Oxidative Palladium(II)-Catalyzed Cross-Dehydrogenative Couplings of Indolines with Arenes and Alkenes at the C-7 Position

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Lin-Yu Jiao
aus Henan, VR China

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Gutachter:	Prof. Dr. Martin Oestreich
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PUBLICATIONS

This work:

[1] "*Oxidative Palladium(II)-Catalyzed Dehydrogenative C–H/C–H Cross-Coupling of 2,3-Substituted Indolines with Arenes at the C-7 Position*",
L.-Y. Jiao, M. Oestreich, *Chem. Eur. J.* **2013**, *19*, 10845–10848.

[2] "*Oxidative Palladium(II)-Catalyzed C-7 Alkenylation of Indolines*",
L.-Y. Jiao, M. Oestreich, *Org. Lett.* **2013**, *15*, 5374–5377.

[3] "*Exceptionally Mild Palladium(II)-Catalyzed Dehydrogenative C–H/C–H Arylation of Indolines at the C-7 Position under Air*",
L.-Y. Jiao, P. Smirnov, M. Oestreich, *Org. Lett.* **2014**, *16*, 6020–6023.

Collaborative work in other projects:

[4] "*Diastereotopic Group Selection in Hydroxy-Directed Intramolecular C–H Alkenylation of Indole under Oxidative Palladium(II) Catalysis*",
S. R. Kandukuri, L.-Y. Jiao, A. B. Machotta, M. Oestreich, *Adv. Synth. Catal.* **2014**, *356*, 1597–1609. (Special Thematic Issue on Directed C–H Functionalization)

[5] "*Synthesis of 2,6-Dihalogenated Purine Nucleosides by Thermostable Nucleoside Phosphorylases*",
X. Zhou, K. Szeker, L.-Y. Jiao, M. Oestreich, I. A. Mikhailopulo, P. Neubauer, *Adv. Synth. Catal.* **2015**, *357*, 1237–1244.

POSTER PRESENTATIONS

[1] L.-Y. Jiao, M. Oestreich*, "*Oxidative Palladium(II)-Catalyzed Cross Dehydrogenative Arylation and Alkenylation of Indolines at the C-7 Position*",
19. Lecture Conference of the Liebig-Vereinigung für Organische Chemie, ORCHEM 2014, Weimar (Germany), September 15–17, **2014**.

[2] L.-Y. Jiao, André V. Ferreira, M. Oestreich*, "*Phosphinic Amide as Directing Group Enabling Palladium(II)-Catalyzed ortho C–H Alkenylation of Anilines without and with Alkylation at the Nitrogen Atom*",
ICIQ-UniCat Summer School in Berlin (Germany), July 6–9, **2015**.

ABSTRACT

Previously, several different kinds of prefunctionlized coupling partners such as boronic acids or organometallic reagents had been used in combination with catalytic amounts of a transition metal to accomplish $C(sp^2)$–$C(sp^2)$ bonds formation. Later, the concept changed to use two unactivated C–H bonds directly under oxidative transition metal catalysis for the same type of reactions.

We describe here an oxidative palladium(II)-catalyzed cross-dehydrogenative arylation of indolines. The palladium(II) catalysis requires TFA as an additive and $Na_2S_2O_8$ as the terminal oxidant. An acetyl group at the indoline nitrogen atom was employed as a directing group, no such group was required at the arene coupling partner. Several mono-, di-, and trisubstituted indolines were subjected to the optimized conditions in moderate to excellent yields. For the annulated indolines, the relative configuration was determined by nOe measurements and was retained throughout the sequence. Remarkably, the amide group alone is not sufficient to allow for this transformation. In addition, NMR experiments showed that the substituent at C-2 position is a crucial factor for the regioselectivity and reactivity. This established protocol, however, requires harsh reaction conditions (100–120 °C) under which less-substituted indolines would undergo oxidation to their corresponding indoles.

Shortly afterwards, we overcame the limitations by using a urea directing group instead of an acetyl group that enabled the same transformation under milder conditions. As a result, the use of either $Cu(OAc)_2$ in an open flask or dioxygen (balloon) at 50 °C tolerates indolines not substituted at C-2 and C-3, thereby extending the scope of the previous method that suffers from indoline-to-indole oxidation. This methodology has been successfully repeated on a gram scale with slightly diminished conversion and yield. It is worth noting that other common directing groups, even a urea with a free N–H group at the terminus, failed to facilitate the C−H bond activation.

By employing the same urea directing group attached to the indoline skeleton, a protocol for the direct alkenylation of indolines at the C-7 position is described. This catalytic system proved to be broadly applicable, mild, and efficient. Both α,β-unsaturated acceptors and styrenes participate in this direct C–H functionalization. Even substituted α,β-unsaturated acceptors reacted, regioselectivities were good to excellent albeit yields were somewhat lower. Notably, with a free N–H group at the urea terminus, the nitrogen atom subsequently cyclizes in a 1,4-fashion to yield a six-membered heterocycle.

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1 INTRODUCTION

It is well known that C–C bond formation is considered as one of the most fundamental synthetic transformations in modern innovative organic chemistry. This challenging object could be realized through several different ways.[1] Among them transition metals,[2] especially palladium-catalyzed cross-coupling reactions[3] present particularly valuable tools. Research in this area is mainly focusing on the invention of efficient catalytic protocols and the extension of the substrate scopes to different types of transformations depending on the nature of the starting materials and coupling partners, such as the MIZOROKI–HECK reaction,[4] KUMADA coupling,[5] STILLE coupling,[6] NEGISHI reaction,[7] SUZUKI–MIYAURA reaction,[8] HIYAMA reaction,[9] as well as TSUJI–TROST allylation.[10] To highlight the great contribution in this field, the NOBEL Prize in Chemistry in 2010 was awarded jointly to these three pioneers of organic chemistry - R. F. HECK, E.-I. NEGISHI, and A. SUZUKI - *for palladium-catalyzed cross couplings in organic synthesis*.[11]

The mechanisms of transition metals, especially palladium catalysis involving C−H bond activation are topics of ongoing discussion in the literature,[12] and several different modes

[1] a) A. Bhunia, S. R. Yetra, A. T. Biju, *Chem. Soc. Rev.* **2012**, *41*, 3140–3152; b) I. D. G. Watson, F. D. Toste, *Chem. Sci.* **2012**, *3*, 2899–2919.

[2] a) T.-Y. Luh, M.-k. Leung, K.-T. Wong, *Chem. Rev.* **2000**, *100*, 3187–3204; b) *Cross-Coupling Reactions: A Practical Guide* (Ed: N. Miyaura), Springer, Berlin, **2002**; c) V. Ritleng, C. Sirlin, M. Pfeffer, *Chem. Rev.* **2002**, *102*, 1731–1770; d) D. A. Colby, R. G. Bergman, J. A. Ellman, *Chem. Rev.* **2010**, *110*, 624–655; e) *Metal-Catalyzed Cross-Coupling Reactions and More* (Ed: A. de Meijere, S. Bräse, M. Oestreich), Wiley-VCH, Weinheim, **2014**.

[3] a) *Handbook of Organopalladium Chemistry for Organic Synthesis* (Ed.: E.-i. Negishi), Wiley, New York, **2002**; b) K. C. Nicolaou, P. G. Bulger, D. Sarlah, *Angew. Chem.* **2005**, *117*, 4516–4563; *Angew. Chem. Int. Ed.* **2005**, *44*, 4442–4489; c) C.-L. Sun, B.-J. Li, Z.-J. Shi, *Chem. Commun.* **2010**, *46*, 677–685; d) X.-F. Wu, P. Anbarasan, H. Neumann, M. Beller, *Angew. Chem.* **2010**, *122*, 9231–9234; *Angew. Chem. Int. Ed.* **2010**, *49*, 9047–9050.

[4] a) I. P. Beletskaya, A. V. Cheprakov, *Chem. Rev.* **2000**, *100*, 3009–3066; b) *The Mizoroki–Heck Reaction* (Ed.: M. Oestreich), Wiley, Chichester, **2009**.

[5] C. E. I. Knappke, A. J. von Wangelin, *Chem. Soc. Rev.* **2011**, *40*, 4948–4962.

[6] a) J. K. Stille, *Angew. Chem.* **1986**, *98*, 504–519; *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 508–524; b) V. Farina, V. Krishnamurthy, W. J. Scott, *Org. React.* **1998**, *50*, 1–652.

[7] E.-i. Negishi, *Acc. Chem. Res.* **1982**, *15*, 340–348.

[8] a) N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, 95, 2457–2483; b) F.-S. Han, *Chem. Soc. Rev.* **2013**, *42*, 5270–5298.

[9] H. F. Sore, W. R. J. D. Galloway, D. R. Spring, *Chem. Soc. Rev.* **2012**, *41*, 1845–1866.

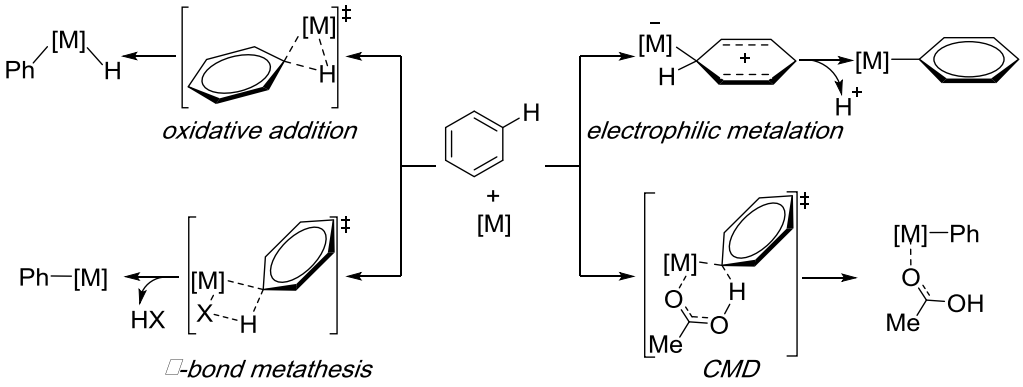
[10] B. M. Trost, M. L. Crawley, *Chem. Rev.* **2003**, *103*, 2921–2944.

[11] a) A. Suzuki, *Angew. Chem.* **2011**, *123*, 6854–6869; *Angew. Chem. Int. Ed.* **2011**, *50*, 6722–6737; b) E.-i. Negishi, *Angew. Chem.* **2011**, *123*, 6870–6897; *Angew. Chem. Int. Ed.* **2011**, *50*, 6738–6764.

[12] For selected reports that summarize mechanistic aspects of C–H bond activation, see: a) A. E. Shilov, G. B. Shul'pin, *Chem. Rev.* **1997**, *97*, 2879–2932; b) J. A. Labinger, J. E. Bercaw, *Nature* **2002**, *417*, 507–514; c) S. Sakaki, *Top. Organomet. Chem.* **2005**, *12*, 31–78; d) *Handbook of C–H Transformations: Applications in Organic Synthesis* (Ed.: G. Dyker), Wiley-VCH, Weinheim, **2005**; e) R. G. Bergman, *Nature* **2007**, *446*, 391–

such as oxidative addition, σ-bond metathesis, electrophilic palladation, and concerted metalation/deprotonation (CMD) have been previously proposed, and the latter two pathways are commonly thought to predominate in these transformations.

The first and most commonly accepted pathway is oxidative addition (Scheme 1.1, upper left). It starts from the coordination of the target C–H bond to a vacant position of palladium and results in the generation of a Pd–C and a Pd–H bond. This intermediate was defined as a "true" metal complex cation by SHILOV and SHUL'PIN.[12a] In this case, the closest interaction between a palladium(II) cation and a C–H bond is obtained. This pathway is typical for electron-rich late transition metals since higher oxidation states are required.



Scheme 1.1: Common mechanisms of transition metal-catalyzed C−H bond activation.

The σ-bond metathesis pathway (Scheme 1.1, lower left), which is common for early transition metals, is favored and characterized by concerted formation and cleavage of bonds in the transition state. It is likely that the metal serves as a LEWIS acid, and as a result, hydrogen atom of the arene is substituted. This pathway is also classified as electrophilic substitution reaction.

The third pathway is the electrophilic metalation (Scheme 1.1, upper right).[13] It involves a rate-determining nucleophilic attack of electron-rich arenes at an electrophilic palladium(II) species, followed by a rapid deprotonation of the intermediate to form a Pd–C bond. In this case, the regioselectivity is governed mainly by the electrophilic metalation at the more nucleophilic position; additional migration occasionally happens, depending most likely on the reaction conditions employed.

The last mode of C–H bond activation is named concerted metalation/deprotonation (CMD) (Scheme 1.1, lower right). In this pathway, the formation of the [M]–C bond occurs simultaneously with the cleavage of the arene's C–H bond to generate a metaloarene

393; f) L. Ackermann, *Chem. Rev.* **2011**, *111*, 1315–1345; g) M. García-Melchor, A. A. C. Braga, A. Lledós, G. Ujaque, F. Maseras, *Acc. Chem. Res.* **2013**, *46*, 2626–2634.

[13] a) C.-H. Park, V. Ryabova, I. V. Seregin, A. W. Sromek, V. Gevorgyan, *Org. Lett.* **2004**, *6*, 1159–1162; b) B. S. Lane, M. A. Brown, D. Sames, *J. Am. Chem. Soc.* **2005**, *127*, 8050–8057.

intermediate. Several research groups have revealed computationally that a carbonate base or acetate ligand coordinated to the [M]–aryl intermediate promote this C–H bond activation pathway,[14] which is in agreement with experimental observations.[15] One of the examples involves the arylation of pentafluorobenzene *via* a six-membered transition state.[16]

Besides, according to the insight observations obtained from advanced computational methods, novel C–H bond activation mechanisms are also presented, such as GODDARD's recent suggestion of an "oxidative hydrogen migration" pathway.[17]

It should definitely be noted that the proposed mechanisms cannot be universally valid since there is substantial difference between the substrates. For instance, DAVIES and MACGREGOR recently proposed a palladium-catalyzed agnostic complex[18] rather than a WHELAND intermediate,[19] which overthrew the previous suggestions proposed by the RYABOV group.[20] By the aid of DFT calculations, these authors demonstrated that the rate-limiting step involves the electrophilic attack of the palladium at an *ortho* arene C−H bond directed by nitrogen atom. The cyclometalation product is then generated by intramolecular deprotonation with acetate *via* a six-membered transition state, which has almost no energy barrier.

Based on the well-established transition metal catalysis, one of the most popular traditional methods for the construction of conjugated structures is the MIZOROKI–HECK reaction, that is the cross-coupling between aryl halides (Cl, Br, I) or aryl triflates (OTf) and alkenes to deliver alkenes with exclusive *trans* selectivity under non-oxidative conditions (Scheme 1.2, **A** → (*E*)-**D**). Likewise, this transformation could also be improved by the use of unactivated aromatic C–H bonds instead in an oxidative pathway which is known as the FUJIWARA–MORITANI reaction or oxidative HECK reaction[21] (Scheme 1.2, **B** → (*E*)-**D**). This

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[14] a) L.-C. Campeau, M. Parisien, M. Leblanc, K. Fagnou, *J. Am. Chem. Soc*. **2004**, *126*, 9186–9187; b) M. Leblanc, K. Fagnou, *Org. Lett.* **2005**, *7*, 2849–2852; c) L.-C. Campeau, M. Parisien, A. Jean, K. Fagnou, *J. Am. Chem. Soc*. **2006**, *128*, 581–590; for a discussion of concerted metalation deprotonation, see: d) M. Lafrance, C. N. Rowley, T. K. Woo, K. Fagnou, *J. Am. Chem. Soc.* **2006**, *128*, 8754–8756; e) H.-Y. Sun, S. I. Gorelsky, D. R. Stuart, L.-C. Campeau, K. Fagnou, *J. Org. Chem.* **2010**, *75*, 8180–8189.

[15] a) D. García-Cuadrado, A. A. C. Braga, F. Maseras, A. M. Echavarren, *J. Am. Chem. Soc.* **2006**, *128*, 1066–1067; b) S. I. Gorelsky, D. Lapointe. K. Fagnou, *J. Am. Chem. Soc.* **2008**, *130*, 10848–10849.

[16] H. Li, J. Liu, C.-L. Sun, B.-J. Li, Z.-J. Shi, *Org. Lett.* **2011**, *13*, 276–279.

[17] J. Oxgaard, R. P. Muller, W. A. Goddard, R. A. Periana, *J. Am. Chem. Soc.* **2004**, *126*, 352–363.

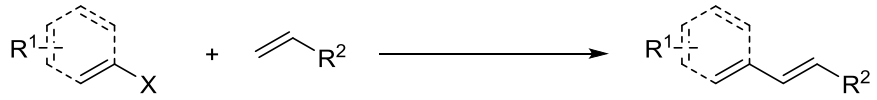
[18] a) Y. Boutadla, D. L. Davies, S. A. Macgregor, A. I. Poblador-Bahamonde, *Dalton Trans.* **2009**, 5820–5831; b) D. L. Davies, S. M. A. Donald, S. A. Macgregor, *J. Am. Chem. Soc.* **2005**, *127*, 13754–13755.

[19] G. W. Wheland, *J. Am. Chem. Soc.* **1942**, *64*, 900–908.

[20] a) A. D. Ryabov, *Chem. Rev*. **1990**, *90*, 403–424; b) A. D. Ryabov, I. K. Sakodinskaya, A. K. Yatsimirsky, *J. Chem. Soc. Dalton Trans*. **1985**, 2629–2638.

[21] For selected reviews, see: a) E. M. Beccalli, G. Broggini, M. Martinelli, S. Sottocornola, *Chem. Rev.* **2007**, *107*, 5318–5365; b) E. M. Ferreira, H. Zhang, B. M. Stoltz in The Mizoroki–Heck Reaction (Ed.: M. Oestreich), Wiley, Chichester, **2009**, pp. 345–382; c) X. Chen, K. M. Engle, D.-H. Wang, J.-Q. Yu, *Angew. Chem.* **2009**, *121*, 5196–5217; *Angew. Chem. Int. Ed.* **2009**, *48*, 5094–5115; d) R. Giri, B.-F. Shi, K. M. Engle, N. Maugel, J.-Q. Yu, *Chem. Soc. Rev*. **2009**, *38*, 3242–3272; e) J. L. Bras, J. Muzart, *Chem. Rev.* **2011**, *111*, 1170–1214; f) C. S. Yeung, V. M. Dong, *Chem. Rev.* **2011**, *111*, 1215–1292; g) K. M. Engle, J.-Q. Yu, *J. Org. Chem*. **2013**, *78*, 8927−8955.

direct reaction would bypass the demand of prefunctionalized coupling partners in a more efficient fashion and found widespread use in synthetic organic chemistry. Additionally, for the FUJIWARA–MORITANI reaction, the regioselectivity is controlled by the introduction of a directing group.



A (X = halide or triflate) **C** (*E*)-**D**
B (X = H)

Scheme 1.2: Palladium(0)- or palladium(II)-catalyzed C(sp^2)–C(sp^2) bond formation through MIZOROKI–HECK and FUJIWARA–MORITANI reactions, respectively.

Compared with the alkenylation of arenes, the synthesis of other aryl containing conjugated compounds through transition metal catalysis are also very interesting and well documented during the past decades.[22] As widely existent and very important motifs in bioactive molecules, natural products, and functional materials, biaryl compounds have captured growing attention from the synthetic organic chemistry community.[23] To date, preparation of biaryl compounds has been accomplished both with stoichiometric[24] and catalytic[25] amounts of palladium salts. In early examples, intramolecular C–C coupling reactions were successfully applied to the synthesis of dibenzofurans.[26,27]

The SUZUKI reaction and other related processes were recently represented of straightforward methods for the construction of these compounds.[8] Importantly, in order to accomplish these types of high yielding transformations, organoboron precursors ($B(OH)_2$, Bpin, BF_3K) and aryl halides (Cl, Br, I) as well as aryl triflates (OTf) are always employed as

[22] For reviews dedicated to direct C–H bond activation, see: a) L. Ackermann, R. Vicente, A. R. Kapdi, *Angew. Chem.* **2009**, *121*, 9976–10011; *Angew. Chem. Int. Ed.* **2009**, *48*, 9792–9826; b) J. A. Ashenhurst, *Chem. Soc. Rev.* **2010**, *39*, 540–548; c) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147–1169; d) C. Liu, H. Zhang, W. Shi, A. Lei, *Chem. Rev.* **2011**, *111*, 1780–1824; e) W. Shi, C. Liu, A. Lei, *Chem. Soc. Rev.* **2011**, *40*, 2761–2776; f) Ref. [21d]; g) S. H. Cho, J. Y. Kim, J. Kwak, S. Chang, *Chem. Soc. Rev.* **2011**, *40*, 5068–5083; h) X. Bugaut, F. Glorius, *Angew. Chem.* **2011**, *123*, 7618–7620; *Angew. Chem. Int. Ed*. **2011**, *50*, 7479–7481; i) N. Kuhl, M. N. Hopkinson, J. Wencel-Delord, F. Glorius, *Angew. Chem.* **2012**, *124*, 10382–10401; *Angew. Chem. Int. Ed.* **2012**, *51*, 10236–10254; j) I. Hussain, T. Singh, *Adv. Synth. Catal*. **2014**, *356*, 1661–1696.

[23] For selected reviews, see: a) G. Bringmann, C. Günther, M. Ochse, O. Schupp, S. Tasler, *Prog. Chem. Org. Nat. Prod.* **2001**, *82*, 1–294; b) G. Bringmann, A. J. Price Mortimer, P. A. Keller, M. J. Gresser, J. Garner, M. Breuning, *Angew. Chem*. **2005**, *117*, 5518–5563; *Angew. Chem. Int. Ed.* **2005**, *44*, 5384–5427; c) L. McMurray, F. O'Hara, M. J. Gaunt, *Chem. Soc. Rev*. **2011**, *40*, 1885–1898.

[24] R. van Helden, G. Verberg, *Recl. Trav. Chim. Pays-Bas.* **1965**, *84*, 1263–1273.

[25] a) H. Iataaki, H. Yoshimoto, *J. Org. Chem.* **1973**, *38*, 76–79; b) H. Yoshimoto, H. Itatani, *J. Catal.* **1973**, *31*, 8–12; c) F. R. S. Clark, R. O. C. Norman, C. B. Thomas, J. S. Wilson, *J. Chem. Soc. Perkin Trans. 2* **1974**, 1289–1295.

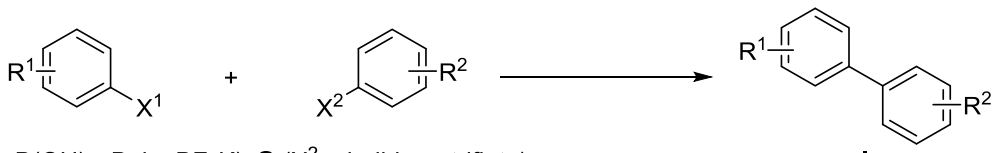
[26] A. Shiotani, H. Itatani, *Angew. Chem.* **1974**, *86*, 478–479; *Angew. Chem. Int. Ed. Engl*. **1974**, *13*, 471–472.

[27] For further early contributions, see: a) H. Yoshimoto, H. Itatani, *Bull. Chem. Soc. Jpn*. **1973**, *46*, 2490–2492; b) B. Akermark, L. Eberson, E. Jonsson, E. Petterson, *J. Org. Chem.* **1975**, *40*, 1365–1367; c) H.-J. Knölker, N. O'Sullivan, *Tetrahedron Lett*. **1994**, *35*, 1695–1698.

cross-coupling partners. However, the advantages of such components were mitigated by the demand for the functionalization prior to use (Scheme 1.3, **E** + **G** → **I**).

As a consequence, a modified route was then disclosed by the replacing of aryl halides with unactivated arenes directly involving a C–H bond activation process (Scheme 1.3, **E** + **H** → **I**). Since C–H bonds are ubiquitous in organic compounds, it exhibits as an atom economic and efficient process. In contrast to reactive C–X bonds, the C–H bond is much more inert. This was proven to be more convenient, although one preactivated coupling partner is still required. With regard to selectivity, it is worthy of mention that in this variant, a "regio-guide factor" such as directing group was always essential to control the regioselectivity.[22]

Spurred by the claim of green and sustainable chemistry, the invention of more efficient alternatives is demanded. In this context, the cross-dehydrogenative coupling (CDC) between two simple arenes moved into the focus of oxidative palladium catalysis and represents a powerful alternative for the preparation of biaryl compound (Scheme 1.3, **F** + **H** → **I**).



E (X^1 = $B(OH)_2$, Bpin, BF_3K) **G** (X^2 = halide or triflate)
F (X^1 = H) **H** (X^2 = H)
I

Scheme 1.3: Palladium(0)- or palladium(II)-catalyzed $C(sp^2)$–$C(sp^2)$ bond formation for the preparation of biaryl compounds through SUZUKI and CDC reactions.

Importantly, the aforementioned FUJIWARA–MORITANI and cross-dehydrogenative arylation reactions are not only advantageous to the overall suppression of the formation of byproducts but also satisfying the demand of streamlining organic syntheses.

1.1 DIRECTING GROUPS IN OXIDATIVE PALLADIUM-CATALYZED C–H BOND FUNCTIONALIZATION

As mentioned, the directing groups, also known as coordinating ligands, are designed and introduced in response to the regioselectivity problems encountered with C–H bond activation and generally play an important role in the transition metal catalysis.[28] They always bind to the metal center selectively and are capable of positively minimizing the

[28] a) K. M. Engle, T.-S. Mei, M. Wasa, J.-Q. Yu, *Acc. Chem. Res*. **2012**, *45*, 788–802; b) S. R. Neufeldt, M. S. Sanford, *Acc. Chem. Res*. **2012**, *45*, 936–946; c) M. Zhang, Y. Zhang, X. Jie, H. Zhao, G. Li, W, Su, *Org. Chem. Front*. **2014**, *1*, 843–895; d) G. Shi, Y. Zhang, *Adv. Synth. Catal*. **2014**, *356*, 1419–1442; e) Q.-Z. Zheng, N. Jiao, *Tetrahedron Lett*. **2014**, 55, 1121–1126.

inherent limitation of the C–H bond to a great extent. Hence, the application of directing groups is to date still the best means to control the chemo- and regioselectivity to enhance/change the reactivity. Based on these principles, major efforts have been made in the organic chemistry community to develop truly practical and powerful directing groups.

Directing groups possess of several advantages, including directing the transition metal into close proximity to the C–H bond to be activated/cleaved, higher effective concentration of the catalyst at the site of interest as well as high levels of regioselectivity and increased reactivity. Furthermore, the introduction of a directing group has also been successfully in avoiding the formation of intractable mixtures of undesired regioisomeric homo- and heterocoupled biaryl compounds.

However, directing groups are disadvantageous because they are sometimes synthetically restrictive owing to their strong coordination properties. Additionally, in most cases, they are serving as *ortho* directing groups, and need to be installed prior to use and removed afterwards which are largely complicated.[29] Therefore, the invention of easily installable and removable or modifiable directing groups remains a critical goal.

1.2 OXIDATIVE PALLADIUM(II)-CATALYZED CROSS-DEHYDROGENATIVE COUPLING REACTIONS WITH ALKENES

Pioneering studies by FUJIWARA, MORITANI and co-workers since the late 1960s focused on the coupling of unactivated C–H bonds with alkenes under palladium catalysis, showcasing the first example of a C–C bond formation through C–H bond activation process.[30] Inspired by these initial achievements, during the past decades, this process has matured to become a valuable approach for the preparation of substituted alkenes from substrates with or without chelation assistance.[31]

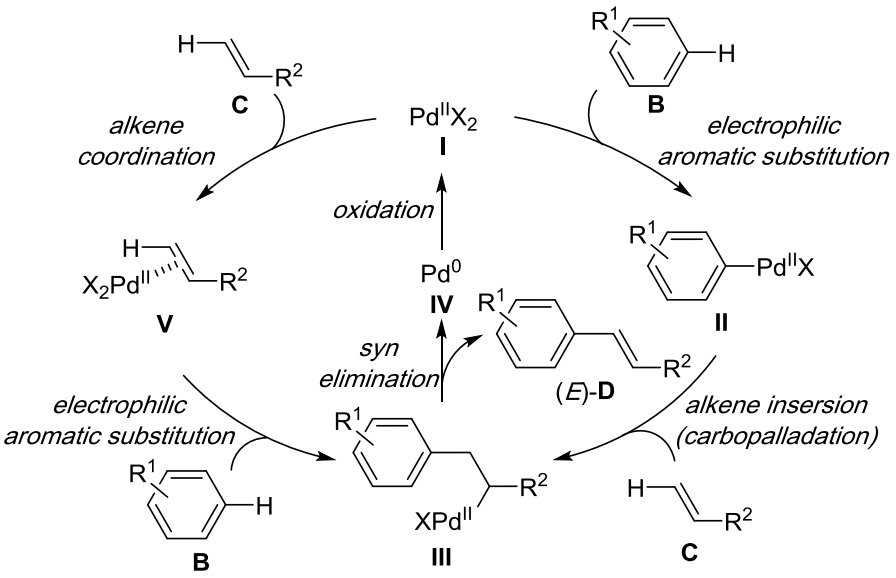
There are two generally plausible pathways of the well-studied FUJIWARA–MORITANI reaction (Scheme 1.4). The first one involves the electrophilic palladation of aryl compounds **B** reacting with a palladium salt to form an arylpalladium intermediate **II** through a C–H bond activation process, followed by a *syn*-alkene insertion of **C** into the Pd–C bond to generate

[29] a) D. W. Robbins, T. A. Boebel, J. F. Hartwig, *J. Am. Chem. Soc.* **2010**, *132*, 4068–4069; b) A. García-Rubia, M. Á. Fernández-Ibáñez, R. G. Arrayás, J. C. Carretero, *Chem. Eur. J.* **2011**, *17*, 3567–3570.

[30] a) I. Moritani, Y. Fujiwara, *Tetrahedron Lett.* **1967**, *8*, 1119–1122; b) Y. Fujiwara, I. Moritani, M. Matsuda, S. Teranishi, *Tetrahedron Lett.* **1968**, *9*, 633–636; c) Y. Fujiwara, I. Moritani, M. Matsuda, S. Teranishi, *Tetrahedron Lett.* **1968**, *9*, 3863–3865; d) Y. Fujiwara, I. Moritani, S. Danno, R. Asano, S. Teranishi, *J. Am. Chem. Soc.* **1969**, *91*, 7166–7169.

[31] a) C. Jia, T. Kitamura, Y. Fujiwara, *Acc. Chem. Res.* **2001**, *34*, 633–639; b) N. Kuhl, M. N. Hopkinson, J. Wencel-Delord, F. Glorius, *Angew. Chem.* **2012**, *124*, 10382–10401; *Angew. Chem. Int. Ed.* **2012**, *51*, 10236–10254.

alkylpalladium complex **III** (Scheme 1.4, right). Afterwards, it undergoes *syn*-β-H elimination to deliver the alkenylation product (*E*)-**D** and palladium(0) species **IV**. The final step is to reoxidize palladium(0) to palladium(II) by a terminal oxidant. Alternatively, the other mechanism is initiated by palladium-catalyzed alkene activation *via* coordination (Scheme 1.4, left). The resulting intermediate **V** is more electrophilic and is prone to undergo nucleophilic addition with electron-rich arenes. After C–C bond formation and rearomatization, the same alkylpalladium complex **III** is formed and undergoes identical process to complete the catalytic cycle.



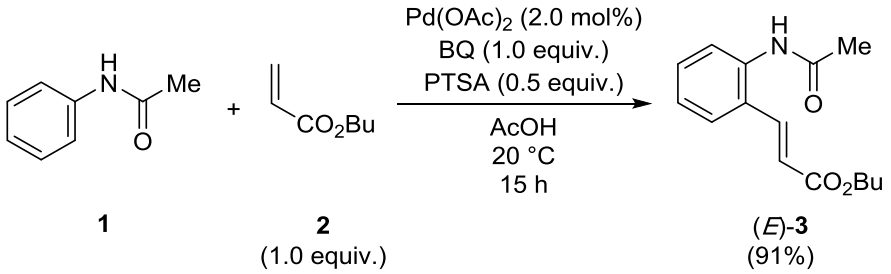
Scheme 1.4: General catalytic cycles for the FUJIWARA–MORITANI reaction.

1.2.1 Oxidative Palladium(II)-Catalyzed Cross-Dehydrogenative Alkenylation with Directing Groups

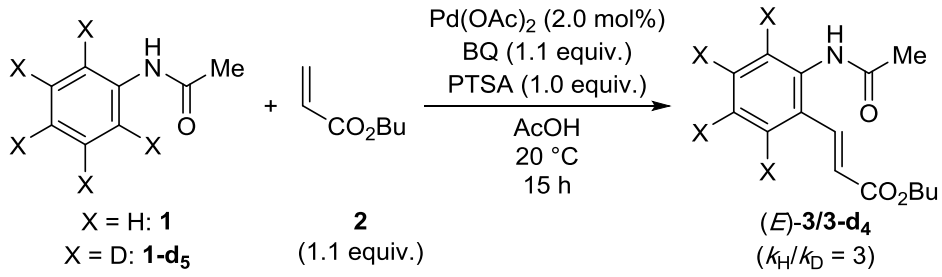
To date, heteroatoms such as nitrogen- and oxygen-containing directing groups have proven to be effective factors to promote C–H bond functionalization. In 2002, a groundbreaking example was disclosed by the DE VRIES and VAN LEEUWEN group (Scheme 1.5).[32] This oxidative palladium(II)-catalyzed alkenylation proceeded at ambient temperature in acidic media between the aniline **1** and *n*-butyl acrylate (**2**). 1,4-Benzoquinone (BQ) as terminal oxidant was essential for efficient catalytic turnover. Several aniline derivatives with different electronic properties were evaluated under the optimized conditions in moderate to excellent yields. Methyl-substituted acetaniline did not provide any product at all. Mechanistic studies exhibited a kinetic isotope effect (KIE) (k_H/k_D = 3), indicating C–H bond activation was the

[32] M. D. K. Boele, G. P. F. van Strijdonck, A. H. M. de Vries, P. C. J. Kamer, J. G. de Vries, P. W. N. M. van Leeuwen, *J. Am. Chem. Soc.* **2002**, *124*, 1586–1587.

rate-determining step (Scheme 1.6).[33] This contribution indeed set the stage for the recent remarkable progress in this area and several examples were highlighted by the use of this widespread acetyl directing group and aniline substrates.[34,35]



Scheme 1.5: Alkenylation between aniline derivatives and acrylate by DE VRIES and VAN LEEUWEN.



Scheme 1.6: Kinetic isotope effect (KIE) study for palladium(II)-catalyzed oxidative *ortho*-alkenylation of anilides at room temperature.

1.2.1.1 Nitrogen- and Oxygen-Containing Directing Groups

In 2010, the YU group disclosed the mono- and dialkenylation of phenylacetic acid **4** with the aid of a carboxylate group under palladium catalysis (Scheme 1.7).[36] The Boc-protected amino acid ligand **L1** was found to be crucial to promote the transformation by substantially increasing the reactivity even with problematic substrates. In the end, the synthetic utility of

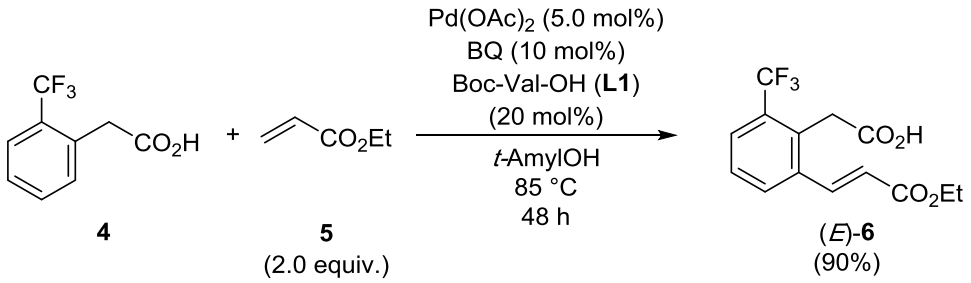
[33] M. Gómez-Gallego, M. A. Sierra, *Chem. Rev.* **2011**, *111*, 4857–4963.

[34] For reports related to palladium-catalyzed C–H bond alkenylation using acetyl as directing groups, see: a) G. T. Lee, X. Jiang, K. Prasad, O. Repič, T. J. Blacklock, *Adv. Synth. Catal.* **2005**, *347*, 1921–1924; b) C. Amatore, C. Cammoun, A. Jutand, *Adv. Synth. Catal.* **2007**, *349*, 292–296; c) B. S. Kim, C. Jang, D. J. Lee, S. W. Youn, *Chem. Asian J.* **2010**, *5*, 2336–2340; d) W. Rauf, A. L. Thompson, J. M. Brown, *Dalton Trans.* **2010**, *39*, 10414–10421; e) T. Nishikata. B. H. Lipshutz, *Org. Lett.* **2010**, *12*, 1972–1975; f) X. Liu, K. K. Hii, *J. Org. Chem.* **2011**, *76*, 8022–8026; g) B. Schmidt, N. Elizarov, *Chem. Commun.* **2012**, *48*, 4350–4352; h) S. R. Kandukuri, J. A. Schiffner, M. Oestreich, *Angew. Chem.* **2012**, *124*, 1291–1295; *Angew. Chem. Int. Ed.* **2012**, *51*, 1265–1269; i) Y. Gao, Y. Huang, W. Wu, K. Huang, H. Jiang, *Chem. Commun.* **2014**, *50*, 8370–8373.

[35] For reports related to palladium-catalyzed C–H bond alkenylation of aniline derivatives, see: a) W. Rauf, A. L. Thompson, J. M. Brown, *Chem. Commun.* **2009**, 3874–3876; b) G. T. Lee, X. Jiang, K. Prasad, O. Repič, T. J. Blacklock, *Adv. Synth. Catal.* **2005**, *347*, 1921–1924; c) J.-R. Wang, C.-T. Yang, L. Liu, Q.-X. Guo, *Tetrahedron Lett.* **2007**, *48*, 5449–5453.

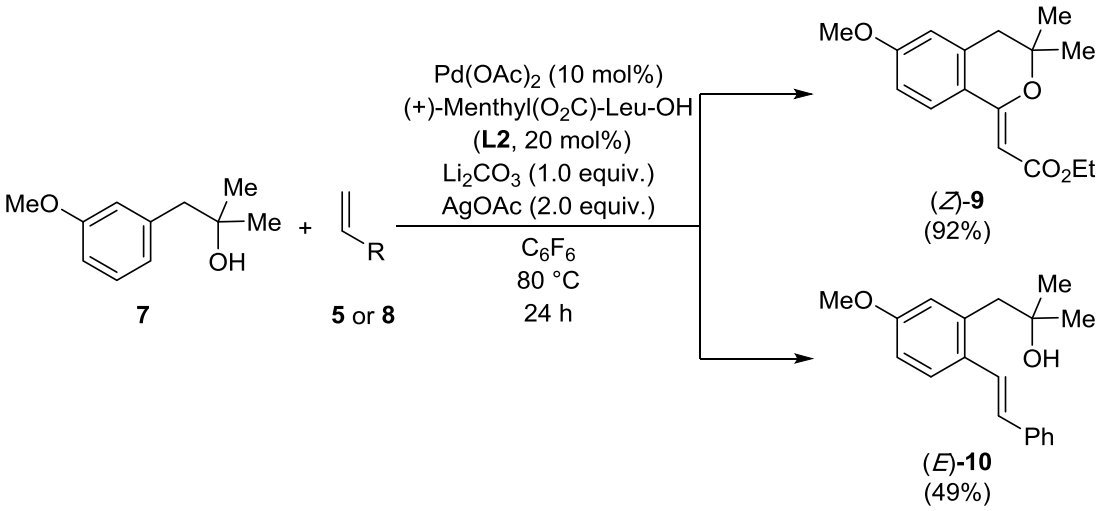
[36] D.-H. Wang, K. M. Engle, B.-F. Shi, J.-Q. Yu, *Science* **2010**, *327*, 315–319.

this method was demonstrated by a highly versatile and scalable alkenylation reaction for concise syntheses of several natural products. This contribution was followed by intensive studies in the same research group.[37]



Scheme 1.7: Carboxylate group-directed alkenylation of arenes under palladium(II) catalysis by YU.

In the same year, the same group reported that the homobenzylic hydroxyl groups were also efficient directing groups in alkenylation of arenes (Scheme 1.8).[38] The reactions were first conducted with tertiary alcohols, which are prone to decomposition under oxidative palladium(II) catalysis.[39] The catalytic efficiency was greatly enhanced when mono-*N*-protected amino acid (MPAA) **L2** was employed as ligands together with Li_2CO_3 as base. Under the optimized conditions, electron-poor alkenes always underwent a domino reaction, resulting in the pyran (*Z*)-**9**; however, electron-neutral alkenes could afford the desired alkenylated target compound (*E*)-**10** only with moderate reactivity.



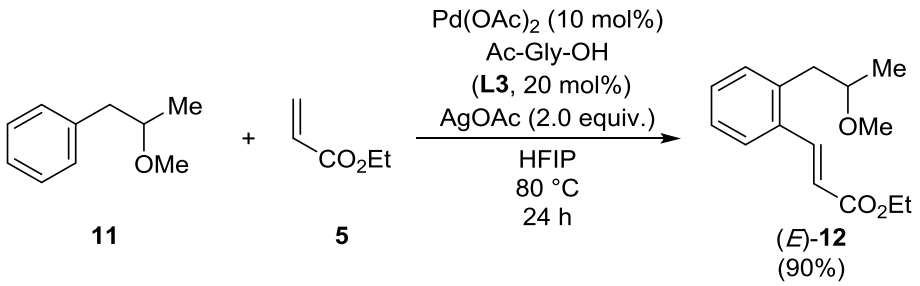
[37] a) K. M. Engle, D.-H. Wang, J.-Q. Yu, *Angew. Chem.* **2010**, *122*, 6305–6309; *Angew. Chem. Int. Ed.* **2010**, *49*, 6169–6173; b) K. M. Engle, D.-H. Wang, J.-Q. Yu, *J. Am. Chem. Soc.* **2010**, *132*, 14137–14151; c) T.-S. Mei, D.-H. Wang, J.-Q. Yu, *Org. Lett.* **2010**, *12*, 3140–3143; d) D.-H. Wang, J.-Q. Yu, *J. Am. Chem. Soc.* **2011**, *133*, 5767–5769; for an asymmetric variant, see: e) B.-F. Shi, Y.-H. Zhang, J. K. Lam, D.-H. Wang, J.-Q. Yu, *J. Am. Chem. Soc.* **2010**, *132*, 460–461.

[38] a) A. Lu, D.-H. Wang, K. M. Engle, J.-Q. Yu, *J. Am. Chem. Soc.* **2010**, *132*, 5916–5921; also see: b) C. Zhang, J. Ji, P. Sun, *J. Org. Chem.* **2014**, *79*, 3200−3205, c) S. R. Kandukuri, L.-Y. Jiao, A. B. Machotta, M. Oestreich, *Adv. Synth. Catal.* **2014**, *356*, 1597–1609.

[39] J. Muzart, *Tetrahedron* **2005**, *61*, 9423–9463.

Scheme 1.8: Benzylic hydroxy group-directed alkenylation of arenes under palladium(II) catalysis by YU.

In addition to the free alcohol, ether or methoxy groups also serve as directing groups in the same transformation, reported by the YU group (Scheme 1.9).[40] The combined precatalyst of palladium(II) and monoprotected amino acid ligand **L3** proven to be effective.



11 **5** (*E*)-**12** (90%)

Scheme 1.9: Methyl-ether-directed alkenylation of arenes under palladium(II) catalysis by YU.

A few years ago, two very interesting studies were published regarding palladium-catalyzed C–H bond activation for C–C bond formation starting from aromatic *N*-oxides **13** and **15**. In 2008, the CHANG group reported with the aid of oxygen attached to nitrogen atom of pyridine, both simple arenes (not shown) and alkenes could couple selectively at the C-2 position (Scheme 1.10, upper).[41] During this work, these authors observed that the separately prepared complex C_5H_5NO–$PdCl_2(PPh_3)$ did not react under the same conditions, indicating that this intermediate was probably not part of the catalytic cycle. Another related report was disclosed by CUI and WU one year later (Scheme 1.10, lower).[42] It is well known that *N*-oxides, especially pyridine *N*-oxides, serve as prototypical oxygen atom transfer reagents.[43] In agreement with this property, the authors found that the quinoline *N*-oxide **15** plays a dual role both as directing group and as internal oxidant. The reactions performed quite well under external-oxidant-free conditions. During the transformation, the N–O bond was cleaved and alkenylated quinoline (*E*)-**16** and isoquinoline were obtained smoothly.[44]

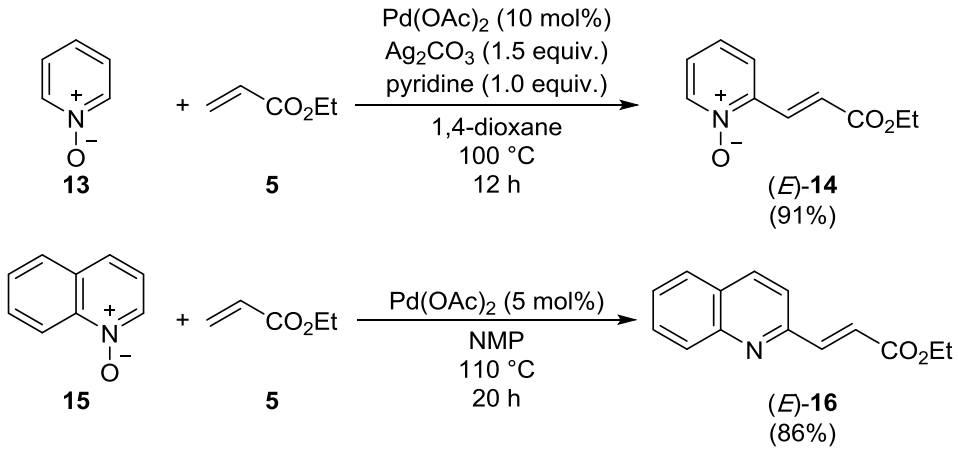
[40] G. Li, D. Leow, L. Wan, J.-Q. Yu, *Angew. Chem.* **2012**, 125, 1283–1285; *Angew. Chem. Int. Ed.* **2012**, *52*, 1245–1247.

[41] S. H. Cho, S. J. Hwang, S. Chang, *J. Am. Chem. Soc.* **2008**, *130*, 9254–9256.

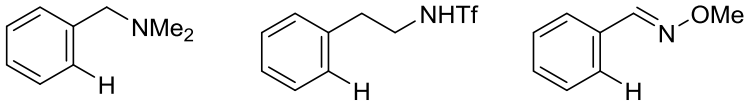
[42] J. Wu, X. Cui, L. Chen, G. Jiang, Y. Wu, *J. Am. Chem. Soc.* **2009**, *131*, 13888–13889.

[43] a) C. C. Cummins, R. R. Schrock, W. M. Davis, *Inorg. Chem.* **1994**, *33*, 1448–1457; b) D. S. J. Arney, C. J. Burns, *J. Am. Chem. Soc.* **1995**, *117*, 9448–9460; c) K.-M. Sung, R. H. Holm, *J. Am. Chem. Soc.* **2001**, *123*, 1931–1943; d) S. M. Mullins, A. P. Duncan, R. G. Bergman, J. Arnold, *Inorg. Chem.* **2001**, *40*, 6952–6963.

[44] For other nitrogen-containing directing groups, see: a) G. Cai, Y. Fu, Y. Li, X. Wan, Z. Shi, *J. Am. Chem. Soc.* **2007**, *129*, 7666–7673; b) J.-J. Li, T.-S. Mei, J.-Q. Yu, *Angew. Chem.* **2008**, *120*, 6552–6555; *Angew. Chem. Int. Ed.* **2008**, *47*, 6452–6455; c) Z. Xu, B. Xiang, P. Sun, *Eur. J. Org. Chem.* **2012**, 3069–3073.



Scheme 1.10: Palladium(II)-catalyzed alkenylation of pyridines and quinolines by CHANG, CUI, and WU.



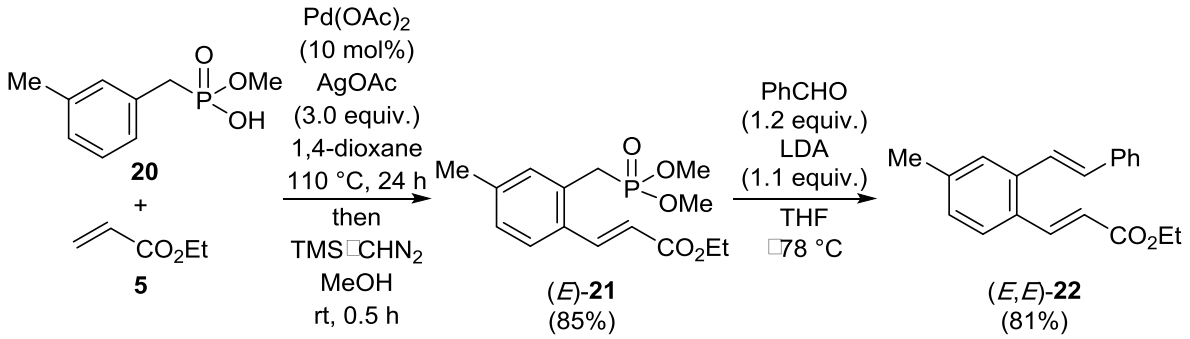
Scheme 1.11: Recent other nitrogen-containing directing groups by SHI, YU, and SUN.

1.2.1.2 Phosphorus -, Silicon-, and Sulfur- Containing Directing Groups

In addition to nitrogen and oxygen, other heteroatoms can also act as directing factors in C–H bond activation. Similar to phenylacetic acids reported by YU and co-workers,[36] the KIM group succeeded recently in developing a monophosphonic acid directing group in C–H bond alkenylation of arenes under oxidative palladium catalysis (Scheme 1.12).[45] AgOAc and 1,4-dioxane were employed as oxidant and solvent, respectively. Interestingly, the resulting product could further undergo a HORNER–WADSWORTH–EMMONS reaction to form dialkene product (*E*,*E*)-**22** in good yield. Furthermore, other phosphorus-related directing groups were also developed for transition metal catalysis.[46]

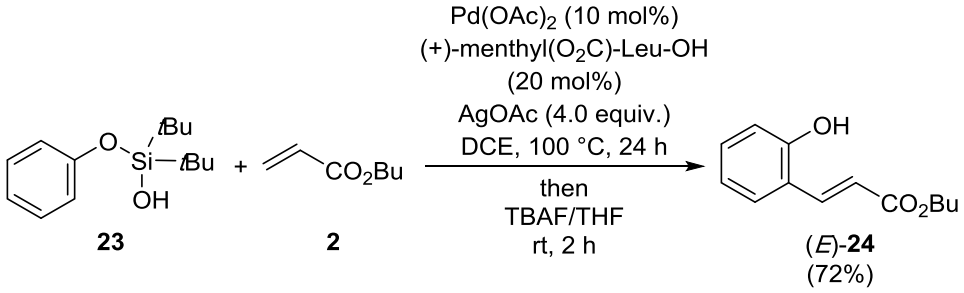
[45] X. Meng, S. Kim, *Org. Lett.* **2013**, *15*, 1910–1913.

[46] a) L. Y. Chan, S. Kim, T. Ryu, P. H. Lee, *Chem. Commun.* **2013**, *49*, 4682–4684; b) J. Seo, Y. Park, I. Jeon, T. Ryu, S. Park, P. H. Lee, *Org. Lett.* **2013**, *15*, 3358–3361; c) X. Meng, S. Kim, *J. Org. Chem.* **2013**, *78*, 11247–11254; d) H.-L. Wang, R.-B. Hu, H. Zhang, A.-X. Zhou, S.-D. Yang, *Org. Lett.* **2013**, *15*, 5302–5305; e) J. Mo, S. Lim, S. Park, T. Ryu, S. Kim, P. H. Lee, *RSC Adv.* **2013**, *3*, 18296–18299; f) D. Zhao, C. Nimphius, M. Lindale, F. Glorius, *Org. Lett.* **2013**, *15*, 4504–4507; g) S. Park, B. Seo, S. Shin, J.-Y. Son, P. H. Lee, *Chem. Commun.* **2013**, *49*, 8671–8673.



Scheme 1.12: Sequential monophosphonic acid-directed alkenylation/HORNER–WADSWORTH–EMMONS reaction by KIM.

Alternatively, as a representative example of silicon-containing groups, a novel traceless silanol directing group **23** was shown to promote the intermolecular alkenylation of arenes as described by the GEVORGYAN group (Scheme 1.13).[47] After C–H bond functionalization, the product could be converted into corresponding phenol (*E*)-**24** smoothly by treatment with TBAF in THF.



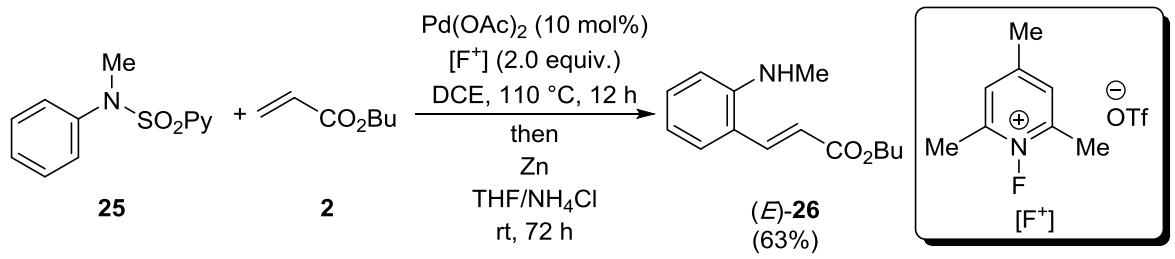
Scheme 1.13: Traceless silanol-directing group promoted C–H bond alkenylations by GEVORGYAN.

In 2011, an easily removable *N*-(2-pyridyl)sulfonyl protecting group was successfully applied as a directing group in palladium(II)-catalyzed alkenylation of anilines by CARRETERO and co-workers (Scheme 1.14).[48] The aniline **25** with an alkyl substituent at the nitrogen atom, which failed to react before,[32] performed well under the optimized conditions. Some other sulfur-related directing groups were also developed recently (Scheme 1.15).[49]

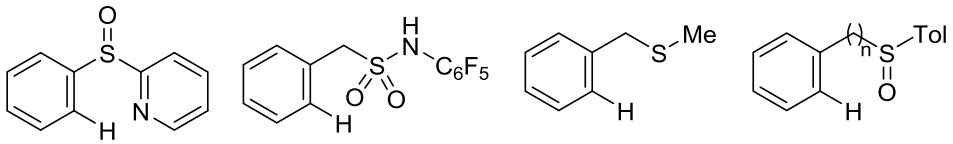
[47] a) C. Huang, B. Chattopadhyay, V. Gevorgyan, *J. Am. Chem. Soc.* **2011**, *133*, 12406–12409; also see: b) C. Wang, H. Ge, *Chem. Eur. J.* **2011**, *17*, 14371–14374; c) M. Mewald, J. A. Schiffner, M. Oestreich, *Angew. Chem.* **2012**, *124*, 1797–1799; *Angew. Chem. Int. Ed.* **2012**, *51*, 1763–1765.

[48] A. García-Rubia, B. Urones, R. G. Arrayás, J. C. Carretero, *Angew. Chem.* **2011**, *123*, 11119–11123; *Angew. Chem. Int. Ed.* **2011**, *50*, 10927–10931.

[49] a) Ref. [29b]; b) M. Yu, Z. Liang, Y. Wang, Y. Zhang, *J. Org. Chem.* **2011**, *76*, 4987–4994; c) H.-X. Dai, A. F. Stepan, M. S. Plummer, Y.-H. Zhang, J.-Q. Yu, *J. Am. Chem. Soc.* **2011**, *133*, 7222–7228; d) M. Yu, Y. Xie, C. Xie,Y. Zhang, *Org. Lett.* **2012**, *14*, 2164–2167; e) B. Wang, C. Shen, J. Yao, H. Yin, Y. Zhang, *Org. Lett.* **2014**, *16*, 46−49.



Scheme 1.14: *N*-(2-Pyridyl)sulfonyl group-promoted C–H bond alkenylation by CARRETERO.



CARRETERO, 2011
ZHANG, 2011
YU, 2011
ZHANG, 2012
ZHANG, 2012

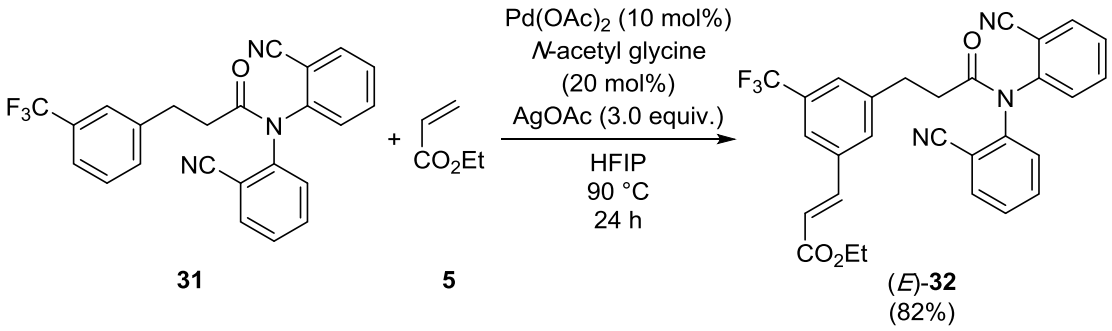
Scheme 1.15: Some other surfur-related directing groups for C–H bond alkenylation.

1.2.1.3 Remote/*meta* Directing Groups

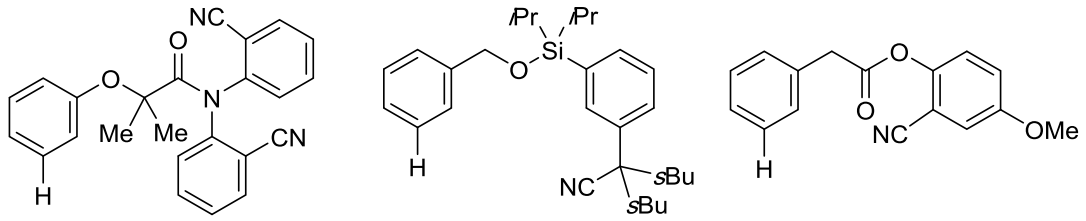
In 2012, the Yu group developed an outstanding remote directing group that enables C–H bond functionalization at the *meta* position (Scheme 1.16).[50] Template-assisted *meta*-selective C–H activation overpowered the inherent *ortho*-directing properties, electronic as well as steric effects of the arene substrates. The weak coordination between palladium(II) and a terminal nitrile group could overcome the difficulties associated with a flexible conformationally 12-membered cyclic transition state. With this kind of template, the *meta* C–H bond undergoes alkenylation with high selectivity. Inspired by this work, several *meta*-directing templates appeared recently and broadened the existing synthetic methodologies (Scheme 1.17).[51]

[50] D. Leow, G. Li, T.-S. Mei, J.-Q. Yu, *Nature* **2012**, *486*, 518–522.

[51] For other *meta*-directing groups, see: a) R. Tang, G. Li, J.-Q. Yu, *Nature* **2014**, *507*, 215–220; b) G. Yang, P. Lindovska, D. Zhu, J. Kim, P. Wang, R.-Y. Tang, M. Movassaghi, J.-Q. Yu, *J. Am. Chem. Soc.* **2014**, *136*, 10807−10813; d) H.-X. Dai, G. Li, X.-G. Zhang, A. F. Stepan, J.-Q. Yu, *J. Am. Chem. Soc.* **2013**, *135*, 7567–7571; d) Y.-F. Yang, G.-J. Cheng, P. Liu, D. Leow, T.-Y. Sun, P. Chen, X. Zhang, J.-Q. Yu, Y.-D. Wu, K. N. Houk, *J. Am. Chem. Soc.* **2014**, *136*, 344–355; e) S. Lee, H. Lee, K. L. Tan, *J. Am. Chem. Soc.* **2013**, *135*, 18778−18781; f) Y. Deng, J.-Q. Yu, *Angew. Chem.* **2015**, *127*, 902–905; *Angew. Chem. Int. Ed.* **2015**, *54*, 888–891; g) M. Bera, A. Modak, T. Patra, A. Maji, D. Maiti, *Org. Lett.* **2014**, *16*, 5760−5763.



Scheme 1.16: Template-assisted remote directing group by YU.



Scheme 1.17: Recent other *meta*-directing groups reported.

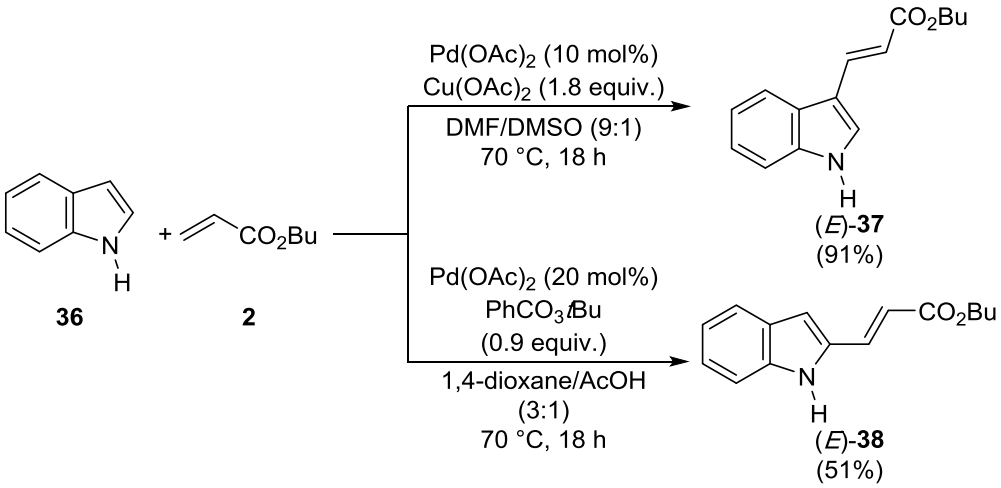
1.2.2 Oxidative Palladium(II)-Catalyzed Cross-Dehydrogenative Alkenylation without Directing Groups

1.2.2.1 Solvent/Oxidant-Controlled Regioselective C–H bond Alkenylation of Indoles

For indole substrates, in most of cases, the C-3 position is preferred to undergo C–H bond functionalization through electrophilic aromatic substitution process. Examples for the C-2 selective alkenylation of indole were rare.[52] Ten years ago, the GAUNT group disclosed a regioselective alkenylation of indole (**36**) with a free N–H group. This regioselectivity and reactivity were controlled by different solvents employed (Scheme 1.18).[53] When strongly coordinating solvents such as DMF and DMSO together with $Cu(OAc)_2$ as terminal oxidant were used, the indole was selectively alkenylated at the C-3 position to form (*E*)-**37** (Scheme 1.18, upper). In contrast, reactions performed in less coordinating solvents such as AcOH and 1,4-dioxane generated the C-2 alkenylated product (*E*)-**38** in the presence of *tert*-butyl perbenzoate as terminal oxidant (Scheme 1.18, lower).

[52] a) E. Capito, J. M. Brown, A. Ricci, *Chem. Commun.* **2005**, 1854–1856; b) G. Fanton, N. M. Coles, A. R. Cowley, J. P. Flemming, J. M. Brown, *Heterocycles* **2010**, *80*, 895–901.

[53] N. P. Grimster, C. Gauntlett, C. R. A. Godfrey, M. J. Gaunt, *Angew. Chem.* **2005**, *117*, 3185–3189; *Angew. Chem. Int. Ed.* **2005**, *44*, 3125–3129.



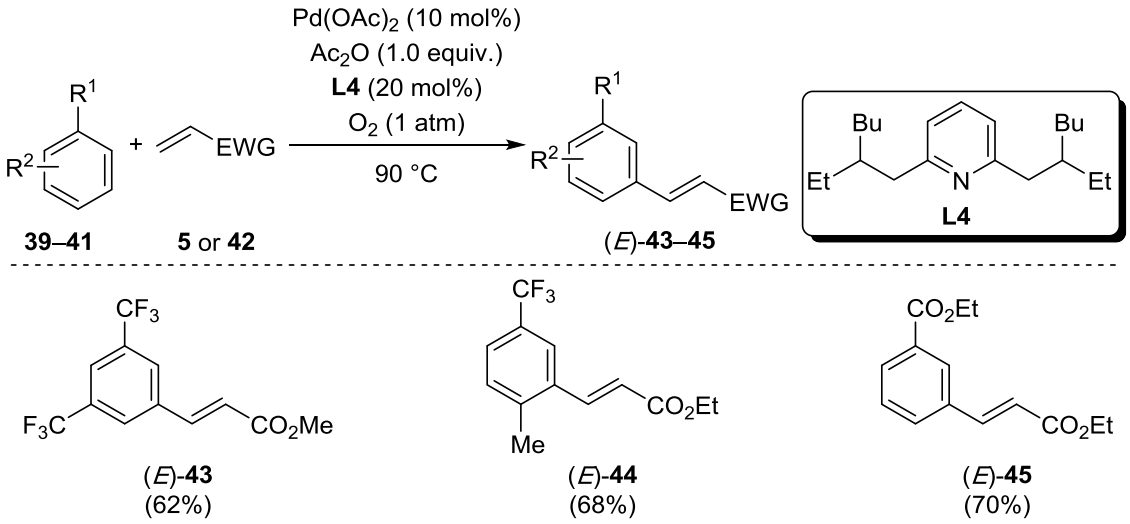
Scheme 1.18: Palladium(II)-catalyzed regioselective intermolecular C–H bond alkenylation of indoles by GAUNT.

1.2.2.2 Electronic Factors Controlled Regioselective C–H Bond Alkenylation of Arenes

Despite the progress, the palladium-catalyzed alkenylation has always been limited to electron-rich arenes. In 2009, the YU group demonstrated that electron-deficient arenes **39**–**41** could undergo alkenylation in an outstanding *meta*-selective fashion under palladium catalysis (Scheme 1.19).[54] Extensive screening established conditions with a sterically encumbered 2,6-dialkylpyridine ligand **L4** with at the exterior to promote the oxidation addition step of the palladium(0) species. In this design, a Pd–N interaction was maintained concurrently imparting the necessary destabilization of dimers required to promote substrate coordination. However, other common pyridine ligands resulted in low reactivities, likely due to their strong Pd–N coordinating ability; this disfavored productive association with the electron-deficient arene partners. Later, detailed mechanistic studies provided further insight in this catalytic transformation.[55]

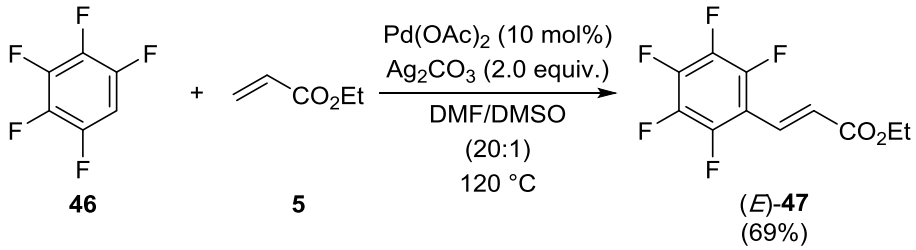
[54] Y.-H. Zhang, B.-F. Shi, J.-Q. Yu, *J. Am. Chem. Soc.* **2009**, *131*, 5072–5074.

[55] S. Zhang, L. Shi, Y. Ding, *J. Am. Chem. Soc.* **2011**, *133*, 20218–20229.



Scheme 1.19: Selective C–H bond alkenylation of electron-deficient arenes by YU.

Since electron-deficient arenes could be selectively alkenylated, it raises the question whether other highly electron-deficient perfluoroarenes perform in the transformation. Perfluoroarenes are considered nontrivial starting materials because the C–H bond activation might result in an intermediate containing a strong Pd(II)–Ar^F bond, probably too stable for catalysis. ZHANG and co-workers showed that this kind of arene **46** could undergo palladium(II)-catalyzed alkenylation with ethyl acrylate (**5**) (Scheme 1.20),[56] where DMSO serves both as co-solvent and as ligand.[57] The use of Ag_2CO_3 seems optimal, and this protocol was compatible with a vast array of alkene coupling partners, including acrylates, acrylamides, and vinylphosphates generally in moderate to excellent yields. Furthermore, the synthetic utility of this methodology was elegantly demonstrated by large-scale synthesis (2.0 g) of (*E*)-ethyl 3-(perfluorophenyl)acrylate from commercially available reagents in 71% yield (not shown).



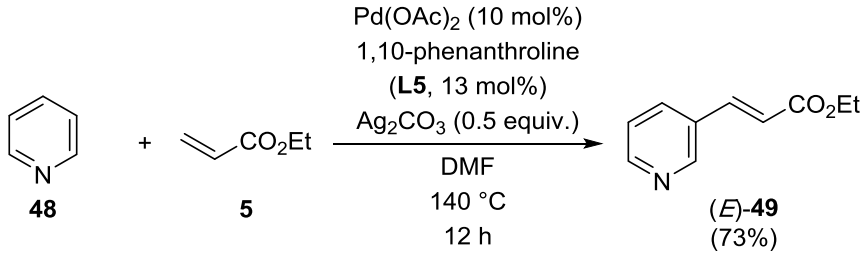
Scheme 1.20: Palladium(II)-catalyzed C–H bond alkenylation of perfluoroarenes by ZHANG.

[56] a) X. Zhang, S. Fan, C.-Y. He, X. Wan, Q.-Q. Min, J. Yang, Z.-X. Jiang, *J. Am. Chem. Soc.* **2010**, *132*, 4506–4507; see also: b) C.-Z. Wu, C.-Y. He, Y. Huang, X. Zhang, *Org. Lett.* **2013**, *15*, 5266–5269.

[57] Examples of DMSO serving as ligand under palladium(II) catalysis, see: a) D. Tanaka, S. P. Romeril, A. G. Myers, *J. Am. Chem. Soc.* **2005**, *127*, 10323-10333; b) B. A. Steinhoff, S. S. Stahl, *J. Am. Chem. Soc.* **2006**, *128*, 4348-4355.

1.2.2.3 Ligand-Promoted Regioselective C–H bond Alkenylation of Arenes

One year later, YU and co-workers developed a palladium-catalyzed C-3-selective C–H bond alkenylation of pyridines promoted by 1,10-phenanthroline ligand (**L5**) for the first time.[58] In contrast to previous examples using an acidic amide[32] or *N*-oxides[41,42] as directing groups, unsubstituted pyridine (**48**) was used as substrate directly in this protocol (Scheme 1.21). Both electron-rich and -deficient substrates exhibited good C-3 regioselectivity. The reaction proceeded under air, and a catalytic amount of Ag_2CO_3 was employed as co-oxidant. Studies on the kinetic isotope effect were conducted under the optimized conditions and provided a high KIE value (k_H/k_D = 4.0), indicating that a palladium-mediated C–H bond cleavage step rather than a LEWIS acid-mediated FRIEDEL–CRAFTS pathway was involved. One later example supported this conclusion from another aspect that the reaction happened mostly at the C-2 position of pyridine in the absence of any ligand.[59]



Scheme 1.21: Palladium(II)-catalyzed C-3-selective C–H bond alkenylation of pyridines by Yu.

1.3 OXIDATIVE PALLADIUM(II)-CATALYZED CROSS-DEHYDROGENATIVE COUPLING REACTIONS WITH ARENES

The mechanism of the cross-dehydrogenative arylation reaction is best viewed from the perspective of the palladium catalyst. A critical and common feature of the catalytic process involves the formation of an aryl palladium(II) intermediate **II** which is subsequently functionalized to form C–C and C–Het bonds. Generally, two different catalytic pathways are involved, including palladium(0)/palladium(II) and palladium(II)/palladium(IV).

For the palladium(0)/palladium(II) cycle (Scheme 1.22, left), firstly, the palladium salt **I** reacts with one molecule of arene **E** selectively rather than with the other coupling partner **F** *via* C–H bond activation. Then the resulting aryl–palladium **II** (**I** → **II**) can react with the other nucleophilic arene **F** selectively to generate a C–Pd–C intermediate (**II** → **III**). During this process, the reactivity and selectivity are entirely reversed. The following reductive

[58] M. Ye, G.-L. Gao, J.-Q. Yu, *J. Am. Chem. Soc.* **2011**, *133*, 6964–6967.

[59] P. Wen, Y. Li, K. Zhou, C. Ma, X. Lan, C. Ma, G. Huang, *Adv. Synth. Catal.* **2012**, *354*, 2135–2140.

elimination step delivers the desired product **G** as well as restores palladium(0) **IV** which can be reoxidized to palladium(II) **I** (**IV** → **I**)participate into the next catalytic cycle.

The palladium(II)/palladium(IV) cycle contains two pathways itself (Scheme 1.22, right). For the first pathway, the generation of C–Pd–C intermediate **III** (**I** → **II** →**III**) is identical as illustrated before. This intermediate **III** can be oxidized directly to form a palladium(IV) species **VI** (**III** →**VI**) (the arrow is not shown), which is followed by a reductive elimination to afford arylation product **G** as well as palladium(II) **I**. The other one starts with the direct oxidation of intermediate **II** to form a palladium(IV) **V** (**II** →**V**) species prior to a electrophilic metalation. The desired product **G** is then generated by following elimination step (**V** → **VI** →**I**).

Considering the oxidation state of palladium during the transformation, it is worthy of mention that normally electron-rich arenes react faster than electron-poor ones. This phenomenon is in accordance with a palladium(0)/palladium(II) catalytic cycle (Scheme 1.22, left).[60] However, when strong oxidants, for instance $Na_2S_2O_8$ with a high redox potential (i.e., 2.01 eV),[61] as introduced, the catalytic cycle is most likely considered to follow a palladium(II)/palladium(IV) pathway (Scheme 1.22, right).[62,63,64] These results emphasize that the mechanisms of oxidative cross-couplings may differ greatly depending on the type of oxidant employed.

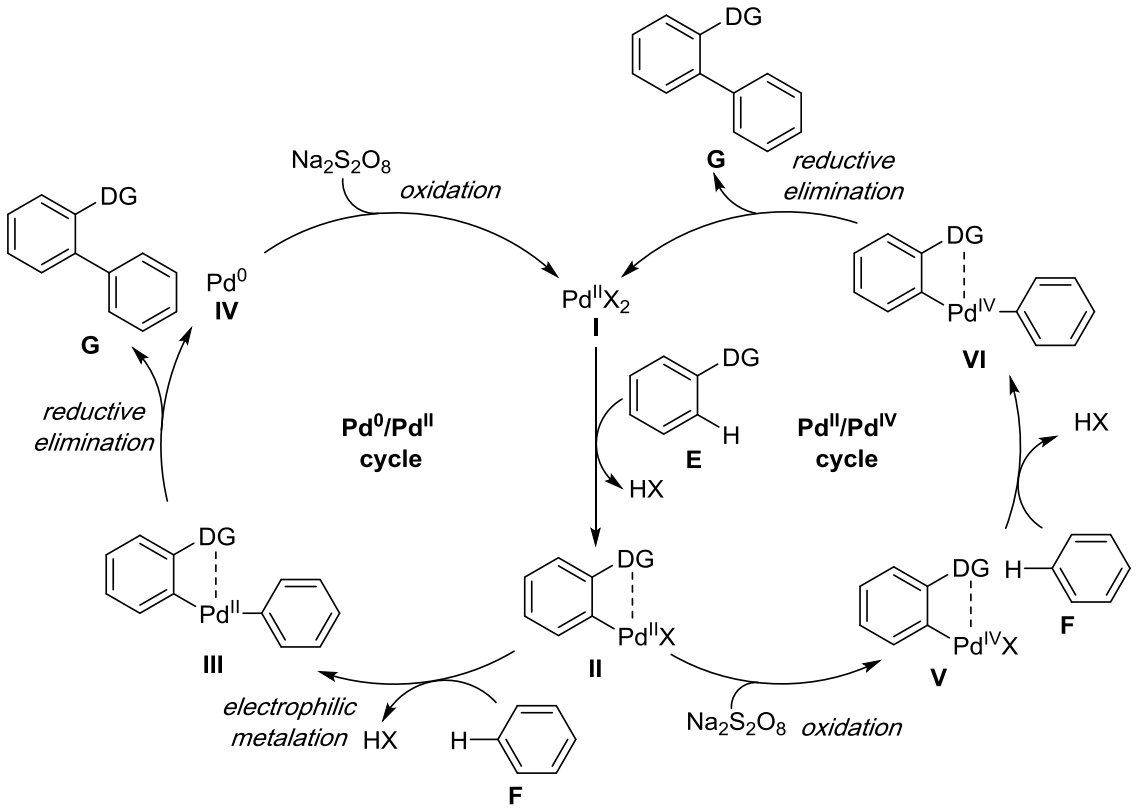
[60] For a review of palladium(0)/palladium(II) catalysis, see: M. Wasa, K. M. Engle, J.-Q. Yu, *Isr. J. Chem.* **2010**, *50*, 605–616.

[61] P. F. Killian, C. J. Bruell, C. Liang, M. C. Marley, *Soil Sediment Contam.* **2007**, *16*, 523–537.

[62] For selected examples, see: a) L. V. Desai, H. A. Malik, M. S. Sanford, *Org. Lett.* **2006**, *8*, 1141–1144; b) G.-W. Wang, T.-T. Yuan, X.-L. Wu, *J. Org. Chem.* **2008**, *73*, 4717–4720; c) H.-Y. Thu, W.-Y. Yu, C.-M. Che, *J. Am. Chem. Soc.* **2006**, *128*, 9048–9049; d) Y.-K. Liu, S.-J. Lou, D.-Q. Xu, Z.-Y. Xu, *Chem. Eur. J.* **2010**, *16*, 13590–13593.

[63] N. R. Deprez, M. S. Sanford, *J. Am. Chem. Soc.* **2009**, *131*, 11234–11241.

[64] For reviews of palladium(II)/palladium(IV) catalysis, see: a) K. Muñiz, *Angew. Chem. Int. Ed.* **2009**, *48*, 9412–9423; b) L.-M. Xu, B.-J. Li, Z. Yang, Z.-J. Shi, *Chem. Soc. Rev.* **2010**, *39*, 712–733; c) P. Sehnal, R. J. K. Taylor, I. J. S. Fairlamb, *Chem. Rev.* **2010**, *110*, 824–889; d) J. J. Topczewski, M. S. Sanford, *Chem. Sci.* **2015**, *6*, 70–76.



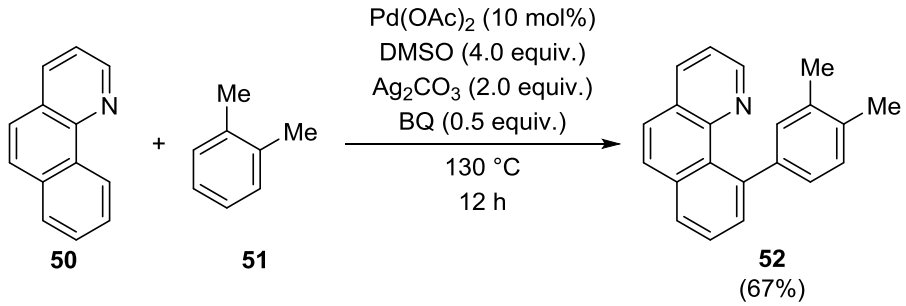
Scheme 1.22: Proposed catalytic cycles for the CDC reactions with the aid of a directing group.

1.3.1 Oxidative Palladium(II)-Catalyzed Cross-Dehydrogenative Arylation with Directing Groups

As with the heteroatom-containing directing groups in the alkenylation reactions, selective catalytic two-fold C–H bond activation occur in the presence of the palladium catalyst by choosing a suitable chelating group.

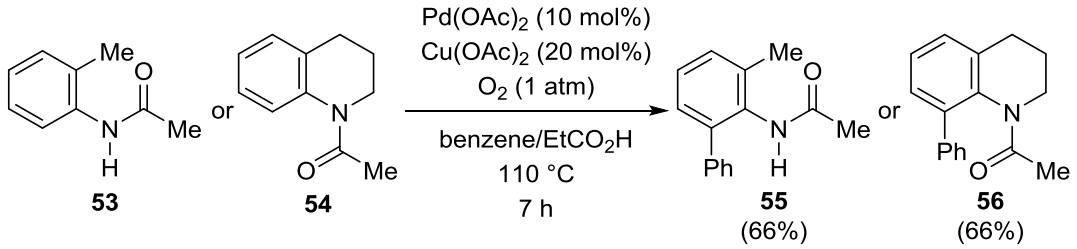
In 2007, the SANFORD group presented that a wide range of arenes could couple through facile CDC arylation with benzo[*h*]quinoline (**50**) selectively at the desired position (Scheme 1.23).[65a] It was proven that $AgCO_3$ serves as the sole oxidizing reagent and BQ is ancillary selectivity-influencing ligand under catalytic transformation, respectively.[64c]

[65] a) K. L. Hull, M. S. Sanford, *J. Am. Chem. Soc.* **2007**, *129*, 11904–11905; b) K. L. Hull, M. S. Sanford, *J. Am. Chem. Soc.* **2009**, *131*, 9651–9653.



Scheme 1.23: Palladium(II)-catalyzed C–H bond arylation of aromatic substrates by SANFORD.

Amides are very effective as directing groups for oxidative C–H bond activation. In 2008, SHI and co-workers reported a complementary oxidative arylation of *N*-acylanilide (**53**) or *N*-acyl-3,4-dihydroquinoline (**54**) with simple arenes to give biologically relevant structures **55**–**56** (Scheme 1.24).[66] Instead of stoichiometric amount of silver salts, the use of oxygen as the terminal oxidant is advantageous because the only byproduct formed is water. Additionally, this coupling can be scaled up (10 mmol) with good efficiencies (73%). In the same year, a related report by the BUCHWALD group demonstrated that a copper-free process is possible in the presence of TFA and a slight excess of the unactivated arene coupling partner.[67]



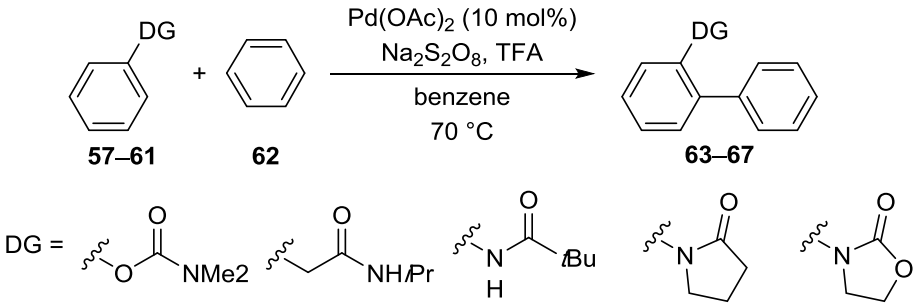
Scheme 1.24: Palladium(II)-catalyzed C–H bond arylation of aromatic substrates in *ortho* position by SHI.

A palladium-catalyzed protocol amenable to a relatively broad class of arenes including phenylacetamides, benzamides, *O*-phenylcarbamates and anilines, was developed by DONG and co-workers recently (Scheme 1.25).[68] As the optimized conditions, TFA was employed as an acidic additive and a relatively benign and inexpensive $Na_2S_2O_8$ was chosen as a terminal oxidant. A wide range of electron-deficient, -neutral, and -rich arenes were well-suited in this process, albeit the simple arene coupling partner was used in large excess (~40 equiv.).

[66] B.-J. Li, S.-L. Tian, Z. Fang, Z.-J. Shi, *Angew. Chem.* **2008**, *120*, 1131–1134; *Angew. Chem. Int. Ed.* **2008**, *47*, 1115–1118.

[67] G. Brasche, J. García-Fortanet, S. L. Buchwald, *Org. Lett.* **2008**, *10*, 2207–2210.

[68] a) X. Zhao, C. S. Yeung, V. M. Dong, *J. Am. Chem. Soc.* **2010**, *132*, 5837–5844; b) C. S. Yeung, X. Zhao, N. Borduas, V. M. Dong, *Chem. Sci.* **2010**, *1*, 331–336.



Scheme 1.25: Palladium(II)-catalyzed C–H bond arylation of aromatic substrates in *ortho* position by DONG.

In addition, Yu and co-workers have extended the scope of the oxidative palladium-catalyzed cross-coupling reactions with benzamide derivatives afterwards.[69] Furthermore, other types of directing groups were reported to accelerate the desired transformation.[70]

1.3.2 Oxidative Palladium(II)-Catalyzed Cross-Dehydrogenative Arylation without Directing Groups

At the early stage of the development of the CDC reaction, the LU group disclosed an interesting example between two different simple arenes under palladium(II) catalysis in the absence of a directing group.[71] As expected, the regioselectivity and undesired homocoupling were big problems. To overcome these obstacles, low concentration of TFA and large excess of one arene coupling partner (up to 100 equiv.) were required, however, the yields of unsymmetrical biaryl products were still low.

Several promising results were achieved in the following years, indicating that other factors such as oxidant, catalyst, steric, as well as electronic factors are essential to control the regioselectivity.

1.3.2.1 Oxidant-Controlled Regioselectivity of CDC Arylations

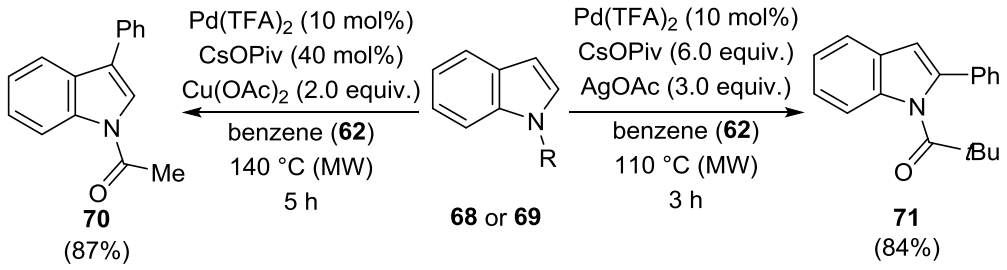
In 2007, a breakthrough work regarding highly regioselective arylation through two-fold C–H bond activation at C-2 and C-3 of indole, respectively, was accomplished by FAGNOU and co-

[69] X. Wang, D. Leow, J.-Q. Yu, *J. Am. Chem. Soc.* **2011**, *133*, 13864–13867.

[70] a) J.-B. Xia, S.-L. You, *Organometallics* **2007**, *26*, 4869–4871; b) Ref. [41]; c) J. Karthikeyan, C.-H. Cheng, *Angew. Chem.* **2011**, *123*, 10054–10057; *Angew. Chem. Int. Ed.* **2011**, *50*, 9880–9883.

[71] R. Li, L. Jiang, W. Lu, *Organometallics* **2006**, *25*, 5973–5975.

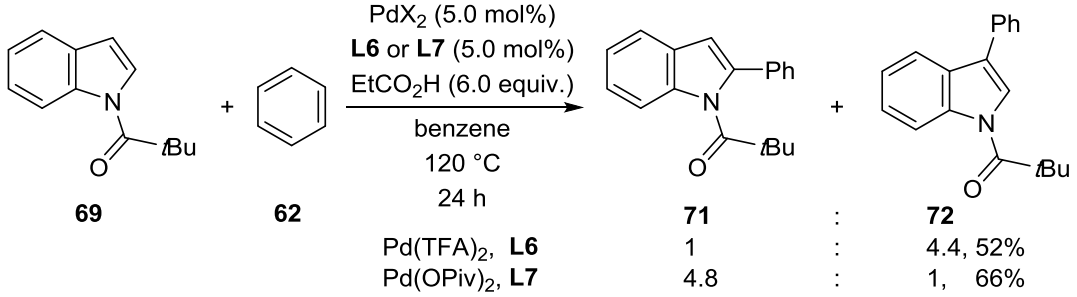
workers (Scheme 1.26).[72] The indole starting material **68** with an acetyl group at the nitrogen atom could undergo palladium-catalyzed oxidative cross-coupling with benzene which served both as coupling partner and solvent at the C-3 position selectively, mediated by $Cu(OAc)_2$ as terminal oxidant. Remarkably, switching both protecting group and oxidant led to the C-2 arylation product **71** with excellent yield and regioselectivity. These promising contributions set the stage for the further development in this area.



Scheme 1.26: Palladium(II)-catalyzed oxidant-controlled regioselective C–H bond arylation of indoles by FAGNOU.

1.3.2.2 Catalyst-Controlled Regioselectivity of CDC Arylations

Recently, the STAHL group showed that the use of different palladium salts cannot only change the efficiency of the reaction but also govern the regioselectivity for indole substrates under aerobic palladium catalysis (Scheme 1.27).[73] For example, the combination of $Pd(TFA)_2$ as catalyst with 9,9-dimethyl-4,5-diazafluorene (**L6**) as ligand favored the formation of the C-3 arylation product **72** smoothly while the use of $Pd(OAc)_2$ and 4,5-diazafluoren-9-one (**L7**) switched the functionalization at the C-2 position to form product **71** efficiently and selectively.



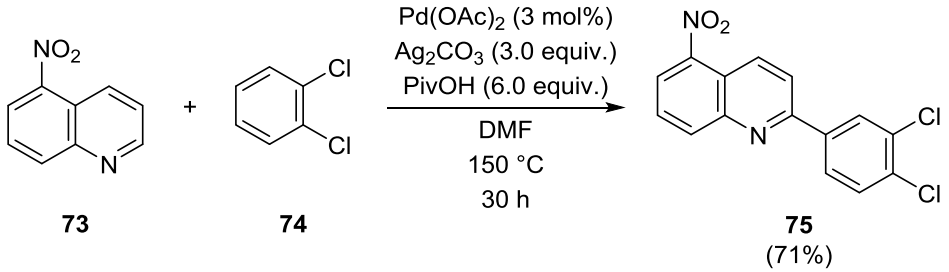
Scheme 1.27: Catalyst-controlled regioselective C–H bond arylation of indoles by STAHL.

[72] a) D. R. Stuart, K. Fagnou, *Science* **2007**, *316*, 1172–1175; b) D. R. Stuart, E. Villemure, K. Fagnou, *J. Am. Chem. Soc.* **2007**, *129*, 12072–12073.

[73] A. N. Campbell, E. B. Meyer, S. S. Stahl, *Chem. Commun.* **2011**, *47*, 10257–10259.

1.3.2.3 Electronic Factors Controlled Regioselectivity of CDC Arylations

2-Arylquinolines are very useful building blocks, and the conventional preparation methods involving CDC arylation require to convert quinolines to the corresponding *N*-oxides due to their low reactivity and the strong coordinating ability of the nitrogen atom.[42] Very recently, the HUANG group documented a simple protocol for the C-2 arylation of quinolines mediated by O_2 and Ag_2CO_3 as co-oxidant (Scheme 1.28).[74] They observed that both coupling partners bearing electron-withdrawing groups favored the transformation while electron-rich quinolines and arenes failed to generate the arylation product. It can be concluded that the electronic properties of the substituents at the quinoline rings are more influential than steric factors. Nevertheless, this strategy still provided a direct and efficient method for C–H bond activation at the C-2 position of quinolines.



73 **74** **75** (71%)

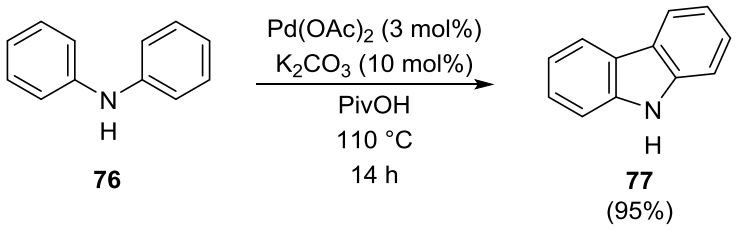
Scheme 1.28: Palladium(II)-catalyzed electronic factors controlled regioselective C–H bond arylation of quinolines by HUANG.

1.3.2.4 Regioselective Intramolecular CDC Arylations

Despite the progress achieved in direct intermolecular arylation reactions, the CDC reaction could also be elaborated in an intramolecular fashion. In 2008, the FAGNOU group described that electron-rich diarylamine **76** could undergo an intramolecular two-fold C–H bond activation to form carbazole (**77**) in the open air (Scheme 1.29).[75] Under the optimized conditions, a series of carbazoles and even dibenzofurans were prepared. Additionally, the applicability of this strategy was highlighted by the synthesis of natural products such as Murrayafoline A, Clausenine, and Mukonine in moderate to excellent yield, respectively.

[74] X. Ren, P. Wen, X. Shi, Y. Wang, J. Li, S. Yang, H. Yan, G. Huang, *Org. Lett.* **2013**, *15*, 5194–5197.

[75] B. Liégault, D. Lee, M. P. Huestis, D. R. Stuart, K. Fagnou, *J. Org. Chem.* **2008**, *73*, 5022–5028.



Scheme 1.29: Palladium(II)-catalyzed regioselective intramolecular C–H bond arylation by FAGNOU.

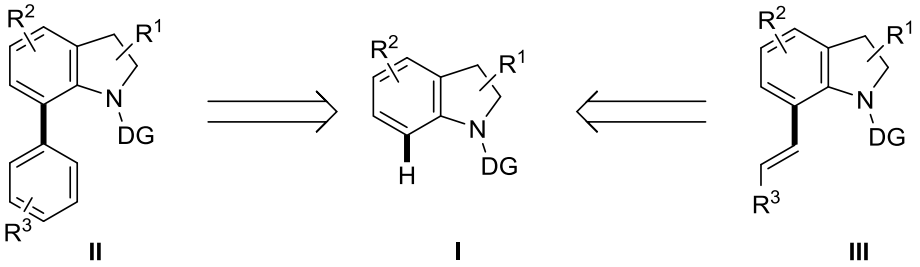
1.4 OBJECTIVE AND TASKS

As highlighted in the previous sections, numerous methods for palladium(II)-catalyzed CDC arylation and FUJIWARA–MORITANI reactions were reported. These contributions mainly concentrated on the modification of arenes, anilines, and pyridines. Additionally, for the most abundant moieties in natural products as well as biologically active compounds, the C–H bond activation at the C-2 and C-3 positions of indole nuclei are well documented. However, as a very promising target, the C–H bond functionalization at the C-7 position has been very rare to date and most of them required prefunctionalized coupling partners. Despite the progress made so far, improving the versatility and practicality of this new reaction remains a tremendous challenge.

Based on the modern chemistry which mostly pursues high efficiency and environmentally benign characteristics, we were interested in realizing the challenging functionalization at the C-7 position of indoline substrates both with alkenes and simple arenes through CDC reaction pathways. In particular, we were trying to investigate methods with ambient conditions or even under aerobic conditions to form useful molecular architectures in accordance with the principles of Green Chemistry.[76]

As mentioned above, the directing group plays important roles both in reactivity and regioselectivity, so we planned to introduce different directing groups at the nitrogen atom of indolines to enhance their reactivity. With the aid of a suitable directing group, the C–H bond activation would take place selectively at the C-7 position. Different coupling partners such as simple arenes and alkenes, which performed well in the CDC arylation (Scheme 1.30, **I** → **II**) and alkenylation (Scheme 1.30, **I** → **III**) reactions, could be employed in these transformations.

[76] P. Anastas, N. Eghbali, *Chem. Soc. Rev.* **2010**, *39*, 301–312.



Scheme 1.30: Palladium(II)-catalyzed CDC arylation and alkenylation of indolines at the C-7 position (DG = acetyl, dimethylcarbamoyl et. al.).

2 OXIDATIVE PALLADIUM(II)-CATALYZED CROSS-DEHYDROGENATIVE ARYLATION OF INDOLINE AT THE C-7 POSITION

2.1 ARYLATION OF INDOLINES AT THE C-7 POSITION – A BRIEF INTRODUCTION

As the most abundant moieties in natural products as well as biologically active compounds, indole nuclei-containing structures have garnered tremendous attention of chemists during the past decades.[77] Consequently, significant research efforts have been devoted towards not only developing new synthetic methods but also doing modification on these structures mainly through C–C or C–Het bond formation.[78]

As part of this promising research area, the modification of indolines especially at the C-7 position is synthetically attractive but less intensively studied.[79] The conventional procedures

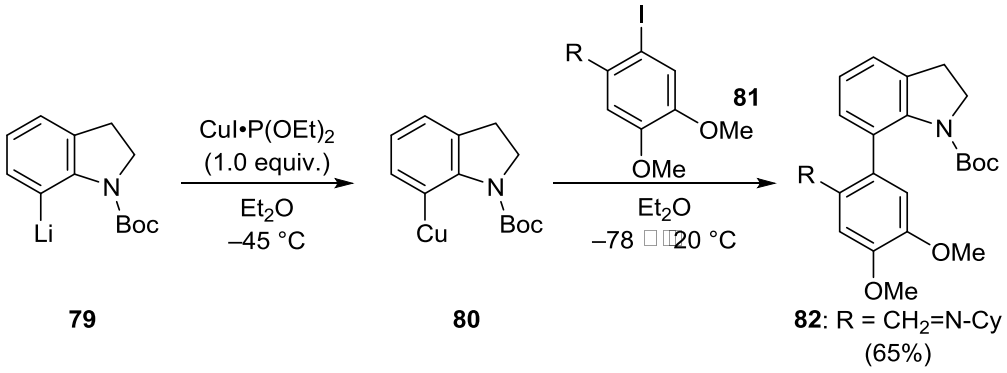
[77] a) R. B. Van Order, H. G. Lindwall, *Chem. Rev.* **1942**, *30*, 69–96; b) A. I. Scott, *Acc. Chem. Res.* **1970**, *3*, 151–157; c) P. Magnus, T. Gallagher, P. Brown, P. Pappalardo, *Acc. Chem. Res.* **1984**, *17*, 35–41; d) D. Crich, A. Banerjee, *Acc. Chem. Res*. **2007**, *40*, 151–161; e) A. J. Kochanowska-Karamyan, M. T. Hamann, *Chem. Rev*. **2010**, *110*, 4489–4497; f) S. Lancianesi, A. Palmieri, M. Petrini, *Chem. Rev*. **2014**, *114*, 7108–7149.

[78] a) S. Cacchi, G. Fabrizi, *Chem. Rev*. **2005**, *105*, 2873–2920; b) S. Cacchi, G. Fabrizi, *Chem. Rev*. **2011**, *111*, PR215–PR283; c) G. Broggini, E. M. Beccalli, A. Fasana, S. Gazzola, *Beilstein J. Org. Chem*. **2012**, *8*, 1730–1746; d) W. Zi, Z. Zuo, D. Ma, *Acc. Chem. Res*. **2015**, *48*, 702–711.

[79] For recent C–H bond alkenylations, see: a) Z. Song, R. Samanta, A. P. Antonchick, *Org. Lett*. **2013**, *15*, 5662–5665; b) S. Pan, T. Wakaki, N. Ryu, T. Shibata, *Chem. Asian J.* **2014**, *9*, 1257–1260; c) J. Park, N. K. Mishra, S. Sharma, S. Han, Y. Shin, T. Jeong, J. S. Oh, J. H. Kwak, Y. H. Jung, I. S. Kim, *J. Org. Chem*. **2015**, *80*, 1818–1827; d) X.-F. Yang, X.-H. Hu, C. Feng, T.-P. Loh, *Chem. Commun.* **2015**, *51*, 2532–2535; e) D. Yang, S. Mao, Y.-R. Gao, D.-D. Guo, S.-H. Guo, Bin Li, Y.-Q. Wang, *RSC Adv*. **2015**, *5*, 23727–23736; for C–H bond alkynylations, see: f) N. Jin, C. Pan, H. Zhang, P. Xu, Y. Cheng, C. Zhu, *Adv. Synth. Catal.* **2015**, *357*, 1149–1153; g) Y. Wu, Y. Yang , B. Zhou, Y. Li, *J. Org. Chem*. **2015**, *80*, 1946–1951; h) Ref. [79d]; for C–H bond methylation and alkylation, see: i) S. R. Neufeldt, C. K. Seigerman, M. S. Sanford, *Org. Lett.* **2013**, *15*, 2302–2305; j) S. Pan, N. Ryu, T. Shibata, *Adv. Synth. Catal.* **2014**, *356*, 929–933; k) W. Ai, X. Yang, Y. Wu, X. Wang, Y. Li, Y. Yang, B. Zhou, *Chem. Eur. J.* **2014**, *20*, 17653–17657; l) Chanchal Premi, Ankit Dixit, and Nidhi Jain, *Org. Lett*. **2015**, *17*, 2598–2601; for C–H bond acylations, see: m) M. Kim, N. K. Mishra, J. Park, S. Han, Y. Shin, S. Sharma, Y. Lee, E.-K. Lee, J. H. Kwak, I. S. Kim, *Chem. Commun.* **2014**, *50*, 14249–14252; n) Y. Shin, S. Sharma, N. K. Mishra, S. Han, J. Park, H. Oh, J. Ha, H. Yoo, Y. H. Jung, I. S. Kim, *Adv. Synth. Catal.* **2015**, *357*, 594–600; for C–H bond cyanation, see: o) N. K. Mishra, T. Jeong, S. Sharma, Y. Shin, S. Han, J. Park, J. S. Oh, J. H. Kwak, Y. H. Jung, I. S. Kim, *Adv. Synth. Catal.* **2015**, *357*, 1293–1298; for C–H bond allylations, see: p) S. Sharma, Y. Shin, N. K. Mishra, J. Park, S. Han, T. Jeong, Y. Oh, Y. Lee, M. Choi, I. S. Kim, *Tetrahedron* **2015**, *71*, 2435–2441; q) J. Park, N. K. Mishra, S. Sharma, S. Han, Y. Shin, T. Jeong, J. S. Oh, J. H. Kwak, Y. H. Jung, I. S. Kim, *J. Org. Chem.* **2015**, *80*, 1818−1827; for C–H bond heterofunctionalizations, see: r) C. Pan, A. Abdukader, J. Han, Y. Cheng, C. Zhu, *Chem. Eur. J.* **2014**, *20*, 3606–3609; s) K. Shin, S. Chang, *J. Org. Chem*. **2014**, *79*, 12197–12204; t) W. Hou, Y. Yang, W. Ai, Y. Wu, X. Wang, B. Zhou, Y. Li, *Eur. J. Org. Chem*. **2015**, 395–400.

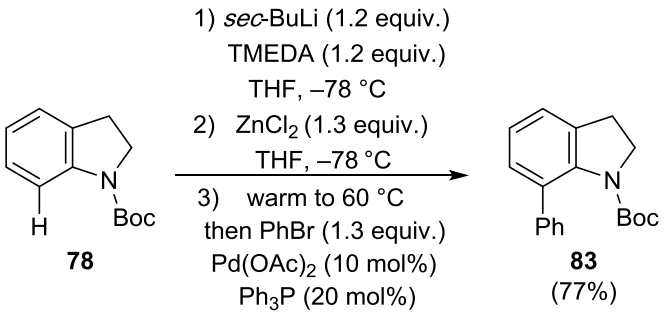
for the arylation at the C-7 position of indoline are mainly involving commonly used organometallic reagents through ULLMANN or NEGISHI coupling pathways.

More than 20 years ago, FLIPPIN and co-workers established a protocol for the construction of biaryl compounds (Scheme 2.1).[80] Firstly, C–H bond lithiation of *N*-Boc-indoline (**78**) to generate 7-lithio-*N*-Boc-indoline intermediate (**79**), followed by treatment with CuI·P(OEt)$_2$ to form an organocopper reagent **80**. Then, this resulting reagent was coupled with another organoiodine compound **81** to install an aryl group on the target position in 65% isolated yield at room temperature under ULLMANN reaction conditions. It is worthy of mention that the resulting biaryl compound **82** could be further functionalized through deprotection/ concomitant cyclization followed by reduction to give Assoanine or by oxidation to yield Oxoassoanine, both of which are natural products isolated from Narcissus assoanus (not shown).



Scheme 2.1: ULLMANN-type arylation of indoline at the C-7 position at room temperature by FLIPPIN.

As shown by LEONORI and COLDHAM in 2009,[81] after similar lithiation with the aforementioned method, the same resulting intermediate **79** reacted with $ZnCl_2$ and bromobenzene to deliver the desired biaryl compound **83** in 77% yield through NEGISHI-type cross-coupling reaction (Scheme 2.2).

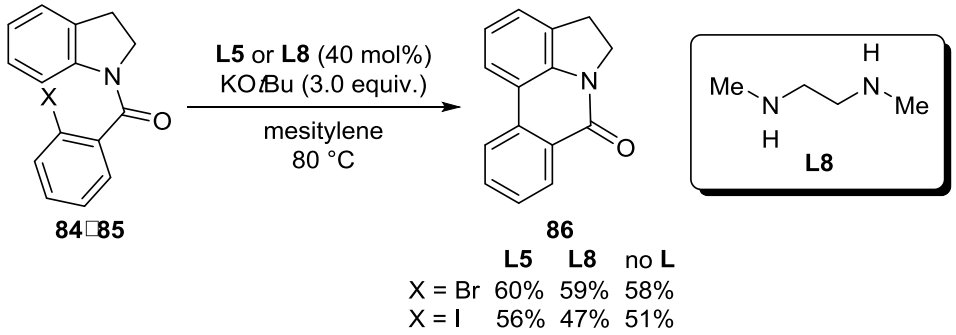


Scheme 2.2: NEGISHI-type arylation at the C-7 position of indoline by LEONORI and COLDHAM.

[80] J. S. Parnes, D. S. Carter, L. J. Kurz, L. A. Flippin, *J. Org. Chem.* **1994**, *59*, 3497–3499.

[81] D. Leonori, I. Coldham, *Adv. Synth. Catal.* **2009**, *351*, 2619–2623.

Despite the attractiveness of the transmetalation pathway, the intramolecular C-7 arylation of indoline could also be achieved by homolytic aromatic substitution (HAS) promoted by KO*t*Bu in a transition-metal-free fashion disclosed by BISAI and co-workers in 2012 (Scheme 2.3).[82] It was observed that KO*t*Bu was solely responsible for the biaryl coupling mediated by aryl radicals *via* radical anions. Both organobromine and organoiodine substrates **84**–**85** could be coupled in moderate to good yields (47–60%). Compared with conventional methods, this protocol was both environmentally friendly and straightforward since the new formed C–C bond was directly formed from a C–H bond without prior transmetalation. Intriguingly, the practical utility of this protocol was highlighted by the efficient synthesis of the Amaryllidaceae alkaloids oxoassoanine and anhydrolycorinone as well as 5,6-dihydrobicolorine (not shown).

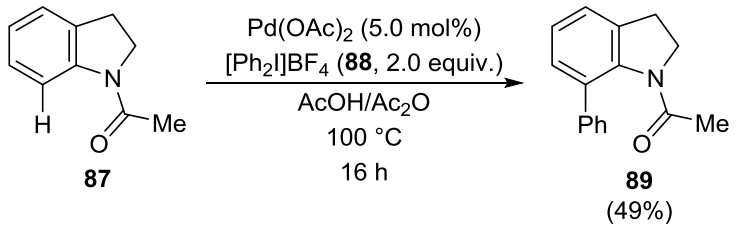


Scheme 2.3: KO*t*Bu-promoted intramolecular direct arylation of indolines at the C-7 position by BISAI.

As one of the most spread methods for the construction of C–C bonds, the SUZUKI reaction might be viewed as a remarkable alternative in this transformation under palladium catalysis. Exactly a decade ago, the SANFORD group accomplished just one example about direct oxidative SUZUKI–MIYAURA coupling between unfunctionalized indoline **87** and a hypervalent iodine(III) reagent **88** under acidic conditions at 100 °C (Scheme 2.4).[83] This example was a remarkable progress albeit only with moderate success (49% yield). These authors introduced an acetyl group which was widely used as a directing group to control the reaction to selectively happen at the C-7 position of indoline. Based on the experimental observations, these authors proposed a Pd(II)/Pd(IV) catalytic cycle, in which the hypervalent iodine(III) reagent **88** played a dual role, both as coupling partner and as terminal oxidant to generate the Pd(IV) intermediate in situ.

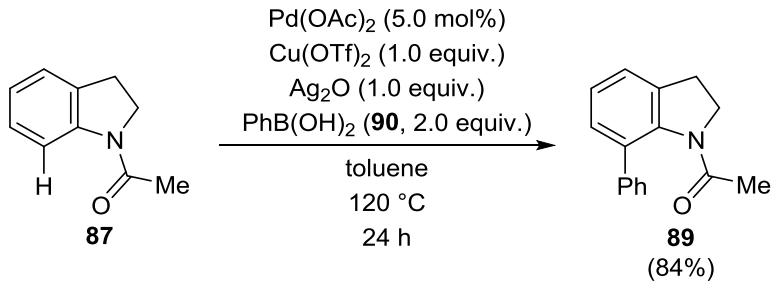
[82] S. De, S. Ghosh, S. Bhunia, J. A. Sheikh, A. Bisai, *Org. Lett.* **2012**, *14*, 4466–4469.

[83] D. Kalyani, N. R. Deprez, L. V. Desai, M. S. Sanford, *J. Am. Chem. Soc.* **2005**, *127*, 7330–7331.



Scheme 2.4: Oxidative SUZUKI–MIYAURA arylation between indolines and hypervalent iodine(III) reagents by SANFORD.

Two year later, SHI and co-workers reported about the bond formation between *N*-acetyl indoline (**87**) and phenyl boronic acid (**90**) catalyzed by $Pd(OAc)_2$ at 120 °C, in which $Cu(OAc)_2$ and Ag_2O served as oxidant and co-oxidant, respectively to promote this transformation efficiently in 84% yield (Scheme 2.5).[84] Additionally, they examined several different kinds of substrates such as acetyl-directed indolines, 1,2,3,4-tetrahydroquinolines, as well as *N*-alkyl acetanilides. Their method exhibited broad functional group tolerance. Furthermore, these authors conducted some preliminary mechanistic studies to gain insight into the mechanism.

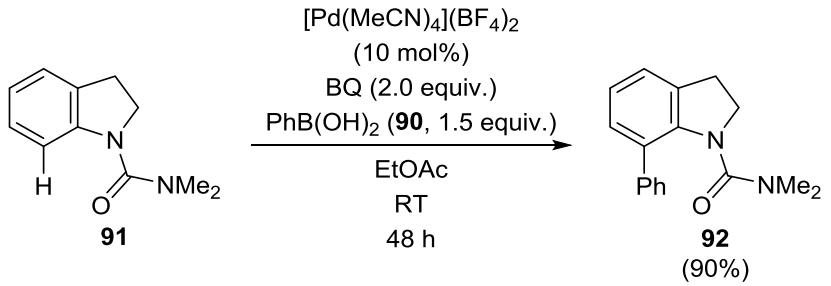


Scheme 2.5: Oxidative SUZUKI–MIYAURA arylation between acetyl-directed indolines and phenyl boronic acids by SHI.

Similar but more exciting progress has been made by LIPSHUTZ and co-workers in 2010. In this case, the use of a urea instead of an acetyl as a directing group made the SUZUKI–MIYAURA arylation proceed under exceptionally mild conditions (room temperature) without losing reactivity (90% yield) (Scheme 2.6).[85] It is noteworthy that palladium salts other than cationic $[Pd(MeCN)_4](BF_4)_2$ were ineffective. 1,4-Benzoquinone (BQ) was used as terminal oxidant and at the same time to promote the reductive elimination step in the transformation. Gratifyingly, compared with the acetyl directing group, this urea group could be easily installed and removed afterwards and this enhanced its synthetic practicality.

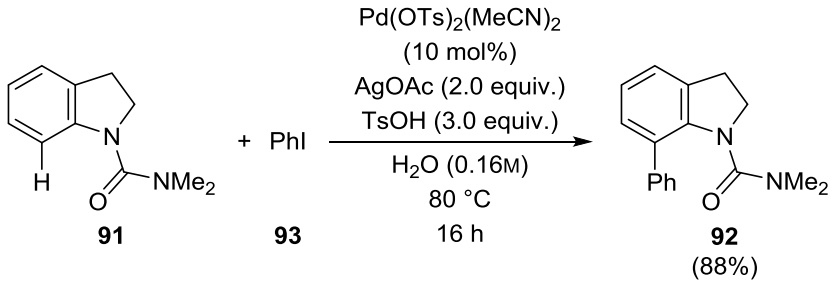
[84] Z. Shi, B. Li, X. Wan, J. Cheng, Z. Fang, B. Cao, C. Qin, Y. Wang, *Angew. Chem.* **2007**, *119*, 5650–5654; *Angew. Chem. Int. Ed.* **2007**, *46*, 5554–5558.

[85] T. Nishikata, A. R. Abela, S. Huang, B. H. Lipshutz, *J. Am. Chem. Soc.* **2010**, *132*, 4978–4979.



Scheme 2.6: Oxidative SUZUKI–MIYAURA arylation between urea-directed indolines and phenyl boronic acids catalyzed by a cationic palladium(II) complex under mild conditions by LIPSHUTZ.

Besides the SUZUKI–MIYAURA reactions, the reaction between unactivated indoline **91** and aryl iodide **93** was also accomplished recently by the FAN group in excellent yield (88%) (Scheme 2.7).[86] The catalysis was proceeded smoothly in aqueous phase and was found to be compatible with different functional groups. However, no reaction was observed when aryl bromides were used instead. This methodology highly extended the scope of the coupling partner scope of this biaryl compound preparation.



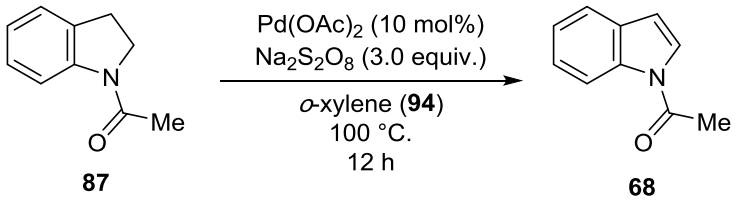
Scheme 2.7: Oxidative C-7 arylation between indolines and aryl iodides in aqueous phase by FAN.

To date, there are only a few examples of the C-7 arylation of indolines, and in all cases, one or even both coupling partner(s) need(s) to be prefunctionalized prior to use, resulting in the formation of undesired byproducts and wastes Given the principle of Green Chemistry, more environmentally benign and economical methodologies in this transformation are highly desired. In combination with the concept of cross-dehydrogenative coupling (CDC) reactions, we devoted our efforts to realize this goal through a CDC approach with which the desired C-7 arylated biaryl compounds could be assembled involving two unfunctionalized coupling partners.

2.2 OXIDATIVE PALLADIUM(II)-CATALYZED CROSS-DEHYDROGENATIVE ARYLATION OF 2,3,3-TRISUBSTITUTED INDOLINES AT THE C-7 POSITION

[86] Z. Jiang, L. Zhang, C. Dong, X. Su, H. Li, W. Tang, L. Xu, Q. Fan, *RSC Adv.* **2013**, *3*, 1025–1028.

We initiated our investigations with conditions similar to those formerly reported by SHI and co-workers.[84] We chose an acetyl as a chelating group because its utility has already been well studied in several kinds of transformations. Our reactions were performed between *N*-acetyl-directed indoline (**87**) and *o*-xylene (**94**), which served as both coupling partner and solvent as in related cases. We found quickly after initial evaluations that the unsubstituted indoline substrate **87** was unstable under this oxidative palladium catalysis reaction setup. Indoline was oxidized mainly to the corresponding indole **68** (Scheme 2.8), indicating that some substituents should be installed at C-2 and C-3 positions to prevent this undesired reaction.



Scheme 2.8: Indoline to indole oxidation under oxidative palladium(II) catalysis conditions.

2.2.1 Synthesis of Mono-, Di-, and Trisubstituted Indoline Starting Materials

Consequently, we turned our attention to indolines substituted at C-2 and/or C-3 positions and annulated indolines which would not easily be oxidized. Accordingly, several potentially useful mono-, di-, as well as trisubstituted indolines **95**–**108** as shown in Figure 2.1 were prepared by straightforward procedures.

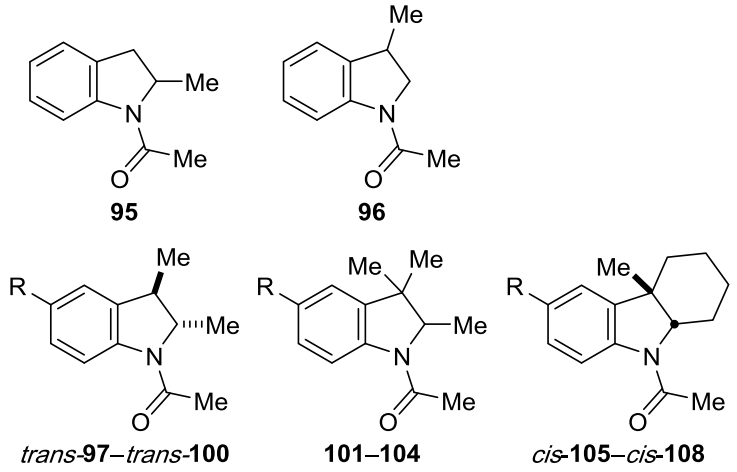
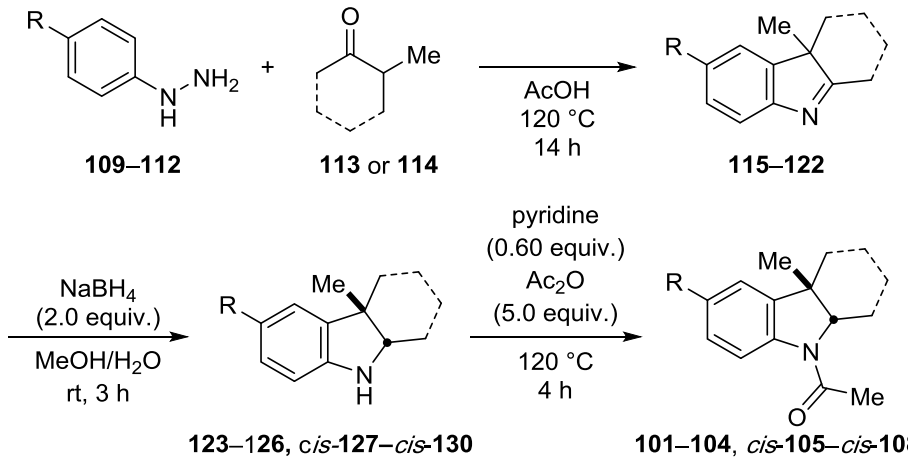


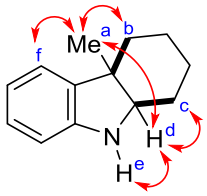
Figure 2.1: Mono-, di-, and trisubstituted indoline motifs surveyed.

2,3,3-Trisubstituted indolines **101–104** and *cis*-**105**–*cis*-**108** were easily accessible through an interrupted FISCHER indole synthesis[87] starting from the indicated ketone [3-methylbutan-2-ol (**113**) or 2-methylcyclohexanon (**114**)] with *para*-substituted phenylhydrazines **109–112**. The resulting indolenine intermediate **115–122** were then reduced with $NaBH_4$ (2.0 equiv.) in aqueous phase ($MeOH/H_2O$, *v*/*v* = 4:1) to give the corresponding indoline **123–126** and *cis*-**127**–*cis*-**130**. Afterwards, the acetyl directing group was introduced by treatment with acetic anhydride mediated by a catalytic amount of pyridine to afford the analytically pure products **101–104** and *cis*-**105**–*cis*-**108** (Scheme 2.9). Both electron-donating and -withdrawing groups were attached to the aromatic ring of the indolines (R = H, Me, OMe, and F).



Scheme 2.9: Preparation of 2,3,3-trisubstituted indolines by an interrupted FISCHER indole synthesis.

The resulting annulated indolines *cis*-**105**–*cis*-**108** were obtained with excellent diastereoselectivity (*cis*:*trans* > 99:1).[88] The relative configuration was assigned by nOe experiments. For example, the nOe spectra of indoline *cis*-**127** are illustrated below (Figure 2.2).



cis-**127**

[87] a) T. Kappe, P. Roschger, B. Schuiki, W. Stadlbauer, *J. Heterocyclic Chem.* **2003**, *40*, 297–302; b) L. Yuan, W. Lin, J. Song, *Chem. Commun.* **2010**, *46*, 7930–7932; c) H. S. Choi, K. Nasr, S. Alyabyev, D. Feith, J. H. Lee, S. H. Kim, Y. Ashitate, H. Hyun, G. Patonay, L. Strekowski, M. Henary, J. V. Frangioni, *Angew. Chem.* **2011**, *123*, 6382–6387; *Angew. Chem. Int. Ed.* **2011**, *50*, 6258 –6263.

[88] a) H. Booth, T. Masamune, *J. Chem. Soc., Perkin Trans. 2* **1972**, 354–356; b) Y. Ban, K. Yoshida, J. Goto, T. Oishi, E. Takeda, *Tetrahedron* **1983**, *39*, 3657–3668.

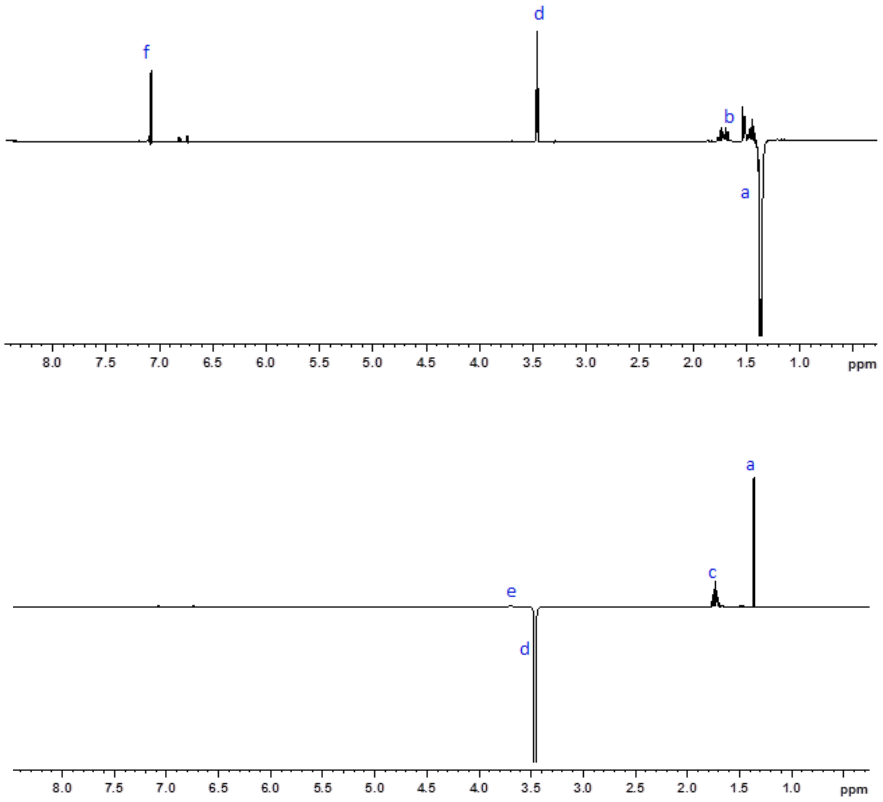
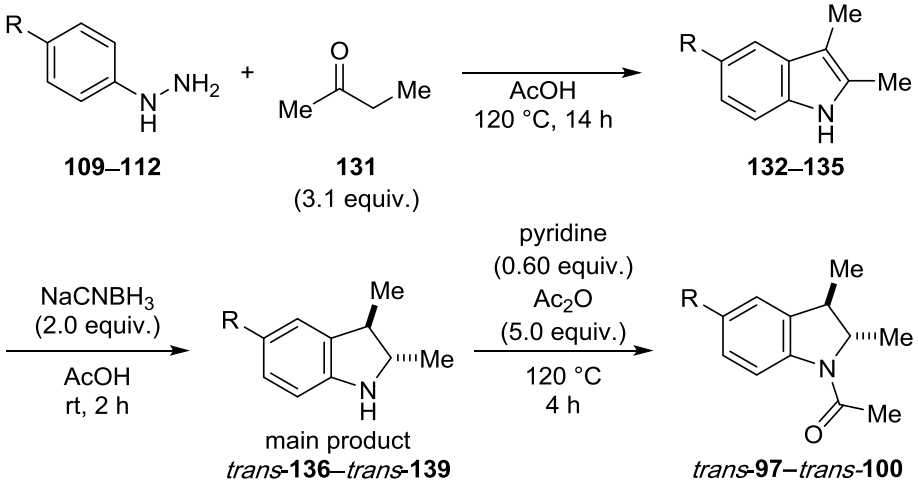


Figure 2.2: Assignment of the relative configuration by nOe interactions.

In addition, 2,3-disubstituted indolines *trans*-**97**–*trans*-**100** were also easily prepared from *para*-substituted phenylhydrazines **109–112** through the FISCHER indole synthesis.[89] The following indole reduction using $NaCNBH_3$ (2.0 equiv.) provided both *trans*- and *cis*- products with a ratio of approximately 80:20 in favor of the *trans* product, which was separated either in this step or in the next step after the introduction of the acetyl group (Scheme 2.10).



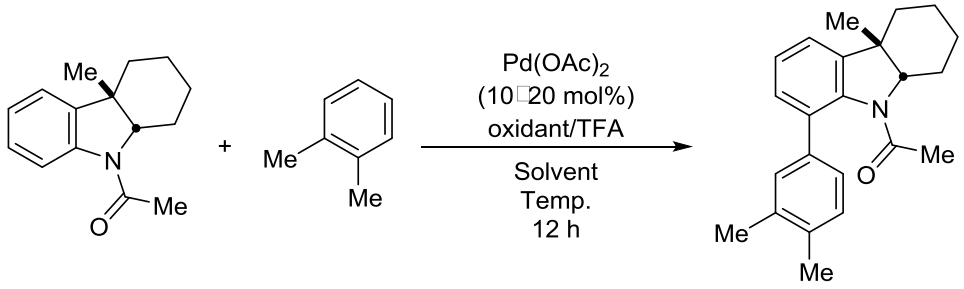
Scheme 2.10: Preparation of 2,3-disubstituted indolines by FISCHER indole synthesis

[89] a) B. Robinson, *Chem. Rev.* **1963**, *63*, 373–401; b) B. Robinson, *Chem. Rev.* **1969**, *69*, 227–250.

2.2.2 Preliminary Investigations and Substrate Scope

Then, we continued our study with the annulated indoline *cis*-**105** in *o*-xylene (**94**). Disappointingly, however, only very low conversion was observed when using $Cu(OAc)_2$ or $Cu(OTf)_2$ which had proven to be the optimal oxidants in SHI's report.[84] (Table 2.1, entries 1 and 2). The addition of trifluoroacetic acid (TFA, 5.0 equiv.) was found to be beneficial to increase the generation of the desired product *cis*-**140** albeit only slightly (Table 2.1, entry 3). To our delight, a switch of oxidant from copper salts to the strong oxidant $Na_2S_2O_8$ (3.0 equiv.)[90] improved the conversion and yield dramatically (Table 2.1, entry 4). The result could be further improved by raising the reaction temperature from 70 °C to 100 °C (Table 2.1, entry 4 versus 5), and the C–H/C–H bonds cross-coupled product *cis*-**140** was isolated in good yield (88%) as a single regioisomer (Table 2.1, entry 5). Full conversion could be achieved when conducting the catalysis under O_2 atmosphere; the yield remained unchanged though (Table 2.1, entry 6). It is not surprising that $Na_2S_2O_8$ and TFA have been recognized as a perfect combination to enable the CDC transformation under oxidative palladium catalysis.[91] Additional evidence for the importance of TFA was obtained when using either AcOH as solvent or altering the optimized conditions; the outcome dropped significantly in any case (Table 2.1, entries 7 and 11). Other organic acids, for example $EtCO_2H$, were detrimental (Table 2.1, entry 8). It is worthy of mention that both the catalyst loading and the amount of oxidant were also essential. Conversions and yields were merely moderate with less $Pd(OAc)_2$ (10 mol% versus 20 mol%) even under O_2 atmosphere (Table 2.1, entries 9–10) and less $Na_2S_2O_8$ (2.0 equiv. versus 3.0 equiv.) was also unfavorable (Table 2.1, entry 12).

Table 2.1: Identification of oxidative palladium(II)-catalyzed CDC arylation catalyst system.[a]



cis-**105** **94** *cis*-**140**

[90] a) Ref. [62a]; b) Ref. [62b]; c) Ref. [70c]; d) V. S. Thirunavukkarasu, C.-H. Cheng, *Chem. Eur. J.* **2011**, *17*, 14723–14726.

[91] a) Ref. [68a]; b) Ref. [68b]; c) N. Borduas, A. J. Lough, V. M. Dong, *Inorg. Chim. Acta* **2011**, *369*, 247–252.

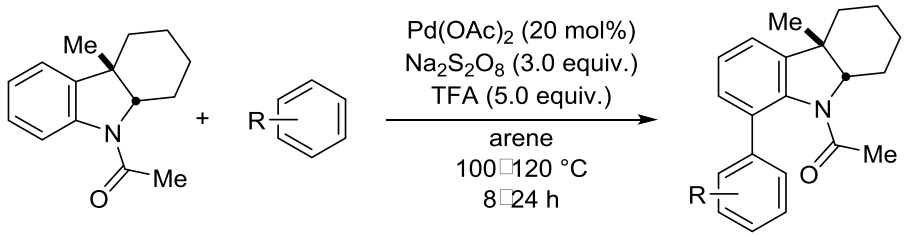
Entry	$Pd(OAc)_2$ [mol%]	Oxidant [equiv.]	TFA [equiv.]	Solvent	Temp. [°C]	Conv. [%][b]	Yield [%][c]
1	20	$Cu(OAc)_2$ [2.0]	—	*o*-xylene	70	<10	—
2	20	$Cu(OTf)_2$ [2.0]	—	*o*-xylene	70	<10	7
3	20	$Cu(OTf)_2$ [2.0]	5.0	*o*-xylene	70	18	12
4	20	$Na_2S_2O_8$ [3.0]	5.0	*o*-xylene	70	63	54
5	20	$Na_2S_2O_8$ [3.0]	5.0	*o*-xylene	100	95	88
6[d]	20	$Na_2S_2O_8$ [3.0]	5.0	*o*-xylene	100	100	89
7[e]	20	$Na_2S_2O_8$ [3.0]	—	AcOH	100	88	45
8[d,e]	20	$Cu(OTf)_2$ [2.0]	—	$EtCO_2H$	100	33	12
9	10	$Na_2S_2O_8$ [3.0]	5.0	*o*-xylene	100	45	38
10[d]	10	$Na_2S_2O_8$ [3.0]	5.0	*o*-xylene	100	60	51
11[f]	20	$Na_2S_2O_8$ [3.0]	—	*o*-xylene	100	28	18
12	20	$Na_2S_2O_8$ [2.0]	5.0	*o*-xylene	100	88	80

[a] All reactions were conducted according to **GP 3**. [b] Determined by GLC analysis with tetracosane as internal standard. [c] Isolated yield after purification by flash column chromatography on silica gel. [d] O_2 atmosphere (balloon) was used as co-oxidant. [e] 10 equiv. of *o*-xylene were used. [f] No product was observed in the absence of TFA.[68]

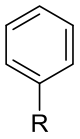
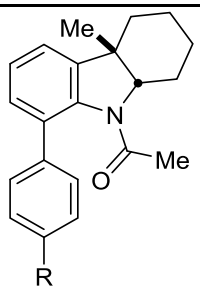
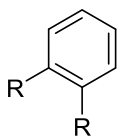
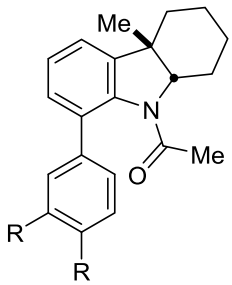
With the optimized conditions in hand, further exploration of the arene scope **62**, **94**, and **141–150** with annulated indoline *cis*-**105** demonstrated the practicality and utility of this protocol (Table 2.2). Benzene (**62**) was sufficiently reactive, resulting in the arylated indoline *cis*-**151** in decent conversion and isolated yield (Table 2.2, entry 1). According to the other results, both electronic and steric effects played a dominant role in both reactivity and selectivity. Generally, electron-rich arenes **62**, **94**, **141–144**, and **147**–**149** provided moderate to good yields (Table 2.2, entries 1–5 and 8–11), except arene **150** with major steric hindrance (Table 2.2, entry 12). Arene bearing electron-withdrawing groups such as fluorine **145** or CF_3 **146** did not result in any product (Table 2.2, entries 6–7). Monosubstituted arenes always gave rise to different regioisomers but interestingly, the ratio between these two regioisomers was highly affected by electronic effects. With the electron-donating ability of the attached group on the aromatic ring increasing, the ratio of *para*/*meta* arylated product also improved. In contrast to toluene (**141**) (Table 2.2, entry 2) and biphenyl (**142**) (Table 2.2, entry 3) showing moderate (53:47) to good (77:23) selectivity, anisole (**143**) (Table 2.2, entry 4) as well as phenetole (**144**) (Table 2.2, entry 5) exhibited good (86:14) to excellent (> 95:5) regioselective control.

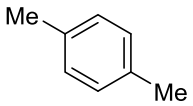
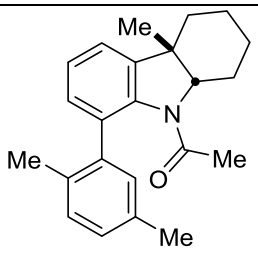
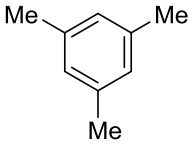
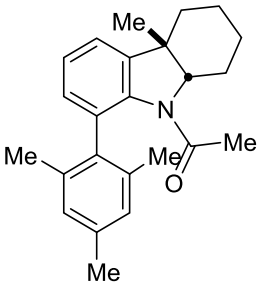
It should be highlighted here that the conversions and yields were relevance in the same range, suggesting that the indoline substrates did not decompose under these oxidative reaction conditions.

Table 2.2: Cross-dehydrogenative arylation of indoline derivatives with different arenes.[a]



cis-**105** **62**, **94**, **141**–**150** *cis*-**140**, *cis*-**151**–*cis*-**161**

Entry	Arene	T [°C]	*t* [h]	Product	Conv. [%][b]	Yield [%][c]
						
1	R = H (**62**)	100	14	R = H (*cis*-**151**)	78	74
2[d]	R = Me (**141**)	100	8	R = Me (*cis*-**152**)	88	72 (53:47)
3[d]	R = Ph (**142**)	120	14	R = Ph (*cis*-**153**)	55	48 (77:23)
4[d]	R = OMe (**143**)	120	14	R = OMe (*cis*-**154**)	96	82 (86:14)
5[d]	R = OEt (**144**)	120	24	R = OEt (*cis*-**155**)	63	50 (> 95:5)
6	R = F (**145**)	120	14	R = F (*cis*-**156**)	78	—
7	R = CF_3 (**146**)	120	14	R = CF_3 (*cis*-**157**)	88	—
						
8	R = Me (**94**)	100	12	R = Me (*cis*-**140**)	95	88
9	R = OMe (**147**)	120	14	R = OMe (*cis*-**158**)	74	71
10	R,R = OCH_2O (**148**)	120	14	R = R,R = OCH_2O (*cis*-**159**)	60	—

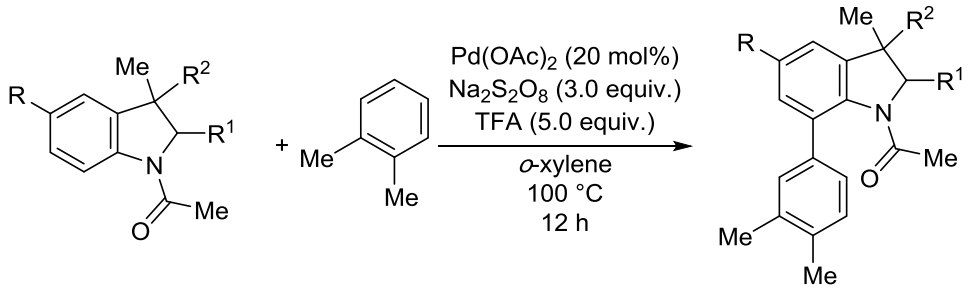
11[e]	 (**149**)	100	14	 (*cis*-**160**)	46	40
12	 (**150**)	120	16	 (*cis*-**161**)	34	—

[a] All reactions were conducted according to **GP 3.** [b] Determined by GLC analysis with tetracosane as internal standard. [c] Isolated yield after purification by flash column chromatography on silica gel; the ratios given in parentheses refer to the relative yield of *para*- to *meta*-substituted product. [d] The ratio of the two isomers was determined by GLC analysis. [e] 40% of starting material was recovered.

The standard protocol was applied to different di- and trisubstituted indolines and the results are shown in Table 2.3. In general, the substituents at the C-2 and C-3 positions exert little effect on the reactivity, even though there is a steric effect on the directing groups. However, the electronic properties of the aromatic ring play a significant role. Several annulated indolines *cis*-**105**–*cis*-**107** containing electron-neutral or -rich rings all converted smoothly to form the corresponding arylated products *cis*-**140** and *cis*-**162**–*cis*-**163** with excellent conversions (95–100%) and yields (88–92%) (Table 2.3, entries 1–3). The starting material *cis*-**108** bearing a fluorine was reluctant to react smoothly, and only moderate yield was obtained (45%) with remaining starting material (23%) even with doubled reaction time (Table 2.3, entry 4).

With the above observations, we envisioned that this potential CDC arylation was highly affected by the electron density of the indoline's aromatic core. As expected, similar results were observed with 2,3,3-trimethyl substituted indolines **101**–**104** (Table 2.3, entries 5–8). 2,3-Disubstituted indolines *trans*-**97**–*trans*-**100** also showed similar reactivity, resulting in equally conversions and yields (Table 2.3, entries 9–12).

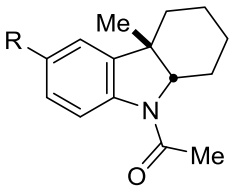
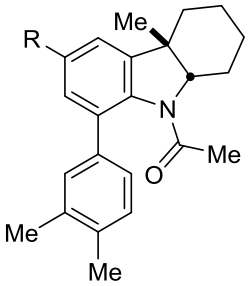
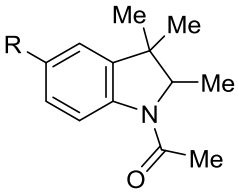
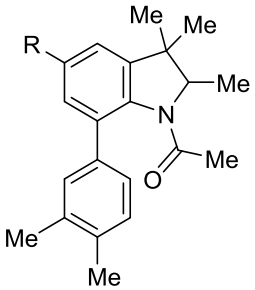
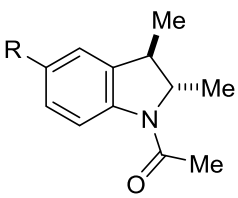
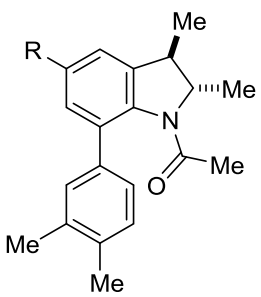
Table 2.3: Cross-dehydrogenative arylation of *o*-xylene with variation of the indoline substitution pattern.[a]



trans-**97**–t*rans*-**100**, **101**–**104**, *cis*-**105**–*cis*-**108**

94

cis-**140**, *cis*-**162**–c*is*-1**64**, **165**–**168**, *trans*-**169**–t*rans*-**172**

Entry	Indoline	R	Product	Conv. [%][b]	Yield [%][c]
					
1	*cis*-**105**	H	*cis*-**140**	95	88
2	*cis*-**106**	Me	*cis*-**162**	99	91
3	*cis*-**107**	OMe	*cis*-**163**	100	92
4	*cis*-**108**	F	*cis*-**164**	55[d]	45[e]
					
5[f]	**101**	H	**165**	97	87
6	**102**	Me	**166**	100	95
7	**103**	OMe	**167**	100	93
8	**104**	F	**168**	58[d]	51[g]
					

9	*trans*-**97**	H	*trans*-**169**	96	88
10	*trans*-**98**	Me	*trans*-**170**	100	93
11	*trans*-**99**	OMe	*trans*-**171**	100	90
12	*trans*-**100**	F	*trans*-**172**	55[d]	50[h]

[a] All reactions were conducted according to **GP 3**. [b] Determined by GLC analysis with tetracosane as internal standard. [c] Isolated yield after purification by flash column chromatography on silica gel. [d] 24 h. [e] 23% starting material recovered. [f] For this reaction, we found that conversion was highly dependent on the purity of the indoline. Out of several runs, 50% was lowest and 97% highest. [g] 26% starting material recovered. [h] 35% starting material recovered.

The relative configuration of the annulated indoline was retained throughout the whole sequence to yield the desired product *cis*-**162** in pure form which was confirmed by both nOe measurements and X-ray crystal structural analysis (Figure 2.3).

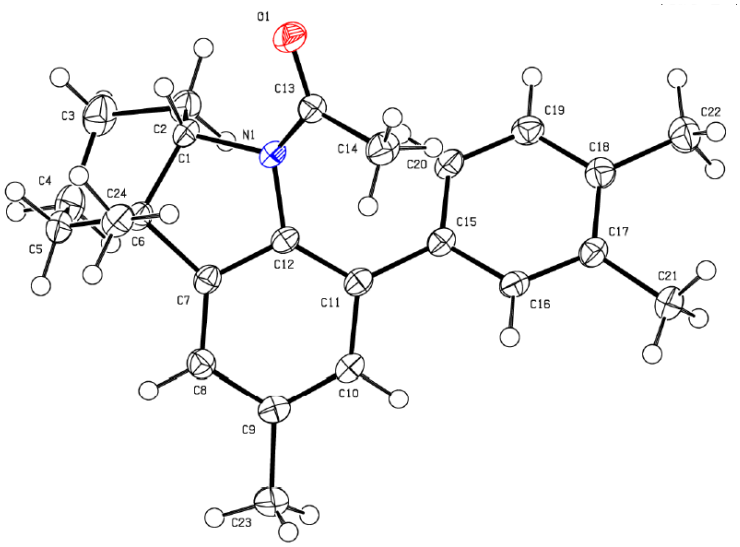
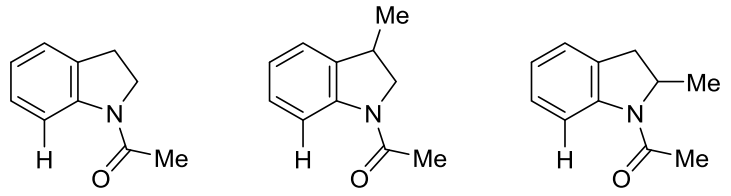


Figure 2.3: Molecular structure of product *cis*-**162**.

2.2.3 NMR Experiments for the Assignment of Amide Rotamers

The most simple indoline substrate **87** encountered indoline-to-indole oxidation problem while 2,3,3-tri- **101**–**104** and *cis*-**105**–*cis*-**108** or 2,3-disubsituted indolines *trans*-**97**–*trans*-**100** survived under the same catalytic conditions. In an effort to continue expanding the scope of this protocol, we explored the further simplification of the substitution pattern to monosubstituted indolines. As mentioned above, we prepared two indolines with a methyl at the C-2 **95** and the C-3 **96** position, respectively assuming that these indolines would not suffer facile oxidation. As a matter of fact, these indolines were quite stable under oxidative catalytic conditions. However, much to our surprise, 2-methyl substituted indoline **95** reacted slowly to form the desired product in moderate yield (38%) accompanied by a small amount

of indoline-to-indole oxidation. Conversely, indoline substrate **96** with a methyl group at the C-3 position showed low reactivity and yielded trace amounts of the arylated product (Figure 2.4).



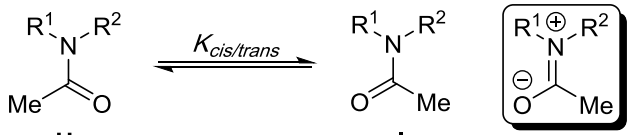
87
sharp doublet
at □= 8.20 ppm
no cross-coupling
(indoline oxidation)

96
sharp doublet
at □= 8.19 ppm
slow cross-coupling

95
broad singlet
at □= 7.88 ppm
69% conv. after 24 h
(38% isolated yield)

Figure 2.4: ^{1}H NMR shifts and signal shapes of the proton at C-7 of differently substituted, acetylated indolines at room temperature and their performance in the C–H/C–H bonds cross-coupling.

Amide groups always exist as two different rotamers because their C–N single bond displays double bond characteristics. As a consequence, there will be an equilibrium between the rotamers if C–N bond rotation is not totally unrestricted (Scheme 2.11).[92]



H
trans-amide

I
cis-amide

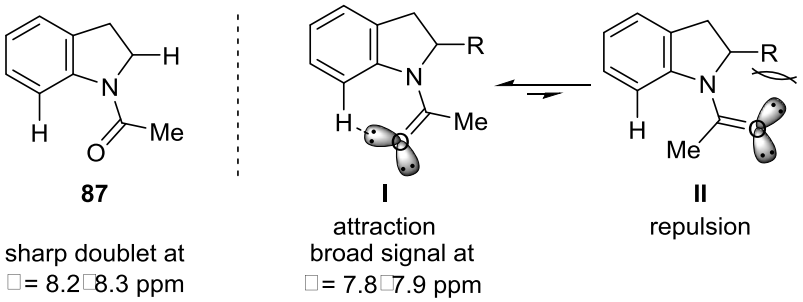
Scheme 2.11: Equilibrium between amide bond rotamers.

This is one of the considerations that motivated our efforts to gain an inside view of this transformation. Much to our delight, more evidence emerged after a few NMR experiments of different kinds of substrates, providing more detailed differences between these indolines. For instance, the unreactive indolines **87** and **96** showed perfectly resolved ^{1}H NMR spectra with the chemical shift of the C-7 proton at around 8.20 ppm as a sharp doublet. In contrast, the ^{1}H NMR spectrum of **95** was less resolved at room temperature (Scheme 2.12). We measured a sample of **95** by using variable temperature (VT) NMR technique. After increasing the temperature step by step, a satisfactory spectra was obtained at 358 K (85 °C) with a broad singlet resonance signal of the C-7 proton at around 7.88 ppm. In addition, other indoline substrates *trans*-**97**–*trans*-**100**, **101**–**104**, and *cis*-**105**–*cis*-**108** also suffered from the same problem, and all of them needed to be measured at 358 K in order to get resolved ^{1}H

[92] a) J. S. Laursen, J. Engel-Andreasen, P. Fristrup, P. Harris, C. A. Olsen, *J. Am. Chem. Soc.* **2013**, *135*, 2835–2844; b) P. Saxena, N. Thirupathi, M. Nethaji, *Organometallics* **2014**, *33*, 5554–5565.

NMR spectra, representing similar shape of peaks with similar chemical shifts (7.80–7.90 ppm). It is evident that the substituent at the C-2 position of indoline remotely affects the reactivity of this desired C-7 arylation reaction.

On the basis of the aforementioned observations and knowledge, we proposed an attraction and repulsion equilibrium as shown below (Scheme 2.12). The repulsion existing in **II** between the electron lone pairs of the amide oxygen atom and the C-2 substituent pushes the amide isomer toward rotamer **I** in which the same oxygen atom approaches the C–H bond at the C-7 position of indoline to engage in a hydrogen bonding. Our hypothesis was supported by the fully assignment of rotamers **I** and **II** through chemical exchange in 2D EXSY and 2D NOESY NMR measurements.



Scheme 2.12: Amide rotamer equilibrium controlled by repulsion (right) and attraction (left) with **I** and **II** assigned by 2D EXSY and 2D NOESY measurements.

Finally, we were able to separate these two rotamers on ^{1}H NMR spectra at 251 K. As shown in Figure 2.5, it is clear to see that with decreasing the measuring temperature, the broad singlet peak of the proton at the C-7 atom (7.8 ppm) separate gradually into two groups of sharp doublet peaks (7.2 and 8.0 ppm, respectively. In addition, a similar phenomenon was also found for the proton at the tertiary C-2 atom (4.2 ppm split into 4.0 and 4.4 ppm). The rotamers ratio of compound **101** was determined as 79:21 in favor of rotamer **I**.

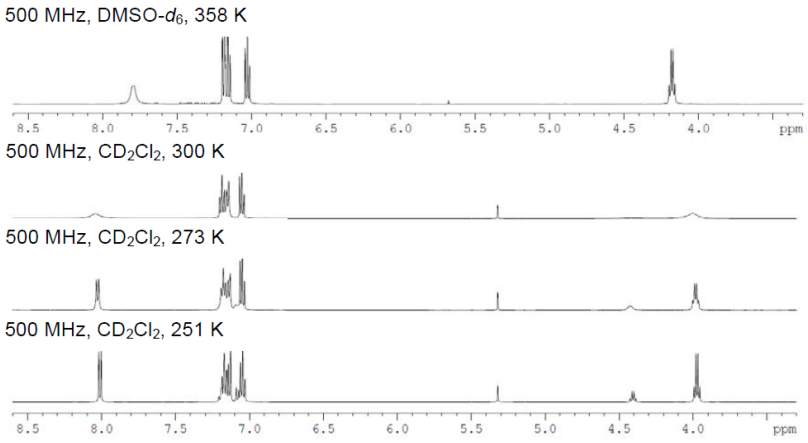


Figure 2.5: Determination of the ratio of amide rotamers.

2.3 Oxidative Palladium(II)-Catalyzed Cross-Dehydrogenative Arylation of Indolines at the C-7 Position Under Exceptionally Mild Conditions in Air

Despite the recent progress made in C-7 selective CDC arylation, the practical utility of this protocol in remained limited due to the need for a very strong oxidant such as $Na_2S_2O_8$. The lack of reactivity of the indoline substrates required harsh reaction conditions.[98]

2.3.1 Urea Directing Groups in Direct C–H Functionalization

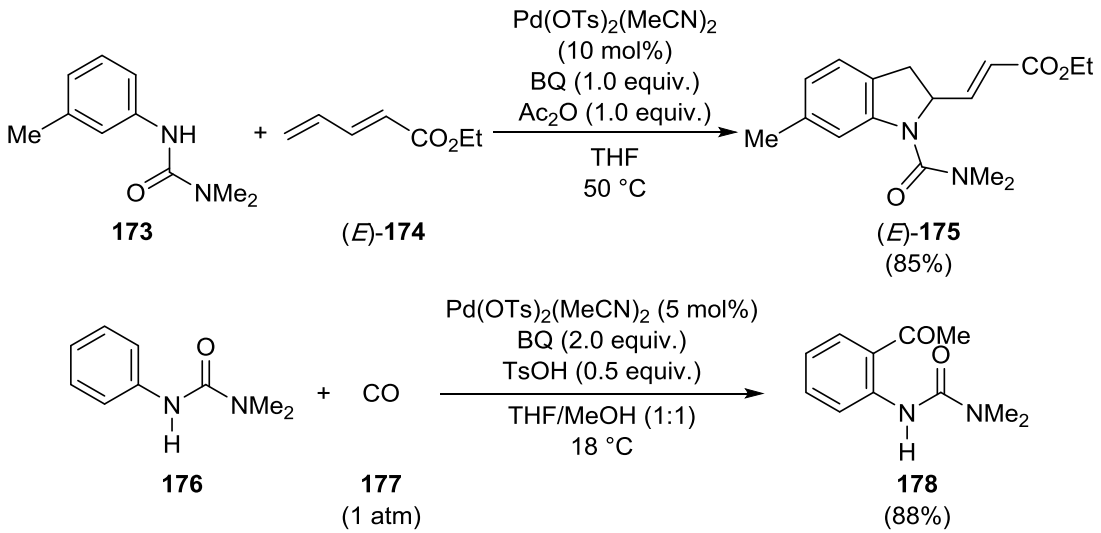
However, according to former experiences, the directing groups sometimes play dual roles, that is not only as a directing tool, but also in changing the reactivity of substrates.
With these considerations in mind, some effort has been made in our group to pursue powerful and practical directing groups that overcome the aforementioned problems and enabling facile preparation of the target molecules. As far as we know, to date, there are several kinds of reported LEWIS basic functional groups and most of them are oxygen- and nitrogen-containing moieties.[28] Among them, a readily accessible and removable urea group was only used occasionally. It was recently introduced by the LLOYD-JONES and BOOKER-MILBURN groups in the C–H 1,2-carboamination of dienes[93] and C–H methoxycarbonylation of aniline derivatives (Scheme 2.13).[94] Afterwards this directing group was independently utilized by the LIPSHUTZ,[95] FAN,[86] and other groups[96] in the C–H arylation of anilines.

[93] C. E. Houlden, C. D. Bailey, J. G. Ford, M. R. Gagné, G. C. Lloyd-Jones, K. I. Booker-Milburn, *J. Am. Chem. Soc.* **2008**, *130*, 10066–10067.

[94] C. E. Houlden, M. Hutchby, C. D. Bailey, J. G. Ford, S. N. G. Tyler, M. R. Gagné, G. C. Lloyd-Jones, K. I. Booker-Milburn, *Angew. Chem.* **2009**, *121*, 1862–1865; *Angew. Chem. Int. Ed.* **2009**, *48*, 1830–1833.

[95] a) Ref. [85]; b) T. Nishikata, A. R. Abela, B. H. Lipshutz, *Angew. Chem.* **2010**, *122*, 793–796; *Angew. Chem. Int. Ed.* **2010**, *49*, 781–784.

[96] a) D. J. Schipper, M. Hutchinson, K. Fagnou, *J. Am. Chem. Soc.* **2010**, *132*, 6910–6911; b) J. Willwacher, S. Rakshit, F. Glorius, *Org. Biomol. Chem.* **2011**, *9*, 4736–4740; c) B. Li, J. Ma, W. Xie, H. Song, S. Xu, B. Wang, *Chem. Eur. J.* **2013**, *19*, 11863–11868; d) B. Li, J. Ma, W. Xie, H. Song, S. Xu, B. Wang, *J. Org. Chem.* **2013**, *78*, 9345−9353.

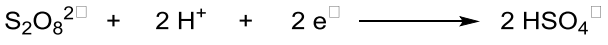


Scheme 2.13: Urea as directing group promote the C–H 1,2-carboamination of dienes and methoxycarbonylation under very mild conditions by LLOYD-JONES and BOOKER-MILBURN.

All these reactions have in common that most of them proceeded under slightly elevated or even ambient conditions from room temperature to 60 °C.[93,94,95] We assumed that this directing group would also show a beneficial effect in our CDC arylation of indolines selective at the C-7 position.

2.3.2 Dioxygen Acting as Oxidant in Direct C–H Functionalization

As for the oxidant, compared with others choices, persulfate salts **J** are indeed quite strong with an oxidation potential of 2.1 V of its persulfate anion **K** (Equation 2.1).



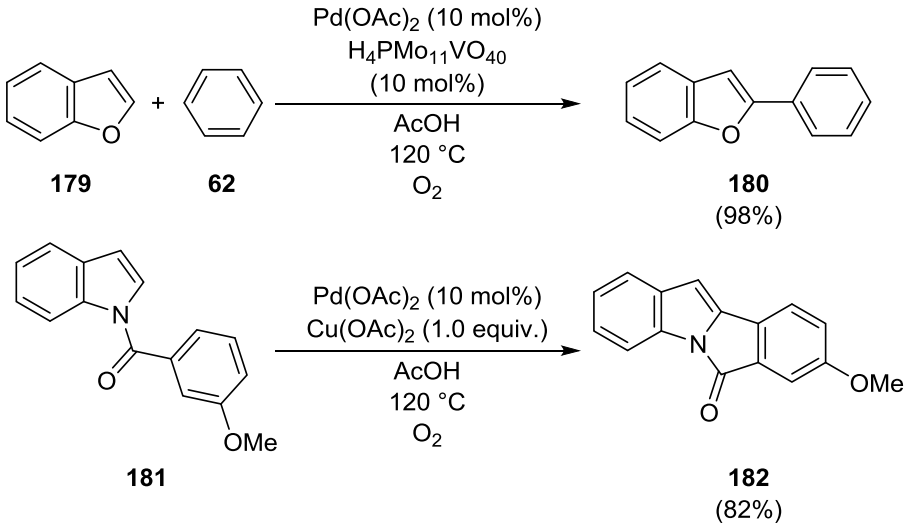
J **K**

Equation 2.1: Persulfate anions as strong oxidants.

In terms of sustainability, air or dioxygen serving as terminal oxidant seems to be a perfect alternative. Until today, however, there are only a few examples associated with CDC arylation using air or dioxygen as oxidant, normally at 100–120 °C.[97] For example, a few years ago, the DEBOEF group accomplished both inter- and intramolecular oxidative CDC arylation of benzofurans and *N*-substituted indoles, respectively in an O_2 atmosphere.[97a]

[97] a) T. A. Dwight, N. R. Rue, D. Charyk, R. Josselyn, B. DeBoef, *Org. Lett.* **2007**, *9*, 3137–3139; b) G. Brasche, J. García-Fortanet, S. L. Buchwald, *Org. Lett.* **2008**, *10*, 2207–2210; c) B. Liégault, D. Lee, M. P. Huestis, D. R. Stuart, K. Fagnou, *J. Org. Chem.* **2008**, *73*, 5022–5028; d) A. N. Campbell, E. B. Meyer, S. S. Stahl, *Chem. Commun.* **2011**, *47*, 10257–10259; e) L. Zhou, W. Lu, *Organometallics* **2012**, *31*, 2124–2127.

This contribution set the stage for performing direct arylation reactions in an atom economic as well as green chemistry fashion. In the arylation of benzofuran (**179**), heteropolymolybdovanadic acid $H_4PMo_{11}VO_{40}$ (HPMV) was introduced to fulfill exclusive regioselective control at the C-2 rather than C-3 position (Scheme 2.14, upper). For the C–C bond formation of *N*-substituted indole **181**, $Cu(OAc)_2$ as a mild oxidant was found to be effective to accelerate the transformation (Scheme 2.14, lower).



Scheme 2.14: Inter- and intramolecular oxidative CDC arylation of benzofuran and *N*-substituted indoles, respectively in O_2 atmosphere by DEBOEF.

Since these early reports, dioxygen as oxidant started to draw more and more attention on CDC reactions due to its environmentally benign and green chemistry properties. Afterwards, this was further highlighted followed by reports of (a) intramolecular arylation to form carbazole in the open air by FAGNOU,[97c] (b) *ortho* arylation of anilides by BUCHWALD,[97b] (c) regioselective oxidative arylation of indoles by STAHL,[97d] and (d) arylation of electron deficient arenes by LU.[97e]

These achievements were a major impetus for us to devote our efforts in developing new catalytic system with more versatility and practicality.

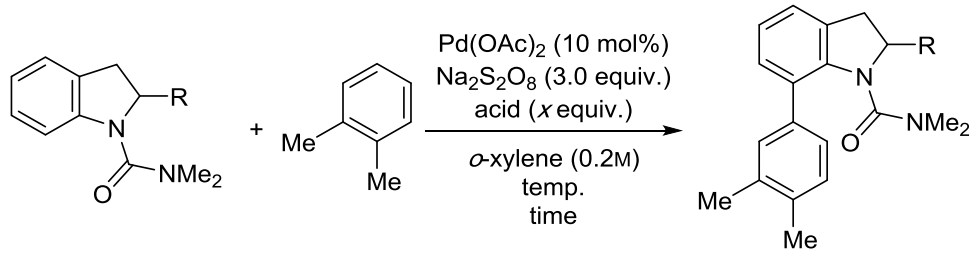
2.3.3 Preliminary Investigations and Substrate Scope

In a continuation of our previous work, we initiated our research by using urea-directed indoline **91** instead of an acetyl-directed substrates at low temperature with strong oxidant $Na_2S_2O_8$ (3.0 equiv.) as done before.[98] We quickly learned that this strategy was promising, both conversion (40%) and yield (34%) were acceptable even at only 30 °C (Table 2.4, entry 1). Encouraged by this observation, more conversion was monitored at raised temperatures

[98] L.-Y. Jiao, M. Oestreich, *Chem. Eur. J.* **2013**, *19*, 10845–10848.

and more product was formed with the temperatures slightly elevated (Table 2.4, entries 2–3). Gratifyingly, full conversion was obtained in 73% yield at 50 °C (Table 2.4, entry 3) but higher temperatures resulted in product decomposition (Table 2.4, entry 4). Under the optimized conditions, indoline with a methyl group at the C-2 position **183** was tested, the result was even better (Table 2.4, entry 5). As previously, TFA was also essential,[99] and no conversion was detected in its absence (Table 2.4, entry 6). With the aid of a urea directing group, catalysis was even conducted in aqueous phase.[86] Inspired by this, one example was attempted, however, decomposition was observed (Table 2.4, entry 7).

Table 2.4: Identification of the CDC arylation catalyst system directed by urea group.[a]



91 or **183** **94** **184–185**

Entry	Indoline	TFA [equiv.]	Temp. [°C]	Time [h]	Conv. [%][b]	Yield [%][c]
1	R = H (**91**)	5.0	30	16	40	34
2	R = H (**91**)	5.0	40	16	86	62
3	R = H (**91**)	5.0	50	18	100	74
4	R = H (**91**)	5.0	90	18	100	—[d]
5	R = Me (**183**)	5.0	50	18	99	83
6	R = H (**91**)	—	50	16	NR[e]	—
7[f]	R = H (**91**)	5.0	50	16	90	—

[a] All reactions were conducted according to **GP 5**. [b] Determined by GLC analysis with tetracosane as internal standard. [c] Isolated yield after purification by flash column chromatography. [d] Decomposition. [e] No reaction. [f] In *o*-xylene/H_2O[100] (*v*/*v*, 1/1), 0.2 equiv. of tetra-*n*-butylammonium bromide (TBAB) was added as phase transfer catalyst (PTC).

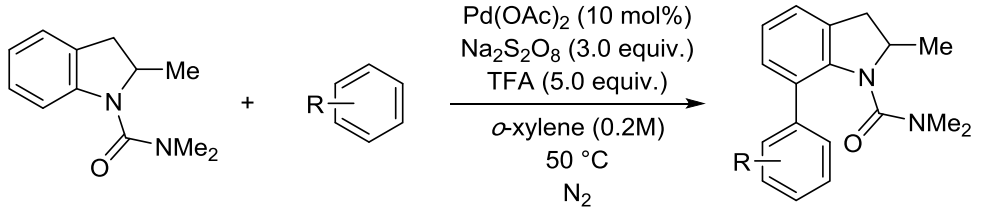
Under these optimized conditions, several arenes were evaluated in the coupling with indoline **183** (Table 2.5). Much to our disappointment, despite the above excellent-yielding *o*-xylene (**94**), none of the other arenes **62**, **141**–**142**, **147**, **149**–**150**, and **186**–**187** led to any

[99] a) A. A. H. Van der Zeijden, H. W. Bosch, H. Berke, *Organometallics* **1992**, *11*, 563–573; b) C. Jia, W. Lu, J. Oyamada, T. Kitamura, K. Matsuda, M. Irie, Y. Fujiwara, *J. Am. Chem. Soc.* **2000**, *122*, 7252–7263; c) C. Jia, D. Piao, J. Oyamada, W. Lu, T. Kitamura, Y. Fujiwara, *Science* **2000**, *287*, 1992–1995.

[100] a) K. Nishiura, Y. Urawa, S. Soda, *Adv. Synth. Catal.* **2004**, *346*, 1679–1684; b) Z. Wu, F. Luo, S. Chen, Z. Li, H. Xiang, X. Zhou, *Chem. Commun.* **2013**, *49*, 7653–7655.

arylated product although generally conversions were quite high (Table 2.5, entries 2–9). We cannot explain this unusual and unexpected behavior.[98]

Table 2.5: Identification of the CDC arylation catalytic system directed by a urea group.[a]



183 **185**, **188–195**

Entry	Arene	Time [h]	Conv. [%][b]	Yield [%][c]
1	*o*-xylene (**94**)	18	99	83
2	*p*-xylene (**149**)	18	85	<5[d]
3	*m*-xylene (**186**)	18	92	<10[d]
4	benzene (**62**)	18	97	<19[d]
5	toluene (**141**)	18	97	<10[d]
6	mesitylene (**150**)	18	92	<10[d]
7	biphenyl (**142**)	18	84	<10[d]
8	veratrole (**147**)	18	78	—[d]
9	*N*,*N*-dimethyl-*o*-toluidine (**187**)	18	32	—[d]

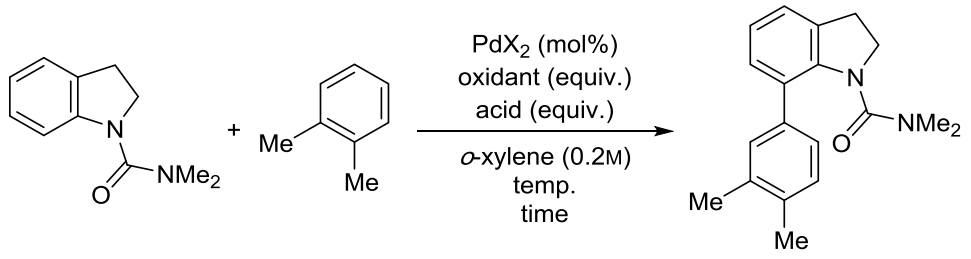
[a] All reactions conducted according to the condition listed in Table 2.4, enty5. [b] Determined by GLC analysis with tetracosane as internal standard. [c] Isolated yield after purification by flash column chromatography. [d] Decomposition.

We then intended to accomplish a more compatible protocol for other arenes as well. Switching to the milder oxidant $Cu(OAc)_2$ (2.5 equiv.) resulted in both low conversion and yield (Table 2.6, entry 1). However, performing the reaction in dioxygen atmosphere improved the yield slightly. (Table 2.6, entry 2). The amount of oxidant seemed not to be crucial for the reaction outcome (Table 2.6, entry 3). In contrast, TFA was still important for this CDC arylation (Table 2.6, entry 4). To our delight, an increase of the amount of TFA (5.0 to 13.0 equiv.) in an open flask indeed accelerated the transformation dramatically. Using pure dioxygen (balloon) as the sole oxidant did not change this result, providing more solid evidence of the important role of TFA (Table 2.6, entries 5–6).

Extensive oxidant screening revealed that either open air or $Cu(OAc)_2$ alone showed less efficiency than the combination of both (Table 2.6, entries 7–8). Moreover, neither Ag_2CO_3 nor BQ which are commonly used in oxidative cross-coupling reactions only led to acceptable results (Table 2.6, entries 9–10). Lowering the catalyst loading from 10 to 5.0 mol% was detrimental (Table 2.6, entry 11), and no reaction was observed without the

addition of $Pd(OAc)_2$ (Table 2.6, entry 12). Additives other than TFA were quite detrimental with no conversion detected after 18 h (Table 2.6, entry 13). It is worthy of mention that neither byproduct nor decomposition was observed in all cases where $Cu(OAc)_2$ was employed as oxidant (Table 2.6, entries 1–3, 5, and 8). Conditions shown in Table 2.6, entries 5 and 6 were best. However, in order to simplify the reaction setup manipulation, we chose the conditions given in Table 2.6, entry 5 as the standard procedure for the following substrate scope extending process.

Table 2.6: Identification of the CDC arylation catalytic system directed by a urea group.[a]



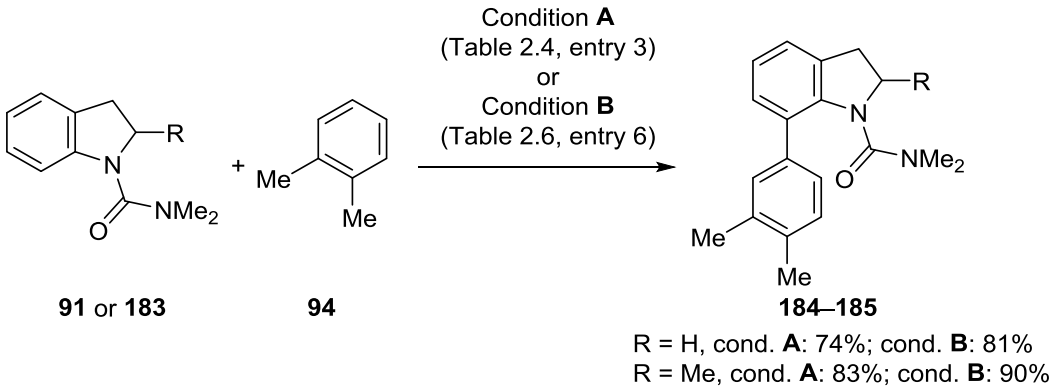
91 **94** **184**

Entry	[Pd] [mol %]	Oxidant [equiv.]	Atm.	Acid [equiv.]	Temp. [°C]	Time [h]	Conv. [%][b]	Yield [%][c]
1	$Pd(OAc)_2$ [10]	$Cu(OAc)_2$ [2.5]	N_2	TFA [5.0]	50	18	25	22
2	$Pd(OAc)_2$ [10]	$Cu(OAc)_2$ [2.5]	O_2[d]	TFA [5.0]	50	18	41	30
3	$Pd(OAc)_2$ [10]	$Cu(OAc)_2$ [1.0]	O_2[d]	TFA [5.0]	50	18	34	28
4	$Pd(TFA)_2$ [10]	$Cu(OAc)_2$ [1.0]	air[e]	—	50	18	NR[f]	—
5	$Pd(OAc)_2$ [10]	$Cu(OAc)_2$ [1.0]	air[e]	TFA [13]	50	22	100	81
6	$Pd(OAc)_2$ [10]	—	O_2[d]	TFA [13]	50	22	100	85
7	$Pd(OAc)_2$ [10]	—	air[e]	TFA [13]	50	18	16	9
8	$Pd(OAc)_2$ [10]	$Cu(OAc)_2$ [1.0]	N_2	TFA [13]	50	42	55	47
9	$Pd(OAc)_2$ [10]	Ag_2CO_3 [1.0]	air[e]	TFA [13]	50	18	10	trace
10	$Pd(OAc)_2$ [10]	BQ [1.0]	air[e]	TFA [13]	50	18	90	trace
11	$Pd(OAc)_2$ [5.0]	$Cu(OAc)_2$ [1.0]	air[e]	TFA [13]	50	42	24	ND[g]
12	—	$Cu(OAc)_2$ [1.0]	air[e]	TFA [13]	50	16	NRf	—
13	$Pd(OAc)_2$ [10]	$Cu(OAc)_2$ [1.0]	air[e]	PivOH [10]	50	18	NRf	—

[a] All reactions were conducted according to **GP 5** or **GP 6**. [b] Determined by GLC analysis with tetracosane as internal standard. [c] Isolated yield after purification by flash column chromatography. [d] Balloon. [e] In the open air. [f] No reaction. [g] Not determined.

Given the encountered problems illustrated above, we subjected the two indoline substrates **91** and **183** to those two kinds of conditions (Table 2.4, entry 3 and Table 2.6, entry 5)

(Scheme 2.15). Both substrates converted to the desired arylated products **184**–**185** smoothly with good to excellent results.

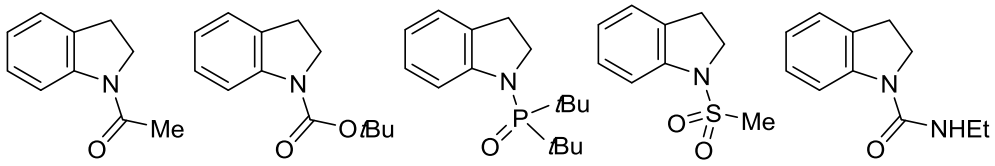


91 or **183** **94** **184**–**185**

R = H, cond. **A**: 74%; cond. **B**: 81%
R = Me, cond. **A**: 83%; cond. **B**: 90%

Scheme 2.15: Testing indoline substrates **91** and **183** under two different conditions.

Having the optimized oxidative palladium(II) catalysis conditions in hand, a variety of indolines bearing different directing groups such as acetyl **87**, Boc **78**, dialkyl phosphine oxide **196**, methyl sulfonyl **197**, and a urea with a free N–H group at the terminus **198** were evaluated (Scheme 2.16). It was disappointing that none of them prove to be effective to deliver the arylated products, indicating that not only the type of the attached directing group but also its substitution were equally important to the transformation.



87 **78** **196** **197** **198**

Scheme 2.16: Different directing groups that do not allow C–H arylation at the C-7 position.

We started to install other arene coupling partners to the indoline substrates **91**, hoping not to encounter the aforementioned problems as with $Na_2S_2O_8$ (Table 2.5, entries 2–9). As hoped, we did observe moderate to good results (Table 2.7).

Firstly, benzene (**62**) served as a coupling partner, yielding the arylated product **92** in decent result (Table 2.7, entry 1). Next, a few more examples with electron-rich monosubstituted arenes **141**, **143**–**144** were examined. These showcased good to excellent yields and regioselectivities. As illustrated, with the electron density of arenes increasing, the product **201** displayed high regioselective control of up to > 99:1 (Table 2.7, entries 3, 5–6).

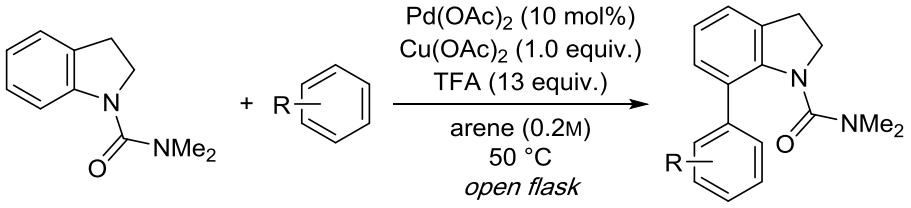
Both conversion and yield decreased slightly with 1,2-diethylbenzene (**199**, 62%, Table 2.7, entry 9) and dropped substantially with tetrahydronaphthalin (**200**, 18%, Table 2.7, entry 10) compared to *o*-xylene (**94**, 81%, Table 2.7, entry 7). The former was a little much bulkier.

Another electron-rich *ortho* disubstituted arenes **147**, exhibited low reactivity even with much longer reaction time probably because of the electronic effects (Table 2.7, entry 11). Similar to 1,2-dimethoxybenzene (**147**), 1,2-dichlorobenzene (**74**) was reluctant to react (Table 2.7, entry 12).

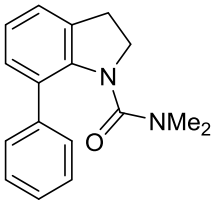
Unlike highly reactive *o*-xylene (**94**), *m*-xylene (**186**), and *p*-xylene (**149**) only gave moderate yield (Table 2.7, entry 13) or traces (Table 2.7, entry 15), respectively, with poor regioselectivity in the former case (rs = 69:31). It was not surprising that mesitylene (**150**) refused to react because of strong steric hindrance (Table 2.7, entry 16). The *N*,*N*-dimethyl toluidine homologue **187** formed only homocoupled compound instead of the desired product **211**[101] (Table 2.7, entry 17).

To test the compatibility of our palladium(II) catalysis in an aerobic fashion (Table 2.6, entry 6), we performed a few examples with a different number of substituents under these conditions (Table 2.7, entries 2, 4, 8, and 14). Slightly better results were obtained in the coupling of benzene (Table 2.7, entries 1 and 2, 76% versus 71%) and *o*-xylene (Table 2.7, entries 7 and 8, 85% versus 81%), however, for toluene (Table 2.7, entry 4) and *p*-xylene (Table 2.7, entry 14), yields dropped while the regioselectivity increasing slightly. Thus, it can be concluded that this aerobic protocol is also versatile and practical.

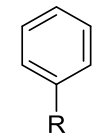
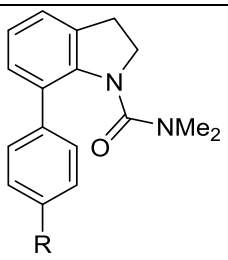
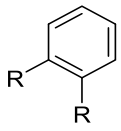
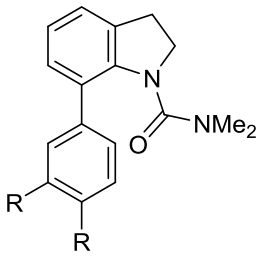
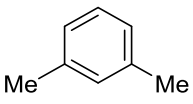
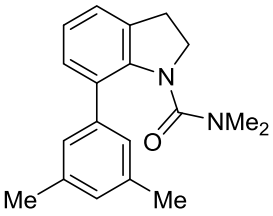
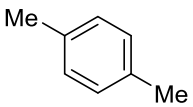
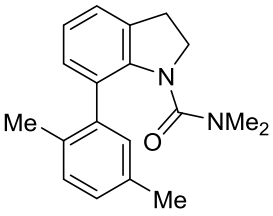
Table 2.7: Open-flask or aerobic CDC arylation of indoline and various arenes.[a]

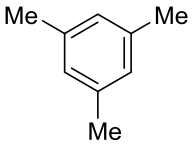
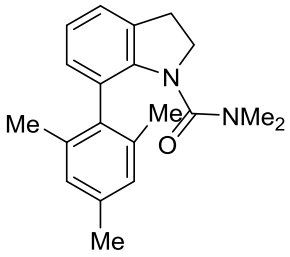
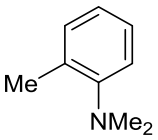
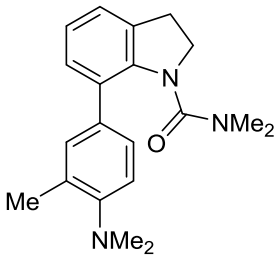


91 **92, 184**, **201**–**211**

Entry	Arenes	Time [h]	Product	Conv. [%][b]	Yield [%][c]
					
1	**62**	20	**92**	99	71
2[d]	**62**	48	**92**	100	76

[101] a) Y. Rong, R. Li, W. Lu, *Organometallics* **2007**, *26*, 4376-4378; b) L. T. Ball, G. C. Lloyd-Jones, C. A. Russell, *Science*, **2012**, *337*, 1644–1648.

					
3	R = Me (**141**)	24	R = Me (**201**)	97	70 (62:38)[e]
4[d]	R = Me (**141**)	48	R = Me (**201**)	60	26 (64:36)[e]
5	R = OMe (**143**)	18	R = OMe (**202**)	74	68 (> 99:1)[e]
6	R = OEt (**144**)	24	R = OEt (**203**)	99	84 (94:6)[e]
					
7	R = Me (**94**)	18	R = Me (**184**)	100	81
8[d]	R = Me (**94**)	22	R = Me (**184**)	100	85
9	R = Et (**199**)	20	R = Et (**204**)	78	62
10	R,R = $(CH_2)_4$ (**200**)	44	R,R = $(CH_2)_4$ (**205**)	20	18 (89:11)[e]
11	R = OMe (**147**)	52	R = OMe (**206**)	21	18
12	R = Cl (**74**)	52	R = Cl (**207**)	42	trace
					
13	**186**	44	**208**	98	55 (69:31)[e]
14[d]	**186**	48	**208**	36	32 (74:26)[e]
					

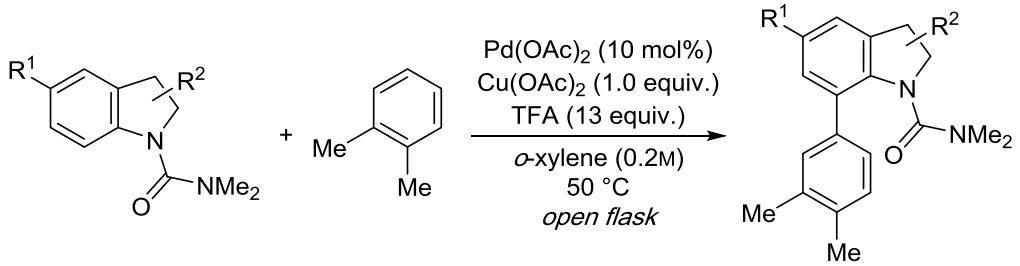
15	**149** 	44	**209** 	98	trace
16	**150** 	44	**210** 	98	trace
17	**187**	20	**211**	99	—

[a] All reactions were conducted according to **GP 5**. [b] Determined by GLC analysis with tetracosane as internal standard. [c] Isolated yield after purification by flash column chromatography. [d] Reactions proceeded under copper-free conditions with dioxygen (balloon) as sole oxidant. [e] Regioselectivity, *para*:*meta*, major regioisomer shown.

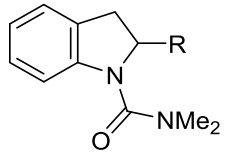
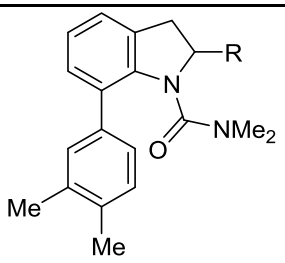
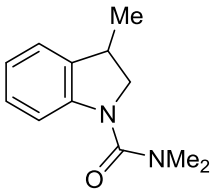
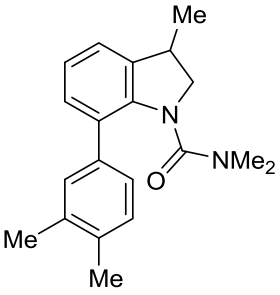
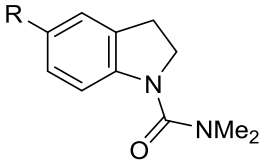
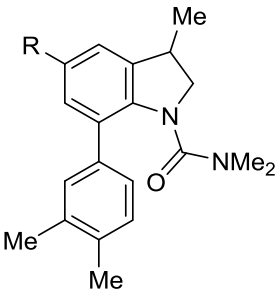
Having ganged the scope of different arenes as coupling partners, several indolines **91**, **183**, **212**–**217**, *cis*-**218**–*cis*-**219** were also subjected to the standard conditions (Table 2.8). Unlike previous results that the functional group at C-2 was essential,[98] the substituent at the C-2 or C-3 position, for example methyl, seemed not to be significant unless a phenyl group was introduced (Table 2.8, entries 1–4). In this case, only 18% yield was formed after prolonged reaction time with most of the starting material remaining unreacted, probably due to steric rather than electronic effects (Table 2.8, entry 3). Furthermore, 2,3,3-trisubstituted indolines underwent the arylation smoothly (Table 2.8, entries 7 and 9).

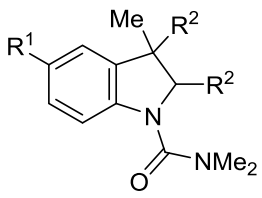
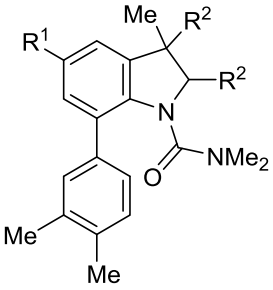
The electronic effect on the aromatic ring affected this transformation dramatically. Indolines bearing electron-donating groups at the C-5 position sometimes reacted well (Table 2.8, entry 10). This phenomenon was however incoherent; for example, there was another unexplained observation where methyl substitution reduced its reactivity significantly (Table 2.8, entry 8). Additionally, a methoxy group substituted substrate **214** exerted an even stronger negative effect (Table 2.8, entry 5). These findings were not consistent with previous data where electron-donating and -withdrawing groups had positive and negative effect on the arylation in opposed ways.[98] On the other hand, however, halogenated indolines gave little conversion under identical conditions (Table 2.8, entry 6).

Table 2.8: Open-flask CDC arylation of various indolines.[a]



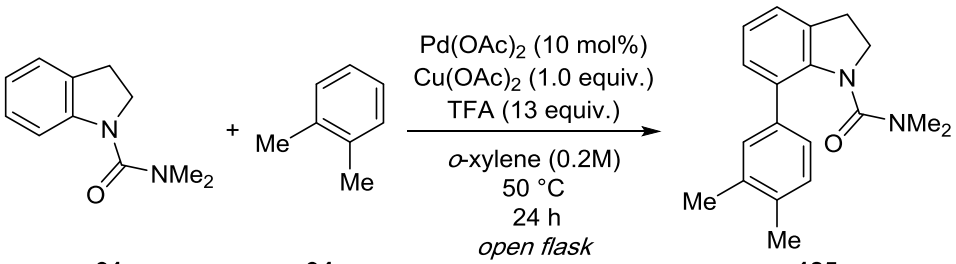
91, **183**, **212**–**217**, *cis*-**218**–*cis*-**219** | **94** | **184**–**185**, **220**–**225**, *cis*-**226**–c*is*-**227**

Entry	Indolines	Time [h]	Product	Conv. [%][b]	Yield [%][c]
					
1	R = H (**91**)	18	R = H (**184**)	100	81
2	R = Me (**183**)	18	R = Me (**185**)	100	90
3	R = Ph (**212**)	48	R = Ph (**220**)	32	18
					
4	**213**	26	**221**	82	67
					
5	R = OMe (**214**)	48	R = OMe (**222**)	56	30
6	R = Br (**215**)	42	R = Br (**223**)	trace	—

					
7	R^1 = H, R^2 = Me (**216**)	24	R^1 = H, R^2 = Me (**224**)	87	71
8	R^1 = R^2 = Me (**217**)	44	R^1 = R^2 = Me (**225**)	64	44
9	R^1 = H, R^2 = $(CH_2)_4$ (*cis*-**218**)	24	R^1 = H, R^2 = $(CH_2)_4$ (*cis*-**226**)	85	75
10	R^1 = Me, R^2 = $(CH_2)_4$ (*cis*-**219**)	17	R^1 = Me, R^2 = $(CH_2)_4$ (*cis*-**227**)	100	85

[a] All reactions were conducted according to **GP 5**. [b] Determined by GLC analysis with tetracosane as internal standard. [c] Isolated yield after purification by flash column chromatography.

It was proven that our easily handed catalytic setup is an alternative protocol for the existing palladium(II)-catalyzed CDC arylation reaction. The next goal was to make it practical for applications in organic synthesis of biaryl compounds. To satisfy this demand, we scaled up our catalysis to gram scale almost without losing much reactivity (conversion 96% versus 100%, isolated yield 72% versus 81%) as shown in Scheme 2.17.



Scheme 2.17: Scale-up experiment.

2.4 CONCLUSION

We accomplished the desired arylation of indolines at the C-7 position with a cross-dehydrogenative C–H/C–H coupling protocol for the first time. Remarkably, the amide group which was employed as a directing group alone is not sufficient to allow for this transformation. In addition, NMR experiments showed that the substituent at C-2 is a crucial

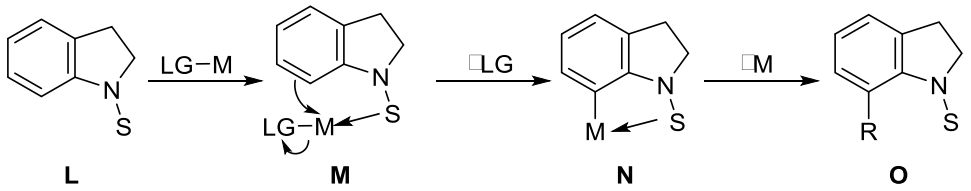
factor for the regioselectivity and reactivity control. The established protocol, however, requires harsh reaction conditions and under which less substituted indolines undergo oxidation to their corresponding indoles.

To our delight, we overcame this limitation shortly afterwards by using a urea directing group instead of an acetyl group that enabled the same transformation under milder conditions in an aerobic atmosphere. This method is operationally simply, thereby substantially extending the scope of the previous protocol that suffered from indoline-to-indole oxidation.

3 OXIDATIVE PALLADIUM(II)-CATALYZED DIRECT ALKENYLATION OF INDOLINES AT THE C-7 POSITION

3.1 ALKENYLATION OF INDOLINES AT THE C-7 POSITION – A BRIEF INTRODUCTION

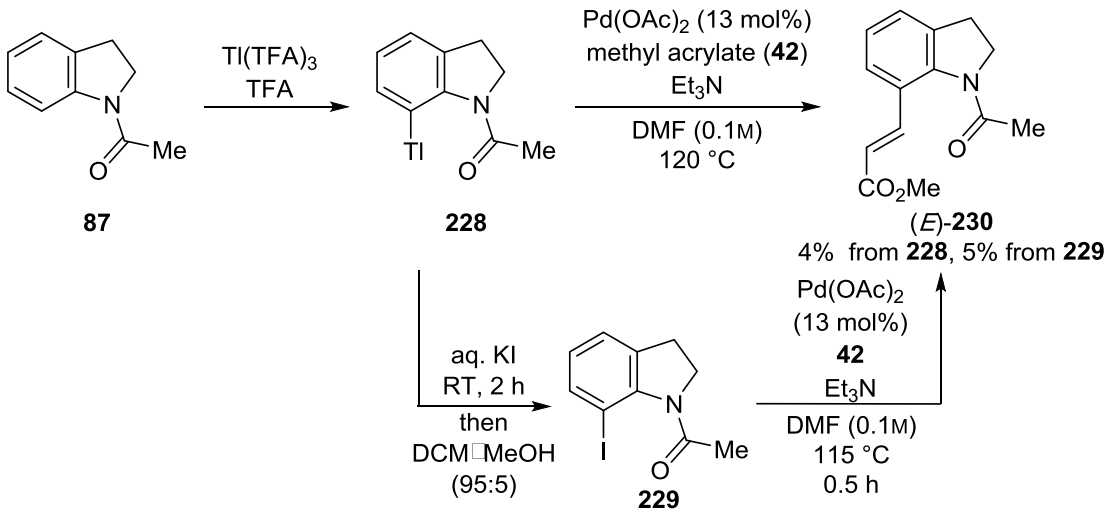
Compared with the aforementioned cross-dehydrogenative arylation of indolines at the C-7 position, the related alkenylation at the same position has been even rare prior to our work.
An early example was disclosed by SOMEI and co-workers in the 1980s.[102] In order to achieve this challenging regioselective transformation, these authors designed an interesting strategy as illustrated in Scheme 3.1. After the introduction of a suitable "ligand" (S) at the nitrogen atom of indoline **L**, it could coordinate to a metal reagent guiding the metal close to the C-7 position to form an intermediate **M**. As a consequence, metalation would occur regioselectively at the desired atom (**M** → **N**), making the carbon susceptible to various functionalizations.



Scheme 3.1: Strategy for the preparation of 7-substituted indolines. (S = ligand; M = metal; LG = leaving group).

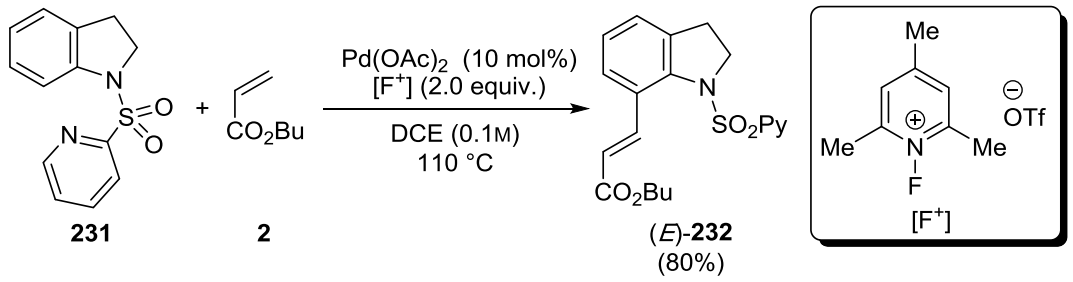
Based on this promising proposal, these authors finally found that the acetyl group could serve as a suitable ligand. By the aid of this directing group, the starting indoline **87** underwent thallation with stoichiometric amount of $Tl(TFA)_3$ in TFA followed by the addition of a catalytic amount of $Pd(OAc)_2$ and an electron-deficient alkene **42** as coupling partner at 120 °C. However, the yield was very low (4%). An alternative pathway involving iodination of the C–Tl bond followed by coupling with an alkene **42**did not give acceptable results either (5%) (Scheme 3.2). Although these results were not as good as expected, this insightful observation set the stage for further development in this area.

[102] a) M. Somei, Y. Saida, T. Funamoto, T. Ohta, *Chem. Pharm. Bull.* **1987**, *35*, 3146–3154; b) M. Somei, T. Kawasaki, *Chem. Pharm. Bull.* **1989**, *37*, 3426–3428.



Scheme 3.2: C-7 alkenylation of acetyl-directed indoline through ligand-directed thallation by SOMEI.

Very recently, the ARRAYÁS/CARRETERO group disclosed an oxidative cross-dehydrogenative alkenylation of carbazoles. In this report, indoline **231** was included as the sole example.[103] And their protocol relied on a 2-pyridyl sulfonyl group linked to the nitrogen atom as a directing group; $Pd(OAc)_2$ (10 mol%) and *N*-fluoro-2,4,6-trimethylpyridinium triflate (2.0 equiv.) were used as catalyst and terminal oxidant, respectively in DCE at 110 °C (Scheme 3.3).



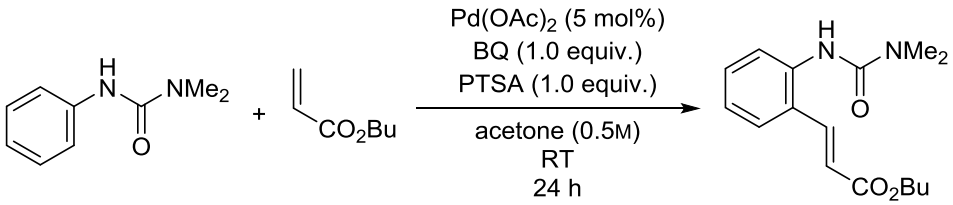
Scheme 3.3: C-7 alkenylation of indoline directed by a 2-pyridylsulfonyl group by CARRETERO.

3.2 ALKENYLATION OF ANILINES DIRECTED BY A UREA GROUP

To date, there have already been several examples reported involving the *ortho* cross-dehydrogenative alkenylation of anilines.[32,35] Among them, the acetyl group was intensively studied as a chelating factor for regioselective control[32], 2-pyridyl sulfonyl[48,103] and urea[35a] were also described.

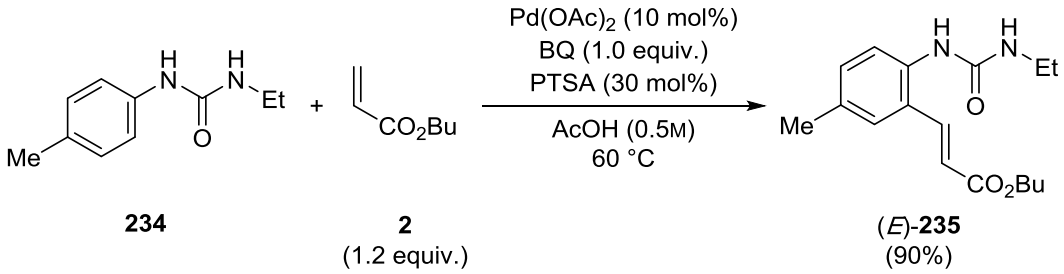
[103] B. Urones, R. G. Arrayás, J. C. Carretero, *Org. Lett.* **2013**, *15*, 1120–1123.

In 2009, BROWN and co-workers developed a palladium-catalyzed oxidative HECK (FUJIWARI–MORITANI) reaction of aniline **176** equipped with a urea directing group (Scheme 3.4).[104] Similar to the palladium(II)-catalyzed arylation described before, this catalysis also proceeded under very mild conditions. It is worthy of mention that these authors compared their results with former reports and concluded that their outcomes were generally better than those using acetanilides as starting materials, indicating that the urea group was superior in this transformation.



Scheme 3.4: Oxidative palladium-catalyzed alkenylation of urea-directed aniline by BROWN.

Two years later, a palladium(II)-catalyzed direct alkenylation of aryl urea derivatives was reported by the YU group (Scheme 3.5).[105] Unlike previously reported urea-based directing groups, there was always a free N–H group at its terminus, and a fully substituted urea was not examined. The reaction was conducted in acetic acid at 60 °C; BQ and *p*-toluenesulfonic acid (PTSA) were introduced as oxidant and additive, respectively. These authors employed *n*-butyl acrylate (**2**) as coupling partner in generally good to excellent yields.



Scheme 3.5: Oxidative palladium-catalyzed alkenylation of arenes by YU.

Inspired by the above outlined achievements and the previous work in our laboratory, we planned to establish a novel protocol for the urea-directed alkenylation of indolines at the C-7 position. To achieve this goal, we therefore envisioned that the promising urea directing group would successfully promote this transformation.

[104] W. Rauf, A. L. Thompson, J. M. Brown, *Chem. Commun.* **2009**, 3874–3876.
[105] L. Wang, S. Liu, Z. Li, Y. Yu, *Org. Lett.* **2011**, *13*, 6137–6139.

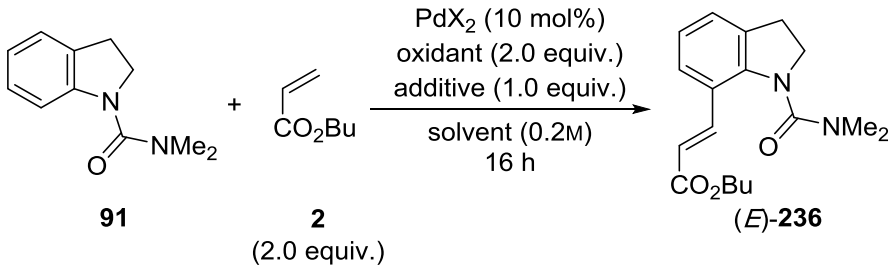
3.3 PRELIMINARY INVESTIGATIONS AND SUBSTRATE SCOPE

To establish the optimal reaction conditions in a systematic fashion, we began with our efforts by the evaluation of different parameters. According to our proposal, we started our study by treatment of urea-directed indoline **91** with $Pd(OAc)_2$ and BQ under acidic conditions (Table 3.1).

In the beginning, to our delight, the desired alkenylated product (*E*)-**236** was formed in good yield (68%) even under exceptionally mild conditions (Table 3.1, entry 1). This result improved slightly at elevated temperature, but the yield started to decrease due to decomposition with further increase of the temperature (Table 3.1, entries 2–3 and 5). The conditions with of alkene **2** (2.0 equiv.) coupling partner and more BQ (2.0 equiv.) seemed to be optimal along with full consumption of the indoline starting material **91** (Table 3.1, entry 6). Either increasing or reducing the amount of alkene led to decreased yields (Table 3.1, entries 4 and 7).

Then, we turned our attention to a systematical screening of further parameters such as catalyst, solvent, additive, as well as oxidant. Other solvents, either polar or nonpolar, were unfavorable to this transformation (Table 3.1, entries 8–11). Likewise, palladium sources rather than $Pd(OAc)_2$ or decreased catalyst loading (10 mol% versus 5.0 mol%) resulted in poor yield or even led to decomposition (Table 3.1, entries 12–15). As an acid additive, TFA exhibited less efficiency; in contrast, bases instead of acids could not provide any conversion at all (Table 3.1, entries 16–18). There are a few common oxidants that might be chosen as useful alternatives such as air or dioxygen or strong oxidants such as $Na_2S_2O_8$ (Table 3.1, entries 19–21). However, silver salts such as Ag_2O and Ag_2CO_3 were reluctant to consume any starting material; the hypervalent iodine reagent $PhI(OAc)_2$ only caused decomposition or high conversion but without any product formation (Table 3.1, entries 22–24).

Table 3.1: Identification of the catalytic system for the oxidative palladium-catalyzed alkenylation of indoline at the C-7 position.[a]



91 **2** (2.0 equiv.) (*E*)-**236**

Entry	PdX_2	Oxidant	Additive	Solvent	Temp. [°C]	Conv. [%][b]	Yield [%][c]

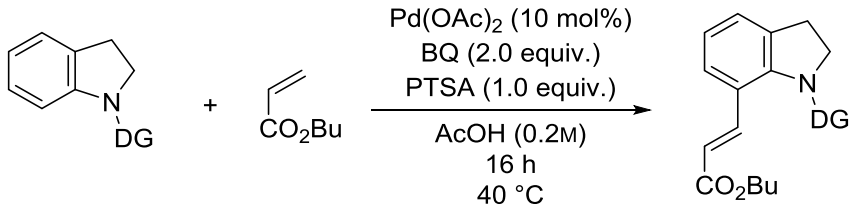
1[d]	$Pd(OAc)_2$	BQ[e]	PTSA	AcOH	RT	72	68
2	$Pd(OAc)_2$	BQ[e]	PTSA	AcOH	40	87	83
3	$Pd(OAc)_2$	BQ[e]	PTSA	AcOH	60	97	57
4[f]	$Pd(OAc)_2$	BQ[e]	PTSA	AcOH	60	89	52
5	$Pd(OAc)_2$	BQ[e]	PTSA	AcOH	80	98	32
6	$Pd(OAc)_2$	BQ	PTSA	AcOH	40	100	89
7[g]	$Pd(OAc)_2$	BQ	PTSA	AcOH	40	92	78
8	$Pd(OAc)_2$	BQ	PTSA	toluene	40	95	36
9	$Pd(OAc)_2$	BQ	PTSA	DMF	40	62	55
10	$Pd(OAc)_2$	BQ	PTSA	NMP	40	43	32
11	$Pd(OAc)_2$	BQ	PTSA	dioxane	40	93	71
12[h]	$Pd(OAc)_2$	BQ	PTSA	AcOH	40	73	63
13	$Pd(TFA)_2$	BQ	PTSA	AcOH	40	94	80
14	$PdCl_2$	BQ	PTSA	AcOH	40	70	49
15	$(MeCN)_2PdCl_2$	BQ	PTSA	AcOH	40	78	52
16	$Pd(OAc)_2$	BQ	TFA	AcOH	40	79	55
17	$Pd(OAc)_2$	BQ	KOAc	AcOH	40	23	—
18	$Pd(OAc)_2$	BQ	KO*t*Bu	AcOH	40	36	—
19	$Pd(OAc)_2$	O_2	PTSA	AcOH	40	90	66
20	$Pd(OAc)_2$	$Na_2S_2O_8$	PTSA	AcOH	40	92	63
21	$Pd(OAc)_2$	$Cu(OAc)_2$	PTSA	AcOH	40	32	25
22	$Pd(OAc)_2$	Ag_2O	PTSA	AcOH	40	—	—
23	$Pd(OAc)_2$	Ag_2CO_3	PTSA	AcOH	40	—	—
24	$Pd(OAc)_2$	$PhI(OAc)_2$	PTSA	AcOH	40	95	—

[a] All reactions were conducted according to **GP 7**. [b] Determined by GLC analysis with tetracosane as internal standard. [c] Isolated yield after purification by flash column chromatography on silica gel. [d] Determined after 17 h. [e] 1.0 Equiv. was used. [f] 3.5 Equiv. of alkene were used. [g] 1.2 Equiv. of alkene were used. [h] With decreased catalyst loading (5.0 mol%).

Several readily accessible directing groups were evaluated afterwards as outlined in Table 3.2. Replacing the methyl groups of the urea group by ethyl groups **237** showed hardly any difference (Table 3.2, entry 1). However, the intensively studied and highly reactive acetyl-directed indoline **87** only resulted in moderate conversion and low yield under the same reaction setup (Table 3.2, entry 2). Directing groups such as Boc **78** and methyl sulfonyl **197**

gave rise to decomposition and no conversion, respectively (Table 3.2, entries 3–4). To our surprise, P(O)*t*Bu$_2$-directed indoline **196** underwent the desired alkenylation product (*E*)-**242** smoothly in moderate yield (Table 3.2, entry 5).[106]

Table 3.2: Variations of indoline directing group for the oxidative palladium(II)-catalyzed alkenylation of indoline at the C-7 position.[a]



78, **87**, **196**–**197**, **237** **2** (2.0 equiv.) (*E*)-**238**–**242**

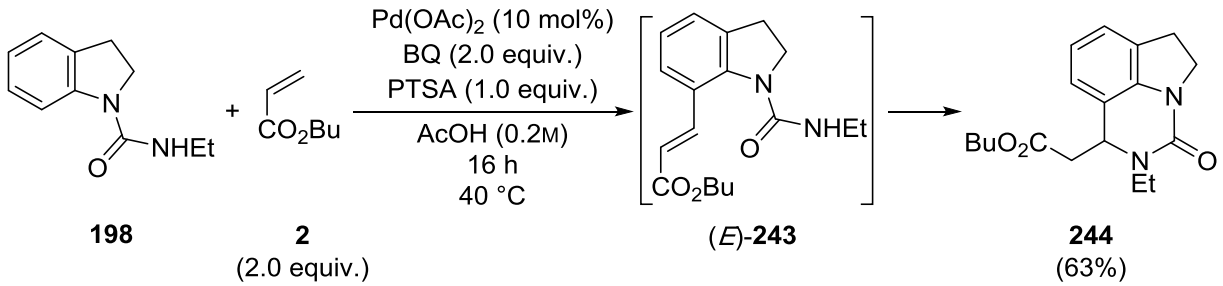
Entry	Indoline	DG[b]	Product	Conv. [%][c]	Yield [%][d]
1	**237**	–C(O)NEt$_2$	(*E*)-**238**	99	85
2	**87**	–C(O)Me	(*E*)-**239**	40	20
3	**78**	–C(O)O*t*Bu	(*E*)-**240**	99	—[e]
4	**197**	–S(O)$_2$Me	(*E*)-**241**	—	—
5	**196**	–P(O)*t*Bu$_2$	(*E*)-**242**	67	47

[a] All reactions were conducted according to **GP 7**. [b] DG = directing groups. [c] Determined by GLC analysis with tetracosane as internal standard. [d] Isolated yield after purification by flash column chromatography on silica gel. [e] Decomposition.

Interestingly, the reported reactive urea with a free N–H group at the terminus **198** also converted under our reaction conditions, but instead of the desired alkenylated product (*E*)-**243**, a six-membered cyclized compound **244** was isolated (Scheme 3.6). It can be assumed that the starting material underwent a domino procedure involving an intermolecular C–H bond alkenylation followed by an intramolecular conjugate C–N bond formation through 1,4-addition fashion. This observation was in accordance with a few former reports[107] but was not detected in the YU group during their alkenylation of urea-directed anilines.[105] The constitution was assigned by nOe interaction measurements.

[106] L.-Y. Jiao, A. V. Ferreira, M. Oestreich, unpublished results, Technische Universität Berlin, **2015**.

[107] a) M. Miura, T. Tsuda, T. Satoh, S. Pivsa-Art, M. Nomura, *J. Org. Chem.* **1998**, *63*, 5211–5215; b) B. S. Kim, S. Y. Lee, S. W. Youn, *Chem. Asian J.* **2011**, *6*, 1952–1957.

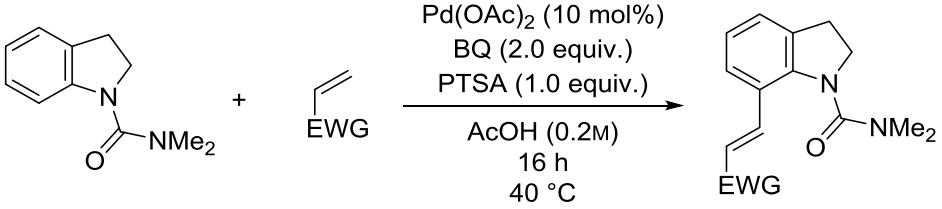


198 **2** (2.0 equiv.) (*E*)-**243** **244** (63%)

Scheme 3.6 Free N–H group at the urea terminus: domino intermolecular C–H bobd alkenylation followed by intramolecular conjugate C–N bond formation.

With this mild and high-yielding protocol in hand, we then investigated different α,β-unsaturated acceptors (Table 3.3). It is obvious that acrylates **2**, **5**, **42**, and **245** are ideal coupling partners with generally high reactivity, providing equally well results (Table 3.3, entries 1–4). Both phosphonate **246** and methyl vinyl ketone (**247**) resulted in high conversions with decent yields. Conversely, acetonitrile (**248**) generated less amount of product (*E*)-**255** although with almost full consumption of the starting material (Table 3.3, entries 5–7). Relatively, phenyl vinyl sulfone (**249**) reacted less efficiently (Table 3.3, entry 8).

Table 3.3: Variation of the alkene: α,β-unsaturated acceptors.[a]

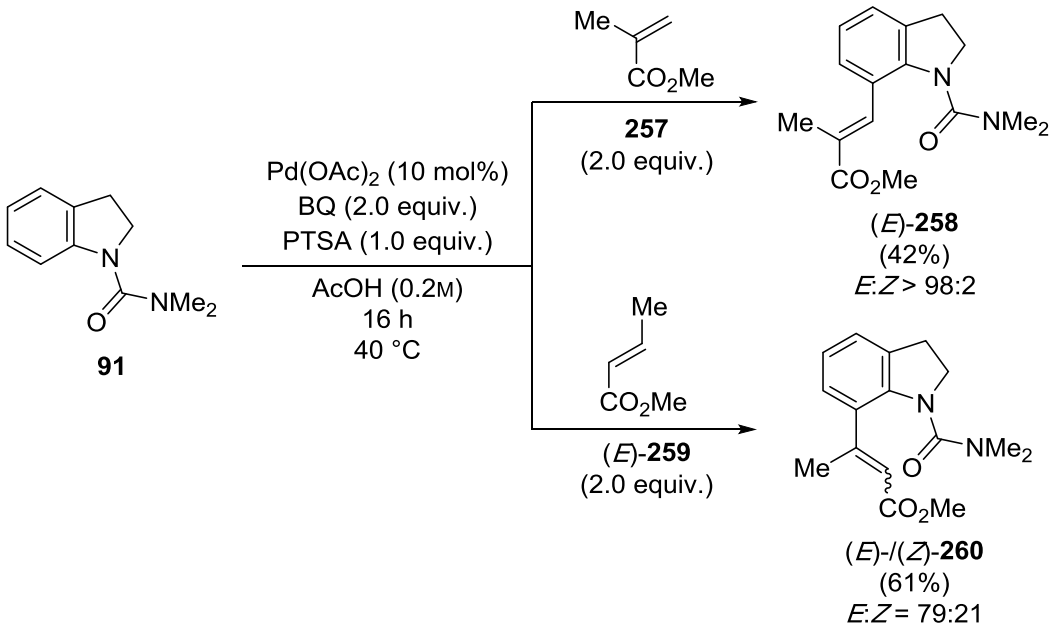


91 **2**, **5**, **42**, **245**–**249** (2.0 equiv.) (*E*)-**236**, (*E*)-**250**–**256**

Entry	Alkene	EWG[b]	Product	Conv. [%][c]	Yield [%][d]
1	**2**	CO_2Bu	(*E*)-**236**	100	89
2	**5**	CO_2Et	(*E*)-**250**	97	82
3	**42**	CO_2Me	(*E*)-**251**	97	80
4	**245**	CO_2Bn	(*E*)-**252**	99	87
5	**246**	$P(O)(OEt)_2$	(*E*)-**253**	100	86
6	**247**	C(O)Me	(*E*)-**254**	92	60
7	**248**	CN	(*E*)-**255**	99	21
8	**249**	$S(O)_2Ph$	(*E*)-**256**	37	—

[a] All reactions were conducted according to **GP 7**. [b] EWG = electron-withdrawing group. [c] Determined by GLC analysis with tetracosane as internal standard. [d] Isolated yield after purification by flash column chromatography on silica gel.

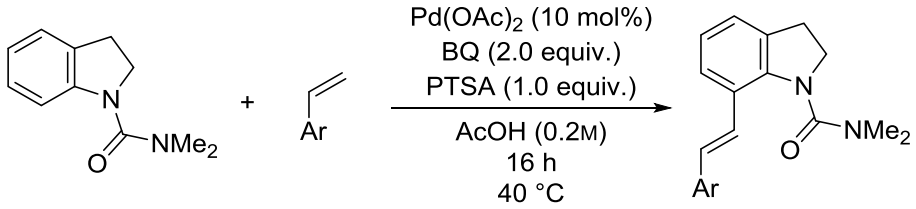
Different from unsubstituted alkenes, α,β-unsaturated acceptors bearing a methyl group at both α and β position displayed reduced reactivity (Scheme 3.7). Methyl methacrylate (**257**) cross-coupled with excellent diastereoselectivity (*E*:*Z* > 98:2) in moderate yield (Scheme 3.7, upper). However, methyl crotonate [(*E*)-**259**] generated a little more product (*E*)-/(*Z*)-**260**, albeit with poor regiocontrol (*E*:*Z* = 79:21) in favor of the *trans* product (Scheme 3.7, lower).



Scheme 3.7: Oxidative palladium(II)-catalyzed C-7-selective C–H bond alkenylation with substituted α,β-unsaturated acceptors.

Apart from α,β-unsaturated acceptors, styrenes have proven to be very good coupling partners in direct C–H bond alkenylations. Therefore, we employed a whole range of styrenes **8**, and **261**–**266** in our catalytic setup as shown in Table 3.4. Encouragingly, these were compatible with our alkenylation reaction, thereby greatly extending the substrate scope of this approach. According to our observations, both electronic and steric effects played an important role in this transformation. For example, styrenes bearing electron-withdrawing groups **8**, and **261**–**264** generally reacted well in moderate to good yields (Table 3.4, entries 1–5). However, styrene with an *ortho* bromo substituent **265** was reluctant to react, probably due to steric hindrance (Table 3.4, entry 6). In contrast, electron-rich styrene **266** failed to provide any product (*E*)-**273** (Table 3.4, entry 7).

Table 3.4: Variation of the alkene: styrene derivatives.[a]



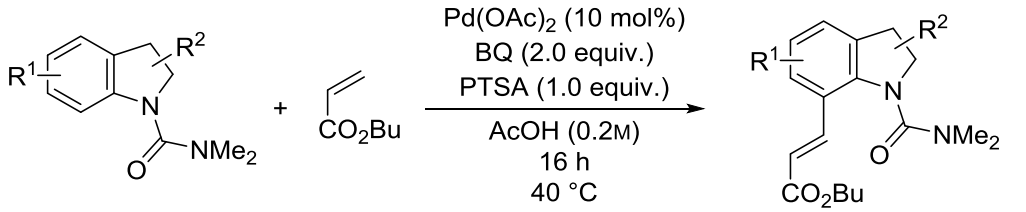
91 **8**, **261**–**266** (2.0 equiv.) (*E*)-**267**–(*E*)-**273**

Entry	Styrene	Ar	Product	Conv. [%][b]	Yield [%][c]
1	**8**	Ph	(*E*)-**267**	82	73
2	**261**	C_6F_5	(*E*)-**268**	100	88
3	**262**	4-F-C_6H_4	(*E*)-**269**	82	63
4	**263**	4-Cl-C_6H_4	(*E*)-**270**	96	82
5	**264**	2-Cl-C_6H_4	(*E*)-**271**	100	85
6	**265**	2-Br-C_6H_4	(*E*)-**272**	63	40
7	**266**	4-OMe-C_6H_4	(*E*)-**273**	13	—

[a] All reactions were conducted according to **GP 7**. [b] Determined by GLC analysis with tetracosane as internal standard. [c] Isolated yield after purification by flash column chromatography on silica gel.

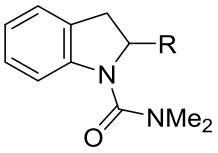
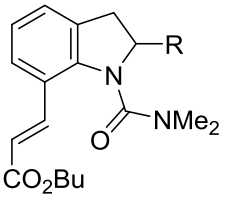
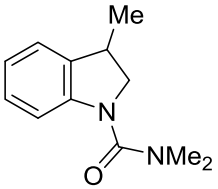
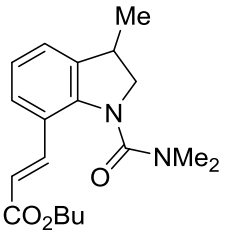
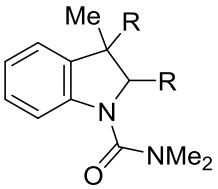
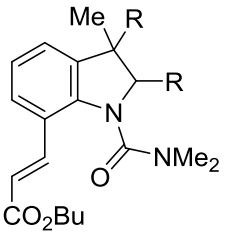
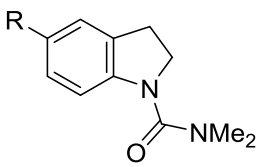
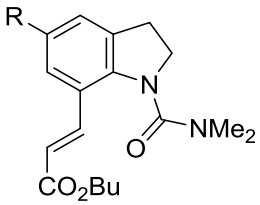
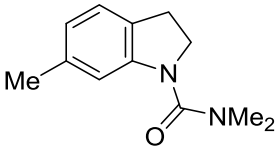
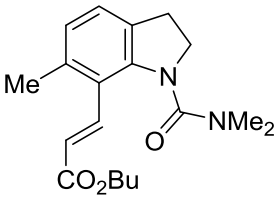
Finally, we went on to evaluate the effect of the substitution pattern at the indoline motif by attaching different substituents at the C-2, C-3, C-5 as well as C-6 positions (Table 3.5). Most of the investigated derivatives performed quite well with full conversions and excellent yields (Table 3.5, entries 1–7). Additionally, the electronic effect seemed to be insignificant as both electron-rich and -deficient indolines reacted equally well (Table 3.5, entries 6–9). The introduction of a methyl group at the C-6 position of indoline was detrimental, maybe due to steric hindrance, and only moderate yield was obtained in this case (Table 3.5, entry 10). Nevertheless, this example showcased the broad applicability of this protocol.

Table 3.5: Variation of the indoline substituents at the C-2, C-3, C-5, and C-6 positions.[a]



91, **183**, **207**, et. al. **2** (2.0 equiv.) (*E*)-**236**, (*E*)-**278**–(*E*)-**286**

Entry	Indoline	Product	Conv. [%][b]	Yield [%][c]

				
1	R = H (**91**)	R = H [(*E*)-**236**]	100	89
2	R = Me (**183**)	R = Me [(*E*)-**278**]	100	82
				
3	**207**	(*E*)-**279**	100	97
				
4	R = Me (**210**)	R = Me [(*E*)-**280**]	100	86
5	R = $(CH_2)_4$ (*cis*-**212**)	R = $(CH_2)_4$ [*cis*-(*E*)-**281**]	100	86
				
6	R = Me (**274**)	R = Me [(*E*)-**282**]	100	88
7	R = OMe (**208**)	R = OMe [(*E*)-**283**]	100	93
8	R = F (**275**)	R = F [(*E*)-**284**]	97	84
9	R = Cl (**276**)	R = Cl [(*E*)-**285**]	99	89
				
10	**277**	(*E*)-**286**	82	46

[a] All reactions were conducted according to **GP 7**. [b] Determined by GLC analysis with tetracosane as internal standard. [c] Isolated yield after purification by flash column chromatography on silica gel.

3.4 CONCLUSION

By employing a urea as directing group attached to the nitrogen atom of the indoline skeleton, we accomplished a broadly applicable, mild, direct C–H bond alkenylation at the C-7 position. The catalytic system was efficient, and both α,β-unsaturated acceptors and styrenes reacted equally well. In addition, substitution at various positions of the indolines was tolerated in moderate to excellent yields. Notably, with a free N–H group at the urea terminus, the nitrogen atom subsequently cyclized in a 1,4-addition fashion to yield a six-membered ring.

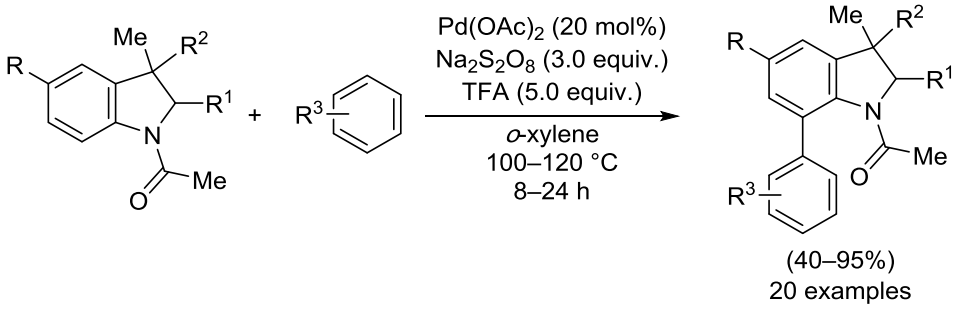
4 SUMMARY

In summary, we have accomplished catalytic protocols to enable oxidative palladium(II)-catalyzed C–H bond functionalization of indolines at the C-7 position with different arenes and alkenes.

For the palladium(II)-catalyzed cross-dehydrogenative arylation reactions, our initial approach was to use conditions similar to those formerly reported by SHI and co-workers.[84] We found that reactions between unsubstituted indoline **87** with an acetyl group at the nitrogen atom serving as a directing group and simple arenes did, however, not give any product in the presence of common oxidants such as BQ, silver salts, or copper salts. Trace amounts of the desired product was observed when the strong oxidant $Na_2S_2O_8$ was employed, accompanied by oxidation of the indoline to its corresponding indole **68**. Then, we turned our attention to substituted indolines to prevent this side reaction.

A series of di- and trisubstituted indolins *trans*-**97**–*trans*-**100**, **101–104**, and *cis*-**105–***cis*-**108** were prepared readily through (interrupted) FISCHER indole synthesis. For the annulated indolines *cis*-**127**, the relative configuration was determined by nOe measurements that was retained throughout the sequence.

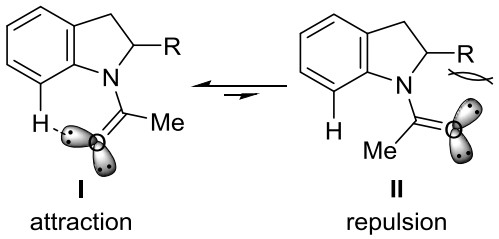
With these indoline substrates, we accomplished this challenging C–C bond formation under oxidative palladium catalysis. From screening of reaction conditions, $Na_2S_2O_8$ was chosen as the optimal terminal oxidant, and the combination of $Pd(OAc)_2$ as catalyst with TFA as additive favored the formation of the C-7 arylation product. Several di- and trisubstituted indolines were subjected to the optimized conditions in moderate to excellent yields (Scheme 4.1).



Scheme 4.1: Palladium(II)-catalyzed cross-dehydrogenative arylation of indolines at the C-7 position mediated by $Na_2S_2O_8$ as terminal oxidant.

Interestingly, we observed that monosubstituted indolines showed different reactivity. 2-Methylindoline **95** could undergo slow arylation albeit indoline-to-indole oxidation still occurred. However, indoline substrate **96** with a methyl at C-3 position did not give any

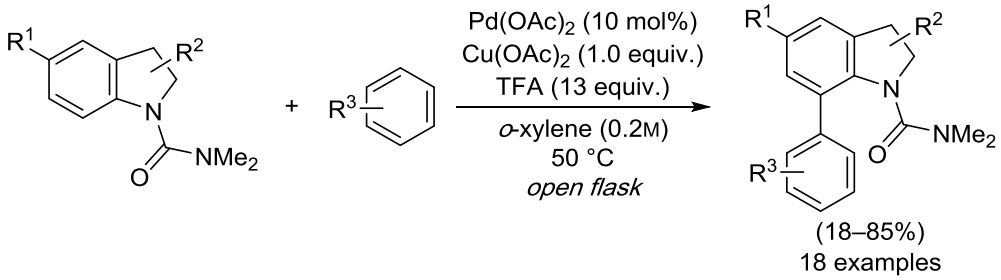
product. This unusual phenomenon brought us to do further study. We found that the amide group alone is not sufficient to allow for this transformation. In addition, NMR experiments showed that the substituent at C-2 position is a crucial factor for regioselectivity and reactivity. Accordingly, we proposed an attraction and repulsion equilibrium as shown below (Scheme 4.2). The repulsion existing in **II** between the electron lone pairs of the amide oxygen atom and the C-2 substituent pushes the amide isomer toward rotamer **I** in which the same oxygen atom approaches the C–H bond at the C-7 position of the indoline to engage in hydrogen bonding. Our hypothesis was supported by full assignment of rotamers **I** and **II** through chemical exchange in 2D EXSY and 2D NOESY NMR measurements.



Scheme 4.2: Amide rotamers equilibrium controlled by repulsion (right) and attraction (left) with **I** and **II** assigned by 2D EXSY and 2D NOESY measurements.

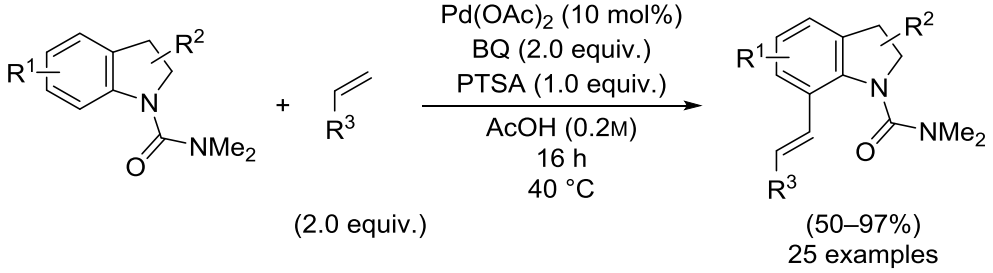
The established catalytic system, however, requires high temperatures (100–120 °C) and a strong oxidant, under which less substituted indolines would undergo oxidation to their corresponding indoles.

We overcame this limitation shortly afterwards by using a urea directing group instead of an acetyl group that enabled the same transformation under milder conditions (50 °C) (Scheme 4.3). As a result, the use of either $Cu(OAc)_2$ in an open flask or dioxygen (balloon) tolerates simple indolines without substitution at the C-2 or C-3 position, thereby substantially extending the substrate scope to more general motifs. This methodology was then successfully scaled up (1.0 g) with slightly diminished conversion and yield. It is worth noting that other common directing groups, even a urea with a free N–H group at the terminus, failed to facilitate the C−H bond activation.



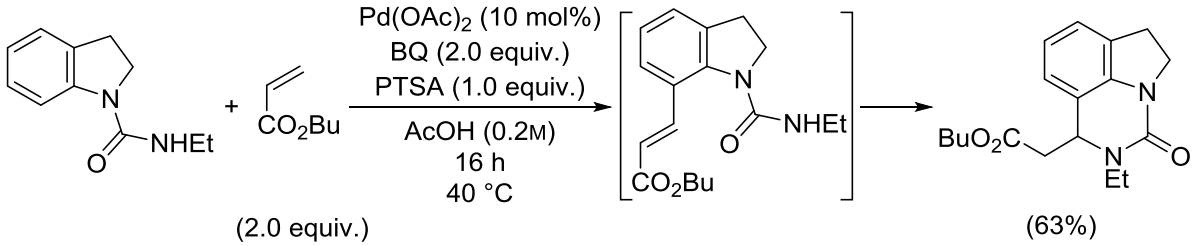
Scheme 4.3: Palladium(II)-catalyzed cross-dehydrogenative arylation of indolines at the C-7 position mediated by $Cu(OAc)_2$ or dioxygen as terminal oxidant.

By employing the same urea directing group attached to the indoline skeleton, a protocol for the direct alkenylation of indolines at the C-7 position is described (Scheme 4.4). This catalytic system proved to be broadly applicable, mild, and efficient. Both α,β-unsaturated acceptors and styrenes participate in this direct C–H functionalization. Even substituted α,β-unsaturated acceptors reacted, regioselectivities were good to excellent albeit yields were somewhat lower.



Scheme 4.4: Palladium(II)-catalyzed oxidative alkenylation of indolines at the C-7 position.

Notably, with a free N–H group at the urea terminus, the nitrogen atom subsequently cyclizes in a 1,4-fashion to yield a six-membered heterocycle (Scheme 4.5).



Scheme 4.5: Free N–H group at the urea terminus: domino intermolecular C–H bond alkenylation followed by intramolecular conjugate C–N bond formation.

Overall, the present work was devoted to the development of new protocols for the oxidative palladium(II)-catalyzed direct arylation and alkenylation through a cross-dehydrogenative way. Although the early results of direct arylation reaction exhibited limitations, we overcame these drawbacks by replacing the directing group, making the methodology more general and simple. The use of environmental friendly molecular oxygen as terminal oxidant possesses several advantages in accordance with the principles of Green Chemistry. As for the palladium(II)-catalyzed alkenylation of indolines, the established catalytic system provided an alternative protocol for the existing choices.

EXPERIMENTAL PART

1 GENERAL INFORMATION

All Reactions except otherwise specified ones were performed under argon or nitrogen atmosphere in previously flame-dried glassware under oil-pump vacuum. For general cleaning, all laboratory glassware was kept overnight in an *i*-PrOH/KOH bath, rinsed with distilled water and dried at 120 °C. At completion of reactions, the used glassware contaminated with transition metals was initially rinsed with aqua regia (conc. HCl and conc. HNO_3 in a ratio of 3:1) prior to further cleaning. For the addition of reagents and solvents through silicon/rubber septa, argon- or nitrogen-flushed disposable syringes and needles were used. All glass syringes and stainless steel needles were used several times and stored at 120 °C after each use. Solids were added in a countercurrent of inert atmosphere or in solution. Low-temperature reactions were either cooled by an EtOH/dry ice bath or by using a cryostat “EK90” from *Haake* or “T 100 -F” from *Huber*.

Solvents

Dichloromethane (CH_2Cl_2), diethyl ether (Et_2O), 1,2-dichloroethane ($ClCH_2CH_2Cl$, DCE), methanol (MeOH), and triethylamine (Et_3N) were heated at reflux over CaH_2 and distilled under argon or nitrogen atmosphere.
Tetrahydrofuran (THF) was distilled from potassium hydroxide, then heated at reflux over potassium with benzophenone as indicator and distilled under argon or nitrogen atmosphere.
Toluene was heated at reflux over sodium with benzophenone as indicator and distilled under argon or nitrogen atmosphere.
Technical grade ethanol (EtOH) and acetone were used without further purification.
N,N-Dimethylformamide (DMF) was distilled and stored over 4Å molecular sieves under argon or nitrogen atmosphere.
For extraction and flash chromatography, technical grade solvents (*tert*-butylmethylether, cyclohexane, *n*-pentane, dichloromethane, diethylether and ethyl acetate) were distilled prior to use.

Physical Data

Melting points (m.p.) were determined using a melting point determination apparatus from *Thompson Scientific* and *Stuart*. The values are not corrected.

Chromatography

Qualitative **thin layer chromatography** (TLC) was performed on glass plates with silica gel 60 F_{254} from *Merck KGaA*.
The following methods were used for the indication of the analyte:

- Exposure of the TLC plate to UV light (λ = 254 nm), UV absorption by the analyte.
- Dipping the TLC plate into a solution of $(NH_4)_3[P(Mo_3O_{10})_4]$ (100 g), $Ce(SO_4)_2$ (4.00 g) and conc. H_2SO_4 (100 mL) in distilled H_2O (900 mL) and then heating with a heat gun.
- Dipping the TLC plate into a solution of $KMnO_4$ (3.0 g), K_2CO_3 (20 g) and KOH (0.30 g) in distilled H_2O (300 mL) and then heating with a heat gun.

Flash chromatography was performed with the silica gel from *Merck-Schuchardt* of the grain size 40–63 µm, 230–400 mesh, ASTM. The required amounts of silica gel, the column diameter and the fraction size was based on the parameters elaborated by STILL.[108]

Analytical **gas-liquid chromatography** (GLC) of reaction mixtures and pure substances were carried out using a gas chromatograph of the type GC-2010 from *Shimadzu* [The device was equipped with a fused silica capillary column of the type SE-54 from *CS-Chromatography Service* (Length: 30 m; inner diameter: 0.32 mm; film thickness of the covalently bonded stationary phase: 0.25 µm)] or type 7890A from *Agilent Technologies* [The device was equipped with a fused silica capillary column of the type HP-5 capillary column (Length: 30 m; inner diameter: 0.32 mm; film thickness of the covalently bonded stationary phase: 0.25 µm)].
All GLC analyses were performed using the following program:

- Carrier gas N_2; injector temperature 250 °C; detector temperature 300 °C; flow rate 1.7 mL/min; temperature program: starting temperature 40 °C, 10 °C/min heating rate, final temperature 280 °C for 10 min.

NMR Spectroscopy

^1H, ^{13}C, ^{19}F, and ^{31}P NMR spectra were recorded in $CDCl_3$ (*Eurisotop*) or in DMSO-d_6 (*Eurisotop*) on AV 400, AV 500, and AV 700 instruments from *Bruker*. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (TMS) and referenced to the residual solvent resonance as the internal standard ($CHCl_3$: δ = 7.26 ppm, $CDCl_3$: δ =

[108] W. C. Still, M. Kahn, A. Mitra, *J. Org. Chem.* **1978**, *43*, 2923–2925.

77.16 ppm; DMSO-d_5: δ = 2.50 ppm, DMSO-d_6: δ = 39.52 ppm). The ^{19}F NMR resonance signals were internally calibrated using the standardized scale for chemical shifts (*unified chemical shift scale*) which is in accordance with the IUPAC recommendation of 2001.[109] Data are reported as follows: chemical shift, multiplicity (br s = broad singlet, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet). The coupling constant "*J*" is mentioned in Hertz (Hz). The assignment of signals refers to the numbering of the structures in the figures and is in accordance with careful interpretations made from 2D NMR spectroscopy: GCOSY [^{1}H,^{1}H-correlation], GHSQC [^1J(^{13}C,^{1}H-correlation)], GHMBC [$^{2,3}J$(^{13}C,^{1}H-correlation)], and 1D NOE measurements. The assignment of ^{13}C NMR signals was secured with the aid of DEPT 90 and DEPT 135 NMR spectral analyses. In the case where the individual assignment of the signal was not possible, corresponding atoms were marked with "*" or "**" and are interchangable. The subscript "Ar" refers to unspecified protons or carbon atoms of an aromatic system. The term "$_{quart}$" in the evaluation of the ^{13}C NMR spectra stands for unspecified "quaternary" carbon atom. The analysis of AB-signals was determined by the formula shown below, where $\delta_{A,B}$ is the chemical shift of signal A or B and the median point ν_s, to which the resonance frequencies as ν_1, ν_2, ν_3, and ν_4 are assigned with ν_r being the frequency of the spectrometer (in MHz).

$$\delta_{A,B} = \frac{\nu_s \pm \frac{1}{2}\sqrt{(\nu_3 - \nu_2)\cdot(\nu_4 - \nu_1)}}{\nu_r}$$

All signals calculated according to this formula are signed with "◊" or "◊◊". These are diastereotopic protons with "A" and "B", where "A" is the highfield-shifted proton and "B" is the downfield-shifted proton. Olefinic protons of terminal double bonds or similar substituents on double bonds are marked "*E*" and "*Z*"; the name is chosen with the higher priority according to their orientation to the substituent. The NMR spectra were processed and evaluated using "TopSpin 3.1" from *Bruker*. The numbering of the atoms is not in accordance with IUPAC recommendations. Symmetric parts of a molecule were numbered only on one side.

Mass Spectrometry

High resolution mass spectrometry (HRMS) were performed by the analytical facilities at the *Institut für Chemie, Technische Universität Berlin*. Equipment (ionization in parentheses)

[109] R. K. Harris, E. D. Becker, S. M. Cabral de Menezes, R. Goodfellow, P. Granger, *Pure Appl. Chem.* **2001**, *73*, 1795–1818.

used for the analyses are as follows: LTQ Orbitrap XL [atmospheric-pressure chemical ionization (APCI)] from *Thermo Scientific*. The in-detail fragmentation has been omitted and only the molecular ion peak or characteristic molecular fragments are considered.

IR Spectroscopy

Infrared (IR) spectra were recorded on a *Varian* 3100 FT-IR spectrophotometer or Cary 630 FT-IR from *Agilent Technologies* equipped with an ATR unit and are reported (br = broad, vw = very weak, w = weak, m = medium, s = strong) in wavenumbers (cm^{-1}).

X-Ray Crystal Structural Analysis

Data sets for X-ray crystal structure analyses were collected by DR. ELISABETH IRRAN and PAULA NIXDORF on a *Nonius KappaCCD* circle diffractometer equipped with Cu-K_α-radiation (λ = 154.178 pm) graphite monochromator in the analytical facility at the *Institut für Chemie, Technische Universität Berlin*. Thermal ellipsoids are shown at the 50% probability level; *R*-values are given for the observed reflections, wR^2-values are given for all reflections

Reagents

AcOH	Supp. *Aldrich*
Acetonitrile	Supp. *Fischer*
$(Ac)_2O$	Supp. *Aldrich*
AgOAc	Supp. *ABCR*
Ag_2CO_3	Supp. *In-house Stock*
Ag_2O	Supp. *Aldrich*
Benzene	Supp. *Aldrich*
1,3-Benzodioxole	Supp. *TCI*
1,4-Benzoquinone (BQ)	Supp. *Aldrich*
Benzylacrylate	Supp. *ABCR*
Biphenyl	Supp. *Acros*
2-Bromostyrene	Supp. *ABCR*
n-BuLi (1.6M in hexane)	Supp. *Aldrich*
2-Butanone	Supp. *Aldrich*
n-Butyl acrylate	Supp. *Aldrich*
2-**C**hlorostyrene	Supp. *ABCR*
4-Chlorostyrene	Supp. *Alfa Aesar*
$Cu(OAc)_2$	Supp. *ABCR*
$Cu(OTf)_2$	Supp. *Alfa Aesar*
(**D**iacetoxyiodo)benzene	Supp. *Fluka*
1,2-Dichlorobenzene	Supp. *Merck*
1,2-Diethylbenzene	Supp. *ABCR*
Diethylcarbamoyl chloride	Supp. *TCI*
Diethyl vinylphosphonate	Supp. *ABCR*
1,2-Dimethoxybenzene	Supp. *Aldrich*
Dimethylcarbamyl chloride	Supp. *Alfa Aesar*
2,3-Dimethylindole	Supp. *TCI*
N,*N*-Dimethyl-*o*-toluidine	Supp. *Acros*
1,4-Dioxane	Supp. *Aldrich*
Di-*tert*-butylpyrocarbonat	Supp. *ABCR*
DMF	Supp. *Acros*

Ethyl acrylate	Supp. *Aldrich*
Ethyl isocyanate	Supp. *Aldrich*
Ethyl phenyl ether	Supp. *Aldrich*
Et_3N	Supp. *Acros*
Fluorobenzene	Supp. *Aldrich*
4-Fluorophenylhydrazine hydrochloride	Supp. *Aldrich*
4-Fluorostyrene	Supp. *TCI*
Indole	Supp. *Aldrich*
Indoline	Supp. *Acros*
Mesitylene	Supp. *Aldrich*
Mesyl chloride	Supp. *Acros*
4-Methoxyphenylhydrazine hydrochloride	Supp. *ABCR*
4-Methoxystyrene	Supp. *TCI*
Methyl acrylate	Supp. *ABCR*
3-Methyl-2-butanone	Supp. *Aldrich*
Methyl crotonate	Supp. *Fluka*
2-Methylcyclohexanone	Supp. *Fluka*
3-Methylindole	Supp. *Alfa Aesar*
5-Methylindole	Supp. *Aldrich*
6-Methylindole	Supp. *Alfa Aesar*
2-Methylindoline	Supp. *Acros*
Methyl methacrylate	Supp. *ABCR*
Methyl phenyl ether	Supp. *Fluka*
4-Methylphenylhydrazine hydrochloride	Supp. *TCI*
N-Methyl-2-pyrrolidone	Supp. *ABCR*
Methyl vinyl ketone	Supp. *Fluka*
NaBH_3CN	Supp. *Aldrich*
$NaBH_4$	Supp. *Aldrich*
$Na_2S_2O_8$	Supp. *Aldrich*
PdCl_2	Supp. *Merck*
$Pd(MeCN)_2Cl_2$	Supp. *Aldrich*
$Pd(OAc)_2$	Supp. *Aldrich*

$Pd(TFA)_2$	Supp. *ABCR*
Pentafluorostyrene	Supp. *ABCR*
Phenylhydrazine	Supp. *ABCR*
2-Phenylindole	Supp. *Aldrich*
Phenyl vinyl sulfoxide	Supp. *Aldrich*
$PhI(OAc)_2$	Supp. *Fluka*
PivOH	Supp. *Aldrich*
Potassium acetate	Supp. *ABCR*
Potassium *t*-butoxide	Supp. *In-house Stock*
Propionic acid	Supp. *Merck*
Pyridine	Supp. *Alfa Aesar*
Styrene	Supp. *Aldrich*
TBAB	Supp. *ABCR*
1,2,3,4-Tetrahydronaphthalene	Supp. *TCI*
Toluene	Supp. *Aldrich*
p-Toluenesulfonic acid monohydrate	Supp. *Alfa Aesar*
Trifluoroacetic acid	Supp. *Merck*
m-**X**ylene	Supp. *Aldrich*
o-Xylene	Supp. *Merck*
p-Xylene	Supp. *ABCR*

Nomenclature

The numbering of compounds was done analogous to their representative structural drawing and does not correspond to the IUPAC recommendations.

2 GENERAL PROCEDURES

The individual substrate and solvent amounts are found in the procedure of the corresponding reaction. In a few cases, general procedures were slightly modified. The molarity (M) of solvents was calculated based on the substrate amount.

2.1 OXIDATIVE PALLADIUM(II)-CATALYZED CROSS-DEHYDROGENATIVE ARYLATION OF INDOLINE AT THE C-7 POSITION

2.1.1 Preparation of 2,3,3-Trisubstituted Indoline Substrates with an Acetyl Directing Group (GP 1)

Step 1: Under inert atmosphere, phenylhydrazine or a substituted phenylhydrazine hydrochloride (1.0 equiv.) is added to a solution of the indicated ketone (3-methylbutan-2-one or 2-methylcyclohexanone, 3.0 equiv.) in acetic acid (0.25–0.50M) and stirred at 120 °C for 14 h.[110] After cooling to ambient temperature, ethyl acetate and H_2O are added, and the phases are separated. The organic phase is washed with brine (2 ×) and saturated aqueous $NaHCO_3$ (1 ×) and is then dried over anhydrous Na_2SO_4. The solvent is removed under reduced pressure, affording the corresponding indolenine.

Step 2: The resulting indolenine is then dissolved in MeOH and H_2O (*v*/*v* = 4:1, 0.2M), and sodium borohydride (2.0 equiv.) is added in portions at 0 °C. After warming to ambient temperature, the mixture is stirred and monitored by TLC (2–3 h).[111] The solvents are removed, and the aqueous phase is extracted with Et_2O (3 ×). The combined organic phases are washed with brine (2 ×), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel with cyclohexane and ethyl acetate solvent mixtures as eluents affords the desired indoline product.

Step 3: The indoline is dissolved in acetic anhydride (5.0–15.0 equiv.) at room temperature, followed by the addition of pyridine (0.60 equiv.). The reaction mixture is heated with an oil bath to 120 °C and maintained at this temperature for 4 h. After quenching by addition of NaOH (2M), the resulting mixture is diluted with ethyl acetate, and the phases are separated. The organic phase is washed with saturated aqueous $NaHCO_3$ (1 ×), dried over anhydrous

[110] L. Yuan, W. Lin, J. Song, *Chem. Commun.* **2010**, *46*, 7930–7932.
[111] T. Kappe, P. Roschger, B. Schuiki, W. Stadlbauer, *J. Heterocyclic Chem.* **2003**, *40*, 297–302.

Na_2SO_4, and concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel using mixtures of cyclohexane and ethyl acetate as eluents affords the analytically pure acetylated product (*cis*:*trans* > 99:1).

2.1.2 Preparation of 2,3-Disubstituted Indoline Substrates with an Acetyl Directing Group (GP 2)

Step 1: Under inert atmosphere, phenylhydrazine or a substituted phenylhydrazine hydrochloride (1.0 equiv.) is added to a solution of butan-2-one (3.1 equiv.) in acetic acid (0.5M) and stirred at 120 °C for 14 h. After cooling to ambient temperature, H_2O and ethyl acetate are added and the phases are separated. The organic phase is washed with brine (2 ×) and saturated aqueous $NaHCO_3$ (1 ×) and is then dried over anhydrous Na_2SO_4. The solvents are removed under reduced pressure and the crude product is characterized and subsequently used in the next step without further purification.[112]

Step 2: Under inert atmosphere, sodium cyanoborohydride (2.0 equiv.) is slowly added to a solution of the 2,3-dimethylindole (1.0 equiv.) in acetic acid (0.20M) at 0 °C and stirred at room temperature.[113] The reaction mixture is monitored by TLC. After evaporation of the solvent under reduced pressure, the residue is neutralized with NaOH (2M) to pH = 7 under ice cooling and extracted with CH_2Cl_2 (3 ×). The extracts are washed with brine (1 ×), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure.

Step 3: The residue is dissolved in acetic anhydride (5.0–15.0 equiv.) at room temperature, followed by addition of pyridine (0.60 equiv.). The reaction mixture is heated with an oil bath to 120 °C and maintained at this temperature for 4 h and afterwards quenched by the addition of NaOH (2M) under ice cooling, and the resulting mixture is then diluted with ethyl acetate. The phases are separated, and the organic phase is washed with saturated aqueous $NaHCO_3$ (1 ×), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel using mixtures of cyclohexane and ethyl acetate as eluents affords the analytically pure product. The *cis*:*trans* ratio of products was determined by GLC analysis of the crude compounds; assignment was done by ^1H NMR spectroscopy.

[112] M. López-Iglesias, E. Busto, V. Gotor, V. Gotor-Fernández, *J. Org. Chem.* **2012**, *77*, 8049–8055.
[113] G. W. Gribble, J. H. Hoffman, *Synthesis* **1977**, 859–860.

2.1.3 Oxidative Palladium(II)-Catalyzed Cross-Dehydrogenative Arylation of Indolines Using $Na_2S_2O_8$ as Oxidant (GP 3)

Under inert atmosphere, a flame-dried SCHLENK tube equipped with a magnetic stir bar is successively charged with the *N*-acetylated indoline (1.0 equiv.), $Pd(OAc)_2$ (20 mol%), $Na_2S_2O_8$ (3.0 equiv.), and excess arene (0.2M). Subsequently, trifluoroacetic acid (5.0 equiv.) is added, and the reaction mixture is stirred at the indicated temperature for the indicated time. After complete consumption of the indoline, as monitored by GLC analysis using indicated amount of tetracosane as internal standard, the reaction mixture is allowed to cool to room temperature and diluted with ethyl acetate. The crude reaction mixture is washed with saturated aqueous $NaHCO_3$ and the phases are separated. The aqueous phase is extracted with ethyl acetate (3 ×), and the combined organic phases are washed with brine (1 ×) and dried over anhydrous Na_2SO_4. After evaporation of the solvents under reduced pressure, purification of the residue by flash column chromatography on silica gel using mixtures of cyclohexane and ethyl acetate as eluents affords the analytically pure arylation products.
The regioisomeric ratio was determined by GLC analysis.

2.1.4 Preparation of Indoline Substrates with a Urea Directing Group (GP 4)

Under inert atmosphere, a flame-dried SCHLENK flask is charged with the indicated indoline (1.0 equiv.) and anhydrous diethyl ether (0.2M) at 0 °C. To this mixture, a solution of *n*-BuLi in hexane (1.3 equiv.) is added dropwise with ice cooling. The resulting mixture is stirred at room temperature for 1 h before cooling down to 0 °C again, and *N*,*N*-dimethylcarbamoyl chloride or *N*,*N*-diethylcarbamoyl chloride (1.2 equiv.) is added dropwise. After being stirred at room temperature for 14 h, the reaction is quenched with saturated aqueous NH_4Cl and extracted with CH_2Cl_2 (3 ×). The combined organic phases are washed with brine (1 ×), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel using mixtures of cyclohexane and ethyl acetate as eluents affords the analytically pure indoline product with the urea directing group.

2.1.5 Oxidative Palladium(II)-Catalyzed Cross-Dehydrogenative Arylation of Indolines Mediated by $Cu(OAc)_2$ in an Open Flask under Mild Condition (GP 5)

A indicated-dried SCHLENK tube equipped with a magnetic stir bar is successively charged with the indoline (1.0 equiv.), $Pd(OAc)_2$ (10 mol%), $Cu(OAc)_2$ (1.0 equiv.), and trifluoroacetic acid (13.0 equiv.) in the corresponding arene (0.2M). The reaction mixture is stirred at 50 °C in open air for the indicated reaction time. After complete consumption of the indoline, as monitored by GLC analysis using the indicated amount of tetracosane as internal standard, the reaction mixture is allowed to cool to room temperature and diluted with ethyl acetate. The crude reaction mixture is washed with saturated aqueous Na_2CO_3 (1 ×) and H_2O (1 ×) and the phases are separated. The organic phase is dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel using mixtures of cyclohexane and ethyl acetate as eluents affords the analytically pure arylation product. The regioisomeric ratio was determined by GLC analysis.

2.1.6 Oxidative Palladium(II)-Catalyzed Cross-Dehydrogenative Arylation of Indolines Using Dioxygen as Oxidant under Mild Condition (GP 6)

Under inert atmosphere, a flame-dried SCHLENK tube equipped with a magnetic stir bar is successively charged with the indicated indoline (1.0 equiv.) and $Pd(OAc)_2$ (10 mol%). The tube is then evacuated and backfilled with O_2 (balloon, 3 cycles) followed by the addition of trifluoroacetic acid (13.0 equiv.) and the corresponding arene (0.2M). The reaction mixture is stirred at 50 °C for the indicated reaction time. After complete consumption of the indoline, as monitored by GLC analysis using the indicated amount of tetracosane as internal standard, the reaction mixture is allowed to cool to room temperature and is diluted with ethyl acetate. The crude reaction mixture is washed with saturated aqueous Na_2CO_3 (1 ×) and H_2O (1 ×) and the phases are separated. The organic phase is dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel using mixtures of cyclohexane and ethyl acetate as eluents affords the analytically pure arylation product. The regioisomeric ratio was determined by GLC analysis.

2.2 OXIDATIVE PALLADIUM(II)-CATALYZED CROSS-DEHYDROGENATIVE ALKENYLATION OF INDOLINE AT THE C-7 POSITION (GP 7)

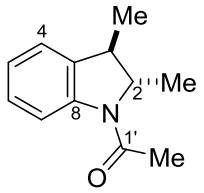
Under inert atmosphere, a flame-dried SCHLENK tube equipped with a magnetic stir bar is successively charged with the indoline substrate (1.0 equiv.), $Pd(OAc)_2$ (10 mol%), BQ (2.0 equiv.), and *p*-toluenesulfonic acid monohydrate (1.0 equiv.) in acetic acid (0.2M). Subsequently, the α,β-unsaturated acceptor (2.0 equiv.) or styrene (2.0 equiv.) is added, and the reaction mixture is stirred at the indicated temperature for the indicated time. After complete consumption of the indoline, as monitored by GLC analysis using indicated amount of tetracosane as internal standard, the reaction mixture is allowed to cool to room temperature and diluted with ethyl acetate. The crude reaction mixture is washed with saturated aqueous Na_2CO_3 (1 ×) and H_2O (1 ×). The organic phase is dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel using mixtures of cyclohexane and ethyl acetate as eluents affords the analytically pure alkenylation product.

3 DESCRIPTION OF EXPERIMENTS

3.1 OXIDATIVE PALLADIUM(II)-CATALYZED CROSS-DEHYDROGENATIVE ARYLATION OF INDOLINE AT THE C-7 POSITION

3.1.1 Preparation of 2,3-Disubstituted Indoline Substrates with an Acetyl as Directing Group

3.1.1.1 *trans*-1-(2,3-Dimethylindolin-1-yl)ethanone (*trans*-97)



trans-**97**
$C_{12}H_{15}NO$
M = 189.26 g/mol

According to a modified protocol of **GP 2**, a flame-dried flask equipped with a magnetic stir bar was charged with 2,3-dimethylindoline (*trans*-**136**, 883 mg, 6.00 mmol, 1.00 equiv.) in acetic acid (30 mL, 0.20M) under inert atmosphere. $NaBH_3CN$ (754 mg, 12.0 mmol, 2.00 equiv.) was added portionwise at 0 °C. The reaction mixture was monitored by TLC and stopped after 2 h. After evaporation of the solvent under reduced pressure, the residue was neutralized with NaOH (2M) to pH = 7 with ice cooling and extracted with CH_2Cl_2 (3 × 20 mL). The extracts were washed with brine (1 × 10 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The obtained indoline was directly used in the next step without further purification.

The intermediate was then dissolved in acetic anhydride (2.9 mL, 30 mmol, 5.0 equiv.) under inert atmosphere at room temperature, followed by addition of pyridine (0.29 mL, 3.6 mmol, 0.60 equiv.). The reaction mixture was heated with an oil bath to 120 °C and maintained at this temperature for 4 h and was afterwards quenched by the addition of NaOH (2M) with ice-cooling, and the resulting mixture was diluted with ethyl acetate (30 mL). The phases were separated, and the organic phase was washed with saturated aqueous $NaHCO_3$ (1 × 5 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (3.5 × 20 cm, cyclohexane:ethyl

acetate = 4:1 → 3:1, 100 mL, #12–19) afforded the analytically pure arylated product *trans*-**97** (681 mg, 60%) as a light brown oil.

R_f = 0.33 (cyclohexane:ethyl acetate = 3:1).

GLC (HP-5): t_R = 14.2 min.

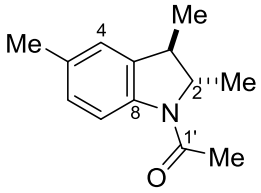
^{1}H NMR (500 MHz, DMSO-d$_6$, 358 K): δ/ppm = 1.23 (d, $^3J_{3–CH_3,3}$ = 7.0 Hz, 3H, 3–CH_3), 1.27 (d, $^3J_{2–CH_3,2}$ = 7.3 Hz, 3H, 2–CH_3), 2.27 (s, 3H, H-2'), 2.91 (q, $^3J_{3,3–CH_3}$ = 7.0 Hz, 1H, H-3), 4.17 (q, $^3J_{2,2–CH_3}$ = 6.5 Hz, 1H, H-2), 7.05 (ddd, $^3J_{5,4}$ = $^3J_{5,6}$ = 7.4 Hz, $^4J_{5,7}$ = 0.9 Hz, 1H, H-5), 7.20 (ddd, $^3J_{6,5}$ = 7.5 Hz, $^3J_{6,7}$ = 7.3 Hz, $^4J_{6,4}$ = 0.9 Hz, 1H, H-6), 7.29 (d, $^3J_{4,5}$ = 7.4 Hz, 1H, H-4), 7.90 (br s, 1H, H-7).

^{13}C NMR (100 MHz, DMSO-d$_6$, 298 K): δ/ppm = 21.8 (3-*C*H$_3$), 22.6 (2-*C*H$_3$), 24.0 (C-2'), 43.7 (C-3), 64.1 (C-2), 117.7 (C-7), 124.4 (C-5), 125.5 (C-4), 128.2 (C-6), 137.3 (C-9), 141.4 (C-8), 169.2 (C-1').

IR (ATR): $\tilde{\nu}$ /cm^{-1} = 2964 (m), 2936 (w), 2918 (vw), 1650 (s), 1599 (m), 1478 (s), 1462 (m), 1379 (s), 1360 (m), 1311 (m), 1281 (s), 1173 (m), 1127 (m), 1023 (m), 982 (m), 753 (s).

HRMS (APCI) for $C_{12}H_{16}NO$ ([M+H]$^+$): calcd. 190.1226
found 190.1221

3.1.1.2 *trans*-1-(2,3,5-Trimethylindolin-1-yl)ethanone (*trans*-98)



trans-**98**
$C_{13}H_{17}NO$
M = 203.29 g/mol

According to **GP 2**, a flame-dried flask equipped with a magnetic stir bar was charged with 4-methylphenylhydrazine hydrochloride (**110**, 475 mg, 3.00 mmol, 1.00 equiv.) and 2-butanone (**131**, 0.83 mL, 9.3 mmol, 3.1 equiv.) in acetic acid (15 mL, 0.5M) and stirred at 120 °C for 14 h under inert atmosphere. After cooling to ambient temperature, H_2O (10 mL) and ethyl

acetate (20 mL) were added and the phases were separated. The organic phase was washed with brine (2 × 10 mL) and saturated aqueous $NaHCO_3$ (1 × 10 mL) and then dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the crude product was subsequently used in the next step without further purification.
In a flame-dried flask, the resulting indole was dissolved in acetic acid (15 mL, 0.20M) under inert atmosphere. $NaBH_3CN$ (377 mg, 6.00 mmol, 2.00 equiv.) was added portionwise at 0 °C. The reaction mixture was monitored by TLC and stopped after 2.5 h. After evaporation of the solvent under reduced pressure, the residue was neutralized with NaOH (2M) to pH = 7 with ice-cooling and extracted with CH_2Cl_2 (3 × 10 mL). The extracts were washed with brine (1 × 5 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The obtained indoline was directly used in the next step without further purification.
The intermediate was then dissolved in acetic anhydride (1.5 mL, 15 mmol, 5.0 equiv.) under inert atmosphere at room temperature, followed by addition of pyridine (0.15 mL, 1.8 mmol, 0.60 equiv.). The reaction mixture was heated with an oil bath to 120 °C and maintained at this temperature for 4 h and was afterwards quenched by the addition of NaOH (2M) with ice-cooling, and the resulting mixture was diluted with ethyl acetate (15 mL). The phases were separated, and the organic phase was washed with saturated aqueous $NaHCO_3$ (1 × 5 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (3.5 × 20 cm, cyclohexane:ethyl acetate = 2.5:1 → 2:1, 100 mL, #18–27) afforded the analytically pure arylated product *trans*-**98** (353 mg, 58%) as a light yellow oil.

R_f = 0.29 (cyclohexane:ethyl acetate = 2:1).

GLC (HP-5): t_R = 15.2 min.

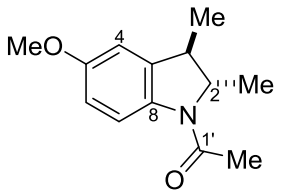
^{1}H NMR (500 MHz, DMSO-d_6, 358 K): δ/ppm = 1.21 (d, $^3J_{3\text{–}CH_3,3}$ = 7.1 Hz, 3H, 3–CH_3), 1.26 (d, $^3J_{2\text{–}CH_3,2}$ = 6.4 Hz, 3H, 2–CH_3), 2.24 (s, 3H, H-2'), 2.31 (s, 3H, 5–CH_3), 2.86 (q, $^3J_{3,3\text{–}CH_3}$ = 7.0 Hz, 1H, H-3), 4.15 (q, $^3J_{2,2\text{–}CH_3}$ = 6.3 Hz, 1H, H-2), 7.01 (d, $^3J_{6,7}$ = 8.1 Hz, 1H, H-6), 7.09 (s, 1H, H-4), 7.77 (br s, 1H, H-7).

^{13}C NMR (100 MHz, DMSO-d_6, 298 K): δ/ppm = 21.6 (5-*C*H$_3$), 21.8 (3-*C*H$_3$), 22.7 (2-*C*H$_3$), 23.9 (C-2'), 43.7 (C-3), 64.3 (C-2), 117.5 (C-7), 126.0 (C-4), 128.5 (C-6), 133.4 (C-5), 137.4 (C-9), 139.2 (C-8), 168.8 (C-1').

IR (ATR): $\tilde{\nu}$ /cm^{-1} = 2965 (br), 2925 (w), 2865 (vw), 1712 (m), 1651 (s), 1486 (s), 1396 (s), 1384 (s), 1370 (s), 1279 (m), 1151 (m), 1123 (m), 1032 (w), 982 (m), 818 (s).

HRMS (APCI) for $C_{13}H_{18}NO$ ($[M+H]^+$): calcd. 204.1383
found 204.1378

3.1.1.3 *trans*-1-(5-Methoxy-2,3-dimethylindolin-1-yl)ethanone (*trans*-99)



trans-**99**
$C_{13}H_{17}NO_2$
M = 219.28 g/mol

According to **GP 2**, a flame-dried flask equipped with a magnetic stir bar was charged with 4-methoxyphenylhydrazine hydrochloride (**111**, 524 mg, 3.00 mmol, 1.00 equiv.) and 2-butanone (**131**, 0.83 mL, 9.3 mmol, 3.1 equiv.) in acetic acid (15 mL, 0.5M) and stirred at 120 °C for 14 h under inert atmosphere. After cooling to ambient temperature, H_2O (10 mL) and ethyl acetate (20 mL) were added and the phases were separated. The organic phase was washed with brine (2 × 10 mL) and saturated aqueous $NaHCO_3$ (1 × 10 mL) and then dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the crude product was subsequently used in the next step without further purification.
In a flame-dried flask, the resulting indole was dissolved in acetic acid (15 mL, 0.20M) under inert atmosphere. $NaBH_3CN$ (377 mg, 6.00 mmol, 2.00 equiv.) was added portionwise at 0 °C. The reaction mixture was monitored by TLC and stopped after 2 h. After evaporation of the solvent under reduced pressure, the residue was neutralized with NaOH (2M) to pH = 7 with ice-cooling and extracted with CH_2Cl_2 (3 × 10 mL). The extracts were washed with brine (1 × 5 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The obtained indoline was directly used in the next step without further purification.
The intermediate was then dissolved in acetic anhydride (1.5 mL, 15 mmol, 5.0 equiv.) under inert atmosphere at room temperature, followed by addition of pyridine (0.15 mL, 1.8 mmol, 0.60 equiv.). The reaction mixture was heated with an oil bath to 120 °C and maintained at this temperature for 4 h and was afterwards quenched by the addition of NaOH (2M) with ice-cooling, and the resulting mixture was diluted with ethyl acetate (15 mL). The phases were separated, and the organic phase was washed with saturated aqueous $NaHCO_3$ (1 × 5 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (3.5 × 20 cm, cyclohexane:ethyl

acetate = 2.5:1 → 2:1, 100 mL, #9–19) afforded the analytically pure arylated product *trans*-**99** (334 mg, 51%) as a light yellow solid.

m.p.: 62–63 °C.

R_f = 0.15 (cyclohexane:ethyl acetate = 2:1).

GLC (HP-5): t_R = 16.8 min.

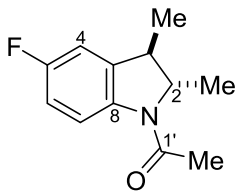
^{1}H NMR (500 MHz, DMSO-d_6, 358 K): δ/ppm = 1.23 (d, $^3J_{3–CH_3,3}$ = 7.1 Hz, 3H, 3–CH_3), 1.26 (d, $^3J_{2–CH_3,2}$ = 6.4 Hz, 3H, 2–CH_3), 2.23 (s, 3H, H-2'), 2.87 (q, $^3J_{3,3–CH_3}$ = 7.0 Hz, 1H, H-3), 3.78 (s, 3H, 5–OCH_3), 4.14 (q, $^3J_{2,2–CH_3}$ = 5.9 Hz, 1H, H-2), 6.77 (dd, $^3J_{6,7}$ = 8.7 Hz, $^4J_{6,4}$ = 2.7 Hz, 1H, C-6), 6.90 (d, $^4J_{4,6}$ = 2.6 Hz, 1H, C-4), 7.82 (br s, 1H, H-7).

^{13}C NMR (100 MHz, DMSO-d_6, 298 K): δ/ppm = 21.8 (3-*C*H$_3$), 22.5 (2-*C*H$_3$), 23.8 (C-2'), 43.9 (C-3), 56.2 (5-O*C*H$_3$), 64.3 (C-2), 111.4 (C-6), 112.9 (C-4), 118.3 (C-7), 135.1 (C-9), 138.9 (C-8), 156.8 (C-5), 168.4 (C-1').

IR (ATR): $\tilde{\nu}$ /cm^{-1} = 2966 (m), 2927 (w), 1715 (s), 1643 (s), 1593 (w), 1479 (s), 1390 (s), 1369 (m), 1276 (m), 1241 (m), 1218 (m), 1124 (w), 1035 (m), 983 (w), 870 (w), 815 (w), 713 (w).

HRMS (APCI) for $C_{13}H_{18}NO_2$ ([M+H]$^+$): calcd. 220.1332
found 220.1326

3.1.1.4 *trans*-1-(5-Fluoro-2,3-dimethylindolin-1-yl)ethanone (*trans*-100)



trans-**100**
$C_{12}H_{14}FNO$
M = 207.25 g/mol

According to **GP 2**, a flame-dried flask equipped with a magnetic stir bar was successively charged with 4-fluorophenylhydrazine hydrochloride (**112**, 976 mg, 6.00 mmol, 1.00 equiv.)

and 2-butanone (**131**, 1.66 mL, 18.6 mmol, 3.10 equiv.) in acetic acid (30 mL, 0.5M) and stirred at 120 °C for 14 h under inert atmosphere. After cooling to ambient temperature, H_2O (10 mL) and ethyl acetate (30 mL) were added and the phases were separated. The organic phase was washed with brine (2 × 10 mL) and saturated aqueous $NaHCO_3$ (1 × 10 mL) and then dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the crude product was subsequently used in the next step without further purification.
In a flame-dried flask, the resulting indole was dissolved in acetic acid (30 mL, 0.20M) under inert atmosphere. $NaBH_3CN$ (754 mg, 12.0 mmol, 2.00 equiv.) was added portionwise at 0 °C. The reaction mixture was monitored by TLC and stopped after 2 h. After evaporation of the solvent under reduced pressure, the residue was neutralized with NaOH (2M) to pH = 7 with ice-cooling and extracted with CH_2Cl_2 (3 × 20 mL). The extracts were washed with brine (1 × 5 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The obtained indoline was directly used in the next step without further purification.
The intermediate was then dissolved in acetic anhydride (2.9 mL, 30 mmol, 5.0 equiv.) under inert atmosphere at room temperature, followed by addition of pyridine (0.29 mL, 3.6 mmol, 0.60 equiv.). The reaction mixture was heated with an oil bath to 120 °C and maintained at this temperature for 4 h and was afterwards quenched by the addition of NaOH (2M) with ice-cooling, and the resulting mixture was diluted with ethyl acetate (30 mL). The phases were separated, and the organic phase was washed with saturated aqueous $NaHCO_3$ (1 × 10 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (3.5 × 20 cm, cyclohexane:ethyl acetate = 2.5:1 → 2:1, 100 mL, #23–28) afforded the analytically pure arylated product *trans*-**100** (634 mg, 51%) as a light yellow solid.

R_f = 0.20 (cyclohexane:ethyl acetate = 3:1).

GLC (HP-5): t_R = 14.1 min.

^{1}H NMR (500 MHz, DMSO-d$_6$, 358 K): δ/ppm = 1.24 (d, $^3J_{3–CH_3,3}$ = 7.1 Hz, 3H, 3–CH_3), 1.27 (d, $^3J_{2–CH_3,2}$ = 6.4 Hz, 3H, 2–CH_3), 2.26 (s, 3H, H-2'), 2.92 (q, $^3J_{3,3–CH_3}$ = 7.0 Hz, 1H, H-3), 4.19 (q, $^3J_{2,2–CH_3}$ = 6.4 Hz, 1H, H-2), 6.99 (ddd, $^3J_{6,5–F}$ = 9.1 Hz, $^3J_{6,7}$ = 9.0 Hz, $^4J_{6,4}$ = 2.8 Hz, 1H, H-6), 7.13 (dd, $^3J_{4,5–F}$ = 8.5 Hz, $^4J_{4,6}$ = 2.7 Hz, 1H, H-4), 7.92 (br s, 1H, H-7).

^{13}C NMR (126 MHz, DMSO-d$_6$, 298 K): δ/ppm = 21.2 (3-*C*H$_3$), 21.7 (2-*C*H$_3$), 23.4 (C-2'), 43.3 (C-3), 64.2 (C-2), 112.2 (d, $^3J_{6,5–F}$ = 23.4 Hz, C-6), 113.8 (d, $^3J_{4,5–F}$ = 22.7 Hz, C-4), 118.0 (d, $^4J_{7,5–F}$ = 7.3 Hz, C-7), 137.5 (C-9), 139.5 (C-8), 159.2 (d, $^1J_{5,5–F}$ = 238.2 Hz, C-5), 168.4 (C-1').

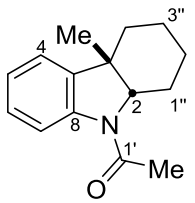
^{19}F NMR (471 MHz, DMSO-d_6, 298 K): δ/ppm = –119.4 (5–F).

IR (ATR): $\tilde{\nu}$ /cm^{-1} = 2967 (m), 2928 (w), 1649 (s), 1607 (s), 1478 (s), 1395 (s), 1131 (m), 1266 (m), 1238 (s), 1177 (m), 1122 (m), 1032 (w), 983 (m), 930 (m), 862 (m), 817 (s), 751 (m), 719 (m).

HRMS (APCI) for $C_{12}H_{15}FNO$ ($[M+H]^+$): calcd. 208.1132
found 208.1126

3.1.2 Preparation of 2,3,3-Trisubstituted Indoline Substrates with an Acetyl as Directing Group

3.1.2.1 *cis*-1-[4a-Methyl-2,3,4,4a-tetrahydro-1*H*-carbazol-9(9a*H*)-yl]ethanone (*cis*-105)



***cis*-105**
$C_{15}H_{19}NO$
M = 229.32 g/mol

According to **GP 1**, a flame-dried flask equipped with a magnetic stir bar was successively charged with phenylhydrazine (**109**, 2.6 g, 24 mmol, 1.0 equiv.) and 2-methylcyclohexanone (**114**, 8.1 g, 72 mmol, 3.0 equiv.) in acetic acid (48 mL, 0.5M) and stirred at 120 °C for 14 h under inert atmosphere. After cooling to ambient temperature, ethyl acetate (100 mL) and H_2O (30 mL) were added and the phases were separated. The organic phase was washed with brine (2 × 20 mL) and saturated aqueous $NaHCO_3$ (1 × 20 mL) and then dried over anhydrous Na_2SO_4. The solvents were removed under reduced pressure and the crude product was subsequently used in the next step without further purification.
In a flame-dried flask, the resulting indolenine was dissolved in MeOH and H_2O (120 mL, *v*/*v* = 4:1, 0.2M) under inert atmosphere. $NaBH_4$ (1.82 g, 48.0 mmol, 2.00 equiv.) was added portionwise at 0 °C. After warming to ambient temperature, the reaction mixture was monitored by TLC and stopped after 2 h. After evaporation of the solvent under reduced pressure, the aqueous phase was extracted with Et_2O (3 × 50 mL). The extracts were washed with brine (2 × 20 mL), dried over anhydrous Na_2SO_4, and concentrated under

reduced pressure. The obtained indoline was directly used in the next step without further purification.

The intermediate was then dissolved in acetic anhydride (12.0 mL, 120 mmol, 5.00 equiv.) under inert atmosphere at room temperature, followed by addition of pyridine (1.16 mL, 14.4 mmol, 0.600 equiv.). The reaction mixture was heated with an oil bath to 120 °C and maintained at this temperature for 4 h and was afterwards quenched by the addition of NaOH (2M) to pH = 7 with ice-cooling, and the resulting mixture was diluted with ethyl acetate (50 mL). The phases were separated, and the organic phase was washed with saturated aqueous $NaHCO_3$ (1 × 20 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (3.5 × 20 cm, cyclohexane:ethyl acetate = 4:1 → 3:1, 100 mL, #19–37) afforded the analytically pure arylated product *cis*-**105** (3.2 g, 59%) as a yellow solid.

m.p.: 94–95 °C.

R_f = 0.29 (cyclohexane:ethyl acetate = 3:1).

GLC (HP-5): t_R = 17.6 min.

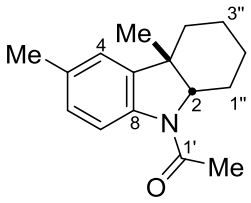
^{1}H NMR (500 MHz, DMSO-d_6, 358 K): δ/ppm = 1.01–1.11 (m, 2H, H-2''), 1.13 (s, 3H, 3–CH_3), 1.25–1.33 (m, 1H, H-3''), 1.54–1.66 (m, 3H, H-3'', H-4''), 2.07–2.10 (m, 1H, H-1''A), 2.27 (s, 3H, H-2'), 2.30–2.32 (m, 1H, H-1''B), 4.09 (dd, $^3J_{2,1''A}$ = 10.0 Hz, $^3J_{2,1''B}$ = 6.3 Hz, 1H, H-2), 7.08 (dd, $^3J_{5,4}$ = 8.0 Hz, $^3J_{5,6}$ = 7.4 Hz, 1H, H-5), 7.19–7.23 (m, 2H, H-4, H-6), 7.88 (br s, 1H, H-7).

^{13}C NMR (126 MHz, DMSO-d_6, 298 K): δ/ppm = 21.9 (C-2'')*, 22.3 (C-3'')*, 23.4 (3–CH$_3$), 29.0 (C-1''), 31.1 (C-2'), 32.1 (C-4''), 43.7 (C-3), 67.8 (C-2), 117.6 (C-7), 122.2 (C-5), 124.0 (C-4), 127.5 (C-6), 139.8 (C-9), 141.4 (C-8), 168.2 (C-1').

IR (ATR): $\tilde{\nu}$ /cm^{-1} = 2925 (br), 2858 (w), 1651 (s), 1599 (m), 1475 (m), 1457 (m), 1399 (w), 1357 (m), 1283 (m), 1187 (w), 1110 (w), 1090 (w), 929 (w), 846 (w), 770 (m), 752 (s).

HRMS (APCI) for $C_{15}H_{20}NO$ ($[M+H]^+$): calcd. 230.1539
found 230.1541

3.1.2.2 *cis*-1-[4a,6-Dimethyl-2,3,4,4a-tetrahydro-1*H*-carbazol-9(9a*H*)-yl]ethanone (*cis*-106)



cis-**106**
$C_{16}H_{21}NO$
M = 243.35 g/mol

According to **GP 1**, a flame-dried flask equipped with a magnetic stir bar was successively charged with 4-methylphenylhydrazine hydrochloride (**110**, 470 mg, 3.00 mmol, 1.00 equiv.) and 2-methylcyclohexanone (**114**, 1.01 g, 9.00 mmol, 3.00 equiv.) in acetic acid (12 mL, 0.25M) and stirred at 120 °C for 14 h under inert atmosphere. After cooling to ambient temperature, ethyl acetate (20 mL) and H_2O (5 mL) were added and the phases were separated. The organic phase was washed with brine (2 × 5 mL) and saturated aqueous $NaHCO_3$ (1 × 5 mL) and then dried over anhydrous Na_2SO_4. The solvents were removed under reduced pressure and the crude product was subsequently used in the next step without further purification.

In a flame-dried flask, the resulting indolenine was dissolved in MeOH and H_2O (15 mL, *v*/*v* = 4:1, 0.2M) under inert atmosphere. $NaBH_4$ (227 mg, 6.00 mmol, 2.00 equiv.) was added portionwise at 0 °C. After warming to ambient temperature, the reaction mixture was monitored by TLC and stopped after 2 h. After evaporation of the solvent under reduced pressure, the aqueous phase was extracted with Et_2O (3 × 15 mL). The extracts were washed with brine (2 × 5 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The obtained indoline was directly used in the next step without further purification.

The intermediate was then dissolved in acetic anhydride (4.5 mL, 45 mmol, 15 equiv.) under inert atmosphere at room temperature, followed by addition of pyridine (0.14 mL, 1.8 mmol, 0.60 equiv.). The reaction mixture was heated with an oil bath to 120 °C and maintained at this temperature for 4 h and was afterwards quenched by the addition of NaOH (2M) to pH = 7 with ice-cooling, and the resulting mixture was diluted with ethyl acetate (20 mL). The phases were separated, and the organic phase was washed with saturated aqueous $NaHCO_3$ (1 × 5 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (3.5 × 20 cm, cyclohexane:ethyl acetate = 2.5:1, 100 mL, #10–20) afforded the analytically pure arylated product *cis*-**106** (392 mg, 54%) as a white solid.

m.p.: 125–126 °C.

R_f = 0.29 (cyclohexane:ethyl acetate = 3:1).

GLC (HP-5): t_R = 15.8 min.

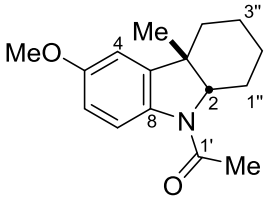
^{1}H NMR (500 MHz, DMSO-d$_6$, 358 K): δ/ppm = 1.01–1.15 (m, 2H, H-2''), 1.12 (s, 3H, 3–CH_3), 1.22–1.33 (m, 1H, H-3''), 1.53–1.64 (m, 3H, H-3'', H-4''), 2.05–2.08 (m, 1H, H-1''A), 2.25 (s, 3H, 5–CH_3), 2.26–2.29 (m, 1H, H-1''B), 2.33 (s, 3H, H-2'), 4.06 (dd, $^3J_{2,1''A}$ = 10.0 Hz, $^3J_{2,1''B}$ = 6.1 Hz, 1H, H-2), 7.00 (d, $^3J_{6,7}$ = 8.1 Hz, 1H, H-6), 7.03 (s, 1H, H-4), 7.75 (br s, 1H, H-7).

^{13}C NMR (126 MHz, DMSO-d$_6$, 298 K): δ/ppm = 21.7 (C-2'')*, 22.7 (C-3'')*, 23.1 (3–*C*H$_3$), 23.8 (5–*C*H$_3$), 29.7 (C-1''), 31.8 (C-2'), 32.4 (C-4''), 44.2 (C-3), 68.2 (C-2), 118.1 (C-7), 123.1 (C-4), 128.4 (C-6), 133.6 (C-5), 139.4 (C-9), 139.9 (C-8), 168.5 (C-1').

IR (ATR): $\tilde{\nu}$ /cm^{-1} = 2950 (w), 2918 (br), 2853 (br), 1644 (s), 1588 (w), 1476 (m), 1426 (m), 1393 (m), 1345 (m), 1280 (m), 1207 (w), 1128 (w), 1007 (m), 926 (w), 885 (w), 853 (w), 830 (s), 739 (s).

HRMS (APCI) for $C_{16}H_{22}NO$ ([M+H]$^+$): calcd. 244.1696
found 244.1689

3.1.2.3 *cis*-1-[6-Methoxy-4a-methyl-2,3,4,4a-tetrahydro-1*H*-carbazol-9(9a*H*)-yl]ethanone (*cis*-107)



cis-**107**
$C_{16}H_{21}NO_2$
M = 259.35 g/mol

According to **GP 1**, a flame-dried flask equipped with a magnetic stir bar was successively charged with 4-methoxyphenylhydrazine hydrochloride (**111**, 520 mg, 3.00 mmol, 1.00 equiv.) and 2-methylcyclohexanone (**114**, 1.01 g, 9.00 mmol, 3.00 equiv.) in acetic acid (12 mL,

0.25M) and stirred at 120 °C for 14 h under inert atmosphere. After cooling to ambient temperature, ethyl acetate (20 mL) and H_2O (5 mL) were added and the phases were separated. The organic phase was washed with brine (2 × 5 mL) and saturated aqueous $NaHCO_3$ (1 × 5 mL) and then dried over anhydrous Na_2SO_4. The solvents were removed under reduced pressure and the crude product was subsequently used in the next step without further purification.

In a flame-dried flask, the resulting indolenine was dissolved in MeOH and H_2O (15 mL, *v*/*v* = 4:1, 0.2M) under inert atmosphere. $NaBH_4$ (227 mg, 6.00 mmol, 2.00 equiv.) was added portionwise at 0 °C. After warming to ambient temperature, the reaction mixture was monitored by TLC and stopped after 2 h. After evaporation of the solvent under reduced pressure, the aqueous phase was extracted with Et_2O (3 × 15 mL). The extracts were washed with brine (2 × 5 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The obtained indoline was directly used in the next step without further purification.

The intermediate was then dissolved in acetic anhydride (4.5 mL, 45 mmol, 15 equiv.) under inert atmosphere at room temperature, followed by addition of pyridine (0.14 mL, 1.8 mmol, 0.60 equiv.). The reaction mixture was heated with an oil bath to 120 °C and maintained at this temperature for 4 h and was afterwards quenched by the addition of NaOH (2M) to pH = 7 with ice-cooling, and the resulting mixture was diluted with ethyl acetate (20 mL). The phases were separated, and the organic phase was washed with saturated aqueous $NaHCO_3$ (1 × 5 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (3.5 × 20 cm, cyclohexane:ethyl acetate = 2.5:1 → 2:1, 100 mL, #14–30) afforded the analytically pure arylated product *cis*-**107** (427 mg, 55%) as a light yellow oil.

R_f = 0.25 (cyclohexane:ethyl acetate = 3:1).

GLC (HP-5): t_R = 19.9 min.

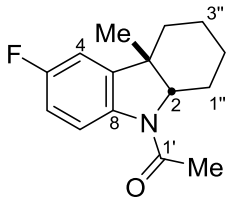
^{1}H NMR (500 MHz, DMSO-d_6, 358 K): δ/ppm = 1.05–1.15 (m, 2H, H-2''), 1.13 (s, 3H, 3–CH_3), 1.24–1.33 (m, 1H, H-3''), 1.54–1.63 (m, 3H, H-3'', H-4''), 2.04–2.08 (m, 1H, H-1''A), 2.24 (s, 3H, H-2'), 2.27–2.30 (m, 1H, H-1''B), 3.79 (s, 3H, 5–OCH_3), 4.07 (dd, $^3J_{2,1''A}$ = 9.4 Hz, $^3J_{2,1''B}$ = 6.4 Hz, 1H, H-2), 6.76 (dd, $^3J_{6,7}$ = 8.7 Hz, $^4J_{6,4}$ = 2.7 Hz, 1H, H-6), 6.82 (d, $^4J_{4,6}$ = 2.6 Hz, 1H, H-4), 7.80 (br s, 1H, H-7).

^{13}C NMR (126 MHz, DMSO-d_6, 298 K): δ/ppm = 22.8 (C-2'')*, 23.2 (C-3'')*, 23.6 (3–*C*H$_3$), 29.7 (C-1''), 31.6 (C-2'), 32.4 (C-4''), 44.4 (C-3), 56.2 (5–O*C*H$_3$), 68.2 (C-2), 109.1 (C-6), 112.2 (C-4), 119.0 (C-7), 135.2 (C-9), 141.6 (C-8), 157.0 (C-5), 168.0 (C-1').

IR (ATR): $\tilde{\nu}$ /cm^{-1} = 2926 (br), 2855 (br), 1640 (s), 1591 (m), 1478 (s), 1446 (m), 1395 (s), 1362 (w), 1323 (m), 1280 (w), 1210 (m), 1184 (m), 1128 (w), 1083 (m), 1034 (s), 927 (w), 820 (m), 800 (m), 694 (w).

HRMS (APCI) for $C_{16}H_{22}NO_2$ ([M+H]$^+$): calcd. 260.1645
found 260.1635

3.1.2.4 *cis*-1-[6-Fluoro-4a-methyl-2,3,4,4a-tetrahydro-1*H*-carbazol-9(9a*H*)-yl]ethanone (*cis*-108)



cis-**108**
$C_{15}H_{18}FNO$
M = 247.31 g/mol

According to **GP 1**, a flame-dried flask equipped with a magnetic stir bar was successively charged with 4-fluorophenylhydrazine hydrochloride (**112**, 490 mg, 3.00 mmol, 1.00 equiv.) and 2-methylcyclohexanone (**114**, 1.01 g, 9.00 mmol, 3.00 equiv.) in acetic acid (12 mL, 0.25M) and stirred at 120 °C for 14 h under inert atmosphere. After cooling to ambient temperature, ethyl acetate (20 mL) and H_2O (5 mL) were added and the phases were separated. The organic phase was washed with brine (2 × 5 mL) and saturated aqueous $NaHCO_3$ (1 × 5 mL) and then dried over anhydrous Na_2SO_4. The solvents were removed under reduced pressure and the crude product was subsequently used in the next step without further purification.
In a flame-dried flask, the resulting indolenine was dissolved in MeOH and H_2O (15 mL, *v*/*v* = 4:1, 0.2M) under inert atmosphere. $NaBH_4$ (227 mg, 6.00 mmol, 2.00 equiv.) was added portionwise at 0 °C. After warming to ambient temperature, the reaction mixture was monitored by TLC and stopped after 2 h. After evaporation of the solvent under reduced pressure, the aqueous phase was extracted with Et_2O (3 × 15 mL). The extracts were washed with brine (2 × 5 mL), dried over anhydrous Na_2SO_4, and concentrated under

reduced pressure. The obtained indoline was directly used in the next step without further purification.

The intermediate was then dissolved in acetic anhydride (2.9 mL, 30 mmol, 10 equiv.) under inert atmosphere at room temperature, followed by addition of pyridine (0.14 mL, 1.8 mmol, 0.60 equiv.). The reaction mixture was heated with an oil bath to 120 °C and maintained at this temperature for 4 h and was afterwards quenched by the addition of NaOH (2M) to pH = 7 with ice-cooling, and the resulting mixture was diluted with ethyl acetate (20 mL). The phases were separated, and the organic phase was washed with saturated aqueous $NaHCO_3$ (1 × 5 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (3.5 × 20 cm, cyclohexane:ethyl acetate = 3:1, 100 mL, #12–25) afforded the analytically pure arylated product *cis*-**108** (363 mg, 49%) as a white solid.

m.p.: 130–131 °C.

R_f = 0.25 (cyclohexane:ethyl acetate = 3:1).

GLC (HP-5): t_R = 17.5 min.

^{1}H NMR (500 MHz, DMSO-d_6, 358 K): δ/ppm = 1.02–1.12 (m, 2H, H-2''), 1.15 (s, 3H, 3–CH_3), 1.23–1.34 (m, 1H, H-3''), 1.55–1.65 (m, 3H, H-3'', H-4''), 2.07–2.13 (m, 1H, H-1''A), 2.26 (s, 3H, H-2'), 2.27–2.30 (m, 1H, H-1''B), 4.11 (dd, $^3J_{2,1''A}$ = 10.2 Hz, $^3J_{2,1''B}$ = 6.2 Hz, 1H, H-2), 6.98 (ddd, $^3J_{6,5-F}$ = 9.8 Hz, $^3J_{6,7}$ = 9.0 Hz, $^4J_{6,4}$ = 2.7 Hz, 1H, H-6), 7.08 (dd, $^3J_{4,5-F}$ = 8.5 Hz, $^4J_{4,6}$ = 2.7 Hz, 1H, H-4), 7.90 (br s, 1H, H-7).

^{13}C NMR (126 MHz, DMSO-d_6, 298 K): δ/ppm = 22.7 (C-2'')*, 23.0 (C-3'')*, 23.7 (3–CH$_3$), 29.7 (C-1''), 31.4 (C-2'), 32.3 (C-4''), 44.4 (C-3), 68.3 (C-2), 110.4 (d, $^2J_{6,5-F}$ = 23.0 Hz, C-6), 114.1 (d, $^2J_{4,5-F}$ = 22.6 Hz, C-4), 119.2 (C-7), 137.9 (C-9), 142.6 (C-8), 159.8 (d, $^1J_{5,5-F}$ = 238.0 Hz, C-5), 168.7 (C-1').

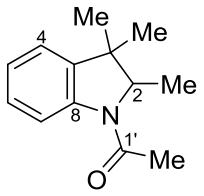
^{19}F NMR (471 MHz, DMSO-d_6, 298 K): δ/ppm = –118.8 (5–F).

IR (ATR): $\tilde{\nu}$ /cm^{-1} = 2959 (w), 2924 (br), 2854 (br), 1649 (s), 1601 (m), 1471 (s), 1457 (m), 1396 (m), 1357 (w), 1253 (m), 1175 (m), 1124 (w), 1007 (w), 938 (w), 875 (m), 836 (s), 692 (w).

HRMS (APCI) for $C_{15}H_{19}FNO$ ([M+H]$^+$): calcd. 248.1445

found 248.1438

3.1.2.5 1-(2,3,3-Trimethylindolin-1-yl)ethanone (101)



101
$C_{13}H_{17}NO$
M = 203.29 g/mol

According to **GP 1**, a flame-dried flask equipped with a magnetic stir bar was successively charged with phenylhydrazine (**109**, 650 mg, 6.00 mmol, 1.00 equiv.) and 3-methylbutan-2-one (**113**, 1.55 g, 18.0 mmol, 3.00 equiv.) in acetic acid (12 mL, 0.5M) and stirred at 120 °C for 14 h under inert atmosphere. After cooling to ambient temperature, ethyl acetate (40 mL) and H_2O (10 mL) were added and the phases were separated. The organic phase was washed with brine (2 × 10 mL) and saturated aqueous $NaHCO_3$ (1 × 10 mL) and then dried over anhydrous Na_2SO_4. The solvents were removed under reduced pressure and the crude product was subsequently used in the next step without further purification.

In a flame-dried flask, the resulting indolenine was dissolved in MeOH and H_2O (30 mL, *v*/*v* = 4:1, 0.2M) under inert atmosphere. $NaBH_4$ (554 mg, 12.0 mmol, 2.00 equiv.) was added portionwise at 0 °C. After warming to ambient temperature, the reaction mixture was monitored by TLC and stopped after 2 h. After evaporation of the solvent under reduced pressure, the aqueous phase was extracted with Et_2O (3 × 20 mL). The extracts were washed with brine (2 × 10 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The obtained indoline was directly used in the next step without further purification.

The intermediate was then dissolved in acetic anhydride (2.9 mL, 30 mmol, 5.0 equiv.) under inert atmosphere at room temperature, followed by addition of pyridine (0.29 mL, 3.6 mmol, 0.60 equiv.). The reaction mixture was heated with an oil bath to 120 °C and maintained at this temperature for 4 h and was afterwards quenched by the addition of NaOH (2M) to pH = 7 with ice-cooling, and the resulting mixture was diluted with ethyl acetate (40 mL). The phases were separated, and the organic phase was washed with saturated aqueous $NaHCO_3$ (1 × 10 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (5 × 20 cm,

cyclohexane:ethyl acetate = 4:1, 10 mL, #23–46) afforded the analytically pure arylated product **101** (902 mg, 74%) as a yellow oil.

R_f = 0.26 (cyclohexane:ethyl acetate = 3:1).

GLC (HP-5): t_R = 14.5 min.

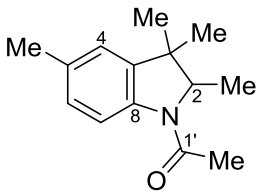
^{1}H NMR (500 MHz, DMSO-d_6, 358 K): δ/ppm = 1.13 (d, $^3J_{2-CH_3,2}$ = 6.6 Hz, 3H, 2–CH_3), 1.20 (s, 3H, 3–CH_3)*, 1.35 (s, 3H, 3–CH_3)*, 2.29 (s, 3H, H-2'), 4.22 (q, $^3J_{2,2-CH_3}$ = 6.5 Hz, 1H, H-2), 7.05–7.08 (m, 1H, H-5), 7.18–7.23 (m, 2H, H-4, H-6), 7.83 (br s, 1H, H-7).

^{13}C NMR (100 MHz, DMSO-d_6, 298 K): δ/ppm = 17.3 (2-CH$_3$), 20.7 (3-CH$_3$)*, 24.0 (3-CH$_3$)*, 31.7 (C-2'), 43.8 (C-3), 67.7 (C-2), 117.7 (C-7), 123.2 (C-5), 124.6 (C-4), 128.1 (C-6), 140.8 (C-9), 141.2 (C-8), 168.8 (C-1').

IR (ATR): $\tilde{\nu}$ /cm^{-1} = 2985 (br), 2961 (br), 1646 (s), 1598 (m), 1479 (s), 1449 (m), 1386 (s), 1308 (m), 1284 (s), 1188 (w), 1133 (w), 1112 (w), 1023 (w), 982 (w), 747 (s).

HRMS (APCI) for $C_{13}H_{17}NNaO$ ([M+Na]$^+$): calcd. 226.1202
found 226.1198

3.1.2.6 1-(2,3,3,5-Tetramethylindolin-1-yl)ethanone (102)



102
$C_{14}H_{19}NO$
M = 217.31 g/mol

According to **GP 1**, a flame-dried flask equipped with a magnetic stir bar was successively charged with 4-methylphenylhydrazine hydrochloride (**110**, 470 mg, 3.00 mmol, 1.00 equiv.) and 3-methylbutan-2-one (**113**, 760 mg, 9.00 mmol, 3.00 equiv.) in acetic acid (0.25 mL, 0.5M) and stirred at 120 °C for 14 h under inert atmosphere. After cooling to ambient temperature, ethyl acetate (20 mL) and H_2O (5 mL) were added and the phases were separated. The organic phase was washed with brine (2 × 5 mL) and saturated aqueous

$NaHCO_3$ (1 × 5 mL) and then dried over anhydrous Na_2SO_4. The solvents were removed under reduced pressure and the crude product was subsequently used in the next step without further purification.

In a flame-dried flask, the resulting indolenine was dissolved in MeOH and H_2O (15 mL, *v*/*v* = 4:1, 0.2M) under inert atmosphere. $NaBH_4$ (277 mg, 6.00 mmol, 2.00 equiv.) was added portionwise at 0 °C. After warming to ambient temperature, the reaction mixture was monitored by TLC and stopped after 2 h. After evaporation of the solvent under reduced pressure, the aqueous phase was extracted with Et_2O (3 × 10 mL). The extracts were washed with brine (2 × 5 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The obtained indoline was directly used in the next step without further purification.

The intermediate was then dissolved in acetic anhydride (2.9 mL, 30 mmol, 10 equiv.) under inert atmosphere at room temperature, followed by addition of pyridine (0.14 mL, 1.8 mmol, 0.60 equiv.). The reaction mixture was heated with an oil bath to 120 °C and maintained at this temperature for 4 h and was afterwards quenched by the addition of NaOH (2M) to pH = 7 with ice-cooling, and the resulting mixture was diluted with ethyl acetate (20 mL). The phases were separated, and the organic phase was washed with saturated aqueous $NaHCO_3$ (1 × 5 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (3.5 × 20 cm, cyclohexane:ethyl acetate = 3:1 → 2.5:1, 100 mL, #10–20) afforded the analytically pure arylated product **102** (385 mg, 59%) as a yellow oil.

R_f = 0.29 (cyclohexane:ethyl acetate = 3:1).

GLC (HP-5): t_R = 15.8 min.

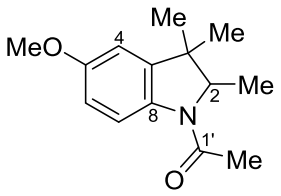
^{1}H NMR (500 MHz, DMSO-d_6, 358 K): δ/ppm = 1.12 (d, $^3J_{2-CH_3,2}$ = 6.6 Hz, 3H, 2–CH_3), 1.19 (s, 3H, 3–CH_3)*, 1.33 (s, 3H, 3–CH_3)*, 2.26 (s, 3H, H-2'), 2.32 (s, 3H, 5–CH_3), 4.20 (q, $^3J_{2,2-CH_3}$ = 6.5 Hz, 1H, H-2), 7.00 (d, $^3J_{6,7}$ = 8.1 Hz, 1H, H-6), 7.03 (s, 1H, H-4), 7.69 (br s, 1H, H-7).

^{13}C NMR (100 MHz, DMSO-d_6, 298 K): δ/ppm = 17.4 (2-*C*H$_3$), 20.7 (3-*C*H$_3$)*, 21.7 (5-*C*H$_3$), 23.9 (3-*C*H$_3$)*, 31.7 (C-2'), 43.8 (C-3), 67.9 (C-2), 117.5 (C-7), 123.7 (C-4), 128.4 (C-6), 133.6 (C-5), 138.5 (C-9), 141.3 (C-8), 168.5 (C-1').

IR (ATR): $\tilde{\nu}$ /cm^{-1} = 2933 (w), 2908 (br), 2873 (br), 1649 (s), 1566 (w), 1432 (m), 1406 (m), 1383 (m), 1347 (m), 1278 (m), 1168 (w), 1017 (m), 913 (w), 891 (w), 855 (w), 840 (s), 746 (s).

HRMS (APCI) for $C_{14}H_{20}NO$ ($[M+H]^+$): calcd. 218.1539
found 218.1532

3.1.2.7 1-(5-Methoxy-2,3,3-trimethylindolin-1-yl)ethanone (103)



103
$C_{14}H_{19}NO_2$
M = 233.31 g/mol

According to **GP 1**, a flame-dried flask equipped with a magnetic stir bar was successively charged with 4-methoxyphenylhydrazine hydrochloride (**111**, 520 mg, 3.00 mmol, 1.00 equiv.) and 3-methylbutan-2-one (**113**, 760 mg, 9.00 mmol, 3.00 equiv.) in acetic acid (0.25 mL, 0.5M) and stirred at 120 °C for 14 h under inert atmosphere. After cooling to ambient temperature, ethyl acetate (20 mL) and H_2O (5 mL) were added and the phases were separated. The organic phase was washed with brine (2 × 5 mL) and saturated aqueous $NaHCO_3$ (1 × 5 mL) and then dried over anhydrous Na_2SO_4. The solvents were removed under reduced pressure and the crude product was subsequently used in the next step without further purification.

In a flame-dried flask, the resulting indolenine was dissolved in MeOH and H_2O (15 mL, *v*/*v* = 4:1, 0.2M) under inert atmosphere. $NaBH_4$ (277 mg, 6.00 mmol, 2.00 equiv.) was added portionwise at 0 °C. After warming to ambient temperature, the reaction mixture was monitored by TLC and stopped after 2 h. After evaporation of the solvent under reduced pressure, the aqueous phase was extracted with Et_2O (3 × 10 mL). The extracts were washed with brine (2 × 5 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The obtained indoline was directly used in the next step without further purification.

The intermediate was then dissolved in acetic anhydride (2.9 mL, 30 mmol, 10 equiv.) under inert atmosphere at room temperature, followed by addition of pyridine (0.14 mL, 1.8 mmol, 0.60 equiv.). The reaction mixture was heated with an oil bath to 120 °C and maintained at this temperature for 4 h and was afterwards quenched by the addition of NaOH (2M) to pH = 7 with ice-cooling, and the resulting mixture was diluted with ethyl acetate (20 mL). The phases were separated, and the organic phase was washed with saturated aqueous $NaHCO_3$ (1 × 5 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced

pressure. Purification of the residue by flash column chromatography on silica gel (3.5 × 20 cm, cyclohexane:ethyl acetate = 2.5:1 → 2:1, 100 mL, #14–30) afforded the analytically pure arylated product **103** (371 mg, 53%) as a yellow oil.

R_f = 0.21 (cyclohexane:ethyl acetate = 3:1).

GLC (HP-5): t_R = 17.3 min.

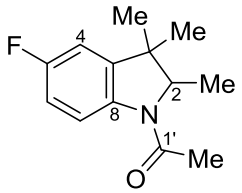
^{1}H NMR (500 MHz, DMSO-d$_6$, 358 K): δ/ppm = 1.13 (d, $^3J_{2-CH_3,2}$ = 6.6 Hz, 3H, 2–CH_3), 1.20 (s, 3H, 3–CH_3)*, 1.33 (s, 3H, 3–CH_3)*, 2.25 (s, 3H, H-2'), 3.79 (s, 3H, 5–OCH_3), 4.20 (q, $^3J_{2,2-CH_3}$ = 6.3 Hz, 1H, H-2), 6.75 (dd, $^3J_{6,7}$ = 8.7 Hz, $^4J_{6,4}$ = 2.6 Hz, 1H, H-6), 6.83 (d, $^4J_{4,6}$ = 2.1 Hz, 1H, H-4), 7.74 (br s, 1H, H-7).

^{13}C NMR (100 MHz, DMSO-d$_6$, 298 K): δ/ppm = 17.4 (2-*C*H$_3$), 20.7 (3-*C*H$_3$)*, 23.7 (3-*C*H$_3$)*, 31.5 (C-2'), 44.0 (C-3), 56.2 (5-O*C*H$_3$), 67.9 (C-2), 109.5 (C-6), 112.5 (C-4), 118.4 (C-7), 134.4 (C-9), 142.9 (C-8), 157.0 (C-5), 168.0 (C-1').

IR (ATR): $\tilde{\nu}$ /cm^{-1} = 2906 (br), 2835 (br), 1648 (s), 1599 (m), 1488 (s), 1459 (m), 1401 (s), 1230 (m), 1194 (m), 1144 (w), 1103 (m), 1054 (s), 946 (w), 840 (m), 799 (w), 699 (w).

HRMS (APCI) for $C_{14}H_{20}NO_2$ ([M+H]$^+$): calcd. 234.1489
found 234.1485

3.1.2.8 1-(5-Fluoro-2,3,3-trimethylindolin-1-yl)ethanone (104)



104
$C_{13}H_{16}FNO$
M = 221:28 g/mol

According to **GP 1**, a flame-dried flask equipped with a magnetic stir bar was successively charged with 4-fluorophenylhydrazine hydrochloride (**112**, 490 mg, 3.00 mmol, 1.00 equiv.) and 3-methylbutan-2-one (**113**, 760 mg, 9.00 mmol, 3.00 equiv.) in acetic acid (0.25 mL, 0.5M) and stirred at 120 °C for 14 h under inert atmosphere. After cooling to ambient

temperature, ethyl acetate (20 mL) and H_2O (5 mL) were added and the phases were separated. The organic phase was washed with brine (2 × 5 mL) and saturated aqueous $NaHCO_3$ (1 × 5 mL) and then dried over anhydrous Na_2SO_4. The solvents were removed under reduced pressure and the crude product was subsequently used in the next step without further purification.

In a flame-dried flask, the resulting indolenine was dissolved in MeOH and H_2O (15 mL, *v*/*v* = 4:1, 0.2M) under inert atmosphere. $NaBH_4$ (277 mg, 6.00 mmol, 2.00 equiv.) was added portionwise at 0 °C. After warming to ambient temperature, the reaction mixture was monitored by TLC and stopped after 2 h. After evaporation of the solvent under reduced pressure, the aqueous phase was extracted with Et_2O (3 × 10 mL). The extracts were washed with brine (2 × 5 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The obtained indoline was directly used in the next step without further purification.

The intermediate was then dissolved in acetic anhydride (2.9 mL, 30 mmol, 10 equiv.) under inert atmosphere at room temperature, followed by addition of pyridine (0.14 mL, 1.8 mmol, 0.60 equiv.). The reaction mixture was heated with an oil bath to 120 °C and maintained at this temperature for 4 h and was afterwards quenched by the addition of NaOH (2M) to pH = 7 with ice-cooling, and the resulting mixture was diluted with ethyl acetate (20 mL). The phases were separated, and the organic phase was washed with saturated aqueous $NaHCO_3$ (1 × 5 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (3.5 × 20 cm, cyclohexane:ethyl acetate = 3:1, 100 mL, #23–43) afforded the analytically pure arylated product **104** (377 mg, 57%) as a light yellow solid.

m.p.: 62–63 °C.

R_f = 0.21 (cyclohexane:ethyl acetate = 3:1).

GLC (HP-5): t_R = 16.5 min.

^{1}H NMR (500 MHz, DMSO-d_6, 358 K): δ/ppm = 1.15 (d, $^3J_{2\text{–}CH_3,2}$ = 6.5 Hz, 3H, 2–C*H*$_3$), 1.22 (s, 3H, 3–C*H*$_3$)*, 1.35 (s, 3H, 3–C*H*$_3$)*, 2.27 (s, 3H, H-2'), 4.24 (q, $^3J_{2,2\text{–}CH_3}$ = 6.5 Hz, 1H, H-2), 6.97 (ddd, $^3J_{6,5\text{–}F}$ = 9.6 Hz, $^3J_{6,7}$ = 9.1 Hz, $^4J_{6,4}$ = 2.8 Hz, 1H, H-6), 7.07 (dd, $^3J_{4,5\text{–}F}$ = 8.5 Hz, $^4J_{4,6}$ = 2.7 Hz, 1H, H-4), 7.86 (br s, 1H, H-7).

^{13}C NMR (100 MHz, DMSO-d_6, 298 K): δ/ppm = 17.3 (2-*C*H$_3$), 20.5 (3-*C*H$_3$)*, 23.8 (3-*C*H$_3$)*, 31.3 (C-2'), 44.0 (C-3), 68.0 (C-2), 110.8 (d, $^3J_{6,5-F}$ = 23.5 Hz, C-6), 114.2 (d, $^3J_{4,5-F}$ = 22.6 Hz, C-4), 118.7 (C-7), 137.1 (C-9), 143.9 (C-8), 159.8 (d, $^2J_{5,5-F}$ = 237.4 Hz, C-5), 168.7 (C-1').

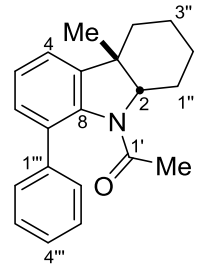
^{19}F NMR (471 MHz, DMSO-d_6, 298 K): δ/ppm = –118.9 (5–F).

IR (ATR): $\tilde{\nu}$ /cm^{-1} = 2983 (w), 2962 (br), 2869 (br), 1650 (s), 1603 (m), 1490 (s), 1395 (s), 1312 (m), 1260 (s), 1177 (s), 1128 (m) 1098 (w), 1074 (w), 988 (w), 922 (w), 870 (s), 831 (s), 799 (m), 683 (m).

HRMS (APCI) for $C_{13}H_{17}FNO$ ([M+H]$^+$): calcd. 222.1289
found 222.1282

3.1.3 Preparation of C-7 Arylated Indolines Using $Na_2S_2O_8$ as Terminal Oxidant

3.1.3.1 *cis*-1-[4a-Methyl-8-phenyl-2,3,4,4a-tetrahydro-1*H*-carbazol-9(9a*H*)-yl]ethanone (*cis*-151)



cis-**151**
$C_{21}H_{23}NO$
M = 305.42 g/mol

According to **GP 3**, a flame-dried SCHLENK tube equipped with a magnetic stir bar was successively charged with *cis*-1-[4a-methyl-2,3,4,4a-tetrahydro-1*H*-carbazol-9(9a*H*)-yl]ethanone (*cis*-**105**, 46 mg, 0.20 mmol, 1.0 equiv.), $Pd(OAc)_2$ (9.0 mg, 0.040 mmol, 20 mol%), $Na_2S_2O_8$ (143 mg, 0.600 mmol, 3.00 equiv.), and TFA (76 µL, 1.0 mmol, 5.0 equiv.) in benzene (**62**, 1.0 mL, 0.2M) under inert atmosphere. The reaction was heated with an oil bath to 100 °C for 14 h and monitored by GLC analysis using tetracosane (10 mg, 0.030 mmol, 15 mol%) as internal standard. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate (5 mL). The crude reaction mixture was washed with

saturated aqueous $NaHCO_3$ (3 mL), and the phases were separated. The aqueous phase was extracted with ethyl acetate (3 × 5 mL), and the combined organic phases were washed with brine (1 × 5 mL) and dried over anhydrous Na_2SO_4. After evaporation of the solvents under reduced pressure, purification of the residue by flash column chromatography on silica gel (2.5 × 20 cm, cyclohexane:ethyl acetate = 4:1, 250 mL, #11–16) afforded the analytically pure arylated product *cis*-**151** (45 mg, 74%) as a white solid.

m.p.: 193–194 °C.

R_f = 0.33 (cyclohexane:ethyl acetate = 3:1).

GLC (HP-5): t_R = 22.4 min.

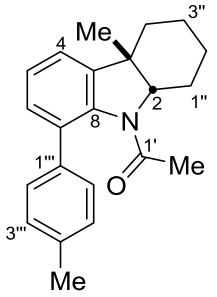
^{1}H NMR (500 MHz, DMSO-d_6, 358 K): δ/ppm = 1.05–1.08 (m, 1H, H-2''), 1.11 (s, 3H, 3–CH_3), 1.29–1.37 (m, 2H, H-2'', H-3''), 1.60–1.65 (m, 3H, H-3'', H-4''), 1.66 (br s, 3H, H-2'), 2.16–2.20 (m, 1H, H-1''A), 2.34–2.37 (m, 1H, H-1''B), 4.30 (dd, $^3J_{2,1''A}$ = 10.0 Hz, $^3J_{2,1''B}$ = 6.1 Hz, 1H, H-2), 7.23–7.29 (m, 3H, H-Ar), 7.32–7.35 (m, 1H, H-Ar), 7.42–7.45 (m, 4H, H-Ar).

^{13}C NMR (126 MHz, DMSO-d_6, 298 K): δ/ppm = 22.8 (C-2'')*, 23.3 (C-3'')*, 23.6 (3–CH$_3$), 29.6 (C-1''), 30.2 (C-2'), 32.9 (C-4''), 44.8 (C-3), 65.9 (C-2), 113.4 (C-4), 117.8 (C-6), 121.9 (C-5), 126.7 (C-4'''), 127.5 (C-2'''), 128.4 (C-3'''), 129.8 (C-7), 139.5 (C-1'''), 143.4 (C-9), 148.0 (C-8), 170.8 (C-1').

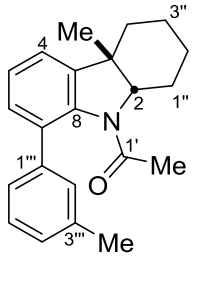
IR (ATR): $\tilde{\nu}$ /cm^{-1} = 3032 (w), 2922 (br), 2855 (w), 1742 (vw), 1650 (s), 1602 (m), 1589 (m), 1511 (w), 1430 (m), 1396 (s), 1378 (m), 1322 (w), 1298 (m), 1241 (w), 1183 (w), 1156 (w), 1058 (w), 1030 (w), 910 (m), 882 (m), 840 (s), 793 (m), 756 (s), 699 (m).

HRMS (APCI) for $C_{21}H_{24}NO$ ($[M+H]^+$): calcd. 306.1852
found 306.1849

3.1.3.2 *cis*-1-[4a-Methyl-8-(*p*-tolyl)-2,3,4,4a-tetrahydro-1*H*-carbazol-9(9a*H*)-yl]ethanone (*cis*-152) and *cis*-1-[4a-methyl-8-(*m*-tolyl)-2,3,4,4a-tetrahydro-1*H*-carbazol-9(9a*H*)-yl]ethanone (*cis*-152')



cis-**152**
$C_{22}H_{25}NO$
M = 319.45 g/mol



cis-**152'**
$C_{22}H_{25}NO$
M = 319.45 g/mol

According to **GP 3**, a flame-dried SCHLENK tube equipped with a magnetic stir bar was successively charged with *cis*-1-[4a-methyl-2,3,4,4a-tetrahydro-1*H*-carbazol-9(9a*H*)-yl]ethanone (*cis*-**105**, 46 mg, 0.20 mmol, 1.0 equiv.), $Pd(OAc)_2$ (9.0 mg, 0.040 mmol, 20 mol%), $Na_2S_2O_8$ (143 mg, 0.600 mmol, 3.00 equiv.), and TFA (76 µL, 1.0 mmol, 5.0 equiv.) in toluene (**141**, 1.0 mL, 0.2M) under inert atmosphere. The reaction was heated with an oil bath to 100 °C for 8 h and monitored by GLC analysis using tetracosane (10 mg, 0.030 mmol, 15 mol%) as internal standard. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate (5 mL). The crude reaction mixture was washed with saturated aqueous $NaHCO_3$ (3 mL), and the phases were separated. The aqueous phase was extracted with ethyl acetate (3 × 5 mL), and the combined organic phases were washed with brine (1 × 5 mL) and dried over anhydrous Na_2SO_4. After evaporation of the solvents under reduced pressure, purification of the residue by flash column chromatography on silica gel (2.5 × 20 cm, cyclohexane:ethyl acetate = 6:1, 50 mL, #9–14) afforded the analytically pure arylated product *cis*-**152** and *cis*-**152'** (46 mg, 72% combined yield; ratio of regioisomers: *cis*-**152**: *cis*-**152'** = 53:47) as a light yellow oil.

Analytical data for *cis*-**152** (major isomer):

R_f = 0.44 (cyclohexane:ethyl acetate = 3:1).

GLC (HP-5): t_R = 23.8 min.

^{1}H NMR (500 MHz, DMSO-d_6, 358 K): δ/ppm = 1.05–1.08 (m, 1H, H-2''), 1.11 (s, 3H, 3–C*H*$_3$), 1.30–1.33 (m, 2H, H-2'', H-3''), 1.61–1.64 (m, 3H, H-3'', H-4''), 1.66 (br s, 3H, H-2'), 2.18–

2.20 (m, 1H, H-1''A), 2.33–2.35 (m, 1H, H-1''B), 2.38 (s, 3H, 4'''–C*H*$_3$), 4.31 (dd, $^3J_{2,1''A}$ = 10.1 Hz, $^3J_{2,1''B}$ = 6.2 Hz, 1H, H-2), 7.08–7.15 (m, 1H, H-Ar), 7.21–7.30 (m, 5H, H-Ar), 7.32 (d, $^3J_{6,5}$ = 8.1 Hz, 1H, H-6).

^{13}C NMR (100 MHz, DMSO-d$_6$, 298 K): δ/ppm = 22.1 (4'''–*C*H$_3$), 22.8 (C-2'')*, 23.6 (C-3'')*, 23.7 (3–*C*H$_3$), 29.5 (C-1''), 30.2 (C-2'), 32.9 (C-4''), 44.9 (C-3), 69.7 (C-2), 117.8 (C-4), 121.8 (C-6), 124.7 (C-5), 126.6 (C-7), 127.6 (C-2'''), 130.5 (C-3'''), 132.6 (C-1'''), 139.5 (C-4'''), 143.4 (C-9), 148.2 (C-8), 170.9 (C-1').

HRMS (APCI) for $C_{22}H_{26}NO$ ([M+H]$^+$): calcd. 320.2009
found 320.2007

Analytical data for *cis*-**152'** (minor isomer):

R_f = 0.44 (cyclohexane:ethyl acetate = 3:1).

GLC (HP-5): t_R = 22.9 min.

^{1}H NMR (500 MHz, DMSO-d$_6$, 358 K): δ/ppm = 1.05–1.08 (m, 1H, H-2''), 1.10 (s, 3H, 3–C*H*$_3$), 1.30–1.33 (m, 2H, H-2'', H-3''), 1.61–1.64 (m, 3H, H-3'', H-4''), 1.66 (br s, 3H, H-2'), 2.18–2.20 (m, 1H, H-1''A), 2.33–2.35 (m, 1H, H-1''B), 2.38 (s, 3H, 3'''–C*H*$_3$), 4.31 (dd, $^3J_{2,1''A}$ = 10.1 Hz, $^3J_{2,1''B}$ = 6.2 Hz, 1H, H-2), 7.08–7.15 (m, 1H, H-Ar), 7.21–7.30 (m, 5H, H-Ar), 7.32 (m, 1H, H-6).

^{13}C NMR (100 MHz, DMSO-d$_6$, 298 K): δ/ppm = 21.7 (3'''–*C*H$_3$), 22.6 (C-2'')*, 23.4 (C-3'')*, 23.6 (3–*C*H$_3$), 29.1 (C-1''), 30.2 (C-2'), 32.5 (C-4''), 44.4 (C-3), 69.5 (C-2), 113.5 (C-4), 117.8 (C-6), 121.7 (C-6'''), 127.3 (C-7), 128.4 (C-2'''), 129.7 (C-4'''), 130.2 (C-7), 132.6 (C-5'''), 132.9 (C-1'''), 138.5 (C-3'''), 143.0 (C-9), 148.2 (C-8), 170.2 (C-1').

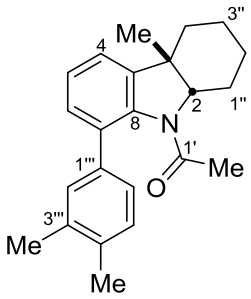
HRMS (APCI) for $C_{22}H_{26}NO$ ([M+H]$^+$): calcd. 320.2009
found 320.2007

IR data for *cis*-**152** and *cis*-**152'**:

IR (ATR): □ /cm^{-1} = 3046 (w), 2924 (br), 2854 (w), 1711 (w), 1655 (s), 1606 (m), 1596 (m), 1500 (w), 1463 (m), 1430 (m), 1413 (w), 1400 (s), 1370 (s), 1333 (m), 1302 (w), 1286 (m),

1248 (s), 1174 (w), 1110 (m), 1054 (m), 998 (w), 965 (w), 929 (w), 843 (w), 822 (m), 794 (m), 758 (s), 738 (m).

3.1.3.3 *cis*-1-[8-(3,4-Dimethylphenyl)-4a-methyl-2,3,4,4a-tetrahydro-1*H*-carbazol-9(9a*H*)-yl]ethanone (*cis*-140)



cis-**140**
$C_{23}H_{27}NO$
M = 333.48 g/mol

According to **GP 3**, a flame-dried SCHLENK tube equipped with a magnetic stir bar was successively charged with *cis*-1-[4a-methyl-2,3,4,4a-tetrahydro-1*H*-carbazol-9(9a*H*)-yl]ethanone (*cis*-**105**, 46 mg, 0.20 mmol, 1.0 equiv.), $Pd(OAc)_2$ (9.0 mg, 0.040 mmol, 20 mol%), $Na_2S_2O_8$ (143 mg, 0.600 mmol, 3.00 equiv.), and TFA (76 µL, 1.0 mmol, 5.0 equiv.) in *o*-xylene (**94**, 1.0 mL, 0.2M) under inert atmosphere. The reaction was heated with an oil bath to 100 °C for 12 h and monitored by GLC analysis using tetracosane (10 mg, 0.030 mmol, 15 mol%) as internal standard. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate (5 mL). The crude reaction mixture was washed with saturated aqueous $NaHCO_3$ (3 mL), and the phases were separated. The aqueous phase was extracted with ethyl acetate (3 × 5 mL), and the combined organic phases were washed with brine (1 × 5 mL) and dried over anhydrous Na_2SO_4. After evaporation of the solvents under reduced pressure, purification of the residue by flash column chromatography on silica gel (2.5 × 20 cm, cyclohexane:ethyl acetate = 6:1, 50 mL, #11–17) afforded the analytically pure arylated product *cis*-**140** (59 mg, 88%) as a yellow solid.

m.p.: 181–182 °C.

R_f = 0.45 (cyclohexane:ethyl acetate = 3:1).

GLC (HP-5): t_R = 23.9 min.

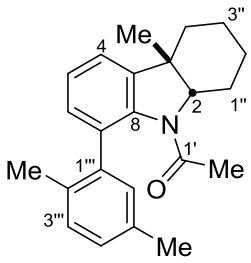
^{1}H NMR (500 MHz, DMSO-d_6, 358 K): δ/ppm = 1.02–1.07 (m, 1H, H-2''), 1.09 (s, 3H, 3–C*H*$_3$), 1.29–1.36 (m, 2H, H-2'', H-3''), 1.58–1.65 (m, 3H, H-3'', H-4''), 1.62 (br s, 3H, H-2'), 2.13–2.17 (m, 1H, H-1''A), 2.28 (s, 6H, 3'''–C*H*$_3$, 4'''–C*H*$_3$), 2.33–2.36 (m, 1H, H-1''B), 4.31 (dd, $^3J_{2,1''A}$ = 10.2 Hz, $^3J_{2,1''B}$ = 6.1 Hz, 1H, H-2), 7.13–7.19 (m, 2H, H-4, H-6), 7.21–7.27 (m, 4H, H-5, H-2''', H-5''', H-6''').

^{13}C NMR (126 MHz, DMSO-d_6, 298 K): δ/ppm = 20.0 (3'''–*C*H$_3$)*, 20.5 (4'''–*C*H$_3$)*, 22.8 (C-2'')**, 23.5 (C-3'')**, 23.7 (3–*C*H$_3$), 29.4 (C-1''), 30.2 (C-2'), 32.9 (C-4''), 45.0 (C-3), 69.5 (C-2), 115.4 (C-4), 123.0 (C-5), 125.8 (C-6'''), 127.4 (C-2'''), 129.6 (C-6), 130.5 (C-5'''), 131.2 (C-7), 131.5 (C-1'''), 137.0 (C-3''')***, 137.4 (C-4''')***, 139.1 (C-9), 145.6 (C-8), 170.2 (C-1').

IR (ATR): $\tilde{\nu}$ /cm^{-1} = 2929 (m), 2857 (w), 1638 (s), 1595 (w), 1505 (w), 1435 (m), 1426 (m), 1385 (m), 1372 (s), 1308 (m), 1275 (w), 1233 (w), 1057 (w), 1031 (w), 882 (w), 827 (w), 793 (s), 754 (s), 718 (w).

HRMS (APCI) for $C_{23}H_{28}NO$ ([M+H]$^+$): calcd. 334.2165
found 334.2164

3.1.3.4 *cis*-1-[8-(2,5-Dimethylphenyl)-4a-methyl-2,3,4,4a-tetrahydro-1*H*-carbazol-9(9a*H*)-yl]ethanone (*cis*-160)



cis-**160**
$C_{23}H_{27}NO$
M = 333.48 g/mol

According to **GP 3**, a flame-dried SCHLENK tube equipped with a magnetic stir bar was successively charged with *cis*-1-[4a-methyl-2,3,4,4a-tetrahydro-1*H*-carbazol-9(9a*H*)-yl]ethanone (*cis*-**105**, 46 mg, 0.20 mmol, 1.0 equiv.), $Pd(OAc)_2$ (9.0 mg, 0.040 mmol, 20 mol%), $Na_2S_2O_8$ (143 mg, 0.600 mmol, 3.00 equiv.), and TFA (76 µL, 1.0 mmol, 5.0 equiv.) in *p*-xylene (**149**, 1.0 mL, 0.2M) under inert atmosphere. The reaction was heated with an oil bath to 100 °C for 14 h and monitored by GLC analysis using tetracosane (10 mg,

0.030 mmol, 15 mol%) as internal standard. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate (5 mL). The crude reaction mixture was washed with saturated aqueous $NaHCO_3$ (3 mL), and the phases were separated. The aqueous phase was extracted with ethyl acetate (3 × 5 mL), and the combined organic phases were washed with brine (1 × 5 mL) and dried over anhydrous Na_2SO_4. After evaporation of the solvents under reduced pressure, purification of the residue by flash column chromatography on silica gel (2.5 × 20 cm, cyclohexane:ethyl acetate = 5:1, 50 mL, #8–13) afforded the analytically pure arylated product *cis*-**160** (27 mg, 14%) as a yellow solid.

m.p.: 177–178 °C.

R_f = 0.39 (cyclohexane:ethyl acetate = 3:1).

GLC (HP-5): t_R = 23.0 min.

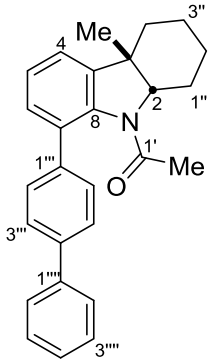
^{1}H NMR (500 MHz, DMSO-d_6, 358 K): δ/ppm = 1.06–1.16 (m, 1H, H-2''), 1.13 (s, 3H, 3–CH_3), 1.28–1.36 (m, 3H, H-2'', H-3''), 1.58–1.67 (m, 2H, H-4''), 1.64 (br s, 3H, H-2'), 2.10–2.18 (m, 1H, H-1''A), 2.29 (s, 3H, 2'''–CH_3)*, 2.32–2.36 (m, 1H, H-1''B), 2.37 (s, 3H, 5'''–CH_3)*, 4.24 (dd, $^3J_{2,1''A}$ = 10.2 Hz, $^3J_{2,1''B}$ = 6.4 Hz, 1H, H-2), 6.89–6.95 (m, 1H, H-4), 7.05 (d, $^3J_{6,5}$ = 8.2 Hz, 1H, H-6), 7.07–7.11 (m, 1H, H-5), 7.16–7.18 (m, 1H, H-3'''), 7.20–7.22 (m, 1H, H-4'''), 7.24 (s, 1H, H-6''').

^{13}C NMR (126 MHz, DMSO-d_6, 298 K): δ/ppm = 21.5 (2'''–CH$_3$)*, 22.6 (5'''–CH$_3$)*, 22.8 (3–CH$_3$), 23.3 (C-2'')**, 23.6 (C-3'')**, 29.4 (C-1''), 32.5 (C-2'), 32.9 (C-4''), 44.4 (C-3), 69.7 (C-2), 113.5 (C-4), 117.8 (C-6), 121.7 (C-5), 125.5 (C-6'''), 125.7 (C-4'''), 128.6 (C-3'''), 129.4 (C-7), 129.7 (C-1'''), 130.4 (C-5''')***, 131.4 (C-2''')***, 131.8 (C-9), 139.9 (C-8), 170.8 (C-1').

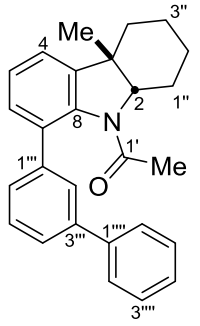
IR (ATR): $\tilde{\nu}$ /cm^{-1} = 2927 (m), 2877 (w), 1711 (w), 1646 (s), 1597 (w), 1512 (m), 1415 (s), 1406 (m), 1382 (m), 1367 (s), 1312 (m), 1298 (w), 1274 (w), 1243 (w), 1118 (w), 1058 (w), 1022 (w), 989 (m), 884 (w), 817 (w), 790 (s), 756 (s), 708 (w), 696 (w).

HRMS (APCI) for $C_{23}H_{28}NO$ ($[M+H]^+$): calcd. 334.2165
found 334.2164

3.1.3.5 *cis*-1-{8-[(1,1'-Biphenyl)-3-yl]-4a-methyl-2,3,4,4a-tetrahydro-1*H*-carbazol-9(9a*H*)-yl}ethanone (*cis*-153) and *cis*-1-{8-[(1,1'-biphenyl)-4-yl]-4a-methyl-2,3,4,4a-tetrahydro-1*H*-carbazol-9(9a*H*)-yl}ethanone (*cis*-153')



cis-**153**
$C_{27}H_{27}NO$
M = 381.52 g/mol



cis-**153'**
$C_{27}H_{27}NO$
M = 381.52 g/mol

According to **GP 3**, a flame-dried SCHLENK tube equipped with a magnetic stir bar was successively charged with *cis*-1-[4a-methyl-2,3,4,4a-tetrahydro-1*H*-carbazol-9(9a*H*)-yl]ethanone (*cis*-**105**, 46 mg, 0.20 mmol, 1.0 equiv.), $Pd(OAc)_2$ (9.0 mg, 0.040 mmol, 20 mol%), $Na_2S_2O_8$ (143 mg, 0.600 mmol, 3.00 equiv.), and TFA (76 µL, 1.0 mmol, 5.0 equiv.) in biphenyl (**142**, 1.0 mL, 0.2M) under inert atmosphere. The reaction mixture was heated with an oil bath to 120 °C for 14 h and monitored by GLC analysis using tetracosane (10 mg, 0.030 mmol, 15 mol%) as internal standard. After cooling to room temperature, the reaction was diluted with ethyl acetate (5 mL). The crude reaction mixture was washed with saturated aqueous $NaHCO_3$ (3 mL) and the phases were separated. The aqueous phase was extracted with ethyl acetate (3 × 5 mL), and the combined organic phases were washed with brine (1 × 5 mL), and dried over anhydrous Na_2SO_4. After evaporation of the solvents under reduced pressure, purification of the residue by flash column chromatography on silica gel (2.5 × 20 cm, cyclohexane:ethyl acetate = 6:1, 50 mL, #15–19) afforded the analytically pure arylated product *cis*-**153** and *cis*-**153'** (37 mg, 48% combined yield; ratio of regioisomers: *cis*-**153**: *cis*-**153'** = 77:23) as a light yellow solid.

Analytical data for *cis*-**153** (major isomer):

R_f = 0.44 (cyclohexane:ethyl acetate = 3:1).

GLC (HP-5): t_R = 31.8 min.

^{1}H NMR (500 MHz, DMSO-d_6, 358 K): δ/ppm = 1.07–1.17 (m, 1H, H-2''), 1.13 (s, 3H, 3–C*H*$_3$), 1.30–1.40 (m, 2H, H-2'', H-3''), 1.57–1.67 (m, 3H, H-3'', H-4''), 1.76 (br s, 3H, H-2'), 2.21–2.24 (m, 1H, H-1''A), 2.35–2.38 (m, 1H, H-1''B), 4.31 (dd, $^3J_{2,1''A}$ = 10.1 Hz, $^3J_{2,1''B}$ = 6.2 Hz, 1H, H-2), 7.24–7.72 (m, 10H, H-Ar), 7.75 (d, $^3J_{2'''',3''''}$ = 8.1 Hz, 2H, H-2'''').

^{13}C NMR (100 MHz, DMSO-d_6, 298 K): δ/ppm = 22.8 (C-2'')*, 23.5 (3–*C*H$_3$), 27.7 (C-3'')*, 30.2 (C-1''), 31.1 (C-2'), 32.9 (C-4''), 45.0 (C-3), 69.7 (C-2), 113.4 (C-4), 117.8 (C-6), 122.1 (C-5), 123.5 (C-3''''), 124.6 (C-7), 126.7 (C-2'''), 126.8 (C-3'''), 127.4 (C-4'''), 127.5 (C-4''''), 127.6 (C-2''''), 128.3 (C-1''''), 128.6 (C-9), 129.9 (C-1'''), 140.5 (C-8), 170.7 (C-1').

HRMS (APCI) for $C_{27}H_{28}NO$ ([M+H]$^+$): calcd. 382.2165
found 382.2163

Analytical data for *cis*-**153'** (minor isomer):

R_f = 0.44 (cyclohexane:ethyl acetate = 3:1).

GLC (HP-5): t_R = 29.7 min.

^{1}H NMR (500 MHz, DMSO-d_6, 358 K): δ/ppm = 1.07–1.17 (m, 1H, H-2''), 1.13 (s, 3H, 3–C*H*$_3$), 1.30–1.40 (m, 2H, H-2'', H-3''), 1.57–1.67 (m, 3H, H-3'', H-4''), 1.76 (br s, 3H, H-2'), 2.21–2.24 (m, 1H, H-1''A), 2.35–2.38 (m, 1H, H-1''B), 4.31 (dd, $^3J_{2,1''A}$ = 10.1 Hz, $^3J_{2,1''B}$ = 6.2 Hz, 1H, H-2), 6.72–6.75 (m, 4H, H-Ar), 6.89–6.91 (m, 1H, H-Ar), 7.18–7.20 (m, 3H, H-Ar), 7.35–7.38 (m, 2H, H-Ar), 7.43–7.45 (m, 2H, H-Ar).

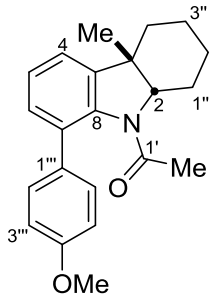
^{13}C NMR (100 MHz, DMSO-d_6, 298 K): δ/ppm = 22.6 (C-2'')*, 23.3 (3–*C*H$_3$), 27.5 (C-3'')*, 29.1 (C-1''), 31.1 (C-2'), 32.5 (C-4''), 44.4 (C-3), 69.5 (C-2), 113.4 (C-4), 117.8 (C-6), 120.6 (C-5), 123.5 (C-6'''), 124.6 (C-7), 126.7 (C-2'''), 126.7 (C-3'''), 126.9 (C-4'''), 127.4 (C-5'''), 127.5 (C-4''''), 127.6 (C-2''''), 128.0 (C-3''''), 128.4 (C-9), 129.8 (C-1''''), 129.9 (C-1'''), 139.4 (C-8), 170.7 (C-1').

HRMS (APCI) for $C_{27}H_{28}NO$ ([M+H]$^+$): calcd. 382.2165
found 382.2163

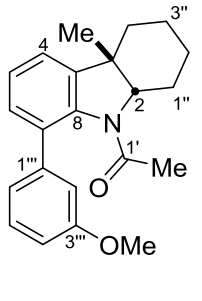
IR data for *cis*-**153** and *cis*-**153'**:

IR (ATR): $\tilde{\nu}$ /cm^{-1} = 2924 (br), 2854 (w), 1711 (w), 1653 (s), 1596 (w), 1440 (m), 1429 (s), 1369 (s), 1302 (m), 1264 (m), 1222 (m), 1182 (w), 1076 (w), 843 (w), 794 (w), 766 (s), 738 (m), 696 (s).

3.1.3.6 *cis*-1-[8-(4-Methoxyphenyl)-4a-methyl-2,3,4,4a-tetrahydro-1*H*-carbazol-9(9a*H*)-yl]ethanone (*cis*-154) and *cis*-1-[8-(3-methoxyphenyl)-4a-methyl-2,3,4,4a-tetrahydro-1*H*-carbazol-9(9a*H*)-yl]ethanone (*cis*-154')



cis-**154**
$C_{22}H_{25}NO_2$
M = 335.45 g/mol



cis-**154'**
$C_{22}H_{25}NO_2$
M = 335.45 g/mol

According to **GP 3**, a flame-dried SCHLENK tube equipped with a magnetic stir bar was successively charged with *cis*-1-[4a-methyl-2,3,4,4a-tetrahydro-1*H*-carbazol-9(9a*H*)-yl]ethanone (*cis*-**105**, 46 mg, 0.20 mmol, 1.0 equiv.), $Pd(OAc)_2$ (9.0 mg, 0.040 mmol, 20 mol%), $Na_2S_2O_8$ (143 mg, 0.600 mmol, 3.00 equiv.), and TFA (76 µL, 1.0 mmol, 5.0 equiv.) in phenyl methyl ether (**143**, 1.0 mL, 0.2M) under inert atmosphere. The reaction was heated with an oil bath to 120 °C for 24 h and monitored by GLC analysis using tetracosane (10 mg, 0.030 mmol, 15 mol%) as internal standard. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate (5 mL). The crude reaction mixture was washed with saturated aqueous $NaHCO_3$ (3 mL) and the phases were separated. The aqueous phase was extracted with ethyl acetate (3 × 5 mL), and the combined organic phases were washed with brine (1 × 5 mL), and dried over anhydrous Na_2SO_4. After evaporation of the solvents under reduced pressure, purification of the residue by flash column chromatography on silica gel (2.5 × 20 cm, cyclohexane:ethyl acetate = 4:1, 50 mL, #9–13) afforded the analytically pure arylated product *cis*-**154** and *cis*-**154'** (55 mg, 82% combined yield; ratio of regioisomers: *cis*-**154**: *cis*-**154'** = 86:14) as a yellow solid.

Analytical data for *cis*-**154** (major isomer):

R_f = 0.33 (cyclohexane:ethyl acetate = 3:1).

GLC (HP-5): t_R = 28.5 min.

^{1}H NMR (500 MHz, DMSO-d$_6$, 358 K): δ/ppm = 1.04–1.09 (m, 1H, H-2''), 1.10 (s, 3H, 3–C*H*$_3$), 1.31–1.35 (m, 2H, H-2'', H-3''), 1.60–1.66 (m, 3H, H-3'', H-4''), 1.67 (br s, 3H, H-2'), 2.13–2.18 (m, 1H, H-1''A), 2.32–2.37 (m, 1H, H-1''B), 3.83 (s, 3H, 4'''–OC*H*$_3$), 4.31 (dd, $^3J_{2,1''A}$ = 10.2 Hz, $^3J_{2,1''B}$ = 6.1 Hz, 1H, H-2), 7.01 (d, $^3J_{3''',2'''}$ = 8.8 Hz, 2H, H-3'''), 7.18–7.24 (m, 3H, H-4, H-5, H-6), 7.38 (d, $^3J_{2''',3'''}$ = 8.8 Hz, 2H, H-2''').

^{13}C NMR (100 MHz, DMSO-d$_6$, 298 K): δ/ppm = 22.8 (C-2'')*, 23.6 (3–*C*H$_3$), 29.5 (C-3'')*, 30.2 (C-1''), 32.4 (C-2'), 33.0 (C-4''), 44.9 (C-3), 56.0 (4'''–O*C*H$_3$), 69.5 (C-2), 113.6 (C-3'''), 115.2 (C-4), 121.4 (C-6), 126.6 (C-5), 128.0 (C-2'''), 128.9 (C-7), 129.6 (C-1'''), 139.4 (C9), 143.5 (C-8), 159.2 (C-4'''), 170.1 (C-1').

HRMS (APCI) for $C_{22}H_{26}NO_2$ ([M+H]$^+$): calcd. 336.1958
found 336.1957

Analytical data for *cis*-**154'** (minor isomer):

R_f = 0.33 (cyclohexane:ethyl acetate = 3:1).

GLC (HP-5): t_R = 27.7 min.

^{1}H NMR (500 MHz, DMSO-d$_6$, 358 K): δ/ppm = 1.04–1.09 (m, 1H, H-2''), 1.10 (s, 3H, 3–C*H*$_3$), 1.31–1.35 (m, 2H, H-2'', H-3''), 1.60–1.66 (m, 3H, H-3'', H-4''), 1.67 (br s, 3H, H-2'), 2.13–2.18 (m, 1H, H-1''A), 2.32–2.37 (m, 1H, H-1''B), 3.93 (s, 3H, 3'''–OC*H*$_3$), 4.31 (dd, $^3J_{2,1''A}$ = 10.2 Hz, $^3J_{2,1''B}$ = 6.1 Hz, 1H, H-2), 6.87–6.89 (m, 2H, H-4, H-6), 7.08–7.10 (m, 1H, H-5), 7.24–7.28 (m, 2H, H-2''', H-5'''), 7.61 (d, $^3J_{6''',5'''}$ = 8.8 Hz, 1H, H-6'''), 7.87 (d, $^3J_{4''',5'''}$ = 9.1 Hz, 1H, H-4''').

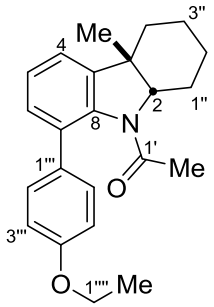
^{13}C NMR (100 MHz, DMSO-d$_6$, 298 K): δ/ppm = 22.7 (C-2'')*, 23.0 (3–*C*H$_3$), 29.5 (C-3'')*, 30.2 (C-1''), 32.4 (C-2'), 33.0 (C-4''), 44.3 (C-3), 55.8 (3'''–O*C*H$_3$), 69.5 (C-2), 115.2 (C-4'''), 118.3 (C-2'''), 124.6 (C-4), 126.6 (C-6), 128.0 (C-5), 129.8 (C-7), 130.7 (C-6'''), 131.0 (C-5'''), 133.0 (C-1'''), 142.0 (C-9), 143.5 (C-8), 160.1 (C-3'''), 170.1 (C-1').

HRMS (APCI) for $C_{22}H_{26}NO_2$ ([M+H]$^+$): calcd. 336.1958
found 336.1957

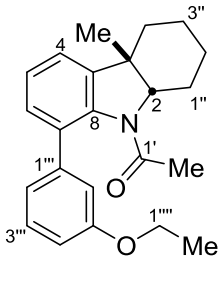
IR data for *cis*-**154** and *cis*-**154'**:

IR (ATR): $\tilde{\nu}$ /cm^{-1} = 3051 (w), 2922 (br), 2855 (br), 1734 (vw), 1642 (s), 1598 (m), 1512 (m), 1473 (m), 1446 (m), 1423 (m), 1402 (s), 1371 (s), 1320 (m), 1305 (w), 1283 (m), 1244 (s), 1173 (m), 1107 (w), 1030 (m), 990 (w), 970 (w), 928 (w), 874 (w), 832 (m), 796 (m), 758 (s), 699 (w).

3.1.3.7 *cis*-1-[8-(4-Ethoxyphenyl)-4a-methyl-2,3,4,4a-tetrahydro-1*H*-carbazol-9(9a*H*)-yl]ethanone (*cis*-155) and *cis*-1-[8-(3-ethoxyphenyl)-4a-methyl-2,3,4,4a-tetrahydro-1*H*-carbazol-9(9a*H*)-yl]ethanone (*cis*-155')



cis-**155**
$C_{23}H_{27}NO_2$
M = 349.47 g/mol



cis-**155'**
$C_{23}H_{27}NO_2$
M = 349.47 g/mol

According to **GP 3**, a flame-dried SCHLENK tube equipped with a magnetic stir bar was successively charged with *cis*-1-[4a-methyl-2,3,4,4a-tetrahydro-1*H*-carbazol-9(9a*H*)-yl]ethanone (*cis*-**105**, 46 mg, 0.20 mmol, 1.0 equiv.), $Pd(OAc)_2$ (9.0 mg, 0.040 mmol, 20 mol%), $Na_2S_2O_8$ (143 mg, 0.600 mmol, 3.00 equiv.), and TFA (76 µL, 1.0 mmol, 5.0 equiv.) in phenyl ethyl ether (**144**, 1.0 mL, 0.2M) under inert atmosphere. The reaction was heated with an oil bath to 120 °C for 14 h and monitored by GLC analysis using tetracosane (10 mg, 0.030 mmol, 15 mol%) as internal standard. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate (5 mL). The crude reaction mixture was washed with saturated aqueous $NaHCO_3$ (3 mL) and the phases were separated. The aqueous phase was extracted with ethyl acetate (3 × 5 mL), and the combined organic phases were washed with brine (1 × 5 mL), and dried over anhydrous Na_2SO_4. After evaporation of the solvents under reduced pressure, purification of the residue by flash column chromatography on silica gel (2.5 × 20 cm, cyclohexane:ethyl acetate = 5:1, 50 mL, #15–20) afforded the analytically pure arylated product *cis*-**155** and *cis*-**155'** (35 mg, 50% combined yield; ratio of regioisomers: *cis*-**155**: *cis*-**155'** > 95:5) as a yellow solid.

Analytical data for *cis*-**155** (major isomer):

R_f = 0.38 (cyclohexane:ethyl acetate = 3:1).

GLC (HP-5): t_R = 25.0 min.

^{1}H NMR (500 MHz, DMSO-d_6, 358 K): δ/ppm = 1.04–1.09 (m, 1H, H-2''), 1.10 (s, 3H, 3–CH_3), 1.30–1.36 (m, 2H, H-2'', H-3''), 1.39 (t, $^3J_{2'''',1''''}$ = 7.0 Hz, 3H, H-2''''), 1.60–1.64 (m, 3H, H-3'', H-4''), 1.66 (br s, 3H, H-2'), 2.13–2.17 (m, 1H, H-1''A), 2.32–2.37 (m, 1H, H-1''B), 4.12 (q, $^3J_{1'''',2''''}$ = 7.4 Hz, 2H, H-1''''), 4.30 (dd, $^3J_{2,1''A}$ = 10.1 Hz, $^3J_{2,1''B}$ = 6.2 Hz, 1H, H-2), 6.99 (d, $^3J_{4,5}$ = 8.9 Hz, 1H, H-4), 7.19 (d, $^3J_{2''',3'''}$ = 7.0 Hz, 2H, H-2'''), 7.21–7.27 (m, 2H, H-5, H-6), 7.36 (d, $^3J_{3''',2'''}$ = 8.6 Hz, 2H, H-3''').

^{13}C NMR (100 MHz, DMSO-d_6, 298 K): δ/ppm = 15.6 (C-2''''), 22.8 (C-2'')*, 23.6 (3–CH$_3$), 29.5 (C-3'')*, 30.2 (C-1''), 31.2 (C-2'), 33.0 (C-4''), 44.9 (C-3), 63.9 (C-1''''), 69.5 (C-2), 113.5 (C-4), 115.7 (C-3'''), 117.8 (C-6), 122.5 (C-5), 128.9 (C-2'''), 129.6 (C-7), 139.5 (C-1'''), 143.5 (C-9), 148.0 (C-8), 159.8 (C-4'''), 170.8 (C-1').

HRMS (APCI) for $C_{23}H_{28}NO_2$ ([M+H]$^+$): calcd. 350.2115
found 350.2113

Analytical data for *cis*-**155'** (minor isomer):

R_f = 0.38 (cyclohexane:ethyl acetate = 3:1).

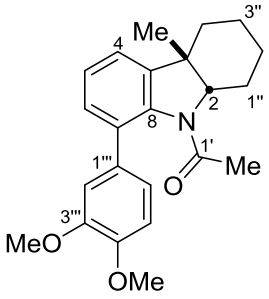
GLC (HP-5): t_R = 26.9 min.

HRMS (APCI) for $C_{23}H_{28}NO_2$ ([M+H]$^+$): calcd. 350.2115
found 350.2113

IR data for *cis*-**155** and *cis*-**155'**:

IR (ATR): $\tilde{\nu}$ /cm^{-1} = 2950 (br), 2922 (br), 2854 (w), 1733 (vw), 1655 (s), 1601 (m), 1580 (w), 1544 (w), 1501 (w), 1489 (m), 1472 (w), 1406 (m), 1358 (w), 1254 (s), 1241 (m), 1209 (w), 1115 (w), 1086 (m), 1070 (w), 989 (w), 864 (m), 830 (m), 788 (m), 746 (s), 695 (m).

3.1.3.8 *cis*-1-[8-(3,4-Dimethoxyphenyl)-4a-methyl-2,3,4,4a-tetrahydro-1*H*-carbazol-9(9a*H*)-yl]-ethanone (*cis*-158)



cis-**158**

$C_{23}H_{27}NO_3$

M = 365.47 g/mol

According to **GP 3**, a flame-dried SCHLENK tube equipped with a magnetic stir bar was successively charged with *cis*-1-[4a-methyl-2,3,4,4a-tetrahydro-1*H*-carbazol-9(9a*H*)-yl]ethanone (*cis*-**105**, 46 mg, 0.20 mmol, 1.0 equiv.), $Pd(OAc)_2$ (9.0 mg, 0.040 mmol, 20 mol%), $Na_2S_2O_8$ (143 mg, 0.600 mmol, 3.00 equiv.), and TFA (76 µL, 1.0 mmol, 5.0 equiv.) in 1,2-dimethoxybenzene (**147**, 1.0 mL, 0.2M) under inert atmosphere. The reaction was heated with an oil bath to 120 °C for 14 h and monitored by GLC analysis using tetracosane (10 mg, 0.030 mmol, 15 mol%) as internal standard. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate (5 mL). The crude reaction was washed with saturated aqueous $NaHCO_3$ (3 mL) and the phases were separated. The aqueous phase was extracted with ethyl acetate (3 × 5 mL), and the combined organic phases were washed with brine (1 × 5 mL), and dried over anhydrous Na_2SO_4. After evaporation of the solvents under reduced pressure, purification of the residue by flash column chromatography on silica gel (2.5 × 20 cm, cyclohexane:ethyl acetate = 2.5:1 → 2:1, 100 mL, #27–35) afforded the analytically pure arylated product *cis*-**158** (52 mg, 71%) as a light brown solid.

m.p.: 156–158 °C.

R_f = 0.15 (cyclohexane:ethyl acetate = 2:1).

GLC (HP-5): t_R = 25.7 min.

^{1}H NMR (500 MHz, DMSO-d_6, 358 K): δ/ppm = 1.05–1.07 (m, 1H, H-2''), 1.11 (s, 3H, 3–C*H*$_3$), 1.31–1.40 (m, 2H, H-2'', H-3''), 1.61–1.66 (m, 3H, H-3'', H-4''), 1.69 (br s, 3H, H-2'), 2.13–2.17 (m, 1H, H-1''A), 2.29–2.35 (m, 1H, H-1''B), 3.79 (s, 3H, 3'''–OC*H*$_3$), 3.84 (s, 3H, 4'''–

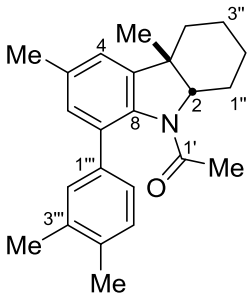
OC*H*$_3$), 4.31 (dd, $^3J_{2,1''A}$ = 10.1 Hz, $^3J_{2,1''B}$ = 6.3 Hz, 1H, H-2), 7.01–7.05 (m, 3H, H-4, H-5, H-6), 7.20 (dd, $^3J_{5''',6'''}$ = 6.9 Hz, 1H, H-5'''), 7.23–7.29 (m, 2H, H-2''', H-6''').

^{13}C NMR (126 MHz, DMSO-d$_6$, 298 K): δ/ppm = 22.8 (C-2'')*, 23.6 (3–*C*H$_3$), 24.8 (C-3'')*, 29.4 (C-1''), 30.2 (C-2'), 33.0 (C-4''), 44.8 (C-3), 56.2 (3'''–O*C*H$_3$), 56.4 (4'''–O*C*H$_3$), 69.5 (C-2), 111.4 (C-5'''), 113.1 (C-2'''), 120.0 (C-6), 121.5 (C-4), 126.6 (C-5), 129.5 (C-6'''), 133.5 (C-7), 135.8 (C-1'''), 139.4 (C-9), 143.5 (C-8), 148.8 (C-4'''), 149.7 (C-3'''), 170.6 (C-1').

IR (ATR): $\tilde{\nu}$ /cm^{-1} = 2950 (w), 2922 (br), 2852 (w), 1716 (w), 1647 (s), 1607 (w), 1513 (m), 1462 (w), 1431 (m), 1402 (m), 1373 (s), 1345 (w), 1248 (s), 1207 (s), 1173 (m), 1137 (m), 1063 (w), 1017 (s), 863 (m), 822 (m), 795 (s), 763 (m), 755 (s).

HRMS (APCI) for $C_{23}H_{28}NO_3$ ([M+H]$^+$): calcd. 366.2064
found 366.2063

3.1.3.9 *cis*-1-[8-(3,4-Dimethylphenyl)-4a,6-dimethyl-2,3,4,4a-tetrahydro-1*H*-carbazol-9(9a*H*)-yl]-ethanone (*cis*-162)



cis-**162**
$C_{24}H_{29}NO$
M = 347.50 g/mol

According to **GP 3**, a flame-dried SCHLENK tube equipped with a magnetic stir bar was successively charged with *cis*-1-[4a,6-dimethyl-2,3,4,4a-tetrahydro-1*H*-carbazol-9(9a*H*)-yl]ethanone (*cis*-**106**, 49 mg, 0.20 mmol, 1.0 equiv.), $Pd(OAc)_2$ (9.0 mg, 0.040 mmol, 20 mol%), $Na_2S_2O_8$ (143 mg, 0.600 mmol, 3.00 equiv.), and TFA (76 µL, 1.0 mmol, 5.0 equiv.) in *o*-xylene (**94**, 1.0 mL, 0.2M) under inert atmosphere. The reaction mixture was heated with an oil bath to 100 °C for 12 h and monitored by GLC analysis using tetracosane (10 mg, 0.030 mmol, 15 mol%) as internal standard. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate (5 mL). The crude reaction mixture was washed with saturated aqueous $NaHCO_3$ (3 mL) and the phases were separated. The aqueous phase

was extracted with ethyl acetate (3 × 5 mL), and the combined organic phases were washed with brine (1 × 5 mL), and dried over anhydrous Na_2SO_4. After evaporation of the solvents under reduced pressure, purification of the residue by flash column chromatography on silica gel (2.5 × 20 cm, cyclohexane:ethyl acetate = 6:1, 50 mL, #10–15) afforded the analytically pure arylated product *cis*-**162** (63 mg, 91%) as a light yellow solid.

m.p.: 190–191 °C.

R_f = 0.41 (cyclohexane:ethyl acetate = 3:1).

GLC (HP-5): t_R = 24.4 min.

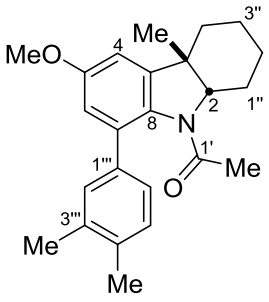
^{1}H NMR (500 MHz, DMSO-d_6, 358 K): δ/ppm = 1.06–1.10 (m, 1H, H-2''), 1.09 (s, 3H, 3–C*H*$_3$), 1.28–1.37 (m, 2H, H-2'', H-3''), 1.57–1.65 (m, 3H, H-3'', H-4''), 1.60 (br s, 3H, H-2'), 2.13–2.17 (m, 1H, H-1''A), 2.29 (s, 6H, 3'''–C*H*$_3$, 4'''–C*H*$_3$), 2.32–2.36 (m, 1H, H-1''B), 2.38 (s, 3H, 5–C*H*$_3$), 4.30 (dd, $^3J_{2,1''A}$ = 10.2 Hz, $^3J_{2,1''B}$ = 6.1 Hz, 1H, H-2), 7.03 (dd, $^4J_{4,6}$ = 2.7 Hz, 1H, H-4), 7.03 (dd, $^4J_{6,4}$ = 2.7 Hz, 1H, H-6), 7.13–7.18 (m, 2H, H-5''', H-6'''), 7.22 (s, 1H, H-2''').

^{13}C NMR (126 MHz, DMSO-d_6, 298 K): δ/ppm = 19.6 (3'''–*C*H$_3$)*, 20.1 (4'''–*C*H$_3$)*, 21.4 (5–*C*H$_3$), 22.3 (C-2'')**, 23.4 (3–*C*H$_3$), 28.5 (C-3'')**, 29.7 (C-1''), 31.0 (C-2'), 33.0 (C-4''), 44.1 (C-3), 69.7 (C-2), 121.5 (C-4), 124.9 (C-6'''), 128.6 (C-6), 129.7 (C-2'''), 130.5 (C-5'''), 132.3 (C-7), 135.5 (C-5), 135.8 (C-1'''), 137.0 (C-3''')***, 137.4 (C-4''')***, 138.0 (C-9), 143.4 (C-8), 171.0 (C-1').

IR (ATR): $\tilde{\nu}$ /cm^{-1} = 2924 (m), 2855 (w), 1714 (m), 1644 (s), 1505 (w), 1445 (w), 1420 (m), 1370 (s), 1346 (m), 1306 (w), 1274 (w), 1218 (m), 1185 (w), 1094 (w), 1032 (w), 949 (w), 860 (m), 826 (m), 801 (vw), 715 (w).

HRMS (APCI) for $C_{24}H_{30}NO$ ($[M+H]^+$): calcd. 348.2322
found 348.2320

3.1.3.10 *cis*-1-[8-(3,4-Dimethylphenyl)-6-methoxy-4a-methyl-2,3,4,4a-tetrahydro-1*H*-carbazol-9-(9a*H*)-yl]ethanone (*cis*-163)



cis-**163**

$C_{24}H_{29}NO_2$

M = 363.50 g/mol

According to **GP 3**, a flame-dried SCHLENK tube equipped with a magnetic stir bar was successively charged with c*is*-1-[6-methoxy-4a-methyl-2,3,4,4a-tetrahydro-1*H*-carbazol-9(9a*H*)-yl]ethanone (*cis*-**107**, 52 mg, 0.20 mmol, 1.0 equiv.), $Pd(OAc)_2$ (9.0 mg, 0.040 mmol, 20 mol%), $Na_2S_2O_8$ (143 mg, 0.600 mmol, 3.00 equiv.), and TFA (76 µL, 1.0 mmol, 5.0 equiv.) in *o*-xylene (**94**, 1.0 mL, 0.2M) under inert atmosphere. The reaction mixture was heated with an oil bath to 100 °C for 12 h and monitored by GLC analysis using tetracosane (10 mg, 0.030 mmol, 15 mol%) as internal standard. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate (5 mL). The crude reaction mixture was washed with saturated aqueous $NaHCO_3$ (3 mL) and the phases were separated. The aqueous phase was extracted with ethyl acetate (3 × 5 mL), and the combined organic phases were washed with brine (1 × 5 mL), and dried over anhydrous Na_2SO_4. After evaporation of the solvents under reduced pressure, purification of the residue by flash column chromatography on silica gel (2.5 × 20 cm, cyclohexane:ethyl acetate = 3:1, 50 mL, #11–17) afforded the analytically pure arylated product *cis*-**163** (66 mg, 92%) as a light yellow solid.

R_f = 0.28 (cyclohexane:ethyl acetate = 3:1).

GLC (HP-5): t_R = 25.7 min.

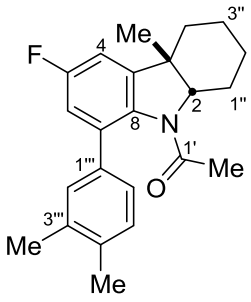
^{1}H NMR (500 MHz, DMSO-d_6, 358 K): δ/ppm = 1.04–1.07 (m, 1H, H-2''), 1.20 (s, 3H, 3–CH_3), 1.30–1.37 (m, 2H, H-2'', H-3''), 1.59–1.65 (m, 3H, H-3'', H-4''), 1.69 (br s, 3H, H-2'), 2.19–2.24 (m, 1H, H-1''A), 2.29 (s, 6H, 3'''–CH_3, 4'''–CH_3), 2.31–2.36 (m, 1H, H-1''B), 3.82 (s, 3H, 5–OCH_3), 4.29 (dd, $^3J_{2,1''A}$ = 10.2 Hz, $^3J_{2,1''B}$ = 6.1 Hz, 1H, H-2), 6.75 (d, $^4J_{6,4}$ = 2.5 Hz, 1H, H-6), 6.81 (d, $^4J_{4,6}$ = 2.5 Hz, 1H, H-4), 7.15–7.19 (m, 2H, H-5''', H-6'''), 7.25 (s, 1H, H-2''').

^{13}C NMR (126 MHz, DMSO-d_6, 298 K): δ/ppm = 20.0 (3'''–*C*H$_3$)*, 20.5 (4'''–*C*H$_3$)*, 22.9 (C-2'')**, 23.7 (3–*C*H$_3$), 29.2 (C-3'')**, 29.3 (C-1''), 30.0 (C-2'), 32.9 (C-4''), 44.8 (C-3), 56.4 (5–O*C*H$_3$), 69.5 (C-2), 108.7 (C-6), 113.5 (C-4), 125.3 (C-5'''), 129.1 (C-2'''), 131.0 (C-6'''), 132.9 (C-7), 133.3 (C-1'''), 135.1 (C-3''')***, 136.5 (C-4''')***, 138.1 (C-9), 145.5 (C-8), 158.5 (C-5), 170.2 (C-1').

IR (ATR): $\tilde{\nu}$ /cm^{-1} = 2924 (br), 2855 (br), 1714 (vw), 1650 (s), 1595 (m), 1449 (m), 1421 (m), 1369 (s), 1306 (m), 1272 (w), 1235 (w), 1213 (w), 1182 (w), 1158 (w), 1030 (w), 994 (vw), 826 (w), 755 (s), 700 (s), 678 (w).

HRMS (APCI) for $C_{24}H_{30}NO_2$ ([M+H]$^+$): calcd. 364.2271
found 364.2270

3.1.3.11 *cis*-1-[8-(3,4-Dimethylphenyl)-6-fluoro-4a-methyl-2,3,4,4a-tetrahydro-1*H*-carbazol-9(9a-*H*)-yl]ethanone (*cis*-164)



cis-**164**
$C_{23}H_{26}FNO$
M = 351.47 g/mol

According to **GP 3**, a flame-dried SCHLENK tube equipped with a magnetic stir bar was successively charged with *cis*-1-[6-fluoro-4a-methyl-2,3,4,4atetrahydro-1*H*-carbazol-9(9a*H*)-yl]ethanone (*cis*-**108**, 49 mg, 0.20 mmol, 1.0 equiv.), $Pd(OAc)_2$ (9.0 mg, 0.040 mmol, 20 mol%), $Na_2S_2O_8$ (143 mg, 0.600 mmol, 3.00 equiv.), and TFA (76 µL, 1.0 mmol, 5.0 equiv.) in *o*-xylene (**94**, 1.0 mL, 0.2M) under inert atmosphere. The reaction mixture was heated with an oil bath to 100 °C for 24 h and monitored by GLC analysis using tetracosane (10 mg, 0.030 mmol, 15 mol%) as internal standard. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate (5 mL). The crude reaction mixture was washed with saturated aqueous $NaHCO_3$ (3 mL) and the phases were separated. The aqueous phase was extracted with ethyl acetate (3 × 5 mL), and the combined organic phases were washed with brine (1 × 5 mL), and dried over anhydrous Na_2SO_4. After evaporation of the solvents

under reduced pressure, purification of the residue by flash column chromatography on silica gel (2.5 × 20 cm, cyclohexane:ethyl acetate = 4:1, 50 mL, #11–15) afforded the analytically pure arylated product *cis*-**164** (32 mg, 45%) as a light yellow solid.

m.p.: 199–200 °C.

R_f = 0.35 (cyclohexane:ethyl acetate = 3:1).

GLC (HP-5): t_R = 23.7 min.

^{1}H NMR (500 MHz, DMSO-d$_6$, 358 K): δ/ppm = 1.03–1.08 (m, 1H, H-2''), 1.11 (s, 3H, 3–C*H*$_3$), 1.30–1.37 (m, 2H, H-2'', H-3''), 1.59–1.65 (m, 3H, H-3'', H-4''), 1.69 (br s, 3H, H-2'), 2.19–2.24 (m, 1H, H-1''A), 2.29 (s, 6H, 3'''–C*H*$_3$, 4'''–C*H*$_3$), 2.31–2.36 (m, 1H, H-1''B), 4.30 (dd, $^3J_{2,1''A}$ = 10.1 Hz, $^3J_{2,1''B}$ = 6.3 Hz, 1H, H-2), 7.01 (dd, $^3J_{4,5–F}$ = 10.3 Hz, $^4J_{4,6}$ = 2.7 Hz, 1H, H-4), 7.07 (dd, $^3J_{6,5–F}$ = 8.1 Hz, $^4J_{6,4}$ = 2.6 Hz, 1H, H-6), 7.15–7.19 (m, 2H, H-5''', H-6'''), 7.24 (s, 1H, H-2''').

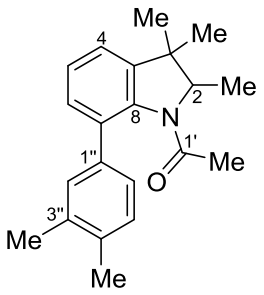
^{13}C NMR (126 MHz, DMSO-d$_6$, 298 K): δ/ppm = 20.1 (3'''–*C*H$_3$)*, 20.5 (4'''–*C*H$_3$)*, 21.7 (H-2'), 22.8 (C-2'')**, 23.5 (C-3'')**, 23.6 (3–C*H*$_3$), 29.8 (C-1''), 32.8 (C-4''), 45.5 (C-3), 69.7 (C-2), 110.3 (d, $^2J_{4,5–F}$ = 23.2 Hz, C-4), 115.8 (d, $^2J_{6,5–F}$ = 22.8 Hz, C-6), 125.3 (C-6'''), 129.1 (C-2'''), 131.2 (C-5'''), 134.3 (C-7), 134.9 (C-1'''), 137.0 (C-3''')***, 138.1 (C-4''')***, 143.2 (C-8), 147.9 (C-9), 161.6 (d, $^1J_{5,5–F}$ = 238.4 Hz, C-5), 170.0 (C-1').

^{19}F NMR (471 MHz, DMSO-d$_6$, 298 K): δ/ppm = –117.5 (5–F).

IR (ATR): $\tilde{\nu}$ /cm^{-1} = 2930 (br), 2891 (br), 1715 (w), 1650 (s), 1577 (m), 1498 (w), 1360 (s), 1333 (w), 1295 (m), 1198 (m), 1126 (w), 1085 (w), 1012 (m), 928 (m), 850 (s), 801 (s), 755 (m), 699 (w).

HRMS (APCI) for $C_{23}H_{27}FNO$ ($[M+H]^+$): calcd. 352.2071
found 352.2072

3.1.3.12 1-[7-(3,4-Dimethylphenyl)-2,3,3-trimethylindolin-1-yl]ethanone (165)



165

$C_{21}H_{25}NO$

M = 307.44 g/mol

According to **GP 3**, a flame-dried SCHLENK tube equipped with a magnetic stir bar was successively charged with 1-(2,3,3-trimethylindolin-1-yl)ethanone (**101**, 41 mg, 0.20 mmol, 1.0 equiv.), $Pd(OAc)_2$ (9.0 mg, 0.040 mmol, 20 mol%), $Na_2S_2O_8$ (143 mg, 0.600 mmol, 3.00 equiv.), and TFA (76 µL, 1.0 mmol, 5.0 equiv.) in *o*-xylene (**94**, 1.0 mL, 0.2M) under inert atmosphere. The reaction mixture was heated with an oil bath to 100 °C for 12 h and monitored by GLC analysis using tetracosane (10 mg, 0.030 mmol, 15 mol%) as internal standard. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate (5 mL). The crude reaction mixture was washed with saturated aqueous $NaHCO_3$ (3 mL) and the phases were separated. The aqueous phase was extracted with ethyl acetate (3 × 5 mL), and the combined organic phases were washed with brine (1 × 5 mL), and dried over anhydrous Na_2SO_4. After evaporation of the solvents under reduced pressure, purification of the residue by flash column chromatography on silica gel (2.5 × 20 cm, cyclohexane:ethyl acetate = 6:1, 50 mL, #11–18) afforded the analytically pure arylated product **165** (53 mg, 87%) as a light yellow solid.

m.p.: 117–178 °C.

R_f = 0.43 (cyclohexane:ethyl acetate = 3:1).

GLC (HP-5): t_R = 21.6 min.

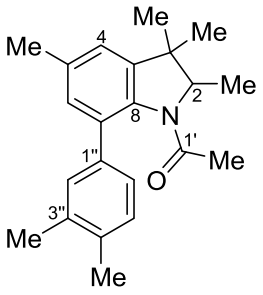
^{1}H NMR (500 MHz, DMSO-d_6, 358 K): δ/ppm = 1.18 (s, 3H, 3–CH_3)*, 1.26 (d, $^3J_{2\text{–}CH_3,2}$ = 6.7 Hz, 3H, 2–CH_3), 1.34 (s, 3H, 3–CH_3)*, 1.60 (br s, 3H, H-2'), 2.30 (s, 6H, 3''–CH_3, 4''–CH_3), 4.43 (q, $^3J_{2,2\text{–}CH_3}$ = 6.7 Hz, 1H, H-2), 7.13–7.16 (m, 1H, H-4), 7.17–7.21 (m, 2H, H-5, H-6), 7.22–7.25 (m, 3H, H-2'', H-5'', H-6'').

^{13}C NMR (126 MHz, DMSO-d_6, 298 K): δ/ppm = 16.7 (2-*C*H$_3$), 20.0 (3''–*C*H$_3$)*, 20.5 (4''–*C*H$_3$)*, 20.8 (3-*C*H$_3$)**, 23.1 (3-*C*H$_3$)**, 30.0 (C-2'), 44.2 (C-3), 69.0 (C-2), 114.6 (C-5), 116.0 (C-4), 122.2 (C-6''), 125.0 (C-6), 126.6 (C-2''), 128.9 (C-5''), 129.7 (C-7), 130.4 (C-1''), 130.4 (C-3'')***, 130.7 (C-4'')***, 138.3 (C-9), 144.8 (C-8), 169.2 (C-1').

IR (ATR): $\tilde{\nu}$ /cm^{-1} = 2921 (br), 2047 (vw), 1857 (br), 1739 (vw), 1715 (vw), 1636 (s), 1598 (m), 1450 (m), 1430 (m), 1376 (s), 1340 (m), 1306 (m), 1251 (m), 1220 (w), 1172 (w), 1088 (w), 1032 (w), 995 (w), 968 (vw), 888 (w), 825 (w), 793 (m), 753 (s), 694 (w).

HRMS (APCI) for $C_{21}H_{26}NO$ ([M+H]$^+$): calcd. 308.2009
found 308.2007

3.1.3.13 1-[7-(3,4-Dimethylphenyl)-2,3,3,5-tetramethylindolin-1-yl]ethanone (166)



166
$C_{22}H_{27}NO$
M = 321.46 g/mol

According to **GP 3**, a flame-dried SCHLENK tube equipped with a magnetic stir bar was successively charged with 1-(2,3,3,5-tetramethylindolin-1-yl)ethanone (**102**, 44 mg, 0.20 mmol, 1.0 equiv.), $Pd(OAc)_2$ (9.0 mg, 0.040 mmol, 20 mol%), $Na_2S_2O_8$ (143 mg, 0.600 mmol, 3.00 equiv.), and TFA (76 µL, 1.0 mmol, 5.0 equiv.) in *o*-xylene (**94**, 1.0 mL, 0.2M) under inert atmosphere. The reaction mixture was heated with an oil bath to 100 °C for 12 h and monitored by GLC analysis using tetracosane (10 mg, 0.030 mmol, 15 mol%) as internal standard. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate (5 mL). The crude reaction mixture was washed with saturated aqueous $NaHCO_3$ (3 mL) and the phases were separated. The aqueous phase was extracted with ethyl acetate (3 × 5 mL) and the combined organic phases were washed with brine (1 × 5 mL) and dried over anhydrous Na_2SO_4. After evaporation of the solvents under reduced pressure, purification of the residue by flash column chromatography on silica gel (2.5 × 20 cm,

cyclohexane:ethyl acetate = 6:1, 50 mL, #10–15) afforded the analytically pure arylated product **166** (61 mg, 95%) as a light yellow solid.

m.p.: 97–98 °C.

R_f = 0.44 (cyclohexane:ethyl acetate = 3:1).

GLC (HP-5): t_R = 22.2 min.

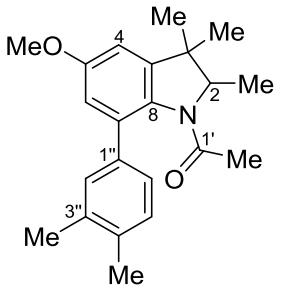
^{1}H NMR (500 MHz, DMSO-d_6, 358 K): δ/ppm = 1.16 (s, 3H, 3–CH_3)*, 1.24 (d, $^3J_{2-CH_3,2}$ = 6.7 Hz, 3H, 2–CH_3), 1.32 (s, 3H, 3–CH_3)*, 1.57 (br s, 3H, H-2'), 2.29 (s, 6H, 3''–CH_3, 4'''–CH_3), 2.37 (s, 3H, 5–CH_3), 4.43 (q, $^3J_{2,2-CH_3}$ = 6.6 Hz, 1H, H-2), 7.01 (d, $^4J_{4,6}$ = 2.4 Hz, 1H, H-4), 7.04 (d, $^4J_{6,4}$ = 2.5 Hz, 1H, H-6), 7.13–7.19 (m, 2H, H-5'', H-6''), 7.23 (s, 1H, H-2'').

^{13}C NMR (126 MHz, DMSO-d_6, 298 K): δ/ppm = 16.6 (2-CH$_3$), 20.0 (3''–CH$_3$)*, 20.5 (4''–CH$_3$)*, 20.8 (3-CH$_3$)**, 21.7 (5-CH$_3$), 23.0 (3-CH$_3$)**, 30.0 (C-2'), 44.0 (C-3), 69.1 (C-2), 122.9 (C-4), 125.1 (C-6), 128.9 (C-2''), 130.1 (C-6''), 130.8 (C-5''), 131.8 (C-7), 135.8 (C-5), 136.1 (C-1''), 137.6 (C-3'')***, 138.8 (C-4'')***, 142.0 (C-9), 144.9 (C-8), 169.7 (C-1').

IR (ATR): $\tilde{\nu}$ /cm^{-1} = 2958 (br), 2922 (br), 2820 (w), 1710 (m), 1651 (s), 1600 (w), 1505 (w), 1445 (m), 1360 (s), 1336 (m), 1306 (m), 1252 (w), 1220 (m), 1170 (w), 1092 (w), 1025 (w), 861 (m), 819 (s), 754 (w).

HRMS (APCI) for $C_{22}H_{28}NO$ ($[M+H]^+$): calcd. 322.2165
found 322.2158

3.1.3.14 1-[7-(3,4-Dimethylphenyl)-5-methoxy-2,3,3-trimethylindolin-1-yl]ethanone (167)



167

$C_{22}H_{27}NO_2$

M = 337.46 g/mol

According to **GP 3**, a flame-dried SCHLENK tube equipped with a magnetic stir bar was successively charged with 1-(5-methoxy-2,3,3-trimethylindolin-1-yl)ethanone (**103**, 47 mg, 0.20 mmol, 1.0 equiv.), $Pd(OAc)_2$ (9.0 mg, 0.040 mmol, 20 mol%), $Na_2S_2O_8$ (143 mg, 0.600 mmol, 3.00 equiv.), and TFA (76 µL, 1.0 mmol, 5.0 equiv.) in *o*-xylene (**94**, 1.0 mL, 0.2M) under inert atmosphere. The reaction mixture was heated with an oil bath to 100 °C for 12 h and monitored by GLC analysis using tetracosane (10 mg, 0.030 mmol, 15 mol%) as internal standard. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate (5 mL). The crude reaction mixture was washed with saturated aqueous $NaHCO_3$ (3 mL) and the phases were separated. The aqueous phase was extracted with ethyl acetate (3 × 5 mL), and the combined organic phases were washed with brine (1 × 5 mL), and dried over anhydrous Na_2SO_4. After evaporation of the solvents under reduced pressure, purification of the residue by flash column chromatography on silica gel (2.5 × 20 cm, cyclohexane:ethyl acetate = 4:1, 50 mL, #15–23) afforded the analytically pure arylated product **167** (62 mg, 93%) as a brown oil.

R_f = 0.33 (cyclohexane:ethyl acetate = 3:1).

GLC (HP-5): t_R = 23.3 min.

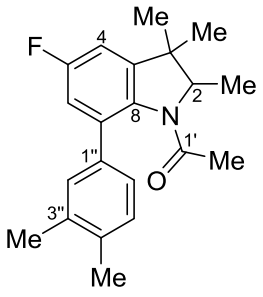
^{1}H NMR (500 MHz, DMSO-d$_6$, 358 K): δ/ppm = 1.17 (s, 3H, 3–CH_3)*, 1.25 (d, $^3J_{2\text{–}CH_3,2}$ = 6.7 Hz, 3H, 2–CH_3), 1.32 (s, 3H, 3–CH_3)*, 1.57 (br s, 3H, H-2'), 2.30 (s, 6H, 3''–CH_3, 4''–CH_3), 3.84 (s, 3H, 5–OCH_3), 4.44 (q, $^3J_{2,2\text{–}CH_3}$ = 6.5 Hz, 1H, H-2), 6.76 (d, $^4J_{4,6}$ = 2.5 Hz, 1H, H-4), 6.82 (d, $^4J_{6,4}$ = 2.5 Hz, 1H, H-6), 7.16–7.20 (m, 2H, H-5'', H-6''), 7.25 (s, 1H, H-2'').

^{13}C NMR (126 MHz, DMSO-d_6, 298 K): δ/ppm = 16.5 (2-*C*H$_3$), 20.0 (3''–*C*H$_3$)*, 20.5 (4''–*C*H$_3$)*, 20.7 (3-*C*H$_3$)**, 22.9 (3-*C*H$_3$)**, 29.8 (C-2'), 44.3 (C-3), 56.4 (5-*C*H$_3$), 69.1 (C-2), 109.0 (C-6), 113.7 (C-4), 125.3 (C-2''), 129.0 (C-6''), 130.9 (C-5''), 131.7 (C-7), 132.7 (C-1''), 136.1 (C-3'')***, 137.9 (C-4'')***, 138.7 (C-9), 146.7 (C-8), 158.5 (C-5), 170.0 (C-1').

IR (ATR): $\tilde{\nu}$ /cm^{-1} = 2952 (br), 2926 (br), 2845 (br), 1733 (vw), 1714 (w), 1651 (s), 1551 (m), 1498 (m), 1469 (s), 1368 (s), 1355 (m), 1300 (w), 1234 (m), 1204 (m), 1179 (w), 1164 (w), 1123 (m), 1071 (s), 977 (w), 866 (m), 830 (m), 801 (s), 754 (m), 687 (w).

HRMS (APCI) for $C_{22}H_{28}NO_2$ ([M+H]$^+$): calcd. 338.2115
found 338.2106

3.1.3.15 1-[7-(3,4-Dimethylphenyl)-5-fluoro-2,3,3-trimethylindolin-1-yl]ethanone (168)



168
$C_{21}H_{24}FNO$
M = 325.43 g/mol

According to **GP 3**, a flame-dried SCHLENK tube equipped with a magnetic stir bar was successively charged with 1-(5-fluoro-2,3,3-trimethylindolin-1-yl)ethanone (**104**, 44 mg, 0.20 mmol, 1.0 equiv.), $Pd(OAc)_2$ (9.0 mg, 0.040 mmol, 20 mol%), $Na_2S_2O_8$ (143 mg, 0.600 mmol, 3.00 equiv.), and TFA (76 µL, 1.0 mmol, 5.0 equiv.) in *o*-xylene (**94**, 1.0 mL, 0.2M) under inert atmosphere. The reaction mixture was heated with an oil bath to 100 °C for 24 h and monitored by GLC analysis using tetracosane (10 mg, 0.030 mmol, 15 mol%) as internal standard. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate (5 mL). The crude reaction mixture was washed with saturated aqueous $NaHCO_3$ (3 mL) and the phases were separated. The aqueous phase was extracted with ethyl acetate (3 × 5 mL), and the combined organic phases were washed with brine (1 × 5 mL), and dried over anhydrous Na_2SO_4. After evaporation of the solvents under reduced pressure, purification of the residue by flash column chromatography on silica gel (2.5 ×

20 cm, cyclohexane:ethyl acetate = 5:1, 50 mL, #12–17) afforded the analytically pure arylated product **168** (33 mg, 51%) as a brown solid.

m.p.: 134–135 °C.

R_f = 0.38 (cyclohexane:ethyl acetate = 3:1).

GLC (HP-5): t_R = 21.4 min.

^{1}H NMR (500 MHz, DMSO-d_6, 358 K): δ/ppm = 1.18 (s, 3H, 3–CH_3)*, 1.27 (d, $^3J_{2–CH_3,2}$ = 6.7 Hz, 3H, 2–CH_3), 1.34 (s, 3H, 3–CH_3)*, 1.65 (br s, 3H, H-2'), 2.29 (s, 6H, 3''–CH_3, 4''–CH_3), 4.43 (q, $^3J_{2,2–CH_3}$ = 6.7 Hz, 1H, H-2), 7.01 (dd, $^3J_{4,5–F}$ = 10.3 Hz, $^4J_{4,6}$ = 2.7 Hz, 1H, H-4), 7.06 (dd, $^3J_{6,5–F}$ = 8.1 Hz, $^4J_{6,4}$ = 2.7 Hz, 1H, H-6), 7.16 (d, $^3J_{6''',5'''}$ = 7.8 Hz, 1H, H-6''), 7.18–7.21 (m, 1H, H-5''), 7.24 (s, 1H, H-2'').

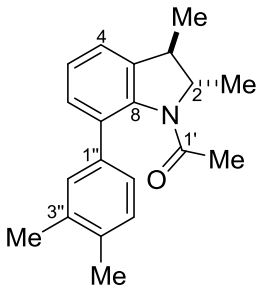
^{13}C NMR (126 MHz, DMSO-d_6, 298 K): δ/ppm = 16.7 (2-*C*H$_3$), 20.1 (3''–*C*H$_3$)*, 20.5 (4''–*C*H$_3$)*, 20.5 (3-*C*H$_3$)**, 23.1 (3-*C*H$_3$)**, 29.6 (C-2'), 44.7 (C-3), 69.3 (C-2), 109.9 (d, $^2J_{4,5–F}$ = 23.0 Hz, C-4), 115.4 (d, $^2J_{6,5–F}$ = 23.9 Hz, C-6), 124.9 (C-6''), 128.7 (C-2''), 130.8 (C-5''), 135.5 (C-7), 136.6 (C-1''), 137.7 (C-3'')***, 138.0 (C-4'')***, 142.7 (C-9), 147.6 (C-8), 161.7 (d, $^1J_{5,5–F}$ = 239.6 Hz, C-5), 169.7 (C-1').

^{19}F NMR (471 MHz, DMSO-d_6, 298 K): δ/ppm = –117.4 (5–F).

IR (ATR): $\tilde{\nu}$ /cm^{-1} = 2963 (br), 2952 (br), 2865 (w), 1739 (vw), 1715 (w), 1648 (s), 1591 (m), 1480 (s), 1405 (s), 1334 (m), 1312 (w), 1261 (s), 1188 (m), 1138 (m), 1110 (w), 1085 (w), 998 (w), 924 (w), 840 (s), 826 (s), 753 (m), 694 (m).

HRMS (APCI) for $C_{21}H_{25}FNO$ ([M+H]$^+$): calcd. 326.1915
found 326.1906

3.1.3.16 *trans*-1-[7-(3,4-Dimethylphenyl)-2,3-dimethylindolin-1-yl]ethanone (*trans*-169)



trans-**169**
$C_{20}H_{23}NO$
M = 293.41 g/mol

According to **GP 3**, a flame-dried SCHLENK tube equipped with a magnetic stir bar was successively charged with *trans*-1-(2,3-dimethylindolin-1-yl)ethanone (*trans*-**97**, 38 mg, 0.20 mmol, 1.0 equiv.), $Pd(OAc)_2$ (9.0 mg, 0.040 mmol, 20 mol%), $Na_2S_2O_8$ (143 mg, 0.600 mmol, 3.00 equiv.), and TFA (76 µL, 1.0 mmol, 5.0 equiv.) in *o*-xylene (**94**, 1.0 mL, 0.2M) under inert atmosphere. The reaction mixture was heated with an oil bath to 100 °C for 12 h and monitored by GLC analysis using tetracosane (10 mg, 0.030 mmol, 15 mol%) as internal standard. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate (5 mL). The crude reaction mixture was washed with saturated aqueous $NaHCO_3$ (3 mL) and the phases were separated. The aqueous phase was extracted with ethyl acetate (3 × 5 mL), and the combined organic phases were washed with brine (1 × 5 mL), and dried over anhydrous Na_2SO_4. After evaporation of the solvents under reduced pressure, purification of the residue by flash column chromatography on silica gel (2.5 × 20 cm, cyclohexane:ethyl acetate = 4:1, 50 mL, #12–16) afforded the analytically pure arylated product *trans*-**169** (51 mg, 88%) as a brown solid.

m.p.: 102–103 °C.

R_f = 0.35 (cyclohexane:ethyl acetate = 3:1).

GLC (HP-5): t_R = 20.9 min.

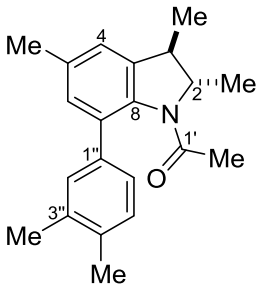
^{1}H NMR (500 MHz, DMSO-d$_6$, 358 K): δ/ppm = 1.20 (d, $^3J_{3–CH_3,3}$ = 7.1 Hz, 3H, 3–CH_3), 1.35 (d, $^3J_{2–CH_3,2}$ = 6.6 Hz, 3H, 2–CH_3), 1.63 (br s, 3H, H-2'), 2.29 (s, 6H, 3''–CH_3, 4''–CH_3), 2.81 (q, $^3J_{3,3–CH_3}$ = 7.0 Hz, 1H, H-3), 4.39 (q, $^3J_{2,2–CH_3}$ = 6.6 Hz, 1H, H-2), 7.14–7.19 (m, 2H, H-4, H-5), 7.23–7.25 (m, 3H, H-2'', H-5'', H-6''), 7.28 (dd, $^3J_{6,5}$ = 6.9 Hz, $^4J_{6,4}$ = 1.0 Hz, 1H, H-6).

^{13}C NMR (126 MHz, DMSO-d_6, 298 K): δ/ppm = 20.0 (3''–*C*H$_3$)*, 20.5 (4''–*C*H$_3$)*, 20.7 (3-*C*H$_3$), 21.4 (2-*C*H$_3$), 23.2 (C-2'), 43.6 (C-3), 65.2 (C-2), 124.4 (C-5), 124.9 (C-4), 126.3 (C-6), 128.7 (C-2''), 129.8 (C-6''), 130.7 (C-5''), 132.4 (C-7), 135.7 (C-1''), 137.5 (C-3'')**, 138.4 (C-4'')**, 139.1 (C-9), 141.1 (C-8), 169.4 (C-1').

IR (ATR): $\tilde{\nu}$ /cm^{-1} = 2982 (vw), 2951 (w), 2918 (br), 2859 (br), 1713 (m), 1646 (s), 1504 (w), 1435 (m), 1370 (s), 1320 (m), 1308 (w), 1255 (w), 1217 (m), 1110 (vw), 1056 (w), 1018 (w), 928 (w), 826 (w), 792 (s), 786 (s), 723 (m).

HRMS (APCI) for $C_{20}H_{24}NO$ ([M+H]$^+$): calcd. 294.1852
found 294.1845

3.1.3.17 *trans*-1-[7-(3,4-Dimethylphenyl)-2,3,5-trimethylindolin-1-yl]ethanone (*trans*-170)



trans-**170**
$C_{21}H_{25}NO$
M = 307.44 g/mol

According to **GP 3**, a flame-dried SCHLENK tube equipped with a magnetic stir bar was successively charged with *trans*-2,3,5-trimethylindolin-1-yl)ethanone (*trans*-**98**, 41 mg, 0.20 mmol, 1.0 equiv.), $Pd(OAc)_2$ (9.0 mg, 0.040 mmol, 20 mol%), $Na_2S_2O_8$ (143 mg, 0.600 mmol, 3.00 equiv.), and TFA (76 µL, 1.0 mmol, 5.0 equiv.) in *o*-xylene (**94**, 1.0 mL, 0.2M) under inert atmosphere. The reaction mixture was heated with an oil bath to 100 °C for 12 h and monitored by GLC analysis using tetracosane (10 mg, 0.030 mmol, 15 mol%) as internal standard. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate (5 mL). The crude reaction mixture was washed with saturated aqueous $NaHCO_3$ (3 mL) and the phases were separated. The aqueous phase was extracted with ethyl acetate (3 × 5 mL), and the combined organic phases were washed with brine (1 × 5 mL), and dried over anhydrous Na_2SO_4. After evaporation of the solvents under reduced pressure, purification of the residue by flash column chromatography on silica gel (2.5 ×

20 cm, cyclohexane:ethyl acetate = 5:1, 50 mL, #10–18) afforded the analytically pure arylated product *trans*-**170** (57 mg, 93%) as a brown solid.

m.p.: 95–96 °C.

R_f = 0.42 (cyclohexane:ethyl acetate = 3:1).

GLC (HP-5): t_R = 21.9 min.

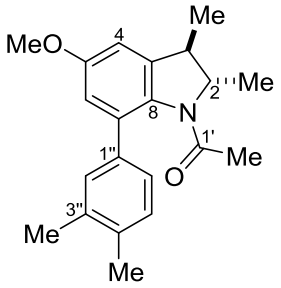
^{1}H NMR (500 MHz, DMSO-d_6, 358 K): δ/ppm = 1.19 (d, $^3J_{3–CH_3,3}$ = 7.0 Hz, 3H, 3–CH_3), 1.33 (d, $^3J_{2–CH_3,2}$ = 6.6 Hz, 3H, 2–CH_3), 1.59 (br s, 3H, H-2'), 2.29 (s, 6H, 3''–CH_3, 4''–CH_3), 2.36 (s, 3H, 5–CH_3), 2.76 (q, $^3J_{3,3–CH_3}$ = 7.0 Hz, 1H, H-3), 4.39 (q, $^3J_{2,2–CH_3}$ = 6.6 Hz, 1H, H-2), 7.05 (s, 1H, H-6), 7.09 (s, 1H, H-4), 7.13–7.18 (m, 2H, H-5'', H-6''), 7.23 (s, 1H, H-2'').

^{13}C NMR (126 MHz, DMSO-d_6, 298 K): δ/ppm = 20.0 (3''–*C*H$_3$)*, 20.5 (4''–*C*H$_3$)*, 20.6 (3-*C*H$_3$), 21.4 (2-*C*H$_3$), 21.5 (5-*C*H$_3$), 23.2 (C-2'), 43.5 (C-3), 65.3 (C-2), 125.0 (C-4), 128.8 (C-6), 130.2 (C-2''), 130.7 (C-6''), 132.0 (C-5''), 133.9 (C-7), 135.5 (C-1''), 135.8 (C-5), 136.2 (C-3'')**, 137.5 (C-4'')**, 139.1 (C-9), 143.1 (C-8), 169.3 (C-1').

IR (ATR): $\tilde{\nu}$ /cm^{-1} = 2957 (br), 2921 (br), 2861 (br), 1740 (vw), 1653 (s), 1503 (vw), 1462 (w), 1446 (m), 1391 (m), 1364 (s), 1345 (m), 1305 (m), 1258 (w), 1204 (w), 1099 (w), 1064 (w), 1023 (w), 942 (w), 858 (s), 826 (s), 801 (m), 767 (w), 718 (m).

HRMS (APCI) for $C_{21}H_{26}NO$ ($[M+H]^+$): calcd. 308.2009
found 308.2003

3.1.3.18 *trans*-1-[7-(3,4-Dimethylphenyl)-5-methoxy-2,3-dimethylindolin-1-yl]ethanone (*trans*-171)



trans-**171**
$C_{21}H_{25}NO_2$
M = 323.44 g/mol

According to **GP 3**, a flame-dried SCHLENK tube equipped with a magnetic stir bar was successively charged with *trans*-5-methoxy-2,3-dimethylindolin-1-yl)ethanone (*trans*-**99**, 44 mg, 0.20 mmol, 1.0 equiv.), $Pd(OAc)_2$ (9.0 mg, 0.040 mmol, 20 mol%), $Na_2S_2O_8$ (143 mg, 0.600 mmol, 3.00 equiv.), and TFA (76 µL, 1.0 mmol, 5.0 equiv.) in *o*-xylene (**94**, 1.0 mL, 0.2M) under inert atmosphere. The reaction mixture was heated with an oil bath to 100 °C for 12 h and monitored by GLC analysis using tetracosane (10 mg, 0.030 mmol, 15 mol%) as internal standard. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate (5 mL). The crude reaction mixture was washed with saturated aqueous $NaHCO_3$ (3 mL) and the phases were separated. The aqueous phase was extracted with ethyl acetate (3 × 5 mL), and the combined organic phases were washed with brine (1 × 5 mL), and dried over anhydrous Na_2SO_4. After evaporation of the solvents under reduced pressure, purification of the residue by flash column chromatography on silica gel (2.5 × 20 cm, cyclohexane:ethyl acetate = 4:1, 50 mL, #19–29) afforded the analytically pure arylated product *trans*-**171** (58 mg, 90%) as a brown solid.

m.p.: 124–126 °C.

R_f = 0.31 (cyclohexane:ethyl acetate = 3:1).

GLC (HP-5): t_R = 22.8 min.

^{1}H NMR (500 MHz, DMSO-d_6, 358 K): δ/ppm = 1.19 (d, $^3J_{3-CH_3,3}$ = 7.0 Hz, 3H, 3–CH_3), 1.34 (d, $^3J_{2-CH_3,2}$ = 6.6 Hz, 3H, 2–CH_3), 1.59 (br s, 3H, H-2'), 2.29 (s, 6H, 3''–CH_3, 4''–CH_3), 2.77 (q, $^3J_{3,3-CH_3}$ = 7.1 Hz, 1H, H-3), 3.83 (s, 3H, 5–OCH_3), 4.39 (q, $^3J_{2,2-CH_3}$ = 6.5 Hz, 1H, H-2), 6.77

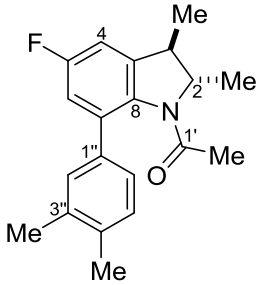
(d, $^4J_{6,4}$ = 3.0 Hz, 1H, H-6), 6.91 (d, $^4J_{4,6}$ = 2.5 Hz, 1H, H-4), 7.15–7.19 (m, 2H, H-5'', H-6''), 7.24 (s, 1H, H-2'').

^{13}C NMR (100 MHz, DMSO-d_6, 298 K): δ/ppm = 20.0 (3''–*C*H$_3$)*, 20.5 (4''–*C*H$_3$)*, 20.6 (3-*C*H$_3$), 21.2 (2-*C*H$_3$), 23.1 (C-2'), 43.9 (C-3), 56.4 (5-O*C*H$_3$), 65.3 (C-2), 110.7 (C-6), 114.2 (C-4), 125.0 (C-6''), 128.8 (C-2''), 130.8 (C-5''), 131.8 (C-7), 133.4 (C-1''), 136.3 (C-3'')**, 137.7 (C-4'')**, 138.8 (C-9), 142.9 (C-8), 158.2 (C-5), 170.1 (C-1').

IR (ATR): $\tilde{\nu}$ /cm^{-1} = 2952 (br), 2921 (br), 2860 (br), 1739 (vw), 1646 (s), 1635 (s), 1608 (m), 1502 (vw), 1467 (m), 1439 (m), 1400 (m), 1385 (m), 1372 (m), 1340 (s), 1311 (m), 1256 (w), 1234 (s), 1192 (w), 1157 (m), 1129 (w), 1109 (vw), 1065 (vw), 1045 (m), 1018 (m), 967 (m), 939 (w), 876 (m), 847 (w), 821 (s), 799 (w), 759 (w), 720 (m), 666 (w).

HRMS (APCI) for $C_{21}H_{26}NO_2$ ([M+H]$^+$): calcd. 324.1958
found 324.1950

3.1.3.19 *trans*-1-[7-(3,4-Dimethylphenyl)-5-methoxy-2,3-dimethylindolin-1-yl]ethanone (*trans*-172)



trans-**172**
$C_{20}H_{22}FNO$
M = 311.40 g/mol

According to **GP 3**, a flame-dried SCHLENK tube equipped with a magnetic stir bar was successively charged with *trans*-5-fluoro-2,3-dimethylindolin-1-yl)ethanone (*trans*-**100**, 41 mg, 0.20 mmol, 1.0 equiv.), $Pd(OAc)_2$ (9.0 mg, 0.040 mmol, 20 mol%), $Na_2S_2O_8$ (143 mg, 0.600 mmol, 3.00 equiv.), and TFA (76 µL, 1.0 mmol, 5.0 equiv.) in *o*-xylene (**94**, 1.0 mL, 0.2M) under inert atmosphere. The reaction mixture was heated with an oil bath to 100 °C for 24 h and monitored by GLC analysis using tetracosane (10 mg, 0.030 mmol, 15 mol%) as internal standard. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate (5 mL). The crude reaction mixture was washed with saturated aqueous

$NaHCO_3$ (3 mL) and the phases were separated. The aqueous phase was extracted with ethyl acetate (3 × 5 mL), and the combined organic phases were washed with brine (1 × 5 mL), and dried over anhydrous Na_2SO_4. After evaporation of the solvents under reduced pressure, purification of the residue by flash column chromatography on silica gel (2.5 × 20 cm, cyclohexane:ethyl acetate = 4:1, 50 mL, #9–17) afforded the analytically pure arylated product *trans*-**172** (31 mg, 50%) as a brown solid.

m.p.: 122–123 °C.

R_f = 0.34 (cyclohexane:ethyl acetate = 3:1).

GLC (HP-5): t_R = 20.8 min.

^{1}H NMR (500 MHz, DMSO-d_6, 358 K): δ/ppm = 1.20 (d, $^3J_{3-CH_3,3}$ = 7.1 Hz, 3H, 3–CH_3), 1.36 (d, $^3J_{2-CH_3,2}$ = 6.6 Hz, 3H, 2–CH_3), 1.67 (br s, 3H, H-2'), 2.29 (s, 6H, 3''–CH_3, 4''–CH_3), 2.83 (q, $^3J_{3,3-CH_3}$ = 7.1 Hz, 1H, H-3), 4.38 (q, $^3J_{2,2-CH_3}$ = 6.6 Hz, 1H, H-2), 7.02 (dd, $^3J_{6,5-F}$ = 10.3 Hz, $^4J_{6,4}$ = 2.7 Hz, 1H, H-6), 7.13–7.19 (m, 3H, H-4, H-5'', H-6''), 7.24 (s, 1H, H-2'').

^{13}C NMR (100 MHz, DMSO-d_6, 298 K): δ/ppm = 20.1 (3''–CH$_3$)*, 20.5 (4''–CH$_3$)*, 20.7 (3-CH$_3$), 21.1 (2-CH$_3$), 23.2 (C-2'), 43.9 (C-3), 65.5 (C-2), 111.7 (d, $^2J_{4,5-F}$ = 22.8 Hz, C-4), 115.6 (d, $^2J_{6,5-F}$ = 23.6 Hz, C-6), 124.8 (C-6''), 128.6 (C-2''), 130.7 (C-5''), 133.9 (C-1''), 134.7 (C-7), 136.3 (C-3'')**, 137.6 (C-4'')**, 138.0 (C-9), 143.6 (C-8), 161.2 (d, $^1J_{5,5-F}$ = 238.2 Hz, C-5), 169.2 (C-1').

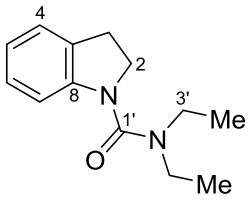
^{19}F NMR (471 MHz, DMSO-d_6, 298 K): δ/ppm = –118.1 (5–F).

IR (ATR): $\tilde{\nu}$ /cm^{-1} = 2965 (br), 2920 (br), 1740 (vw), 1714 (w), 1655 (s), 1620 (s), 1585 (m), 1482 (s), 1453 (s), 1385 (m), 1346 (s), 1311 (m), 1291 (w), 1222 (m), 1210 (w), 1114 (m), 1095 (w), 1075 (vw), 1002 (w), 988 (m), 940 (m), 866 (m), 805 (s), 761 (m), 722 (s), 685 (m).

HRMS (APCI) for $C_{20}H_{23}FNO$ ($[M+H]^+$): calcd. 312.1758
found 312.1751

3.1.4 Preparation of Indoline Substrates with a Urea as Directing Group

3.1.4.1 *N,N*-Diethylindoline-1-carboxamide (91)



91

$C_{13}H_{18}N_2O$

M = 218.30 g/mol

According to **GP 4**, to a flame-dried SCHLENK flask containing a solution of indoline (357 mg, 3.00 mmol, 1.00 equiv.) in anhydrous diethyl ether (15 mL, 0.2M) under inert atmosphere, a solution of *n*-BuLi (1.6M in hexane, 2.44 mL, 3.90 mmol, 1.30 equiv.) was added dropwise with ice-cooling. The resulting mixture was stirred at room temperature for 1 h before cooling down to 0 °C, and *N,N*-diethylcarbamoyl chloride (488 mg, 3.60 mmol, 1.20 equiv.) was added over a period of 1 h. After being stirred at room temperature for 14 h, the reaction was quenched with saturated aqueous NH_4Cl (5 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were washed with brine (1 × 5 mL) and dried over anhydrous Na_2SO_4. After evaporation of the solvents under reduced pressure, purification of the residue by flash column chromatography on silica gel (3.5 × 20 cm, cyclohexane:ethyl acetate = 4:1, 100 mL, #6–16) afforded the analytically pure indoline with urea directing group **91** (593 mg, 95%) as a light yellow oil. The spectroscopic data are in accordance with those reported.[114]

R_f = 0.71 (cyclohexane:ethyl acetate = 2:1).

GLC (HP-5): t_R = 16.7 min.

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ/ppm = 1.18 (t, $^3J_{4',3'}$ = 7.4 Hz, 6H, H-4'), 3.02 (t, $^3J_{3,2}$ = 8.4 Hz, 2H, H-3), 3.34 (q, $^3J_{3',4'}$ = 7.4 Hz, 4H, H-3'), 3.88 (t, $^3J_{2,3}$ = 8.4 Hz, 2H, H-2), 6.86 (ddd, $^3J_{5,4}$ = $^3J_{5,6}$ = 7.4 Hz, $^4J_{5,7}$ = 0.9 Hz, 1H, H-5), 6.96 (d, $^3J_{4,5}$ = 8.1 Hz, 1H, H-4), 7.11 (dd, $^3J_{6,5}$ = $^3J_{6,7}$ = 7.8 Hz, 1H, H-6), 7.16 (d, $^3J_{7,6}$ = 7.4 Hz, 1H, H-7).

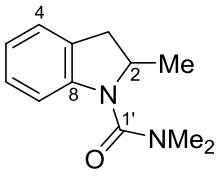
^{13}C NMR (126 MHz, $CDCl_3$, 298 K): δ/ppm = 13.7 (C-4'), 28.2 (C-3), 42.0 (C-3'), 50.5 (C-2), 112.9 (C-4), 121.3 (C-5), 124.9 (C-7), 127.1 (C-6), 131.5 (C-9), 144.9 (C-8), 159.7 (C-1').

[114] K. P. Landge, K. S. Jang, S. Y. Lee, D. Y. Chi, *J. Org. Chem.* **2012**, *77*, 5705–5713.

IR (ATR): $\tilde{\nu}$ /cm^{-1} = 2966 (w), 2873 (w), 1645 (s), 1585 (m), 1476 (s), 1406 (s), 1348 (m), 1249 (s), 1210 (m), 1071 (w), 928 (w), 873 (w), 746 (s).

HRMS (APCI) for $C_{13}H_{19}N_2O$ ([M+H]$^+$): calcd. 219.1492
found 219.1492

3.1.4.2 *N,N*,2-Trimethylindoline-1-carboxamide (183)



183
$C_{12}H_{16}N_2O$
M = 204.27 g/mol

According to **GP 4**, to a flame-dried SCHLENK flask containing a solution of 2-methylindoline (400 mg, 3.00 mmol, 1.00 equiv.) in anhydrous diethyl ether (15 mL, 0.2M) under inert atmosphere, a solution of *n*-BuLi (1.6M in hexane, 2.44 mL, 3.90 mmol, 1.30 equiv.) was added dropwise with ice-cooling. The resulting mixture was stirred at room temperature for 1 h before cooling down to 0 °C, and *N,N*-dimethylcarbamoyl chloride (387 mg, 3.60 mmol, 1.20 equiv.) was added over a period of 1 h. After being stirred at room temperature for 14 h, the reaction was quenched with saturated aqueous NH_4Cl (5 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were washed with brine (1 × 5 mL) and dried over anhydrous Na_2SO_4. After evaporation of the solvents under reduced pressure, purification of the residue by flash column chromatography on silica gel (3.5 × 20 cm, cyclohexane:ethyl acetate = 4:1, 50 mL, #12–29) afforded the analytically indoline with urea directing group **183** (600 mg, 98%) as a light yellow oil.

R_f = 0.37 (cyclohexane:ethyl acetate = 3:1).

GLC (HP-5): t_R = 15.1 min.

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ/ppm = 1.37 (d, $^3J_{2-CH_3,2}$ = 6.2 Hz, 3H, 2–CH_3), 2.66 (dd, $^2J_{3A,3B}$ = 15.4 Hz, $^3J_{3A,2}$ = 8.4 Hz, 1H, H-3A), 2.95 (s, 6H, N(CH_3)$_2$), 3.17 (dd, $^2J_{3B,3A}$ = 15.7 Hz, $^3J_{3B,2}$ = 8.8 Hz, 1H, H-3B), 4.44–4.51 (m, 1H, H-2), 6.72 (d, $^3J_{4,5}$ = 7.9 Hz, 1H, H-4), 6.83 (ddd,

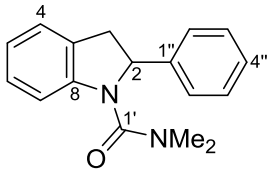
$^3J_{5,4}$ = $^3J_{5,6}$ = 7.5 Hz, $^4J_{5,7}$ = 0.6 Hz, 1H, H-5), 7.10 (dd, $^3J_{6,5}$ = $^3J_{6,7}$ = 7.4 Hz, 1H, H-6), 7.12 (d, $^3J_{7,6}$ = 7.5 Hz, 1H, H-7).

^{13}C NMR (126 MHz, $CDCl_3$, 298 K): δ/ppm = 20.0 (2–*C*H$_3$), 36.6 (C-3), 37.9 (N(*C*H$_3$)$_2$), 58.1 (C-2), 111.9 (C-4), 121.0 (C-5), 125.0 (C-7), 127.1 (C-6), 130.2 (C-9), 144.7 (C-8), 159.6 (C-1').

IR (ATR): $\tilde{\nu}$ /cm^{-1} = 2961 (w), 2920 (w), 1648 (s), 1603 (m), 1477 (s), 1439 (m), 1375 (s), 1347 (s), 1262 (s), 1244 (s), 1196 (s), 1107 (w), 1061 (w), 1026 (m), 958 (w), 932 (w), 821 (vw), 740 (s), 715 (w).

HRMS (APCI) for $C_{12}H_{17}N_2O$ ([M+H]$^+$): calcd. 205.1335
found 205.1331

3.1.4.3 *N,N*-Dimethyl-2-phenylindoline-1-carboxamide (212)



212
$C_{17}H_{18}N_2O$
M = 266.34 g/mol

According to **GP 4**, to a flame-dried SCHLENK flask containing a solution of 2-phenylindoline (196 mg, 1.00 mmol, 1.00 equiv.) in anhydrous diethyl ether (5.0 mL, 0.2M) under inert atmosphere, a solution of *n*-BuLi (1.6M in hexane, 0.81 mL, 1.3 mmol, 1.3 equiv.) was added dropwise with ice-cooling. The resulting mixture was stirred at room temperature for 1 h before cooling down to 0 °C, and *N,N*-dimethylcarbamoyl chloride (129 mg, 1.20 mmol, 1.20 equiv.) was added over a period of 1 h. After being stirred at room temperature for 14 h, the reaction was quenched with saturated aqueous NH_4Cl (5 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were washed with brine (1 × 5 mL) and dried over anhydrous Na_2SO_4. After evaporation of the solvents under reduced pressure, purification of the residue by flash column chromatography on silica gel (3.5 × 20 cm, cyclohexane:ethyl acetate = 2:1 → 1.5:1, 50 mL, #7–17) afforded the analytically pure indoline with urea directing group **212** (244 mg, 92%) as a white solid.

m.p.: 93–94 °C.

R_f = 0.70 (cyclohexane:ethyl acetate = 2:1).

GLC (HP-5): t_R = 20.4 min.

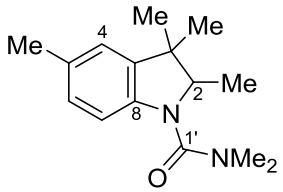
^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ/ppm = 2.93 (s, 6H, N(CH_3)$_2$), 3.02 (dd, $^2J_{3A,3B}$ = 15.7 Hz, $^3J_{3A,2}$ = 9.7 Hz, 1H, H-3A), 3.45 (dd, $^2J_{3B,3A}$ = 15.7 Hz, $^3J_{3B,2}$ = 9.3 Hz, 1H, H-3B), 5.42 (t, $^3J_{2,3}$ = 9.7 Hz, 1H, H-2), 6.79 (d, $^3J_{4,5}$ = 8.1 Hz, 1H, H-4), 6.90 (dd, $^3J_{5,4}$ = $^3J_{5,6}$ = 7.4 Hz, 1H, H-5), 7.14 (d, $^3J_{7,6}$ = 7.4 Hz, 1H, H-7), 7.16 (dd, $^3J_{6,5}$ = $^3J_{6,7}$ = 7.7 Hz, 1H, H-6), 7.23–7.26 (m, 1H, H-4''), 7.31 (dd, $^3J_{3'',2''}$ = $^3J_{3'',4''}$ = 7.4 Hz, 2H, H-3''), 7.38 (dd, $^3J_{2'',3''}$ = 8.3 Hz, $^4J_{2'',4''}$ = 1.1 Hz, 2H, H-2'').

^{13}C NMR (126 MHz, $CDCl_3$, 298 K): δ/ppm = 37.7 (N(*C*H$_3$)$_2$), 38.9 (C-3), 65.8 (C-2), 111.6 (C-4), 121.4 (C-5), 124.9 (C-7), 126.6 (C-2''), 127.5 (C-6), 127.5 (C-4''), 128.7 (C-3''), 129.4 (C-9), 142.9 (C-8), 145.3 (C-1''), 159.4 (C-1').

IR (ATR): $\tilde{\nu}$ /cm^{-1} = 2922 (br), 2850 (w), 1657 (s), 1600 (m), 1475 (s), 1457 (m), 1361 (m), 1241 (m), 1196 (m), 1056 (w), 1002 (w), 944 (w), 842 (vw), 745 (s), 704 (m).

HRMS (APCI) for $C_{17}H_{19}N_2O$ ([M+H]$^+$): calcd. 267.1492
found 267.1482

3.1.4.4 *N,N*,2,3,3,5-Hexamethylindoline-1-carboxamide (217)



217
$C_{15}H_{22}N_2O$
M = 246.35 g/mol

According to **GP 4**, to a flame-dried SCHLENK flask containing a solution of 2,3,3,5-tetramethylindoline (**124**, 200 mg, 1.14 mmol, 1.00 equiv.) in anhydrous diethyl ether (5.7 mL, 0.2M) under inert atmosphere, a solution of *n*-BuLi (1.6M in hexane, 0.93 mL, 1.5 mmol, 1.3 equiv.) was added dropwise with ice-cooling. The resulting mixture was stirred at room

temperature for 1 h before cooling down to 0 °C, and *N*,*N*-dimethylcarbamoyl chloride (147 mg, 1.37 mmol, 1.20 equiv.) was added over a period of 1 h. After being stirred at room temperature for 14 h, the reaction was quenched with saturated aqueous NH_4Cl (5 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were washed with brine (1 × 5 mL) and dried over anhydrous Na_2SO_4. After evaporation of the solvents under reduced pressure, purification of the residue by flash column chromatography on silica gel (3.5 × 20 cm, cyclohexane:ethyl acetate = 4:1, 50 mL, #10–22) afforded the analytically pure indoline with urea directing group **217** (257 mg, 92%) as a yellow solid.

m.p.: 60–61 °C.

R_f = 0.36 (cyclohexane:ethyl acetate = 3:1).

GLC (HP-5): t_R = 16.8 min.

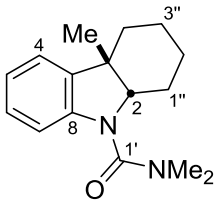
^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ/ppm = 1.08 (s, 3H, 3–C*H*$_3$)*, 1.25 (d, $^3J_{2\text{–}CH_3,2}$ = 6.3 Hz, 3H, 2–C*H*$_3$), 1.28 (s, 3H, 3–C*H*$_3$)*, 2.29 (s, 3H, 5–C*H*$_3$), 2.96 (s, 6H, N(C*H*$_3$)$_2$), 3.90 (q, $^3J_{2,2\text{–}CH_3}$ = 6.3 Hz, 1H, H-2), 6.57 (d, $^3J_{7,6}$ = 8.6 Hz, 1H, H-7), 6.90 (d, $^3J_{6,7}$ = 8.0 Hz, 1H, H-6), 6.91 (s, 1H, H-4).

^{13}C NMR (126 MHz, $CDCl_3$, 298 K): δ/ppm = 13.1 (2–*C*H$_3$), 21.0 (5–*C*H$_3$), 23.1 (3–*C*H$_3$)*, 25.9 (3–*C*H$_3$)*, 37.8 (N(*C*H$_3$)$_2$), 42.3 (C-3), 67.6 (C-2), 111.4 (C-7), 123.2 (C-4), 127.5 (C-6), 130.6 (C-5), 140.1 (C-9), 141.1 (C-8), 159.8 (C-1').

IR (ATR): $\tilde{\nu}$ /cm^{-1} = 2955 (w), 2921 (w), 2863 (w), 1637 (s), 1482 (s), 1445 (m), 1385 (s), 1325 (m), 1262 (m), 1185 (s), 1106 (w), 1040 (w), 943 (w), 895 (w), 820 (m), 771 (w), 716 (w), 686 (w).

HRMS (APCI) for $C_{15}H_{23}N_2O$ ($[M+H]^+$): calcd. 247.1805
found 247.1797

3.1.4.5 *cis*-*N*,*N*,4a-Trimethyl-2,3,4,4a-tetrahydro-1*H*-carbazole-9(9a*H*)-carboxamide (*cis*-218)



cis-**218**
$C_{16}H_{22}N_2O$
M = 258.37 g/mol

According to **GP 4**, to a flame-dried SCHLENK flask containing a solution of *cis*-4a-methyl-2,3,4,4a,9,9a-hexahydro-1*H*-carbazole (*cis*-**127**, 187 mg, 1.00 mmol, 1.00 equiv.) in anhydrous diethyl ether (5.0 mL, 0.2M) under inert atmosphere, a solution of *n*-BuLi (1.6M in hexane, 0.81 mL, 1.3 mmol, 1.3 equiv.) was added dropwise with ice-cooling. The resulting mixture was stirred at room temperature for 1 h before cooling down to 0 °C, and *N*,*N*-dimethylcarbamoyl chloride (129 mg, 1.20 mmol, 1.20 equiv.) was added over a period of 1 h. After being stirred at room temperature for 14 h, the reaction was quenched with saturated aqueous NH_4Cl (5 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were washed with brine (1 × 5 mL) and dried over anhydrous Na_2SO_4. After evaporation of the solvents under reduced pressure, purification of the residue by flash column chromatography on silica gel (3.5 × 20 cm, cyclohexane:ethyl acetate = 3:1, 50 mL, #9–13) afforded the analytically pure indoline with urea directing group *cis*-**218** (220 mg, 85%) as a yellow oil.

R_f = 0.40 (cyclohexane:ethyl acetate = 2:1).

GLC (HP-5): t_R = 18.7 min.

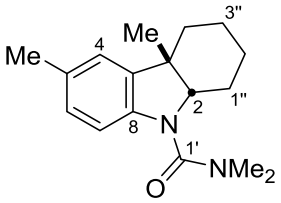
^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ/ppm = 1.31 (s, 3H, 3–CH_3), 1.37–1.45 (m, 4H, H-2'', H-3''), 1.52–1.56 (m, 1H, H-4''), 1.59–1.63 (m, 1H, H-4''), 1.81–1.92 (m, 2H, H-1''), 2.98 (s, 6H, N(CH_3)$_2$), 3.83 (t, $^3J_{2,1''}$ = 4.5 Hz, 1H, H-2), 6.74 (d, $^3J_{4,5}$ = 7.8 Hz, 1H, H-4), 6.89 (ddd, $^3J_{6,5}$ = 7.6 Hz, $^3J_{6,7}$ = 7.5 Hz, $^4J_{6,4}$ = 0.9 Hz, 1H, H-6), 7.07 (dd, $^3J_{7,6}$ = 7.4 Hz, $^3J_{7,5}$ = 0.9 Hz, 1H, H-7), 7.11 (ddd, $^3J_{5,4}$ = 7.9 Hz, $^3J_{5,6}$ = 7.8 Hz, $^4J_{5,7}$ = 1.3 Hz, 1H, H-5).

^{13}C NMR (126 MHz, $CDCl_3$, 298 K): δ/ppm = 21.7 (C-2'')*, 21.8 (C-3'')*, 23.8 (3–CH$_3$), 24.8 (C-1''), 35.7 (C-4''), 37.8 (N(CH$_3$)$_2$), 42.1 (C-3), 68.3 (C-2), 112.4 (C-4), 121.2 (C-6), 121.8 (C-7), 127.0 (C-5), 140.3 (C-9), 143.5 (C-8), 159.6 (C-1').

IR (ATR): $\tilde{\nu}$ /cm^{-1} = 2932 (w), 1655 (s), 1599 (m), 1465 (s), 1251 (s), 1226 (m), 1200 (m), 1189 (w), 1092 (w), 1066 (w), 1002 (w), 989 (m), 852 (w).

HRMS (APCI) for $C_{16}H_{23}N_2O$ ([M+H]$^+$): calcd. 259.1805
found 259.1796

3.1.4.6 *cis*-*N*,*N*,4a,6-Tetramethyl-1,2,3,4,4a,9a-hexahydro-9*H*-carbazole-9-carboxamide (*cis*-219)



cis-**219**
$C_{17}H_{24}N_2O$
M = 272.39 g/mol

According to **GP 4**, to a flame-dried SCHLENK flask containing a solution of *cis*-4a,6-dimethyl-2,3,4,4a,9,9a-hexahydro-1*H*-carbazole (*cis*-**128**, 230 mg, 1.14 mmol, 1.00 equiv.) in anhydrous diethyl ether (5.7 mL, 0.2M) under inert atmosphere, a solution of *n*-BuLi (1.6M in hexane, 0.93 mL, 1.5 mmol, 1.3 equiv.) was added dropwise with ice-cooling. The resulting mixture was stirred at room temperature for 1 h before cooling down to 0 °C, and *N*,*N*-dimethylcarbamoyl chloride (147 mg, 1.37 mmol, 1.20 equiv.) was added over a period of 1 h. After being stirred at room temperature for 14 h, the reaction was quenched with saturated aqueous NH_4Cl (5 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were washed with brine (1 × 5 mL) and dried over anhydrous Na_2SO_4. After evaporation of the solvents under reduced pressure, purification of the residue by flash column chromatography on silica gel (3.5 × 20 cm, cyclohexane:ethyl acetate = 4:1, 50 mL, #11–23) afforded the analytically pure indoline with urea directing group *cis*-**219** (279 mg, 90%) as a white solid.

m.p.: 91–92 °C.

R_f = 0.41 (cyclohexane:ethyl acetate = 1:1).

GLC (HP-5): t_R = 17.3 min.

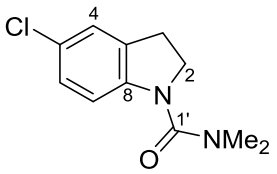
^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ/ppm = 1.28 (s, 3H, 3–C*H*$_3$), 1.35–1.43 (m, 4H, H-2'', H-3''), 1.50–1.55 (m, 1H, H-4''), 1.60–1.65 (m, 1H, H-4''), 1.83–1.87 (m, 2H, H-1''), 2.30 (s, 3H, H-5), 2.96 (s, 6H, N(C*H*$_3$)$_2$), 3.80 (t, $^3J_{1'',2}$ = 5.0 Hz, 1H, H-2), 6.64 (d, $^3J_{7,6}$ = 8.0 Hz, 1H, H-7), 6.89 (s, 1H, H-4), 6.91 (dd, $^3J_{6,7}$ = 8.1 Hz, 1H, H-6).

^{13}C NMR (100 MHz, $CDCl_3$, 298 K): δ/ppm = 21.1 (C-2'')*, 21.8 (C-3'')*, 21.8 (5–*C*H$_3$), 24.0 (3–*C*H$_3$), 24.9 (C-1''), 35.6 (C-4''), 37.8 (N(*C*H$_3$)$_2$), 42.1 (C-3), 68.4 (C-2), 112.3 (C-7), 122.6 (C-4), 127.3 (C-6), 130.6 (C-5), 140.4 (C-9), 141.1 (C-8), 159.7 (C-1').

IR (ATR): $\tilde{\nu}$ /cm^{-1} = 2914 (s), 2873 (w), 1658 (s), 1481 (s), 1444 (m), 1383 (s), 1334 (m), 1239 (m), 1188 (s), 1156 (m), 1058 (m), 991 (w), 885 (w), 811 (s), 688 (w).

HRMS (APCI) for $C_{17}H_{25}N_2O$ ([M+H]$^+$): calcd. 273.1961
found 273.1953

3.1.4.7 5-Chloro-*N,N*-dimethylindoline-1-carboxamide (276)



276
$C_{11}H_{13}ClN_2O$
M = 224.69 g/mol

According to **GP 4**, to a flame-dried SCHLENK flask containing a solution of 5-chloroindoline (154 mg, 1.00 mmol, 1.00 equiv.) in anhydrous diethyl ether (5.0 mL, 0.2M) under inert atmosphere, a solution of *n*-BuLi (1.6M in hexane, 0.81 mL, 1.3 mmol, 1.3 equiv.) was added dropwise with ice-cooling. The resulting mixture was stirred at room temperature for 1 h before cooling down to 0 °C, and *N,N*-dimethylcarbamoyl chloride (129 mg, 1.20 mmol, 1.20 equiv.) was added over a period of 1 h. After being stirred at room temperature for 14 h, the reaction was quenched with saturated aqueous NH_4Cl (5 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were washed with brine (1 × 5 mL) and dried over anhydrous Na_2SO_4. After evaporation of the solvents under reduced pressure, purification of the residue by flash column chromatography on silica gel (3.0 × 20 cm,

cyclohexane:ethyl acetate = 2:1 → 1.5:1, 100 mL, #19–29) afforded the analytically pure indoline with urea directing group **276** (188 mg, 83%) as a dark brown oil.

R_f = 0.20 (cyclohexane:ethyl acetate = 2:1).

GLC (HP-5): t_R = 17.9 min.

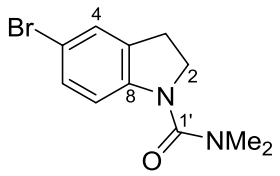
^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ/ppm = 2.89 (s, 6H, N(CH_3)$_2$), 2.98 (t, $^3J_{3,2}$ = 7.9 Hz, 2H, H-3), 3.87 (t, $^3J_{2,3}$ = 8.3 Hz, 2H, H-2), 6.85 (d, $^3J_{7,6}$ = 8.5 Hz, 1H, H-7), 7.05 (dd, $^3J_{6,7}$ = 8.5 Hz, $^4J_{6,4}$ = 2.2 Hz, 1H, H-6), 7.08 (s, 1H, H-4).

^{13}C NMR (126 MHz, $CDCl_3$, 298 K): δ/ppm = 28.1 (C-3), 38.1 (N(*C*H$_3$)$_2$), 50.6 (C-2), 114.4 (C-7), 125.0 (C-4), 126.2 (C-5), 126.9 (C-6), 133.3 (C-9), 143.2 (C-8), 160.1 (C-1').

IR (ATR): $\tilde{\nu}$ /cm^{-1} = 2891 (w), 1651 (s), 1596 (m), 1470 (s), 1437 (m), 1375 (s), 1251 (s), 1179 (s), 1093 (w), 1068 (w), 1050 (w), 1003 (w), 805 (m), 764 (m), 600 (m).

HRMS (APCI) for $C_{11}H_{14}ClN_2O$ ([M+H]$^+$): calcd. 225.0789
found 225.0784

3.1.4.8 5-Bromo-*N*,*N*-dimethylindoline-1-carboxamide (215)



215
$C_{11}H_{13}BrN_2O$
M = 269.14 g/mol

According to **GP 4**, to a flame-dried SCHLENK flask containing a solution of 5-bromoindoline (650 mg, 3.28 mmol, 1.00 equiv.) in anhydrous diethyl ether (16 mL, 0.2M) under inert atmosphere, a solution of *n*-BuLi (1.6M in hexane, 2.67 mL, 4.26 mmol, 1.30 equiv.) was added dropwise with ice-cooling. The resulting mixture was stirred at room temperature for 1 h before cooling down to 0 °C, and *N*,*N*-dimethylcarbamoyl chloride (1.17 g, 3.93 mmol, 1.20 equiv.) was added over a period of 1 h. After being stirred at room temperature for 14 h, the reaction was quenched with saturated aqueous NH_4Cl (10 mL) and extracted with CH_2Cl_2

(3 × 15 mL). The combined organic phases were washed with brine (1 × 10 mL) and dried over anhydrous Na_2SO_4. After evaporation of the solvents under reduced pressure, purification of the residue by flash column chromatography on silica gel (3.5 × 25 cm, cyclohexane:ethyl acetate = 1:1, 100 mL, #9–20) afforded the analytically pure indoline with urea directing group **215** (653 mg, 74%) as a white solid.

m.p.: 65–66 °C.

R_f = 0.40 (cyclohexane:ethyl acetate = 1:2).

GLC (HP-5): t_R = 15.5 min.

^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ/ppm = 2.92 (s, 6H, N(CH_3)$_2$), 3.02 (t, $^3J_{3,2}$ = 8.4 Hz, 2H, H-3), 3.90 (t, $^3J_{2,3}$ = 8.4 Hz, 2H, H-2), 6.82 (d, $^3J_{7,6}$ = 8.8 Hz, 1H, H-7), 7.21–7.24 (m, 1H, H-6), 7.27 (s, 1H, H-4).

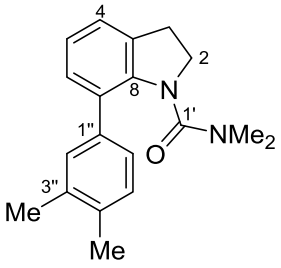
^{13}C NMR (100 MHz, $CDCl_3$, 298 K): δ/ppm = 28.1 (C-3), 38.3 (N(*C*H$_3$)$_2$), 50.6 (C-2), 113.6 (C-5), 115.0 (C-7), 128.0 (C-4), 129.9 (C-6), 133.8 (C-9), 143.8 (C-8), 160.1 (C-1').

IR (ATR): $\tilde{\nu}$ /cm^{-1} = 2887 (br), 1646 (s), 1465 (s), 1355 (s), 1248 (m), 1177 (m), 1091 (w), 1053 (w), 1001 (w), 929 (vw), 872 (w), 802 (m), 760 (m), 660 (m).

HRMS (APCI) for $C_{11}H_{14}BrN_2O$ ($[M+H]^+$): calcd. 269.0284
found 269.0277

3.1.5 Preparation of C-7 Arylated Indolines Using $Cu(OAc)_2$ or Dioxygen as Terminal Oxidant

3.1.5.1 7-(3,4-Dimethylphenyl)-*N*,*N*-dimethylindoline-1-carboxamide (184)



184
$C_{19}H_{22}N_2O$
M = 294.40 g/mol

According to **GP 6**, a flame-dried SCHLENK tube equipped with a magnetic stir bar was successively charged with *N*,*N*-dimethylindoline-1-carboxamide (**91**, 38 mg, 0.20 mmol, 1.0 equiv.) and $Pd(OAc)_2$ (4.5 mg, 0.020 mmol, 10 mol%) under inert atmosphere. The tube was then evacuated and backfilled with O_2 (balloon, 3 cycles) followed by the addition of TFA (0.20 mL, 0.26 mmol, 13 equiv.) and *o*-xylene (**94**, 1.0 mL, 0.2 M). The reaction mixture was stirred at 50 °C for 18 h. After complete consumption of the indoline, as monitored by GLC analysis using tetracosane (10 mg, 0.030 mmol, 15 mol%) as internal standard, the reaction mixture was allowed to cool to room temperature and diluted with ethyl acetate (5 mL). The crude reaction mixture was washed with saturated aqueous Na_2CO_3 (1 × 5 mL) and H_2O (1 × 5 mL), phases were separated. The organic layer was dried over anhydrous Na_2SO_4. After evaporation of the solvents under reduced pressure, purification of the residue by flash column chromatography on silica gel (2.5 × 20 cm, cyclohexane:ethyl acetate = 1:1.5 → 1:2, 50 mL, #11–18) afforded the analytically pure arylated product **184** (50 mg, 85%) as a brown solid.

Alternatively, according to **GP 5**, a flame-dried SCHLENK tube equipped with a magnetic stir bar was successively charged with *N*,*N*-dimethylindoline-1-carboxamide (**91**, 38 mg, 0.20 mmol, 1.0 equiv.), $Pd(OAc)_2$ (4.5 mg, 0.020 mmol, 10 mol%), $Cu(OAc)_2$ (36 mg, 0.20 mmol 1.0 equiv.), TFA (0.20 mL, 0.26 mmol, 13 equiv.), and *o*-xylene (**94**, 1.0 mL, 0.2 M) in the open air. The reaction mixture was stirred at 50 °C for 18 h. After complete consumption of the indoline, as monitored by GLC analysis using tetracosane (10 mg, 0.030 mmol, 15 mol%) as internal standard, the reaction mixture was allowed to cool to room temperature and diluted with ethyl acetate (5 mL). The crude reaction mixture was washed

with saturated aqueous Na_2CO_3 (1 × 5 mL) and H_2O (1 × 5 mL), phases were separated. The organic layer was dried over anhydrous Na_2SO_4. After evaporation of the solvents under reduced pressure, purification of the residue by flash column chromatography on silica gel (2.5 × 20 cm, cyclohexane:ethyl acetate = 1:1.5 → 1:2, 50 mL, #13–19) afforded the analytically pure arylated product **184** (48 mg, 81%) as a brown solid.

m.p.: 132–133 °C.

R_f = 0.21 (cyclohexane:ethyl acetate = 1:2).

GLC (HP-5): t_R = 22.1 min.

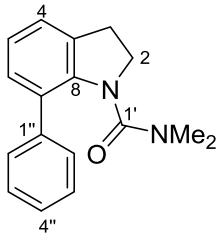
^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ/ppm = 2.26 (s, 3H, 3''–C*H*$_3$)*, 2.28 (s, 3H, 4''–C*H*$_3$)*, 2.61 (s, 6H, N(C*H*$_3$)$_2$), 3.10 (t, $^3J_{3,2}$ = 7.8 Hz, 2H, H-3), 3.97 (t, $^3J_{2,3}$ = 7.8 Hz, 2H, H-2), 7.01 (dd, $^3J_{5,4}$ = 7.5 Hz, $^3J_{5,6}$ = 7.4 Hz, 1H, H-5), 7.11–7.14 (m, 2H, H-4, H-6), 7.16 (d, $^3J_{5'',6''}$ = 7.7 Hz, 1H, H-5''), 7.20 (d, $^3J_{6'',5''}$ = 7.7 Hz, 1H, H-6''), 7.24 (s, 1H, H-2'').

^{13}C NMR (126 MHz, $CDCl_3$, 298 K): δ/ppm = 19.6 (3''–*C*H$_3$)*, 20.0 (4''–*C*H$_3$)*, 29.9 (C-3), 36.9 (N(*C*H$_3$)$_2$), 52.0 (C-2), 123.1 (C-5), 123.4 (C-6), 124.4 (C-4), 128.2 (C-2''), 129.0 (C-7), 129.2 (C-5''), 129.6 (C-6''), 133.7 (C-1''), 135.0 (C-3'')**, 136.2 (C-4'')**, 137.9 (C-9), 142.4 (C-8), 159.9 (C-1').

IR (ATR): $\tilde{\nu}$ /cm^{-1} = 2916 (br), 2849 (br), 1653 (s), 1589 (w), 1434 (m), 1376 (s), 1257 (m), 1165 (m), 1102 (w), 1061 (w), 1004 (w), 884 (vw), 811 (w), 776 (m), 761 (s), 677 (w).

HRMS (APCI) for $C_{19}H_{23}N_2O$ ($[M+H]^+$): calcd. 295.1805
found 295.1805

3.1.5.2 *N,N*-Dimethyl-7-phenylindoline-1-carboxamide (92)



92
$C_{17}H_{18}N_2O$
M = 266.34 g/mol

According to **GP 5**, a flame-dried SCHLENK tube equipped with a magnetic stir bar was successively charged with *N,N*-dimethylindoline-1-carboxamide (**91**, 38 mg, 0.20 mmol, 1.0 equiv.), $Pd(OAc)_2$ (4.5 mg, 0.020 mmol, 10 mol%), $Cu(OAc)_2$ (36 mg, 0.20 mmol 1.0 equiv.), TFA (0.20 mL, 0.26 mmol, 13 equiv.), and benzene (**62**, 1.0 mL, 0.2M) in the open air. The reaction mixture was stirred at 50 °C for 20 h. After complete consumption of the indoline, as monitored by GLC analysis using tetracosane (10 mg, 0.030 mmol, 15 mol%) as internal standard, the reaction mixture was allowed to cool to room temperature and diluted with ethyl acetate (5 mL). The crude reaction mixture was washed with saturated aqueous Na_2CO_3 (1 × 5 mL) and H_2O (1 × 5 mL), phases were separated. The organic layer was dried over anhydrous Na_2SO_4. After evaporation of the solvents under reduced pressure, purification of the residue by flash column chromatography on silica gel (2.5 × 20 cm, cyclohexane:ethyl acetate = 1:1 → 1:2, 50 mL, #12–21) afforded the analytically pure arylated product **92** (38 mg, 71%) as a light yellow solid.

m.p.: 140–141 °C.

R_f = 0.35 (cyclohexane:ethyl acetate = 1:2).

GLC (HP-5): t_R = 20.6 min.

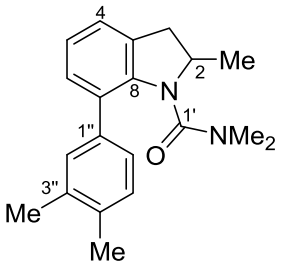
^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ/ppm = 2.54 (s, 6H, N(C*H*$_3$)$_2$), 3.10 (t, $^3J_{3,2}$ = 8.0 Hz, 2H, H-3), 3.97 (t, $^3J_{2,3}$ = 8.0 Hz, 2H, H-2), 7.02 (d, $^3J_{4,5}$ = 7.5 Hz, 1H, H-4), 7.14–7.18 (m, 2H, H-Ar), 7.24–7.27 (m, 1H, H-Ar), 7.34–7.37 (m, 2H, H-Ar), 7.42–7.45 (m, 2H, H-Ar).

^{13}C NMR (126 MHz, $CDCl_3$, 298 K): δ/ppm = 29.8 (C-3), 36.9 (N(*C*H$_3$)$_2$), 52.0 (C-2), 123.1 (C-6), 123.8 (C-4), 126.8 (C-5), 127.2 (C-2''), 128.3 (C-7), 129.1 (C-4''), 129.2 (C-3''), 133.8 (C-9), 140.5 (C-1''), 142.5 (C-8), 159.8 (C-1').

IR (ATR): $\tilde{\nu}$ /cm^{-1} = 2917 (br), 1736 (vw), 1650 (s), 1455 (m), 1376 (s), 1265 (m), 1219 (m), 1169 (m), 1102 (s), 1069 (w), 1024 (w), 962 (w), 895 (w), 753 (s), 700 (s).

HRMS (APCI) for $C_{17}H_{19}N_2O$ ([M+H]$^+$): calcd. 267.1492
found 267.1482

3.1.5.3 7-(3,4-Dimethylphenyl)-*N,N*,2-trimethylindoline-1-carboxamide (185)



185
$C_{20}H_{24}N_2O$
M = 308.43 g/mol

According to **GP 5**, a flame-dried SCHLENK tube equipped with a magnetic stir bar was successively charged *N,N*,2-trimethylindoline-1-carboxamide (**183**, 41 mg, 0.20 mmol, 1.0 equiv.), $Pd(OAc)_2$ (4.5 mg, 0.020 mmol, 10 mol%), $Cu(OAc)_2$ (36 mg, 0.20 mmol 1.0 equiv.), TFA (0.20 mL, 0.26 mmol, 13 equiv.), and *o*-xylene (**94**, 1.0 mL, 0.2M) in the open air. The reaction mixture was stirred at 50 °C for 20 h. After complete consumption of the indoline, as monitored by GLC analysis using tetracosane (10 mg, 0.030 mmol, 15 mol%) as internal standard, the reaction mixture was allowed to cool to room temperature and diluted with ethyl acetate (5 mL). The crude reaction mixture was washed with saturated aqueous Na_2CO_3 (1 × 5 mL) and H_2O (1 × 5 mL), phases were separated. The organic layer was dried over anhydrous Na_2SO_4. After evaporation of the solvents under reduced pressure, purification of the residue by flash column chromatography on silica gel (2.5 × 20 cm, cyclohexane:ethyl acetate = 4:1 → 3:1, 50 mL, #14–21) afforded the analytically pure arylated product **185** (56 mg, 90%) as a light yellow oil.

R_f = 0.35 (cyclohexane:ethyl acetate = 2:1).

GLC (HP-5): t_R = 21.6 min.

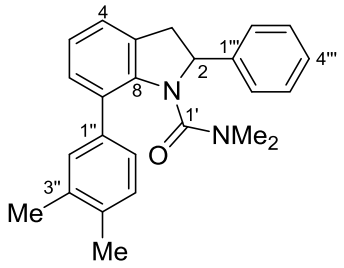
^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ/ppm = 1.44 (d, $^3J_{2-CH_3,2}$ = 6.0 Hz, 3H, 2–CH_3), 2.26 (s, 6H, 3''–CH_3, 4''–CH_3), 2.29 (s, 6H, N(CH_3)$_2$), 2.60 (dd, $^2J_{3A,3B}$ = 15.3 Hz, $^3J_{3A,2}$ = 3.6 Hz, 1H, H-3A), 3.27 (dd, $^2J_{3B,3A}$ = 15.3 Hz, $^3J_{3B,2}$ = 8.0 Hz, 1H, H-3B), 4.35–4.41 (m, 1H, H-2), 6.95 (dd, $^3J_{5,4}$ = 7.5 Hz, $^3J_{5,6}$ = 7.3 Hz, 1H, H-5), 7.10 (d, $^3J_{6'',5''}$ = 7.5 Hz, 1H, H-6''), 7.11–7.14 (m, 3H, H-4, H-6, H-5''), 7.17 (s, 1H, H-2'').

^{13}C NMR (126 MHz, $CDCl_3$, 298 K): δ/ppm = 19.5 (3''–CH$_3$)*, 19.9 (4''–CH$_3$)*, 20.5 (2–CH$_3$), 36.6 (C-3), 37.3 (N(CH$_3$)$_2$), 59.3 (C-2), 122.2 (C-5), 123.9 (C-6), 124.7 (C-4), 128.1 (C-2''), 128.5 (C-7), 129.4 (C-6''), 129.5 (C-5''), 132.3 (C-1''), 135.2 (C-3'')**, 136.3 (C-4'')**, 137.3 (C-9), 141.3 (C-8), 158.4 (C-1').

IR (ATR): $\tilde{\nu}$ /cm^{-1} = 2919 (br), 1736 (vw), 1639 (s), 1486 (m), 1434 (s), 1381 (s), 1271 (s), 1212 (m), 1105 (w), 1061 (w), 1031 (w), 959 (w), 886 (w), 821 (w), 772 (m), 744 (m), 687 (w).

HRMS (APCI) for $C_{20}H_{25}N_2O$ ([M+H]$^+$): calcd. 309.1961
found 309.1956

3.1.5.4 7-(3,4-Dimethylphenyl)-*N,N*-dimethyl-2-phenylindoline-1-carboxamide (220)



220
$C_{25}H_{26}N_2O$
M = 370.50 g/mol

According to **GP 5**, a flame-dried SCHLENK tube equipped with a magnetic stir bar was successively charged with *N,N*-dimethyl-2-phenylindoline-1-carboxamide (**212**, 53 mg, 0.20 mmol, 1.0 equiv.), $Pd(OAc)_2$ (4.5 mg, 0.020 mmol, 10 mol%), $Cu(OAc)_2$ (36 mg, 0.20 mmol 1.0 equiv.), TFA (0.20 mL, 0.26 mmol, 13 equiv.), and *o*-xylene (**94**, 1.0 mL, 0.2M) in the open air. The reaction mixture was stirred at 50 °C for 20 h. After complete consumption of the indoline, as monitored by GLC analysis using tetracosane (10 mg, 0.030 mmol, 15 mol%) as internal standard, the reaction mixture was allowed to cool to room temperature and diluted with ethyl acetate (5 mL). The crude reaction mixture was washed

with saturated aqueous Na_2CO_3 (1 × 5 mL) and H_2O (1 × 5 mL), phases were separated. The organic layer was dried over anhydrous Na_2SO_4. After evaporation of the solvents under reduced pressure, purification of the residue by flash column chromatography on silica gel (2.5 × 20 cm, cyclohexane:ethyl acetate = 3:1 → 2:1, 50 mL, #11–18) afforded the analytically pure arylated product **220** (14 mg, 18%) as a light yellow oil.

R_f = 0.31 (cyclohexane:ethyl acetate = 2:1).

GLC (HP-5): t_R = 26.0 min.

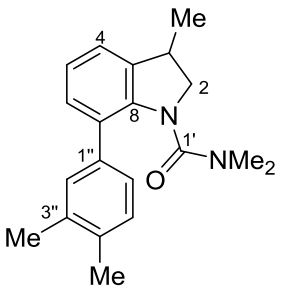
^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ/ppm = 2.25 (s, 3H, 3''–CH_3)*, 2.26 (s, 3H, 4''–CH_3)*, 2.41 (s, 6H, N(CH_3)$_2$), 2.99 (dd, $^2J_{3A,3B}$ = 16.0 Hz, $^3J_{3A,2}$ = 4.8 Hz, 1H, H-3A), 3.68 (dd, $^2J_{3B,3A}$ = 15.2 Hz, $^3J_{3B,2}$ = 8.8 Hz, 1H, H-3B), 5.21 (dd, $^3J_{2,3A}$ = 9.1 Hz, $^3J_{2,3B}$ = 4.3 Hz, 1H, H-2), 7.03 (dd, $^3J_{5,4}$ = 7.6 Hz, $^3J_{5,6}$ = 7.4 Hz, 1H, H-5), 7.11 (dd, $^3J_{3''',2'''}$ = 7.7 Hz, $^3J_{3''',4'''}$ = 7.4 Hz, 2H, H-3'''), 7.20 (d, $^3J_{6'',5''}$ = 7.7 Hz, 1H, H-6''), 7.23–7.27 (m, 2H, H-4, H-6), 7.30–7.34 (m, 3H, H-2'', H-5'', H-4'''), 7.39 (d, $^3J_{2''',3'''}$ = 7.3 Hz, 2H, H-2''').

^{13}C NMR (126 MHz, $CDCl_3$, 298 K): δ/ppm = 19.6 (3''–CH_3)*, 20.0 (4''–CH_3)*, 37.1 (N(CH_3)$_2$), 39.9 (C-3), 67.2 (C-2), 123.3 (C-5), 123.8 (C-6), 124.7 (C-4), 126.2 (C-4'''), 127.5 (C-2'''), 128.6 (C-3'''), 128.8 (C-2''), 128.9 (C-7), 129.5 (C-5''), 129.6 (C-6''), 132.0 (C-1''), 135.2 (C-3'')**, 136.3 (C-4'')**, 137.6 (C-9), 143.1 (C-8), 143.7 (C-1'''), 160.1 (C-1').

IR (ATR): $\tilde{\nu}$ /cm^{-1} = 3025 (w), 2922 (br), 1735 (w), 1661 (s), 1489 (m), 1438 (s), 1380 (s), 1261 (m), 1181 (m), 1063 (w), 1018 (w), 881 (w), 799 (w), 769 (m), 700 (m).

HRMS (APCI) for $C_{25}H_{27}N_2O$ ($[M+H]^+$): calcd. 371.2118
found 371.2112

3.1.5.5 7-(3,4-Dimethylphenyl)-*N*,*N*,3-trimethylindoline-1-carboxamide (221)



221

$C_{20}H_{24}N_2O$

M = 308.43 g/mol

According to **GP 5**, a flame-dried SCHLENK tube equipped with a magnetic stir bar was successively charged with *N*,*N*,3-trimethylindoline-1-carboxamide (**213**, 41 mg, 0.20 mmol, 1.0 equiv.), $Pd(OAc)_2$ (4.5 mg, 0.020 mmol, 10 mol%), $Cu(OAc)_2$ (36 mg, 0.20 mmol 1.0 equiv.), TFA (0.20 mL, 0.26 mmol, 13 equiv.), and *o*-xylene (**94**, 1.0 mL, 0.2M) in the open air. The reaction mixture was stirred at 50 °C for 26 h. After complete consumption of the indoline, as monitored by GLC analysis using tetracosane (10 mg, 0.030 mmol, 15 mol%) as internal standard, the reaction mixture was allowed to cool to room temperature and diluted with ethyl acetate (5 mL). The crude reaction mixture was washed with saturated aqueous Na_2CO_3 (1 × 5 mL) and H_2O (1 × 5 mL), phases were separated. The organic layer was dried over anhydrous Na_2SO_4. After evaporation of the solvents under reduced pressure, purification of the residue by flash column chromatography on silica gel (2.5 × 20 cm, cyclohexane:ethyl acetate = 1:1 → 1:1.5, 50 mL, #12–20) afforded the analytically pure arylated product **221** (41 mg, 67%) as a light yellow oil.

R_f = 0.36 (cyclohexane:ethyl acetate = 1:2).

GLC (HP-5): t_R = 22.2 min.

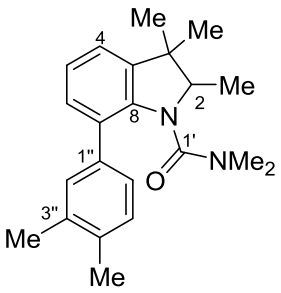
^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ/ppm = 1.34 (d, $^3J_{3-CH_3,3}$ = 6.6 Hz, 3H, 3–CH_3), 2.26 (s, 3H, 3''–CH_3)*, 2.27 (s, 3H, 4''–CH_3)*, 2.57 (s, 6H, N(CH_3)$_2$), 3.40 (dd, $^2J_{2A,2B}$ = 14.5 Hz, $^3J_{2A,3}$ = 7.5 Hz, 1H, H-2A), 3.55 (dd, $^2J_{2B,2A}$ = 10.0 Hz, $^3J_{2B,3}$ = 7.9 Hz, 1H, H-2B), 4.08 (dd, $^3J_{3,2A}$ = 9.7 Hz, $^3J_{3,2B}$ = 8.5 Hz, 1H, H-3), 7.03 (dd, $^3J_{5,4}$ = 7.5 Hz, $^3J_{5,6}$ = 7.3 Hz, 1H, H-5), 7.10 (d, $^3J_{5'',6''}$ = 7.3 Hz, 1H, H-5''), 7.11 (d, $^3J_{6'',5''}$ = 7.4 Hz, 1H, H-6''), 7.16–7.20 (m, 2H, H-4, H-6), 7.23 (s, 1H, H-2'').

^{13}C NMR (126 MHz, $CDCl_3$, 298 K): δ/ppm = 18.9 (3''–*C*H$_3$)*, 19.6 (4''–*C*H$_3$)*, 20.0 (3–*C*H$_3$), 36.4 (C-3), 37.0 (N(*C*H$_3$)$_2$), 59.8 (C-2), 122.2 (C-6), 123.3 (C-5), 124.5 (C-4), 128.3 (C-2''), 129.2 (C-5''), 129.2 (C-6''), 129.7 (C-7), 135.1 (C-1''), 136.3 (C-3'')**, 137.8 (C-4'')**, 138.9 (C-9), 141.9 (C-8), 159.8 (C-1').

IR (ATR): $\tilde{\nu}$ /cm^{-1} = 2921 (br), 2864 (w), 1782 (vw), 1652 (s), 1437 (s), 1377 (s), 1276 (m), 1173 (m), 1162 (w), 1128 (w), 906 (w), 786 (s), 727 (s).

HRMS (APCI) for $C_{20}H_{25}N_2O$ ([M+H]$^+$): calcd. 309.1961
found 309.1956

3.1.5.6 7-(3,4-Dimethylphenyl)-*N,N*,2,3,3-pentamethylindoline-1-carboxamide (224)



224
$C_{22}H_{28}N_2O$
M = 336.48 g/mol

According to **GP 5**, a flame-dried SCHLENK tube equipped with a magnetic stir bar was successively charged with *N,N*,2,3,3-pentamethylindoline-1-carboxamide (**216**, 46 mg, 0.20 mmol, 1.0 equiv.), $Pd(OAc)_2$ (4.5 mg, 0.020 mmol, 10 mol%), $Cu(OAc)_2$ (36 mg, 0.20 mmol 1.0 equiv.), TFA (0.20 mL, 0.26 mmol, 13 equiv.), and *o*-xylene (**94**, 1.0 mL, 0.2M) in the open air. The reaction mixture was stirred at 50 °C for 24 h. After complete consumption of the indoline, as monitored by GLC analysis using tetracosane (10 mg, 0.030 mmol, 15 mol%) as internal standard, the reaction mixture was allowed to cool to room temperature and diluted with ethyl acetate (5 mL). The crude reaction mixture was washed with saturated aqueous Na_2CO_3 (1 × 5 mL) and H_2O (1 × 5 mL), phases were separated. The organic layer was dried over anhydrous Na_2SO_4. After evaporation of the solvents under reduced pressure, purification of the residue by flash column chromatography on silica gel (2.5 × 20 cm, cyclohexane:ethyl acetate = 3:1 → 2:1, 50 mL, #15–23) afforded the analytically pure arylated product **224** (46 mg, 71%) as a light brown oil.

R_f = 0.36 (cyclohexane:ethyl acetate = 2:1).

GLC (HP-5): t_R = 22.3 min.

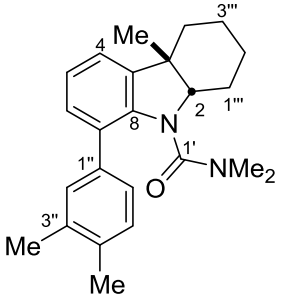
^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ/ppm = 1.21 (br s, 3H, 3–C*H*$_3$)*, 1.28 (s, 3H, 3–C*H*$_3$)*, 1.36 (d, $^3J_{2\text{–}CH_3,2}$ = 6.6 Hz, 3H, 2–C*H*$_3$), 2.24 (br s, 6H, N(C*H*$_3$)$_2$), 2.27 (s, 3H, 3''–C*H*$_3$)**, 2.29 (s, 3H, 4''–C*H*$_3$)**, 3.97 (q, $^3J_{2,2\text{–}CH_3}$ = 6.6 Hz, 1H, H-2), 6.99 (dd, $^3J_{5,4}$ = 7.5 Hz, $^3J_{5,6}$ = 7.3 Hz, 1H, H-5), 7.05–7.11 (m, 3H, H-6, H-5'', H-6''), 7.14 (d, $^3J_{4,5}$ = 7.6 Hz, 1H, H-4), 7.15 (s, 1H, H-2'').

^{13}C NMR (126 MHz, $CDCl_3$, 298 K): δ/ppm = 14.7 (2–*C*H$_3$), 19.5 (3''–*C*H$_3$)*, 19.9 (4''–*C*H$_3$)*, 21.8 (3–*C*H$_3$)**, 36.5 (3–*C*H$_3$)**, 37.8 (N(*C*H$_3$)$_2$), 43.2 (C-3), 69.6 (C-2), 121.3 (C-5), 122.4 (C-6), 124.8 (C-4), 127.6 (C-2''), 128.7 (C-7), 129.5 (C-5'')***, 129.7 (C-6'')***, 129.9 (C-1''), 135.3 (C-3'')****, 136.3 (C-4'')****, 137.2 (C-7), 141.6 (C-8), 158.1 (C-1').

IR (ATR): $\tilde{\nu}$ /cm^{-1} = 2961 (w), 2921 (w), 2863 (w), 1775 (vw), 1639 (s), 1488 (m), 1431 (s), 1383 (s), 1281 (w), 1206 (w), 1165 (m), 1036 (w), 908 (w), 822 (w), 789 (w), 728 (s).

HRMS (APCI) for $C_{22}H_{29}N_2O$ ([M+H]$^+$): calcd. 337.2274
found 337.2267

3.1.5.7 *cis*-8-(3,4-Dimethylphenyl)-*N*,*N*,4a-trimethyl-1,2,3,4,4a,9a-hexahydro-9*H*-carbazole-9-carboxamide (*cis*-226)



cis-**226**
$C_{24}H_{30}N_2O$
M = 362.52 g/mol

According to **GP 5**, a flame-dried SCHLENK tube equipped with a magnetic stir bar was successively charged with *cis*-*N*,*N*,4a-trimethyl-1,2,3,4,4a,9a-hexahydro-9*H*-carbazole-9-

carboxamide (*cis*-**218**, 52 mg, 0.20 mmol, 1.0 equiv.), $Pd(OAc)_2$ (4.5 mg, 0.020 mmol, 10 mol%), $Cu(OAc)_2$ (36 mg, 0.20 mmol 1.0 equiv.), TFA (0.20 mL, 0.26 mmol, 13 equiv.), and *o*-xylene (**94**, 1.0 mL, 0.2M) in the open air. The reaction mixture was stirred at 50 °C for 24 h. After complete consumption of the indoline, as monitored by GLC analysis using tetracosane (10 mg, 0.030 mmol, 15 mol%) as internal standard, the reaction mixture was allowed to cool to room temperature and diluted with ethyl acetate (5 mL). The crude reaction mixture was washed with saturated aqueous Na_2CO_3 (1 × 5 mL) and H_2O (1 × 5 mL), phases were separated. The organic layer was dried over anhydrous Na_2SO_4. After evaporation of the solvents under reduced pressure, purification of the residue by flash column chromatography on silica gel (2.5 × 20 cm, cyclohexane:ethyl acetate = 4:1 → 3:1, 50 mL, #21–28) afforded the analytically pure arylated product *cis*-**226** (55 mg, 75%) as a light brown oil.

R_f = 0.45 (cyclohexane:ethyl acetate = 2:1).

GLC (HP-5): t_R = 24.6 min.

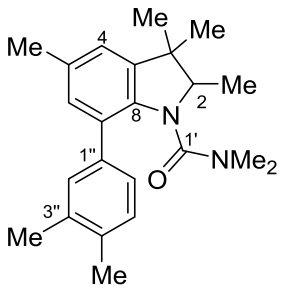
^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ/ppm = 1.23 (s, 3H, 3–CH_3), 1.25–1.31 (m, 3H, H-3’’’, H-2’’’), 1.51–1.59 (m, 4H, H-1’’’, H-2’’’, H-4’’’), 2.04–2.08 (m, 1H, H-1’’’), 2.26 (s, 3H, 3’’–CH_3)*, 2.29 (s, 3H, 4’’–CH_3)*, 2.30 (br s, 6H, N(CH_3)$_2$), 3.83 (dd, $^3J_{2,1'''A}$ = 8.1 Hz, $^3J_{2,1'''B}$ = 5.7 Hz, 1H, H-2), 7.00 (dd, $^3J_{5,4}$ = $^3J_{5,6}$ = 7.3 Hz, 1H, H-5), 7.04 (dd, $^3J_{4,5}$ = 7.3 Hz, $^4J_{4,6}$ = 1.5 Hz, 1H, H-4), 7.09 (dd, $^3J_{6,5}$ = 7.6 Hz, $^4J_{6,4}$ = 1.5 Hz, 1H, H-6), 7.12–7.14 (m, 2H, H-5’’, H-6’’), 7.16 (s, 1H, H-1’’).

^{13}C NMR (126 MHz, $CDCl_3$, 298 K): δ/ppm = 19.5 (3’’–CH$_3$)*, 19.9 (4’’–CH$_3$)*, 22.2 (C-2’’’)**, 22.7 (C-3’’’)**, 26.8 (3–CH$_3$), 28.0 (C-1’’’), 34.2 (C-4’’’), 36.6 (N(CH$_3$)$_2$), 43.4 (C-3), 70.3 (C-2), 120.6 (C-5), 122.4 (C-6), 124.8 (C-4), 128.6 (C-2’’), 128.6 (C-7), 129.4 (C-5’’), 129.5 (C-6’’), 135.2 (C-1’’), 136.2 (C-3’’)***, 137.3 (C-4’’)***, 140.3 (C-9), 140.9 (C-8), 158.2 (C-1’).

IR (ATR): □ /cm^{-1} = 3016 (w), 2922 (w), 2854 (w), 1637 (s), 1488 (m), 1431 (s), 1383 (s), 1265 (m), 1180 (m), 1064 (w), 987 (w), 908 (w), 824 (w), 787 (w), 727 (s).

HRMS (APCI) for $C_{24}H_{31}N_2O$ ($[M+H]^+$): calcd. 363.2431
found 363.2424

3.1.5.8 7-(3,4-Dimethylphenyl)-*N*,*N*,2,3,3,5-hexamethylindoline-1-carboxamide (225)



225

$C_{23}H_{30}N_2O$

M = 350.51 g/mol

According to **GP 5**, a flame-dried SCHLENK tube equipped with a magnetic stir bar was successively charged with *N*,*N*,2,3,3,5-hexamethylindoline-1-carboxamide (**217**, 49 mg, 0.20 mmol, 1.0 equiv.), $Pd(OAc)_2$ (4.5 mg, 0.020 mmol, 10 mol%), $Cu(OAc)_2$ (36 mg, 0.20 mmol 1.0 equiv.), TFA (0.20 mL, 0.26 mmol, 13 equiv.), and *o*-xylene (**94**, 1.0 mL, 0.2M) in the open air. The reaction mixture was stirred at 50 °C for 44 h. After complete consumption of the indoline, as monitored by GLC analysis using tetracosane (10 mg, 0.030 mmol, 15 mol%) as internal standard, the reaction mixture was allowed to cool to room temperature and diluted with ethyl acetate (5 mL). The crude reaction mixture was washed with saturated aqueous Na_2CO_3 (1 × 5 mL) and H_2O (1 × 5 mL), phases were separated. The organic layer was dried over anhydrous Na_2SO_4. After evaporation of the solvents under reduced pressure, purification of the residue by flash column chromatography on silica gel (2.5 × 20 cm, cyclohexane:ethyl acetate = 4:1 → 3:1, 50 mL, #16–24) afforded the analytically pure arylated product **225** (31 mg, 44%) as a light brown oil.

R_f = 0.40 (cyclohexane:ethyl acetate = 2:1).

GLC (HP-5): t_R = 22.9 min.

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ/ppm = 1.20 (s, 3H, 3–CH_3)*, 1.26 (s, 3H, 3–CH_3)*, 1.35 (d, $^3J_{2\text{–}CH_3,2}$ = 6.1 Hz, 3H, 2–CH_3), 2.22 (br s, 6H, N(CH_3)$_2$), 2.26 (s, 3H, 3''–CH_3)**, 2.28 (s, 3H, 4''–CH_3)**, 2.32 (s, 3H, 5–CH_3), 3.94 (q, $^3J_{2,2\text{–}CH_3}$ = 6.3 Hz, 1H, H-2), 6.87 (s, 1H, H-6), 6.89 (s, 1H, H-4), 7.08–7.13 (m, 3H, H-1'', H-5'', H-6'').

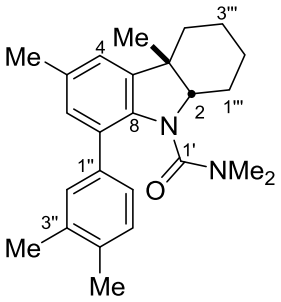
^{13}C NMR (126 MHz, $CDCl_3$, 298 K): δ/ppm = 19.5 (2–*C*H$_3$), 19.9 (4''–*C*H$_3$)*, 21.1 (3''–*C*H$_3$)*, 21.2 (5–*C*H$_3$), 27.1 (3–*C*H$_3$)**, 36.4 (3–*C*H$_3$)**, 37.8 (N(*C*H$_3$)$_2$), 43.2 (C-3), 69.7 (C-2), 122.1

(C-4), 123.2 (C-6), 124.8 (C-7), 127.4 (C-2''), 128.6 (C-5'')***, 129.4 (C-6'')***, 130.0 (C-5), 131.8 (C-1''), 135.2 (C-3'')****, 136.2 (C-4'')****, 137.3 (C-9), 141.7 (C-8), 158.2 (C-1').

IR (ATR): $\tilde{\nu}$ /cm^{-1} = 2919 (w), 2859 (w), 1639 (s), 1444 (m), 1381 (s), 1282 (m), 1229 (m), 1171 (m), 1114 (w), 1030 (w), 961 (w), 859 (w), 820 (w), 751 (w), 719 (w).

HRMS (APCI) for $C_{23}H_{31}N_2O$ ($[M+H]^+$): calcd. 351.2431
found 351.2427

3.1.5.9 *cis*-8-(3,4-Dimethylphenyl)-*N*,*N*,4a,6-tetramethyl-1,2,3,4,4a,9a-hexahydro-9*H*-carbazole-9-carboxamide (*cis*-227)



cis-**227**
$C_{25}H_{32}N_2O$
M = 376.54 g/mol

According to **GP 5**, a flame-dried SCHLENK tube equipped with a magnetic stir bar was successively charged with *cis*-*N*,*N*,4a,6-tetramethyl-1,2,3,4,4a,9a-hexahydro-9*H*-carbazole-9-carboxamide (*cis*-**219**, 54 mg, 0.20 mmol, 1.0 equiv.), $Pd(OAc)_2$ (4.5 mg, 0.020 mmol, 10 mol%), $Cu(OAc)_2$ (36 mg, 0.20 mmol 1.0 equiv.), TFA (0.20 mL, 0.26 mmol, 13 equiv.), and *o*-xylene (**94**, 1.0 mL, 0.2M) in the open air. The reaction mixture was stirred at 50 °C for 17 h. After complete consumption of the indoline, as monitored by GLC analysis using tetracosane (10 mg, 0.030 mmol, 15 mol%) as internal standard, the reaction mixture was allowed to cool to room temperature and diluted with ethyl acetate (5 mL). The crude reaction mixture was washed with saturated aqueous Na_2CO_3 (1 × 5 mL) and H_2O (1 × 5 mL), phases were separated. The organic layer was dried over anhydrous Na_2SO_4. After evaporation of the solvents under reduced pressure, purification of the residue by flash column chromatography on silica gel (2.5 × 20 cm, cyclohexane:ethyl acetate = 4:1 → 3:1, 50 mL, #13–20) afforded the analytically pure arylated product *cis*-**227** (64 mg, 85%) as a light brown oil.

R_f = 0.35 (cyclohexane:ethyl acetate = 2:1).

GLC (HP-5): t_R = 25.1 min.

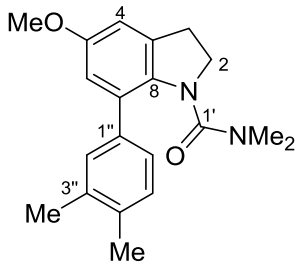
^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ/ppm = 1.19 (s, 3H, 3–C*H*$_3$), 1.20–1.31 (m, 3H, H-2’’’, H-3’’’), 1.51–1.58 (m, 3H, H-1’’’, H-2’’’, H-4’’’), 1.67–1.77 (m, 1H, H-4’’’), 2.06–2.10 (m, 1H, H-1’’’), 2.26 (s, 3H, 3’’–C*H*$_3$)*, 2.28 (s, 3H, 4’’–C*H*$_3$)*, 2.29 (br s, 6H, N(C*H*$_3$)$_2$), 2.33 (s, 3H, 5–C*H*$_3$), 3.82 (dd, $^3J_{2,1'''A}$ = 8.0 Hz, $^3J_{2,1'''B}$ = 5.9 Hz, 1H, H-2), 6.86 (s, 1H, H-4), 6.91 (s, 1H, H-6), 7.10–7.13 (m, 2H, H-5’’, H-6’’), 7.15 (s, 1H, H-1’’).

^{13}C NMR (126 MHz, $CDCl_3$, 298 K): δ/ppm = 19.5 (3’’–*C*H$_3$)*, 19.9 (4’’–*C*H$_3$)*, 21.1 (5–*C*H$_3$), 22.2 (C-2’’’)**, 22.8 (C-3’’’)**, 27.0 (3–*C*H$_3$), 27.1 (C-1’’’), 34.1 (C-4’’’), 36.6 (N(*C*H$_3$)$_2$), 43.5 (C-3), 70.4 (C-2), 121.4 (C-4), 124.8 (C-6), 128.4 (C-7), 128.6 (C-2’’), 129.4 (C-5’’)***, 129.8 (C-6’’)***, 132.0 (C-1’’), 135.1 (C-5), 136.1 (C-3’’)****, 137.3 (C-4’’)****, 137.9 (C-9), 141.0 (C-8), 158.4 (C-1’).

IR (ATR): $\tilde{\nu}$ /cm^{-1} = 2921 (w), 2854 (w), 1635 (s), 1488 (m), 1441 (s), 1383 (s), 1264 (w), 1222 (w), 1180 (m), 1063 (w), 1030 (w), 987 (w), 908 (m), 858 (m), 820 (m), 726 (s), 679 (w).

HRMS (APCI) for $C_{25}H_{33}N_2O$ ([M+H]$^+$): calcd. 377.2587
found 377.2579

3.1.5.10 7-(3,4-Dimethylphenyl)-5-methoxy-*N*,*N*-dimethylindoline-1-carboxamide (222)



222

$C_{20}H_{24}N_2O_2$
M = 324.42 g/mol

According to **GP 5**, a flame-dried SCHLENK tube equipped with a magnetic stir bar was successively charged with 5-methoxy-*N*,*N*-dimethylindoline-1-carboxamide (**214**, 44 mg,

0.20 mmol, 1.0 equiv.), $Pd(OAc)_2$ (4.5 mg, 0.020 mmol, 10 mol%), $Cu(OAc)_2$ (36 mg, 0.20 mmol 1.0 equiv.), TFA (0.20 mL, 0.26 mmol, 13 equiv.), and *o*-xylene (**94**, 1.0 mL, 0.2M) in the open air. The reaction mixture was stirred at 50 °C for 48 h. After complete consumption of the indoline, as monitored by GLC analysis using tetracosane (10 mg, 0.030 mmol, 15 mol%) as internal standard, the reaction mixture was allowed to cool to room temperature and diluted with ethyl acetate (5 mL). The crude reaction mixture was washed with saturated aqueous Na_2CO_3 (1 × 5 mL) and H_2O (1 × 5 mL), phases were separated. The organic layer was dried over anhydrous Na_2SO_4. After evaporation of the solvents under reduced pressure, purification of the residue by flash column chromatography on silica gel (2.5 × 20 cm, cyclohexane:ethyl acetate = 1:1 → 1:2, 50 mL, #16–20) afforded the analytically pure arylated product **222** (19 mg, 30%) as a brown oil.

R_f = 0.28 (cyclohexane:ethyl acetate = 1:2).

GLC (HP-5): t_R = 24.0 min.

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ/ppm = 2.25 (s, 3H, 3''–C*H*$_3$)*, 2.27 (s, 3H, 4''–C*H*$_3$)*, 2.63 (s, 6H, N(C*H*$_3$)$_2$, 3.06 (t, $^3J_{3,2}$ = 8.0 Hz, 2H, H-3), 3.79 (s, 3H, 5–C*H*$_3$), 3.95 (t, $^3J_{2,3}$ = 8.0 Hz, 2H, H-2), 6.71–6.74 (m, 2H, H-4, H-6), 7.11 (d, $^3J_{5'',6''}$ = 7.7 Hz, 1H, H-5''), 7.21 (d, $^3J_{6'',5''}$ = 7.8 Hz, 1H, H-6''), 7.27 (s, 1H, H-2'').

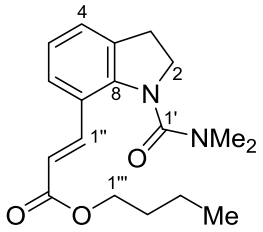
^{13}C NMR (126 MHz, $CDCl_3$, 298 K): δ/ppm = 19.6 (3''–*C*H$_3$)*, 20.0 (4''–*C*H$_3$)*, 30.5 (C-3), 37.1 (N(*C*H$_3$)$_2$), 52.4 (C-2), 55.9 (5–O*C*H$_3$), 110.1 (C-4), 113.6 (C-6), 124.4 (C-7), 128.2 (C-2''), 129.8 (C-5''), 130.2 (C-6''), 135.3 (C-1''), 135.5 (C-3'')**, 136.0 (C-4'')**, 136.4 (C-9), 137.9 (C-8), 156.5 (C-5), 160.6 (C-1').

IR (ATR): $\tilde{\nu}$ /cm^{-1} = 2921 (br), 1734 (w), 1663 (s), 1608 (s), 1438 (s), 1377 (s), 1275 (m), 1234 (m), 1189 (w), 1155 (w), 1097 (w), 1041 (w), 996 (w), 829 (m), 766 (w), 701 (w).

HRMS (APCI) for $C_{20}H_{25}N_2O_2$ ($[M+H]^+$): calcd. 325.1911
found 325.1907

3.2 Oxidative Palladium(II)-Catalyzed Alkenylation of Indolines at the C-7 Position

3.2.1 (*E*)-Butyl 3-[1-(dimethylcarbamoyl)indolin-7-yl]acrylate [(*E*)-236]



(*E*)-**236**
$C_{18}H_{24}N_2O_3$
M = 316.40 g/mol

According to **GP 7**, a flame-dried SCHLENK tube equipped with a magnetic stir bar was successively charged with *N*,*N*-dimethylindoline-1-carboxamide (**91**, 38 mg, 0.20 mmol, 1.0 equiv.), $Pd(OAc)_2$ (4.5 mg, 0.020 mmol, 10 mol%), BQ (43 mg, 0.40 mmol, 2.0 equiv.), and *p*-toluenesulfonic acid monohydrate (38 mg, 0.20 mmol, 1.0 equiv.) in acetic acid (1.0 mL, 0.2M) under inert atmosphere. Subsequently, butyl acrylate (**2**, 58 µL, 0.40 mmol, 2.0 equiv.) was added, and the reaction mixture was stirred at 40 °C for 16 h. After complete consumption of the indoline, as monitored by GLC analysis using tetracosane (10 mg, 0.030 mmol, 15 mol%) as internal standard, the reaction mixture was allowed to cool to room temperature and diluted with ethyl acetate (10 mL). The crude reaction mixture was washed with saturated aqueous Na_2CO_3 (1 × 5 mL) and H_2O (1 × 5 mL). The organic phase was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (2.5 × 20 cm, cyclohexane:ethyl acetate = 1:1.5, 20 mL, #19–37) afforded the analytically pure alkenylated product *(E)*-**236** (56 mg, 89%) as a brown oil.

R_f = 0.23 (cyclohexane:ethyl acetate = 1:1).

GLC (HP-5): t_R = 23.6 min.

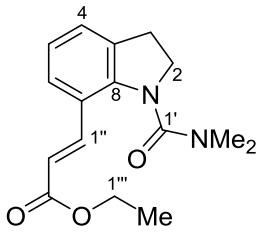
^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ/ppm = 0.95 (t, $^3J_{4''',3'''}$ = 7.6 Hz, 3H, H-4'''), 1.38–1.46 (m, 2H, H-3'''), 1.62–1.68 (m, 2H, H-2'''), 2.98 (s, 6H, N(CH_3)$_2$), 3.07 (t, $^3J_{3,2}$ = 8.2 Hz, 2H, H-3), 3.93 (t, $^3J_{2,3}$ = 7.9 Hz, 2H, H-2), 4.15 (t, $^3J_{1''',2'''}$ = 6.7 Hz, 2H, H-1'''), 6.30 (d, $^3J_{2'',1''}$ = 16.0 Hz, 1H, H-2''), 6.97 (dd, $^3J_{5,4}$ = 7.6 Hz, $^3J_{5,6}$ = 7.5 Hz, 1H, H-5), 7.17 (dd, $^3J_{6,5}$ = 7.3 Hz, $^4J_{6,4}$ = 0.8 Hz, 1H, H-6), 7.35 (d, $^3J_{4,5}$ = 7.9 Hz, 1H, H-4), 7.50 (d, $^3J_{1'',2''}$ = 15.8 Hz, 1H, H-1'').

^{13}C NMR (126 MHz, $CDCl_3$, 298 K): δ/ppm = 13.9 (C-4'''), 19.3 (C-3'''), 30.0 (C-3), 30.9 (C-2'''), 37.6 (N(CH_3)$_2$), 52.7 (C-2), 64.2 (C-1'''), 117.3 (C-2''), 123.6 (C-5)*, 123.7 (C-7)*, 125.6 (C-4), 126.0 (C-6), 134.3 (C-9), 141.5 (C-1''), 144.9 (C-8), 161.7 (C-1'), 167.3 (C-3'').

IR (ATR): $\tilde{\nu}$ /cm^{-1} = 2955 (w), 2920 (w), 2873 (w), 1702 (s), 1653 (s), 1625 (s), 1447 (m), 1376 (s), 1341 (m), 1298 (m), 1251 (s), 1158 (s), 1063 (m), 979 (s), 899 (w), 860 (m), 742 (m), 690 (w).

HRMS (APCI) for $C_{18}H_{25}N_2O_3$ ([M+H]$^+$): calcd. 317.1860
found 317.1857

3.2.2 (*E*)-Ethyl 3-[1-(dimethylcarbamoyl)indolin-7-yl]acrylate [(*E*)-250]



(*E*)-**250**
$C_{16}H_{20}N_2O_3$
M = 288.35 g/mol

According to **GP 7**, a flame-dried SCHLENK tube equipped with a magnetic stir bar was successively charged with *N*,*N*-dimethylindoline-1-carboxamide (**91**, 38 mg, 0.20 mmol, 1.0 equiv.), $Pd(OAc)_2$ (4.5 mg, 0.020 mmol, 10 mol%), BQ (43 mg, 0.40 mmol, 2.0 equiv.), and *p*-toluenesulfonic acid monohydrate (38 mg, 0.20 mmol, 1.0 equiv.) in acetic acid (1.0 mL, 0.2M) under inert atmosphere. Subsequently, ethyl acrylate (**5**, 43 µL, 0.40 mmol, 2.0 equiv.) was added, and the reaction mixture was stirred at 40 °C for 16 h. After complete consumption of the indoline, as monitored by GLC analysis using tetracosane (10 mg, 0.030 mmol, 15 mol%) as internal standard, the reaction mixture was allowed to cool to room temperature and diluted with ethyl acetate (10 mL). The crude reaction mixture was washed with saturated aqueous Na_2CO_3 (1 × 5 mL) and H_2O (1 × 5 mL). The organic phase was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (2.5 × 20 cm, cyclohexane:ethyl acetate = 3:1, 50 mL, #11–30) afforded the analytically pure alkenylated product *(E)*-**250** (47 mg, 82%) as a brown solid.

m.p.: 118–119 °C.

R_f = 0.31 (cyclohexane:ethyl acetate = 1:2).

GLC (HP-5): t_R = 22.0 min.

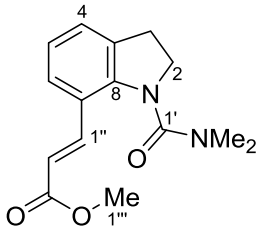
^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ/ppm = 1.29 (t, $^3J_{2''',1'''}$ = 7.2 Hz, 3H, H-2'''), 2.98 (s, 6H, N(CH_3)$_2$), 3.07 (t, $^3J_{3,2}$ = 7.8 Hz, 2H, H-3), 3.93 (t, $^3J_{2,3}$ = 7.8 Hz, 2H, H-2), 4.20 (q, $^3J_{2''',1'''}$ = 7.2 Hz, 2H, H-2'''), 6.30 (d, $^3J_{2'',1''}$ = 15.7 Hz, 1H, H-2''), 6.97 (dd, $^3J_{5,4}$ = $^3J_{5,6}$ = 7.7 Hz, 1H, H-5), 7.17 (dd, $^3J_{6,5}$ = 7.3 Hz, $^4J_{6,4}$ = 0.7 Hz, 1H, H-6), 7.35 (d, $^3J_{4,5}$ = 7.8 Hz, 1H, H-4), 7.51 (d, $^3J_{1'',2''}$ = 15.9 Hz, 1H, H-1'').

^{13}C NMR (126 MHz, $CDCl_3$, 298 K): δ/ppm = 14.4 (C-2'''), 30.0 (C-3), 37.6 (N(*C*H$_3$)$_2$), 52.7 (C-2), 60.3 (C-1'''), 117.3 (C-2''), 123.6 (C-5)*, 123.6 (C-7)*, 125.6 (C-4), 126.0 (C-6), 134.2 (C-9), 141.5 (C-1''), 144.8 (C-8), 161.6 (C-1'), 167.2 (C-3'').

IR (ATR): $\tilde{\nu}$ /cm^{-1} = 2948 (w), 1706 (s), 1651 (s), 1624 (s), 1475 (w), 1446 (m), 1383 (s), 1363 (s), 1300 (s), 1253 (s), 1160 (s), 1150 (s), 1092 (w), 1062 (w), 1038 (m), 1007 (w), 977 (m), 907 (w), 862 (m), 779 (m), 759 (m), 712 (w), 689 (w).

HRMS (APCI) for $C_{16}H_{21}N_2O_3$ ([M+H]$^+$): calcd. 289.1547
found 289.1542

3.2.3 (*E*)-Methyl 3-[1-(dimethylcarbamoyl)indolin-7-yl]acrylate [(*E*)-251]



(*E*)-**251**
$C_{15}H_{18}N_2O_3$
M = 274.32 g/mol

According to **GP 7**, a flame-dried SCHLENK tube equipped with a magnetic stir bar was successively charged with *N*,*N*-dimethylindoline-1-carboxamide (**91**, 38 mg, 0.20 mmol,

1.0 equiv.), $Pd(OAc)_2$ (4.5 mg, 0.020 mmol, 10 mol%), BQ (43 mg, 0.40 mmol, 2.0 equiv.), and *p*-toluenesulfonic acid monohydrate (38 mg, 0.20 mmol, 1.0 equiv.) in acetic acid (1.0 mL, 0.2M) under inert atmosphere. Subsequently, methyl acrylate (**42**, 37 µL, 0.40 mmol, 2.0 equiv.) was added, and the reaction mixture was stirred at 40 °C for 16 h. After complete consumption of the indoline, as monitored by GLC analysis using tetracosane (10 mg, 0.030 mmol, 15 mol%) as internal standard, the reaction mixture was allowed to cool to room temperature and diluted with ethyl acetate (10 mL). The crude reaction mixture was washed with saturated aqueous Na_2CO_3 (1 × 5 mL) and H_2O (1 × 5 mL). The organic phase was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (2.5 × 20 cm, cyclohexane:ethyl acetate = 1:3, 50 mL, #11–18) afforded the analytically pure alkenylated product (*E*)-**251** (44 mg, 80%) as a brown solid.

m.p.: 134–135 °C.

R_f = 0.26 (cyclohexane:ethyl acetate = 1:2).

GLC (HP-5): t_R = 21.4 min.

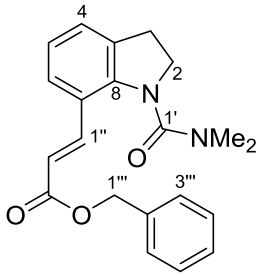
^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ/ppm = 2.99 (s, 6H, N(CH_3)$_2$), 3.08 (t, $^3J_{3,2}$ = 7.7 Hz, 2H, H-3), 3.75 (s, 3H, H-1'''), 3.94 (t, $^3J_{2,3}$ = 8.1 Hz, 2H, H-2), 6.31 (d, $^3J_{2'',1''}$ = 16.1 Hz, 1H, H-2''), 6.98 (dd, $^3J_{5,4}$ = 7.8 Hz, $^3J_{5,6}$ = 7.5 Hz, 1H, H-5), 7.18 (dd, $^3J_{6,5}$ = 7.3 Hz, $^4J_{6,4}$ = 0.9 Hz, 1H, H-6), 7.35 (d, $^3J_{4,5}$ = 7.7 Hz, 1H, H-4), 7.52 (d, $^3J_{1'',2''}$ = 16.0 Hz, 1H, H-1'').

^{13}C NMR (126 MHz, $CDCl_3$, 298 K): δ/ppm = 30.0 (C-3), 37.7 (N(*C*H$_3$)$_2$), 51.6 (C-1'''), 52.8 (C-2), 116.9 (C-2''), 123.6 (C-5), 123.7 (C-7), 125.8 (C-6), 126.1 (C-4), 134.3 (C-9), 141.9 (C-1''), 144.9 (C-8), 161.7 (C-1'), 167.8 (C-3'').

IR (ATR): $\tilde{\nu}$ /cm^{-1} = 2917 (w), 1709 (m), 1658 (m), 1634 (s), 1435 (m), 1368 (w), 1345 (m), 1296 (m), 1252 (s), 1150 (s), 1021 (m), 981 (m), 902 (w), 859 (m), 764 (m), 692 (w).

HRMS (APCI) for $C_{15}H_{19}N_2O_3$ ($[M+H]^+$): calcd. 275.1390
found 275.1386

3.2.4 (*E*)-Benzyl 3-[1-(dimethylcarbamoyl)indolin-7-yl]acrylate [(*E*)-252]



(*E*)-**252**
$C_{21}H_{22}N_2O_3$
M = 350.42 g/mol

According to **GP 7**, a flame-dried SCHLENK tube equipped with a magnetic stir bar was successively charged with *N*,*N*-dimethylindoline-1-carboxamide (**91**, 38 mg, 0.20 mmol, 1.0 equiv.), $Pd(OAc)_2$ (4.5 mg, 0.020 mmol, 10 mol%), BQ (43 mg, 0.40 mmol, 2.0 equiv.), and *p*-toluenesulfonic acid monohydrate (38 mg, 0.20 mmol, 1.0 equiv.) in acetic acid (1.0 mL, 0.2M) under inert atmosphere. Subsequently, benzyl acrylate (**245**, 61 µL, 0.40 mmol, 2.0 equiv.) was added, and the reaction mixture was stirred at 40 °C for 16 h. After complete consumption of the indoline, as monitored by GLC analysis using tetracosane (10 mg, 0.030 mmol, 15 mol%) as internal standard, the reaction mixture was allowed to cool to room temperature and diluted with ethyl acetate (10 mL). The crude reaction mixture was washed with saturated aqueous Na_2CO_3 (1 × 5 mL) and H_2O (1 × 5 mL). The organic phase was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (2.5 × 20 cm, cyclohexane:ethyl acetate = 1:1.5, 50 mL, #11–21) afforded the analytically pure alkenylated product *(E)*-**252** (61 mg, 87%) as a brown solid.

m.p.: 81–82 °C.

R_f = 0.39 (cyclohexane:ethyl acetate = 1:2).

GLC (HP-5): t_R = 27.9 min.

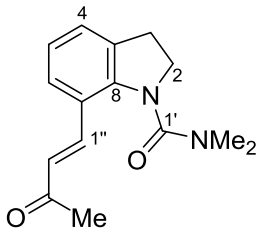
^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ/ppm = 2.95 (s, 6H, N(CH_3)$_2$), 3.08 (t, $^3J_{3,2}$ = 8.0 Hz, 2H, H-3), 3.93 (t, $^3J_{2,3}$ = 8.0 Hz, 2H, H-2), 5.20 (s, 2H, H-1'''), 6.37 (d, $^3J_{2'',1''}$ = 15.8 Hz, 1H, H-2''), 6.98 (dd, $^3J_{5,4}$ = 7.9 Hz, $^3J_{5,6}$ = 7.5 Hz, 1H, H-5), 7.18 (dd, $^3J_{6,5}$ = 7.4 Hz, $^4J_{6,4}$ = 0.8 Hz, 1H, H-6), 7.31–7.41 (m, 6H, H-Ar), 7.57 (d, $^3J_{1'',2''}$ = 15.8 Hz, 1H, H-1'').

^{13}C NMR (126 MHz, $CDCl_3$, 298 K): δ/ppm = 29.9 (C-3), 37.5 (N(CH_3)$_2$), 52.6 (C-2), 66.2 (C-1'''), 116.7 (C-2''), 123.4 (C-5)*, 123.5 (C-7)*, 125.5 (C-4), 126.1 (C-6), 128.1 (C-Ar), 128.2 (C-Ar), 128.5 (C-Ar), 134.2 (C-9), 136.3 (C-2'''), 142.0 (C-1''), 144.9 (C-8), 161.6 (C-1'), 166.9 (C-3'').

IR (ATR): $\tilde{\nu}$ /cm^{-1} = 2925 (w), 2885 (w), 1707 (s), 1654 (s), 1631 (s), 1496 (w), 1448 (m), 1371 (s), 1341 (w), 1296 (m), 1244 (s), 1150 (s), 1089 (w), 1009 (w), 979 (w), 906 (w), 862 (w), 783 (w), 733 (m), 696 (m).

HRMS (APCI) for $C_{21}H_{23}N_2O_3$ ([M+H]$^+$): calcd. 351.1703
found 351.1698

3.2.5 (*E*)-*N*,*N*-Dimethyl-7-(3-oxobut-1-en-1-yl)indoline-1-carboxamide [(*E*)-254]



(*E*)-**254**
$C_{15}H_{18}N_2O_2$
M = 258.32 g/mol

According to **GP 7**, a flame-dried SCHLENK tube equipped with a magnetic stir bar was successively charged with *N*,*N*-dimethylindoline-1-carboxamide (**91**, 38 mg, 0.20 mmol, 1.0 equiv.), $Pd(OAc)_2$ (4.5 mg, 0.020 mmol, 10 mol%), BQ (43 mg, 0.40 mmol, 2.0 equiv.), and *p*-toluenesulfonic acid monohydrate (38 mg, 0.20 mmol, 1.0 equiv.) in acetic acid (1.0 mL, 0.2M) under inert atmosphere. Subsequently, methyl vinyl ketone (**247**, 34 µL, 0.40 mmol, 2.0 equiv.) was added, and the reaction mixture was stirred at 40 °C for 16 h. After complete consumption of the indoline, as monitored by GLC analysis using tetracosane (10 mg, 0.030 mmol, 15 mol%) as internal standard, the reaction mixture was allowed to cool to room temperature and diluted with ethyl acetate (10 mL). The crude reaction mixture was washed with saturated aqueous Na_2CO_3 (1 × 5 mL) and H_2O (1 × 5 mL). The organic phase was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (2.5 × 20 cm, ethyl acetate as eluent, 100 mL, #24–46) afforded the analytically pure alkenylated product *(E)*-**254** (31 mg, 60%) as a brown solid.

m.p.: 93–94 °C.

R_f = 0.31 (ethyl acetate).

GLC (HP-5): t_R = 21.2 min.

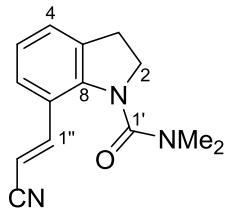
^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ/ppm = 2.31 (s, 3H, 3''–C*H*$_3$), 3.01 (s, 6H, N(C*H*$_3$)$_2$), 3.11 (t, $^3J_{3,2}$ = 7.9 Hz, 2H, H-3), 3.96 (t, $^3J_{2,3}$ = 7.9 Hz, 2H, H-2), 6.57 (d, $^3J_{2'',1''}$ = 16.3 Hz, 1H, H-2''), 7.01 (dd, $^3J_{5,4}$ = 7.8 Hz, $^3J_{5,6}$ = 7.7 Hz, 1H, H-5), 7.21 (dd, $^3J_{6,5}$ = 7.4 Hz, $^4J_{6,4}$ = 0.9 Hz, 1H, H-6), 7.37 (d, $^3J_{4,5}$ = 8.0 Hz, 1H, H-4), 7.37 (d, $^3J_{1'',2''}$ = 16.2 Hz, 1H, H-1'').

^{13}C NMR (100 MHz, $CDCl_3$, 298 K): δ/ppm = 27.2 (3''–*C*H$_3$), 30.1 (C-3), 37.7 (N(*C*H$_3$)$_2$), 52.8 (C-2), 123.7 (C-2''), 123.8 (C-5), 125.8 (C-7), 126.4 (C-4), 126.6 (C-6), 134.4 (C-9), 140.9 (C-1''), 145.1 (C-8), 161.3 (C-1'), 198.8 (C-3'').

IR (ATR): $\tilde{\nu}$ /cm^{-1} = 2922 (w), 1653 (s), 1598 (s), 1490 (w), 1436 (m) 1380 (s), 1361 (s), 1294 (m), 1250 (s), 1160 (s), 1089 (w), 1062 (w), 1007 (w), 982 (w), 934 (w), 913 (w), 835 (w), 771 (s).

HRMS (APCI) for $C_{15}H_{19}N_2O_2$ ([M+H]$^+$): calcd. 259.1441
found 259.1440

3.2.6 (*E*)-7-(2-Cyanovinyl)-*N*,*N*-dimethylindoline-1-carboxamide [(*E*)-255]



(*E*)-**255**
$C_{14}H_{15}N_3O$
M = 241.29 g/mol

According to **GP 7**, a flame-dried SCHLENK tube equipped with a magnetic stir bar was successively charged with *N*,*N*-dimethylindoline-1-carboxamide (**91**, 38 mg, 0.20 mmol, 1.0 equiv.), $Pd(OAc)_2$ (4.5 mg, 0.020 mmol, 10 mol%), BQ (43 mg, 0.40 mmol, 2.0 equiv.), and *p*-toluenesulfonic acid monohydrate (38 mg, 0.20 mmol, 1.0 equiv.) in acetic acid

(1.0 mL, 0.2M) under inert atmosphere. Subsequently, acrylonitrile (**248**, 27 µL, 0.40 mmol, 2.0 equiv.) was added, and the reaction mixture was stirred at 40 °C for 16 h. After complete consumption of the indoline, as monitored by GLC analysis using tetracosane (10 mg, 0.030 mmol, 15 mol%) as internal standard, the reaction mixture was allowed to cool to room temperature and diluted with ethyl acetate (10 mL). The crude reaction mixture was washed with saturated aqueous Na_2CO_3 (1 × 5 mL) and H_2O (1 × 5 mL). The organic phase was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (2.5 × 20 cm, cyclohexane:ethyl acetate = 1:1.5, 50 mL, #20–29) afforded the analytically pure alkenylated product *(E)*-**255** (10 mg, 21%) as a yellow solid.

m.p.: 158–159 °C.

R_f = 0.34 (cyclohexane:ethyl acetate = 1:2).

GLC (HP-5): t_R = 20.9 min.

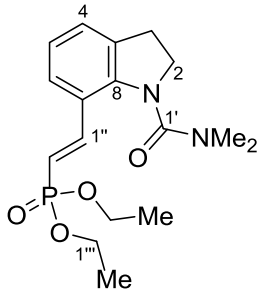
^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ/ppm = 3.03 (s, 6H, N(C*H*$_3$)$_2$), 3.10 (t, $^3J_{3,2}$ = 8.2 Hz, 2H, H-3), 3.95 (t, $^3J_{2,3}$ = 7.9 Hz, 2H, H-2), 5.75 (d, $^3J_{2'',1''}$ = 16.7 Hz, 1H, H-2''), 7.10 (ddd, $^3J_{5,4}$ = $^3J_{5,6}$ = 7.6 Hz, 1H, H-5), 7.22–7.24 (m, 1H, H-4), 7.24 (d, $^3J_{1'',2''}$ = 17.0 Hz, 1H, H-1''), 7.29 (br s, 1H, H-6).

^{13}C NMR (100 MHz, $CDCl_3$, 298 K): δ/ppm = 30.1 (C-3), 37.8 (N(*C*H$_3$)$_2$), 52.9 (C-2), 95.2 (C-2''), 118.9 (2''–*C*N), 123.3 (C-5), 124.0 (C-7), 124.6 (C-4), 127.0 (C-6), 134.7 (C-9), 144.6 (C-8), 148.0 (C-1''), 161.6 (C-1').

IR (ATR): $\tilde{\nu}$ /cm^{-1} = 2983 (w), 2323 (m), 1665 (s), 1599 (m), 1485 (m), 1437 (m), 1150 (w), 1086 (w), 976 (w), 862 (w).

HRMS (APCI) for $C_{14}H_{16}N_3O$ ($[M+H]^+$): calcd. 242.1288
found 242.1287

3.2.7 (*E*)-Diethyl {2-[1-(dimethylcarbamoyl)indolin-7-yl]vinyl}phosphonate [(*E*)-253]



(*E*)-**253**
$C_{17}H_{25}N_2O_4P$
M = 352.37 g/mol

According to **GP 7**, a flame-dried SCHLENK tube equipped with a magnetic stir bar was successively charged with *N*,*N*-dimethylindoline-1-carboxamide (**91**, 38 mg, 0.20 mmol, 1.0 equiv.), $Pd(OAc)_2$ (4.5 mg, 0.020 mmol, 10 mol%), BQ (43 mg, 0.40 mmol, 2.0 equiv.), and *p*-toluenesulfonic acid monohydrate (38 mg, 0.20 mmol, 1.0 equiv.) in acetic acid (1.0 mL, 0.2M) under inert atmosphere. Subsequently, diethyl vinylphosphonate (**246**, 62 µL, 0.40 mmol, 2.0 equiv.) was added, and the reaction mixture was stirred at 40 °C for 16 h. After complete consumption of the indoline, as monitored by GLC analysis using tetracosane (10 mg, 0.030 mmol, 15 mol%) as internal standard, the reaction mixture was allowed to cool to room temperature and diluted with ethyl acetate (10 mL). The crude reaction mixture was washed with saturated aqueous Na_2CO_3 (1 × 5 mL) and H_2O (1 × 5 mL). The organic phase was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (2.5 × 20 cm, methanol:ethyl acetate = 1:7, 50 mL, #17–25) afforded the analytically pure alkenylated product *(E)*-**253** (61 mg, 86%) as a brown oil.

R_f = 0.50 (methanol:ethyl acetate = 1:5).

GLC (HP-5): t_R = 24.2 min.

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ/ppm = 1.37 (t, $^3J_{2''',1'''}$ = 7.3 Hz, 6H, H-2'''), 3.01 (s, 6H, N(CH_3)$_2$), 3.11 (t, $^3J_{3,2}$ = 8.3 Hz, 2H, H-3), 3.96 (t, $^3J_{2,3}$ = 8.3 Hz, 2H, H-2), 4.13–4.19 (m, 4H H-1'''), 6.11 (dd, $^2J_{2'',P}$ = 18.7 Hz, $^3J_{2'',1''}$ = 17.5 Hz, 1H, H-2''), 7.02 (dd, $^3J_{5,4}$ = 7.9 Hz, $^3J_{5,6}$ = 7.6 Hz, 1H, H-5), 7.21 (d, $^3J_{6,5}$ = 7.1 Hz, 1H, H-6), 7.29–7.36 (m, 2H, H-4, H-1'').

^{13}C NMR (126 MHz, $CDCl_3$, 298 K): δ/ppm = 6.4 (d, $^3J_{2''',P}$ = 6.6 Hz, C-2'''), 30.0 (C-3), 37.5 (N(*C*H$_3$)$_2$), 52.7 (C-2), 61.9 (d, $^2J_{1''',P}$ = 5.2 Hz, C-1'''), 112.6 (d, $^1J_{2'',P}$ = 191.1 Hz, C-2''), 123.5

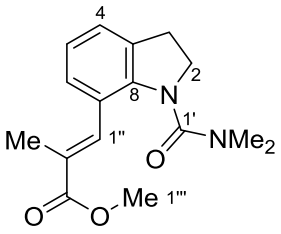
(C-4), 124.3 (C-6), 125.4 (C-5), 125.9 (C-7), 134.2 (C-9), 144.4 (C-8), 145.9 (d, $^{2}J_{1'',P}$ = 6.9 Hz, C-1''), 161.4 (C-1').

^{31}P NMR (202 MHz, $CDCl_3$, 298 K): δ/ppm = 19.8.

IR (ATR): $\tilde{\nu}$ /cm^{-1} = 2980 (w), 2828 (w), 1717 (vw), 1654 (s), 1618 (m), 1586 (w), 1491 (w), 1444 (m), 1380 (s), 1290 (m), 1245 (m), 1200 (m), 1159 (m), 1094 (w), 1047 (s), 1022 (s), 951 (s), 866 (m), 825 (w), 764 (s).

HRMS (APCI) for $C_{17}H_{26}N_2O_4P$ ([M+H]$^+$): calcd. 353.1625
found 353.1621

3.2.8 (*E*)-Methyl 3-[1-(dimethylcarbamoyl)indolin-7-yl]-2-methylacrylate [(*E*)-258]



(*E*)-**258**
$C_{16}H_{20}N_2O_3$
M = 288.35 g/mol

According to **GP 7**, a flame-dried SCHLENK tube equipped with a magnetic stir bar was successively charged with *N*,*N*-dimethylindoline-1-carboxamide (**91**, 38 mg, 0.20 mmol, 1.0 equiv.), $Pd(OAc)_2$ (4.5 mg, 0.020 mmol, 10 mol%), BQ (43 mg, 0.40 mmol, 2.0 equiv.), and *p*-toluenesulfonic acid monohydrate (38 mg, 0.20 mmol, 1.0 equiv.) in acetic acid (1.0 mL, 0.2M) under inert atmosphere. Subsequently, methyl methacrylate (**257**, 43 µL, 0.40 mmol, 2.0 equiv.) was added, and the reaction mixture was stirred at 40 °C for 16 h. After complete consumption of the indoline, as monitored by GLC analysis using tetracosane (10 mg, 0.030 mmol, 15 mol%) as internal standard, the reaction mixture was allowed to cool to room temperature and diluted with ethyl acetate (10 mL). The crude reaction mixture was washed with saturated aqueous Na_2CO_3 (1 × 5 mL) and H_2O (1 × 5 mL). The organic phase was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (2.5 × 20 cm, cyclohexane:ethyl acetate = 1:2, 50 mL, #24–39) afforded the analytically pure alkenylated product *(E)*-**258** (24 mg, 42%, *E*:*Z* > 98:2) as a brown oil.

R_f = 0.26 (cyclohexane:ethyl acetate = 1:2).

GLC (HP-5): t_R = 20.9 min.

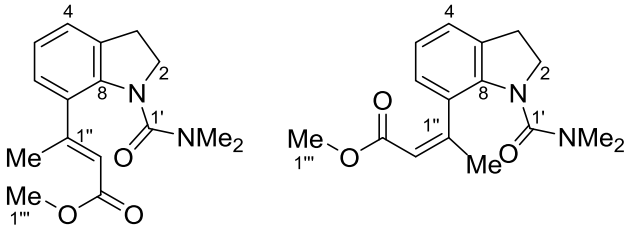
^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ/ppm = 2.03 (d, $^4J_{2''–CH_3,1''}$ = 1.4 Hz, 3H, 2''–C*H*$_3$), 2.90 (s, 6H, N(C*H*$_3$)$_2$), 3.09 (t, $^3J_{3,2}$ = 8.0 Hz, 2H, H-3), 3.77 (s, 3H, H-1'''), 3.93 (t, $^3J_{2,3}$ = 8.0 Hz, 2H, H-2), 6.97 (ddd, $^3J_{5,4}$ = 7.8 Hz, $^3J_{5,6}$ = 7.5 Hz, 1H, H-5), 7.11 (ddd, $^3J_{6,5}$ = 7.9 Hz, $^4J_{6,4}$= 1.2 Hz, $^4J_{6,1''}$ = 0.6 Hz, 1H, H-6), 7.39 (dd, $^3J_{4,5}$ = 7.3 Hz, $^4J_{4,6}$ = 0.9 Hz, 1H, H-4), 7.43 (d, $^4J_{1'',6}$ = 0.6 Hz, 1H, H-1'').

^{13}C NMR (126 MHz, $CDCl_3$, 298 K): δ/ppm = 14.3 (2''–*C*H$_3$), 29.9 (C-3), 37.6 (N(*C*H$_3$)$_2$), 52.0 (C-2), 52.4 (C-1'''), 122.6 (C-2''), 124.1 (C-5), 124.7 (C-7), 127.0 (C-4), 128.0 (C-6), 133.4 (C-9), 137.0 (C-1''), 144.2 (C-8), 160.8 (C-1'), 169.3 (C-3'').

IR (ATR): $\tilde{\nu}$ /cm^{-1} = 2949 (w), 1705 (s), 1652 (s), 1491 (w), 1432 (s), 1377 (s), 1264 (s), 1218 (m), 1193 (m), 1112 (s), 1021 (w), 933 (vw), 763 (m), 744 (m), 583 (m).

HRMS (APCI) for $C_{16}H_{21}N_2O_3$ ([M+H]$^+$): calcd. 289.1547
found 289.1540

3.2.9 (*E*)-Methyl 3-[1-(dimethylcarbamoyl)indolin-7-yl]-2-methylacrylate [(*E*)-260] and (*Z*)-methyl 3-[1-(dimethylcarbamoyl)indolin-7-yl]but-2-enoate [(*Z*)-260]



(*E*)-**260**
$C_{16}H_{20}N_2O_3$
M = 288.35 g/mol

(*Z*)-**260**
$C_{16}H_{20}N_2O_3$
M = 288.35 g/mol

According to **GP 7**, a flame-dried SCHLENK tube equipped with a magnetic stir bar was successively charged with *N*,*N*-dimethylindoline-1-carboxamide (**91**, 38 mg, 0.20 mmol, 1.0 equiv.), $Pd(OAc)_2$ (4.5 mg, 0.020 mmol, 10 mol%), BQ (43 mg, 0.40 mmol, 2.0 equiv.), and *p*-toluenesulfonic acid monohydrate (38 mg, 0.20 mmol, 1.0 equiv.) in acetic acid

(1.0 mL, 0.2M) under inert atmosphere. Subsequently, methyl crotonate [(*E*)-**259**, 43 µL, 0.40 mmol, 2.0 equiv.] was added, and the reaction mixture was stirred at 40 °C for 16 h. After complete consumption of the indoline, as monitored by GLC analysis using tetracosane (10 mg, 0.030 mmol, 15 mol%) as internal standard, the reaction mixture was allowed to cool to room temperature and diluted with ethyl acetate (10 mL). The crude reaction mixture was washed with saturated aqueous Na_2CO_3 (1 × 5 mL) and H_2O (1 × 5 mL). The organic phase was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (2.5 × 20 cm, cyclohexane:ethyl acetate = 1:1 → 1:2, 100 mL, #29–43) afforded the analytically pure alkenylated product *(E)- and (Z)*-**260** (35 mg, 61%, *E*:*Z* = 79:21) as a brown oil.

Analytical data for (*E*)-**260** (major isomer):

R_f = 0.16 (cyclohexane:ethyl acetate = 1:1).

GLC (HP-5): t_R = 20.9 min.

^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ/ppm = 2.40 (d, $^4J_{1''-CH_3,2''}$ = 1.5 Hz, 3H, 1''–CH_3), 2.91 (s, 6H, N(CH_3)$_2$), 3.10 (t, $^3J_{3,2}$ = 8.0 Hz, 2H, H-3), 3.71 (s, 3H, H-1'''), 3.92 (t, $^3J_{2,3}$ = 8.2 Hz, 2H, H-2), 5.94 (q, $^4J_{2'',1''-CH_3}$ = 1.3 Hz, 1H, H-2''), 6.97 (dd, $^3J_{5,4}$ = $^3J_{5,6}$ = 7.8 Hz, 1H, H-5), 7.06 (dd, $^3J_{4,5}$ = 7.8 Hz, $^4J_{4,6}$ = 1.3 Hz, 1H, H-4), 7.15 (dq, $^3J_{6,5}$ = 7.3 Hz, $^5J_{6,1''-CH_3}$ = 1.0 Hz, 1H, H-6).

^{13}C NMR (126 MHz, $CDCl_3$, 298 K): δ/ppm = 18.4 (1''–*C*H$_3$), 30.0 (C-3), 37.4 (N(*C*H$_3$)$_2$), 51.0 (C-2), 52.0 (C-1'''), 116.0 (C-2''), 123.1 (C-4), 124.7 (C-6), 127.0 (C-5), 131.7 (C-7), 133.8 (C-9), 142.3 (C-8), 157.0 (C-1''), 161.2 (C-1'), 167.5 (C-3'').

HRMS (APCI) for $C_{16}H_{21}N_2O_3$ ([M+H]$^+$): calcd. 289.1547
found 289.1540

Analytical data for (*Z*)-**260** (minor isomer):

R_f = 0.16 (cyclohexane:ethyl acetate = 1:1).

GLC (HP-5): t_R = 19.6 min.

^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ/ppm = 2.23 (d, $^4J_{1''-CH_3,2''}$ = 1.5 Hz, 3H, 1''–CH_3), 2.87 (s, 6H, N(CH_3)$_2$), 3.10 (t, $^3J_{3,2}$ = 8.0 Hz, 2H, H-3), 3.51 (s, 3H, H-1'''), 3.85 (t, $^3J_{2,3}$ = 8.2 Hz, 2H,

H-2), 5.71 (q, $^{4}J_{2'',1''-CH_3}$ = 1.3 Hz, 1H, H-2''), 6.97–7.01 (m, 2H, H-4, H-5), 7.12 (dq, $^{5}J_{6,5}$ = 7.3 Hz, $^{5}J_{6,1''-CH_3}$ = 1.0 Hz, 1H, H-6).

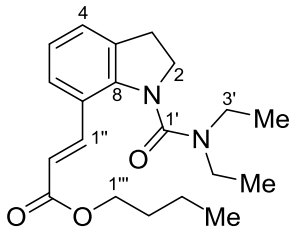
^{13}C NMR (126 MHz, $CDCl_3$, 298 K): δ/ppm = 25.8 (1''–*C*H$_3$), 31.0 (C-3), 37.5 (N(*C*H$_3$)$_2$), 50.8 (C-2), 52.1 (C-1'''), 115.4 (C-2''), 123.0 (C-4), 124.1 (C-6), 125.5 (C-5), 129.3 (C-7), 132.9 (C-9), 146.3 (C-8), 155.8 (C-1''), 161.5 (C-1'), 166.1 (C-3'').

HRMS (APCI) for $C_{16}H_{21}N_2O_3$ ([M+H]$^+$): calcd. 289.1547
found 289.1540

IR data for (*E*)-**260** and (*Z*)-**260**:

IR (ATR): $\tilde{\nu}$ /cm^{-1} = 2957 (w), 1701 (s), 1659 (s), 1631 (s), 1586 (w), 1491 (w), 1470 (w), 1429 (s), 1376 (s), 1336 (w), 1291 (w), 1260 (w), 1184 (m), 1158 (s), 1080 (m), 1029 (m), 865 (m), 785 (m), 765 (m), 750 (m), 686 (w).

3.2.10 (*E*)-Butyl 3-[1-(diethylcarbamoyl)indolin-7-yl]acrylate [(*E*)-238]



(*E*)-**238**
$C_{20}H_{28}N_2O_3$
M = 344.46 g/mol

According to **GP 7**, a flame-dried SCHLENK tube equipped with a magnetic stir bar was successively charged with *N*,*N*-diethylindoline-1-carboxamide (**237**, 44 mg, 0.20 mmol, 1.0 equiv.), $Pd(OAc)_2$ (4.5 mg, 0.020 mmol, 10 mol%), BQ (43 mg, 0.40 mmol, 2.0 equiv.), and *p*-toluenesulfonic acid monohydrate (38 mg, 0.20 mmol, 1.0 equiv.) in acetic acid (1.0 mL, 0.2M) under inert atmosphere. Subsequently, *n*-butyl acrylate (**2**, 58 µL, 0.40 mmol, 2.0 equiv.) was added, and the reaction mixture was stirred at 40 °C for 16 h. After complete consumption of the indoline, as monitored by GLC analysis using tetracosane (10 mg, 0.030 mmol, 15 mol%) as internal standard, the reaction mixture was allowed to cool to room temperature and diluted with ethyl acetate (10 mL). The crude reaction mixture was washed with saturated aqueous Na_2CO_3 (1 × 5 mL) and H_2O (1 × 5 mL). The organic phase was

dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (2.5 × 20 cm, cyclohexane:ethyl acetate = 1:1 → 1:1.2, 100 mL, #24–35) afforded the analytically pure alkenylated product *(E)*-**238** (59 mg, 85%) as a yellow oil.

R_f = 0.62 (cyclohexane:ethyl acetate = 1:2).

GLC (HP-5): t_R = 24.5 min.

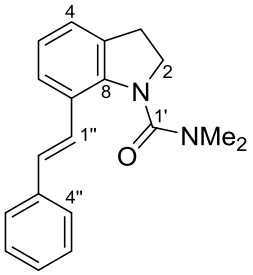
^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ/ppm = 0.91 (t, $^3J_{4''',3'''}$ = 6.8 Hz, 3H, H-4'''), 1.24 (t, $^3J_{4',3'}$ = 7.6 Hz, 6H, H-4'), 1.36–1.43 (m, 2H, H-3'''), 1.60–1.66 (m, 2H, H-2'''), 3.08 (t, $^3J_{3,2}$ = 7.6 Hz, 2H, H-3), 3.41 (q, $^3J_{3',4'}$ = 7.6 Hz, 4H, H-3'), 3.89 (t, $^3J_{2,3}$ = 7.6 Hz, 2H, H-2), 4.13 (t, $^3J_{1''',2'''}$ = 6.8 Hz, 2H, H-1'''), 6.27 (d, $^3J_{2'',1''}$ = 16.1 Hz, 1H, H-2''), 6.95 (dd, $^3J_{5,4}$ = $^3J_{5,6}$ = 7.2 Hz, 1H, H-5), 7.15 (d, $^3J_{6,5}$ = 7.2, 1H, H-6), 7.31 (d, $^3J_{4,5}$ = 8.1 Hz, 1H, H-4), 7.49 (d, $^3J_{1'',2''}$ = 16.1 Hz, 1H, H-1'').

^{13}C NMR (126 MHz, $CDCl_3$, 298 K): δ/ppm = 13.4 (C-4'''), 13.9 (C-4'), 19.3 (C-3'''), 30.2 (C-3), 30.9 (C-2'''), 41.6 (C-3'), 53.1 (C-2), 64.3 (C-1'''), 117.4 (C-2''), 123.6 (C-5), 123.8 (C-7), 125.6 (C-4), 126.0 (C-6), 134.2 (C-9), 141.6 (C-1''), 145.4 (C-8), 161.7 (C-1'), 167.4 (C-3'').

IR (ATR): $\tilde{\nu}$ /cm^{-1} = 2958 (w), 1704 (m), 1626 (s), 1509 (s), 1421 (s), 1348 (w), 1301 (m), 1245 (s), 1187 (s), 1045 (w), 979 (w), 909 (w), 827 (m), 758 (m).

HRMS (APCI) for $C_{20}H_{29}N_2O_3$ ([M+H]$^+$): calcd. 345.2173
found 345.2172

3.2.11 (*E*)-*N,N*-Dimethyl-7-styrylindoline-1-carboxamide [(*E*)-267]



(*E*)-**267**
$C_{19}H_{20}N_2O$
M = 292.38 g/mol

According to **GP 7**, a flame-dried SCHLENK tube equipped with a magnetic stir bar was successively charged with *N*,*N*-dimethylindoline-1-carboxamide (**91**, 38 mg, 0.20 mmol, 1.0 equiv.), $Pd(OAc)_2$ (4.5 mg, 0.020 mmol, 10 mol%), BQ (43 mg, 0.40 mmol, 2.0 equiv.), and *p*-toluenesulfonic acid monohydrate (38 mg, 0.20 mmol, 1.0 equiv.) in acetic acid (1.0 mL, 0.2M) under inert atmosphere. Subsequently, styrene (**8**, 47 µL, 0.40 mmol, 2.0 equiv.) was added, and the reaction mixture was stirred at 40 °C for 16 h. After complete consumption of the indoline, as monitored by GLC analysis using tetracosane (10 mg, 0.030 mmol, 15 mol%) as internal standard, the reaction mixture was allowed to cool to room temperature and diluted with ethyl acetate (10 mL). The crude reaction mixture was washed with saturated aqueous Na_2CO_3 (1 × 5 mL) and H_2O (1 × 5 mL). The organic phase was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (2.5 × 20 cm, cyclohexane:ethyl acetate = 1:1 → 1:1.5, 50 mL, #14–24) afforded the analytically pure alkenylated product *(E)*-**267** (42 mg, 73%) as a brown solid.

m.p.: 85–86 °C.

R_f = 0.35 (cyclohexane:ethyl acetate = 1:2).

GLC (HP-5): t_R = 24.0 min.

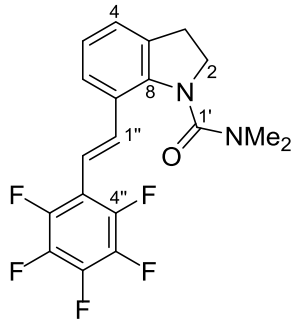
^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ/ppm = 2.94 (s, 6H, N(C*H*$_3$)$_2$), 3.07 (t, $^3J_{3,2}$ = 7.9 Hz, 2H, H-3), 3.95 (t, $^3J_{2,3}$ = 7.7 Hz, 2H, H-2), 6.96–6.99 (m, 2H, H-5, H-1''), 7.00 (d, $^3J_{4,5}$ = 7.6 Hz, 1H, H-4), 7.11 (d, $^3J_{2'',1''}$ = 16.4 Hz, 1H, H-2''), 7.21–7.24 (m, 1H, H-6''), 7.23 (dd, $^3J_{5'',6''}$ = 7.6 Hz, $^3J_{5'',4''}$ = 7.5 Hz, 2H, H-5''), 7.41 (d, $^3J_{6,5}$ = 7.9 Hz, 1H, H-6), 7.45 (d, $^3J_{4'',5''}$ = 7.5 Hz, 2H, H-4'').

^{13}C NMR (126 MHz, $CDCl_3$, 298 K): δ/ppm = 30.1 (C-3), 37.6 (N(*C*H$_3$)$_2$), 52.8 (C-2), 123.5 (C-1''), 123.8 (C-4), 125.0 (C-5), 125.8 (C-2''), 126.3 (C-6), 126.6 (C-5''), 127.5 (C-6''), 128.5 (C-4''), 128.7 (C-7), 134.0 (C-3''), 137.9 (C-9), 143.1 (C-8), 161.2 (C-1').

IR (ATR): $\tilde{\nu}$ /cm^{-1} = 3022 (w), 2853 (w), 1738 (vw), 1655 (s), 1586 (m), 1489 (m), 1451 (m), 1371 (s), 1263 (w), 1204 (w), 1169 (w), 1089 (w), 1061 (w), 1004 (w), 960 (m), 911 (w), 844 (w), 783 (w), 765 (w), 724 (w), 689 (m).

HRMS (APCI) for $C_{19}H_{21}N_2O$ ($[M+H]^+$): calcd. 293.1648
found 293.1642

3.2.12 (*E*)-*N*,*N*-Dimethyl-7-[2-(perfluorophenyl)vinyl]indoline-1-carboxamide [(*E*)-268]



(*E*)-**268**
$C_{19}H_{15}F_5N_2O$
M = 382.33 g/mol

According to **GP 7**, a flame-dried SCHLENK tube equipped with a magnetic stir bar was successively charged with *N*,*N*-dimethylindoline-1-carboxamide (**91**, 38 mg, 0.20 mol, 1.0 equiv.), $Pd(OAc)_2$ (4.5 mg, 0.020 mmol, 10 mol%), BQ (43 mg, 0.40 mmol, 2.0 equiv.), and *p*-toluenesulfonic acid monohydrate (38 mg, 0.20 mmol, 1.0 equiv.) in acetic acid (1.0 mL, 0.2M) under inert atmosphere. Subsequently, pentafluorostyrene (**261**, 56 µL, 0.40 mmol, 2.0 equiv.) was added, and the reaction mixture was stirred at 40 °C for 16 h. After complete consumption of the indoline, as monitored by GLC analysis using tetracosane (10 mg, 0.030 mmol, 15 mol%) as internal standard, the reaction mixture was allowed to cool to room temperature and diluted with ethyl acetate (10 mL). The crude reaction mixture was washed with saturated aqueous Na_2CO_3 (1 × 5 mL) and H_2O (1 × 5 mL). The organic phase was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (2.5 × 20 cm, cyclohexane:ethyl acetate = 1:1, 50 mL, #13–27) afforded the analytically pure alkenylated product *(E)*-**268** (67 mg, 88%) as a brown solid.

m.p.: 140–141 °C.

R_f = 0.48 (cyclohexane:ethyl acetate = 1:1).

GLC (HP-5): t_R = 22.9 min.

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ/ppm = 3.03 (s, 6H, N(C*H*$_3$)$_2$), 3.10 (t, $^3J_{3,2}$ = 8.0 Hz, 2H, H-3), 3.95 (t, $^3J_{2,3}$ = 8.0 Hz, 2H, H-2), 6.85 (d, $^3J_{1'',2''}$ = 16.7 Hz, 1H, H-1''), 7.03 (dd, $^3J_{5,4}$ = 8.0

Hz, $^{3}J_{5,6}$ = 7.7 Hz, 1H, H-5), 7.16 (d, $^{3}J_{4,5}$ = 7.1 Hz, 1H, H-4), 7.26 (d, $^{3}J_{2'',1''}$ = 17.0 Hz, 1H, H-2''), 7.40 (d, $^{3}J_{6,5}$ = 7.7 Hz, 1H, H-6).

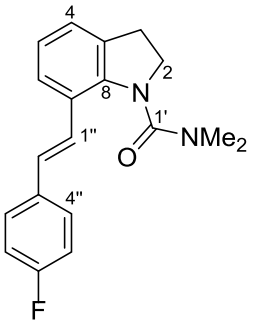
^{13}C NMR (126 MHz, $CDCl_3$, 298 K): δ/ppm = 30.3 (C-3), 37.6 (N(CH_3)$_2$), 52.9 (C-2), 106.0 (C-4), 111.8 (d, *J* = 65.0 Hz, C-Ar), 113.0 (td, *J* = 14.0 Hz, *J* = 4.5 Hz, C-2''), 115.6 (d, *J* = 59.2 Hz, C-Ar), 124.7 (C-6), 124.9 (C-5), 124.9 (d, *J* = 242.4 Hz, C-Ar), 134.3 (dd, *J* = 9.8 Hz, *J* = 2.2 Hz, C-1''), 134.4 (C-9), 137.8 (dm, *J* = 248.3 Hz, C-Ar), 144.9 (dm, *J* = 248.3 Hz, C-Ar), 149.7 (C-8), 161.9 (C-1').

^{19}F NMR (471 MHz, $CDCl_3$, 298 K): δ/ppm = −163.4 (td, *J* = 21.3 Hz, *J* = 7.5 Hz), −157.4 (t, *J* = 20.7 Hz), −143.3 (dd, *J* = 21.9 Hz, *J* = 7.7 Hz).

IR (ATR): $\tilde{\nu}$ /cm^{-1} = 2921 (w), 1734 (vw), 1661 (m), 1617 (m), 1519 (s), 1485 (s), 1439 (m), 1378 (m), 1344 (m), 1314 (w), 1291 (w), 1252 (w), 1193 (w), 1173 (w), 1142 (w), 1090 (w), 999 (s), 970 (s), 955 (s), 904 (w), 760 (w), 742 (w), 671 (w).

HRMS (APCI) for $C_{19}H_{16}F_5N_2O$ ([M+H]$^+$): calcd. 383.1177
found 383.1170

3.2.13 (*E*)-7-(4-Fluorostyryl)-*N*,*N*-dimethylindoline-1-carboxamide [(*E*)-269]



(*E*)-**269**
$C_{19}H_{19}FN_2O$
M = 310.37 g/mol

According to **GP 7**, a flame-dried SCHLENK tube equipped with a magnetic stir bar was successively charged with *N*,*N*-dimethylindoline-1-carboxamide (**91**, 38 mg, 0.20 mmol, 1.0 equiv.), $Pd(OAc)_2$ (4.5 mg, 0.020 mmol, 10 mol%), BQ (43 mg, 0.40 mmol, 2.0 equiv.), and *p*-toluenesulfonic acid monohydrate (38 mg, 0.20 mmol, 1.0 equiv.) in acetic acid (1.0 mL, 0.2M) under inert atmosphere. Subsequently, 1-fluoro-4-vinylbenzene (**262**, 49 µL,

0.40 mmol, 2.0 equiv.) was added, and the reaction mixture was stirred at 40 °C for 16 h. After complete consumption of the indoline, as monitored by GLC analysis using tetracosane (10 mg, 0.030 mmol, 15 mol%) as internal standard, the reaction mixture was allowed to cool to room temperature and diluted with ethyl acetate (10 mL). The crude reaction mixture was washed with saturated aqueous Na_2CO_3 (1 × 5 mL) and H_2O (1 × 5 mL). The organic phase was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (2.5 × 20 cm, cyclohexane:ethyl acetate = 1:1 → 1:1.5, 50 mL, #9–19) afforded the analytically pure alkenylated product *(E)*-**269** (39 mg, 63%) as a brown solid.

m.p.: 110–111 °C.

R_f = 0.51 (cyclohexane:ethyl acetate = 1:2).

GLC (HP-5): t_R = 23.8 min.

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ/ppm = 2.95 (s, 6H, N(CH_3)$_2$), 3.07 (t, $^3J_{3,2}$ = 7.9 Hz, 2H, H-3), 3.95 (t, $^3J_{2,3}$ = 7.9 Hz, 2H, H-2), 6.87–6.92 (m, 2H, H-Ar), 6.98–7.02 (m, 3H, H-Ar), 7.09–7.11 (m, 1H, H-Ar), 7.37–7.41 (m, 3H, H-Ar).

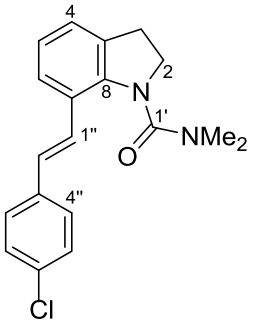
^{13}C NMR (126 MHz, $CDCl_3$, 298 K): δ/ppm = 30.1 (C-3), 37.7 (N(*C*H$_3$)$_2$), 52.8 (C-2), 115.6 (d, $^2J_{5'',6''-F}$ = 21.7 Hz, C-5''), 123.6 (C-1''), 123.8 (C-4), 124.9 (C-5), 125.6 (C-6), 126.3 (C-2''), 127.3 (C-7), 128.1 (d, $^3J_{4'',6''-F}$ = 8.1 Hz, C-4''), 134.0 (C-9), 134.1 (d, $^4J_{3'',6''-F}$ = 3.3 Hz, C-3''), 143.1 (C-8), 161.3 (C-1'), 162.3 (d, $^1J_{6'',6''-F}$ = 247.2 Hz, C-6'').

^{19}F NMR (471 MHz, $CDCl_3$, 298 K): δ/ppm = –114.7 (6''–F).

IR (ATR): $\tilde{\nu}$ /cm^{-1} = 2919 (w), 2820 (w), 1734 (vw), 1647 (s), 1599 (m), 1500 (s), 1448 (s), 1370 (s), 1266 (m), 1224 (s), 1148 (s), 1095 (w), 1060 (w), 1004 (w), 967 (m), 909 (w), 862 (w), 820 (s), 797 (m), 760 (s), 714 (m).

HRMS (APCI) for $C_{19}H_{20}FN_2O$ ([M+H]$^+$): calcd. 311.1554
found 311.1548

3.2.14 (*E*)-7-(4-Chlorostyryl)-*N*,*N*-dimethylindoline-1-carboxamide [(*E*)-270]



(*E*)-**270**
$C_{19}H_{19}ClN_2O$
M = 326.82 g/mol

According to **GP 7**, a flame-dried SCHLENK tube equipped with a magnetic stir bar was successively charged with *N*,*N*-dimethylindoline-1-carboxamide (**91**, 38 mg, 0.20 mmol, 1.0 equiv.), $Pd(OAc)_2$ (4.5 mg, 0.020 mmol, 10 mol%), BQ (43 mg, 0.40 mmol, 2.0 equiv.), and *p*-toluenesulfonic acid monohydrate (38 mg, 0.20 mmol, 1.0 equiv.) in acetic acid (1.0 mL, 0.2M) under inert atmosphere. Subsequently, 1-chloro-4-vinylbenzene (**263**, 52 µL, 0.40 mmol, 2.0 equiv.) was added, and the reaction mixture was stirred at 40 °C for 16 h. After complete consumption of the indoline, as monitored by GLC analysis using tetracosane (10 mg, 0.030 mmol, 15 mol%) as internal standard, the reaction mixture was allowed to cool to room temperature and diluted with ethyl acetate (10 mL). The crude reaction mixture was washed with saturated aqueous Na_2CO_3 (1 × 5 mL) and H_2O (1 × 5 mL). The organic phase was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (2.5 × 20 cm, cyclohexane:ethyl acetate = 1:1 → 1:1.5, 50 mL, #10–22) afforded the analytically pure alkenylated product *(E)*-**270** (52 mg, 82%) as a brown solid.

m.p.: 164–165 °C.

R_f = 0.50 (cyclohexane:ethyl acetate = 1:2).

GLC (HP-5): t_R = 25.7 min.

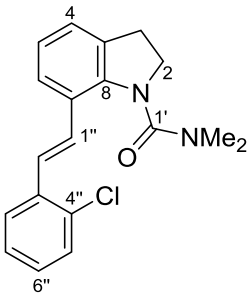
^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ/ppm = 2.95 (s, 6H, N(C*H*$_3$)$_2$), 3.07 (t, $^3J_{3,2}$ = 7.8 Hz, 2H, H-3), 3.95 (t, $^3J_{2,3}$ = 8.1 Hz, 2H, H-2), 6.90 (d, $^3J_{1'',2''}$ = 16.1 Hz, 1H, H-1''), 6.93 (d, $^3J_{4,5}$ = 8.6 Hz, 1H, H-4), 6.99 (dd, $^3J_{5,4}$ = 7.5 Hz, $^3J_{5,6}$ = 7.2 Hz, 1H, H-5), 7.11 (d, $^3J_{6,5}$ = 7.2 Hz, 1H, H-6), 7.28 (d, $^3J_{5'',4''}$ = 8.4 Hz, 2H, H-5''), 7.35 (d, $^3J_{4'',5''}$ = 8.4 Hz, 2H, H-4''), 7.38 (d, $^3J_{2'',1''}$ = 16.1 Hz, 1H, H-2'').

^{13}C NMR (126 MHz, $CDCl_3$, 298 K): δ/ppm = 30.1 (C-3), 37.6 (N(CH_3)$_2$), 52.8 (C-2), 123.6 (C-1''), 124.0 (C-4), 124.9 (C-5), 126.1 (C-2''), 126.5 (C-6), 127.1 (C-2''), 127.7 (C-4''), 128.8 (C-5''), 132.9 (C-6''), 134.0 (C-3''), 136.4 (C-9), 143.2 (C-8), 161.3 (C-1').

IR (ATR): $\tilde{\nu}$ /cm^{-1} = 2921 (w), 1651 (s), 1585 (m), 1488 (m), 1449 (s), 1374 (s), 1340 (m), 1290 (w), 1263 (m), 1204 (w), 1186 (m), 1088 (s), 1059 (m), 1008 (m), 970 (m), 910 (vw), 895 (w), 810 (s), 766 (m), 733 (m), 680 (s).

HRMS (APCI) for $C_{19}H_{20}ClN_2O$ ([M+H]$^+$): calcd. 327.1259
found 327.1258

3.2.15 (*E*)-7-(2-Chlorostyryl)-*N*,*N*-dimethylindoline-1-carboxamide [(*E*)-271]



(*E*)-**271**
$C_{19}H_{19}ClN_2O$
M = 326.82 g/mol

According to **GP 7**, a flame-dried SCHLENK tube equipped with a magnetic stir bar was successively charged with *N*,*N*-dimethylindoline-1-carboxamide (**91**, 38 mg, 0.20 mmol, 1.0 equiv.), $Pd(OAc)_2$ (4.5 mg, 0.020 mmol, 10 mol%), BQ (43 mg, 0.40 mmol, 2.0 equiv.), and *p*-toluenesulfonic acid monohydrate (38 mg, 0.20 mmol, 1.0 equiv.) in acetic acid (1.0 mL, 0.2M) under inert atmosphere. Subsequently, 1-chloro-2-vinylbenzene (**264**, 51 µL, 0.40 mmol, 2.0 equiv.) was added, and the reaction mixture was stirred at 40 °C for 16 h. After complete consumption of the indoline, as monitored by GLC analysis using tetracosane (10 mg, 0.030 mmol, 15 mol%) as internal standard, the reaction mixture was allowed to cool to room temperature and diluted with ethyl acetate (10 mL). The crude reaction mixture was washed with saturated aqueous Na_2CO_3 (1 × 5 mL) and H_2O (1 × 5 mL). The organic phase was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (2.5 × 20 cm, cyclohexane:ethyl

acetate = 1:1 → 1:1.5, 50 mL, #15–27) afforded the analytically pure alkenylated product *(E)*-**271** (59 mg, 90%) as a brown solid.

m.p.: 95–96 °C.

R_f = 0.43 (cyclohexane:ethyl acetate = 1:2).

GLC (HP-5): t_R = 25.5 min.

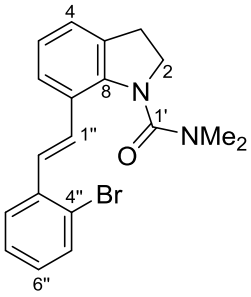
^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ/ppm = 2.95 (s, 6H, N(CH_3)$_2$), 3.07 (t, $^3J_{3,2}$ = 8.1 Hz, 2H, H-3), 3.95 (t, $^3J_{2,3}$ = 7.9 Hz, 2H, H-2), 6.96 (d, $^3J_{1'',2''}$ = 16.1 Hz, 1H, H-1''), 7.01 (dd, $^3J_{5,4}$ = 7.9 Hz, $^3J_{5,6}$ = 7.6 Hz, 1H, H-5), 7.11–7.14 (m, 1H, H-6''), 7.16 (dd, $^3J_{4,5}$ = 8.0 Hz, $^4J_{4,6}$ = 1.7 Hz, 1H, H-4), 7.20–7.24 (m, 1H, H-7''), 7.35 (d, $^3J_{2'',1''}$ = 16.2 Hz, 1H, H-2''), 7.35 (dd, $^3J_{6,5}$ = 8.0 Hz, $^4J_{6,4}$ = 1.1 Hz, 1H, H-6), 7.43 (d, $^3J_{8'',7''}$ = 7.8 Hz, 1H, H-8''), 7.61 (dd, $^3J_{5'',6''}$ = 7.8 Hz, $^4J_{5'',7''}$ = 1.4 Hz, 1H, H-5'').

^{13}C NMR (126 MHz, $CDCl_3$, 298 K): δ/ppm = 30.1 (C-3), 37.7 (N(*C*H$_3$)$_2$), 52.8 (C-2), 123.6 (C-1''), 124.2 (C-4), 124.5 (C-5), 125.7 (C-6), 126.2 (C-2''), 126.8 (C-7''), 126.9 (C-8''), 128.3 (C-6''), 128.7 (C-7), 129.8 (C-5''), 133.3 (C-3''), 134.1 (C-4''), 136.0 (C-9), 143.2 (C-8), 161.2 (C-1').

IR (ATR): $\tilde{\nu}$ /cm^{-1} = 2922 (w), 2901 (w), 1733 (vw), 1645 (s), 1589 (m), 1467 (m), 1445 (m), 1370 (s), 1301 (w), 1261 (m), 1207 (w), 1170 (m), 1125 (w), 1093 (w), 1049 (w), 1031 (w), 1002 (w), 964 (m), 904 (w), 836 (w), 759 (m), 738 (s), 686 (w).

HRMS (APCI) for $C_{19}H_{20}ClN_2O$ ([M+H]$^+$): calcd. 327.1259
found 327.1258

3.2.16 (*E*)-7-(2-Bromostyryl)-*N*,*N*-dimethylindoline-1-carboxamide [(*E*)-272]



(*E*)-**272**
$C_{19}H_{19}BrN_2O$
M = 371.28 g/mol

According to **GP 7**, a flame-dried SCHLENK tube equipped with a magnetic stir bar was successively charged with *N*,*N*-dimethylindoline-1-carboxamide (**91**, 38 mg, 0.20 mmol, 1.0 equiv.), $Pd(OAc)_2$ (4.5 mg, 0.020 mmol, 10 mol%), BQ (43 mg, 0.40 mmol, 2.0 equiv.), and *p*-toluenesulfonic acid monohydrate (38 mg, 0.20 mmol, 1.0 equiv.) in acetic acid (1.0 mL, 0.2M) under inert atmosphere. Subsequently, 1-bromo-4-vinylbenzene (**265**, 51 µL, 0.40 mmol, 2.0 equiv.) was added, and the reaction mixture was stirred at 40 °C for 16 h. After complete consumption of the indoline, as monitored by GLC analysis using tetracosane (10 mg, 0.030 mmol, 15 mol%) as internal standard, the reaction mixture was allowed to cool to room temperature and diluted with ethyl acetate (10 mL). The crude reaction mixture was washed with saturated aqueous Na_2CO_3 (1 × 5 mL) and H_2O (1 × 5 mL). The organic phase was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (2.5 × 20 cm, cyclohexane:ethyl acetate = 1:1 → 1:1.5, 50 mL, #15–24) afforded the analytically pure alkenylated product *(E)*-**272** (30 mg, 40%) as a brown oil.

R_f = 0.47 (cyclohexane:ethyl acetate = 1:2).

GLC (HP-5): t_R = 26.4 min.

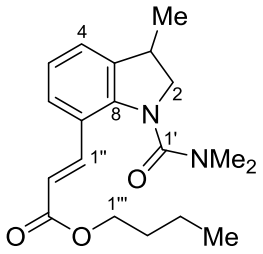
^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ/ppm = 2.95 (s, 6H, N(CH_3)$_2$), 3.08 (t, $^3J_{3,2}$ = 7.9 Hz, 2H, H-3), 3.96 (t, $^3J_{2,3}$ = 8.2 Hz, 2H, H-2), 6.94 (d, $^3J_{1'',2''}$ = 16.1 Hz, 1H, H-1''), 7.01 (dd, $^3J_{5,6}$ = 7.7 Hz, $^3J_{5,4}$ = 7.5 Hz, 1H, H-5), 7.06–7.14 (m, 3H, H-4, H-6'', H-7''), 7.30 (d, $^3J_{2'',1''}$ = 16.1 Hz, 1H, H-2''), 7.44 (dd, $^3J_{6,5}$ = 7.8 Hz, $^4J_{6,4}$ = 0.5 Hz, 1H, H-6), 7.55 (dd, $^3J_{8'',7''}$ = 8.1 Hz, $^4J_{8'',6''}$ = 1.2 Hz, 1H, H-8''), 7.59 (dd, $^3J_{5'',6''}$ = 8.0 Hz, $^4J_{5'',7''}$ = 1.7 Hz, 1H, H-5'').

^{13}C NMR (100 MHz, $CDCl_3$, 298 K): δ/ppm = 30.9 (C-3), 37.7 (N(CH_3)$_2$), 52.8 (C-2), 123.7 (C-1''), 124.1 (C-4''), 124.2 (C-4), 125.7 (C-5), 126.1 (C-2''), 127.2 (C-6), 127.2 (C-8''), 127.6 (C-6''), 128.6 (C-7''), 128.9 (C-7), 133.1 (C-5''), 134.0 (C-3''), 137.8 (C-9), 143.3 (C-8), 161.2 (C-1').

IR (ATR): $\tilde{\nu}$ /cm^{-1} = 3059 (w), 2916 (w), 2845 (w), 1736 (m), 1653 (m), 1623 (s), 1584 (m), 1491 (w), 1465 (m), 1431 (s), 1377 (s), 1340 (w), 1304 (w), 1230 (w), 1186 (m) 1169 (s), 1091 (m), 1045 (s), 1026 (s), 960 (s), 909 (w), 813 (w), 767 (m), 725 (s), 672 (w).

HRMS (APCI) for $C_{19}H_{20}BrN_2O$ ([M+H]$^+$): calcd. 371.0754
found 371.0752

3.2.17 (*E*)-Butyl 3-[1-(dimethylcarbamoyl)-3-methylindolin-7-yl]acrylate [(*E*)-279]



(*E*)-**279**
$C_{19}H_{26}N_2O_3$
M = 330.43 g/mol

According to **GP 7**, a flame-dried SCHLENK tube equipped with a magnetic stir bar was successively charged with *N*,*N*,3-trimethylindoline-1-carboxamide (**207**, 41 mg, 0.20 mmol, 1.0 equiv.), $Pd(OAc)_2$ (4.5 mg, 0.020 mmol, 10 mol%), BQ (43 mg, 0.40 mmol, 2.0 equiv.), and *p*-toluenesulfonic acid monohydrate (38 mg, 0.20 mmol, 1.0 equiv.) in acetic acid (1.0 mL, 0.2M) under inert atmosphere. Subsequently, *n*-butyl acrylate (**2**, 58 µL, 0.40 mmol, 2.0 equiv.) was added, and the reaction mixture was stirred at 40 °C for 16 h. After complete consumption of the indoline, as monitored by GLC analysis using tetracosane (10 mg, 0.030 mmol, 15 mol%) as internal standard, the reaction mixture was allowed to cool to room temperature and diluted with ethyl acetate (10 mL). The crude reaction mixture was washed with saturated aqueous Na_2CO_3 (1 × 5 mL) and H_2O (1 × 5 mL). The organic phase was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (2.5 × 20 cm, cyclohexane:ethyl acetate = 2:1 → 1:1, 20 mL, #23–34) afforded the analytically pure alkenylated product *(E)*-**279** (64 mg, 97%) as a brown oil.

R_f = 0.20 (cyclohexane:ethyl acetate = 2:1).

GLC (HP-5): t_R = 23.7 min.

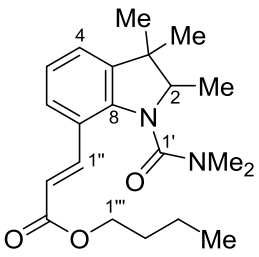
^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ/ppm = 0.94 (t, $^3J_{4''',3'''}$ = 7.3 Hz, 3H, H-4'''), 1.28 (d, $^3J_{3\text{–}CH_3,3}$ = 6.6 Hz, 3H, 3–CH_3), 1.38–1.45 (m, 2H, H-3'''), 1.62–1.67 (m, 2H, H-2'''), 2.97 (s, 6H, N(CH_3)$_2$), 3.36–3.44 (m, 1H, H-3), 3.48 (dd, $^2J_{2A,2B}$ = 10.4 Hz, $^3J_{2A,3}$ = 7.5 Hz, 1H, H-2A), 4.03 (dd, $^2J_{2B,2A}$ = 10.0 Hz, $^3J_{2B,3}$ = 8.1 Hz, 1H, H-2B), 4.14 (t, $^3J_{1''',2'''}$ = 6.5 Hz, 2H, H-1'''), 6.29 (d, $^3J_{2'',1''}$ = 16.2 Hz, 1H, H-2''), 7.00 (dd, $^3J_{5,4}$ = 8.1 Hz, $^3J_{5,6}$ = 7.8 Hz, 1H, H-5), 7.13 (d, $^3J_{6,5}$ = 7.1 Hz, 1H, H-6), 7.35 (d, $^3J_{4,5}$ = 7.8 Hz, 1H, H-4), 7.50 (d, $^3J_{1'',2''}$ = 15.9 Hz, 1H, H-1'').

^{13}C NMR (126 MHz, $CDCl_3$, 298 K): δ/ppm = 13.8 (C-4'''), 19.0 (3–CH$_3$), 19.3 (C-3'''), 30.8 (C-2'''), 36.7 (C-3), 37.6 (N(CH$_3$)$_2$), 60.7 (C-2), 64.2 (C-1'''), 117.4 (C-2''), 123.5 (C-5), 123.8 (C-7), 124.9 (C-4), 125.7 (C-6), 139.4 (C-9), 141.4 (C-1''), 144.4 (C-8), 161.6 (C-1'), 167.3 (C-3'').

IR (ATR): $\tilde{\nu}$ /cm^{-1} = 2958 (w), 2931 (w), 2871 (w), 1706 (s), 1655 (s), 1630 (s), 1491 (m), 1438 (s), 1368 (s), 1341 (m), 1281 (m), 1254 (s), 1154 (s), 1118 (m), 1062 (m), 979 (m), 862 (w), 792 (w), 761 (m), 742 (m), 718 (w), 684 (w).

HRMS (APCI) for $C_{19}H_{27}N_2O_3$ ([M+H]$^+$): calcd. 331.2016
found 331.2017

3.2.18 (*E*)-Butyl 3-[1-(dimethylcarbamoyl)-2,3,3-trimethylindolin-7-yl]acrylate [(*E*)-280]



(*E*)-**280**
$C_{21}H_{30}N_2O_3$
M = 358.48 g/mol

According to **GP 7**, a flame-dried SCHLENK tube equipped with a magnetic stir bar was successively charged with *N,N*,2,3,3-pentamethylindoline-1-carboxamide (**210**, 46 mg, 0.20 mmol, 1.0 equiv.), $Pd(OAc)_2$ (4.5 mg, 0.020 mmol, 10 mol%), BQ (43 mg, 0.40 mmol, 2.0 equiv.), and *p*-toluenesulfonic acid monohydrate (38 mg, 0.20 mmol, 1.0 equiv.) in acetic acid (1.0 mL, 0.2M) under inert atmosphere. Subsequently, *n*-butyl acrylate (**2**, 58 µL, 0.40 mmol, 2.0 equiv.) was added, and the reaction mixture was stirred at 40 °C for 16 h. After complete consumption of the indoline, as monitored by GLC analysis using tetracosane (10 mg, 0.030 mmol, 15 mol%) as internal standard, the reaction mixture was allowed to cool to room temperature and diluted with ethyl acetate (10 mL). The crude reaction mixture was washed with saturated aqueous Na_2CO_3 (1 × 5 mL) and H_2O (1 × 5 mL). The organic phase was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (2.5 × 20 cm, cyclohexane:ethyl acetate = 3:1 → 2:1, 50 mL, #16–31) afforded the analytically pure alkenylated product *(E)*-**280** (62 mg, 86%) as a yellow oil.

R_f = 0.63 (cyclohexane:ethyl acetate = 1:1).

GLC (HP-5): t_R = 23.6 min.

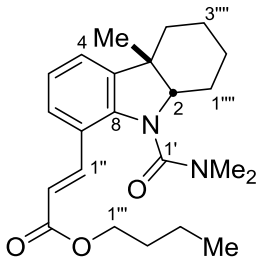
^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ/ppm = 0.94 (t, $^3J_{4''',3'''}$ = 7.2 Hz, 3H, H-4'''), 1.17 (s, 3H, 3–CH_3)*, 1.23 (s, 3H, 3–CH_3)*, 1.25 (d, $^3J_{2-CH_3,2}$ = 6.7 Hz, 3H, 2–CH_3), 1.36–1.46 (m, 2H, H-3'''), 1.62–1.69 (m, 2H, H-2'''), 2.86 (s, 6H, N(CH_3)$_2$), 3.89 (q, $^3J_{2,2-CH_3}$ = 6.3 Hz, 1H, H-2), 4.17 (t, $^3J_{1''',2'''}$ = 7.8 Hz, 2H, H-1'''), 6.27 (d, $^3J_{2'',1''}$ = 16.0 Hz, 1H, H-2''), 6.94 (ddd, $^3J_{5,4}$ = 8.3 Hz, $^3J_{5,6}$ = 7.9 Hz, 1H, H-5), 7.08 (dd, $^3J_{6,5}$ = 7.3 Hz, $^4J_{6,4}$ = 1.2 Hz, 1H, H-6), 7.28 (dd, $^3J_{4,5}$ = 7.9 Hz, $^4J_{4,6}$ = 0.8 Hz, 1H, H-4), 7.57 (d, $^3J_{1'',2''}$ = 16.0 Hz, 1H, H-1'').

^{13}C NMR (126 MHz, $CDCl_3$, 298 K): δ/ppm = 13.8 (C-4'''), 14.7 (2–CH$_3$), 19.3 (C-3'''), 21.8 (3–CH$_3$)*, 27.6 (3–CH$_3$)*, 30.9 (C-2'''), 37.4 (N(CH$_3$)$_2$), 43.7 (C-3), 64.4 (C-1'''), 70.2 (C-2), 117.8 (C-2''), 121.3 (C-5), 122.2 (C-7), 122.8 (C-4), 124.1 (C-6), 126.0 (C-8), 140.8 (C-1''), 142.1 (C-9), 160.1 (C-1'), 167.1 (C-3'').

IR (ATR): $\tilde{\nu}$ /cm^{-1} = 2960 (w), 1685 (m), 1626 (s), 1510 (s), 1437 (s), 1390 (s), 1265 (m), 1180 (s), 1093 (w), 1066 (w), 1028 (w), 983 (w), 863 (w), 828 (m), 758 (m).

HRMS (APCI) for $C_{21}H_{31}N_2O_3$ ($[M+H]^+$): calcd. 359.2329
found 359.2329

3.2.19 *cis*-(*E*)-Butyl 3-[9-(dimethylcarbamoyl)-4a-methyl-2,3,4,4a,9,9a-hexahydro-1*H*-carbazol-8-yl]acrylate [*cis*-(*E*)-281]



cis-(*E*)-**281**
$C_{23}H_{32}N_2O_3$
M = 384.52 g/mol

According to **GP 7**, a flame-dried SCHLENK tube equipped with a magnetic stir bar was successively charged with *cis*-*N*,*N*,4a-trimethyl-1,2,3,4,4a,9a-hexahydro-9*H*-carbazole-9-carboxamide (*cis*-**212**, 52 mg, 0.20 mmol, 1.0 equiv.), $Pd(OAc)_2$ (4.5 mg, 0.020 mmol, 10 mol%), BQ (43 mg, 0.40 mmol, 2.0 equiv.), and *p*-toluenesulfonic acid monohydrate (38 mg, 0.20 mmol, 1.0 equiv.) in acetic acid (1.0 mL, 0.2M) under inert atmosphere. Subsequently, *n*-butyl acrylate (**2**, 58 µL, 0.40 mmol, 2.0 equiv.) was added, and the reaction mixture was stirred at 40 °C for 16 h. After complete consumption of the indoline, as monitored by GLC analysis using tetracosane (10 mg, 0.030 mmol, 15 mol%) as internal standard, the reaction mixture was allowed to cool to room temperature and diluted with ethyl acetate (10 mL). The crude reaction mixture was washed with saturated aqueous Na_2CO_3 (1 × 5 mL) and H_2O (1 × 5 mL). The organic phase was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (2.5 × 20 cm, cyclohexane:ethyl acetate = 3:1 → 2:1, 50 mL, #11–19) afforded the analytically pure alkenylated product *cis*-*(E)*-**281** (66 mg, 86%) as a yellow oil.

R_f = 0.30 (cyclohexane:ethyl acetate = 3:1).

GLC (HP-5): t_R = 26.2 min.

^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ/ppm = 0.94 (t, $^3J_{4''',3'''}$ = 7.5 Hz, 3H, H-4'''), 1.18 (s, 3H, 3–C*H*$_3$), 1.23–1.28 (m, 2H, H-1''''), 1.36–1.44 (m, 2H, H-3'''), 1.46–1.57 (m, 4H, H-3'''', H-4''''), 1.62–1.69 (m, 2H, H-2'''), 1.98–2.02 (m, 1H, H-2''''A), 2.08–2.15 (m, 1H, H-2''''B), 2.90 (s, 6H, N(C*H*$_3$)$_2$), 3.76 (dd, $^3J_{2A,2B}$ = 8.4 Hz, $^3J_{2,1''''}$ = 2.7 Hz, 1H, H-2), 4.16 (t, $^3J_{1''',2'''}$ = 6.7 Hz, 2H, H-1'''), 6.29 (d, $^3J_{2'',1''}$ = 16.1 Hz, 1H, H-2''), 6.98 (ddd, $^3J_{5,4}$ = 8.1 Hz, $^3J_{5,6}$ = 7.5 Hz, 1H, H-5),

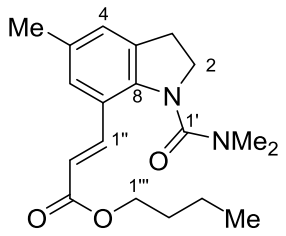
7.07 (dd, $^{3}J_{6,5}$ = 7.2 Hz, $^{4}J_{6,4}$ = 1.2 Hz, 1H, H-6), 7.31 (dd, $^{3}J_{4,5}$ = 7.9 Hz, $^{4}J_{4,6}$ = 0.8 Hz, 1H, H-4), 7.58 (d, $^{3}J_{1'',2''}$ = 16.0 Hz, 1H, H-1'').

^{13}C NMR (126 MHz, $CDCl_3$, 298 K): δ/ppm = 13.8 (C-4'''), 19.3 (C-3'''), 22.0 (C-2'''')*, 22.9 (C-3'''')*, 27.6 (3–*C*H$_3$), 28.1 (C-1''''), 30.9 (C-2'''), 34.0 (C-4''''), 37.6 (N(*C*H$_3$)$_2$), 44.4 (C-3), 64.4 (C-1'''), 71.1 (C-2), 117.8 (C-2''), 122.2 (C-5), 123.1 (C-7), 123.3 (C-4), 123.4 (C-6), 125.8 (C-8), 140.9 (C-1''), 141.8 (C-9), 160.6 (C-1'), 167.2 (C-3'').

IR (ATR): $\tilde{\nu}$ /cm^{-1} = 2929 (w), 2858 (w), 1760 (w), 1708 (s), 1630 (s), 1599 (w), 1508 (w), 1489 (w), 1433 (s), 1379 (s), 1261 (s), 1167 (s), 1064 (m), 1032 (m), 980 (m), 909 (w), 774 (w), 729 (m).

HRMS (APCI) for $C_{23}H_{33}N_2O_3$ ([M+H]$^+$): calcd. 385.2486
found 385.2476

3.2.20 (*E*)-Butyl 3-[1-(dimethylcarbamoyl)-5-methylindolin-7-yl]acrylate [(*E*)-282]



(*E*)-**282**
$C_{19}H_{26}N_2O_3$
M = 330.43 g/mol

According to **GP 7**, a flame-dried SCHLENK tube equipped with a magnetic stir bar was successively charged with *N*,*N*,5-trimethylindoline-1-carboxamide (**274**, 41 mg, 0.20 mmol, 1.0 equiv.), $Pd(OAc)_2$ (4.5 mg, 0.020 mmol, 10 mol%), BQ (43 mg, 0.40 mmol, 2.0 equiv.), and *p*-toluenesulfonic acid monohydrate (38 mg, 0.20 mmol, 1.0 equiv.) in acetic acid (1.0 mL, 0.2M) under inert atmosphere. Subsequently, *n*-butyl acrylate (**2**, 58 µL, 0.40 mmol, 2.0 equiv.) was added, and the reaction mixture was stirred at 40 °C for 16 h. After complete consumption of the indoline, as monitored by GLC analysis using tetracosane (10 mg, 0.030 mmol, 15 mol%) as internal standard, the reaction mixture was allowed to cool to room temperature and diluted with ethyl acetate (10 mL). The crude reaction mixture was washed with saturated aqueous Na_2CO_3 (1 × 5 mL) and H_2O (1 × 5 mL). The organic phase was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification of the

residue by flash column chromatography on silica gel (2.5 × 20 cm, cyclohexane:ethyl acetate = 1:1, 50 mL, #17–34) afforded the analytically pure alkenylated product *(E)*-**282** (58 mg, 88%) as a yellow solid.

m.p.: 77–79 °C.

R_f = 0.29 (cyclohexane:ethyl acetate = 1:1).

GLC (HP-5): t_R = 24.3 min.

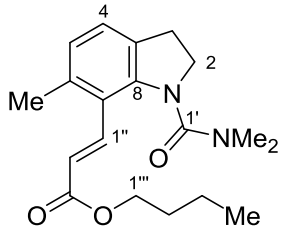
^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ/ppm = 0.94 (t, $^3J_{4''',3'''}$ = 7.3 Hz, 3H, H-4'''), 1.39–1.46 (m, 2H, H-3'''), 1.62–1.68 (m, 2H, H-2'''), 2.29 (s, 3H, 5–CH_3), 2.97 (s, 6H, N(CH_3)$_2$), 3.02 (t, $^3J_{3,2}$ = 7.6 Hz, 2H, H-3), 3.91 (t, $^3J_{2,3}$ = 8.2 Hz, 2H, H-2), 4.15 (t, $^3J_{1''',2'''}$ = 6.5 Hz, 2H, H-1'''), 6.29 (d, $^3J_{2'',1''}$ = 16.0 Hz, 1H, H-2''), 7.00 (s, 1H, H-4), 7.17 (s, 1H, H-6), 7.49 (d, $^3J_{1'',2''}$ = 16.0 Hz, 1H, H-1'').

^{13}C NMR (126 MHz, $CDCl_3$, 298 K): δ/ppm = 13.9 (C-4'''), 19.3 (C-3'''), 21.0 (5–CH$_3$), 30.0 (C-3), 30.9 (C-2'''), 37.6 (N(CH$_3$)$_2$), 52.9 (C-2), 64.2 (C-1'''), 117.2 (C-2''), 123.3 (C-7), 125.9 (C-4), 127.0 (C-6), 133.2 (C-5), 134.5 (C-9), 141.5 (C-1''), 142.6 (C-8), 161.9 (C-1'), 167.4 (C-3'').

IR (ATR): $\tilde{\nu}$ /cm^{-1} = 2955 (w), 2933 (w), 2870 (w), 1705 (s), 1656 (s), 1636 (m), 1466 (m), 1448 (m), 1373 (s), 1268 (s), 1248 (s), 1235 (m), 1196 (w), 1170 (s), 1065 (m), 1027 (m), 974 (w), 871 (w), 853 (w), 819 (w), 767 (w), 707 (w).

HRMS (APCI) for $C_{19}H_{27}N_2O_3$ ($[M+H]^+$): calcd. 331.2016
found 331.2017

3.2.21 (*E*)-Butyl 3-[1-(dimethylcarbamoyl)-6-methylindolin-7-yl]acrylate [(*E*)-286]



(*E*)-**286**
$C_{19}H_{26}N_2O_3$
M = 330.43 g/mol

According to **GP 7**, a flame-dried SCHLENK tube equipped with a magnetic stir bar was successively charged with *N*,*N*,6-trimethylindoline-1-carboxamide (**277**, 41 mg, 0.20 mmol, 1.0 equiv.), $Pd(OAc)_2$ (4.5 mg, 0.020 mmol, 10 mol%), BQ (43 mg, 0.40 mmol, 2.0 equiv.), and *p*-toluenesulfonic acid monohydrate (38 mg, 0.20 mmol, 1.0 equiv.) in acetic acid (1.0 mL, 0.2M) under inert atmosphere. Subsequently, *n*-butyl acrylate (**2**, 58 µL, 0.40 mmol, 2.0 equiv.) was added, and the reaction mixture was stirred at 40 °C for 16 h. After complete consumption of the indoline, as monitored by GLC analysis using tetracosane (10 mg, 0.030 mmol, 15 mol%) as internal standard, the reaction mixture was allowed to cool to room temperature and diluted with ethyl acetate (10 mL). The crude reaction mixture was washed with saturated aqueous Na_2CO_3 (1 × 5 mL) and H_2O (1 × 5 mL). The organic phase was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (2.5 × 20 cm, cyclohexane:ethyl acetate = 1:1, 50 mL, #19–23) afforded the analytically pure alkenylated product *(E)*-**286** (30 mg, 46%) as a brown oil.

R_f = 0.21 (cyclohexane:ethyl acetate = 1:1).

GLC (HP-5): t_R = 23.6 min.

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ/ppm = 0.96 (t, $^3J_{4''',3'''}$ = 7.4 Hz, 3H, H-4'''), 1.39–1.46 (m, 2H, H-3'''), 1.64–1.69 (m, 2H, H-2'''), 2.36 (s, 3H, 6–C*H*$_3$), 2.98 (s, 6H, N(C*H*$_3$)$_2$), 3.06 (t, $^3J_{3,2}$ = 8.2 Hz, 2H, H-3), 3.88–3.93 (m, 2H, H-2), 4.17 (t, $^3J_{1''',2'''}$ = 6.6 Hz, 2H, H-1'''), 6.12 (d, $^3J_{2'',1''}$ = 16.3 Hz, 1H, H-2''), 6.84 (d, $^3J_{5,4}$ = 7.4 Hz, 1H, H-5), 7.05 (d, $^3J_{4,5}$ = 7.4 Hz, 1H, H-4), 7.68 (d, $^3J_{1'',2''}$ = 16.3 Hz, 1H, H-1'').

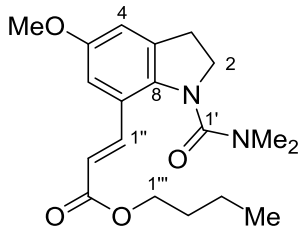
^{13}C NMR (100 MHz, $CDCl_3$, 298 K): δ/ppm = 13.9 (C-4'''), 19.4 (C-3'''), 20.7 (6–*C*H$_3$), 30.4 (3-*C*H$_3$), 31.0 (C-2'''), 37.4 (N(*C*H$_3$)$_2$), 52.9 (C-2), 64.3 (C-1'''), 116.3 (C-2''), 118.4 (C-4), 120.4

(C-5), 125.0 (C-7), 125.9 (C-6), 131.9 (C-9), 136.4 (C-1''), 141.5 (C-8), 161.6 (C-1'), 167.5 (C-3'').

IR (ATR): $\tilde{\nu}$ /cm^{-1} = 2956 (w), 1709 (m), 1634 (s), 1488 (s), 1444 (s), 1376 (s), 1242 (w), 1221 (w), 1201 (w), 1166 (s), 1093 (w), 1063 (w), 912 (w), 869 (w), 834 (w), 809 (w), 761 (w), 730 (w).

HRMS (APCI) for $C_{19}H_{27}N_2O_3$ ([M+H]$^+$): calcd. 331.2016
found 331.2017

3.2.22 (*E*)-Butyl 3-[1-(dimethylcarbamoyl)-5-methoxyindolin-7-yl]acrylate [(*E*)-283]



(*E*)-**283**
$C_{19}H_{26}N_2O_4$
M = 346.43 g/mol

According to **GP 7**, a flame-dried SCHLENK tube equipped with a magnetic stir bar was successively charged with 5-methoxy-*N*,*N*-dimethylindoline-1-carboxamide (**208**, 44 mg, 0.20 mmol, 1.0 equiv.), $Pd(OAc)_2$ (4.5 mg, 0.020 mmol, 10 mol%), BQ (43 mg, 0.40 mmol, 2.0 equiv.), and *p*-toluenesulfonic acid monohydrate (38 mg, 0.20 mmol, 1.0 equiv.) in acetic acid (1.0 mL, 0.2M) under inert atmosphere. Subsequently, *n*-butyl acrylate (**2**, 58 µL, 0.40 mmol, 2.0 equiv.) was added, and the reaction mixture was stirred at 40 °C for 16 h. After complete consumption of the indoline, as monitored by GLC analysis using tetracosane (10 mg, 0.030 mmol, 15 mol%) as internal standard, the reaction mixture was allowed to cool to room temperature and diluted with ethyl acetate (10 mL). The crude reaction mixture was washed with saturated aqueous Na_2CO_3 (1 × 5 mL) and H_2O (1 × 5 mL). The organic phase was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (2.5 × 2 cm, cyclohexane:ethyl acetate = 1:1 → 1:1.5, 50 mL, #24–40) afforded the analytically pure alkenylated product *(E)*-**283** (63 mg, 93%) as a brown oil.

R_f = 0.42 (cyclohexane:ethyl acetate = 1:2).

GLC (HP-5): t_R = 25.5 min.

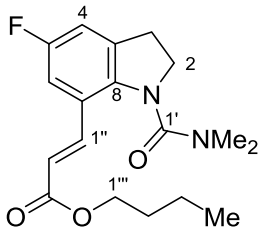
^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ/ppm = 0.95 (t, $^3J_{4''',3'''}$ = 7.3 Hz, 3H, H-4'''), 1.38–1.46 (m, 2H, H-3'''), 1.62–1.68 (m, 2H, H-2'''), 2.98 (s, 6H, N(CH_3)$_2$), 3.03 (t, $^3J_{3,2}$ = 8.0 Hz, 2H, H-3), 3.77 (s, 3H, 5–OCH_3), 3.91 (t, $^3J_{2,3}$ = 8.0 Hz, 2H, H-2), 4.15 (t, $^3J_{1''',2'''}$ = 6.6 Hz, 2H, H-1'''), 6.29 (d, $^3J_{2'',1''}$ = 15.9 Hz, 1H, H-2''), 6.79 (d, $^3J_{4,6}$ = 2.3 Hz, 1H, H-4), 6.86 (d, $^3J_{6,4}$ = 2.3 Hz, 1H, H-6), 7.47 (d, $^3J_{1'',2''}$ = 15.9 Hz, 1H, H-1'').

^{13}C NMR (126 MHz, $CDCl_3$, 298 K): δ/ppm = 13.9 (C-4'''), 19.3 (C-3'''), 30.4 (C-3), 30.9 (C-2'''), 37.7 (N(*C*H$_3$)$_2$), 53.1 (C-2), 55.9 (5–O*C*H$_3$), 64.3 (C-1'''), 109.3 (C-4), 113.5 (C-6), 117.6 (C-2''), 124.1 (C-7), 136.0 (C-1''), 138.8 (C-9), 141.4 (C-8), 156.6 (C-5), 162.2 (C-1'), 167.2 (C-3'').

IR (ATR): $\tilde{\nu}$ /cm^{-1} = 2956 (w), 2933 (w), 1709 (s), 1657 (s), 1485 (m), 1441 (m), 1382 (s), 1348 (m), 1260 (m), 1232 (m), 1155 (s), 1136 (m), 1089 (w), 1064 (w), 1041 (w), 1028 (w), 979 (w), 862 (w), 770 (w), 704 (w).

HRMS (APCI) for $C_{19}H_{27}N_2O_4$ ([M+H]$^+$): calcd. 347.1965
found 347.1964

3.2.23 (*E*)-Butyl 3-[1-(dimethylcarbamoyl)-5-fluoroindolin-7-yl]acrylate [(*E*)-284]



(*E*)-**284**
$C_{18}H_{23}FN_2O_3$
M = 334.39 g/mol

According to **GP 7**, a flame-dried SCHLENK tube equipped with a magnetic stir bar was successively charged with 5-fluoro-*N*,*N*-dimethylindoline-1-carboxamide (**275**, 42 mg, 0.20 mmol, 1.0 equiv.), $Pd(OAc)_2$ (4.5 mg, 0.020 mmol, 10 mol%), BQ (43 mg, 0.40 mmol, 2.0 equiv.), and *p*-toluenesulfonic acid monohydrate (38 mg, 0.20 mmol, 1.0 equiv.) in acetic acid (1.0 mL, 0.2M) under inert atmosphere. Subsequently, *n*-butyl acrylate (**2**, 58 µL,

0.40 mmol, 2.0 equiv.) was added, and the reaction mixture was stirred at 40 °C for 16 h. After complete consumption of the indoline, as monitored by GLC analysis using tetracosane (10 mg, 0.030 mmol, 15 mol%) as internal standard, the reaction mixture was allowed to cool to room temperature and diluted with ethyl acetate (10 mL). The crude reaction mixture was washed with saturated aqueous Na_2CO_3 (1 × 5 mL) and H_2O (1 × 5 mL). The organic phase was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (2.5 × 20 cm, cyclohexane:ethyl acetate = 1:1 → 1:2, 50 mL, #18–34) afforded the analytically pure alkenylated product *(E)*-**284** (63 mg, 93%) as a yellow solid.

m.p.: 113–114 °C.

R_f = 0.23 (cyclohexane:ethyl acetate = 1:1).

GLC (HP-5): t_R = 23.4 min.

^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ/ppm = 0.94 (t, $^3J_{4''',3'''}$ = 7.4 Hz, 3H, H-4'''), 1.37–1.46 (m, 2H, H-3'''), 1.61–1.68 (m, 2H, H-2'''), 2.99 (s, 6H, N(CH_3)$_2$), 3.06 (t, $^3J_{3,2}$ = 8.1 Hz, 2H, H-3), 3.93 (t, $^3J_{2,3}$ = 8.1 Hz, 2H, H-2), 4.15 (t, $^3J_{1''',2'''}$ = 6.7 Hz, 2H, H-1'''), 6.27 (d, $^3J_{2'',1''}$ = 15.8 Hz, 1H, H-2''), 6.89 (dd, $^3J_{4,5–F}$ = 7.6 Hz, $^4J_{4,6}$ = 1.2 Hz, 1H, H-4), 7.04 (dd, $^3J_{6,5–F}$ = 10.0 Hz, $^4J_{6,4}$ = 2.5 Hz, 1H, H-6), 7.41 (dd, $^3J_{1'',2''}$ = 15.9 Hz, $^4J_{1'',6}$ = 1.3 Hz, 1H, H-1'').

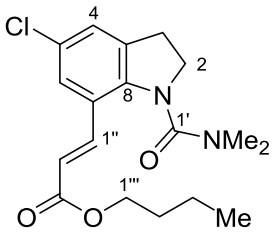
^{13}C NMR (100 MHz, $CDCl_3$, 298 K): δ/ppm = 13.8 (C-4'''), 19.3 (C-3'''), 30.3 (d, $^4J_{C\text{-}3,5–F}$ = 1.6 Hz, C-3), 30.8 (C-2'''), 37.6 (N(*C*H$_3$)$_2$), 53.1 (C-2), 64.3 (C-1'''), 111.2 (d, $^2J_{C\text{-}4,5–F}$ = 25.1 Hz, C-4), 113.4 (d, $^2J_{C\text{-}6,5–F}$ = 25.1 Hz, C-6), 118.5 (C-2''), 124.7 (d, $^3J_{C\text{-}7,5–F}$ = 8.5 Hz, C-7), 136.4 (d, $^3J_{C\text{-}9,5–F}$ = 9.6 Hz, C-9), 140.4 (d, $^4J_{C\text{-}1'',5–F}$ = 2.3 Hz, C-1''), 141.1 (d, $^4J_{C\text{-}8,5–F}$ = 2.1 Hz, C-8), 159.5 (d, $^1J_{C\text{-}5,5–F}$ = 241.7 Hz, C-5), 161.9 (C-1'), 166.9 (C-3'').

^{19}F NMR (471 MHz, $CDCl_3$, 298 K): δ/ppm = −120.2 (5–F).

IR (ATR): $\tilde{\nu}$ /cm^{-1} = 2933 (w), 1690 (s), 1655 (s), 1463 (m), 1435 (m), 1376 (s), 1347 (m), 1251 (s), 1210 (s), 1185 (m), 1162 (w), 1119 (w), 1091 (w), 1064 (w), 1009 (s), 978 (s), 870 (m), 859 (m).

HRMS (APCI) for $C_{18}H_{24}FN_2O_3$ ([M+H]$^+$): calcd. 335.1765
found 335.1759

3.2.24 (*E*)-Butyl 3-[5-chloro-1-(dimethylcarbamoyl)indolin-7-yl]acrylate [(*E*)-285]



(*E*)-**285**
$C_{18}H_{23}ClN_2O_3$
M = 350.84 g/mol

According to **GP 7**, a flame-dried SCHLENK tube equipped with a magnetic stir bar was successively charged with 5-chloro-*N*,*N*-dimethylindoline-1-carboxamide (**276**, 45 mg, 0.20 mmol, 1.0 equiv.), $Pd(OAc)_2$ (4.5 mg, 0.020 mmol, 10 mol%), BQ (43 mg, 0.40 mmol, 2.0 equiv.), and *p*-toluenesulfonic acid monohydrate (38 mg, 0.20 mmol, 1.0 equiv.) in acetic acid (1.0 mL, 0.2M) under inert atmosphere. Subsequently, *n*-butyl acrylate (**2**, 58 µL, 0.40 mmol, 2.0 equiv.) was added, and the reaction mixture was stirred at 40 °C for 16 h. After complete consumption of the indoline, as monitored by GLC analysis using tetracosane (10 mg, 0.030 mmol, 15 mol%) as internal standard, the reaction mixture was allowed to cool to room temperature and diluted with ethyl acetate (10 mL). The crude reaction mixture was washed with saturated aqueous Na_2CO_3 (1 × 5 mL) and H_2O (1 × 5 mL). The organic phase was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (2.5 × 20 cm, cyclohexane:ethyl acetate = 1:1 → 1:2, 50 mL, #18–26) afforded the analytically pure alkenylated product *(E)*-**285** (62 mg, 89%) as a yellow solid.

m.p.: 94–95 °C.

R_f = 0.25 (cyclohexane:ethyl acetate = 1:1).

GLC (HP-5): t_R = 25.2 min.

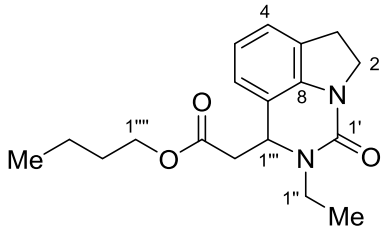
^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ/ppm = 0.94 (t, $^3J_{4''',3'''}$ = 7.2 Hz, 3H, H-4'''), 1.37–1.46 (m, 2H, H-3'''), 1.61–1.68 (m, 2H, H-2'''), 2.98 (s, 6H, N(C*H*$_3$)$_2$), 3.05 (t, $^3J_{3,2}$ = 8.3 Hz, 2H, H-3), 3.92 (t, $^3J_{2,3}$ = 8.0 Hz, 2H, H-2), 4.14 (t, $^3J_{1''',2'''}$ = 6.8 Hz, 2H, H-1'''), 6.28 (d, $^3J_{2'',1''}$ = 15.9 Hz, 1H, H-2''), 7.11–7.14 (m, 1H, H-4), 7.30–7.33 (m, 1H, H-6), 7.39 (d, $^3J_{1'',2''}$ = 15.9 Hz, 1H, H-1'').

^{13}C NMR (100 MHz, $CDCl_3$, 298 K): δ/ppm = 13.8 (C-4'''), 19.3 (C-3'''), 29.9 (3–*C*H_3), 30.8 (C-2'''), 37.6 (N(*C*H_3)$_2$), 52.9 (C-2), 64.4 (C-1'''), 118.5 (C-2''), 124.7 (C-4), 125.2 (C-6), 125.9 (C-5), 128.8 (C-7), 136.2 (C-1''), 140.1 (C-9), 143.6 (C-8), 161.4 (C-1'), 166.9 (C-3'').

IR (ATR): $\tilde{\nu}$ /cm^{-1} = 2954 (w), 2929 (w), 1702 (s), 1655 (s), 1488 (w), 1452 (m), 1428 (m), 1381 (s), 1373 (s), 1356 (m), 1290 (m), 1272 (m), 1249 (s), 1215 (m), 1192 (m), 1166 (m), 1062 (m), 1025 (w), 972 (m), 885 (m), 876 (m), 765 (w), 702 (w).

HRMS (APCI) for $C_{18}H_{24}ClN_2O_3$ ([M+H]$^+$): calcd. 351.1470
found 351.1465

3.2.25 Butyl 2-(2-ethyl-3-oxo-2,3,5,6-tetrahydro-1*H*-pyrrolo[3,2,1-ij]quinazolin-1-yl)acetate (244)



244
$C_{18}H_{24}N_2O_3$
M = 316.40 g/mol

According to **GP 7**, a flame-dried SCHLENK tube equipped with a magnetic stir bar was successively charged with *N*-ethylindoline-1-carboxamide (**198**, 38 mg, 0.20 mmol, 1.0 equiv.), $Pd(OAc)_2$ (4.5 mg, 0.020 mmol, 10 mol%), BQ (43 mg, 0.40 mmol, 2.0 equiv.), and *p*-toluenesulfonic acid monohydrate (38 mg, 0.20 mmol, 1.0 equiv.) in acetic acid (1.0 mL, 0.2M) under inert atmosphere. Subsequently, *n*-butyl acrylate (**2**, 58 µL, 0.40 mmol, 2.0 equiv.) was added, and the reaction mixture was stirred at 40 °C for 16 h. After complete consumption of the indoline, as monitored by GLC analysis using tetracosane (10 mg, 0.030 mmol, 15 mol%) as internal standard, the reaction mixture was allowed to cool to room temperature and diluted with ethyl acetate (10 mL). The crude reaction mixture was washed with saturated aqueous Na_2CO_3 (1 × 5 mL) and H_2O (1 × 5 mL). The organic phase was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (2.5 × 20 cm, cyclohexane:ethyl

acetate = 3:1 → 2:1, 50 mL, #25–34) afforded the analytically pure cyclized product **244** (40 mg, 63%) as a brown oil.

R_f = 0.18 (cyclohexane:ethyl acetate = 3:1).

GLC (HP-5): t_R = 22.6 min.

^{1}H NMR (700 MHz, $CDCl_3$, 298 K): δ/ppm = 0.90 (t, $^3J_{4'''',3''''}$ = 7.7 Hz, 3H, H-4’’’’), 1.19 (t, $^3J_{2'',1''}$ = 7.1 Hz, 3H, H-2’’), 1.27–1.32 (m, 2H, H-3’’’’), 1.53–1.57 (m, 2H, H-2’’’’), 2.61 (dd, $^2J_{2'''A,2'''B}$ = 15.0 Hz, $^3J_{2'''A,1'''}$ = 9.5 Hz, 1H, H-2’’’A), 2.77 (dd, $^2J_{2'''B,2'''A}$ = 15.0 Hz, $^3J_{2'''B,1'''}$ = 4.7 Hz, 1H, H-2’’’B), 3.05–3.10 (m, 1H, H-3A), 3.16–3.20 (m, 2H, H-2A, H-3B), 3.94–4.00 (m, 1H, H-2B), 4.01–4.07 (m, 2H, H-1’’), 4.05 (t, $^3J_{1'''',2''''}$ = 6.4 Hz, 2H, H-1’’’’), 4.95 (dd, $^3J_{1''',2'''A}$ = 8.9 Hz, $^3J_{1''',2'''B}$ = 4.3 Hz, 1H, H-1’’’), 6.86 (dd, $^3J_{5,4}$ = $^3J_{5,4}$ = 7.5 Hz, 1H, H-5), 6.93 (d, $^3J_{4,6}$ = 7.5 Hz, 1H, H-4), 7.08 (d, $^3J_{6,5}$ = 7.5 Hz, 1H, H-6).

^{13}C NMR (126 MHz, $CDCl_3$, 298 K): δ/ppm = 13.8 (C-4’’’’), 13.9 (C-2’’), 19.2 (C-3’’’’), 28.4 (C-3), 30.6 (C-2’’’’), 40.7 (C-2’’’), 40.8 (C-1’’), 46.9 (C-1’’’), 56.1 (C-2), 64.9 (C-1’’’’), 117.9 (C-4), 122.5 (C-6), 122.9 (C-5), 124.3 (C-7), 128.2 (C-9), 141.5 (C-8), 154.3 (C-1’), 170.8 (C-3’’’).

IR (ATR): $\tilde{\nu}$ /cm^{-1} = 2958 (w), 1726 (m), 1629 (s), 1570 (s), 1480 (s), 1458 (s), 1405 (s), 1354 (w), 1297 (w), 1215 (w), 1154 (w), 1059 (w), 828 (w), 755 (s).

HRMS (APCI) for $C_{18}H_{25}N_2O_3$ ($[M+H]^+$): calcd. 317.1860
found 317.1857

APPENDIX

A1 X-RAY CRYSTAL STRUCTURE DATA

A1.1 *cis*-1-[8-(3,4-Dimethylphenyl)-4a,6-dimethyl-2,3,4,4a-tetrahydro-1*H*-carbazol-9(9a*H*)-yl]-ethanone (*cis*-162)

Structural Analysis Reference: cu-52 L.-Y. JIAO / Prof. Dr. M. OESTREICH

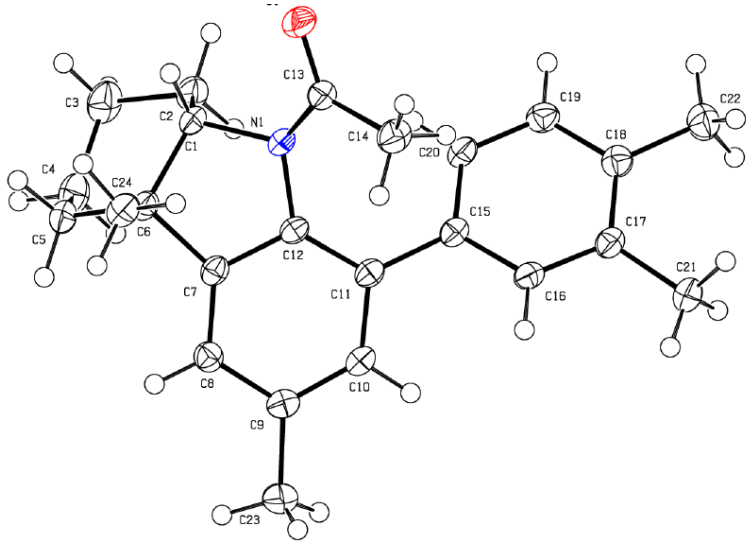


Figure A1.1: X-ray structure for compound *cis*-**162**.

Table 1: Crystal data and structure refinement for cu-52.

Identification code	cu-52
Empirical formula	C_{24} H_{29} N O
Formula weight	347.48
Temperature	150(2) K
Wavelength	1.54184 Å
Crystal system, space group	monoclinic, P21/c
Unit cell dimension	a = 13.4649(3) Å
	b = 11.28794(14) Å, β = 117.787(3)°
	c = 14.4128(3) Å
Volume	1938.00(7) $Å^3$
Z, Calculated density	4, 1.191 Mg/m^3
Absorption coefficient	0.548 mm^{-1}
F(000)	752

Crystal size	0.68 × 0.13 × 0.13 mm
Theta range for data collection	3.71 to 67.49°
Limiting indices	–15<=h<=16, –13<=k<=13, –15<=l<=17
Reflections collected / unique	14806 / 3479 [R(int) = 0.0355]
Completeness to theta = 67.49	99.7 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9322 and 0.7071
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3479 / 0 / 240
Goodness-of-fit on F^2	1.038
Final R indices [I>2σ(I)]	R1 = 0.0385, wR^2 = 0.1027
R indices (all data)	R1 = 0.0410, wR^2 = 0.1057
Largest diff. peak and hole	0.255 and –0.201 e.$Å^{-3}$

Table 2: Atomic coordinates (× 10^4) and equivalent isotropic displacement parameters ($Å^2$ × 10^3) for cu-52. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
O(1)	8408(1)	9995(1)	5061(1)	34(1)
N(1)	8305(1)	8184(1)	4360(1)	21(1)
C(1)	9520(1)	8141(1)	4655(1)	22(1)
C(2)	10109(1)	7278(1)	5570(1)	29(1)
C(3)	11219(1)	6811(1)	5671(1)	36(1)
C(4)	11015(1)	6225(1)	4646(1)	33(1)
C(5)	10577(1)	7133(1)	3764(1)	26(1)
C(6)	9493(1)	7745(1)	3610(1)	22(1)
C(7)	8458(1)	6953(1)	3160(1)	21(1)
C(8)	8138(1)	6084(1)	2401(1)	23(1)
C(9)	7131(1)	5471(1)	2112(1)	24(1)
C(10)	6518(1)	5715(1)	2641(1)	23(1)
C(11)	6821(1)	6582(1)	3424(1)	21(1)
C(12)	7783(1)	7242(1)	3627(1)	20(1)
C(13)	7831(1)	9217(1)	4457(1)	23(1)
C(14)	6587(1)	9388(1)	3789(1)	30(1)
C(15)	6172(1)	6675(1)	4020(1)	21(1)
C(16)	5006(1)	6523(1)	3507(1)	23(1)
C(17)	4368(1)	6519(1)	4038(1)	23(1)

C(18)	4905(1)	6715(1)	5126(1)	24(1)
C(19)	6065(1)	6875(1)	5637(1)	25(1)
C(20)	6694(1)	6848(1)	5102(1)	24(1)
C(21)	3124(1)	6291(1)	3444(1)	31(1)
C(22)	4248(1)	6749(1)	5731(1)	34(1)
C(23)	6726(1)	4541(1)	1268(1)	36(1)
C(24)	9266(1)	8827(1)	2887(1)	27(1)

Table 3: Bond lengths [Å] and angles [°] for cu-52.

O(1)-C(13)	1.2251(14)	C(3)-C(4)-C(5)	110.01(11)
N(1)-C(13)	1.3682(15)	C(4)-C(5)-C(6)	113.41(10)
N(1)-C(12)	1.4311(14)	C(7)-C(6)-C(5)	114.63(10)
N(1)-C(1)	1.4860(13)	C(7)-C(6)-C(24)	108.94(9)
C(1)-C(2)	1.5306(16)	C(5)-C(6)-C(24)	109.32(9)
C(1)-C(6)	1.5562(15)	C(7)-C(6)-C(1)	100.58(9)
C(2)-C(3)	1.5274(17)	C(5)-C(6)-C(1)	113.43(9)
C(3)-C(4)	1.5210(19)	C(24)-C(6)-C(1)	109.57(9)
C(4)-C(5)	1.5216(17)	C(8)-C(7)-C(12)	120.93(10)
C(5)-C(6)	1.5336(15)	C(8)-C(7)-C(6)	129.82(10)
C(6)-C(7)	1.5235(15)	C(12)-C(7)-C(6)	109.23(9)
C(6)-C(24)	1.5401(16)	C(7)-C(8)-C(9)	119.26(10)
C(7)-C(8)	1.3797(16)	C(10)-C(9)-C(8)	118.66(10)
C(7)-C(12)	1.3981(16)	C(10)-C(9)-C(23)	119.87(10)
C(8)-C(9)	1.4010(16)	C(8)-C(9)-C(23)	121.45(11)
C(9)-C(10)	1.3877(16)	C(9)-C(10)-C(11)	123.73(10)
C(9)-C(23)	1.5038(16)	C(12)-C(11)-C(10)	115.62(10)
C(10)-C(11)	1.4038(16)	C(12)-C(11)-C(15)	125.26(10)
C(11)-C(12)	1.4022(15)	C(10)-C(11)-C(15)	118.96(10)
C(11)-C(15)	1.4874(16)	C(7)-C(12)-C(11)	121.36(10)
C(13)-C(14)	1.5054(16)	C(7)-C(12)-N(1)	108.83(9)
C(15)-C(20)	1.3937(16)	C(11)-C(12)-N(1)	129.55(10)
C(15)-C(16)	1.3993(15)	O(1)-C(13)-N(1)	120.80(10)
C(16)-C(17)	1.3907(16)	O(1)-C(13)-C(14)	120.73(11)
C(17)-C(18)	1.4049(17)	N(1)-C(13)-C(14)	118.46(10)
C(17)-C(21)	1.5059(15)	C(20)-C(15)-C(16)	117.71(10)
C(18)-C(19)	1.3932(17)	C(20)-C(15)-C(11)	121.96(10)

C(18)-C(22)	1.5052(17)	C(16)-C(15)-C(11)	120.23(10)
C(19)-C(20)	1.3868(17)	C(17)-C(16)-C(15)	122.57(10)
C(13)-N(1)-C(12)	128.09(9)	C(16)-C(17)-C(18)	119.01(10)
C(13)-N(1)-C(1)	120.12(9)	C(16)-C(17)-C(21)	119.77(10)
C(12)-N(1)-C(1)	106.49(8)	C(18)-C(17)-C(21)	121.21(11)
N(1)-C(1)-C(2)	109.05(9)	C(19)-C(18)-C(17)	118.49(11)
N(1)-C(1)-C(6)	101.92(8)	C(19)-C(18)-C(22)	120.49(11)
C(2)-C(1)-C(6)	114.85(10)	C(17)-C(18)-C(22)	121.02(11)
C(3)-C(2)-C(1)	113.11(10)	C(20)-C(19)-C(18)	121.90(11)
C(4)-C(3)-C(2)	109.39(10)	C(19)-C(20)-C(15)	120.29(10)

Table 4: Anisotropic displacement parameters ($Å^2 \times 10^3$) for cu-52. The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U_{11} + \ldots + 2 h k a^* b^* U_{12}]$.

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O(1)	27(1)	32(1)	43(1)	-16(1)	16(1)	-7(1)
N(1)	16(1)	24(1)	21(1)	-3(1)	6(1)	-4(1)
C(1)	15(1)	25(1)	22(1)	-2(1)	6(1)	-3(1)
C(2)	22(1)	38(1)	21(1)	4(1)	7(1)	0(1)
C(3)	23(1)	47(1)	29(1)	11(1)	6(1)	6(1)
C(4)	22(1)	33(1)	42(1)	6(1)	14(1)	5(1)
C(5)	19(1)	32(1)	28(1)	-1(1)	11(1)	-1(1)
C(6)	17(1)	25(1)	20(1)	0(1)	7(1)	-2(1)
C(7)	17(1)	23(1)	20(1)	3(1)	6(1)	0(1)
C(8)	21(1)	25(1)	22(1)	1(1)	10(1)	2(1)
C(9)	24(1)	22(1)	22(1)	-1(1)	8(1)	-1(1)
C(10)	18(1)	24(1)	23(1)	-1(1)	7(1)	-3(1)
C(11)	17(1)	22(1)	20(1)	1(1)	5(1)	0(1)
C(12)	17(1)	22(1)	18(1)	1(1)	5(1)	0(1)
C(13)	23(1)	24(1)	24(1)	-2(1)	11(1)	-3(1)
C(14)	24(1)	27(1)	33(1)	-1(1)	9(1)	3(1)
C(15)	19(1)	19(1)	23(1)	0(1)	8(1)	-2(1)
C(16)	20(1)	23(1)	21(1)	-3(1)	7(1)	-2(1)
C(17)	20(1)	20(1)	27(1)	-1(1)	10(1)	-1(1)
C(18)	26(1)	21(1)	27(1)	1(1)	13(1)	-1(1)
C(19)	26(1)	27(1)	20(1)	0(1)	8(1)	-3(1)
C(20)	18(1)	27(1)	22(1)	0(1)	6(1)	-3(1)

C(21)	20(1)	37(1)	33(1)	-4(1)	12(1)	-3(1)
C(22)	31(1)	42(1)	31(1)	0(1)	17(1)	-2(1)
C(23)	38(1)	36(1)	38(1)	-15(1)	21(1)	-11(1)
C(24)	25(1)	30(1)	24(1)	4(1)	9(1)	-4(1)

A1.2 (*E*)-*N*,*N*-Dimethyl-7-(3-oxobut-1-en-1-yl)indoline-1-carboxamide [(*E*)-251]

Structural Analysis Reference: p21c L.-Y. JIAO / Prof. Dr. M. OESTREICH

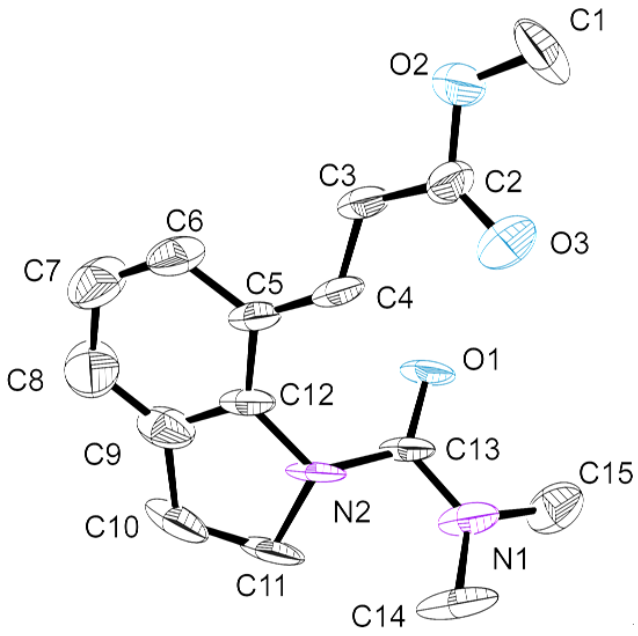


Figure A2.1: X-ray structure for compound (*E*)-251.

Table 1: Crystal data and structure refinement for p21c.

Identification code	p21c
Empirical formula	C_{15} H_{18} N_2 O_3
Formula weight	274.31
Temperature	150(2) K
Wavelength	1.54178 Å
Crystal system, space group	monoclinic, P2(1)/c
Unit cell dimension	a = 6.32670(10) Å
	b = 15.2222(6) Å, β = 91.848(2)°
	c = 14.4727(5) Å
Volume	1393.09(8) $Å^3$
Z, Calculated density	4, 1.308 Mg/m^3
Absorption coefficient	0.752 mm^{-1}
F(000)	584
Crystal size	0.34 × 0.07 × 0.04 mm
Theta range for data collection	4.22 to 67.46°
Limiting indices	–5<=h<=7, –18<=k<=17, –16<=l<=17

Reflections collected / unique	5134 / 2501 [R(int) = 0.1233]
Completeness to theta = 67.46	99.6 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9720 and 0.7825
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2501 / 0 / 196
Goodness-of-fit on F^2	1.043
Final R indices [I>2σ(I)]	R1 = 0.1135, wR^2 = 0.2918
R indices (all data)	R1 = 0.1415, wR^2 = 0.3380
Extinction coefficient	0.0000(17)
Largest diff. peak and hole	0.400 and –0.490 e.Å^{-3}

Table 2: Atomic coordinates (× 10^4) and equivalent isotropic displacement parameters (Å^2 × 10^3) for p21c. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
O(1)	11149(3)	4018(2)	357(2)	47(1)
O(2)	16368(4)	1309(3)	1531(2)	65(1)
O(3)	13687(5)	1264(3)	504(2)	76(1)
N(1)	8382(5)	3694(3)	-601(3)	56(1)
N(2)	7945(4)	3676(2)	976()3	51(1)
C(1)	17470(20)	731(19)	1020(12)	76(5)
C(1A)	17420(80)	400(30)	1050(30)	59(9)
C(2)	14473(6)	1555(3)	1194(3)	49(1)
C(3)	13523(5)	2197(3)	1803(3)	47(1)
C(4)	11609(5)	2544(3)	1633(2)	42(1)
C(5)	10504(5)	3140(3)	2221(3)	42(1)
C(6)	11038(7)	3223(3)	3172(3)	55(1)
C(7)	9879(9)	3726(4)	3746(4)	71(2)
C(8)	8103(9)	4174(4)	3421(4)	72(2)
C(9)	7550(6)	4123(3)	2495(4)	60(1)
C(10)	5728(6)	4552(4)	1969(4)	77(2)
C(11)	5949(5)	4205(4)	991(4)	79(2)
C(12)	8763(5)	3635(3)	1896(3)	46(1)
C(13)	9292(5)	3810(3)	236(3)	43(1)
C(14)	6460(7)	3191(4)	-792(4)	79(2)
C(15)	9480(8)	4004(4)	-1401(3)	64(1)

Table 3: Bond lengths [Å] and angles [°] for p21c.

O(1)-C(13)	1.224(4)	O(1)-C(13)-N(1)	122.9(4)
N(2)-C(13)	1.405(5)	O(1)-C(13)-N(2)	122.2(4)
N(2)-C(12)	1.414(5)	N(1)-C(13)-N(2)	114.9(3)
N(2)-C(11)	1.499(6)	C(9)-C(12)-C(5)	121.4(4)
O(2)-C(2)	1.334(5)	C(9)-C(12)-N(2)	111.7(3)
O(2)-C(1)	1.36(2)	C(5)-C(12)-N(2)	126.8(4)
O(2)-C(1A)	1.70(4)	C(12)-C(5)-C(6)	116.1(4)
C(4)-C(3)	1.337(5)	C(12)-C(5)-C(4)	122.0(4)
C(4)-C(5)	1.441(6)	C(6)-C(5)-C(4)	121.8(3)
C(4)-H(4A)	0.9500	C(4)-C(3)-C(2)	122.8(3)
N(1)-C(13)	1.349(6)	C(4)-C(3)-H(3A)	118.6
N(1)-C(15)	1.437(6)	C(2)-C(3)-H(3A)	118.6
N(1)-C(14)	1.454(5)	C(7)-C(6)-C(5)	121.9(4)
C(2)-O(3)	1.187(5)	C(7)-C(6)-H(6A)	119.1
C(2)-C(3)	1.458(6)	C(5)-C(6)-H(6A)	119.1
C(12)-C(9)	1.391(7)	C(8)-C(9)-C(12)	120.6(4)
C(12)-C(5)	1.403(5)	C(8)-C(9)-C(10)	129.3(5)
C(5)-C(6)	1.412(6)	C(12)-C(9)-C(10)	110.1(5)
C(3)-H(3A)	0.9500	N(1)-C(14)-H(14A)	109.5
C(6)-C(7)	1.361(7)	N(1)-C(14)-H(14B)	109.5
C(6)-H(6A)	0.9500	H(14A)-C(14)-H(14B)	109.5
C(9)-C(8)	1.376(8)	N(1)-C(14)-H(14C)	109.5
C(9)-C(10)	1.509(5)	H(14A)-C(14)-H(14C)	109.5
C(14)-H(14A)	0.9800	H(14B)-C(14)-H(14C)	109.5
C(14)-H(14B)	0.9800	C(9)-C(10)-C(11)	103.2(4)
C(14)-H(14C)	0.9800	C(9)-C(10)-H(10A)	111.1
C(10)-C(11)	1.521(9)	C(11)-C(10)-H(10A)	111.1
C(10)-H(10A)	0.9900	C(9)-C(10)-H(10B)	111.1
C(10)-H(10B)	0.9900	C(11)-C(10)-H(10B)	111.1
C(11)-H(11A)	0.9900	H(10A)-C(10)-H(10B)	109.1
C(11)-H(11B)	0.9900	N(2)-C(11)-C(10)	107.6(3)
C(8)-C(7)	1.384(7)	N(2)-C(11)-H(11A)	110.2
C(8)-H(8A)	0.9500	C(10)-C(11)-H(11A)	110.2
C(7)-H(7A)	0.9500	N(2)-C(11)-H(11B)	110.2
C(15)-H(15A)	0.9800	C(10)-C(11)-H(11B)	110.2

C(15)-H(15B)	0.9800	H(11A)-C(11)-H(11B)	108.5
C(15)-H(15C)	0.9800	C(9)-C(8)-C(7)	118.8(5)
C(1)-H(1A)	0.9800	C(9)-C(8)-H(8A)	120.6
C(1)-H(1B)	0.9800	C(7)-C(8)-H(8A)	120.6
C(1)-H(1C)	0.9800	C(6)-C(7)-C(8)	121.1(5)
C(1A)-H(1AA)	0.9800	C(6)-C(7)-H(7A)	119.5
C(1A)-H(1AB)	0.9800	C(8)-C(7)-H(7A)	119.5
C(1A)-H(1AC)	0.9800	N(1)-C(15)-H(15A)	109.5
C(13)-N(2)-C(12)	120.7(3)	N(1)-C(15)-H(15B)	109.5
C(13)-N(2)-C(11)	117.7(3)	H(15A)-C(15)-H(15B)	109.5
C(12)-N(2)-C(11)	107.1(4)	N(1)-C(15)-H(15C)	109.5
C(2)-O(2)-C(1)	116.9(8)	H(15A)-C(15)-H(15C)	109.5
C(2)-O(2)-C(1A)	116.2(15)	H(15B)-C(15)-H(15C)	109.5
C(1)-O(2)-C(1A)	14(2)	O(2)-C(1)-H(1A)	109.5
C(3)-C(4)-C(5)	126.4(3)	O(2)-C(1)-H(1B)	109.5
C(3)-C(4)-H(4A)	116.8	H(1A)-C(1)-H(1B)	109.5
C(5)-C(4)-H(4A)	116.8	O(2)-C(1)-H(1C)	109.5
C(13)-N(1)-C(15)	118.5(3)	H(1A)-C(1)-H(1C)	109.5
C(13)-N(1)-C(14)	124.3(4)	H(1B)-C(1)-H(1C)	109.5
C(15)-N(1)-C(14)	116.9(4)	O(2)-C(1A)-H(1AA)	109.5
O(3)-C(2)-O(2)	123.4(5)	O(2)-C(1A)-H(1AB)	109.5
O(3)-C(2)-C(3)	126.1(4)	O(2)-C(1A)-H(1AC)	109.5
O(2)-C(2)-C(3)	110.5(3)		

Table 4: Anisotropic displacement parameters ($Å^2 \times 10^3$) for p21c. The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U_{11} + \ldots + 2 h k a^* b^* U_{12}]$.

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O(1)	15(1)	64(2)	62(2)	17(1)	-12(1)	-12(1)
O(2)	36(1)	99(3)	59(2)	-26(2)	-8(1)	12(2)
O(3)	69(2)	107(3)	52(2)	26(2)	-19(2)	-6(2)
N(1)	40(2)	69(3)	57(2)	26(2)	-25(2)	-21(2)
N(2)	15(1)	70(2)	65(2)	43(2)	-19(1)	-13(1)
C(1)	37(4)	88(12)	104(8)	-56(8)	28(4)	-9(7)
C(1A)	46(13)	50(19)	80(15)	-35(14)	-4(11)	17(15)
C(2)	39(2)	72(3)	35(2)	2(2)	-6(2)	-14(2)
C(3)	34(2)	64(3)	42(2)	-6(2)	-19(2)	2(2)
C(4)	32(2)	54(2)	37(2)	16(2)	-20(1)	-13(2)

C(5)	28(2)	50(2)	47(2)	13(2)	-17(2)	-3(2)
C(6)	52(2)	56(3)	56(3)	3(2)	-22(2)	14(2)
C(7)	84(3)	73(3)	55(3)	7(3)	-19(3)	24(3)
C(8)	77(3)	74(3)	66(3)	15(3)	5(3)	27(3)
C(9)	37(2)	65(3)	76(3)	36(3)	-2(2)	7(2)
C(10)	23(2)	100(4)	108(4)	66(4)	12(2)	14(2)
C(11)	13(2)	136(5)	88(3)	69(4)	-10(2)	-1(2)
C(12)	22(2)	59(3)	57(2)	26(2)	-17(2)	-9(2)
C(13)	19(1)	53(2)	55(2)	27(2)	-17(2)	-13(2)
C(14)	57(3)	80(4)	96(4)	34(3)	-55(3)	-26(3)
C(15)	76(3)	65(3)	49(2)	14(2)	-14(2)	-8(2)

Table 5: Hydrogen coordinates (× 10^4) and isotropic displacement parameters (Å^2 × 10^3) for p21c.

	x	y	z	U(eq)
H(1A)	17722	988	413	114
H(1B)	16647	188	940	114
H(1C)	18821	599	1336	114
H(1AA)	18907	507	921	88
H(1AB)	16636	254	479	88
H(1AC)	17329	-95	1487	88
H(3A)	14297	2376	2344	57
H(4A)	10908	2381	1068	50
H(6A)	12241	2919	3418	66
H(7A)	10296	3770	4381	86
H(8A)	7281	4511	3829	86
H(10A)	5850	5200	1986	92
H(10B)	4356	4377	2223	92
H(11A)	4718	3833	813	95
H(11B)	6017	4699	548	95
H(14A)	6092	2869	-233	118
H(14B)	6688	2774	-1295	118
H(14C)	5304	118	-971	3591
H(15A)	11005	3924	-1294	95
H(15B)	9171	4628	-1498	95
H(15C)	9012	3670	-1949	95

A2 ABBREVIATIONS

δ	Chemical Shift
Δ	Reflux Temperature
σ	Substituent Constant
°C	Degree
□̃	Wave Number

Ac	Acetyl
Ac_2O	Acetic Anhydride
AcOH	Acetic Acid
AgOAc	Silver(I) Acetate
Ag_2CO_3	Silver(I) Carbonate
Ag_2O	Silver(I) Oxide
APCI	Atmospheric-Pressure Chemical Ionization
Ar	Aryl
ATR	Attenuated Total Reflection

Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
b.p.	Boiling Point
BQ	1,4-Benzoquinone
br	Broad
br s	Broad Singlet
Bu	Butyl
n-Bu	*n*-Butyl
n-BuLi	*n*-Butyllithium
t-Bu	*t*-Butyl

calcd.	Calculated
CDC	Cross Dehydrogenative Coupling
$CDCl_3$	Deuterated Chloroform
$CHCl_3$	Chloroform
CH_2Cl_2	Dichloromethane
CMD	Concerted Metallation/Deprotonation
CO	Carbon Monoxide

conc.	Concentrated
conv,	Conversion
COSY	Correlation Spectroscopy
$Cu(OAc)_2$	Copper(II) Acetate
$Cu(OTf)_2$	Copper(II) Triflate
d	Doublet
DCE	1,2-Dichloroethane
DEPT	Distortionless Enhancement by Polarization Transfer
DFT	Density Functional Theory
DG	Directing Group
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethylsulfoxide
DMSO-d_6	Deuterated Dimethylsulfoxide
E	Entgegen
equiv.	Equivalent
Et	Ethyl
Et_2O	Diethylether
Et_3N	Triethylamine
EXSY	EXchange SpectroscopY
g	Gram
GCOSY	^{1}H,^{1}H-Correlation Spectroscopy
GHMBC	$^{2,3}J(^{13}C,^1H)$-Correlation Spectroscopy
GHSQC	$^1J(^{13}C,^1H)$-Correlation Spectroscopy
GLC	Gas-Liquid Chromatography
GP	General Procedure
h	Hour(s)
HAS	Homolytic Aromatic Substitution
HCl	Hydrochloric Acid
Het	Heteroatom
HFIP	Hexafluoro-2-propanol
H_2O	Water
HRMS	High Resolution Mass Spectrometry
Hz	Hertz

IR	Infrared Spectroscopy
J	NMR-Coupling Constant
K	Kelvin
KIE	Kinetic Isotope Effect
K_2CO_3	Potassium Carbonate
$KMnO_4$	Potassium Permanganate
KOH	Potassium Hydroxide
KO*t*Bu	Potassium *t*-Butoxide,
LDA	Lithium Diisopropylamide
Lit.	Literature
M	Molar
M	Molecular Weight
m-	*meta*-
[M]	Transition Metal Complex
m	Multiplet or Medium
Me	Methyl
MeCN	Acetonitrile
MeOH	Methanol
mg	Milligram
$MgSO_4$	Magnesium Sulfate
MHz	Megahertz
min	Minute(s)
mL	Milliliter
mol%	Mole Percent
MPAA	Mono-protected Amino Acid
m.p.	Melting Point
MS	Mass Spectrometry
MS 4Å	Molecular Sieves 4Å
MW	Microwave
n	Number of Units
$NaBH_4$	Sodium Borohydride

$NaBH_3CN$	Sodium Cyanoborohydride
$NaHCO_3$	Sodium Bicarbonate
NaOH	Sodium Hydroxide
$Na_2S_2O_8$	Sodium Persulfate
ND	No Determined
NH_4Cl	Ammonium Chloride
NMP	*N*-Methyl-2-pyrrolidone
NMR	Nuclear Magnetic Resonance
nOe	Nuclear Overhauser Effect
NOESY	Nuclear Overhauser Enhancement SpectroscopY
NR	No Reaction
o-	*ortho*-
O_2	Dioxygen
p-	*para*-
[Pd]	Palladium Complex
$Pd(OAc)_2$	Palladium(II) Acetate
$Pd(TFA)_2$	Palladium(II) Trifluoroacetate
PG	Protecting Group
Ph	Phenyl
$PhB(OH)_2$	Phenylboronic Acid
$PhI(OAc)_2$	(Diacetoxyiodo)benzene
PivOH	Pivalic Acid
ppm	Parts Per Million
*i*Pr	*iso*-Oropyl
PTSA	*p*-Toluenesulfonic Acid Monohydrate
q	quartet
R	Organic Substituent
rac-	Racemic
R_f	Retention Factor
rs	Regioselectivity
RT	Room Temperature
s	Singlet or Strong
Supp.	Supplier

t	Time or Triplet
T	Temperature
TBAB	Tetra-*n*-Butylammonium Bromide
TBAF	Tetra-*n*-Butylammonium Fluoride
tert-	Tertiary
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic Acid
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
$Tl(TFA)_3$	Thallium(III) Trifluoroacetate
TMS	Trimethylsilyl
Tol	Toluyl (4-Methylphenyl)
t_R	Retention Time
p-TsOH	*para*-Toluenesulfonic Acid
UV	Ultraviolet
V	Voltage
vs	Versus
VT	Variable Tmerature
vw	Very Weak
w	Weak
X	Halogen or Triflate or Boron
Z	Zusammen
$ZnCl_2$	Zinc Chloride

A3 BIBLIOGRAPHY

[1] a) A. Bhunia, S. R. Yetra, A. T. Biju, *Chem. Soc. Rev*. **2012**, *41*, 3140–3152; b) I. D. G. Watson, F. D. Toste, *Chem. Sci*. **2012**, *3*, 2899–2919.

[2] a) T.-Y. Luh, M.-k. Leung, K.-T. Wong, *Chem. Rev*. **2000**, *100*, 3187–3204; b) *Cross-Coupling Reactions: A Practical Guide* (Ed: N. Miyaura), Springer, Berlin, **2002**; c) V. Ritleng, C. Sirlin, M. Pfeffer, *Chem. Rev*. **2002**, *102*, 1731–1770; d) D. A. Colby, R. G. Bergman, J. A. Ellman, *Chem. Rev*. **2010**, *110*, 624–655; e) *Metal-Catalyzed Cross-Coupling Reactions and More* (Ed: A. de Meijere, S. Bräse, M. Oestreich), Wiley-VCH, Weinheim, **2014**.

[3] a) *Handbook of Organopalladium Chemistry for Organic Synthesis* (Ed.: E.-i. Negishi), Wiley, New York, **2002**; b) K. C. Nicolaou, P. G. Bulger, D. Sarlah, *Angew. Chem*. **2005**, *117*, 4516–4563; *Angew. Chem. Int. Ed*. **2005**, *44*, 4442–4489; c) C.-L. Sun, B.-J. Li, Z.-J. Shi, *Chem. Commun*. **2010**, *46*, 677–685; d) X.-F. Wu, P. Anbarasan, H. Neumann, M. Beller, *Angew. Chem*. **2010**, *122*, 9231–9234; *Angew. Chem. Int. Ed*. **2010**, *49*, 9047–9050.

[4] a) I. P. Beletskaya, A. V. Cheprakov, *Chem. Rev*. **2000**, *100*, 3009–3066; b) *The Mizoroki–Heck Reaction* (Ed.: M. Oestreich), Wiley, Chichester, **2009**.

[5] C. E. I. Knappke, A. J. von Wangelin, *Chem. Soc. Rev*. **2011**, *40*, 4948–4962.

[6] a) J. K. Stille, *Angew. Chem*. **1986**, *98*, 504–519; *Angew. Chem. Int. Ed. Engl*. **1986**, *25*, 508–524; b) V. Farina, V. Krishnamurthy, W. J. Scott, *Org. React.* **1998**, *50*, 1–652.

[7] E.-i. Negishi, *Acc. Chem. Res*. **1982**, *15*, 340–348.

[8] a) N. Miyaura, A. Suzuki, *Chem. Rev*. **1995**, 95, 2457–2483; b) F.-S. Han, *Chem. Soc. Rev.* **2013**, *42*, 5270–5298.

[9] H. F. Sore, W. R. J. D. Galloway, D. R. Spring, *Chem. Soc. Rev.* **2012**, *41*, 1845–1866.

[10] B. M. Trost, M. L. Crawley, *Chem. Rev.* **2003**, *103*, 2921–2944.

[11] a) A. Suzuki, *Angew. Chem.* **2011**, *123*, 6854–6869; *Angew. Chem. Int. Ed*. **2011**, *50*, 6722–6737; b) E.-i. Negishi, *Angew. Chem*. **2011**, *123*, 6870–6897; *Angew. Chem. Int. Ed*. **2011**, *50*, 6738–6764.

[12] For selected reports that summarize mechanistic aspects of C–H bond activation, see: a) A. E. Shilov, G. B. Shul'pin, *Chem. Rev*. **1997**, *97*, 2879–2932; b) J. A. Labinger, J. E. Bercaw, *Nature* **2002**, *417*, 507–514; c) S. Sakaki, *Top. Organomet. Chem*. **2005**, *12*, 31–78; d) *Handbook of C–H Transformations: Applications in Organic Synthesis* (Ed.: G. Dyker), Wiley-VCH, Weinheim, **2005**; e) R. G. Bergman,

Nature **2007**, *446*, 391–393; f) L. Ackermann, *Chem. Rev.* **2011**, *111*, 1315–1345; g) M. García-Melchor, A. A. C. Braga, A. Lledós, G. Ujaque, F. Maseras, *Acc. Chem. Res.* **2013**, *46*, 2626–2634.

[13] a) C.-H. Park, V. Ryabova, I. V. Seregin, A. W. Sromek, V. Gevorgyan, *Org. Lett.* **2004**, *6*, 1159–1162; b) B. S. Lane, M. A. Brown, D. Sames, *J. Am. Chem. Soc.* **2005**, *127*, 8050–8057.

[14] a) L.-C. Campeau, M. Parisien, M. Leblanc, K. Fagnou, *J. Am. Chem. Soc*. **2004**, *126*, 9186–9187; b) M. Leblanc, K. Fagnou, *Org. Lett.* **2005**, *7*, 2849–2852; c) L.-C. Campeau, M. Parisien, A. Jean, K. Fagnou, *J. Am. Chem. Soc.* **2006**, *128*, 581–590; for a discussion of concerted metalation deprotonation, see: d) M. Lafrance, C. N. Rowley, T. K. Woo, K. Fagnou, *J. Am. Chem. Soc.* **2006**, *128*, 8754–8756; e) H.-Y. Sun, S. I. Gorelsky, D. R. Stuart, L.-C. Campeau, K. Fagnou, *J. Org. Chem.* **2010**, *75*, 8180–8189.

[15] a) D. García-Cuadrado, A. A. C. Braga, F. Maseras, A. M. Echavarren, *J. Am. Chem. Soc.* **2006**, *128*, 1066–1067; b) S. I. Gorelsky, D. Lapointe. K. Fagnou, *J. Am. Chem. Soc.* **2008**, *130*, 10848–10849.

[16] H. Li, J. Liu, C.-L. Sun, B.-J. Li, Z.-J. Shi, *Org. Lett.* **2011**, *13*, 276–279.

[17] J. Oxgaard, R. P. Muller, W. A. Goddard, R. A. Periana, *J. Am. Chem. Soc.* **2004**, *126*, 352–363.

[18] a) Y. Boutadla, D. L. Davies, S. A. Macgregor, A. I. Poblador-Bahamonde, *Dalton Trans.* **2009**, 5820–5831; b) D. L. Davies, S. M. A. Donald, S. A. Macgregor, *J. Am. Chem. Soc.* **2005**, *127*, 13754–13755.

[19] G. W. Wheland, *J. Am. Chem. Soc.* **1942**, *64*, 900–908.

[20] a) A. D. Ryabov, *Chem. Rev*. **1990**, *90*, 403–424; b) A. D. Ryabov, I. K. Sakodinskaya, A. K. Yatsimirsky, *J. Chem. Soc. Dalton Trans*. **1985**, 2629–2638.

[21] For selected reviews, see: a) E. M. Beccalli, G. Broggini, M. Martinelli, S. Sottocornola, *Chem. Rev.* **2007**, *107*, 5318–5365; b) E. M. Ferreira, H. Zhang, B. M. Stoltz in The Mizoroki–Heck Reaction (Ed.: M. Oestreich), Wiley, Chichester, **2009**, pp. 345–382; c) X. Chen, K. M. Engle, D.-H. Wang, J.-Q. Yu, *Angew. Chem.* **2009**, *121*, 5196–5217; *Angew. Chem. Int. Ed.* **2009**, *48*, 5094–5115; d) R. Giri, B.-F. Shi, K. M. Engle, N. Maugel, J.-Q. Yu, *Chem. Soc. Rev*. **2009**, *38*, 3242–3272; e) J. L. Bras, J. Muzart, *Chem. Rev*. **2011**, *111*, 1170–1214; f) C. S. Yeung, V. M. Dong, *Chem. Rev.* **2011**, *111*, 1215–1292; g) K. M. Engle, J.-Q. Yu, *J. Org. Chem*. **2013**, *78*, 8927−8955.

[22] For reviews dedicated to direct C–H bond activation, see: a) L. Ackermann, R. Vicente, A. R. Kapdi, *Angew. Chem.* **2009**, *121*, 9976–10011; *Angew. Chem. Int. Ed.* **2009**, *48*, 9792–9826; b) J. A. Ashenhurst, *Chem. Soc. Rev.* **2010**, *39*, 540–

548; c) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147–1169; d) C. Liu, H. Zhang, W. Shi, A. Lei, *Chem. Rev.* **2011**, *111*, 1780–1824; e) W. Shi, C. Liu, A. Lei, *Chem. Soc. Rev.* **2011**, *40*, 2761–2776; f) Ref. [21d]; g) S. H. Cho, J. Y. Kim, J. Kwak, S. Chang, *Chem. Soc. Rev.* **2011**, *40*, 5068–5083; h) X. Bugaut, F. Glorius, *Angew. Chem.* **2011**, *123*, 7618–7620; *Angew. Chem. Int. Ed*. **2011**, *50*, 7479–7481; i) N. Kuhl, M. N. Hopkinson, J. Wencel-Delord, F. Glorius, *Angew. Chem.* **2012**, *124*, 10382–10401; *Angew. Chem. Int. Ed.* **2012**, *51*, 10236–10254; j) I. Hussain, T. Singh, *Adv. Synth. Catal*. **2014**, *356*, 1661–1696.

[23] For selected reviews, see: a) G. Bringmann, C. Günther, M. Ochse, O. Schupp, S. Tasler, *Prog. Chem. Org. Nat. Prod.* **2001**, *82*, 1–294; b) G. Bringmann, A. J. Price Mortimer, P. A. Keller, M. J. Gresser, J. Garner, M. Breuning, *Angew. Chem*. **2005**, *117*, 5518–5563; *Angew. Chem. Int. Ed.* **2005**, *44*, 5384–5427; c) L. McMurray, F. O'Hara, M. J. Gaunt, *Chem. Soc. Rev*. **2011**, *40*, 1885–1898.

[24] R. van Helden, G. Verberg, *Recl. Trav. Chim. Pays-Bas.* **1965**, *84*, 1263–1273.

[25] a) H. Iataaki, H. Yoshimoto, *J. Org. Chem.* **1973**, *38*, 76–79; b) H. Yoshimoto, H. Itatani, *J. Catal.* **1973**, *31*, 8–12; c) F. R. S. Clark, R. O. C. Norman, C. B. Thomas, J. S. Wilson, *J. Chem. Soc. Perkin Trans. 2* **1974**, 1289–1295.

[26] A. Shiotani, H. Itatani, *Angew. Chem.* **1974**, *86*, 478–479; *Angew. Chem. Int. Ed. Engl*. **1974**, *13*, 471–472.

[27] For further early contributions, see: a) H. Yoshimoto, H. Itatani, *Bull. Chem. Soc. Jpn*. **1973**, *46*, 2490–2492; b) B. Akermark, L. Eberson, E. Jonsson, E. Petterson, *J. Org. Chem.* **1975**, *40*, 1365–1367; c) H.-J. Knölker, N. O'Sullivan, *Tetrahedron Lett*. **1994**, *35*, 1695–1698.

[28] a) K. M. Engle, T.-S. Mei, M. Wasa, J.-Q. Yu, *Acc. Chem. Res*. **2012**, *45*, 788–802; b) S. R. Neufeldt, M. S. Sanford, *Acc. Chem. Res*. **2012**, *45*, 936–946; c) M. Zhang, Y. Zhang, X. Jie, H. Zhao, G. Li, W, Su, *Org. Chem. Front*. **2014**, *1*, 843–895; d) G. Shi, Y. Zhang, *Adv. Synth. Catal*. **2014**, *356*, 1419–1442; e) Q.-Z. Zheng, N. Jiao, *Tetrahedron Lett*. **2014**, 55, 1121–1126.

[29] a) D. W. Robbins, T. A. Boebel, J. F. Hartwig, *J. Am. Chem. Soc*. **2010**, *132*, 4068–4069; b) A. García-Rubia, M. Á. Fernández-Ibáñez, R. G. Arrayás, J. C. Carretero, *Chem. Eur. J.* **2011**, *17*, 3567–3570.

[30] a) I. Moritani, Y. Fujiwara, *Tetrahedron Lett.* **1967**, *8*, 1119–1122; b) Y. Fujiwara, I. Moritani, M. Matsuda, S. Teranishi, *Tetrahedron Lett*. **1968**, *9*, 633–636; c) Y. Fujiwara, I. Moritani, M. Matsuda, S. Teranishi, *Tetrahedron Lett*. **1968**, *9*, 3863–3865; d) Y. Fujiwara, I. Moritani, S. Danno, R. Asano, S. Teranishi, *J. Am. Chem. Soc.* **1969**, *91*, 7166–7169.

[31] a) C. Jia, T. Kitamura, Y. Fujiwara, *Acc. Chem. Res*. **2001**, *34*, 633–639; b) N. Kuhl, M. N. Hopkinson, J. Wencel-Delord, F. Glorius, *Angew. Chem.* **2012**, *124*, 10382–10401; *Angew. Chem. Int. Ed*. **2012**, *51*, 10236–10254.

[32] M. D. K. Boele, G. P. F. van Strijdonck, A. H. M. de Vries, P. C. J. Kamer, J. G. de Vries, P. W. N. M. van Leeuwen, *J. Am. Chem. Soc.* **2002**, *124*, 1586–1587.

[33] M. Gómez-Gallego, M. A. Sierra, *Chem. Rev*. **2011**, *111*, 4857–4963.

[34] For reports related to palladium-catalyzed C–H bond alkenylation using acetyl as directing groups, see: a) G. T. Lee, X. Jiang, K. Prasad, O. Repič, T. J. Blacklock, *Adv. Synth. Catal.* **2005**, *347*, 1921–1924; b) C. Amatore, C. Cammoun, A. Jutand, *Adv. Synth. Catal.* **2007**, *349*, 292–296; c) B. S. Kim, C. Jang, D. J. Lee, S. W. Youn, *Chem. Asian J*. **2010**, *5*, 2336–2340; d) W. Rauf, A. L. Thompson, J. M. Brown, *Dalton Trans*. **2010**, *39*, 10414–10421; e) T. Nishikata. B. H. Lipshutz, *Org. Lett.* **2010**, *12*, 1972–1975; f) X. Liu, K. K. Hii, *J. Org. Chem*. **2011**, *76*, 8022–8026; g) B. Schmidt, N. Elizarov, *Chem. Commun.* **2012**, *48*, 4350–4352; h) S. R. Kandukuri, J. A. Schiffner, M. Oestreich, *Angew. Chem*. **2012**, *124*, 1291–1295; *Angew. Chem. Int. Ed*. **2012**, *51*, 1265–1269; i) Y. Gao, Y. Huang, W. Wu, K. Huang, H. Jiang, *Chem. Commun.* **2014**, *50*, 8370–8373.

[35] For reports related to palladium-catalyzed C–H bond alkenylation of aniline derivatives, see: a) W. Rauf, A. L. Thompson, J. M. Brown, *Chem. Commun*. **2009**, 3874–3876; b) G. T. Lee, X. Jiang, K. Prasad, O. Repič, T. J. Blacklock, *Adv. Synth. Catal.* **2005**, *347*, 1921–1924; c) J.-R. Wang, C.-T. Yang, L. Liu, Q.-X. Guo, *Tetrahedron Lett.* **2007**, *48*, 5449–5453.

[36] D.-H. Wang, K. M. Engle, B.-F. Shi, J.-Q. Yu, *Science* **2010**, *327*, 315–319.

[37] a) K. M. Engle, D.-H. Wang, J.-Q. Yu, *Angew. Chem*. **2010**, *122*, 6305–6309; *Angew. Chem. Int. Ed.* **2010**, *49*, 6169–6173; b) K. M. Engle, D.-H. Wang, J.-Q. Yu, *J. Am. Chem. Soc*. **2010**, *132*, 14137–14151; c) T.-S. Mei, D.-H. Wang, J.-Q. Yu, *Org. Lett.* **2010**, *12*, 3140–3143; d) D.-H. Wang, J.-Q. Yu, *J. Am. Chem. Soc.* **2011**, *133*, 5767–5769; for an asymmetric variant, see: e) B.-F. Shi, Y.-H. Zhang, J. K. Lam, D.-H. Wang, J.-Q. Yu, *J. Am. Chem. Soc.* **2010**, *132*, 460–461.

[38] a) A. Lu, D.-H. Wang, K. M. Engle, J.-Q. Yu, *J. Am. Chem. Soc.* **2010**, *132*, 5916–5921; also see: b) C. Zhang, J. Ji, P. Sun, *J. Org. Chem.* **2014**, *79*, 3200−3205, c) S. R. Kandukuri, L.-Y. Jiao, A. B. Machotta, M. Oestreich, *Adv. Synth. Catal.* **2014**, *356*, 1597–1609.

[39] J. Muzart, *Tetrahedron* **2005**, *61*, 9423–9463.

[40] G. Li, D. Leow, L. Wan, J.-Q. Yu, *Angew. Chem.* **2012**, 125, 1283–1285; *Angew. Chem. Int. Ed.* **2012**, *52*, 1245–1247.

[41] S. H. Cho, S. J. Hwang, S. Chang, *J. Am. Chem. Soc*. **2008**, *130*, 9254–9256.

[42] J. Wu, X. Cui, L. Chen, G. Jiang, Y. Wu, *J. Am. Chem. Soc*. **2009**, *131*, 13888–13889.

[43] a) C. C. Cummins, R. R. Schrock, W. M. Davis, *Inorg. Chem.* **1994**, *33*, 1448–1457; b) D. S. J. Arney, C. J. Burns, *J. Am. Chem. Soc*. **1995**, *117*, 9448–9460; c) K.-M. Sung, R. H. Holm, *J. Am. Chem. Soc.* **2001**, *123*, 1931–1943; d) S. M. Mullins, A. P. Duncan, R. G. Bergman, J. Arnold, *Inorg. Chem.* **2001**, *40*, 6952–6963.

[44] For other nitrogen-containing directing groups, see: a) G. Cai, Y. Fu, Y. Li, X. Wan, Z. Shi, *J. Am. Chem. Soc.* **2007**, *129*, 7666–7673; b) J.-J. Li, T.-S. Mei, J.-Q. Yu, *Angew. Chem.* **2008**, *120*, 6552–6555; *Angew. Chem. Int. Ed.* **2008**, *47*, 6452–6455; c) Z. Xu, B. Xiang, P. Sun, *Eur. J. Org. Chem*. **2012**, 3069–3073.

[45] X. Meng, S. Kim, *Org. Lett*. **2013**, *15*, 1910–1913.

[46] a) L. Y. Chan, S. Kim, T. Ryu, P. H. Lee, *Chem. Commun.* **2013**, *49*, 4682–4684; b) J. Seo, Y. Park, I. Jeon, T. Ryu, S. Park, P. H. Lee, *Org. Lett*. **2013**, *15*, 3358–3361; c) X. Meng, S. Kim, *J. Org. Chem.* **2013**, *78*, 11247–11254; d) H.-L. Wang, R.-B. Hu, H. Zhang, A.-X. Zhou, S.-D. Yang, *Org. Lett*. **2013**, *15*, 5302–5305; e) J. Mo, S. Lim, S. Park, T. Ryu, S. Kim, P. H. Lee, *RSC Adv.* **2013**, *3*, 18296–18299; f) D. Zhao, C. Nimphius, M. Lindale, F. Glorius, *Org. Lett.* **2013**, *15*, 4504–4507; g) S. Park, B. Seo, S. Shin, J.-Y. Son, P. H. Lee, *Chem. Commun*. **2013**, *49*, 8671–8673.

[47] a) C. Huang, B. Chattopadhyay, V. Gevorgyan, *J. Am. Chem. Soc.* **2011**, *133*, 12406–12409; also see: b) C. Wang, H. Ge, *Chem. Eur. J*. **2011**, *17*, 14371–14374; c) M. Mewald, J. A. Schiffner, M. Oestreich, *Angew. Chem.* **2012**, *124*, 1797–1799; *Angew. Chem. Int. Ed.* **2012**, *51*, 1763–1765.

[48] A. García-Rubia, B. Urones, R. G. Arrayás, J. C. Carretero, *Angew. Chem.* **2011**, *123*, 11119–11123; *Angew. Chem. Int. Ed.* **2011**, *50*, 10927–10931.

[49] a) Ref. [29b]; b) M. Yu, Z. Liang, Y. Wang, Y. Zhang, *J. Org. Chem.* **2011**, *76*, 4987–4994; c) H.-X. Dai, A. F. Stepan, M. S. Plummer, Y.-H. Zhang, J.-Q. Yu, *J. Am. Chem. Soc.* **2011**, *133*, 7222–7228; d) M. Yu, Y. Xie, C. Xie,Y. Zhang, *Org. Lett.* **2012**, *14*, 2164–2167; e) B. Wang, C. Shen, J. Yao, H. Yin, Y. Zhang, *Org. Lett.* **2014**, *16*, 46−49.

[50] D. Leow, G. Li, T.-S. Mei, J.-Q. Yu, *Nature* **2012**, *486*, 518–522.

[51] For other *meta*-directing groups, see: a) R. Tang, G. Li, J.-Q. Yu, *Nature* **2014**, *507*, 215–220; b) G. Yang, P. Lindovska, D. Zhu, J. Kim, P. Wang, R.-Y. Tang, M. Movassaghi, J.-Q. Yu, *J. Am. Chem. Soc*. **2014**, *136*, 10807−10813; d) H.-X. Dai, G. Li, X.-G. Zhang, A. F. Stepan, J.-Q. Yu, *J. Am. Chem. Soc*. **2013**, *135*, 7567–7571; d) Y.-F. Yang, G.-J. Cheng, P. Liu, D. Leow, T.-Y. Sun, P. Chen, X. Zhang, J.-Q. Yu, Y.-D. Wu, K. N. Houk, *J. Am. Chem. Soc.* **2014**, *136*, 344–355; e) S. Lee, H. Lee, K. L. Tan, *J. Am. Chem. Soc*. **2013**, *135*, 18778−18781; f) Y. Deng, J.-Q. Yu,

Angew. Chem. **2015**, *127*, 902–905; *Angew. Chem. Int. Ed*. **2015**, *54*, 888–891; g) M. Bera, A. Modak, T. Patra, A. Maji, D. Maiti, *Org. Lett*. **2014**, *16*, 5760−5763.

[52] a) E. Capito, J. M. Brown, A. Ricci, *Chem. Commun*. **2005**, 1854–1856; b) G. Fanton, N. M. Coles, A. R. Cowley, J. P. Flemming, J. M. Brown, *Heterocycles* **2010**, *80*, 895–901.

[53] N. P. Grimster, C. Gauntlett, C. R. A. Godfrey, M. J. Gaunt, *Angew. Chem*. **2005**, *117*, 3185–3189; *Angew. Chem. Int. Ed.* **2005**, *44*, 3125–3129.

[54] Y.-H. Zhang, B.-F. Shi, J.-Q. Yu, *J. Am. Chem. Soc*. **2009**, *131*, 5072–5074.

[55] S. Zhang, L. Shi, Y. Ding, *J. Am. Chem. Soc*. **2011**, *133*, 20218–20229.

[56] a) X. Zhang, S. Fan, C.-Y. He, X. Wan, Q.-Q. Min, J. Yang, Z.-X. Jiang, *J. Am. Chem. Soc*. **2010**, *132*, 4506–4507; see also: b) C.-Z. Wu, C.-Y. He, Y. Huang, X. Zhang, *Org. Lett.* **2013**, *15*, 5266–5269.

[57] Examples of DMSO serving as ligand under palladium(II) catalysis, see: a) D. Tanaka, S. P. Romeril, A. G. Myers, *J. Am. Chem. Soc.* **2005**, *127*, 10323-10333; b) B. A. Steinhoff, S. S. Stahl, *J. Am. Chem. Soc*. **2006**, *128*, 4348-4355.

[58] M. Ye, G.-L. Gao, J.-Q. Yu, *J. Am. Chem. Soc*. **2011**, *133*, 6964–6967.

[59] P. Wen, Y. Li, K. Zhou, C. Ma, X. Lan, C. Ma, G. Huang, *Adv. Synth. Catal*. **2012**, *354*, 2135–2140.

[60] For a review of palladium(0)/palladium(II) catalysis, see: M. Wasa, K. M. Engle, J.-Q. Yu, *Isr. J. Chem*. **2010**, *50*, 605–616.

[61] P. F. Killian, C. J. Bruell, C. Liang, M. C. Marley, *Soil Sediment Contam*. **2007**, *16*, 523–537.

[62] For selected examples, see: a) L. V. Desai, H. A. Malik, M. S. Sanford, *Org. Lett*. **2006**, *8*, 1141–1144; b) G.-W. Wang, T.-T. Yuan, X.-L. Wu, *J. Org. Chem.* **2008**, *73*, 4717–4720; c) H.-Y. Thu, W.-Y. Yu, C.-M. Che, *J. Am. Chem. Soc.* **2006**, *128*, 9048–9049; d) Y.-K. Liu, S.-J. Lou, D.-Q. Xu, Z.-Y. Xu, *Chem. Eur. J.* **2010**, *16*, 13590–13593.

[63] N. R. Deprez, M. S. Sanford, *J. Am. Chem. Soc*. **2009**, *131*, 11234–11241.

[64] For reviews of palladium(II)/palladium(IV) catalysis, see: a) K. Muñiz, *Angew. Chem. Int. Ed*. **2009**, *48*, 9412–9423; b) L.-M. Xu, B.-J. Li, Z. Yang, Z.-J. Shi, *Chem. Soc. Rev*. **2010**, *39*, 712–733; c) P. Sehnal, R. J. K. Taylor, I. J. S. Fairlamb, *Chem. Rev.* **2010**, *110*, 824–889; d) J. J. Topczewski, M. S. Sanford, *Chem. Sci*. **2015**, *6*, 70–76.

[65] a) K. L. Hull, M. S. Sanford, *J. Am. Chem. Soc.* **2007**, *129*, 11904–11905; b) K. L. Hull, M. S. Sanford, *J. Am. Chem. Soc*. **2009**, *131*, 9651–9653.

[66] B.-J. Li, S.-L. Tian, Z. Fang, Z.-J. Shi, *Angew. Chem*. **2008**, *120*, 1131–1134; *Angew. Chem. Int. Ed*. **2008**, *47*, 1115–1118.

[67] G. Brasche, J. García-Fortanet, S. L. Buchwald, *Org. Lett*. **2008**, *10*, 2207–2210.

[68] a) X. Zhao, C. S. Yeung, V. M. Dong, *J. Am. Chem. Soc.* **2010**, *132*, 5837–5844; b) C. S. Yeung, X. Zhao, N. Borduas, V. M. Dong, *Chem. Sci*. **2010**, *1*, 331–336.

[69] X. Wang, D. Leow, J.-Q. Yu, *J. Am. Chem. Soc.* **2011**, *133*, 13864–13867.

[70] a) J.-B. Xia, S.-L. You, *Organometallics* **2007**, *26*, 4869–4871; b) Ref. [41]; c) J. Karthikeyan, C.-H. Cheng, *Angew. Chem.* **2011**, *123*, 10054–10057; *Angew. Chem. Int. Ed.* **2011**, *50*, 9880–9883.

[71] R. Li, L. Jiang, W. Lu, *Organometallics* **2006**, *25*, 5973–5975.

[72] a) D. R. Stuart, K. Fagnou, *Science* **2007**, *316*, 1172–1175; b) D. R. Stuart, E. Villemure, K. Fagnou, *J. Am. Chem. Soc.* **2007**, *129*, 12072–12073.

[73] A. N. Campbell, E. B. Meyer, S. S. Stahl, *Chem. Commun*. **2011**, *47*, 10257–10259.

[74] X. Ren, P. Wen, X. Shi, Y. Wang, J. Li, S. Yang, H. Yan, G. Huang, *Org. Lett*. **2013**, *15*, 5194–5197.

[75] B. Liégault, D. Lee, M. P. Huestis, D. R. Stuart, K. Fagnou, *J. Org. Chem*. **2008**, *73*, 5022–5028.

[76] P. Anastas, N. Eghbali, *Chem. Soc. Rev*. **2010**, *39*, 301–312.

[77] a) R. B. Van Order, H. G. Lindwall, *Chem. Rev.* **1942**, *30*, 69–96; b) A. I. Scott, *Acc. Chem. Res.* **1970**, *3*, 151–157; c) P. Magnus, T. Gallagher, P. Brown, P. Pappalardo, *Acc. Chem. Res.* **1984**, *17*, 35–41; d) D. Crich, A. Banerjee, *Acc. Chem. Res*. **2007**, *40*, 151–161; e) A. J. Kochanowska-Karamyan, M. T. Hamann, *Chem. Rev*. **2010**, *110*, 4489–4497; f) S. Lancianesi, A. Palmieri, M. Petrini, *Chem. Rev*. **2014**, *114*, 7108–7149.

[78] a) S. Cacchi, G. Fabrizi, *Chem. Rev*. **2005**, *105*, 2873–2920; b) S. Cacchi, G. Fabrizi, *Chem. Rev*. **2011**, *111*, PR215–PR283; c) G. Broggini, E. M. Beccalli, A. Fasana, S. Gazzola, *Beilstein J. Org. Chem*. **2012**, *8*, 1730–1746; d) W. Zi, Z. Zuo, D. Ma, *Acc. Chem. Res*. **2015**, *48*, 702–711.

[79] For recent C–H bond alkenylations, see: a) Z. Song, R. Samanta, A. P. Antonchick, *Org. Lett*. **2013**, *15*, 5662–5665; b) S. Pan, T. Wakaki, N. Ryu, T. Shibata, *Chem. Asian J.* **2014**, *9*, 1257–1260; c) J. Park, N. K. Mishra, S. Sharma, S. Han, Y. Shin, T. Jeong, J. S. Oh, J. H. Kwak, Y. H. Jung, I. S. Kim, *J. Org. Chem*. **2015**, *80*, 1818–1827; d) X.-F. Yang, X.-H. Hu, C. Feng, T.-P. Loh, *Chem. Commun.* **2015**, *51*, 2532–2535; e) D. Yang, S. Mao, Y.-R. Gao, D.-D. Guo, S.-H. Guo, Bin Li, Y.-Q. Wang, *RSC Adv*. **2015**, *5*, 23727–23736; for C–H bond alkynylations, see: f) N. Jin, C. Pan, H. Zhang, P. Xu, Y. Cheng, C. Zhu, *Adv. Synth. Catal.* **2015**, *357*, 1149–1153; g) Y. Wu, Y. Yang , B. Zhou, Y. Li, *J. Org. Chem*. **2015**, *80*, 1946–1951; h) Ref. [79d]; for C–H bond methylation and alkylation, see: i) S. R. Neufeldt, C. K. Seigerman, M. S. Sanford, *Org. Lett.* **2013**, *15*, 2302–2305; j) S. Pan, N. Ryu, T.

Shibata, *Adv. Synth. Catal.* **2014**, *356*, 929–933; k) W. Ai, X. Yang, Y. Wu, X. Wang, Y. Li, Y. Yang, B. Zhou, *Chem. Eur. J.* **2014**, *20*, 17653–17657; l) Chanchal Premi, Ankit Dixit, and Nidhi Jain, *Org. Lett*. **2015**, *17*, 2598–2601; for C–H bond acylations, see: m) M. Kim, N. K. Mishra, J. Park, S. Han, Y. Shin, S. Sharma, Y. Lee, E.-K. Lee, J. H. Kwak, I. S. Kim, *Chem. Commun.* **2014**, *50*, 14249–14252; n) Y. Shin, S. Sharma, N. K. Mishra, S. Han, J. Park, H. Oh, J. Ha, H. Yoo, Y. H. Jung, I. S. Kim, *Adv. Synth. Catal.* **2015**, *357*, 594–600; for C–H bond cyanation, see: o) N. K. Mishra, T. Jeong, S. Sharma, Y. Shin, S. Han, J. Park, J. S. Oh, J. H. Kwak, Y. H. Jung, I. S. Kim, *Adv. Synth. Catal.* **2015**, *357*, 1293–1298; for C–H bond allylations, see: p) S. Sharma, Y. Shin, N. K. Mishra, J. Park, S. Han, T. Jeong, Y. Oh, Y. Lee, M. Choi, I. S. Kim, *Tetrahedron* **2015**, *71*, 2435–2441; q) J. Park, N. K. Mishra, S. Sharma, S. Han, Y. Shin, T. Jeong, J. S. Oh, J. H. Kwak, Y. H. Jung, I. S. Kim, *J. Org. Chem.* **2015**, *80*, 1818−1827; for C–H bond heterofunctionalizations, see: r) C. Pan, A. Abdukader, J. Han, Y. Cheng, C. Zhu, *Chem. Eur. J.* **2014**, *20*, 3606–3609; s) K. Shin, S. Chang, *J. Org. Chem*. **2014**, *79*, 12197–12204; t) W. Hou, Y. Yang, W. Ai, Y. Wu, X. Wang, B. Zhou, Y. Li, *Eur. J. Org. Chem*. **2015**, 395–400.

[80] J. S. Parnes, D. S. Carter, L. J. Kurz, L. A. Flippin, *J. Org. Chem.* **1994**, *59*, 3497–3499.

[81] D. Leonori, I. Coldham, *Adv. Synth. Catal.* **2009**, *351*, 2619–2623.

[82] S. De, S. Ghosh, S. Bhunia, J. A. Sheikh, A. Bisai, *Org. Lett.* **2012**, *14*, 4466–4469.

[83] D. Kalyani, N. R. Deprez, L. V. Desai, M. S. Sanford, *J. Am. Chem. Soc.* **2005**, *127*, 7330–7331.

[84] Z. Shi, B. Li, X. Wan, J. Cheng, Z. Fang, B. Cao, C. Qin, Y. Wang, *Angew. Chem.* **2007**, *119*, 5650–5654; *Angew. Chem. Int. Ed.* **2007**, *46*, 5554–5558.

[85] T. Nishikata, A. R. Abela, S. Huang, B. H. Lipshutz, *J. Am. Chem. Soc.* **2010**, *132*, 4978–4979.

[86] Z. Jiang, L. Zhang, C. Dong, X. Su, H. Li, W. Tang, L. Xu, Q. Fan, *RSC Adv*. **2013**, *3*, 1025–1028.

[87] a) T. Kappe, P. Roschger, B. Schuiki, W. Stadlbauer, *J. Heterocyclic Chem*. **2003**, *40*, 297–302; b) L. Yuan, W. Lin, J. Song, *Chem. Commun*. **2010**, *46*, 7930–7932; c) H. S. Choi, K. Nasr, S. Alyabyev, D. Feith, J. H. Lee, S. H. Kim, Y. Ashitate, H. Hyun, G. Patonay, L. Strekowski, M. Henary, J. V. Frangioni, *Angew. Chem.* **2011**, *123*, 6382–6387; *Angew. Chem. Int. Ed.* **2011**, *50*, 6258 –6263.

[88] a) H. Booth, T. Masamune, *J. Chem. Soc., Perkin Trans. 2* **1972**, 354–356; b) Y. Ban, K. Yoshida, J. Goto, T. Oishi, E. Takeda, *Tetrahedron* **1983**, *39*, 3657–3668.

[89] a) B. Robinson, *Chem. Rev*. **1963**, *63*, 373–401; b) B. Robinson, *Chem. Rev*. **1969**, *69*, 227–250.

[90] a) Ref. [62a]; b) Ref. [62b]; c) Ref. [70c]; d) V. S. Thirunavukkarasu, C.-H. Cheng, *Chem. Eur. J.* **2011**, *17*, 14723–14726.

[91] a) Ref. [68a]; b) Ref. [68b]; c) N. Borduas, A. J. Lough, V. M. Dong, *Inorg. Chim. Acta* **2011**, *369*, 247–252.

[92] a) J. S. Laursen, J. Engel-Andreasen, P. Fristrup, P. Harris, C. A. Olsen, *J. Am. Chem. Soc.* **2013**, *135*, 2835–2844; b) P. Saxena, N. Thirupathi, M. Nethaji, *Organometallics* **2014**, *33*, 5554–5565.

[93] C. E. Houlden, C. D. Bailey, J. G. Ford, M. R. Gagné, G. C. Lloyd-Jones, K. I. Booker-Milburn, *J. Am. Chem. Soc.* **2008**, *130*, 10066–10067.

[94] C. E. Houlden, M. Hutchby, C. D. Bailey, J. G. Ford, S. N. G. Tyler, M. R. Gagné, G. C. Lloyd-Jones, K. I. Booker-Milburn, *Angew. Chem.* **2009**, *121*, 1862–1865; *Angew. Chem. Int. Ed*. **2009**, *48*, 1830–1833.

[95] a) Ref. [85]; b) T. Nishikata, A. R. Abela, B. H. Lipshutz, *Angew. Chem.* **2010**, *122*, 793–796; *Angew. Chem. Int. Ed*. **2010**, *49*, 781–784.

[96] a) D. J. Schipper, M. Hutchinson, K. Fagnou, *J. Am. Chem. Soc*. **2010**, *132*, 6910–6911; b) J. Willwacher, S. Rakshit, F. Glorius, *Org. Biomol. Chem*. **2011**, *9*, 4736–4740; c) B. Li, J. Ma, W. Xie, H. Song, S. Xu, B. Wang, *Chem. Eur. J*. **2013**, *19*, 11863–11868; d) B. Li, J. Ma, W. Xie, H. Song, S. Xu, B. Wang, *J. Org. Chem*. **2013**, *78*, 9345−9353.

[97] a) T. A. Dwight, N. R. Rue, D. Charyk, R. Josselyn, B. DeBoef, *Org. Lett*. **2007**, *9*, 3137–3139; b) G. Brasche, J. García-Fortanet, S. L. Buchwald, *Org. Lett.* **2008**, *10*, 2207–2210; c) B. Liégault, D. Lee, M. P. Huestis, D. R. Stuart, K. Fagnou, *J. Org. Chem*. **2008**, *73*, 5022–5028; d) A. N. Campbell, E. B. Meyer, S. S. Stahl, *Chem. Commun.* **2011**, *47*, 10257–10259; e) L. Zhou, W. Lu, *Organometallics* **2012**, *31*, 2124–2127.

[98] L.-Y. Jiao, M. Oestreich, *Chem. Eur. J.* **2013**, *19*, 10845–10848.

[99] a) A. A. H. Van der Zeijden, H. W. Bosch, H. Berke, *Organometallics* **1992**, *11*, 563–573; b) C. Jia, W. Lu, J. Oyamada, T. Kitamura, K. Matsuda, M. Irie, Y. Fujiwara, *J. Am. Chem. Soc*. **2000**, *122*, 7252–7263; c) C. Jia, D. Piao, J. Oyamada, W. Lu, T. Kitamura, Y. Fujiwara, *Science* **2000**, *287*, 1992–1995.

[100] a) K. Nishiura, Y. Urawa, S. Soda, *Adv. Synth. Catal*. **2004**, *346*, 1679–1684; b) Z. Wu, F. Luo, S. Chen, Z. Li, H. Xiang, X. Zhou, *Chem. Commun.* **2013**, *49*, 7653–7655.

[101] a) Y. Rong, R. Li, W. Lu, *Organometallics* **2007**, *26*, 4376-4378; b) L. T. Ball, G. C. Lloyd-Jones, C. A. Russell, *Science*, **2012**, *337*, 1644–1648.

[102] a) M. Somei, Y. Saida, T. Funamoto, T. Ohta, *Chem. Pharm. Bull.* **1987**, *35*, 3146–3154; b) M. Somei, T. Kawasaki, *Chem. Pharm. Bull.* **1989**, *37*, 3426–3428.

[103] B. Urones, R. G. Arrayás, J. C. Carretero, *Org. Lett*. **2013**, *15*, 1120–1123.

[104] W. Rauf, A. L. Thompson, J. M. Brown, *Chem. Commun*. **2009**, 3874–3876.

[105] L. Wang, S. Liu, Z. Li, Y. Yu, *Org. Lett*. **2011**, *13*, 6137–6139.

[106] L.-Y. Jiao, A. V. Ferreira, M. Oestreich, unpublished results, Technische Universität Berlin, **2015**.

[107] a) M. Miura, T. Tsuda, T. Satoh, S. Pivsa-Art, M. Nomura, *J. Org. Chem.* **1998**, *63*, 5211–5215; b) B. S. Kim, S. Y. Lee, S. W. Youn, *Chem. Asian J*. **2011**, *6*, 1952–1957.

[108] W. C. Still, M. Kahn, A. Mitra, *J. Org. Chem.* **1978**, *43*, 2923–2925.

[109] R. K. Harris, E. D. Becker, S. M. Cabral de Menezes, R. Goodfellow, P. Granger, *Pure Appl. Chem.* **2001**, *73*, 1795–1818.

[110] L. Yuan, W. Lin, J. Song, *Chem. Commun.* **2010**, *46*, 7930–7932.

[111] T. Kappe, P. Roschger, B. Schuiki, W. Stadlbauer, *J. Heterocyclic Chem*. **2003**, *40*, 297–302.

[112] M. López-Iglesias, E. Busto, V. Gotor, V. Gotor-Fernández, *J. Org. Chem*. **2012**, *77*, 8049–8055.

[113] G. W. Gribble, J. H. Hoffman, *Synthesis* **1977**, 859–860.

[114] K. P. Landge, K. S. Jang, S. Y. Lee, D. Y. Chi, *J. Org. Chem*. **2012**, *77*, 5705–5713.