Carboxylate-Assisted Ruthenium-Catalyzed Direct C–H Bond Functionalizations

Dissertation

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Lianhui Wang

from Puyang (China)

Göttingen, 2014

Thesis Committee

Prof. Dr. L. Ackermann, Institute of Organic and Biomolecular Chemistry

Prof. Dr. D. Stalke, Institute of Inorganic Chemistry

Members of the Examination Board

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Second Reviewer: Prof. Dr. D. Stalke, Institute of Inorganic Chemistry

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Dr. A. Breder, Institute of Organic and Biomolecular Chemistry

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1.1.1 Metal-Catalyzed Direct C−H Bond Functionalizations: An Overview

The catalytic functionalization of unreactive C−H bonds represents one of the most powerful tools for sustainable syntheses and for opening new routes to pharmaceuticals and natural products.[1,2] These methods are economically attractive alternatives to conventional cross-coupling reactions (Scheme 1).[3,4] For instance, the prefunctionalized organometallics or main-group element arylating reagents **2** (M = MgX, ZnX, BR$_2$, SnR$_3$, SiR$_3$, etc.) are often sensitive to air or are relatively expensive, and their preparation from the corresponding arenes **1** usually involves a number of synthetic operations (Scheme 1a).[3a] In contrast, direct C−H bond activations such as the direct arylation reactions represent an environmentally and economically more attractive strategy,
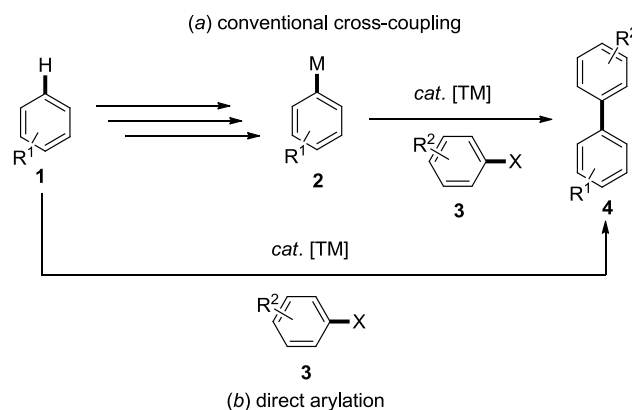
Scheme 1 Conventional cross-coupling (a) *versus* direct arylation (b)

1   For recent reviews on C–H functionalizations in organic synthesis, see: (a) D. Y.-K. Chen, S. W. Youn, *Chem. – Eur. J.* **2012**, *18*, 9452–9474; (b) W. R. Gutekunst, P. S. Baran, *Chem. Soc. Rev.* **2011**, *40*, 1976–1991; (c) L. McMurray, F. O'Hara, M. J. Gaunt, *Chem. Soc. Rev.* **2011**, *40*, 1885–1898.

2   (a) J. Yamaguchi, A. D. Yamaguchi, K. Itami, *Angew. Chem. Int. Ed.* **2012**, *51*, 8960–9009; (c) *Modern Heterocyclic Chemistry*; J. Alvarez-Builla, J. J. Vaquero, J. Barluenga, Eds.; Wiley-VCH: Weinheim, Germany, **2011**.

3   (a) *Modern Arylation Methods*; L. Ackermann, Ed.; Wiley-VCH: Weinheim, Germany, **2009**; For recent reviews on conventional cross-coupling reactions, see: (b) C. C. C. Johansson Seechurn, M. O. Kitching, T. J. Colacot, V. Snieckus, *Angew. Chem. Int. Ed.* **2012**, *51*, 5062–5085; (c) *Chem. Soc. Rev.* **2011**, *40*, Special Issue 10 "Cross coupling reactions in organic synthesis", pp 4877–5208; (d) B. M. Rosen, K. W. Quasdorf, D. A. Wilson, N. Zhang, A.-M. Resmerita, N. K. Garg, V. Percec, *Chem. Rev.* **2011**, *111*, 1346–1416; (e) G. Cahiez, A. Moyeux, A. *Chem. Rev.* **2010**, *110*, 1435–1462.

4   For representative general reviews on C−H bond functionalizations, see: (a) K. M. Engle, J.-Q. Yu, *J. Org. Chem.* **2013**, *78*, 8927–8955; (b) J. J. Mousseau, A. B. Charrette, *Acc. Chem. Res.* **2013**, *46*, 412–424; (c) N. Kuhl, M. N. Hopkinson, J. Wencel-Delord, F. Glorius, *Angew. Chem. Int. Ed.* **2012**, *51*, 10236–10254; (d) C. S. Yeung, V. M. Dong, *Chem. Rev.* **2011**, *111*, 1215–1292; (e) D. A. Colby, R. G. Bergman, J. A. Ellman, *Chem. Rev.* **2010**, *110*, 624–655; (f) I. A. I. Mkhalid, J. H. Barnard, T. B. Marder, J. M. Murphy, J. F. Hartwig, *Chem. Rev.* **2010**, *110*, 890−931; (g) P. Sehnal, R. J. K. Taylor, I. J. S. Fairlamb, *Chem. Rev.* **2010**, *110*, 824–889; (h) M. C. Willis, *Chem. Rev.* **2010**, *110*, 725−748; (i) G. E. Dobereiner, R. H. Crabtree, *Chem. Rev.* **2010**, *110*, 681−703; (j) P. Thansandote, M. Lautens, *Chem. –Eur. J.* **2009**, *15*, 5874–5883; (k) L. Ackermann, R. Vicente, A. R. Kapdi, *Angew. Chem. Int. Ed.* **2009**, *48*, 9792−9826; (l) L.-C. Campeau, D. R. Stuart, K. Fagnou, *Aldrichim. Acta* **2007**, *40*, 35−41; (m) D. Alberico, M. E. Scott, M. Lautens, *Chem. Rev.* **2007**, *107*, 174−238; (n) R. G. Bergman, *Nature* **2007**, *446*, 391−393; (o) K. Godula, D. Sames, *Science* **2006**, *312*, 67−72 and references cited therein.

which are not only advantageous with respect to the overall minimization of byproduct formation, but also allow for a streamlining of organic syntheses (Scheme 1b).[3a,4k,5]

Early studies in the catalytic functionalization of unreactive C−H bonds were largely directed toward the challenging C–H bond activation of methane.[6] However, during the past two decades, intensive research efforts have led to the development of C−H bond functionalizations[4] with increasingly viable metal catalysts to improve the atom economy and more importantly the step-economy of organic syntheses.[5] By far, a large variety of transition-metal catalysts have set the stage for efficient chemo-, site-, and enantioselective C−H bond functionalizations.[1,4]

1.1.2 Mechanisms for Transition-Metal-Catalyzed C−H Bond Metalation

Key to the success to the direct C–H bond functionalizations was generally a detailed mechanistic understanding of the elementary C–H bond metalation step. Traditionally, three different modes of action were primarily considered for C–H bond metalations,[7] namely, (i) oxidative addition with electron-rich late transition metals, (ii) σ-bond metathesis with early transition metals, and (iii) electrophilic activation with electron-deficient late transition metals (Scheme 2).
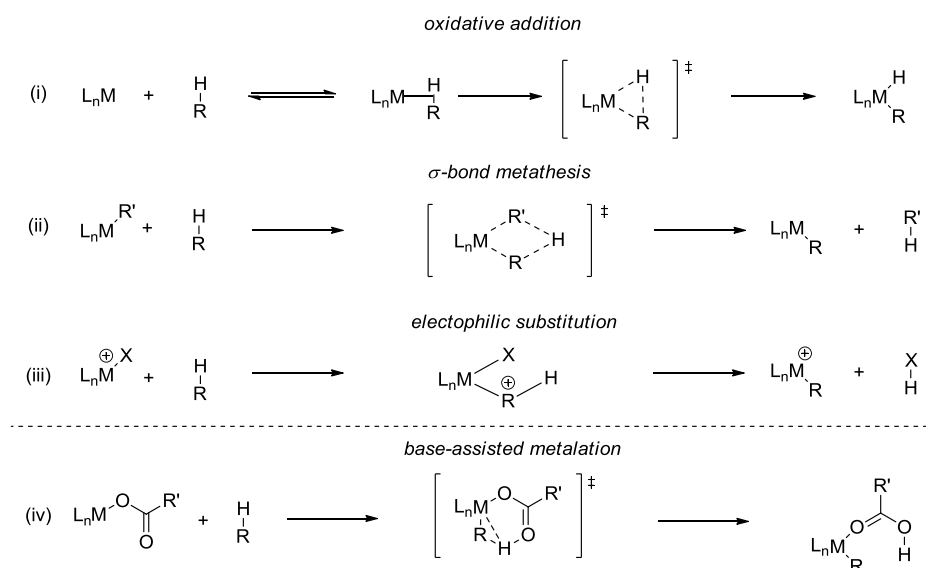
Scheme 2 Mechanisms for C−H bond metalation

However, studies in the past years also indicated the existence of a continuum of electrophilic, ambiphilic, and nucleophilic interactions as well as base-assisted metalation reactions.[8] As early as 1970s, the Shaw group[9a] observed the beneficial effect exerted by NaOAc for stoichiometric

5   (a) P. A. Wender, V. A. Verma, T. J. Paxton, T, H. Pillow, *Acc. Chem. Res.* **2008**, *41*, 40–49; (b) B. M. Trost, *Acc. Chem. Res.* **2002**, *35*, 695–705; (c) B. M. Trost, *Science* **1991**, *254*, 1471–1477.

6   (a) B. G. Hashiguchi, S. M. Bischof, M. M. Konnick, R. A. Periana, *Acc. Chem. Res.* **2012**, *45*, 885–898; (b) H. Schwarz, *Angew. Chem. Int. Ed.* **2011**, *50*, 10096–10115; (c) S. J. Blanksby, G. B. Ellison, *Acc. Chem. Res.* **2003**, *36*, 255–263.

7   For selected reviews on mechanistic aspects of C−H bond functionalizations, see: (a) D. Balcells, E. Clot, O. Eisenstein, *Chem. Rev.* **2010**, *110*, 749−823; (b) M. Lersch, M. Tilset, *Chem. Rev.* **2005**, *105*, 2471−2526; (c) V. Ritleng, C. Sirlin, M. Pfeffer, *Chem. Rev.* **2002**, *102*, 1731−1770 and references cited therein.

8   L. Ackermann, *Chem. Rev.* **2011**, *111*, 1315–1345.

9   (a) J. C. Gaunt, B. L. Shaw, *J. Organomet. Chem.* **1975**, *102*, 511–516; (b) V. I. Sokolov, L. L. Troitskaya, O. A. Reutov, *J. Organomet. Chem.* **1979**, *182*, 537–546.

cyclometalation reactions (Scheme 3). Thus, detailed experimental and computational analysis by Davies and coworkers [10] provided strong evidence for this novel C–H bond metalation mechanisms relying on the assistance of a bifunctional ligand bearing an additional Lewis-basic heteroatom or most prominently carboxylates (Scheme 2, iv).

no additive: —
NaOAc (1.0 equiv): 84%
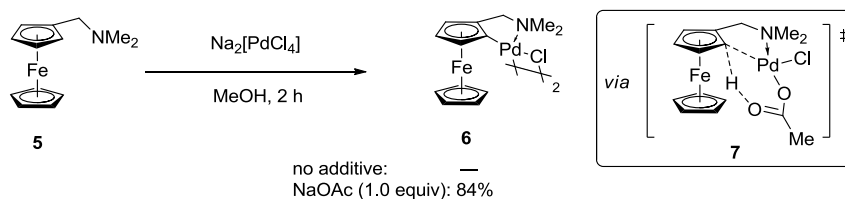
Scheme 3 Stoichiometric acetate-mediated cyclometalation

This novel insight into metalations has thus served as stimulus for the development of C–H bond transformations based on cocatalytic amounts of carboxylates.[8] To differentiate this type of base-assisted metalations mechanistically, new concepts have recently been introduced (Scheme 4). It has been proposed that a bidentate base is operating by the concerted-metalation-deprotonation pathway (CMD) [11] or by the ambiphilic metal-ligand activation (AMLA) mechanism, [12] both of which favor a six-membered transition state. Theoretical calculation[13] disclose that the metal-acetate complexes have an ambiphilic character due to an intramolecular electrophilic activation of a C–H bond followed by deprotonation with an internal base. On the other hand, the mode of action of monodentate anionic ligands has been explored by the research groups of Oxgaard and Goddard as well as Gunnoe.[14] DFT-studies favor an internal electrophilic substitution (IES) prior to traditional σ-bond metathesis.

CMD   AMLA   IES

Scheme 4 Proposed transition states during C−H bond metalations

1.1.3 Carboxylate-Assisted Ruthenium-Catalyzed Direct C–H Bond Functionalizations

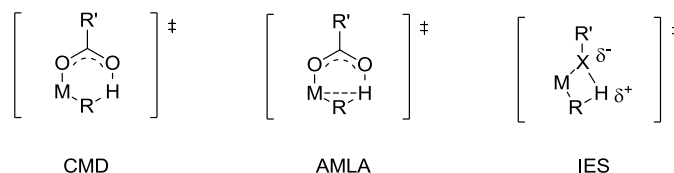The contributions for C−H bond functionalization brought by palladium catalysts[1,4] have motivated the search for less expensive, active ruthenium catalysts.[15] Notably, the pioneering

[10] D. L. Davies, O. Al-Duaij, J. Fawcett, M. Giardiello, S. T. Hilton, D. R. Russell, *Dalton Trans.* **2003**, 4132–4138 and references cited therein.

[11] D. Lapointe, K. Fagnou, *Chem. Lett.* **2010**, *39*, 1118–1126.

[12] (a) Y. Boutadla, D. L. Davies, S. A. Macgregor, A. I. Poblador-Bahamonde, *Dalton Trans.* **2009**, 5820−5831; (b) Y. Boutadla, D. L. Davies, S. A. Macgregor, A. I. Poblador-Bahamonde, *Dalton Trans.* **2009**, 5887−5893.

[13] D. H. Ess, S. M. Bischof, J. Oxgaard, R. A. Periana, W. A. Goddard, III, *Organometallics* **2008**, *27*, 6440–6445.

[14] (a) J. Oxgaard, W. J. Trenn, III, R. J. Nielsen, R. A. Periana, W. A. Goddard, III, *Organometallics* **2007**, *26*, 1565–1567; (b) D. Conner, K. N. Jayaprakash, T. R. Cundari, T. B. Gunnoe, *Organometallics* **2004**, *23*, 2724–2733; (c) a review: J. R. Webb, T. BolaÇo, T. B. Gunnoe, *ChemSusChem* **2011**, *4*, 37–49.

[15] February 2014, http://taxfreegold.co.uk/precious metalpricesusdollars.html: prices of gold, platinum, rhodium, iridium, palladium and ruthenium: $1244, $1377, $1053, $400, $705, and $56 US per troy ounce, respectively.

studies on ruthenium-catalyzed direct hydroarylations of alkenes by Lewis[16] as well as Murai[17] highlighted the potential of efficient ruthenium catalysis for site-selective reactions of C–H bonds onto C–C and C−Het multiple bonds (see Chapter **1.4**).

The subsequent intensive search for easy-to-prepare and more stable ruthenium(II) catalysts during the following decades resulted in the discovery efficient ruthenium catalysts, milder reaction conditions and new ruthenium-catalyzed reactions, as was demonstrated by Oi and Inoue in 2001 (Scheme 5).[18] However, essential progress in ruthenium-catalyzed direct arylations of arenes with aryl halides was achieved employing ruthenium complexes *in situ* derived from phosphine-[19] or *N*-heterocyclic carbene[20] (NHC) ligands. Notably, all of these reactions required the use of highly polar *N*-methylpyrrolidinone (NMP) as solvent, which led to catalytic systems with lower robustness,[21] particularly when being applied to more challenging substrate combinations.
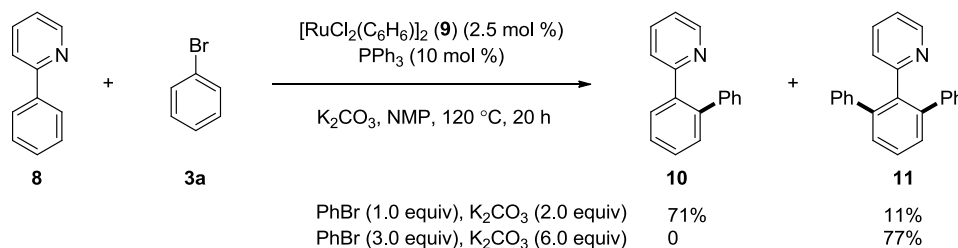
Scheme 5 Ruthenium-catalyzed direct arylation with aryl halides by Oi and Inoue

Until 2008, carboxylates have not been used as efficient cocatalytic additives in ruthenium-catalyzed C−H bond functionalizations. Primary studies from the Ackermann group highlighted a significant reaction rate acceleration applying bifunctional secondary phosphine oxides (SPO) preligand[22] in ruthenium-catalyzed direct arylations with organic electrophiles.[23] Concerning the catalysis working mode,[23] a base assistance with an intermediacy of the five-membered transition state **12** was proposed to be the decisive feature (Figure 1). Analogously, further studies from the same group showed that bifunctional ligands, especially carboxylates, were expected to give rise to six-membered transition state **13** (Figure 1).[8]

16   L. N. Lewis, J. F. Smith, *J. Am. Chem. Soc.* **1986**, *108*, 2728–2735.

17   S. Murai, F. Kakiuchi, S. Sekine, Y. Tanaka, A. Kamatani, M. Sonoda, N. Chatani, *Nature* **1993**, *366*, 529–531.

18   (a) S. Oi, S. Fukita, N. Hirata, N. Watanuki, S. Miyano, Y. Inoue, *Org. Lett.* **2001**, *3*, 2579−2581; (b) S. Oi, Y. Ogino, S. Fukita, Y. Inoue, *Org. Lett.* **2002**, *4*, 1783−1785.

19   L. Ackermann, R. Vicente, *Top. Curr. Chem.* **2010**, *292*, 211−229.

20   (a) W. A. Herrmann, *Angew. Chem. Int. Ed.* **2002**, *41*, 1290−1309; (b) D. Bourissou, O. Guerret, F. P. Gabbaie, G. Bertrand, *Chem. Rev.* **2000**, *100*, 39−92; (c) *N-Heterocyclic Carbenes in Synthesis*; S. P. Nolan, Ed.; Wiley-VCH: Weinheim, Germany, **2006**.

21   S. G. Ouellet, A. Roy, C. Molinaro, R. Angelaud, J.-F., P. D. O'Shea, I. W. Davies, *J. Org. Chem.* **2011**, *76*, 1436–1439.

22   (a) L. Ackermann, *Isr. J. Chem.* **2010**, *50*, 652–663; (b) L. Ackermann, *Synthesis* **2006**, 1557–1571.

23   (a) L. Ackermann, *Org. Lett.* **2005**, *7*, 3123–3125; (b) L. Ackermann, A. Althammer, R. Born, *Angew. Chem. Int. Ed.* **2006**, *45*, 2619–2622; (c) L. Ackermann, R. Born, P. Álvarez-Bercedo, *Angew. Chem. Int. Ed.* **2007**, *46*, 6364–6367.
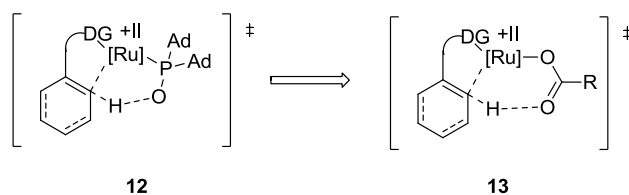
Figure 1 Proposed transition states for base-assisted ruthenations

Hence, the Ackermann group investigated the order of efficacy for various cocatalytic additives in direct arylations using toluene as inert solvent and *N*-aryl-substitued 1,2,3-triazoles **14** as substrates (Scheme 6).[24] Herein, complexes of previously used ligands, such as NHC precursors or tertiary phosphines, demonstrated only poor activity. On the contrary, bifunctional sterically hindered SPO preligand (1-Ad)$_2$P(O)H enabled more efficient catalysis. Further screening showed that acids were superior, with optimal results being obtained with sterically congested MesCO$_2$H.
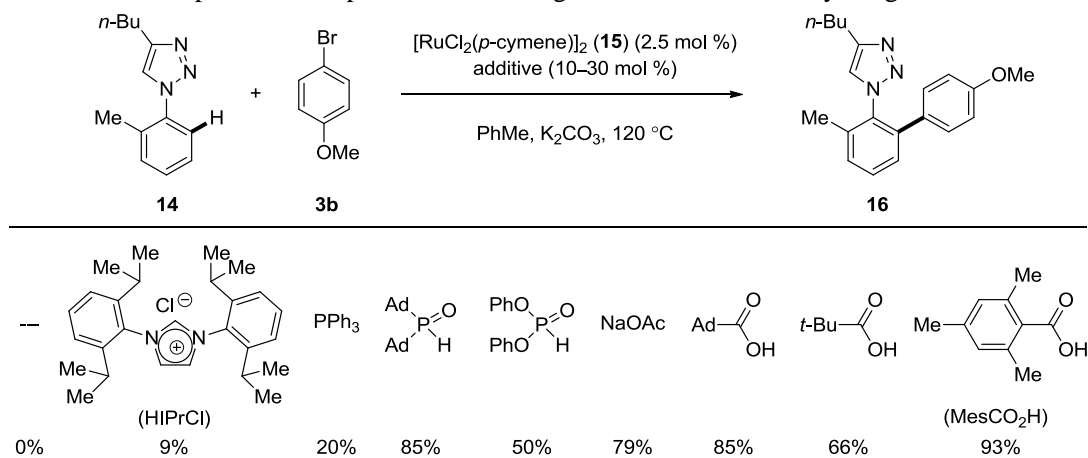
Scheme 6 Cocatalytic additives in the ruthenium-catalyzed direct arylation

The subsequent intensive mechanistic studies[24,25] disclosed the ruthenium(II)-catalyzed direct arylations to involve initial C−H bond activations *via* carboxylate-assisted and thus deprotonative ruthenations *via* the transition state **19** (Scheme 7).

24   L. Ackermann, R. Vicente, A. Althammer, *Org. Lett.* **2008**, *10*, 2299−2302.
25   L. Ackermann, R. Vicente, H. K. Potukuchi, V. Pirovano, *Org. Lett.* **2010**, *12*, 5032–5035.
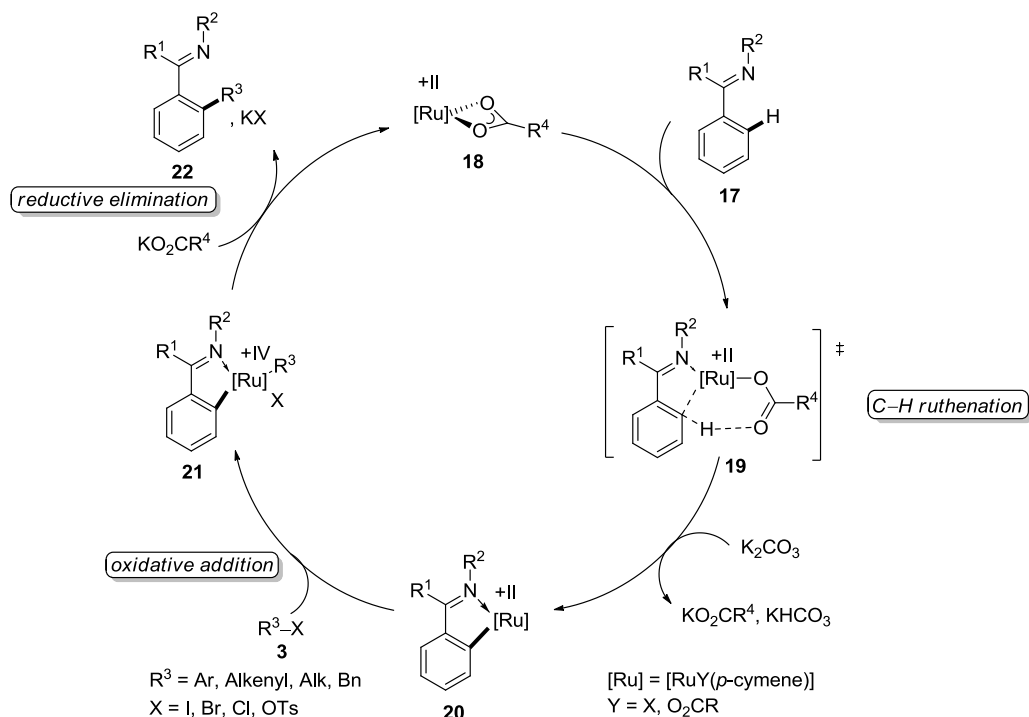
Scheme 7 Proposed mechanism for direct arylations and alkylations by carboxylate assistance

To address the mechanistic understanding, a ruthenium(II) biscarboxylate complex **23** was prepared (Scheme 8a).[25] Notably, the well-defined complex **23** displayed a broad substrate scope in that various arenes were directly functionalized with (Het)ArCl in a highly regioselective fashion (Scheme 8b).[25]
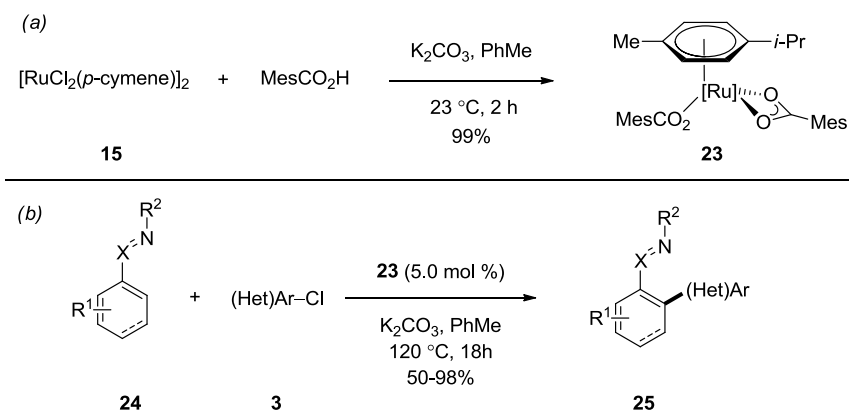
Scheme 8 Direct arylations catalyzed by ruthenium(II) biscarboxylate **23**

On the basis of experimental findings in ruthenium-catalyzed direct arylations (Scheme 9, **27**) as well as alkylations (**28** and **29**),[4k,8,19,22,26] the Ackermann group intensively examined carboxylates as effective cocatalytic additives in ruthenium-catalyzed C−H bond functionalizations, such as

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26   For selected reviews on ruthenium-catalyzed C–H bond functionalization, see also: (a) B. Li, P. H. Dixneuf, *Chem. Soc. Rev.* **2013**, *42*, 5744–5767; (b) P. B. Arockiam, C. Bruneau, P. H. Dixneuf, *Chem. Rev.* **2012**, *112*, 5879–5918; (c) L. Ackermann, *Pure Appl. Chem.* **2010**, *82*, 1403–1413; (d) L. Ackermann, *Chem. Commun.* **2010**, *46*, 4866–4877; (e) L. Ackermann, *Synlett* **2007**, 507–526.

hydroarylations with alkenes (**30**),[27] as well as oxidative C−C (**32** and **33**),[28,29] C−O (**34**)[30] and C−N (**35**)[30] bond formations (Scheme 9). This thesis herein focuses on carboxylate-assisted ruthenium-catalyzed oxidative C−H bond functionalizations (**32** and **33**) and C(sp^3)−H alkylations (**31**) with alkenes as well as direct *ortho*-C−Hal bond formations (**36**), which will be described in details in the following Chapters.
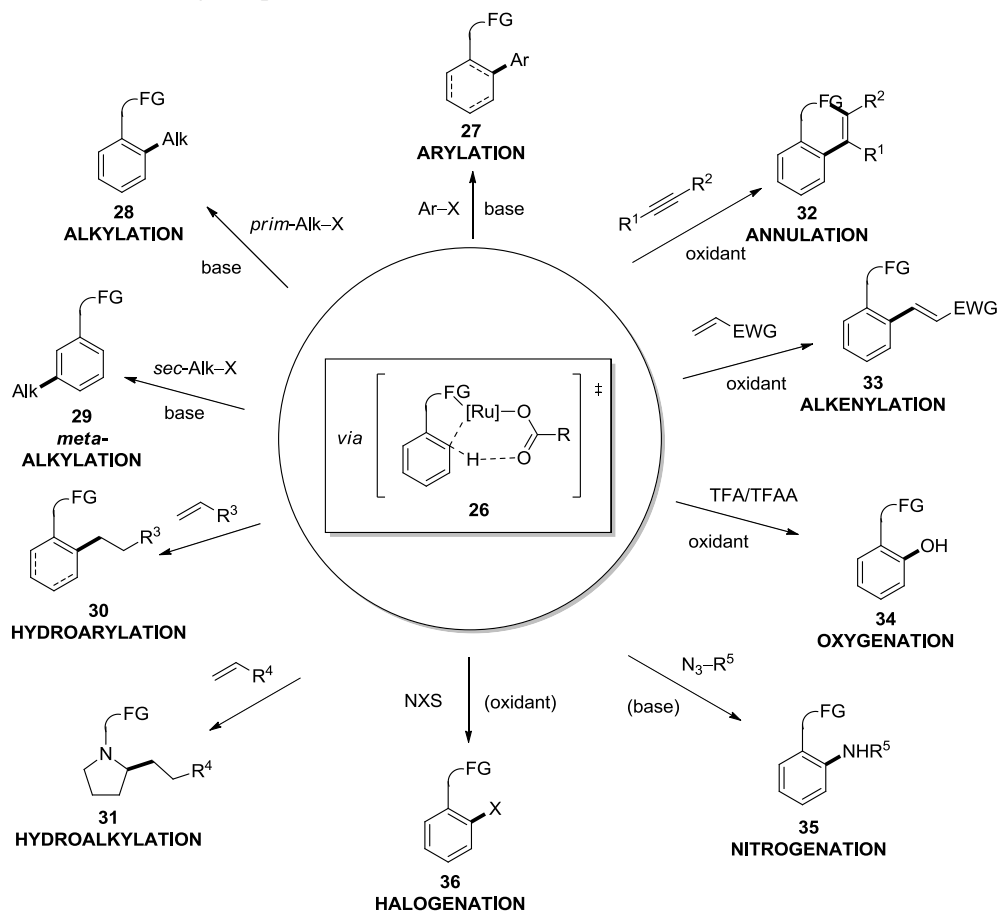
Scheme 9 Carboxylate-assisted ruthenium-catalyzed direct C−H bond functionalizations

1.2 Ruthenium-Catalyzed Alkyne Annulations by C−H/Het−H Bond Functionalizations

Proceeding with the previously reported experimental results on direct arylations, the Ackermann group first tested carboxylates as cocatalytic additives for ruthenium-catalyzed oxidative C−H bond functionalizations,[28,29] a research area that had thus far largely been dominated by the use of

27   Selected reviews: (a) J. R. Andreatta, B. A. McKeown, T. B. Gunnoe, *J. Organomet. Chem.* **2011**, *696*, 305–315; (b) N. A. Foley, J. P. Lee, Z. Ke, T. B. Gunnoe, T. R. Cundari, *Acc. Chem. Res.* **2009**, *42*, 585–597; (c) F. Kakiuchi, *Top. Organomet. Chem.* **2007**, *24*, 1–33; (d) C. Nevado, A. M. Echavarren, *Synthesis* **2005**, 167–182; (e) F. Kakiuchi, N. Chatani, *Adv. Synth. Catal.* **2003**, *345*, 1077–1101; (f) C. Jia, T. Kitamura, Y. Fujiwara, *Acc. Chem. Res.* **2001**, *34*, 633–639.

28   L. Ackermann, *Acc. Chem. Res.* **2014**, *47*, 281–295.

29   S. I. Kozhushkov, L. Ackermann, *Chem. Sci.* **2013**, *4*, 886−896.

30   V. S. Thirunavukkarasu, S. I. Kozhushkov, L. Ackermann, *Chem. Commun.* **2014**, *50*, 29–39.

more expensive palladium[31] or rhodium complexes.[32]

Considering the importance for step-economical syntheses of bioactive heterocycles, Ackermann and coworkers hence set out to develop ruthenium-catalyzed oxidative annulations of alkynes **38** through C−H and N−H bond cleavages for isoquinolones **39** synthesis (Scheme 10).[33] Notably, preliminary studies[33a] revealed [RuCl$_2$(*p*-cymene)]$_2$ (**15**) to be optimal among a variety of ruthenium complexes, while Cu(OAc)$_2$ H$_2$O was found to be the terminal oxidant of choice.[33a] The optimized ruthenium(II) catalyst **15** proved to be tolerant to valuable electrophilic functional groups, and was found to be applicable to benzamides **37** with different substituents on nitrogen atom. Furthermore, the annulation process proceeded with excellent regioselectivity with unsymmetrical internal alkynes.[33]
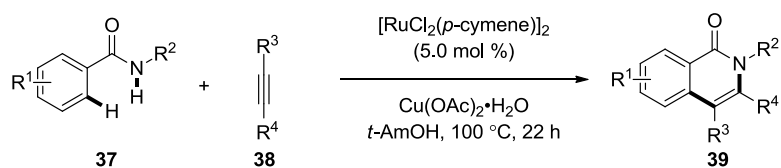
Scheme 10 Ruthenium-catalyzed oxidative annulation *via* C−H/N−H bond cleavage

Based on mechanistic studies, the ruthenium(II)-catalyzed oxidative annulation was proposed to proceed by an initial carboruthenation *via* acetate-assisted C−H bond cleavage,[8,28] followed by migratory insertion, C−N bond-forming reductive elimination, and final reoxidation of the ruthenium(0) intermediate (Scheme 11).[33a] Additional support for this proposed mechanism was recently provided through the independent synthesis and isolation of key intermediates by the groups of Li and Wang as well as Dixneuf.[34]

[31]   A review on palladium-catalyzed oxidative annulation of alkynes: C. Zhu, R. Wang, J. R. Falck, *Chem. Asian J.* **2012**, *7*, 1502–1514 and references cited therein.

[32]   Selected reviews on rhodium-catalyzed oxidative annulation of alkynes: (a) G. Song, F. Wang, X. Li, *Chem. Soc. Rev.* **2012**, *41*, 3651–3678; (b) F. W. Patureau, J. Wencel-Delord, F. Glorius, *Aldrichimica Acta* **2012**, *45*, 31-41; (c) T. Satoh, M. Miura, *Chem.–Eur. J.* **2010**, *16*, 11212–11222 and references cited therein.

[33]   (a) L. Ackermann, A. V. Lygin, N. Hofmann, *Angew. Chem. Int. Ed.* **2011**, *50*, 6379–6382; (b) M. Deponti, S. I. Kozhushkov, D. S. Yufit, L. Ackermann, *Org. Biomol. Chem.* **2013**, *11*, 142–148.

[34]   (a) B. Li, H. Feng, N. Wang, J. Ma, H. Song, S. Xu, B. Wang, *Chem. –Eur. J.* **2012**, *18*, 12873–12879; (b) B. Li, T. Roisnel, C. Darcel, P. H. Dixneuf, *Dalton Trans.* **2012**, *41*, 10934–10937.
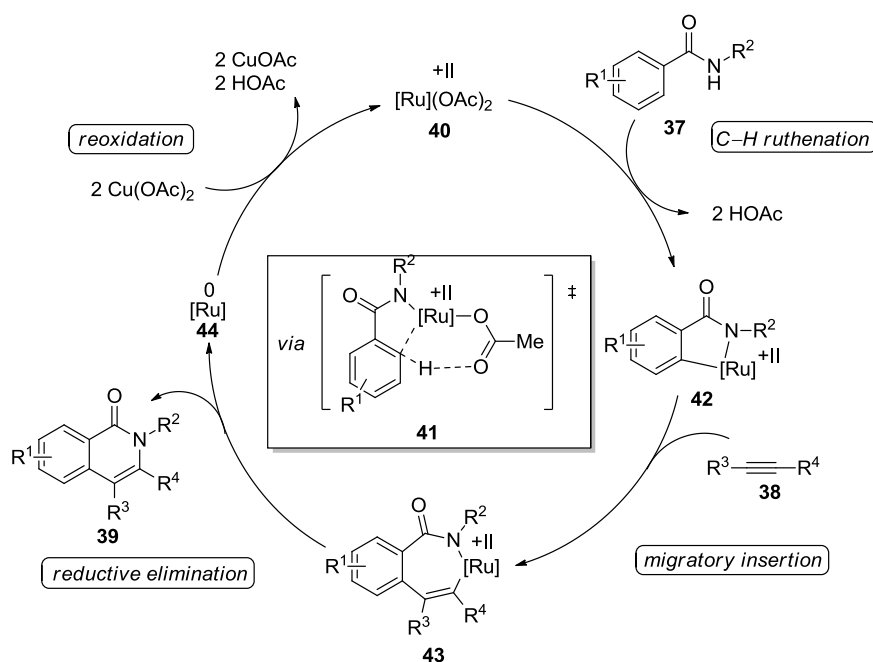
Scheme 11 Catalytic cycle for ruthenium-catalyzed oxidative annulation of alkynes

Subsequently, acrylamides **45** turned out to be competent substrates through alkenylic C−H bond activation with the same ruthenium(II) catalytic system (Scheme 12). Likewise, $Cu(OAc)_2$ H_2O as the oxidant led to the most efficient transformation, again being indicative of acetate assistance.[35]
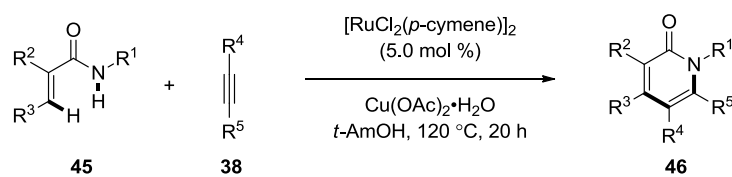
Scheme 12 Ruthenium-catalyzed synthesis of 2-pyridones **46**

Recently, Jeganmohan developed a route to isoquinolones **49** through ruthenium-catalyzed aerobic oxidative cyclization of (hetero)aromatic nitriles **47** with alkynes (Scheme 13).[36] Mechanistic studies showed an acetamide intermediate **48** was generated with AcOH in the presence of $Cu(OAc)_2$ H_2O prior to oxidative annulation with alkynes.

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[35] L. Ackermann, A. V. Lygin, N. Hofmann, *Org. Lett.* **2011**, *13*, 3278–3281.

[36] M. C. Reddy, R. Manikandan, M. Jeganmohan, *Chem. Commun.*, **2013**, *49*, 6060−6062.
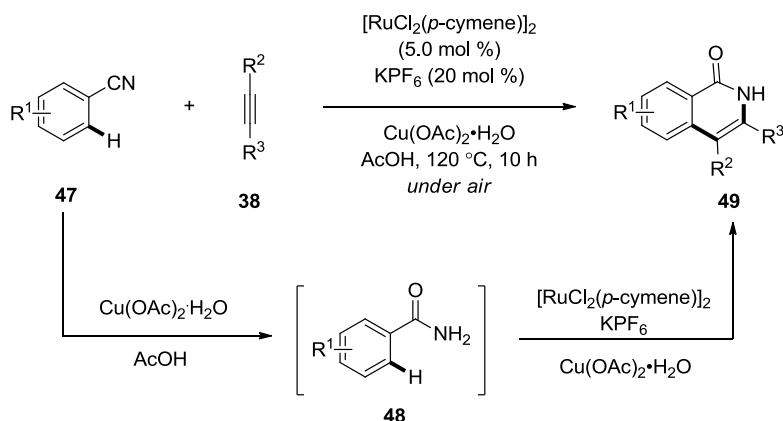
Scheme 13 Ruthenium-catalyzed oxidative cyclization of aromatic nitriles **47** with alkynes **38**

The C−H/N−H bond functionalization strategy was not restricted to arenes bearing electron-withdrawing directing groups. Indeed, the cationic ruthenium(II) complexes derived from KPF$_6$ facilitated oxidative C−H bond functionalizations with electron-rich anilines **50** through acetate assistance (Scheme 14).[37a] A notable feature of this protocol was represented by the use of substrates bearing easily removable directing groups.[38] The C−H/N−H bond cleavages occurred most efficiently in water as a green reaction medium and provided general access to indole derivatives **51**.
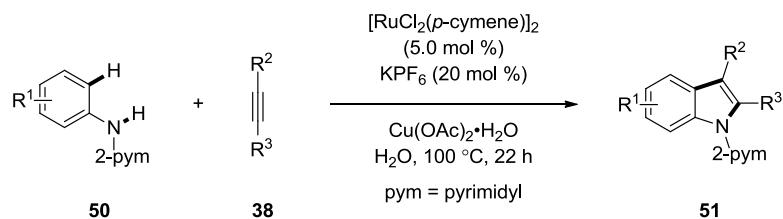
Scheme 14 Oxidative annulation with electron-rich anilines **50** bearing a removable directing group

Furthermore, Ackermann and coworkers found the cationic ruthenium(II) complexes derived from AgSbF$_6$ additives allowed for highly efficient oxidative annulations of aryl- and alkyl-substituted alkynes **38** by 5-aryl-1*H*-pyrazoles **52** under aerobic conditions (Scheme 15).[39]
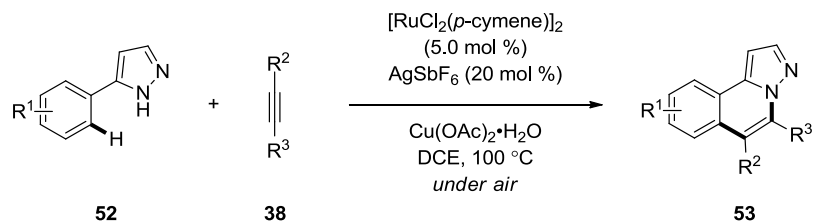
Scheme 15 Oxidative annulation of alkynes **38** by 5-aryl-1*H*-pyrazoles **52**

37 (a) L. Ackermann, A. V. Lygin, *Org. Lett.* **2012**, *14*, 764–767; (b) for nickel-catalyzed alkyne annulation by anilines, see: W. Song, L. Ackermann, *Chem. Commun.* **2013**, *49*, 6638–6640.

38 Representative reviews on removable directing groups: (a) C. Wang, Y. Huang, *Synlett* **2013**, *24*, 145–149; (b) G. Rousseau, B. Breit, *Angew. Chem. Int. Ed.* **2011**, *50*, 2450–2494.

39 W. Ma, K. Graczyk, L. Ackermann, *Org. Lett.* **2012**, *14*, 6318–6321.

Very recently, the same group developed a ruthenium-catalyzed oxidative annulation of alkynes by ketimines **54** to furnish exo-methylene-1,2-dihydroisoquinolines **55**. Particularly, carboxylate-assisted ruthenium(II) catalysis proved to be key to success for the synthesis of diversely decorated products in high yields (Scheme 16).[40]
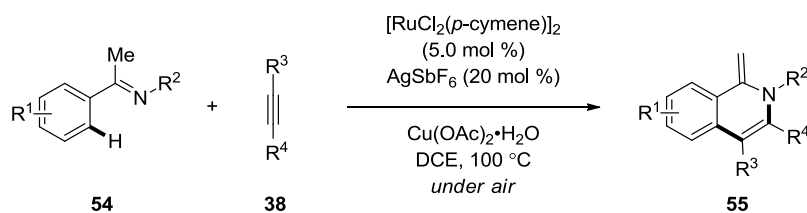
Scheme 16 Oxidative annulation of alkynes **38** by ketimines **54**

Besides this, oxidative annulations of alkynes **38** through C−H/O−H bond cleavages were independently achieved with ruthenium(II) complexes by the research groups of Ackermann and Jaganmohan (Scheme 17).[41,42] Likewise, a cationic ruthenium(II) catalyst derived from KPF_6 or $AgSbF_6$ was employed for the synthesis of isocoumarins **57** through oxidative annulations of alkynes by (hetero)aromatic acids **56**. Detailed optimization studies revealed acetates to be crucial additives and provided support for a kinetically relevant C−H bond ruthenation.[41]
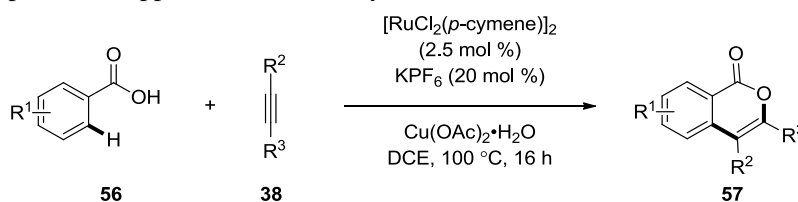
Scheme 17 Synthesis of isocoumarins **57** by Ackermann

Moreover, acetate assistance was found to be key to success for ruthenium(II)-catalyzed oxidative alkyne annulations with hydroxyl groups.[43] Thus, hydroxyl-assisted C−H bond functionalizations provided step-economical access to diversely decorated fluorescent coumarins **59** and quinolin-2-ones **61**, respectively (Scheme 18).
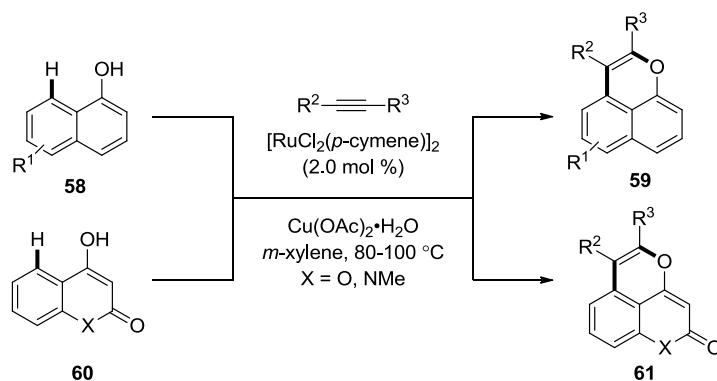
Scheme 18 Hydroxyl-directed alkyne annulations

40   J. Li, L. Ackermann, *Tetrahedron* **2014**, *70*, doi: 10.1016/j.tet.2013.10.003.
41   L. Ackermann, J. Pospech, K. Graczyk, K. Rauch, *Org. Lett.* **2012**, *14*, 930–933.
42   R. K. Chinnagolla, M. Jeganmohan, *Chem. Commun.* **2012**, *48*, 2030–2032.
43   V. S. Thirunavukkarasu, M. Donati, L. Ackermann, *Org. Lett.* **2012**, *14*, 3416–3419.

Along with the rapid development on C−H/N−H and C−H/O−H bond functionalizations, Lee developed the first ruthenium-catalyzed oxidative cyclization of phosphonic acid monoesters or phosphinic acids **62** with alkynes for the synthesis of phosphaisocoumarins **63** under aerobic conditions. A variety of arylphosphonic acid monoesters as well as arylphosphinic acids bearing electron-donating and -withdrawing groups were efficiently converted under aerobic reaction conditions (Scheme 19).[44]
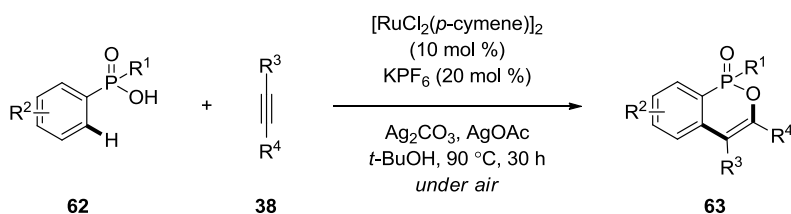
Scheme 19 Ruthenium-catalyzed annulation of alkynes **38** with phosphonic acid derivatives **62**

Furthermore, Jeganmohan developed a highly regioselective ruthenium-catalyzed cyclization of aromatic ketones **64** with alkynes. This methodology offers a simple and mild method for the synthesis of indenols **65** and benzofulvenes **66** in a highly regioselective manner. Herein, the amount of silver salt determined the nature of the product: In the presence of 8 mol % of $AgSbF_6$ favored the formation of indenols **65** (Scheme 20, left), whereas with 20 mol % of $AgSbF_6$ benzofulvenes **66** were obtained (Scheme 20, right).[45]
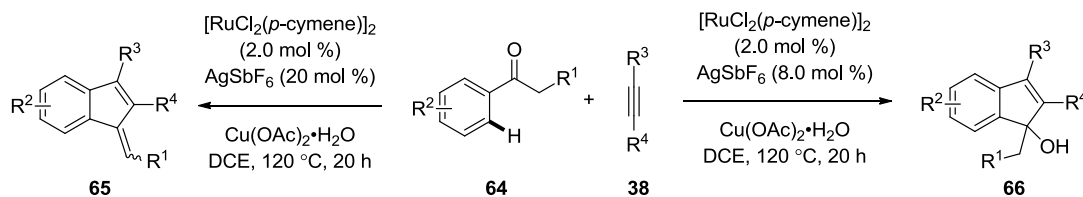
Scheme 20 Ketone-directed alkyne annulations

Lam recently reported a catalytic alkyne oxidative annulation by 2-aryl-1,3-dicarbonyl compounds **67** involving the (formal) functionalization of $C(sp^3)$−H bond and $C(sp^2$−H) bond (Scheme 21a). Notably, this ruthenium-catalyzed process led to the synthesis of indenes **69** with the formation of an all-carbon quaternary center.[46a] In analogy, Luan's intermolecular annulation reactions of 1-aryl-2-naphthols **70** with alkynes proceeded efficiently in the presence of the same ruthenium catalyst to generate spirocyclic compounds **71** by sequential cleavage of the $C(sp^2)$–H bond, migratory insertion of the alkyne, and dearomatization of the naphthyl ring (Scheme 21b).[47]

44 Y. Park, I. Jeon, S. Shin, J. Min, P. H. Lee, *J. Org. Chem.* **2013**, *78*, 10209−10220.

45 R. K. Chinnagolla, M. Jeganmohan, *Eur. J. Org. Chem.* **2012**, 417−423.

46 (a) S. R. Chidipudi, I. Khan, H. W. Lam, *Angew. Chem. Int. Ed.* **2012**, *51*, 12115–12119; (b) for similar research with palladium catalysis, see: J. D. Dooley, S. R. Chidipudi, H. W. Lam, *J. Am. Chem. Soc.* **2013**, *135*, 10829−10836.

47 J. Nan, Z. Zuo, L. Luo, L. Bai, H. Zheng, Y. Yuan, J. Liu, X. Luan, Y. Wang, *J. Am. Chem. Soc.* **2013**, *135*, 17306–17309.

a)

67   **68**   **69**

b)

70   **38**   **71**
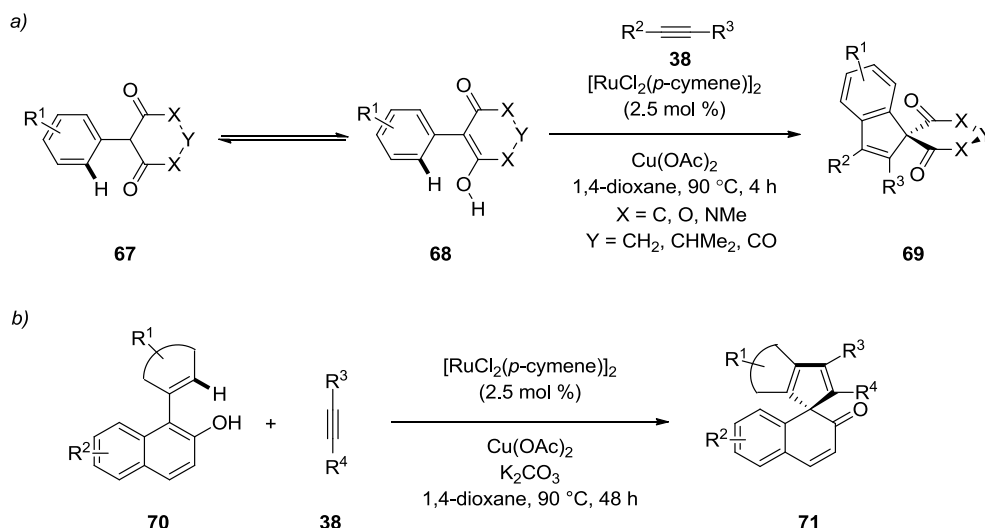
Scheme 21 Ruthenium-catalyzed carbocycles by (formal) C(sp^3)−H/C(sp^2)−H bond cleavage

However, the success of the above-discussed ruthenium(II)-catalyzed annulations always relied on the use of an external oxidant in stoichiometric or cocatalytic amounts (*vide supra*). Thus, Cu(OAc)$_2$ H$_2$O proved to be essential for these transformations, since it not only acted as the (co)oxidant but also served as the source of acetate for the carboxylate-assisted C−H bond activation step. Conversely, an alternative strategy was viable through the use of substrates bearing N−O bonds as "internal"[48] oxidants.

Herein, *N*-methoxybenzamides and free hydroxamic acid **72** were utilized by Ackermann and Fenner for highly selective syntheses of isoquinolones **49** in the absence of an external oxidant under notably mild reaction conditions (Scheme 22).[49] Remarkably, cocatalytic amounts of carboxylates were found to be indispensable for achieving efficient C−H bond functionalizations, with optimal results being accomplished with KO$_2$CMes as the co-catalyst and H$_2$O as the reaction medium.[49] Meanwhile, an alternative protocol by Li and Wang employed NaOAc as the additive in MeOH as the solvent,[50] which was also rationalized in terms of acetate-assisted C−H bond ruthenation.

72   **38**   **49**
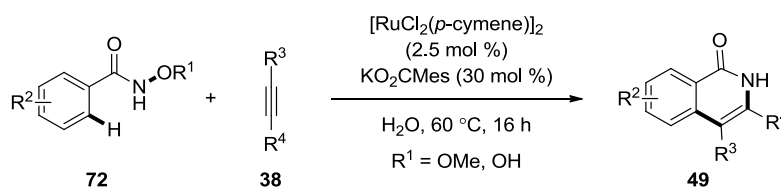
Scheme 22 Synthesis of isoquinolones **49** by C−H/N−O bond cleavages

In analogy, this "internal" oxidant approach set the stage for an extension to the synthesis of isoquinolines **74** (Scheme 23).[51,52] Thus, ketoximes **73** were selectively converted, with base

48   F. W. Patureau, F. Glorius, *Angew. Chem., Int. Ed.* **2011**, *50*, 1977–1979.

49   L. Ackermann, S. Fenner, *Org. Lett.* **2011**, *13*, 6548–6551.

50   B. Li, H. Feng, S. Xu, B. Wang, *Chem. –Eur. J.* **2011**, *17*, 12573–12577.

51   C. Kornhaaß, J. Li, L. Ackermann, *J. Org. Chem.* **2012**, *77*, 9190–9198.

52   (a) R. K. Chinnagolla, S. Pimparkar, M. Jeganmohan, *Org. Lett.* **2012**, *14*, 3032–3035; (b) see also: K. Parthasarathy, N. Senthilkumar, J. Jayakumar, C.-H. Cheng, *Org. Lett.* **2012**, *14*, 3478–3481; (c) P. Villuendas, E. P. Urriobeitia, *J. Org. Chem.* **2013**, *78*, 5254–5263.

assistance proving to be essential for the dehydrative alkyne annulation to occur in an efficient manner.[51]
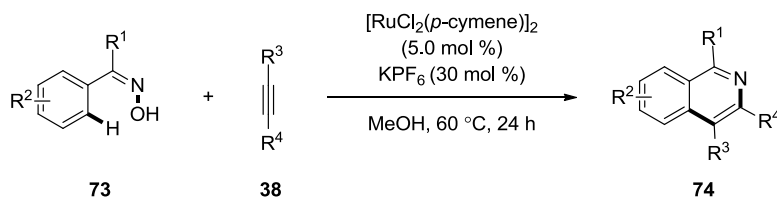
Scheme 23 Synthesis of isoquinolines **74** by dehydrative alkyne annulations

1.3 Ruthenium-Catalyzed Direct Oxidative Alkenylation of Arenes

Styrene derivatives are useful intermediates in synthetic organic chemistry and represent key structural motifs in natural products as well as in medicinal chemistry.[53] Conventional transition metal-catalyzed cross-coupling reactions,[3] such as the Mizoroki–Heck reaction,[54] have matured to being reliable tools for the preparation of styrene derivatives (Scheme 24a). Besides, alkenylation *via* transmetallation employing stoichiometric amounts of palladium chloride and organomercury, -tin, or -lead arenes *in lieu* of aryl halides were also reported (Scheme 24b).[3,54] However, the Mizoroki–Heck reaction is accompanied by the formation of a stoichiometric amount of potentially hazardous halide salt and transmetallation reactions always require organometallic nucleophilic reagents, which are, however, often not commercially available or are relatively expensive.

In contrast, the catalytic oxidative dehydrogenative alkenylation *via* a twofold C–H bond activation approach, as initially demonstrated by Fujiwara and Moritani,[55] presents a powerful tool for the synthesis of styrene derivatives (Scheme 24c).[56] Importantly, this approach is not only advantageous with respect to the overall minimization of byproduct formation (atom-economy),[5b,c] but also allows for significantly reducing the number of required reaction steps (step-economy).[5a] Subsequently, a variety of synthetically useful protocols for palladium-catalyzed direct oxidative couplings between arenes and alkenes have been achieved by *inter alia* Miura and Satoh, as well as Yu.[56] Efficient and selective rhodium catalysts have also been developed in recent years.[32]

[53]   (a) M. Sova, *Mini-Rev. Med. Chem.* **2012**, *12*, 749–767; (b) B. S. Siddiqui, H. Aslan, S. Begus, S. T. Ali, *Nat. Prod. Res.* **2007**, *21*, 736–741.

[54]   *The Mizoroki–Heck Reaction*, M. Oestreich, ed.; Wiley, Chichester, **2009**.

[55]   (a) I. Moritani, Y. Fujiwara, *Tetrahedron Lett.* **1967**, *8*, 1119–1122; (b) Y. Fujiwara, I. Moritani, M. Matsuda, *Tetrahedron* **1968**, *24*, 4819–4824.

[56]   Reviews: (a) L. Zhou, W. Lu, *Chem. –Eur. J.* **2014**, *20*, 634–642; (b) J. Le Bras, J. Muzart, *Chem. Rev.* **2011**, *111*, 1170–1214; (c) B. Karimi, H. Behzadnia, D. Elhamifar, P. F. Akhavan, F. K. Esfahani, *Synthesis* **2010**, 1399–1427; (d) M. Wasa, K. M. Engle, J.-Q. Yu, *Isr. J. Chem.* **2010**, *50*, 605–616.
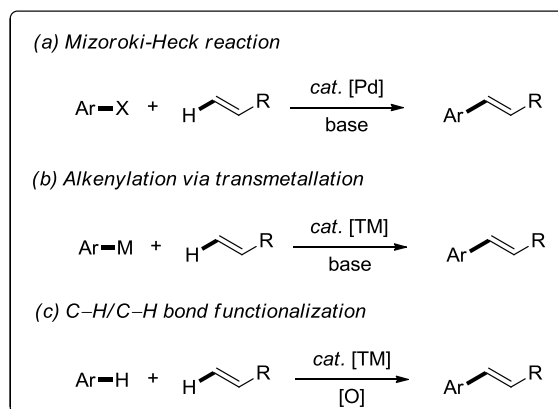
Scheme 24 Strategies for streamlining of styrene synthesis

However, less expensive ruthenium complexes have only recently been exploited as catalysts for oxidative C–H bond alkenylations on arenes, starting from the work by Milstein and coworkers in 2001 (Scheme 25).[57] According to this protocol, styrene derivatives **77** were obtained from substituted arenes **75**. Unfortunately, major limitations of this protocol were represented by the low reactivity of unactivated alkenes as well as the poor site-selectivities with substituted arenes.

77a
34% (*p/m/o* = 1/2/0)

77b
41%

77c
44% (*p/m/o* = 1/1.6/0)

77d
47% (*p/m/o* = 1/1.3/1.1)

77e
3%

77f
4% (*p/m/o* = 1/1.6/0)
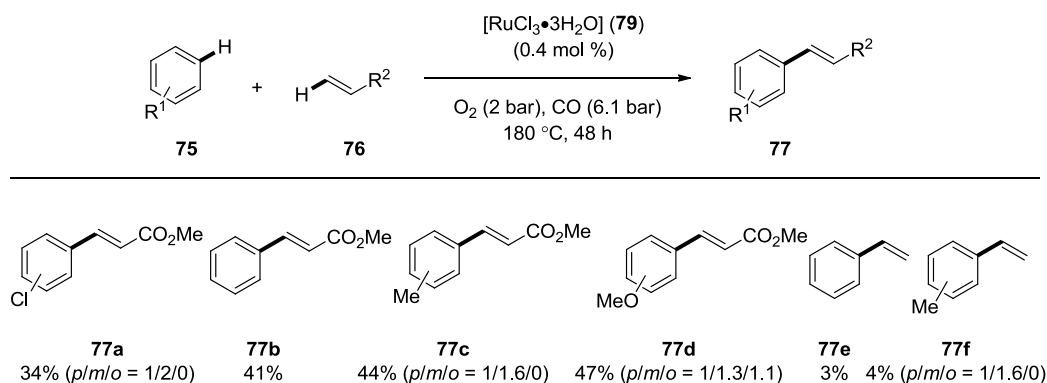
Scheme 25 Ruthenium-catalyzed direct alkenylations with simple arenes **75**

The low selectivities observed in reactions of simple arenes were successfully addressed with the aid of Lewis-basic functional groups. Thus, a cationic ruthenium hydride complex **80** enabled highly site-selective oxidative C–H bond alkenylations of benzamides **78** (Scheme 26), as described by Yi and coworkers.[58a] Since an external oxidant was not employed, an excess of the alkene **79** as well as the newly formed alkenylated benzamide **81** served as the hydrogen scavenger. Therefore, the products **81** were unfortunately contaminated with hydrogenated benzamides **82**.

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57   H. Weissman, X. Song, D. Milstein, *J. Am. Chem. Soc.* **2001**, *123*, 337–338.

58   (a) K.-H. Kwon, D. W. Lee, C. S. Yi, *Organometallics* **2010**, *29*, 5748–5750; (b) C. S. Yi, D. W. Lee, *Organometallics* **2009**, *28*, 4266−4268.
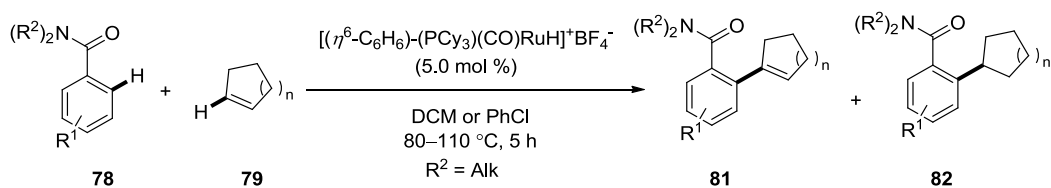
Scheme 26 Direct oxidative alkenylation of benzamides **78** with unactivated alkenes **79**

The major breakthrough on the ruthenium-catalyzed oxidative alkenylaltions with directing groups was achieved by *inter alia* Ackermann as well as Miura and Satoh in recent years.[29]

In 2011, Ackermann and Pospech disclosed the ruthenium(II)-catalyzed oxidative C–H bond alkenylation of benzoic acids **56** to smoothly proceed in water with Cu(OAc)$_2$ H$_2$O as the oxidant (Scheme 27).[59] Yet, the expected alkenylated benzoic acids **84** were not isolated, but the alkenylation products **84** immediately underwent a subsequent intramolecular oxa-Michael reaction, affording isobenzofuran-1(3*H*)-ones **85** in high yields. Experimental studies with isotopically labelled substrates suggested a kinetically relevant C–H bond ruthenation through acetate assistance in the transition state.[59]
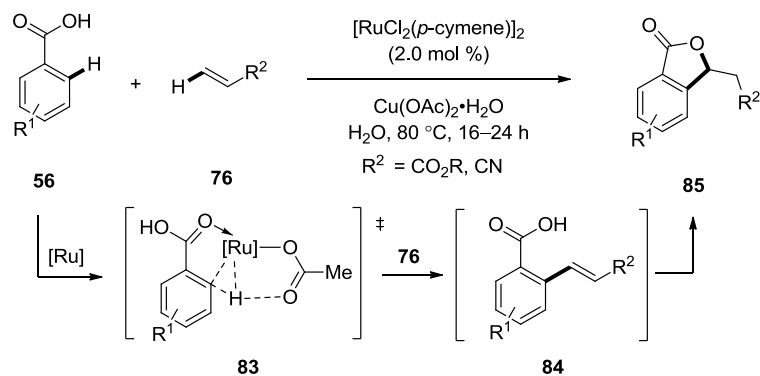
Scheme 27 Ruthenium-catalyzed oxidative alkenylation of benzoic acids **56** in water

Satoh and Miura reported on the use of a cationic ruthenium catalyst, *in situ* generated from [RuCl$_2$(*p*-cymene)]$_2$ and AgSbF$_6$, for oxidative alkenylations of benzamides **78** (Scheme 28).[60a] Notably, the reaction did not proceed in the absence of AgSbF$_6$. Besides, Loh developed a ruthenium catalytic system with KPF$_6$ as the efficient additive for the direct cross-coupling of acrylamides with electron-deficient alkenes forming (*Z,E*)-dienamides.[60b]
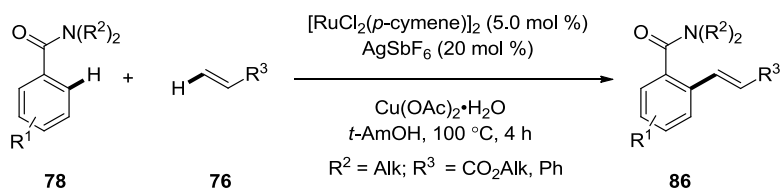
Scheme 28 Ruthenium-catalyzed oxidative alkenylation of benzamides **78** with AgSbF$_6$ as the additive

Alternatively, ruthenium-catalyzed C–H bond alkenylations can also be realized with

[59] L. Ackermann, J. Pospech, *Org. Lett.* **2011**, *13*, 4153–4155.
[60] (a) Y. Hashimoto, T. Ortloff, K. Hirano, T. Satoh, C. Bolm, M. Miura, *Chem. Lett.* **2012**, *41*, 151–153; (b) J. Zhang, T.-P. Loh, *Chem. Commun.* **2012**, *48*, 11232–11234; (c) for a ruthenium-catalyzed amide directed *ortho*-C−H alkylation, see: J. Qi, L. Huang, Z. Wang, H. Jiang, *Org. Biomol. Chem.* **2013**, *11*, 8009–8013.

pre-functionalized starting materials bearing an "internal" oxidizing directing group.[48] Notably, the reactions with acrylates **76** resulted in C–H bond alkenylations of methoxybenzamides **72**, affording olefinated benzamides **87** (Scheme 29).[61]
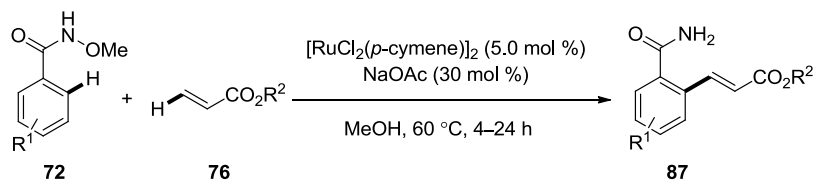
Scheme 29 Ruthenium-catalyzed C−H bond alkenylation with an "internal" oxidazing directing group

With the success of chelation-assisted alkenylations on benzamides, analogous ruthenium-catalyzed oxidative functionalizations of weakly coordinating esters has until recently proven elusive. The research groups of Ackermann[62] and Jeganmohan[63] disclosed reaction conditions for the versatile oxidative direct functionalization of aromatic esters **88** (Scheme 30). Thus, a catalytic system comprising [RuCl$_2$(p-cymene)]$_2$, AgSbF$_6$ and cocatalytic amounts of Cu(OAc)$_2$ H$_2$O utilizing air as the ideal terminal oxidant allowed for efficient aerobic C–H bond alkenylations in a highly site-selective fashion.[62]
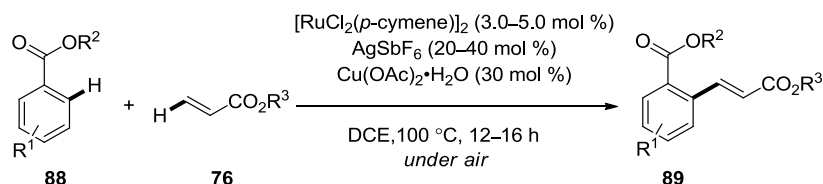
Scheme 30 Ruthenium-catalyzed oxidative alkenylations of weakly coordinating aromatic esters **88**

This catalytic system was also found to be effective for alkenylations of aromatic ketones and benzaldehydes **90** (Scheme 31).[64,65] Thus, the ruthenium-catalyzed C–H bond functionalization provided alkenylated products **91** in moderate to good yields with acrylates and styrenes.
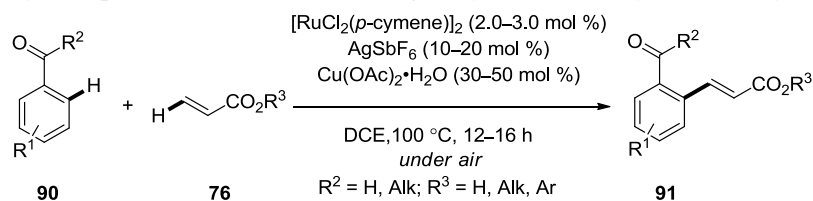
Scheme 31 Ruthenium-catalyzed oxidative alkenylation of phenones and benzaldhydes **90**

Moreover, the ruthenium catalytic system enabled oxidative alkenylations of electron-rich aryl carbamates **92** with weakly coordinating and removable directing groups[38] in a chemo- and

[61]   B. Li, J. Ma, N. Wang, H. Feng, S. Xu, B. Wang, *Org. Lett.* **2012**, *14*, 736–739.

[62]   K. Graczyk, W. Ma, L. Ackermann, *Org. Lett.* **2012**, *14*, 4110–4113.

[63]   K. Padala, S. Pimparkar, P. Madasamy, M. Jeganmohan, *Chem. Commun.* **2012**, *48*, 7140–7142.

[64]   K. Padala, M. Jeganmohan, *Org. Lett.* **2011**, *13*, 6144–6147.

[65]   K. Padala, M. Jeganmohan, *Org. Lett.* **2012**, *14*, 1134–1137.

site-selective fashion, affording diversely decorated phenol derivatives **93** (Scheme 32).[66a]
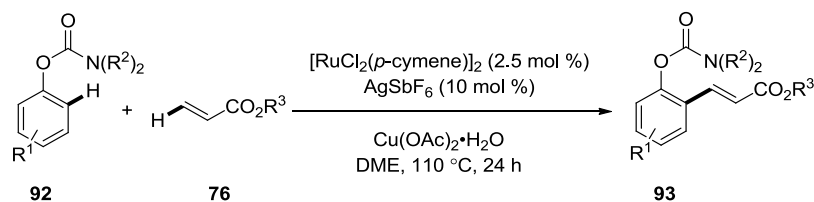
Scheme 32 Ruthenium-catalyzed oxidative alkenylation of aryl carbamates **92**

Recently, the ruthenium(II)-promoted oxidative alkenylations of phenols **94** bearing easily cleavable directing groups[38] was reported (Scheme 33).[67] The double C−H functionalization process proceeded with excellent chemo-, site-, and diastereoselectivities in an aerobic fashion.
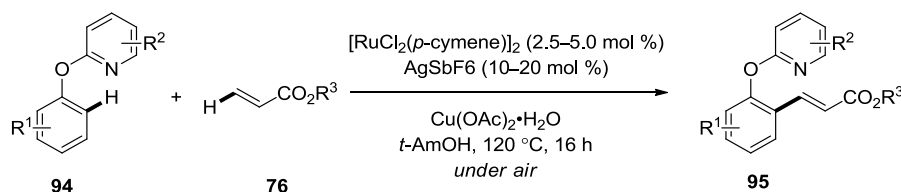
Scheme 33 Ruthenium(II)-catalyzed C−H alkenylations of arenes **94** with removable directing groups

Besides, Dixneuf and Bruneau reported on ruthenium-catalyzed oxidative alkenylation of *N*-phenylpyrazole (**96**) with acrylates and acrylamides (Scheme 34).[68] Unfortunately, in many cases the products **97** were contaminated with by-products **98** generated through dehydrogenative homocoupling of substrates **96**.
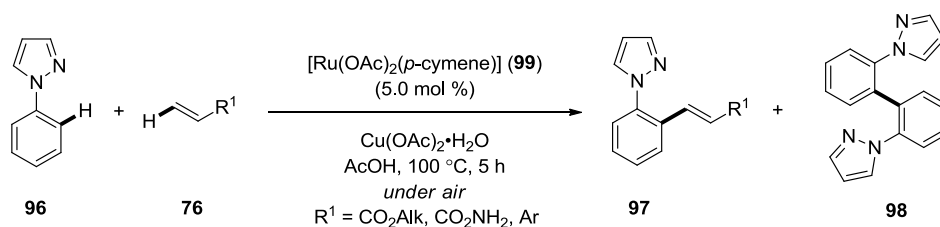
Scheme 34 Ruthenium-catalyzed oxidative alkenylation of *N*-phenylpyrazole **96**

However, employing [RuCl$_2$(*p*-cymene)]$_2$ complex instead of the above mentioned [Ru(OAc)$_2$(*p*-cymene)] analog, along with a higher loading of Cu(OAc)$_2$ H$_2$O, efficiently suppressed the competitive homocoupling reaction.[69] Hence, alkenylations of 2-phenylazoles **100** with [RuCl$_2$(*p*-cymene)]$_2$ in *t*-AmOH as the solvent was achieved, albeit with a significantly lower yields (Scheme 35).[60a]

[66] (a) J. Li, C. Kornhaaß, L. Ackermann, *Chem. Commun.* **2012**, *48*, 11343–11345; (b) for subsequent report: M. C. Reddy, M. Jeganmohan, *Eur. J. Org. Chem.* **2013**, 1150−1157; (c) B. Li, J. Ma, Y. Liang, N. Wang, S. Xu, H. Song, B. Wang, *Eur. J. Org. Chem.* **2013**, 1950–1962; (d) for hydroalkenylation of alkynes, see: M. C. Reddy, M. Jeganmohan, *Chem. Commun.* **2013**, *49*, 481−483.

[67] W. Ma, L. Ackermann, *Chem.−Eur. J.* **2013**, *19*, 13925–13928.

[68] P. B. Arockiam, C. Fischmeister, C. Bruneau, P. H. Dixneuf, *Green Chem.* **2011**, *13*, 3075–3078.

[69] Y. Hashimoto, T. Ueyama, T. Fukutani, K. Hirano, T. Satoh, M. Miura, *Chem. Lett.* **2011**, *40*, 1165–1166.
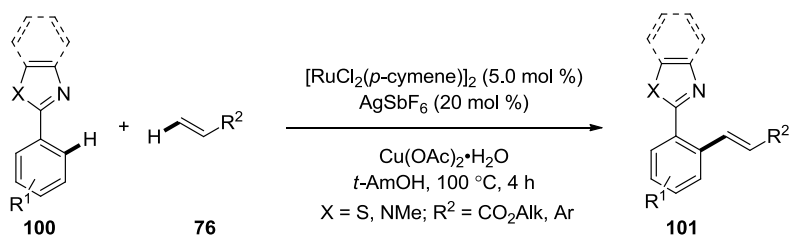
Scheme 35 Ruthenium-catalyzed oxidative alkenylation of 2-phenylazoles **100**

Furthermore, monoalkenylations of aromatic C–H bonds directed by an oxazoline group were found by the same group to take place efficiently using [RuCl$_2$(p-cymene)]$_2$ along with rac-BNPAN (**104**) as an efficient ligand (Scheme 36).[70]
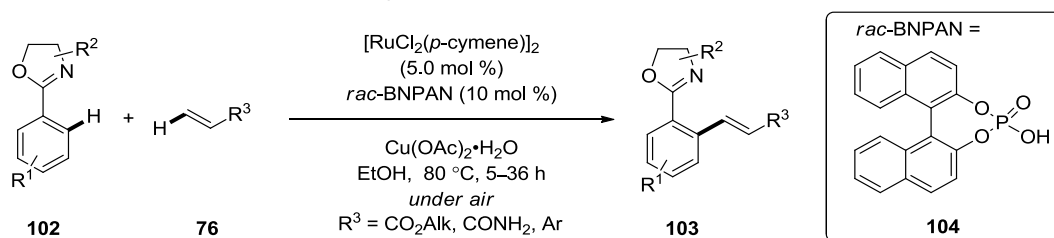
Scheme 36 Ruthenium-catalyzed oxidative alkenylation of 2-phenyloxazolines **102**

Essentially, ruthenium-catalyzed alkenylations of heteroarenes **105** with various directing groups were achieved with the catalytic systems described above, albeit with different catalytic efficacies.[71,72] The experimental results are summarized in Scheme 37 and highlight various esters, benzamides, aldehydes and carbamates could be employed for chemo- and site-selective ruthenium-catalyzed twofold C–H bond functionalizations.

[70] B. Li, K. Devaraj, C. Darcel, P. Dixneuf, *Green Chem.* **2012**, *14*, 2706–2709.

[71] T. Ueyama, S. Mochida, T. Fukutani, K. Hirano, T. Satoh, M. Miura, *Org. Lett.* **2011**, *13*, 706–708.

[72] (a) B. Li, J. Ma, W. Xie, H. Song, S. Xu, B. Wang, *J. Org. Chem.* **2013**, *78*, 9345−9353; (b) L.-Q. Zhang, S. Yang, X. Huang, J. You, F. Sodirectng, *Chem. Commun.* **2013**, *49*, 8830−8832.

106a: 94% [71]   **106b**: 84% [71]   X = O (**106c**):   66% [71]   **106f**: 66% [61]   **106g**: 58% [61]

X = S (**106d**):   95% [71]

X = NMe (**106e**): 84% [71]

106h: 69% [65]   **106i**: 67% [65]   **106j**: 47% [62]   **106k**: 81% [63]   **106l**: 64% [63]

106m: 47% [63]   **106n**: 88% [72a]   **106o**: 56% [72a]
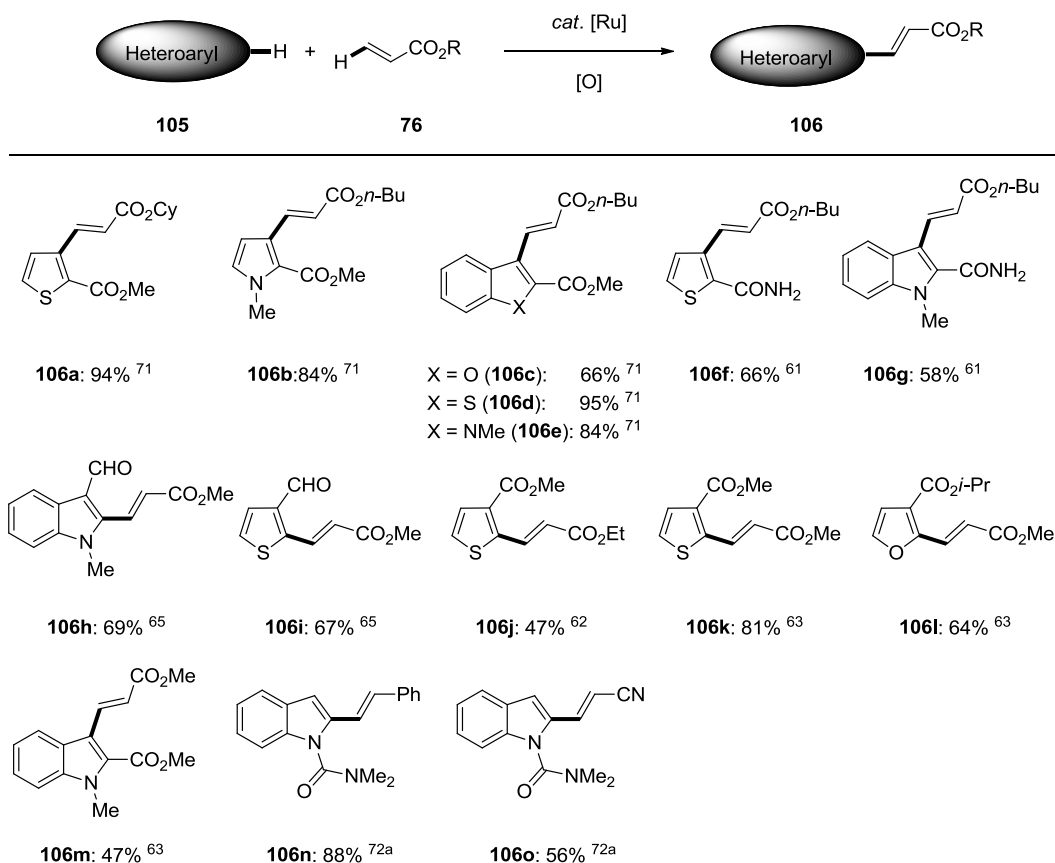
Scheme 37 Ruthenium-catalyzed oxidative alkenylation of substituted heteroarenes

1.4 Ruthenium-Catalyzed Direct Hydroarylations

1.4.1 Ruthenium-Catalyzed Direct Hydroarylations

As discussed above, the oxidative direct functionalization with unreactive C−H bonds is a powerful tool for the construction of C−C bonds in a step-economical fashion. On the other hand, the prospects to develop metal-catalyzed hydroarylation reactions are alternatively attractive due to their perfect atom economy, with notable progress being accomplished with versatile ruthenium catalysts.[27]

As early as 1986, Lewis reported the first *ortho*-selective hydroarylation of phenol (**107**) with alkenes catalyzed by the *ortho*-metalated ruthenium complex **110** (Scheme 38).[16]
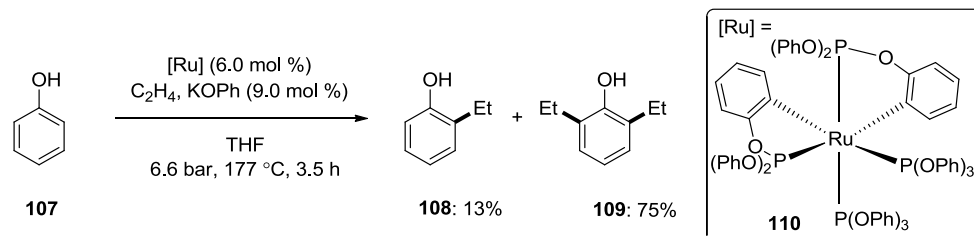
Scheme 38 Ruthenium-catalyzed direct C−H alkylation by Lewis

However, a major breakthrough in the ruthenium-catalyzed directed hydroarylations was achieved by Murai in 1993 (Scheme 39).[17] According to this protocol, chelation-assistance resulted in

highly site-selective C−H bond cleavage, leading to addition of aromatic ketone **90** to alkenes **111** with a C−C bond formation.[17]
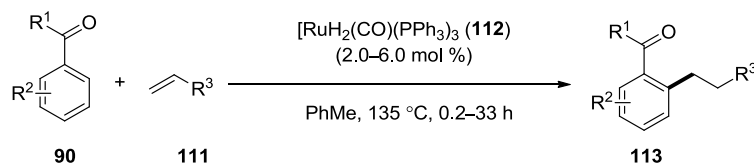
Scheme 39 Ruthenium-catalyzed direct C−H alkylation by Murai

Intensive mechanistic studies[73,74] on the Murai reaction showed that the initial formation of intermediate **117** *via* transition state **116**, subsequent coordination of alkene **111** and migratory insertion to the Ru–H bond are reversible (Scheme 40). Finally, reductive elimination of complex **119** delivers the target product **113** and regenerates the active ruthenium species **114**. Besides, isotopically labelled experiment with substrates suggested that a branched species **119'** is also probably formed, which, however, seems not to undergo reductive elimination, since no corresponding branched product was obtained.[74] Further studies[75] showed that the C−C bond formation is the rate determining step.
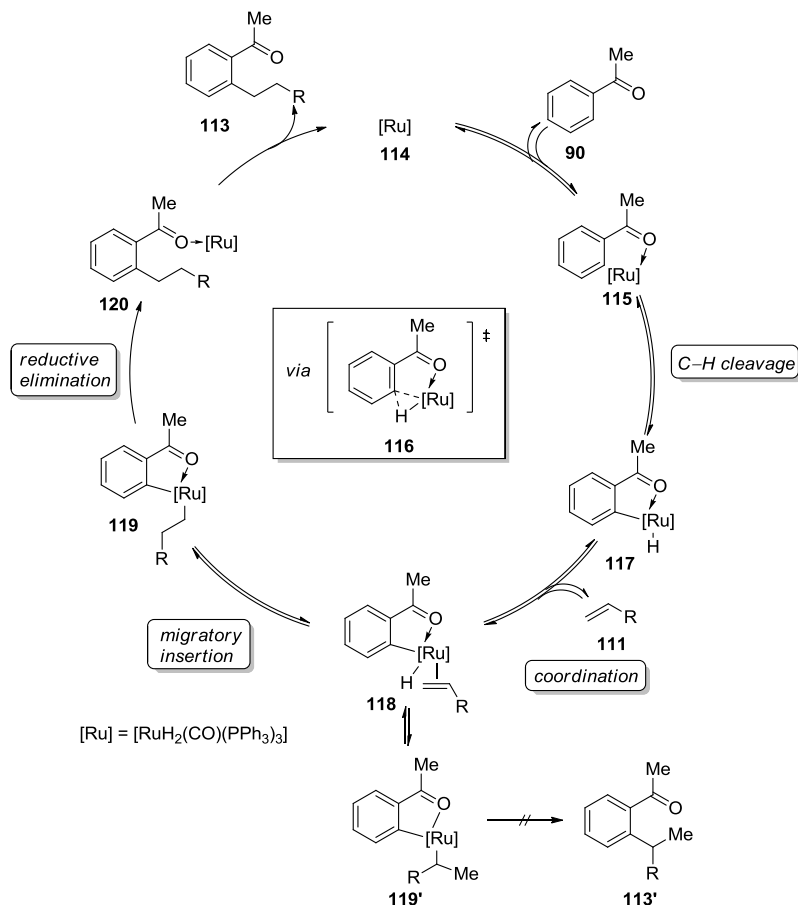
Scheme 40 Catalytic cycle for the Murai reaction

[73] F. Kakiuchi, H. Ohtaki, M. Sonoda, N. Chatani, S. Murai, *Chem. Lett.* **2001**, 918–919.

[74] F. Kakiuchi, T. Kochi, E. Mizushima, S. Murai, *J. Am. Chem. Soc.* **2010**, *132*, 17741–17750.

[75] (a) F. Kakiuchi, T. Sato, T. Tsujimoto, M. Yamauchi, N. Chatani, S. Murai, *Chem. Lett.* **1998**, 1053–1054; (b) T. Matsubara, N. Koga, D. G. Musaev, K. Morokuma, *J. Am. Chem. Soc.* **1998**, *120*, 12692–12693; (c) T. Matsubara, N. Koga, D. G. Musaev, K. Morokuma, *Organometallics* **2000**, *19*, 2318–2329.

In the following years,[76] Murai and coworkers extended the application of hydroarylations including replacement of the terminal alkenes **111** by acetylenes [77] and the use of esters,[78] imines,[79] oxazoline[80] and aldehydes[81] as efficient directing groups. Coinciding with Murai's alkylations of cyclic and acyclic α,β-enones, [82] Trost successfully applied the precatalyst [RuH$_2$(CO)(PPh$_3$)$_3$] (**114**) to the alkylation of acrylic acid esters.[83]

However, a major disadvantage of Murai's protocol is the air sensitivity of catalyst [RuH$_2$(CO)(PPh$_3$)$_3$] (**114**). This promoted Darses and Genet to develop a new hydroarylating system through the elegant *in situ* formation of catalyst [RuH$_2$(PPh$_3$)$_4$] (**121**) from [RuCl$_2$(*p*-cymene)]$_2$ (**15**) and sodium formate, in association with a phosphine ligand (Scheme 41).[84] This novel system showed high activity in the *ortho*-hydroarylations of tetralone and acetophenone **122** with active alkenes, such as vinylsilane and styrene derivatives **111** (Scheme 41).[84,85]
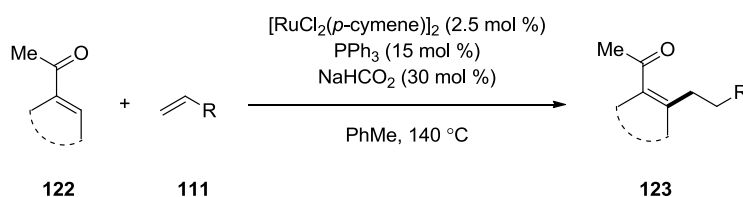
Scheme 41 Ruthenium-catalyzed direct C−H alkylation by Genet and Darses

Besides, Ackermann and coworkers achieved the hydroarylation of highly strained methylenecyclopropanes **124** by the combination of [RuCl$_2$(cod)]$_n$ (**125**) and XPhos, which furnished *anti*-Markovnikov products **126** with complete conservation of all cyclopropane rings (Scheme 42).[86]

[76] (a) F. Kakiuchi, T. Kochi, *Synthesis* **2008**, 3013−3039; (b) F. Kakiuchi, S. Murai, *Acc. Chem. Res.* **2002**, *35*, 826–834; (c) S. Murai, F. Kakiuchi, S. Sekine, Y. Tanaka, A. Kamatani, M. Sonoda, N. Chatani, *Pure Appl. Chem.* **1994**, *66*, 1527–1534; (d) S. Murai, N. Chatani, F. Kakiuchi, *Pure Appl. Chem.* **1997**, *69*, 589–594; (e) M. Sonoda, F. Kakiuchi, N. Chatani, S. Murai, *Bull. Chem. Soc. Jpn.* **1997**, *70*, 3117–3128.

[77] F. Kakiuchi, Y. Yamamoto, N. Chatani, S. Murai, *Chem. Lett.* **1995**, 681–682.

[78] M. Sonoda, F. Kakiuchi, A. Kamatani, N. Chatani, S. Murai, *Chem. Lett.* **1996**, 109–110.

[79] F. Kakiuchi, M. Yamauchi, N. Chatani, S. Murai, *Chem. Lett.* **1996**, 111–112.

[80] F. Kakiuchi, T. Sato, M. Yamauchi, N. Chatani, S. Murai, *Chem. Lett.* **1999**, 19–20.

[81] F. Kakiuchi, T. Sato, K. Igi, N. Chatani, S. Murai, *Chem. Lett.* **2001**, 386–387.

[82] (a) F. Kakiuchi, Y. Tanaka, T. Sato, N. Chatani, S. Murai, *Chem. Lett.* **1995**, 679–680; (b) T. Sato, F. Kakiuchi, N. Chatani, S. Murai, *Chem. Lett.* **1998**, 893–894.

[83] B. M. Trost, K. Imi, I. W. Davies, *J. Am. Chem. Soc.* **1995**, *117*, 5371–5372.

[84] (a) R. Martinez, R. Chevalier, S. Darses, J.-P. Genet, *Angew. Chem. Int. Ed.* **2006**, *45*, 8232–8235; (b) R. Martinez, M.-O. Simon, R. Chevalier, C. Pautigny, J.-P. Genet, S. Darses, *J. Am. Chem. Soc.* **2009**, *131*, 7887–7895.

[85] (a) R. Martinez, J.-P. Genet, S. Darses, *Chem. Commun.* **2008**, 3855–3857; (b) M.-O. Simon, R. Martinez, J.-P. Genet, S. Darses, *Adv. Synth. Catal.* **2009**, *351*, 153–157; (c) M.-O. Simon, R. Martinez, J.-P. Genet, S. Darses, *J. Org. Chem.* **2009**, 75, 208–210; (d) M.-O. Simon, J.-P. Genet, S. Darses, *Org. Lett.* **2010**, *12*, 3038–3041; (e) M.-O. Simon, G. Ung, S. Darses, *Adv. Synth. Catal.* **2011**, *353*, 1045–1048; (c) M.-O. Simon, S. Darses, *J. Org. Chem.* **2013**, 78, 9981–9985.

[86] (a) S. I. Kozhushkov, D. S. Yufit, L. Ackermann, *Org. Lett.* **2008**, *10*, 3409–3412; (b) L. Ackermann, S. I. Kozhushkov, D. S. Yufit, *Chem. –Eur. J.* **2012**, *18*, 12068–12077.
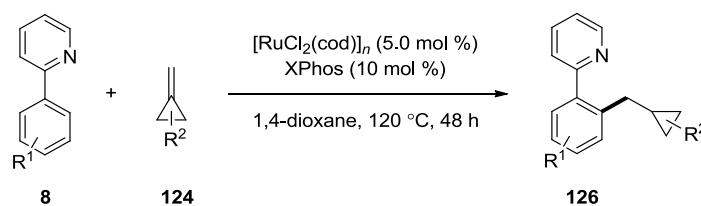
Scheme 42 Ruthenium-catalyzed hydroarylation of methylenecyclopropanes

Despite notable advances in the oxidative C–H bond functionalizations,[8] metal carboxylates were as of yet not exploited as cocatalytic additives for ruthenium-catalyzed hydroarylations. Very recently, Ackermann and co-workers reported on highly efficient carboxylate-assisted ruthenium-catalyzed hydroarylations of unactivated alkenes **111** and of methylenecyclopropanes **124** employing various (hetero)arenes **17** with ample scope (Scheme 43).[87]
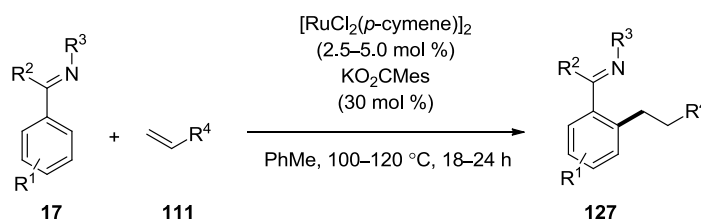
Scheme 43 Carboxylate-assisted ruthenium-catalyzed hydroarylations

Ruthenium-catalyzed hydroarylations of aromatic amides **129** with various α,β-unsaturated ketones **130** using a removable 8-aminoquinoline bidentate directing group[38,88] has been recently developed by Chatani (Scheme 44).[89] This methodology represented the first efficient utilization of active enones in the *ortho*-directed ruthenium-catalyzed addition of C–H bonds to C–C double bonds.
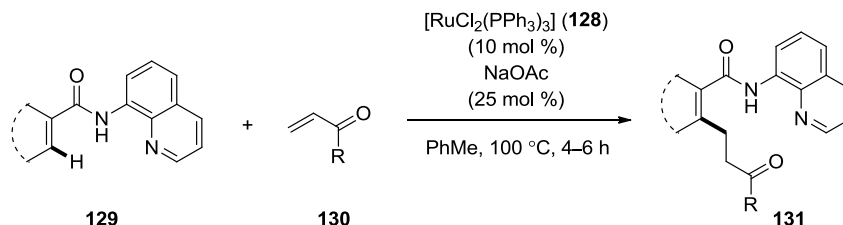
Scheme 44 Ruthenium-catalyzed *ortho*-hydroarylation with α,β-unsaturated ketones

Along with the obvious progress in the ruthenium-catalyzed chelation-assisted hydroarylations, Nakamura and Yoshikai independently reported on the first examples of cobalt-catalyzed

[87] (a) M. Schinkel, I. Marek, L. Ackermann, *Angew. Chem. Int. Ed.* **2013**, *52*, 3977–3980; (b) M. Schinkel, J. Wallbaum, S. I. Kozhushkov, I. Marek, L. Ackermann, *Org. Lett.* **2013**, *15*, 4482–4484.

[88] A recent review on catalytic functionalization of C(sp^2)−H and C(sp^3)−H bonds by using bidentate directing groups: G. Rouquet, N. Chatani, *Angew. Chem. Int. Ed.* **2013**, *52*, 11726–11743.

[89] (a) G. Rouquet, N. Chatani, *Chem. Sci.* **2013**, *4*, 2201–2208; selected examples of Rh(I) catalysis: (b) L. Yang, B. Qian, H. Huang, *Chem. –Eur. J.* **2012**, *18*, 9511−9515; (b) L. Yang, C. A. Correia, C.-J. Li, *Org. Biomol. Chem.* **2011**, *9*, 7176−7179; (c) S.-G. Lim, J.-A. Ahn, C.-H. Jun, *Org. Lett.* **2004**, *6*, 4687−4690.

hydroarylation of terminal alkenes[90,91] and internal alkynes[92] using ketimines, *N*-methyl amide and pyridine as directing groups. However, the employment of this catalytic system was limited by low tolerance of many important functional groups. Besides, the first manganese-catalyzed hydroarylation of terminal alkynes was recently reported.[93]

1.4.2 Ruthenium-Catalyzed Direct C(sp³)−H Alkylations

In contrast to the direct transformations of C(sp²)–H bonds, catalytic alkylations with alkenes involving the cleavage of the C(sp³)–H bonds[94] have unfortunately thus far met with limited success. In 1998, Jun achieved the first chelation-assisted C(sp³)−H alkylation on benzylamines **133** employing Ru₃(CO)₁₂ (**132**). However, only benzylic C−H bonds enabled addition to alkenes **134** under these conditions (Scheme 45).[95]
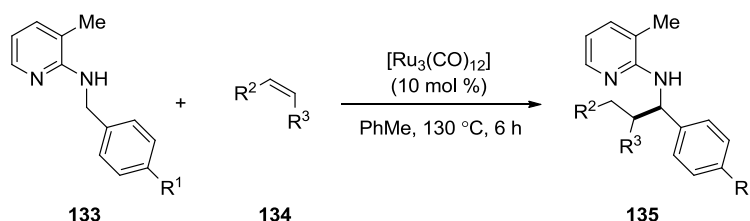
Scheme 45 Ruthenium-catalyzed hydroalkylation of benzylamines **133** with alkenes **134**

Promoted by the success of rhodium-catalyzed *α*-carbonylation of C(sp³)−H bonds to cyclic amino and amido groups,[96] Murai, Kakiuchi and Chatani observed that Ru₃(CO)₁₂ (**132**) enabled the addition of C(sp³)−H bond across the alkene bond to give the corresponding alkylated products **137** (Scheme 46).[97] Intensive studies showed that the reactivity was improved using *iso*-propanol as the solvent. Various alkenes, including terminal, internal and cyclic alkenes, proved to be suitable applying this protocol, and the substrates were successfully extended to five-, six- and seven-membered rings.

90   L. Ilies, Q. Chen, X. Zeng, E. Nakamura, *J. Am. Chem. Soc.* **2011**, *133*, 5219–5223.

91   (a) K. Gao, N. Yoshikai, *Angew. Chem. Int. Ed.* **2011**, *50*, 6888–6892; (b) K. Gao, N. Yoshikai, *J. Am. Chem. Soc.* **2011**, *133*, 400–402. See also: (c) W. Song, L. Ackermann, *Angew. Chem. Int. Ed.* **2012**, *51*, 8251−8254.

92   K. Gao, P.-S. Lee, T. Fujita, N. Yoshikai, *J. Am. Chem. Soc.* **2010**, *132*, 12249–12251.

93   B. Zhou, H. Chen, C. Wang, *J. Am. Chem. Soc.* **2013**, *135*, 1264–1267.

94   For selected reviews on C(sp³)−H bond transformations, see: (a) S. A. Girard, T. Knauber, C.-J. Li, *Angew. Chem. Int. Ed.* **2014**, *53*, 74–100; (b) H. Li, B.-J. Li, Z.-J. Shi, *Catal. Sci. Technol.* **2011**, *1*, 191; (c) O. Baudoin, *Chem. Soc. Rev.* **2011**, *40*, 4902; (d) M. Wasa, K. M. Engle, J.-Q. Yu, *Isr. J. Chem.* **2010**, *50*, 605; (e) R. Jazzar, J. Hitce, A. Renaudat, J. Sofack-Kreutzer, O. Baudoin, *Chem. –Eur. J.* **2010**, *16*, 2654.

95   C.-H. Jun, D.-C. Hwang, S.-J. Na, *Chem. Commun.* **1998**, 1405–1406.

96   (a) N. Chatani, T. Asaumi, T. Ikeda, S. Yorimitsu, Y. Ishii, F. Kakiuchi, S. Murai, *J. Am. Chem. Soc.* **2000,** *122*, 12882–12883; (b) Y. Ishii, N. Chatani, F. Kakiuchi, S. Murai, *Organometallics* **1997**, *16*, 3615–3622; (c) Y. Ishii, N. Chatani, F. Kakiuchi, S. Murai, *Tetrahedron Lett.* **1997,** *38*, 7565–7568.

97   N. Chatani, T. Asaumi, S. Yorimitsu, T. Ikeda, F. Kakiuchi, S. Murai, *J. Am. Chem. Soc.* **2001,** *123*, 10935–110941.
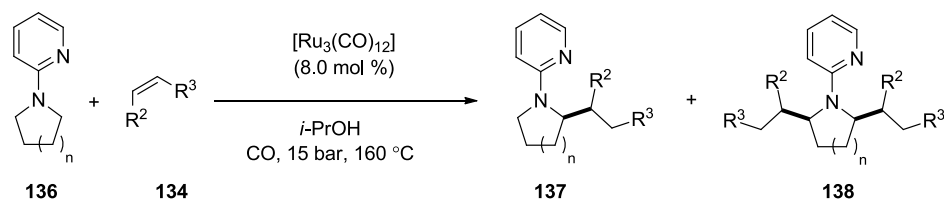
Scheme 46 Ruthenium-catalyzed alkylation of cyclic amines **136** with alkenes **134**

The reaction mechanism proposed for Murai's C(sp^3)−H alkylation was similar to the mechanisms of C(sp^2)−H bond functionalizations discussed above (Scheme 47).[73–75,98] First, coordination of substrate **136** to ruthenium provides complex **140**, in which the C−H bond undergoes cleavage to give a Ru–H complex **141**. Subsequently, coordination of alkene **134** and its migratory insertion furnishes the Ru–alkyl complex **143**, from which reductive elimination affords the final product **137**, with the active ruthenium complex being regenerate.
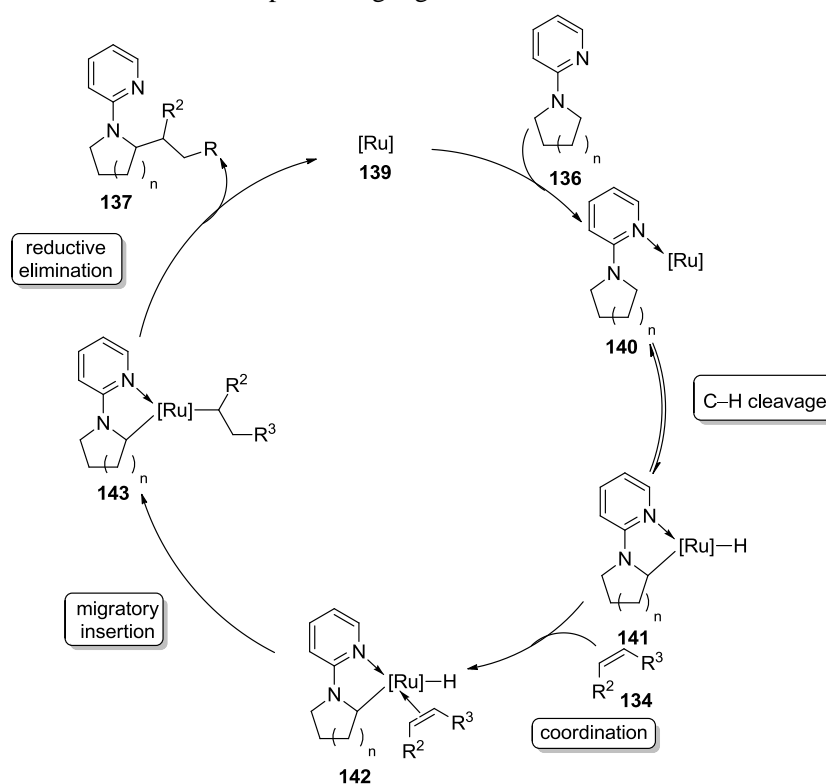
Scheme 47 Proposed mechanism for the ruthenium-catalyzed hydroalkylation

Very recently, Maes reported a ruthenium(0)-catalyzed α-alkylation and -arylation of piperidines **144** with terminal alkenes **111a**.[99] Control experiments showed the carboxylic acid can efficiently increase the catalyst activation and longevity, along with that the alcohol reduces the side reactions (Scheme 48).[99a]

98   Analogous mechanism with Iridium catalysis: (a) E. Clot, J. Chen, D.-H. Lee, S. Y. Sung, L. N. Appelhans, J. W. Faller, R. H. Crabtree, O. Eisenstein, *J. Am. Chem. Soc.* **2004**, *126*, 8795–8804; (b) D.-H. Lee, J. Chen, J. W. Faller, R. H. Crabtree, *Chem. Commun.* **2001**, 213–214.

99   (a) S. D. Bergman, T. E. Storr, H. Prokopcová, K. Aelvoet, G. Diels, L. Meerpoel, B. U. W. Maes, *Chem. –Eur. J.* **2012**, *18*, 10393–10398; (b) A. Peschiulli, V. Smout, T. E. Storr, E. A. Mitchell, Z. Eliáš, W. Herrebout, D. Berthelot, L. Meerpoel, B. U. W. Maes, *Chem.– Eur. J.* **2013**, *19*, 10378–10387.
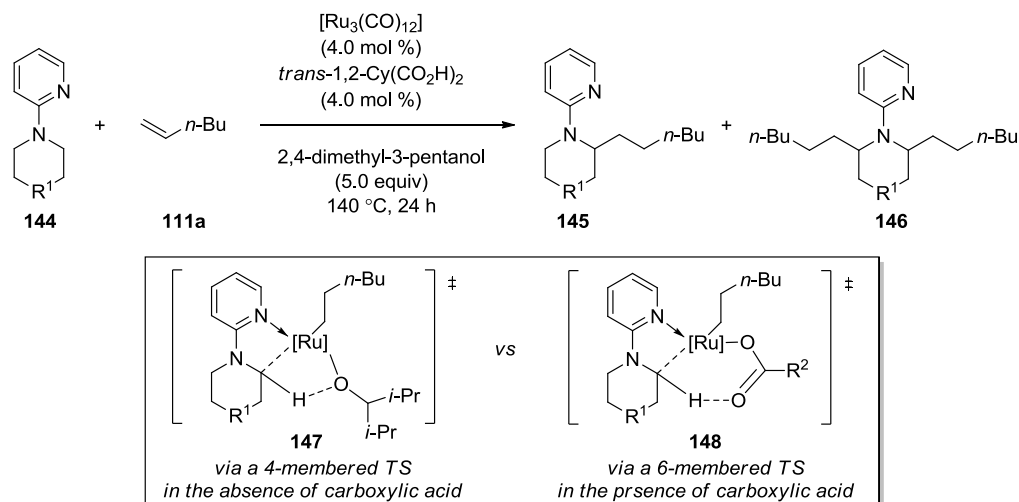
Scheme 48 Ruthenium-catalyzed alkylation of amines in the presence of carboxylate acid

Besides, using the ruthenium-hydride complex **150**, Yi showed that the alkylation of cyclic amines **149** without additional directing group can be achieved by invoking the dehydrogenation of amine and subsequent α-C−H imine bond activation/alkene insertion sequence (Scheme 49).[100]
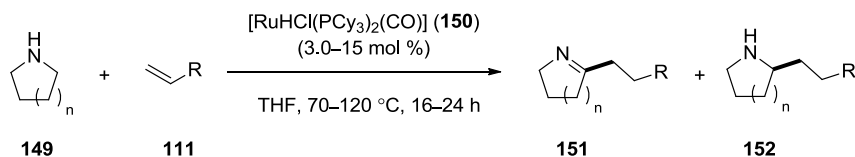
Scheme 49 Ruthenium-catalyzed alkylation of unprotected cyclic amines with alkenes

1.5 Metal-Catalyzed *ortho*-C−H Halogenations

Aromatic halides are key intermediates in organic synthesis, and have been broadly utilized for natural products synthesis, material sciences and medicinal chemistry.[101] As a consequence, the development of efficient and selective methods for their syntheses continues to be of prime importance. Conventionally, the most useful strategies for their synthesis rely on the electrophilic aromatic substitution (S_E^{Ar}), the Sandmeyer reaction or the directed *ortho*-lithiation approach (Scheme 50a–c).[102] Unfortunately, these methods face considerable limitations, including tedious and/or hazardous reaction procedures, poor site selectivities, and harsh reaction conditions, resulting in low chemo-selectivities. In recent years, metal-catalyzed C−H activation has emerged as an increasingly viable tool for C−X bond formations (Scheme 50d).[4] In this context, methods for the palladium-catalyzed chelation-assisted direct C−H bond functionalization with

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[100] C. S. Yi, S. Y. Yun, I. A. Guzei, *Organometallics* **2004**, *23*, 5392−5395.

[101] Selected reviews: (a) S. Johansson, C. C. Carin, M. O. Kitching, T. J. Colacot, V. Snieckus, *Angew. Chem. Int. Ed.* **2012**, *51*, 5062−5085; (b) G. Evano, N. Blanchard, M. Toumi, *Chem. Rev.* **2008**, *108*, 3054−3131; (c) K. C. Nicolaou, P. G. Bulger, D. Sarlah, *Angew. Chem. Int. Ed.* **2005**, *44*, 4442−4489; (d) P. Knochel, W. Dohle, N. Gommermann, F. F. Kneisel, F. Kopp, T. Korn, I. Sapountzis, V. A. Vu, *Angew. Chem. Int. Ed.* **2003**, *42*, 4302−4320 and cited references.

[102] (a) Y. L. Janin, *Chem. Rev.* **2012**, *112*, 3924−3958; (b) S. D. Roughley, A. M. Jordan, *J. Med. Chem.* **2011**, *54*, 3451−3479; (c) A. Podgorsek, M. Zupan, J. Iskra, *Angew. Chem. Int. Ed.* **2009**, *48*, 8424−8450; (d) E. B. Merkushev, *Synthesis* **1988**, 923−937; (e) E. J.-G. Anctil, V. Snieckus, in *Metal-Catalyzed Cross-Coupling Reactions*; A. de Meijere, F. Diederich, eds.; Wiley-VCH: Weinheim, Germany, **2004**, pp761−814.

electrophilic halogenating reagents have been developed by several groups.[103]
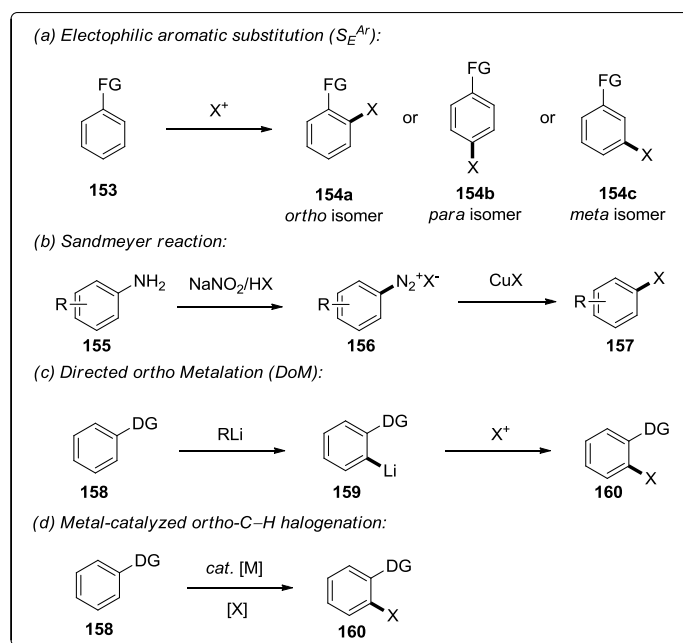
Scheme 50 Conventional approaches for halogenation reactions

An early report on palladium catalysis involved the *ortho*-halogenation of azobenzene **161** with X_2 (Scheme 51),[104] which afforded a mixture of mono-, di-, tri-, and tetra-halogenated products. While this work elegantly demonstrated the viability of such transformations, the requirement for X_2 as the oxidant limited its widespread application in organic synthesis.
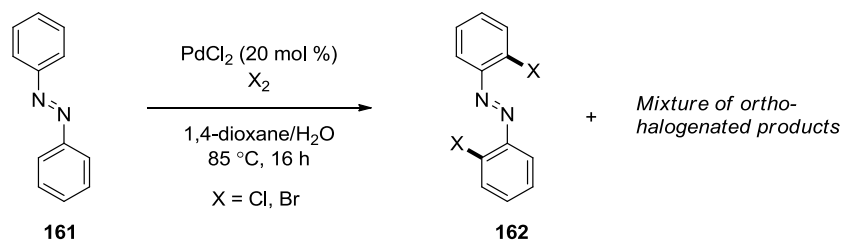
Scheme 51 Pd-catalyzed direct *ortho*-halogenation of azobenzene **161**

In 2005, Yu and coworkers reported an auxiliary approach for the chemo- and stereo- selective ambient-temperature iodination of methyl groups with oxazoline as directing group (Table 1, entry 1). This protocol has also been successfully applied to the activation of cyclopropanes (C−H bond β to the carboxy group) and arenes (C−H bond γ to the carboxy group).[105a,b] Furthermore, they developed *ortho*-iodination and bromination of arene carboxylic acids **56** with Suárez reagents

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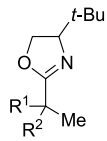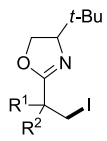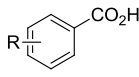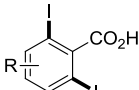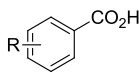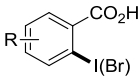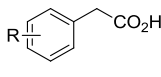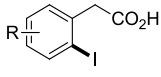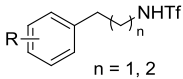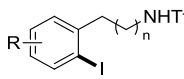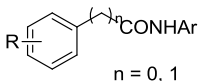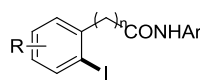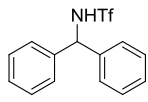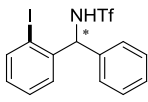
[103] Reviews: (a) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147−1169; (b) S. R. Neufeldt, M. S. Sanford, *Acc. Chem. Res.* **2012**, *45*, 936−946.

[104] D. R. Fahey, *J. Organomet. Chem.* **1971**, *27*, 283−292.

[105] (a) R. Giri, X. Chen, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2005**, *44*, 2112−2115; (b) R. Giri, X. Chen, X.-S. Hao, J.-J. Li, J. Liang, Z.-P. Fan, J.-Q. Yu, *Tetrahedron Asym.* **2005**, *16*, 3502−3505; (c) T.-S. Mei, R. Giri, N. Maugel, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2008**, *47*, 5215−5219; (d) T.-S. Mei, D.-H. Wang, J.-Q. Yu, *Org. Lett.* **2010**, *12*, 3140−3143; (e) J.-J. Li, T.-S. Mei, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2008**, *47*, 6452−6455; (f) X.-C. Wang, Y. Hu, S. Bonacorsi, Y. Hong, R. Burrell, J.-Q. Yu, *J. Am. Chem. Soc.* **2013**, *135*, 10326−10329; (g) L. Chu, X.-C. Wang, C. E. Moore, A. L. Rheingold, J.-Q. Yu, *J. Am. Chem. Soc.* **2013**, *135*, 16344−16347.

(XOAc) as the halogen source as well as the terminal oxidant (entries 2–3).[105c] In this case, mechanistic study shows that employment of the large tetraalkylammonium cation can efficiently prevent the formation of dihalogenated product.[105c] In 2010, this group extended this protocol to phenylacetic acid **167** (entry 4)[105d] as well as triflamide (NHTf) directing groups (entry 5).[105e] Very recently, palladium-catalyzed *ortho*-C−H iodination directed by a weakly coordinating amide auxiliary (**171**) using I_2 as the sole oxidant was developed (entry 6).[105f] This reaction is compatible with a wide range of heterocycles including pyridines, imidazoles, oxazoles, thiazoles, isoxazoles, and pyrazoles. Furthermore, a similar protocol realized the enantioselective C−H iodination reaction using a mono-*N*-benzoyl-protected amino acid for the synthesis of chiral diarylmethylamines **174** (entry 7).[105g]

Table 1 Palladium-catalyzed direct C−H halogenations reported by the Yu group

Entry	Substrate	Product	Conditions	Ref.
1	**163**	**164**	I_2 (1.0 equiv), Pd(OAc)$_2$ (10 mol %), PhI(OAc)$_2$ (1.0 equiv), CH$_2$Cl$_2$, 24 ℃, 48–72 h.	105a
2	**56**	**165**	IOAc (2.0 equiv), Pd(OAc)$_2$ (5.0 mol %), DCE, 76 ℃, 2 h.	105c
3	**56**	**166**	IOAc (4.0 equiv), Pd(OAc)$_2$ (5.0 mol %), Bu$_4$NX (1.5 equiv), DCE, 100 ℃, 24 h.	105c
4	**167**	**168**	I_2 (0.75 equiv), Pd(OAc)$_2$ (10 mol %), PhI(OAc)$_2$ (0.75 equiv), DMF, 60 ℃, 24 h, no light.	105d
5	**169** n = 1, 2	**170**	I_2 (2.0 equiv), Pd(OAc)$_2$ (10 mol %), PhI(OAc)$_2$ (2.0 equiv), NaHCO$_3$ (2.0 equiv), DMF, 130 ℃, 72 h.	105e
6	**171** n = 0, 1	**172**	I_2 (2.5 equiv), Pd(OAc)$_2$ (2.0 mol%), CsOAc (1.2 equiv), NaHCO$_3$ (1.0 equiv), 4 Å molecular sieves, *t*-AmOH/DMF (1:1) 65 ℃, 20 h.	105f
7	**173**	**174**	I_2 (2.5 equiv), Pd(OAc)$_2$ (10 mol %), Bz-Leu-OH (40 mol %), CsOAc (3.0 equiv), Na$_2$CO$_3$ (3.0 equiv), DMSO (15 equiv), *t*-AmOH, 30 ℃, air, 48 h.	105g

Meanwhile, distinct contributions arose also from the Sanford group. In 2004, Sanford and coworkers disclosed a highly regio- and chemo-selective palladium-catalyzed *ortho*-halogenation on benzo[*h*]quinolone (**175**), using NCS or NBS in place of PhI(OAc)$_2$ as the stoichiometric

oxidant.[106a] These transformations have been subsequently applied to a wide array of substrates and can provide products that are complementary to those obtained *via* conventional electrophilic aromatic substitution (S_E^{Ar}) reactions.[106b] Further studies showed that the nature of the directing group and the substitution pattern on the arene ring of the substrate both led to different reactivity profiles, and often different and complementary products in the presence and absence of the catalyst (Scheme 52).[106c] In other words, arene C−H functionalization with an electrophilic oxidant can occurred by either a palladium-catalyzed pathway or an uncatalyzed electrophilic aromatic substitution (S_E^{Ar}). In certain cases, these two pathways afforded different and complementary site selectivity. For example, the halogenation of electron-rich oxime ether **176** (which selectively affords **178** in the absence of Pd and **177** under Pd catalysis), pyrazole **96** (forming **179** and **180**, respectively), and quinolone **181** (generating **182** and **183**) (Scheme 52).[106c−d]
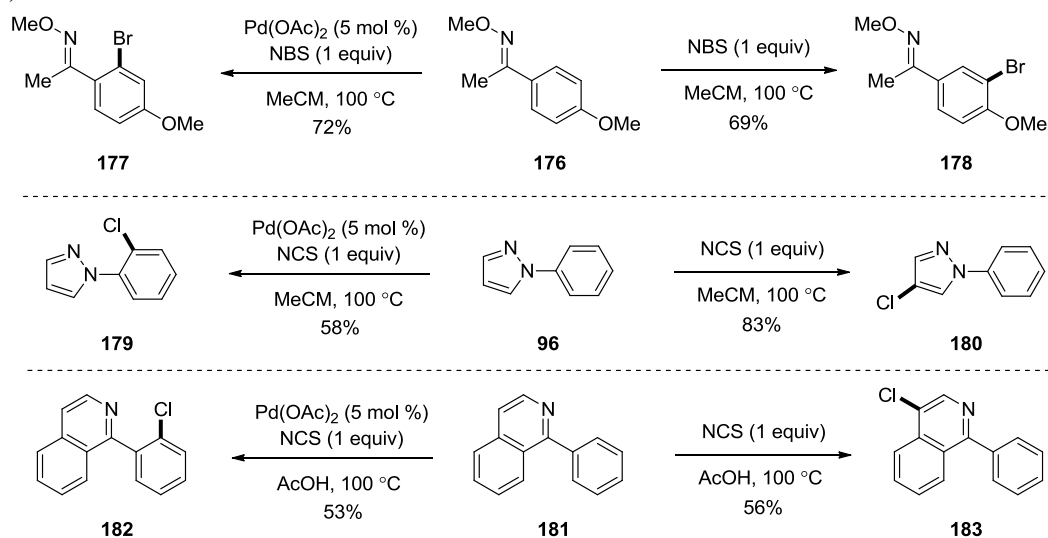
Scheme 52 Complementary site selectivity of halogenation in the presence and absence of palladium catalyst

Along with Yu's and Sanford's independent work, Shi reported a highly regioselective C−H functionalization/halogenation of acetanilides **184** catalyzed by Pd(OAc)$_2$ and Cu(OAc)$_2$ with CuX$_2$ as the halogen source (Scheme 53).[107a]
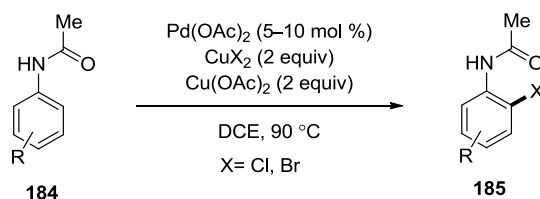
Scheme 53 Palladium-catalyzed C−H halogenation of acetanilides **184** with CuX$_2$ as the halogen source

[106] (a) A. R. Dick, K. L. Hull, M. S. Sanford, *J. Am. Chem. Soc.* **2004**, *126*, 2300−2301; (b) D. Kalyani, A. R. Dick, W. Q. Anani, M. S. Sanford, *Org. Lett.* **2006**, *8*, 2523−2526; (c) D. Kalyani, A. R. Dick, W. Q. Anani, M. S. Sanford, *Tetrahedron* **2006**, *62*,11483−11498; (d) S. R. Whitfield, M. S. Sanford, *J. Am. Chem. Soc.* **2007**, *129*, 15142−15143.

[107] (a) X. Wan, Z. Ma, B. Li, K. Zhang, S. Cao, S. Zhang, Z. Shi, *J. Am. Chem. Soc.* **2006**, *128*, 7416−7417; for similar research, see: (b) R. B. Bedford, J. U. Engelhart, M. F. Haddow, C. J. Mitchell, R. L. Webster, *Dalton Trans.* **2010**, *39*, 10464−10472; (c) B. Song, X. Zheng, J. Mo, B. Xu, *Adv. Synth. Catal.* **2010**, *352*, 329–335; (d) X. Zheng, B. Song, G. Li, B. Liu, H. Deng, B. Xu, *Tetrahedron Lett.* **2010**, *52*, 6641–6645; (e) X. Zhao, E. Dimitrijević, V. M. Dong, *J. Am. Chem. Soc.* **2009**, *131*, 3466−3467.

In 2011, Bedford achieved a facile palladium-catalyzed *ortho*-selective bromination and chlorination of anilides **186** under aerobic conditions at ambient temperature with *N*-halosuccinimides (NXS) as the halogen source (Scheme 54a).[108a] Mechanistic studies showed that *p*-toluenesulfonic acid (PTSA) plays a key role in the catalytic process. Following this report, analogous work was achieved with varieties of directing groups in the presence of PTSA as efficient additive.[109] Likewise, Rao very recently reported a palladium-catalyzed regio- and chemoselective chlorination for the facile synthesis of aromatic chlorides **189**. The reaction demonstrates excellent reactivity, good functional-group tolerance, and high yields. Control experiment showed that TfOH could accelerate the halogenation efficiently and that a co-oxidant was necessary (Scheme 54b).[108b,c]
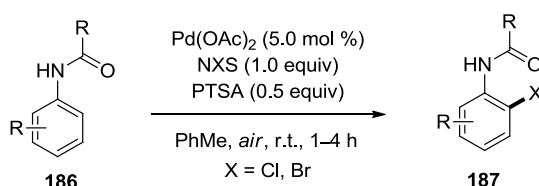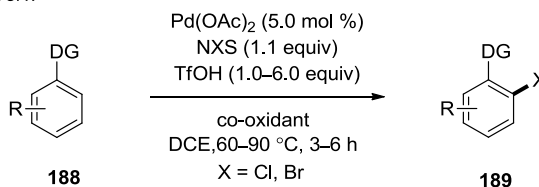
Scheme 54 Palladium-catalyzed C−H halogenation in the presence of acid additives

Meanwhile, Gevorgyan developed an efficient strategy for the synthesis of 1,2-ambiphilic aromatic and heteroannulated aromatic synthons (Scheme 55).[110] This method featured installation of the removable/modifiable PyDipSi directing group on haloarenes and subsequent palladium-catalyzed directed *ortho*-halogenation reaction to give the *ortho*-halogenated PyDipSi-arene derivatives **191**. The synthetic usefulness of these 1,2-ambiphilic building blocks was demonstrated in a variety of transformations, involving reactions on both nucleophilic aryl silane and electrophilic aryl iodide moieties.

[108] (a) R. B. Bedford, M. F. Haddow, C. J. Mitchell, R. L. Webster, *Angew. Chem. Int. Ed.* **2011**, *50*, 5524−5527; (b) X. Sun, G. Shan, Y. Sun, Y. Rao, *Angew. Chem. Int. Ed.* **2013**, *52*, 4440−4444; (c) X. Sun, Y. Sun, C. Zhang, Y. Rao, *Chem. Commun.* **2014**, *50*, 1262−1264.

[109] (a) B. Du, X. Jiang, P. Sun, *J. Org. Chem.* **2013**, *78*, 2786−2791; (b) P. Sadhu, S. K. Alla, T. Punniyamurthy, *J. Org. Chem.* **2013**, *78*, 6104−6111; (c) A. John, K. M. Nicholas, *J. Org. Chem.* **2012**, *77*, 5600−5605; (d) X.-T. Ma, S.-K. Tian, *Adv. Synth. Catal.* **2013**, *355*, 337−340; (e) E. Dubost, C. Fossey, T. Cailly, S. Rault, F. Fabis, *J. Org. Chem.* **2011**, *76*, 6414−6420.

[110] (a) A. S. Dudnik, N. Chernyak, C. Huang, V. Gevorgyan, *Angew. Chem. Int. Ed.* **2010**, *49*, 8729–8732; (b) D. Sarkar, F. S. Melkonyan, A. V. Gulevich, V. Gevorgyan, *Angew. Chem. Int. Ed.* **2013**, *52*, 10800–10804.
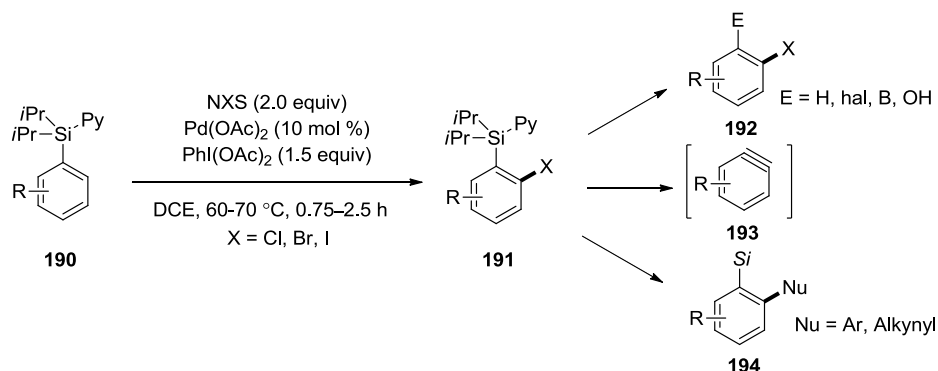
Scheme 55 Palladium-catalyzed *ortho*-halogenation of aryl silanes **190**

Distinguished from the above protocols, Kakiuchi described a new strategy for catalytic halogenation of C−H bonds by means of electrochemical oxidation. Herein, combination of palladium-catalyzed aromatic C−H bond cleavage and halogenation with electrochemically generated halonium ions enables highly efficient, selective halogenations of aromatic compounds **195** in a green-sustainable manner (Scheme 56).[111]
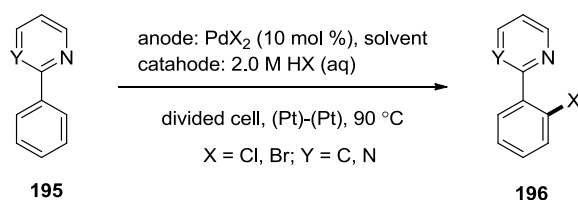
Scheme 56 Palladium-catalyzed regioselective halogenantion *via* electrochemical oxidation

In addition to palladium-catalyzed halogenation protocols, versatile copper-catalyzed/promoted *ortho*-halogenation strategies have also been applied to arenes. These reactions were usually directed by pyridyl or related heteroaryl directing groups along with employment of a proper halogen source (Table 2).[112]

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[111] F. Kakiuchi, T. Kochi, H. Mutsutani, N. Kobayashi, S. Urano, M. Sato, S. Nishiyama, T. Tanabe, *J. Am. Chem. Soc.* **2009**, *131*, 11310−11311.

[112] (a) X. Chen, X. S. Hao, C. E. Goodhue, J.-Q. Yu, *J. Am. Chem. Soc.* **2006**, *128*, 6790–6791; (b) W. Wang, C. Pan, F. Chen, J. Chen, *Chem. Commun.* **2011**, *47*, 3978−3980; (c) S. Mo, Y. Zhu, Z. Shen, *Org. Biomol. Chem.* **2013**, *11*, 2756−2760; (d) B. Urones, Á. M. Martínez, N. Rodríguez, R. G. Arrayás, J. C. Carretero, *Chem. Commun.* **2013**, 49, 11044−11046; (e) Z.-J. Du, L.-X. Gao, Y.-J. Lin, F.-S. Han, *ChemCatChem* **2014**, *6*, 123−126.

Table 2 Copper-catalyzed direct C−H halogenations

Entry	Substrate	Product	Conditions	Ref.
1	Py / R **8**	Py, Cl **197** or Cl, Py, Cl **198**	$CuCl_2$ (20 mol %), $Cl_2CHCHCl_2$, O_2 (1 atm), 130 °C, 24 h	112a
2	Py / R **8**	Py, X **197** & X, Py, X **198** (X = Br, I)	X = Br: $Cu(OAc)_2$ (1.0 equiv), air, $Br_2CHCHBr_2$, 130 °C, 24 h. X = I: $Cu(OAc)_2$ (1.0 equiv), I_2 (1.0 equiv), air, DCE, 100 °C, 24 h.	112a
3	Py / R **8**	Py, Cl / R **197**	$Cu(OAc)_2$ (20 mol %), benzoyl chloride (3.0 equiv), Li_2CO_3 (2.0 equiv), PhMe, O_2, 145 °C, 48 h	112b
4	Py / R **8**	Py, Cl **197** or Cl, Py, Cl **198**	$Cu(NO_3)_2$ $3H_2O$ (20 mol %), LiCl (3.0 equiv), HOAc, O_2 (1 atm), 150 °C.	112c
5	$NHSO_2Py$ / R **202**	$NHSO_2Py$, X / R **203** (X = Cl, Br)	CuX_2 (10 mol %), NXS (1.2 equiv), MeCN, O_2 (1 atm), 100 °C, 4–8 h	112d
6	Py / R **8**	Py, X / R **197** (X = Cl, Br)	CuX (1.0 equiv, NXS (2.0 equiv), HOAc (0.5 equiv), MeCN, 100 °C, 24 h	112e

Furthermore, [RhCp*Cl₂]₂ (**201**)[32] was very recently demonstrated to be a competent catalyst for the halogenation of aromatic C−H bonds in arenes **202**, as reported by Glorius (Scheme 57).[113a] In addition, this protocol was realized for the iodination and bromination of vinylic C−H bonds which provides a variety of (Z)-haloacrylic acid derivatives.[113b]
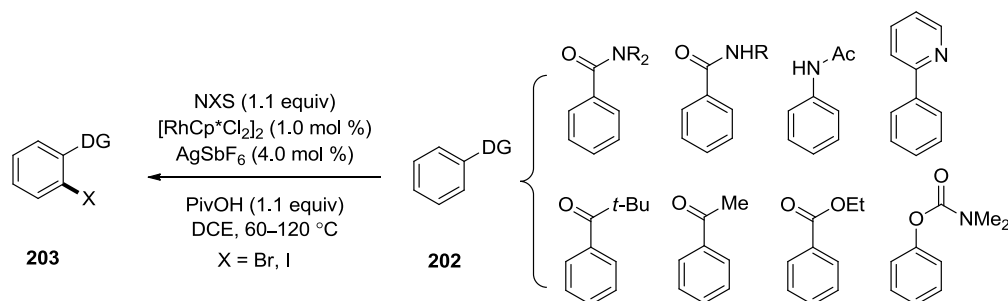
Scheme 57 Rh(III)-catalyzed *ortho*-halogenations

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113 (a) N. Schröder, J. Wencel-Delord, F. Glorius, *J. Am. Chem. Soc.* **2012**, *134*, 8298−8301; (b) N. Kuhl, N. Schröder, F. Glorius, *Org. Lett.* **2013**, *15*, 3860−3863.

Recently, Jeganmohan reported an intramolecular halogenation of *O*-methylbenzohydroximoyl halides **204** in the presence of the widely used ruthenium complex [RuCl$_2$(*p*-cymene)]$_2$ (**15**)[26–30] along with diphenylacetylene (**38a**) as the ligand, yielding substituted halo aromatic nitriles under base- and oxidant-free conditions (Scheme 58).[114]
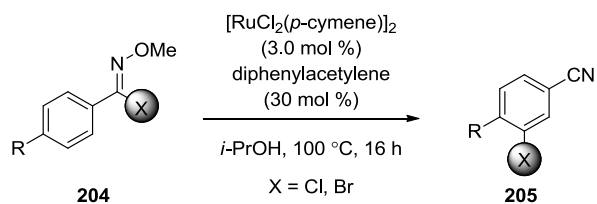
Scheme 58 Ruthenium-catalyzed intramolecular halogenations

[114] R. K. Chinnagolla, S. Pimparkar, M. Jeganmohan, *Chem. Commun.* **2013**, *49*, 3146−3148.

2 Objectives

During the past decade, remarkable progress in organometallic chemistry has set the stage for the development of increasingly viable metal catalysts for C−H bond activation reactions. Among these methods, oxidative C−H bond functionalizations are particularly attractive because they avoid the use of prefunctionalized starting materials.[4] Among such protocols, oxidative annulations that involve sequential C−H and heteroatom−H bond cleavages allow for the modular assembly of regioselectively decorated heterocycles.[28–32] While other researchers have devised palladium[31] or rhodium[32] complexes for oxidative alkyne annulations, our group has focused on the application of significantly less expensive, yet highly selective ruthenium complexes in recent years.[28]

Carboxylate-assisted oxidative annulations of alkynes by benzamides employing ruthenium catalysts were only disclosed in 2011.[33] Unfortunately, these ruthenium-catalyzed transformations were as of yet restricted to the use of superstoichiometric amounts of copper(II) or silver(I) salts as the sacrificial oxidants, thereby leading to the formation of stoichiometric amounts of undesired heavy metal by-products.[115] During our studies on ruthenium-catalyzed oxidative C–H bond functionalizations with substituted pyrroles, we focused on developing carboxylate-assisted ruthenium-catalyzed oxidative annulations with air as an ideal oxidant (Scheme 59). Thereby, we established a novel access to pyrrolo[2,1-*a*]isoquinolines **209**, which are indispensable structural motifs of *inter alia* bioactive lamellarine alkaloid.[116] An additional asset of our ruthenium-catalyzed process is represented by its complementary scope and chemoselectivity as compared to the previously reported rhodium-catalyzed transformation that was found by Miura and coworkers.[117]
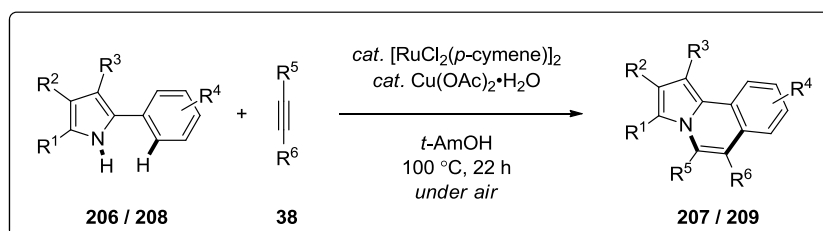
Scheme 59 Ruthenium-catalyzed aerobic oxidative annulation with substituted pyrroles

The recent years witnessed a rapid development of the ruthenium-catalyzed oxidative C−H/N−H bond functionalizations.[28] However, these C−H/N−H bond functionalizations were hitherto restricted to electron-deficient Michael acceptors decorated with electron-withdrawing carbonyl groups. Herein, we wanted to devise a new protocol that could achieve the ruthenium-catalyzed oxidative alkyne annulations with challenging electron-rich alkenes **210** for an expedient pyrrole synthesis, which was also accomplished in an aerobic manner with air as the ideal terminal oxidant (Scheme 60).

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[115] Notably, ruthenium-catalyzed oxidative alkyne annulations with air as ideal oxidant were also achieved during the preparation of this thesis, see ref. 36, 39, 40 and 44.

[116] T. Fukuda, F. Ishibashi, M. Iwao, *Heterocycles* **2011**, *83*, 491–529.

[117] K. Morimoto, K. Hirano, T. Satoh, M. Miura, *Org. Lett.* **2010**, *12*, 2068–2071.
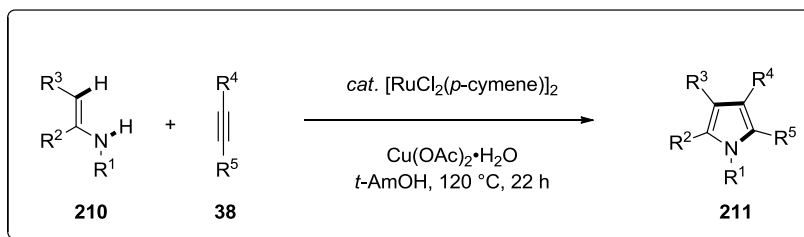
Scheme 60 Ruthenium(II)-catalyzed oxidative pyrrole synthesis

Along with the rapidly developing oxidative annulation with alkynes, significant progress has been accomplished in direct alkenylations through twofold C–H bond functionalization of arenes and heteroarenes employing ruthenium catalysts.[29] Herein, we were interested in the use of [RuCl$_2$(p-cymene)]$_2$ and KPF$_6$ for efficient oxidative alkenylations of electron-rich anilides **212** in water as a green solvent (Scheme 61). Notably, this reaction also proved to be applicable to electron-deficient (hetero)aromatic amides **214**. Mechanistic studies showed that the transformations of these two types of substrates displayed different rate-limiting steps, with an irreversible C−H bond metalation in the case of oxidative alkenylations with benzamides **214**.
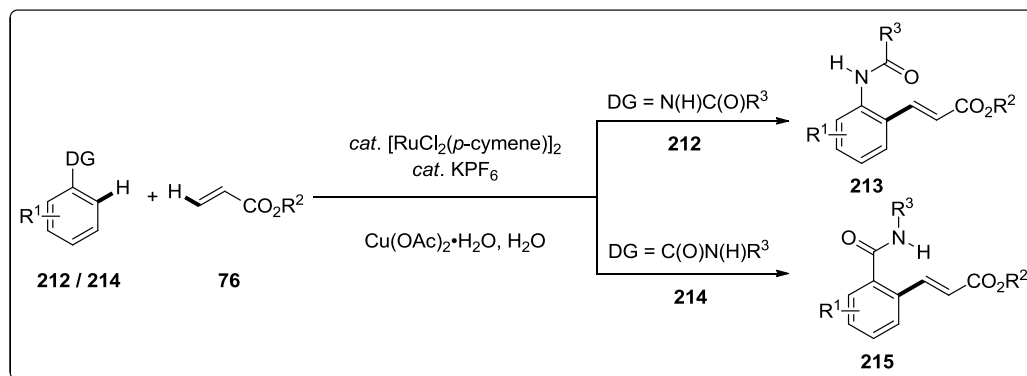
Scheme 61 Ruthenium-catalyzed oxidative C−H alkenylations of anilides **212** and benzamides **214** in water

Despite the progress in the ruthenium-catalyzed C(sp^3)−H alkylations with unactivated alkenes in the past years, all protocols were restricted to Ru$_3$(CO)$_{12}$ catalyst under relatively harsh reaction conditions and with high catalyst loadings. Thus, we became attached by developing a general procedure for ruthenium-catalyzed C(sp^3)−H alkylations of unactivated alkenes **111** with pyrrolidines **216** employing ruthenium(II) catalyst. Complementing to the above-discussed oxidative protocols, this procedure would be a new powerful tool to construct C−C bonds. Furthermore, the pyridyl directing group can easily be removed to furnish the corresponding (*NH*)-free cyclic amines **218** (Scheme 62).
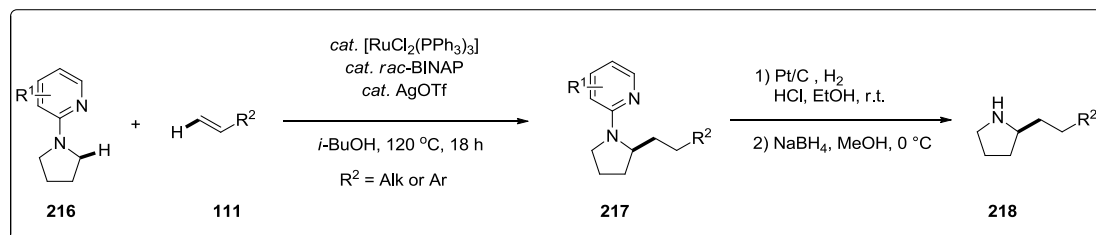
Scheme 62 Ruthenium(II)-catalyzed direct C(sp^3)−H bond alkylations with alkenes **111**

In addition to the C−C bond formations, ruthenium complexes have been identified as powerful catalysts for the oxidative transformation of otherwise unreactive C−H bonds into C−O and C−N bonds.[30] In strict contrast, ruthenium-catalyzed intermolecular[114] C−Hal bond forming processes were unfortunately thus far not available. As a consequence, we became intrigued by a catalytic system comprising of [Ru$_3$(CO)$_{12}$] and AgO$_2$CAd for first ruthenium-catalyzed intermolecular brominations and iodinations of electron-rich and electron-deficient benzamides **219** using *N*-halosuccinimides as halogen source (Scheme 63).
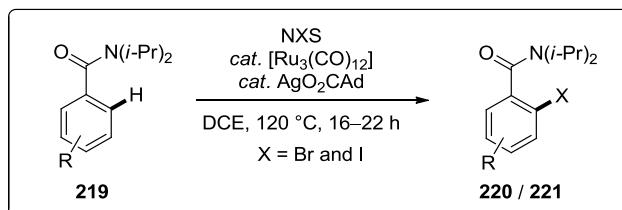
Scheme 63 Ruthenium-catalyzed direct *ortho*-halogenations

3 Ruthenium-Catalyzed Oxidative Annulation of Alkynes Through C−H/N−H Bond Functionalizations

3.1 Ruthenium-Catalyzed Aerobic Oxidative Annulation of Alkynes with 2-Aryl-Substituted Indoles and Pyrroles

As indicated in Chapter **1.2**, transition metal-catalyzed oxidative annulations that involve sequential C−H and heteroatom−H bond cleavages allow for the modular assembly of regioselectively decorated heterocycles.[31,32] Publications on carboxylate-assisted oxidative annulations of alkynes employing less expensive, yet highly selective ruthenium catalysts,[26,28−30] appeared only since the pionnering work in 2011.[33a] Unfortunately, these transformations were as of yet restricted to the use of superstoichiometric amounts of copper(II) or silver(I) salts as the sacrificial oxidants. We established a novel access to pyrrolo[2,1-*a*]isoquinolines **207** through ruthenium-catalyzed oxidative C–H bond functionalizations with cocatalytic amounts of $Cu(OAc)_2 \cdot H_2O$ under an atmosphere of ambient air.[118]

3.1.1 Optimization Studies

At the outset of our studies, we explored representative oxidants and additives for the envisioned ruthenium-catalyzed annulation of tolane (**38a**) by indole **206a** (Table 3). Thus, the C–H/N−H bond functionalization was achieved with $[RuCl_2(p\text{-cymene})]_2$ and stoichiometric amounts of $Cu(OAc)_2 \cdot H_2O$ as the terminal oxidant (entries 1–3). Interestingly, catalytic amounts of $Cu(OAc)_2 \cdot H_2O$ were found to be sufficient, provided that reactions were conducted under an atmosphere of air (entry 4). Furthermore, the use of cocatalytic additive KPF_6 that forms cationic ruthenium(II) catalyst did not improve the catalytic activity (entry 5).[119] While reactions with $CuBr_2$ as the co-oxidant did not furnish the desired product (entry 6), cocatalytic amounts of metal acetates restored the catalytic efficacy (entries 7–10), thus providing strong evidence for carboxylate-assisted aerobic oxidations.[8]

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[118] L. Ackermann, L. Wang, A. V. Lygin, *Chem. Sci.* **2012**, *3*, 177–180.

[119] (a) S. Fernández, M. Pfeffer, V. Ritleng, C. Sirlin, *Organometallics* **1999**, *18*, 2390–2394; (b) M. A. Bennett, A. K. Smith, *J. Chem. Soc., Dalton Trans.* **1974**, 233–241.

Table 3 Optimization of oxidative annulation with indole **206a**[a]
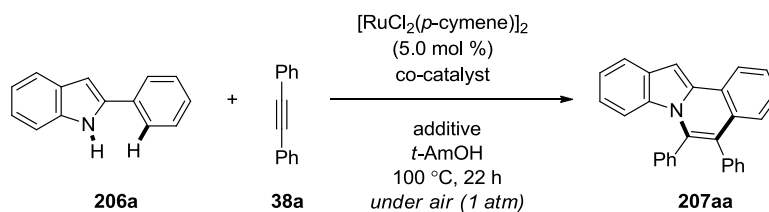
Entry	Co-catalyst (mol %)	Additive (mol %)	207aa (%)
1	—	—	<5[b]
2	$Cu(OAc)_2 H_2O$ (200)	—	84[c]
3	$Cu(OAc)_2 H_2O$ (10)	—	21[c]
4	$Cu(OAc)_2 H_2O$ (10)	—	82
5	$Cu(OAc)_2 H_2O$ (10)	KPF_6 (20)	84
6	$CuBr_2$ (10)	—	<5[b]
7	$CuBr_2$ (10)	KPF_6 (20)	<5[b]
8	$CuBr_2$ (10)	$LiOAc H_2O$ (20)	16[b]
9	$CuBr_2$ (10)	NaOAc (20)	51
10	$CuBr_2$ (10)	CsOAc (20)	50

[a] Reaction conditions: **206a** (0.5 mmol), **38a** (1.0 mmol), [RuCl$_2$(p-cymene)]$_2$ (5.0 mol %), cocatalyst, t-AmOH (2.0 mL), 100 °C, 22 h, under air (1 atm); isolated yields. [b] GC-conversion. [c] Under N$_2$.

3.1.2 Scope of the Annulation with 2-Aryl-Substituted Indoles

With an optimized catalytic system in hand, we explored the scope of this ruthenium-catalyzed aerobic oxidative annulation of alkynes **38** by indoles **206** (Table 4). Notably, the aerobic annulation proved to be broadly applicable, and occurred chemoselectively at the N–H functionality of indoles **206**. Valuable functional groups, such as fluoro, bromo, nitro or ester substituents, were well tolerated by the catalytic system. Electron-deficient heteroarenes **206** were efficiently converted, generally furnishing moderate to high isolated yields (entries 1–3 and 5–8). Unfortunately, electron-rich heteroarenes **206e** and **206k** (entries 4 and 10) as well as substrates **206j** and **206m** (entries 9 and 12) gave low conversion. However, improved yields were obtained when switching to stoichiometric amounts of the terminal oxidant Cu(OAc)$_2$ H$_2$O. On the other hand, the aerobic annulation tolerated decorated tolane derivatives **38** as well (entries 13–14).[118] Likewise, dichlorotolane **38c** delivered the desired annulated product **207** in good yield with stoichiometric amounts of Cu(OAc)$_2$ H$_2$O (entry 14).

Table 4 Aerobic oxidative annulation of alkynes **38** with indoles **206**[a]
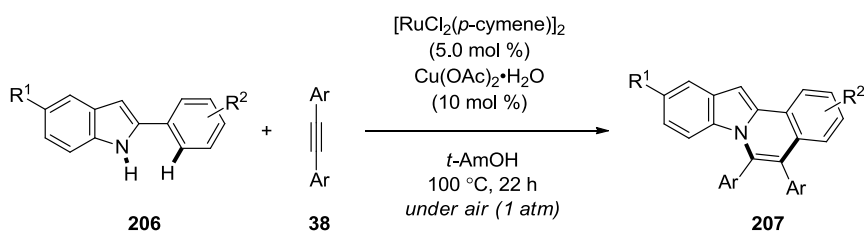
Entry	Indole 206	Alkyne 38	Product 207		Yield (%)
1	R = F (**206b**)			**207ba**	54
2	R = Br (**206c**)	Ph——Ph		**207ca**	32
3	**206b–d** R = NO₂ (**206d**)	**38a**	**207ba–207da**	**207da**	71
4	**206e**	**38a**	**207ea**		7, 65[b]
5	R = F (**206f**)			**207fa**	84
6	R = CF₃ (**206g**)	**38a**		**207ga**	72
7	**206f–i** R = NO₂ (**206h**)		**207fa–207ia**	**207ha**	44
8	R = CO₂Me(**206i**)			**207ia**	57
9	**206j**	**38a**	**207ja**		13, 51[b]
10	**206k**	**38a**	**207ka**		6, 55[b]
11	**206l**	**38a**	**207la**		46
12	**206m**	**38a**	**207ma**		6, 46[b]

(*continued*)

Table 4 *(continued)*

Entry	Indole 206	Alkyne 38	Product 207	Yield (%)
13	206a	38b	207ab	54
14	206a	38c	207ac	6, 82[b]

a Reaction conditions: **206** (0.5 mmol), **38** (1.0 mmol), [RuCl$_2$(*p*-cymene)]$_2$ (5.0 mol %), Cu(OAc)$_2$ H$_2$O (10 mol %), *t*-AmOH (2.0 mL), 100 ℃, 22 h, under air (1 atm); isolated yields. *b* Cu(OAc)$_2$ H$_2$O (1.0 mmol), under N$_2$.
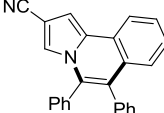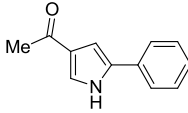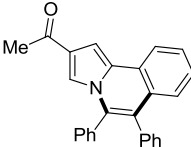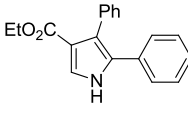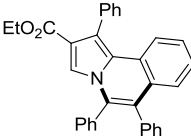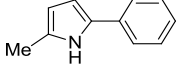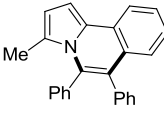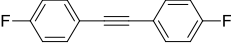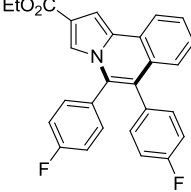
3.1.3 Scope of the Annulation with 2-Aryl-Substituted Pyrroles

Importantly, the ruthenium catalysis was not restricted to the use of 2-aryl-substituted indoles **206**, but also allowed for the first metal-catalyzed oxidative annulations with pyrroles **208** (Table 5). The remarkable chemoselectivity of the catalytic system enabled the preparation of substituted pyrrolo[2,1-*a*]isoquinolines **209** in a highly regioselective fashion (entries 1−4), a structural motif found among others in the biologically active lamellarine alkaloids.[115] Likewise, the ruthenium system proved tolerant of various electrophilic functional groups, such as esters, cyano or enolizable ketones (entries 1–4), although 5-methylpyrrole derivative **208e** failed to deliver the desired product (entry 5). Electron-rich as well as electron-deficient tolanes **38** were efficiently converted, with the latter furnishing higher isolated yields (entry 6).[118]

Table 5 Aerobic oxidative annulation with pyrroles **208**[a]

Entry	Pyrrole 208	Alkyne 38	Product 209	Yield (%)
1	208a	Ph—≡—Ph 38a	209aa	93

Table 5 *(continued)*

Entry	Pyrrole 208	Alkyne 38	Product 209	Yield (%)
1	**208a** (EtO$_2$C, Ph substituted pyrrole)	Ph—≡—Ph **38a**	**209aa**	93
2	**208b** (NC, Ph substituted pyrrole)	**38a**	**209ba**	40
3	**208c** (Me-CO, Ph substituted pyrrole)	**38a**	**209ca**	76
4	**208d** (EtO$_2$C, Ph, Ph substituted pyrrole)	**38a**	**209da**	75
5	**208e** (Me, Ph substituted pyrrole)	**38a**	**209ea**	0
6	**208a**	F–C$_6$H$_4$–≡–C$_6$H$_4$–F **38d**	**209ad**	54

*^{a} Reaction conditions: **208** (0.5 mmol), **38** (1.0 mmol), [RuCl$_2$(*p*-cymene)]$_2$ (5.0 mol %), Cu(OAc)$_2$ H$_2$O (10 mol %), *t*-AmOH (2.0 mL), 100 °C, 22 h, under air (1 atm); isolated yields.*

Further, the aerobic ruthenium-catalyzed annulation displayed an improved chemoselectivity as compared to the reported rhodium-catalyzed process.[117] For instance, alkyl-substituted alkynes **38** gave access to the desired products without the formation of structural isomers (Table 6). Hence, the annulated heteroarenes **209** were isolated in high yields with slightly increased loadings of Cu(OAc)$_2$ H$_2$O (entry 1 *vs* entry 2), while the related rhodium catalysis was shown to deliver a mixture of products.[117] The selective transformation of *n*-alkyl-substituted alkynes **38** also enabled aerobic oxidative annulations with unsymmetrically-substituted alkynes **38g** and **38h**, which proceeded with synthetically useful regiocontrol (entries 6−8).

Table 6 Aerobic oxidative annulation with pyrroles **208**[a]

Entry	Pyrrole 208	Alkyne 38	Product 209	Yield (%)
1	**208f**	n-Pr──────n-Pr **38e**	**209fe**	48[b]
2				74
3	**208d**	**38e**	**209de**	77%
4	**208f**	Et──────Et **38f**	**209ff**	86
5	**208d**	**38f**	**209df**	76
6	**208f**	Ar──────n-Bu (Ar = 4-MeOC$_6$H$_4$) **38g**	**209fg**	74 (6:1)[c]
7	**208a**	**38g**	**209ag**	76 (8:1)[c]

(*continued*)

Table 6 (*continued*)

Entry	Pyrrole 208	Alkyne 38	Product 209	Yield (%)
8	**208a**	Ph———Me **38h**	**209ah**	73 (6:1)[c]

[a] Reaction conditions: **208** (0.5 mmol), **38** (1.0 mmol), [RuCl₂(*p*-cymene)]₂ (5.0 mol %), Cu(OAc)₂ H₂O (30 mol %), *t*-AmOH (2.0 mL), 100 ℃, 22 h, under air (1 atm); isolated yields. [b] Cu(OAc)₂ H₂O (10 mol %). [c] The ratio of isomers was determined by ¹H-NMR spectroscopy.
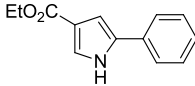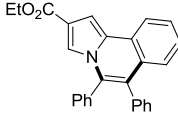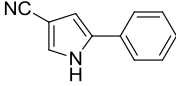
3.1.4 Mechanistic Studies

3.1.4.1 Inter- and Intramolercular Competition Experiments

Considering the unique selectivity and outstanding efficacy of our ruthenium catalyst, we became interested in understanding its mode of action. For this purpose, intermolecular competition experiments with indoles **206b** and **206o** were performed and selectively yielded fluoro-substituted indole **207ba** as the sole product (Scheme 64a). Furthermore, electron-deficient alkyne **38b** was preferentially reacted with indole **206a** under the optimized reaction conditions (Scheme 64b).
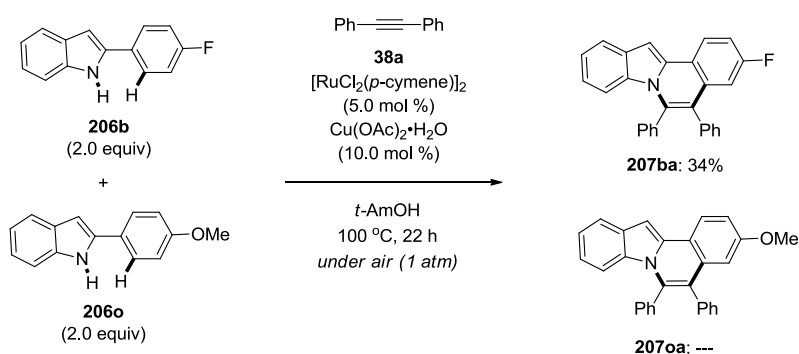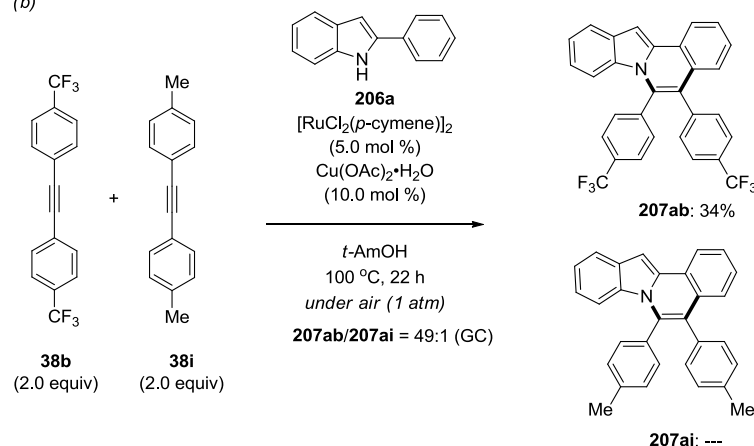
Scheme 64 Intermolecular competition experiments

Additionally, an intramolecular competition experiment with *meta*-fluoro-substituted indole **206p** predominantly gave isomer **207'pa** (Scheme 65), which can be rationalized with a deprotonative ruthenation manifold.[7c,8,120]
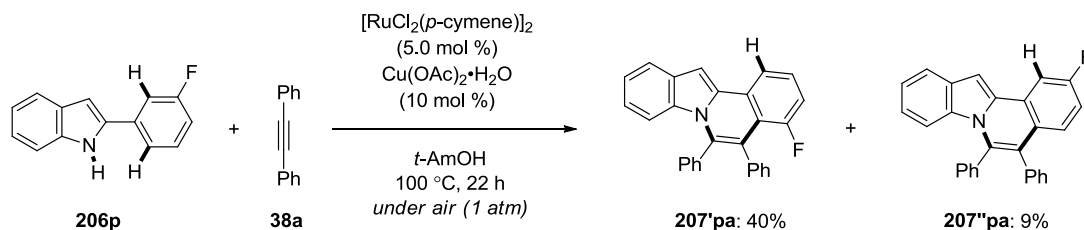
Scheme 65 Annulation with *meta*-fluorophenyl-substituted indole **206p**

3.1.4.2 Reactions in Isotopically Labelled Solvents

Furthermore, no significant H/D scrambling was observed in the oxidative annulations with indole substrate **206d** in $[D]_4$-MeOH under otherwise identical reaction conditions (Scheme 66). These results can be rationalized in terms of an irreversible carboxylate-assisted C−H bond metalation step with the ruthenium complex (Scheme 67).
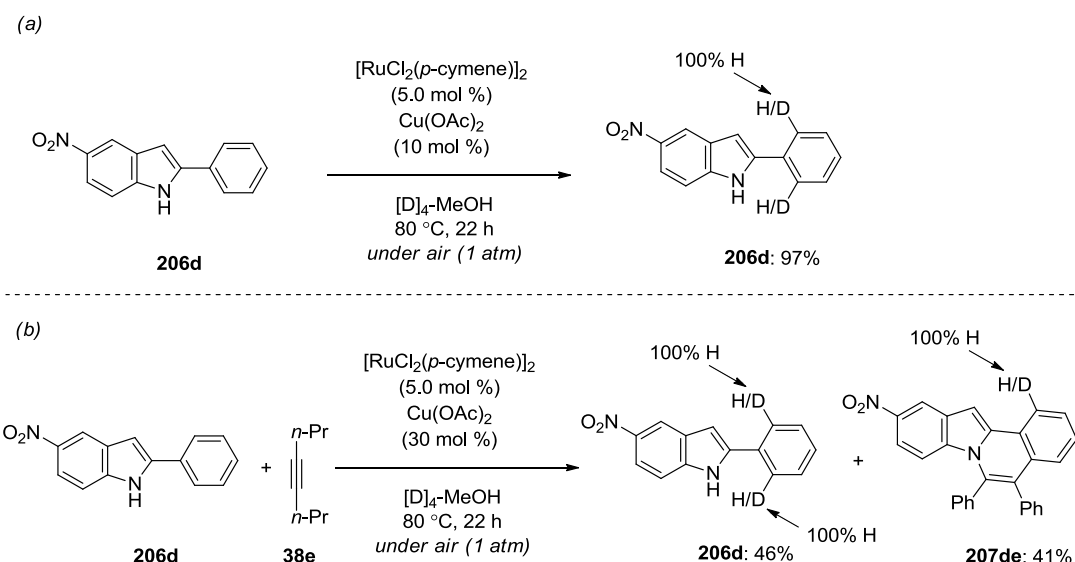
Scheme 66 Aerobic oxidative annulation in $[D]_4$-MeOH

3.1.5 Proposed Catalytic Cycle

Based on our experimental mechanistic studies, the following catalytic cycle for the ruthenium(II)-catalyzed aerobic oxidative annulation is proposed (Scheme 67).[28] Initially, the ruthenium-dimer is expected to form an acetate complex **222**, similar to those observed in the ruthenium-catalyzed carboxylate-assisted direct arylation.[8] Subsequently, N–H bond ruthenation of free N−H group followed by irreversible C–H bond metalation *via* a key transition state **223** with a loss of two molecules of acetic acid affords ruthenacycle **224**. Coordination of alkyne **38** and regioselective migratory insertion delivers seven-membered ruthenacycle **225** as a key intermediate. Finally, the intermediate **225** releases the desired product **207** or **209** through

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[120] 2-Aryl-substituted indoles bearing electron-donating groups on the aryl moiety led to low conversion.

reductive elimination, which is followed by reoxidation of the resulting ruthenium(0) species core **226** by the copper (II)-acetate.
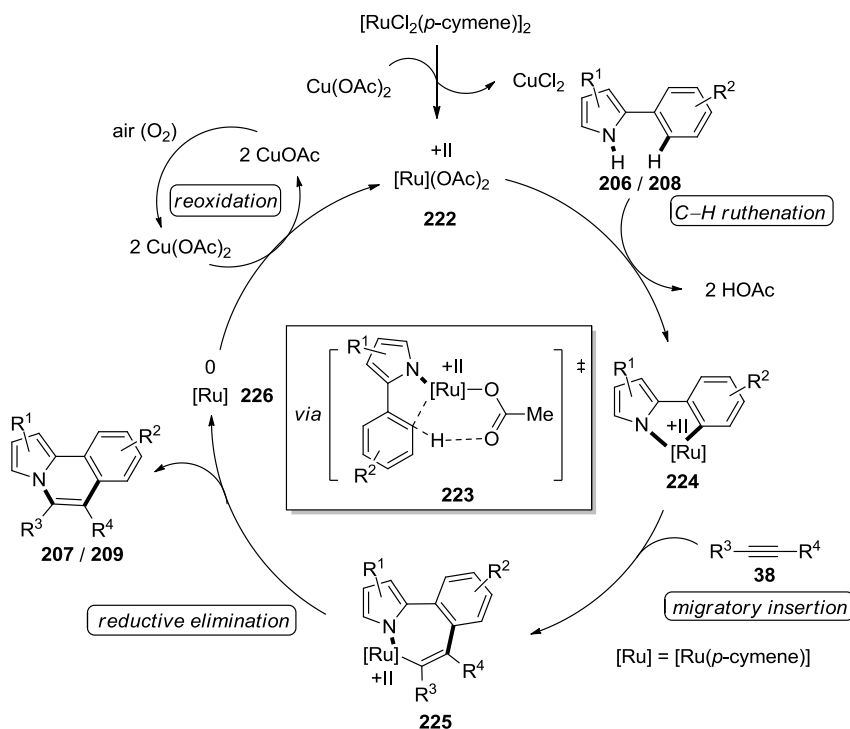
Scheme 67 Proposed catalytic cycle for the aerobic oxidative alkyne annulations

3.2 Ruthenium-Catalyzed Oxidative Annulation of Alkynes with Enamines for Pyrrole Synthesis

Pyrroles are among the most abundant heterocycles and represent indispensable structural motifs in bioactive natural products or material sciences.[121a,b] Therefore, there is a continued strong demand for methods that give broad access to this important heteroaromatic scaffold after the pioneering Knorr-pyrrole synthesis.[121c,d] Among these methods, transition-metal-catalyzed C–H bond functionalization strategy for the pyrrole synthesis provides a more atom-economical approach and thus receives much recent attention.[2]

The seminal work by the research groups of Glorius[122] as well as Stuart and Fagnou[123] have revealed novel syntheses of polysubstituted pyrroles through rhodium(III)-catalyzed C−H activation of enamines followed by the cyclization with an internal alkyne. Unfortunately, the high costs of the required rhodium(III) catalyst were identified as a limitation of this approach.[15] The past three years witness a rapid development of the ruthenium-catalyzed oxidative C−H/N−H bond functionalizations.[28] However, these protocols were restricted to alkenes activated with electron-withdrawing carbonyl groups. To overcome these restrictions, we hence became intrigued

[121] (a) V. Estevéz, M. Villacampa, J. C. Menendéz, *Chem. Soc. Rev.* **2010**, *39*, 4402–4421, and references cited therein; (b) D. S. Bhakuni, D. S. Rawat, *Bioactive Marine Natural Products*, Springer: New York, **2005**; (c) C. Paal, *Ber. Dtsch. Chem. Ges.* **1885**, *18*, 367–371; (d) A. Hantzch, *Ber. Dtsch. Chem. Ges.* **1890**, *23*, 1474–1476.

[122] S. Rakshit, F. W. Patureau, F. Glorius, *J. Am. Chem. Soc.* **2010**, *132*, 9585−9587.

[123] (a) M. P. Huestis, L. Chan, D. R. Stuart, K. Fagnou, *Angew. Chem. Int. Ed.* **2011**, *50*, 1338−1341; (b) D. R. Stuart, P. Alsabeh, M. Kuhn, K. Fagnou, *J. Am. Chem. Soc.* **2010**, *132*, 18326−18339.

by developing a new ruthenium(II)-catalyzed oxidative alkyne annulations with challenging electron-rich alkenes for the pyrrole synthesis.[124,125]

3.2.1 Optimization Studies

We commenced our studies by probing oxidative annulations with differently *N*-substituted enamines **210** (Scheme 68). Among starting materials **210** bearing a variety of functional substituents, such as Boc, Ts, acetyl, solely the *N*-acetylated substrate delivered the product **211aa** in a satisfactory yield of 70%, while the corresponding trifluoroacetylated starting material led to the *NH*-free product **212aa**, albeit in low yield (15%).
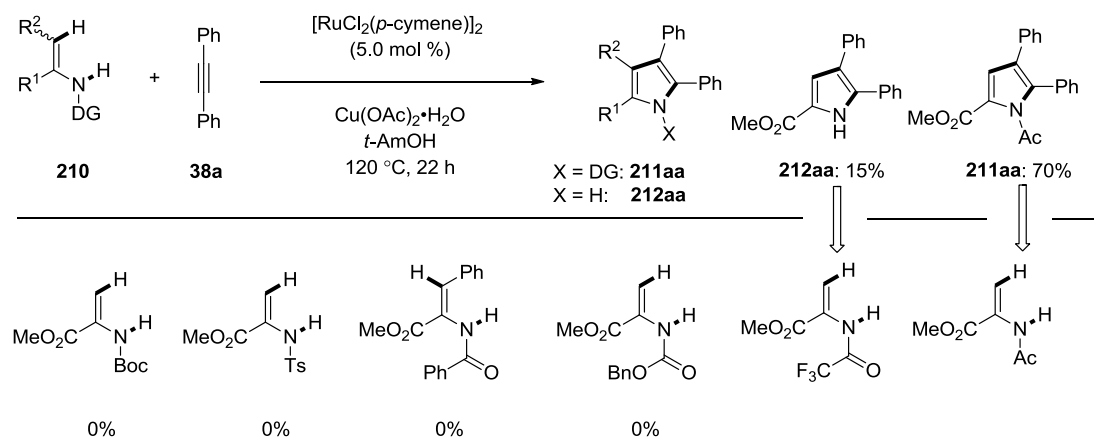
Scheme 68 Ruthenium(II)-catalyzed oxidative pyrrole synthesis

Thereafter, we tested the influence of reaction conditions on the activaty of the ruthenium(II) catalyst (Table 7). In the absence of either the ruthenium complex or the copper oxidant, the desired product **211aa** was not formed (entries 1 and 2). Likewise, the use of cocatalytic additive KPF_6 that forms cationic ruthenium(II) catalyst did not improve the catalytic activity (entries 3−5),[118] whereas the replacement with $AgSbF_6$ led to **211aa** in 39% yield, along with the formation of *NH*-free product **212aa** in 19% yield (entry 6). Further, a series of solvents, including DCE, H_2O, DMF, NMP, PhMe, DMA and *t*-AmOH (entries 3−11), were tested and disclosed the latter to be the most efficient one. Moreover, the use of $CuBr_2$ instead of $Cu(OAc)_2 H_2O^8$ as the sacrificial oxidant did not deliver the desired product **211aa** (entries 12–14). Besides, the complex $RuCl_3 xH_2O$ applied instead of $[RuCl_2(p\text{-cymene})]_2$ displayed no catalytic activity in the pyrrole synthesis (entry 15).

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[124] L. Wang, L. Ackermann, *Org. Lett.* **2013**, *15*, 176–179.

[125] For similar subsequent reports on ruthenium(II)-catalyzed pyrrole synthesis, see: (a) B. Li, N. Wang, Y. Liang, S. Xu, B. Wang, *Org. Lett.* **2013**, *15*, 136–139; (b) K. Murugan, S.-T. Liu, *Tetrahedron Lett.* **2013**, *54*, 2608–2611; for recent palladium-catalyzed oxidative substituted pyrrole synthesis, see: (c) M.-N. Zhao, Z.-H. Ren, Y.-Y. Wang, Z.-H. Guan, *Org. Lett.* **2014**, *16*, 608–611.

Table 7 Optimization study for the oxidative pyrrole synthesis[a]
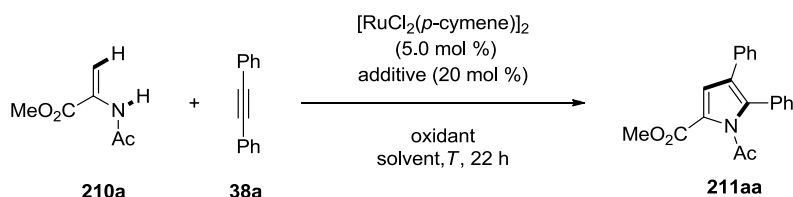
Entry	Oxidant	Additive	Solvent	T (°C)	211aa (%)
1	—	—	t-AmOH	100	0
2	Cu(OAc)₂ H₂O	—	t-AmOH	100	0[b]
3	Cu(OAc)₂ H₂O	—	t-AmOH	100	70
4	Cu(OAc)₂ H₂O	—	t-AmOH	120	68
5	Cu(OAc)₂ H₂O	KPF₆	t-AmOH	120	68
6	Cu(OAc)₂ H₂O	AgSbF₆	DCE	100	39[c]
7	Cu(OAc)₂ H₂O	—	H₂O	100	35
8	Cu(OAc)₂ H₂O	—	DMF	100	55
9	Cu(OAc)₂ H₂O	—	NMP	100	53
10	Cu(OAc)₂ H₂O	—	PhMe	100	38
11	Cu(OAc)₂ H₂O	—	DMA	100	63
12	CuBr₂	—	t-AmOH	100	0
13	CuBr₂	NaOAc	t-AmOH	100	0
14	CuBr₂	CsOAc	t-AmOH	100	0
15	Cu(OAc)₂ H₂O	—	t-AmOH	100	0[d]

[a] Reaction conditions: **210a** (0.5 mmol), **38a** (1.0 mmol), [RuCl₂(p-cymene)]₂ (5.0 mol %), oxidant (0.5 mmol), solvent (2.0 mL), 22 h; isolated yields. [b] In the absence of [RuCl₂(p-cymene)]₂. [c] **212aa** (19%) was also isolated. [d] RuCl₃ xH₂O (10 mol %) was used instead of [RuCl₂(p-cymene)]₂.

3.2.2 Scope of the Oxidative Pyrrole Synthesis

To evaluate the scope of the optimized ruthenium(II) catalyst, we tested its versatility in oxidative annulations of tolane (**38a**) utilizing representative enamines **210** (Table 8). We were delighted to observe that numerous useful electrophilic functional groups were well tolerated, including ester, vinyl, bromo, cyano, and nitro substituents. Substrates **210d** and **210e** with a ketone moiety or without an additional substituent, respectively, provided only low conversion under the optimized reaction conditions (entries 3 and 4). Transformations of 1-aryl-substituted enamines (entries 6–15) proceeded very smoothly in most cases. However, electron-rich methyl and methoxy (entries 12, 13) as well as cyclopropyl groups only delivered the target product in low yields, while more sterically congested substrate **210p** was efficiently converted to product **211pa** (entry 15). Moreover, 1-heteroaryl-substituted substrates **210q** and **210r** furnished the desired pyrroles **211q** and **211ra** as well (entries 16 and 17), albeit in lower yields. In the latter case, the *NH*-free pyrrole **212ra** was formed in a comparable yield, and the substrate **210s** afforded analogous compound **212sa** as a sole product in moderate yield (entry 18).

Table 8 Oxidative annulation of tolane (**38a**) by enamides **210**[a]
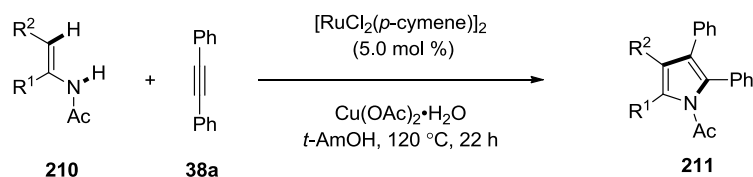
Entry	Enamine 210		Product 211		Yield (%)
1	R = CO$_2$Et (**210b**)			**211ba**	68
2	R = CO$_2i$-Pr (**210c**)			**211ca**	66
3	R = COMe (**210d**)			**211da**	7
4	**210b−e** R = H (**210e**)		**211ba−211ea**	**211ea**	7
5	**210f**		**219fa**		43
6	R = H (**210g**)			**211ga**	52
7	R = CF$_3$ (**210h**)			**211ha**	68
8	R = F (**210i**)			**211ia**	53
9	R = Br (**210j**)			**211ja**	58
10	R = CN (**210k**)			**211ka**	74
11	**210g−n** R = NO$_2$ (**210l**)		**211ga−211na**	**211la**	71
12	R = Me (**210m**)			**211ma**	18
13	R = OMe (**210n**)			**211na**	28
14	**210o**		**211oa**		72
15	**210p**		**211pa**		68
16	**210q**		**211qa**		32
17	**210r**		X = Ac (**211ra**)		33
			X = H (**212ra**)		30

(continued)

Table 8 *(continued)*

Entry	Enamine 210	Product 211	Yield (%)
18	**210s**	**212sa**	48

[a] Reaction conditions: **210** (0.5 mmol), **38a** (1.0 mmol), [RuCl$_2$(*p*-cymene)]$_2$ (5.0 mol %), Cu(OAc)$_2$ H$_2$O (0.5 mmol), *t*-AmOH (2.0 mL), 22 h; isolated yields.

Thereafter, we probed different tolane derivatives **38** in the oxidative pyrrole synthesis (Table 9). The optimized ruthenium catalyst proved to be tolerant of functional groups in the *para*-, *meta*- and *ortho*-position of tolane (entries 1–8), but was not restricted to aryl alkynes **38**. Dialkyl-substituted substrates **38e** and **38f** delivered the desired products **211ae** and **211af**, respectively, in high yields (entries 9 and 10). Notably, oxidative annulations of unsymmetrical alkynes **38h** and **38o** occurred with synthetically useful levels of regiocontrol, furnishing exclusively the products **211lh**, **211ah** and **211ao** (entries 11–13). This selectivity pattern is in good agreement with the previously observed one for a related indole synthesis.[37]

Table 9 Oxidative annulation of alkynes **38** by enamines **210**[a]
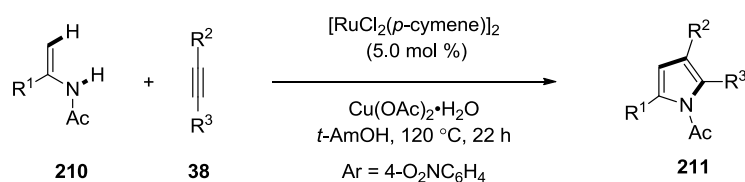
Entry	Enamine 210	Alkyne 38		Product 211	Yield (%)
1		R = Me (**38i**)		**211li**	63
2		R = OMe (**38j**)		**211lj**	52
3		R = CF$_3$ (**38b**)	R—⟨benzene⟩—C≡C—⟨benzene⟩—R	**211b**	67
4	**210l**	R = F (**38k**)	**38i–l**	**211lk**	67
5		R = Cl (**38c**)		**211lc**	68
6		R = CO$_2$Et (**38l**)	**211li–211ll**	**211ll**	64
7	**210l**	**38m**		**211lm**	67
8	**210a**	**38n**		**211an**	57

Table 9 *(continued)*

Entry	Enamine 210	Alkyne 38		Product 211	Yield (%)
9	**210a**	$R \equiv\!\!\!\equiv\!\!\!\equiv R$ **38e–f**	R = *n*-Pr (**38e**)	**211ae**	57
10			R = Et (**38f**)	**211af**	71
11	**210l**	Ph $\equiv\!\!\!\equiv\!\!\!\equiv$ Me **38h**		**211lh**	45
12	**210a**	Ph $\equiv\!\!\!\equiv\!\!\!\equiv$ R **38h–o**	R = Me (**38h**)	**211ah**	66
13			R = Et (**38o**)	**211ao**	54

a Reaction conditions: **210** (0.5 mmol), **38** (1.0 mmol), [RuCl₂(*p*-cymene)]₂ (5.0 mol %), Cu(OAc)₂ H₂O (0.5 mmol), *t*-AmOH (2.0 mL), 22 h; isolated yields.

3.2.3 Ruthenium(II)-Catalyzed Aerobic Oxidative Pyrrole Synthesis

We were pleased that the C–H/N–H bond functionalization was also achieved in an aerobic fashion employing cocatalytic amounts of Cu(OAc)₂ H₂O under an ambient atmosphere of air as the ideal oxidant (Scheme 69).
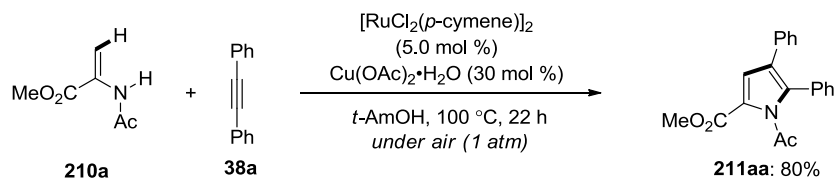
Scheme 69 Aerobic oxidative C–H/N–H bond functionalization under ambient air

3.2.4 Mechanistic Studies

3.2.4.1 Intermolecular Competition Experiments

Given the remarkable catalytic activity of the ruthenium(II) catalyst, we became interested in elucidating the mechanistic aspects of this transformation. We conducted intermolecular competition experiments with alkynes **38**, which revealed more electron-rich alkyne **38j** to react preferentially (Scheme 70).
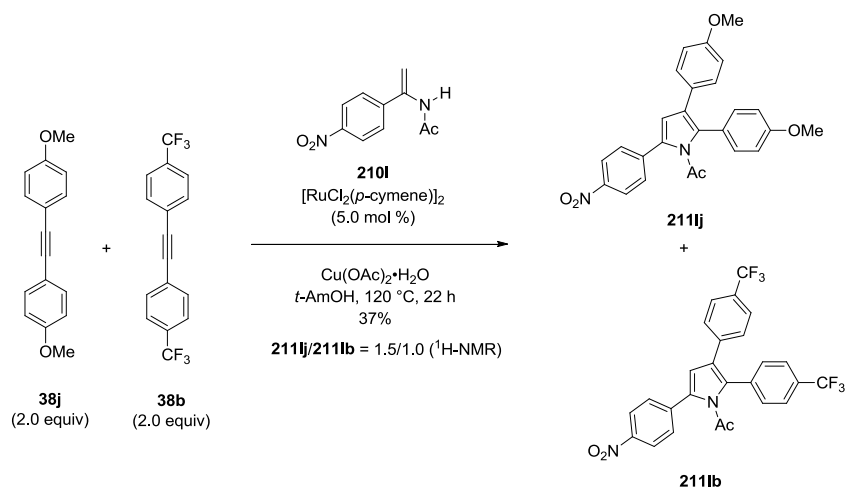
Scheme 70 Intermolecular competition between alkynes **38**

Additionally, competition experiments with differently 2-aryl-substituted enamines **210** highlighted electron-donating substituents on the aryl moiety to be beneficial (Scheme 71).
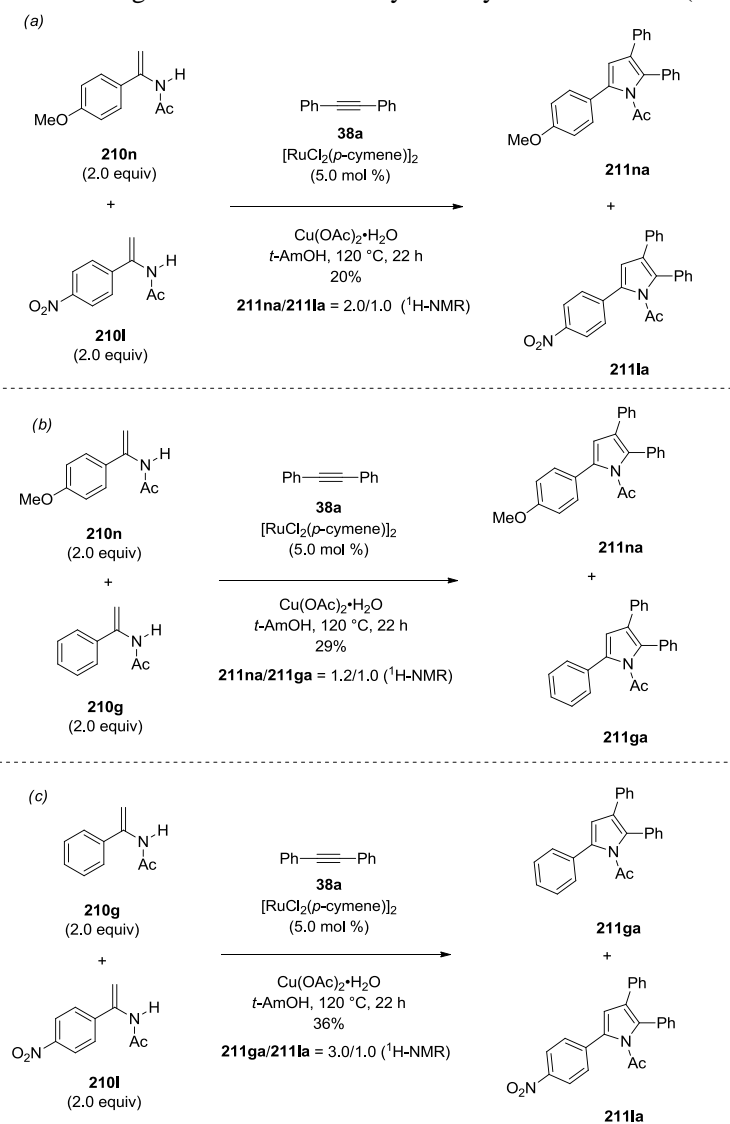
Scheme 71 Intermolecular competition between enamines **210**

3.2.4.2 Reactions in Isotopically Labelled Solvents

Oxidative annulations in isotopically labeled solvent [D]$_4$-MeOH unraveled the C–H bond activation on enamines **210** to be reversible in nature (Scheme 72a). Yet, the H/D scrambling was not observed in the presence of alkyne **38e** under otherwise identical reaction conditions (Scheme 72b). These results can be rationalized in terms of an alkyne-coordinated ruthenium complex undergoing an irreversible C–H bond metalation step.
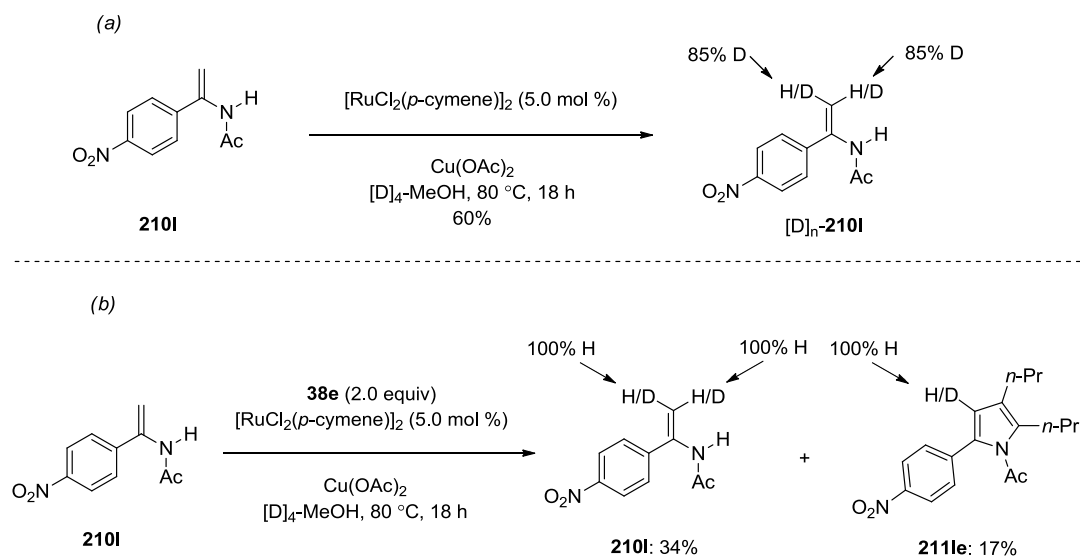
Scheme 72 Oxidative annulations in [D]$_4$-MeOH

3.2.5 Proposed Catalytic Cycle

Based on the above discussed experiments and on the known mechanisms of transition-on-metal-catalyzed oxidative annulation reactions,[28] a plausible catalytic cycle for the ruthenium(II)-catalyzed pyrrole synthesis is proposed (Scheme 73). Initially, the ruthenium-dimer reacts with Cu(OAc)$_2$·H$_2$O to form an acetate-ligated species **227**, which is subsequently coordinated by **210** *via* the amide oxygen to generate complex **228**. Then an alkyne-coordinate ruthenium complex undergoes an irreversible C–H bond metalation step to deliver a six-membered ruthenacycle **230** with concomitant formation of acetic acid *via* an acetate-assisted transition state **229**. Regioselectively migratory insertion into the Ru–C bond and cleavage of N–H bond furnish a six-membered ruthenacycle intermediate **231**. Subsequently, the oxidative coupling of the C–N bond takes place to form the pyrrole product **211** with the reduction of the ruthenium core from ruthenium(II) to ruthenium(0). Finally, the ruthenium(0) species **232** undergoes oxidation to regenerate the active ruthenium(II) complex with the aid of the copper oxidant.
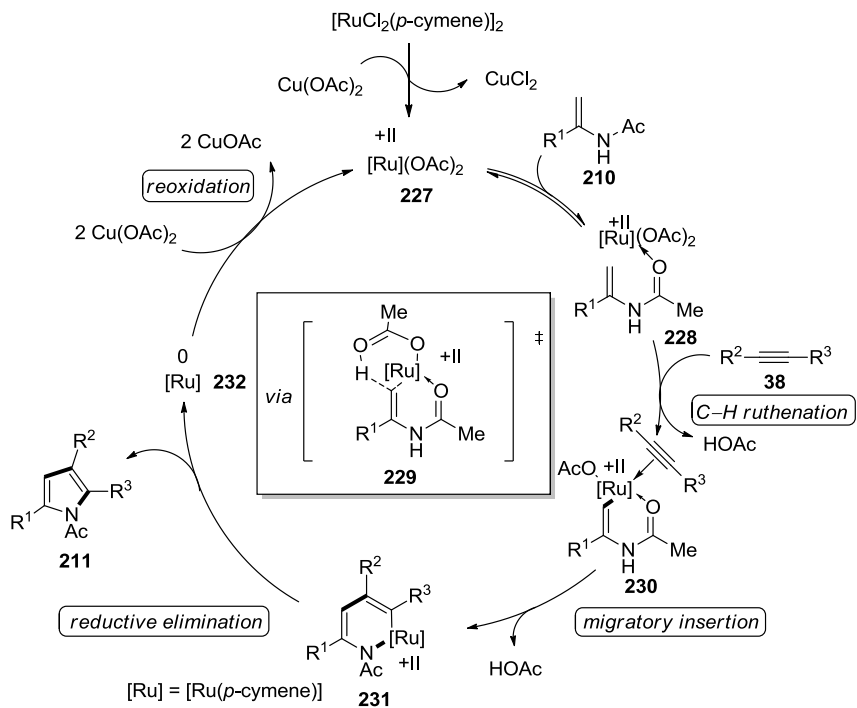
Scheme 73 Proposed catalytic cycle for the pyrrole synthesis

4 Ruthenium-Catalyzed Oxidative C–H Alkenylations

4.1 Ruthenium-Catalyzed Oxidative C–H Alkenylations of Anilides

Along with the rapid developing oxidative annulations of alkynes,[28] significant progress has been accomplished in direct oxidative alkenylations of (hetero)arenes *via* twofold C–H bond cleavages employing ruthenium catalysts.[29] However, ruthenium-catalyzed direct oxidative alkenylations continue to be limited to (hetero)arenes bearing electron-withdrawing directing groups.[126] Given the importance of anilines as key intermediates for the preparation of bioactive compounds and functional materials,[127] we set out to develop the first ruthenium-catalyzed oxidative olefinations with electron-rich anilines.[128]

4.1.1 Optimization Studies

At the outset of our studies, we optimized reaction conditions for the oxidative alkenylation of acetanilide **212a** with alkene **76a** in water (Table 10). In the absence of an additive, only trace amounts of the desired product **213aa** were formed (entries 1 and 2). However, high catalytic efficiency was ensured by a complex generated *in situ* from $[RuCl_2(p\text{-cymene})]_2$ and cocatalytic amounts of KPF_6 (entries 3–9), reaction conditions previously established for the generation of cationic ruthenium(II) complexes.[119] An aerobic oxidative alkenylation with cocatalytic amounts of $Cu(OAc)_2 H_2O$ was viable, albeit with reduced efficacy (entry 10). Further, the use of silver(I) salts as terminal oxidants provided less satisfactory results but indicated a strong dependence of the catalyst's performance on the presence of acetates (entries 11 and 12).[8]

Table 10 Optimization of alkenylation with acetanilide **212a**[a]
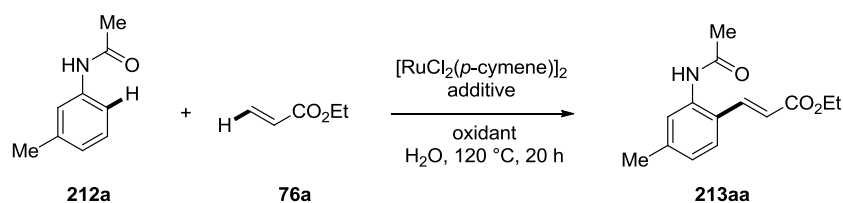
Entry	$[RuCl_2(p\text{-cymene})]_2$ (mol %)	Oxidant (equiv)	Additive (mol %)	213aa (%)
1	—	$Cu(OAc)_2 H_2O$ (1.0)	KPF_6 (10)	0
2	2.5	$Cu(OAc)_2 H_2O$ (1.0)	—	2^b
3	1.0	$Cu(OAc)_2 H_2O$ (1.0)	KPF_6 (5)	43^b
4	2.5	$Cu(OAc)_2 H_2O$ (1.0)	$AgSbF_6$ (10)	54
5	2.5	$Cu(OAc)_2 H_2O$ (1.0)	KPF_6 (10)	87
6	2.5	$Cu(OAc)_2 H_2O$ (1.0)	KPF_6 (5)	76
7	2.5	$Cu(OAc)_2 H_2O$ (2.0)	KPF_6 (10)	84
8	5.0	$Cu(OAc)_2 H_2O$ (1.0)	KPF_6 (20)	86

(continued)

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[126] For the recent reports on ruthenium-catalyzed oxidative olefinations with electron-rich arenes appeared during the preparation of this thesis, see ref. 66 and 67.

[127] *Amino Group Chemistry*; A. Ricci, Ed.; Wiley-VCH: Weinheim, **2008**.

[128] L. Ackermann, L. Wang, R. Wolfram, A. V. Lygin, *Org. Lett.* **2012**, *14*, 728–731.

Table 10 (continued)

Entry	[RuCl$_2$(p-cymene)]$_2$ (mol %)	Oxidant (equiv)	Additive (mol %)	213aa (%)
9	2.5	Cu(OAc)$_2$ H$_2$O (1.0)	KPF$_6$ (10)	77^c
10	2.5	Cu(OAc)$_2$ H$_2$O (0.05)	KPF$_6$ (10)	48^{b,c,d}
11	2.5	Ag$_2$CO$_3$ (1.0)	KPF$_6$ (10)	0
12	2.5	AgOAc (1.0)	KPF$_6$ (10)	40^b

^{a} Reaction conditions: **212a** (0.50 mmol), **76a** (0.75 mmol), [RuCl$_2$(p-cymene)]$_2$ (2.5 mol %), additive (10 mol %), oxidant (0.5 mmol), H$_2$O (2.0 mL), 120 ℃, 20 h, under N$_2$; isolated yields. ^{b} GC conversion. ^{c} 100 ℃. ^{d} Under air (1 atm).

Notably, the replacement of water by organic solvents, such as t-AmOH and DMF, led to lower-yielding reactions (Table 11, entries 2−6). Hence, the reaction mixture was biphasic, which suggested that the reaction occured "on" water, rather than "in water".[129] However, addition of surfactants, such as Triton X-100, surprisingly delivered the alkenylated product in similar yield in H$_2$O (entry 7 *vs* entry 1).

Table 11 Influence of solvent on the alkenylation with acetanilide **212a**^{a}
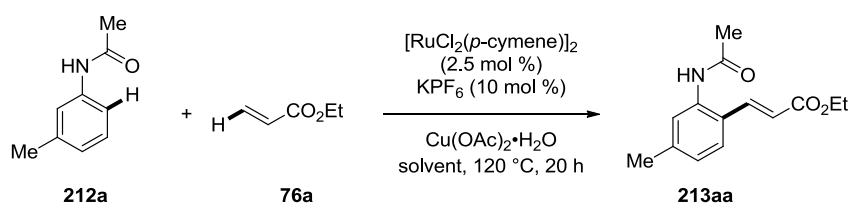
Entry	Solvent	Surfactant	213aa (%)
1	H$_2$O	—	87
2	t-AmOH	—	54
3	DMF	—	55
4	H$_2$O/DMF (9:1)	—	75
5	H$_2$O/DMF (1:1)	—	10^b
6	H$_2$O/DMF (1:9)	—	11^b
7	H$_2$O	Triton X-100 (10 mol %)	81

^{a} Reaction conditions: **212a** (0.50 mmol), **76a** (0.75 mmol), [RuCl$_2$(p-cymene)]$_2$ (2.5 mol %), KPF$_6$ (10 mol %), Cu(OAc)$_2$ H$_2$O (0.5 mmol), solvent (2.0 mL), 120 ℃, 20 h, under N$_2$; isolated yields. ^{b} GC conversion.

4.1.2 Effect of Directing Groups

Furthermore, we probed the ruthenium-catalyzed oxidative alkenylation with differently N-substituted substrates **212** (Scheme 74). Among a variety of starting materials **212**, N-phenylacetamide (**212d**) delivered the product **213da** in best yield in H$_2$O (68%), while the corresponding N,N-disubstituted substrate **212f** led to the target product **213fa** with a low conversion (15%).

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[129] For recent reviews on transition-metal-catalyzed coupling reactions in or on water, see: (a) M.-O. Simon, C.-J. Li, *Chem. Soc. Rev.* **2012**, *41*, 1415–1427; (b) C.-J. Li, *Acc. Chem. Res.* **2010**, *43*, 581–590; (c) B. H. Lipshutz, A. R. Abela, Z. V. Boskovic, T. Nishikata, C. Duplais, A. Krasovskiy, *Top. Catal.* **2010**, *53*, 985–990; (d) R. N. Butler, A. G. Coyne, *Chem. Rev.* **2010**, *110*, 6302–6337.

212 + **76a** $\xrightarrow[\substack{Cu(OAc)_2 \cdot H_2O \\ t\text{-AmOH, 120 °C, 20 h}}]{\substack{[RuCl_2(p\text{-cymene})]_2 \\ (2.5 \text{ mol\%}) \\ KPF_6 (10 \text{ mol\%})}}$ **213**

213ba: 6%   **213ca**: 0   **213da**: 68%[a]   **213ea**: 40% 62%[a]   **213fa**: 15%

[a] H_2O as solvent; isolated yield.
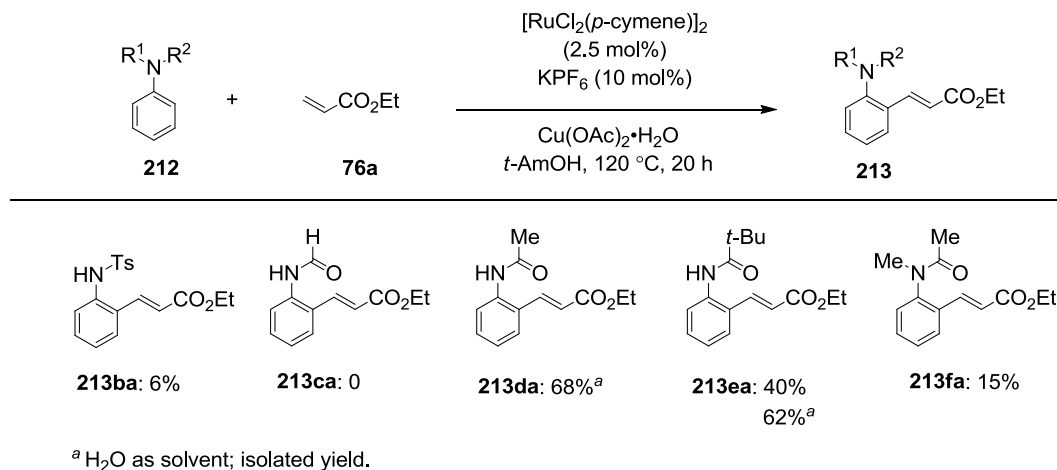
Scheme 74 Ruthenium(II)-catalyzed oxidative alkenylations

4.1.3 Scope and Limitations

With the optimized catalytic system in hand, we explored the scope in the ruthenium-catalyzed oxidative alkenylation of anilides **212** (Table 12). Thus, the catalytic C–H bond functionalization in water allowed for the efficient conversion of *para*-substituted substrates **212g−i** *via* chemoselective monoalkenylations (entries 1–5). Intramolecular competition experiments with *meta*-substituted anilides **212** site selectively delivered the products **213** through alkenylation in position C-6, likely due to steric interactions (entries 6−10). Notably, this reactivity pattern was not observed when using *meta*-fluoro-substituted anilide **212m** (entry 11), as was previously noted for ruthenium-catalyzed C–H bond functionalization with organic electrophiles.[24] Unfortunately, *ortho*-substituted substrate **212n** delivered the alkenylated product **213na** in only 41% conversion (entry 13). However, hydroarylation of alkenes surprisingly occurred with methy vinyl ketone (**76c**), yielding the corresponding alkylated product **213ac** in 31% yield (entry 12).[130]

Table 12 Oxidative alkenylations with anilides **212**[a]

212 + **76** $\xrightarrow[\substack{Cu(OAc)_2 \cdot H_2O \\ H_2O, 120 °C, 20 h}]{\substack{[RuCl_2(p\text{-cymene})]_2 \\ (5.0 \text{ mol \%}) \\ KPF_6 (20 \text{ mol \%})}}$ **213**

Entry	Anilide 212	Alkene 76	Product 213		Yield (%)
1		CO_2Et **76a**		R = Et (**213ga**)	67
2	**212g**	CO_2Bu **76b**	**213ga−213gb**	R = Bu (**213gb**)	55

(continued)

[130] For a similar subsequent example, see: L. Huang, Q. Wang, J. Qi, X. Wu, K. Huang, H. Jiang, *Chem. Sci.* **2013**, *4*, 2665−2669.

Table 12 *(continued)*
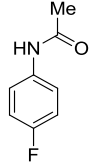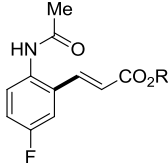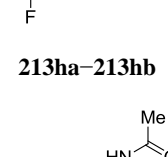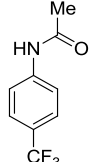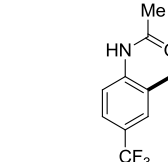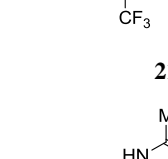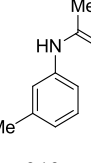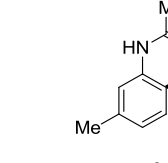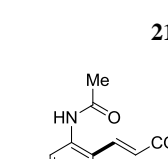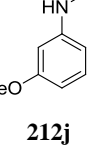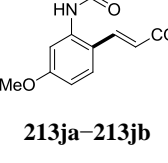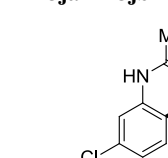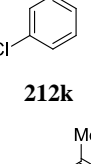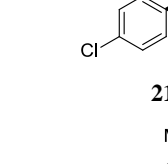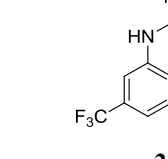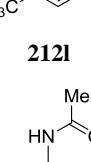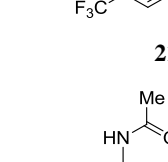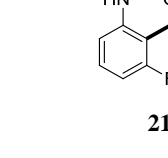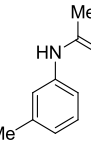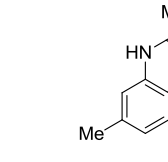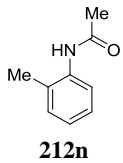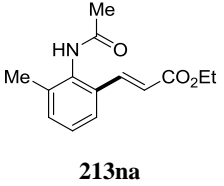
Entry	Anilide 212	Alkene 76	Product 213	Yield (%)
3	**212h**	**76a**	**213ha−213hb** R = Et (**213ha**)	74
4		**76b**	R = Bu (**213hb**)	53
5	**212i**	**76a**	**213ia**	46
6	**212a**	**76b**	**213ab**	56 (1:0)[b]
7	**212j**	**76a**	**213ja−213jb** R = Et (**213ja**)	58 (10:1)[b]
8		**76b**	R = Bu (**213jb**)	52 (6:1)[b]
9	**212k**	**76a**	**213ka**	66 (17:1)[b]
10	**212l**	**76a**	**213la**	53 (1:0)[b]
11	**212m**	**76a**	**213ma**	70 (4:1)[b]
12	**212a**	**76c**	**213ac**	31 (1:0)[b]

Table 12 (continued)

Entry	Anilide 212	Alkene 76	Product 213	Yield (%)
13	212n	76a	213na	41[c]
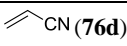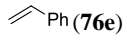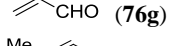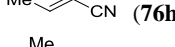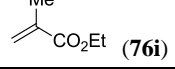
[a] Reaction conditions: **212** (0.50 mmol), **76** (0.75 mmol), [RuCl$_2$(p-cymene)]$_2$ (5.0 mol %), KPF$_6$ (10 mol %), Cu(OAc)$_2$ H$_2$O (0.5 mmol), H$_2$O (2.0 mL), 120 °C, 20 h, under N$_2$; isolated yields (of the major isomers). [b] Ratio of the regioisomers determined by GC. [c] GC conversion.

Furthermore, we were pleased to observe that this ruthenium-catalyzed oxidative C–H alkenylation proceeded smoothly even on a large scale (0.5g–5.0 g).[131] Herein, 5 mmol scale anilide loadings delivered the target product **213aa** in 73% yield (Scheme 75).
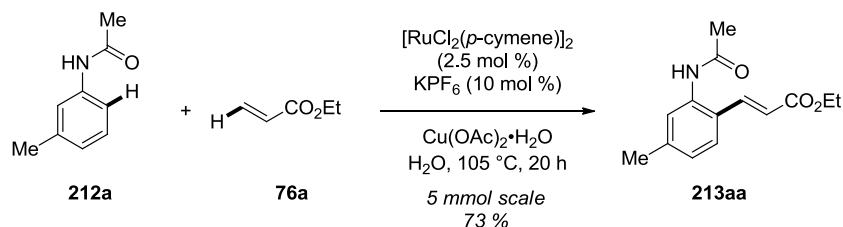
Scheme 75 Ruthenium(II)-catalyzed oxidative alkenylations of anilide **212a** in 5 mmol scale

The cationic ruthenium(II) system unfortunately led to low conversions with acrylonitrile (**76d**), styrene (**76e**), *tert*-butyl acrylate (**76f**), acrolein (**76g**) and α- or β-substituted alkenes (**76h−k**) (Table 13), even when switching H$_2$O to the organic solvent *t*-AmOH (entry 3).
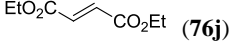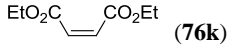
Table 13 Oxidative alkenylations with alkene derivatives **76**[a]

Entry	Alkene 76	213 (%)
1	CN (**76d**)	13
2	Ph (**76e**)	13
3		36[b]
4	CO$_2$tBu (**76f**)	0
5	CHO (**76g**)	0
6	Me CN (**76h**)	0
7	Me CO$_2$Et (**76i**)	0

(continued)

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[131] L. Wang, K. Rauch, A. V. Lygin, S. I. Kozhushkov, L. Ackermann, *Org. Synth.* submitted.

Table 13 *(continued)*

Entry	Alkene 76	213 (%)
8	EtO$_2$C$\diagup\!\diagdown$CO$_2$Et **(76j)**	3
9	EtO$_2$C$\diagdown\diagup$CO$_2$Et **(76k)**	0

^{a} Reaction conditions: **212a** (0.50 mmol), **76** (0.75 mmol), [RuCl$_2$(*p*-cymene)]$_2$ (5.0 mol %), KPF$_6$ (20 mol %), Cu(OAc)$_2$ H$_2$O (0.5 mmol), H$_2$O (2.0 mL), 120 ℃, 20 h, under N$_2$; GC conversion. ^{b} *t*-AmOH as solvent.

4.1.4 Mechanistic Studies

4.1.4.1 Intermolercular Competition Experiments

Considering the unique features of our ruthenium catalyst, we became interested in understanding its mode of action. Thus, intermolecular competition experiments revealed electron-rich anilides **212** to be preferentially functionalized (Scheme 76), which is in good agreement with an electrophilic activation manifold.
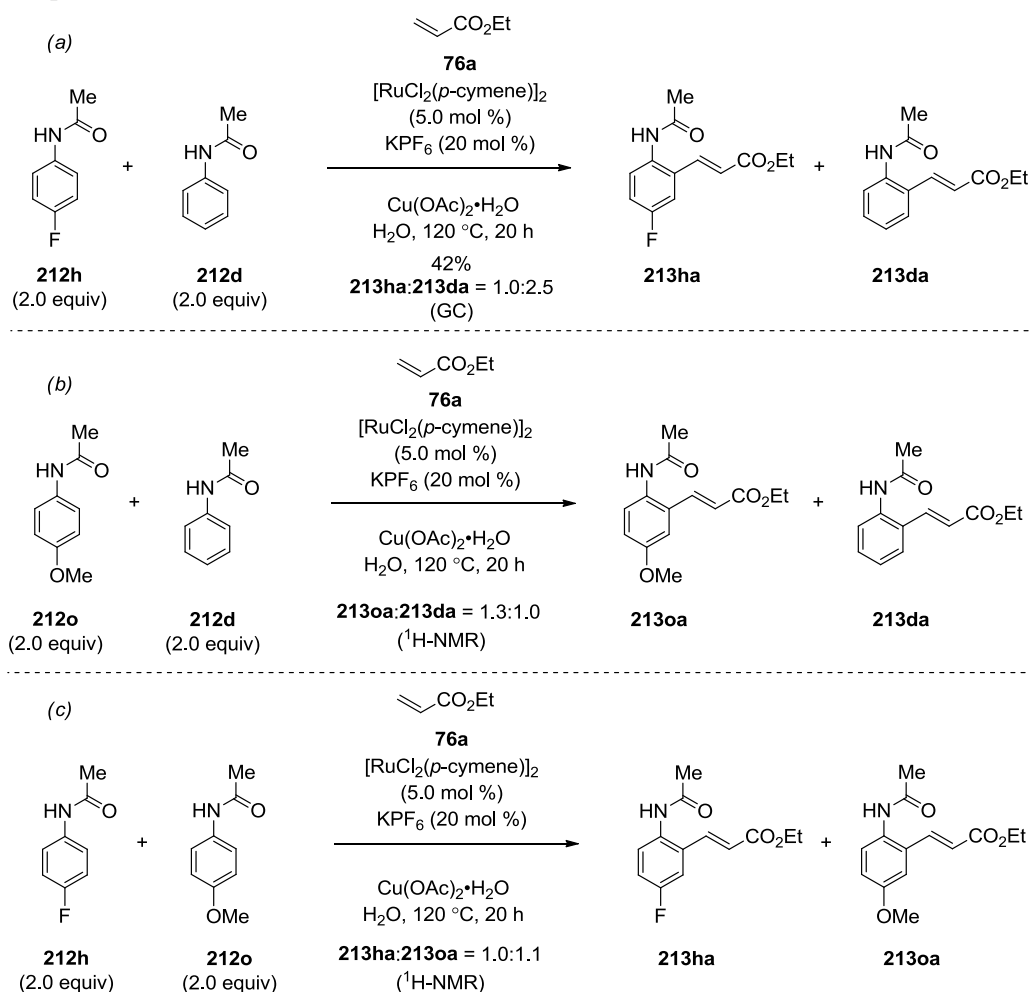
Scheme 76 Intermolecular Competition Experiments

4.1.4.2 Reactions in Isotopically Labelled Solvents

Oxidative alkenylation in D_2O unraveled the C–H bond activation in anilide **212d** to be reversible in nature (Scheme 77a).[128] Consistence with this result, an obvious H/D scrambling on both the recycled starting material [D]$_n$-**212a** and target product [D]$_n$-**213aa** were observed in the presence of alkene **76a** under identical reaction conditions in D_2O (Scheme 77b). These findings can be rationalized in that the ruthenium-catalyzed alkenylation proceeds by a reversible C–H bond metalation step.
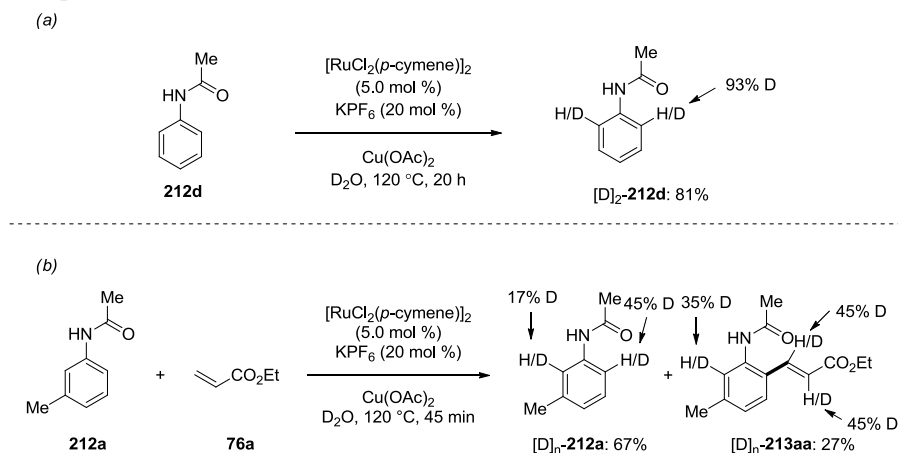
Scheme 77 Ruthenium-Catalyzed H/D Exchange in D_2O

4.1.5 Proposed Catalytic Cycle

Based on our mechanistic studies, we propose the catalytic cycle to involve an initial reversible acetate-assisted[8] cycloruthenation of the cationic species **233** with anilide **212** to form complex **235** through a transition state **234** (Scheme 78), which subsequently undergoes a migratory insertion with alkene **76** to furnish the six-membered intermediate **236**. Finally, β-hydride elimination yields the desired product **213**, and oxidation of [RuH] species with $Cu(OAc)_2$ regenerates the catalytically active cationic catalyst **233**.
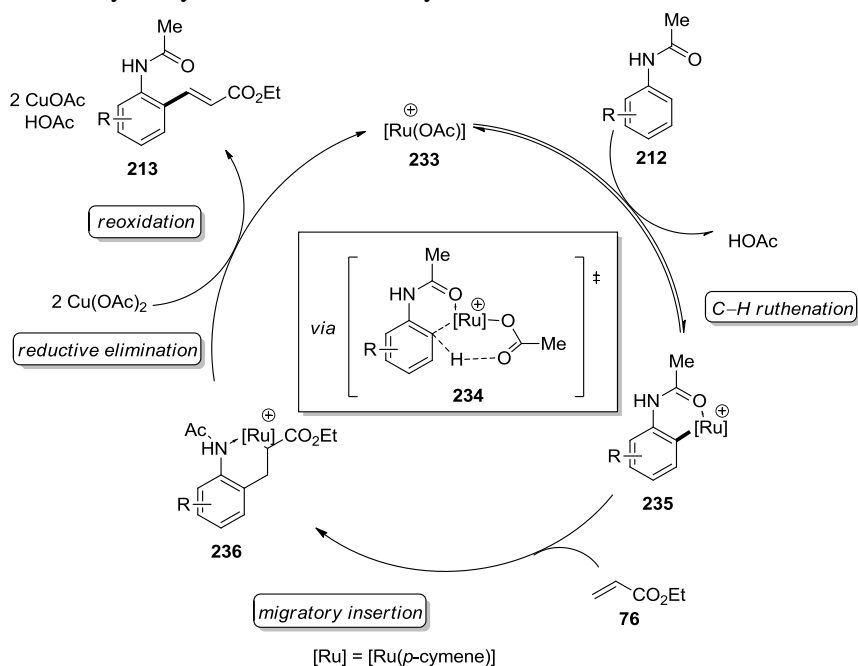
Scheme 78 Proposed mechanism for the ruthenium-catalyzed oxidative alkenylation

4.2 Ruthenium-Catalyzed Oxidative C–H Alkenylations of Benzamides

Notably, the efficient catalysis achieved with the cationic ruthenium(II) complex in water allowed for efficient oxidative alkenylations of benzamides.[128] Thus, direct C−H bond functionalization of heteroaromatic amides **214** occurred with high catalytic efficacy and excellent site selectivity (Table 14). However, the alkenylation of *NH*-free indole **214c** did not proceed under the identical reaction conditions (entry 3).

Table 14 Oxidative alkenylation of heteroaromatic amides **214**[a]

Entry	Amide 214	Alkene 76	Product 215	Yield (%)
1	**214a**	**76a**	**215aa**	52
2	**214b**	**76a**	**215ba**	71
3	**214c**	**76a**	**215ca**	0
4	**214d**	**76a**	**215da**	36, 64[b]
5	**214e**	**76a**	R = Et (**215ea**)	76
6	**214e**	**76b**	R = Bu (**215eb**) 215ea−215eb	72

[a] Reaction conditions: **214** (0.50 mmol), **76** (0.75 mmol), [RuCl$_2$(*p*-cymene)]$_2$ (5.0 mol %), KPF$_6$ (20 mol %), Cu(OAc)$_2$ H$_2$O (0.5 mmol), H$_2$O (2.0 mL), 120 °C, 20 h, under N$_2$; isolated yield. [b] *t*-AmOH as solvent.

Furthermore, the site selectivity within intramolecular competition experiments with heteroaromatic amides was largely governed by electrophilic effects. Hence, substrate **214f** was

preferentially functionalized at its C-2 position (Scheme 79).
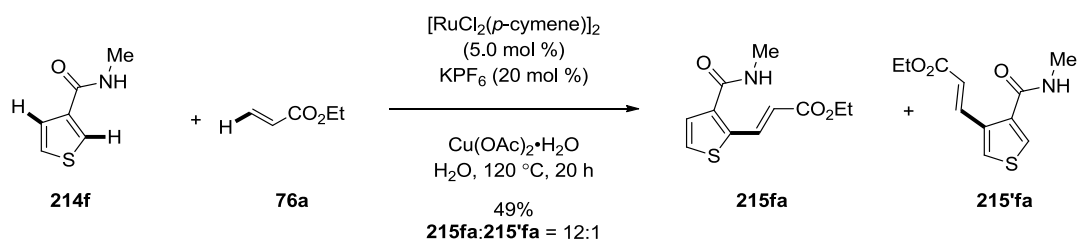
Scheme 79 Intramolecular competition experiments with amide **214f**

5 Ruthenium(II)-Catalyzed C(sp^3)−H α-Alkylation of Pyrrolidines with Alkenes

In spite of the progress on ruthenium-catalyzed C(sp^3)−H alkylations with alkenes in the past years, these protocols were largely restricted to Ru$_3$(CO)$_{12}$ catalysis under harsh conditions, i.e. relatively high pressure and reaction temperature.[95,97,99] Taking into consideration our group's recent report on ruthenium-catalyzed hydroarylations with unactivated alkenes through carboxylate-assistance,[87] we hence set out to develop a novel directed C(sp^3)−H alkylations of alkenes on pyrrolidines by ruthenium(II) catalyst.

5.1 Optimization Studies

Based on recently obtained results from our group,[132] we were interested in exploring representative cocatalytic additives for the envisioned hydroalkylation of unactivated alkenes **111a** (Table 15). Not surprisingly, test reactions clearly illustrated the importance of [RuCl$_2$(PPh$_3$)$_3$] as well as of *rac*-BINAP. Indeed, simple [RuCl$_2$(PPh$_3$)$_3$] did not affect the desired C−H bond functionalization in the absence of ligands and additives (entry 1). Likewise, in the absence of *rac*-BINAP satisfactory results were not obtained (entries 2–4). Notably, more promising results were achieved utilizing metal triflate as additives, and AgOTf was identified as being optimal (entries 5–7).

Table 15 Further screenings of the ruthenium(II)-catalyzed C(sp^3)−H alkylation of pyrrolidine **216a**[a]

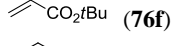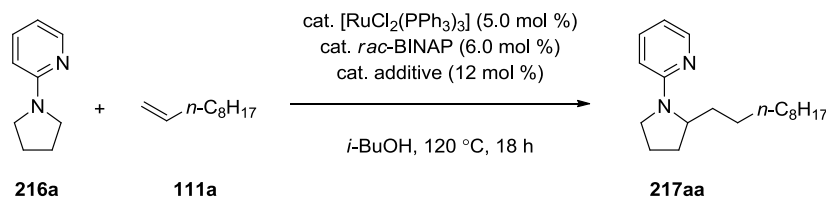| Entry	Additive	217aa (%)
1	—	4[b]
2	—	8
3	AgOTf	0[c]
4	AgOTf	<1[b]
5	AgOTf	73[d]
6	AgOAc	7
7	NaOTf	70[d]

[a] Reaction conditions: **216a** (1.5 mmol), **111a** (0.5 mmol), [RuCl$_2$(PPh$_3$)$_3$] (5.0 mol %), *rac*-BINAP (6.0 mol %), additive (12 mol %), 120 ˚C, 18 h; GC analysis with *n*-tridecane as an internal standard. [b] Without *rac*-BINAP. [c] Without [RuCl$_2$(PPh$_3$)$_3$] [d] Isolated yield.

5.2 Scope and Limitations

With a highly selective catalytic system in hand (Table 15, entry 5), we next examined the influence exerted by substituents at the heteroaromatic moiety (Table 16). Thus, the optimized

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[132] Ph.D Dissertation, M. Schinkel, University of Göttingen, Göttingen, Germany, **2013**.

ruthenium catalyst proved applicable to high-yielding transformations of pyrrolidines with 3-, 4- or 5-substituents on the pyridyl group, thereby selectively delivering the monoalkylated products **217ba–217ea** (entries 1−4). Notably, the optimized catalyst system was not restricted to pyridine moieties, but also enabled the C–H activation using an isoquinoline (entry 6). Contrarily, methyl groups either on the pyridine (**216f**) or on the pyrrolidine (**216h**) had a detrimental effect (entries 5 and 7).
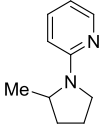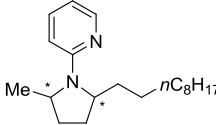
Table 16 Ruthenium(II)-catalyzed C(sp^3)−H alkylation with pyrrolidine **216**^{a}
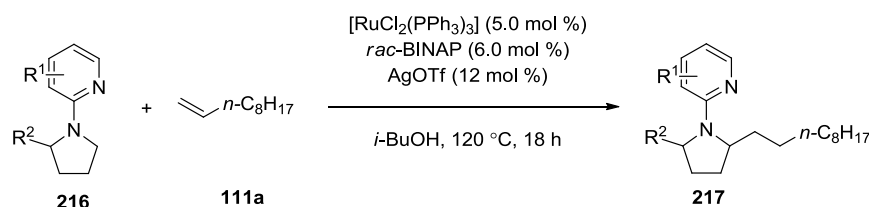
Entry	Pyrrolidine 216	Product 217		Yield (%)
1			R = Me (**217ba**)	94
2	**216b–c**	**217ba–217ca**	R = CF$_3$ (**217ca**)	72
3	**216d**	**217da**		64
4	**216e**	**217ea**		76
5	**216f**	**217fa**		1^b
6	**216g**	**217ga**		67
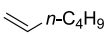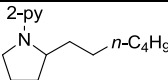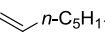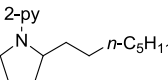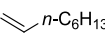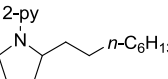
(continued)

Table 16 (*continued*)

Entry	Pyrrolidine 216	Product 217	Yield
7	 Me **216h**	 Me–*–N–*–nC$_8$H$_{17}$ **217ha**	7[b]

^{a} Reaction conditions: **216** (1.5 mmol), **111a** (0.5 mmol), [RuCl$_2$(PPh$_3$)$_3$] (5.0 mol %), *rac*-BINAP (6.0 mol %), AgOTf (12 mol %), 120 ˚C, 18 h; isolated yield. ^{b} GC analysis with *n*-tridecane as the internal standard.

Thereafter, we explored the versatility of this method by testing a representative set of unactivated alkenes **111** (Table 17). Different alkenes **111b–h** furnished the corresponding products **217bb–bh** in high yields even at a significantly reduced temperature of 80 ˚C (entries 1−7). Notably, the catalytic system tolerated functional groups, such as silanes (**111i** and **111j**) or ethers (**111k**) (entries 8−10). Intriguingly, competition experiments with haloalkenes **111l** and **111m** highlighted the excellent chemoselectivity of the C(sp^3)−H alkylations with substrates **111l–n** (entries 11−12), in that products stemming from direct C–H bond alkylations with the alkyl halide moieties were not observed.[26, 133] Likewise, styrene derivatives **111o–s** proved to be suitable substrates, delivering the corresponding alkylated products **217bo−217bs** in good yields (entries 13−18).
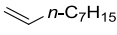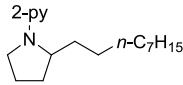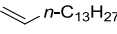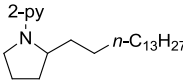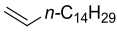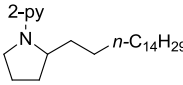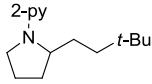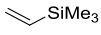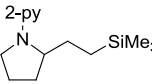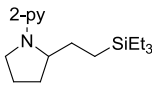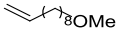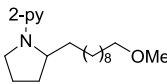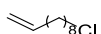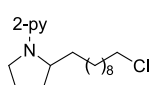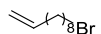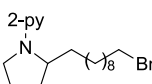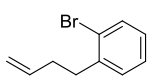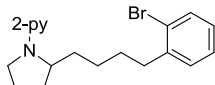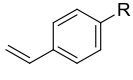
Table 17 Ruthenium(II)-catalyzed C(sp^3)−H alkylation with alkene **111**^{a}
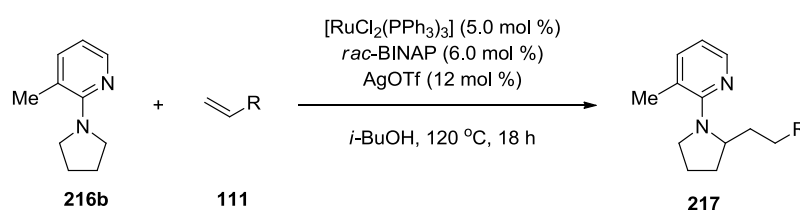
Entry	Alkene 111	Product 217	Yield (%)
1	n-C$_4$H$_9$ **111b**	2-py n-C$_4$H$_9$ **217bb**	73[b]
2	n-C$_5$H$_{11}$ **111c**	2-py n-C$_5$H$_{11}$ **217bc**	78[b]
3	n-C$_6$H$_{13}$ **111d**	2-py n-C$_6$H$_{13}$ **217bd**	90

(*continued*)

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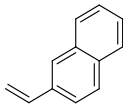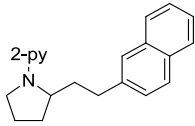
[133] Selected examples on ruthenium-catalyzed direct alkylations with alkyl halides: *ortho*-Alkylations: (a) L. Ackermann, P. Novák, R. Vicente, N. Hofmann, *Angew. Chem. Int. Ed.* **2009**, *48*, 6045–6048; (b) L. Ackermann, N. Hofmann, R. Vicente, *Org. Lett.* **2011**, *13*, 1875–1877; *meta*-Alkylations: (c) N. Hofmann, L. Ackermann, *J. Am. Chem. Soc.* **2013**, *135*, 5877–5884; Highlight article: (d) F. Juliá-Hernández, M. Simonetti, I. Larrosa, *Angew. Chem. Int. Ed.* **2013**, *52*, 11458–11460.

Table 17 *(continued)*

Entry	Alkene 111	Product 217		Yield (%)
4	*n*-C$_7$H$_{15}$ **111e**	2-py ... *n*-C$_7$H$_{15}$ **217be**		89
5	*n*-C$_{13}$H$_{27}$ **111f**	2-py ... *n*-C$_{13}$H$_{27}$ **217bf**		85
6	*n*-C$_{14}$H$_{29}$ **111g**	2-py ... *n*-C$_{14}$H$_{29}$ **217bg**		87
7	*t*-Bu **111h**	2-py ... *t*-Bu **217bh**		50^{b,c}
8	SiMe$_3$ **111i**	2-py ... SiMe$_3$ **217bi**		59^b
9	SiEt$_3$ **111j**	2-py ... SiEt$_3$ **217bj**		86
10	$\}_8$OMe **111k**	2-py ... $\}_8$OMe **217bk**		65^d
11	$\}_8$Cl **111l**	2-py ... $\}_8$Cl **217bl**		82
12	$\}_8$Br **111m**	2-py ... $\}_8$Br **217bm**		60
13	Br **111n**	2-py ... Br **217bn**		82
14	R **111o–r**	2-py ... R **217bo–217br**	R = H (**217bo**)	73
15			R = OMe (**217bp**)	70
16			R = Br (**217bq**)	65
17			R = F (**217br**)	64

(continued)

Table 17 (*continued*)

Entry	Alkene 111	Product 217	Yield (%)
18	**111s**	**217bs**	57

^{a} Reaction conditions: **216b** (1.5 mmol), **111** (0.5 mmol), [RuCl$_2$(PPh$_3$)$_3$] (5.0 mol %), *rac*-BINAP (6.0 mol %), AgOTf (12 mol %), 120 °C, 18 h; Isolated yield. ^{b} 80 °C. ^{c} **216b** (0.5 mmol), **111h** (1.5 mmol). ^{d} DCE as solvent.

However, nucleophilic substitution occurred upon alkylation of the substrate **111t** in the protic solvent *i*-BuOH, affording product **219'bt** (Scheme 80a). Fortunately, simply switching the solvent to aprotic DCE delivered the target product **219bt** in good yield applying the optimized ruthenium catalyst. Besides, alkene **111u** with a ketone moiety was well tolerated, while alkylation along with unexpected hydrogen transfer generated the reduced product **217bv** in a moderate yield (Scheme 80b).
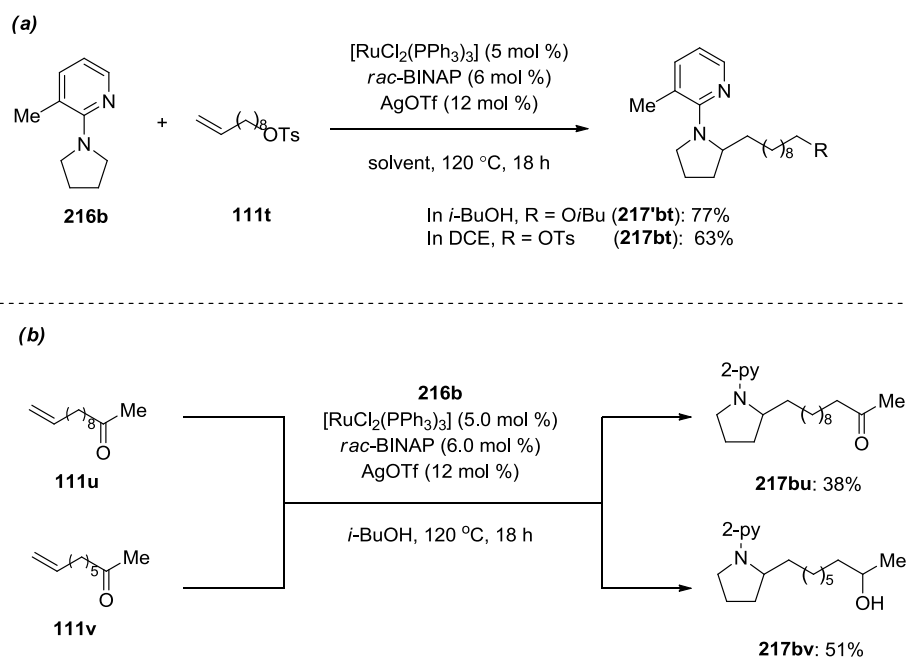
Scheme 80 Ruthenium(II)-catalyzed C(sp^3)−H alkylation with alkenes **111t–v**

Unfortunately, substrates with six- or seven-membered rings fused to a pyrrolidine moiety, and among others compounds **237a–b** gave unsatisfactory results under the identical conditions (Scheme 81).[134] Furthermore, substrates **237c–g** bearing oxazole, pyrrole, imine, acetyl or cyano directing groups proved inefficient. On the other hand, products of reduction were obtained in low yield from activated alkenes **76a**, **76c** and **238a–c**. Terminal, internal and cyclic alkenes **238d–g** and diene **238h** as well as alkynes **238i–j** and **38a** were inactive under the standard reaction conditions.

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[134] For details, see also: B.Sc. Thesis, K. Bielefeld, University of Göttingen, Göttingen, Germany, **2012**.

237a
No conv.

237b
No conv.

237c
No conv.

237d
9% conv.

237e
No conv.

237f
No conv.

237g
No target procuct.

76a
No conv.

76c
29% (reductive prod.)

238a
No conv.

238b
No conv.

238c
No conv.

238d
No conv.

238e
11 % (isomerization)

238f
No conv.

238g
No conv.

238h
No conv.

238i
14%

238j
22%

38a
10%
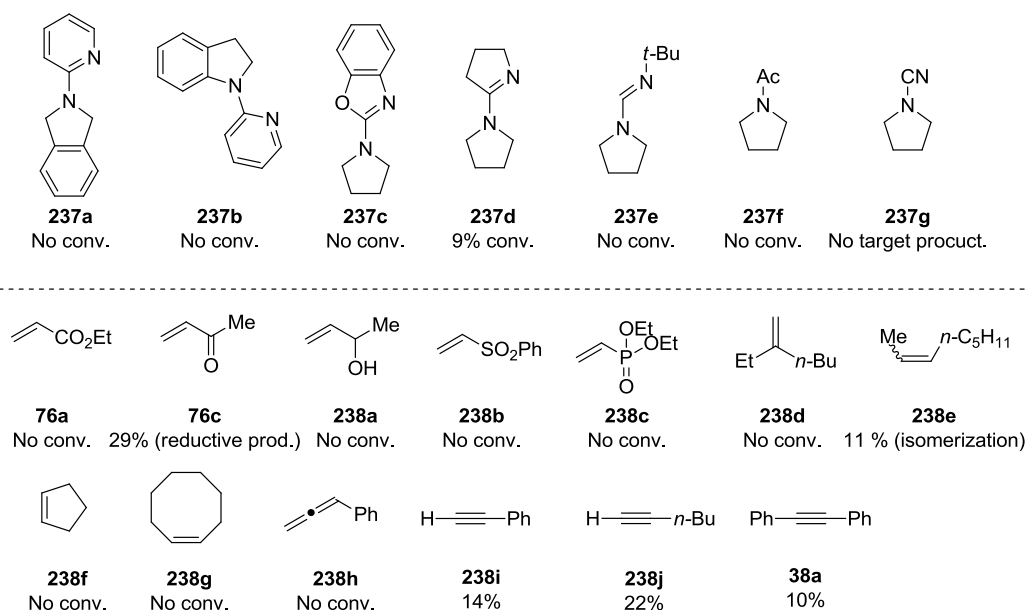
Scheme 81 Limitations of substrate scope under the identical conditions

5.3 Mechanistic Studies

5.3.1 Reactions in the Presence of Radical Scavengers

Given the unique reactivity profile of the novel ruthenium(II) catalyst, we subsequently performed mechanistic studies to rationalize its mode of action. Thus, SET-type processes could be ruled out by successfully performing the C(sp^3)–H alkylation in the presence of stoichiometric amounts of the radical scavenger TEMPO (Scheme 82).

[RuCl$_2$(PPh$_3$)$_3$] (5.0 mol %)
rac-BINAP (6.0 mol %)
AgOTf (12 mol %)

i-BuOH, 120 °C, 18 h

216b   **111a**

with TEMPO (3.0 equiv):   **217ba**: 70%
without TEMPO: **217ba**: 94%
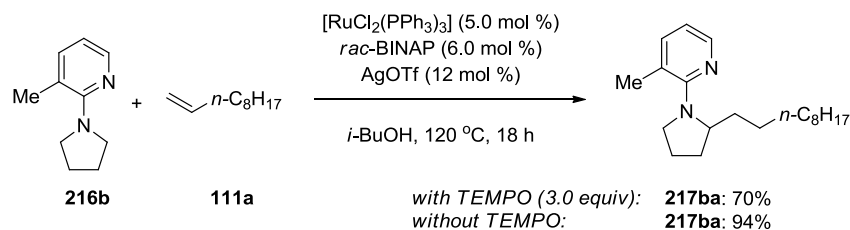
Scheme 82 Mechanistic studies with TEMPO

5.3.2 Reactions in Isotopically Labelled Reagents

Next, the H/D exchange reaction was undertaken to obtain information concerning the reaction mechanism. In the present case, ruthenium(II)-catalyzed C(sp^3)–H alkylation in [D]$_4$-MeOH (Schemes 83a–b) or with isotopically enriched substrate [D]$_n$-**216b** (Scheme 84) indicated the C–H bond metalation step to be reversible. Surprisingly, the treatment of **216b** under catalytic reaction conditions (either in the absence or presence of **111a**) in [D]$_4$-MeOH showed significant deuterium incorporation at the β-positions of the pyrrolidine (Scheme 83a–b). However, this result is in line with the observation reported by Murai and coworkers for ruthenium(0) catalyst (Scheme 83c).[96]

(a)

(b)
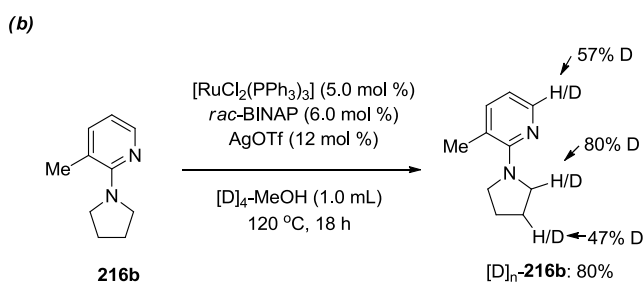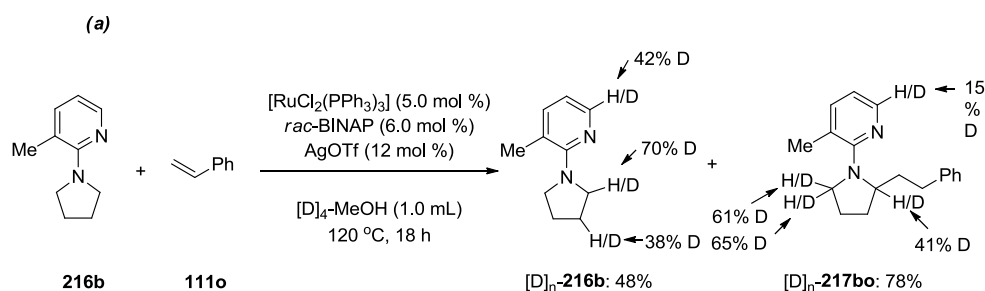
(c) H/D exchange experiment performed by Murai:
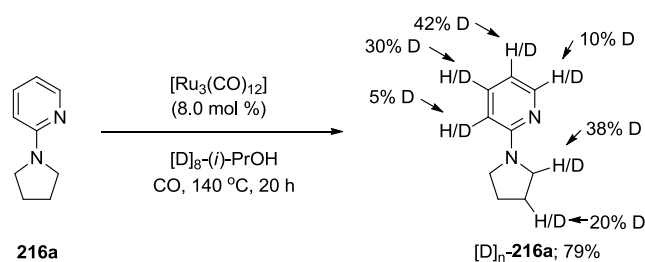
Scheme 83 Studies in isotopically labelled solvents
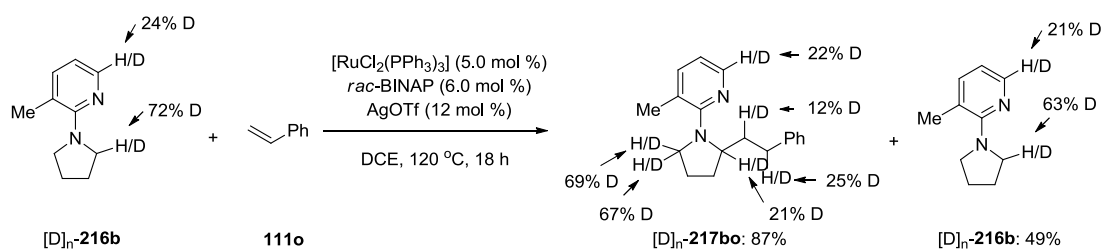
Scheme 84 Studies in isotopically labelled compounds

5.4 Proposed Catalytic Cycle

Based on our experimental mechanistic studies, the following catalytic cycle for the ruthenium(II)-catalyzed C(sp^3)−H alkylation of pyrrolidines **216** is postulated (Scheme 85). Initially, the active species **239** is *in situ* formed from ruthenium precursor. Subsequently, reversible C–H bond metalation *via* transition state **240** forms ruthenacycle **241**, which is similar to those observed in the carboxylate-assisted ruthenium-catalyzed oxidative direct C–H activations.[8] Coordination of alkene **111** followed by its regioselective migratory insertion deliver a key intermediate **243**. Finally, reductive elimination of **243** affords complex **244**, which subsequently releases the desired product **217** and regenerates the active species **239**. However, it should be noted that a precise investigation of the exact intermediate structures in terms of the

ligand sphere is required. Due to the important role of *rac*-BINAP in the process (Table15, entry 1), it remains questionable as to whether exchange of *rac*-BINAP with PPh$_3$ as a ligand occurs.[84]
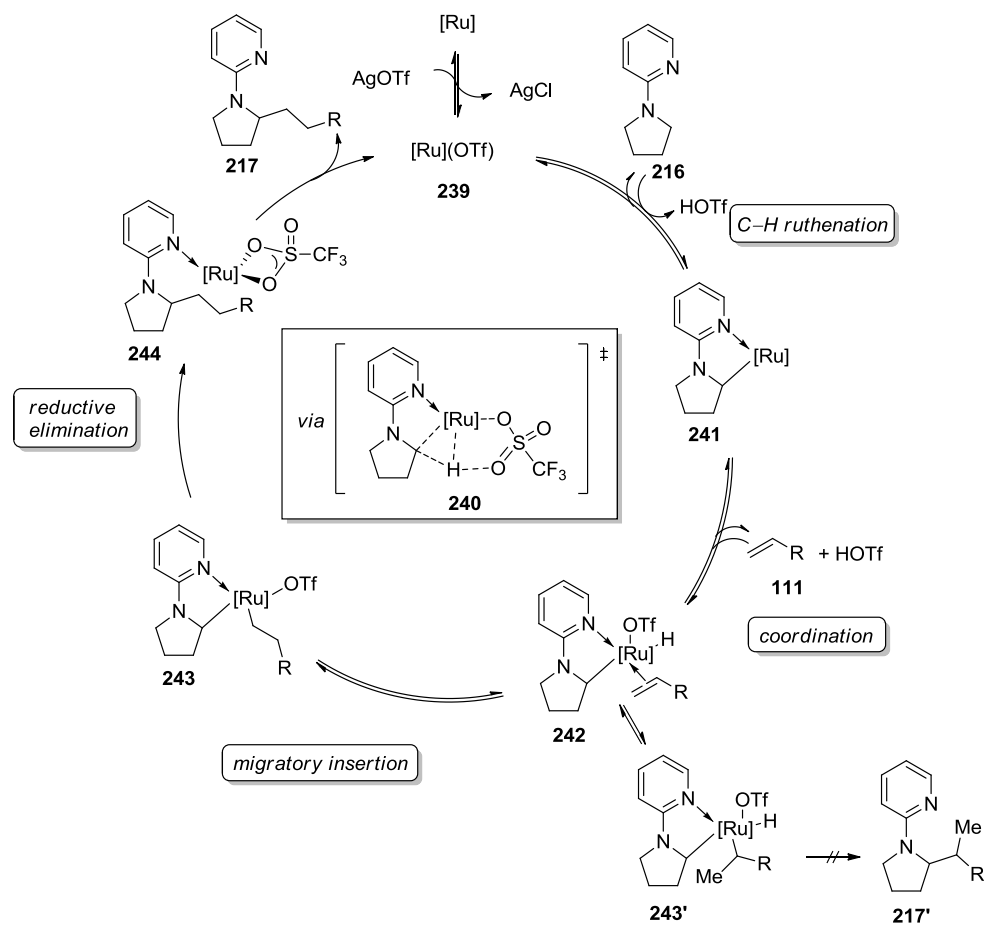
Scheme 85 Proposed reaction mechanism

5.5 Removal of the Directing Groups

The pyridyl directing group was efficiently removed according to Maes' recent "one-pot" protocols, namely, hydrogenation/hydride reduction and quaternization/hydride reduction strategies (Scheme 86).[135] Thus, the hydrogenation/hydride reduction protocol was successfully applied to substrate **217ba** and **217bj**, delivering the desired (*NH*)-free pyrrolidines under comparably mild conditions (Scheme 86a). Although the pyridine directing group in substrate **217bo** was removed under the hydrogenation/hydride reduction strategy as well, the arene ring of the phenethyl moiety was simultaneously reduced. Further switching to the quaternization/hydride reduction strategy led to unsatisfactory result (Scheme 86b).

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[135] V. Smout, A. Peschiulli, S. Verbeeck, E. A. Mitchell, W. Herrebout, P. Bultinck, C. M. L. Vande Velde, D. Berthelot, L. Meerpoel, B. U. W. Maes, *J. Org. Chem.* **2013**, *78*, 9803−9814.

(a) "Hydrogenation Hydride Reduction" Strategy

1) Pt/C (10 mol %), H$_2$ (1 atm)
   HCl (1.2 equiv), EtOH
   23 °C, 24 h

2) NaBH$_4$ (4.0 equiv)
   MeOH, 0 °C, 15 min

217

R = n-C$_8$H$_{17}$ (**218ba**): 70%
R = SiEt$_3$ (**218bj**): 61%

1) Pt/C (10 mol %), H$_2$ (1 atm)
   HCl (1.2 equiv), EtOH
   23 °C, 24 h

2) NaBH$_4$ (4.0 equiv)
   MeOH, 0 °C, 15 min

218bo: 58%

217bo

1) MeOTf (3.6 equiv)
   MeCN, 23 °C, 5 min

2) NaBH$_4$ (10.0 equiv)
   MeOH, 0 °C, 15 min

S.M. was recovered,
no target ptoduct
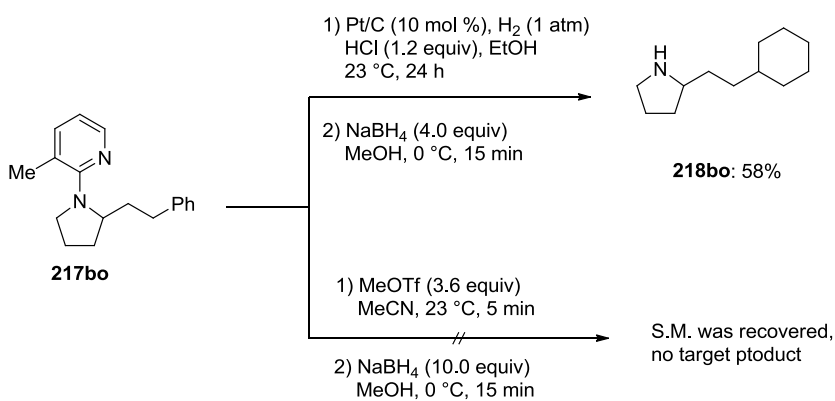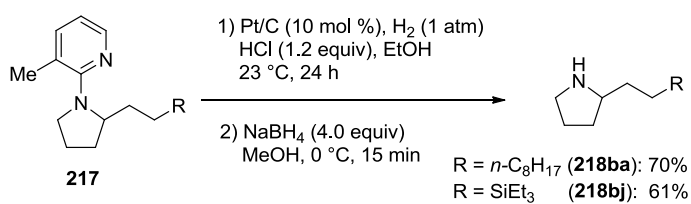
(b) "Quaternization Hydride Reduction" Strategy

Scheme 86 Removal of the directing groups

6 Ruthenium-Catalyzed *ortho*-C−H Halogenations

In addition to the C−C bond formations, ruthenium complexes have been identified as powerful catalysts for the oxidative transformation of otherwise unreactive C−H bonds into C−O and C−N bonds.[30] In strict contrast, ruthenium-catalyzed intermolecular[114] C−Hal bond forming processes are unfortunately not available. Herein, we established a ruthenium catalytic system which enabled the first ruthenium-catalyzed intermolecular brominations and iodinations of benzamides using *N*-halosuccinimides as halogen sources.[136]

6.1 Preliminary Studies with Ruthenium(II)-Catalysis

6.1.1 *ortho*-Halogenations of Electron-Rich Arenes

At the outset of our studies, we explored the widely used [RuCl$_2$(*p*-cymene)]$_2$ complex for the halogenation of electron-rich anilide **184a** with CuBr$_2$ or NBS as a halogen source (Table 18). To our disappointment, only classical electrophilic aromatic substitution (S$_E^{Ar}$) occurred delivering the corresponding *para*-brominated product **245a** both in the absence and presence of the catalyst. Further efforts to probe parameters, including oxidant, additive and solvent, unfortunately did not offer the target *ortho*-brominated product even at the lower reaction temperature (entries 2, 10 and 11). In addition, no conversion was observed with CuCl$_2$ as a halogenating reagent (entries 7 and 8).

Table 18 Screenings of the ruthenium(II)-catalyzed C–H halogenations of acetanilide **184a**[a]
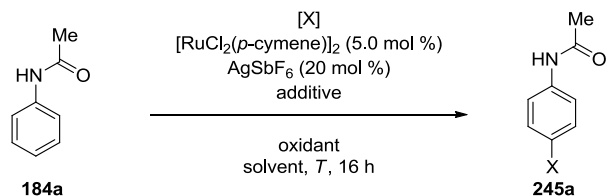
Entry	[X] (equiv)	Oxidant (equiv)	Additive (equiv)	Solvent	T (°C)	245a (%)
1	CuBr$_2$ (2.0)	—	PivOH (1.1)	MeCN	100	76[b]
2	CuBr$_2$ (2.0)	—	—	DCE	60	10
3	CuBr$_2$ (2.0)	Cu(OAc)$_2$ (2.0)	—	DCE	100	49
4	CuBr$_2$ (2.0)	—	PTSA H$_2$O (1.1)	DCE	100	7
5	CuBr$_2$ (2.0)	Cu(OAc)$_2$ (2.0)	PivOH (1.1)	AcOH	100	11
6	CuBr$_2$ (2.0)	Cu(OAc)$_2$ (2.0)	PivOH (1.1)	MeCN	100	63
7	CuCl$_2$ (2.0)	—	—	DCE	60	0
8	CuCl$_2$ (2.0)	Cu(OAc)$_2$ (2.0)	—	DCE	90	0
9	NBS (1.1)	Cu(OAc)$_2$ (2.0)	—	DCE	120	100[b]
10	NBS (1.1)	—	—	DCE	60	71
11	NBS (1.1)	—	PTSA H$_2$O (0.5)	DCE	60	100

[a] Reaction conditions: **187a** (0.5 mmol), halogen source [X], [RuCl$_2$(*p*-cymene)]$_2$ (5.0 mol %), AgSbF$_6$ (20 mol %), additive, solvent (2.0 mL), 60−120 °C, 16 h; GC conversion. [b] Without [RuCl$_2$(*p*-cymene)]$_2$.

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[136] L. Wang, L. Ackermann, *Chem. Commun.* **2014**, *50*, 1083–1085.

Further screenings of directing groups (DG) with [RuCl$_2$(*p*-cymene)]$_2$ as the catalyst gave unsatisfactory results as well (Scheme 87). For instance, the use of **184b** and **184c** delivered *para*-brominated products in low yields, whereas no conversion was observed for electron-rich substrates **184d–g**.
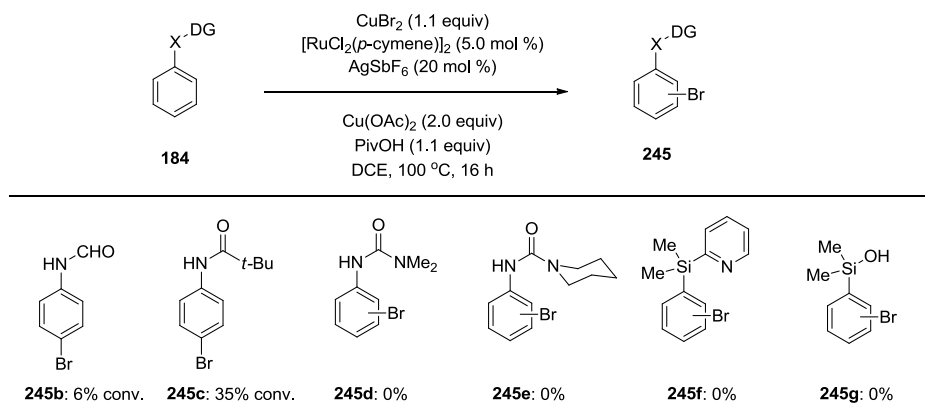
Scheme 87 Ruthenium(II)-catalyzed C–H halogenations of electron-rich arenes **184**

6.1.2 *ortho*-Halogenations of Electron-Deficient Arenes

As the bromination of electron-rich substrates always led to significant formation of *para* electrophilic substitution products, we subsequently turned to more challenging electron-deficient arenes (Table 19). Herein, *ortho*-bromination on benzamide **219a** was observed employing CuBr$_2$ as the halogen source, yet with low conversion (6%). However, further screenings proved *N*-bromosuccinimide (NBS) to be more efficient for ruthenium(II)-catalyzed *ortho*-C−H halogenations under otherwise identical reaction conditions (entry 2). In spite of acids are known to serve as critical additives in the palladium-[107,108] and rhodium-catalyzed[113] *ortho*-C−H halogenations, to our disappointment, no better results were obtained with acidic additives in our ruthenium(II) system. The reason for this is obviously a competitive *ortho*-C–O bond formation (**246a**) (entries 3−14), and addition of an external oxidant did not improve the situation (entries 8 and 12). However, we were pleased to observe that switching to a catalytic amount of the corresponding silver(I) carboxylate salt significantly improved the efficacy (entries 15−20), and the target product **220a** was obtained in 43% isolated yield with AgO$_2$CCF$_3$ (entry 16). In addition, base additives did shut down the reaction almost completely (entries 21−22).

Table 19 Screenings of the ruthenium(II)-catalyzed C–H brominations of benzamide **219a**[a]
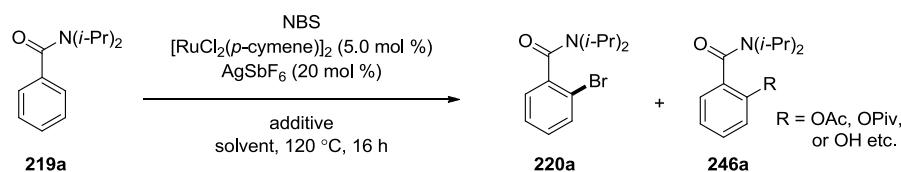
Entry	Additive (equiv)	Solvent	Yield of 220a (%)	246a (%)
1[b]	—	DCE	0	0
2	—	DCE	27	0
3	PTSA H$_2$O (1.1)	DCE	0	0
4	TfOH (1.1)	DCE	11	0

Table 19 *(continued)*

Entry	Additive (equiv)	Solvent	Yield of 220a (%)	246a (%)
5	MesCO$_2$H (1.1)	DCE	9	9
6	(1-Ad)CO$_2$H (1.1)	DCE	0	0
7	PivOH (1.1)	DCE	20	39
8[c]	PivOH (1.1)	DCE	12	33
9	TFA (1.1)	DCE	21	32
10	TFA (1.1)	MeCN	1	4
11	TFA (1.1)	AcOH	7	3
12[d]	TFA (1.1)	DCE	2	0
13	TFAA (1.1)	DCE	31	22
14[e]	TFA (1.1)	DCE	0	0
15[b]	AgO$_2$CCF$_3$ (0.2)	DCE	0	0
16	AgO$_2$CCF$_3$ (0.2)	DCE	51 (43[f])	18
17	AgO$_2$CCF$_3$ (0.5)	DCE	13	32
18[g]	AgO$_2$CCF$_3$ (0.2)	DCE	32	16
19	Ag$_2$O (0.2)	DCE	5	0
20	AgOTf (0.2)	DCE	11	2
21	KO$_2$CCF$_3$ (0.2)	DCE	5	2
22	CsOPiv (1.1)	DCE	0	7

[a] Reaction conditions: **219a** (0.5 mmol), NBS (1.0 mmol), [RuCl$_2$(*p*-cymene)]$_2$ (5.0 mol %), AgSbF$_6$ (20 mol %), additive, solvent (2.0 mL), 100−120 ℃, 16 h; GC-yield. [b] Without [RuCl$_2$(*p*-cymene)]$_2$. [c] Cu(OAc)$_2$ (1.0 mmol). [d] CuBr$_2$ (0.1 mmol). [e] KPF$_6$ was used instead of AgSbF$_6$. [f] Isolated yield. [g] 100 ℃.

Functional directing groups, such as amide, ester, ketone and pyridine (Scheme 88), were also examined under the optimal reaction conditions (Table 19, entry 16). Unfortunately, only low conversions to the *ortho*-brominated products were observed. Moreover, significant side reactions such as bromination of the methyl group and *ortho*-oxygenation occurred in acetophenone (**247e**) and 2-phenylpyridine (**247f**), respectively.
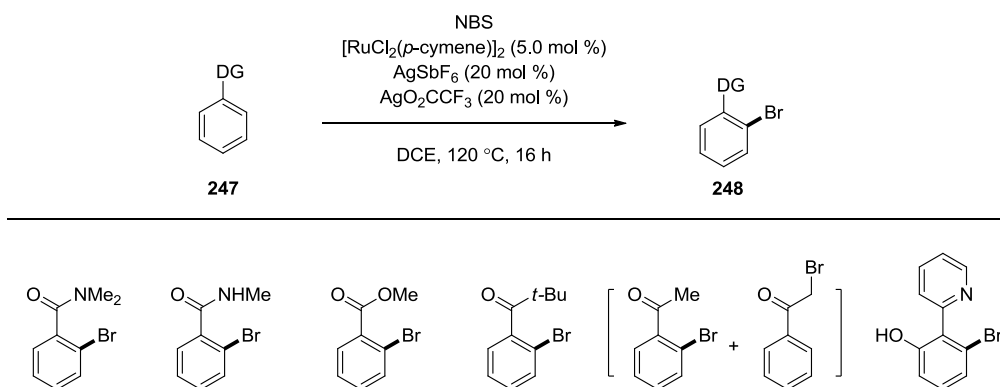
Scheme 88 Ruthenium(II)-catalyzed *ortho*-C–H halogenations of electron-deficient arenes **247**

6.2 Ruthenium(0)-Catalyzed *ortho*-C−H Halogenations of Benzamides

6.2.1 Optimization Studies

To our delight, simply switching the catalyst to $Ru_3(CO)_{12}$ for the *ortho*-C−H halogenations of benzamide **219a** successfully delivered the desired product **220a** in 27% yield (Table 20, entry 1). Notably, control experiment showed that no conversion of the starting material **219a** was detected in the absence of $Ru_3(CO)_{12}$, highlighting the efficiency of the ruthenium(0)-catalyzed pathway (entries 2 and 14). Further investigations indicated that stoichiometric quantities of carboxylate acid not only promoted the *ortho*-halogenation, but also provoked *ortho*-oxygenation affording small amounts of the by-product **246a** (entries 3−13). Maes has recently reported that alcohol additives were efficient in ruthenium(0)-catalyzed $C(sp^3)$−H $α$-alkylation reactions.[99] However, alcohol additives herein completely inhibited the halogenation process (entry 16). It is noteworthy that the use of additional oxidants, such as copper(II) salts, did not improve the yield (entries 5 and 15). Furthermore, switching the solvent to AcOH, MeCN, or even neat reaction did not improve the reaction efficacy (entries 17−19).

Table 20 Screenings of the ruthenium(0)-catalyzed *ortho*-C–H halogenations with acids as additives[a]
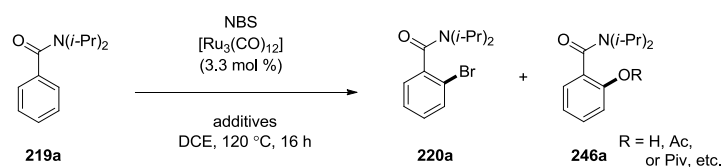
Entry	Additive A (equiv)	Additive B (equiv)	Solvent	Yield of 220a (%)	246a (%)
1	—	—	DCE	27	0
2[b]	—	—	DCE	<2	0
3	PTSA H$_2$O (2.0)	—	DCE	5	0
4	TFA (2.0)	—	DCE	39	0
5	TFA (2.0)	Cu(OAc)$_2$ (2.0)	DCE	43	7
6	AcOH (1.0)	—	DCE	56	7
7	Ac$_2$O (1.0)	—	DCE	55	5
8	AcOH (1.0) + Ac$_2$O (1.0)	—	DCE	54	5
9	MesCO$_2$H (2.0)	—	DCE	9	0
10	PhCO$_2$H (2.0)	—	DCE	24	0
11	(1-Ad)CO$_2$H (2.0)	—	DCE	57	<3
12	PivOH (2.0)	—	DCE	57	11
13	PivOH (0.2)	—	DCE	19	0
14[b]	PivOH (0.2)	—	DCE	<2	0
15	PivOH (2.0)	CuBr$_2$ (2.0)	DCE	16	0
16	PivOH (2.0)	*i*-PrCHOH (5.0)	DCE	0	0
17	PivOH (0.2)	—	AcOH	41	4
18	PivOH (0.2)	—	MeCN	14	0
19	PivOH (0.2)	—	neat	43	10
20[c]	—	—	DCE	0	0

[a] Reaction conditions: **219a** (0.5 mmol), NBS (1.0 mmol), $Ru_3(CO)_{12}$ (3.3 mol %), additives, solvent (2.0 mL), 120 ℃, 16 h; ^{1}H-NMR yield with 1,3,5-trimethoxybenzene (0.1 mmol) as an internal standard. [b] without $Ru_3(CO)_{12}$. [c] RuCl$_3$ (10 mol %) was used instead of $Ru_3(CO)_{12}$.

Further investigations revealed that, as in the case of the above-discussed catalytic system from [RuCl$_2$(*p*-cymene)]$_2$ (Table 19), base additives did not accelerate the halogenation process catalyzed with Ru$_3$(CO)$_{12}$ (Table 21, entry 1). On the other hand, replacing carboxylic acid with a catalytic amount of silver(I) carboxylate salt significantly improved the desired formation of target product **220a** (entries 3−20). To our delight, AgO$_2$C(1-Ad) delivered the best isolated yield, and meanwhile no C−O bond formation was detected due to the steric effect of the adamantyl moiety (entry 19). It is noteworthy to mention that 0.05 equivalent amount of phosphine ligand slightly accelerated the transformation, while increasing the loadings to 0.2 equivalent completely inhibited the process (entry 11 *vs* entry 12). Further screenings proved 1,2-dichloroethane (DCE) to be superior to other solvents with this ruthenium(0) catalyst (entries 14−17).

Table 21 Screenings of the ruthenium(0)-catalyzed *ortho*-C–H halogenations with metal salts as additives[a]
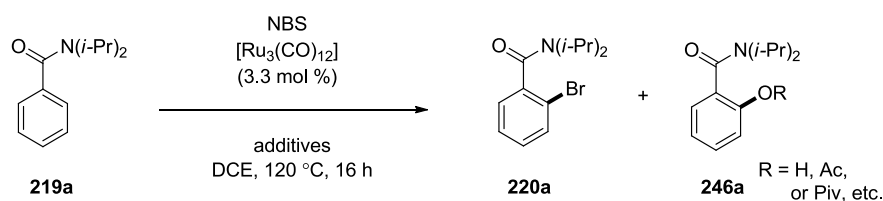
Entry	Additive A (equiv)	Additive B (equiv)	Solvent	Yield of 220a (%)	246a (%)
1	CsOAc (0.2)	—	DCE	24	0
2	KPF$_6$ (0.2)	—	DCE	0	0
3	AgSbF$_6$ (0.2)	—	DCE	18	0
4	AgCl (0.2)	—	DCE	20	0
5	Ag$_2$CO$_3$ (0.2)	—	DCE	34	0
6	AgO$_2$CCF$_3$ (0.2)	—	DCE	41	4
7	AgOAc (0.2)	—	DCE	58	7
8	AgOAc (0.05)	—	DCE	21	0
9	AgOAc (0.5)	—	DCE	48	5
10	—	PPh$_3$ (0.05)	DCE	9	0
11	AgOAc (0.2)	PPh$_3$ (0.05)	DCE	53	0
12	AgOAc (0.2)	PPh$_3$ (0.2)	DCE	2	0
13	AgOAc (0.2)	PivOH (1.1)	DCE	51	10
14	AgOAc (0.2)	—	*t*-BuOH	10	0
15	AgOAc (0.2)	—	PhMe	2	0
16	AgOAc (0.2)	—	Pinacolone	35	0
17	AgOAc (0.2)	—	NMP	<1	0
18	AgOPiv (0.2)	—	DCE	60	6
19	AgO$_2$C(1-Ad) (0.2)	—	DCE	64 (60[b])	0
20[c]	AgO$_2$C(1-Ad) (0.2)	—	DCE	<2	0

[a] Reaction conditions: **219a** (0.5 mmol), NBS (1.0 mmol), [Ru$_3$(CO)$_{12}$] (3.3 mol %), additives, solvent (2.0 mL), 120 ℃, 16 h; ^{1}H-NMR yield with 1,3,5-trimethoxybenzene (0.1 mmol) as an internal standard. [b] Isolated yield. [c] without [Ru$_3$(CO)$_{12}$].

6.2.2 Scope of the Ruthenium(0)-Catalyzed *ortho*-C−H halogenations

With the optimized conditions in hand (Table 21, entry 19), we initially examined the influence of different amide *N*-substituents on the efficacy of the corresponding brominations as well as iodinations (Table 22).[137] Thus, a variety of benzamides **219** provided the desired halogenated products **220** and **221** in good yields. Herein, electron-donating amide group gave a slightly better performance and bulky substituent such as *N,N*-diisopropylamide efficiently directed the bromination as well. In contrast to brominations, successive addition of *N*-iodosuccinimide (NIS) in two equal portions was required to deliver the iodinated products **221** in best yield. Besides, control experiments demonstrated that omission of the ruthenium(0) catalyst proved to be detrimental.

Table 22 Effect of *N*-substituents on C−H halogenations[a]

Entry	Arene 219	Product 220 / 219		Yield (%) Cond. (*A*)	Yield (%) Cond. (*B*)	Yield (%) Cond. (*C*)
1	**219b**		X = Br (**220b**)	68	—[b]	8
2			X = I (**221b**)	74	78	0
3	**219c**		X = Br (**220c**)	56	—[b]	0
4			X = I (**221c**)	54	71	0
5[c]	**219d**		X = Br (**220d**)	89	—[b]	0
6			X = I (**221d**)	70	85	0
7	**219e**		X = Br (**220e**)	36	36	2
8			X = I (**221e**)	72	76	0
9	**219f**		X = Br (**220f**)	62	—[b]	25
10			X = I (**221f**)	62	76	0

(continued)

[137] Primary and secondary benzamides provided thus far only unsatisfactory results (<15% conversion).

Table 22 *(continued)*

Entry	Arene 219	Product 220 / 219	Yield (%) Cond. (*A*)	Yield (%) Cond. (*B*)	Yield (%) Cond. (*C*)
11	**219g**	X = Br (**220g**)	52	—[b]	25
12		X = I (**221g**)	54	72	1

[a] Reaction conditions *A*: **219** (1.0 mmol), NXS (2.0 mmol), [Ru$_3$(CO)$_{12}$] (3.3 mol %), AgO$_2$C(1-Ad) (20 mol %), DCE (3.0 mL), 120 °C, 16 h; *B*: **219** (1.0 mmol), [Ru$_3$(CO)$_{12}$] (3.3 mol %), AgO$_2$C(1-Ad) (20 mol %), DCE (3.0 mL), 120 °C, NXS (1.0 equiv) was added and stirred for 8 h, then the second equiv of NXS was added and the stirring was continued for 14 h; *C*: **219** (0.5 mmol), NXS (1.0 mmol), DCE (2.0 mL), 120 °C, 16 h; GC analysis. [b] Not tested. [c] 80 °C.

Thereafter, we probed the scope of the C–H bromination with differently decorated benzamides **219** (Table 23). Intramolecular competition experiments with *meta*-methyl arene **219h** bearing two chemically inequivalent *ortho* C–H bonds showed the less hindered C–H bond to be predominantly brominated (entry 1). In contrast, the electron-deficient benzamide **219i** afforded mainly isomer **220i**, most probably because of the secondary directing group effect (entry 2).[7a] The C–H functionalizations of substrates bearing additional (hetero)aromatic moieties proceeded with excellent site-selectivities in the *ortho*-position to the amide (entries 3−10). Thereby, synthetically useful heterocycles (**220q**) and functional groups, such as acetyl (**220n** and **220o**) or ester (**220p**), were well tolerated by the catalyst.[138]
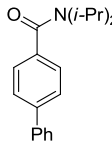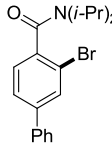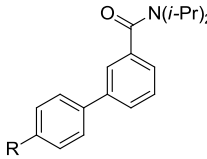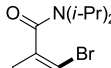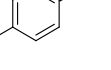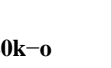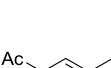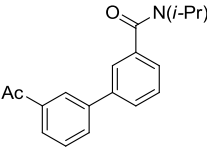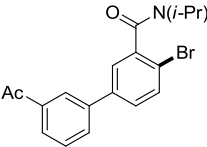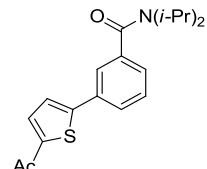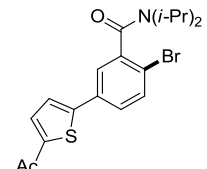
Table 23 Ruthenium(0)-catalyzed *ortho*-C–H bromination on benzamides **219**[a]
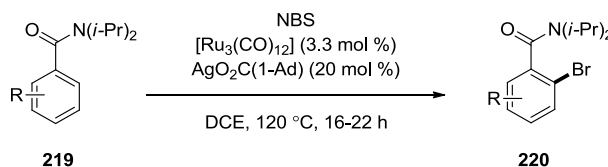
Entry	Benzamide 219	Product 220	A/B	Yield (%)
1	**219h**	**220h**	*A*	64 (3:1)[b]
2	**219i**	**220i**	*B*	55 (3:1)[b]

(continued)

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[138] Under the optimized reaction conditions, the mass balance accounted for the unreacted starting materials as well as the second regioisomers in case of *meta*-substituted substrates **219**.

Table 23 *(continued)*

Entry	Benzamide 219	Product 220	*A/B*	Yield (%)
3	**219j**	**220j**	*B*	48
4	**219k−o**	R = H (**220k**) **220k−o**	*B*	65[c]
5		R = Me (**220l**)	*B*	47[c]
6		R = F (**220m**)	*B*	54[c]
7		R = CO$_2$Me (**220n**)	*B*	57[c]
8		R = Ac (**220o**)	*B*	34[c]
9	**219p**	**220p**	*B*	46[c]
10	**219q**	**220q**	*B*	37[c]

[a] Reaction conditions *A*: **219** (0.5–1.0 mmol), NBS (1.0–2.0 mmol), [Ru$_3$(CO)$_{12}$] (3.3 mol %), AgO$_2$C(1-Ad) (20 mol %), DCE (3.0 mL), 120 °C, 16 h; *B*: **219** (0.5–1.0 mmol), [Ru$_3$(CO)$_{12}$] (3.3 mol %), AgO$_2$C(1-Ad) (20 mol %), DCE (2.0 mL), 120 °C, NBS (1.0 equiv) was added and stirred for 8 h, then the second equiv of NBS was added and the stirring was continued for 14 h; Isolated yield. [b] Isolated yields of the major isomer; ratio of regioisomers (major: minor) in the crude reaction mixture, as determined by GC analysis in parenthesis. [c] Only one isomer was observed by GC analysis.

However, *ortho*-substitution turned out to be detrimental for this transformation, due to the sterically demanding tertiary benzamide directing group: The brominated product **220r** was detected in 13% conversion by GC analysis of the crude reaction mixture (Scheme 89).[139] Besides, electron-withdrawing groups at the *para*-position, such as F (**219s**) and CF$_3$ (**219t**), only led to low conversions. *para*-Methoxyl benzamide **219u** proceeded in high reactivity, however, poor regioselectivities were obtained.

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[139] Similar result was obtained applying rhodium(I) catalyst, see ref. 113.
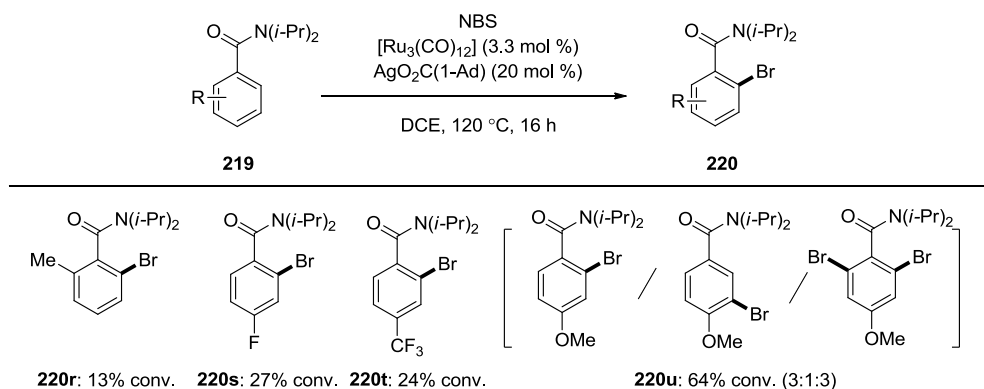
Scheme 89 Limitations of benzamide scope

Furthermore, the versatile ruthenium(0) catalyst displayed a broad substrate scope and allowed for C−H iodinations of differently substituted arenes **219** (Table 24). Thus, benzamide **219a** provided the mono-halogenated products **221a** in moderate yield (entry 1). Importantly, *meta*-substituted arenes **219** gave the desired products **221** with useful site-selectivities (entries 2–8). As was observed for the bromination (*vide supra*), the C−H iodination herein was neither viable in the absence of the ruthenium(0) catalyst nor of the additive AgO$_2$C(1-Ad) for all benzamides **219**.
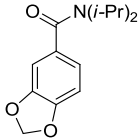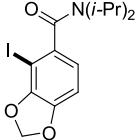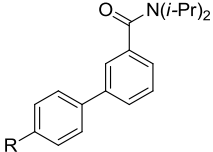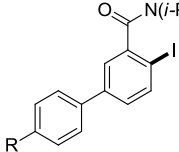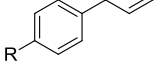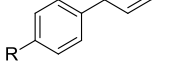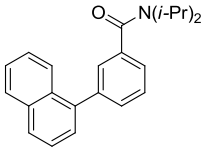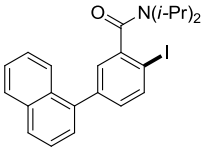
Table 24 Ruthenium(0)-catalyzed *ortho*-C–H iodination on benzamides **219**[a]

Entry	Benzamide 219	Product 221	Yield (%)
1	219a	221a	53
2	219h	221h	64 (3:1)[b]
3	219v	221v	52 (5:1)[b]
4	219i	221i	36 (4:1)[b]

Table 24 *(continued)*

Entry	Benzamide 219	Product 221		Yield (%)
5	**219w**	**221w**		73 (5:1)[b]
6	**219k–l**	**221k−211l**	R = H (**221k**)	64[c]
7			R = Me (**221l**)	68[c]
8	**219x**	**221x**		59[c]

[a] Reaction conditions: **219** (0.5–1.0 mmol), [Ru$_3$(CO)$_{12}$] (3.3 mol %), AgO$_2$C(1-Ad) (20 mol %), DCE (2.0 mL), 120 °C, NIS (1.0 equiv) was added and stirred for 8 h, then the second equiv of NIS was added and the stirring was continued for 14 h; Isolated yield. [b] Isolated yields of the major isomer; ratio of regioisomers (major: minor) in the crude reaction mixture, as determined by GC analysis in parenthesis. [c] Only one isomer was observed by GC analysis.

6.2.3 Mechanistic Studies

6.2.3.1 Reactions in the Presence of Radical Scavengers

In consideration of the unique reactivity profile of the novel ruthenium(0) catalyst, we performed mechanistic studies to delineate its mode of action. To this end, (co)catalysis with a Brønsted acid could be ruled out by successfully performing the C−H bromination in the presence of stoichiometric amounts of 2,6-di-*tert*-butylpyridine (**249a**)[140] (Table 25, entry 1). Furthermore, a radical inhibition test was next carried out in order to get insight into whether the reaction proceeds *via* radical intermediates. When such known effective radical scavengers as 2,2,6,6-tetramethylpiperidin-1-yloxy (TEMPO, **249b**), 2,2-diphenyl-1-picrylhydrazyl (DPPH, **249c**), 2,6-di-*tert*-butyl-4-methylphenol (BHT, **249d**), *trans*-stilbene (**249e**) or 1,1-diphenylethylene (**249f**) were added to the reaction mixture under otherwise identical conditions, the reaction process was significantly suppressed (Table 25, entries 2−7). The latter could be rationalized in terms of SET-type processes[141] being operative.

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[140] T. C. Wabnitz, J.-Q. Yu, J. B. Spencer, *Chem.–Eur. J.* **2004**, *10*, 484–493.

[141] (a) E. C. Ashby, *Acc. Chem. Res.* **1988**, *21*, 414–421; (b) A. Pross, *Acc. Chem. Res.* **1985**, *18*, 212–219.

Table 25 Effect of additives on the *ortho*-C–H bromination of benzamide **219a**[*a*]
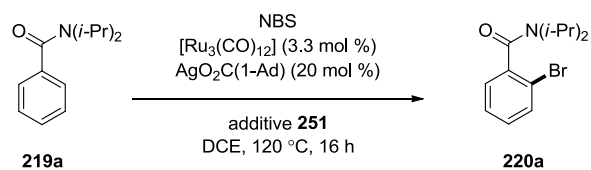
Entry	Additive 249 (equiv)	220a (%)
1	2,6-di-*tert*-Butylpyridine (**249a**) (1.0)	61
2	TEMPO (**249b**) (0.2)	9
3	TEMPO (**249b**) (2.0)	0
4	DPPH (**249c**) (2.0)	0
5	BHT (**249d**) (2.0)	0
6	*trans*-Stilbene (**249e**) (2.0)	16
7	1,1-Diphenylethene (**249f**) (2.0)	0

[*a*] Reaction conditions: **219a** (0.5 mmol), NBS (1.0 mmol), [Ru$_3$(CO)$_{12}$] (3.3 mol %), AgO$_2$C(1-Ad) (20 mol %), additive **249** (0.5−1.0 mmol), DCE (2.0 mL), 120 ℃, 16 h; ^{1}H-NMR yield with 1,3,5-trimethoxybenzene (0.1 mmol) as an internal standard.

6.2.3.2 Reactions in Isotopically Labelled Reagents

Furthermore, the catalytic C−H functionalization in the presence of isotopically labelled additive [D]$_1$-**250** highlighted a reversible C−H ruthenation event (Scheme 90).
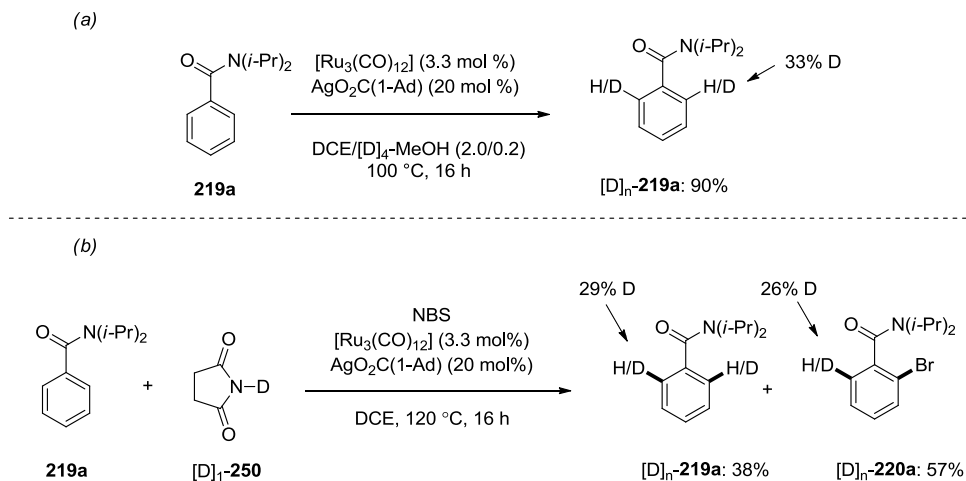
Scheme 90 C−H Functionalization with isotopically labelled reagents

In good agreement with these observations were the results of kinetic isotope effect (KIE)[142] measurements. The independent experiments with substrates **219a** and [D]$_5$-**219a** disclosed a KIE of $k_H/k_D \approx 1.0$, hence indicating the C−H cleavage step not to be kinetically relevant (Scheme 91).

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[142] E. M. Simmons, J. F. Hartwig, *Angew. Chem. Int. Ed.* **2012**, *51*, 3066–3072.
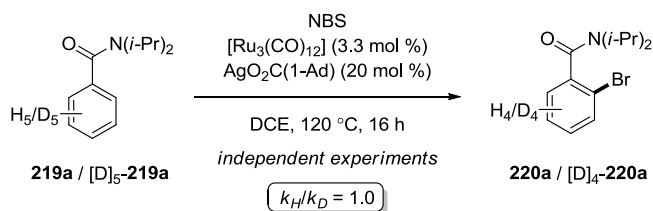
Scheme 91 Kinetic isotope effect studies

6.2.4 Proposed Catalytic Cycle

Based on our experimental mechanistic studies and independent kinetic isotope effect measurements, the following catalytic cycle for the ruthenium(0)-catalyzed C–H halogenation is proposed (Scheme 92). Analogously to the general mechanism of the carboxylate-assisted ruthenium-catalyzed oxidative direct C–H activations,[8] after chelation with amide substituent, the ruthenium species is expected to form initially a ruthenacycle **254** through reversible C–H bond metalation *via* transition state **253**. Subsequently, migratory insertion of *N*-halosuccinimide (NXS) through a SET sequence delivers intermediate **255**. Finally, reductive elimination of intermediate **255** releases the desired product **220** or **221** and regenerates ruthenium (0) species **251**.
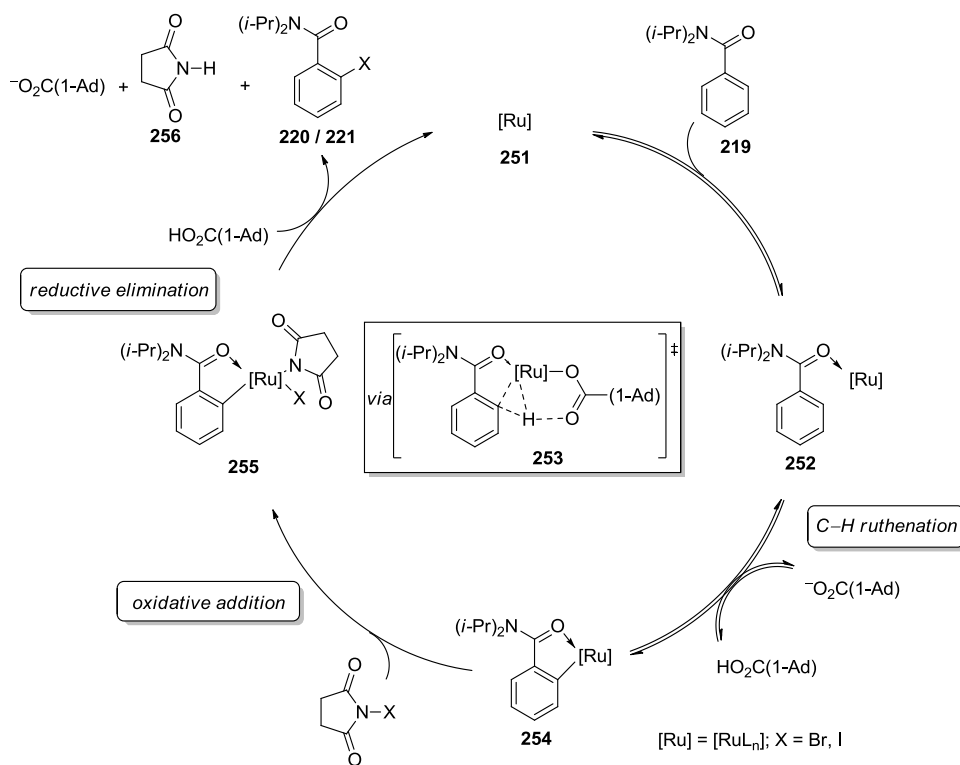
Scheme 92 Proposed catalytic cycle for the ruthenium(0)-catalyzed *ortho*-C–H halogenations

7 Summary and Outlook

Ruthenium-catalyzed direct C–H bond functionalizations was shown to be an attractive approach for the development of sustainable chemical processes. The significant rate acceleration of cycloruthenations by carboxylates has provided the bases for various catalyzed C–H bond functionalizations.

In a first project, ruthenium(II)-catalyzed oxidative annulations were realized in an aerobic fashion with cocatalytic amounts of $Cu(OAc)_2 \cdot H_2O$ under an atmosphere of ambient air. Pleasingly, the C–H/N–H bond functionalization occurred with unparalleled selectivities and ample scope to deliver indole **207** and pyrrole derivatives **209** (Scheme 93). While reactions with $CuBr_2$ as the co-oxidant did not furnish the desired products, cocatalytic amounts of metal acetates restored the catalytic efficacy, thus providing strong evidence for carboxylate-assisted aerobic oxidations. Furthermore, the highly selective conversion of unsymmetrical alkynes **38** constituted a strong testament to the unique features of chemoselective ruthenium catalysts.
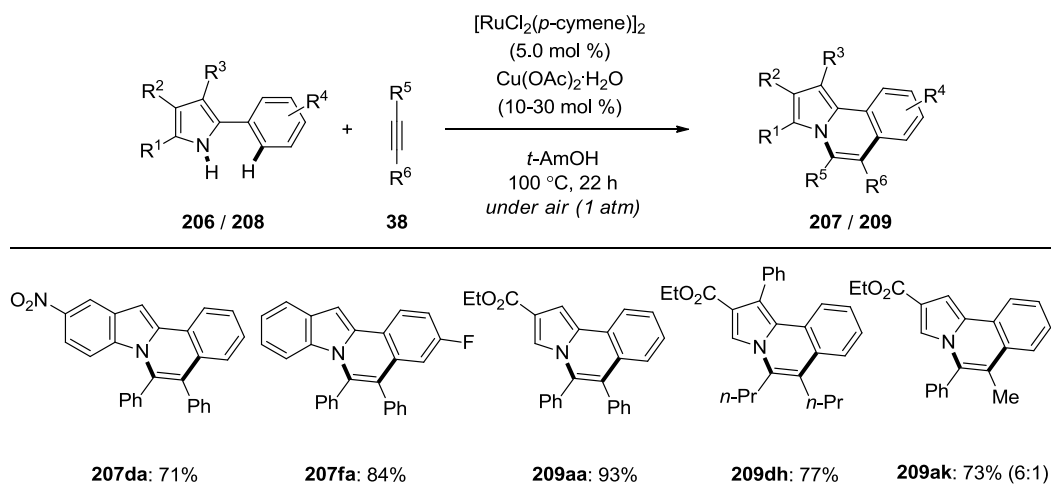
Scheme 93 Ruthenium(II)-catalyzed aerobic oxidative annulation

This efficient ruthenium(II) catalyst also enabled broadly applicable oxidative alkyne annulations with electron-rich enamines **210** to provide diversely decorated pyrroles **211**, even with air as the ideal oxidant (Scheme 94). We were delighted to observe that numerous useful electrophilic functional groups were well tolerated, including ester, vinyl, bromo, cyano, and nitro substituents. Notably, oxidative annulations of unsymmetrical alkynes **38** occurred with synthetically useful levels of regiocontrol.
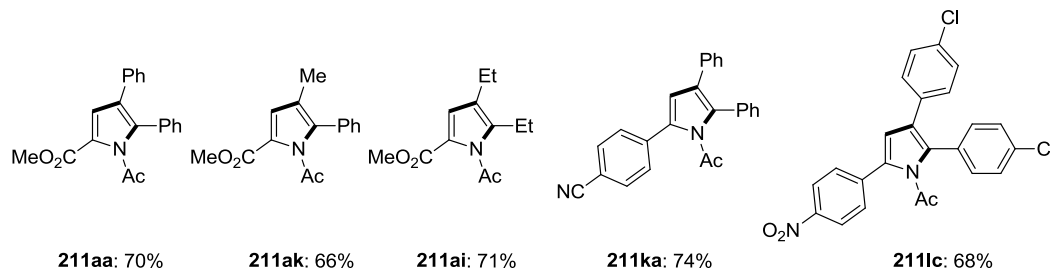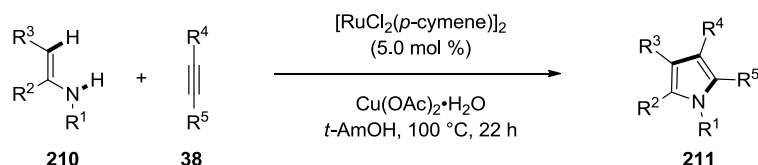
Scheme 94 Ruthenium(II)-catalyzed oxidative pyrrole synthesis by C−H activation

Along with the rapid development of the oxidative annulations, challenging oxidative olefinations with electron-rich anilides **212** as well as electron-deficient benzamides **214** were elaborated with [RuCl$_2$(*p*-cymene)]$_2$, KPF$_6$ and Cu(OAc)$_2$ H$_2$O as the catalytic system (Scheme 95). Remarkably, this protocol proved to be most effective with water as the reaction medium and provided an expedient access to differently decorated arenes **213** and **215**. Furthermore, we were pleased to observe that this ruthenium-catalyzed oxidative C–H alkenylations proceeded smoothly even on a large scale.
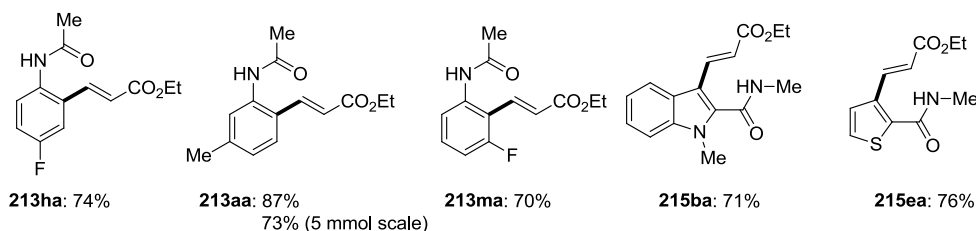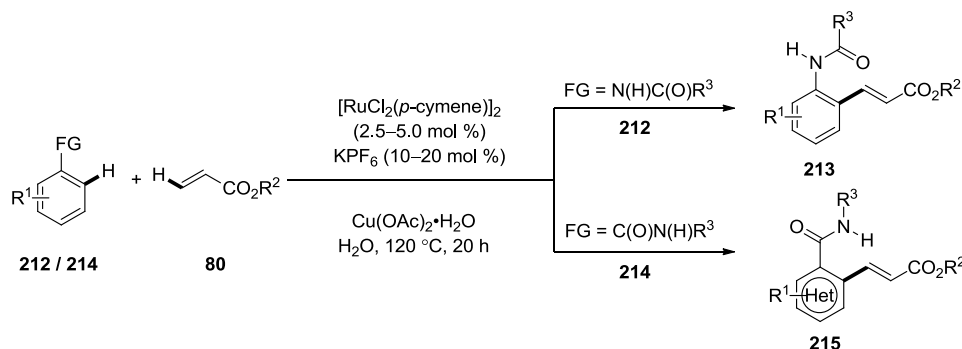
Scheme 95 Ruthenium-catalyzed oxidative alkenylation

A catalytic system comprising of [RuCl$_2$(PPh$_3$)$_3$], AgOTf and *rac*-BINAP enabled step-economical additions of C(sp^3)–H bonds (**216**) onto unactivated alkenes **111** with ample scope under comparably mild reaction conditions (Scheme 96). Furthermore, the pyridyl directing group was efficiently removed to furnish (*NH*)-free pyrrolidines **218**.
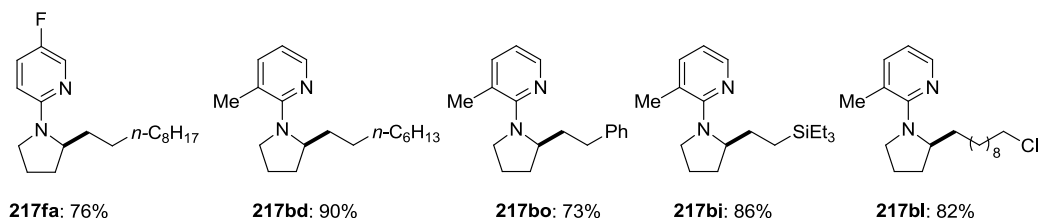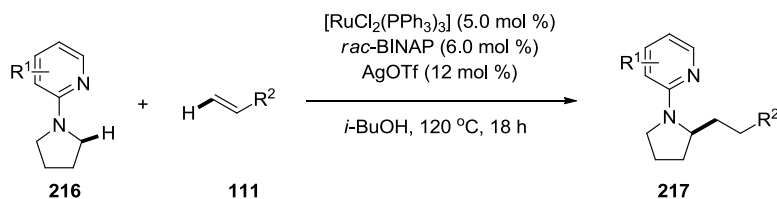
Scheme 96 Ruthenium(II)-catalyzed direct C(sp^3)−H alkylations with alkenes

Finally, [Ru$_3$(CO)$_{12}$] and AgO$_2$C(1-Ad) enabled the first ruthenium-catalyzed intermolecular *ortho*-selective halogenations of benzamides **219** *via* C−H activation (Scheme 97). Thereby, brominations and iodinations of electron-rich and electron-deficient benzamides were achieved in a highly selective fashion as well as with excellent functional group tolerance. Preliminary mechanistic studies provided evidence for a reversible C−H metalation event in this process.
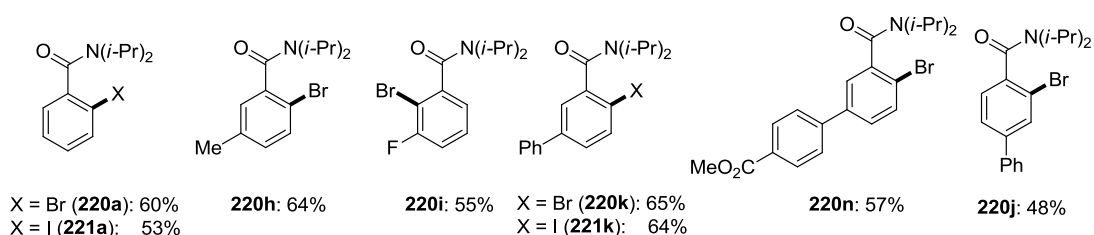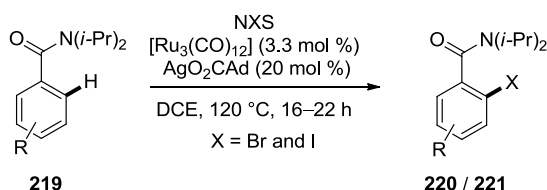
Scheme 97 Ruthenium-catalyzed direct *ortho*-halogenations

In summary, recent years have witnessed significant progress in transition-metal-catalyzed C−H bond functionalizations. Importantly, direct C−H arylations, alkylations and hydroarylations with alkenes, as well as challenging oxidative C−C, C−O, C−N and C−Hal bond formations have proven viable with ruthenium complexes with considerable progress being accomplished in the past several years. Notable features of the most user-friendly ruthenium catalysts include the remarkably broad substrate scope and the extraordinarily high chemo- and site-selectivity. Particularly, the significant rate acceleration of stoichiometric cyclometalations by carboxylates along with recent detailed experimental and computational studies has provided strong evidence for various C−H bond ruthenations to proceed by base-assisted deprotonations. Considering the highly sustainable nature of ruthenium-catalyzed direct C−H bond functionalizations, along with

the improved mechanistic understanding of base-assisted metalations, further exciting developments are expected in this rapidly evolving research area.

8 Experimental Section

8.1 General Remarks

Unless otherwise noticed, all reactions were performed under a N_2 atmosphere using pre-dried glassware and standard Schlenk techniques.

Solvents

All solvents for reactions involving moisture-sensitive reagents were dried, distilled and stored under inert atmosphere (argon or nitrogen) according to the following standard procedures. *tert*-Amylalcohol (*t*-AmOH) was used as supplied by Merck or stirred over sodium chips for 5 h at 120 ℃ and distilled under ambient pressure; water (H_2O) was degassed before its use applying repeated Freeze-Pump-Thaw degassing procedure; 1,2-dichloroethane (DCE), *i*-BuOH, *N*,*N*-dimethylformamide (DMF), acetonitrile (MeCN) and dimethylacetamide (DMA) were dried over CaH_2 for 8 h, degassed and distilled under reduced pressure; dichloromethane (DCM) and tetrahydrofuran (THF) were purified using a solvent purification system (SPS) from MBRAUN; *N*-methyl-2-pyrrolidone (NMP) was stirred over CaH_2 for 4 h at 150 ℃ and subsequently distilled under reduced pressure; methanol (MeOH) was distilled from magnesium methanolate; toluene (PhMe) was either pre-dried over KH followed by distillation from sodium benzophenone ketyl; 1,4-dioxane was dried by distillation from sodium benzophenone ketyl.

Vacuum

The following pressures were measured on the used vacuum pump and were not corrected: membrane pump vacuum (MPV): 0.5 mbar, oil pump vacuum (OPV): 0.1 mbar.

Melting Points (M. p.)

Melting points were measured using a *Stuart® Melting Point Apparatus SMP3* from BARLOWORLD SCIENTIFIC. Reported values are uncorrected.

Chromatography

Analytical thin layer chromatography (TLC) was performed on 0.25 mm silica gel 60F-plates (MACHEREY-NAGEL) with 254 nm fluorescent indicator from MERCK. Plates were visualized under UV-light or developed by treatment with a $KMnO_4$ solution followed by careful applying a heat gun. Chromatographic purification of products was accomplished by flash column chromatography on MERCK silica gel, grade 60 (0.040–0.063 mm and 0.063–0.200 mm).

Gas Chromatograpgy (GC)

The conversion of the reactions was monitored applying coupled gas chromatography/mass spectrometry using *G1760C GCDplus* with mass detector *HP 5971*, *5890 Series II* with mass detector *HP 5972* from HEWLETT-PACKARD and *7890A GC-System* with mass detector *5975C (Triplex-Axis-Detector)* from AGILENT TECHNOLOGIES equipped with *HP-5MS* columns (30 m × 0.25 mm × 0.25 m) were used.

High Performance Liquid Chromatography (HPLC)

Preparative and analytical separations were performed on an HPLC-System from KNAUER (*Smartline Pump 100*, Dynamic Mixing Chamber, Injection- and Control-Valve, *Smartline UV*

Detector 2500). Separation normal phase column (250 × 10 mm) from MACHEREY-NAGEL (MN) was used. Organic solvents of HPLC grade were employed. All samples were filtered through Polytetrafluorethylen Filter from ROTH (Ø 25 mm, 0.2 μm) or VWR (Ø 13 mm, 0.2 μm) prior to separation.

Nuclear Magnetic Resonance Spectroscopy (NMR)

Nuclear magnetic resonance (NMR) spectroscopy was performed at 300 or 600 MHz (^{1}H-NMR), 75 or 125 MHz (^{13}C-NMR, APT) and 283 MHz (^{19}F-NMR) on BRUKER *AM 250*, VARIAN *Unity-300* and *Inova 500* instruments. Chemical shifts are reported as *δ*-values in ppm relative to the residual proton peak of the deuterated solvent or its carbon atom, respectively, or the standard trimethylsilyl (TMS) peak. For characterization of the observed resonance multiplicities the following abbrevations were applied: *s* (singlet), *d* (doublet), *t* (triplet), *q* (quartet), *m* (multiplet), *dd* (doublet of doublet), *dt* (doublet of triplet), or analogue representations. The coupling constants *J* are reported in Hertz (Hz).

Infrared Spectroscopy (IR)

Infrared spectra were recorded on a BRUKER *Alpha-P* ATR-spectrometer. Liquid probes have been measured as film and solid probes neat. Analysis of the spectral data has been done by using the *OPUS 3.1* software from BRUKER, respectively *OPUS 6*. Absorption ($\tilde{\nu}$) is given in wave numbers (cm^{-1}). Spectra were recorded in the range of 4000 to 400 cm^{-1}.

Mass Spectrometry (MS)

MS (EI) and HR-MS (EI) were measured on a *Time-of-Flight* mass spectrometer *AccuTOF* from JOEL. ESI-mass spectra were recorded on an *Ion-Trap* mass spectrometer *LCQ* from FINNIGAN or on a *Time-of-Flight* mass spectrometer *microTOF* from BRUKER. ESI-HR-MS spectra were recorded on a BRUKER *APEX IV* or a BRUKER *DALTONIC* {7T, Fourier Transform Ion Cyclotron Resonance (FTICR)} mass spectrometer. The ratios of mass to charge (*m/z*) are indicated, intensities relative to the base peak (I = 100) are written in parentheses.

Reagents

Chemicals obtained from commercial sources with purity above 95% were used without further purification.

8.2 Synthesis of Starting Materials

The following starting materials were synthesized according to previously described methods: Alkynes **38b−f**,[143] **38j**,[144] **38l−o**,[143] **38q**;[144] 1,1-dimethyl-3-phenylurea (**184d**),[145] *N*-phenylpiperidine-1-carboxamide (**184e**),[146] 2-{dimethyl(phenyl)silyl}pyridine (**184f**),[147]

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dimethyl(phenyl)silanol (**184g**);[148] 2-aryl-substituted indoles **206b−c**,[149] **206d**,[150] **206e−h**,[149] **206i**,[151 , 152] **206j−n**;[149] 2-aryl-substituted pyrroles **208a−d**,[153] **208e**,[154] **208f**;[155] enamines **210a−b**,[156] **210c**,[157] **210d**,[158] **210f**,[121] **210g−t**,[159] anilides **212a**,[160] **212b**,[161] **212c**,[162] **212d−e**,[161] **212f**,[163] **212g−o**;[161] (hetero)amides **214a**,[164,165] **214b**,[166,167] **214c**,[164,168] **214d**,[166,168] **214e**,[164,167] **214f**;[164–166] pyrrolidines **216a−l**;[169] benzamides **219a−j**,[113a] **219r−u**,[113a] **219k−q**,[113a, 170 , 171] 2-(pyridin-2-yl)isoindoline (**237a**)[172] 1-(pyridin-2-yl)indoline (**237b**),[169] 2-(pyrrolidin-1-yl)-benzo[*d*]oxazole (**237c**),[173] 5-(pyrrolidin-1-yl)-3,4-dihydro-2*H*-pyrrole (**237d**),[174] (*E*)-2-methyl-*N*-(pyrrolidin-1-ylmethylene)propan-2-amine (**237e**),[175] 1-(pyrrolidin-1-yl)ethanone (**237f**),[160] propa-1,2-dien-1-ylbenzene (**238h**),[176] [D]$_1$-succinimide ([D]$_1$-**250**).[177]

The following compounds were obtained by the generous courtesy of the persons named below:

Dr. Marvin Schinkel: alkenes **111k–n**,[132] **111t–v**.[132]

Karsten Rauch: [RuCl$_2$(*p*-cymene)]$_2$.

8.3 General Procedures

General procedure A for ruthenium-catalyzed aerobic coupling of substituted indoles 206 and pyrroles 208 with alkynes 38:

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A mixture of 2-aryl indole **206** or pyrrole **208** (0.50 mmol), alkyne **38** (1.00 mmol), [RuCl$_2$(*p*-cymene)]$_2$ (15.3 mg, 5.0 mol %) and Cu(OAc)$_2$ H$_2$O (10 mg, 10.0 mol % or 30 mg, 30.0 mol %) in *t*-AmOH (2.0 mL) was stirred at 100 ℃ under air (1 atm) for 22 h. At ambient temperature, the reaction mixture was diluted with H$_2$O (75 mL) and extracted with EtOAc (3 × 75 mL). The combined organic phase was washed with brine (50 mL) and dried over anhydrous Na$_2$SO$_4$. After filtration and evaporation of the solvents under reduced pressure, the crude product was purified by column chromatography on silica gel (*n*-hexane/EtOAc or *n*-hexane/CH$_2$Cl$_2$) to yield compound **207** and **209**.

General procedure B for ruthenium-catalyzed oxidative coupling of substituted indoles 206 and pyrroles 208 with alkynes 38:

A mixture of 2-aryl indole **206** or pyrrole **208** (0.50 mmol), alkyne **38** (1.00 mmol), [RuCl$_2$(*p*-cymene)]$_2$ (15.3 mg, 5.0 mol %) and Cu(OAc)$_2$ H$_2$O (200 mg, 1.00 mmol) in *t*-AmOH (2.0 mL) was stirred at 100 ℃ under N$_2$ for 22 h. At ambient temperature, the reaction mixture was diluted with H$_2$O (75 mL) and extracted with EtOAc (3 × 75 mL). The combined organic phase was washed with brine (50 mL) and dried over anhydrous Na$_2$SO$_4$. After filtration and evaporation of the solvents under reduced pressure, the crude product was purified by column chromatography on silica gel (*n*-hexane/EtOAc or *n*-hexane/CH$_2$Cl$_2$) to yield compound **207** and **209**.

General procedure C for ruthenium-catalyzed oxidative annulation of alkynes 38 with enamines 210:

A mixture of enamine **210** (0.50 mmol), alkyne **38** (1.00 mmol), [RuCl$_2$(*p*-cymene)]$_2$ (15.3 mg, 5.0 mol %) and Cu(OAc)$_2$ H$_2$O (200 mg, 1.00 mmol) in *t*-AmOH (2.0 mL) was stirred at 120 ℃ under N$_2$ for 22 h. At ambient temperature, the reaction mixture was diluted with sat. aq. NH$_4$Cl/NH$_3$ (1:1, 75 mL) and extracted with EtOAc (3 × 75 mL). The combined organic phase was washed with sat. aq. NH$_4$Cl/NH$_3$ (1:1, 50 mL) and dried over anhydrous Na$_2$SO$_4$. After filtration and evaporation of the solvents under reduced pressure, the crude product was purified by column chromatography on silica gel (*n*-hexane/EtOAc) to yield compound **211**.

General procedure D for ruthenium-catalyzed oxidative alkenylation of anilides 212 and heteroamides 214:

A mixture of anilide **212** or heteroarylamide **214** (0.50 mmol), acrylate **76** (0.75 mmol), [RuCl$_2$(*p*-cymene)]$_2$ (15.3 mg, 5.0 mol %), KPF$_6$ (18.4 mg, 20 mol %) and Cu(OAc)$_2$ H$_2$O (99.5 mg, 1.00 mmol) in H$_2$O (2.0 mL) (sealed tube) was stirred at 120 ℃ under N$_2$ for 20 h. At ambient temperature, the mixture was diluted with H$_2$O (75 mL) and extracted with EtOAc (3 × 75 mL). The combined organic phase was washed with brine (50 mL) and dried over anhydrous Na$_2$SO$_4$. After filtration and evaporation of the solvents under reduced pressure, the crude product was purified by column chromatography on silica gel (*n*-hexane/EtOAc) to yield compound **213** and **215**.

General procedure E for ruthenium-catalyzed C(sp^3)−H α-alkylation of pyrrolidine 216 with alkene 111:

A suspension of [RuCl$_2$(PPh$_3$)$_3$] (24.0 mg, 5.0 mol %), *rac*-BINAP (18.7 mg, 6.0 mol %), AgOTf (15.4 mg, 12 mol %), pyrrolidine **216** (1.5 mmol) and alkene **111** (0.5 mmol) in *i*-BuOH (1.0 mL)

was stirred at 120 ℃ under N$_2$ for 18 h. At ambient temperature, CuCl (50 mg), tridecane (25 μL) and EtOAc (5 mL) were added to the reaction mixture. After GC analysis, the solvents were evaporated in reduced pressure. Purification by column chromatography on silica gel (*n*-hexane/EtOAc) yielded compound **217**.

General procedure F for the removal of 2-pyrridyl directing groups (217):[135]
Step 1: A 25 mL Schlenk flask was charged with compound **217** (0.5 mmol) and Pt/C (5% Pt, 195 mg, 10 mol %). Under N$_2$, EtOH (4.5 mL) was added. To the resulting black suspension was added 1.25 M HCl in EtOH (0.5 mL, 0.6 mmol), and the reaction mixture was subsequently flushed twice with H$_2$. The reaction mixture was then stirred under H$_2$ (1 atm) at 23 ℃ for 24 h. The solids were removed by filtration through a short pad of celite, the pad was washed with CH$_2$Cl$_2$ (3 × 10 mL), and the combined filtrate was evaporated to dryness.
Step 2: The residue was dissolved in MeOH (5 mL), and the resulting solution was cooled to 0 ℃ using an ice/water bath. NaBH$_4$ (76 mg, 2.0 mmol) was added portionwise to the cooled solution under magnetic stirring at 0 ℃. After complete addition of NaBH$_4$, the reaction mixture was stirred further at 0 ℃ for 15 min. The volatiles were removed in reduced pressure. Purification by column chromatography on silica gel (CH$_2$Cl$_2$/MeOH) yielded compound **218**.

General procedure G for ruthenium-catalyzed *ortho*-C−H halogenation of benzamide 219:
To a seal tube equipped with a magnetic stir bar were added Ru$_3$(CO)$_{12}$ (10.5 mg, 3.3 mol %), AgO$_2$C(1-Ad) (28.7 mg, 20 mol %) and DCE (2.0 mL) under N$_2$. Benzamide substrate **219** (0.5 mmol) and *N*-halosuccinimide (1.0 mmol) were added. After being stirred at ambient temperature for 10 min, the tube was placed in a pre-heated oil-bath and stirred at 120 ℃ for 16 h. The reaction mixture was then allowed to cool to ambient temperature, diluted with EtOAc (5 mL) and filtered through a short pad of silica gel and eluted with EtOAc (50 mL). After removing the solvent under reduced pressure, purification by column chromatography on silica gel (*n*-hexane/EtOAc) yielded the corresponding compound **220**.

General procedure H for ruthenium-catalyzed *ortho*-C−H halogenation of benzamides 219:
To a seal tube equipped with a magnetic stir bar were added Ru$_3$(CO)$_{12}$ (10.5 mg, 3.3 mol %), AgO$_2$C(1-Ad) (28.7 mg, 20 mol %) and DCE (2.0 mL) under N$_2$. Benzamide substrate **219** (0.5 mmol) and the first portion of *N*-halosuccinimide (0.5 mmol) were added. After being stirred at ambient temperature for 10 min, the tube was placed in a pre-heated oil-bath and stirred at 120 ℃ for 8 h. The mixture was then allowed to cool to ambient temperature, the second portion of *N*-halosuccinimide (0.5 mmol) was added under N$_2$ and the stirring was continued for further 14 h at 120 ℃. The mixture was then allowed to cool to ambient temperature, diluted with EtOAc (5 mL) and filtered through a short pad of silica gel and eluted with EtOAc (50 mL). After removing the solvent under reduced pressure, purification by column chromatography on silica gel (*n*-hexane/EtOAc) yielded the corresponding compound **220** and **221**.

8.4 Analytical Data

8.4.1 Analytical Data for the Products of Ruthenium-Catalyzed Aerobic Coupling of Substituted Indoles 206 or Pyrroles 208 with Alkynes 38

Synthesis of 5,6-diphenylindolo[2,1-*a*]isoquinoline (207aa)
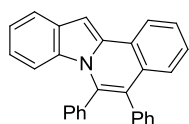
The general procedure **A** was followed using 2-phenylindole (**206a**) (96.5 mg, 0.50 mmol), diphenylacetylene (**38a**) (178 mg, 1.00 mmol) and $Cu(OAc)_2$ H_2O (10 mg, 10.0 mol %). After 22 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 20/1) yielded **207aa** (151 mg, 82%) as a white solid.

M. p. = 205−206 °C.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 8.31 (d, J = 6.7 Hz, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.51 (ddd, J = 7.7, 7.2, 1.3 Hz, 1H), 7.38 (s, 1H), 7.38−7.14 (m, 13H), 6.82 (ddd, J = 7.8, 7.0, 1.3 Hz, 1H), 6.01 (d, J = 8.7 Hz, 1H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 136.7 (C$_q$), 136.0 (C$_q$), 135.9 (C$_q$), 135.3 (C$_q$), 132.7 (C$_q$), 131.8 (CH), 130.8 (CH), 130.2 (C$_q$), 129.7 (C$_q$), 128.7 (CH), 128.6 (CH), 127.8 (CH), 127.3 (CH), 127.0 (CH), 126.7 (CH), 126.2 (CH), 125.4 (C$_q$), 123.3 (CH), 121.6 (CH), 121.4 (C$_q$), 120.2 (CH), 120.1 (CH), 114.6 (CH), 94.2 (CH).

IR (ATR): $\tilde{\nu}$ = 1543, 1484, 1443, 1377, 1338, 1245, 1030, 756, 736, 696 cm^{-1}.

MS (EI) *m/z* (relative intensity): 369 (100) [M$^+$], 291 (13).

HR-MS (EI) *m/z* calcd for C$_{28}$H$_{19}$NO$^+$ 369.1517, found 369.1518.

The spectral data were in accordance with those reported in the literature.[117]

Synthesis of 10-fluoro-5,6-diphenylindolo[2,1-*a*]isoquinoline (207ba)
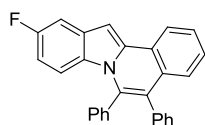
The general procedure **A** was followed using 5-fluoro-2-phenyl-1*H*-indole (**206b**) (106 mg, 0.50 mmol), diphenylacetylene (**38a**) (178 mg, 1.00 mmol) and $Cu(OAc)_2$ H_2O (10 mg, 10.0 mol %). After 22 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 50/1) yielded **207ba** (102 mg, 54%) as a yellow solid.

M. p. = 227−228 °C.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 8.26 (d, J = 7.8 Hz, 1H), 7.49 (ddd, J = 7.8, 7.8, 1.2 Hz, 1H), 7.39−7.11 (m, 14H), 6.52 (ddd, J = 9.2, 9.1, 2.6 Hz. 1H), 5.86 (dd, J = 9.4, 4.6 Hz, 1H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 158.6 (d, $^1J_{C-F}$ = 238 Hz, C$_q$), 137.4 (C$_q$), 136.5 (C$_q$), 135.7 (C$_q$), 135.0 (C$_q$), 131.7 (CH), 130.8 (CH), 130.3 (d, $^3J_{C-F}$ = 10 Hz, C$_q$), 130.2 (C$_q$), 129.4 (C$_q$), 128.8 (CH), 128.7 (CH), 127.8 (CH), 127.6 (CH), 127.1 (CH), 126.8 (CH), 126.2 (CH), 124.9 (C$_q$), 123.4 (CH), 121.6 (C$_q$), 111.6 (d, $^3J_{C-F}$ = 9 Hz, CH), 108.5 (d, $^2J_{C-F}$ = 26 Hz, CH), 104.3 (d, $^2J_{C-F}$ = 23 Hz, CH), 94.0 (d, $^4J_{C-F}$ = 4 Hz, CH).

^{19}F-NMR (283 MHz, CDCl$_3$): δ = −(121.7–121.8) (m).

IR (ATR): $\tilde{\nu}$ = 3054, 1610, 1539, 1485, 1441, 1117, 855, 787, 753, 696 cm^{-1}.

MS (EI) *m/z* (relative intensity): 387 (100) [M$^+$], 309 (30).

HR-MS (EI) *m/z* calcd for C$_{28}$H$_{18}$FN$^+$ 387.1383, found 387.1382.

Synthesis of 10-bromo-5,6-diphenylindolo[2,1-*a*]isoquinoline (207ca)
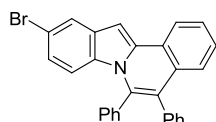
The general procedure **A** was followed using 5-bromo-2-phenyl-1*H*-indole (**206c**) (136 mg, 0.50 mmol), diphenylacetylene (**38a**) (178 mg, 1.00 mmol) and $Cu(OAc)_2$ H_2O (10 mg, 10.0 mol %). After 22 h, purification by column chromatography on silica gel (*n*-hexane/CH$_2$Cl$_2$: 5/1) yielded **207ca** (72 mg, 32%) as a yellow solid.

M. p. = 213−214 °C.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 8.29 (d, J = 8.0 Hz, 1H), 7.90 (d, J = 2.0 Hz, 1H), 7.53 (dd, J = 7.6, 7.2 Hz, 1H), 7.38−7.12 (m, 13H), 6.87 (dd, J = 9.0, 2.0 Hz, 1H), 5.81 (d, J = 9.0 Hz, 1H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 136.9 (C$_q$), 136.4 (C$_q$), 135.6 (C$_q$), 134.9 (C$_q$), 131.7 (CH), 131.3 (C$_q$), 131.2 (C$_q$), 130.7 (CH), 130.3 (C$_q$), 128.9 (CH), 128.8 (CH), 127.9 (CH), 127.7 (CH), 127.2 (CH), 126.9 (CH), 126.3 (CH), 125.0 (C$_q$), 123.4 (CH), 122.8 (CH), 122.4 (CH), 122.0 (C$_q$), 111.9 (CH), 111.2 (C$_q$), 93.5 (CH).

IR (ATR): $\tilde{\nu}$ = 3056, 1620, 1487, 1377, 1030, 725, 696 cm^{-1}.

MS (EI) m/z (relative intensity): 449 (100) [M$^+$] (^{81}Br), 447 (97) [M$^+$] (^{79}Br), 367 (44), 291 (37).

HR-MS (ESI) m/z calcd for C$_{28}$H$_{18}$BrN$^+$ 447.0623, found 447.0634.

Synthesis of 10-nitro-5,6-diphenylindolo[2,1-*a*]isoquinoline (207da)
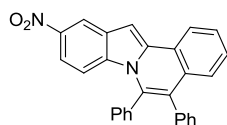
The general procedure **A** was followed using 5-nitro-2-phenyl-1*H*-indole (**206d**) (119 mg, 0.50 mmol), diphenylacetylene (**38a**) (178 mg, 1.00 mmol) and Cu(OAc)$_2$ H$_2$O (10 mg, 10.0 mol %). After 22 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 25/1) yielded **207da** (141 mg, 71%) as a yellow solid.

M. p. = 281−282 °C.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 8.66 (s, 1H), 8.28 (d, J = 7.8 Hz, 1H), 7.63 (dd, J = 9.4, 2.3 Hz, 1H), 7.58−7.45 (m, 2H), 7.44−7.30 (m, 4H), 7.30−7.08 (m, 8H), 5.96 (d, J = 9.4 Hz, 1H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 138.5 (C$_q$), 138.8 (CH), 135.9 (C$_q$), 135.3 (C$_q$), 134.9 (C$_q$), 134.5 (CH), 131.4 (CH), 130.7 (C$_q$), 130.2 (CH), 129.2 (CH), 128.9 (CH), 128.8 (CH), 128.4 (CH), 128.0 (CH), 127.7 (CH), 127.1 (CH), 126.6 (C$_q$), 124.7 (C$_q$), 123.6 (CH), 123.6 (C$_q$), 116.7 (C$_q$), 114.8 (C$_q$), 114.6 (CH), 95.9 (CH).

IR (ATR): $\tilde{\nu}$ = 3060, 1600, 1545, 1505, 1487, 1336, 1073, 759, 731, 696 cm^{-1}.

MS (EI) *m/z* (relative intensity): 414 (100) [M$^+$], 384 (27), 368 (30), 291 (13).

HR-MS (EI) *m/z* calcd for C$_{28}$H$_{18}$N$_2$O$_2$$^+$ 414.1368, found 414.1384.

Synthesis of 10-methyl-5,6-diphenylindolo[2,1-*a*]isoquinoline (207ea)

The general procedure **A** was followed using 5-methyl-2-phenyl-1*H*-indole (**206e**) (103 mg, 0.50 mmol), diphenylacetylene (**38a**) (178 mg, 1.00 mmol) and Cu(OAc)$_2$ H$_2$O (10 mg, 10.0 mol %). After 22 h, purification by column chromatography on silica gel (*n*-hexane/CH$_2$Cl$_2$: 4/1) yielded **207ea** (14 mg, 7%) as a yellow solid.

The general procedure **B** was followed using 5-methyl-2-phenyl-1*H*-indole (**206e**) (103 mg, 0.50 mmol) and diphenylacetylene (**38a**) (178 mg, 1.00 mmol). After 22 h, purification by column chromatography on silica gel (*n*-hexane/CH$_2$Cl$_2$: 4/1) yielded **207ea** (126 mg, 65%) as a yellow solid.

M. p. = 236−237 °C.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 8.29 (d, J = 8.0 Hz, 1H), 7.57 (s, 1H), 7.51 (dd, J = 8.0, 7.2 Hz, 1H), 7.40−7.29 (m, 7H), 7.27−7.12 (m, 6H), 6.66 (dd, J = 8.8, 2.7 Hz, 1H), 5.87 (d, J = 8.8 Hz, 1H), 2.44 (s, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 136.8 (C$_q$), 136.0 (C$_q$), 135.4 (C$_q$), 135.2 (C$_q$), 131.8 (CH), 131.1 (C$_q$), 130.9 (CH), 130.8 (CH), 130.2 (C$_q$), 130.0 (C$_q$), 128.6 (CH), 128.5 (CH), 127.8 (CH), 127.1 (CH), 126.9 (CH), 126.7 (CH), 126.1 (CH), 125.5 (C$_q$), 123.2 (C$_q$), 121.9 (CH), 121.0 (C$_q$), 119.7 (CH), 114.2 (CH), 93.7 (CH), 21.3 (CH$_3$).

IR (ATR): $\tilde{\nu}$ = 3047, 1614, 1574, 1443, 1376, 745, 697, 650 cm^{-1}.

MS (EI) m/z (relative intensity): 383 (100) [M$^+$], 367 (25), 306 (10).

HR-MS (EI) m/z calcd for C$_{29}$H$_{21}$N$^+$ 383.1674, found 399.1676.

Synthesis of 3-fluoro-5,6-diphenylindolo[2,1-*a*]isoquinoline (207fa)

The general procedure **A** was followed using 2-(4-fluorophenyl)-1*H*-indole (**206f**) (106 mg, 0.50 mmol), diphenylacetylene (**38a**) (178 mg, 1.00 mmol) and Cu(OAc)$_2$ H$_2$O (10 mg, 10.0 mol %). After 22 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 10/1) yielded **207fa** (164 mg, 84%) as a yellow solid.

M. p. = 178−179 °C.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 8.26 (dd, J = 8.7, 5.5 Hz, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.40−7.28 (m, 6H), 7.28−7.11 (m, 7H), 6.87−6.76 (m, 2H), 6.00 (d, J = 8.7 Hz, 1H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 162.0 (d, $^1J_{C-F}$ = 246 Hz, C$_q$), 137.1 (C$_q$), 136.1 (C$_q$), 135.4 (C$_q$), 135.0 (C$_q$), 132.6 (C$_q$), 132.3 (d, $^3J_{C-F}$ = 9 Hz, C$_q$), 131.6 (CH), 130.6 (CH), 129.7 (C$_q$), 128.8 (CH), 128.6 (CH), 128.0 (CH), 127.0 (CH), 125.4 (d, $^3J_{C-F}$ = 9 Hz, CH), 121.9 (C$_q$), 121.9 (CH), 121.8 (CH), 120.8 (d, $^4J_{C-F}$ = 3 Hz, C$_q$), 120.1 (CH), 111.2 (d, $^2J_{C-F}$ = 23 Hz, CH), 114.6 (CH), 111.6 (d, $^2J_{C-F}$ = 23 Hz, CH), 93.9 (CH).

^{19}F-NMR (283 MHz, CDCl$_3$): δ = −(112.6−112.7) (m).

IR (ATR): $\tilde{\nu}$ = 3055, 1609, 1546, 1481, 1438, 1273, 775, 738, 724, 693 cm^{-1}.

MS (EI) m/z (relative intensity): 387 (100) [M$^+$], 309 (37).

HR-MS (EI) m/z calcd for C$_{28}$H$_{18}$FN$^+$ 387.1383, found 387.1412.

Synthesis of 5,6-diphenyl-3-(trifluoromethyl)indolo[2,1-*a*]isoquinoline (207ga)

The general procedure **A** was followed using 2-{4-(trifluoromethyl)phenyl}-1*H*-indole (**207g**) (131 mg, 0.50 mmol), diphenylacetylene (**38a**) (178 mg, 1.00 mmol) and Cu(OAc)$_2$ H$_2$O (10 mg, 10.0 mol %). After 22 h, purification by column chromatography on silica gel (*n*-hexane/CH$_2$Cl$_2$: 5/1) yielded **207ga** (158 mg, 72%) as a yellow solid.

M. p. = 225−226 °C.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 8.38 (d, J = 8.4 Hz, 1H), 7.82 (d, J = 8.0 Hz, 1H), 7.71 (d, J = 8.4 Hz, 1H), 7.51 (s, 1H), 7.41−7.28 (m, 6H), 7.28−7.20 (m, 4H), 7.20−7.12 (m, 2H), 6.86 (ddd, J = 7.8, 7.8, 1.3 Hz, 1H), 6.00 (d, J = 8.8 Hz, 1H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 137.3 (C$_q$), 135.7 (C$_q$), 134.8 (C$_q$), 134.6 (C$_q$), 132.9 (C$_q$), 131.7 (CH), 130.6 (CH), 130.1 (C$_q$), 129.5 (C$_q$), 129.3 (q, $^2J_{C-F}$ = 22 Hz, C$_q$), 128.9 (CH), 128.1 (CH), 127.9 (C$_q$), 127.2 (CH), 124.1 (q, $^1J_{C-F}$ = 273 Hz, C$_q$), 123.8 (CH), 123.2 (q, $^2J_{C-F}$ = 19 Hz, CH), 123.2 (q, $^3J_{C-F}$ = 11 Hz, CH), 123.2 (q, $^4J_{C-F}$ = 4 Hz, CH), 122.0 (CH), 121.0 (CH), 120.9 (C$_q$), 120.6 (CH), 114.7 (CH), 96.0 (CH).

^{19}F-NMR (283 MHz, CDCl$_3$): δ = −62.3 (s).

IR (ATR): $\tilde{\nu}$ = 3062, 1618, 1544, 1485, 1345, 1272, 1017, 977, 744, 695 cm^{-1}.

MS (EI) m/z (relative intensity): 437 (100) [M$^+$], 359 (11).

HR-MS (EI) m/z calcd for C$_{29}$H$_{18}$F$_3$N$^+$ 437.1391, found 437.1376.

Synthesis of 3-nitro-5,6-diphenylindolo[2,1-*a*]isoquinoline (207ha)

The general procedure **A** was followed using 2-(4-nitrophenyl)-1*H*-indole (**206h**) (119 mg, 0.50 mmol), diphenylacetylene (**38a**) (178 mg, 1.00 mmol) and Cu(OAc)$_2$ H$_2$O (10 mg, 10.0 mol %). After 22 h, purification by column chromatography on silica gel (*n*-hexane/CH$_2$Cl$_2$: 7/1) yielded **207ha** (92 mg, 44%) as a yellow solid.

M. p. = 224−225 °C.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 8.38 (d, *J* = 8.2 Hz, 1H), 7.83 (d, *J* = 7.8 Hz, 1H), 7.71 (d, *J* = 8.2 Hz, 1H), 7.51 (s, 1H), 7.45−7.08 (m, 12H), 6.87 (dd, *J* = 8.2, 7.4 Hz, 1H), 6.01 (d, *J* = 8.8 Hz, 1H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 137.3 (C$_q$), 135.7 (C$_q$), 134.9 (C$_q$), 134.7 (C$_q$), 132.9 (C$_q$), 131.7 (CH), 130.6 (CH), 130.2 (C$_q$), 129.5 (C$_q$), 128.9 (CH), 128.7 (CH), 128.1 (CH), 127.9 (C$_q$), 127.2 (CH), 125.9 (C$_q$), 123.8 (CH), 123.2 (CH), 123.1 (CH), 122.0 (CH), 121.0 (CH), 120.9 (C$_q$), 120.6 (CH), 114.7 (CH), 96.0 (CH).

IR (ATR): $\tilde{v}$ = 3061, 3032, 1618, 1597, 1544, 1485, 1444, 1169, 825, 658 cm^{-1}.

MS (EI) *m/z* (relative intensity): 414 (100) [M$^+$], 384 (27), 368 (30).

HR-MS (EI) *m/z* calcd for C$_{28}$H$_{18}$N$_2$O$_2$$^+$ 414.1368, found 414.1368.
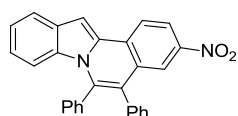
Synthesis of methyl 5,6-diphenylindolo[2,1-*a*]isoquinoline-3-carboxylate (207ia)
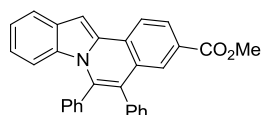
The general procedure **A** was followed using methyl 4-(1*H*-indol-2-yl)benzoate (**206i**) (126 mg, 0.50 mmol), diphenylacetylene (**38a**) (178 mg, 1.00 mmol) and Cu(OAc)$_2$ H$_2$O (10 mg, 10.0 mol %). After 22 h, purification by column chromatography on silica gel (*n*-hexane/CH$_2$Cl$_2$: 2/1) yielded **207ia** (122 mg, 57%) as a yellow solid.

M. p. = 256−257 °C.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 8.33 (d, *J* = 8.3 Hz, 1H), 8.13 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.86 (s, 1H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.51 (s, 1H), 7.39−7.28 (m, 5H), 7.27−7.15 (m, 6H), 6.86 (dd, *J* = 7.8, 7.7 Hz, 1H), 6.00 (d, *J* = 8.7 Hz, 1H), 3.86 (s, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 166.8 (C$_q$), 136.7 (C$_q$), 135.9 (C$_q$), 135.0 (C$_q$), 134.9 (C$_q$), 133.0 (C$_q$), 131.7 (CH), 130.7 (CH), 129.9 (C$_q$), 129.5 (C$_q$), 128.9 (C$_q$), 128.8 (CH), 128.6 (CH), 128.5 (C$_q$), 128.0 (CH), 127.8 (CH), 127.5 (CH), 127.0 (CH), 123.2 (CH), 121.9 (CH), 121.3 (C$_q$), 120.9 (CH), 120.6 (CH), 114.7 (CH), 96.3 (CH), 52.1 (CH$_3$).

IR (ATR): $\tilde{v}$ = 3025, 1708, 1604, 1544, 1484, 1441, 1382, 762, 738, 701 cm^{-1}.

MS (EI) *m/z* (relative intensity): 387 (100) [M$^+$], 367 (9), 291 (10).

HR-MS (EI) *m/z* calcd for C$_{30}$H$_{21}$NO$_2$$^+$ 387.1572, found 387.1578.

The spectral data were in accordance with those reported in the literature.[117]

Synthesis of 3-chloro-5,6-diphenylindolo[2,1-*a*]isoquinoline (207ja)

The general procedure **A** was followed using 2-2-(4-chlorophenyl)-1*H*-indole (**206j**) (113 mg, 0.50 mmol), diphenylacetylene (**38a**) (178 mg, 1.00 mmol) and Cu(OAc)$_2$ H$_2$O (10 mg, 10.0 mol %). After 22 h, purification by column chromatography on silica gel (*n*-hexane/CH$_2$Cl$_2$: 10/1) yielded **207ja** (26mg, 13%) as a yellow solid.

The general procedure **B** was followed using 2-2-(4-chlorophenyl)-1*H*-indole (**206j**) (113 mg, 0.50 mmol) and diphenylacetylene (**38a**) (178 mg, 1.00 mmol). After 22 h, purification by column

chromatography on silica gel (*n*-hexane/CH$_2$Cl$_2$: 10/1) yielded **207ja** (104 mg, 51%) as a yellow solid.

M. p. = 241−238 ℃.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 8.17 (d, *J* = 8.7 Hz, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.48−7.10 (m, 14H), 6.92 (dd, *J* = 8.2, 7.1 Hz, 1H), 6.03 (d, *J* = 8.2 Hz, 1H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 137.1 (C$_q$), 135.9 (C$_q$), 135.0 (C$_q$), 134.9 (C$_q$), 133.1 (C$_q$), 132.7 (C$_q$), 131.6 (CH), 131.6 (C$_q$), 130.6 (CH), 129.6 (C$_q$), 128.8 (CH), 128.6 (CH), 128.0 (CH), 127.2 (CH), 127.0 (CH), 125.4 (CH), 124.7 (CH), 123.7 (C$_q$), 121.8 (CH), 120.4 (CH), 120.4 (C$_q$), 120.3 (CH), 114.6 (CH), 94.6 (CH).

IR (ATR): $\tilde{v}$ = 3048, 1594, 1546, 1479, 1441, 1417, 1071, 759, 700 cm^{-1}.

MS (EI) *m/z* (relative intensity): 403 (100) [M$^+$], 367 (10), 291 (10).

HR-MS (ESI) *m/z* calcd for C$_{28}$H$_{18}$ClN$^+$ 403.1128, found 403.1118.

The spectral data were in accordance with those reported in the literature.[117]

Synthesis of 3-methyl-5,6-diphenylindolo[2,1-*a*]isoquinoline (207ka)

The general procedure **A** was followed using 2-2-(*p*-tolyl)-1*H*-indole (**206k**) (104 mg, 0.50 mmol), diphenylacetylene (**38a**) (178 mg, 1.00 mmol) and Cu(OAc)$_2$ H$_2$O (10 mg, 10.0 mol %). After 22 h, purification by column chromatography on silica gel (*n*-hexane/CH$_2$Cl$_2$: 10/1) yielded **207ka** (11 mg, 6%) as a yellow solid.

The general procedure **B** was followed using 2-2-(*p*-tolyl)-1*H*-indole (**206k**) (104 mg, 0.50 mmol) and diphenylacetylene (**38a**) (178 mg, 1.00 mmol). After 22 h, purification by column chromatography on silica gel (*n*-hexane/CH$_2$Cl$_2$: 10/1) yielded **207ka** (106 mg, 55%) as a yellow solid.

M. p. = 249−250 ℃.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 8.21 (d, *J* = 8.2 Hz, 1H), 7.78 (d, *J* = 7.9 Hz, 1H), 7.43−7.14 (m, 12H), 6.95 (s, 1H), 6.81 (dd, *J* = 7.8, 7.8 Hz, 1H), 5.99 (d, *J* = 8.7 Hz, 1H), 2.36 (s, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 137.3 (C$_q$), 136.8 (C$_q$), 136.1 (C$_q$), 136.0 (C$_q$), 135.4 (C$_q$), 132.6 (C$_q$), 131.8 (CH), 130.8 (CH), 130.2 (C$_q$), 129.8 (C$_q$), 128.6 (CH), 128.5 (CH), 128.4 (CH), 127.8 (CH), 126.7 (CH), 126.0 (CH), 123.3 (CH), 123.0 (C$_q$), 121.5 (CH), 121.3 (C$_q$), 120.0 (CH), 119.8 (CH), 114.5 (CH), 93.4 (CH), 21.7 (CH$_3$).

IR (ATR): $\tilde{v}$ = 3024, 1595, 1541, 1483, 1341, 1021, 759, 692 cm^{-1}.

MS (EI) *m/z* (relative intensity): 383 (100) [M$^+$], 367 (7), 207 (10).

HR-MS (EI) *m/z* calcd for C$_{29}$H$_{21}$N$^+$ 383.1674, found 383.1664.

The spectral data were in accordance with those reported in the literature.[117]

Synthesis of 7, 8-diphenylbenzo[*h*]indolo[2,1-*a*]isoquinoline (207la)

The general procedure **A** was followed using 2-(naphthalen-1-yl)-1*H*-indole (**206l**) (122 mg, 0.50 mmol), diphenylacetylene (**38a**) (178 mg, 1.00 mmol) and Cu(OAc)$_2$ H$_2$O (10 mg, 10.0 mol %). After 22 h, purification by column chromatography on silica gel (*n*-hexane/CH$_2$Cl$_2$: 5/1) yielded **207la** (97 mg, 46%) as a yellow solid.

M. p. = 213−215 ℃.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 9.40 (d, *J* = 8.6 Hz, 1H), 8.06 (s, 1H), 7.96 (dd, *J* = 9.0, 8.6 Hz, 2H), 7.84 (ddd, *J* = 7.6, 7.6, 1.2 Hz, 1H), 7.76 (d, *J* = 8.6 Hz, 1H), 7.66 (dd, *J* = 7.3, 7.3 Hz, 1H),

7.46−7.18 (m, 12H), 6.92 (ddd, 8.0, 7.8, 1.2 Hz, 1H), 6.17 (d, J = 8.7 Hz, 1H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 137.2 (C$_q$), 136.6 (C$_q$), 135.6 (C$_q$), 134.9 (C$_q$), 132.8 (C$_q$), 132.0 (CH), 131.7 (C$_q$), 130.7 (CH), 130.2 (C$_q$), 129.5 (C$_q$), 129.5 (C$_q$), 128.9 (CH), 128.6 (CH), 128.6 (CH), 127.9 (CH), 127.9 (CH), 127.2 (CH), 126.8 (CH), 125.9 (CH), 125.7 (CH), 124.2 (CH), 122.1 (C$_q$), 122.0 (CH), 121.2 (C$_q$), 120.3 (CH), 120.2 (CH), 114.9 (CH), 99.3 (CH).

IR (ATR): $\tilde{\nu}$ = 3057, 1588, 1543, 1467, 1360, 1208, 1017, 818, 730, 695 cm^{-1}.

MS (EI) m/z (relative intensity): 419 (100) [M$^+$], 341 (20).

HR-MS (EI) m/z calcd for C$_{32}$H$_{21}$N$^+$ 419.1674, found 419.1678.

The spectral data were in accordance with those reported in the literature.[117]

Synthesis of 6,7-Diphenylbenzo[g]indolo[2,1-*a*]isoquinoline (207ma)

The general procedure **A** was followed using 2-(naphthalen-2-yl)-1*H*-indole (**206m**) (121 mg, 0.50 mmol), diphenylacetylene (**38a**) (178 mg, 1.00 mmol) and Cu(OAc)$_2$ H$_2$O (10 mg, 10.0 mol %). After 22 h, purification by column chromatography on silica gel (*n*-hexane/ CH$_2$Cl$_2$: 5/1) yielded **207ma** (13 mg, 6%) as a yellow solid.

The general procedure **B** was followed using 2-(naphthalen-2-yl)-1*H*-indole (**206m**) (121 mg, 0.50 mmol) and diphenylacetylene (**38a**) (178 mg, 1.00 mmol). After 22 h, purification by column chromatography on silica gel (*n*-hexane/CH$_2$Cl$_2$: 5/1) yielded **207ma** (97 mg, 46%) as a yellow solid.

M. p. = 262−263 °C.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 8.73 (s, 1H), 8.00 (d, J = 8.1 Hz, 1H), 7.83 (d, J = 7.7 Hz, 1H), 7.74 (d, J = 7.8 Hz, 1H), 7.59 (d, J = 2.8 Hz, 2H), 7.54−7.16 (m, 13H), 6.89 (dd, J = 7.8, 7.8 Hz, 1H), 5.99 (d, J = 8.2 Hz, 1H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 136.8 (C$_q$), 135.8 (C$_q$), 135.6 (C$_q$), 135.3 (C$_q$), 133.6 (C$_q$), 132.6 (C$_q$), 132.2 (C$_q$), 131.9 (CH), 130.9 (CH), 129.5 (C$_q$), 129.2 (C$_q$), 128.6 (CH), 128.4 (CH), 128.1 (CH), 127.9 (CH), 127.6 (CH), 126.8 (CH), 126.0 (CH), 125.8 (CH), 124.8 (CH), 124.2 (C$_q$), 121.9 (CH), 121.7 (CH), 121.4 (C$_q$), 120.8 (CH), 120.3 (CH), 114.4 (CH), 96.7 (CH).

IR (ATR): $\tilde{\nu}$ = 3051, 3021, 1625, 1487, 1375, 1022, 736, 722, 694 cm^{-1}.

MS (EI) m/z (relative intensity): 419 (100) [M$^+$], 341 (18).

HR-MS (EI) m/z calcd for C$_{32}$H$_{21}$N$^+$ 419.1674, found 419.1678.

Synthesis of 5,6-bis{4-(trifluoromethyl)phenyl}indolo[2,1-*a*]isoquinoline (207ab)

The general procedure **A** was followed using 2-phenyl-1*H*-indole (**206a**) (97.0 mg, 0.50 mmol), 1,2-bis{4-(trifluoromethyl)phenyl}ethyne (**38b**) (314 mg, 1.00 mmol) and Cu(OAc)$_2$ H$_2$O (10 mg, 10.0 mol %). After 22 h, purification by column chromatography on silica gel (*n*-hexane/CH$_2$Cl$_2$: 10/1) yielded **207ab** (137 mg, 54%) as a yellow solid.

M. p. = 287−288 °C.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 8.32 (d, J = 7.8 Hz, 1H), 7.82 (d, J = 7.8 Hz, 1H), 7.64 (d, J = 7.8 Hz, 2H), 7.59−7.48 (m, 3H), 7.48−7.33 (m, 4H), 7.33−7.18 (m, 3H), 7.05 (d, J = 7.8 Hz, 1H), 6.88 (dd, J = 7.8, 7.8 Hz, 1H), 5.95 (d, J = 8.6 Hz, 1H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 140.2 (C$_q$), 138.5 (C$_q$), 135.7 (C$_q$), 134.5 (C$_q$), 132.5 (C$_q$), 132.1 (CH), 131.2 (q, $^2J_{C-F}$ = 33 Hz, C$_q$), 131.2 (CH), 129.8 (C$_q$), 129.7 (q, $^2J_{C-F}$ = 33 Hz, C$_q$), 129.2 (C$_q$), 127.8 (q, $^3J_{C-F}$ = 11 Hz, CH), 125.9 (CH), 125.8 (q, $^4J_{C-F}$ = 4 Hz, CH), 125.6 (C$_q$), 125.1 (q,

$^3J_{C-F}$ = 11 Hz, CH), 125.1 (q, $^4J_{C-F}$ = 4 Hz, CH), 124.0 (q, $^1J_{C-F}$ = 272 Hz, C$_q$). 123.7 (q, $^1J_{C-F}$ = 272 Hz, C$_q$), 123.5 (CH), 122.1 (CH), 120.7 (CH), 120.7 (C$_q$), 120.6 (CH), 114.0 (CH), 94.9 (CH).

^{19}F-NMR (283 MHz, CDCl$_3$): δ = −62.6 (s), −62.7 (s).

IR (ATR): $\tilde{v}$ = 3065, 1612, 1576, 1545, 1446, 1322, 1171, 1105, 1066, 759 cm^{-1}.

MS (EI) m/z (relative intensity): 505 (100) [M$^+$], 435 (10), 359 (15), 291 (10).

HR-MS (EI) m/z calcd for C$_{30}$H$_{17}$F$_6$N$^+$ 505.1265, found 505.1269.

The spectral data were in accordance with those reported in the literature.[117]

Synthesis of 5,6-di-(*p*-tolyl)indolo[2,1-*a*]isoquinoline (207ac)

The general procedure **A** was followed using 2-phenyl-1*H*-indole (**206a**) (97 mg, 0.50 mmol), 1,2-bis(4-chlorophenyl)ethyne (**38c**) (247 mg, 1.00 mmol) and Cu(OAc)$_2$ H$_2$O (10 mg, 10.0 mol %). After 22 h, purification by column chromatography on silica gel (*n*-hexane/CH$_2$Cl$_2$: 10/1) yielded **207ac** (14 mg, 6%) as a yellow solid.

The general procedure **B** was followed using 2-phenyl-1*H*-indole (**206a**) (97 mg, 0.50 mmol) and 1,2-bis(4-chlorophenyl)ethyne (**38c**) (247 mg, 1.00 mmol). After 22 h, purification by column chromatography on silica gel (*n*-hexane/CH$_2$Cl$_2$: 10/1) yielded **207ac** (176 mg, 82%) as a yellow solid.

M. p. = 251−252 ℃.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 8.29 (d, J = 8.2 Hz, 1H), 7.81 (d, J = 7.8 Hz, 1H), 7.50 (ddd, J = 7.8, 7.5, 1.2 Hz, 1H), 7.38 (s, 1H), 7.39−7.35 (m, 3H), 7.29−7.21 (m, 5H), 7.13−7.06 (m, 3H), 6.90 (ddd, J = 7.8, 7.8, 1.2 Hz, 1H), 6.09 (d, J = 8.6 Hz, 1H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 135.7 (C$_q$), 135.0 (C$_q$), 134.9 (C$_q$), 134.9 (C$_q$), 133.5 (C$_q$), 133.0 (C$_q$), 133.0 (CH), 132.5 (C$_q$), 132.1 (CH), 129.7 (C$_q$), 129.6 (C$_q$), 129.2 (CH), 128.3 (CH), 127.5 (CH), 127.4 (CH), 125.9 (CH), 125.4 (C$_q$), 123.4 (CH), 121.9 (CH), 120.6 (C$_q$), 120.5 (CH), 120.4 (CH), 114.2 (CH), 94.6 (CH).
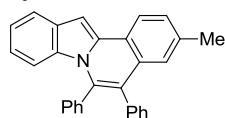
IR (ATR): $\tilde{v}$ = 3064, 1619, 1591, 1538, 1484, 1443, 1393, 1087, 1014, 737 cm^{-1}.

MS (EI) m/z (relative intensity): 437 (100) [M$^+$], 401 (9), 365 (11), 291 (10), 182 (18).

HR-MS (EI) m/z calcd for C$_{28}$H$_{17}$Cl$_2$N$^+$ 437.0738, found 437.0728.

The spectral data were in accordance with those reported in the literature.[117]

Synthesis of ethyl 5,6-diphenylpyrrolo[2,1-*a*]isoquinoline-2-carboxylate (209aa)

The general procedure **A** was followed using ethyl 5-phenyl-1*H*-pyrrole-3-carboxylate (**208a**) (108 mg, 0.50 mmol), diphenylacetylene (**38a**) (178 mg, 1.00 mmol) and Cu(OAc)$_2$ H$_2$O (10 mg, 10.0 mol %). After 22 h, purification by column chromatography on silica gel (*n*-hexane/CH$_2$Cl$_2$: 5/1) yielded **209aa** (182 mg, 93%) as a yellow solid.

M. p. = 200−201 ℃.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 8.15 (d, J = 8.0 Hz, 1H), 7.54−7.37 (m, 2H), 7.38 (d, J = 1.6 Hz, 1H), 7.36−7.19 (m, 10H), 7.19−7.11 (m, 2H), 4.33 (q, J = 7.1 Hz, 2H), 1.37 (t, J = 7.1 Hz, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 165.1 (C$_q$), 136.2 (C$_q$), 133.8 (C$_q$), 133.3 (C$_q$), 131.3 (CH), 130.8 (C$_q$), 130.5 (CH), 128.7 (CH), 128.7 (CH), 128.4 (C$_q$), 127.9 (CH), 127.7 (CH), 127.1 (CH), 126.6 (CH), 126.2 (CH), 125.7 (C$_q$), 124.6 (C$_q$), 122.1 (CH), 118.7 (CH), 118.3 (C$_q$), 101.3 (CH), 60.1 (CH$_2$), 14.5 (CH$_3$).

IR (ATR): $\tilde{v}$ = 2979, 1702, 1513, 1454, 1418, 1235, 1207, 1144, 749, 700 cm^{-1}.

MS (EI) m/z (relative intensity): 391 (100) [M$^+$], 318 (90).

HR-MS (EI) m/z calcd for $C_{27}H_{21}NO_2^+$ 391.1572, found 391.1576.

Synthesis of 5,6-diphenylpyrrolo[2,1-*a*]isoquinoline-2-carbonitrile (209ba)

The general procedure **A** was followed using 5-phenyl-1*H*-pyrrole-3-carbonitrile (**208b**) (84.0 mg, 0.50 mmol), diphenylacetylene (**38a**) (178 mg, 1.00 mmol) and Cu(OAc)$_2$ H$_2$O (10 mg, 10.0 mol %). After 22 h, purification by column chromatography on silica gel (*n*-hexane/CH$_2$Cl$_2$: 10/1) yielded **209ba** (70 mg, 40%) as a white solid.

M. p. = 228−229 °C.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 8.11 (d, J = 8.0 Hz, 1H), 7.55 (ddd, J = 7.6, 7.4, 1.3 Hz, 1H), 7.40−7.30 (m, 4H), 7.30−7.21 (m, 8H), 7.21−7.10 (m, 2H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 135.7 (C$_q$), 133.2 (C$_q$), 132.7 (C$_q$), 131.1 (CH), 130.9 (C$_q$), 130.3 (CH), 129.1 (CH), 128.9 (CH), 128.5 (C$_q$), 128.0 (CH), 128.0 (CH), 127.3 (CH), 127.0 (CH), 126.8 (CH), 125.3 (C$_q$), 124.7 (C$_q$), 122.2 (CH), 120.7 (CH), 116.5 (C$_q$), 103.0 (CH), 95.5 (C$_q$).

IR (ATR): $\tilde{v}$ = 3132, 2107, 1598, 1513, 1487, 1389, 1131, 760, 754, 697 cm^{-1}.

MS (EI) m/z (relative intensity): 344 (100) [M$^+$], 266 (10).

HR-MS (EI) m/z calcd for $C_{25}H_{16}N_2^+$ 344.1313, found 344.1324.

Synthesis of 1-(5,6-diphenylpyrrolo[2,1-*a*]isoquinolin-2-yl)ethanone (209ca)

The general procedure **A** was followed using 1-(5-phenyl-1*H*-pyrrol-3-yl)ethanone (**208c**) (93.0 mg, 0.50 mmol), diphenylacetylene (**38a**) (178 mg, 1.00 mmol) and Cu(OAc)$_2$ H$_2$O (10 mg, 10.0 mol %). After 22 h, purification by column chromatography on silica gel (*n*-hexane/CH$_2$Cl$_2$: 10/1) yielded **209ca** (137 mg, 76%) as a white solid.

M. p. = 206 °C (dec.).

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 8.15 (d. J = 8.2 Hz, 1H), 7.56−7.38 (m, 2H), 7.39−7.10 (m, 13H), 2.49 (s, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 194.6 (C$_q$), 136.1 (C$_q$), 133.8 (C$_q$), 133.2 (C$_q$), 131.3 (C$_q$), 131.2 (CH), 130.4 (CH), 128.8 (CH), 128.8 (CH), 128.5 (C$_q$), 128.0 (CH), 127.8 (CH), 127.1 (CH), 127.0 (C$_q$), 126.7 (CH), 126.4 (CH), 125.8 (C$_q$), 125.0 (C$_q$), 122.1 (CH), 118.2 (CH), 100.3 (CH), 27.5 (CH$_3$).

IR (ATR): $\tilde{v}$ = 3023, 1651, 1511, 1458, 1241, 1143, 799, 773, 700, 644 cm^{-1}.

MS (EI) m/z (relative intensity): 361 (100) [M$^+$], 346 (27), 318 (30).

HR-MS (EI) m/z calcd for $C_{26}H_{19}NO^+$ 361.1467, found 361.1456.

Synthesis of ethyl 1,5,6-triphenylpyrrolo[2,1-*a*]isoquinoline-2-carboxylate (209da)

The general procedure **A** was followed using ethyl 4,5-diphenyl-1*H*-pyrrole-3-carboxylate (**208d**) (146 mg, 0.50 mmol), diphenylacetylene (**38a**) (178 mg, 1.00 mmol) and Cu(OAc)$_2$ H$_2$O (10 mg, 10.0 mol %). After 22 h, purification by column chromatography on silica gel (*n*-hexane/CH$_2$Cl$_2$: 10/1) yielded **209da** (176 mg, 75%) as a white solid.

M. p. = 243−244 °C.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.57−7.38 (m, 7H), 7.41−7.29 (m, 5H), 7.29−7.06 (m, 8H), 4.08 (q, J = 7.0 Hz, 2H), 1.04 (t, J = 7.0 Hz, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 164.8 (C$_q$), 136.8 (C$_q$), 136.4 (C$_q$), 133.6 (C$_q$), 133.3 (C$_q$), 131.3 (CH), 130.6 (CH), 130.5 (CH), 129.1 (C$_q$), 128.8 (CH), 128.8 (CH), 128.4 (CH), 127.9 (CH), 127.2 (CH), 127.1 (CH), 127.0 (CH), 126.7 (C$_q$), 126.6 (CH), 126.4 (C$_q$), 125.7 (CH), 124.7 (C$_q$), 122.7 (CH), 119.9 (C$_q$), 118.9 (CH), 117.6 (C$_q$), 59.6 (CH$_2$), 13.9 (CH$_3$).

IR (ATR): $\tilde{\nu}$ = 3049, 1713, 1601, 1514, 1456, 1206, 1137, 776, 761, 699 cm^{-1}.

MS (EI) m/z (relative intensity): 467 (100) [M$^+$], 394 (30).

HR-MS (EI) m/z calcd for C$_{33}$H$_{25}$NO$_2$$^+$ 467.1885, found 467.1872.
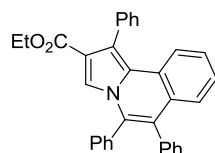
Synthesis of ethyl 5,6-di(4-fluorophenyl)pyrrolo[2,1-*a*]isoquinoline-2-carboxylate (209ad)
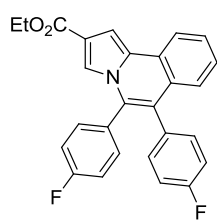
The general procedure **A** was followed using ethyl 5-phenyl-1*H*-pyrrole-3-carboxylate (**208a**) (108 mg, 0.50 mmol) and 1,2-bis(4-fluorophenyl)ethyne (**38d**) (206 mg, 1.00 mmol) and Cu(OAc)$_2$ H$_2$O (10 mg, 10.0 mol %). After 22 h, purification by column chromatography on silica gel (*n*-hexane/CH$_2$Cl$_2$: 10/1) yielded **209ad** (116 mg, 54%) as a yellow solid.

M. p. = 240−241°C.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 8.14 (d, J = 8.0 Hz, 1H), 7.56−7.41 (m, 2H), 7.41−6.84 (m, 11H); 4.34 (q, J = 7.1 Hz, 2H), 1.37 (t, J = 7.1 Hz, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 164.9 (C$_q$), 162.6 (d, $^1J_{C-F}$ = 250 Hz, C$_q$), 161.9 (d, $^1J_{C-F}$ = 247 Hz, C$_q$), 133.0 (C$_q$), 132.9 (d, $^3J_{C-F}$ = 8 Hz, CH), 132.4 (d, $^3J_{C-F}$ = 8 Hz, CH), 132.0 (d, $^4J_{C-F}$ = 4 Hz, C$_q$), 130.8 (C$_q$), 129.2 (d, $^4J_{C-F}$ = 4 Hz, C$_q$), 128.1 (C$_q$), 128.0 (CH), 126.4 (CH), 126.4 (CH), 125.8 (C$_q$), 124.0 (C$_q$), 122.2 (CH), 118.6 (C$_q$), 118.4 (CH), 116.2 (d, $^2J_{C-F}$ = 22 Hz, CH), 111.2 (d, $^2J_{C-F}$ = 22 Hz, CH), 101.6 (CH), 60.2 (CH$_2$), 14.4 (CH$_3$).

^{19}F-NMR (283 MHz, CDCl$_3$): δ = −(111.2−111.4) (m), −(114.3−114.5) (m).

IR (ATR): $\tilde{\nu}$ = 3144, 2989, 1697, 1598, 1545, 1501, 1216, 816, 789, 756 cm^{-1}.

MS (EI) m/z (relative intensity): 387 (100) [M$^+$], 354 (60).

HR-MS (EI) m/z calcd for C$_{27}$H$_{19}$F$_2$NO$_2$$^+$ 387.1384, found 387.1379.

Synthesis of dimethyl 3-methyl-5,6-di(*n*-propyl)pyrrolo[2,1-*a*]isoquinoline-1,2-dicarboxylate (209fe)

The general procedure **A** was followed using dimethyl 2-methyl-5-phenyl-1*H*-pyrrole- 3,4-dicarboxylate (**208f**) (137 mg, 0.50 mmol), 4-octyne (**38e**) (110 mg, 1.00 mmol) and Cu(OAc)$_2$ H$_2$O (10.0 mg, 10.0 mol %). After 22 h, purification by column chromatography on silica gel (*n*-hexane/ EtOAc: 10/1) yielded **209fe** (99 mg, 48%) as a yellow oil.

The general procedure **A** was followed using dimethyl 2-methyl-5-phenyl-1*H*-pyrrole-3,4-dicarboxylate (**208f**) (137 mg, 0.50 mmol), 4-octyne (**38e**) (110 mg, 1.00 mmol) and Cu(OAc)$_2$ H$_2$O (30.0 mg, 30.0 mol %). After 22 h, purification by column chromatography on silica gel (*n*-hexane/ EtOAc: 10/1) yielded **209fe** (141 mg, 74%) as a yellow oil.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 8.17 (d, J = 7.2 Hz, 1H), 7.67 (d, J = 7.0 Hz, 1H), 7.46−7.36 (m, 2H), 3.99 (s, 3H), 3.87 (s, 3H), 3.12 (t, J = 8.2 Hz, 2H), 2.97 (s, 3H), 2.79 (t, J = 8.2 Hz, 2H), 1.70−1.52 (m, 4H), 1.09 (t, J = 7.3 Hz, 3H), 1.02 (t, J = 7.3 Hz, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 169.0 (C$_q$), 165.7 (C$_q$), 154.7 (C$_q$), 128.8 (C$_q$), 128.4 (C$_q$), 127.9 (C$_q$), 126.9 (CH), 126.8 (CH), 124.7 (C$_q$), 123.6 (CH), 123.1 (CH), 122.2 (C$_q$), 116.4 (C$_q$), 109.2

(C$_q$), 52.5 (CH$_3$), 51.7 (CH$_3$), 50.5 (CH$_2$), 50.2 (CH$_2$), 25.4 (CH$_2$), 25.0 (CH$_2$), 14.8 (CH$_3$), 14.4 (CH$_3$), 13.4 (CH$_3$).

IR (ATR): $\tilde{v}$ = 2954, 1708, 1526, 1455, 1438, 1199, 1118, 1091, 755, 730 cm^{-1}.

MS (EI) m/z (relative intensity): 381 (100) [M$^+$], 350 (30), 334 (38), 263 (28).

HR-MS (EI) m/z calcd for C$_{23}$H$_{27}$NO$_4^+$ 381.1940, found 381.1933.

Synthesis of ethyl 5,6-dimethyl-1-phenylpyrrolo[2,1-a]isoquinoline-2-carboxylate (209de)

The general procedure **A** was followed using ethyl 4,5-diphenyl-1H-pyrrole-3-carboxylate (**208d**) (72.8 mg, 0.25 mmol), 4-octyne (**38e**) (55.0 mg, 0.50 mmol) and Cu(OAc)$_2$ H$_2$O (15.0 mg, 30.0 mol %). After 22 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 20/1) yielded **209de** (77 mg, 77%) as a yellow oil.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.97 (s, 1H), 7.69 (d, J = 8.2 Hz, 1H), 7.65−7.57 (m, 6H), 7.32 (ddd, J = 7.7, 7.7, 1.2 Hz, 1H), 7.09 (ddd, J = 7.7, 7.7, 1.2 Hz, 1H), 4.15 (q, J = 7.1 Hz, 2H), 3.02 (t, J = 8.0 Hz, 2H), 2.87 (t, J = 8.0 Hz, 2H), 1.92−1.77 (m, 2H), 1.75−1.61 (m, 2H), 1.22−1.01 (m, 9H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 166.0 (C$_q$), 157.2 (C$_q$), 152.5 (C$_q$), 150.6 (CH), 128.5 (CH), 127.7 (C$_q$), 127.0 (CH), 126.5 (C$_q$), 126.5 (C$_q$), 126.1 (CH), 125.7 (CH), 123.6 (CH), 123.1 (CH), 119.8 (C$_q$), 119.4 (C$_q$), 117.4 (C$_q$), 116.5 (CH), 59.6 (CH$_2$), 30.7 (CH$_2$), 30.0 (CH$_2$), 23.4 (CH$_2$), 20.3 (CH$_2$), 14.5 (CH$_3$), 14.3 (CH$_3$), 13.9 (CH$_3$).

IR (ATR): $\tilde{v}$ = 2958, 1698, 1604, 1519, 1457, 1202, 1111, 758, 731, 698 cm^{-1}.

MS (EI) m/z (relative intensity): 399 (100) [M$^+$], 370 (45), 282 (35).

HR-MS (EI) m/z calcd for C$_{27}$H$_{29}$NO$_2^+$ 399.2178, found 399.2178.

Synthesis of dimethyl 5,6-diethyl-3-methylpyrrolo[2,1-a]isoquinoline-1,2-dicarboxylate (209ff)

The general procedure **A** was followed using dimethyl 2-methyl-5-phenyl-1H-pyrrole- 3,4-dicarboxylate (**208f**) (137 mg, 0.50 mmol), 3-hexyne (**38f**) (82.0 mg, 1.00 mmol) and Cu(OAc)$_2$ H$_2$O (30.0 mg, 30.0 mol %). After 22 h, purification by column chromatography on silica gel (n-hexane/ EtOAc: 10/1) yielded **209ff** (152 mg, 86%) as a yellow oil.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 8.17 (d, J = 6.8 Hz, 1H), 7.71 (d, J = 6.7 Hz, 1H), 7.46−7.34 (m, 2H), 3.99 (s, 3H), 3.88 (s, 3H), 3.21 (q, J = 7.4 Hz, 2H), 3.01 (s, 3H), 2.89 (q, J = 7.5 Hz, 2H), 1.25 (t, J = 7.5 Hz, 3H), 1.24 (t, J = 7.4 Hz, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 168.8 (C$_q$), 165.7 (C$_q$), 155.7 (C$_q$), 128.6 (C$_q$), 128.5 (C$_q$), 127.6 (C$_q$), 126.9 (CH), 126.8 (CH), 125.0 (C$_q$), 125.4 (CH), 125.4 (CH), 125.2 (C$_q$), 116.6 (C$_q$), 109.6 (C$_q$), 52.4 (CH$_3$), 51.6 (CH$_3$), 21.6 (CH$_2$), 20.9 (CH$_2$), 14.9 (CH$_3$), 14.4 (CH$_3$), 14.4 (CH$_3$). IR (ATR): $\tilde{v}$ = 2948, 1706, 1525, 1482, 1439, 1200, 1131, 1083, 784, 755 cm^{-1}.

MS (EI) m/z (relative intensity): 353 (76) [M$^+$], 322 (38), 306 (100), 235 (74).

HR-MS (EI) m/z calcd for C$_{21}$H$_{23}$NO$_4^+$ 353.1627, found 353.1636.

Synthesis of ethyl 5,6-diethyl-1-phenylpyrrolo[2,1-a]isoquinoline-2-carboxylate (209df)

The general procedure **A** was followed using ethyl 2-methyl-4,5-diphenyl-1H-pyrrole-3-carboxylate (**208d**) (72.8 mg, 0.25 mmol), 3-hexyne (**38f**) (55.0 mg, 0.50 mmol) and Cu(OAc)$_2$ H$_2$O (15.0 mg, 30.0 mol %). After 22 h,

purification by column chromatography on silica gel (*n*-hexane/EtOAc: 20/1) yielded **209df** (74 mg, 76%) as a white solid. M. p. = 141−138 °C.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 8.01 (s, 1H), 7.73 (d, J = 8.4 Hz, 1H), 7.64−7.38 (m, 6H), 7.32 (ddd, J = 7.7, 7.6, 1.3 Hz, 1H), 7.09 (ddd, J = 7.7, 7.6, 1.2 Hz, 1H), 4.16 (q, J = 7.4 Hz, 2H), 3.09 (q, J = 7.6 Hz, 2H), 2.96 (q, J = 7.6 Hz, 2H), 1.45 (t, J = 7.6 Hz, 3H), 1.31 (t, J = 7.6 Hz, 3H), 1.11 (t, J = 7.4 Hz, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 166.0 (C$_q$), 157.3 (C$_q$), 155.4 (C$_q$), 150.7 (CH), 128.5 (CH), 127.6 (C$_q$), 127.0 (CH), 126.5 (C$_q$), 126.5 (C$_q$), 126.2 (CH), 125.8 (CH), 123.6 (CH), 123.3 (CH), 120.8 (C$_q$), 119.6 (C$_q$), 117.7 (C$_q$), 116.4 (CH), 59.6 (CH$_2$), 21.8 (CH$_2$), 20.8 (CH$_2$), 14.7 (CH$_3$), 14.0 (CH$_3$), 11.7 (CH$_3$).

IR (ATR): $\tilde{v}$ = 2966, 1695, 1602, 1521, 1444, 1268, 1219, 1034, 757, 703 cm^{-1}.

MS (EI) *m/z* (relative intensity): 371 (100) [M$^+$], 298 (23), 282 (20).

HR-MS (EI) *m/z* calcd for C$_{25}$H$_{25}$NO$_2^+$ 371.1885, found 371.1887.

Synthesis of dimethyl 6-(*n*-butyl)-5-(4-methoxyphenyl)-3-methylpyrrolo[2,1-*a*]isoquinoline-1,2-di-caboxylate (209fg)

The general procedure **A** was followed using dimethyl 2-methyl-5-phenyl-1*H*-pyrrole- 3,4-dicarboxylate (**208f**) (137 mg, 0.50 mmol), 1-(hex-1-yn-1-yl)-4-methoxybenzene (**38g**) (188 mg, 1.00 mmol) and Cu(OAc)$_2$ H$_2$O (30 mg, 30.0 mol %). After 22 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 10/1) yielded **209fg** (169 mg, 74%, 6:1 mixture of regioisomers according to ^{1}H-NMR as a yellow oil. Purification by a second column chromatography on silica gel (*n*-hexane/EtOAc: 20/1) yielded the major regioisomer (146 mg, 64%) as a yellow solid.

M. p. = 138−143 °C.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 8.31−8.24 (d, J = 7.1 Hz, 1H), 7.76−7.71 (d, J = 7.0 Hz, 1H), 7.50−7.45 (m, 2H), 7.27 (d, J = 10.8 Hz, 2H), 6.99 (d, J = 10.8 Hz, 2H), 4.00 (s, 3H), 3.90 (s, 3H), 3.82 (s, 3H), 2.49 (t, J = 8.2 Hz, 2H), 1.92 (s, 3H), 1.52−1.39 (m, 2H), 1.31−1.18 (m, 2H), 0.76 (t, J = 7.3 Hz, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 168.9 (C$_q$), 165.6 (C$_q$), 160.0 (C$_q$), 133.2 (C$_q$), 132.0 (CH), 130.1 (C$_q$), 127.6 (C$_q$), 127.5 (C$_q$), 127.4 (CH), 126.9 (CH), 125.3 (C$_q$), 124.1 (CH), 124.0 (C$_q$), 123.4 (CH), 111.9 (C$_q$), 113.6 (CH), 112.2 (C$_q$), 109.0 (C$_q$), 55.3 (CH$_3$), 52.5 (CH$_3$), 51.6 (CH$_3$), 32.3 (CH$_2$), 28.2 (CH$_2$), 22.9 (CH$_2$), 14.1 (CH$_3$), 13.6 (CH$_3$).

IR (ATR): $\tilde{v}$ = 2954, 1705, 1604, 1525, 1509, 1438, 1240, 1171, 1021, 798 cm^{-1}.

MS (EI) *m/z* (relative intensity): 459 (100) [M$^+$], 386 (70), 341 (60).

HR-MS (EI) *m/z* calcd for C$_{28}$H$_{29}$NO$_5^+$ 459.2046, found 459.2041.

Synthesis of ethyl 6-butyl-5-(4-methoxyphenyl)pyrrolo[2,1-*a*]isoquinoline-2-carboxylate (209ag)

The general procedure **A** was followed using ethyl 5-phenyl-1*H*-pyrrole-3-carboxylate (**208a**) (108 mg, 0.50 mmol), 1-(hex-1-yn-1-yl)-4-methoxybenzene (**38g**) (188 mg, 1.00 mmol) and Cu(OAc)$_2$ H$_2$O (30.0 mg, 30.0 mol%). After 22 h, purification by column chromatography on silica gel (*n*-hexane/ EtOAc: 30/1) yielded **209ag** (160 mg, 76%, 8:1 mixture of regioisomers according to ^{1}H-NMR) as a

yellow oil. Purification by a second column chromatography on silica gel (*n*-hexane/EtOAc: 30/1) yielded the major regioisomer (95 mg, 47%) as a yellow oil.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 8.10 (d, *J* = 7.6 Hz, 1H), 7.76 (d, *J* = 7.8 Hz, 1H), 7.55−7.45 (m, 2H), 7.40 (s, 1H), 7.51 (d, *J* = 8.4 Hz, 2H), 7.20 (s, 1H), 7.10 (d, *J* = 8.4 Hz, 2H), 4.52 (q, *J* = 7.4 Hz, 2H), 3.92 (s, 3H), 2.60 (t, *J* = 8.0 Hz, 2H), 1.61−1.49 (m, 2H), 1.36 (t, *J* = 7.0 Hz, 3H), 1.29 (m, 2H), 0.85 (t, *J* = 7.4 Hz, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 165.1 (C$_q$), 160.0 (C$_q$), 152.8 (C$_q$), 131.2 (CH), 130.4 (C$_q$), 127.2 (CH), 127.1 (C$_q$), 126.2 (C$_q$), 126.2 (CH), 125.9 (C$_q$), 124.5 (CH), 122.6 (CH), 121.7 (C$_q$), 118.4 (CH), 117.6 (C$_q$), 114.8 (CH), 100.9 (CH), 60.0 (CH$_2$), 55.3 (CH$_3$), 32.5 (CH$_2$), 28.2 (CH$_2$), 22.9 (CH$_2$), 14.4 (CH$_3$), 13.7 (CH$_3$).

IR (ATR): $\tilde{v}$ = 2955, 1705, 1607, 1508, 1454, 1289, 1241, 1173, 1025, 751 cm^{-1}.

MS (EI) *m/z* (relative intensity): 401 (100) [M$^+$], 358 (20), 285 (35).

HR-MS (EI) *m/z* calcd for C$_{26}$H$_{27}$NO$_3$$^+$ 401.1991, found 401.1989.
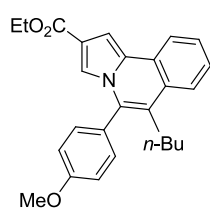
Synthesis of ethyl 6-methyl-5-phenylpyrrolo[2,1-*a*]isoquinoline-2-carboxylate (209ah)
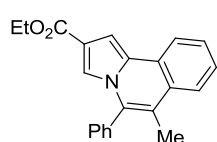
The general procedure **A** was followed using ethyl 5-phenyl-1*H*-pyrrole-3-carboxylate (108 mg, 0.50 mmol) (**208a**), 1-phenyl-1-propyne (**38h**) (116 mg, 1.00 mmol) and Cu(OAc)$_2$ H$_2$O (30.0 mg, 30.0 mol%). After 22 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 20/1) yielded **209ah** (120 mg, 73%, 5:1 mixture of regioisomers according to ^{1}H-NMR) as a yellow solid. Purification by a second column chromatography on silica gel (*n*-hexane/EtOAc: 30/1) yielded the major regioisomer (41 mg, 25%) as a yellow solid.

M. p. = 114−111 °C.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 8.10 (d, *J* = 7.8 Hz, 1H), 7.76 (d, *J* = 7.8 Hz, 1H), 7.60−7.38 (m, 8H), 7.25 (d, *J* = 1.6 Hz, 1H), 4.51 (q, *J* = 7.1 Hz, 2H), 2.21 (s, 3H), 1.55 (t, *J* = 7.1 Hz, 3H).
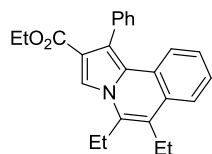
^{13}C-NMR (75 MHz, CDCl$_3$): δ = 165.2 (C$_q$), 153.9 (C$_q$), 153.0 (C$_q$), 150.6 (C$_q$), 150.1 (CH), 129.6 (CH), 129.5 (CH), 128.1 (C$_q$), 127.6 (CH), 126.5 (CH), 125.9 (C$_q$), 124.2 (CH), 122.5 (CH), 118.5 (CH), 117.7 (C$_q$), 116.6 (C$_q$), 101.1 (CH), 60.0 (CH$_2$), 15.0 (CH$_3$), 14.4 (CH$_3$).

IR (ATR): $\tilde{v}$ = 2974, 1695, 1544, 1516, 1454, 1240, 1178, 1019, 747, 703 cm^{-1}.

MS (EI) *m/z* (relative intensity): 329 (100) [M$^+$], 256 (55).

HR-MS (EI) *m/z* calcd for C$_{22}$H$_{19}$NO$_2$$^+$ 329.1416, found 329.1417.

Intermolecular competition experiment with indoles 206b and 206o (Scheme 64a)

A mixture of 2-(4-fluorophenyl)-1*H*-indole (**206b**) (219 mg, 1.00 mmol), 2-(4-methoxyphenyl)-1*H*-indole (**206o**) (209 mg, 1.00 mmol), diphenylacetylene (**38a**) (89.0 mg, 0.50 mmol), [RuCl$_2$(*p*-cymene)]$_2$ (15.3 mg, 5.0 mol %) and Cu(OAc)$_2$ H$_2$O (10.0 mg, 10.0 mol %)

in *t*-AmOH (2.0 mL) was stirred at 100 ℃ under air for 22 h. At ambient temperature, the mixture was diluted with H$_2$O (75 mL) and extracted with EtOAc (3 × 75 mL). The combined organic phase was washed with brine (50 mL) and dried over anhydrous Na$_2$SO$_4$. After filtration and evaporation of the solvents under reduced pressure, the crude product was purified by column chromatography on silica gel (*n*-hexane/EtOAc: 50/1) to yield **207ba** as a yellow solid (66 mg, 34%).

Intermolecular competition experiment with alkynes 38b and 38i (Scheme 64b)

A mixture of 2-phenylindole (**206a**) (48.0 mg, 0.25 mmol), 1,2-di-(*p*-tolyl)ethyne (**38i**) (103 mg, 0.50 mmol), 1,2-bis{4-(trifluoromethyl)phenyl}ethyne (**38b**) (157 mg, 0.50 mmol), [RuCl$_2$(*p*-cymene)]$_2$ (7.7 mg, 5.0 mol %) and Cu(OAc)$_2$ H$_2$O (5.0 mg, 10.0 mol %) in *t*-AmOH (2.0 mL) was stirred at 100 ℃ under air for 22 h. At ambient temperature, the mixture was diluted with H$_2$O (75 mL) and extracted with EtOAc (3 × 75 mL). The combined organic phase was washed with brine (50 mL) and dried over anhydrous Na$_2$SO$_4$. After filtration and evaporation of the solvents under reduced pressure, the crude product was purified by column chromatography on silica gel (*n*-hexane/EtOAc: 50/1) to yield **207ab** as a yellow solid (43 mg, 34%).

Annulation with *meta*-fluorophenyl-substituted indole 206p (Scheme 65)

A mixture of 2-(3-fluorophenyl)-1*H*-indole (**206p**) (106 mg, 0.50 mmol), diphenylacetylene (**38a**) (178 mg, 1.00 mmol), [RuCl$_2$(*p*-cymene)]$_2$ (15.3 mg, 5.0 mol%) and Cu(OAc)$_2$ H$_2$O (10.0 mg, 10.0 mol %) in *t*-AmOH (2.0 mL) was stirred at 100 ℃ under air for 22 h. At ambient temperature, the mixture was diluted with H$_2$O (75 mL) and extracted with EtOAc (3 × 75 mL). The combined organic phase was washed with brine (50 mL) and dried over anhydrous Na$_2$SO$_4$. After filtration and evaporation of the solvents under reduced pressure, the crude product was purified by column chromatography on silica gel (*n*-hexane/CH$_2$Cl$_2$: 10/1) to yield **207'pa** (78 mg, 40%) as yellow solid and **207''pa** (17 mg, 9%) as yellow solid.

4-Fluoro-5,6-diphenylindolo[2,1-*a*]isoquinoline (207'pa)

M. p. = 209−210 °C.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 8.12 (d, J = 7.8 Hz, 1H), 7.83 (d, J = 7.8 Hz, 1H), 7.52−7.10 (m, 13H), 7.05 (dd, J = 12.4, 7.8 Hz, 1H), 6.88 (dd, J = 7.8, 7.8 Hz, 1H), 5.96 (d, J = 8.8 Hz, 1H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 159.1 (d, $^1J_{C-F}$ = 254 Hz, C$_q$), 138.7 (d, $^4J_{C-F}$ = 3 Hz, C$_q$), 137.5 (C$_q$), 134.9 (d, $^4J_{C-F}$ = 3 Hz, C$_q$), 134.8 (C$_q$), 132.8 (C$_q$), 131.0 (CH), 130.9 (CH), 129.6 (C$_q$), 128.7 (CH), 128.5 (CH), 128.0 (d, $^3J_{C-F}$ = 9 Hz, CH), 127.7 (d, $^3J_{C-F}$ = 4 Hz, C$_q$), 127.1 (CH), 126.3 (CH), 121.9 (CH), 120.6 (CH), 120.4 (CH), 119.4 (d, $^4J_{C-F}$ = 4 Hz, CH), 118.6 (d, $^2J_{C-F}$ = 9 Hz, C$_q$), 117.0 (d, $^4J_{C-F}$ = 3 Hz, C$_q$), 114.7 (CH), 114.4 (d, $^2J_{C-F}$ = 22 Hz, CH), 96.1 (CH).

^{19}F-NMR (283 MHz, CDCl$_3$): δ = −(107.8−108.9) (m).

IR (ATR): $\tilde{v}$ = 3056, 1608, 1539, 1487, 1461, 1440, 1230, 773, 739, 693 cm^{-1}.

MS (EI) *m/z* (relative intensity): 387 (100) [M$^+$], 309 (13).

HR-MS (EI) *m/z* calcd for C$_{28}$H$_{18}$FN$^+$ 387.1383, found 387.1411.

2-Fluoro-5,6-diphenylindolo[2,1-*a*]isoquinoline (207''pa)

M. p. = 226−227 °C.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.93 (dd, J = 9.7, 2.6 Hz, 1H), 7.81 (d, J = 8.0 Hz, 1H), 7.43−7.27 (m, 6H), 7.27−7.09 (m, 7H), 7.05 (ddd, J = 8.8, 8.6, 2.6 Hz, 1H), 6.84 (ddd, J = 8.0, 7.7, 1.3 Hz, 1H), 6.01 (d, J = 8.8 Hz, 1H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 161.8 (d, $^1J_{C-F}$ = 247 Hz, C$_q$), 136.7 (C$_q$), 136.7 (C$_q$), 135.3 (C$_q$), 135.3 (C$_q$), 133.0 (C$_q$), 131.8 (CH), 131.0 (CH), 129.6 (C$_q$), 129 (CH), 128.6 (CH), 128.5 (d, $^3J_{C-F}$ = 9 Hz, CH), 127.9 (CH), 127.2 (d, $^3J_{C-F}$ = 9 Hz, C$_q$), 126.9 (CH), 126.8 (d, $^4J_{C-F}$ = 2 Hz, C$_q$), 121.9 (CH), 121.0 (C$_q$), 120.6 (CH), 120.5 (CH), 111.3 (CH, $^2J_{C-F}$ = 23 Hz), 114.7 (CH), 108.7 (d, $^2J_{C-F}$ = 23 Hz, CH), 96.1 (CH).

^{19}F-NMR (283 MHz, CDCl$_3$): δ = −(113.7−113.8) (m).

IR (ATR): $\tilde{v}$ = 3061, 1608, 1538, 1487, 1340, 1167, 956, 732, 694, 651 cm^{-1}.

MS (EI) *m/z* (relative intensity): 387 (100) [M$^+$], 309 (9).

HR-MS (EI) *m/z* calcd for C$_{28}$H$_{18}$FN$^+$ 387.1383, found 387.1419.

Aerobic oxidative annulation in [D]$_4$-MeOH (Scheme 66a)

A mixture of 5-nitro-2-phenyl-1*H*-indole (**206d**) (119 mg, 0.50 mmol), [RuCl$_2$(*p*-cymene)]$_2$ (15.3 mg, 5.0 mol %) and Cu(OAc)$_2$ (9.1 mg, 10.0 mol %) in [D]$_4$-MeOH (2.0 mL) was stirred at 76 °C under air for 22 h. At ambient temperature, the crude mixture was evaporated under reduced pressure and purified by column chromatography on silica gel (*n*-hexane/EtOAc: 10/1) to yield **206d** (116 mg, 97%) as a yellow solid. No deuterium incorporation was detected by ^{1}H-NMR spectroscopy.

Aerobic oxidative annulation in [D]₄-MeOH (Scheme 66b)

A mixture of 5-nitro-2-phenyl-1H-indole (**206d**) (119 mg, 0.50 mmol), 4-octyne (**38e**) (110 mg, 1.00 mmol), [RuCl₂(p-cymene)]₂ (15.3 mg, 5.0 mol %) and Cu(OAc)₂ (27.1 mg, 30.0 mol %) in [D]₄-MeOH (2.0 mL) was stirred at 76 ℃ under air for 22 h. At ambient temperature, the mixture was diluted with H₂O (75 mL) and extracted with EtOAc (3 × 75 mL). The combined organic phase was washed with brine (50 mL) and dried over anhydrous Na₂SO₄. After filtration and evaporation of the solvents under reduced pressure, the crude product was purified by column chromatography on silica gel (n-hexane/EtOAc: 40/1→10/1) to yield **207de** (76 mg, 46%) as a yellow solid and **206d** (49 mg, 41%) as a yellow solid. No deuterium incorporation was detected by ¹H-NMR spectroscopy.

8.4.2 Analytical Data for the Products of Ruthenium-Catalyzed Oxidative Annulation of Alkynes 38 with Enamines 210

Synthesis of methyl 1-acetyl-4,5-diphenyl-1H-pyrrole-2-carboxylate (211aa)

The general procedure **C** was followed using 2-acetamidoacrylate (**210a**) (71.5 mg, 0.50 mmol) and diphenylacetylene (**38a**) (178 mg, 1.00 mmol). After 22 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 10/1) yielded **211aa** (111 mg, 70%) as a yellow oil.

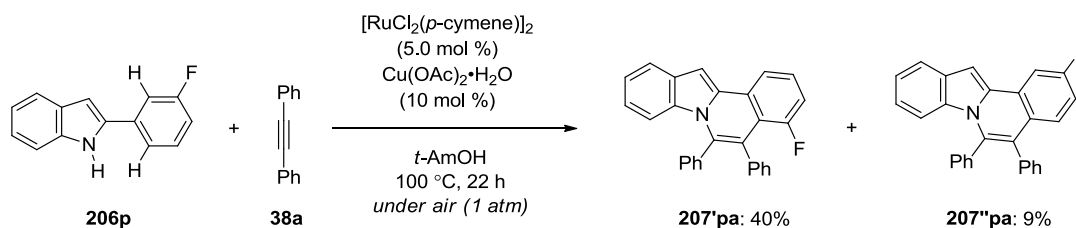¹H-NMR (300 MHz, CDCl₃): δ = 7.48−7.28 (m, 5H), 7.28−7.07 (m, 6H), 3.89 (s, 3H), 2.33 (s, 3H).

¹³C-NMR (75 MHz, CDCl₃): δ = 173.8 (C_q), 161.0 (C_q), 134.5 (C_q), 133.9 (C_q), 130.6 (C_q), 130.6 (CH), 128.8 (CH), 128.5 (CH), 128.2 (CH), 128.0 (CH), 126.4 (CH), 124.8 (C_q), 122.9 (C_q), 118.3 (CH), 51.8 (CH₃), 28.8 (CH₃).

IR (ATR): $\tilde{v}$ = 3060, 2953, 1759, 1702, 1440, 1381, 1253, 1207, 756, 694 cm⁻¹.

MS (EI) m/z (relative intensity): 319 (18) [M⁺], 277 (100), 245 (33), 215 (34), 43 (27).

HR-MS (EI) m/z calcd for C₂₀H₁₇NO₃⁺ 319.1206, found 319.1197.

The spectral data were in accordance with those reported in the literature.[123a]

Synthesis of methyl 4,5-diphenyl-1H-pyrrole-2-carboxylate (212aa)

The general procedure **C** was followed using 2-(2,2,2-trifluoroacetamido)acrylate (98.5 mg, 0.50 mmol), and diphenylacetylene (**38a**) (178 mg, 1.00 mmol). After 22 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 10/1) yielded **212aa** as a white solid (21 mg, 15%).

M.p. = 174−175 ℃.

¹H-NMR (300 MHz, CDCl₃): δ = 9.56 (s_br, 1H), 7.55−7.18 (m, 10H), 7.07 (d, J = 2.8 Hz, 1H),

3.85 (s, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 161.7 (C$_q$), 136.3 (C$_q$), 133.4 (C$_q$), 131.8 (C$_q$), 128.6 (CH), 128.4 (CH), 128.3 (CH), 128.0 (CH), 127.9 (CH), 126.3 (CH), 124.1 (C$_q$), 122.0 (C$_q$), 116.8 (CH), 51.6 (CH$_3$).

IR (ATR): $\tilde{v}$ = 3257, 1668, 1602, 1454, 1440, 1225, 1203, 1009, 762, 692 cm^{-1}.

MS (EI) m/z (relative intensity): 277 (100) [M$^+$], 245 (72), 215 (70), 189 (28), 43 (20).

HR-MS (EI) m/z calcd for C$_{18}$H$_{15}$NO$_2$$^+$ 277.1103, found 277.1094.
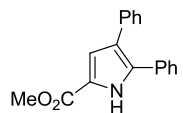
Synthesis of ethyl 1-acetyl-4,5-diphenyl-1*H*-pyrrole-2-carboxylate (211ba)
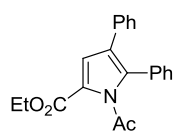
The general procedure **C** was followed using ethyl 2-acetamidoacrylate (**210b**) (78.5 mg, 0.50 mmol) and diphenylacetylene (**38a**) (178 mg, 1.00 mmol). After 22 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 20/1) yielded **211ba** (113 mg, 68%) as a white solid.

M.p. = 94−95 °C.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.49−7.26 (m, 5H), 7.25−7.03 (m, 6H), 4.36 (q, J = 7.2 Hz, 2H), 3.00 (s, 3H), 1.39 (t, J = 7.2 Hz, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 173.9 (C$_q$), 160.6 (C$_q$), 134.4 (C$_q$), 134.0 (C$_q$), 130.7 (C$_q$), 130.7 (CH), 128.8 (CH), 128.5 (CH), 128.2 (CH), 128.0 (CH), 126.4 (CH), 124.7 (C$_q$), 123.3 (C$_q$), 118.2 (CH), 60.8 (CH$_2$), 28.9 (CH$_3$), 14.3 (CH$_3$).

IR (ATR): $\tilde{v}$ = 2998, 1753, 1697, 1499, 1460, 1258, 1219, 1190, 770, 701 cm^{-1}.

MS (EI) m/z (relative intensity): 333 (5) [M$^+$], 291 (100), 245 (62), 215 (38), 189 (20).

HR-MS (EI) m/z calcd for C$_{21}$H$_{19}$NO$_3$$^+$ 333.1365, found 333.1356.

Synthesis of isopropyl 1-acetyl-4,5-diphenyl-1*H*-pyrrole-2-carboxylate (211ca)

The general procedure **C** was followed using isopropyl 2-acetamidoacrylate (**210c**) (85.5 mg, 0.50 mmol) and diphenylacetylene (**38a**) (178 mg, 1.00 mmol). After 22 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 30/1) yielded **210ca** (111 mg, 66%) as a colorless oil.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.38−7.27 (m, 5H), 7.21−7.11 (m, 6H), 5.21 (sept., J = 6.2 Hz, 1H), 2.30 (s, 3H), 1.36 (d, J = 6.2 Hz, 6H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 173.9 (C$_q$), 160.2 (C$_q$), 134.2 (C$_q$), 134.0 (C$_q$), 130.7 (C$_q$), 130.7 (CH), 128.8 (CH), 128.5 (CH), 128.2 (CH), 128.0 (CH), 126.3 (CH), 124.7 (C$_q$), 123.7 (C$_q$), 118.0 (CH), 68.5 (CH), 28.9 (CH$_3$), 21.9 (CH$_3$).

IR (ATR): $\tilde{v}$ = 3030, 1760, 1695, 1460, 1385, 1254, 1206, 1104, 757, 695 cm^{-1}.

MS (EI) m/z (relative intensity): 347 (9) [M$^+$], 305 (100), 263 (70), 245 (77), 214 (47), 191 (22).

HR-MS (EI) m/z calcd for C$_{22}$H$_{21}$NO$_3$$^+$ 347.1521, found 347.1516.
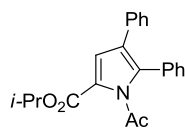
Synthesis of 1-acetyl-2-methyl-4,5-diphenyl-1*H*-pyrrole-3-carbonitrile (211fa)
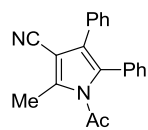
The general procedure **C** was followed using *N*-(1-cyanoprop-1-en-2-yl)acetamide (**210f**) (62.0 mg, 0.50 mmol) and diphenylacetylene (**38a**) (178 mg, 1.00 mmol). After 22 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 10/1) yielded **211fa** (65 mg, 43%) as a white solid.

M.p. = 243−244 °C.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.39−7.31 (m, 3H), 7.28−7.14 (m, 7H), 2.64 (s, 3H), 1.95 (s, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 172.2 (C$_q$), 140.8 (C$_q$), 131.4 (C$_q$), 131.4 (C$_q$), 130.2 (CH), 129.6 (C$_q$), 129.1 (CH), 129.0 (CH), 128.8 (CH), 128.3 (CH), 127.4 (CH), 125.4 (C$_q$), 111.6 (C$_q$), 97.2 (C$_q$), 27.9 (CH$_3$), 14.2 (CH$_3$).

IR (ATR): $\tilde{\nu}$ = 2977, 2198, 1521, 1441, 1362, 1072, 1003, 717, 703, 574 cm^{-1}.

MS (EI) m/z (relative intensity): 300 (20) [M$^+$], 258 (100), 238 (20), 43 (32).

HR-MS (EI) m/z calcd for C$_{20}$H$_{16}$N$_2$O$^+$ 300.1263, found 300.1259.

The spectral data were in accordance with those reported in the literature.[122]

Synthesis of 1-(2,3,5-triphenyl-1*H*-pyrrol-1-yl)ethanone (211ga)
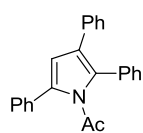
The general procedure **C** was followed using *N*-(1-phenylvinyl)acetamide (**210g**) (76.5 mg, 0.50 mmol) and diphenylacetylene (**38a**) (178 mg, 1.00 mmol). After 22 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 30/1) yielded **211ga** (88 mg, 52%) as a yellow solid.

M.p. = 131−132 ℃.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.46−7.40 (m, 4H), 7.38−7.33 (m, 6H), 7.21−7.14 (m, 5H), 6.54 (s, 1H), 2.02 (s, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 172.8 (C$_q$), 134.8 (C$_q$), 134.7 (C$_q$), 133.4 (C$_q$), 132.8 (C$_q$), 131.0 (CH), 130.9 (C$_q$), 128.5 (CH), 128.4 (CH), 128.4 (CH), 128.1 (CH), 128.1 (CH), 128.1 (CH), 127.6 (CH), 126.2 (CH), 125.5 (C$_q$), 113.6 (CH), 28.6 (CH$_3$).

IR (ATR): $\tilde{\nu}$ = 3061, 3029, 1721, 1620, 1485, 1288, 1268, 1026, 789, 762 cm^{-1}.

MS (EI) m/z (relative intensity): 337 (23) [M$^+$], 295 (100), 189 (23), 43 (33).

HR-MS (EI) m/z calcd for C$_{24}$H$_{19}$NO$^+$ 337.1467, found 337.1461.

Synthesis of 1-{5-[4-(trifluoromethyl)phenyl]-2,3-diphenyl-1*H*-pyrrol-1-yl}ethanone (211ha)
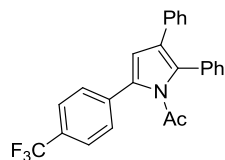
The general procedure **C** was followed using *N*-{1-[4-(trifluoromethyl)phenyl]vinyl}-acetamide (**210h**) (111 mg, 0.50 mmol) and diphenylacetylene (**38a**) (178 mg, 1.00 mmol). After 22 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 40/1) yielded **211ha** (138 mg, 68%) as a white solid.

M.p. = 133−134 ℃.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.67 (d, J = 8.2 Hz, 2H), 7.53 (d, J = 8.2 Hz, 2H), 7.43−7.33 (m, 5H), 7.24−7.13 (m, 5H), 6.59 (s, 1H), 2.03 (s, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 172.5 (C$_q$), 137.0 (C$_q$), 134.4 (C$_q$), 133.6 (C$_q$), 132.5 (C$_q$), 131.5 (C$_q$), 130.9 (CH), 129.7 (q, $^2J_{C-F}$ = 32 Hz, C$_q$), 128.6 (CH), 128.5 (CH), 128.5 (CH), 128.2 (CH), 128.1 (CH), 127.7 (q, $^1J_{C-F}$ = 273 Hz, C$_q$), 126.4 (CH), 125.9 (C$_q$), 125.3 (q, $^3J_{C-F}$ = 4 Hz, CH), 114.8 (CH), 28.5 (CH$_3$).

^{19}F-NMR (283 MHz, CDCl$_3$): δ = −62.5 (s).

IR (ATR): $\tilde{\nu}$ = 3063, 3032, 1723, 1615, 1268, 1111, 1064, 847, 766, 694 cm^{-1}.

MS (EI) m/z (relative intensity): 405 (18) [M$^+$], 363 (100), 293 (4), 189 (10), 43 (15).

HR-MS (EI) m/z calcd for C$_{25}$H$_{18}$F$_3$NO$^+$ 405.1340, found 405.1346.

Synthesis of 1-{5-(4-fluorophenyl)-2,3-diphenyl-1*H*-pyrrol-1-yl}ethanone (211ia)
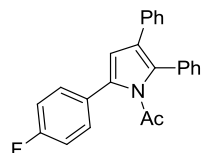
The general procedure **C** was followed using *N*-{1-(4-fluorophenyl)vinyl}acetamide (**210i**) (89.5 mg, 0.50 mmol) and diphenylacetylene (**38a**) (178 mg, 1.00 mmol). After 22 h, purification by

column chromatography on silica gel (*n*-hexane/EtOAc: 30/1) yielded **211ia** (94 mg, 53%) as a white solid.

M.p. = 144−145 ℃.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.46−7.30 (m, 7H), 7.24−7.07 (m, 7H), 6.51 (s, 1H), 2.01 (s, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 172.7 (C$_q$), 162.3 (d, $^1J_{C-F}$ = 248 Hz, C$_q$), 134.7 (C$_q$), 133.9 (C$_q$), 132.8 (C$_q$), 130.8 (CH), 130.7 (C$_q$), 130.4 (d, $^3J_{C-F}$ = 8 Hz, CH), 129.5 (d, $^4J_{C-F}$ = 3 Hz, C$_q$), 128.5 (CH), 128.2 (CH), 128.2 (CH), 128.1 (CH), 126.3 (CH), 125.5 (C$_q$), 111.4 (d, $^2J_{C-F}$ = 21 Hz, CH), 113.7 (CH), 28.6 (CH$_3$).

^{19}F-NMR (283 MHz, CDCl$_3$): δ = −(114.1−114.2) (m).

IR (ATR): $\tilde{v}$ = 3024, 1722, 1585, 1493, 1365, 1279, 958, 840, 767, 694 cm^{-1}.

MS (EI) *m/z* (relative intensity): 355 (15) [M$^+$], 313 (100), 207 (7), 189 (7), 43 (13).

HR-MS (EI) *m/z* calcd for C$_{24}$H$_{18}$FNO$^+$ 355.1372, found 355.1384.

Synthesis of 1-{5-(4-bromophenyl)-2,3-diphenyl-1*H*-pyrrol-1-yl}ethanone (211ja)
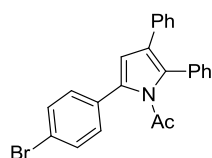
The general procedure **C** was followed using *N*-{1-(4-bromophenyl)vinyl}acetamide (**210j**) (119 mg, 0.50 mmol) and diphenylacetylene (**38a**) (178 mg, 1.00 mmol). After 22 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 30/1) yielded **211ja** (120 mg, 58%) as a white solid.

M.p. = 120−121 ℃.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.54 (d, *J* = 8.6 Hz, 2H), 7.40−7.34 (m, 5H), 7.31 (d, *J* = 8.6 Hz, 2H), 7.23−7.14 (m, 5H), 6.53 (s, 1H), 2.02 (s, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 172.5 (C$_q$), 134.5 (C$_q$), 133.7 (C$_q$), 132.6 (C$_q$), 132.3 (C$_q$), 131.5 (CH), 131.0 (C$_q$), 130.8 (CH), 130.0 (CH), 128.5 (CH), 128.2 (CH), 128.1 (CH), 128.1 (CH), 126.3 (CH), 125.7 (C$_q$), 121.6 (C$_q$), 114.0 (CH), 28.5 (CH$_3$).

IR (ATR): $\tilde{v}$ = 3060, 3026, 1722, 1585, 1482, 1365, 1278, 1069, 1011, 743 cm^{-1}.

MS (EI) *m/z* (relative intensity): 417 (17) [M$^+$] (^{81}Br), 415 (17) [M$^+$] (^{79}Br), 373 (100), 293 (20), 189 (27), 43 (52).

HR-MS (EI) *m/z* calcd for C$_{24}$H$_{18}$BrNO$^+$ 415.0572, found 415.0589.

Synthesis of 4-(1-acetyl-4,5-diphenyl-1*H*-pyrrol-2-yl)benzonitrile (211ka)
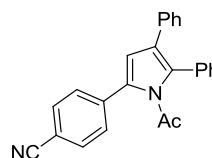
The general procedure **C** was followed using *N*-{1-(4-cyanophenyl)vinyl}acetamide (**210k**) (93.0 mg, 0.50 mmol) and diphenylacetylene (**38a**) (178 mg, 1.00 mmol). After 22 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 20/1) yielded **211ka** (134 mg, 74%) as a yellow solid.

M.p. = 145−146 ℃.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.66 (d, *J* = 8.5 Hz, 2H), 7.48 (d, *J* = 8.5 Hz, 2H), 7.41−7.31 (m, 5H), 7.21−7.10 (m, 5H), 6.59 (s, 1H), 2.00 (s, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 172.4 (C$_q$), 138.0 (C$_q$), 134.2 (C$_q$), 133.3 (C$_q$), 132.3 (C$_q$), 132.0 (CH), 132.0 (C$_q$), 130.9 (CH), 128.7 (CH), 128.7 (CH), 128.7 (CH), 128.2 (CH), 128.1 (CH), 126.6 (CH), 126.2 (C$_q$), 118.8 (C$_q$), 111.4 (CH), 110.7 (C$_q$), 28.4 (CH$_3$).

IR (ATR): $\tilde{v}$ = 3061, 2103, 1731, 1603, 1490, 1267, 1208, 824, 696, 552 cm^{-1}.

MS (EI) *m/z* (relative intensity): 362 (10) [M$^+$], 320 (100), 214 (6), 189 (8), 43 (15).

HR-MS (EI) m/z calcd for $C_{25}H_{18}N_2O^+$ 362.1419, found 362.1416.

Synthesis of 1-{5-(4-nitrophenyl)-2,3-diphenyl-1*H*-pyrrol-1-yl}ethanone (211la)
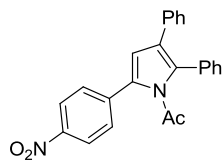
The general procedure **C** was followed using *N*-{1-(4-nitrophenyl)vinyl}acetamide (**211l**) (103 mg, 0.50 mmol) and diphenylacetylene (**38a**) (178 mg, 1.00 mmol). After 22 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 20/1) yielded **211la** (136 mg, 71%) as a yellow solid.

M.p. = 184−185 °C.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 8.27 (d, J = 8.6 Hz, 2H), 7.55 (d, J = 8.6 Hz, 2H), 7.44−7.32 (m, 5H), 7.24−7.11 (m, 5H), 6.66 (s, 1H), 2.03 (s, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 172.3 (C$_q$), 146.6 (C$_q$), 139.9 (C$_q$), 134.1 (C$_q$), 133.0 (C$_q$), 132.3 (C$_q$), 132.2 (C$_q$), 130.9 (CH), 128.8 (CH), 128.8 (CH), 128.7 (CH), 128.3 (CH), 128.1 (CH), 126.6 (CH), 126.4 (C$_q$), 123.6 (CH), 111.9 (CH), 28.4 (CH$_3$).

IR (ATR): $\tilde{v}$ = 3104, 1733, 1595, 1508, 1338, 1264, 1206, 784, 692, 491 cm^{-1}.

MS (EI) m/z (relative intensity): 382 (10) [M$^+$], 340 (100), 310 (17), 294 (30), 189 (20), 43 (50).

HR-MS (EI) m/z calcd for $C_{24}H_{18}N_2O_3^+$ 382.1317, found 382.1330.

Synthesis of 1-{2,3-diphenyl-5-(*p*-tolyl)-1*H*-pyrrol-1-yl}ethanone (211ma)
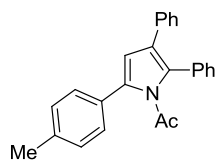
The general procedure **C** was followed using *N*-{1-(*p*-tolyl)vinyl}acetamide (**210m**) (87.5 mg, 0.50 mmol) and diphenylacetylene (**38a**) (178 mg, 1.00 mmol). After 22 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 10/1) yielded **211ma** (32 mg, 18%) as a white solid.

M.p. = 104−105 °C.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.44−7.30 (m, 7H), 7.26−7.13 (m, 7H), 6.53 (s, 1H), 2.38 (s, 3H), 2.05 (s, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 172.9 (C$_q$), 137.5 (C$_q$), 134.9 (C$_q$), 134.8 (C$_q$), 132.9 (C$_q$), 130.9 (CH), 130.6 (C$_q$), 130.5 (C$_q$), 129.2 (CH), 128.3 (CH), 128.3 (CH), 128.1 (CH), 128.1 (CH), 128.0 (CH), 126.1 (CH), 125.4 (C$_q$), 113.2 (CH), 28.6 (CH$_3$), 21.2 (CH$_3$).

IR (ATR): $\tilde{v}$ = 3050, 1723, 1601, 1495, 1276, 1206, 957, 764, 694, 546 cm^{-1}.

MS (EI) m/z (relative intensity): 351 (13) [M$^+$], 309 (100), 189 (7), 43 (10).

HR-MS (EI) m/z calcd for $C_{25}H_{21}NO^+$ 351.1623, found 351.1627.

Synthesis of 1-{5-(4-methoxyphenyl)-2,3-diphenyl-1*H*-pyrrol-1-yl}ethanone (211na)
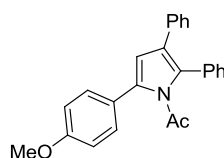
The general procedure **C** was followed using *N*-{1-(4-methoxyphenyl)vinyl}acetamide (**210n**) (95.5 mg, 0.50 mmol) and diphenylacetylene (**38a**) (178 mg, 1.00 mmol). After 22 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 20/1) yielded **211na** (52 mg, 28%) as a white solid.

M.p. = 105−106 °C.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.38−7.32 (m, 7H), 7.23−7.11 (m, 5H), 6.97 (d, J = 8.4 Hz, 2H), 6.48 (s, 1H), 3.86 (s, 3H), 2.03 (s, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 172.9 (C$_q$), 159.2 (C$_q$), 134.9 (C$_q$), 134.6 (C$_q$), 132.9 (C$_q$), 130.9 (CH), 130.4 (C$_q$), 129.8 (CH), 128.3 (CH), 128.1 (CH), 128.1 (CH), 127.9 (CH), 126.1 (CH), 125.8 (C$_q$), 125.4 (C$_q$), 113.9 (CH), 113.0 (CH), 55.3 (CH$_3$), 28.6 (CH$_3$).

IR (ATR): $\tilde{\nu}$ = 3058, 3028, 1730, 1599, 1281, 1246, 1174, 1023, 764, 694 cm^{-1}.

MS (EI) m/z (relative intensity): 367 (30) [M$^+$], 325 (100), 310 (27), 276 (13), 178 (14), 43 (52).

HR-MS (EI) m/z calcd for C$_{25}$H$_{21}$NO$_2$$^+$ 367.1572, found 367.1562.

Synthesis of 1-{5-[3-(trifluoromethyl)phenyl]-2,3-diphenyl-1*H*-pyrrol-1-yl}ethanone (211oa)

The general procedure **C** was followed using *N*-{1-[3-(trifluoromethyl)phenyl]vinyl}-acetamide (**210o**) (111 mg, 0.50 mmol) and diphenylacetylene (**38a**) (178 mg, 1.00 mmol). After 22 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 30/1) yielded **211oa** (146 mg, 72%) as a white solid.

M.p. = 111−112 °C.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.70 (s, 1H), 7.59 (d, J = 7.3 Hz, 1H), 7.59 (d, J = 7.8 Hz, 1H), 7.50 (dd, J = 7.8, 7.3 Hz, 1H), 7.38−7.31 (m, 5H), 7.22−7.12 (m, 5H), 6.56 (s, 1H), 1.99 (s, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 172.4 (C$_q$), 134.4 (C$_q$), 134.3 (C$_q$), 133.6 (C$_q$), 132.6 (C$_q$), 131.8 (q, $^4J_{C–F}$ = 1 Hz, CH), 131.2 (C$_q$), 130.9 (CH), 130.7 (q, $^2J_{C–F}$ = 32 Hz, C$_q$), 128.7 (CH), 128.6 (CH), 128.4 (CH), 128.2 (CH), 128.2 (CH), 127.7 (q, $^1J_{C–F}$ = 272 Hz, C$_q$), 126.4 (CH), 125.9 (C$_q$), 125.3 (q, $^3J_{C–F}$ = 4 Hz, CH), 124.1 (q, $^3J_{C–F}$ = 4 Hz, CH), 114.7 (CH), 28.5 (CH$_3$).

^{19}F-NMR (283 MHz, CDCl$_3$): δ = −62.7 (s).

IR (ATR): $\tilde{\nu}$ = 3072, 1733, 1585, 1446, 1365, 1119, 1111, 1072, 763, 693 cm^{-1}.

MS (EI) m/z (relative intensity): 405 (10) [M$^+$], 363 (100), 189 (9), 43 (12).

HR-MS (EI) m/z calcd for C$_{25}$H$_{18}$F$_3$NO$^+$ 405.1340, found 405.1327.

Synthesis of 1-{2,3-diphenyl-5-(*o*-tolyl)-1*H*-pyrrol-1-yl}ethanone (211pa)

The general procedure **C** was followed using *N*-{1-(*o*-tolyl)vinyl}acetamide (**210p**) (87.5 mg, 0.50 mmol) and diphenylacetylene (**38**) (178 mg, 1.00 mmol). After 22 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 30/1) yielded **211pa** (120 mg, 68%) as a yellow solid.

M.p. = 145−146 °C.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.46−7.15 (m, 14H), 6.45 (s, 1H), 2.37 (s, 3H), 1.94 (s, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 171.6 (C$_q$), 137.6 (C$_q$), 137.6 (C$_q$), 134.8 (C$_q$), 133.8 (C$_q$), 133.7 (C$_q$), 133.3 (C$_q$), 130.7 (CH), 130.3 (CH), 129.9 (CH), 128.4 (CH), 128.3 (CH), 128.1 (CH), 128.1 (CH), 127.8 (CH), 126.1 (CH), 125.6 (CH), 125.5 (C$_q$), 113.7 (CH), 27.6 (CH$_3$), 20.2 (CH$_3$).

IR (ATR): $\tilde{\nu}$ = 3053, 1733, 1615, 1445, 1318, 1267, 1111, 1071, 762, 692 cm^{-1}.

MS (EI) m/z (relative intensity): 351 (25) [M$^+$], 309 (100), 230 (11), 202 (12), 191 (10), 43 (65).

HR-MS (EI) m/z calcd for C$_{25}$H$_{21}$NO$^+$ 351.1623, found 351.1634.

Synthesis of 1-{2,3-diphenyl-5-(pyridin-3-yl)-1*H*-pyrrol-1-yl}ethanone (211qa)

The general procedure **C** was followed using *N*-{1-(pyridin-3-yl)vinyl}acetamide (**211q**) (81.0 mg, 0.50 mmol) and diphenylacetylene (**38a**) (178 mg, 1.00 mmol). After 22 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 3/1) yielded **211qa** (54 mg, 32%) as a yellow solid.

M.p. = 100−101 °C.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 8.71 (s, 1H), 7.57 (d. J = 5.2 Hz, 1H), 7.75 (dt, J = 7.8, 1.6 Hz, 1H), 7.48−7.30 (m, 6H), 7.26−7.13 (m, 5H), 6.56 (s, 1H), 1.99 (s, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 172.2 (C$_q$), 149.2 (CH), 148.4 (CH), 136.1 (CH), 134.3 (C$_q$), 132.6 (C$_q$), 131.7 (C$_q$), 131.2 (C$_q$), 130.7 (CH), 129.5 (C$_q$), 128.7 (CH), 128.4 (CH), 128.2 (CH), 128.1 (CH), 126.4 (CH), 126.0 (C$_q$), 122.8 (CH), 114.8 (CH), 28.3 (CH$_3$).

IR (ATR): $\tilde{\nu}$ = 3060, 3030, 1720, 1672, 1599, 1571, 1267, 1208, 764, 693 cm^{-1}.

MS (EI) m/z (relative intensity): 338 (20) [M$^+$], 296 (100), 191 (11), 43 (12).

HR-MS (EI) m/z calcd for C$_{23}$H$_{18}$N$_2$O$^+$ 338.1419, found 338.1410.

Synthesis of 1-{2,3-diphenyl-5-(thiophen-2-yl)-1H-pyrrol-1-yl}ethanone (211ra) and 2,3-diphenyl-5-(thiophen-2-yl)-1H-pyrrole (212ra)

The general procedure **C** was followed using N-{1-(thiophen-2-yl)vinyl}acetamide (**210r**) (83.5 mg, 0.50 mmol) and diphenylacetylene (**38a**) (178 mg, 1.00 mmol). After 22 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 30/1) yielded **211ra** (57 mg, 33%) as a yellow solid and **212ra** (46 mg, 30%) as a yellow solid.

1-{2,3-diphenyl-5-(thiophen-2-yl)-1H-pyrrol-1-yl}ethanone (211ra):

M.p. = 171−172 °C.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.38−7.29 (m, 6H), 7.21−7.12 (m, 6H), 7.06 (dd, J = 5.1, 5.1 Hz, 1H), 6.59 (s, 1H), 2.02 (s, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 172.8 (C$_q$), 134.6 (C$_q$), 134.0 (C$_q$), 132.6 (C$_q$), 131.0 (C$_q$), 130.6 (CH), 128.5 (CH), 128.2 (CH), 128.2 (CH), 128.1 (CH), 127.6 (CH), 127.2 (CH), 127.1 (C$_q$), 126.3 (CH), 126.1 (CH), 125.6 (C$_q$), 114.8 (CH), 28.3 (CH$_3$).

IR (ATR): $\tilde{\nu}$ = 3097, 1722, 1600, 1496, 1363, 1277, 1197, 1028, 767, 695 cm^{-1}.

MS (EI) m/z (relative intensity): 343 (13) [M$^+$], 301 (100), 267 (10), 197 (10), 43 (17).

HR-MS (EI) m/z calcd for C$_{22}$H$_{17}$NOS$^+$ 343.1031, found 343.1043.

2,3-Diphenyl-5-(thiophen-2-yl)-1H-pyrrole (212ra):

M.p. = 92−94 °C.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 8.27 (s$_{br}$, 1H), 7.44−7.16 (m, 11H), 7.11 (d, J = 3.5 Hz, 1H), 7.05 (dd, J = 5.1, 5.1 Hz, 1H), 6.61 (d, J = 2.7 Hz, 1H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 136.0 (C$_q$), 135.6 (C$_q$), 132.8 (C$_q$), 128.9 (C$_q$), 128.7 (CH), 128.4 (CH), 128.3 (CH), 127.7 (CH), 127.4 (CH), 127.0 (CH), 126.9 (C$_q$), 126.0 (CH), 123.6 (C$_q$), 123.0 (CH), 121.1 (CH), 109.2 (CH).

IR (ATR): $\tilde{\nu}$ = 3411, 3055, 3024, 1600, 1492, 1439, 1199, 1070, 759, 689 cm^{-1}.

MS (EI) m/z (relative intensity): 301 (100) [M$^+$], 267 (7), 197 (10).

HR-MS (EI) m/z calcd for C$_{20}$H$_{15}$NS$^+$ 301.0925, found 301.0939.

Synthesis of (E)-2,3-diphenyl-5-styryl-1H-pyrrole (212sa)

The general procedure **C** was followed using (E)-N-(4-phenylbuta-1,3-dien-2-yl)acetamide (**210s**) (87.5 mg, 0.50 mmol) and diphenylacetylene (**38a**) (178 mg, 1.00 mmol). After 22 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 10/1) yielded **211sa** (78 mg, 48%) as a yellow solid.

M.p. = 87−88 °C.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 8.35 (s$_{br}$, 1H), 7.54−7.44 (m, 2H), 7.38−7.23 (m, 13 H), 7.01 (d, J = 16.6 Hz, 1H), 6.77 (d, J = 16.6 Hz, 1H), 6.55 (d, J = 2.7 Hz, 1H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 137.3 (C$_q$), 136.2 (C$_q$), 132.8 (C$_q$), 130.9 (C$_q$), 129.5 (C$_q$), 128.7 (CH), 128.7 (CH), 128.4 (CH), 128.3 (CH), 127.4 (CH), 127.1 (CH), 127.0 (CH), 125.9 (CH),

125.9 (CH), 123.9 (CH), 123.8 (C$_q$), 118.3 (CH), 111.7 (CH).

IR (ATR): $\tilde{\nu}$ = 3058, 3026, 2951, 2925, 1684, 1598, 1504, 1447, 1261, 760, 693 cm^{-1}.

MS (EI) *m/z* (relative intensity): 321 (100) [M$^+$], 243 (9), 213 (8).

HR-MS (EI) *m/z* calcd for C$_{24}$H$_{19}$N$^+$ 321.1517, found 321.1519.

Synthesis of 1-{5-(4-nitrophenyl)-2,3-di-*p*-tolyl-1*H*-pyrrol-1-yl}ethanone (211li)

The general procedure **C** was followed using *N*-{1-(4-nitrophenyl)vinyl}acetamide (**210l**) (103 mg, 0.50 mmol) and 1,2-di-*p*-tolylacetylene (**38i**) (206 mg, 1.00 mmol). After 22 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 30/1) yielded **211li** (130 mg, 63%) as a yellow solid.

M.p. = 143−144 ℃.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 8.23 (d, *J* = 8.6 Hz, 2H), 7.52 (d, *J* = 8.6 Hz, 2H), 7.24 (d, *J* = 8.2 Hz, 2H), 7.19 (d, *J* = 8.0 Hz, 2H), 7.06 (d, *J* = 8.2 Hz, 2H), 7.01 (d, *J* = 8.0 Hz, 2H), 6.61 (s, 1H), 2.39 (CH$_3$), 2.28 (CH$_3$), 2.01 (CH$_3$).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 172.5 (C$_q$), 146.4 (C$_q$), 140.1 (C$_q$), 138.7 (C$_q$), 136.2 (C$_q$), 132.8 (C$_q$), 132.2 (C$_q$), 131.2 (C$_q$), 130.7 (CH), 129.5 (CH), 129.3 (C$_q$), 129.0 (CH), 128.6 (CH), 127.9 (CH), 126.1 (C$_q$), 123.6 (CH), 116.0 (CH), 28.4 (CH$_3$), 21.4 (CH$_3$), 21.1 (CH$_3$).

IR (ATR): $\tilde{\nu}$ = 3025, 2905, 1723, 1593, 1502, 1334, 1262, 1108, 817, 752 cm^{-1}.

MS (EI) *m/z* (relative intensity): 410 (20) [M$^+$], 368 (100), 322 (23), 43 (17).

HR-MS (EI) *m/z* calcd for C$_{26}$H$_{22}$N$_2$O$_3$$^+$ 410.1630, found 410.1633.
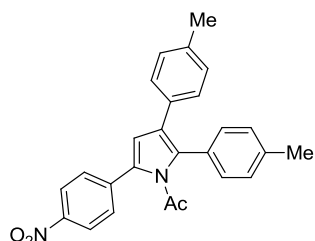
Synthesis of 1-{2,3-bis(4-methoxyphenyl)-5-(4-nitrophenyl)-1*H*-pyrrol-1-yl}ethanone (211lj)
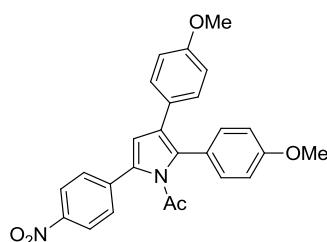
The general procedure **C** was followed using *N*-{1-(4-nitrophenyl)vinyl}acetamide (**210l**) (103 mg, 0.50 mmol) and 1,2-bis(4-methoxyphenyl)ethyne (**38j**) (238 mg, 1.00 mmol). After 22 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 10/1) yielded **210lj** (111 mg, 52%) as a yellow solid.

M.p. = 117−118 ℃.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 8.22 (d, *J* = 8.8 Hz, 2H), 7.51 (d, *J* = 8.8 Hz, 2H), 7.26 (d, *J* = 8.8 Hz, 2H), 7.08 (d, *J* = 8.7 Hz, 2H), 6.92 (d, *J* = 8.7 Hz, 2H), 6.75 (d, *J* = 8.8 Hz, 2H), 6.59 (s, 1H), 3.84 (s, 3H), 3.75 (s, 3H), 2.01 (s, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 172.4 (C$_q$), 159.8 (C$_q$), 158.3 (C$_q$), 146.4 (C$_q$), 140.1 (C$_q$), 132.7 (C$_q$), 132.2 (CH), 131.8 (C$_q$), 129.1 (CH), 128.5 (CH), 126.6 (C$_q$), 125.9 (C$_q$), 124.4 (C$_q$), 123.6 (CH), 111.9 (CH), 114.2 (CH), 113.7 (CH), 55.2 (CH$_3$), 55.1 (CH$_3$), 28.4 (CH$_3$).

IR (ATR): $\tilde{\nu}$ = 2952, 2836, 1726, 1595, 1515, 1493, 1339, 1245, 1029, 752 cm^{-1}.

MS (EI) *m/z* (relative intensity): 438 (26) [M$^+$], 400 (100), 385 (23), 354 (17), 339 (15), 43 (26).

HR-MS (EI) *m/z* calcd for C$_{26}$H$_{22}$N$_2$O$_5$$^+$ 438.1529, found 438.1511.

Synthesis of 1-{2,3-bis[4-(trifluoromethyl)phenyl]-5-(4-nitrophenyl)-1*H*-pyrrol-1-yl}ethanone (211lb)

The general procedure **C** was followed using *N*-{1-(4-nitrophenyl)vinyl}acetamide (**210l**) (103 mg, 0.50 mmol) and 1,2-bis{4-(trifluoromethyl)phenyl}acetylene (**38b**) (314 mg, 1.00 mmol). After 22 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 20/1) yielded **211lb** (174 mg, 67%) as a yellow solid.

M.p. = 161−162 °C.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 8.30 (d, *J* = 8.9 Hz, 2H), 7.68 (d, *J* = 7.2 Hz, 2H), 7.60 (d, *J* = 8.4 Hz, 2H), 7.54−7.43 (m, 4H), 7.22 (d, *J* = 8.4 Hz, 2H), 6.68 (s, 1H), 2.07 (s, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 171.7 (C$_q$), 147.0 (C$_q$), 139.0 (C$_q$), 137.3 (q, $^4J_{C-F}$ = 1 Hz, C$_q$), 135.2 (q, $^4J_{C-F}$ = 1 Hz, C$_q$), 133.5 (C$_q$), 131.3 (C$_q$), 131.2 (CH), 130.8 ($^2J_{C-F}$ = 32 Hz, C$_q$), 128.9 (q, $^2J_{C-F}$ = 32 Hz, C$_q$), 128.7 (CH), 128.3 (CH), 125.8 (C$_q$), 125.7 (q, $^3J_{C-F}$ = 4 Hz, CH), 125.4 (q, $^3J_{C-F}$ = 4 Hz, CH), 124.1 (d, $^1J_{C-F}$ = 272 Hz, C$_q$), 123.9 (CH), 123.7 (q, $^1J_{C-F}$ = 272 Hz, C$_q$), 111.5 (CH), 28.8 (CH$_3$).

^{19}F-NMR (283 MHz, CDCl$_3$): δ = −62.6 (s), −62.7 (s).

IR (ATR): $\tilde{v}$ = 1727, 1613, 1593, 1514, 1338, 1321, 1265, 1117, 854, 832 cm^{-1}.

MS (EI) *m/z* (relative intensity): 518 (4) [M$^+$], 476 (100), 446 (28), 430 (30), 43 (52).

HR-MS (EI) *m/z* calcd for C$_{26}$H$_{16}$F$_6$N$_2$O$_3$$^+$ 518.1065, found 518.1081.
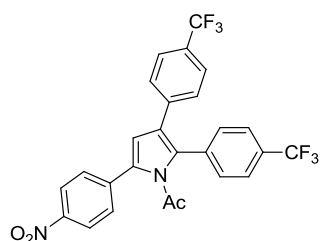
Synthesis of 1-{2,3-bis(4-fluorophenyl)-5-(4-nitrophenyl)-1*H*-pyrrol-1-yl}ethanone (211lk)
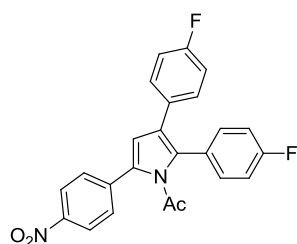
The general procedure **C** was followed using *N*-{1-(4-nitrophenyl)vinyl}acetamide (**210l**) (103 mg, 0.50 mmol) and 1,2-bis(4-fluorophenyl)acetylene (**38k**) (212 mg, 1.00 mmol). After 22 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 20/1) yielded **211lk** (140 mg, 67%) as a yellow solid.

M.p. = 172−173 °C.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 8.25 (d, *J* = 9.0 Hz, 2H), 7.53 (d, *J* = 9.0 Hz, 2H), 7.31 (dd, *J* = 8.8, 8.4 Hz, 2H), 7.14−7.03 (m, 4H), 6.90 (dd, *J* = 8.8, 8.7 Hz, 2H), 6.59 (s, 1H), 2.04 (s, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 172.0 (C$_q$), 162.7 (d, $^1J_{C-F}$ = 251 Hz, C$_q$), 161.9 (d, $^1J_{C-F}$ = 245 Hz, C$_q$), 146.7 (C$_q$), 139.6 (C$_q$), 132.9 (C$_q$), 132.9 (d, $^3J_{C-F}$ = 8 Hz, CH), 131.2 (C$_q$), 130.0 (d, $^4J_{C-F}$ = 3 Hz, C$_q$), 129.7 (d, $^3J_{C-F}$ = 8 Hz, CH), 128.5 (CH), 127.9 (d, $^4J_{C-F}$ = 3 Hz, C$_q$), 125.8 (C$_q$), 123.8 (CH), 116.0 (d, $^2J_{C-F}$ = 22 Hz, CH), 111.7 (CH), 111.3 (d, $^2J_{C-F}$ = 22 Hz, CH), 28.5 (CH$_3$).

^{19}F-NMR (283 MHz, CDCl$_3$): δ = −(114.4−114.7) (m), −(111.2−111.5) (m).

IR (ATR): $\tilde{v}$ = 1721, 1595, 1492, 1333, 1217, 1118, 1104, 847, 816, 523 cm^{-1}.

MS (EI) *m/z* (relative intensity): 418 (10) [M$^+$], 376 (100), 346 (20), 330 (30), 207 (12), 43 (20).

HR-MS (EI) *m/z* calcd for C$_{24}$H$_{16}$F$_2$N$_2$O$_3$$^+$ 418.1129, found 418.1125.

Synthesis of 1-{2,3-bis(4-chlorophenyl)-5-(4-nitrophenyl)-1*H*-pyrrol-1-yl}ethanone (211lc)

The general procedure **C** was followed using *N*-{1-(4-nitrophenyl)vinyl}acetamide (**210l**) (103 mg, 0.50 mmol) and 1,2-bis(4-chlorophenyl)acetylene (**38c**) (247 mg, 1.00 mmol). After 22 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 30/1) yielded **211lc** (154 mg, 68%) as a yellow solid.

M.p. = 117−118 ℃.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 8.25 (d, *J* = 8.6 Hz, 2H), 7.54 (d, *J* = 8.6 Hz, 2H), 7.37 (d, *J* = 8.6 Hz, 2H), 7.26 (d, *J* = 8.6 Hz, 2H), 7.19 (d, *J* = 8.6 Hz, 2H), 7.04 (d, *J* = 8.6 Hz, 2H), 6.59 (s, 1H), 2.04 (s, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 171.8 (C$_q$), 146.7 (C$_q$), 139.3 (C$_q$), 135.0 (C$_q$), 133.1 (C$_q$), 132.6 (C$_q$), 132.3 (C$_q$), 132.1 (CH), 131.2 (C$_q$), 130.2 (C$_q$), 129.3 (CH), 129.0 (CH), 128.6 (CH), 128.5 (CH), 125.6 (C$_q$), 123.7 (CH), 111.5 (CH), 28.7 (CH$_3$).

IR (ATR): $\tilde{\nu}$ = 3104, 1729, 1514, 1486, 1341, 1257, 1091, 1012, 832 cm^{-1}.

MS (EI) *m/z* (relative intensity): 450 (9) [M$^+$], 408 (100), 378 (20), 362 (28), 327 (13), 291 (15), 189 (12), 43 (43).

HR-MS (EI) *m/z* calcd for C$_{24}$H$_{16}$Cl$_2$N$_2$O$_3^+$ 450.0538, found 450.0539.

Synthesis of diethyl 4,4'-{1-acetyl-5-(4-nitrophenyl)-1*H*-pyrrole-2,3-diyl}dibenzoate (211ll)

The general procedure **C** was followed using *N*-{1-(4-nitrophenyl)vinyl}acetamide (**210l**) (103 mg, 0.50 mmol) and diethyl 4,4'-(ethyne-1,2-diyl)dibenzoate (**38l**) (322 mg, 1.00 mmol). After 22 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 5/1) yielded **211ll** (168 mg, 64%) as a yellow solid.

M.p. = 188−189 ℃.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 8.26 (d. *J* = 9.0 Hz, 2H), 8.06 (d, *J* = 8.2 Hz, 2H), 7.87 (d, *J* = 8.2 Hz. 2H), 7.56 (d, *J* = 9.0 Hz, 2H), 7.40 (d, *J* = 8.7 Hz, 2H), 7.16 (d, *J* = 8.7 Hz, 2H), 6.66 (s, 1H), 4.39 (q, *J* = 7.2 Hz, 2H), 4.32 (q, *J* = 7.2 Hz, 2H), 2.04 (s, 3H), 1.40 (t, *J* = 7.2 Hz, 3H), 1.37 (t, *J* = 7.2 Hz, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 171.8 (C$_q$), 166.1 (C$_q$), 165.8 (C$_q$), 146.9 (C$_q$), 139.2 (C$_q$), 138.4 (C$_q$), 136.2 (C$_q$), 133.5 (C$_q$), 131.8 (C$_q$), 130.7 (CH), 129.8 (CH), 129.6 (CH), 128.8 (CH), 128.7 (C$_q$), 128.7 (C$_q$), 127.9 (CH), 126.1 (C$_q$), 123.7 (CH), 111.5 (CH), 61.3 (CH$_2$), 61.0 (CH$_2$), 28.7 (CH$_3$), 14.4 (CH$_3$), 14.4 (CH$_3$).

IR (ATR): $\tilde{\nu}$ = 2995, 1723, 1707, 1594, 1514, 1341, 1269, 1104, 1024, 752 cm^{-1}.

MS (EI) *m/z* (relative intensity): 526 (7) [M$^+$], 484 (100), 454 (38), 438 (17), 291 (11), 43 (77).

HR-MS (EI) *m/z* calcd for C$_{30}$H$_{26}$N$_2$O$_7^+$ 526.1740, found 526.1735.

Synthesis of 1-{2,3-bis(3-chlorophenyl)-5-(4-nitrophenyl)-1*H*-pyrrol-1-yl}ethanone (211lm)

The general procedure **C** was followed using *N*-{1-(4-nitrophenyl)vinyl}acetamide (**210l**) (103 mg, 0.50 mmol) and 1,2-bis(3-chlorophenyl)acetylene (**38m**) (247 mg, 1.00 mmol). After 22 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 20/1) yielded **211lm** (152 mg, 67%) as a yellow solid.

M.p. = 120−121 ℃.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 8.25 (d, J = 9.0 Hz, 2H), 7.54 (d, J = 9.0 Hz, 2H), 7.38−7.30 (m, 3H), 7.24 (dt, J = 7.2, 1.4 Hz, 1H), 7.18 (s, 1H), 7.16−7.08 (m, 2H), 6.94 (dt, J = 7.2, 1.7 Hz, 1H), 6.61 (s, 1H), 2.06 (s, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 171.8 (C$_q$), 146.9 (C$_q$), 139.4 (C$_q$), 135.6 (C$_q$), 134.7 (C$_q$), 134.3 (C$_q$), 133.5 (C$_q$), 133.3 (C$_q$), 131.0 (C$_q$), 130.8 (CH), 130.0 (CH), 129.6 (CH), 129.2 (CH), 129.1 (CH), 128.7 (CH), 128.2 (CH), 126.9 (CH), 126.2 (CH), 125.6 (C$_q$), 123.8 (CH), 111.5 (CH), 28.6 (CH$_3$).

IR (ATR): $\tilde{v}$ = 3062, 1749, 1593, 1565, 1508, 1340, 1200, 1096, 853, 789 cm^{-1}.

MS (EI) m/z (relative intensity): 450 (10) [M$^+$], 408 (100), 362 (22), 327 (15), 291 (15), 43 (39).

HR-MS (EI) m/z calcd for C$_{24}$H$_{16}$Cl$_2$N$_2$O$_3$$^+$ 450.0538, found 450.0534.

Synthesis of methyl 1-acetyl-4,5-di(naphthalen-1-yl)-1*H*-pyrrole-2-carboxylate (211an)
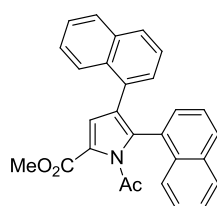
The general procedure **C** was followed using methyl 2-acetamidoacrylate (**210a**) (71.5 mg, 0.50 mmol), and 1,2-di(naphthalen-1-yl)acetylene (**38n**) (278 mg, 1.00 mmol). After 22 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 10/1) yielded **211an** (120 mg, 57%) as a white solid.

M.p. = 176−181 ℃.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 8.11 (d, J = 7.2 Hz, 1H), 7.84−7.71 (m, 3H), 7.70−7.55 (m, 2H), 7.52−7.27 (m 7H), 7.16−7.03 (m, 2H), 3.93 (s, 3H), 2.16 (s, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 172.7 (C$_q$), 161.4 (C$_q$), 134.6 (C$_q$), 133.5 (C$_q$), 133.2 (C$_q$), 133.1 (C$_q$), 132.3 (C$_q$), 131.5 (C$_q$), 129.8 (CH), 129.5 (CH), 128.3 (CH), 128.2 (C$_q$), 128.2 (CH), 127.6 (CH), 127.5 (CH), 126.7 (CH), 126.1 (CH), 125.9 (CH), 125.7 (CH), 125.6 (CH), 125.3 (CH), 125.1 (C$_q$), 125.0 (CH), 124.9 (CH), 123.8 (C$_q$), 121.4 (CH), 52.0 (CH$_3$), 27.7 (CH$_3$).

IR (ATR): $\tilde{v}$ = 3056, 1744, 1708, 1486, 1382, 1249, 1230, 760, 775 cm^{-1}.

MS (EI) m/z (relative intensity): 419 (16) [M$^+$], 377 (100), 317 (70), 289 (25), 163 (7).

HR-MS (EI) m/z calcd for C$_{29}$H$_{21}$NO$_3$$^+$ 419.1521, found 419.1519.

Synthesis of methyl 1-acetyl-4,5-dipropyl-1*H*-pyrrole-2-carboxylate (211ae)

The general procedure **C** was followed using methyl 2-acetamidoacrylate (**210a**) (71.5 mg, 0.50 mmol), and 4-octyne (**38e**) (110 mg, 1.00 mmol). After 22 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 20/1) yielded **211ae** (72 mg, 57%) as a colorless oil.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 6.82 (s, 1H), 3.76 (s, 3H), 2.57 (t, J = 7.6 Hz, 2H), 2.50 (s, 3H), 2.32 (t, J = 7.4 Hz, 2H), 1.63−1.43 (m, 4H), 0.93 (t, J = 7.2 Hz, 3H), 0.91 (t, J = 7.2 Hz, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 174.0 (C$_q$), 161.1 (C$_q$), 138.4 (C$_q$), 123.3 (C$_q$), 121.5 (C$_q$), 121.4 (CH), 51.5 (CH$_3$), 28.5 (CH$_3$), 27.4 (CH$_2$), 27.0 (CH$_2$), 23.6 (CH$_2$), 23.6 (CH$_2$), 13.9 (CH$_3$), 13.9 (CH$_3$).

IR (ATR): $\tilde{v}$ = 2960, 1738, 1702, 1478, 1437, 1374, 1227, 1186, 1054, 762 cm^{-1}.

MS (EI) m/z (relative intensity): 251 (5) [M$^+$], 207 (36), 176 (100), 148 (25), 43 (34).

HR-MS (EI) m/z calcd for C$_{14}$H$_{21}$NO$_3$$^+$ 251.1521, found 251.1525.
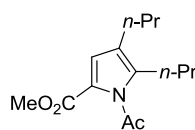
The spectral data were in accordance with those reported in the literature.[123a]

Synthesis of methyl 1-acetyl-4,5-diethyl-1H-pyrrole-2-carboxylate (211af)
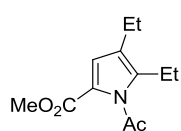
The general procedure **C** was followed using methyl 2-acetamidoacrylate (**210a**) (71.5 mg, 0.50 mmol), and 3-hexyne (**38f**) (82 mg, 1.00 mmol). After 22 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 20/1) yielded **211af** (76 mg, 71%) as a colorless oil.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 6.84 (s, 1H), 3.79 (s, 3H), 2.62 (q, J = 7.2 Hz, 2H), 2.50 (s, 3H), 2.37 (q, J = 7.2 Hz, 2H), 1.14 (t, J = 7.2 Hz, 3H), 1.11 (t, J = 7.2 Hz, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 173.9 (C$_q$), 161.0 (C$_q$), 139.4 (C$_q$), 124.3 (C$_q$), 121.4 (C$_q$), 120.9 (CH), 51.5 (CH$_3$), 28.4 (CH$_3$), 18.4 (CH$_2$), 18.4 (CH$_2$), 14.9 (CH$_3$), 14.7 (CH$_3$).

IR (ATR): $\tilde{v}$ = 2966, 1738, 1698, 1481, 1437, 1378, 1239, 1186, 940, 762 cm^{-1}.

MS (EI) *m/z* (relative intensity): 219 (5) [M$^+$], 181 (52), 166 (100), 134 (43).

HR-MS (EI) *m/z* calcd for C$_{12}$H$_{17}$NO$_3^+$ 219.1206, found 219.1208.

Synthesis of 1-{3-methyl-5-(4-nitrophenyl)-2-phenyl-1H-pyrrol-1-yl}ethanone (211lh)
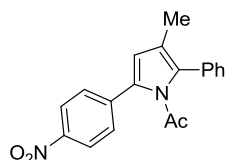
The general procedure **C** was followed using *N*-{1-(4-nitrophenyl)vinyl}acetamide (**210l**) (103 mg, 0.50 mmol) and propyn-1-benzene (**38h**) (116 mg, 1.00 mmol). After 22 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 30/1) yielded **211lh** (72 mg, 45%) as a yellow solid.
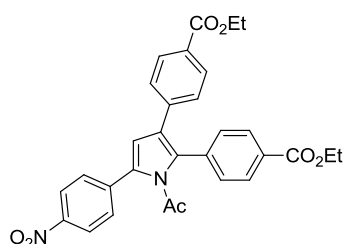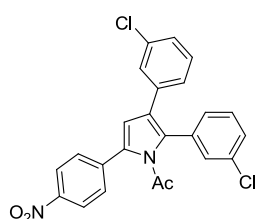
M.p. = 149−150 °C.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 8.19 (d, J = 8.9 Hz, 2H), 7.50−7.38 (m, 5H), 7.36−7.28 (m, 2H), 6.32 (s, 1H), 1.99 (s, 3H), 1.99 (s, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 171.8 (C$_q$), 146.3 (C$_q$), 140.4 (C$_q$), 133.1 (C$_q$), 132.7 (C$_q$), 132.7 (C$_q$), 130.0 (CH), 128.7 (CH), 128.6 (CH), 128.2 (CH), 123.4 (CH), 121.9 (C$_q$), 117.7 (CH), 28.1 (CH$_3$), 11.3 (CH$_3$).

IR (ATR): $\tilde{v}$ = 2924, 1720, 1592, 1506, 1344, 1264, 1107, 853, 752, 701 cm^{-1}.

MS (EI) *m/z* (relative intensity): 320 (15) [M$^+$], 278 (100), 248 (12), 232 (30), 43 (27).

HR-MS (EI) *m/z* calcd for C$_{19}$H$_{16}$N$_2$O$_3^+$ 320.1161, found 320.1114.

Synthesis of methyl 1-acetyl-4-methyl-5-phenyl-1H-pyrrole-2-carboxylate (211ah)
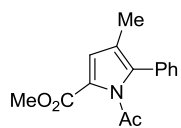
The general procedure **C** was followed using methyl 2-acetamidoacrylate (**210a**) (71.5 mg, 0.50 mmol), and prop-1-yn-1-ylbenzene (**38h**) (116 mg, 1.00 mmol). After 22 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 30/1) yielded **211ah** (85 mg, 66%) as a white solid.

M.p. = 109−110 °C.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.46−7.37 (m, 3H), 7.32−7.26 (m, 2H), 6.85 (s, 1H), 3.84 (s, 3H), 2.27 (s, 3H), 1.99 (s, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 173.5 (C$_q$), 161.2 (C$_q$), 135.6 (C$_q$), 131.0 (C$_q$), 129.8 (CH), 128.4 (CH), 128.4 (CH), 122.6 (C$_q$), 120.5 (CH), 119.6 (C$_q$), 51.7 (CH$_3$), 28.5 (CH$_3$), 11.1 (CH$_3$).

IR (ATR): $\tilde{v}$ = 2952, 1747, 1696, 1556, 1464, 1443, 1375, 1230, 772, 584 cm^{-1}. MS (EI) *m/z* (relative intensity): 257 (7) [M$^+$], 213 (100), 183 (63), 155 (39), 43 (25).

HR-MS (EI) *m/z* calcd for C$_{15}$H$_{15}$NO$_3^+$ 257.1052, found 257.1056.

The spectral data were in accordance with those reported in the literature.[123a]

Synthesis of methyl 1-acetyl-4-ethyl-5-phenyl-1*H*-pyrrole-2-carboxylate (211ao)
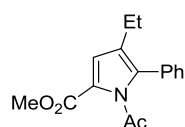
The general procedure **C** was followed using methyl 2-acetamidoacrylate (**210a**) (71.5 mg, 0.50 mmol), and but-1-yn-1-ylbenzene (**38o**) (130 mg, 1.00 mmol). After 22 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 30/1) yielded **211ao** (74 mg, 54%) as a yellow oil.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.45−7.37 (m 3H), 7.32−7.26 (m, 2H), 6.92 (s, 1H), 3.85 (s, 3H), 2.34 (q, *J* = 7.2 Hz, 2H), 2.26 (s, 3H), 1.11 (t, *J* = 7.2 Hz, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 173.3 (C$_q$), 161.0 (C$_q$), 135.0 (C$_q$), 131.0 (C$_q$), 129.9 (CH), 128.4 (CH), 128.3 (CH), 126.3 (C$_q$), 122.7 (C$_q$), 118.8 (CH), 51.8 (CH$_3$), 28.5 (CH$_3$), 18.8 (CH$_2$), 15.2 (CH$_3$).

IR (ATR): $\tilde{v}$ = 2961, 2927, 1726, 1599, 1448, 1261, 1070, 759, 699 cm^{-1}.

MS (EI) *m/z* (relative intensity): 271 (4) [M$^+$], 229 (100), 212 (73), 197 (20), 182 (40), 169 (15), 154 (32), 43 (57).

HR-MS (EI) *m/z* calcd for C$_{16}$H$_{17}$NO$_3{}^+$ 271.1206, found 271.1211.

Ruthenium-catalyzed aerobic oxidative coupling with enamine 210a (Scheme 69)
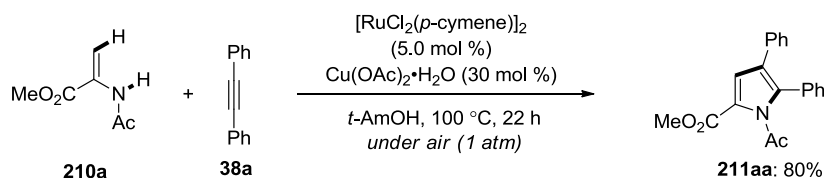
A mixture of methyl 2-acetamidoacrylate (**210a**) (71.5 mg, 0.50 mmol), diphenylacetylene (**38a**) (178 mg, 1.00 mmol), [RuCl$_2$(*p*-cymene)]$_2$ (15.3 mg, 5.0 mol %) and Cu(OAc)$_2$ H$_2$O (30.0 mg, 30 mol %) in *t*-AmOH (2.0 mL) was stirred at 100 ℃ under ambient air for 22 h. At ambient temperature, the reaction mixture was diluted with sat. aq. NH$_4$Cl/NH$_3$ (1:1, 75 mL) and extracted with EtOAc (3 × 75 mL). The combined organic phase was washed with sat. aq. NH$_4$Cl/NH$_3$ (1:1, 50 mL) and dried over anhydrous Na$_2$SO$_4$. After filtration and evaporation of the solvents under reduced pressure, the crude product was purified by column chromatography on silica gel (*n*-hexane/EtOAc: 10/1) to yield **211aa** (128 mg, 76%) as a yellow oil.

Intermolecular competition experiment with alkynes 38m and 38b (Scheme 70)
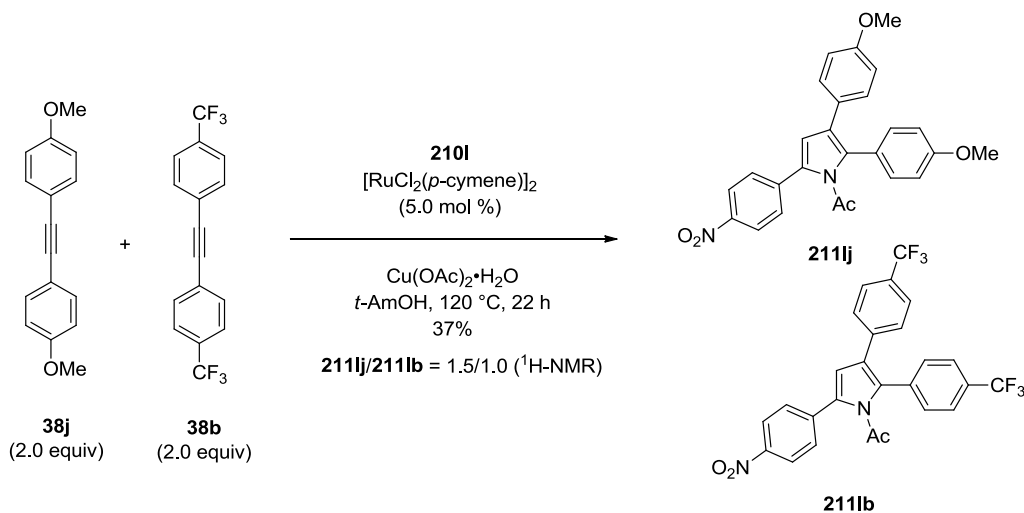
A mixture of *N*-{1-(4-nitrophenyl)vinyl}acetamide (**210l**) (103 mg, 0.50 mmol),

1,2-bis(4-methoxyphenyl)acetylene (**38j**) (238 mg, 1.00 mmol), 1,2-bis{4-(trifluoromethyl)phenyl}acetylene (**38b**) (314 mg, 1.00 mmol), [RuCl$_2$(*p*-cymene)]$_2$ (15.3 mg, 5.0 mol %) and Cu(OAc)$_2$ H$_2$O (200 mg, 1.00 mmol) in *t*-AmOH (2.0 mL) was stirred at 120 ℃ under N$_2$ for 22 h. At ambient temperature, the reaction mixture was diluted with sat. aq. NH$_4$Cl/NH$_3$ (1:1, 75 mL) and extracted with EtOAc (3 × 75 mL). The combined organic phase was washed with sat. aq. NH$_4$Cl/NH$_3$ (1:1, 50 mL) and dried over anhydrous Na$_2$SO$_4$. After filtration and evaporation of the solvents under reduced pressure, the crude product was purified by column chromatography on silica gel (*n*-hexane/EtOAc: 20/1) to yield a mixture of **211lj** and **211lb** as a yellow solid. The ratio of products **211lj/211lb** was found to be 1.5/1.0 by ^{1}H-NMR spectroscopy.

Intermolecular competition experiment with enamines 210n and 210l (Scheme 71a)

A mixture of N-{1-(4-methoxyphenyl)vinyl}acetamide (**210n**) (191 mg, 1.00 mmol), N-{1-(4-nitrophenyl)vinyl}acetamide (**210l**) (206 mg, 1.00 mmol), diphenylacetylene (**38a**) (89.0 mg, 0.50 mmol), [RuCl$_2$(*p*-cymene)]$_2$ (15.3 mg, 5.0 mol %) and Cu(OAc)$_2$ H$_2$O (200 mg, 1.00 mmol) in *t*-AmOH (2.0 mL) was stirred at 120 ℃ under N$_2$ for 22 h. At ambient temperature, the reaction mixture was diluted with sat. aq. NH$_4$Cl/NH$_3$ (1:1, 75 mL) and extracted with EtOAc (3 × 75 mL). The combined organic phase was washed with sat. aq. NH$_4$Cl/NH$_3$ (1:1, 50 mL) and dried over anhydrous Na$_2$SO$_4$. After filtration and evaporation of the solvents under reduced pressure, the crude product was purified by column chromatography on silica gel (*n*-hexane/EtOAc: 20/1) to yield a mixture of **211na** and **211la** as a yellow oil. The ratio of products **211na/211la** was found to be 2.0/1.0 by ^{1}H-NMR spectroscopy.

Intermolecular competition experiment with enamines 210n and 210g (Scheme 71b)
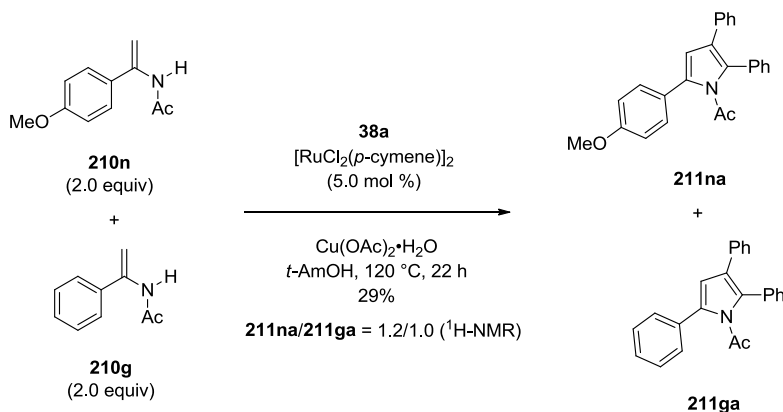
A mixture of *N*-{1-(4-methoxyphenyl)vinyl}acetamide (**210n**) (191 mg, 1.00 mmol), *N*-(1-phenylvinyl)acetamide (**210g**) (161 mg, 1.00 mmol), diphenylacetylene (**38a**) (89.0 mg, 0.50 mmol), [RuCl$_2$(*p*-cymene)]$_2$ (15.3 mg, 5.0 mol %) and Cu(OAc)$_2$ H$_2$O (200 mg, 1.00 mmol) in *t*-AmOH (2.0 mL) was stirred at 120 ℃ under N$_2$ for 22 h. At ambient temperature, the reaction mixture was diluted with sat. aq. NH$_4$Cl/NH$_3$ (1:1, 75 mL) and extracted with EtOAc (3 × 75 mL). The combined organic phase was washed with sat. aq. NH$_4$Cl/NH$_3$ (1:1, 50 mL) and dried over anhydrous Na$_2$SO$_4$. After filtration and evaporation of the solvents under reduced pressure, the crude product was purified by column chromatography on silica gel (*n*-hexane/EtOAc: 20/1) to yield a mixture of **211na** and **211ga** as a yellow oil. The ratio of products **211na**/**211ga** was found to be 1.2/1.0 by ^{1}H-NMR spectroscopy.

Intermolecular competition experiment with enamines 210g and 210l (Scheme 71c)
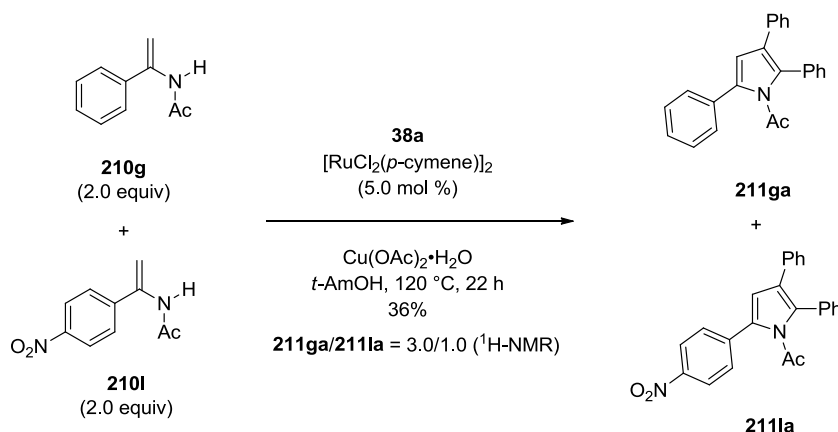
A mixture of *N*-(1-phenylvinyl)acetamide (**210g**) (161 mg, 1.00 mmol), *N*-{1-(4-nitrophenyl)vinyl}acetamide (**210l**) (206 mg, 1.00 mmol), diphenylacetylene (**38a**) (89.0 mg, 0.50 mmol), [RuCl$_2$(*p*-cymene)]$_2$ (15.3 mg, 5.0 mol %) and Cu(OAc)$_2$ H$_2$O (200 mg, 1.00 mmol) in *t*-AmOH (2.0 mL) was stirred at 120 ℃ under N$_2$ for 22 h. At ambient temperature, the reaction mixture was diluted with sat. aq. NH$_4$Cl/NH$_3$ (1:1, 75 mL) and extracted with EtOAc (3 × 75 mL). The combined organic phase was washed with sat. aq. NH$_4$Cl/NH$_3$ (1:1, 50 mL) and dried over anhydrous Na$_2$SO$_4$. After filtration and evaporation of the solvents under reduced pressure, the crude product was purified by column chromatography on silica gel (*n*-hexane/EtOAc: 20/1) to yield a mixture of **211ga** and **211la** as a yellow oil. The ratio of products **211ga**/**211la** was found to be 3.0/1.0 by ^{1}H-NMR spectroscopy.

Ruthenium-catalyzed H/D exchange with 210l (Scheme 72a)

A mixture of *N*-{1-(4-nitrophenyl)vinyl}acetamide (**210**) (103 mg, 0.50 mmol), [RuCl$_2$(*p*-cymene)]$_2$ (15.3 mg, 5.0 mol %), and Cu(OAc)$_2$ (182 mg, 1.00 mmol) in [D]$_4$-MeOH (2.0 mL) was stirred at 80 ℃ under N$_2$ for 18 h. After cooling to ambient temperature, the reaction mixture was diluted with sat. aq. NH$_4$Cl/NH$_3$ (50 mL) and extracted with EtOAc (3 × 40 mL). The combined organic phase was washed with brine (30 mL) and dried over Na$_2$SO$_4$. After filtration

and evaporation of the solvents under reduced pressure, the crude product was purified by column chromatography on silica gel (*n*-hexane/EtOAc: 1/1) to give the mixture of [D]$_n$-**210l** and **210l** as a white solid (63 mg, 60%). The deuterium incorporation was estimated to be 85% by ^{1}H-NMR spectroscopy.

Ruthenium-catalyzed oxidative annulation of alkyne with enamine 210l in [D]$_4$-MeOH (Scheme 72b)
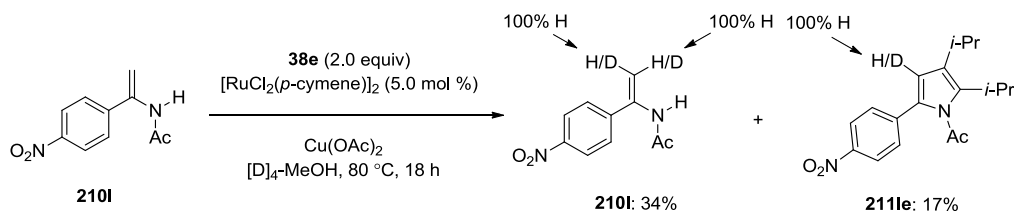
A mixture of *N*-{1-(4-nitrophenyl)vinyl}acetamide (**210l**) (103 mg, 0.50 mmol), diphenylacetylene (**38e**) (178 mg, 1.00 mmol), [RuCl$_2$(*p*-cymene)]$_2$ (15.3 mg, 5.0 mol %), and Cu(OAc)$_2$ (182 mg, 1.00 mmol) in [D]$_4$-MeOH (2.0 mL) was stirred at 80 ℃ under N$_2$ for 18 h. After cooling to ambient temperature, the reaction mixture was diluted with sat. aq. NH$_4$Cl/NH$_3$ (50 mL) and extracted with EtOAc (3 × 40 mL). The combined organic phase was washed with brine (30 mL) and dried over Na$_2$SO$_4$. After filtration and evaporation of the solvents under reduced pressure, the mixture was separated by column chromatography on silica gel (*n*-hexane/EtOAc: 10/1 to 1/1) to give **211le** as a red solid (33 mg, 17%) and **210l** as a white solid (35 mg, 34%). No deuterium incorporation was detected by ^{1}H-NMR spectroscopy.

8.4.3 Analytical Data for the Products of Ruthenium-Catalyzed Oxidative Alkenylation of Anilides 212 and Heteroamides 214

Synthesis of (*E*)-ethyl 3-(2-acetamido-4-methylphenyl)acrylate (213aa)
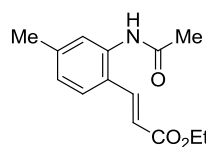
 The general procedure **D** was followed using acetanilide **212a** (74.5 mg, 0.50 mmol), ethyl acrylate (**76a**) (75.0 mg, 0.75 mmol), [RuCl$_2$(*p*-cymene)]$_2$ (7.7 mg, 5.0 mol %) and KPF$_6$ (9.2 mg, 10 mol %). After 20 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 3/1) yielded **213aa** (108 mg, 87%) as a white solid.

M.p. = 155−156 ℃.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.76 (d, *J* = 15.6 Hz, 1H), 7.54 (s$_{br}$, 1H), 7.50 (s, 1H), 7.43 (d, *J* = 8.2 Hz, 1H), 6.99 (d, *J* = 8.2 Hz, 1H), 6.33 (d, *J* = 15.6 Hz, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 2.38 (s, 3H), 2.20 (s, 3H), 1.30 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 168.9 (C$_q$), 166.9 (C$_q$), 141.4 (C$_q$), 139.2 (CH), 135.7 (C$_q$), 126.9 (CH), 126.9 (CH), 125.9 (CH), 124.9 (C$_q$), 119.3 (CH), 60.6 (CH$_2$), 24.1 (CH$_3$), 21.4 (CH$_3$), 14.2 (CH$_3$).

IR (ATR): $\tilde{v}$ = 3226, 1711, 1660, 1635, 1609, 1537, 1493, 1163, 984, 814 cm^{-1}.

MS (EI) *m/z* (relative intensity): 247 (28) [M$^+$], 204 (25), 160 (97), 138 (20) 132 (92), 117 (22).

HR-MS (EI) *m/z* calcd for C$_{14}$H$_{17}$NO$_3$$^+$ 247.1206, found 247.1209.

Synthesis of (*E*)-ethyl 3-(2-pivalamidophenyl)acrylate (213ea)
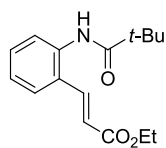
The representative procedure **D** was followed using acetanilide **213e** (88.5 mg, 0.50 mmol), ethyl acrylate (**76a**) (75.0 mg, 0.75 mmol), [RuCl$_2$(*p*-cymene)]$_2$ (15.3 mg, 5.0 mol %) and KPF$_6$ (18.4 mg, 20 mol %). After 20 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 5/1) yielded **213ea** (86 mg, 62%) as a white solid.

M.p. = 81−82 °C.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.75 (d, *J* = 16.4 Hz, 1H), 7.70 (d, *J* = 8.4 Hz, 1H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.40 (s$_{br}$, 1H), 7.37 (dd, *J* = 8.4, 7.8 Hz, 1H), 7.20 (dd, *J* = 8.0, 7.8 Hz, 1H), 6.38 (d, *J* = 16.4 Hz, 1H), 4.34 (q, *J* = 7.1 Hz, 2H), 1.36 (s, 9H), 1.32 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 176.9 (C$_q$), 166.5 (C$_q$), 139.2 (CH), 136.1 (C$_q$), 130.6 (CH), 128.1 (C$_q$), 127.1 (CH), 125.8 (CH), 125.1 (CH), 120.8 (CH), 60.3 (CH$_2$), 39.6 (C$_q$), 27.6 (CH$_3$), 14.2 (CH$_3$).

IR (ATR): $\tilde{v}$ = 3266, 2979, 1711, 1638, 1477, 1365, 1173, 1036, 984, 760 cm^{-1}.

MS (EI) *m/z* (relative intensity): 275 (20) [M$^+$], 190 (22), 174 (12), 146 (38), 117 (36), 90 (15), 57 (100).

HR-MS (EI) *m/z* calcd for C$_{16}$H$_{21}$NO$_3^+$ 275.1521, found 275.1522.

Synthesis of (*E*)-ethyl 3-(2-acetamido-5-methylphenyl)acrylate (213ga)
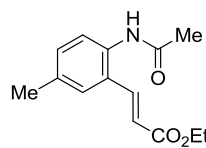
The general procedure **D** was followed using acetanilide **212g** (74.5 mg, 0.50 mmol), ethyl acrylate (**76a**) (75.0 mg, 0.75 mmol), [RuCl$_2$(*p*-cymene)]$_2$ (15.3 mg, 5.0 mol %) and KPF$_6$ (18.4 mg, 20 mol %). After 20 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 2/1) yielded **213ga** (83 mg, 67%) as a white solid.

M.p. = 134−135 °C.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.76 (d, *J* = 15.8 Hz, 1H), 7.53 (d, *J* = 8.2 Hz, 1H), 7.38 (s, 1H), 7.35 (s$_{br}$, 1H), 7.17 (d, *J* = 8.2 Hz, 1H), 6.37 (d, *J* = 15.8 Hz, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 2.32 (s, 3H), 2.20 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 169.0 (C$_q$), 166.8 (C$_q$), 139.4 (CH), 135.7 (C$_q$), 133.4 (C$_q$), 131.5 (CH), 127.8 (C$_q$), 127.3 (CH), 125.5 (CH), 120.2 (CH), 60.6 (CH$_2$), 24.0 (CH$_3$), 20.9 (CH$_3$), 14.2 (CH$_3$).

IR (ATR): $\tilde{v}$ = 3269, 1712, 1658, 1636, 1525, 1363, 1299, 1174, 970, 815 cm^{-1}.

MS (EI) *m/z* (relative intensity): 247 (40) [M$^+$], 205 (37), 160 (100), 132 (76), 117 (12).

HR-MS (EI) *m/z* calcd for C$_{14}$H$_{17}$NO$_3^+$ 247.1206, found 247.1204.

Synthesis of (*E*)-(*n*)-butyl 3-(2-acetamido-5-methylphenyl)acrylate (213gb)
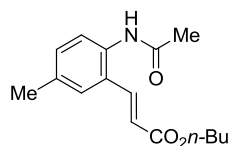
The general procedure **D** was followed using acetanilide **212g** (74.5 mg, 0.50 mmol), *n*-butyl acrylate (**76b**) (96.0 mg, 0.75 mmol), [RuCl$_2$(*p*-cymene)]$_2$ (15.3 mg, 5.0 mol %) and KPF$_6$ (18.4 mg, 20 mol %). After 20 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 1/1) yielded **213gb** (75 mg, 55%) as a white solid.

M.p. = 112−113 °C.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.76 (d, *J* = 16.0 Hz, 1H), 7.51 (d, *J* = 8.4 Hz, 1H), 7.37 (s, 1H), 7.34 (s$_{br}$, 1H), 7.16 (d, *J* = 8.4 Hz, 1H), 6.35 (d, *J* = 16.0 Hz, 1H), 4.16 (t, *J* = 6.7 Hz, 2H), 2.30 (s, 3H), 2.18 (s, 3H), 1.70−1.59 (m, 2H), 1.47−1.32 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 168.9 (C$_q$), 166.9 (C$_q$), 139.4 (CH), 135.7 (C$_q$), 133.3 (C$_q$), 131.5 (CH), 127.8 (C$_q$), 127.3 (CH), 125.6 (CH), 120.2 (CH), 64.5 (CH$_2$), 30.7 (CH$_2$), 24.0 (CH$_3$), 20.9 (CH$_3$), 19.1 (CH$_2$), 13.7 (CH$_3$).

IR (ATR): $\tilde{\nu}$ = 3269, 1711, 1656, 1584, 1527, 1277, 1241, 1161, 979, 812 cm^{-1}.

MS (EI) m/z (relative intensity): 275 (25) [M$^+$], 233 (20), 160 (100), 132 (64), 117 (9).

HR-MS (EI) m/z calcd for C$_{16}$H$_{21}$NO$_3^+$ 275.1521, found 275.1529.

The spectral data were in accordance with those reported in the literature.[178]

Synthesis of (*E*)-ethyl 3-(2-acetamido-5-fluorophenyl)acrylate (213ha)
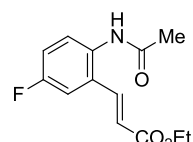
The general procedure **D** was followed using acetanilide **212h** (76.5 mg, 0.50 mmol), ethyl acrylate (**76a**) (75.0 mg, 0.75 mmol), [RuCl$_2$(*p*-cymene)]$_2$ (15.3 mg, 5.0 mol %) and KPF$_6$ (18.4 mg, 20 mol %). After 20 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 2/1) yielded **213ha** (93 mg, 74%) as a white solid.

M.p. = 143−144 ℃.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.72 (d, J = 15.6 Hz, 1H), 7.59 (s, 1H), 7.55 (d, J = 7.6 Hz, 1H), 7.21 (d, J = 8.2 Hz, 1H), 7.05 (dd, J = 8.2, 8.0 Hz, 1H), 6.34 (d, J = 15.6 Hz, 1H), 4.24 (q, J = 7.1 Hz, 2H), 2.19 (s, 3H), 1.32 (t, J = 7.1 Hz, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 169.3 (C$_q$), 166.4 (C$_q$), 160.2 (d, $^1J_{C-F}$ = 247 Hz, C$_q$), 138.3 (d, $^4J_{C-F}$ = 2 Hz, CH), 131.9 (d, $^4J_{C-F}$ = 3 Hz, C$_q$), 130.2 (d, $^3J_{C-F}$ = 8 Hz, C$_q$), 127.9 (d, $^3J_{C-F}$ = 8 Hz, CH), 121.4 (CH), 117.7 (d, $^2J_{C-F}$ = 23 Hz, CH), 113.1 (d, $^2J_{C-F}$ = 23 Hz, CH), 60.8 (CH$_2$), 23.8 (CH$_3$), 14.2 (CH$_3$).

^{19}F-NMR (CDCl$_3$, 283 MHz): δ = −(111.3−111.5) (m).

IR (ATR): $\tilde{\nu}$ = 3249, 1717, 1656, 1636, 1527, 1486, 1419, 1264, 1177, 971, 852 cm^{-1}.

MS (EI) m/z (relative intensity): 251 (20) [M$^+$], 207 (32), 164 (100), 146 (22), 136 (70), 108 (16).

HR-MS (EI) m/z calcd for C$_{13}$H$_{14}$FNO$_3^+$ 251.0958, found 251.0956.

Synthesis of (*E*)-(*n*)-butyl 3-(2-acetamido-5-fluorophenyl)acrylate (213hb)
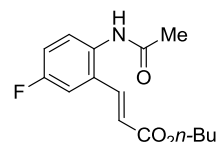
The general procedure **D** was followed using acetanilide **212h** (76.5 mg, 0.50 mmol), *n*-butyl acrylate (**76b**) (96.0 mg, 0.75 mmol), [RuCl$_2$(*p*-cymene)]$_2$ (15.3 mg, 5.0 mol %) and KPF$_6$ (18.4 mg, 20 mol %). After 20 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 1/1) yielded **213hb** (74 mg, 53%) as a white solid.

M.p. = 138−139 ℃.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.71 (s, 1H), 7.68 (d, J = 15.8 Hz, 1H), 7.51 (dd, J = 8.8, 5.4 Hz, 1H), 7.18 (d, J = 8.8 Hz, 1H), 7.01 (dd, J = 8.2, 2.9 Hz, 1H), 6.30 (d, J = 15.8 Hz, 1H), 4.14 (t, J = 6.5 Hz, 2H), 2.15 (s, 3H), 1.70−1.56 (m, 2H), 1.46−1.31 (m, 2H), 0.92 (t, J = 7.3 Hz, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 169.3 (C$_q$), 166.5 (C$_q$), 160.3 (d, $^1J_{C-F}$ = 246 Hz, C$_q$), 138.3 (CH), 131.8 (d, $^4J_{C-F}$ = 2 Hz, C$_q$), 130.3 (d, $^3J_{C-F}$ = 8 Hz, C$_q$), 128.0 (d, $^3J_{C-F}$ = 8 Hz, CH), 121.2 (CH), 117.6 (d, $^2J_{C-F}$ = 22 Hz, CH), 113.0 (d, $^2J_{C-F}$ = 22 Hz, CH), 64.7 (CH$_2$), 30.6 (CH$_2$), 23.7 (CH$_3$), 19.1 (CH$_2$), 13.6 (CH$_3$).

^{19}F-NMR (CDCl$_3$, 283 MHz): δ = −111.4 (m).

IR (ATR): $\tilde{\nu}$ = 3255, 2955, 1717, 1656, 1636, 1527, 1486, 1174, 1015, 852 cm^{-1}.

[178] L. L. Chng, J. Zhang, J. Yang, M. Amoura, J. Y. Ying, *Adv. Synth. Catal.* **2011**, *353*, 2988–2998.

MS (EI) m/z (relative intensity): 279 (11) [M$^+$], 237 (16), 164 (100), 136 (55), 108 (10).

HR-MS (EI) m/z calcd for $C_{15}H_{18}FNO_3^+$ 279.1271, found 279.1268.

The spectral data were in accordance with those reported in the literature.[178]

Synthesis of (*E*)-ethyl 3-{2-acetamido-5-(trifluoromethyl)phenyl}acrylate (213ia)
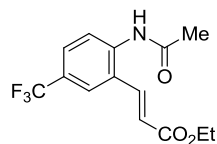
The general procedure **D** was followed using acetanilide **212i** (101.5 mg, 0.50 mmol), ethyl acrylate (**76a**) (75.0 mg, 0.75 mmol), [RuCl$_2$(*p*-cymene)]$_2$ (15.3 mg, 5.0 mol %) and KPF$_6$ (18.4 mg, 20 mol %). After 20 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 3/1) yielded **213ia** (69 mg, 46%) as a white solid.

M.p. = 168−169 ℃.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 8.01 (s$_{br}$, 1H), 7.78 (d, J = 16.3 Hz, 1H), 7.77 (d, J = 8.4 Hz, 1H), 7.73 (s, 1H), 7.57 (d, J = 8.4 Hz, 1H), 6.43 (d, J = 16.3 Hz, 1H), 4.25 (q, J = 7.1 Hz, 2H), 2.23 (s, 3H), 1.32 (t, J = 7.1 Hz, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 169.0 (C$_q$), 166.3 (C$_q$), 138.8 (C$_q$), 137.8 (CH), 127.2 (q, $^3J_{C-F}$ = 10 Hz, CH), 127.0 (q, $^2J_{C-F}$ = 33 Hz, C$_q$), 124.4 (q, $^4J_{C-F}$ = 4 Hz, CH), 124.2 (q, $^3J_{C-F}$ = 11 Hz, CH), 123.6 (q, $^1J_{C-F}$ = 273 Hz, C$_q$), 122.4 (CH), 121.8 (C$_q$), 61.0 (CH$_2$), 24.2 (CH$_3$), 14.2 (CH$_3$).

^{19}F-NMR (CDCl$_3$, 283 MHz): δ = −62.6 (s).

IR (ATR): $\tilde{\nu}$ = 3269, 1719, 1661, 1585, 1527, 1369, 1278, 1108, 1039, 834 cm^{-1}.

MS (EI) m/z (relative intensity): 301 (12) [M$^+$], 259 (20), 212 (100), 196 (20), 186 (55), 166 (21), 43 (38).

HR-MS (EI) m/z calcd for $C_{14}H_{14}F_3NO_3^+$ 301.0926, found 301.0920.

Synthesis of (*E*)-(*n*)-butyl 3-(2-acetamido-4-methylphenyl)acrylate (213ab)
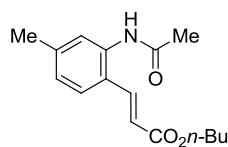
The general procedure **D** was followed using acetanilide **212a** (74.5 mg, 0.50 mmol), *n*-butyl acrylate (**76b**) (96.0 mg, 0.75 mmol), [RuCl$_2$(*p*-cymene)]$_2$ (15.3 mg, 5.0 mol %) and KPF$_6$ (18.4 mg, 20 mol %). After 20 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 3/1) yielded **213ab** (77 mg, 56%) as a white solid.

M.p. = 138−139 ℃.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.77 (d, J = 16.0 Hz, 1H), 7.51 (s$_{br}$, 1H), 7.51 (s, 1H), 7.44 (d, J = 8.0 Hz, 1H), 6.99 (d, J = 8.0 Hz, 1H), 6.33 (d, J = 16.0 Hz, 1H), 4.17 (t, J = 6.7 Hz, 2H), 2.38 (s, 3H), 2.20 (s, 3H), 1.72−1.59 (m, 2H), 1.48−1.33 (m, 2H), 0.94 (t, J = 7.4 Hz, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 168.9 (C$_q$), 167.0 (C$_q$), 141.4 (C$_q$), 139.2 (CH), 135.7 (C$_q$), 126.9 (CH), 126.8 (CH), 125.9 (C$_q$), 124.9 (CH), 119.3 (CH), 64.5 (CH$_2$), 30.7 (CH$_2$), 24.1 (CH$_3$), 21.4 (CH$_3$), 19.1 (CH$_2$), 13.7 (CH$_3$).

IR (ATR): $\tilde{\nu}$ = 3267, 2958, 1708, 1656, 1569, 1532, 1251, 1067, 973, 813 cm^{-1}.

MS (EI) m/z (relative intensity): 275 (17) [M$^+$], 233 (10), 160 (92), 138 (20), 132 (100), 117 (13).

HR-MS (EI) m/z calcd for $C_{14}H_{17}NO_3^+$ 275.1521, found 275.1525.

The spectral data were in accordance with those reported in the literature.[178]

Synthesis of (*E*)-ethyl 3-(2-acetamido-4-methoxyphenyl)acrylate (213ja)
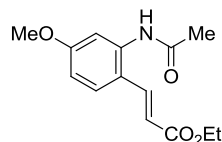
The general procedure **D** was followed using acetanilide **212j** (82.5 mg, 0.50 mmol), ethyl acrylate (**76a**) (75.0 mg, 0.75 mmol), [RuCl$_2$(*p*-cymene)]$_2$ (15.3 mg, 5.0 mol %) and KPF$_6$ (18.4 mg, 20 mol %). After 20 h,

purification by column chromatography on silica gel (*n*-hexane/EtOAc: 2/1) yielded **213ja** (77 mg, 58%) as a white solid.

M.p. = 132−133 ℃.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.75 (d. *J* = 15.7 Hz, 1H), 7.58 (s$_{br}$, 1H), 7.47 (d, *J* = 8.4 Hz, 1H), 7.40 (s, 1H), 7.72 (d, *J* = 8.4 Hz, 1H), 6.26 (d, *J* = 15.7 Hz, 1H), 4.23 (q, *J* = 7.1 Hz, 2H), 3.76 (s, 3H), 2.22 (s, 3H), 1.31 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 168.8 (C$_q$), 167.1 (C$_q$), 161.6 (C$_q$), 138.7 (CH), 137.4 (C$_q$), 128.2 (CH), 119.3 (C$_q$), 117.8 (CH), 112.5 (CH), 109.2 (CH), 60.5 (CH$_2$), 55.4 (CH$_3$), 14.3 (CH$_3$), 14.3 (CH$_3$).

IR (ATR): $\tilde{v}$ = 3258, 2976, 1697, 1660, 1610, 1573, 1435, 1259, 1110, 768 cm^{-1}.

MS (EI) *m/z* (relative intensity): 263 (30) [M$^+$], 218 (20), 176 (65), 148 (70), 132 (38), 104 (22).

HR-MS (EI) *m/z* calcd for C$_{14}$H$_{17}$NO$_4^+$ 263.1118, found 263.1114.

Synthesis of (*E*)-(*n*)-butyl 3-(2-acetamido-4-methoxyphenyl)acrylate (213jb)
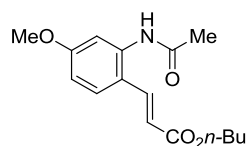
The general procedure **D** was followed using acetanilide **212j** (82.5 mg, 0.50 mmol), *n*-butyl acrylate (**76b**) (96.0 mg, 0.75 mmol), [RuCl$_2$(*p*-cymene)]$_2$ (15.3 mg, 5.0 mol %) and KPF$_6$ (18.4 mg, 20 mol %). After 20 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 3/1) yielded **213jb** (76 mg, 52%) as a white solid.

M.p. = 138−139 ℃.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.75 (d, *J* = 16.4 Hz, 1H), 7.61 (s$_{br}$, 1H), 7.47 (d, *J* = 8.8 Hz, 1H), 7.40 (s, 1H), 6.72 (d, *J* = 8.8 Hz, 1H), 6.27 (d, *J* = 16.4 Hz, 1H), 4.16 (t, *J* = 6.4 Hz, 2H), 3.76 (s, 3H), 2.22 (s, 3H) 1.78−1.59 (m, 2H), 1.51−1.33 (m, 2H), 0.94 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 167.1 (C$_q$), 161.8 (C$_q$), 138.7 (CH), 137.6 (C$_q$), 137.6 (C$_q$), 128.4 (CH), 118.2 (CH), 112.6 (CH), 112.6 (C$_q$), 109.3 (CH), 64.4 (CH$_2$), 55.5 (CH$_3$), 30.8 (CH$_2$), 24.2 (CH$_3$), 19.2 (CH$_2$), 13.6 (CH$_3$).

IR (ATR): $\tilde{v}$ = 3266, 2952, 1697, 1660, 1609, 1573, 1244, 1110, 972, 767 cm^{-1}.

MS (EI) *m/z* (relative intensity): 291 (25) [M$^+$], 249 (20), 176 (65), 148 (100), 132 (26), 104 (13).

HR-MS (EI) *m/z* calcd for C$_{14}$H$_{17}$NO$_3^+$ 291.1471, found 291.1472.

The spectral data were in accordance with those reported in the literature.[178]

Synthesis of (*E*)-ethyl 3-(2-acetamido-4-chlorophenyl)acrylate (213ka)
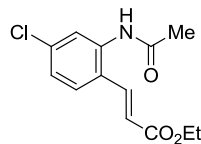
The general procedure **D** was followed using acetanilide **212k** (84.5 mg, 0.50 mmol), ethyl acrylate (**76a**) (150 mg, 1.50 mmol), [RuCl$_2$(*p*-cymene)]$_2$ (15.3 mg, 5.0 mol %) and KPF$_6$ (18.4 mg, 20 mol %). After 20 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 1/1) yielded **213ka** (88 mg, 66%) as a white solid.

M.p. = 167−168 ℃.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.87 (s, 1H), 7.75 (s$_{br}$, 1H), 7.69 (d, *J* = 15.8 Hz, 1H), 7.39 (d, *J* = 8.6 Hz, 1H), 7.09 (d, *J* = 8.6 Hz, 1H), 6.30 (d, *J* = 15.8 Hz, 1H), 4.22 (q, *J* = 7.3 Hz, 2H), 2.19 (s, 3H), 1.30 (t, *J* = 7.3 Hz, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 169.1 (C$_q$), 166.6 (C$_q$), 138.2 (CH), 136.8 (C$_q$), 136.3 (C$_q$), 127.8 (CH), 125.8 (CH), 125.6 (C$_q$), 124.9 (CH), 120.6 (CH), 60.8 (CH$_2$), 24.0 (CH$_3$), 14.2 (CH$_3$).

IR (ATR): $\tilde{v}$ = 3249, 1712, 1665, 1568, 1521, 1474, 1266, 1244, 975, 810 cm^{-1}.

MS (EI) *m/z* (relative intensity): 267 (18) [M$^+$], 225 (25), 176 (100), 152 (90), 117 (30), 89 (32).

HR-MS (EI) *m/z* calcd for $C_{13}H_{14}ClNO_3^+$ 267.0662, found 267.0622.

Synthesis of (*E*)-ethyl 3-{2-acetamido-4-(trifluoromethyl)phenyl}acrylate (213la)
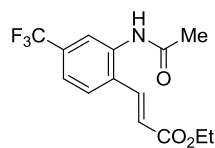
The general procedure **D** was followed using acetanilide **213l** (102 mg, 0.50 mmol), ethyl acrylate (**76a**) (75.0 mg, 0.75 mmol), [RuCl$_2$(*p*-cymene)]$_2$ (15.3 mg, 5.0 mol %) and KPF$_6$ (18.4 mg, 20 mol %). After 20 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 4/1) yielded **213la** (76 mg, 53%) as a white solid.

M.p. = 138−139 C.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.98 (s, 1H), 7.96 (s$_{br}$, 1H), 7.73 (d, *J* = 15.8 Hz, 1H), 7.55 (d, *J* = 8.2 Hz, 1H), 7.36 (d, *J* = 8.2 Hz, 1H), 6.48 (d, *J* = 15.8 Hz, 1H), 4.23 (q, *J* = 7.1 Hz, 2H), 2.20 (s, 3H), 1.31 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 169.3 (C$_q$), 166.2 (C$_q$), 138.0 (CH), 136.2 (C$_q$), 132.1 (q, $^2J_{C-F}$ = 33 Hz, C$_q$), 130.6 (C$_q$), 127.4 (CH), 123.4 (q, $^1J_{C-F}$ = 273 Hz, C$_q$), 122.5 (CH), 122.1 (q, $^3J_{C-F}$ = 14 Hz, CH), 121.7 (q, $^3J_{C-F}$ = 12 Hz, CH), 60.9 (CH$_2$), 23.9 (CH$_3$), 14.1 (CH$_3$).

^{19}F-NMR (CDCl$_3$, 283 MHz): δ = −63.0 (s).

IR (ATR): $\tilde{v}$ = 3255, 2984, 1712, 1661, 1531, 1387, 1328, 1110, 822, 553 cm^{-1}.

MS (EI) *m/z* (relative intensity): 301 (10) [M$^+$], 259 (20), 212 (100), 196 (20), 186 (65), 166 (25).

HR-MS (EI) *m/z* calcd for $C_{14}H_{14}F_3NO_3^+$ 301.0926, found 301.0918.

Synthesis of (*E*)-ethyl 3-(2-acetamido-6-fluorophenyl)acrylate (213ma)
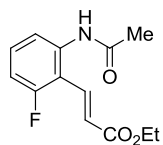
The general procedure **D** was followed using acetanilide **212m** (76.5 mg, 0.50 mmol), ethyl acrylate (**76a**) (75.0 mg, 0.75 mmol), [RuCl$_2$(*p*-cymene)]$_2$ (15.3 mg, 5.0 mol %) and KPF$_6$ (18.4 mg, 20 mol %). After 20 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 2/1) yielded **213ma** (88 mg, 70%) as a white solid.

M.p. = 138−143 ℃.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.65–7.52 (m, 2H), 7.60 (d, *J* = 16.9 Hz, 1H), 7.30 (dd, *J* = 9.6, 9.6 Hz, 1H), 6.93 (dd, *J* = 9.6, 8.7 Hz, 1H), 6.57 (d, *J* = 16.9 Hz, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 2.21 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 168.8 (C$_q$), 166.9 (C$_q$), 161.3 (d, $^1J_{C-F}$ = 252 Hz, C$_q$), 137.3 (d, $^4J_{C-F}$ = 4 Hz, C$_q$), 133.3 (CH), 130.8 (d, $^3J_{C-F}$ = 10 Hz, CH), 124.8 (d, $^3J_{C-F}$ = 11 Hz, CH), 120.5 (CH), 116.1 (d, $^2J_{C-F}$ = 10 Hz, C$_q$), 112.8 (d, $^2J_{C-F}$ = 24 Hz, CH), 60.8 (CH$_2$), 24.2 (CH$_3$), 14.2 (CH$_3$).

^{19}F-NMR (CDCl$_3$, 283 MHz): δ = −110.4 (s).

IR (ATR): $\tilde{v}$ = 3264, 1719, 1664, 1636, 1572, 1364, 1184, 1029, 751, 530 cm^{-1}.

MS (EI) *m/z* (relative intensity): 251 (10) [M$^+$], 207 (8), 164 (58), 146 (15), 136 (38), 108 (10).

HR-MS (EI) *m/z* calcd for $C_{13}H_{14}FNO_3^+$ 251.0958, found 251.0959.

Synthesis of *N*-{5-methyl-2-(3-oxobutyl)phenyl}acetamide (213ac)
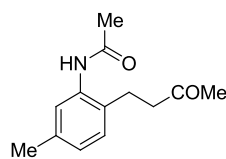
The general procedure **D** was followed using *N*-(*m*-tolyl)acetamide **212a** (74.5 mg, 0.50 mmol), 3-buten-2-one (**76c**) (52.5 mg, 0.75 mmol), [RuCl$_2$(*p*-cymene)]$_2$ (15.3 mg, 5.0 mol %) and KPF$_6$ (18.4 mg, 20 mol %). After 20 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 3/1→2/1) yielded **213ac** (34 mg, 31%) as a white solid.

M.p. = 132−133 °C.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 9.00 (s$_{br}$, 1H), 7.62 (s, 1H), 6.99 (d, J = 8.0 Hz, 1H), 6.88 (d, J = 8.0 Hz, 1H), 2.88 (t, J = 6.7 Hz, 2H), 2.76 (t, J = 6.7 Hz, 2H), 2.30 (s, 3H), 2.27 (s, 3H), 2.13 (s, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 208.7 (C$_q$), 169.1 (C$_q$), 137.0 (C$_q$), 135.6 (C$_q$), 129.8 (CH), 129.7 (C$_q$), 126.2 (CH), 125.0 (CH), 45.7 (CH$_2$), 30.2 (CH$_3$), 24.5 (CH$_3$), 23.7 (CH$_2$), 21.3 (CH$_3$).

IR (ATR): $\tilde{\nu}$ = 3276, 2949, 1708, 1650, 1576, 1531, 1370, 1284, 1161, 814, 553 cm^{-1}.

MS (EI) m/z (relative intensity): 217 (28) [M$^+$], 176 (67), 158 (25), 134 (100), 120 (90), 107 (20).

HR-MS (EI) m/z calcd for C$_{13}$H$_{17}$NO$_2^+$ 217.1259, found 217.1257.

Ruthenium-catalyzed oxidative alkenylations of anilide 212a in 5 mmol scale (Scheme 75)
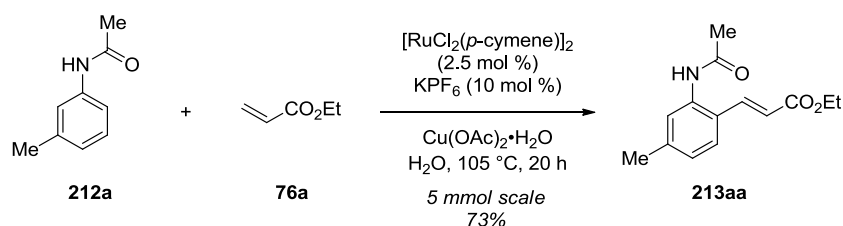
A mixture of acetanilide **212a** (715 mg, 5.0 mmol), ethyl acrylate (**76a**) (750 mg, 7.5 mmol), [RuCl$_2$(p-cymene)]$_2$ (76.5 mg, 2.5 mol %), KPF$_6$ (92.0 mg, 10 mol %) and Cu(OAc)$_2$ H$_2$O (1.0 g, 5.0 mmol) in H$_2$O (2.0 mL) was stirred at 105 °C under N$_2$ for 20 h. At ambient temperature, the mixture was diluted with sat. aq. NH$_4$Cl/NH$_3$ (1:1, 100 mL) and extracted with EtOAc (2 × 100 mL). The combined organic phase was dried over anhydrous Na$_2$SO$_4$ (50 g). After filtration and evaporation of the solvents under reduced pressure, the crude product was purified by column chromatography on silica gel (n-hexane/EtOAc/CH$_2$Cl$_2$: 9/5/1→6/4/1) to yield **213aa** (901 mg, 73%) as a white solid.

Intermolecular competition experiment with anilides 212h and 212d (Scheme 76a)
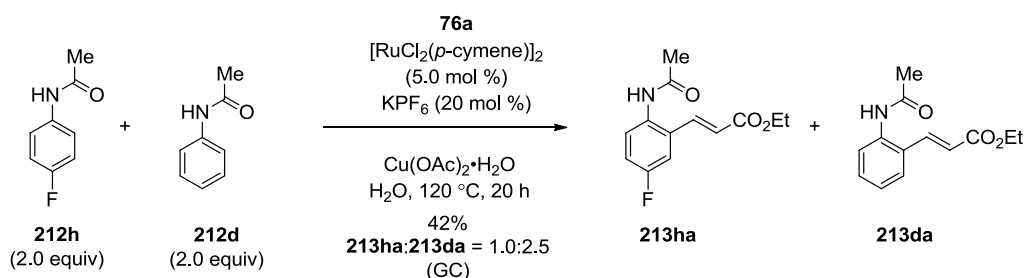
A mixture of N-(4-fluorophenyl)acetamide (**212h**) (153 mg, 1.00 mmol), N-phenylacetamide (**212d**) (135 mg, 1.00 mmol), ethyl acrylate (**76a**) (50.0 mg, 0.50 mmol), [RuCl$_2$(p-cymene)]$_2$ (15.3 mg, 5.0 mol %), KPF$_6$ (18.4 mg, 20 mol%) and Cu(OAc)$_2$ H$_2$O (99.5 mg, 1.00 mmol) in H$_2$O (2.0 mL) was stirred at 120 °C under N$_2$ for 20 h. At ambient temperature, the mixture was diluted with H$_2$O (75 mL) and extracted with EtOAc (3 × 75 mL). The combined organic phase was washed with brine (50 mL) and dried over anhydrous Na$_2$SO$_4$. After filtration and evaporation of the solvents under reduced pressure, the conversion of the crude mixture was determined by GC (38%, **213ha**:**213da** = 1.0:2.5).

Intermolecular competition experiment with anilides 212o and 212d (Scheme 76b)
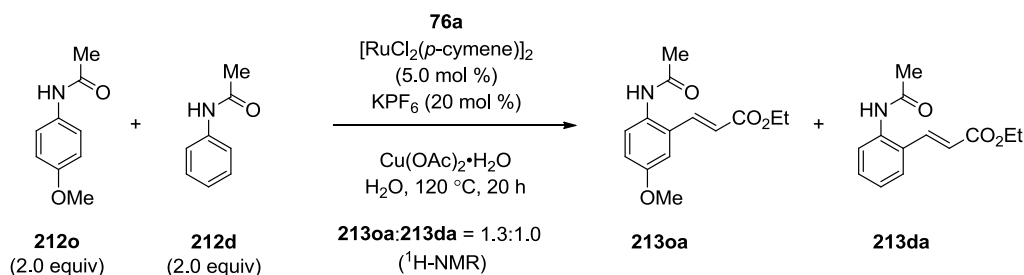
A mixture of *N*-(4-methoxyphenyl)acetamide (**212o**) (165 mg, 1.00 mmol), *N*-phenylacetamide (**212d**) (135 mg, 1.00 mmol), ethyl acrylate (**76a**) (50.0 mg, 0.50 mmol), [RuCl$_2$(*p*-cymene)]$_2$ (15.3 mg, 5.0 mol %), KPF$_6$ (18.4 mg, 20 mol %) and Cu(OAc)$_2$ H$_2$O (99.5 mg, 1.00 mmol) in H$_2$O (2.0 mL) was stirred at 120 ℃ under N$_2$ for 20 h. At ambient temperature, the mixture was diluted with H$_2$O (75 mL) and extracted with EtOAc (3 × 75 mL). The combined organic phase was washed with brine (50 mL) and dried over anhydrous Na$_2$SO$_4$. After filtration and evaporation of the solvents under reduced pressure, the crude product was purified by column chromatography on silica gel (*n*-hexane/EtOAc: 2/1) to yield a mixture of **213oa** and **213da** as a white solid. The ratio of products **213oa:213da** was found to be 1.3:1.0 by ¹H-NMR spectroscopy.

Intermolecular competition experiment with anilides 212h and 212o (Scheme 76c)
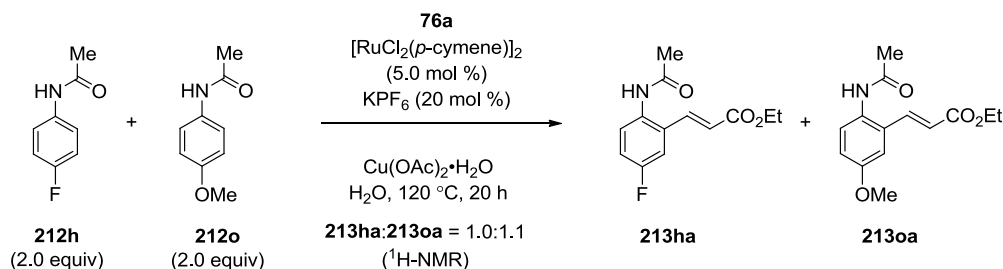
A mixture of *N*-(4-fluorophenyl)acetamide (**212h**) (153 mg, 1.00 mmol), *N*-(4-methoxyphenyl)acetamide (**212o**) (165 mg, 1.00 mmol), ethyl acrylate (**76a**) (50.0 mg, 0.50 mmol), [RuCl$_2$(*p*-cymene)]$_2$ (15.3 mg, 5.0 mol %), KPF$_6$ (18.4 mg, 20 mol %) and Cu(OAc)$_2$ H$_2$O (99.5 mg, 1.00 mmol) in H$_2$O (2.0 mL) was stirred at 120 ℃ under N$_2$ for 20 h. At ambient temperature, the mixture was diluted with H$_2$O (75 mL) and extracted with EtOAc (3 × 75 mL). The combined organic phase was washed with brine (50 mL) and dried over anhydrous Na$_2$SO$_4$. After filtration and evaporation of the solvents under reduced pressure, the crude product was purified by column chromatography on silica gel (*n*-hexane/EtOAc: 2/1) to yield a mixture of **213ha** and **213oa** as a white solid. The ratio of products **213ha:213oa** was found to be 1.0:1.1 by ¹H-NMR spectroscopy.

Ruthenium-catalyzed H/D exchange in D$_2$O (Scheme 77b)
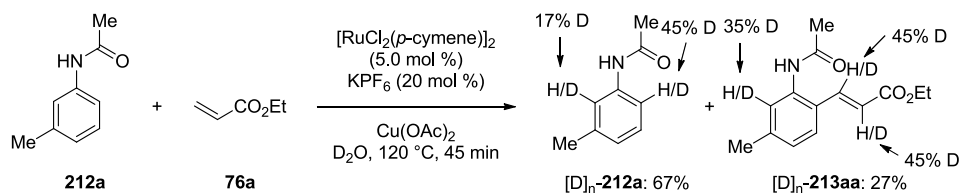
A mixture of acetanilide (**212a**) (149 mg, 1.00 mmol), ethyl acylate (**76a**) (150 mg, 1.50 mmol), [RuCl$_2$(*p*-cymene)]$_2$ (30.6 mg, 5.0 mol %), KPF$_6$ (36.8 mg, 20 mol %) and Cu(OAc)$_2$ (181 mg,

1.00 mmol) in D_2O (3.0 mL) was stirred at 120 °C under N_2 for 45 min. At ambient temperature, the mixture was diluted with sat. aq. NH_4Cl/NH_3 (1:1, 50 mL) and extracted with EtOAc (3 × 50 mL). The combined organic phase was washed with brine (50 mL) and dried over anhydrous Na_2SO_4. After filtration and evaporation of the solvents under reduced pressure, the crude product was purified by column chromatography on silica gel (*n*-hexane/EtOAc: 2/1→1/1) to yield [D]$_n$-**212a** (100 mg, 67%) as a white solid and [D]$_n$-**213aa** (67 mg, 27%) as a white solid. The deuterium incorporation was estimated by ^{1}H-NMR spectroscopy.

Synthesis of (*E*)-ethyl 3-{1-methyl-3-(methylcarbamoyl)-1*H*-indol-2-yl}acrylate (215aa)
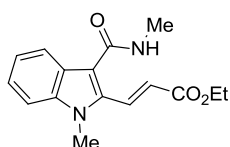
The general procedure **D** was followed using indole **214a** (94 mg, 0.50 mmol), ethyl acrylate (**76a**) (75 mg, 0.75 mmol), [RuCl$_2$(*p*-cymene)]$_2$ (15.3 mg, 5.0 mol %) and KPF$_6$ (18.4 mg, 20 mol %). After 20 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 1/1) yielded **215aa** (75mg, 52%) as a white solid.

M.p. = 193−194 °C.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 8.08 (d, *J* = 16.3 Hz, 1H), 7.79 (d, *J* =8.0 Hz, 1H), 7.36−7.30 (m, 2H), 7.21 (dd, *J* = 8.0, 5.1 Hz, 1H), 6.53 (d, *J* = 16.3 Hz, 1H), 6.00 (s$_{br}$, 1H), 4.28 (q, *J* = 7.1 Hz, 2H), 3.78 (CH$_3$), 3.05 (d, *J* = 5.0 Hz, 3H), 1.35 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 166.4 (C$_q$), 165.7 (C$_q$), 138.1 (C$_q$), 135.1 (C$_q$), 132.1 (CH), 125.2 (C$_q$), 124.2 (CH), 123.4 (CH), 121.7 (CH), 120.2 (CH), 113.8 (C$_q$), 110.1 (CH), 60.8 (CH$_2$), 31.4 (CH$_3$), 26.6 (CH$_3$), 14.3 (CH$_3$).

IR (ATR): $\tilde{\nu}$ = 3264, 1698, 1628, 1543, 1467, 1400, 1237, 1173, 1027, 731 cm^{-1}.

MS (EI) *m/z* (relative intensity): 286 (30) [M$^+$], 219 (100), 199 (40), 184 (25), 128 (10).

HR-MS (EI) *m/z* calcd for C$_{16}$H$_{18}$N$_2$O$_3^+$ 286.1317, found 286.1321.

Synthesis of (*E*)-ethyl 3-{1-methyl-2-(methylcarbamoyl)-1*H*-indol-3-yl}acrylate (215ba)
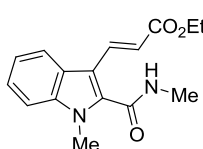
The general procedure **D** was followed using indole **214b** (94 mg, 0.50 mmol), ethyl acrylate (**76a**) (75 mg, 0.75 mmol), [RuCl$_2$(*p*-cymene)]$_2$ (15.3 mg, 5.0 mol %) and KPF$_6$ (18.4 mg, 20 mol %). After 20 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 1/1) yielded **215ba** (102 mg, 71%) as a white solid.

M.p. = 173−174 °C.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.97 (d, *J* = 16.0 Hz, 1H), 7.91 (d, *J* = 8.2 Hz, 1H), 7.46−7.32 (m, 2H), 7.26 (dd, *J* = 8.8, 4.0 Hz, 1H), 6.48 (d, *J* = 16.0 Hz, 1H), 6.30 (s$_{br}$, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.85 (s, 3H), 3.10 (d, *J* = 5.1 Hz, 3H), 1.29 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 167.9 (C$_q$), 162.2 (C$_q$), 138.1 (C$_q$), 136.4 (C$_q$), 136.3 (CH), 124.6 (C$_q$), 124.5 (CH), 122.0 (CH), 121.4 (CH), 116.1 (CH), 111.3 (CH), 110.4 (C$_q$), 60.3 (CH$_2$), 31.3 (CH$_3$), 26.9 (CH$_3$), 14.3 (CH$_3$).

IR (ATR): $\tilde{\nu}$ = 3271, 2981, 1709, 1623, 1547, 1469, 1368, 1131, 977, 730 cm^{-1}.

MS (EI) *m/z* (relative intensity): 286 (40) [M$^+$], 228 (26), 219 (100), 200 (32), 184 (25), 111 (15).

HR-MS (EI) *m/z* calcd for C$_{16}$H$_{18}$N$_2$O$_3^+$ 286.1317, found 286.1321.

Synthesis of (*E*)-ethyl 3-{2-(methylcarbamoyl)benzofuran-3-yl}acrylate (215da)
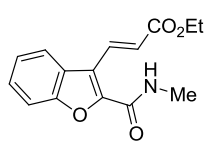
The general procedure **D** was followed using benzofurane **214d** (87.5 mg, 0.50 mmol), ethyl acrylate (**76a**) (75 mg, 0.75 mmol), [RuCl$_2$(*p*-cymene)]$_2$ (15.3 mg, 5.0 mol %) and KPF$_6$ (18.4 mg, 20 mol %) in H$_2$O (2.0 mL). After 20 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 2/1) yielded **215da** as a white solid (49 mg, 36%).

The general procedure **D** was followed using benzofurane **214d** (87.5 mg, 0.50 mmol), ethyl acrylate (**76a**) (75 mg, 0.75 mmol), [RuCl$_2$(*p*-cymene)]$_2$ (15.3 mg, 5.0 mol %) and KPF$_6$ (18.4 mg, 20 mol %) in *t*-AmOH (2.0 mL). After 20 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 2/1) yielded **215da** as a white solid (87 mg, 64%).

M.p. = 141−138 ℃.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 8.66 (d, *J* = 16.0 Hz, 1H), 7.88 (d, *J* = 7.9 Hz, 1H), 7.52−7.30 (m, 3H), 6.86 (s$_{br}$, 1H), 6.69 (d, *J* = 16.0 Hz, 1H), 4.28 (q, *J* = 7.1 Hz, 2H), 3.04 (d, *J* = 5.1 Hz, 3H), 1.34 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 166.5 (C$_q$), 159.6 (C$_q$), 153.5 (C$_q$), 145.5 (C$_q$), 124.8 (CH), 127.4 (CH), 125.7 (C$_q$), 124.4 (CH), 122.7 (CH), 122.3 (CH), 120.1 (C$_q$), 111.9 (CH), 60.6 (CH$_2$), 26.0 (CH$_3$), 14.3 (CH$_3$).

IR (ATR): $\tilde{v}$ = 3308, 1714, 1649, 1569, 1523, 1269, 1170, 1146, 743, 692 cm^{-1}.

MS (EI) *m/z* (relative intensity): 273 (5) [M$^+$], 200 (100), 187 (9), 111 (10).

HR-MS (EI) *m/z* calcd for C$_{15}$H$_{15}$NO$_4$$^+$ 273.1001, found 273.0997.

Synthesis of (*E*)-ethyl 3-{2-(methylcarbamoyl)thiophen-3-yl}acrylate (215ea)

The general procedure **D** was followed using thiophene **214e** (70.5 mg, 0.50 mmol), ethyl acrylate (**76a**) (75 mg, 0.75 mmol), [RuCl$_2$(*p*-cymene)]$_2$ (15.3 mg, 5.0 mol %) and KPF$_6$ (18.4 mg, 20 mol %). After 20 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 1/1) yielded **215ea** (92 mg, 76%) as a white solid.

M.p. = 92−93 °C.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 8.25 (d, *J* = 16.0 Hz, 1H), 7.31 (dd, *J* = 6.1, 5.4 Hz, 1H), 7.29 (dd, *J* = 6.1, 5.4 Hz, 1H), 6.32 (d, *J* = 16.0 Hz, 1H), 5.94 (s$_{br}$, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 3.00 (d, *J* = 4.9 Hz, 3H), 1.32 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 166.7 (C$_q$), 162.2 (C$_q$), 138.4 (C$_q$), 136.4 (CH), 136.0 (C$_q$), 127.0 (CH), 126.7 (CH), 121.4 (CH), 60.6 (CH$_2$), 27.0 (CH$_3$), 14.3 (CH$_3$).

IR (ATR): $\tilde{v}$ = 3266, 2976, 1707, 1624, 1539, 1247, 1119, 1036, 981, 613 cm^{-1}.

MS (EI) *m/z* (relative intensity): 239 (25) [M$^+$], 166 (76), 152 (100), 137 (23), 125 (22), 97 (25).

HR-MS (EI) *m/z* calcd for C$_{11}$H$_{13}$NO$_3$S$^+$ 239.0616, found 239.0615.

Synthesis of (*E*)-(*n*)-butyl 3-{2-(methylcarbamoyl)thiophen-3-yl}acrylate (215eb)

The general procedure **D** was followed using thiophene **214e** (70.5 mg, 0.50 mmol), *n*-butyl acrylate (**76b**) (96 mg, 0.75 mmol), [RuCl$_2$(*p*-cymene)]$_2$ (15.3 mg, 5.0 mol %) and KPF$_6$ (18.4 mg, 20 mol %). After 20 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 2/1) yielded **215eb** (96 mg, 72%) as a white solid.

M.p. = 93−94 °C.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 8.18 (d, *J* = 16.1 Hz, 1H), 7.26 (d, *J* = 5.2 Hz, 1H), 7.22 (d, *J* =

5.2 Hz, 1H), 6.25 (d, J = 16.1 Hz, 1H), 6.20 (s$_{br}$, 1H), 4.14 (q, J = 6.4 Hz, 2H), 2.93 (d, J = 5.0 Hz, 1H), 1.69−1.57 (m, 2H), 1.44−1.29 (m, 2H), 0.90 (t, J = 7.3 Hz, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 166.8 (C$_q$), 162.6 (C$_q$), 138.2 (C$_q$), 136.4 (CH), 126.9 (CH), 126.5 (CH), 121.0 (CH), 109.1 (C$_q$), 64.3 (CH$_2$), 30.7 (CH$_2$), 26.9 (CH$_3$), 18.8 (CH$_2$), 13.7 (CH$_3$).

IR (ATR): $\tilde{v}$ = 3272, 2952, 1706, 1625, 1541, 1270, 1227, 1066, 987, 737 cm^{-1}.

MS (EI) m/z (relative intensity): 267 (25) [M$^+$], 208 (10), 166 (100), 152 (16).

HR-MS (EI) m/z calcd for C$_{13}$H$_{17}$NO$_3$S$^+$ 267.0929, found 267.0922.

Intramolecular competition experiments with amide 214f (Scheme 81)

A mixture of thiophene **214f** (70.5 mg, 0.50 mmol), ethyl acrylate (**76a**) (75 mg, 0.75 mmol), [RuCl$_2$(p-cymene)]$_2$ (15.3 mg, 5.0 mol %), KPF$_6$ (18.4 mg, 20 mol %) and Cu(OAc)$_2$ H$_2$O (99.5 mg, 1.00 mmol) in H$_2$O (2.0 mL) was stirred under N$_2$ for 20 h at 120 ℃. At ambient temperature, the mixture was diluted with H$_2$O (75 mL) and extracted with EtOAc (3 × 75 mL). The combined organic phase was washed with brine (50 mL) and dried over anhydrous Na$_2$SO$_4$. After filtration and evaporation of the solvents under reduced pressure, the crude product was purified by column chromatography on silica gel (n-hexane/EtOAc: 1/1) to yield a mixture of **215fa** and **215'fa** (59 mg, 49%, 12:1 mixture of regioisomers according to ^{1}H-NMR) as a white solid. Recrystallization (n-hexane/CH$_2$Cl$_2$: 2/1) gave the major regioisomer **215fa** (44 mg, 37%) as a white solid.

(E)-Ethyl 3-{3-(methylcarbamoyl)thiophen-2-yl}acrylate (215fa)

M.p. = 128−129 °C.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 8.32 (d, J = 15.9 Hz, 1H), 7.25 (d, J = 5.1 Hz, 1H), 7.14 (d, J = 5.1 Hz, 1H), 6.26 (d, J = 15.9 Hz, 1H), 6.03 (s$_{br}$, 1H), 4.21 (q, J = 7.1 Hz, 2H), 2.96 (d, J = 4.5 Hz, 3H), 1.29 (t, J = 7.1 Hz, 3H).

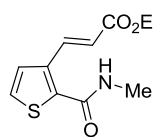^{13}C-NMR (75 MHz, CDCl$_3$): δ = 166.2 (C$_q$), 164.3 (C$_q$), 141.0 (C$_q$), 137.3 (C$_q$), 135.4 (CH), 127.6 (CH), 126.9 (CH), 120.0 (CH), 60.6 (CH$_2$), 26.7 (CH$_3$), 14.3 (CH$_3$).

IR (ATR): $\tilde{v}$ = 3381, 3103, 1712, 1626, 1549, 1436, 1296, 1252, 982, 719 cm^{-1}.

MS (EI) m/z (relative intensity): 239 (13) [M$^+$], 166 (100), 152 (20), 137 (20) 109 (10).

HR-MS (EI) m/z calcd for C$_{11}$H$_{13}$NO$_3$S$^+$ 239.0616, found 239.0611.

8.4.4 Analytical Data for the Products of Ruthenium-Catalyzed C(sp^3)−H α-Alkylation of Pyrrolidine 209 with Alkene 111

Synthesis of 2-(2-n-decylpyrrolidin-1-yl)-3-methylpyridine (217ba)

The general procedure **E** was followed using 3-methyl-2-(pyrrolidin-1-yl)pyridine (**216b**) (243 mg, 1.5 mmol) and 1-decene (**111a**) (70.1 mg, 0.5 mmol). After 18 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 40/1→30/1) yielded **217ba** (138 mg, 94%) as a colorless oil.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 8.06 (dd, J = 5.0, 2.0 Hz, 1H), 7.30–7.27 (m, 1H), 6.65 (dd, J = 7.1, 5.0 Hz, 1H), 4.28–4.20 (m, 1H), 3.70–3.62 (m, 1H), 3.23–3.11 (m, 1H), 2.23 (s, 3H), 2.19–2.09 (m, 1H), 1.95–1.54 (m, 4H), 1.29–1.17 (m, 17H), 0.89–0.85 (m, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 159.6 (C$_q$), 144.6 (CH), 139.1 (CH), 121.9 (C$_q$), 114.6 (CH), 58.2 (CH), 51.7 (CH$_2$), 34.2 (CH$_2$), 31.9 (CH$_2$), 31.2 (CH$_2$), 29.9 (CH$_2$), 29.6 (CH$_2$), 29.6 (CH$_2$),

29.6 (CH$_2$), 29.3 (CH$_2$), 25.9 (CH$_2$), 24.9 (CH$_2$), 22.7 (CH$_2$), 20.1 (CH$_3$), 14.1 (CH$_3$).

IR (ATR): $\tilde{v}$ = 2922, 2853, 1588, 1564, 1384, 1346, 1186, 993, 775 cm^{-1}.

MS (EI) m/z (relative intensity): 302 (5) [M$^+$], 287 (3), 208 (5), 161 (100), 133 (10), 107 (9), 92 (14), 43 (10).

HR-MS (EI) m/z calcd for C$_{20}$H$_{34}$N$_2^+$ 302.2722, found 302.2724.

Synthesis of 2-(2-*n*-decylpyrrolidin-1-yl)-3-(trifluoromethyl)pyridine (217ca)

The general procedure **E** was followed using 2-(pyrrolidin-1-yl)-3-(trifluoromethyl)pyridine (**216c**) (324 mg, 1.5 mmol) and 1-decene (**2a**) (70.1 mg, 0.5 mmol). After 18 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 100/1) yielded **217ca** (128 mg, 72%) as a colorless oil.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 8.25 (dd, J = 4.9, 1.8 Hz, 1H), 7.75 (d, J = 7.4 Hz, 1H), 6.61 (dd, J = 7.4, 4.9 Hz, 1H), 4.47−4.36 (m, 1H), 3.65−3.53 (m, 1H), 3.41−3.31 (m, 1H), 2.14−2.04 (m, 1H), 1.97−1.87 (m, 1H), 1.82−1.56 (m, 3H), 1.35−1.16 (m, 17H), 0.85 (t, J = 6.6 Hz, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 155.7 (C$_q$), 150.4 (CH), 137.0 (q, $^3J_{C-F}$ = 6 Hz, CH), 124.6 (q, $^1J_{C-F}$ = 272 Hz, C$_q$), 111.8 (CH), 110.7 (q, $^2J_{C-F}$ = 32 Hz, C$_q$), 58.9 (CH), 51.6 (q, J_{C-F} = 5 Hz, CH$_2$), 33.6 (CH$_2$), 31.9 (CH$_2$), 30.5 (CH$_2$), 29.8 (CH$_2$), 29.6 (CH$_2$), 29.6 (CH$_2$), 29.6 (CH$_2$), 29.3 (CH$_2$), 25.6 (CH$_2$), 25.5 (CH$_2$), 22.7 (CH$_2$), 14.1 (CH$_3$).

^{19}F-NMR (283 MHz, CDCl$_3$): δ = −56.6 (s).

IR (ATR): $\tilde{v}$ = 2923, 2854, 1596, 1556, 1449, 1369, 1302, 1097, 1019, 767 cm^{-1}.

MS (EI) m/z (relative intensity): 356 (4) [M$^+$], 213 (100), 175 (4), 146 (5).

HR-MS (EI) m/z calcd for C$_{20}$H$_{31}$F$_3$N$_2^+$ 356.2439, found 356.2432.

Synthesis of 3-methyl-2-(2-*n*-nonylpyrrolidin-1-yl)pyridine (217da)

The general procedure **E** was followed using 4-methyl-2-(pyrrolidin-1-yl)pyridine (**216d**) (243 mg, 1.5 mmol) and 1-decene (**111a**) (70.1 mg, 0.5 mmol). After 18 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 20/1→10/1) yielded **217da** (97 mg, 64%) as a colorless oil.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.99 (d, J = 5.2 Hz, 1H), 6.32 (dd, J = 5.2, 1.2 Hz, 1H), 6.12 (s, 1H), 3.93−3.82 (m, 1H), 3.56−3.46 (m, 1H), 3.41−3.29 (m, 1H), 2.22 (s, 3H), 2.04−1.65 (m, 5H), 1.38−1.12 (m, 17H), 0.86 (t, J = 6.6 Hz, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 157.4 (C$_q$), 147.9 (CH), 147.4 (C$_q$), 112.5 (CH), 106.8 (CH), 57.6 (CH), 47.4 (CH$_2$), 33.0 (CH$_2$), 31.9 (CH$_2$), 30.1 (CH$_2$), 29.8 (CH$_2$), 29.7 (CH$_2$), 29.6 (CH$_2$), 29.6 (CH$_2$), 29.3 (CH$_2$), 26.4 (CH$_2$), 23.4 (CH$_2$), 22.7 (CH$_2$), 21.3 (CH$_3$), 14.1 (CH$_3$).

IR (ATR): $\tilde{v}$ = 2921, 2852, 1708, 1604, 1553, 1453, 1297, 1176, 792, 447 cm^{-1}.

MS (EI) m/z (relative intensity): 302 (5) [M$^+$], 161 (100), 133 (7), 92 (9), 41 (7).

HR-MS (EI) m/z calcd for C$_{20}$H$_{34}$N$_2^+$ 302.2722, found 302.2722.

Synthesis of 2-(2-*n*-decylpyrrolidin-1-yl)-5-fluoropyridine (217ea)

The general procedure **E** was followed using 5-fluoro-2-(pyrrolidin-1-yl)pyridine (**216e**) (249 mg, 1.5 mmol) and 1-decene (**111a**) (70.1 mg, 0.5 mmol). After 18 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 40/1) yielded **217ea** (116 mg,

76%) as a colorless oil.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.99 (d, J = 3.0 Hz, 1H), 7.17 (ddd, J = 8.8, 3.0, 1.1 Hz, 1H), 6.24 (dd, J = 8.8, 3.0 Hz, 1H), 3.87−3.78 (m, 1H), 3.52−3.43 (m, 1H), 3.35−3.25 (m, 1H), 2.04−1.65 (m, 5H), 1.34−1.16 (m, 17H), 0.86 (t, J = 6.6 Hz, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 154.1 (C$_q$), 152.4 (d, $^{1}J_{C-F}$ = 240 Hz, C$_q$), 134.6 (d, $^{2}J_{C-F}$ = 24 Hz, CH), 124.6 (d, $^{2}J_{C-F}$ = 20 Hz, CH), 106.4 (d, $^{3}J_{C-F}$ = 4 Hz, CH), 58.2 (CH), 47.4 (CH$_2$), 33.1 (CH$_2$), 31.9 (CH$_2$), 30.2 (CH$_2$), 29.8 (CH$_2$), 29.7 (CH$_2$), 29.6 (CH$_2$), 29.6 (CH$_2$), 29.3 (CH$_2$), 26.5 (CH$_2$), 23.5 (CH$_2$), 22.7 (CH$_2$), 14.1 (CH$_3$).

^{19}F−NMR (283 MHz, CDCl$_3$): δ = −(146.91−146.95) (m).

IR (ATR): $\tilde{v}$ = 2922, 2852, 1613, 1492, 1407, 1224, 762 cm^{-1}.

MS (EI) m/z (relative intensity): 306 (22) [M$^+$], 305 (100) [(M−H)$^+$], 165 (18).

HR-MS (EI) m/z calcd for C$_{19}$H$_{31}$FN$_2$$^+$ 306.2471, found 306.2387.
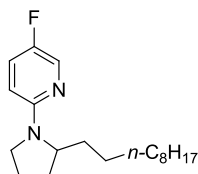
Synthesis of 1-(2-*n*-decylpyrrolidin-1-yl)isoquinoline (217ga)
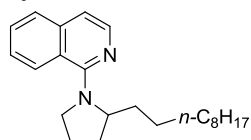
The general procedure **E** was followed using 1-(pyrrolidin-1-yl)isoquinoline (**216g**) (297 mg, 1.5 mmol) and 1-decene (**111a**) (70.1 mg, 0.5 mmol). After 18 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 40/1) yielded **217ga** (113 mg, 67%) as a colorless oil.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 8.10 (d, J = 8.6 Hz, 1H), 8.03 (d, J = 5.7 Hz, 1H), 7.65 (d, J = 8.2 Hz, 1H), 7.52 (ddd, J = 8.2, 8.2, 1.2 Hz, 1H), 7.38 (ddd, J = 8.6, 8.2, 1.2 Hz, 1H), 7.01 (d, J = 5.7 Hz, 1H), 4.61−4.50 (m, 1H), 4.02−3.92 (m, 1H), 3.65−3.56 (m, 1H), 2.26−2.13 (m, 1H), 1.99−1.81 (m, 2H), 1.81−1.61 (m, 2H), 1.43−1.16 (m, 17H), 0.87 (t, J = 6.7 Hz, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 158.8 (C$_q$), 140.9 (CH), 138.6 (C$_q$), 129.0 (CH), 126.5 (CH), 126.3 (CH), 124.4 (CH), 121.4 (C$_q$), 112.4 (CH), 58.9 (CH), 54.8 (CH$_2$), 34.0 (CH$_2$), 31.9 (CH$_2$), 31.2 (CH$_2$), 29.9 (CH$_2$), 29.6 (CH$_2$), 29.6 (CH$_2$), 29.6 (CH$_2$), 29.3 (CH$_2$), 25.9 (CH$_2$), 25.9 (CH$_2$), 22.7 (CH$_2$), 14.1 (CH$_3$).

IR (ATR): $\tilde{v}$ = 2921, 2852, 1585, 1551, 1503, 1408, 1346, 761, 743, 681 cm^{-1}.

MS (EI) m/z (relative intensity): 338 (14) [M$^+$], 255 (7), 225 (6), 197 (100), 183 (15), 169 (22), 143 (33), 128 (27).

HR-MS (EI) m/z calcd for C$_{23}$H$_{34}$N$_2$$^+$ 338.2722, found 338.2730.

Synthesis of 2-(2-*n*-hexylpyrrolidin-1-yl)-3-methylpyridine (217bb)

The general procedure **E** was followed using 3-methyl-2-(pyrrolidin-1-yl)pyridine (**216b**) (243 mg, 1.5 mmol) and 1-hexene (**111b**) (38.0 mg, 0.5 mmol) at 80 ℃. After 18 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 40/1) yielded **217bb** (90 mg, 73%) as a colorless oil.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 8.04 (dd, J = 5.0, 1.8 Hz, 1H), 7.26 (dd, J = 7.4, 1.8 Hz, 1H), 6.62 (dd, J = 7.4, 5.0 Hz, 1H), 4.29−4.16 (m, 1H), 3.70−3.58 (m, 1H), 3.21−3.09 (m, 1H), 2.20 (s, 3H), 2.17−2.05 (m, 1H), 1.93−1.52 (m, 4H), 1.29−1.14 (m, 9H), 0.83 (t, J = 6.3 Hz, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 159.7 (C$_q$), 144.7 (CH), 138.9 (CH), 121.9 (C$_q$), 114.7 (CH), 58.1 (CH), 51.7 (CH$_2$), 34.3 (CH$_2$), 31.9 (CH$_2$), 31.2 (CH$_2$), 29.6 (CH$_2$), 25.9 (CH$_2$), 24.9 (CH$_2$), 22.6 (CH$_2$), 20.0 (CH$_3$), 14.1 (CH$_3$).

IR (ATR): $\tilde{v}$ = 2922, 2856, 1588, 1563, 1383, 1345, 975, 774 cm^{-1}. MS (EI) m/z (relative

intensity): 246 (7) [M$^+$], 161 (100), 154 (8), 133 (12), 92 (17).

HR-MS (EI) *m/z* calcd for C$_{16}$H$_{26}$N$_2^+$ 246.2076, found 226.2068.

Synthesis of 2-(2-*n*-heptylpyrrolidin-1-yl)-3-methylpyridine (217bc)

The general procedure **E** was followed using 3-methyl-2-(pyrrolidin-1-yl)pyridine (**216b**) (243 mg, 1.5 mmol) and 1-heptene (**111c**) (49.0 mg, 0.5 mmol) at 80 °C. After 18 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 40/1) yielded **217bc** (103 mg, 78%) as a colorless oil.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 8.04 (dd, *J* = 4.9, 1.8 Hz, 1H), 7.26 (dd, *J* = 7.4, 1.8 Hz, 1H), 6.62 (dd, *J* = 7.4, 4.9 Hz, 1H), 4.28−4.15 (m, 1H), 3.70−3.57 (m, 1H), 3.21−3.09 (m, 1H), 2.21 (s, 3H), 2.17−2.05 (m, 1H), 1.95−1.52 (m, 5H), 1.35−1.11 (m, 10H), 0.84 (t, *J* = 6.1 Hz, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 159.7 (C$_q$), 144.7 (CH), 138.9 (CH), 121.8 (C$_q$), 114.7 (CH), 58.1 (CH), 51.7 (CH$_2$), 34.2 (CH$_2$), 31.8 (CH$_2$), 31.2 (CH$_2$), 29.8 (CH$_2$), 29.3 (CH$_2$), 25.9 (CH$_2$), 24.9 (CH$_2$), 22.6 (CH$_2$), 20.0 (CH$_3$), 14.1 (CH$_3$).

IR (ATR): $\tilde{v}$ = 2922, 2854, 1588, 1564, 1383, 1346, 774 cm^{-1}.

MS (EI) *m/z* (relative intensity): 260 (5) [M$^+$], 168 (5), 161 (100), 133 (10), 92 (16).

HR-MS (EI) *m/z* calcd for C$_{17}$H$_{28}$N$_2^+$ 260.2252, found 260.2244.

Synthesis of 3-methyl-2-(2-*n*-octylpyrrolidin-1-yl)pyridine (217bd)

The general procedure **E** was followed using 3-methyl-2-(pyrrolidin-1-yl)pyridine (**216b**) (243 mg, 1.5 mmol) and 1-octene (**111d**) (56.1 mg, 0.5 mmol). After 18 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 40/1→30/1) yielded **217bd** (123 mg, 90%) as a colorless oil.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 8.04 (dd, *J* = 4.9, 1.8 Hz, 1H), 7.26 (dd, *J* = 7.4, 1.8 Hz, 1H), 6.62 (dd, *J* = 7.4, 4.9 Hz, 1H), 4.28−4.16 (m, 1H), 3.69−3.58 (m, 1H), 3.20−3.10 (m, 1H), 2.20 (s, 3H), 2.17−2.06 (m, 1H), 1.95−1.50 (m, 5H), 1.34−1.11 (m, 12H), 0.84 (t, *J* = 6.1 Hz, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 159.7 (C$_q$), 144.7 (CH), 138.9 (CH), 121.8 (C$_q$), 114.7 (CH), 58.1 (CH), 51.7 (CH$_2$), 34.2 (CH$_2$), 31.9 (CH$_2$), 31.2 (CH$_2$), 29.9 (CH$_2$), 29.6 (CH$_2$), 29.2 (CH$_2$), 25.9 (CH$_2$), 24.9 (CH$_2$), 22.6 (CH$_2$), 20.0 (CH$_3$), 14.1 (CH$_3$).

IR (ATR): $\tilde{v}$ = 2921, 2853, 1588, 1383, 1346, 775 cm^{-1}.

MS (EI) *m/z* (relative intensity): 274 (5) [M$^+$], 182 (6), 161 (100), 133 (7), 84 (17).

HR-MS (EI) *m/z* calcd for C$_{18}$H$_{30}$N$_2^+$ 274.2409, found 274.2405.

Synthesis of 3-methyl-2-(2-*n*-nonylpyrrolidin-1-yl)pyridine (217be)

The general procedure **E** was followed using 3-methyl-2-(pyrrolidin-1-yl)pyridine (**216b**) (243 mg, 1.5 mmol) and 1-nonene (**111e**) (63.0 mg, 0.5 mmol). After 18 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 40/1→30/1) yielded **217be** (129 mg, 89%) as a colorless oil.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 8.04 (dd, *J* = 4.9, 1.8 Hz, 1H), 7.26 (dd, *J* = 7.4, 1.8 Hz, 1H), 6.62 (dd, *J* = 7.4, 4.9 Hz, 1H), 4.28−4.15 (m, 1H), 3.69−3.58 (m, 1H), 3.20−3.10 (m, 1H), 2.21 (s, 3H), 2.17−2.06 (m, 1H), 1.95−1.51 (m, 5H), 1.32−1.12 (m, 14H), 0.85 (t, *J* = 6.1 Hz, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 159.7 (C$_q$), 144.7 (CH), 139.0 (CH), 121.9 (C$_q$), 114.7 (CH),

58.2 (CH), 51.7 (CH$_2$), 34.2 (CH$_2$), 31.9 (CH$_2$), 31.2 (CH$_2$), 29.9 (CH$_2$), 29.6 (CH$_2$), 29.6 (CH$_2$), 29.3 (CH$_2$), 25.9 (CH$_2$), 24.9 (CH$_2$), 22.7 (CH$_2$), 20.0 (CH$_3$), 14.1 (CH$_3$).

IR (ATR): $\tilde{\nu}$ = 2921, 2853, 1588, 1564, 1383, 1345, 775 cm^{-1}.

MS (EI) *m/z* (relative intensity): 288 (5) [M$^+$], 196 (5), 161 (100), 133 (7), 92 (7).

HR-MS (EI) *m/z* calcd for C$_{19}$H$_{32}$N$_2$$^+$ 288.2565, found 288.2562.

Synthesis of 3-methyl-2-(2-*n*-pentadecylpyrrolidin-1-yl)pyridine (217bf)
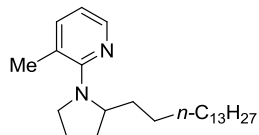
The general procedure **E** was followed using 3-methyl-2-(pyrrolidin-1-yl)pyridine (**216b**) (243 mg, 1.5 mmol) and 1-pentadecene (**111f**) (105 mg, 0.5 mmol). After 18 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 30/1) yielded **217bf** (159 mg, 85%) as a colorless oil.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 8.04 (dd, *J* = 4.9, 2.0 Hz, 1H), 7.26 (dd, *J* = 7.4, 2.0 Hz, 1H), 6.62 (dd, *J* = 7.4, 4.9 Hz, 1H), 4.27−4.16 (m, 1H), 3.69−3.59 (m, 1H), 3.20−3.11 (m, 1H), 2.21 (s, 3H), 2.17−2.06 (m, 1H), 1.95−1.51 (m, 5H), 1.35−1.10 (m, 26H), 0.86 (t, *J* = 6.6 Hz, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 159.6 (C$_q$), 144.6 (CH), 138.9 (CH), 121.8 (C$_q$), 114.6 (CH), 58.2 (CH), 51.7 (CH$_2$), 34.3 (CH$_2$), 32.0 (CH$_2$), 31.3 (CH$_2$), 30.0 (CH$_2$), 29.8 (CH$_2$), 29.8 (CH$_2$), 29.8 (CH$_2$), 29.8 (CH$_2$), 29.7 (CH$_2$), 29.7 (CH$_2$), 29.7 (CH$_2$), 29.7 (CH$_2$), 29.4 (CH$_2$), 26.0 (CH$_2$), 25.0 (CH$_2$), 22.8 (CH$_2$), 20.1 (CH$_3$), 14.2 (CH$_3$).

IR (ATR): $\tilde{\nu}$ = 2920, 2851, 1588, 1384, 1346, 1186, 992, 775 cm^{-1}.

MS (EI) *m/z* (relative intensity): 372 (4) [M$^+$], 276 (6), 161 (100), 133 (7), 107 (7), 92 (8).

HR-MS (EI) *m/z* calcd for C$_{25}$H$_{44}$N$_2$$^+$ 372.3504.0572, found 372.3510.

Synthesis of 2-(2-*n*-hexadecylpyrrolidin-1-yl)-3-methylpyridine (217bg)

The general procedure **E** was followed using 3-methyl-2-(pyrrolidin-1-yl)pyridine (**216b**) (243 mg, 1.5 mmol) and 1-hexadecene (**111g**) (112 mg, 0.5 mmol). After 18 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 40/1) yielded **217bg** (168 mg, 87%) as a colorless oil.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 8.04 (dd, *J* = 4.9, 1.9 Hz, 1H), 7.26 (dd, *J* = 7.4, 1.9 Hz, 1H), 6.62 (dd, *J* = 7.4, 4.9 Hz, 1H), 4.27−4.16 (m, 1H), 3.68−3.58 (m, 1H), 3.20−3.11 (m, 1H), 2.21 (s, 3H), 2.17−2.06 (m, 1H), 1.98−1.50 (m, 5H), 1.30−1.15 (m, 28H), 0.86 (t, *J* = 6.6 Hz, 3H).
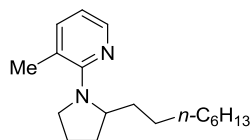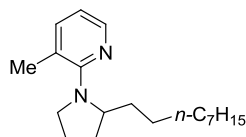
^{13}C-NMR (75 MHz, CDCl$_3$): δ = 159.7 (C$_q$), 144.7 (CH), 139.0 (CH), 121.9 (C$_q$), 114.7 (CH), 58.2 (CH), 51.7 (CH$_2$), 34.3 (CH$_2$), 31.9 (CH$_2$), 31.2 (CH$_2$), 29.9 (CH$_2$), 29.7 (CH$_2$), 29.7 (CH$_2$), 29.7 (CH$_2$), 29.7 (CH$_2$), 29.7 (CH$_2$), 29.7 (CH$_2$), 29.7 (CH$_2$), 29.6 (CH$_2$), 29.4 (CH$_2$), 25.9 (CH$_2$), 24.9 (CH$_2$), 22.7 (CH$_2$), 20.0 (CH$_3$), 14.1 (CH$_3$).

IR (ATR): $\tilde{\nu}$ = 2920, 2851, 1588, 1384, 1346, 992, 775 cm^{-1}.

MS (EI) *m/z* (relative intensity): 386 (5) [M$^+$], 371 (4), 294 (7), 161 (100), 133 (7), 107 (8), 92 (7).

HR-MS (EI) *m/z* calcd for C$_{26}$H$_{46}$N$_2$$^+$ 386.3661, found 386.3662.
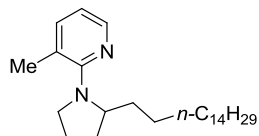
Synthesis of 2-{2-(3,3-dimethylbutyl)pyrrolidin-1-yl}-3-methylpyridine (217bh)
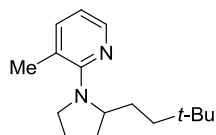
The general procedure **E** was followed using 3-methyl-2-(pyrrolidin-1-yl)pyridine (**216b**) (81.0 mg, 0.5 mmol) and 3,3-dimethyl-1-butene (**111h**) (63.1 mg, 1.5 mmol) at 80 ℃. After 18 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 30/1)

yielded **217bh** (62 mg, 50%) as a colorless oil.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 8.04 (dd, J = 5.0, 1.9 Hz, 1H), 7.26 (dd, J = 7.2, 1.9 Hz, 1H), 6.62 (dd, J = 7.2, 5.0 Hz, 1H), 4.22−4.12 (m, 1H), 3.69−3.59 (m, 1H), 3.22−3.13 (m, 1H), 2.21 (s, 3H), 2.16−2.06 (m, 1H), 1.91−1.53 (m, 4H), 1.20−1.07 (m, 3H), 0.78 (s, 9H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 159.5 (C$_q$), 144.7 (CH), 139.0 (CH), 121.7 (C$_q$), 114.6 (CH), 58.6 (CH), 51.7 (CH$_2$), 39.8 (CH$_2$), 31.2 (CH$_2$), 30.1 (C$_q$), 29.3 (CH$_3$), 29.0 (CH$_2$), 24.9 (CH$_2$), 20.0 (CH$_3$).

IR (ATR): $\tilde{\nu}$ = 2951, 2864, 1588, 1383, 1343, 992, 775 cm^{-1}.

MS (EI) m/z (relative intensity): 246 (7) [M$^+$], 161 (100), 143 (5), 92 (5).

HR-MS (EI) m/z calcd for C$_{16}$H$_{26}$N$_2{}^+$ 246.2076, found 246.2078.

Synthesis of 3-methyl-2-{2-[2-(trimethylsilyl)ethyl]pyrrolidin-1-yl}pyridine (217bi)
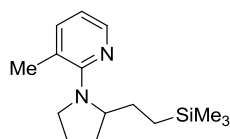
The general procedure **E** was followed using 3-methyl-2-(pyrrolidin-1-yl)pyridine (**216b**) (243 mg, 1.5 mmol) and trimethyl(vinyl)silane (**111i**) (50.1 mg, 0.5 mmol) at 80 ℃. After 18 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 40/1) yielded **217bi** (78 mg, 59%) as a colorless oil.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 8.03 (dd, J = 5.0, 1.9 Hz, 1H), 7.25 (dd, J = 7.2, 1.9 Hz, 1H), 6.62 (dd, J = 7.2, 5.0 Hz, 1H), 4.25−4.13 (m, 1H), 3.71−3.60 (m, 1H), 3.24−3.15 (m, 1H), 2.21 (s, 3H), 2.17−2.07 (m, 1H), 1.94−1.55 (m, 4H), 1.25−1.11 (m, 1H), 0.54−0.31 (m, 2H), −0.11 (s, 9H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 159.5 (C$_q$), 144.7 (CH), 139.0 (CH), 121.5 (C$_q$), 114.5 (CH), 60.4 (CH), 52.0 (CH$_2$), 30.7 (CH$_2$), 27.9 (CH$_2$), 24.8 (CH$_2$), 20.1 (CH$_3$), 12.1 (CH$_2$), −1.8 (CH$_3$).

IR (ATR): $\tilde{\nu}$ = 2952, 2870, 1588, 1384, 1348, 1245, 1186, 832, 774, 691 cm^{-1}.

MS (EI) m/z (relative intensity): 262 (6) [M$^+$], 261 (10) [(M−H)$^+$], 161 (100), 92 (18), 73 (20).

HR-MS (ESI) m/z calcd for [(C$_{15}$H$_{26}$N$_2$Si)H]$^+$ 263.1938, found 263.1940.

Synthesis of 3-methyl-2-{2-[2-(triethylsilyl)ethyl]pyrrolidin-1-yl}pyridine (217bj)
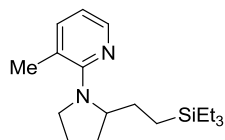
The general procedure **E** was followed using 3-methyl-2-(pyrrolidin-1-yl)pyridine (**216b**) (243 mg, 1.5 mmol) and triethyl(vinyl)silane (**111j**) (71.2 mg, 0.5 mmol). After 18 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 40/1) yielded **217bj** (131 mg, 86%) as a colorless oil.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 8.03 (dd, J = 4.9, 1.9 Hz, 1H), 7.24 (dd, J = 7.2, 1.9 Hz, 1H), 6.60 (dd, J = 7.2, 4.9 Hz, 1H), 4.25−4.13 (m, 1H), 3.71−3.60 (m, 1H), 3.25−3.15 (m, 1H), 2.20 (s, 3H), 2.18−2.08 (m, 1H), 1.94−1.53 (m, 4H), 1.27−1.14 (m, 1H), 0.84 (t, J = 7.4 Hz, 9H), 0.49−0.35 (m, 8H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 159.4 (C$_q$), 144.7 (CH), 138.9 (CH), 121.5 (C$_q$), 114.5 (CH), 60.6 (CH), 51.9 (CH$_2$), 30.6 (CH$_2$), 27.6 (CH$_2$), 24.8 (CH$_2$), 20.1 (CH$_3$), 7.3 (CH$_3$), 6.4 (CH$_2$), 3.2 (CH$_2$). IR (ATR): $\tilde{\nu}$ = 2950, 2872, 1588, 1385, 1347, 1186, 1014, 772, 725 cm^{-1}.

MS (EI) m/z (relative intensity): 304 (3) [M$^+$], 275 (4), 161 (100), 92 (5).

HR-MS (EI) m/z calcd for C$_{18}$H$_{32}$N$_2$Si$^+$ 304.2335, found 304.2299.

Synthesis of 2-{2-(10-methoxy-*n*-decyl)pyrrolidin-1-yl}-3-methylpyridine (**217bk**)
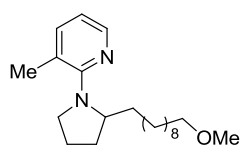
The general procedure **E** was followed using 3-methyl-2-(pyrrolidin-1-yl)pyridine (**216b**) (243 mg, 1.5 mmol) and 10-methoxy-1-decene (**111k**) (79.1 mg, 0.5 mmol) in DCE. After 18 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 30/1→20/1) yielded **217bk** (104 mg, 65%) as a colorless oil.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 8.03 (dd, J = 4.9, 2.0 Hz, 1H), 7.25 (dd, J = 7.4, 2.0 Hz, 1H), 6.62 (dd, J = 7.4, 4.9 Hz, 1H), 4.27−4.16 (m, 1H), 3.68−3.58 (m, 1H), 3.33 (t, J = 6.76 Hz, 2H), 3.30 (s, 3H), 3.19−3.10 (m, 1H), 2.20 (s, 3H), 2.17−2.06 (m, 1H), 1.94−1.46 (m, 6H), 1.32−1.15 (m, 15H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 159.7 (C$_q$), 144.6 (CH), 138.9 (CH), 121.8 (C$_q$), 114.7 (CH), 72.9 (CH$_2$), 58.5 (CH), 58.1 (CH$_3$), 51.7 (CH$_2$), 34.2 (CH$_2$), 31.2 (CH$_2$), 29.9 (CH$_2$), 29.6 (CH$_2$), 29.6 (CH$_2$), 29.5 (CH$_2$), 29.5 (CH$_2$), 29.4 (CH$_2$), 26.1 (CH$_2$), 25.9 (CH$_2$), 24.9 (CH$_2$), 20.0 (CH$_3$).

IR (ATR): $\tilde{\nu}$ = 2922, 2853, 1588, 1384, 1346, 1116, 992, 775 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 332 (5) [M$^+$], 240 (7), 161 (100), 133 (12), 92 (13).

HR-MS (ESI) *m/z* calcd for C$_{21}$H$_{26}$N$_2$O$^+$ 332.2828, found 332.2826.

Synthesis of 2-{2-(10-chloro-*n*-decyl)pyrrolidin-1-yl}-3-methylpyridine (**217bl**)
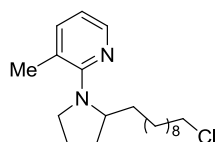
The general procedure **E** was followed using 3-methyl-2-(pyrrolidin-1-yl)pyridine (**216b**) (243 mg, 1.5 mmol) and 10-chloro-1-decene (**111l**) (87.3 mg, 0.5 mmol). After 18 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 30/1) yielded **217bl** (138 mg, 82%) as a colorless oil.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 8.04 (dd, J = 4.9, 1.9 Hz, 1H), 7.26 (dd, J = 7.4, 1.9 Hz, 1H), 6.62 (dd, J = 7.4, 4.9 Hz, 1H), 4.27−4.16 (m, 1H), 3.68−3.59 (m, 1H), 3.50 (t, J = 7.4 Hz, 2H), 3.19−3.10 (m, 1H), 2.21 (s, 3H), 2.17−2.06 (m, 1H), 1.93−1.54 (m, 6H), 1.44−1.14 (m, 15H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 159.7 (C$_q$), 144.7 (CH), 138.9 (CH), 121.8 (C$_q$), 114.7 (CH), 58.1 (CH), 51.7 (CH$_2$), 45.2 (CH$_2$), 34.2 (CH$_2$), 32.6 (CH$_2$), 31.2 (CH$_2$), 29.8 (CH$_2$), 29.5 (CH$_2$), 29.4 (CH$_2$), 29.4 (CH$_2$), 28.8 (CH$_2$), 26.8 (CH$_2$), 25.9 (CH$_2$), 24.9 (CH$_2$), 20.0 (CH$_3$).

IR (ATR): $\tilde{\nu}$ = 2923, 2853, 1588, 1383, 1346, 992, 776, 650 cm^{-1}.

MS (EI) *m/z* (relative intensity): 336 (4) [M$^+$], 244 (4), 161 (100), 133 (8), 92 (11).

HR-MS (EI) *m/z* calcd for C$_{20}$H$_{33}$ClN$_2^+$ 336.2332, found 336.2336.

Synthesis of 2-{2-(10-bromo-*n*-decyl)pyrrolidin-1-yl}-3-methylpyridine (**217bm**)
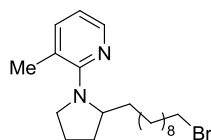
The general procedure **E** was followed using 3-methyl-2-(pyrrolidin-1-yl)pyridine (**216b**) (243 mg, 1.5 mmol) and 10-bromo-1-decene (**111m**) (110 mg, 0.5 mmol) in DCE. After 18 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 30/1) yielded **217bm** (114 mg, 60%) as a colorless oil.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 8.04 (dd, J = 4.9, 1.9 Hz, 1H), 7.25 (dd, J = 7.2, 1.9 Hz, 1H), 6.62 (dd, J = 7.2, 4.9 Hz, 1H), 4.28−4.17 (m, 1H), 3.69−3.58 (m, 1H), 3.50 (t, J = 7.2 Hz, 2H), 3.19−3.10 (m, 1H), 2.20 (s, 3H), 2.16−2.05 (m, 1H), 1.94−1.52 (m, 6H), 1.43−1.12 (m, 15H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 159.7 (C$_q$), 144.7 (CH), 138.9 (CH), 121.8 (C$_q$), 114.7 (CH), 58.1 (CH), 51.7 (CH$_2$), 45.1 (CH$_2$), 34.2 (CH$_2$), 32.6 (CH$_2$), 31.2 (CH$_2$), 29.8 (CH$_2$), 29.5 (CH$_2$), 29.4 (CH$_2$), 29.4 (CH$_2$), 28.8 (CH$_2$), 26.8 (CH$_2$), 25.9 (CH$_2$), 24.9 (CH$_2$), 20.0 (CH$_3$).

IR (ATR): $\tilde{v}$ = 2923, 2853, 1707, 1588, 1384, 1346, 992, 775, 650 cm^{-1}.

MS (ESI) m/z (relative intensity): 383 (100) [(M+H)$^+$] (^{81}Br), 381 (100) [(M+H)$^+$] (^{79}Br).

HR-MS (ESI) m/z calcd for [(C$_{20}$H$_{33}$BrN$_2$)H]$^+$ 381.1900, found 381.1897.

Synthesis of 2-{2-[4-(2-bromophenyl)butyl]pyrrolidin-1-yl}-3-methylpyridine (217bn)
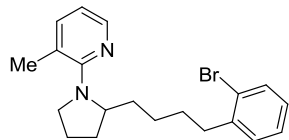
The general procedure **E** was followed using 3-methyl-2-(pyrrolidin-1-yl)pyridine (**216b**) (243 mg, 1.5 mmol) and 1-bromo-2-(but-3-en-1-yl)benzene (**111n**) (105 mg, 0.5 mmol). After 18 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 30/1) yielded **217bn** (152 mg, 82%) as a colorless oil.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 8.05 (dd, J = 4.9, 1.9 Hz, 1H), 7.48 (dd, J = 8.1, 1.1 Hz, 1H), 7.26 (dd, J = 7.4, 1.9 Hz, 1H), 7.21−7.11 (m, 2H), 7.00 (ddd, J = 7.4, 7.4, 2.6 Hz, 1H), 6.62 (dd, J = 7.4, 4.9 Hz, 1H), 4.34−4.23 (m, 1H), 3.70−3.60 (m, 1H), 3.19−3.10 (m, 1H), 3.50 (td, J = 7.4, 2.1 Hz, 2H), 2.21 (s, 3H), 2.18−2.07 (m, 1H), 1.96−1.83 (m, 1H), 1.82−1.67 (m, 2H), 1.65−1.49 (m, 3H), 1.46−1.21 (m, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 159.7 (C$_q$), 144.6 (CH), 138.0 (C$_q$), 139.0 (CH), 132.6 (CH), 130.2 (CH), 127.2 (CH), 127.2 (CH), 124.4 (C$_q$), 121.9 (C$_q$), 114.8 (CH), 58.0 (CH), 51.9 (CH$_2$), 36.0 (CH$_2$), 33.9 (CH$_2$), 31.1 (CH$_2$), 30.0 (CH$_2$), 25.6 (CH$_2$), 25.0 (CH$_2$), 20.0 (CH$_3$).

IR (ATR): $\tilde{v}$ = 2930, 2858, 1587, 1382, 1346, 1020, 776, 746 cm^{-1}.

MS (EI) m/z (relative intensity): 373 (100) [M$^+$] (^{81}Br), 371 (100) [M$^+$] (^{79}Br), 317 (6), 265 (13), 171 (35), 161 (40), 33 (22), 92 (17).

HR-MS (ESI) m/z calcd for [(C$_{20}$H$_{25}$BrN$_2$)H]$^+$ 373.1274, found 373.1274.

Synthesis of 3-methyl-2-(2-phenethylpyrrolidin-1-yl)pyridine (217bo)
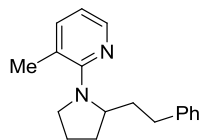
The general procedure **E** was followed using 3-methyl-2-(pyrrolidin-1-yl)pyridine (**216b**) (243 mg, 1.5 mmol) and styrene (**111o**) (52.1 mg, 0.5 mmol). After 18 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 25/1) yielded **217bo** (98 mg, 73%) as a colorless oil.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 8.06 (dd, J = 4.9, 1.9 Hz, 1H), 7.30−7.18 (m, 3H), 7.17−7.09 (m, 3H), 6.65 (dd, J = 7.2, 4.9 Hz, 1H), 4.41−4.31 (m, 1H), 3.73−3.64 (m, 1H), 3.22−3.14 (m, 1H), 2.68−2.56 (m, 2H), 2.25−2.14 (m, 1H), 2.19 (s, 3H), 2.06−1.90 (m, 2H), 1.84−1.54 (m, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 159.7 (C$_q$), 144.8 (CH), 138.8 (C$_q$), 139.1 (CH), 128.3 (CH), 128.2 (CH), 125.5 (CH), 122.1 (C$_q$), 111.0 (CH), 57.8 (CH), 51.7 (CH$_2$), 35.9 (CH$_2$), 32.2 (CH$_2$), 31.1 (CH$_2$), 24.9 (CH$_2$), 19.8 (CH$_3$).

IR (ATR): $\tilde{v}$ = 2956, 2862, 1587, 1382, 1346, 1186, 1099, 776, 696 cm^{-1}.

MS (EI) m/z (relative intensity): 266 (5) [M$^+$], 175 (26), 161 (100), 133 (7), 92 (17).

HR-MS (EI) m/z calcd for C$_{18}$H$_{22}$N$_2{}^+$ 266.1783, found 266.1792.

Synthesis of 2-{2-(4-methoxyphenethyl)pyrrolidin-1-yl}-3-methylpyridine (217bp)
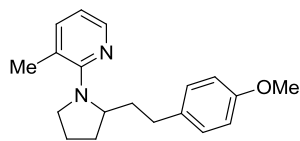
The general procedure **E** was followed using 3-methyl-2-(pyrrolidin-1-yl)pyridine (**216b**) (243 mg, 1.5 mmol) and 4-methoxystyrene (**111p**) (67.1 mg, 0.5 mmol). After 18 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 30/1→20/1) yielded **217bp** (104 mg, 70%) as a colorless oil.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 8.04 (dd, J = 5.0, 1.9 Hz, 1H), 7.26 (dd, J = 7.3, 1.9 Hz, 1H), 7.04 (d, J = 8.6 Hz, 2H), 6.76 (d, J = 8.6 Hz, 2H), 6.65 (dd, J = 7.3, 5.0 Hz, 1H), 4.38−4.26 (m, 1H), 3.75 (s, 3H), 3.70−3.61 (m, 1H), 3.20−3.12 (m, 1H), 2.61−2.47 (m, 2H), 2.24−2.11 (m, 1H), 2.18 (s, 3H), 2.01−1.49 (m, 5H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 159.6 (C$_q$), 157.5 (C$_q$), 144.7 (CH), 139.0 (CH), 134.8 (C$_q$), 129.1 (CH), 122.1 (C$_q$), 114.9 (CH), 113.6 (CH), 57.8 (CH), 55.2 (CH$_3$), 51.8 (CH$_2$), 36.2 (CH$_2$), 31.3 (CH$_2$), 31.2 (CH$_2$), 25.0 (CH$_2$), 19.9 (CH$_3$).

IR (ATR): $\tilde{\nu}$ = 2952, 2862, 1587, 1510, 1382, 1347, 1241, 1176, 1035, 820, 776 cm^{-1}.

MS (EI) m/z (relative intensity): 296 (10) [M$^+$], 281 (10), 175 (35), 161 (100), 133 (13), 121 (25), 92 (27).

HR-MS (EI) m/z calcd for C$_{19}$H$_{24}$N$_2$O$^+$ 296.1889, found 296.1887.

Synthesis of 2-{2-(4-bromophenethyl)pyrrolidin-1-yl}-3-methylpyridine (217bq)
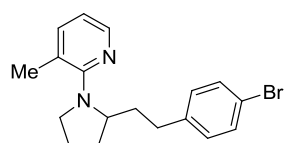
The general procedure **E** was followed using 3-methyl-2-(pyrrolidin-1-yl)pyridine (**216b**) (243 mg, 1.5 mmol) and 4-bromostyrene (**111q**) (91.5 mg, 0.5 mmol). After 18 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 30/1) yielded **217bq** (112 mg, 65%) as a colorless oil.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 8.05 (dd, J = 4.9, 1.9 Hz, 1H), 7.32 (d, J = 8.6 Hz, 2H), 7.26 (dd, J = 7.4, 1.9 Hz, 1H), 6.99 (d, J = 8.6 Hz, 2H), 6.65 (dd, J = 7.4, 4.9 Hz, 1H), 4.40−4.29 (m, 1H), 3.72−3.61 (m, 1H), 3.20−3.09 (m, 1H), 2.65−2.48 (m, 2H), 2.19 (s, 3H), 2.17−2.10 (m, 1H), 2.04−1.51 (m, 5H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 159.6 (C$_q$), 144.6 (CH), 141.6 (C$_q$), 139.0 (CH), 131.1 (CH), 130.0 (CH), 122.0 (C$_q$), 119.1 (C$_q$), 111.0 (CH), 57.7 (CH), 52.0 (CH$_2$), 35.7 (CH$_2$), 31.7 (CH$_2$), 31.1 (CH$_2$), 25.0 (CH$_2$), 19.8 (CH$_3$).

IR (ATR): $\tilde{\nu}$ = 2958, 2862, 1587, 1487, 1382, 1347, 1010, 776 cm^{-1}.

MS (EI) m/z (relative intensity): 346 (4) [M$^+$] (^{81}Br), 344 (4) [M$^+$] (^{79}Br), 175 (38), 161 (100), 147 (10), 133 (18), 92 (23).

HR-MS (EI) m/z calcd for C$_{18}$H$_{21}$BrN$_2$$^+$ 344.0888, found 344.0879.

Synthesis of 2-{2-(4-fluorophenethyl)pyrrolidin-1-yl}-3-methylpyridine (217br)
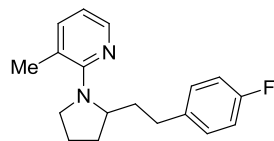
The general procedure **E** was followed using 3-methyl-2-(pyrrolidin-1-yl)pyridine (**216b**) (243 mg, 1.5 mmol) and 4-fluorostyrene (**111r**) (61.1 mg, 0.5 mmol). After 18 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 30/1→20/1) yielded **217br** (91 mg, 64%) as a colorless oil.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 8.05 (dd, J = 4.9, 1.9 Hz, 1H), 7.27 (dd, J = 7.3, 1.9 Hz, 1H), 7.07 (ddd, J = 8.7, 8.7, 2.3 Hz, 2H), 6.76 (dd, J = 8.7, 8.7 Hz, 2H), 6.65 (dd, J = 7.3, 4.9 Hz, 1H), 4.41−4.29 (m, 1H), 3.73−3.62 (m, 1H), 3.21−3.11 (m, 1H), 2.66−2.51 (m, 2H), 2.23−2.12 (m, 1H), 2.19 (s, 3H), 2.03−1.51 (m, 5H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 161.1 (d, $^1J_{C-F}$ = 243 Hz, C$_q$), 159.7 (C$_q$), 144.6 (CH), 139.0 (CH), 138.2 (d, $^4J_{C-F}$ = 3 Hz, C$_q$), 129.5 (d, $^3J_{C-F}$ = 8 Hz, CH), 122.0 (C$_q$), 111.0 (CH), 114.7 (d, $^2J_{C-F}$ = 21 Hz, CH), 57.7 (CH), 51.9 (CH$_2$), 36.0 (CH$_2$), 31.4 (CH$_2$), 31.1 (CH$_2$), 25.0 (CH$_2$), 19.8 (CH$_3$).

^{19}F-NMR (283 MHz, CDCl$_3$): δ = −(118.2−118.3) (m).

IR (ATR): $\tilde{v}$ = 2955, 2864, 1587, 1508, 1382, 1348, 1216, 822, 776 cm^{-1}.

MS (EI) m/z (relative intensity): 284 (5) [M$^+$], 175 (32), 161 (100), 133 (12), 109 (17), 92 (27).

HR-MS (EI) m/z calcd for C$_{18}$H$_{21}$FN$_2^+$ 284.1689, found 284.1692.

Synthesis of 3-methyl-2-{2-[2-(naphthalen-2-yl)ethyl]pyrrolidin-1-yl}pyridine (217bs)
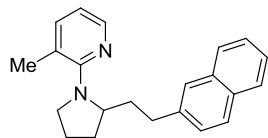
The general procedure **E** was followed using 3-methyl-2-(pyrrolidin-1-yl)pyridine (**216b**) (243 mg, 1.5 mmol) and 2-vinylnaphthalene (**111s**) (77.1 mg, 0.5 mmol). After 18 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 25/1) yielded **217bs** (91 mg, 57%) as a white solid.

M.p. = 93−94 ℃.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 8.09 (dd, J = 4.9, 2.0 Hz, 1H), 7.79−7.69 (m, 3H), 7.58 (s, 1H), 7.45−7.35 (m, 2H), 7.31−7.25 (m, 2H), 6.67 (dd, J = 7.4, 4.9 Hz, 1H), 4.48−4.36 (m, 1H), 3.75−3.65 (m, 1H), 3.23−3.14 (m, 1H), 2.87−2.72 (m, 2H), 2.27−2.07 (m, 2H), 2.20 (s, 3H), 2.00−1.64 (m, 4H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 159.7 (C$_q$), 144.7 (CH), 140.2 (C$_q$), 139.0 (CH), 133.6 (C$_q$), 131.8 (C$_q$), 127.6 (CH), 127.5 (CH), 127.4 (CH), 127.3 (CH), 126.0 (CH), 125.7 (CH), 124.9 (CH), 122.0 (C$_q$), 111.0 (CH), 57.9 (CH), 51.9 (CH$_2$), 35.7 (CH$_2$), 32.4 (CH$_2$), 31.2 (CH$_2$), 25.0 (CH$_2$), 19.9 (CH$_3$).

IR (ATR): $\tilde{v}$ = 2963, 2919, 2858, 1588, 1563, 1382, 1320, 862, 815, 786, 475 cm^{-1}.

MS (EI) m/z (relative intensity): 316 (10) [M$^+$], 175 (50), 161 (100), 141 (20), 111 (15), 92 (30).

HR-MS (EI) m/z calcd for C$_{22}$H$_{24}$N$_2^+$ 316.1939, found 316.1927.

Synthesis of 2-{2-(10-isobutoxy-n-decyl)pyrrolidin-1-yl}-3-methylpyridine (217'bt)
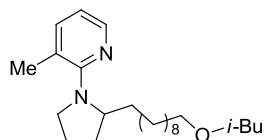
The general procedure **E** was followed using 3-methyl-2-(pyrrolidin-1-yl)pyridine (**216b**) (243 mg, 1.5 mmol) and 9-decen-1-yl 4-methylbenzenesulfonate (**111t**) (155 mg, 0.5 mmol). After 18 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 40/1→30/1) yielded **217'bt** (144 mg, 77%) as a colorless oil.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 8.04 (dd, J = 4.9, 2.0 Hz, 1H), 7.25 (dd, J = 7.4, 2.0 Hz, 1H), 6.61 (dd, J = 7.4, 4.9 Hz, 1H), 4.27−4.16 (m, 1H), 3.68−3.58 (m, 1H), 3.35 (t, J = 6.7 Hz, 2H), 3.31 (d, J = 6.7 Hz, 2H), 2.20 (s, 3H), 2.17−2.06 (m, 1H), 1.95−1.47 (m, 8H), 1.33−1.13 (m, 15H), 0.87 (d, J = 7.0 Hz, 6H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 159.7 (C$_q$), 144.7 (CH), 138.9 (CH), 121.8 (C$_q$), 114.7 (CH), 77.8 (CH$_2$), 71.0 (CH$_2$), 58.1 (CH), 51.7 (CH$_2$), 34.2 (CH$_2$), 31.2 (CH$_2$), 29.9 (CH$_2$), 29.7 (CH$_2$), 29.6 (CH$_2$), 29.6 (CH$_2$), 29.5 (CH$_2$), 29.5 (CH$_2$), 28.4 (CH), 26.2 (CH$_2$), 25.9 (CH$_2$), 24.9 (CH$_2$), 20.0 (CH$_3$), 19.4 (CH$_3$).

IR (ATR): $\tilde{v}$ = 2923, 2852, 1588, 1565, 1384, 1346, 1110, 992, 775 cm^{-1}.

MS (EI) m/z (relative intensity): 374 (5) [M$^+$], 331 (6), 282 (5), 161 (100), 133 (7), 107 (96), 92 (6).

HR-MS (EI) m/z calcd for C$_{24}$H$_{38}$N$_2$O 374.3297, found 374.3285.

Synthesis of 10-{1-(3-methylpyridin-2-yl)pyrrolidin-2-yl}-*n*-decyl 4-methylbenzenesulfonate (217bt)
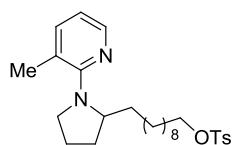
The general procedure **E** was followed using 3-methyl-2-(pyrrolidin-1-yl)pyridine (**216b**) (243 mg, 1.5 mmol) and 9-decen-1-yl 4-methylbenzenesulfonate (**111t**) (155 mg, 0.5 mmol) in DCE. After 18 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 15/1→5/1) yielded **217bt** (148 mg, 63%) as a colorless oil.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 8.03 (dd, J = 4.9, 1.9 Hz, 1H), 7.75 (d, J = 8.3 Hz, 2H), 7.31 (d, J = 8.3 Hz, 2H), 7.25 (dd, J = 7.2, 1.9 Hz, 1H), 6.61 (dd, J = 7.2, 4.9 Hz, 1H), 4.28−4.15 (m, 1H), 3.98 (t, J = 6.6 Hz, 2H), 3.69−3.58 (m, 1H), 3.21−3.08 (m, 1H), 2.41 (s, 3H), 2.20 (s, 3H), 2.16−2.05 (m, 1H), 1.94−1.52 (m, 6H), 1.30−1.09 (m, 15H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 159.6 (C$_q$), 144.5 (CH), 144.5 (C$_q$), 139.0 (CH), 133.2 (C$_q$), 129.7 (CH), 127.8 (CH), 121.9 (C$_q$), 114.6 (CH), 70.6 (CH$_2$), 58.1 (CH), 51.7 (CH$_2$), 34.2 (CH$_2$), 31.2 (CH$_2$), 29.8 (CH$_2$), 29.5 (CH$_2$), 29.3 (CH$_2$), 29.3 (CH$_2$), 28.8 (CH$_2$), 28.7 (CH$_2$), 25.8 (CH$_2$), 25.2 (CH$_2$), 24.9 (CH$_2$), 21.6 (CH$_3$), 20.0 (CH$_3$).

IR (ATR): $\tilde{v}$ = 2923, 2851, 1588, 1385, 1356, 1174, 1097, 956, 775, 553 cm^{-1}.

MS (EI) *m/z* (relative intensity): 472 (3) [M$^+$], 376 (3), 161 (100), 133 (10), 107 (14), 92 (13).

HR-MS (EI) *m/z* calcd for C$_{27}$H$_{40}$N$_2$O$_3$S$^+$ 472.2760, found 472.2767.

Synthesis of 12-{1-(3-methylpyridin-2-yl)pyrrolidin-2-yl}dodecan-2-one (217bu)
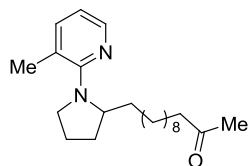
The general procedure **E** was followed using 3-methyl-2-(pyrrolidin-1-yl)pyridine (**216b**) (243 mg, 1.5 mmol) and 11-dodecen-2-one (**111u**) (99.1 mg, 0.5 mmol) in DCE. After 18 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 10/1) yielded **217bu** (69 mg, 38%) as a white solid.

M.p. = 62−63 °C.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 8.01 (dd, J = 4.9, 1.9 Hz, 1H), 7.23 (dd, J = 7.2, 1.9 Hz, 1H), 6.60 (dd, J = 7.2, 4.9 Hz, 1H), 4.27−4.15 (m, 1H), 3.68−3.56 (m, 1H), 3.17−3.06 (m, 1H), 2.36 (t, J = 6.9 Hz, 2H), 2.18 (s, 3H), 2.15−2.01 (m, 1H), 2.08 (s, 3H), 1.92−1.45 (m, 6H), 1.28−1.12 (m, 15H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 207.1 (C$_q$), 159.7 (C$_q$), 144.6 (CH), 138.9 (CH), 121.8 (C$_q$), 114.6 (CH), 58.1 (CH), 51.6 (CH$_2$), 43.7 (CH$_2$), 34.2 (CH$_2$), 31.1 (CH$_2$), 29.8 (CH$_2$), 29.7 (CH$_3$), 29.5 (CH$_2$), 29.4 (CH$_2$), 29.4 (CH$_2$), 29.3 (CH$_2$), 29.1 (CH$_2$), 25.8 (CH$_2$), 24.8 (CH$_2$), 23.8 (CH$_2$), 19.9 (CH$_3$).

IR (ATR): $\tilde{v}$ = 2922, 2853, 1714, 1588, 1384, 1347, 1164, 776, 731 cm^{-1}.

MS (EI) *m/z* (relative intensity): 344 (4) [M$^+$], 252 (6), 161 (100), 133 (12), 92 (16).

HR-MS (ESI) *m/z* calcd for [(C$_{22}$H$_{36}$N$_2$O)H]$^+$ 345.2900, found 345.2900.

Synthesis of 9-{1-(3-methylpyridin-2-yl)pyrrolidin-2-yl}nonan-2-ol (217bv)
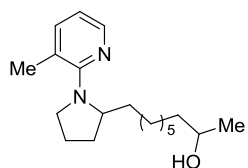
The general procedure **E** was followed using 3-methyl-2-(pyrrolidin-1-yl)pyridine (**216b**) (243 mg, 1.5 mmol) and 8-nonen-2-one (**111v**) (70.0 mg, 0.5 mmol). After 18 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 10/1→5/1) yielded **217bv** (77 mg, 51%) as a colorless oil.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 8.02 (dd, J = 4.9, 1.8 Hz, 1H), 7.26 (dd, J = 7.2, 1.8 Hz, 1H),

6.62 (dd, J = 7.2, 4.9 Hz, 1H), 4.27−4.15 (m, 1H), 3.76−3.68 (m, 1H), 3.68−3.58 (m, 1H), 3.19−3.09 (m, 1H), 2.20 (s, 3H), 2.16−2.05 (m, 1H), 1.94−1.50 (m, 5H), 1.44−1.14 (m, 13H), 1.13 (d, J = 6.4 Hz, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 159.6 (C$_q$), 144.6 (CH), 139.0 (CH), 121.9 (C$_q$), 114.6 (CH), 68.0 (CH), 58.1 (CH), 51.7 (CH$_2$), 39.3 (CH$_2$), 34.2 (CH$_2$), 31.2 (CH$_2$), 29.8 (CH$_2$), 29.5 (CH$_2$), 29.5 (CH$_2$), 25.8 (CH$_2$), 25.7 (CH$_2$), 24.9 (CH$_2$), 23.4 (CH$_3$), 20.0 (CH$_3$).

IR (ATR): $\tilde{v}$ = 3364, 2924, 2854, 1588, 1384, 1346, 1102, 776, 730 cm^{-1}.

MS (EI) m/z (relative intensity): 304 (5) [M$^+$], 289 (5), 161 (100), 133 (12), 92 (18).

HR-MS (EI) m/z calcd for C$_{19}$H$_{32}$N$_2$O$^+$ 304.2515, found 304.2519.

Mechanistic studies with TEMPO (Scheme 82)
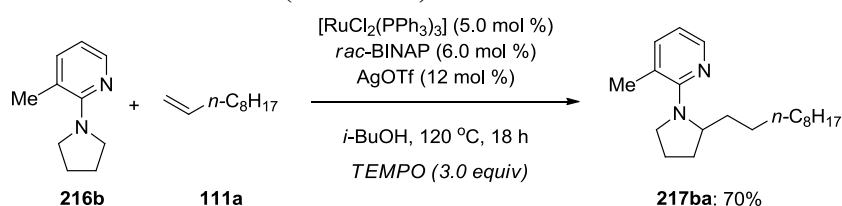
A suspension of [RuCl$_2$(PPh$_3$)$_3$] (24.0 mg, 5.0 mol %), rac-BINAP (18.7 mg, 6.0 mol %), AgOTf (15.4 mg, 12 mol %), TEMPO (234 mg, 1.5 mmol), 3-methyl-2-(pyrrolidin-1-yl)pyridine (**216b**) (243 mg, 1.5 mmol) and 1-decene (**111a**) (70.1 mg, 0.5 mmol) in i-BuOH (1.0 mL) was stirred at 120 ℃ under N$_2$ for 18 h. At ambient temperature, EtOAc (5 mL) and silica (1.5 g) were added to the reaction mixture and the solvents were evaporated in reduced pressure. Purification by column chromatography on silica gel (n-hexane/EtOAc: 40/1→30/1) yielded **217ba** (106 mg, 70%) as a colorless oil.

Studies with isotopically labelled [D]$_4$-MeOH (Scheme 83a)
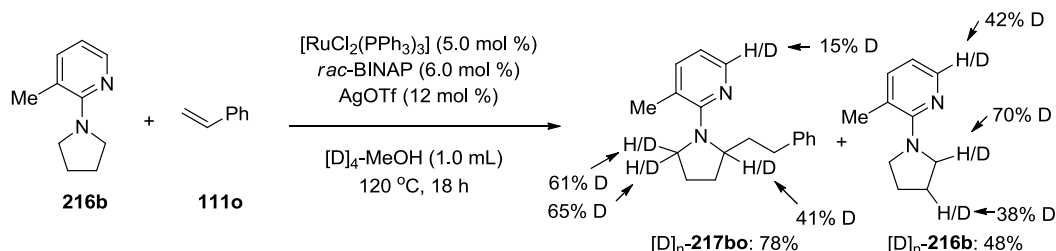
A suspension of [RuCl$_2$(PPh$_3$)$_3$] (24.0 mg, 5.0 mol %), rac-BINAP (18.7 mg, 6.0 mol %), AgOTf (15.4 mg, 12 mol %), 3-methyl-2-(pyrrolidin-1-yl)pyridine (**216b**) (243 mg, 1.5 mmol) and styrene (**111o**) (52.1 mg, 0.5 mmol) in [D]$_4$-MeOH (1.0 mL) was stirred at 120 ℃ under N$_2$ for 18 h. CuCl (50 mg), EtOAc (5 mL) and silica (1.5 g) were added to the cold reaction mixture and the solvents were evaporated in $vacuo$. Purification by column chromatography on silica gel (n-hexane/EtOAc: 20/1→10/1) to give [D]$_n$-**217bo** (104 mg, 78%) as a colorless oil and [D]$_n$-**216b** (118 mg, 48%) as a colorless oil. The deuterium incorporation was estimated by ^{1}H-NMR spectroscopy.

Studies with isotopically labelled [D]$_4$-MeOH (Scheme 83b)
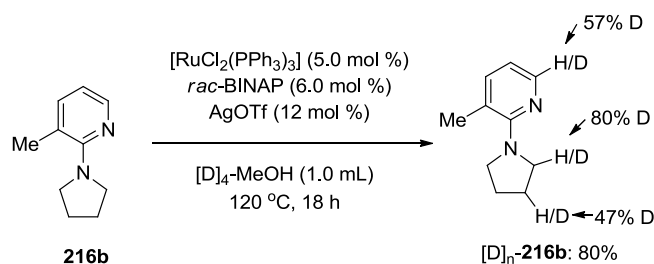
A suspension of [RuCl$_2$(PPh$_3$)$_3$] (24.0 mg, 5.0 mol %), *rac*-BINAP (18.7 mg, 6.0 mol %), AgOTf (15.4 mg, 12 mol %) and 3-methyl-2-(pyrrolidin-1-yl)pyridine (**216b**) (81.0 mg, 0.5 mmol) in [D]$_4$-MeOH (1.0 mL) was stirred at 120 ℃ under N$_2$ for 18 h. EtOAc (5 mL) and silica (1.5 g) were added to the cold reaction mixture and the solvents were evaporated *in vacuo*. Purification by column chromatography on silica gel (*n*-hexane/EtOAc: 20/1→10/1) yielded compound [D]$_n$-**216b** (65 mg, 76%) as a colorless oil. The deuterium incorporation was estimated by ^{1}H-NMR spectroscopy.

Studies with isotopically labelled compounds (Scheme 84)
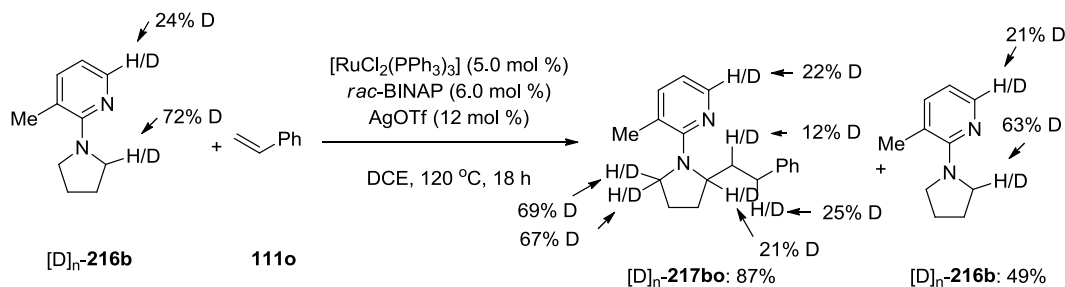
A suspension of [RuCl$_2$(PPh$_3$)$_3$] (24.0 mg, 5.0 mol %), *rac*-BINAP (18.7 mg, 6.0 mol %), AgOTf (15.4 mg, 12 mol %), [D]$_n$-**216b** (243 mg, 1.5 mmol) and **111o** (52.1 mg, 0.5 mmol) in DCE (1.0 mL) was stirred at 120 ℃ under N$_2$ for 18 h. CuCl (50 mg), EtOAc (5 mL) and silica (1.5 g) were added to the cold reaction mixture and the solvents were evaporated *in vacuo*. Purification by column chromatography on silica gel (*n*-hexane/EtOAc: 25/1→10/1) to give [D]$_n$-**217bo** (116 mg, 87%) as a colorless oil and [D]$_n$-**216b** (120 mg, 49%) as a colorless oil. The deuterium incorporation was estimated by ^{1}H-NMR spectroscopy.

Synthesis of 2-decylpyrrolidine (218ba)
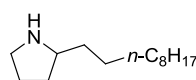
The general procedure **F** was followed using 2-(2-decylpyrrolidin-1-yl)-3-methylpyridine (**217ba**) (151 mg, 0.5 mmol). Purification by column chromatography on silica gel (CH$_2$Cl$_2$/MeOH: 20/1→10/1) yielded **218ba** (74 mg, 70%) as a white solid.

M.p. = 88−89 ℃.

^{1}H-NMR (300 MHz, [d]$_6$-DMSO): δ = 9.34 (s$_{br}$, 1H), 3.38−3.24 (m, 1H), 3.19−3.00 (m, 2H), 2.11−1.98 (m, 1H), 1.96−1.38 (m, 6H), 1.39−1.18 (m, 16H), 0.85 (t, J = 6.7 Hz, 3H).

^{13}C-NMR (75 MHz, [d]$_6$-DMSO): δ = 59.3 (CH), 43.7 (CH$_2$), 31.3 (CH$_2$), 31.2 (CH$_2$), 29.7 (CH$_2$), 28.9 (CH$_2$), 28.8 (CH$_2$), 28.7 (CH$_2$), 28.6 (CH$_2$), 28.6 (CH$_2$), 26.1 (CH$_2$), 22.9 (CH$_2$), 22.0 (CH$_2$), 13.8 (CH$_3$).

IR (ATR): $\tilde{\nu}$ = 2919, 2850, 2744, 1461, 1385, 1030, 730 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 210 (100) [(M+H)$^+$].

HR-MS (ESI) m/z calcd for $[(C_{14}H_{29}N)H]^+$ 210.2373, found 210.2375.

Synthesis of 2-{2-(triethylsilyl)ethyl}pyrrolidine (218bj)
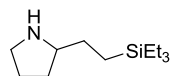
The general procedure **F** was followed using 3-methyl-2-{2-[2-(triethylsilyl)ethyl]pyrrolidin-1-yl}pyridine (**217bj**) (152 mg, 0.5 mmol). Purification by column chromatography on silica gel (CH$_2$Cl$_2$/MeOH: 20/1→10/1→5/1) yielded **218bj** (65 mg, 61%) as a white solid.

M.p. = 52−53 °C.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.52 (s$_{br}$, 1H), 3.35−3.09 (m, 3H), 2.16−2.00 (m, 1H), 2.00−1.69 (m, 3H), 1.64−1.43 (m, 2H), 0.91 (t, J = 7.8 Hz, 9H), 0.67−0.38 (m, 8H).

^{13}C-NMR (75 MHz, [d]$_6$-DMSO): δ = 62.1 (CH), 44.1 (CH$_2$), 29.4 (CH$_2$), 26.3 (CH$_2$), 23.1 (CH$_2$), 8.0 (CH$_2$), 7.2 (CH$_3$), 2.7 (CH$_2$).

IR (ATR): $\tilde{\nu}$ = 2950, 2873, 2730, 1459, 1414, 1015, 758, 720 cm^{-1}.

MS (ESI) m/z (relative intensity): 212 (100) [(M+H)$^+$].

HR-MS (ESI) m/z calcd for $[(C_{12}H_{27}NSi)H]^+$ 212.1986, found 212.1987.

Synthesis of 2-(2-cyclohexylethyl)pyrrolidine (218bo)
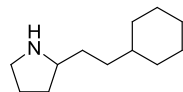
The general procedure **F** was followed using 3-methyl-2-(2-phenethylpyrrolidin-1-yl)pyridine (**217bo**) (195 mg, 0.5 mmol). Purification by column chromatography on silica gel (CH$_2$Cl$_2$/MeOH: 10/1→5/1→3/1) yielded **218bo** (53 mg, 58%) as a white solid.

M.p. = 99−100 °C.

^{1}H-NMR (300 MHz [D]$_6$-DMSO): δ = 6.93 (s$_{br}$, 1H), 3.33−3.18 (m, 1H), 3.17−2.95 (m, 2H), 2.12−1.96 (m, 1H), 1.95−1.37 (m, 10H), 1.33−1.00 (m, 6H), 0.96−0.75 (m, 2H).

^{13}C-NMR (75 MHz, [d]$_6$-DMSO): δ = 59.5 (CH), 43.8 (CH$_2$), 36.7 (CH), 33.7 (CH$_2$), 32.6 (CH$_2$), 29.8 (CH$_2$), 28.9 (CH$_2$), 26.0 (CH$_2$), 25.6 (CH$_2$), 23.0 (CH$_2$).

IR (ATR): $\tilde{\nu}$ = 1917, 1851, 1575, 1588, 1448, 1412, 1027, 387 cm^{-1}.

MS (ESI) m/z (relative intensity): 182 (100) [(M+H)$^+$].

HR-MS (ESI) m/z calcd for $[(C_{12}H_{23}N)H]^+$ 182.1903, found 182.1905.

8.3.5 Analytical Data for the Products of Ruthenium-Catalyzed *ortho*-C−H Halogenation of Benzamide 219

Synthesis of 2-bromo-*N,N*-diisopropylbenzamide (220a)
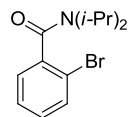
The general procedure **G** was followed using *N,N*-diisopropylbenzamide (**219a**) (103 mg, 0.5 mmol) and NBS (178 mg, 1.0 mmol). After 16 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 10/1→5/1) yielded **220a** (86 mg, 60%) as a white solid.

M.p. = 73−74 °C.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.57 (d, J = 7.6 Hz, 1H), 7.53 (dd, J = 7.6, 7.6 Hz, 1H), 7.22−7.12 (m, 2H), 3.65−3.43 (m, 2H), 1.56 (d, J = 6.7 Hz, 3H), 1.55 (d, J = 6.7 Hz, 3H), 1.22 (d, J = 6.7 Hz, 3H), 1.04 (d, J = 6.7 Hz, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 168.0 (C$_q$), 140.1 (C$_q$), 132.7 (CH), 129.3 (CH), 127.4 (CH), 126.5 (CH), 118.8 (C$_q$), 51.1 (CH), 45.9 (CH), 20.7 (CH$_3$), 20.6 (CH$_3$), 20.5 (CH$_3$), 20.0 (CH$_3$).

IR (ATR): $\tilde{\nu}$ = 2975, 2930, 1626, 1438, 1339, 1019, 770 cm^{-1}.

MS (EI) m/z (relative intensity): 285 (7) [M$^+$] (^{81}Br), 283 (7) [M$^+$] (^{79}Br), 238 (25), 240 (26), 185 (98), 185 (100).

HR-MS (EI) m/z calcd for C$_{13}$H$_{18}$BrNO$^+$ 283.0572, found 283.0567.

The spectral data were in accordance with those reported in the literature.[113a]

Synthesis of 2-bromo-*N,N*,3,5-tetramethylbenzamide (220b)
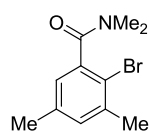
The general procedure **G** was followed using *N,N*,3,5-tetramethylbenzamide (**219b**) (177 mg, 1.0 mmol) and NBS (356 mg, 2.0 mmol). After 16 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 3/1→2/1) yielded **220b** (175 mg, 68%) as a yellow solid.

M.p. = 103−104 ℃.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.02 (s, 1H), 6.86 (s, 1H), 3.10 (s, 3H), 2.84 (s, 3H), 2.35 (s, 3H), 2.25 (s, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 169.8 (C$_q$), 138.9 (C$_q$), 138.5 (C$_q$), 137.6 (C$_q$), 131.7 (CH), 125.5 (CH), 117.9 (C$_q$), 38.2 (CH$_3$), 34.5 (CH$_3$), 23.0 (CH$_3$), 20.7 (CH$_3$).

IR (ATR): $\tilde{v}$ = 2918, 2871, 1626, 1508, 1441, 1392, 1257, 1130, 1020, 865, 665 cm^{-1}.

MS (EI) m/z (relative intensity): 257 (17) [M$^+$] (^{81}Br), 255 (20) [M$^+$] (^{79}Br), 219 (97), 209 (100), 104 (35).

HR-MS (EI) m/z calcd for C$_{11}$H$_{14}$BrNO$^+$ 255.0259, found 255.0249.

Synthesis of 2-iodo-*N,N*,3,5-tetramethylbenzamide (221b)
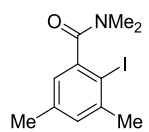
The general procedure **G** was followed using *N,N*,3,5-tetramethylbenzamide (**219b**) (177 mg, 1.0 mmol) and NIS (450 mg, 2.0 mmol). After 16 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 3/1) yielded **221b** (224 mg, 74%) as a yellow solid.

The general procedure **H** was followed using *N,N*,3,5-tetramethylbenzamide (**219b**) (177 mg, 1.0 mmol) and NIS (450 mg, 2.0 mmol). After 22 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 3/1) yielded **221b** (237 mg, 78%) as a yellow solid.

M.p. = 82−83 ℃.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 6.98 (s, 1H), 6.76 (s, 1H), 3.07 (s, 3H), 2.79 (s, 3H), 2.36 (s, 3H), 2.21 (s, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 171.3 (C$_q$), 143.5 (C$_q$), 138.0 (C$_q$), 138.4 (C$_q$), 130.3 (CH), 124.8 (CH), 94.9 (C$_q$), 38.3 (CH$_3$), 34.5 (CH$_3$), 28.4 (CH$_3$), 20.6 (CH$_3$).

IR (ATR): $\tilde{v}$ = 2913, 2853, 1626, 1505, 1441, 1399, 1125, 1003, 863, 663 cm^{-1}.

MS (EI) m/z (relative intensity): 303 (38) [M$^+$], 259 (100), 231 (24), 104 (20).

HR-MS (EI) m/z calcd for C$_{11}$H$_{14}$INO$^+$ 303.0120, found 303.0118.

Synthesis of 2-bromo-*N,N*-diethyl-3,5-dimethylbenzamide (220c)
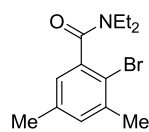
The general procedure **G** was followed using *N,N*-diethyl-3,5-dimethylbenzamide (**219c**) (205 mg, 1.0 mmol) and NBS (356 mg, 2.0 mmol). After 16 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 5/1) yielded **220c** (159 mg, 56%) as a colorless oil.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.02 (s, 1H), 6.85 (s, 1H), 3.79 (hex, J = 6.9 Hz, 1H), 3.31 (hex, J = 6.9 Hz, 1H), 3.19−3.05 (m, 2H), 2.35 (s, 3H), 2.25 (s, 3H), 1.25 (t, J = 6.9 Hz, 3H), 1.04 (t, J = 6.9 Hz, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 169.0 (C$_q$), 139.0 (C$_q$), 138.4 (C$_q$), 137.2 (C$_q$), 131.4 (CH), 125.3 (CH), 117.9 (C$_q$), 38.5 (CH$_2$), 38.6 (CH$_2$), 23.0 (CH$_3$), 20.6 (CH$_3$), 13.8 (CH$_3$), 12.4 (CH$_3$).

IR (ATR): $\tilde{\nu}$ = 2973, 2932, 1631, 1433, 1132, 1023, 767, 649 cm^{-1}.

MS (EI) m/z (relative intensity): 285 (27) [M$^+$] (^{81}Br), 283 (28) [M$^+$] (^{79}Br), 219 (98), 209 (100), 133 (22), 104 (48).

HR-MS (ESI) m/z calcd for [(C$_{13}$H$_{18}$BrNO)H]$^+$ 284.0645, found 284.0645.

Synthesis of *N,N*-diethyl-2-iodo-3,5-dimethylbenzamide (221c)
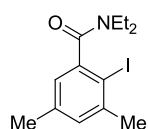
The general procedure **G** was followed using *N,N*-diethyl-3,5-dimethylbenzamide (**219c**) (205 mg, 1.0 mmol) and NIS (450 mg, 2.0 mmol). After 16 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 10/1→5/1) and normal phase HPLC (*n*-hexane/EtOAc: 15/1→7/1) yielded **221c** (179 mg, 54%) as a colorless oil.

The general procedure **H** was followed using *N,N*-diethyl-3,5-dimethylbenzamide (**219c**) (205 mg, 1.0 mmol) and NIS (450 mg, 2.0 mmol). After 22 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 10/1→5/1) and normal phase HPLC (*n*-hexane/EtOAc: 15/1→7/1) yielded **221c** (235 mg, 71%) as a colorless oil.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.02 (s, 1H), 6.79 (s, 1H), 3.84 (hex, J = 6.9 Hz, 1H), 3.28 (hex, J = 6.9 Hz, 1H), 3.20−3.03 (m, 2H), 2.39 (s, 3H), 2.24 (s, 3H), 1.28 (t, J = 6.9 Hz, 3H), 1.05 (t, J = 6.9 Hz, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 170.7 (C$_q$), 143.6 (C$_q$), 138.1 (C$_q$), 138.2 (C$_q$), 130.2 (CH), 124.8 (CH), 95.4 (C$_q$), 38.6 (CH$_2$), 38.7 (CH$_2$), 28.5 (CH$_3$), 20.7 (CH$_3$), 13.8 (CH$_3$), 12.3 (CH$_3$).

IR (ATR): $\tilde{\nu}$ = 2972, 2932, 1628, 1432, 1317, 1129, 1008, 857, 766, 648 cm^{-1}.

MS (EI) m/z (relative intensity): 331 (57) [M$^+$], 259 (100), 231 (32), 204 (50), 135 (33), 104 (37).

HR-MS (EI) m/z calcd for C$_{13}$H$_{18}$INO$^+$ 331.0433, found 331.0432.

Synthesis of 2-bromo-*N,N*-diisopropyl-3,5-dimethylbenzamide (220d)
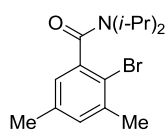
The general procedure **G** was followed using *N,N*-diisopropyl-3,5-dimethylbenzamide (**219d**) (233 mg, 1.0 mmol) and NBS (356 mg, 2.0 mmol) at 80 ℃. After 16 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 10/1) yielded **220d** (277 mg, 89%) as a white solid.

M.p. = 200−201 ℃.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.00 (s, 1H), 6.76 (s, 1H), 3.63 (sept, J = 6.7 Hz, 1H), 3.50 (sept, J = 6.7 Hz, 1H), 2.36 (s, 3H), 2.25 (s, 3H), 1.57 (d, J = 6.7 Hz, 3H), 1.55 (d, J = 6.7 Hz, 3H), 1.22 (d, J = 6.7 Hz, 3H), 1.05 (d, J = 6.7 Hz, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 168.7 (C$_q$), 140.4 (C$_q$), 138.4 (C$_q$), 137.2 (C$_q$), 130.9 (CH), 124.4 (CH), 117.7 (C$_q$), 51.0 (CH), 45.7 (CH), 23.0 (CH$_3$), 20.7 (CH$_3$), 20.6 (CH$_3$), 20.6 (CH$_3$), 20.5 (CH$_3$), 19.9 (CH$_3$).

IR (ATR): $\tilde{\nu}$ = 2960, 2928, 1626, 1438, 1368, 1346, 1207, 1026, 865, 778 cm^{-1}.

MS (EI) m/z (relative intensity): 313 (15) [M$^+$] (^{81}Br), 311 (15) [M$^+$] (^{79}Br), 270 (28), 268 (28), 219 (98), 209 (100), 104 (17).

HR-MS (EI) m/z calcd for C$_{15}$H$_{22}$BrNO$^+$ 311.0885, found 311.0877.

Synthesis of 2-iodo-*N*,*N*-diisopropyl-3,5-dimethylbenzamide (221d)
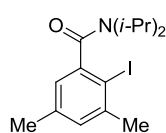
The general procedure **G** was followed using *N*,*N*-diisopropyl-3,5-dimethylbenzamide (**219d**) (233 mg, 1.0 mmol) and NIS (450 mg, 2.0 mmol). After 16 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 10/1) yielded **221d** (251 mg, 70%) as a white solid.

The general procedure **H** was followed using *N*,*N*-diisopropyl-3,5-dimethylbenzamide (**219d**) (233 mg, 1.0 mmol) and NIS (450 mg, 2.0 mmol). After 22 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 10/1) yielded **221d** (305 mg, 85%) as a white solid.

M.p. = 195−196 ℃.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 6.98 (s, 1H), 6.71 (s, 1H), 3.59 (hept, *J* = 6.8 Hz, 1H), 3.48 (hept, *J* = 6.8 Hz, 1H), 2.39 (s, 3H), 2.23 (s, 3H), 1.60 (d, *J* = 6.8 Hz, 3H), 1.54 (d, *J* = 6.8 Hz, 3H), 1.24 (d, *J* = 6.8 Hz, 3H), 1.03 (d, *J* = 6.8 Hz, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 170.5 (C$_q$), 145.0 (C$_q$), 138.2 (C$_q$), 138.2 (C$_q$), 129.9 (CH), 123.8 (CH), 95.0 (C$_q$), 51.1 (CH), 45.8 (CH), 28.5 (CH$_3$), 20.7 (CH$_3$), 20.7 (CH$_3$), 20.7 (CH$_3$), 20.6 (CH$_3$), 19.9 (CH$_3$).

IR (ATR): $\tilde{v}$ = 2958, 2926, 1625, 1438, 1368, 1344, 1206, 864, 777, 630 cm^{-1}.

MS (EI) *m/z* (relative intensity): 359 (40) [M$^+$], 316 (48), 259 (100), 232 (40), 133 (32), 104 (32).

HR-MS (ESI) *m/z* calcd for [(C$_{15}$H$_{22}$INO)H]$^+$ 360.0824, found 360.0817.

Synthesis of (2-bromo-3,5-dimethylphenyl)(pyrrolidin-1-yl)methanone (220e)

The general procedure **G** was followed using (3,5-dimethylphenyl)(pyrrolidin-1-yl)methanone (**219e**) (203 mg, 1.0 mmol) and NBS (356 mg, 2.0 mmol). After 16 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 2/1→1/1) and normal phase HPLC (*n*-hexane/EtOAc: 3/1→2/1) yielded **220e** (102 mg, 36%) as a white solid.

The general procedure **H** was followed using (3,5-dimethylphenyl)(pyrrolidin-1-yl)methanone (**219e**) (203 mg, 1.0 mmol) and NBS (356 mg, 2.0 mmol). After 22 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 2/1→1/1) and normal phase HPLC (*n*-hexane/EtOAc: 3/1→2/1) yielded **220e** (102 mg, 36%) as a white solid.

M.p. = 68−69 ℃.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.03 (s, 1H), 6.90 (s, 1H), 3.64 (t, *J* = 6.7 Hz, 2H), 3.31−3.08 (m, 2H), 2.36 (s, 3H), 2.26 (s, 3H), 2.00−1.83 (m, 4H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 168.0 (C$_q$), 139.9 (C$_q$), 138.5 (C$_q$), 137.6 (C$_q$), 131.6 (CH), 125.3 (CH), 117.5 (C$_q$), 43.0 (CH$_2$), 45.3 (CH$_2$), 25.8 (CH$_3$), 24.6 (CH$_2$), 23.0 (CH$_2$), 20.7 (CH$_3$).

IR (ATR): $\tilde{v}$ = 2971, 2874, 1629, 1433, 1023, 859, 706, 621 cm^{-1}.

MS (EI) *m/z* (relative intensity): 283 (30) [M$^+$] (^{81}Br), 281 (31) [M$^+$] (^{79}Br), 219 (98), 209 (100), 202 (37), 104 (38).

HR-MS (EI) *m/z* calcd for C$_{13}$H$_{16}$BrNO$^+$ 281.0415, found 281.0405.

Synthesis of (2-iodo-3,5-dimethylphenyl)(pyrrolidin-1-yl)methanone (221e)
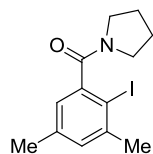
The general procedure **G** was followed using (3,5-dimethylphenyl)(pyrrolidin-1-yl)methanone (**219e**) (203 mg, 1.0 mmol) and NIS (450 mg, 2.0 mmol). After 16 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 10/1) yielded **221e** (238 mg, 72%) as a white solid.

The general procedure **H** was followed using (3,5-dimethylphenyl)(pyrrolidin-1-yl)methanone (**219e**) (203 mg, 1.0 mmol) and NIS (450 mg, 2.0 mmol). After 22 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 10/1) yielded **221e** (250 mg, 76%) as a white solid.

M.p. = 107−108 ℃.

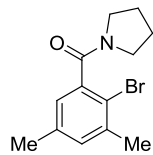^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.00 (s, 1H), 6.76 (s, 1H), 3.61 (t, *J* = 6.7 Hz, 2H), 3.25−3.01 (m, 2H), 2.38 (s, 3H), 2.23 (s, 3H), 1.99−1.76 (m, 4H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 169.5 (C$_q$), 144.7 (C$_q$), 138.1 (C$_q$), 138.5 (C$_q$), 130.4 (CH), 124.6 (CH), 94.7 (C$_q$), 48.3 (CH$_2$), 45.4 (CH$_2$), 28.4 (CH$_3$), 25.9 (CH$_2$), 24.5 (CH$_2$), 20.7 (CH$_3$).

IR (ATR): $\tilde{\nu}$ = 2963, 2930, 1626, 1434, 1364, 1322, 1148, 1036, 816, 608 cm^{-1}.

MS (EI) *m/z* (relative intensity): 329 (67) [M$^+$], 259 (100), 231 (34), 202 (49), 133 (37), 104 (38).

HR-MS (EI) *m/z* calcd for C$_{13}$H$_{16}$INO 329.0277, found 329.0275.

Synthesis of (2-bromo-3,5-dimethylphenyl)(piperidin-1-yl)methanone (220f)
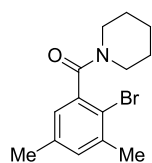
The general procedure **D** was followed using (3,5-dimethylphenyl)(piperidin-1-yl)methanone (**219f**) (215 mg, 1.0 mmol) and NBS (356 mg, 2.0 mmol). After 16 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 5/1→4/1) and normal phase HPLC (*n*-hexane/EtOAc: 10/1→5/1) yielded **220f** (198 mg, 67%) as a white solid.

M.p. = 107−108 ℃.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 6.99 (s, 1H), 6.76 (s, 1H), 3.76−3.58 (m, 2H), 3.22−3.05 (m, 2H), 2.32 (s, 3H), 2.22 (s, 3H), 1.71−1.50 (m, 5H), 1.48−1.31 (m, 1H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 168.0 (C$_q$), 138.8 (C$_q$), 138.4 (C$_q$), 137.3 (C$_q$), 131.4 (CH), 125.2 (CH), 117.8 (C$_q$), 47.7 (CH$_2$), 38.2 (CH$_2$), 26.1 (CH$_3$), 25.3 (CH$_2$), 24.4 (CH$_2$), 23.0 (CH$_2$), 20.6 (CH$_3$).

IR (ATR): $\tilde{\nu}$ = 2937, 2855, 1624, 1439, 1217, 1021, 792, 659 cm^{-1}.

MS (EI) *m/z* (relative intensity): 297 (32) [M$^+$] (^{81}Br), 295 (34) [M$^+$] (^{79}Br), 219 (98), 209 (100), 135 (27), 104 (38).

HR-MS (EI) *m/z* calcd for C$_{14}$H$_{18}$BrNO$^+$ 295.0572, found 295.0576.

Synthesis of (2-iodo-3,5-dimethylphenyl)(piperidin-1-yl)methanone (221f)
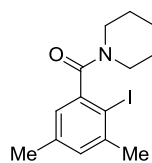
The general procedure **G** was followed using (3,5-dimethylphenyl)(piperidin-1-yl)methanone (**219f**) (215 mg, 1.0 mmol) and NIS (450 mg, 2.0 mmol). After 16 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 5/1→4/1) yielded **221f** (219 mg, 62%) as a white solid.

The general procedure **H** was followed using (3,5-dimethylphenyl)(piperidin-1-yl)methanone (**219f**) (215 mg, 1.0 mmol) and NIS (450 mg, 2.0 mmol). After 22 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 5/1→4/1) yielded **221f** (275 mg, 76%) as a white solid.

M.p. = 77−78 ℃.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.01 (s, 1H), 6.77 (s, 1H), 3.84−3.74 (m, 1H), 3.70−3.60 (m, 1H), 3.25−3.07 (m, 2H), 2.41 (s, 3H), 2.25 (s, 3H), 1.76−1.54 (m, 5H), 1.53−1.35 (m, 1H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 169.8 (C$_q$), 143.6 (C$_q$), 138.2 (C$_q$), 138.4 (C$_q$), 130.3 (CH), 124.7 (CH), 95.1 (C$_q$), 47.8 (CH$_2$), 38.3 (CH$_2$), 28.5 (CH$_3$), 26.1 (CH$_2$), 25.3 (CH$_2$), 24.5 (CH$_2$), 20.7

(CH$_3$).

IR (ATR): $\tilde{\nu}$ = 2936, 2852, 1625, 1435, 1215, 1006, 855, 658 cm^{-1}.

MS (EI) m/z (relative intensity): 343 (52) [M$^+$], 338 (100), 259 (93), 231 (23), 214 (43), 104 (28).

HR-MS (EI) m/z calcd for C$_{14}$H$_{18}$INO$^+$ 343.0433, found 343.0438.

Synthesis of (2-bromo-3,5-dimethylphenyl)(morpholino)methanone (220g)
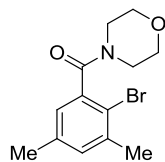
The general procedure **G** was followed using (3,5-dimethylphenyl)(morpholino)methanone (**219g**) (217 mg, 1.0 mmol) and NBS (356 mg, 2.0 mmol). After 16 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 3/1→2/1) and normal phase HPLC (*n*-hexane/EtOAc: 5/1→3/1) yielded **220g** (155 mg, 52%) as a white solid.

M.p. = 118−119 ℃.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.05 (s, 1H), 6.85 (s, 1H), 3.92−3.63 (m, 5H), 3.33−3.13 (m, 1H), 3.32−3.11 (m, 2H), 2.34 (s, 3H), 2.25 (s, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 168.3 (C$_q$), 138.7 (C$_q$), 137.8 (C$_q$), 137.7 (C$_q$), 132.0 (CH), 125.5 (CH), 117.9 (C$_q$), 66.7 (CH$_2$), 66.6 (CH$_2$), 47.1 (CH$_2$), 41.9 (CH$_2$), 23.0 (CH$_3$), 20.7 (CH$_3$).

IR (ATR): $\tilde{\nu}$ = 2913, 2848, 1630, 1436, 1112, 1020, 860, 618 cm^{-1}.

MS (EI) m/z (relative intensity): 299 (16) [M$^+$] (^{81}Br), 297 (18) [M$^+$] (^{79}Br), 219 (100), 209 (98), 104 (33).

HR-MS (ESI) m/z calcd for [(C$_{13}$H$_{16}$INO$_2$)H]$^+$ 298.0437, found 298.0445.

Synthesis of (2-iodo-3,5-dimethylphenyl)(morpholino)methanone (221g)
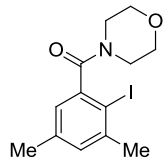
The general procedure **G** was followed using (3,5-dimethylphenyl)(morpholino)methanone (**219g**) (217 mg, 1.0 mmol) and NIS (450 mg, 2.0 mmol). After 16 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 3/1→2/1) and normal phase HPLC (*n*-hexane/EtOAc: 7/1→3/1) yielded **221g** (186 mg, 54%) as a white solid.

The general procedure **H** was followed using (3,5-dimethylphenyl)(morpholino)methanone (**219g**) (217 mg, 1.0 mmol) and NIS (450 mg, 2.0 mmol). After 22 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 3/1→2/1) and normal phase HPLC (*n*-hexane/EtOAc: 7/1→3/1) yielded **221g** (248 mg, 72%) as a white solid.

M.p. = 135−136 ℃.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.03 (s, 1H), 6.77 (s, 1H), 3.86−3.68 (m, 5H), 3.60−3.50 (m, 1H), 3.32−3.11 (m, 2H), 2.40 (s, 3H), 2.25 (s, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 170.0 (C$_q$), 138.5 (C$_q$), 138.2 (C$_q$), 138.6 (C$_q$), 130.8 (CH), 124.9 (CH), 95.0 (C$_q$), 66.6 (CH$_2$), 66.5 (CH$_2$), 47.1 (CH$_2$), 41.8 (CH$_2$), 28.5 (CH$_3$), 20.7 (CH$_3$).

IR (ATR): $\tilde{\nu}$ = 2901, 2856, 1627, 1460, 1434, 1106, 1007, 860, 662 cm^{-1}.

MS (EI) m/z (relative intensity): 345 (30) [M$^+$], 359 (100), 2313 (17), 104 (20).

HR-MS (EI) m/z calcd for C$_{13}$H$_{16}$INO$_2$$^+$ 345.0226, found 345.0209.

Synthesis of 2-bromo-*N,N*-diisopropyl-5-methylbenzamide (220h)
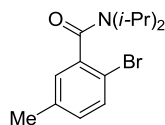
The general procedure **G** was followed using *N,N*-diisopropyl-3-methylbenzamide (**219h**) (110 mg, 0.5 mmol) and NBS (178 mg, 1.0 mmol). After 16 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 10/1→5/1) yielded **220h** (95 mg, 64%) as a white solid.

M.p. = 162−163 ℃.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.40 (d, J = 8.2 Hz, 1H), 7.03−6.94 (m, 2H), 3.61 (sept, J = 6.7 Hz, 1H), 3.51 (sept, J = 6.7 Hz, 1H), 2.29 (s, 3H), 1.57 (d, J = 6.7 Hz, 3H), 1.55 (d, J = 6.7 Hz, 3H), 1.23 (d, J = 6.7 Hz, 3H), 1.06 (d, J = 6.7 Hz, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 168.3 (C$_q$), 139.9 (C$_q$), 137.6 (C$_q$), 132.5 (CH), 130.2 (CH), 127.1 (CH), 111.4 (C$_q$), 51.1 (CH), 45.9 (CH), 20.8 (CH$_3$), 20.8 (CH$_3$), 20.6 (CH$_3$), 20.6 (CH$_3$), 20.1 (CH$_3$).

IR (ATR): $\tilde{\nu}$ = 2960, 2928, 1626, 1441, 1337, 1044, 831, 764, 622, 459 cm^{-1}.

MS (EI) m/z (relative intensity): 299 (5) [M$^+$] (^{81}Br), 297 (5) [M$^+$] (^{79}Br), 256 (25), 254 (25), 199 (97), 197 (100).

HR-MS (EI) m/z calcd for C$_{14}$H$_{20}$BrNO$^+$ 297.0728, found 297.0721.

The spectral data were in accordance with those reported in the literature.[113a]

Synthesis of 2-bromo-3-fluoro-*N,N*-diisopropylbenzamide (220i)
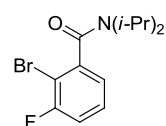
The general procedure **H** was followed using 3-fluoro-*N,N*-diisopropylbenzamide (**219i**) (219 mg, 1.0 mmol) and NBS (356 mg, 2.0 mmol). After 22 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 5/1) yielded **220i** (165 mg, 55%) as a white solid.

M.p. = 134−135 ℃.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.28 (dddd, J = 8.2, 7.8, 4.9, 0.8 Hz, 1H), 7.06 (ddd, J = 8.2, 8.2, 1.5 Hz, 1H), 6.95 (dq, J = 7.8, 0.8 Hz, 1H), 3.63−3.43 (m, 2H), 1.56 (d, J = 6.7 Hz, 3H), 1.54 (d, J = 6.7 Hz, 3H), 1.21 (d, J = 6.7 Hz, 3H), 1.05 (d, J = 6.7 Hz, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 166.9 (d, $^4J_{C–F}$ = 2 Hz, C$_q$), 159.2 (d, $^1J_{C–F}$ = 249 Hz, C$_q$), 138.2 (C$_q$), 129.2 (d, $^3J_{C–F}$ = 8 Hz, CH), 121.8 (d, $^4J_{C–F}$ = 4 Hz, CH), 111.8 (d, $^2J_{C–F}$ = 22 Hz, CH), 106.4 (d, $^2J_{C–F}$ = 22 Hz, C$_q$), 51.2 (CH), 46.1 (CH), 20.7 (CH$_3$), 20.6 (CH$_3$), 20.6 (CH$_3$), 20.1 (CH$_3$).

^{19}F-NMR (283 MHz, CDCl$_3$): δ = −(105.1−105.2) (m).

IR (ATR): $\tilde{\nu}$ = 2970, 2932, 2874, 1625, 1437, 1339, 1205, 1041, 790, 603 cm^{-1}.

MS (EI) m/z (relative intensity): 303 (4) [M$^+$] (^{81}Br), 301 (4) [M$^+$] (^{79}Br), 202 (90), 200 (100), 174 (16), 172 (18), 57 (48).

HR-MS (ESI) m/z calcd for [(C$_{13}$H$_{17}$FBrNO)H]$^+$ 302.0556, found 302.0551.

Synthesis of 3-bromo-*N,N*-diisopropyl-[1,1'-biphenyl]-4-carboxamide (220j)
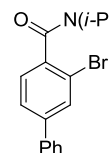
The general procedure **H** was followed using 3-bromo-*N,N*-diisopropyl-[1,1'-biphenyl]-4-carboxamide (**219j**) (281 mg, 1.0 mmol) and NBS (712 mg, 4.0 mmol). After 22 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 5/1) and normal phase HPLC (*n*-hexane/EtOAc: 15/1→1/9) yielded **220j** (173 mg, 48%) as a colorless oil.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.76 (d, J = 1.6 Hz, 1H), 7.57−7.49 (m, 3H), 7.47−7.39 (m 2H), 7.39−7.32 (m, 1H), 7.22 (d, J = 7.8 Hz, 1H), 3.68 (sept, J = 6.7 Hz, 1H), 3.53 (sept, J = 6.7 Hz, 1H), 1.59 (d, J = 6.7 Hz, 3H), 1.57 (d, J = 6.7 Hz, 3H), 1.25 (d, J = 6.7 Hz, 3H), 1.08 (d, J = 6.7 Hz, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 168.1 (C$_q$), 138.6 (C$_q$), 139.0 (C$_q$), 138.7 (C$_q$), 131.3 (CH), 128.9 (CH), 128.0 (CH), 127.0 (CH), 126.8 (CH), 126.3 (CH), 119.3 (C$_q$), 51.2 (CH), 46.0 (CH), 20.8 (CH$_3$), 20.7 (CH$_3$), 20.6 (CH$_3$), 20.1 (CH$_3$).

IR (ATR): $\tilde{\nu}$ = 2968, 2931, 1631, 1437, 1336, 1044, 754, 696 cm^{-1}.

MS (EI) m/z (relative intensity): 361 (10) [M$^+$] (^{81}Br), 359 (10) [M$^+$] (^{79}Br), 318 (32), 316 (33), 261 (99), 259 (100), 152 (70).

HR-MS (EI) m/z calcd for $C_{19}H_{22}BrNO^+$ 359.0885, found 359.0885.

Synthesis of 4-bromo-*N,N*-diisopropyl-[1,1'-biphenyl]-3-carboxamide (220k)
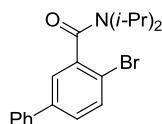
The general procedure **H** was followed using *N,N*-diisopropyl-[1,1'-biphenyl]-3-carboxamide (**219k**) (141 mg, 0.5 mmol) and NBS (267 mg, 1.5 mmol). After 22 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 20/1→10/1) yielded **220k** (117 mg, 65%) as a white solid.

M.p. = 151−152 ℃.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.61 (d, J = 8.2 Hz, 1H), 7.55 (d, J = 7.8 Hz, 2H), 7.51−7.37 (m, 4H), 7.36 (d, J = 2.2 Hz, 1H), 3.69 (sept, J = 6.6 Hz, 1H), 3.55 (sept, J = 6.6 Hz, 1H), 1.61 (d, J = 6.6 Hz, 3H), 1.59 (d, J = 6.6 Hz, 3H), 1.26 (d, J = 6.6 Hz, 3H), 1.08 (d, J = 6.6 Hz, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 168.0 (C$_q$), 140.8 (C$_q$), 140.5 (C$_q$), 139.4 (C$_q$), 133.2 (CH), 128.9 (CH), 128.1 (CH), 127.9 (CH), 127.0 (CH), 125.1 (CH), 117.9 (C$_q$), 51.2 (CH), 46.0 (CH), 20.9 (CH$_3$), 20.7 (CH$_3$), 20.6 (CH$_3$), 20.1 (CH$_3$).

IR (ATR): $\tilde{v}$ = 2931, 2873, 1631, 1444, 1369, 1337, 1039, 786 cm^{-1}.

MS (EI) m/z (relative intensity): 361 (8) [M$^+$] (^{81}Br), 359 (8) [M$^+$] (^{79}Br), 318 (38), 316 (37), 261 (98), 259 (100), 152 (85).

HR-MS (EI) m/z calcd for $C_{19}H_{22}BrNO^+$ 359.0885, found 359.0882.

The spectral data were in accordance with those reported in the literature.[113a]

Synthesis of 4-bromo-*N,N*-diisopropyl-4'-methyl-[1,1'-biphenyl]-3-carboxamide (220l)
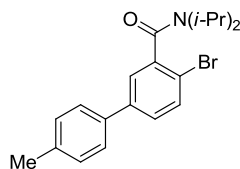
The general procedure **H** was followed using *N,N*-diisopropyl-4'-methyl-[1,1'-biphenyl]-3-carboxamide (**219l**) (148 mg, 0.5 mmol) and NBS (178 mg, 1.0 mmol). After 22 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 20/1→10/1) yielded **220l** (88 mg, 47%) as a white solid.

M.p. = 193−194 ℃.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.57 (dd, J = 8.1, 0.5 Hz, 1H), 7.44 (dt, J = 8.1, 0.5 Hz, 2H), 7.37 (dd, J = 8.2, 2.2 Hz, 1H), 7.34 (d, J = 2.0 Hz, 1H), 7.23 (d, J = 8.2 Hz, 2H), 3.67 (sept, J = 6.7 Hz, 1H), 3.52 (sept, J = 6.7 Hz, 1H), 2.37 (s, 3H), 1.59 (d, J = 6.7 Hz, 3H), 1.57 (d, J = 6.7 Hz, 3H), 1.24 (d, J = 6.7 Hz, 3H), 1.05 (d, J = 6.7 Hz, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 168.1 (C$_q$), 140.7 (C$_q$), 140.4 (C$_q$), 137.8 (C$_q$), 136.5 (C$_q$), 133.1 (CH), 129.6 (CH), 127.9 (CH), 126.8 (CH), 124.8 (CH), 117.5 (C$_q$), 51.2 (CH), 46.0 (CH), 21.1 (CH$_3$), 20.9 (CH$_3$), 20.7 (CH$_3$), 20.6 (CH$_3$), 20.1 (CH$_3$).

IR (ATR): $\tilde{v}$ = 2969, 2929, 1631, 1441, 1336, 1021, 763, 514 cm^{-1}.

MS (ESI) m/z (relative intensity): 396 (28) [(M+Na)$^+$], 749 (100) [(2M+H)$^+$].

HR-MS (ESI) m/z calcd for [(C$_{20}$H$_{24}$BrNO)H]$^+$ 374.1114, found 374.1107.

Synthesis of 4-bromo-4'-fluoro-*N,N*-diisopropyl-[1,1'-biphenyl]-3-carboxamide (220m)
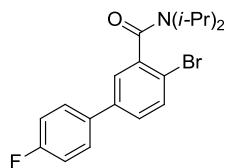
The general procedure **H** was followed using 4'-fluoro-*N,N*-diisopropyl-[1,1'-biphenyl]-3-carboxamide (**219m**) (150 mg, 0.5 mmol) and NBS (178 mg, 1.0 mmol). After 22 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 20/1→10/1) yielded **220m** (102 mg, 54%) as a white solid.

M.p. = 156−157 ℃.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.59 (d, J = 8.2 Hz, 1H), 7.49 (dd, J = 8.6, 8.6 Hz, 2H), 7.33 (dd, J = 8.2, 2.3 Hz, 1H), 7.30 (d, J = 2.3 Hz, 1H), 7.11 (dd, J = 8.6, 8.6 Hz, 2H), 3.66 (sept, J = 6.6 Hz, 1H), 3.63 (sept, J = 6.6 Hz, 1H), 1.58 (d, J = 6.6 Hz, 3H), 1.56 (d, J = 6.6 Hz, 3H), 1.25 (d, J = 6.6 Hz, 3H), 1.07 (d, J = 6.6 Hz, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 167.9 (C$_q$), 162.7 (d, $^{1}J_{C-F}$ = 247 Hz, C$_q$), 140.5 (C$_q$), 139.9 (C$_q$), 135.6 (d, $^{4}J_{C-F}$ = 3 Hz, C$_q$), 133.2 (CH), 128.7 (d, $^{3}J_{C-F}$ = 9 Hz, CH), 128.0 (CH), 124.9 (CH), 117.9 (C$_q$), 111.9 (d, $^{2}J_{C-F}$ = 22 Hz, CH), 51.2 (CH), 46.1 (CH), 20.9 (CH$_3$), 20.7 (CH$_3$), 20.6 (CH$_3$), 20.1 (CH$_3$).

^{19}F-NMR (283 MHz, CDCl$_3$): δ = −(114.3−114.6) (m).

IR (ATR): $\tilde{v}$ = 2966, 2928, 1631, 1599, 1438, 1337, 1226, 849, 813 cm^{-1}.

MS (EI) *m/z* (relative intensity): 379 (9) [M$^+$] (^{81}Br), 377 (9) [M$^+$] (^{79}Br), 336 (35), 334 (36), 279 (99), 277 (100), 170 (75), 135 (60).

HR-MS (EI) *m/z* calcd for C$_{19}$H$_{21}$FBrNO$^+$ 377.0791, found 377.0790.

Synthesis of methyl 4'-bromo-3'-(diisopropylcarbamoyl)-[1,1'-biphenyl]-4-carboxylate (220n)
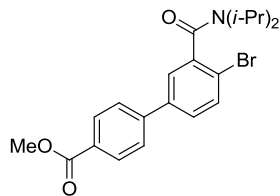
The general procedure **H** was followed using methyl 4'-bromo-3'-(diisopropylcarbamoyl)-[1,1'-biphenyl]-4-carboxylate (**219n**) (170 mg, 0.5 mmol) and NBS (178 mg, 1.0 mmol). After 22 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 10/1→4/1) yielded **220n** (120 mg, 57%) as a white solid.

M.p. = 182−183 ℃.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 8.08 (dt, J = 8.4, 1.8 Hz, 2H), 7.62 (d, J = 8.2 Hz, 1H), 7.59 (dt, J = 8.4, 1.8 Hz, 2H), 7.41 (dd, J = 8.2, 2.2 Hz, 1H), 7.38 (d, J = 2.2 Hz, 1H), 3.94 (s, 3H), 3.65 (sept, J = 6.7 Hz, 1H), 3.53 (sept, J = 6.7 Hz, 1H), 1.58 (d, J = 6.7 Hz, 3H), 1.57 (d, J = 6.7 Hz, 3H), 1.25 (d, J = 6.7 Hz, 3H), 1.07 (d, J = 6.7 Hz, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 167.8 (C$_q$), 166.7 (C$_q$), 143.7 (C$_q$), 140.7 (C$_q$), 139.6 (C$_q$), 133.4 (CH), 130.2 (CH), 129.5 (C$_q$), 128.2 (CH), 126.9 (CH), 125.1 (CH), 118.9 (C$_q$), 52.2 (CH$_3$), 51.2 (CH), 46.1 (CH), 20.9 (CH$_3$), 20.7 (CH$_3$), 20.6 (CH$_3$), 20.0 (CH$_3$).

IR (ATR): $\tilde{v}$ = 2960, 1719, 1629, 1435, 1368, 1340, 1271, 1102, 769, 710 cm^{-1}.

MS (EI) *m/z* (relative intensity): 419 (10) [M$^+$] (^{81}Br), 417 (10) [M$^+$] (^{79}Br), 376 (38), 374 (38), 319 (98), 317 (100), 151 (19).

HR-MS (EI) *m/z* calcd for C$_{21}$H$_{24}$BrNO$_3^+$ 417.0940, found 417.0934.

Synthesis of 4'-acetyl-4-bromo-*N*,*N*-diisopropyl-[1,1'-biphenyl]-3-carboxamide (220o)
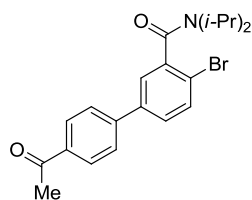
The general procedure **H** was followed using 4'-acetyl-*N*,*N*-diisopropyl-[1,1'-biphenyl]-3-carboxamide (**219o**) (162 mg, 0.5 mmol) and NBS (178 mg, 1.0 mmol). After 22 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 5/1→3/1) yielded **220o** (70 mg, 34%) as a white solid.

M.p. = 203−204 ℃.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 8.01 (d, *J* = 8.2 Hz, 2H), 7.66−7.58 (m, 3H), 7.38 (dd, *J* = 8.2, 2.2 Hz, 1H), 7.38 (d, *J* = 2.2 Hz, 1H), 3.65 (sept, *J* = 6.7 Hz, 1H), 3.53 (sept, *J* = 6.7 Hz, 1H), 2.62 (s, 3H), 1.58 (d, *J* = 6.7 Hz, 3H), 1.57 (d, *J* = 6.7 Hz, 3H), 1.25 (d, *J* = 6.7 Hz, 3H), 1.07 (d, *J* = 6.7 Hz, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 197.5 (C$_q$), 167.8 (C$_q$), 143.8 (C$_q$), 140.7 (C$_q$), 139.5 (C$_q$), 136.3 (C$_q$), 133.4 (CH), 129.0 (CH), 128.2 (CH), 127.1 (CH), 125.1 (CH), 119.0 (C$_q$), 51.3 (CH), 46.1 (CH), 26.7 (CH$_3$), 20.9 (CH$_3$), 20.7 (CH$_3$), 20.6 (CH$_3$), 20.0 (CH$_3$).

IR (ATR): $\tilde{v}$ = 2989, 1681, 1637, 1603, 1441, 1337, 1257, 1016, 813, 604 cm^{-1}.

MS (EI) *m/z* (relative intensity): 403 (11) [M$^+$] (^{81}Br), 401 (11) [M$^+$] (^{79}Br), 360 (43), 358 (43), 303 (99), 301 (100), 151 (18), 43 (41).

HR-MS (EI) *m/z* calcd for C$_{21}$H$_{24}$BrNO$_2^+$ 401.0990, found 401.0990.

Synthesis of 3'-acetyl-4-bromo-*N*,*N*-diisopropyl-[1,1'-biphenyl]-3-carboxamide (220p)

The general procedure **H** was followed using 3'-acetyl-*N*,*N*-diisopropyl-[1,1'-biphenyl]-3-carboxamide (**219p**) (162 mg, 0.5 mmol) and NBS (178 mg, 1.0 mmol). After 22 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 10/1→4/1) yielded **220p** (93 mg, 46%) as a white solid.
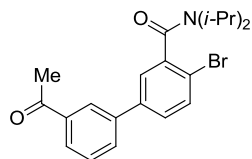
M.p. = 159−160 ℃.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 8.11 (t, *J* = 1.6 Hz, 1H), 7.93 (dt, *J* = 7.8, 1.6 Hz, 1H), 7.72 (dq, *J* = 7.6, 1.1 Hz, 1H), 7.62 (d, *J* = 8.2 Hz, 1H), 7.52 (dd, *J* = 7.8, 7.6 Hz, 1H), 7.41 (dd, *J* = 8.2, 2.3 Hz, 1H), 7.37 (d, *J* = 2.3 Hz, 1H), 3.65 (sept, *J* = 6.7 Hz, 1H), 3.53 (sept, *J* = 6.7 Hz, 1H), 2.63 (s, 3H), 1.58 (d, *J* = 6.7 Hz, 3H), 1.57 (d, *J* = 6.7 Hz, 3H), 1.24 (d, *J* = 6.7 Hz, 3H), 1.06 (d, *J* = 6.7 Hz, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 197.8 (C$_q$), 167.8 (C$_q$), 140.6 (C$_q$), 140.0 (C$_q$), 139.8 (C$_q$), 137.7 (C$_q$), 133.4 (CH), 131.5 (CH), 129.2 (CH), 128.2 (CH), 127.8 (CH), 126.7 (CH), 125.1 (CH), 118.7 (C$_q$), 51.2 (CH), 46.1 (CH), 26.8 (CH$_3$), 20.9 (CH$_3$), 20.7 (CH$_3$), 20.6 (CH$_3$), 20.0 (CH$_3$).

IR (ATR): $\tilde{v}$ = 2982, 2934, 1677, 1629, 1451, 1367, 1397, 1036, 767, 602 cm^{-1}.

MS (EI) *m/z* (relative intensity): 403 (11) [M$^+$] (^{81}Br), 401 (11) [M$^+$] (^{79}Br), 360 (46), 358 (46), 303 (98), 301 (100), 151 (15).

HR-MS (EI) *m/z* calcd for C$_{21}$H$_{24}$BrNO$_2^+$ 401.0990, found 401.0991.

Synthesis of 5-(5'-acetylthiophen-2-yl)-2-bromo-*N*,*N*-diisopropylbenzamide (220q)

The general procedure **H** was followed using 3-(5'-acetylthiophen-2-yl)-*N*,*N*-diisopropylbenzamide (**219q**) (165 mg, 0.5 mmol) and NBS (178 mg, 1.0 mmol). After 22 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 4/1→3/1) yielded **220q** (76 mg, 37%) as a white solid.
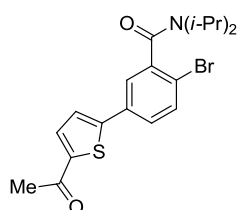
M.p. = 181−183 °C.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.62 (d, J = 4.0 Hz, 1H), 7.58 (d, J = 8.2 Hz, 1H), 7.43 (dd, J = 8.2, 2.2 Hz, 1H), 7.40 (d, J = 2.2 Hz, 1H), 7.29 (d, J = 4.0 Hz, 1H), 3.62 (sept, J = 6.7 Hz, 1H), 3.53 (sept, J = 6.7 Hz, 1H), 2.54 (s, 3H), 1.59 (d, J = 6.7 Hz, 3H), 1.55 (d, J = 6.7 Hz, 3H), 1.24 (d, J = 6.7 Hz, 3H), 1.07 (d, J = 6.7 Hz, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 190.5 (C$_q$), 167.3 (C$_q$), 150.3 (C$_q$), 143.8 (C$_q$), 140.9 (C$_q$), 133.6 (CH), 133.3 (CH), 133.0 (C$_q$), 127.0 (CH), 124.6 (CH), 124.0 (CH), 119.5 (C$_q$), 51.3 (CH), 46.1 (CH), 26.5 (CH$_3$), 20.9 (CH$_3$), 20.6 (CH$_3$), 20.6 (CH$_3$), 20.0 (CH$_3$).

IR (ATR): $\tilde{\nu}$ = 2977, 2936, 1653, 1621, 1435, 1340, 1281, 1021, 827, 796, 599 cm^{-1}.

MS (EI) m/z (relative intensity): 409 (10) [M$^+$] (^{81}Br), 407 (10) [M$^+$] (^{79}Br), 366 (40), 364 (40), 309 (100), 307 (100), 185 (14).

HR-MS (ESI) m/z calcd for [(C$_{19}$H$_{22}$BrNO$_2$S)H]$^+$ 408.0627, found 408.0620.

Synthesis of 2-iodo-*N,N*-diisopropylbenzamide (221a)

The general procedure **H** was followed using *N,N*-diisopropylbenzamide (**219a**) (103 mg, 0.5 mmol) and NIS (225 mg, 1.0 mmol). After 22 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 10/1→5/1) and normal phase HPLC (*n*-hexane/EtOAc: 19/1→9/1) yielded **221a** (88 mg, 53%) as a white solid.

M.p. = 188−189 °C.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.76 (dd, J = 8.0, 1.0 Hz, 1H), 7.34 (ddd, J = 7.6, 7.5, 1.0 Hz, 1H), 7.11 (dd, J = 7.6, 1.6 Hz, 1H), 7.00 (ddd, J = 8.0, 7.5, 1.6 Hz, 1H), 3.63−3.38 (m, 2H), 1.58 (d, J = 6.8 Hz, 3H), 1.54 (d, J = 6.8 Hz, 3H), 1.25 (d, J = 6.8 Hz, 3H), 1.04 (d, J = 6.8 Hz, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 169.8 (C$_q$), 144.2 (C$_q$), 139.3 (CH), 129.4 (CH), 128.2 (CH), 125.8 (CH), 92.2 (C$_q$), 51.2 (CH), 46.0 (CH), 20.7 (CH$_3$), 20.7 (CH$_3$), 20.6 (CH$_3$), 20.0 (CH$_3$).
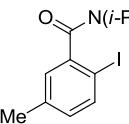
IR (neat): $\tilde{\nu}$ = 2967, 2929, 1618, 1581, 1435, 1339, 1012, 771 cm^{-1}.

MS (EI) m/z (relative intensity): 331 (7) [M$^+$], 288 (27), 230 (100), 202 (21), 43 (23).

HR-MS (EI) m/z calcd for C$_{13}$H$_{18}$INO$^+$ 331.0433, found 331.0414.

The spectral data were in accordance with those reported in the literature.[113a]

Synthesis of 2-iodo-*N,N*-diisopropyl-5-methylbenzamide (221h)

The general procedure **H** was followed using *N,N*-diisopropyl-3-methylbenzamide (**219h**) (217 mg, 1.0 mmol) and NIS (450 mg, 2.0 mmol). After 22 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 10/1) and normal phase HPLC (*n*-hexane/EtOAc: 19/1→9/1) yielded **221h** (219 mg, 64%) as a white solid.

M.p. = 161−162 °C.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.63 (d, J = 8.0 Hz, 1H), 6.93 (d, J = 2.0 Hz, 1H), 6.82 (dt, J = 8.0, 0.7 Hz, 1H), 3.58 (sept, J = 6.7 Hz, 1H), 3.49 (sept, J = 6.7 Hz, 1H), 2.27 (s, 3H), 1.57 (d, J = 6.7 Hz, 3H), 1.54 (d, J = 6.7 Hz, 3H), 1.25 (d, J = 6.7 Hz, 3H), 1.05 (d, J = 6.7 Hz, 3H).
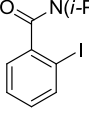
^{13}C-NMR (75 MHz, CDCl$_3$): δ = 169.9 (C$_q$), 144.0 (C$_q$), 139.0 (CH), 138.4 (C$_q$), 130.4 (CH), 126.5 (CH), 88.0 (C$_q$), 51.2 (CH), 45.9 (CH), 20.9 (CH$_3$), 20.8 (CH$_3$), 20.7 (CH$_3$), 20.6 (CH$_3$), 20.0 (CH$_3$).

IR (ATR): $\tilde{\nu}$ = 2966, 2928, 1621, 1441, 1337, 1012, 834, 763, 621, 455 cm^{-1}.

MS (EI) m/z (relative intensity): 345 (11) [M$^+$], 302 (23), 245 (100), 216 (16), 90 (22).

HR-MS (ESI) m/z calcd for [(C$_{14}$H$_{20}$INO)H]$^+$ 346.0668, found 346.0662.

The spectral data were in accordance with those reported in the literature.[179]

Synthesis of 2-iodo-*N*,*N*-diisopropyl-4,5-dimethylbenzamide (**219v**)
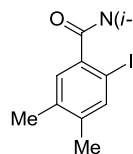
The general procedure **H** was followed using *N*,*N*-diisopropyl-3,4-dimethylbenzamide (**219v**) (233 mg, 1.0 mmol) and NIS (450 mg, 2.0 mmol). After 22 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 20/1→10/1) yielded **221v** (187 mg, 52%) as a white solid.

M.p. = 106−107 °C.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.55 (s, 1H), 6.94 (s, 1H), 3.62 (sept, *J* = 6.7 Hz, 1H), 3.49 (sept, *J* = 6.7 Hz, 1H), 2.21 (s, 3H), 2.17 (s, 3H), 1.58 (d, *J* = 6.7 Hz, 3H), 1.56 (d, *J* = 6.7 Hz, 3H), 1.26 (d, *J* = 6.7 Hz, 3H), 1.06 (d, *J* = 6.7 Hz, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 170.0 (C$_q$), 141.8 (C$_q$), 139.7 (CH), 138.4 (C$_q$), 137.0 (C$_q$), 126.8 (CH), 88.3 (C$_q$), 51.1 (CH), 45.8 (CH), 20.8 (CH$_3$), 20.7 (CH$_3$), 20.6 (CH$_3$), 20.0 (CH$_3$), 19.3 (CH$_3$), 19.1 (CH$_3$).
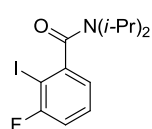
IR (ATR): $\tilde{v}$ = 2970, 2929, 1623, 1435, 1359, 1322, 1043, 817, 609 cm^{-1}.

MS (EI) *m/z* (relative intensity): 359 (10) [M$^+$], 316 (28), 259 (100), 232 (17), 104 (13).

HR-MS (EI) *m/z* calcd for C$_{15}$H$_{22}$INO$^+$ 359.0746, found 359.0745.

Synthesis of 3-fluoro-2-iodo-*N*,*N*-diisopropylbenzamide (**219i**)

The general procedure **H** was followed using 3-fluoro-*N*,*N*-diisopropylbenzamide (**219i**) (219 mg, 1.0 mmol) and NIS (450 mg, 2.0 mmol). After 22 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 5/1) yielded **221i** (128 mg, 36%) as a white solid.

M.p. = 124−125 °C.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.32 (ddd, *J* = 8.0, 5.2, 0.7 Hz, 1H), 7.00 (ddd, *J* = 8.0, 7.6, 1.5 Hz, 1H), 6.93 (dd, *J* = 7.6, 1.0 Hz, 1H), 3.62−3.43 (m, 2H), 1.60 (d, *J* = 6.6 Hz, 3H), 1.56 (d, *J* = 6.6 Hz, 3H), 1.26 (d, *J* = 6.6 Hz, 3H), 1.07 (d, *J* = 6.6 Hz, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 168.6 (d, $^4J_{C-F}$ = 2 Hz, C$_q$), 161.8 (d, $^1J_{C-F}$ = 246 Hz, C$_q$), 146.4 (d, $^3J_{C-F}$ = 8 Hz, C$_q$), 130.3 (d, $^3J_{C-F}$ = 8 Hz, CH), 121.4 (d, $^4J_{C-F}$ = 3 Hz, CH), 114.8 (d, $^2J_{C-F}$ = 24 Hz, CH), 76.5 (d, $^2J_{C-F}$ = 26 Hz, C$_q$), 51.3 (CH), 46.1 (CH), 20.8 (CH$_3$), 20.7 (CH$_3$), 20.6 (CH$_3$), 20.0 (CH$_3$).

^{19}F-NMR (283 MHz, CDCl$_3$): δ = −(90.8−90.9) (m).

IR (ATR): $\tilde{v}$ = 2967, 2930, 1620, 1435, 1340, 1203, 1041, 788, 604 cm^{-1}.

MS (EI) *m/z* (relative intensity): 349 (10) [M$^+$], 306 (28), 249 (100), 218 (18), 43 (16).

HR-MS (EI) *m/z* calcd for C$_{13}$H$_{17}$FINO$^+$ 349.0339, found 349.0339.

Synthesis of 4-iodo-*N*,*N*-diisopropylbenzo[*d*][1,3]dioxole-5-carboxamide (**221w**)
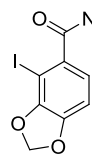
The general procedure **H** was followed using 4-iodo-*N*,*N*-diisopropylbenzo[*d*][1,3]dioxole-5-carboxamide (**219w**) (249 mg, 1.0 mmol) and NIS (450 mg, 2.0 mmol). After 22 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 5/1) yielded **221w** (277 mg, 73%) as a white solid.

M.p. = 149−150 °C.

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[179] V. S. Chan, R. G. Bergman, F. D. Toste, *J. Am. Chem. Soc.* **2007**, *129*, 15122–15123.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 6.73 (d, J = 7.8 Hz, 1H), 6.61 (d, J = 7.8 Hz, 1H), 6.02 (dd, J = 7.0, 1.2 Hz, 2H), 3.62 (sept, J = 6.7 Hz, 1H), 3.47 (sept, J = 6.7 Hz, 1H), 1.55 (d, J = 6.7 Hz, 3H), 1.52 (d, J = 6.7 Hz, 3H), 1.22 (d, J = 6.7 Hz, 3H), 1.04 (d, J = 6.7 Hz, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 169.1 (C$_q$), 149.7 (C$_q$), 145.5 (C$_q$), 137.5 (C$_q$), 119.1 (CH), 108.3 (CH), 100.7 (C$_q$), 70.0 (CH$_2$), 51.2 (CH), 46.0 (CH), 20.8 (CH$_3$), 20.7 (CH$_3$), 20.6 (CH$_3$), 20.2 (CH$_3$).

IR (ATR): $\tilde{v}$ = 2961, 2927, 1621, 1445, 1339, 1238, 1033, 898, 763, 593 cm^{-1}.

MS (EI) m/z (relative intensity): 375 (13) [M$^+$], 332 (20), 275 (100), 149 (12).

HR-MS (EI) m/z calcd for C$_{14}$H$_{18}$INO$_3{}^+$ 375.0331, found 375.0329.

Synthesis of 4-iodo-*N*,*N*-diisopropyl-[1,1'-biphenyl]-3-carboxamide (221k)

The general procedure **H** was followed using *N*,*N*-diisopropyl-[1,1'-biphenyl]-3-carboxamide (**219k**) (141 mg, 0.5 mmol) and NIS (338 mg, 1.5 mmol). After 22 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 20/1→10/1) yielded **221k** (130 mg, 64%) as a white solid.
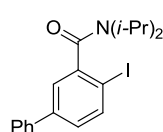
M.p. = 171−172 °C.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.84 (d, J = 8.2 Hz, 1H), 7.53 (dt, J = 7.0, 2.0 Hz, 2H), 7.43 (dt, J = 7.0, 2.0 Hz, 2H), 7.36 (dt, J = 7.0, 1.3 Hz, 1H), 7.32 (d, J = 2.2 Hz, 1H), 7.23 (dd, J = 8.2, 2.2 Hz, 1H), 3.65 (sept, J = 6.7 Hz, 1H), 3.52 (sept, J = 6.7 Hz, 1H), 1.60 (d, J = 6.7 Hz, 3H), 1.58 (d, J = 6.7 Hz, 3H), 1.28 (d, J = 6.7 Hz, 3H), 1.06 (d, J = 6.7 Hz, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 169.6 (C$_q$), 144.5 (C$_q$), 141.4 (C$_q$), 139.6 (CH), 139.4 (C$_q$), 128.9 (CH), 128.1 (CH), 127.9 (CH), 126.9 (CH), 124.3 (CH), 90.8 (C$_q$), 51.2 (CH), 46.0 (CH), 20.8 (CH$_3$), 20.7 (CH$_3$), 20.6 (CH$_3$), 20.0 (CH$_3$).

IR (ATR): $\tilde{v}$ = 2967, 2930, 1622, 1444, 1337, 1207, 785, 608 cm^{-1}.

MS (EI) m/z (relative intensity): 407 (15) [M$^+$], 364 (35), 307 (100), 276 (25), 152 (45).

HR-MS (EI) m/z calcd for C$_{19}$H$_{22}$INO$^+$ 407.0746, found 407.0727.

Synthesis of 4-iodo-*N*,*N*-diisopropyl-4'-methyl-[1,1'-biphenyl]-3-carboxamide (221l)
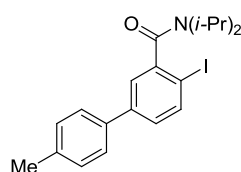
The general procedure **H** was followed using *N*,*N*-diisopropyl-4'-methyl-[1,1'-biphenyl]-3-carboxamide (**219l**) (148 mg, 0.5 mmol) and NIS (225 mg, 1.0 mmol). After 22 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 20/1→10/1) yielded **219l** (145 mg, 68%) as a white solid.

M.p. = 208−210 °C.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.82 (d, J = 8.2 Hz, 1H), 7.43 (dt, J = 8.1, 1.8 Hz, 2H), 7.30 (d, J = 2.2 Hz, 1H), 7.26−7.19 (m, 3H), 3.65 (sept, J = 6.6 Hz, 1H), 3.52 (sept, J = 6.6 Hz, 1H), 2.37 (s, 3H), 1.60 (d, J = 6.6 Hz, 3H), 1.57 (d, J = 6.6 Hz, 3H), 1.27 (d, J = 6.6 Hz, 3H), 1.06 (d, J = 6.6 Hz, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 169.8 (C$_q$), 144.5 (C$_q$), 141.4 (C$_q$), 139.6 (CH), 137.8 (C$_q$), 136.6 (C$_q$), 129.6 (CH), 128.0 (CH), 126.7 (CH), 124.1 (CH), 90.4 (C$_q$), 51.2 (CH), 46.0 (CH), 21.1 (CH$_3$), 20.8 (CH$_3$), 20.7 (CH$_3$), 20.7 (CH$_3$), 20.0 (CH$_3$).

IR (ATR): $\tilde{v}$ = 2968, 2929, 1627, 1440, 1335, 1034, 762, 515 cm^{-1}.

MS (ESI) m/z (relative intensity): 382 (82) [(M+H)$^+$], 444 (37) [(M+Na)$^+$], 843 (100) [(2M+H)$^+$].

HR-MS (ESI) m/z calcd for [(C$_{20}$H$_{24}$INO)H]$^+$ 382.0975, found 382.0970.

Synthesis of 2-iodo-*N*,*N*-diisopropyl-5-(naphthalen-1-yl)benzamide (221x)
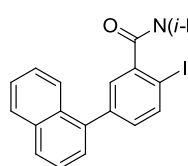
The general procedure **H** was followed using *N*,*N*-diisopropyl-3-(naphthalen-1-yl)benzamide (**219x**) (166 mg, 0.5 mmol) and NIS (225 mg, 1.0 mmol). After 22 h, purification by column chromatography on silica gel (*n*-hexane/EtOAc: 20/1→10/1) yielded **221x** (134 mg, 59%) as a white solid.

M.p. = 161−162 °C.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.91 (d, *J* = 8.2 Hz, 1H), 7.89 (d, *J* = 8.2 Hz, 1H), 7.86 (d, *J* = 8.6 Hz, 1H), 7.82 (d, *J* = 8.6 Hz, 1H), 7.50 (dd, *J* = 8.2, 7.0 Hz, 1H), 7.46 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H), 7.38 (ddd, *J* = 7.6, 7.5, 1.5 Hz, 1H), 7.37 (dd, *J* = 7.5, 1.1 Hz, 1H), 7.25 (dd, *J* = 2.2, 2.1 Hz, 1H), 7.15 (dd, *J* = 8.2, 2.1 Hz, 1H), 3.77 (sept, *J* = 6.6 Hz, 1H), 3.51 (sept, *J* = 6.6 Hz, 1H), 1.61 (d, *J* = 6.7 Hz, 3H), 1.51 (d, *J* = 6.7 Hz, 3H), 1.33 (d, *J* = 6.7 Hz, 3H), 1.09 (d, *J* = 6.7 Hz, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 169.6 (C$_q$), 144.2 (C$_q$), 141.0 (C$_q$), 139.3 (CH), 138.3 (C$_q$), 133.7 (C$_q$), 131.1 (CH), 128.4 (CH), 128.2 (CH), 127.4 (CH), 126.9 (CH), 126.3 (CH), 126.0 (CH), 125.5 (CH), 125.3 (CH), 91.0 (C$_q$), 51.4 (CH), 46.0 (CH), 20.9 (CH$_3$), 20.7 (CH$_3$), 20.6 (CH$_3$), 20.1 (CH$_3$) (One C$_q$ is invisible).

IR (ATR): $\tilde{v}$ = 2968, 2933, 1624, 1439, 1368, 1331, 1119, 1038, 1011, 778 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 458 [(M+H)$^+$] (46), 915 [(2M+H)$^+$] (100).

HR-MS (ESI) *m/z* calcd for [(C$_{25}$H$_{18}$F$_3$NO)H]$^+$ 458.0975, found 458.0968.

Studies with isotopically labelled [D]$_4$-MeOH (Scheme 90a)
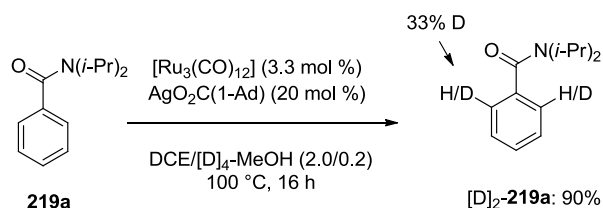
A mixture of *N*,*N*-diisopropylbenzamide (**219a**) (103 mg, 0.5 mmol), Ru$_3$(CO)$_{12}$ (10.5 mg, 3.3 mol %) and AgO$_2$C(1-Ad) (28.7 mg, 20 mol %) in DCE (2.0 mL) and [D]$_4$-MeOH (0.2 mL) was stirred at 100 °C under N$_2$ for 16 h. The mixture was then allowed to cool to ambient temperature, diluted with EtOAc (5 mL), filtered through a short pad of silica gel and eluted with EtOAc (50 mL). After removing the solvent under reduced pressure, the product was purified by column chromatography on silica gel (*n*-hexane/EtOAc: 4/1) to yield a mixture **219a** and [D]$_2$-**219a** (93 mg, 90%) as a white solid. The deuterium incorporation was estimated to be 33% by ^{1}H-NMR spectroscopy.

Studies with isotopically labelled compound [D]$_1$-250 (Scheme 90b)
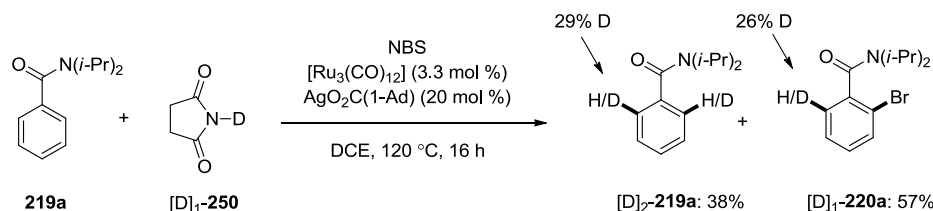
A mixture of *N*,*N*-diisopropylbenzamide (**219a**) (205 mg, 1.0 mmol), NBS (356 mg, 2.0 mmol),

$Ru_3(CO)_{12}$ (21.1 mg, 3.3 mol %), AgO_2C(1-Ad) (57.4 mg, 20 mol %) and [D]$_1$-**250** (200 mg, 2.0 mmol) in DCE (3.0 mL) was stirred at 120 °C under N_2 for 16 h. The mixture was then allowed to cool down to ambient temperature, diluted with EtOAc (5 mL), filtered through a short pad of silica gel and eluted with EtOAc (50 mL). After removing the solvent under reduced pressure, the product was purified by column chromatography on silica gel (*n*-hexane/EtOAc: 10/1→5/1) to give [D]$_1$-**220a** (164 mg, 57%) as a white solid and [D]$_2$-**219a** (79 mg, 38%) as a white solid. The deuterium incorporation was estimated by ^{1}H-NMR spectroscopy.

Kinetic isotope effect studies by parallel experiments (Scheme 91)
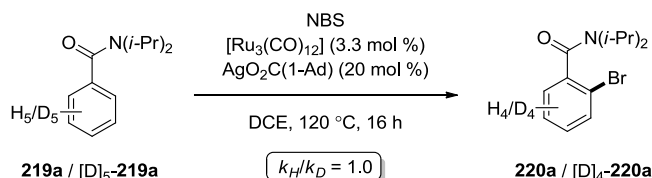
A mixture of benzamide **219a** or [D]$_5$-**219a** (1.0 mmol), NBS (356 mg, 2.0 mmol), $Ru_3(CO)_{12}$ (21.1 mg, 3.3 mol %), AgO_2C(1-Ad) (57.4 mg, 20 mol %) and the internal standard 1,3,5-tri-*tert*-butylbenzene (246 mg, 1.0 mmol) in DCE (8.0 mL) was stirred at 120 °C under N_2. For three hours, an aliquot (0.2 mL) was collected every fifteen minutes and submitted to GC analysis to determine the conversion.
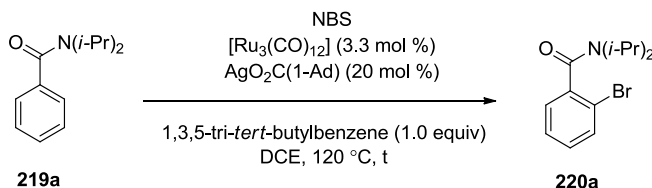
Entry	1	2	3	4	5	6	7	8	9	10	11	12
220a	2	9	20	25	31	35	39	38	44	46	48	49
219a	98	91	76	75	69	65	61	58	56	54	52	51
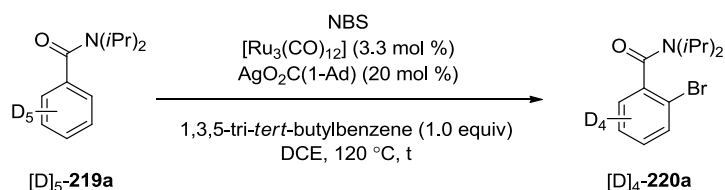
Entry	1	2	3	4	5	6	7	8	9	10	11	12
[D]$_4$-**220a**	2	9	19	25	31	35	39	41	43	44	46	46
[D]$_5$-**219a**	98	91	81	75	69	65	61	59	57	56	54	54

9 List of Abbreviations

Å	Ångström		ESI	electrospray ionization
Ac	acetyl		Et	ethyl
Ad	adamantly		FG	functional group
Alk	alkyl		g	gram
AMLA	ambiphilic metal-ligand activation		GC	gas chromatography
aq.	aqueous		h	hour
Ar	aryl		Het	Hetero(aryl)
APT	attached proton test		Hept	heptyl
atm	atmospheric pressure		HPLC	high performance liquid chromatography
ATR	attenuated total reflectance		HR-MS	high resolution mass spectrometry
BHT	2,6-di-*tert*-butyl-4-methylphenol		Hz	Hertz
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl		*i*	*iso*
Bn	benzyl		IES	internal electrophilic substitution
Boc	*tert*-butyloxycarbonyl		IR	infrared spectroscopy
Bu	Butyl		*J*	coupling constant
Bz	benzoyl		KIE	kinetic isotope effect
calc.	calculated		L	ligand
cat.	catalyst		Leu	leucine
CMD	concerted-metalation-deprotonation		*m*	meta
cod	1,5-cyclooctadien		m	multiplet
conv.	conversion		M	molar
Cp	cyclopentadienyl		[M$^+$]	molecular ion peak
Cy	cyclohexyl		Me	methyl
δ	chemical shift		Mes	mesityl
d	doublet		mg	milligram
DCE	1,2-dichloroethane		MHz	megahertz
DCM	dichloromethane		min	minute
dd	doublet of doublet		mL	milliliter
DFT	density functional theory		mmol	millimol
DG	directing group		M. p.	melting point
DMA	*N*,*N*-dimethylacetamide		MPV	membrane pump vacuum
DME	dimethoxyethane		MS	mass spectrometry
DMF	*N*,*N*-dimethylformamide		*m/z*	mass-to-charge ratio
DMSO	dimethyl sulfoxide		*n*	*normal*
DoM	directed *ortho* metalation		NBS	*N*-bromosuccinimide
DPPH	2,2-diphenyl-1-picrylhydrazyl		NHC	*N*- heterocyclic carbene
dt	doublet of triplet		NIS	*N*-iodosuccinimide
Ed.	editor		NMP	*N*-methylpyrrolidinone
EI	electron ionization		NMR	nuclear magnetic resonance
equiv	equivalent		NXS	*N*-halosuccinimides

o	*ortho*		SPS	solvent purification system
OPV	oil pump vacuum		*t*	*tert*
p	*para*		t	triplet
Ph	phenyl		*T*	temperature
Piv	pivaloyl		TEMPO	2,2,6,6-tetramethylpiperidin-1-yloxy
ppm	parts per million		Tf	trifluoromethanesulfonate
Pr	propyl		TFA	trifluoroacetic acid
PTSA	*p*-toluenesulfonic acid		TFAA	trifluoroacetic anhydride
Py	pyridyl		THF	tetrahydrofuran
PyDipSi	pyridyldiisopropylsilyl		TLC	thin layer chromatography
pym	pyrimidyl		TM	transition metal
q	quartet		TMS	trimethylsilyl
R	rest		Ts	*para*-toluenesulfonyl
rac	*racemic*		TS	transition state
ref.	reference		$\tilde{\nu}$	absorption
s	singlet		wt%	weight by volume
sat.	saturated		X	(pseudo)halide
sec	*secondary*		PyDipSi	pyridyldiisopropylsilyl
S_E^{Ar}	electrophilic aromatic substitution		XPhos	2-dicyclohexylphosphino-2′,4′,6′-tri-
SET	single electron transfer			isopropylbiphenyl
SPO	secondary phosphine oxides			

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Lianhui Wang （王连会）

Curriculum Vitae

Date of birth: March 8th, 1983
Place of birth: Puyang (China)
Nationality: Chinese

Education

10/2010 – 02/2014	Studies for a doctorate under the supervision of Prof. Dr. Lutz Ackermann, Institute of Organic and Biomolecular Chemistry
	Georg-August University of Göttingen, Göttingen, Germany
	Research topic: "Carboxylate-Assisted Ruthenium-Catalyzed Direct C−H Bond Functionalizations"
09/2007 – 07/2010	M. Sc. in Organic Chemistry
	Supervisors: Prof. Dr. Xiuling Cui and Prof. Dr. Zhiwu Zhu
	Department of Chemistry, Zhengzhou University, Zhengzhou, China
	Research topic: "Application of Cyclopalladated Ferrocenylimine Complexes in the Synthesis of Arylboronate Esters and Suzuki-Miyaura Reaction"
09/2003 – 07/2007	B. Sc. in Chemistry
	Department of Chemistry, Zhengzhou University, Zhengzhou, China

Experience

08/2011 – 03/2013	Teaching Assistant
	Institute of Organic and Biomolecular Chemistry
	Georg-August University of Göttingen, Göttingen, Germany

Publications

1. **Lianhui Wang** and Lutz Ackermann*: Ruthenium-catalyzed *ortho*-C−H halogenation of benzamides. *Chem. Commun.* **2014**, *50*, 1083−1085.

2. M. Schinkel, **Lianhui Wang**, K. Bielefeld, L. Ackermann*: Ruthenium(II)-Catalyzed C(sp^3)−H α-Alkylation of Pyrrolidines. *Org. Lett.* **2014**, *16*, Accepted for publication.

3. **Lianhui Wang** and Lutz Ackermann*: Versatile pyrrole synthesis through ruthenium(II)-catalyzed alkene C−H bond functionalization on enamines. *Org. Lett.* **2013**, *15*, 176−179.

4. Lutz Ackermann*, **Lianhui Wang**, Ratnakancana Wolfram and Alexander V. Lygin: Ruthenium-catalyzed oxidative C−H alkenylations of anilides and benzamides in water. *Org. Lett.* **2012**, *14*, 728−731.

5. Lutz Ackermann*, **Lianhui Wang** and Alexander V. Lygin: Ruthenium-catalyzed aerobic oxidative coupling of alkynes with 2-aryl-substituted pyrroles. *Chem. Sci.* **2012**, *3*, 177−180. (highlighted by the *Royal Society of Chemistry*)

6. **Lianhui Wang**, Xiuling Cui*, Jingya Li, Yusheng Wu, Zhiwu Zhu and Yangjie Wu*: Synthesis of biaryls through a one-pot tandem borylation/Suzuki–Miyaura cross-coupling reaction catalyzed by a palladacycle. *Eur. J. Org. Chem.* **2012**, 595−603.

7. **Lianhui Wang**, Jingya Li, Xiuling Cui*, Yusheng Wu, Zhiwu Zhu and Yangjie Wu*: Cyclopalladated ferrocenylimines as efficient catalysts for the synthesis of arylboronate esters. *Adv. Synth. Catal.* **2010**, *352*, 2002−2010.