Dehydrogenative C–N Cross-Coupling

DOI: 10.1002/anie.201308601

Ruthenium-Catalyzed Cross-Dehydrogenative *ortho*-N-Carbazolation of Diarylamines: Versatile Access to Unsymmetrical Diamines**

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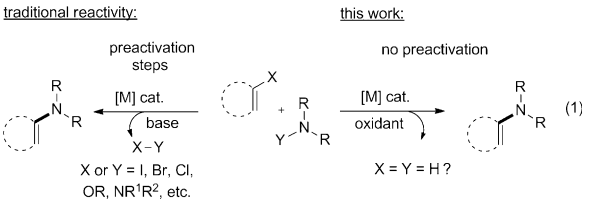
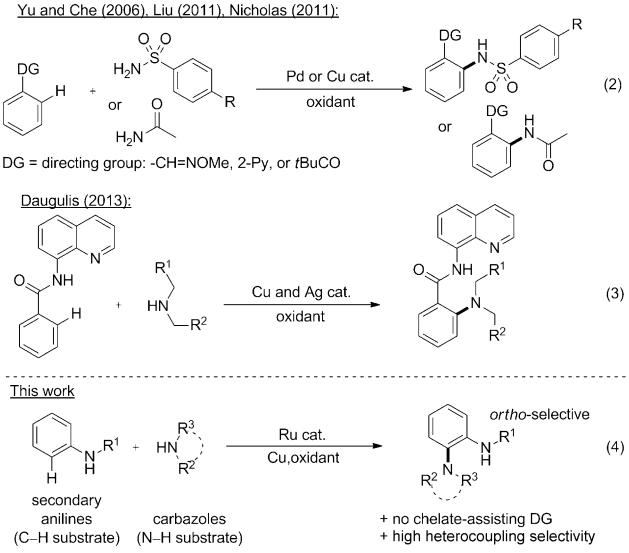
Abstract: *The dehydrogenative C–N cross-coupling of unprotected, secondary anilines through ortho-N-carbazolation has been achieved using a Ru catalytic system with O_2 as the terminal oxidant. The reactions proceed in an intermolecular fashion, selectively in the ortho position. Implications for the field of organic synthesis are discussed.*

The development of novel cross-coupling methods has considerably expanded over the past decade, due to recent exceptional discoveries in the field of metal-catalyzed C–H activation.[1] These methods are becoming very popular in the field of chemistry as they usually allow useful and unprecedented reactivity. Those classified as cross-dehydrogenative couplings (CDCs) are particularly attractive because they typically do not require preactivation and/or preoxidation of either coupling partners, and they are also more atom-economical [Eq. (1)].[2] The formation of C–N bonds is immensely important for the construction of biologically



relevant scaffolds.[3] Very few CDC-amination methods exist however,[4] due to pK_a incompatibility issues (C–H activation methods usually require acidic conditions),[5] but also thermodynamic limitations (the reductive elimination with formation of the C–N bond and/or the transmetalation step are reputed to be energetically difficult).[6] In spite of these challenges, inspiring seminal works from Yu and Che,[7] Su,[8] Liu,[9] Nicholas,[10] Daugulis,[11] and others[12] have appeared recently, showcasing the feasibility of the concept of intermolecular CDC-amination reactions [Eqs. (2) and (3)], although unpractical, strongly coordinating directing groups are often required.



We recently reported promising C–N bond-forming reactivity in a Ru-catalyzed method for the intermolecular homodimerization of carbazoles leading to an interesting class of dicarbazole products: lauternazoles.[13] We now turn our attention to the C–H activation and CDC-amination of highly ubiquitous diarylamines.[3] Initial investigations using Ru as catalyst[14] rapidly established that diphenylamine can be selectively *ortho* N-carbazolated to yield diamine **3a** as an exclusive cross-coupling product [Eq. (4), Scheme 1]. This new reactivity is particularly synthetically relevant because: 1) it constitutes a rare case of intermolecular hetero CDC-amination; 2) it is a surprisingly regioselective reaction with respect to the C–H functionalization (diarylamine), as well as the N–H functionalization (carbazole), in spite of multiple possibilities; 3) it does not require a conventional, strongly coordinating, chelate-assisting directing group; 4) it utilizes O_2 as the terminal oxidant.

We optimized the reaction as follows. The carbazole (1 mmol), the diarylamine (3 mmol), [{(*p*-cymene)$RuCl_2$}$_2$] (5 mol%), anhydrous $Cu(OAc)_2$ (2.2 equiv), cumene (0.5 mL), tetrachloroethylene (TCE, 2 mL), and acetic acid (0.5 mL) are united in a screw-cap vessel and flushed with O_2. The vessel is then sealed and heated at 150 °C for 24 h. Treatment with acetylacetonate (neutralization of metal salts) followed by column chromatography affords the cross-coupling products **3a–w** in moderate to excellent yields [Scheme 1, Scheme 2, Scheme 3, Eq. (5)].[15] For convenience,

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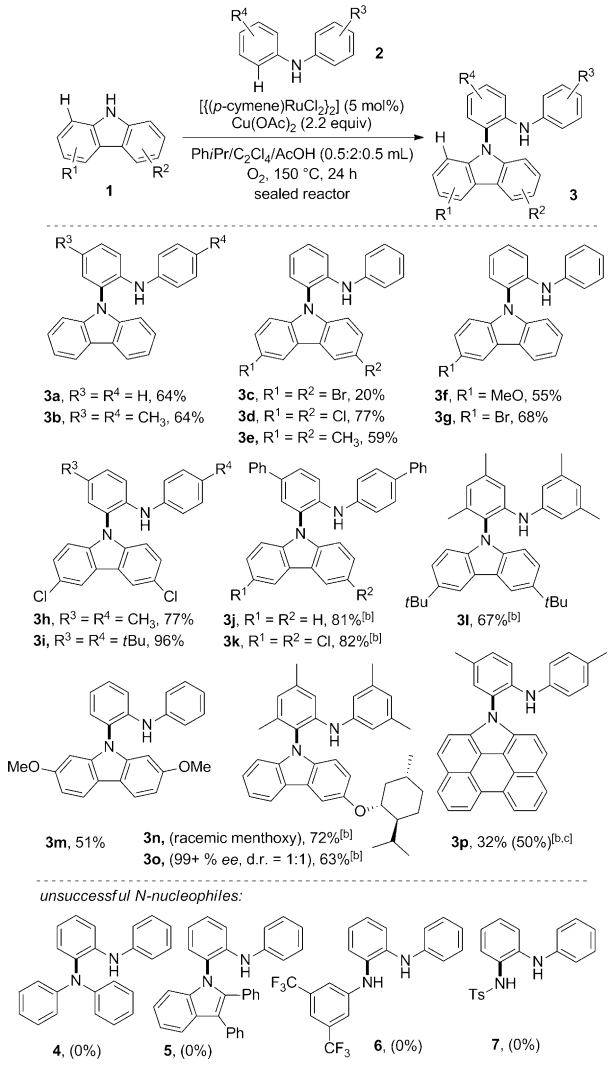
[**] This work was supported by the DFG-funded transregional collaborative research center SFB/TRR 88 "Cooperative effects in homo- and heterometallic complexes (http://3MET.de)". Corinna Nimphius is also acknowledged.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201308601.

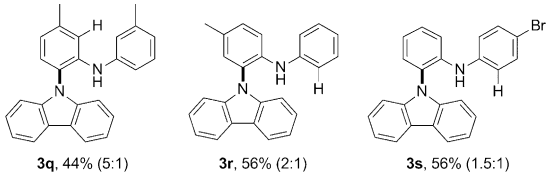


Scheme 1. Substrate scope, yields of isolated products. [a] All reactions are carried out in a sealed reactor of circa 170 mL, on a 1 mmol scale of N-coupling partner (carbazole), and 3 mmol of C-coupling partner (diarylamine). [b] Those entries were carried out on 0.5 mmol scale, in a circa 70 mL sealed reactor. [c] Entry **3p** gives 50% NMR yield of the expected product, but only 32% were isolated due to a difficult separation.

we refer to this novel class of diamine compounds as lauternamines. It should be noted that: 1) cumene is a significantly better cosolvent than chlorobenzene, toluene, *tert*-butylbenzene, or even *para*-cymene (the ligand on the Ru precursor); 2) TCE is a necessary component of the reaction, its omission typically leads to low conversion and/or decomposition;[16] 3) O_2 is the preferred oxidant, its replacement by N_2 ($Cu(OAc)_2$ as sole oxidant) decreases the yield of **3a** from 64 to 39%; 4) neither primary aniline nor acetanilide react with carbazole, making diarylamines a privileged substrate class in this reaction.

With these conditions in hand, we found this novel cross-dehydrogenative amination reaction to tolerate a number of functional groups, including halides such as Cl and Br (**3c**,**d**,**g**–**i**,**k**). Selected substrates react with high efficiency, notably 3,6-dichlorocarbazole (**3d**,**h**,**i**,**k** isolated in 77, 77, 96, and 82% yield, respectively) as well as 4,4′-diphenyldiarylamine (**3j**,**k**). It is interesting to note that "perycarbazole" **1p**, a compound of industrial interest in high-performance semiconducting devices,[17] undergoes our reaction, affording **3p** in 50% yield (Scheme 1). Intriguingly, diphenylamine is not effective as an N-nucleophile (no homocoupling product **4**). Neither are 2,3-diphenylindole (electronically similar to carbazole, **5**), 3,5-trifluoromethylaniline (**6**), nor tosylamine (**7**).

Furthermore, sterics do not seem to alter reactivity. For instance 2,7-dimethoxycarbazole still leads to **3m** in 51% yield. Even more illustrative, 1,3,5-dixylylamine still affords **3l**,**n**,**o** in 67, 72, and 63% yield, respectively, in spite of a methyl group *ortho* to the C–H functionalization position. Steric pressure could be utilized in order to induce regioselective C–N bond formation (product **3q**, 5:1 in favor of the less sterically hindered C–H position, Scheme 2). Electronic

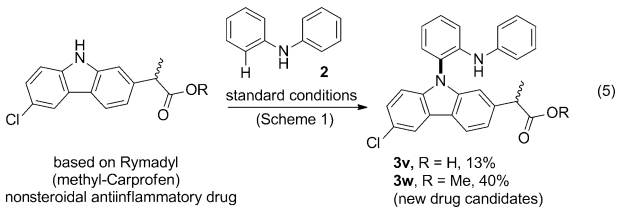


Scheme 2. Steering the regioselectivity by means of sterics and/or electronics, reaction conditions: see Scheme 1. The ratio of regioisomers is given in parentheses.

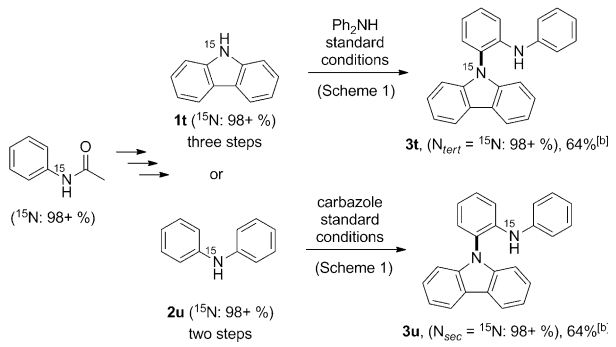
effects are somewhat less efficient in inducing a regioselective reaction, however, whether with electron-donating or withdrawing substituents (**3r** and **3s**, 2:1 and 1.5:1, respectively, in favor of functionalization at the most electron-rich position).

Our method is also remarkably efficient for the preparation of unsymmetrical selectively isotopically labeled *ortho* diamine compounds. For example, **3t** (tertiary ^{15}N, 98+%), and **3u** (secondary ^{15}N, 98+%), were both readily prepared in 64% yield (Scheme 3).[15]

A biologically active carbazole could also be engaged: Carprofen, a nonsteroidal antiinflammatory drug, notably commercialized by Pfizer as a racemate under the trade name Rimadyl.[18] The corresponding coupling product **3w** could be obtained with a promising 40% yield.[15,19] We expect that our late-stage CDC-amination method could be used to generate rapidly libraries of new drug candidates [Eq. (5)].



Surprisingly, engaging nonsymmetrical carbazoles systematically leads to chiral C–N cross-coupling products, due to constrained rotation about the C–N_{tert} axis. We suspect that the intramolecular N–H···N hydrogen bond is partly respon-



Scheme 3. Access to unsymmetrically semi-labeled ^{15}N-^{14}N *ortho*-diamines, with absolute regio-isotopic control.

sible for this constraint.[20] For example, the racemic product **3f**, obtained from the condensation of simple 3-methoxycarbazole with diphenylamine, can be separated readily into its enantiomers by analytical HPLC on a chiral stationary phase (OD-H column, Figure 1). Likewise, product **3v**, based on

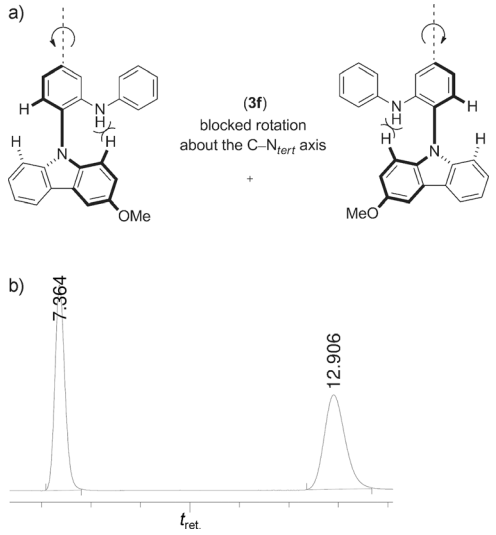
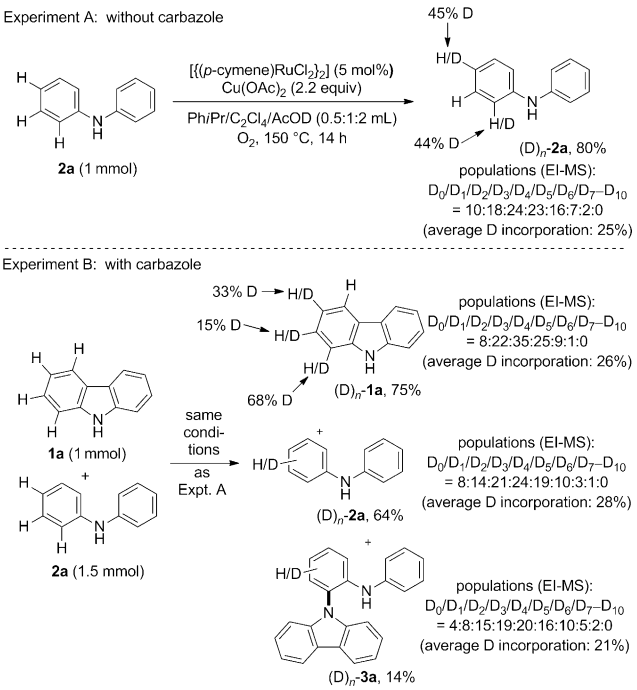


Figure 1. OD-H HPLC profile of **3f**, flow: 1 mL min^{-1} in hexane/*i*PrOH (97:3), detection 254 nm. Horizontal axis: retention time (t = 7.36 min., 50.8% of integration, first enantiomer, t = 12.91 min., 49.2% of integration, second enantiomer).

(racemic) Carprofen, is characterized by NMR spectroscopy as two diastereomers. It should be noted that increasing the temperature to 160 °C in [D_6]-DMSO did not lead to internal rotation about the C–N_{tert} axis on the NMR timescale. NMR data at temperatures above 160 °C could not be obtained for compound **3v** because of thermal decomposition.[15] In the same spirit, chiral product **3o**, bearing an enantiomerically pure menthoxy auxiliary, was obtained in 63% yield as a 1:1 mixture of diastereomers. We expect that this new kind of C–N_{tert} axial chirality will find interesting future applications, for example in ligands in metal-catalyzed enantioselective transformations.

Initial mechanistic experiments were carried out by first engaging diphenylamine under pseudo-reaction conditions,



Scheme 4. H–D scrambling experiments.

with [D_1]-acetic acid, and initially without carbazole coupling partner (for simplicity, Experiment A, Scheme 4).[15] As expected, significant reversible metalation–deuteration occurs in the *ortho* position (44% D), and in the *para* position (46% D), with an overall average D incorporation of 25% (determined by MS). It is interesting to note that C–H metalation occurs at the most nucleophilic *ortho* and *para* positions, but only the former reacts further to give the C–N cross-coupling product. We then performed the experiment in the presence of carbazole (Experiment B, Scheme 4). The unreacted diphenylamine was again found with a consistent average deuterium incorporation of 28%. In other words, the C–H activation step is reversible under the reaction conditions, and is therefore not rate limiting. We assume the C–N bond-forming reductive elimination to be the most likely rate-limiting step. Interestingly, in this experiment the unreacted carbazole was measured with an average D incorporation of 26%. In other words, although carbazole acts as the N-coupling partner, it is still significantly (reversibly) C–H activated under the reaction conditions. It is also interesting to note that Experiment A can still result in significant H–D scrambling on diphenylamine (D incorporation of 36%) if both $Cu(OAc)_2$ and O_2 are omitted, highlighting that those components do not operate at the C–H activation stage, but later on in the catalytic cycle.[21] This means the current reaction mechanism is significantly different from the previously reported homodimerization of carbazoles.[13]

In summary, we have developed an efficient Ru-catalyzed method to N-carbazolate diarylamines in the *ortho* position by direct intermolecular CDC-amination, leading to unprecedented unsymmetrical diamines. This intermolecular hetero-CDC-amination method is exceptional because it obviates the need for the preoxidation of either coupling

partners, and it operates without a chelate-assisting directing group. We are now working on translating this new reactivity to simple primary anilines, phenols, and other useful C–H activation substrates.[22] More in-depth mechanistic investigations are also underway.

Received: October 2, 2013
Revised: October 31, 2013
Published online: February 19, 2014

Keywords: axial chirality · C–H activation · dehydrogenative cross-couplings · lauternamines · oxidative amination

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[15] See the Experimental Section in the Supporting Information.

[16] Replacement of TCE with any other standard chlorinated or brominated cosolvent/additive (for example, chloro- or bromobenzene, dichloro- or dibromobenzenes, hexabromobenzene, tribromoethylene, hexachlorobutadiene, etc.) typically leads to significant loss of conversion. It should be noted that traces of chlorination of the substrates or products were not detected. In addition, omitting TCE while using a stoichiometric amount of Ru salt leads to a significantly lower yield of **3a** (19% instead of 64% under standard conditions). We therefore assume that TCE is not specifically involved in the (re-)oxidation of the Ru catalyst.

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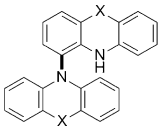
[19] In Equation (5), the low yield of **3v** (13%) can probably be explained by competing decomposition pathways, perhaps through undesired decarboxylation. The Carprofen starting material (**1v**) could not be detected at all in the reaction mixture due to heavy decomposition. Lowering the reaction temperature did not improve the yield of **3v**, however. Fortunately, protecting the carboxylic acid in its methyl ester form (**1w**) proved more effective, and the corresponding product **3w** was obtained in 40% yield.

[20] Chirality based on the slow or hindered pyramidal inversion of the secondary NH atom was also considered but estimated to be improbable. Supporting this point, no racemate separation was evident when nonfunctionalized product **3a** was analyzed by HPLC on a chiral stationary phase (OD-H). Only a single sharp peak was observed (see the Supporting Information).

[21] A control experiment in which the $[\{(p\text{-cymene})RuCl_2\}_2]$ precatalyst is replaced by $[(p\text{-cymene})Ru(OAc)_2]$ was carried out, without any Cu salt. Only a very small nonisolable trace of expected product **3a** was detected by GC–MS, suggesting that the role of Cu is far more than just an acetate source.



8a, X = O, 82%
8b, X = S, 43%

[22] Phenoxazine and phenothiazine show promising reactivity, but only in homocoupling reactions. Attempts at heterocoupling with diarylamines typically lead to poorly useful mixture of homo- and heterocoupling products. Optimized conditions for homocouplings: Phenoxazine (1.0 mmol), $[\{(p\text{-cymene})RuCl_2\}_2]$ (0.0125 mmol), $Cu(OAc)_2$ (0.55 mmol), C_2Cl_4 (2 mL), cumene (0.5 mL), and AcOH (0.125 mL) under otherwise standard conditions. Phenothiazine (2.0 mmol), $[\{(p\text{-cymene})RuCl_2\}_2]$ (0.025 mmol), $Cu(OAc)_2$ (0.25 mmol), C_2Cl_4 (4 mL), cumene (1 mL), and AcOH (0.250 mL) under otherwise standard conditions.

