C–H Activation

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8-Aminoquinoline: A Powerful Directing Group in Metal-Catalyzed Direct Functionalization of C–H Bonds

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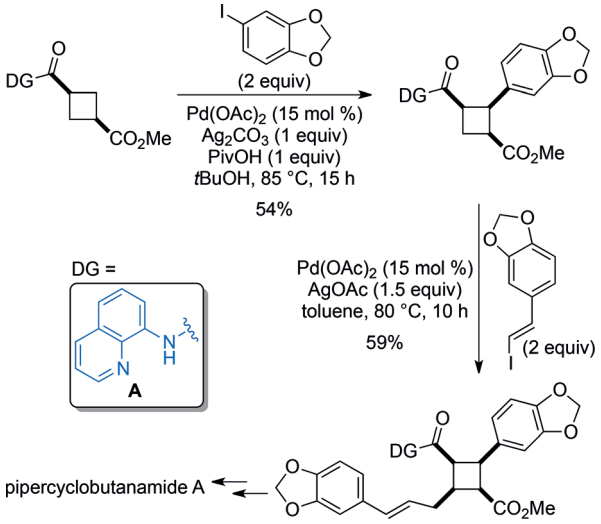
C–H activation · chelates · heterocycles · palladium · synthetic methods

In the context of a growing demand for cleaner, shorter, and even more regioselective reaction sequences, the direct formation of carbon–carbon or carbon–heteroatom bonds through C–H activation has emerged as a unique methodology.[1] In this active research area, non-acidic β C–H bond functionalization requires the assistance of a directing group embedded in the substrate. However, not all of them are equally effective and the 8-aminoquinoline group (**A**; see Scheme 1) has become one of the most versatile chelating auxiliaries which affects a wider and wider range of transformations. Herein, we highlight the latest developments in the realm of C–H activation employing this simple, yet powerful bidentate directing group, which has also the advantages of being readily available, and easily incorporated and removed.

Since the seminal work of Daugulis et al. on the use of the 8-aminoquinoline moiety in $Pd(OAc)_2$-catalyzed arylations of C_{sp^2}–H and unactivated C_{sp^3}–H bonds,[2] the β functionalization of the corresponding carboxylic amides was extended to more challenging substrates as well as to a diverse set of other coupling partners such as alkyl halides, sometimes under even less demanding reaction conditions.[3] Striking examples of successful applications in total syntheses were also reported recently.[3c,j] For instance, the potent antimitotic agent celogentin C was efficiently prepared by a palladium(II)-catalyzed C_{sp^3}–H bond indolylation of a leucine derivative in perfect regio- and diastereoselectivity.[3c] Similarly, Baran and co-workers ingeniously designed their approach to pipercyclobutanamide A around a direct C_{sp^3}–H bond arylation/olefination sequence of a cyclobutane ring, a reaction which was not yet described (Scheme 1).[3j]

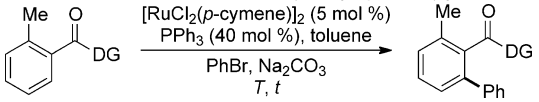
At the end of 2012, Chatani and Aihara showed that less expensive ruthenium-based catalysts were also very efficient in the direct arylation of *ortho* C–H bonds in aromatic amides.[4] While the source of ruthenium(II) was not crucial, a careful choice of the base and the presence of PPh_3 were essential to secure high yields of the desired arylated compounds. Notably, 8-aminoquinoline was found to perform best among the bidentate auxiliaries screened, thus allowing the reaction of the corresponding amide with bromobenzene to proceed under smoother reaction conditions (Table 1). Later on, it was also deemed mandatory in the ruthenium(II)-catalyzed direct *ortho* C–H bond alkylations with α,β-unsaturated ketones.[5]

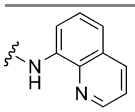
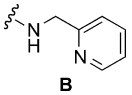
Almost simultaneously, the even more challenging nickel(II)-catalyzed direct alkylation of C_{sp^2}–H bonds with



Scheme 1. Sequential C_{sp^3}–H bond arylation/olefination reactions as key steps in total synthesis.[3j] DG = directing group.

Table 1: Directing group effect in the ruthenium(II)-catalyzed direct arylation of the β C–H bond in 2-methyl-*N*-(8-quinolinyl)benzamide.[4]



DG	PhBr (equiv)	Na_2CO_3 (equiv)	*T* [°C]	*t* [h]	Yield [%]
 **A**	1.2	2	130	15	80
 **B**	2	3	140	18	82

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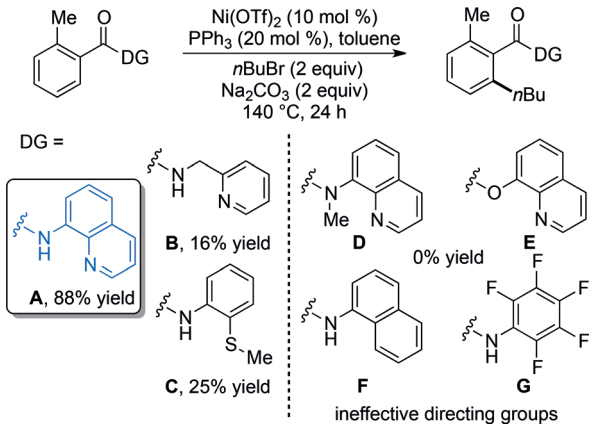
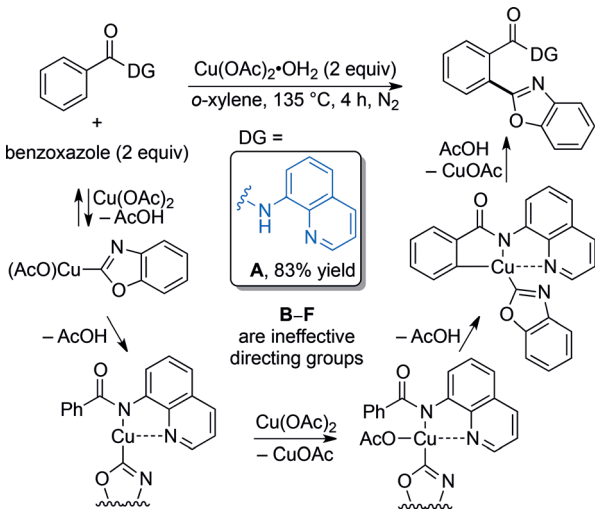


Scheme 2. Directing group effect in the nickel(II)-catalyzed direct alkylation of the β C–H bond in 2-methyl-*N*-(8-quinolinyl)benzamide.[6] Tf = trifluoromethanesulfonyl.



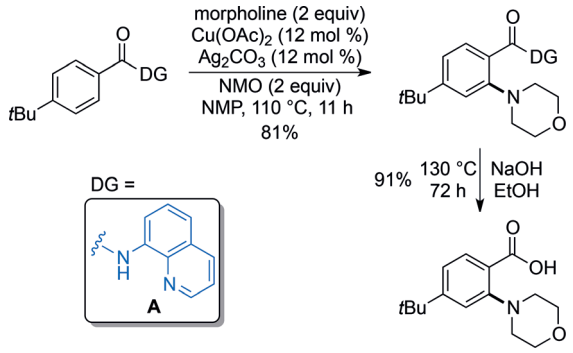
Scheme 3. Copper(II)-mediated C–H/C–H coupling of benzamides with benzoxazole.[8]

unactivated alkyl halides was reported.[6] Again, the superiority of 8-aminoquinoline (**A**), over other bidentate auxiliaries such as **B** or **C** and monodentate ones, was confirmed (Scheme 2).

Remarkably, 8-aminoquinoline-assisted C–H activation is also achievable using even cheaper and greener metal sources such as copper(II). In this respect, Daugulis et al. demonstrated that different carboxylic acid derivatives could be efficiently trifluoromethylsulfenylated with the corresponding disulfide.[7] The scope of the reaction is rather broad but, unfortunately, monosulfenylated compounds cannot be obtained. While analogous bidentate auxiliaries were not tested in this study, benzylamine derivatives bearing a picolinic acid directing group could also be functionalized, albeit with stoichiometric amounts of metal complex and higher reaction temperatures.

Subsequently, another example of copper-mediated direct *ortho* functionalization of C_{sp^2}–H bonds was published.[8] Although not yet catalytic in $Cu(OAc)_2$, C–H/C–H couplings of a variety of benzoic acid derivatives with 1,3-azoles involving the 8-aminoquinoline functional group delivered the desired biaryls in useful synthetic yields. Control experiments were performed with monodentate and other non-N,N-bidentate directing groups, thus demonstrating that the 8-aminoquinoline motif was beneficial in the transformation (Scheme 3). Interestingly, mechanistic investigations with deuterium-labeled substrates and reactants suggested that the β C_{sp^2}–H bond cleavage of the benzamide was irreversible, whereas it was found to be reversible in other related studies (e.g. with ruthenium).[4–6]

Last but not least, direct intermolecular non-nitrenoid aminations of aryl β C_{sp^2}–H bonds catalyzed by a copper/silver system was just reported.[9] In this study, morpholine was shown to react readily with different 8-aminoquinoline-containing benzamides using $Cu(OAc)_2$ as the catalyst along with a silver-based additive and a stoichiometric oxidant. It is worth highlighting that this amination reaction affords the monofunctionalized products selectively. It can be easily scaled-up and benefits from a broad functional-group tolerance. For instance, 4-(*tert*-butyl)-2-morpholinobenzoic acid can be prepared in a two-step, high-yielding sequence (Scheme 4). Furthermore, the scope of the reaction is not limited to morpholine since many secondary and primary aliphatic amines reacted smoothly, but no examples with aromatic amines were included.



Scheme 4. Straightforward and high-yielding access to 4-(*tert*-butyl)-2-morpholinobenzoic acid.[9] NMO = *N*-methylmorpholine-*N*-oxide, NMP = *N*-methylpyrrolidone .

In summary, the 8-aminoquilonine auxiliary has recently gained much attention because of its versatility as a directing group in many metal-catalyzed direct C–H bond functionalizations. Its chelating ability, its rigid backbone, and relatively acidic N–H bond have proven to be critical in most transformations. Even though clues on the mechanisms have already been gathered,[3e,i,4–6] the case-by-case picture remains to be fully elucidated. Sure enough, current and subsequent developments in the field of C–H bond functionalization by C–H activation hold great potential for future industrial applications.[10]

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[1] "C–H Activation": *Topics in Current Chemistry*, *Vol. 292* (Eds.: J.-Q. Yu, Z. Shi), Springer, Berlin, **2010**, pp. 1 – 384.
[2] V. G. Zaitsev, D. Shabashov, O. Daugulis, *J. Am. Chem. Soc.* **2005**, *127*, 13154 – 13155.
[3] Other palladium(II)-catalyzed systems with the assistance of the 8-aminoquinoline auxiliary: C_{sp^3}–H acetoxylations and arylations: a) B. V. S. Reddy, L. R. Reddy, E. J. Corey, *Org. Lett.* **2006**, *8*, 3391 – 3394; C_{sp^2}–H acetoxylations: b) F.-R. Gou, X.-C. Wang, P.-F. Huo, H.-P. Bi, Z.-H. Guan, Y.-M. Liang, *Org. Lett.* **2009**, *11*, 5726 – 5729; C_{sp^3}–H heteroarylation in total synthesis: c) Y. Feng, G. Chen, *Angew. Chem.* **2010**, *122*, 970 – 973; *Angew. Chem. Int. Ed.* **2010**, *49*, 958 – 961; same approach to celogentin C: d) B. T. Y. Li, J. M. White, C. A. Hutton, *Aust. J. Chem.* **2010**, *63*, 438 – 444; C_{sp^2}–H/C_{sp^3}–H arylations and alkylations: e) D. Shabashov, O. Daugulis, *J. Am. Chem. Soc.* **2010**, *132*, 3965 – 3972; C_{sp^3}–H intramolecular arylations: f) Y. Feng, Y. Wang, B. Landgraf, S. Liu, G. Chen, *Org. Lett.* **2010**, *12*, 3414 – 3417; C_{sp^3}–H alkynylation: g) Y. Ano, M. Tobisu, N. Chatani, *J. Am. Chem. Soc.* **2011**, *133*, 12984 – 12986; C_{sp^2}–H alkynylation: h) Y. Ano, M. Tobisu, N. Chatani, *Org. Lett.* **2012**, *14*, 354 – 357; C_{sp^3}–H arylations of non-natural amino acids: i) L. D. Tran, O. Daugulis, *Angew. Chem.* **2012**, *124*, 5278 – 5281; *Angew. Chem. Int. Ed.* **2012**, *51*, 5188 – 5191; sequential C_{sp^3}–H arylation/alkenylation in total synthesis: j) W. R. Gutekunst, R. Gianatassio, P. S. Baran, *Angew. Chem.* **2012**, *124*, 7625 – 7628; *Angew. Chem. Int. Ed.* **2012**, *51*, 7507 – 7510.
[4] Y. Aihara, N. Chatani, *Chem. Sci.* **2013**, *4*, 664 – 670.
[5] G. Rouquet, N. Chatani, *Chem. Sci.* **2013**, *4*, 2201 – 2208.
[6] Y. Aihara, N. Chatani, *J. Am. Chem. Soc.* **2013**, *135*, 5308 – 5311.
[7] L. D. Tran, I. Popov, O. Daugulis, *J. Am. Chem. Soc.* **2012**, *134*, 18237 – 18240.
[8] M. Nishino, K. Hirano, T. Satoh, M. Miura, *Angew. Chem.* **2013**, *125*, 4553 – 4557; *Angew. Chem. Int. Ed.* **2013**, *52*, 4457 – 5191.
[9] L. D. Tran, J. Roane, O. Daugulis, *Angew. Chem.* **2013**, *125*, 6159 – 6162; *Angew. Chem. Int. Ed.* **2013**, *52*, 6043 – 6046.
[10] Since submission of this manuscript two other reports appeared on the 8-aminoquinoline-assisted direct functionalization of C–H bonds: a) C_{sp^3}–H arylations catalyzed by iron(III): R. Shang, L. Ilies, A. Matsumoto, E. Nakamura, *J. Am. Chem. Soc.* **2013**, *135*, 6030 – 6032; b) C_{sp^2}–H mono- and difluorination of arenes catalyzed by copper(I): T. Truong, K. Klimovica, O. Daugulis, *J. Am. Chem. Soc.* **2013**, *135*, 9342 – 9345.

