C–H Activation Hot Paper

Deutsche Ausgabe: DOI: 10.1002/ange.201510743
Internationale Ausgabe: DOI: 10.1002/anie.201510743

A General Strategy for the Nickel-Catalyzed C–H Alkylation of Anilines

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Abstract: *The C–H alkylation of aniline derivatives with both primary and secondary alkyl halides was achieved with a versatile nickel catalyst of a vicinal diamine ligand. Step-economic access to functionalized 2-pyrimidyl anilines, key structural motifs in anticancer drugs, is thus provided. The C–H functionalization proceeded through facile C–H activation and SET-type C–X bond cleavage with the assistance of a monodentate directing group, which could be removed in a traceless fashion.*

Methods for the functionalization of unreactive C–H bonds have emerged as transformative tools in synthetic chemistry,[1] with applications to natural product syntheses,[2] drug discovery,[3] or material sciences,[4] among others. Recently, considerable progress has been accomplished in C–H alkylations with alkyl halides for site-selective arene functionalizations by chelation assistance.[5] In spite of undisputed advances, these C–H alkylations have been dominated by expensive catalysts of precious 4d and 5d transition metals.[6] In consideration of the beneficial features associated with the use of naturally abundant 3d transition metals, focus has recently shifted to less expensive base-metal catalysts for C–H activations.[7] In this regard, considerable advances have been realized with versatile nickel[8] catalysts for powerful arene[9] functionalizations, with major contributions by the groups of Chatani[10] and Ge,[11] us,[12] and Shi, among others.[13] A variety of nickel-catalyzed C–H functionalization methods have thus been established that have proven instrumental for organic synthesis. Unfortunately, nickel-catalyzed arene functionalization has thus far been limited to electron-deficient carboxylic amides derived from the bidentate auxiliaries 8-aminoquinoline (Q) or (pyridin-2-yl)isopropyl (PIP) amine. Within our program on step-economic C–H activation for sustainable synthesis,[14] we have now addressed this restriction by developing a nickel-catalyzed C–H alkylation of synthetically useful aniline derivatives bearing monodentate directing groups. Our methods enables the direct preparation of *ortho*-functionalized 2-pyrimidyl anilines, which are key structural motifs of numerous bioactive compounds used in crop protection and medicinal chemistry, such as the anticancer drug Gleevec (Figure 1).[15] Notable features of our general strategy include 1) an unparalleled broad substrate scope with both primary and secondary alkyl halides, 2) an unusual ligand design based on a vicinal diamine, 3) a rare six-membered[16] nickelacycle as a key intermediate of the C–H activation process, 4) a removable[17] monodentate directing group, and 5) in contrast to previous reports on carboxylic acid derivatives, nickel-catalyzed C–H functionalizations on inherently electron-rich anilines. Moreover, this approach complements our recently developed remote *meta*-alkylation by ruthenium(II) catalysis.[6c]

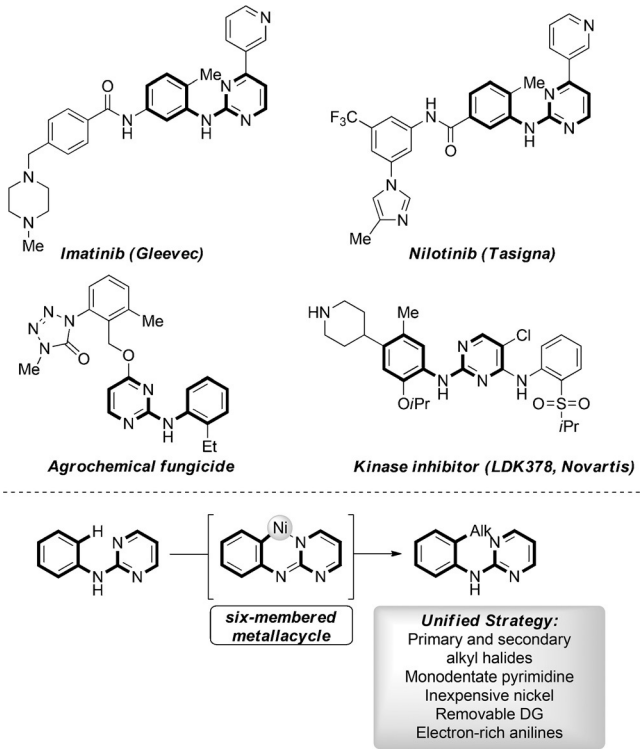

Figure 1. Nickel-catalyzed C–H activation for the assembly of bioactive 2-pyrimidyl anilines.

At the outset, we probed various reaction conditions for the envisioned C–H alkylation of aniline **1a**, which bears a monodentate *N*-pyrimidyl substituent, with the primary alkyl halide **2a** (Table 1; see also the Supporting Information, Table S1).[18] Interestingly, reaction conditions previously employed for nickel-catalyzed C–H alkylations assisted by the bidentate Q auxiliary[10e] proved ineffective for the C–H activation of aniline **1a**, reflecting the challenging nature of transformations with monodentate groups via six-membered

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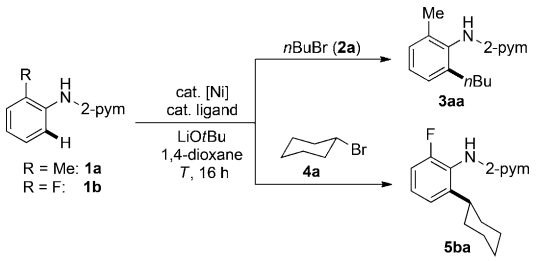
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201510743.

Table 1: Optimization of the nickel-catalyzed C–H alkylation of anilines **1**.[a]

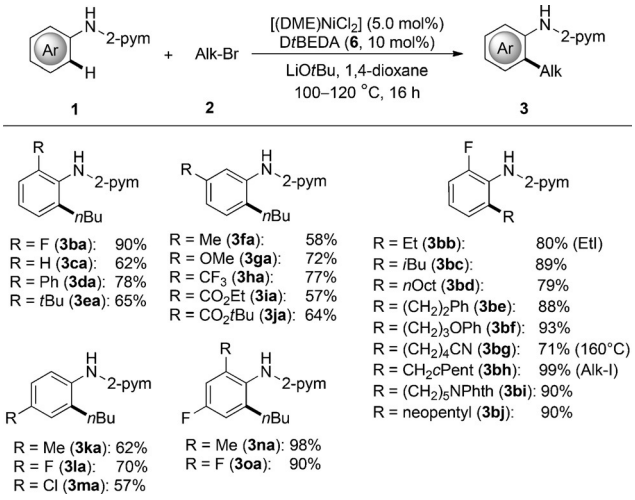


Entry	Nickel source	Ligand	Yield [%]	
			3aa	**5ba**
1	$[(DME)NiCl_2]$	–	18[b]	–
2	$Ni(OTf)_2$	PPh_3	19[b]	5[c,d]
3	$[(DME)NiCl_2]$	PPh_3	26[b]	–
4	$[(DME)NiCl_2]$	PPh_3	47	42[c,d]
5	$[(DME)NiCl_2]$	IPr·HCl	54	66[c,d]
6	$[(DME)NiCl_2]$	TMEDA	–	19[c]
		R–NH HN–R		
7	$[(DME)NiCl_2]$	R = Cy	43	–
8	$[(DME)NiCl_2]$	R = Ad	84	18[c,d]
9	**$[(DME)NiCl_2]$**	**R = *t*Bu (6)**	**87**	**99**[c]
10	–	R = *t*Bu (**6**)	–	–
11	$[(DME)NiCl_2]$	–	45	24[c,d]

[a] Reaction conditions: **1a** or **1b** (0.5 mmol), **2a** or **4a** (1.0 mmol), nickel source (5.0 mol%), ligand (10 mol%), LiO*t*Bu (2.0 equiv), 1,4-dioxane (1.5 mL), 120°C, 16 h; yields of isolated products are given. [b] Ni source (10 mol%), ligand (20 mol%), toluene (1.5 mL), 160°C. [c] Ni source (2.5 mol%), ligand (5.0 mol%), 1,4-dioxane (1.5 mL), 100°C. [d] Determined by ^{19}F NMR analysis with C_6F_6 as the internal standard. Ad = adamantyl, DME = 1,2-dimethoxyethane, pym = pyrimidyl.

metallacycles (entries 1–4). Likewise, the use of N-heterocyclic carbene[19] preligands resulted in unsatisfactory results (entry 5). In contrast, detailed optimizations revealed vicinal diamines to be particularly powerful ligands, with optimal results being achieved with the secondary diamine D*t*BEDA (**6**) in 1,4-dioxane as the solvent of choice (entries 6–11). The efficacy of the optimized catalytic system was illustrated by a reduced reaction temperature. C–H alkylations with secondary alkyl halides are more challenging because of a more difficult oxidative addition and facile β-hydride elimination of the thus formed alkyl metal species.[5] Hence, we were particularly delighted to observe that the optimized nickel catalyst derived from vicinal diamine **6** was not limited to reactions with primary alkyl halides. Indeed, the versatile catalyst set the stage for a general C–H alkylation strategy, also enabling C–H functionalization with secondary alkyl halide **4a** under otherwise identical reaction conditions (Table 1, right column).

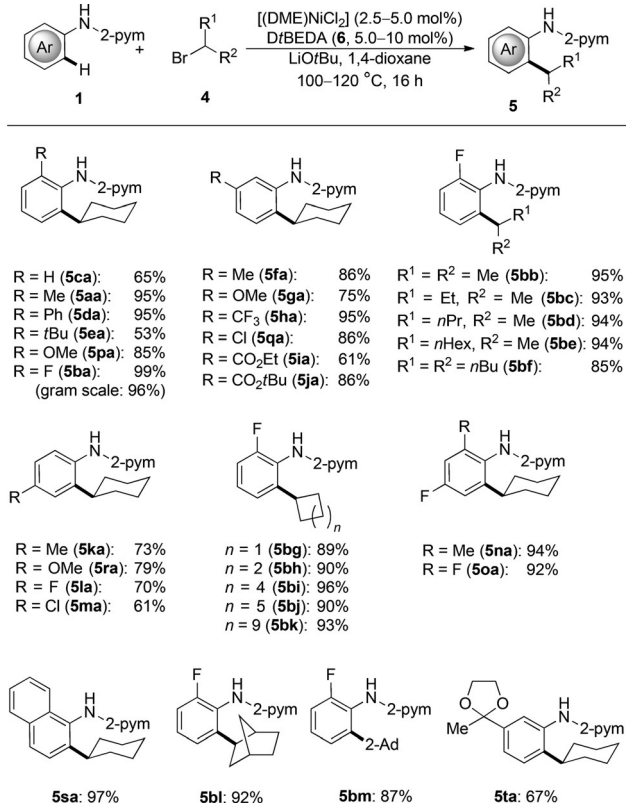
With the optimized catalytic system in hand, we probed its versatility in the C–H alkylation of aniline derivatives **1** with primary alkyl bromides **2** (Scheme 1). The nickel-catalyzed C–H functionalization method enabled chemoselective transformations of *ortho*- and *para*-substituted[20] arenes **1** with a variety of functionalized alkyl halides **2**, displaying halo, ether, amide, ester, or cyano substituents. *meta*-Substituted



Scheme 1. Scope of the nickel-catalyzed C–H alkylation with primary halides **2**. Phth = phthaloyl.

anilines **1f–1j** delivered the desired products **3** with excellent positional selectivity, which was governed by steric interactions. It is noteworthy that even a sterically hindered neopentyl substituent could be directly introduced by the nickel-catalyzed C–H activation approach to selectively furnish product **3bj**.[21]

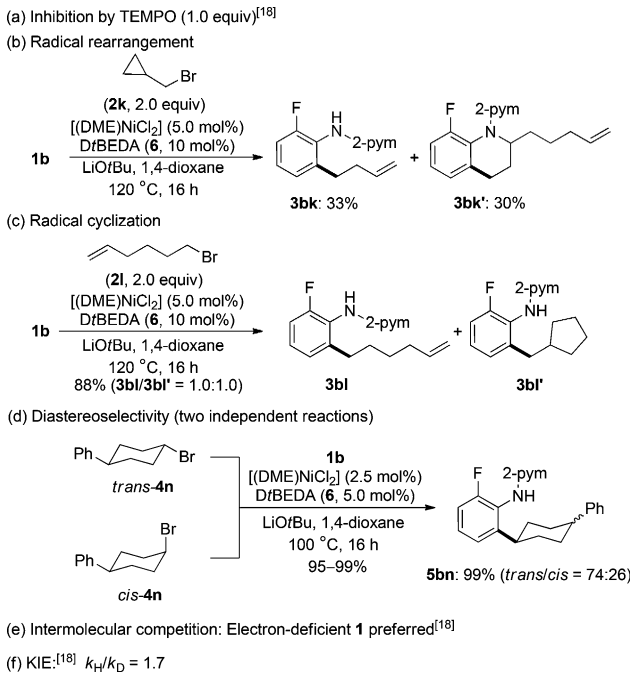
Thereafter, we explored the efficacy of the optimized nickel catalyst derived from ligand **6** in challenging transformations with secondary alkyl halides (Scheme 2). The



Scheme 2. Scope of the nickel-catalyzed C–H alkylation with secondary halides **4**.

robustness of our method was highlighted by successful C–H alkylations with a broad range of secondary alkyl halides **4** displaying valuable functional groups, as well as by reactions performed on gram scale, which reached comparable levels of efficiency (**5ba**). The reactions with secondary alkyl halides proved viable with *ortho*-, *meta*-, and *para*-substituted anilines **1** in a site-selective fashion. Furthermore, the inexpensive nickel catalyst could not only be used for reactions with cyclic alkyl halides **4**. Indeed, the acyclic electrophiles **4b–4f** also delivered the desired products **5** in a chemoselective manner. Notably, C–H alkylation with norbornyl bromide **4l** furnished the *exo* product **5bl** with retention of configuration.

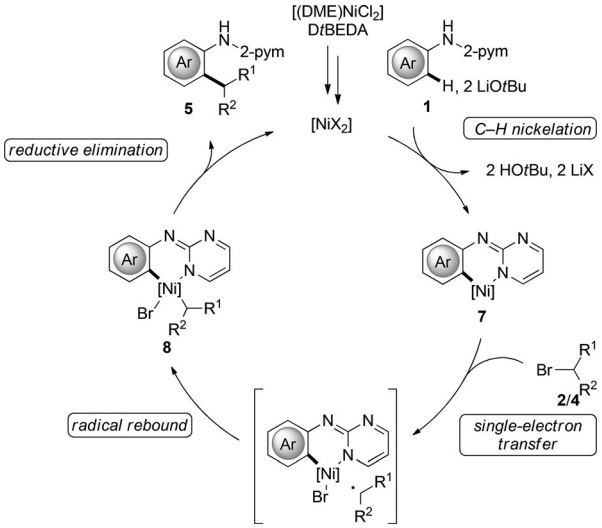
Considering the unique versatility and efficacy of the nickel-catalyzed C–H alkylation process by monodentate chelation, we wanted to unravel its mode of action. To this end, C–H alkylations performed in the presence of stoichiometric amounts of TEMPO led to catalyst inhibition by the radical scavenger, and the coupling product of the reaction of TEMPO with an alkyl radical was observed (Scheme 3).[18] In



Scheme 3. Key mechanistic findings for the C–X cleavage process.

good agreement with this finding, cyclopropylmethyl bromide (**2k**) exclusively delivered alkylation products resulting from a cyclopropylmethyl/homoallyl rearrangement, with the notable formation of the 2-substituted tetrahydroquinoline **3bk′**. Likewise, the involvement of radical intermediates was confirmed through the partial cyclization of substrate **2l**, and the diastereoconvergent nature of the C–H alkylation with the *cis* and *trans* isomers of **4n** in two independent reactions.

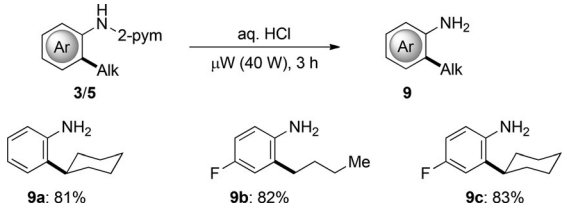
As to the key elementary C–H activation step, we observed considerable H/D scrambling with $[D]_5$-**1c** and a minor kinetic isotope effect (KIE) of $k_H/k_D \approx 1.7$ in independent experiments,[18] suggesting that C–H metalation is facile. A Hammett correlation plot furthermore indicated the crucial importance of the kinetic acidity of the C–H bond as electron-withdrawing substituents considerably increased the relative reaction rate.[18] Based on our mechanistic studies and literature precedence,[22] we propose a plausible catalytic cycle to be initiated by reversible C–H nickelation, delivering the six-membered[16] metallacycle **7** (Scheme 4). Thereafter,



Scheme 4. Proposed catalytic cycle.

reaction with the alkyl radical is suggested to occur, which is followed by radical rebound to generate intermediate **8**. Finally, reductive elimination delivers the desired product and regenerates the catalytically active species. Whereas there is strong precedence for the formation of nickel(IV) species by the action of organic electrophiles,[22a,b] radical addition[9i] or Ni^{I}/Ni^{III} mechanisms[10a] cannot be ruled out at this stage.

Finally, we illustrated the synthetic utility of our strategy by the facile removal of the pyrimidyl group in a traceless fashion, yielding the corresponding anilines **9a–9c** (Scheme 5).



Scheme 5. Facile removal of the pyrimidyl group.

In summary, we have reported the first nickel-catalyzed C–H alkylations of aniline derivatives through chelation assistance. An inexpensive catalyst derived from the diamine ligand D*t*BEDA set the stage for a unified strategy for C–H alkylations of 2-pyrimidyl anilines with primary and secondary alkyl halides. The corresponding products are key structural motifs of numerous bioactive compounds and

blockbuster drugs. The inexpensive nickel catalyst proved broadly applicable and enabled C–H alkylations with excellent levels of positional selectivity. Mechanistic studies were indicative of a facile C–H nickelation step and SET-type C–X cleavage. The C–H functionalization reaction proceeded via an unusual six-membered metallacycle and is based on the use of a removable, monodentate directing group.

Acknowledgements

Generous support by the European Research Council under the European Community's Seventh Framework Program (FP7 2007–2013; ERC Grant 307535), the CSC (fellowship to Z.R.), and the DFG (SPP 1807) is gratefully acknowledged.

Keywords: alkylation · anilines · C–H activation · nickel · reaction mechanisms

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 3153–3157
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Received: November 19, 2015
Published online: January 28, 2016

