C–H Activation Hot Paper

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Nickel-Catalyzed C–H Alkylations: Direct Secondary Alkylations and Trifluoroethylations of Arenes**

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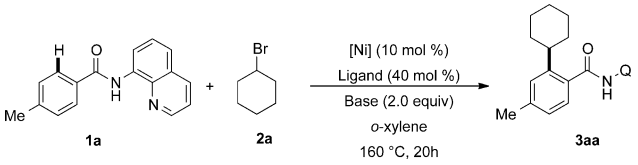
Abstract: *A versatile nickel catalyst allowed for C–H alkylations of unactivated arenes with challenging secondary alkyl bromides and chlorides. The high catalytic efficacy also set the stage for direct secondary alkylations of indoles as well as C–H trifluoroethylations with ample substrate scope.*

C–H activation has emerged as an increasingly viable tool for improving the step-economy in organic synthesis.[1] While various useful methods for catalytic direct arylations have been developed during the past few years, significantly more challenging C–H bond alkylations with unactivated alkyl halides continue to be scarce.[2] Indeed, only few methods for direct alkylations with primary alkyl halides are thus far available.[2a–j] C–H Functionalizations with secondary alkyl halides are even more difficult because of their reluctance to undergo oxidative additions onto transition metals and the pronounced tendency of the thus formed alkyl metal complexes to undergo undesired β-hydride eliminations.[2,3] As a direct consequence, secondary C–H alkylations[4] on arenes are currently largely limited to very recently developed ruthenium-[5] and cobalt-catalyzed transformations.[6]

In recent years, bidentate auxiliaries have attracted considerable attention owing to their unique potential for the activation of otherwise inert C–H bonds.[7] Since the seminal studies by Daugulis,[8] a variety of reactions utilizing auxiliary-assisted C–H bond transformations have been developed,[9] including a very recent nickel-catalyzed direct C–H alkylation with primary alkyl halides.[10] In consideration of the key challenges associated with the use of secondary alkyl halides in C–H activation chemistry, we became attracted by devising direct C–H alkylations of arenes with unactivated secondary alkyl halides. We report herein robust nickel(II) catalysts that allow for expedient secondary alkylations with both alkyl bromides and chlorides. It is further noteworthy that unprecedented C–H trifluoroethylations[11,12] of arenes are achieved with the inexpensive nickel(II) catalyst.

Table 1: Optimization of nickel-catalyzed secondary alkylation.[a]



Entry	Catalyst	Ligand	Base	Yield [%]
1	$Ni(OTf)_2$	PPh_3	Na_2CO_3	–[b]
2	$[Ni(acac)_2]$	–	LiO*t*Bu	10
3	$[Ni(cod)_2]$	–	LiO*t*Bu	52
4	$Ni(OTf)_2$	–	LiO*t*Bu	33
5	$NiCl_2$	–	LiO*t*Bu	–
6	$[(diglyme)NiBr_2]$	–	LiO*t*Bu	40
7	$[(DME)NiCl_2]$	–	LiO*t*Bu	55
8	$[(DME)NiCl_2]$	PPh_3	LiO*t*Bu	30
9	$[(DME)NiCl_2]$	IPrHCl	LiO*t*Bu	–
10	$[(DME)NiCl_2]$	Xantphos	LiO*t*Bu	20
11	$[(DME)NiCl_2]$	DME	LiO*t*Bu	60
12	$[(DME)NiCl_2]$	BDMAE	LiO*t*Bu	70
13	$[(DME)NiCl_2]$	L-proline	LiO*t*Bu	22
14	$[(DME)NiCl_2]$	TMEDA	LiO*t*Bu	45
15	$[(DME)NiCl_2]$	BDMAE	Na_2CO_3	–
16	$[(DME)NiCl_2]$	BDMAE	Cs_2CO_3	–
17	$[(DME)NiCl_2]$	BDMAE	NaOAc	–
18[c]	$[(DME)NiCl_2]$	BDMAE	LiO*t*Bu	71
19[d]	$[(DME)NiCl_2]$	BDMAE	LiO*t*Bu	76
20[e]	**$[(DME)NiCl_2]$**	**BDMAE**	**LiO*t*Bu**	**86[d]**

[a] Reaction conditions: **1a** (0.50 mmol), **2a** (1.0 mmol), [Ni] (10 mol%), ligand (20 mol%), base (2.0 equiv), solvent (1.0 mL), 160°C, 20 h; yields of isolated product. [b] PPh_3 (20 mol%), 89% of re-isolated **1a**. [c] 1,4-Dioxane (1.0 mL). [d] PhMe (1.0 mL). [e] BDMAE (40 mol%). OTf = trifluoromethane sulfonate, acac = acetylacetonate, Q = 8-quinolinyl, BDMAE = bis(2-dimethylaminoethyl)ether, DME = dimethoxyethane. Optimized system highlighted in bold.

We initiated our studies by exploring reaction conditions for the envisioned direct alkylation of benzamide **1a** with bromocyclohexane (**2a**; Table 1). At the outset, we observed that the nickel catalyst previously used for C–H transformations with primary alkyl halides[10] was completely ineffective for the desired secondary C–H alkylation (entry 1). After considerable optimizations we found that among a set of nickel precursors $[(DME)NiCl_2]$ was most suitable (entries 2–7). Thereafter, we explored various stabilizing ligands, with BDMAE and DME furnishing particularly effective catalysts (entries 8–14). As to the nature of the base and the solvent, the most effective C–H secondary alkylation was accomplished with LiO*t*Bu (entries 15–17) in toluene (entries 18–20).

With the optimized catalytic system in hand, we probed its scope in the C–H functionalization of diversely decorated

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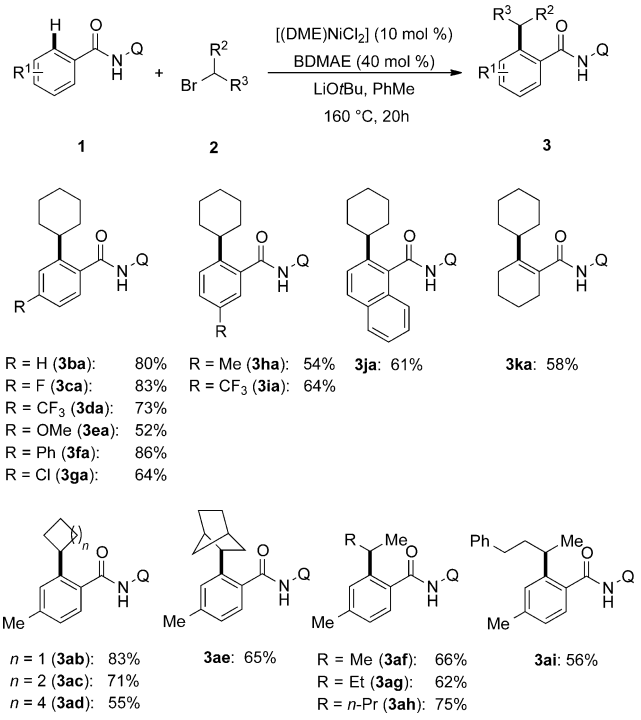
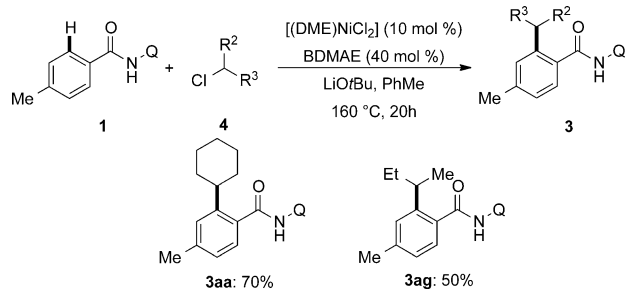


Scheme 1. Scope of nickel-catalyzed secondary C–H alkylations.

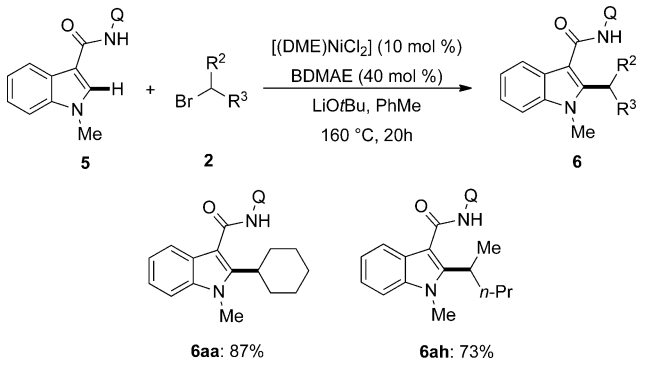
amides **1** with secondary alkyl bromides **2** (Scheme 1). To our delight, a variety of electrophilic functional groups was well tolerated by the versatile nickel catalyst to deliver the desired products **3** with excellent selectivities for the mono-substituted form. The transformations of *meta*-substituted substrates **1h** and **1i** resulted in highly site-selective direct alkylations, exclusively occurring at the less-hindered C–H bonds. Notably, α,β-unsaturated amide **1k** proved to be a viable substrate for the secondary alkylation reaction on alkenes as well. Cyclic alkyl bromides **2b–d** with different ring size afforded the corresponding mono-substituted products **3ab–ad** in good yields. Intriguingly, the alkylation with *exo*-2-bromonorbornane (**2e**) delivered product **3ae** with retention of the configuration. Moreover, acyclic secondary alkyl bromides **2f–i** were found to be amenable to the nickel-catalyzed C–H functionalization, proceeding without the formation of any isomerized or rearranged side-products.

Likewise, significantly less-reactive secondary alkyl chlorides **4** turned out to be viable electrophiles (Scheme 2).



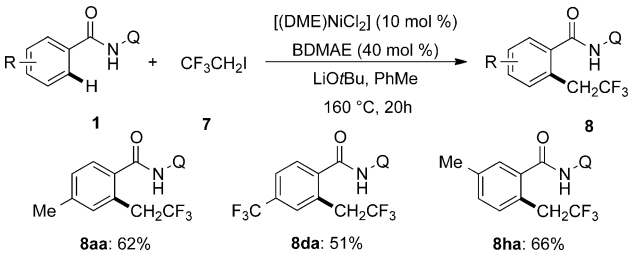
Scheme 2. C–H alkylations with secondary alkyl chlorides **4**.

The inexpensive nickel catalyst was not limited to the functionalization of arenes **1**, but heterocyclic indoles **5** served as valuable substrates for the secondary C–H bond alkylation as well (Scheme 3). Both cyclic and acyclic alkyl bromides **2** delivered the desired products **6** with high catalytic efficacy.



Scheme 3. Secondary C–H alkylations of indoles **5**.

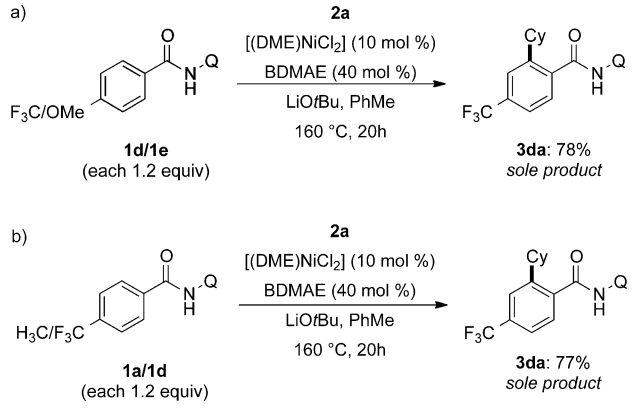
Approximately 30% of all agrochemicals and 20% of all pharmaceuticals contain fluorine, including top-selling antidepressant fluoxetine (Prozac).[11] Fluorine uniquely affects the properties of organic molecules, and thus enhances solubility, bioavailability, and metabolic stability as compared to the nonfluorinated analogues. Therefore, there is a significant demand for selective syntheses of fluorinated organic molecules.[11] Thus, it is noteworthy that the versatile nickel catalyst also enabled challenging direct trifluoroethylation[12] reactions (Scheme 4). Indeed, the trifluoroethylation through chelation-assisted C–H cleavage was realized with commercially available trifluoroethyl iodide (**7**) under otherwise identical reaction condition.



Scheme 4. Nickel-catalyzed C–H trifluoroethylations.

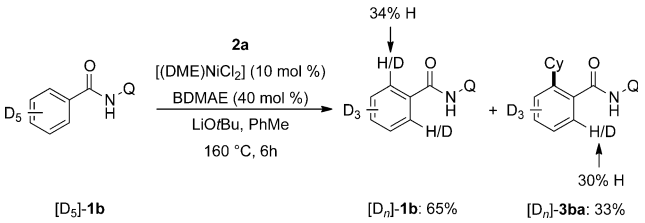
In light of the unique reactivity profile of the nickel catalyst, we became interested in probing its mode of action. To this end, competition experiments between differently substituted arenes **1** revealed substrates with electron-withdrawing groups to be preferentially converted (Scheme 5). These findings show that the acidity of the C–H bond being cleaved is clearly important.

Additionally, we performed studies with isotopically labeled substrate [D]$_5$-**1b**, revealing a considerable H/D exchange, exclusively in the *ortho*-positions of the re-isolated



Scheme 5. Intermolecular competition experiments.

substrate $[D]_n$-**1b** and product $[D]_n$-**3ba** arenes (Scheme 6). This finding provided strong support for the occurrence of a reversible C–H bond metalation event.



Scheme 6. Direct secondary alkylation with labeled arene $[D]_5$-**1b**.

In conclusion, we have developed a first nickel-catalyzed C–H arene alkylation with challenging secondary alkyl halides. Thus, a robust nickel(II) catalyst enabled C–H activations with cyclic and acyclic alkyl bromides and chlorides with ample substrate scope. Preliminary mechanistic studies indicated the C–H metalation to be reversible in nature, and identified the acidity of the C–H to be cleaved to be of importance. Notably, the versatile nickel(II) catalyst also formed the basis for unprecedented trifluoroethylations of unactivated C–H bonds.

Experimental Section

PhMe (1.0 mL) was added to a mixture of benzamide (**1a**; 131 mg, 0.50 mmol), bromocyclohexane (**2a**; 163 mg, 1.00 mmol), [(DME)-$NiCl_2$] (11 mg, 10.0 mol%), BDMAE (32 mg, 40 mol%), and LiO*t*Bu (80 mg, 1.00 mmol). Thereafter, the reaction mixture was stirred under N_2 at 160°C for 20 h. At ambient temperature, the crude product was purified by column chromatography on silica gel (*n*-hexane/EtOAc 20:1) to yield **3aa** as a white solid (148 mg, 86%).

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