ORGANIC
LETTERS

2013
Vol. 15, No. 18
4872–4875

Copper-Catalyzed Electrophilic Amination of Organolithiums Mediated by Recoverable Siloxane Transfer Agents

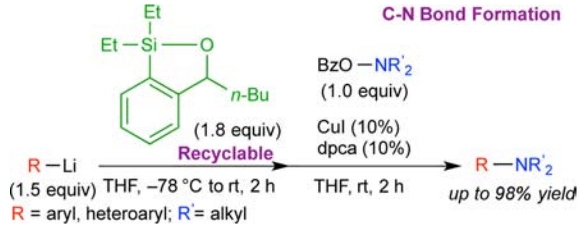
Minh H. Nguyen and Amos B. Smith, III*

Department of Chemistry, University of Pennsylvania, Philadelphia,
Pennsylvania 19104, United States

smithab@sas.upenn.edu

Received August 13, 2013

ABSTRACT



The development and validation of copper-catalyzed, electrophilic amination of aryl and heteroaryl organolithiums with *N,N*-dialkyl-*O*-benzoylhydroxylamines have been achieved exploiting recoverable siloxane transfer agents. Given the ready availability of organolithium compounds, the mild reaction conditions, the ease of product purification, and the ready recovery of the siloxane transfer agents, this transformation comprises a useful tactic to access diverse aryl and heteroaryl amines.

Transition-metal-mediated C–N bond construction is one of the most important transformations in organic synthesis for the elaboration of diverse aryl and heteroaryl amines, given the prevalence of this structural motif in natural products, pharmaceutical agents, and functional materials.[1] Among them, the Buchwald–Hartwig palladium-catalyzed cross-coupling of aryl halides with amines, the Ullmann-type copper-catalyzed cross-coupling of aryl halides with amines, and the Chan–Lam copper-mediated oxidative coupling of aryl metals with amines have proven to be powerful methods for C–N bond formation.[2] An umpolung tactic, involving transition-metal-catalyzed amination of organometallic reagents with electrophilic aminating reagents (e.g., chloroamines and hydroxylamines), provides a valuable complementary approach.[3] Indeed, various organometallic reagents are known to undergo electrophilic amination, including organomagnesiums,[4] -zincs,[5] -tins,[6] -borons,[6,7] -silicons,[8] and -titaniums.[9] These reagents however are frequently prepared from the corresponding organolithium reagents. The direct use of organolithiums would eliminate the need for additional synthetic manipulations and/or the isolation of suitable nucleophilic partners. Although organolithium reagents

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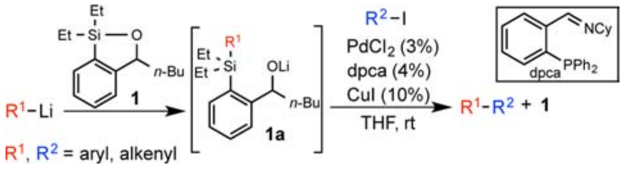
10.1021/ol4023084

are commercially available and/or readily accessible via a simple metal−halogen exchange or metalation, the direct application of these agents in electrophilic amination remains a challenge, often hampered by low yields, limited substrate scope, and in some cases the need for excess reagents.[3a,d]

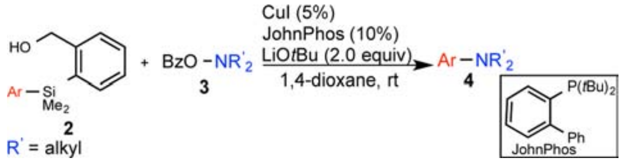
Recently we reported a highly atom-efficient tactic for the palladium-catalyzed cross-coupling of aryl and alkenyl organolithium reagents with aryl and alkenyl iodides (Scheme 1), exploiting readily recoverable and/or polymeric siloxane transfer agents.[10,11] As part of the ongoing program to expand the siloxane transfer agent tactic, we report here the copper-catalyzed electrophilic amination of aryl and heteroaryl organolithiums with electrophilic aminating reagents, mediated by recoverable siloxanes.

Scheme 1. Siloxane Based Cross-Coupling Reactions



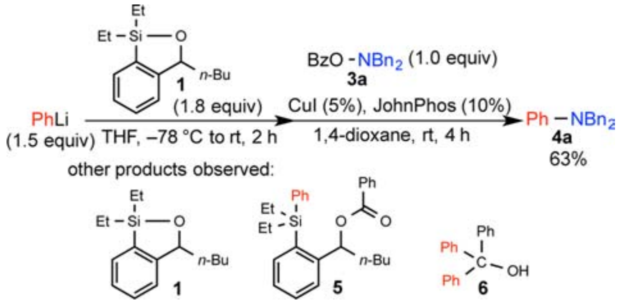
Based on the similarities between the reactive intermediate involved in siloxane-based cross-coupling reactions (alkoxide **1a**, Scheme 1) and arylsilanes **2**, recently employed in electrophilic aminations reported by Miura and co-workers (Scheme 2),[8] we reasoned that we could intersect this reaction manifold via a siloxane transfer agent. Success would provide a valuable and practical method for the direct amination of organolithium compounds with electrophilic aminating reagents, such as *N*,*N*-dialkyl-*O*-benzoyl hydroxylamines. To the best of our knowledge, there are no reports of an effective, general method to employ *directly* organolithium reagents for the preparation of *N*,*N*-dialkyl aryl and heteroaryl amines, an important structural motif in many biologically active compounds.[12]

Scheme 2. Miura's Electrophilic Amination of Aryl Silanes

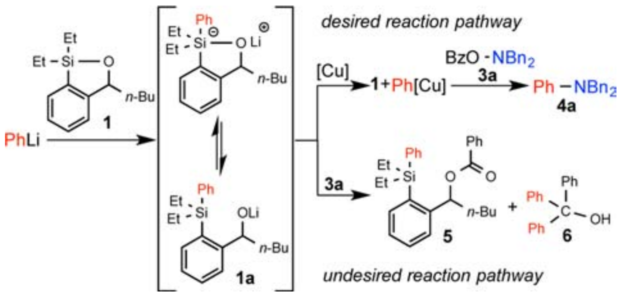


To explore this thesis, we began by subjecting alkoxide intermediate **1a**, derived from the reaction of PhLi and **1**, to conditions similar to those reported by Miura and coworkers, employing *N*,*N*-dibenzyl-*O*-benzoyl hydroxylamine as the electrophile (Scheme 3). Pleasingly, the desired product, dibenzyl aniline, was obtained in 63% yield. Although the majority of siloxane **1** could be recovered from the reaction mixture, the siloxane-derived benzoate **5** and triphenyl methanol were also isolated. We envision that under the conditions the reaction proceeds via two pathways (Scheme 4). The desired reaction involves transmetalation from silicon to copper, with subsequent electrophilic amination of the aryl copper intermediate to generate **4a**. Alternatively, the lithium alkoxide (**1a**) can *O*-acylate **3a** to generate silane **5** or transfer the phenyl group to **3a** to generate triphenyl methanol **6**.

Scheme 3. Initial Attempt at the Electrophilic Amination of Phenyl Lithium Employing Siloxane Transfer Agent



Scheme 4. Proposed Reaction Pathways



With these preliminary, albeit intriguing results in hand, we turned to optimize the reaction, including both product yield and siloxane recovery (Table 1). Changing the solvent from 1,4-dioxane to THF increased the yield of **4a** (entry 1). Importantly the reaction proceeded effectively at *room temperature* within a 2 h time period. An increase in product yield and siloxane recovery was also realized when the catalyst loading was increased (entries 2 and 3); a further increase in the copper catalyst (40 mol %) however proved ineffective (entry 4). Particularly pleasing, a significant increase

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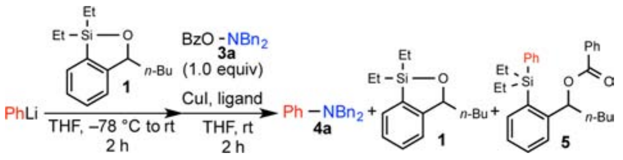
in the efficiency of the process was observed when *N*-[2-(diphenylphosphino)benzylidene]cyclohexylamine (dpca), the optimal ligand employed in siloxane mediated cross-coupling reactions,[10,11] was employed. The use of 10 mol % CuI and 10 mol % dpca proved optimal, leading to complete conversion of **3a** within 2 h at room temperature to furnish **4a** in 98% isolated yield, with full recovery of the siloxane transfer agent (entry 5). Attempts to reduce the amount of PhLi or the catalyst loading, while maintaining the efficiency of the process, provided no enhancement (entries 6 and 7). Importantly, as a control experiment only 7% of **4a** was obtained in the absence of the siloxane transfer agent (entry 8). Also as expected, reaction of PhLi with the electrophilic aminating reagent **3a** provided triphenyl methanol as the major product; no amination product could be detected (entry 9).

Table 1. Optimization of the Electrophilic Amination of Organolithiums Employing Siloxane Transfer Agent[a]

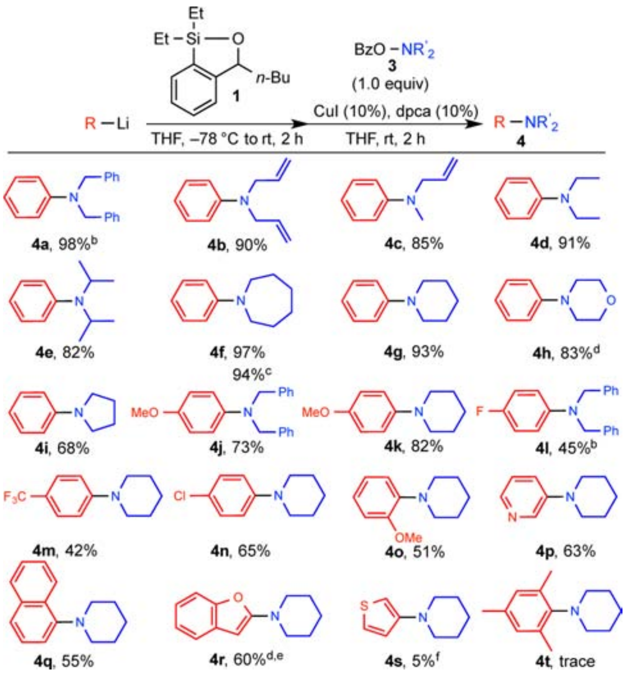


entry	equiv PhLi	equiv **1**	mol % CuI	ligand (mol %)	yield of **4a**	product ratio[b] **1**:**5**
1	1.5	1.8	5%	JohnPhos (10%)	67%	5:1
2	1.5	1.8	10%	JohnPhos (10%)	81%	10:1
3	1.5	1.8	20%	JohnPhos (10%)	91%	19:1
4	1.5	1.8	40%	JohnPhos (10%)	84%	>20:1
5	1.5	1.8	10%	dpca (10%)	98%	>20:1
6	1.2	1.5	10%	dpca (10%)	88%	>20:1
7	1.5	1.8	5%	dpca (5%)	73%	11:1
8[c]	1.5	–	10%	dpca (10%)	7%	–
9[c]	1.5	–	–	–	nd	–

[a] All reactions were performed on a 0.3 mmol scale. [b] Determined by ^{1}H NMR analysis of the reaction mixture following an aqueous work-up and extraction with Et_2O. [c] Ph_3COH as the major product. nd = not detected.

We next explored the scope of the Cu-catalyzed electrophilic amination of organolithium agents, employing siloxane transfer agent **1** under the optimized reaction conditions (Scheme 5). Various acyclic and cyclic amines underwent effective coupling with PhLi to form the corresponding anilines in good to excellent yields (**4a**–**i**). The resultant *N*-allyl and *N*-benzyl moieties (**4a**–**c**) can serve as useful synthetic handles upon removal of the benzyl or allyl groups to access either unsubstituted or monosubstituted anilines (e.g., **4c**).[14] Notably, the reaction of PhLi and the sterically hindered electrophile *N*,*N*-diisopropyl-*O*-benzoyl hydroxylamine proceeds to form the coressponding aniline in good yield (**4e**). Electrophilic amination was also effective with a variety of organolithium agents. In particular, the electron-rich *p*-methoxyphenyl lithium readily underwent electrophilic amination to provide the corresponding amination products in good yield (**4j** and **4k**). On the other hand, electron-deficient organolithiums proceeded with somewhat lower efficiency (**4l**–**n**). Pleasingly however, the aryl-Cl moiety remained intact in the amination of *p*-chlorophenyl lithium with piperidine-1-yl benzoate to furnish **4n**, providing an opportunity for additional transformations, such as palladium-catalyzed cross-coupling reactions. Sterically hindered organolithiums such as *o*-methoxyphenyl lithium

Scheme 5. Substrate-Scope Study of the Electrophilic Amination of Organolithiums Employing Siloxane Transfer Agent[a]



[a] All reactions were performed on 0.3 mmol scale. The organolithiums were generated via lithium–halogen exchange between *t*-BuLi and the corressponding organohalides. The siloxane was recovered via flash chromatography (average recovery = 85%). [b] Siloxane coelutes with product and was oxidized[13] with H_2O_2 in NaOH to facilitate product purification. [c] Reaction was run on 3 mmol scale. [d] 20% CuI was used. [e] The organolithium was generated by treating 2,3-benzofurane with *n*-BuLi. [f] Estimated via H NMR analysis of the crude reaction mixture.

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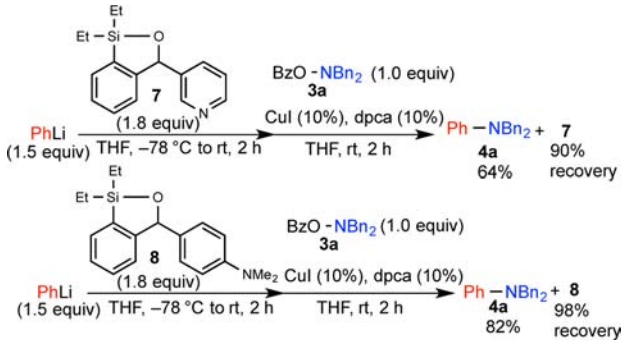
and 1-naphthyl lithium also proceeded, albeit in moderate yield (**4o** and **4q**). Importantly, heteroaryl lithiums such as 3-pyridyl lithium and 2-benzofuryl lithium were also tolerated in the amination (**4p** and **4r**), with the latter accessed via a direct ortho lithiation/amination sequence of benzofuran. Use of 3-thienyl lithium and the sterically hinderred mesityl lithium however proved unsuccessful (**4s** and **4t**). Gratifyingly, the amination protocol can be carried out on a gram scale to provide an excellent yield of the desired product (**4f**, 94%), indicating both the scalability and reliability of the method. Equally important, in this case, the siloxane transfer agent was recovered in 92% yield via Kugelrohr distillation, with the amination product **4f** conveniently isolated via acid–base extraction.

We next explored the use of other siloxane transfer agents, focusing on the ability to recycle the transfer agent via a simple and easy protocol. Success here should facilitate adoption of the siloxane tactic by the chemical community.

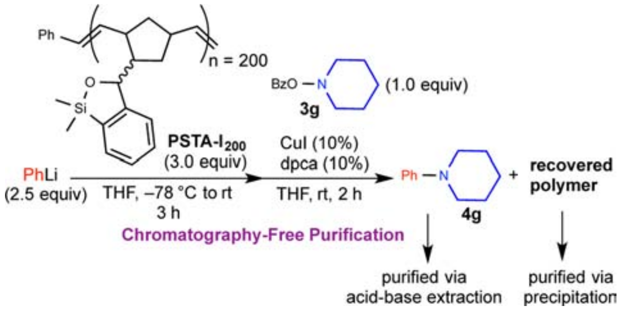
As shown in Scheme 6, Brønsted base incorporated siloxane transfer agents **7** and **8** were found to be effective in the electrophilic amination between PhLi and *N*,*N*-dibenzyl-*O*-benzoyl hydroxylamine, providing the amination product in 64% and 82% yield, respectively with near-quantitative recovery of the transfer agents via acid–base extraction,[10b] exploiting the differential basicity of the siloxanes and the amine products.

Scheme 6. Performance of Brønsted Base Containing Siloxanes



Finally we examined the utility of our recently introduced polymer-supported siloxane transfer agent PSTA-I$_{200}$,[11] now for electrophilic amination between PhLi and piperidine-1-yl benzoate (Table 2). Pleasingly, the polymer can be used for at least three cycles, providing excellent to good yields of the desired amination product **4g**, abeit with a small decrease in efficiency after each cycle. In all cases, the amination product was purified via acid–base extraction and the polymer was recovered in near-quantitative yield via precipitation in CH$_3$CN, thus featuring a chromatography-free purification strategy.

Table 2. Recyclability of Polymer-Supported Siloxane Transfer Agent



cycle	isolated yield of **4g**	polymer recovered
first	92%	95%
second	80%	92%
third	71%	90%

In summary, we have developed and validated the direct copper-catalyzed, electrophilic amination of aryl and heteroaryl organolithiums with *N*,*N*-dialkyl-*O*-benzoyl hydroxylamines. Importantly, the use of siloxane transfer agents offers, for the first time, a viable solution for the direct application of organolithiums in electrophilic amination and, in turn, eliminates the need for multiple synthetic manipulation and/or isolation of the required organometallic reagents (e.g., organoborons and organosilicons), as well as the requirement for a stoichiometric amount of toxic, heavy metals (e.g., Zn, Sn, and Ti). The mild, room temperature reaction conditions, in conjunction with the ease of product purification, make this approach a valuable addition to methods for C–N bond construction. Studies to expand the scope of this reaction, as well as the application of siloxane transfer agents in other transformations, continue in our laboratory.

Acknowledgment. Financial support was provided by the NIH through Grant CA-19033. We thank Dr. Rakesh Kohli at the University of Pennsylvania for assistance in obtaining HRMS.

Supporting Information Available. Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.