Facile and Atom-Efficient Amidolithium-Catalyzed C−C and C−N Formation for the Construction of Substituted Guanidines and Propiolamidines

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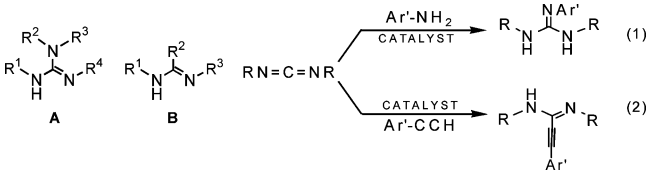
Summary: Lithium hexamethyldisilazide ($LiN(SiMe_3)_2$) is an excellent precatalyst for the room-temperature guanylation of a variety of aryl amines with carbodiimides and for the C−C coupling reaction between terminal alkynes and carbodiimides to yield propiolamidines. Tetramethylethylenediamine (TMEDA), presumably through modulation of the lithium coordination sphere, increases the reactivity of this catalyst system.

Organometallic compounds of the s-block metals are beginning to receive appropriate attention as catalyst precursors, an aspect that compliments their well-established role as stoichiometric reagents.[1−7] Among the fundamental characteristics of these species that are key to their application in catalysis are a bifunctional nature, originating from the Lewis acidity of the main group center and the nucleophilicity of the substituents/ligands, and the redox stability of the metal centers. Guanidines (**A**) and amidines (**B**) have received considerable recent attention as ancillary ligands in the preparation of a variety of metal complexes, including those of the main group, transition metals, and lanthanides.[8,9] Our interest in the application of **A** and **B** as ligands and in preparing these compounds with a variety of substituents prompted our consideration of facile methods for the synthesis of substituted guanidines and amidines. More specifically, our efforts to reveal catalytic methods for assembling guanidines from a diverse set of amines targeted the activation of the amine component. This strategy was employed for the catalytic guanylation of amines using Ti- and V-imido catalysts as well as half-sandwich yttrium alkyl complexes.[10−12] We noted that the reactivity features associated with alkali metal organometallic reagents could provide a similar catalytic pathway for the synthesis of guanidines and amidines. We now present an efficient catalytic route for the guanylation of aromatic and heterocyclic amines directly with carbodiimides employing readily available lithium hexamethyldisilazide ($LiN(SiMe_3)_2$) as the catalyst precursor (eq 1).[13] In addition, we demonstrate that this catalyst system can be extended to catalytic C−C bond formation through addition of alkyne C−H bonds to carbodiimides to provide a high-yield, atom-economical route to propiolamidines (R^2 = alkynyl) (eq 2).[14,15]



In the absence of a catalyst, aromatic amines do not react with diisopropylcarbodiimide to any detectable degree even with prolonged heating at 140 °C. We were gratified to find that the addition of 2 mol % of commercially available $LiN(SiMe_3)_2$ led to efficient catalytic guanylation of 2,6-dimethylaniline with diisopropylcarbodiimide to give a quantitative yield of guanidine **1** within 5 h at room temperature. This result is generalized to other substituted anilines and other carbodiimides in Table 1. The resulting guanidines could be isolated by simple crystallization in good to excellent yield. These results represent a significant improvement over the previously reported Ti-catalyzed reactions by employing milder reaction conditions and providing improved yields, features that are clearly demonstrated with the synthesis of compound **7**. Specifically, the amido-

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Table 1. Room-Temperature Guanylation of Aromatic Amines with Carbodiimide Using $LiN(SiMe_3)_2$

entry	Ar′NH_2	RNCNR′	prod	yield (%)[a,c]
1	2,6-$Me_2C_6H_3NH_2$	^{i}PrNCN^{i}Pr	1	98[b] (90)
2	$C_6H_5NH_2$	^{i}PrNCN^{i}Pr	2	96
3	$C_6F_5NH_2$	^{i}PrNCN^{i}Pr	3	96
4	*p*-$MeOC_6H_4NH_2$	^{i}PrNCN^{i}Pr	4	98
5	*o*-$MeOC_6H_4NH_2$	^{i}PrNCN^{i}Pr	5	58; (96)[d]
6	*o*-$ClC_6H_4NH_2$	^{i}PrNCN^{i}Pr	6	(72)[e]
7	*p*-$NCCH_2C_6H_4NH_2$	^{i}PrNCN^{i}Pr	7	83
8	*p*-$H_2NCH_2C_6H_4NH_2$	^{i}PrNCN^{i}Pr	**8**[f]	96 (90)
9	*o*-$BrC_6H_4NH_2$	^{i}PrNCN^{i}Pr	9	(71.2)[d]
10	*p*-$MeOC_6H_4NH_2$	^{t}BuNCNPh	10	0; 95[e,g] (90)[e,g]
11	$C_6H_5NH_2$	^{t}BuNCNPh	11	70[e,g] (62.0)[e,g]
12	*p*-$MeOC_6H_4NH_2$	CyNCNCy	12	(95)[e]
13	*o*-$BrC_6H_4NH_2$	PhNCNPh	13	(66)[d]

[a] All reactions were run for 18 h with 2 mol % catalyst unless otherwise specified. Yields determined by integration of ^{1}H NMR relative to internal standard of 1,3-$(MeO)_2C_6H_4$. [b] Quantitative yield was obtained after 5 h. [c] Isolated yields given in parentheses. [d] Yield for reaction at 100 °C. [e] Reaction run with 5% catalyst loading. [f] Product is $H_2NCH_2(C_6H_4)$-N=C(^{i}PrNH)$_2$. [g] Reaction run with addition of 10 mol % TMEDA.

lithium-catalyzed reaction provided an 83% yield of **7** at room temperature, while the reaction catalyzed by our Ti-imido complex, [{$(Me_2N)C(N^iPr)_2$}$_2$Ti=N(2,6-$Me_2C_6H_3$)], at reaction temperatures in excess of 100 °C, provided only a 47% yield.[10] While we achieved excellent yields with a variety of substituted aryl groups at room temperature, the two *ortho*-substituted amines *o*-$MeOC_6H_4NH_2$ and *o*-$BrC_6H_4NH_2$ (entries 5, 9, and 13) required slightly elevated reaction temperatures to get high yields. It is noteworthy that *p*-benzylaminoaniline affords only the anilide-substituted guanidine, **8**, indicating a high chemoselectivity for this reaction. These results provide a unique demonstration of the potential of alkali metal-catalyzed guanylation under mild conditions.

The applicability of $LiN(SiMe_3)_2$ as a catalyst precursor for guanylation of amines with other carbodiimides is demonstrated with entries 10−13 in Table 1. Carbodiimides possessing a combination of aliphatic and aromatic substituents proved to be resistant to reaction, as demonstrated by a comparison of entries 2 and 11. The addition of amines that can modulate the coordination environment of the cationic Li center is known to accelerate the reactions of $LiN(SiMe_3)_2$,[16] and the addition of 10 mol % TMEDA dramatically increases the activity of this reaction system and leads to very good yields of the appropriate trisubstituted guanidines **10** and **11**.

In an effort to obtain more detailed information on these reactions, we attempted to isolate crystalline compounds from active catalyst systems and were successful for the reactions represented by entries 2 and 5 in Table 1. Furthermore we were able to carry out single-crystal X-ray analysis on these two materials and present, in Figure 1, the structures of **I** and **II** as trapped intermediates in the syntheses of compounds **2** and **5**, respectively.[17] Compound **I**, [Li(^{i}PrNC(HN^{i}Pr)N(C_6H_5)(THF)]$_2$, is a dimeric species derived from the lithium salt of the guanidinate anion of **2**, each of which is coordinated by a THF molecule. Compound **II**, [Li(^{i}PrNC(HN^{i}Pr)N(C_6H_4OMe)]$_2$, displayed a similar dimeric structure, consisting of deprotonated **5**. In this case, the coordinated THF molecule is replaced by a chelating interaction from the *ortho* OMe group of the guanidinate. In both **I** and **II** the dimeric cores display guanidinates in μ-η^1,η^2-bridging modes between two lithium centers. Related dimeric structures have been observed in a number of metal amidinate[18] and guanidinate[19] compounds. Both molecules display three fused four-membered rings in a folded ladder-type arrangement with a cis-arrangement about the central Li_2N_2 metallacycle. Most importantly, in terms of providing details on the reaction pathway, both **I** and **II** appear to originate from the insertion of carbodiimide into the amidolithium species C_6H_5-(H)NLi and *o*-$MeOC_6H_4$(H)NLi.

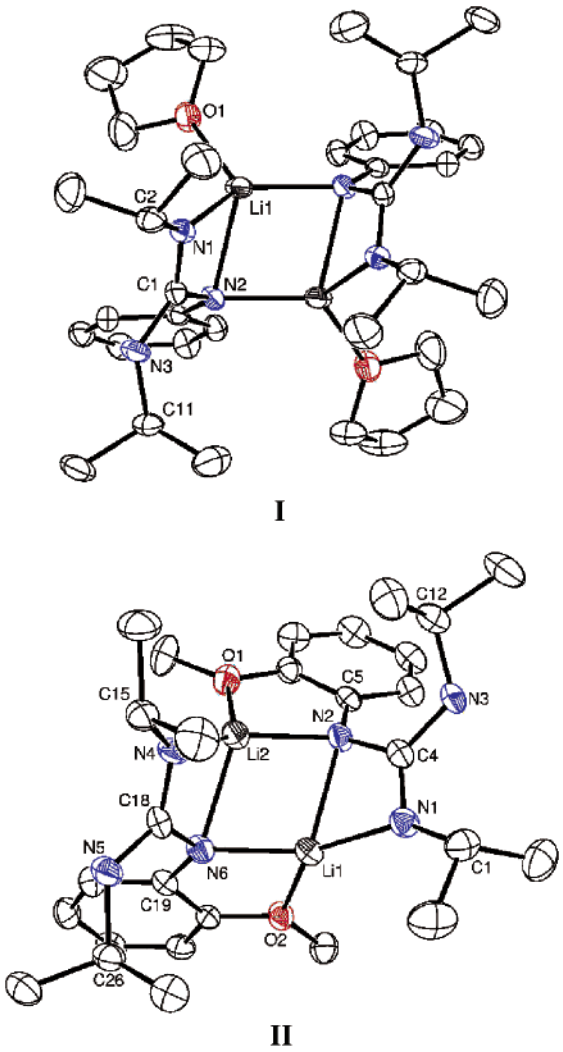

Figure 1. Molecular structure and partial atom-numbering schemes for [Li(^{i}PrNC(HN^{i}Pr)N(C_6H_5)(THF)]$_2$ (**I**) and [Li(^{i}PrNC(HN^{i}Pr)N-(C_6H_4OMe)]$_2$ (**II**). In both cases, thermal ellipsoids are shown at 30% probability and hydrogen atoms have been omitted for clarity.[17]

Preliminary examination of the catalyzed guanylation of heterocyclic amines and amides is presented in eqs 3 and 4. Efficient guanylations of 2,3-dimethylindole and acetamide, to

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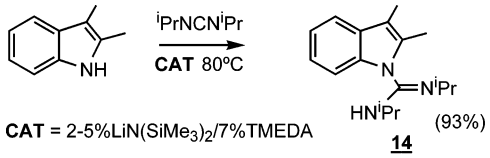
Table 2. Catalytic Formation of Propiolamidine by Addition of Alkyne to Carbodiimides at 80 °C Using 5 mol % $LiN(SiMe_3)_2$

entry	carbodiimide	alkyne	product (time)[a]	yield (%)[b]
1	^{i}PrN=C=N^{i}Pr	HCCPh	**16** (120)	95
2	CyN=C=NCy	HCCPh	**17** (90)	95
3	^{i}PrN=C=N^{i}Pr	HCC(*p*-C_6H_4OMe)	**18** (90)	93
4	CyN=C=NCy	HCC(*p*-$C_6H_4CF_3$)	**19** (75)	95

[a] Reaction time in min is given in parentheses. [b] Yields determined by integration of ^{1}H NMR relative to internal standard of 1,3-$(MeO)_2C_6H_4$.

yield **14** and **15**, respectively, were achieved with $LiN(SiMe_3)_2$. In both cases, efficient catalysis required the addition of TMEDA.



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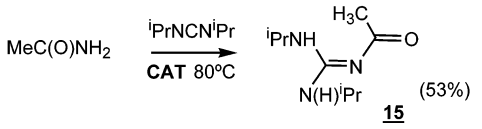
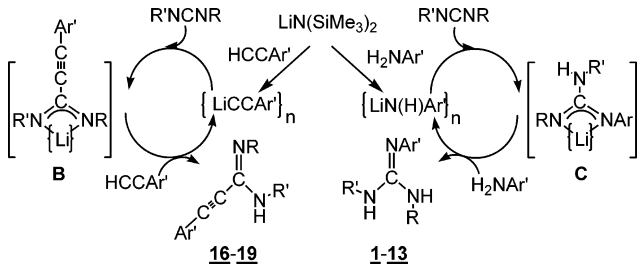


(4)

The excellent results obtained for the construction of C−N bonds encouraged an effort to expand the scope of this catalytic process into the realm of C−C coupling. The addition of terminal alkynes across carbodiimides could, in principle, provide a straightforward route to propiolamidines. In fact, synthetic routes to propiolamidines remain scarce, and the only clearly documented precedent for this reaction is the recent report that half-sandwich rare-earth metal complexes bearing silylene-linked cyclopentadienyl-amido ligands act as catalysts for eq 2.[15] Again, the highly polar nature of the rare-earth metal−amido linkage along with the lack of redox activity from these metals suggested that we might successfully implement amidolithium for this transformation. Initial screens were conducted at 80 °C for the reaction of 1,3-diisopropylcarbodiimide with phenylacetylene at 5 mol % $LiN(SiMe_3)_2$ loading. From these reactions propiolamidine **16** was obtained quantitatively in less than 2 h. Similar reactions with other substituted terminal acetylenes and carbodiimides are summarized in Table 2. Attempts to access *N*,*N*′-diaryl-substituted amidines from 1,3-diphenylcarbodiimide yielded only an uncharacterized insoluble gel that may be the product of carbodiimide polymerization.

A proposed mechanism for the reactions given in eqs 1 and 2 is summarized in Scheme 1. Initial generation of either lithium

Scheme 1



amide or acetylide is followed by carbodiimide insertion to yield the appropriate guanidinate or amidinate species. Transfer protonation then releases the product with concomitant regeneration of the catalytically active species. This proposition is supported by the isolation of the two lithium guanidinates (**I** and **II**) in the production of **2** and **5** shown in Figure 1.

Other organolithium compounds (e.g., ^{n}BuLi) and lithium amides were also effective precatalysts for these transformations, and these reagents exhibited conversion yields and rates similar to $LiN(SiMe_3)_2$. These observations are consistent with the initiation step being formation of lithium acetylide or amide as shown in Scheme 1. The proposed mechanism further suggests that other alkali metal species may function as catalysts for eqs 1 and 2. In fact our preliminary screen of other alkali metal amides revealed that both $NaN(SiMe_3)_2$ and $KN(SiMe_3)_2$ are equally effective in the catalytic guanylation reactions.

In summary, we have demonstrated an efficient and direct catalytic method for the guanylation of amines and the addition of alkyne C−H bonds to carbodiimides that can be achieved under mild reaction conditions with an amidolithium precatalyst. To the best of our knowledge, this is the first report of the application of readily accessible and economical $LiN(SiMe_3)_2$ to such reactions. This novel catalytic procedure opens avenues for the rapid assembly of a variety of new π-excessive, nitrogen-rich molecules and materials. Our ongoing efforts focus on exploring the generality of these concepts, expanding the range of substrates, and developing new catalyst precursors and additives in an effort to investigate enantioselective versions of related reactions.

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Supporting Information Available: Experimental procedures and characterization of new compounds and the cif files for [Li(^{i}PrNC(HN^{i}Pr)N(C_6H_5)(THF)]$_2$ (**I**) and [Li(^{i}PrNC(HN^{i}Pr)N(C_6H_4OMe)]$_2$ (**II**). The material is available free of charge on the Internet at http://pubs.acs.org.

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