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Facile Double-Lithiation of a Transient Urea: Vicarious *ortho*-Metalation of Aniline Derivatives

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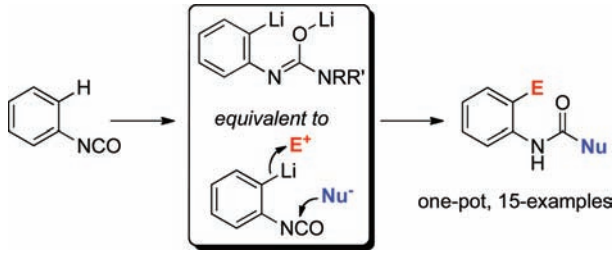
ABSTRACT



A convenient one-pot method for the conversion of phenylisocyanate into *ortho*-functionalized aniline derivatives has been developed. The reaction proceeds *via* the selective *ortho*-metalation of a transient labile urea, which can be considered as a synthetic equivalent of 2-lithiophenylisocyanate, a highly improbable intermediate.

A number of efficient methods are available for the regioselective *ortho*-functionalization of aniline derivatives,[1] including *catalytic* methodologies proceeding via C−H activation.[2] Nonetheless, for the past 3 decades the stoichiometric directed *ortho*-metalation (DoM) reaction has reigned supreme as the most reliable and broad-ranging procedure.[3] DoM of anilines requires a *directed metalation group* (DMG), for example, *N*-pivaloyl,[4] *N*-Boc,[5] or urea[6,7] moieties, to facilitate the *ortho*-metalation. Herein we report on the DoM of highly hindered, *N*,*N*-dialkyl-*N*′-aryl ureas. Not only are these moieties potent DMGs, but they also provide a unique advantage: upon protonation, isocyanate-like reactivity is restored, allowing rapid access to a range of *ortho*-functionalized aniline derivatives.

We recently reported that a "proton switch" mechanism allows protic nucleophiles to liberate and then capture aryl isocyanates from *N*,*N*-dialkyl-*N*′-aryl ureas under neutral conditions, provided that there is substantial steric hindrance

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(2) (a) Selective functionalization of C−H bonds. *Chem. Rev* **2010**, *110*. (b) Kakiuchi, F.; Kochi, T. *Synthesis* **2008**, *19*, 3013. (c) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (d) Li, B. J.; Yang, S. D.; Shi, Z. J. *Synlett* **2008**, *7*, 949. (e) Campeau, L.-C.; Stuart, D. R.; Fagnou, K. *Aldrichimica Acta* **2007**, *40*, 35.

(3) (a) Clayden, J. *Organolithiums: Selectivity for Synthesis*; Pergamon: Oxford, 2002. (b) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879. (c) Beak, P.; Zajdel, W. J. *Chem. Rev.* **1984**, *84*, 471.

(4) Fuhrer, W.; Gschwend, H. W. *J. Org. Chem.* **1979**, *44*, 1133.

(5) (a) Muchowski, J. M.; Venuti, M. C. *J. Org. Chem.* **1980**, *45*, 479. (b) Stanetty, P.; Koller, H.; Mihovilovic, M. *J. Org. Chem.* **1992**, *57*, 6833.

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(7) The utility of ureas for directed metallation has been recently been substantially expanded by Clayden and co-workers: (a) Bach, R.; Clayden, J.; Hennecke, U. *Synlett* **2009**, 421. (b) Clayden, J.; Turner, H.; Helliwell, M.; Moir, E. *J. Org. Chem.* **2008**, *73*, 4415. (c) Clayden, J.; Hennecke, U. *Org. Lett.* **2008**, *10*, 3567. (d) Clayden, J.; Dufour, J.; Grainger, D. M.; Helliwell, M. *J. Am. Chem. Soc.* **2007**, *129*, 7488. (e) Clayden, J.; Dufour, J. *Tetrahedron Lett.* **2006**, *47*, 6945. (f) Clayden, J.; Turner, H.; Pickworth, M.; Adler, T. *Org. Lett.* **2005**, *7*, 3147.

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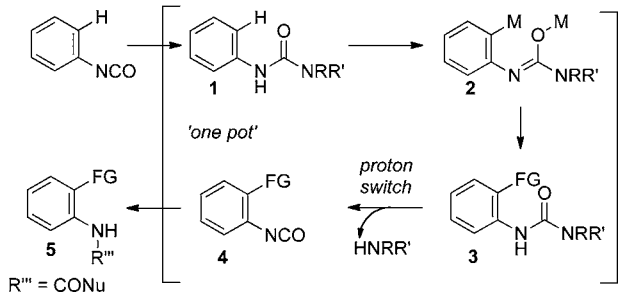
at the dialkyl urea terminus.[8] This lability has thwarted the application of such substrates in our methodology for Pd(II)-catalyzed *ortho* C−H activation.[9] We have thus sought to develop a strategy for their *ortho*-functionalization that takes advantage of rather than suffers from this remarkable lability.

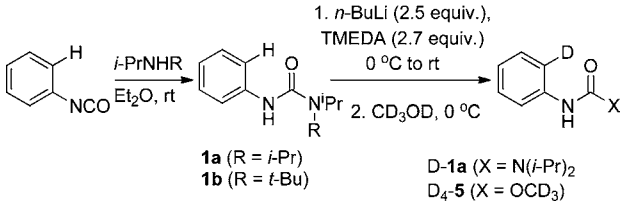
Scheme 1. One-Pot Process for the Vicarious *ortho*-Metallation of Aniline Derivatives (**5**) via Double-Lithiation of an *in Situ* Generated *N*,*N*-Dialkyl-*N*′-aryl Urea



Our concept involves in situ generation of a highly hindered *N*,*N*-dialkyl-*N*′-aryl urea (**1**), followed by deprotonation (NH), *ortho*-metalation (→ **2**), electrophilic quench (→ **3**), and then liberation of the aniline derivative (**5**), via proton-switch release of isocyanate **4**. The sequence **1** → **4** represents a formal *ortho*-lithiation/trapping of an aryl isocyanate; a process for which there is no direct route. Moreover, since the aryl isocyanate is readily trapped, the net transformation to **5** provides a vicarious route for the *ortho*-metalation of aniline derivatives.

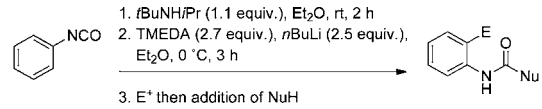
We began by investigating the lithiation of *N*,*N*-diisopropyl-*N*′-phenyl urea **1a,** Scheme 2, (R = *i*-Pr) formed *in situ*

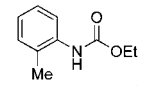
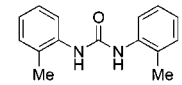
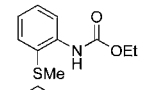
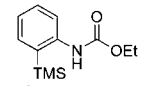
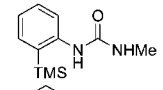
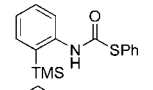
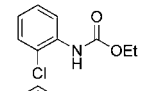
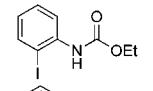
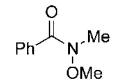
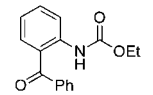
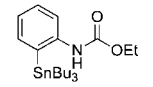
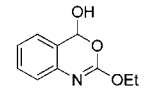
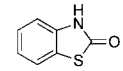
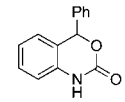
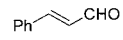
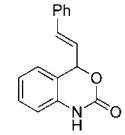
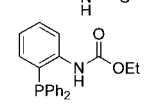
Scheme 2. Preliminary Studies on the Double Lithiation of *in Situ* Generated Hindered Ureas



from phenyl isocyanate. Quantitative DoM was achieved in under 12 h, using *n*-BuLi/TMEDA in Et_2O at room temperature, with the recovery of D-**1a** (>99% D) after quenching with CD_3OD. When TMEDA was excluded, deuterium

Table 1. One-Pot Difunctionalization of Phenyl Isocyanate



entry	E^+	NuH	product	yield (%)
1	MeI	EtOH		82
2	MeI	H_2O		54
3	$(MeS)_2$	EtOH		76
4	TMSCl	EtOH		84
5	TMSCl	$MeNH_2$		81
6	TMSCl	PhSH		82
7	C_2Cl_6	EtOH		85
8	I_2	EtOH		52
9		EtOH		65
10	Bu_3SnCl	EtOH		82
11	DMF	EtOH		55
12	S_8	EtOH		72
13		EtOH		74
14		EtOH		87
15	Ph_2PCl	EtOH		77

incorporation was not observed.This facile lithiation stands in stark contrast to the DoM of *N*-Boc aniline, which requires the use of *t*-BuLi to avoid nucleophilic attack on the more electrophilic carbonyl group.[5] The more labile urea **1b** (R = *t*-Bu) proved even more effective, undergoing quantitative lithiation in just 2 h, and on quenching with CD_3OD provided the *ortho* deuterated *carbamate* **5** (X = OCD_3) in excellent

(8) Hutchby, M.; Houlden, C. E.; Ford, J. G.; Tyler, S. N. G.; Gagné, M. R.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *Angew. Chem. Int. Ed* **2009**, *48*, 8721. For a related neutral hydrolysis of sterically encumbered ureas, see ref.7c

(9) (a) Houlden, C. E.; Bailey, C. D.; Ford, J. G.; Gagné, M. R.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *J. Am. Chem. Soc.* **2008**, *130*, 10066. (b) Houlden, C. E.; Hutchby, M.; Bailey, C. D.; Ford, J. G.; Tyler, S. N. G.; Gagné, M. R. *Angew. Chem., Int Ed.* **2009**, *48*, 1830.

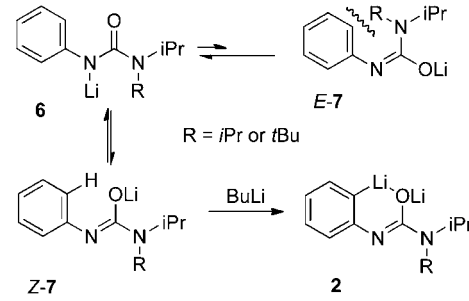
yield, confirming the rapid solvolysis of the hindered urea under the quenching conditions (<1 h at rt.).

With these conditions in hand we examined the scope of the reaction by utilizing a range of different electrophilic and nucleophilic partners (Table 1). In general the reaction is successful for a wide range of electrophiles and gave good overall yields of the resulting difunctionalized products. The intermediate dilithiated species proved to be very reactive, and electrophilic quench was complete within 5 min, after which *in situ* isocyanate liberation and capture was initiated by "proton switch" using a range of nucleophiles and solvents. Ethanol was generally used as nucleophile as the carbamates generated were readily isolated.

The diversity of products formed hints at the versatility of this transformation. For example, sulfide, silane, halogen, stannane, and phosphine moieties (entries 3, 4, 7, 8, 10, 15) could all be introduced cleanly, leading to a range of *ortho*-functionalized carbamates on ethanol workup. By using alternative nucleophiles in the workup other *N*-acyl derivatives could be obtained (e.g., entries 6 and 7). *ortho*-Substituted aryl ketones and aldehydes could be prepared using a Weinreb amide and DMF electrophilic quench respectively (entries 10 and 11); the latter is isolated as the corresponding hemiacetal. Electrophilic quench with elemental sulfur gave novel access to benzothiazolone (entry 12). The reactions of aldehydes are interesting as cyclization of the intermediate benzhydrols leads to the isolation of cyclic carbamates (entries 13 and 14).

It is not entirely clear why these hindered ureas are such good directing groups. When Smith and co-workers studied the *ortho*-lithiation of dimethylphenylurea, they found that unless the aryl ring was electron-deficient, methyl deprotonation was favored over *ortho*-lithiation.[6b] Clearly the hindered ureas used in our study are much less likely to undergo alkyl deprotonation. The initially generated lithium amide **6** can undergo lithiotropic tautomerization to *E*/*Z* isomers of alkoxide **7**. We note that severe steric repulsion between the phenyl group and the hindered *N*-alkyl substituent will disfavor *E*-**7**. However, in *Z*-**7** the oxygen atom is suitably orientated[10] to direct the metalation event[11] that generates **2**, Scheme 3. The equilibrium position, with respect to *Z*-**7**, may be a contributing factor in the ca. 6-fold more rapid *ortho*-lithiation when R = *t*-Bu as compared to R = *i*-Pr.

Scheme 3. Configurational Control in Selective *ortho*-Lithiation of **7**



In conclusion, we have demonstrated a powerful and highly adaptable transformation that is of broad use for the synthesis of aniline derivatives and heterocycles from commercially available starting materials in a simple, high-yielding one-pot operation. Future work will involve investigating the scope of the reaction to ring substitution and nucleophile/electrophile variaition. Furthermore, we hope to develop a procedure utilizing the same hindered urea intermediates but with anilines as starting materials.

Acknowledgment. We thank the EPSRC (E061575) for support. GCLJ is a Royal Society Wolfson Research Merit Award Holder.

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.

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(10) Whisler, M. C.; MacNeil, S.; Snieckus, V.; Beak, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 2206.

(11) *ortho*-Lithiation is a distinct process from *ortho*-deprotonation; see ref 10 and Dyke, A. M.; Gill, D. M.; Harvey, J. N.; Hester, A. J.; Lloyd-Jones, G. C.; Muñoz, M. P.; Shepperson, I. R. *Angew. Chem., Int. Ed.* **2008**, *47*, 5067.