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Cine Substitution of Arenes Using the Aryl Carbamate as a Removable Directing Group

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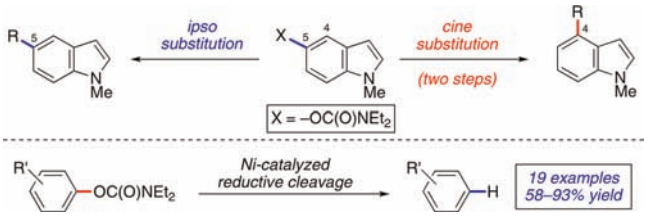
ABSTRACT



An efficient and controlled means to achieve a rare cine substitution of arenes is reported. The methodology relies on the strategic use of aryl *O*-carbamates as readily removable directing groups for arene functionalization. The removal of aryl carbamates is achieved by employing an air-stable Ni(II) precatalyst, along with an inexpensive reducing agent, to give synthetically useful yields across a range of substrates. The net cine substitution process offers a new strategy for analogue synthesis, which complements the well-established logic for achieving arene functionalization by ipso substitution.

Arene substitution processes are some of the most important and frequently used transformations in organic synthesis.[1] Whereas ipso substitution can be readily achieved through numerous means, including metal-catalyzed cross-coupling[2] and nucleophilic aromatic substitution,[3] methods to achieve other patterns of arene substitution are rare. For example, cine substitution of aromatics,[4] where a new substituent is introduced adjacent to the position of the departing leaving group, has seen little use beyond reactions of nitroaromatics[5] and in reactions that invoke aryne[6] intermediates. A controlled and selective method to achieve the net cine substitution of arenes would provide a valuable means for arene functionalization and a versatile new tool for analogue synthesis.

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(2) For recent reviews of transition metal-catalyzed cross-couplings, see: (a) Negishi, E. *Acc. Chem. Res.* **1982**, *15*, 340–348. (b) *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998. (c) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359–1469. (d) *Topics in Current Chemistry*, Vol. 219; Miyaura, N., Ed.; Springer-Verlag: New York, 2002. (e) Corbet, J.; Mignani, G. *Chem. Rev.* **2006**, *106*, 2651–2710. (f) Negishi, E. *Bull. Chem. Soc. Jpn.* **2007**, *80*, 233–257.

(3) For reviews, see: (a) Terrier, F. *Nucleophilic Aromatic Displacement, The Influence of the Nitro Group*; VCH Publishers Inc.: New York, 1991. (b) van der Plas, H. C.; Chupakhin, O. N.; Charushin, V. N. *Nucleophilic Aromatic Substitution of Hydrogen*; Academic Press: San Diego, 1994. (c) Makosza, M. *Russ. Chem. Bull.* **1996**, *45*, 491–504.

(4) For a review of cine substitution, see: Suwinski, J.; Swierczek, K. *Tetrahedron* **2001**, *57*, 1639–1662.

(5) Nitroarenes can be converted to aryl carboxylic acid derivatives via the von Richter reaction; for a pertinent study, see: Bunnett, J. F. *Q. Rev. Chem. Soc.* **1958**, *12*, 1–16.

(6) Arynes may give rise to products of net ipso or cine substitution. For reviews of aryne chemistry, see: (a) Sanz, R. *Org. Prep. Proced. Int.* **2008**, *40*, 215–291. (b) Peña, D.; Pérez, D.; Guitián, E. *Heterocycles* **2007**, *74*, 89–100. (c) Dyke, A. M.; Hester, A. J.; Lloyd-Jones, G. C. *Synthesis* **2006**, 4093–4112. (d) Pellissier, H.; Santelli, M. *Tetrahedron* **2003**, *59*, 701–730. (e) Wenk, H. H.; Winkler, M.; Sander, W. *Angew. Chem., Int. Ed.* **2003**, *42*, 502–528. For recent studies of regioselectivity in additions to unsymmetrical arynes, see: (f) Cheong, P. H.-Y.; Paton, R. S.; Bronner, S. M.; Im, G.-Y. J.; Garg, N. K.; Houk, K. N. *J. Am. Chem. Soc.* **2010**, *132*, 1267–1269. (g) Im, G.-Y. J.; Bronner, S. M.; Goetz, A. E.; Paton, R. S.; Cheong, P. H.-Y.; Houk, K. N.; Garg, N. K. *J. Am. Chem. Soc.* **2010**, *132*, 17933–17944.

(7) A Reaxys search shows that over 500 examples of ortho-functionalization of *N,N*-dialkyl carbamates have been reported on aryl or heteroaryl substrates, using directed ortho-lithiation or transition-metal-catalyzed C–H functionalization methodologies.

(8) Of the various phenol derivatives, the aryl carbamate possesses superior ability in directed metallation reactions (see ref 10).

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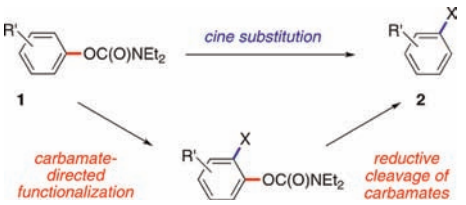

Figure 1. Cine substitution of aryl *O*-carbamates.

Bearing in mind the unique ability of aryl carbamates[7,8] to participate efficiently in directed metallation reactions,[9] most commonly using organolithium chemistry pioneered by Snieckus,[10] we considered the net arene cine substitution process shown in Figure 1. Aryl carbamates **1** would undergo ortho-functionalization, followed by reductive aryl C−O bond cleavage, to afford the net cine substituted products **2**. Although methods for aryl C−O bond cleavage of aryl sulfonates are well-known,[11] and recent examples pertaining to phenol-derived esters[12,13] and ethers have been reported,[12,14,15] no methodology exists for the reductive removal of synthetically useful aryl carbamates. In fact, the cleavage of aryl carbamates through C−O bond reduction has only been observed as a minor undesired reaction pathway in the attempted coupling of aryl carbamates with alkyl Grignard reagents.[16]

We report the first method to achieve the reductive cleavage of aryl *O*-carbamates, which utilizes an air-stable Ni(II) precatalyst and an inexpensive silane reducing agent. When employed subsequently to carbamate-directed arene functionalization, this methodology provides an efficient means to achieve the desired arene cine substitution process. Our approach provides a new method for analogue synthesis, which augments the conventional logic for achieving arene functionalization by ipso substitution.

We first explored the sequential ortho-functionalization/reduction of methoxycarbamate **3** to give cine substituted products **5** (Figure 2). Carbamate-directed lithiation of **3** proceeded smoothly, without competitive metallation ortho to the methoxy substituent. This observation, which is consistent with literature data,[17] reflects the superior directing group ability of carbamates compared to ethers. Quenching of the lithiated intermediate with various electrophiles gave products **4a**−**c**.

Next, we developed conditions for the unexplored aryl carbamate cleavage. We,[18] and others,[16,19] have shown that the aryl C−O bond of aryl carbamates may be activated by specific Ni/ligand combinations to ultimately construct C−C or C−N bonds.[20] The Ni(II) precatalyst $NiCl_2(PCy_3)_2$,[21] which was used in the Suzuki−Miyaura coupling of aryl carbamates, was considered ideal because of its low cost and pronounced stability to air and water.[22] Despite the fact that this complex has not been used in reductive aryl C−O bond cleavage reactions, we tested its performance in the desired transformation using **4a** as the substrate, in conjunction with various reducing agents. After considerable experimentation, it was found that reductive cleavage occurred efficiently using cat. $NiCl_2(PCy_3)_2$, 1,1,3,3-tetramethyldisiloxane (TMDSO),[23] and K_3PO_4 in toluene at 115 °C to afford meta substituted arene **5a** in 69% yield (Figure 2). Of note, the methoxy substituent remained intact despite the removability of aryl ethers under Ni-based reductive conditions.[14] Removal of the carbamate from ortho-substituted substrates **4b** and **4c** using our Ni-catalyzed conditions provided

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(16) Sengupta, S.; Leite, M.; Raslan, D. S.; Quesnelle, C.; Snieckus, V. *J. Org. Chem.* **1992**, *57*, 4066–4068.

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(20) For a pertinent review, see: Rosen, B. M.; Quasdorf, K. W.; Wilson, D. A.; Zhang, B.; Resmerita, A.-M.; Garg, N. K.; Percec, V. *Chem. Rev.* **2011**, *111*, 1346–1416.

(21) $NiCl_2(PCy_3)_2$ is commercially available from Strem Chemicals Inc. or Sigma-Aldrich (CAS #19999-87-2). For more information on this catalyst, see: Quasdorf, K. W.; Garg, N. K. *Encyclopedia of Reagents for Organic Synthesis* **2010**, DOI: 10.1002/047084289X.rn01201.

(22) Current methods for the reductive removal of aryl esters or ethers utilize $Ni(cod)_2$ as the precatalyst, which requires glovebox handling; see refs 12 and 14.

(23) TMDSO was also an effective reducing agent for the reductive removal of aryl ethers reported by Martin et al. (see ref 14a).

meta-substituted products **5b** and **5c**, respectively. Given the rich precedent for the controlled ortho-functionalization of aryl carbamates and the efficiency of the carbamate removal methodology (vida infra), this cine substitution process provides a useful tool for the conversion of para- to meta-substituted arenes.

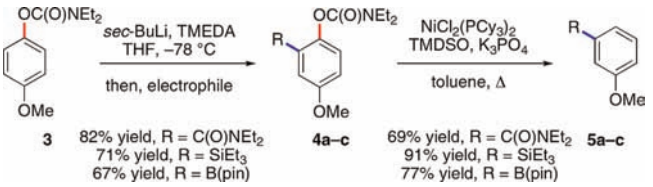

Figure 2. Cine substitution of *para*-methoxycarbamate **3** to give *meta*-substituted products **5a**–**c**.

The cine substitution sequence was also tested on 5-hydroxyindole derivative **6** (Figure 3). Lithiation of **6** proceeded selectively at C4; subsequent functionalization of the resulting organolithium species gave ortho-substituted carbamate products **7**–**9**. Amide **7** was obtained through a Fries rearrangement/carbamoylation sequence, whereas products **8** and **9** came from direct quenching of the intermediate lithiated species with MeI or TMSCl, respectively. Reductive cleavage of **7**–**9** under our Ni-catalyzed reaction conditions furnished the desired products **10**–**12**. The cine substitution of indolylcarbamate **6** demonstrates (a) the unrivaled directing group ability of the *N*,*N*-diethylcarbamate, as competitive C2 lithiation was not observed;[24] (b) that the Ni-catalyzed carbamate removal methodology may be used on heterocyclic, ortho-substituted substrates; and (c) that C4-substituted indoles can be readily synthesized from more accessible C5-substituted precursors.[25]

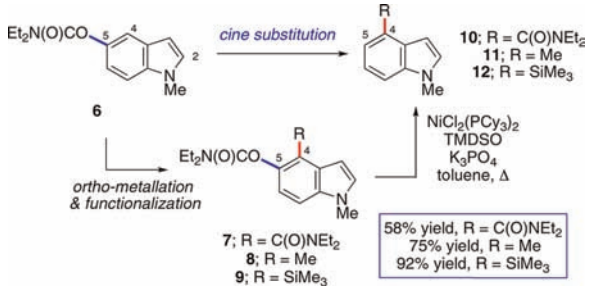

Figure 3. Cine substitution of indolylcarbamate **6**.

(24) The acidity of C2–H of *N*-methylindole is approximately 10^7 times greater than the acidity of C4–H according to computational studies; see: Shen, K.; Fu, Y.; Li, J.-N.; Liu, L.; Guo, Q.-X. *Tetrahedron* **2007**, *63*, 1568–1576.

(25) The ability to access C4 substituted indoles is of importance for natural product synthesis and drug discovery. A Reaxys search indicates that more than 600 C4-substituted indole-containing natural products exist and nearly 10 000 bioactive C4-substituted indoles have been reported.

Figure 4 highlights the ability to employ carbamates in either ipso or cine substitution reactions, in a highly controlled manner, using transition metal-catalyzed reactions. Using Ni-catalysis, direct coupling of carbamate **6** affords products **14** or **15**, via C–N[18c] or C–C[18a,b] bond formation, respectively. Alternatively, borylation of **6** with cine substitution provides boronic ester **13**. Boronate **13** could be elaborated to either amine **16** or arylated product **17**, via Chan–Lam[26] or Suzuki–Miyaura coupling,

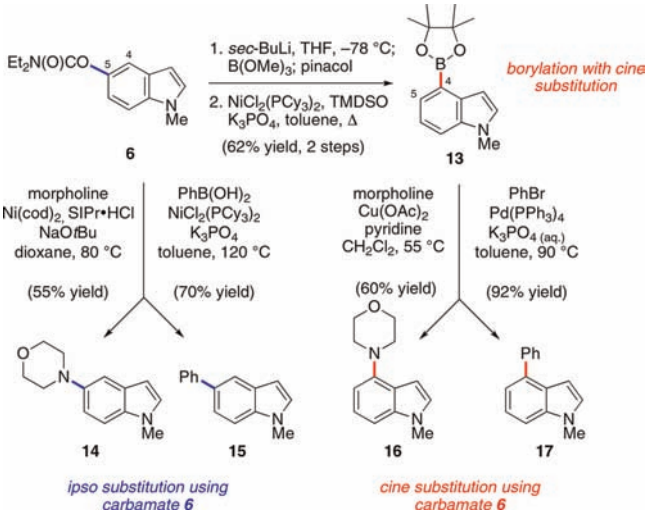

Figure 4. Cross-coupling approaches to ipso or cine substituted products from carbamate **6**.

respectively. Given the widespread use of transition metal-catalyzed reactions in medicinal chemistry,[27] we expect the complementary means to achieve C–C and C–N bond formation using aryl carbamates, with controlled ipso or cine substitution, will add to the arsenal of tools needed to efficiently synthesize analogues of lead compounds.

Finally, we explored the generality of our reaction conditions for the reductive cleavage of various carbamate substrates, as no general methodology exists for this transformation (Figure 5). Fused aromatics were excellent substrates, giving rise to products **18**–**21**. Of note, a double-decarbamoylation proceeded smoothly to give naphthalene (**18**) in 82% yield. Nonfused aromatics were also tolerated, as were a variety of functional groups. For instance, an electron-deficient ester survived the transformation to provide **20**, and electron-donating substituents did not cause difficulty as suggested by the smooth formation of **21** and **22**. The successful reduction of an estrone derivative demonstrates the use of this methodology on a complex system bearing a ketal protecting group to furnish **23**. Several heterocyclic substrates

(26) Qiao, J. X.; Lam, P. Y. S. *Synthesis* **2011**, 829–856.

(27) (a) Torborg, C.; Beller, M. *Adv. Synth. Catal.* **2009**, *351*, 3027–3043. (b) *Modern Drug Synthesis*; Li, J. J., Johnson, D. S., Eds.; Wiley: New York, 2010. (c) Djakovitch, L.; Batail, N.; Genelot, M. *Molecules* **2011**, *16*, 5241–5267.

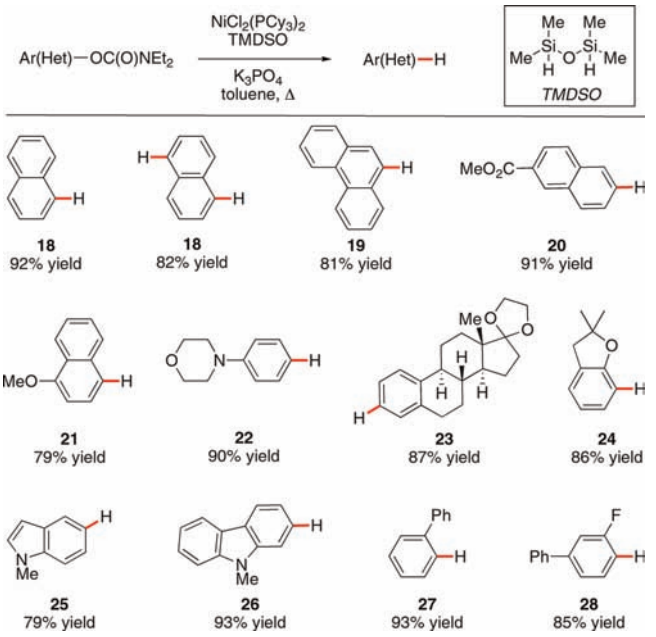

Figure 5. Reductive cleavage of aryl carbamates. Reaction conditions: Aryl carbamate (1 equiv), $NiCl_2(PCy_3)_2$ (5−20 mol %), TMDSO (2.5 equiv), K_3PO_4 (4.5 equiv), toluene (0.27 M), 115−125 °C for 15 h (see Supporting Information). Isolated yields provided.

were evaluated to provide **24**−**26** in synthetically useful yields. Two additional ortho-substituted carbamates were examined, which demonstrate that both phenyl and fluoro substituents positioned ortho to the carbamate are tolerated by this methodology.

In summary, we have developed an efficient means to achieve a rare arene cine substitution process. The methodology relies on the strategic use of aryl *O*-carbamates as readily removable directing groups for arene functionalization. We expect that our parent method for carbamate removal will prove useful for aryl C−O bond cleavage reactions. Moreover, the cine substitution process offers a new tool for arene functionalization that is intended to complement the prevalent logic of arene ipso substitution as a means to prepare analogues of important scaffolds.

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Supporting Information Available. Experimental details and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.