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Stereoselective Bis-functionalizations of Arene Chromium Tricarbonyl Complexes via Brook Rearrangements

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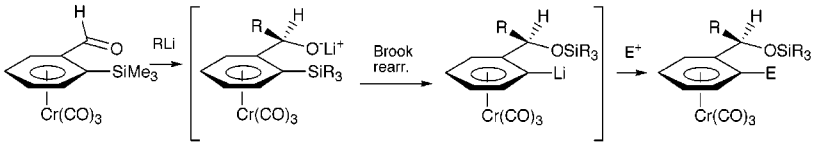
ABSTRACT



An efficient method has been developed for the stereoselective bis-functionalization of arene chromium tricarbonyl complexes. Initial nucleophilic addition of organolithium reagents to a carbonyl moiety is followed by a 1,4-carbon to oxygen silyl migration (Brook rearrangement) and alkylation of the resultant aryl anion.

Arene chromium tricarbonyl complexes are important tools in organic synthesis,[1] both as intermediates in synthetic endeavors[2] and as catalysts in a variety of processes.[3] As advances in these areas continue to be demonstrated, the development of efficient methods for the stereoselective synthesis of highly functionalized arene chromium tricarbonyl complexes becomes increasingly important.

Although the characteristic reactivity of arene chromium tricarbonyl complexes readily provides opportunities for regioselective functionalizations, the planar chirality conferred on unsymmetrical *ortho*- or *meta*-disubstituted arene complexes by the chromium tricarbonyl moiety has rendered stereoselective functionalization a more challenging issue. Stereoselective formation of new bonds to the aromatic ring requires the differentiation between enantiotopic *ortho*-protons of achiral monosubstituted arene complexes or diastereotopic *ortho*-protons of arene complexes containing an additional stereogenic center. A related difficulty is encountered in the elaboration of functional groups attached to the aromatic ring. That is, reactant partners must distinguish between enantiotopic or diastereotopic faces of a prochiral reaction center. Methods to circumvent these difficulties have largely been based on the use of chiral bases

(1) For reviews, see: (a) Uemura, M. *Adv. Met. Org. Chem.* **1991**, *2*, 195. (b) Semmelhack, M. F. In *Comprehensive Organometallic Chemistry II*; Wilkinson, G., Stone, F. G. A., Abel, E. W., Eds.; Pergamon Press: New York, 1995; Vol. 12, pp 929−1015. (c) Hegedus, L. S. *Transition Metals in the Synthesis of Complex Organic Molecules*, 2nd ed.; University Science Books: Sausalito, 1999; Chapter 10.

(2) For recent examples, see: (a) Semmelhack, M. F.; Knochel, P.; Singleton, T. *Tetrahedron Lett.* **1993**, *34*, 5051. (b) Tamaka, T.; Mikamiyama, H.; Maeda, K.; Ishida, T.; In, Y.; Iwata, C. *J. Chem. Soc., Chem. Commun.* **1997**, 2401. (c) Watanabe, T.; Uemura, M. *J. Chem. Soc., Chem. Commun.* **1998**, 871. (d) Schellhaas, K.; Schmalz, H. G.; Bats, J. W. *Chem. Eur. J.* **1998**, *4*, 57. (e) Horstermann, D.; Schmalz, H. G.; Kociok-Kohn, G. *Tetrahedron* **1999**, *55*, 6905.

(3) For recent examples, see: (a) Uemura, M.; Miyake, R.; Nakayama, K.; Shiro, M.; Hayashi, Y. *J. Org. Chem.* **1993**, *58*, 1238. (b) Sodeoka, M.; Shibasaki, M. *Synthesis* **1993**, 643. (c) Jones, G. B.; Heaton, S. B.; Chapman, B. J.; Guzel, M. *Tetrahedron: Asymmetry* **1997**, *8*, 3625. (d) Pasquier, C.; Naill, S.; Pelinski, L.; Brocard, J.; Mortreux, A.; Agbossou, F. *Tetrahedron: Asymmetry* **1998**, *9*, 193. (e) Malfait, S.; Pelinski, L.; Brocard, J. *Tetrahedron: Asymmetry* **1998**, *9*, 2595. (f) Nelson, S. G.; Hilfiker, M. A. *Org. Lett.* **1999**, *1*, 1379.

(4) (a) Kundig, E. P.; Quattropani, A. *Tetrahedron Lett.* **1994**, *35*, 3497. (b) Ariffin, A.; Blake, A. J.; Ewin, R. A.; Simpkins, N. S. *Tetrahedron: Asymmetry* **1998**, *9*, 2563. (c) Gibson, S. E.; O'Brien, P.; Rahimian, E.; Smith, M. H. *J. Chem. Soc., Perkin Trans. 1* **1999**, 909.

(5) For an excellent review, see: Bolm, C.; Muniz, K. *Chem. Soc. Rev.* **1999**, *28*, 51. For other representative references, see: (a) Aube, J.; Heppert, J. A.; Milligan, M. L.; Smith, M. J.; Zenk, P. *J. Org. Chem.* **1992**, *57*, 3563. (b) Davies, S. G.; Donohoe, T. J.; Williams, J. M. J. *Pure Appl. Chem.* **1992**, *64*, 379. (c) Kondo, Y.; Green, J. R.; Ho, J. *J. Org. Chem.* **1993**, *58*, 6182. (d) Davies, S. G.; Loveridge, T.; Clough, J. M. *J. Chem. Soc., Chem. Commun.* **1995**, 817. (e) Alexakis, A.; Kanger, T.; Mangeney, P.; Rose-Munch, F.; Perrotey, A.; Rose, E. *Tetrahedron: Asymmetry* **1995**, *6*, 2135. (f) Fretzen, A.; Kundig, E. P. *Helv. Chim. Acta* **1997**, *80*, 2023. (g) Han, J. W.; Son, S. U.; Chung. Y. K. *J. Org. Chem.* **1997**, *62*, 8264.

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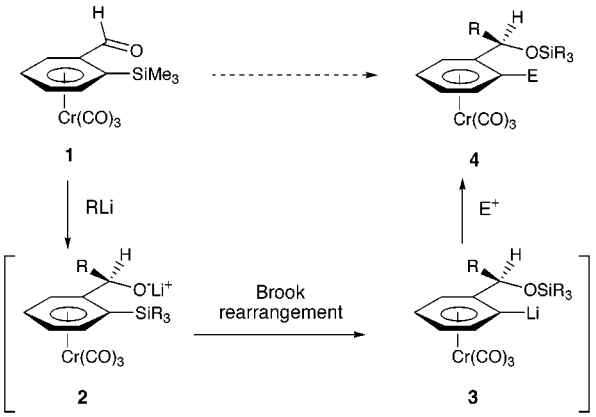
to effect selective deprotonations[4] or chiral auxiliaries that allow for the differentiation of diastereotopic protons or reactant faces.[5] Although these methods have successfully allowed the formation of chiral functionalized arene complexes, they often face the inefficiency associated with the synthesis of chiral bases or the protection/deprotection strategies of chiral auxiliaries. In addition, all of these methods are limited to the formation of a single bond in each reaction step. Indeed, additional methods to effect multiple stereoselective bond formations are highly desirable.

We are currently developing the use of silyl migrations as a novel method for achieving this goal.[6] Our strategy, outlined in Scheme 1, involves initial addition of an

Scheme 1



organolithium reagent to an *o*-silyl-substituted benzaldehyde chromium tricarbonyl complex, generating oxyanion **2**. Subsequent 1,4 carbon-to-oxygen silyl migration was anticipated to be a favorable process, as the resultant aryl anion would be stabilized by the powerful electron-withdrawing capability of the $Cr(CO)_3$ moiety. A second bond-forming step would then be accomplished by treatment of **3** with various electrophiles. Importantly, we recognized that the silyl group would provide an element of stereocontrol in *both* bond-forming steps. That is, the silyl group serves not only to influence the facial selectivity of the initial nucleophilic attack (vide infra) but also to ensure maintenance of the sense of planar chirality through the final alkylation.

Studies began with racemic arene chromium tricarbonyl complex **1**, which is prepared on a multigram scale according to literature precedence.[7] As previously demonstrated by Davies and co-workers, addition of methyllithium to **1** at −78 °C occurs with good facial selectivity (88/12), which is attributed to the ability of the sterically bulky chromium tricarbonyl and trimethylsilyl groups to favor nucleophilic attack on a single rotameric isomer.[8] Although oxyanion **2** is stable at low temperature, the anticipated carbon-to-oxygen migration is observed upon gradual warming of the reaction solution. Indeed, silyl ether **4a** can be isolated in near quantitative yield by warming the reaction to room temperature for 2 h and quenching with H_2O (Figure 1). Similar

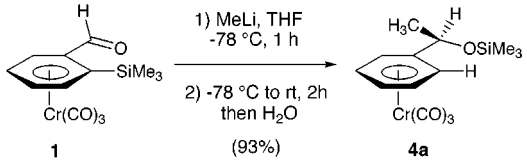
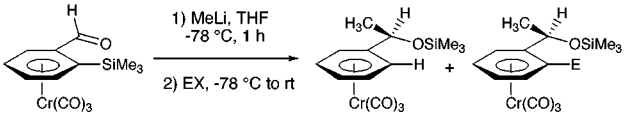


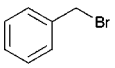
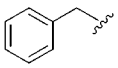
Figure 1. Initial demonstration of silyl migration.

results were obtained with a variety of solvents (THF, Et_2O, DME). The addition of cosolvents (HMPA, DMPU, TMEDA) did not have a significant effect on the rate of silyl migration.

The next set of experiments involved the in situ trapping of aryl anion **3** with electrophiles. As indicated in Table 1, a variety of carbon- and heteroatom-based electrophiles could

Table 1. Bis-alkylations of Arene Complex **1**



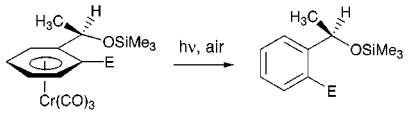
Entry	EX	E	Products[a] (% yield)
1			**4b** (58) + **4a** (36)
2			**4c** (52) + **4a** (33)
3	CH_3I	CH_3	**4d** (65) + **4a** (15)
4	PhCHO	PhCH(OH)	**4e** (72) + **4a** (<5)
5[b]	$Ph_2C(O)$	$Ph_2C(OH)$	**4f** (77)[c] + **4a** (<5)
6	PhSSPh	SPh	**4g** (83) + **4a** (<5)
7	BrF_2CCF_2Br	Br	**4h** (66) + **4a** (<5)

[a] Products **4b-4d** and **4g-4h** were obtained as ca. 9:1 mixtures of diastereomers. Product **4e** was initially obtained as a mixture of 4 diastereomers. The yield refers to a 6:1 mixture of the two major diastereomers isolated after purification. [b] A 95/5 mixture of THF:HMPA was necessary for addition to benzophenone. [c] Product **4f** was isolated as the corresponding alcohol rather than the silyl ether. The yield refers to recrystallized product, obtained as a single diastereomer.

(6) For other examples using silyl migrations for tandem bond formations, see: (a) Matsuda, I.; Murata, S.; Ishii, Y. *J. Chem. Soc., Perkin Trans. 1* **1979**, 26. (b) Isobe, M.; Kitamura, M.; Goto, T. *Tetrahedron Lett.* **1979**, 3465. (c) Fleming, I.; Floyd, C. D. J. *Chem. Soc., Perkin Trans. 1* **1981**, 969. (d) Tietze, L. F.; Geissler, H.; Gewert, J. A.; Jakobi, U. *Synlett* **1994**, 511. (e) Shinokubo, H.; Miura, K.; Oshima, K.; Utimoto, K. *Tetrahedron* **1996**, *52*, 503. (f) Smith, A. B., III.; Boldi, A. M. *J. Am. Chem. Soc.* **1997**, *119*, 6925. (g) Takeda, K.; Nakajima, A.; Takeda, M.; Okamoto, Y.; Sato, T.; Yoshii, E.; Koizumi, T.; Shiro, M. *J. Am. Chem. Soc.* **1998**, *120*, 4947. (h) Brauer, N.; Dreessen, S.; Schaumann, E. *Tetrahedron Lett.* **1999**, *40*, 2921.

(7) Davies, S. G.; Goodfellow, C. L. *J. Chem. Soc., Perkin Trans. 1* **1990**, 393.

Table 2. Removal of Chromium Moiety from Arene Complexes **4**



4b-h **5b-h**

Arene complex	Product (% yield)
4b	**5b** (96)
4c	**5c** (94)
4d	**5d** (82)
4e	**5e** (92)[a]
4f[b]	**5f** (89)[c]
4g	**5g** (94)
4h	**5h** (95)

[a] Complex **5e** was isolated as a 4:1 mixture of diastereomers. [b] Complex **4f** was obtained as the corresponding alcohol rather than the silyl ether. [c] Product **5f** was obtained as the corresponding alcohol rather than the silyl ether.

be utilized in this process, generating bis-functionalized arene complexes **4b**−**h**.[9] The diastereoselectivity observed in the initial addition step was maintained in this step, as evidenced by the isolation of products **4** as approximately 9/1 mixtures of diastereoisomers. These results suggest that the electrophile replaces the silyl group in a site-selective manner with no proton transfer. Notably, significant amounts of product **4a**, apparently arising from protonation of intermediate **3**, were only observed in entries 1−3. A reasonable hypothesis is that the silyl migration is the slowest step of the sequence; thus products **4b**−**d**, containing acidic protons in the benzylic position, could serve as a proton source for intermediate **3**.

Removal of the chromium moiety was readily effected in all trials by exposure of ethereal solutions of the arene complexes to air and sunlight, providing bis-functionalized aryl products **5b**−**h** in excellent yield (Table 2).

In summary, a novel method for the stereoselective bis-functionalization of arene chromium tricarbonyl complexes based on silyl migrations has been demonstrated. The silyl group not only mediates multiple bond formation but also provides an element of stereocontrol in each bond-forming step. Further assessment of the stereoselectivity of this process, asymmetric variants, and applications to synthetic endeavors are currently underway.

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Supporting Information Available: Detailed experimental procedures and complete spectral data for compounds **4b**−**h** and **5b**−**h**. This information is available free of charge via the Internet at http://pubs.acs.org.

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(8) All of the studies involve *racemic* arene complex **1**. The relative stereochemistry of the major product diastereomers is illustrated, and is in agreement with the work of Davies.

(9) All new compounds were characterized by ^{1}H NMR, ^{13}C NMR, IR, and high-resolution mass spectroscopy.