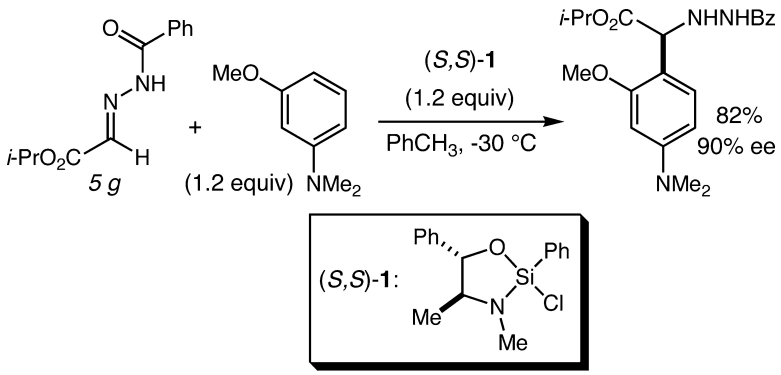
Communication

Enantioselective Friedel–Crafts Alkylations with Benzoylhydrazones Promoted by a Simple Strained Silacycle Reagent

Seiji Shirakawa, Richard Berger, and James L. Leighton

J. Am. Chem. Soc., **2005**, 127 (9), 2858-2859• DOI: 10.1021/ja042522a • Publication Date (Web): 11 February 2005



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 8 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

J|A|C|S
COMMUNICATIONS

Published on Web 02/11/2005

Enantioselective Friedel−Crafts Alkylations with Benzoylhydrazones Promoted by a Simple Strained Silacycle Reagent

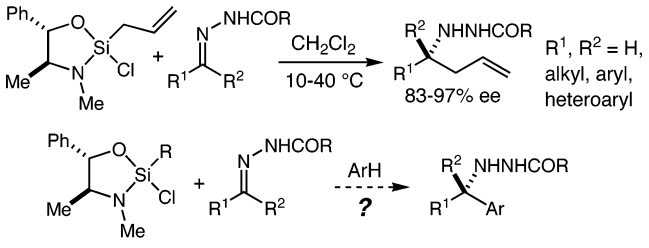
Seiji Shirakawa, Richard Berger, and James L. Leighton*

Department of Chemistry, Columbia University, New York, New York 10027

Received December 13, 2004; E-mail: leighton@chem.columbia.edu

Chemists have for decades been captivated by the notion that chiral ligand/substituent-modified silanes might be used as Lewis acids for asymmetric synthesis, due both to the significant practical advantages that the use of silicon might offer and to the intellectual challenge of rendering silicon Lewis acidic enough to mediate/catalyze carbon−carbon bond forming reactions.[1] To date, significant success has been achieved by Denmark, who has developed an elegant chiral Lewis base-modified silicon Lewis acid system for enantioselective allylation,[2] aldol,[3] and Passerini[4] reactions. Our strategy for inducing Lewis acidity in silanes focuses on the use of ring-strain,[5,6] and we have documented that simply constraining allyl- and crotylsilanes in a five-membered ring leads to enantioselective type I[7] allylation reagents for both aldehydes and acylhydrazones (Scheme 1).[8] Seeking to harness this phenomenon for the development of an effective and general chiral silane Lewis acid, we wondered whether simple chiral silacycles could effectively mediate carbon−carbon bond forming reactions. The enantioselective Friedel−Crafts alkylation of arenes with imine derivatives[9,10] is particularly attractive in this regard both because the nucleophiles require no preactivation and because the products are chiral benzylic amines, a substructure found in natural products and in many medicinal chemistry programs. Herein, we report the development of a simple chiral silane that mediates the enantioselective Friedel−Crafts reaction of electron-rich arenes and heteroarenes with the benzoylhydrazone of isopropyl glyoxylate, leading to a practical synthesis of arylglycines.

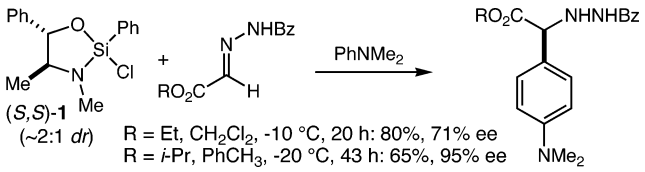
Scheme 1



Our studies began with the benzoylhydrazone of ethyl glyoxylate and *N*,*N*-dimethylaniline (Scheme 2). The allyl group of the silane was simply replaced with a presumably inert phenyl group, leading to silanes **1**, easily prepared (as a ∼2:1 mixture of diastereomers) in a single step from pseudoephedrine and phenyltrichlorosilane. An initial experiment in CH_2Cl_2 was highly encouraging, giving the product in 80% yield and 71% ee. The use of toluene as solvent led to a significantly more enantioselective (85% ee), albeit less efficient, reaction. By switching to the isopropyl ester and lowering the reaction temperature to −20 °C, we obtained the product in 95% ee. The *tert*-butyl glyoxylate-derived hydrazone was examined as well, but led only to a very sluggish and inefficient reaction.

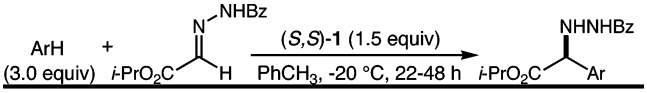
Having established the feasibility of and optimal conditions for the reaction, we carried out a survey of the scope with respect to

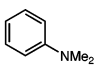
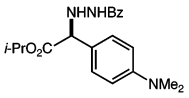
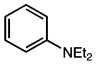
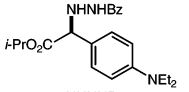
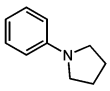
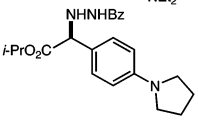
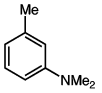
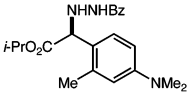
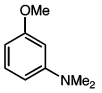
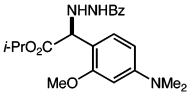
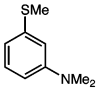
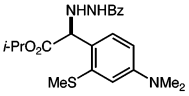
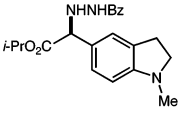
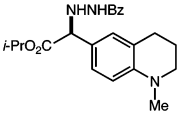
Scheme 2



the arene (Table 1). Although it was found that a strongly activating amino group is required for the reaction to occur at a reasonable rate, substitution on the arene ring was otherwise tolerated, notably, at the position *ortho* to the site of alkylation.

Table 1. Enantioselective Friedel−Crafts Alkylations with Arenes



entry	ArH	product	yield (%)	ee (%)[a]
1			65	95
2			54	94
3[b]			72	93
4			62	87
5[b]			92	90
6			64	88
7			84	90
8			86	87

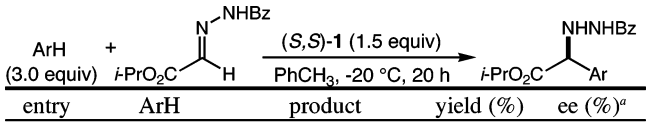
[a] Determined by chiral HPLC. [b] Temperature = −30 °C.

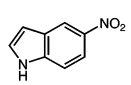
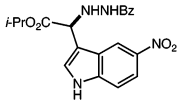
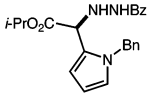
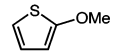
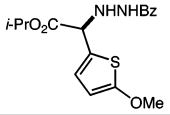
The reaction was investigated with heteroaromatic substrates as well (Table 2). As shown, derivatives of several heterocyclic systems (indole, pyrrole, and thiophene) gave results similar to those

10.1021/ja042522a CCC: $30.25

of the aniline derivatives described in Table 1. Entry 1 is noteworthy in demonstrating that an unprotected indole NH group is compatible with the reaction. We note as well that indole itself provides the corresponding product with significantly reduced enantioselectivity (24% ee). At present, this surprisingly large drop in selectivity is not well-understood, although the hypothesis that led us to employ the 5-nitroindole is that a racemization pathway is kinetically accessible with very reactive arenes and can be avoided by attenuation of the reactivity of the arene.

Table 2. Enantioselective Friedel−Crafts Alkylations with Heteroarenes

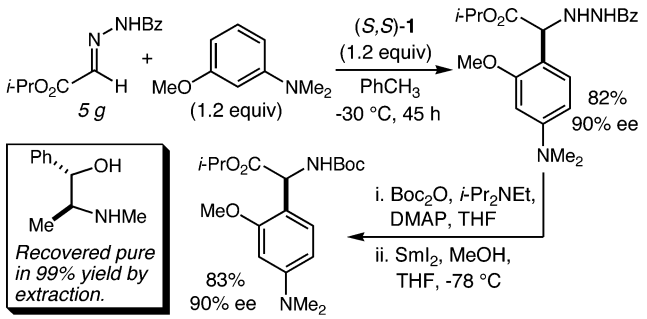


entry	ArH	product	yield (%)	ee (%)[a]
1			74	88
2			76	88
3[b]			91	89

[a] Determined by chiral HPLC. [b] This reaction was run at −30 °C for 48 h.

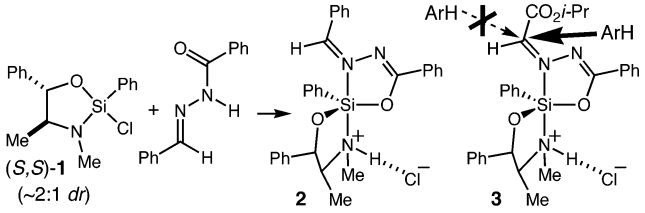
To establish that the reaction is easily practicable on a larger scale, the reaction of 3-methoxy-*N*,*N*-dimethylaniline was carried out using 5 g of the hydrazone (Scheme 3). Employing only 1.2 equiv of both the arene and silanes **1**, we obtained the product in 82% yield and 90% ee. In addition, it proved trivial to recover pure pseudoephedrine in 99% yield by simple extraction during the workup. Boc protection and hydrazide reduction[11] were then demonstrated to provide the protected amino acid in 83% overall yield. Importantly, this two-step sequence was completely unaccompanied by racemization of these sensitive compounds.

Scheme 3



In a previous study, it was demonstrated that the reaction of silanes **1** with the benzaldehyde-derived benzoylhydrazone leads to structure **2** (Scheme 4).[8d] Notable features of this structure include (1) the coalescence of both diastereomers of **1** into a single structure, (2) the protonation of the pseudoephedrine amino group, presumably leading to a significant increase in silane Lewis acidity,[12] and (3) the isomerization of the C═N bond from *trans* (in the hydrazone) to *cis* (in the complex). Assuming the corresponding structure **3** obtains with the glyoxylate-derived hydrazone, a simple and plausible model for the enantioselectivity of the Friedel−Crafts reaction may be advanced. Thus, the pseudoephedrine determines the placement of the phenyl group on the trigonal bipyramidal silane, and in turn, this phenyl group blocks access to the back (*re*) face of the silane-activated hydrazone. The arene preferentially approaches from the exposed front (*si*) face, consistent with the observed major enantiomer.

Scheme 4



We have described a method for the synthesis of an array of aryl- and heteroarylglycines mediated by an extraordinarily simple chiral silane Lewis acid. Silanes **1** can be prepared in bulk in a single step from (*S*,*S* or *R*,*R*) pseudoephedrine and $PhSiCl_3$. The former is trivially recoverable in near quantitative yield, and the latter is available at a nominal cost.[13] The process may thus lay a formidable claim to a high degree of practicality despite the requirement for a full equivalent of silanes **1**. Current efforts are focused on expanding the scope of this Friedel−Crafts reaction as well as on the development of new reactions.

Acknowledgment. S.S. is a recipient of a Japan Society for the Promotion of Science Research Fellowship for Young Scientists. We thank Merck Research Laboratories for fellowship support of R.B. Generous support from Amgen and the Yamanouchi U.S.A. Foundation is also gratefully acknowledged.

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

References

(1) Dilman, A. D.; Ioffe, S. L. *Chem. Rev.* **2003**, *103*, 733.
(2) Denmark, S. E.; Wynn, T. *J. Am. Chem. Soc.* **2001**, *123*, 6199.
(3) (a) Denmark, S. E.; Wynn, T.; Beutner, G. L. *J. Am. Chem. Soc.* **2002**, *124*, 13405. (b) Denmark, S. E.; Beutner, G. L. *J. Am. Chem. Soc.* **2003**, *125*, 7800.
(4) Denmark, S. E.; Fan, Y. *J. Am. Chem. Soc.* **2003**, *125*, 7825.
(5) (a) Myers, A. G.; Kephart, S. E.; Chen, H. *J. Am. Chem. Soc.* **1992**, *114*, 7922. (b) Denmark, S. E.; Griedel, B. D.; Coe, D. M.; Schnute, M. E. *J. Am. Chem. Soc.* **1994**, *116*, 7026. (c) Matsumoto, K.; Oshima, K.; Utimoto, K. *J. Org. Chem.* **1994**, *59*, 7152.
(6) For a related approach to chiral aluminum Lewis acids, see: Nelson, S. G.; Kim, B.-K.; Peelen, T. J. *J. Am. Chem. Soc.* **2000**, *122*, 9318.
(7) Denmark, S. E.; Weber, E. J. *Helv. Chim. Acta* **1983**, *66*, 1655.
(8) (a) Kinnaird, J. W. A.; Ng, P. Y.; Kubota, K.; Wang, X.; Leighton, J. L. *J. Am. Chem. Soc.* **2002**, *124*, 7920. (b) Kubota, K.; Leighton, J. L. *Angew. Chem., Int. Ed.* **2003**, *42*, 946. (c) Berger, R.; Rabbat, P. M. A.; Leighton, J. L. *J. Am. Chem. Soc.* **2003**, *125*, 9596. (d) Berger, R.; Duff, K.; Leighton, J. L. *J. Am. Chem. Soc.* **2004**, *126*, 5686. (e) Hackman, B. M.; Lombardi, P. J.; Leighton, J. L. *Org. Lett.* **2004**, *6*, 4375.
(9) (a) Johannsen, M. *Chem. Commun.* **1999**, 2233. (b) Saaby, S.; Fang, X.; Gathergood, N.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 4114. (c) Saaby, S.; Bayón, P.; Aburel, P. S.; Jørgensen, K. A. *J. Org. Chem.* **2002**, *67*, 4352. (d) Gong, Y.; Kato, K. *Tetrahedron: Asymmetry* **2001**, *12*, 2121. (e) Uraguchi, D.; Sorimachi, K.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 11804.
(10) For a review of recent advances in enantioselective Friedel−Crafts reactions, see: Bandini, M.; Umani-Ronchi, A.; Melloni, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 550.
(11) (a) Burk, M. J.; Martinez, J. P.; Feaster, J. E.; Cosford, N. *Tetrahedron* **1994**, *50*, 4399. (b) Hamada, T.; Manabe, K.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 3927.
(12) (a) Ryu, D. H.; Lee, T. W.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 9992. (b) Ryu, D. H.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 6388.
(13) The 2003−2004 Aldrich catalog lists phenyltrichlorosilane at $37.70/L.

JA042522A