J|A|C|S
COMMUNICATIONS

Published on Web 07/18/2003

Toward a Versatile Allylation Reagent: Practical, Enantioselective Allylation of Acylhydrazones Using Strained Silacycles

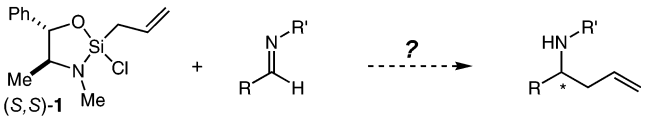
Richard Berger, Philippe M. A. Rabbat, and James L. Leighton*

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

Received March 5, 2003; E-mail: leighton@chem.columbia.edu

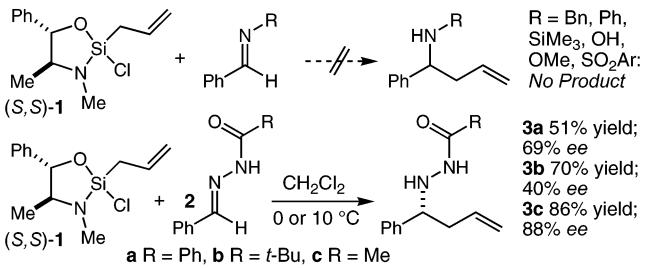
The development of practical enantioselective syntheses of chiral amines is of great importance to synthetic organic and medicinal chemistry. Despite much effort directed at enantioselective aldehyde allylation and crotylation, the development of chiral reagents and catalysts for the enantioselective allyl(crotyl)ation of aldimine derivatives has lagged behind. While creative and noteworthy advances have been recorded,[1,2] a truly practical and general method remains elusive. We recently reported a conceptually new and practical class of allylsilane reagents (e.g., **1**) for aldehyde allylation that derive their reactivity from ring strain-induced Lewis acidity,[3] and it was of interest to investigate these reagents in the context of aldimine allylation reactions (Scheme 1).

Scheme 1



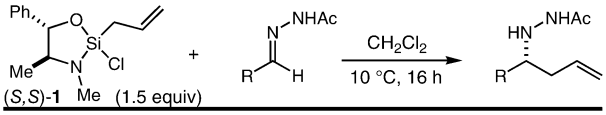
Several imine derivatives of benzaldehyde were subjected to reaction with **1**, and in no case was any allylation observed (Scheme 2). Kobayashi has reported that benzoylhydrazones undergo smooth allylation with allyltrichlorosilane especially in the presence of Lewis basic solvents such as DMF.[4] Reaction of benzoylhydrazone **2a** with allylsilane **1** in CH_2Cl_2 at 0 °C led to hydrazide **3a** in 51% yield and in 69% ee. A series of aroyl- and alkanoylhydrazones of benzaldehyde were prepared and reacted with allylsilane **1**. Significant variations in enantioselectivity were observed (e.g., pivaloylhydrazone **2b** gave **3b** in only 40% ee), and optimal results were obtained with the simple acetylhydrazone **2c**. Optimization revealed CH_2Cl_2 as the solvent of choice and 10 °C as the optimal reaction temperature. Under these conditions, the reaction of **1** and **2c** proceeded to give **3c** in 86% yield and 88% ee.[5]

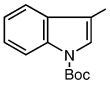
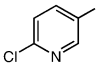
Scheme 2



As outlined in Table 1, a wide variety of aromatic and heterocyclic aldehyde-derived acetylhydrazones performed admirably in the reaction (entries 1−10). An exception was the 3-pyridyl acetylhydrazone, which was allylated in only 23% ee (entry 11). Hypothesizing that the Lewis basic nitrogen was interacting with the Lewis acidic silicon, we screened the 2-chloropyridyl substrate and were delighted to find that most of the lost selectivity was restored (entry 12). The 2-pyrrolyl acetylhydrazone was also a problematic substrate (entry 13). While the mechanistic basis for the poor selectivity in this case is less obvious, the corresponding *N*-Boc pyrrole was prepared. This substrate proved very effective, albeit sluggish, resulting in product of 92% ee (entry 14). Finally, although aliphatic aldehyde-derived hydrazones generally provide only low to moderate enantioselectivities, the pivalaldehyde-derived substrate is an exception, providing the highest enantioselectivity observed to date (97% ee, entry 15).

Table 1. Enantioselective Allylation of Acylhydrazones



entry	R	yield (%)	*ee* (%)[a]
1	Ph	86	88
2	*o*-Me-C_6H_4	75	85
3	*p*-Br-C_6H_4	88	85
4	*p*-MeO-C_6H_4	82	86
5		93	83
6	2-Naphthyl	85	87
7	2-Furyl	89	88
8	3-Furyl	78	86
9		76	89
10		96	83
11		89	23
12		90	80
13		70	48
14		49[b]	92
15	*t*-Bu	88	97

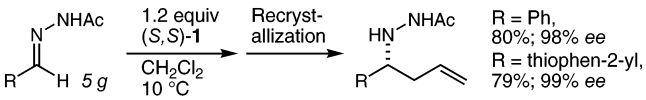
[a] Enantiomeric excess was determined by chiral HPLC. [b] 40% of recovered starting material was isolated as well.

In a demonstration of the practicality of this reaction, the reactions of two substrates were carried out on a 5 g scale (Scheme 3). Only 1.2 equiv of reagent **1** was employed, the products were isolated without chromatography, and highly enantiomerically enriched materials (≥98% ee) were obtained in good yield upon a single recrystallization. Combined with the experimentally trivial preparation of reagent **1**,[6] these data establish the true practicality

10.1021/ja035001g CCC: $25.00

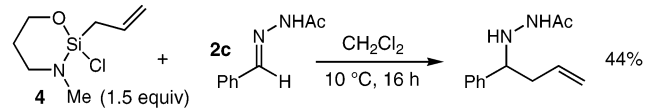
of this reaction, despite the only moderately high enantioselectivities of some of the substrates.

Scheme 3



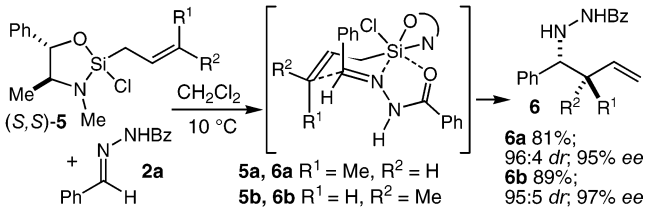
The observations (1) that of the aldimine derivatives screened, only acylhydrazones undergo allylation and (2) that the structure of the acyl group has a dramatic effect on the reaction (see Scheme 2) suggest a secondary interaction between the Lewis basic amide and the Lewis acidic silane. This in turn calls into question whether the ring strain-induced Lewis acidity in reagents such as **1**, which has been shown to be necessary for aldehyde allylation,[2a] is necessary in the reactions with acylhydrazones. We prepared allylsilane **4** and have found that it indeed allylates acetylhydrazone **2c**, albeit with reduced efficiency (Scheme 4). We may thus conclude that strain-induced Lewis acidity, while helpful for efficiency, is not necessary for acylhydrazone allylation, in stark contrast to the corresponding aldehyde allylations.[7]

Scheme 4



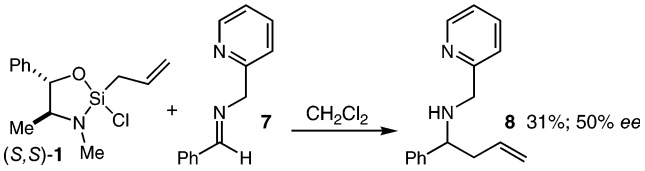
cis-Crotylsilane and *trans*-crotylsilane (*S*,*S*)-**5a**,**b** were prepared and reacted with benzoylhydrazone **2a**, giving *anti*-hydrazide **6a** in 81% yield with 96:4 dr and 95% ee and *syn*-hydrazide **6b** in 89% yield with 95:5 dr and 97% ee, respectively (Scheme 5). In addition to establishing the superior performance of the crotylation reagents **5**, these results are mechanistically revealing. As shown, two-point binding/double activation of the type proposed is completely consistent with the unusual observation of an *anti* product from a *cis*-crotylsilane, and a *syn* from a *trans*-crotylsilane. Kobayshi has made similar observations in the additions of crotyltrichlorosilanes to benzoylhydrazones,[4] and related observations have been made during studies of intramolecular aldehyde crotylsilylations.[8]

Scheme 5



An important consequence of this mechanism is that Lewis basic groups other than acylhydrazones might be expected to promote the reaction. Indeed, aldimine **7** was prepared and, upon reaction with allylsilane **1**, gave amine **8** in 31% yield and 50% ee (Scheme 6). Albeit unoptimized, this reaction stands in contrast to the corresponding benzylimine, which does not undergo allylation with allylsilane **1** (see Scheme 2).

Scheme 6



We have developed a highly practical enantioselective allylation of acetylhydrazones. The reagent is trivially prepared in bulk and is stable to storage. The products may be isolated without chromatography and in high ee by simple recrystallization. A mechanistic paradigm distinct from aldehyde allylation has been established, and more effective Lewis base-containing imine derivatives may be imagined.

Acknowledgment. We are grateful to Merck Research Laboratories for unrestricted research support and fellowship support of R.B. J.L.L. is the recipient of a Pfizer Award for Creativity in Organic Chemistry.

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

References

(1) For chiral reagents, see: (a) Panek, J. S.; Jain, N. F. *J. Org. Chem.* **1994**, *59*, 2674−2675. (b) Schaus, J. V.; Jain, N. F.; Panek, J. S. *Tetrahedron* **2000**, *56*, 10263−10274. (c) Nakamura, M.; Hirai, A.; Nakamura, E. *J. Am. Chem. Soc.* **1996**, *118*, 8489−8490. (d) Itsuno, S.; Watanabe, K.; Ito, K.; El-Shehawy, A. A.; Sarhan, A. A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 109−110. (e) Watanabe, K.; Kuroda, S.; Yokoi, A.; Ito, K.; Itsuno, S. *J. Organomet. Chem.* **1999**, *581*, 103−107. (f) Itsuno, S.; Watanabe, K.; Matsumoto, T.; Kuroda, S.; Yokoi, A.; El-Shahawy, A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2011−2016. (g) Itsuno, S.; Yokoi, A.; Kuroda, S. *Synlett* **1999**, 1987−1989. (h) Chen, G.-M.; Ramachandran, P. V.; Brown, H. C. *Angew. Chem., Int. Ed.* **1999**, *38*, 825−826. (i) Teng, X.; Takayama, Y.; Okamoto, S.; Sato, F. *J. Am. Chem. Soc.* **1999**, *121*, 11916−11917. (j) Marshall, J. A.; Gill, K.; Seletsky, B. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 953−956. For catalysts, see: (k) Nakamura, H.; Nakamura, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **1998**, *120*, 4242−4243. (l) Nakamura, K.; Nakamura, H.; Yamamoto, Y. *J. Org. Chem.* **1999**, *64*, 2614−2615. (m) Fang, X.; Johannsen, M.; Yao, S.; Gathergood, N.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **1999**, *64*, 4844−4849. (n) Gastner, T.; Ishitani, H.; Akiyama, R.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2001**, *40*, 1896−1898.

(2) For reviews of enantioselective amine synthesis by nucleophilic addition to imines, see: (a) Enders, D.; Reinhold, U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895−1946. (b) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407−1438. (c) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069−1094. (d) Puentes, C. O.; Kouznetsov, V. *J. Heterocycl. Chem.* **2002**, *39*, 595−614.

(3) (a) Kinnaird, J. W. A.; Ng, P. Y.; Kubota, K.; Wang, X.; Leighton, J. L. *J. Am. Chem. Soc.* **2002**, *124*, 7920−7921. (b) Kubota, K.; Leighton, J. L. *Angew. Chem., Int. Ed.* **2003**, *42*, 946−948.

(4) (a) Kobayashi, S.; Hirabayashi, R. *J. Am. Chem. Soc.* **1999**, *121*, 6942−6943. (b) Hirabayashi, R.; Ogawa, C.; Sugiura, M.; Kobayashi, S. *J. Am. Chem. Soc.* **2001**, *123*, 9493−9499. (c) Ogawa, C.; Sugiura, M.; Kobayashi, S. *J. Org. Chem.* **2002**, *67*, 5359−5364.

(5) Reagent **1** is an inseparable 2:1 mixture of diastereomers (see ref 3a). When **2c** was reacted in separate experiments with 0.5 and 5.0 equiv of **1**, **3c** was obtained in 85.4% and 87.5% ee, respectively. These data are inconsistent with the possibility that the diastereomers of **1** react independently with significantly different rates and enantioselectivities and suggest instead that they interconvert and react by a common pathway or pathways.

(6) The preparation of reagent **1** was recently carried out on ∼150 g scale in 92% yield. See the Supporting Information.

(7) Allylsilane **4** is unreactive with aldehydes even at 50 °C.

(8) (a) Kira, M.; Sato, K.; Kazushi, S.; Gewald, R.; Sakurai, H. *Chem. Lett.* **1995**, 281−282. (b) Chemler, S. R.; Roush, W. R. *J. Org. Chem.* **1998**, *63*, 3800−3801. (c) Chemler, S. R.; Roush, W. R. *J. Org. Chem.* **2003**, *68*, 1319−1333. (d) Wang, X.; Meng, Q.; Nation, A. J.; Leighton, J. L. *J. Am. Chem. Soc.* **2002**, *124*, 10672−10673.

JA035001G