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Proline-Based *N*-Oxides as Readily Available and Modular Chiral Catalysts. Enantioselective Reactions of Allyltrichlorosilane with Aldehydes

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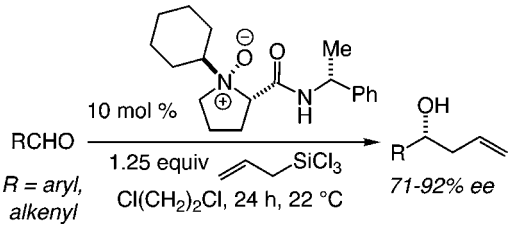
ABSTRACT



A proline-based *N*-oxide is identified that serves as an effective catalyst for the reaction of allyltrichlorosilane with aryl and α,β-unsaturated aldehydes at room temperature to afford the desired homoallylic alcohols in up to 92% ee. The chiral catalyst can be easily prepared from optically pure proline in three simple steps and 60% overall yield.

Amino acid based chiral molecules have emerged as versatile and effective platforms in the development of catalysts that promote a range of enantioselective transformations.[1] The lure of this class of catalyst candidates is due to several important reasons.[2] A number of amino acids are available in optically pure form (both antipodes). Furthermore, catalyst candidates can be easily altered, not only by variations in the identity of amino acid constituent(s) but also by incorporation of additional structural features through the amide bond linkage. Such characteristics render amino acid based catalysts easily modular: a diverse set of catalyst candidates can be readily prepared (on solid support or in solution) and examined in parallel to search for optimal reactivity and selectivity.

Research in these laboratories during the past few years has focused on the development of amino acid based ligands that can participate in metal-catalyzed C−C bond-forming reactions.[3] The aforementioned attributes have played a critical role in allowing us to introduce metal-catalyzed enantioselective reactions that offer unique levels of efficiency and enantioselectivity. More recently, we have set out to introduce a new class of easily accessible and readily modifiable amino acid-based *N*-oxides that can serve as chiral nucleophilic catalysts. This initiative was partly inspired by the observation that chiral *N*-oxides have been shown to promote several synthetically useful transformations efficiently.[4] Our efforts were encouraged by the fact that the majority of chiral *N*-oxide catalysts developed thus far are molecules that are prepared through nontrivial synthesis

(1) For recent reviews, see: (a) Berkessel, A.; Gröger, H.; MacMillan, D. *Asymmetric Organocatalysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis*; Wiley-VCH: Weinheim, 2005; pp 1−454. (b) Hoveyda, A. H.; Hird, A. W.; Kacprzynski, M. A. *Chem. Commun.* **2004**, 1779−1785. (c) Miller, S. J. *Acc. Chem. Res.* **2004**, *37*, 601−610. (d) Groeger, H.; Wilken, J.; Berkessel, A. *Org. Synth. Highlights V* **2003**, 178−186.

(2) For a discussion, see: Hoveyda, A. H. In *Handbook of Combinatorial Chemistry*; Nicolaou, K. C., Hanko, R., Hartwig, W., Eds.: Wiley-VCH: Weinheim, 2002; pp 991−1016.

(3) For representative examples, see: (a) Cole, B. M.; Shimizu, K. D.; Krueger, C. A.; Harrity, J. P. A.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **1996**, *35*, 1668−1671. (b) Krueger, C. A.; Kuntz, K. W.; Dzierba, C. D.; Wirschun, W. G.; Gleason, J. D.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 4284−4285. (c) Luchaco-Cullis, C. A.; Mizutani, H.; Murphy, K. E.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2001**, *40*, 1456−1460. (d) Degrado, S. J.; Mizutani, H.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 755−756. (e) Akullian, L. C.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4244−4247. (f) Josephsohn, N. S.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 3734−3735.

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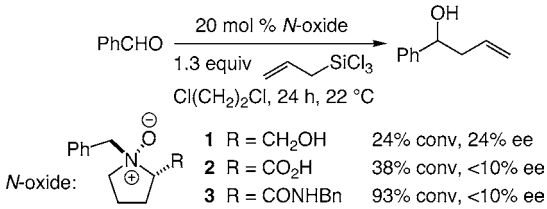
routes and their structural modification often requires lengthy and cumbersome manipulations.

As the first step in the development of amino acid-based chiral *N*-oxide catalysts, we decided to explore the possibility of an enantioselective method for allylation of aldehydes. Syntheses of optically enriched homoallylic alcohols through addition of B-,[5] Ti-,[6] and Si-based[7] reagents as well as catalytic protocols involving allylstannanes[8] and allylsilanes[9] have been reported.[10] In several cases, chiral *N*-oxides are used as catalysts.[4d−i,11] Nonetheless, in many of the reported cases, the requisite catalysts are not easily prepared and the available synthesis methods require low reaction temperatures (≤ −40 °C) to ensure high asymmetric induction.

Herein, we report the catalytic activity of a proline-based *N*-oxide that promotes the reaction of trichloroallylsilane with aryl and α,*β*-unsaturated aldehydes in up to 92% ee. The catalyst is easily prepared from commercially available optically pure proline in three straightforward steps in 60% overall isolated yield without the need for silica gel chromatography. The structural modularity of this new class of chiral Lewis base catalysts is exploited in efforts to optimize reaction efficiency and enantioselectivity.

We initiated our studies by examining the ability of proline-based *N*-oxides **1**−**3**,[12] prepared by directed oxidation of the tertiary amine with *m*-CPBA,[13] as catalysts for the transformation in Scheme 1.[14] These initial investigations

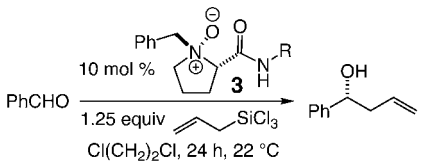
Scheme 1. Allylation Reactions Promoted by *N*-Oxides **1**−**3**

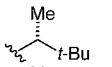
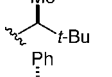
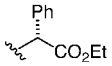
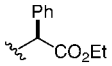
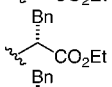
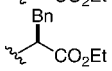
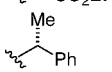
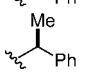


proved promising. Although low enantioselectivity was observed, there was appreciable conversion for reactions at ambient temperature. Notably, with catalyst **3**, >90% conversion was detected within 12 h at 22 °C. It should be noted that there is <2% conversion in the absence of *N*-oxides **1**−**3**.

Encouraged by the above findings, we set out to identify a more effective chiral catalyst by systematic modification of the catalyst's *C*- and *N*-termini. Accordingly, we prepared various proline-based *N*-oxides with different *C*-termini (**3a**−**m**) and examined their ability to promote enantioselective allylations at 22 °C. The results of these studies are summarized in Table 1.

Table 1. Effect of the Identity of the *C*-Terminus of Catalyst on Efficiency and Enantioselectivity of Allylations of Benzaldehyde



entry	R		conv. (%)[a]	ee (%)[b]
1	*n*-Bu	**3a**	94	13
2	*i*-Pr	**3b**	98	12
3	*t*-Bu	**3c**	98	<10
4	$CHPh_2$	**3d**	96	<10
5	Ph	**3e**	82	<10
6		**3f**	93	11
7		**3g**	96	<10
8		**3h**	73	<10
9		**3i**	61	<10
10		**3j**	47	<10
11		**3k**	51	<10
12		**3l**	***98***	***45***
13		**3m**	>98	−31

[a] Determined by the analysis of 400 MHz ^{1}H NMR spectra. [b] Determined by chiral HPLC analysis; see the Supporting Information for details.

(4) (a) O'Neil, I. A.; Turner, C. D.; Kalindjian, S. B. *Synlett* **1997**, 777−780. (b) Tao, B.; Lo, M. M−C.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 353−354. (c) Denmark, S. E.; Fan, Y. *J. Am. Chem. Soc.* **2002**, *124*, 4233−4235. (d) Shimada, T.; Kina, A.; Ikeda, S.; Hayashi, T. *Org. Lett.* **2002**, *4*, 2799−2801. (e) Malkov, A. V.; Orsini, M.; Pernazza, D.; Muir, K. W.; Langer, V.; Meghani, P.; Kocovsky, P. *Org. Lett.* **2002**, *4*, 1047−1049. (f) Malkov, A. V.; Bell, M.; Orsini, M.; Parnazza, D.; Massa, A.; Herrmann, P.; Meghani, P.; Kocovsky, P. *J. Org. Chem.* **2003**, *68*, 9659−9668. (g) Malkov, A. V.; Dufkova, L.; Farrugia, L.; Kocovsky, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 3674−3677. (h) Shimada, T.; Kina, A.; Hayashi, T. *J. Org. Chem.* **2003**, *68*, 6329−6337. (i) Kina, A.; Shimada, T.; Hayashi, T. *Adv. Synth. Catal.* **2004**, *346*, 1169−1174.

(5) For representative examples, see: (a) Gung, B. W.; Xue, X.; Roush, W. R. *J. Am. Chem. Soc.* **2002**, *124*, 10692−10697. (b) Racherla, U. S.; Liao, Y.; Brown, H. C. *J. Org. Chem.* **1992**, *57*, 6614−6617.

(6) Duthaler, R.; Hafner, A.; Bold, G. *Chem. Rev.* **1992**, *92*, 807−832.

(7) For select examples, see: (a) Kubota, K.; Leighton, J. L. *Angew. Chem., Int. Ed.* **2003**, *43*, 946−948. (b) Kinnard, J. W. A.; Ng, P. Y.; Kubota, K.; Wang, X.; Leighton, J. L. *J. Am. Chem. Soc.* **2002**, *124*, 7920−7921.

(8) For representative examples, see: (a) Yanagisawa, A.; Nakashima, H.; Ishiba, A.; Yamamoto, H. *J. Am. Chem. Soc.* **1996**, *118*, 4723−4724. (b) Denmark, S. E.; Wynn, T. *J. Am. Chem. Soc.* **2001**, *123*, 6199−6200. (c) Lu, J.; Hong, M.-L.; Ji, S.-J.; Loh, T.-P. *Chem. Commun.* **2005**, 1010−1012 and references therein.

(9) (a) Furuta, K.; Mouri, M.; Yamamoto, H. *Synlett* **1991**, 561−563. (b) Ishihara, K.; Mouri, M.; Gao, Q.; Maruyama, T.; Furuta, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1993**, *115*, 11490−11495. (c) Gauthier, D. R.; Carreira, E. M. *Angew. Chem., Int. Ed.* **1996**, *35*, 2363−2365. (d) Bode, J. W.; Gauthier, D. R.; Carreira, E. M. *Chem. Commun.* **2001**, 2560−2561.

(10) (a) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763−2794. (b) Masse, C. E.; Panek, J. S. *Chem. Rev.* **1995**, *95*, 1293−1316.

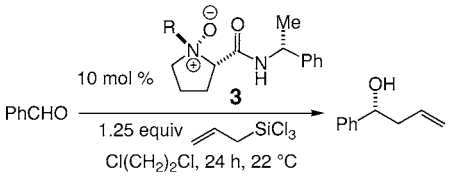
(11) For a review of pyridine *N*-oxides as chiral catalysts, see: Chelucci, G.; Murineddu, G.; Pinna, G. A. *Tetrahedron: Asymmetry* **2004**, *15*, 1373−1389.

(12) O'Neil, I. A.; Potter, A. J. *Chem. Commun.* **1998**, 1487−1488 and references therein.

(13) For a review of directed reactions, see: Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1306−1360.

(14) Catalysts bearing a secondary amide with the indicated relative stereochemistry were selected, since the intramolecular H-bonding between the amide and *N*-oxide is reported to be critical to stability of these compounds. See: O'Neil, I. A.; Miller, N. D.; Peake, J.; Barkley, J. V.; Low, C. M. R.; Kalindjian, S. B. *Synlett* **1993**, 515−518.

Table 2. Effect of the Catalyst *N*-Terminus on Efficiency and Enantioselectivity of Allylations of Benzaldehyde



entry	R		conv. (%)[a]	ee (%)[b]
1	Me	**3n**	92	56
2	*i*-Pr	**3o**	64	75
3	$CHEt_2$	**3p**	90	75
4	cyclopent.	**3q**	58	80
5	cyclohex.	**3r**	***91***	***87***
6		**3s**	94	83
7	cyclohept.	**3t**	77	69
8	cyclooct.	**3u**	62	77

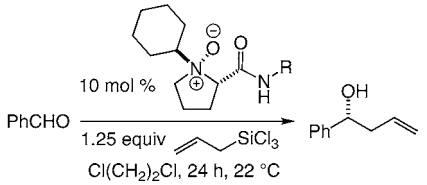
[a,b] See Table 1.

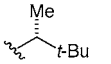
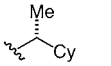
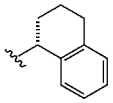
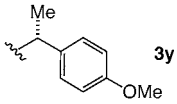
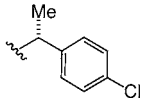
As illustrated in entries 1−5 (Table 1), a change in the amide substituent (**3a**−**e**) results in little or no difference in efficiency or enantioselectivity. When a chiral group is incorporated within the catalyst structure, a more notable effect is observed in some cases. Processes in entries 6−7 remain efficient but nonselective, whereas reactions in entries 8−11 are inefficient as well. A significant enhancement in enantioselectivity arises, as depicted in entry 12, when (*R*)-α-methylbenzylamine was incorporated within the amide terminus (catalyst **3l**): the desired homoallylic alcohol was isolated in 45% ee while the reaction proceeded to 98% conv (12 h). The alternative catalyst diastereomer (**3m**, entry 13) promotes a significantly less selective transformation to afford the alternative product antipode (−31% ee).

Next, we investigated the effect of altering the catalyst *N*-terminus (Bn in **3l**); a variety of proline *N*-oxides, bearing the optimal (*R*)-α-methylbenzylamide terminus, were prepared and examined. These studies, the results of which are summarized in Table 2, led us to establish that when the proline *N*-oxide bears a cyclohexyl group (**3r**, entry 5), reaction enantioselectivity improves significantly: the desired homoallylic alcohol is obtained in 87% ee (91% conv; 12 h at 22 °C). Increasing the size of the amine substituent leads to higher product optical purity (entries 1−5), although catalysts **3t** and **3u** (entries 7 and 8), bearing a cycloheptyl and a cyclooctylamine, promote reactions less efficiently and with lower enantioselectivity than **3r**.

To determine whether cooperative effects involving the two termini of the catalyst can give rise to a more effective catalyst, chiral proline *N*-oxides with a cyclohexyl *N*-terminus but different *C*-termini (see Table 1) were prepared and investigated (Table 3). Catalysts bearing electron-rich (**3y**, entry 4) and electron-poor (**3z**, entry 5) (*R*)-α-methylbenzylamine derivatives were included in this search. A more effective catalyst than **3r** was not identified. Nonethless, the data in Table 3 suggest that the presence of an aryl-containing *C*-terminus leads to higher asymmetric induction. Finally, the diastereomer of *N*-oxide **3r** is a significantly less effective

Table 3. Reexamination of the Catalyst *C*-Terminus



entry	R		conv. (%)[a]	ee (%)[b]
1		**3v**	68	34
2		**3w**	92	43
3		**3x**	93	20
4		**3y**	91	85
5		**3z**	87	85

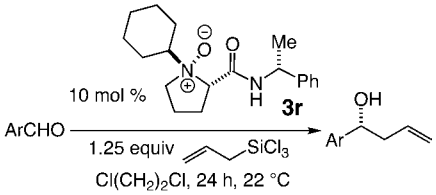
[a,b] See Table 1.

catalyst (>98% conversion, −18% ee under identical conditions shown in Table 3).

Further optimization studies indicated that dichloroethane is the solvent of choice.[15] Lowering of the reaction temperature results in reduced conversion[16] without improvement in enantioselectivity (e.g., 85% ee and 48% conversion at 4 °C, 24 h). When the representative allylation is carried out at elevated temperatures, enantioselectivity suffers (e.g., 77% ee at 40 °C).

As the data summarized in Table 4 indicate, catalyst **3r** can be used to promote the enantioselective allylation of a

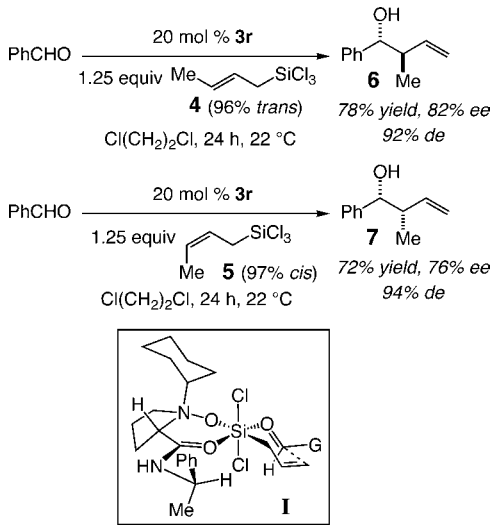
Table 4. Enantioselective Reactions of Allyltrichlorosilane Catalyzed by **3r**



entry	Ar	yield[a] (%)	ee[b] (%)
1	Ph	82	87
2	2-BrC_6H_4	81	82
3	4-ClC_6H_4	74	85
4	3-$NO_2C_6H_4$	76	72
5	4-$OMeC_6H_4$	81	88
6[c]	3,4-$(OMe)_2C_6H_3$	73	92
7	1-napththyl	89	79
8	2-naphthyl	89	83
9	2-furyl	59	71
10	3-furyl	64	82

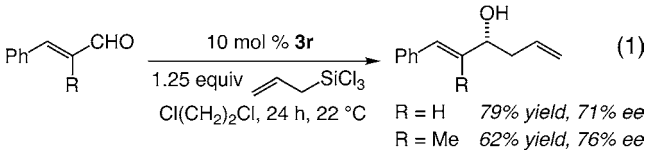
[a] Yield after chromatography. [b] See Table 1. [c] 15 mol % catalyst loading used.

Scheme 2. Reactions of *E*- and *Z*-Crotyltrichlorosilanes **4** and **5** Promoted by **3r** and a Proposed Transition Model



variety of aromatic aldehydes at 22 °C. All reactions proceed to >98% conversion within 24 h. Electron-rich and electron-poor substrates give rise to appreciable levels of asymmetric induction; the highest optical purity is observed with electron-rich 3,4-dimethoxybenzaldehyde (92% ee, entry 6). Reactions of sterically hindered aldehydes (entry 8) and those that bear a heterocyclic substituent can be effected in 71−83% ee (entries 9 and 10).

As the examples in eq 1 indicate, catalytic enantioselective allylations promoted by *N*-oxide **3r** are not limited to aromatic aldehydes. Although their transformations proceed with lower enantioselectivity, α,*β*-unsaturated aldehydes can also be utilized as substrates.[17]

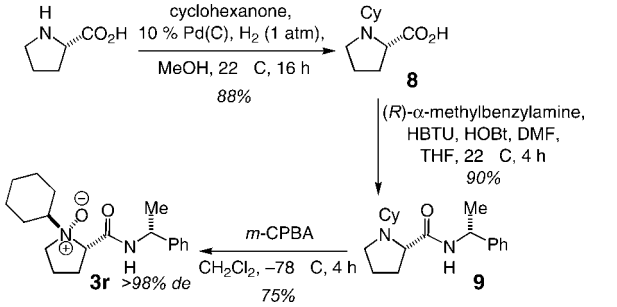


(1)

As depicted in Scheme 2, *E*- and *Z*-crotyltrichlorosilanes **4** and **5** can be employed in enantio- and diastereoselective additions promoted by **3r**. The high levels of diastereoselectivity (92 and 94% de), where the *E*-silane leads to the formation of the anti product diastereomer **6** and *Z*-silane affords the syn isomer **7**, suggest that a six-membered ring transition structure, such as **I** (Scheme 2), is involved in this class of asymmetric allylations. The nucleophilicity of the allyl group may thus be enhanced as it is situated *trans* to the donor *N*-oxide, and the aldehyde carbonyl might be activated through coordination *trans* to the electron-withdrawing amide carbonyl.[18] It is plausible that the large *N*-terminus moiety (cyclohexyl group) ensures that substrate coordination proceeds so as to minimize unfavorable steric interactions with the cyclohexyl substituent; the presence of the phenethylamine at the *C*-terminus may be required so that aldehyde association with the Si center cis to the bulky chiral moiety is discouraged. Nonetheless, it is difficult to explain why other sizable *C*-termini or the alternative diastereomer (Table 1) give rise to significantly lower enantioselectivity.

As mentioned previously, one of the strengths of the present protocol is that the requisite catalyst can be prepared in three steps in high yield (60% overall) from commercially available optically pure proline. Thus, the synthesis route used to access **3r** (Scheme 3) involves a reductive amination

Scheme 3. Synthesis of Chiral Catalyst **3r** from Proline



in the presence of cyclohexanone to afford **8** (88% yield), followed by formation of amide **9** (90% yield) and directed amine oxidation to generate **3r** as a single diastereomer in 75% isolated yield. The only purification required in the above procedure is a simple precipitation of **3r** from CH_2Cl_2 (addition of hexanes).

In summary, we have identified a readily available and modifiable chiral amino acid based Lewis base catalyst that promotes the enantioselective allylation of unsaturated aldehydes. Attractive features of the method include the ease of catalyst preparation and mild reaction conditions (22 °C). Future studies will include design of new amino acid based *N*-oxides and examination of their utility as catalysts for useful catalytic asymmetric protocols.

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Supporting Information Available: Experimental and analytical data for substrates and products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) THF, CH_3CN, and toluene led to 80−82% ee but low conversion (<30%). Use of dichloromethane and CH_3NO_2 gives rise to low conversion and ee. With DMF >98% conversion and <2% ee is observed (see: Kobayashi, S.; Nishio, K. J. *J. Org. Chem.* **1994**, *59*, 6620−6628).

(16) The lower conversion at higher temperatures can be attributed to loss of catalyst through reduction of the *N*-oxide; the derived reduced product was isolated in several representative cases.

(17) Presumably due to formation of *O*-silyl chlorohydrins, attempts to effect additions to aliphatic aldehydes were unsuccessful. See: Denmark, S. E.; Fu, J. *Org. Lett.* **2002**, *4*, 1951−1953.

(18) Cotton, F. A. *Advanced Inorganic Chemistry*, 5th ed.; John Wiley & Sons: New York, 1988; pp 1299−1300.