http://dx.doi.org/10.5012/bkcs.2013.34.9.2571

Highly Diastereoselective Indium-Mediated Allylation of Proline-Derived Hydrazones

Apuri Satyender and Doo Ok Jang*

*Department of Chemistry, Yonsei University, Wonju 220-710, Korea. *E-mail: dojang@yonsei.ac.kr*
Received July 7, 2013, Accepted July 12, 2013

Key Words : Asymmetric, Diastereoselective, Homoallylic amine, Allylation, Indium

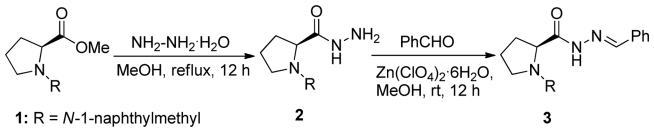
Diastereoselective allylation of imines bearing a chiral auxiliary is a reliable, efficient, and powerful strategy for the construction of optically pure homoallylic amines,[1] which are important precursors and key intermediates in syntheses of natural products.[2] Many chiral imines, such as chiral *N*-aliphatic imines,[3] hydrazones,[4] and *N*-sulfinyl imines,[5] have been used for diastereoselective allylations. Of these surrogates, chiral hydrazones have proven to be candidates of choice as they offer many advantages including high reactivity and high regioselectivity.[6]

It is well known that (*S*)-1-amino-2-methoxymethylpyrrolidine[4c] and (*S*)-4-isopropyl- or (*S*)-4-phenylmethyl-oxazolidin-2-one-derived hydrazones[4d] have been used for metal-mediated diastereoselective allylation additions to produce chiral homoallylic amines. However, the optically pure hydrazine precursors are either commercially expensive and/or involve laborious synthetic procedures employing toxic reagents for their preparation. Thus, the design of novel classes of chiral hydrazines that would further broaden the scope of asymmetric synthesis to access optically pure homoallylic amines is highly desirable.

In recent decades, stereoselective reactions of allylindium species have gained new impetus because of attractive features such as diversity of reagent reactivity, high degree of diastereoselectivity, and access to contiguous arrays of stereocenters.[7] In view of these antecedents, we herein present diastereoselective additions of allylindium bromide to various *N*-substituted L-proline-based hydrazones.[8]

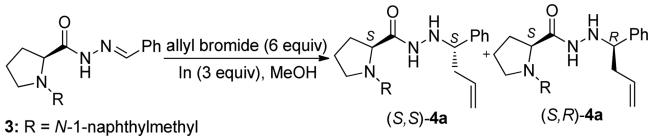
Our research commenced with the synthesis of chiral auxiliary, (*S*)-1-napthylmethyl-pyrrolidine-2-carbohydrazide **2**, from readily available *N*-substituted L-proline ester **1**.[9] This carbohydrazide **2** was then treated with benzaldehyde to afford hydrazone **3** (Scheme 1).

Next, we investigated *N*-protected carbohydrazide as auxiliary for the asymmetric allylation of benzhydrazone (Table 1). Allylation reaction of chiral hydrazone **3** was carried out in the presence of 3 equiv of indium powder and 6 equiv of allyl bromide in absolute methanol as solvent at ambient temperature (Table 1, entry 1). Hydrazone **3** showed high



Scheme 1. Synthesis of hydrazone **3**.

Table 1. Allylation of hydrazone **3** under various reaction conditions



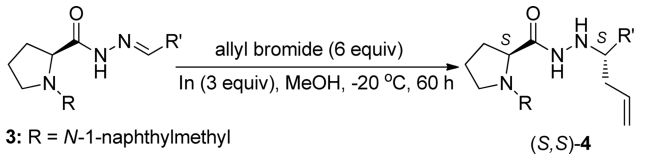
Entry	Temp (°C)	Time (h)	Yield (%)[a]	dr (*S*,*S*: *S*,*R*)[b]
1	rt	15	86	80:20
2	0	24	80	92:8
3	-5	24	82	94:6
4	-10	48	84	96:4
5	-20	60	87	98:2

[a]Isolated yields. [b]Diastereomeric ratio was determined by ^{1}H NMR spectroscopy.

diastereoselectivity and turned out to be a good chiral auxiliary presumably due to its bulkiness. To accomplish high stereoselectivity, allylation reactions were performed under various reaction conditions. Gratifyingly, lowering the reaction temperature had a significant impact, and the highest selectivity was achieved by performing the reaction at –20 °C (Table 1, entries 2-5).

Having identified optimal reaction conditions, we studied

Table 2. Allylation of various hydrazones



Entry	R'	Product	Yield (%)[a]	dr (*S*,*S*:*S*,*R*)[b]
1	4-Me_2N-C_6H_4	**4b**	88	96:4
2	4-MeO-C_6H_4	**4c**	91	98:2
3	4-Et-C_6H_4	**4d**	89	98:2
4	2-Me-C_6H_4	**4e**	88	97:3
5	3-F-C_6H_4	**4f**	89	96:4
6	4-Cl-C_6H_4	**4g**	92	98:2
7	2-Br-C_6H_4	**4h**	90	98:2
8	4-O_2N-C_6H_4	**4i**	32	90:10
9	cinnamyl	**4j**	91	97:3
10	furyl	**4k**	86	98:2

[a]Isolated yield. [b]Diastereomeric ratio was determined by ^{1}H NMR spectroscopy.

the substrate generality and scope of the indium-mediated allylation reaction with various *N*-1-naphthylmethyl-based hydrazones, and the results are summarized in Table 2. Reactions with aromatic aldehyde-derived substrates with electron-donating groups as well as electron-withdrawing groups gave high yields and excellent diastereoselectivities (entries 1-7). The reaction has substrate generality for aromatic derivatives with the exception of substrates with strongly electron-withdrawing substituents such as the 4-nitrophenyl group, which gave low yields of product although the diastereoselectivity was high (entry 8). The cinnamaldehyde derived α,β-unsaturated hydrazone underwent regioselective addition to the C=N bond (entry 9). This adduct offers the potential for further functionalization of the olefinic moiety. Surprisingly, the simple acetophenone derivative did not react under the present reaction conditions.

The allylated product **4a** was protected with Boc_2O and was then subjected to *N-N* bond cleavage using 3 equiv of SmI_2[4d] in methanol to afford the corresponding homoallylic amine derivative. The enantiomeric excess of the compound, determined by chiral HPLC, was found to be 98:2, and an identical optical rotation to the literature value was obtained.[10]

In summary, a highly diastereoselective indium-mediated addition reaction to L-proline-derived hydrazones has been developed. The method affords an efficient and general synthesis of homoallylic amines of high optically purity in high yields and diastereomeric ratios up to 98:2.

General Procedure for Allylation of Hydrazones. To a solution of chiral hydrazone **3** (0.1 mmol) and indium powder (0.3 mmol) in absolute methanol (3 mL) at –20 °C was added allyl bromide (0.6 mmol). The reaction mixture was stirred for 60 h. After completion of the reaction (confirmed by TLC), the solvent was evaporated, quenched with saturated NH_4Cl and extracted with ethyl acetate. The organic phase was separated, dried and further purified by flash column chromatography over silica gel (*n*-hexane/EtOAc, 7:3) to afford desired addition products. For **4a**: Syrup, $[\alpha]_D^{20} = -48.0^o$ (c 0.01, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.53-1.72 (m, 2H), 1.75-1.83 (m, 1H), 2.23-2.30 (m, 3H), 2.86-2.90 (m, 1H), 3.27 (m, 1H,), 3.81-3.92 (m, 3H), 4.67 (br, 1H), 5.00-5.07 (m, 2H), 5.61-5.71 (m, 1H), 6.86 (t, 1H, *J* = 7.6 Hz), 6.97-7.04 (m, 3H), 7.14 (d, 2H, *J* = 7.6 Hz), 7.22-7.28 (m, 1H), 7.36-7.47 (m, 1H), 7.43 (t, 1H, *J* = 7.8 Hz), 7.68 (d, 1H, *J* = 8.4 Hz), 7.81 (m, 2H), 8.18 (br, 1H). ^{13}C NMR ($CDCl_3$) δ 23.9, 30.4, 40.2, 54.0, 56.7, 63.8, 67.1, 117.8, 123.1, 125.4, 126.1, 127.3, 127.4, 128.2, 131.6, 133.6, 134.4, 141.1, 172.8. Anal. Calcd for $C_{26}H_{29}N_3O$: C, 78.16; H, 7.32; N, 10.52. Found: C, 78.14; H, 7.34; N, 10.50.

Acknowledgments. This work was supported by the National Research Foundation of Korea (NRF-2009-0074839: NRF-2011-0021279).

References

1. (a) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207. (b) Ding, H.; Friestad, G. K. *Synthesis* **2005**, 2815. (c) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069.
2. Breuer, M.; Ditrich, K.; Habicher, T.; Hauer, B.; Kesseler, M.; Stuermer, R.; Zelinski, T. *Angew. Chem. Int. Ed.* **2004**, *43*, 788.
3. (a) Ken Lee, C.-L.; Ling, H. Y.; Loh, T.-P. *J. Org. Chem.* **2004**, *69*, 7787. (b) van der Sluis, M.; Dalmolen, J.; de Lange, B.; Kaptein, B.; Kellogg, R. M.; Broxterman, Q. B. *Org. Lett.* **2001**, *3*, 3943. (c) Loh, T.-P.; Ho, D. S.-C.; Xu, K.-C.; Sim, K.-Y. *Tetrahedron Lett.* **1997**, *38*, 865.
4. (a) Enders, D.; Chelain, E.; Raabe, G. *Bull. Soc. Chim. Fr.* **1997**, *134*, 299. (b) Friestad, G. K.; Ding, H. *Angew. Chem. Int. Ed.* **2001**, *40*, 4491. (c) Lebrun, S.; Couture, A.; Deniau, E.; Grandclaudon, P. *Org. Lett.* **2007**, *9*, 2473. (d) Cook, G. R.; Maity, B. C.; Kargbo, R. *Org. Lett.* **2004**, *6*, 1741.
5. (a) Cogan, D. A.; Liu, G.-C.; Ellman, J. *Tetrahedron* **1999**, *55*, 8883. (b) Foubelo, F.; Yus, M. *Tetrahedron: Asymmetry* **2004**, *15*, 3823.
6. Lazny, R.; Nodzewska, A. *Chem. Rev.* **2010**, *110*, 1386.
7. For review: (a) Shen, Z.-L.; Shun-Yi Wang, S.-Y.; Chok, Y.-K.; Xu, Y.-H.; Loh, T.-P. *Chem. Rev.* **2013**, *113*, 271.
8. For recent reports for indium-mediated diastereoselective allylation: (a) Guo, T.; Song, R.; Yuan, B.-H.; Chen, X.-Y.; Sun, X.-W.; Lin, G.-Q. *Chem. Commun.* **2013**, *49*, 5402. (b) Sirivent, J. A.; Foubelo, F.; Yus, M. *Chem. Commun.* **2012**, *48*, 2543. (c) Arena, G.; Zill, N.; Salvadori, J.; Girard, N.; Mann, A.; Taddei, M. *Org. Lett.* **2011**, *13*, 2294. (d) Min, Q.-Q.; He, C.-Y.; Zhou, H.; Zhang, X. *Chem. Commun.* **2010**, *46*, 8029. (e) Gonzalez-Gomez, J. C.; Medjahdi, M.; Foubelo, F.; Yus, M. *J. Org. Chem.* **2010**, *75*, 6308.
9. Almansa, R.; Guijarro, D.; Yus, M. *Tetrahedron: Asymmetry* **2007**, *18*, 2828.
10. Chandrasekhar, S.; Kiran Babu, G. S.; Raji Reddy, Ch. *Tetrahedron: Asymmetry* **2009**, *20*, 2216.