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Chiral *N*-phosphonyl imine chemistry: asymmetric 1,2-additions of allylmagnesium bromides

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Abstract

Chiral *N*-phosphonyl homoallylic amines were synthesized by the reaction of allylmagnesium bromide with chiral *N*-phosphonyl imines. The C_2-symmetric chiral *N*-phosphonyl group was optimized for this reaction. Excellent yields and good diastereoselectivities were obtained for eight examples.

Keywords: Chiral *N*-phosphonyl imines; Homoallylic amines; Grignard reagents; Allylmagnesium bromide; 1,2-Addition

Homoallylic amines are key building blocks for the synthesis of complex natural products and biologically active compounds.[1] Asymmetric 1,2-addition of allylic nucleophiles to chiral imines is one of the most commonly used strategies for generating these compounds in optically pure forms. Several chiral imines derived from amino acid derivatives, chiral *N*-sulfinyl imines and hydrazones have been used for this purpose.[2–4] Among these known cases, the chiral *N*-sulfinyl imines are particularly effective[5,6] in directing allylic nucleophilic attack onto imine carbon to afford *N*-sulfinyl homoallylic amines with excellent diastereoselectivities and very good yields. Very recently, Lin and co-workers have reported an interesting methodology to synthesize *N*-sulfinyl homoallylic amines by using chiral *N*-*tert*-butanesulfinyl imines.[7] They found that the asymmetric induction can be reversed by simply changing the reaction conditions.

Recently, in our labs we have synthesized some new chiral *N*-phosphonyl imines and successfully proven that the C_2-symmetric chiral *N*-phosphonyl group could efficiently control the diastereoselectivity of nucleophilic addition reactions such as aza-Darzens reaction and aza-Henry reaction (Scheme 1).[8,9] Very good results were obtained in terms of both yields and diastereoselectivities.

In continuation of our efforts on using chiral *N*-phosphonyl imines in various nucleophilic addition reactions, we sought to explore the reaction of Grignard reagents with these chiral *N*-phosphonyl imines. Herein, we report our preliminary results of the reaction of allylmagnesium bromides with chiral *N*-phosphonyl imines derived from different aromatic aldehydes.

Initially, the reaction of chiral *N*-phosphonyl imine having *N*-benzyl groups in the auxiliary (**1**) with allylmagnesium bromide was examined (Scheme 2).

Even though the reaction provided quantitative yield of product, the diastereoselectivity was only moderate (dr 70:30). In order to investigate the effect of non-coordinating solvents for the reaction shown in Scheme 2, methylene chloride and toluene were used. However, in contrast to *N*-sulfinyl imines where significant improvements in diastereoselectivities were observed,[4b] the use of both methylene chloride and toluene as reaction media resulted in decreased diastereoselectivities (methylene chloride: dr 60:40; toluene: dr 65:35).[10] The use of diethyl ether as a solvent did not improve the diastereoselectivity either.

At this point, attempts were made to optimize the chiral *N*-phosphonyl auxiliary by changing different alkyl groups (R^1, Table 1) on C_2-symmetric nitrogens of chiral

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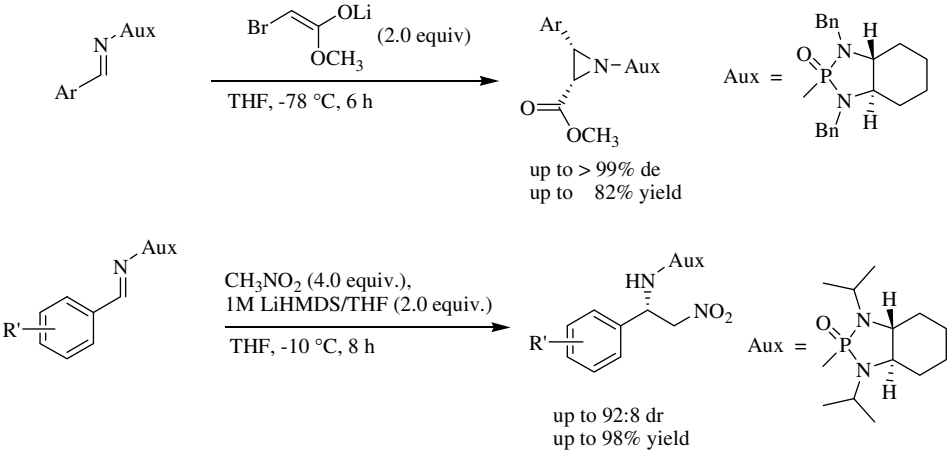
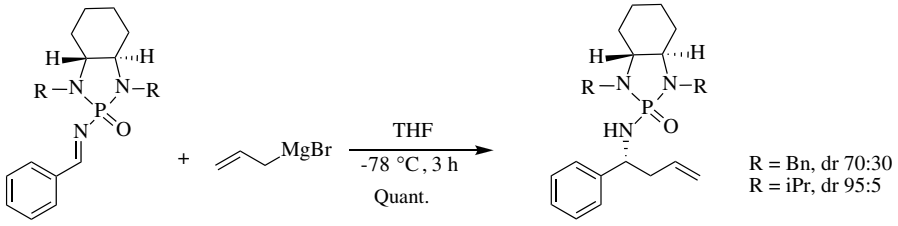


Scheme 1. Asymmetric aza-Darzens and aza-Henry reactions using chiral *N*-phosphonyl imines.

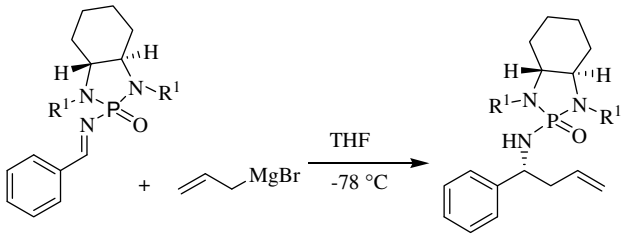


Scheme 2. Reaction of allylmagnesium bromide with chiral *N*-phosphonyl imine **1**.

N-phosphonyl group. Results of these optimization studies are summarized in Table 1.

The presence of *N*-benzyl group (entry 1) in the auxiliary provided only moderate diastereoselectivity of 70:30. When *iso*-butyl group were utilized (entry 2) to replace benzyl group, dramatic decrease in diastereomeric ratio was observed. No significant improvement in stereoselectivity was obtained even when the bulkier *neo*-pentyl groups (entry 3) was used for this purpose. Pleasantly, when *iso*-propyl groups were attached onto C_2-symmetric nitrogens of chiral *N*-phosphonyl group of the auxiliary, dramatic improvement in diastereoselectivity was observed; and the product was obtained in near quantitative yield. The improved diastereoselectivity with *iso*-propyl groups in the auxiliary could be attributed to increased steric bulkiness at C_2-symmetric nitrogens of the chiral auxiliary. This result was in complementary to what we observed in the case of aza-Henry reaction using chiral *N*-phosphonyl imines.[9]

Table 1
The results of optimization of chiral *N*-phosphonyl auxiliary



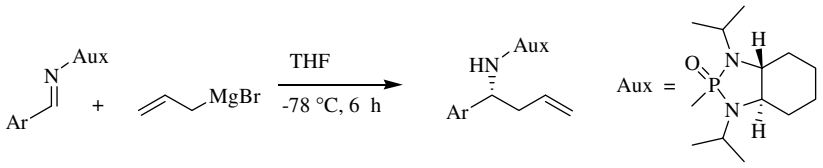
Entry	R^1	Time (h)	% Yield[a,b]	dr[c]
1	$-CH_2Ph$	3	Quant.	70:30
2	$-CH_2-CH(CH_3)_2$	3	Quant.	55:45
3	$-CH_2-C(CH_3)_3$	6	84[d]	65:35
4	$-CH(CH_3)_2$	6	Quant.	95:5

[a] Isolated yield after standard aqueous work-up.
[b] Combined yields of both diastereomers.
[c] Determined by ^1H NMR and ^{31}P NMR analysis of crude reaction products.
[d] Yield after trituration with ether.

Encouraged by this result, different chiral *N*-phosphonyl imines derived from various aldehydes were synthesized[9] and subjected to reaction with allylmagnesium bromide. The results are presented in Table 2. As can be seen from Table 2, nearly quantitative yields of *N*-phosphonyl homoallylic amines were obtained in all the cases that were studied.[11] The diastereoselectivities, in general, were good. Slightly decreased diastereoselectivities were observed in the cases when ortho-substituents (entries 4 and 5) and electron-withdrawing substituents were present on the aromatic rings (entries 6 and 7). Chiral *N*-phosphonyl imine derived from heteroaromatic aldehyde (thiophene-2-carboxaldehyde) also worked well for this reaction (entry 8). The absolute stereochemistry of the products was assigned by converting product **3b** into a known compound and by comparing their optical rotation values.[12,2a]

In summary, several chiral *N*-phosphonyl imines were synthesized and utilized for nuclephilic addition reactions with allylmagnesium bromide. The C_2-symmetric chiral phosphonyl auxiliary was optimized for this reaction. Excellent yields and good diastereoselectivities were

Table 2
Reaction of allylmagnesium bromide with chiral *N*-phosphonyl imines **2a–h**



Entry	Ar	Product	% Yield[a,b]	dr[c]	$[\alpha]_D^{25}$, $CHCl_3$[d]
1	Phenyl	**3a**	Quant.	95:5	−18.7 (*c* 1.03)
2	4-MeO–phenyl	**3b**	Quant.	100:0	−6.9 (*c* 0.64)
3	4-Me–phenyl	**3c**	Quant.	95:5	−9.4 (*c* 0.34)
4	2-MeO–phenyl	**3d**	96	86:14	−28.8 (*c* 0.84)
5	2-Me–phenyl	**3e**	Quant.	90:10	−18.0 (*c* 3.15)
6	4-F–phenyl	**3f**	Quant.	85:15	−26.5 (*c* 1.45)
7	4-Cl–phenyl	**3g**	Quant.	81:19	−20.3 (*c* 1.32)
8	2-Thienyl	**3h**	Quant.	95:5	−21.3 (*c* 0.86)

[a] Isolated yield after standard aqueous work-up.
[b] Combined yields of both diastereomers.
[c] Determined by ^1H NMR and ^{31}P NMR analysis of crude reaction products.
[d] Concentration in g/100 mL.

obtained in all the examples examined. Studies are in progress in our laboratory to extend this methodology to other non-stabilized and more basic Grignard reagents such as methyl- and ethylmagnesium bromides. Furthermore, the work is also being pursued to use other organometallics such as organoindium, organozinc, and organolithium compounds as nucleophiles and the results would be reported in the due course.

Acknowledgments

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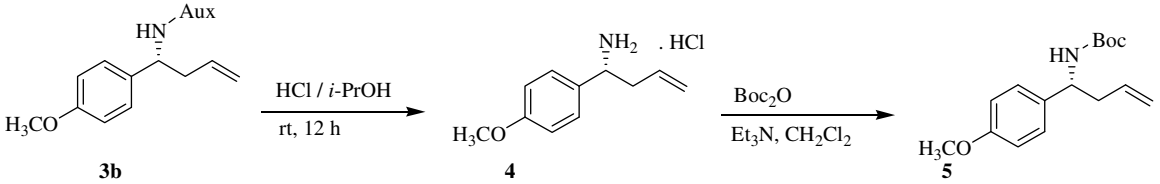
References and notes

1. (a) Ochoa-Puentes, C.; Kouznetsov, V. *J. Heterocycl. Chem.* **2002**, *39*, 595; (b) Ding, H.; Friestad, G. K. *Synthesis* **2005**, 2815.
2. (a) Vilaivan, T.; Winotapan, C.; Banphavichit, V.; Shinada, T.; Ohfune, Y. *J. Org. Chem.* **2005**, *70*, 3464; (b) Basile, T.; Bocoum, A.; Savoia, D.; Umani-Ronchi, A. *J. Org. Chem.* **1994**, *59*, 7766; (c) Ken Lee, C.-L.; Ling, H. Y.; Loh, T.-P. *J. Org. Chem.* **2004**, *69*, 7787.
3. (a) Hua, D. H.; Miao, S. W.; Chen, J. S.; Iguchi, S. *J. Org. Chem.* **1991**, *56*, 4; (b) Yang, T.-K.; Chen, R.-Y.; Lee, D.-S.; Peng, W.-S.; Jiang, Y.-Z.; Mi, A.-Q.; Jong, T.-T. *J. Org. Chem.* **1994**, *59*, 914; (c) Hua, D. H.; Lagneau, N.; Wang, H.; Chen, J. *Tetrahedron: Asymmetry* **1995**, *6*, 349; (d) Cogan, D. A.; Liu, G.-C.; Ellman, J. *Tetrahedron* **1999**, *55*, 8883; (e) Foubelo, F.; Yus, M. *Tetrahedron: Asymmetry* **2004**, *15*, 3823.
4. (a) Friestad, G. K.; Ding, H. *Angew. Chem., Int. Ed.* **2001**, *40*, 4491; (b) Cook, G. R.; Maity, B. C.; Kargbo, R. *Org. Lett.* **2004**, *6*, 1741.
5. (a) Davis, F. A.; Zhou, P.; Chen, B. C. *Chem. Soc. Rev.* **1998**, *27*, 13–18; (b) Davis, F. A. *J. Org. Chem.* **2006**, *71*, 8993–9003.
6. (a) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984–995; (b) Ellman, J. A. *Pure Appl. Chem.* **2003**, *75*, 39–46.
7. Sun, X.-W.; Xu, M.-H.; Lin, G.-Q. *Org. Lett.* **2006**, *8*, 4979.
8. Kattuboina, A.; Li, G. *Tetrahedron Lett.* **2008**, *49*, 1573–1577.
9. Kattuboina, A.; Kaur, P.; Ai, T.; Li, G. *Chem. Biol. Drug Des.* **2008**, 216–223.
10. Reaction was stirred for 9 h with toluene as a solvent.
11. Typical procedure for the reaction of allylmagnesium bromide with chiral *N*-phosphonyl imines is as follows. Into an oven dried 25 mL round-bottomed flask flushed with N_2 was taken a solution of chiral *N*-phosphonyl imine (0.5 mmol) in 10.0 mL of dry THF. The flask was cooled to −78 °C, and 1.0 mmol of allylmagnesium bromide (1.0 mL, 1.0 M solution in THF) was added drop wise. After stirring for 6 h at this temperature the reaction was quenched with 1.0 mL of saturated NH_4Cl and brought to room temperature. 5.0 mL of water was then added to the reaction and extracted with 2 × 20 mL of ethylacetate. The combined organic layers were washed with water (1 × 10 mL) and dried over anhydrous Na_2SO_4. Sodium sulfate was filtered off, and the solvent was evaporated to obtain crude product as a pale yellow solid. This was washed with minimum amount of hexanes to get pure product as a white solid.
12.



$[\alpha]_D^{25}$ + 82.4 ($CHCl_3$, c 0.85)

Lit.[2a] $[\alpha]_D^{24}$ + 76.0 ($CHCl_3$, c 1.00)
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