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Asymmetric Allylboration of α,β-Enals as a Surrogate for the Enantioselective Synthesis of Allylic Amines and α-Amino Acids

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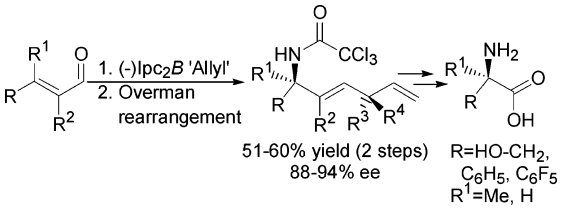

Optically pure allylic amines have been synthesized from α,β-unsaturated aldehydes via allylboration with (−)-*B*-allyldiisopinocampheylborane, followed by Overman rearrangement. By incorporating crotyl and alkoxyallylboration, functionalization at δ-position was readily accomplished. By applying this methodology, the synthesis of several chiral α-amino acids has been achieved.

Allylic amines are very useful synthons in organic synthesis.[1] They are widely used for the preparation of alkaloids, carbohydrates, and other synthetic intermediates.[2] Dienylamines have been recently evaluated as linkers in the synthesis of taxoid analogues.[3] Conversion of analogous amines to δ-amino ketones, precursors for the synthesis of α-methyl piperidines, which are common structural features found in numerous natural products, has also been reported.[4] Allylic amines are also attractive starting materials for the synthesis of α- and β-amino acids.[5] Owing to their importance, there have been many reports in the literature for the preparation of allylic amines.[6,7] Preparation of homoallylic alcohols in high enantiomeric excess via asymmetric allylboration is a well-established protocol.[8] Our recent work[9] on the applications of allylboration using α-pinene-based chiral auxiliaries prompted us to undertake a project involving tandem asymmetric allylboration-Overman rearrangement[7] for the synthesis of optically active allylic amines and α-amino acids. We chose three α-pinene-based reagents for asymmetric allylboration (**1**−**3**, Figure 1).[10]

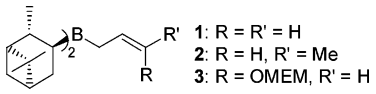

FIGURE 1. α-Pinene-based "allyl" borating reagents.

We selected several α,β-unsaturated aldehydes, containing a variety of functional groups and substitutions. The required aldehydes **4b**−**g** were synthesized using several literature procedures. Aldehyde **4b** was prepared via $LiAlH_4$ reduction of commercially available ethyl β-methyl cinnamate and subsequent Dess−Martin periodinane (DMP) oxidation.[11] Compound **4c** was made via S_N2' substitution with ethylmagnesium bromide on ethyl 2-[(acetyloxy)(phenyl)methyl]acrylate,[12] followed by a $LiAlH_4$ reduction−DMP oxidation sequence, and **4d** was made from (2*Z*)-butene-1,4-diol.[13] Aldehydes **4e**−**g** were prepared from methyl (2*S*)-3-hydroxy-2-methylpropanoate via Wittig−Horner olefination with (triphenylphosphoranylidene)acetaldehyde.[5c,14] The aldehydes **4a**−**g** were reacted with (−)-*B*-allyldiisopinocampheylborane (**1**), followed by oxidative workup to afford the desired homoallylic allylic alcohols **5a**−**g** in 68−83% yields and in 89−94% ee as determined by HPLC analysis (Scheme 1, Table 1, entries 1−7). On the basis of previous reports,[10a] the *S* isomer of homoallylic alcohols was obtained. These alcohols were converted to the corresponding trichloroacetimidates by treatment with 0.1 equiv of sodium bis(trimethylsilyl)amide in THF at −42 °C, followed by the addition of trichloroacetonitrile and warming to room temperature. THF was removed in vacuo and the crude trichloroacetimidates were diluted with xylene and refluxed for 6−14 h (TLC analysis) in the presence of 1.1 equiv of K_2CO_3.[15] The desired amides **6a**−**g** were obtained in good yields (74−89%) (Scheme 1, Table 1, entries 1−7). Overman rearrangement has been reported to proceed with complete retention of stereo-

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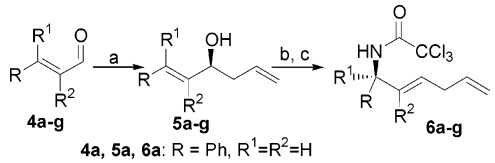
TABLE 1. Synthesis of α,β-unsaturated Homoallylic Alcohols and Allylic Amides

		homoallylic alcohol								amide	
entry	enal no.	no.	R	R^1	R^2	R^3	R^4	% yield[a]	% ee[b] (de)[c]	no.	% yield[a]
1	**4a**	**5a**	Ph	H	H	H	H	73	94	**6a**	89
2	**4b**	**5b**	Ph	Me	H	H	H	73	91	**6b**	79
3	**4c**	**5c**	Ph	H	*n*-Pr	H	H	71	91	**6c**	89
4	**4d**	**5d**	TBSO-CH_2-	H	H	H	H	68	91	**6d**	86
5	**4e**	**5e**	C_6F_5	H	H	H	H	74	93	**6e**	74
6	**4f**	**5f**	(*S*)-TBSO-CH_2-CH(CH_3)-	H	H	H	H	79	89 (>98)	**6f**	75
7	**4g**	**5g**	(*S*)-PMBO-CH_2-CH(CH_3)-	H	H	H	H	83	88 (30)[d]	**6g**	84
8	**4a**	**7a**	Ph	H	H	Me	H	69	89 (>98)	**9a**	74
9	**4a**	**8a**	Ph	H	H	H	OMEM	76	94 (>98)	**10a**	80
10	**4b**	**8b**	Ph	Me	H	H	OMEM	78	93 (>98)	**10b**	77

[a] All yields are of pure isolated products. [b] Percent enantiomeric excess was determined by HPLC using Chiracel OD-H column and isopropyl alcohol/hexanes as the mobile phase. [c] Ratio of diastereomers was determined with ^{1}H NMR spectroscopy. [d] The low de could be due to the partial racemization of the starting aldehyde during Wittig−Horner reaction.

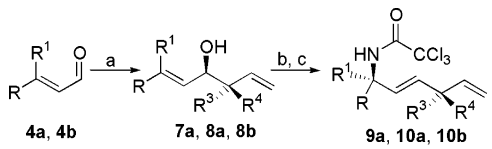
SCHEME 1[a]



4a, 5a, 6a: R = Ph, R^1=R^2=H
4b, 5b, 6b: R = Ph, R^1=Me, R^2=H
4c, 5c, 6c: R = Ph, R^1=H, R^2=*n*-Pr
4d, 5d, 6d: R = $TBSOCH_2$, R^1=R^2=H
4e, 5e, 6e: R = C_6F_5, R^1=R^2=H
4f, 5f, 6f: R = (*S*)-$TBSOCH_2$CH(Me), R^1=R^2=H
4g, 5g, 6g: R = (*S*)-$PMBOCH_2$CH(Me), R^1=R^2=H

[a] Reagents and conditions: (a) (1) **1**, then **4a**−**g**; −100 → −78 °C, 3 h, (2) NaOH, H_2O_2; −78 °C → rt, 14 h. (b) (1) $NaN(SiMe_3)_2$; THF, −42 °C, 0.5 h, (2) Cl_3CCN; −42 °C → rt, 1 h. (c) K_2CO_3; xylene reflux, 6−14 h.

SCHEME 2[a]



4a: R=Ph,R^1=H
4b: R=Ph,R^1=Me

7a, **9a**: R=Ph, R^1=R^4=H, R^3=Me
8a, **10a**: R=Ph, R^1=R^3=H, R^4=OMEM
8b, **10b**: R=Ph, R^1=Me, R^3=H, R^4=OMEM

[a] Reagents and conditions: (a) (1) **2** or **3**, then **4a** or **4b**; −78 °C, 5 h, (2) NaOH, H_2O_2; −78 °C → rt, 14 h. (b) (1) $NaN(SiMe_3)_2$; THF, −42 °C, 0.5 h, (2) Cl_3CCN; −42 °C → rt, 1 h. (c) K_2CO_3; xylene reflux, 10−14 h.

chemistry.[7] Verification of the enantioselectivity of amides **6a**, **6b**, and **6e** using HPLC revealed that they retained the high optical purity, 94%, 91%, and 93% ee, respectively, of the homoallylic alcohols achieved during allylboration.

Additionally, to show the versatility of the current protocol in the synthesis of more functionalized allylic amines, we incorporated crotyl and alkoxyallylboration using **2** and **3**. These reagents,[10] upon reaction with **4a** or **4b**, furnished the corresponding homoallylic alcohols **7a**, **8a**, and **8b** in >98% de and 89%, 94%, and 93% ee, respectively, as determined by HPLC analysis (Scheme 2, Table 1, entries 8−10). These densely functionalized alcohols were converted to the corresponding amides **9a**, **10a**, and **10b** via the trichloroacetimidates, followed by rearrangement as described above, without loss of optical activity (HPLC analysis of **10b** indicated 92% ee).

Unnatural amino acids are very important in bioorganic chemistry.[16] Having achieved the preparation of the allylic amines in high ee, we demonstrated an application of this methodology by preparing representative α-amino acids **11a**, **11b**, **11d**, and **11e** from trichloroacetamides **6a**, **6b**, **6d**, and **6e**, respectively. Accordingly, ozonolysis of **6a** in CH_2Cl_2 at −78 °C, followed by quenching with Me_2S gave the intermediate aldehyde, which upon oxidation with sodium chlorite in *tert*-butyl alcohol in the presence of 2-methylbut-2-ene and aqueous NaH_2PO_4 provided the corresponding acid in good yield. We found this 2-step procedure to be more convenient and reliable than a one-step oxidation with $NaIO_4$−$RuCl_3$, which gave varying results. Removal of the trichloroacetamide group required refluxing of the material with concentrated HCl for 1 h. (2*R*)-Aminophenyl acetic acid hydrochloride (**11a**) and (2*R*)-2-amino-2-phenylpropionic acid hydrochloride (**11b**) were obtained by this sequence in 64% and 62% yield, respectively. Alternatively, we first deprotected **6a** by stirring with aqueous alcoholic NaOH for 24 h (the reaction could be shortened to 2 h by refluxing the mixture), followed by the protection of the amine using di-*tert*-butyl dicarbonate. This *N*-Boc-protected amine was subjected to ozonolysis and oxidation with $NaClO_2$ to afford *N*-Boc-protected amino acid. The Boc group was then conveniently removed by treatment with ethereal hydrogen chloride for 0.5 h at room temperature. The amino acid **11a** was obtained in 73% yield. We applied the latter method for the synthesis of an aliphatic α-amino-β-hydroxy acid **11d** and a fluorinated amino acid **11e** (Scheme 3). Comparison of the optical rotation of the obtained amino acids with those reported in the literature[17] revealed the configuration and assured that the enantioselectivity induced

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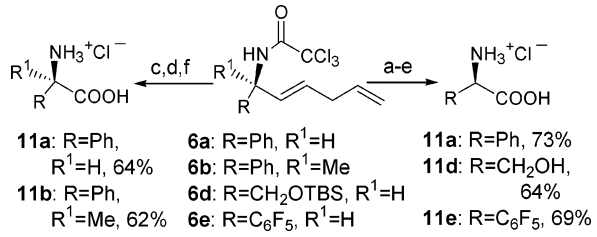
(17) (a) **5a**: $[\alpha]^{20}_D$ = −84° (D_2O, *c* 1.0), $[\alpha]^{20}_D$ = −138° (10% aqueous HCl, *c* 0.5; 93% ee) (lit.: Badorrey, R.; Cativiela, C.; Díaz-de-Villegas, M.; Gálvez, J. A. *Tetrahedron* **1997**, *53*, 1411. $[\alpha]^{25}_D$ = −155° (1 M HCl, *c* 1.0)). (b) **5b**: $[\alpha]^{20}_D$ = −77° (10% aqueous HCl, *c* 0.2; 91% ee) (lit.: Davis, F. A.; Lee, S.; Zhang, H.; Fanelli, D. L. *J. Org. Chem.* **2000**, *65*, 8704. $[\alpha]^{20}_D$ = −85° (1 M HCl, *c* 0.7)). (c) **5d**: $[\alpha]^{20}_D$ = +10° (D_2O, *c* 0.4, 90% ee) (lit.: Rose, J. E.; Leeson, P. D.; Gani, D. *J. Chem. Soc., Perkin Trans. 1* **1995**, 157. [α] = +11° (H_2O, *c* 0.5). (d) **5e**: $[\alpha]^{20}_D$ = +36° (D_2O, *c* 0.7).

SCHEME 3[a]



[a] Reagents and conditions: (a) NaOH; aq EtOH, rt, 24 h. (b) Boc_2O; Et_2O, rt, 3 h. (c) (1) O_3, CH_2Cl_2, −78 °C, (2) Me_2S, −78 °C → rt, 3 h. (d) $NaClO_2$, 2-methylbut-2-ene, NaH_2PO_4; *t*-BuOH, H_2O, rt, 0.5 h. (e) HCl; Et_2O, rt, 0.5 h. (f) concd aq HCl; reflux, 1 h.

during the preparation of homoallylic alcohols has been transferred during the Overman rearrangement.

In conclusion, we have developed an efficient protocol for the enantioselective synthesis of allylic amines via asymmetric allylboration and Overman rearrangement. We have demonstrated the utility of this procedure for the synthesis of several chiral α-amino acids. The simplicity of the protocol, high enantioselectivities in the allylboration step, complete retention of stereochemistry during the rearrangement, and the importance of allylic amines and unnatural α-amino acids make this methodology very attractive. We believe that the presented procedure will find further applications in organic synthesis.

Experimental Section

Representative Experimental Procedures. Preparation of (2*E*)-3-Phenylbut-2-enal (4b). To ethyl (2*E*)-3-phenylbut-2-enoate (1.0 mL, 5.4 mmol), diluted with THF (20 mL) and cooled to 0 °C, was added $LiAlH_4$ (1 M in THF; 5.5 mL, 5.5 mmol) and the reaction was stirred at room temperature for 1 h. Excess $LiAlH_4$ was quenched with water; the product was extracted with Et_2O (3 × 30 mL) and dried with $MgSO_4$. After removal of the solvent under reduced pressure, the resulting alcohol was diluted with CH_2Cl_2 and Dess−Martin periodinane (2.8 g, 6.6 mmol) was added. After stirring at room temperature for 0.5 h, the solvent was removed; the residue was extracted with pentane (3 × 50 mL) and filtered through Celite. After evaporation of the solvent, the obtained product was purified on silica gel (flash; 96:4 hexanes/ethyl acetate) to afford 0.7 g (4.8 mmol, 89% yield) of **4b**. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 2.57 (d, J = 0.72 Hz, 3H), 6.40 (dq, J = 1.24 Hz, 7.88 Hz, 1H), 7.40−7.55 (m, 5H), 10.19 (d, J = 7.83 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 16.4, 126.3, 127.3, 128.8, 130.1, 140.6, 157.7, 191.3.

Preparation of (4*S*,5*E*)-6-Phenylhepta-1,5-dien-4-ol (5b). To **1** (1 M in pentane; 6 mL, 6 mmol), diluted with Et_2O (3 mL) and cooled to −100 °C, was added **4b** (0.7 g, 4.8 mmol) diluted with Et_2O (6 mL) precooled to −78 °C. The mixture was stirred for 3 h, while it was allowed to warm to −78 °C. To the reaction mixture at −78 °C was added 3 M aqueous NaOH (1.6 mL) and (slowly!) 30% aqueous H_2O_2 (1.3 mL), and the reaction was left stirring for 14 h under positive N_2 pressure while it slowly warmed to room temperature. The product was then extracted with Et_2O (3 × 20 mL), washed with brine, and dried with $MgSO_4$, and the solvent was removed under reduced pressure, and the residue was purified on silica gel (flash; 200:1 hexanes/ethyl acetate) to furnish **5b** in 73% yield (0.66 g, 3.5 mmol) and 91% ee as analyzed by HPLC using Chiracel OD-H column and hexanes/2-propanol as the mobile phase. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.95 (br s, 1H), 2.13 (d, J = 1.32 Hz, 3H), 2.42 (t, J = 6.48 Hz, 2H), 4.63 (q, J = 7.05 Hz, 1H), 5.15−5.23 (m, 2H), 5.79−5.95 (m, 2H), 7.28−7.44 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 16.7, 42.4, 68.4, 118.5, 126.1, 127.6, 128.5, 130.2, 134.5, 137.6, 143.1.

Preparation of 2,2,2-Trichloro-*N*-[(1*S*,2*E*)-1-methyl-1-phenylhexa-2,5-dienyl]acetamide (6b). To **5b** (0.5 g, 2.7 mmol), diluted with THF (13 mL) and cooled to −42 °C, was added sodium bis(trimethylsilyl)amide (1 M in THF; 0.27 mL, 0.27 mmol) and the reaction was stirred for 0.5 h, when trichloroacetonitrile (0.3 mL, 2.9 mmol) was added. The reaction was then allowed to warm to room temperature and the solvent was removed under reduced pressure. To the obtained crude trichloroacetimidates, diluted with xylenes (6 mL), was added potassium carbonate (0.4 g, 2.9 mmol) and the mixture was stirred at reflux (150 °C) for 10 h. The mixture was then filtered through Celite, concentrated under reduced pressure, and purified on silica gel (flash; 99:1 hexanes/ethyl acetate) to afford 0.76 g (2.6 mmol, 79% yield) of allylic amide **6b** as an oily substance with 91% ee as analyzed by HPLC. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.89 (s, 3H), 2.87 (t, J = 6.35 Hz, 2H), 5.03−5.09 (m, 2H), 5.58−5.68 (m, 1H), 5.78−5.97 (m, 2H), 6.96 (br s, 1H), 7.29−7.39 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 26.4, 36.6, 61.2, 76.9, 93.6, 116.3, 125.7, 126.6, 127.9, 128.7, 129.3, 134.3, 136.4, 144.0, 160.1.

Preparation of (2*R*)-2-Amino-2-phenylpropionic Acid Hydrochloride (11b). Ozone was passed through a solution of **6b** (0.6 g, 1.8 mmol) in CH_2Cl_2 (200 mL) and MeOH (200 mL) at −78 °C until it turned dark blue. The reaction was then quenched with Me_2S (1 mL) and stirred overnight while it was warming to room temperature. After evaporation of the solvents, the obtained product was purified on silica gel to give 0.5 g (1.7 mmol, 94% yield) of 2,2,2-trichloro-*N*-[(1*R*)-1-methyl-2-oxo-1-phenylethyl]acetamide. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 2.00 (s, 3H), 7.34−7.47 (m, 5H), 8.21 (br s, 1H), 9.21 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 17.9, 66.3, 92.8, 126.7, 129.3, 129.7, 134.7, 160.4, 194.3. To the obtained aldehyde, diluted with 2-methylpropan-2-ol (25 mL) and 2-methylbut-2-ene (5 mL), was added sodium chlorite (0.7 g, 7.7 mmol), sodium phosphate monobasic (0.6 g, 4.3 mmol), and water (5 mL). The mixture was stirred at room temperature for 0.5 h, and the product was extracted with ethyl acetate (3 × 30 mL) and filtered through a short plug of silica gel. The solvent was removed under reduced pressure and the obtained material was refluxed with concentrated HCl (6 mL) for 1 h. Following the evaporation of HCl, the obtained solid was washed with Et_2O and dried to give **11b** in 62% yield (0.2 g, 1.0 mmol) from **6b**. ^{1}H NMR (300 MHz, D_2O, δ): 2.00 (s, 3H), 7.48−7.53 (m, 5H). ^{13}C NMR (75 MHz, D_2O, δ): 21.5, 69.1, 125.0, 127.0, 129.2, 129.4, 137.1, 175.8. $[\alpha]^{20}_D$ = −77° (10% aqueous HCl, *c* 0.2).

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Supporting Information Available: Spectral data (^{1}H, ^{13}C, and ^{19}F NMR spectra) and other physical characteristics of the compounds described. This material is available free of charge via the Internet at http://pubs.acs.org.

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