Organocatalytic Asymmetric Intramolecular Allylic Substitutions of Morita-Baylis-Hillman Acetates: Synthesis of Chiral 2-(α-Methylene)-Pyrrolidines

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The Morita-Baylis-Hillman (MBH) reaction is a very useful carbon-carbon bond forming reaction and affords α-methylene-β-hydroxy carbonyl compounds, which are versatile intermediates in the synthesis of pharmaceutical and biologically active natural products.1 Considerable effort has been devoted to the development of MBH reactions that can be applied to the synthesis of biologically potent compounds. Recently, various organocatalytic allylic substitutions, which proceed via a tandem S_n2′-S_n2′ mechanism, have carried out on MBH acetates with different types of nucleophiles.2,3 However, to the best of our knowledge, there is no report on the intramolecular version of the organocatalytic allylic substitutions of MBH acetates, although these reactions afford versatile heterocyclic intermediates for pharmaceutical and natural product synthesis. In this paper, we report the first example of the intramolecular organocatalytic asymmetric allylic substitutions of MBH acetates containing a protected amine moiety (nucleophile) to obtain various chiral 2-[(α-methylene)]-pyrrolidine derivatives,4 which are important moieties of a large number of pharmaceutical and biologically active natural products (Scheme 1).

To realize the proposed transformation, MBH acetate 1 is reacted with 20 mol% DABCO in 0.1 M THF to afford the desired 2-[(α-methylene)]-pyrrolidine derivative 2 in 98% yield via a tandem S_n2′-S_n2′ mechanism without the formation of any dimerized by-products (Scheme 2). The amine-protecting p-nitrobenzenesulfonyl group in the p-nitrobenzenesulfonylamide moiety of 1 acts as the substituent for increase of nucleophilicity as well as the good protecting group.

Scheme 1. Organocatalytic asymmetric intramolecular allylic substitutions of MBH acetates.

Scheme 2. DABCO-catalyzed intramolecular allylic substitution of MBH acetate 1.

Scheme 3. Synthesis of the substrate 1 for the organocatalytic intramolecular allylic substitutions.
Optimization of organocatalytic asymmetric intramolecular allylic substitutions of MBH acetate

<table>
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<tr>
<th>Entry</th>
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<th>Ee (%)</th>
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<td>VII</td>
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<td>VII</td>
<td>CICH2CH2Cl</td>
<td>43</td>
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Procedure: To a reaction vessel charged with 1 (0.5 mmol, 100 mol%) and catalyst (0.1 mmol, 20 mol%) was added the solvent (10.0 mL, 0.05 M). The reaction was stirred for 96 h, at which point the reaction mixture was evaporated onto silica gel. The product was isolated by silica gel chromatography. Enantioselective excess was determined by chiral stationary phase HPLC analysis using a Chiralcel OD-H column. Reaction was carried out in 0.1 M CICH2CH2Cl.

An effective synthetic route to 1 was adopted to overcome the difficulties involved in the synthesis of this substrate (Scheme 3). Elaboration of commercially available 4-aminobutanal diethyl acetal (3) to 1 was achieved in six steps. Sulfonlation of 3 with p-nitrobenzenesulfonyl chloride in the presence of Et3N and DMAP in dichloromethane yielded the sulfonamide 4 in 93% yield. The sulfonamide group of 4 had to be protected during its conversion to the aldehyde product, as direct acetal deprotection afforded a carbinolamine as the by-product. Therefore, Boc protection of the amine moiety in 4 was carried out using (Boc)2O in the presence of Et3N and DMAP in ethyl acetate to afford the doubly N-protected product 5 in 97% yield. Subsequent deprotection of the acetal group of 5 with PPTS in an acetone-water mixture afforded the aldehyde 6 in 95% yield. Synthesis of the allylic alcohol 7 was initially attempted using a MBH coupling of 6 with ethyl acrylate. MBH coupling of 6 with various nucleophilic promoters failed to give the desired allylic alcohol 7 in good yield; however, vinylalumination of ethyl propiolate and 6 using DIBAL-H and HMPTA in THF gave 7 in 73% yield. Subsequent treatment of 7 with acetyl chloride and Et3N in toluene afforded the allylic acetate 8 in 79% yield. Finally, removal of Boc from the amine moiety of 8 using sulfuric acid in 1,4-dioxane gave the desired product 1 in 98% yield.

To expand the scope of substrates in the DABCO-catalyzed intramolecular allylic substitutions of MBH acetates, the substitution reactions were carried out under the optimized condition using methyl vinyl ketone-derived substrate 9 and acrylonitrile-derived substrate 11 (Scheme 4). Substrates 9 and 11, which were prepared according to the synthetic method of substrate 1, underwent the organocatalytic intramolecular allylic substitutions to afford 2-(α-methylene)-pyrrolidine derivatives 10 and 12, respectively, in good yields, and no dimerized by-products were formed.

To explore the feasibility of an enantioselective variant, the intramolecular allylic substitutions of 1 in 0.05 M toluene solution were carried out in the presence of a wide variety of chiral organocatalysts (Table 1, entries 1-7), and the best result was obtained with hydroquinidine 4-methyl-2-quinolyl ether (VII) (Table 1, entry 7). Reactions carried out in various solvents (Table 1, entries 7-10) revealed that dichlorehane was the ideal solvent, affording a 74% enantiomeric excess of 2 in 37% yield (Table 1, entry 10). When the concentration of dichlorehane was increased to 0.1 M under the same condition, the yield of 2 was magnified increased to 43%. But the enantiomeric excess of 2 was slightly decreased to 70% (Table 1, entry 11).

To expand the scope of substrates in the organocatalytic asymmetric intramolecular allylic substitutions of MBH acetates, the reaction was performed under the optimized condition using methyl vinyl ketone-derived substrate 9 (Scheme 5). The results showed that 9 underwent the asymmetric intramolecular allylic substitution to afford the chiral 2-(α-methylene)-pyrrolidine derivative 10 in 77% isolated yield and 73% ee; no dimerized by-products were formed in this reaction.

In conclusion, the intramolecular allylic substitution of MBH acetates 1, 9 and 11 in the presence of DABCO catalyst afforded a series of 2-(α-methylene)-pyrrolidine derivatives as the corresponding intramolecular substitution products in good to excel-
lent yields; the substitution proceeded via a tandem S$_2$2′-S$_2$2′ substitution mechanism, and no dimerized by-products were formed. To the best of our knowledge, there are no reported examples of the organocatalytic intramolecular allylic substitutions of MBH acetates. Therefore, this is the first example of an intramolecular variant of the organocatalytic allylic substitutions of MBH acetates having a protected amine moiety as the nucleophile. The asymmetric version of this substitution reaction using hydroquinidine 4-methyl-2-quinolyl ether (VII) as the chiral organocatalyst afforded chiral 2-(α-methylene)-pyrrolidine derivatives 8 and 10 as the corresponding chiral substitution products with up to 74% ee.

**Experimental Section**

Typical procedure for the asymmetric intramolecular allylic substitutions. To a reaction vessel charged with substrate (0.5 mmol, 100 mol%) and catalyst (0.1 mmol, 20 mol%) was added the solvent (10.0 mL, 0.05 M). The reaction was stirred for 96 h, at which point the reaction mixture was evaporated onto silica gel. The product was isolated by silica gel chromatography.

Enantiomeric excess was determined by chiral stationary phase HPLC using a Chiralcel OD-H column. The spectroscopic data of 1, 2 and 4-12 are as follows. Ethyl 2-[1-(4-nitrophenylsulfonyl)pyrrolidin-2-yl] acrylate (8): White solid, mp 131-132 °C; IR (neat) 3233, 2925, 1720, 1531, 1353, 1283, 1103, 1034, 855, 736 cm$^{-1}$; 1H NMR (300 MHz, CDCl$_3$) δ 8.35 (d, J = 9.2 Hz, 2H), 8.10 (d, J = 8.8 Hz, 2H), 4.52 (t, J = 5.4 Hz, 1H), 3.86 (t, J = 7.4 Hz, 2H), 3.65 (m, 2H), 3.50 (m, 2H), 3.46 (m, 2H), 2.06 (m, 3H), 1.82 (m, 2H), 1.30 (t, J = 7.3 Hz, 3H), 1.23 (m, 12H), 1.10 (m, 12H), 1.06 (m, 12H), 0.96 (m, 12H); 13C NMR (100 MHz, CDCl$_3$) δ 170.0, 165.3, 150.0, 146.0, 139.6, 128.3, 125.1, 124.4, 70.6, 61.2, 42.6, 31.1, 25.4, 21.0, 14.1; HRMS caleld for [M+Na] C$_{19}$H$_{30}$O$_8$N$_2$SNa 469.1621, found 469.1617.

tert-Butyl 4,4-diethoxybutyl(4-nitrophenylsulfonyl)carbamate (5): A solution of di-tert-butyl dicarbonate (4.67 g, 21.4 mmol) in ethyl acetate (5.0 mL) was added to a stirred mixture of N-(4,4-diethoxybutyl)-4-nitrobenzenesulfonamide (4, 3.70 g, 10.7 mmol), triethylamine (1.80 mL, 12.8 mmol) and 4-(dimethylamino)pyridine (1.57 g, 12.8 mmol) in ethyl acetate (6.0 mL) at ambient temperature. After 30 min, the mixture was quenched withaq. 2.0 M HCl and extracted with ethyl acetate. The organic layer was washed with water, dried over MgSO$_4$, and concentrated in vacuo. The product was purified by flash column chromatography to afford the compound 5 (4.69 g, 97%) as white solid. mp 57 – 58 °C; IR (neat) 2983, 1731, 1533, 1328, 1217, 1182, 852, 743, 716 cm$^{-1}$; 1H NMR (300 MHz, CDCl$_3$) δ 8.35 (d, J = 9.2 Hz, 2H), 8.10 (d, J = 8.8 Hz, 2H), 4.52 (t, J = 5.4 Hz, 1H), 3.86 (t, J = 7.4 Hz, 2H), 3.65 (m, 2H), 3.50 (m, 2H), 3.46 (m, 2H), 2.06 (m, 3H), 1.82 (m, 2H), 1.30 (t, J = 7.3 Hz, 3H), 1.23 (m, 12H), 1.10 (m, 12H), 1.06 (m, 12H), 0.96 (m, 12H); 13C NMR (100 MHz, CDCl$_3$) δ 170.0, 165.3, 150.0, 146.0, 139.6, 128.3, 125.1, 124.4, 70.6, 61.2, 42.6, 31.1, 25.4, 21.0, 14.1; HRMS caleld for [M+Na] C$_{19}$H$_{30}$O$_8$N$_2$SNa 469.1621, found 469.1617.

Ethyl 2-[1-(4-nitrophenylsulfonyl)]pyrrolidin-2-yl] acrylate (2): White solid, mp 130 – 131 °C; IR (neat) 3455, 2925, 1701, 1526, 1535, 1297, 1167, 1033, 739 cm$^{-1}$; 1H NMR (300 MHz, CDCl$_3$) δ 8.40-8.37 (m, 2H), 8.05-8.02 (m, 2H), 5.67 (s, 1H), 5.94 (d, J = 0.9 Hz, 1H), 4.65 (d, J = 4.2 Hz, 1H), 4.28-4.12 (m, 2H), 3.68-3.60 (m, 1H), 2.93-2.71 (m, 1H), 1.90-1.65 (m, 4H), 1.31 (t, J = 7.3 Hz, 3H); 13C NMR (75 MHz, CDCl$_3$) δ 165.5, 140.5, 135.1, 128.1, 126.0, 124.4, 61.0, 60.2, 49.3, 32.6, 23.3, 14.1; HRMS caleld for [M+1] C$_{17}$H$_{23}$O$_8$N$_2$S 355.0964, found 355.0966; HPLC condition to determine enantiomeric excess: chiralcel OD-H column, Hexane/2-Propanol = 80/20, flow rate = 0.8 mL/min, detection wavelength = 254 nm, retention time: 21.9 min (minor isomer), 26.9 min (major isomer).

N-(4,4-Diethoxybutyl)-4-nitrobenzenesulfonamide (4): A solution of 4-nitrobenzenesulfon chloride (4.83 g, 27.0 mmol) in CH$_2$Cl$_2$ (45 mL) was added to a vigorously stirred mixture of 4-aminobutylaldehyde diethyl acetel (3, 6.58 g, 29.1 mmol), triethylamine (4.52 mL, 32.4 mmol) and 4-(dimethylamino)pyridine (1.32 g, 10.8 mmol) in CH$_2$Cl$_2$ (45 mL). After 45 min, the mixture was quenched with sat. aq. NH$_4$Cl and extracted with CH$_2$Cl$_2$. The organic layer was washed with brine, dried over MgSO$_4$, and concentrated in vacuo. The product was purified by flash column chromatography to afford the compound 4 (8.69 g, 93%) as white solid. mp 72 – 73 °C; IR (neat) 3233, 2981, 2886, 1533, 1343, 1034, 855, 736 cm$^{-1}$; 1H NMR (300 MHz, CDCl$_3$) δ 8.34 (d, J = 8.8 Hz, 2H), 8.03 (d, J = 8.8 Hz, 2H), 5.51 (t, J = 5.5 Hz, 1H), 4.41 (t, J = 4.8 Hz, 1H), 3.60 (m, 2H), 3.43 (m, 2H), 3.02 (m, 2H), 1.58 (m, 4H), 1.16 (t, J = 7.2 Hz, 6H); 13C NMR (100 MHz, CDCl$_3$) δ 149.9, 146.1, 128.5, 128.2, 124.3, 102.4, 61.9, 43.2, 30.9, 24.2, 15.2; HRMS caleld for [M+Na] C$_{17}$H$_{23}$O$_8$N$_2$SNa 369.1096, found 369.1092.

mixture stirred for 0.5 h. Ethyl propiolate (0.89 mL, 8.8 mmol) was added, and the mixture was stirred at 0 °C for 1 h, followed by the addition of tert-butyl 4-nitrophensulfonyl(4-oxobutyl) carbamate (6, 3.28 g, 8.8 mmol). The mixture was warmed to room temperature and stirred for 18 h. The mixture was quenched with aq. 1.0 M HCl and extracted with Et2O. The combined ether layers were washed with brine and dried over MgSO4. Removal of the solvents and purification by column chromatography over silica gel provided the compound 7 (3.03 g, 73%) as colorless oil. IR (neat) 3545, 2981, 1732, 1534, 1351, 1283, 1153, 1086, 742 cm−1; 1H NMR (300 MHz, CDCl3) δ 8.37-8.34 (m, 1H), 8.06 (d, J = 8.6 Hz, 2H), 8.05 (d, J = 8.6 Hz, 2H), 8.01 (s, 1H), 7.53-7.52 (m, 1H, 5.12 (t, J = 6.0 Hz, 1H), 3.90-3.92 (m, 2H), 2.10 (s, 3H), 1.89-1.77 (m, 2H), 1.65-1.52 (m, 2H); 13C NMR (75 MHz, CDCl3) δ 169.8, 150.1, 148.6, 147.7, 146.0, 128.5, 123.9, 123.5, 85.2, 71.1, 60.9, 47.1, 31.2, 27.8, 26.5, 14.1; HRMS calcd for [M+Na] C20H19NO9NSNa 396.0973, found 396.0975.

Ethyl 3-acetoxy-6-[N-(tert-butoxycarbonyl)-4-nitrophensulfonylamido]-2-methylenexanate (8): To a stirred solution of ethyl 6-[N-(tert-butoxycarbonyl)-4-nitrophensulfonylamido]-3-oxo-2-methylhexanenitrate (7, 3.07 g, 6.5 mmol) in toluene (22 mL) was added acetyl chloride (1.11 mL, 15.6 mmol) and triethylamine (1.81 mL, 13 mmol) at ambient temperature. After 1 hour, the mixture was quenched with sat. aq. NH4Cl and extracted with ethyl acetate. The organic layer was washed with brine, dried over MgSO4, and concentrated in vacuo.


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References and Notes


7. In the case of the substrate 11, the asymmetric intramolecular allylic substitution afforded the corresponding product 12 in 58% yield and only 6% enantiomeric excess.