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Asymmetric Michael Addition of a Recyclable Chiral Amine: Inversion of Stereoselectivity Caused by the Difference of Ethereal Solvents

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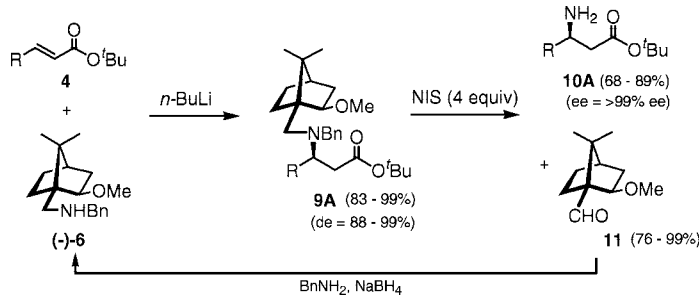
ABSTRACT



The Michael addition of a chiral amine [(−)-6] to α,β-unsaturated esters (4) was attained and the stereoselectivity was inverted by changing the solvent from diethyl ether to tetrahydrofuran when α,β-unsaturated esters having an aromatic ring at the β-position were employed. In addition, the chiral auxiliary in the Michael adducts (9A) was facilely removed with *N*-iodosuccinimide to afford β-amino esters (10A) and 2-methoxy-*d*-bornylaldehyde (11), which can be reclaimed to the chiral amine (6) by reductive amination.

Asymmetric Michael additions of amines to α,β-unsaturated esters are very promising because they afford units of β-amino acids that are a part of a number of naturally occurring bioactive compounds. Many methods of stereoselective Michael addition, with amines or amides utilized as nucleophiles, have been developed up to date in either catalytic or stoichiometric ways. For example, Davis employed a chiral phenethyl amide as a nucleophile to attack α,β-unsaturated esters to afford derivatives of β-amino acids,[1] while Tomioka achieved the Michael addition of an achiral silyllithium amide in the presence of a chiral ligand.[2] Enders developed a recyclable *N*-silylated amide carrying (*S*)-2-methoxymethylpyrrolidine as a nucleophile.[3]

On the other hand, we recently reported the asymmetric Michael addition of a chiral thiol (**1**) to α,β-unsaturated ketones, which was followed by spontaneous Meerwein−Pondorf−Varley reduction to afford β-mercapto alcohols.[4,5] The Michael addition of **1** was further applied to α,β-

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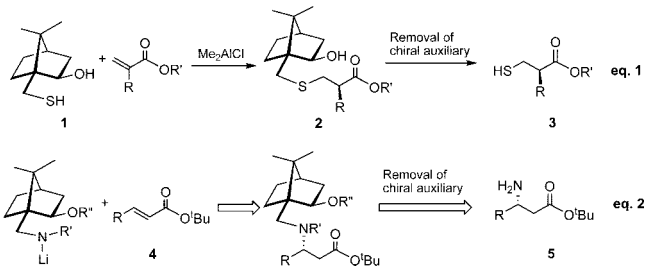
unsaturated esters to afford β-sulfinyl esters (**2**), of which the reaction was next developed to yield β-mercapto esters (**3**) by taking advantage of the Wagner−Meerwein rearrangement (Scheme 1, eq 1).[6]

Scheme 1. Strategy for the Asymmetric Michael Addition of H_2S and NH_3

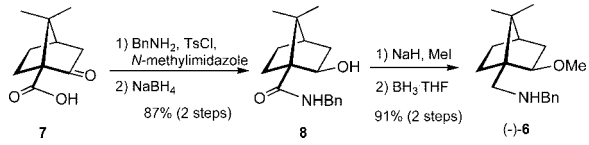


On the basis of these backgrounds, we embarked on the development of a novel asymmetric Michael addition to α,β-unsaturated esters (**4**) using a chiral amine with a bicycle[2.2.1] system as a nucleophile, which could be prepared from commercially available ketopinic acid,[7] for establishing an alternative synthetic pathway for both (*R*)- and (*S*)-β-amino acids (Scheme 1, eq 2).

Furthermore, increasing the utility of the Michael addition in terms of atom economy and a method to remove the chiral auxiliary, norbornane, in recyclable form from the Michael adducts to afford β-amino esters **5** were established together.

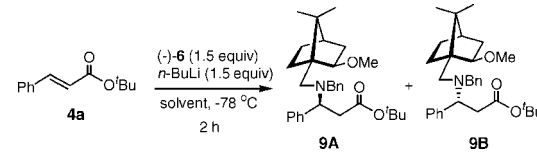
At the beginning of this study, the chiral amine (−)-**6** was prepared as follows. Ketopinic acid (**7**) was treated with benzylamine and *p*-toluenesulfonyl chloride in the presence of *N*-methylimidazole[8] to afford amide **8**,[9,10] the hydroxyl group of which was methylated by a conventional method followed by reduction of the amide group with borane to give (−)-**6** (Scheme 2).

Scheme 2. Synthesis of Chiral Amino Reagents (**6**)



Next, the effects of solvents on the Michael addition were scrutinized by fixing the reaction conditions, i.e., adding a solution of *tert*-butyl cinnamate **4a** in an appropriate organic solvent to the amide prepared (−)-**6** (1.5 equiv) and *n*-butyllithium (1.5 equiv) and stirring the mixture at −78 °C for 2 h (Table 1). The reaction conducted in a nonpolar solvent, such as toluene or hexane, did not proceed well in terms of chemical yield and diastereoselectivity (Table 1, entries 11 and 12). However, the reactions in diethyl ether (Table 1, entry 1) and tetrahydrofuran (Table 1, entry 7) proceeded with satisfactory yields and an excellent contrast of product ratios, i.e., the diastereoselectivities were completely inverted by changing the solvent from cyclic to acyclic ethers (Table 1, entries 1, 4−7, and 10). The reaction solution of tetrahydrofuran maintained a transparent red color during the reaction while that of diethyl ether was transparent yellow.

Table 1. Effects of Solvents on the Ratios of the Michael Adducts (**9A**, **9B**)



entry	solvent	yield (%)[a]	**9A**:**9B**[b]
1	Et_2O	74	15:85
2	Et_2O + HMPA (6 equiv)[c]	52	88:12
3	Et_2O + HMPA (30 equiv)[d]	61	94:6
4	*i*-Pr_2O	45	15:85
5	*n*-Bu_2O	56	17:83
6	CPME	59	10:90
7	THF	62	81:19
8	THF + HMPA (6 equiv)[c]	99	86:14
9	THF + HMPA (30 equiv)[d]	63	91:9
10	oxetane	34	89:11
11	toluene	48	52:48
12	hexane	36	28:72

[a] Isolated yield. [b] Ratio determined by ^{1}H NMR.. [c] −50 °C. [d] −20 °C.

On the basis of the difference in the solutions' colors, the inversion of the diastereoslectivity could be attributed to the differences of aggregation forms of the lithium amide in the solutions, of which forms A and B would be dissociated by adding *tert*-butyl cinnamate **4a** to construct the transition states **TS-A** and **TS-B** (Figure 1).

An experiment with HMPA, a well-known dissociating agent for organometals, as an additive supported the hypothesis, i.e., addition of HMPA to the reaction solution of diethyl ether changed the color from yellow to red and inverted the diastereoslectivity of the products, similar to the reaction performed in tetrahydrofuran (Table 1, entries 2 and 3). Addition of HMPA in THF solution gave the same type of aggregation as in diethyl ether in the presence of HMPA (Table 1, entries 8 and 9).

Considering the results above, several Michael acceptors carrying another group instead of the phenyl group were

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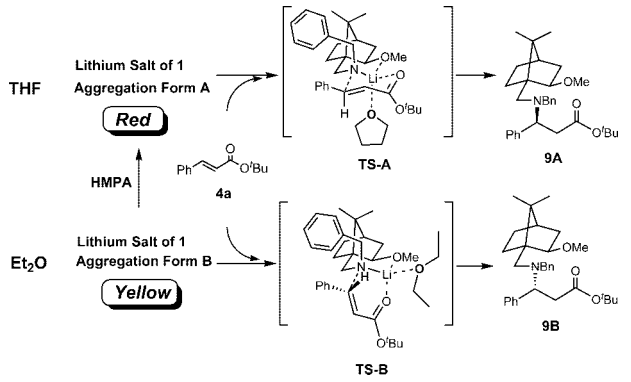
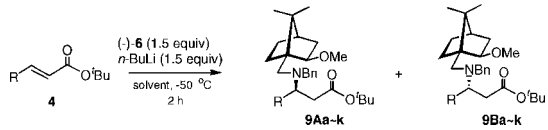


Figure 1. Assumed transition states of the Michael addition in Et_2O and THF solution.

subjected to the Michael addition to investigate the influence of the functional groups on the β-carbon toward the solvent effect (Table 2). With the substrates employed in our

Table 2. Substrate Specificity of the Michael Addition



		solvent			
		THF		Et_2O	
entry	substrates **4**, R	yield (%)[b]	**9A**:**9B**[c]	yield (%)[b]	**9A**:**9B**[c]
1	**a**: Ph	90 (99)[a]	93:7 (94:6)[d]	74[a]	15:85[a]
2	**b**: 4-Cl-Ph	80 (91)[a]	91:9 (94:6)[d]	50[a]	7:93[a]
3	**c**: 4-MeO-Ph	90 (97)	94:6 (96:4)[d]	65	23:77
4	**d**: 4-Me-Ph	83(80)	91:9 (94:6)[d]	79	22:78
5	**e**: 2-Naph	70 (88)	92:8 (96:4)[d]	79	21:79
6	**f**: *n*-Hex	83[a] (81)[a]	95:5[a] (95:5)[d]	29	44:56
7	**g**: *c*-Hex	99 (92)	>99:1 (>99:1)[d]		
8	**h**: *i*-Pr	90 (95)	>99:1) (93:7)[d]		
9	**i**: *n*-Pr	83 (95)	91:9 (91:9)[d]		
10	**j**: 3-Pen	76 (88)	92:8 (96:4)[d]		
11	**k**: *c*-Pen	99 (99)	97:3 (97:3)[d]		

[a] Performed at −78 °C. [b] Isolated yield. [c] Ratio was determined by ^{1}H NMR. [d] The value in parentheses was the result of the reaction with LiOTf (0.5 equiv).

experiment (−50 °C), reactions of the α,β-unsaturated esters having an aromatic ring at the β-position **4a**−**e** showed good contrast depending on the solvents (Table 2, entries 1−5). Meanwhile, the reaction of **4f** having a *n*-hexyl group afforded almost no selectivity in diethyl ether (Table 2, entry 6) and those of substrates having another aliphatic group at the β-position **4g**−**k** afforded inseparable products composed of many components with diethyl ether as the solvent. Interestingly, higher diastereoselectivities were generally obtained with the substrates **4f**−**k** than the reactions of **4a**−**e** on using tetrahydrofuran as the solvent (Table 2, entries 6−11). Moreover, effects of additives on the reactions of **4a**−**k** in tetrahydrofuran solution were tested (Table 2, see the values in parenthses). Interestingly, addition of 0.5 equiv of lithium salts, such as lithium trifluoromethanesulfonate, generally increased both chemical yield and diastereoselectivity.

The additive exhibited a positive effect in the reaction with a cinnamate derivative having an electron-withdrawing or -donating group, especially in the reaction of *p*-chlorocinnamate (**4b**), where the chemical yield was increased from 80% to 91% and the diastereoselectivity was improved from 91:9 to 94:6 by adding lithium triflate (Table 2, entry 2). Unfortunately, additives such as lithium triflate and trifuoroacetate in diethyl ether solution afforded no satisfactory results.

The newly generated chiral center was first determined to have an *S*-configuration by X-ray chrystallography of **9Ad**, which was obtained in the reaction of *tert*-butyl *p*-methylcinnamate and (−)-**6**. The absolute configurations of other products were speculated on the basis of comparison of chemical shifts of methoxy and methyl groups of the chiral auxiliary in ^{1}H NMR spectra with those of **9Ad**.[11]

Herein, to develop the Michael addition as a general method to synthesize β-amino acids or esters, the chiral auxiliary has to be removed from the Michael adducts. Although cleavage reactions of the carbon−nitrogen bond are difficult in general, many methods have been developed.[12] Notably, the oxidative dealkylation of secondary amines can be conducted a little more facilely due to the ease of forming a Schiff base. In fact, Tomioka reported a practical debenzylation of secondary amines by *N*-chlorosuccin-imide (NCS), dehydrochlorination, and successive transoximation;[13] however, the method did not apply to dealkylation on an amino group except for debenzylation. Therefore, we tried to cleave the chiral auxiliary by using *N*-iodosuccin-imide (NIS), a softer halonium source than NCS.[14] Namely, the Michael adducts (**9A**) were treated with 4 equiv of NIS to afford the β-amino esters (**10A**)[15] and 2-methoxybornyl

(11) The signals assigned for methyl and methoxy groups of **9Ad** in the ^{1}H NMR spectrum were observed at 0.50 and 3.17, respectively, while those of **9Bd** appeared at 0.61 and 3.19.

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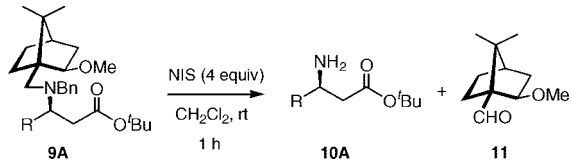
(15) The absolute configuration of **10Aa** was determined by the optical rotation ($[\alpha]^{21}_D$ −24.5) on the basis of values in the literature ($[\alpha]_D$ −13.3, 74% ee)[16] and the values of ee (>99% ee) were further confirmed by converting to *N*-protected derivatives with a Boc group, which were analyzed by HPLC with a chiral column. In addition, the absolute configuration and the ee value of the enantiomer of **10Aa** (**10Ba**) derived from **9Ba** were also determined in a similar way ($[\alpha]^{21}_D$ +22.8, lit.[17] $[\alpha]^{21}_D$ +22.4, >96% ee).

aldehyde (**11**) in good yield (Table 3). It is noteworthy to emphasize that this is the first reaction where an alkyl group except methyl and benzyl groups on an amino group was cleaved efficiently by oxidation with NIS.

Table 3. Complete Deprotection of the Michael Adducts with NIS (4 equiv)



9A **10A** **11**

			yield	
entry	substrate	R	**10A**	**11**
1	**9Aa**	Ph	76	93
2	**9Ac**	4-MeO-Ph	84	99
3	**9Ad**	4-Me-Ph	80	97
4	**9Af**	*n*-Hex[a]	69	76
5	**9Ag**	*c*-Hex	89	93
6	**9Ah**	*i*-Pr[a]	68	88

[a] It is noteworthy to emphasize that adding 4 equiv of NIS at once into the reaction mixture reduced the chemical yield; therefore, 2 equiv of NIS was added twice at an interval of 1 h.

Another advantage of the protocol is that the 2-methoxy-*d*-bornylaldehyde (**11**) can be reformed to the chiral amine (−)-**6** in 85% yield by reductive amination with benzylamine in the presence of sodium borohydride.

In conclusion, we succeeded in establishing a novel stereoselective Michael addition to *tert*-butyl esters of α,*β*-unsaturated acids by using the chiral amine (−)-**6** as a nucleophile. The diastereoselectivity was dramatically inverted by changing the solvent from diethyl ether to tetrahydrofuran when aromatic substrates, such as cinnamate, were employed as the Michael acceptor. The addition of lithium triflate to the reaction by using *tert*-butyl cinnamate and its derivatives as the substrate increased the chemical yield and enhanced the stereoselectivity. Moreover, the chiral auxiliary in (−)-**6** was facilely cleaved with 4 equiv of NIS to afford *β*-amino esters **10A** and 2-methoxy-*d*-bornylaldehyde (**11**), which was reclaimable to (−)-**6** by reductive amination with benzylamine. Our method seems to be practical because of high chemical and optical yields,[18] and no observation of a decrease in optical purity during the removal of the chiral auxiliary from Michael adducts to afford *β*-amino esters.[2] An application to the synthesis of (+)-negamycin will appear in a future publication.[19]

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Supporting Information Available: Experimental details and spectroscopic data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) *n*-Butyllithium (2.77 M solution in *n*-hexane, 107 μL, 0.295 mmol) was added to a solution of (1*S*,2*R*)-(−)-2-methoxybornyl-10-benzylamine [(−)-**6**] (80.7 mg, 0.295 mmol) in tetrahydrofuran (2 mL) at −50 °C and the mixture was stirred for 30 min. Then, a solution of (*E*)-*tert*-butyl 3-phenyl-2-propenoate (**4a**) (40.2 mg, 0.197 mmol) in tetrahydrofuran (1 mL) was added to the reaction mixture, which was stirred for another 1 h. The reaction was quenched by adding a saturated aqueous solution of sodium bicarbonate and the mixture was extracted with diethy ether. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried over sodium sulfate, and evaporated. The residue was purified by silica gel column chromatography (*n*-hexane:ethyl acetate = 10:1) to afford a mixture of *tert*-butyl (*S*)-(−)-3-phenyl-3-[(1*S*,2*R*)-2-methoxybornyl-10-benzylamino]propanoate [(−)-**9Aa**] (79.1 mg, 85%) and **9Ba** (5.9 mg, 5.4%) as colorless needles. *N*-Iodosuccinimide (NIS: 119.4 mg, 0.53 mmol) was added to a solution of **9Aa** (63.4 mg, 0.133 mmol) in dichloromethane (1.5 mL) at room temperature and the mixture was stirred for 1 h. The reaction was quenched by adding a saturated aqueous solution of sodium bicarbonate and the mixture was extracted with chloroform. The organic layer was successively washed with a saturated aqueous solution of sodium chloride and sodium thiosulfate, dried over potassium carbonate, and evaporated. The residue was purified by silica gel column chromatography (*n*-hexane: ethyl acetate = 15:1 to 5:1, and then chloroform:methanol = 30:1) to afford **10Aa** (22.3 mg, 76%) and **11** (22.4 mg, 93%).

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