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Enantioselective Conjugate Addition to α,β-Unsaturated Esters and Amides Mediated by Lithium Perchlorate

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An efficient method for the enantioselective 1,4-conjugate addition of amines to α,β-unsaturated esters containing an inexpensive chiral auxiliary, such as (*S*)-2-methyl-1-butanol and fenchyl alcohol, in solvent-free conditions mediated by solid lithium perchlorate is reported. Over 12 examples of the products are generated in excellent yields, accompanied by moderate enantioselectivity. The concentrated solution of $LiClO_4$ in a diethyl ether system works well for the enantioselective 1,4-addition of organolithium compounds to α,β-unsaturated amides without any side reactions.

Keywords: Enantioselective, Conjugate addition**,** Chiral auxiliary**,** Solvent-free, Unsaturated esters, Lithium perchlorate

INTRODUCTION

Functionalized β-amino acids or β-amino esters are key components of a variety of bioactive molecules [1-4]. One of the simplest and widely used methods for the preparation of these compounds is the conjugate addition of a nucleophile to an α,β-unsaturated acid derivative [5-7]. Asymmetric conjugate additions of amines or organolithium reagents to electron deficient olefins are among the most popular reactions due to their usefulness in preparing intermediates for the synthesis of biologically important molecules [8-10]. An asymmetric conjugate addition reaction requires the design of a chiral auxiliary and many recent studies have focused on the use of chiral ligands or the development of chiral conjugated esters and amides, each bearing a chiral auxiliary [11-13]. A variety of nucleophiles add to α,β-unsaturated esters and amides in a conjugate manner. If the alcohol or amine from which the system is derived has a chiral unit, there is a potential for asymmetric induction. Hydrolysis would then release the original chiral auxiliary group as well as a chiral acid or ester [14-25]. Mukaiyama and co-workers have reported that the reactions of α,β-unsaturated amides derived from (1*R*,2*S*)-(-)-ephedrine and Grignard reagents result in products with relatively high enantioselectivity [26]. Although the reported chiral auxiliaries or chiral ligands gave high *de* or *ee* values in good yields, unfortunately they are prepared from very expensive chiral starting materials.

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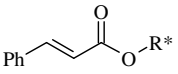
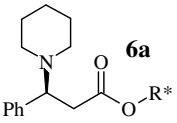
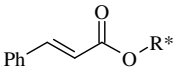
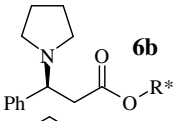
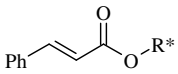
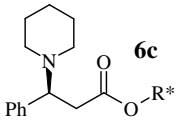
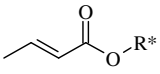
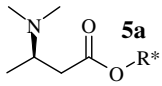
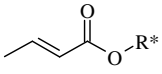
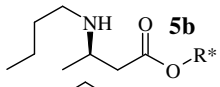
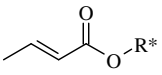
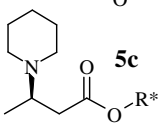
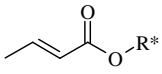
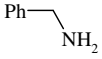
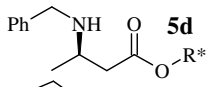
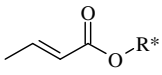
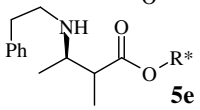
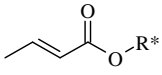
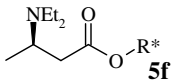
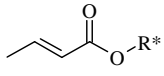
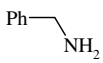
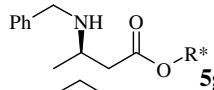
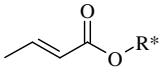
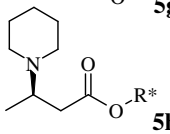
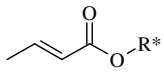
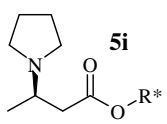
EXPERIMENTAL

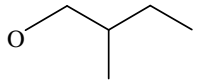
General Procedure for the 1,4-Conjugate Addition of Amines to α,β-Unsaturated Esters

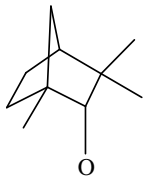
An amine (1.5 mmol) was added to a mixture of solid anhydrous $LiClO_4$ (0.1 g, 1 mmol) and chiral ester (0.5 mmol) and was stirred in a test tube fitted with a rubber septum at room temperature for the time indicated in Table 1. The

Table 1. 1,4-Conjugate Addition of Secondary and Primary Amine to α,β-Unsaturated Chiral Esters

Entry	Chiral Ester	R*	Amine	Product	Dias. ratio[a]	yield (%)	Time (h)
1		A		 **6a**	89 : 11	92	5
2		B		 **6b**	62 : 38	87	5
3		B		 **6c**	60 : 40	85	5
4		A	Me_3SiNMe_2	 **5a**	74 : 26	89	6
5		A	$n\text{-}BuNH_2$	 **5b**	79 : 21	87	5
6		A		 **5c**	91 : 9	93	3
7		A		 **5d**	89 : 11	84	5
8		A		 **5e**	90 : 10	81	4
9		A	Et_2NH	 **5f**	75.5 : 24.5	93	3
10		B		 **5g**	61 : 39	79	5
11		B		 **5h**	60.5 : 39.5	83	3
12		B		 **5i**	66 : 34	85	3

[a]Measured by ^{13}C NMR, with conversion yields > 98%.

A, OR* = 

B, OR* = 

reaction was monitored by TLC. After completion of the reaction, water (5 ml) was added and the organic materials were extracted with diethyl ether (2 × 5 ml). The combined organic layers were dried over anhydrous Na_2SO_4, and the solvent removed under reduced pressure. The crude product was purified by column chromatography on silica gel (ethyl acetate, petroleum ether, 10:90) if needed. The 1,4-adduct products were reduced with $LiAlH_4$ to give the corresponding β-amino alcohols. The β-amino alcohols were characterized on the basis of their spectroscopic data (^{1}H NMR, ^{13}C NMR or MS), and by comparison with those reported in the literature [33].

General Procedure for the 1,4-Conjugate Addition of Organolithium Compounds to α,β-Unsaturated Amides

Dry diethyl ether (1.5 ml) was added to anhydrous $LiClO_4$ (0.63 g, 6 mmol) in a test tube fitted with rubber septum and a stirring bar under argon in an ice-bath. The mixture was stirred until the lithium perchlorate had dissolved. Then chiral amide (0.5 mmol) was added and the mixture was stirred at 0 ^{o}C for 10 min. Then 1.5 mmol of an organolithium compound was added and the mixture was stirred at room temperature for 1 h. After completion of the reaction, water (5 ml) was added dropwise, and the organic materials were extracted with diethyl ether (2 × 5 ml). The combined organic layers dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. NMR spectra showed almost pure product with no starting material or any side products. All compounds were characterized on the basis of their spectroscopic data (^{1}H NMR, ^{13}C NMR), and by comparison with those reported in the literature.

Selected Spectroscopic Data

Chiral ester 3a. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.94 (m, 6H), 1.12 (m, 1H), 1.47 (m, 1H), 1.75 (m, 1H), 3.12 (d, J = 6.7 Hz, 3H), 3.91 (m, 1H), 3.98 (m, 1H), 5.28 (d, J = 14.7 Hz, 1H), 5.91 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.1, 16.3, 17.8, 25.7, 34.2, 68.4, 122.8, 144.2, 166.6; IR (KBr), 1708 cm^{-1}.

Chiral ester 4a. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.92 (m, 6H), 1.21 (m, 1H), 1.51 (m, 1H), 1.81 (m, 1H), 3.98 (m, 1H), 4.08 (m, 1H), 6.44 (d, J = 16.3 Hz, 1H), 7.42 (m, 5H), 7.70 (d, J = 16.3 Hz, 1H): ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.3, 16.7, 26.1, 34.3, 69.2, 118.3, 128.3, 128.7, 130.2, 134.5, 144.5, 167.1; IR (KBr), 1710 cm^{-1}.

Chiral amino ester 5d. ^{13}C NMR (100 MHz, $CDCl_3$) for major diastereomer: δ 11.2, 16.4, 20.7, 26.1, 34.1, 41.7, 46.2, 51.2, 68.8, 127.4, 128.1, 128.5, 140.3, 172.5.

Chiral amino ester 5f. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.81-1.00 (m, 15H), 1.14 (m, 1H), 1.41 (m, 1H), 1.68 (m, 1H), 1.88 (m, 1H), 2.18 (m, 1H), 2.41 (m, 4H), 3.31 (m, 1H), 3.89 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) for major diastereomer: δ 10.5, 13.6, 14.4, 15.7, 25.3, 33.5, 38.2, 42.7, 51.5, 68.1, 172.2.

Chiral amide 7a. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.55 (d, J = 6.8 Hz, 3H), 1.82 (d, J = 6.5 Hz, 3H), 5.19 (q, J = 6.8 Hz, 1H), 5.87 (d, J = 16.2 Hz, 1H), 6.85 (m, 1H), 7.38 (s, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.8, 21.7, 48.8, 124.8, 126.3, 127.4, 128.7, 140.5, 143.2, 165.3.

Chiral amide 7b. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.61 (d, J = 6.8 Hz, 3H), 5.32 (q, J = 6.8 Hz, 1H), 6.04 (bs, 1H), 6.42 (d, J = 16.3 Hz, 1H), 7.34 (m, 10H), 7.65 (d, J = 16.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.8, 48.9, 120.8, 126.3, 127.4, 127.8, 128.6, 128.7, 129.1, 134.9, 141.1, 143.2, 165.1.

Chiral amide 8a. ^{13}C NMR (100 MHz, $CDCl_3$) for major diastereomer: δ 14.5, 19.6, 21.7, 23.0, 29.1, 32.7, 36.7, 44.6, 48.5, 126.2, 127.2, 128.5143.4, 171.8.

Chiral amide 8d. ^{13}C NMR (100 MHz, $CDCl_3$) for major diastereomer: δ 21.8, 27.5, 32.7, 33.2, 45.8, 60.3, 125.2, 125.3, 125.5, 126.1, 128.8, 128.5, 140.3, 142.5, 172.1.

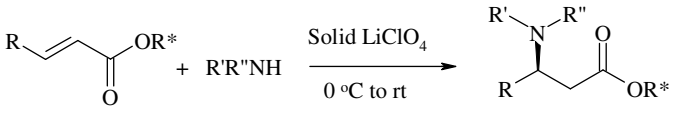
RESULTS AND DISCUSSION

Recently, $LiClO_4$ has emerged as a powerful promoter for various chemical processes. In this context it is worth noting that there is a remarkable tolerance of $LiClO_4$ reactions toward substrates having strongly coordinating functional groups [27-31]. We also reported that the conjugate addition of amines to α,β-unsaturated olefins under solvent-free conditions was accelerated by $LiClO_4$ [32].

We report here an enantioselective conjugate addition of amines to α,β-unsaturated esters, bearing the inexpensive chiral auxiliaries (*S*)-2-methyl-1-butanol and (1*R*)-endo-(+)-fenchyl alcohol, catalyzed by solid $LiClO_4$ [29,35].

The conjugate addition reaction of different primary and

secondary amines to chiral esters **3a**,**b** with (*S*)-2-methyl-1-butanol as the chiral auxiliary in the presence of solid $LiClO_4$ gave chiral adducts in high yields with diastereomeric ratios between 90/10 and 75/25 (Scheme 1). The results, summarized in Table 1, show that reaction of different aliphatic amines with ester **3** gave the corresponding chiral β-amino ester **5(a-f)** in high yield at room temperature without using any solvent. No side product was observed when using primary amines. The diastereomeric ratio was about 60/40 when the chiral auxiliary was (1*R*)-endo-(+)-fenchyl alcohol, which is lower than the diastereomeric ratio when (*S*)-2-methyl-1-butanol was used. Subsequently, we studied the conjugate addition reaction of different primary and secondary amines to chiral esters **4a**,**b** in the presence of solid $LiClO_4$. As is indicated in Table 1, only the cyclic secondary amines, pyrrolidine and piperidine, reacted with esters **4a**,**b** to give the corresponding amino ester **6**. No products were obtained by the reaction of other primary or secondary amines with **4a**,**b**.



3a [R* = (*S*)-2-Methyl-1-butanol; R = Me]

3b [R* = (1*R*)-*endo*-(+)-Fenchy alcohol; R = Me]

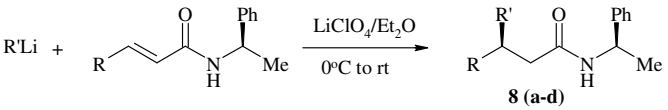
4a [R* = (*S*)-2-Methyl-1-butanol; R = Ph]

4b [R* = (1*R*)-*endo*-(+)-Fenchy alcohol; R = Ph]

5 (R = Me)

6 (R = Ph)

Scheme 1



7a, R = Me

7b, R = Ph

8 (a-d)

R	R'		Dist. Ratio[a]	Yields[b]
Me	n-BuLi	**8a**	89 : 11	92
Me	t-BuLi	**8b**	91 : 9	93
Ph	n-BuLi	**8c**	59 : 41	94
Ph	t-BuLi	**8d**	61 : 39	90

[a]Diastereomeric ratio were measured by ^{13}C NMR. [b]Isolated yields.

Scheme 2

Without using solid $LiClO_4$ the reactions did not take place.

The above results prompted us to extend this study and explore whether enantioselective conjugate addition takes place with organolithium reagents to amide **7a**,**b** bearing (*R*)-phenylethyl amine as an inexpensive chiral auxiliary under these conditions. Scheme 2 shows the conjugate addition of the organolithium reagents *n*-BuLi and *tert*-BuLi, to chiral amides **7a**,**b** mediated by $LiClO_4$ in diethyl ether (LPDE). Both *n*-BuLi and *tert*-BuLi react with **7a**,**b** in a very short time at 0 °C or room temperature with diastereomeric ratios between 91/9 and 59/41, resulting in complete 1,4-addition in excellent yields. Diastereomeric ratios were measured by ^{13}C NMR, and ^{1}H NMR of the crude products did not show any peaks corresponding to the starting materials.

Without using LPDE, the reaction of *n*-BuLi or *tert*-BuLi with **7a**,**b** gave a tarry material. The reactions of alkyllithiums with chiral amides **7a**,**b** in LPDE were very clean with high yields and no side products were formed. Aside from the stereoselectivity, which is mainly due to the chiral auxiliary, LPDE is a very good medium for the 1,4-conjugate addition of organolithium reagents to α,β-unsaturated amides without any 1,2-addition as a side product. It has been known that unsaturated amides prefer the s-*cis* conformation. By assuming a nucleophilic attack on the less hindered side, and by comparison of our results to the literature, we assigned the structure of the major diastereomers. The low diastereoselectivity could be a consequence of the presence of rotamers in comparable amounts [13,25].

In conclusion, solid $LiClO_4$ and a concentrated solution of LPDE are good media for the 1,4-conjugate addition of primary and secondary amines and organolithium reagents to α,β-unsaturated esters and amides, respectively. Our method for the enantioselective conjugate addition to chiral α,β-unsaturated esters and amides, bearing inexpensive chiral auxiliaries, proved to be very efficient with high yields.

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