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TETRAHEDRON: *ASYMMETRY*

A new protocol for the one-pot preparation of highly diastereomerically enriched secondary amines and β-amino esters mediated by lithium perchlorate solution in diethyl ether

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Abstract—A highly diastereoselective one-pot, three-component method for the preparation of several secondary amines and amino esters is reported. Treatment of aldehydes (aliphatic or aromatic) with chiral amines and functionalized organozinc reagents (e.g. $BrZnCH_2COOR$, allylzinc bromide) in the presence of trimethylsilylchloride with 5 M lithium perchlorate in diethyl ether produces *N*-alkylamino esters or *N*,*N*-dialkylamines in good yields and high diastereoselectivities. The diastereomeric ratios of the secondary amines prepared by this method were lower in comparison to those of the *N*-alkylamino esters formed in the same way.

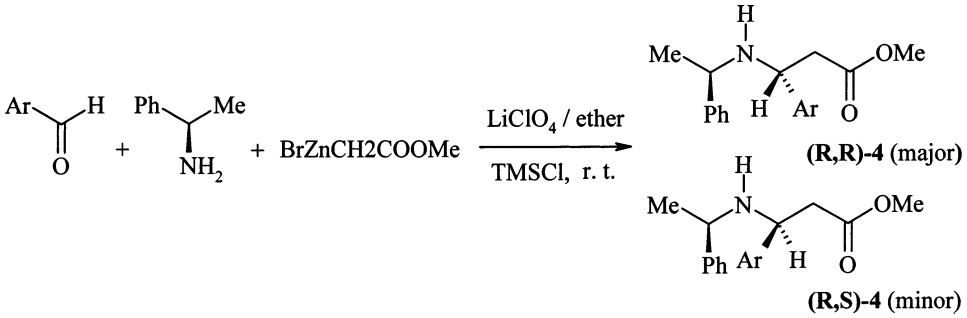
1. Introduction

β-Amino acids are components of naturally occurring and biologically active compounds and in some cases they show interesting pharmacological properties themselves.[1] β-Amino esters and secondary amines are also of great interest due to their wide use as plant growth regulators and plant growth promoters as well as their other chemical and pharmaceutical activities.[2] There are two excellent reviews for the synthesis of β-amino acids in diastereomerically enriched form and a number of procedures for the production of these compounds in racemic form.[3]

The Mannich reaction is one of the most important three-component processes in organic synthesis and biosynthesis.[4] Recently, we reported the Mannich-type aminoalkylation of aldehydes with chiral amines mediated by lithium perchlorate solution in diethyl ether. Herein, we describe an efficient and straightforward one-pot, three-component method for the preparation of several highly diastereomerically enriched secondary amino esters with chiral amines mediated by lithium perchlorate.[5] The diastereomeric excesses of the prepared secondary amines were lower in comparison to those of *N*-alkylamino esters formed using this method.

2. Results and discussion

The diastereoselective addition of organozinc regents to imines containing an enantiopure amine moiety remains



Scheme 1.

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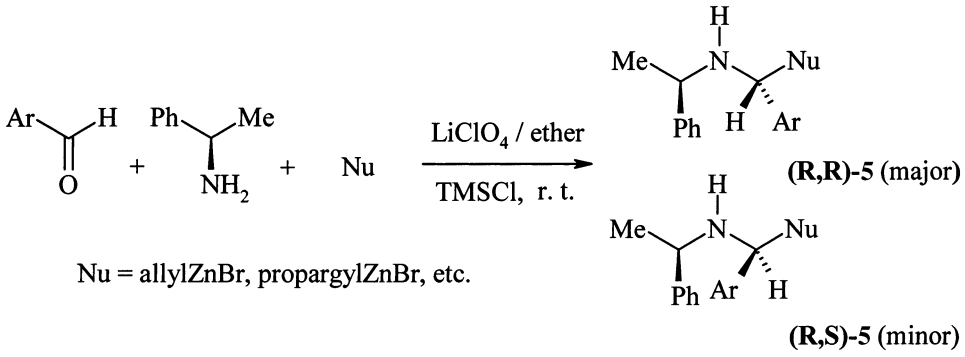
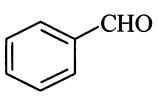
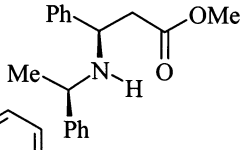
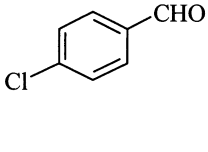
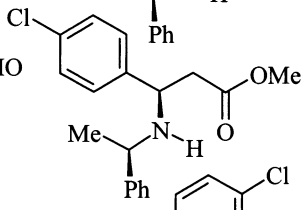
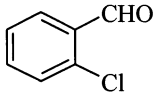
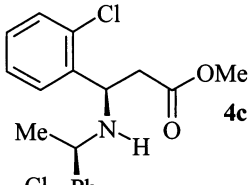
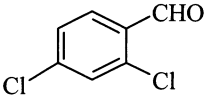
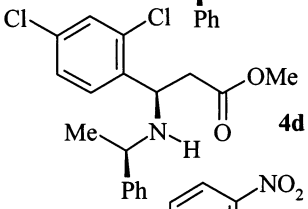
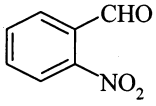
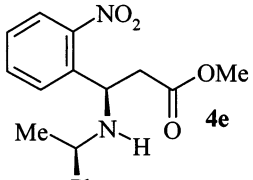
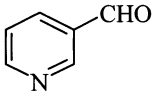
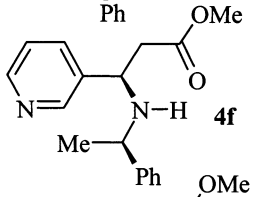
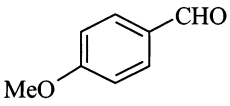
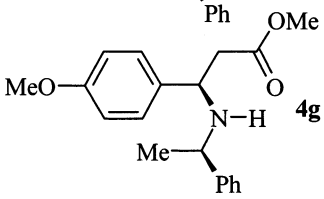


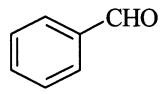
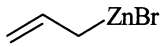
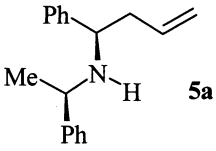
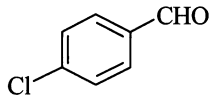
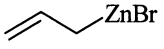
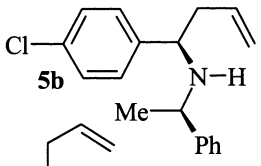
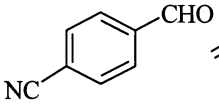
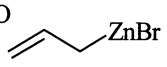
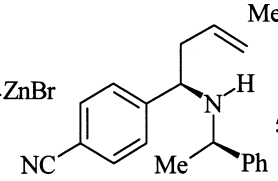
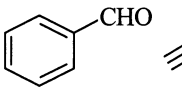
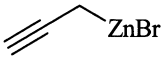
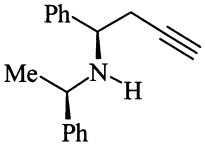
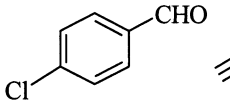
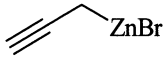
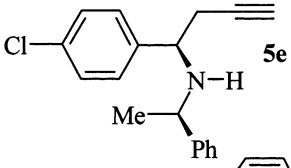
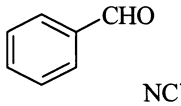
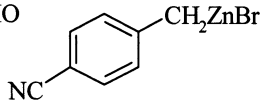
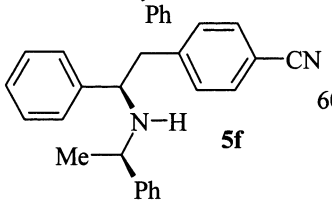
Scheme 2.

Table 1. Chiral amino esters obtained from the reaction of in situ pre-formed chiral imines with α-bromoalkylzinc ester

Aldehyde	Product		%Yield[a]	de, %
		**4a**	90	95
		**4b**	88	95
		**4c**	83	90
		**4d**	85	95
		**4e**	83	90
		**4f**	94	95
		**4g**	76	82

[a]isolated yields for the mixture of diastereoisomers.

Table 2. Chiral amines obtained from the reaction of in situ pre-formed chiral imines with alkylzinc bromide reagents

Aldehyde	RZnBr	Product	%Yield[a]	de %
		 **5a**	78	70
		 **5b**	76	65
		 **5c**	78	68
		 **5d**	70	60
		 **5e**	68	65
		 **5f**	60	70

[a]isolated yields for the mixture of diastereoisomers.

the focus of much research activity in recent years. In continuation of our research studies on Mannich type reactions, we now report the highly diastereoselective one-pot synthesis of several secondary amino esters and secondary amines from chiral imines, generated in situ in 5 M ethereal lithium perchlorate solution. Thus, in the concentrated ethereal lithium perchlorate solution, aldehyde **1** and enantiopure (*R*)-1-phenylethylamine **2**, readily accessible in both enantiopure forms, produce the chiral imine **3** as an intermediate at room temperature. Upon addition of α-bromoalkylzinc ester, $BrZnCH_2COOMe$, or a bromoalkylzinc reagent to the reaction mixture, the zinc alkoxide of chiral amino esters **4a–h** or chiral secondary amines **5a–f** were formed. Addition of water converts the intermediate zinc alkoxide to the corresponding products in moderate to high yields and with diastereoselectivities (dr) from 65 to >95% (Schemes 1 and 2).

As can be seen from Tables 1 and 2, the diastereoselectivity is generally higher for the reaction of α-bromoalkylzinc ester reagents with chiral imines (82–95%) than the reactions of alkylzinc bromides with chiral imines (65–70%). The yields of chiral amino esters **4** were also significantly higher than those obtained with secondary chiral amines **5**. Thus, by the addition of α-bromoalkylzinc esters or alkylzinc bromide reagents to a series of in situ pre-formed imines, chiral amino ester **4** and chiral secondary amines **5** were prepared. The results are summarized in Tables 1 and 2. The structures of the compounds have been unambiguously characterized on the basis of their IR, NMR (^1H, ^{13}C) and mass spectra. The ^1H and ^{13}C NMR spectra display the characteristic signals for protons and carbons of all the substituents.

In summary, a one-pot, three-component method for the preparation of chiral amino ester **4** and chiral secondary amines **5** has been achieved in good to moderate yields and with very high to moderate diastereoselectivity. The structures of all products were determined by comparison of the spectroscopic data those reported in the literature.

3. Experimental

3.1. General procedure for the diastereoselective synthesis of chiral amino esters 4 and 5

A mixture of benzaldehyde (2 mmol, 0.21 g) and 5 M $LiClO_4$ (4 mL) in diethyl ether were placed in a 50 mL flask under argon and stirred for 2 min at room temperature. (*R*)-(+)-1-Phenylethylamine (3 mmol, 0.36 g) and TMSCl (1 mmol) were added via syringe. After addition of TMSCl, a white solid was formed. At this time α-bromoalkylzinc ester or bromoalkylzinc (3 mmol), which were prepared in diethyl ether[5] was added. Following the progress of the reaction by TLC and ^1H NMR, the reaction mixture was stirred at room temperature for 2 h. Water (10 mL) and ethyl acetate (10 mL) were added. The organic phase was separated, dried over $MgSO_4$, and the solvent was removed using a rotary evaporator. The crude product was further purified by column chromatography on basic alumina eluting with petroleum ether/ethyl acetate. All compounds were characterized on the basis of spectroscopic data (IR, NMR, MS) by comparison with those reported in the literature.[10]

Caution: Although we did not have any accidents while using $LiClO_4$, it is advisable to dry lithium perchlorate in a fume hood using a suitable lab-shield.

Acknowledgements

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10. Selected spectroscopic data for the major diastereoisomers:
Compound 4a:[6b] IR (CH_2Cl_2), 3407 (NH), 1738 (CO) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.38 (d, $J=6.5$ Hz, 3H), 2.71 (m, 2H), 3.67 (m, 1H), 3.68 (s, 3H), 4.25 (m, 1H), 7.25–7.38 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.6 (CH_3), 42.8 (CH_2), 52.0 (CH), 55.1 (CH), 57.0 (CH_3), 127.0 (CH), 127.2 (CH), 127.8 (CH), 128.7 (CH), 129.1 (CH), 131.1 (CH), 131.0 (CH), 143.0 (C), 146.2 (C), 172.4 (CO); MS: 283 (M^+), 268 (78), 210 (60), 178 (21), 121 (56), 106 (100, base peak), 77 (21).
Compound 4b:[6b] IR (CH_2Cl_2), 3407 (NH), 1738 (CO) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.39 (d, $J=7$ Hz, 3H), 2.81 (m, 2H), 3.66 (m, 1H), 3.67 (s, 3H), 4.20 (m, 1H), 7.20–7.60 (m, 9H).
Compound 4c:[4a] IR (CH_2Cl_2), 3384 (NH), 1732 (CO) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.36 (d, $J=6.8$ Hz, 3H), 2.72 (m, 2H), 3.66 (s, 3H), 3.67 (m, 1H), 4.20 (m, 1H), 7.1–7.40 (m, 9H).
Compound 4d:[6b] IR (CH_2Cl_2), 3390 (NH), 1735 (CO) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.40 (d, $J=7.1$ Hz), 2.81 (m, 2H), 3.67 (s, 3H), 3.98 (m 1H), 4.18 (m, 1H), 7.12–7.92 (m, 8H).
Compound 4e:[4a] IR (CH_2Cl_2), 3386 (NH), 1738 (CO) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.39 (d, $J=6.9$ Hz), 2.68 (m, 2H), 3.64 (m, 1H), 3.67 (s, 3H), 4.20 (m, 1H), 7.12–7.98 (m, 8H).
Compound 4f:[4a] IR (CH_2Cl_2), 3246 (NH), 1740 (CO) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.36 (d, $J=7.0$ Hz, 3H), 2.72 (m, 2H), 3.67 (s, 3H), 3.91 (m, 1H), 4.30 (m, 1H), 7.30–8.40 (m, 9H).

Compound 4g:[7] IR (CH_2Cl_2), 3380 (NH), 1738 (CO) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.38 (d, $J=6.9$ Hz, 3H), 2.68 (m, 2H), 3.66 (s, 3H), 3.91 (m, 1H), 4.15 (m, 1H), 7.01–7.5 (m, 9H).

Compound 5a:[6b] IR (CH_2Cl_2) 3284 (NH) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.55 (d, $J=6.62$ Hz, 3H), 2.61 (m, 2H), 3.40 (m, 1H), 3.81 (m, 1H), 5.20 (m, 2H), 5.6 (m, 1H), 7.31–7.42 (m, 10H).

Compound 5b:[7] IR (CH_2Cl_2), 3300 (NH) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.36 (d, $J=6.5$ Hz, 3H), 2.46 (m, 2H), 2.71 (m, 2H), 3.61 (m, 1H), 3.78 (m, 1H), 5.07 (m, 2H), 5.75 (m, 1H), 7.19–7.36 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.0 (CH_3), 42.5 (CH_2), 55.3 (CH), 58.9 (CH), 118.1 (CH), 127.0 (CH), 127.5 (CH), 127.8 (CH), 128.8 (CH) 129.0 (CH_2), 132.1 (CH), 135.3 (C), 142.9 (C), 146.1 (C).

Compound 5c:[4a] IR (CH_2Cl_2), 3453 (NH), 2230 (CN) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.54 (d, $J=6.6$ Hz, 3H), 2.81 (m, 2H), 3.44 (m, 1H), 3.82 (m, 1H), 5.20 (m, 2H), 5.63 (m, 1H), 7.31–7.87 (m, 9H).

Compound 5d:[8] IR (CH_2Cl_2), 3340 (NH), cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.36 (d, $J=6.8$ Hz, 3H), 1.84 (m, 2H), 3.82 (q, $J=7.2$, 1H), 3.94 (m, 1H), 7.11–7.62 (m, 10H).

Compound 5e:[9] IR (CH_2Cl_2), 3380 (NH) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.35 (d, $J=6.9$ Hz, 3H), 1.90 (m, 2H), 3.78 (q, $J=7.2$, 1H), 3.96 (m, 1H), 7.12–7.88 (m, 9H).

Compound 5f:[8] IR (CH_2Cl_2), 3353 (NH), 2225 (CN) cm^{-1}; 1.32 (d, $J=9.8$ Hz), 2.41 (d, $J=6.4$ Hz, 2H), 3.74 (m, 2H), 3.95 (m, 1H), 7.10–7.89 (m, 14H).