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Diastereoselective addition of organozinc reagents to chiral α-imino esters

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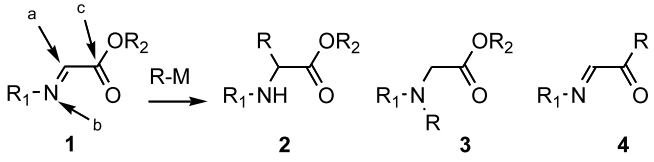
Abstract—The addition of organozinc reagents to chiral α-imino esters pre-complexed with zinc bromide, occurred with complete regioselectivity at the imino carbon. The influence of the solvent, temperature and different chiral auxiliaries was studied. The best diastereoselectivities were obtained in Et_2O or CH_2Cl_2 at 0°C, using phenylglycinol methyl ether as the chiral inductor.

1. Introduction

The reaction of α-imino esters **1** with organometallic reagents[1] is an interesting and potentially useful reaction for the synthesis of chiral, non-racemic amino acids and related compounds such as amino alcohols. Nevertheless, the selective formation of the carbon–carbon bond exclusively at the imino carbon has proved a major problem and several studies have demonstrated that the regioselectivity of this reaction is closely related to the nature of the organometallic species. Indeed, α-imino esters can behave as conjugated heterodienes and the nucleophile may attack three possible electrophilic centers via paths a, b, or c, leading respectively to α-amino ester **2**, the *N*-alkylated derivative **3** or the α-imino ketone **4** (Scheme 1). Kagan et al. reported that allyl- and *tert*-butylmagnesium halides and organocadmium reagents exclusively attack the imino carbon of **1** via path a, whereas simple Grignard reagents such as ethyl-, propyl-, benzyl- and *iso*-butyl magnesium halides react predominantly through path b.[2] It was demonstrated later by Yamamoto that the less basic but more reactive allylic boron and benzylzinc reagents react regioselectively with **1** at the expected imino carbon (path a).[3] Bertrand et al. reported recently that radical additions of alkyl halides to α-imino esters also proceed regioselectively at the imino carbon.[4] Diastereoselective syntheses of α-amino acid derivatives were realized using α-imino esters bearing a chiral auxiliary as the R_1 and/or the R_2 group of **1**. Enantioselective and catalytic additions of silyl enol ethers to glyoxylimines and enantioselective ene-reactions of α-imino esters have also been reported recently.[5]



Scheme 1.

Following on from our previous studies on the addition of *tert*-butyl organometallics to chiral 1,2-bisimines,[6] we decided to explore the same reaction on chiral α-imino esters. Herein, we wish to report our study concerning the influence of solvents, additives and chiral auxiliaries on the regio- and diastereoselectivity of the addition of organomagnesium and organozinc reagents to α-imino esters.

2. Results and discussion

2.1. Influence of the metal

We started our study with the reaction of **1a** with *tert*-butyl organometallics (Scheme 2) first used by Kagan and Fiaud.[7] The results are presented in Table 1. In a first attempt, we carried out the addition of

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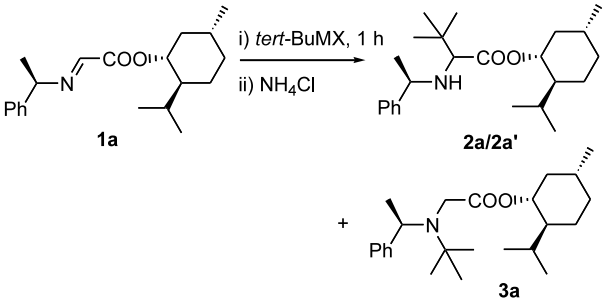
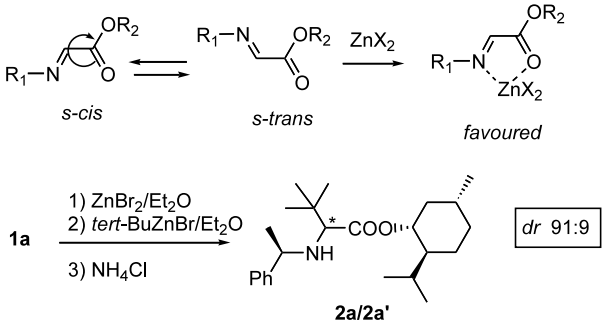


Scheme 2.



Scheme 3.

tert-butylmagnesium chloride at −78°C to a solution of **1a** in THF. Surprisingly, this reaction led to very poor regioselectivity since the *N*-alkylated adduct **3a** was obtained in 55% yield, with only 45% of the expected products **2a** and **2a′** (entry 1). However, the same reaction at 20°C gave a 91:09 ratio of **2**/**3a** (entry 2).[8] As previously reported by Yamamoto for the addition of benzyl organometallic reagents to imino esters, the zinc reagent seemed to be more appropriate in terms of regioselectivity. Indeed, the addition of *tert*-butylzinc bromide in THF led to the exclusive formation of **2a**/**2a′** (entry 3). Nevertheless, the best diastereoselectivity, in THF, was obtained with *tert*-BuMgCl (83:17) when a 71:29 ratio of the two diastereomers was obtained with the zinc reagent (entry 3). The 'mismatched' analog of **1a**, synthesized from (*S*)-(−)-1-phenylethylamine and (−)-menthyl glyoxylate gave a d.r. of 53:47 in the addition of *tert*-BuMgCl. Finally, the use of Et_2O as the solvent gave the best d.r. (80:20) with the zinc reagent (entry 5). The diastereoselectivity was slightly lower in hexane (entry 4). The regioselectivity was complete for the reactions using *tert*-BuZnBr in hexane or ether.

2.2. Influence of zinc salts

In order to increase the diasteroselectivity of the addition, we studied the influence of zinc salts as additives. We anticipated that complexation of the imino ester with a Lewis acid, prior to the addition of the organozinc reagent, should enhance the diastereoselectivity by forming a rigid cyclic precursor and also by displacing the possible equilibrium between the *s-cis* and *s-trans* forms of the imino ester in favor of the *s-cis*-form (Scheme 3).

Thus, we carried out the addition of 1.1 equiv. of $ZnBr_2$ (1 M in Et_2O) to a solution of **1a** in Et_2O at 20°C. The zinc complex immediately precipitated during the addition. After stirring for 0.5 h, *tert*-BuZnBr was added dropwise and the mixture stirred for 1 h. The result of this experiment (Scheme 3) confirmed the importance of this complexation since the diastereomeric ratio increased from 80:20 without Lewis acid to 91:9 in the presence of $ZnBr_2$. This first result was encouraging. Nevertheless, all our attempts to increase the diastereoselectivity, by changing the solvent (THF, hexane), the zinc salt ($ZnCl_2$) or the temperature (from –20 to +35°C) were unsuccessful. The best diastereoselectivity was obtained by performing the reaction at room temperature in Et_2O.

2.3. Influence of the chiral ester

The same reactions were carried out with imino esters **1b** and **1c**, derived respectively from ethyl- or isopropyl glyoxylate and (*R*)-(+)-1-phenylethylamine, to estimate the influence of the (−)-menthyl group on the diastereoselectivity (Scheme 4). These two substrates each gave a lower diastereoselectivity (close to 40%), showing the importance of the chiral ester group in **1a**.[9]

Scheme 4.

Table 1. Addition of *tert*-BuMX on imino ester **1a**

Entry	MX	*T* (°C)	Yield (%)	Solvent	**2**/**3a**[b]	**2a**/**2a′**[b]
1	MgCl	−78→20	99[a]	THF	45:55	75:25
2	MgCl	20	68 (98[a])	THF	91:09	83:17
3	ZnBr	20	52 (80[a])	THF	100:0	71:29
4	ZnBr	20	55 (88[a])	Hexane	100:0	76:24
5	ZnBr	20	64 (91[a])	Et_2O	**100:0**	**80:20**

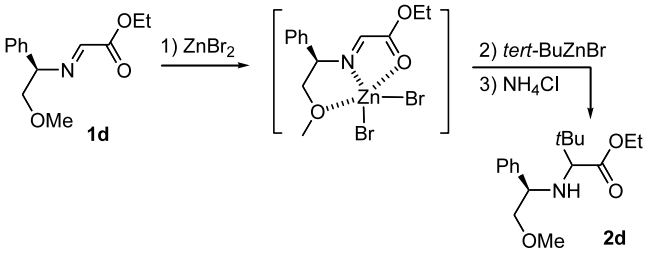
Typical procedure: To a solution of **1a** (1 mmol) in the appropriate solvent (15 ml) was added dropwise a solution of *tert*-BuMgCl (2 M in Et_2O; 1.5 equiv.) or *tert*-BuZnBr (0.5 M in THF; 1.5 equiv.). The mixture was stirred for 1 h at 20°C. The reaction was hydrolyzed with aqueous NH_4Cl satd (5 ml), extracted with ether, dried over $MgSO_4$ and concentrated. The crude was purified by silica gel chromatography (pentane/Et_2O, 95:5).

[a] Crude yield.

[b] Ratio determined by ^1H NMR (400 MHz). Compound **3a** was not separable from the minor diastereoisomer by chromatography on silica gel.

2.4. Influence of the chiral amine

High levels of diastereoselectivity are often obtained in the addition of organometallic compounds to chiral imines which have a heteroatom in the chiral auxiliary group attached to nitrogen, owing to the formation of rigid chelated intermediates.[10] Our focus, after obtaining the preliminary results described above, was to test the addition of *tert*-BuZnBr to **1d**, which has a chelating methoxy group (Scheme 5). Compound **1d** was synthesized as previously described[7] from (*R*)-phenylglycinol methyl ether[11] and ethyl glyoxylate. The results are presented in Table 2. First of all, comparison of the diastereoselectivities obtained with the similar imino esters **1b** and **1d** (Scheme 4 and Table 2, entry 2), clearly demonstrated the importance of the chelating methoxy group in **1d** since the d.r. significantly increased from 70:30 to 93:7. Performing the addition of *t*-BuZnBr at 0°C after complexation with $ZnBr_2$ at room temperature, gave the best yield of isolated product (68%, entry 3) with d.r. of >95:5. The use of two equivalents of $ZnBr_2$ did not change the outcome of the reaction significantly (entry 4). Diastereomeric ratio of >95:5 was also obtained in THF at 0°C (entry 6) and comparable results were observed in toluene (entry 7). This study showed that the conditions did not have a marked influence on this reaction although small variations were observed in the yields and diastereoselectivities.



Scheme 5.

Table 2. Addition of *tert*-BuZnBr to **1d**

Entry	Additive	Conditions	Yield (%)	d.r.[b]
1	–	Et_2O, +20°C	41 (83[a])	70:30
2	$ZnBr_2$	Et_2O, +20°C	58 (82[a])	93:7
3	$ZnBr_2$	Et_2O, 0°C	**68** (86[a])	96:4
4	2($ZnBr_2$)	Et_2O, +20°C	64 (82[a])	94:6 (96:4[c])
5	$ZnBr_2$	THF, +20°C	52 (80[a])	95:5
6	$ZnBr_2$	THF, 0°C	58 (83[a])	**97:3**
7	$ZnBr_2$	$PhCH_3$, +20°C	**68** (84[a])	94:6 (95:5[c])

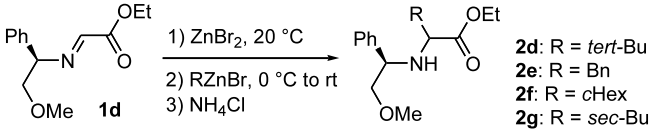
Typical procedure: To a solution of **1d** (1 mmol.; 235 mg) in the appropriate solvent (10 ml) was added dropwise at 20°C, a solution of $ZnBr_2$ 1 M in Et_2O (1.1 ml). The mixture was stirred for 30 min. at 20°C. The zinc reagent (0.5 M in THF, 1.5 equiv.) was added dropwise at the appropriate temperature (0 or 20°C). After the addition, the mixture was stirred for 1 h at 20°C. The reaction was hydrolyzed with NH_4Cl satd (5 ml), extracted with ether, dried on $MgSO_4$ and concentrated. The crude was purified by silica gel chromatography (pentane/Et_2O, 9:1).

[a] Crude yields.

[b] Ratio determined by ^1H NMR spectroscopy (400 MHz) Hα (C*H*-*tert*-Bu).

[c] Ratio determined on the purified compound.

The reaction was extended to other organozinc reagents using the same procedure (Scheme 6). The results are presented in Table 3. The reaction of benzylzinc bromide with **1d** for 1 h at 20°C, afforded in 58% isolated yield, the expected adduct **2e** with a d.r. of 93:7 (entry 2). The reactivity and the stereoselectivity in this case were similar to those obtained with *tert*-butylzinc bromide. The addition was slower using secondary zinc reagents such as cyclohexylzinc bromide (*c*HexZnBr) or *sec*-butylzinc bromide. Indeed, after 1 h at rt the cyclohexyl adduct **2f** was isolated in only 25% yield with a d.r. of 80:20 (entry 3). About 50% of **1d** was recovered at the end of the reaction. The use of CH_2Cl_2 as the solvent with a longer reaction time (5 h) gave a complete conversion and **2f** was then isolated in 58% yield with a better d.r. of 89:11 (entry 4). The same procedure was applied to the addition of *sec*-BuZnBr to give **2g** as a mixture of four diastereomers in a 50:40:5:5 ratio (entry 6).[12]



Scheme 6.

Table 3. Addition of RZnBr to **1d**

Entry	R	Conditions[a]	Yield (%)	d.r.[c]
1	*tert*-Bu	Et_2O, 1 h	68 (86[b])	96:4
2	Bn	Et_2O, 1 h	62 (91[b])	93:7 (90:10[d])
3	*c*Hex	Et_2O, 1 h	25 (72[b])	80:20 (87:13[d])
4	*c*Hex	CH_2Cl_2, 5 h	58 (93[b])	89:11 (88:12[d])
5	*sec*-Bu	Et_2O, 5 h	40 (68[b])	41:41:10:8
6	*sec*-Bu	CH_2Cl_2, 5 h	50 (72[b])	50:40:5:5

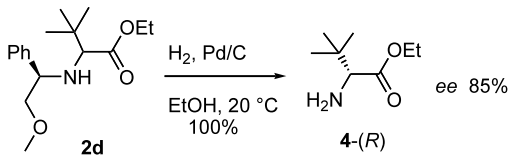
[a] The mixture was stirred for the indicated time at 20°C after addition of the zinc reagent dropwise at 0°C. The crudes were purified by silica gel chromatography (pentane/Et_2O, 9:1).

[b] Crude yields.

[c] Ratio determined by ^1H NMR spectroscopy (400 MHz) Hα (C*H*-R).

[d] Ratio determined after purification. The two diastereomers are separable on silica gel.

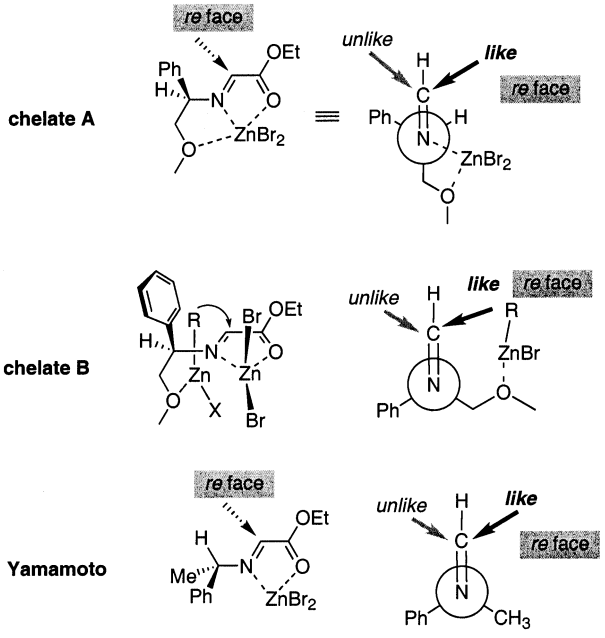
The absolute configuration at the α-carbon of **2d** (bearing the *tert*-butyl group) was determined by chemical correlation. Hydrogenolysis of **2d** in EtOH, in the presence of catalytic Pd/C led to ethyl 2-amino-3,3-dimethyl butanoate **4** in quantitative yield (Scheme 7). The *R* absolute configuration was assigned to this compound after establishment of its specific rotation value ($[\alpha]_D^{25} = -40.7$ (*c* 0.52, $CHCl_3$)) and comparison with the values reported in the literature.[13]



Scheme 7.

The stereochemical outcome of this reaction can be rationalized by two possible chelate models presented in Scheme 8, both of which lead to the (*R*)-adduct. In chelate **A**, $ZnBr_2$ is associated to the nitrogen atom of the imine and to two oxygens (from the methoxy group and the ester) forming two rigid five-membered rings and the zinc reagent adds to the less hindered *re* face. In chelate **B**, $ZnBr_2$ may form only one five-membered ring but, the delivery of the nucleophile could be assisted by the oxygen of the methoxy group, leading to preferential attack from the *re* face also.[10a] The increase in diastereoselectivity when using phenylglycinol derivatives instead of 1-phenylethylamine can be explained by comparing the chelate models and the model proposed by Yamamoto in the second case. Indeed, it is easily seen that in chelate **A**, the phenyl group of the chiral auxiliary is closer to the prochiral center to be attacked (the carbon of the imino group) than in Yamamoto's model. In chelate **B**, the major conformation of the imino ester could be similar to the one described by Yamamoto (same position of the phenyl group) but chelation of the methoxy group to the organozinc reagent should lead to almost exclusive delivery of the nucleophile from the *re* face.

In conclusion, we have developed a totally regioselective addition of organozinc reagents to α-imino esters pre-complexed with zinc bromide. High levels of diastereoselectivity were obtained using phenylglycinol methyl ether as the chiral auxiliary. This method allows the synthesis of various functionalized amino esters and this could be of interest for the preparation of the corresponding amino acids or amino alcohols such as *tert*-butylglycinol. The α-amino esters **2** are also potential ligands for asymmetric catalysis.



Scheme 8.

References

1. For reviews on the addition of organometallics to CN double bonds, see: (a) Enders, D.; Reinhold, U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895–1946; (b) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407–1438.
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7. Compound **1a** was prepared at 20°C from (−)-menthyl glyoxylate (1 mmol) and (*R*)-(+)-1-phenylethylamine (1 mmol) in CH_2Cl_2 (5 ml) in the presence of $MgSO_4$. Stirring for 1 h, filtration and concentration afforded the crude imino ester quantitatively, which was used without further purification. Compounds **1b–d** were obtained by the same procedure.
8. Kagan and Fiaud in 1971 (see Ref. 2b) reported a complete regioselectivity in this reaction.
9. Good stereoselectivities were obtained by Yamamoto with R_2=(−)-8-phenylmenthyl (see Ref. 3b).
10. (a) Spero, D. M.; Kapadia, S. R. *J. Org. Chem.* **1997**, *62*, 5537–5541; (b) Yamada, T.; Suzuki, H.; Mukaiyama, T. *Chem. Lett.* **1987**, *2*, 293–296.
11. (*R*)-Phenylglycinol was prepared by $LiAlH_4$ reduction of phenylglycine in refluxing THF. The methyl ether was synthesized according to: Hiroi, K.; Sato, S. *Chem. Pharm. Bull.* **1985**, *33*, 2331–2338. A modified representative procedure for this preparation is outlined as follows: To a solution of (*R*)-phenylglycinol (5 mmol) in CH_2Cl_2 (20 ml), were added benzaldehyde (560 μl, 5.5 mmol) and $MgSO_4$. The mixture was stirred for 2 h at 20°C, filtered through a pad of Celite and concentrated under vacuum at 20°C. The crude iminoalcohol was dissolved in dry THF (10 ml) and NaH (50% w/w dispersion in mineral

oil, 720 mg, 15 mmol) was added in portions. The suspension was stirred for 15 min at 20°C. The alkyl halide (7.5 mmol) was then added and the mixture heated at 40°C for 2 h. After cooling to 20°C, HCl 3N (10 ml) was slowly added followed by Et_2O (10 ml). The mixture was stirred vigorously for 3 h. The aqueous layer was separated and the organic layer was extracted with HCl 1N (2×10 ml). The combined aqueous layers were washed with pentane (3×10 ml) and solid NaOH was added slowly until pH 10. The aqueous layer was extracted with Et_2O (3×15 ml). The combined extracts were dried over K_2CO_3, filtered and concentrated at 20°C to give the aminoether in 85% yield. This procedure is applicable to hindered aminoalcohols such as norephedrine.

12. We supposed that in this case, the *syn*/*anti* selectivity was very low. This implied that the stereoselectivity must be 9:1 at the α-carbon.
13. Jaeger, D. A.; Broadhurst, M. D.; Cram, D. J. *J. Am. Chem. Soc.* **1979**, *101*, 717–732. (+)-(*S*)-Ethyl 2-amino-3,3-dimethyl butanoate $[\alpha]_D^{25} = +47.8$ (*c* 1, $CHCl_3$).