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Application of the addition of triorganozincates to *N*-(*tert*-butanesulfinyl)imines to the enantioselective synthesis of α-amino acids

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ABSTRACT

Highly enantiomerically enriched N-protected α-amino acids can be easily prepared from optically pure *N*-(*tert*-butanesulfinyl)imines by a four-step sequence involving: diastereoselective addition of a triorganozincate to the imine, removal of the sulfinyl group, benzoylation of the nitrogen atom of the obtained primary amine and oxidation of one of the substituents on the carbon atom α to the nitrogen. Using the same configuration in the sulfinyl chiral auxiliary, amino acids with the (*R*) or the (*S*) configuration can be prepared by choosing the proper combination of imine and organozincate. α,α-Disubstituted α-amino esters with high optical purity can also be prepared by the diastereoselective addition of trialkylzincates to α-imino esters.

The asymmetric synthesis of α-amino acids[1] is a research field that continues attracting numerous organic chemists due to the importance of these chiral building blocks for the construction of natural structures.[2] Besides their biological role as constituents of peptides and proteins, α-amino acids have found applications in the preparation of agrochemical and pharmaceutical compounds[2] and are commonly used as chiral auxiliaries and catalysts in a variety of synthetic methods.[3] Among the wide range of methods available for the synthesis of optically active α-amino acids, one can encounter several of them which rely on the stereoselective addition of carboxylate synthons to C=N bonds, such as the Strecker reaction or the Ugi condensation.[1a,b] Some alkenyl,[4] aryl[4c,5] and heteroaryl[4c,5c,6] groups can be considered as synthetic equivalents for the carboxylic acid, since they can be oxidatively cleaved to that function. The addition of such oxidizable groups to imines bearing a removable chiral auxiliary with the aid of organometallic reagents is the key step in several methods of preparation of α-amino acids found in the literature.[4c,d,g,6b] Another efficient approach is to introduce these groups as substituents of the imine substrates.[4b,5d,6a,d–f] We have recently reported the highly diastereoselective addition of triorganozincates to *N*-(*tert*-butanesulfinyl)imines,[7] which are very useful substrates for the preparation of chiral primary amines.[8] By using an excess of a previously formed triorganozincate, very good yields and diastereoselectivities were obtained in the addition products, which could be easily transformed into the corresponding enantiomerically enriched amines by desulfinylation of the nitrogen atom. We have developed a new version of this method that uses only a catalytic amount of a dialkylzinc to generate the organozincate.[9] Herein we present our preliminary results on the application of this methodology to the asymmetric synthesis of α-amino acids.

In our previous work, we found that the triorganozincate generated by mixing CH_2=CHMgBr (1.5 equiv) and Me_2Zn (1.7 equiv) added the vinyl group to benzaldimine **1a** (Scheme 1) in a highly diastereoselective manner.[7] This result prompted us to try to apply this addition methodology to the asymmetric synthesis of α-amino acids, since it was well known that the vinyl group could be oxidatively cleaved to the corresponding carboxylic acid.[4] Thus, the addition product **2a** was desulfinylated by reaction with a solution of HCl in methanol[10] and the obtained free primary amine was benzoylated[10] with the aim of facilitating the isolation of the final amino acid. Treatment of benzamide **3a** with $NaIO_4$ in the presence of a catalytic amount of $RuCl_3$ gave *N*-benzoyl (*S*)-phenylglycine with an 88% ee (Scheme 1, Table 1, entry 1). The same reaction sequence applied to imines **1b** and **1c** gave the expected protected amino acids **4b** and **4c** with enantioselectivities of up to 85% (Scheme 1, Table 1, entries 3 and 5). Since we have recently found that the generation of the triorganozincate using only a catalytic amount of Me_2Zn improves results in comparison with the use of an excess of that reagent,[9] we decided to test this addition procedure in our synthesis of amino acids. As it can be seen in Table 1, in all cases the enantioselectivities obtained in the final benzoylated amino acids are higher than the ones observed before (entries 2, 4 and 6). It is worth noting that, since $Me_2(CH_2$=CH)ZnMgBr and CH_2=CHMgBr have shown opposite diastereoselectivities in their addition to *N*-(*tert*-butanesulfinyl)benzaldimines,[7,11] either

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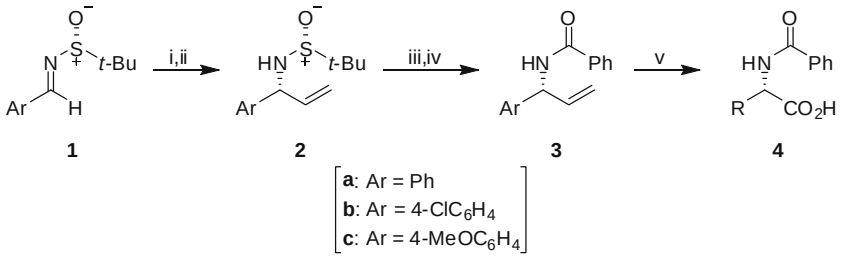


Scheme 1. Reagents and conditions: (i) Method A: CH_2=CHMgBr (1.5 equiv for **1a**–**b**, 2.25 equiv for **1c**), Me_2Zn (1.7 equiv for **1a**–**b**, 2.5 equiv for **1c**), THF, −78 °C; Method B: CH_2=CHMgBr (1.3 equiv), Me_2Zn (0.15 equiv), THF, −78 °C; (ii) NH_4Cl (aq); (iii) HCl, MeOH; (iv) PhCOCl (2.8 equiv), Et_3N (2.8 equiv), $CHCl_3$, 0–20 °C; (v) $RuCl_3{\cdot}xH_2O$ (1.2 mol %), $NaIO_4$ (4 equiv), MeCN:H_2O:CCl_4 (1:1.5:1), 20 °C.

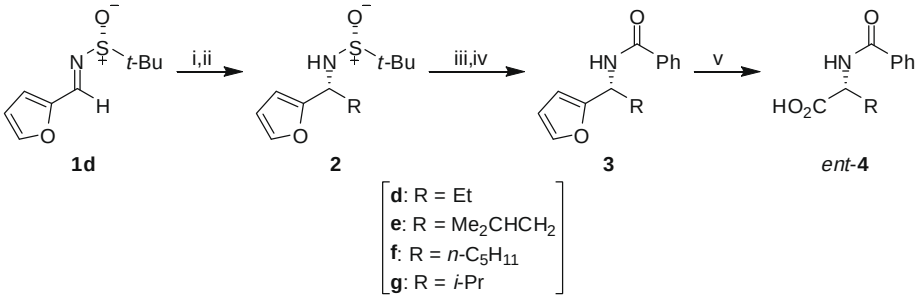
Table 1
Asymmetric synthesis of α-amino acids via the diastereoselective addition of triorganozincates to *N*-(*tert*-butanesulfinyl)imines

Entry	Imine	Method[a]	Sulfinamide			Benzamide		Amino acid			
			No.[b]	Yield[c] (%)	dr[d]	No.[e]	Yield[f] (%)	No.[e]	R	Yield[g] (%)	ee[h] (%)
1	**1a**	A	**2a**	93	95:5	**3a**	66	**4a**	Ph	95	88
2	**1a**	B	**2a**	94	98:2	**3a**	65	**4a**	Ph	94	94
3	**1b**	A	**2b**	82	88:12	**3b**	72	**4b**	4-ClC_6H_4	94	76
4	**1b**	B	**2b**	78	96:4	**3b**	64	**4b**	4-ClC_6H_4	89	92
5	**1c**	A	**2c**	92	93:7	**3c**	64	**4c**	4-$MeOC_6H_4$	99	85
6	**1c**	B	**2c**	90	94:6	**3c**	60	**4c**	4-$MeOC_6H_4$	96	86
7	**1d**	A	**2d**	99	94:6	**3d**	52	*ent*-**4d**	Et	75	86
8	**1d**	B	**2d**	91	97:3	**3d**	41	*ent*-**4d**	Et	75	92
9	**1d**	A	**2e**	83	80:20	**3e**	59	*ent*-**4e**	Me_2CHCH_2	98	58
10	**1d**	B	**2e**	79	98:2	**3e**	73	*ent*-**4e**	Me_2CHCH_2	98	96
11	**1d**	A	**2f**	90	93:7	**3f**	59	*ent*-**4f**	*n*-C_5H_{11}	77	86
12	**1d**	B	**2f**	98	96:4	**3f**	59	*ent*-**4f**	*n*-C_5H_{11}	77	92
13	**1d**	A	**2g**	92	94:6	**3g**	64	*ent*-**4g**	*i*-Pr	96	88
14	**5**	A	**6**	85	91:9	—	—	**7**	—	60[f]	82
15	**5**	A[i]	**6**	96	96:4	—	—	**7**	—	70[f]	92

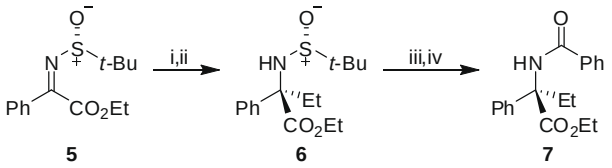
[a] Method A: The solution of the triorganozincate prepared by mixing the corresponding Grignard reagent and Me_2Zn (see Schemes 1–3) was added to a solution of the imine (0.5 mmol) in THF (3 mL) at −78 °C and the reaction mixture was stirred for 1 h at the same temperature (see Ref. 7b). Method B: The corresponding Grignard reagent (1.3 equiv) and Me_2Zn (0.15 equiv) were added to the imine in a stepwise procedure (see Ref. 9). The reaction time was 2 h at −78 °C.
[b] Product number corresponding to the major diastereoisomer.
[c] The crude reaction mixture only showed the mixture of diastereoisomers of the addition products **2** (300 MHz ^{1}H NMR) without any noticeable by-product. The yields are calculated according to the amount of crude mixture that was obtained after work-up.
[d] Diastereomeric ratio determined from the crude reaction mixture by HPLC using a ChiralCel OD-H column. The absolute configuration of the major diastereoisomer was deduced by removal of the *N*-sulfinyl group and comparison of the sign of the specific rotation of the free primary amines with the reported data.
[e] Product number corresponding to the major enantiomer.
[f] Overall isolated yield for the desulfinylation and the benzoylation steps based on sulfinamide **2** or **6**.
[g] Isolated yield after column chromatography (hexane/ethyl acetate/methanol) based on the benzoylated amine **3**. All isolated compounds were ⩾95% pure (GC and/or 300 MHz ^{1}H NMR).
[h] Determined for the corresponding methyl ester by HPLC using a ChiralCel OD-H column.
[i] The reaction was performed at −100 °C. The reaction time was 1 h.

enantiomer of the amino acid could be prepared by an appropriate selection of the nucleophile.

Since the oxidation of the furyl group to a carboxylic acid is also well documented in the literature,[4c,5c,6] we tried an alternative approach to amino acids with the (*R*) absolute configuration. The addition of primary and secondary alkyl groups to the heterocyclic imine **1d** (Scheme 2) through the corresponding alkyldimethylzincates gave the expected sulfinamides **2d**–**g** in high diastereomeric ratios (Table 1, entries 7–13). As it was the case with imines **1a**–**c**, in all cases the diastereoselectivities were higher with a catalytic generation of the organozincate (Table 1, entries 8, 10 and 12) than with an excess of it (Table 1, entries 7, 9, 11 and 13), the improvement observed in sulfinamide **2e** being especially remarkable (Table 1, entries 9 and 10). Sulfinamides **2d**–**g** were then converted



Scheme 2. Reagents and conditions: (i) Method A: RMgBr (1.5 equiv), Me_2Zn (1.7 equiv), THF, −78 °C. Method B: RMgBr (1.3 equiv), Me_2Zn (0.15 equiv), THF, −78 °C; (ii) NH_4Cl (aq); (iii) HCl, MeOH; (iv) PhCOCl (2.8 equiv), Et_3N (2.8 equiv), $CHCl_3$, 0–20 °C. (v) $RuCl_3{\cdot}xH_2O$ (5 mol %), $NaIO_4$ (6 equiv), MeCN:H_2O:CCl_4 (1.5:1.5:1), 20 °C.



Scheme 3. Reagents and conditions: (i) EtMgBr (2.25 equiv), Me_2Zn (2.5 equiv), THF, −78 or −100 °C; (ii) NH_4Cl (aq); (iii) HCl, MeOH; (iv) PhCOCl (2.8 equiv), Et_3N (2.8 equiv), $CHCl_3$, 0–20 °C.

into the corresponding primary amines, which were benzoylated and submitted to oxidation with $NaIO_4$ catalyzed by $RuCl_3$, leading to the expected *N*-benzoyl (*R*)-amino acids *ent*-**4d–g** with ee values of up to 96% (Table 1, entries 7–13). Our methodology is complementary to other reported approaches to α-amino acids involving the stereoselective addition of organolithium[6a] or dialkylzinc[6e] reagents to imines derived from furfural, since we obtain the opposite enantiomer of the final amino acid.

In all cases, the two diastereoisomers of sulfinamides **2** were the only products that could be detected in the crude reaction mixtures after the addition of the triorganozincates to imines **1**. Therefore, they could be submitted to the desulfinylation procedure without further purification, affording the expected primary amines without any detectable racemization.[12] By comparison of the sign of their specific rotations with the data reported in the literature, the absolute configuration of the asymmetric carbon atoms of the major diastereoisomers of **2** could be determined. The oxidation of benzamides **3** was performed following the literature procedures.[13] The enantiomeric excesses of the N-protected amino acids **4** and *ent*-**4** were determined for their corresponding methyl esters[14] by HPLC analysis using a ChiralCel OD-H column. As can be seen in Table 1, in some cases there is a very slight loss of optical purity (2% maximum) during the whole process from the imines to the amino acids: the ee values of the final amino acids match very well with the diastereomeric ratios of the corresponding sulfinamides **2**.

In an attempt to prepare α-amino acids with a quaternary stereogenic centre, the addition of $EtMe_2ZnMgBr$ to the imino ester **5** (Scheme 3) was performed at −78 °C and the addition product **6** was obtained with a 91:9 diastereomeric ratio. Desulfinylation followed by benzoylation afforded the protected amino ester **7** with an 82% ee (Table 1, entry 14). We were glad to see that the diastereoselectivity of the addition reaction improved to 96:4 when it was carried out at −100 °C, which led to the final amino ester with a 92% ee (Table 1, entry 15). An interesting point to remark is that a reversal of the diastereoselectivity was observed when EtMgBr was added to **5** instead of the trialkylzincate (15:85 diastereomeric ratio at −78 °C).[7b] Thus, both enantiomers of the final amino ester could be prepared from the same imine substrate just by changing the nucleophilic reagent.

In conclusion, the addition of triorganozincates to *N*-(*tert*-butanesulfinyl)imines can be used as a key step in an asymmetric synthesis of α-amino acids and derivatives. The absolute configuration of the final amino acid can be controlled by an appropriate choice of the way in which the synthetic equivalent of the carboxy group is introduced. The methodology is applicable to the synthesis of α,α-disubstituted α-amino acids with high optical purity by using α-imino esters as substrates. Further efforts to extend the substrate scope and to find more synthetic applications of this addition methodology are currently underway in our laboratories.

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