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Synthesis of highly enantiomerically enriched amines by the diastereoselective addition of triorganozincates to *N*-(*tert*-butanesulfinyl)imines

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This paper is dedicated to Professor Ernesto Carmona on the occasion of his 60th anniversary

ABSTRACT

The reaction of triorganozincates with (*R*)-*N*-(*tert*-butanesulfinyl)imines gives the expected α-branched sulfinamides in good to excellent yields with diastereomeric ratios of up to 98:2. The *N*-sulfinyl group of the products can be easily removed by acidic treatment, affording the corresponding chiral primary amines in enantiomeric excesses of up to 96%. The reactivity and the selectivity shown by the triorganozincates are different from the ones observed with the corresponding Grignard reagents, which allows, in several cases, the preparation of both enantiomers of an amine from the same imine substrate. When mixed triorganozincates are used, one can take advantage of the slow transfer rate of the methyl group to use it as a non-transferable one. Both aromatic and aliphatic aldimines, as well as activated ketimines, are good substrates for these addition reactions.

1. Introduction

The asymmetric preparation of chiral amines has been a subject of great interest over the last few years due to the fact that the amine functionality is present in many pharmaceuticals, natural products and biologically active compounds.[1] Optically active amines are also extensively used as resolving agents[2] and chiral auxiliaries in asymmetric synthesis.[3] A valuable method for the synthesis of amines is the addition of organometallic reagents to imines.[4] The asymmetric version of this reaction is very convenient,[5] and the diastereoselective addition of carbon nucleophiles to imines bearing removable chiral auxiliaries connected to the nitrogen atom represents an attractive approach for the preparation of α-branched chiral primary amines.[4c,5a] One of these chiral auxiliaries, which has turned out to be very efficient, is the sulfinyl group. Enantiomerically pure *N*-sulfinylimines have shown to be versatile substrates for asymmetric synthesis,[6] especially for the preparation of chiral primary amines.[6b,c,f] The chiral and electron-withdrawing sulfinyl group plays a dual role as an activating and a stereodirecting group. The addition of Grignard and organolithium reagents to the C=N bond takes place in a diastereoselective manner[6] and provides sulfinamides that can be readily converted into primary amines by desulfinylation of the nitrogen atom by simple acidic treatment.[7] However, the high basicity of these organometallic reagents can be a problem when the substrate is an enolisable imine and their high reactivity makes them incompatible with other functional groups in either the imine or the nucleophile. In contrast to these groups, organozinc reagents[8] tolerate several functional groups and can lead to polyfunctionalised organic compounds by reaction with electrophiles. However, the reactivity of the most common organozinc reagents, dialkylzincs and alkylzinc halides, is quite limited.[9] Triorganozincates[8d,10] have emerged as very useful zinc reagents since they are generally more reactive than organozinc halides and diorganozincs. They have been involved in reactions such as additions to aldehydes and ketones,[11] conjugate additions to α,β-unsaturated ketones,[8d,9b] cross-couplings,[12] nucleophilic substitutions[12b,13] and halogen-zinc exchanges with alkyl,[13,14] alkenyl[12a] and aryl halides.[13] However, to the best of our knowledge, there are only two reports on the addition of organozincates to imines derived from a phenethylamine, an α-aminoester or an O-protected β-aminoalcohol.[15] The participation of trialkylzincates in the zinc chloride catalysed addition of Grignard reagents to *N*-phenyl- and *N*-tosylimines has also been postulated.[11b] Continuing our research on the addition of organozinc reagents to imines,[16] we herein report our results on the diastereoselective addition of triorganozincates to *N*-(*tert*-butanesulfinyl)imines[17] and the application to the synthesis of highly enantiomerically enriched amines.

2. Results and discussion

We were interested in the addition of organozinc reagents to *N*-sulfinylimines. First, we attempted the reaction between Et_2Zn and (*R*)-*N*-(*tert*-butanesulfinyl)benzaldimine **1a** (Scheme 1), but no reaction was observed after stirring for several hours at room temperature. As a result, we decided to change to more reactive

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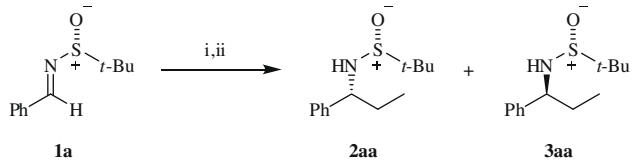
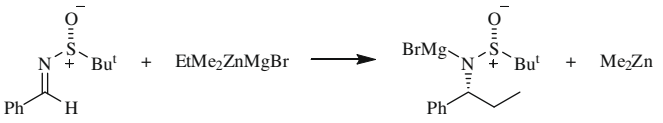


Scheme 1. Reagents and conditions: (i) R^2MgBr, R^3_2Zn, solvent, *T*; (ii) NH_4Cl (aq).

organozinc reagents, such as the triorganozincates. Since trialkylzincates can be prepared by the reaction of dialkylzincs with Grignard reagents,[8d,18] we added MeMgBr (1 equiv) to a solution of Et_2Zn and imine **1a** (1 equiv each) in THF at 0 °C and obtained a very promising 93:7 ratio of diastereomeric products **2aa** and **3aa** (Scheme 1); however, the yield was very low after stirring for 5 h (Table 1, entry 1). We then tried to mix the organometallic reagents before adding them to the imine. Thus, MeMgBr and Et_2Zn (1 equiv each) were stirred for 15 min at room temperature and the resulting solution of the mixed trialkylzincate was transferred to a solution of imine **1a** at 0 °C. The reaction was complete after only 1 h and the expected addition products **2aa** and **3aa** were obtained in 91% yield with a diastereomeric ratio of 86:14, respectively (Table 1, entry 2). Encouraged by this result, we tried to optimise the reaction conditions. We were pleased to see that the diastereomeric ratio increased when the temperature was lowered (Table 1, entries 2–5), reaching a 98:2 value at −78 °C, although the yield was only 66% (Table 1, entry 5). In order to try and improve the yield, the latter reaction was repeated while increasing the amounts of MeMgBr (1.5 equiv) and Et_2Zn (1.7 equiv). These conditions afforded product **2aa** in quantitative yield and with a 97:3 diastereomeric ratio (Table 1, entry 6). A further decrease in the temperature was detrimental for both the yield and diastereoselectivity (Table 1, entry 7).

Two interesting features of this reaction could be extracted from all these experiments: (a) only the ethyl group added to the imine, the corresponding methylation product could not be detected in the crude mixture; (b) despite the presence of two ethyl groups in the mixed trialkylzincate, only one of them was transferred. These observations made us think about interchanging the alkyl groups on the organometallic reagents utilised to prepare the zincate. The use of Me_2Zn and EtMgBr could allow us to completely transfer the ethyl group of the Grignard reagent, which would be very convenient in the case of using more sophisticated R^2 groups. In this way, the methyl group would act as a non-transferable group.[19] Thus, a mixture of EtMgBr (1.5 equiv) and Me_2Zn (1.7 equiv) was added to a solution of imine **1a** in THF at −78 °C and, after 1 h, an 85% yield of the addition products was obtained with a **2aa**:**3aa** ratio of 98:2 (Table 1, entry 8). In order to prove that the Grignard reagent itself was not the actual nucleophile, the latter reaction was repeated in the absence of Me_2Zn, which gave a lower diastereoselectivity (Table 1, entry 9). The effect of the solvent was also studied. The reactions in CH_2Cl_2 and toluene were much slower than the reactions in THF: after stirring for 12 h, the addition products were obtained in low yields and with a diastereoselectivity of 88:12 in both solvents (Table 1, entries 10 and 11).

We assumed that Me_2Zn was regenerated after the transfer of the ethyl group from the mixed trialkylzincate to the imine, according to Eq. 1. For this reason, we decided to try the reaction using a substoichiometric amount of Me_2Zn, with the hope that the regenerated Me_2Zn would react with another molecule of EtMgBr, regenerating in this way the trialkylzincate and closing a possible catalytic cycle. Unfortunately, when EtMgBr (1.5 equiv) was added dropwise to a solution of Me_2Zn (0.5 equiv) and imine **1a** in THF at −78 °C, only a 47% yield of the addition products was obtained after stirring for 12 h, although the diastereoselectivity was as high as 94:6 (Table 1, entry 12). At the moment, we do not have a good explanation for this slow reaction rate.



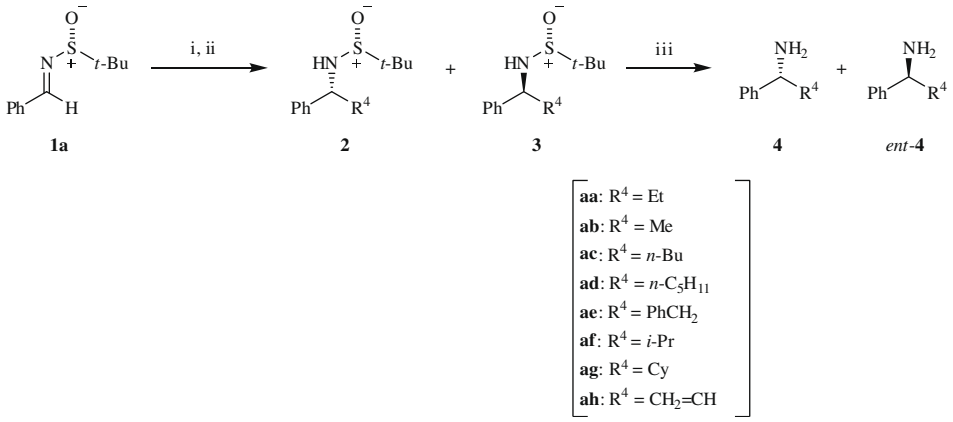
(1)

Having established the optimum reaction conditions, we then tested the transfer of other alkyl groups to imine **1a** (Scheme 2 and Table 2). The transfer of the methyl group was attempted by using trimethylzincate as the nucleophile. Imine **1a** was treated with a mixture of MeMgBr (1.5 equiv) and Me_2Zn (1.7 equiv) at −78 °C. After stirring for 12 h at the same temperature, only 13%

Table 1
Diastereoselective addition of triorganozincates to *N*-(*tert*-butanesulfinyl)benzaldimine **1a**[a]: Optimisation of the reaction conditions.

Entry	R^2MgBr		R^3_2Zn		Solvent	*T* (°C)	Time (h)	Product		
	R^2	Equiv	R^3	Equiv				No.[b]	Yield[c] (%)	**2**:**3** ratio[d]
1[e]	Me	1	Et	1	THF	0	5	**2aa**	22[f]	93:7
2	Me	1	Et	1	THF	0	1	**2aa**	91	86:14
3	Me	1	Et	1	THF	−30	1	**2aa**	83	91:9
4	Me	1	Et	1	THF	−50	1	**2aa**	94	95:5
5	Me	1	Et	1	THF	−78	1	**2aa**	66[f]	98:2
6	Me	1.5	Et	1.7	THF	−78	1	**2aa**	99	97:3
7	Me	1.5	Et	1.7	THF	−100	1	**2aa**	56[f]	87:13
8	Et	1.5	Me	1.7	THF	−78	1	**2aa**	85	98:2
9	Et	1.5	—	—	THF	−78	1	**2aa**	91	79:21
10	Et	1.5	Me	1.7	CH_2Cl_2	−78	12	**2aa**	43[f]	88:12
11	Et	1.5	Me	1.7	Toluene	−78	12	**2aa**	37[f]	88:12
12	Et	1.5	Me	0.5	THF	−78	12	**2aa**	47[f]	94:6

[a] All reactions were performed by the dropwise addition of a mixture of dialkylzinc and the Grignard reagents over ca. 5 min to a stirred solution of imine **1a** (0.5 mmol) in anhydrous THF (3 mL) under argon at the indicated temperature.
[b] Product number corresponding to the major diastereoisomer.
[c] The crude reaction mixture only showed the mixture of diastereoisomers **2aa** + **3aa** (300 MHz ^1H NMR) without any noticeable by-product. The yields are calculated according to the amount of crude mixture that was obtained after work-up, and are based on the starting imine **1a**.
[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 by comparison of the sign of the specific rotation of the free primary amine with the reported data.
[e] The Grignard reagent was added over ca. 10 min to a stirred solution of imine **1a** (0.5 mmol) and Et_2Zn in anhydrous THF (3 mL) under argon at the temperature indicated.
[f] Yield estimated by ^1H NMR using diphenylmethane as an internal standard. The reaction was not complete.



Scheme 2. Reagents and conditions: (i) R^2MgBr, R^3_2Zn, THF, −78 °C; (ii) NH_4Cl (aq); (iii) HCl, MeOH.

Table 2
Diastereoselective addition of triorganozincates to *N*-(*tert*-butanesulfinyl)benzaldimine **1a**[a]: Preparation of amines **4**.

Entry	R^2MgBr		R^3_2Zn		Time (h)	Sulfinamides **2** + **3**			Amines **4** + *ent*-**4**		
	R^2	Equiv	R^3	Equiv		R^4	Yield[b] (%)	**2**:**3** ratio[c]	No.[d]	Yield[e] (%)	ee[f] (%)
1	Et	1.5	Me	1.7	1	Et	85	98:2	**4aa**	77	96
2	Et	1.5	—	—	1	Et	91	79:21	**4aa**	82	58
3	Me	1.5	Me	1.7	12	Me	13[g]	54:46	**4ab**	—[h]	—[h]
4	Me	1.5	*n*-Bu	1.7	1	*n*-Bu	94	94:6	**4ac**	68	88
5	Me[i]	1.5	*n*-Bu	1.7	1	*n*-Bu	99	96:4	**4ac**	72	92
6	*n*-Bu[j]	1.5	Me	1.7	1	*n*-Bu	98	94:6	**4ac**	70	88
7	*n*-Bu[j]	1.5	—	—	1	*n*-Bu	88	77:23	**4ac**	65	54
8	n-C_5H_{11}	1.5	Me	1.7	1	n-C_5H_{11}	92	96:4	**4ad**	70	92
9	n-C_5H_{11}	1.5	—	—	12	n-C_5H_{11}	70[g]	49:51	**4ad**	—[h]	—[h]
10	$PhCH_2$[k]	1.5	Me	1.7	1	$PhCH_2$	99	90:10	**4ae**	80	80
11	*i*-Pr	1.5	Me	1.7	3	*i*-Pr	81	94:6	**4af**	72	88
12	*i*-Pr	1.5	—	—	12	*i*-Pr	21[g]	60:40	**4af**	—[h]	—[h]
13	Me	1.5	*i*-Pr	1.7	1	*i*-Pr	99	92:8	**4af**	74	84
14	Cy[l]	1.5	Me	1.7	1	Cy	80	93:7	**4ag**	45	86
15	CH_2=CH	1.5	Me	1.7	1	CH_2=CH	93	95:5	**4ah**	75	90
16	CH_2=CH	1.5	—	—	12	CH_2=CH	28[g]	44:56	**4ah**	—[h]	—[h]

[a] All addition reactions were performed by the dropwise addition of the mixture of the dialkylzinc and the Grignard reagents over ca. 5 min to a stirred solution of imine **1a** (0.5 mmol) in anhydrous THF (3 mL) under argon at −78 °C and stirring was continued for the time indicated.
[b] The crude reaction mixture only showed a mixture of diastereoisomers **2** + **3** (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.
[c] The diastereomeric ratio was 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 by comparison of the sign of the specific rotation of the free primary amine with the reported data.
[d] Product number corresponding to the major enantiomer.
[e] Isolated yield of the free primary amine based on the starting imine **1a**. All isolated compounds were ⩾95% pure (GC and/or 300 MHz ^{1}H NMR).
[f] Determined for the *N*-benzoyl amine by HPLC using a ChiralCel OD-H column. The absolute configuration of the major enantiomer of the amine was (*R*).
[g] Yield estimated by ^{1}H NMR using diphenylmethane as an internal standard. The reaction was not complete.
[h] Not determined.
[i] MeLi was used instead of MeMgBr.
[j] *n*-BuLi was used instead of *n*-BuMgBr.
[k] $PhCH_2MgCl$ was used.
[l] CyMgCl was used.

of the expected addition product was obtained as a 54:46 mixture of diastereoisomers (Table 2, entry 3). This result shows the slow rate for the transfer of the methyl group and supports our idea of using this group as a non-transferable one. Thus, Me_2Zn was combined with several Grignard reagents and the generated triorganozincates were added to imine **1a**. In all cases, the R^2 group of the Grignard reagent was the only one that added to the imine, irrespective of its nature. Primary (Table 2, entries 1, 8 and 10) and secondary alkyls (Table 2, entries 11 and 14) and the vinyl group (Table 2, entry 15) were effectively transferred to imine **1a**, giving, after desulfinylation, the expected amines **4a** in good yields and with ee's ranging from 80% to 96%. With the aim of proving that the reactivities of the triorganozincate solutions and the corresponding Grignard reagents were different, the imine **1a** was treated with EtMgBr, n-$C_5H_{11}MgBr$, *i*-PrMgBr and CH_2=CHMgBr (1.5 equiv of each) in four separate experiments. Except in the case of EtMgBr, all reactions were very slow, and were not complete after stirring for 12 h at −78 °C. The yield was high only with Grignard reagents bearing a primary alkyl group and in all cases the **2**:**3** ratio was much lower than in the reactions with the corresponding organozincates (compare entry 1 with entry 2, entry 8 with entry 9, entry 11 with entry 12 and entry 15 with entry 16 in Table 2).

The addition of the *n*-butyl and the isopropyl groups by using the combination $(n\text{-Bu})_2Zn$ or $(i\text{-Pr})_2Zn$, respectively, and MeMgBr was also attempted, giving the expected sulfinamides in very good yields and with high diastereomeric ratios (Table 2, entries 4 and 13). It is interesting to note that when the two possible combina-

tions to prepare the mixed trialkylzincates were tested, namely, RMgBr + Me_2Zn or MeMgBr + R_2Zn (R being the desired group to be added), the diastereoselectivities were very similar in both cases and the yield was slightly higher in the latter combination (compare entry 6 with entry 8 in Table 1 or entry 11 with entry 13 in Table 2). The combination MeMgBr + R_2Zn could be very useful, especially when considering that the R_2Zn is more easily accessible than the RMgBr or when the R group of interest is functionalised, although at the expense of transferring only one R group.

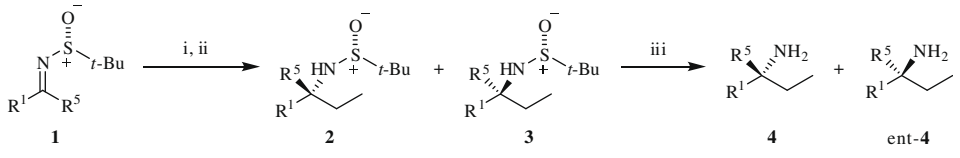
Organolithium compounds could be used instead of Grignard reagents as precursors of the trialkylzincates. The reactions proceeded with the same efficiency as with the Grignard reagents, while both yields and diastereoselectivities were very good (Table 2, entries 5 and 6). The change of magnesium to lithium as the countercation of the trialkylzincate only gave a slight improvement of the diastereoselectivity (compare entries 4 and 5 in Table 2). As was the case with the Grignard reagents, the reactivity of the triorganozincate generated by mixing an organolithium compound and Me_2Zn was different from the reactivity of the alkyllithium itself. For instance, the zincate prepared from *n*-BuLi and Me_2Zn gave a **2**:**3** ratio of 94:6 (Table 2, entry 6), much higher than the 77:23 ratio obtained with *n*-BuLi alone (Table 2, entry 7).

After the addition of the triorganozincates to the imine, the **2**:**3** ratios were determined in the crude reaction mixtures by HPLC using a ChiralCel OD-H column. In all the reactions that reached completion, the only products that could be detected in the crude reaction mixtures were the two diastereoisomers **2** and **3**, which were submitted to the desulfinylation procedure without further purification. The removal of the *N*-sulfinyl group was easily achieved by treatment of the crude reaction mixtures with HCl in MeOH, affording the expected primary amines. By comparison of the sign of their specific rotation with the data reported in the literature, the absolute configuration of the major enantiomer **4** or *ent*-**4** (Scheme 2) could be determined. The enantiomeric excesses of the free primary amines were determined by benzoylation of the nitrogen atom and by analysis of the obtained benzamides by HPLC using a ChiralCel OD-H column. Table 2 shows all the results obtained, including both the diastereoselectivities of the sulfinamides **2** + **3** and the enantioselectivities of the free amines **4**. As can be seen from Table 2, there was no loss of enantiomeric purity during the desulfinylation process: the ee values of the free amines match perfectly well with the corresponding **2**:**3** diastereomeric ratios.[20]

We also tried to add an aryl group to imine **1a**. *p*-Tolylmagnesium bromide (2.25 equiv) and Me_2Zn (2.5 equiv) were mixed and then added to the solution of the imine. It was necessary to use a higher excess of the nucleophilic mixture and to perform the reaction at room temperature in order to obtain a fast reaction. After 1 h, the expected sulfinamides were quantitatively formed in a 20:80 diastereomeric ratio, which was exactly the same as that obtained when the reaction was set up only with *p*-tolylmagnesium bromide. According to these results, it seems that the aryldimethylzincate did not form, and the Grignard reagent itself was the only one which gave the addition reaction.

Next, we decided to investigate the scope of this reaction by testing some other imine substrates **1b**–**i** (Scheme 3 and Table 3). All the imines **1** were prepared from the corresponding aldehydes or ketones according to literature procedures.[21] Et$Me_2ZnMgBr$[22] was used as the nucleophile in all the reactions, which were stirred for 1 h at −78 °C and then hydrolysed. The **2**:**3** ratio was determined in the crude reaction mixtures by HPLC using a ChiralCel OD-H column. These crude mixtures were submitted to the desulfinylation process, giving the expected primary amines without any detectable racemisation. The absolute configurations and the enantiomeric excesses of the amines **4** or *ent*-**4** (Scheme 3) were determined as indicated above. All the results are listed in Table 3. As can be seen, all imines **1a**–**c**, derived from aromatic aldehydes, gave the (*R*) amines **4aa**–**c** with very good ees regardless of the electronic nature of the substituents on the aromatic ring (Table 3, entries 1, 3 and 4). At this point, the influence of the substituent on the sulfur atom was studied by using *N*-(*p*-toluenesulfinyl)benzaldimine as a substrate, which led to amine **4aa** with only 24% ee (Table 3, entry 2). This result shows the importance of using the *tert*-butyl group on the sulfur atom of the imine in order to obtain high stereoselectivities. The heteroaromatic imine **1d** gave an 83% yield of the amine **4d** with an ee of 88% (Table 3, entry 5), which was much higher than the one obtained under the same reaction conditions but in the absence of Me_2Zn (40% ee).

The addition of Et$Me_2ZnMgBr$ to the aliphatic imines **1e**–**f** gave the expected mixtures of sulfinamides in good yields but with moderate 2:3 ratios. The (R_S,*S*)-diastereoisomer **3f** was the major product of the addition to imine **1f** (Table 3, entry 8). Unfortunately, all attempts to determine the absolute configuration of the major product of the addition to imine **1e** were unsuccessful. The absolute configuration of amine 4e was tentatively assigned according to the order of elution of the two benzoylated enantiomers in the HPLC analysis by analogy to compounds *N*-benzoyl **4f** and *N*-benzoyl *ent*-**4f**. It is interesting to note that the addition of EtMgBr to the same substrates gave the reverse diastereoselectivity (compare entry 6 with entry 7 and entry 8 with entry 9 in Table 3).[23] This could be very useful, since it would allow the preparation of both enantiomers of the final amine, **4** and *ent*-**4**, from a common imine substrate just by choosing the right nucleo-



a: R^1 = Ph, R^5 = H
b: R^1 = 4-ClC_6H_4, R^5 = H
c: R^1 = 4-$MeOC_6H_4$, R^5 = H
d: R^1 = 2-furyl, R^5 = H
e: R^1 = $Me(CH_2)_7$, R^5 = H
f: R^1 = $PhCH_2CH_2$, R^5 = H
g: R^1 = $MeO_2C(CH_2)_3$, R^5 = H
h: R^1 = Ph, R^5 = CO_2Et
i: R^1 = Ph, R^5 = CO_2*i*-Pr

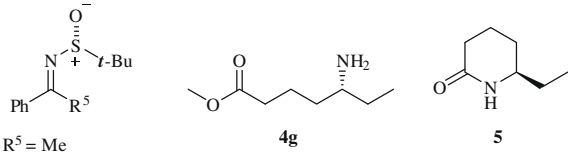
Scheme 3. Reagents and conditions: (i) EtMgBr, Me_2Zn, THF, −78 °C; (ii) NH_4Cl (aq); (iii) HCl, MeOH.

Table 3
Diastereoselective addition of $EtMe_2ZnMgBr$ to *N*-(*tert*-butanesulfinyl)imines **1**[a]: Preparation of amines **4**.

Entry	Imine	Equiv EtMgBr	Equiv Me_2Zn	Sulfinamides **2** + **3**		Amines **4** + *ent*-**4**			
				Yield[b] (%)	**2**:**3** ratio[c]	No.[d]	Yield[e] (%)	ee[f] (%)	Config.[g]
1	**1a**	1.5	1.7	85	98:2	**4aa**	77	96	(*R*)
2	**1a**[h]	1.5	1.7	96	62:38	**4aa**	80	24	(*R*)
3	**1b**	1.5	1.7	92	98:2	**4b**	72	96	(*R*)
4	**1c**	2.25	2.5	86	96:4	**4c**	67	92	(*R*)
5	**1d**	1.5	1.7	99	94:6	**4d**	83	88	(*R*)
6	**1e**	2.25	2.5	75	70:30	**4e**	70	40	(*R*)[i]
7	**1e**	2.25	—	77	32:68	*ent*-**4e**	61	36	(*S*)[i]
8	**1f**	2.25	2.5	81	29:71	*ent*-**4f**	60	42	(*S*)
9	**1f**	2.25	—	69	83:17	**4f**	64	66	(*R*)
10	**1g**	2.25	2.5	64	81:19	**5**	63	62	(*R*)
11	**1h**	2.25	2.5	87	91:9	**4h**	60	82	(*R*)
12	**1h**	2.25	—	79	15:85	*ent*-**4h**	60	70	(*S*)
13	**1i**	2.25	2.5	82	79:21	**4i**	65	58	(*R*)[j]
14	**1i**	2.25	—	78	21:79	*ent*-**4i**	66	58	(*S*)[j]

[a] All addition reactions were performed by the dropwise addition of the mixture of Me_2Zn and EtMgBr over ca. 5 min to a stirred solution of imine **1** (0.5 mmol) in anhydrous THF (3 mL) under argon at −78 °C, and stirring was continued for 1 h.
[b] The crude reaction mixture only showed the mixture of diastereoisomers **2** + **3** (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.
[c] The diastereomeric ratio was 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 by comparison of the sign of the specific rotation of the free primary amine with the reported data.
[d] Product number corresponding to the major enantiomer.
[e] Isolated yield of the free primary amine based on the starting imine **1**. All isolated compounds were ⩾95% pure (GC and/or 300 MHz ^{1}H NMR).
[f] Determined for the *N*-benzoyl amine by HPLC using a ChiralCel OD-H column.
[g] The absolute configuration of the major enantiomer was determined by comparison of the sign of the specific rotation of the free primary amine with the one reported in the literature.
[h] The *N*-(*p*-toluenesulfinyl)benzaldimine was used as a substrate instead of the *N*-(*tert*-butanesulfinyl)benzaldimine **1a**. The reaction was performed in toluene at room temperature for 1 h.
[i] The absolute configuration of the major enantiomer was tentatively assigned according to the order of elution of the two benzoylated enantiomers in the HPLC analysis by analogy to compounds *N*-benzoyl **4f** and *N*-benzoyl *ent*-**4f**.
[j] The absolute configuration of the major enantiomer was tentatively assigned according to the order of elution of the two benzoylated enantiomers in the HPLC analysis by analogy to compounds *N*-benzoyl 4**h** and *N*-benzoyl *ent*-**4h**.

philic reagent. Aliphatic imine **1g**, bearing an ester group, gave sulfinamides **2g** and **3g** in an 81:19 ratio (Table 3, entry 10). However, when this mixture was submitted to the desulfinylation process, the major product was lactam **5** instead of the expected amine **4g** (Fig. 1). The formation of product **5** can be explained by intramolecular nucleophilic substitution on the ester moiety of **4g** by the initially formed free amino group.



1j: R^5 = Me
1k: R^5 = *i*-Pr
1l: R^5 = 4-MeC_6H_4

4g **5**

Figure 1.

We also tested the reaction between $EtMe_2ZnMgBr$ and several *N*-(*tert*-butanesulfinyl)ketimines. Unfortunately, all attempts to perform the addition of the ethyl group to imines **1j** and **1k** (Fig. 1), derived from the corresponding phenones, were unsuccessful, and the starting material was recovered unchanged. The reaction between $EtMe_2ZnMgBr$ and imine **1l** (Fig. 1) gave an almost 1:1 mixture of the corresponding sulfinamides after stirring for 2 h at −78 °C. However, we were glad to see that the results improved when imines **1h** and **1i**, derived from the corresponding ketoesters, were used as substrates. The ethylation products were obtained in good yields and with 2:3 ratios of 91:9 and 79:21, respectively (Table 3, entries 11 and 13). Interestingly, as was the case with imines **1e** and **1f**, when the nucleophile was the Grignard reagent instead of the trialkylzincate, a reversal of the diastereoselectivity was observed, the 2:3 ratios were in this case 15:85 and 21:79, respectively (Table 3, entries 12 and 14). The products of the reaction between the nucleophile and the ester moieties of **1h** and **1i** were not detected.

As can be seen in Table 3, in order to obtain completion of the reactions in 1 h under the reaction conditions, a higher excess of the nucleophilic mixture (2.25 equiv of EtMgBr and 2.5 equiv of Me_2Zn) had to be used with the aromatic imine **1c** (bearing an electron-releasing group on the aromatic ring), with all the aliphatic imines **1e–g** and with the ketimines **1h–i** derived from ketoesters.

3. Conclusions

In conclusion, the reaction of triorganozincates with *N*-(*tert*-butanesulfinyl)imines is a very efficient procedure to effect the diastereoselective addition of alkyl and alkenyl groups to the imine carbon atom. Reactions are fast and provide the expected sulfinamide products in good yields and with very high diastereomeric ratios. Due to the low transfer ability of the methyl group, it can be used as a non-transferable group in mixed triorganozincates. Although the diastereoselectivities obtained with aliphatic aldimines and activated ketimines are lower, a very interesting reversal of the diastereoselectivity is observed when the reactions with the trialkylzincates and the corresponding Grignard reagents are compared. Since the *N*-sulfinyl group can be easily removed, this methodology represents a new and very efficient procedure for the asymmetric synthesis of primary amines. Further efforts to elucidate the mechanism of the reaction and to find synthetic

applications of this methodology are currently underway in our laboratories.

4. Experimental

4.1. General

For general experimental information, see Ref. 16a. When mentioned, an R_f value measured on deactivated silica gel means that the TLC plate was eluted with a mixture of 5% triethylamine in hexane and dried before applying the sample. All starting materials needed for the synthesis of imines **1** and the solutions of MeMgBr (3 M in Et_2O, Aldrich), EtMgBr (1 M in THF, Aldrich), *n*-BuLi (1.6 M in hexane, Chemetall), *n*-$C_5H_{11}MgBr$ (2 M in Et_2O, Aldrich), $PhCH_2MgCl$ (1 M in THF, Acros), *i*-PrMgBr (2 M in THF, Aldrich), CyMgCl (2 M in THF, Aldrich), CH_2=CHMgBr (1 M in THF, Aldrich), Me_2Zn (2 M in toluene, Aldrich), Et_2Zn (1.1 M in toluene, Aldrich), $(n\text{-}Bu)_2Zn$ (1 M in heptane, Fluka) and $(i\text{-}Pr)_2Zn$ (1 M in toluene, Aldrich) were commercially available and were used as received. Optical rotations were measured on a Perkin–Elmer 341 polarimeter. HPLC analyses were performed at 25 °C on a JASCO apparatus, equipped with a PU-2089 Plus pump, a MD-2010 Plus detector and an AS-2059 Plus automatic injector. The HRMS (EI) were performed by the Technical Services of the University of Alicante on a Finnigan MAT 95S apparatus.

4.2. Synthesis of imines 1

Imines **1** were prepared by reaction of the corresponding aldehydes or ketone with (*R*)-*tert*-butanesulfinamide, according to literature procedures.[21] Compounds **1a**,[21a] **1b**,[24] **1c**,[24] **1d**[25] and **1f**[26] were characterised by comparison of their physical and spectroscopic data with the ones reported in the literature. The corresponding physical, spectroscopic and analytical data for compounds **1e**, **1g**, **1h** and **1i** follow.

4.2.1. (*R*)-2-Methyl-*N*-nonylidenepropane-2-sulfinamide 1e

60% Yield; yellow oil; R_f 0.30 (hexane/ethyl acetate: 4:1); $[\alpha]_D^{20} = -207.0$ (*c* 0.4, $CHCl_3$); *v*(film) 1622 (C=N), 1088 cm^{-1} (SO); δ_H 0.88 (3H, t, *J* = 6.7 Hz, *Me*CH_2), 1.20 (9H, s, 3 × *Me*C), 1.23–1.43, 1.57–1.67, 2.48–2.55 (10H, 2H and 2H, respectively, 3m, 7 × CH_2), 8.07 (1H, t, *J* = 4.7 Hz, CHN); δ_C 14.1 (*Me*CH_2), 22.3 (3C, 3 × *Me*C), 22.6, 25.5, 29.1, 29.2, 29.3, 31.8, 36.1 (7 × CH_2), 56.5 (C), 169.8 (CHN); *m/z* 245 (M^+, 2%), 205 (12), 189 (15), 149 (17), 141 (11), 83 (10), 71 (12), 70 (14), 69 (16), 57 (100), 55 (18), 43 (40), 41 (27).

4.2.2. (*R*)-Methyl 5-[(*tert*-butylsulfinyl)imino]pentanoate 1g

78% Yield; colourless oil; R_f 0.12 (hexane/ethyl acetate: 1:1); $[\alpha]_D^{20} = -206.4$ (*c* 1.7, $CHCl_3$); *v*(film) 1737 (C=O), 1622 (C=N), 1163 (CO), 1081 cm^{-1} (SO); δ_H 1.20 (9H, s, 3 × MeC), 1.92–2.05, 2.40–2.44, 2.56–2.61 (2H each, 3m, 3 × CH_2), 3.69 (3H, s, MeO), 8.08 (1H, t, *J* = 4.1 Hz, CHN); δ_C 20.4 ($CH_2CH_2CH_2$), 22.2 (3C, 3 × *Me*C), 33.1 (CH_2CN), 35.1 (CH_2CO), 51.6 (MeO), 56.5 (CMe_3), 168.3 (CHN), 173.3 (C=O); *m/z* 233 (M^+, <1%), 177 (19), 146 (14), 145 (15), 129 (86), 57 (100), 56 (23), 55 (19), 41(27). HRMS: M^+ found 202.0937, $C_9H_{16}NSO_2$ requires 202.0902.

4.2.3. (*R*)-Ethyl [(*tert*-butylsulfinyl)imino](phenyl)acetate 1h

90% Yield; yellow oil; R_f 0.30 (hexane/ethyl acetate: 1:1); $[\alpha]_D^{20} = -95.8$ (*c* 0.9, $CHCl_3$); *v*(film) 3112, 3092, 3065, 1571 (HC=C), 1738 (C=O), 1601 (C=N), 1206 (CO), 1093 cm^{-1} (SO); δ_H 1.35 (9H, s, 3 × MeC), 1.41 (3H, t, *J* = 7.1 Hz, *Me*CH_2), 4.39–4.52 (1H, m, CH_2), 7.43–7.55, 7.76–7.78 (3H and 2H, respectively, 2m, ArH); δ_C 13.9 (*Me*CH_2), 23.0 (3C, 3 × *Me*C), 59.5 (CMe_3), 62.3 (CH_2), 127.8 (2C), 128.8 (2C), 132.6, 133.1 (ArC), 163.3 (C=N), 165.8 (C=O); *m/z* 281 (M^+, <1%), 225 (35), 179 (29), 152 (10), 151 (100), 105 (11), 104 (28), 103 (24), 57 (34), 41 (10). HRMS: M^+ found 224.0362, $C_{10}H_{10}NSO_3$ requires 224.0381.

4.2.4. (*R*)-Isopropyl [(*tert*-butylsulfinyl)imino](phenyl)-acetate 1i

92% Yield; yellow oil; R_f 0.30 (hexane/ethyl acetate: 1:1); $[\alpha]_D^{20} = -115.0$ (*c* 1.0, $CHCl_3$); *v*(film) 3083, 3065, 3022, 1572 (HC=C), 1732 (C=O), 1603 (C=N), 1210 (CO), 1097 cm^{-1} (SO); δ_H 1.34 (9H, s, 3 × MeC), 1.40, 1.42 (3H each, 2 d, *J* = 6.4 Hz each, 2 × *Me*CH), 5.36 (1H, heptet, *J* = 6.4 Hz, CHO), 7.41–7.57, 7.73–7.81 (3H and 2H, respectively, 2m, ArH); δ_C 21.6, 21.8 (2 × *Me*CH), 23.0 (3C, 3 × *Me*C), 59.4 (CMe_3), 70.5 (CHO), 127.8 (2C), 128.8 (2C), 132.5, 133.2 (ArC), 163.4 (C=N), 165.2 (C=O); *m/z* 295 (M^+, <1%), 239 (29), 197 (42), 179 (22), 152 (12), 151 (100), 118 (16), 105 (49), 104 (29), 103 (25), 77 (20), 57 (64), 43 (34), 41 (24). HRMS: M^+ found 236.0744, $C_{12}H_{14}NSO_2$ requires 236.0745.

4.3. Addition of triorganozincates to imines 1. Preparation of sulfinamides 2 and 3. General procedure

A solution of the Grignard reagent (0.75 mmol for imines **1a**, **1b** and **1d**; 1.1 mmol for imines **1c** and **1e–i**) was added to the solution of the dialkylzinc reagent (0.86 mmol for imines **1a**, **1b** and **1d**; 1.3 mmol for imines **1c** and **1e–i**) under argon at room temperature and the mixture stirred for 15 min. The resulting solution of the triorganozincate was then transferred dropwise via syringe over ca. 5 min to a solution of the sulfinylimine **1** (0.5 mmol) in anhydrous THF (3 mL) under argon at −78 °C, and the mixture was stirred for 1 h at the same temperature. The reaction was hydrolysed with an aqueous saturated solution of NH_4Cl (2 mL). Water (5 mL) was added and the mixture was extracted with diethyl ether (3 × 5 mL). The combined organic layers were washed with brine (5 mL) and then dried over Na_2SO_4. After filtration and evaporation of the solvents, the mixtures of *tert*-butanesulfinamides **2** and **3** were obtained in yields as shown in Tables 1–3. These mixtures were analysed by HPLC on a ChiralCel OD-H column using a 254 nm UV detector, 10% *i*-PrOH in hexane as eluent and a flow rate of 0.5 mL/min. The retention times were 8.7 (**2aa**), 10.8 (**3aa**), 9.5 (**2ab**), 14.4 (**3ab**), 6.5 (**2ac**), 9.2 (**3ac**), 7.9 (**2ad**), 9.7 (**3ad**), 11.0 (**2ae**), 12.8 (**3ae**), 7.8 (**2af**), 12.1 (**3af**), 10.6 (**2ag**), 16.9 (**3ag**), 9.5 (**2ah**), 11.1 (**3ah**), 9.0 (**2b**), 11.4 (**3b**), 10.9 (**2c**), 12.1 (**3c**), 9.8 (**2d**), 10.8 (**3d**), 10.8 (**2e**), 7.8 (**3e**), 13.9 (**2f**), 12.2 (**3f**), 11.5 (**2g**), 8.6 (**3g**), 12.9 (**2h**; ChiralCel AD column, 254 nm UV detector, 5% *i*-PrOH in hexane as eluent), 14.1 (**3h**; ChiralCel AD column, 254 nm UV detector, 5% *i*-PrOH in hexane as eluent), 8.4 (**2i**) and 10.6 (**3i**). The diastereomeric ratios are indicated in Tables 1–3. The absolute configuration of the asymmetric carbon atom of the major diastereoisomers was determined by treatment of the crude reaction mixtures with HCl in methanol and by comparison of the sign of the specific rotation of the obtained free amines with the reported data.

4.4. Desulfinylation of compounds 2 and 3. Isolation of amines 4. General procedure

The crude mixture of the addition reaction was dissolved in a 1.5 M solution of HCl in methanol (4 mL; prepared by dropwise addition of $SOCl_2$ to methanol at 0 °C) and stirred overnight at room temperature. Then, the solvent was evaporated, a 2 M aqueous HCl solution (5 mL) was added and the mixture was extracted with ethyl acetate (3 × 5 mL). The organic layers were discarded. The aqueous layer was basified with a buffer solution of NH_3 (1 M)/NH_4Cl (1 M) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried over Na_2SO_4. After filtration

and evaporation of the solvent, pure amines **4** were obtained in the yields indicated in Tables 2 and 3. Amine **4aa**, commercially available, was characterised by comparison with an authentic sample. Amines **4ac**,[27] **4ad**,[28] **4ae**,[27] **4ah**,[29] and **4d**[30] were characterised by comparison of their physical and spectroscopic data with the ones reported in the literature. The corresponding physical, spectroscopic and analytical data for the other amines **4** and lactam **5** follow.

4.4.1. (*R*)-2-Methyl-1-phenylpropan-1-amine 4af[31]

Colourless oil; R_f 0.14 (ethyl acetate, deactivated silica gel); $[\alpha]_D^{20} = +6.4$ (*c* 0.6, $CHCl_3$, 88% ee); *ν*(film) 3305 (NH), 3085, 3061, 3027, 1602, 1492 (HC=C), 1121 cm^{-1} (CN); δ_H 0.77, 0.98 (3H each, 2d, *J* = 6.7 Hz each, 2 × Me), 1.60 (2H, br s, NH_2), 1.80–1.91 (1H, m, C*H*Me), 3.60 (1H, d, *J* = 7.3 Hz, CHN), 7.20–7.35 (5H, m, ArH); δ_C 18.9, 19.8 (2 × Me), 35.4 (*C*HMe), 62.4 (CN), 126.7, 127.0 (2C), 128.1 (2C), 145.4 (ArC); *m/z* 149 (M^+, <1%), 106 (100), 79 (15).

4.4.2. (*R*)-Cyclohexyl(phenyl)methanamine 4ag[32]

White solid; R_f 0.15 (ethyl acetate, deactivated silica gel); mp 97 °C; $[\alpha]_D^{20} = +9.3$ (*c* 1.0, EtOH, 86% ee); *ν*(film) 3379 (NH), 3091, 3058, 3018, 1602, 1449 (HC=C), 1262 cm^{-1} (CN); δ_H 0.85–1.29, 1.40–1.80 (5H and 7H, respectively, 2m, 5 × CH_2 ring and NH_2), 1.97–2.04 (1H, m, *CH*CN), 3.59–3.64 (1H, m, CHN), 7.26–7.34 (5H, m, ArH); δ_C 26.2 (2C), 26.4, 29.5, 30.1 (5 × CH_2 ring), 45.2 (*C*HCN), 61.7 (CN), 126.7, 127.1 (2C), 128.1 (2C), 145.5 (ArC); *m/z* 189 (M^+, <1%), 106 (100), 104 (14), 79 (13), 77 (10).

4.4.3. (*R*)-1-(4-Chlorophenyl)propan-1-amine 4b[33]

Colourless oil; R_f 0.20 (ethyl acetate, deactivated silica gel); $[\alpha]_D^{20} = +15.0$ (*c* 1.2, $CHCl_3$, 96% ee); *ν*(film) 3365, 3307 (NH), 3089, 3052, 3021, 1594, 1491 (HC=C), 1091 cm^{-1} (CN); δ_H 0.85 (3H, t, *J* = 7.3 Hz, Me), 1.44–1.80 (4H, m, NH_2 and CH_2), 3.80 (1H, t, *J* = 6.7 Hz, CHN), 7.23–7.31 (4H, m, ArH); δ_C 10.8 (Me), 32.4 (CH_2), 57.1 (CN), 127.8 (2C), 128.4 (2C), 132.3, 144.8 (ArC); *m/z* 169 (M^+, <1%), 142 (32), 140 (100), 77 (14).

4.4.4. (*R*)-1-(4-Methoxyphenyl)propan-1-amine 4c[34]

Colourless oil; R_f 0.20 (ethyl acetate, deactivated silica gel); $[\alpha]_D^{20} = +15.0$ (*c* 1.0, EtOH, 92% ee); *ν*(film) 3335 (NH), 3072, 3032, 3005, 1584, 1513 (HC=C), 1248 cm^{-1} (CN); δ_H 0.85 (3H, t, *J* = 7.3 Hz, *Me*CH_2), 1.57 (2H, br s, NH_2), 1.61–1.77 (2H, m, CH_2), 3.76 (1H, t, *J* = 6.9 Hz, CHN), 3.80 (3H, s, MeO), 6.84–6.89, 7.21–7.26 (2H and 2H, respectively, 2m, ArH); δ_C 11.0 (*Me*CH_2), 32.4 (CH_2), 55.2 (MeO), 57.2 (CN), 113.7 (2C), 127.4 (2C), 138.5, 158.5 (ArC); *m/z* 165 (M^+, <1%), 136 (100), 109 (12).

4.4.5. (*R*)-Undecan-3-amine 4e

Colourless oil; R_f 0.10 (ethyl acetate, deactivated silica gel); $[\alpha]_D^{20} = -2.3$ (*c* 1.2, $CHCl_3$, 40% ee); *ν*(film) 3376, 3345 (NH), 1135 cm^{-1} (CN); δ_H 0.86–0.93 (6H, m, 2 Me), 1.19–1.50 (18H, m, 8 × CH_2 and NH_2), 2.58–2.64 (1H, m, CH); δ_C 10.4, 14.1 (2 × Me), 22.7, 26.2, 29.3, 29.6, 29.8, 30.7, 31.9, 37.6 (8 × CH_2), 52.7 (CN); *m/z* 171 (M^+, <1%), 143 (10), 142 (99), 58 (100), 56 (16), 55 (11). HRMS: M^+ found 171.1963, $C_{11}H_{25}N$ requires 171.1987.

4.4.6. (*S*)-1-Phenylpentan-3-amine *ent*-4f[35]

Colourless oil; R_f 0.14 (ethyl acetate, deactivated silica gel); $[\alpha]_D^{20} = +7.5$ (*c* 1.0, MeOH, 42% ee); $[\alpha]_D^{20}$ for *ent*-**4f**·HCl[36] −4.0 (*c* 1.5, MeOH, 42% ee) {literature[37] $[\alpha]_D^{23} = -17.8$ (*c* 1.58, MeOH)}; *ν*(film) 3334 (NH), 3092, 3065, 3026, 1581, 1495 (HC=C), 1181 cm^{-1} (CN); δ_H 0.93 (3H, t, *J* = 7.5 Hz, Me), 1.23–1.42, 1.45–1.66 (2H each, 2m, CH_2CHCH_2), 1.81 (2H, br s, NH_2), 2.58–2.80 (3H, m, CH_2Ph and CHN), 7.16–7.30 (5H, m, ArH); δ_C 10.3 (Me), 30.4, 32.5, 39.0 (3 × CH_2), 52.3 (CN), 125.7 (2C), 128.2 (2C), 128.3, 142.3 (ArC); *m/z* 163 (M^+, 3%), 146 (26), 134 (56), 117 (35), 91 (100), 65 (11), 58 (94).

4.4.7. (*R*)-Ethyl 2-amino-2-phenylbutanoate 4h[38]

Yellow oil; R_f 0.40 (ethyl acetate, deactivated silica gel); $[\alpha]_D^{20} = -11.6$ (*c* 1.0, EtOH, 82% ee); *ν*(film) 3400 (NH), 3088, 3063, 3027, 1612, 1502, (HC=C), 1728 (C=O), 1228 (CO), 1104 cm^{-1} (CN); δ_H 0.89 (3H, t, *J* = 7.3 Hz, *Me*CH_2C), 1.23 (3H, t, *J* = 7.2 Hz, *Me*CH_2O), 1.91 (2H, br s, NH_2), 1.96–2.08, 2.12–2.26 (1H each, 2 m, CH_2C), 4.08–4.25 (2H, m, CH_2O), 7.24–7.44, 7.47–7.52 (3H and 2H, respectively, 2m, ArH); δ_C 8.4 (*Me*CH_2C), 14.1 (*Me*CH_2O), 32.7 (*C*H_2C), 61.3 (CH_2O), 64.0 (CN), 125.5 (2C), 127.2, 128.2 (2C), 143.2 (ArC), 175.6 (C=O); *m/z* 207 (M^+ <1%), 135 (16), 134 (100), 117 (11), 104 (32), 77 (12), 56 (12).

4.4.8. (*R*)-Isopropyl 2-amino-2-phenylbutanoate 4i

Yellow oil; R_f 0.36 (ethyl acetate, deactivated silica gel); $[\alpha]_D^{20} = -56.0$ (*c* 1, $CHCl_3$, 58% ee); *ν*(film) 3400 (NH), 3078, 3050, 3018, 1600, 1494, (HC=C), 1721 (C=O), 1231 (CO), 1106 cm^{-1} (CN); δ_H 0.90 (3H, t, *J* = 7.3 Hz, *Me*CH_2), 1.16–1.24 (6H, m, 2 × *Me*CH), 1.97–2.04, 2.12–2.35 (1H and 3H, respectively, 2m, CH_2 and NH_2), 5.04 (1H, *J* = 6.2 Hz, heptet, C*H*Me_2), 7.23–7.37, 7.47–7.53 (3H and 2H, respectively, 2m, ArH); δ_C 8.4 (*Me*CH_2) 21.5, 21.6 (2 × *Me*CH), 32.4 (CH_2), 64.0 (CN), 68.9 (CO), 125.5 (2C), 127.2, 128.3 (2C), 143.0 (ArC), 174.9 (C=O); *m/z* 221 (M^+ <1%), 134 (36), 121 (55), 120 (22), 104 (100), 91 (11), 87 (10), 77 (10). HRMS: $M^+ - CO_2Pr^i$ found 134.1013, $C_9H_{12}N$ requires 134.0970.

4.4.9. (*R*)-6-Ethylpiperidin-2-one 5[39]

Colourless oil; R_f 0.15 (ethyl acetate, deactivated silica gel); $[\alpha]_D^{20} = -3.0$ (*c* 1, $CHCl_3$, 62% ee) {literature[40] $[\alpha]_D^{20}$ for *ent*-**5** +10.5 (*c* 0.4, $CHCl_3$)}; *ν*(film) 3211 (NH), 1658 (C=O), 1265 cm^{-1} (CN); δ_H 0.95 (3H, t, *J* = 7.5 Hz, Me), 1.20–1.45, 1.47–1.57, 1.61–1.77, 1.85–1.97 (1H, 2H, 1H and 2H, respectively, 4m, CH_2CH_2CH and CH_2Me), 2.21–2.43 (2H, m, CH_2CO), 3.25–3.33 (1H, m, CH); δ_C 9.4 (Me), 19.4 (CH_2CH_2CO), 27.5 (CH_2Me), 29.5 (CH_2CH_2CH), 30.9 (CH_2CO), 54.5 (CH), 159.9 (C=O); *m/z* 127 (M^+, 5%), 98 (100), 55 (39).

4.5. Determination of the enantiomeric excesses of amines 4

Benzoyl chloride (1.4 mmol) was added to a solution of amine **4** (0.5 mmol) and triethylamine (1.4 mmol) in $CHCl_3$ (0.9 mL) at 0 °C. After stirring for 3 h at room temperature, a 2 M aqueous HCl solution (0.5 mL) was added and the mixture was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layers were washed with water (5 mL) and then dried over Na_2SO_4. After filtration and evaporation of the solvents, the expected benzamides were purified by column chromatography (silica gel, hexane/ethyl acetate). These benzamides were analysed by HPLC on a ChiralCel OD-H column using a 254 nm UV detector, 10% *i*-PrOH in hexane as eluent and a flow rate of 0.5 mL/min. The retention times were 17.8 (*N*-benzoyl **4aa**), 29.0 (*N*-benzoyl *ent*-**4aa**), 15.4 (*N*-benzoyl **4ac**), 26.6 (*N*-benzoyl *ent*-**4ac**), 15.6 (*N*-benzoyl **4ad**), 29.7 (*N*-benzoyl *ent*-**4ad**), 33.0 (*N*-benzoyl **4ae**), 47.8 (*N*-benzoyl *ent*-**4ae**), 14.5 (*N*-benzoyl **4af**), 18.5 (*N*-benzoyl *ent*-**4af**), 13.0 (*N*-benzoyl **4ag**), 20.1 (*N*-benzoyl *ent*-**4ag**), 19.7 (*N*-benzoyl **4ah**), 30.7 (*N*-benzoyl *ent*-**4ah**), 19.3 (*N*-benzoyl **4b**), 28.3 (*N*-benzoyl *ent*-**4b**), 15.4 (*N*-benzoyl **4c**), 27.1 (*N*-benzoyl *ent*-**4c**), 15.8 (*N*-benzoyl **4d**), 19.2 (*N*-benzoyl *ent*-**4d**), 15.2 (*N*-benzoyl **4e**), 12.4 (*N*-benzoyl *ent*-**4e**), 35.0 (*N*-benzoyl **4f**), 26.4 (*N*-benzoyl *ent*-**4f**), 14.6 (*N*-benzoyl **4h**; 5% *i*-PrOH in hexane as eluent), 21.1 (*N*-benzoyl *ent*-**4h**; 5% *i*-PrOH in hexane as eluent), 17.5 (*N*-benzoyl **4i**), 24.3 (*N*-benzoyl *ent*-**4i**), 21.4 (*N*-benzoyl **5**), and 19.0 (*N*-benzoyl *ent*-**5**). The enantiomeric excesses obtained are collected in Tables 2 and 3.

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