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Triorganozincates as efficient nucleophiles for the diastereoselective addition to *N*-(*tert*-butanesulfinyl)imines

Raquel Almansa, David Guijarro* and Miguel Yus*

Departamento de Química Orgánica, Facultad de Ciencias and Instituto de Síntesis Orgánica (ISO),
Universidad de Alicante, Apdo. 99, 03080 Alicante, Spain

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Dedicated to the memory of Dr. C. V. Asokan from Mahatma Gandhi University, Kottayam (India)

Abstract—Triorganozincates, generated by mixing a Grignard reagent and a dialkylzinc reagent, effectively react with (*R*)-*N*-(*tert*-butanesulfinyl)benzaldimine to give the expected α-branched sulfinamides in good to excellent yields and with diastereomeric ratios of up to 98:2. When the R group of the organomagnesium and the R′ group of the diorganozinc are different, the selective transfer of only one of them to the imine can be achieved by the proper choice of the organometallic reagents. One can take advantage of the slow transfer rate of the methyl group to use it as a non-transferable one. The *N*-sulfinyl group of the products can be easily removed by acidic treatment, affording the corresponding chiral primary amines without the loss in enantiomeric purity.

1. Introduction

Enantiomerically pure *N*-sulfinylimines have been shown to be versatile substrates for asymmetric synthesis,[1] especially for the preparation of chiral primary amines.[1b,c] The electron-withdrawing sulfinyl group plays two important roles: (a) it activates the imine for nucleophilic addition and (b) it acts as a powerful stereodirecting group. The addition of organometallics, mainly Grignard and organolithium reagents, to the C=N bond takes place in a diastereoselective manner and provides sulfinamides that can be readily transformed into primary amines, since the *N*-sulfinyl group can be easily removed under mild acidic conditions.[2] Among the carbon nucleophiles, organozinc reagents[3] are very useful since they tolerate several functional groups and can lead to polyfunctionalised organic compounds by reaction with electrophiles. However, the reactivity of the most common dialkylzincs and alkylzinc halides is quite limited.[4] Dialkylzincs react very slowly with activated imines, leading to low yields of addition products over very long reaction times. Organozincates are generally more reactive than organozinc halides and diorganozincs. They can be readily added to aldehydes and ketones[5] and lead to 1,4-addition products with α,β-unsaturated ketones.[3c,4b] Solutions of triorganozincates have been found to give reactions not important for dialkylzincs or alkylzinc halides, including halogen-zinc exchange with a range of 1,1-dibromoalkenes[6] or –alkanes[3c] and with aryl iodides.[3c] 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.[7] The participation of trialkylzincates in the zinc chloride catalysed addition of Grignard reagents to *N*-phenyl- and *N*-tosylimines has also been postulated.[5b] Continuing our research on the addition or organozinc reagents to imines,[8] we herein report our preliminary results on the diastereoselective addition of organozincates to *N*-(*tert*-butanesulfinyl)imines.

2. Results and discussion

Triorganozincates can be prepared by the reaction of dialkylzincs with Grignard reagents.[3c,9] In our initial experiment, MeMgBr and Et_2Zn (1 equiv each) were stirred for 15 min and the resulting solution of the mixed organozincate was then transferred into a solution of (*R*)-*N*-(*tert*-butanesulfinyl)benzaldimine **1** (Scheme 1) at 0 °C. The reaction was completed after only 1 h and the expected addition products (R_S,*R*)-**2a** and (R_S,*S*)-**3a** were obtained

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* Corresponding authors. Fax: +34 965903549 (D.G.); e-mail addresses: dguijarro@ua.es; yus@ua.es

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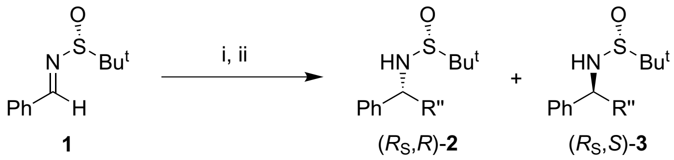

Scheme 1. Reagents and conditions: (i) RMgBr, R'_2Zn, THF, *T*; (ii) NH_4Cl (aq).

in 91% yield with a diastereomeric ratio of 86:14, respectively (Table 1, entry 1). Only the ethyl group was transferred from the organozincate to the imine, the corresponding methylation product not being detected in the crude mixture. We were pleased to see that the diastereomeric ratio increased when the temperature was lowered (Table 1, entries 2–4), reaching a 98:2 value at −78 °C, although the yield was only 66% (Table 1, entry 4). To try to improve the yield, the latter reaction was repeated, increasing the amounts of MeMgBr (1.5 equiv) and Et_2Zn (1.7 equiv). These conditions afforded the product (R_S,*R*)-**2a** in quantitative yield and with a 97:3 diastereomeric ratio (Table 1, entry 5). A further decrease in the temperature was detrimental for both the yield and the diastereoselectivity (Table 1, entry 6).

To prove the slow rate for the transfer of the methyl group, imine **1** 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% of the expected addition product was obtained as a 54:46 mixture of diastereoisomers. This result led us to think about using methyl as a non-transferable group.[10] Thus, Me_2Zn was combined with several Grignard reagents and the organozincates generated were added to imine **1** (Table 1, entries 7, 9, 11 and 13). $EtMe_2ZnMgBr$[11] gave the ethylation product (R_S,*R*)-**2a** in 85% yield and a 98:2 dr (Table 1, entry 7). When $C_5H_{11}MgBr$ was used as the Grignard component, the product (R_S,*R*)-**2b** resulting from the addition of the pentyl group was obtained in 92% yield with a 96:4 dr (Table 1, entry 9). The use of $Pr^iMe_2ZnMgBr$[11] and (vinyl)-$Me_2ZnMgBr$[11] gave compounds **2c** and **2d**, respectively, as the major products with very high diastereomeric ratios (Table 1, entries 11 and 13, respectively). In both cases, only the R group of the Grignard reagent was transferred to the imine.

With the aim of proving that the reactivities of the organozincate solutions and the corresponding Grignard reagents were different, imine **1** was treated with EtMgBr, $C_5H_{11}MgBr$, Pr^iMgBr and $CH_2{=}CHMgBr$ (1.5 equiv of each) in four separate experiments. Except for the case of EtMgBr, all reactions were much slower, not being complete after stirring for 12 h at −78 °C. The yield was high only with the Grignard reagents bearing a primary alkyl group while in all other cases, the diastereoselectivity was much lower than in the reactions with the corresponding organozincates (compare entries 7 with 8, 9 with 10, 11 with 12 and 13 with 14 in Table 1).

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**. Therefore, they could be submitted to the deprotection procedure without further purification. The removal of the *N*-sulfinyl group could be easily achieved by the treatment of the crude reaction mixtures with HCl in MeOH, to afford the expected primary amines without any detectable racemisation. By comparison of the sign of their specific rotation with the data reported in the literature, the absolute configuration

Table 1. Diastereoselective addition of triorganozincates to *N*-(*tert*-butanesulfinyl)imine **1**: Preparation of compounds **2** and **3**

Entry	RMgBr		R'_2Zn		*T* (°C)	Time (h)	Product			
	R	Equiv	R′	Equiv			No.[a]	R″	Yield[b] (%)	**2**:**3** ratio[c]
1	Me	1	Et	1	0	1	**2a**	Et	91	86:14
2	Me	1	Et	1	−30	1	**2a**	Et	83	91:9
3	Me	1	Et	1	−50	1	**2a**	Et	94	95:5
4	Me	1	Et	1	−78	1	**2a**	Et	66[d]	98:2
5	Me	1.5	Et	1.7	−78	1	**2a**	Et	99	97:3
6	Me	1.5	Et	1.7	−100	1	**2a**	Et	56[d]	87:13
7	Et	1.5	Me	1.7	−78	1	**2a**	Et	85	98:2
8	Et	1.5	—	—	−78	1	**2a**	Et	91	79:21
9	*n*-C_5H_{11}	1.5	Me	1.7	−78	1	**2b**	*n*-C_5H_{11}	92	96:4
10	*n*-C_5H_{11}	1.5	—	—	−78	12	**3b**	*n*-C_5H_{11}	70[d]	49:51
11	Pr^i	1.5	Me	1.7	−78	3	**2c**	Pr^i	81	94:6
12	Pr^i	1.5	—	—	−78	12	**2c**	Pr^i	21[d]	60:40
13	$CH{=}CH_2$	1.5	Me	1.7	−78	1	**2d**	$CH{=}CH_2$	93	95:5
14	$CH{=}CH_2$	1.5	—	—	−78	12	**3d**	$CH{=}CH_2$	28[d]	44:56

[a] Product number corresponding to the major diastereoisomer.

[b] The crude reaction mixture only showed the mixture of diastereoisomers **2** and **3** (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.

[c] 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 the removal of the *N*-sulfinyl group and comparison of the sign of the specific rotation of the free primary amines with the reported data.

[d] Yield estimated by ^1H NMR using diphenylmethane as an internal standard. The reaction was not complete.

of the asymmetric carbon atom of the major diastereoisomer **2** or **3** could be determined. The enantiomeric ratios of the free primary amines were determined by benzoylation of the nitrogen atom and analysis of the benzamides obtained by HPLC using a ChiralCel OD-H column under the same elution conditions as for the diastereoisomers **2** and **3** (see below). In every case, the enantiomeric ratio of the free primary amine was equal to the corresponding **2**:**3** diastereomeric ratio as determined by HPLC.[12]

As has been described above, the reaction of triorganozincates with *N*-(*tert*-butanesulfinyl)imine **1** is a very efficient procedure to effect the diastereoselective addition of alkyl groups to the imine carbon atom. Further efforts to extend the substrate scope and to elucidate the mechanism of the reaction are currently underway in our laboratories.

3. Conclusions

In conclusion, organozincates have been shown to be very useful nucleophiles for the diastereoselective addition to *N*-(*tert*-butanesulfinyl)imines. Reactions are fast and provide the expected sulfinamide products in good yields and with very high diastereomeric ratios with all the alkyl groups that were transferred, except for methyl. Due to the low transfer ability of the methyl group, it can be used as a non-transferable group in mixed triorganozincates. 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.

4. Experimental

4.1. Typical experimental procedure (Table 1, entry 7)

EtMgBr (0.75 mmol, 0.75 mL of a 1.0 M solution in THF) was added to Me_2Zn (0.86 mmol, 0.43 mL of a 2.0 M solution in toluene) under argon at room temperature and the mixture was stirred for 15 min. The resulting solution of the organozincate was then transferred dropwise via syringe to a solution of the sulfinylimine **1** (105 mg, 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, pure *tert*-butanesulfinamides **2a** and **3a** were obtained in 85% combined yield. This mixture was analyzed 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 (**2a**) and 10.8 (**3a**).[13] The diastereomeric ratio was 98:2 (**2a**:**3a**). The absolute configuration of the asymmetric carbon atom of the major diastereoisomer was determined by treatment of the mixture of products with HCl in methanol and comparison of the sign of the specific rotation of the obtained free amine with the reported data.[14–17]

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12. A referee suggested that the determination of the relative proportion of **2** and **3** by HPLC using UV detection is an estimate unless it has been proven that both diastereoisomers have the same UV response. The fact that the enantiomeric

ratios of the free primary amines are equal to the corresponding **2**:**3** diastereomeric ratios determined by HPLC indicates that the latter technique is appropriate for determining the diastereomeric ratio of this kind of sulfinamides.

13. The retention times for the other addition products under the same elution conditions were 7.9 (**2b**), 9.7 (**3b**), 7.8 (**2c**), 12.1 (**3c**), 9.5 (**2d**) and 11.1 (**3d**).
14. For 1-phenylpropan-1-amine, observed $[\alpha]_D^{20} = +11.9$ (*c* 1.1, $CHCl_3$) 90% ee. Lit.: $[\alpha]_D^{25} = +8.8$ [(*c* 1.0, $CHCl_3$) 61.5% ee (*R*)]. Ref.: Andersson, P. G.; Guijarro, D.; Tanner, D. *J. Org. Chem.* **1997**, *62*, 7364–7375.
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17. For 1-phenylprop-2-en-1-amine, observed $[\alpha]_D^{20} = +9.3$ (*c* 1, $CHCl_3$) 90% ee. Lit.: $[\alpha]_D^{20} = +10.2$ [(*c* 1, $CHCl_3$) (*R*)]. Ref.: Atobe, M.; Yamazaki, N.; Kibayashi, C. *J. Org. Chem.* **2004**, *69*, 5595–5607.