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An improved procedure for the diastereoselective addition of triorganozincates to *N*-(*tert*-butanesulfinyl)imines: use of catalytic dialkylzinc

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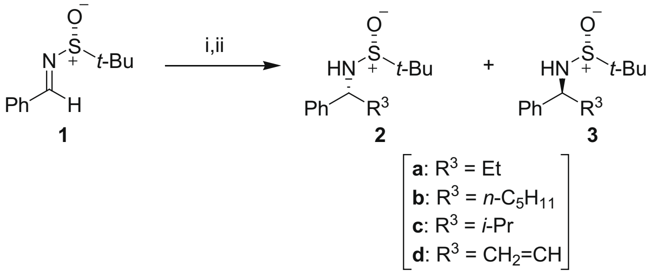
ABSTRACT

The addition of triorganozincates to (*R*)-*N*-(*tert*-butanesulfinyl)benzaldimine has been performed with very good results by using a catalytic amount of Me_2Zn (0.15 equiv) to generate the organozincate. Yields and/or diastereoselectivities of the formed α-branched sulfinamides improve in comparison with the values obtained in the same reactions carried out with an excess of a previously formed triorganozincate. On the other hand, the transfer of the two alkyl groups of a dialkylzinc reagent to the imine has been achieved by using 0.5 equiv of dialkylzinc and 1.5 equiv of MeMgBr to generate the trialkylzincate. In both methods, good to excellent yields and diastereomeric ratios (up to 98:2) have been obtained.

Triorganozincates[1] are a class of zinc reagents which are more reactive than the most common dialkylzincs and alkylzinc halides. They have found several synthetic applications, such as addition to aldehydes and ketones,[2] conjugate addition to α,β-unsaturated ketones,[1b,3] cross-coupling,[4] nucleophilic substitution[4b,5] and halogen-zinc exchanges with alkyl,[5,6] alkenyl[4a] and aryl halides.[5] Organozincates have also been used as nucleophiles in the addition to imines bearing a chiral auxiliary derived from a phenethylamine, an α-aminoester or an O-protected β-aminoalcohol.[7] The participation of trialkylzincates in the zinc chloride-catalyzed addition of Grignard reagents to *N*-phenyl- and *N*-tosylimines has also been postulated.[2b] Recently, we have reported on the use of triorganozincates as very efficient nucleophiles to perform the addition of alkyl or alkenyl groups to *N*-(*tert*-butanesulfinyl)imines,[8] a class of imines that have been shown to be versatile substrates for asymmetric synthesis,[9] especially for the preparation of chiral primary amines.[9b,c,f] By using an excess of a dialkylzinc and a Grignard reagent to generate the triorganozincate, very good yields and diastereoselectivities were observed in the addition products, which could be easily transformed into the corresponding enantiomerically enriched amines by desulfinylation of the nitrogen atom under mild reaction conditions. Herein, we present our preliminary results on the generation of triorganozincates by employing a catalytic amount of the precursor dialkylzincs and the diastereoselective addition of those triorganozincates to *N*-(*tert*-butanesulfinyl)imines.

In our previous work, we had tried to carry out the addition of $EtMe_2ZnMgBr$[10] to *N*-(*tert*-butanesulfinyl)benzaldimine **1** (Scheme 1) by utilizing 0.5 equiv of Me_2Zn to generate the mixed trialkylzincate.[8b] We assumed that Me_2Zn was regenerating after the transfer of the ethyl group from the trialkylzincate to the imine, and we hoped that the formed Me_2Zn would react with another molecule of EtMgBr, regenerating in this way the trialkylzincate and closing a possible catalytic cycle. Unfortunately, when



Scheme 1. Reagents and conditions: (i) R^1MgBr, R^2_2Zn (cat.), THF, −78 °C. (ii) NH_4Cl (aq.).

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Table 1

Diastereoselective addition of triorganozincates to *N*-(*tert*-butanesulfinyl)benzaldimine **1** using a catalytic amount of the dialkylzinc reagent

Ent.	Proced.	R^1MgBr		R^2_2Zn		Time (h)	Product			
		R^1	Equiv	R^2	Equiv		No.[a]	R^3	Yield[b] (%)	**2:3** ratio[c]
1	A[d]	Et	1.5	Me	0.5	12	**2a**	Et	47	94:6
2	B[e]	Et	1.5	Me	0.5	1	**2a**	Et	90	97:3
3	B[e]	Et	1.5	Me	0.25[f]	1	**2a**	Et	77	90:10
4	B[e]	Et	1.5	Me	0.1[g]	1	**2a**	Et	20[h]	93:7
5	C[i]	Et	1.5	Me	0.5	1	**2a**	Et	87	97:3
6	C[i]	Et	1.5	Me	0.25[f]	1.75	**2a**	Et	88	97:3
7	C[i]	Et	1.5	Me	0.1[g]	3.25	**2a**	Et	54[h]	97:3
8	D[j]	Et	1.125	Me	0.125	2.25	**2a**	Et	78[h]	97:3
9	E[k]	Et	1.3	Me	0.15	2	**2a**	Et	93	97:3
10	E[k]	n-C_5H_{11}	1.3	Me	0.15	2	**2b**	n-C_5H_{11}	99	93:7
11	E[k]	*i*-Pr	1.3	Me	0.15	2	**2c**	*i*-Pr	83	94:6
12	E[k]	CH_2=CH	1.3	Me	0.15	2	**2d**	CH_2=CH	94	98:2
13	F[l]	Me	1.5	Et	0.5	1	**2a**	Et	84[m]	97:3
14	F[l]	Me	1.5	*i*-Pr	0.5	1	**2c**	*i*-Pr	90[m]	94:6

[a] Product number corresponding to the major diastereoisomer.

[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] 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 amine with the reported data.

[d] EtMgBr (0.75 mmol) was added dropwise to a mixture of Me_2Zn (0.25 mmol) and imine **1** (0.5 mmol) in THF (3 mL) at −78 °C, and the reaction mixture was stirred at that temperature.

[e] The solution of imine **1** (0.5 mmol) in THF (3 mL) was added dropwise over ca. 30 min to the mixture of Me_2Zn (0.25 mmol) and EtMgBr (0.75 mmol) at −78 °C, and the reaction mixture was stirred at that temperature.

[f] The reaction was performed by following the indicated procedure, but by using 0.25 equiv of Me_2Zn with regard to imine **1**.

[g] The reaction was performed by following the indicated procedure, but by using 0.1 equiv of Me_2Zn with regard to imine **1**.

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

[i] A mixture of Me_2Zn (0.25 mmol) and EtMgBr (0.25 mmol) was stirred for 10 min at room temperature. After cooling to −78 °C, a fraction (1 mL, 0.17 mmol) of the solution of imine **1** (prepared by dissolving 0.50 mmol of the imine in 3 mL of THF) was added dropwise over ca. 5 min, and the mixture was stirred for additional 10 min. Then, a fraction of EtMgBr (0.25 mmol) was added dropwise over ca. 5 min and the mixture was stirred for additional 10 min. This process of alternate addition of imine and EtMgBr was repeated until the total amount of both reagents had been added.

[j] A mixture of Me_2Zn (0.25 mmol) and R^1MgBr (0.75 mmol) was stirred for 10 min at room temperature. After cooling to −78 °C, a fraction (3 mL, 0.50 mmol) of the solution of imine **1** (prepared by dissolving 2.0 mmol of the imine in 12 mL of THF) was added dropwise over ca. 20 min using a syringe pump. Immediately after the addition was finished, a fraction of R^1MgBr (0.50 mmol) was added dropwise over ca. 5 min, and the mixture was stirred for additional 10 min. This process of alternate addition of imine and R^1MgBr was repeated until the total amount of both reagents had been added.

[k] Like procedure D, but the solution of imine **1** was prepared by dissolving 1.7 mmol of it in 10 mL of THF. Three fractions of 2.9 mL (0.50 mmol) and a last fraction of 1.3 mL (0.20 mmol) of this solution were added. The time needed to add the last fraction was 9 min.

[l] The solution of imine **1** (1.0 mmol) in THF (6 mL) was added with a syringe pump over ca. 40 min to the mixture of R^2_2Zn (0.50 mmol) and MeMgBr (1.50 mmol) at −78 °C, and the reaction mixture was stirred at that temperature.

[m] Yield calculated for the stoichiometry 1 $R^2_2Zn \rightarrow 2$ **2**.

EtMgBr was added dropwise to the mixture of Me_2Zn and imine **1** in THF at −78 °C, the reaction was not complete after stirring for 12 h and afforded the expected sulfinamides in 47% yield and a **2a**:**3a** ratio of 94:6 (procedure A, Table 1, entry 1). Since the diastereoselectivity was quite good, we decided to carefully screen the reaction conditions with the aim of improving the conversion and reducing the reaction time and the amount of Me_2Zn. First, the order of addition of the reagents was changed in order to assure the presence of the trialkylzincate in the reaction medium when the imine was added. By slowly adding the imine to the mixture of Me_2Zn (0.5 equiv) and EtMgBr (1.5 equiv) at −78 °C, a 90% yield and a diastereomeric ratio of 97:3 were obtained (procedure B, Table 1, entry 2). The improvement in both the conversion and the diastereoselectivity encouraged us to perform some tests with lower loadings of Me_2Zn. When 0.25 and 0.1 equiv of the latter were used, maintaining the ratios between the rest of the reagents and the addition rate, both yield and diastereoselectivity were reduced (Table 1, entries 3 and 4). The conversion decreases as the amount of Me_2Zn is reduced. Accordingly, it seemed that it was necessary to have a minimum amount of the preformed triorganozincate in the reaction flask before the addition of the imine in order for the reaction to work successfully. The presence of a large excess of the Grignard reagent with regard to the amount of trialkylzincate should be also avoided, since we had already proved that the results obtained with those two organometallic species were different.[8]

In order to fulfil these two requirements, we thought about performing the addition of the Grignard reagent and the imine in several steps. The solution of the imine **1** (0.50 mmol in 3 mL of THF) was divided into three fractions of 1 mL each. After the addition of one of these fractions to the preformed trialkylzincate (0.25 mmol) for ca. 5 min and stirring for additional 10 min, a fraction of EtMgBr (0.25 mmol) was added dropwise for ca. 5 min and the mixture was stirred for 10 min to allow the regeneration of the triorganozincate before the entrance of a new fraction of the imine, by reaction of the excess of EtMgBr with the Me_2Zn formed after the addition reaction. This process of alternate addition of imine and EtMgBr was repeated until the total amount of both reagents had been added, which afforded results almost same as for procedure B (compare entries 2 and 5 in Table 1). This stepwise procedure C (Table 1, footnote i) was repeated with 0.25 and 0.1 equiv of Me_2Zn. In the first case, the results were identical to the ones obtained with 0.5 equiv of Me_2Zn (compare entries 5 and 6 in Table 1), whereas the reaction with 0.1 equiv did not reach completion (Table 1, entry 7). We were pleased to see that the diastereoselectivity was as high as 97:3 in the three assays performed following procedure C.

With the idea of adjusting Me_2Zn loading to the minimum amount that allowed for completion of the reaction, a slight modification in the addition procedure was made consisting in adding the fractions of the solution of imine **1** for ca. 20 min by using a syringe pump and starting the addition of a fraction of EtMgBr immediately after the end of the addition of the fraction of the imine (procedure D, Table 1, entry 8, footnote j). This modification allowed the use of 0.125 equiv of Me_2Zn and 1.125 equiv of EtMgBr, and gave a 78% yield and a 97:3 diastereomeric ratio. Since the reaction was not complete, the amount of the imine was reduced in order to increase the number of equiv of Me_2Zn and EtMgBr to 0.15 and 1.3, respectively. This last modification led to a 93% yield and a **2a**:**3a** ratio of 97:3 in a reaction time of only 2 h (procedure E, Table 1, entry 9). Procedure E was chosen as the optimum reaction conditions.

We then tested the transfer of some other alkyl groups to imine **1** (Scheme 1 and Table 1). Primary alkyls (Table 1, entries 9 and 10), the isopropyl group (Table 1, entry 11) and the vinyl group (Table 1, entry 12) were effectively transferred to the imine, giving the expected sulfinamides in very good yields and diastereomeric ratios. In all cases, yields were higher than the ones obtained when an excess of the previously formed zincate was used.[8] The diastereoselectivity was of the order same as the ones observed in our previous report, being even higher for the addition of the vinyl group (98:2 in this catalytic addition against 95:5 in the stoichiometric version[8]).

As was the case in the reactions with an excess of the triorganozincate,[8] in all cases the R^1 group of the Grignard reagent was the only one adding to the imine, the corresponding methylation product being not detected in the crude mixtures. Thus, the methyl group acted as a non-transferable group,[11] which allowed the regeneration of Me_2Zn after the addition reaction and the complete transfer of the R^1 group. To the best of our knowledge, this is the first time that a catalytically generated triorganozincate has been used as nucleophile in a diastereoselective addition to an imine.

The very slow transfer rate of the methyl group gave us another idea: we thought that by using 0.5 equiv of a dialkylzinc reagent and an excess of MeMgBr, we would be able to transfer the two R^2 groups of the dialkylzinc to the imine. After the reaction between the initially generated $R^2_2MeZnMgBr$ and the imine, an R^2 group would have been transferred and R^2ZnMe would have been formed. The reaction of the latter with MeMgBr would generate $R^2Me_2ZnMgBr$, which would transfer the second R^2 group to the imine. Thus, the solution of imine **1** was added dropwise to the stirred mixture of Et_2Zn or *i*-Pr_2Zn (0.5 equiv) and MeMgBr (1.5 equiv) at −78 °C (procedure F, Table 1, entries 13 and 14, footnote l), and after only 1 h, yields of the expected addition products of 84% (for **2a**) and 90% (for **2c**) were obtained, the diastereoselectivities being exactly the same as the ones achieved with procedure E (compare entry 9 with entry 13 and entry 11 with entry 14 in Table 1). It is worth noting that these yields are based on the starting amounts of the imine **1**, and the fact that they are much higher than 50% imply that two mmol of the addition products has been formed for each mmol of R^2_2Zn. To the best of our knowledge, this is the first time that the two alkyl groups of a dialkylzinc reagent have been transferred in an addition reaction. This feature makes procedure F very useful from a synthetic point of view, especially when the $R^2{}_2Zn$ is more easily accessible than the R^1MgBr or when the R group that one wishes to be transferred is functionalized.

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 asymmetric carbon atom of the major diastereoisomer of the addition products could be determined. The enantiomeric excesses of the free primary amines were determined by benzoylation of the nitrogen atom and analysis of the obtained benzamides by HPLC using a ChiralCel OD-H column. There was no loss of optical purity during the desulfinylation process: the ee values of the free amines matched perfectly well with the corresponding **2**:**3** ratios.[12]

In conclusion, we have presented here two new and very efficient procedures to perform the highly diastereoselective addition of triorganozincates to *N*-(*tert*-butanesulfinyl)imines using a catalytic amount of a dialkylzinc reagent as a precursor or the organozincates. Reactions are fast and provide the expected sulfinamide products in excellent yields and very high diastereomeric ratios. The low transfer ability of the methyl group allows for (a) the success of the addition reaction by using only a small amount (0.15 equiv) of dimethylzinc, which reduces the reaction cost in comparison with the same reaction carried out with an excess of the triorganozincate, and (b) the transfer of both alkyl groups of a dialkylzinc reagent to the imine via the corresponding mixed zincate. Since the *N*-sulfinyl group can be easily removed, these methodologies represent two new and very efficient procedures for the asymmetric synthesis of primary amines. Further efforts to elucidate the mechanism of the reaction and to find synthetic applications of these methodologies are currently underway in our laboratories.

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Supplementary data

Supplementary data (complete experimental details for procedures E and F) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.01.136.

References and notes

1. (a) Harada, T.; Oku, A. In *Organozinc Reagents: A Practical Approach*; Knochel, P., Jones, P., Eds.; Oxford University Press: Oxford, 1999; pp 101–117; (b) Knochel, P. *Science of Synthesis* **2004**, *3*, 5–90.
2. See, for instance: (a) Musser, C. A.; Richey, H. G., Jr. *J. Org. Chem.* **2000**, *65*, 7750–7756; (b) Hatano, M.; Suzuki, S.; Ishihara, K. *J. Am. Chem. Soc.* **2006**, *128*, 9998–9999; (c) Gosselin, F.; Britton, R. A.; Mowat, J.; O'Shea, P. D.; Davies, I. W. *Synlett* **2007**, 2193–2196.
3. Lee, V. J. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Semmelhack, M. F., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, section 1.2.2.1.4.
4. (a) Harada, T.; Katsuhira, T.; Hara, D.; Kotani, Y.; Maejima, K.; Kaji, R.; Oku, A. *J. Org. Chem.* **1993**, *58*, 4897–4907; (b) Kondo, Y.; Takazawa, N.; Yamazaki, C.; Sakamoto, T. *J. Org. Chem.* **1994**, *59*, 4717–4718; (c) Gauthier, D. R., Jr.; Szumigala, R. H., Jr.; Dormer, P. G.; Armstrong, J. D., III; Volante, R. P.; Reider, P. J. *Org. Lett.* **2002**, *4*, 375–378.
5. Kondo, Y.; Fujinami, M.; Uchiyama, M.; Sakamoto, T. *J. Chem. Soc., Perkin Trans. 1* **1997**, 799–800.
6. Harada, T.; Kotani, Y.; Katsuhira, T.; Oku, A. *Tetrahedron Lett.* **1991**, *32*, 1573–1576.
7. (a) Alvaro, G.; Pacioni, P.; Savoia, D. *Chem. Eur. J.* **1997**, *3*, 726–731; (b) Alvaro, G.; Martelli, G.; Savoia, D. *J. Chem. Soc., Perkin Trans. 1* **1998**, 775–784.
8. (a) Almansa, R.; Guijarro, D.; Yus, M. *Tetrahedron: Asymmetry* **2008**, *19*, 603–606; (b) Almansa, R.; Guijarro, D.; Yus, M. *Tetrahedron: Asymmetry* **2008**, *19*, 2484–2491.
9. For reviews, see: (a) Davis, F. A.; Chen, B.-C. *Chem. Soc. Rev.* **1998**, *27*, 13–18; (b) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984–995; (c) Ellman, J. A. *Pure Appl. Chem.* **2003**, *75*, 39–46; (d) Zhou, P.; Chen, B.-C.; Davis, F. A. *Tetrahedron* **2004**, *60*, 8003–8030; (e) Morton, D.; Stockman, R. A. *Tetrahedron* **2006**, *62*, 8869–8905; (f) Lin, G.-Q.; Xu, M.-H.; Zhong, Y.-W.; Sun, X.-W. *Acc. Chem. Res.* **2008**, *41*, 831–840.

10. This formula indicates only composition of the organometallic mixture and implies neither the molecular formula nor the dominant species in solution. For a study about the possible reactive species in a reaction between Et_3ZnLi and di-*tert*-butyl ketone, see: Maclin, K. M.; Richey, H. G., Jr. *J. Org. Chem.* **2002**, *67*, 4602–4604.
11. The low transfer ability of the methyl group from triorganozincates has been shown in other addition reactions. For instance, see Refs. 1b,3,7a.
12. 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 estimating the diastereomeric ratios of this type of sulfinamides.