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Selective Diethylzinc Reduction of Imines in the Presence of Ketones Catalyzed by Ni(acac)$_2$

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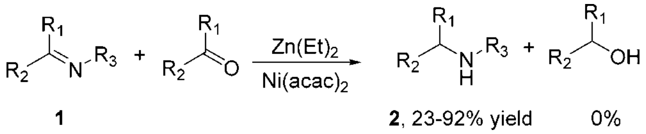
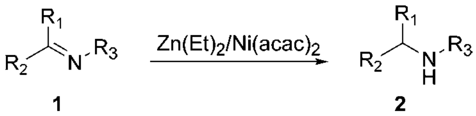
ABSTRACT



A selective reduction method of an electronically deficient imine in the presence of ketone was developed by employing Et$_2$Zn and 5 mol % of Ni(acac)$_2$. The method was applied in the reduction of *S_S-tert*-butanesulfinyl ketimines 1 to afford amines 2 in 23–92% yields and 73:27 to 98:2 diastereoselectivities. A plausible mechanism was proposed on the basis of an NMR study.

The amine functional group is widely present in bioactive natural products and many pharmaceutically important substances. A large number of methods have been developed to prepare amine. The most used method is the reduction of imine by commonly used reductants such as DIBAL, LiAiH$_4$, NaBH$_4$, BH$_3$, and 9-BBN.[1] Although high yields were achieved in the reduction of imines, those reductants were not compatible with a variety of functional groups such as ketones, esters, and nitriles. In this letter, we report an effective reduction of imines by employing diethylzinc as a reductant in the presence of a catalytic amount of Ni(acac)$_2$ (Scheme 1) as an important complement to imine reduction protocols.

Scheme 1



Although the C═N double bond of an imine is potentially susceptible to attack of alkylmetals,[2] direct addition of diethylzinc to imine has proved to be difficult without the aid of a ligand;[3] sometimes, additional metal salts were also necessary for a successful addition.[4] In Hoveyda's study of diethylzinc addition to *o*-anisidyl imines catalyzed by dipeptide and Zr(O^{i}Pr)$_4$, variable amounts of the reduction product were observed along with the addition product.[4d] During the course of our study to screen metal salts for catalyzing diethylzinc addition to phenyl methyl *tert*-butanesulfinyl ketimine **1a**,[5] we found that the ketimine **1a** was predominantly reduced to provide sulfonamide **2a** as a mixture of two diastereoisomers with 5 equiv of Et$_2$Zn in the presence of 5 mol % of Ni(acac)$_2$ in CH$_2$Cl$_2$ at room temperature.[6]

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(1) Larock, R. C. *Comprehensive Organic Transformations*; Wiley-VCH: New York, 1999 and references therein.

(2) For reviews on asymmetric addition to imines, see: (a) Ding, H.; Friestad, G. K. *Synthesis* **2005**, 2815. (b) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069.

(3) For ligand-aided dialkylzinc addition to imines, see: (a) Jiang, B.; Si, Y. *Angew Chem., Int. Ed.* **2004**, *43*, 216. (b) Keith, J.; Jacobsen, E. N. *Org. Lett.* **2004**, *6*, 153. (c) Wang, Ch.-J.; Shi, M. *J. Org. Chem.* **2003**, *68*, 6229. (d) Soeta, T.; Nagai, K.; Fujihara, H.; Kuriyama, M.; Tomioka, K. *J. Org. Chem.* **2003**, *68*, 9723. (e) Zhang, X.-M.; Zhang, H.-L.; Lin, W.-Q.; Gong, L.-Zh.; Mi, A.-Q.; Cui, X.; Jiang, Y.-Zh.; Yu, K.-B. *J. Org. Chem.* **2003**, *68*, 4322. (f) Dahmen, S.; Brase, S. *J. Am. Chem. Soc.* **2002**, *124*, 5940. (g) Fujihara, H.; Nagai, K.; Tomioka, K. *J. Am. Chem. Soc.* **2000**, *122*, 12055. (h) Jimeno, C.; Reddy, K. S.; Sola, L.; Moyano, A.; Pericas, M. A.; Riera, A. *Org. Lett.* **2000**, *2*, 3157.

(4) (a) Boezio, A. A.; Charette, A. B. *J. Am. Chem. Soc.* **2003**, *125* 1692. (b) Boezio, A. A.; Pytkowicz, J.; Cote, A.; Charette, A. *J. Am. Chem. Soc.* **2003**, *125*, 14260. (c) Porter, J. R.; Traverse, J. F.; Hoveyda, A. H.; Snapper, M. L. *J. Am. Chem. Soc.* **2001**, *123*, 10409. (d) Porter, J. R.; Traverse, J. F.; Hoveyda, A. H.; Snapper, M. L. *J. Am. Chem. Soc.* **2001**, *123*, 984.

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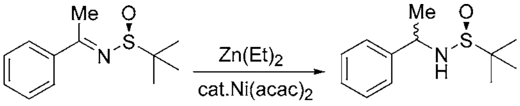
This unexpected observation encouraged us to investigate the details of $Ni(acac)_2$-catalyzed diethylzinc reduction of ketimine **1** and general imines.

Initially, the effect of a variety of solvents on the reduction of racemic **1a** by Et_2Zn was investigated in the presence of 5 mol % of $Ni(acac)_2$ at room temperature. As shown in Table 1, the reduction of **1a** with 5 equiv of Et_2Zn proceeded slowly to give moderate yield when halogenated solvents such as CH_2Cl_2 and CH_2ClCH_2Cl were used (Table 1, entries 1 and 2). Since a dark precipitate was formed immediately after the injection of diethylzinc into the mixture of **1a** and $Ni(acac)_2$ in $CHCl_3$ or CCl_4, $CHCl_3$ and CCl_4 were not suitable for this reaction (Table 1, entries 3 and 4). Acetonitrile did not improve the yield compared with halogenated solvent, while toluene gave a high yield (Table 1, entries 5 and 6). Ethereal solvents were the best choice of solvents; the reduction of **1a** afforded **2a** in high yields (Table 1, entries 7−11). Notably, among the tested ethereal solvents, dioxane generated the strongest reducing system, and the reduction of **1a** was completed within 0.5 h to give **2a** in 89% yield. Further screening the quantity of Et_2Zn needed in the reduction reaction in dioxane, we found that 3 equiv of Et_2Zn was enough to drive the reaction to completion (Table 1, entries 11−15).

Table 1. Reduction of **1a** by Diethylzinc and Catalytic $Ni(acac)_2$



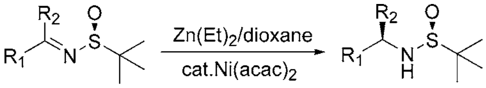
racemic-1a **racemic-2a**

entry	solvent	Et_2Zn (equiv)	time (h)	yield[a] (%)
1	CH_2Cl_2	5	24	42
2	dichloroethane	5	24	63
3	$CHCl_3$[b]	5		
4	CCl_4[b]	5		
5	CH_3CN	5	8	52
6	toluene	5	10	89
7	DME	5	6	79
8	$^iPr_2O$	5	6	85
9	Et_2O	5	10	91
10	THF	5	10	89
11	dioxane	5	0.5	89
12	dioxane	4	0.5	87
13	dioxane	3	0.5	88
14	dioxane	2	1	82
15	dioxane	1	20	71

[a] Isolated yields. [b] A dark precipitate was formed.

The effects of solvents and temperature on the diastereoslectivity of reduction reaction were studied using enantiopure phenylmethyl ketimine S_S-**1a** as a substrate. As shown in Table 2, a similar diastereoselectivity of around 96:4 was observed either using toluene or ethereal solvents (Table 2, entries 1−3 and 7). We had tested the reduction of S_S-**1a** at different temperatures such as 25, 0, −20, and −45 °C, respectively, in THF (Table 2, entries 3−6). The results indicated that lowering the temperature did not improve the diastereoselectivity but dramatically decreased the reductant capability of Et_2Zn to S_S-**1a**.

Table 2. Reduction of Ketimine S_S-**1** by Diethylzinc in the Presence of 5 mol % of $Ni(acac)_2$[a]



S_S**-1** S_S**-2**

entry	1	R_1	R_2	solvent	yield[b] (%)	dr and config[c]
1	**1a**	Ph	Me	toluene	87	95:5 (*S*)[d]
2	**1a**	Ph	Me	Et_2O	90	96:4 (*S*)[d]
3	**1a**	Ph	Me	THF	89	96:4 (*S*)[d]
4[f]	**1a**	Ph	Me	THF	84	96:4 (*S*)[d]
5[g]	**1a**	Ph	Me	THF	81	96:4 (*S*)[d]
6[h]	**1a**	Ph	Me	THF	9	
7	**1a**	Ph	Me	dioxane	88	96:4 (*S*)[d]
8	**1b**	4-MeO-Ph	Me	dioxane	92	98:2 (*S*)[d]
9	**1c**	Ph	Et	dioxane	90	89:11 (*S*)[d]
10	**1d**	Ph	^iPr	dioxane	82	85:15 (*S*)[e]
11	**1e**	Ph	^tBu	dioxane	23	96:4 (*R*)[d]
12	**1f**	Pr	Me	dioxane	88	73:27 (*S*)[d]
13	**1g**	^iPr	Me	dioxane	71	82:18 (*S*)[e]
14	**1h**	^iBu	Me	dioxane	81	95:5 (*R*)[d]

[a] Reactions were conducted at room temperature with 3 equiv of Et_2Zn and 5 mol % of $Ni(acac)_2$. [b] Isolated yield. [c] Absolute configuration of amine was determined by comparing rotation with that of known amine after removing the *tert*-butanesulfinyl group of **2**. [d] Diastereomeric ratio was determined by HPLC. [e] Diastereomeric ratio was determined by ^1H NMR of the crude product. [f] At 0 °C. [g] At −20 °C. [h] At −45 °C.

Since dioxane could generate the most powerful reduction system, studies of dialkylzinc reduction to a variety of enantiopure ketimines S_S-**1** were conducted in dioxane at room temperature using 3 equiv of Et_2Zn and 5 mol % of $Ni(acac)_2$.[7] As shown in Table 2, for both aryl alkyl ketimines and dialkyl ketimines, the dialkylzinc reduction of S_S-**1** was completed within 1 h to afford S_S-**2** in high yields and

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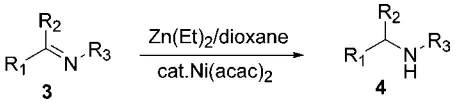
(5) For reviews on chiral sulfinylimine chemistry, see: (a) Zhou, P.; Chen, B.-C.; Davis, F. A. *Tetrahedron* **2004**, *60*, 8003. (b) Ellman, J. A.; Owens, T. D. *Pure Appl. Chem.* **2003**, *75*, 39. (c) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984. (d) Davis, F. A.; Zhou, P.; Chen, B.-C. *Chem. Soc. Rev.* **1998**, *27*, 13.

(6) A mixture of dialkylzinc with a catalytic amount of nickel has been known to be an effective reagent for the alkylative carboxylation of alkynes for the intramolecular cyclization of allenyl aldehyde, homoallylation of aldehyde and aldimines with 1,3-dienes and with alkeyne, selective addition of cyclic anhydrides, Reformatsky-type imine addition, and conjugate aldol addtion; see: (a) Bercot, E. A.; Rovis, T. *J. Am. Chem. Soc.* **2005**, *127*, 247. (b) Kimura, M.; Miyachi, A.; Kojima, K.; Tanaka, Sh.; Tamaru, Y. *J. Am. Chem. Soc.* **2004**, *126*, 14360. (c) Adrian, J. C., Jr.; Snapper, M. L. *J. Org. Chem.* **2003**, *68*, 2143. (d) Montgomery, J.; Subburaj, K. *J. Am. Chem. Soc.* **2003**, *125*, 11210. (e) Montgomery, J.; Lozanov, M. *J. Am. Chem. Soc.* **2002**, *124*, 2106. (f) Montgomery, J.; Song, M. *Org. Lett.* **2002**, *4*, 4009. (g) Loh, T.-P.; Song, H.-Y.; Zhou, Y. *Org. Lett.* **2002**, *4*, 2715. (h) Bercot, E. A.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 174. (i) Takimoto, M.; Shimizu, K.; Mori, M. *Org. Lett.* **2001**, *3*, 3345. (j) Kimura, M.; Fujimatsu, H.; Ezoe, A.; Shibata, K.; Shimizu, M.; Matsumoto, S.; Tamaru, Y. *Angew. Chem., Int. Ed.* **1999**, *38*, 8, 397. (k) Oblinger, E.; Montgomery, J. *J. Am. Chem. Soc.* **1997**, *119*, 9065.

moderate to high diastereoselectivities (Table 2, entries 7−14). The exception was the reduction with sterically hindered phenyl *tert*-butyl ketimine **1e**, where the reduction was very sluggish to yield **2e** in a low yield (Table 2, entry 11). The reductions with aromatic ketimines usually provided higher diastereoselectivity than the reduction with aliphatic ketimines.

The applicable scope of Ni(acac)$_2$-catalyzed diethylzinc reduction to both electronically deficient and electronically rich imine[8] was then tested. As shown in Table 3, reduction of electronically deficient aromatic imines **3a**−**d** with 3 equiv of Et$_2$Zn and 5 mol % of Ni(acac)$_2$ in dioxane gave amines **4a**−**d** in high yields (Table 3, entries 1−4), while the reduction of aliphatic imines **3e**−**f** under the same conditions gave poor yields (Table 3, entries 5−6). In contrast to the reduction of electronically deficient imines, the reduction of electronically rich imine **3g** was unsuccessful (Table 3, entry 7).

Table 3. Reduction of Imine **3** by Diethylzinc in the Presence of 5 mol % of Ni(acac)$_2$[a]



entry	3	R$_1$	R$_2$	R$_3$	yield of **4**[b] (%)
1	**3a**	Ph	H	Ts	**4a** (83)
2	**3b**	Ph	Me	Ts	**4b** (78)
3	**3c**	Ph	Ph	Ts	**4c** (92)
4	**3d**	Ph	Et	^{t}BuSO$_2$	**4d** (88)
5	**3e**	Pr	Me	^{t}BuSO$_2$	**4e** (19)
6	**3f**	^{i}Bu	Me	^{t}BuSO$_2$	**4f** (22)
7	**3g**	Ph	Me	Ph	**4g** (0)

[a] Reactions were conducted at room temperature with 3 equiv of Et$_2$Zn and 5 mol % of Ni(acac)$_2$. [b] Isolated yield.

It was interesting to know whether the selective reduction of imine in the presence of ketone could be achieved by employing the current reduction method, since selective reduction between imine and ketone was always problematic using common reductants such as DIBAL, LiAiH$_4$, NaBH$_4$, BH$_3$, and 9-BBN. Three competitive reactions were designed to test the possibility. Thus, under our best condition (3 equiv of Et$_2$Zn, 5 mol % of Ni(acac)$_2$ in dioxane), reduction of a 1:1 mixture of *S*$_S$-**1a** and acetophenone **5** (1 equiv) afforded *S*$_S$-**2a** in 88% yield, ketone **5** totally remained unchanged as shown by HPLC analysis of the crude product (Figure 1, eq 1). Reduction of a 1:1 mixture of *S*$_S$-**1h** and isobutyl methyl ketone **7** gave *S*$_S$-**2h** in 80% yield, and ketone **7** completely survived the reaction as shown by GC analysis of the crude product (Figure 1, eq 2). Similarly, *N*-Ts imine **3b** was reduced to afford **4b** in 78% yield without affecting the acetophenone **5** under the same conditions (Figure 1, eq 3).

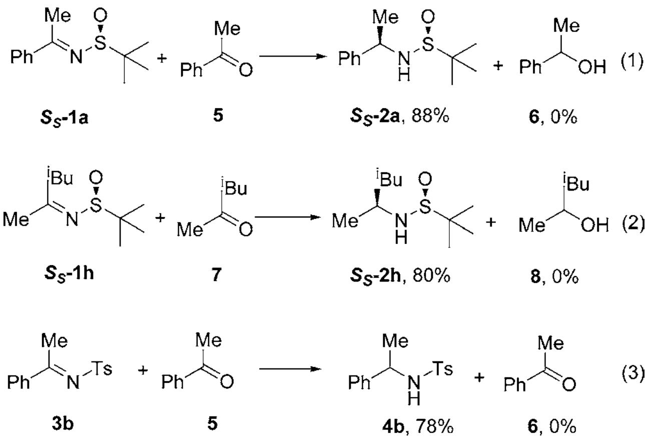


Figure 1.

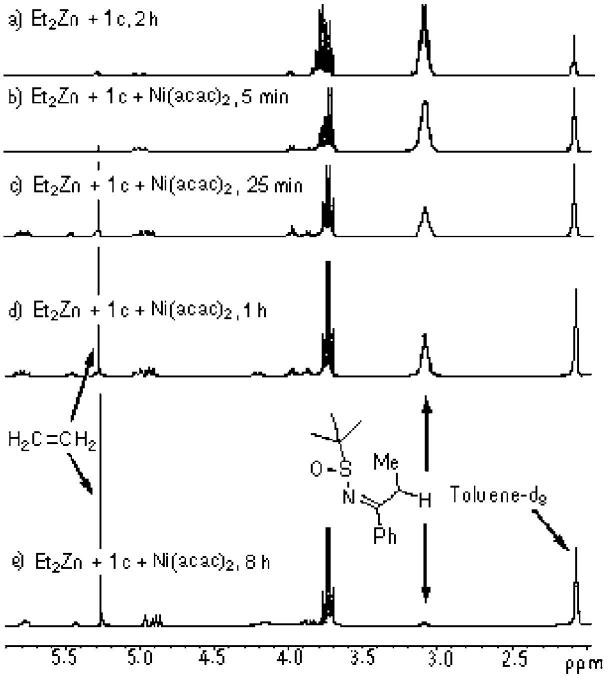


Figure 2.

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[7] The diastereoselective reduction of *tert*-butanesulfinyl ketimines by Ti(O^{i}Pr)$_4$-mediated NaBH$_4$ was reported by Ellman; see: Borg, G.; Cogan, D. A.; Ellman, J. A. *Tetrahedron Lett.* **1999**, *40*, 6709.

[8] For the preparation of *N*-sulfonyl imines, see: (a) Ruano, J. L. J.; Aleman, J.; Cid, M. B.; Parra, A. *Org. Lett.* **2005**, *7*, 179. (b) Jin, T.; Feng, G.; Yang, M.; Li, T. *Synth. Commun.* **2004**, *34*, 1277. (c) Wolf, J.; Ney, J. E. *Org. Lett.* **2003**, *5*, 4607. (d) Lee, K. Y.; Lee, C. C.; Kim, J. N. *Tetrahedron Lett.* **2003**, *44*, 1231. (e) Ram, R. N.; Khan, A. A. *Synth. Commun.* **2001**, *31*, 841. (f) Chemla, F.; Hebbe, V.; Notmant, J.-F. *Synthesis* **2000**, *11*, 75. (g) Sandrinelli, F.; Perrio, S.; Belsin, P. *J. Org. Chem.* **1997**, *62*, 8626. (h) Georg, G. I.; Harriman, G. B.; Peterson, S. A. *J. Org. Chem.* **1995**, *60*, 7366. (i) Boger, D. L.; Corbett, W. L. *J. Org. Chem.* **1992**, *57*, 4777. (j) Trost, B. M.; Christopher, M. *J. Org. Chem.* **1991**, *56*, 6468. (k) Jennings, W. B.; Lovely, C. J. *Tetrahedron* **1991**, *47*, 5561. (l) Davis, F. A.; Lamendola, J., Jr.; Nadir, U.; Kluger, E. W.; Sedergran, T. C.; Panunto, T. W.; Billmers, R.; Jenkins, R., Jr.; Turchi, I. J.; Watson, W. H.; Chen, J. S.; Kimura, M. *J. Am. Chem. Soc.* **1980**, *102*, 2000.

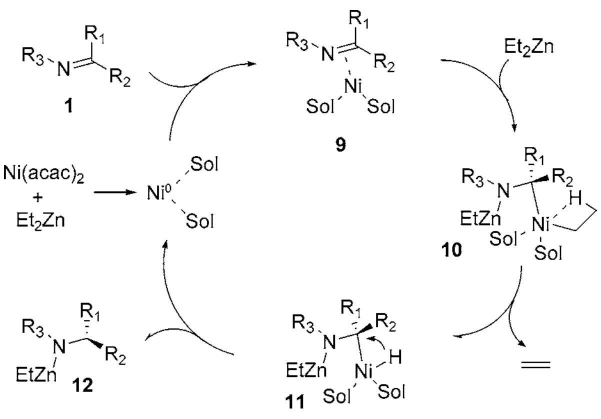

Figure 3. Plausible mechanism of Et_2Zn reduction of imine catalyzed by $Ni(acac)_2$.

To understand the reaction mechanism, we had conducted the reduction of S_S-**1c** in an NMR tube in toluene-d_8 at room temperature. The reaction procedure was tracked by measuring ^1H NMR signals corresponding to the constituents of reaction mixture. The ^1H NMR spectra truncated between 2.0 and 6.0 ppm are compiled in Figure 2. When ketimine S_S-**1c** was mixed with Et_2Zn in the absence of $Ni(acac)_2$ for 2 h, we did not observe any change of the ^1H NMR spectrum of reaction mixture (Figure 2, spectrum a). Once the $Ni(acac)_2$ (5 mol %) was added into the reaction mixture, the NMR tube was then sealed to record the ^1H NMR spectra at different times. As shown in spectrum b of Figure 2, only a trace amount of ethylene was detected at 5.28 ppm at 5 min after adding $Ni(acac)_2$. With the reaction proceeding smoothly, more ethylene was released into the reaction mixture. As a result, the peak at 5.28 ppm ascribed to ethylene proton became a major peak (Figure 2, spectra c and d). At the same time, an apparent shrinking of the methylene proton peak of S_S-**1c** at 3.05 ppm occurred, which indicated the gradual consumption of S_S-**1c** during the reaction. The methylene proton peak of S_S-**1c** disappeared when the reaction was completed at 8 h after adding $Ni(acac)_2$ (Figure 2, spectrum e).

Based on the NMR study of the reduction reaction, a plausible mechanism is suggested for the $Ni(acac)_2$-catalyzed diethylzinc reduction of imines (Figure 3).

Ni(II) is first reduced by diethylzinc to give Ni(0) as a catalytically active species. The resulting Ni(0) coordinates to the C═N double bond of imine **1** with the aid of solvent to form a complex **9**. Transmetalation of **9** with Et_2Zn affords the ethyl nickel complex **10**. β-Hydrogen elimination of ethyl in **10** releases elthylene to form hydride nickel complex **11**. Reductive elimination of Ni(0) provides intermediate **12** and releases Ni(0) to complete one catalytic cycle.

In summary, we have described a highly efficient reduction method to reduce *tert*-butanesulfinyl ketimines in moderate to high yields and diastereoselectivityies by employing Et_2Zn and a catalytic amount of $Ni(acac)_2$. This method can be expanded to the reduction of electronically deficient imines. The remarkable aspect of this method is that the imine reduction can be achieved in the presence of ketone, which is an important complement to known methods. Further study will be focused on the application of current method in asymmetric reduction of achiral imines catalyzed by a chiral nickel complex.

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Supporting Information Available: Experimental details, spectra data of of compounds **2** and **4**, and GC and HPLC analysis data. This material is available free of charge via the Internet at http://pubs.acs.org.

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