ORGANIC LETTERS

2011
Vol. 13, No. 5
964–967

Asymmetric Synthesis of Amines by the Knochel-Type $MgCl_2$-Enhanced Addition of Benzyl Zinc Reagents to *N-tert*-Butanesulfinyl Aldimines

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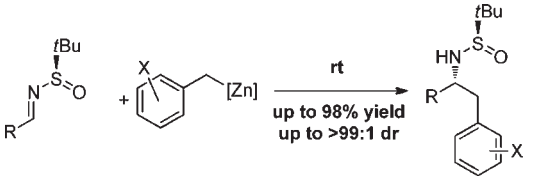
Received December 10, 2010

ABSTRACT



The $MgCl_2$-enhanced addition of benzyl zinc reagents to *N-tert*-butanesulfinyl imines proceeds readily at room temperature to afford the *N-tert*-butanesulfinyl-protected amine products in good yields and diastereomeric ratios. This method is functional group tolerant in both the imine substrate and benzyl zinc coupling partner. Moreover, benzyl zinc reagent addition to the *N-tert*-butanesulfinyl imine 3o prepared from isopropylidene-protected glyceraldehyde proceeds in high yield and with exceptional selectivity to provide rapid entry to hydroxyethylamine-based aspartyl protease inhibitors.

The addition of organometallic reagents to *N-tert*-butanesulfinyl imines is one of the most extensively used approaches for the asymmetric synthesis of amines.[1] The addition of Grignard and organolithium reagents was developed first and proceeded with high yields and diastereoselectivities for a broad range of coupling partners.[2] Still, these methods suffer from poor functional group compatibility and require low reaction temperatures. Rhodium-catalyzed additions of boron reagents to *N-tert*-butanesulfinyl aldimines greatly expanded the breadth of functionality that may be present during the addition step.[3] However, these methods are currently limited to the coupling of aryl and vinyl boron reagents, which are sp^2 hybridized. Therefore, additions of sp^3 hybridized organometallic reagents that also proceed with broad functional group compatibility would represent a significant advance, but to date functional group tolerant additions of allylzinc[4] and allylindium reagents[5] have primarily been reported.

Recently, Knochel and co-workers reported that while organozinc halides normally do not react with aldehydes or ketones, the preparation of alkyl and benzyl reagents using a mixture of Mg^0, LiCl, and $ZnCl_2$ (Scheme 1) results in a species that adds efficiently in high yields and with good functional group compatibility.[6] Herein we report

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(2) For initial reports, see: (a) Cogan, D. A.; Liu, G.; Ellman, J. *Tetrahedron* **1999**, *55*, 8883. (b) Liu, G.; Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1997**, *119*, 9913. (c) Pflum, D. A.; Krishnamurthy, D.; Han, Z.; Wald, S. A.; Senanayake, C. H. *Tetrahedron Lett.* **2002**, *43*, 923. (d) Plobeck, N.; Powell, D. *Tetrahedron: Asymmetry* **2002**, *13*, 303.

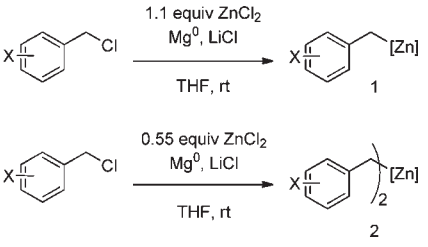
(3) For rhodium-catalyzed additions to *N-tert*-butanesulfinyl imines, see: (a) Weix, D. J.; Shi, Y.; Ellman, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 1092. (b) Bolshan, Y.; Batey, R. A. *Org. Lett.* **2005**, *7*, 1481. (c) Beenen, M. A.; Weix, D. J.; Ellman, J. A. *J. Am. Chem. Soc.* **2006**, *128*, 6304. (d) Truong, V. L.; Pfeiffer, J. Y. *Tetrahedron Lett.* **2009**, *50*, 1633. (e) Brak, K.; Ellman, J. A. *J. Am. Chem. Soc.* **2009**, *131*, 3850. (f) Brak, K.; Ellman, J. A. *J. Org. Chem.* **2010**, *75*, 3147.

(4) (a) Sun, X.-W.; Xu, M.-H.; Lin, G.-Q. *Org. Lett.* **2006**, *8*, 4979. (b) Kolodney, G.; Sklute, G.; Perrone, S.; Knochel, P.; Marek, I. *Angew. Chem., Int. Ed.* **2007**, *46*, 9291. (c) Sun, X.-W.; Liu, M.; Xu, M.-H. Lin, G.-Q. *Org. Lett.* **2008**, *10*, 1259. (d) Reddy, L. R.; Hu, B.; Prashad, M. *Org. Lett.* **2008**, *10*, 3109. (e) Shen, A.; Liu, M.; Jia, Z.-S.; Xu, M.-H.; Lin, G.-Q. *Org. Lett.* **2010**, *12*, 5154.

(5) (a) Cooper, I. R.; Grigg, R.; MacLachlan, W. S.; Thornton-Pett, M.; Sridharan, V. *Chem. Commun.* **2002**, 1372. (b) Foubelo, F.; Yus, M. *Tetrahedron: Asymmetry* **2004**, *15*, 3823. (c) Gonzalez-Gomez, J. C.; Medjahdi, M.; Foubelo, F.; Yus, M. *J. Org. Chem.* **2010**, *75*, 6308.

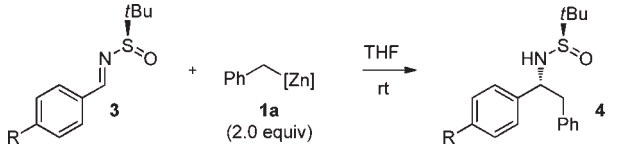
10.1021/ol103002t
Published on Web 02/09/2011

Scheme 1. Preparation of Benzyl Zinc Reagents



the application of this new methodology for the diastereoselective addition of a variety of benzyl zinc reagents to *N-tert*-butanesulfinyl imine substrates with excellent functional group tolerance.[7,8]

Table 1. Optimization of Benzyl Zinc Additions

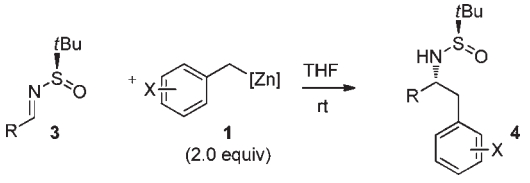


entry	reagent preparation	R	4	yield,[a] %	dr[b]
1	30 min	OMe	**4a**	70	92:8
2	3 h	OMe	**4a**	76	81:19
3	30 min	CO_2Me	**4b**	77	93:7
4	3 h	CO_2Me	**4b**	overaddition[c]	nd[d]
5[e]	30 min	CO_2Me	**4b**	83	90:10
6[f]	30 min	CO_2Me	**4b**	88	93:7

[a] Determined by ^1H NMR relative to an external standard. [b] Determined by ^1H NMR. [c] 57% triple addition product, 37% double addition product. [d] Not determined. [e] Reagent stored in a Schlenk flask under static N_2 for 20 days. [f] 4.0 equiv of **1a**.

We began by investigating the addition of the unsubstituted benzyl zinc reagent **1a** to the *p*-methoxy- and *p*-methylcarboxy-substituted aromatic imine substrates **3** (Table 1). Appropriate reagent preparation time was found to vary with the quality of the magnesium used, and therefore initial reagent preparations were monitored by following consumption of the benzyl chloride by GC. For benzyl zinc reagent **1a**, a 30 min reagent preparation time and 2.0 equiv of reagent in the addition were found to produce the optimal results (entries 1 and 3). Extended reagent preparation time was found to result in lower diastereoselectivity (entry 2) and overaddition into the ester functional group (entry 4). These negative effects were not observed when the reagent was filtered away from excess magnesium immediately after consumption of the benzyl chloride starting material. Despite a decrease in reagent concentration from 0.33 to 0.19 M,[9] reagent stored in a Schlenk flask for 20 days reacted similarly to freshly prepared reagent (entry 5). Furthermore, overaddition was not observed with a large excess of benzyl zinc reagent prepared under the standard conditions (entry 6). Together, these results suggest that the presence of excess Mg^0 after formation of the initial desired benzyl zinc reagent leads to the formation of a second more reactive and less selective organometallic reagent.

Table 2. Benzyl Zinc Additions to *N-tert*-Butanesulfinyl Aldimines



entry	R	1	X	4	yield,[a] %	dr[b]
1	4-$OMeC_6H_4$	**1a**	H	**4a**	85	90:10[c]
2	4-$CO_2MeC_6H_4$	**1a**	H	**4b**	86	92:8
3	4-ClC_6H_4	**1a**	H	**4c**	87	92:8
4	3-ClC_6H_4	**1a**	H	**4d**	86	92:8
5	2-ClC_6H_4	**1a**	H	**4e**	79	>99:1
6	3-Py	**1a**	H	**4f**	98	96:4
7	4-$CO_2MeC_6H_4$	**1b**	4-OMe	**4g**	69	94:6[d]
8	3-Py	**1b**	4-OMe	**4h**	42	98:2
9	4-$CO_2MeC_6H_4$	**1c**	4-F	**4i**	86	94:6
10	4-CNC_6H_4	**1c**	4-F	**4j**	83	98:2
11	*t*Bu	**1c**	4-F	**4k**	77	76:24[d,e]
12	$PhCH_2CH_2$	**1c**	4-F	**41**	76	77:23[f]

[a] Isolated yield of mixture of diastereomers after purification by chromatography. [b] Determined by HPLC comparison to authentic diastereomers. [c] Absolute configuration determined by comparison of the optical rotation of the amine obtained upon sulfinyl deprotection to literature values (see the Supporting Information). [d] Absolute configuration was determined by X-ray crystallography. [e] Determined by mass balance of separately isolated diastereomers. [f] Determined by ^1H and ^{19}F NMR.

The optimal conditions were next evaluated for a range of *N-tert*-butanesulfinyl aldimine substrates and organozinc coupling partners (Table 2). Reactions with both electron-rich (entry 1) and electron-poor aromatic imines (entries 2−5) proceeded with excellent yields and good diastereoselectivity. Para-, meta-, and ortho-substitution were all well tolerated (entries 3−5). As expected, ortho-substitution resulted in a slightly diminished yield but proceeded with very high diastereoselectivity. Additions

(6) (a) Metzger, A.; Bernhardt, S.; Manolikakes, G.; Knochel, P. *Angew. Chem., Int. Ed.* **2010**, *49*, 4665. (b) Piller, F. M.; Metzger, A.; Schade, M. A.; Haag, B. A.; Gavryushin, A.; Knochel, P. *Chem.—Eur. J.* **2009**, *15*, 7192.

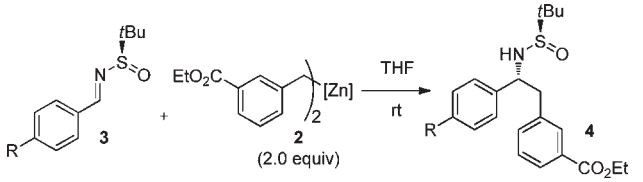
(7) For studies on the addition of organozincates, prepared from Grignard and dialkylzinc reagents, to *N-tert*-butanesulfinyl imines, see: (a) Almansa, R.; Guijarro, D.; Yus, M. *Tetrahedron: Asymmetry* **2008**, *19*, 603. (b) Almansa, R.; Guijarro, D.; Yus, M. *Tetrahedron: Asymmetry* **2008**, *19*, 2484. (c) Almansa, R.; Guijarro, D.; Yus, M. *Tetrahedron. Lett.* **2009**, *50*, 3198.

(8) For an important application of substituted benzyl Grignard reagent addition to *N-tert*-butanesulfinyl imines for the preparation of inhibitors of aspartyl proteases such as HIV protease and β-secretase, see: Harried, S. S.; Croghan, M. D.; Kaller, M. R.; Lopez, P.; Zhong, W.; Hungate, R.; Reider, P. J. *J. Org. Chem.* **2009**, *74*, 5975.

(9) Determined by iodometric titration.

to ester- and nitrile-substituted imines (entries 2, 7, 9, and 10) demonstrated the functional group compatibility of this method. Furthermore, the benzyl reagent added to the 3-pyridyl imine substrate in high yield and with good diastereoselectivity, indicating that nitrogen heterocycles that often interfere with transition metal-catalyzed additions, such as Rh-catalyzed arylboronic acid additions,[3] do not interfere with these $MgCl_2$-enhanced benzyl reagent additions. Additions to alkyl imine substrates (entries 11 and 12) also proceeded in good yields although with only moderate selectivity. Finally, electron-neutral (entry 2), electron-rich (entry 7), and electron-poor (entry 9) organozinc coupling partners reacted smoothly and provided good stereoselectivity and functional group tolerance.

Table 3. Ester-Substituted Dibenzyl Zinc Additions



entry	R	4	yield,[a] %	dr[b]
1	H	**4m**	73	80:20
2	CN	**4n**	74	97:3[c]

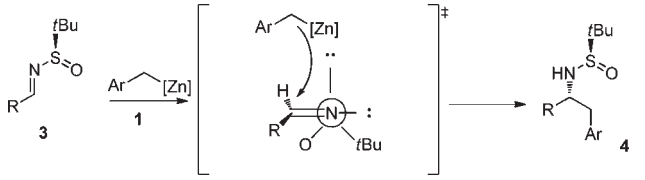
[a] Isolated yield of a mixture of diastereomers after purification by chromatography. [b] Determined by HPLC comparison to authentic diastereomers. [c] HPLC of the crude material suggested a dr of 87:13.

Further highlighting the functional group compatibility of this method, ester-substituted organozinc reagents were added to both unsubstituted and nitrile-substituted aromatic imines with good yields and moderate to good selectivity (Table 3). However, these reactions required the more reactive dibenzyl zinc reagent, prepared with 0.55 equiv of $ZnCl_2$ (Scheme 1).

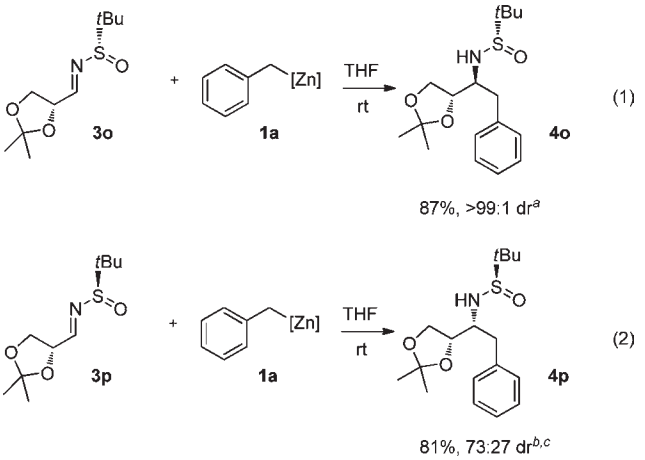
The sense of induction for these addition reactions was determined by rigorously establishing the absolute configurations of addition product **4a** by chemical correlation and products **4k** and **4g** by X-ray structural analysis.[10] The sense of induction is consistent with an open transition state as proposed for a number of *N*-*tert*-butanesulfinyl imine addition reactions (Scheme 2).[1] Presumably, the excess of coordinating ions in conjunction with the use of a coordinating solvent favor this transition state over a chelating transition state.

The utility of the method was demonstrated by the synthesis of *anti*-3-amino-4-arylbutane-1,2-diol derivatives (Scheme 3), which are useful intermediates in the preparation of hydroxyethylamine-based inhibitors of aspartyl proteases such as HIV protease and β-secretase (BACE 1).[8,11] Benzyl zinc reagent **1a** added to imine **3o** prepared from isopropylidene-protected glyceraldehyde in high yield and with exceptionally high selectivity (eq 1). Importantly, the stereochemistry obtained is that most commonly found in hydroxyethylamine-based protease inhibitors. Addition to imine **3p** also proceeded in high yield but with modest selectivity for the syn diastereomer (eq 2).

Scheme 2. Stereochemical Rationale



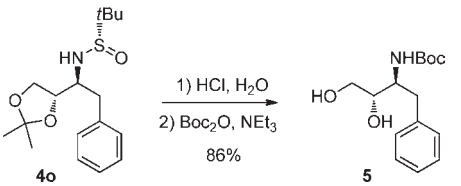
Scheme 3. Addition to Glyceraldehyde-Derived Imines[c]



[a] Determined by HPLC comparison to authentic diastereomers. [b] Determined by mass balance of separately isolated diastereomers. [c] ^1H NMR of the crude material suggested a dr of 67:33.

Diastereomer **4o** was readily converted to *N*-Boc amino diol **5** by simultaneous deprotection of the sulfinyl and isopropylidene protecting groups followed by Boc-protection of the amine functionality (Scheme 4). *N*-Boc-3-amino-1,2-diols with the stereochemistry present in **5** provide direct access to hydroxyethylamine inhibitors.[12]

Scheme 4. Elaboration of Amine **4o**



(10) See the Supporting Information for more details.

(11) For reviews of aspartyl protease inhibitors and their synthesis, see: (a) Ghosh, A. K. *J. Med. Chem.* **2009**, *52*, 2163. (b) Izawa, K.; Onishi, T. *Chem. Rev.* **2006**, *106*, 2811. (c) Huang, W.-H.; Sheng, R.; Hu, Y.-Z. *Curr. Med. Chem.* **2009**, *16*, 1806–1820.

Oxidative conversion of **5** to *N*-Boc-(*S*)-phenylalanine also enabled rigorous assignment of the configuration at the amine stereocenter.[13]

In conclusion, the $MgCl_2$-enhanced addition of benzyl zinc reagents to *N*-*tert*-butanesulfinyl imines occurs readily at room temperature. Good yields, selectivity, and functional group tolerance are observed for a variety of aromatic imines. Moreover, ester-substituted dibenzyl zinc reagents readily add to nitrile-substituted imines without cross-reactivity, further highlighting the functional-group compatible nature of the transformation. Although benzyl additions to aliphatic imines generally showed only moderate selectivity, addition to sulfinyl imine **3o** prepared from isopropylidene-protected glyceraldehyde proceeded in high yield and with very high selectivity, indicating that this method should allow the rapid introduction of a variety of functionalized benzyl substituents into hydroxyethylamine-based aspartyl protease inhibitors.

Acknowledgment. This work was supported by the NSF (CHE-1049571).

Supporting Information Available. Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

(12) For literature procedures for the straightforward conversion of Boc amino diol **5** to the corresponding *anti*-*N*-protected-3-amino-1,2-epoxide, see: Branalt, J.; Kvarnstrom, I.; Classon, B.; Samuelsson, B.; Nillroth, U.; Danielson, U. H.; Karlen, A.; Hallberg, A. *Tetrahedron Lett*. **1997**, *38*, 3483.

(13) See the Supporting Information.