JOC Article

Modular Stereocontrolled Assembly of R_2Zn, Cyclic Enones and *N-tert*-Butanesulfinyl Imines†

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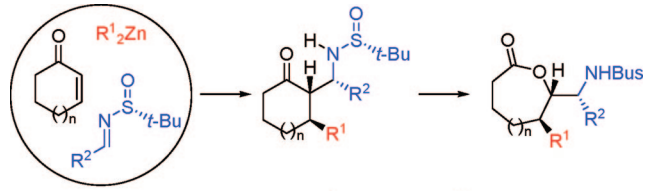

[n = 0, 1, 2; R^1 = alkyl, aryl; R^2 = alkyl, aryl]

The assembly of a wide range of dialkylzincs, cyclic enones, and chiral *N-tert*-butylsulfinyl imines in the presence of the appropriate phosphoramidite ligands allowed the formation of β-amino ketones with three consecutive stereogenic centers in a stereocontrolled manner. The Baeyer−Villiger oxidation of the resulting amino ketones led to the corresponding aminolactones with excellent regio- and stereoselectivities.

Introduction

The development of new stereoselective multicomponent reactions (MCRs) is of fundamental importance for the advancement of organic synthesis. Reactions that build up carbon−carbon and carbon−nitrogen bonds and, at the same time, introduce heteroatom-containing functionality into the structural framework are particularly attractive for the rapid construction of organic molecules. Coupled with the challenge of controlling the stereoselective outcome of any elementary reaction implicated in the final cascade, MCRs offer a unique opportunity to create building blocks of high molecular complexity.[1]

Chiral β-amino ketones are important building blocks for the asymmetric synthesis of biologically active molecules;[2] these compounds have been used in the stereoselective synthesis of 1,3-aminoalcohols,[3] homoallylic amines,[4] piperidines,[5] indolizidines,[6] and other alkaloids.[7] A particularly inspiring contribution to the asymmetric synthesis of α-substituted β-amino ketones is the diastereoselective addition of lithium enolates to chiral *N*-sulfinyl imines (sulfinimines), which was recently developed by Davis.[8] Chiral sulfinimines have been widely studied, particularly by Davis[9] and Ellman,[10] who developed the use of *N-p*-tolylsulfinimines and *N-tert*-butyl derivatives, respectively. Indeed, one of the most direct and reliable methods for the asymmetric synthesis of amine derivatives is the addition of an organometallic reagent to the C=N bond of enantiopure sulfinimines.[11]

The copper-catalyzed addition of dialkylzinc reagents to cyclic enones in the presence of phosphoramidite ligand **L1** developed by Feringa leads to chiral enolates in high yields and stereoselectivities (ee > 98%).[12] It has been reported that these chiral enolates react with different electrophiles to give predominantly

† Dedicated to Professor Josep Font on occasion of his 70th birthday.

(1) Recent discussions of asymmetric multicomponent reactions:(a) Marcaccini, S.; Torroba, T. In *Multicomponent Reactions*; Zhu, J., Bienayme, H., Eds.; Wiley-VCH: Wienheim, 2005; p 33. (b) Ramón, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602. (c) Guo, H.-C.; Ma, J.-A. *Angew. Chem., Int. Ed.* **2006**, *45*, 354. (d) Enders, D.; Hüttl, M. R.; Grondal, C.; Raabe, G. *Nature* **2006**, *441*, 861. (e) Dömling, A. *Chem. Rev.* **2006**, *106*, 17. (f) *Domino Reactions in Organic Synthesis*; Tietze, L. F., Brasche, G., Gericke, K., Eds.; Wiley-VCH: Weinheim, 2006.

(2) Kleinman, E. F. In *Comprehensive Organic Synthesis*; Heathcock, C. H., Ed.; Pergamon Press: Oxford, 1991; Vol. 2, Chapter 4, p 893.

(3) For a review see:Bates, R. W.; Sa-Ei, K. *Tetrahedron* **2002**, *58*, 5957.

(4) For leading references see:(a) Ishimaru, K.; Kojima, T. *J. Org. Chem.* **2000**, *65*, 8395. (b) Davis, F. A.; Song, M.; Augustine, A. *J. Org. Chem.* **2006**, *71*, 2779.

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(7) (a) Shultz, A. G.; Dai, M. *Tetrahedron Lett.* **1999**, *40*, 645. (b) Chan, C.; Zheng, S.; Zhou, B.; Guo, J.; Heid, R. M.; Wright, B. J. D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 1749.

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(9) (a) Davis, F. A. *J. Org. Chem.* **2006**, *71*, 8993. (b) Zhou, P.; Chen, B.-C.; Davis, F. A. *Tetrahedron* **2004**, *60*, 8003.

(10) (a) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984. (b) Fernández, I.; Khiar, N.; Llera, J. M.; Alcudia, F. *J. Org. Chem.* **1992**, *57*, 6789.

(11) For a recent review see:(a) Morton, D.; Stockman, R. A. *Tetrahedron* **2006**, *62*, 8869.

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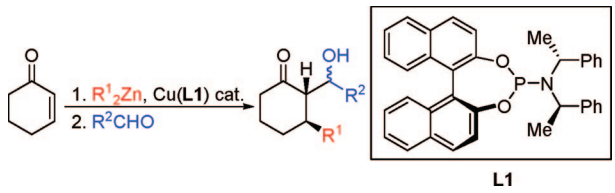
SCHEME 1. Tandem Enantioselective Conjugate Addition−Aldol Reaction



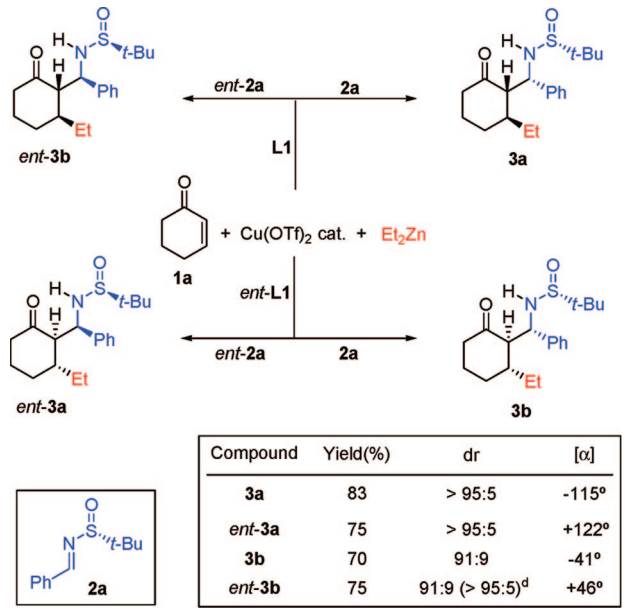
trans substitution. However, when prostereogenic aldehydes are used, the newly generated stereogenic center β to the carbonyl group is usually formed in a stereorandom manner (Scheme 1).[13] In this context, we recently reported a modular route to chiral β-amino ketones that involved trapping the in situ-generated homochiral enolates with chiral *N*-sulfinimines.[14] We report here a full account of our studies of the first highly stereoselective multicomponent assembly of dialkylzinc reagents, cyclic enones, and chiral sulfinimines. The scope of the reaction has also been expanded and an interesting new synthetic application of chiral β-amino ketones is described.

Results and Discussion

N-tert-Butanesulfinimines (*t*-BS imines) are known to be less reactive toward metal enolates than other chiral sulfinimines.[15] However, we initially explored the reactivity of these compounds due to the ready availability of both antipodes[16] and the high stereoinduction of the *tert*-butyl group.[17] Since it was reasoned that chiral *t*-BS imines would overcome the directing effect of a chiral enolate at the Mannich stereocenter,[18] we anticipated that this tandem enantioselective conjugate addition−Mannich reaction could provide a selective route to four diastereomeric β-amino ketones. The results of the initial screening are summarized in Scheme 2.

After some experimentation, we determined that 3 mol % of copper, 4 equiv of Et_2Zn, and 3 equiv of enone **1a** were required for a good conversion of the aromatic sulfinimine **2a**. We were pleased to find that the use of chiral phosphoramidite **L1** in the test reaction gave the expected compound **3a** in good yield as a single diastereoisomer (Scheme 2). Importantly, similar results were obtained when Et_2Zn was added either before or after the sulfinimine, indicating that enolate formation is possible in the presence of the electrophile, this process being therefore a truly multicomponent reaction.[19] Considering that copper-catalyzed alkylation or reduction of imines with dialkylzinc reagents is a known process,[20] the high selectivity achieved in this tandem process is notable. Compound *ent*-**3a** was obtained under these optimized conditions in enantiomerically pure form in the reaction between the *S*-sulfinimine *ent*-**2a** and the enantiomer of ligand **L1** (*ent*-**L1**). When the pairs *ent*-**L1** ligand/*R*-sulfinimine (**2a**) or **L1** ligand/*S*-sulfinimine (*ent*-**2a**) were used, compounds **3b** and *ent*-**3b** were the major products, respectively (Scheme 2). The slightly worse stereoselectivity observed in these cases (about 9:1 dr) would seem to point to a moderate mismatch effect between the corresponding homochiral enolate and the chiral sulfinimine. Interestingly, we observed that this possible mismatch effect could be overcome by using a larger excess of Et_2Zn.

SCHEME 2. Development of a Tandem Stereoselective Conjugate Addition−Mannich Reaction[a−c]



Compound	Yield(%)	dr	[α]
3a	83	> 95:5	-115°
ent-**3a**	75	> 95:5	+122°
3b	70	91:9	-41°
ent-**3b**	75	91:9 (> 95:5)[d]	+46°

[a] Reactions carried out at −20 °C using 3 mol % of $Cu(OTf)_2$, 6 mol % of **L1**, 3 equiv of cyclohexenone, and 4 equiv of Et_2Zn. [b] Yields reported are based on *N*-sulfinimine conversion and determined by ^1H NMR. [c] Diastereoselectivities were determined by ^1H NMR analysis of the crude reaction mixtures, assuming >95:5 when signals for only one diastereoisomer were observed. [d] Five equivalents of Et_2Zn were used.

The substrate scope was found to be broad for aromatic and aliphatic sulfinimines, when Et_2Zn and cyclohexenone were used (Table 1). In general, under the previously optimized conditions, only one of four possible diastereoisomers was observed for all sulfinimines used. The electronic nature of the substituents on the aromatic sulfinimines had a marked impact on the reactivity. Electron-deficient aromatic sulfinimines reacted smoothly to afford compounds **3a** and **3c**, respectively, in moderate yields. However, the electron rich aromatic sulfinimine **2c** did not react under our standard conditions. It is noteworthy that aliphatic unbranched imines were more reactive than aromatic substrates and this allowed us to decrease the amount

(12) For leading references see:(a) De Vries, A. H. M.; Meetsma, A.; Feringa, B. L. *Angew. Chem., Int. Ed.* **1996**, *35*, 2374. (b) Feringa, B. L. *Acc. Chem. Res.* **2000**, *33*, 346. (c) Alexakis, A.; Benhaim, C. *Eur. J. Org. Chem.* **2002**, 3221.

(13) (a) Kitamura, M.; Miki, T.; Nakano, K.; Noyori, R. *Tetrahedron Lett.* **1996**, *37*, 5141. (b) Feringa, B. L.; Pineschi, M.; Arnold, L. A.; Imbos, R.; de Vries, A. H. M. *Angew. Chem., Int. Ed.* **1997**, *36*, 2620. (c) For an isolated example where the three stereogenic centers are controled by the chiral ligand **L1** see:(d) Arnold, L. A.; Naasz, R.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2001**, *123*, 5841.

(14) A portion of these studies have been previously communicated, see:(a) González-Gómez, J. C.; Foubelo, F.; Yus, M. *Tetrahedron Lett.* **2008**, *49*, 2343. (b) Highlights: *Synfacts* **2008**, *7*. 0725.

(15) (a) Davis, F. A.; Song, M. *Org. Lett.* **2007**, *9*, 2413. (b) Scott, M. E.; Lautens, M. *J. Org. Chem.* **2008**, *73*, 8154.

(16) *N-tert*-Butanesulfinyl imines are readily prepared from aldehydes and *N-tert*-butanesulfinamides (*Ss* and *Rs* are commercially available in >99% ee), following the procedure reported in: Liu, G.; Cogan, D. A.; Owens, T. D.; Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 1278.

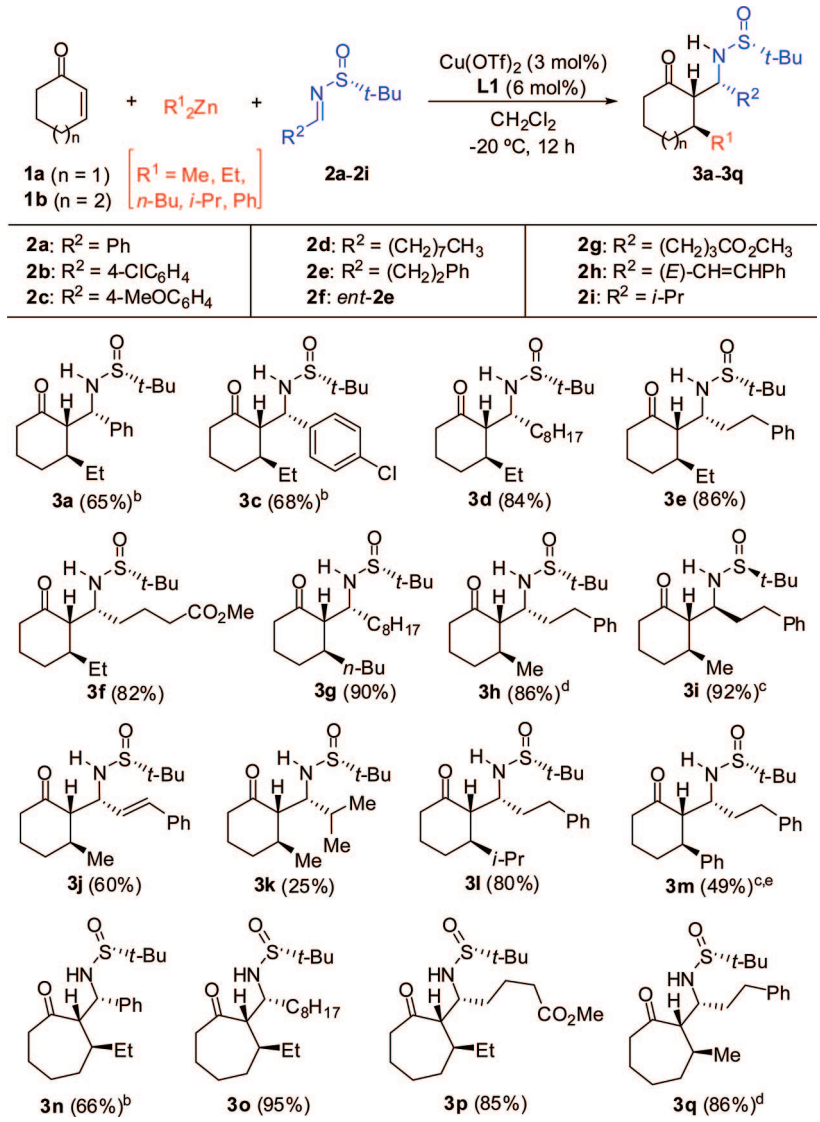
(17) In the aziridination of sulfinimines it was recognized early that the replacement of the *p*-toluene motif with a *tert*-butyl group significantly increased the stereoinduction: García Ruano, J. L.; Fernandez, I.; Hamdouchi, C. *Tetrahedron Lett.* **1995**, *36*, 295.

(18) For an example where a chiral acetal overcome the directing induction of the chiral enolate in a tandem enantioselective conjugate addition-aldol reaction, see:(a) Alexakis, A.; Trevitt, G. P.; Bernardinelli, G. *J. Am. Chem. Soc.* **2001**, *123*, 4358.

(19) To the best of our knowledge, only a few examples of multicomponent reactions that include chiral sulfinimines have been recently reported:(a) Kamimura, A.; Okawa, H.; Morisaki, Y.; Ishikawa, S.; Uno, H. *J. Org. Chem.* **2007**, *72*, 3569. (b) Huang, H.; Guo, X.; Hu, W. *Angew. Chem., Int. Ed.* **2007**, *46*, 1337.

(20) Yamada, K.-I.; Tomioka, K. *Chem. Rev.* **2008**, *108*, 2874.

TABLE 1. Reaction Scope Using 2-Cyclohexenone or 2-Cycloheptenone[a]



[a] In all cases, a single stereoisomer was observed by ^{1}H NMR analysis of crude reaction mixtures, except for **3l**. Quoted yields are of isolated pure compounds. Standard conditions employs 1.5 equiv of enone **1**, 3 equiv of R^1_2Zn, and 1 equiv of imine **2** (0.50 mmol). [b] 4 equiv of R^1_2Zn and 3 equiv of enone **1** were used. [c] 4 equiv of R^1_2Zn were used. [d] 2.4 mmol of enone **1** and 2 mmol of imine **2** were used. [e] 26% of another diastereoisomer was also isolated; see Supporting Information.

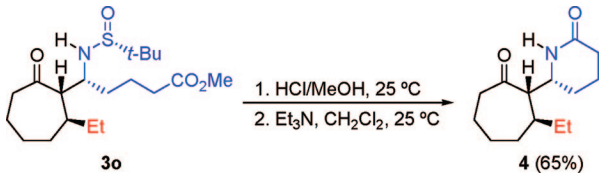
of enone to 1.5 equiv, compounds **3d**−**3i** being obtained in excellent yields.[21] Importantly, the *tert*-butanesulfinyl group minimizes the competitive α-deprotonation of the imines, allowing the otherwise problematic use of enolizable imines. The mild conditions used were also compatible with the ester group, so providing access to the highly functionalized compound **3f** in high yield.

Similar levels of efficiency and asymmetric induction were observed when *n*-Bu_2Zn was used (product **3g**) and even with the poorly reactive Me_2Zn (products **3h**−**3k**, Table 1). As previously observed for *ent*-**3b**, when the *S*-sulfinimine **2f** was used to afford compound **3i**, 4 equiv of Me_2Zn was added in order to achieve good diastereoselectivity. The α,β-unsaturated sulfinimine **2h** was also compatible with this protocol, and the expected product **3j** was isolated as a single stereoisomer in fairly good yield. Although α-branched sulfinimines were not very reactive (**3k**), we were pleased to observe that *i*-Pr_2Zn reacted smoothly under our optimized conditions (**3l**). Notably, when Ph_2Zn was used, the phenyl group was transferred and the major diastereoisomer **3m** was isolated in a pure state, after column chromatography, in a 49% yield. Surprisingly, in this case we also isolated a minor diastereoisomer, arising from poor enantioselection in the conjugate addition step,[22] in a 26% yield after column chromatography. Finally, we also explored the use of cycloheptenone in this reaction, observing a performance similar to cyclohexenone (products **3n**−**3q**).

(21) The scope of the reaction was studied using 0.5 mmol of sulfinimines and 1.5 equiv of enone. However, compounds **3h** and **3q** were prepared using 1.2 equiv of enone, on a 2 mmol scale, observing similar isolated yields and stereoselectivities.

(22) Good enantioselection was reported for the Ph_2Zn conjugate addition to cyclohexenone using **L1**, see:(a) Peña, D.; López, F.; Harutyunyan, S.-R.; Minnaard, A. J.; Feringa, B. L. *Chem. Commun.* **2004**, 1836.

SCHEME 3. Synthesis of Compound 4



3o **4 (65%)**

Following a recently reported procedure,[23] piperidone **4** was obtained in good yield by acidic deprotection of compound **3k** and subsequent cyclization mediated by Et_3N. Crystals of **4** obtained from Et_2O were suitable for single crystal X-ray analysis.[24] Coupled with the known absolute configuration of the first two stereocenters created in the asymmetric conjugate addition to cyclohexenone and cycloheptenone, this X-ray structure supports an *S* configuration for the Mannich stereocenter in compounds **3a**, **3c**, and **3n**, and *R* configuration in the rest of compounds (Scheme 3).

Given the success obtained with 2-cyclohexenone (**1a**) and 2-cycloheptenone (**1b**) in this methodology, we decided to extend the scope of this reaction to include the more challenging reactant cyclopentenone (**1c**). This enone is a special case due to: (a) its flatness, which makes it less sensitive to the steric requirements of the chiral ligand, and (b) the resulting enolate is reactive enough to undergo Michael addition to the remaning cyclopentenone. Conjugate addition to cyclopentenone (**1c**) takes place generally with lower ee values than for cyclohexenone (**1a**) and cycloheptenone (**1b**), and products are isolated in lower yields. In an effort to circumvent these problems, specific ligands have been developed for this Michael acceptor, and isolated yields are best calculated after trapping the generated enolate with an appropiate electrophile.[25]

We initially preformed the corresponding enolate by adding Et_2Zn to cyclopentenone (**2c**) in the presence of the diphosphite-type ligand **L3**, for which good ee values were reported.[26] After quenching with (*R*)-*tert*-butanesulfinimine **2e**, a modest diastereoselection was observed (method A, Table 2, entry 1). Interestingly, similar or slightly better stereoselection was observed when Et_2Zn was added shortly after mixing the other reactants (multicomponent protocol, method B, Table 2, entry 2). It is worth mentioning that this ligand induces the opposite absolute configuration on the enolate, compared with cyclohexenone (**1a**), the same major compound observed when phosphoramidite **L1** was used as the ligand. To our surprise, a good diastereoselection (dr 85:5:10) was observed when our multicomponent protocol was used with **L1** (Table 2, entry 4). This excellent diastereoselection is in marked contrast with the very poor enantioselection reported for the conjugate addition of $R^1{}_2Zn$ to cyclopentenone using ligand **L1**.[27] Interestingly, when *ent*-**L1** was used as the ligand in the sequential procedure (method A), lower and opposite diastereoselection was observed (Table 2, entries 3 and 5). When the reaction was conducted in the presence of ligand *ent*-**L1**, using the multicomponent protocol, similar levels of diastereoselection were achieved as in cases where the ligand was not added (Table 2, entries 6 and 7). The fact that similar and opposite diastereoselection was observed in the reaction of enantiomeric enolates (enone:imine, 3:1 molar ratio) with the same chiral *N*-sulfinimine **2e**, using the sequential procedure (method A), suggests that classical kinetic resolution is not taking place. However, when the multicomponent protocol was used (method B), a matched combination was observed for ligand **L1**/(*R*s)-*N*-sulfinimine **2e** (Table 2, entries 4 and 6). Only one diastereoisomer was observed by ^{1}H NMR when the bulky *i*-Pr_2Zn was used (entry 8). More interestingly, similar diastereoselection was observed when only 1.25 equiv of cyclopentenone (**1c**) was used in the presence of ligands **L1** or **L2** (Table 2, entries 9 and 10).

We next examined the scope of the reaction by using cyclopentenone, diisopropylzinc, and different chiral *N*-sulfinimines (Table 3). Unfortunately, the diastereoselection was very dependent on the *N*-sulfinimine moiety, and the products of these reactions ranged from a single isomer to 70:30 dr. Very good diastereoselection was achieved when unbranched aliphatic **2e** and neutral aromatic **2a** sulfinimines were used. Modest diastereoselectivity was observed for the *p*-methoxysulfinimine **2c**, as well as for α,β-unsaturated sulfinimine **2h**. Full conversion of the *p*-methoxysulfinimine **2c** and isopropylsulfinimine **2i** were observed (products **5d**, **5e**/**5f**) while either no conversion or very poor conversion was observed for the cyclohexenone enolate. This result is consistent with the higher reactivity described for cyclopentenone enolates. The lowest diastereoselectivity was observed for the isopropyl sulfinimine (**5f**/**5g** 70:30), where the minor diastereoisomer (**5g**) was isolated after column chromatography.

The ^{1}H NMR coupling constants between Ha and Hb (J = 12 Hz) for compounds **5f** and **5g** are consistent with a trans substitution of the ring.[28] Moreover, the ^{1}H NMR coupling constant between Hb and Hc was found to be 5.5 Hz for **5f**, and coupling was not observed for **5g**. This data supports the anti-threo configuration assigned to **5f** and anti-erythro configuration assigned to **5g**, according to recent studies by Noyori on the stereochemistry of cyclopentanone aldols.[29] As expected, excellent diastereocontrol is exerted by the *N*-*tert*-butylsulfinyl group at the Mannich stereocenter, and the minor stereoisomer arises due to poor enantioselection in the conjugate addition to the cyclopentenone.

We next studied the Baeyer−Villiger oxidation of β-aminoketones **3** and **5**, since the corresponding aminolactones **6** (Table 4) would constitute versatile chiral building blocks in organic synthesis. The use of MCPBA in dichloromethane for the oxidation of β-aminoketones **3h**, led to rapid oxidation to give the *N*-*tert*-butylsulfonyl (Bus) derivative, but the corresponding aminolactone **6a** was obtained in only a 15% yield. To our delight, this compound was obtained with excellent region- and diastereoselectivity. After some experimentation, we found that the best procedure for this transformation was to add 4 equiv of MCPBA and 5 equiv of $NaHCO_3$ to a dichloromethane solution of substrate, and then remove the solvent carefully.[30] Under these experimental conditions, good

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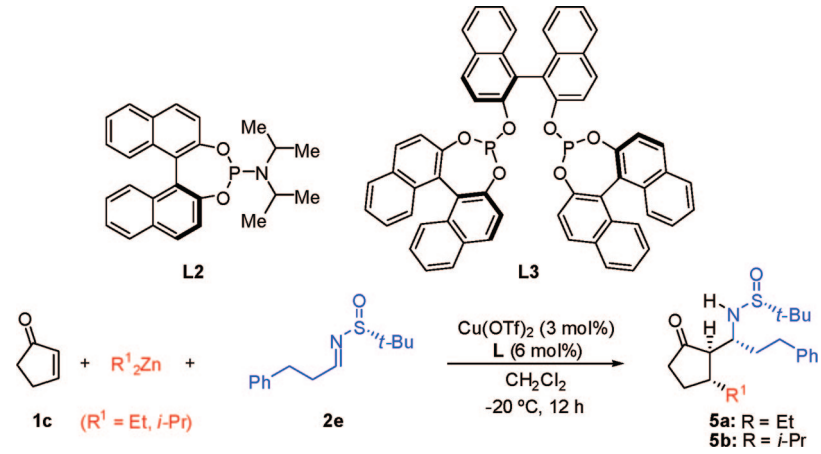
(24) Crystal data (excluding structure factors) deposited at the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 671456.
(25) Alexakis, A.; Backwall, J. E.; Krause, N.; Pamies, O.; Dieguez, M. *Chem. Rev.* **2008**, *108*, 2796.
(26) (a) Yan, M.; Yan, L.-W.; Wong, K.-Y.; Chan, A. S. C. *Chem. Commun.* **1999**, 11. (b) Liang, L.; Yan, M.; Li, Y.-M.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2004**, *15*, 2575.
(27) (a) Feringa, B. L.; Pineschi, M.; Arnold, L. A.; Imbos, R.; de Vries, A. H. M. *Angew. Chem., Int. Ed.* **1997**, *36*, 2620. (b) Naasz, R.; Arnold, L. A.; Pineshi, M.; Keller, E.; Feringa, B. L. *J. Am. Chem. Soc.* **1999**, *121*, 1104.
(28) For comparison with 1H NMR data of related aldol systems, see:(a) Kitamura, M.; Miki, T.; Nakano, K.; Noyori, R. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 999.
(29) Kitamura, M.; Nakano, K.; Miki, T.; Okada, M.; Noyori, R. *J. Am. Chem. Soc.* **2001**, *123*, 8939.
(30) Yakura, T.; Kitano, T.; Ikeda, M.; Uenishi, J. *Tetrahedron Lett.* **2002**, *43*, 6925.

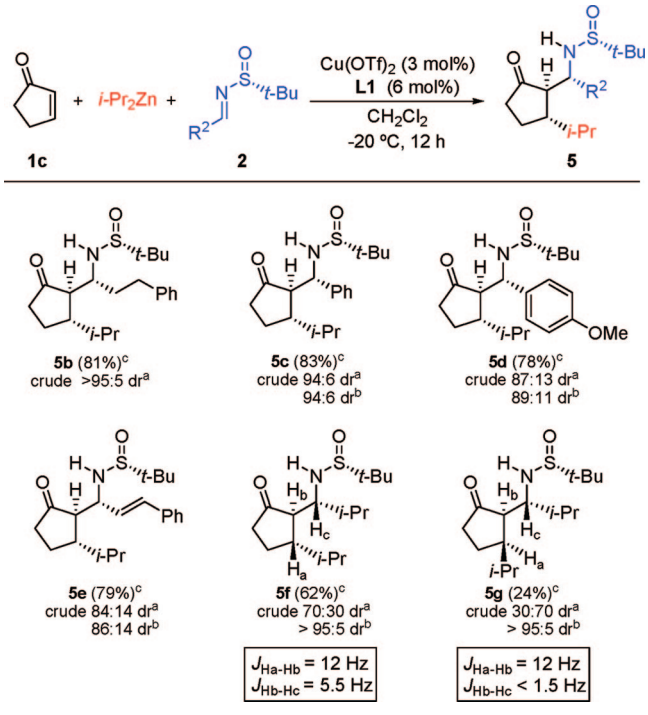
TABLE 2. Selected Optimization Studies Using Cyclopentenone (1c)



entry	enone equiv	R^1_2 Zn	L	method[a]	product	dr[b]
1	3.0	Et_2Zn	**L3**	A	**5a**	73:6:6:18
2	3.0	Et_2Zn	**L3**	B	**5a**	75:5:20
3	3.0	Et_2Zn	**L1**	A	**5a**	71:29
4	3.0	Et_2Zn	**L1**	B	**5a**	85:5:10
5	3.0	Et_2Zn	*ent*-**L1**	A	**5a**	28:72
6	3.0	Et_2Zn	*ent*-**L1**	B	**5a**	37:63
7	3.0	Et_2Zn	none	B	**5a**	67:33[c]
8	3.0	*i*-Pr_2Zn	**L1**	B	**5b**	>95:5[d]
9	1.25	*i*-Pr_2Zn	**L1**	B	**5b**	>95:5[d]
10	1.25	*i*-Pr_2Zn	**L2**	B	**5b**	95:5
11	1.25	*i*-Pr_2Zn	*ent*-**L1**	B	**5b**	39:10:51

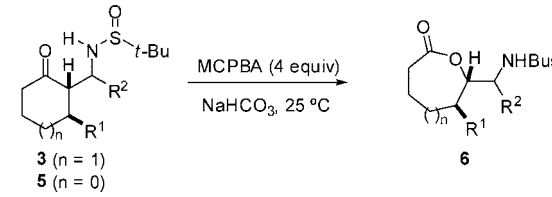
[a] Method A: the sulfinimine **2e** was added 3 h after R^1_2Zn. Method B: R^1_2Zn was added to the mixture of all reagents. [b] Determined by ^{1}H NMR analysis of crude reaction mixture after full conversion of sulfinimine **2e**. [c] Only 20% conversion was detected by ^{1}H NMR analysis. [d] Signals of only one diastereoisomer were detected by ^{1}H NMR analysis.

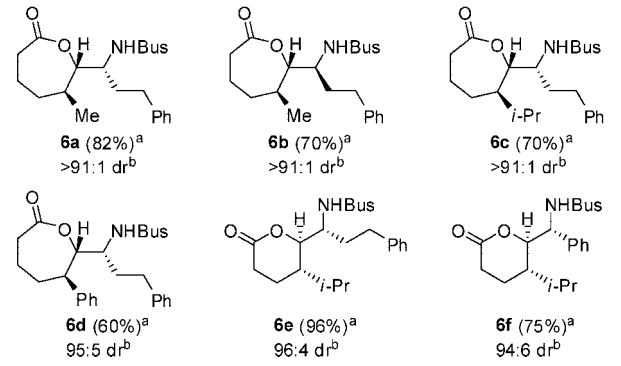
TABLE 3. Scope of the Reaction of Cyclopentenone with Diisopropylzinc and Chiral *N*-Sulfinimines



[a] Determined by ^{1}H NMR analysis of crude reaction mixture. [b] Determined by ^{1}H NMR analysis after purification by column chromatography. [c] Isolated yields after purification by column chromatography. Standard conditions employ 1.25 equiv of enone **1c**, 4 equiv of *i*-Pr_2Zn, and 1 equiv of imine **2** (0.50 mmol).

TABLE 4. Baeyer−Villiger Oxidation of Selected *β*-Aminoketones

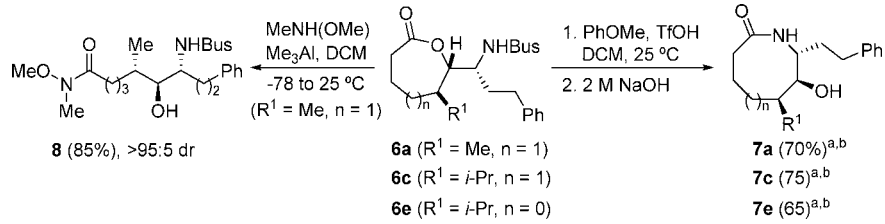




[a] Pure isolated compound after column chromatography. [b] Determined by GC after chromatography.

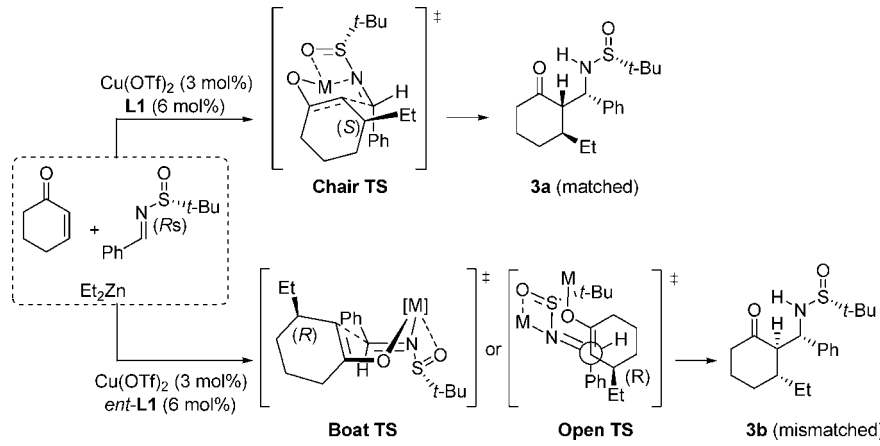
isolated yields and excellent regio- and diastereoselectivities were observed for lactones with seven-membered (products **6a**−**6d**) and six-membered (**6e**, **6f**) rings. Unfortunately, when cycloheptanone derivative **3q** (Table 1) was submitted to these experimental conditions, less than a 10% conversion into the corresponding eight-membered ring lactone was observed. Importantly, when *β*-aminoketone **3i** was submitted to these

SCHEME 4. Lactone Ring-Opening[a,b]



[a] Yields refer to pure isolated compound. [b] Only one diastereoisomer is observed by ^{1}H NMR.

SCHEME 5. Proposed Transition States for (*R* or *S*)-Cyclohexenone (Cycloheptenone) Enolate Addition to (*R*)-*t*-BS Sulfinimines



optimized conditions, compound **6b** was obtained and the ^{1}H and ^{13}C NMR spectra are clearly different from that of **6a** (diastereoisomers).

The former results clearly show that while in the tandem conjugate addition−Mannich reaction an (*R*s)-sulfinimine dictates an *R*-configuration on the Mannich stereocenter, for nonaromatic imines **2**; the opposite configuration is dictated at this stereocenter with the starting (*S*s)-sulfinimine. These data support our presumption that the stereocontrol at the Mannich stereocenter arises purely as a result of the asymmetric *t*-BS imine induction and diastereoconvergence is not taking place.

In order to briefly explore the synthetic potential of aminolactones **6**, we deprotected the amino group under Weinreb conditions,[31] and after in situ cyclization, the corresponding aminolactams **7** were obtained in good yields. We were also able to obtain the acyclic Weinreb-amide **8** in good yield by ring-opening of the aminolactones **6a**. It is noteworthy that only three synthetic operations were necessary for the stereoselective synthesis of this highly functionalized acyclic β-aminoalcohol from readily available starting materials (Scheme 4).

Stereochemical Analysis. Given the absolute configuration observed for β-aminoketones **3a**−**3q** (cyclohexanones and cycloheptanones), a reasonable explanation for the observed matched/mismatched combination can be proposed on the basis of classical stereochemical models. The approach of the (3*S*)-enolates from the *Si*-face of the (*R*s)-sulfinimine (far from the bulky *t*-Bu group) in a six-membered chairlike transition state could explain the absolute configuration of the matched products (e.g., **3a**).[32] The absolute configuration of the mismatched products is also consistent with an approach of the (3*R*)-enolates from the *Si*-face of the (*R*s)-sulfinimine. This approach mode could be explained by invoking a six-membered boatlike (or twist-boat-like) transition state or an open transition state. Six-membered cyclic transition states in a chair conformation usually offer better diastereoselection than the corresponding boat conformation or open transition states. This fact could account for the moderate matched−mismatched combination observed. The beneficial effect of a larger excess of $R^1{}_2Zn$ used in the stereoinduction of the mismatch combination could support the open transition state, since the $R^1{}_2Zn$ could act as a Lewis acid that fixes the necessary s-trans conformation of the (Rs)-sulfinimine (Scheme 5).

The stereochemical outcome for cyclopentenone derivatives **5** is less clear. A different mechanism must be considered to explain the good-to-excellent diastereoselection observed with ligand **L1** for cyclopentenone. At this point we believe that either the chiral *N*-sulfinimine or the resultant β-aminoketone is involved in the initial conjugate addition, but further mechanistic studies must be carried out to elucidate the most rational pathway. An alternative copper-catalyzed oxidative-coupling of cyclopentenone (**1c**) and *N*-sulfinimine could explain the better diastereoselection. However, this pathway can be ruled out since *cis*-cyclopentanones should be formed, and the ^{1}H NMR data obtained for **5a** and **5b** clearly support the *trans*-cyclopentanone moiety.

Conclusions

A simple multicomponent protocol allows the assembly of dialkylzinc reagents, cyclic enones, and chiral *N*-*t*-BS imines with stereocontrolled construction of three consecutive stereogenic centers. The same reaction conditions can be applied to a wide range of dialkylzincs (including Ph_2Zn), aromatic and aliphatic N-*t*-BS imines, and cyclic enones (5−7 membered rings) with good-to-excellent stereocontrol and isolated yields.

(31) Sun, P.; Weinreb, S. M. *J. Org. Chem.* **1997**, *62*, 8604.
(32) Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **2002**, *67*, 7819.

By simply choosing the appropriate ligand (**L1** vs *ent*-**L1**)/chiral sulfinimine combination (*R*s vs *S*s), the present methodology allows access to four diastereomeric β-amino ketones in enantiomerically pure form, when cyclohexenone or cycloheptenone are used. Moreover, excellent regioselectivities and isolated yields were obtained for the Baeyer−Villiger oxidation of some five- and six-membered ring β-amino ketones obtained by the present methodology. This Baeyer−Villiger transformation greatly expands the synthetic utility of the methodology disclosed in this work since the resulting aminolactones **6** are versatile building blocks for synthetic applications.

Experimental Section

General Procedure for the Tandem Conjugate Addition−Mannich Reaction. $Cu(OTf)_2$ (6 mg, 0.016 mmol), phosphoramidite **L1** (18 mg, 0.032 mmol), the enone **1** (0.75 mmol), and the corresponding sulfinimine **2** (0.50 mmol) were suspended in CH_2Cl_2 (4.0 mL), and the suspension was stirred at room temperature for 15 min before cooling to −40 °C. A solution of $R^1{}_2Zn$ (1.50 mL, 1.0 M in toluene) was added dropwise, and the reaction mixture was allowed to reach −20 °C while stirring overnight (12−14 h). The reaction was quenched at −20 °C by adding a saturated solution of NH_4Cl in 1:1 H_2O/MeOH (1.50 mL), and the mixture was stirred for 15 min at room temperature. The resulting precipitate was filtered through a short pad of celite, and after evaporation of solvents, ^1H NMR analysis of the crude sample was performed to determine the imine conversion and diasteromeric ratio of products. Purification by silica gel column chromatography, using EtOAc/hexane, gave the analytically pure compound.

(*R*$_S$,2*S*,3*S*,1′*R*)-*N*-(*tert*-Butylsulfinyl)-3-methyl-2-(1-amino-3-phenylpropyl)cyclohexanone (3 h). Following the general procedure, but using 2 mmol of starting *N*-sulfinimine **2e**, after workup, chromatography on silica gel eluting first with 3:1 and then 2:1 hexane/ethyl acetate afforded 630 mg (91% yield) of **3h** as a colorless oil: $[\alpha]_D^{20}$ −27.7 (*c* 0.92, $CHCl_3$); R_f 0.19 (1:1 *n*-hexane/EtOAc); ^1H NMR δ 7.26 (m, 3H), 7.17 (m, 2H), 4.64 (d, J = 10.8, 1H), 3.28 (t, J = 11.0, 1H), 2.90 (m, 1H), 2.80 (dd, J = 11.7, 3.9, 1H), 2.53 (m, 1H), 2.30 (m, 2H), 1.95 (m, 1H), 1.77 (m, 1H), 1.60 (m, 3H), 1.44 (m, 1H), 1.26 (s, 9H), 0.83 (d, J = 6.4, 3H); ^{13}C NMR δ 213.9, 141.9, 128.7 (CH), 128.5 (CH), 126.0 (CH), 61.7 (CH), 56.3 (CH), 56.2, 42.6 (CH_2), 36.6 (CH), 34.2 (CH_2), 33.0 (CH_2), 32.0 (CH_2), 25.5 (CH_2), 22.9 (CH_3), 19.4 (CH_3); IR ν (cm^{-1}) 3301 (broad), 2956 (s), 2867 (m), 1697 (s), 1455 (m), 1066 (s); MS (MALDI) *m*/*z* 372 $[M + Na]^+$. HRMS (MALDI) Calcd for $C_{20}H_{31}NNaO_2S$ $[M + Na]^+$ 372.1973. Found 372.1979.

(*R*$_S$,2*R*,3*S*,1′*R*)-*N*-(*tert*-Butylsulfinyl)-3-isopropyl-2-(1-amino-1-phenylmethyl)cyclopentanone (5c). Following the general procedure, sulfinimine **2a** (209 mg, 0.53 mmol) and cyclopentenone **1c** (60 μL, 0.70 mmol) were used. After workup, purification by chromatography on silica gel was carried out using first 3:1 and then 7:3 hexane/ethyl acetate, affording 152 mg (83% yield) of a colorless oil with 94:6 dr according to ^1H NMR: $[\alpha]_D^{20}$ −112.7 (*c* 3.00, $CHCl_3$); ^1H NMR δ 7.30 (m, 3H), 7.15 (m, 2H), 5.95 (d, J = 8.7, 1H), 4.57 (dd, J = 8.7, 5.1, 1H), 2.79 (dd, J = 9.3, 5.1, 1H), 2.25 (m, 1H), 1.95 (m, 1H), 1.70 (m, 3H), 1.44 (m, 1H), 1.23 (s, 9H), 1.01 (d, J = 6.9, 3H), 0.96 (d, J = 6.9, 3H); ^{13}C NMR δ 222.5, 140.3, 128.5 (CH), 127.8 (CH), 127.6 (CH), 60.6 (CH), 57.6 (CH), 55.9, 45.3 (CH), 39.6 (CH_2), 28.9 (CH), 22.8 (CH_3), 21.5 (CH_2), 21.4 (CH_3), 17.2 (CH_3); IR ν (cm^{-1}) 3272 (broad), 2956 (s), 1724 (s), 1454, 1068 (s); HRMS (MALDI) Calcd for $C_{19}H_{29}NNaO_2S$ $[M + Na]^+$ 358.1817. Found 358.1812.

General Procedure for Baeyer−Villiger Oxidation of β-Aminoketones. To a solution of β-aminoketones **3** or **5** (0.34 mmol) in CH_2Cl_2 (2 mL) was added MCPBA (300 mg, 1.20 mmol) at 0−5 °C, and the mixture was stirred at the same temperature. After 30 min, finely ground $NaHCO_3$ (100 mg, 1.20 mmol) was added, and the suspension was concentrated to give a solid residue. The solid was allowed to stand for 3 h at room temperature, a small volume of CH_2Cl_2 was added to the mixture, and the suspension was carefully concentrated to a solid. When the reaction was not completed, the process of dissolution and evaporation was repeated. After completion (TLC monitoring), the reaction was quenched by diluting with EtOAc (10 mL) and adding a solution of Na_2SO_3 (800 mg) in H_2O (10 mL). After stirring for 15 min at room temperature, the phases were separated and the aqueous phase extracted with more EtOAc (2 × 10 mL). The combined organic layers were washed with a saturated solution of $NaHCO_3$, followed by brine. The organic layers were dried over $MgSO_4$, and the solution was concentrated in vacuo and chromatographied on silica gel (hexane/EtOAc) to afford the pure corresponding β-aminolactone.

(6*S*,7*S*,1′*R*)-*N*-(*tert*-Butylsulfonyl)-6-methyl-7-(1-amino-3-phenylpropyl)oxepan-2-one (6a). Following the general procedure, after workup, column chromatography purification was carried out using 2:1 hexane/ethyl acetate, affording 107 mg (83% yield) of a colorless foam with >99:1 dr according to GC: $[\alpha]_D^{20}$ +73.1 (*c* 1.0, $CHCl_3$); GC t_r (major) = 21.96 min; ^1H NMR δ 7.28 (m, 2H), 7.16 (m, 3H), 4.53 (d, J = 10.2, 1H, 1H), 4.37 (dd, J = 9.05, 2.0, 1H), 3.70 (m, 1H), 2.98 (m, 1H), 2.60 (m, 3H), 1.95 (m, 1H), 1.90−1.55 (m, 6H), 1.45 (s, 9H), 1.40 (m, 1H), 0.87 (d, J = 6.8, 3H); ^{13}C NMR δ 175.4, 141.4, 128.7 (CH), 128.6 (CH), 126.3 (CH), 87.6 (CH), 60.2, 56.0 (CH), 37.2 (CH_2), 34.8 (CH), 33.8 (CH_2), 33.1 (CH_2), 30.5 (CH_2), 24.4 (CH_3), 21.7 (CH_2), 17.4 (CH_3); IR ν (cm^{-1}) 3295 (broad), 2928, 1731 (s), 1454 (s), 1127; MS (EI) *m*/*z* (%) 382.1 (2, $M^+ + 1$), 381.1 (3, M^+), 254 (15), 156 (9), 134 (100), 117 (6), 91 (25), 70 (5), 57 (45); HRMS (EI) Calcd for $C_{20}H_{31}NO_4S$ $[M]^+$ 381.1974. Found 381.1925.

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Supporting Information Available: Experimental procedures, full characterization, copies of ^1H and ^{13}C NMR spectra of all compounds, and X-ray crystal data for compound **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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