Chiral Magnesium Bis(sulfonamide) Complexes as Catalysts for the Merged Enolization and Enantioselective Amination of *N*-Acyloxazolidinones. A Catalytic Approach to the Synthesis of Arylglycines

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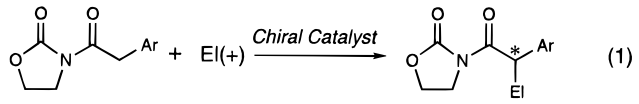
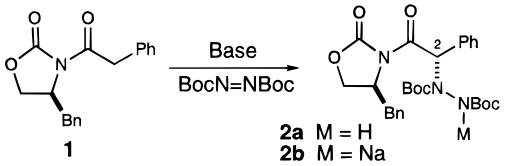
There is considerable interest in the development of catalyzed enantioselective enolate-electrophile bond constructions to complement existing procedures which typically employ stoichiometric chiral controllers. In the design of these catalytic processes it would be highly desirable to merge the enolization event with the desired enantioselective bond construction. Catalyzed β-ketoester conjugate additions,[2] isocyanoacetic ester aldol reactions,[3] and nitro aldol reactions[4] are among the few examples that meet this design criterion. The purpose of this Communication is to disclose a chiral metal complex that will mediate the enolization and enantioselective electrophilic amination (El(+) = BocN═NBoc) of aryl-substituted carboximides (eq 1) that possess a considerably lower predisposition toward enolization than the substrates employed in those studies cited above.[2−4]



(1)

Catalyzed Enolization. Aryl-substituted carboximides were selected for the development of these processes with the expectation that they would be moderately activated toward enolization and would afford structurally well-defined enolate complexes.[5] Azodicarboxylate esters (El(+) = $RO_2CN{=}NCO_2R$) were chosen as the electrophilic reaction component to provide a vehicle for evaluating catalyst-enolate structure and catalyst turnover.[6,7] We have previously demonstrated that oxazolidinone imide enolates generated using prototypical stoichiometric conditions (1.0 equiv of LDA) undergo stereoselective electrophilic amination using di-*tert*-butyl azodicarboxylate as the electrophilic nitrogen source [2(*S*):2(*R*) = 97:3] (eq 2).[6c,e] As a precondition for the catalyzed reaction variant, we first demonstrated that substoichiometric quantities (5 mol %) of bases such as La(O*t*-Bu)$_3$ or NaO*t*-Bu also catalyze the amination of imide **1** to afford the hydrazide **2a** in ≥95:5 [2(*S*):2(*R*)] diastereoselectivity (eq 2). In an attempt to identify the



(2)

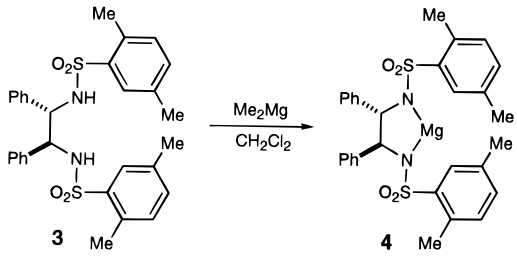
1

2a M = H
2b M = Na

base	2 (*S*) : 2 (*R*)
1.0 equiv LDA	97 : 3
5 mol% La(O*t*-Bu)$_3$	97 : 3
5 mol% NaO*t*-Bu	95 : 5
5 mol% **2b**	95 : 5

participating base in the catalytic cycle, the competency of the hydrazide conjugate base **2b** in promoting enolization was investigated. Indeed, 5 mol % of the sodium anion **2b** catalyzed the electrophilic amination of **1** with diastereoselectivity identical to that obtained under NaO*t*-Bu catalysis, indicating that the metal alkoxide is probably serving simply as an initiator, while the hydrazide conjugate base functions as the base in the catalytic cycle. This observation strongly suggests that hydrazide anions (pK_a DMSO ≈ 17−18)[8] are effective bases for the enolization of carboximides such as **1**.

Enantioselective Catalysis. The preceding observations suggested that sulfonamide-derived bases should be sufficiently basic to effect substrate enolization. Accordingly, we were attracted to metallo−bis(sulfonamide) complexes derived from chiral diamines as potential chiral catalysts. In conjunction with the optimization process, diamine, metal, and sulfonamide moieties were systematically screened to maximize turnover rates and enantioselection. The most successful of this family of promoters was generated by treating *(S,S)*-bis(sulfonamide) **3**[9] with dimethylmagnesium[10] in dichloromethane to provide the magnesium bis(sulfonamide) complex **4** (eq 3).[11,12] The catalyzed amination of phenylacetylimide **5a**, employing mag-



(3)

3 **4**

nesium complex **4** (10 mol %) and *N*-methyl-*p*-toluenesulfonamide (20 mol %) in 2:1 CH_2Cl_2/Et_2O, afforded the hydrazide **6a** with an enantiomeric ratio of 2(*S*):2(*R*) = 93:7 in 92% yield (eq 4). This amination procedure is applicable to a variety of aryl-substituted imides (Table 1); substrates incorporating either

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(2) (a) Feringa, B. l.; de Vries, A. H. M. *Advances in Catalytic Processes*; JAI Press: London, 1995; pp 151−192 and references cited therein. (b) Sasai, H.; Arai, T.; Satow, Y.; Houk, K. N.; Shibasaki, M. *J. Am. Chem. Soc.* **1995**, *117*, 6194−6198.

(3) Ito, Y.; Sawamura, M.; Hayashi, T. *J. Am. Chem. Soc.* **1986**, *108*, 6405−6406.

(4) (a) Sasai, H.; Suzuki, T.; Arai, S.; Arai, T.; Shibasaki, M. *J. Am. Chem. Soc.* **1992**, *114*, 4418−4420. (b) Reference 2b, footnote 2.

(5) Alkali metal enolates of oxazolidinone-derived imides exhibit a strong proclivity for adopting chelated (*Z*) enolate structures, see: (a) Evans, D. A. *Aldrichimica Acta* **1982**, *15*, 23−32. (b) Evans, D. A.; Britton, T. C.; Ellman, J. A.; Dorow, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 4011−4030. (c) Evans, D. A.; Rieger, D. L.; Bilodeau, M. T.; Urpi, F. *J. Am. Chem. Soc.* **1991**, *113*, 1047−1049.

(6) For the electrophilic amination of enolates using azodicarboxylate esters, see: (a) Gennari, C.; Colombo, L.; Bertolini, G. *J. Am. Chem. Soc.* **1986**, *108*, 6394−6395. (b) Oppolzer, W.; Moretti, R. *Helv. Chim. Acta.* **1986**, *69*, 1923−1926. (c) Evans, D. A.; Britton, T. C.; Dorow, R. L.; Dellaria, Jr., J. F. *J. Am. Chem. Soc.* **1986**, *108*, 6395−6397. (d) Trimble, L. A.; Vederas, J, C. *J. Am. Chem. Soc.* **1986**, *108*, 6397−6399. (e) Evans, D. A.; Britton, T. C.; Dorow, R. L.; Dellaria, J. F., Jr. *Tetrahedron* **1988**, *44*, 5525−5540.

(7) Vederas has recently reported the diastereoselective amination of enolates using chiral azodicarboxylate reagents: Harris, J. M.; McDonald, R.; Vederas, J. C. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2669−2674.

(8) This value is an estimate of the pK_a of the hydrazide in DMSO derived from values reported for related functional groups, see: Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456−463.

(9) Bis(sulfonamide) **3** was prepared by treating (1*S*,2*S*)-diphenylethylenediamine with 2,5-dimethylbenzenesulfonyl chloride; see Supporting Information for full procedural details.

(10) The dimethylmagnesium employed in this study was prepared as an ∼0.5 M solution in diethyl ether, see: Ashby, E. C.; Arnott, R. *J. Organomet. Chem.* **1968**, *14*, 1−11.

(11) Structure **4** is provided to represent metal−ligand stoichiometry. Catalyst aggregation, alluded to by ^{1}H NMR spectroscopy, may affect the exact nature of the catalytic species.

(12) Catalyst architecture, specifically the structure of the diamine backbone and of the sulfonamide aryl moiety, dramatically influences the catalytic competency of the derived magnesium complex. The catalyst complex optimized for each of these variables is reported herein.

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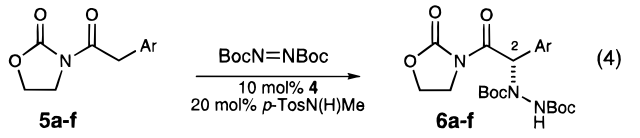
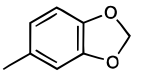
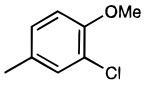
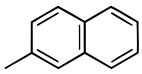
Table 1. Enantioselective Amination of *N*-Acyloxazolidinones **5**[a,b]



entry	aryl group	reaction time, h (temp, °C)	2(*S*):2(*R*) (% yield)[c,d]	% ee (mp °C)[e]
a	C_6H_5–	48 (–75)	93:7 (92)	>99 (185-7)
b	*p*-F-C_6H_4–	48 (–65)	95:5 (97)	>99 (207-8)
c	*p*-CH_3O-C_6H_4–	48 (–65)	93:7 (93)	99 (201-2)
d		72 (–75)	91:9 (85)	>99 (182-3)
e		60 (–75)	90:10 (84)	97 (191-3)
f		48 (–65)	91:9 (87)	96 (201-2)

[a] Reactions were carried out using the conditions given in ref 14 at the indicated times and temperatures. [b] Absolute configuration of adducts **6** were assigned by the procedure outlined in ref 13. [c] Enantiomeric purity was determined by chiral HPLC assay (Daicel Chiralcel OD-H). [d] Values reported are those for chromatographically purified hydrazides. [e] Values reported are those for recrystallized hydrazides.

electron-withdrawing (entry b) or electron-donating substituents (entry c) as well as disubstituted aryl substituents (entries d−f) afford relatively high enantiomeric ratios [2(*S*):2(*R*) = 95:5 to 90:10].[13] The amination adducts **6a**−**f** illustrated in Table 1 are all highly crystalline. In each instance, a single recrystallization of the product hydrazides leads to enantiomer enrichment (96 → 99% ee).[14] Finally, the potential for utilizing lower catalyst loadings was demonstrated by the preparation of hydrazide **6c** from imide **5c** in >99% ee and 81% yield after recrystallization using 5 mol % of **4** and 10 mol % *N*-methyl-*p*-toluenesulfonamide.

The role of *N*-methyl-*p*-toluenesulfonamide in this catalytic process has not yet been completely elucidated; however, this addend clearly accelerates the reaction. A kinetic investigation reveals a first-order dependence of this addend on reaction rate.

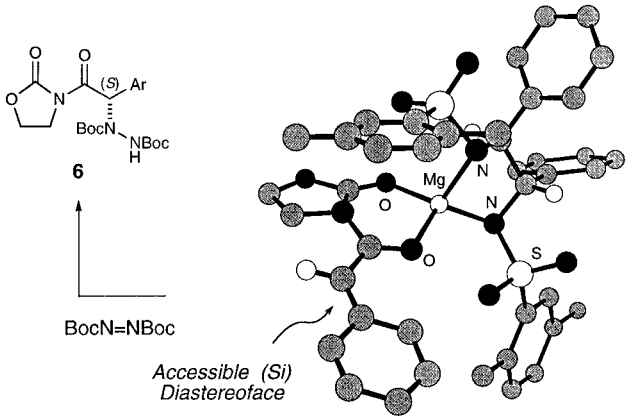


Figure 1. Chiral magnesium bis(sulfonamide)−enolate complex.

Our analysis leads us to conclude that catalyst turnover, rather than enolization, is the rate-determining step in this reaction and that the observed first order dependence on *N*-methyl-*p*-toluenesulfonamide results from an accelerated rate of hydrazide conjugate protonation and the associated liberation of the active catalyst.

The sense of asymmetric induction in the preceding reactions can be rationalized by assuming that the reaction proceeds via the intermediacy of the chelated tetrahedral magnesium enolate complex depicted in Figure 1.[15] Important structural attributes of this complex include the (*Z*) enolate geometry and the conformational rigidity enforced by chelation of both the imide enolate and bis(sulfonamide) ligand to the tetrahedral magnesium ion. Our studies on chiral oxazolidinone-derived imide enolate mediated bond constructions that uniformly proceed through analogous structures with chelating metals (Li, Na, Mg, Ti), provide circumstantial support for this assumption.[5] Gearing between the aryl groups resident within the diamine backbone and the arylsulfonamide residues forces one aromatic ring to project over the enolate π-system, exposing the (*Si*) enolate α carbon diastereoface to the incoming electrophile.[16]

The present study establishes that lanthanide and alkali metal alkoxides as well as magnesium-bis(sulfonamide) complexes are effective catalysts for executing enantioselective enolate amination in simple carboxylate ester synthons. Extension of these concepts to a general catalytic enantioselective approach to the synthesis of α-amino acids as well as other enolate-electrophile bond constructions is the subject of ongoing investigations.

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Supporting Information Available: Experimental procedures and enantiomeric purity assays for all compounds are provided (6 pages). See any current masthead page for ordering and Internet access instructions.

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(13) The absolute configuration of the α-hydrazido imides **6** (Table 1) were established by conversion to the corresponding α-hydrazido carboxylic acids and correlation of their optical rotation to those of authentic samples of known configuration. See ref 6d.

(14) Typical experimental procedure: Under an inert atmosphere (Ar or N_2), 15 mg (25 μmol) of bis(sulfonamide) **3** in 0.5 mL of CH_2Cl_2 is treated with 1.0 equiv (25 μmol) of dimethylmagnesium at ambient temperature. After stirring 1 h, the turbid catalyst solution is cooled to −78 °C and a solution of 0.25 mmol of imide **5**, 69 mg (1.2 equiv, 0.30 mmol) of di-*tert*-butylazodicarboxylate, and 9.4 mg (50 μmol) of *N*-methyl-*p*-toluenesulfonamide in 1 mL of 1:1 CH_2Cl_2/Et_2O is added via cannula. The reaction mixture is then warmed to −65 °C and stirred 48−72 h. The reaction is quenched at −65 °C by the addition of glacial acetic acid (200 μL), and the reaction mixture is then poured into a saturated aqueous sodium bicarbonate solution. The crude product is isolated by extraction with dichloromethane and concentration of the organic extracts *in vacuo*. Purification of the product mixture by flash chromatography affords the desired hydrazide **6** with the indicated yield and enantioselectivity, along with recovered bis(sulfonamide) **3**. The enantiomeric excess of the isolated hydrazide **6** is ≥96% after a single recrystallization (ethyl acetate−hexane).

(15) The magnesium enolate complex depicted in Figure 1 was minimized using the Spartan Modeling Package (Version 4.0). Geometry optimizations were performed using the PM3 parameter set.

(16) For a discussion of "gearing" in related bis(sulfonamide) ligands, see: Corey, E. J.; Imwinkelried, R.; Pikul, S.; Xiang, Y. B. *J. Am. Chem. Soc.* **1989**, *111*, 5493−5495.