JOC*Article*

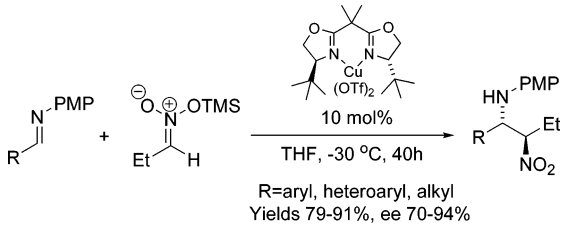
An Asymmetric Nitro-Mannich Reaction Applicable to Alkyl, Aryl, and Heterocyclic Imines

James C. Anderson,*[,†] Gareth P. Howell,[†] Ron M. Lawrence,[‡] and Claire S. Wilson[†,§]

School of Chemistry, University of Nottingham, NG7 2RD, United Kingdom, and GlaxoSmithKline Research and Development, Medicines Research Centre, Gunnels Wood Road, Stevenage, Hertfordshire, SG1 2NY, United Kingdom

j.anderson@nottingham.ac.uk

Received April 15, 2005



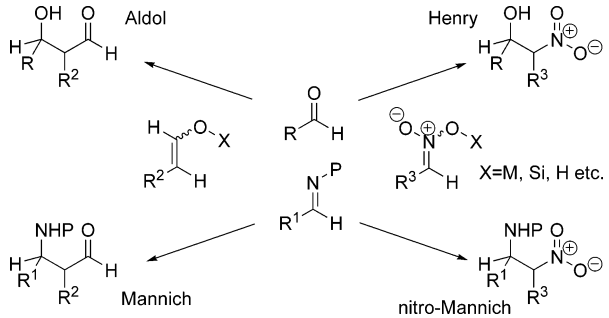
A protocol for the enantioselective nitro-Mannich coupling between alkyl, aryl, and heterocyclic *p*-methoxybenzylimines and trimethylsilylnitropropanate catalyzed by a chiral ^{t}Bu-BOX Cu(II) catalyst is described. It uses the lowest reported loading of commercially available metal catalyst and chiral ligand, and gives the highest yields and selectivities for a broad substrate range including nonaromatic aldimines. The resultant β-nitroamines are obtained in 70−94% enantiomeric excess in good yield and can be readily reduced to synthetically useful 1,2-diamines.

Introduction

Bearing close resemblance to three of the most fundamental carbon−carbon bond forming reactions (aldol, Mannich, and Henry), nitro-Mannich coupling allows access to synthetically useful β-nitroamines (Scheme 1).[1] These structures can be derivatized in a number of ways, principally, via simple reduction of the nitro-function to yield 1,2-diamines and their subsequent derivatives. This structural motif is of considerable importance in many areas of chemistry: 1,2-diamines are remarkably abundant in natural products and pharmaceutical targets, and have been elegantly utilized in asymmetric ligand and base chemistry.[2] We believe a robust and general asymmetric nitro-Mannich reaction would be of great use to synthetic chemistry and we report our efforts here.

Our initial report of the Lewis acid catalyzed nitro-Mannich addition of *O*-trimethylsilyl nitropropanate to imines (Scheme 1: R^1 = alkyl, aryl; R^3 = Et; P = 4-methoxybenzyl, 4-methoxyphenyl; X = $SiMe_3$)[3] was further utilized by Jørgensen et al. to afford efficient enantiocontrol through incorporation of a chiral, nonracemic Lewis acid.[4] Excellent levels of enantiomeric excess were displayed, but the protocol was only described for the imino-ester substrate (Scheme 1: R^1 = COOEt; R^3 = Me, Et, ^{n}Pn; P = 4-methoxybenzyl; X = $SiMe_3$), with the α-carboxylate group deemed necessary for 2-point catalyst binding. This procedure was subsequently developed into a simplified, direct-coupling procedure negating the use of preformed silyl nitronates.[5] Utilizing a different

SCHEME 1. Relationship of Nitro-Mannich Reaction to Fundamental Carbonyl Based Coupling Reactions



† School of Chemistry, University of Nottingham.
‡ GlaxoWellcome Research and Development.
§ Address questions on X-ray crystal structure to this author.

(1) Westermann, N. *Angew. Chem., Int. Ed.* (*Highlight*) **2003**, *42*, 151.
(2) Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem.*, *Int. Ed.* **1998**, *37*, 2581.
(3) Anderson, J. C.; Peace, S.; Pih, S. *Synlett* **2000**, 850.
(4) Knudsen, K. R.; Risgaard, T.; Nishiwaki, N.; Gothelf, K. V.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2001**, *123*, 5843.

10.1021/jo050762i CCC: $30.25
Published on Web 06/16/2005

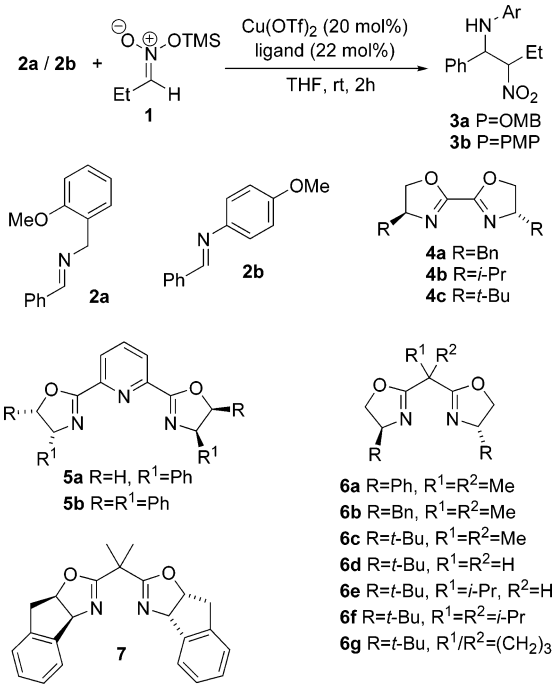
approach, Shibasaki et al. have demonstrated enantioselective nitro-Mannich coupling using heterobimetallic Lewis acidic/Brønsted basic complexes (Scheme 1: R^1 = aryl; R^3 = H, Me; P = $POPh_2$; X = H).[6,7] The aromatic aldimines screened afforded *β*-nitroamines in moderate to high ee, but a large loading (60%) of the BINOL ligand was required. The latest publications in this field describe the application of organic catalysis.[8] Catalytic 1,1,3,3-tetramethylguanidine led to the coupling of a variety of nitroalkanes to *N*-phosphinoyl aldimines in good yields and diastereoselectivities.[9] The use of chiral thio-urea catalysts to promote nitro-Mannich addition to aromatic aldimines has been achieved with high enantioselectivities by Okino et al.[10] and more recently by Yoon and Jacobsen.[11] Johnston et al. have employed a chiral ammonium species to furnish aromatic *β*-nitroamines, with three examples with >85% ee described.[12] Despite a number of well-designed and inventive nitro-Mannich protocols being reported, there is still a need for a general, enantioselective procedure applicable to simple alkyl and aryl imines.

Results and Discussion

Our recent studies on the nitro-Mannich reaction have shown the nature of the imine *N*-substituent (P in Scheme 1) to be significant to the stereoselectivity of reaction.[13] Imine **2a**, bearing a 2-methoxybenzyl (OMB) substituent, underwent higher yielding nitro-Mannich coupling relative to imine **2b**, bearing a 4-methoxyphenyl (PMP) group. The higher yield was also accompanied by superior diastereoselectivity, possibly due to a combination of chelation and steric factors. To further study the possible effects of imine−LA chelate binding we elected to study both imine **2a** (OMB, potentially bidentate) and **2b** (PMP, monodentate) in asymmetric studies. Both **2a** and **2b** were treated with trimethylsilyl nitropropanate (**1**) in the presence of Cu(II)/known chiral ligand systems (Scheme 2 and Table 1).

The first conclusion to be drawn from these results (Table 1) is that imine **2a** reacts to give *racemic* *β*-nitroamines under all of the conditions described (entries 2−7). Lowering the reaction temperature and changing solvent (DCM, MeCN) offered no advantage. The explanation for this finding appears to lie in the presence of a facile (uncatalyzed) background reaction. In a control run with the omission of Cu(II) and ligand we noted ∼30% conversion after 4 h at room temperature (anti:syn 3:1). The use of $Cu(OTf)_2$ alone as catalyst gives reasonable

SCHEME 2



rate acceleration and high diastereoselectivity (entry 1, >95% conversion in less than 5 min at −78 °C). The addition of donor ligands to the $Cu(OTf)_2$ catalyst (entries 2−7) results in significant rate deceleration (>95% conversion needed 1−3 h at room temperature) and erosion of the diastereoselectivity to levels comparable to the uncatalyzed reaction. The electron rich chelate ligands would be expected to reduce the Lewis acidity of the copper catalyst and would reduce the rate of the reaction. Chelation by the OMB-imine function (if operative) to the copper catalyst could render the coordination sphere around the copper (and the electron count) incapable of accepting the chiral ligand in a bidentate coordination mode. Monodentate coordination of the chiral ligand would then compromise its stereoinducing effect.

Conversely, imine **2b** does not undergo any significant nitro-Mannich coupling with nitronate **1** in the absence of Lewis acid catalyst. Moreover, *β*-nitroamine **3b** can be obtained in moderate to high levels of enantioselectivity with use of simple, commercially available bisoxazoline (BOX) ligands (entries 13−15). The application of Cu(II) salts in conjunction with unbridged-BOX ligands **4a**−**c** resulted in lower enantioselectivity (entries 8−10); pyridine-BOX ligands **5a**,**b** afforded only racemic *β*-nitroamine **5b** (entries 11 and 12). In the hope of increasing the level of enantiocontrol, we synthesized a range of structural (*S*)-^{t}Bu-BOX analogues **6d**−**g**.[14] It is apparent that while the nature of the bridging methylene substituents has a pronounced effect on enantioselectivity (entries 16−19), the commercially available 2,2-dimethyl ligand (*S*)-**6c** appears optimal (entry 15).

Simple variation of the reaction conditions revealed that a decrease in temperature to −30 °C afforded

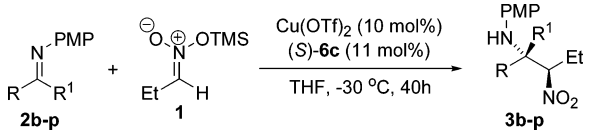
(5) Nishiwaki, N.; Knudsen, K. R.; Gothelf, K. V.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 2992.
(6) Yamada, K.; Harwood, S.; Groger, H.; Shibasaki, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 3504.
(7) Yamada, K. I.; Moll, G.; Shibasaki, M. *Synlett* **2001**, 980.
(8) Two recent contributions that do not involve organic catalysis are: (a) Lee, A.; Kim, W.; Lee, J.; Hyeon, T.; Kim, B. M. *Tetrahedron: Asymmetry* **2004**, *15*, 2595. (b) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2005**, *127*, 3672.
(9) Bernardi, L.; Bonini, B. F.; Capitò, E.; Dessole, G.; Comes-Franchini, M.; Fochi, M.; Ricci, A. *J. Org. Chem.* **2004**, *69*, 8168.
(10) Okino, T.; Nakamura, S.; Furukawa, T.; Takemoto, Y. *Org. Lett.* **2004**, *6*, 625.
(11) Yoon, T. P.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2005**, *44*, 466.
(12) Nugent, B. M.; Yoder, R. A.; Johnston, J. N. *J. Am. Chem. Soc.* **2004**, *126*, 3418.
(13) Anderson, J. C.; Blake, A. J.; Howell, G. P.; Wilson, C. S. *J. Org. Chem.* **2005**, *70*, 549−55.
(14) Denmark has shown that structural variation (**6d**−**g**) of ^{t}Bu-BOX ligand **6c** had a pronounced effect on the enantioselective addition of organolithiums to PMP imines. See: Denmark, S. E.; Stiff, C. M. *J. Org. Chem.* **2000**, *65*, 5875.

TABLE 1. Screening of Chiral Ligands in Cu(II) Catalyzed Nitro-Mannich Reactions[a]

entry	imine	ligand	**3** anti:syn[b]	**3** ee (anti)[c]	entry	imine	ligand	**3** anti:syn[b]	**3** ee (anti)[c]
1	**2a**	none	9:1	n/a	11	**2b**	**5a**	9:1	rac
2	**2a**	**4a**	2:1	rac	12	**2b**	**5b**	9:1	rac
3	**2a**	**5a**	2:1	rac	13	**2b**	**6a**	9:1	51%
4	**2a**	**5b**	5:2	rac	14	**2b**	**6b**	9:1	20%
5	**2a**	**6a**	6:1	rac	15	**2b**	**6c**	>15:1	80%
6	**2a**	**6b**	2:1	rac	16	**2b**	**6d**	>15:1	rac
7	**2a**	**6c**	2:1	rac	17	**2b**	**6e**	>15:1	68%
8	**2b**	**4a**	6:1	16%	18	**2b**	**6f**	6:1	6%
9	**2b**	**4b**	6:1	8%	19	**2b**	**6g**	10:1	36%
10	**2b**	**4c**	6:1	8%	20	**2b**	**7**	9:1	12%

[a] 5.0 equiv of nitronate **1** was used throughout. Full (>95%) conversion was measured throughout based on ^{1}H NMR and mass balance. [b] Diastereoselectivity was measured from ^{1}H NMR, using baseline resolved signals. The major diastereomer was assigned anti based on subsequent derivatization and analysis of products **3a** and **3b**. [c] Major (anti) diastereoisomer measured by chiral HPLC, using Chiralcel OD-H and Chiralpak AS columns with ^{i}PrOH and hexane eluents. The minor (syn) enantiomers proved inseparable.

SCHEME 3



β-nitroamine **3b** with greatly increased enantioselectivity (94% ee, Scheme 3; Table 2, entry 1). We also found that both the catalyst and ligand loading could be reduced to 10% and 11%, respectively; similarly, the loading of nitronate **1** could be reduced to 1.5 equiv. Other pertinent observations include the following: replacement of the reaction solvent (THF) with non-ethereal solvents leads to racemic β-nitroamine products and other Cu(II) catalysts such as $CuCl_2$ and $Cu(OAc)_2$ also led to complete loss of enantiocontrol. While these observations are interesting, we have no conclusive rationale for this behavior.

With this high yielding and highly stereoselective process in-hand, we synthesized and characterized a wide range of PMP imines including alkyl, aryl,[15] and heterocyclic derivatives. The aldimines **2c**−**k** were synthesized via simple condensation reactions and were isolated as crystalline solids (aryl imines **2c**−**h**) or viscous oils (alkyl imines **2j**,**k**). The ketimines derived from benzophenone,[16] acetophenone,[17] and acetone[18] were synthesized with use of literature procedures. Each of the PMP-imines **2b**−**p** was treated with nitronate **1** in the presence of $Cu(OTf)_2$ and (*S*)-^{t}Bu-BOX ligand (*S*)-**6c** (Scheme 3 and Table 2).

The data in Table 2 show that this asymmetric protocol for nitro-Mannich coupling is particularly efficient for the conversion of simple aryl and 4-substituted aryl aldimines (entries 1, 2, and 5) to the corresponding β-nitroamines with excellent levels of diastero- and enantioselectivity. Lower levels of enantio- and diastereocontrol were observed with 2-substituted aryl aldimines (entries 3 and 6); the ortho and para isomers (compare **2c** with **2d** and **2f** with **2g**) should display similar electronic properties, thus, we would ascribe this disparity to steric factors. The heterocyclic imine **2h** also reacted smoothly and efficiently to yield the corresponding β-nitroamine in 94% ee. We found the magnitude of enantioselectivity in this particular reaction (entry 7) to be dependent on the purity and quality of the starting 2-furylimine **2h**.[19] The 2,6-dichloroimine **2e** (entry 4) was found to be unreactive with use of this methodology, presumably due to sterics that cause the aromatic ring to lie out of plane with respect to C=N and hinder nucleophilic attack.

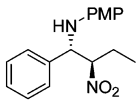
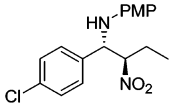
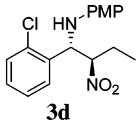
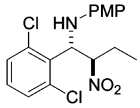
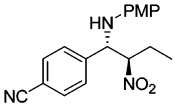
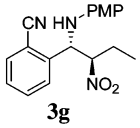
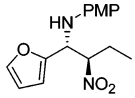
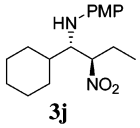
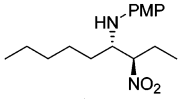
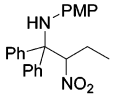
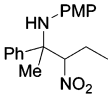
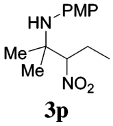
The alkylimine substrates **2j** and **2k**, while displaying moderate stability at ambient conditions (imines **2j** and **2k** were prepared and used immediately) also showed excellent levels of enantioselectivity, although the latter reaction proceeded in a nondiastereoselective manner. These two results (entries 8 and 9) represent the first enantioselective examples of nitro-Mannich addition into alkyl-derived aldimines. The lack of diastereoselectivity with substrate **2k** is curious and very dependent on the imine protecting group.[20] Somewhat disappointingly, the ketimine substrates tested (**2m**−**p**) were found to be wholly unreactive in this system. Ketone-derived imines are of lower reactivity than their aldimine analogues and it would seem apparent that the Cu(II) catalyst offers insufficient activation to promote nucleophilic attack toward these substrates.

To determine the sense of enantioinduction in our nitro-Mannich protocol, we converted two of the β-nitroamine products (**3b**, **3h**) to the corresponding thioimidazolidinones via SmI_2 reduction[21] and reaction with $CSCl_2$ (Scheme 4). We have previously shown that conversion of β-nitroamines to the corresponding imidazolidinone (SmI_2 reduction followed by reaction with $COCl_2$) affords stable, solid products.[13] Accordingly, we expected the thioimidazolidinones **8b** and **8h** to be crystalline solids, allowing determination of absolute stereochemistry by single-crystal X-ray analysis (with S as a "heavy atom").

The reduction/cyclization protocol proceeded smoothly in both cases. The diastereomeric ratio was conserved throughout this procedure, which would suggest that no epimerization had occurred. The 2-furyl product **8h** was found to be an amorphous solid and we were unable to gain a crystalline sample suitable for analysis. Conversely, the phenyl-substituted product **8b** was found to

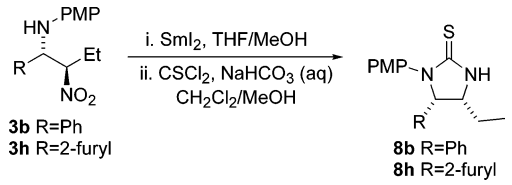
(15) In retrospect we surveyed only aryl groups with electron withdrawing substituents. No donor groups, such as Me or MeO, were screened, but we anticipate they should also be satisfactory substrates.
(16) Sisti, A. J.; Milstein, S. R. *J. Org. Chem.* **1974**, *39*, 3932−3936.
(17) Barluenga, J.; Alejandro, M.; Fernández, F.; Aznar, F.; Valdés, C. *Chem. Eur. J.* **2004**, *10*, 494.
(18) Iwamura, H. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 193.
(19) Highly colored samples of this imine afforded the product **3h** in lower ee (70−80%). The origins of this effect are unknown.
(20) The OMB protected imine of hexanal gives a diastereoselectivity of 90:10 without chiral ligand (ref 13).
(21) Sturgess, M. A.; Yarberry, D. J. *Tetrahedron Lett.* **1993**, *34*, 4743−6.

TABLE 2. Screening of Imines in Asymmetric Nitro-Mannich Reactions[a]

Entry	Imine	R	R[1]	Product **3**[b]	Yield **3**[c]	*anti/syn*[d]	*ee* (*anti*)[e]
1	**2b**	Ph	H	 **3b**	84%	>15:1	94%
2	**2c**	4-Cl-C_6H_4	H	 **3c**	84%	>15:1	92%
3	**2d**	2-Cl-C_6H_4	H	 **3d**	79%	8:1	73%
4	**2e**	2,6-Cl_2-C_6H_4	H	 **3e**	<5%	n/a	n/a
5	**2f**	4-CN-C_6H_4	H	 **3f**	82%	>15:1	92%
6	**2g**	2-CN-C_6H_4	H	 **3g**	91%	7:1	70%
7	**2h**	2-furyl	H	 **3h**	89%	11:1	94%
8	**2j**	*c*-hexyl	H	 **3j**	88%	>15:1	87%
9	**2k**	*n*-pentyl	H	 **3k**	88%[f]	1:1	86%
10	**2m**	Ph	Ph	 **3m**	<5%	n/a	n/a
11	**2n**	Ph	Me	 **3n**	<5%	n/a	n/a
12	**2p**	Me	Me	 **3p**	<5%	n/a	n/a

[a] 1.5 equiv of nitronate **1** was used throughout. [b] The absolute stereochemistry of products **3** was tentatively assigned as (1*S*,2*R*) based on subsequent derivatization and analysis of nitro-amine **3b**. [c] Purified isolated yield of inseparable diastereomeric mixture. [d] Diastereoselectivity was measured from ^{1}H NMR, using baseline resolved signals. Samples quoted as >15:1 showed no minor diastereoisomer. The major diastereomer is assigned anti based on subsequent derivatization and analysis of products **3b** and **3h**. [e] Measured by chiral HPLC, using Chiralcel OD-H and Chiralpak AS columns with ^{i}PrOH and hexane eluents. [f] Careful chromatography allowed a diasteromerically enriched sample to be analyzed by chiral HPLC.

SCHEME 4



be crystalline and X-ray analysis revealed the absolute stereochemistry to be 4*R*,5*S* as depicted in Scheme 4. On the basis of this finding, we tentatively assigned the absolute stereochemistry of the other β-nitroamine products **3b**−**k** as (1*S*,2*R*).[22] Although ongoing, our experiments to determine the origins of enantioselectivity remain inconclusive due to no firm evidence as to the geometry of the imine and silyl nitronate in the reactive complex.[23]

We believe this protocol to be the most general and efficient version of the nitro-Mannich reaction reported to date. Although this protocol requires prederivatization of the nitro species, it uses the lowest reported loading of commercially available metal catalyst and chiral ligand, and gives the highest yields and selectivities for such a broad substrate range including nonaromatic aldimines. These results go some way to characterizing the nitro-Mannich process as a general route to enantiomerically pure β-nitroamines and compliments existing asymmetric methodology for the aldol, Henry, and nitroaldol reactions (Scheme 1). The β-nitroamine products are readily reduced to enantiomerically pure 1,2-diamines, which is a prominent structural feature of many biologically important molecules, and will therefore be of great use as building blocks in asymmetric synthesis.

Experimental Section

General Procedure for the Synthesis of Imines. Basic Al_2O_3 (1.0 g per mmol) was added to a solution of *p*-anisidine (purified by dissolution in Et_2O, followed by treatment with activated charcoal, filtration, and evaporation; stored in a darkened container <0 °C) in DCM (5 mL per mmol) under N_2 at room temperature and after a period of 5 min carbonyl compound (1 equiv) was added. The mixture was left to stir for 14 h at room temperature before filtration through Celite and removal of solvents in vacuo, to yield the crude imine. Recrystallization from hexane/EtOAc afforded analytically pure imines.

2b. Prepared using the general procedure above, *p*-anisidine (1.23 g, 10.0 mmol) and benzaldehyde (1.06 g, 10.0 mmol) gave crude **2b** as a pale-brown solid. Recrystallization afforded off-white platelets (1.86 g, 88%): mp 68−70 °C (lit.[24] mp 65 °C); ^{1}H NMR ($CDCl_3$) δ 3.85 (3H, s), 6.95 (2H, d, J = 8.9 Hz), 7.25 (2H, d, J = 8.9 Hz), 7.40−7.55 (3H, m), 7.80−7.95 (2H, m), 8.50 (1H, s). ^{1}H NMR data correspond to literature values .[3]

General Procedure for Asymmetric Nitro-Mannich Coupling. Rigorously dried $Cu(OTf)_2$ (7.3 mg, 20 μmol, 0.10 equiv) and (*S*)-^{t}Bu-BOX ligand (6.5 mg, 22 μmol, 0.11 equiv) were added to a vial containing a stirrer bar in an inert atmosphere box. A septum was fitted and the vial was removed from the box and placed under N_2. Dry THF (1.0 mL) was added and the mixture was stirred for 1 h at room temperature then cooled to −30 °C. During this time, a vivid, sea-green solution was obtained (any blue coloration indicates formation of the hydrated catalyst complex). To a second vial, also in an inert atmosphere box, was added imine (0.20 mmol, 1.00 equiv). A septum was fitted and the vial was removed from the box and placed under N_2. Dry THF (1.0 mL) was added and the solution was added via cannula transfer to the catalyst solution at −30 °C. The catalyst/imine solution was stirred for 5 min at −30 °C before addition of trimethylsilyl nitropropanate **1** (80 μL, 1.50 equiv). The mixture was stirred for 40 h[25] at −30 °C, then warmed to room temperature. The mixture was partitioned between petroleum ether and saturated aqueous EDTA, the aqueous layer was discarded, and the organic phase was further washed with EDTA. The organic phase was dried with $MgSO_4$ and evaporated to yield crude β-nitroamine **3**. Purification was achieved by flash column chromatography with a short (~5 cm) column of silica.

3b. Prepared using general procedure above from **2b**, chromatography (6:1, hexanes:EtOAc) gave a pure major diastereoisomer as a yellow oil (52 mg, 84%): ^{1}H NMR for (1*S*,2*R*)-**3b** (C_6D_6) δ 0.46 (3H, t, J = 7.3 Hz), 1.40−1.60 (1H, m), 1.71 (1H, dqd, J = 14.5, 10.9, 7.3 Hz), 3.11 (3H, s), 3.90 (1H, br d), 4.29 (1H, ddd, J = 10.9, 6.7, 3.1 Hz), 4.49 (1H, br t, J = 6.8 Hz), 6.23 (2H, d, J = 8.9 Hz), 6.44 (2H, d, J = 8.9 Hz), 6.75−7.00 (5H, m); ^{1}H NMR data correspond to literature values;[3] HPLC (Chiralpak AS 150 mm column with guard, 95:5 hexane:IPA, 0.15 mL/min), 15.6 min (minor), 17.3 min (major) shows 94% ee.

General Procedure for Reduction of the Nitro Group and Subsequent Formation of Imidazolidinone. Samarium metal (40 mesh, 0.21 g, 1.40 mmol) and 1,2-diiodoethane (0.37 g, 1.30 mmol) were added to a rigorously flame-dried Schlenk tube. A triple evacuation/N_2 fill was carried out, then THF (2 mL) was added and the mixture was stirred for 1 h under N_2. A further 10 mL of THF was added and the mixture was stirred for 2 h until an intense, deep blue solution was obtained. To this was added crude β-nitroamine (0.20 mmol) in MeOH (1 mL) and THF (3 mL) via cannula transfer. The mixture was left to stir for 16 h. After addition of oxalic acid (0.25 g, 2.80 mmol) in water (10 mL) the mixture was filtered (Celite) and THF was removed in vacuo. The resulting aqueous phase was basified to pH >12 (NaOH) and EtOAc (10 mL) was added. The aqueous phase was washed with EtOAc (3 × 10 mL). The combined organics were washed with saturated sodium thiosulfate (10 mL) and saturated brine (10 mL) before drying ($MgSO_4$) and evaporation to yield crude, monoprotected 1,2-diamine. The crude product was dissolved in DCM (6 mL) and MeOH (3 mL), then saturated $NaHCO_3$ (1 mL) and water (1 mL) were added. The mixture was stirred under N_2 at room temperature for 5 min then $CSCl_2$ (23 μL, 0.30 mmol) was added and the mixture was left to stir for 16 h. The mixture was partitioned between water (10 mL) and DCM (10 mL) and the water phase was further washed with DCM (2 × 10 mL). The combined organics were dried with $MgSO_4$ and concentrated in vacuo to give crude product as a brown semisolid. Column chromatography (4:1 hexane:EtOAc) followed by recrystallization (hexane/EtOAc) afforded the pure thioimidazolidinone.

8b. Prepared using the general procedure above from **3b**, recrystallization (hexane/EtOAc) of crude material afforded diastereomerically pure **8b** as small, clear needles (38 mg, 61%): mp 148−150 °C; IR (solid) 3188, 1500, 1249, 1031 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.83 (3H, t, J = 7.6) Hz, 1.18 (2H, m), 3.73 (3H, s), 4.22 (1H, q, J = 6.0 Hz), 5.26 (1H, d, J = 9.2 Hz), 6.40 (1H, br s), 6.78 (2H, d, J = 8.4 Hz), 7.20−7.30 (7H, m); ^{13}C NMR ($CDCl_3$) δ 10.9, 23.9, 55.4, 60.7, 71.3, 114.0, 128.2, 128.3,

(22) **3h** has 1*R*,2*R* stereochemistry, but the sense of stereoinduction is as drawn.

(23) One could forward a plausible mechanism along the lines of that offered by Evans for enantioselective Henry reactions catalyzed by a copper acetate−bis(oxazoline) catalyst, but we feel this system is more complicated and awaits further investigation. See: Evans, D. A.; Seidel, D.; Rueping, M.; Lam, H. W.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2004**, *125*, 12692.

(24) Aly, M. F.; Grigg, R. *Tetrahedron* **1988**, *44*, 7271.

(25) All substrates screened needed 35−40 h to give good conversion.

128.7, 128.7, 131.9, 135.1, 158.2, 184.0; *m/z* (ES^+) 335 (10%, $M^+ + Na$), 313 (30%, MH^+), 281 (100%), 214 (5%); HRMS $C_{18}H_{21}N_2OS$ calcd 313.1375, found 313.1389; $[\alpha]_D$ +54.0 ($CHCl_3$, *c* 1.280).

Acknowledgment. This work is part of the Ph.D. Thesis of G.P.H., University of Nottingham, 2004. We thank the EPSRC and GlaxoSmithKline for financial support, Dr. A. Ross for helpful discussions, Mr. T. Hollingworth and Mr. D. Hooper for providing mass spectra, and Mr. T. J. Spencer for microanalytical data. We thank the EPSRC-funded synchrotron crystallography service and its director Professor W. Clegg for collection of single-crystal diffraction data at Daresbury SRS Station 9.8.

Supporting Information Available: General experimental details, spectroscopic data for compounds **2** and **3**, copies of ^1H and ^{13}C NMR data for **3c**,**d**,**f**−**h**,**j**,**k** and **8b**,**h**, HPLC traces for **3b**−**d**,**f**−**h**,**j**,**k**, and CIF for **8b**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO050762I