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Scope and Limitations of the Nitro-Mannich Reaction for the Stereoselective Synthesis of 1,2-Diamines

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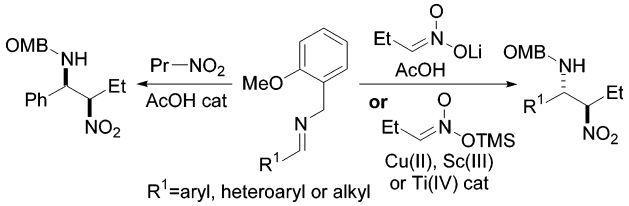

The acetic acid-promoted addition of lithium nitropropanate and the Lewis acid-catalyzed [Sc(OTf)$_3$, Cu(OTf)$_2$, or Ti(O*i*Pr)$_4$] addition of trimethylsilyl nitropropanate to a range of heteroaromatic and simple aliphatic aldimines gave *anti*-rich (~3−19:1) *β*-nitroamines in >95% yields as the kinetic products. It was found that a nonpolar *N*-imine protecting group was essential for reactivity with the *o*-methoxybenzyl (OMB) group giving better selectivities and yields than *p*-methoxybenzyl (PMB) or *p*-methoxyphenyl (PMP) in the Lewis acid-catalyzed addition reactions. Reduction with SmI_2, treatment with $COCl_2$, followed by OMB deprotection gave diastereomerically pure *cis*-imidazolidinones in 55−79% overall yield from imine. Preliminary results have shown that acetic acid can catalyze the reaction of *N*-OMB-benzylideneamine with nitropropane, used as solvent, to give the thermodynamically more stable *syn*-*β*-nitroamine product.

Introduction

The development of stereoselective reactions that create carbon−carbon bonds and heteroatom functionality can provide valuable building blocks for organic synthesis. Due to the importance of the 1,2-diamine structural motif in biologically active natural products, medicinal agents, and more recently as chiral auxiliaries and chiral ligands in asymmetric catalysis,[1] we set out to develop a general method to synthesize this class of compounds that did not rely upon the use of naturally occurring amino acids or amino alcohols. Guided by the notion that a closed six-membered transition state structure could help to maximize stereocontrol, due to the associated conformational energies of the defined six-membered ring, we concentrated on searching for potential α-aza carbanions possessing an extra donor group (X in **1**, Scheme 1) that would add to imines. We eventually discovered that under very precise conditions lithium nitronates would add to imines in the presence of a Brønsted acid to give *β*-nitroamines **2** in good yield and diastereoselectivites in certain cases (Scheme 1).[2]

As this protocol starts with a preformed imine, it represents a stepwise method of conducting the classic

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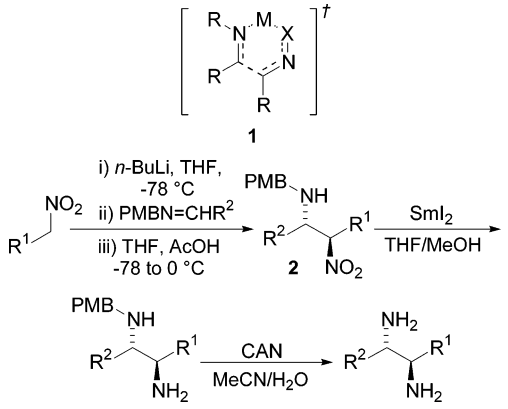

nitro-Mannich reaction[3] that had previously been described in a different guise over 100 years ago,[4] but for which no stereoselective examples had ever been reported.[5] Reduction of the nitro function is complicated with retroaddition and/or *β*-elimination of **2**,[6] but samarium di-iodide was found to perform the reduction in

† Corresponding authors for X-ray crystal structures.

(1) Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2580.

(2) Adams, H.; Anderson, J. C.; Peace, S.; Pennell, A. M. K. *J. Org. Chem.* **1998**, *63*, 9932.

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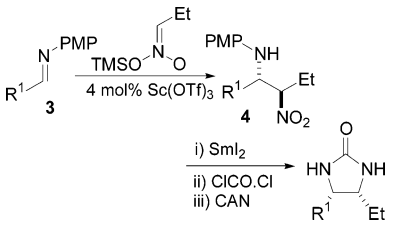
SCHEME 2



high yield and with no erosion in stereochemical integrity.[6b,7] This stepwise protocol that combines an imine, derived from an aromatic or aliphatic carbaldehyde, with a nitro compound under nonbasic conditions represents a more high yielding and stereoselective synthesis of 1,2-diamines than the condensation of amines with formaldehyde and nitroalkanes under reducing conditions, which had been reported over fifty years ago.[8] An asymmetric variant of the nitro-Mannich reaction with *N*-phosphinoylaldimines was then developed by Shibasaki et al.[9] They employed their heterobimetallic asymmetric complexes which contain both Brønsted basic and Lewis acidic sites,[10] first with nitromethane[9] and then extended to other nitroalkanes,[11] but only with imines derived from aromatic aldehydes. Our results had led us to postulate that activation of the imine by protonation is a prerequisite for nitronate addition. Extending this idea with the knowledge of metal-catalyzed additions of silyl ketene acetals and silyl enol ethers to imines[12] and the fluoride induced addition of silyl nitronates to carbonyl compounds,[13] we reported that $Sc(OTf)_3$ catalyzed the addition of 1-trimethylsilyl nitropropanate to aryl and aliphatic imines in good yield with variable diastereoselectivity (Scheme 2).[14] We found that PMP-protected imines (**3**) gave generally higher diastereoselectivities than the analogous PMB-protected imines and could be removed after reduction of the nitro functionality and oxazilidinone formation. Throughout our studies the sensitivity of β-nitroamines **2** and **4** toward retro-addition meant that reduction with SmI_2 to stable monoprotected 1,2-diamines should be performed immediately.

After this report Jørgensen et al. reported that the Cu-catalyzed addition of trimethylsilyl nitronates to *N*-PMP α-imino esters could give optically active β-nitro-α-amino acids and α,β-diamino acid derivatives in high yield, with generally good diastereoselectivity and excellent enantioselectivity using bisoxazoline-type chiral ligands.[15] These catalysts were simultaneously developed for the efficient asymmetric addition of nitroalkanes to *N*-PMP α-imino esters in the presence of catalytic Et_3N.[16] The high selectivity of these two processes can be attributed in part to the bidentate chelation of the α-imino esters to the Lewis acid metal centers. The β-nitro-α-amino esters generated by Jørgensen seem more stable than simple β-nitroamines (**2**) and can be readily reduced with Raney Ni/H_2 in good yields with no erosion of stereochemical integrity. Other workers have shown that $Yb(OiPr)_3$ can catalyze the addition of nitromethane to *N*-sulfonylaldimines derived from aromatic aldehydes.[17] The catalytic asymmetric synthesis of ICI-199441 and CP-99994 by Shibasaki et al. using the nitro-Mannich reaction has demonstrated that the products from the nitro-Mannich reaction are useful synthetic building blocks and should stimulate their use in other target syntheses.[18] Most recently chiral organic Brønsted acid catalysts have been developed to provide aromatic β-nitroamines in good enantioselectivities.[19,20]

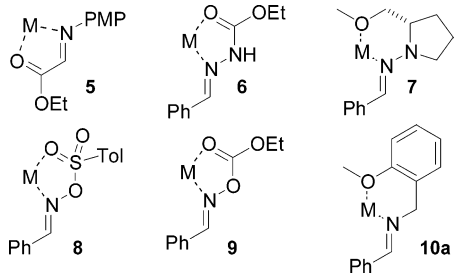


FIGURE 1. Imine substrates.

Despite the considerable advances made in this area there remain limitations to the general applicability of the nitro-Mannich reaction. We set out to develop a flexible methodology that would allow the synthesis of a variety of 1,2-diamines through the coupling of a range of nitroalkanes with aromatic and aliphatic imines. This is in direct contrast to Shibasaki's system, which uses aromatic aldimines, and Jørgensen's, which is necessarily restricted to α-imino esters. This paper reports our efforts to tackle this difficult goal and the results prepare the ground for our asymmetric studies which are currently under investigation.

Results and Discussion

Inspired by Jørgensen's work with α-imino esters (**5**, Figure 1)[15,16] and that of Yamamoto's group concerning the use of *o*-alkoxy aniline-derived aldimines in Lewis acid-catalyzed Mannich-type reactions,[21] we focused on the bidentate coordination of imine substrates to Lewis acid metal centers which would reduce the degrees of freedom of the reaction system. To mimic this effect, but

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(20) Nugent, B. M.; Yoder, R. A.; Johnston, J. N. *J. Am. Chem. Soc.* **2004**, *126*, 3418.

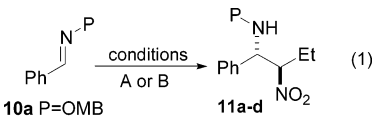
TABLE 1. Comparison of the Imine Protecting Group

entry	imine	method[a]	*t*	yield of **11** (%)[b]	anti/syn[c]
1	**10a**	A	1 h	>95	90/10
2	**10a**	B $Cu(OTf)_2$	5 min	>95	90/10
3	**10a**	B $Sc(OTf)_3$	5 min	>95	80/20
4	**10a**	B $Ti(Oi\text{-}Pr)_4$	5 min	>95	80/20
5	**10b**	A	1 h	90	90/10
6	**10b**	B $Sc(OTf)_3$	2 h	70	65/35
7	**10c**	B $Sc(OTf)_3$	2 h	90	90/10
8	**10d**	B $Cu(OTf)_2$	2 h	>95	85/15

[a] Method A: AcOH (2.4 equiv) was added to a solution of lithium 1-nitropropanate (1.4 equiv) and imine (1.0 mmol) in THF at −78 °C then rt. Method B: 1-trimehtylsilyl nitropropanate (2.4 equiv) was added to imine (0.40 mmol) and Lewis acid (5 mol %) in THF at −78 °C. [b] Crude yield estimated from the mass balance and ^{1}H NMR. [c] From crude ^{1}H NMR rounded to the nearest 5%.

without limiting variation in the imine substrate, we investigated imines bearing potentially chelating protecting groups (Figure 1). A range of possible candidates were synthesized and screened in both the acetic acid-promoted nitro-Mannich reaction (Scheme 1) with nitropropane and the Lewis acid-catalyzed nitro-Mannich reaction (Scheme 2) with trimethylsilyl nitropropanate previously developed by us.

Imines **6**−**9** were found to be wholly unreactive under nitro-Mannich reaction conditions employing either AcOH or Lewis acids $Cu(OTf)_2$, $Sc(OTf)_3$, and $Ti(Oi\text{-}Pr)_4$. Conversely the *N*-(2-methoxybenzyl) (OMB)-protected imine **10a** was found to be highly reactive under both sets of reaction conditions to give *anti*-**11a** in good yields and diastereoselectivities (Table 1, entries 1−4). The additional α-heteroatoms in imines **6**−**9** could be diminishing the electrophilicity of the imine carbon through electron donation or there are alternate binding modes of the Lewis acid, which may not include the imine nitrogen, that lead to inactive complexes. To compare the efficiency of the OMB group we compared similar reactions with PMB (**10b** entries 5 and 6) and PMP (**10c** entry 7) protected imines of benzaldehyde (eq 1). The OMB imine **10a** gave consistently higher selectivities and/or yields under both sets of reaction conditions. To explore whether the increased selectivity attributed to the OMB group was due to sterics or the presence of a coordinating group in the ortho position, we synthesized the *N*-(2-methylbenzyl)-protected imine **10d** and subjected it to the $Cu(OTf)_2$ Lewis acid-catalyzed reaction conditions. The results (entry 8) did not illuminate the coordination mode of **10a** in these reactions.



Mindful of our goal to develop a broad and robust method for nitro-Mannich coupling we synthesized and screened a range of OMB imines (Figure 2). Imines **12**−**15** are heterocyclic-Schiff bases, **16** and **17** are aldimines derived from simple aliphatic aldehydes, and **18** is a ketimine derived from acetone. Despite considerable effort we were unable to synthesize significant quantities of analogous imines derived from acetophenone or benzophenone due to incomplete reactions and difficulties with purification.

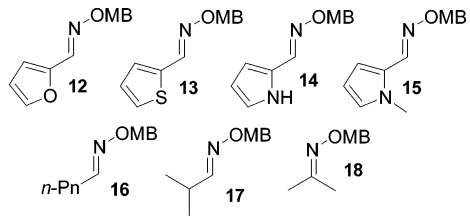
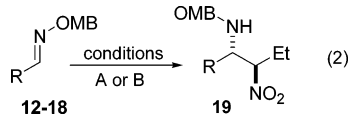


FIGURE 2. OMB protected imines.

Each of the imines (Figure 2) were subjected to both the acetic acid-promoted and Lewis acid-promoted nitro-Mannich reaction (eq 2, Table 2). Purification of the



β-nitroamines **19** by chromatography was not possible due to degradation and the data were collected from the crude reaction mixtures. The relative stereochemistry was assigned based on ^{1}H NMR coupling constants and was confirmed by single-crystal X-ray analysis of derivatives (vide supra). The diastereomeric ratios were measured from distinct signals in the ^{1}H NMR spectrum.[22] The diastereoselectivities of OMB-imines **12** and **16** are far superior in comparison to our previous studies with the corresponding PMB or PMP imines[14] and were another justification for us choosing to optimize diastereoselectivites for OMB-imines.

General patterns in the data (Table 2) show both methods A and B to be typically high yielding with method A (acetic acid promoted) showing higher anti-diastereoselectivity in most cases. Within method B, among the Lewis acid catalysts $Cu(OTf)_2$, $Sc(OTf)_3$, and $Ti(Oi\text{-}Pr)_4$, the diastereoselectivity seems independent of the Lewis acid used, but the use of $Ti(Oi\text{-}Pr)_4$ often resulted in the lowest conversion. Pyrrole imine **14** was practically inert under all reaction conditions (entries 9−12). Possibly the existing hydrogen bonding between the pyrrole NH and the imine lone pair interferes with coordination of an acid. This was supported by the *N*-methyl analogue **15** undergoing satisfactory reaction (entries 13−16). Imine **16** derived from a straight chain aldehyde gave up to a 90:10 diastereomeric ratio (entries 17−20) whereas the more sterically demanding isopropyl imine **17** gave diastereomeric ratios closer to 1:1 (entries 21−24).

The crude β-nitroamines were subjected to SmI_2 reduction to give 1,2-diamines to confirm the yields and sense of diastereoselectivity assigned (eq 3, Table 3). We took

this opportunity to survey other common reducing sys-

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TABLE 2. Addition of Nitronate Species to Imines

entry	imine	method[a]	*t*	**19**	R	yield of **19** (%)[b]	anti/syn[c]
1	**12**	A	1 h	**b**	2-furyl	91	95/5
2	**12**	B $Cu(OTf)_2$	5 min	**b**	2-furyl	>95	85/15
3	**12**	B $Sc(OTf)_3$	5 min	**b**	2-furyl	>95	80/20
4	**12**	B $Ti(Oi\text{-}Pr)_4$	5 min	**b**	2-furyl	89	65/35
5	**13**	A	2 h	**c**	2-thiophenyl	71	95/5
6	**13**	B $Cu(OTf)_2$	45 min	**c**	2-thiophenyl	86	75/25
7	**13**	B $Sc(OTf)_3$	45 min	**c**	2-thiophenyl	>95	80/20
8	**13**	B $Ti(Oi\text{-}Pr)_4$	45 min	**c**	2-thiophenyl	72	75/25
9	**14**	A	6 h	**d**	2-pyrrole	<5	
10	**14**	B $Cu(OTf)_2$	3 h	**d**	2-pyrrole	<5	
11	**14**	B $Sc(OTf)_3$	3 h	**d**	2-pyrrole	<5	
12	**14**	B $Ti(Oi\text{-}Pr)_4$	3 h	**d**	2-pyrrole	<5	
13	**15**	A	3 h	**e**	2-(*N*-methyl)pyrrole	89	75/25
14	**15**	B $Cu(OTf)_2$	1 h	**e**	2-(*N*-methyl)pyrrole	>95	75/25
15	**15**	B $Sc(OTf)_3$	1 h	**e**	2-(*N*-methyl)pyrrole	>95	75/25
16	**15**	B $Ti(Oi\text{-}Pr)_4$	1 h	**e**	2-(*N*-methyl)pyrrole	60	80/20
17	**16**	A	1 h	**f**	*n*-hexyl	>95	90/10
18	**16**	B $Cu(OTf)_2$	5 min	**f**	*n*-hexyl	>95	90/10
19	**16**	B $Sc(OTf)_3$	5 min	**f**	*n*-hexyl	>95	85/15
20	**16**	B $Ti(Oi\text{-}Pr)_4$	5 min	**f**	*n*-hexyl	>95	80/20
21	**17**	A	1 h	**g**	*i*-Pr	92	60/40
22	**17**	B $Cu(OTf)_2$	5 min	**g**	*i*-Pr	90	50/50
23	**17**	B $Sc(OTf)_3$	5 min	**g**	*i*-Pr	>95	65/35
24	**17**	B $Ti(Oi\text{-}Pr)_4$	5 min	**g**	*i*-Pr	82	50/50
25	**18**	A	1 h	**h**	Me_2	93	
26	**18**	B $Cu(OTf)_2$	5 min	**h**	Me_2	>95	
27	**18**	B $Sc(OTf)_3$	5 min	**h**	Me_2	90	
28	**18**	B $Ti(Oi\text{-}Pr)_4$	5 min	**h**	Me_2	89	

[a] Method A: AcOH (2.4 equiv) was added to a solution of lithium 1-nitropropanate (1.4 equiv) and imine (1.0 mmol) in THF at −78 °C then rt. Method B: 1-trimehtylsilyl nitropropanate (2.4 equiv) was added to imine (0.40 mmol) and Lewis acid (5 mol %) in THF at −78 °C. [b] Crude yield estimated from the mass balance and ^{1}H NMR. [c] From crude ^{1}H NMR rounded to the nearest 5%.

TABLE 3. Isolated Yields of 1,2-Diamine Derivatives

20	R^1	yield (%)[a]
20a	Ph	74
20b	2-furyl	87[b]
20c	2-thiophenyl	59[b]
20e	2-(*N*-methyl)pyrrole	69[b]
20f	*n*-hexyl	83[b]
20g	*i*-Pr	26[c]
20h	Me_2	—[d]

[a] Yield over three steps from imine to diastereomerically pure *cis*-**20**. [b] Minor isomer removed by recrystallization. [c] Separated by chromatography from a 1:1 mixture of nitro-Mannich product after cyclic urea formation. [d] *N*-OMB-isopropylamine isolated in 76% yield after reduction.

tems, which had been used for the reduction of nitroalkanes, on crude *β*-nitroamine **11a**. Standard Fe or Sn metal reduction under acidic conditions gave a complex mixture of products.[23] Treatment with $LiAlH_4$ furnished OMB-benzylamine (55%) from reduction of the iminium ion from retroaddition of nitropropane from **11a**.[24] The use of nickel borohydride[25] gave unreacted starting material among a mixture of degradation products. Hydrogenolysis[26] with Pt/H_2 or with Raney nickel alone gave recovered starting material. Raney nickel reduction in the presence of atmospheric H_2 gave only ∼10% reduced product along with recovered starting material after 24 h.[15] In keeping with our previous studies we found SmI_2 in THF/MeOH to be an effective and mild system for this reduction as long as the reagent was freshly prepared.[6b] We encountered difficulties in purifying the 1,2-diamines with significant loss of mass upon chromatography and found bulb-to-bulb distillation unsatisfactory. The 1,2-diamines visibly degraded in the atmosphere over 24 h. As a consequence we found it convenient to treat the crude reduction mixture with phosgene to generate the cyclic ureas, OMB-imidazolidinones (eq 3, Table 3). The isolated yield quoted is for three steps from imine to diastereomerically pure **20**.

The three-step sequence of nitro-Mannich coupling of OMB-imines with a nitroalkane, followed by reduction and cyclic urea formation can give *cis*-diamine derivatives in moderate to good overall yields. It appears that *β*-nitroamines derived from ketimines suffer from retroaddition during the reduction step when an OMB protecting group is used (**20h**). In our original acetic acid-promoted reaction the nitroamine from 2-nitropropane and *N*-PMB benzylideneamine furnished a moderate yield of the desired 1,2-diamine (48%).[2] This suggests that diamines possessing tertiary centers can only be derived from secondary nitro compounds and not ketimines. The Single-crystal X-ray analysis of **20a**−**c**,**e**,**g** confirmed the cis-stereochemistry which we had assumed from ^{1}H NMR analysis.[27] Diamine derivative **20f** was assigned cis by analogy of its ^{1}H NMR spectrum.

To complete the synthesis of 1,2-diamine derivatives we wanted to demonstrate the removal of the OMB protecting group. Inspection of the literature revealed no precedent for cleavage of N−OMB bonds so we studied analogous methods used for the cleavage of N−PMB groups using **20a** (R = Ph). The use of one-electron donors CAN[28] and DDQ[29] was ineffective, either giving no reaction or eliminated product **22**. Hydrogenolysis was

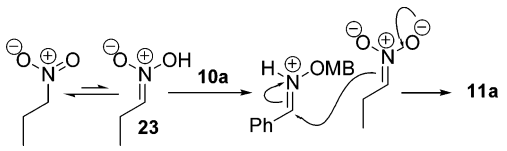
(22) See Supporting Information.
(23) Johnson, K.; Degering, E. F. *J. Am. Chem. Soc.* **1939**, *61*, 3194.
(24) Bunce, S. C.; Clemans, S. D.; Bennett, B. A. *J. Org. Chem.* **1975**, *40*, 961.
(25) Osby, J. O.; Ganem, B. *Tetrahedron Lett.* **1985**, *26*, 6413.
(26) Iffland, D. C.; Cassis, F. A. *J. Am. Chem. Soc.* **1952**, *74*, 6284.

TABLE 4. Removal of the OMB Protecting Group

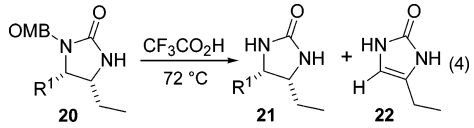
20	R^1	yield of **21** (%)[a]	yield of **22** (%)[a]
20a	Ph	95	
20b	2-furyl	87	
20c	2-thiophenyl	94	
20e	2-(*N*-methyl)pyrrole	-	75
20f	*n*-hexyl	95	
20g	*i*-Pr	-	

[a] Isolated yield.

SCHEME 3



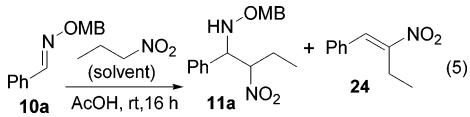
similarly ineffective and the use of harsher conditons employing $AlCl_3$ in refluxing anisole[30] caused complete degradation. Clean deprotection of the OMB group was achieved by refluxing in neat TFA (eq 4) to give high yields of **21** (Table 4).[31] This method proved successful for most of the diamines **20**, except *N*-methylpyrrole derivative **20e** underwent facile elimination to **22** and the *i*-Pr diamine **20g** proved unstable to the reaction conditions.



The two nitro-Mannich protocols presented above give inherently *anti*-β-nitroamines, identical with similar processes reported in the literature.[11,15,16,18] We have investigated modifications of our protocols to produce syn products. We found that imine **10a** bearing an OMB protecting group underwent a slow nitro-Mannich reaction in neat nitropropane at room temperature. After 16 h, 35% of imine had been consumed giving β-nitro-amine product **11a** with an anti/syn ratio of 4:1. Conversion tended to a maximum of ~75% (>72 h), but with an eroded diastereoselectivity of 2:1. We attribute this reaction to the small concentration of nitronic acid tautomer **23** that can protonate imine **10a** to allow addition of the nitronate anion (Scheme 3).[2]

The nitro/nitronic acid tautomeric equilibrium lies heavily in favor of the nitro species and we postulate that it is only in neat nitropropane that a significant concentration of **23** is attainable. This is supported by the observation that decreasing the level of nitropropane from solvent to 5 or 10 equiv in CH_2Cl_2, THF, or MeCN results in <5% reaction in 16 h.

The nitro-Mannich reaction of OMB-imine **10a** in neat nitropropane was significantly accelerated by the addition of substoichiometric amounts of AcOH. We found that the optimum amount of AcOH for the most syn-selective reaction appeared to be 20 mol %, where *syn*-**11a** was formed in 71% yield of the reaction mixture (eq 5, *anti*-**11a**/*syn*-**11a**/**24**, 20:75:5). We may expect a Brønsted acid to raise the levels of **23** by analogy with keto/enol tautomerism and thus promote this reaction. Elimination product **24** was formed in exclusively the *E*-form[32] and is derived from standard acid-catalyzed Henry elimination of OMB-NH_2.



Conversion of syn-rich **11a** to the 1,2-diamine derivative, imidazolidinone *trans*-**20a**, proceeded as before by reduction with SmI_2 followed by cyclization with phosgene in 41% isolated yield from starting imine. This variant of the nitro-Mannich reaction is the subject of further investigations to engineer a general syn-selective process.

We have investigated the Lewis acid-catalyzed and AcOH-promoted nitro-Mannich reaction as a diastereoselective route to certain 1,2-diamine derivatives. Only carbon benzyl or phenyl *N*-imine protecting groups were successful with OMB better than PMB and PMP. The anti-rich β-nitroamines were reduced to 1,2-diamines with SmI_2 and the OMB group readily removed by refluxing TFA from the imidazoline derivatives in high isolated yields and diastereomeric purity. Work is continuing to understand the sense and magnitude of diastereoselection under the different reaction conditions reported in this paper. The Lewis acid-catalyzed examples will form the basis of enantioselective studies with the use of chiral multidentate ligands and Cu(II), Sc(III), or Ti(IV) complexes. Preliminary results show that acetic acid can catalyze a syn-selective nitro-Mannich reaction with OMB-imine in neat nitropropane and we are currently looking at other Brønsted acids and bases which may facilitate an efficient and general enantio- and syn-selective process.

Experimental Section

General Procedure for the Synthesis of Imines. Rigorously dried 4 Å molecular sieves (1.0 g per mmol) were added to a solution of amine 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. Imines were judged >95% pure by ^1H NMR, but were purified if possible. For spectroscopic data see the Supporting Information.

(27) Crystallographic data (excluding structure factors) for *cis*-**20a** and **20c**,**e**,**g** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 242114−7, respectively. Copies of the data can be obtained free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax +44-(0)1223-336033 or e-mail deposit@ccdc.cam.ac.uk]. Although we have clearly established the stereochemistry by single-crystal X-ray diffraction methods for compound **20b**, there were significant problems with crystal quality and the resulting structure was not of sufficient quality for publication.

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(31) This method was developed from the known cleavage of PMB groups from amides with neat TFA at room temperature. Brooke, G. M.; Mohammed, S.; Whiting, M. C. *Chem. Commun.* **1997**, 1511.

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General Procedure for the AcOH-Promoted Nitro-Mannich Reaction (method A, Tables 1 and 2). A solution of *n*-butyllithium (2.5 M in hexanes, 0.56 mL, 1.40 mmol) was added to a solution of 1-nitropropane (0.13 mL, 1.40 mmol) in THF (20 mL) over 10 min at −78 °C under N_2 and the mixture was stirred for a 10 min. A solution of imine (1.00 mmol) in THF (10 mL) was then added, the mixture was stirred for 10 min at −78 °C, and then AcOH (0.14 mL, 2.4 mmol) was added and the mixture was stirred for a further 20 min before being allowed to warm to 25 °C over 30 min. Saturated aq $NaHCO_3$ (10 mL) and Et_2O (20 mL) were then added, and the organic phase was separated, washed with satd aq $NaHCO_3$ (10 mL), dried ($MgSO_4$), and evaporated to yield crude β-nitroamine. These were analyzed by ^{1}H NMR. Purification (chromatography on silica or alumina) was attempted with some crude mixtures but gave very little of the desired material. MS under a variety of techniques causes retroaddition and no collection was made.

General Procedure for the Lewis Acid-Catalyzed Nitro-Mannich Reaction (method B, Tables 1 and 2). A solution of imine (0.40 mmol) and Lewis acid catalyst [Cu(OTf)$_2$, Sc(OTf)$_3$, or Ti(O*i*-OPr)$_4$, 5 mol %) in THF (1 mL) was stirred for 5 min at room temperature and then cooled to −78 °C. A solution of *O*-trimethylsilyl nitropropanate in THF (3 mL) was then added over a period of 15 min via cannula. The mixture was left to stir at −78 °C for 30 min before filtration through poly(4-vinylpyridine) to remove Cu catalysts, or neutral alumina to remove Sc or Ti catalyst. Removal of solvent in vacuo gave the crude β-nitroamine. These were analyzed by ^{1}H NMR. Purification (chromatography on silica or alumina) was attempted with some crude mixtures but gave very little of the desired material. MS under a variety of techniques causes retroaddition and no t collection was made.

11a: Isolated as a yellow oil. NMR data for anti (1*S**,2*R**) ^{1}H NMR δ 0.60 (3H, t, J = 7.4 Hz), 1.67 (1H, dqd, J = 14.9, 7.4, 3.0 Hz), 1.97 (1H, ddq, J = 14.7, 10.9, 7.3 Hz), 3.31 (3H, s), 3.54 (1H, d, J = 13.5 Hz), 3.80 (1H, d, J = 13.5 Hz), 4.04 (1H, d, J = 6.1 Hz), 4.39 (1H, ddd, J = 11.1, 6.1, 3.0 Hz), 6.49 (1H, m), 6.82 (1H, m), 6.86 (2H, m), 7.00−7.20 (5H, m); ^{13}C NMR δ 10.4, 22.5, 47.5, 54.8, 64.4, 95.2, 110.6, 120.9, 127.8, 128.7, 128.9, 130.0, 130.6, 139.2, 158.1; NMR data for syn (1*R**,2*R**) ^{1}H NMR δ 0.50 (3H, t, J = 7.4 Hz), 1.53 (1H, ddq, J = 14.9, 10.8, 7.2 Hz), 3.28 (3H, s), 3.52 (1H, d, J = 13.9 Hz), 3.78 (1H, d, J = 13.9 Hz), 3.97 (1H, d, J = 9.7 Hz), 4.46 (1H, ddd, J = 11.0, 9.7, 3.3 Hz), 6.49 (1H, m), 6.82 (1H, m), 6.86 (2H, m), 7.00−7.20 (5H, m);^{13}C NMR δ 10.2, 20.1, 47.2, 54.7, 64.5, 95.8, 110.5, 120.6, 127.8, 128.6, 128.8, 130.2, 130.6, 139.1, 158.1.

11b: For characterization data see ref 2.

11c: For characterization data see ref 13.

11d: Prepared using general procedure B, isolated as a yellow oil. NMR data for major anti (1*S**,2*R**) ^{1}H NMR δ 0.75 (3H, t, J = 7.4 Hz), 1.75−2.05 (2H, m), 2.21 (3H, s), 3.38 (1H, d, J = 12.6 Hz), 3.52 (1H, d, J = 12.6 Hz), 4.05 (1H, d, J = 7.2 Hz), 4.41 (1H, m), 7.10−7.30 (9H, m); ^{13}C NMR δ 10.4, 19.1, 25.2, 49.9, 65.0, 95.0, 126.2, 127.9, 128.4, 129.1, 129.3, 129.4, 130.8, 137.2, 138.1, 139.3.

19b: Isolated as a yellow oil. NMR data for major anti (1*S**,2*R**) ^{1}H NMR δ 0.67 (3H, t, J = 7.4 Hz), 1.88 (2H, m), 3.28 (6H, s), 3.62 (2H, m), 3.80 (2H, m), 4.13 (1H, d, J = 7.3 Hz), 4.51 (1H, ddd, J = 10.1, 7.5, 3.9 Hz), 6.00 (1H, m), 6.06 (1H, m), 6.50 (2H, m), 6.84 (2H, m), 6.95−7.25 (6H, m); ^{13}C NMR δ 10.1, 23.7, 47.4, 54.8, 58.7, 92.8, 108.8, 110.4, 120.9, 128.3, 128.4, 128.7, 129.9, 142.5, 152.0, 157.9; NMR data for minor syn (1*R**,2*R**) ^{1}H NMR δ 0.57 (3H, t, J = 7.3 Hz), 1.11 (1H, m), 1.62 (1H, m), 3.28 (6H, s), 3.62 (2H, m), 3.80 (2H, m), 4.09 (1H, d, J = 9.9 Hz), 4.61 (1H, td, J = 10.2, 3.3 Hz), 5.83 (1H, d, J = 3.2 Hz), 5.96 (1H, m), 6.50 (2H, m), 6.84 (2H, m), 6.95−7.25 (6H, m).

19c: Isolated as a yellow oil. NMR data for major anti (1*S**,2*R**) ^{1}H NMR δ 0.59 (3H, t, J = 7.4 Hz), 1.74 (1H, m), 1.95 (1H, m), 3.31 (3H, s), 3.62 (1H, d, J = 13.5 Hz), 3.92 (1H, d, J = 13.4 Hz), 3.34−3.42 (2H, m), 6.40−6.55 (1H, m), 6.66−6.73 (2H, m), 6.82−6.90 (2H, m), 7.08 (2H, m); ^{13}C NMR δ 10.3, 23.0, 47.6, 54.9, 60.1, 95.4, 110.4, 120.7, 125.5, 126.8, 127.1, 128.7, 130.3, 143.6, 154.9, 158.1.

19e: Isolated as a yellow oil. NMR data for major anti (1*S**,2*R**) ^{1}H NMR δ 0.71 (3H, t, J = 7.2 Hz), 1.52 (1H, m), 1.97 (2H, m), 2.95 (3H, s), 3.26 (3H, s), 3.62 (2H, m), 3.80 (2H, m), 4.12 (1H, d, J = 7.2 Hz), 4.41 (1H, ddd, J = 11.1, 7.4, 3.8 Hz), 6.19−6.28 (5H, m), 6.45−6.51 (2H, m), 6.80 (2H, m), 7.02−7.15 (4H, m); ^{13}C NMR δ 10.3, 23.5, 33.3, 47.1, 54.8, 56.5, 94.1, 107.7, 108.0, 110.4, 120.6, 122.9, 128.3, 128.6, 130.1, 154.0, 158.2; NMR data for minor syn (1*R**, *R**) ^{1}H NMR δ 0.56 (3H, t, J = 7.3 Hz), 1.18 (1H, m), 2.90 (3H, s), 3.29 (3H, s), 3.62 (2H, m), 3.80 (2H, m), 4.16 (1H, d, J = 10.0 Hz), 4.61 (1H, td, J = 10.2, 2.7 Hz), 5.98 (1H, m), 6.19−6.28 (5H, m), 6.45−6.51 (2H, m), 6.80 (2H, m), 7.02−7.15 (4H, m).

19f: Isolated as a yellow oil. NMR data for major anti (1*S**,2*R**) ^{1}H NMR δ 0.87 (3H, t, J = 7.2 Hz), 0.97 (3H, t, J = 7.4 Hz), 1.10−1.48 (8H, m), 1.81−2.16 (2H, m), 2.89 (1H, m), 3.78 (1H, d, J = 13.1 Hz), 3.84 (4H, m), 4.47 (1H, ddd, J = 10.6, 5.9, 3.5 Hz), 6.88 (1H, d, J = 8.0 Hz), 6.93 (1H, td, J = 7.4, 0.9 Hz), 7.20−7.30 (2H, m); ^{13}C NMR δ 10.8, 14.0, 22.1, 22.8, 25.4, 30.8, 31.8, 47.5, 55.2, 59.4, 93.6, 110.2, 120.6, 128.5, 128.6, 130.1, 157.7.

19g: Isolated as a yellow oil. NMR data for major anti (1*S**,2*R**) ^{1}H NMR δ 0.57 (3H, d, J = 6.6 Hz), 0.67−0.81 (9H, m), 1.27 (1H, dqd, J = 14.7, 7.3, 3.7 Hz), 1.53 (1H, hepd, J = 6.8, 4.3 Hz), 1.74 (1H, ddq, J = 14.6, 10.7, 7.2 Hz), 2.76 (1H, dd, J = 7.8, 4.3 Hz), 3.29 (3H, s), 3.90 (2H, s), 4.27 (2H, m), 6.50, (2H, dd, J = 8.1, 2.2 Hz), 6.87 (2H, tdd, J = 7.4, 3.2, 1.0 Hz), 7.08 (2H, tdd, J = 8.0, 3.3, 1.7 Hz), 7.19 (1H, dd, J = 7.3, 1.7 Hz); ^{13}C NMR δ 10.5, 16.4, 20.3, 24.4, 29.9, 50.4, 54.7, 65.0, 94.2, 110.5, 120.9, 128.6, 129.2, 130.3, 157.9; NMR data for minor syn (1*R**,2*R**) ^{1}H NMR δ 0.67−0.81 (9H, m), 1.64 (1H, hepd, J = 6.8, 3.7 Hz), 1.88 (1H, dqd, J = 14.7, 7.4, 3.2 Hz), 1.97 (1H, ddq, J = 14.6, 10.9, 7.2 Hz), 2.88 (1H, dd, J = 7.9, 3.7 Hz), 3.31 (3H, s), 3.78 (2H, d, J = 13.0 Hz), 4.27 (2H, m), 6.50, (2H, dd, J = 8.1, 2.2 Hz), 6.87 (2H, tdd, J = 7.4, 3.2, 1.0 Hz), 7.08 (2H, tdd, J = 8.0, 3.3, 1.7 Hz), 7.36 (1H, dd, J = 7.3, 1.7 Hz); ^{13}C NMR δ 10.8, 16.1, 20.2, 24.0, 30.1, 50.7, 54.7, 65.3, 93.6, 110.4, 120.9, 128.9, 129.4, 130.3, 157.9.

19h: Isolated as a yellow oil. ^{1}H NMR δ 0.78 (3H, t, J = 7.4 Hz), 1.08 (3H, s), 1.16 (3H, s), 1.49 (1H, m), 2.01 (1H, m), 3.48 (3H, s), 3.76 (1H, d, J = 12.7 Hz), 3.86 (1H, d, J = 12.8 Hz), 4.40 (1H, dd, J = 11.9, 2.4 Hz), 6.64 (1H, d, J = 8.1 Hz), 6.99 (1H, t, J = 7.4 Hz), 7.20 (1H, t, J = 9.7), 7.47 (1H, d, J = 7.4 Hz); ^{13}C NMR δ 11.0, 21.9, 23.8, 41.3, 54.7, 55.3, 97.7, 110.3, 120.9, 128.1, 128.3, 129.5, 129.8, 157.7.

General Procedure for Reduction of the Nitro Group[6b] and Subsequent Formation of Imidazolidinone. A triple evacuation/N_2 fill was carried out on a suspension of samarium metal (40 mesh, 5.26 g, 35.0 mmol) and 1,2-diiodoethane (9.16 g, 32.5 mmol) in a Schlenk tube. The mixture was diluted with THF (50 mL) and stirred for 1 h under N_2. A further 150 mL of THF was added and the mixture was stirred for 2 h until an intense, deep blue solution was obtained. Crude β-nitroamine (5.00 mmol) in MeOH/THF (1:1, 30 mL) was added and the mixture was stirred for 16 h at room temperature. A solution of oxalic acid (8.60 g) in water (100 mL) was added and the mixture was filtered (Celite) and the organics removed in vacuo. The resulting aqueous phase was basified to pH >12 (2 M, NaOH) and extracted with EtOAc. The combined organics were washed with satd aq $Na_2S_2O_3$ and satd brine before drying ($MgSO_4$) and evaporation to yield crude, mono-protected 1,2-diamine.

A solution of phosgene (20% in toluene, 2.65 mL, 5.00 mmol) was added dropwise to a solution of the crude diamine from above in CH_2Cl_2 (30 mL) and Et_3N (1.50 mL, 10.0 mmol) at −20 °C. After addition the mixture was allowed to warm to 25 °C over 30 min, 5 M NaOH (20 mL) was added, and the organic phase was separated, dried ($MgSO_4$), and evaporated to a yellow/brown highly viscous oil. After being dissolved in

the minimum amount of hot EtOAc/petroleum ether, the product imidazolidinone was crystallized and obtained as a solid. Further recrystallization (EtOAc/petroleum ether mixtures) to remove the minor diastereoisomer was carried out where indicated. For spectroscopic data see the Supporting Information.

General Procedure for the Removal of the 2-Methoxybenzyl Group. A solution of OMB-imidazolidinone (0.5 mmol) in TFA (5 mL) was stirred at reflux (∼95 °C). After consumption of starting material (TLC) the TFA was removed in vacuo to yield a dark red, viscous oil. After addition of EtOAc and washing with saturated $NaHCO_3$, the organic phase was dried ($MgSO_4$) and evaporated to give a viscous, yellow oil. Flash-column chromatography (1:2 EtOAc/petroleum ether) gave the imidazolidinone product as a white solid.

21a:. According to the general procedure above **20a** (155 mg, 0.50 mmol) gave **21a** as a white solid (94 mg, >99%): mp 191.0−193.0 °C (lit.[2] mp 192.0−194.0 °C); all other spectroscopic data were in agreement with those already published by us.[2]

21b: According to the general procedure above **20b** (150 mg, 0.5 mmol) gave **21b** as a white solid (78 mg, 87%): mp 182.0−184.0 °C; IR ν_{max} (solid) 3206, 1698, 1455, 1260, 1148, 1003, 750, 719 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.84 (3H, t, J = 7.5 Hz), 1.22 (2H, m), 3.90 (1H, dt, J = 8.3, 5.6 Hz), 4.88 (1H, d, J = 8.2 Hz), 5.25 (1H, br s), 5.60 (1H, br s), 6.33 (2H, m), 7.36 (1H, s); ^{13}CNMR ($CDCl_3$) δ 10.7, 24.4, 54.4, 58.7, 108.1, 110.5, 142.5, 152.2, 163.5; *m/z* (EI^+) 180 (100%, M^+), 109 (53%), 94 (26%), 67 (30%), 59 (26%); HRMS $C_9H_{12}N_2O_2$ calcd 180.0899, found 180.0893.

21c: According to the general procedure above **20c** (158 mg, 0.5 mmol) gave **21c** as a white solid (92 mg, 94%): mp 161.0−163.0 °C; IR ν_{max} (solid) 3199, 1693, 1456, 1236, 773, 687 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.84 (3H, t, J = 7.4 Hz), 1.23 (2H, m), 3.87 (1H, q, J = 6.1 Hz), 5.12 (1H, d, J = 8.0 Hz), 5.23 (1H, br s), 5.49 (1H, br s), 6.98 (2H, m), 7.26 (1H, s); ^{13}C NMR ($CDCl_3$) δ 10.8, 22.2, 56.3, 59.2, 125.1, 125.6, 128.0, 142.0, 163.8; *m/z* (EI^+) 196 (32%, M^+), 136 (22%), 135 (100%), 88 (34%), 78 (65%); HRMS $C_9H_{12}N_2OS$ calcd 196.0670, found 196.0679.

21f: According to the general procedure above **20f** (152 mg, 0.5 mmol) gave **21f** as a white solid (92 mg, >99%): mp 85.1−87.5 °C; IR ν_{max} (solid) 3217, 1698, 1463, 770 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87−0.98 (6H, m), 1.18−1.40 (6H, m), 1.41−1.59 (4H, m), 3.61 (1H, q, J = 7.0 Hz), 3.71 (1H, ddd, J = 8.9, 7.8, 4.6 Hz), 4.84 (1H, br s), 4.98 (1H, br s); ^{13}C NMR ($CDCl_3$) δ 10.8, 14.0, 22.5, 22.7, 26.0, 29.6, 31.8, 56.2, 57.8, 164.5; *m/z* (EI^+) 184 (6%, M^+), 155 (68%, M^+ − Et), 113 (100%, M^+ − *n*-pen), 75 (12%), 58 (32%); HRMS $C_{10}H_{20}N_2O$ calcd 184.1576, found 184.1569.

General Procedure for Thermodynamic Reactions. To a solution of imine **10a** (0.40 mmol) in 1-nitropropane (2.50 mL) was added acetic acid (20 mol %) and the mixture was stirred for 18 h at room temperature. Filtration through poly(4-vinylpyridine) and removal of solvent at ∼40 °C in vacuo gave the crude β-nitroamine product, which was analyzed by NMR spectroscopy: 95% conversion, *anti*-**11a**/*syn*-**11a**/**24**, 20:75:5.

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Supporting Information Available: General experimental, spectroscopic data for compounds **10a**−**d**, **12**−**18**, *cis*- and *trans*-**20a**, **20b**,**c**,**e**,**f**, and *cis*- and *trans*-**20g** and copies of ^1H and ^{13}C NMR data. This material is available free of charge via the Internet at http://pubs.acs.org.

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