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Secondary–secondary diamine catalysts for the enantioselective Michael addition of cyclic ketones to nitroalkenes

Sunil V. Pansare *, Raie Lene Kirby

Department of Chemistry, Memorial University, St. John's, Newfoundland, Canada A1B 3X7

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ABSTRACT

Secondary–secondary diamines derived from *S*-proline are efficient catalysts for the ketone–nitroalkene Michael addition reaction. The stereoselectivity of the Michael addition is dependant on the pK_a of the *N*-substituted aminomethyl pendant in these diamines. *N*′-Aryl aminomethyl pyrrolidines provide γ-nitroketones with moderate to good enantiomeric excess (65–92%). Removal of the hydrogen-bond donor group by N-methylation results in a dramatic reduction of enantioselectivity (average ee 6%).

1. Introduction

The organocatalytic Michael addition of carbon nucleophiles to a variety of acceptors has been extensively investigated in recent years.[1] One particular class of these reactions, namely the conjugate addition of aldehydes or ketones to nitroalkenes, is of special interest. The ready availability of starting materials, the inherent simplicity of the process, the opportunity to construct enantiomerically pure γ-nitrocarbonyl compounds with contiguous stereocenters, and the synthetic versatility of the nitro group have all contributed to the notable interest in the asymmetric catalysis of this reaction.[2] An array of organocatalysts is available for the enamine-mediated Michael addition reaction.[3] However, the search for new and more efficient catalysts continues at a remarkable pace. Herein, we report preliminary results on the application of pyrrolidine-based secondary–secondary diamines as catalysts for the ketone–nitroalkene conjugate addition reaction.

The secondary–secondary diamine motif, which was examined by Yamamoto in asymmetric aldol reactions,[4] has been mostly overlooked in organocatalytic conjugate addition studies. A potential difficulty with secondary–secondary diamines is irreversible aminal formation with the carbonyl substrate, a competing reaction which is known to predominate.[5] Nonetheless, such diamines are readily amenable to structural modifications in the *N*-substituents. This feature is particularly attractive for studying catalyst performance as a function of steric and electronic changes in the *N*-substituent. Consequently, the objectives of the present study were twofold: a) to determine the applicability of secondary–secondary diamines as catalysts in the ketone–nitroalkene Michael addition reactions and b) to understand the role of catalyst–nitroalkene hydrogen bonding in the stereoselectivity of these reactions. As regards the first objective, we were curious to see if aminal formation with the carbonyl substrate would be reversible under the reaction conditions, thereby allowing enamine formation and catalyst turnover (Fig. 1).

If turnover was achieved with secondary–secondary diamines, we hoped to address the second objective by modulating the hydrogen-bonding abilities of the amine pendant in the catalyst. In principle, the H-bond donor properties of the pendant can be controlled by altering the acidity of the secondary amine[6] as a function of the *N*-substituent. Such an approach could lead to simple diamine catalysts that are designed to maximize the stereoselectivity of Michael addition for a particular combination of donor and acceptor. It may be noted that hydrogen-bonding interactions between the catalyst and the Michael acceptor have been proposed in several organocatalytic reactions[7] and theoretical studies have also implied a role for hydrogen bonding in deciding stereoselectivity.[8] However, within the context of enamine catalysis, very few studies[9] have established a direct relationship between the H-bond donor ability of the catalyst and the reaction stereoselectivity. Alternatively, a steric model has also been proposed for the enamine-mediated nitro-Michael addition.[10] Clearly, a better understanding of hydrogen bonding and/or steric interactions between the reacting partners would be helpful in the development of improved catalysts.

A series of proline-derived diamines **1**–**5** (Fig. 2) were chosen as catalyst candidates for this study. The approximate pK_a value for the secondary amine pendant in diamines **1**–**4** was calculated.[11] As anticipated, diamine **4** has the most acidic pendant (pK_a=21) and diamine **1**[12] the least acidic (pK_a=34). At the outset, it seemed reasonable that a direct comparison of stereoselectivities obtained

* Corresponding author. Tel.: +1 709 737 8535; fax: +1 709 737 3702.
E-mail address: spansare@mun.ca (S.V. Pansare).

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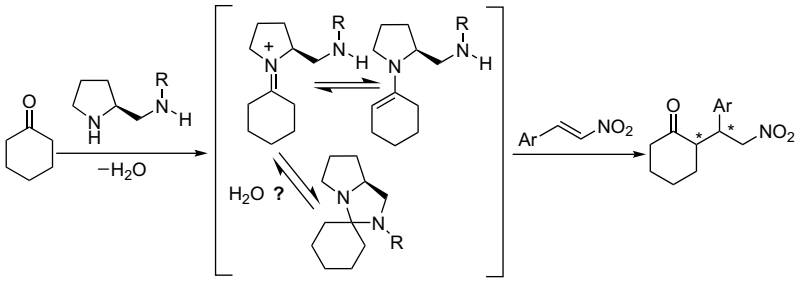


Figure 1. Proposed iminium ion–aminal–enamine equilibration with secondary–secondary diamine catalysts.

with diamines **2**–**4** (*N*-aryl side chain) and diamine **1** (*N*-alkyl side chain) would assist in the identification of a possible role of catalyst–nitroalkene hydrogen bonding and/or steric effects (*N*-aryl vs *N*-alkyl) in the transition state assembly. Also, a comparison of stereoselectivities among the catalysts **2**–**4** (increasing acidity of the secondary amine pendant) as a function of the nitroalkene (electron donating or withdrawing groups on the aryl ring of the nitroalkene) would provide insight into the role of hydrogen bonding in the transition state assembly. Finally, the stereoselectivity for catalyst **5** (secondary–tertiary amine) would either support or negate the necessity of a hydrogen-bond donor group in the pendant.

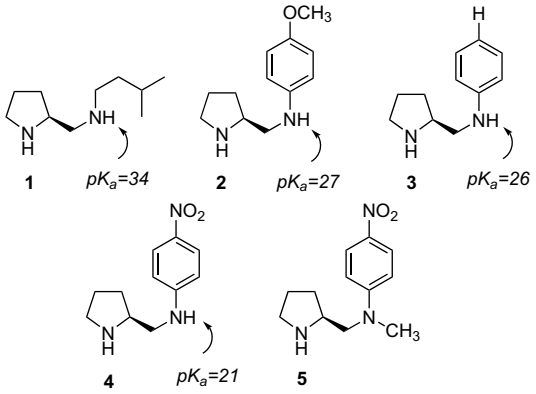
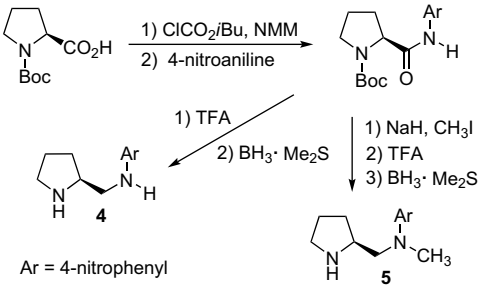


Figure 2. Selected diamine catalysts and their side-chain pK_a values.

2. Results and discussion

Diamines **1**[12] and **2**[13] were prepared according to the literature procedure from *N*-protected '*S*'-proline derivatives by conventional amidation followed by reduction of the amide. Diamine **3** is commercially available. Diamine **4** was readily prepared from *N*-Boc '*S*'-proline as shown in Scheme 1. Diamine **5** was prepared by N-methylation of the amide intermediate in the preparation of **4**, followed by removal of the Boc protection and reduction of the amide (Scheme 1).



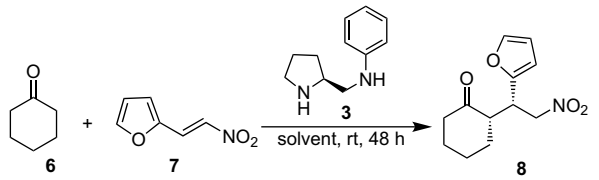
Scheme 1.

Orienting experiments were conducted with diamine **3** for the conjugate addition of cyclohexanone and 2-nitrovinylfuran in dichloromethane as the solvent. Interestingly, catalyst deactivation by aminal formation did not appear to be an issue and the *syn* Michael adduct **6** was obtained in moderate yield (61%) and enantiomeric excess (48%). A brief solvent study identified toluene as the solvent of choice in terms of product yield (89%) and reaction stereoselectivity (10/1 dr, 89% ee). Somewhat surprisingly, practically no product (<1%) was obtained when ethanol was used as the solvent (Table 1).

The results with diamine **3** were encouraging and suggested that the secondary–secondary diamines **1**, **2** and **4** would also function as catalysts. Since the utility of proline-derived secondary–tertiary diamines in enamine catalysis is well known[14] it was anticipated that catalytic turnover with **5** would not be an issue. Based on the solvent screening study with **3**, we proceeded to examine diamines **1**–**5** in conjugate addition reactions employing a variety of cyclic ketones and 2-aryl nitroethylenes. All reactions were conducted in toluene at ambient temperature with 2.5 equiv of the ketone. The results from these studies are summarized in Table 2.

Notably, diamines **1**–**4** provided the Michael adducts **8**–**15** in good to excellent yield and useful enantiomeric excess. For Michael adducts **8**–**10**, catalyst **3** showed the highest enantioselectivity, good diasterioselectivity and high yields, the other catalysts did not show any general trend. Catalyst **1** (*N*-isoamyl) showed the highest stereocontrol for Michael adducts **12** and **13**. Interestingly, a distinct trend in side-chain pK_a versus stereoselectivity was observed within the *N*-aryl catalyst series. Thus, catalyst **4** (lowest side-chain pK_a), provided the highest enantiomeric excess in the series, whereas catalyst **2**, provided the lowest stereoselectivity. Although these results were anticipated for the *N*-aryl catalysts, catalyst **1** (*N*-isoamyl) that has a calculated side-chain pK_a that is higher than catalyst **2**, **3**, or **4** provided the highest stereoselectivity for adducts **12** and **13**. The precise reasons for this are not clear and we hypothesize that steric effects may be responsible.

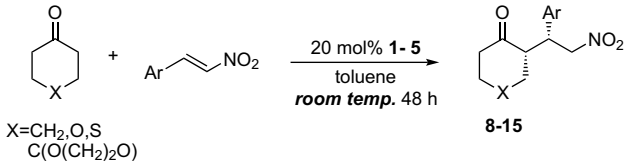
Table 1

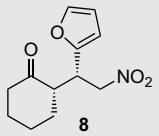
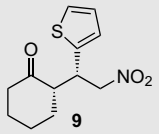
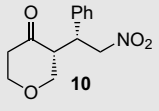
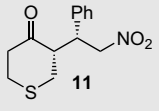
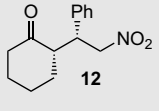
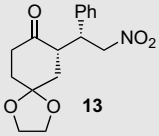
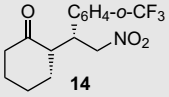
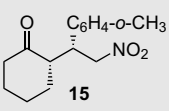


Entry	Solvent	Yield[a] (%)	dr[b] (*syn*/*anti*)	ee[c] (%) (*syn*)
1	CH_2Cl_2	61	6/1	48
2	DMF	53	5/1	68
3	**Toluene**	**89**	**10/1**	**89**
4	Ethanol	<1	—	—

[a] Isolated yields.
[b] Determined by ^{1}H NMR of crude product.
[c] Chiral HPLC analysis.

Table 2



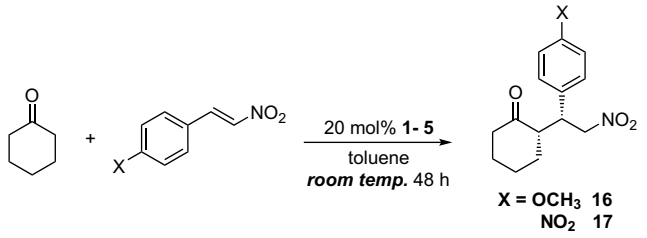
Entry	Product	Cat	Yield[a] (%)	dr[b] (*syn*/*anti*)	ee[c] (%) (*syn*)
1		1	80	11/1	84
2		2	93	11/1	83
3		**3**	**89**	**10/1**	**89**
4		4	81	3/1	82
5	**8**	5	64	3/1	1
6		1	97	6/1	71
7		2	20	16/1	79
8		**3**	**77**	**12/1**	**82**
9		4	89	9/1	77
10	**9**	5	80	7/1	9
11		1	72	10/1	25
12		2	74	15/1	80
13		**3**	**96**	**11/1**	**89**
14		4	81	15/1	68
15	**10**	5	80	15/1	9
16		**1**	**71**	**9/1**	**73**
17		2	90	9/1	71
18		3	86	10/1	59
19		4	74	8/1	72
20	**11**	5	98	10/1	16
21		**1**	**69**	**15/1**	**86**
22		2	99	15/1	65
23		3	80	17/1	**77**
24		4	67	10/1	86
25	**12**	5	77	15/1	3
26		**1**	**79**	**20/1**	**92**
27		2	97	3/1	76
28		3	**77**	3/1	79
29		4	73	5/1	88
30	**13**	5	71	3/1	4
31		1	72	8/1	65
32		2	74	19/1	64
33		3	80	11/1	60
34		**4**	**82**	**20/1**	**76**
35	**14**	5	78	10/1	3
36		1	97	15/1	80
37		**2**	**74**	**>20/1**	**90**
38		3	99	15/1	86
39		4	91	18/1	82
40	**15**	5	75	20/1	14

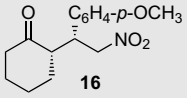
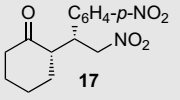
[a] Isolated yields; 2.5 equiv ketone.
[b] Determined by ^{1}H NMR of the crude product.
[c] Chiral HPLC analysis.

Results for Michael adduct **14** show a pK_a dependant trend for catalysts **1**–**4**. For product **15**, catalyst **2** gave the best result (90% ee). It is noteworthy that for all cases examined, the secondary–tertiary diamine **5** showed very low enantioselectivity compared to any of the other catalysts (Table 2). This observation highlights the efficiency of the secondary–secondary diamine motif. At the same time, it contrasts the known efficiency of other, pyrrolidine-based, secondary–tertiary catalysts[14] that provide ketone–nitroalkene Michael adducts in moderate to good enantioselectivity. Clearly, the nature of the *N*-substituents in the tertiary amine pendant has a profound influence on the enantioselectivity.

The nitroalkene substrates that provide adducts **14** and **15** have '*ortho*' substituents in the aromatic ring. Previous studies in our laboratories with triamine/protonic acid catalysts[12] had indicated that stereoselectivities with such nitroalkenes were lower than the sterically less crowded *para* isomers. Hence, in order to minimize steric contributions from the substrate, the 4-methoxynitroalkene isomer was examined as a substrate. At the same time, we wondered if catalyst–substrate interaction could be better established by changing the electronic properties of the nitroalkene in conjunction with electronic changes in the catalyst side chains. Consequently, 4-nitro-nitrostyrene was examined as a direct comparison to 4-methoxynitrostyrene. The results of these studies are summarized in Table 3.

Table 3



Entry	Product	Cat	Yield[a] (%)	dr[b] (*syn*/*anti*)	ee[c] (%) (*syn*)
1		1	97	25/1	50
2		2	78	12/1	55
3		3	99	20/1	68
4		**4**	**87**	**25/1**	**73**
5	**16**	5	80	20/1	3
6		1	73	10/1	74
7		**2**	**76**	**20/1**	**89**
8		3	88	9/1	86
9		4	53	16/1	87
10	**17**	5	30	16/1	−2

[a] Isolated yields.
[b] Determined by ^{1}H NMR of crude product.
[c] Chiral HPLC analysis.

Interestingly, the enantioselectivity for **16** (electron-rich nitroalkene) shows a direct dependence on catalyst side-chain pK_a (lowest ee with **1** (50%), highest ee with **4** (73%)). This observation supports a hydrogen-bonding interaction between the catalyst and the nitroalkene. A similar trend was observed for the adduct **17**. In this case catalyst **1** is again the least selective, but the difference in selectivity between catalysts **2**–**4** is not as pronounced as it is for **16**. Curiously, the highest enantioselectivity for **16** (Table 3, entry 4) is with catalyst **4** (electron deficient side chain) and for **17** (Table 3, entry 7) is with catalyst **2** (electron-rich side chain). These results may be indicative of synergistic interactions between the catalyst side chain and the nitroalkene. Evidently, more than one interaction between the nitroalkene and the catalyst may be responsible for the origin of stereoselectivity with the catalysts examined in this study.

3. Conclusion

In conclusion, the above study highlights the utility of the secondary–secondary diamine motif for stereoselective Michael additions of cyclic ketones to nitroalkenes. A predictable trend in enantioselectivity versus side-chain pK_a was observed within the *N*-aryl catalysts **2**–**4** in a few cases. More importantly, a distinct trend in average enantioselectivity versus catalyst side chain pK_a is identified (average ee for ten reactions: **1**, 72%; **2**, 75%; **3**, 77%; and **4**, 79%). This observation, combined with the low average enantiomeric excess obtained with the secondary–tertiary catalyst **5** (6%), emphasizes the importance of a hydrogen-bond donor functionality in the catalysts examined in this study. This hydrogen-bond donor most likely participates in organizing the enamine and nitroalkene by hydrogen bonding.

4. Experimental

4.1. General

Reactions requiring anhydrous conditions were performed under a positive pressure of nitrogen using oven-dried glassware (100 °C). All organic layers obtained from extractions were dried over anhydrous sodium sulfate. THF was distilled from sodium benzophenone ketyl, and dichloromethane was distilled from calcium hydride prior to use. All melting points are uncorrected. IR spectra were recorded on a Brucker TENSOR 27 spectrometer and are reported in wavenumbers (cm^{-1}). Mass spectra (APCI or ESI) were obtained on an Atmospheric Pressure Ionization-Mass Spectrometer (API-MS, Agilent 1100 series LC/MSD chromatographic system) at an ionization potential of 70 eV. High-resolution mass spectra (HRMS) were obtained on a Waters/Micromass GCT Time of Flight Mass Spectrometer. Optical rotations were measured at the sodium D line on a JASCO DIP-370 polarimeter at ambient temperature. Enantiomeric excess (ee) was determined by high performance liquid chromatography (HPLC) on a Waters instrument.

4.2. Synthesis of the diamine catalysts

Diamines **1**[12] and **2**[13] were prepared according to the literature procedures. Diamine **3** is commercially available.

4.3. 4-Nitro-*N*-(((*S*)-pyrrolidin-2-yl)methyl)benzenamine (4)

A solution of Boc-'*S*'-proline (3.23 g, 15 mmol) in 40 mL dry THF under N_2 was cooled to −15 °C and stirred for 15 min. *N*-Methylmorpholine (1.7 mL, 15 mmol) was added and the mixture was stirred for an additional 15 min after which isobutylchloroformate (2.0 mL, 15 mmol) was added followed by stirring for 15 min. 4-Nitroaniline (2.13 g, 15.5 mmol) was added and the mixture was stirred at room temperature for 24 h. EtOAc (150 mL) was added, and the solution was washed with H_2O (1×50 mL), saturated aqueous $NaHCO_3$ (1×20 mL), 0.5 N HCl (1×20 mL), and brine (1×10 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting solid was triturated with hexanes to provide 4 g (80%) of the *N*-Boc amide (*S*)-*tert-butyl 2-(4-nitrophenylcarbamoyl)pyrrolidine-1-carboxylate* as a pale yellow solid that was pure by ^1H NMR and was directly used further.

^1H NMR (500 MHz, $CDCl_3$): δ 10.22 (br s, 1H, N*H*), 8.17 (d, 2H, *J*=8.73, Ar*H*, *ortho* to NO_2), 7.66 (d, 2H, *J*=8.73, Ar*H*), 4.48 (br m, 1H, C*H*CO), 3.48–3.33 (br m, 2H, CH_2N), 2.57 (br m, 1H, CH_2CH), 1.94 (br m, 3H, CH_2CH, CH_2CH$_2$N), 1.50 (br s, 9H, C(CH_3)$_3$).

To a solution of the above *N*-Boc amide (3.62 g, 10.7 mmol) in dry CH_2Cl_2 (15 mL) at 0 °C under N_2 was added TFA (13.3 mL, 162 mmol). The reaction mixture was stirred at room temperature for 20 h and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (20 mL) and the solution was extracted with H_2O (2×15 mL). The aqueous layer was cooled (<5 °C), basified to pH 12 with NaOH pellets, and extracted with CH_2Cl_2 (2×15 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The resulting solid was recrystallized (EtOAc/hexanes) to provide 1.78 g (69%) of the amide *(S)-N-(4-nitrophenyl)pyrrolidine-2-carboxamide* as a yellow solid.

^1H NMR (500 MHz, $CDCl_3$): δ 10.16 (s, 1H, N*H*CO), 8.19 (d, 2H, *J*=10, Ar*H*, *ortho* to NO_2), 7.76 (d, 2H, *J*=10, Ar*H*), 3.88 (dd, 1H, *J*=5.17, 9.35, C*H*CO), 3.09 (dt, 1H, *J*=6.77, 10.31, CH_2N), 2.98 (dt 1H, *J*=6.30, 10.31, CH_2N), 2.02 (m, 2H, NH, CH_2CH), 2.20 (m, 1H, CH$_2$C*H*), 1.74 (m, 2H, CH_2CH$_2$NH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 174.3 (*C*O), 143.7 (*C*NO$_2$ (*ipso*)), 143.4 (*C*NHCO (*ipso*)), 125.2 (Ar*C* (*ortho* to NO_2)), 118.8 (Ar*C*), 61.2 (*C*HCO), 47.5 (*C*H$_2$NH), 30.8 (*C*H$_2$CH), 26.5 (*C*H$_2$CH$_2$NH). IR (neat): MS (APCI, positive): *m*/*z* 236.1 (M+1, 100). HRMS (EI): *m*/*z* 235.0958 (235.0957 calcd for $C_{11}H_{13}N_3O_3$ (M+)).

The above amide (1.9 g, 8.1 mmol) was dissolved in borane–methyl sulfide complex (2.0 M in THF, 16 mL, 32 mmol) and the solution was stirred at room temperature under N_2 for 48 h. The reaction mixture was cooled to 0 °C, 6 N HCl (30 mL) was added followed by stirring for 3 h. The resulting mixture was then concentrated under reduced pressure. The residue was dissolved in H_2O (20 mL) and the solution was washed with EtOAc (2×10 mL). The aqueous layer was basified with 2 N NaOH and extracted with EtOAc (3×10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The crude product was purified using flash chromatography on silica gel (15/85 to 70/30 EtOAc/hexanes) to provide 644 mg (36%) of diamine **4** as a yellow solid.

^1H NMR (500 MHz, $CDCl_3$): δ 8.03 (d, 2H, *J*=9.16, Ar*H*, *ortho* to NO_2), 6.51 (d, 2H, *J*=9.16, Ar*H*), 5.15 (br s, 1H, N*H*Ar), 3.40 (m, 1H, C*H*CH$_2$NH), 3.19 (dt, 1H, *J*=5.17, 12.22, CH_2NH), 3.00–2.90 (m, 3H, CH_2NH, CH_2NH (ring)), 1.98–1.85 (m, 2H, NH, CH_2CH$_2$NH), 1.85–1.75 (m, 1H, CH$_2$CH$_2$), 1.75–1.67 (m, 1H, CH$_2$CH$_2$), 1.50–1.40 (m, 1H, CH$_2$CH$_2$). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 153.8 (*C*NO$_2$ (*ipso*)), 137.8 (*C*NH (*ipso*)), 126.5 (Ar*C* (*ortho* to NO_2)), 111.3 (Ar*C*), 57.2 (*C*HNH (ring)), 47.4 (*C*H$_2$NH), 46.6 (*C*H$_2$NH), 29.6 (*C*H$_2$CH), 25.9 (*C*H$_2$CH$_2$). IR (neat): 1600, 1474, 1304, 1111, 827 cm^{-1}. HRMS (EI): *m*/*z* 221.1163 (221.1164 calcd for $C_{11}H_{15}N_3O_2$ (M+)).

4.4. (*S*)-*N*-Methyl-4-nitro-*N*-(pyrrolidin-2-ylmethyl)-benzenamine (5)

A solution of *(S)-tert-butyl 2-(4-nitrophenylcarbamoyl)-pyrrolidine-1-carboxylate* (1.44 g, 4.3 mmol, prepared as described above) in THF (15 mL) was cooled (5 °C) under N_2 and NaH (170 mg, 1.5 mmol) was added cautiously. After 10 min, CH_3I (2 mL, 32.5 mmol) was added and the reaction mixture was stirred at room temperature for 24 h. The mixture was concentrated and then diluted with EtOAc (40 mL). The resulting solution was washed with H_2O (1×10 mL) and brine (1×10 mL). The organic layer was then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue obtained was purified using flash chromatography on silica gel (50/50 EtOAc/hexanes) to provide 1 g (70%) of the amide *(S)-tert-butyl-2-(methyl-(4-nitrophenyl)carbamoyl)pyrrolidine-1-carboxylate* as a pale yellow gum.

^1H NMR (500 MHz, $CDCl_3$): Major rotamer: δ 8.28 (d, 2H, *J*=8.48, Ar*H*, *ortho* to NO_2), 7.58 (d, 2H, *J*=8.48, Ar*H*), 4.32 (br, 1H, C*H*CO), 3.56–3.51 (br m, 2H, CH_2*N*-Boc), 3.45–3.32 (br s, 3H, NCH_3), 2.04–1.74 (m, 4H, CH_2CH_2), 1.45 (br s, 9H, C(CH_3)$_3$).Visible signals for the minor rotamer: 8.28 (d, 2H, *J*=8.68, Ar*H*, *ortho* to NO_2), 7.41 (d, 1H, *J*=8.68, ArH), 4.24 (br, 1H, C*H*CO). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 173, 154.8, 153.9, 149.6, 146.9, 128.7, 125.4, 80.3, 79.9. 57.5, 57.3, 47.5, 47.4, 38.1, 38, 30.6, 29, 28.9, 24.7, 23.8, 14.6. IR (neat): 3279, 1703, 1509, 1407, 1338, 1159, 1111, 853 cm^{-1}. HRMS (EI): *m*/*z* 350.1723 (350.1716 calcd for $C_{17}H_{23}N_3O_5$ (M+H)).

To a solution of the above *N*-methyl amide (1 g, 2.86 mmol) in dry CH_2Cl_2 (5 mL) at 0 °C under N_2 was added TFA (2.4 mL, 28.6 mmol). The reaction mixture was stirred at room temperature for 3 h and concentrated under reduced pressure to remove CH_2Cl_2 and TFA. The resulting residue was dissolved in EtOAc (30 mL) and the solution was extracted with H_2O (2×15 mL). The aqueous layer was cooled (<5 °C), basified to pH 12 with NaOH pellets, and extracted with CH_2Cl_2 (2×15 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated to provide 571 mg (80%) of *(S)-N-methyl-N-(4-nitrophenyl)pyrrolidine-2-carboxamide* as a yellow solid that was pure by ^1H NMR and was directly used further.

^1H NMR (500 MHz, $CDCl_3$): δ 8.14 (d, 2H, *J*=9.25, Ar*H*, *ortho* to NO_2), 6.56 (d, 2H, *J*=9.25, ArH), 4.19–4.17 (m, 1H, C*H*CO), 3.69 (m, 1H, CH_2N), 3.40–3.35 (dd, 1H, *J*=2.94, 8.23, CH_2NH), 2.80 (br s, 3H, NCH_3), 2.31 (m, 2H, CH_2CH$_2$), 2.12 (m, 1H, CH_2CH$_2$), 2.02 (m, 1H, CH$_2$CH_2). The above amino amide (160 mg, 0.10 mmol) was dissolved in borane–methyl sulfide complex (2.0 M in THF, 1.9 mL,

3.80 mmol) and the solution was stirred at room temperature under N_2 for 48 h. The reaction mixture was cooled to 0 °C, treated with 6 N HCl (2 mL), and stirred for 3 h after which time the resulting mixture was concentrated under reduced pressure. The residue obtained was dissolved in H_2O (5 mL) and the solution was washed with EtOAc (2×5 mL). The aqueous layer was basified with 6 N NaOH and extracted with EtOAc (3×10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The crude product was purified using flash chromatography on silica gel (95/5 CH_2Cl_2/CH_3OH to 90/10 CH_2Cl_2/CH_3OH) to provide 95 mg (63%) of diamine **5** as a yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.11 (d, 2H, J=9.35, ArH, *ortho* to NO_2), 6.57 (d, 2H, J=9.35, ArH), 3.96 (m, 1H, C*H*CH_2), 3.47 (m, 1H, CH_2N), 3.27 (m, 1H, CH_2N), 2.75 (dd, 1H, J=3.58, 12.06, CH_2NCH$_3$), 2.55 (dd, 1H, J=8.65, 12.06, CH_2NCH$_3$), 2.48 (s, 3H, NCH_3), 2.12–2.01 (m, 4H, CH_2CH_2). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 152 (ArCNO$_2$), 137.4 (Ar*C*N), 126.7 (Ar*C*, *ortho* to NO_2), 111.3 (Ar*C*), 59.1 (*C*HN), 53.5 (*C*H$_2$N), 49 (*C*H$_2$N), 37.1 (NCH$_3$), 29.8 (*C*H$_2$), 23.5 (*C*H$_2$). IR (neat): 1594, 1478, 1288, 1195, 1108, 822 cm^{-1}. MS: m/z 236.1 (M+1, 100). HRMS: m/z 235.1324 (235.1321 calcd for $C_{12}H_{17}N_3O_2$ (M+)).

4.5. General experimental procedure for the Michael addition of ketones to nitroalkenes

To a solution of the amine catalyst (0.1 mmol) and the nitroalkene (0.5 mmol) in toluene (1 mL) was added the ketone (2.5 mmol), and the solution was stirred at ambient temperature for 48–72 h except when noted otherwise. Ethyl acetate (10 vol) was added and the solution was washed with water, aqueous 0.5 N HCl, dried (Na_2SO_4), filtered, and concentrated to give the crude product, which was purified by flash chromatography on silica gel.

The relative configurations of the products (*syn* or *anti*) were determined by comparison of ^{1}H NMR spectral data with those reported in the literature. The absolute configurations of each product were determined either by comparison of optical rotation values with those reported in the literature or by comparison of HPLC retention times. Spectral data for compounds **8**–**17** are in agreement with literature reports.

*4.5.1. (S)-2-[(R)-2-Nitro-1-phenylethyl]-4-[1,3-dioxolanyl]-cyclohexanone (**13**)*[8b,14a]

Reaction of 4-(1,3-dioxolanyl)-cyclohexanone (395 mg, 2.5 mmol) and 1-((*E*)-2-nitrovinyl)benzene (74.5 mg, 0.5 mmol) in the presence of catalyst **1** (16.7 mg, 0.1 mmol) according to the general procedure gave, after purification by flash chromatography on silica gel (ethyl acetate/hexane: 40/60), 121 mg (79%) of **13** as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35–7.28 (m, 3H, Ar*H*), 7.21 (d, 2H, J=7.50, *ortho* Ar*H*), 4.95 (dd, 1H, J=12.50, 4.71, CH_2NO$_2$), 4.63 (dd, 1H, J=12.50, 9.82, CH_2NO$_2$), 4.04–3.81 (m, 5H, PhC*H*, OCH_2CH_2O), 3.10–3.05 (m, 1H, C*H*C(O)), 2.71 (dt, 1H, J=6.41, 13.43, CH_2CH$_2$), 2.42 (ddd, 1H, J=13.81, 3.59, 1.52, CH_2CH$_2$), 2.04–2.01 (m, 1H, CH_2CH$_2$), 2.00–1.91 (m, 1H, CH_2CH$_2$), 1.72–1.66 (ddd, 1H, J=13.37, 3.52, 1.87, CH_2CH), 1.60–1.52 (m, 1H, CH_2CH).

HPLC (Chiralpak AS-H): (hexane/*i*-PrOH, 90/10, flow rate 0.5 mL min^{-1}, λ=254 nm): t_{major}=59.6 min, t_{minor}=47.5 min, ee: 92%

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Supplementary data

Experimental details and data for compounds **8**–**17**.

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.03.093.

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