A bifunctional B,N-based asymmetric catalytic nitrostyrene-Michael addition acting through a 10-membered ring cyclic transition state.

Yihao Du,[a] Ozlem Sari,[b] Safiye S. Erdem*[c] and Andrew Whiting[a]*

[a] Department of Chemistry, Durham University, Science Laboratories, South Road, Durham, DH1 3QZ, UK, email andy.whiting@durham.ac.uk

[b] Network Technologies Department, TUBITAK ULAKBIM, 06800, Ankara, Turkey.

[c] Chemistry Department, Faculty of Arts & Sciences, Marmara University, 34722, Goztepe, Istanbul, Turkey, email erdem@marmara.edu.tr

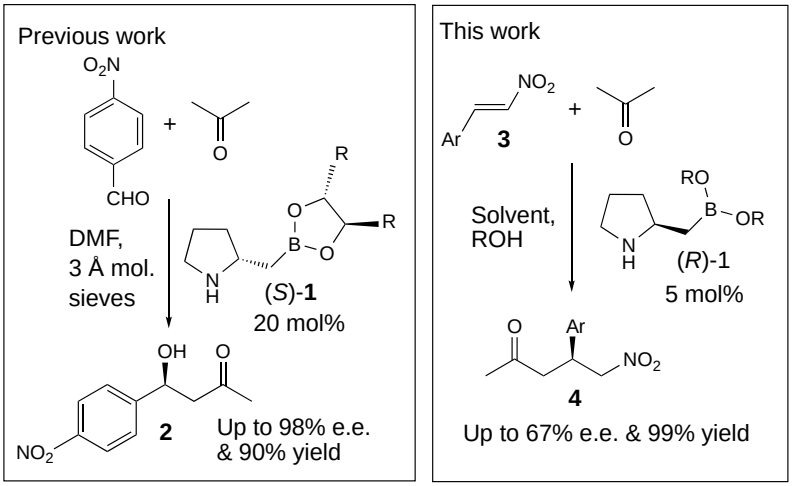
Dedicated to Peter Kündig on the occasion of his 75th birthday

The B,N-bifunctional catalyst homoboroproline has been applied to a catalytic asymmetric nitroalkene-Michael addition to β-nitrostyrene analogues, showing broad substrate tolerance, high conversions and moderate to good asymmetric induction. The ability of homoboroproline to act as an efficient catalyst based on enamine-formation of the secondary amine, coupled with intramolecular Lewis-acid chelation of the nitro function, in a non-FLP manner, to effect efficient and enantioselective catalysis *via* a proposed large 10-membered ring transition state is remarkable and reinforced by theoretical calculations.

Keywords: amino-boronic acid • B,N-bifunctional catalysis • homoboroproline • asymmetric Michael addition • nitroalkene

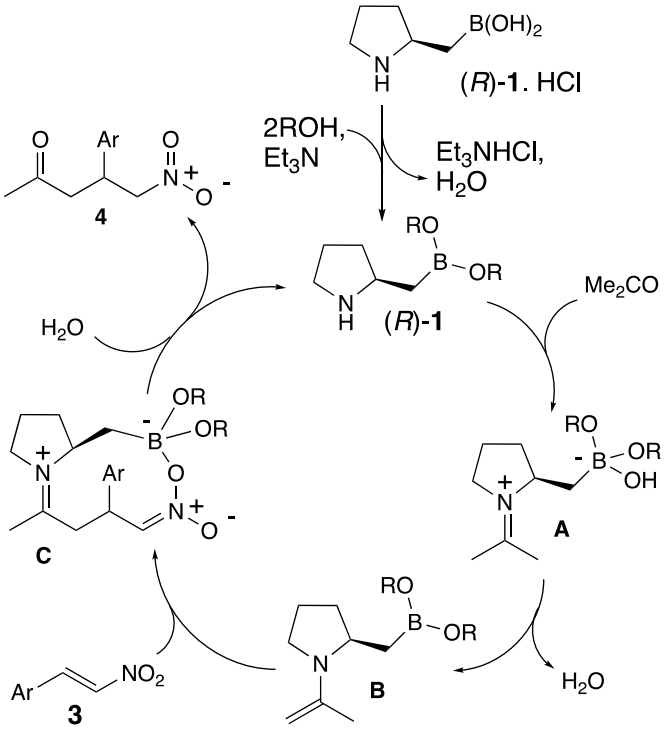
Introduction

Aminoboronate-based bifunctional catalysts are finding increasing utility for a number of transformations since their discovery,[1]-[7] including asymmetric variants for the construction of new C-C bonds in order to access enantiomerically enriched compounds.[8],[9] Aminoboronate bifunctional catalysts of this type work cooperatively through both Lewis acid complexation of the boronate function and Lewis base interaction via the amino function, which represents a fine balance in minimising intramolecular B,N-deactivation *versus* intermolecular effects, through substrate activation. Hence, the design of the catalyst, including the relative Lewis acidity and basicity of the boronate amino functions respectively, and their relative arrangements are crucial to efficient catalytic processes.[9]-[11] Hence, by avoiding the extreme levels of activation represented by frustrated Lewis pair systems,[12] less reactive aminoboronate-derived bifunctional catalysts provide the potential for more subtle and tunable catalysts to be designed, which in turn, may be applicable to different reactions.[7] Exemplifying this idea in previous work (Scheme 1), we reported the proline-related boronate ester **1** as a proof-of-concept that a B,N-bifunctional asymmetric catalyst system could be developed that employed an enamine-mediated asymmetric aldol reactions, together boronate-mediated Lewis acid activation of a substrate aldehyde. The important finding was that Lewis-acid tuning of the boronate function was readily affected to optimise asymmetric induction through *in situ* esterification (see Scheme 1); a process and mechanism which was reiforced by subsequent theoretical calculations.[13] However, there were major limitations to the application of this efficient asymmetric reaction to *para*-nitrobenzaldehyde, because less electrophilic aldehydes were either not sufficiently reactive or the product of addition reacted with the catalyst intermmediate through transesterification, deactivating the catalyst and preventing further reaction.[10] As a result, we theorised that the catalyst might be better suited to substrates where the addition product does not contain a nucleophilic function that is able to react with catalyst causing deactivation, i.e. avoiding the formation hydroxylic products such as that formed in an aldol reaction. We surmised, therefore, that a particularly attractive proposition would be the application of B,N-bifunctional catalyst homoboroproline to the asymmetric nitroalkene-Michael addition reaction.[14]-[37] In this work (see Scheme 1), we report our endeavours in this area and demonstrate a wide substrate scope to matching the reactivity of the catalyst to that of the substrates, while avoiding products that could react with the catalyst and trigger deactivation.



Scheme 1. In previous work, catalysts of type (*S*)-**1** required 20 mol% loading and achieved high e.e. for the aldol reaction but was limited *para*-nitrobenzaldehyde, whereas, in this work, a number of nitroalkenes could be converted with catalysts of type (*R*)-**1** (only 5 mol% loading) providing nitro-Michael adducts **4** in up to 67% e.e. and with complete conversion.

Recognising the limitations of the B,N-bifunctional catalyst homoboroproline catalyst **1** in asymmetric aldol reactions and that such a system would likely be better matched to reactions that do not produce nucleophilic, *i.e.* hydroxyl, functions that could react at the boronate ester, causing catalyst deactivation, led us to examine the potential mechanism that might be involved in a nitro-alkene Michael addition (see Scheme 2). We envisaged that an enamine system of type **B** derived from *in situ* reaction of homoboroproline **1** and acetone would be reactive towards nitroalkenes **3** to give Michael adduct, iminium intermediate **C** (Scheme 2), hydrolysis of which would provide a keto-nitroalkyl product **4** which we predicted would not interfere with the catalytic process through catalyst deactivation due to the lack of any function which could react back at the boron centre. Assuming that the boronate Lewis-acid function of the enamine **B** could achieve sufficiently strong nitro-coordination to the nitroalkene, then potentially a facially-selective addition might take place according to Fig. 1. However, such a process would rely upon a complex involving a 10-membered ring transition state, which might not be suitablet for an enantioselectively controlled reaction due too much conformational freedom in the transition state. However, in order to try and tighten the transition state as much as possible to optimise boronate-nitro Lewis-acid coordination, inherent in Scheme 2 is the option to tune boronate Lewis acidity *via* different alcohols ROH. In this paper, we report the realisation of this approach and show that tuning boronate Lewis acidity does play a role in being able to improve catalytic efficiency, and that theoretical calculations broadly support not only the catalytic cycle, but also the proposed transition state implied in Fig. 1, which results in perhaps surprisingly good asymmetric induction.



Scheme 2. Proposed catalytic cycle for the action of homoboroproline (*R*)-**1** *via* enamine formation acting as a reactive nitroalkene Michael nucleophile.

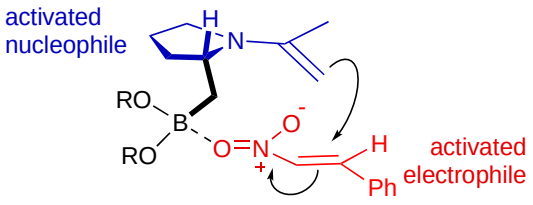
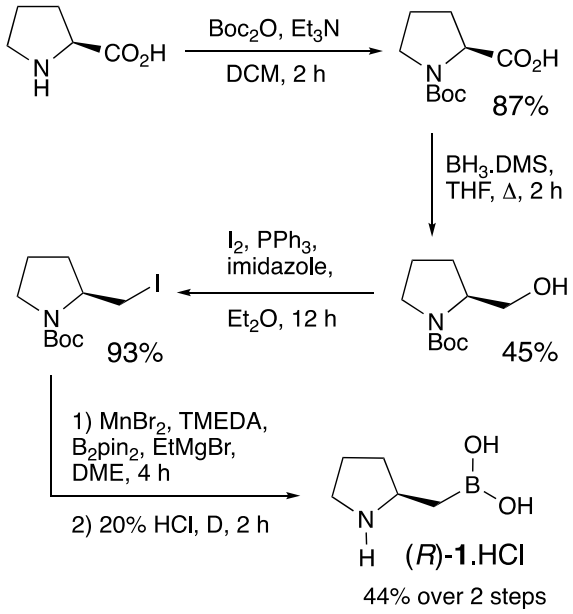


Figure 1. Proposed 10-membered ring transition-state of the nitro-Michael addition catalysed by homoboroproline (*R*)-**1**.

Results and Discussion

Homoboroproline catalyst synthesis

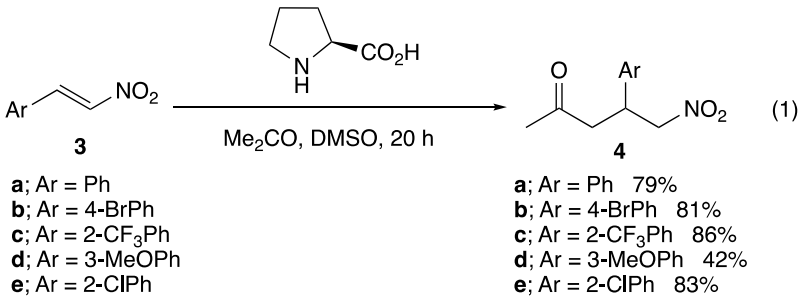
Homoboroproline analogues (*S*)-**1**, particularly esterified as either the tartrate and hydrobenzoin esters and applied as B,N-bifunctional enamine-boronate Lewis acid catalysts for application in asymmetric aldol reaction,[8] were prepared using an asymmetric sparteine-directed deprotonation strategy.[38] However, the challenge of obtaining sparteine and the development of alkyl halide catalytic borylation reactions,[39],[40] paved the way for a direct synthesis of the enantiomeric analogues, i.e. (*R*)-**1**.[41] Our preliminary synthesis involved an (*S*)-proline protection, reduction, iodination, borylation and deprotection sequence, followed by a lithium tert-butoxide copper-based borylation step which was found to be highly capricious and unsuitable for scale up. Hence, this borylation step needed to be replaced with a reproducible and scalable method, and after experimentation, a manganese(II)-catalysed borylation[42] (Scheme 3) was utilised which required both lower catalyst loading (5 mol%), shorter reaction time (4 h) and reproducibly produced cleaner reaction product (*R*)-**1** as the hydrochloride salt (Scheme 3).



Scheme 3. Synthetic strategy towards the homoboroproline (*R*)-**1**.HCl.

Racemic nitrostyrene-acetone adducts

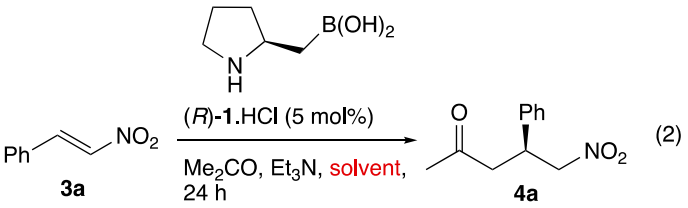
The racemic β-nitrostyrene-acetone adducts were accessed using the procedure reported by Barbas *et al.*[34] to provide the racemic (as determined by chiral HPLC analysis in all cases) products **4** (Eqn. 1). Interestingly, catalytic L-proline failed to provide any asymmetric induction but was an efficient catalytic approach to racemic Michael adducts.



*Screening and optimisation of homoboroproline (R)-**1** catalysed asymmetric synthesis of nitrostyrene-acetone adduct **4a***

For initial screening of reaction conditions for the catalytic use of homoboroproline catalyst (*R*)-**1** for the nitroalkene Michael addition, β-nitrostyrene was reacted at 5 mol% of catalyst (*R*)-**1**.HCl (neutralised with triethylamine in situ) loading in acetone, as both solvent and ketone for enamine formation (Eqn. 2) at room temperature for 24 hours. Gratifyingly, the nitroketone adduct **4a** was isolated in 63% yield and 36% e.e., immediately demonstrating the utility of the homoboroproline system for this type of Michael reaction. We therefore turned to optimise and examine the reaction further, starting by examining solvent effects, the addition of molecular sieves and the use of *in situ* boronate esterification using hydrobenzoin, since this had been a useful strategy for optimising catalyst reactivity in the corresponding aldol reactions.[4] The results of all these screening reactions are reported in Table 1.

Table 1. Solvent test of catalytic nitroalkene-Michael addition.



Entry	Solvent	Yield (%)	E.e. (%)
1	Acetone	63, 33,[a] 99[b]	15, 30,[a] 44[b]
2	DMF	18, 20,[a] 50[b]	8, 16,[a] 20[b]
3	DMSO	14, 20[a]	0, 0[a]
4	2-Me-THF	12, 35,[a] 99[b]	37, 40,[a] 54[b]
5	Toluene	0, 5,[a] 99[b]	-, 5,[a] 49[b]
5	THF	48	14
6	MTBE	0	-
7	Acetonitrile	44	5
8	^{i}Pr-CN	15	10
9	MeOH	39, 15[a]	33, 36[a]
10	EtOH	95, 95[a]	35, 35[a]
11	^{i}Pr-OH	34	33
12	1,4-Dioxane	41	20
13	DME	41	24
14	DCM	0, 29,[a] 99[b]	-, 5,[a] 36[b]

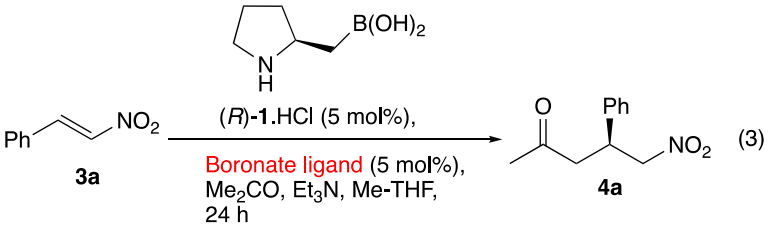
[a]Reaction carried out in the presence of activated 3 Å molecular sieves (General Procedure D). [b](*S,S*)-(-)-Hydrobenzoin (5 mol%) added as boronate esterification diol (General procedure E).[9]-[11]

As can be seen from the results in Table 1, the initial screening reactions carried out in different solvents without any purification, showed wide variation in terms of yields, from no or low conversion (e.g. for MTBE, DCM, $CHCl_3$, DMF and DMSO, Entries 6, 14, 15, 2 and 3 respectively, Table 1) through to high conversion, such as in ethanol (Entry 10, Table 1). In addition, in all cases the acetone-nitroalkene Michael adduct was produced exceptionally cleanly with no signs of any by-products; however, the enantiomeric excesses were also generally low, and all less than 37% (Entry 10, Table 1). At this stage of the reaction screening we had not taken any precautions to control solvent hydration levels in any of these solvents, and because we were aware the importance of water levels in such amine-ketone dependent condensation reactions deriving enamines both from the literature[43],[44] and from our own studies on the homoboroproline-catalysed aldol reaction,[9]-[11] we then examined the impact of drying the solvent *in situ* by the addition of activated 3 Å molecular sieves. Interestingly, there was quite wide variation on the impact of adding a drying agent, with some conversions improving and others reducing over the standard 24 h reaction timescale, however, generally there was improvement. For example, in the case of acetone (Entry 1, Table 1), reducing the water content reduced the conversion by half (63 to 33%), while doubling the e.e. (15 to 30%), showing that a water content aids conversion, but reduces e.e., at least in acetone (though DMF was similar as shown by Entry 2, Table 1). However, generally the e.e.s only improved marginally upon adding a drying agent with the exception of ethanol (Entry 10, Table 1) which showed almost no effect, which could be understood from its low water content commercially. Of all these different solvents examined, the highest e.e. observed was with 2-Me-THF (40% e.e., Entry 4, Table 1) and this result was sufficiently encouraging to see if we could improve upon both conversion and e.e. using the Lewis-acidity tuning protocol through *in situ* esterification of the boronic acid function used for the application of homoboroproline **1** for aldol reactions, i.e. through *in situ* esterification with hydrobenzoin.[9]-[11] This subtle electronic tuning was effective for application on asymmetric aldol reactions, and therefore, we also examined whether the addition of (*S,S*)-(-)-hydrobenzoin as an exemplar 1,2-diol used effectively previously,[9]-[11] would be effective here. Hence, the reaction outlined in Eqn. 1 was exposed

to diol addition, and Entries 1, 2, 4, 5, and 9 (Table 1) all showed an improved yield and e.e. as a result, with the 2-Me-THF system still showing the highest e.e. (54%), as well as essentially quantitative conversion to the Michael adduct **4a** (Entry 4, Table 1), though the results in toluene and acetone (Entries 5 and 1, Table 1, respectively) were also encouraging.

In order to be sure that the use of hydrobenzoin represented the optimal diol for this application, we examined one entry, i.e. Entry 4 (Table 1) with other potentially better diol systems, including systems that should be more activating towards increasing the Lewis acidity at boron, as listed in Table 2.

Table 2. Ligand screening of bifunctional catalytic nitro-Michael addition.



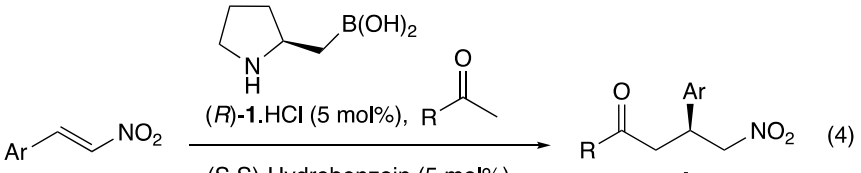
Entry	Ligand[a]	Yield (%)	E.e. (%)
1	(*S,S*)-(-)-Hydrobenzoin	99	54
2	(*R,R*)-(+)-Hydrobenzoin	71	57
3	2,2-Dihydroxybiphenyl	14	56
4	1,2-Dihydroxylbenzene	11	48
5	Tetrabromocatechol	32	6
6	Benzilic acid	43	42

[a] Carried out according to General Procedure E, using the stipulated diol in place of hydrobenzoin.

According to the data shown in Table 2, it is clear that different diol (and one hydroxy acid system, Entry 6, Table 2) have variable effects upon the catalytic process, with none of the systems showing improvements over hydrobenzoin. Part of the explanation for this may be a play-off between ester stability and catalytic reactivity of the different boronate species resulting; however, the net result is that hydrobenzoin remains the diol of choice compared to cyclic phenol analogues (Entries 3-4, Table 2) and a system that might form an acyloxy cyclic ester system, i.e. benzilic acid. These reactions were all both slower and providing lower e.e. than hydrobenzoin. It is also noteworthy that the stereocentres on the hydrobenzoin have essentially no, or very little, impacted through double diastereoselectivity effects from the diol ligand chirality, acting predominantly through sigma-bond electronic tuning effects.[9]-[11] Hence, use of the (*S,S*)- *versus* (*R,R*)-hydrobenzoin enantiomers results in 99 and 71% isolated yields, and 54 and 57% e.e.s, respectively (Entries 1 and 2, Table 2).

With the optimised conditions for using homoboroproline **1** as an enamine catalyst for the nitroalkene Michael-addition identified as requiring Me-THF as solvent with hydrobenzoin as *in situ* esterification diol ligand for the boronic acid, we proceeded to apply this system for examination of substrate scope and application upon different arylnitroalkenes and using two additional methyl ketone nucleophiles. The results are summarised by Table 3 and Eqn. 4.

Table 3. Substrate scope of bifunctional catalytic nitroalkene-Michael addition.



a; Ar = Ph
b; Ar = 4-BrPh
c; Ar = 2-CF_3Ph
d; Ar = 3-MeOPh
e; Ar = 2-ClPh

a; R = Me, Ar = Ph
b; R = Me, Ar = 4-BrPh
c; R = Me, Ar = 2-CF_3Ph
d; R = Me, Ar = 3-MeOPh
e; R = Me, Ar = 2-ClPh
f; R = Ph, Ar = Ph
g; R = iPr, Ar = Ph

Entry	Nitro alkene 3	Ketone	Yield 4 (%)	E.e. 4 (%)
1	a	Me_2CO	**a**, 99	54
2	b	Me_2CO	**b**, 99	41
3	c	Me_2CO	**c**, 99, 99[b]	67, 65[b]
4	d	Me_2CO	**d**, 38	43
5	e	Me_2CO	**e**, 99	55
6	a	PhCOMe[a]	**f**, -	-
7	a	^{i}PrCOMe[a]	**g**, 10	-

[a] Carried out according to General Procedure E, using the stipulated diol in place of hydrobenzoin.

Table 3, Entries 1-5 show that the arylnitroalkene substrate has varying effects upon the reaction conversion and only a marginal effect upon the e.e. The *ortho*-trifluoromethyl nitroalkene **3c** stood out in terms of a 13% increase in e.e. compared with the phenyl system **3a** suggesting that both steric and electronic effects may be beneficial to enantiocontrol in these reactions (Entry 3, Table 3). Interestingly, there was no improvement in conversion when this reaction was carried out at 55 °C *versus* RT, with only a marginal drop in e.e. being observed (67 to 65%). Considering the proposed **TS** shown in Figure 1, it would be expected that a strong *ortho*-electron withdrawing group, such as CF_3 (*i.e.* **3c**) should enhance nucleophilic attack at the α-aryl alkene carbon to improve the enantiocontrol due to the CF_3's strong sigma-electron withdrawing effect. Certainly, the proposed transition state **TS**, involving a 10-membered Lewis-acid-nitro alkene complex as drawn can explain the observed absolute stereocontrol, i.e. through attack of the enamine on the *Si*-face of the nitroalkene.

In terms of ketone reactivity, other methylketone systems did not show the high levels of reactivity observed with acetone, as evidenced by Entries 6 and 7, Table 3. Hence acetophenone showed zero reactivity, providing no adduct **4f** (Entry 6, Table 3). Use of *iso*propylmethylketone (Entry 7, Table 3) did show low reactivity, together with no enantiocontrol.

Theoretical studies

In order to provide insight into the enantioselectivity in homoboroproline catalyzed asymmetric nitro alkene reactions, we employed density functional theory calculations with M06-2X/6-31G(d,p) method. Since enantioselective reactions are assumed to be kinetically-controlled, the selectivity is governed by the relative stabilities of the transition state (TS) structures ($\Delta\Delta G^*$ values) for the selectivity-determining steps of the alternative mechanisms having different stereochemistry.[45] Therefore, in this study, TS structures corresponding to four stereochemical aspects of the reaction between homoboroproline catalyst (*R*)-**1** and nitroalkene **3a** are considered (Fig. 2): The first aspect is the relative orientation of the double bond of the proposed enamine intermediate. As it is known in previous computational studies of similar proline-based asymmetric reactions it can adopt either *syn*- or *anti*-orientation with respect to the group substituted at the chiral carbon of the proline ring. The second aspect is the two alternative enantio-faces of the nitroalkene "b" carbon center where the enamine can attack either at the *Re*-face or *Si*-face (Fig. 2). These considerations give rise to four different transition state alternatives, *Si-anti, Si-syn, Re-anti* and *Re-syn*.

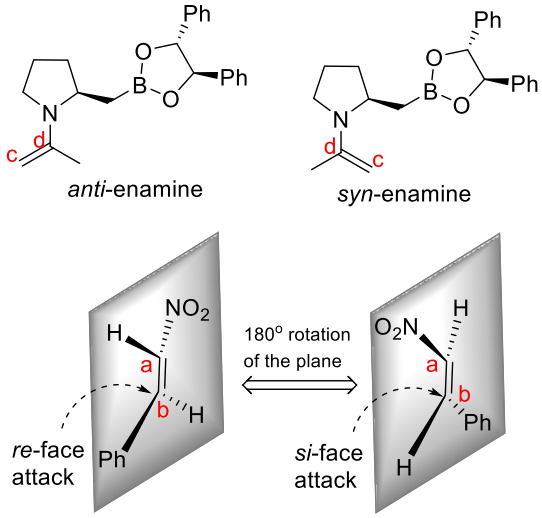


Figure 2. Main stereochemical considerations: *anti/syn* conformations of the enamine and *Re/Si*-faces of the nitroalkene. Note: *Re*-face/*Si*-face notations represent the case where enamine attacks through the backside of the plane forming a new bond between C_b and C_c.

Moreover, for each of these four TS structures, different conformational possibilities with respect to the rotation around the newly forming C_b-C_c bond represented by C_a-C_b-C_c-C_d dihedral angle are available. We have taken into account all reasonable staggered (60° and -60°) and slightly eclipsed conformations that maintain interactions between the boronate moiety of the catalyst and the nitro group of the nitroalkene. Overall, eight different TS structures are analysed to explain the enantioselectivity.

The reaction of **3a** with *(R)*-homoboroproline **1** involving (*R,R*)-(+)-hydrobenzoin, resulting in 57% e.e. (entry 2 in Table 2) was selected for computational modeling. For this reaction, Newman projections of all the optimized TS structures with respect to partially formed C_b-C_c bond are given in Fig. 3. For *Si-anti,* we have characterised three conformational TSs corresponding to slightly staggered and eclipsed orientations; *Si-anti*(52), *Si-anti*(-75), and *Si-anti*(19) bearing dihedral angles 52°, -75°, and 19° respectively in the fully optimised structures. Please note that the other staggered alternative, 180° dihedral angle, is not a reasonable TS since it puts the nitro group away from the catalyst. For *Si-syn*, both 180° and 60° dihedral angles are not reasonable candidates and only *Si-syn*(-62) was obtained. Among TS structures involving an attack from *Re*-face of nitroalkene, *Re-anti* gives rise to stagger *Re-anti*(50) and slightly eclipsed/staggered *Re-anti*(34) TSs while *Re-syn* results *in Re-syn*(-64), and *Re-syn*(-7) conformations. Remaining conformations are not relevant.

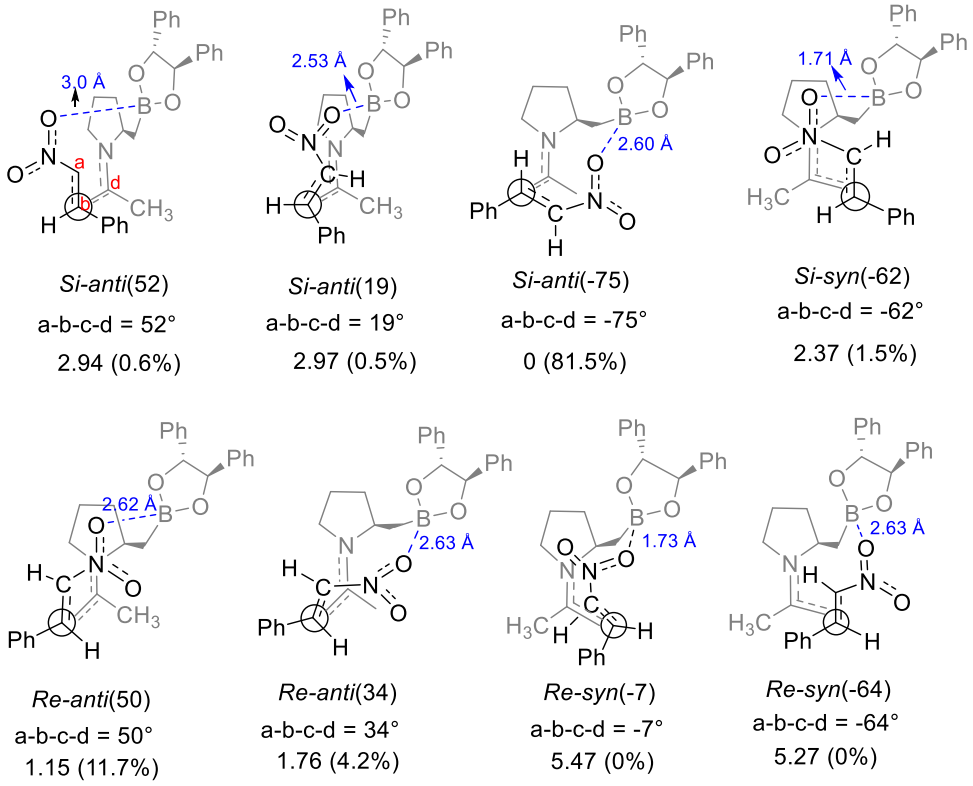


Figure 3. Newman projections of all reasonable TS structures optimized with M06-2X/6-31G(d,p) method, relative Gibbs free energies (ΔΔG*) in kcal/mol with respect to *Si-anti*(-75), and Boltzman percentages. Please note that the numbers in the designation of TSs are the optimised values of C_a-C_b-C_c-C_d dihedral angles.

In order to provide insight into the enantioselectivity, we have examined the 3-D structure of each TS in detail. As displayed in Fig.4, several C-H---O nonbonded interactions and boron-oxygen interaction are observed in these TSs. There are several factors influencing the enantioselectivity of homoproline catalyzed nitro-Michael addition. Based on our previous computational study[13] on aldol reaction with the same catalyst, the main factor is expected to be the favorable Lewis-acid/base type interaction between boron and the oxygen of the nitro group. Almost all TS structures involve boron-oxygen interactions where interatomic distances vary from 1.71 Å to 2.64 Å. On the other hand, the interaction distance *in Si-anti*(52) is relatively longer (3.0 Å) revealing that the interaction is negligible for this conformation. Surprisingly, *Si-syn*(-62) and *Re-syn*(-7) which exhibit quite strong B-O interactions with noticeably shorter distances (1.71 and 1.73 Å, respectively), are not the most stable structures. Thus, we further explored all the TS structures and compared them to the ones obtained from the aldol reaction in the previous work.[13] The nitro-Michael addition reaction differs from the aldol reaction since there are two oxygen atoms from the nitro group that may interact with boron. Also, there are two additional atoms (C_a and N) between C_b and the O-atom interacting with boron. This gives rise to several rotamer possibilities around newly forming C_b-C_c bond as shown in Fig. 3. It also leads to larger ring (ten-membered) structures in the TSs relative to the eight-membered rings in the TSs of the aldol reaction.

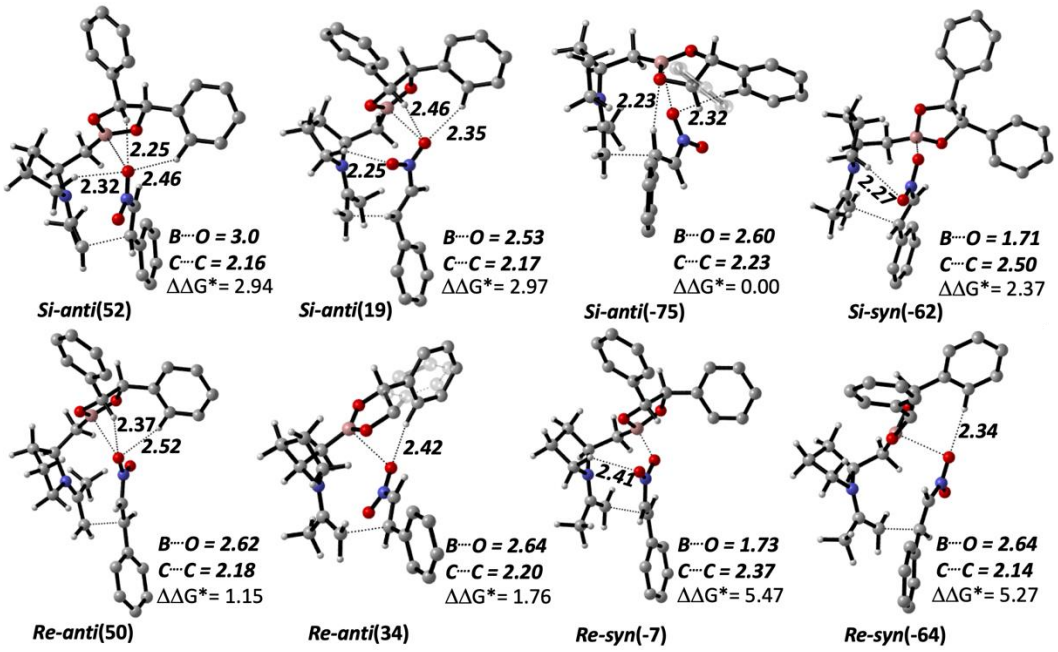


Figure 4. 3-D views of the optimized TSs generated from *Si*-face attack and *Re*-face attack, their ΔΔG* values in kcal/mol and important interaction distances. Hydrogens of the phenyl rings are not shown for clarity. C-H···O interaction distances are shown on dotted lines. Atom colors: B: light pink, O: red, N: blue, C: gray

Since C_a–N bond of nitroalkene exhibits partial double bond character at the TSs, the relative positions of oxygen atoms interacting with boron can be distinguished as *cis* or *trans* with respect to C_b of the nitroalkene. As can be seen from Fig. 3 and 4, in majority of the TS structures, oxygen atom interacting with boron adopts *trans*-orientation. On the contrary, in the most stable TS *Si-anti*(-75), its *cis*-oxygen is properly oriented to interact with boron. Presumably, this may be associated with the greater stability of *Si-anti*(-75) since it may be a significant factor influencing the relative stabilities of the ten-membered rings establishing at the TSs. Please note that *Re-syn*(-7) also exhibits a *cis*-nitro oxygen and strong B-O interaction but its eclipsed conformation suffers from several torsional repulsions making it the least stable conformation among all.

It appears from the percentages in Fig. 3 that enantioselectivity mostly originates from the relative contributions of *Si-anti*(-75) (81.5%) and *Re-anti*(50) (11.7%) since the population of the remaining TSs are notably smaller, and therefore, we focused on these two structures. Interestingly, their B-O interaction distances are quite similar (2.60 and 2.62 Å, respectively) revealing that they gain comparable stabilisation due to B-O interaction. Presumably, 1.15 kcal/mol difference in their relative stability is likely to be related to their distinctive ring-like structures. Therefore, in order to compare the relative stability of the ring systems in *Si-anti*(-75) and *Re-anti*(50), we obtained their reduced structures in Fig. 5 by truncating their phenyl groups and canceling the chirality. Single point energy calculations on these two ring systems resulted in 1.05 kcal/mol higher energy for the reduced *Re-anti*(50) structure which is parallel to the relative stability between S*i-anti*(-75) and *Re-anti*(50), supporting our hypothesis.

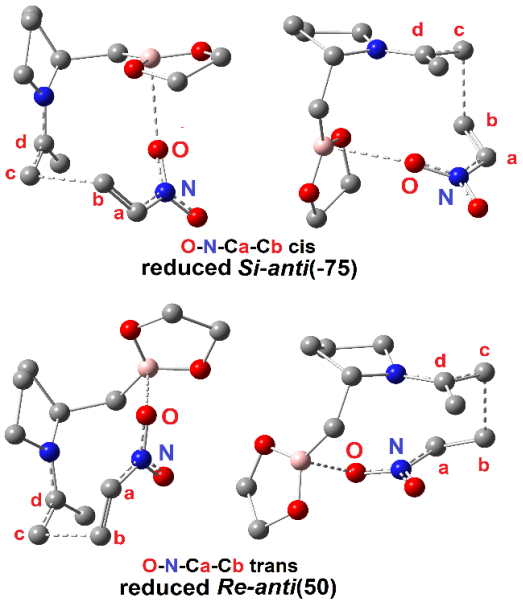


Figure 5. Two different views of the ring systems truncated from the TSs of *Si-anti*(-75) and *Re-anti*(50). Hydrogen atoms are not shown for clarity.

As a result, computational study predicts that the *Si*-face attack is more favorable than the *Re*-face attack at the TS leading to 68% e.e. The conformational possibilities related to C_a-C_b-C_c-C_d dihedral angle generate eight ring-like TS structures for *Si*-face and *Re*-face attacks. Among them, *Si-anti*(-75) (81.5%) and *Re-anti*(50) (11.7%) make the greatest contribution. Both TSs have comparable B-O interactions with about 2.6 Å interaction distances. We propose that the TSs ring-like structures consisting of *cis*-pattern of nitro-oxygen in *Si-anti*(-75) and the *trans*-pattern in *Re-anti*(50) are the major factor for enantioselectivity.

As a consequence of the conformational possibilities investigated here, the ring-like structure developing at the TS is assumed to be more flexible than the case in aldol reaction.[13] Ignoring the contribution of the remaining conformations and re-calculating the Boltzman percentages for only *Si-anti*(-75) and *Re-anti*(50) resulted in 87.5% and 12.5% contributions, respectively, leading to 75% e.e. Thus, it appears that the flexibility of the larger ring size decreases e.e. by at least 7% in homoboroproline-catalysed nitro-Michael additions.

Conclusions

The application of catalysts involving B,N-bifunctional catalysts in asymmetric synthesis is still in its infancy, perhaps due to the challenges of accessing suitable catalysts that allow both the Lewis-acidic and Lewis-basic functions to behave cooperatively without either self-interaction causing deactivation, or without creating catalysts which are difficult to prepare and use.[12] Homoboroproline-based B,N-bifunctional catalysts based around **1** do show early utility in both aldol reactions,[9]-[11] and reported herein, nitro-Michael asymmetric additions involving an enolate equivalent (enamine) nucleophile. Although asymmetric induction is moderate to good, our initial envisaged asymmetric nucleophilic addition mode seems to bourne out in practice, and in fact, through Lewis-acidity tuning of the boronate function, one can generate *in situ* (through diol esterification of the boronic acid moiety) a highly efficient enamine-generating catalyst. This catalyst shows a good balance between stability of the boronate ester (depending upon the diol) and reactivity, so that catalyst loadings and reaction temperatures enable straighforward use. Through the presence of the pendant boronate Lewis-acidic ester, the catalyst is also able to bind and orientate the substrate nitroalkene Michael acceptor, and hence, direct asymmetric induction through the transition state structures described above. That fact this process appears to work through a 10-membered-ring transition state is quite remarkable and suggests that wider applications for catalysts are likely to be accessible.

Experimental Section

General experimental

All the reactions were performed under air unless otherwise specified. The reagents were purchased directly from standard chemical suppliers and used as received from the supplier without further purification. All solvents were used as received from the supplier, except THF, MeOH and ^{i}PrOH which were stored over a dehydrating agent and deoxygenated before use. Molecular sieves (4 Å 1-2 mm beads) were supplied from Alfa Aesar and stored at 220 °C (>48 h) heated under vacuum before use. The purification of crude reaction products was performed using medium-pressure column chromatography, which was carried out using different supports as supplied from Sigma Aldrich; Silica gel (230-400 mesh, 40-63 µm, 60 Å); activated magnesium silicate FLORISIL® (100-200 mesh, 289 m^2g^{-1}) and monitored in both cases by TLC analysis using POLYGRAM® SIL G/UV254 (40 x 80 mm) TLC plates; and activated neutral aluminium oxide Alumina monitored using TLC-PET foils of aluminium oxide with fluorescent indicator 254 nm (40 x 80 mm). In all cases the TLC plates were visualized under a UV lamp operating at short (254 nm) and long (365 nm) wavelength ranges. Visualization was aided by dipping the plates into an alkaline potassium permanganate solution or a *p*-anisaldehyde solution.

Liquid chromatographic mass spectrometry (LCMS) was obtained using a Waters (UK) TQD mass spectrometer (low resolution ESI+, electrospray in positive ion mode, ES+) unless stated elsewhere. Accurate mass spectrometry was obtained on a Finnigan LTQ-FT. IR spectra were recorded on a Perkin Elmer Paragon 1000 FT-IR spectrometer with an ATR attachment.

tert-*Butoxycarbonyl-(L)-proline*

Add Et_3N (14.2 ml, 102.4 mmol) to an ice-cold suspension of *L*-proline (4.50 g, 39.1 mmol) in DCM (90 ml), followed by Boc_2O (12.0 g, 54.8 mmol) in DCM (10 ml). After stirring at rt for 2h, 5% HCl (150 ml) was added. Mixture was extracted into Et_2O, organic layer washed with brine (60 ml), water (60 ml) and dried to give crude product. It was recrystallised from hot EtOAc by adding hexane and leaving the mixture in the freezer overnight to yield 7.30 g (87%) of *N*-Boc-proline as a solid white product. All spectroscopic and analytical properties were identical to those repeated in the literature.[41]

tert-*Butyl (S)-2-(hydroxymethyl)pyrrolidine-1-carboxylate*

To a solution of (tert-butoxycarbonyl)-(*L*)-proline (7.25 g, 33.7 mmol) in dry THF (60 ml) under Ar, BH_3.DMS (3.00 g, 37.1 mmol) was added dropwise and the reaction mixture was refluxed for 2 h. After cooling to rt, ice was added, the aqueous layer was extracted with Et_2O, washed with 5% aq. NaOH twice, then with water, separated, dried and evaporated to yield 2.49 (37%) of *N*-Boc-prolinol as a colourless oil, which crystallized overnight. All spectroscopic and analytical properties were identical to those repeated in the literature.[41]

tert-*Butyl (S)-2-(iodomethyl)pyrrolidine-1-carboxylate*

To a suspension of imidazole (1.66 g, 24.4 mmol) and PPh_3 (4.87 g, 18.6 mmol) in Et_2O (150 ml) at 0 °C under Ar, iodine, ground into a fine powder, (4.74 g, 18.60 mmol) was added in portions over 30 min during intense stirring with mechanical stirrer. Solution of tert-butyl (*S*)-2-(hydroxymethyl) pyrrolidine-1-carboxylate (2.49 g, 12.4 mmol) in DCM (20 ml) was added, and the mixture stirred overnight at r.t. The whole reaction mixture was then dissolved in DCM, mixed with silica gel and columned (EtOAc:hexane = 1:1) to yield 3.59 g (93%) of iodomethyl-*N*-Boc-pyrrolidine as white solid. All spectroscopic and analytical properties were identical to those repeated in the literature.[41]

tert-*Butyl (R)-2-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)pyrrolidine-1-carboxylate*

To a mixture of manganese(II) bromide (5.5 mg, 5 mol%), B_2Pin_2 (0.17 g, 0.65 mmol) and TMEDA (3.8 µL, 5 mol%) dissolved in DME (0.5 ml), ethylmagnesium bromide (220 µL, 0.65 mmol) was added, followed by the *tert*-butyl (*S*)-2-(iodomethyl)pyrrolidine-1-carboxylate (0.16 g, 0.50 mmol) under Ar. Reaction mixture turned grey and was stirred at rt for 1.5 h. The reaction mixture was quenched with 5 ml 20% HCl, extracted with Et_2O, dried, and evaporated to give the crude oil, which was then purified by silica gel chromatography (EtOAc:hexane 1:4) to yield 76 mg (49%) of N-Boc-homoboroproline pinacol ester as a colourless oil. All spectroscopic and analytical properties were identical to those repeated in the literature.[41]

*(R)-2-(Boronomethyl)pyrrolidin-1-ium chloride **1***

To *tert*-butyl (*R*)-2-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl) pyrrolidine-1-carboxylate (80 mg, 0.26 mmol) was added 20% HCl (1.7 ml), and refluxed for 2 h. The mixture was cooled to rt, washed with Et_2O (3 x 20 mL) and evaporated fully, to isolate homoboroproline hydrochloride **8** a pale brown oil (30 mg, 38%). All spectroscopic and analytical properties were identical to those repeated in the literature.[41]

General procedure A: preparation of nitroalkenes[46]

A 3.5 M solution of NaOH was dropped into a cooled solution of nitromethane (0.50 ml, 10 mmol, 1 equiv.) and aromatic aldehyde (10 mmol, 1 equiv.) in methanol (50 ml) at 10 ℃. After the mixture was stirred for 15 min, crushed ice was added until the solid was completely dissolved. The clear solution was dropped into a vigorously stirred solution of 5 M HCl and some solid product appeared. Then the mixture was kept in the refrigerator for another 4 h to generate more solid. The solid product was obtained by filtration, washed with water and dried under vacuum.

1-Bromo-4-[(1E)-2-nitroethenyl]benzene ***3b***

According to general procedure A, 4-bromobenzaldehyde (1.83 g, 10 mmol) was applied in the reaction, and a pale-yellow solid was obtained (1.84 g, 81%): All spectroscopic and analytical properties were identical to those reported in the literature.[46]

1-Trifluormethyl-2-[(1E)-2-nitroethenyl]benzene ***3c***

According to general procedure A, *2*-trifluoromethylbenzaldehyde (1.70 g, 10 mmol) was applied in the reaction, and a yellow solid was obtained (1.86 g, 86%): All spectroscopic and analytical properties were identical to those reported in the literature. [46]

1-Methoxy-3-[(1E)-2-nitroethenyl]benzene ***3d***

According to general procedure A, 3-methoxybenzaldehyde (1.40 g, 10 mmol) was applied in the reaction, and a pale solid was obtained (1.43 g, 80%): All spectroscopic and analytical properties were identical to those reported in the literature. [46]

1-Chloro-2-[(1E)-2-nitroethenyl]benzene ***3e***

According to general procedure A, 2-chlorobenzaldehyde (1.40 g, 10 mmol) was applied in the reaction, and a pale-yellow solid was obtained (1.59 g, 86%): All spectroscopic and analytical properties were identical to those reported in the literature. [46]

General procedure B: racemic nitroalkene-Michael addition using L-proline [34]

To a mixture of nitrostyrene (1.0 mmol) and acetone (2.0 ml) dissolved in DMSO (8.0 ml), *L*-proline (23 mg) was added. The reaction mixture was stirred at rt. for 24 h before being quenched with saturated NH_4Cl (5 ml), extracted with Et_2O, dried ($MgSO_4$), and evaporated to give the crude. Purification by silica gel chromatography (EtOAc:hexane gradient, 1:4 - 2:1) to yield the product. The enantiomeric excess was determined by chiral HPLC using an AS-H-CHIRALCEL column (250 x 4.60 mm) fitted with guard cartridge (50 x 4.6 mm), 25 ℃, flow rate 1.00 ml/min, 210 nm, hexane:IPA (60:40).

General procedure C: homoboroproline catalytic nitroalkene-Michael addition

To a mixture of catalyst (*R*)-**1a** (5 mol%) and triethylamine (5 mol%) in solvent (4.0 ml), nitrostyrene (1.0 mmol) in solvent (1.0 ml) was added after 30 min. Next, acetone (1.0 mmol) was added to the reaction mixture which then stirred at r.t. for 24 h before extraction with Et_2O (3 x 10 ml), dried with $MgSO_4$, and evaporated *in vacuo* to give the crude. Silica gel column chromatography gave the pure product. The enantiomeric excess was determined by chiral HPLC using an AS-H-CHIRALCEL column (250 x 4.60 mm) fitted with guard cartridge (50 x 4.6 mm), 25 ℃, flow rate 1.00 ml/min, 210 nm, hexane:IPA (60:40).

General procedure D: homoboroproline catalytic nitroalkene-Michael addition with molecular sieves

To a mixture of catalyst (*R*)-**1a** (5 mol%) and triethylamine (5 mol%) in solvent (4.0 ml), 3Å molecular sieves (1-2 mm, 10 beads, 64 mg) were added, nitrostyrene (1.0 mmol) in the stipulated solvent (1.0 ml) was added after 30 min stirring. Next, acetone (1.0 mmol) was added to the reaction mixture which then stirred at r.t. for 24 h before extraction with Et_2O (3 x 10 ml), dried with $MgSO_4$, and evaporated *in vacuo* to give the crude. Silica gel column chromatography give the pure product. The enantiomeric excess was determined by chiral HPLC using an AS-H-CHIRALCEL column (250 x 4.60 mm) fitted with guard cartridge (50 x 4.6 mm), 25 ℃, flow rate 1.00 ml/min, 210 nm, hexane: IPA (60:40).

General procedure E: homoboroproline catalytic nitroalkene-Michael addition with molecular sieves and hydrobenzoin

To a mixture of catalyst (*R*)-**1a** (5 mol%) and triethylamine (5 mol%) in solvent (4.0 ml), 3 Å molecular sieves (1-2 mm, 10 beads, 64 mg) and (*S,S*)-(-)-hydrobenzoin (5 mol%) were added, nitrostyrene (1.0 mmol) in the stipulated solvent (1.0 ml) was added after 30 min stirring. Next, acetone (1.0 mmol) was added to the reaction mixture which then stirred at r.t. for 24 h before extraction with Et_2O (3 x 10 ml), dried with $MgSO_4$, and evaporated *in vacuo* to give the crude. Silica gel column chromatography gave the pure product. The enantiomeric excess was determined by chiral HPLC using an AS-H-CHIRALCEL column (250 x 4.60 mm) fitted with guard cartridge (50 x 4.6 mm), 25 ℃, flow rate 1.00 ml/min, 210 nm, hexane: IPA (60:40).

5-Nitro-4-phenylpentan-2-one ***4a***

According to general procedure B, nitrostyrene (0.15 g, 1.0 mmol) and acetone were applied. The resulting product was yielded 0.15 g (73%) as a white solid. The enantiomeric excess was determined by chiral HPLC: t_R (S) = 11.3 min; t_R *(R)* = 15.3 min. All the other spectroscopic and analytical properties were identical to those reported in the literature.[47]

(R)-5-Nitro-4-phenylpentan-2-one ***4a***

According to general procedure C, reaction mixture was dissolved in Me-THF (5.0 ml), before addition of (*S,S*)-(-)-hydrobenzoin. The reaction stirred at r.t. for 24 h before being extracted with Et_2O, dried ($MgSO_4$), and evaporated to give the crude, which was then purified by silica gel chromatography (EtOAc:hexane gradient, 1:5 - 1:1) to yield 0.64 g (61 %) of white solid. The enantiomeric excess was determined by chiral HPLC: t_R (minor) = 10.7 min; t_R (major) = 14.4 min. All the other spectroscopic and analytical properties were identical to those reported in the literature. [47]

4-(4-Bromophenyl)-5-nitropentan-2-one ***4b***

According to general procedure B, (*E*)-1-bromo-4-(2-nitrovinyl)benzene (0.22 g, 1.0 mmol) and acetone (2.0 ml) were applied. The resulting product was obtained0.15 g (73 %) as a white solid. The enantiomeric excess was determined by chiral HPLC: t_R (*S*) = 17.1 min; t_R (*R*) = 21.9 min. All the other spectroscopic and analytical properties were identical to those reported in the literature. [47]

(4R)-4-(4-Bromophenyl)-5-nitropentan-2-one ***4b***

According to general procedure C, (*E*)-1-bromo-4-(2-nitrovinyl)benzene (0.22 g, 1.0 mmol) and acetone were dissolved in Me-THF (5.0 ml), before addition of (*S,S*)-(-)-hydrobenzoin. The reaction stirred at r.t. for 24 h before being extracted with Et_2O, dried ($MgSO_4$), and evaporated to give the crude, which was then purified by silica gel chromatography (EtOAc:hexane gradient, 1:5 - 1:1) to yield 0.64 g (61 %) of white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (s, 3H), 2.88 (d, *J* 7.0, 2H), 3.92-4.03 (m, 1H), 4.57 (dd, *J* 12.5, 7.9, 1H), 4.68 (dd, *J* 12.5, 7.9, 1H), 7.06-7.18 (m, 3H), 7.41-7.50 (m, 1H). The enantiomeric excess was determined by chiral HPLC: t_R (minor) = 18.2 min; t_R (major) = 23.6 min. All the other spectroscopic and analytical properties were identical to those reported in the literature. [47]

5-Nitro-4-(2-trifluoromethylphenyl)pentan-2-one ***4c***

According to general procedure B, (*E*)-1-trifluoromethyl-2-(2-nitrovinyl)benzene (0.18 g, 1.0 mmol) and acetone (2.0 ml) were applied. The resulting product was obtained 0.15 g (73 %) as a white solid. The enantiomeric excess was determined by chiral HPLC: t_R (*S*) = 7.2 min; t_R (*R*) = 8.0 min. All the other spectroscopic and analytical properties were identical to those reported in the literature. [47]

(*R)-5-Nitro-4-(2-trifluoromethylphenyl)pentan-2-one* ***4c***

According to general procedure C, (*E*)-1-trifluoromethyl-2-(2-nitrovinyl)benzene (0.18 g, 1.0 mmol) and acetone were dissolved in Me-THF (5.0 ml), before addition of (*S,S*)-(-)-hydrobenzoin. The reaction stirred at r.t. for 24 h before being extracted with Et_2O, dried ($MgSO_4$), and evaporated to give the crude, which was then purified by silica gel chromatography (EtOAc:hexane gradient, 1:5 - 1:1) to yield 0.64 g (61%) of white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.16 (s, 3H), 2.90 (dd, *J* 17.9, 5.3, 1H), 3.03 (dd, *J* 17.9, 8.4, 1H), 4.35-4.47 (m, 1H), 4.74 (d, *J* 6.7, 2H), 7.35 (d, *J* 7.9, 1H), 7.41 (d, *J* 7.8, 1H), 7.54 (d, *J* 7.6, 1H), 7.70 (dd, *J* 7.9, 1H). The enantiomeric excess was determined by chiral HPLC: t_R (minor) = 10.7 min; t_R (major) = 14.4 min. All the other spectroscopic and analytical properties were identical to those reported in the literature. [47]

4-(3-Methoxyphenyl)-5-nitropentan-2-one ***4d***

According to general procedure B, (*E*)-1-methoxyl-3-(2-nitrovinyl)benzene (0.18 g, 1.0 mmol) and acetone (2.0 ml) were applied. The resulting product was 0.10 g (42%) and obtained as a white solid. The enantiomeric excess was determined by chiral HPLC: t_R (*S*) = 18.9 min; t_R (R) = 23.0 min. All the other spectroscopic and analytical properties were identical to those reported in the literature. [21]

(R)-4-(3-Methoxyphenyl)-5-nitropentan-2-one ***4d***

According to general procedure C, (*E*)-1-methoxyl-3-(2-nitrovinyl)benzene (0.18 g, 1.0 mmol) and acetone were dissolved in Me-THF (5.0 ml), before addition of (*S,S*)-(-)-hydrobenzoin. The reaction stirred at r.t. for 24 h before being extracted with Et_2O, dried ($MgSO_4$), and evaporated to give the crude product, which was then purified by silica gel chromatography (EtOAc:hexane gradient, 1:5 - 1:1) to yield 0.09 g (38%) of white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22-1.28 (s, 3H), 2.90 (d, *J* 7.0, 1H), 3.76-3.82 (m, 2H), 4.59 (dd, *J* 12.4, 7.6, 1H), 4.67 (dd, *J* 12.4, 7.0, 1H), 7.09-7.18 (m, 2H), 7.20-7.26 (m, 2H). The enantiomeric excess was determined by chiral HPLC: t_R (minor) = 18.9 min; t_R (major) = 23.0 min. All the other spectroscopic and analytical properties were identical to those reported in the literature. [47]

4-(2-Chlorophenyl)-5-nitropentan-2-one ***4e***

According to general procedure B, (*E*)-1-chloro-2-(2-nitrovinyl)benzene (0.14 g, 1.0 mmol) and acetone (2.0 ml) were applied. The resulting product was obtained 0.20 g (83 %) as a white solid. The enantiomeric excess was determined by chiral HPLC: t_R (S) = 15.6 min; t_R (R) = 17.2 min. All the other spectroscopic and analytical properties were identical to those reported in the literature. [47]

(4R)-4-(2-Chlorophenyl)-5-nitropentan-2-one ***4e***

According to general procedure C, (*E*)-1-chloro-2-(2-nitrovinyl)benzene (0.14 g, 1.0 mmol) and acetone were dissolved in Me-THF (5.0 ml), before addition of (*S,S*)-(-)-hydrobenzoin. The reaction stirred at r.t. for 24 h before being extracted with Et_2O, dried ($MgSO_4$), and evaporated to give the crude product, which was then purified by silica gel chromatography (EtOAc:hexane gradient, 1:5 - 1:1) to yield 0.24 g (99 %) of white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.14 (s, 3H), 2.95 (dd, *J* 17.9, 7.7, 1H), 3.04 (dd, *J* 17.9, 7.7, 1H), 4.39-4.50 (m, 1H), 4.74 (d, *J* 6.4, 2H), 7.17-7.25 (m, 3H), 7.35-7.42 (m, 1H). The enantiomeric excess was determined by chiral HPLC: t_R (minor) = 16.7 min; t_R (major) = 18.5 min. All the other spectroscopic and analytical properties were identical to those reported in the literature. [47]

Computational methodology

All calculations were conducted by Gaussian 09[48] software package. M06-2X[49],[50]/6-31G(d,p) method was employed based on its success in our previous computational study for the asymmetric aldol reaction with homoboroproline catalyst[13] as well as in modeling the proline-catalysed nitro-Michael addition.[51] Conformational analysis of the homoboroproline catalyst (*R*)-**1** was previously conducted[13] and the same stable anti and syn enamine conformations were used throughout this study. All TS structures were optimized with DFT M06-2X/6-31G(d,p) method in THF solvent. Solvent effect was included implicitly using SMD[52] solvation model. Harmonic frequency calculations were employed to characterize each TS with only one imaginary frequency corresponding to the stretching vibration of C_b-C_c bond. Thermodynamic corrections were obtained at 298 K and 1 atm. Structural representations were generated using CYLview.[53]

Supplementary Material

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/MS-number.

Acknowledgements

The numerical calculations reported in this paper were partially performed at TUBITAK ULAKBIM, High Performance and Grid Computing Center (TRUBA resources) and the resources of Computational Chemistry Group funded by Marmara University Scientific Research Projects Commission.

Author Contribution Statement

A. W. conceived the overall concept and led the project. *Y. D.* carried out the reactions. *S. S. E.* designed and directed the computational project. *O. S.* carried out the computational work. All authors helped prepare the manuscript and all have read and agreed to the published version of the manuscript.

References

[1] R. L. Letsinger, J. M. Smith, J. Gilpin, Organoboron compounds. XX. Chemistry of some 1-naphthaleneboronic acids with substituents in the 8-position, *J. Org. Chem.*, **1965**, *30*, 807-812.

[2] R. L. Letsinger, A. J. Wysocki, Organoboron compounds. XVII. Chemistry of a compound with neighboring borono, ethynyl, and amine functional groups, *J. Org. Chem.*, **1963**, *28*, 3199-3202.

[3] R. L. Letsinger, D. B. Maclean, Organoboron compounds. XVI. Coöperative functional group effects in reactions of boronoarylbenzimidazoles, *J. Am. Chem. Soc.*, **1963**, *85*, 2230-2236.

[4] R. L. Letsinger, J. D. Morrison, Organoboron compounds. XV. Stereochemistry of the reaction of 8-quinolineboronic acid with chloroalcohols, *J. Am. Chem. Soc.*, **1963**, *85*, 2227-2229.

[5] R. L. Letsinger, J. R. Nazy, Organoboron compounds. XI. Isomerization of 2,2'-tolandiboronic acid, *J. Am. Chem. Soc.*, **1959**, *81*, 3013-3017.

[6] R. L. Letsinger, S. Dandegaonker, J. D. Morrison, Organoboron compounds. XIV. Polyfunctional catalysis by 8-quinolineboronic acid, *J. Am. Chem. Soc.*, **1963**, *85*, 2223-2227.

[7] I. Georgiou, G. Ilyashenko, A. Whiting, Synthesis of aminoboronic acids and their applications in bifunctional catalysis, *Acc. Chem. Res.*, **2009,** *42*, 756-768.

[8] K. Arnold, B. Davies, D. Hérault, A. Whiting, Asymmetric direct amide synthesis by kinetic amine resolution: A chiral bifunctional aminoboronic acid catalyzed reaction between a racemic amine and an achiral carboxylic acid, *Angew. Chem.*, **2008**, *47*, 2673-2676.

[9] K. Arnold, A. S. Batsanov, B. Davies, C. Grosjean, T. Schütz, A. Whiting, K. Zawatzky, The first example of enamine–Lewis acid cooperative bifunctional catalysis: application to the asymmetric aldol reaction, *Chem. Commun.*, **2008**, 3879-3881

[10] I. Georgiou, A. Whiting, Mechanism and optimisation of the homoboroproline bifunctional catalytic asymmetric aldol reaction: Lewis acid tuning through *in situ* esterification, *Org. Biomol. Chem.,* **2012**, *10*, 2422-2430.

[11] A. S. Batsanov, I. Georgiou, P. R. Girling, L. Pommier, H. C. Shen, A. Whiting, Asymmetric synthesis and application of homologous pyrroline-2-alkylboronic acids : identification of the B-N distance for eliciting bifunctional catalysis of an asymmetric aldol reaction, *Asian J. Org. Chem.*, **2014**, *3*, 470-479.

[12] S. Arkhipenko, A. Whiting, Broadening the synthetic organic applications of frustrated Lewis pairs, *Arkivoc*, 2017, Part I, 26-40.

[13] H. Dulger, Ö. Sari, N. Demirel, S. S. Erdem, Computational insight into the enantioselectivity of homoboroproline catalyzed asymmetric aldol reaction, *ChemistrySelect*, **2019**, *4*, 7959-7967.

[14] N. Hayama, R. Kuramoto, I. Pápai, Mechanistic insight into asymmetric hetero-Michael addition of α,β-unsaturated carboxylic acids catalyzed by multifunctional thioureas, *J. Am. Chem. Soc.*, **2018**, *140*, 12216-12225.

[15] R. E. Gawley, J. Aubé, Principles of asymmetric synthesis, 2nd. edition, *Elsevier*, **2012**, Boston, USA.

[16] O. M. Berner, L. Tedeschi, Asymmetric Michael additions to nitroalkenes, *Eur. J. Org. Chem.*, **2002**, 1877-1894

[17] S. B. Tsogoeva, Recent advances in asymmetric organocatalytic 1,4-conjugate additions, *Eur. J. Org. Chem.*, **2007**, 1701-1716.

[18] M. S. Sigman, E. N. Jacobsen, Schiff base catalysts for the asymmetric Strecker reaction identified and optimized from parallel synthetic libraries, *J. Am. Chem. Soc.*, **1998**, *120*, 4901-4902.

[19] S. B. Tsogoeva, D. A. Yalalov, K. Huthmacher, Asymmetric organocatalysis with novel chiral thiourea derivatives: Bifunctional catalysts for the Strecker and nitro-Michael reactions, *Eur. J. Org. Chem.*, **2005**, 4995-5000.

[20] L. Y. Chen, S. Guillarme, A. Whiting, C. Saluzzo, Asymmetric Michael addition of acetone to β-nitrostyrenes catalyzed by novel organocatalysts derived from D-isomannide or L-isoidide, *Arkivoc*, **2014**, *4*, 215-227.

[21] T. Mandal, C. G. Zhao, Modularly designed organocatalytic assemblies for direct nitro-Michael addition reactions, *Angew. Chem.,* **2008**, *47*, 7714-7717.

[22] S. Wei, D. A. Yalalov, S. Schmatz, New highly enantioselective thiourea-based bifunctional organocatalysts for nitro-Michael addition reactions, *Catal. Today*, **2007**, *121*, 151-157.

[23] J. M. Andres, R. Manzano, R. Pedrosa, Novel bifunctional chiral urea and thiourea derivatives as organocatalysts: enantioselective nitro-Michael reaction of malonates and diketones, *Chemistry*, **2008**, *14*, 5116-5119.

[24] X. Jiang, Y. Zhang, R. Wang, Highly enantioselective synthesis of γ-nitro heteroaromatic ketones in a doubly stereocontrolled manner catalyzed by bifunctional thiourea catalysts based on dehydroabietic amine: A doubly stereocontrolled approach to pyrrolidine carboxylic acids, *Org. Lett.*, **2008**, *11*, 153-156.

[25] R. Manzano, J. M. Andres, R. Pedrosa, Stereocontrolled construction of quaternary stereocenters by inter- and intramolecular nitro-Michael additions catalyzed by bifunctional thioureas, *Adv. Syn. Catal.*, **2010**, *352*, 3364-3372.

[26] T. E. Shubina, M. Freund, S. B. Tsogoeva, Synthesis and evaluation of new guanidine-thiourea organocatalyst for the nitro-Michael reaction: Theoretical studies on mechanism and enantioselectivity, *Beilstein J. Org. Chem.*, **2012**, *8*, 1485-1498.

[27] M. Tsakos, C. G. Kokotos, G. Kokotos, Primary amine-thioureas with improved catalytic properties for "difficult" Michael reactions. efficient organocatalytic syntheses of (S)-, (R)-Baclofen and (S)-Phenibut, *Adv. Syn. Catal.*, **2012**, *354*, 740-746.

[28] J. M. Andres, M. Ceballos, R. Pedrosa, Supported bifunctional thioureas as recoverable and reusable catalysts for enantioselective nitro-Michael reactions, *J. Org. Chem.*, **2016**, *12*, 628-635.

[29] L. Tuchman-Shukron, M. Portnoy, Polymer-supported highly enantioselective catalyst for nitro-Michael addition: Tuning through variation of the number of H-bond donors and spacer length, *Adv. Syn. Catal.*, **2009**, *351*, 541-546.

[30] L. Tuchman-Shukron, S. J. Miller, M. Portnoy, Nitro-Michael addition using polymer-supported Bifunctional Catalysts, *Chemistry*, **2012**, *18*, 2290-2296.

[31] D. A. Yalalov, S. B. Tsogoeva, S. Schmatz, Chiral thiourea-based bifunctional organocatalysts in the asymmetric nitro-Michael addition: a joint experimental-theoretical study, *Adv. Syn. Catal.*, **2006**, *348*, 826-832.

[32] L. Peng, X. Y. Xu, L.-X. Wang, Noyori's Ts-DPEN ligand: Simple yet effective catalyst for the highly enantioselective Michael addition of acetone to nitroalkenes, *Eur. J. Org. Chem.*, **2010**, 1849-1853.

[33] B. List, P. Pojarliev, Efficient proline-catalyzed Michael additions of unmodified ketones to nitro olefins, *J. Am. Chem. Soc.,* **2001**, *3*, 2423-2425.

[34] K. Sakthivel, W. Notz, C. F. Barbas, Amino acid catalyzed direct asymmetric aldol reactions: a bioorganic approach to catalytic asymmetric carbon– carbon bond-forming reactions, *J. Am. Chem. Soc.,* **2001**, *123*, 5260-5267.

[35] J. M. Betancort, J. M.; C. F. Barbas, Catalytic direct asymmetric Michael reactions: Taming naked aldehyde donors, *Org. Lett.*, **2001**, *3,* 3737-3740.

[36] H. Yang, M. W. Wong, (*S*)-Proline-catalyzed nitro-Michael reactions: towards a better understanding of the catalytic mechanism and enantioselectivity, *Org. Bio. Chem.*, **2012**, *10*, 3229-3235.

[37] D. Xu, J. Wang, Y. Wang, Novel bifunctional l-prolinamide derivatives as highly efficient organocatalysts for asymmetric nitro-Michael reactions, *Tetrahedron: Asymmetry*, **2016**, *27*, 1121-1132.

[38] A. S. Batsanov, C. Grosjean, T. Schütz, A. Whiting, A (−)-sparteine-directed highly enantioselective synthesis of boroproline. Solid- and solution-state structure and properties, *J. Org. Chem.*, **2007**, *72*, 6276-6279.

[39] I.-H. Chen, L. Yin, W. Itano, M. Kanal, M. Shibasaki, Catalytic asymmetric synthesis of chiral tertiary organoboronic esters through conjugate boration of β-substituted cyclic enones, *J. Am. Chem. Soc.* **2009**, *131*, 11664–11665.

[40] C. T. Yang, Z. Q. Zhang, H. Tajuddin, C. C. Wu, J. Liang, J. H. Liu, Y. Fu, M. Czyzewska, P. G. Steel, T. B. Marder, L. Liu, Alkylboronic esters from copper-catalyzed borylation of primary and secondary alkyl halides and pseudohalides, *Angew. Chem. Int. Ed.* **2012**, *51*, 528–532.

[41] I. Georgiou, A. Whiting, Enantioselective synthesis of (*R*)-homoboroproline from (*S*)-proline using a borylation approach, *Eur. J. Org. Chem.*, **2012**, 4110–4113.

[42] T. C. Atack, S. P. Cook, Manganese-catalyzed borylation of unactivated alkyl chlorides, *J. Am. Chem. Soc.,* **2016**, *138*, 6139-6142.

[43] S. Saito, H. Yamamoto, Design of acid-base catalysis for the asymmetric direct Aldol reaction, *Acc. Chem. Res.* **2004**, *37*, 570-579.

[44] S. Mukherjee, J. W. Yang, S. Hoffmann, B. J. List, Asymmetric enamine catalysis, *Chem. Rev.*, **2007**, *107*, 5471-5569.

[45] Q. Peng, F. Duarte, R. S. Paton, Computing organic stereoselectivity – from concepts to quantitative calculations and predictions, *Chem. Soc. Rev.,* **2016**, *45*, 6093-6107.

[46] C. Xu, J. Du, L. Ma, G. Li, M. Tao and W. Zhang, Tertiary amine functionalized polyacrylonitrile fiber catalyst for the synthesis of tetrahydrothiophenes, *Tetrahedron*, **2013**, *69*, 4749-4757.

[47] L. Peng, X.-Y. Xu, L.-L. Wang, J. Huang, J.-F. Bai, Q.-C. Huang, L.-X. Wang, Effective construction of quaternary stereocenters by highly enantioselective α-amination of branched aldehydes, *Eur. J. Org. Chem.*, **2010**, *10*, 1849-1853.

[48] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox, Gaussian 09, Revision B.01, Gaussian, Inc., Wallingford CT, 2009. (Wallingford CT: Gaussian, Inc. 2009).

[49] Y. Zhao, D. G. Truhlar, The M06 suite of density functionals for main group thermochemistry, thermochemical kinetics, noncovalent interactions, excited states, and transition elements: two new functionals and systematic testing of four M06-class functionals and 12 other functionals, *Theor. Chem. Acc*. **2008**, *120*, 215-241.

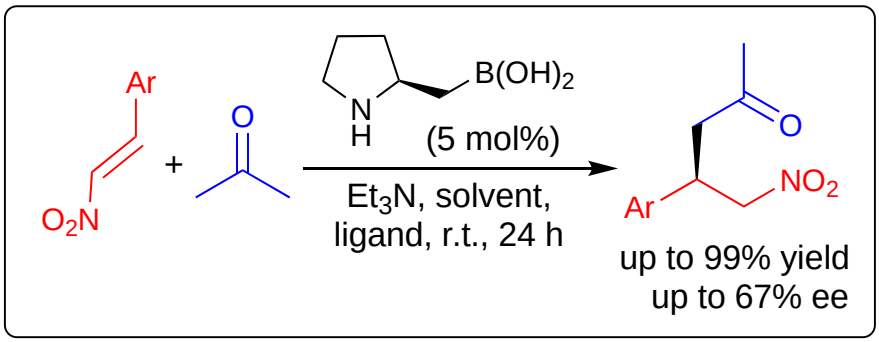
[50] Y. Zhao, D. G. Truhlar, Density functionals with broad applicability in chemistry, *Acc. Chem. Res*. **2008**, *41*, 157–167.

[51] H. Yang, M. W. Wong, (*S*)-Proline-catalyzed nitro-Michael reactions: Towards a better understanding of the catalytic mechanism and enantioselectivity, *Org. Biomol. Chem*., **2012**, *10*, 3229-3235.

[52] A. V. Marenich, C. J. Cramer, D. G. Truhlar, Universal solvation model based on solute electron density and on a continuum model of the solvent defined by the bulk dielectric constant and atomic surface tensions, *J. Phys. Chem. B*, **2009**, *113*, 6378−6396.

[53] *CYLview,* version 1.0b; Université de Sherbrooke: Sherbrooke, Québec, Canada, **2009**, http://www.cylview.org.

Entry for the Table of Contents



Twitter

A B,N-bifunctional proline-related asymmetric catalysts affects a nitro-Michael addition of a ketone to a nitro-alkene operating through a proposed 10-membered ring transition state providing moderate asymmetric induction.