DOI: 10.1002/chem.200903537

# A 4-Hydroxypyrrolidine-Catalyzed Mannich Reaction of Aldehydes: Control of *anti*-Selectivity by Hydrogen Bonding Assisted by Brønsted Acids

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*Dedicated to Professor Josep M. Ribó on the occasion of his 70th birthday*

**Abstract:** An *anti*-selective Mannich reaction of aldehydes with *N*-sulfonyl imines has been developed by using a 4-hydroxypyrrolidine in combination with an external Brønsted acid. The catalyst design is based on three elements: the α-substituent of the pyrrolidine, the 4-hydroxy group, and the Brønsted acid, the combination of which is essential for high chemical and stereochemical efficiency. The reaction works with aromatic aldehyde-derived imines, which have rarely been employed in previously reported enamine-based *anti*-Mannich reactions. Additionally, both *N*-tosyl and *N*-nosyl imines can be successfully used and the Mannich adducts can be easily reduced or oxidized, and after *N*-deprotection the corresponding β-amino acids and β-amino alcohols can be obtained with good yields. The results also show that this ternary catalytic system may be practical in other enamine-based reactions.

**Keywords:** asymmetric catalysis · Brønsted acids · enamine activation · hydrogen bonds · Mannich reaction

## Introduction

Inspired by the efficiency, elegance, and selectivity of enzymatic catalysis, the design of organic molecules capable of the efficient and enantioselective promotion of carbon–carbon or carbon–heteroatom bond processes is a formidable challenge that is currently receiving considerable attention. In this context, several examples of chiral Brønsted acid[1] and chiral Brønsted base[2] promoted organocatalytic transformations are known. More significantly, molecules that combine a site with Brønsted base character and another site with hydrogen-bond donor ability (ambifunctional catalysts) that are capable of activating concurrently both the donor and acceptor components have emerged as a better alternative to achieve high levels of reaction enantioselection.[3] Besides the thiourea/amine-based catalysts,[4] relevant examples in the above context are some secondary amines that activate the donor aldehyde or ketone through enamine[5] formation and the electrophile through hydrogen-bond interactions (Scheme 1a). Prototypical catalysts of this type are proline **1**,[5a,6] the analogues **2**[7] and **3**,[6d,8] and some prolylamides[9] in which the hydrogen-bond donor is located in the substituent at the α-position of the pyrrolidine nitrogen. A related family of amine catalysts works only through steric control (Scheme 1b). These molecules activate the donor via enamine formation and possess a sterically hindered group that directs the approach of the electrophile from the less-hindered enamine face and thereby controls the stereoselectivity of the reaction. In this second group, the most representative small organic molecules are MacMillan's imidazolidinones[10] and α,α-diarylprolinol ethers[11] (**4** in Scheme 1), which have been shown to be very general for a broad range of reactions. However, catalysts of this latter family with an additional hydrogen-bond donor that could also activate the pronucleophile concurrently (Scheme 1c) are quite scarce despite the fact that they

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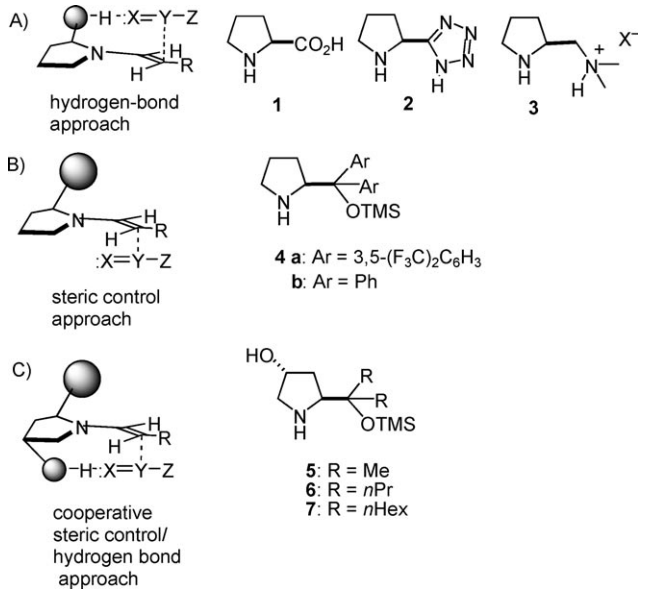
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200903537.



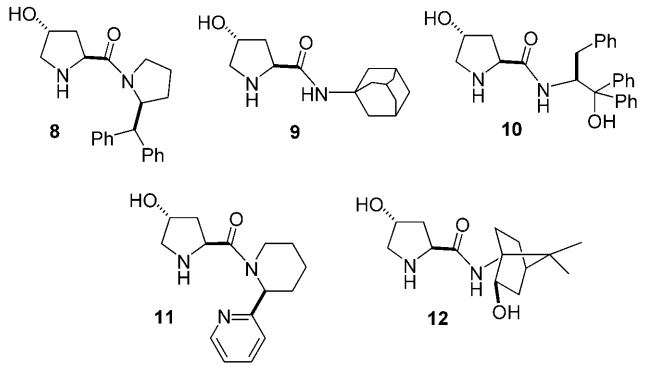

Scheme 1. Prototypical organocatalysts for enamine and iminium ion based reactions and their mode of action for enamine reactions. a) Hydrogen-bond approach. b) Steric-control approach. c) Proposed model.

would be, in principle, more active as a result of this synergic action.

Herein we report a new simple family of amine catalysts, *trans*-4-hydroxy-2-dialkylsilyl pyrrolidines, that fulfils these structural requirements and we demonstrate their capability of promoting *anti*-selective Mannich reactions with very high diastereo- and enantioselectivity.

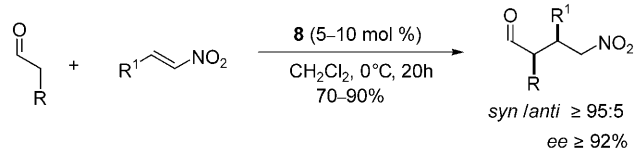
## Results and Discussion

**Background and working plan**: Previously we introduced *trans*-4-hydroxyprolylamide **8** as an efficient catalyst for conjugate addition reactions of aldehydes to nitroalkenes.[12] In




a subsequent related investigation by Feng[13] it has been shown that catalyst **9** is capable of promoting the Biginelli reaction with good to moderate levels of enantioselectivity, and more recently, Nakano/Takeshit,[14] Gao,[15] and Chen[16] independently revealed catalysts **10**, **11**, and **12**, respectively, to be effective for the conjugate addition of aldehydes to nitroalkenes, with the former being also efficient in aldol reactions. In all these cases, it was assumed that the hydroxy group of each catalyst played an important role in reaction efficiency and stereoselectivity.

In our initial studies on this subject, the addition reaction of a survey of enolizable aldehydes to either β-alkyl or β-aryl-substituted nitroalkenes promoted by catalyst **8** was observed to proceed with excellent *syn/anti* ratios, typically greater than 95:5, and with very high enantiomeric excess (*ee*) values for the major *syn* diastereomer (>92% *ee*; Scheme 2). The optimum results were achieved when the reactions were carried out in $CH_2Cl_2$ at room temperature in the presence of 10% of catalyst **8** for β-branched aldehydes and 5 mol% for linear-chain aldehydes at 0°C. Under these conditions, the enantioselectivities obtained were above 90% for essentially all substrates that were explored. Even the more challenging β-alkyl-substituted nitroalkenes gave adducts with diastereomeric ratios greater than 99:1 and enantioselectivities of up to 99%, results that were attributed to a cooperative effect between the hydroxy group and the substituent of the catalyst according to our proposal (Scheme 1c).



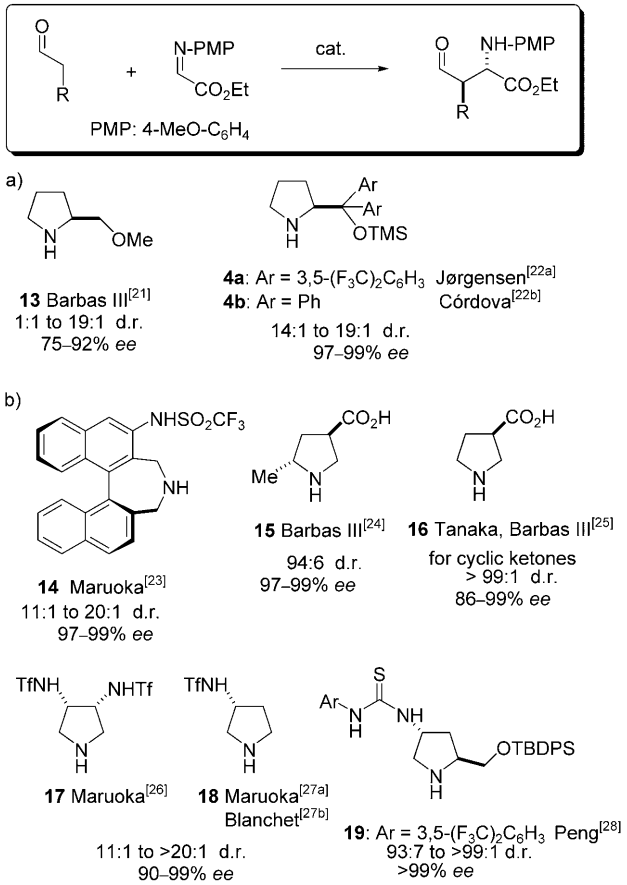

Scheme 2. Catalytic conjugate addition of aldehydes to nitroalkenes and representative examples.

Given these results, it was considered to be instructive to evaluate the scope of this concept and the Mannich reaction was elected for that purpose. Not only does this transformation establish one carbon–carbon bond and up to two stereogenic centers in a single synthetic operation, it also plays a pivotal strategic role in the synthesis of numerous nitrogen-containing compounds.[17] As a result, both the activation of the reaction and control of its stereochemical outcome have been and continue to be the subject of intensive research activity.[18] However, despite the recent progress made in the area, methods based on direct approaches leading to *anti*-α,β-disubstituted β-amino carbonyl compounds are still demanding. To date the most common practice to access *anti*-β-amino α-substituted carbonyl compounds is the alkylation of their corresponding α-unsubstituted derivatives, which can be readily obtained by several catalytic enantioselective procedures.[19]

**Early formulations and challenges**: At the outset of our investigation, however, it was not clear which kind of imines would be best suited for the Mannich reaction. Whilst imines derived from aromatic aldehydes are effective in the

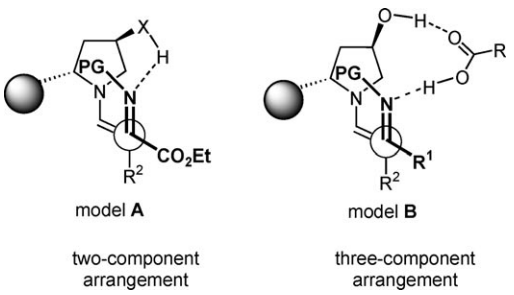
reactions promoted by proline and its congeners to give *syn* adducts with high enantioselectivity, they are rarely employed in the reported *anti*-selective Mannich reactions.[18,20] The first example of an *anti*-selective Mannich reaction by enamine catalysis was described in 2002 by Barbas III[21] by using (*S*)-2-methoxymethylpyrrolidine (**13**, Scheme 3) and




Scheme 3. Representative chiral pyrrolidines for *anti*-Mannich reactions with glyoxylate derived imines. a) Catalysts working through steric control. b) Catalysts working through hydrogen-bond control.

glyoxylate imines. The identification by Jørgensen[22a] of the diaryl prolinol silyl ether **4a** led to significant improvements in terms of yields and enantioselectivity. Maruoka[23]reported the first bifunctional catalyst for the same reaction, the axially chiral amino sulfonamide **14**. Although its preparation involves tedious multistep synthesis, the catalyst has the ability of activating concurrently the aldehyde via enamine formation and the Mannich acceptor through hydrogen bonding. Later, Barbas III and Tanaka showed that the installation of a carboxyl group at the β-position of the pyrrolidine nitrogen (catalyst **15**[24] and **16**[25]) suffices for high enantio- and *anti*-diastereocontrol of this reaction. Pyrrolidines **17**[26] and **18**[27] that work through the same model have also been reported by Blanchet and Maruoka, independently. More recently, the thiourea-based catalyst **19** that combines structural features of catalysts **13** and **18** has been reported by Peng for the same reaction.[28] Accordingly, the main limitation of all these contributions is that only α-imino esters appear to be sufficiently reactive to give Mannich adducts with both chemical and stereochemical efficiency.[29] One solution has been recently presented by Maruoka who has revealed that *N*-Boc (*tert*-butoxycarbonyl) imines from arylaldehydes may be utilized in the Mannich reaction by using chiral sulfonamide **14**.[30] On the other hand, catalyst **4b**, which is more readily available, seems to be less active since long reaction times (4–7 days) are needed for the reaction with this kind of imines to occur with good yields. In this instance, glyoxylate-derived imines are, once again, the best substrates to give the Mannich adducts with high *anti*-selectivity and enantioselectivity.[31]

In most of the above catalytic systems, a transition-state model A (Scheme 4) is invoked in which a hydrogen-bond




Scheme 4. Features of the proposed models for *anti*-Mannich reactions.

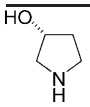
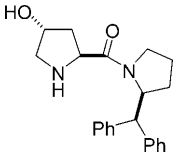
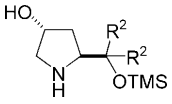
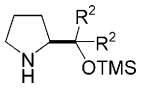
interaction with the imine nitrogen is postulated to be the key organizational element in a two-component arrangement in analogy with our proposal for conjugate additions. Apparently, glyoxylate imines have the appropriate bond lengths and angles to fit properly in this model.[32] We reasoned that in the presence of an external Brønsted acid a more fluxional model could be provided in which other imines could be accommodated in a three-component arrangement, such as model B (Scheme 4).

To evaluate this assumption, *N*-sulfonyl imines[33] were chosen because of the poor coordinating ability of the oxygen atoms toward hydrogen bonding that would ensure an effective imine activation.

**Catalyst screening and conditions**: The validity of the above hypothesis soon became clear. Whilst hydroxypyrrolidine **20** alone (Table 1, entry 1) was quite inefficient in promoting the reaction of butyraldehyde **22** (R = Et) with *N*-tosylimine **23a** at −20 °C, in combination with a 20 mol % of *p*-nitrobenzoic acid (PNBA), higher yield and diastereo- and enantioselectivity were attained (Table 1, entry 2). Decreasing the temperature to −60 °C (Table 1, entry 3) provided a higher *ee*, although with similar diastereoselectivity and a lower yield. By using catalyst **8**, a further improvement was achieved albeit still insufficient providing the amino alcohol **29a**, after in situ reduction of the intermediate Mannich

Table 1. Catalyst screening for the Mannich reaction of butyraldehyde **22** (R = Et) with imine **23a** in DMF as the solvent to give **32a**.[a]

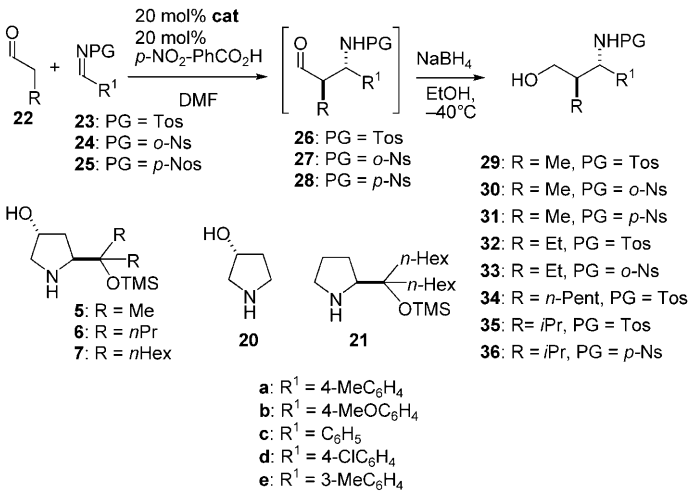
| | Entry | Cat. | $T$ [°C] | Conv. [%][b] | Yield [%][c] | d.r.[b] | *ee* [%][d] |
|---|---|---|---|---|---|---|---|
|  | 1 | **20** | −20 | nd[e] | 37 | 55:45 | 47[f,g] |
| | 2 | **20** | −20 | nd [e] | 70 | 75:25 | 67[g] |
| | 3 | **20** | −60 | >99 | 29 | 77:23 | 83[g] |
|  | 4 | **8** | −60 | >99 | 88 | 96:4 | 75 |
|  | 5 | **5** ($R^2$ = Me) | −60 | >99 | 75 | 93:7 | 92 |
| | 6 | **6** ($R^2$ = *n*Pr) | −60 | 50 | 43 | 90:10 | 93 |
| | 7 | **7** ($R^2$ = *n*Hex) | −60 | >99 | 77 | 98:2 | 95 |
| | 8 | **7** ($R^2$ = *n*Hex) | −20 | >99 | 99 | 80:20 | 76[f] |
| | 9 | **7** ($R^2$ = *n*Hex) | −20 | >99 | 92 | 76:24 | 86 |
|  | 10 | **4a** ($R^2$ = 3,5-$(F_3C)_2C_6H_3$) | −60 | 0 | 0 | – | –[h] |
| | 11 | **4b** ($R^2$ = Ph) | −60 | 40 | 15 | 75:25 | 63 |
| | 12 | **21** ($R^2$ = *n*Hex) | −40 | >99 | 98 | 78:22 | 67 |
| | 13 | **21** ($R^2$ = *n*Hex) | −60 | >99 | 24 | 78:22 | 58 |

[a] Reactions performed at 0.5 mmol scale in DMF (2 mL) and by using catalysts **4a**, **4b**, **5**, **6**, **7**, and **21** (20 mol%), PNBA (20 mol%), and imine **23a** (3 equiv). Data related to **32a** after in situ reduction of **26a**. Reaction time 20 h. [b] Determined by $^1$H NMR spectroscopy on the crude material. [c] Isolated yield of **32a** after flash column chromatography. [d] Determined by HPLC analysis; see the Supporting Information for details. [e] nd: not determined. [f] No Brønsted acid was used. [g] Reactions conducted by using 3 equiv of aldehyde. [h] Reaction time 3 days.

adduct, with a good diastereomeric ratio and moderate *ee* (Table 1, entry 4).

Subsequent efforts to increase stereoselectivity by increasing the steric bulk of the α-substituent of the pyrrolidine ring resulted in the development of 4-hydroxy derivatives **5**, **6**, and **7** (Scheme 5).[34] Concordant with our expectations, the aminoalcohol product **29a** obtained from the reaction of aldehyde **22** (R = Et) and imine **23a** promoted by catalyst **5** in the presence of PNBA was indeed formed after reduction of the intermediate aldehyde with an excellent high diastereomeric ratio (93:7) and 92% *ee* (Table 1, entry 5). Catalyst **6** enabled further stereochemical improvement, and catalyst **7** proved to be the best giving the *anti*-Mannich adduct **29a** in 77% yield and with a remarkably high diastereomeric ratio (98:2) and 95% *ee* (entries 6, 7). The less acidic benzoic acid is also effective under the same conditions but a longer reaction time is needed for reaction completion, whilst *p*-methoxybenzoic acid leads to lower yield after 20 h. Additionally, decreasing or increasing the amount of PNBA to 10 or 40%, respectively, while maintaining the catalyst loading at 20% affords similar enantio- and diastereoselectivity, but significantly lower yields for the same reaction time (50 and 58% yield, respectively). As the results in Table 1 show, in the absence of PNBA (entry 8), the reaction only proceeded at −20°C, and low diastereo- and enantioselectivity were obtained. No variations were observed with the aid of PNBA in this instance (Table 1, entry 9), thus suggesting that a low reaction temperature is also needed for achieving good results and that the acid co-catalyst is necessary not only for reactivity,[35] but also for stereocontrol. To further prove these observations catalysts **4a** and **4b**, which work well when glyoxylate imines are employed,[11] were evaluated. Whilst catalyst **4a** in combination with PNBA was totally ineffective under the conditions examined, catalyst **4b** afforded a 15% yield and poor diastereo- and enantioselectivity (Table 1, entries 10, 11).

To further demonstrate the influence of the hydroxy group in catalyst **7**, the reaction of butyraldehyde with imine **23a** was conducted under the same conditions in the presence of the analogous catalyst **21** lacking the hydroxyl group (Table 1, entries 12 and 13). These data show that all three elements, the external Brønsted acid, the α-substituent in the pyrrolidine, and the 4-hydroxy group of the ring are essential for high chemical and stereochemical efficiency.

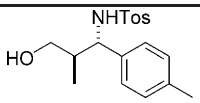
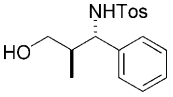
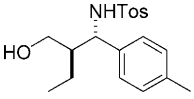
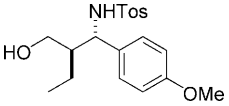
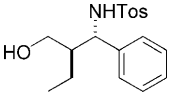
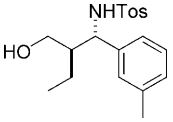
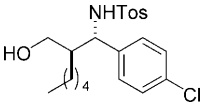
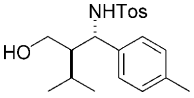



Scheme 5. Mannich reaction between aldehydes **22** and *N*-sulfonyl-imines **23**–**25** catalyzed by **5**, **6**, **7**, **20**, and **21**.

**Scope of the Mannich reaction**: The generality of the enantioselective Mannich reaction catalyzed by **7** was then explored with different aldehydes and *N*-*p*-toluensulfonyl imines under the optimized conditions (Table 2). The results show that the reaction is quite general with respect the aldehyde donor and imine acceptor. *N*-Tosyl imines derived from aromatic aldehydes with electron-poor and -rich substituents can be employed leading to the *anti* adducts in up to 78% yield, 97:3 diastereomeric ratio, and 99% *ee*. Initial-

Table 2. Catalytic asymmetric Mannich reactions of aldehydes **22** with *N*-tosyl imines **23** promoted by **7**.[a]

| Entry | Product | | *T* [°C] | Yield [%][b] | d.r.[c] | *ee* [%][d] |
|---|---|---|---|---|---|---|
| 1 |  | **29a** | −60 | 68 (78) | 96:4 | 97 |
| 2 |  | **29c** | −60 | 40 (77) | 96:4 | >99 |
| 3 |  | **32a** | −60 | 77 | 98:2 | 95 |
| 4 |  | **32b** | −60 | 63 | 98:2 | 86 |
| 5 |  | **32c** | −60 | 67 (68) | 94:6 | 91 |
| 6 |  | **32e** | −60 | 60 | 93:7 | 91 |
| 7 |  | **34d** | −40 | – (76) | 87:13 | 91 |
| 8 |  | **35a** | −60 | – (76) | 97:3 | >99 |

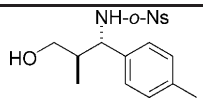
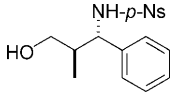
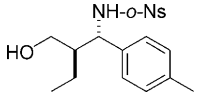
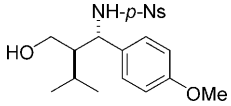
[a] Reactions performed at 0.5 mmol scale in DMF (2 mL) and by using catalyst **7** (20 mol%), *p*-nitrobenzoic acid (20 mol%), aldehydes **22**, and imines **23** (3 equiv). [b] Isolated yield of aminoalcohols **29**, **32**, and **34** after flash column chromatography. Yields in brackets were obtained by using a ratio of aldehyde/imine of 3:1. [c] Determined by $^1$H NMR spectroscopy on the crude material. [d] Determined by HPLC analysis after flash chromatography; see the Supporting Information for details.

ly, reactions were performed in a 3:1 molar ratio of imine/aldehyde. However changing the stoichiometry to 3:1 aldehyde/imine led to significantly higher yields without apparent changes in the stereoselectivity.

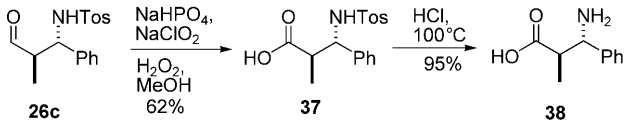
Given the utility of the nitrobenzenesulfonyl group as both activating and protecting group of the amine function,[36] we next extended the method to nosyl imines. As the results in Table 3 show, the Mannich reaction also proceeded efficiently with *o*-nosyl- and *p*-nosyl-protected imines. In these cases, both benzoic acid and *p*-nitrobenzoic acid can be used, with the latter slightly superior in terms of yield.

The assigned absolute configuration of the major products was established by a single-crystal X-ray analysis of **29a** and by assuming an uniform reaction mechanism.[37,38] In addition, the β-amino aldehyde **26c** upon oxidation under standard conditions provided the *N*-tosyl-protected derivative **37**, which then was converted into the known β-amino acid **38** (Scheme 6).[39]

Table 3. Catalytic asymmetric Mannich reactions of aldehydes **22** with *N*-nosyl imines **24** and **25** promoted by **7**.[a]

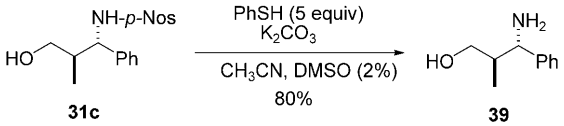
| Entry | Product | | *T* [°C] | Yield [%][b] | d.r.[c] | *ee* [%][d] |
|---|---|---|---|---|---|---|
| 1 |  | **30a** | −60 | – (61) | 93:7 | 93 |
| 2 |  | **31c** | −60 | – (59)[e] | 91:9 | 97 |
| 3 |  | **33a** | −60 | – (71) | 93:7 | 91 |
| 4 |  | **36b** | −60 | – (51)[e] | 99:1 | >99 |

[a] Reactions performed at 0.5 mmol scale in DMF (2 mL) and by using catalyst **7** (20 mol%), *p*-nitrobenzoic acid (20 mol%), aldehydes **22** (3 equiv), and imines **24** and **25**. [b] Isolated yield of aminoalcohols after flash column chromatography. Yields in brackets were obtained by using a ratio of aldehyde/imine of 3:1. [c] Determined by $^1$H NMR spectroscopy on the crude material. [d] Determined by HPLC analysis after flash chromatography; see the Supporting Information for details. [e] Benzoic acid (20 mol%) was used as cocatalyst.




Scheme 6. Oxidation and deprotection of Mannich adducts.

Complementing this protocol, the *N*-nosyl derivatives can also be easily deprotected[40] under the conditions shown in Scheme 7 to afford the free aminoalcohols. For example, treatment of **31c** with tiophenol and potassium carbonate in acetonitrile and some drops of DMSO afforded amino alcohol **39** in 80% yield.



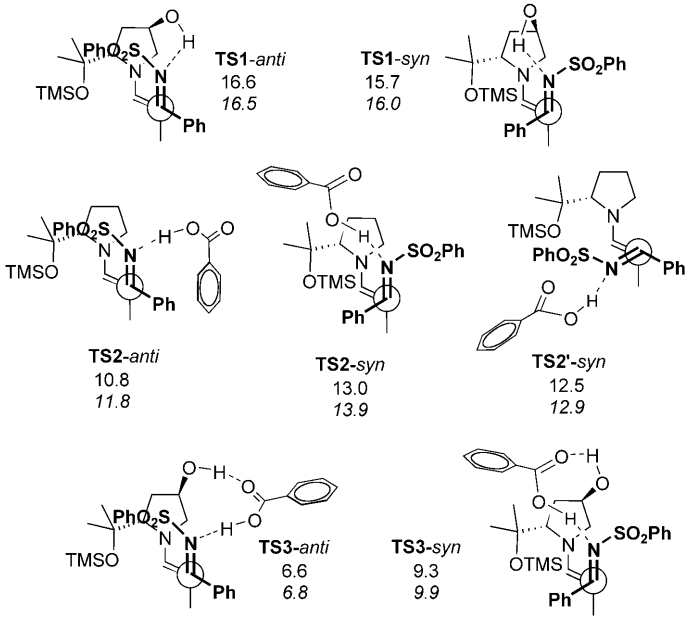

Scheme 7. Deprotection of the *N*-nosyl adducts.

**Mechanistic insights**: The above results suggest that the initially invoked three-component arrangement for the Mannich reaction to proceed with *anti* selectivity is indeed operating. To get a better understanding of this activation mechanism and provide a rationale for the stereochemical outcome of the reaction, some quantum calculations were carried out.

On the basis of enamine formation,[41] we assumed the reaction to proceed through an enamine mechanism[38] rather

than an enol intermediate.[42] Accordingly, computational DFT[43] data based on the model shown in Scheme 8 indicated that the activation of the iminic N by the pyrrolidine OH




Scheme 8. Representation of the computed transition structures optimized at B3LYP/6-31-G*. Single-point values [Kcal mol$^{-1}$] at the B3LYP/6-311++G** level are shown in italics.

group is of similar magnitude for *anti* or *syn* transition states, anticipating an almost equal ratio of diastereomers (TS1-*anti* vs TS1-*syn*, Scheme 8). Better activation of the iminic nitrogen was obtained by replacing the intramolecular hydrogen bonding by an intermolecular hydrogen-bond interaction with the aid of an external Brønsted acid (TS2, Scheme 8). However, the *anti* stereoselectivity is still predicted to be low. In fact, TS2-*syn* and TS2′-*syn* staggered conformations equally contribute to the formation of the *syn* isomer in this case. Remarkably, however, the combination of both tools, the catalyst hydroxy group and the external Brønsted acid, led to a model that correctly predicts the results obtained, differentiating TS3-*anti* and TS3-*syn* by 3 kcal mol$^{-1}$ (Scheme 8).

## Conclusion

In summary, we have reported a highly efficient catalytic system for the *anti*-selective Mannich reaction of aldehydes with *N*-sulfonyl imines. This catalyst system combines an amino group to activate the aldehyde donor substrate, and a hydroxy group together with an external Brønsted acid to activate the imine acceptor component, while controlling the stereochemistry of the process. The Mannich adducts can be easily reduced or oxidized and then deprotected to give the corresponding β-amino acids and β-amino alcohols. Specifically, the synthetic utility of the present *anti*-selective Mannich reaction has been significantly expanded by the utilization of imines other than those derived from glyoxylate. The results also show that this ternary system may be of utility in the development of other enamine-based reactions.

## Experimental Section

**General methods**: All reactions were carried out under a nitrogen atmosphere in flame-dried glassware with efficient magnetic stirring. Methylene chloride ($CH_2Cl_2$) was distilled from $CaH_2$, and toluene was dried in the presence of sodium metal. Ethyl acetate and DMF were used as reagent grade. Purification of reaction products was carried out by flash column chromatography by using silica gel 60 (0.040–0.063 mm, 230–400 mesh). Analytical TLC was performed on 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light and a solution obtained by admixing in 470 mL of water ammonium molybdate (21 g), cerium sulphate (1 g), and concentrated sulphuric acid (31 mL), followed by heating. Melting points were measured with a Buchi SMP-20 melting point apparatus and are uncorrected. $^1$H and $^{13}$C NMR spectra were recorded on Bruker Advance-300 and are reported in ppm from internal tetramethylsilane (TMS). Analytical HPLC was performed on waters-600E controller chromatographs, equipped with 2996 and 2998 photodiode array UV detector, by using Daicel Chiralpak AD-H, IC and IA columns. Optical rotations were recorded on a Jasco P-2000 polarimeter. MS spectra were recorded on an ESI-ion trap mass spectrometer (Agilent 1100 series LC/MSD, SL model). Diarylprolinol trimethylsilyl ether catalysts **4a** and **4b** were purchased from Aldrich and used without further purification.

**General procedure for the Mannich reaction**: The aldehyde (1.5 mmol, 3 equiv) was added to a solution of the imine (0.5 mmol, 1 equiv), the acid (0.1 mmol, 20 mol%), and the catalyst (0.1 mmol, 20 mol%) in DMF (2 mL) at −60 °C. The resulting solution was stirred at −60 °C for 24 h. EtOH (1 mL) and $NaBH_4$ (4.5 mmol, 8 equiv) were successively added at the same temperature, and after stirring for 30 min at −40 °C, the reaction was quenched with brine (2 mL) and allowed to reach room temperature. After extraction with $Et_2O$ (3×4 mL), the combined organic phases were washed with brine and dried over $MgSO_4$, concentrated under reduced pressure, and purified over silica gel by flash column chromatography to afford the expected adducts. The diastereoselectivity of the process was determined by $^1$H NMR spectroscopic analysis on the crude material.

***N*-[(1*S*,2*R*)-3-Hydroxy-2-methyl-1-*p*-tolylpropyl]-4-methylbenzenesulfonamide (29a)**: Prepared according to the general procedure by starting from propanal (0.11 mL, 1.5 mmol) and *N*-tosyl-tolylimine (**23a**) (137 mg, 0.5 mmol). The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate 80:20) and then disagregated with $Et_2O$ to give the title compound as a white solid. Yield: 78% (130 mg); m.p. 104–06 °C; $[\alpha]_D^{20} = -68.2$ ($c = 1$ in $CH_2Cl_2$); $^1$H NMR (300 MHz, $CDCl_3$): $\delta = 7.53$ (d, $J = 8.3$ Hz, 2H), 7.13 (d, $J = 8.0$ Hz, 2H), 6.97 (d, $J = 7.9$ Hz, 2H), 6.84 (d, $J = 8.1$ Hz, 2H), 5.65 (d, $J = 7.5$ Hz, 1H), 4.17 (t, $J = 8.0$ Hz, 1H), 3.97 (dd, $J = 11.0$, 11.0 Hz, 1H), 3.58 (dd, $J = 4.5$, 11.2 Hz, 1H), 2.39 (s, 3H), 2.30 (s, 3H), 2.02–1.89 (m, 1H), 0.81 ppm (d, $J = 7.0$ Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta = 142.8$, 137.5, 137.0, 136.8, 129.27, 128.9, 127.1, 126.9, 65.0, 61.4, 40.9, 21.4, 21.0, 14.5 ppm; the enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/2-propanol 97:3): flow rate = 1 mL min$^{-1}$; retention times: 126.7 (minor), 137.5 min (major).

***N*-[(1*S*,2*R*)-3-Hydroxy-2-methyl-1-phenylpropyl]-4-methylbenzenesulfonamide (29c)**: Prepared according to the general procedure by starting from propanal (0.11 mL, 1.5 mmol) and *N*-tosyl-phenylimine (**23c**) (129 mg, 0.5 mmol). The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate 80:20) and then disgregated with $Et_2O$ to give the title compound as a white solid. Yield: 77% (123 mg); m.p. 127–130 °C.; $[\alpha]_D^{20} = -82.2$ ($c = 1$ in $CH_2Cl_2$); $^1$H NMR (300 MHz, $CDCl_3$): $\delta = 7.52$ (d, $J = 8.3$ Hz, 2H), 7.18–

7.08 (m, 5H), 7.00–6.96 (m, 2H), 5.81 (s, 1H), 4.22 (m, 1H), 3.96 (dd, $J$= 3.1, 11.2 Hz, 1H), 3.59 (dd, $J$=4.6, 11,2 Hz, 1H), 2.38 (s, 3H), 1.98 (m, 1H), 0.82 ppm (d, $J$=7.0 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$= 142.9, 139.9, 137.3, 129.6, 129.2, 128.2, 127.1, 126.4, 64.9, 61.5, 40.9, 21.4, 14.5 ppm; the enantiomeric purity of the major diastereoisomer was determined by HPLC analysis (Daicel Chiralpak IA, hexane/2-propanol 95:5): flow rate = 0.8 mL min$^{-1}$; retention times: 36.7 (minor), 43.7 min (major).

***N*-[(1*S*,2*R*)-2-(Hydroxymethyl)-1-p-tolylbutyl]-4-methylbenzenesulfonamide (32a)**: Prepared according to the general procedure by starting from butanal (0.14 mL, 1.5 mmol) and *N*-tosyl-tolylimine (**23a**) (137 mg, 0.5 mmol). The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate 80:20) to give the title compound as a yellow oil. Yield: 77% (134 mg); $[\alpha]_D^{20}=-19.8$ ($c$= 0.5 in $CH_2Cl_2$); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$=7.54 (d, $J$=8.3 Hz, 2H), 7.13 (d, $J$=8.2 Hz, 2H), 6.97 (d, $J$=7.9 Hz, 2H), 6.87 (d, $J$=8.1 Hz, 2H), 5.81 (d, $J$=7.9 Hz, 1H), 4.35 (t, $J$=7.8, Hz, 1H), 3.93 (d, $J$=11.1 Hz, 1H), 3.72–3.63 (m, 1H), 2.39 (s, 3H), 2.30 (s, 3H), 1.66–1.53 (m, 1H), 1.44–1.18 (m, 2H), 0.88 ppm (t, $J$=7.4, 7.4 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$=142.8, 137.7, 137.4, 136.8, 129.2, 128.9, 127.1, 126.6, 61.2, 60.0, 47.6, 29.7, 21.4, 21.0, 11.6 ppm; the enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/2-propanol 95:5): flow rate = 0.8 mL min$^{-1}$; retention times: 51.5 (minor), 61.8 min (major).

***N*-[(1*S*,2*R*)-2-(Hydroxymethyl)-1-(4-methoxyphenyl)butyl]-4-methylbenzene sulfonamide (32b)**: Prepared according to the general procedure by starting from butanal (0.14 mL, 1.5 mmol) and *N*-tosyl-4-methoxyphenylimine (**23b**) (145 mg, 0.5 mmol). The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate 80:20) and then disgregated with $Et_2O$ to give the title compound as a white solid. Yield: 63% (114 mg); m.p. 117–121 °C; $[\alpha]_D^{20}=-54.8$ ($c$=1 in $CH_2Cl_2$); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$=7.53 (d, $J$=8.3 Hz, 2H), 7.13 (d, $J$=8.0 Hz, 2H), 6.91 (d, $J$=8.6 Hz, 2H), 6.68 (d, $J$=8.7 Hz, 2H), 5.97 (d, $J$=7.8 Hz, 1H), 4.33 (t, $J$=7.7, 7.7 Hz, 1H), 3.94 (d, $J$=11.19 Hz, 1H), 3.77 (s, 3H), 3.68 (d, $J$=8.0 Hz, 1H), 2.38 (s, 3H), 2.29 (s, 1H), 1.67–1.55 (m, 1H), 1.44–1.16 (m, 2H), 0.87 ppm (t, $J$=7.4, 7.4 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$=158.7, 142.8, 137.7, 132.5, 129.2, 127.9, 127.1, 113.6, 61.3, 59.8, 55.2, 47.6, 21.4, 21.0, 11.6 ppm; the enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak IA, hexane/2-propanol 95:5): flow rate = 0.75 mL min$^{-1}$; retention times: 79.6 (minor), 92.3 min (major).

***N*-[(1*S*,2*R*)-2-(Hydroxymethyl)-1-phenylbutyl]-4-methylbenzenesulfonamide (32c)**: Prepared according to the general procedure by starting from butanal (0.14 mL, 1.5 mmol) and *N*-tosyl-phenylimine (**23c**) (129 mg, 0.5 mmol). The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate 80:20) and then disgregated with $Et_2O$ to give the compound as a white solid. Yield: 68% (122 mg); m.p. 123–125 °C; $[\alpha]_D^{20}=-72.7$ ($c$=1 in $CH_2Cl_2$); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$=7.53 (d, $J$=8.3 Hz, 2H), 7.17–7.08 (m, 5H), 7.02–6.99 (m, 2H), 5.95 (d, $J$=8.07 Hz, 1H), 4.42 (t, $J$=7.7, 7.7 Hz, 1H), 3.91 (m, 1H), 3.38 (m, 1H), 2.38 (s, 3H), 1.69–1.59 (m, 1H), 1.49–1.21 (m, 2H), 0.89 ppm (t, $J$=7.4, 7.4 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$=142.8, 140.4, 137.7, 129.2, 128.3, 127.0, 126.7, 61.3, 60.2, 47.5, 21.4, 21.1, 11.6 ppm; the enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak IA, hexane/2-propanol 95:5): flow rate = 0.75 mL min$^{-1}$; retention times: 51.3 (minor), 57.7 min (major).

***N*-[(1*S*,2*R*)-2-(Hydroxymethyl)-1-*m*-tolylbutyl]-4-methylbenzenesulfonamide (32e)**: Prepared according to the general procedure by starting from butanal (0.14 mL, 1.5 mmol) and *N*-tosyl-3-methylphenylimine (**23e**) (137 mg, 0.5 mmol). The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate 80:20) to give the title compound as a yellow oil. Yield: 60% (104 mg); $[\alpha]_D^{20}=-39.8$ ($c$=1 in $CH_2Cl_2$); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$=7.51 (d, $J$=8.3 Hz, 2H), 7.13–7.01 (m, 3H), 6.94 (d, $J$=7.5 Hz, 1H), 6.83 (d, $J$= 7.6 Hz, 1H), 6.68 (s, 1H), 6.10 (d, $J$=8.1 Hz, 1H), 4.33 (t, $J$=7.9, 7.9 Hz, 1H), 3.93 (d, $J$=11.1 Hz, 1H), 3.68 (d, $J$=10.7 Hz, 1H), 2.51 (brs, 1H), 2.37(s, 3H), 2.17(s, 3H), 1.70–1.57 (m, 1H), 1.47–1.20 (m, 2H), 0.88 ppm (t, $J$=7.4, 7.4 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$=142.7, 140.1, 137.7, 129.1, 128.2, 127.7, 127.1, 123.8, 61.2, 60.2, 47.4, 21.4, 21.2, 21.0, 11.6 ppm; the enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak IA, hexane/2-propanol 98:2): flow rate = 0.7 mL min$^{-1}$; retention times: 91.1 (minor), and 98.8 min (major).

***N*-[(1*S*,2*R*)-1-(4-Chlorophenyl)-2-(hydroxymethyl)heptyl]-4-methylbenzene sulfonamide (34d)**: Prepared according to the general procedure by starting from heptanal (0.21 mL, 1.5 mmol) and *N*-tosyl-4-chlorophenylimine (**23d**) (147 mg, 0.5 mmol). The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate 80:20) and then disgregated with $Et_2O$ to give the compound as a white solid. Yield: 76% (161 mg); m.p. 120–124 °C; $[\alpha]_D^{20}=-58.9$ ($c$=1 in $CH_2Cl_2$); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$=7.54 (d, $J$=8.3 Hz, 2H), 7.13 (m, 4H), 7.01 (d, $J$=8.5 Hz, 2H), 6.39 (d, $J$=7.4 Hz, 1H), 4.40 (t, $J$= 7.0 Hz, 1H), 3.81 (d, $J$=11.2 Hz, 1H), 3.61 (m, 1H), 2.40 (s, 3H), 2.31 (m, 1H), 1.65 (m, 1H) 1.40–1.05 (m, 8H), 0.86 ppm (t, $J$=7.0 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$=143.1, 139.2, 137.7, 132.8, 129.3, 128.3, 127.0, 61.9, 60.1, 45.6, 31.8, 28.2, 26.7, 22.4, 21.4, 14.0 ppm; the enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/2-propanol 95:5): flow rate = 0.8 mL min$^{-1}$; retention times: 31.7 (minor), 49.1 min (major).

***N*-[(1*S*,2*R*)-2-(Hydroxymethyl)-3-methyl-1-*p*-tolylbutyl]-4-methylbenzene sulfonamide (35a)**: Prepared according to the general procedure by starting from isovaleraldehyde (0.16 mL, 1.5 mmol) and *N*-tosyl-tolylimine (**23a**) (137 mg, 0.5 mmol). The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate 80:20) and then disgregated with $Et_2O$ to give the title compound as a white solid. Yield: 76% (134 mg); m.p. 145–148 °C; $[\alpha]_D^{20}=-70.8$ ($c$=1 in $CH_2Cl_2$); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$=7.50 (d, $J$=8.2 Hz, 2H), 7.08 (d, $J$=8.1 Hz, 2H), 6.97–6.90 (m, 4H), 6.70–6.55 (brs, 1H), 4.60 (d, $J$= 6.8 Hz, 1H), 3.82–3.68 (m, 2H), 2.36 (s, 3H), 2.28 (s, 3H), 1.80–1.65 (m, 1H), 1.46–1.36 (m, 1H), 1.34–1.24 (brs, 1H), 0.92 ppm (dd, $J$=6.7, 20.5 Hz, 6H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$=142.6, 138.0, 137.7, 136.4, 129.0, 128.7, 127.0, 126.9, 60.3, 59.6, 53.5, 51.9, 25.7, 21.3, 20.9, 18.8 ppm; the enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak IA, hexane/2-propanol 95:5): flow rate = 0.5 mL min$^{-1}$; retention times: 50.1 (minor), 54.4 min (major).

***N*-[(1*S*,2*R*)-3-Hydroxy-2-methyl-1-*p*-tolylpropyl]-2-nitrobenzenesulfonamide (30a)**: Prepared according to the general procedure by starting from propanal (0.12 mL, 1.5 mmol) and *N*-*o*-nosyl-*p*-methyl-phenylimine (**24a**) (152 mg, 0.5 mmol). The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate 80:20) to give the title compound as a yellowish oil and as a diastereomeric mixture *syn*/*anti* in a ratio of 7:93. Yield: 61% (111 mg); spectroscopic data of the major *anti* diastereomer: $^1$H NMR (300 MHz, $CDCl_3$): $\delta$=7.76–7.67 (m, 2H), 7.62–7.53 (m, 1H), 7.48–7.40 (m, 1H) 6.98–6.83 (m, 4H), 6.62 (d, $J$=8.7 Hz, 1H), 4.49 (t, $J$=8.3 Hz, 1H), 4.00—3.88 (m, 1H), 3.74–3.62 (m, 1H), 2.22 (s, 3H), 2.08–1.90 (m, 2H), 0.95 ppm (d, $J$= 7.0, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$=137.2, 136.2, 134.7, 132.5, 132.2, 130.8, 130.6, 128.9, 126.8, 124.8, 64.5, 62.2, 40.7, 20.9, 14.6 ppm; the enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak IC, hexane/2-propanol 70:30): flow rate = 0.5 mL min$^{-1}$; retention times: 108.5 (minor), 116.5 min (major).

***N*-[(1*S*,2*R*)-3-Hydroxy-2-methyl-1-phenylpropyl]-4-nitrobenzenesulfonamide (31c)**: Prepared according to the general procedure by starting from propanal (0.12 mL, 1.5 mmol) and *N*-*p*-nosyl-phenylimine (**25c**) (145 mg, 0.5 mmol). The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate 80:20) to give the title compound as a white solid and as a diastereomeric mixture *syn*/*anti* in a ratio of 9:91. Yield: 59% (90 mg); spectroscopic data of the major *anti* diastereomer: $^1$H NMR (300 MHz, $CDCl_3$): $\delta$=8.12–8.05 (m, 2H), 7.75–7.69 (m, 2H), 7.19–7.10 (m, 3H), 7.04–6.98 (m, 2H), 4.43 (d, $J$=7.7 Hz, 1H), 3.93–3.83 (m, 1H), 3.70–3.62 (m, 1H), 2.05–1.95 (m, 1H), 0.91 ppm (d, $J$=7.0 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$= 149.5, 146.7, 139.3, 128.4, 128.1, 127.7, 127.1, 123.6, 65.4, 63.0, 40.3, 14.7 ppm; the enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak IC, hexane/2-propanol

80:20): flow rate = 0.5 mL min$^{-1}$; retention times: 34.4 (minor), 42.8 min (major).

***N*-[(1*S*,2*R*)-2-(Hydroxymethyl)-1-*p*-tolylbutyl]-2-nitrobenzenesulfonamide (33a)**: Prepared according to the general procedure by starting from butanal (0.2 mL, 1.5 mmol) and *N*-*o*-nosyl-*p*-methyl-phenylimine (**24a**) (152 mg, 0.5 mmol). The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate 80:20) to give the title compound as a yellowish oil and as a diastereomeric mixture *syn*/*anti* in a ratio of 7:93. Yield: 71% (134 mg); spectroscopic data of the major *anti* diastereomer: $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 7.71 (dd, $J$ = 7.9, 25.2 Hz, 2H), 7.55 (t, $J$ = 7.7 Hz, 1H), 7.40 (t, $J$ = 7.7 Hz, 1H), 6.99 (d, $J$ = 7.9 Hz, 2H), 6.95 (d, $J$ = 13.5 Hz, 1H), 6.87 (d, $J$ = 7.8 Hz, 2H), 4.72–4.64 (m, 1H), 3.98–3.82 (m, 1H), 3.80–3.69 (m, 1H), 1.86–1.79 (m, 1H), 1.72–1.61(m, 1H), 1.56 (s, 3H), 1.54–1.43 (m, 2H), 0.97 ppm (t, $J$ = 7.4 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 137.4, 137.0, 135.4, 132.8, 132.5, 131.1, 129.2, 127.2, 125.1, 61.7, 61.3, 47.6, 21.7, 21.3, 12.0 ppm; the enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak IC, hexane/2-propanol 80:20): flow rate = 0.5 mL min$^{-1}$; retention times: 112.2 (minor), 123.3 min (major).

***N*-[(1*S*,2*R*)-2-(Hydroxymethyl)-1-(4-methoxyphenyl)-3-methylbutyl]-4-nitrobenzene sulfonamide (36b)**: Prepared according to the general procedure by starting from isovaleraldehyde (0.16 mL, 1.5 mmol) and *N*-*p*-nosyl-4-methoxy-phenylimine (**25b**) (160 mg, 0.5 mmol). The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate 80:20) to give the title compound as a white solid and as a diastereomeric mixture *syn*/*anti* in a ratio of 1:99. Yield: 52% (106 mg); spectroscopic data of the major *anti* diastereomer: $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 8.12–8.02 (m, 2H), 7.74–7.64 (m, 2H), 6.99–6.87 (m, 2H), 6.68–6.56 (m, 2H), 4.81–4.74 (m, 1H), 3.87–3.78 (m, 2H), 3.73 (s, 3H), 1.90–177 (m, 1H), 1.47–1.35 (m, 1H), 1.06 (d, $J$ = 7.8 Hz, 3H), 0.94 ppm (d, $J$ = 6.8 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 158.9, 149.2, 147.1, 131.7, 128.1, 123.5, 113.6, 60.7, 60.0, 55.3, 51.6, 25.6, 21.2, 18.8 ppm; the enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak IC, hexane/2-propanol 90:10): flow rate = 0.8 mL min$^{-1}$; retention times: 57.8 (minor), 65.6 min (major).

**Deprotection and elaboration of the Mannich adducts**

**Preparation of 38**: Propanal (1.5 mmol, 3 equiv) was added to a solution of *N*-tosyl phenylimine (**23c**) (0.5 mmol, 1 equiv), *p*-nitrobenzoic acid (0.1 mmol, 20 mol%), and catalyst **7** (0.1 mmol, 20 mol%) in DMF (2 mL) at −60 °C. The resulting solution was stirred at −60 °C for 24 h. Then MeOH (2.5 mL), $KH_2PO_4$ (570 mg, 4.15 mmol), and $NaClO_2$ (338 mg, 3.15 mmol) were added. The reaction was allowed to reach 0 °C and after the injection of $H_2O_2$ (35% solution, 4.5 mL), the mixture was warmed up to RT and stirred for 2 h. The pH was adjusted to 3 by the addition of 1 M HCl and saturated $Na_2SO_3$ solution (10 mL) was added. The resulting mixture was extracted with $Et_2O$ (3 × 10 mL), the combined organic layers were washed with sat. NaCl solution (4 × 15 mL) and dried over $MgSO_4$. The organic layer was concentrated in vacuo to give the title crude compound, which was then purified by flash column chromatography on silica gel (eluent: $CH_2Cl_2$/MeOH 98:2). This yielded the protected derivative **37** as a white solid. Yield: 62% (100 mg); spectroscopic and physical properties were in agreement with those previously reported.[39c] Deprotection of the tosyl group was carried out by treatment of **36** with HCl at 100 °C; this yielded compound **38** in 95% yield.[39]

**Preparation of 39**: $K_2CO_3$ (277 mg, 2 mmol), PhSH (0.26 mL, 2.5 mmol), and DMSO (2 mol%) were added to a solution of Mannich adduct **31c** (diastereomeric ratio (d.r.) = 91:9, 143 mg, 0.5 mmol) in anhydrous $CH_3CN$ (1 mL) under a $N_2$ atmosphere. The mixture was stirred at room temperature for 24 h. The solvents were evaporated under reduced pressure and then $CH_2Cl_2$ (5 mL) and NaOH (1 M, 5 mL) were added to the resulting residue. The organic phase was separated, dried, and evaporated under reduced pressure. The crude product was purified by flash column chromatography ($CH_2Cl_2$ to $CH_2Cl_2$/$NH_3$ (7 N MeOH solution) 90:10) to give a colorless oil. Yield: 80% (66 mg); spectroscopic data of the major *anti* diastereomer: $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 7.40–7.21 (m, 5H), 3.80–3.58 (m, 3H), 2.58 (br s, 2H), 2.08–1.92 (m, 1H), 0.65 ppm (d, $J$ = 6.9 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 128.9, 127.5, 127.05, 126.5, 69.1, 40.2, 29.7, 15.1 ppm.

## Acknowledgements

This work was financially supported by The University of the Basque Country (UPV/EHU), and Ministerio de Educación y Ciencia (MEC, Grant CTQ2007-68095-C02, Spain). Predoctoral grants to I.O. (from GV) and I.V. (from UPV/EHU) are also acknowledged. We also thank SGIker (UPV/EHU) for NMR, HRMS, and computational facilities.

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Received: December 23, 2009
Published online: March 22, 2010

  