Tetrahedron 67 (2011) 4412–4416

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Development of an *N*-sulfinyl prolinamide for the asymmetric aldol reaction

MaryAnn T. Robak [a], Melissa A. Herbage [a], Jonathan A. Ellman [b,*]

[a] Department of Chemistry, University of California, Berkeley, CA 94720, USA
[b] Department of Chemistry, Yale University, New Haven, CT 06520, USA

ARTICLE INFO

Article history:
Received 11 January 2011
Received in revised form 9 March 2011
Accepted 11 March 2011
Available online 21 March 2011

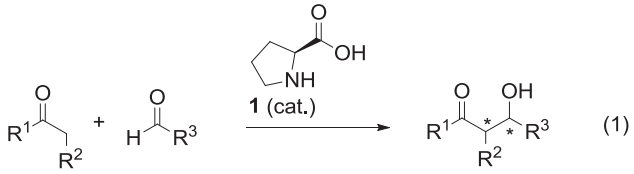
Keywords:
Asymmetric catalysis
Aldol reaction
Proline
tert-Butanesulfinamide
Organocatalysis

ABSTRACT

A new class of organocatalysts is reported that incorporates an *N*-sulfinyl amide in place of the carboxylic acid of proline to serve as a hydrogen bond donor, chiral directing group, and solubilizing element. The successful application of this type of catalyst to the asymmetric aldol reaction of acetone and aryl aldehydes, for which proline performs poorly, is also described.

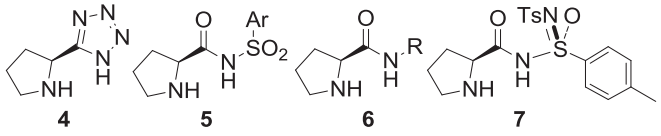
1. Introduction

The proline-catalyzed enantioselective intermolecular aldol reaction was first reported by List and co-workers in 2000, and since that time proline (**1**) has been utilized to efficiently catalyze many aldol reactions (Eq. 1).[1–4] This reaction, a prototypical example of enamine-based organocatalysis, proceeds via reversible condensation of the catalytic amine with a ketone to provide a nucleophilic enamine intermediate. In this reaction, the carboxylic acid functionality on proline was found to be important and is postulated to activate and orient the aldehyde acceptor via a hydrogen-bonding interaction.



(1)

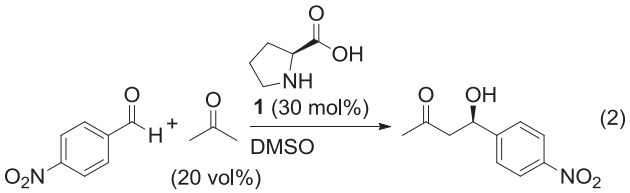
However, proline is not an effective catalyst for all aldol coupling partners. For example, high proline catalyst loading is required and moderate enantioselectivities are observed for acetone and aryl aldehyde substrate combinations (Eq. 2). Many researchers have therefore investigated the replacement of the carboxylic acid of proline (**1**) with other H-bond donors with the goal of improving catalyst solubility, activity, stability, and level of asymmetric induction (Fig. 1),[2,3] including achiral acid replacements, such as



4 **5** **6** **7**

Fig. 1. Selected proline derivatives used as organocatalysts for the aldol reaction.

tetrazole (**4**)[5–15] or sulfonyl amides (**5**).[4,9,16–20] The prolinamide scaffold (**6**) has also been explored, and while it is less acidic, also provides opportunity for incorporation of additional chiral centers as well as additional tethered hydrogen bond donors or amines.[21–40] Worch and Bolm recently detailed replacement of the carboxylic acid with a chiral sulfonimidamide (**7**), which represents the first example of a carboxylic acid derivative, that is, both chiral and acidic.[41] In their study of the aldol condensation of cyclohexanone with aromatic aldehydes, evaluation of each diastereomer of the catalyst revealed that for most substrates, the configuration of the stereogenic sulfur in the catalyst had only a minor impact on the enantiomeric purity of the products obtained.



(2)

2a **3a**: 68%, 76% *ee*

* Corresponding author. Tel.: +1 203 432 3647; e-mail address: jonathan.ellman@yale.edu (J.A. Ellman).

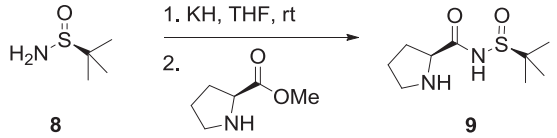
0040-4020/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2011.03.030

The utility of the *N*-sulfinyl group[42–45] as both a chiral directing group and acidifying element in hydrogen-bonding organocatalysts has been demonstrated by the successful application of *N*-sulfinyl ureas, initially in the addition of nitroalkanes to imines (the aza-Henry reaction),[46] and more recently the addition of thioacetic acid to nitroalkenes.[47] In these reactions, the sulfinyl N–H is postulated to activate the substrates by the formation of key hydrogen bonding interactions. The inductive electron-withdrawing effect of the sulfinyl group acidifies this N–H bond, which serves to modulate hydrogen bonding interactions. Additionally, close proximity of the stereogenic sulfur to the active site of the catalyst contributes to high levels of stereocontrol in these reactions (vide infra). Finally, the sulfinyl group enhances the solubility of the catalyst in organic solvents.

On the basis of the success of *N*-sulfinyl ureas in hydrogen-bonding organocatalysis, we sought to extend this concept to enamine-based organocatalysis. Specifically, we postulated that the incorporation of an *N*-sulfinyl amide in place of the carboxylic acid of proline would maintain the level of acidity required to act as an efficient hydrogen bond donor, while at the same time the chiral nature of the sulfinamide substituent could contribute to the achievement of high levels of stereocontrol in the aldol reaction.

2. Results and discussion

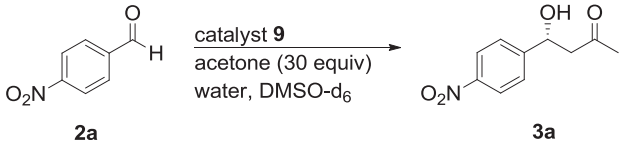
In order to test this hypothesis, *N*-prolyl sulfinamide **9** was first synthesized (Eq. 3). A simple procedure was developed whereby deprotonation of enantiomerically pure *tert*-butanesulfinamide **8** with KH followed by addition of inexpensive (*S*)-proline methyl ester provides catalyst **9** in 82% yield. A preliminary survey of solvents for the addition of acetone to 4-nitrobenzyaldehyde as catalyzed by **9** revealed that the highest enantioselectivities were obtained in DMSO. Therefore, optimization of the reaction parameters was undertaken with catalyst **9** in DMSO-d_6 (Table 1). Significantly, it was discovered that addition of a small amount of water to the reaction mixture was important both for reaction rate and selectivity (entries 1–5), while larger amounts of water were detrimental (entry 6). The effects of water on reaction rate observed in our studies are consistent with the complex role of water in the proline-mediated aldol reaction as described by Blackmond and co-workers.[48] The catalyst loading could be decreased at the expense of reaction rate (entries 7–9). The reaction was relatively independent of the amount of DMSO used, allowing the reaction to be conducted at higher concentrations (entries 8, 10, and 11). A direct correlation was observed between the reaction rate and the amount of acetone added (entries 10 vs 12).



(3)

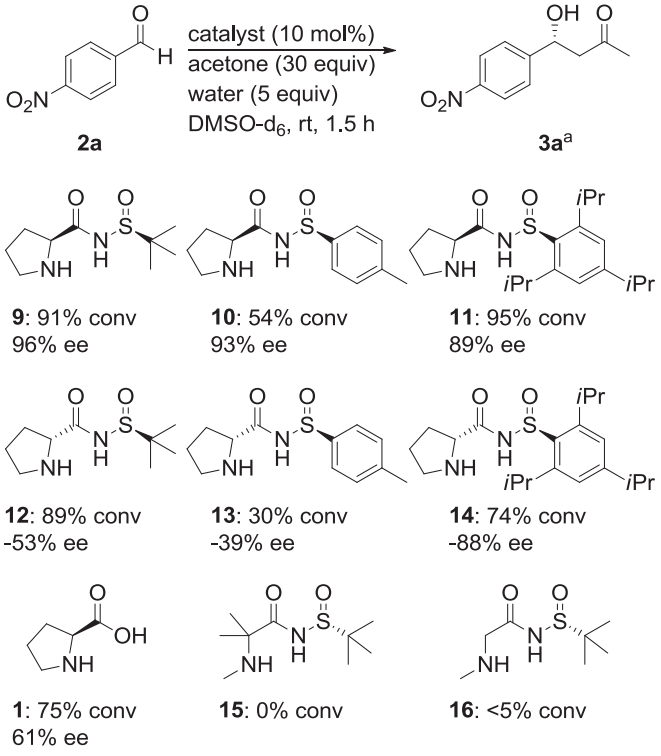
With optimal reaction conditions established, the performance of several different *N*-aminoacyl sulfinamide catalysts was evaluated (Scheme 1). For each sulfinamide input both diastereomers of the *N*-prolyl sulfinamide were prepared in order to systematically evaluate the effect of the sulfinyl substituent and stereocenter on the selectivity of the aldol reaction (see Experimental section for catalyst synthesis and analytical characterization). While a dramatic difference in enantioselectivity was observed for the *tert*-butanesulfinamide diastereomers **9** and **12**, very little effect of the sulfur stereocenter was observed for trisylsulfinamides **11** and **14**. Additionally, the reaction was significantly slower in the presence of the arenesulfinamide derivatives **10**, **13**, and **14**. Catalysts **15** and **16**, which incorporate achiral secondary amino acids, clearly demonstrate the importance of the proline scaffold for good reaction efficiency. This is consistent with the report by List and co-workers,[1] in which *N*-methyl valine provided poor conversion for this aldol reaction. Overall, catalyst **9** is superior to the other *N*-aminoacyl sulfinamide catalysts surveyed, providing the highest enantioselectivity with high conversion.

Table 1
Optimization of reaction conditions



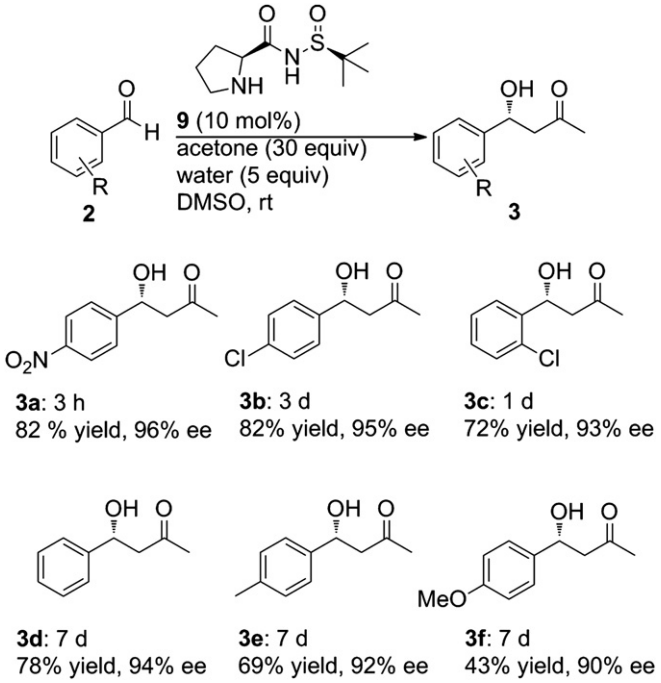
Entry	Equiv **9**	[**2a**] in DMSO (M)	Equiv water	Time[a] (h)	Conv[a] (%)	ee[b] (%)
1	0.2	0.125	0	>1.5[c]	45	89
2	0.2	0.125	1	0.5	89	92
3	0.2	0.125	2	0.5	88	94
4	0.2	0.125	5	0.5	86	96
5	0.2	0.125	10	0.5	83	96
6	0.2	0.125	30	>1.5[d]	66	93
7	0.1	0.125	5	4	88	95
8	0.05	0.125	5	48	87	96
9	0.025	0.125	5	>96[e]	77	94
10	0.05	0.25	5	48	92	95
11	0.05	0.5	5	48	91	94
12[f]	0.05	0.25	5	96	94	95

[a] Time required for >97% consumption of **2a** and conversion to **3a** with the time determined by ^{1}H NMR using trimethoxybenzene as an internal standard.
[b] Enantioselectivity was determined by chiral HPLC.
[c] Compound **2a** (29%) remains after 1.5 h.
[d] Compound **2a** (14%) remains after 1.5 h.
[e] Compound **2a** (18%) remains after 96 h.
[f] Acetone (15 equiv) used.



Scheme 1. Catalyst evaluation for enantioselective aldol reaction.

Next, the scope of the reaction was evaluated (Scheme 2). The aldol reaction of acetone with a variety of aryl aldehydes proceeded smoothly, providing the products with 90–96% ee. For aldehydes with electron-withdrawing substituents the reaction proceeded in high conversion within 3 days, and the aldol products were isolated in high yields (**3a**–**c**). However, in the case of the less reactive aldehydes much longer reaction times were necessary (1 week) to achieve reasonable conversion (**3d**–**f**).



Scheme 2. Substrate scope.

3. Conclusions

We have demonstrated the utility of the *N*-sulfinyl amide as a chiral carboxylic acid replacement in the proline scaffold for the highly enantioselective intermolecular aldol reaction. The dramatic difference in stereoselectivity between the diastereomeric *N*-*tert*-butanesulfinyl amides demonstrates that the chirality of the sulfinyl substituent in addition to its acidifying nature is important for reactivity.

4. Experimental

4.1. General methods

All reagents were obtained from commercial suppliers and used without further purification unless otherwise noted. Flash column chromatography was carried out either with Merck 60 230–240 mesh silica gel, or using a Biotage SP Flash Purification System (Biotage No. SP1-B1A) with Flash+cartridges (Biotage No. FPK0-1107-16046). ^{1}H and ^{13}C NMR chemical shifts are reported in parts per million relative to either the residual solvent peak (^{1}H, ^{13}C) or TMS (^{1}H) as an internal standard. IR spectra were recorded as thin films on a Nicolet Avatar 360 FTIR spectrometer equipped with an attenuated total reflectance accessory or as KBr pellets on a Nicolet MAGNA-IR 850 spectrometer, and only partial data are listed. Mass spectrometry (HRMS) was carried out by the University of California at Berkeley Mass Spectrometry Facility.

The syntheses of catalysts **9**–**14** were carried out under nitrogen in flame-dried glassware, using dry tetrahydrofuran (THF) that was passed through columns of activated alumina under nitrogen pressure immediately prior to use. Enantiomerically pure proline methyl esters were purchased as the corresponding hydrochloride salts and were isolated as the free bases by extraction with CH_2Cl_2 and aqueous K_2CO_3. The proline methyl esters contained up to 1 equiv of residual CH_2Cl_2 after concentration (as determined by ^{1}H NMR) and the mass of material used was adjusted in each case to account for the presence of the CH_2Cl_2. The aldol reactions were carried out using commercial solvents and reagents without further drying, and were set up in vials without any precautions to exclude air.

4.2. Catalyst synthesis

Compound **9**. A solution of (*S*)-*tert*-butanesulfinamide (1.21 g, 10.0 mmol) in THF (40 mL) was added to a stirred suspension of KH (0.420 g, 10.5 mmol) in THF (40 mL), resulting in the evolution of hydrogen gas as the sulfinamide was deprotonated. The reaction mixture was stirred for 3 h at rt, providing a white slurry. (L)-Proline methyl ester (10.8 mmol) was added via syringe, and the white slurry dissolved within 3 min to provide a clear solution. After 30 min, the reaction was quenched by addition of acetic acid (0.630 g, 10.5 mmol) and water (1 mL). The crude mixture was concentrated to remove the THF and then purified by reverse phase chromatography without buffers (Biotage 40+M C_{18} column, 1%–100% MeOH in H_2O). The product was concentrated to remove the water, then recrystallized from hot EtOAc in the presence of a trace amount of MeOH. The crystals were collected by vacuum filtration and rinsed with additional EtOAc and hexanes, to yield 1.79 g (82%) of **9** as a white crystalline solid, mp 149.5–150.0 °C (phase change at 139 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.19 (s, 9H), 1.86 (m, 2H), 2.03 (m, 1H), 2.25 (m, 1H), 3.24 (m, 1H), 3.33 (m, 1H), 4.16 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 22.1, 25.4, 30.9, 47.0, 53.6, 61.3, 178.0. IR (neat): 3646, 3451, 3095, 2659, 1586, 1537, 1367, 1369, 1321, 811, 546 cm^{-1}. Exact mass calcd for $C_9H_{18}N_2O_2S$ requires *m*/*z* 219.1162, found *m*/*z* 219.1165 (M+H$^+$, ESI).

Compound **10**. A solution of (*S*)-toluenesulfinamide (0.388 g, 2.50 mmol) in THF (10 mL) was added to a stirred suspension of KH (0.105 g, 2.63 mmol) in THF (10 mL) resulting in the evolution of hydrogen gas as the sulfinamide was deprotonated. The reaction mixture was stirred for 3 h at rt. (L)-Proline methyl ester (3.0 mmol) was added via syringe. After 30 min, the reaction was quenched by addition of acetic acid (0.158 g, 2.63 mmol) and water (8 mL). The crude mixture was concentrated to remove the THF, and the resulting white precipitate was collected by vacuum filtration and rinsed on the filter with small amounts of water. The crude product was recrystallized from EtOAc in the presence of trace amounts of MeOH. The solids were collected by vacuum filtration and rinsed with additional EtOAc to yield 0.30 g (48%) of **10** as a white crystalline solid, mp 126.0–127.0 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.80 (m, 1H), 1.90 (m, 1H), 2.08 (m, 1H), 2.26 (m, 1H), 2.39 (s, 3H), 3.23 (m, 1H), 3.35 (m, 1H), 4.21 (m, 1H), 7.27 (d, *J*=8.0 Hz, 2H), 7.61 (d, *J*=8.0 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 21.4, 25.6, 30.7, 47.1, 61.4, 125.0, 129.7, 141.3, 142.8, 177.5. Exact mass calcd for $C_{12}H_{16}N_2O_2SNa$ requires *m*/*z* 275.0825, found *m*/*z* 275.0832 (M+Na$^+$, ESI).

Compound **11**. A solution of (*S*)-(1,3,5)-triisopropylbenzenesulfinamide (0.669 g, 2.50 mmol) in THF (10 mL) was added to a flask containing a suspension of KH (0.105 g, 2.63 mmol), resulting in the evolution of hydrogen gas as the sulfinamide was deprotonated. The reaction mixture was stirred for 3 h at rt. (L)-Proline methyl ester (3.0 mmol) was added via syringe. After 30 min, the reaction was quenched by addition of acetic acid (0.160 g, 2.66 mmol) and water (8 mL), and the resulting mixture was

concentrated to remove the THF. The crude product was extracted into EtOAc, and the organic layer from the extraction was loaded onto a silica plug and side products were eluted with 100% EtOAc. The product was eluted using a mobile phase gradient of 20%–50% MeOH in EtOAc. Fractions containing the desired product were concentrated several times from EtOAc and the resulting residue was redissolved in warm EtOAc and filtered. The filtrate was concentrated, and then the white solid was recrystallized from 5 mL of hexanes. The solids were collected by vacuum filtration and rinsed with additional hexanes, to yield 0.66 g (73%) of **11** as a white powder, mp 170.5–172.0 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.23 (m, 12H), 1.35 (d, J=6.9 Hz, 6H), 1.83 (m, 2H), 2.07 (m, 1H), 2.26 (m, 2H), 2.88 (m, 1H), 3.15 (m, 1H), 3.22 (m, 1H), 3.98 (m, 1H), 4.05 (m, 2H), 7.08 (s, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 23.6, 24.0, 24.4, 25.7, 28.6, 30.8, 34.2, 46.9, 61.0, 122.8, 137.1, 148.7, 151.9, 176.3. Exact mass calcd for $C_{20}H_{32}N_2O_2SNa$ requires m/z 387.2077, found m/z 387.2087 (M+Na^+, ESI).

Compound **12**. A solution of (*S*)-*tert*-butanesulfinamide (0.303 g, 2.50 mmol) in THF (10 mL) was added to a stirred suspension of KH (0.105 g, 2.63 mmol) in THF (10 mL), resulting in the evolution of hydrogen gas as the sulfinamide was deprotonated. The reaction mixture was stirred for 3 h at rt, providing a white slurry. (D)-Proline methyl ester (3.0 mmol) was added via syringe, and the white slurry dissolved within 3 min to provide a clear solution. After 30 min, the reaction was quenched by addition of acetic acid (0.158 g, 2.63 mmol) and water (1 mL). The crude mixture was concentrated to remove most of the THF, and the resulting white precipitate was collected by vacuum filtration and then rinsed on the filter with small amounts of water and Et_2O. The crude product was dissolved in 100 mL of hot EtOAc, and the resulting solution was filtered twice to remove insoluble white solids. The filtrate was concentrated, then recrystallized from approximately 5 mL of EtOAc. The solids were collected by vacuum filtration and rinsed with additional EtOAc, to yield 0.22 g (41%) of **12** as a white powder, mp 149.5–150.0 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.25 (s, 9H), 1.75 (m, 2H), 1.96 (m, 1H), 2.19 (m, 1H), 2.95 (m, 1H), 3.09 (m, 1H) 3.89 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 22.1, 26.2, 30.8, 47.2, 56.1, 61.1, 176.5. IR (neat): 3651, 3368, 2981, 2888, 1566, 1298, 1270, 935, 599 cm^{-1}. Exact mass calcd for $C_9H_{18}N_2O_2S$ requires m/z 219.1162, found m/z 219.1162 (M+H^+, ESI).

Compound **13**. THF (10 mL) was added to a flask containing (*S*)-toluenesulfinamide (0.388 g, 2.50 mmol) and KH (0.100 g, 2.50 mmol), resulting in the evolution of hydrogen gas as the sulfinamide was deprotonated. The reaction mixture was stirred for 1.5 h at rt. (D)-Proline methyl ester (3.0 mmol) was added via syringe. After 2 h, the reaction was quenched by addition of acetic acid (0.150 g, 2.50 mmol), and resulting mixture was stirred for 20 min. The crude mixture in THF was loaded onto a silica plug and side products were eluted with 100% EtOAc. The mobile phase was switched to 50:40:10 EtOAc:MeOH:NH_4OH, resulting in rapid elution of the product. Fractions containing the desired product were concentrated several times from EtOAc, and then the white solid was dissolved in CH_2Cl_2 and filtered to remove a white solid byproduct. The filtrated was concentrated and then recrystallized from EtOAc. The solids were collected by vacuum filtration and rinsed with additional EtOAc, to yield 0.21 g (34%) of **13** as a white powder, mp 115.0–117.5 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.70 (m, 2H), 1.99 (m, 1H), 2.20 (m, 1H), 2.43 (s, 3H), 2.79 (m, 1H), 2.98 (m, 1H), 3.88 (m, 1H), 7.34 (d, J=8.1 Hz, 2H), 7.59 (d, J=8.1 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 21.4, 26.1, 30.7, 47.1, 61.0, 124.6, 130.0, 141.3, 142.2, 176.6. Exact mass calcd for $C_{12}H_{16}N_2O_2SNa$ requires m/z 275.0825, found m/z 275.0836 (M+Na^+, ESI).

Compound **14**. A solution of (*S*)-(1,3,5)-triisopropylbenzenesulfinamide (0.669 g, 2.50 mmol) in THF (10 mL) was added to a flask containing a suspension of KH (0.105 g, 2.63 mmol), resulting in the evolution of hydrogen gas as the sulfinamide was deprotonated. The reaction mixture was stirred for 3 h at rt. (D)-Proline methyl ester (3.0 mmol) was added via syringe. After 30 min, the reaction was quenched by addition of acetic acid (0.160 g, 2.66 mmol) and water (8 mL), and the resulting mixture was concentrated to remove the THF. The crude product was extracted into EtOAc, and the organic layer was dried (Na_2SO_4), filtered, and concentrated. The crude product was loaded onto a silica plug and side products were eluted with 100% EtOAc. The product was eluted using 50% MeOH in EtOAc. Fractions containing the desired product were concentrated several times from EtOAc, and then the material was redissolved in warm EtOAc and filtered. The filtrate was concentrated, and then the white solid was recrystallized from 1 mL of EtOAc. The solids were collected by vacuum filtration and rinsed with additional EtOAc (3×0.3 mL) to yield 0.52 g (57%) of **14** as a white crystalline solid, mp 152.5–154.0 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.25 (m, 12H), 1.35 (d, J=6.9 Hz, 6H), 1.60 (m, 1H), 1.69 (m, 1H), 1.90 (m, 1H), 2.17 (m, 1H), 2.76 (m, 1H), 2.91 (m, 1H), 2.98 (m, 1H), 3.90 (m, 1H), 3.97 (m, 2H), 7.12 (s, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 23.6, 24.0, 24.4, 26.0, 28.5, 30.5, 34.2, 47.1, 60.8, 123.1, 136.0, 148.7, 152.8, 176.1. Exact mass calcd for $C_{20}H_{32}N_2O_2SNa$ requires m/z 387.2077, found m/z 387.2086 (M+Na^+, ESI).

4.3. Representative procedure for catalyst screen (Scheme 1)

A reaction vial was equipped with a stir bar and charged with catalyst **9** (4.4 mg, 0.020 mmol, 0.10 equiv), acetone (0.44 mL, 6.0 mmol, 30 equiv), water (18 μL, 1.0 mmol, 5 equiv), and DMSO-d_6 (0.40 mL). After stirring for 15 min, a freshly prepared stock solution (0.40 mL) containing 4-nitrobenzaldehyde (0.20 mmol, 1.0 equiv) and 1,3,5-trimethoxybenzene (0.067 mmol, 0.33 equiv) was added, and the vial was sealed with a cap. The resulting mixture was stirred for 90 min, and then a 0.8 mL aliquot was transferred to an NMR tube and analyzed by ^{1}H NMR. The conversion to product was determined to be 91% by integration of the product peak at 5.2 ppm relative to the trimethoxybenzene peak at 6.1 ppm. No remaining aldehyde was observed. A second aliquot of the reaction mixture (approx. 100 μL) was diluted with 1 mL of EtOAc and washed with 1 mL of water. The organic layer was filtered through a plug of silica, eluting with EtOAc and then concentrated. The ee of this sample was determined to be 96% by chiral HPLC analysis (Chiralpak AS-H, hexanes/^{i}PrOH 70/30, 1 mL min^{-1}): t_R (major)= 12.6 min, t_R (minor)=16.3 min.

4.4. General procedure for the preparation of products listed in Scheme 2

The aldehyde (1.0 mmol) was weighed into a reaction vial. A freshly prepared stock solution containing catalyst **9** (0.20 mmol), acetone (30.0 mmol), water (5.0 mmol), and DMSO (4.0 mL) were added by mass, and then the vial was sealed with an airtight cap. The mixture was stirred for the indicated amount of time. The reaction mixture was diluted with EtOAc (40 mL), washed with water (10 mL) and brine (10 mL), and then dried over Na_2SO_4, filtered, and concentrated. The product was purified by silica gel chromatography (EtOAc/Hexanes).

The ee of each product was determined by chiral HPLC analysis. Authentic racemic standards for the HPLC analysis were synthesized using pyrrolidine as a catalyst according to a literature procedure.[49]

Compound **3a**: The general procedure was followed using 4-nitrobenzaldehyde. After 3 h, 0.17 g (82%) of the desired product was isolated. The ee of this sample was determined to be 96% by chiral HPLC analysis (Chiralpak AS-H, hexanes/^{i}PrOH 70/30, 1 mL min^{-1}): t_R (major)=11.7 min, t_R (minor)=15.3 min. The ^{1}H NMR is consistent with literature reports.[22]

Compound **3b**: The general procedure was followed using 4-chlorobenzaldehyde. After 3 days, 0.17 g (82%) of the desired product was isolated. The ee of this sample was determined to be 95% by chiral HPLC analysis (Chiralpak AS-H, hexanes/^{i}PrOH 90/10, 1 mL min^{-1}): t_R (major)=14.1 min, t_R (minor)=18.4 min. The ^{1}H NMR is consistent with literature reports.[22]

Compound **3c**: The general procedure was followed using 2-chlorobenzaldehyde. After 1 day, 0.14 g (73%) of the desired product was isolated. The ee of this sample was determined to be 93% by chiral HPLC analysis (Chiralpak AS-H, hexanes/^{i}PrOH 90/10, 1 mL min^{-1}): t_R (minor)=10.4 min, t_R (major)=13.9 min. The ^{1}H NMR is consistent with literature reports.[22]

Compound **3d**: The general procedure was followed using benzaldehyde. After 7 days, 0.13 g (78%) of the desired product was isolated. The ee of this sample was determined to be 94% by chiral HPLC analysis (Chiralpak AS-H, hexanes/^{i}PrOH 90/10, 1 mL min^{-1}): t_R (major)=14.4 min, t_R (minor)=16.9 min. The ^{1}H NMR is consistent with literature reports.[22]

Compound **3e**: The general procedure was followed using 4-tolualdehyde. After 7 days, 0.12 g (69%) of the desired product was isolated. The ee of this sample was determined to be 92% by chiral HPLC analysis (Chiralpak AS-H, hexanes/^{i}PrOH 90/10, 1 mL min^{-1}): t_R (major)=13.4 min, t_R (major)=17.0 min. The ^{1}H NMR is consistent with literature reports.[22]

Compound **3f**: The general procedure was followed using 4-methoxybenzaldehyde. After 7 days, 0.082 g (43%) of the desired product was isolated. The ee of this sample was determined to be 90% by chiral HPLC analysis (Chiralpak AS-H, hexanes/^{i}PrOH 90/10, 1 mL min^{-1}): t_R (minor)=31.0 min, t_R (major)=35.8 min. The ^{1}H NMR is consistent with literature reports.[50]

Acknowledgements

We gratefully acknowledge the National Science Foundation (CHE-1049571) for support of this work. M. T. R. thanks Eli Lilly for a graduate fellowship.

References and notes

1. List, B.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396.
2. Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471–5569.
3. Trost, B. M.; Brindle, C. S. *Chem. Soc. Rev.* **2010**, *39*, 1600–1632.
4. Yang, H.; Carter, R. G. *Synlett* **2010**, 2827–2838 2010(EFirst).
5. Hartikka, A.; Arvidsson, P. I. *Tetrahedron: Asymmetry* **2004**, *15*, 1831–1834.
6. Thayumanavan, R.; Tanaka, F.; Barbas, C. F., III. *Org. Lett.* **2004**, *6*, 3541–3544.
7. Torii, H.; Nakadai, M.; Ishihara, K.; Saito, S.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 1983–1986.
8. Arno, M.; Zaragoza, R. J.; Domingo, L. R. *Tetrahedron: Asymmetry* **2005**, *16*, 2764–2770.
9. Cobb, A. J. A.; Shaw, D. M.; Longbottom, D. A.; Gold, J. B.; Ley, S. V. *Org. Biomol. Chem.* **2005**, *3*, 84–96.
10. Hartikka, A.; Arvidsson, P. I. *Eur. J. Org. Chem.* **2005**, *20*, 4287–4295.
11. Suri, J. T.; Ramachary, D. B.; Barbas, C. F., III. *Org. Lett.* **2005**, *7*, 1383–1385.
12. Samanta, S.; Zhao, C.-G. *Tetrahedron Lett.* **2006**, *47*, 3383–3386.
13. Tong, S.-T.; Harris, P. W. R.; Barker, D.; Brimble, M. A. *Eur. J. Org. Chem.* **2008**, *1*, 164–170.
14. Odedra, A.; Seeberger, P. H. *Angew. Chem., Int. Ed.* **2009**, *48*, 2699–2702.
15. Xue, F.; Zhang, S.; Liu, L.; Duan, W.; Wang, W. *Chem.—Asian J.* **2009**, *4*, 1664–1667.
16. Berkessel, A.; Koch, B.; Lex, J. *Adv. Synth. Catal.* **2004**, *346*, 1141–1146.
17. Bellis, E.; Vasilatou, K.; Kokotos, G. *Synthesis* **2005**, *14*, 2407–2413.
18. Maria, M.; Toma, S.; Berkessel, A.; Koch, B. *Lett. Org. Chem.* **2006**, *3*, 437–441.
19. Wu, Y.; Zhang, Y.; Yu, M.; Zhao, G.; Wang, S. *Org. Lett.* **2006**, *8*, 4417–4420.
20. Yang, H.; Carter, R. G. *Org. Lett.* **2008**, *10*, 4649–4652.
21. Martin, H. J.; List, B. *Synlett* **2003**, *12*, 1901–1902.
22. Tang, Z.; Jiang, F.; Yu, L.-T.; Cui, X.; Gong, L.-Z.; Qiao, A.; Jiang, Y.-Z.; Wu, Y.-D. *J. Am. Chem. Soc.* **2003**, *125*, 5262–5263.
23. Tang, Z.; Jiang, F.; Cui, X.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z.; Wu, Y.-D. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5755–5760.
24. Chimni, S. S.; Mahajan, D.; Babu, V. V. S. *Tetrahedron Lett.* **2005**, *46*, 5617–5619.
25. Samanta, S.; Liu, J.; Dodda, R.; Zhao, C.-G. *Org. Lett.* **2005**, *7*, 5321–5323.
26. Tang, Z.; Yang, Z.-H.; Chen, X.-H.; Cun, L.-F.; Mi, A.-Q.; Jiang, Y.-Z.; Gong, L.-Z. *J. Am. Chem. Soc.* **2005**, *127*, 9285–9289.
27. Chen, J.-R.; Li, X.-Y.; Xing, X.-N.; Xiao, W.-J. *J. Org. Chem.* **2006**, *71*, 8198–8202.
28. Chimni, S. S.; Mahajan, D. *Tetrahedron: Asymmetry* **2006**, *17*, 2108–2119.
29. Guillena, G.; Hita, M. d. C.; Najera, C. *Tetrahedron: Asymmetry* **2006**, *17*, 1493–1497.
30. Guizzetti, S.; Benaglia, M.; Pignataro, L.; Puglisi, A. *Tetrahedron: Asymmetry* **2006**, *17*, 2754–2760.
31. Jiang, M.; Zhu, S.-F.; Yang, Y.; Gong, L.-Z.; Zhou, X.-G.; Zhou, Q.-L. *Tetrahedron: Asymmetry* **2006**, *17*, 384–387.
32. Raj, M.; Vishnumaya, V.; Ginotra, S. K.; Singh, V. K. *Org. Lett.* **2006**, *8*, 4097–4099.
33. Tsogoeva, S. B.; Jagtap, S. B.; Ardemasova, Z. A. *Tetrahedron: Asymmetry* **2006**, *17*, 989–992.
34. Puleo, G. L.; Masi, M.; Iuliano, A. *Tetrahedron: Asymmetry* **2007**, *18*, 1364–1375.
35. Russo, A.; Botta, G.; Lattanzi, A. *Tetrahedron* **2007**, *63*, 11886–11892.
36. Chen, F.; Huang, S.; Zhang, H.; Liu, F.; Peng, Y. *Tetrahedron* **2008**, *64*, 9585–9591.
37. Chen, J.-R.; An, X.-L.; Zhu, X.-Y.; Wang, X.-F.; Xiao, W.-J. *J. Org. Chem.* **2008**, *73*, 6006–6009.
38. Sato, K.; Kuriyama, M.; Shimazawa, R.; Morimoto, T.; Kakiuchi, K.; Shirai, R. *Tetrahedron Lett.* **2008**, *49*, 2402–2406.
39. Chandrasekhar, S.; Johny, K.; Reddy, C. R. *Tetrahedron: Asymmetry* **2009**, *20*, 1742–1745.
40. Jia, Y.-N.; Wu, F.-C.; Ma, X.; Zhu, G.-J.; Da, C.-S. *Tetrahedron Lett.* **2009**, *50*, 3059–3062.
41. Worch, C.; Bolm, C. *Synlett* **2009**, *15*, 2425–2428.
42. Ferreira, F.; Botuha, C.; Chemla, F.; Perez-Luna, A. *Chem. Soc. Rev.* **2009**, *38*, 1162–1186.
43. Morton, D.; Stockman, R. A. *Tetrahedron* **2006**, *62*, 8869–8905.
44. Robak, M. T.; Herbage, M. A.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 3600–3740.
45. Zhou, P.; Chen, B.-C.; Davis, F. A. *Tetrahedron* **2004**, *60*, 8003–8030.
46. Robak, M. T.; Trincado, M.; Ellman, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 15110–15111.
47. Kimmel, K. L.; Robak, M. T.; Ellman, J. A. *J. Am. Chem. Soc.* **2009**, *131*, 8754–8755.
48. Zotova, N.; Franzke, A.; Armstrong, A.; Blackmond, D. G. *J. Am. Chem. Soc.* **2007**, *129*, 15100–15101.
49. Chimni, S. S.; Mahajan, D. *Tetrahedron* **2005**, *61*, 5019–5025.
50. Zhou, Y.; Shan, Z. *Tetrahedron: Asymmetry* **2006**, *17*, 1671–1677.