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Graphical Abstract

Prolinal dithioacetals: Highly efficient organocatalysts for the direct nitro-Michael additions in both organic and aqueous Media

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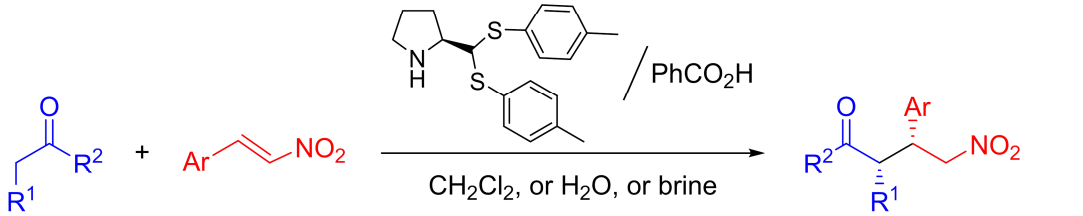

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Prolinal dithioacetals: Highly efficient organocatalysts for the direct nitro-Michael additions in both organic and aqueous media

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ABSTRACT

Some novel prolinal dithioacetal derivatives have been synthesized and applied as the organocatalysts for the direct Michael addition of ketones and aldehydes to nitroalkenes. High enantioselectivities and diastereoselectivities have been obtained in both organic and aqueous media (dichloromethane, water, or brine).

1. Introduction

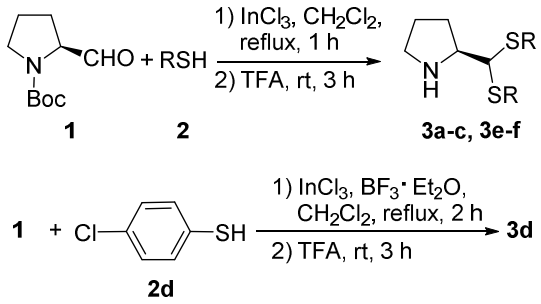
The Michael addition reaction is arguably one of the most convenient and powerful methods for building new carbon-carbon bonds.[1] Since List[2] and Barbas[3] reported the first examples of the amine-catalyzed intermolecular Michael addition of ketones and aldehydes to nitroalkenes (the nitro-Michael reaction), numerous organocatalysts have been reported in the last sixteen years for the enantioselective nitro-Michael reactions and excellent stereoselectivities have been achieved in many cases.[4,5] In recent years, conducting traditional organic reactions in aqueous media has been an important topic in organic research due to the green nature of water as a solvent and its dramatic solvent effects on organic reactions.[6] Not surprisingly, some organocatalytic reactions have also been realized either in water or on water.[6c,e] Nevertheless, despite the fact that numerous organocatalysts have been developed for the asymmetric nitro-Michael reaction between aldehydes and ketones to nitroalkenes, catalytic systems that can operate in aqueous media are relatively few.[7,8] Apparently, finding novel catalysts that can operate in aqueous media is still warranted. Our group is interested in developing novel catalysts for the nitro-Michael reaction.[9] In this regard, a few years ago we briefly reported that prolinal dithioacetal derivatives[10] are highly stereoselective catalysts for the nitro-Michael reaction of aldehydes and ketones in organic solvents.[9a] Recently we found that these catalysts could also catalyze the nitro-Michael reaction in water and brine with high enantio- and diastereoselectivities. Herein we wish to report a detailed study of the nitro-Michael reaction using these derivatives as the catalysts in both organic and aqueous media.

2. Results and Discussion

We are interested in using prolinal dithioacetals (**3**, Scheme 1) as potential organocatalysts for the direct nitro-Michael reaction because the formation of the dithioacetal functional group is much easier than that of C-C bonds and there are many different thiol structures available.[11] These features make the modification and fine-tuning the catalyst structure much easier. Indeed, most of the prolinal dithioacetal catalysts used in the current study were easily synthesized in high yields using a one-pot two-step reaction between the commercially available (*S*)-*N*-Boc-prolinal (**1**) and the corresponding thiols (**2**) using indium(III) chloride as the catalyst (Scheme 1).[9a,10] Nonetheless, catalyst **3d** derived from 4-chlorobenzenethiol (**2d**) needed boron trifluoride diethyl etherate as an additional catalyst for the synthesis, and it was obtained also in a much lower yield (68%, Scheme 1). All of these catalysts were found to be very stable under our reaction conditions.

With these catalysts in hand, we initially screened them in the direct nitro-Michael reaction in CH_2Cl_2 at rt with benzoic acid as the cocatalyt, using cyclohexanone (**4a**) and *trans*-β-nitrostyrene (**5a**) as the model substrates. The results are collected in Table 1. As the results in Table 1 show, with a 10 mol % loading of the benzenethiol-derived catalyst **3a**, the desired *syn* nitro-Michael adduct **6a** was obtained in 81% yield, 97:3 dr, and 97% ee in 29 h (entry 1). With the 4-methylbenzenethiol-derived catalyst **3b**, a slightly improved yield (88%), dr (99:1), and ee value (>99%) of **6a** was obtained (entry 2). Excellent results were also obtained with catalysts **3c** and **3d**, derived from 4-methoxybenzenethiol, and 4-chlorobenzenethiol, respectively (entries 3 and 4). When

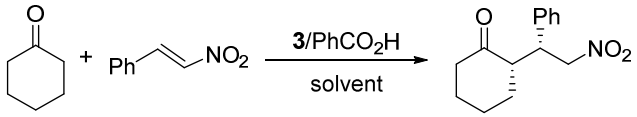
the thioacetal moiety in the catalyst contains two sterically demanding beneficial effects on both the reactivity and stereoselectivity of the reaction, but it is not essential. Next, using the best catalyst **3b**, some common



3a: R = C_6H_5-, yield = 94%;
3b: R = 4-MeC_6H_4-, yield = 93%;
3c: R = 4-$MeOC_6H_4$-, yield = 82%;
3d: R = 4-ClC_6H_4- ; yield = 68%
3e: R = 2,6-$Me_2C_6H_3$-; yield = 91%;
3f: R = *t*-Bu; yield = 88%.

Scheme 1. Synthesis of the prolinal dithioacetal catalysts

Table 1. Catalyst screening and reaction condition optimizations[a]

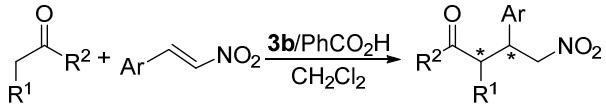


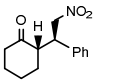
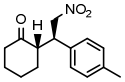
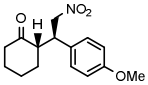
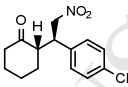
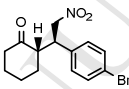
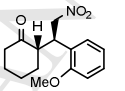
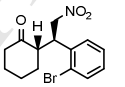
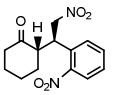
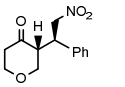
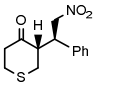
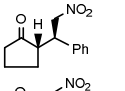
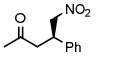
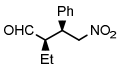
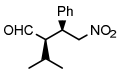
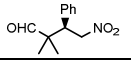
Entry	Catalyst	Solvent	Time (h)	Yield (%)[b]	dr[c] (*syn*/*anti*)	ee (%)[d]
1	**3a**	CH_2Cl_2	29	81	97:3	97
2	**3b**	CH_2Cl_2	28	88	99:1	>99
3	**3c**	CH_2Cl_2	28	81	98:2	97
4	**3d**	CH_2Cl_2	30	82	98:2	98
5	**3e**	CH_2Cl_2	30	85	97:3	95
6	**3f**	CH_2Cl_2	40	75	95:5	80
7[e]	**3b**	CH_2Cl_2	40	76	96:4	96
8	**3b**	$CHCl_3$	30	80	98:2	95
9	**3b**	DMF	33	75	94:6	96
10	**3b**	hexane	30	81	96:4	97
11	**3b**	toluene	29	78	97:3	97
12[f]	**3b**	brine	31	79	98:2	98
13[f,g]	**3b**	water	26	90	97:3	98

[a]Unless otherwise specified, all the reactions were carried out with cyclohexanone (**4a**, 0.30 mmol), *trans*-β-nitrostyrene (**5a**, 0.10 mmol), catalyst **3** (0.01 mmol, 10 mol %), and benzoic acid (0.01 mmol, 10 mol %) in the specified solvent (0.5 mL) at room temperature. [b]Yield of the isolated product after column chromatography. [c]Determined by ^{1}H NMR analysis of the crude product. [d]Value of the major diastereomer was determined by HPLC analysis on a Chiralpak AD-H column. Absolute configuration was determined by comparison of the measured optical rotation with the reported data.[12] [e]Without benzoic acid. [f]Reaction was conducted in 1.0 mL of solvent. [g]Reaction was carried out at 5 °C.

2,6-dimethylphenyl groups (**3e**), the stereoselectivities of the reaction dropped slightly (entry 5). In contrast, an alkylthiol-derived catalyst **3f** gave a much lower ee value of the product (80%), although the diastereoselectivity was only slightly lower than the other arylthiol derivatives (entry 6). With the best catalyst **3b** (entry 2), we found that slightly lower yield, dr, and ee value of **6a** were obtained without adding benzoic acid as the cocatalyst (entry 7 vs. entry 2). Thus, benzoic acid has some

Table 2. Asymmetric Michael addition ketones and aldehydes to *trans*-β-nitrostyrenes in CH_2Cl_2[a]



Entry	Product		Time (h)	Yield (%)[b]	dr[c] (*syn*/*anti*)	ee (%)[d]
1		**6a**	28	88	99:1	>99
2		**6b**	33	90	99:1	99
3		**6c**	36	79	>99:1	97
4		**6d**	20	86	99:1	99
5		**6e**	20	90	99:1	99
6[e]		**6f**	38	77	>99:1	97
7		**6g**	25	81	99:1	97
8		**6h**	30	85	97:3	95
9		**6i**	27	79	99:1	96
10		**6j**	29	76	98:2	95
11		**6k**	26	80	90:10[f]	98
12[g]		**6l**	40	78	---	50
13[h]		**6m**	46	70	99:1	99
14[h,i]		**6n**	59	70	96:4	85
15[h,i]		**6o**	72	60	---	76

[a]Unless otherwise specified, all the reactions were carried out with **4** (0.30 mmol), *trans*-β-nitrostyrene **5** (0.10 mmol), catalyst **3b** (0.01 mmol, 10 mol %), and benzoic acid (0.01 mmol) in CH_2Cl_2 (0.5 mL) at room temperature. [b]Yield of the isolated product after column chromatography. [c]Determined by ^{1}H NMR analysis of the crude product. [d]Value of the major diastereomer; unless otherwise indicated, the ee value was determined by HPLC analysis on a ChiralPak AD-H column. Absolute configuration was determined by comparison of the measured optical rotation with the reported data.[3b,12,14] [e]On a ChiralPak AS column. [f]The ee value of the minor diastereomer was >99% ee. [g]The reaction was carried out at -25 °C. [h]The reaction was carried out at 0 °C without adding benzoic acid. [i]The reaction was conducted with 0.02 mmol (20 mol %) catalyst.

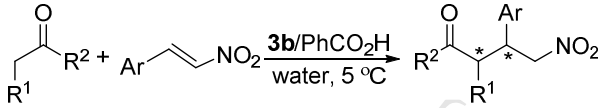
organic solvents were screened, and it were found slightly worse results were obtained in $CHCl_3$ (entry 8), DMF (entry 9), hexane (entry 10), and toluene (entry 11). Therefore, CH_2Cl_2 was identified as the best organic solvent for this reaction.

Recently there has been substantial interest in conducting the direct nitro-Michael reactions in water and brine,[7,8] since these two solvents are both cheap, green, and renewable.[6] We also evaluated catalyst **3b** in these two solvents. As the results in Table 1 show, when the reaction of **4a** and **5a** was conducted in brine (saturated NaCl solution in water) at rt, the desired product **6a** was obtained in 79% yield with an ee value of 98% and a dr of 98:2 (entry 12). A slightly lower ee value (92% ee) of **6a** was obtained when water was used as the solvent under similar conditions; Nonetheless, when the reaction was carried out at 5 °C, **6a** was obtained in 90% yield with an ee value of 98% and a dr of 97:3 (entry 13). We speculate that these observations are due to the slight differences of the catalyst conformation in these two solvents. Thus, both water and brine are almost equally good solvents as CH_2Cl_2 for this reaction, except that the reaction using water as solvent has to be carried out at subambient temperature.

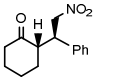
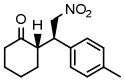
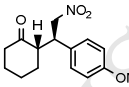
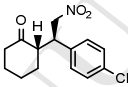
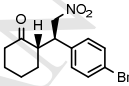
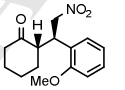
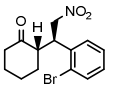
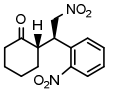
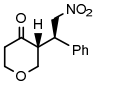
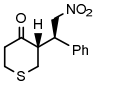
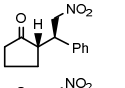
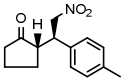
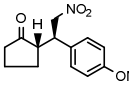
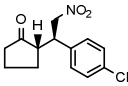
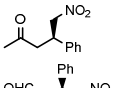
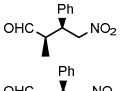
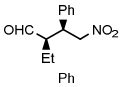
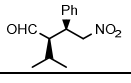
The scope of this reaction were initially studied in the best organic solvent (CH_2Cl_2). The results are presented in Table 2. As the data in Table 2 show, besides *trans*-β-nitrostyrene (**5a**, entry 1), substituted *trans*-β-nitrostyrenes also reacted with cyclohexanone under the optimized conditions to yield the desired *syn* nitro-Michael adducts in high yields and excellent diastereo- and enantioselectivities (**6b**-**h**, entries 2-8). Neither the electronic nature of the *para*-substituent (entries 1-5) nor the position of the substituent on the phenyl ring (entries 6-8) has any meaningful effects on the reactivity or the stereoselectivities of the reaction. Nevertheless, our attempt to react an aliphatic nitroalkene (*trans*-1-nitroprop-1-ene) with cyclohexanone failed to produce any desired product under the optimized conditions (data not shown). Good product yields and high stereoselectivities were obtained for the products of other cyclic ketones, such as 4-oxacyclohexanone (**6i**, entry 9), 4-thiacyclohexanone (**6j**, entry 10), and cyclopentanone (**6k**, entry 11). In contrast, acetone appears to be a more challenging substrate for this reaction in terms of stereoselectivity. After careful optimizations, an ee value of only 50% was obtained for the product **6l** at -25 °C (entry 12). In addition to ketones, aldehydes may also be applied in this reaction. Nonetheless, in the case of aldehyde substrates, it was found that adding benzoic acid actually slowed down the reaction and, therefore, these reactions were carried out without benzoic acid. Under these new conditions, the Michael addition product of butanal could be obtained in 99% ee with a dr of 99:1 for the major *syn* product **6m** (entry 13). However, with the increase of the steric hindrance next to the aldehyde group, the product ee value decreases. For examples, the best results of the Michael addition of 3-methylbutanal and 2-methylpropanal to *trans*-β-nitrostyrene were achieved only when the reactions were carried out 0 °C. Under these optimized conditions, the ee value of the Michael adduct of 3-methylbutanal **6n** was only 85% (entry 14) and that of the even more sterically demanding 2-methylpropanal (**6o**) was only 76% (entry 15). In addition, these aldehydes are also much less reactive and the catalyst loading has to be increased (entry 15). It should be pointed out that, with the same catalyst, opposite enantiomers of the *syn* diastereomers were obtained for cyclic ketones and aldehydes. Similar phenomenon has been observed before.[13]

Next the same nitro-Michael reactions were conducted using water or brine as the solvent under their respective optimized conditions (cf. Table 1). As the results in Tables 3 and 4 show, with a few exceptions, catalyst **3b** yields very similar results in terms of yields, diastereoselectivities, and ee values in these two green solvents as compared with those obtained in CH_2Cl_2.

Table 3. Asymmetric Michael addition of ketones and aldehydes to *trans*-β-nitrostyrenes in water[a]

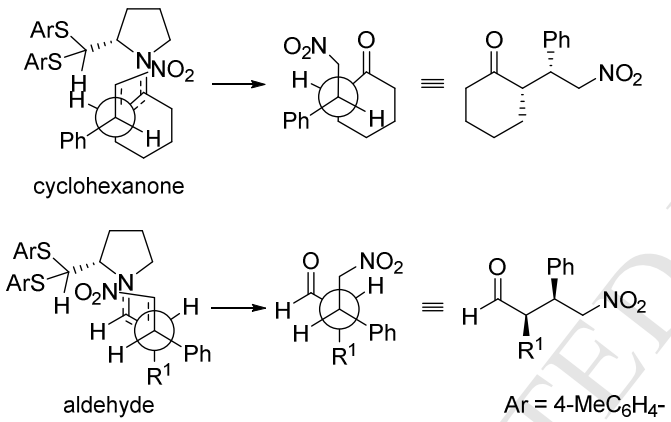


4 **5** **6**

Entry	Product		Time (h)	Yield (%)[b]	dr[c] (*syn*/*anti*)	ee (%)[d]
1		**6a**	26	90	97:3	98
2		**6b**	30	89	97:3	97
3		**6c**	33	82	97:3	95
4		**6d**	24	88	98:2	97
5		**6e**	27	79	94:6	97
6[e]		**6f**	34	82	98:2	96
7		**6g**	26	81	95:5	95
8		**6h**	25	83	98:2	97
9		**6i**	32	80	97:3	93
10		**6j**	34	78	97:3	95
11		**6k**	27	78	84:16	96
12		**6p**	36	65	90:10	97
13		**6q**	38	60	89:11	95
14		**6r**	31	69	88:12	98
15		**6l**	16	75	---	47
16[f,g]		**6s**	40	80	88:12	81
17[g]		**6m**	42	75	90:10	80
18[g,h]		**6n**	60	71	92:8	82

[a]Unless otherwise specified, all the reactions were carried out with **4** (0.30 mmol), *trans*-β-nitrostyrenes **5** (0.10 mmol), catalyst **3b** (0.01 mmol, 10 mol %), and benzoic acid (0.01 mmol) in water (1.0 mL) at 5 °C. [b]Yield of the isolated product after column chromatography. [c]Determined by ^{1}H NMR analysis of the crude product. [d]Value of the major diastereomer, unless otherwise indicated, was determined by HPLC analysis on a ChiralPak AD-H column. [e]On a ChiralPak AS column. [f]On a ChiralCel OD-H column. [g]The reaction was carried out without adding benzoic acid. [h]The reaction was conducted with 0.02 mmol (20 mol %) catalyst.

The formation of opposite enantiomers of the *syn* diastereomers in the nitro-Michael addition of ketones vs. aldehydes to *trans*-β-nitrostyrenes may be explained by the different conformations of the enamine intermediates[13] in the favored acyclic synclinal transition states.[15] As shown in Scheme 2, for cyclohexanone (top equation), in the favored transition state, the enamine double bond is next to the thioacetal group, and attacking of the enamine onto *Re* face of nitrostyrene leads to the observed major *syn* enantiomer. In contrast, for aldehyde substrate (bottom equation), in the favored transition state, the *trans*-enamine double bond is away from the thioacetal group and the attack of this enamine onto the *Si* face of the nitrostyrene leads to the formation of the observed opposite enantiomer of the *syn* diastereomer. Acetone and sterically demanding aldehydes yield much lower product ee values most likely because, for these substrates, the energy gap between these two possible enamine conformations is less, such that both approaches are possible for these substrates.

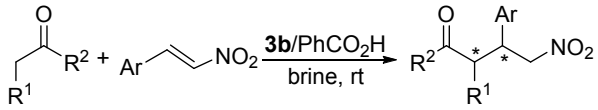


Scheme 2. Proposed transition state models

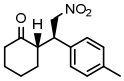
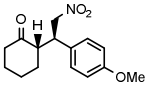
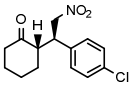
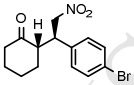
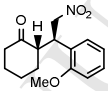
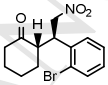
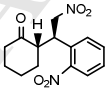
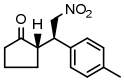
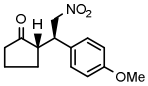
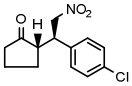
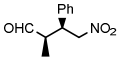
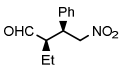
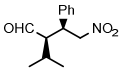
3. Conclusion

We have synthesized some readily accessible and highly tunable prolinal dithioacetal catalysts for the direct Michael addition of both ketones and aldehydes to β-nitrostyrenes. These catalysts cannot only catalyze the nitro-Michael reaction in organic solvents, but also in aqueous media, such as water and brine. With the exception of acetone and sterically demanding aldehydes, high diastereoselectivities and enantioselectivities have been uniformly obtained for both ketone and aldehyde substrates in all of these three reaction media.

Table 4. Asymmetric Michael addition of ketones and aldehydes to *trans*-β-nitrostyrenes in brine[a]



4 **5** **6**

Entry	Product		Time (h)	Yield (%)[b]	dr[c] (*syn*/*anti*)	ee (%)[d]
1		**6a**	31	79	98:2	98
2		**6b**	32	82	97:3	97
3		**6c**	39	80	96:4	97
4		**6d**	30	83	97:3	96
5		**6e**	25	85	95:5	98
6[e]		**6f**	40	74	97:3	93
7		**6g**	28	81	96:4	94
8		**6h**	27	76	97:3	95
9		**6i**	31	75	97:3	91
10		**6j**	30	77	96:4	94
11		**6k**	31	63	80:20	94
12		**6p**	35	62	88:12	93
13		**6q**	36	59	86:14	92
14		**6r**	31	63	86:14	94
15		**6l**	25	73	---	46
16[f,g]		**6s**	27	79	87:13	80
17[g]		**6m**	28	76	92:8	82
18[g,h]		**6n**	45	70	92:8	85

[a]Unless otherwise specified, all the reactions were carried out with **4** (0.30 mmol), *trans*-β-nitrostyrenes **5** (0.10 mmol), catalyst **3b** (0.01 mmol, 10 mol %), and benzoic acid (0.01 mmol) in brine (1.0 mL) at room temperature. [b]Yield of the isolated product after column chromatography. [c]Determined by ^{1}H NMR analysis of the crude product. [d]Value of the major diastereomer; unless otherwise indicated, was determined by HPLC analysis on a ChiralPak AD-H column. [e]On a ChiralPak AS column. [f]On a ChiralCel OD-H column.

[g]The reaction was carried out without adding benzoic acid. [h]The reaction was conducted with 0.02 mmol (20 mol%) catalyst.

4. Experimental Section

4.1. General

All reactions were carried out in oven-dried glass vials. Solvents were dried using standard protocols. ^{1}H NMR (300 or 500 MHz) and ^{13}C NMR (75 or 125 MHz, respectively) spectra were recorded at 25 ºC using $CDCl_3$ as solvent. TLC was conducted on aluminum-backed TLC plates and the spots were visualized with UV. Column chromatography was performed on silica gel. HPLC were conducted with a ChiralCel OD-H, a ChiralPak AS, or a ChiralPak AD-H column using a mixture of hexanes/*i*-PrOH as the eluent.

4.2. General experimental procedure for the synthesis of the catalysts (3a-c, e and f)

To a solution of (*S*)-*N*-Boc-prolinal (**1**, 199.0 mg, 1.0 mmol) and the thiol (2.2 mol) in CH_2Cl_2 (5.0 mL) was added indium(III) chloride (44.2 mg, 0.20 mmol, 20 mol %) at room temperature with stirring. The reaction mixture was then refluxed for 1 h. After the reaction mixture was cooled down to room temperature, trifluoroacetic acid (0.25 mL) was then added and stirring was continued for another 3 h. Then the reaction mixture was made alkaline (pH ≈ 9) by adding 1.0 M aqueous NaOH solution and extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were washed with brine (2 × 10 mL) and dried over Na_2SO_4. Evaporation of the organic solvent provided the crude product, which was purified by column chromatography over silica gel with ethyl acetate/hexane (50:50) as the eluent to furnish the desired product.

*4.2.1. (S)-2-[(Diphenylthio)methyl]pyrrolidine (**3a**).* Yellowish viscous liquid, yield 283.3 mg (94%). $[\alpha]_D^{24}$ -29.5 (c 1.0, $CHCl_3$); IR (KBr): 3054, 3017, 2962, 2865, 1580, 1477 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.48-7.43 (m, 4H), 7.30-7.25 (m, 6H), 4.50 (d, *J* = 5.0 Hz, 1H), 3.50-3.46 (m, 1H), 3.13-3.08 (m, 1H), 2.93-2.88 (m, 1H), 2.28 (br s, 1H), 1.99-1.73 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 134.9, 134.8, 132.8, 132.7, 129.2, 129.1, 127.9, 127.8, 65.4, 62.1, 47.1, 29.8, 25.9; Anal. Calcd. for $C_{17}H_{19}NS_2$: C, 67.73; H, 6.53; N, 4.65. Found: C, 67.91; H, 6.47; N, 4.65.

*4.2.2. (S)-2-[Bis(4-methylphenylthio)methyl]pyrrolidine (**3b**).* Pale yellow viscous liquid, yield 306.2 mg (93%). $[\alpha]_D^{23}$ -86.8 (c 1.0, $CHCl_3$); IR (KBr): 3017, 2947, 2918, 2864, 1564, 1490 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39-7.27 (m, 4H), 7.11-7.09 (m, 4H), 4.38 (d, *J* = 5.0 Hz, 1H), 3.44-3.40 (m, 1H), 3.11-3.07 (m, 1H), 2.90-2.86 (m, 1H), 2.34 (s, 6H), 2.26 (br s, 1H), 1.99-1.73 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.0, 137.9, 133.4, 133.3, 131.2, 131.1, 130.0, 129.9, 66.3, 61.9, 47.0, 29.8, 25.9, 21.4; Anal. Calcd. for $C_{19}H_{23}NS_2$: C, 69.25; H, 7.04; N, 4.25. Found: C, 69.41; H, 7.05; N, 4.16.

*4.2.3. (S)-2-[Bis(4-methoxyphenylthio)methyl]pyrrolidine (**3c**).* Colourless viscous liquid, yield 296.9 mg (82%). $[\alpha]_D^{23}$ -39.3 (c 1.0, $CHCl_3$); IR (KBr): 2999, 2938, 2865, 2833, 1589, 1569, 1490 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42-7.37 (m, 4H), 6.84-6.82 (m, 4H), 4.19 (d, *J* = 5.5 Hz, 1H), 3.81 (s, 6H), 3.39-3.35 (m, 1H), 3.11-3.07 (m, 1H), 2.90-2.86 (m, 1H), 2.08 (br s, 1H), 1.99-1.92 (m, 1H), 1.88-1.73 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.9, 135.9, 135.8, 125.2, 125.1, 114.7, 114.6, 68.2, 62.0, 55.6, 46.9, 29.8, 25.8; Anal. Calcd. for $C_{19}H_{23}NO_2S_2$: C, 63.12; H, 6.41; N, 3.87. Found C, 62.97; H, 6.38; N, 3.84.

*4.2.4. (S)-2-[Bis(2,6-dimethylphenylthio)methyl]pyrrolidine (**3e**).* Yellowish viscous liquid, yield 325.8 mg (91%); $[\alpha]_D^{24}$ = -25.7 (c 1.0, $CHCl_3$); IR (KBr) 3053, 2952, 2921, 2869, 1458 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.14-7.05 (m, 6H), 4.10 (d, *J* = 4.0 Hz, 1H), 3.33-3.29 (m, 1H), 3.19-3.15 (m, 1H), 2.89-2.84 (m, 1H), 2.44 (s, 6H), 2.35 (s, 6H), 2.02-1.75 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.0, 137.9, 133.4, 133.3, 131.2, 131.1, 130.0, 129.9, 66.3, 61.9, 47.0, 29.8, 25.9, 21.4. Anal. Calcd. for $C_{21}H_{27}NS_2$: C, 70.54; H, 7.61; N, 3.92. Found C, 70.27; H, 7.79; N, 3.84.

*4.2.5. (S)-2-[Bis(tert-butylthio)methyl]pyrrolidine (**3f**).* Pale yellow viscous liquid, yield 230.0 mg (88%); $[\alpha]_D^{23}$ = -82.6 (c 1.0, $CHCl_3$); IR (KBr) 3108, 2963, 2865, 1463 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.19 (d, *J* = 4.0 Hz, 1H), 3.53-3.49 (m, 1H), 3.17-3.12 (m, 1H), 2.86-2.82 (m, 1H), 2.22 (br s, 1H), 1.95-1.91 (m, 1H), 1.79-1.73 (m, 2H), 1.62-1.58 (m, 1H), 1.41 (m, 18H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 64.6, 49.9, 47.6, 45.0, 44.8, 32.0, 31.8, 28.4, 26.0. HRMS Calcd. for $C_{13}H_{28}NS_2$ ($[M+H]^+$): 262.1658. Found: 262.1657.

4.3. Synthesis of (*S*)-2-[bis(4-chlorophenylthio)methyl]-pyrrolidine (3d)

To a solution of (*S*)-*N*-Boc-prolinal (**1**, 199.0 mg, 1.0 mmol) and 4-chlorobenzenethiol (317.0 mg, 2.2 mol) in CH_2Cl_2 (5.0 mL) were added indium(III) chloride (44.2 mg, 0.2 mmol) and $BF_3{\cdot}OEt_2$ (13 μL, 0.10 mmol) at room temperature with stirring. The reaction mixture was then refluxed for 2 h. After the reaction mixture was cooled down to room temperature, trifluoroacetic acid (0.25 mL) was then added and stirring was continued for another 3 h. The reaction mixture was made alkaline (pH ≈ 9) by adding 1.0 M aqueous NaOH solution and extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were washed with brine (2 × 10 mL) and dried over Na_2SO_4. Evaporation of the organic solvent provided the crude product, which was purified by column chromatography over silica gel with ethyl acetate/hexane (50:50) as the eluent to furnish the desired product as a colorless viscous liquid (252.8 mg, 68% yield). $[\alpha]_D^{23}$ -25.6 (c 1.0, $CHCl_3$); IR (KBr) 3049, 2962, 2865, 1572, 1473 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41-7.32 (m, 4H), 7.28-7.24 (m, 4H), 4.39 (d, *J* = 5.5 Hz, 1H), 3.46-3.42 (m, 1H), 3.11-3.07 (m, 1H), 2.94-2.89 (m, 1H), 2.01-1.96 (m, 1H), 1.94-1.85 (m, 2H), 1.82-1.74 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 134.3, 134.2, 133.1, 132.9, 129.4, 129.3, 66.4, 61.9, 47.1, 30.0, 25.9; HRMS Calcd. for $C_{17}H_{18}Cl_2NS_2$ ($[M+H]^+$): 370.0252, found: 370.0252.

4.4. General experimental procedure for the Michael addition of ketones to *trans*-β-nitrostyrenes in CH_2Cl_2

To a mixture of catalyst **3b** (3.3 mg, 0.010 mmol, 10 mol %) and ketone **4** (0.30 mmol) in CH_2Cl_2 (0.5 mL) was added benzoic acid (1.2 mg, 0.010 mmol, 10 mol %) at room temperature. The reaction mixture was stirred for 4 min, then *trans*-β-nitrostyrene **5** (0.10 mmol) was added. The reaction mixture was further stirred for the desired time (monitored by TLC). After that the reaction mixture was extracted with ethyl acetate (3 x 1 mL). The combined extracts were washed with water (1 x 1 mL) and brine (1 x 1 mL) and then dried over Na_2SO_4. Evaporation of the organic solvent provided the crude product, which was purified by column chromatography over silica gel with ethyl acetate/hexane (15:85) as an eluent to afford the desired product. Diastereoselectivity was determined by ^{1}H NMR analysis of the crude reaction mixture. All the nitro-Michael addition products are known compounds and have identical spectroscopic data as those reported.

4.5. General experimental procedure for the Michael addition of aldehydes to *trans*-*β*-nitrostyrene in CH_2Cl_2

To a solution of *trans*-β-nitrostyrene (**5a**, 14.9 mg, 0.1 mmol) and catalyst **3b** (3.3 mg, 0.010 mmol, 01 mol %) in CH_2Cl_2 (0.5 mL) was added aldehyde **4** (0.40 mmol) at 0 °C. Then the reaction mixture was allowed to stir for the desired time (monitored by TLC). After that the reaction mixture was quenched by adding aq. 1N HCl (0.1 mL). Organic materials were then extracted with ethyl acetate (3 x 1 mL) and washed with water (1 x 1 mL) and brine (1 x 1 mL). The combined extracts were dried over Na_2SO_4. The solvent was evaporated to provide the crude product, which was purified by column chromatography over silica gel with ethyl acetate/hexane (15:85) as an eluent to afford the desired product. Diastereoselectivity was determined by ^{1}H NMR analysis of the crude reaction mixture. All the nitro-Michael addition products are known compounds and have identical spectroscopic data as those reported.

4.6. General experimental procedure for the Michael addition in water

To a mixture of catalyst **3b** (3.3 mg, 0.010 mmol, 10 mol %), *trans*-β-nitrostyrene **5** (0.10 mmol) in water (1.0 mL) was added benzoic acid (1.2 mg, 0.010 mmol, 10 mol %) at 5 °C. The reaction mixture was stirred for 5 min, then ketone **4** (0.30 mmol) was added. The reaction mixture was further stirred for the desired time (monitored by TLC). After that the reaction mixture was extracted with ethyl acetate (3 x 1 mL) and the combined extracts were washed with brine (1 x 1 mL). The organic layer was dried over Na_2SO_4. Evaporation of the solvent provided the crude product, which was purified by column chromatography over silica gel with ethyl acetate/hexane (15:85) as an eluent to afford the desired product. Diastereoselectivity was determined by ^{1}H NMR analysis of the crude reaction mixture. For aldehyde substrates, benzoic acid was not added.

4.7. General experimental procedure for the Michael addition in brine

To a mixture of catalyst **3b** (3.3 mg, 0.01 mmol, 10 mol %), *trans*-β-nitrostyrene **5** (0.10 mmol) in brine (1.0 mL) was added benzoic acid (1.2 mg, 0.01 mmol, 10 mol %) at room temperature. The reaction mixture was stirred for 4 min, then ketone **4** (0.30 mmol) was added. The reaction mixture was further stirred for the desired time (monitored by TLC). After that the reaction mixture was extracted with ethyl acetate (3 x 1 mL) and the combined organic extracts were dried over Na_2SO_4. Evaporation of the solvent provided the crude product, which was purified by column chromatography over silica gel with ethyl acetate/hexane (15:85) as an eluent to afford the desired product. Diastereoselectivity was determined by ^{1}H NMR analysis of the crude reaction mixture. For aldehyde substrates, benzoic acid was not added.

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Supplementary data

Supplementary data related to this article can be found at

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