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Enantioselective conjugate addition of ketones to β-nitrostyrenes catalyzed by 1,2-amino alcohol-derived prolinamides

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Abstract—Various L-prolinamides **14**, prepared from L-proline and chiral β-amino alcohols, are active bifunctional catalysts for the direct nitro-Michael addition of ketones to β-nitrostyrenes. In particular, catalyst **14e** prepared from L-proline and (1*S*,2*R*)-*cis*-1-amino-2-indanol exhibits the highest catalytic performance working in polar aprotic solvents such as NMP. High *syn*-diastereoselectivities (up to 94% de) and good enantioselectivities (up to 80% ee) were obtained at rt.

1. Introduction

The Michael addition is one of the most frequently used C–C bond forming reactions in organic synthesis.[1] The conjugate addition of a carbon nucleophile to a nitroalkene is a very useful synthetic method for the preparation of nitroalkanes, which are valuable building blocks in organic synthesis. Nitro compounds can be transformed into amines, ketones, carboxylic acids, nitrile oxides, etc.[2] Asymmetric reactions catalyzed by organocatalysts[3] have become very attractive in recent years since environmentally friendly and metal-free transformations are desired. Barbas,[4] List,[5] and Enders[6] independently reported the first organocatalytic addition of ketones to *trans*-β-nitrostyrene using L-proline **1** as a catalyst with good yields but very low enantioselectivities. Since then, very effective catalytic systems have been developed for the asymmetric Michael reaction of aldehydes[7] and ketones[7b–f,h,i,k,l,8] with nitroalkenes.[9] The best improvements to this reaction have mostly been achieved using pyrrolidine-based catalytic derivatives **2**–**10**,[7d–j,8b,d,e] as well as chiral acyclic primary amines such as alanine **11**,[8g] thiourea–amine bifunctional catalysts[8f,h] such as **12**, and small dipeptides[7k,8a] such as (*S*)-ala-(*R*)-ala **13** (Scheme 1). L-Prolinamide and its derivatives have been shown as highly efficient catalysts for the direct aldol reaction of aldehydes with simple ketones in organic,[10] ionic,[11] and aqueous solvents.[12] These types of organocatalysts have also been demonstrated to promote the enantioselective α-hydroxyamination reaction of α-branched aldehydes with good yields and moderate enantioselectivities.[13] To the best of our knowledge, no examples have so far been reported of the organocatalytic direct Michael reaction of ketones with β-nitrostyrenes catalyzed by these types of prolinamides. As part of our program aimed at developing new organocatalysts for asymmetric organic transformations,[14] we herein report the asymmetric Michael addition of ketones to nitrostyrenes catalyzed by chiral prolinamide derivatives **14** acting as bifunctional organocatalysts. A transient activation of ketone donors through the formation of an enamine on the secondary amino group was anticipated.[15] Furthermore, the amide and hydroxyl groups were expected to interact via double hydrogen bonding with the nitro group of the electrophile in order to enhance their reactivity as depicted in Scheme 2.

2. Results and discussion

L-Pro-derived catalysts **14** were prepared in moderate to excellent yields from Cbz-L-proline and the corresponding commercially available chiral amines and β-amino alcohols (Scheme 3).[16]

We initially screened the library of prolinamide-derived catalysts **14** (20 mol %) for the 1,4-addition between 3-pentanone and β-nitrostyrene in typical polar protic solvents such as MeOH at rt[17] (Scheme 4, Table 1). Most of the

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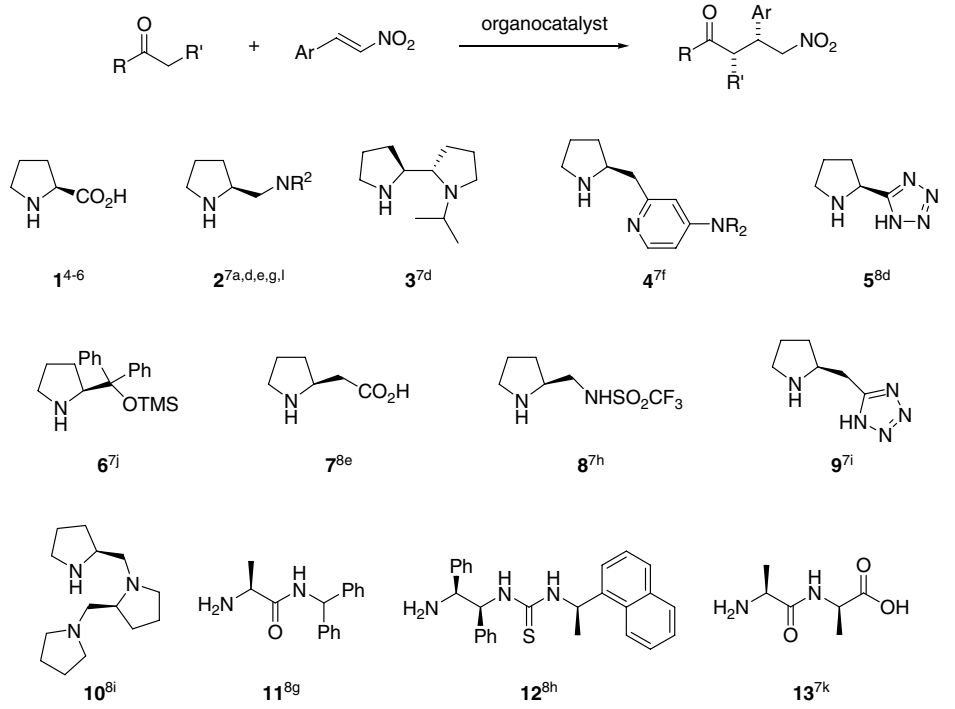
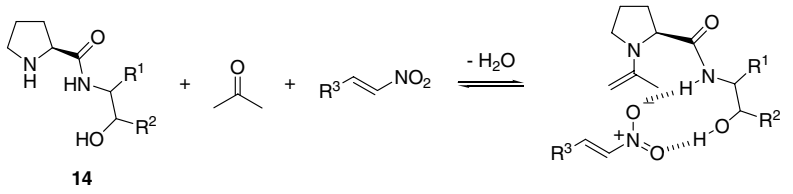
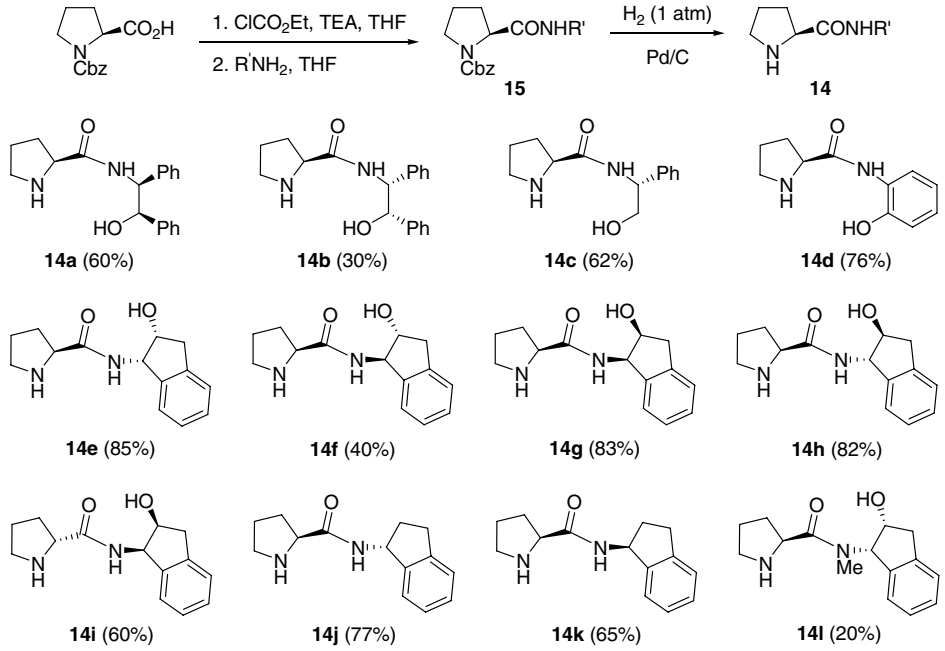


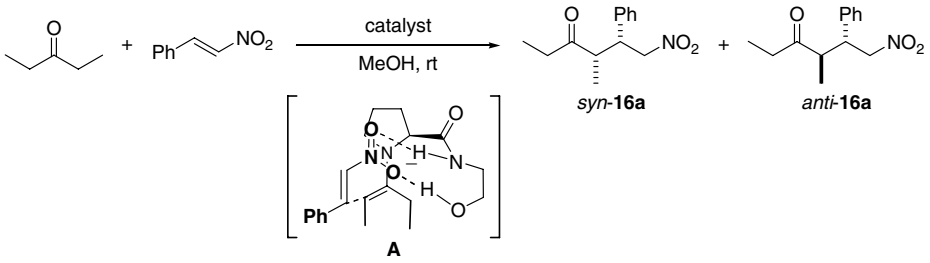
Scheme 1. Organocatalysts for 1,4-addition of aldehydes and ketones to nitro olefins.



Scheme 2. Prolinamide-derived bifunctional organocatalysts.



Scheme 3. Synthesis of organocatalysts **14**.



Scheme 4. Catalyst study for the direct asymmetric 1,4-addition.

Table 1. Asymmetric 1,4-addition of 3-pentanone to β-nitrostyrene

Entry	Catalyst	*t* (days)	Yield[b] (%)	*syn*/*anti*[b]	ee[c] (%)
1	**14a**	2	87	92/8	39
2	**14b**	1.5	96	85/15	52
3	**14c**	1	>99	83/17	36
4	**14d**	6	80	89/11	42
5	**14e**	3	95	93/7	64
6	**14f**	2	>99	88/12	38
7	**14g**	3	>99	92/8	53
8	**14h**	2	>99	86/14	52
9	**14i**	3	99	91/9	62[d]
10	**14j**	3	48	91/9	48
11	**14k**	3	48	82/18	32
12	**14l**	3	>99	88/12	34

Catalyst study.[a]

[a] To a solution of catalyst **14** (20 mol %) in MeOH (0.2 mL) were added 3-pentanone (4 mmol) and β-nitrostyrene (0.4 mmol) and the resulting mixture was stirred at rt for the time shown in the table.

[b] Determined by ^{1}HNMR and/or GC analysis.

[c] ee for the *syn* diastereoisomer. Determined by chiral-phase HPLC analysis. The relative and absolute configurations of **16a** were determined by comparison with the literature data.[7d]

[d] The *syn*-(4*R*,5*S*)-**16a** enantiomer was obtained.

L-prolinamides exhibited high catalytic activities to give the *syn* adduct **16a** as the favored product in a (4*S*,5*R*)-configuration according to transition state **A** (Scheme 4). Prolinamides **14a** and **14b**, derived from 1,2-diphenyl-2-aminoethanol, which have been successfully used in the direct aldol reaction of ketones with aldehydes,[10] showed good activity with high reaction conversions and good diastereoselectivity, *syn*/*anti*: 92/8 and 85/15, respectively, and enantioselectivities 39% and 52% ee for the major diastereomer, respectively (Table 1, entries 1 and 2). This meant that **14b** was the matched diastereomer. Catalyst **14c**, derived from 2-phenyl-2-aminoethanol, with a primary alcohol unit group, showed very high catalytic activity to afford after 1 day the Michael adduct in high yield but with lower diastereo- and enantioselectivity (*syn*/*anti*: 83/17, 36% ee, for the *syn* isomer) (Table 1, entry 3). The presence of the chiral hydroxyl moiety seemed to be important for the selectivity of the process. This was further supported with catalyst **14d**, derived from 2-aminophenol, which gave a 42% ee for the *syn* adduct after 6 days (Table 1, entry 4). The reaction time was decreased to 3 days and a noticeable increase in yield (95%) and enantioselectivity (64% ee) was obtained with (1*S*,2*R*)-*cis*-1-amino-2-indanol-derived prolinamide **14e** as catalyst (Table 1, entry 5). This result demonstrated that increasing the conformational rigidity of the amino alcohol moiety seemed to be beneficial for the selectivity of the process. This was probably due to the more favored double hydrogen-bonding interactions of the more rigid derivative **14e** with the electrophile. Diastereomeric catalysts **14e**, **14f**, **14g**, and **14h** showed very high catalytic activities in the 1,4-addition (Table 1, entries 5–8), the highest enantioselectivity (64% ee) being observed with prolinamide **14e**. This finding indicates that the (1*S*,2*R*)-configuration of the chiral 1-aminoindanol matched the (*S*)-configuration of the L-proline to enhance the stereochemical control. This was corroborated with catalyst **14i**, prepared from D-proline and (1*R*,2*S*)-*cis*-1-amino-2-indanol, which gave the enantiomeric (4*R*,5*S*)-*syn*-adduct **16** in 62% ee (Table 1, entry 9). This experiment also showed that the enantioselectivity of the process was controlled by the proline moiety since diastereomeric catalysts **14g** and **14i**, derived from the same (1*R*,2*S*)-*cis*-1-amino-2-indanol and L- and D-proline, respectively, afforded the corresponding enantiomers of the *syn* adduct **16** (Table 1, entries 7 and 9).

Catalysts **14j** and **14k**, derived from L-proline and (*R*)- and (*S*)-1-aminoindane, respectively, mediated the formation of the Michael product **16** in lower yields (48%) and enantioselectivities, 48% and 32%, respectively (Table 1, entries 10 and 11), than the corresponding aminoalcohol-derived prolinamides **14a**–**i**. These results and the very low enantioselectivity (34% ee) observed with N-methylated derivative **14l** of L-proline and *N*-methyl-(1*S*,2*R*)-*cis*-1-amino-2-indanol (Table 1, entry 12) showed that the presence of the hydroxyl group and a hydrogen in the amido group was important for good conversion and selectivity in the 1,4-addition. The amide and hydroxyl groups are most likely involved in the catalysis and stereoselection of the 1,4-addition through hydrogen bonding interactions with the substrate (Scheme 3). To explain the *syn*-diastereoselectivity and the absolute configuration observed, we proposed transition state **A** (Scheme 4) based upon Seebach's model assuming intramolecular hydrogen bonds.[18]

We next screened a range of solvents with the best catalyst **14e** (Table 2). The optimum results were obtained with polar nonprotic solvents, such as DMF and NMP (Table 2, entries 5–7), providing high conversions and good enantioselectivities being the highest 80% ee for NMP. This represents a significant improvement in the ee value over that initially obtained in MeOH as a solvent (Table 2,

Table 2. Asymmetric 1,4-addition of 3-pentanone to β-nitrostyrene

Entry	Solvent	*t* (days)	Yield[b] (%)	*syn*/*anti*[b]	ee[c] (%)
1	MeOH	3	95	93/7	64
2	Toluene	8	91	91/9	56
3	$CHCl_3$	3	97	91/9	58
4	CH_3CN	7	99	90/10	65
5	DMF	10	<99	92/8	76
6	NMP	7	97	90/10	80
7	NMP[d]	3	80	91/9	78

Solvent study.[a]

[a] To a solution of catalyst **14e** (20 mol %) in the corresponding solvent (0.2 mL) were added 3-pentanone (4 mmol) and β-nitrostyrene (0.4 mmol) and the resulting mixture was stirred at rt (see column).

[b] Determined by ^{1}H NMR and/or GC analysis.

[c] ee for the *syn* diastereoisomer. Determined by chiral-phase HPLC analysis.

[d] A mixture of catalyst **14e** (20 mol %) and 3-pentanone (4 mmol) was stirred for 20 min in NMP (0.2 mL) at rt. Then, β-nitrostyrene (0.4 mmol) was added to the mixture and the reaction was stirred at rt for 3 days.

compare entries 1 and 6). With respect to the diastereoselectivity, all the solvents tested afforded similar levels ranging from *syn*/*anti*: 90/10, for CH_3CN, to 93/7 for MeOH. Interestingly, the reaction time was reduced in NMP from 7 to 3 days by simply stirring the catalyst and ketone at rt for 20 min prior to the addition of the electrophile (Table 2, entry 7). These conditions still afforded high conversions and similar selectivities (Table 2, compare entries 6 and 7).

Under the best reaction conditions established, various nitrostyrenes were then evaluated as substrates (Scheme 5 and Table 3).[19] The reaction appears quite general with respect to the nature of the aromatic Michael acceptor. Generally, excellent yields and good enantioselectivities were observed. The introduction of electron-withdrawing or electron-donating groups on the aromatic ring of the nitroolefin did not affect the enantioselectivities. Thus, 4-tolyl, 4-chloro, 4-methoxy, and 3,5-dichlorosubstituted aryl nitrostyrenes gave compounds **16b–e** in 92–98% yields, 92/8–93/7 diastereomeric ratios and 73–78% enantioselectivities in 4 days reaction time (Table 3, entries 2–5). However, in the case of the 4-(trifluoromethyl)phenyl derivative, a 50% ee for the major diastereoisomer *syn*-**16f** was obtained (Table 3, entry 6). In general, a *syn*-diastereoselectivity was slightly higher when electron poor styrenes were used (Table 3, entries 3, 5, and 6). Finally, it is noteworthy to mention that prolinamide catalyst **14e** can be easily recovered (80% recovery) from the reaction mixture after extractive workup and reused after flash chromatography with similar results (Table 3, entry 1) since no loss of optical activity is detected $\{[\alpha]_D^{20} = -24.4$ (c 1.0, CH_2Cl_2)$\}$.

Table 3. Asymmetric 1,4-addition of 3-pentanone to nitroolefins[a]

Entry	Ar	Conv.[b] (%)	No.	*syn*/*anti*[b]	ee[c] (%)
1	Ph	90	**16a**	91/9	78[d]
2	4-MeC_6H_4	98	**16b**	93/7	74
3	4-ClC_6H_4	93	**16c**	95/5	78
4	4-$MeOC_6H_4$	92	**16d**	92/8	73
5	3,5-$(Cl)_2C_6H_3$	95	**16e**	97/3	73
6	4-$CF_3C_6H_4$	>99	**16f**	97/3	50

[a] A mixture of catalyst **14e** (20 mol %) and 3-pentanone (4 mmol) was stirred in NMP (0.2 mL) for 20 min at rt. Then, nitroolefin (0.4 mmol) was added to the mixture and the reaction was stirred at rt for 4 days.

[b] Determined by ^{1}HNMR and/or GC analysis.

[c] For the *syn* diastereoisomer. Determined by chiral-phase HPLC analysis. Absolute configuration not determined except for **16a**.

[d] Similar results were obtained with recycled **14e** (88% yield, *syn*/*anti*: 91/9, 78% ee).

3. Conclusions

From the first direct enantioselective conjugate addition of ketones to β-nitrostyrenes catalyzed by 1,2-amino alcohol-derived prolinamide studies, it can be deduced that 1,2-amino alcohol-derived prolinamides promote the *syn*-diastereo- and enantioselective Michael addition of ketones to nitrostyrenes. The best catalyst derived from L-proline and (1*S*,2*R*)-*cis*-1-amino-2-indanol gave de's up to 94% and 80% ee of the *syn* adduct. It seems that both the amide hydrogen and the chiral hydroxyl group of the catalysts play an important role in the process. Furthermore, prolinamide catalysts can be recovered and reused. Further studies on the scope of prolinamide-derived catalysts **14** in Michael and other organocatalytic asymmetric C–C bond-forming reactions are currently underway.

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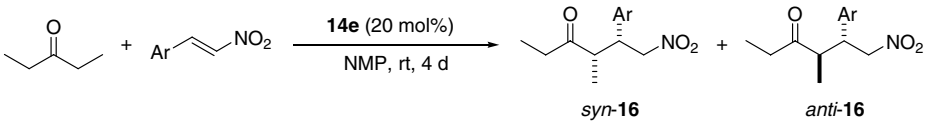

Scheme 5. Michael addition of 3-pentanone to nitroolefins under optimized conditions.

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19. All new compounds gave satisfactory physical, analytical, and spectroscopic data. Typical procedure for the synthesis of **18**: A mixture of **14e** (0.08 mmol, 19.6 mg) and 3-pentanone (4 mmol, 423 μL) in NMP (0.2 mL) was stirred for 20 min at rt. Then, *trans*-4-chloro-β-nitrostyrene (0.4 mmol, 73.4 mg) was added and the mixture was stirred for 4 days. The reaction was extracted with EtOAc (3×5 mL), dried over Na_2SO_4, filtered, and the solvent evaporated. The residue was purified by flash chromatography (hexane/AcOEt: 12/1) to afford pure **18**. The catalyst was recovered from the column with AcOEt/MeOH: 2/1 (15.8 g, 80% recovery). Selected data for **18**: $[\alpha]_D^{20} = +5.7$ (*c* 1.0, CH_2Cl_2) for 78% ee; R_f 0.2 (hexane/AcOEt: 5/1); IR (KBr) *ν* 1553 (NO_2), 1711 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): *δ* 0.96 (d, $J = 7.1$ Hz, 3H, CH_3CH), 1.07 (t, $J = 7.1$ Hz, 3H, CH_3CH_2), 2.41, 2.62 (2dq, $J = 17.9$, 7.1 Hz, 2H, CH_3CH_2), 2.95 (dq, $J = 9.3$, 7.2 Hz, 1H, CH_3CH), 3.69 (dt, $J = 9.3$, 4.9 Hz, 1H, $CHCH_2N$), 4.58 (dd, $J = 12.4$, 4.8 Hz, 1HxCH_2NO_2), 4.64 (dd, $J = 12.4$, 9.0 Hz, 1Hx CH_2NO_2), 7.11 (d, $J = 8.3$ Hz, 2H, ArH), 7.31 (dd, $J = 6.6$ Hz, 2H, HAr); ^{13}C NMR ($CDCl_3$, 100 MHz): *δ* 7.6 (CH_3CH_2), 16.2 (CH_3CH), 35.4 (CH_2CH_3), 45.4 ($CHCH_2N$), 48.1 ($CHCH_3$), 78.0 (CH_2NO_2), 129.2, 129.3, 133.8, 136.0 (ArC), 213.1 (C═O); *m*/*z* (EI) 269 (M^+-29, <1%), 193 (19), 138 (18), 115 (10), 57 (100). HRMS calcd for $C_{13}H_{16}ClNO_3 = 269.0819$, ($M^+-NO_2$) 223.0884, found 223.0874. HPLC (Chiralcel OD-H, 1 mL/min, 99:1 hexane/IPA, $\lambda = 210$ nm), retention time **22.6** min (major)/25.8 min (minor).