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Tetrahedron: *Asymmetry* 19 (2008) 495–499
Tetrahedron: *Asymmetry*

Chiral pyrrolidine–triazole conjugate catalyst for asymmetric Michael and Aldol reactions

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Received 13 December 2007; accepted 25 January 2008

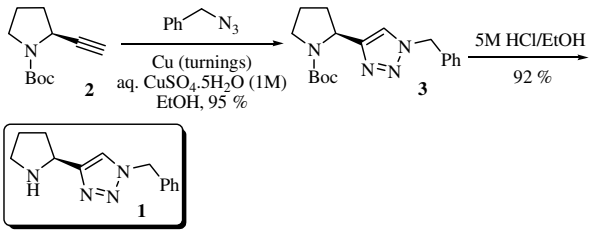
Abstract—A new pyrrolidine–triazole conjugate organocatalyst is synthesized using a Huisgen 1,3-dipolar cycloaddition reaction. The application of this catalyst in an asymmetric Michael addition and in an Aldol reaction is described, showing good catalytic activity. The reactions proceeded to give the products in good yield and in a highly selective manner.

1. Introduction

Over the past decade, there has been increasing interest towards the synthesis and application of various asymmetric organocatalysts, especially those derived from natural proline.[1] These derivatives have been shown to exhibit catalytic activities in a diverse range of organic reactions. Our interest in proline-catalyzed asymmetric reactions,[2] as well as in the copper(I)-catalyzed 1,3-dipolar cycloaddition reaction[3] directed us to prepare a new pyrrolidine based organocatalyst from proline using the Huisgen 1,3-dipolar cycloaddition 'click' reaction.[4,5] We have designed our catalyst **1** in such a way that alkyne **2** could participate in a 1,3-dipolar cycloaddition with benzyl azide to furnish **3**, which on deblocking the *tert*-butoxycarbonyl group (Boc) would yield the desired catalyst. This synthetic approach in principle enables us to prepare various analogues involving both aryl and alkyl azides. This hybrid pyrrolidine–triazole catalyst was utilized in classical Michael additions[6] and Aldol reactions[7] with various substrates. We herein report the results of this study.

2. Results and discussion

The chiral pyrrolidine–triazole catalyst **1** was synthesized from alkyne **2**, which was obtained from L-proline using a known literature method.[8] Alkyne **2** was treated with benzyl azide under copper(I)-catalyzed Huisgen 1,3-dipolar cycloaddition reaction conditions to give the pyrrolidine–triazole derivative **3** in 95% yield. Next, the deprotection of the Boc-group was carried out using 5 M HCl to give the desired organocatalyst **1** in 92% yield (Scheme 1).



Scheme 1. Synthesis of pyrrolidine–triazole asymmetric organocatalyst.

After the preparation of catalyst **1**, we initially tested its efficiency in the asymmetric Michael addition reaction, which is one of the most important C–C bond forming reactions in organic chemistry. As a model reaction, the Michael addition of cyclohexanone **4a** to β-nitrostyrene **5a** was selected to study the activity of catalyst **1**. Initially, in order to optimize the reaction conditions, the above reaction was studied in the presence of various additives (2 mol %), such as CSA, *p*-TSA and TFA at 0 °C; the results are summarized in Table 1. We were pleased to find that the 5 mol % of pyrrolidine–triazole **1** was able to catalyze the reaction efficiently in the presence of 2 mol % of trifluoroacetic acid (Table 1, entry 4). Interestingly, the yield of the product and enantioselectivity improved with 10 mol % of **1** (Table 1, entry 5). However, a further increase in the loading of the catalyst had no effect on the

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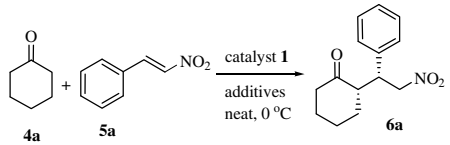
doi:10.1016/j.tetasy.2008.01.033

yield and selectivity (Table 1, entry 6). It is noteworthy to mention that all the reactions were carried out under solvent-free conditions.

Table 1. Effect of additives and catalyst loading



4a 5a 6a

Entry	Additive (2 mol %)	Catalyst (mol %)	Yield[a] (%)	*syn*/*anti*[b] (ratio)	ee[c] (%)
1	None	10	76	7:3	62
2	CSA	10	87	9:1	76
3	*p*-TSA	10	86	9:1	73
4	TFA	05	90	98:2	89
5	TFA	10	95	98:2	91
6	TFA	20	95	98:2	92

[a] Isolated yields.
[b] Determined by the ^{1}H NMR of the crude product.
[c] Determined by chiral HPLC of the *syn*-product.

With the optimized conditions in hand, the reactions of a variety of nitroolefin substrates with ketones, such as cyclohexanone **4a**, cyclopentanone **4b** and acetone **4c**, were investigated to check the generality of this procedure. All the β-nitrostyrenes **5a**–**5h** bearing electron-donating aryl groups, as well as electron-withdrawing aryl groups, reacted smoothly with cyclohexanone **4a** to give the corresponding Michael adducts, **6a**–**6h** in good yields, and with high diastereoselectivity and enantioselectivity (Table 2, entries 1–8). However, other ketones, such as cyclopentanone **4b** and acetone **4c**, gave the Michael adduct **6i** and **6j**, respectively, with β-nitrostyrene in low yield, low selectivity and required longer reaction times (Table 2, entries 9 and 10).

After the above success, we sought to extend the catalytic activity of pyrrolidine–triazole **1** in an Aldol reaction. Accordingly, the reaction of benzaldehyde **7a** with cyclohexanone **4a** in the presence of catalyst **1** (10 mol %) and TFA was carried out at 0 °C under solvent-free conditions. The reaction proceeded efficiently to give the corresponding product **8a** in 86% yield with good diastereoselectivity (94:6, *anti*:*syn*) (Table 3, entry 1). However, the enantioselectivity of this reaction was low (26%). In order to determine the reactivity of diverse substrates, several aldehydes were reacted with cyclohexanone **4a** under above reaction condition and we found that the reaction proceeded to give the corresponding Aldol products **8b**–**8d** in good yields.

3. Conclusions

In conclusion, we have developed a new proline derived organocatalyst for the asymmetric Michael addition reaction of ketones to nitroolefins and for the Aldol reaction, which was easily prepared from alkyne **2** using a 'click' reaction. The reactions were highly efficient in terms of yield and selectivity for Michael addition. In the case of Aldol reaction, the products were obtained with low enantioselectivity. Further applications to extend the scope of the catalyst are currently in progress.

4. Experimental

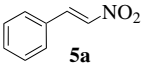
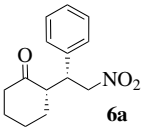
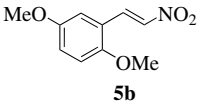
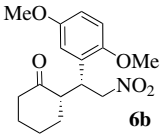
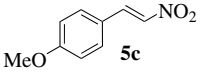
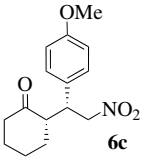
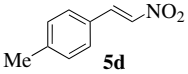
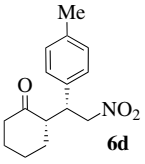
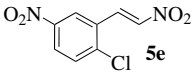
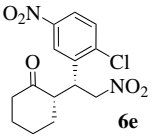
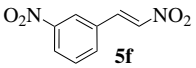
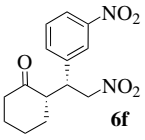
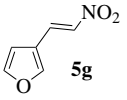
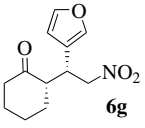
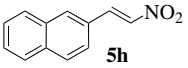
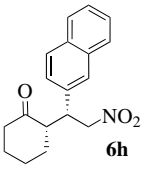
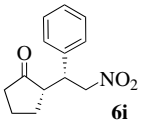
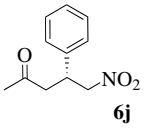
4.1. General

All solvents and reagents were purified by standard techniques. Crude products were purified by column chromatography on a Silica Gel of 60–120 mesh. IR spectra were recorded on Perkin–Elmer 683 spectrometer. Optical rotations were obtained on Jasco Dip 360 digital polarimeter. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution on a Varian Gemini 200, Brucker Avance 300 and Unity 400. Chemical shifts were reported in parts per million with respect to internal TMS. Coupling constants (J) are quoted in Hz. Mass spectra were obtained on an Agilent Technologies LC/MSD Trap SL. Chiral HPLC was carried out on chiral pak AD columns using isopropanol/hexanes as a eluent.

4.1.1. (*S*)-*tert*-Butyl-2-(1-benzyl-1*H*-1,2,3-triazol-4-yl) pyrrolidine-1-carboxylate 3. To a mixture of alkyne **2** (300 mg, 1.5 mmol) in ethanol (10 mL) were successively added benzyl azide (239 mg, 1.8 mmol), Cu-turnings (10 mg, 0.15 mmol) and aq saturated copper sulfate solution (300 μL, 1 M) and refluxed for 4 h. After completion of the reaction, the reaction mixture was filtered, concentrated in vacuo and purified by silica-gel chromatography to afford Boc-protected triazole **3** (479 mg) in 95% yield as a white solid: $[\alpha]_D^{25} = -42.7$ (c 0.8, $CHCl_3$); mp 100–102 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.46–7.14 (m, 6H), 5.57–5.37 (m, 2H), 4.99–4.87 (m, 1H), 3.53–3.31 (m, 2H), 2.33–2.11 (m, 2H), 2.02–1.82 (m, 1H), 1.49–1.12 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 154.2, 151.4, 134.8, 129.0, 128.6, 128.0, 120.6, 79.4, 54.0, 53.6, 46.6, 32.9, 28.2, 24.4; IR (KBr): ν 3114, 2930, 2882, 1689, 1400 cm^{-1}; ESIMS: m/z 329 $(M+1)^+$; HRMS calcd for $C_{18}H_{24}N_4O_2Na$: 351.1796 $(M+Na)^+$, found: 351.1798.

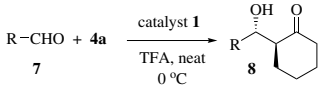
4.1.2. (*S*)-1-Benzyl-4-(pyrrolidin-2-yl)-1*H*-1,2,3-triazole 1. 5M HCl (0.5 mL) was added to a solution of triazole **3** (100 mg, 0.43 mmol) in ethanol (3 mL) at 0 °C and stirred for 2 h at rt. After removal of the solvent, the reaction mixture was dissolved in CH_2Cl_2 and quenched with saturated $NaHCO_3$ solution. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layer was dried over Na_2SO_4, concentrated in vacuo and purified by silica-gel chromatography to afford organocatalyst **1** (96 mg) in 92% yield as a pale yellow solid: $[\alpha]_D^{25} = -15.0$ (c 1.0, $CHCl_3$); mp 98–100 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.63 (s, 1H), 7.36–7.22 (m, 5H), 5.47 (s, 2H), 5.13 (br s, 1H), 4.42 (t, 1H, $J = 7.8$ Hz), 3.31–2.98 (m, 2H), 2.30–1.83 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 147.7, 134.6, 129.0, 128.6, 128.1, 122.0, 54.4, 54.1, 45.6, 31.6, 24.6; IR (neat): ν 3426, 3227, 3120, 2948, 2498, 1457 cm^{-1}; ESIMS: m/z 229 $(M+1)^+$; HRMS calcd for $C_{13}H_{17}N_4$: 229.1453 $(M+H)^+$, found: 229.1449.

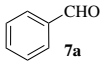
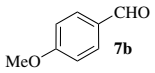
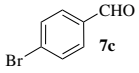
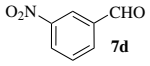
Table 2. Asymmetric Michael addition of **4a** to β-nitrostyrenes using organocatalyst **1**

Entry	Nitrostyrene	*t* (h)	Product	Yield[a] (%)	*syn*/*anti*[b] (ratio)	ee[c] (%)
1	 **5a**	12	 **6a**	95	98:2	91
2	 **5b**	16	 **6b**	96	99:1	94
3	 **5c**	19	 **6c**	92	99:1	92
4	 **5d**	13	 **6d**	90	99:2	94
5	 **5e**	15	 **6e**	97	99:1	87
6	 **5f**	16	 **6f**	98	99:1	90
7	 **5g**	12	 **6g**	89	98:2	91
8	 **5h**	18	 **6h**	92	99:1	92
9[d]	**5a**	30	 **6i**	85	80:2	83
10[e]	**5a**	36	 **6j**	68	—	58

[a] Isolated yields.
[b] Determined by ^{1}H NMR of the crude product.
[c] Determined by chiral HPLC of the syn product.
[d] Cyclopentanone **4b** was used instead of **4a**.
[e] Acetone **4c** was used instead of **4a**.

Table 3. Asymmetric Aldol reaction of aromatic aldehydes with **4a** using organocatalyst **1**



Entry	Aldehyde	Time (h)	Product	Yield[a] (%)	*anti*/*syn*[b] (ratio)	ee[c] (%)
1	 **7a**	12	**8a**	86	94:6	26
2	 **7b**	14	**8b**	91	96:4	28
3	 **7c**	10	**8c**	89	95:5	28
4	 **7d**	10	**8d**	93	92:8	23

[a] Isolated yields.
[b] Determined by ^{1}H NMR of the crude product.
[c] Determined by chiral HPLC of the *anti* product.

4.1.3. Representative procedure for the Michael reaction

4.1.3.1. (*S*)-2-((*R*)-1-(2,5-Dimethoxyphenyl)-2-nitroethyl) cyclohexanone 6b. Catalyst **1** (10.8 mg, 0.047 mmol) was added to a mixture of cyclohexanone **4a** (0.39 mL, 3.8 mmol) and TFA (0.008 mmol) at room temperature and stirred for 15 min. 2,5-Dimethoxy nitrostyrene **5b** (100 mg, 0.47 mmol) at 0 °C was then added and stirred for 16 h at the same temperature. The reaction mixture was directly loaded on a silica-gel column to give adduct **6b** (140.1 mg, 96% yield) as a semi solid: $[\alpha]_D^{25} = -25.1$ (*c* 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.78–6.67 (m, 2H), 6.61 (d, 1H, $J = 3.0$ Hz), 4.77 (d, 1H, $J = 2.2$ Hz), 4.75 (s, 1H), 3.90–3.83 (m, 1H), 3.81 (s, 3H), 3.73 (s, 3H), 2.97–2.86 (m, 1H), 2.50–2.30 (m, 2H), 2.12–2.03 (m, 1H), 1.84–1.52 (m, 4H), 1.28–1.19 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 212.4, 153.5, 151.7, 127.8, 126.5, 117.3, 112.7, 112.0, 55.8, 55.5, 50.6, 42.6, 41.4, 33.1, 28.4, 25.1; IR (Neat): *v* 2940, 2860, 1706, 1550, 1503, 1448, 1380 cm^{-1}; ESIMS: *m*/*z* 330 $(M+Na)^+$ HRMS calcd for $C_{16}H_{21}NO_5Na$: 330.1317 $(M+Na)^+$, found: 330.1321.

4.1.3.2. (*S*)-2-((*R*)-1-(2-Chloro-5-nitrophenyl)-2-nitroethyl) cyclohexanone 6e. $[\alpha]_D^{25} = -8.0$ (*c* 0.45, $CHCl_3$); mp 145–147 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.19–8.14 (m, 1H), 8.09 (dd, 1H, $J = 2.9$, 8.7 Hz), 7.59 (dd, 1H, $J = 3.6$, 8.7 Hz), 4.99–4.81 (m, 2H), 4.43–4.29 (m, 1H), 2.95–2.78 (m, 1H), 2.56–2.29 (m, 2H), 2.22–2.08 (m, 1H), 1.91–1.59 (m, 4H), 1.53–1.35 (m, 1H): ^{13}C NMR ($CDCl_3$,75 MHz): δ 210.6, 146.8, 141.6, 138.0, 131.2, 124.0, 123.5, 76.5, 51.7, 42.7, 40.7, 32.9, 28.3, 25.2; IR (KBr): *v* 3082, 2946, 2866, 1703, 1555, 1519, 1447, 1377, 1351 cm^{-1}; ESIMS: *m*/*z* 349 $(M+Na)^+$.

4.1.3.3. (*S*)-2-((*R*)-(Furan-3-yl)-2-nitroethyl) cyclohexanone 6g. $[\alpha]_D^{25} = -12.5$ (*c* 0.75, $CHCl_3$); mp 61–63 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.32 (d, 2H, $J = 15.6$ Hz), 6.23 (s, 1H), 4.70 (dd, 1H, $J = 5.2$, 6.9 Hz), 4.56 (dd, 1H, $J = 3.4$, 8.6 Hz), 3.75 (dt, 1H, $J = 2.6$, 7.8 Hz), 2.70–2.52 (m, 1H), 2.50–2.24 (m, 2H), 2.17–1.80 (m, 3H), 1.73–1.56 (m, 2H), 1.45–1.20 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 211.2, 143.5, 140.7, 121.3, 109.1, 78.2, 51.7, 42.5, 34.5, 32.3, 28.0, 24.9; IR (KBr): *v* 3133, 2937, 2866, 1707, 1551, 1504, 1442, 1382, 1312 cm^{-1}; ESIMS: *m*/*z* 260 $(M+Na)^+$; HRMS calcd for $C_{12}H_{15}NO_4Na$: 260.0898 $(M+Na)^+$, found: 260.0895.

4.1.4. Representative procedure for the Aldol reaction. To a mixture of cyclohexanone **4a** (0.92 mL, 9.4 mmol) and TFA (0.015 mmol) was added catalyst **1** (20.4 mg, 0.09 mmol) at rt. The reaction mixture was vigorously stirred for 15 min and benzaldehyde **7a** (100 mg, 0.94 mmol) then added at 0 °C. After stirring for 12 h at 0 °C, the reaction mixture was loaded directly onto a silica-gel column to give the pure Aldol product **8a** (165.5 mg, 86% yield) as a white solid. IR, ^{1}H, ^{13}C NMR and mass spectral data of the known products were identical with the reported data.[5b,9]

Acknowledgement

B.T. and B.B.P. thank the CSIR, New Delhi for financial assistance.

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