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Combining proline and 'click chemistry': a class of versatile organocatalysts for the highly diastereo- and enantioselective Michael addition in water

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Abstract—Based on 'click chemistry' conditions, a class of novel, facile, versatile pyrrolidine-based triazole derivatives were prepared, and proved to be efficient catalysts for the highly diastereoselective and enantioselective Michael addition of ketones to nitroalkenes. The Cu(I)-catalyzed 1,3-dipolar 'click' azide–alkyne cycloaddition provides modular and tunable features for the pyrrolidine-based triazole organocatalysts, and the resulting triazole moiety can serve as a phase tag to complete the reaction in water with an excellent yield and high enantiomeric excess.

1. Introduction

The Michael addition reaction is one of the most important carbon–carbon bond-forming reactions in organic synthesis.[1] Among the variants of this methodology, a direct Michael addition of carbonyl compounds to nitroalkenes offers an attractive approach to afford versatile difunctional products.[2] In recent years, an intense research effort has been made to find chiral organic molecules as catalysts for this enantioselective reaction. List and Barbas pioneered L-proline-catalyzed asymmetric Michael addition reactions.[3] Further investigations have also demonstrated that proline-based derivatives are more efficient catalysts for the asymmetric Michael reaction of carbonyl compounds to nitroolefins.[4] For example, Alexakis,[5] Kotsuki,[6] Wang,[2b] and Hayashi[7] reported excellent highly enantioselective Michael conjugate additions catalyzed by chiral pyrrolidine-based catalysts. On the other hand, there has been increasing recognition that organic reactions in water may offer advantages over those occurring in organic solvents, and the development of enantioselective reactions in water is an extensively investigated topic.[8] Compared to the widely reported aldol reaction in aqueous medium,[9] only a few organocatalysts have been able to catalyze the Michael addition reaction in water with high enantioselectivity and good yields.[10] Therefore, the development of novel small organic molecules that catalyze enantioselective reactions in water is currently a desirable goal in synthetic chemistry.

Very recently, Sharpless introduced 'click chemistry' as a new way of categorizing organic reactions that are modular, widely applicable, and relatively insensitive to solvents and pH value; they result in stereoselective conversions in high to very high yields.[11] Due to their efficiency and simplicity, these reactions have been used frequently in recent years. We were especially interested in the Cu(I)-catalyzed 1,3-dipolar 'click' azide–alkyne cycloaddition,[12] since the special feature of this reaction is that it is biocompatible and takes place particularly well in aqueous media, with the resulting 1,4-disubstituted 1,2,3-triazoles is chemically stable.

Ley[13] prepared a proline-derived tetrazole catalyst to perform asymmetric Michael addition reactions. Unfortunately, only a moderate enantioselectivity was obtained because the nature of the tetrazole group prevents further optimization of catalyst **4**, that is, by attaching the

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substituents of various electronic and steric properties. We envisioned that the implementation of a click-reaction in the synthetic scheme of a ligand should lead to a novel class of chiral pyrrolidine-type triazoles by introducing versatile substrates of varying electronic and steric groups, which might catalyze the Michael addition of carbonyl compounds and nitroolefins in water.

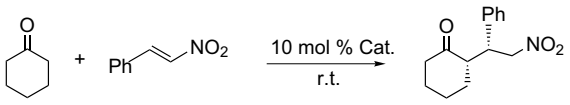
2. Results and discussion

The chiral pyrrolidine–triazole catalysts were prepared as depicted in Figure 1. The reduction of *N*-Boc-L-proline generated the corresponding (*S*)-prolinol. Treating the protected prolinol with tosyl chloride gave sulfonyl ester. Displacing the tosylate with sodium azide resulted in the formation of *N*-Boc-(*S*)-2-azidomethylpyrrlidine in a 95% yield.[14] Under 'click chemistry' conditions,[12b] the various protected pyrrolidine triazoles **2** were easily obtained from azide **1** in high yields, followed by the removal of the carbamate using trifluoroacetic acid to give the desired catalysts.

The asymmetric Michael addition reactions of cyclohexanone with β-nitrostyrene were investigated using the new catalysts (Table 1). Tetrazole **4** catalyzed the Michael reaction in DMSO in a good yield with a low ee value;[13] however, the attempt in water gave a poor yield (entries 1 and 2). As can be seen in Table 1, the reactivity and enantioselectivity of triazoles **3a–e** is considerably different. Initially, the use of **3a** failed to complete the reaction. Nitrostyrene (94%) was recovered after 96 h (entry 3). Changing the R group to *n*-pentyl, a substantial change was observed in $CHCl_3$, and H_2O, the desired product was obtained in a good yield and in a high enantioselectivity (entries 4 and 5). Stimulated by this positive result, we continued to prepare other triazole ligands from **3c** to **3e**. To our delight, catalysts **3c–e** also gave good results. It is noteworthy that the reaction could be proceeded in various solvents, such as $CHCl_3$, DMSO, and H_2O, a substantial change in the nature of the solvent only has a small effect on the yield and enantioselectivity (entries 6–8), and the best result was obtained in water using ligand **3c** (entry 8). The introduction of some acids in water, such as TFA, *p*-TsOH, 2,4-dinitrobenzenesulfonic acid, failed to give a reaction, and only 10–20% of the product was produced.[4c]

Under the optimized conditions, the addition reactions of a variety of nitroolefins and ketones were investigated to establish the generality of this methodology (Table 2). In order to emphasize the versatility and potential of this new triazole catalyst, all reactions were performed in $CHCl_3$ and water at an ambient temperature. As shown in Table 2, the reactions of cyclohexanone with substituted nitroolefins all gave a very high diastereoselectivity (up to 99:1) and with an excellent ee values (entries 2–6). For 1-naphthylnitroolefin, the reaction went to completion with nearly perfect stereo- and enantiocontrol (entries 7 and 8). Furylnitroolefin provided the desired adduct in excellent enantioselectivity, but in moderate diastereoselectivity (entries 11–14). Acetone was also a suitable Michael donor to produce the desired adduct with a good yield and a moderate enantioselectivity (entries 15 and 16). Although the reactions proceeded smoothly in both solvents, we found that aqueous media could efficiently promote the process to push the reaction to completion within a shorter time (entries 1–16). Compared to the reaction in $CHCl_3$, the addition reaction in water generally showed a better reactivity and enantioselectivity (Table 2).[15]

Table 1. Catalytic asymmetric Michael addition of cyclohexanone **5** to nitrostyrene **6** under various conditions[a]



5 **6** **7**

Entry	Cat.	Solvent	Time (h)	Yield[b] (%)	dr[c] (*syn*/*anti*)	ee[d] (%) (*syn*)
1	**4**	DMSO	48	93	14/1	23
2	**4**	H_2O	48	Trace	—	—
3	**3a**	$CHCl_3$	96	0	—	—
4	**3b**	$CHCl_3$	48	72	6/1	95
5	**3b**	H_2O	22	94	7/1	97
6	**3c**	$CHCl_3$	48	83	23/1	96
7	**3c**	DMSO	48	87	21/1	94
8	**3c**	H_2O	13	98	34/1	96
9	**3d**	H_2O	26	93	4/1	97
10	**3e**	H_2O	12	93	15/1	96

[a] Reactions conducted in solvent (2 mL) using **5** (2.5 mmoL), **6** (0.5 mmol), and 10 mol % of the catalyst.
[b] Isolated yield.
[c] Determined by ^1H NMR and HPLC.
[d] Determined by chiral HPLC analysis (Chiralpak AD-H, hexane–2-propanol = 92:8).

A possible model to rationalize the present enantio- and diastereoselective Michael addition reaction is shown in Figure 1. Since the relative and absolute configurations of the product generated from pyrrolidine–pyridine organocatalysts are the same as those with triazole **3c** as a catalyst,[6]

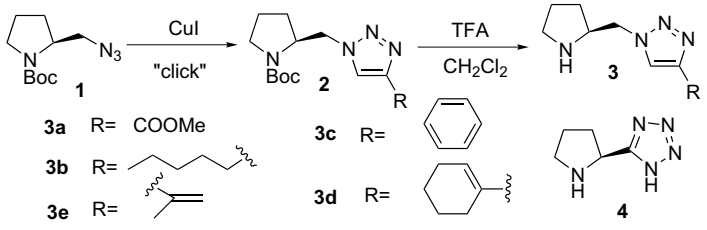
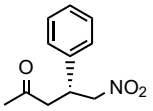
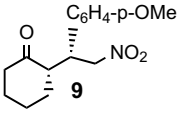
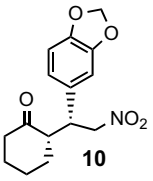
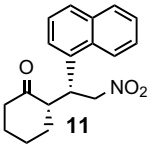
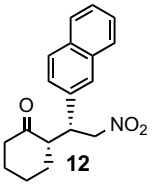
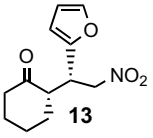
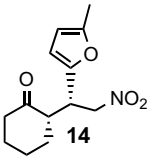
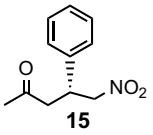


Figure 1. Organocatalysts for the Michael addition.

Table 2. Catalytic asymmetric Michael addition of ketone to nitroolefins[a]

Entry	Solvent	Time (h)	Product	Yield[b] (%)	dr[c] (*syn*/*anti*)	ee (%)[d] (*syn*)
1	$CHCl_3$	36	 **8**	75	14/1	99
2	H_2O	17		94	29/1	98
3	$CHCl_3$	36	 **9**	76	14/1	99
4	H_2O	13		96	38/1	99
5	$CHCl_3$	48	 **10**	79	43/1	93
6	H_2O	20		97	54/1	99
7	$CHCl_3$	48	 **11**	77	>99/1	>99
8	H_2O	17		99	>99/1	>99
9	$CHCl_3$	48	 **12**	71	11/1	>99
10	H_2O	24		94	23/1	>99
11	$CHCl_3$	15	 **13**	91	10/1	88
12	H_2O	7		90	11/1	98
13	$CHCl_3$	26	 **14**	94	9/1	98
14	H_2O	12		94	9/1	>99
15	$CHCl_3$	40	 **15**	83	—	50
16	H_2O	11		89	—	65

[a] Reactions were conducted on a 0.5-mmol scale in solvent (2 mL) using ketone (2.5 mmol) and 10 mol % of **3c**.
[b] Isolated yield.
[c] Determined by HPLC.
[d] Determined by chiral HPLC analysis (Chiralpak AD-H).

a transition state similar to the pyrrolidine–pyridine catalyst was proposed for triazole **3c** catalyzed Michael addition (Fig. 2). The R group occupies a larger space than a pyrrolidine to become a more efficient shield of the *si*-face of an

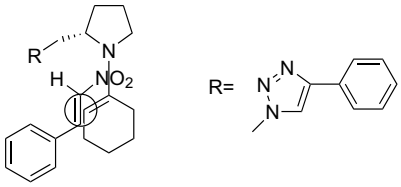


Figure 2. Proposed transition state.

enamine double bond,[6] which might be a possible reason for the highly stereoselective outcome.[16]

3. Conclusion

In conclusion, we have developed a series of novel asymmetric pyrrolidine–triazole organocatalysts and demonstrated their potential for Michael reactions. The pyrrolidine–triazole catalysts show several interesting features: (a) they can efficiently catalyze the Michael additions with high yields, excellent enantioselectivity, and a very good diastereoselectivity; (b) the Cu(I)-catalyzed 1,3-dipolar 'click' azide–alkyne cycloaddition provides the modular and tunable features for the present catalyst; (c) the triazole moiety cannot only act as a phase tag to complete the reaction in a broad range of solvents (including water), but can also serve as an efficient chiral-induction group to ensure a high selectivity. Further improvements of the present catalysts and the application of them to other types of reactions are currently underway in our laboratory.

4. Experimental

4.1. General

Column chromatography was carried out on silica gel (200–300 mesh). Melting points were measured using an electrothermal melting point apparatus, and are uncorrected. Commercial reagents were used as received, unless otherwise stated. ^{1}H and ^{13}C NMR were recorded on 300 or 400 MHz spectrometer. Chemical shifts are reported in parts per million from tetramethylsilane with the solvent resonance as the internal standard. The following abbreviations were used to designate chemical shift mutiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Splitting patterns that could not be easily interpreted are designated as multiplet (m) or broad (br). Optical rotations were measured using a 1 mL cell with a 1 dm path length on a digital polarimeter and are reported as follows: $[\alpha]_D^{20}$ (c in g per 100 mL of solvent). HPLC analysis was performed on Varian-ProStar using a ChiralPak AD-H columns purchased from Daicel Chemical Industries, Ltd.

4.2. Typical experimental procedure for the asymmetric Michael addition of cyclohexanone to nitroolefins

To a mixture of nitroolefin (0.5 mmol) and a chiral pyrrolidine–triazole organocatalyst (0.05 mmol) in solvent ($CHCl_3$ or H_2O) was added cyclohexanone (1.0 mL, 9.6 mmol). The mixture was stirred vigorously at an ambient temperature until completion of the reaction by monitoring on TLC. The solution was quenched with 1 M HCl (10 mL) and extracted with CH_2Cl_2 (3 × 15). The organic phase was washed with saturated NaCl solution (3 × 10 mL). The combined extracts were dried over Na_2SO_4, and evaporated, and purified by flash column chromatography on silica gel using a mixture of petroleum–ethyl acetate (8:1) to give the Michael adduct.

The relative configurations of the products (*syn* and *anti*) were determined by the comparison of ^{1}H NMR spectral data with those reported in the literature. The absolute configurations of the product were determined by comparison of specific rotation values with those reported in the literature. With the exception of compound **14**, all other compounds in Table 2 are known in the literature.[6]

4.3. 4-Phenyl-1-(((*S*)-pyrrolidin-2-yl)methyl)-1*H*-1,2,3-triazole 3c

Under the click chemistry conditions,[12b] *N*-Boc-(*S*)-2-azidomethylpyrrolidine **1** (2.26 g, 10.0 mmol) was dissolved in a 9:1 mixture of DMSO (36 mL) and H_2O (4 mL). Phenylacetylene (1.02 g, 10.0 mmol) was added, followed by CuI (191 mg, 1.0 mmol). At room temperature, the heterogeneous mixture was vigorously stirred overnight, until all the starting material had been consumed by TLC analysis (about 24–30 h). The reaction mixture was then diluted with CH_2Cl_2 (200 mL). The organic phase was washed with H_2O (3 × 100 mL) and NaCl (2 × 100 mL), dried over Na_2SO_4, and the solvent was evaporated. The intermediate *N*-Boc-pyrrolidine derivative **2** was obtained in quantitative yield as a white solid (3.35 g), and used without additional purification.

The crude product **2** (3.35 g) was dissolved in a 1:4 mixture of trifluoroacetic acid and dichloromethane (37 mL) and the solution was stirred for 6 h at an ambient temperature, at which time the solvent was evaporated under reduced pressure. The residue was dissolved in 30 mL of $CHCl_3$, followed by the addition of 10% aqueous ammonia. The mixture was stirred for 10 min and diluted with 30 mL of $CHCl_3$. The solution was washed with brine, and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to afford pure compound **3c**. Other organocatalysts **3a** and **3b** and **3d–e** were also obtained via similar processes. The total yield of **3c** in two steps: 1.99 g (87%). Yellow solid, mp 77–78 °C. $[\alpha]_D^{20} = +18$ (c 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.36–1.47 (m, 1H), 1.60–1.76 (m, 2H), 1.82–1.99 (m, 1H), 1.95 (s, 1H), 2.87 (t, $J = 6.6$ Hz, 2H), 3.50–3.59 (m, 1H), 4.14 (dd, $J = 7.5$, 13.5 Hz, 1H), 4.36 (dd, $J = 4.8$, 13.5 Hz, 1H), 7.27 (t, $J = 2.4$ Hz, 1H), 7.36 (t, $J = 7.5$ Hz, 2H), 7.80 (t, $J = 8.4$ Hz, 2H), 7.89 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.8, 29.3, 46.8, 55.7, 58.1, 120.9, 125.8, 128.2, 129.0, 131.0, 147.6.

4.4. 1-(((*S*)-Pyrrolidin-2-yl)methyl)-1*H*-1,2,3-triazole-4-carboxylic acid methyl ester 3a

Compound **3a** was obtained in a 72% yield from **1** (two steps) as a yellowish oil. $[\alpha]_D^{20} = +12$ (c 1.0, $CHCl_3$). ^{1}H

NMR (300 MHz, $CDCl_3$): δ 1.49–1.58 (m, 1H), 1.75–1.83 (m, 2H), 1.95–2.04 (m, 1H), 2.77 (s, 1H), 2.94–3.02 (m, 2H), 3.68–3.71 (m, 1H), 3.95 (s, 3H), 4.31 (dd, $J = 8.4$, 13.5 Hz, 1H), 4.49 (dd, $J = 4.5$, 14.1 Hz, 1H), 8.32 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.5, 28.9, 46.5, 52.1, 55.2, 57.7, 128.5, 139.6, 161.4.

4.5. 4-Pentyl-1-(((*S*)-pyrrolidin-2-yl)methyl)-1*H*-1,2,3-triazole 3b

Compound **3b** was obtained in an 83% yield from **1** (two steps) as a brown oil. $[\alpha]_D^{20} = -13$ (*c* 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 0.87–0.95 (m, 3H), 1.31–1.36 (m, 4H), 1.41–1.53 (m, 1H), 1.62–1.81 (m, 4H), 1.88–1.99 (m, 1H), 2.37 (br, 1H), 2.70 (t, $J = 8.1$ Hz, 2H), 2.95 (t, $J = 7.2$ Hz, 2H), 3.55–3.64 (m, 1H), 4.18 (dd, $J = 7.8$, 13.5 Hz, 1H), 4.37 (dd, $J = 4.5$, 13.2 Hz, 1H), 7.41 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9, 22.3, 25.3, 25.6, 28.9, 29.0, 31.4, 46.4, 55.1, 57.9, 121.4, 148.2.

4.6. 4-Cyclohexenyl-1-(((*S*)-pyrrolidin-2-yl)methyl)-1*H*-1,2,3-triazole 3d

Compound **3d** was obtained in an 84% yield from **1** (two steps) as a brown oil. $[\alpha]_D^{20} = -4$ (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 1.43–1.52 (m, 1H), 1.64–1.70 (m, 3H), 1.72–1.84 (m, 4H), 1.90–1.98 (m, 1H), 2.20 (t, $J = 3.2$ Hz, 2H), 2.39 (t, $J = 1.6$ Hz, 1H), 2.53 (s, 1H), 2.95 (t, $J = 6.8$ Hz, 2H), 3.56–3.63 (m, 1H), 4.19 (dd, $J = 8.0$, 14.0 Hz, 1H), 4.39 (dd, $J = 4.4$, 13.6 Hz, 1H), 6.50 (s, 1H), 7.56 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.1, 22.4, 25.2, 25.3, 26.3, 28.9, 46.4, 55.1, 57.9, 119.1, 124.7, 127.3, 149.2.

4.7. 4-(Prop-1-en-2-yl)-1-(((*S*)-pyrrolidin-2-yl)methyl)-1*H*-1,2,3-triazole 3e

Compound **3e** was obtained in an 88% yield from **1** (two steps) as a brown oil. $[\alpha]_D^{20} = +12$ (*c* 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 1.43–1.54 (m, 1H), 1.69–1.84 (m, 2H), 1.90–2.04 (m, 1H), 2.13 (s, 3H), 2.64 (s, 1H), 2.95 (dd, $J = 2.4$, 3.9 Hz, 2H), 3.57–3.66 (m, 1H), 4.20 (dd, $J = 8.1$, 13.5 Hz, 1H), 4.41 (dd, $J = 4.5$, 13.5 Hz, 1H), 5.08 (s, 1H), 5.70 (s, 1H), 7.68 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.5, 25.3, 28.9, 46.4, 55.1, 57.9, 112.1, 120.5, 133.5, 148.4.

4.8. (*S*)-2-((*S*)-1-(5-Methylfuran-2-yl)-2-nitroethyl)cyclohexanone 14

Yellow solid, mp 63–65 °C. $[\alpha]_D^{20} = -11$ (*c* 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 1.25–1.34 (m, 1H), 1.60–1.71 (m, 2H), 1.78–1.86 (m, 2H), 2.08–2.19 (m, 1H), 2.24 (s, 3H), 2.33–2.48 (m, 2H), 2.69–2.76 (m, 1H), 3.85–3.90 (m, 1H), 4.62–4.67 (m, 1H), 4.70–4.80 (m, 1H), 6.02 (dd, $J = 2.4$, 5.4 Hz, 1H), 6.04 (m, 1H).^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.5, 25.0, 28.2, 32.5, 37.6, 42.5, 51.0, 76.7, 106.1, 109.6, 148.9, 151.9, 211.1. The enantiomeric excess was determined by HPLC with a chiral Chiralpak AD-H column at 280 nm (hexane–2-propanol = 98:2), 1.0 mL/min, $t_R = 13.5$ min (*syn*), 14.1 (*anti*, minor), 15.2 min (*anti*, major), >99% ee.

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16. While this manuscript was in submission, an independent, similar pyrrolidine–triazole catalyzed Michael addition reaction was achieved in the presence of TFA under solvent-free condition, which was published on web on November 4, 2006, by Cheng et al. To review the updated reference: Luo, S.; Xu, H.; Mi, X.; Li, J.; Zheng, X.; Cheng, J.-P. *J. Org. Chem.* **2006**, *71*, 9244–9247.