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Hydroxyphthalimide allied triazole-pyrrolidine catalyst for asymmetric Michael additions in water

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ABSTRACT

A new hydroxyphthalimide-coupled triazole-pyrrolidine derivative has been synthesized and demonstrated as an efficient and stereoselective organocatalyst for the asymmetric Michael addition reaction of ketones to nitro olefins at room temperature. Good yields and high selectivities were achieved when benzoic acid was used in combination with organocatalyst **1**, employing water as the reaction medium.

1. Introduction

The asymmetric Michael addition is one of the most powerful synthetic tools for the construction of stereoselective carbon–carbon bonds.[1] In recent years, this process has gained prominence from synthetic organic chemists working in the field of organocatalysis due to the formation of stereoenriched adducts with multiple stereogenic centres in a single step.[2] In particular, the use of nitroolefins as Michael acceptors has received large attention for the efficient formation of chiral γ-nitro carbonyl compounds, which serve as versatile building blocks for the synthesis of complex organic molecules.[3] Over the past few years, various proline-based organocatalysts, such as pyrrolidine-triazole,[4] pyrrolidine-tetrazole,[5] pyrrolidine-thiourea,[6] pyrrolidine-sulfonamide,[7] pyrrolidine-pyridine,[8] pyrrolidine-imidazolium,[9] 2,2-bipyrrolidine[3b,10] have been successfully employed for asymmetric Michael additions with diverse range of stereoselectivities. Further work in this field to develop new organocatalysts would be a useful addition to the existing methods. With our continued interest on organocatalysts,[11,12] we have developed a new hydroxyphthalimide-linked triazole-pyrrolidine catalyst (Fig. 1) from proline using the Huisgen 1,3-dipolar cycloaddition, 'click reaction'.[13] We envisioned that *N*-propargyloxyphthalimide **3** could participate in a click reaction with Boc-protected proline azide **2** to afford **4**, which upon deprotection of the Boc group would yield a new hydroxyphthalimide-linked triazole-pyrrolidine **1** (Scheme 1). Structurally it possesses a privileged chiral pyrrolidine backbone as the catalytically active site, which efficiently activates the carbonyl compounds via the formation of an enamine intermediate and planar triazole ring as the steric controller, which directs the reactivity towards the less hindered stereotopic face of the enamine double bond furnishing the Michael products with high stereoselectivity.[14] Herein, we report the use of a hydroxyphthalimide-linked triazole-pyrrolidine in the asymmetric Michael addition reaction of ketones with various nitroolefins.

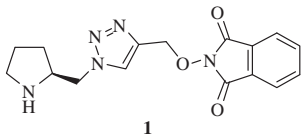

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Figure 1. Structure of organocatalyst **1**.

2. Results and discussion

The hydroxyphthalimide-linked organocatalyst **1** was synthesized from the known azide **2** (readily obtained from L-proline)[15] as illustrated in Scheme 1. Accordingly, the Boc-protected proline azide **2** was treated with commercially available *N*-propargyloxyphthalimide **3** under click conditions to furnish the protected derivative **4** in 92% yield, which upon deprotection of the Boc group with 5 M HCl/EtOH resulted in the desired organocatalyst **1** (89% yield, Scheme 1). The efficiency of the catalyst **1** was evaluated in a model reaction of cyclohexanone **5a** with β-nitrostyrene **6a** (Scheme 2). Initially, the reaction was performed in THF with 10 mol % of the catalyst at rt, and it was found that the reaction proceeded in 24 h to provide the Michael product **7a** in 65% yield. The *syn*/*anti* ratio of the product obtained was 7:3 (determined by ^{1}H NMR of the crude product) and the enantiomeric excess was 72% (determined by chiral HPLC, Table 1, entry 1).

To further improve the yield as well as the stereoselectivity, we investigated the effect of different solvents such as CH_2Cl_2, MeOH, DMF, toluene and H_2O. The results are summarized in Table 1. The reaction proceeded well in polar solvents such as MeOH, DMF and H_2O resulting in the Michael adduct in good yield, diastereoselectivity and enantioselectivity. In non-polar solvents, the reaction

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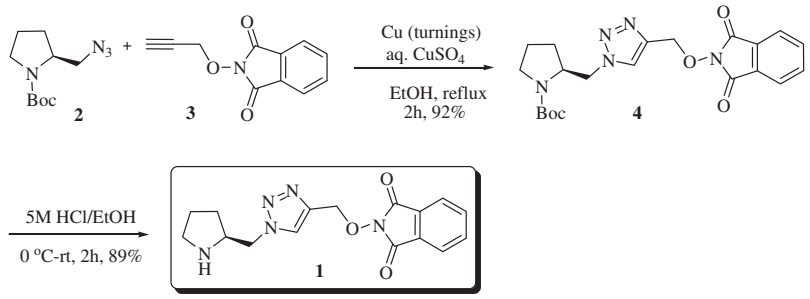
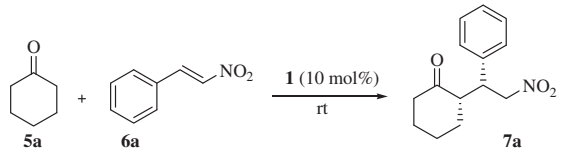


Scheme 1. Synthesis of catalyst **1**.



Scheme 2. Michael addition of cyclohexanone to nitrostyrene.

Table 1
Screening of solvents

Entry	Solvent	Time (h)	Yield[a] (%)	*syn*/*anti*[b]	ee[c] (%)
1	THF	24	65	7:3	72
2	CH_2C1_2	24	68	6:4	70
3	DMF	18	84	8:2	79
4	Toluene	24	56	6:4	61
5	MeOH	18	87	9:1	82
6	H_2O	18	92	9:1	88
7	—	18	80	9:1	85

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

was slow and the products were formed in low yield with less stereoselectivity. The reaction was also performed under solvent-free conditions, in which the reaction was completed in 18 h with 80% yield (9:1, 85% ee) (Table 1, entry 7). The best result was observed when H_2O was used as the solvent (Table 1, entry 6). With the hope of improving the yield and selectivity, we next examined the effect of various acid additives such as CSA, TFA, pTSA, PhOH, PhCOOH and formic acid. From these experiments, we found that the use of PhCOOH as an additive improved the selectivity as well as the yield, as shown in Table 2.

Table 2
Screening of additives

Entry	Additive[d] (5 mol %)	Yield[a] (%)	*syn*/*anti*[b]	ee[c] (%)
1	CSA	85	92:8	84
2	TFA	82	93:7	80
3	*p*-TSA	87	94:6	85
4	PhOH	86	92:8	82
5	PhCOOH	95	96:4	91
6	HCOOH	90	94:6	89

[a] Isolated yields.
[b] Determined by the ^{1}H NMR of the crude product.
[c] Determined by chiral HPLC.
[d] Reactions performed in water for 18 h.

With the established reaction conditions in hand, a series of nitroolefins (Michael acceptors) with different ketones (Michael donors) were examined to expand the substrate scope and the results are summarized in Table 3. All β-nitrostyrenes irrespective of the nature of substituents on aryl group were reacted smoothly with cyclohexanone (Table 3, entries 1–8) and also equally with cyclopentanone (Table 3, entries 9 and 10) to give the corresponding Michael adducts in good yields with high diastereoselectivity and enantioselectivity. The reaction of β-nitrostyrene with acetone was very sluggish and afforded the desired product in low yield with low selectivity even after prolonged reaction time (Table 3, entries 11 and 12).

Based on the above-mentioned experimental results, we propose two potential transition states (Fig. 2) to rationalize the stereochemical outcome of the asymmetric Michael addition reaction performed by catalyst **1**. TS-1 is an acyclic synclinal transition state in which the planar triazole ring effectively shields the *Si* face of the enamine double bond in the ketone and allows the reaction to occur via *Re*–*Re* approach.[16,9a] The addition of water improved the efficiency of catalyst towards yield and selectivity, this suggests that TS-2 may be more favorable.

3. Conclusions

In conclusion, we have developed a new hydroxyphthalimide linked triazole-pyrrolidine organocatalyst by employing click reaction for the asymmetric Michael addition of ketones to nitro olefins. The reactions were performed in water with the aid of an acid co-catalyst leading to the desired products in good yield and high selectivity. Further investigations to extend the scope of this catalyst are under way in our laboratory.

4. Experimental section

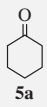
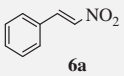
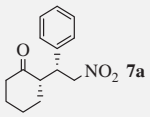
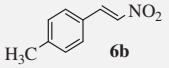
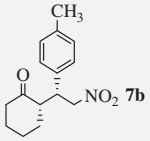
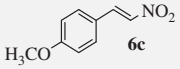
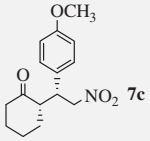
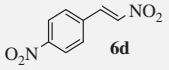
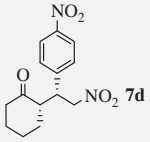
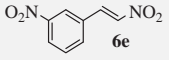
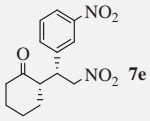
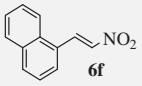
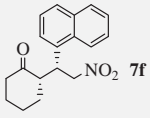
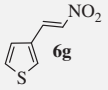
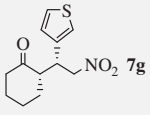
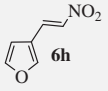
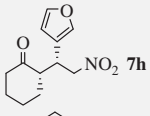
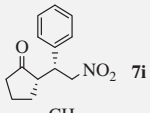
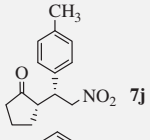
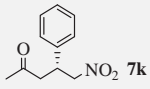
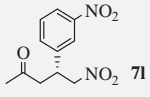
4.1. General

All solvents and reagents were purified by standard techniques. Crude products were purified by column chromatography on 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 and a Brucker Avance 300. Chemical shifts were reported in parts per million with respect to internal TMS. Coupling constants (*J*) are quoted in Hertz. Mass spectra were obtained on an Agilent Technologies LC/MSD Trap SL. Chiral HPLC analysis was carried out on chiral pak OD-H, IC or IA columns using a mixture of isopropanol and hexanes as the eluent.

4.1.1. (*S*)-*tert*-Butyl-2-((4-((1,3-dioxoisoindolin-2-yloxy)-1*H*-1,2,3-triazol-1-yl)methyl)pyrrolidine-1-carboxylate 4

To a mixture of *N*-propargyloxyphthalimide **3** (200 mg, 0.99 mmol) in ethanol (5 ml) was added *N*-Boc-proline azide **2** (240 mg, 1.09 mmol), Cu turnings (5 mg), aq saturated copper sulfate solution (0.1 mL) and refluxed for 2 h. After completion of the reaction (monitored by TLC), ethanol was removed in vacuo

Table 3
Asymmetric Michael addition of ketones to nitroolefins using organocatalyst **1**

Entry	Ketone	Nitroolefin	Time (h)	Product	Yield[a] (%)	*syn*/*anti*[b]	ee[c] (%)
1	 **5a**	 **6a**	18	 **7a**	95	96:4	91
2	**5a**	 **6b**	18	 **7b**	94	95:5	90
3	**5a**	 **6c**	18	 **7c**	96	97:3	87
4	**5a**	 **6d**	18	 **7d**	93	98:2	95
5	**5a**	 **6e**	18	 **7e**	95	94:6	94
6	**5a**	 **6f**	20	 **7f**	92	93:7	86
7	**5a**	 **6g**	20	 **7g**	89	94:6	85
8	**5a**	 **6h**	20	 **7h**	90	92:8	86
9	 **5b**	**6a**	24	 **7i**	86	93:7	84
10	**5b**	**6b**	24	 **7j**	82	90:10	82
11	 **5c**	**6a**	48	 **7k**	75	—	41
12	**5c**	**6e**	48	 **7l**	64	—	36

[a] Isolated yields.
[b] Determined by ^{1}H NMR and HPLC analysis.
[c] Determined by chiral HPLC using chiral pak-IA, IC or OD-H columns.

and purified by silica-gel column chromatography to afford Boc-protected triazole **4** (380 mg, 92% yield) as a white solid: mp: 122–124 °C; $[\alpha]_D^{27} = -39.6$ (*c* 0.6, $CHCl_3$); IR (Neat): *ν* 2927, 2361, 1791, 1732, 1698, 1465, 1397, 1170, 1050 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): *δ* 7.76–7.72 (m, 5H), 5.35–5.31 (m, 2H), 4.61–4.58 (m, 2H), 4.12–4.08 (m, 1H), 3.45–3.41 (m, 2H), 1.88–1.83 (m, 3H), 1.52 (s, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz): *δ* 163.1, 134.2, 129.1, 125.3, 124.9, 123.5, 79.9, 70.1, 57.2, 52.6, 51.5, 47.0, 29.7, 28.7, 22.6; ESIMS: *m*/*z* 428 $[M+H]^+$; HRMS calcd for $C_{21}H_{26}N_5O_5$: 428.1928, found: 428.1945.

4.1.2. (*S*)-2-((1-(Pyrrolidin-2-ylmethyl)-1*H*-1,2,3-triazol-4-yl)methoxy)isoindoline-1,3-dione 1

Five molar HCl (0.5 mL) was added to a solution of triazole **4** (100 mg) in ethanol at 0 °C and stirred for 2 h at rt. After completion of the reaction, the solvent was removed in vacuo and the

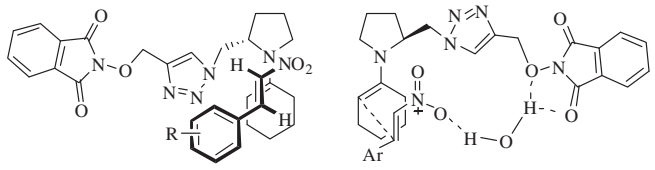


Figure 2. Proposed transition state for Michael additions.

reaction mixture was dissolved in CH_2Cl_2 (10 mL) and quenched with saturated $NaHCO_3$ solution. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layer was dried over Na_2SO_4, concentrated in vacuo and purified by silica-gel column chromatography to afford organocatalyst **1** (67 mg, 89% yield) as a white solid: mp: 128–131 °C; $[\alpha]_D^{27} = -18.4$ (*c* 0.3, $CHCl_3$); IR (Neat): *ν* 2924, 1731, 1694, 1462, 1217, 1133, 1051 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): *δ* 7.74–7.70 (m, 5H), 5.35–5.32 (s, 2H), 4.68 (br s, 1H), 4.24–4.21 (m, 2H), 3.86–3.82 (m, 1H), 2.85–2.82 (m, 2H), 1.79–1.74 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): *δ* 163.4, 134.6, 129.2, 125.3, 124.9, 123.2, 70.3, 57.7, 51.5, 46.8, 30.9, 23.4; ESIMS: *m*/*z* 328 $[M+H]^+$; HRMS calcd for $C_{16}H_{18}N_5O_3$: 328.1404, found: 328.1415.

4.1.3. General procedure for the Michael addition of cyclohexanone to β-nitrostyrene

To a mixture of catalyst **1** (10 mol %), PhCOOH (5 mol %) and corresponding nitroolefin in water (0.5 mL) was added cyclohexanone (5 equiv) and stirred for appropriate time (Table 3) at rt. After completion of the reaction (monitored by TLC), the reaction mixture was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic layer was dried over Na_2SO_4, concentrated in vacuo and purified by silica-gel column chromatography to afford the desired product. Relative and absolute configurations of the products were determined by comparison of ^1H NMR, ^{13}C NMR and specific rotation values with those reported in the literature.

4.1.3.1. (*S*)-2-((*R*)-2-Nitro-1-tolylethyl)cyclopentanone 7j. Thick liquid; $[\alpha]_D^{25} = -12.8$ (*c* 0.5, $CHCl_3$); IR (Neat): *ν* 2924, 2862, 1708, 1552, 1437, 1373, 1251 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): *δ* 7.12 (d, 2H, *J* = 7.6 Hz), 7.02 (d, 2H, *J* = 7.6 Hz), 4.86 (dd, 1H, *J* = 4.7, 12.4 Hz), 4.58 (dd, 1H, *J* = 9.6, 12.4 Hz), 3.32 (td, 1H, *J* = 4.6, 9.4, 14.2 Hz), 2.48 (td, 1H, *J* = 4.5, 9.8, 14.6 Hz), 2.24 (s, 3H), 2.10–2.01 (m, 4H), 1.92–1.88 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): *δ* 216.6, 135.5, 134.2, 126.4, 125.2, 75.8, 64.3, 39.5, 28.8, 23.8, 17.6, 14.4; ESIMS: *m*/*z* 248 $[M+H]^+$; HRMS calcd for $C_{14}H_{18}NO_3$: 248.1614, found: 248.1511; HPLC: chiral pak-IA, hexane/isopropanol = 95:5, 1.0 mL/min, R_t = 17.7 (major) and 20.8 (minor), 82% ee, *syn*/*anti* = 90/10.

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