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Highly efficient and recoverable dendritic organocatalyst from click chemistry for the asymmetric michael addition of ketones to nitroolefins without the use of organic solvent

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ABSTRACT

A series of pyrrolidine-triazole based dendritic catalysts have been synthesized and applied directly in the asymmetric Michael addition of ketones to nitroolefins without the use of an organic solvent. Good yields (up to 99%), and high diastereoselectivities (up to *syn*/*anti* = 45:1) and enantioselectivities (up to 95% ee) have been obtained. Furthermore, the third generation catalyst can be reused at least five times without significant loss of catalytic activity.

1. Introduction

Interest has greatly increased in the recent years on development of organocatalysts for organic reactions because they are environmentally benign, easy to handle, and highly efficient. Several excellent organocatalysts for asymmetric reactions that achieve high enantioselectivities have been reported.[1] Though the advances are great, there are still disadvantages associated with the use of organocatalysts. One major limitation of organocatalyzed reactions is the high-catalyst loadings that are generally required (10–30 mol %) to complete the reactions thoroughly. This causes cost problems, especially in industrial applications when a large amount of expensive chiral raw materials are needed to prepare the catalysts. Thus, the development of recyclable organocatalysts is of great significance to expand upon the scope to encompass further industrial applications. Recently, great efforts have been devoted to immobilizing and further recycling these organocatalysts using supports such as ionic liquids,[2] polystyrenes,[3] flourous tags,[4] PEG,[5] silica gel,[6] and dendrimers.[7]

The asymmetric Michael addition of ketones or aldehydes to nitroolefins is a powerful method for the construction of enantiomerically enriched nitroalkanes, which are versatile synthetic intermediates in organic synthesis. Over the past decade, great progress has been made in the organocatalytic asymmetric version of these reactions to give synthetically useful products with high enantiopurities.[8] Within these reported catalysts, pyrrolidine derivates bearing 1,2,3-triazole substituents, which are easy to prepare via a click reaction, show high catalytic activity and enantioselectivity.[9]

Dendrimers are well-defined macromolecules with tunable structures, shapes, sizes, and solubilities. Since the first report in 1994, dendritic catalysts have been become a subject of intensive research.[10] Such novel catalysts can be used under homogeneous conditions, and be readily recovered via simple precipitation or nanofiltration methods. To the best of our knowledge, a dendritic organocatalyst system has yet to be investigated in the asymmetric Michael addition of ketones to nitroolefins. Therefore, we attempted to anchor the pyrrolidine derivates to dendrimers via a click reaction, and investigate their catalytic activity in asymmetric Michael addition of ketones to nitroolefins. Herein, we report dendritic catalysts derived from pyrrolidine derivates via a click reaction which are highly active and selective for the asymmetric Michael addition of ketones to nitroolefins. Moreover, the catalysts can be easily recovered after the reaction is over, and recycled up to five times with only a slight loss in catalytic activity.

2. Results and discussion

The synthetic route to a series of polyether dendrimers-supported pyrrolidine-triazole organocatalysts **5a–c** is shown in Scheme 1. Azidomethylpyrrolidine **1** was prepared according to a reported literature method.[9a] On the other hand, brominated polyether dendrimers **2a–c** are treated with 4-ethynylbenzyl alcohol **3** under basic conditions (NaH, DMF/THF = 1:1) to give alkyne-functionalized polyether dendrimers **4a–c**. Azide **1** was then grafted to dendrimers **4a–c** by a Cu(I)-catalyzed click reaction to afford the desired dendrimer-supported organocatalysts **5a–c**. The detailed experimental procedures and the spectroscopic data

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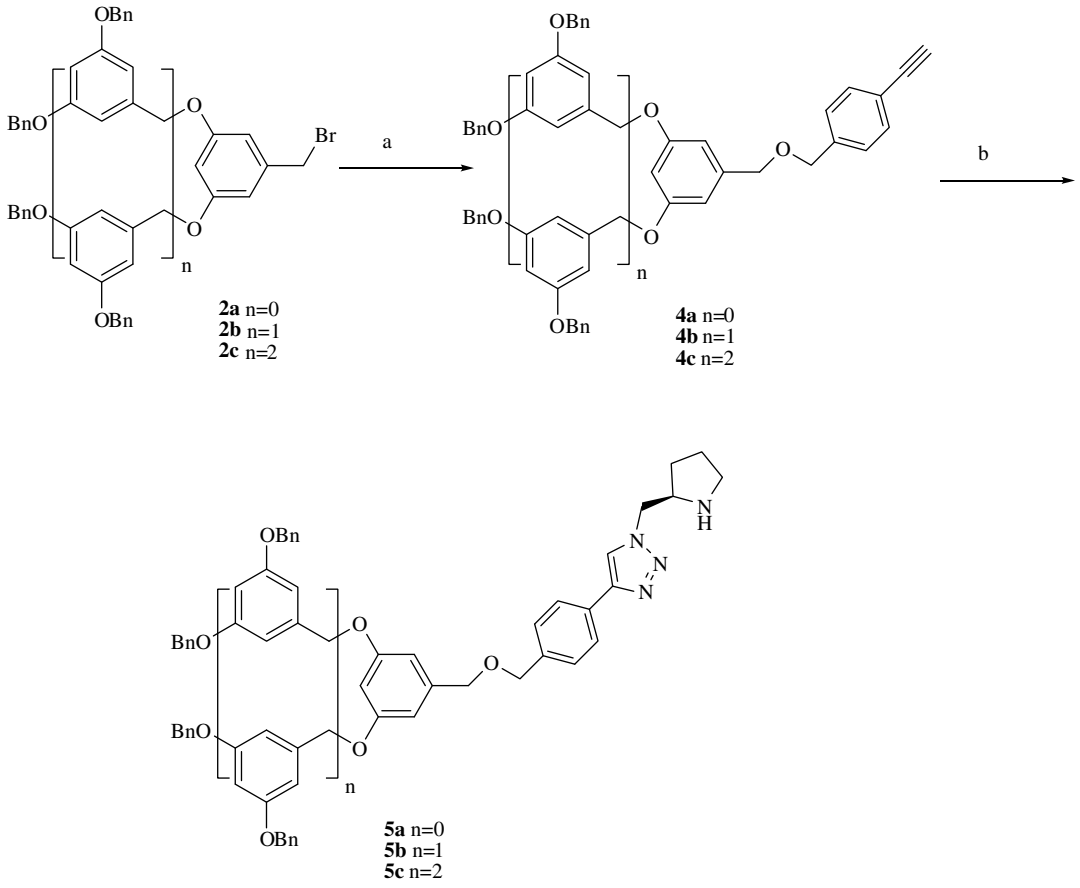


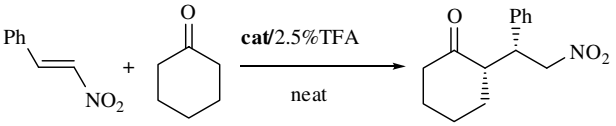
Scheme 1. Reaction and conditions: (a) 4-ethynylbenzyl alcohol **3**, NaH, DMF/THF = 1:1, rt, 24 h; (b) azidomethylpyrrolidine **1**, CuI, DIPEA, toluene/*t*-BuOH = 4:1.

are summarized in Section 4. These catalysts were purified by flash column chromatography, and were characterized by ^{1}H NMR/^{13}CNMR spectroscopy and elemental analysis.

The catalytic activity of **5a–c** for the asymmetric Michael addition of ketones to nitroolefins is investigated by performing a model reaction of *trans*-β-nitrostyrene with cyclohexanone under various reaction conditions. The results are summarized in Table 1. As can be seen from Table 1, with dendritic catalysts **5a–c**, the Michael addition reaction proceeded smoothly with trifluoroacetic acid (TFA) as an additive under neat conditions; the *syn*-Michael adducts were obtained as the major products in excellent yields (96–99%) and with high diastereoselectivity and enantioselectivity (entries 1–3). Notably, the third generation catalyst **5c** provides the best results in terms of the catalytic activity and selectivity under the same reaction conditions. Therefore, **5c** was chosen for the subsequent studies of the effects of other conditions on the reaction. First, the influence of catalyst loading was examined (entries 4–6). It is found that no change had been observed by increasing the amount of **5c** to 20%. A sharp drop in both the yield and the enantioselectivity was observed when reducing the catalyst loading to 5% and further to 2%. Attention was also paid to the effect of reactant ratios on the reaction (entries 7–9). The results in Table 1 show that 5 equiv of cyclohexanone to 1 equiv of *trans*-β-nitrostyrene gave the best results. We also studied the effect of water on the reaction (entries 10 and 11); this showed that a slight drop in enantioselectivity but a sharp increase in diastereoselectivity was observed in the presence of water when using 5 equiv of cyclohexanone. Thus, the optimum reaction conditions were obtained by performing the reaction of 5 equiv of cyclohexanone with 1 equiv of nitroolefin, 10 mol % **5c**, and 2.5 mol % of TFA as additive without the use of an organic solvent.

To establish the scope of the reaction with **5c**, a series of substrates were tested under the optimized reaction conditions, and the results are summarized in Table 2. β-Nitroolefins, which possess either neutral (entries 1 and 8), electron- withdrawing (entries 2, 3 and 7), or -donating (entries 4–6), and heterocyclic groups

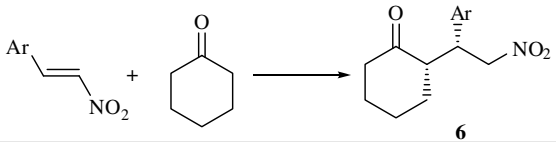
Table 1
Optimization of the reaction conditions[a]



Entry	Catalyst	Catalyst loading (%)	Reactant ratios[b]	Time (h)	Yield[c] (%)	*syn*/*anti*[d]	ee[e] (%)
1	**5a**	10	20	18	96	40:1	91
2	**5b**	10	20	18	96	42:1	91
3	**5c**	10	20	18	99	45:1	94
4	**5c**	20	20	18	98	45:1	94
5	**5c**	5	20	18	89	35:1	89
6	**5c**	2	20	18	78	26:1	86
7	**5c**	10	10	18	98	45:1	94
8	**5c**	10	5	18	98	45:1	94
9	**5c**	10	2	18	96	25:1	90
10[f]	**5c**	10	5	24	98	>99:1	90
11[f]	**5c**	10	2	24	97	22:1	89

[a] Unless otherwise stated, all the reactions were performed with 2.5% TFA.
[b] Cyclohexanone/*trans*-β-nitrostyrene.
[c] Isolated yield.
[d] Determined by ^{1}H NMR of the crude product.
[e] Determined by HPLC analysis of the *syn*-product (chiral pak AD-H column).
[f] 0.25 mL water was added.

Table 2
Substrate scope of dendritic catalyst **5c**[a]



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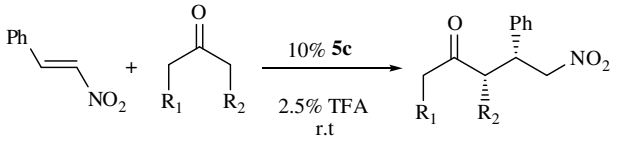
Entry	Ar	Product	Yield[b] (%)	*syn*/*anti*[c]	ee[d] (%)
1	C_6H_5–	**6a**	99	45:1	93
2	4-ClC_6H_4–	**6b**	93	40:1	93
3	4-BrC_6H_4–	**6c**	94	45:1	95
4	2,4-$MeO_2C_6H_3$–	**6d**	92	35:1	91
5	4-MeC_6H_4–	**6e**	96	45:1	92
6	4-$MeOC_6H_4$–	**6f**	94	35:1	88
7	3-$O_2NC_6H_4$–	**6g**	91	35:1	93
8	2-Naphthyl–	**6h**	99	25:1	92
9	2-Furanyl–	**6i**	93	25:1	92
10	2-Thiophenyl–	**6j**	95	16:1	89

[a] Reaction condition: **5c** (0.025 mmol), TFA (0.00625 mmol), β-nitroolefin (0.25 mmol), and cyclohexanone (0.14 mL, 1.25 mmol) at rt for 18 h.
[b] Isolated yield.
[c] Determined by ^{1}H NMR of the crude product.
[d] Determined by HPLC analysis of the *syn*-product (chiral pak AD-H column).

Table 3
The reactions of other Michael donors with *trans*-β-nitrostyrene catalyzed by **5c**



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Entry	R^1, R^2	Product	Yield[a] (%)	*syn*/*anti*[b]	ee[c] (%) *syn*/*anti*
1	R^1, R^2 = CH_2CH_2	**6k**	58	7:4	72/66
2	R^1, R^2 = H, H	**6l**	65	—	38
3	R^1 = H, R^2 = Me	**6m**	60	8:1	68

[a] Isolated yield.
[b] Determined by ^{1}H NMR of the crude product.
[c] Determined by HPLC analysis of the *syn*-product (chiral pak AD-H column).

(entries 9 and 10) and contain a variety of substitution patterns (*ortho*- and *meta*-, entries 4 and 7), were all tested as Michael acceptors. The results showed that the reactions proceeded efficiently (92–99% yield) with high to excellent levels of enantioselectivity (88–95% ee) and diastereoselectivity (*syn*/*anti* = 45:1), regardless of the electronic or steric properties of the substrate.

The use of ketones other than cyclohexanone as Michael donors was evaluated as well, and the results are shown in Table 3. The use of cyclopentanone as a Michael donor resulted in a moderate yield but a dramatic drop in both enantioselectivity and diastereoselectivity. With acetone and butanone, the desired adducts were produced with moderate yields but low enantioselectivities.

The recovery and the reuse of the catalyst **5c** were also investigated (Table 4). After reaction, the unreacted cyclohexanone was removed in vacuo, followed by the addition of ether (5 times) to extract the product thoroughly. The catalyst is almost quantitatively left in the reaction vessel, and is used directly in the next run. The catalyst can be used for four consecutive runs with no decrease in the isolated yield of adduct **6a** or in the stereoselectivity; however, in the fifth run a slight loss of product yield was observed while high levels of enantioselectivity and diastereoselectivity still remain even in the sixth run.

Table 4
Recycling of dendritic catalyst **5c** in the asymmetric catalysis of the reaction of *trans*-β-nitrostyrene with cyclohexanone[a]

Run	Time (h)	Yield[b] (%)	*syn*/*anti*[c]	ee[d] (%)
1	18	98	45:1	94
2	18	95	45:1	92
3	18	95	45:1	93
4	24	93	42:1	91
5	30	88	40:1	92
6	36	80	40:1	90

[a] Reaction conditions: **5c** (0.025 mmol), TFA (0.00625 mmol), β-nitrostyrene (0.25 mmol), cyclohexanone (0.14 mL, 1.25 mmol) at rt.
[b] Isolated yield.
[c] Determined by ^{1}H NMR of the crude product.
[d] Determined by HPLC (chiral pak AD-H column).

3. Conclusions

In conclusion, a highly efficient, dendritic organocatalyst for the diastereo- and enantioselective Michael addition of ketones to nitroolefins has been developed using a click chemistry method. The catalyst system represents the first dendritic organocatalyst for this type of reaction. The catalyst can be easily separated from the reaction system, and reused for several runs without significant loss in both the catalytic activity and the stereoselectivity. Due to the importance of the reuse of the organocatalyst, the development and application of other dendritic organocatalysts are currently in progress.

4. Experimental

4.1. General

All commercial reagents were used as received, and all reactions were carried out directly under open air, unless otherwise stated. All solvents were dried before use. Flash chromatography was performed on silica from QingDao Haiyang chemical Co.Ltd. FT-IR spectra were recorded on a Boi-Rad FTS135 infrared spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AV400. Chemical shifts were reported in ppm using tetramethylsilane (TMS, 0.00 ppm) as internal standard. Elemental analyses were carried out in a GmbH VarioEL V2.8 instrument. Optical rotations were measured with Perkin–Elmer digital polarimeter. High performance liquid chromatography (HPLC) was performed on Shimadzu L6AD, using Chiralpak AD-H column.

4.2. General procedure for the synthesis of 4a–c

Typical procedure: To a suspension of sodium hydride (60% dispersion in mineral oil; 0.16 g, 4 mmol) in a mixture of THF (10 mL) and DMF (10 mL) under nitrogen was added 4-ethynylbenzyl alcohol (0.396 g, 3 mmol) at 0 °C. The mixture was allowed to warm to room temperature, and stirred for 1 h. Compound **2a–c** (2 mmol) was then added at 0 °C. The mixture was then allowed to warm to room temperature and stirred for 24 h. The mixture was cooled to 0 °C and water (0.5 mL) was added to quench the reaction, and then the residue was purified by flash chromatography on silica gel (CH_2Cl_2) to give **4a–c**.

Compound **4a**: Prepared according to the above general procedure, the resulting residue was purified by column chromatography on silica gel (CH_2Cl_2) to give **4a** as a white liquid. Yield: 90%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 3.09 (s, 1H), 4.51 (s, 2H), 4.53 (s, 2H), 5.05 (s, 4H), 6.58 (s, 1H), 6.63 (s, 2H), 7.29–7.51 (m, 14H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 70.06, 71.51, 72.15, 83.54, 101.44, 106.63, 127.5, 128, 128.6, 132.2, 136.9, 139.1, 140.5, 160.1. Anal. Calcd for $C_{30}H_{26}O_3$: C, 82.92; H, 6.03. Found: C, 82.96; H, 6.00.

Compound **4b**: Prepared according to the above general procedure, the resulting residue was purified by column chromatography on silica gel (CH_2Cl_2) to give **4b** as a white foam. Yield: 83%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 3.07 (s, 1H), 4.50 (s, 2H), 4.52 (s, 2H), 4.98 (s, 4H), 5.04 (s, 8H), 6.58 (s, 1H), 6.59 (s, 2H), 6.61 (s, 2H), 6.69 (s, 4H), 7.31–7.47 (m, 24H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 70.00, 70.1, 71.53, 72.15, 83.55, 101.44, 101.56, 106.35, 106.66, 127.55, 128.00, 128.6, 132.2, 136.8, 139.3, 140.5, 160.0, 160.1. Anal. Calcd for $C_{58}H_{50}O_7$: C, 81.10; H, 5.87. Found: C, 81.23; H, 5.79.

Compound **4c**: Prepared according to the above general procedure, the resulting residue was purified by column chromatography on silica gel (CH_2Cl_2) to give **4b** as a white foam. Yield: 75%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 3.08 (s, 1H), 4.50 (s, 2H), 4.52 (s, 2H), 4.99–5.05 (m, 28H), 6.60–6.72 (m, 21H), 7.31–7.50 (m, 44H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 70.00, 70.1, 71.51, 72.11, 83.52, 101.38, 101.58, 106.37, 106.63, 127.51, 127.95, 128.54, 132.14, 136.75, 139.04, 139.18, 139.28, 140.52, 160.04, 160.13. Anal. Calcd for $C_{114}H_{98}O_{15}$: C, 80.17; H, 5.78. Found: C, 80.21; H, 5.81.

4.3. General procedure for the synthesis of 5a–c

Typical procedure: To a solution of **4a–c** (2 mmol) with azidomethylpyrrolidine **1** (0.252 g, 2 mmol) in toluene/*t*BuOH (15 mL, v:v = 4/1) under argon were added CuI (38.2 mg, 0.2 mmol), DIPEA (1 mL), the reaction mixture was stirred at room temperature overnight. After removal of the solvents, the resulting residue was purified by flash chromatography on silica gel (MeOH–CH_2Cl_2 = 1:100) to give **5a–c** as a pale yellow foam.

Compound **5a**: Prepared according to the above general procedure, the resulting residue was purified by column chromatography on silica gel (MeOH–CH_2Cl_2 = 1:100) to give **5a** as a pale yellow foam. Yield: 72%; $[\alpha]_D^{20} = +9.1$ (*c* 1, CH_2Cl_2), ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 1.53 (m, 1H), 1.78 (m, 2H), 1.98 (m, 1H), 2.99 (m, 2H), 3.69 (m, 1H), 4.30 (m, 1H), 4.45 (m, 1H), 4.50 (s, 2H), 4.54 (s, 2H), 5.03 (s, 4H), 6.56 (s, 1H), 6.63 (s, 2H), 7.29–7.43 (m, 12H), 7.80 (d, 2H), 7.95 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 25.14, 28.94, 29.66, 46.40, 54.60, 59.19, 70.04, 71.74, 72.03, 101.38, 106.63, 125.69, 127.49, 127.93, 128.25, 128.54, 129.89, 136.84, 138.15, 140.65, 147.3, 160.04. Anal. Calcd for $C_{35}H_{36}N_4O_3$: C, 74.98; H, 6.47; N, 9.99. Found: C, 74.87; H, 6.41; N, 10.08.

Compound **5b**: Prepared according to the above general procedure, the resulting residue was purified by column chromatography on silica gel (MeOH–CH_2Cl_2 = 1:100) to give **5b** as a pale yellow foam. Yield: 56%; $[\alpha]_D^{20} = +4.5$ (*c* 1, CH_2Cl_2), ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 1.58 (m, 1H), 1.83 (m, 2H), 2.03 (m, 1H), 3.05 (m, 2H), 3.77 (m, 1H), 4.47 (m, 2H), 4.51 (s, 2H), 4.54 (s, 2H), 4.98 (s, 4H), 5.03 (s, 8H), 6.54 (s, 1H), 6.58 (s, 2H), 6.63 (s, 2H), 6.69 (s, 4H), 7.30–7.42 (m, 42H), 7.72 (d, 2H), 7.88 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 25.12, 28.93, 29.62, 46.38, 54.60, 59.19, 69.93, 70.04, 71.76, 72.03, 101.43, 101.57, 106.34, 106.64, 125.70, 127.53, 127.96, 128.27, 128.54, 129.89, 136.76, 138.19, 139.32, 140.68, 147.3, 159.96, 160.14. Anal. Calcd for $C_{63}H_{60}N_4O_7$: C, 76.81; H, 6.14; N, 5.69. Found: C, 76.76; H, 6.09; N, 5.81.

Compound **5c**: Prepared according to the above general procedure, the resulting residue was purified by column chromatography on silica gel (MeOH–CH_2Cl_2 = 1:100) to give **5c** as a pale yellow foam. Yield: 40%; $[\alpha]_D^{20} = +2.8$ (*c* 1, CH_2Cl_2), ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 1.53 (m, 1H), 1.77 (m, 2H), 1.98 (m, 1H), 2.99 (m, 2H), 3.71 (m, 1H), 4.37 (m, 2H), 4.47 (s, 2H), 4.50 (s, 2H), 4.93 (s, 8H), 4.94 (s, 4H), 4.98 (s, 16H), 6.53 (m, 6H), 6.61 (m, 3H), 6.65 (m, 12H), 7.30–7.39 (m, 22H), 7.77 (d, 2H), 7.96 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 24.77, 28.67, 29.65, 46.18, 53.43, 58.44, 69.92, 70.03, 71.71, 72.01, 101.42, 101.57, 106.02, 106.34, 106.60, 125.64, 127.49, 127.92, 128.21, 128.51, 129.61, 136.72, 138.21, 139.19, 139.31, 140.70, 147.27, 159.95, 160.01, 160.09. Anal. Calcd for $C_{119}H_{108}N_4O_{15}$: C, 77.93; H, 5.94; N, 3.05. Found: C, 77.86; H, 5.87; N, 3.13.

4.4. General procedure for the dendritic catalysts 5a–c catalyzed Michael addition reaction of ketones with nitroolefins

Nitroolefin (0.25 mmol) and **5c** (45.6 mg, 10 mol %) were mixed with ketones (1.25 mmol) in the presence of TFA (2.5 mol %)[11] at room temperature. The homogeneous reaction mixture was stirred at room temperature for 18 h. The unreacted cyclohexanone was removed in vacuo, followed by the addition of ether (5 × 20 mL) to extract the product thoroughly. The ether solution was combined, and the solvent was reduced under reduced pressure and was loaded onto a silica gel column to afford the Michael adducts **6a–j** as a white solid.

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