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Stereoselective synthesis of functionalised cyclopropanes from nitroalkenes via an organocatalysed Michael-initiated ring-closure approach

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Dedicated with admiration to Professor Henri B. Kagan on the occasion of his 80th birthday

ABSTRACT

Synthetically useful nitrocyclopropanes are easily obtained via Michael addition of dimethyl bromomalonate to nitrostyrenes promoted by commercially available (*S*)-α,α-di-β-naphthlyl-2-pyrrolidinemethanol as the catalyst, followed by DABCO-mediated intramolecular nucleophilic substitution. The functionalised nitrocyclopropanes are obtained in good yield, excellent diastereoselectivity and up to 49% ee.

1. Introduction

Chiral cyclopropane is the key-structural motif of a variety of natural products, agrochemical targets and biologically active compounds including a notable number of therapeutic agents.[1] Moreover, cyclopropyl containing compounds are attractive synthetic intermediates and building blocks.[2]

Consequently, many synthetic efforts have been focused on the development of efficient and stereoselective methodologies of cyclopropanation of alkenes essentially based through the generation of organometallic carbenoid species and ylides.[3] The organocatalytic approach has been gaining importance in this context as demonstrated by several reports showing the ability of various L-proline derivatives to promote the process via iminium activation of α,β-unsaturated aldehydes and ketones.[4] Excellent results in terms of diastereo- and enantioselectivity have been achieved by Gaunt et al. in the cyclopropanation of acrylate esters or amides, using in situ generation of chiral ylides by using readily available cinchona alkaloid derivatives.[5] Intramolecular variants have also been established.[6] Connon et al. reported that bifunctional cinchona alkaloid-derived thioureas are able to catalyse the enantioselective cyclopropanation of nitroalkenes with dimethyl chloromalonate via Michael-initiated ring-closure reaction (MIRC)[7] (Scheme 1).

Firstly, the enantioselective Michael addition occurs, followed by DBU-mediated intramolecular nucleophilic substitution on the adduct. The stereocontrol of the reaction is established through non-covalent activation of nitroalkene and dimethyl chloromalonate by the acid and basic sites of the thiourea catalyst, respectively. Nitrocyclopropanes have been isolated in good yield, complete control of the diastereoselectivity and up to 47% ee. This simple approach has been recently improved by Yan using 6′-demethyl-quinine as the catalyst and dimethyl bromomalonate as the nucleophile.[8] In this case, DABCO in DMF rather than DBU in less environmentally friendly hexamethylphosphoramide (HMPA) was found to be more effective conditions for the ring closure. Excellent diastereo- and enantioselectivity and good yields of product were obtained for a variety of aryl and heteroaromatic nitroalkenes. A similar approach has been recently developed by Takemoto using chiral bifunctional thioureas to access densely functionalised cyclopropanes.[9]

Recently, we have demonstrated that easily accessible L-α,α-diaryl prolinols are useful promoters of the organocatalysed Michael addition and ring-opening reactions for the formation of carbon–carbon and carbon–heteroatom bonds.[10] Herein, we report a further example of their potential as organocatalysts in the stereoselective synthesis of nitrocyclopropanes. Indeed, we previously demonstrated that L-α,α-diaryl prolinols behave as bifunctional organocatalysts in the Michael addition of malonates to aryl and heteroaryl nitroalkenes, affording the adducts in good to high yield and moderate enantioselectivity (up to 56% ee).[11] Hydrogen bonding interactions of the nitroalkene and the malonate ester with the hydroxyl group and the secondary basic moiety of the catalyst have been suggested to be involved in substrates activation. Hence, the sequence in Scheme 1 was thought to be a viable access to enantiomerically enriched nitrocyclopropanes using α,α-diaryl prolinols as a novel class of organic promoters.

2. Results and discussion

At the outset a variety of aryl-substituted prolinols were screened in different reaction conditions at room temperature in the model reaction between *trans*-nitrostyrene **1a** and dimethyl

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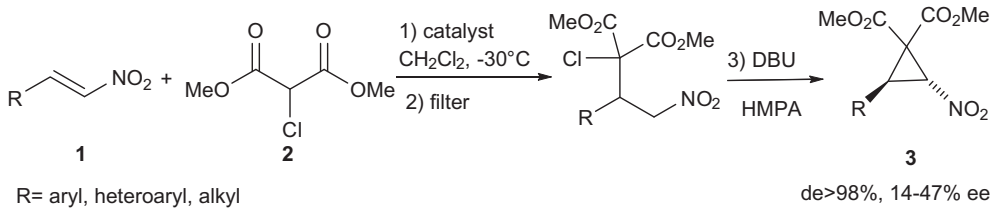


Scheme 1. MIRC strategy to nitrocyclopropanes.

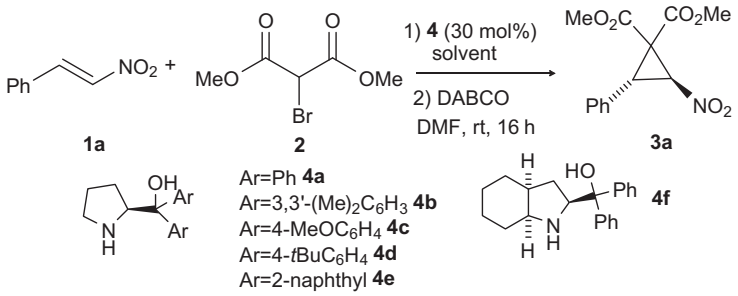
bromomalonate **2** for the conjugate addition process, whereas the ring-closure step was carried out on the crude mixture using DABCO in DMF as a solvent (Table 1).

Catalysts **4a**–**d** led exclusively to *trans*-nitrocyclopropane product **3a**, as confirmed by ^{1}H NMR analysis, as the prevalent (2*S*,3*R*)-enantiomer in generally good yield over the two steps and up to 31% ee (entries 1–4).[12] Commercially available α,α-(2-naphthyl)prolinol **4e** significantly improved the ee of the product (entry 5). More sterically demanding perhydroindolinol **4f**, recently employed as silyl ether derivative in enamine catalysis,[13] proved to be poorly efficient compared to prolinols **4a**–**e**. The reaction using the most effective catalyst **4e**, carried out at −16 °C led to a negligible enhancement of the enantioselectivity (entry 7). The reaction performed with diethyl bromomalonate proceeded sluggishly (entry 8). Alternative solvents were detrimental in all respects (entries 9 and 10). Various aromatic solvents were also checked (entries 11–13) and amongst them, the best result was achieved with chlorobenzene (entry 13). Catalyst loading can be eventually reduced to 15 mol % without significantly affecting the efficiency of the process (entry 14).

To investigate the scope of the stereoselective nitrocyclopropane MIRC approach, the reaction of compound **2** with a series of *trans*-nitroalkenes was explored under optimised reaction conditions (Table 2).[14]

Electron-donating or withdrawing substituents at the *para*-position on the phenyl ring were generally well tolerated, achieving the products in good yield and up to 49% ee (entries 2–6). A lower efficiency in terms of yield and enantiocontrol was observed in the case of *ortho*-phenyl substituted compounds or the sterically hindered 1-naphthyl-derivative (entries 7 and 8), in analogy to previously reported findings on the same process promoted by cinchona-derived thioureas and 6′-demethyl-quinine. Heteroaryl nitroalkenes afforded comparable results (entries 9 and 10), while the β-alkyl substituted nitroalkene did not react, which was in

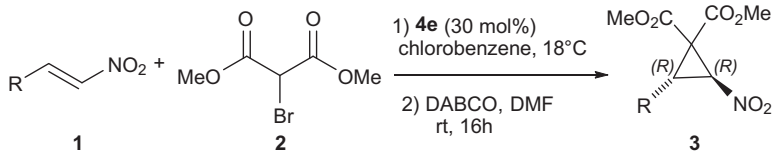
Table 1
Optimisation study for the synthesis of model nitrocyclopropane **3a** promoted by catalyst **4**[a]



Entry	4	Solvent	*T* (°C)	*t*[b] (h)	Yield **3a**[c] (%)	ee **3a**[d] (%) (abs. conf.)
1	**4a**	Toluene	18	91	68	28 (2*S*,3*R*)
2	**4b**	Toluene	18	95	70	31 (2*S*,3*R*)
3	**4c**	Toluene	18	76	81	21 (2*S*,3*R*)
4	**4d**	Toluene	18	65	90	29 (2*S*,3*R*)
5	**4e**	Toluene	18	67	67	40 (2*S*,3*R*)
6	**4f**	Toluene	18	64	51	9 (2*S*,3*R*)
7	**4e**	Toluene	−16	110	56	43 (2*S*,3*R*)
8[e]	**4e**	Toluene	18	86	25	—[f]
9	**4e**	CH_2Cl_2	18	70	30	33 (2*S*,3*R*)
10	**4e**	THF	18	66	36	rac
11	**4e**	*p*-Xylene	18	72	58	40 (2*S*,3*R*)
12	**4e**	Anisole	18	45	38	36 (2*S*,3*R*)
13	**4e**	Chlorobenzene	18	65	75	43 (2*S*,3*R*)
14[g]	**4e**	Chlorobenzene	18	75	62	40 (2*S*,3*R*)

[a] Conjugate addition was performed with **1a** (0.2 mmol), dimethyl bromomalonate (0.22 mmol), **4** (0.06 mmol) in chlorobenzene (0.4 mL). The intramolecular cyclopropanation on the crude mixture was performed using DABCO (0.15 mmol) in DMF (1 mL).
[b] Reaction time of the first step.
[c] Combined yield of two steps.
[d] Determined by HPLC analysis. Absolute configuration was determined by comparison of specific rotation and elution order of HPLC retention times with those reported in the literature.[7]
[e] Reaction performed with diethyl bromomalonate.
[f] Not determined.
[g] 15 mol % of catalyst was used.

Table 2
Stereoselective cyclopropanation of *trans*-nitroalkenes mediated by catalyst **4e**[a]



1 2 3

Entry	R	t[b] (h)	Yield **3**[c] (%)	ee **3**[d] (%) (abs. conf.)
1	Ph	65	75	43 (2*S*,3*R*)
2	4-$CH_3C_6H_4$	65	73	44 (2*S*,3*R*)
3	4-$CF_3C_6H_4$	69	68	35 (2*S*,3*R*)
4	4-BrC_6H_4	69	69	46 (2*S*,3*R*)
5	4-$CH_3OC_6H_4$	85	63	49 (2*S*,3*R*)
6	4-ClC_6H_4	77	61	49 (2*S*,3*R*)
7	2-ClC_6H_4	77	50	35 (2*S*,3*R*)
8	1-Naphthyl	87	45	17 (2*S*,3*R*)
9	2-Furyl	112	49	42 (2*S*,3*R*)
10	2-Thienyl	112	68	32 (2*S*,3*R*)
11	Cyclohexyl	98	—	—

[a] Conjugate addition was performed with **1** (0.2 mmol), dimethyl bromomalonate **2** (0.22 mmol), **4e** (0.06 mmol) in chlorobenzene (0.4 mL). The intramolecular cyclopropanation on the crude mixture was performed using DABCO (0.15 mmol) in DMF (1 mL) affording exclusively *trans*-**3**.
[b] Reaction time of the first step.
[c] Combined yield of two steps.
[d] Determined by HPLC analysis. Absolute configuration was determined by comparison of specific rotation and elution order of enantiomers via chiral HPLC with those reported in the literature.[7]

agreement with our previous findings on conjugate addition of malonate esters to nitroalkenes promoted by the same catalysts (entry 11). Finally, the Michael addition to the trisubstituted alkene *trans*-β-methyl-β-nitrostyrene did not proceed. Although the levels of enantioselectivity are still moderate, α,α-diaryl-prolinols afford comparable results to cinchona alkaloid derived thioureas as catalysts, working at room temperature and using more environmentally friendly reaction conditions for the ring-closure step.

3. Conclusion

In conclusion, we have shown that besides cinchona-modified alkaloids and chiral thioureas, α,α-diaryl prolinols are a new class of organocatalysts employable in the stereoselective MIRC approach to cyclopropanes. A convenient protocol to synthetically useful nitrocyclopropanes has been developed by using commercially available α,α-(2-naphthyl)prolinol and bromomalonate with easily accessible *trans*-nitrostyrenes. The functionalised products are obtained as diastereoisomerically pure *trans*-isomers, in good yield and moderate enantioselectivity. We are currently working on the improvement of MIRC strategy for the stereoselective cyclopropanation of electron-poor alkenes.

Acknowledgements

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12. A control experiment was carried out with catalyst **4a** (0.06 mmol) and compound **2** (0.24 mmol) stirred in toluene at room temperature for 72 h. ^{1}H NMR analysis of the crude reaction mixture substantially showed the resonances of the catalyst and compound **2** and resonances of a side-product, which might correspond to the N-alkylated catalyst. Catalyst **4a** was recovered after silica gel chromatography in 76% yield. The alkylation of the secondary amine moiety of catalysts **4** is a negligible process with respect to Brønsted base activation of compound **2**.
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14. *Representative procedure for the stereoselective synthesis of nitrocyclopropanes*: A reaction vial containing a stirring bar was charged with **1** (0.20 mmol), dimethyl bromomalonate (28.8 μL, 0.22 mmol) and catalyst **4e** (21.2 mg, 0.060 mmol) in chlorobenzene (400 μL) and stirred at room temperature. The reaction was quenched until almost complete consume of **1** as monitored by TLC (petroleum ether/diethyl ether 7/3). The reaction mixture was diluted with DMF (1 mL) and DABCO (22.4 mg, 0.20 mmol) was added at room temperature. Stirring was maintained overnight, then the reaction mixture was diluted with EtOAc (30 mL). The organic layer was washed with water (40 mL × 4), dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by flash column chromatography (petroleum ether/diethyl ether 9/1) to give the product. Spectroscopic and analytical data of compounds *trans*-**3** matched those reported in the literature.[7,8]