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Stereoselective Synthesis of Highly Functionalized Nitrocyclopropanes via Organocatalyic Conjugate Addition to Nitroalkenes

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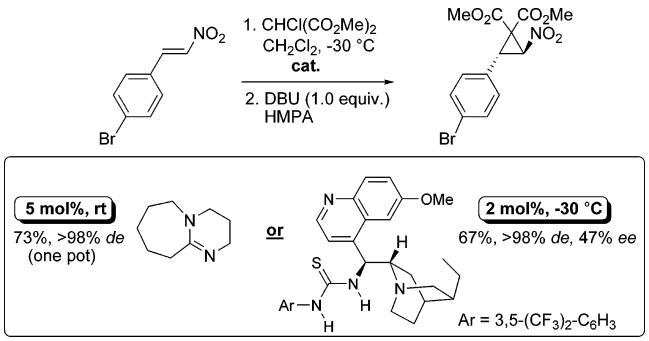

A convenient and novel one-pot organocatalytic methodology for the stereoselective synthesis of highly functionalized nitrocyclopropanes is reported. The addition of dimethyl chloromalonate to a variety of nitroolefins catalyzed by tertiary amines leads to a Michael adduct which cyclizes to form the cyclopropane in the presence of DBU under carefully controlled reaction conditions with outstanding diastereoselectivity.

The cyclopropane ring is a constituent of a diverse assortment of natural products[1] and biologically active agents. In addition to serving as drug and agrichemical targets, cyclopropyl derivatives are also valuable as (inter alia) synthetic building blocks[2,3] and as templates for the construction of conformationally restricted amino acids and peptides.[4,5] It is therefore unsurprising that the development of new, efficient methodologies for the stereocontrolled synthesis of these materials continues to command considerable attention.[6] Aggarwal,[7,8] Gaunt,[9] and MacMillan[10] have recently developed asymmetric organocatalytic strategies for the cyclopropanation of α,β-unsaturated aldehydes,[10] ketones,[7,9,10] amides,[9] esters,[8,9] nitriles,[9a] and sulfones[9a] using either preformed[10] or in situ generated[7−9] ylides[11,12] which complement asymmetric Simmons−Smith[6,13] and metal−carbenoid methodologies often better suited to relatively electron-rich olefinic substrates.[6,14,15]

Nitroolefins are readily accessible synthetic building blocks of widespread use in preparative organic chemistry.[16,17] It is somewhat surprising therefore that no efficient catalytic methodologies for their catalytic asymmetric cyclopropantion have thus far been reported.[18] In addition, existing methods for the synthesis of racemic nitrocyclopropanes from nitroolefins (via the addition of sulfoxonium/phosphonium ylides and diazomethanes) are often characterized by both variable yields and (where applicable) diastereoselectivity.[19,20] This dearth of methodological flexibility, together with our interest in organocatalytic Michael addition reactions[21] and the recent confirmation of the first biologically active natural product structure to contain a chiral nitrocyclopropane moiety[22] prompted us to

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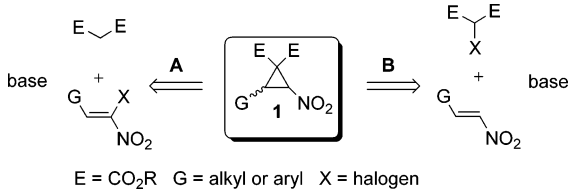
SCHEME 1. Potential Strategies for the Organocatalytic Cyclopropanation of Nitroolefins

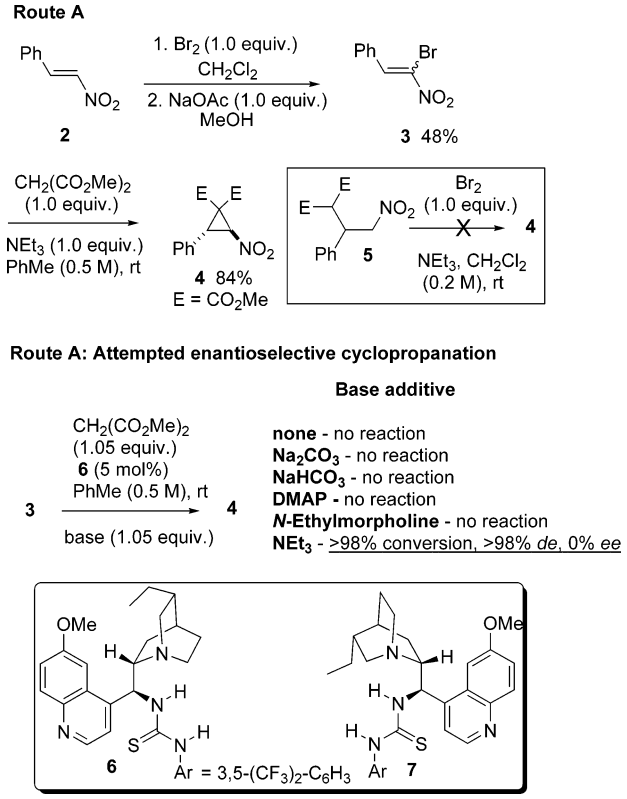


undertake the development of a convenient, organocatalytic Michael-based route to functionalized nitrocyclopropanes of high potential synthetic utility.

At the outset, it was decided that for such a methodology to be of use it must (a) represent a convenient, mild process, (b) furnish nitrocyclopropane products readily amenable to further modification in good yield and diastereoselectivity (across a range of readily available substrates), and (c) incorporate a *catalyzed* stereocenter-forming step. With this in mind, two Michael-initiated ring-closure (MIRC) strategies[1b,6] to malonate-substituted cyclopropanes of general type **1** were considered (Scheme 1): a base-mediated additon of a malonate pronucleophile to a halonitroolefin (route A), or a base-catalyzed reaction between an α-halomalonate and a nitroalkene (route B).

A preliminary investigation of route A was encouraging (Scheme 2); bromination of nitrostyrene gave bromo nitrooolefin **3**, which afforded cyclopropane **4** on treatment with triethylamine in moderate overall yield (40%) from **2**. In an attempt to avoid the requirement for the preparation of **3**, the generation of the presumed cyclization reaction precusor via the bromination of the Michael adduct from the reaction of dimethyl malonate with **2** (i.e., **5**, Scheme 2) was attempted in the presence of base; however, no cyclopropane was detected under these conditions (Scheme 2). The addition of dimethyl malonate to **3** promoted by chiral bifunctional organocatalyst **6**—known to possess excellent reactivity and selectivity in the promotion of similar conjugate addition reactions[21a,23,24]—in the presence of Brønsted-base additives was then attempted (Scheme 2). These experiments exposed route A as unsatisfactory from an asymmetric catalysis standpoint: of the additives tested only NEt_3 furnished **4** in racemic form. The incompatibility of less hindered yet both comparable and less basic amines[25] to NEt_3

SCHEME 2. Route A (Preliminary Investigations)



and the isolation of racemic **4** from the reaction mediated by NEt_3 indicate that the relatively unhindered **6** is not involved catalytically in this reaction.

To circumvent these difficulties, route B was examined. While this route held some promise, as both substrates were commercially available and elecrophilic α-bromonitroalkane intermediates could be avoided, initial experiments identified a new challenge: ring-closure must now occur at an electron-deficient quaternary carbon atom. The addition of dimethyl chloromalonate to **2** in the presence of either stoichiometric or catalytic amounts of an amine base (hindered or unhindered) gave excellent yields of adduct **8** but no cyclized material. After considerable experimentation,[26] it was found that tertiary amine bases in polar aprotic solvents (no reaction was observed in protic solvents) gave trace amounts of cyclopropane products from **8**, with *the combination of 1,8-diazabicyclo[5.4.0]undec-7-ene*, (*DBU*) *and hexamethylphosphoramide* (*HMPA*) *solvent providing efficient ring closure* (Scheme 3).[27]

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SCHEME 3. Route B

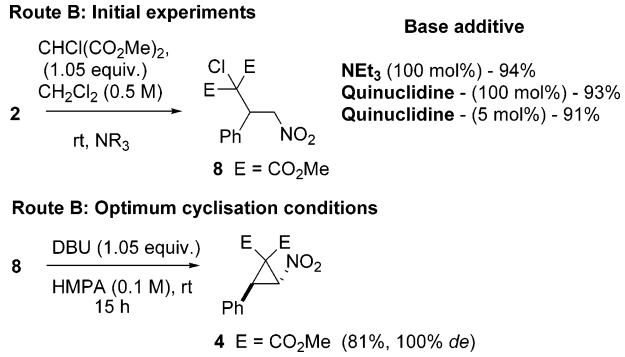
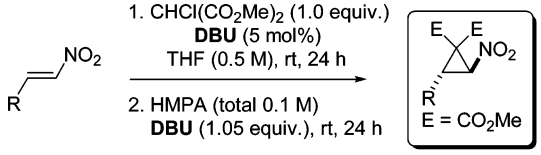


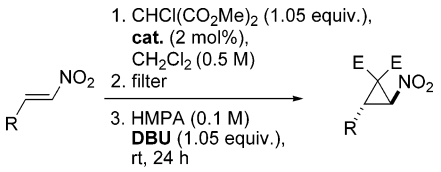
TABLE 1. One-pot Organocatalytic Nitrocyclopropane Synthesis



entry	nitroolefin	product	yield (%)[a]	*de* (%)[b]
1	**2**	**4**	75	>98
2	**9**	**15**	73	>98
3	**10**	**16**	74	>98
4	**11**	**17**	72	>98
5	**12**	**18**	72	>98
6	**13**	**19**	71	>98
7	**14**	**20**	70	>98

[a] Isolated yield. [b] Determined by ^{1}H NMR spectroscopy.

TABLE 2. Asymmetric Organocatalytic Cyclopropanation



entry	catalyst	time (h)[a]	*T* (°C)[a]	product	yield (%)[b]	de (%)[c]	ee (%)[d]
1	**DHQD**	24	−30	**4**	66	>98	7
2	**6**	92	−20	**4**	73	>98	37[e]
3	**6**	22	−30	**4**	69	>98	38
4	**6**	25	−30	**15**	67	>98	47
5	**6**	25	−30	**16**	65	>98	14
6	**6**	24	−30	**17**	64	>98	18
7	**6**	30	−30	**18**	66	>98	25
8	**6**	22	−30	**19**	65	>98	31
9	**6**	24	−30	**20**	66	>98	17
10	**6**	40	−30	**22**	65	>98	26
11	**7**	24	−30	**4**	64	>98	−30

[a] Refers to the Michael reaction. [b] Isolated yield. [c] Determined by ^{1}H NMR spectroscopy. [d] Determined by CSP−HPLC (see Supporting Information). [e] 5 mol % **6**, 0.05 M CH_2Cl_2, 0.3 M HMPA.

We were thus encouraged to develop a one-pot cyclopropanation involving the controlled DBU-catalyzed addition of dimethyl chloromalonate to nitroolefins, followed by DBU-mediated cyclization in the presence of HMPA (Table 1). Gratifyingly, this protocol allowed the convenient synthesis of nitrocyclopropanes **4** and **15**−**20** *as a single diastereomer* from a range of readily accessible aliphatic and aromatic nitroolefins of variable steric and electronic character (**2** and **9**−**14**) in uniformly good yields (Table 1). The anti relative stereochemistry was confirmed using ^{1}H NMR spectroscopic (NOE)[28] and X-ray crystallographic studies of cyclopropane **18**.

With an efficient organocatalytic protocol in hand, attention now turned to the question of asymmetric induction. In a modification of the diastereoselective methodology outlined above, the initial Michael addition of dimethyl chloromalonate to a selection of nitroolefins was promoted by modified cinchona alkaloids in CH_2Cl_2,[29] with subsequent DBU-mediated ring-closure. The results of these experiments are outlined in Table 2. While use of dihydroquinidine (**DHQD**) afforded essentially racemic product,[30] the bifunctional quinine-based catalyst **6** (and its *pseudo*enantiomer **7**) afforded the nitrocyclopropanes with poor to moderate enantioselectivity up to a maximum of 47% ee. While the enantioselectivity exhibited in these reactions is lower than those we observed previously in the addition of

(27) Kohler found that an α-bromoadduct similar to **8** could be cyclized in poor yield (>30%) on reflux in excess methanolic KOAc (see ref 20d). A later report suggested that a *p*-Me analogue of **4** could be prepared via electroreduction of the chloromalonate in the presence of the Michael acceptor (no yield given): Le Menn, J.-C.; Tallec, A.; Sarrazin, J. *Can. J. Chem.* **1991**, *69*, 761. For a useful oxidative cyclization using KF/alumina of the Michael adducts between malonate esters and electron deficient olefins (including nitroolefins): Villemin, D.; Thibault-Starzyk, F.; Hachemi, M. *Synth. Commun.* **1994**, *24*, 1425.

(28) See Supporting Information for details.

(29) The Michael addition reaction promoted by **6** and **7** proceeded to completion in all cases.

(30) It is interesting to note that the quinidine derived **DHQD** furnished the same major product enantiomer as the quinine-derived **6**. This is contrary to the trend previously observed in the corresponding catalyzed addition of dimethyl malonate to **2** (see ref 21a).

dimethyl malonate to nitrostyrenes,[31] to the best of our knowledge these represent the first examples of catalytic asymmetric cyclopropanations of nitroolefin derivatives.

In summary an operationally simple and completely diastereoselective one-pot synthesis of densely functionalized nitrocyclopropanes from readily available starting materials has been developed which represents a most convenient and efficient method for the synthesis of these compounds of excellent potential synthetic utility. Catalysis of the initial conjugate addition by a chiral bifunctional cinchona alkaloid-based organocatalyst (at low loadings) in place of DBU has resulted in the first examples of a catalytic asymmetric Michael addition−cyclopropanation reaction sequence involving nitroolefin substrates.

Experimental Section

One-Pot Synthesis of Racemic *trans*-Nitrocylopropanes: Procedure A. A reaction vial containing a stirring bar was charged with the appropriate β-nitrostyrene (0.200 mmol) and THF (0.40 mL). Dimethyl chloromalonate (29 μL, 0.224 mmol) was added via syringe. After 5 min, DBU (1.5 μL, 0.010 mmol) was added to the reaction. The solution was left to stir for 24 h with precipitation of the Michael adduct as a white solid. The reaction was then diluted with HMPA to give a total volume of 2 mL (0.1 M). To this a solution of DBU (31 μL, 0.210 mmol) in THF (100 μL) was added dropwise over 20 min with vigorous stirring. When conversion was adjudged to be complete (TLC), the HMPA solution was diluted with 30 mL EtOAc, and the organic layer was washed with water (4 × 200 mL) to remove the HMPA. The organic extracts were combined, dried ($MgSO_4$), and concentrated in vacuo. The crude residue was purified by column chromatography.

***trans*-2-Phenyl-3-nitrocyclopropane-1,1-dicarboxylic Acid Dimethylester (4).** Prepared according to procedure A using **2** (30 mg, 0.20 mmol). After workup, flash chromatography (1:15 EtOAc−hexane) gave **4** (42 mg, 75%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 3.57 (s, 3H), 3.88 (s, 3H), 4.23 (d, 1H, J = 6.0 Hz), 5.43 (d, 1H, J = 6.0 Hz), 7.27−7.30 (m, 2H), 7.33−7.37 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 37.3, 45.6, 53.0, 53.5, 65.8, 127.8, 128.2, 128.4, 129.6, 163.1, 163.4. IR (film): 1742, 1557, 1437, 1367, 1292, 1121 cm^{-1}. Anal. Calcd for $C_{13}H_{13}NO_6$: C, 55.91; H, 4.69; N, 5.02. Found: C, 56.16; H, 4.90; N, 5.12.

(31) Racemization of the product by DBU has been discounted as the ee of enantioenriched **4** remained unchanged after stirring in THF (1.0 M) in the presence of DBU (1.0 equiv) for 24 h at room temperature.

Catalytic Asymmetric Cyclopropanation: Procedure B. A reaction vial containing a stirring bar was charged with β-nitrostyrene (0.200 mmol), and **6** (2.4 mg, 0.04 mmol). The vial was fitted with a septum and placed under an Ar atmosphere (balloon). CH_2Cl_2 (0.400 mL) was added via syringe, and the resulting solution was cooled to −30 °C. The solution was allowed to equilibrate at this temperature (ca. 30 min), and dimethyl chloromalonate (29 μL, 0.224 mmol) was added via syringe. The resulting solution stirred for the time indicated in Table 2 resulting in precipitation of the Michael adduct as a white solid. The reaction mixture was filtered, and the resulting solid was dissolved in 2.0 mL HMPA (0.1 M). To this a solution of DBU (31 μL, 0.210 mmol) in THF (100 μL) was added dropwise over 20 min with vigorous stirring. When conversion was adjudged to be complete (TLC), the HMPA solution was diluted with 30 mL EtOAc, and the organic layer was washed with water (4 × 200 mL) to remove the HMPA. The organic extracts were combined, dried ($MgSO_4$), and concentrated in vacuo. The crude residue was purified by column chromatography.

(+)-*trans*-2-(4-Bromo-phenyl)-3-nitrocyclopropane-1,1-dicarboxylic Acid Dimethylester (15). Prepared according to procedure B using **9** (46 mg, 0.20 mmol). After workup, flash chromatography (1:15 EtOAc−hexane) gave **(+)-15** (48 mg, 67%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 3.61 (s, 3H), 3.87 (s, 3H), 4.15 (d, 1H, J = 6.0 Hz), 5.39 (d, 1H, J = 6.0 Hz), 7.17 (d, 2H, J = 8.3 Hz), 7.50 (d, 2H, J = 8.3 Hz). ^{13}C NMR ($CDCl_3$): δ 36.6, 45.5, 53.2, 53.6, 65.6, 122.4, 128.6, 129.5, 131.6, 162.9, 163.1. IR (film): 1741, 1557, 1437, 1368, 1293, 1121 cm^{-1}. Anal. Calcd for $C_{13}H_{12}BrNO_6$: C, 43.60; H, 3.38; N, 3.91. Found: C, 43.93; H, 3.67; N, 3.56. $[\alpha]^{23}_D$ = +23.3 (c 0.09, $CHCl_3$, 47% ee). Enatiomeric excess was determined using a CSP−HPLC with a Chiralcel AD-H column (4.6 mm × 25 cm), hexane/IPA, 90/10, 1.0 mL min^{-1}, RT, UV detection at 220 nm, retention times: 11.3 min (minor enantiomer) and 15.0 min (major enantiomer).

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Supporting Information Available: General experimental procedures, ^{1}H and ^{13}C NMR spectra, characterization data for all unknown compounds; crystal structure of **18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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