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An efficient organocatalytic enantioselective synthesis of spironitrocyclopropanes†

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An organocatalytic asymmetric synthesis of spironitrocyclopropanes has been demonstrated starting from 2-arylidene-1,3-indandiones and bromonitroalkanes catalyzed by a cinchona-derived bifunctional organocatalyst. The products were obtained with excellent enantioselectivities, diastereoselectivities and with good yields.

Several biologically active compounds and natural products are known to have cyclopropane rings as important structural subunits.[1] Among them, nitrocyclopropanes are of special interest because they can be found in various biologically active natural products.[2] Moreover, they serve as the key intermediates for many useful synthetic transformations.[3] As a result, asymmetric cyclopropanations have been well explored, including enantioselective versions of Simmons–Smith reactions[4] and transition metal catalyzed reactions using carbene intermediates.[5] An alternative path for catalytic cyclopropanation was introduced by Aggarwal,[6] Gaunt[7] and MacMillan[8] involving ylides[9] as intermediates.

In recent years, organocatalytic asymmetric cyclopropanation reactions were found to be an attractive alternative, and many elegant strategies were reported.[10] However, the direct organocatalytic synthesis of spirofused nitrocyclopropanes is very limited[10a,d] and that employing 2-arylidene-1,3-indandiones (**1**) has not yet been reported. The substrates **1** are known as a restricted class of trisubstituted electron poor alkenes and have rarely been used in organocatalysis.[11] Very recently, Lattanzi and co-workers[11a] described an elegant Michael-initiated cascade reaction to prepare spirocyclopropanes starting from **1**. However, their attempted base-catalyzed cyclopropanation of **1** with bromonitromethane (**2**) was not successful. As evident in the literature,[10a,d] cinchona alkaloid derived thioureas[12] are well known for their bifunctional behavior to activate electron poor alkenes and pronucleophiles simultaneously. Accordingly, we planned to use bifunctional catalysts (**I–IV**) for our study of nitrocyclopropanation. Thiourea catalysts **V–VI** derived from cyclohexane diamine were also included for our study. In a continuation of our recent efforts,[13] herein we wish to report our attempts to prepare enantioenriched spironitrocyclopropane derivatives.[14] We began our study by using **1a** (alkene component) and bromonitromethane (**2a**, pronucleophile) as the model reaction partners in the presence of quinidine derived bifunctional tertiary amine-thiourea catalyst **I**. Na_2CO_3 was used to neutralize the liberated HBr. However, our initial attempt at the predicted nitrocyclopropanation was unsuccessful, and only a trace amount of the expected product was detected (Table 1, entry 1). We reasoned that this failure was due to a lack of hydrogen-bond interactions between the N–H bonds of thiourea and the 1,3-dicarbonyl groups of **1a**. Water is well known for its ability to participate in hydrogen bonding interactions and many organocatalytic reactions are known to proceed in water.[15] Unfortunately, we did not observe any conversion of starting material when the reaction was conducted in water (entry 2). To our surprise, we noted that precise quantities of water were critical for the reaction to proceed. In the presence of one equivalent of water the reaction proceeded smoothly to furnish the nitrocyclopropanation adduct (**3a**) in 49% isolated yield in just two hours with 75% ee at room temperature (entry 3). Lowering of the reaction temperature to 0 °C was beneficial as product **3a** was obtained in 76% yield with a diasteremeric ratio of 11 : 1 and 91% enantiomeric excess (entry 4).

Encouraged by this promising output, we also evaluated other cinchona alkaloid derived catalysts (**II–IV**) and catalysts **V–VI**, and the results are presented in Table 1 (entries 5–9). Although all the catalysts (**I–IV**) could promote the reaction, catalyst **I** was found to be better in terms of chemical yield and enantioselectivity. However catalysts **V** and **VI** turned to be very poor, as not only did the reaction take longer (<70% conversion in the indicated time), but also the obtained products

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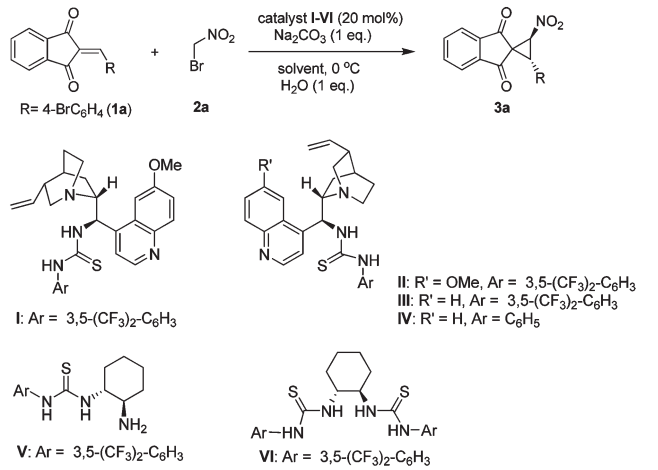
†Electronic supplementary information (ESI) available: Experimental procedure, spectral data of new compounds. CCDC 892806 (**3a**) and 892808 (**3k**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2ob26943k

Table 1 Optimization of enantioselective nitrocyclopropanation reaction between **1a** and **2a**[a]



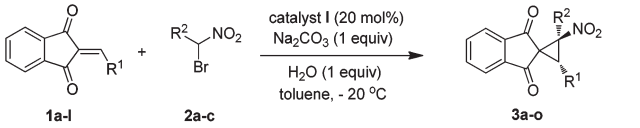
Entry	Cat.	Solvent	t (h)	**3a**[b] (%)	dr[c]	ee[d] (%)
1[e,f]	**I**	Toluene	24	—	—	—
2[e]	**I**	H_2O	24	—	—	—
3[e]	**I**	Toluene	2	49	6.5 : 1	75
4	**I**	Toluene	5	76	11 : 1	91
5	**II**	Toluene	5	69	11 : 1	−91
6	**III**	Toluene	5	65	10 : 1	−88
7	**IV**	Toluene	6	79	12 : 1	−75
8	**V**	Toluene	48	49	—	±
9	**VI**	Toluene	30	49	—	±
10	**I**	CH_2Cl_2	6	78	6.5 : 1	87
11	**I**	THF	6	64	4.3 : 1	67
12[g]	**I**	Toluene	48	49	11 : 1	90
13[h]	**I**	**Toluene**	**6**	**79**	**19 : 1**	**94**
14[h,i]	**I**	Toluene	14	79	16 : 1	88

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (1.5 equiv.), cat. (20 mol%), base (1 equiv.) in 0.5 mL anhydrous solvent. [b] Isolated yield. [c] Diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [d] Enantiomeric excess was determined by HPLC analysis. [e] At room temperature. [f] No water was used as an additive. [g] $NaHCO_3$ was used. [h] The reaction was performed at −20 °C in 0.2 mL toluene. [i] 10 mol% **I** was used.

were racemic. The organocatalytic nitrocyclopropanation reaction for the formation of **3a** was then further optimized. A number of different solvents and bases were screened (entries 10–13, for details see ESI†), and the results indicate that proper choice of solvent and base play an important role. Adduct **3a** was afforded in reduced diastereoselectivity and enantioselectivity when the reaction was conducted in dichloromethane or tetrahydrofuran (entries 10 and 11). Product **3a** could be formed with a similar product profile (entry 12) using the weaker sodium bicarbonate base, but the progress of reaction was too slow. When the reaction temperature was further lowered to −20 °C, **3a** was furnished in 94% ee coupled with 19 : 1 diastereoselectivity and 79% yield (entry 13). It is worth mentioning that both the diastereoselectivity and enantioselectivity of **3a** dropped upon lowering of catalyst loading (10 mol%) under these reaction conditions (entry 14).

With an effective protocol for the enantioselective formation of spironitrocyclopropane in hand, the substrate

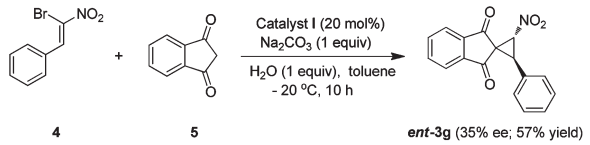
Table 2 Substrate scope for the enantioselective spironitrocyclopropanation[a]



Entry	R^1	R^2	t (h)	**3**,[b] (%)	dr[c]	ee[d] (%)
1	4-BrC_6H_4	H	6	**3a**, 79	19 : 1	96 (>99)
2	4-ClC_6H_4	H	8	**3b**, 68	19 : 1	95
3	4-$NO_2C_6H_4$	H	8	**3c**, 68	18 : 1	86
4	4-CNC_6H_4	H	12	**3d**, 78	19 : 1	92
5	2-BrC_6H_4	H	8	**3e**, 68	19 : 1	96 (>99)
6	3-FC_6H_4	H	7	**3f**, 71	16 : 1	86
7	C_6H_5	H	10	**3g**, 78	18 : 1	96
8	4-MeC_6H_4	H	5	**3h**, 68	18 : 1	96
9	2-MeC_6H_4	H	5	**3i**, 65	18 : 1	96
10	4-^{t}BuC_6H_4	H	6	**3j**, 63	18 : 1	98
11	4-BrC_6H_4	Me	12	**3k**, 81	19 : 1	96 (>99)
12	C_6H_5	Me	24	**3l**, 88	19 : 1	93
13	4-MeC_6H_4	Me	36	**3m**, 78	19 : 1	96
14	4-BrC_6H_4	Et	72	**3n**, 65	16 : 1	56
15[e]	Cyclohexyl	H	8	—	—	—
16	4-$OMeC_6H_4$	H	24	—	—	—

[a] Reaction conditions: **1a–l** (0.1 mmol), **2a–c** (1.5 equiv.), **I** (20 mol%), Na_2CO_3 (1 equiv.) in 0.2 mL anhydrous toluene. [b] Isolated yield. [c] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [d] ee for the major isomer (ee after single recrystallization). [e] A mixture of three compounds (70% ee, 87% ee and 72% ee) were obtained (please also see ESI†).

scope and generality of the methodology were examined. A variety of substituents on 2-arylidene-1,3-indandiones (**1a–l**) and different bromonitroalkanes (**2a–c**) could be employed to provide spironitrocyclopropanes (**3a–n**) in good yields (up to 88%), excellent diastereoselectivities (up to 19 : 1) and enantioselectivities (up to 98%) (Table 2). The electronic nature, bulkiness or positions of substituents in the aryl group seems to have little effect on the results (entries 1–10). Slightly reduced enantioselectivities were observed in the cases of 4-nitrophenyl and 3-fluorophenyl substituted arylidene-1,3-indandiones (**1c** and **1f**). We have also evaluated substituted bromonitroalkanes (**2b** and **2c**) as pronucleophile (entries 11–14) for synthesis of the products **3k–n** bearing a quaternary stereocenter, which is considered a challenging task in organic synthesis.[16] Thus the reaction of 1-bromo-1-nitroethane (**2b**) with substituted 2-arylidene-1,3-indandiones having different electronic natures proceeded smoothly to give the desired products (**3k–m**) in good yields, excellent diastereoselectivities and enantioselectivities (entries 11–13). It is noteworthy that the reaction between 1-bromo-1-nitropropane (**2c**) and **1a** was slower and the product (**3n**) was obtained in moderate enantioselectivity (56%) albeit with good yield and diastereoselectivity (entry 14 *vs.* 1 and 11). Less reactive cyclohexyl substituted alkylidene-1,3-indandiones were also examined with **2a**. However, a poor result was obtained under our reaction conditions (entry 15).[17] Additionally, cyclopropanation of 4-methoxyphenyl substituted arylidene-1,3-indandione (**1l**) and **2a** did not take place under identical reaction conditions



Scheme 1 Synthesis of ***ent*-3g** starting from **4** and **5**.

(entry 16).[18] The absolute configuration of **3a** and **3k** were determined by single crystal X-ray data analyses and those of the others were assigned by analogy.[19]

We believe that the reaction proceeds through simultaneous activation of the pronucleophile (bromonitroalkane) and electrophilic 2-arylidene-1,3-indandiones *via* water assisted H-bonding interaction by the bifunctional catalyst. Nucleophilic addition of bromonitroalkane and subsequent intramolecular cyclisation furnished the desired spirocyclopropane products (see ref. 10*d*).

Furthermore, we envisioned that spirocyclopropane product (**3g**) can also be accessed by employing bromonitrostyrene, such as **4**, as a dielectrophilic component[10*a*,20] and 1,3-indandione (**5**) as a dinucleophile in presence of appropriate catalyst. However, our initial attempt to use the present optimized reaction conditions was not very successful and the adduct ***ent*-3g** was obtained with only 35% ee and moderate yield (57%) (Scheme 1).

In summary, we have developed an efficient asymmetric pathway for the preparation of spironitrocyclopropanes catalyzed by cinchona-derived bifunctional organocatalysts. To the best of our knowledge, this is the first asymmetric route to prepare spironitrocyclopropanes starting from 2-arylidene-1,3-indandiones and bromonitroalkanes. The products were obtained in good yields (up to 88%), excellent enantioselectivities (up to 98%) and diastereoselectivities (up to 19 : 1). Further investigation of the synthetic route described in Scheme 1, biological evaluation of spironitrocyclopropanes and investigation of the reaction mechanism are currently underway in our laboratory.

Acknowledgements

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17 Preparation of primary or tertiary alkyl substituted alkylidene-1,3-indandiones was not successful, and therefore a secondary alkyl substituted alkylidene-1,3-indandione such as **1k** was examined for our study. However, a mixture of three compounds were obtained, and their polarities are too close to be separated by flash column chromatography.

18 No product formation was also observed in the case of using heteroaromatic residue (*e.g.* 2-furyl, 2-thienyl) as R^1 in our preliminary study.

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