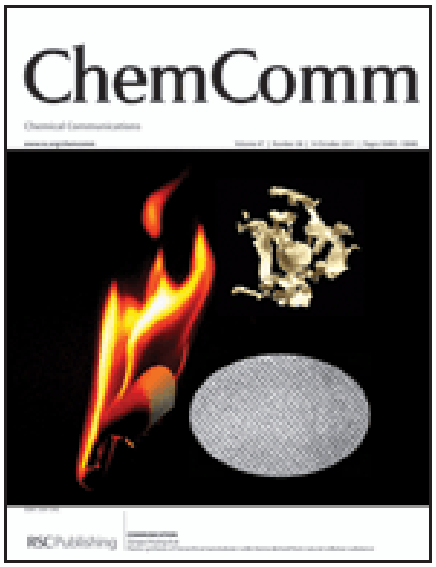

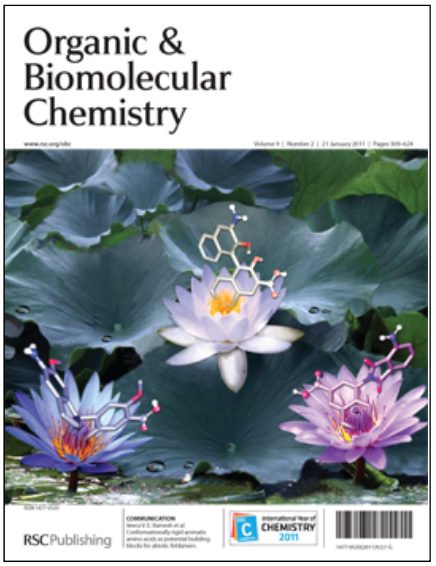

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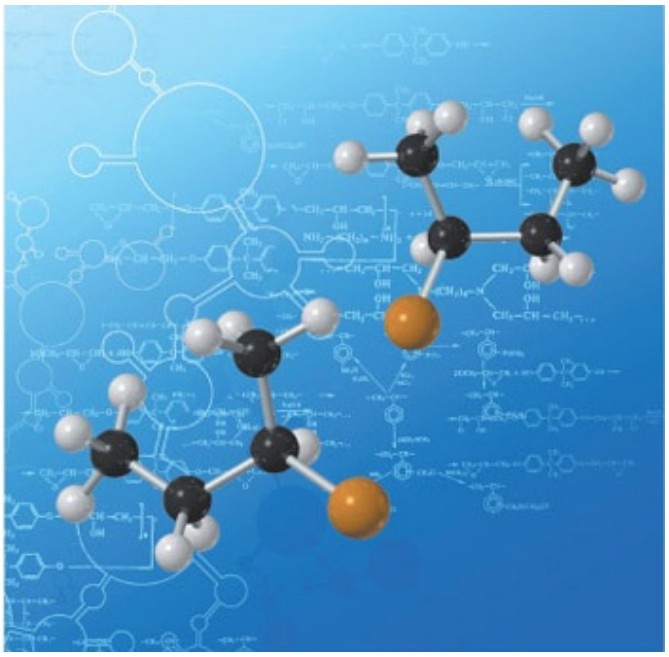

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COMMUNICATION

Chiral squaramide-catalyzed highly diastereo- and enantioselective direct Michael addition of nitroalkanes to nitroalkenes†‡

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An efficient highly diastereo- and enantioselective direct Michael addition of nitroalkanes to nitroalkenes catalyzed by chiral squaramide catalyst has been developed. This organocatalytic reaction with a low catalyst loading (2 mol%) proceeded well to afford synthetically useful 1,3-dinitro compounds in high yields with high diastereoselectivities (up to 95 : 5 dr) and excellent enantioselectivities (up to 97% ee).

The conjugate addition of carboanion nucleophiles to electron-deficient alkenes is widely recognized as one of the most important carbon–carbon bond-forming reactions in organic synthesis.[1,2] Owing to the strong electron-withdrawing character of the nitro group and its facile transformations to other useful functional groups, nitroalkanes are a valuable source of stabilized carboanions as good Michael donors,[3] and nitroalkenes serve as excellent Michael acceptors.[4] The Michael addition of nitroalkanes to nitroalkenes is extremely attractive because it can directly afford 1,3-dinitro compounds, which are useful intermediates for a variety of further elaborated structures.[5] Our group reported the first asymmetric version of this reaction catalyzed by bis(oxazoline) or bis(thiazoline)–zinc(II) complexes, which provided an easy access to optically active 1,3-dinitro compounds.[6] In recent years, some efforts have been also devoted to this asymmetric Michael addition by other groups, and a few efficient catalytic systems have been reported.[7] Wang *et al*. revealed that a simply modified cinchona alkaloid was a good promoter, albeit with moderate to good enantioselectivities.[7a] Feng and co-workers employed a $La(OTf)_3$/*N*,*N*′-dioxide complex to promote this reaction, and high diastereoselectivities and excellent enantioselectivities were obtained.[7b] Subsequently, two organocatalytic systems for this process with excellent results were reported. Wulff and Rabalakos developed a bifunctional DMAP-thiourea,[7c] while Wang *et al*. reported a bifunctional amine-thiourea bearing multiple hydrogen-bonding donors.[7d] Moreover, Maruoka *et al*. described an *N*-spiro chiral ammonium bifluoride catalyzed indirect Michael addition with silyl nitronates.[8] Despite these successes, the development of efficient catalytic systems in pursuit of excellent enantioselectivity, low catalyst loading, and mild reaction conditions is still challenging and in great demand.

The utilization of hydrogen bonding as an activation force is widespread in organocatalysis.[9] Chiral squaramide is a novel type of good hydrogen-bonding donor organocatalyst.[10,11] After the pioneering work reported by Rawal *et al*.,[11a] a series of chiral squaramide organocatalysts have been developed and successfully applied in various asymmetric reactions.[11] Recently, our group also reported the chiral squaramide-catalyzed asymmetric Michael addition reactions.[11f,g] Herein, we would like to report our new advance on the highly diastereo- and enantioselective Michael addition of nitroalkanes to nitroalkenes catalyzed by chiral squaramide catalysts.

Initially, a small library of squaramide catalysts **I–X** (Fig. 1) was readily prepared and their catalytic performance to promote the Michael addition of nitroalkanes to nitroalkenes was evaluated. The addition of nitroethane to β-nitrostyrene as a model reaction for catalyst screening was performed in CH_2Cl_2 in the presence of 5 mol% catalyst loading at room temperature for 12 h. The screening results are shown in Table 1. Both squaramides **I** and **II** derived from chiral cyclohexane-1,2-diamine gave good yield and diastereoselectivity, but the former exhibited much better enantioselectivity (79% ee) (entries 1 and 2). The substituent of the tertiary amino group as a Lewis base has an effect on the enantioselectivity. When squaramides **III** and **IV** bearing a piperidinyl group were

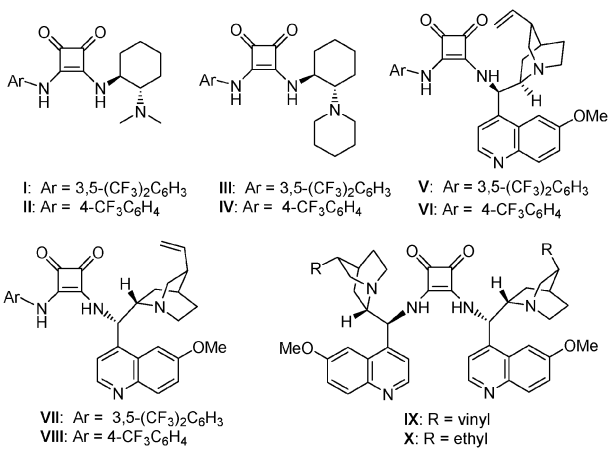

Fig. 1 Screened squaramide catalysts.

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† Electronic supplementary information (ESI) available: Experimental procedures, characterization data, copies of NMR spectra and HPLC chromatographs. See DOI: 10.1039/c1cc15946a

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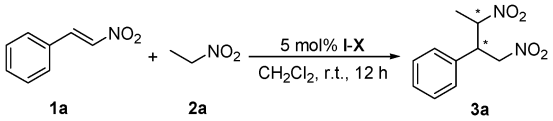
Table 1 Screening of squaramide catalysts for the asymmetric Michael addition of nitroethane to β-nitrostyrene[a]



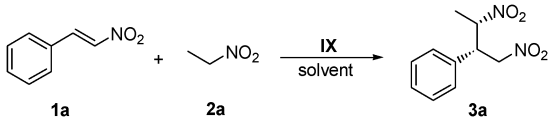
Entry	Catalyst	Yield[b] (%)	dr[c] (*syn*/*anti*)	ee[d] (%)
1	**I**	70	85 : 15	79
2	**II**	74	80 : 20	43
3	**III**	82	75 : 25	88
4	**IV**	32	80 : 20	87
5	**V**	75	83 : 17	−82
6	**VI**	67	83 : 17	−67
7	**VII**	90	83 : 17	91
8	**VIII**	62	81 : 19	86
9	**IX**	94	85 : 15	93
10	**X**	96	80 : 20	91

[a] Reactions were carried out with β-nitrostyrene (0.2 mmol) and nitroethane (1.0 mmol) in CH_2Cl_2 (0.5 mL). [b] Isolated yields after column chromatography purification. [c] Determined by chiral HPLC analysis. [d] Enantiomeric excess for the major *syn*-diastereomer was determined by chiral HPLC analysis.

employed, an obvious increase in enantioselectivity was observed (88% ee and 87% ee, respectively); however, squaramide **III** only gave moderate diastereoselectivity and squaramide **IV** afforded the product in low yield (entries 3 and 4). Squaramides **V–VIII** derived from cinchona alkaloid, developed in our previous report, were then screened (entries 5–8). Gratifyingly, quinine-derived squaramide **VII** achieved a very good result (90% yield, 83 : 17 dr, 91% ee). Subsequently, C_2-symmetric quinine/hydroquinine-derived squaramides **IX** and **X** were tested, and a better result (94% yield, 85 : 15 dr, 93% ee) was obtained for squaramide **IX**. Therefore, squaramide **IX** was selected as the best catalyst for further optimization.

With the optimal catalyst in hand, the effect of solvents, temperature, and catalyst loading was further investigated for the optimal reaction conditions. The results are summarized in Table 2. A solvent screening was first performed, and CH_2Cl_2 was proved to be the best reaction medium (entries 1–7). Notably, when the model reaction was carried out in neat nitroethane, lower yield and enantioselectivity were obtained (entry 8). Lowering the temperature led to an increase in both diastereoselectivity and enantioselectivity (entries 9 and 10). When the reaction was performed at −20 °C for 48 h, the adduct was obtained in high yield with high diastereoselectivity and excellent enantioselectivity (95 : 5 dr, 97% ee). Subsequently, catalyst loading was screened. Interestingly, increasing the catalyst loading (10 mol%) resulted in a decrease in both diastereoselectivity and enantioselectivity, while high diastereoselectivity and excellent enantioselectivity were maintained with a reduced catalyst loading (2 or 1 mol%) (entries 11–13). The phenomenon of increased enantioselectivity with decreased catalyst loading may be ascribed to the decreased self-association of this type of hydrogen-bonding catalyst, as it is reported that urea and thiourea based organocatalysts can form hydrogen-bonded aggregates.[12] This phenomenon is a notable feature in squaramide-catalyzed reactions. Considering the yield, 2 mol% catalyst loading was chosen. Additionally, the loading of

Table 2 Optimization of reaction conditions for the asymmetric Michael addition of nitroethane to β-nitrostyrene[a]



Entry	Solvent	Loading	*T*/ °C	*t*/h	Yield[b] (%)	dr[c] (*syn*/*anti*)	ee[d,e] (%)
1	CH_2Cl_2	5	rt	12	94	85 : 15	93
2	THF	5	rt	12	58	91 : 9	86
3	PhMe	5	rt	12	20	90 : 10	93
4	MeOH	5	rt	12	72	83 : 17	53
5	$CHCl_3$	5	rt	12	78	82 : 18	91
6	CH_2ClCH_2Cl	5	rt	12	62	87 : 13	90
7	CCl_4	5	rt	12	93	66 : 34	83
8	$EtNO_2$	5	rt	12	69	83 : 17	82
9	CH_2Cl_2	5	0	24	85	91 : 9	94
10	CH_2Cl_2	5	−20	48	92	95 : 5	97
11	CH_2Cl_2	10	−20	48	84	90 : 10	95
12	CH_2Cl_2	2	−20	48	94	95 : 5	97
13	CH_2Cl_2	1	−20	48	85	94 : 6	97
14[f]	CH_2Cl_2	2	−20	48	79	94 : 6	97
15[g]	CH_2Cl_2	2	−20	48	96	90 : 10	95

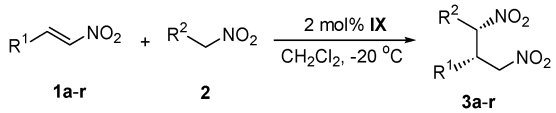
[a] Reactions were carried out with β-nitrostyrene (0.2 mmol) and nitroethane (1.0 mmol) in solvent (0.5 mL). [b] Isolated yields after column chromatography purification. [c] Determined by chiral HPLC analysis. [d] Enantiomeric excess for the major *syn*-diastereomer was determined by chiral HPLC analysis. [e] The configuration of the major *syn*-diastereomer was assigned to be (*S*,*S*) by comparison of the optical rotation with literature data.[6,7] [f] Nitroethane (0.4 mmol) was used. [g] Nitroethane (2.0 mmol) was used.

nitroethane **2a** was also simply examined, but no better result was observed (entries 14 and 15).

Having established the optimal reaction conditions, we explored the scope of the asymmetric Michael addition of nitroalkanes to nitroalkenes. The results are presented in Table 3. Generally, a wide array of aromatic nitroalkenes bearing electron-neutral, electron-withdrawing or electron-donating substitutions reacted smoothly with nitroethane **2a** to afford the corresponding adducts in good to high yields with high diastereoselectivities and excellent enantioselectivities (95–97% ee) (entries 1–10). These results indicated that the position and the electronic property of the substituent on the aromatic ring had a limited effect on both diastereoselectivity and enantioselectivity. Heteroaromatic nitroalkenes were also suitable substrates, and the desired products were obtained with excellent enantioselectivities albeit with lower yields (entries 11 and 12). When aliphatic nitroalkene **1m** served as an acceptor, very low yield (16%) and a significant decrease in both diastereoselectivity and enantioselectivity (67 : 33 dr, 80% ee) were observed (entry 13). Nitropropane **2b** as a donor worked well with aromatic nitroalkenes to give good to high diastereoselectivities and excellent enantioselectivities albeit with lower reactivity (entries 14–18).

Further substrate scope was investigated. The reaction of branched 2-nitropropane **4** and β-nitrostyrene **1a** was performed, but no reaction occurred. Nitrodienes **5** as acceptors reacted with nitroethane **2a** to afford the 1,4-addition product **6** in moderate yields with good diastereoselectivities and high enantioselectivities (Scheme 1). To further evaluate the synthetic potential of this squaramide catalytic system, the gram-scale preparation and transformation of **3a** were performed. As shown in Scheme 2, **1a**

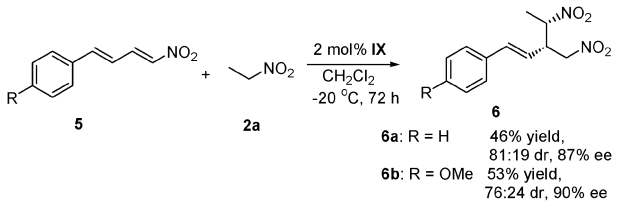
Table 3 Scope of the Michael addition of nitroalkanes to nitroalkenes[a]



1a-r **2** **3a-r**

Entry	R^1	R^2	t/h	Product	Yield[b] (%)	dr[c] (*syn*/*anti*)	ee[d,e] (%)
1	C_6H_5	Me	48	**3a**	94	95 : 5	97
2	4-FC_6H_4	Me	48	**3b**	98	94 : 6	96
3	4-ClC_6H_4	Me	48	**3c**	95	92 : 8	96
4	2-ClC_6H_4	Me	48	**3d**	83	88 : 12	95
5	4-BrC_6H_4	Me	48	**3e**	91	94 : 6	96
6	4-MeC_6H_4	Me	60	**3f**	91	91 : 9	96
7	4-$MeOC_6H_4$	Me	60	**3g**	90	94 : 6	97
8	2-$MeOC_6H_4$	Me	60	**3h**	88	94 : 6	97
9	3,4-$(MeO)_2C_6H_3$	Me	60	**3i**	71	88 : 12	96
10	1-Naphthyl	Me	60	**3j**	79	92 : 8	95
11	2-Furanyl	Me	60	**3k**	64	89 : 11	96
12	2-Thienyl	Me	60	**3l**	63	79 : 21	95
13	*i*-Propyl	Me	96	**3m**	16	67 : 33	80
14	C_6H_5	Et	60	**3n**	79	88 : 12	92
15	4-ClC_6H_4	Et	60	**3o**	88	89 : 11	96
16	2-ClC_6H_4	Et	60	**3p**	72	81 : 19	96
17	4-$MeOC_6H_4$	Et	72	**3q**	64	92 : 8	97
18	2-$MeOC_6H_4$	Et	72	**3r**	58	90 : 10	96

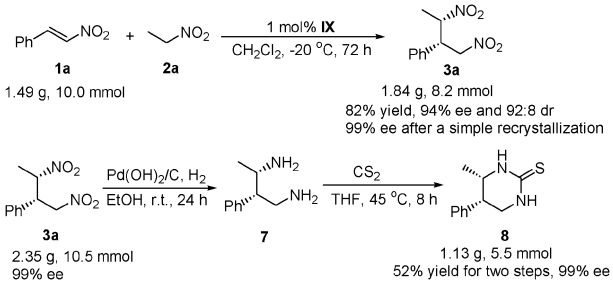
[a] Reactions were carried out with nitroalkene (0.2 mmol) and nitroalkane (1.0 mmol) in CH_2Cl_2 (0.5 mL). [b] Isolated yields after column chromatography purification. [c] Determined by chiral HPLC analysis. [d] Enantiomeric excess for the major *syn*-diastereomer was determined by chiral HPLC analysis. [e] The configuration of the major *syn*-diastereomer was assigned to be (*S*,*S*) by comparison of the optical rotation with literature data.[6,7]



Scheme 1 Further investigation of substrate scope.

(1.49 g, 10.0 mmol) reacted with nitroethane **2a** with 1 mol% catalyst **IX** to afford the product **3a** in 82% yield with 92 : 8 dr and 94% ee (99% ee was obtained after a simple crystallization). The transformation of the 1,3-dinitro compound **3a** (2.35 g, 10.5 mmol) to the corresponding chiral cyclic thiourea **8** was also readily gram-scaled without change in enantioselectivity.

In summary, we have developed a squaramide-catalyzed highly diastereo- and enantioselective direct Michael addition of nitroalkanes to nitroalkenes. This catalytic system with a low catalyst loading (2 mol%) was very effective to afford the corresponding Michael adducts in high yields with high diastereoselectivities (up to 95 : 5 dr) and enantioselectivities (up to 97% ee). This process provides an easy access to optically active 1,3-dinitro compounds. Moreover, the gram-scale preparation and transformation of the 1,3-dinitro compounds to chiral cyclic thiourea can be performed well, demonstrating the synthetic potential of this chiral squaramide organocatalytic system. Further studies on asymmetric reactions catalyzed by squaramides are underway in our laboratory.



Scheme 2 The gram-scale preparation and transformation of **3a**.

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