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Chiral squaramide-catalyzed asymmetric synthesis of pyranones and pyranonaphthoquinones *via* cascade reactions of 1,3-dicarbonyls with Morita–Baylis–Hillman acetates of nitroalkenes†‡

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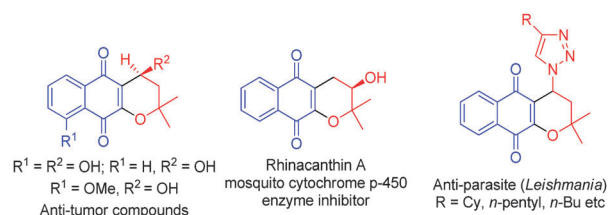
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Cascade reactions of 1,3-dicarbonyls with Morita–Baylis–Hillman acetates of nitroalkenes using a quinine derived chiral squaramide organocatalyst led to the formation of pyranones and pyranonaphthoquinones in good to excellent yields and high diastereo- and enantioselectivities. Representative examples of the reaction scale-up with a much lower catalyst loading without an appreciable loss of selectivities and synthetic transformations of the products are also reported here. The compounds described herein for the first time were evaluated against the infective bloodstream form of *Trypanosoma cruzi*, the etiological agent of Chagas disease, since the structures are related to bioactive α -lapachones.

Naturally occurring naphthoquinones are widely distributed in the plant kingdom, exhibit redox properties and are involved in processes such as photosynthesis and electron transfer reactions.¹ These compounds exhibit several activities against various diseases, *e.g.* Chagas disease, caused by the protozoan *Trypanosoma cruzi*, which affects approximately eight million individuals in Latin America.^{1,2} Pyranonaphthoquinones, in particular, display anti-cancer properties, besides being active against bacteria, fungi and mycoplasmas.³

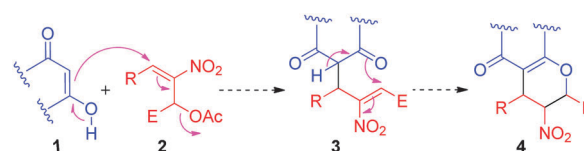
Although α -lapachones (*e.g.* Fig. 1) inherently possess weaker trypanocidal activity,¹ structural modifications could lead to enhanced activity.⁴ Moreover, α -lapachones exhibit a variety of other biological activities such as anti-tumor,⁵ anti-parasite (*Leishmania*),⁶ and mosquito cytochrome P450 enzyme inhibitory properties,⁷

Fig. 1 Selected biologically active α -lapachones.

to name a few. Recently, an asymmetric total synthesis of an α -lapachone natural product rhinacanthin A (Fig. 1) has been reported.⁸

The diverse biological profiles of α -lapachones inspired us to pursue their synthesis, especially in an asymmetric fashion. Although enantioselective conjugate addition of hydroxynaphthoquinone to different electron deficient alkenes, such as nitroalkenes,⁹ enones,¹⁰ unsaturated esters¹¹ and phosphonates,¹² in the presence of various chiral catalysts has been reported, there are only two such reactions, to our knowledge, that lead to α -lapachones¹³ and neither uses Morita–Baylis–Hillman adducts of activated alkenes as the key substrates.

Recently, we reported the synthesis of furans, pyrans,¹⁴ and imidazopyridines¹⁵ as well as arenofurans¹⁶ *via* cascade S_N2' -intramolecular Michael addition of binucleophiles such as 1,3-dicarbonyl compounds, 2-aminopyridines and arenols, respectively, to Morita–Baylis–Hillman (MBH) acetates of nitroalkenes (*e.g.* 2, E = CO₂Et, Scheme 1). Chen *et al.* also cleverly exploited the bielectrophilic nature of MBH acetates of nitroalkenes 2 (E = CO₂Et) for the synthesis of various carbocycles and heterocycles.¹⁷ The primary MBH acetate 2 (E = H), on the other hand, received less attention in such cascade reactions.^{18,19}

Scheme 1 S_N2' -intramolecular Michael addition.

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† Dedicated to Professor H. Ila on the occasion of her 70th birthday.

‡ Electronic supplementary information (ESI) available: Also complete experimental procedures, characterization data and copies of NMR spectra for all the new compounds. CCDC 993968. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4cc02279c

In the above scenario, we decided to employ 1,3-dicarbonyl compounds **1**, including 2-hydroxy-1,4-naphthoquinone (lawsone), as binucleophiles in the reaction with primary MBH-acetates of nitroalkenes **2** ($E = H$) in anticipation that the exclusive products would be pyrans **4** (Scheme 1). It appeared that such a cascade reaction in the presence of a suitable chiral catalyst would lead to enantioenriched pyrans and dihydropyranonaphthoquinones (lapachones). Therefore, we realized that the reaction sequence should begin with an enantioselective Michael addition of 1,3-dicarbonyls **1** to MBH acetate **2** ($E = H$) in an S_N2' manner to give intermediate **3**, followed by a diastereoselective intramolecular oxa-Michael addition of **3** to afford the desired pyrans **4**. We hypothesized that this cascade reaction can be efficiently triggered by a chiral bifunctional catalyst which can simultaneously activate MBH-acetate **2** and deprotonate diketone **1**.

In order to identify suitable reaction conditions for the asymmetric S_N2' -intramolecular Michael addition cascade, we have chosen dimedone **1a** and MBH-acetate **2a** as the model substrates and 10 mol% of **C1**–**C10** as the catalysts (Fig. 2 and Table 1). When the reaction was carried out in THF using (–)-sparteine **C1** as the catalyst, complete conversion was observed in 1 h to give the product in 80% yield, but, unfortunately, there was no selectivity at all (entry 1). This prompted us to switch to bifunctional catalysts with a Lewis basic moiety which can deprotonate 1,3-dicarbonyl **1** and a Bronsted acid moiety which can activate MBH acetate **2**. Thus cinchona-derived thiourea catalysts **C2**–**C8**²⁰ were screened (entries 2–10). Although product **4a** was isolated in good to excellent yield (78–94%), to our dismay, the selectivity remained low to moderate (24–69% ee).

At this juncture, we turned to quinine-squaramide catalysts **C9**–**C10**,²¹ in anticipation that their stronger H-bonding capability vis-à-vis their thiourea counterparts **C2**–**C8** would enhance the selectivities. Accordingly, we were pleased to note a dramatic rate acceleration and an equally dramatic rise in the enantioselectivity when squaramide **C9** was employed (90% yield, 92% ee, 15 min, entry 11). A slight improvement in the yield with a marginal drop in the selectivity was observed in the presence of squaramide **C10** (92% yield, 86% ee, 15 min, entry 12). After zeroing in on the catalyst, several solvents were screened at room temperature with the aim of further improving the selectivity (entries 13–19). Thus the ee remained $\geq 90\%$ in solvents such as CHCl_3 , CH_2Cl_2 , DCE, CH_3CN and EtOAc (entries 13–15, 17 and 18),

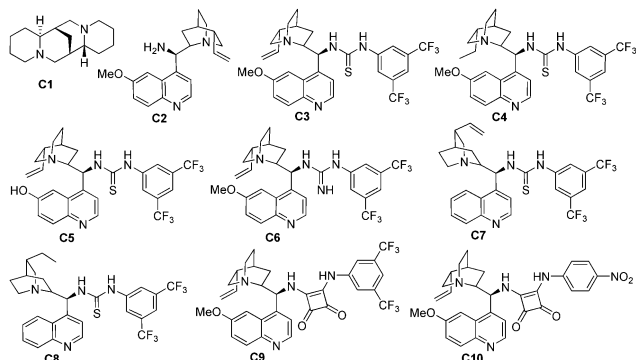


Fig. 2 Catalysts screened.

Table 1 Optimization of catalysts and solvents^a

Entry	Cat.	Solvent	Time	Yield ^b (%)	ee ^c (%)
1	C1	THF	1 h	80	0
2	C2	THF	2 h	78	24
3	C3	THF	4 h	89	50
4	C3	THF	7 h	90	57
5	C4	THF	5 h	88	51
6	C5	THF	5 h	85	65
7	C6	THF	3 h	94	69
8 ^d	C6	THF	48 h	88	60
9	C7	THF	5 h	87	52
10	C8	THF	5.5 h	85	54
11	C9	THF	15 min	90	92
12	C10	THF	15 min	92	86
13	C9	CHCl_3	20 min	83	91
14	C9	CH_2Cl_2	20 min	86	92
15	C9	DCE	20 min	83	90
16	C9	Dioxane	15 min	92	95
17	C9	CH_3CN	30 min	86	90
18	C9	EtOAc	25 min	90	91
19	C9	Toluene	3 h	76	50

^a Optimizations were done with 0.11 mmol of **1a**, 0.1 mmol of **2a** and 0.01 mmol of catalyst **C** in 0.5 mL solvent under N_2 . ^b After silica gel column chromatography. ^c Determined by chiral HPLC using an AD-H column for the major diastereomer (dr, determined by ^1H NMR spectroscopy, were in the range of 88 : 12 to 91 : 09). ^d -40°C .

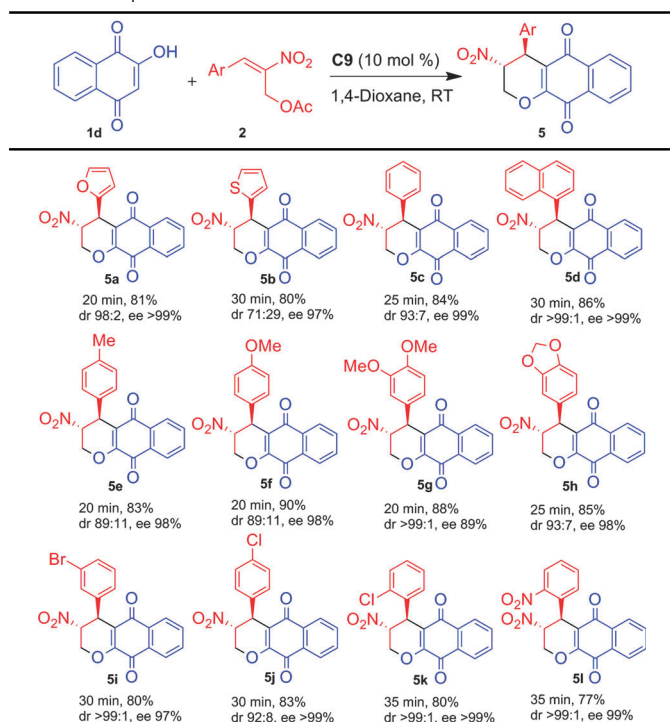
but dropped in toluene (50%, entry 19) while maintaining the yields in the range of 76–90%. However, a considerable improvement in the ee (to 95%) was observed in 1,4-dioxane (92% yield, 15 min, entry 16). Finally, 10 mol% of catalyst **C9** in 1,4-dioxane at rt was identified as the best condition for our further reactions.

Initially, the scope of 1,3-dicarbonyls was investigated under the above optimized conditions using MBH acetate **2a** as the representative substrate (Table 2). The results with cyclohexane-1,3-dione **1b** were inferior to what we obtained with dimedone **1a** (**4b**: 81% yield, 88 : 12 dr, 92% ee). Cyclic β -keto ester hydroxy

Table 2 Screening of 1,3-dicarbonyls **1**^{a–c}

Substrate	Yield (%)	Time	dr	ee (%)
1a (dimedone)	92%	25 min	91:9	95%
1b (cyclohexane-1,3-dione)	81%	20 min	88:12	92%
1c (cyclic β -keto ester)	93%	60 min	99:1	49%
1d (hydroxy cyclic β -keto ester)	81%	20 min	98:2	>99%

^a Yields after silica gel column chromatography. ^b dr was determined by ^1H NMR spectroscopy of the crude product and ee (for the major diastereomer) by chiral HPLC using an AD-H column. ^c All the reactions were carried out with 0.55 mmol of **1a**, 0.5 mmol of **2a** and 0.05 mmol of **C9** in 2.5 mL 1,4-dioxane under N_2 .

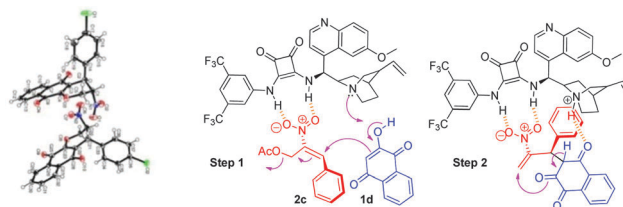
Table 3 Scope of MBH acetates 2^{a-d}

^a Yields after silica gel column chromatography. ^b dr was determined by ¹H NMR spectroscopy of the crude product and ee (for the major diastereomer) by chiral HPLC using an AD-H column. ^c All the reactions were carried out with 0.55 mmol of **1a**, 0.5 mmol of **3** and 0.05 mmol of **C9** in 2.5 mL 1,4-dioxane under N₂. ^d **5a** = **4e**.

chromenone **1c** also reacted with MBH acetate **2a** to afford product **4c** in excellent yield (93%). However, while the diastereoselectivity was high (99:1), the enantioselectivity was moderate (49% ee). Finally, to our delight, lawsone **1d** turned out to be an excellent binucleophile, providing product **5a** in high yield (81%) and with impressive selectivities (98:2 dr, >99% ee).

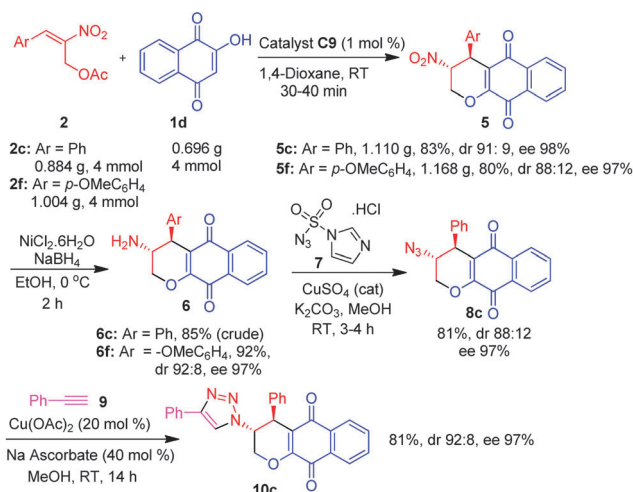
Having achieved nearly absolute selectivities using lawsone **1d** as the binucleophile, we proceeded to investigate the scope of MBH acetates **2** under the optimized conditions (Table 3). As in the case of 2-furyl MBH acetate **2a**, the thienyl analog **2b** also reacted well with lawsone **1d** to afford pyranonaphthoquinone **5b** in high (80%) yield and enantioselectivity (97% ee), though with moderate diastereoselectivity (71:29 dr). The MBH acetates **2d**, **2j**, and **2k**, with fused or chloro-substituted aromatic rings, reacted with lawsone **1d** to give products **5d**, **5j**, and **5k** with high diastereo- (>92:8) and enantioselectivities (>99). The yields (80–90%) and enantioselectivities (97 to >99%) were excellent for dihydropyranonaphthoquinones **5c**, **5e**, **5f**, **5h**, and **5i**, with unsubstituted or *para*-substituted aromatic rings, though there was a marginal drop in the diastereoselectivities (89:11 to 93:7). High yield (88%) and absolute diastereoselectivity (>99:1) with marginally lower enantioselectivity (89% ee) for product **5g** were observed in the case of MBH acetate **2g** with multiple electron donating substituents.

The structure and relative configuration of the products were determined by detailed spectral analysis (see the ESI[†]) which were further confirmed by single crystal X-ray analysis of

Fig. 3 X-ray structure of **5j** and the proposed mechanistic model.

a representative compound **5j** (Fig. 3, also see the ESI[†]). Furthermore, the absolute configuration of **5j** was also assigned (3*R*, 4*S*) based on X-ray data and that of the analogs **4** and **5** by analogy. A plausible mechanism, using lawsone **1d** and MBH acetate **2c** as the representative substrates, is outlined in Fig. 3. The first step is initiated by deprotonation of **1d** by the tertiary amine of the quinuclidine moiety resulting in an enolate. The enolate then adds to MBH acetate **2c** from the *Si* face in a Michael fashion, which is facilitated by activation of the nitro group by double H-bonding with the squaramide moiety of the chiral catalyst, leading to elimination of the acetate in the overall S_N2' reaction. In the second step, the enolate generated by H-bonding of the carbonyl group with the protonated quinuclidine moiety adds to the nitroalkene activated by the squaramide moiety from the *Re* face in a 6-*endo*-trig intramolecular oxa-Michael fashion, giving rise to the desired dihydropyran. Our solvent screening (Table 1, entries 11, 13–19) suggests that polar aprotic solvents (*e.g.* dioxane) that do not interfere with the catalyst are suitable for this transformation.

Our methodology was applicable to the gram scale reaction as well with a catalyst loading as low as 1 mol% (Scheme 2, see also the ESI[†]). Addition of 696 mg (4 mmol) of lawsone **1d** to 0.884 g of MBH acetate **2c** or 1.004 g of **2f** (4 mmol) in the presence of 30 mg (0.04 mmol, 1 mol%) of catalyst **C9** afforded 1.110 g (3.64 mmol, 83%) of nitroquinone **5c** or 1.168 g (3.20 mmol, 80%) of **5f** without any appreciable change in the diastereo- and enantioselectivities. The nitro group of quinones **5c** and **5f** could be transformed to the amino group using NiCl₂·6H₂O/NaBH₄ to afford aminoquinones **6c** and **6f**. While **6f** was isolated in

Scheme 2 Synthetic applications of α -lapachones **5**.

excellent yield (92%) without any loss of stereochemical integrity (dr 92:8, ee 97%), crude **6c**, due to its instability, was treated with azide **7** to furnish azidoquinone **8c** in high yield (81%) and selectivities (dr 88:12, ee 97%). Finally, the click reaction²² of azidoquinone **8c** with phenylacetylene **9** provided triazole **10c** in high yield (81%) and selectivities (dr 92:8, ee 97%).

Due to the potential trypanocidal activity of the lapachone derivatives (*vide supra*), we evaluated compounds **5a–5g** and **5i–5l** against the infective bloodstream form of *Trypanosoma cruzi*, the etiological agent of Chagas disease. Benznidazole (IC₅₀/24 h = 103.6 ± 0.6 μM),²³ the standard anti-*T. cruzi* drug, was used as the positive control. Preliminary experiments showed that our compounds at concentrations of up to 0.5% in DMSO had no deleterious effects on the parasites. The compounds evaluated were not active against *T. cruzi* with IC₅₀ values > 1000.0 μM (see the ESI†). Possible enhancement of trypanocidal activity *via* structural modifications and studies on other biological activities of α-lapachones **5** are being currently investigated in our laboratories and will be reported in due course.

In conclusion, a chiral squaramide-catalysed cascade reaction of 1,3-dicarbonyl compounds, including 2-hydroxy-1,4-naphthoquinone (lawsone), with Morita–Baylis–Hillman acetates of nitroalkenes affords pyrans and pyranonaphthoquinones (α-lapachones) in high yields and excellent diastereo- and enantioselectivities. The transformation which involves an S_N2'-intramolecular oxa-Michael addition sequence is amenable for scale-up even with a very low catalyst loading (1 mol%) without an appreciable loss in yield or selectivity. The multi-step transformation of a representative product to a naphthoquinone-based 1,2,3-triazole *via* nitro group reduction, conversion to azide and click reactions as well as preliminary evaluation of the α-lapachones for trypanocidal activity have been carried out.

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