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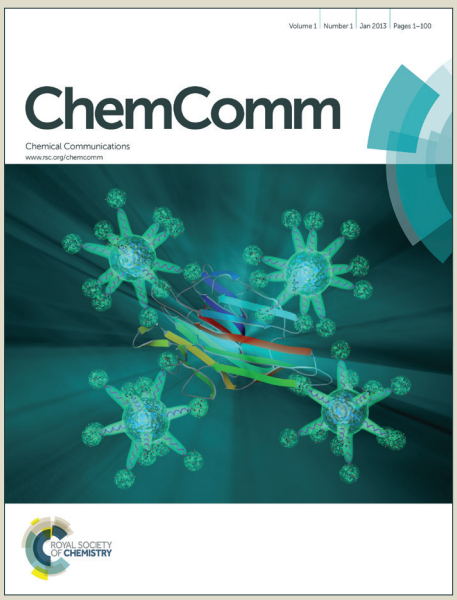

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Chiral squaramide catalyzed asymmetric synthesis of pyranones and pyranonaphthoquinones via cascade reactions of 1,3-dicarbonyls with Morita-Baylis-Hillman acetates of nitroalkenes

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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 reaction scale up with much lower catalyst loading without appreciable loss in 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 present several activities against various diseases, e.g. Chagas, caused by the protozoan *Trypanosoma cruzi*, that affects approximately eight million individuals in Latin America.[1,2] Pyranonaphthoquinones, in particular, display anti-cancer properties, besides being active against bacteria, fungi and mycoplasms.[3]

Although α-lapachones (e.g. Figure 1) inherently possess weaker trypanocidal activity,[1] structural modification 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 p-450 enzyme inhibitory properties,[7] to name a few. Recently, an asymmetric total synthesis of α-lapachone natural product rhinacanthin A (Figure 1) has been reported.[8]

The diverse biological profile 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 esters[11] 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-lapachones[13] and none using Morita-Baylis-Hillman adducts of activated alkenes as the key substrates.

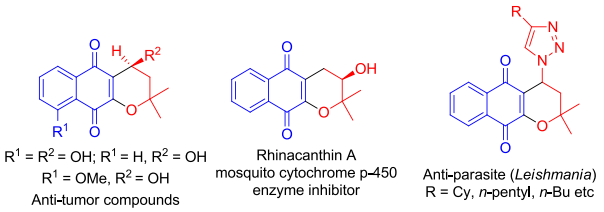
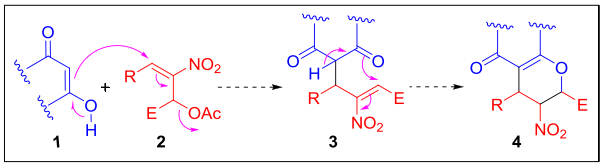


Figure 1 Selected biologically active α-lapachones

Recently, we reported the synthesis of furans and pyrans,[14] imidazopyridines[15] as well as arenofurans[16] 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 nitroakenes (e.g. **2**, E = CO_2Et, Scheme 1). Chen et al also cleverly exploited the bielectrophilic nature of MBH-acetates of nitroalkenes **2** (E = CO_2Et) 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]

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 enantio-enriched 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 the MBH-acetate **2** and deprotonate the diketone **1**.



Scheme 1 S_N2'-Intramolecular Michael addition

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 (Figure 2 and Table 1). When the reaction was carried out in THF with (-)-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 the 1,3-dicarbonyl **1** and a Bronsted acid moiety which can activate the MBH acetate **2**. Thus cinchona-derived thiourea catalysts **C2-C8**[20] were screened (entries 2-10). Although the product **4a** was isolated in good to excellent yield (78-94%), to our dismay, the selectivity remained low to moderate (24-69% ee).

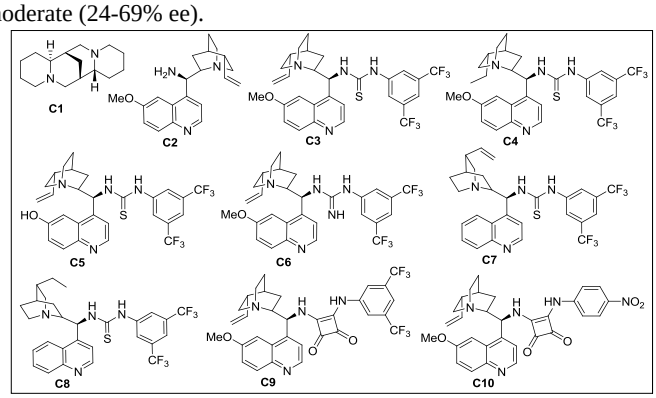
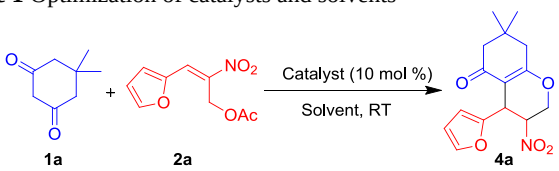


Figure 2 Catalysts screened

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). Slight improvement in the yield with a marginal drop in the selectivity was encountered 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 aimed at further improving the selectivity (entries 13-19). Thus the ee remained ≥90% in solvents such as $CHCl_3$, CH_2Cl_2, DCE, CH_3CN and EtOAc (entries 13-15 and 17-18), 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 taking MBH-acetate **2a** as the representative substrate (Table 2). The results with cyclohexan-1,3-dione **1b** was inferior to what we obtained with dimedone **1a** (**4b:** 81% yield, 88:12 dr, 92% ee). Cyclic *β*-keto ester hydroxy chromenone **1c** also reacted with MBH acetate **2a** to afford the 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 the product **5a** in high yield (81%) and with impressive selectivities (98:2 dr, > 99% ee).

Table 1 Optimization of catalysts and solvents[a]

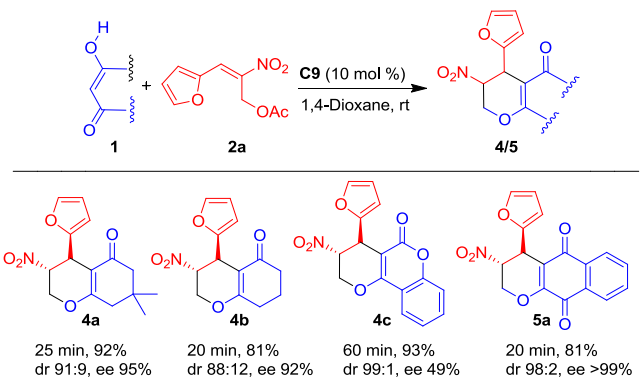


1a 2a 4a

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 AD-H column for the major diastereomer (dr, determined by ^1H NMR, were in the range of 88:12 to 91:09). [d] -40ºC.

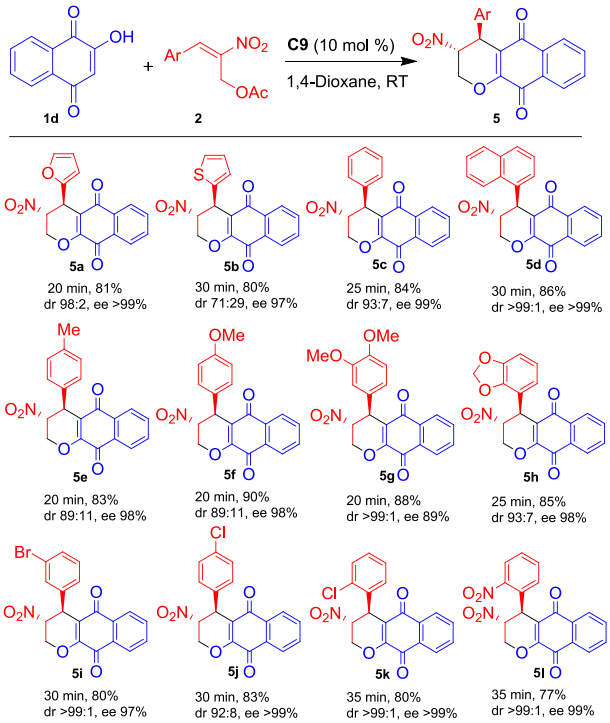
Table 2 Screening of 1,3-dicarbonyls **1**[a,b,c]



[a]Yields after silica gel column chromatography, [b]dr was determined by ^1H NMR of the crude product and ee (for the major diastereomer) by chiral HPLC using 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.

Having achieved nearly absolute selectivities with 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 the pyranonaphthoquinone **5b** in high (80%) yield and enantioselectivity (97% ee), though with moderate diastereselectivity (71:29 dr). The MBH acetates **2d** and **2j-k**, with fused or chloro-substituted aromatic rings, reacted with lawsone **1d** to give the products **5d** and **5j-k** with high diastereo- (≥ 92:8) and enantioselectivities (≥99). The yields (84-90%) and enantioselectivities (97 to >99%) were excellent for dihydropyranonaphthoquinones **5c**, **5e-f** and **5h-i**, with unsubstituted or *para*-substituted aromatic rings, though there was a marginal drop in the diastereoselectivities (89:11 to 93:7). High yield (88%), absolute diastereoselectivity (>99:1) with marginally lower enantioselectivity (89% ee) for the product **5g** were encountered in the case of MBH acetate **2g** with multiple electron donating substituents.

Table 3 Scope of MBH acetates **2**[a,b,c,d]



[a]Yields after silica gel column chromatography, [b]dr was determined ^{1}H NMR of the crude product and ee (for the major diastereomer) by chiral HPLC using 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 N_2. [d]**5a** = **4e**

The structure and relative configuration of the products were determined by detailed spectral analysis (see the Supporting Information) which were further confirmed by single crystal X-ray analysis of a representative compound **5j** (Figure 3, see also the ESI). Further the absolute configuration of **5j** was also assigned (3*R*, 4*S*) based on X-ray data and that of all the analogs **4** and **5** by analogy. A plausible mechanism, taking lawsone **1d** and MBH-acetate **2c** as the representative substrates, is outlined in Figure 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 acetate in an 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.

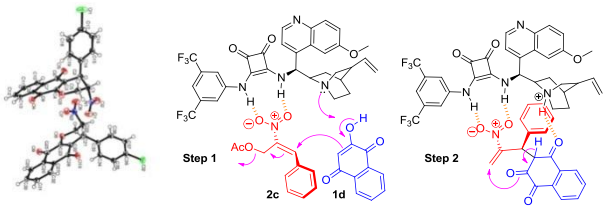
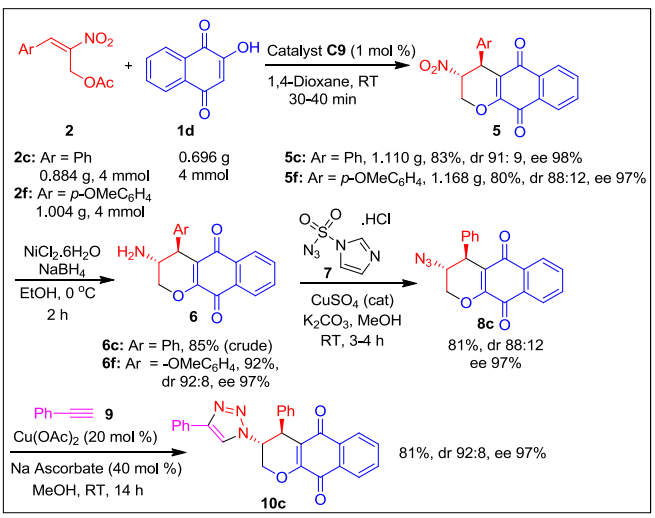


Figure 3 X-ray structure of **5j** and proposed mechanistic model

Our methodology was applicable for 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 the 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 amino group using $NiCl_2.6H_2O/NaBH_4$ to afford aminoquinones **6c** and **6f**. While **6f** was isolated in 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, click reaction[22] of azidoquinone **8c** with phenylacetylene **9** provided triazole **10c** in high yield (81%) and selectivities (dr 92:8, ee 97%).

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



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 (IC_{50}/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 effect on the parasites. The compounds evaluated were not active against *T. cruzi* with IC_{50} values >1000.0 μM (see the ESI). Possible enhancement of trypanocidal activity via structural modification 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 appreciable loss in yield or selectivity. Multi-step transformation of a representative product to a naphthoquinone-based 1,2,3-triazole via nitro group reduction, conversion to azide and click reaction as well as preliminary evaluation of the α-lapachones for trypanocidal activity have been carried out.

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Notes and references

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† Electronic Supplementary Information (ESI) available: CCDC 993968, also complete experimental procedures, characterization data and copies of NMR spectra for all the new compounds. See DOI: 10.1039/c000000x/

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