Organocatalysis

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Asymmetric Iminium Ion Catalysis: An Efficient Enantioselective Synthesis of Pyranonaphthoquinones and β-Lapachones**

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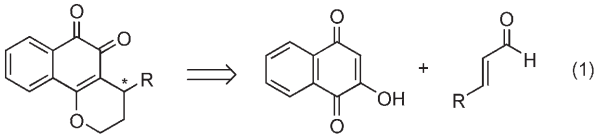
Naphthoquinones are common in the plant kingdom. As a result of their molecular structure they exhibit redox properties that influence various regulatory cellular processes. Their cytotoxic activity is a result of the quinone core structure, which is an important pharmacophore.[1] Furthermore, a number of naturally occurring 1,4- and 1,2-naphthoquinones are associated with diverse biological activities[2] and are components of antibacterial, fungicidal, antimalarial, antiparasitic, and antitumoral agents.[3] Based on their biological and structural properties, the 1,2- and 1,4-naphthoquinones are considered privileged structures in medicinal chemistry.

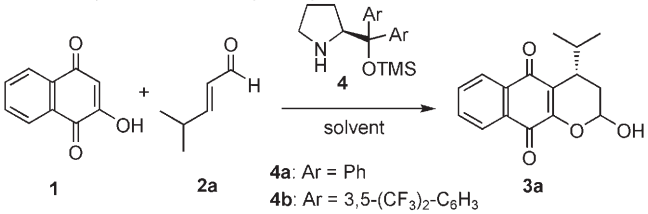
Following previous studies on the activation of aldimines and carbonyl functionalities with chiral Brønsted acids,[4] we decided to examine an enantioselective Brønsted acid catalyzed synthesis of 1,2-pyranonaphthoquinones starting from hydroxynaphthoquinone and α,β-unsaturated aldehydes [Eq. (1)]. However, in initial experiments we did not obtain satisfactory results with regard to reactivity and selectivity.



(1)

Therefore, we decided to investigate an alternative reaction with a chiral secondary amine as the organocatalyst. In contrast to primary amines previously employed, which are known to lead to the condensation product,[5] we assumed that it should be feasible to activate α,β-unsaturated aldehydes **2** using secondary amines through the formation of an intermediary iminium ion.[6] The subsequent 1,4-addition reaction to 2-hydroxy-1,4-naphthoquinone **1**, followed by an acetalization should give the corresponding enantiomerically enriched 1,4-pyranonaphthoquinones **3**. The initial experiments showed that the reaction of **1** with the α,β-unsaturated aldehyde **2a** could be carried out in the presence of diarylprolinol ethers[7] **4a** and **4b** in DMSO to give the corresponding 1,2-pyranonaphthoquinone **3a** in good yields and excellent enantioselectivities (Table 1, entries 1 and 2).[8] This new asymmetric addition–cyclization cascade[9] can also be performed in other solvents, whereby the best enantioselectivities (up to 99% *ee*) and yields were obtained with dichloromethane as the solvent in combination with catalyst **4b** (Table 1, entry 8).

Table 1: Solvent survey of the diarylprolinol ether catalyzed enantioselective synthesis of 1,4-naphthoquinones.[a]



Entry[b]	*T* [°C]	Catalyst	Solvent	Yield [%][d]	*ee* [%][e]
1	RT	**4a**	DMSO	86	82
2	RT	**4b**	DMSO	78	98
3	0	**4a**	Et_2O	48	90
4	0	**4a**	Bu_2O	24	85
5	0	**4a**	CH_2Cl_2	71	90
6	0	**4a**	toluene	54	66
7[c]	−20	**4a**	CH_2Cl_2	76	92
8[c]	−20	**4b**	CH_2Cl_2	77	99
9	−20	**4a**	toluene	34	92
10[c]	−20	**4b**	toluene	69	98

[a] TMS = trimethylsilyl. [b] Reactions were performed with hydroxyquinone **1**, aldehyde **2a** (1.5 equiv) and 20 mol% **4** for 20 h. [c] 40 h. [d] Yield of isolated product after column chromatography. [e] Enantiomeric excess was determined by HPLC.

Further reaction optimization focused on the solvent concentration and catalyst loading of **4a** and **4b** (Table 2). While lower catalyst loadings resulted in slightly reduced enantioselectivities, the variation of the concentration did not have any significant influence (Table 2, entries 1–5). Again catalyst **4b** gave the best results when the reaction was carried out in dichloromethane (0.2 M **1**, 0.2 M **2a**) (Table 2, entries 6–8).

Using the optimized reaction conditions we investigated the scope of the diarylprolinol ether catalyzed enantioselective addition–cyclization reaction cascade using various α,β-unsaturated aldehydes **2** (Table 3). In general, aliphatic (Table 3, entries 1–6) as well as aromatic (Table 3, entries 7–15) α,β-unsaturated aldehydes could be employed successfully in this new transformation, and a diverse set of 1,4-

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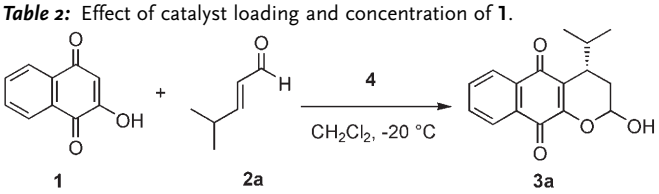
Table 2: Effect of catalyst loading and concentration of **1**.

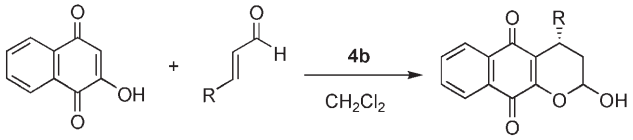


1 **2a** **3a**

Entry[a]	Catalyst (mol%)	Concentration	Yield [%][b]	*ee* [%][c]
1	**4a** (5)	0.2 M	47	87
2	**4a** (10)	0.2 M	76	88
3	**4a** (20)	0.1 M	53	90
4	**4a** (20)	0.2 M	76	92
5	**4a** (20)	0.3 M	69	91
6	**4b** (5)	0.2 M	40	99
7	**4b** (10)	0.2 M	41	99
8	**4b** (20)	0.2 M	77	99

[a] Reactions were performed with hydroxyquinone **1** and aldehyde **2a** (1.5 equiv). [b] Yield of isolated product after column chromatography. [c] Enantiomeric excess was determined by HPLC using a Chiralpak AD-H column.

Table 3: Scope of the diarylprolinol-catalyzed addition–cyclization cascade reaction.



1 **2** **3**

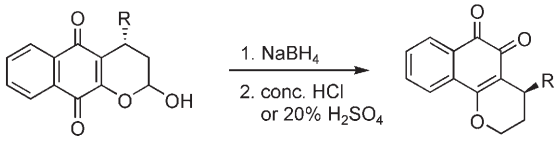
Entry[a]	Product	R	*T* [°C]	Yield [%][e]	*ee* [%][f]
1	**3a**[b]	$CH(CH_3)_2$	−20	77	99
2	**3b**	C_2H_5	−20	55	98
3	**3c**	C_3H_7	−20	75	99
4	**3d**	C_4H_9	−20	52	98
5	**3e**	C_7H_{15}	−20	46	98
6	**3f**	$C_{10}H_{21}$	−20	43	99
7	**3g**	Ph	−20	56	91
8	**3h**[c]	2-ClC_6H_4	RT	50	99
9	**3h**[d]	2-ClC_6H_4	RT	57	99
10	**3i**[d]	2-BrC_6H_4	RT	84	99
11	**3j**[d]	2-$CH_3C_6H_4$	RT	57	96
12	**3k**[d]	2-$CF_3C_6H_4$	RT	49	95
13	**3l**	3-BrC_6H_4	0	82	90
14	**3m**	4-BrC_6H_4	0	87	92
15	**3n**	4-$CH_3OC_6H_4$	0	51	93

[a] Reactions were performed with hydroxyquinone **1**, aldehyde **2** (1.3 equiv), and 20 mol% **4b** for 3 d. [b] 40 h. [c] 24 h. [d] Performed with 20 mol% **4a** at RT for 24 h. [e] Yield of isolated product after column chromatography. [f] Enantiomeric excess was determined by HPLC on a chiral stationary phase.

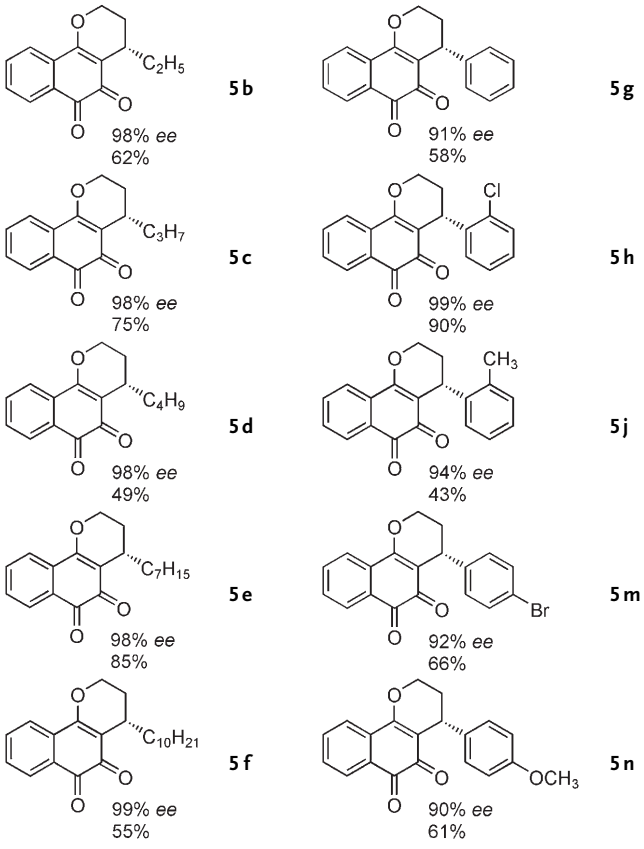
pyranonaphthoquinones **3a–n** was isolated in good yields and with excellent enantioselectivities (90–99% *ee*).

Having developed an efficient and highly enantioselective method for the synthesis of 1,4-pyranonaphthoquinones **3**, we decided to transform the new products to the desired biologically active 1,2-pyranonaphthoquinones **5** (Table 4). It was thereby shown that application of sodium borohydride and concentrated hydrochloric or sulfuric acid resulted in the corresponding β-lapachone derivatives **5** without loss of enantiopurity.[10] The 1,4-naphthoquinone **3** can also be

Table 4: Transformation of 1,4-naphthoquinones to 1,2-naphthoquinones.

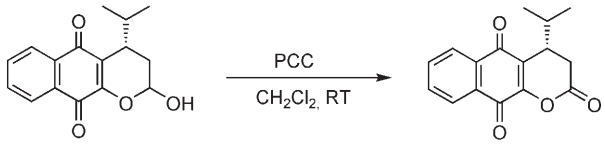


3 **5**



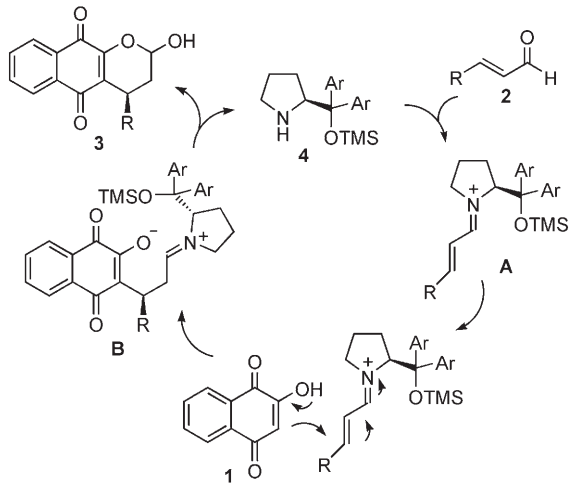
transformed to further interesting derivatives. For instance, oxidation of **3a** with PCC provides the corresponding lactone **6a**, which again can be isolated without loss of enantiopurity (Scheme 1).[10]

With regard to the mechanism, we assume that the reaction of the diphenylprolinol ether **4** with the α,β-unsaturated aldehyde **2** results in the intermediary iminium ion **A** (Scheme 2). Subsequent 1,4-addition to 2-hydroxy-1,4-naphthoquinone (**1**) followed by an isomerization gives rise to adduct **B**, which after hydrolysis and acetylization yields the desired 1,4-naphthoquinone **3** with regeneration of the catalyst.



3a 99% *ee* **6a** 99% *ee*

Scheme 1. Oxidation of 1,4-pyranonaphthoquinone **3a**. PCC = pyridinium chlorochromate.



Scheme 2. Diarylprolinol ether catalyzed reaction of 2-hydroxy-1,4-naphthoquinone (**1**) with α,β-unsaturated aldehyde **2**.

The constitution and absolute configuration of the new products was proven by X-ray crystal structure analysis, as we were able to obtain suitable single crystals of the 1,4-naphthoquinone **3j** as well as the 1,2-naphthoquinone **5c** (Figure 1).

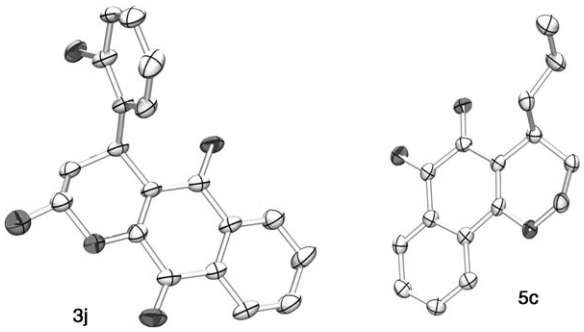


Figure 1. X-ray crystal structures of 1,4-naphthoquinone **3j** and 1,2-naphthoquinone **5c** (ellipsoids drawn at the 50% probability level).

In summary we have developed a Lewis base catalyzed enantioselective addition cyclization cascade which results in biologically interesting quinones. In this efficient transformation not only aliphatic but also aromatic α,β-unsaturated aldehydes can be applied to provide 1,4-pyranonaphthoquinones in good yields and with excellent enantioselectivities (90–99% *ee*). The 1,4-naphthoquinones obtained can be further reacted to provide the valuable 1,2-pyranonaphthoquinones and lapachones as well as useful 1,4-naphthoquinonelactones. These transformations proceed without loss of enantiopurity. In current work we are subjecting further substrates to this efficient transformation.

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[10] A detailed description is given in the Supporting Information.

