Organocatalysis

DOI: 10.1002/anie.200701009

Organocatalytic Highly Enantioselective α-Arylation of β-Ketoesters**

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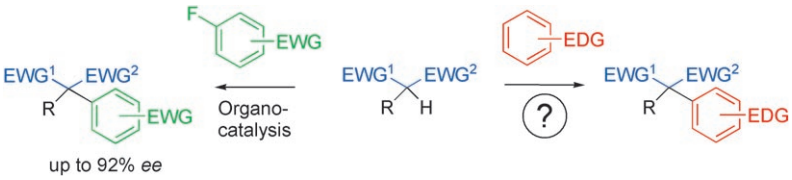
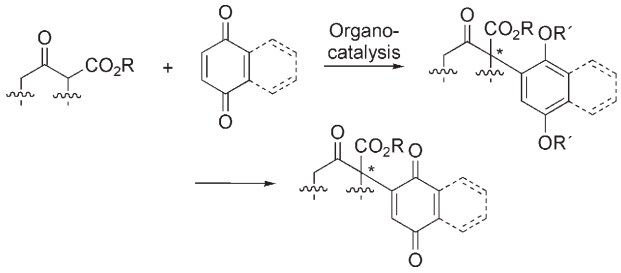
Dedicated to Prof. Roald Hoffmann on the occasion of his 70th birthday

During the last years, the field of organocatalysis has received much attention and become a powerful tool in the field of organic chemistry.[1] The aromatic substitution reaction (S_NAr) is a fundamental reaction in organic chemistry which normally requires aromatic compounds that have electron-withdrawing substituents to activate the aromatic moiety for nucleophilic attack.[2] A number of nucleophiles can be used, such as carbon-, oxygen-, and amine-type nucleophiles, with aromatic compounds that have electron-withdrawing substituents.[3] Recently, the first asymmetric nucleophilic aromatic substitution was presented, allowing the synthesis of optically active α-aryl-β-ketoesters (Scheme 1, left),[4] by addition of activated β-ketoesters to activated aryl compounds and applying organocatalysis. However, this reaction allows the synthesis of optically active electron-poor aromatic systems only; therefore it is desirable to have a complementary procedure for obtaining α-aryl-β-ketoesters that contain electron-rich aromatic rings (Scheme 1, right).



Scheme 1. Synthetic approaches of electron-poor α-aryl β-ketoesters and the complementary electron-rich α-arylation. EWG: electron-withdrawing group; EDG: electron-donating group.

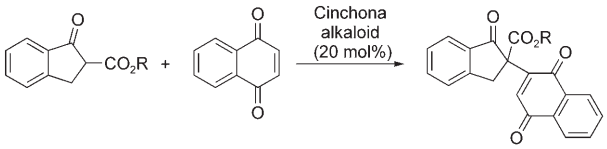
Herein, we present the first organocatalytic enantioselective addition of β-ketoesters to quinones leading to optically active hydroquinones or quinones, depending on the reaction conditions (Scheme 2). Furthermore, we show that this is an easy procedure for the synthesis of optically active α-aryl-β-ketoesters, in which various transformations of the electron-rich aromatic ring have been performed.



Scheme 2. Organocatalytic addition of β-ketoesters to quinones for the synthesis of optically active hydroquinones and quinones.

Quinones are important compounds which are widely distributed in nature and undergo a number of biochemical transformations. From a biological point of view quinones are significant in many compounds,[5] and furthermore they are also used in industry on the ton scale as dye reagents. As a result of their importance, a large number of reactions have been performed with quinones. One class of reagents which have been widely used for the functionalization of quinones are nucleophiles such as thiols and nitrogen-, oxygen-, halogen-, phosphorus-, and activated methylene-based nucleophiles.[6] In all these cases, the addition has been applied in a racemic version, most likely as a result of the incompatibility of the different asymmetric catalytic metal systems with the redox quinine–hydroquinone system.[7]

Thus, we decided to perform the addition of substituted β-ketoesters to 1,4-naphthoquinone under organocatalysis. We started out by studying the reaction under phase-transfer conditions using cinchona alkaloids. Unfortunately, the reaction failed under these conditions, probably owing to the instability of the quinone–hydroquinone system under the basic aqueous conditions. Therefore, we attempted the reaction of β-ketoester **1a** with 1,4-naphthoquinone (**2a**) in the presence of cinchona alkaloids as chiral base catalysts [Eq. (1)].[8]



(1)

1a (R = *t*Bu)
1a' (R = Me)

2a

3a (R = *t*Bu)
3a' (R = Me)

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[**] This work was made possible by a grant from the Danish National Research Foundation. J.A. thanks the Ministerio de Educación y Ciencia of Spain for a postdoctoral fellowship. We thank Dr. Jacob Overgaard for performing X-ray analysis, Dr. Kim Frisch for conversations about quinone systems, and Dr. Peter Dinér for help in DFT calculations.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

We were pleased to find that by using, for example, quinine as the catalyst, the optically active 1,4-naphthoquinone **3a′** was obtained with a moderate enantioselectivity of 47% *ee* and in 59% yield (Table 1, entry 1). We then screened

Table 1: Representative screening results for the enantioselective organocatalytic addition of the indanone-derived β-ketoester **1a** to 1,4-naphthoquinone **2a** under various reaction conditions.[a]

Entry	Solvent	Catalyst	R	*T* [°C]	Yield [%][b]	*ee* [%][c]
1	toluene	quinine	Me	RT	59	+47
2	toluene	quinine	Me	−20	60	+33
3	DCE	quinine	Me	−20	42	+69
4	$CHCl_3$	quinine	Me	−20	27	+61
5	CH_2Cl_2	quinine	Me	−20	68	+67
6	CH_3CN	quinine	Me	−20	nd	+37
7	CH_2Cl_2	quinine	Me	−10	94	+56
8	CH_2Cl_2	quinine	Me	+4	71	+55
9	CH_2Cl_2	quinidine	Me	−20	68	−72
10	CH_2Cl_2	quinidine	Me	−40	nd	−42
11	CH_2Cl_2	cinchonine	Me	−20	43	−60
12	CH_2Cl_2	$(DHQD)_2AQN$	Me	−20	29	−16
13	CH_2Cl_2	$(DHQD)_2PYR$[d]	Me	−20	49	+74
14	CH_2Cl_2	$(DHQ)_2AQN$	Me	−20	86	−36
15	CH_2Cl_2	$(DHQ)_2PYR$	Me	−20	89	+28
16	CH_2Cl_2	quinine	*t*Bu	−20	76	+94

[a] A solution of the β-ketoester **1a** (0.1 mmol) and the quinone **2a** (0.1 mmol) in CH_2Cl_2 (0.2 mL) was cooled (to the indicated temperature). After approximately 15 min, the corresponding catalyst (20 mol%) was added. The final product was isolated after full conversion. DCE: dichloroethane; $(DHQD)_2AQN$: hydroquinidine(anthraquinone-1,4-diyl)diether; $(DHQD)_2PYR$: hydroquinidine-2,5-diphenyl-4,6-pyrimidinediyl diether. [b] Yield of isolated product. [c] The enantiomeric excess was determined by chiral HPLC (see the Supporting Information). [d] The reaction did not go to full conversion after 24 h.

different solvents and temperatures (Table 1, entries 1–8) using quinine as catalyst as well as other catalysts (entries 9–15) and finally by changing the ester moiety (entry 16). These screening investigations gave the fundamental key parameters of this reaction: temperature at −20 °C, CH_2Cl_2 as solvent, the *tert*-butyl moiety of the β-ketoester, and finally quinine as the base. Using these conditions, compound **3a** was formed in 76% yield and with 94% *ee* (Table 1, entry 16). Table 1 presents some representative results from the screening process for the reaction shown in Equation (1).

Surprisingly, the product formed in the reaction in Equation (1) was the oxidation product, 1,4-quinone derivative **3a**, rather than the expected hydroquinone. This oxidation of the hydroquinone to the quinone is probably carried out by molecular oxygen or in a catalytic manner with the quinone starting material. Our proposed catalytic cycle for both the formation of the hydroquinone and quinone addition products is presented in Figure 1. The first step in the reaction is the formation of the chiral ion-pair **I** between the organocatalyst and the β-ketoester enolate. This step is followed by the enantioselective addition of the enolate to the quinone, generating the corresponding chiral quinone-enolate system **II**, which by protonation leads to **III**. Abstraction of the proton in the α position of the quinone gives **IV**, and the hydroquinone **V** is formed by protonation. This hydroquinone **V** could be oxidized to the quinone **VI** (depending on the redox potential).[9] However, if the reaction is performed under Ar followed by protection of the hydroxy functional groups (e.g. AcCl; see Scheme 3), the reaction leads to the protected hydroquinone **VII** (see below).

With the optimal conditions in hand, the scope of the reaction was studied for different β-ketoesters with various quinones to give both the quinone and hydroquinone addition products (Table 2). The 2-indanone derivatives (Table 2, entries 1–3) were found to be the best substrates in terms of enantioselectivity and yield. The reaction proceeds well for substrates that have both electron-donating and electron-withdrawing substituents in the aromatic ring of the β-ketoester. For the dimethoxy-substituted β-ketoester derivative **1b**, the optically active quinone product **3b** was formed with a high enantioselectivity of 94% *ee* (Table 2, entry 2), and nearly similar results were obtained for the chloro derivative which gave **3c** in 80% yield and 88% *ee* (entry 3). The non-aromatic β-ketoester *tert*-butyl 2-oxocyclopentanecarboxylate was also found to be a good substrate for the reaction with 1,4-naphthoquinone, and the corresponding product **3d** was obtained in lower yield and an excellent enantioselectivity of 96% *ee* (Table 2, entry 4).

Changing to 1,2-naphthoquinone leads to a reaction with lower enantioselectivity (Table 2, entry 5; see also Table S1 in the Supporting Information for the optimization of this

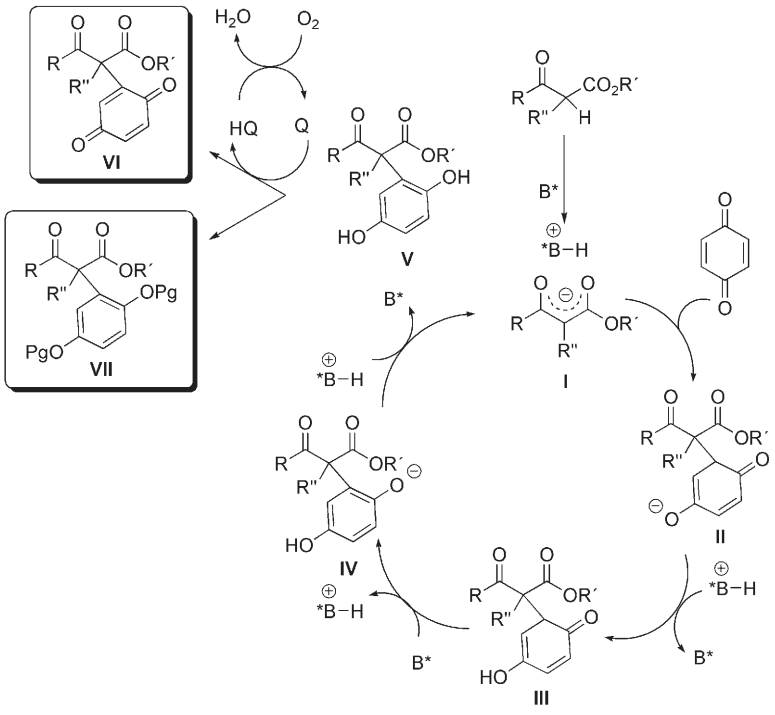
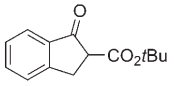
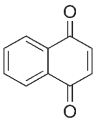
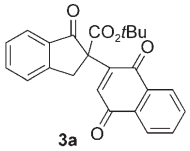
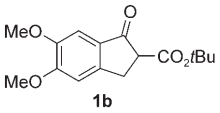
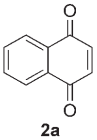
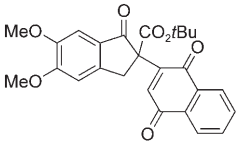
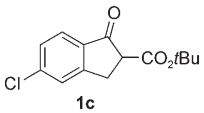
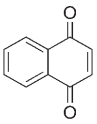
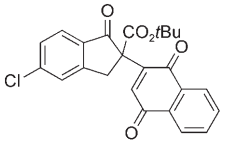
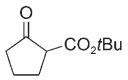
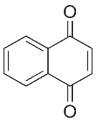
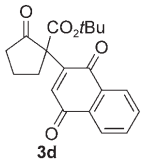
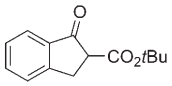
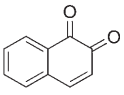
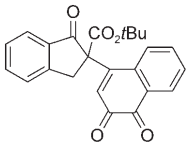
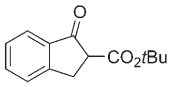
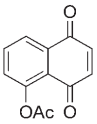
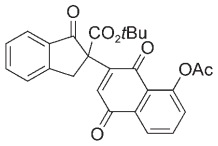
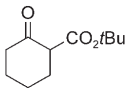
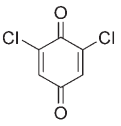
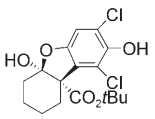
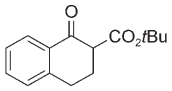
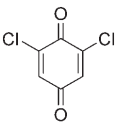
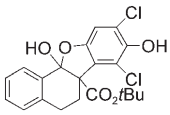
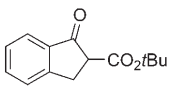
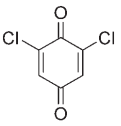
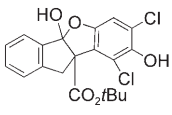


Figure 1. Proposed mechanism for the organocatalyzed asymmetric reaction of β-ketoesters with quinones under the formation of β-ketoester-derived quinones (Q) and hydroquinones (HQ). B: base; Pg: protecting group.

Table 2: Representative screening of different β-ketoesters and quinones.[a]

Entry	β-Ketoester	Quinone	Product	Yield [%]	*ee* [%][b]
1	 **1a**	 **2a**	 **3a**	76	94
2	 **1b**	 **2a**	 **3b**	69	94
3	 **1c**	 **2a**	 **3c**	80	88
4	 **1d**	 **2a**	 **3d**	59	96
5	 **1a**	 **2b**	 **3e**	58	44[c]
6	 **1a**	 **2c**	 **3f**	72	80
7	 **1e**	 **2d**	 **3g (*ent*-3g)**	66[d] (87)[e]	90[d] (−92)[e]
8	 **1f**	 **2d**	 **3h**	88[d]	94[d]
9	 **1a**	 **2d**	 **3i (*ent*-3i)**	66[d] (92)[e]	80[d] (−72)[e]

[a] A solution of the β-ketoester **1** (0.2 mmol) and **2** (0.2 mmol) in CH_2Cl_2 (0.4 mL) was cooled to −20 °C. Quinine (20 mol %) was then added at this temperature, and the product was isolated after 3–6 h (see the Supporting Information). The products were purified by flash chromatography. [b] The *ee* values were determined by chiral HPLC. [c] Reaction performed at −40 °C. [d] Result obtained when (−)-cinchonidine was used as catalyst at −32 °C and DCE as solvent (see Tables S2 and S3 in the Supporting Information). [e] Values in parentheses correspond to the yield and *ee* obtained using 20 mol % of (+)-cinchonine as catalyst at −32 °C and DCE as solvent (see Tables S2 and S3 in the Supporting Information).

reaction), while the introduction of a substituent in the aromatic ring, such as for the acetyljuglone **2c**, leads to good enantioselectivity (entry 6) as well as regioselectivity.[5c]

For six-membered-ring β-ketoesters lower reactivity was observed; in order to perform the reaction, more activated quinones have to be applied. We were very pleased to find that when the more reactive dichlorosubstituted quinone was used the reactions proceeded very well, and surprisingly we could isolate the corresponding hydroquinone, rather than the 1,4-quinone, in good yield and enantioselectivity (Table 2, entries 7 and 8). These results could be explained according to easier oxidation of the 1,4-naphthoquinone compared to 2,6-dichloro-1,4-quinone.[9]

To obtain these results it was necessary to carry out a screening, which indicated that (−)-cinchonidine is the best catalyst (see Tables S2 and S3 in the Supporting Information). The reaction can also be performed with the pseudo-enantiomer (+)-cinchonine, and for the six-membered-ring β-ketoester derivative **1e** the corresponding enantiomer *ent*-**3g** could be obtained in good yield (87 %) with an enantioselectivity of −92 % *ee* (Table 2, entry 8). The reaction of the β-ketoester **1a** was also performed with the pseudo-enantiomer catalyst (+)-cinchonine; however, lower enantioselectivity was obtained (results in parentheses, entry 9, Table 2). Note that the reaction can be performed with, for example, the quinone **2d** using only 1 mol % of (−)-cinchonidine as the catalyst, without appreciable loss of enantioselectivity or yield (67 % yield and 82 % *ee*, see Table S2, entry 10, in the Supporting Information); however, a longer reaction time is required. Furthermore, this reaction can also be carried out on the 5 mmol scale with 1 mol % of the catalyst to give the product

with a yield of 57% and 80% *ee* (Table S2, entry 11, in the Supporting Information).

Interestingly the products are isolated as hemiacetals of the corresponding ketones, and only one diastereoisomer is observed in the formation of hydroquinones **3g–i** (entries 7–9, Table 2).[10] The absolute configuration was determined by X-ray crystallographic analysis[11] of *ent*-**3g**, which gave the *R* configuration of the hemiacetal and *S* configuration at the ester (see the Supporting Information).

Note that the present catalytic system does not accommodate relatively flexible substrates as they are probably not reactive enough. For example, the noncyclic β-ketoester *tert*-butyl 2-methyl-3-oxo-3-phenylpropanoate did not react either with the quinone **2a** or with the more reactive 2,6-dichloro-1,4-quinone **2d**.

Finally, we investigated some elaboration products of the optically active quinones formed. These results indicated the possibility of trapping intermediate **V** (Figure 1) by using, for example, acetyl chloride. Therefore, it was possible to carry out the reaction and obtain the protected hydroquinone **4** (upper reaction, Scheme 3). More interestingly, if the reaction yielding **3i** was treated with TfOH at 0°C, a rupture of the corresponding hemiacetal compound and cyclization (by activation with the acid) of the ester yielded the spiro compound **5**.[12] This compound was obtained without loss of optical purity (lower reaction, Scheme 3), even when the reaction was performed as a one-pot reaction. The spiro structure of compound **5** was confirmed by X-ray analysis (see the Supporting Information).

In conclusion, we have demonstrated that the reaction of β-ketoesters with 1,4-quinones is a good strategy to carry out α-arylations enantioselectively for aromatic compounds that contain electron-donating groups using organocatalysts. This reaction can be performed with different β-ketoesters and quinones and allows an easy-to-control one-pot synthesis of complicated polycyclic and spiro chiral compounds.

Experimental Section

A solution of **1** (0.2 mmol) and **2** (0.2 mmol) in CH_2Cl_2 (0.4 mL) in a vial equipped with a magnetic stirring bar was cooled to −32°C during 15 min. After this time, catalyst (20 mol%) was added. Stirring was maintained at the indicated temperature until completion of the reaction. The crude reaction mixture was directly charged on silica gel and subjected to flash chromatography. See the Supporting Information for full experimental details.

Received: March 7, 2007
Revised: April 10, 2007
Published online: May 24, 2007

Keywords: α-arylation · β-ketoesters · organocatalysis · quinine · quinones

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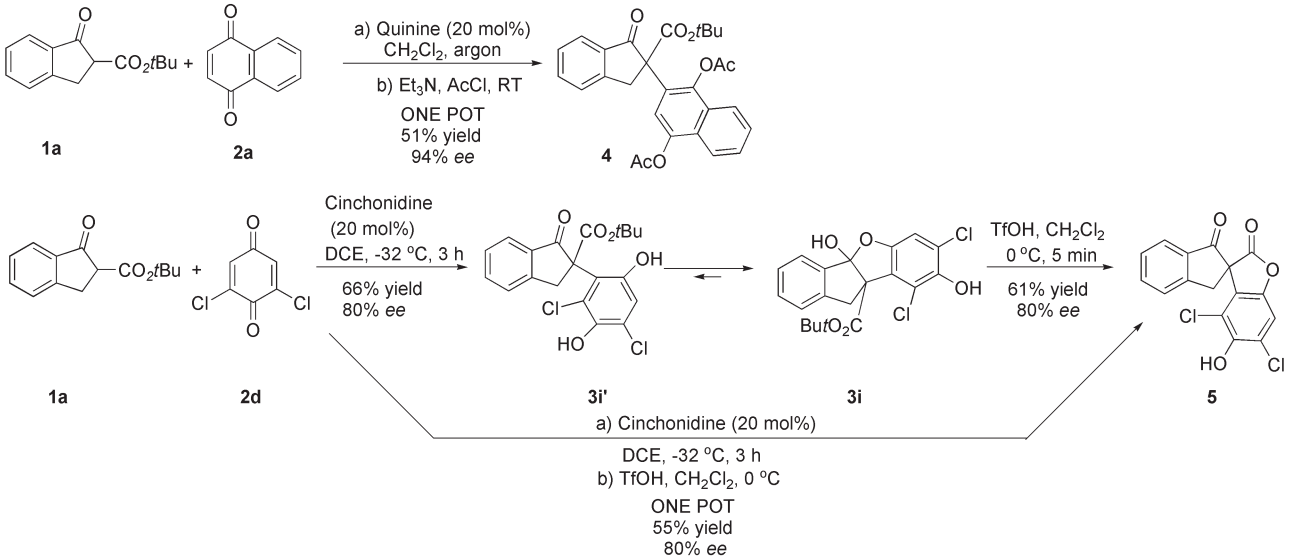

Scheme 3. Some transformations to obtain spiro and polycyclic skeletons. Tf: trifluoromethanesulfonyl.

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