Organocatalysis

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Asymmetric Organocatalytic α-Arylation of Aldehydes**

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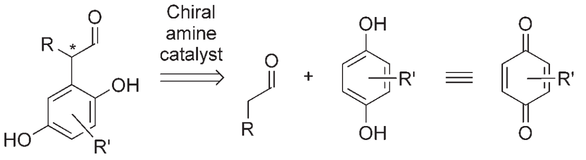
Dedicated to Prof. Roald Hoffmann on the occasion of his 70th birthday

The transition-metal-catalyzed α-arylation of carbonyl compounds is a useful and general synthetic method in chemistry which has been used for the synthesis of a number of important molecules. Recently, with the application of aryl halides, in particular, and chiral palladium complexes as catalysts, it is now also possible to perform enantioselective α-arylation of activated compounds.[1] A challenge in arylation chemistry is the direct enantioselective α-arylation of aldehydes, because of the importance of the optically active aromatic compounds formed.

Organocatalysis[2] has, in the last few years, been the subject of intensive development. Two different mechanistic approaches are generally considered in organocatalysis:[2c] covalent and noncovalent catalysis. For covalent catalysis, chiral secondary amines have shown to be a powerful tool for the enantioselective functionalization of, for example, carbonyl compounds. A large number of α-,[3] β-,[4] and γ-functionalization[5] reactions have been reported and are considered to proceed via enamine, iminium, and dienamine intermediates, respectively. However, the direct formation of a stereoselective C(sp^3)–C(sp^2) bond by arylation in the α-position to an aldehyde remains elusive as a result of difficulties associated with this kind of reaction.

Herein, we present the first highly asymmetric direct α-arylation of aldehydes using quinones as the aromatic partner, leading to optically active α-arylated aldehydes in which the aromatic fragment has electron-rich substituents (Scheme 1).

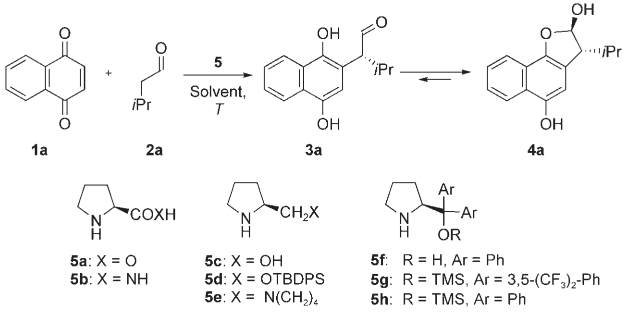


Scheme 1. Organocatalytic asymmetric α-arylation of aldehydes.

In nature, quinones have a relevant role in a great number of biological processes, and therefore a large number of reactions have been performed with these compounds.[6] The direct α-arylation of aldehydes described here affords also a new method for the formation of optically active hydroquinones and quinones by using simple and easily available starting materials.

As a model reaction, we studied the reactivity of the naphthoquinone (**1a**) with 3-methylbutanal (**2a**) in the presence of various catalysts and under different reaction conditions (Table 1). The optically active α-arylated aldehyde **3a** that is formed in the reaction exists in equilibrium with its hemiacetal form **4a**, which can easily be isolated as a

Table 1: Screening of reaction conditions for the addition of 1,4-naphthoquinone (**1a**) to 3-methylbutanal (**2a**) to yield **4a**.[a]



Entry	Solvent	Cat.	Conv.[b] [%]	*ee*[c] [%]
1	CH_2Cl_2	**5a**	nr	–
2	CH_3CN	**5a**	66	33
3	DMF	**5a**	71	30
4	DMSO/7% H_2O	**5a**	100	20
5	DMSO/7% H_2O	**5b**	100	74
6	DMSO/7% H_2O	**5c**	90	49
7	DMSO/7% H_2O	**5d**	93	94
8	DMSO/7% H_2O	**5e**	100	65
9	DMSO/7% H_2O	**5f**	96	88
10	DMSO/7% H_2O	**5g**	nr	–
11	DMSO/7% H_2O	**5h**	100 (86)[d]	> 99
12	DMSO/7% H_2O	**5h**[e]	79	> 99
13	DMSO/7% H_2O	**5h**[f]	44	> 99
14	H_2O	**5h**	100 (99)[d]	93
15	EtOH/7% H_2O	**5h**	100	97
16	EtOH/H_2O (2:1)	**5h**	100 (75)[d]	95
17	DMSO (dried)	**5h**	nr	–

[a] Performed with **1a** (0.3 mmol) and **2a** (0.6 mmol) with 20 mol% of catalyst loading at room temperature; all reactions were stopped after 18 h. TBDPS: *tert*-butyldiphenylsilyl; TMS: trimethylsilyl; DMF: *N*,*N*-dimethylformamide; DMSO: dimethyl sulfoxide. [b] Conversion and *de* values (> 99%) determined by ^1H NMR spectroscopy. Nr: no reacvtion. [c] Determined by chiral HPLC by derivatization to the quinone **6** (see Scheme 2). [d] Yield of isolated product. [e] 10 mol% catalyst loading. [f] 5 mol% catalyst loading.

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diastereomerically pure compound by flash chromatography using iatrobeads. It appears from the results given in entries 1–4 (Table 1) that proline (**5a**) is an effective catalyst for the reaction in terms of the extent of conversion, especially in wet DMSO; however, only low enantioselectivity is obtained. Proline amide **5b** also turned out to be an effective catalyst for the reaction and led to an improvement of the enantioselectivity of **4a** to 74% *ee* (Table 1, entry 5). The screening of different solvents showed that reactions performed in DMSO gave the best results; however, the presence of water is essential for success in this reaction. Thus, a number of other catalysts were tested in wet DMSO for the direct α-arylation (Table 1, entries 6–13). These results showed that a number of chiral secondary amines can catalyze the α-arylation of **2a** in moderate to excellent enantioselectivity.

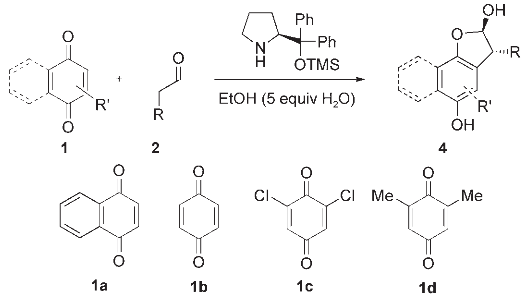
Surprisingly, we found that (*S*)-2-[bis(3,5-bistrifluoromethylphenyl)trimethylsilanyloxymethyl]pyrrolidine (**5g**), which has shown to be a general catalyst, for example, for the α-functionalization of aldehydes, was not active in the present reaction while (*S*)-2-(diphenyltrimethylsilanyloxymethyl)pyrrolidine (**5h**)[7] was an effective catalyst and provided full conversion and an excellent enantioselectivity of over 99% *ee* with a loading down to 5 mol% (Table 1, entries 11–13).

A very important advantage of the enantioselective direct α-arylation of aldehydes is that it can also proceed with full conversion in H_2O and EtOH with only a minor decrease in enantioselectivity (Table 1, entries 14–16). It turned out that H_2O is of utmost importance for the reaction as the reaction did not proceed in dry DMSO (entry 17). The solvent composition and the ratio of quinone to aldehyde are also important in relation to oxidation–reduction chemistry, as 1,4-dihydronaphthol is formed when other aldehydes are used (see Table S1 in the Supporting Information).

The organocatalytic α-arylation of aldehydes is a general reaction that can proceed for different quinones reacting with various aldehydes, and the scope of the reaction in EtOH–H_2O as solvent is presented in Table 2.

Entries 1–6 in Table 2 show the results for the reaction of a series of different aldehydes with naphthoquinone (**1a**), and it appears that the corresponding α-arylated products **4a–f** are formed in high yields from 80% to quantitative yield and with excellent enantioselectivities up to 99% *ee*. Next, some representative aldehydes that have isopropyl, propyl, and benzyl substituents were reacted with benzoquinone (**1b**), 2,6-dichlorobenzoquinone (**1c**), and 2,6-dimethylbenzoquinone (**1d**), respectively. The α-arylation of 3-methylbutanal using **1b** as the aromatic partner proceeds with an enantioselectivity of 92% *ee*; however, the yield is moderate, which is a result of the formation of the hydroquinone as by-product (Table 2, entry 7). With **1c**, the reaction proceeds well for a number of aldehydes and high yields and excellent enantioselectivities of 98–99% *ee* are obtained (Table 2, entries 8–11). For the benzoquinone bearing an electron-donating group (**1d**), the direct α-arylation reaction also proceeds well both in terms of yield and enantioselectivity (Table 2, entries 12 and 13).

Table 2: Scope of the organocatalytic α-arylation of aldehydes.[a]



Entry	Quinone	R	*T* [°C]	Product	Yield [%][b]	*ee* [%][c]
1	**1a**	*i*Pr	RT	**4a**	90[d]	99
2	**1a**	$PhCH_2$	4	**4b**	86	98
3	**1a**	Pr	−24	**4c**	98[e]	96
4	**1a**	Et	−24	**4d**	85	98
5	**1a**	*n*-Hex	−24	**4e**	86	99
6	**1a**	*n*-Oct	4	**4f**	80	99
7	**1b**	*i*Pr	−24	**4g**	68	92
8	**1c**	$PhCH_2$	4	**4h**	76	99
9	**1c**	$PhCH_2$	4	*ent*-**4h**	65[f]	99
10	**1c**	*i*Pr	4	**4i**	95	98
11	**1c**	Pr	−24	**4j**	65[g]	98
12	**1d**	$PhCH_2$	4	**4k**	55	99
13	**1d**	Pr	4	**4l**	82	99

[a] Performed with **1** (0.3 mmol), **2** (1.5 mmol), and 20 mol% of catalyst **5h** in EtOH (0.3 mL) with 5 equiv of H_2O at the temperature given. [b] Isolated yield. [c] Determined by chiral HPLC. [d] This reaction was carried out in DMSO/7% H_2O. [e] H_2O was used as solvent (see Table S2 in the Supporting Information). [f] (*R*)-**5h** was used for this reaction. [g] *ee* value determined after transformation into the corresponding protected acetal (see the Supporting Information for details).

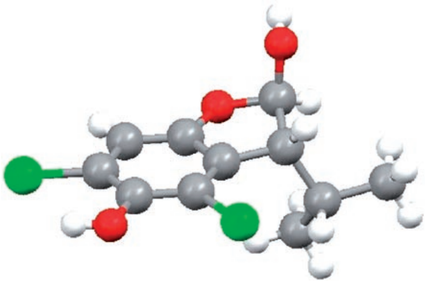
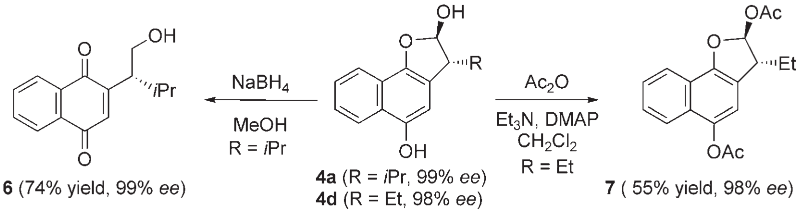


Figure 1. X-ray crystal structure of compound **4i**. C gray, H white, O red, Cl green.

The absolute configuration of the optically active α-arylated product formed was determined by X-ray analysis of the hemiacetal **4i** to be 2*R*,3*R* (Figure 1).[8] The absolute configuration of the stereogenic center formed indicates that the quinone approaches the *Si* face in the enamine intermediate in the catalytic cycle (on the right in Figure 2).

Scheme 2 outlines some transformations of the optically active α-arylated product formed. Reduction of compound **4a** leads to the optically active quinone **6** in 74% yield and with 99% *ee*. Furthermore, both hydroxy groups in compound **4d** can be acetylated by Ac_2O leading to **7**, also without loss of enantiopurity.



Scheme 2. Some product transformations: reduction and acetylation. DMAP: 4-dimethylaminopyridine.

The proposed mechanism for the direct α-arylation consists of two catalytic cycles. The first cycle, in which the stereogenic center is formed, is the reaction of the enamine intermediate with the quinone, and the second cycle is a series of proton-transfer reaction leading to the optically active α-arylated aldehyde that has a dihydroquinone functionality (see Figure 2). The proton-transfer reactions might involve H_2O, as no reaction occurs in its absence.

In conclusion, we have developed the first direct organocatalytic enantioselective α-arylation by reacting aldehydes with quinones. The α-arylation proceeds in high yields under environmentally friendly conditions,[9] and the optically active α-arylated aldehydes are obtained with excellent enantioselectivities. Furthermore, some transformations of the products formed have also been presented.

Experimental Section

α-Arylation of aldehydes: In an ordinary vial, the corresponding quinone (0.3 mmol) was added to a stirred solution of catalyst **5h** (0.06 mmol) and aldehyde (1.5 mmol) in EtOH (0.3 mL) and H_2O (30 μL) at the temperature indicated in Table 2. After complete consumption of the quinone (as monitored by ^1H NMR spectroscopy), the crude product was directly charged on a flash chromatography column (eluent indicated in each case) to afford the pure products. See the Supporting Information for full experimental details.

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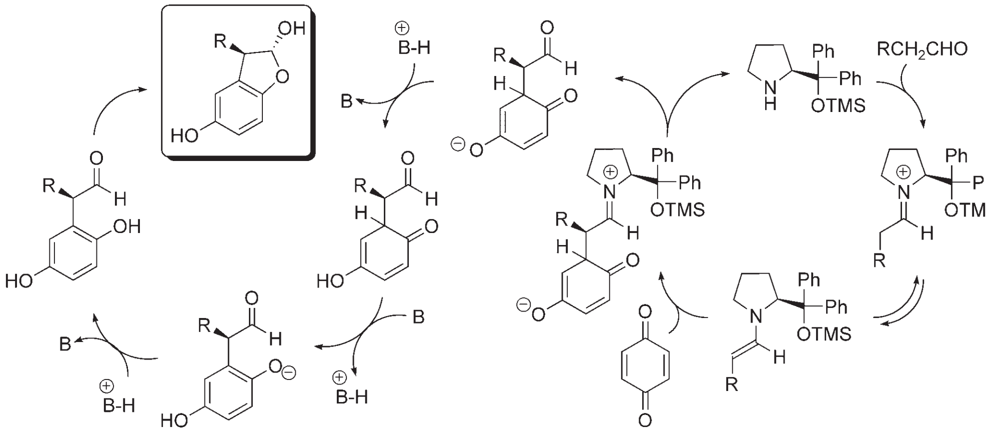

Figure 2. Proposed mechanism for the α-arylation of aldehydes catalyzed by **5h**. B: base.

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