Asymmetric Organocatalytic α -Arylation of Aldehydes

José Alemán, Silvia Cabrera, Eddy Maerten, Jacob Overgaard, Karl Anker Jørgensen

► To cite this version:

José Alemán, Silvia Cabrera, Eddy Maerten, Jacob Overgaard, Karl Anker Jørgensen. Asymmetric Organocatalytic α -Arylation of Aldehydes. *Angewandte Chemie International Edition*, 2007, 46 (29), pp.5520 - 5523. 10.1002/anie.200701207 . hal-03412834

HAL Id: hal-03412834

<https://hal.science/hal-03412834>

Submitted on 3 Nov 2021

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

DOI: 10.1002/anie.200123456

Asymmetric Organocatalytic α -Arylation of Aldehydes**

José Alemán, Silvia Cabrera, Eddy Maerten, Jacob Overgaard and Karl Anker Jørgensen*

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 especially aryl halides and chiral palladium complexes as the 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 in an intensive development. Two different mechanistic approaches are generally considered in organocatalysis:^[2c] covalent and non-covalent catalysis. For the covalent catalysis, chiral secondary amines have shown to be a powerful tool for the enantioselective functionalization of *e.g.* carbonyl compounds and a large number of α -,^[3] β -^[4] and γ -functionalization^[5] reactions have been reported. These reactions are considered to proceed *via* enamine, iminium and dienamine intermediates, respectively. However, the direct formation of a stereoselective Csp³–Csp² bond by an arylation reaction in the α -position to an aldehyde in this field remains elusive to be carried out due to difficulties associated to this kind of reaction.

In this paper 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, the 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 present new

development of the direct α -arylation of aldehydes, affords also a new method for the formation of optically active hydroquinones and quinones using simple and easy-available starting materials.

As a model reaction, we studied the reactivity of the naphthoquinone **1a** with 3-methyl butanal **2a** in the presence of various catalysts and reaction conditions, and some representative results are presented in Table 1. The optically active α -arylated aldehyde (**3a**) formed in the reaction exists in equilibrium with its hemiacetal form **4a**, which can easily be isolated as a diastereomerically pure compound by flash chromatography using iatrobeads. It appears from the results given in entries 1–4, that proline **5a** is an effective catalyst for the reaction in terms of conversion, especially in wet DMSO; however, only low enantioselectivity is obtained. Proline amide **5b** turned out to also be an effective catalyst for the reaction leading to an improvement of the enantioselectivity of **4a** to 74% *ee* (entry 5). The screening of different solvents showed that reactions performed in DMSO gave the best results; however, water is essential for success in this reaction. Thus, a number of other catalysts were tested in wet DMSO for the direct α -arylation and the results are given in 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.

Table 1: Screening of Reaction Conditions for the Addition of 1,4-Naphthoquinone **1a** to 3-Methyl Butanal **2a** to Yield **4a**.^[a]

<div style="display: flex; justify-content: space-around; align-items: flex-start;"> <div style="text-align: center;"> 5a: X = O 5b: X = NH </div> <div style="text-align: center;"> 5c: X = OH 5d: X = OTBDPS 5e: X = N(CH₂)₄ </div> <div style="text-align: center;"> 5f: R = H, Ar = Ph 5g: R = TMS, Ar = 3,5-(CF₃)₂-Ph 5h: R = TMS, Ar = Ph </div> </div>				
Ent	Solvent	Cat.	Conv. ^[b]	<i>ee</i> ^[c]
1	CH ₂ Cl ₂	5a	nr	-
2	CH ₃ CN	5a	66	33
3	DMF	5a	71	30
4	DMSO-7% H ₂ O	5a	100	20
5	DMSO-7% H ₂ O	5b	100	74
6	DMSO-7% H ₂ O	5c	90	49
7	DMSO-7% H ₂ O	5d	93	94
8	DMSO-7% H ₂ O	5e	100	65
9	DMSO-7% H ₂ O	5f	96	88
10	DMSO-7% H ₂ O	5g	nr	-
11	DMSO-7% H ₂ O	5h	100 (86) ^[d]	>99
12	DMSO-7% H ₂ O	5h ^[e]	79	>99
13	DMSO-7% H ₂ O	5h ^[f]	44	>99
14	H ₂ O	5h	100 (99) ^[d]	93
15	EtOH-7% H ₂ O	5h	100	97
16	EtOH/H ₂ O (2/1)	5h	100 (75) ^[d]	95
17	DMSO (dried)	5h	nr	-

[a] Performed with **1a** (0.3 mmol), **2a** (0.6 mmol) with 20 mol% of catalyst loading at rt and all reactions stopped after 18 h. [b] Conversion and *de* (>99%) determined by ¹H NMR. [c] Determined by chiral HPLC by derivatization to the quinone **6** (see Scheme 2). [d] Isolated yield. [e] 10 mol% catalyst loading. [f] 5 mol% catalyst loading.

[*] Dr. J. Alemán, Dr. S. Cabrera, Dr. E. Maerten, Dr. J. Overgaard, Professor Dr. K. A. Jørgensen.
Danish National Research Foundation: Center for Catalysis
Department of Chemistry, Aarhus University
DK-8000 Aarhus C, Denmark
Fax: (+45) 8919 6199
E-mail: kaj@chem.au.dk

[**] This work was made possible by a grant from Danish National Research Foundation. J. A. and S. C. thank Ministerio de Educación y Ciencia of Spain for a post-doctoral fellowship.

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

Surprisingly, we found that (*S*)-2-[bis(3,5-bis(trifluoromethyl)phenyl)-trimethyl-silyloxymethyl]-pyrrolidine **5g**, which has shown to be a general catalyst for *e.g.* the α -functionalization of aldehydes, in the present reaction was not active, while (*S*)-2-(diphenyl-trimethyl-silyloxymethyl)-pyrrolidine **5h**⁷ was an effective catalyst providing full conversion and an excellent enantioselectivity of >99% *ee* with a loading down to 5 mol% (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 H₂O and EtOH with only a minor decrease in enantioselectivity (entries 14-16). It turned out that H₂O 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-aldehyde are also important in relation to oxidation-reduction chemistry as 1,4-dihydronaphthol is formed when other aldehydes were used (see Table S1 in Supporting Information).

The organocatalytic α -arylation of aldehydes is a general reaction which can proceed for different quinones reacting with various aldehydes and the scope of the reaction in a EtOH-H₂O composition is presented in Table 2.

Table 2: Scope of the Organocatalytic α -Arylation of Aldehydes.^[a]

Ent.	Quin.	R	T [°C]	Yield [%] ^[b]	ee [%] ^[c]
1	1a	<i>i</i> -Pr	rt	4a – 90 ^[d]	99
2	1a	PhCH ₂	4	4b – 86	98
3	1a	<i>n</i> -Pr	-24	4c – 98 ^[e]	96
4	1a	<i>n</i> -Et	-24	4d – 85	98
5	1a	<i>n</i> -Hex	-24	4e – 86	99
6	1a	<i>n</i> -Oct	4	4f – 80	99
7	1b	<i>i</i> -Pr	-24	4g – 68	92
8	1c	PhCH ₂	4	4h – 76	99
9	1c	PhCH ₂	4	<i>ent</i> - 4h – 65 ^[f]	99
10	1c	<i>i</i> -Pr	4	4i – 95	98
11	1c	<i>n</i> -Pr	-24	4j – 65 ^[g]	98
12	1d	PhCH ₂	4	4k – 55	99
13	1d	<i>n</i> -Pr	4	4l – 82	99

[a] Performed with **1** (0.3 mmol), **2** (1.5 mmol) and 20 mol% of catalyst **5h** in 0.3 mL of EtOH and 5 equiv. of H₂O at the temperature given. [b] Isolated yield. [c] Determined by chiral HPLC. [d] This reaction has been carried out in DMSO-7% H₂O. [e] H₂O was used as solvent (see Table S2 in Supporting Information). [f] (*R*)-**5h** was used for this reaction. [g] *Ee* determined after transformation into the corresponding protected acetal (see Supporting Information for details).

The first six entries in Table 2 show the results for a series of different aldehydes reacting 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 excellent enantioselectivities up to 99% *ee*. Next, some representative aldehydes having *iso*-propyl, propyl and benzyl substituents were reacted with benzoquinone **1b**, and 2,6-dichloro- and 2,6-dimethyl-benzoquinones, **1c** and **1d**, respectively. The α -arylation of 3-methyl butanal using **1b** as the aromatic partner proceeds with an enantioselectivity of 92% *ee*; however, the yield is moderate, which is due to the formation of the hydroquinone as by-product (entry 7). For 2,6-dichloro benzoquinone **1c**, the reaction proceeds well for a number of aldehydes and high yields and excellent enantioselectivities of 98-99% *ee* are obtained (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 (entries 12, 13).

The absolute configuration of the optically active α -arylated product formed has been determined by X-ray analysis of the hemiacetal **4i** to be 2*R* and 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 to the right in Figure 2.

Figure 1. X-Ray structure of compound **4i**. Carbon: grey, hydrogen: white, oxygen: red, chloride: green.

In Scheme 2 is outlined 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 maintaining the enantioselectivity of 99% *ee*. Furthermore, both hydroxyl groups in compound **4d** can be acetylated by Ac₂O leading to **7**, also without losing enantiopurity.

Scheme 2. Some Product Transformations: Reduction and Acetylation.

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 optically active α -arylated aldehyde having the dihydroquinone functionality (see Figure 2). The proton-transfer reactions might involve H₂O as no reaction occurs in its absence.

Figure 2. Proposed Mechanism for the α -Arylation of Aldehydes Catalyzed by **5h**.

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 environmental-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 H₂O (30 μ L) at the indicated temperature in Table 2. After complete consumption of the quinone (as monitored by ¹H NMR spectroscopy), the crude was directly charged in FC (eluent indicated in each case), affording the pure products. See Supporting Information for full experimental details.

Received: ((will be filled in by the editorial staff))

Published online on ((will be filled in by the editorial staff))

Keywords: Aldehydes, α -arylation, quinones, organocatalysis.

- [1] See e.g.: a) J. Ahman, J. P. Wolfe, M. V. Troutman, M. Palucki, S. L. Buchwald, *J. Am. Chem. Soc.* **1998**, 120, 1918. b) T. Hamada, A. Chieffi, J. Ahman, S. L. Buchwald, *J. Am. Chem. Soc.* **2002**, 124, 1261; c) D. J. Spielvogel, S. L. Buchwald, *J. Am. Chem. Soc.* **2002**, 124, 3500 and references cited in there; d) G. C. Lloyd-Jones, *Angew. Chem. Int. Ed.* **2002**, 41, 953; e) D. A. Culkin, J. F. Hartwig, *Acc. Chem. Res.* **2003**, 36, 234 and references therein.
- [2] For recent reviews on organocatalysis see e.g.: a) P. L. Dalko, L. Moisan, *Angew. Chem. Int. Ed.* **2004**, 43, 5138; b) *Acc. Chem. Res.* **2004**, 37 (8), special issue on organocatalysis; c) A. Berkessel, H. Gröger, *Asymmetric Organocatalysis*; VCH: Weinheim, Germany, **2005**; d) J. Seayed, B. List, *Org. Biomol. Chem.* **2005**, 3, 719; e) B. List, J.-W. Yang, *Science* **2006**, 313, 1584; f) M. J. Gaunt, C. C. C. Johansson, A. McNally, N. C. Vo, *Drug Discovery Today* **2007**, 2, 8; g) B. List, *Chem. Commun.* **2006**, 819; h) P. I. Dalko, *Enantioselective Organocatalysis*, Wiley-VCH, Weinheim, **2007**.
- [3] See e.g.: a) M. Marigo, K. A. Jørgensen, *Chem. Commun.* **2006**, 2001; b) G. Guillena, D. J. Ramón, *Tetrahedron Asymmetry* **2006**, 17, 1465; c) N. Mase, K. Watanabe, H. Yoda, K. Tanabe,

- F. Tanaka, C. F. Barbas III, *J. Am. Chem. Soc.* **2006**, 128, 4966; d) S. Samanta, C.-G. Zhao, *J. Am. Chem. Soc.* **2006**, 128, 7442; e) Y. Hayashi, T. Sumiya, J. Takahashi, H. Gotoh, T. Urushima, M. Shoji, *Angew. Chem. Int. Ed.* **2006**, 45, 958; f) T. Kano, M. Ueda, J. Takai, K. Maruoka, *J. Am. Chem. Soc.* **2006**, 128, 6046.
- [4] See e.g.: a) K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, 122, 4243; b) S. G. Ouellet, J. B. Tuttle, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2005**, 127, 32; c) S. Mayer, B. List, *Angew. Chem. Int. Ed.* **2006**, 45, 4193; d) M. Marigo, M., T. Schulte, J. Franzén, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, 127, 15710; e) S. Brandau, A. Landa, J. Franzén, M. Marigo, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2006**, 45, 4305; f) H. Gotoh, R. Masui, H. Ogino, M. Shoji, Y. Hayashi, *Angew. Chem. Int. Ed.* **2006**, 45, 6853; g) W. Wang, H. Li, J. Wang, L. Zu, *J. Am. Chem. Soc.* **2006**, 128, 10354; h) S. Brandau, E. Maerten, K. A. Jørgensen, *J. Am. Chem. Soc.* **2006**, 128, 14986; i) Y. K. Chen, M. Yoshida, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2006**, 128, 9328; j) H. Sundén, I. Ibrahim, G.-L. Zhao, L. Eriksson, A. Córdova, *Chem. Eur. J.* **2007**, 13, 574; k) For a general review of β -functionalization see: S. B. Tsogoeva, *Eur. J. Org. Chem.* **2007**, 1701.
- [5] S. Bertelsen, M. Marigo, S. Brandes, P. Dinér, K. A. Jørgensen, *J. Am. Chem. Soc.* **2006**, 128, 12973.
- [6] a) "The Chemistry of the Quinoid Compounds" (Eds: S. Patai, Z. Rapoport), Wiley, New York, 1988; b) For a review of quinone chemistry see: A. Kutyrev, *Tetrahedron* **1991**, 47, 8043. c) See also: M. E. Kuehne, *J. Am. Chem. Soc.* **1961**, 84, 837.
- [7] See e.g.: a) J. Franzén, M. Marigo, D. Fielenbach, T. C. Wabnitz, A. Kjærsgaard, K. J. Jørgensen, *J. Am. Chem. Soc.* **2005**, 127, 18296; b) C. Palomo, A. Mielgo, *Angew. Chem. Int. Ed.* **2006**, 45, 7876. c) G.-L. Zhao, A. Córdova, *Tet. Lett.* **2006**, 47, 7417. d) T. Govender, L. Hojabri, F. M. Moghaddam, P. I. Arvidsson *Tet. Asymmetry*, **2006**, 17, 1763. e) D. Enders, M. R. M. Hüttl, C. Grondal, G. Raabe, *Nature* **2006**, 441, 441. f) I. Ibrahim, G.-L. Zhao, H. Sundén, A. Córdova, *Tet. Lett.* **2006**, 47, 4659. g) Y. Chi, S. H. Gellman, *J. Am. Chem. Soc.* **2006**, 128, 6804. h) S. S. Chow, M. Nevalainen, C. A. Evans, C. W. Johannes, *Tet. Lett.* **2007**, 48, 277. i) See also references: 4f, 4g,
- [8] CCDC 639134 contains the supplementary crystallographic data. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (internat.) +44(1223)336-033, e-mail: deposit@ccdc.cam.ac.uk].
- [9] For a recent discussion about water in organocatalytic processes see: D. G. Blackmond, A. Armstrong, V. Coombe, A. Wells, *Angew. Chem. Int. Ed.* **2007**, 46, early view and references cited therein.

Organocatalysis

José Alemán, Silvia Cabrera, Eddy Maerten, Jacob Overgaard and Karl Anker Jørgensen*

Asymmetric Organocatalytic α -Arylation of Aldehydes

The first catalytic enantioselective α -arylation of aldehydes is presented using quinones as the aromatic partner. The organocatalytic reaction takes place under environmental-friendly conditions such as H₂O and EtOH-H₂O as the solvent. The corresponding optically active α -arylated aldehydes are obtained in high yields and with an excellent enantioselectivity of up to >99% ee. It is demonstrated that the organocatalytic asymmetric α -arylation reaction of aldehydes can proceed for a number of different aldehydes reacting with different quinones.