Organocatalytic asymmetric vinylogous addition to quinones – formation of optically active α-aryl ketones†

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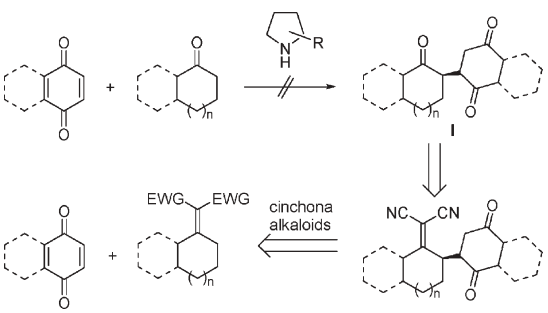
The first organocatalytic addition of dicyanoalkylidenes to quinones catalyzed by Cinchona alkaloids leading to formation of 1,4-diketone derivatives with high diastereomeric ratios (up to >98 : <2 dr) and enantioselectivities (up to 99% ee) has been developed; the optically active compounds obtained are useful for a number of transformations, *e.g.* the synthesis of optically active α-aryl ketones.

Stereoselective C–C bond formation is an important goal in organic chemistry, and especially organocatalysis has in the past years provided the chemist with different asymmetric strategies to reach this goal.[1] Limitations of these strategies have been Csp^3–Csp^2 and Csp^3–Csp organocatalytic asymmetric reactions. However, recent strategies for the development of methods for the formation of these types of bonds, allowing the synthesis of a stereocenter attached to double[2a,b] or propargylic triple bond,[2c] have been presented.

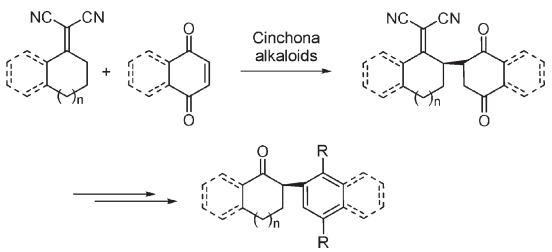
In nature, quinones have an important role in biological processes and therefore a large number of reactions have been performed with these compounds.[3] Recently, the first asymmetric organocatalytic α-arylations of β-keto esters[4a] and aldehydes[4b] by addition to quinones were presented. However, the organocatalytic α-arylation of ketones, in a direct or indirect way, is also attractive but has been elusive until now. In this communication we present our efforts to achieve this goal.

In our initial attempts, we focused on performing the reaction with enamine chemistry (top, Scheme 1). However, in our hands, after several diverse attempts, with different catalysts,[5] we found that the system was completely non-reactive using various reaction conditions (See Tables S1 and S2 in the ESI†).[6] Consequently, the retro-analysis of the final product (**I**) was considered, and it was found that **I** might be formed by functionalization of the dicyanoalkylidenes,[7] followed by oxidative cleavage, allowing the synthesis of the same type of compound in an indirect manner (Scheme 1).



Scheme 1 Two main strategies for the α-addition of ketones to quinones.

In this paper, we present the first asymmetric addition of dicyanoalkylidenes to quinones catalyzed by Cinchona alkaloids. Furthermore, further derivatization of the products to *e.g.* α-aromatic ketones is also included (Scheme 2).



Scheme 2 The allylic C–C formation.

The screenings of the appropriate conditions and catalysts are presented in Table 1 for the reaction of dicyanoalkylidene **1a** with 1,4-naphthoquinone **2a**. The reaction can be catalyzed by quinine **3a** with good conversion and moderate diastereomeric ratio; however, the enantioselectivity was poor (entry 1). Further modification of the catalyst, such as protection at the hydroxy group with 1-naphthalene (**3b**), improved the enantioselectivity to 39% ee; nevertheless, longer reaction time was required (entry 2). Other aromatic rings have also been introduced as the linker (**3c** and **3d**) leading to a further improvement to 52% ee (entries 3, 4). However, on applying the adamantoyl ester **3e** as the catalyst, the enantioselectivity was not improved further (entry 5), indicating that not only steric effects, but also electronic effects might be of importance for the reaction.

The dimeric catalysts **3f**–**3j** were also screened (entries 6–10) and these catalysts gave more satisfactory results in terms of conversion and stereoselectivity than the monomeric catalysts. The best catalyst was **3j** which gives **4a** with 61% ee (entry 10).

The effect of solvents on the reaction course using catalyst **3j** was also studied (entries 10–15). Chlorinated solvents, such as 1,2-dichloroethane (DCE), CH_2Cl_2, and $CHCl_3$, gave a slower reaction, compared to acetone, leading to lower conversion. In order to obtain both high conversion and stereoselectivity, it was found that a mixture of $CHCl_3$–acetone (7 : 1) allowed us to decrease the temperature to −40 °C. By increasing the catalytic loading from 10 to 20 mol%, product **4a** was formed with high conversion, a dr of 14 : 1 and with 67% and 81% ee of the major

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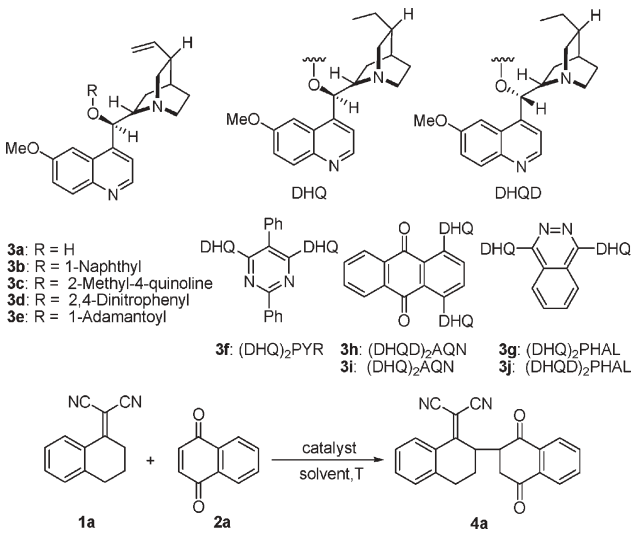
† Electronic supplementary information (ESI) available: Experimental details and NMR spectra. See DOI: 10.1039/b716485h

Table 1 Screening and optimization conditions for the addition of dicyanoalkylidene **1a** to quinone **2a**[a]



Entry	Catalyst (mol %)	Solvent	T/°C	Time (h)	Conv.[b] (%)	dr[b]	ee[c] (%)
1	**3a** (10)	CH_2Cl_2	−20	18	78	2 : 1	2
2	**3b** (10)	CH_2Cl_2	−20	89	36	13 : 1	39
3	**3c** (10)	CH_2Cl_2	−20	44	88	3 : 1	52
4	**3d** (10)	CH_2Cl_2	−20	72	26	8 : 1	−47
5	**3e** (10)	CH_2Cl_2	−20	12	95	4 : 1	30
6	**3f** (10)	CH_2Cl_2	−20	47	89	4 : 1	17
7	**3g** (10)	CH_2Cl_2	−20	72	85	3 : 1	56
8	**3h** (10)	CH_2Cl_2	−20	72	98	10 : 1	−43
9	**3i** (10)	CH_2Cl_2	−20	16	96	4 : 1	−46
10	**3j** (10)	CH_2Cl_2	−20	48	79	4 : 1	−61
11	**3j** (10)	DCE	−20	43	91	5 : 1	−53
12	**3j** (10)	$CHCl_3$	−20	43	67	4 : 1	−65
13	**3j** (10)	Acetone	−20	18	98	3 : 1	−59
14	**3j** (10)	Toluene	−20	72	82	5 : 1	−30
15	**3j** (10)	THF	−20	43	82	2 : 1	−63
16	**3j** (10)	$CHCl_3$–Acetone (7 : 1)	−40	20	90	5 : 1	−60 (44)[d]
17	**3j** (20)	$CHCl_3$–Acetone (7 : 1)	−40	20	80	14 : 1	−67 (81)[d]
18	**3j** (20)	$CHCl_3$–Acetone (7 : 1)	−20	20	95	14 : 1	−75

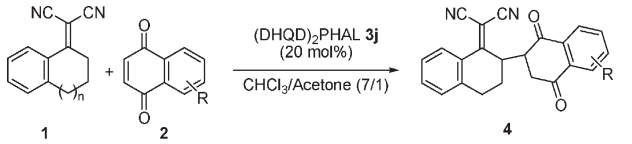
[a] All the reactions were performed on a 0.10 mmol scale (0.1 M). [b] Conversion and diastereomeric ratio were determined by ^{1}H NMR spectroscopy. [c] The ee was determined by HPLC using a chiral stationary phase. [d] Ee of minor diastereoisomer.

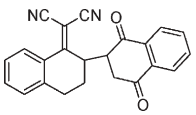
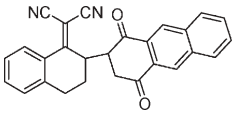
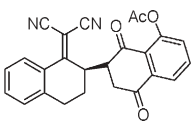
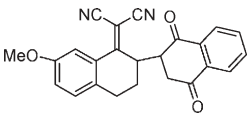
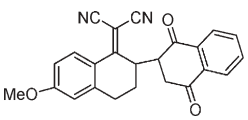
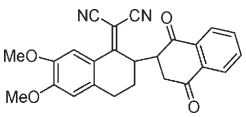
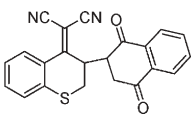
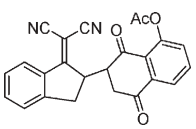
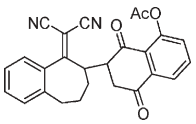
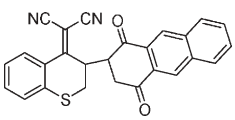
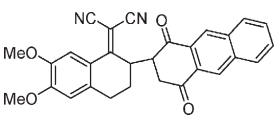
and minor diastereomer, respectively (entries 16, 17). Finally, it was found that slightly higher temperature led to an increase of the enantioselectivity to 75% ee (entry 18).

With these key conditions, we decided to investigate the scope of the reaction (Table 2). Surprisingly, when the reaction was carried out with the 1,4-anthraquinone, compared with the 1,4-naphthoquinone, the enantioselectivity was improved to >99% ee (entries 1, 2). However, the yield of **4b** was only moderate, which might be due to insolubility problems of the final product. Substitution at the 1,4-naphthoquinone led to a minor decrease in the enantioselectivity of the reaction, as observed for the reaction with the acetyl juglone (entry 3).[8]

The 6-methoxy-dicyanoalkylidene derivative **1b** reacted with quinone **2a** to give the corresponding adduct **4d** in good yield and moderate enantioselectivity (entry 4). Interestingly, when a

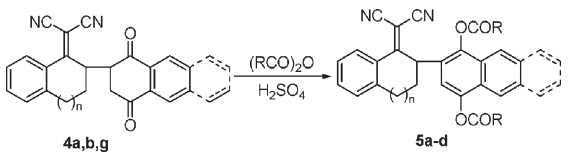
Table 2 Screening for the addition of dicyanoalkylidenes **1a**–**g** to quinones **2a**–**c**[a]



Entry	1	2	Product 4	Yield[b] (%)	(dr)[c]	ee (%)[d]
1	**1a**	**2a**		**4a** 84	(14 : 1)	75
2	**1a**	**2b**		**4b** 39	(>98 : <2)	>99
3	**1a**	**2c**		**4c** 80	(8 : 1)	60
4	**1b**	**2a**		**4d** 81	(5 : 1)	63
5	**1c**	**2a**		**4e** 76	(14 : 1)	99
6	**1d**	**2a**		**4f** 69	(>98 : <2)	96
7	**1e**	**2a**		**4g** 81	(4 : 1)	65
8	**1f**	**2c**		**4h** 67	(11 : 1)	68
9	**1g**	**2c**		**4i** 83	(>98 : <2)	80
10	**1e**	**2b**		**4j** 50	(12 : 1)	93
11	**1d**	**2b**		**4k** 51	(>98 : <2)	92

[a] In all cases the reaction was carried out at −20 °C on a 0.2 mmol scale and stopped after 24–48 h, after the consumption of the starting material (see ESI). [b] Global isolated yield. [c] Diastereomeric ratio determined by ^{1}H NMR spectroscopy. [d] The enantiomeric excess was determined by HPLC using a chiral stationary phase (see ESI).

Table 3 Acid-catalyzed aromatization of compounds **4a**, **4b** and **4g**[a]



Entry	Starting material	R	Product	Yield (%)
1	**4a**	Me	**5a**	74 (69)[b]
2	**4b**	Et	**5b**	71
3	**4g**	Me	**5c**	71
4	**4a**	Et	**5d**	93

[a] All the reactions were performed on a 0.10 mmol scale. [b] Reaction done on the 6.0 mmol scale.

methoxy group was placed at the 5-position as in 5-methoxy-dicyanoalkylidene **1c** or 5,6-dimethoxy-dicyanoalkylidene **1d**, the reaction with quinone **2a** gave **4e** and **4f** in good yields and 96 and 99% ee, respectively (entries 5, 6). The non-phenyl-fused dicyanoalkylidene—derived from cyclohexanone—only gave 10% ee of the desired product (**4l**, see ESI†).

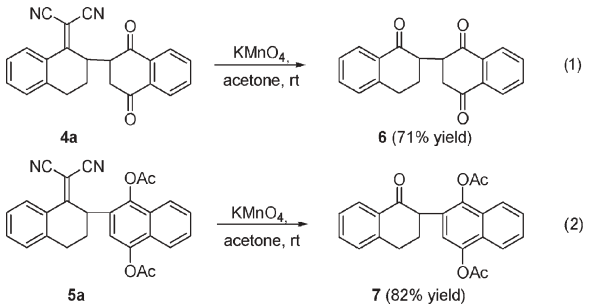
Substrates with heteroatoms in the nucleophile, such as the sulfur derivative **1e**, also reacted smoothly with quinone **2a** to give the corresponding product **4g** with moderate enantiomeric excess and good yield (entry 7). It is also interesting that the reaction can be performed with five and seven membered rings (**1f** and **1g**), obtaining in both cases the compounds **4h** and **4i** in good yields and diastereoselectivities with moderate enantioselectivity (entries 8, 9).

Finally, the reaction could be performed with the 1,4-anthraquinone **2b**, and both reactions studied, the products **4j** and **4k** were obtained with excellent enantioselectivities (entries 10, 11). The configuration of the products was determined by X-ray crystal analysis of compound **4j**,‡ and also based on previous results[7b,e] (see ESI for more details†).

The reaction also proceeds well on a larger scale. Compound **4a** could be obtained in 90% yield on a 20 mmol scale, allowing in this way different derivatizations. For all the compounds that we have studied, we did not detect aromatization to the corresponding 1,4-hydroquinones under the base-catalyzed conditions as we observed before.[4] However, compounds **4a**, **4b** and **4g** instantaneously aromatized in solvent-free conditions using acid catalysis[9] and the products were trapped using different anhydrides, giving the α-aromatic compounds **5a**–**5d** in good yields and without any significant loss of enantiopurity (Table 3).

In addition, compound **4a** could be subjected to oxidative cleavage conditions,[7b] giving the tri-ketone **6** in good yield (eqn (1), Scheme 3); also, the α-aromatic ketone from **5a** gives **7** in good yield (eqn (2), Scheme 3) and in both cases without any significant loss of enantiopurity.

In conclusion, we have presented the first organocatalytic allylic addition of alkylidene derivatives to quinones by using Cinchona alkaloid catalysts. This reaction proceeds with good yields, diastereoselectivities, and gives up to 99% ee. The adducts can be derivatized to different useful products such as α-arylated alkylidenes and ketone compounds.



Scheme 3 Different transformations of the alkylidenes **4a** and **5a**.

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Notes and references

‡ CCDC 666377. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b716485h

1 For reviews on organocatalysis, see *e.g.*: (*a*) P. I. Dalko and L. Moisan, *Angew. Chem.*, 2001, **113**, 3840, (*Angew. Chem., Int. Ed.*, 2001, **40**, 3726); (*b*) E. R. Jarvo and S. J. Miller, *Tetrahedron*, 2002, **58**, 2481; (*c*) P. I. Dalko and L. Moisan, *Angew. Chem.*, 2004, **116**, 5248, (*Angew. Chem., Int. Ed.*, 2004, **43**, 5138); (*d*) *Acc. Chem. Res.*, 2004, **37**(8), special issue on organocatalysis; (*e*) A. Berkessel and H. Gröger, *Asymmetric Organocatalysis*, Wiley-VCH, Weinheim, 2005; (*f*) J. Seayad and B. List, *Org. Biomol. Chem.*, 2005, **3**, 719; (*g*) M. J. Gaunt, C. C. C. Johansson, A. McNally and N. T. Vo, *Drug Discovery Today*, 2007, **12**, 8; (*h*) P. I. Dalko, *Enantioselective Organocatalysis*, Wiley-VCH, Weinheim, 2007.

2 (*a*) T. B. Poulsen, L. Bernardi, M. Bell and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2006, **45**, 6551; (*b*) J. Alemán, E. Reyes, B. Richter, J. Overgaard and K. A. Jørgensen, *Chem. Commun.*, 2007, 3921; (*c*) T. B. Poulsen, L. Benardi, J. Alemán, J. Overgaard and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2007, **129**, 441.

3 (*a*) *The Chemistry of the Quinoid Compounds*, ed. S. Patai and Z. Rapoport, Wiley, New York, 1988. For a review of quinone chemistry see: (*b*) A. Kutyrev, *Tetrahedron*, 1991, **47**, 8043.

4 (*a*) J. Alemán, B. Richter and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2007, **46**, 5515; (*b*) J. Alemán, S. Cabrera, E. Maerten, J. Overgaard and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2007, **46**, 5520. A racemic addition of alkyl phenylcyanoacetate to *in situ* formed 1,2-quinones was recently described: (*c*) K. Bogle, D. J. Hirst and D. J. Dixon, *Org. Lett.*, 2007, **9**, 4901.

5 Different attempts with 3-pentanone and cyclohexanone have been carried out with the quinone **2a**, however in different conditions and with different catalysts no reaction took place. See ESI Tables S1 and S2†.

6 Although highly successful direct asymmetric funtionalizations of ketones have been achieved using enamine catalysis, the corresponding functionalization of α-tetralone cannot be carried out.

7 (*a*) T. B. Poulsen, C. Alemparte and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2005, **127**, 11614; (*b*) T. B. Poulsen, M. Bell and K. A. Jørgensen, *Org. Biomol. Chem.*, 2006, **4**, 63; (*c*) M. Bell, K. Frisch and K. A. Jørgensen, *J. Org. Chem.*, 2006, **71**, 5407; (*d*) B. Niess and K. A. Jørgensen, *Chem. Commun.*, 2007, 1620. For related work from other groups, see: (*e*) D. Xue, Y.-C. Chen, Q.-W. Wang, L.-F. Cun, J. Zhu and J.-G. Deng, *Org. Lett.*, 2005, **7**, 5293; (*f*) J.-W. Xie, L. Yue, D. Xue, X.-L. Ma, Y.-C. Chen, Y. Wu, J. Zhu and J.-G. Deng, *Chem. Commun.*, 2006, 1563; (*g*) J.-W. Xie, W. Chen, R. Li, M. Zeng, W. Du, L. Yue, Y.-C. Chen, Y. Wu, J. Zhu and J.-G. Deng, *Angew. Chem., Int. Ed.*, 2007, **46**, 389.

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