Organocatalysis

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Quinine-Catalyzed Asymmetric Synthesis of 2,2′-Binaphthol-Type Biaryls under Mild Reaction Conditions

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Abstract: *Simple quinine as an organocatalyst mediates the addition of various naphthols to halogenated quinones to afford non-C_2-symmetrical, axially chiral biaryl products, which are promising compounds as chiral ligands and organocatalysts. The rotational barrier required to have two distinct atropisomers has been evaluated in the products generated from the addition of naphthols to various quinones by means of DFT calculations and HPLC. The use of halogenated quinones as reagents was necessary to have configurationally stable enantiomeric products which can be obtained in good yield and stereoselectivity. These compounds have also been prepared in gram quantities and recrystallized to near enantiopurity.*

Biaryl moieties bearing a chiral axis are present in a number of natural products[1a] and are widely exploited in asymmetric catalysis.[1b–f] A key molecule belonging to this class is 2,2′-binaphthol (BINOL), which is produced on large scale by oxidative coupling and resolved by *Cinchona* alkaloids.[2a,b] Over the years, several chiral ligands and catalysts derived from the privileged BINOL framework have been successfully employed in asymmetric synthesis (Figure 1).[2a–f]

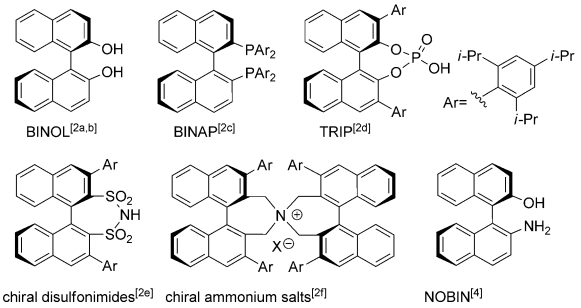

Figure 1. Some widely exploited axially chiral ligands and catalysts.[2]

A C_2-symmetry axis was once considered a key feature for obtaining high enantioselectivity in asymmetric catalysis,[3] but over the years, several authors have also demonstrated the efficiency of non-C_2-symmetrical ligands and catalysts, such as NOBIN.[4] Despite their wide popularity in asymmetric catalysis, the large scale synthesis of these molecules suffers from two critical issues. First, the formation of C–C bonds in an industrial process is a significant challenge, especially $C(sp^2)$–$C(sp^2)$ couplings which are mediated by transition metals and oxidants. The use of metals represents a technical and economic issue for industry.[5a,b] Second, most scalable syntheses only afford racemic products, which need to be resolved by processes having a maximum theoretical yield of 50%.[2,5c] Therefore, an efficient organocatalytic (transition-metal-free) approach to prepare these compounds could represent a major breakthrough. Recently, the groups of Miller[6a,b] and Matsubara[6c] demonstrated the possibility of obtaining axially chiral biaryls through dynamic kinetic resolution by using an organocatalytic bromination reaction. Despite this process being of scientific value within academia, the elaboration of the products into effective ligands and catalysts does not appear straightforward and it has not been demonstrated yet. Moreover, the synthesis of the achiral precursors still requires a transition metal catalyzed reaction. Therefore, a practical synthesis of a structure which closely resembles BINOL, a structure already proven to be highly effective as a chiral ligand and catalyst, might be preferable and open new horizons in the field of asymmetric catalysis.

Prakash and co-workers reported that *Cinchona* alkaloid-derived chiral bases could activate indoles, which would add in an asymmetric way to ethyl trifluoropiruvate.[7a] Jørgensen, Bella, and co-workers described a similar activation mode of the corresponding 2-naphthols, which after addition to azodicarboxylates, produced C–N axially chiral compounds (Figure 2).[7b,c] We thought that this information could be exploited to develop a $C(sp^2)$–$C(sp^2)$ coupling between

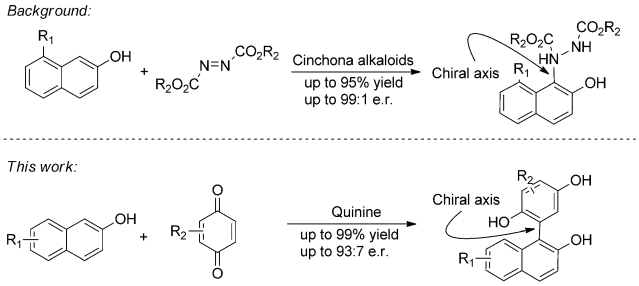

Figure 2. Previous and current work.

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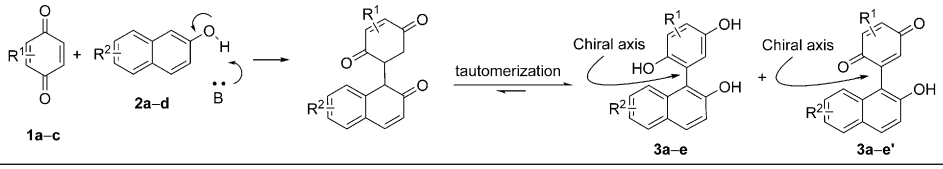
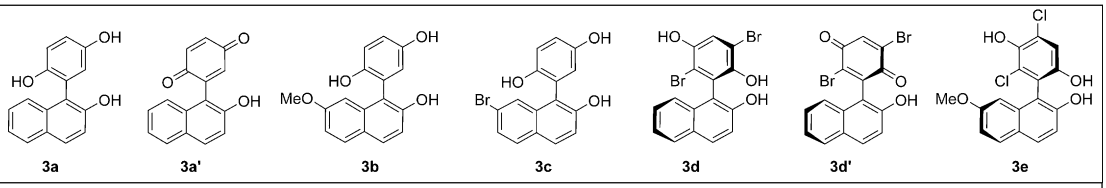




	3a	3a'	3b	3c	3d	3d'	3e
Calculated							
$\Delta G^{\#}$ (kcal/mol)	22.9	11.9	22.1	22.8	45.8	32.4	40.2
$t_{1/2}$ rac (s)	7800	6.3×10^{-5}	2000	6600	5.5×10^{20}	7.6×10^{10}	4.2×10^{16}
Determined							
$\Delta G^{\#}$ (kcal/mol)	22.0 ± 0.1		21.3 ± 0.1	21.9 ±0.1			
$t_{1/2}$ rac (s)	1650 ± 250		510 ± 80	1340 ± 270			

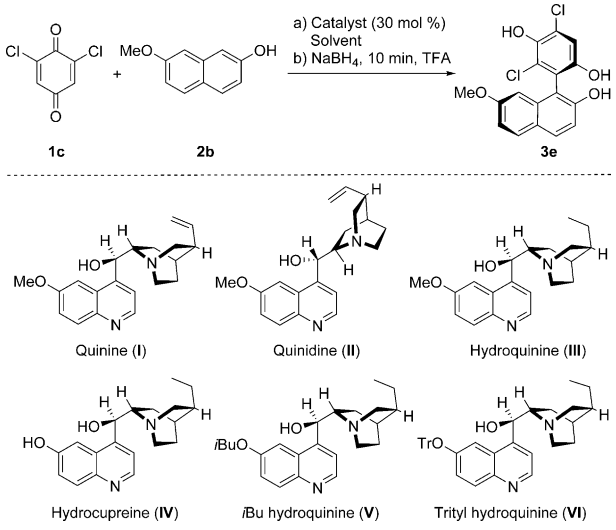
Scheme 1. Base-catalyzed addition of naphthols (**2**) to quinones (**1**) to afford biaryls (**3**) bearing a stereogenic axis (top). Energy of rotational barrier calculated (b3lyp/6-311 + g(d,p)// b3lyp/6-311 + g(d,p)) using Gaussian09[9a] and determined by HPLC[9b] (bottom, see the Supporting Information for details).

activated aromatic compounds and quinones, as electrophiles,[8] to afford C–C axially chiral molecules which closely resemble the skeleton of BINOLs. The configurational stability of BINOLs stems from the hindered rotation along the C–C axis because of the presence of the hydroxy groups (in the 2,2′-positions) and the *peri* protons (in the 8,8′-positions). Since our compounds were missing this feature, a preliminary aspect to be investigated was the substituent pattern allowing a sufficient rotational barrier along the newly formed chiral axis to obtain configurationally stable atropisomers (Scheme 1).

While the rotational barriers of BINOL-like molecules are known, we could not find data in the literature about the specific compounds reported in our paper. The compound **3a** (Scheme 1) was separated into two enantiomers by HPLC using a chiral stationary phase, but the shape of the chromatogram is anomalous because of the appearance of peaks with a plateau between them (this is known as a "Batman" profile).[10] Such peaks can be observed in the case of atropisomers, with hindered rotation, which are interconverting on a time-scale comparable to the retention time of the HPLC run. Indeed, analytical chiral separations can be used to determine the rotational barriers of racemization.[9b] In contrast, we could not get any separation for the enantiomers of **3a′**, thus pointing to a fast interconversion. Accordingly, ab initio calculations indicate a low interconversion barrier for **3a′**, but the calculated energy barrier for the enantiomer interconversion of **3a** (22.9 kcal mol^{-1}) is compatible with a chromatogram of species interconverting on an HPLC time scale and it is in reasonable agreement with that determined by integration of the areas of HPLC peaks (22.0 kcal mol^{-1}).[9] We then prepared **3b** and **3c**, bearing a methoxy and a bromo substituent, respectively, at the 7-position and the rotational barrier still remains similar to that of **3a**. Finally, we tested the same reaction starting from 2,5-dibromo 1,4-benzoquinone (**1b**), thus obtaining a mixture of **3d** and its oxidized form **3d′.** Both in silico and experimental data indicate that the two compounds have a high rotational barrier and consequently are configurationally stable. Also the presence of a chloro substituent on the quinone moiety results in a significant rotational barrier (**3e**), and we find a similar agreement between the calculated and experimental data. Therefore, to obtain configurationally stable enantiomers, it was necessary to employ halogenated quinones such as **1b** and **1c**. The DFT calculations turn out to be useful to predict whether the enantiomers can have an interconversion rate comparable to the HPLC timescale and therefore whether a plateau between the peaks of the enantiomers can be observed.

We then chose as a model the reaction of 7-methoxy 2-naphthol (**2b**) and 2,6-dichloro 1,4-benzoquinone (**1c**), and we investigated which reaction conditions could afford higher yield and stereoselectivity. Previous attempts to run the reaction under argon gave rise anyway to the formation of a mixture of **3e** and its oxidized quinonic form in variable ratios. This oxidation process might be due to the presence of **1c** as it can act as an oxidant. We then added sodium borohydride to the reaction mixture to reduce any oxidized quinone product, and then TFA to reprotonate the naphthol sodium salts. We loaded the crude reaction mixture on a short pad of silica gel and quick filtration afforded a substantially pure sample of **3e**. The combination of THF as the solvent and quinine (**I**) as the catalyst (Table 1, entry 1) afforded **3e** in nearly quantitative yield and with 83:17 e.r. Chloroform or toluene, which are common solvents employed for *Cinchona* alkaloid-derived catalysis, were not as effective (entries 2 and 3). The temperature of 4°C, which can be conveniently achieved, appeared ideal so as to maximize the enantiomeric ratio; the reaction run at −20°C did not increase enantioselectivity (entry 4) and the one conducted at room temperature also produced products in less satisfactory enantioselectivity (entry 5). A minor amount of catalyst and higher dilution were instead beneficial and when we combined these findings we achieved the highest enantioselectivity (entry 6). It is important to stress that simple **I** was the most effective

Table 1: Screening of reaction conditions for the organocatalyzed addition of **2b** to **1c** to afford the axially chiral **3e** (see the Supporting Information for additional screening of reaction conditions and catalysts).

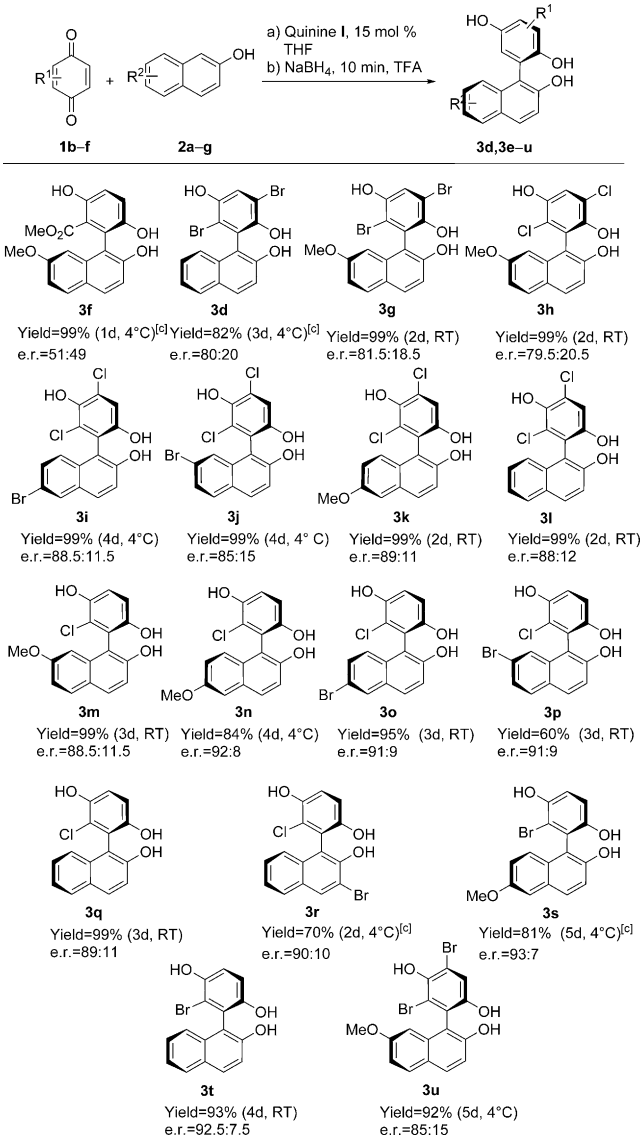


Entry[a]	Cat	Solvent	t [h]	T [°C]	Yield [%][b]	e.r.[c]
1	**I**	THF	24	4	98	83:17
2	**I**	$CHCl_3$	18	4	65	63:37
3	**I**	toluene	18	4	99	63:37
4	**I**	THF	3	−20	50	83:17
5	**I**	THF	24	RT	90	79:21
6[d,e]	**I**	THF	48	4	99	86:14
7	**II**	THF	48	4	99	21:79
8	**III**	THF	4	4	50	83:17
9	**IV**	THF	72	4	<10	50:50
10	**V**	THF	24	4	99	85:15
11	**VI**	toluene	72	4	99	56:44
12[d,e,f]	**I**	THF	5	4	99	87:13

[a] Reaction performed employing 50 mg (0.28 mmol,1.2 equiv) of **1c** and 40 mg (0.23 mmol, 1 equiv) of **2b** with 4 mL of solvent (concentration: 0.057 M). [b] Yield of isolated product. [c] The e.r. value was determined by HPLC on CSP using Chiralpack ID column and *n*-hexane/isopropyl alcohol (88:12; flow 0.9 mL min). [d] Concentration of 0.0275 M. [e] Used 15 mol% catalyst. [f] Used 2 equiv of **1c**. TFA = trifluoroacetic acid, THF = tetrahydrofuran.

catalyst, at least in our hands. None of the other natural and synthetic *Cinchona* alkaloid derivatives we tested performed better. In particular, the pseudoenantiomer quinidine (**II**) gave rise to the formation of the enantiomer of **3e** with similar stereocontrol (entry 7). The hydroquinine **III** did not perform better (entry 8) and hydrocupreine **IV** afforded essentially racemic material (entry 9). The substitution of the 6-methoxy group with other bulkier groups (**V**; entry 10 and **VI**; entry 11) did not afford better results. The reaction employing 2 equivalents of **1c** was faster (entry 12 versus entry 6). Although the enantioselectivity was not the highest possible, our experience regarding one of our asymmetric reactions,[11a] which became a large-scale industrial process[11b] suggested that for the wide applicability of a novel process this was not a major issue. Specifically, mild reaction conditions (RT or 4°C), high yield (above 95%), cheap and commercially available catalysts (quinine) and reagents, plus the potential to avoid chromatography to purify the products are aspects which are more important than finding a catalyst which would afford a higher enantiomeric ratio.

With our optimized reaction conditions, we explored the scope of our reaction by testing several combinations of halogenated 1,4-benzoquinones (**1**) and naphthols (**2**; Scheme 2). To maximize the enantiomeric ratio, we ran the reactions at high dilution. When compatible with reasonably reaction times, we employed only a small excess of the quinones **1** and ran the reactions at 4°C. At first, we tested carbomethoxy 1,4-benzoquinone (**1d**), which is the most reactive quinone (reaction completed within a day and quantitative yield), but it produced the corresponding biaryl **3f** only as a racemic mixture. The lack of stereocontrol might



Scheme 2. Scope of the quinine-catalyzed addition reaction of naphthols (**2**) to quinones (**1**) to produce axially chiral compounds (**3**) in enantioenriched form. [a] Reaction performed employing 2.0 equiv of quinones (**1**), 1.0 equiv of naphthol **2b** (0.15 mmol), and with 5.5 mL of solvent (concentration: 0.0275 M). [b] Values within parentheses are reaction time in days. [c] Used 1.2 equiv of **1**. See the Supporting Information for the determination of the absolute configuration.

be due to the fast, nonselective reaction. The use of dihalogenated benzoquinones [**1b**,**c** and **1e** (2,5-dichloro 1,4-benzoquinone)] afforded the biaryls **3d** and **3g–l** in good yield and moderate to good enantioselectivity (82–99% yield, 80:20 to 89:11 e.r.). Chloro 1,4-benzoquinone (**1f**) presented a similar reactivity, even if the reactions required a longer reaction time. However, the products **3m–r** were formed in better stereoselectivity (60–99% yield, 88.5:11.5 to 92:8 e.r.).

Finally, we tested bromo 1,4-benzoquinone (**1g**) and 2,6-dibromo 1,4-benzoquinone (**1h**), which afforded the products **3s–u** after a longer reaction time, but in comparable stereoselectivity with that of the corresponding chloroquinones **1c** and **1f** (81–93% yield, 85:15 to 93:7 e.r.). For a full report of all reaction conditions tested see Schemes S5 and S6 in the Supporting Information.

A possible rationalization regarding the formation of the major enantiomer is depicted in Figure 3. According to this scenario, the deprotonated hydroxy function on the naphthol unit would interact with the protonated quinuclidine unit of quinine and the quinone reagent would be activated by hydrogen bonding at the 9-hydroxy functionality of the

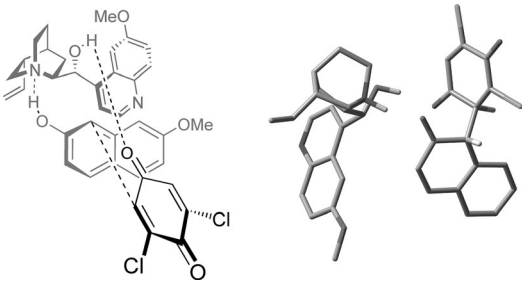
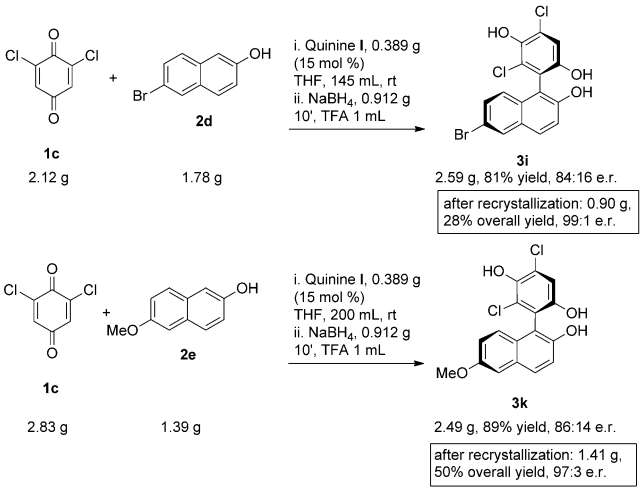


Figure 3. Proposed transition state leading to the major enantiomer and corresponding DFT optimized structure (b3lyp/6-31g*//b3lyp/6-31g*; some atoms are omitted for clarity).

catalyst. The π–π staking between the aromatic moiety of the reagents and the quinoline part of the catalyst does not seem to play any major role. DFT calculations and the inversion of stereoinduction when employing catalysts lacking the free 9-hydroxy group support this hypothesis.

To show the preparative usefulness of our transformation, we performed two reactions on gram scale by employing a higher concentration of reagents. The products **3i** and **3k** were obtained in high yield and with minimal erosion of enantiopurity, and have been recrystallized with high enantiomeric excess (Scheme 3).

In conclusion, we have presented a new organocatalyzed reaction for the synthesis of a class of novel biaryl compounds and we have discussed the features necessary to prepare configurationally stable atropisomers. We believe that the mild reaction conditions of our reaction, coupled with the use of a cheap and commercially available catalyst should render it attractive for the large-scale preparation of these important compounds, at the very least in a research laboratory. Furthermore, the presence of various halogen atoms offers the possibility to functionalize these compounds by using



Scheme 3. Preparative large-scale reactions for **3i** and **3k**.

several transformations. Studies are ongoing in our group as well as others[12,13] to apply these compounds as useful ligands and catalysts for highly enantioselective asymmetric reactions.

Experimental Section

Typical experimental procedure: To a cooled (4°C) suspension of the naphthol **2** (0.15 mmol) and quinine **I** (7 mg, 0.0225 mmol, 15 mol %) in THF (4.5 mL) was added a cooled (4°C) solution of the halogenated 1,4 benzoquinone **1** (0.30 mmol, 2 equiv) dissolved in 1 mL of THF. The reaction mixture was stirred at 4°C for 48 h, and then the resulting dark solution was cooled to 0°C (ice bath) and $NaBH_4$ (17 mg, 0.45 mmol) was added, followed by the dropwise addition of 1 mL of MeOH. After 5 min to the solution was added TFA (trifluoroacetic acid, 0.1 mL) and 1 g of silica gel, and the solvent was removed by rotary evaporation. The resulting white solid was loaded on the top of a column, and quickly filtered over a pad of silica gel (20 gr) using diethyl ether/dichloromethane (1:20) as an eluent. The solvent of the fraction containing the desired compound **3** was evaporated, to give chemically pure material.

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Keywords: atropisomers · biaryls · chirality · density-functional calculations · organocatalysis

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[12] While this manuscript was in preparation, an important paper by Tan, Liu, and co-workers appeared and described a similar reaction catalyzed by chiral phosphoric acids rather than bases. The authors demonstrated in a preliminary experiment the effectiveness of the aryl diols as chiral ligands in the asymmetric addition of diethyl zinc to aldehydes, and the enantioselectivity achieved by the chiral diols in this reaction was even superior to C_2-symmetrical 2,2′ binaphthol. We believe that the two methodologies can be complementary with regards to the reaction conditions and scope. Y. H. Chen, D. J. Cheng, J. Zhang, Y. Wang, X. Y. Liu, B. Tan, *J. Am. Chem. Soc.* **2015**, *137*, 15062 – 15065.

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