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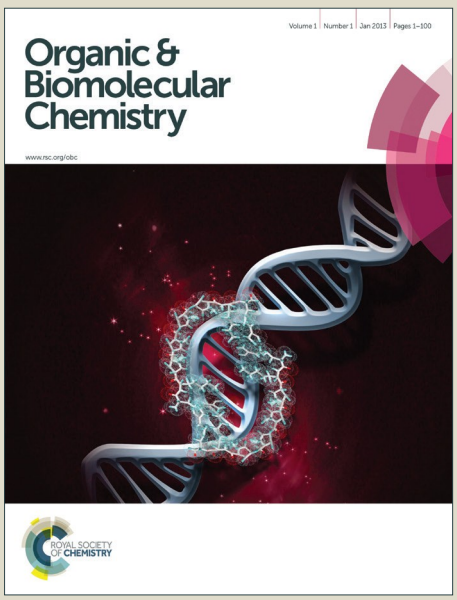

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A Novel Enantioselective Synthesis of 6*H*-Dibenzopyran Derivatives by Combined Palladium/Norbornene and Cinchona Alkaloid Catalysis

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Organometallic and organo-catalysts are cooperatively at work in the enantioselective synthesis of dibenzopyran derivatives; palladium/norbornene and a cinchona alkaloid base guarantee good yields and satisfactory enantioselectivities in a one-pot reaction.

Inspired by their important biological activity, many efforts have been made to prepare benzopyran and dibenzopyran derivatives.[1] They are widely present in natural compounds and pharmaceuticals (Fig. 1).[2] The synthesis of chiral dibenzopyran skeletons is an important issue for further modification to therapeutic compounds.[3]

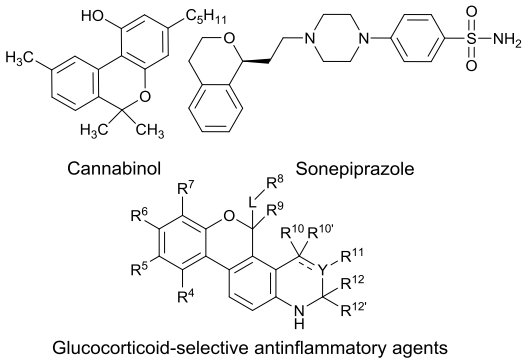


Fig. 1 Bioactive and pharmacologically active molecules containing benzopyran and dibenzopyran moieties

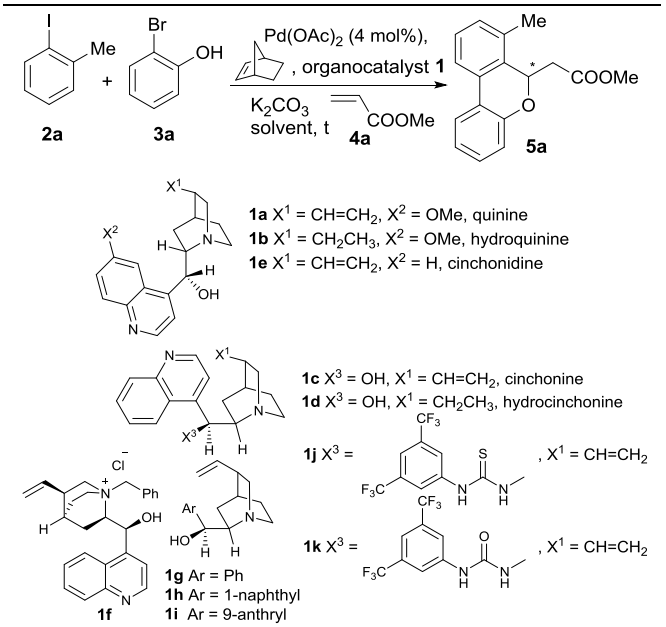
The development of organocatalytic enantioselective cascade reactions has greatly helped in the ready construction of complex molecules with stereogenic centers.[4] Recently, the concept of metal catalysis combined with asymmetric organocatalysis has been developed.[5] To obtain chiral dibenzopyran structures, organocatalysts[6,7] were used. Previous studies have exploited cooperative catalysis through palladium and norbornene to yield racemic 6*H*-dibenzopyran derivatives. However, this transformation was not achieved with any enantioinduction.[8] Herein, we describe a novel synthesis of chiral dibenzopyran compounds by a sequential one-pot reaction catalyzed by palladium/norbornene in combination with a cinchona alkaloid base, acting as organocatalyst, in good yields and satisfactory enantioselectivities.

The reaction involves unsymmetrical aryl-aryl coupling by palladium/norbornene catalysis, Heck reaction, and final enantioselective oxa-Michael addition. Considering that the formation of the stereogenic center occurs in the last step without the involvement of palladium species, a variety of organocatalysts were prepared and tested for this reaction (Table 1 and Scheme 1).

Initially, very low yields and essentially no enantioselectivity were obtained with the commonly used proline derivatives.[9] To our delight, the attempt of using quinine (**1a**) and cinchonine (**1c**) as the chiral base led to good and excellent enantiomeric excess (*ee*) values (Table 1, entries 1 and 3). The vinyl side chain of the cinchona alkaloid appears to be necessary, since hydroquinine (**1b**) and hydrocinchonine (**1d**), bearing the corresponding hydrogenated ethyl chain, gave only very poor or unsatisfactory results (entries 2 and 4). Under these conditions, however, the reactions (entries 1 and 3) proceeded slowly providing the desired products (**5a**) in low yield together with the unconverted starting halides (**2a** and **3a**).

An extensive screening of reaction parameters such as inorganic bases, temperature and solvents was performed using cinchonine as the organocatalyst, without improving both yields and *ee* values at the same time (entries 5–9). For instance, the use of the more alkaline base Cs_2CO_3 in place of K_2CO_3 slightly increased the yield but decreased the enantioselectivity (entries 3 and 8). The reaction occurred well at 80 ℃ but gave poor results at lower temperature. At 150 ℃ the desired product **5a** readily formed in 82% yield but with very low enantioselectivity (entry 9). It was noticed that the addition of cinchona alkaloids slowed down the reaction rate (i.e. entry 3, 35% yield) compared with the reaction without organocatalyst (24 h, 83% yield).[8] Therefore, a longer reaction time was required to obtain a better yield and maintain a satisfactory enantioselectivity (entries 3 and 10).

Table 1 Screening of reaction conditions[a]



Entry	Chiral catalyst	Solvent	Time (h)	Yield[b] (%)	*ee*[c] (%)
1	**1a**	DMF	24	32	80
2	**1b**	DMF	24	5	n.d.[d]
3	**1c**	DMF	24	35	99
4	**1d**	DMF	24	22	75
5	**1c**[e]	DMF	24	6	>99
6	**1c**[f]	DMF	24	45	51
7	**1c**[e,f]	DMF	24	35	97
8	**1c**[g]	DMF	24	43	85
9	**1c**[h]	DMF	24	82	12
10[i]	**1c**	DMF	96	72	94
11	**1e**	DMF	96	69	89
12	**1f**	DMF	96	75	2
13	**1g**	DMF	96	77	82
14[j]	**1h**	DMF	96	75	95
15[k]	**1i**	DMF	96	74	95
16	**1j**	DMF	96	43	73
17	**1k**	DMF	96	42	75
18	**1h**	NMP	96	21	62
19	**1h**	Dioxane	96	33	82
20	**1h**	DMA	96	56	91
21	**1h**	THF	96	38	88
22	**1h**	Toluene	96	23	85

[a] Unless otherwise noted, all reactions were carried out with **2a** (0.223 mmol), **3a** (0.223 mmol), **4a** (0.714 mmol), K_2CO_3 (0.714 mmol), norbornene (0.178 mmol), $Pd(OAc)_2$ (0.009 mmol), and organocatalyst **1** (0.112 mmol) in solvent (4.0 mL) at 80 °C. [b] Isolated yield. [c] Determined by chiral HPLC analysis (Daicel OD-H, hexane/*i*-propane = 95/5). [d] Not determined. [e] **1** (0.335 mmol). [f] $Pd(OAc)_2$ (0.026 mmol). [g] Cs_2CO_3 in place of K_2CO_3. [h] T = 150 °C. [i] with **2** = 1-iodo-2,4-dimethylbenzene, 51% yield and 77% *ee*. [j] with **2** = 1-iodo-2,4-dimethylbenzene, 73% yield, 92% *ee*. [k] with **2** = 1-iodo-2,4-dimethylbenzene, 62% yield, 75% *ee*.

Furthermore, the influence of quaternary ammonium salts on the cascade reaction was studied. NBu_4Br, NH_4Cl and Et_3NMeI were used but poor results both in yield and enantioselectivity were obtained.[9] The phase transfer catalyst **1f** was also prepared[10] and its effect was evaluated but the results did not improve (entry 12). DMF proved to be the best solvent while toluene, THF, dioxane and others gave lower yields (entries 18–22).[8]

Some time ago Soós[11] reported that cinchona alkaloid-derived chiral bifunctional thiourea organocatalysts could give both high *ee* values and yields in the Michael addition of nitromethane to chalcones. Recently Matsubara[12] described the successful use of bifunctional amino(thio)urea catalysts for the asymmetric synthesis of 2-substituted indolines. We thus decided to investigate the behavior of compounds **1j** and **1k** as bifunctional catalysts in this reaction (entries 16 and 17). The results, however, indicated that thiourea and urea moieties negatively affected the conversion of the reaction, which remained low, without improving the *ee* values. The detrimental effect of nitrogen containing compounds on the yield of product **5a** was also ascertained by adding pyridine (0.5:1 molar ratio to the substrate) to the reaction mixture (64% yield). These unfavorable results are possibly to be ascribed to interference in the coordination to palladium by sulphur and nitrogen containing species.

A higher catalyst loading led to a better conversion but with a concomitant decrease of the *ee* value (entry 6). To counteract the negative effect of palladium acetate concentration, also that of cinchonine was increased. However, the reaction carried out in the presence of $Pd(OAc)_2$ and cinchonine (0.12 and 1.5:1 molar ratio to the substrate, respectively), became sluggish and the yield dropped (entry 7).

Then we checked the influence of a hydroxyl group and found that the addition of EtOH (0.5:1 molar ratio to the substrate) to the reaction mixture did not reduce the yield (82%), demonstrating that the OH group of alcohols was well tolerated.

On the basis of these experimental results, we reasoned that an organocatalyst, containing a low number of nitrogen atoms and bearing a hydroxyl group could lead to good results both in terms of yield and enantioselectivity. Accordingly, we reduced the content of nitrogen in the cinchona alkaloid base by replacing the 1-quinolin-4-yl ring with a phenyl, 1-naphthyl or 9-anthryl group, leaving unchanged the quinuclidine moiety which should play a fundamental role in the terminal asymmetric oxa-Michael addition. The hydroxyl group was also essential in the process of interaction, via hydrogen bonding, with the double bond of the cinnamate moiety of the open precursor **6** (Scheme 1 and Fig. 2). In addition, the size of the cinchona alkaloid catalyst was also crucial (entries 13–15). The reaction was very sensitive; small changes in the reaction conditions could significantly influence the results. However, satisfactory results were obtained under appropriate conditions.

At this point, further optimization was carried out in the presence of organocatalysts **1g**–**1i**,[13] all containing the vinyl and the hydroxyl groups, and a phenyl, 1-naphthyl or 9-antryl ring (entries 13–15). Catalyst **1h** showed the broadest scope and highest flexibility.[9]

The absolute configuration of dibenzopyran products **5** was determined by comparing its optical rotation with that of the known cores of chromane acetates and benzodihydrofuranyl acetates.[7b,14] In the presence of cinchonine as organocatalyst, the chiral product (+)–**5a** was formed in its *S* configuration. According to Merschaert,[14] in the presence of cinchonine as catalyst, the *E* isomer of α,β-

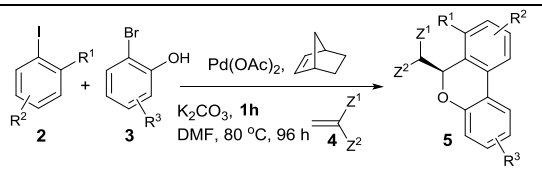
unsaturated esters cyclized into *S*–chromane. Uncyclized intermediate **6** (Scheme 1) was isolated as *E* isomer, in the synthesis of 6-methoxycarbonylmethyl-7-methyl-2-nitro-6*H*-dibenzopyran.[8]

Finally, under the best experimental conditions, we evaluated the scope of the reaction by varying the *o*-substituted aryl iodide (**1**), the *o*-bromophenol (**2**) and the electron–deficient terminal alkene (**3**) (Table 2). The presence of ortho electron-donating substituents in the iodoarene **2** is needed to obtain unsymmetrical aryl-aryl coupling as previously shown.[8,15] Generally, the reactions proceeded well under the organocatalysis of **1h**, forming dibenzopyran derivatives in moderate to good yields (40–75%) and satisfactory enantioselectivities (80–97%). The effect of the substituent R^3 in the o-bromophenol follows the trend previously observed in the absence of an organocatalyst.[8] Although the yield was low for 4-methyl-2-bromophenol, the enantioselectivity was quite high (Table 2, entry 8). The 1,1-disubstituted alkenes could work (Table 2, entry 10), but both yield and *ee* decreased likely because of steric hindrance. Nitroalkenes did not lead to the expected compound and the main product resulted from the direct Heck reaction of the nitroalkene itself with the aryl iodide (Scheme 2, styrene derivative). Acrylonitrile gave compound **5** (R^1 = Me, R^2, R^3 = H) only in very poor yield (12%).

This procedure allows access to a large number of 6*H*-dibenzopyran derivatives, which are useful intermediates for fragrances, pharmaceuticals, and other fine chemicals. Indeed, functionalization can be readily achieved, for example through the intermediacy of an iodide derivative such as **5k** (Figure 2).

The needed amount of organocatalyst varied considerably depending on the substrate. The electron-rich aryl rings of the substrate could coordinate better to the organocatalyst through π–π interaction[16] and as a consequence the catalyst loading of **1h** was generally lower (0.25:1 molar ratio to the substrate) when using electron-rich aryl iodides (Table 2, entries 2 and 3).

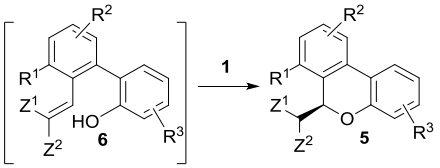
Table 2 Investigating the reaction scope[a]



Entry	R^1, R^2	R^3	Z^1	Z^2	5	Yield[b] (%)	*ee*[c] (%)
1	2-Me	H	CO_2Me	H	**5a**	75	95
2	2,4-Me	H	CO_2Me	H	**5b**	73	92
3	2,3-Me	H	CO_2Me	H	**5c**	68	93
4	2-CF_3	H	CO_2Me	H	**5d**	59	83
5	2-Me 3,4-OMe	H	CO_2Me	H	**5e**	61	88
6	2-Me 4-NMe_2	H	CO_2Me	H	**5f**	56	90
7	4-OMe-naphthyl	H	CO_2Me	H	**5g**	68	91
8	2-Me	4-Me	CO_2Me	H	**5h**	40	97
9	2-Me	5-NO_2	CO_2Me	H	**5i**	63	80
10[e]	2-Me	H	CO_2Et	CO_2Et	**5j**	66	84

[a] Unless otherwise noted, all reactions were carried out with **2** (0.223 mmol), **3** (0.223 mmol), **4** (0.714 mmol), K_2CO_3 (0.714 mmol), norbornene (0.178 mmol), $Pd(OAc)_2$ (0.0089 mmol), and **1h** (0.056 mmol for entries 2 and 3, 0.112 mmol for entries 1, 4-10; (for more experimental data, see SI) in DMF (4.0 mL) at 80 °C. [b] Isolated yield. [c] Determined by chiral HPLC analysis (Daicel OD-H, hexane/*i*-propane = 95/5−99/1).

The proposed reaction pathway is similar to that previously reported[8,17] and the formation of the chiral compound **5** from the open precursor is depicted in Scheme 1. The vinylbiphenyl intermediate **6** undergoes an intramolecular Michael-type reaction by attack of the ortho hydroxyl group, originally belonging to the aryl bromide, onto the vinyl group, to yield the dibenzopyran derivative **5** (Scheme 1).



Scheme 1 Enantioselective cyclisation of the open precursor to 6*H*-dibenzopyran by Michael reaction in the presence of alkaloid base **1**.

A plausible transition state for the interaction between the intermediate vinylbiphenyl derivative **6** and organocatalyst **1**, and the X-ray structure of **5k** obtained by iodination from **5e** are shown in Fig. 2. The hydroxyl group of **1** interacts with the double bond of the vinyl part of the cinnamate moiety of **6** via hydrogen bonding. Meanwhile, the hydroxyl group of intermediate **6** can also interact with the organocatalyst via hydrogen bonding. The aryl moiety of **1** can coordinate with the aryl ring of **6**. An appropriate conformation could enhance the π–π interaction. As a result, a six-member ring with the pro-*S* structure was favored.[13]

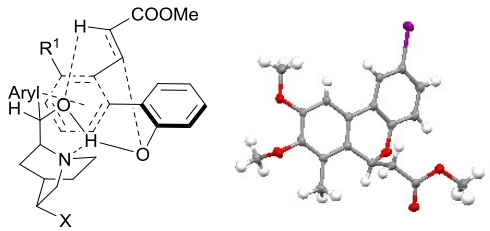
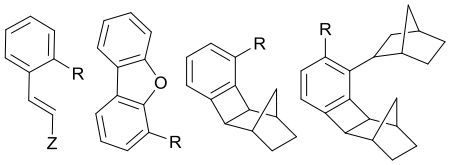


Fig. 2 Proposed transition state model from **6** to **5** via oxa-Michael addition and X-Ray crystal structure of compound **5k**

The main previously reported byproducts are shown in Scheme 2.



Scheme 2 Byproducts

In summary, we have developed a promising approach for the synthesis of chiral substituted dibenzopyran derivatives employing the cinchona alkaloid, as an organo-catalyst, in combination, for the first time, with the palladium/norbornene catalytic system. A study of the effect of the organo-catalyst structure on the model reaction was accomplished. The reaction has several noteworthy features: 1) substrates and catalysts are commercially available or can be easily

prepared; 2) a broad range of aryl halides can be used; 3) good to excellent enantioselectivities and high yields were achieved for most of the substrates under mild conditions. Further extension, biological evaluation and screening application of the method and products will be pursued.

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Notes and references

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† Supporting Information (SI) available: Experimental procedures, spectroscopic data, and NMR spectra. See DOI:10.1039/c000000x/

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