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# Organocatalytic Enantio- and Diastereoselective Synthesis of 1,2-Dihydronaphthalenes from Isobenzopyrylium Ions

Hui Qian, Wanxiang Zhao, Zhaobin Wang, and Jianwei Sun*

Department of Chemistry, The Hong Kong University of Science and Technology, Clear Water Bay, Kowloon, Hong Kong SAR, China

Supporting Information

**ABSTRACT:** A highly efficient asymmetric synthesis of dihydronaphthalenes is disclosed. The process represents a new addition to the limited asymmetric reactions of isobenzopyryliums, a family of versatile 10$\pi$-electron aromatic species. Excellent asymmetric induction is achieved for the first time without an anchoring group in the 4-position or a metal catalyst, both of which were required previously in these reactions. The success is attributed to the unusual chiral counteranion (meanwhile also the nucleophile) generated in situ from the chiral phosphate and the boronic acid as well as the leaving group. Preliminary control experiments provided important insight into the reaction mechanism.

1,2-Dihydronaphthalenes represent an important structural motif in many natural products and biologically active molecules, such as podophyllic aldehyde and pycnanthulignenes A–D.[1] They are also important synthetic intermediates toward various tetrahydronaphthalene molecules (e.g., natural product podophyllotoxin).[1] Consequently, many strategies have been developed for their synthesis (achiral or racemic).[2] However, regarding their asymmetric synthesis, for a long time the traditional dearomatization of electron-deficient naphthalenes has been the major approach, although it not only suffers from limited substrate scope (electron-deficient) but also requires the use of either chiral auxiliary or stoichiometric chiral ligands.[3] Indeed, truly catalytic asymmetric approaches remain scarce. Among the few known approaches, the desymmetrization of oxabenzonorbornadienes is probably the most explored.[4] Therefore, additional catalytic asymmetric strategies remain in high demand. Here we report an efficient organocatalytic approach using isobenzopyrylium ions.

Isobenzopyrylium ions are a family of versatile species, serving as key intermediates or substrates in a range of useful reactions.[5−7] Their unique reactivity and stability are probably owing to the 10$\pi$-electron aromatic structure. Unfortunately, it is also this aromatic planar structural feature that impedes the development of their asymmetric reactions, presumably due to the lack of obvious coordination sites to interact with chiral catalysts for efficient chiral induction. Indeed, catalytic asymmetric transformations of isobenzopyryliums are surprisingly underdeveloped, despite their significant synthetic utility.[7] Moreover, in all these limited examples, an anchoring group, either a metal or a hydrogen bond donor/acceptor (e.g., OH or $O^-$), is required in the 4-position (Figure 1).[7] The anchoring

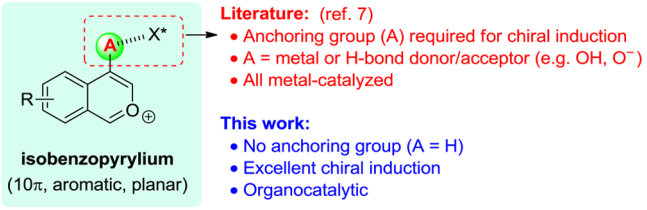


**Figure 1.** Isobenzopyryliums in catalytic asymmetric reactions.

group is believed to provide key interaction with the chiral catalyst/ligand for efficient asymmetric induction. It is also worth noting that all these reactions employed metal catalysts. In the present work, we address the challenge by achieving excellent chiral induction without an anchoring group (A = H) or a metal catalyst.

We began the study with acetal **1aa** as the isobenzopyrylium precursor and (*E*)-(4-methoxystyryl)boronic acid **2a** as the nucleophile. The chiral phosphoric acid **A1** was initially employed as the catalyst.[8,9] We were pleased to observe the smooth formation of the desired dihydronaphthalene product **3a**, albeit with moderate efficiency and almost no enantioselectivity (Table 1, entry 1). Dicarbonyl **1a-A** was also observed, presumably resulting from the decomposition of acetal **1aa**. Further evaluation of other BINOL-derived phosphoric acids identified **A6** as the catalyst of choice, providing almost quantitative transformation to **3a** with excellent diastereoselectivity and good enantioselectivity (>20:1 dr, 84% ee, entry 6). Other solvents (e.g., $CHCl_3$, toluene, ether, MeCN, DCE, and hexane) could not improve the enantioselectivity. Other acids derived from spiroindane or VAPOL proved inferior (entries 7−11).

Aiming at further improving the enantioselectivity of the process, we next evaluated the effect of the acetal leaving group. Interestingly, as shown in Table 2, slightly increased enantioselectivity was observed with ethylene glycol as the leaving group (**1ad**). Leaving groups with a longer alkyl chain or a larger size or protected ethylene glycol could not further improve the results. Subsequent optimization with different parameters achieved the best results with $MgSO_4$ as the additive at 0 °C (84% yield, 93% ee, entry 10). It is worth noting that the reaction efficiency and enantioselectivity both decreased significantly when substrate **1aa** and ethylene glycol (1 equiv) were used together to mimic substrate **1ad** (entry 11). The corresponding boronate (**2b**, vide

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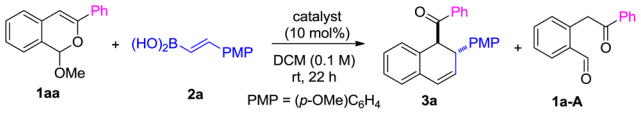
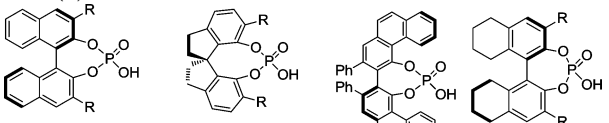
**Table 1. Catalyst Screening**[a]




| entry | catalyst | conv (%) | yield of **3a** (**1a-A**) (%) | dr of **3a** | ee of **3a** (%) |
|---|---|---|---|---|---|
| 1 | (*R*)-**A1** | 87 | 43 (6) | 6.2:1 | 2 |
| 2 | (*R*)-**A2** | 87 | 68 (5) | 13:1 | 2 |
| 3 | (*R*)-**A3** | 88 | 62 (10) | 6.8:1 | 22 |
| 4 | (*R*)-**A4** | >99 | 88 | 5.8:1 | 25 |
| 5 | (*R*)-**A5** | >99 | 91 | 6.6:1 | 42 |
| ***6*** | ***(R)-A6*** | ***>99*** | ***99*** | ***>20:1*** | ***84*** |
| 7 | (*R*)-**B1** | >99 | 69 | 8.9:1 | −2 |
| 8 | (*R*)-**B2** | 69 | 41 | 13:1 | −14 |
| 9 | (*S*)-**B3** | >99 | 88 | 10:1 | 56 |
| 10 | (*R*)-**B4** | 91 | 64 (7) | 10:1 | −38 |
| 11 | (*R*)-**C** | 60 | 24 | 4.0:1 | 0 |



**A1**: R = Ph
**A2**: R = $SiPh_3$
**A3**: R = 2,4,6-($^i$Pr)$_3$C$_6$H$_2$
**A4**: R = 1-naphthyl
**A5**: R = 9-phenanthryl
**A6**: R = 9-anthryl



**B1**: R = 3,5-(CF$_3$)$_2$C$_6$H$_3$
**B2**: R = 2,4,6-($^i$Pr)$_3$C$_6$H$_2$
**B3**: R = 9-phenanthryl
**B4**: R = 9-anthryl



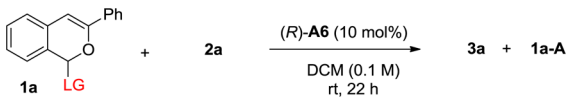
**C**

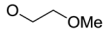
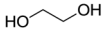
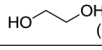


**D**: R = 9-anthryl

[a]Reaction scale: **1aa** (0.05 mmol), **2** (0.15 mmol). The conversion, yield, and dr values are based on NMR analysis of the crude product using $CH_2Br_2$ as internal standard. The ee values were determined by HPLC with a chiral column.

**Table 2. Effect of the Leaving Group**[a]




| entry | LG (**1a**) | conv. | yield **3a** (**1a-A**) | dr (**3a**) | ee (**3a**) |
|---|---|---|---|---|---|
| 1 | O$^i$Pr (**1ab**) | >99% | >99% | >20:1 | 85% |
| 2 | OBn (**1ac**) | >99% | 94% | >20:1 | 82% |
| 3 |  (**1ad**) | 90% | 62% (20%) | >20:1 | 88% |
| 4 |  (**1ae**) | >99% | >99% | >20:1 | 84% |
| 5 |  (**1af**) | >99% | 55% (21%) | >20:1 | 82% |
| 6 |  (**1ag**) | 89% | 73% (7%) | 11:1 | 56% |
| 7 |  (**1ah**) | >99% | 90% (2%) | >20:1 | 47% |
| 8[b] | **1ad** | >99% | 82% (14%) | >20:1 | 91% |
| 9[b,c] | **1ad** | >99% | 70% (15%) | >20:1 | 82% |
| 10[b,d] | **1ad** | >99% | 84% (10%) | >20:1 | 93% |
| 11[b,d] | **1aa** +  (1 eq.) | 81% | 39% (16%) | >20:1 | 61% |
| 12[b,d] | **1aa** +  (0.1 eq.) | >99% | 86% | >20:1 | 90% |

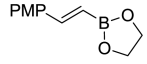
[a]The conversion, yield, and dr values are based on NMR analysis of the crude product using $CH_2Br_2$ as internal standard. The ee values were determined by HPLC with a chiral column. [b]Run at 0 °C. [c]Run with 4 Å MS (10 mg/0.05 mmol **1a**) as additive. [d]Run with $MgSO_4$ (10 mg/0.05 mmol **1a**) as additive.

infra) might be generated in situ and affect the reaction efficiency. However, with only a catalytic amount of ethylene glycol, good results could still be observed (entry 12).

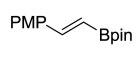
With the optimized conditions, we next examined the reaction scope. As shown in Scheme 1, a wide range of acetal substrates with different substituents at different positions all reacted smoothly with **2a** to form the corresponding dihydronaphthalene products **3** with good to excellent efficiency and stereoselectivity. The reaction is amenable to both electron-withdrawing and electron-donating groups. Various functional groups, including nitrile, ester, ketone, acetal, halogen, and silyl-protected alcohol, are well tolerated. It is worth mentioning that although substrates with an aryl substituent at the 3-position generally gave excellent enantioselectivity, the reaction of an alkyl- or non-substituted analogues resulted in low enantioselectivity under the standard conditions (28% ee for **3p** and 36% ee for **3x**). However, a brief survey of different catalysts established that the [$H_8$]BINOL- and spiroindane-derived chiral phosphoric acids **D** and **B3** (structures shown in Table 1) could catalyze the formation of **3p** and **3x** in 84% ee and 50% ee, respectively. Other boronic acids are also suitable nucleophiles. Heterocycles such as thiophene can also be incorporated in the products (**3m** and **4h**). It is noteworthy that in all these cases the stereocontrol was achieved without the presence of an anchoring group in the 4-position of the hypothetical isobenzopyrylium intermediates.

Our proposed mechanism is depicted in Scheme 2. We believe that the acetal substrate **1** may equilibrate with dicarbonyl **1-A** and acetal **1-B**. These equilibria can be facilitated by the acid catalyst. Indeed, **1-A** could be observed initially and then gradually consumed during the reaction progress. Moreover, in the absence of a boronic acid nucleophile, treatment of substrate **1** with the acid catalyst could quickly establish the equilibrium, with **1A** being major. It is believed that all these species could react to form the key isobenzopyrylium intermediate **5**,[10] in which the leaving alkoxy group, the boronic acid, and the chiral phosphate may combine to form a well-organized cyclic counteranion.[11] This intimate interaction could be regarded as the formation of a tight boronate anion with the negative charge shifted to the boron center, which might also be induced to be chiral.[12] Such an unusual chiral counteranion, also serving as the reactive nucleophile with chiral moiety in close proximity, might make a key contribution to the observed excellent asymmetric induction, even in the absence of an anchoring group in the cation moiety.[13] Subsequent [4+2] cycloaddition forms the bicyclic zwitterion **6**, which then undergoes intramolecular elimination to form the observed dihydronaphthalene product.[14] Further investigations are required to provide more detail on the mechanism.

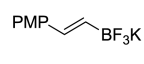
We also evaluated other boron-based nucleophiles, **2b**−**d**. Unfortunately, all of them gave inferior results with **1ad** under




**2b** (36% yield, 70% ee)




**2c** (no desired prdt.)




**2d** (43% yield, 0% ee)

the standard conditions. Notably, the outcome with boronate **2b** suggests that the possible in situ generation of **2b** from ethylene glycol and boronic acid **2a** is not involved under our standard conditions. The pinacol boronate **2c** and trifluoroborate **2d** resulted in either no product formation or no enantioselectivity. These results are consistent with the possible involvement of the boronic acid hemiester with a hydroxy group for effective interaction with the phosphate moiety.

Acetal **7** was also subjected to the standard conditions. Product **8** was obtained, but with no enantioselectivity (eq 1).[15] The



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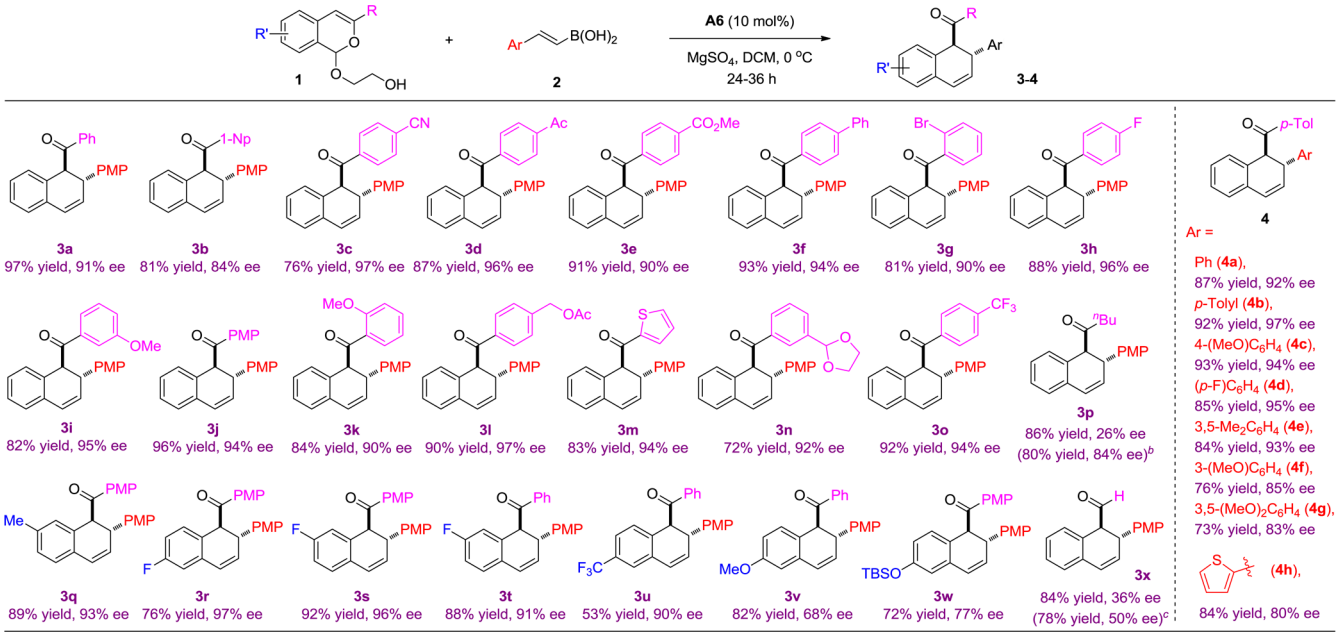
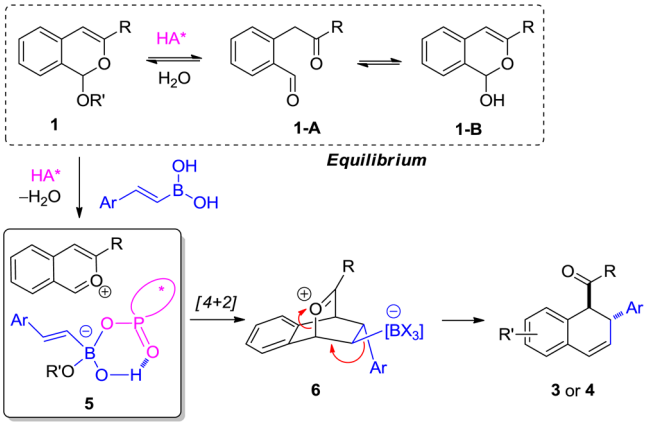
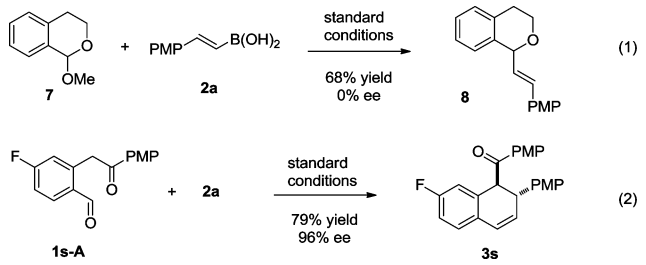
**Scheme 1. Substrate Scope**[a]



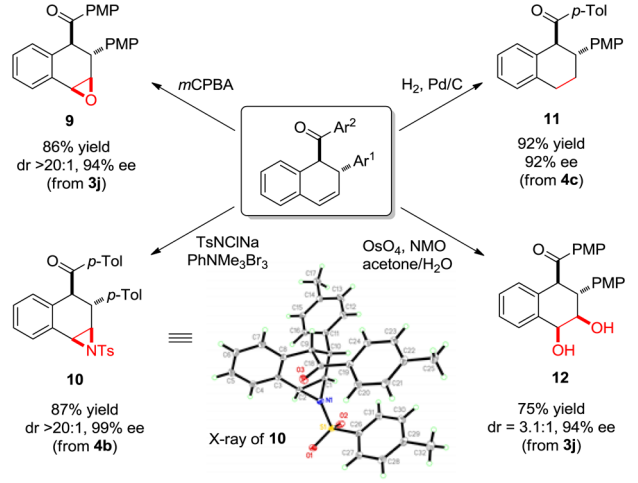

[a]Reaction scale: **1** (0.2 mmol) and **2** (0.6 mmol). Isolated yield, all with >20:1 dr. [b]Run with catalyst (*R*)-**D**. [c]Run with catalyst (*S*)-**B3**.

**Scheme 2. Proposed Mechanism**




**Scheme 3. Representative Product Transformations**




results suggest that boronic acid **2a** is chemically competent for nucleophilic addition to oxocarbenium species. Next, dicarbonyl **1s-A** could also react to form the desired product **3s** with comparable efficiency and enantioselectivity (eq 2), consistent with the proposed equilibrium in Scheme 2.

Finally, we have done some derivatizations to demonstrate the utility of our dihydronaphthalene products (Scheme 3). The C=C bond can easily undergo epoxidation, aziridination, hydrogenation, and dihydroxylation to form the corresponding tetrahydronaphthalene products **9**–**12** in excellent enantiomeric excess. The *X*-ray crystallography of the aziridine **10** also confirmed the product structure and absolute stereochemistry.

In summary, we have developed a highly efficient enantio- and diastereoselective synthesis of dihydronaphthalenes from isobenzopyrylium ions. It is not only a new addition to the small family of catalytic asymmetric synthesis of the important dihydronaphthalene scaffolds, but also a new example of the asymmetric reactions of the versatile isobenzopyrylium species, which has received limited development previously. More importantly, our reaction represents the first demonstration of excellent asymmetric induction on the planar isobenzopyryliums without an anchoring group or a metal catalyst, both of which were employed previously. The excellent stereocontrol is presumably attributed to the unusual chiral counteranion generated in situ from the chiral phosphate and the boronic acid nucleophile as well as the leaving group. The mild reaction exhibits good substrate scope and functional group compatibility. The highly enantioenriched dihydronaphthalene products can be



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easily transformed to other useful molecules. Preliminary control experiments provided insight into the reaction mechanism. Additional mechanistic investigations are underway.

## ■ ASSOCIATED CONTENT

### Supporting Information

Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

## ■ AUTHOR INFORMATION


### Corresponding Author

*sunjw@ust.hk


### Notes

The authors declare no competing financial interest.

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