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Letter

Regulation of Chiral Phosphoric Acid Catalyzed Asymmetric Reaction through Crown Ether Based Host–Guest Chemistry

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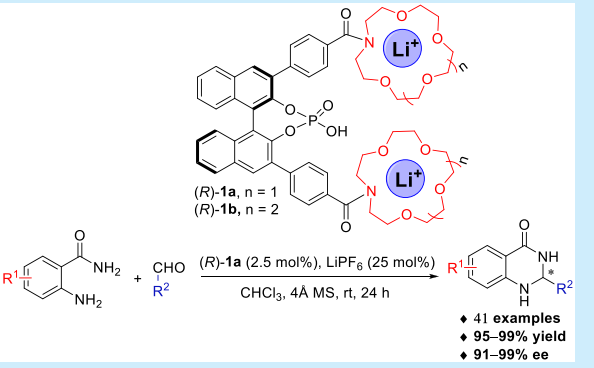
ABSTRACT: Supramolecular asymmetric catalysis has arisen from the in-depth intersection of supramolecular chemistry and asymmetric catalysis due to its unique advantages in building chiral catalyst libraries and regulating performance of catalysts. Herein, we combine crown ether based host–guest chemistry with chiral phosphoric acid mediated asymmetric catalysis to actualize the supramolecular regulation of catalytic asymmetric two-component tandem acetalization reactions. By comparison with the catalytic reaction without host–guest interaction, improvement of up to 72% in yield and increases of up to 13% in enantioselectivity were acquired after addition of the alkali metal guests, which demonstrated the great advantages of this supramolecular regulation strategy.



Over the past two decades, the combination of supramolecular chemistry and catalysis has aroused the new field of supramolecular catalysis.[1] Supramolecular interactions have the characteristics of self-selectivity, dynamic reversibility, and controllability, which is very appropriate for the construction of catalysts or regulation of electronic and steric properties of catalysts.[1,2] The activity and selectivity of catalysts can be easily controlled by introducing supramolecular recognition motifs into the sites around the catalytic active centers, making the artificial catalysts like enzymes to undergo self-assembly first and then catalysis, thereby providing the possibility to remarkably improve the effectiveness and selectivity of the catalytic systems.[3]

Crown ethers have attracted extensive attention in the past decades and have aroused the rapid development of host–guest chemistry.[4] The most prominent feature of crown ethers is able to complex with inorganic/organic cations, such as alkali metal ions, ammoniums, and pyridiniums.[5] The crown ether based host–guest chemistry has been widely utilized in the construction of mechanically interlocked structures, molecular machines, supramolecular polymers, and stimuli-responsive materials.[6] The selective molecular recognition and strong binding ability of crown ethers with cations have also been employed in supramolecular asymmetric catalysis.[7] The application of crown ethers in asymmetric catalysis has gained significant success in chiral phase-transfer catalysis,[8] whereas it remains a great challenge to regulate chiral catalysts by using crown ether-based host–guest chemistry to achieve high enantioselectivity.[9]

In the past decade, chiral phosphoric acids (CPAs) have been a class of very useful organocatalysts for asymmetric catalysis.[10] CPAs derived from BINOL (1,1′-bi-2,2′-naphthol) are one of the most outstanding representatives due to their good catalytic activity.[11] Herein, we present a supramolecular strategy to conveniently regulate the catalysis performance of BINOL-based CPA by using host–guest chemistry of crown ethers. Crown ether attached CPA catalysts were designed, synthesized, and applied in the asymmetric tandem acetalization, in which the introduction of crown ethers and their complexation with alkali metal cations were found to play a significant role in improving the activity and enantioselectivity of the catalysts.

First, we synthesized 3,3′-bis(aza-crown ether)-derived CPA (*R*)-**1a** and (*R*)-**1b** in six steps (Scheme 1). After iodination of (*R*)-**2**, the resulting iodide (*R*)-**3** underwent the Pd-catalyzed Suzuki–Miyaura coupling reaction with (4-(methoxycarbonyl)phenyl)boronic acid to generate (*R*)-**4** in 61% yield. Hydrolysis of (*R*)-**4** and then amidation of dicarboxylic acid (*R*)-**5** with aza-15-crown-5 or aza-18-crown-6 furnished (*R*)-**6a** and (*R*)-**6b**, respectively. The MOM protection was removed by trifluoroacetic acid (TFA), and phosphorylation was carried out to produce (*R*)-**1a** and (*R*)-**1b** in 95% and 97% yields, respectively.

The crown ether-appended CPAs were subsequently employed as catalysts for the asymmetric acetalization reaction, which has been proven to be one of the most efficient methods

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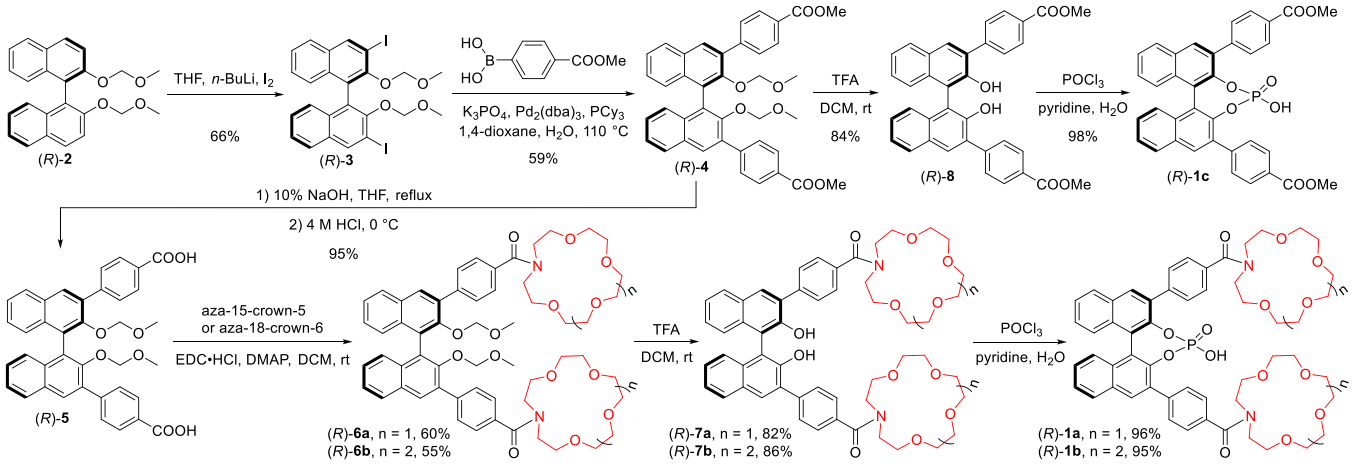
Scheme 1. Synthesis of Crown Ether Derived CPAs (*R*)-1a and (*R*)-1b



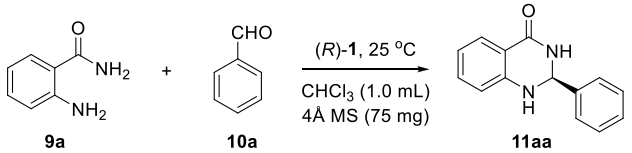
for the synthesis of optically active 2,3-dihydroquinazolinones[12−16] that extensively showed valuable pharmacological activities.[17]

With 2-aminobenzamide **9a** and benzaldehyde **10a** as the model substrates, a preliminary attempt of the reaction in $CHCl_3$ at room temperature in the presence of 75 mg 4 Å molecular sieves (MS) demonstrated that (*R*)-**1a** is an effective catalyst for the asymmetric acetalization to deliver the product **11aa** in >99% yield and 99% ee (Table 1, entry 1). $LiPF_6$ (100 mol %) was then added to investigate the influence of host−guest complexation between alkali metal ions and crown ethers on the reaction. The result showed that the addition of $LiPF_6$ could greatly improve catalytic activity, shortening the complete reaction time to 2 h with an identical high enantioselectivity of 99% ee (entry 3), while the reaction without addition of $LiPF_6$ only provided an 11% yield and 95% ee in 2 h (entry 2). In consideration of the high catalytic activity, reduced catalyst usage was investigated. A half or quarter catalyst loading led to extension of the reaction time but no decrease of enantioselectivity (entries 4−5 vs entry 3), while further decrement of the catalyst amount to 1 mol % caused a diminished enantioselectivity of 95% ee (entry 6). The impact of $LiPF_6$ on the reaction was further confirmed by using 2.5 mol % catalyst. It was found that only a 59% yield and 94% ee were obtained in the absence of $LiPF_6$ (entry 7).

When the reaction temperature was decreased to 0 °C or raised to 35 °C, there was almost no influence on the reaction found (Table 1, entries 8−9). A variety of alkali metal salts were then examined under a given set of reaction conditions (entries 10−14). All guests enhanced the reaction activity, except $NaBAr_F$, but had insignificant effect on the enantioselectivity as compared to that without guests (entries 10−13 vs entry 7). Only the addition of $LiPF_6$ induced simultaneous improvement of the reactivity and enantioselectivity (entry 5 vs entry 7). As the usage of $LiPF_6$ decreased from 100 mol % to 5 mol %, completion of the reaction was prolonged from 20 to 36 h, while maintaining quantitative yields and excellent ee's (entries 15−17 vs entry 5). To ensure sufficient reactivity, 25 mol % $LiPF_6$ was chosen as the optimal dosage.

To verify the occurrence of host−guest interaction, complexation of (*R*)-**1a** with $LiPF_6$ was investigated by ^1H NMR and mass spectrometry spectra. By comparing the ^1H NMR spectra of (*R*)-**1a** and [(*R*)-**1a** + $LiPF_6$] (Figure S36), apparent differences in both chemical shifts and peak shapes were observed. The signals of oxyethylene protons (H^c) and aromatic hydrogens changed apparently (Figure S36b vs S36a), which confirmed the presence of host−guest complexation between the aza-crown ethers and $LiPF_6$. Mass spectrometry further provided solid evidence for the complexation. In the ESI-MS spectrum of a mixture of (*R*)-**1a** and $LiPF_6$, two peaks belonging to a host−guest complex of one (*R*)-**1a** molecule with two Li^+ ions were found (Figure S37), at *m*/*z* = 1148.3298 and 502.1843, attributed to [M + 2Li +

Table 1. Optimization of Reaction Conditions[a]



9a 10a 11aa

Entry	Cat. (mol %)	Guest (mol %)	Time (h)	Yield (%)[b]	Ee (%)[c]
1	(*R*)-**1a** (10)	none	18	>99	99
2	(*R*)-**1a** (10)	none	2	11	95
3	(*R*)-**1a** (10)	$LiPF_6$ (100)	2	>99	99
4	(*R*)-**1a** (5.0)	$LiPF_6$ (100)	3	>99	99
5	(*R*)-**1a** (2.5)	$LiPF_6$ (100)	24	>99	99
6	(*R*)-**1a** (1.0)	$LiPF_6$ (100)	48	>99	95
7	(*R*)-**1a** (2.5)	none	24	59	94
8[d]	(*R*)-**1a** (2.5)	$LiPF_6$ (100)	36	>99	99
9[e]	(*R*)-**1a** (2.5)	$LiPF_6$ (100)	24	>99	98
10	(*R*)-**1a** (2.5)	KPF_6 (100)	48	>99	93
11	(*R*)-**1a** (2.5)	NH_4PF_6 (100)	48	>99	92
12	(*R*)-**1a** (2.5)	$NaPF_6$ (100)	48	>99	95
13	(*R*)-**1a** (2.5)	$LiBF_4$ (100)	24	>99	95
14	(*R*)-**1a** (2.5)	$NaBAr_F$ (100)	48	67	24
15	(*R*)-**1a** (2.5)	$LiPF_6$ (50)	24	>99	99
16	(*R*)-**1a** (2.5)	$LiPF_6$ (25)	24	>99	99
17	(*R*)-**1a** (2.5)	$LiPF_6$ (5)	36	>99	99
18	(*R*)-**1b** (2.5)	none	96	53	35
19	(*R*)-**1b** (2.5)	$LiPF_6$ (25)	96	73	71
20	(*R*)-**1c** (2.5)	none	96	54	30
21	(*R*)-**1c** (2.5)	$LiPF_6$ (25)	96	62	32

[a]Reaction conditions: **9a** (0.05 mmol), **10a** (0.055 mmol), $CHCl_3$ (1.0 mL), 4 Å MS (75 mg). [b]Isolated yield. [c]Determined by chiral HPLC analysis. [d]Carried out at 0 °C. [e]Carried out at 35 °C.

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$PF_6]^+$ and $[M + 2Li]^{2+}$, respectively. No peaks corresponding to the complexes with other stoichiometries were observed, indicative that both crown ethers on (*R*)-**1a** were bound by Li^+, forming a 1:2 complex [(*R*)-**1a** + 2Li]. Meanwhile, the compared ^1H NMR spectra of (*R*)-**1c** with and without addition of $LiPF_6$ (Figure S38) displayed no changes in either chemical shifts or peak shapes, which further proved that Li^+ did not interact with the phosphoric acid, but complexed with the aza-crown ethers of (*R*)-**1a**.

The catalysts modified with other substituents were further investigated (Table 1, entries 18−21). The catalysts **1b** with 1-aza-18-crown-6 and **1c** without crown ethers were found to be much more inferior than their analogue **1a** with 1-aza-15-crown-5. Both the catalysts **1b** and **1c** initially provided similar low yields and enantioselectivities. Addition of 25 mol % $LiPF_6$ could obviously improve the activity and enantioselectivity of **1b** (entry 19 vs entry 18), but they were still lower than those of **1a**, while the addition of $LiPF_6$ to the catalytic system of **1c** without crown ethers had very slight effect on reactivity and enantioselectivity (entry 21 vs entry 20). These results indicated that the presence of crown ethers on the catalysts could significantly enhance the catalytic activity and enantioselectivity, and introduction of Li^+ for the host−guest complexation is beneficial to further improve catalytic activity and enantioselectivity.

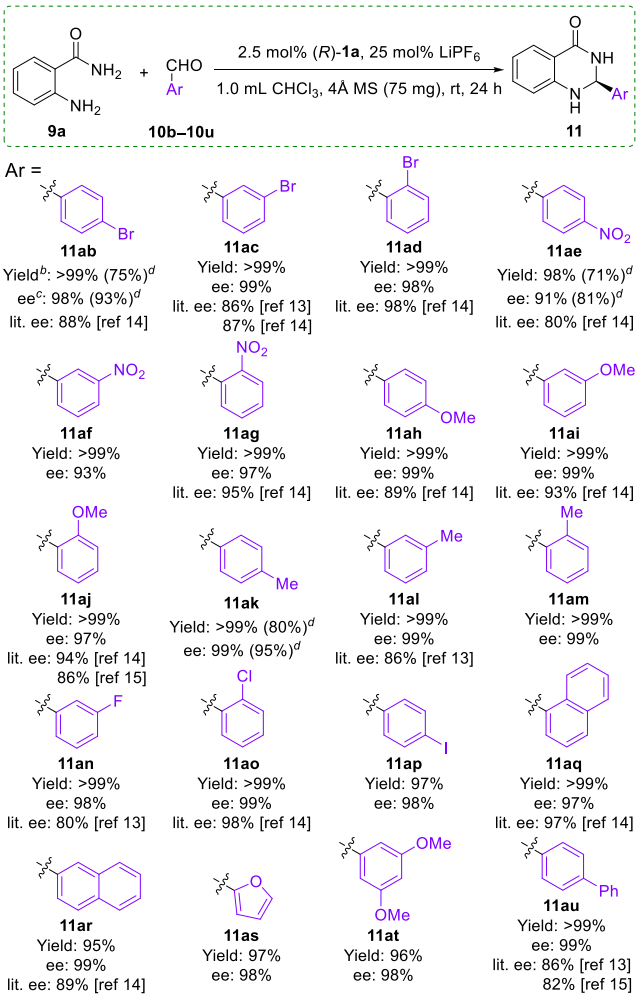
The effect of solvent on the reaction was subsequently studied (Table S1). When dichloromethane (DCM), 1,2-dichloroethane (DCE), toluene, or tetrahydrofuran (THF) was used, the reaction could complete within 20−48 h, but the ee of the product decreased somewhat by comparison with that in $CHCl_3$ (Table S1, entries 1−4 vs Table 1, entry 16). There was almost no catalytic activity in Et_2O (Table S1, entry 5), while a 56% yield and 89% ee were achieved in CH_3CN (Table S1, entry 6).

After optimization of reaction conditions, we systematically studied the generality of the presented catalytic system in catalyzing various aromatic or aliphatic aldehydes and 2-aminobenzamide derivatives substituted at different positions.

All of the electron-withdrawing and electron-donating substituents (−F, −Cl, −Br, −I, $-NO_2$, −OMe, −Me) on the benzaldehydes could be tolerated, affording their desired products **11ab**−**11ap** and **11at** (Scheme 2). It is noteworthy that different positions of the same substituents on the benzaldehydes appear to have no remarkable effect on the enantioselectivity, except for the nitro group. When a nitro substituent is presented (**11ae**−**11ag**), an apparent steric hindrance effect was observed. The enantioselectivity of the products was gradually enhanced with the increase of steric hindrance, from *para* to *meta* and to *ortho*. The nitro substitution on the *ortho* position makes it possible to participate in transition state formation through hydrogen bonding, thus leading to the increase of enantioselectivity from 91% ee to 97% ee. Reaction of 1-naphthaldehyde, 2-naphthaldehyde, and furan-2-carbaldehyde furnished the desired products **11aq**, **11ar**, and **11as**, respectively, also in excellent yields and enantioselectivities. The substrate *p*-phenylbenzaldehyde was further used to generate the adduct **11au**, which has good anticancer activity as a potent tubulin inhibitor,[14] in >99% yield and 99% ee.

To further testify the effect of host−guest complexation on this asymmetric reaction, three other substrates were selected to perform reactions without addition of alkali metal ions (Scheme 2, **11ab**, **11ae**, and **11ak**). With the other conditions

Scheme 2. Substrate Scope of Aromatic Aldehydes[a]



[a]Reaction scale: 0.05 mmol of **9a** and 0.055 mmol of **10**. [b]Isolated yield. [c]Determined by chiral HPLC analysis. [d]Without $LiPF_6$.

unchanged, the presence of guest could increase the reaction yields by 19−27% and the enantioselectivities by 4−10%, which further indicated the universality of modifying electronic properties of the catalyst through host−guest complexation between the crown ethers and alkali metal cations, thereby improving the catalytic performances.

The applicability of aliphatic aldehydes, such as *n*-butanal, *n*-heptanal, isovaleraldehyde, isobutyraldehyde, and C3∼C6 cycloalkanecarbaldehydes, was also investigated for this catalytic system. All of the selected aliphatic and alkenyl aldehydes gained quantitative yields and excellent enantioselectivities in 93−99% ee (Scheme 3, **13aa**−**13ai**). As compared with the literature results, enantioselectivities of all of the products are higher than the highest values that had been previously reported (Scheme 3).

The substrate scope of this cascade reaction was further expanded to different substituted 2-aminobenzamides (Scheme 4). Reaction of *m*-bromobenzaldehyde **10c** and *p*-methoxybenzaldehyde **10h** with 2-amino-5-methylbenzamide **9b**, 2-amino-4-methylbenzamide **9c**, 2-amino-3-methylbenzamide **9d**, 2-amino-4-fluorobenzamide **9e**, 2-amino-5-fluorobenzamide **9f**, and 2-amino-6-fluorobenzamide **9g**, respectively, released the corresponding optically enriched products in

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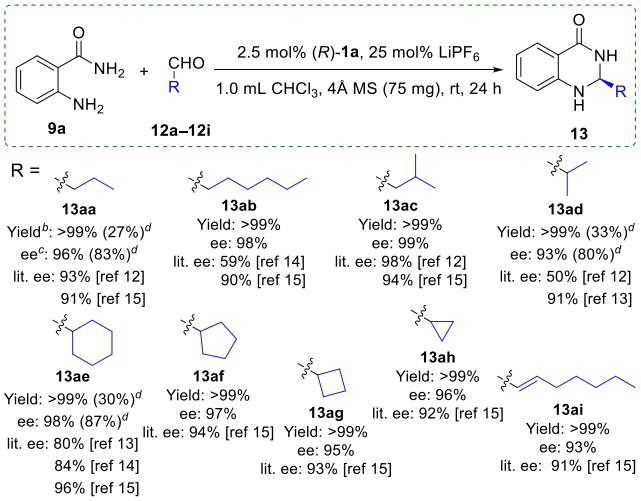
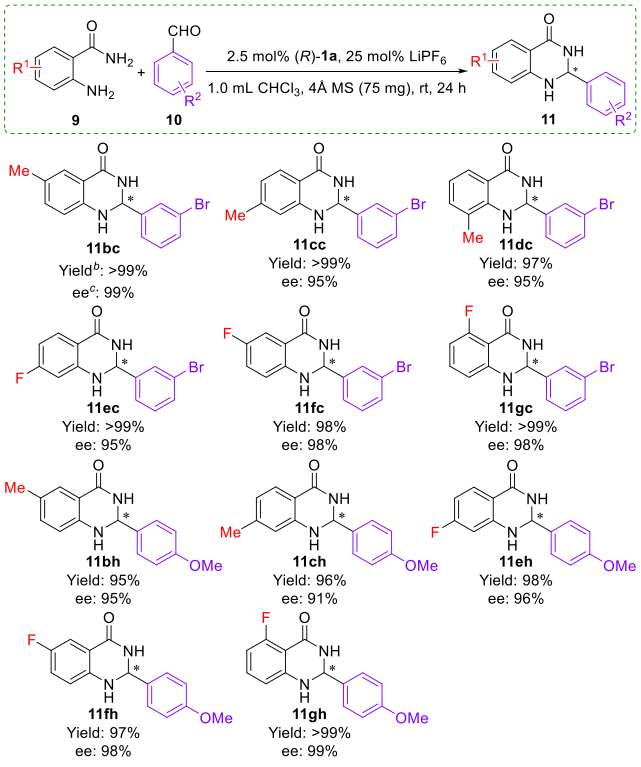
Scheme 3. Substrate Scope of Aliphatic and Alkenyl Aldehydes[a]



[a]Reaction scale: 0.05 mmol **9a** and 0.055 mmol **10**. [b]Isolated yield. [c]Determined by chiral HPLC analysis. [d]Without $LiPF_6$.

Scheme 4. Substrate Scope of 2-Aminobenzamides[a]



[a]Reaction scale: 0.05 mmol **9a** and 0.055 mmol **10**. [b]Isolated yield. [c]Determined by chiral HPLC analysis.

excellent yields (95−99%) and enantioselectivities (91−99% ee) with no apparent substituent effect.

In summary, CPAs functionalized with crown ethers were synthesized and applied in the asymmetric tandem acetalization of 2-aminobenzamide with aldehydes. By regulating the host−guest complexation of crown ethers with alkali metal cations, all substrates were transformed to 2,3-dihydroquinazolinones in high yields (95−99%) and excellent enantioselectivities (91−99% ee) with low catalyst usage. Up to 72% enhancements in yield and up to 13% increases in enantioselectivity were achieved by comparison with those obtained in the absence of alkali metal cations. In the previous reports, all of the catalysts could not simultaneously provide high enantioselectivities for the transformation of both aliphatic and aromatic aldehydes,[12−16] while this catalytic system has no limitation on the substrates. Whether from aromatic or aliphatic aldehydes, the enantioselectivities of the known products are all superior or at least equal to the highest values that had been previously reported. Studies aimed at elucidating the reaction mechanism and expanding these supramolecular catalysts to other asymmetric reactions are in progress in our laboratories.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.2c03091.

Experimental details and characterization data of the catalysts and catalytic products. (PDF)

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Notes

The authors declare no competing financial interest.

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