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Enantioselective PCCP Brønsted Acid Catalyzed Aminalization of Aldehydes

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Abstract:

Here we present an enantioselective aminalization of aldehydes catalyzed by Brønsted acids based on pentacarboxycyclopentadienes (PCCPs). Cyclization reaction using readily available anthranilamides as building-blocks provides an access to valuable 2,3-dihydroquinazolinones containing one stereogenic carbon center with high degree of enantioselectivities (*ee* up to 81 %) and excellent yields (up to 97%).

Keywords:

Pentacarboxycyclopentadiene, PCCP, Brønsted acid, aminalization, organocatalysis

Introduction:

Nitrogen-containing heterocyclic compounds are commonly occurring in nature and constitute the core structures of many biologically important compounds. An important example of such heterocycles are 2,3-dihydroquinazolinones which scaffold can be found in various compounds exhibiting pharmacological properties.[1–6] Some of them are currently used to treat numerous diseases, such as diuretic Fenquizone used for the treatment of hypertension,[7,8] or Evodiamine, a stimulant used in fat reduction or inflammation.[9–11] Moreover, it was reported that both enantiomers of 2,3-dihydroquinazolinones exhibit different bioactivities.[12,13] Thus, the development of enantioselective synthetic strategies towards 2,3-dihydroquinazolinone derivatives draw the attention of organic chemists for a long time,[14–18] even though the aminal stereocenter is sensitive to racemization.[19]

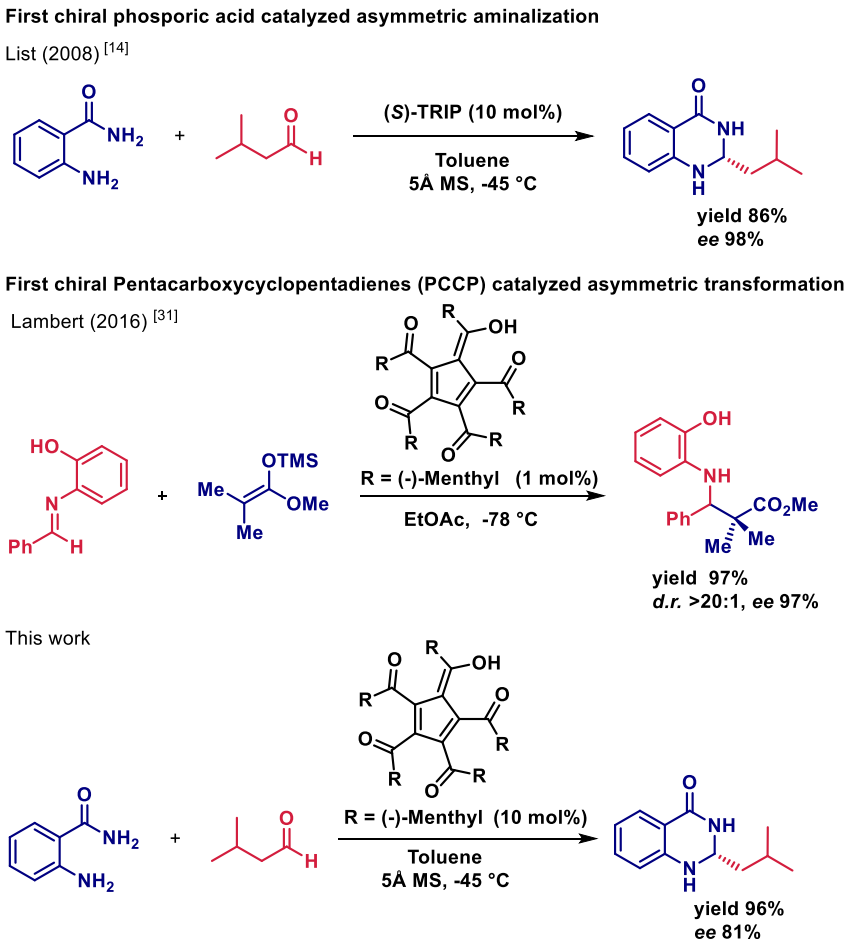


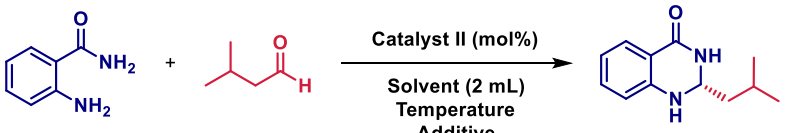
Figure 1: Synthetic strategies employing chiral Brønsted acid catalysis.

The well-established and straightforward approach in the asymmetric organocatalytic synthesis of molecules with this moiety uses the reaction between aldehydes and anthranilamide building blocks. The advantage of his methodology lies in the fact that both starting materials are readily available, and the enantioselectivity of such cyclization reaction can be controlled by chiral Brønsted acids. In the scope of Brønsted acids catalysis, chiral phosphoric acids (CPA) are dominated as potent catalysts in various asymmetric transformations,[20–24] although the synthesis of these catalysts is expensive and laborious[25]. One of the most frequent examples of CPAs is the binaphthol (BINOL)-derived phosphoric acid class of catalysts, firstly reported by Akiyama[26] and Terada[27]. Soon after, BINOL-derived phosphoric acids were employed in the enantioselective synthesis of 2,3-dihydroquinazolinones. The initial report in this area was made by List and co-workers, using (*S*)-TRIP derivative as a chiral catalyst (Figure 1).[14] Soon after, Rueping *et al*. developed a similar

methodology catalyzed by other chiral BINOL-phosphoric acids.[15] However, the reaction suffered from limited scope to aromatic aldehydes without an *ortho* substitution; corresponding dihydroquinazolinones were obtained in high yields and with high enantiomeric purities. In 2013 Lin and co-workers published the application of chiral SPINOL-phosphoric acid in the asymmetric aminalization reaction.[28] Tian´s research group developed the synthesis of dihydroquinazolinones from preformed imines instead of aldehydes catalyzed by BINOL-phosphoric acid.[17] Corresponding aminals were prepared with a wide range of substitutions using aromatic, α,β-unsaturated, or aliphatic imines. Apart from chiral phosphoric acids, chiral quaternary ammonium salts were successfully employed as catalysts in asymmetric dihydroquinazolinones synthesis.[18] Regarding the above-mentioned strategies involving chiral Brønsted acids, we envisioned that chiral pentacarboxycyclopentadiene (PCCP) derivatives could be used in enantioselective aminalization of aldehydes with anthranilamide derivatives. PCCPs were firstly reported by Otto Diels,[29,30] but recently, Lambert and co-workers introduced a new generation, chiral PCCPs (Figure 1).[29] Due to the high stability of aromatic cyclopentadienyl anion, PCCPs exhibit a low degree of pKa comparable to pKa of phosphoric acids. Contrary to chiral phosphoric acids, PCCPs offer less laborious and inexpensive preparation protocol[30,31], which makes them an interesting alternative in chiral Brønsted acid-catalyzed transformations.[29,32–35]

Results and discussion:

Table 1: Optimization of reaction condition for aminalization between **1a** and **2a**.



1a 2a 3a

Entry	Solvent	Temperature (°C)	Cat loading (mol%)	Additive	Time (h)	Yield (%)[a]	Ee (%)[b]
1	Toluene	25	10	-	0.5	97	50
2	THF	25	10	-	1	72	50
3	MTBE	25	10	-	1	50	40
4	DCM	25	10	-	1	93	45
5	EtOAc	25	10	-	1	86	44
6	Toluene	0	10	-	12	96	58
7	Toluene	-45	10	-	20	90	66
8	Toluene	-65	10	-	48	65	60
9	Toluene	-45	10	3Å MS	20	81	71
10	Toluene	-45	10	4Å MS	21	73	73
11	Toluene	-45	10	5Å MS	21	96	81
12	Toluene	-45	5	5Å MS	18	91	74
13	Toluene	-45	2	5Å MS	16	86	74

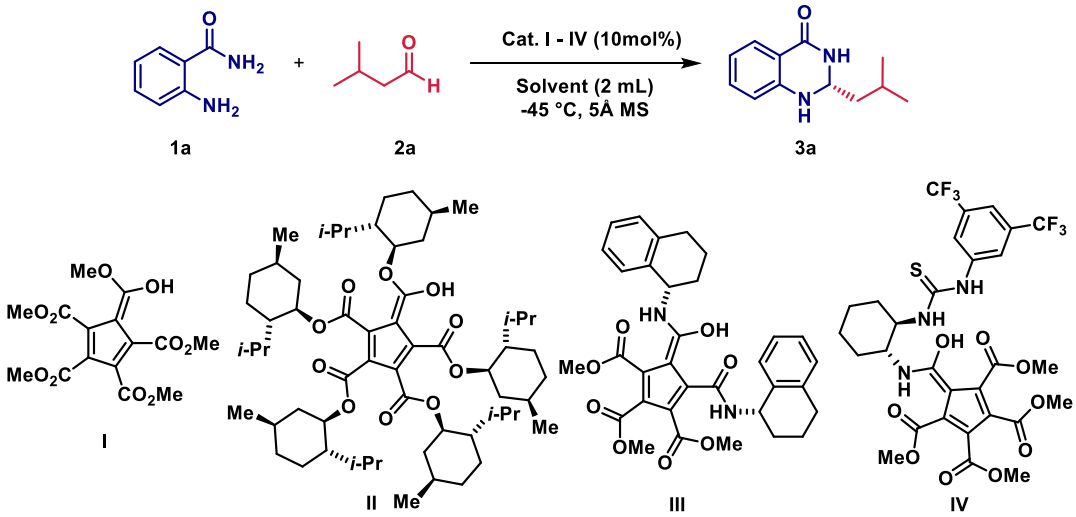
[a] isolated yield; [b] determined by chiral HPLC.

Herein, we describe our findings regarding aminalization of aldehydes using PCCP catalysis. Our investigation commenced with the screening of the reaction between anthranilamide (**1a**) and isovaleraldehyde (**2a**) in the presence of 10mol% of catalyst **II** (Table 1). First, we turned our attention to the solvent and temperature effect concerning the yield and the enantioselectivity of aminalization reaction. While most solvents showed to be effective at room temperature, the enantiomeric purity of the corresponding aminal **3a** was low in all cases (Table 1, entries 1-5). On the other hand, the yield of **3a** was satisfactory in all reactions. In particular, when the reaction between **1a** and **2a** was performed in toluene, the isolated yield of **3a** was almost quantitative (97%, entry 1). In our pursuit of better enantioselectivity, we continued with the reaction proceeded in toluene at lower temperatures. We found temperature of -45 °C as optimal for the enantiocontrol of the model reaction, affording the product **3a** in 90% yield with enantiomeric purity of 66% *ee* (entry 7). Additionally, the effect of molecular sieves on the course of the reaction was investigated. Obtained results demonstrated that molecular sieves dramatically boost the enantioselectivity (entries 9-11). In particular, when the

aminalization reaction between **1a** and **2a** was carried out in the presence of 5Å molecular sieves, corresponding product **3a** was delivered in high yield (96%) and with enantiomeric purity 81% *ee* (entry 11). In addition, the effect of catalyst loading on the course of the reaction was examined. Our data clearly show that a drop in catalyst loading of **II** has caused a significant decrease in enantioselectivity (entries 12-13).

Next, the small set of functionalized derivatives of cyclopentadienes as organocatalysts was surveyed in a model reaction (Table 2). Apart from model catalyst **II**, equipped with five (−)-menthol units, also sterically less demanding amide type of catalyst **III** and thiourea derivative (**IV**) were tested (table 2). First, the diamide type of catalyst (**III**) was examined (entry 4). Although complete conversion of **1a** and **2a** was achieved after a significantly prolonged time (7 days), aminal **3a** was isolated in a good yield of 60%. Unfortunately, the reaction proceeded nearly in a racemic fashion. An inefficient catalyst showed up to be PCCP catalyst derivatized with thiourea functional unit (**IV**), a formation of **3a** was not observed even after prolonged reaction time (entry 5). It is also worth mentioning that the non-catalyzed reaction did not deliver corresponding product **3a** even after 40 hours (entry 1). Based on the results summarized in table 2, the chiral PCCP **II** was selected as the optimal catalyst.

Table 2: Catalyst screening of aminalization reaction between **1a** and **2a**.



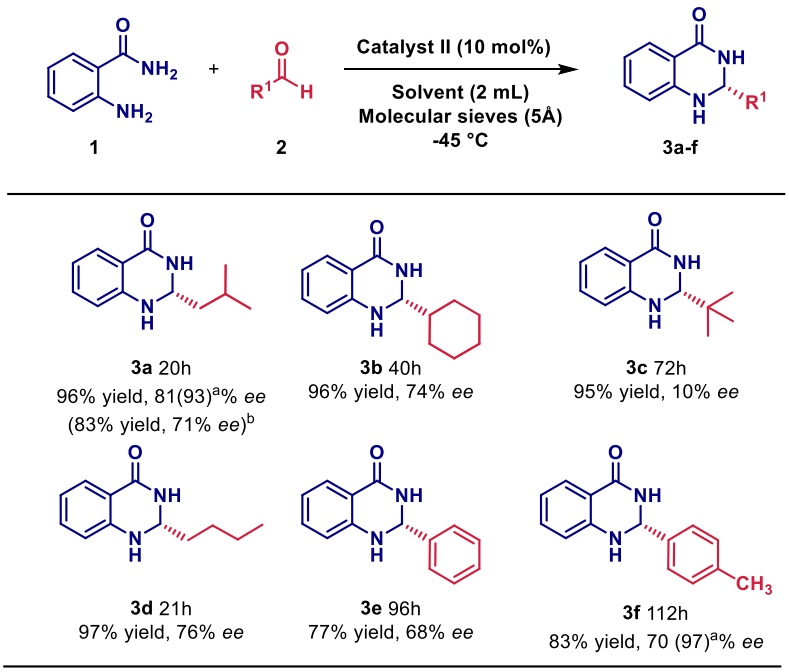
Entry	Catalyst	Time (h)	Yield (%)[a]	Ee (%)[b]
1	-	40	n.d.	n.d.
2	**I**	16	95	0
3	**II**	21	96	81
4	**III**	168	60	2
5	**IV**	168	n.d.	n.d.

[a] isolated yield; [b] determined by chiral HPLC.

With optimized reaction conditions in our hand, we continued investigating the scope of the reaction. First, we focused on the reactivity of anthranilamide **4a** with various aldehydes **2a-f** (Table 3). Generally, aliphatic aldehydes delivered cyclic aminals **3a-d** in excellent yields between 95-97% and enantiomeric purity between 74-81% *ee* (entries 1-2, 4). However, sterically demanding pivalaldehyde (**5c**) needed a prolonged reaction time to reach the complete conversion. In addition, a significant drop in enantioselectivity (10% *ee*) was observed (entry 3). Also, benzaldehyde derivatives were successfully tested in the aminalizition reaction (entries 5-6); however, a decrease in reactivity was observed when compared to aliphatic aldehydes. The corresponding products **3e-f** were isolated in lower yields (77-83%) with enantiomeric purity ranging from 68 to 70% *ee*. We have also tested the reaction between anthranilamine **1a** and isovaleraldehyde **2a** in 1 mmol scale. Obtained results suggested that reaction proceeded with slightly lower efficiency giving product **3a** in 83% yield and enantiopurity of 71% *ee*. On the other hand, we found that the desired product of aminalization reaction could be readily obtained in higher enantiomeric purity after crystallization from ethyl

acetate. That was demonstrated for products **3a** and **3f**, obtained in enantiomeric purity 93% and 97% *ee*, respectively (Table 3).

Table 3: The substrate scope of aminalization reaction for different aldehydes.

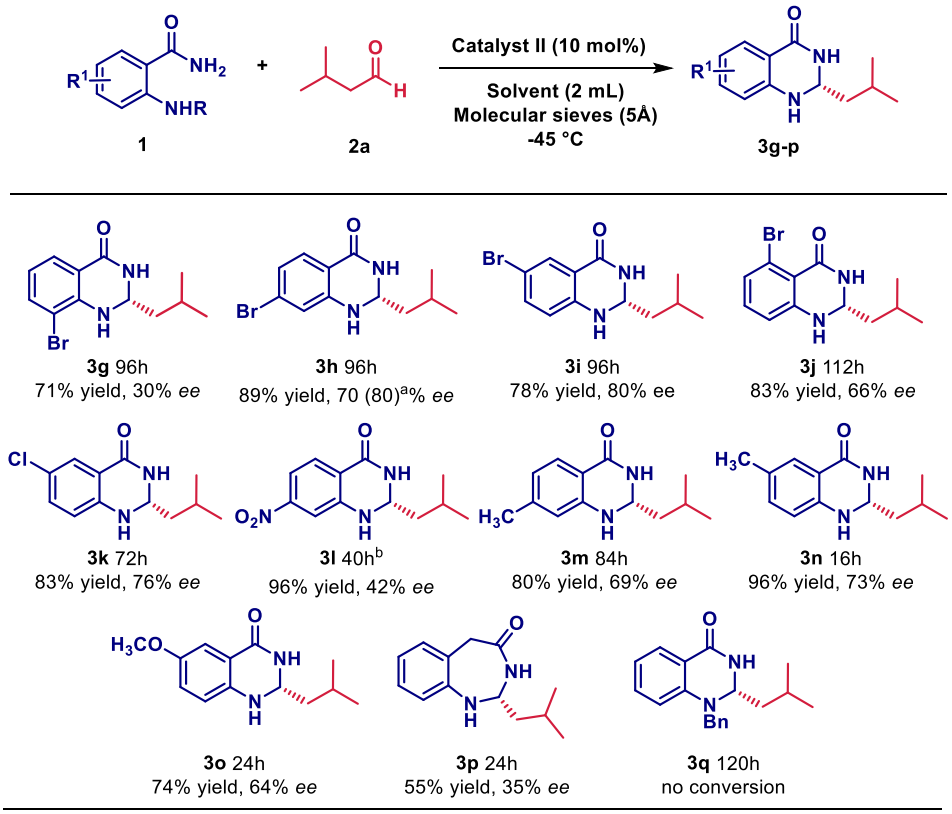


[a] after recrystalization; [b] reaction run in 1 mmol scale.

Next, we turned our attention to the substitution of anthranilamide (Table 4). First, the effect of bromine as a slightly electron-withdrawing substituent on aromatic ring was investigated. The position of bromine on the aromatic ring has a dramatic effect on the enantiomeric purity of formed products **3g-j**. When bromine is introduced in a position "3" of anthranilamide, enantiomeric enrichment of aminal **3g** reached only 30% *ee*. In contrast, substitution with bromine either in position "4", and "5" led to a formation of **3h-i** with enantiomeric purity of 70% *ee* and 80% *ee*, respectively. Finally, reaction with anthranilamide substituted with bromine in position "6" led to corresponding aminal **3j** with the enantiomeric excess of 66% *ee*. We also increased the enantiomeric purity of **3h** from 70% to 80% of *ee* after crystallization from ethyl acetate. When anthranilamide substituted with chlorine in a position "5" was introduced, enantioselectivity of the reaction reached a value of 76% *ee*, and the yield of the corresponding aminal **3k** exceeded 80 %. Next, the effect of strongly electron-withdrawing nitro group present on anthranilamide moiety was investigated. The reaction carried out in toluene did not reach the complete conversion even after a prolonged reaction time. When more polar THF was used,

the corresponding product **3l** was obtained after 40 hours in an excellent yield of 96%; however, the enantiomeric purity of **3l** was only 40% *ee*. Anthranilamides containing electron-donating methyl and methoxy group are also well-tolerated in aminalization reaction. For example, reaction with anthranilamide bearing methyl in a position "4" delivered product **3m** in good yield (80%) and enantiopurity (69% *ee*). Higher yield (yield 96%) and enantiopurity (73% *ee*) was reached when anthranilamide **1m**, having methyl group in a position "5", was employed. To broaden the scope of the aminalization reaction, we prepared 2-(2-aminophenyl)acetamide (**1p**) and tested it in reaction with isovaleraldehyde **2a** to access benzodiazepinone derivatives. The reaction proceeded smoothly with complete conversion in 24 hours, yielding the desired benzodiazepinone derivative **3p** in 55%. However, the enantiomeric purity dropped significantly to 35% *ee*. Additionally, we tested the influence of substitution of aromatic amine and prepared benzyl protected anthranilamide **1q**. Unfortunately, the reaction between **1q** and isovaleraldehyde **2a** did not deliver the corresponding product **3q** even after a prolonged reaction time.

Table 3: The substrate scope of intermolecular aminalization reaction for anthranilamines derivatives.



[a] after recrystalization; [b] THF used as a reaction solvent.

To determine an absolute configuration of aminals **3a-p**, derivative **3h** was subjected to X-ray crystallographic analysis. The absolute configuration on stereogenic center (C1) was assigned as (*R*) (Fig. 2, for details see the ESI†)[36], which is in agreement with the configuration of aminals obtained by List and co-workers.[14]

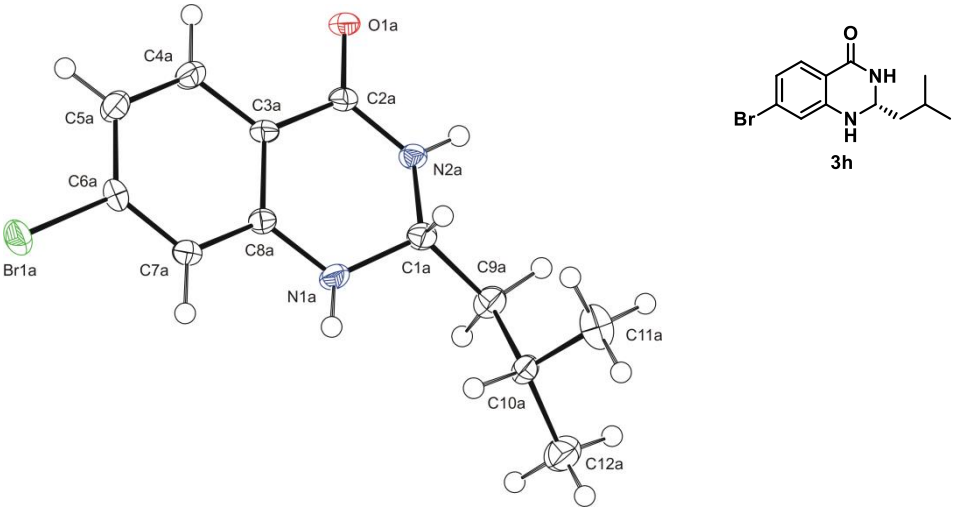


Figure 2: X-ray single-crystal structure of aminal **3h** with the displacement ellipsoids at 30% probability level.

Conclusion:

In summary, we have reported organocatalytic asymmetric aminalization reaction between aldehydes and anthranilamides catalyzed PCCP catalyst as a cheap and readily available option to conventional chiral BINOL phosphoric acids. The reaction tolerates a wide range of substitutions of anthranilamides and aromatic and aliphatic aldehydes, yielding corresponding dihydroquinazolinones in excellent yields (up to 97%) with a high degree of enantiopurity (*ee* up to 81%). We demonstrated that bulkiness of aldehydes negatively affected enantiocontrol of the process, and highly enantiomerically enriched dihydroquinazolinones can be achieved by crystallization (up to 97% ee). The developed methodology can also be used to form tetrahydrobenzodiazepinones; however, a significant drop in the yield and enantioselectivity was observed.

Supporting information:

General synthetic procedures, characteristics of compounds, X-ray experimental data and copies of ^{1}H and ^{13}C NMR spectra.

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