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Catalytic Enantioselective Desymmetrization of Cyclobutane-1,3-diones by Carbonyl-Amine Condensation

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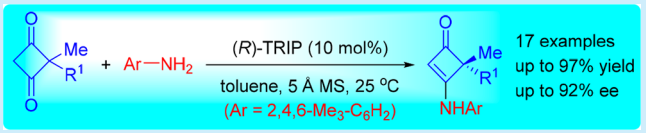
ABSTRACT: A chiral phosphoric acid-catalyzed enantioselective condensation of 2,2-disubstituted cyclobutane-1,3-diones with a primary amine is described. This reaction offered a mild and efficient protocol for constructing quaternary carbon-containing cyclobutanes in good to high yields and enantioselectivities. This reaction is the first catalytic desymmetrizing carbonyl-amine condensation reaction and also represents the first catalytic desymmetrizing reaction of prochiral cyclobutane-1,3-dione.

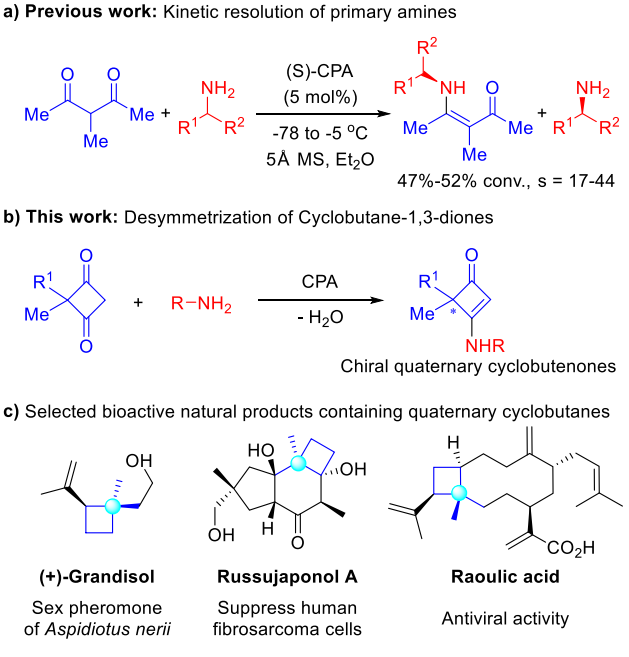


As a fundamental organic reaction, the dehydration condensation of carbonyl compounds with amines played a significant role in chemical synthesis.[1] Very interestingly, however, the enantioselective version of this reaction was largely unexplored. Because the condensation reaction itself does not create a new chiral center, an asymmetric version of this reaction could be realized by only either kinetic resolution of racemic substrates or desymmetrization of prochiral substrates. Pioneering contributions to this field were made by List and co-workers in 2017. They reported that the kinetic resolution of primary amines could be achieved via catalytic asymmetric carbonyl-amine condensation using a chiral Brønsted acid catalyst and a 1,3-diketone as the reaction counterpart (Scheme 1a).[2] Unfortunately, such groundbreaking progress did not attract enough attention, as no follow-up report was found, to the best of our knowledge.

Chiral quaternary carbon-containing cyclobutanes and their derivatives are important structural units that exist in bioactive natural products and pharmaceutically relevant small molecules (Scheme 1c).[3] Moreover, they also served as useful precursors for the synthesis of other value-added organic compounds.[4] Therefore, much effort has been devoted to developing efficient and enantioselective methods for the construction of functionalized chiral quaternary carbon-containing cyclobutanes.[5] Despite these significant advances, the development of mild and efficient protocols remains highly desirable.

On the contrary, the desymmetrization of cyclic 1,3-diketones has been identified as a powerful synthesis of cyclic chiral molecules. Previously, the catalytic desymmetrizing reactions of prochiral cyclopentane-1,3-diones and cyclohexane-1,3-diones have been well established and applied to the total synthesis of natural products and bioactive compounds.[6] Nevertheless, the catalytic desymmetrization of prochiral cyclobutane-1,3-dione to construct quaternary carbon-containing cyclobutane has never been documented, although several catalytic desymmetrizations of other prochiral four-membered cyclic substrates have been reported.[7]

Scheme 1. Catalytic Asymmetric Carbonyl-Amine Condensation



Inspired by List's seminal research work, together with our interest in catalytic asymmetric desymmetrizing reactions, we report herein a chiral phosphoric acid-catalyzed enantioselective condensation reaction of quaternary cyclobutane-1,3-

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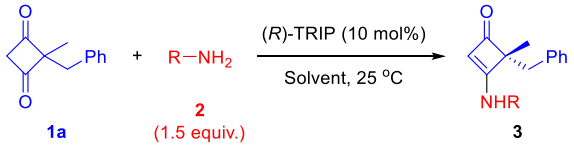
diones with a primary amine, which offered an alternative access to quaternary carbon-containing chiral cyclobutanones in good to high yields and enantioselectivities (Scheme 1b). This reaction is the first catalytic desymmetrizing carbonyl-amine condensation reaction and also represents the first catalytic desymmetrizing reaction of prochiral cyclobutane-1,3-dione.

An inherent problem in the development of the catalytic carbonyl-amine condensation reaction is the identification of an amine with suitable basicity and nucleophilicity. In other words, a good amine counterpart should not quench the chiral Brønsted acid catalysts or cause serious noncatalytic background reaction. We commenced our reaction development by reacting prochiral cyclobutane-1,3-dione **1a** with various amines in DCE using (*R*)-TRIP as the catalyst at 25 °C (Table 1).[8]

Table 1. Reaction Development[a]



entry	R	solvent	t (h)	yield (%)	ee (%)
1	Bn (**2a**)	DCE	24	no reaction	–
2	Ph (**2b**)	DCE	2	97	9
3	*p*-Ts (**2c**)	DCE	24	no reaction	–
4	4-MeO-C_6H_4 (**2d**)	DCE	2	97	6
5	3,5-Me_2-C_6H_3 (**2e**)	DCE	2	96	16
6	2,4,6-Me_3-C_6H_2 (**2f**)	DCE	72	81	89
7	2,6-(^{i}Pr)$_2$-C_6H_3 (**2g**)	DCE	72	no reaction	–
8	4-NO_2-C_6H_4 (**2h**)	DCE	12	97	24
9	C_6F_5- (**2i**)	DCE	72	59	53
10	3,5-(CF_3)$_2$-C_6H_3 (**2j**)	DCE	12	94	38
11	**2f**	CH_2Cl_2	72	65	90
12	**2f**	toluene	72	89	89
13	**2f**	$PhCF_3$	72	88	87
14	**2f**	*n*-C_6H_{14}	72	60	89
15[b]	**2f**	toluene	72	79	91
16[c]	**2f**	toluene	48	97	90
17[d]	**2f**	toluene	48	89	89
18[c,e]	**2f**	toluene	72	<10	91
19[f]	**2f**	toluene	24	97	90

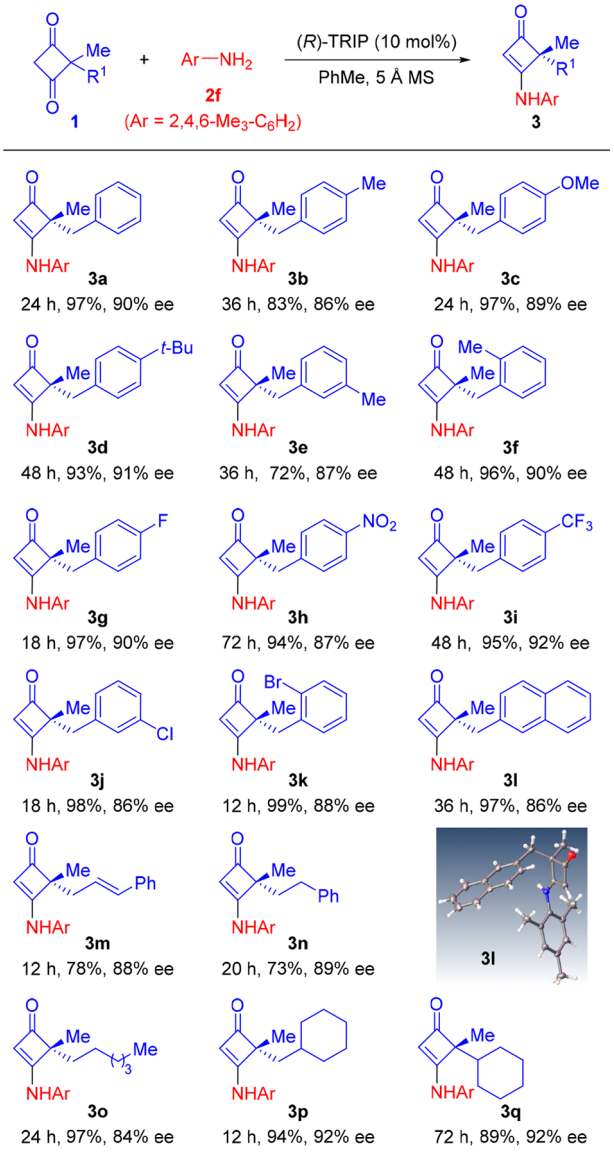
[a]All reactions were conducted using **1a** (0.2 mmol), **2** (0.3 mmol), and (*R*)-TRIP (10 mol %) in 2 mL of solvent at 25 °C, unless noted otherwise. [b]With 4 Å MS (100 mg). [c]With 5 Å MS (100 mg). [d]With 13 X MS (100 mg). [e]At 0 °C. [f]With 5 Å MS (50 mg).

Initially, we tried to use benzyl amine (**2a**), but no reaction took place, possibly because of its high basicity (entry 1). To our delight, when the less basic aniline (**2b**) was subjected to the conditions described above, the reaction proceeded smoothly to give the desired chiral quaternary cyclobutenone in 97% yield, albeit with only 9% ee values (entry 2). The more electron-deficient amines, such as *p*-$TsNH_2$ and H_2NBoc, showed no reactivity (entry 3). In the following, we examined the steric and electronic effects of anilines on the reaction outcome, aiming to improve the enantioselectivity (entries 4–10). It was found that when 2,4,6-trimethyl aniline (**2f**), which is moderate in both nucleophilicity and steric hindrance, was used as the amine nucleophile, the desired condensation products could be obtained in 89% ee and 81% yield (entry 6).

Solvent effect optimization revealed toluene as the optimal choice, in which the reaction could give the highest yield of 89% (entries 11–14). Considering that the current reaction is a dehydration process, we tried to add activated molecular sieves (MS) to remove the byproduct H_2O from the organic phase and, thus, accelerate the reaction. After several trials (entries 15–17), we found the addition of 5 Å MS could afford the best results, in terms of both yield and enantioselectivity (entry 16). When the reaction temperature was decreased to 0 °C, the reaction became rather sluggish and no significant improvement in the ee value was observed (entry 18). Further optimization revealed that decreasing the amount of 5 Å MS to 50 mg could promote the reaction to reach completion within 24 h and afford the desired product in 97% yield and 90% enantioselectivity (entry 19).

The scope of this catalytic desymmetrizing carbonyl-amine condensation reaction was then examined using the optimized reaction conditions described above (Scheme 2). The effect of the substituents on the benzene ring of the benzyl group was first evaluated. In general, the introduction of both an electron-

Scheme 2. Substrate Scope



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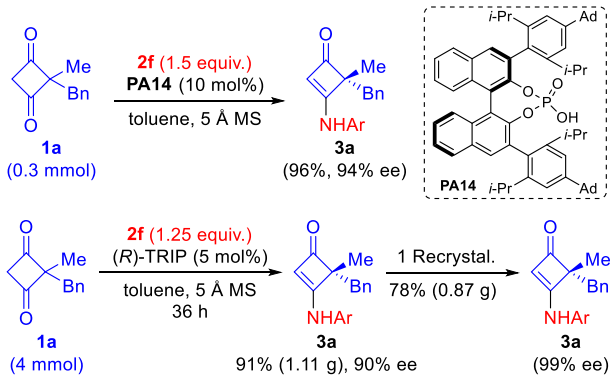
donating and an electron-withdrawing group on the *ortho* and *meta* position of the benzene ring did not have a significant effect on the enantioselectivities of the reaction, as is shown by 86−90% ee values for products **3a−c**, **3e−h**, **3j**, and **3k**, whereas the existence of steric substituents at the *para* position could slightly improve the ee, as exemplified by the 91% and 92% ee values for **3d** and **3i**, respectively. The condensation of naphthalen-1-ylmethyl-substituted cyclobutane-1,3-dione **1l** with aniline **2f** also proceeded well to deliver a 97% yield and an 86% ee for product **3l**, the absolute configuration of which has been determined by X-ray crystallography analysis (see the Supporting Information for details). Besides benzyl groups, allyl and other linear aliphatic substituents were also well tolerated, giving products **3m−o** in 84−89% enantioselectivities. Additionally, when the more steric substrates **1p** and **1q** were subjected to the conditions described above, the corresponding products **3p** and **3q** could be obtained in 89−94% yields with 92% ee.

It should be mentioned that the ee values of the product could be further improved by using more steric (*R*)-TRIP analogues as the catalyst or recrystallization (Scheme 3). When

Scheme 3. Further Efforts to Improve the ee Value of Products 3

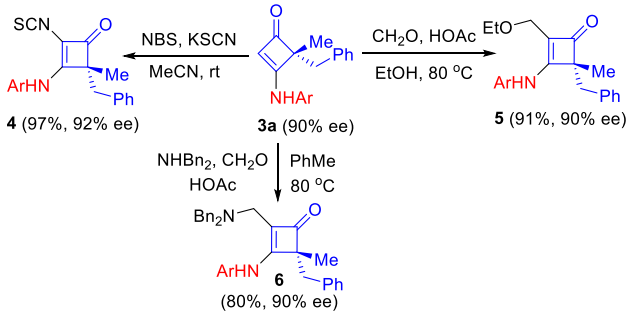


chiral phosphoric acid **PA14** was used instead of (*R*)-TRIP, the reaction of **1a** and **2f** could give product **3a** in 96% yield with 94% ee. To demonstrate the practicability of the current method, we conducted a gram-scale reaction of cyclobutane-1,3-dione **1a** and 2,4,6- trimethyl aniline **2f** (Scheme 3). In the presence of only 5 mol % (*R*)-TRIP, the reaction of **1a** (4.0 mmol) with **2f** (1.25 equiv) could deliver product **3a** in 91% yield (1.11 g) with 90% ee. The ee value of **3a** could be improved from 90% to 99% via a single recrystallization from acetone and petroleum ether in 78% yield.

The thus obtained chiral cyclobutenone could undergo various elaborations to give a series of fully substituted cyclobutenone derivatives. Upon treatment with NBS and KSCN, **3a** could be transformed into **4** in 97% yield without a loss of enantiopurity.[9] In addition, the enamine nature of **3a** enabled it to participate in nucleophilic addition reactions, as exemplified by the synthesis of 2-ethoxymethyl cyclobutenone **5** and 2-aminomethyl cyclobutenone **6** in 91% and 80% yields, respectively.[10] We also tried the reaction of **3a** with α,β-unsaturated ketones and nitroalkenes, but no reaction was observed in the presence of either Brønsted acid or base catalyst (Scheme 4).

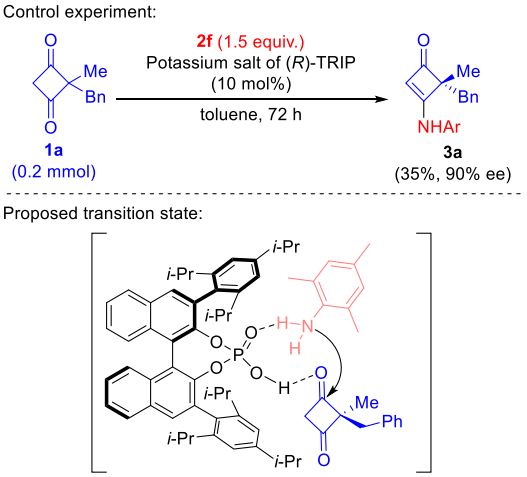
To gain preliminary insight into the mechanism of the current reaction, a control experiment was conducted. As

Scheme 4. Product Elaboration



shown in Scheme 5, reaction of **1a** and **2f** became rather sluggish when the potassium salt of (*R*)-TRIP [prepared from

Scheme 5. Control Experiment and Proposed Transition State



(*R*)-TRIP and *t*-BuOK] was used as the catalyst and the corresponding product **3a** was obtained in only 35% yield even after 72 h. This result indicates that the hydroxyl group in the phosphoric acid catalyst played a vital in the success of the current reaction. On the basis of this observation and literature reports, a transition state for the enantio-determining step was proposed, in which the phosphoric acid serves as a bifunctional catalyst to activate both reactants via hydrogen-bonding interactions.

In conclusion, the first catalytic desymmetrizing carbonyl-amine condensation reaction of 2,2-disubstituted cyclobutane-1,3-diones with a primary amine has been developed using chiral phosphoric acid catalysis. The current reaction offered a mild and efficient protocol for obtaining quaternary carbon-containing cyclobutanes in good to high yields and enantioselectivities. The enamine nature of the obtained products enabled it to undergo various elaborations to give a series of fully substituted cyclobutenone derivatives. Noticeably, this reaction also represents the first catalytic desymmetrizing reaction of prochiral 2,2-disubstituted cyclobutane-1,3-diones.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00067.

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General procedures and experimental details for all compounds, crystallographic details for **3l**, copies of NMR spectra of **1** and **3**, and HPLC chromatograms of **3** (PDF)

Accession Codes

CCDC 2047438 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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