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Desymmetric Enantioselective Reduction of Cyclic 1,3-Diketones Catalyzed by a Recyclable *P*-Chiral Phosphinamide Organocatalyst

Xu-Long Qin, Ang Li, and Fu-She Han*

Cite This: *J. Am. Chem. Soc.* 2021, 143, 2994−3002
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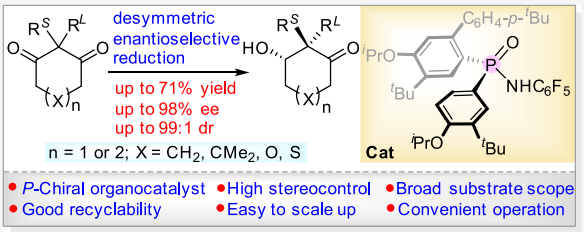
ABSTRACT: The *P*-stereogenic phosphinamides are a structurally novel skeletal class which has not been investigated as chiral organocatalysts. However, chiral cyclic 3-hydroxy ketones are widely used as building blocks in the synthesis of natural products and bioactive compounds. However, general and practical methods for the synthesis of such chiral compounds remain underdeveloped. Herein, we demonstrate that the *P*-stereogenic phosphinamides are powerful organocatalysts for the desymmetric enantioselective reduction of cyclic 1,3-diketones, providing a useful method for the synthesis of chiral cyclic 3-hydroxy ketones. The protocol displays a broad substrate scope that is amenable to a series of cyclic 2,2-disubstituted five- and six-membered 1,3-diketones. The chiral cyclic 3-hydroxy ketone products bearing an all-carbon chiral quaternary center could be obtained with high enantioselectivities (up to 98% ee) and diastereoselectivities (up to 99:1 dr). Most importantly, the reactions could be practically performed on the gram scale and the catalysts could be reused without compromising the catalytic efficiency. Mechanistic studies revealed that an intermediate formed from *P*-stereogenic phosphinamide and catecholborane is the real catalytically active species. The results disclosed herein bode well for designing and developing other reactions using *P*-stereogenic phosphinamides as new organocatalysts.



INTRODUCTION

The chiral cyclic 3-hydroxy ketones (**1** in Figure 1) with an all-carbon quaternary chiral center at 2-position are widely used as versatile intermediates for the enantioselective synthesis of bioactive compounds. Specifically, numerous natural products with different skeletal classes as represented by estrone methyl ether (**2**),[1,2] aplysiasecosterol A (**3**),[3] cyathane terpenoids (**4** and **5**),[4,5] hamigerans (**6** and **7**),[6] crotogoudin (**8**),[7] cortistatin A (**9**),[8,9] and paspaline (**10**)[10,11] have been synthesized using the five- or six-membered chiral cyclic 3-hydroxy ketones as the key building blocks.

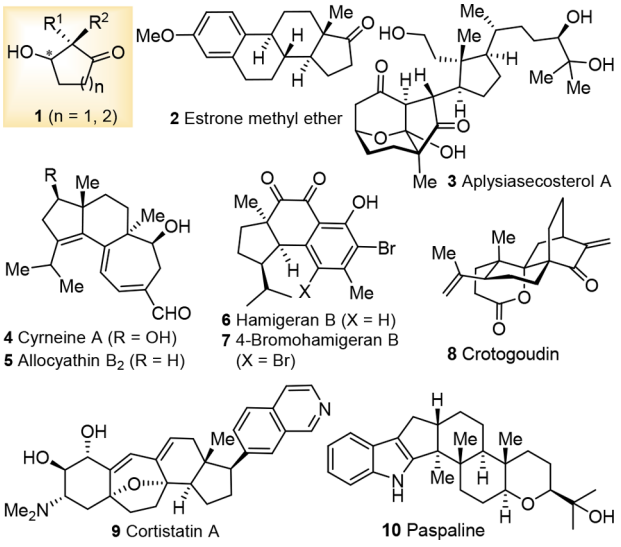


Figure 1. Selected natural products synthesized from chiral cyclic 3-hydroxy ketones.

Desymmetric enantioselective reduction of 2,2-disubstituted 1,3-diketones has been the most frequently investigated strategy for the synthesis of chiral cyclic 3-hydroxy ketones. Early methods include the oxazaborolidine-[1,8,12] (CBS) and enzyme-catalyzed reduction,[7,10,11,13−15] and the transition-metal-catalyzed hydrogenation.[2,9,16−18] While high to excellent enantioselectivity could be obtained by employing these methods, they suffer at least one of the following drawbacks, such as limited substrate scope, low to moderate diastereoselectivity, and poor stability of the catalysts toward air and moisture. Apart from these, the CBS reduction always requires a slow addition of the substrates or reductants which is problematic for reliable scale up; whereas the enzymatic reduction suffers from troublesome isolation of the products

Received: January 9, 2021
Published: February 10, 2021

https://dx.doi.org/10.1021/jacs.1c00277
J. Am. Chem. Soc. 2021, 143, 2994−3002

due to the severe foaming and emulsification, and the need to use large volumes. In fact, we did encounter these problems during our syntheses of diterpenoid natural products.[4−6] Conscious of these disadvantages, we turned toward developing an alternative catalyst system aimed at overcoming these issues.

Chiral phosphorus compounds have been extensively used in catalytic asymmetric reactions as ligands[19−23] or organocatalysts.[24−28] Specifically, the *P*-stereogenic phosphorus compounds have been compellingly demonstrated to exhibit a prominent chiral inducing property stemming from chirality proximate to the catalytic center.[29−32] However, extensive investigations of *P*-stereogenic compounds with structural diversity as well as novelty in the area of asymmetric catalysis remain restricted due to the paucity of efficient methods for their synthesis. In our recent works, we have established an efficient and versatile synthetic platform that could access on the gram level the various types of skeletally novel *P*-stereogenic phosphinamides[33−35] such as acyclic (thio)-phosphinamides (**11** and **12**) and cyclic (thio)phosphinamides (**13** and **14**) (Figure 2A).

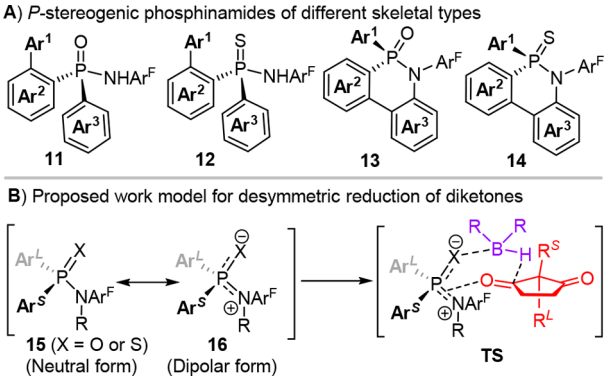


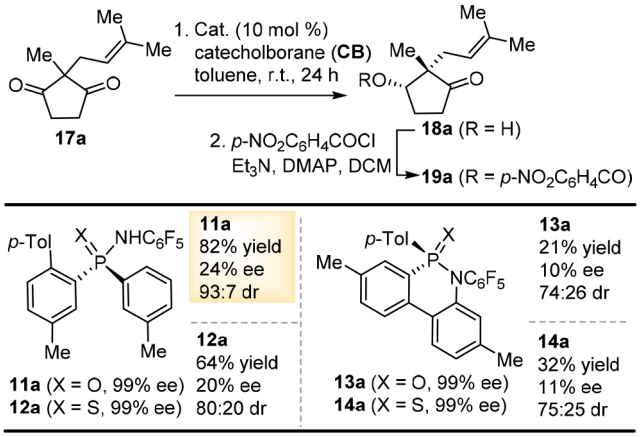
Figure 2. Structural skeleton of *P*-stereogenic phosphinamides (A) and the tentatively proposed working model for desymmetric reduction of diketones (B).

In earlier reports, the carbon-centered chiral phosphinamides were investigated as catalysts for asymmetric reduction of ketone compounds.[36−49] However, the enantioselectivity of such catalysts was less prominent, and moreover, their use in desymmetric enantioselective reduction of diketones has remained underexplored. Herein, taking the advantages of the *P*-stereogenic feature and the skeletal diversity of our chiral phosphinamides, we envisioned they could serve as a potential organocatalyst platform toward the challenging desymmetric enantioselective reduction of 1,3-cyclic diketones. As tentatively illustrated in Figure 2B, the N−P═O unit of a phosphinamide **15**, which provides both Lewis basic and acidic sites via its dipolar form **16**,[50,51] may coordinate with borane and diketone to form a well-positioned transition state **TS**. As a result, such a working model would not only activate both borane and diketone via bifunctional interactions but also impose a beneficial impact on stereochemistry owing to the close proximity of activating center to chiral inducing center. The successful demonstration of *P*-stereogenic phosphinamides as efficient catalysts for the desymmetric enantioselective reduction of 1,3-cyclic diketones and the investigation of the reaction mechanism will be presented herein.

RESULTS AND DISCUSSION

Optimization of the Reaction Conditions. To identify the potential catalysts with an appropriate skeletal type, we initially evaluated the catalytic efficiency of four types of skeletally different *P*-stereogenic catalysts **11a**−**14a** by using 1,3-cyclopentanedione **17a** (Table 1) as a model substrate

Table 1. Evaluation of the Category of the Catalysts[a]



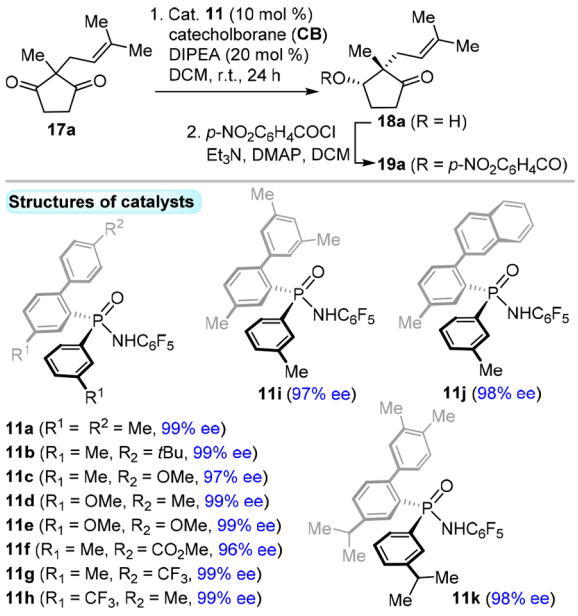
[a]Conditions: **17a** (0.2 mmol, 36.0 mg), CB (1.1 equiv), and cat. (10 mol %) in 1 mL of anhydrous toluene at room temperature for 24 h. The yields were isolated yields for two steps, the ee%, and dr were determined by chiral HPLC by converting the product **18a** into the corresponding ester **19a**.

because the chiral product **18a** was demonstrated to be a useful intermediate for the synthesis various diterpenoid natural products.[4−6] A brief screening of the reaction parameters revealed that among the four different types of catalysts, the acyclic phosphinamide **11a** provided the best results by using catecholborane (CB) as reducing reagent in toluene solvent in term of yield (82%), enantioselectivity (24% ee), and diastereoselectivity (93:7 dr) as determined by converting the product **18a** into the corresponding *p*-nitrobenzoyl ester **19a**. Notably, these initial results showed that **11a** displayed a much better diastereoselectivity than the conventional CBS reduction. Accordingly, a further screening of solvents was carried out by employing **11a** as catalyst (Table S1 of the Supporting Information, SI). Dichloromethane (DCM) afforded a slightly improved outcome (75% yield, 28% ee, and 95:5 dr of **19a**). Next, the effect of *N*-containing compounds was examined as additives because prior literature[1] for CBS reduction revealed that the amine additives influence profoundly the reaction efficiency. After a systematic evaluation on the structures of an array of commercially available amines and pyridine derivatives (Table S2), following additionally an optimization of the loading amounts of the optimal amine (Table S3) and the reaction temperature (Table S4), we found that the addition of diisopropylethylamine (DIPEA) could markedly improve the reaction efficiency. **19a** could be obtained in 72% yield with 75% ee and 97:3 dr in the presence of 10 mol % **11a** and 20 mol % of DIPEA at 23 °C in dichloromethane (Table 2, entry 1).

Under these preliminary conditions, we then investigated the effect of *P*-stereogenic phosphinamide catalysts of type **11** on the catalytic efficiency. Various catalysts bearing electron donating and electron-withdrawing groups on the phenyl ring were synthesized and evaluated (Table 2). It was found that

https://dx.doi.org/10.1021/jacs.1c00277
J. Am. Chem. Soc. 2021, 143, 2994−3002

Table 2. Optimization of the Catalysts[a]



entry	catalyst (10 mol %)	CB (equiv)	yield (%)	ee (%)	dr
1	**11a**	1.1	68	75	97:3
2	**11b**	1.1	68	76	97.5:2.5
3	**11c**	1.1	65	77.5	98:2
4	**11d**	1.1	68	77	97.5:2.5
5	**11e**	1.1	64	76	96:4
6	**11f**	1.1	72	58.5	96:4
7	**11g**	1.1	62	43.5	97:3
8	**11h**	1.1	68	38	93:7
9	**11i**	1.1	72	68	97:3
10	**11j**	1.1	70	64.5	96.5:3.5
11	**11k**	1.1	70	78	97:3
12	**11k**	1.5	68	83	97:3
13	**11k**	1.6	62	86	97:3
14	**11k**	1.7	50	88	97:3
15	**11k**	1.8	39	92.5	97:3

[a]Conditions: **17a** (0.2 mmol, 36.0 mg), CB (1.1 equiv), catalyst (10 mol %), and DIPEA (20 mol %) in 1 mL of anhydrous DCM at room temperature for 24 h. The yields were isolated yields of **19a** for two steps, the ee% and dr were determined by chiral HPLC by converting **18a** into the corresponding ester **19a**.

catalysts decorated by electron-donating substituents such as alkyl and alkoxy groups (entries 1−5 and 9−11) afforded **19a** in >75% ee and excellent diastereoselectivity of uniformly >24:1 dr, and catalyst **11k** (entry 11) bearing bulky isopropyl groups provided the best overall results. In comparison, incorporation of electron-deficient groups such as CO_2Me (entry 6), CF_3 (entries 7 and 8), and naphthyl (entry 10) on any phenyl ring resulted in an apparently diminished enantioselectivity. Although we could not discover a satisfactory catalyst from the survey of this round, we gained an important clue that incorporation of functional groups with appropriate electron-donating nature and steric hindrance would be a feasible way to improve the efficiency of the catalysts.

An interesting point we observed during this survey was that, while the yield of **18a** was decreased with the increase of the loading amounts of CB reductant resulting from the over reduction of **18a**, the enantioselectivity was gradually increased (entries 11−15) to reaching 92.5% ee in the presence of 1.8 equiv of CB (entry 15). These results imply that the over reduction of **18a** and its enantiomer *ent*-**18a** should proceed via a kinetic resolution manner, during which the *ent*-**18a** was reduced faster than **18a**. In addition, we also noted that the reduction of **17a** proceeded very fast virtually when the amounts of CB was increased to higher than 1.3 equiv. The conversion of **17a** could be completed within ca. 5 min. As a comparison, the substrate could not be entirely reacted within 24 h when 1.1 equiv of CB was used (entries 1−11). Our later investigation revealed the incomplete conversion of the substrate with 1.1 equiv of CB was indeed ascribed to the insufficient amounts of CB in the reaction system because part of which was consumed by the over reduction of **18a** and by the formation of catalytically active species with phosphinamide catalyst (vide infra). These observations provided useful clue not only for further optimization of the reaction conditions but also for an indepth understanding of the reaction mechanism.

To clarify the origin of the kinetic resolution reduction, a series of control experiments were implemented. Accordingly, the **11k**-catalyzed reduction of racemic **18a** (rac-**18a**) was carried out by varying the molar equivalents of CB (Table S5). Surprisingly, only racemic **18a** was recovered for all cases (Figure 3A). In contrast, when chiral borate **22** prepared from CB and enantiomerically pure **21** was added to the reaction system, the recovered **18a** was optically active. Specifically, as shown in Figure 3B (see also Table S6 for detailed data), with the increase of the amounts of CB, the recovery yields of **18a** decreased gradually (blue curve), whereas the ee% values

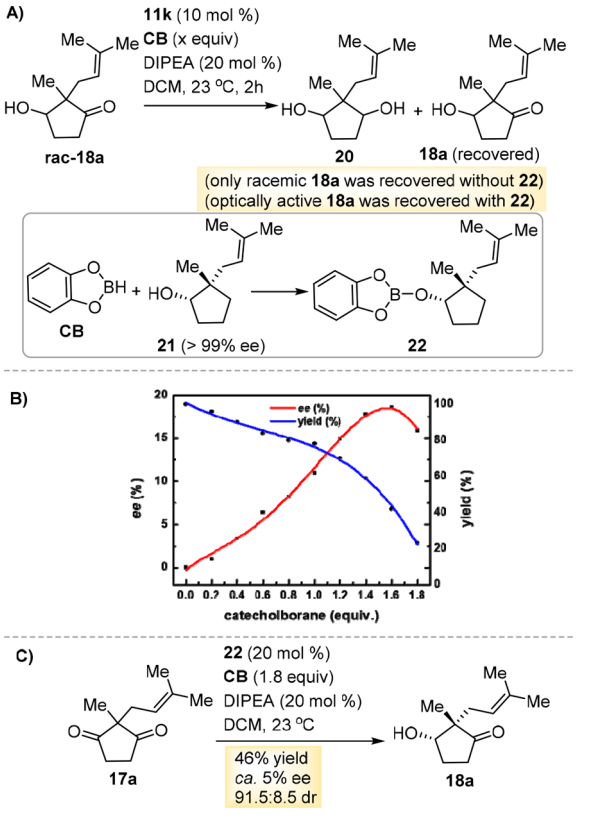


Figure 3. Control experiments: reduction of racemic **18** (A), profile of the course of the reduction in the presence of **22** (B), and desymmetric reduction of **17a** catalyzed by **22** (C).

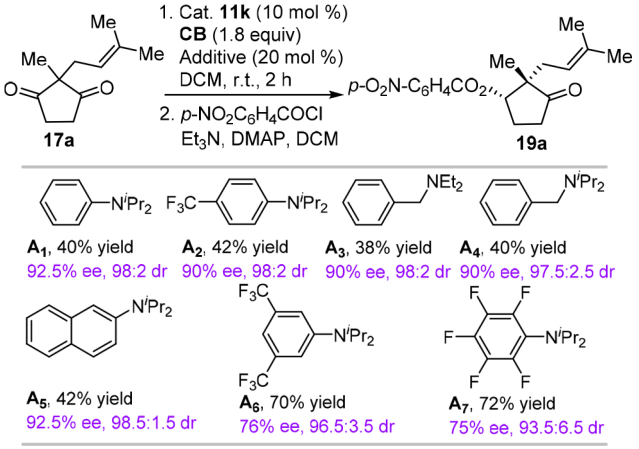
https://dx.doi.org/10.1021/jacs.1c00277
J. Am. Chem. Soc. 2021, 143, 2994−3002

increased gradually to reach a peak data of 18.6% ee and then decreased (red curve). The results of these control experiments unambiguously affirmed that the over reduction of **18a** in the real reaction system did proceed via a kinetic resolution manner which was exclusively catalyzed by the borate that formed in situ from chiral **18a** and CB rather than the phosphinamide **11k**.

Here, a question rising from the above results is whether the desymmetric enatioselective reduction of diketone **17a** is governed by the *P*-stereogenic phosphinamide or by the chiral borate formed from chiral **18a** and CB. To clarify this issue, we performed the desymmetric reduction of **17a** with the presence of chiral borate **22** without **11k** (Figure 3C). The acquisition of almost racemic **18a** (ca. 5% ee) associated with a somewhat lowered dr (91.5:8.5) clearly indicated that the desymmetric enantioselective reduction of diketone **17a** was overwhelmingly governed by the phosphinamide catalyst but not the borate **22**. Thus, on the basis of the results of a series of control experiments, we demonstrated that the overall outcome including the yield and stereoselectivity for the desymmetric enantioselective reduction of diketone **17a** was virtually controlled by two processes. The major one is the *P*-stereogenic phosphinamide-catalyzed desymmetric enantioselective reduction of **17a**, generating chiral hydroxy ketone **18a**. The minor one is the partial over reduction of the product **18a** via a kinetic resolution mediated by the borate in situ formed from CB and chiral **18a**.

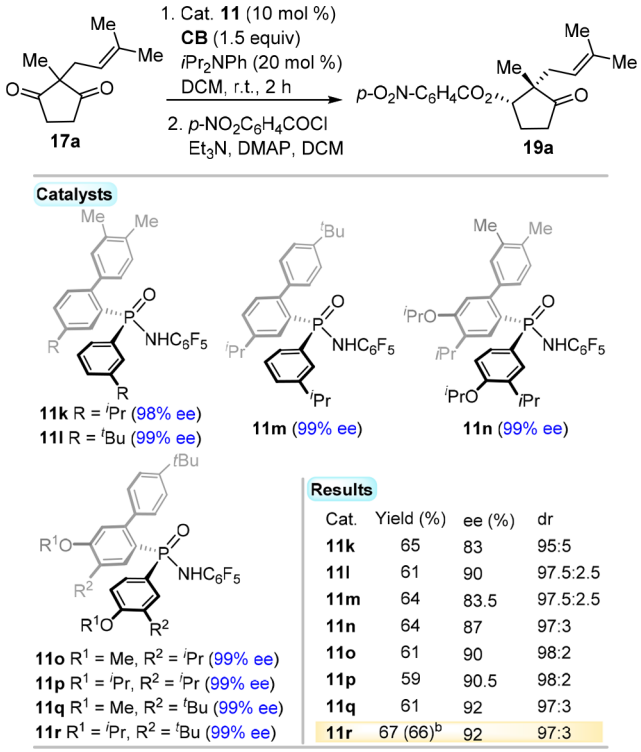
Thus, on the basis of the results from Table 2 and the control experiments, we learned that the key toward further improving the reaction efficiency should be concentrated on finding an appropriate combination of catalysts, additives, and the equivalents of CB to adjust the two processes as mentioned above. At first, an array of amines were synthesized and re-evaluated because, as mentioned above, DIPEA may lead the reaction to proceed so fast that it would be troublesome for large scale operation. Through an extensive survey (Tables 3 and S7), we identified five additional amines ($\mathbf{A_1}$–$\mathbf{A_5}$) that could provide **19a** with the results almost identical to those of DIPEA (entry 15 in Table 2) in the presence of 1.8 equiv of CB catalyzed by **11k**. However, to compare with DIPEA, these additives allowed the conversion to complete within 0.5–2 h, which would facilitate the control of reaction process. A parallel comparison showed that the electron-deficient amine additives resulted in a significantly diminished enantioselectivity ($\mathbf{A_6}$ and $\mathbf{A_7}$) albeit the yields were improved. The effects of electronic nature on the outcomes are congruous with those of catalysts (Table 2). Considering the overall performances, we choose ^{i}Pr$_2$NPh ($\mathbf{A_1}$) as the most suitable additive. Next, a brief examination of the amounts of CB showed that 1.5 equiv was suitable, giving **19a** in 65% yield with 83% ee and 95:5 dr in the presence of **11k** catalyst (Table 4).

Table 3. Re-optimization of the Amine Additives[a]



[a]Conditions: **17a** (0.2 mmol, 36.0 mg), CB (1.8 equiv), catalyst (10 mol %), and additive (20 mol %) in 1 mL of anhydrous DCM at room temperature for 2 h. The yields were isolated yields of **19a** for two steps, the ee% and dr were determined by chiral HPLC by converting **18a** into the corresponding ester **19a**.

Table 4. Re-optimization of the Catalysts[a]



Results

Cat.	Yield (%)	ee (%)	dr
11k	65	83	95:5
11l	61	90	97.5:2.5
11m	64	83.5	97.5:2.5
11n	64	87	97:3
11o	61	90	98:2
11p	59	90.5	98:2
11q	61	92	97:3
11r	67 (66)[b]	92	97:3

[a]Conditions: **17a** (0.2 mmol, 36.0 mg), CB (1.5 equiv), catalyst (10 mol %), and iPr$_2$NPh (20 mol %) in 1 mL of anhydrous DCM at room temperature for 2 h. The yields were isolated yields for two steps, the ee% and dr were determined by chiral HPLC by converting the product **18a** into the corresponding ester **19a**. [b]Yield obtained from 5 mol % catalyst loading.

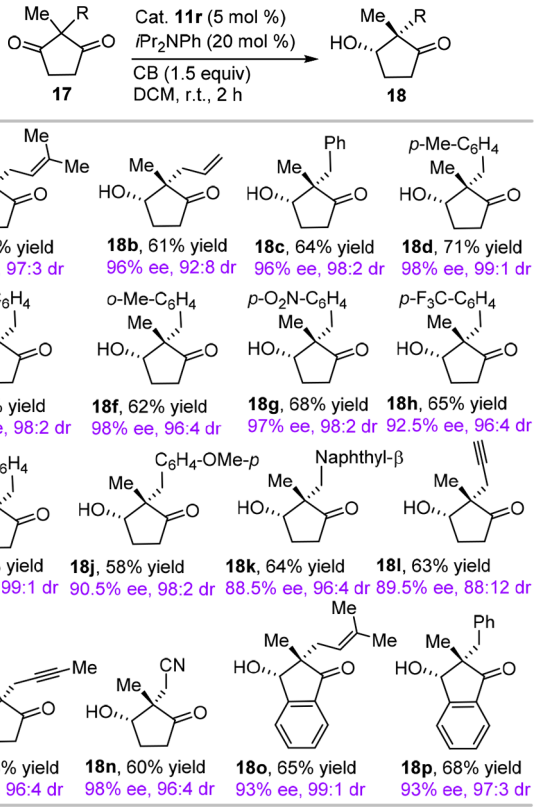
Finally, we reoptimized the catalysts by precisely tuning the steric hindrance and electron-donating nature (Table 4, **11l**–**11r**) based on the general rule drawn from the results in Table 2. An extensive survey along this line eventually led to the discovery of a satisfactory catalyst **11r** bearing bulky ^{t}Bu and electron rich O^{i}Pr groups, which afforded **19a** in 67% yield with 92% ee and 97:3 dr. Further inspection revealed that the catalyst loading of **11r** could be decreased to as low as 5 mol % without eroding the outcomes of the reaction. Thus, through an exhaustive and patient optimization, we could established a set of satisfactory conditions for the desymmetric enantioselective reduction of the 1,3-diketone **17a**, that is, 5 mol % of *P*-stereogenic catalyst **11r**, 20 mol % of iPr$_2$NPh additive, and 1.5 equiv of CB reductant in CH_2Cl_2 at room temperature for 2 h. Under these conditions, the corresponding *p*-nitrobenzoyl

https://dx.doi.org/10.1021/jacs.1c00277
J. Am. Chem. Soc. 2021, 143, 2994–3002

ester **19a** was isolated in 66% yield over two steps with 92% ee and 97:3 dr.

Substrate Scope, Application for Gram Scale Synthesis, and Recyclability. To examine the compatibility of the protocol, an array of 2,2-disubstituted 1,3-cyclopentanedione substrates were investigated (Table 5). The substrates

Table 5. Substrate Scope for 1,3-Cyclopentanediones[a]

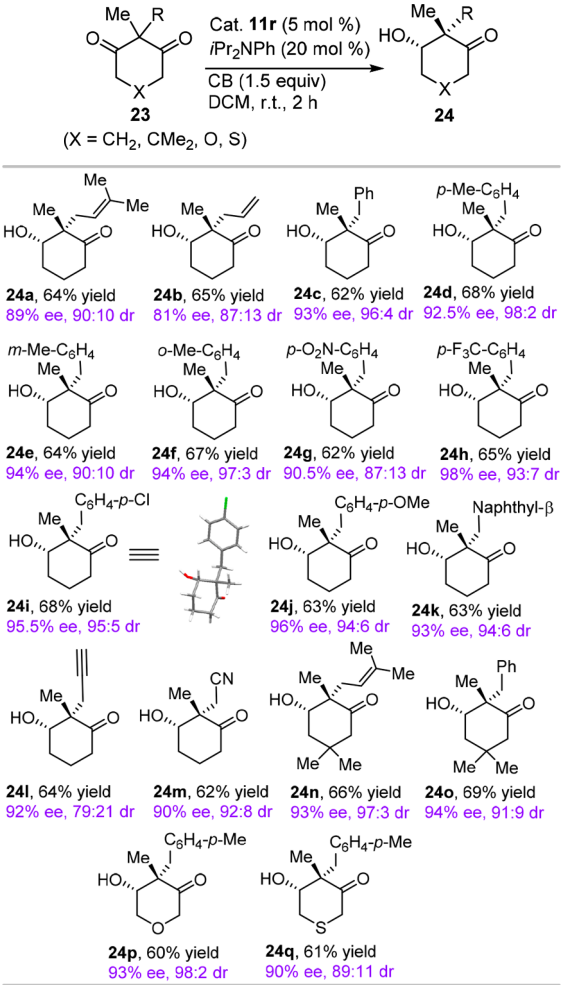


[a]Conditions: **17** (0.5 mmol), CB (1.5 equiv), catalyst (5 mol %), and iPr$_2$NPh (20 mol %) in 1 mL of anhydrous DCM at room temperature for 2 h. The yields were isolated yields, the ee% and dr were determined by chiral HPLC (the ee% and dr for **18a**, **18b**, **18l**, **18m**, and **18n** were determined by converting the products into the corresponding *p*-nitrobenzoyl ester).

substituted with allyl groups were viable substrates, affording the products in excellent enantioselectivities as well as diastereoselectivities (**18a** and **18b**). In addition, various substrates with aryl substituents were also well tolerated. Satisfactory yields as well as high to excellent enantio- and diastereoselectivities were obtained no matter whether the aryl group was undecorated or decorated by electron-donating as well as electron-withdrawing groups at different position on the benzene ring (**18c**–**18k**). Importantly, the alkynyl and cyano functionalities were also compatible (**18l**–**18n**). Finally, the method could also be extended to the disubstituted indandiones, giving the desired products in high yields and excellent enantio- and diastereoselectivities (**18o** and **18p**). Thus, we have successfully developed an efficient and generally applicable organocatalyst for the desymmetric enantioselective reduction of 2,2-disubstituted 1,3-cyclopentanediones. The absolute configuration of the products was *S*,*S* as determined from the known compounds **18a** and **18b**. Moreover, this protocol also provides a complementary way for the efficient and versatile synthesis of the diastereoisomers to Zhang's Ir-catalyzed[2] and Zhou's Pd-catalyzed[17] hydrogenation, which afforded *R*,*R* and *S*,*R* stereoisomers, respectively.

To further demonstrate the broad applicability of the method, we extended the reaction to the six-membered 2,2-disubstituted 1,3-diketones. Prior literature[2] showed that, compared with the five-membered 1,3-cyclodiketones, the desymmetric enantioselective reduction of the six-membered 1,3-cyclodiketones was much more challenging and has rarely been investigated. To the best of our knowledge, only very few methods using transition-metal-catalyzed hydrogenative desymmetrization have been reported.[18] Herein, by employing our standard conditions, we examined a broad variety of 2,2-disubstituted and 2,2,5,5-tetrasubstituted 1,3-cyclohexanedione derivatives, as well as the 4,4-disubstituted six-membered 3,5-cyclodiketones containing heteroatoms (**23**) (Table 6). The method exhibited broad compatibility with various functional groups, such as allyl (**24a**, **24b**, and **24n**), benzyl (**24c**–**24k**, and **24o**), alkynyl (**24l**), and cyano (**24m**) groups. High to excellent enantioselectivities as well as diastereoselectivities were observed for a wide range of the products, except for **24b**

Table 6. Substrate Scope for 1,3-Cyclohexanediones[a]



[a]Conditions: **23** (0.5 mmol), CB (1.5 equiv), catalyst (5 mol %), and iPr$_2$NPh (20 mol %) in 1 mL of anhydrous DCM at room temperature for 2 h. The yields were isolated yields, and the ee% and dr were determined by chiral HPLC (the ee% and dr for **24a**, **24b**, **24l**, **24m**, and **24n** were determined by converting the products into the corresponding *p*-nitrobenzoyl ester).

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which was obtained with a slightly diminished ee (81%) and moderate dr (87:13). It is worth mentioning that, as an individual example reported in prior literature,[2] compound **24c** was also synthesized through Ir-catalyzed desymmetric enantioselective hydrogenation with 82% ee and 6:1 dr. In comparison, a much better outcome with up to 93% ee and 24:1 dr was afforded by employing our *P*-stereogenic organocatalyst. Also noteworthy, substrates containing heteroatoms were also viable, giving the desired products in satisfactory yields and high stereoselectivity (**24p** and **24q**). These overall results demonstrated that the protocol could also be extensively used for the desymmetric enantioselective reduction of six-membered cyclodiketones. The absolute configuration of the products was *S*,*S* as assigned based on the X-ray single crystal diffraction of **24i** (CCDC 2044061).

Having demonstrated the substrate scope of the method, we then investigated the practicality by conducting gram scale syntheses and examining the recyclability of recovered catalyst, respectively (Figure 4). Happily, the reactions could be reliably

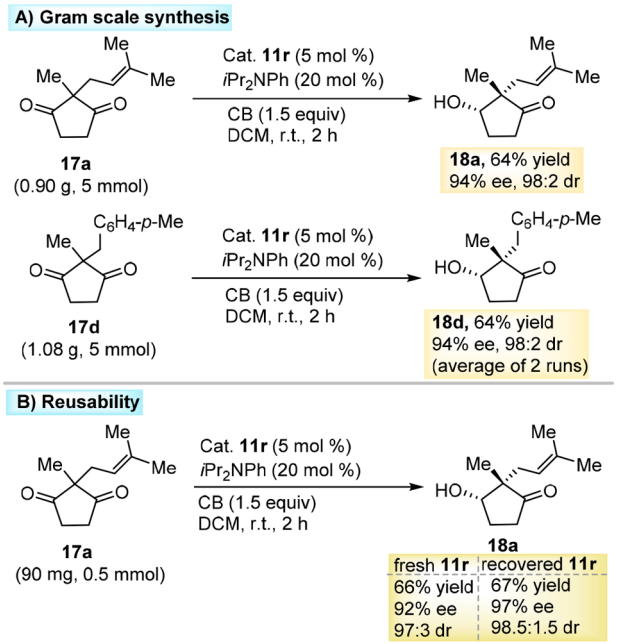

Figure 4. Gram scale reaction (A) and recyclability (B).

performed on the gram scale and exhibited excellent reproducibility as seen from the two representative reactions (**18a** and **18d**) (Figure 4A). Notably, unlike the CBS reduction which usually requires slow addition of the reductants or substrates, the reaction catalyzed by *P*-stereogenic phosphinamide was carried out by adding all the substances in one portion, allowing for a much more convenient operation. Most importantly, it was demonstrated that the catalyst could be readily recovered in >90% yield by simple column chromatography and reused with entirely retained catalytic efficiency to compare with the freshly prepared catalyst (Figure 4B).

Mechanistic Study. To understand the reaction mechanism of the protocol, we sought to identify the possible reaction intermediates by monitoring the detailed reaction course using ^{1}H, ^{31}P, and ^{11}B NMR spectroscopies. More to the point, this study would also set an important basis for designing other asymmetric reactions catalyzed by *P*-stereogenic catalysts. The NMR monitoring studies were carried out using **11r** as catalyst, iPr$_2$NPh (**A$_1$**) as additive, catecholborane (CB) as reductant, and 2-methyl-2-(4-methylbenzyl)-1,3-cyclopentanedione **17d** as substrate in CD_2Cl_2 solvent at ambient temperature. For a 1:1 mixture of catalyst **11r** and CB, the ^{1}H (Figure S1) and ^{31}P NMR (Figure 5) spectra showed

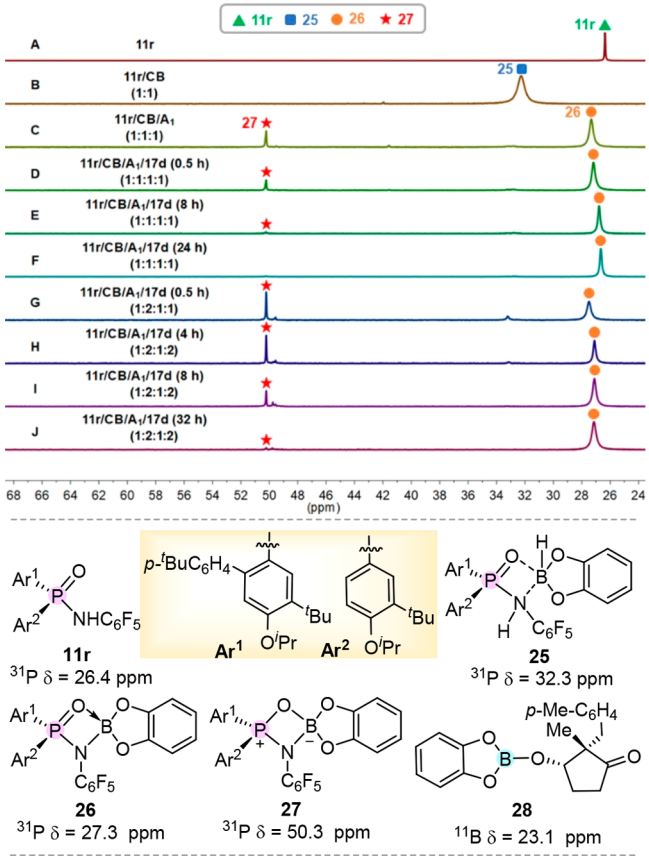

Figure 5. Mechanistic investigation: The ^{31}P NMR spectra in CD_2Cl_2 (upper) and the structures of possible intermediates (lower).

that resonance signals of the proton of NH and phosphorus for catalyst **11r** shifted apparently toward the downfield region from 4.63 to 5.16 ppm (Figure S1, A vs B) and 26.4 to 32.3 ppm (Figure 5, A vs B), respectively, to compare with those of the free catalyst **11r**. Associated with these changes, the peak of boron for CB in the ^{11}B NMR spectrum became broad and shifted upfield from ca. 29.0 to 15.0 ppm (Figure S2, A vs B). These observations imply that a complex **25** should be formed from the Lewis basic **11r** and acidic CB. Control experiments revealed that this complex should not be the catalytically active species since the reduction reaction proceeded very slowly under this system without amine additive.

In stark contrast, remarkable changes were observed when **11r**, CB, and ^{i}Pr$_2$NPh (**A$_1$**) were mixed in a 1:1:1 ratio. Specifically, the proton of NH for **11r** almost disappeared and the protons of CH on both the isopropyl groups for **11r** and **A$_1$** were split into two sets of peaks as seen from the ^{1}H NMR spectrum (Figure S1, A–C vs D and E); in the ^{31}P NMR spectrum, two peaks were observed, one of which shifted upfield to 27.3 ppm and the other moved largely downfield to 50.3 ppm (Figure 5, C vs B); in line with the changes of ^{1}H and ^{31}P NMR spectra, two peaks at 14.2 and 8.1 ppm appeared in the ^{11}B NMR spectrum (Figure S2, B vs C). The spectroscopic data suggest that a couple of species correspond-

https://dx.doi.org/10.1021/jacs.1c00277
J. Am. Chem. Soc. 2021, 143, 2994–3002

ing to boraphosphinimidate **26** and boraphosphonium **27** should be formed from **11r** and **CB** by extrusion of a molecule of H_2 under the assistance of $\mathbf{A_1}$ base, which may then interact with $\mathbf{A_1}$ through Lewis base-acid coordination. More interestingly, upon adding 1 equiv of 1,3-cyclopentanedione **17d** to the 1:1:1 mixture composed of **11r**/CB/$\mathbf{A_1}$, forming a 1:1:1:1 mixture of **11r**/CB/$\mathbf{A_1}$/**17d**, the peak at 50.3 ppm corresponding to **27** decreased gradually with the prolongation of standing time and eventually disappeared (Figure 5, D–F). Correlated with this variation, the intensity of the peak at 27.3 ppm increased gradually and shifted very slightly upfield to 26.8 ppm. These spectroscopic variations should result rationally from the coordination effect between **26** and diketone **17d**, which in turn may act as the driving force to promote the interconversion of boraphosphinimidate **27** into **26**.

The above assumption was strongly supported by the results obtained from the reduction of diketone **17d** with CB. Namely, upon adding the 2nd equiv of CB to the above 1:1:1:1 mixture composed of **11r**/CB/$\mathbf{A_1}$/**17d**, providing a mixture of **11r**/CB/$\mathbf{A_1}$/**17d** in 1:2:1:1 ratio, the peak at 50.33 ppm corresponding to **27** reappeared rapidly within 30 min (Figure 5, G), indicating the reducing reaction proceeded quickly; meanwhile, in the ^{11}B NMR spectrum (Figure S2, E), a new peak at 23.1 ppm was observed which could be assigned to the borate **28** produced from the product **18d** and CB. The spectroscopic data clearly indicated that accompanied by the consumption of diketone **17d**, boraphosphinimidate **26** was regenerated which then interconverted into a pair of equilibrium intermediates **26** and **27**, and ultimately, completing the first catalytic cycle. The NMR monitoring experiments revealed that **26** and **27** were catalytically active and promoted the desymmetric reduction of diketone **17d**.

Coincidently with the profile of the NMR changes as seen in the first catalytic cycle, subsequent addition of the second equivalent of diketone **17d** to the above reaction mixture (the final ratio of **11r**/CB/$\mathbf{A_1}$/**17d** = 1:2:1:2) again resulted in a gradual decrease of the ^{31}P peak at 50.3 ppm corresponding to **27** until it almost disappeared; synchronously, a gradual increase of the intensity associated with a slight upfield shift of the peak corresponding to **26** at 27.3 ppm was observed (Figure 5, H–J). These observations suggested that the reaction entered into the next catalytic cycle upon the addition of the 2nd equiv of diketone **17d**. In the end, product **18d** was obtained from the NMR monitoring experiments and displayed high enantioselectivity with 84% ee, indicating apparently that the reaction proceeded in a highly stereoselective manner during the course of NMR monitoring.

Thus, on the basis of the extensive NMR tracking experiments, we could propose a plausible reaction mechanism (Figure 6). The *P*-stereogenic phosphinamide catalyst forms complex **A** with CB which is then transformed to boraphosphinimidate **B** by extrusion of a molecule of H_2 under the assistance of the $^{i}Pr_2NPh$ base. Tautomerization of **B** produces boraphosphonium **C** which exists with **B** as a couple of equilibrium intermediates. Acting as a bifunctional catalytically active species, the intermediate **B** then coordinates with diketone **17** or **23** to preferentially form the sterically favored **D** over the disfavored **E**. Successively, the Lewis basic site of **D** bonds with Lewis acidic CB to afford the complex **F**. As a result, both diketone and CB are activated through coordination interactions with **B**. Finally, face-selective hydride transfer from CB to diketone regenerates the boraphosphinimidate **B** and delivers borate **G**. Finally, **B** brings the desymmetric enantioselective reduction into the next cycle. As has been demonstrated by the control experiments and NMR monitoring experiments, the stereochemistry of the reaction is predominantly controlled by this catalytic cycle. Alternatively, a small part of borate **G** is over-reduced by a self-mediated kinetic resolution reduction, which makes a minor, yet non-negligible contribution to improve the stereoselectivity of the final products **18** and **24**.

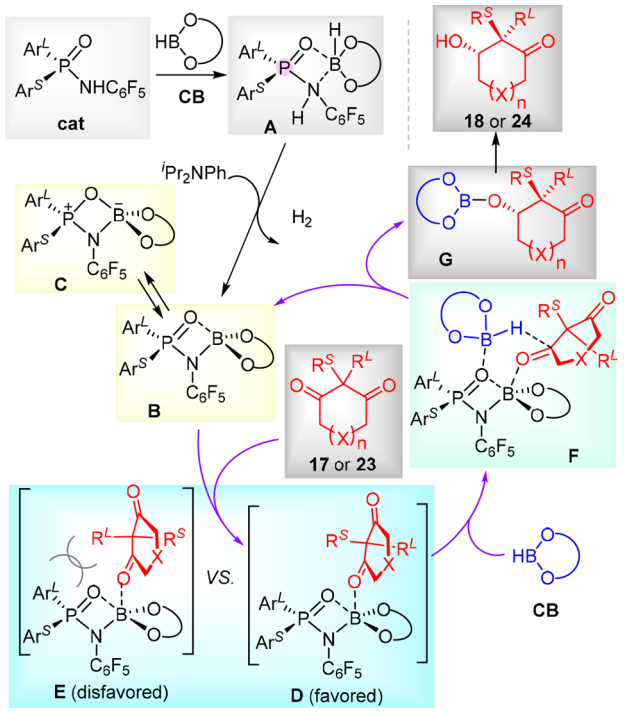

Figure 6. Proposed reaction mechanism.

CONCLUSIONS

In summary, through a patient and thorough investigation, we have developed an efficient and practical protocol for the desymmetric enantioselective reduction of 2,2-disubstituted 1,3-cyclodiketones using the *P*-stereogenic phoshphinamides as a type of novel organocatalyst. This protocol is highlighted by a number of indisputable advantages compared with the reported methods as listed below: (i) it displays a wide substrate scope that works well with both five- and six-membered substrates. High to excellent enantio- and diastereoselectivity are obtained for a series of substrates of both types; (ii) the reaction could be reliably performed on the gram scale and easily operated by adding all substances in one portion; and (iii) most importantly, the catalysts could be readily recovered and reused without losing the catalytic efficiency. These advantages render the current protocol to have great potential for practical application. Also significantly, the identification of the intermediates **B** and **C** derived from *P*-stereogenic phoshpinamide and catecholborane (CB) as the bifunctional catalytic active intermediates should have further implications beyond this work for the de novo design of other relevant asymmetric reactions. These works are currently underway in our laboratory.

https://dx.doi.org/10.1021/jacs.1c00277
J. Am. Chem. Soc. 2021, 143, 2994–3002

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c00277.

Detailed procedures for the optimization of reaction conditions; the preparation of amine additives, *P*-stereogenic catalysts, and 1,3-diketone substrates; the desymmetric enantioselective reduction of 1,3-diketones; chemical compound information including NMR and HRMS data and copies of NMR spectra for all compounds; ^{1}H and ^{11}B NMR spectra for mechanistic study; single X-ray crystal data of **24i** (CIF); and HPLC charts of chiral catalysts and cyclic 3-hydroxy ketone products (PDF)

Accession Codes

CCDC 2044061 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, U.K.; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

Fu-She Han − *CAS Key Lab of High-Performance Synthetic Rubber and its Composite Materials, Changchun Institute of Applied Chemistry, Chinese Academy of Sciences, Changchun, Jilin 130022, P. R. China; University of Science and Technology of China, Hefei, Anhui 230026, P. R. China;* orcid.org/0000-0003-0456-7461; Email: fshan@ciac.ac.cn

Authors

Xu-Long Qin − *CAS Key Lab of High-Performance Synthetic Rubber and its Composite Materials, Changchun Institute of Applied Chemistry, Chinese Academy of Sciences, Changchun, Jilin 130022, P. R. China; University of Science and Technology of China, Hefei, Anhui 230026, P. R. China*

Ang Li − *CAS Key Lab of High-Performance Synthetic Rubber and its Composite Materials, Changchun Institute of Applied Chemistry, Chinese Academy of Sciences, Changchun, Jilin 130022, P. R. China; University of Science and Technology of China, Hefei, Anhui 230026, P. R. China*

Complete contact information is available at: https://pubs.acs.org/10.1021/jacs.1c00277

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from National Natural Science Foundation of China (22071235) is acknowledged.

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