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Communication

Borane-Catalyzed Direct Asymmetric Vinylogous Mannich Reactions of Acyclic α,β-Unsaturated Ketones

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Cite This: J. Am. Chem. Soc. 2021, 143, 3054−3059
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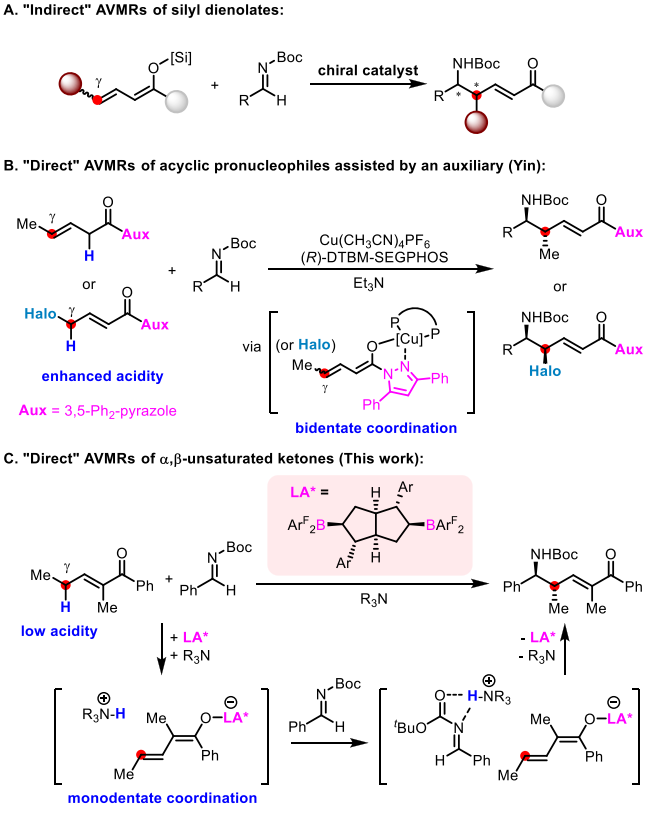
ABSTRACT: Herein, we report that, by using chiral bicyclic bisborane catalysts, we have achieved the first highly regio-, diastereo-, and enantioselective direct asymmetric vinylogous Mannich reactions of acyclic α,β-unsaturated ketones. The strong Lewis acidity and steric bulk of the bisborane catalysts were essential for the observed high yields and selectivities.

Asymmetric vinylogous Mannich reactions (AVMRs) of α,β-unsaturated carbonyl compounds provide efficient access to optically active amino-functionalized derivatives, which are useful building blocks for natural product synthesis.[1] However, the low acidity of the γ proton of the starting carbonyl compound has led to the development of many protocols for "indirect" AVMRs (Scheme 1A) in which the carbonyl compound is first converted to a silyl dienolate by reaction with a silyl donor (e.g., TMSCl or TMSOTf) and a strong base (e.g., LDA or KHMDS), and the silyl dienolate serves as the nucleophile in the AVMR.[1,2] Despite the progress achieved with this workaround, the preparation of the silyl-protected nucleophile is an additional step and usually generates an inseparable mixture of *E* and *Z* isomers,[3] which limits the attractiveness of this method. In contrast, "direct" AVMRs, in which a vinylogous nucleophile is formed in situ by reaction of an unsaturated compound and a base, are atom-economical and more convenient. However, to date, the pronucleophiles used for direct AVMR have been confined mostly to cyclic compounds, such as α,β-unsaturated γ-butenolides,[4] γ-butyrolactams,[5] and cyclic α,α-dicyanoalkenes,[6] because the γ protons of these compounds are relatively acidic, and their rigid cyclic skeletons are considered to be crucial for controlling the regiochemistry (reaction at the α or γ carbon) and stereochemistry. Controlling the selectivity of the reactions of acyclic pronucleophiles is much more challenging.

In a recent breakthrough, the Yin group achieved highly regio-, diastereo-, and enantioselective direct AVMRs of acyclic β,γ-unsaturated *N*-acylpyrazoles and γ-halogenated α,β-unsaturated *N*-acylpyrazoles by using a chiral Cu(I)/diphosphine complex as a catalyst and triethylamine as a base (Scheme 1B).[7] Enhancement of the acidity of the C−H bond by either the adjacent carbonyl group or the halogen atom facilitates base-mediated deprotonation. Moreover, the pyrazole auxiliary is considered to be essential for selectivity, not only because its steric bulk inhibits reaction at the α position but also because the group functions as a bidentate auxiliary ligand for the copper catalyst, forming a complex that decreases the conformational flexibility of the acyclic compound. There have been only a few other successful examples of direct AVMRs of acyclic pronucleophiles.[8]

Scheme 1. Asymmetric Vinylogous Mannich Reactions of Acyclic Dienolates



Received: January 1, 2021
Published: February 11, 2021

https://dx.doi.org/10.1021/jacs.1c00006
J. Am. Chem. Soc. 2021, 143, 3054−3059

In comparison to β,γ-unsaturated carbonyls whose deprotonation was relatively easy to achieve by using organocatalysts[9] or soft Lewis acid/Brønsted base catalysts,[7c,10] a strong Lewis acid catalyst would be preferable for unactivated α,β-unsaturated carbonyls. Theoretically, coordination of the carbonyl oxygen with a strong Lewis acid catalyst would facilitate deprotonation by inductively increasing the acidity of the γ proton and thus favor enolization of the substrate.[11]

However, strong Lewis acids are more prone to being quenched by the bases. We reasoned that this problem could potentially be circumvented by using a frustrated Lewis pair,[12] in which quenching of a Lewis acid by a Lewis base is prohibited by steric hindrance. The most commonly used Lewis acids in such pairs are fluoroaryl-substituted boranes because of their strong acidity and sterically hindered boron center. In principle, the properties of these boranes make them ideally suited for use as AVMR catalysts. Indeed, in mechanistically relevant chemistry, the combination of a fluoroaryl-substituted borane with an amine has been used to promote ketone enolization for various addition reactions at the α position.[13]

Recently, our group developed a series of chiral bicyclic bisborane catalysts for asymmetric reductions,[14] and extending the use of these catalysts to reactions other than reductions has been a goal of our research program. Herein, we report that by combining these boranes with a tertiary amine, we were able to accomplish direct AVMRs of α,β-unsaturated ketones with Boc-protected imines with excellent regio-, diastereo-, and enantioselectivities (Scheme 1C). In these reactions, the Lewis acid catalyst and the base cooperatively deprotonated the substrate to generate a borane-ligated vinylogous dienolate and an ammonium cation, which then presumably served as a Brønsted acid to activate the imine while the borane controlled the selectivity of the Mannich reaction. Notably, these reactions directly used monodentate substrates rather than substrates containing an auxiliary, which simplified the procedures. Furthermore, this is the first time that direct AVMRs of acyclic α,β-unsaturated ketones have been achieved.

We began by testing conditions for direct VMR of α,β-unsaturated ketone **1a** with aldimine **2a** (Figure 1A). Initially, we screened combinations of Et_3N (**B1**, 20 mol %) and a number of achiral borane Lewis acids (10 mol %) whose Lewis acidities were determined by means of the Gutmann–Beckett method.[15] The Lewis acidities of these boranes decreased in the order $B(3,4,5\text{-}F_3C_6H_2)_3$ (**LA1**) > $B(C_6F_5)_3$ (**LA2**) > $PhC_2H_4B(C_6F_5)_2$ (**LA3**) > $B(2,4,6\text{-}F_3C_6H_2)_3$ (**LA4**) > BPh_3 (**LA5**), as indicated by their acceptor numbers (ANs), which are a quantitative measure of Lewis acidity. The strong Lewis acids **LA1** and **LA2** showed excellent activity (87% yield and 91% yield, respectively). **LA3** was moderately active, affording **3a** in 47% yield with a 3.2/1 diastereomeric ratio (dr). **LA4** was poorly active while **LA5** was inactive.

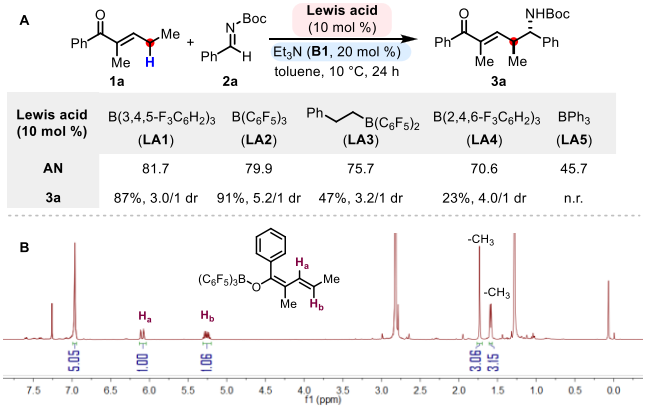
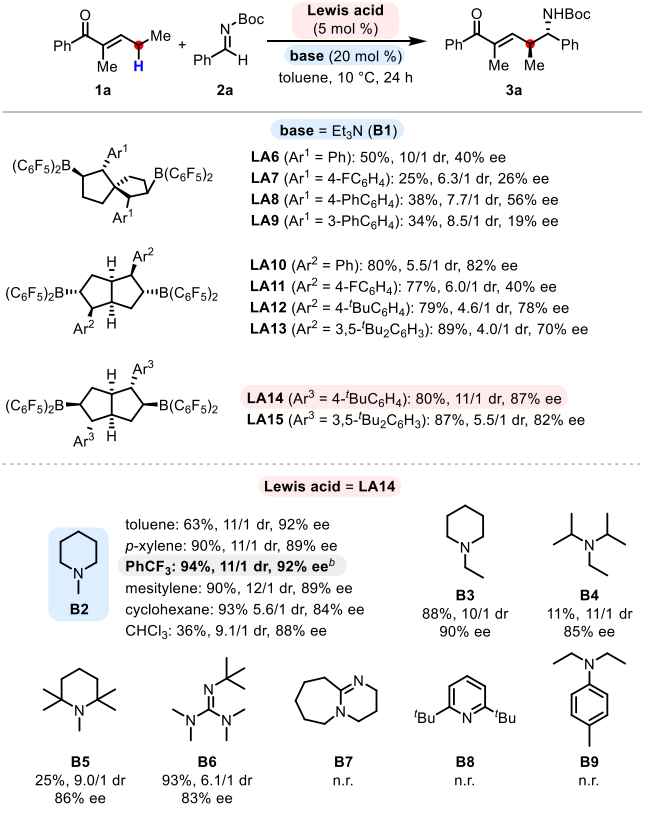


Figure 1. (A) Screening of achiral Lewis acids. (B) ^{1}H NMR spectrum of a mixture of **1a** (1 equiv), $B(C_6F_5)_3$ (1 equiv), and Barton's base (2 equiv).

We used NMR spectroscopy to elucidate the dienoate formation process. Addition of Barton's base (2-*tert*-butyl-1,1,3,3-tetramethylguanidine, 2 equiv)[16] to the mixture of **1a** and $B(C_6F_5)_3$ produced two new olefinic proton signals, one at δ 6.09 (H_a, dd, J = 15.3, 1.5 Hz) and one at δ 5.27 (H_b, dq, J = 15.3, 6.6 Hz) (Figure 1B). The H_a–H_b coupling constant of 15.3 Hz and a 2D-NOESY experiment[17] suggest the formation of an (*E*, *E*)-dienolate. In addition, mixing **1a** with Barton's base in the absence of $B(C_6F_5)_3$ did not result in dienolate formation. These experiments clearly demonstrate that a strongly Lewis acidic borane and an organic base could efficiently promote dienolate formation.

These results, particularly that of **LA3**, whose Lewis acidity should be similar to chiral boranes $R\text{–}B(C_6F_5)_2$, encouraged us to test chiral boranes in the hopes of achieving enantioselective reactions (Table 1). Spirobicyclic bisboranes[14b] **LA6**–**LA9** (5 mol %) exhibited moderate activity and enantioselectivity (up to 56% ee). Fused bicyclic bisboranes[14c] generated by hydroboration of the corresponding diene with $HB(C_6F_5)_2$ at 25 °C were also tested. Phenyl-substituted catalyst **LA10** provided **3a** in 80% yield with 5.5/1 dr and 82% ee, whereas 4-

Table 1. Optimization of Reaction Conditions[a]



[a]Unless otherwise specified, all reactions were performed with 0.2 mmol of **1a** and 0.3 mmol of **2a** in 0.5 mL of toluene under N_2. NMR yields are provided. [b]Used 1 mL of $PhCF_3$.

https://dx.doi.org/10.1021/jacs.1c00006
J. Am. Chem. Soc. 2021, 143, 3054–3059

fluorophenyl-, 4-*tert*-butylphenyl-, and 3,5-di-*tert*-butylphenyl-substituted catalysts (**LA11**−**LA13**, respectively) gave lower enantioselectivities. To our delight, bisborane **LA14** (a diastereomer of **LA12**), which was generated by hydroboration of the corresponding 4-*tert*-butylphenyl-substituted diene at 80 °C, gave a dr of 11/1 and an ee of 87%. Similarly, **LA15** showed better stereoselectivity than diastereomer **LA13** but was not as selective as **LA14**.

Using **LA14** as the Lewis acid, we screened various bases. When *N*-methylpiperidine (**B2**) was the base, reaction in toluene gave **3a** with an ee of 92%, but the yield decreased to 63%. *N*-Ethylpiperidine (**B3**) was more active but slightly less selective. Bulky amines (diisopropylethylamine [**B4**] and 1,2,2,6,6-pentamethylpiperidine [**B5**]) markedly reduced the yield and had a deleterious effect on the enantioselectivity. Barton's base (**B6**) increased the yield to 93% but decreased the ee to 83%. In contrast, DBU (**B7**) shut down the reaction completely, perhaps because of coordination of the imine to the borane catalyst. 2,6-Di-*tert*-butylpyridine (**B8**) and *N*,*N*-diethylaniline (**B9**) also did not give the desired product, probably because these bases were too weak to remove the γ proton. Similarly, in the absence of a base, the borane was unable to catalyze the reaction. To further optimize the reaction conditions, we tested the combination of **LA14** and **B2** in various solvents. *p*-Xylene, $PhCF_3$, mesitylene, and cyclohexane improved the yield to >90%, but only $PhCF_3$ maintained the high enantioselectivity (92% ee) that was observed in toluene. The polar solvent $CHCl_3$ was detrimental to both the yield and the stereoselectivity. Taken together, the results of our experiments indicated that the optimal reaction conditions involved the use of 5 mol % **LA14**, and 20 mol % **B2** in $PhCF_3$ at 10 °C (for optimization of reaction temperature, see the Supporting Information). Notably, the formation of the α-addition product was not observed at any point during the optimization of the conditions for reaction of **1a** with **2a**.

Next, we used imines **2a** and **2c** to investigate the scope of the reaction with respect to the α,β-unsaturated ketone (Table 2). First, we tested ketones with various substituted aryl groups connected to the carbonyl carbon. Compounds with an electron-donating group (e.g., methoxy) or an electron-withdrawing group (e.g., trifluoromethyl) at the *para*, *ortho*, or *meta* position of the phenyl ring were suitable, giving the desired products (**3b**−**3q**) in high isolated yields (82−98%) with excellent diastereoselectivity (>10/1 dr) and enantioselectivity (>90% ee). Substrates with a halogen atom (F, Cl, or Br; **3e**−**3g**, **3n**, and **3o**), an alkenyl group (**3i**), or an alkynyl group (**3j**) were well tolerated. Moreover, the phenyl ring could be replaced by a 2-thienyl (**3r**) or 5-benzofuranyl (**3s**) ring without decreasing the selectivities.

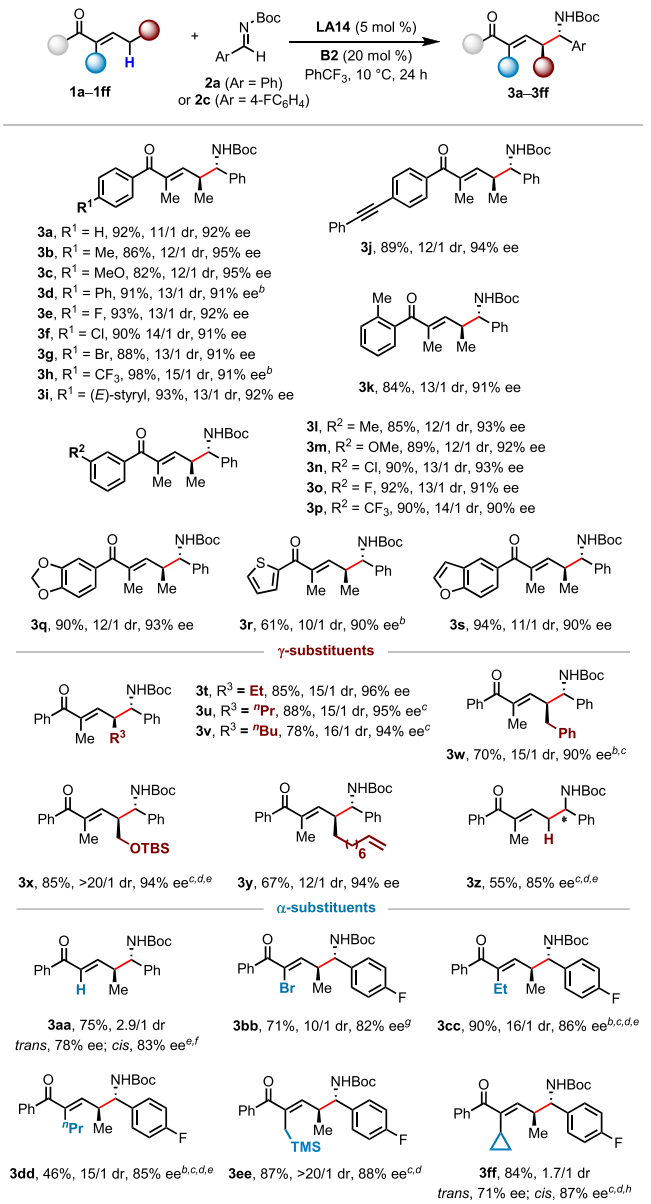
Subsequently, the γ methyl group was changed to ethyl (**3t**), *n*-propyl (**3u**), *n*-butyl (**3v**), or benzyl (**3w**) as well as to a linear alkyl group with a terminal OTBS (**3x**) or olefin (**3y**); the corresponding products were obtained in 67−88% yields with excellent diastereo- and enantioselectivities. However, when the γ carbon was unsubstituted (**3z**), both the yield and the enantioselectivity decreased (to 55% and 85% ee, respectively).

Substrates with various α substituents were studied as well. When there was no α substituent, the diastereoselectivity was poor (**3aa**, dr = 2.9/1), and the enantioselectivity was moderate (78% ee for the *trans* isomer, 83% ee for the *cis* isomer). In contrast, reactions of α-bromo (**3bb**), α-ethyl (**3cc**), α-*n*-propyl (**3dd**), and α-CH_2TMS (**3ee**) substrates provided high diastereoselectivities and 82−88% ee. The reaction of an α-cyclopropyl-substituted compound gave **3ff** with moderate diastereoselectivity and enantioselectivity.

It is worth mentioning that none of the α,β-unsaturated ketones shown in Table 2 gave any α-addition products. This result may be attributable to blocking of the α position by the bulky chiral bisborane. Furthermore, we also evaluated less acidic pronucleophiles, such as α,β-unsaturated esters and α,β-unsaturated amides, but they failed to give the corresponding products.[17]

Next, an array of aldimine electrophiles were studied in reactions with **1a** as the pronucleophile (Table 3). Electron-

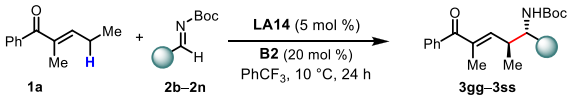
Table 2. Scope with Respect to the α,β-Unsaturated Ketone[a]

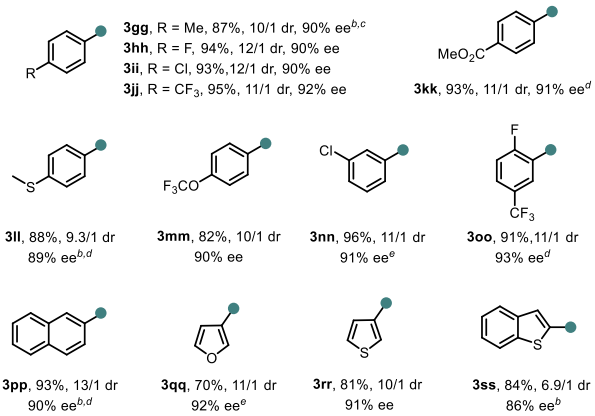


[a]Unless otherwise specified, all reactions were performed with 0.2 mmol of **1** and 0.3 mmol of **2** in 1 mL of $PhCF_3$ under N_2. Isolated yields are provided. [b]At 0 °C. [c]Used 0.4 mmol of **2**. [d]Used 10 mol % of **LA14** and 40 mol % of **B2**. [e]Used 1.5 mL of $PhCF_3$. [f]At −20 °C. [g]At −10 °C. [h]36 h.

https://dx.doi.org/10.1021/jacs.1c00006
J. Am. Chem. Soc. 2021, 143, 3054−3059

Table 3. Scope with Respect to the Imine[a]



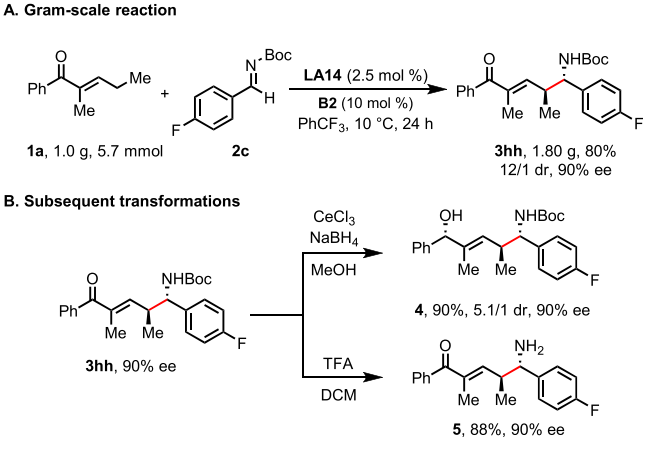


[a]Unless otherwise specified, all reactions were performed with 0.2 mmol of **1a** and 0.4 mmol of **2** in 1 mL of $PhCF_3$ under N_2. Isolated yields are provided. [b]At −10 °C. [c]Used 2 mL of $PhCF_3$. [d]Used 1.5 mL of $PhCF_3$. [e]At 0 °C.

donating and electron-withdrawing groups on the phenyl rings were tolerated, and the corresponding products (**3gg**−**3oo**) were obtained in high yields with excellent dr and ee values. Notably, ester (**3kk**), methylthio (**3ll**), and trifluoromethoxy (**3mm**) functional groups had no effect on the yield or stereoselectivity. Furthermore, 2-naphthyl (**3pp**), 3-furyl (**3qq**), 3-thienyl (**3rr**), and 2-benzothienyl (**3ss**) moieties were compatible with the reaction conditions. In contrast, aliphatic imines were poorly reactive or completely unreactive.[17]

To demonstrate the utility of our AVMR protocol, we performed a gram-scale reaction of **1a** with **2c** in the presence of **LA14** (2.5 mol %) and **B2** (10 mol %), which afforded **3hh** in 80% yield with 12/1 dr and 90% ee (Scheme 2A). Subsequently, the major diastereomer of **3hh** was purified and subjected to two transformations (Scheme 2B). First, treatment with $NaBH_4$ and $CeCl_3$ reduced the carbonyl group to give allyl alcohol **4** in 90% yield with 5.1/1 dr and 90% ee; the olefin remained intact. Second, the Boc protecting group was removed easily by treatment with trifluoroacetic acid to afford chiral δ-amino-α,β-unsaturated ketone **5** in 88% yield with retention of the ee value.

Scheme 2. Synthetic Applications



In conclusion, we have developed the first protocol for direct AVMRs of acyclic α,β-unsaturated ketones. The protocol efficiently and atom-economically affords optically active δ-amino-α,β-unsaturated carbonyl derivatives. The strong Lewis acidity of the borane catalysts was crucial for deprotonation of the poorly acidic γ-C−H bond of the substrates by the tertiary amine, and the steric bulk and structural rigidity of the catalysts were pivotal for achieving selectivities. Currently, we are investigating other α,β-unsaturated carbonyl compounds and other electrophiles in borane-catalyzed asymmetric addition reactions to determine whether chiral borane catalysts can overcome the limitations of existing catalytic systems.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c00006.

Experimental procedures, characterization data for new compounds, NMR spectra, and HPLC traces (PDF)

Accession Codes

CCDC 2052961−2052962 and 2052994 contain 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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Author Contributions

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful for financial support from the National Natural Science Foundation of China (Nos. 91956106 and 21871147), the Natural Science Foundation of Tianjin (Nos. 20JCZDJC-

00720 and 20JCJQJC00030), the NCC Fund (No. NCC2020-PY10), and the Fundamental Research Funds for Central Universities (No. 2122018165). X.-C.W. thanks the Tencent Foundation for support via the Xplorer Prize. This paper is dedicated to the 100th anniversary of Chemistry at Nankai University.

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