JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

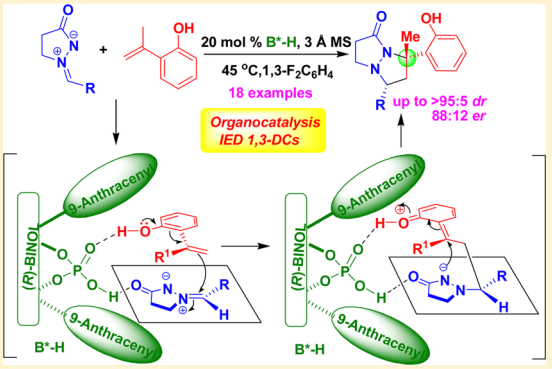
Organocatalytic Asymmetric Inverse-Electron-Demand 1,3-Dipolar Cycloaddition of *N,N′*-Cyclic Azomethine Imines

Ren-Yi Zhu, Cong-Shuai Wang, Jian Zheng, Feng Shi,* and Shu-Jiang Tu

School of Chemistry & Chemical Engineering, and Jiangsu Key Laboratory of Green Synthetic Chemistry for Functional Materials, Jiangsu Normal University, Xuzhou, 221116, China

Supporting Information

ABSTRACT: The first organocatalytic asymmetric inverse-electron-demand 1,3-dipolar cycloaddition (IED 1,3-DC) of *N,N′*-cyclic azomethine imines has been established in the presence of chiral phosphoric acid. This approach assembles *N,N′*-cyclic azomethine imines and *o*-hydroxystyrenes into chiral *N,N*-bicyclic pyrazolidin-3-one derivatives with the creation of two stereogenic centers, one of which is quaternary, in excellent diastereoselectivities and good enantioselectivities (up to >95:5 dr, 88:12 er). The investigation of the activation mode of the reaction revealed that the dual hydrogen-bonding interaction between the two substrates and the catalyst together with the conjugative effect initiated by the *o*-hydroxyl group played a crucial role in the designed IED 1,3-DC. This study will not only greatly enrich the underdeveloped research potential of catalytic asymmetric IED 1,3-DCs but will also facilitate the design of other enantioselective IED 1,3-DCs based on different activation modes.



INTRODUCTION

1,3-Dipolar cycloadditions (1,3-DCs) have proven to be a class of robust methods to synthesize five-membered heterocycles.[1] Among them, 1,3-DCs of *N,N′*-cyclic azomethine imines[2−5] have emerged as powerful tools to access *N,N*-bicyclic pyrazolidin-3-one derivatives, which possess significant bioactivities[6] such as antibiotic[6a] and herbicidal[6b] and are inhibitors of acetyl-CoA carboxylase[6c] and sarco(endo)plasmic reticulum Ca^{2+}-ATPase[6d] (Figure 1).

As a result, much attention has been paid to the catalytic asymmetric 1,3-DCs of *N,N′*-cyclic azomethine imines[2,3] to construct optically pure *N,N*-bicyclic pyrazolidin-3-one frameworks due to the promising bioactivities of chiral heterocycles.

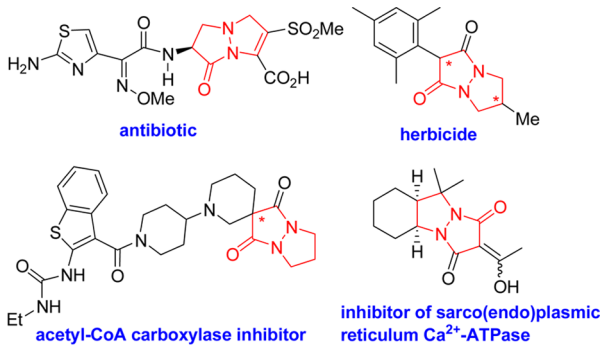
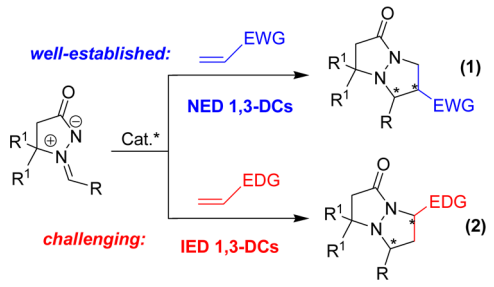


Figure 1. Some biologically important *N,N*-bicyclic pyrazolidin-3-one derivatives.

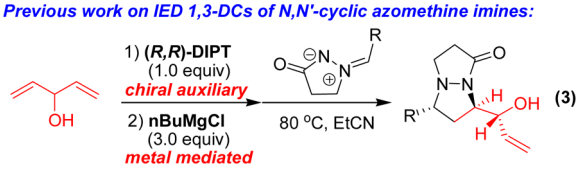
However, the established enantioselective transformations mainly focused on normal-electron-demand (NED) 1,3-DCs of *N,N′*-cyclic azomethine imines with electron-deficient alkenes in the presence of chiral metal-based catalysts[2c,d,g] or organocatalysts[3] (eq 1). *In sharp contrast, inverse-electron-demand (IED) 1,3-DCs of such 1,3-dipoles with electron-rich alkenes have met with little success* (eq 2).[4] In fact, IED 1,3-DCs are far underdeveloped compared with well-established NED 1,3-DCs because the dominant frontier molecular orbital (FMO) interaction in IED 1,3-DCs is between the HOMO of alkenes and the LUMO of dipoles, which is quite opposite to that of NED 1,3-DCs.[1f,7] So, developing catalytic asymmetric IED 1,3-DCs of *N,N′*-cyclic azomethine imines with electron-rich alkenes is highly desirable but full of challenge.



Received: August 10, 2014
Published: September 10, 2014

dx.doi.org/10.1021/jo5018469 | J. Org. Chem. 2014, 79, 9305−9312

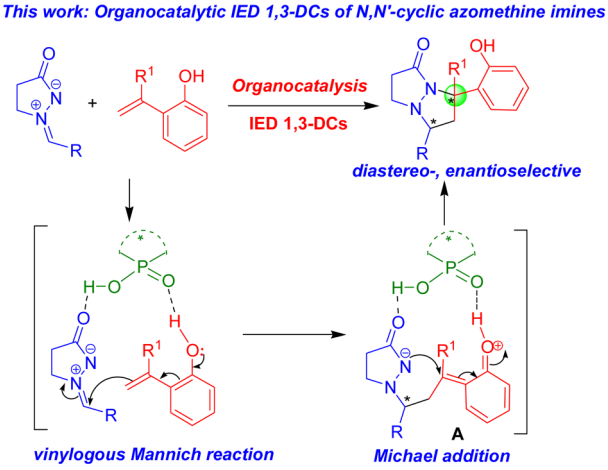
Ukaji and co-workers recently developed an asymmetric IED 1,3-DC of *N,N′*-cyclic azomethine imines with allylic alcohols via a magnesium-mediated, multinucleating chiral reaction system using diisopropyl (*R,R*)-tartrate [(*R,R*)-DIPT] as the chiral auxiliary (eq 3).[4d] Despite this elegant work, the catalytic



asymmetric IED 1,3-DCs of *N,N′*-cyclic azomethine imines with electron-rich olefins, especially those employing organocatalysts, are still unknown and in great demand due to the significant advantages of asymmetric organocatalysis in synthesizing chiral pharmaceuticals.[8]

Considering the challenge in catalytic asymmetric IED 1,3-DCs of *N,N′*-cyclic azomethine imines with electron-rich olefins, we decided to design an organocatalytic asymmetric IED 1,3-DC of this type of 1,3-dipole with styrenes. Chiral phosphoric acids (CPAs) belong to a class of privileged organocatalysts, which have enabled a variety of enantioselective transformations.[9] Our previous attempts on CPA-catalyzed tandem reactions revealed that the dual activation of CPA on both of the substrates or intermediates via hydrogen-bonding interaction played a crucial role in enantioselective control.[10] So, we envisage that the introduction of a hydroxyl group as an electron-donating group in the styrene moiety will not only increase the nucleophilicity of the vinyl group but will also form a hydrogen bond with CPA, which will benefit the desired enantioselective IED 1,3-DCs. As illustrated in Scheme 1, the two substrates of *N,N′*-cyclic

Scheme 1. Design of Organocatalytic Asymmetric IED 1,3-DCs of *N,N′*-Cyclic Azomethine Imines



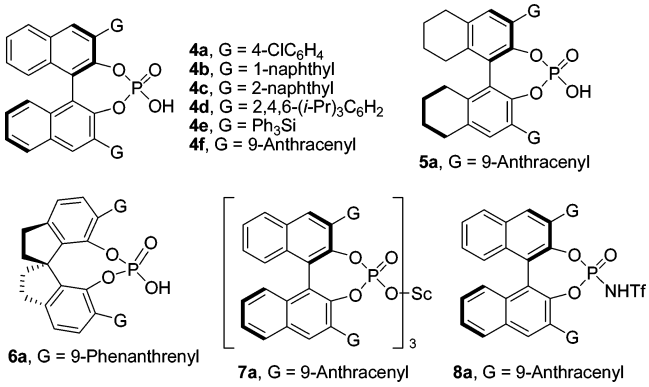
azomethine imines and *o*-hydroxystyrenes[11] would be principally activated by CPA through dual hydrogen bonds to undergo an asymmetric vinylogous Mannich reaction. Then the transient intermediate **A** would further undergo an intramolecular Michael addition to generate the diastereo- and enantioselective cycloaddition products.

We report herein the first organocatalytic asymmetric IED 1,3-DC of *N,N′*-cyclic azomethine imines, which directly assembles this type of 1,3-dipole and *o*-hydroxystyrene into chiral *N,N*-bicyclic pyrazolidin-3-one derivatives with creation of two stereogenic centers, one of which is quaternary, in good diastereo- and enantioselectivities (up to >95:5 dr, 88:12 er).

RESULTS AND DISCUSSION

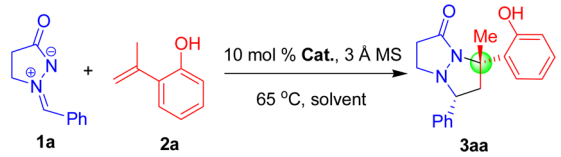
The initial experiment to test our hypothesis commenced with the reaction of *N,N′*-cyclic azomethine imine **1a** with *o*-hydroxystyrene **2a** catalyzed by a variety of CPAs **4a–f** (Scheme 2) in 1,2-dichloroethane (DCE) at 65 °C (Table 1,

Scheme 2. Chiral Catalysts Employed in the Model Reaction



entries 1–6). However, the preliminary results were very unsatisfactory. As shown in entries 1–6, the yields of the desired cycloaddition product **3aa** were poor even after reacting for 48 h, and CPA **4e** only gave a trace amount of the product

Table 1. Screening of Catalysts and Solvents[a]



entry	solvent	cat.	yield (%)[b]	er[c]
1	DCE	**4a**	34	52:48
2	DCE	**4b**	28	58:42
3	DCE	**4c**	32	50:50
4	DCE	**4d**	24	58:42
5	DCE	**4e**	trace	–
6	DCE	**4f**	30	60:40
7	$CHCl_3$	**4f**	30	53:47
8	THF	**4f**	trace	–
9	CH_3CN	**4f**	trace	–
10	ClC_6H_5	**4f**	18	57:43
11	FC_6H_5	**4f**	33	73:27
12	FC_6H_5	**5a**	26	72:28
13	FC_6H_5	**6a**	trace	–
14	$1,2\text{-}F_2C_6H_4$	**4f**	23	64:36
15	$1,3\text{-}F_2C_6H_4$	**4f**	33	77:23
16	$1,4\text{-}F_2C_6H_4$	**4f**	17	76:24
17	2-F-1-MeC_6H_4	**4f**	13	76:24
18	3-F-1-MeC_6H_4	**4f**	17	74:26

[a]Unless indicated otherwise, the reaction was carried out in 0.1 mmol scale in a solvent (1 mL) with 3 Å MS (100 mg) at 65 °C for 48 h, and the mole ratio of **1a**:**2a** was 1:1.2. [b]Isolated yield, and a single diastereomer was observed unless indicated otherwise. [c]The enantiomeric ratio (er) was determined by HPLC.

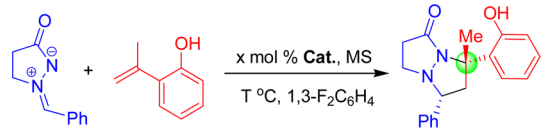
dx.doi.org/10.1021/jo5018469 | J. Org. Chem. 2014, 79, 9305–9312

(entry 5). Moreover, the enantioselectivities of these cases were also very low (less than 60:40 er) although only one diastereomer was observed in all cases. These results indicated that the IED 1,3-DC of *N,N′*-cyclic azomethine imines was indeed a formidable task. Because CPA **4f** with bulky 3,3′-(9-anthracenyl) groups delivered the designed IED 1,3-DC in a relatively higher enantioselectivity of 60:40 er (entry 6), a subsequent evaluation of solvents was performed in the presence of this catalyst. As illustrated in entries 6−11, different types of solvents including haloalkanes, ether, nitrile, and aryl halides were utilized in the model reaction, which revealed that ether and nitrile could hardly facilitate the reaction (entries 8 and 9), while fluorobenzene offered the product **3aa** in the highest enantioselectivity of 73:27 er (entry 11). To further improve the yield and the enantioselectivity, CPAs **5a** and **6a** with a structurally more rigid H_8-BINOL or SPINOL[12] backbone (in Scheme 2) were employed in the reaction using fluorobenzene as a solvent (entries 12 and 13). Nevertheless, H_8-BINOL-derived CPA **5a** did not exhibit obvious superiority over its BINOL-derived counterpart **4f** (entry 12 vs 11), and spiro-CPA **6a** failed to catalyze the reaction (entry 13). Because of the good performance of fluorobenzene, we further screened a variety of fluorinated arenes (entries 14−18) and found that 1,3-difluorobenzene was the most suitable solvent for the reaction, affording the target product in the highest enantioselectivity of 77:23 er (entry 15).

After the screening of CPAs and solvents, the enantioselectivity of the model reaction was improved to a moderate level, but the yield was still low (Table 2, entry 1). For the aim to increase the yield, we also investigated the effect of some achiral Lewis acids as catalysts on the reaction, which disclosed that $Sc(OTf)_3$ and $GaBr_3$ could improve the yield of racemic product to a moderate level.[13] So, we tried to use chiral scandium phosphate **7a**[14] (in Scheme 2) as a catalyst for the reaction. However, the yield was not enhanced at all, and the enantioselectivity was decreased to some extent (entry 2 vs 1). Then, still under the catalysis of CPA **4f**, the molecular sieves (MS) were evaluated (entries 1, 3, 4).The 4 Å MS could improve the yield to 55% and enhance the enantioselectivity to 80:20 er (entry 3). Only a trace of the desired product was obtained in the absence of MS, and instead a dimer of substrate **1a** was formed in this case.[16] So, the role of MS in this reaction was to prevent homo-1,3-dipolar cycloadditions of *N,N′*-cyclic azomethine imines. The subsequent variation on the reaction temperature revealed that elevating the temperature greatly increased the yield but with a dramatically deteriorated enantioselectivity (entry 5), while lowering the temperature was detrimental to the yield albeit with a better enantioselectivity (entry 6). Considering the promising er value at 45 °C, the study on the catalyst loading was performed at this temperature (entries 6−9), which showed that 20 mol % CPA **4f** promoted the desired reaction in the highest yield of 43% and a considerable enantioselectivity of 87:13 er (entry 7). Although the stoichiometric reaction improved the enantioselectivity to the highest level of 90:10 er, the yield was still unsatisfactory (entry 9). Then, inspired by the concept of asymmetric binary acid catalysis,[15] we attempted to employ the combined catalytic system of chiral CPA **4f** and achiral Lewis acid $GaBr_3$ in the reaction, but no synergic effect was observed (entry 10 vs 7). Furthermore, chiral phosphoramide **8a** (in Scheme 2) with stronger acidity than CPA **4f** was also employed in the reaction, but it was unable to catalyze the reaction (entry 11). So, final optimization of conditions was focused on changing the mole ratio of the two reactants in the presence of 20 mol % catalyst **4f** (entries 7, 12−16). Obviously, increasing the stoichiometric ratio of substrate **2a** led to diminished enantioselectivities with almost unchanged yields (entries 12−14 vs 7). On the contrary, elevating the stoichiometric ratio of substrate **1a** resulted in greatly reduced yields (entries 15 and 16) because the dimer of substrate **1a** was easily generated in these cases.[16] On the basis of the above experiments, the relative optimal reaction condition was set as illustrated in entry 7, which realized the organocatalytic asymmetric IED 1,3-DC of *N,N′*-cyclic azomethine imines in an acceptable yield of 43%, excellent diastereoselectivity of >95:5 dr, and good enantioselectivity of 87:13 er. Notably, after 48 h of reaction time, TLC indicated that the remaining two reactants remained intact with the generation of the dimer as a main byproduct. But when the reaction time was prolonged to 72 h, the yield could not be improved at all. So, the moderate yield of the reaction should be mainly ascribed to the relatively low reactivity of *N,N′*-cyclic azomethine imines in organocatalytic IED 1,3-DCs with electron-rich olefins.

With the established optimal reaction conditions in hand, we carried out the investigation of the substrate scope of *N,N′*-cyclic azomethine imines **1** by the reaction with *o*-hydroxystyrene **2a**. As shown in Table 3, this protocol is applicable to a wide range of aldehyde-derived *N,N′*-cyclic azomethine imines, which afforded chiral *N,N*-bicyclic pyrazolidin-3-one derivatives containing two stereogenic centers with structural diversity in generally excellent diastereoselectivities and good enantioselectivities. In detail, various benzaldehyde-derived *N,N′*-cyclic azomethine imines

Table 2. Further Optimization of Reaction Conditions[a]



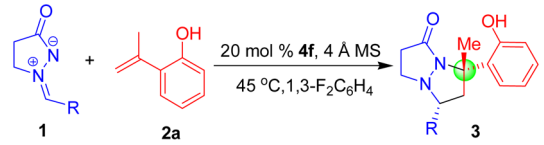
1a 2a 3aa

entry	1a:2a	T (°C)	MS (Å)	x	cat.	yield (%)[b]	er[c]
1	1:1.2	65	3	10	**4f**	33	77:23
2	1:1.2	65	3	10	**7a**	34	67:33
3	1:1.2	65	4	10	**4f**	55	80:20
4	1:1.2	65	5	10	**4f**	22	73:27
5	1:1.2	80	4	10	**4f**	78	60:40
6	1:1.2	45	4	10	**4f**	33	85:15
7	1:1.2	45	4	20	**4f**	43	87:13
8	1:1.2	45	4	30	**4f**	34	85:15
9	1:1.2	45	4	100	**4f**	37	90:10
10	1:1.2	45	4	25	$GaBr_3$/**4f**[d]	39	78:22
11	1:1.2	45	4	10	**8a**	trace	–
12	1:2.5	45	4	20	**4f**	41	78:22
13	1:5	45	4	20	**4f**	41	70:30
14	1:6	45	4	20	**4f**	43	65:35
15	2:1	45	4	20	**4f**	28	87:13
16	3:1	45	4	20	**4f**	trace	–

[a]Unless indicated otherwise, the reaction was carried out in 0.1 mmol scale in 1,2-difluorobenzene (1 mL) with MS (100 mg) for 48 h. [b]Isolated yield and a single diastereomer was observed unless indicated otherwise. [c]The enantiomeric ratio (er) was determined by HPLC. [d]Using the combination of 5 mol % $GaBr_3$ with 20 mol % **4f** as catalysts.

dx.doi.org/10.1021/jo5018469 | J. Org. Chem. 2014, 79, 9305−9312

Table 3. Substrate Scope of *N,N′*-Cyclic Azomethine Imines 1[a]



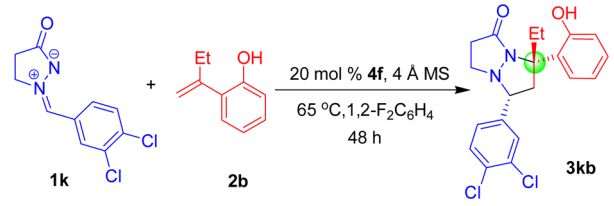
entry	3	R (1)	yield (%)[b]	dr[c]	er[d]
1	**3ba**	4-FC_6H_4 (**1b**)	59	84:16	84:16
2	**3ca**	4-ClC_6H_4 (**1c**)	54	>95:5	83:17
3	**3da**	4-BrC_6H_4 (**1d**)	58	91:9	87:13
4	**3ea**	4-$MeCO_2C_6H_4$ (**1e**)	68	92:8	88:12
5	**3fa**	3-$NO_2C_6H_4$ (**1f**)	53	>95:5	85:15
6	**3aa**	Ph (**1a**)	43	>95:5	87:13
7[e]	**3ga**	1-naphthyl (**1g**)	54	77:23	83:17
8[e]	**3ha**	2-naphthyl (**1h**)	61	94:6	85:15
9[e]	**3ia**	4-Ph-C_6H_4 (**1i**)	67	>95:5	86:14
10[e]	**3ja**	4-Me (**1j**)	69	>95:5	80:20
11	**3ka**	3,4-$Cl_2C_6H_3$ (**1k**)	76	>95:5	88:12
12	**3la**	3-Cl-4-F-C_6H_3 (**1l**)	50	93:7	86:14
13	**3ma**	4-Cl-3-F-C_6H_3 (**1m**)	56	92:8	88:12
14	**3na**	3,4-$F_2C_6H_3$ (**1n**)	47	92:8	83:17
15	**3oa**	3,4,5-$F_3C_6H_2$ (**1o**)	63	94:6	83:17
16[f]	**3pa**	2-thiophenyl (**1p**)	33	92:8	87:13
17[e]	**3qa**	cyclohexyl (**1q**)	67	>95:5	75:25

[a]Unless indicated otherwise, the reaction was carried out in 0.1 mmol scale in 1,2-difluorobenzene (1 mL) with 4 Å MS (100 mg) at 45 °C for 48 h, and the mole ratio of **1**:**2a** was 1:1.2. [b]Isolated yield. [c]The enantiomeric ratio (er) was determined by HPLC. [d]The diastereomeric ratio (dr) was determined by ^{1}H NMR. [e]The reaction was performed at 65 °C. [f]The reaction was performed at 70 °C for 48 h in the presence of 20 mol % **4f**, and then 5 mol % $GaBr_3$ was added to react for another 12 h.

bearing either electronically poor (entries 1−5), neutral (entries 6−9), or rich (entry 10) substituents could be successful employed in the asymmetric IED 1,3-DCs in overall acceptable yields (up to 69%) and good stereoselectivities (up to >95:5 dr, 88:12 er). Among *N,N′*-cyclic azomethine imines substituted with electron-withdrawing groups, substrate **1e** exhibited the highest capability both in reactivity and in enantioselectivity (entry 4 vs 1−3). Furthermore, bromo-substituted substrate **1d** was much superior to its fluoro- or chloro-substituted counterparts **1b** and **1c** in terms of enantioselectivity (entry 3 vs 1, 2). Evidently, electronically rich *N,N′*-cyclic azomethine imine as exemplified by **1j** was inferior to its electronically poor or neutral analogues with regard to the enantioselective control (entry 10 vs 1−9). Furthermore, this approach is also amenable to di- or trisubstituted benzaldehyde-derived *N,N′*-cyclic azomethine imines **1k−o** in excellent diastereoselectivities and considerable enantioselectivities (entries 11−15). Notably, 3,4-dichlorobenzaldehyde-derived substrate **1k** delivered the designed asymmetric IED 1,3-DC in the highest yield of 76% and the best stereoselectivity of >95:5 dr and 88:12 er (entry 11). As exemplified by substrate **1p**, this IED 1,3-DC is also adaptable to heteroaromatic aldehyde-derived *N,N′*-cyclic azomethine imine in a good stereoselectivity (92:8 dr, 87:13 er) albeit with an unsatisfactory yield (entry 16). Importantly, aliphatic aldehyde-generated substrate **1q** could smoothly participate in the desired reaction in a good yield of 67% and excellent diastereoselectivity of >95:5 dr although the enantioselectivity was moderate (entry 17). So, this strategy not only confronted the great challenge in organocatalytic asymmetric IED 1,3-DCs of *N,N′*-cyclic azomethine imines but also afforded a series of chiral *N,N*-bicyclic pyrazolidin-3-one derivatives which may be used for possible bioassay.

Interestingly, *o*-hydroxystyrene **2b** bearing an elongated alkyl group (Et) at the vinylic position proved to be a suitable reaction partner, which took part in the asymmetric IED 1,3-DC with azomethine imine **1k** in an acceptable yield of 42% and good stereoselectivity of 92:8 dr and 88:12 er (Scheme 3).

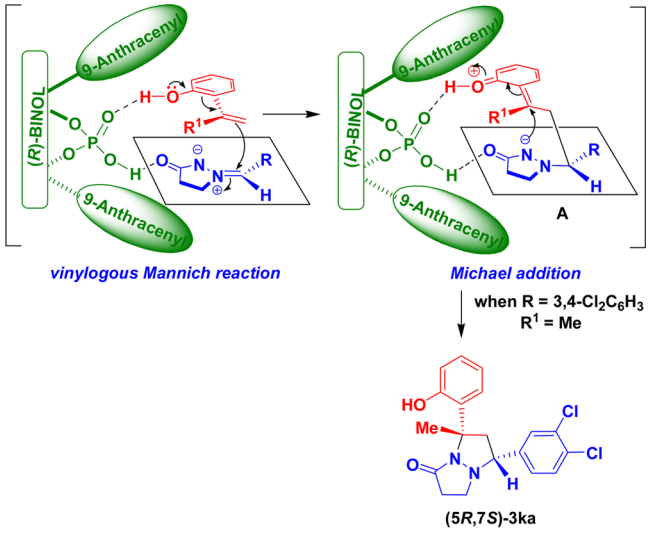
Scheme 3. Using *o*-Hydroxystyrene 2b as a Substrate



Nevertheless, compared with the experimental results of its analogue **2a** (Table 3, entry 11), the reactivity of *o*-hydroxystyrenes seemed to decrease to some extent with the elongation of the alkyl group.

The absolute configuration of product **3ka** (95:5 er after recrystallization) was unambiguously determined to be (5*R*,7*S*) by single crystal X-ray diffraction analysis (in Scheme 4).[17] The

Scheme 4. Absolute Configuration of 3ka and Proposed Transition States of the IED 1,3-DC



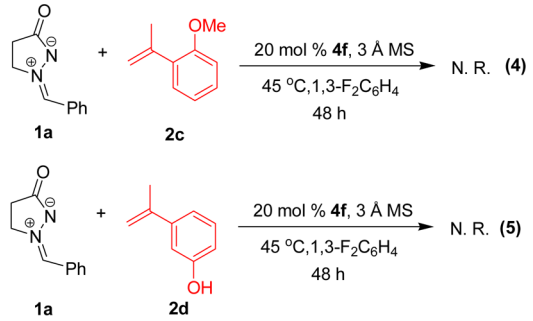
absolute configuration of other products **3** was assigned by analogy. On the basis of the experimental results, we suggested possible transition states to explain the stereochemistry of this organocatalytic asymmetric IED 1,3-DC. As illustrated in Scheme 4, in the presence of CPA **4f**, *N,N′*-cyclic azomethine imines and *o*-hydroxystyrenes were simultaneously activated via dual hydrogen-bonding interaction. At the same time, a conjugative effect was generated by the *o*-hydroxyl group in *o*-hydroxystyrenes, which made the terminal vinyl group readily undergo an enantioselective vinylogous Mannich reaction, affording transient intermediate **A**. Again, under activation of

dx.doi.org/10.1021/jo5018469 | J. Org. Chem. 2014, 79, 9305−9312

the same catalyst via dual hydrogen bonds, intermediate **A** then underwent a stereoselective intramolecular Michael addition to generate the final IED 1,3-DC products. In our proposed transition states, the chiral environment originated bythe (*R*)-BINOL backbone and the bulky 3,3′-(9-anthracenyl) groups of CPA **4f** led to the experimentally observed (5*R*,7*S*)-configured products.

To investigate the role of *o*-hydroxyl group in *o*-hydroxystyrenes, some control experiments were carried out (Scheme 5). First, *o*-methoxy-substituted styrene **2c** was

Scheme 5. Control Experiments To Demonstrate the Role of the *o*-Hydroxyl Group



utilized in the reaction under the optimal reaction conditions (eq 4). But no reaction (N.R.) occurred, which demonstrated that the OH group in *o*-hydroxystyrenes played a crucial role in forming a hydrogen bond with the P═O group of CPA. In the absence of this hydrogen-bonding activation, CPA could only form a single hydrogen bond with the carbonyl group of *N*,*N*′-cyclic azomethine imine. Obviously, this single hydrogen-bond activation mode was much inferior to dual hydrogen-bonding interaction, thus resulting in the failure of the reaction. Second, *m*-hydroxy-substituted styrene **2d** was also employed in the reaction (eq 5). Although this substrate possessed a OH group capable of generating a hydrogen bond with CPA, the desired IED 1,3-DC still did not take place. This result indicated that the hydrogen-bonding interaction between the hydroxyl group of styrene and CPA was not sufficient to ensure the designed reaction. The success of *o*-hydroxystyrenes in IED 1,3-DC with *N*,*N*′-cyclic azomethine imines also relied on the conjugative effect initiated by the *o*-hydroxyl group, which increased the nucleophilicity of the terminal vinyl group to attack the imine functionality of the 1,3-dipoles, thus facilitating the designed IED 1,3-DC. So, the *m*-hydroxyl group could not impose a conjugative effect on the vinyl group to promote the first step of the vinylogous Mannich reaction; therefore, the desired reaction could not be performed. These control experiments demonstrated that the dual hydrogen-bonding activation and the conjugative effect of the *o*-hydroxyl group cooperatively contributed to the designed IED 1,3-DC.

CONCLUSIONS

In summary, we have established the first organocatalytic asymmetric IED 1,3-DC of *N*,*N*′-cyclic azomethine imines, which directly assembles this type of 1,3-dipole and *o*-hydroxystyrene into chiral *N*,*N*-bicyclic pyrazolidin-3-one derivatives with the creation of two stereogenic centers, one of which is quaternary, in excellent diastereoselectivities and good enantioselectivities (up to >95:5 dr, 88:12 er). This protocol not only met the great challenge in organocatalytic asymmetric IED 1,3-DC of *N*,*N*′-cyclic azomethine imines but also afforded a series of chiral *N*,*N*-bicyclic pyrazolidin-3-one derivatives, which may find pharmaceutical applications after related bioassays. The investigation of the activation mode of the reaction revealed that the dual hydrogen-bonding interaction between the two substrates and the catalyst together with the conjugative effect initiated by the *o*-hydroxyl group played a crucial role in the designed IED 1,3-DC. This study will not only greatly enrich the underdeveloped research potential of catalytic asymmetric IED 1,3-DCs, but also will facilitate the design of other enantioselective IED 1,3-DCs based on different activation modes.

EXPERIMENTAL SECTION

General Information. ^{1}H and ^{13}C NMR spectra were measured, respectively, at 400 and 100 MHz, respectively. The solvent used for NMR spectroscopy was $CDCl_3$, using tetramethylsilane as the internal reference. HRMS spectra were recorded on a LTQ-Orbitrap mass spectrometer. Enantiomeric ratios (er) were determined by chiral high-performance liquid chromatography (chiral HPLC). The chiral column used for the determination of enantiomeric ratios by chiral HPLC was Chiralpak IC column. Optical rotation values were measured with instruments operating at λ = 589 nm, corresponding to the sodium D line at the temperatures indicated. Analytical grade solvents for the column chromatography and commercially available reagents were used as received. All starting materials commercially available were used directly. Substrates **1** and **2** were synthesized according to the literature methods.[18,19]

Typical Procedure for the Organocatalytic Asymmetric IED 1,3-DC of *N*,*N*′-Cyclic Azomethine Imines with *o*-Hydroxystyrenes. 1,3-Difluorobenzene (1 mL) and *o*-hydroxystyrenes **2** (0.12 mmol) were sequentially added to the mixture of *N*,*N*′-cyclic azomethine imines **1** (0.1 mmol), 4 Å MS (100 mg), and catalyst **4f** (0.02 mmol). The reaction mixture was stirred at 45 °C for 48 h. Although TLC indicated that the reaction did not go to completion, the reaction was terminated after 48 h because it was found that the yield could not be improved with prolonged reaction time. Then the reaction mixture was filtered to remove the molecular sieves, and the solid powder was washed with ethyl acetate. The resultant solution was concentrated under reduced pressure to give a residue, which was purified through preparative thin layer chromatography on silica gel to afford pure products **3**.

(5*R*,7*S*)-7-(2-Hydroxyphenyl)-7-methyl-5-phenyltetrahydropyrazolo[1,2-*a*]pyrazol-1(5*H*)-one (3aa). Preparative thin layer chromatography (ethyl acetate/petroleum ether = 2/1; reaction time = 48 h; yield: 43% (13.2 mg); >95:5 dr; colorless sticky oil; $[\alpha]_D^{20}$ = −151.0 (*c* 0.10, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.89 (s, 1H), 7.52−7.46 (m, 2H), 7.46−7.37 (m, 3H), 7.37−7.32 (m, 1H), 7.25−7.19 (m, 1H), 6.97 (dd, *J* = 8.1, 1.2 Hz, 1H), 6.91−6.85 (m, 1H), 3.88 (dd, *J* = 11.3, 6.2 Hz, 1H), 3.53−3.44 (m, 1H), 3.05−2.86 (m, 3H), 2.80−2.69 (m, 2H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4, 154.7, 135.1, 129.3, 129.1, 128.9, 128.2, 127.3, 126.3, 119.5, 118.4, 70.6, 59.8, 54.3, 49.0, 36.1, 24.4; IR (KBr): 3626, 1588, 1497, 1449, 1385, 1297, 1228, 1111, 1024, 985, 796, 755 cm^{-1}; ESI FTMS exact mass calcd for $(C_{19}H_{20}N_2O_2 - H)^-$ requires *m*/*z* 307.1447, found *m*/*z* 307.1436; enantiomeric ratio: 87:13; determined by HPLC (Daicel Chirapak IC, hexane/2-propanol = 70/30, flow rate 1.0 mL/min, *T* = 30 °C, 254 nm): t_R = 8.48 min (minor), t_R = 10.94 min (major).

(5*R*,7*S*)-5-(4-Fluorophenyl)-7-(2-hydroxyphenyl)-7-methyltetrahydropyrazolo[1,2-*a*]pyrazol-1(5*H*)-one (3ba). Preparative thin layer chromatography (ethyl acetate/petroleum ether = 2/1; reaction time = 48 h; yield: 59% (19.2 mg); 84:16 dr; colorless sticky oil; $[\alpha]_D^{20}$ = −48.4 (*c* 0.12, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.78 (s, 1H), 7.50−7.45 (m, 2H), 7.34 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.25−7.20 (m, 1H), 7.15−7.08 (m, 2H), 6.96 (dd, *J* = 8.1, 1.3 Hz, 1H), 6.91−6.87 (m, 1H), 3.86 (dd, *J* = 11.3, 6.2 Hz, 1H), 3.50−3.44 (m, 1H), 3.05−2.85 (m, 3H), 2.80−2.67 (m, 2H),2.16 (s,3H); ^{13}C NMR

dx.doi.org/10.1021/jo5018469 | J. Org. Chem. 2014, 79, 9305−9312

(100 MHz, $CDCl_3$) δ 163.4, 154.1, 148.2, 143.0, 129.5, 128.1, 128.0, 126.4, 124.3, 119.9, 118.2, 69.7, 60.3, 54.4, 49.6, 36.0, 24.4; IR (KBr): 3625, 2982, 1638, 1601, 1511, 1421, 1248, 1094, 1075, 752, cm^{-1}; ESI FTMS exact mass calcd for $(C_{19}H_{19}FN_2O_2 - H)^-$ requires m/z 325.1353, found m/z 325.1359; enantiomeric ratio: 84:16; determined by HPLC (Daicel Chirapak IC, hexane/2-propanol = 70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 7.70 min (minor), t_R = 9.00 min (major).

(5*R*,7*S*)-5-(4-Chlorophenyl)-7-(2-hydroxyphenyl)-7-methyltetrahydropyrazolo[1,2-*a*]pyrazol-1(5*H*)-one (3ca). Preparative thin layer chromatography (ethyl acetate/petroleum ether = 2/1; reaction time = 48 h; yield: 54% (18.5 mg); >95:5 dr; colorless sticky oil; $[\alpha]_D^{20}$ = −48.3 (c 0.12, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.66 (s, 1H), 7.46−7.36 (m, 4H), 7.33 (dd, J = 7.9, 1.5 Hz, 1H), 7.24−7.20 (m, 1H), 6.95 (dd, J = 8.1, 1.2 Hz, 1H), 6.91−6.86 (m, 1H), 3.84 (dd, J = 11.3, 6.2 Hz, 1H), 3.50−3.45 (m, 1H), 3.06−2.84 (m, 3H), 2.81−2.72 (m, 2H), 2.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4, 154.5, 134.8, 133.8, 129.4, 129.3, 128.7, 128.2, 126.4, 119.7, 118.3, 69.9, 60.0, 54.3, 49.2, 36.0, 24.3; IR (KBr): 3625, 1594, 1508, 1489, 1435, 1395, 1300, 1085, 814, 752, cm^{-1}; ESI FTMS exact mass calcd for $(C_{19}H_{19}ClN_2O_2 - H)^-$ requires m/z 341.1057, found m/z 341.1071; enantiomeric ratio: 83:17; determined by HPLC (Daicel Chirapak IC, hexane/2-propanol = 70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 7.60 min (minor), t_R = 8.57 min (major).

(5*R*,7*S*)-5-(4-Bromophenyl)-7-(2-hydroxyphenyl)-7-methyltetrahydropyrazolo[1,2-*a*]pyrazol-1(5*H*)-one (3da). Preparative thin layer chromatography (ethyl acetate/petroleum ether = 2/1; reaction time = 48 h; yield: 58% (22.4 mg); 91:9 dr; colorless sticky oil; $[\alpha]_D^{20}$ = −58.2 (c 0.18, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.61 (s, 1H), 7.55 (d, J = 8.2 Hz, 2H), 7.38−7.32 (m, 3H), 7.22 (t, J = 7.7 Hz, 1H), 6.95 (d, J = 8.1 Hz, 1H), 6.89 (t, J = 7.6 Hz, 1H), 3.83 (dd, J = 11.2, 6.2 Hz, 1H), 3.48 (t, J = 8.7 Hz, 1H), 3.05−2.86 (m, 3H), 2.81−2.68 (m, 2H), 2.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4, 154.5, 134.3, 132.3, 129.4, 129.0, 128.2, 126.4, 122.9, 119.7, 118.3, 70.0, 60.0, 54.3, 49.2, 36.1, 24.4; IR (KBr): 3626, 2977, 1648, 1600, 1486, 1445, 1364, 1252, 1069, 813, cm^{-1}; ESI FTMS exact mass calcd for $(C_{19}H_{19}BrN_2O_2 - H)^-$ requires m/z 385.0552, found m/z 385.0561; enantiomeric ratio: 87:13; determined by HPLC (Daicel Chirapak IC, hexane/2-propanol = 70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 7.76 min (minor), t_R = 8.73 min (major).

(5*R*,7*S*)-Methyl-4-(3-(2-hydroxyphenyl)-3-methyl-5-oxohexahydropyrazolo[1,2-*a*]pyrazol-1-yl)benzoate (3ea). Preparative thin layer chromatography (ethyl acetate/petroleum ether = 2/1; reaction time = 48 h; yield: 68% (24.9 mg); 92:8 dr; colorless sticky oil; $[\alpha]_D^{20}$ = −3.8 (c 0.53, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.54 (s, 1H), 8.08 (d, J = 8.3 Hz, 2H), 7.56 (d, J = 8.3 Hz, 2H), 7.33 (dd, J = 7.9, 1.4 Hz, 1H), 7.25−7.18 (m, 1H), 6.95 (dd, J = 8.0, 1.0 Hz, 1H), 6.91−6.86 (m, 1H), 3.95 (s, 3H), 3.94−3.90 (m, 1H), 3.54−3.46 (m, 1H), 3.07−2.88 (m, 3H), 2.82−2.76 (m, 2H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 163.4, 154.4, 140.5, 130.7, 130.3, 129.4, 128.1, 127.3, 126.4, 119.7, 118.3, 70.3, 60.2, 54.3, 52.3, 49.4, 36.1, 24.4; IR (KBr): 3630, 1719, 1655, 1560, 1508, 1418, 1002, 764, cm^{-1}; ESI FTMS exact mass calcd for $(C_{21}H_{22}N_2O_4 - H)^-$ requires m/z 365.1502, found m/z 365.1510; enantiomeric ratio: 88:12; determined by HPLC (Daicel Chirapak IC, hexane/2-propanol = 70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 12.67 min (minor), t_R = 16.61 min (major).

(5*R*,7*S*)-7-(2-Hydroxyphenyl)-7-methyl-5-(3-nitrophenyl)-tetrahydropyrazolo[1,2-*a*]pyrazol-1(5*H*)-one (3fa). Preparative thin layer chromatograph (ethyl acetate/petroleum ether = 2/1; reaction time = 48 h; yield: 53% (18.7 mg); >95:5 dr; colorless sticky oil; $[\alpha]_D^{20}$ = −33.3 (c 0.34, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.01 (s, 1H), 8.30 (t, J = 1.8 Hz, 1H), 8.27−8.21 (m, 1H), 7.88 (d, J = 7.8 Hz, 1H), 7.63 (t, J = 8.0 Hz, 1H), 7.33 (dd, J = 7.9, 1.5 Hz, 1H), 7.25−7.19 (m, 1H), 6.97−6.87 (m, 2H), 3.99 (dd, J = 11.0, 6.4 Hz, 1H), 3.56−3.46 (m, 1H), 3.11−3.02 (m, 1H), 2.98−2.78 (m, 4H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5, 154.1, 148.6, 138.1, 133.0, 130.3, 129.4, 128.2, 126.4, 123.8, 122.7, 119.9, 118.2, 69.6, 60.6, 54.4, 49.8, 36.1, 24.4; IR (KBr): 3627, 1631, 1601, 1457, 1394, 1228, 1078, 1017, 807, 765 cm^{-1}; ESI FTMS exact mass calcd for $(C_{19}H_{19}N_3O_4 - H)^-$ requires m/z 352.1298, found m/z 352.1315; enantiomeric ratio: 85:15; determined by HPLC (Daicel Chirapak IC, hexane/2-propanol = 70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 14.57 min (minor), t_R = 13.48 min (major).

(5*R*,7*S*)-7-(2-Hydroxyphenyl)-7-methyl-5-(naphthalen-1-yl)-tetrahydropyrazolo[1,2-*a*]pyrazol-1(5*H*)-one (3ga). Preparative thin layer chromatography (ethyl acetate/petroleum ether = 2/1; reaction time = 48 h; yield: 54% (19.4 mg); 77:23 dr; colorless sticky oil; $[\alpha]_D^{20}$ = −16.8 (c 0.32, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.69 (s, 1H), 8.00 (d, J = 8.3 Hz, 1H), 7.91 (d, J = 7.8 Hz, 1H), 7.83 (t, J = 8.6 Hz, 2H), 7.64−7.48 (m, 3H), 7.33 (d, J = 7.9 Hz, 1H), 7.18 (t, J = 7.7 Hz, 1H), 6.92 (d, J = 7.9 Hz, 1H), 6.85 (t, J = 7.6 Hz, 1H), 4.71 (dd, J = 11.2, 6.1 Hz, 1H), 3.69 (t, J = 8.9 Hz, 1H), 3.14−2.98 (m, 2H), 2.97−2.73 (m, 3H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5, 154.5, 133.9, 131.5, 131.0, 129.4, 129.3, 128.6, 128.1, 126.6, 126.4, 126.0, 125.9, 122.7, 122.0, 119.6, 118.3, 66.3, 60.1, 54.1, 49.6, 36.1, 24.7; IR (KBr): 3630, 2963, 1655, 1591, 1509, 1454, 1373, 1261, 1096, 1020, 765 cm^{-1}; ESI FTMS exact mass calcd for $(C_{23}H_{22}N_2O_2 - H)^-$ requires m/z 357.1603, found m/z 357.1602; enantiomeric ratio: 83:17; determined by HPLC (Daicel Chirapak IC, hexane/2-propanol = 70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 8.32 min (minor), t_R = 9.41 min (major).

(5*R*,7*S*)-7-(2-Hydroxyphenyl)-7-methyl-5-(naphthalen-2-yl)-tetrahydropyrazolo[1,2-*a*]pyrazol-1(5*H*)-one (3ha). Preparative thin layer chromatography (ethyl acetate/petroleum ether = 2/1; reaction time = 48 h; yield: 61% (21.9 mg); 94:6 dr; colorless sticky oil; $[\alpha]_D^{20}$ = −43.4 (c 0.26, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.86 (s, 1H), 7.92−7.87 (m, 5H), 7.66−7.59 (m, 1H), 7.57−7.51 (m, 2H), 7.38−7.35 (m, 1H), 7.27−7.18 (m, 1H), 7.00−6.98 (m, 1H), 6.93−6.85 (m, 1H), 4.04 (dd, J = 11.3, 6.2 Hz, 1H), 3.52−3.46 (m,1H), 3.14−2.90 (m, 3H), 2.81−2.76 (m, 2H), 2.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5, 154.7, 133.5, 133.3, 132.6, 129.4, 129.1, 128.3, 127.9, 127.8, 127.0, 126.6, 126.5, 126.4, 124.3, 119.6, 118.4, 70.9, 60.1, 54.3, 49.2, 36.2, 24.4; IR (KBr): 3628, 2924, 1655, 1601, 1507, 1374, 1298, 1261, 1113, 1075, 820 cm^{-1}; ESI FTMS exact mass calcd for $(C_{23}H_{22}N_2O_2 - H)^-$ requires m/z 357.1603, found m/z 357.1604; enantiomeric ratio: 85:15; determined by HPLC (Daicel Chirapak IC, hexane/2-propanol = 80/20, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 15.61 min (minor), t_R = 21.88 min (major).

(5*R*,7*S*)-5-([1,1′-Biphenyl]-4-yl)-7-(2-hydroxyphenyl)-7-methyltetrahydropyrazolo[1,2-*a*]pyrazol-1(5*H*)-one (3ia). Preparative thin layer chromatography (ethyl acetate/petroleum ether = 2/1; reaction time = 48 h; yield: 67% (25.8 mg); >95:5 dr; colorless sticky oil; $[\alpha]_D^{20}$ = −55.9 (c 0.19, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.91 (s, 1H), 7.66−7.60 (m, 4H), 7.56 (d, J = 8.2 Hz, 2H), 7.48 (t, J = 7.6 Hz, 2H), 7.42−7.33 (m, 2H), 7.26−7.20 (m, 1H), 6.98 (d, J = 8.1 Hz, 1H), 6.89 (dd, J = 10.8, 4.3 Hz, 1H), 3.93 (dd, J = 11.3, 6.2 Hz, 1H), 3.53 (dd, J = 11.1, 6.3 Hz, 1H), 3.08−2.89 (m, 3H), 2.83−2.70 (m, 2H), 2.19 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4, 154.7, 141.9, 140.3, 134.1, 129.4, 128.9, 128.3, 127.8, 127.6, 127.1, 126.4, 119.6, 118.4, 70.4, 60.0, 54.3, 49.2, 36.1, 24.4; IR (KBr): 3627, 2925, 1590, 1487, 1416, 1298, 1262, 1106, 1009, 765, 751 cm^{-1}; ESI FTMS exact mass calcd for $(C_{25}H_{24}N_2O_2 - H)^-$ requires m/z 383.1760, found m/z 383.1760; enantiomeric ratio: 86:14; determined by HPLC (Daicel Chirapak IC, hexane/2-propanol = 80/20, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 16.92 min (minor), t_R = 24.12 min (major).

(5*R*,7*S*)-7-(2-Hydroxyphenyl)-7-methyl-5-(*p*-tolyl)tetrahydropyrazolo[1,2-*a*]pyrazol-1(5*H*)-one (3ja). Preparative thin layer chromatography (ethyl acetate/petroleum ether = 2/1; reaction time = 48 h; yield: 69% (22.2 mg); >95:5 dr; colorless sticky oil; $[\alpha]_D^{20}$ = −50.4 (c 0.24, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.95 (s, 1H), 7.39−7.33 (m, 3H), 7.24−7.20 (m, 3H), 6.97 (d, J = 8.1 Hz, 1H), 6.88 (t, J = 7.6 Hz, 1H), 3.84 (dd, J = 11.3, 6.2 Hz, 1H), 3.46 (dd, J = 11.9, 6.1 Hz, 1H), 3.05−2.85 (m, 3H), 2.81−2.65 (m, 2H), 2.38 (s, 3H), 2.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4, 154.8, 138.9, 132.0, 129.8, 129.4, 128.3, 127.3, 126.4, 119.5, 118.4, 70.5, 59.8, 54.3, 49.0, 36.1, 24.4, 21.2; IR (KBr): 3624, 2963, 1642, 1587, 1448, 1370, 1262, 1103, 855, 802, 747 cm^{-1}; ESI FTMS exact mass calcd for

dx.doi.org/10.1021/jo5018469 | J. Org. Chem. 2014, 79, 9305−9312

($C_{20}H_{22}N\ _2O_2 - H)^-$ requires m/z 321.1603, found m/z 321.1606; enantiomeric ratio: 80:20; determined by HPLC (Daicel Chirapak IC, hexane/2-propanol = 80/20, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 15.25 min (minor), t_R = 22.93 min (major).

(5*R*,7*S*)-5-(3,4-Dichlorophenyl)-7-(2-hydroxyphenyl)-7-methyltetrahydropyrazolo[1,2-*a*]pyrazol-1(5*H*)-one (3ka). Preparative thin layer chromatography (ethyl acetate/petroleum ether = 2/1; reaction time = 48 h; yield: 76% (28.7 mg); >95:5 dr; white solid; $[\alpha]_D^{20}$ = −14.7 (*c* 0.61, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.20 (s, 1H), 7.55 (d, J = 2.0 Hz, 1H), 7.51−7.47 (m, 1H), 7.36−7.30 (m, 2H), 7.25−7.18 (m, 1H), 6.95−6.85 (m, 2H), 3.81 (dd, J = 11.1, 6.3 Hz, 1H), 3.53−3.48 (m, 1H), 3.07−2.98 (m, 1H), 2.93−2.85 (m, 2H), 2.82−2.73 (m, 2H), 2.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5, 154.3, 135.9, 133.3, 133.0, 131.1, 129.4, 128.2, 126.5, 126.3, 119.8, 118.2, 69.4, 60.4, 60.3, 54.3, 49.6, 36.1, 24.4; IR (KBr): 3628, 1668, 1642, 1541, 1455, 1261, 1097, 1028, 866, 802, 702 cm^{-1}; ESI FTMS exact mass calcd for ($C_{19}H_{18}Cl\ _2N_2O_2 - H)^-$ requires m/z 375.0667, found m/z 375.0674; enantiomeric ratio: 88:12; determined by HPLC (Daicel Chirapak IC, hexane/2-propanol = 80/20, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 11.21 min (minor), t_R = 12.15 min (major).

(5*R*,7*S*)-5-(3-Chloro-4-fluorophenyl)-7-(2-hydroxyphenyl)-7-methyltetrahydropyrazolo[1,2-*a*]pyrazol-1(5*H*)-one (3la). Preparative thin layer chromatography (ethyl acetate/petroleum ether = 2/1; reaction time = 48 h; yield: 50% (18.1 mg); 93:7 dr (inseparable diastereomers); colorless sticky oil; $[\alpha]_D^{20}$ = −51.3 (*c* 0.16, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.25 (s, 1H), 7.51 (dd, J = 6.9, 2.2 Hz,1H), 7.39−7.35 (m,1H), 7.31 (dd, J = 7.9, 1.5 Hz, 1H), 7.23−7.15 (m, 2H), 6.92 (dd, J = 8.0, 1.0 Hz, 1H), 6.90−6.84 (m, 1H), 3.80 (dd, J = 11.1, 6.3 Hz, 1H), 3.53−3.47 (m, 1H), 3.08−2.99 (m, 1H), 2.92−2.84 (m, 2H), 2.82−2.74 (m, 2H), 2.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5, 154.2, 132.8, 129.6, 129.3, 128.3, 127.0, 126.3, 121.7, 119.7, 118.1, 117.4, 117.2, 69.4, 60.5, 54.4, 49.6, 36.1, 24.3; IR (KBr): 3630, 1654, 1630, 1590, 1501, 1465, 1418, 1254, 1148, 1060, 754 cm^{-1}; ESI FTMS exact mass calcd for ($C_{19}H_{18}ClFN\ _2O_2 - H)^-$ requires m/z 359.0963, found m/z 359.0963; enantiomeric ratio: 86:14; determined by HPLC (Daicel Chirapak IC, hexane/2-propanol = 80/20, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 11.32 min (minor), t_R = 12.40 min (major).

(5*R*,7*S*)-5-(4-Chloro-3-fluorophenyl)-7-(2-hydroxyphenyl)-7-methyltetrahydropyrazolo[1,2-*a*]pyrazol-1(5*H*)-one (3ma). Preparative thin layer chromatography (ethyl acetate/petroleum ether = 2/1; reaction time = 48 h; yield: 56% (20.2 mg); 92:8 dr (inseparable diastereomers); colorless sticky oil; $[\alpha]_D^{20}$ = −30.8 (*c* 0.31, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.29 (s, 1H), 7.44 (t, J = 7.8 Hz, 1H), 7.35−7.30 (m, 2H), 7.25−7.20 (m, 2H), 6.94 (d, J = 8.1 Hz,1H), 6.91−6.86 (m, 1H), 3.84 (dd, J = 11.2, 6.3 Hz, 1H), 3.54−3.48 (m, 1H), 3.07−2.85 (m, 3H), 2.82−2.73 (m, 2H), 2.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4, 154.3, 136.5, 131.3, 129.4, 128.1, 126.3, 123.7, 123.6, 119.8, 118.3, 115.7, 115.4, 69.5, 60.2, 54.3, 49.5, 36.1, 24.4; IR (KBr): 3627, 2963, 1650, 1594, 1458, 1261, 1097, 1020, 866, 801, 702 cm^{-1}; ESI FTMS exact mass calcd for ($C_{19}H_{18}ClFN\ _2O_2 - H)^-$ requires m/z 359.0963, found m/z 359.0962; enantiomeric ratio: 88:12; determined by HPLC (Daicel Chirapak IC, hexane/2-propanol = 80/20, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 11.13 min (minor), t_R = 11.90 min (major).

(5*R*,7*S*)-5-(3,4-Difluorophenyl)-7-(2-hydroxyphenyl)-7-methyltetrahydropyrazolo[1,2-*a*]pyrazol-1(5*H*)-one (3na). Preparative thin layer chromatography (ethyl acetate/petroleum ether = 2/1; reaction time = 48 h; yield: 47% (16.2 mg); 92:8 dr (inseparable diastereomers); colorless sticky oil; $[\alpha]_D^{20}$ = −55.0 (*c* 0.22, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.45 (s, 1H), 7.36−7.32 (m, 2H), 7.26−7.16 (m, 3H), 6.95 (d, J = 8.0 Hz, 1H), 6.89 (t, J = 8.0 Hz, 1H), 3.83 (dd, J = 11.2, 6.3 Hz, 1H), 3.49 (dd, J = 12.7, 5.5 Hz, 1H), 3.06−2.98 (m, 1H), 2.98−2.85 (m, 2H), 2.83−2.70 (m, 2H), 2.15 (s,3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4, 154.3, 151.7, 129.5, 128.1, 126.4, 123.5, 119.8, 118.4, 118.1, 117.9, 116.5, 116.3, 69.6, 60.1, 54.3, 49.4, 36.0, 24.4; IR (KBr): 3630, 2963, 1655, 1522, 1457, 1261, 875, 802, 757 cm^{-1}; ESI FTMS exact mass calcd for ($C_{19}H_{18}F\ _2N_2O_2 - H)^-$ requires m/z 343.1258, found m/z 343.1265; enantiomeric ratio: 83:17; determined by HPLC (Daicel Chirapak IC, hexane/2-propanol = 80/20, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 11.21 min (minor), t_R = 12.19 min (major).

(5*R*,7*S*)-7-(2-Hydroxyphenyl)-7-methyl-5-(3,4,5-trifluorophenyl)tetrahydropyrazolo[1,2-*a*]pyrazol-1(5*H*)-one (3oa). Preparative thin layer chromatography (ethyl acetate/petroleum ether = 2/1; reaction time = 48 h; yield: 63% (22.8 mg); 94:6 dr (inseparable diastereomers); colorless sticky oil; $[\alpha]_D^{20}$ = −129.0 (*c* 0.46, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 (s, 1H), 7.32−7.30 (m, 1H), 7.23−7.19 (m, 1H), 7.15−7.11 (m, 2H), 6.93−6.87 (m, 2H), 3.78 (dd, J = 10.7, 6.6 Hz, 1H), 3.55−3.50 (m, 1H), 3.08−2.99 (m, 1H), 2.92−2.74 (m, 4H), 2.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5, 154.1, 129.4, 128.2, 126.3, 119.9, 118.2, 111.6, 111.5, 111.4, 111.3, 69.2, 60.5, 54.3, 49.7, 36.1, 24.3; IR (KBr): 3628, 2963, 1651, 1594, 1558, 1449, 1418, 1383, 1261, 1097, 1043, 802 cm^{-1}; ESI FTMS exact mass calcd for ($C_{19}H_{17}F\ _3N_2O_2 - H)^-$ requires m/z 36l.1164, found m/z 361.1175; enantiomeric ratio: 83:17; determined by HPLC (Daicel Chirapak IC, hexane/2-propanol = 90/10, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 23.80 min (minor), t_R = 25.59 min (major).

(5*R*,7*S*)-7-(2-Hydroxyphenyl)-7-methyl-5-(thiophen-2-yl)-tetrahydropyrazolo[1,2-*a*]pyrazol-1(5*H*)-one (3pa). Preparative thin layer chromatography (ethyl acetate/petroleum ether = 2/1; reaction time = 48 h; yield: 33% (10.4 mg); 92:8 dr (inseparable diastereomers); colorless sticky oil; $[\alpha]_D^{20}$ = −145.2 (*c* 0.10, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.55 (s, 1H), 7.37−7.32 (m, 2H), 7.25−7.20 (m, 1H), 7.16 (dd, J = 3.5, 0.7 Hz, 1H), 7.04 (dd, J = 5.1, 3.5 Hz, 1H), 6.96 (dd, J = 8.0, 1.3 Hz, 1H), 6.88 (td, J = 7.8, 1.3 Hz, 1H), 4.18 (dd, J = 11.1, 6.2 Hz, 1H), 3.62−3.56 (m, 1H), 3.13−2.94 (m, 3H), 2.85−2.74 (m, 2H), 2.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4, 154.7, 137.8, 129.4, 128.1, 127.1, 126.4, 126.3, 126.0, 119.5, 118.5, 65.7, 60.0, 54.6, 49.2, 36.0, 24.4; IR (KBr): 3650, 1655, 1629, 1456, 1374, 1200, 866, 802, 756 cm^{-1}; ESI FTMS exact mass calcd for ($C_{17}H_{18}N\ _2O_2\ S - H)^-$ requires m/z 313.1011, found m/z 313.1023; enantiomeric ratio: 87:13; determined by HPLC (Daicel Chirapak IC, hexane/2-propanol = 80/20, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 14.29 min (minor), t_R = 22.72 min (major).

(5*R*,7*S*)-5-Cyclohexyl-7-(2-hydroxyphenyl)-7-methyltetrahydropyrazolo[1,2-*a*]pyrazol-1(5*H*)-one (3qa). Preparative thin layer chromatography (ethyl acetate/petroleum ether = 2/1; reaction time = 48 h; yield: 67% (21.0 mg); >95:5 dr; colorless sticky oil; $[\alpha]_D^{20}$ = −16.6 (*c* 0.32, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.83 (s, 1H), 7.33−7.24 (m, 1H), 7.21−7.15 (m, 1H), 6.89 (dd, J = 8.1, 1.3 Hz, 1H), 6.86−6.81 (m, 1H), 3.72−3.65 (m, 1H), 3.02−2.86 (m, 2H), 2.77−2.60 (m, 3H), 2.40 (dd, J = 11.9, 5.1 Hz, 1H), 2.06 (s, 3H), 1.88−1.63 (m, 7H), 1.22−1.04 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5, 154.7, 129.1, 128.6, 126.2, 119.3, 118.3, 71.1, 58.5, 51.2, 49.1, 38.7, 36.3, 30.6, 28.4, 26.2, 26.1, 25.9, 24.5; IR (KBr): 3630, 2982, 1643, 1451, 1382, 1348, 1299, 1214, 1101, 1045, 801, 756 cm^{-1}; ESI FTMS exact mass calcd for ($C_{19}H_{26}N\ _2O_2 - H)^-$ requires m/z 313.1916, found m/z 313.1909; enantiomeric ratio: 75:25; determined by HPLC (Daicel Chirapak IC, hexane/2-propanol = 80/20, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 21.05 min (minor), t_R = 38.47 min (major).

(5*R*,7*S*)-5-(3,4-Dichlorophenyl)-7-ethyl-7-(2-hydroxyphenyl)-tetrahydropyrazolo[1,2-*a*]pyrazol-1(5*H*)-one (3kb). Preparative thin layer chromatography (ethyl acetate/petroleum ether = 2/1; reaction time = 48 h; yield: 42% (16.4 mg); 92:8 dr (inseparable diastereomers); colorless sticky oil; $[\alpha]_D^{20}$ = −72.1 (*c* 0.15, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.27 (s, 1H), 7.54 (d, J = 2.0 Hz, 1H), 7.48 (d, J = 8.3 Hz, 1H), 7.35−7.32 (m, 2H), 7.23−7.19 (m, 1H), 6.93 (dd, J = 8.1, 1.3 Hz, 1H), 6.91−6.85 (m, 1H), 3.74 (dd, J = 10.9, 6.9 Hz, 1H), 3.56−3.50 (m, 1H), 3.12−3.02 (m, 1H), 2.96−2.74 (m, 5H), 2.44−2.34 (m, 1H), 1.17 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5, 154.3, 136.5, 133.2, 132.9, 131.1, 129.4, 129.3, 129.0, 126.4, 126.3, 119.8, 118.5, 69.9, 63.8, 51.4, 49.7, 36.3, 27.4, 9.6; IR (KBr): 3626, 2962, 1660, 1630, 1561, 1453, 1370, 1261, 1098, 1024, 802, 755 cm^{-1}; ESI FTMS exact mass calcd for ($C_{20}H_{20}Cl\ _2N_2O_2 -$

dx.doi.org/10.1021/jo5018469 | J. Org. Chem. 2014, 79, 9305−9312

H)$^-$ requires m/z 389.0824, found m/z 389.0826; enantiomeric ratio: 88:12; determined by HPLC (Daicel Chirapak IC, hexane/2-propanol = 80/20, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 8.67 min (minor), t_R = 37.80 min (major).

■ ASSOCIATED CONTENT

Supporting Information

Characterization data (including ^{1}H, ^{13}C NMR and HPLC spectra) for all products **3**; crystal data for compound **3ka**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: fshi@jsnu.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful for financial support from NSFC (21372002 and 21232007), Open Foundation of Jiangsu Key Laboratory (K201314), PAPD, and Qing Lan Project of Jiangsu Province.

■ REFERENCES

(1) (a) Padwa, A.; Pearson, W. H. *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; John Wiley & Sons, Inc.: New York, 2002. For some reviews, see:. (b) Coldham, I.; Hufton, R. *Chem. Rev.* **2005**, *105*, 2765. (c) Nájera, J.; Sansano, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 6272. (d) Pandey, G.; Banerjee, P.; Gadre, S. R. *Chem. Rev.* **2006**, *106*, 4484. (e) Nair, V.; Suja, T. D. *Tetrahedron* **2007**, *63*, 12247. (f) Pellissier, H. *Tetrahedron* **2007**, *63*, 3235. (g) Stanley, L. M.; Sibi, M. P. *Chem. Rev.* **2008**, *108*, 2887. (h) Marie, K.; Anita, R. M. *Chem. Soc. Rev.* **2010**, *39*, 845. (i) Adrio, J.; Carretero, J. C. *Chem. Commun.* **2011**, *47*, 6784. (j) Narayan, R.; Potowski, M.; Jia, Z.-J.; Antonchick, A. P.; Waldmann, H. *Acc. Chem. Res.* **2014**, *47*, 1296.

(2) For metal-catalyzed asymmetric 1,3-DCs of *N*,*N*′-cyclic azomethine imines and related reactions, see: (a) Shintani, R.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 10778. (b) Suárez, A.; Downey, C. W.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 11244. (c) Suga, H.; Funyu, A.; Kakehi, A. *Org. Lett.* **2007**, *9*, 97. (d) Sibi, M. P.; Rane, D.; Stanley, L. M.; Soeta, T. *Org. Lett.* **2008**, *10*, 2971. (e) Arai, T.; Ogino, Y. *Molecules* **2012**, *17*, 6170. (f) Imaizumi, T.; Yamashita, Y.; Kobayashi, S. *J. Am. Chem. Soc.* **2012**, *134*, 20049. (g) Li, J.; Lian, X.; Liu, X.; Lin, L.; Feng, X. *Chem.—Eur. J.* **2013**, *19*, 5134. (h) Wang, M.; Huang, Z. J.; Xu, J. F.; Chi, Y. R. *J. Am. Chem. Soc.* **2014**, *136*, 1214.

(3) For organocatalytic asymmetric 1,3-DCs of *N*,*N*′-cyclic azomethine imines, see: (a) Chen, W.; Yuan, X.-H.; Li, R.; Du, W.; Wu, Y.; Ding, L.-S.; Chen, Y.-C. *Adv. Synth. Catal.* **2006**, *348*, 1818. (b) Chen, W.; Du, W.; Duan, Y.-Z.; Wu, Y.; Yang, S.-Y.; Chen, Y.-C. *Angew. Chem., Int. Ed.* **2007**, *46*, 7667. (c) Suga, H.; Arikawa, T.; Itoh, K.; Okumura, Y.; Kakehi, A.; Shiro, M. *Heterocycles* **2010**, *81*, 1669. (d) Hong, L.; Kai, M.; Wu, C.-Y.; Sun, W.-S.; Zhu, G.-M.; Li, G.-F.; Yao, X.-J.; Wang, R. *Chem. Commun.* **2013**, *49*, 6713.

(4) For asymmetric IED 1,3-DCs of *N*,*N*′-cyclic azomethine imines with alkenes, see: (a) Kato, T.; Fujinami, S.; Ukaji, Y.; Inomata, K. *Chem. Lett.* **2008**, *37*, 342. (b) Tanaka, K.; Kato, T.; Ukaji, Y.; Inomata, K. *Heterocycles* **2010**, *80*, 887. (c) Tanaka, K.; Kato, T.; Fujinami, S.; Ukaji, Y.; Inomata, K. *Chem. Lett.* **2010**, *39*, 1036. (d) Yoshida, M.; Sassa, N.; Kato, T.; Fujinami, S.; Soeta, T.; Inomata, K.; Ukaji, Y. *Chem.—Eur. J.* **2014**, *20*, 2058.

(5) For some representative racemic reactions of *N*,*N*′-cyclic azomethine imines, see: (a) Shintani, R.; Hayashi, T. *J. Am. Chem. Soc.* **2006**, *128*, 6330. (b) Chan, A.; Scheidt, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 5334. (c) Shapiro, N. D.; Shi, Y.; Toste, F. D. *J. Am. Chem. Soc.* **2009**, *131*, 11654. (d) Na, R.; Jing, C.; Xu, Q.; Jiang, H.; Wu, X.; Shi, J.; Zhong, J.; Wang, M.; Benitez, D.; Tkatchouk, E.; Goddard, W. A.; Guo, H.; Kwon, O. *J. Am. Chem. Soc.* **2011**, *133*, 13337. (e) Yu, Q.; Peter, J. Z.; Hu, W.; Doyle, M. P. *Org. Lett.* **2013**, *15*, 1564. (f) Zhu, G. M.; Sun, W. S.; Wu, C. Y.; Li, G. F.; Hong, L.; Wang, R. *Org. Lett.* **2013**, *15*, 4988. (g) Li, Z.; Yu, H.; Liu, L. H.; Zhang, L.; Jiang, H.; Wang, B.; Guo, H. C. *Chem.—Eur. J.* **2014**, *20*, 1731.

(6) (a) Boyd, D. B. *J. Med. Chem.* **1993**, *36*, 1443. (b) Michel, M.; Manfred, B.; Fredrik, C.; Derek, C.; Friedmann, A. A.; Jutta, G.; Thierry, N.; Andre, S.; Trixie, W. *Bioorg. Med. Chem.* **2009**, *17*, 4241. (c) Kamata, M.; Yamashita, T.; Kina, A.; Tawada, M.; Endo, S.; Mizukami, A.; Sasaki, M.; Tani, A.; Nakano, Y.; Watanabe, Y.; Furuyama, N.; Funami, M.; Amano, N.; Fukatsu, K. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 4769. (d) Sheng, Y.; Daniel, G.; Katharina, W.; Bettina, L.; Michael, S.; Juergen, S. *Bioorg. Med. Chem.* **2011**, *19*, 4669.

(7) Hashimoto, T.; Omote, M.; Maruoka, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 3489.

(8) For a review: de Graaff, C.; Ruijter, E.; Orru, R. V. A. *Chem. Soc. Rev.* **2012**, *41*, 3969.

(9) For early examples: (a) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 1566. (b) Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356. For reviews: (c) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744. (d) Terada, M. *Chem. Commun.* **2008**, *35*, 4097. (e) Terada, M. *Synthesis* **2010**, 1929. (f) Yu, J.; Shi, F.; Gong, L. Z. *Acc. Chem. Res.* **2011**, *44*, 1156.

(10) (a) Shi, F.; Zhu, R.-Y.; Liang, X.; Tu, S.-J. *Adv. Synth. Catal.* **2013**, *355*, 2447. (b) Tan, W.; Du, B.-X.; Li, X.; Zhu, X.; Shi, F.; Tu, S.-J. *J. Org. Chem.* **2014**, *79*, 4635. (c) Shi, F.; Zhu, R.-Y.; Dai, W.; Wang, C.-S.; Tu, S.-J. *Chem.—Eur. J.* **2014**, *20*, 2597.

(11) (a) Shi, F.; Xing, G.-J.; Tao, Z.-L.; Luo, S.-W.; Tu, S.-J.; Gong, L.-Z. *J. Org. Chem.* **2012**, *77*, 6970. (b) Shi, F.; Xing, G.-J.; Zhu, R.-Y.; Tan, W.; Tu, S. *Org. Lett.* **2013**, *15*, 128. (c) Yu, S.-Y.; Zhang, H.; Gao, Y.; Mo, L.; Wang, S.; Yao, Z.-J. *J. Am. Chem. Soc.* **2013**, *135*, 11402.

(12) (a) Čorić, I.; Müller, S.; List, B. *J. Am. Chem. Soc.* **2010**, *132*, 17370. (b) Xing, C.; Liao, Y.; Ng, J.; Hu, Q. *J. Org. Chem.* **2011**, *76*, 4125. (c) Xu, B.; Zhu, S.; Xie, X.; Shen, J.; Zhou, Q. *Angew. Chem., Int. Ed.* **2011**, *50*, 11483. (d) Xu, F.; Huang, D.; Han, C.; Shen, W.; Lin, X. F.; Wang, Y. *J. Org. Chem.* **2010**, *75*, 8677.

(13) See the Supporting Information for details.

(14) For a review: Parra, A.; Reboredo, S.; Castroa, A. M. M.; Alemán, J. *Org. Biomol. Chem.* **2012**, *10*, 5001.

(15) Lv, J.; Luo, S.-Z. *Chem. Commun.* **2013**, *49*, 847.

(16) Helmut, D.; Thomas, K. *Tetrahedron Lett.* **1988**, *29*, 2939.

(17) CCDC 1006959 for compound **3ka**. See the Supporting Information for details.

(18) (a) Shao, C. W. *Eur. J. .Org. Chem.* **2013**, *28*, 6443. (b) Xin, Y. *J. Fluorine. Chem.* **2011**, *132*, 402.

(19) (a) Elias, X.; Pleixats, R.; Man, M. W. C. *Tetrahedron* **2008**, *64*, 6770. (b) Chatterjee, A. K.; Toste, F. D.; Goldberg, S. D.; Grubbs, R. H. *Pure Appl. Chem.* **2003**, *75*, 421.