JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

(1,2-Diaminoethane-1,2-diyl)bis(*N*-methylpyridinium) Salts as a Prospective Platform for Designing Recyclable Prolinamide-Based Organocatalysts

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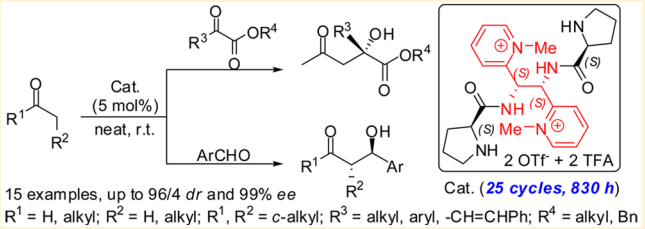
Supporting Information

ABSTRACT: A new efficient and highly recyclable organocatalyst has been developed for asymmetric cross-aldol reactions under neat conditions in ketone−ketone, ketone−aldehyde, and aldehyde−aldehyde systems. The catalyst features two prolinamide fragments and a C_2-symmetrical (1,2-diaminoethane-1,2-diyl)bis(*N*-methylpyridinium) group. The catalyst retained high activity and excellent stereoselection over the operating period of more than 830 h (25 cycles). An ab initio theoretical investigation explained the absolute configuration of the products and different stereoinduction levels for designed diastereomeric organocatalysts.



INTRODUCTION

Design of sustainable and recyclable organocatalysts that combine structural simplicity with a high-level asymmetric induction is one of the most promising areas of asymmetric catalysis.[1,2] Impressive instances of use of such catalysis have been demonstrated over the past decade at multiscale production facilities in the pharmaceutical industry.[3−7] A significant portion of these results are associated with the asymmetric aldol reaction, extensively used for the enantioselective formation of the carbon−carbon bond in organic (particularly bioactive) compounds.[8−15] Prolinamides are among the most active and enantioselective catalysts for this reaction.[16−23] Known recyclable prolinamide derivatives modified with polymeric[24−28] or ionic[29−34] groups (see, e.g., Scheme 1, catalysts of type **I**) have much lower solubility in reaction masses than the original unsupported catalysts (heterogeneous catalysis), which simplifies their separation from products and enables multiple usages. However, the incorporation of these "heterogenizing" structural units, commonly attached to peripheral areas of the catalyst molecule by means of bi- or polyfunctional spacer groups, requires additional protection/deprotection steps and complicates the synthesis of the catalysts.[35,36] Furthermore, these groups are located distally with respect to the active sites and commonly are not involved in the stereoselection process or, in some cases, even reduce the enantioselectivity of catalytic reactions due to nonspecific interactions with reagents in the transition state.[37]

Herein we propose a new approach to the design of recyclable Brønsted-base-type organocatalysts and, potentially, of catalysts capable of other activation modes. Our approach is to link two catalytically active fragments (e.g., prolinamide-derived) by means of a C_2-symmetrical (1,2-diaminoethane-1,2-diyl)bis(*N*-methylpyridinium) group that acts as a spacer and an ionic tag simultaneously (Scheme 1, catalyst **II**). Our hypothesis was that the pyridinium cations in compound **II**—located proximally with respect to the active sites (amino and amido groups)—would not only facilitate the catalyst recovery by creating a heterogeneous reaction environment, but also play an important role in the catalytic reaction. In particular, we expected that the protons of the amido groups in such hybrid systems[38] would attain higher acidity and hydrogen-bonding ability than in corresponding catalysts without ionic groups and thus lead to a more favorable binding of a reagent in the enamine transition state. Furthermore, the neighboring sterically hindered *N*-methylpyridinium fragments should be able to enhance the enantioselectivity by increasing the energetic gap between the transition states that lead to the enantiomeric products.

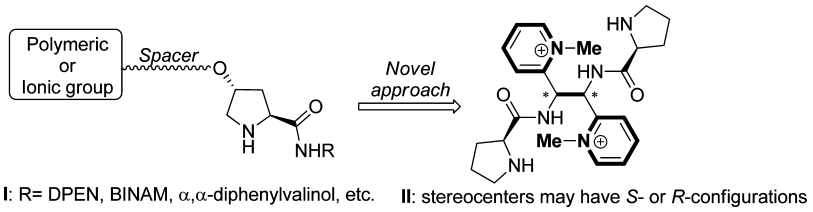
RESULTS AND DISCUSSION

To test our hypothesis, we prepared (*rac*)-1,2-bis(pyridin-2-yl)ethane-1,2-diamine (*rac*-**1**) from 2-pyridinecarboxaldehyde by the literature procedure[39] and separated the enantiomers through diastereomeric recrystallization of the corresponding salts with (*R*)- or (*S*)-mandelic acid (Scheme 2). In this manner, optically pure amines (*R*,*R*)-**1** and (*S*,*S*)-**1** (>99% ee

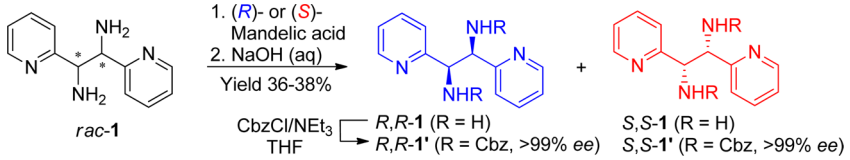
Received: July 7, 2015
Published: September 16, 2015

DOI: 10.1021/acs.joc.5b01555
J. Org. Chem. 2015, 80, 9570−9577

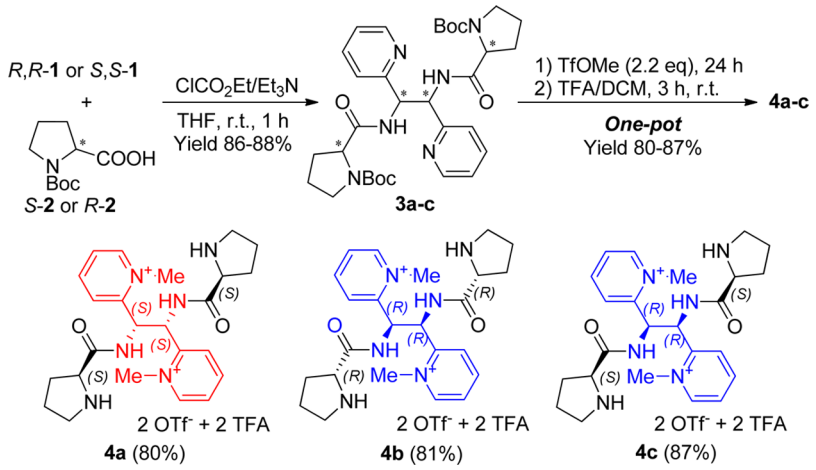
Scheme 1. Research Strategy



Scheme 2. Synthesis of (*S*,*S*)-1 and (*R*,*R*)-1



Scheme 3. Synthesis of Organocatalysts 4a–c



according to an HPLC analysis of the corresponding bis-Cbz derivatives, (*S*,*S*)-**1**′ and (*R*,*R*)-**1**′) were obtained in 38% and 36% yields, respectively. The diamine (*S*,*S*)-**1** ($[\alpha]_D^{20}$ +107.2 (*c* 1.40, $CHCl_3$)) obtained from 2,2′-((1*S*,2*S*)-1,2-diaminoethane-1,2-diyl)diphenol (hpen) and 2-pyridinecarboxaldehyde by stereospecific[40,41] diaza-Cope rearrangement (see the Experimental Section) had the same sign of the optical rotation as the sample obtained from *rac*-**1** and (*S*)-mandelic acid ($[\alpha]_D^{20}$ +104.6 (*c* 0.99, $CHCl_3$)), thus establishing its absolute (*S*,*S*)-configuration.

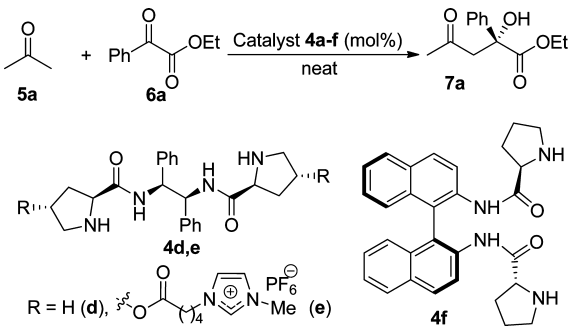
Compounds (*R*,*R*)-**1** and (*S*,*S*)-**1** were further converted to bisamides **3a–c** by a treatment with N-protected proline derivative (*S*)-**2** or (*R*)-**2** in the presence of $ClCO_2Et/Et_3N$ in THF (Scheme 3). Our attempts to alkylate both pyridine nitrogen atoms in **3a** with MeI did not succeed: an inseparable mixture of mono- and bisalkylation products was generated even in the presence of a significant (15–20 equiv) excess of MeI in a sealed tube at 70–80 °C.[42] However, the desired bisalkylation products were generated in the presence of a stronger alkylating agent (MeOTf) under mild conditions (ambient temperature). One-pot deprotection of the latter with TFA/DCM afforded the corresponding diastereo- and enantiomeric bisprolinamides **4a–c** in 80–87% yield with respect to compounds **3**.

Then we tested the catalytic performance of prolinamides **4a–c** in asymmetric aldol reactions of acetone **5a** with α-ketoesters **6a–g**. The reaction products, chiral α-hydroxy-γ-ketoesters **7**, are used as precursors for the synthesis of natural compounds and ingredients of pharmaceutically valuable compositions.[43−47] Known organocatalysts usually exhibit only a moderate enantioselectivity in these reactions.[48−51] The enantioselectivity can be improved by carrying out the reactions at a lower reaction temperature (−20 to −30 °C) and/or in the presence of an excess acidic cocatalyst, although the latter significantly complicates recycling of binary catalytic systems.[52−55] Efficient supported organocatalysts for asymmetric cross-aldol reactions between two ketone molecules have not been reported so far.

To identify the best catalyst and optimize the reaction conditions, we examined the activity and stereoselection of catalysts **4a–c** in the model reaction between acetone (**5a**) and ethyl 2-oxo-2-phenylacetate (**6a**). To meet green chemistry requirements, all experiments were performed in neat acetone typically at ambient temperature and with a catalyst loading of 2–10 mol % (Table 1). At first, we observed that the increase of the **5a**/**6a** molar ratio from 4 to 20 exerted a favorable impact on the activity of catalyst **4a** and enantioselectivity of the model reaction (entries 1–3). The chemical yield and ee value of aldol **7a** in the **4a**-catalyzed (10 mol %) reaction between **5a** and **6a** were significantly higher than in the corresponding reaction catalyzed by diastereomer **4c** (Table 1, entry 3 vs entry 4) (for other examples of the mismatched effect in prolinamides attached to structures bearing additional stereocenters, see ref 56). The enantiomeric enrichment of

DOI: 10.1021/acs.joc.5b01555
J. Org. Chem. 2015, 80, 9570−9577

Table 1. Testing of Catalysts 4a−c in the Model Reaction between 5a and 6a[a]



entry	4 (concn, mol %)	5a/6a molar ratio	T (°C)	time (h)	yield of 7a[b] (%)	ee[c] (%)
1	**4a** (10)	4	20	96	84	80 (*R*)
2	**4a** (10)	10	20	48	61	85 (*R*)
3	**4a** (10)	20	20	48	88	86 (*R*)
4	**4c** (10)	20	20	48	9	64 (*R*)
5	**4a** (5)	20	20	48	84	89 (*R*)
6	**4a** (5)	20	3	48	44	82 (*R*)
7	**4b** (5)	20	20	48	86	89 (*S*)
8[d]	*ent*-**4d** (15)	27	−20	16	92	93 (*S*)
9[e]	**4e** (20)	5	−30	24	99	84 (*R*)
10[f]	**4f** (20)	5	0	75	90	68 (*S*)

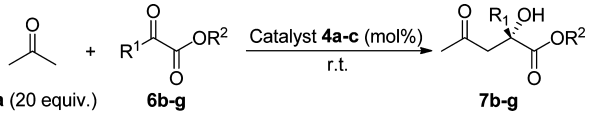
[a]The reactions were carried out with catalyst **4** (5−20 mol %), ketone **5a** (2−10 mmol), and ketoester **6a** (0.50 mmol). [b]Isolated yield. [c]HPLC data were obtained on the chiral phase. [d]Reported[52] data for catalyst *ent*-**4d** with AcOH (1.5 equiv) additive. [e]Reported[57] data for supported catalyst **4e** with H_2O (4 equiv) and AcOH (0.5 equiv) additive. [f]Reported[50] data for catalyst **4f** with $ClCH_2CO_2H$ (1 equiv) additive.

aldol **7a** was raised to 89% ee by reducing the **4a** loading to 5 mol % (entry 5). A lower reaction temperature decreased the reaction rate and reduced the enantioselectivity (entry 6). In the presence of enantiomeric catalyst **4b** (5 mol %) under optimal conditions (rt, 48 h), the reaction afforded the (*S*)-antipode of product **7a** in 86% yield and with 89% ee (entry 7). Catalysts **4a** and **4b** exhibited noticeably better stereoselection in the studied reactions than the ionic liquid-supported bisprolinamide **4e** bearing the 1,2-diphenylethylene unit (entry 9),[57] or BINOL-derived bisprolinamide **4f** (entry 10);[50] however, it appeared somewhat inferior to the unsupported analogue **4d** (entry 8).[52] Nevertheless, catalysts **4a** and **4b** are advantageous as they can be used in lower amounts and the developed procedure allows catalytic reactions to run at ambient temperature without an acidic additive.

2-Oxo-2-phenylacetic esters **6b−d**, in particular compounds **6c** and **6d** bearing substituents in the aromatic ring, efficiently reacted with **5a** under the proposed conditions to produce the corresponding aldols **7b−d** in a nearly quantitative yield and with enantioselectivities of 90−92% ee (Table 2, entries 1−3). *β*,*γ*-Unsaturated *α*-ketoester **6e** also appeared to be a suitable acceptor, to afford aldol **7e**, though stereoinduction was somewhat lower in this case (entry 4). In the presence of **4a** (5 mol %), aliphatic 2-carboxylic esters **6f** and **6g** reacting with **5a** produced aldol products **7f** and **7g** with 84% and 90% ee, respectively (entries 5 and 6). Further reduction of the catalyst **4a** loading (2 mol %) allowed the synthesis of aldol **7g** in a highly enantioselective manner (99% ee), though at the expense of a prolonged reaction time (entry 7). Enantiomeric catalyst **4b** produced antipode *ent*-**7g** with the same extremely high enantioselectivity, whereas diastereomer **4c** performed much worse (entries 8 and 9). The scalability of the developed procedure was demonstrated by the **4a**-catalyzed (2 mol %) enantioselective batch synthesis of compound **7g** on a 7.0 g scale. The absolute (*R*)-configuration was assigned[49,55] to products **7a−e** and the (*S*)-configuration[58] to product **7f** of **4a**- and **4c**-catalyzed aldol reactions on the basis of the similarity of their optical rotation signs with the reported data. The geometrically similar (*S*)-configuration was assigned to product **7g** by analogy. The similarity of the absolute configurations for asymmetric products produced in **4a**- and **4c**-catalyzed aldol reactions shows that the enantioselection is dictated by the stereochemistry of the prolinamide component of the catalyst, whereas the absolute configuration of the 1,2-bis(pyridin-2-yl)ethane-1,2-diamine unit plays an important but auxiliary role in the catalytic process.

To probe the sustainability and versatility of catalyst **4a** in asymmetric aldol reactions, we ran a series of catalytic experiments using various carbonyl compounds. Note that these experiments were performed under neat conditions in the presence of the same sample of **4a** (5 mol %) recovered from the previous aldol reaction via the product extraction with diethyl ether, in which bisamide **4a** is nearly insoluble and is

Table 2. Catalytic Asymmetric Aldol Reactions of Acetone (5a) with *α*-Ketoesters 6b−g[a]

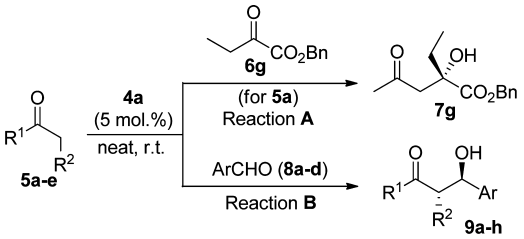


entry	R^1, R^2	4 (concn, mol %)	time (h)	yield[b] (%)	ee[c] (%)
1	Ph, Me (**6b**)	**4a** (5)	24	94 (**7b**)	90 (*R*)
2	4-$MeOC_6H_4$, Me (**6c**)	**4a** (5)	24	95 (**7c**)	91 (*R*)
3	3-ClC_6H_4, Me (**6d**)	**4a** (5)	24	87 (**7d**)	92 (*R*)
4	(*E*)-PhCH=CH−, Me (**6e**)	**4b** (5)	20	96 (**7e**)	80 (*S*)
5	Me, Bn (**6f**)	**4a** (5)	24	95 (**7f**)	84 (*S*)
6	Et, Bn (**6g**)	**4a** (5)	24	96 (**7g**)	90 (*S*)
7	Et, Bn (**6g**)	**4a** (2)	72	90 (96[d]) (**7g**)	99 (98[d]) (*S*)
8	Et, Bn (**6g**)	**4b** (2)	72	88 (*ent*-**7g**)	99 (*R*)
9	Et, Bn (**6g**)	**4c** (2)	72	12 (**7g**)	44 (*S*)

[a]The reactions were carried out with catalyst **4** (2−5 mol %), ketone **5a** (10 mmol), and ketoester **6** (0.50 mmol). [b]Isolated yield. [c]HPLC data were obtained on the chiral phase. [d]The reaction was carried out with **4a** (2 mol %), **5a** (45 mL, 0.62 mol), and **6g** (6.0 g, 31 mmol).

DOI: 10.1021/acs.joc.5b01555
J. Org. Chem. 2015, 80, 9570−9577

Table 3. Applicability and Recyclability of Catalyst 4a



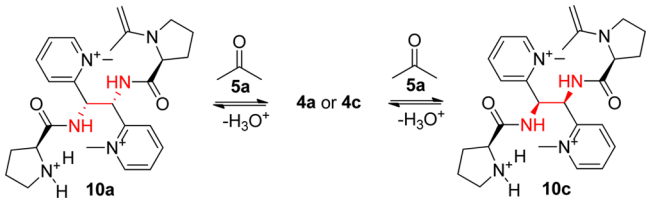
cycle	reaction[a]	R_1, R_2	Ar	time (h)	yield[b] (%)	dr (*anti*/*syn*)	ee (*anti*) (%)
1–5	A	CH_3, H (**5a**)		24	94–96 (**7g**)		90–91
6–15	B	$-(CH_2)_4-$ (**5b**)	4-$O_2NC_6H_4$ (**8a**)	24	88–92 (**9a**)	93/7 to 95/5	88–92
16	B		2-$O_2NC_6H_4$ (**8b**)	48	50 (53[c]) (**9b**)	96/4 (97/3)	99 (99[c])
17	B		4-$MeO_2CC_6H_4$ (**8c**)	48	69 (74[c]) (**9c**)	95/5 (95/5)	94 (91[c])
18	B		2-BrC_6H_4 (**8d**)	48	73 (73[c]) (**9d**)	92/8 (92/8)	84 (86[c])
19	B		4-$O_2NC_6H_4$ (**8a**)	24	95 (**9a**)	92/8	90
20	B	$-(CH_2)_3-$ (**5c**)		40	97 (**9e**)	32/68	80 (52[d])
21[e]	B	CH_3, H (**5a**)		72	75 (**9f**)		90
22	B	Et, H (**5d**)		48	52 (**9g**)		84
23	B	H, CH_3 (**5e**)		24	90 (**9h**)	93/7	97[f]
24	A	CH_3, H (**5a**)		60	90 (**7g**)		99
25	A			60	91 (**7g**)		99

[a]Conditions for reaction A: catalyst **4a** obtained from the previous cycle (0.025 mmol, 5 mol %), **5a** (10 mmol), **6g** (0.5 mmol), neat, at rt for the specified time. Conditions for reaction B: catalyst **4a** obtained from the previous cycle (0.025 mmol, 5 mol %), **5** (2 mmol), **8** (0.5 mmol), neat at rt for the specified time. [b]Isolated yield. [c]Data for a fresh portion of catalyst **4a**. [d]Data for the *syn*-isomer. [e]The reaction was performed at 3 °C. [f]The ee was determined for the corresponding diol after reduction of **9f** with $NaBH_4$.

used in the next cycle without further purification or activation. First, we found that the catalyst retained its activity and a stereoselecting function in the reaction between **5a** and **6g** over five consecutive cycles (Table 3, cycles 1–5). Afterward, catalyst **4a** recovered from the fifth cycle was tested in asymmetric aldol reactions of cycloalkanone **5b** or **5c** (4 equiv) with arylaldehydes **8a–d** (cycles 6–20) with only a slight drop in its activity observed in the 16th and 17th cycles relative to the freshly prepared **4a**; the diastereo- and enantioselectivities were perfect in most cases. Next, a sample of the same catalyst operated over 20 cycles was applied to asymmetric aldol reactions of methylketones **5a** and **5d** with aldehyde **8a** (cycles 21 and 22). The corresponding aldols **9f** and **9g** were generated in these reactions in moderate yields but with relatively high enantiomeric purity (90% and 84% ee, respectively). The 22-fold recovered sample of **4a** retained its activity as a catalyst in asymmetric cross-aldol reactions between two aldehydes. In its presence, propanal **5e** reacted with aldehyde **8a** in the studied conditions to afford *β*-hydroxyaldehyde **9h** in 90% yield and with excellent *anti*-diastereo- and enantioselectivity (cycle 23). Finally, we re-examined the test sample of catalyst **4a** in the reaction of acetone (**5a**) with ketoester **6g** and were pleased to discover that the yield of aldol **7g** remained nearly the same as in the first five cycles, whereas the reaction enantioselectivities improved from 91% to 99% ee (cycles 24 and 25). The rising enantioselectivity and increasing reaction time (from 24 to 60 h) may be attributed in this case to a loss of the recovered catalyst mass due to its gradual leaching to the organic solution during multiple workups (for comparison, see Table 2, entries 6 and 7). Hence, the developed catalyst actually retained its catalytic performance in asymmetric aldol reactions of various types over more than 830 h. The excellent recoverability of **4a** may be caused by the favorable impact of the incorporated acidic units (TFA), which apparently suppress the formation of parasitic imidazolidinone byproducts[59] and prolong the lifetime of **4a**. Given a favorable combination of the catalytic properties (activity, selectivity, and sustainability) and a remarkably wide application area of catalyst **4a**, it is arguably one of the most prospective recyclable organocatalysts for these reactions.

To rationalize the differences in catalytic activity and stereoselectivity of diastereomeric catalysts **4a** and **4c**, we investigated theoretically the model catalytic asymmetric aldol reaction between acetone (**5a**) and ketoester **6g** under the assumption that **4a** and **4c** reversibly generate merely the corresponding mono-*trans*-enamine intermediates **10a** and **10c** with **5a** under the proposed acidic conditions (Scheme 4).[50,52]

Scheme 4. Enamine Formation



For each catalyst, we obtained geometries for two plausible transition states, **TS-10-R** and **TS-10-S** (Figure 1), each having a single imaginary frequency corresponding to the newly formed C–C bond, at the HF/6-31G(d) level[60] with the IEFPCM (integral equation formalism polarizable continuum model) (acetone) implicit solvation model[61] using the Gaussian 09 package[62] (Figure 1). Using the intrinsic reaction coordinate (IRC) method,[63] we confirmed that these transition states were connected by the minimum energy path to the corresponding prereaction complexes and products (the Cartesian geometries of all complexes are given in the Supporting Information).

According to our calculations, the common feature of all enamine-derived TSs and prereaction complexes is the

DOI: 10.1021/acs.joc.5b01555
J. Org. Chem. 2015, 80, 9570–9577

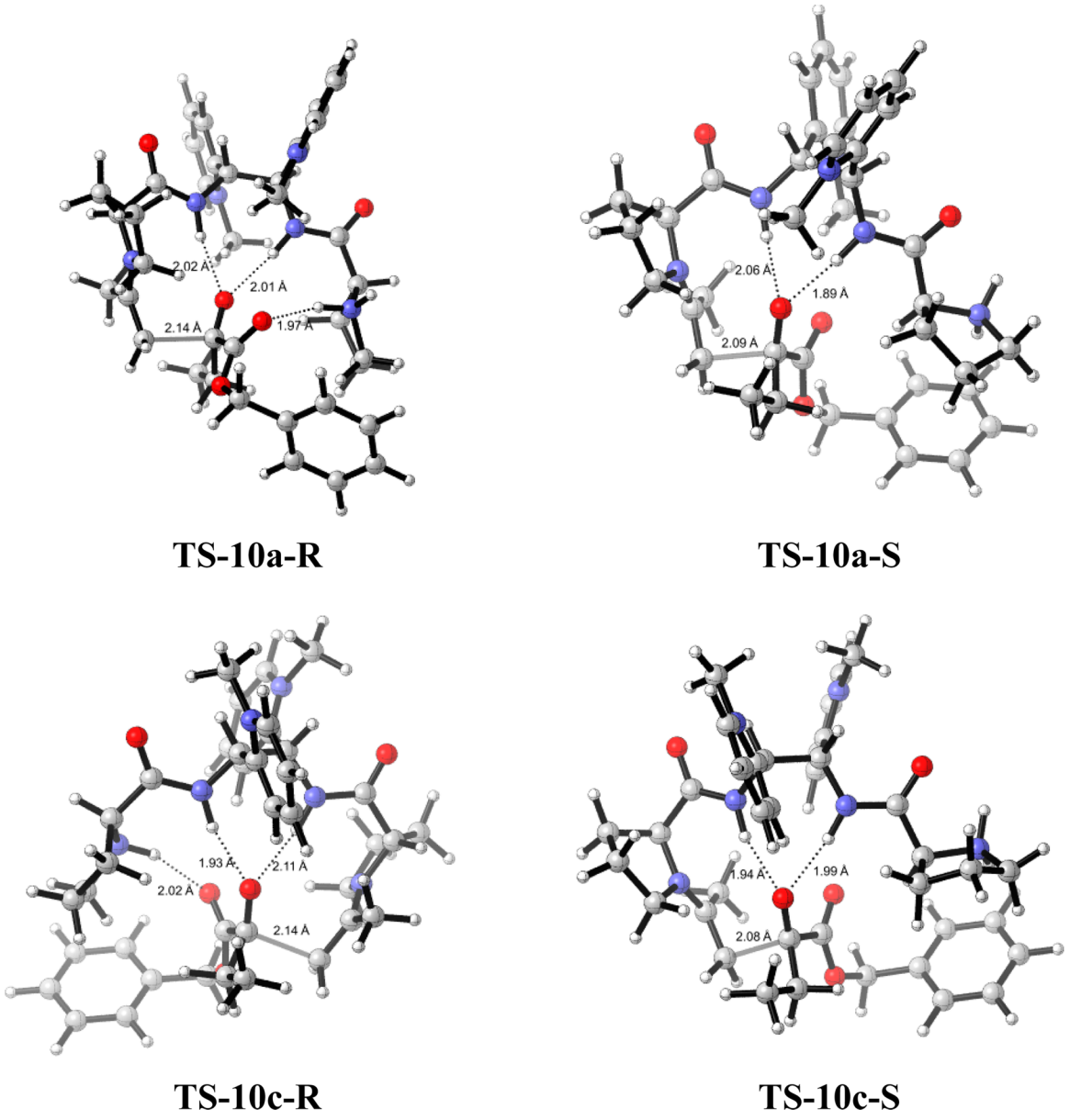


Figure 1. Transition states for the **4a**- or **4c**-catalyzed model reaction of **5a** with **6d**.

presence of two symmetrical hydrogen bonds between the keto group of **6g** and acidic NH protons of the amido group of enamines **10**; these hydrogen bonds make the keto group more electrophilic and stabilize the resulting zwitterion.[64] The (*R*)-enantiomeric TSs and complexes are further stabilized by a hydrogen bond between the protonated pyrrolidinium unit and the ester group of **6g**; such a hydrogen bond is not observed for the (*S*)-counterparts. Note that, to allow both amide protons to bind to the substrate, the N−C−C−N torsion angle must be restricted (from −60° to +60°); we hypothesize that this is achieved by steric interactions between the adjacent bulky *N*-methylpyridinium fragments attached to the diamine framework (highlighted in red in Scheme 4). The more favorable (smaller in magnitude) torsion angles within the optimal range are afforded in the case of enamine **10a**-derived transition states (Table 4).

Next, to gauge the accuracy of the Hartree−Fock-predicted relative energies of enamine **10a**- or **10c**-derived prereaction complexes and transition states, we recalculated their single-point energies using the density functional theory (using the B3LYP/cc-pVTZ level of theory)[65,66] with the IEFPCM (acetone) implicit solvent model (zero-point energy correction was included in all reported energies). Although the Kohn−

Table 4. Calculated Activation Energies for the 4a- or 4c-Catalyzed Model Reaction of 5a with 6g

		$\Delta H^{\ddagger}$(0 K) (kcal/mol)		ee (%)		
		calcd values*				
transition state	torsion (N−C−C−N) angle (deg)	A	B	A	B	exptl data
TS-10a-S	25	1.7	9.0	75	87	99
TS-10a-R	33	2.9	10.5	75	87	99
TS-10c-S	−53	2.1	9.6	33	30	44
TS-10c-R	−59	2.5	9.9	33	30	44

*Method A: B3LYP/cc-pVTZ//HF/6-31G(d). Method B: HF/6-31G(d).

DOI: 10.1021/acs.joc.5b01555
J. Org. Chem. 2015, 80, 9570−9577

Sham DFT methods are typically much more accurate than the Hartree−Fock method due to the efficient inclusion of electron correlation, DFT is notorious for underestimating the reaction barriers and for its propensity for excessive charge over-delocalization, due to the so-called self-interaction error,[67] which does not affect the Hartree−Fock method. Thus, while the activation energies predicted by DFT are dramatically lower than those obtained at the Hartree−Fock level, in agreement with other studies,[68] we found an excellent agreement between DFT and HF predictions for the relative energetics of the enantiomeric transition states. For enamine **10a**, the energy barrier between **TS-10a-S** and the corresponding (*S*)-enantiomeric prereaction complex is predicted by DFT to be 1.2 kcal/mol lower than the barrier between **TS-10a-R** and the (*R*)-enantiomeric prereaction complex (Hartree−Fock predicts a 1.5 kcal/mol difference); this corresponds[69] to 75% ee (B3LYP/cc-pVTZ) or 87% ee (HF/6-31G(d)) toward the (*S*)-enantiomer (Table 3). On the other hand, the difference in activation energies between (*S*)- and (*R*)-transition states (**TS-10c-S** and **TS-10c-R**, respectively) for enamine **10c** is predicted by DFT to be just 0.4 kcal/mol (HF predicts 0.3 kcal/mol); this corresponds to 33% ee (B3LYP/cc-pVTZ) or 30% ee (HF/6-31G(d)) toward the (*S*)-enantiomer. The excellent agreement of these predictions with the experimental observations (99% and 44% ee, respectively; see Table 2) lends further credibility to the mechanistic insights provided by the ab initio theory.

CONCLUSIONS

We have proposed a novel approach to the design of sustainable and recoverable organocatalysts for the asymmetric synthesis. It is based on the linkage of two chiral amide fragments by means of the C_2-symmetrical (1,2-diaminoethane-1,2-diyl)bis(*N*-methylpyridinium) group. This pattern produced highly recyclable prolinamide-derived organocatalysts for asymmetric cross-aldol reactions in ketone−ketone, ketone−aldehyde, and aldehyde−aldehyde systems under simple experimental conditions (rt, solvent-free). The novel catalysts retained high activity and excellent stereoselection over the operating period of more than 830 h. Theoretical predictions for the geometries and relative energetics of plausible prereaction complexes and transition states clearly rationalized the observed absolute configuration of the products and the relative stereoselectivity for diastereomeric organocatalysts.

EXPERIMENTAL SECTION

General Procedures. HRMS (high-resolution mass spectrometry) spectra were measured using electrospray ionization (ESI) and a time-of-flight (TOF) mass analyzer. The measurements were taken in the positive ion mode (interface capillary voltage 4500 V) in the mass range from m/z = 50 Da to m/z = 3000 Da; external or internal calibration was done with an electrospray calibrant solution. NMR spectra were recorded on a 300 or 600 MHz spectrometer. Optical rotations were measured on a polarimeter and calibrated with pure solvent as a blank. HPLC analyses were performed on an HPLC system equipped with chiral stationary phase columns, detection at 220 or 254 nm. Silica gel (0.060−0.200 mm) was used for column chromatography. All reagents and solvents were purified and dried according to common methods.

Synthesis of Organocatalysts 4a−c. *(1S,2S)-1,2-Bis(pyridin-2-yl)ethane-1,2-diamine ((S,S)-**1**). Method A.* (*S*)-Mandelic acid (4.20 g, 27.6 mmol) was dissolved in hot EtOAc (50 mL), and the resulting solution was added to *rac*-**1** (3.00 g, 14.0 mmol). The resulting suspension was refluxed for 40 min until a white precipitate was formed. It was filtered and washed with hot EtOAc (3 × 50 mL) to give the corresponding dimandelate salt, which was further dissolved in a 10 M aqueous solution of NaOH (5 mL). The mixture was diluted with CH_2Cl_2 (20 mL), and the phases were separated. The organic phase was successively washed with a small volume of water and brine. It was dried over anhydrous sodium sulfate and concentrated to give (*S*,*S*)-**1** as a colorless oil (1.08 g, 36%; >99% ee). $[\alpha]_D^{20}$: +104.6 (*c* 0.99, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.53 (d, J = 4.3 Hz, 2H), 7.46 (td, J = 7.7, 1.5 Hz, 2H), 7.09−7.02 (m, 4H), 4.22 (s, 2H), 1.99 (s(br), 4H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.3, 149.0, 136.1, 122.2, 121.9, 62.2 ppm. HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{12}H_{15}N_4^+$ 215.1291, found 215.1288.

Method B. This compound was synthesized by analogy with the literature procedure.[70] Yield: 74% (0.13 g, starting from 0.20 g of (*S*,*S*)-hpen). $[\alpha]_D^{20}$: +107.2 (*c* 1.40, $CHCl_3$). HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{12}H_{15}N_4^+$ 215.1291, found 215.1290.

*(1R,2R)-1,2-Bis(pyridin-2-yl)ethane-1,2-diamine ((R,R)-**1**).* The (*R*,*R*)-enantiomer was synthesized by method A using (*R*)-mandelic acid and *rac*-**1** (4.24 g) to afford (*R*,*R*)-**1** (1.59 g, 38%; 99% ee). $[\alpha]_D^{20}$: −100.5 (*c* 0.70, $CHCl_3$). The ^{1}H and ^{13}C NMR data corresponded to those for enantiomer (*S*,*S*)-**1**.

*Dibenzyl ((1S,2S)-1,2-Bis(pyridin-2-yl)ethane-1,2-diyl)-dicarbamate ((S,S)-**1′**).* To the solution of (*S*,*S*)-**1** (0.10 g, 0.5 mmol) in dry THF (1 mL) were sequentially added Et_3N (140 μL, 1.0 mmol) and CbzCl (150 μL, 1.0 mmol). The resulting solution was stirred for 24 h at room temperature. Then the reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate) to give (*S*,*S*)-**1′** in 73% yield (0.16 g). Mp: 135−137 °C. $[\alpha]_D^{20}$: −6.8 (*c* 1.0, $CHCl_3$). Ee: 99%. For HPLC data see the Supporting Information. ^{1}H NMR ($CDCl_3$): δ 8.44 (m, 2H), 7.25−7.43 (m, 12H), 7.07 (m, 2H), 6.87 (m, 2H), 6.65 (s(br), 2H), 5.27 (s, J = 6.2 Hz, 2H), 5.08 (m, 4H) ppm. ^{13}C NMR ($CDCl_3$): δ 157.6, 156.3, 149.0, 136.7, 136.6, 128.5, 128.0, 127.8, 122.5, 122.4, 66.8, 59.9 ppm. HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{28}H_{27}N_4O_4^+$ 483.2027, found 483.2029.

*Dibenzyl ((1R,2R)-1,2-Bis(pyridin-2-yl)ethane-1,2-diyl)-dicarbamate ((R,R)-**1′**).* The compound was prepared similarly from (*R*,*R*)-**1** (0.10 g, 0.5 mmol). Yield: 0.15 g (70%). Colorless solid. Mp: 136−138 °C. $[\alpha]_D^{20}$: +6.1 (*c* 0.9, $CHCl_3$). Ee: 99%. For HPLC data see the Supporting Information. The ^{1}H and ^{13}C NMR data corresponded to those for enantiomer (*S*,*S*)-**1′**.

*(1S,2S)-N,N′-Bis[(S)-Boc-prolyl]-1,2-bis(pyridin-2-yl)ethane-1,2-diamine (**3a**).* Et_3N (0.32 mL, 0.24 g, 2.34 mmol) and ethyl chloroformate (0.22 mL, 0.25 g, 2.34 mmol) were sequentially added to a solution of Boc-(*S*)-proline ((*S*)-**2**) (0.50 g, 2.34 mmol) in THF (5 mL). After 0.5 h of stirring at rt, a solution of (*S*,*S*)-**1** (0.25 g, 1.17 mmol) in THF (2 mL) was added, and stirring was continued for another 0.5 h. The reaction mixture was then filtered, and the filtrate was concentrated under reduced pressure. The resulting crude product was purified by column chromatography (EtOAc/MeOH = 20/1) to give **3a** (0.61 g, 86%) as a colorless solid. Mp: 81−84 °C. $[\alpha]_D^{20}$: −103.4 (*c* 1.0, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.78−9.23 (m, 2H), 8.45 (m, 2H), 7.41−7.44 (m, 2H), 7.22−7.04 (m, 4H), 5.43 (m, 2H), 4.40 (m, 2H), 3.73−3.53 (m, 4H), 1.98−2.22 (m, 8H), 1.48 (s, 9H), 1.37 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.5, 158.5, 154.4, 148.4, 136.5, 122.3, 121.3, 80.22, 61.6, 60.0, 56.2, 46.8, 31.2, 30.14, 28.3, 24.4, 23.4 ppm. HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{32}H_{44}N_6O_6^+$ 609.3395, found 609.3391.

*(1R,2R)-N,N′-Bis[(R)-Boc-prolyl]-1,2-bis(pyridin-2-yl)ethane-1,2-diamine (**3b**).* The compound was prepared similarly from (*R*,*R*)-**1** (0.17 g) and Boc-(*R*)-proline ((*R*)-**2**). Yield: 0.42 g (88%). Colorless solid. Mp: 82−84 °C. $[\alpha]_D^{20}$: +112.9 (*c* 1.1, MeOH). The ^{1}H and ^{13}C NMR data corresponded to those for enantiomer **3a**. HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{32}H_{44}N_6O_6^+$ 609.3395, found 609.3393.

*(1R,2R)-N,N′-Bis[(S)-Boc-prolyl]-1,2-bis(pyridin-2-yl)ethane-1,2-diamine (**3c**).* The compound was prepared similarly from (*R*,*R*)-**1** (0.29 g) and Boc-(*S*)-proline ((*S*)-**2**). Yield: 0.72 g (88%). Colorless solid. Mp: 79−82 °C. $[\alpha]_D^{20}$: −11.9 (*c* 1.0, MeOH). ^{1}H NMR (300 MHz,

DOI: 10.1021/acs.joc.5b01555
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$CDCl_3$): δ 8.96−8.72 (m, 2H), 8.45 (m, 2H), 7.42 (m, 2H), 7.05−6.91 (m, 4H), 5.51 (d, J = 5.8 Hz, 2H), 4.37−4.32 (m, 2H), 3.55−3.40 (m, 4H), 2.25−1.76 (m, 8H), 1.43 (s, 9H), 1.35 (s, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.5, 158.3, 154.3, 148.5, 136.4, 122.3, 121.9, 80.3, 61.1, 60.2, 56.8, 46.7, 31.0, 28.3, 24.5, 23.7 ppm. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{32}H_{44}N_6O_6^+$ 609.3395, found 609.3393.

*(1S,2S)-N,N′-Bis[(S)-prolyl]-1,2-bis(1-methylpyridin-2-yl)ethane-1,2-diamine Bis(triflate)/Bis(trifluoroacetate) (**4a**).* Freshly distilled methyl trifluoromethansulfonate (0.20 mL, 0.30 g, 1.85 mmol) was added to a solution of **3a** (0.50 g, 0.84 mmol) in CH_2Cl_2 (5 mL) The reaction mixture was stirred for 24 h at rt. Then TFA was gradually added (1 mL, 13.07 mmol) while the reaction mixture was stirred. After 2 h the solution was concentrated under reduced pressure, and the residue was washed with Et_2O (3 × 10 mL) to afford **4a** as a colorless solid (0.62 g, 80%). Mp: 175−177 °C dec. $[\alpha]_D^{20}$: −30.2 (*c* 1.0, MeOH). ^1H NMR (600 MHz, d_6-DMSO): δ 10.14 (m, 2H), 9.09 (m, 2H), 8.51 (m, 2H), 8.30 (m, 2H), 8.09 (m, 2H), 6.13 (d, J = 4.3 Hz, 2H), 4.40 (s, 6H), 4.31 (m, 2H), 3.21 (m, 4H), 2.31−1.71 (m, 8H). ^{13}C NMR (150 MHz, d_6-DMSO): δ 169.5, 152.0, 148.7, 146.6, 128.4, 128.2, 59.5, 50.6, 46.8, 46.0, 29.1, 23.8 ppm. ^{19}F NMR (282 MHz, d_6-DMSO): δ −73.78, −77.76 ppm. Anal. Calcd for $C_{30}H_{36}F_{12}N_6O_{12}S_2$: C, 37.35; H, 3.76; N, 8.71. Found: C, 37.71; H, 3.80; N, 8.61.

*(1R,2R)-N,N′-Bis[(R)-prolyl]-1,2-bis(1-methylpyridin-2-yl)ethane-1,2-diamine Bis(triflate)/Bis(trifluoroacetate) (**4b**).* The compound was prepared similarly from **3b** (0.37 g). Yield: 0.46 g (81%). Colorless solid. Mp: 170−173 °C dec. $[\alpha]_D^{20}$: +28.9 (*c* 1.0, MeOH). The ^1H, ^{19}F, and ^{13}C NMR data corresponded to those for enantiomer **4a**. Anal. Calcd for $C_{30}H_{36}F_{12}N_6O_{12}S_2$: C, 37.35; H, 3.76; N, 8.71. Found: C, 37.66; H, 3.88; N, 8.64.

*(1R,2R)-N,N′-Bis[(S)-prolyl]-1,2-bis(1-methylpyridin-2-yl)ethane-1,2-diamine Bis(triflate)/Bis(trifluoroacetate) (**4c**).* The compound was prepared similarly from **3c** (0.48 g). Yield: 0.64 g (87%). Colorless solid. Mp: 129−132 °C dec. $[\alpha]_D^{20}$: −17.2 (*c* 1.0, MeOH). ^1H NMR (600 MHz, d_6-DMSO): δ 10.50 (s, 2H), 9.03 (m, 2H), 8.67 (m, 2H), 8.47 (m, 2H), 8,12 (m, 2H), 6.20 (s, 2H), 4.54 (m, 2H), 4.43 (s, 6H), 3.22 (m, 4H), 2.33−1.93 (m, 8H) ppm. ^{13}C NMR (150 MHz, d_6-DMSO): δ 170.2, 153.0, 148.8, 147.4, 128.9, 128.8, 59.8, 51.3, 47.3, 46.7, 30.0, 24.2 ppm. ^{19}F NMR (282 MHz, d_6-DMSO): δ −74.32, −77.76 ppm. Anal. Calcd for $C_{30}H_{36}F_{12}N_6O_{12}S_2$: C, 37.35; H, 3.76; N, 8.71. Found: C, 37.54; H, 3.82; N, 8.62.

General Procedure for Catalytic Aldol Reactions of 5a with α-Ketoesters 6a−g. Acetone (**5a**) (10 mmol, 0.58 g, 0.73 mL) was added to a vial containing catalyst **4a** (0.025 mmol, 5 mol %, 23.4 mg). After vigorous stirring for 10 min, α-ketoester **6** (0.5 mmol) was added, and the resulting mixture was stirred at ambient temperature for the specified time (Table 2). The mixture was concentrated under reduced pressure (10 Torr). The residue was further extracted with Et_2O (3 × 7 mL) and purified by flash column chromatography (hexane/ethyl acetate) to afford aldol **7**. Spectroscopic data for **7a−g** are in agreement with those reported in the literature.[55,71]

*(S)-Benzyl 2-Ethyl-2-hydroxy-4-oxopentanoate (**7g**).* Acetone (**5a**) (36.0 g, 45.5 mL, 0.624 mol) was added to a vial containing **4a** (0.58 g, 2 mol %, 0.6 mmol). After vigorous stirring for 10 min, ketoester **6g** (6.00 g, 31.2 mmol) was added, and the resulting mixture was stirred at ambient temperature for 72 h. Then the mixture was concentrated under reduced pressure (10 Torr). The residue was extracted with Et_2O (3 × 10 mL) and purified by flash column chromatography (*n*-hexane/EtOAc = 4/1) to give **7g** as a colorless oil (7.03 g, 96% yield). $[\alpha]_D^{20}$: +61.2 (*c* 1.6, $CHCl_3$). Ee: 99%. For HPLC data see the Supporting Information). ^1H NMR (300 MHz, $CDCl_3$): δ 7.38−7.27 (m, 5H), 5.18 (s, 2H), 3.77 (s(br), 1H), 3.03 (d, J = 17.4 Hz, 1H), 2.82 (d, J = 17.4 Hz, 1H), 2.10 (s, 3H), 1.69 (d, J = 7.4 Hz, 2H), 0.84 (t, J = 7.5 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 207.39, 175.10, 135.43, 128.53, 128.38, 128.35, 75.41, 67.38, 51.26, 32.20, 30.63, 7.31 ppm. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{14}H_{19}O_4^+$ 251.1278, found 251.1275.

General Procedure for Catalytic Aldol Reactions of 5a−e with Aldehydes 8a−d. Ketone or aldehyde **5** (2.0 mmol) was added to a vial containing aldehyde **8** (0.5 mmol) and freshly prepared or recycled catalyst **4a** (0.025 mmol, 5 mol %, 23.4 mg). The resulting mixture was stirred at ambient temperature for the specified time (Table 3). The residue was extracted with Et_2O (3 × 7 mL) and purified by flash column chromatography (*n*-hexane/EtOAc) to afford **9**. Spectroscopic data for **9a−h** were in agreement with those reported in the literature.[72−76]

General Procedure for 4a Recycling. Catalyst **4a** that remained after extraction of product **7**/**9** with Et_2O was dried under reduced pressure (1.0 Torr) for 10 min, fresh portions of reagents **5** and **6**/**8** were added, and the reaction was reperformed at room temperature for the specified time (Table 2).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01555.

^1H, ^{13}C, and ^{19}F NMR spectra of new compounds, HPLC chromatograms of (*S*,*S*)-**1′**, (*R*,*R*)-**1′**, **7**, and **9**, and Cartesian coordinates and absolute energies for the transition states and complexes (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This research was financially supported by the Russian Science Foundation (Project 14-50-00126). E.F.V. also acknowledges the support of the ab initio theoretical investigations from the U.S. National Science Foundation (Awards CHE-0741927 and CHE-1362655).

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DOI: 10.1021/acs.joc.5b01555
J. Org. Chem. 2015, 80, 9570−9577