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Organocatalytic Asymmetric Synthesis of Chiral Pyrrolizines by Cascade Conjugate Addition−Aldol Reactions

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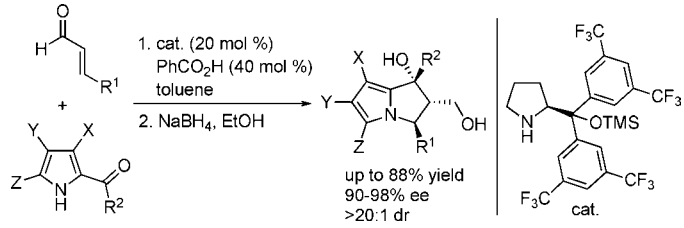
ABSTRACT



As the first *N*-centered heteroaromatic nucleophile for organocatalytic cascade reactions, pyrroles underwent the enantio- and diastereoselective organocatalytic cascade conjugate addition−aldol reactions of α,β-unsaturated aldehydes that afford the highly functionalized chiral pyrrolizines bearing three consecutive stereocenters in good yields, high enantioselectivities (90−98% ee), and excellent diastereoselectivities (>20:1 dr in all cases).

Nitrogen-containing heterocycles and their derivatives have broad applications in organic, biological, and materials chemistry,[1] and accordingly, synthesis of *N*-heteroaromatic compounds, especially optically pure ones, via catalytic routes has been a subject of active research.[2,3] Recently, intensive efforts have been devoted to the development of organocatalytic asymmetric cascade reactions[4,5] because they provide powerful tools for the rapid and efficient construction of complex structures from simple precursors. In organocatalytic asymmetric cascade reactions, the use of *N*-centered heteroaromatic nucleophiles remains unexplored in contrast to the widely studied *C*-centered nucleophiles. Specifically, pyrroles have never been used as *N*-centered nucleophiles in the cascade reactions,[6] in spite of the importance of pyrroles as optically pure *N*-heteroaromatic pharmacophores in biologically active natural products.[3a,7] Here, we report

(1) (a) Eicher, T.; Hauptmann, S. *The Chemistry of Heterocycles*, 2nd ed.; Wiley-VCH: New York, 2003. (b) Katritzky, A. R.; Pozharskii, A. F. *Handbook of Heterocyclic Chemistry*, 2nd ed.; Pergamon: Oxford, 2002. (c) Joule, J. A.; Mills, K. *Heterocyclic Chemistry*, 4th ed.; Blackwell Science: Oxford, 2000.

(2) For examples of enantioselective organocatalyses using *N*-centered heteroaromatic nucleophiles, see: (a) Dinér, P.; Nielsen, M.; Marigo, M.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 1983. (b) Wang, J.; Li, H.; Zu, L.; Wang, W. *Org. Lett.* **2006**, *8*, 1391.

(3) For examples of enantioselective transition-metal catalyses using *N*-centered heteroaromatic nucleophiles, see: (a) Trost, B. M.; Dong, G. *J. Am. Chem. Soc.* **2006**, *128*, 6054. (b) Gandelman, M.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2005**, *44*, 2393.

(4) For recent reviews of organocatalytic asymmetric cascade reactions, see: (a) Grondal, C.; Jeanty, M.; Enders, D. *Nature Chem.* **2010**, *2*, 167. (b) Alba, A.-N.; Companyo, X.; Viciano, M.; Rios, R. *Curr. Org. Chem.* **2009**, *13*, 1432. (c) Yu, X.; Wang, W. *Org. Biomol. Chem.* **2008**, *6*, 2037. (d) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570.

(5) For synthesis of chiral heterocycles via organocatalytic cascade Michael−aldol reactions, see: (a) Luo, G.; Zhang, S.; Duan, W.; Wang, W. *Tetrahedron Lett.* **2009**, *50*, 2946, and references cited therein. (b) Sundén, H.; Rios, R.; Ibrahem, I.; Zhao, G.-L.; Eriksson, L.; Córdova, A. *Adv. Synth. Catal.* **2007**, *349*, 827. (c) Sundén, H.; Ibrahem, I.; Zhao, G.-L.; Eriksson, L.; Córdova, A. *Chem. Eur. J.* **2007**, *13*, 574. (d) Hong, L.; Sun, W.; Liu, C.; Wang, L.; Wang, R. *Chem. Eur. J.* **2010**, *16*, 440.

(6) For examples of pyrroles as *C*-centered nucleophiles for enantioselective organocatalyses, see the following. (a) α-Heteroarylation of aldehydes: Beeson, T. D.; Mastracchio, A.; Hong, J.-B.; Ashton, K.; MacMillan, D. W. C. *Science* **2007**, *316*, 582. (b) Friedel−Crafts alkylation with imines: Li, G.; Rowland, G. B.; Rowland, E. B.; Antilla, J. C. *Org. Lett.* **2007**, *9*, 4065. (c) Friedel−Crafts alkylation with heteroarenes: Shirakawa, S.; Berger, R.; Leighton, J. L. *J. Am. Chem. Soc.* **2005**, *127*, 2858. (d) Friedel−Crafts alkylation with α,β-unsaturated aldehydes: Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 4370.

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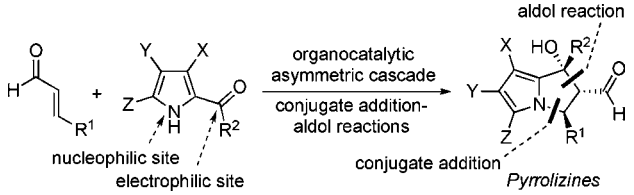
the first use of pyrroles as the *N*-centered heteroaromatic nucleophiles in the organocatalytic asymmetric cascade conjugate addition−aldol reactions of α,β-unsaturated aldehydes that provide highly functionalized chiral pyrrolizines containing three consecutive stereogenic centers (Scheme 1).

Scheme 1. Organocatalytic Asymmetric Cascade Conjugate Addition−Aldol Reactions of Pyrroles to α,β-Unsaturated Aldehydes

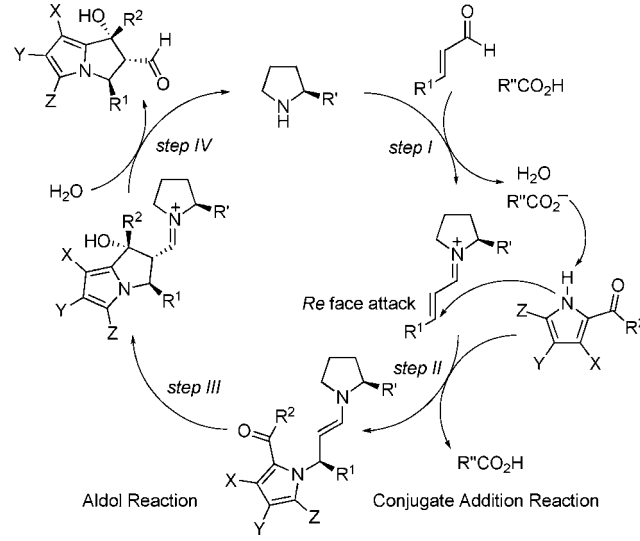


Although pyrrolizines have potent cytostatic effects and thus are potentially useful for the development of antitumor and antiviral agents,[8] synthesis of chiral pyrrolizines has been sparsely reported. Chiral auxiliary-mediated diastereoselective intramolecular cycloadditions of pyrrole-based nitrone intermediates have been reported only for the synthesis of chiral pyrrolizines.[9] Therefore, the development of a new route for the efficient synthesis of chiral pyrrolizines from simple starting materials in a single step is highly desirable.

To develop the catalytic cascade reaction, the NH of the pyrrole should be acidic enough to be deprotonated by a base such as the carboxylate anion; the resulting pyrrole anions then can act as nucleophiles for the initial conjugate addition to α,β-unsaturated aldehydes in the catalytic cycle (Scheme 2, step II). At the same time, the nucleophilic pyrrole species should be compatible with an electrophilic carbonyl functionality in one pyrrole entity, which serves as the electrophile for the subsequent aldol reaction (Scheme 2, step III).

To explore the feasibility of pyrroles as the *N*-centered nucleophiles in the organocatalytic asymmetric cascade conjugate addition−aldol reactions of α,β-unsaturated aldehydes, we optimized the cascade reactions stepwise: first, optimization for the conjugate step and, second, optimization

Scheme 2. Proposed Catalytic Cycle of the Cascade Conjugate Addition−Aldol Reactions Using a Chiral Diarylprolinol Ether Catalyst



for the whole cascade reaction (Table 1). All of the products were obtained after in situ reduction of the cascade aldehyde products into the alcohols using $NaBH_4$ in EtOH. The results from the first optimization, the enantioselective organocatalytic conjugate addition of pyrroles to α,β-unsaturated aldehydes, are listed in Table 1 as entries 1−8. The organocatalytic conjugate additions using pyrroles as *N*-centered heteroaromatic nucleophiles are not known.[10] The enantioselective conjugate addition of 2,4-dicyanopyrrole **2a**, whose pK_a is lower than those of pyrrole and 2-cyanopyrrole, to crotonaldehyde **1** using $PhCO_2H$ (20 mol %) as the acid additive in toluene at ambient temperature was performed in the presence of several chiral organocatalysts (Table 1, entries 1−4).[11] Among the organocatalysts assayed, the catalyst **IV** proved superior, providing the corresponding conjugate product **3a** in 72% yield and 67% enantiomeric excess (ee). However, in the case of 2-cyanopyrrole, the conjugate addition afforded the corresponding product in a very poor yield under the same conditions. We speculated that the benzoate anion was not sufficiently basic to deprotonate the 2-cyanopyrrole.[12] At −10 °C, the conjugate addition product **3a** showed an increased ee of 81%, but a decreased yield of 45% (Table 1, entry 6 vs entry 4). The yield increased to 58% with a slight increase in the

(7) (a) Seiple, I. B.; Su, S.; Young, I. S.; Lewis, C. A.; Yamaguchi, J.; Baran, P. S. *Angew. Chem., Int. Ed.* **2010**, *49*, 1095. (b) When, P. M.; Bois, J. D. *Angew. Chem., Int. Ed.* **2009**, *48*, 3802. (c) Imaoka, T.; Iwamato, O.; Noguchi, K.-i.; Nagasawa, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 3799. (d) Jacquot, D. E. N.; Lindel, T. *Curr. Org. Chem.* **2005**, *9*, 1551. (e) Poullennec, K. G.; Romo, D. *J. Am. Chem. Soc.* **2003**, *125*, 6344.

(8) (a) Liedtke, A. J.; Keck, P. R. W. E. F.; Lehmann, F.; Koeberle, A.; Werz, O.; Laufer, S. A. *J. Med. Chem.* **2009**, *52*, 4968. (b) Michael, J. P. *Nat. Prod. Rep.* **2005**, *22*, 603. (c) Liddell, J. R. *Nat. Prod. Rep.* **2002**, *19*, 773. (d) Atwell, G. J.; Fan, J.-Y.; Tan, K.; Denny, W. A. *J. Med. Chem.* **1998**, *41*, 4744. (e) Das, P. C.; Roberts, J. D.; White, S. L.; Olden, K. *Oncology Res.* **1995**, *7*, 425. (f) Laufer, S. A.; Augustin, J.; Dannhardt, G.; Kiefer, W. *J. Med. Chem.* **1994**, *37*, 1894. (g) Gruters, R. A.; Neefjes, J. J.; Tersmette, M.; de Goede, R. A. Y.; Tulp, A.; Huisman, H. G.; Miedema, F.; Ploegh, H. L. *Nature* **1987**, *330*, 74. (h) Zalkow, L. H.; Glinski, J. A.; Gelbaum, L. T.; Fleischmann, T. J.; McGowan, L. S.; Gordon, M. M. *J. Med. Chem.* **1985**, *28*, 687.

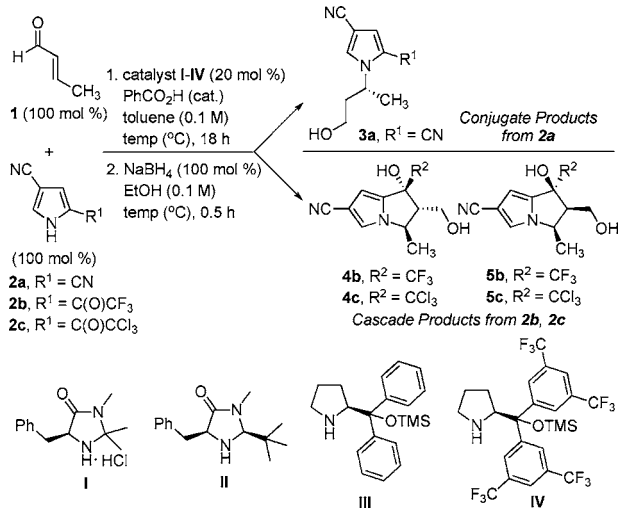
(9) (a) Borsini, E.; Broggini, G.; Contini, A.; Zecchi, G. *Eur. J. Org. Chem.* **2008**, 2808. (b) Beccalli, E. M.; Broggini, G.; Farina, A.; Malpezzi, L.; Terraneo, A.; Zecchi, G. *Eur. J. Org. Chem.* **2002**, 2080. (c) Arnone, A.; Broggini, G.; Passarella, D.; Terraneo, A.; Zecchi, G. *J. Org. Chem.* **1998**, *63*, 9279.

(10) For recent reviews of organocatalytic asymmetric conjugate addition reactions, see: (a) Sulzer-Mossé, S.; Alexakis, A. *Chem. Commun.* **2007**, 3123. (b) Alamaşi, D.; Alonso, D. A.; Nájera, C. *Tetrahedron: Asymmetry* **2007**, *18*, 299. (c) Tsogoeva, S. B. *Eur. J. Org. Chem.* **2007**, 1701.

(11) For the first development of diarylprolinol silyl ethers as organocatalysts, see: (a) Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 794. (b) Marigo, M.; Fielenbach, D.; Braunton, A.; Kjœrsgaad, A.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 3703. (c) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212.

(12) In addition to $PhCO_2H$, we also surveyed a series of acid additives having various pK_a values such as Ph_3CCO_2H, 3,5-$(NO_2)_2PhCO_2H$, CH_3CO_2H, Cl_2CHCO_2H, and Cl_3CCO_2H. Among the additives surveyed, $PhCO_2H$ was the best reagent.

Table 1. Optimization of Enantio- and Diastereoselective Organocatalytic Cascade Conjugate Addition−Aldol Reactions of Pyrroles **2** with Crotonaldehyde **1**[a]



entry	Nu **2**	cat.	$PhCO_2H$ (mol %)	temp (°C)	product	yield[b] (%)	ee[c] (%)	dr[d] [**4**:**5**]
1	**2a**	**I**	none	rt	**3a**	n.r.[e]		
2	**2a**	**II**	20	rt	**3a**	23	51	
3	**2a**	**III**	20	rt	**3a**	31	5	
4	**2a**	**IV**	20	rt	**3a**	72	67	
5	**2a**	**IV**	20	0	**3a**	67	76	
6	**2a**	**IV**	20	−10	**3a**	45	81	
7[f]	**2a**	**IV**	20	−10	**3a**	58	83	
8[f]	**2a**	**IV**	40	−10	**3a**	73	82	
9[f]	**2b**	**IV**	40	−10	**4b**	67	88	>20:1
10[f]	**2b**	**IV**	40	−20	**4b**	61	92	>20:1
11[f]	**2c**	**IV**	40	−10	**4c**	62	96	>20:1

[a] Procedure: To a mixture of pyrrole **2** (100 mol %), catalyst (20 mol %), and $PhCO_2H$ (20 or 40 mol %) in toluene (0.1 M) was added crotonaldehyde **1** (100 or 200 mol %) in one portion. The reaction mixture was allowed to stir at rt, 0, −10, or −20 °C for 18 h, at which point the aldehyde was directly reduced to the alcohol with $NaBH_4$ (100 mol %) in EtOH (0.1 M). The reaction mixture was adsorbed onto silica gel by evaporation of the solvent, and the product was isolated by silica gel chromatography. [b] Isolated yield for two steps. [c] Determined by chiral HPLC analysis (Chiralcel OD-H or Chiralpak AD-H). [d] Determined by ^{1}H NMR. [e] No reaction. [f] 200 mol % **1** and 100 mol % **2** were used.

enantioselectivity (83% ee) by increasing the loading of **1** to 200 mol %, which suggests that crotonaldehyde **1** may decompose gradually as the reaction proceeds (Table 1, entry 7). When we increased the loading of $PhCO_2H$ to 40 mol %, the addition yield of product **3a** increased to 73% with 82% ee (Table 1, entry 8). These optimized reaction conditions for the enantioselective organocatalytic conjugate addition were directly applied to the next optimization for the whole cascade conjugate addition−aldol reaction with 4-cyano-2-trihaloacetylpyrroles **2b** and **2c** as pronucleophiles, whose carbonyl groups act as the electrophilic site for the subsequent aldol reaction after the conjugate addition (Table 1, entries 9−11). Gratifyingly, when pyrrole **2b** containing a trifluoromethyl group, an important pharmacophore,[13] was used as the pronucleophile in the cascade reaction of **1** under the optimized reaction conditions, the highly functionalized chiral pyrrolizine **4b** was obtained in 67% yield and 88% ee as a single diastereomer, as determined by ^{1}H NMR analysis (Table 1, entry 9). By lowering the reaction temperature to −20 °C, the ee of **4b** increased to 92% (Table 1, entry 10). Similarly, pyrrole **2c** containing a 2-trichloroacetyl group also underwent the cascade reaction at −10 °C to afford **4c** in 62% yield and 96% ee as a single diastereomer (Table 1, entry 11).[14]

Next, we examined the scope of pyrroles as nucleophiles in the enantio- and diastereoselective organocatalytic cascade conjugate addition−aldol reaction of crotonaldehyde **1** under the optimized conditions. A series of 2-trichloroacetylpyrroles bearing various substituents, such as 4-cyano, 4-nitro, 4,5-dihalo, and 3,4,5-trihalo, were examined (Figure 1). In all

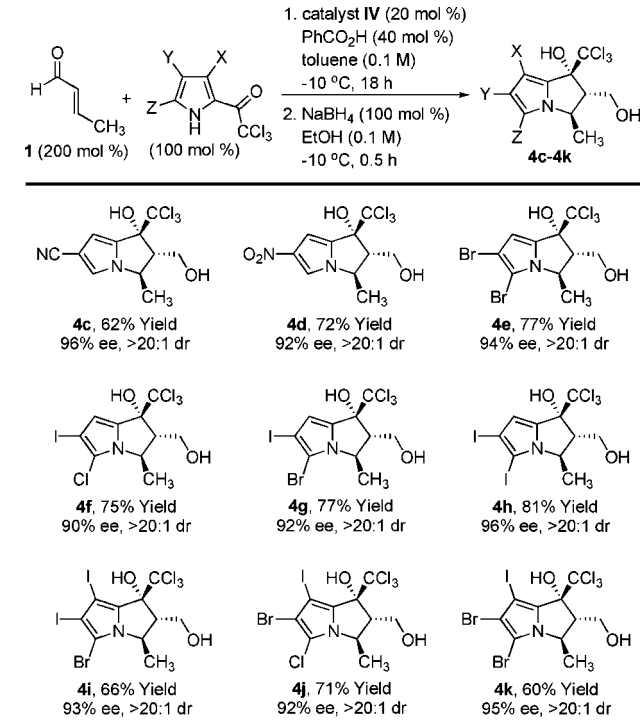


Figure 1. Enantio- and diastereoselective organocatalytic cascade conjugate addition−aldol reactions of crotonaldehyde **1** with various pyrroles. See the Supporting Information for detailed experimental procedures. Cited yields are of isolated material for two steps. Enantiomeric excess was determined by chiral HPLC analysis (Chiralpak AD-H). Diastereomeric ratio was determined by ^{1}H NMR.

cases, chiral pyrrolizines **4c**−**k** were obtained as single diastereomers in good yields and excellent enantioselectivities. The halo groups on the pyrrole moiety in pyrrolizines **4e**−**k** can be used for carbon−carbon coupling reactions to synthesize a variety of chiral pyrrolizine derivatives.[15] In particular, the dibromopyrrole moiety in **4e** occurs in a large

(13) For general reviews in this area, see: (a) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320. (b) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881. (c) Isanbor, C.; O'Hagan, D. *J. Fluorine Chem.* **2006**, *127*, 303. (d) Schlosser, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 5432.

(14) Under the optimized reaction conditions, the cascade reaction did not proceed with pyrroles bearing less electrophilic carbonyl substituent such as 2-acetylpyrrole and 2-acetyl-4-cyanopyrrole.

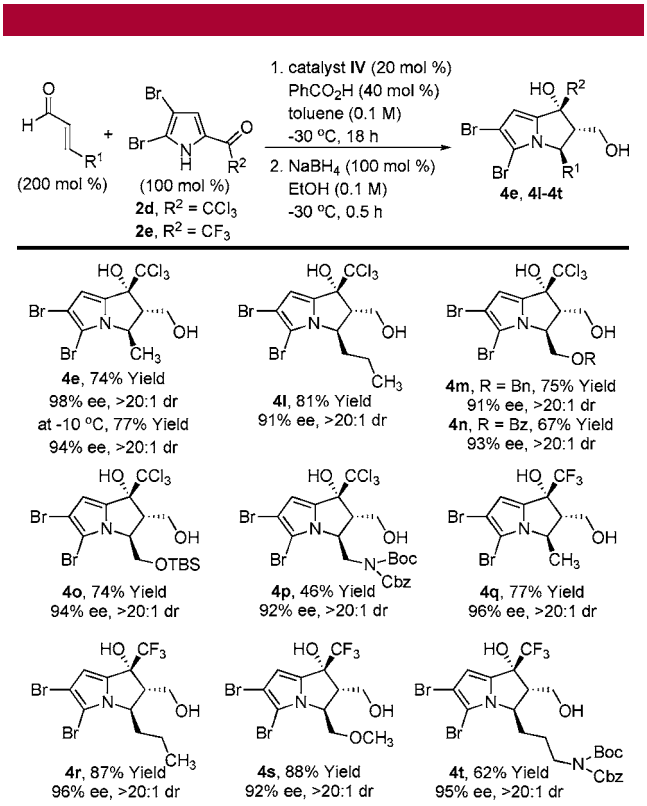


Figure 2. Enantio- and diastereoselective organocatalytic cascade conjugate addition−aldol reactions of dibromopyrroles **2d** and **2e** with various α,β-unsaturated aldehydes. See the Supporting Information for detailed experimental procedures. Cited yields are of isolated material for two steps. Enantiomeric excess was determined by chiral HPLC analysis (Chiralcel OD-H or Chiralpak AD-H). Diastereomeric ratio was determined by ^{1}H NMR.

class of marine natural products that show various interesting biological properties.[16]

Therefore, we further explored the organocatalytic reaction for dibromopyrroles **2d** and **2e** by varying the α,β-unsaturated aldehyde at −30 °C, under otherwise identical conditions, because −30 °C provided the cascade product in slightly higher ee than the reaction conducted at −10 °C, while still sustaining a good yield (Figure 2, **4e**). The results are summarized in Figure 2. The cascade reactions of dibromopyrrole **2d** with α,β-unsaturated aldehydes bearing aliphatic, variously protected hydroxymethyl, and doubly *N*-protected aminomethyl substituents afforded the desired pyrrolizines **4e** and **4l**−**p** as single diastereomers in excellent enantioselectivities. Similarly, dibromopyrrole **2e** underwent the cascade reactions with α,β-unsaturated aldehydes bearing aliphatic, Me-protected hydroxymethyl, and doubly *N*-protected aminoalkyl substituents to afford the desired pyrolizines **4q**−**t** as single diastereomers in good yields and excellent enantioselectivities. The absolute stereochemical assignment of all cascade products is based upon single crystal X-ray diffraction analysis of the pyrrolizine **4e**. From the absolute stereochemistry of the pyrrolizines, the course of asymmetric induction in the cascade reaction was confirmed to be as that already described in the proposed catalytic cycle in Scheme 2.

In summary, the enantio- and diastereoselective cascade conjugate addition−aldol reaction between α,β-unsaturated aldehydes and 2-trihaloacetylpyrroles has been achieved using (*S*)-α,α-bis[3,5-bis(trifluoromethyl)phenyl]-2-pyrrolidinemethanol trimethylsilyl ether as the organocatalyst and benzoic acid as acid additive. The catalytic reaction provides various chiral pyrrolizines containing three consecutive stereogenic centers in good yields with high enantioselectivities (90−98% ee) and excellent diastereoselectivities (>20:1 dr in all cases). This is the first example of organocatalytic cascade reactions in which pyrroles act as *N*-centered heteroaromatic nucleophiles. This organocatalytic process provides an efficient route for the synthesis of various chiral pyrrolizines of biologically potent natural products and drugs. Further investigations on the scope of the cascade reaction and its application to the synthesis of biologically active compounds are underway.

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Supporting Information Available: Spectral data (^{1}H NMR, ^{13}C NMR, IR, HRMS) and chiral HPLC analysis data for all new compounds. Single-crystal X-ray diffraction data of **4e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) (a) Morrison, M. D.; Hanthorn, J. J.; Pratt, D. A. *Org. Lett.* **2009**, *11*, 1051. (b) Smith, J. A.; Ng, S.; White, J. *Org. Biomol. Chem.* **2006**, *4*, 2477.

(16) (a) Berlinck, R. G.; Kosuga, M. H. *Nat. Prod. Rep.* **2005**, *22*, 516. (b) Faulkner, D. J. *Nat. Prod. Rep.* **2002**, *19*, 1. (c) Hao, E.; Fromont, J.; Jardine, D.; Karuso, P. *Molecules* **2001**, *6*, 130. (d) Gribble, G. W. *J. Nat. Prod.* **1992**, *55*, 1353.