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Peptide-Catalyzed Diastereo- and Enantioselective Cyclopropanation of Aromatic α,β-Unsaturated Aldehydes

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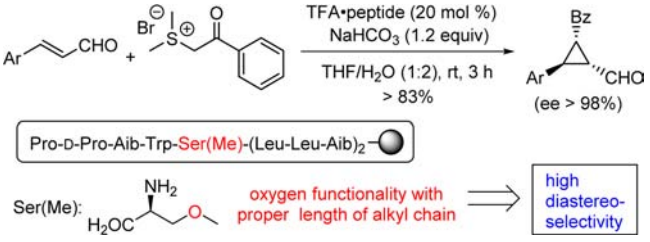
ABSTRACT



Highly diastereo- and enantioselective cyclopropanation of aromatic α,β-unsaturated aldehydes was achieved using a resin-supported peptide catalyst under aqueous conditions. In the peptide sequence, the residue possessing an oxygen atom with the appropriate length of the side chain was essential for attaining good diastereoselectivity.

Cyclopropane structures are widely found in natural products and pharmaceuticals,[1] and also the key intermediates for further chemical transformations.[2] Thus, a variety of the synthetic methods for stereoselective construction of cyclopropane rings have been developed.[3] Compared to the procedures using auxiliaries or a stoichiometric amount of chiral reagents, controlling the stereochemistry of cyclopropanation in a catalytic manner is advantageous for the synthesis of optically active cyclopropanes. In addition to metal-catalyzed asymmetric reactions,[4] much attention has been paid to organocatalytic cyclopropanation over the past decade.[5,6] After pioneering works by Aggarwal et al.[7] and Gaunt et al.[8] using chiral sulfides and cinchona alkaloid-derived catalysts, respectively, MacMillan et al. achieved enantioselective cyclopropanation of α,β-unsaturated aldehydes with sulfur ylides in the presence of an amine catalyst to afford 1,2,3-trisubstitued cyclopropanes **1** (Scheme 1).[9] Since such trisubstituted cyclopropanes possess three stereogenic centers, deliberate control of diastereoselectivity as well as for enantioselectivity is requisite, and developing a new catalytic system suitable for this purpose is a challenging subject. In 2011, Ye et al. reported the stereoselective synthesis of diastereomerically complementary cyclopropane **2** catalyzed by a diphenylprolinol silyl ether, in which a wide scope of α,β-unsaturated aldehydes was demonstrated.[10] On the other hand, the applicability of cyclopropanation for obtaining diastereomers **1** with aromatic α,β-unsaturated aldehydes is still limited. For example, although the reaction with cinnamaldehyde is reported to give product **1** with

(1) For reviews, see: (a) Donaldson, W. A. *Tetrahedron* **2001**, *57*, 8589–8627. (b) Chen, D. Y.-K.; Pouwer, R. H.; Richard, J.-A. *Chem. Soc. Rev.* **2012**, *41*, 4631–4642. (c) Pietruszka, J. *Chem. Rev.* **2003**, *103*, 1051–1070. (d) Brackmann, F.; de Meijere, A. *Chem. Rev.* **2007**, *107*, 4493–4537.

(2) For reviews, see: (a) Reissig, H.-U.; Zimmer, R. *Chem. Rev.* **2003**, *103*, 1151–1196. (b) Wessjohann, L. A.; Brandt, W. *Chem. Rev.* **2003**, *103*, 1625–1647. For selected examples, see: (c) Sohn, S. S.; Bode, J. W. *Angew. Chem., Int. Ed.* **2006**, *45*, 6021–6024. (d) Bode, J. W.; Sohn, S. S. *J. Am. Chem. Soc.* **2007**, *129*, 13798–13799. (e) Li, G.-Q.; Dai, L.-X.; You, S.-L. *Org. Lett.* **2009**, *11*, 1623–1625. (f) Lv, H.; Mo, J.; Fang, X.; Chi, Y. R. *Org. Lett.* **2011**, *13*, 5366–5369.

(3) For reviews, see: (a) Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977–1050. (b) Pellissier, H. *Tetrahedron* **2008**, *64*, 7041–7095.

(4) For recent selected examples, see: (a) Kakei, H.; Sone, T.; Sohtome, Y.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2007**, *129*, 13410–13411. (b) Zhu, S.; Perman, J. A.; Zhang, X. P. *Angew. Chem., Int. Ed.* **2008**, *47*, 8460–8463. (c) Sherrill, W. M.; Rubin, M. *J. Am. Chem. Soc.* **2008**, *130*, 13804–13809. (d) Phan, D. H. T.; Kou, K. G. M.; Dong, V. M. *J. Am. Chem. Soc.* **2010**, *132*, 16354–16355. (e) Gao, L.; Hwang, G.-S.; Ryu, D. H. *J. Am. Chem. Soc.* **2011**, *133*, 20708–20711.

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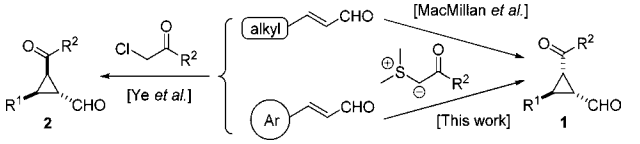
89% ee,[9a] enantioselectivity decreases to 79% ee with 4-methoxycinnamaldehyde,[2e] and there is no example for other substituents on the aromatic ring.[11] This type of reaction was also extended to *N*-heterocyclic carbene-catalyzed oxidative cyclopropanation of α,β-unsaturated aldehydes[12] and the use of β,γ-unsaturated α-ketoesters[13] or α,β-unsaturated ketones[14] as substrates. However, the reactions with substituted aromatic groups have the drawback that either the yield or stereoselectivity is only low to moderate. In this context, we set out to develop a catalyst for asymmetric cyclopropanation with aromatic α,β-unsaturated aldehydes to afford products **1** with high yield and stereoselectivity.

Scheme 1. Organo-catalyzed Cyclopropanation of α,β-Unsaturated Aldehydes



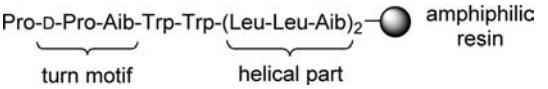


Figure 1. Resin-supported peptide catalyst.

In recent years, we have focused on resin-supported peptide catalysts as secondary amine organocatalysts (Figure 1).[15,16] The peptide consisting of a β-turn motif, D-Pro-Aib (Aib = 2-aminoisobutyric acid),[17] and a helical part is a versatile catalyst promoting various asymmetric organocatalytic reactions especially in aqueous media. The turn structure formed by the terminal five residues is essential for controlling enantioselectivity, and the hydrophobic helical part enhances reactions and stabilizes the whole peptide structure under aqueous conditions.[15a] We envisioned that this type of catalyst might be also effective for regulating the diastereoselectivity of the reaction because of the highly customizable property of peptides by modifying sequences with various kinds of amino acids. Herein, we report the diastereo- and enantioselective cyclopropanation of aromatic α,β-unsaturated aldehydes with a resin-supported peptide catalyst.

Cyclopropanation of 4-nitrocinnamaldehyde with a sulfur ylide was chosen as a model reaction (Table 1). Initially, we checked the general tendency of this reaction with some typical amine catalysts in chloroform for 24 h. When the reaction was performed with indoline-2-carboxylic acid **4** which was employed in MacMillan's report,[9] three diastereomers were generated with low reaction efficiency (Table 1, entry 1). Although diastereomer **1** was produced selectively to some extent, the enantioselectivity was quite low. With L-proline as a catalyst, enhancement of the reaction rate and enantioselectivity was observed with lowered diastereoselectivity (Table 1, entry 2). A versatile secondary amine catalyst, diphenylprolinol silyl ether **6**,[18] promoted the

(5) For selected examples, see: (a) Vignola, N.; List, B. *J. Am. Chem. Soc.* **2004**, *126*, 450–451. (b) Deng, X.-M.; Cai, P.; Ye, S.; Sun, X.-L.; Liao, W.-W.; Li, K.; Tang, Y.; Wu, Y.-D.; Dai, L.-X. *J. Am. Chem. Soc.* **2006**, *128*, 9730–9740. (c) McCooey, S. H.; McCabe, T.; Connon, S. J. *J. Org. Chem.* **2006**, *71*, 7494–7497. (d) Kojima, S.; Suzuki, M.; Watanabe, A.; Ohkata, K. *Tetrahedron Lett.* **2006**, *47*, 9061–9065. (e) Xie, H.; Zu, L.; Li, H.; Wang, J.; Wang, W. *J. Am. Chem. Soc.* **2007**, *129*, 10886–10984. (f) Fan, R.; Ye, Y.; Li, W.; Wang, L. *Adv. Synth. Catal.* **2008**, *350*, 2488–2492. (g) Ibrahem, I.; Zhao, G.-L.; Rios, R.; Vesely, J.; Sundén, H.; Dziedzic, P.; Córdova, A. *Chem.—Eur. J.* **2008**, *14*, 7867–7879. (h) Wascholowski, V.; Hansen, H. M.; Longbottom, D. A.; Ley, S. V. *Synthesis* **2008**, 1269–1275. (i) Vesely, J.; Zhao, G.-L.; Bartoszewicz, A.; Córdova, A. *Tetrahedron Lett.* **2008**, *49*, 4209–4212. (j) Marini, F.; Sternativo, S.; Del Verme, F.; Testaferri, L.; Tiecco, M. *Adv. Synth. Catal.* **2009**, *351*, 1801–1806. (k) Lv, J.; Zhang, J.; Lin, Z.; Wang, Y. *Chem.—Eur. J.* **2009**, *15*, 972–979. (l) Companyó, X.; Alba, A.-N.; Cárdenas, F.; Moyano, A.; Rios, R. *Eur. J. Org. Chem.* **2009**, 3075–3080. (m) Zhang, J.-M.; Hu, Z.-P.; Dong, L.-T.; Xuan, Y.-N.; Lou, C.-L.; Yan, M. *Tetrahedron: Asymmetry* **2009**, *20*, 355–361. (n) Terrasson, V.; van der Lee, A.; de Figueiredo, R. M.; Campagne, J. M. *Chem.—Eur. J.* **2010**, *16*, 7875–7880. (o) Pesciaioli, F.; Righi, P.; Mazzanti, A.; Bartoli, G.; Bencivenni, G. *Chem.—Eur. J.* **2011**, *17*, 2842–2845. (p) Russo, A.; Meninno, S.; Tedesco, C.; Lattanzi, A. *Eur. J. Org. Chem.* **2011**, 5096–5103. (q) Rueping, M.; Sundén, H.; Hubener, L.; Sugiono, E. *Chem. Commun.* **2012**, *48*, 2201–2203. (r) Del Fiandra, C.; Piras, L.; Fini, F.; Disetti, P.; Moccia, M.; Adamo, M. F. A. *Chem. Commun.* **2012**, *48*, 3863–3865. (s) Dou, X.; Lu, Y. *Chem.—Eur. J.* **2012**, *18*, 8315–8319. (u) Das, U.; Tsai, Y.-L.; Lin, W. *Org. Biomol. Chem.* **2013**, *11*, 44–47. (v) Raveendran, A. E.; Paul, R. R.; Suresh, E.; Nair, V. *Org. Biomol. Chem.* **2010**, *8*, 901–905.

(6) For reviews of organocatalysis, see: (a) Erkkilä, A.; Majander, I.; Pihko, P. M. *Chem. Rev.* **2007**, *107*, 5416–5470. (b) Mukherjee, S.; Yang, J. W.; Hoffman, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471–5569. (c) Dondoni, A.; Massi, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 4638–4660. (d) Melchiorre, P.; Marigo, M.; Carlone, A.; Bartoli, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 6138–6171. (e) Bertelsen, S.; Jørgensen, K. A. *Chem. Soc. Rev.* **2009**, *38*, 2178–2189.

(7) (a) Aggarwal, V. K.; Smith, H. W.; Jones, R. V. H.; Fieldhouse, R. *Chem. Commun.* **1997**, 1785–1786. (b) Aggarwal, V. K.; Alonso, E.; Fang, G.; Ferrara, M.; Hynd, G.; Porcelloni, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 1433–1436.

(8) (a) Papageorgiou, C. D.; de Dios, M. A. C.; Ley, S. V.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2004**, *43*, 4641–4644. (b) Johansson, C. C. C.; Bremeyer, N.; Ley, S. V.; Owen, D. R.; Smith, S. C.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 6024–6028.

(9) (a) Kunz, R. K.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 3240–3241. (b) Lakhdar, S.; Appel, R.; Mayr, H. *Angew. Chem., Int. Ed.* **2009**, *48*, 5034–5037.

(10) Li, W.; Li, X.; Ye, T.; Wu, W.; Liang, X.; Ye, J. *Tetrahedron Lett.* **2011**, *52*, 2715–2718.

(11) (a) Hartikka, A.; Arvidsson, P. I. *J. Org. Chem.* **2007**, *72*, 5874–5877. (b) Hartikka, A.; Ślósarczyk, A. T.; Arvidsson, P. I. *Tetrahedron: Asymmetry* **2007**, *18*, 1403–1409. (c) Zhao, Y.-H.; Zhao, G.; Cao, W.-G. *Tetrahedron: Asymmetry* **2007**, *18*, 2462–2467. (d) Zhao, Y.-H.; Zheng, C.-W.; Zhao, G.; Cao, W.-G. *Tetrahedron: Asymmetry* **2008**, *19*, 701–708.

(12) Biswas, A.; De Sarkar, S.; Tebben, L.; Studer, A. *Chem. Commun.* **2012**, *48*, 5190–5192.

(13) Cheng, Y.; An, J.; Lu, L.-Q.; Luo, L.; Wang, Z.-Y.; Chen, J.-R.; Xiao, W.-J. *J. Org. Chem.* **2011**, *76*, 281–284.

(14) Wang, J.; Liu, X.; Dong, S.; Lin, L.; Feng, X. *J. Org. Chem.* **2013**, *78*, 6322–6327.

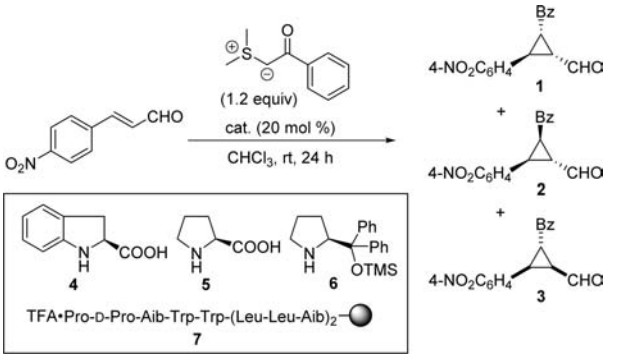
(15) (a) Akagawa, K.; Suzuki, R.; Kudo, K. *Adv. Synth. Catal.* **2012**, *354*, 1280–1286. (b) Akagawa, K.; Umezawa, R.; Kudo, K. *Beilstein J. Org. Chem.* **2012**, *8*, 1333–1337. (c) Akagawa, K.; Kudo, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 12786–12789.

(16) For reviews of peptide catalysts, see: (a) Miller, S. J. *Acc. Chem. Res.* **2004**, *37*, 601–610. (b) Davie, E. A. C.; Mennen, S. M.; Xu, Y.; Miller, S. J. *Chem. Rev.* **2007**, *107*, 5759–5812. (c) Wennemers, H. *Chem. Commun.* **2011**, *47*, 12036–12041.

(17) (a) Haque, T. S.; Little, J. C.; Gellman, S. H. *J. Am. Chem. Soc.* **1996**, *118*, 6975–6985. (b) Blank, J. T.; Miller, S. J. *Biopolymers* **2006**, *84*, 38–47.

(18) Mielgo, A.; Palomo, C. *Chem.—Asian J.* **2008**, *3*, 922–948.

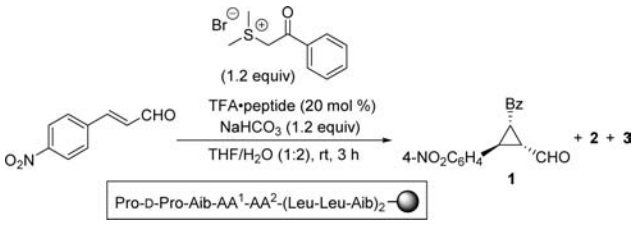
Table 1. Cyclopropanation of an α,β-Unsaturated Aromatic Aldehyde



entry	cat.	conversion (%)[a]	1/2/3[a]	ee (%) of 1 (2)
1	**4**	18	71:11:18	27 (3)
2	**5**	84	37:15:48	−45 (−65)
3	**6**	51	67:11:22	75 (61)
4	**7**	98	35:56:9	89 (98)
5[b]	**7**	97	65:28:7	95 (96)

[a] Determined by ^{1}H NMR spectroscopy of crude mixture. [b] Reaction was performed in THF/H_2O (1:2) for 3 h using 1.2 equiv each of dimethylphenacylsulfonium bromide and sodium bicarbonate.

Table 2. Screening of Peptide Sequences



entry	AA[1]	AA[2]	conversion (%)	1/2/3	ee (%) of 1
1	Ser	Ser	97	83:11:6	90
2	Thr	Thr	81	83:8:9	89
3	Hse	Hse	80	85:9:6	95
4	Hse	Ala	76	74:13:13	81
5	Hse	Trp	51	63:18:19	81
6	Ala	Hse	80	88:9:3	96
7	Trp	Hse	84	89:9:2	99
8	Trp	Ser	87	84:12:4	97
9	Trp	Ser(Me)	92	93:5:2	99
10	Trp	Nva	92	80:14:6	96
11	Trp	Hse(Me)	82	85:11:4	96
12	Trp	Met	95	81:13:6	95
13	Trp	Nle	93	79:13:8	94

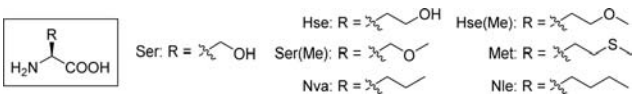
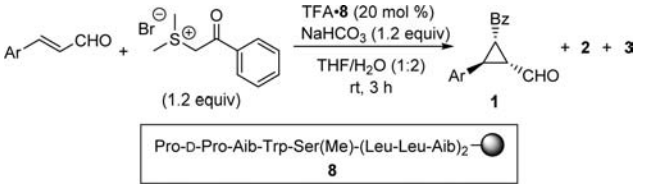
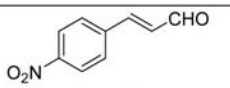
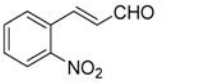
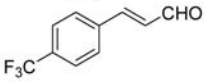
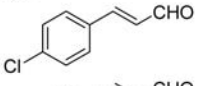
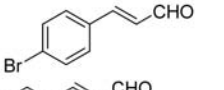
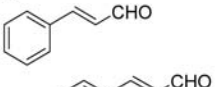
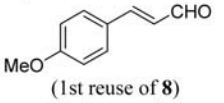
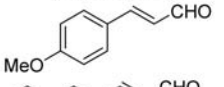
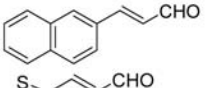
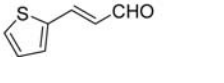


Table 3. Substrate Scope for Diastereoselective Asymmetric Cyclopropanation of α,β-Unsaturated Aromatic Aldehydes[a]



entry	substrate	1	1/2/3	yield(%) of 1	ee(%) of 1
1		**1a**	93:5:2	83	99
2		**1b**	96:2:2	84	99
3		**1c**	95:3:2	87	99
4		**1d**	93:4:3	85	98
5		**1e**	95:3:2	88	99
6		**1f**	94:3:3	87	99
7		**1g**	95:2:3	87	99
8	(1st reuse of **8**)		94:4:2	87	99
9	(2nd reuse of **8**)		94:4:2	85	99
10	(3rd reuse of **8**)		95:3:2	86	99
11	(4th reuse of **8**)		95:3:2	85	99
12	(5th reuse of **8**)		95:3:2	83	99
13[b]		**1g**	95:3:2	82	99
14		**1h**	97:1:2	88	99
15		**1i**	92:3:5	83	99

[a] Unless otherwise noted, the reaction was performed in 0.05 mmol scale. [b] The reaction was performed in 0.4 mmol scale with 10 mol % of peptide catalyst **8** and 1.0 equiv each of dimethylphenacylsulfonium bromide and sodium bicarbonate.

reaction with moderate efficiency and stereoselectivity (Table 1, entry 3). Compared to these cases, a better reaction efficiency and enantioselectivity were attained by using peptide catalyst **7** despite the low diastereoselectivity (Table 1, entry 4). With this peptide catalyst, the reaction rate was dramatically increased under aqueous conditions; the reaction almost completed in 3 h to afford diastereomer **1** as a major product with good enantioselectivity (Table 1, entry 5).[19]

(19) For cyclopropanation of α,β-unsaturated aldehydes using water as reaction media, see: (a) Uria, U.; Vicario, J. L.; Badía, D.; Carrillo, L.; Reyes, E.; Pesquera, A. *Synthesis* **2010**, 701–713. For a review of organocatalytic reactions under aqueous conditions, see: Gruttadauria, M.; Giacalone, F.; Noto, R. *Adv. Synth. Catal.* **2009**, *351*, 33–57.

Performing the reaction in aqueous media has another merit in the fact that a water-soluble sulfonium salt can be used and is converted to the ylide in situ by adding an inorganic base such as sodium bicarbonate; hence, the use of a generally unstable sulfur ylide can be avoided.

Next, in order to achieve high diastereoselectivity for this reaction, the peptide sequence was optimized (Table 2). When the D-Pro-Aib moiety in peptide catalyst **7** takes a turn structure, the Trp-Trp part is likely to be located around the substrate aldehyde attached to the terminal prolyl group as an iminium intermediate.[20] Therefore, we considered that this part largely affected the stereoselectivity of the reaction and replaced the Trp-Trp with other amino acid residues. First, this position was scanned with the pairwise use of amino acids, and we found that those possessing hydroxyl groups gave promising results with respect to diastereoselectivity (Table 2, entries 1 to 3). To determine which of the two consecutive amino acids is critical for the stereoselectivity, one of the homoserines in the catalyst used in entry 3 was altered to alanine or tryptophan (Table 2, entries 4, 5 vs entries 6, 7). It turned out that the hydroxy-substituted amino acid at the fifth residue (AA^2) was crucial for good diastereoselectivity. Then, by fixing the fourth residue (AA^1) with tryptophan, further optimization for the fifth position was conducted. While introducing serine instead of homoserine somewhat decreased the diastereoselectivity (Table 2, entry 8), the use of the methyl ether of serine improved the selectivity (Table 2, entry 9). The methyl ether of homoserine was not as good as that of serine (Table 2, entry 11). These data indicate that both the position of the oxygen atom and the length of the side chain affect the diastereochemical outcome of the reaction. With other residues having no oxygen atom such as norvaline, methionine, and norleucine, the diastereoselectivity was lowered in all cases (Table 2, entries 10, 12, and 13). Although the role of the oxygen functionality is not clear at present, it is presumed that an attracting interaction between the oxygen atom on the amino acid side chain and the sulfonium moiety in the reaction intermediate might increase the selectivity for the three-membered-ring-closing step.[21] This hypothesis is supported by the result that the use of a bulky amino acid residue causing large steric repulsion decreases the diastereoselectivity (Table 1, entry 5), compared to the cases with less bulky side chains at the AA^2 position (Table 2, entries 10 and 13).

Finally, the substrate scope for the diastereo- and enantioselective cyclopropanation of aromatic α,β-unsaturated aldehydes using the optimum peptide catalyst **8** was investigated (Table 3). Regardless of the nature of the substituents on the phenyl ring, the reaction proceeded with high diastereoselectivity to afford products **1** in good yield and excellent enantioselectivity (Table 3, entries 1 to 7, and 13). The substrates with naphthyl and thienyl groups were also applicable for this reaction system (Table 3, entries 14 and 15). These results demonstrate the high generality of the peptide-catalyzed cyclopropanation of aromatic substrates for the stereoselective synthesis of diastereomer **1**.[22] Because a resin-supported catalyst has the advantage of high reusability, the reaction with the catalyst **8** recovered by filtration was examined (Table 3, entries 8 to 12). A significant decrease in the catalytic ability was not observed until the fifth reuse of the catalyst.

In conclusion, highly diastereo- and enantioselective cyclopropanation of aromatic α,β-unsaturated aldehydes was realized with a resin-supported peptide catalyst. Introducing the amino acid residue having an oxygen atom at the appropriate position in the side chain with the proper length was important for the diastereoselectivity. This study shows the high potential and customizability of peptide catalysts, and further application for other stereoselective reactions can be expected.

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Supporting Information Available. Experimental procedure and spectroscopic data for products. This material is available free of charge via the Internet at http://pubs.acs.org.

(20) Akagawa, K.; Akabane, H.; Sakamoto, S.; Kudo, K. *Tetrahedron: Asymmetry* **2009**, *20*, 461–466.

(21) Allwood, B. L.; Crosby, J.; Pears, D. A.; Stoddart, J. F.; Williams, D. J. *Angew. Chem., Int. Ed.* **1984**, *23*, 977–979.

(22) The reaction with an aliphatic aldehyde resulted in low diastereoselectivity. For example, the use of 3-cyclohexylacrylaldehyde as a substrate gave a mixture (ca. 1:1) of products **1** and **2**.

The authors declare no competing financial interest.