Peptide Catalysis

DOI: 10.1002/anie.201305004

Peptide-Catalyzed Regio- and Enantioselective Reduction of α,β,γ,δ-Unsaturated Aldehydes**

*Kengo Akagawa, Jun Sen, and Kazuaki Kudo**

Regiochemistry of organic reactions is generally governed by the intrinsic reactivity of each functional group in a substrate, and this sometimes renders the synthetic route of a target compound complicated. Catalytic regioselective reactions have great potential for realizing straightforward synthesis. However, compared to stereoselective ones, there have been much less reports on regioselective catalysts.[1–4] One of the major subjects in the catalytic regioselective reactions is the nucleophilic addition to α,β,γ,δ-unsaturated carbonyl compounds.[5] While transition metal catalysts have mainly been employed for the regioselective reactions with such substrates,[6] only a few examples with organocatalysts have been reported.[7,8] Because organocatalysis has potential advantages, such as mild reaction conditions and wide applicability for various reactions,[9] exploring novel regioselective organocatalysts is highly desirable.

Considering the fact that enzymes catalyze reactions with high regioselectivity,[10] their simplified forms, peptides, are attractive candidates for regioselective catalysts.[11] So far, Miller and co-workers[3] and Kawabata and co-workers[4] have developed peptide or peptide-related catalysts for regioselective reactions such as derivatization of polyols and epoxidation of polyenes. Meanwhile, our group has reported a resin-supported peptide catalyst (Figure 1) for enantioselective transfer hydrogenation of α,β-unsaturated aldehydes with a Hantzsch ester.[12–14] The peptide consists of a turn motif[15] and a helical part, and the whole peptide chain is attached to a polyethylene glycol grafted polystyrene resin. This catalyst can be easily prepared through the polymerization with leucine *N*-carboxyanhydride followed by the standard Fmoc solid-phase peptide synthesis.[16] The amphiphilic nature of the resin facilitates the use of the hydrophobic peptide while avoiding problems with solubility.[17] Because of the formation of a secondary structure, the peptide catalyst can be expected to create a larger reaction site effective for controlling regioselectivity than low-molecular-weight catalysts. Herein, we report the first regio- and enantioselective transfer hydrogenation of α,β,γ,δ-unsaturated aldehydes with a resin-supported peptide catalyst.

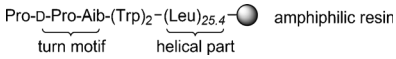


Figure 1. Resin-supported peptide catalyst. Aib = α-aminoisobutyric acid.

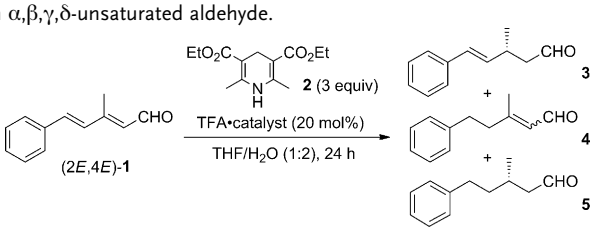
For organocatalytic regioselective reduction using a Hantzsch ester, α,β,γ,δ-unsaturated aldehyde **1** with a methyl group at the β-position was chosen as a starting material (Table 1). Because of the presence of the stereogenic center in the reduced products **3** and **5**, the catalytic ability for enantioselectivity as well as for regioselectivity can be evaluated. The reaction is considered to proceed through the formation of the iminium intermediate with an amine catalyst. Compounds **3** and **4** are the products of 1,4- and 1,6-reduction, respectively. Only compound **4** can be reduced further to afford fully hydrogenated product **5**. To check the intrinsic regiochemistry in the reaction of this substrate, we first tried the reaction with simple secondary amine catalysts, pyrrolidine and morpholine, in chloroform. In both cases, compound **3** was mainly obtained with low conversion (Table 1, entries 1 and 2). These results are consistent with the report by Hayashi et al. for an amine-catalyzed Michael addition of nucleophiles to α,β,γ,δ-unsaturated aldehydes, in which 1,4-addition predominantly took place.[18] On the basis of an ab initio calculation, they concluded that such regioselectivity originates from the electronic nature of the iminium intermediate, i.e., a larger π-orbital coefficient of the LUMO and a more positive charge at the β-position. Melchiorre and co-workers[19] and Jørgensen and co-workers[20] attained 1,6-addition to α,β,γ,δ-unsaturated carbonyl compounds through the iminium activation. In those cases, however, the use of cyclic substrates for the Michael acceptors or finely designed nucleophiles is essential to suppress 1,4-addition. This type of regioselectivity is considered to be controlled by the substrate, and not regulated by a catalyst. When imidazolidinone **8** was used as a catalyst, the distribution of the products changed (Table 1, entry 3). This result implies a possibility for the controlled selective formation of compound **5** by a catalyst. In terms of stereochemistry, both products **3** and **5** were nearly racemic, although this catalyst is known to effectively promote asymmetric reduction of α,β-unsaturated aldehydes.[13b] We then tried the reaction with peptide catalysts. The use of peptide catalyst **9** enhanced 1,6-selectivity to give compound **5** as a major product with good enantioselectivity (Table 1, entry 5). The combination of the terminal five residues including the turn motif and the polyleucine part was essential for regio- and enantioselectivity (Table 1, entries 5–7). Replacing α-helical polyleucine with a 3_{10}-helical unit,

[*] Dr. K. Akagawa, J. Sen, Prof. Dr. K. Kudo
Institute of Industrial Science, University of Tokyo
4-6-1 Komaba, Meguro-ku, Tokyo 153-8505 (Japan)
E-mail: kkudo@iis.u-tokyo.ac.jp

[**] This work was supported by JSPS KAKENHI Grant Number 23750171 (to K.A.) and 23550116 (to K.K.), and by MEXT KAKENHI Grant number 24105506 (to K.K.).

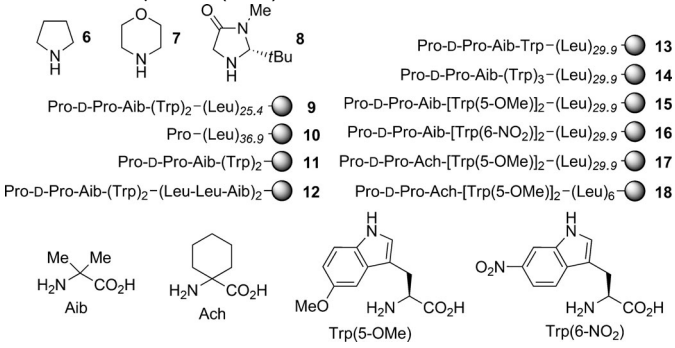
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201305004.

Table 1: Catalyst screening for regio- and enantioselective reduction of an α,β,γ,δ-unsaturated aldehyde.



Entry	Catalyst	*T* [°C]	Conversion[a] [%]	**3**/**4**/**5**[a]	*ee* [%] of **5** (**3**)
1[b]	**6**	20	12	76:0:24	–
2[b]	**7**	20	26	73:8:19	–
3[b]	**8**	20	79	59:9:32	1 (2)
4	**8**	20	93	59:0:41	3 (1)
5	**9**	20	52	11:36:53	88 (51)
6	**10**	20	51	41:28:31	29 (15)
7	**11**	20	19	14:66:20	62 (40)
8	**12**	20	56	23:19:58	86 (54)
9	**9**	30	86	15:10:75	86 (46)
10	**13**	30	97	35:1:64	78 (61)
11	**14**	30	99	15:0:85	90 (69)
12	**15**	30	32	16:50:34	97 (76)
13	**16**	30	95	19:5:76	82 (44)
14	**17**	30	95	13:8:79	93 (68)
15	**18**	30	98	13:0:87	96 (58)
16[c]	**18**	10	99	10:0:90	99 (78)

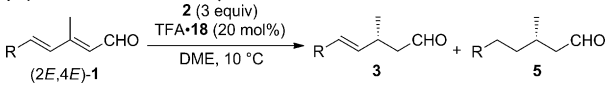
[a] Determined from ^{1}H NMR spectra of the crude mixture. [b] The reaction was performed in $CHCl_3$ for 3 h. [c] The reaction was performed in 1,2-dimethoxyethane (DME) for 48 h.



(Leu-Leu-Aib)$_2$,[21] also decreased 1,6-selectivity (Table 1, entry 8). Notably, a subtle difference in the helical structure influences the regioselectivity of the reaction, although this part is somewhat distant from the catalytically active prolyl group. This demonstrates the importance of the whole peptide secondary structure for regioselective reduction. The reaction in the presence of catalyst **9** at slightly higher temperature gave product **5** in moderate ratio and enantioselectivity (Table 1, entry 9). Then, we set out further screening for the peptide sequences. In the peptide chain, tryptophan residues are most likely to affect the regio- and enantioselectivity, since this part is considered to be allocated near the iminium intermediate, when the D-Pro-Aib unit[15] formed a turn structure.[12b] First, the effect of the number of tryptophan residues between Aib and polyleucine was investigated. The catalyst with one tryptophan residue lowered the 1,6-selectivity (Table 1, entry 10), whereas the catalyst with three tryptophan residues showed the same regioselectivity for the first step of the reduction as the catalyst **9** (entry 11). Next, the electronic nature of the indole rings of the tryptophan residues was modified. The use of tryptophan residues with an electron-donating methoxy group afforded product **5** in excellent enantioselectivity with a significant decrease in conversion (Table 1, entry 12). In contrast, introducing an electron-withdrawing nitro group to the tryptophan residues promoted the reaction, but the regio- and enantioselectivity were slightly lowered (Table 1, entry 13). To overcome the low-efficiency problem of catalyst **15**, the Aib residue in the turn motif was replaced by Ach according to our previous experience for peptide-catalyzed asymmetric epoxidation.[22] In the present case as well, a remarkable acceleration of the reaction occurred (Table 1, entry 14). Furthermore, changing the polyleucine part to hexaleucine[23] gave a slightly better result (Table 1, entry 15), and we regarded peptide **18** as the optimum catalyst. After screening the reaction conditions, a highly regio- and enantioselective reduction of α,β,γ,δ-unsaturated aldehyde **1** was achieved (Table 1, entry 16). The detailed mechanism accounting for the regioselectivity of the peptide-catalyzed reaction is not clear to date. Considering the poor regioselectivity with catalyst **13** lacking one tryptophan and somewhat lowered 1,6-selectivity with catalyst **16** possessing the electron-withdrawing groups on the tryptophan residues, the electron-rich nature of the tryptophan residues seems to be important for increasing the regioselectivity through the interaction with the iminium intermediate.

Next, the substrate scope for this type of reaction was examined (Table 2). Regardless of the kinds of substituents on the benzene ring, the reduction proceeded regioselectively to give compound **5** as a major product with excellent enantioselectivity (Table 2, entries 2 and 5–8). The substrates with 2-naphthyl and 3-thienyl groups showed similar regio- and enantioselectivity (Table 2, entries 9 and 10). Alkyl

Table 2: Peptide-catalyzed regio- and enantioselective reduction of α,β,γ,δ-unsaturated aldehydes.

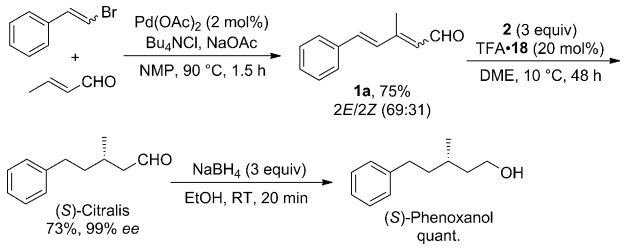


Entry	R	**5**	*t* [h]	**3**/**5**[a]	Yield [%] of **5**[b]	*ee* [%] of **5**
1	C_6H_5	**5a**	48	10:90	79	99
2	4-$NO_2C_6H_4$	**5b**	36	10:90	75	97
3[c]	4-$NO_2C_6H_4$	**5b**	36	9:91	71	97
4[d]	4-$NO_2C_6H_4$	**5b**	36	6:94	70	97
5	4-ClC_6H_4	**5c**	36	10:90	79	97
6	3-ClC_6H_4	**5d**	36	8:92	74	98
7	4-BrC_6H_4	**5e**	36	10:90	71	98
8	4-$MeOC_6H_4$	**5f**	60	9:91	65	98
9	2-naphthyl	**5g**	36	10:90	71	98
10	3-thienyl	**5h**	48	10:90	64	98
11	*n*Bu	**5i**	36	$<1:>99$	55	99
12	c-Hex	**5j**	36	$<1:>99$	65	97
13	C_6H_5-$(CH_2)_2$	**5k**	36	$<1:>99$	67	97

[a] Determined from ^{1}H NMR spectra of the crude mixture. [b] Yields of isolated products. [c] The mixture of (2*E*,4*E*)/(2*Z*,4*E*) (67:33) was used as a starting material. [d] The mixture of (2*E*,4*E*)/(2*E*,4*Z*)/(2*Z*,4*E*)/(2*Z*,4*Z*) (27:45:8:20) was used as a starting material.

substituents at the δ-position enhanced the 1,6-selectivity in the first reduction step (Table 2, entries 11–13). The amine-catalyzed asymmetric transfer hydrogenation of α,β-unsaturated aldehydes with a Hantzsch ester is known to be stereoconvergent; despite the different geometry of a starting material, the same enantiomer can be obtained.[13,24] In the present reaction, such a phenomenon was also observed. A 2*E*/2*Z* mixture of substrate **1b** afforded the products with the same regio- and enantioselectivity (Table 2, entry 3) as the reaction using a single isomer of **1b** (entry 2). Even when a mixture of four geometric isomers was used, the reaction still proceeded in a highly regio- and enantioselective manner (Table 2, entry 4). This is practically advantageous, because geometric isomers are usually generated in the synthesis of this type of substrate.

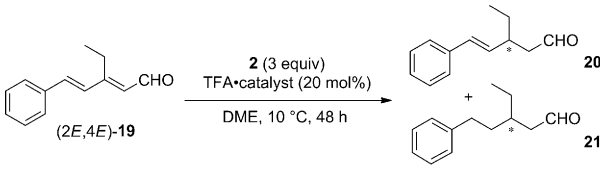
As a demonstration, fragrance compounds, Citralis and Phenoxanol, were synthesized according to Scheme 1. The 2*E*/2*Z* mixture of **1a** obtained by a Heck reaction[25] was



Scheme 1. Short asymmetric synthesis of fragrance compounds.

applied to the peptide-catalyzed reduction to afford Citralis with high enantiomeric excess,[26] which could be easily derivatized to Phenoxanol. Compared to the reports for the synthesis of these compounds,[27] the present regio- and enantioselective reaction offers a simpler synthetic pathway.

In the case of β-ethylated substrate **19**, the inherent reactivity resulted in a preferred 1,4-selectivity (Scheme 2), which was demonstrated by the fact that catalyst **8** exclusively



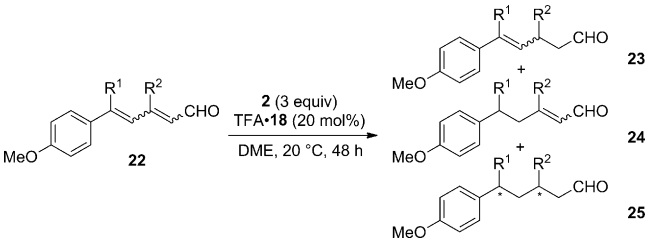
Catalyst	Conversion [%]	**20** : **21**	Yield [%] of **21**	*ee* [%] of **21** (**20**)
8	81	96 : 4	1	<1 (6)
18	86	37 : 63	47	97 (87)

Scheme 2. Reduction of a β-ethyl-substituted substrate.

afforded the 1,4-reduced product **20**. The use of peptide catalyst **18** overturned the regioselectivity of the reaction, and gave compound **21** in a moderate yield with high enantioselectivity.

Finally, δ-substituted substrates were tested in the peptide-catalyzed reduction (Table 3). The reaction with substrate **22a** having only one methyl group at the δ-position was

Table 3: Regio- and stereoselectivity of the reaction with δ-substituted substrates.



Entry	**22**	Conversion [%]	**23**/**24**/**25**	d.r. of **25**	*ee* [%] of **25**
1	**22a** (R^1 = Me, R^2 = H) (2*E*,4*E*)	87	31:0:69	–	87
2	**22b** (R^1 = Me, R^2 = Me) (2*E*,4*E*)	97	9:1:90	57:43	93, 95
3	**22b** (R^1 = Me, R^2 = Me) (2*Z*,4*E*)/(2*Z*,4*Z*) (87:13)	70	11:3:86	53:47	90, 95
4	**22c** (R^1 = Et, R^2 = Me) (2*Z*,4*E*)/(2*Z*,4*Z*) (60:40)	80	14:11:75	55:45	93, 81

also 1,6-selective in the first step of the reduction, in spite of steric congestion at the δ-position (Table 3, entry 1). In the case of substrate **22b** with β,δ-dimethyl substituents, the 1,6-selective reduction predominantly proceeded, and after the subsequent 1,4-reduction, the fully hydrogenated compound **25b** was obtained as a major product (Table 3, entry 2). Although **25b** was a mixture of two diastereomers, the enantioselectivity for each compound was high (see the Supporting Information for a hydrogenation experiment, which suggests that the low diastereoselectivity is caused by the initial 1,6-reduction step). For this type of substrate, good stereoconvergence was observed as well, while the reactivity is low with 2*Z* isomers (Table 3, entry 3). Substrate **22c** with an ethyl substituent at the δ-position showed a comparable 1,6-selectivity for the first reduction step (Table 3, entry 4).

In conclusion, a new peptide catalyst suitable for regio- and enantioselective reduction of α,β,γ,δ-unsaturated aldehydes was developed. It was applicable for the stereoconvergent synthesis using a mixture of geometric isomers. In this study, a high regioselectivity was attained by catalyst control, not by intrinsic reactivity of a substrate. Further application of peptide catalysts for other regioselective reactions can be expected.

Experimental Section

1,2-Dimethoxyethane (0.5 mL) was added at 10 °C to a round-bottom flask containing aldehyde **1** (0.05 mmol), Hantzsch ester **2** (0.15 mmol), and resin-supported peptide **18** (57 mg, 0.01 mmol of the terminal prolyl group). The mixture was stirred with a magnetic stirrer at 200 rpm for the given time. Then, the peptide catalyst was filtered off and washed with chloroform. After removal of the solvent, the residue was purified by preparative TLC using hexanes/ethyl acetate (4:1) as eluent to afford product **5**. For compound **5b**, preparative TLC was performed with hexanes/ethyl acetate (2:1) as eluent.

Received: June 11, 2013
Published online: ■■ ■■, ■■■■

Keywords: asymmetric synthesis · heterogeneous catalysis · peptides · reduction · regioselectivity

[1] A review: J. Mahatthananchai, A. M. Dumas, J. W. Bode, *Angew. Chem.* **2012**, *124*, 11114 – 11152; *Angew. Chem. Int. Ed.* **2012**, *51*, 10954 – 10990.

[2] Selected examples: a) M. J. Martinelli, R. Vaidyanathan, J. M. Pawlak, N. K. Nayyar, U. P. Dhokte, C. W. Doecke, L. M. H. Zollars, E. D. Moher, V. Van Khau, B. Košmrlj, *J. Am. Chem. Soc.* **2002**, *124*, 3578; b) T. Fujihara, K. Semba, J. Terao, Y. Tsuji, *Angew. Chem.* **2010**, *122*, 1514 – 1518; *Angew. Chem. Int. Ed.* **2010**, *49*, 1472 – 1476; c) A. D. Worthy, X. Sun, K. L. Tan, *J. Am. Chem. Soc.* **2012**, *134*, 7321 – 7324; d) A. Di Giuseppe, R. Castarlenas, J. J. Pérez-Torrente, M. Crucianelli, V. Polo, R. Sancho, F. J. Lahoz, L. A. Oro, *J. Am. Chem. Soc.* **2012**, *134*, 8171 – 8183; e) J. Lv, L. Zhang, Y. Zhou, Z. Nie, S. Luo, J.-P. Cheng, *Angew. Chem.* **2011**, *123*, 6740 – 6744; *Angew. Chem. Int. Ed.* **2011**, *50*, 6610 – 6614; f) L. Gremaud, A. Alexakis, *Angew. Chem.* **2012**, *124*, 818 – 821; *Angew. Chem. Int. Ed.* **2012**, *51*, 794 – 797; g) C. Zheng, D. Wang, S. S. Stahl, *J. Am. Chem. Soc.* **2012**, *134*, 16496 – 16499; h) J. L. Farmer, H. N. Hunter, M. G. Organ, *J. Am. Chem. Soc.* **2012**, *134*, 17470 – 17473; i) D. Lee, M. S. Taylor, *J. Am. Chem. Soc.* **2011**, *133*, 3724 – 3727; j) W. Muramatsu, Y. Takemoto, *J. Org. Chem.* **2013**, *78*, 2336 – 2345.

[3] a) C. A. Lewis, S. J. Miller, *Angew. Chem.* **2006**, *118*, 5744 – 5747; *Angew. Chem. Int. Ed.* **2006**, *45*, 5616 – 5619; b) P. A. Jordan, S. J. Miller, *Angew. Chem.* **2012**, *124*, 2961 – 2965; *Angew. Chem. Int. Ed.* **2012**, *51*, 2907 – 2911; c) P. A. Lichtor, S. J. Miller, *Nat. Chem.* **2012**, *4*, 990 – 995.

[4] a) T. Kawabata, T. Furuta, *Chem. Lett.* **2009**, *38*, 640 – 647; b) K. Yoshida, T. Shigeta, T. Furuta, T. Kawabata, *Chem. Commun.* **2012**, *48*, 6981 – 6983.

[5] Reviews: a) N. Krause, S. Thorand, *Inorg. Chim. Acta* **1999**, *296*, 1 – 11; b) A. G. Csákÿ, G. de La Herrán, M. C. Murcia, *Chem. Soc. Rev.* **2010**, *39*, 4080 – 4102.

[6] Selected examples: a) J. Munch-Petersen, C. Bretting, P. M. Jørgensen, S. Refn, V. K. Andersen, A. Jart, *Acta Chem. Scand.* **1961**, *15*, 277 – 292; b) Y. Yamamoto, K. Maruyama, *J. Am. Chem. Soc.* **1978**, *100*, 3240 – 3241; c) T. den Hartog, S. R. Harutyunyan, D. Font, A. J. Minnaard, B. L. Feringa, *Angew. Chem.* **2008**, *120*, 404 – 407; *Angew. Chem. Int. Ed.* **2008**, *47*, 398 – 401; d) S. Okada, K. Arayama, R. Murayama, T. Ishizuka, K. Hara, N. Hirone, T. Hata, H. Urabe, *Angew. Chem.* **2008**, *120*, 6966 – 6970; *Angew. Chem. Int. Ed.* **2008**, *47*, 6860 – 6864; e) H. Hénon, M. Mauduit, A. Alexakis, *Angew. Chem.* **2008**, *120*, 9262 – 9264; *Angew. Chem. Int. Ed.* **2008**, *47*, 9122 – 9124; f) T. Nishimura, Y. Yasuhara, T. Sawano, T. Hayashi, *J. Am. Chem. Soc.* **2010**, *132*, 7872 – 7873; g) T. Sawano, A. Ashouri, T. Nishimura, T. Hayashi, *J. Am. Chem. Soc.* **2012**, *134*, 18936 – 18939.

[7] a) L. Bernardi, J. López-Cantarero, B. Niess, K. A. Jørgensen, *J. Am. Chem. Soc.* **2007**, *129*, 5772 – 5778; b) D. Uraguchi, K. Yoshida, Y. Ueki, T. Ooi, *J. Am. Chem. Soc.* **2012**, *134*, 19370 – 19373.

[8] Other selected examples of organocatalytic regioselective reactions: a) S. Belot, A. Quintard, N. Krause, A. Alexakis, *Adv. Synth. Catal.* **2010**, *352*, 667 – 695; b) D. Enders, C. Wang, A. Greb, *Adv. Synth. Catal.* **2010**, *352*, 987 – 992; c) P. Chauhan, S. S. Chimni, *Adv. Synth. Catal.* **2011**, *353*, 3203 – 3212; d) J. J. Murphy, A. Quintard, P. McArdle, A. Alexakis, J. C. Stephens, *Angew. Chem.* **2011**, *123*, 5201 – 5204; *Angew. Chem. Int. Ed.* **2011**, *50*, 5095 – 5098; e) J. Wang, J. Chen, C. W. Kee, C.-H. Tan, *Angew. Chem.* **2012**, *124*, 2432 – 2436; *Angew. Chem. Int. Ed.* **2012**, *51*, 2382 – 2386; f) Ł. Albrecht, G. Dickmeiss, F. C. Acosta, C. Rodríguez-Escrich, R. L. Davis, K. A. Jørgensen, *J. Am. Chem. Soc.* **2012**, *134*, 2543 – 2546; g) F. Zhong, J. Luo, G.-Y. Chen, X. Dou, Y. Lu, *J. Am. Chem. Soc.* **2012**, *134*, 10222 – 10227; h) K. S. Halskov, T. K. Johansen, R. L. Davis, M. Steurer, F. Jensen, K. A. Jørgensen, *J. Am. Chem. Soc.* **2012**, *134*, 12943 – 12946.

[9] Reviews: a) A. Erkkilä, I. Majander, P. M. Pihko, *Chem. Rev.* **2007**, *107*, 5416 – 5470; b) S. Mukherjee, J. W. Yang, S. Hoffman, B. List, *Chem. Rev.* **2007**, *107*, 5471 – 5569.

[10] Recent selected examples: a) W. Zhang, W. L. Tang, Z. Wang, Z. Li, *Adv. Synth. Catal.* **2010**, *352*, 3380 – 3390; b) R. C. Simon, B. Grischek, F. Zepeck, A. Steinreiber, F. Belaj, W. Kroutil, *Angew. Chem.* **2012**, *124*, 6817 – 6820; *Angew. Chem. Int. Ed.* **2012**, *51*, 6713 – 6716; c) A. Bariotaki, D. Kalaitzakis, I. Smonou, *Org. Lett.* **2012**, *14*, 1792 – 1795.

[11] Reviews of peptide catalysts: a) E. A. C. Davie, S. M. Mennen, Y. Xu, S. J. Miller, *Chem. Rev.* **2007**, *107*, 5759 – 5812; b) H. Wennemers, *Chem. Commun.* **2011**, *47*, 12036 – 12041.

[12] a) K. Akagawa, H. Akabane, S. Sakamoto, K. Kudo, *Org. Lett.* **2008**, *10*, 2035 – 2037; b) K. Akagawa, H. Akabane, S. Sakamoto, K. Kudo, *Tetrahedron: Asymmetry* **2009**, *20*, 461 – 466.

[13] a) J. W. Yang, M. T. H. Fonseca, N. Vignola, B. List, *Angew. Chem.* **2005**, *117*, 110 – 112; *Angew. Chem. Int. Ed.* **2005**, *44*, 108 – 110; b) S. G. Ouellet, J. B. Tuttle, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2005**, *127*, 32 – 33.

[14] Reviews of organocatalytic reductions with Hantzsch esters: a) S. G. Ouellet, A. M. Walji, D. W. C. MacMillan, *Acc. Chem. Res.* **2007**, *40*, 1327 – 1339; b) S.-L. You, *Chem. Asian J.* **2007**, *2*, 820 – 827; c) M. Rueping, E. Sugiono, F. R. Schoepke, *Synlett* **2010**, 852 – 865.

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

[16] G. B. Fields, R. L. Noble, *Int. J. Pept. Protein Res.* **1990**, *35*, 161 – 214.

[17] Detaching a peptide from the resin leads to a decrease in both reactivity and stereoselectivity, probably because of low solubility, see: K. Akagawa, R. Suzuki, K. Kudo, *Adv. Synth. Catal.* **2012**, *354*, 1280 – 1286.

[18] Y. Hayashi, D. Okamura, S. Umemiya, T. Uchimaru, *ChemCatChem* **2012**, *4*, 959 – 962.

[19] a) X. Tian, Y. Liu, P. Melchiorre, *Angew. Chem.* **2012**, *124*, 6545 – 6548; *Angew. Chem. Int. Ed.* **2012**, *51*, 6439 – 6442; b) X. Tian, P. Melchiorre, *Angew. Chem.* **2013**, *125*, 5468 – 5471; *Angew. Chem. Int. Ed.* **2013**, *52*, 5360 – 5363.

[20] a) L. Dell'Amico, Ł. Albrecht, T. Naicker, P. H. Poulsen, K. A. Jørgensen, *J. Am. Chem. Soc.* **2013**, *135*, 8063 – 8070; b) K. S. Halskov, T. Naicker, M. E. Jensen, K. A. Jørgensen, *Chem. Commun.* **2013**, *49*, 6382.

[21] Y. Demizu, M. Doi, Y. Sato, M. Tanaka, H. Okuda, M. Kurihara, *J. Pept. Sci.* **2011**, *17*, 420 – 426.

[22] K. Akagawa, K. Kudo, *Adv. Synth. Catal.* **2011**, *353*, 843 – 847.

[23] A. Weyer, D. Díaz, A. Nierth, N. E. Schlörer, A. Berkessel, *ChemCatChem* **2012**, *4*, 337 – 340.

[24] H. Maeda, S. Yamada, H. Itoh, Y. Hori, *Chem. Commun.* **2012**, *48*, 1772 – 1774.

[25] M. Stadler, B. List, *Synlett* **2008**, 597 – 599.

[26] In this case, the ratio of products **3** and **5** was 14:86.

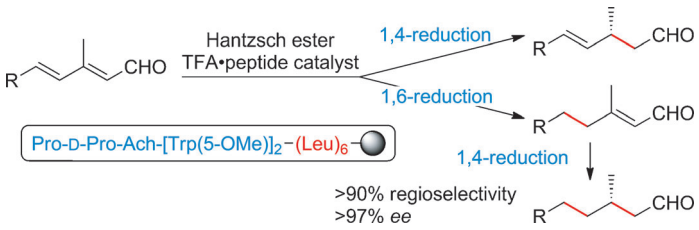
[27] a) U. Matteoli, A. Ciappa, S. Bovo, M. Bertoldini, A. Scrivanti, *Tetrahedron: Asymmetry* **2007**, *18*, 797 – 802; b) S. Superchi, V. Marchitiello, L. Pisani, P. Scafato, *Chirality* **2011**, *23*, 761 – 767.

Communications

Peptide Catalysis

K. Akagawa, J. Sen,
K. Kudo* ——————— ■■■■–■■■■

Peptide-Catalyzed Regio- and Enantioselective Reduction of α,β,γ,δ-Unsaturated Aldehydes



A resin-supported peptide catalyst (see box in the scheme) was used in the title reaction. The inherent regioselectivity was overcome by the peptide catalyst to promote the 1,6-selective reaction prior to 1,4-reduction. High stereoconvergence was also achieved when using a mixture of geometric isomers of the starting aldehydes. Ach = 1-amino-1-cyclohexanecarboxylic acid.