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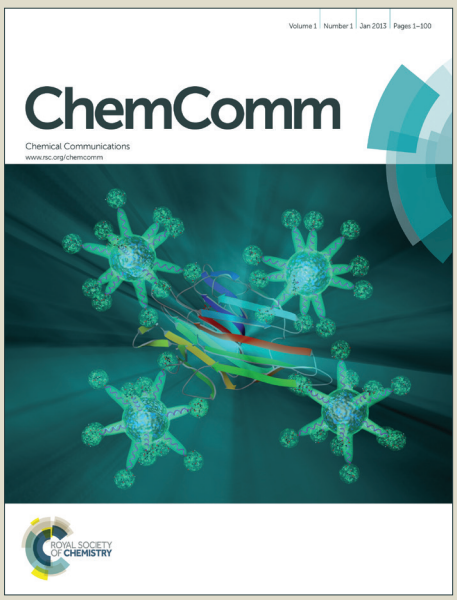

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Peptide-Catalyzed Kinetic Resolution of Planar-Chiral Metallocenes

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Kinetic resolution of racemic planar-chiral metallocenes was performed through the conjugate addition of a nucleophile to the enal part of substrates. While no enantiomeric discrimination was found with low-molecular-weight organocatalysts, a properly designed resin-supported peptide catalyzed the reaction in a highly selective manner.

Planar chirality can be found in the groups of the molecules with planar structures such as metallocenes, π-ligand complexes, and cyclophanes, and enantioselective synthesis of them is necessary for the applications to chiral chemistry.[1] In spite of the recent remarkable progress in the field of asymmetric catalysts, the development of a versatile method for synthesizing chiral planar compounds in a catalytic manner is still a challenging subject.[2]

Planar-chiral ferrocenes represent an important class of chiral compounds, and they have been mainly used as the ligands for metal-catalysts[3] and organocatalysts.[1c,4] Enantioenriched planar-chiral ferrocenes are usually obtained through the resolution of a racemic compound by a chiral chromatography,[3,4] the diastereoselective transformation with the aid of a chiral directing group,[5] or the reaction with a stoichiometric amount of a chiral reagent.[5a-c,6] There are also some reports for the catalytic asymmetric synthesis of planar-chiral ferrocenes.[5c,7] In most cases, however, the applicability of these catalytic reactions is quite limited, and elaborately designed substrates are required to attain good enantioselectivity. Because planar chirality is the nature of the whole shape of a molecule, a catalyst with a large-scale asymmetric environment is necessary.

On the other hand, peptide catalysts can provide the large reaction sites suitable for substrate recognitions by their specific three-dimensional structures.[8] Miller and co-workers[9] and Kawabata and co-workers[10] have reported regioselective reactions with peptide- and peptide-related catalysts, respectively, in which small catalysts were not effective. Meanwhile, we have developed a resin-supported peptide catalyst consisting of a turn motif, D-Pro-Aib,[11] and a helical part (Fig. 1).[12] The N-terminal prolyl residue forms the iminium-ion intermediate with an α,β-unsaturated aldehyde to promote Michael addition of nucleophiles.[13] The turn structure of this peptide plays a key role for enantioselectivity of the reaction by covering one face of the peptide-bound substrate. The helical part is indispensable for stabilizing the turn structure. Because of a fairly large molecular size of the peptide, it is expected to be applicable for an enantioselective synthesis of planar chiral compounds. Herein, we report the kinetic resolution of racemic planar-chiral metallocene derivatives with a resin-supported peptide catalyst.

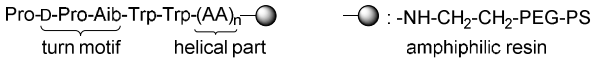


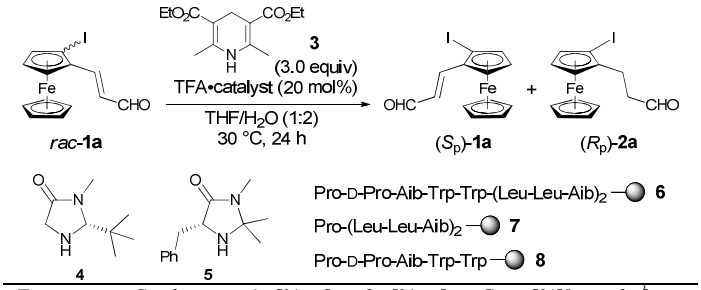
Fig. 1 Resin-supported peptide catalyst. Aib = 2-aminoisobutyric acid, AA = amino acid.

We first examined a kinetic resolution of racemic 1,2-disubstituted ferrocene **1a** in the 1,4-reduction of the enal part with a Hantzsch ester through the iminium-ion intermediate (Table 1).[14] The formyl group of this substrate is distant from the ferrocenyl moiety, hence it might be difficult for a low-molecular-weight chiral amine catalyst to discriminate the enantiomers. In fact, when the reaction was performed with an imidazolidinone catalyst **4** or **5**,[15] both the recovered starting material **1a** and reduced product **2a** were obtained as racemates (Table 1, entries 1 to 3). In contrast, the kinetic resolution took place by peptide catalyst **6** to give enantioenriched compounds **1a** and **2a** with the relative reaction rate (k_{rel}) value[16] of 4.0 (Table 1, entry 4). The use of peptides **7** and **8**, which lack either the terminal turn structure or the helical part resulted in lower k_{rel} values. This indicates the importance of the structural motif of catalyst **6** (Table 1, entries 5 and 6).

The fifth amino acid residue from the N-terminus of the peptide was scanned to achieve higher selectivity because, according to our previous results,[12] the residue is likely to be located around the ferrocenyl part of the iminium-ion intermediate (Table 2). The replacement of the fifth tryptophan to alanine increased the selectivity of the reaction (Table 2, entry 1), and introducing an

amino acid with an unbranched alkyl side chain further enhanced the k_{rel} value (entry 2). Moreover, the incorporation of an oxygen or a sulfur atom in the linear side chain was effective to improve the selectivity (Table 2, entries 3 to 5). Among them, the peptide possessing homoserine methyl ether was the best for the k_{rel} value (Table 2, entry 4). After the optimization for the counter anion of the ammonio group of the terminal prolyl residue and the length of the helical part, the k_{rel} value of 11.7 was achieved (Table 2, entry 6).

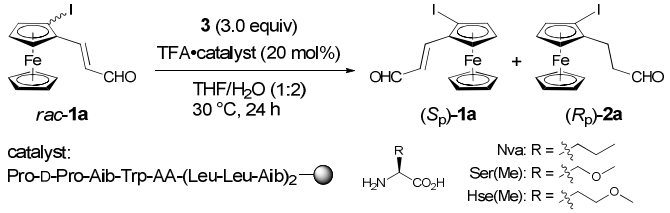
Table 1 Kinetic resolution of a planar-chiral ferrocene through the reduction of an unsaturated bond



Entry	Catalyst	**1a** [% *ee*]	**2a** [% *ee*]	C_{HPLC} [%][a]	k_{rel}[b]
1[c,d]	**4**	<1	<1	11[e]	1.0
2[c]	**4**	<1	<1	42[e]	1.0
3[c,d,f]	**5**	<1	<1	3[e]	1.0
4	**6**	27	51	35	4.0
5	**7**	11	4	73	1.2
6	**8**	10	35	22	2.3

[a] Conversion calculated from ees of **1a** and **2a** (ref. 18a). [b] Selectivity factor: $k_{rel} = k(R_p)/k(S_p)$ (ref. 18). [c] The reaction was performed with 0.5 equiv of **3** for 3 h. [d] The reaction was performed in $CHCl_3$. [e] Determined from ^1H NMR spectra of the crude mixture. [f] The hydrochloric acid salt of **5** was used.

Table 2 Screening for the 5th residue of the peptide catalyst



Entry	AA	**1a** [% *ee*]	**2a** [% *ee*]	C_{HPLC} [%][a]	k_{rel}[b]
1	Ala	74	40	65	4.9
2	Nva	45	61	43	6.4
3	Ser(Me)	48	66	42	7.8
4	Hse(Me)	63	66	49	9.2
5	Met	70	61	53	8.4
6[c]	Hse(Me)	64	72	47	11.7

[a] Conversion calculated from ees of **1a** and **2a**. [b] Selectivity factor. [c] The hydrochloric acid salt of a peptide with $(Leu\text{-}Leu\text{-}Aib)_3$ for the helical part was used.

On the basis of the preference for the absolute configurations of the major enantiomers obtained by the peptide-catalyzed reaction, we postulated a possible mechanism for the kinetic resolution of planar-chiral ferrocene **1a** (Fig. 2). The conformation of the iminium-ion intermediate is considered to be regulated to avoid the steric repulsion between the iodo group on the cyclopentadienyl (Cp) ring and the vinylic hydrogen next to the iminium group (Fig. 2 a). For the S_p enantiomer of **1a**, the both faces of the iminium-ion intermediate are covered either by the Cp ring or by the peptide chain with a turn structure (Fig. 2 b).[12] On the other hand, one face of the intermediate for the R_p enantiomer is accessible by the reagent, thus, the reaction proceeds faster than the case of the S_p isomer. For the highly selective kinetic resolution, the fifth residue of the peptide catalyst should prohibit the nucleophilic attack of the reductant from the upper side of the S_p enantiomer, whereas the formation of the iminium-ion intermediate with the R_p enantiomer should not be prevented by the steric repulsion with the Cp ring.

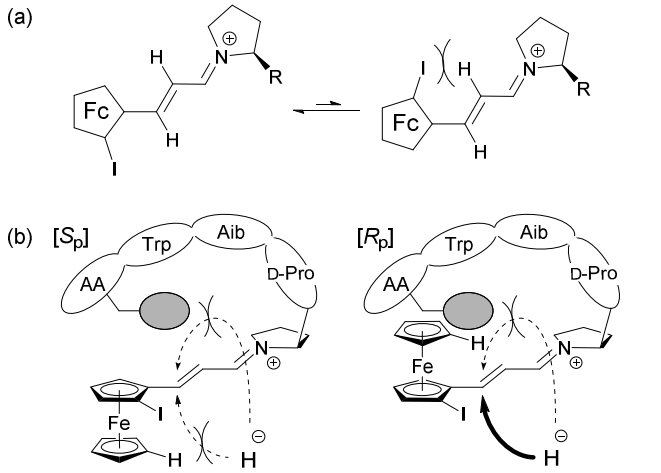


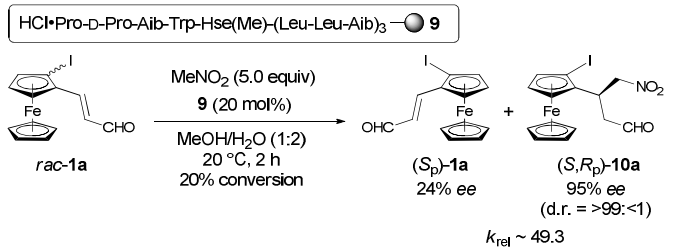
Fig. 2 Plausible mechanism for the kinetic resolution by the peptide catalyst.

Compared to the case with the bulky side chain at the fifth residue of catalyst **6** (Table 1, entry 4), the introduction of the linear side chain in the catalyst was considered to be effective for this purpose (Table 2, entry 3). Although the role of the oxygen atom is not clear at present, an interaction with the cationic iminium-ion part might enhance the formation of the reactive intermediate for the R_p isomer, resulting in the higher selectivity (Table 2, entries 4 and 5).[17]

This type of kinetic resolution is potentially extendable to the reactions with other nucleophiles. Because the Michael addition of nitromethane to α,β-unsaturated aldehydes is a convenient method for the synthesis of γ-amino acid derivatives,[18] we employed nitromethane as a nucleophile. In the presence of the optimum catalyst **9**, the kinetic resolution proceeded with higher enantioselectivity than the case with Hantzsch ester **3** (Scheme 1). In this reaction, a new stereogenic center is created at the β-position of the aldehyde group. The configuration of the major product was consistent with the proposed model shown in Fig. 2, in which the addition occurred from the *Re* face of the R_p isomer of substrate **1a**. The high diastereoselectivity of the reaction indicates the well-controlled conformation of the iminium-ion intermediate with regard to the direction of the ferrocenyl part (Fig. 2a).

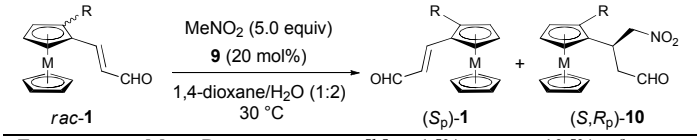
Next, the scope of substrates for the kinetic resolution through the Michael addition of nitromethane by peptide **9** was examined under optimized reaction conditions (Table 3). For the planar-chiral ferrocenes with halogen and alkynyl substituents, both unreacted starting material **1** and product **10** were obtained as highly enantioenriched forms (Table 3, entries 1 to 8). The reaction in a shorter reaction time afforded product **10** with a high ee value (Table 3, entries 1, 3, 5, and 7). Meanwhile, as increasing the conversion by

elongating the reaction time, starting material **1** was obtained in a highly enantioselective manner (Table 3, entries 2, 4, 6, and 8). As to the substrate with an aromatic group, good enantioselectivity was achieved only for the product (Table 3, entry 9). In this case, a reaction conversion could not be increased even in a prolonged reaction time because of the low solubility of the substrate. In addition to the ferrocenes, ruthenocenyl substrate **1f** could be used in this catalytic system (Table 3, entries 10 and 11).



Scheme 1 Peptide-catalyzed kinetic resolution through Michael addition of nitromethane.

Table 3 Peptide-catalyzed kinetic resolution of planar-chiral metallocenes

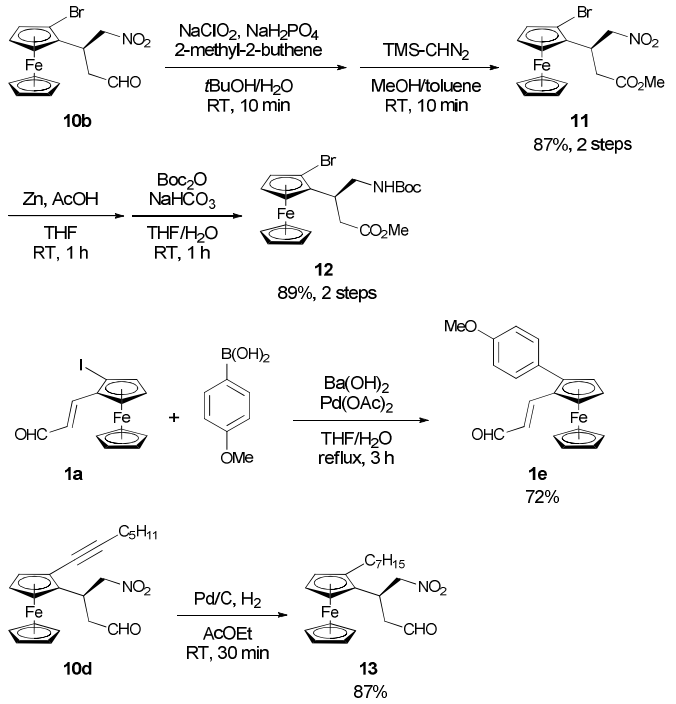


Entry	**1**	M	R	*t* [h]	**1** [% *ee* (% Yield)]	**10** [% *ee*[a] (% Yield, d.r.)]
1	**1a**	Fe	I	10	65 (44)	92 (36, 98:2)
2	**1a**	Fe	I	12	90 (34)	59 (49, 93:7)
3	**1b**	Fe	Br	5	35 (53)	89 (25, 97:3)
4	**1b**	Fe	Br	12	83 (31)	86 (43, 93:7)
5	**1c**	Fe	Cl	8	31 (48)	93 (18, >99:<1)
6	**1c**	Fe	Cl	14	77 (27)	80 (31, 94:6)
7	**1d**	Fe	1-heptynyl	21	60 (38)	83 (37, 88:12)
8	**1d**	Fe	1-heptynyl	36	84 (30)	70 (44, 83:17)
9	**1e**	Fe	*p*-MeOC$_6$H$_4$	10	42 (51)	85 (33, 95:5)
10	**1f**	Ru	I	4	48 (55)	87 (27, 92:8)
11	**1f**	Ru	I	5	87 (50)	66 (38, 82:18)

[a] Ee of the major diastereomer.

Finally, the derivatizations of the obtained materials were conducted to demonstrate the utility of the present resolution method (Scheme 2). The Pinnick oxidation of product **10c** followed by an esterification afforded compound **11**, and this could be further transformed to amino acid derivative **12** via a reduction and an N-protection. Because there are only limited examples for the asymmetric synthesis of amino acid derivatives with planar chirality,[19] this procedure offers a valuable way to prepare them. Halogen-substituted ferrocenyl compounds are synthetically useful, because they can easily be transformed by a coupling reaction.[20] The Suzuki–Miyaura reaction with iodine-containing **1a** and *p*-methoxyphenylboronic acid afforded coupling product **1e**. Alkyl ferrocene **13** could be prepared by the catalytic hydrogenation of product **10d**.

In conclusion, we have successfully shown that the peptide catalyst is applicable for the kinetic resolution of planar-chiral metallocenes which cannot be realized by low-molecular-weight organocatalysts. The use of the amino acid with a sterically less demanding, heteroatom-containing side chain at an appropriate position of the peptide sequence was the key for the high enantioselectivity. Planar chiral ferrocenes could tolerate for several reaction conditions including oxidation and reduction. Further application of peptide catalysts for synthesizing other planar-chiral compounds can be expected.



Scheme 2 Transformation into planar-chiral derivatives.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental procedures and full compound characterization, including NMR spectra and HPLC traces (PDF). See DOI: 10.1039/c000000x/

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