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Stereoselective Pinacol Coupling of Chiral Formylferrocene Using Divalent Samarium Triflate: Preparation of a New Chiral Bisferrocenyl Oxazoline Ligand and Its Application to Asymmetric Diels–Alder Reactions

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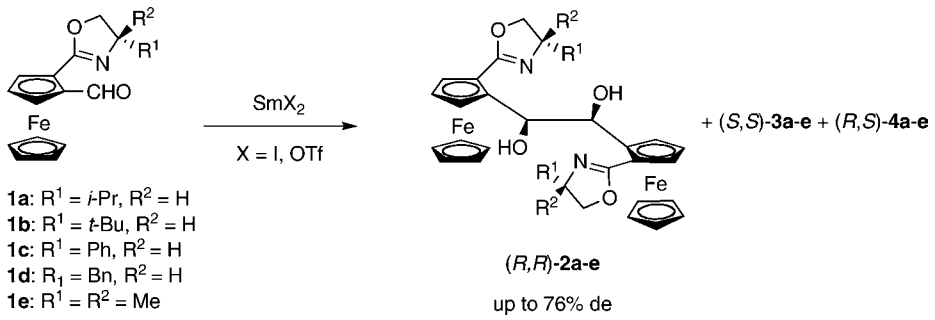
ABSTRACT



1a: R^1 = *i*-Pr, R^2 = H
1b: R^1 = *t*-Bu, R^2 = H
1c: R^1 = Ph, R^2 = H
1d: R_1 = Bn, R^2 = H
1e: R^1 = R^2 = Me

The pinacol coupling reaction of planar chiral *ortho*-oxazoline-substituted formylferrocene was smoothly mediated by SmI_2 or $Sm(OTf)_3$ to give the (*R*,*R*) isomer selectivity (up to 76% diastereomeric excess). The combination of $Yb(OTf)_3$ and the (*R*,*R*)-ferrocenyl diol was revealed to be a good catalyst for the asymmetric Diels–Alder reaction of 3-acyloxazolidinone with cyclopentadiene, and the *endo* adduct was produced in up to 80% enantiomeric excess.

Optically active 1,2-ethane diols are useful chiral auxiliaries and ligands for asymmetric synthesis.[1] These diols had been accessible by resolution of racemates[2] before recent reports on diastereo- and enantioselective pinacol coupling of ketones and aldehydes. Enantioselective pinacol coupling reactions have been achieved using chiral titanium and chromium catalysts to give 1,2-diols in high enantioselectivity.[3]

Diastereoselective pinacol coupling of aldehydes and ketones having chiral auxiliaries can be an alternative and

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(3) For examples, see: (a) Takenaka, N.; Xia, G.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 13198−13199. (b) Li, Y.-G.; Tian, Q.-S.; Zhao, J.; Feng, Y.; Li, M.-J.; You, T.-P. *Tetrahedron: Asymmetry* **2004**, *15*, 1707−1710. (c) Chatterjee, A.; Bennur, T. H.; Joshi, N. N. *J. Org. Chem.* **2003**, *68*, 5668−5671. (d) Bensari, A.; Renaud, J.-L.; Riant, O. *Org. Lett.* **2001**, *3*, 3863−3865. (e) Hashimoto, Y.; Mizuno, U.; Matsuoka, H.; Miyaura, T.; Takakura, M.; Yoshimoto, M.; Oshima, K.; Utimoto, K.; Matsubara, S. *J. Am. Chem. Soc.* **2001**, *123*, 1503−1504. SmI_2 has recently been tried for enantioselective pinacol coupling using chiral ligands: Aspinall, H. C.; Greeves, N.; Valla, C. *Org. Lett.* **2005**, *7*, 1919−1922.

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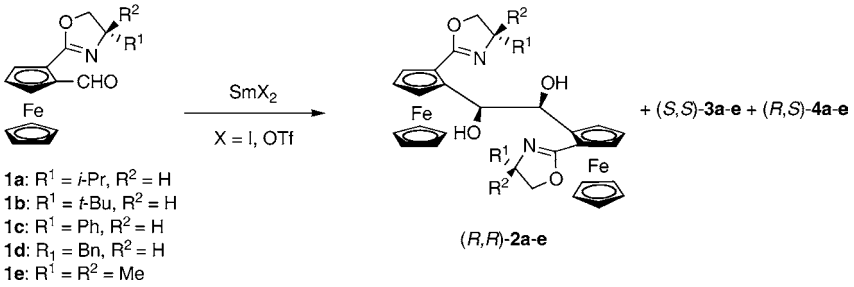
Scheme 1



effective way to access them. For example, samarium(II) iodide promoted the pinacol coupling of chiral α-ketoamide and ester giving the corresponding quaternary tartaric acids in high diastereoselectivities in the presence of HMPA and alcohol.[4] Diastereoselective pinacol coupling of a planar chiral formylferrocene can be achieved by using SmI_2 as a reducing agent.[5] These reactions with *ortho*-methyl and halogeno-substituted formylferrrocenes proceed with excellent diastereoselectivity to give a single diastereomer in high yields; however, the reaction with *ortho*-phosphino-substituted ferrocene produces a mixture of three diastereomers, (*R*,*R*), (*S*,*S*), and (*R*,*S*).[5,6] When we tried the pinacol coupling reaction with chiral *ortho*-oxazoline-substituted formylferrocene using SmI_2, the product was obtained as a mixture of (*R*,*R*), (*S*,*S*), and (*R*,*S*) in the ratio of 24:31:45. We have now found that the use of samarium(II) triflate, "$Sm(OTf)_2$", prepared by the reduction of samarium(III) triflate with *s*-BuLi enhanced the (*R*,*R*) selectivity.[7] We would like to present here the highly diastereoselective pinacol coupling of *ortho*-oxazoline-substituted formylferrocene using $Sm(OTf)_2$ and the successful application of the ferrocenyl pinacol to a ligand for a Lewis-acid-catalyzed asymmetric Diels−Alder reaction.

We first tested the pinacol coupling reaction of planar chiral *ortho*-(*S*,*Rp*)-4-isopropyloxazolinyl formylferrocene **1a** (R^1 = *i*-Pr, R^2 = H) with SmI_2 in THF at room temperature (Scheme 1). The product was a mixture of three diastereomers, (*R*,*R*)-**2a**, (*S*,*S*)-**3a**, and (*R*,*S*)-**4a** (meso), which could be isolated by flash column chromatography on silica gel (hexane/ethyl acetate as eluent). (*R*,*S*)-Isomer **4a** was easily confirmed by the ^{1}H NMR spectrum. The structure of each (*R*,*R*)-**2a** and (*S*,*S*)-**3a** was determined by X-ray crystallographic analysis; the X-ray structure of (*R*,*R*)-**2a** is shown in Figure 1. The isomer ratio was determined by HPLC analysis of the crude product: (*R*,*R*)-**2a**/(*S*,*S*)-**3a**/(*R*,*S*)-**4a** = 24:31:45. Because the addition of HMPA is known to increase the diastereoselectivity in samarium(II)-mediated pinacol coupling reactions,[4] the reaction was carried out by adding 4 equiv of HMPA to SmI_2. The percentage of (*R*,*R*)-**2a** increased, but the percentage of unwanted *meso*-**4a** also increased. Overall diastereoselectivity for (*R*,*R*)-**2a** or (*S*,*S*)-**3a** was not improved: (*R*,*R*)-**2a**/(*S*,*S*)-**3a**/(*R*,*S*)-**4a** = 35:10:55. The other choice of the divalent samarium reagents such as samarium(II) triflate [$Sm(OTf)_2$] reminded us of the possibility of enhancing the selectivity.[7] We and other research groups have reported that $Sm(OTf)_2$ tends to give higher stereoselectivity in the Barbier-type reaction between ketones and alkyl halides[7a−b] and the pinacol coupling reaction of acetophenone than SmI_2.[7d] $Sm(OTf)_2$ can be prepared by the reduction of samarium(III) triflate [$Sm(OTf)_3$] with appropriate organolithium and magnesium reagents. We first carried out the pinacol coupling of **1a** using $Sm(OTf)_2$, which was prepared by the reduction of $Sm(OTf)_3$

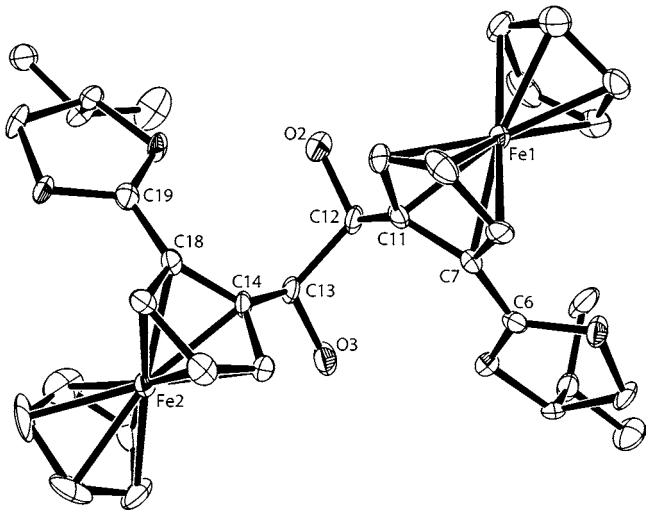


Figure 1. Molecular structure of (*R*,*R*)-**2a** (ORTEP plot). Selected bond lengths (Å): C(6)−C(7) = 1.45, N(1)−C(6) = 1.28, C(18)−C(19) = 1.46, N(2)−C(19) = 1.26, C(11)−C(12) = 1.49, O(2)−C(12) = 1.41, C(12)−C(13) = 1.59, O(3)−C(13) = 1.38. Selected bond angles (deg): C(7)−C(6)−N(1) = 128.1, O(2)−C(12)−C(11) = 111.2, N(2)−C(19)−C(18) = 126.5, O(3)−C(13)−C(12) = 111.0.

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with *s*-BuLi at 0 °C for 1 h in THF. The HPLC and ^{1}H NMR analyses revealed that the selectivity for (*R*,*R*)-**2a** was remarkably enhanced and that the production of unwanted (*R*,*S*)-**4a** significantly decreased; the ratio of (*R*,*R*)-**2a**/(*S*,*S*)-**3a**/(*R*,*S*)-**4a** = 88:3:9, and the diastereomeric excess (de) percentage of **2a** = 76. This result encouraged us to search for more effective organometallic reagents. Table 1 surveys

Table 1. Pinacol Coupling of the Formylferrocene (**1a**) Using $Sm(OTf)_3$/RM[a]

entry	RM	% yield[b]	*R*,*R*/*S*,*S*/*R*,*S*[c]
1[d]		95	24:31:45
2[d,e]		90	35:10:55
3	*s*-BuLi	96	88:3:9
4[f]	*s*-BuLi	73	75:2:23
5[e]	*s*-BuLi	87	87:5:8
6	*n*-BuLi	93	73:2:25
7	*t*-BuLi	64	76:2:22
8	EtMgBr	68	41:10:49
9	*s*-BuMgCl	36	13:8:79

[a] $Sm(OTf)_3$ (1.0 mmol), RM (1.0 mmol), THF (5 mL), **1a** (0.5 mmol) at 0 °C for 1 h. [b] Isolated yield. [c] Determined by HPLC. [d] SmI_2 (THF, 10 mL) was used. [e] HMPA (4.0 mmol) was added. [f] The reaction was carried out at room temperature for 1 h.

the results with $Sm(OTf)_2$ prepared by the reduction with representative organolithium and magnesium reagents. *n*-BuLi was inferior to *s*-BuLi because the Sm(II) species decreased the (*R*,*R*)-**2a** selectivity to some extent. The addition of HMPA hardly affected the selectivity. EtMgBr and *sec*-BuMgCl were not appropriate choices of organometallic reagents, as the Sm(II) species with these Grignard reagents rather enhanced the yield of the unwanted (*R*,*S*)-**4a**.[8]

On the basis of the above experiments, we employed the combination of $Sm(OTf)_3$ and *s*-BuLi for preparing the Sm(II) reagent to examine the pinacol coupling reaction with several ortho 4-substituted oxazolinyl chiral formylferrocene derivatives. (4*S*)-*tert*-Butyl (**1b**), phenyl (**1c**), benzyl (**1d**), and 4,4-dimethyl (**1e**) -oxazolines were examined as ortho substituents for formylferrocene derivatives in addition to the 4-isopropyl derivative (**1a**). The results of the pinacol coupling reaction of these *ortho*-oxazolinyl formylferrocenes using $Sm(OTf)_2$ are summarized in Table 2. The pinacol coupling reaction of the 4-*tert*-butyl oxazoline derivative **1b** with $Sm(OTf)_2$ gave the (*R*,*R*) isomer with diastereoselectivity (entry 2, 74% de) as high as that with **1a**, and the use of SmI_2 gave the unwanted (*R*,*S*) isomer as the major product. The reaction with 4-phenyl derivatives (**1c**) also gave the (*R*,*R*) isomer as the major product; however, its selectivity (12% de) was not as high as that of **1a**,**b**, though the (*R*,*R*) selectivity was improved compared to that of SmI_2. The reaction with the benzyl derivative **1d**, however, produced the (*R*,*S*) isomer as the major product.

(8) The large difference in stereoselectivity between Sm(II) species with alkyllithium and with alkylmagnesium suggests that the formula of $Sm(OTf)_2$ should not represent the correct structure of Sm(II) species. $Sm(OTf)_2$ may form a complex with LiOTf or $Mg(OTf)_2$, and this complex may control the stereoselectivity.

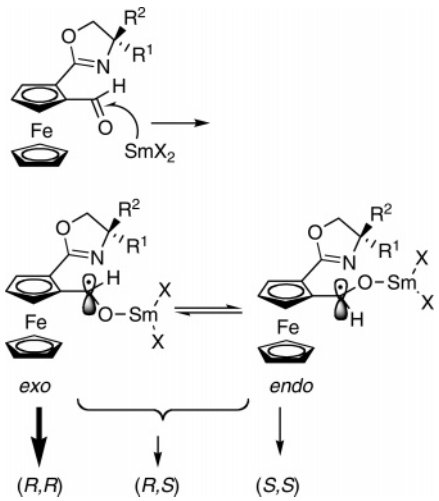
Table 2. Pinacol Coupling of Formylferrocenes (**1a**−**e**) Using $Sm(OTf)_2$[a]

entry	R^1	R^2	% yield[b]	*R*,*R*/*S*,*S*/*R*,*S*[c]
1	H	*i*-Pr	96	88:3:9
2	H	*t*-Bu	99	87:2:11
3[d]	H	*t*-Bu	55	9:44:47
4	H	Ph	58	56:24:20
5[d]	H	Ph	70	36:22:42
6	H	Bn	74	43:10:47
7	Me	Me	70	70:1:29

[a] $Sm(OTf)_3$ (1.0 mmol), *s*-BuLi (1.0 mmol), THF (5 mL), **1a**−**e** (0.5 mmol) at 0 °C for 1 h. [b] Isolated yield. [c] Determined by HPLC. [d] SmI_2 (THF, 10 mL) was used.

The reaction with the 4,4′-dimethyloxazoline derivative **1e**, which has the only planar chirality (*Rp*) (*without central chirality*), gave the (*R*,*R*) pinacol as the major product (40% de), similar to the reaction with **1a**−**d** having *Rp* configuration (Table 2, entry 7). Pinacol coupling of the (*S*,*Sp*) aldehyde **1f** (planar chirality reverse to **1a**) gave the (*S*,*S*) pinacol preferentially (65% de). These results suggest that the central chirality of the oxazoline group may not be involved in the selectivity in pinacol coupling; rather, the planar chirality and size of the 4-substituent should control the stereochemistry and selectivity. The stereochemistry may be explained by Uemura's transition-state model of pinacol coupling of planar chiral formylferrocene.[5] The carbonyl oxygen is oriented away from the *ortho* substituent by steric

Scheme 2

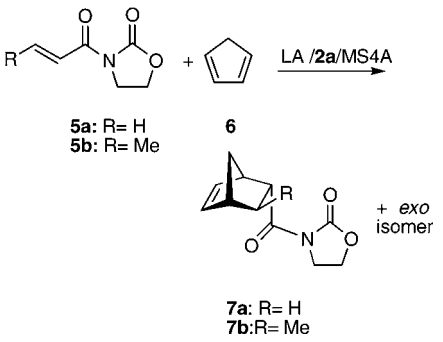


effects, and Sm(II) attacks the carbonyl group from the *exo* side to form the corresponding *exo*-ketyl radical intermediate. The sterically demanding triflate group would allow as little diastereomerical isomerization as possible, and the mostly existing *exo*-ketyl radicals could couple each other to give the (*R*,*R*) pinacol.[9] On the other hand, a less-hindered iodo group would allow coordination of the oxazoline group to the samarium atom; the *exo*-ketyl radical would then isomer-

ize to a diastereoisomeric configuration (equilibrium of *exo*- and *endo*-ketyl radicals), and each radical isomer would cross- or self-couple to form the *dl* and *meso* isomers (Scheme 2).

Representative Lewis acids were examined for the complex formation with **2a** and their catalytic efficiency in the benchmark asymmetric Diels−Alder reaction (Scheme 3).[10]

Scheme 3



The reaction was usually carried out as follows. The Lewis acid complex with (*R*,*R*)-**2a** was first prepared at 0 °C in CH_2Cl_2 or toluene in the presence of MS4A. After 1 h of aging, 3-acryloyloxazolidin-2-one (**5a**) and cyclopentadiene (**6**) were added to the solution at the same temperature, and the resulting mixture was stirred for 2 h. The product was isolated by preparative TLC, and the isomer ratio (*endo*/*exo*) and enantiomeric excess (% ee) were determined by HPLC using a chiral column (Daicel Chiralcel OD). Table 3 summarizes the results of the reaction using a representative Lewis acid/**2a** complex as the catalyst (10 mol % to **5**). Among the various metal salts, rare-earth triflates tended to give moderate to good enantioselectivity; the complex with $Yb(OTf)_3$ was the most effective giving the (*R*) *endo* adduct (**7**) in a high yield with 70% ee.[11] The Lewis acids other than the rare-earth triflates have exhibited lower enantioselectivities (entries 9−13). Addition of a tertiary amine such as 2,6-lutidine has been known to improve enantioselectivity in some asymmetric reactions with rare-earth triflate/chiral ligand complexes;[12] however, the addition of 2,6-lutidine rather spoiled the selectivity in this reaction, with the ee being decreased to 7%. The reaction of 3-crotonoyloxazolidin-2-one (**5b**) and cyclopentadiene (**6**) using the combination of $Yb(OTf)_3$ and **2a** proceeded at 0 °C slowly to give the *endo* (2*R*,3*S*) adduct in high enantioselectivity and 80% ee. Combinations of $Yb(OTf)_3$ and other ferrocenyl pinacol derivatives were studied in the asymmetric Diels−Alder reaction of **5a** with **6**: (*S*,*S*)-**3a**, 7% ee (*S*); (*R*,*R*)-**2b**, 39% ee (*R*); (*R*,*R*)-**2c**, 64% ee (*R*), (*R*,*R*)-**2d**, 47% ee (*R*); (*R*,*R*)-**2e**, 58% ee (*R*); (*S*,*S*)-**2f**, 9% ee (*S*).

Table 3. Diels−Alder Reaction of 3-Acryloyloxazolidin-2-one (**5**) with Cyclopentadiene (**6**) by Lewis Acid/Ferrocenyl Pinacols (**2a**)[a]

entry	LA	% conv[b]	*endo*/*exo*[b]	% ee (*endo*) (config)[c]
1	$La(OTf)_3$	99	88:12	16 (*R*)
2	$Sc(OTf)_3$	99	77:23	48 (*R*)
3	$Sm(OTf)_3$	99	81:19	15 (*R*)
4	$Yb(OTf)_3$	99	80:20	70 (*R*)
5[d]	$Yb(OTf)_3$	99	83:17	7 (*R*)
6[e]	$Yb(OTf)_3$	95	80:20	80 (2*R*,3*S*)
7	$Yb(ClO_4)_3$	77	74:26	15 (*S*)
8	$Y(OTf)_3$	99	74:26	50 (*R*)
9	$Mg(OTf)_2$	trace		
10	$Mg(ClO_4)_2$	63	82:18	40 (*R*)
11	$Cu(OTf)_2$	trace		
12[f]	$TiCl_2(O^iPr)_2$	65	94:6	2
13[f]	$Ti(O^iPr)_4$	80	93:7	1

[a] LA (0.025 mmol), pinacol (0.03 mmol), MS4A (80 mg), 3-acryloyloxazolidin-2-one (**5a**) (0.25 mmol), cyclopentadiene (0.75 mmol) in CH_2Cl_2 (3 mL) at 0 °C for 3 h. [b] Determined by GC. [c] Determined by HPLC (chiralcel OD). [d] 2,6-Lutidine (0.05 mmol) was added. [e] Reaction with 3-crotonoyloxazolidine-2-one (**5b**) at 0 °C for 24 h. [f] The reaction was carried out in toluene (3 mL).

In conclusion, $Sm(OTf)_2$ mediated the pinacol coupling reaction with *ortho*-oxazoline-substituted formylferrocene highly stereoselectively, and ferrocenyl pinacols were first demonstrated as useful ligands for the ytterbium-catalyzed asymmetric Diels−Alder reaction to give the endo adduct in up to 80% ee.

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Supporting Information Available: The experimental details of the pinacol reaction and the Diels−Alder reaction and ^1H and ^{13}C NMR spectra for ferrocenyl compounds, **1a**−**1f**, **2a**−**2f**, **3a**, and **4a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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