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Kinetic Resolution of Racemic 1-Alkyl-2-methylenecyclopropanes via Palladium-Catalyzed Silaborative C−C Cleavage

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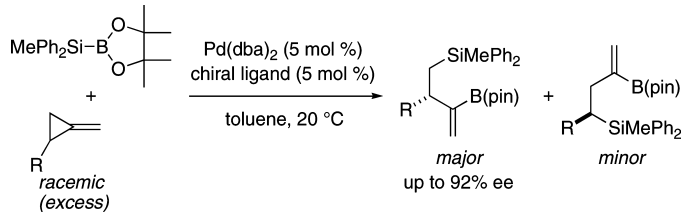
ABSTRACT



Kinetic resolution of racemic 1-alkyl-2-methylenecyclopropanes via silaborative C−C cleavage was efficiently catalyzed by a palladium complex bearing a chiral phosphoramidite, affording 2-boryl-3-silylmethyl-1-alkenes as major products with up to 92% ee. Enantioenrichment through parallel kinetic resolution, where the slower reacting enantiomer was converted to the constitutional isomer of the major product, may be involved as the crucial stereodiscriminating step.

Methylenecyclopropanes (MCPs) have become important starting materials in organic synthesis because of the unique reactivity with sufficient stability.[1] A variety of reactions of MCPs, including transition-metal-catalyzed bond formation with or without opening of the cyclopropane ring, have been developed,[1b−d] presenting a potential applicability of MCPs in asymmetric synthesis. However, limited successes have been achieved for asymmetric reactions utilizing MCPs.[2]

Kinetic resolution of racemic MCPs is an unexplored yet potentially attractive method for obtaining enantioenriched chiral products as well as for recovering highly enantioenriched MCPs.[3] During the course of our study on the asymmetric silaboration of *meso*-MCPs,[4,5] we became interested in the possibility of the kinetic resolution of racemic MCPs through a transition-metal-catalyzed reaction with silylborane.[6] In this paper, we describe a unique kinetic resolution system with palladium-catalyzed silaborative C−C

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(2) (a) Takaya, H.; Hayashi, N.; Ishigami, T.; Noyori, R. *Chem. Lett.* **1973**, 813. (b) Binger, P.; Schäfer, B. *Tetrahedron Lett.* **1988**, *29*, 529. (c) Binger, P.; Brinkmann, A.; Roefke, P.; Schäfer, B. *Liebigs Ann. Chem.* **1989**, 739. (d) Stolle, A.; Becker, H.; Salaün, J.; de Meijere, A. *Tetrahedron Lett.* **1994**, *35*, 3521. (e) Scott, M. E.; Han, W.; Lautens, M. *Org. Lett.* **2004**, *6*, 3309. (f) Taillier, C.; Lautens, M. *Org. Lett.* **2007**, *9*, 591.

(3) Reviews on kinetic resolution, see: (a) Kagan, H. B. *Tetrahedron* **2001**, *57*, 2449. (b) Dehli, J. R.; Gotor, V. *Chem. Soc. Rev.* **2002**, *31*, 365. (c) Vedejs, E.; Jure, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 3974. (d) Gansäuer, A.; Fan, C.-A.; Keller, F.; Karbaum, P. *Chem.—Eur. J.* **2007**, *13*, 8084.

(4) Ohmura, T.; Taniguchi, H.; Kondo, Y.; Suginome, M. *J. Am. Chem. Soc.* **2007**, *129*, 3518.

(5) For related studies on asymmetric silaboration, see: (a) Suginome, M.; Ohmura, T.; Miyake, Y.; Mitani, S.; Ito, Y.; Murakami, M. *J. Am. Chem. Soc.* **2003**, *125*, 11174. (b) Ohmura, T.; Suginome, M. *Org. Lett.* **2006**, *8*, 2503. (c) Ohmura, T.; Taniguchi, H.; Suginome, M. *J. Am. Chem. Soc.* **2006**, *128*, 13682. For recent reviews on bismetallation of unsaturated hydrocarbons, see: (d) Beletskaya, I.; Moberg, C. *Chem. Rev.* **2006**, *106*, 2320. (e) Suginome, M.; Matsuda, T.; Ohmura, T.; Seki, A.; Murakami, M. In *Comprehensive Organometallic Chemistry III*; Crabtree, R. H., Mingos, D. M. P., Eds.; Ojima, I., Vol. Ed.; Elsevier: Oxford, 2007; Vol. 10, p 725. (f) Burks, H. E.; Morken, J. P. *Chem. Commun.* **2007**, 4717. (g) Ohmura, T.; Suginome, M. *Bull. Chem. Soc. Jpn.* **2009**, *82*, 29.

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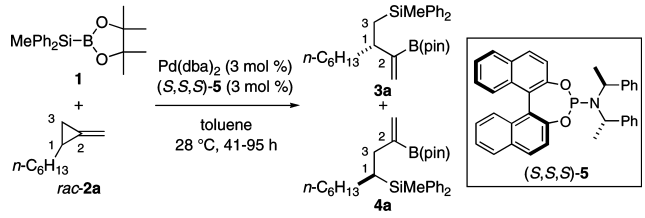
Table 1. Silaborative C−C Cleavage of **2a** with **1** in the Presence of Pd/(*S*,*S*,*S*)-**5** Catalyst[a]



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						path selectivities[e]		
entry	equiv of **2a**	% yield **3a**+**4a**[b]	**3a**:**4a**[c]	% ee of **3a**[d]	% ee of **4a**[d]	**I**:**II**	***a***:***b***	***a′***:***b′***
1	1.0	84	62:38	**71**	**70**	59:41	90:10	78:22
2	1.5	93	70:30	**82**	**51**	71:29	90:10	78:22
3	3.0	96	76:24	**88**	**30**	80:20	89:11	77:23
4[f]	3.0	99 (90)[g,h]	78:22	**91**	**39**	81:19	92:8	81:19

[a] $Pd(dba)_2$ (3 mol %), (*S*,*S*,*S*)-**5** (3 mol %), **1** (0.2 mmol), and **2a** (0.2−0.6 mmol) were reacted in toluene (0.1 mL) at 28 °C for 41−95 h. [b] GC yield based on **1**. [c] Determined by GC. [d] Determined after conversion to the corresponding β-silyl ketones that analyzed by HPLC with a chiral stationary-phase column. [e] Calculated from the product distribution. See Scheme 1 and the Supporting Information. [f] Reaction carried out at 20 °C for 92 h in the presence of 5 mol % of catalyst. [g] Isolated yield. [h] Containing dba (<5%) as an inseparable impurity.

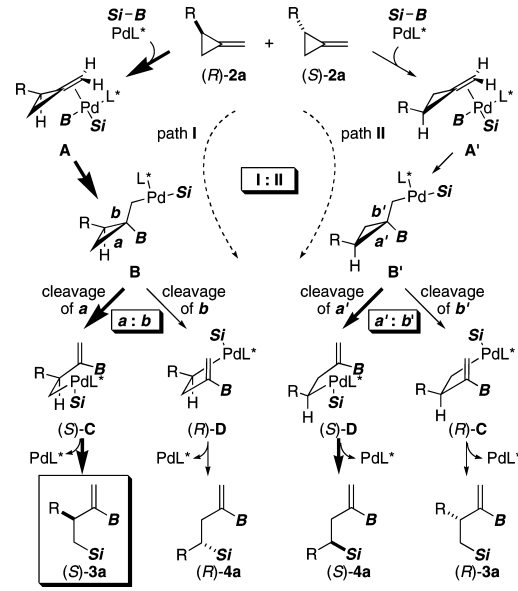
cleavage of 1-alkyl-2-methylenecyclopropanes, which provides highly enantioenriched alkenylboronic acid derivatives.

Reaction of $MePh_2Si$−B(pin) (**1**) with 1 equiv of 1-hexyl-2-methylenecyclopropane (**2a**) was carried out in toluene at 28 °C in the presence of 3 mol % of $Pd(dba)_2$ with chiral phosphoramidite (*S*,*S*,*S*)-**5** (entry 1, Table 1). Silaborative C−C cleavage of **2a** took place to give alkenylboranes **3a** and **4a**, which were formed via cleavage of the less sterically hindered C2−C3 bond and more hindered C2−C1 bond, respectively, in 84% yield in a ratio of 62:38. The enantiomeric excesses (ee's) of **3a** and **4a** were determined to be 71% and 70%, respectively. These results suggested that one enantiomer of **2a** was selectively converted to **3a** and the other enantiomer to **4a**.

The product distribution and enantioselectivity changed significantly when the reaction was carried out with excess amounts of **2a** (entries 2 and 3). Use of 3 equiv of **2a** afforded **3a** more selectively (**3a**:**4a** = 76:24, entry 3), with a higher ee (88% ee). We eventually found that **3a** was formed with 91% ee at 20 °C with an improved ratio of **3a**:**4a** (entry 4).

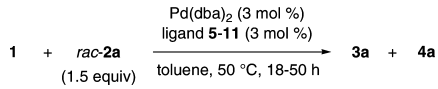
A plausible rationale for the observed enantioenrichment is depicted in Scheme 1. The C−C double bond in (*R*)-**2a** coordinates to the B−Pd−Si complex on the less sterically congested π-face opposite to the hexyl group in the cyclopropane ring to form **A**. The intermediate **A** then undergoes insertion of the C═C bond into the B−Pd bond to form the (cyclopropylmethyl)palladium species **B**. Diastereomeric intermediate **B′** is similarly formed from (*S*)-**2a**. The selectivity for path **I** over path **II** (**I**:**II**), which arises from the primary kinetic resolution of (*R*)- and (*S*)-**2a**, is not very high: around 3:2−4:1 (Table 1). The high enantiopurities of the final product (*S*)-**3a** may be attributed to the secondary resolution in the stage of β-carbon elimination of intermediates **B** and **B′**: The β-carbon elimination of **B** and **B′** proceeds preferentially at the C−C bonds ***a*** and ***a′***, respectively, which have a common spatial arrangement relative to the Pd−C bond that is to be cleaved. This second resolution arises from chiral induction by the ligand (*S*,*S*,*S*)-**5**, which preferably induces β-carbon cleavage at the C−C bonds, corresponding to ***a*** and ***a′***, irrespective of the substituents in the cyclopropane ring. Although neither the primary (**I**:**II** = 3:2−4:1) nor the secondary resolution (***a***:***b*** = ca. 9:1, ***a′***:***b′*** = ca. 8:2) is very selective, their combination allows the formation of an enantioenriched product with high ee.

Scheme 1. Plausible Reaction Pathways [R = n-C_6H_{13}, ***Si*** = $SiMePh_2$, ***B*** = B(pin), L* = (*S*,*S*,*S*)-**5**]



(6) Suginome, M.; Matsuda, T.; Ito, Y. *J. Am. Chem. Soc.* **2000**, *122*, 11015.

Table 2. Comparison of Ligands[a]



entry	ligand	% yield **3a**+**4a**[b]	**3a**:**4a**[c]	% ee of **3a**[d]	% ee of **4a**[d]	path selectivities[e] **I**:**II**	***a***:***b***	***a′***:***b′***
1	(*S*,*S*,*S*)-**5**	92	67:33	75	32	70:30	84:16	72:28
2	(*R*)-**6**	76	54:46	89	70	58:42	88:12	93:7
3	(*R*,*S*,*S*)-**5**	96	55:45	−36	−26	46:54	38:62	31:69
4	(*S*,*S*)-**7**	90	60:40	28	12	56:44	69:31	51:49
5	(*S*)-**8**	71	46:54	67	48	52:48	73:27	84:16
6	(*S*)-**9**	70	46:54	58	42	52:48	70:30	80:20
7	(*S*)-**10**	83	55:45	18	36	47:53	69:31	58:42
8	(*R*,*R*)-**11**	51	69:31	−64	−26	32:68	39:61	17:83

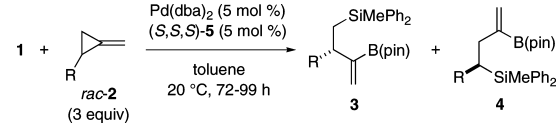
[a] $Pd(dba)_2$ (3 mol %), ligand (3 mol %), **1** (0.2 mmol), and **2a** (0.3 mmol) were reacted in toluene (0.1 mL) at 50 °C for 18−50 h. [b] GC yield based on **1**. [c] Determined by GC. [d] Determined after conversion to the corresponding β-silyl ketones that were analyzed by HPLC with a chiral stationary phase column. A negative value means major formation of the other enantiomer. [e] Calculated from the product distribution. See Scheme 1 and the Supporting Information.

Our kinetic resolution system may be regarded as a unique parallel kinetic resolution system[7] in which the total efficiency of the kinetic resolution also relies on the reactivity difference between the enantiomeric reactants.[8] It suggests that even if each of the two chiral discriminations is not very effective, their synergism in the catalytic cycle affords high enantioselectivity.[9]

It was interesting to compare the characteristic catalyst ability of Pd/(*S*,*S*,*S*)-**5** with that of several other palladium catalysts (Table 2). To enable comparison with some less active catalysts, the reactions were carried out at 50 °C with 1.5 equiv of **2a**. The reaction with Pd/(*S*,*S*,*S*)-**5** catalyst gave **3a** and **4a** in a ratio of 67:33, with 75% and 32% ee, respectively, indicating good path selectivities (**I**:**II** = 70:30, ***a***:***b*** = 84:16, ***a′***:***b′*** = 72:28) (entry 1). Very different results were obtained for the reaction with Pd/(*R*)-**6**, which was the most effective catalyst for the asymmetric desymmetrization of *meso*-MCPs (entry 2).[4] Although the reaction afforded **3a** and **4a** in a ratio of almost 1:1, the ee's of the products were 89 and 70%, respectively, indicating that the (*R*)-**6**-based catalyst is more selective in the β-carbon elimination step (***a***:***b***, ***a′***:***b′***) but less selective in the primary stereodiscrimination (**I**:**II**). Palladium catalysts bearing (*R*,*S*,*S*)-**5**, (*S*,*S*)-**7**, (*S*)-**8**, (*S*)-**9**, and (*S*)-**10** gave inferior results in terms of primary resolution (**I**:**II** = 47:53−56:44) as well as secondary resolution (***a***:***b*** and ***a′***:***b′*** = ca. 5:5−8:2) (entries 3−7). It should be noted that TADDOL-derived (*R*,*R*)-**11** gave product selectivity comparable with (*S*,*S*,*S*)-**5**, despite low product yield (entry 8).

Various racemic MCPs **2** were subjected to the kinetic resolution using the Pd/(*S*,*S*,*S*)-**5** catalyst at 20 °C (Table 3). Selective formation of **3b** (90% ee) was realized with high total yield (97%, **3b**:**4b** = 80:20) (entry 1). The reaction of **2c**−**e** bearing siloxyalkyl and acetoxypropyl groups also gave **3c**−**e** with 90−92% ee's in high yields with good product selectivity (entries 2−4). Products **3f** (87% ee) and

Table 3. Kinetic Resolution of *rac*-**2** via Pd/(*S*,*S*,*S*)-**5**-Catalyzed Silaborative C−C Cleavage[a]

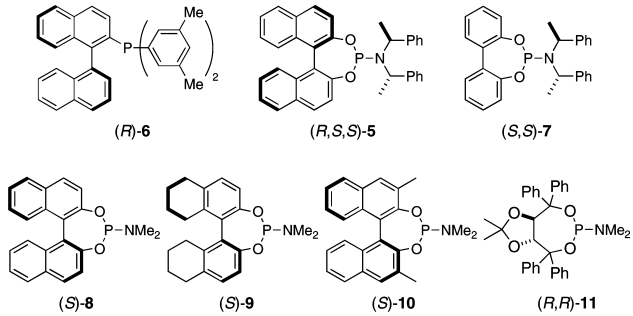


entry	**2**	% yield (**3** + **4**)[b]	**3**:**4**[c]	% ee of **3**[d]
1	**2b** [R = $(CH_2)_2$Ph]	97[e]	80:20	90[f] (**3b**)
2	**2c** [R = $CH_2OSiMe_2(t\text{-Bu})$]	85[e]	86:14	92 (**3c**)
3	**2d** [R = $(CH_2)_3OSiMe_2(t\text{-Bu})$]	97[e]	77:23[g]	90 (**3d**)
4	**2e** [R = $(CH_2)_2$OAc]	71[e]	80:20	90 (**3e**)
5	**2f** [R = $(CH_2)_3$Cl]	69[h]	77:23	87 (**3f**)
6	**2g** [R = $(CH_2)_2$N(phthaloyl)]	84	81:19	85 (**3g**)

[a] $Pd(dba)_2$ (5 mol %), (*S*,*S*,*S*)-**5** (5 mol %), **1** (0.2 mmol), and **2** (0.6 mmol) were reacted in toluene (0.1 mL) at 20 °C for 72−99 h. [b] Isolated yield. [c] Determined by GC. [d] Determined after conversion to the corresponding β-silyl ketones that were analyzed by HPLC with a chiral stationary-phase column. The ee's of **4** were 6−55%. [e] Containing dba (<5%) as inseparable impurity. [f] Determined by direct analysis of **3b**. [g] Determined by ^{1}H NMR. [h] Yield after conversion to the β-silyl ketone.

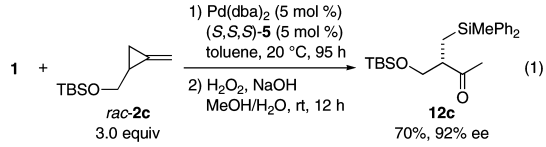
(7) In this paper, we used the term "parallel kinetic resolution" for the reaction in which each enantiomer of racemic substrate was separately converted into constitutional isomers.

(8) Examples of parallel kinetic resolution using chiral transition-metal catalyst : (a) Hayashi, T.; Yamamoto, A.; Ito, Y. *Chem. Lett.* **1987**, 177. (b) Martin, S. F.; Spaller, M. R.; Liras, S.; Hartmann, B. *J. Am. Chem. Soc.* **1994**, *116*, 4493. (c) Visser, M. S.; Hoveyda, A. H. *Tetrahedron* **1995**, *51*, 4383. (d) Doyle, M. P.; Dyatkin, A. B.; Kalinin, A. V.; Ruppar, D. A.; Martin, S. F.; Spaller, M. R.; Liras, S. *J. Am. Chem. Soc.* **1995**, *117*, 11021. (e) Bolm, C.; Schlingloff, G. *J. Chem. Soc., Chem. Commun.* **1995**, 1247. (f) Bertozzi, F.; Crotti, P.; Macchia, F.; Pineschi, M.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2001**, *40*, 930. (g) Tanaka, K.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 8078. (h) Pineschi, M.; Moro, F. D.; Crotti, P.; Bussolo, V. D.; Macchia, F. *J. Org. Chem.* **2004**, *69*, 2099. (i) Tanaka, K.; Hagiwara, Y.; Hirano, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 2734. (j) Gansäuer, A.; Fan, C.-A.; Keller, F.; Keil, J. *J. Am. Chem. Soc.* **2007**, *129*, 3484. (k) Kumar, C.; Studer, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 6542. (l) Webster, R.; Böing, C.; Lautens, M. *J. Am. Chem. Soc.* **2009**, *131*, 444.



3g (85% ee) were obtained with comparable ee's in the reaction of **2f** and **2g** bearing chloro and phthalimido groups at the termini of the alkyl chains (entries 5 and 6).[10]

The enantioenriched alkenylborane **3** would be a useful intermediate in asymmetric synthesis. An example is shown by the synthesis of β-silyl ketone (eq 1).[11] A mixture of **3c**



and **4c**, which was obtained by the reaction of **1** with *rac*-**2c**, was treated with basic hydrogen peroxide. Optically active β-silyl ketone **12c** (92% ee) was isolated in 70% yield for the two steps.[12]

In conclusion, we have reported the kinetic resolution of racemic MCPs via Pd-catalyzed silaborative C−C cleavage, which may prompt further development of asymmetric synthesis on the basis of kinetic resolution of MCPs.

Acknowledgment. H.T. acknowledges JSPS for financial support.

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

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(9) The kinetic resolution system in which secondary selection is operating synergistically has been reported recently in the ring opening of unsymmetrically substituted *cis*-epoxides: Arai, K.; Lucarini, S.; Salter, M. M.; Ohta, K.; Yamashita, Y.; Kobayashi, S. *J. Am. Chem. Soc.* **2007**, *129*, 8103.

(10) The reactions of sterically demanding **2** (R = Ph and cyclohexyl) took place slowly under the same reaction conditions (63% conversion after 48 h, R = cyclohexyl), although we have not been able to find conditions for HPLC analysis with chiral stationary phase column.

(11) For a review on β-silyl carbonyl compounds, see: Fleming, I. In *Science of Synthesis*; Fleming, I., Ed.; Thieme: Stuttgart, 2002; Vol. 4, p 927.

(12) Further synthetic applications of alkenylboronates **3** are being undertaken in this laboratory. A preliminary attempt at Suzuki−Miyaura coupling using a mixture of **3b** and **4b** (80:20) with ethyl 4-bromobenzoate in 1,4-dioxane at 100 °C in the presence of Pd[P(*t*-Bu)$_3$]$_2$ (5 mol %) with 5 N NaOH (3 equiv) resulted in the formation of the corresponding coupling products in 70% total yield after 6 h.