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Rhodium-Catalyzed Highly Enantio- and Diastereoselective Cotrimerization of Alkenes and Dialkyl Acetylenedicarboxylates Leading to Furylcyclopropanes

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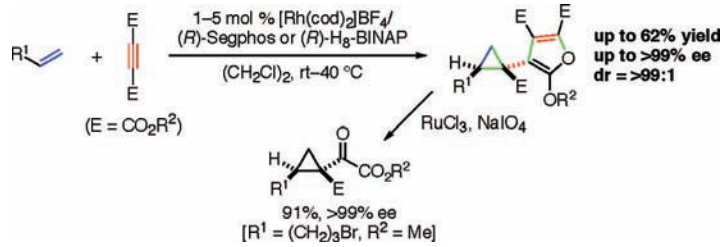
ABSTRACT



A cationic rhodium(I)/Segphos or H_8−BINAP complex catalyzes the unprecedented cotrimerization of commercially available monoenes and dialkyl acetylenedicarboxylates, leading to functionalized furylcyclopropanes with excellent enantioselectivity and perfect diastereoselectivity.

The transition-metal-catalyzed intermolecular cotrimerization of two or three different monoynes leading to substituted benzenes has been extensively studied because of its highly atom-economical nature.[1] The intermolecular cotrimerization of two monoynes and one monoene leading to conjugated cyclohexadienes has also been studied using a number of transition-metal catalysts.[2,3] Enantioselective variants have been realized by a Ni-catalyzed reaction between cyclic enones and electron-rich monoynes, but with moderate enantioselectivity (4−62% ee).[4] On the other hand, our research group demonstrated that a cationic rhodium(I)/

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(1) For recent reviews, see: (a) Agenet, N.; Buisine, O.; Slowinski, F.; Gandon, V.; Aubert, C.; Malacria, M. In *Organic Reactions*; Overman, L. E., Ed.; John Wiley & Sons: Hoboken, 2007; vol. 68, p 1. (b) Chopade, P. R.; Louie, J. *Adv. Synth. Catal.* **2006**, *348*, 2307. (c) Gandon, V.; Aubert, C.; Malacria, M. *Chem. Commun.* **2006**, 2209. (d) Kotha, S.; Brahmachary, E.; Lahiri, K. *Eur. J. Org. Chem.* **2005**, 4741. (e) Yamamoto, Y. *Curr. Org. Chem.* **2005**, *9*, 503. (f) Robinson, J. E. In *Modern Rhodium-Catalyzed Organic Reactions*; Evans, P. A., Ed.; Wiley-VCH: Weinheim, 2005; p 129.

(2) For examples of transition-metal-catalyzed intermolecular cotrimerizations of one monoene and two monoalkynes leading to cyclohexadienes, see: (a) Yamamoto, Y.; Ohno, T.; Itoh, K. *Organometallics* **2003**, *22*, 2267. (b) Ikeda, S.; Mori, N.; Sato, Y. *J. Am. Chem. Soc.* **1997**, *119*, 4779. (c) Mori, N.; Ikeda, S.; Sato, Y. *J. Am. Chem. Soc.* **1999**, *121*, 2722. (d) Itoh, K.; Hirai, K.; Sasaki, M. *Chem. Lett.* **1981**, 865. (e) Brown, L. D.; Itoh, K.; Suzuki, H.; Hirai, K.; Ibers, J. A. *J. Am. Chem. Soc.* **1978**, *100*, 8232. (f) Suzuki, H.; Itoh, K.; Ishii, Y.; Simon, K.; Ibers, J. A. *J. Am. Chem. Soc.* **1976**, *98*, 8494. (g) Chark, A. J. *J. Am. Chem. Soc.* **1972**, *94*, 5928. For Ni-catalyzed intermolecular cotrimerizations of ethyl cyclopropylideneacetate and two monoalkynes leading to cycloheptadienes, see: (h) Komagawa, S.; Saito, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 2446. (i) Saito, S.; Masuda, M.; Komagawa, S. *J. Am. Chem. Soc.* **2004**, *126*, 10540.

(3) The complete intermolecular cyclohexadiene formation by using the CpCo system requires prior formation of a stoichiometric amount of a cobaltacyclopentadiene, see: (a) Wakatsuki, Y.; Aoki, K.; Yamazaki, H. *J. Am. Chem. Soc.* **1974**, *96*, 5284. (b) Macomber, D. W.; Verma, A. G. *Organometallics* **1988**, *7*, 1241.

(4) Ikeda, S.; Kondo, H.; Arii, T.; Odashima, K. *Chem. Commun.* **2002**, 2422.

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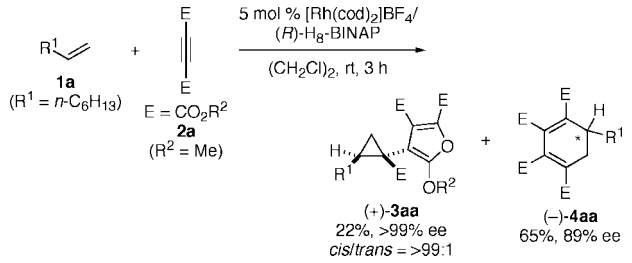
H_8−BINAP complex can catalyze highly chemo- and regioselective cotrimerization of two electron-rich terminal monoynes and one dialkyl acetylenedicarboxylate, leading to tetrasubstituted benzenes at room temperature.[5] In this paper, we describe unprecedented cotrimerization of one electron-rich monoene and two dialkyl acetylenedicarboxylates, leading to furylcyclopropanes with excellent enantioselectivity and perfect diastereoselectivity by using a cationic rhodium(I)/Segphos or H_8−BINAP complex as a catalyst.

We first investigated the reaction of dimethyl acetylenedicarboxylate (**2a**) with a large excess of 1-octene (**1a**, 5 equiv) in the presence of a $[Rh(cod)_2]BF_4$/(*R*)-H_8−BINAP catalyst. Surprisingly, the reaction proceeded at room temperature to give an unprecedented cotrimerization product, chiral furylcyclopropane **3aa**, with perfect enantio- and diastereoselectivity along with conventional cotrimerization product **4aa** (Scheme 1).[6] Although chiral cyclohexadiene

Scheme 1

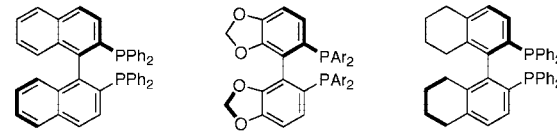


4aa was obtained as a major product with high ee, **4aa** was unstable and gradually decomposed.

To improve the yield of furylcyclopropane **3aa**, various axially chiral biarylbisphosphine ligands were screened as shown in Table 1. The study revealed that the yield of **3aa** is dependent on the dihedral angle of the biarylbisphosphine ligands [dihedral angle: H_8−BINAP (entry 1) > BINAP (entry 2) > Segphos (entry 3),[7] yield of **3aa**: entry 1 < entry 2 < entry 3]. The use of Segphos that possesses the narrowest dihedral angle furnished **3aa** in the highest yield with excellent enantioselectivity (entry 3). The effect of the steric bulk of the aryl group on the phosphorus was also examined, which revealed that increasing the steric bulk decreases the yield of **3aa** and increases the ratio of **4aa**/**3aa** (entries 3−6).

Next, the effect of alkoxy groups on the dialkyl acetylenedicarboxylates was examined as shown in Table 2. The use of diethyl acetylenedicarboxylate (**2b**, entry 2) furnished the cyclopropane product in higher yield than that using

Table 1. Screening of Ligands for Rh-Catalyzed Enantio- and Diastereoselective Cotrimerization of **1a** and **2a**[a]



(*R*)-BINAP (*R*)-Segphos (Ar = Ph) (*R*)-H_8-BINAP
(*R*)-tol-Segphos (Ar = 4-MeC_6H_4)
(*R*)-xyl-Segphos (Ar = 3,5-$Me_2C_6H_3$)
(*R*)-DTBM-Segphos (Ar = 4-MeO-3,5-*t*-$Bu_2C_6H_2$)

entry	ligand	% yield[b] of **3aa** (cis/trans, % ee)	% yield[b] of **4aa** (% ee)
1	(*R*)-H_8−BINAP	22 (>99:1, >99)	65 (89)
2	(*R*)-BINAP	24 (>99:1, >99)	46 (95)
3	(*R*)-Segphos	43 (>99:1, 99)	43 (90)
4	(*S*)-tol-Segphos	32 (>99:1, 98)	41 (93)
5	(*S*)-xyl-Segphos	30 (>99:1, >99)	37 (89)
6	(*R*)-DTBM-Segphos	10 (>99:1, >99)	74 (>99)

[a] Reactions were conducted using $[Rh(cod)_2]BF_4$ (0.015 mmol), ligand (0.015 mmol), **1a** (1.50 mmol), **2a** (0.300 mmol), and $(CH_2Cl)_2$ (3.0 mL) at rt for 3 h. [b] Isolated yield.

dimethyl acetylenedicarboxylate (**2a**, entry 1). However, di-*tert*-butyl acetylenedicarboxylate (**2c**) failed to react with **1a** (entry 3). Finally, the amount of **1a** could be reduced to 1.1 equiv with only slight erosion of the yield of **3ab** (entry 4), but further reduction in the amount of **1a** to 0.5 equiv decreased the yield to 43% (entry 5).

Table 2. $Rh(I)^+$/(*R*)-Segphos-Catalyzed Enantio- and Diastereoselective Cotrimerization of **1a** and **2a**−**c**[a]

entry	**2** (R^2)	**1a** (equiv)	% yield[b] of **3** (cis/trans, % ee)	% yield[b] of **4** (% ee)
1	**2a** (Me)	5.0	43 (>99:1, 99)	43 (90)
2	**2b** (Et)	5.0	58 (>99:1, 98)	32 (90)
3	**2c** (*t*-Bu)	5.0	0 (−)	0 (−)
4	**2b** (Et)	1.1	54 (>99:1, 98)	33 (90)
5	**2b** (Et)	0.5	43 (>99:1, 98)	27 (90)

[a] Reactions were conducted using $[Rh(cod)_2]BF_4$ (0.015 mmol), (*R*)-Segphos (0.015 mmol), **1a** (0.150−1.50 mmol), **2a**−**c** (0.300 mmol), and $(CH_2Cl)_2$ (3.0 mL) at rt for 3 h. [b] Isolated yield.

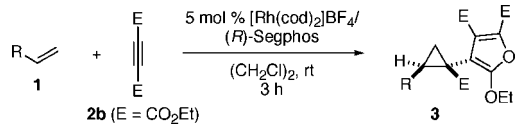
A variety of monoenes were subjected to the reaction with **2b** in the presence of the cationic rhodium(I)/(*R*)-Segphos catalyst as shown in Table 3. Not only 1-octene (**1a**, entry 1) but also a range of primary and secondary alkyl-substituted 1-alkenes (**1b**−**e**, entries 3−6) could participate in this reaction. The reactions involving haloalkyl (**1f** and **1g**, entries 7−9) and oxygen-functionalized alkyl (**1h**−**j**, entries 10−12) substituted 1-alkenes proceeded with excellent ee's. Importantly, all reactions shown in Table 3 furnished the trisubstituted cyclopropanes with perfect diastereoselectivity. Furthermore, the catalytic activity of this rhodium catalyst

(5) (a) Tanaka, K.; Shirasaka, K. *Org. Lett.* **2003**, *5*, 4697. (b) Tanaka, K.; Toyoda, K.; Wada, A.; Shirasaka, K.; Hirano, M. *Chem.*−*Eur. J.* **2005**, *11*, 1145.

(6) For reviews of the transition-metal-catalyzed cyclopropanation of olefins with diazo reagents, see: (a) Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977. (b) Davies, H. M. L.; Antoulinakis, E. *Org. React.* **2001**, *57*, 1. (c) Doyle, M. P.; Forbes, D. C. *Chem. Rev.* **1998**, *98*, 911. (d) Padwa, A.; Krumpe, K. E. *Tetrahedron* **1992**, *48*, 5385.

(7) Shimizu, H.; Nagasaki, I.; Saito, T. *Tetrahedron* **2005**, *61*, 5405.

Table 3. $Rh(I)^+$/(*R*)-Segphos-Catalyzed Enantio- and Diastereoselective Cotrimerization of **1a**−**j** and **2b** Leading to Furylcyclopropanes[a]



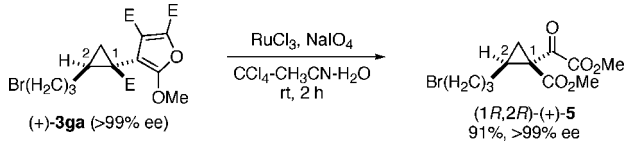
entry	**1** (R)	**3**	yield (%)[b]	cis/trans	ee (%)
1	**1a** (n-C_6H_{13})	(+)-**3ab**	54	>99:1	98
2[c]	**1a** (n-C_6H_{13})	(+)-**3ab**	55	>99:1	98
3	**1b** (n-$C_{12}H_{25}$)	(+)-**3bb**	56	>99:1	97
4[d]	**1c** [$(CH_2)_2Ph$]	(+)-**3cb**	50	>99:1	98
5	**1d** (i-Bu)	(+)-**3db**	62	>99:1	99
6[e]	**1e** (Cy)	(+)-**3eb**	58	>99:1	97
7	**1f** [$(CH_2)_4Cl$]	(+)-**3fb**	48	>99:1	>99
8	**1g** [$(CH_2)_3Br$]	(+)-**3gb**	50	>99:1	99
9[f]	**1g** [$(CH_2)_3Br$]	(+)-**3ga**	34	>99:1	>99
10[d]	**1h** [$(CH_2)_2Ac$]	(+)-**3hb**	46	>99:1	98
11[d]	**1i** [$(CH_2)_4OAc$]	(+)-**3ib**	49	>99:1	98
12	**1j** [$(CH_2)_8CO_2Me$]	(+)-**3jb**	53	>99:1	99

[a] $[Rh(cod)_2]BF_4$ (0.015 mmol), (*R*)-Segphos (0.015 mmol), **1a**−**j** (0.330 mmol), **2b** (0.300 mmol), and $(CH_2Cl)_2$ (3.0 mL) were used. [b] Isolated yield. [c] Catalyst: 1 mol %. For 16 h. [d] At 40 °C. [e] Ligand: (*R*)-H_8−BINAP. [f] **1g** (1.50 mmol) and **2a** (0.300 mmol) were used.

is very high so that the reaction could be carried out even with 1 mol % of the catalyst (entry 2). The structure of the cyclopropane product was unambiguously determined by X-ray crystallographic analysis of (±)-**3ed** prepared by the reaction of **1e** and di-4-bromobenzyl acetylenedicarboxylate (**2d**).

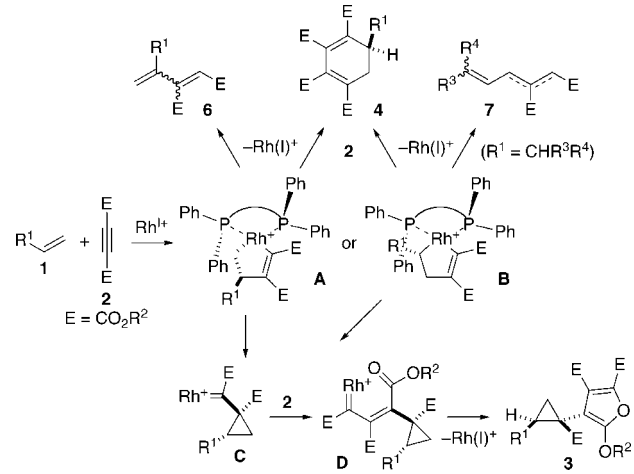
The synthetic utility of the furylcyclopropanes is demonstrated in Scheme 2. A Ru-catalyzed oxidation of furylcyclopropane (+)-**3ga** furnished ketoester (+)-**5** in high yield. Its absolute configuration was determined to be (1*R*,2*R*) by X-ray crystallographic analysis of the corresponding 2,4-dinitrophenylhydrazone.

Scheme 2



Although the precise mechanism cannot be determined at the present stage, our proposed mechanism for the formation of furylcyclopropane **3** is shown in Scheme 3. Monoene **1** and dialkyl acetylenedicarboxylate **2** react with rhodium to give rhodacyclopentene **A** or **B** depending on the steric interaction between the substituent (R^1) of monoene or the Rh-CH_2 moiety and the equatorial P-Ph group of (*R*)-Segphos. Ring contraction of **A** or **B** occurs to form rhodium carbene **C** bearing a cyclopropane ring with R^1 and E in a cis configuration.[8,9] The reaction of **2** with **C** furnishes intermediate **D**, which subsequently furnishes (1*R*,2*R*)-furylcyclopropane **3**. The higher reactivity of dialkyl acetylenedicarboxylate **2** than that of monoene **1** to the cationic rhodium might promote the formation of **D**.

Scheme 3



Alternatively, two molecules of **2** react with rhodium to give rhodacyclopentadiene **E** (Scheme 4). Insertion of **1** to **E** followed by ring contraction or cyclopropanation via rhodacyclopentatriene **G** might furnish intermediate **H**. In this mechanism, *E*/*Z* isomerization of intermediate **H** to intermediate **I** is necessary to form furylcyclopropane **3**.

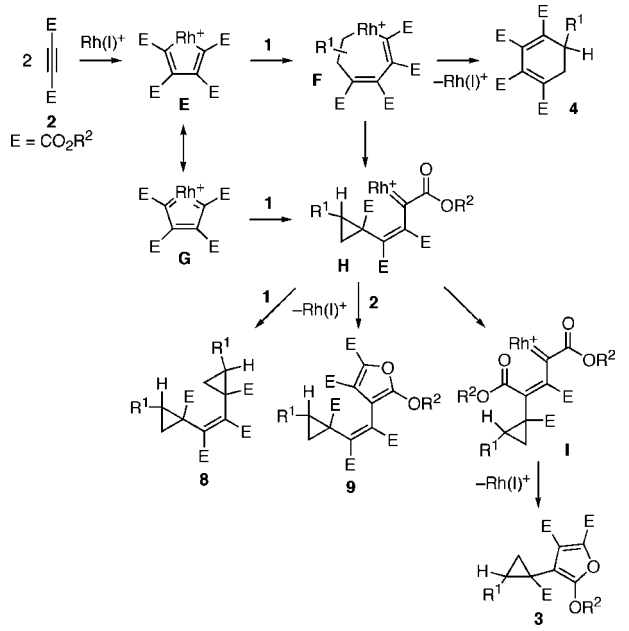
In accordance with the mechanism shown in Scheme 3, the reaction of **1a** and **1e** with **2a** in the presence of the cationic rhodium(I)/(*R*)-Segphos catalyst furnished dienes **6** and **7** as byproducts presumably through β-hydride elimination from intermediates **A** and **B**, respectively (Scheme 5). On the other hand, the reaction of sterically demanding monoene **1k** with **2a** furnished cyclohexadiene **4ka** as a sole product presumably through intermediate **E**, thereby supporting the mechanism shown in Scheme 4.[10,11]

(8) In the intramolecular [2 + 2 + 2] cycloaddition of dienynes with the Cp*RuCl(cod) catalyst, the formation of tandem cyclopropanation products was observed. The authors proposed the formation of a ruthenium carbene complex through ring contraction of an initially formed ruthenacyclopentene intermediate; see: (a) Tanaka, D.; Sato, Y.; Mori, M. *J. Am. Chem. Soc.* **2007**, *129*, 7730.

(9) When the carbonyl group is conjugated with the alkyne moiety of enynes, the Cp*RuCl(cod)-catalyzed cyclopropanation of ethylene with the enynes proceeded in high yield. The authors proposed that the reaction proceeds through a ruthenium carbene complex, which is in equilibrium with oxaruthenacyclobutene; see: (a) Tanaka, D.; Sato, Y.; Mori, M. *Organometallics* **2006**, *25*, 799.

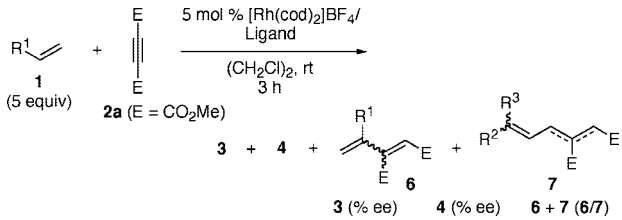
(10) Importantly, ee values of cyclohexadiene **4** are lower than those of furylcyclopropane **3** (Scheme 5). We anticipated that cyclohexadienes **4** generated through intermediate **E** possess the absolute configurations opposite to those generated through intermediates **A** and **B**. Sterically less demanding monoene **1a** reacts with **2a** to give (−)-**4aa** through intermediates **A** and **B**, which might result in the high ee value of (−)-**4aa**. On the other hand, sterically demanding monoene **1e** reacts with **2a** to give (−)-**4ea** through not only intermediates **A** and **B** but also intermediate **E**, which might result in the low ee value of (−)-**4ea**. In the reaction of sterically more demanding monoene **1k** with **2a**, intermediate **E** might be formed predominantly to give cyclohexadiene (+)-**4ka** as a sole product with high ee. The opposite optical rotations, (−)-**4aa**/(−)-**4ea** vs (+)-**4ka**, might be correlated with the opposite absolute configurations.

Scheme 4



To gain more mechanistic insights, the reaction of ethoxycarbonyl-substituted 1,6-diyne **10** with **1a** was investigated (Scheme 6). As *E*/*Z* isomerization of intermediate **H** to intermediate **I** is impossible in this case, tandem cyclopropanation product **8** or furan **9** shown in Scheme 4 might be

Scheme 5

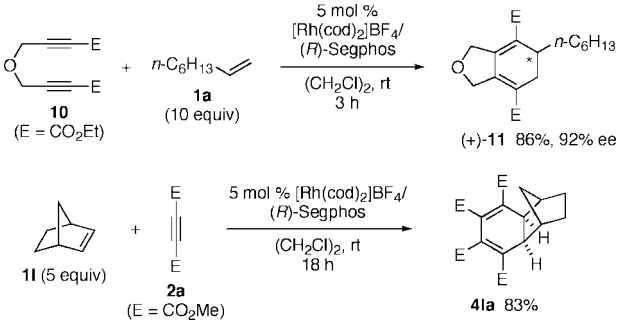


	3 (% ee)	4 (% ee)	6 + 7 (6/7)
1a [R^1 = *n*-C_6H_{13}, (*R*)-Segphos]	43 (99, +)	43 (90, –)	10 (11:89)
1e [R^1 = Cy, (*R*)-Segphos]	57 (90, +)	19 (49, –)	18 (23:77)
1k [R^1 = *t*-Bu, (*R*)-H_8-BINAP]	<1	30 (97, +)	<1

generated. However, cyclohexadiene **11** was obtained as a sole product, and **8** and **9** were not obtained at all. Itoh,

(11) In this reaction, no conversion of **1k** was observed using (*R*)-Segphos as a ligand.

Scheme 6



Yamamoto, and co-workers reported the Ru(II)-catalyzed cotrimerization of norbornene and 1,6-diynes leading to tandem cyclopropanation products via a ruthenacyclopentatriene intermediate.[12] Therefore, the reaction of norbornene **1l** with **2a** was also investigated, which revealed that cyclohexadiene **4la** was obtained as a sole product and **3**, **8**, and **9** were not obtained at all (Scheme 6). According to these results, the mechanism shown in Scheme 3 is more likely than that shown in Scheme 4 at the present stage.

In conclusion, we have demonstrated that a cationic rhodium(I)/Segphos or H_8−BINAP complex catalyzes the unprecedented cotrimerization of commercially available monoenes and dialkyl acetylenedicarboxylates, leading to functionalized furylcyclopropanes with excellent enantioselectivity and perfect diastereoselectivity. Mechanistic studies revealed that furylcyclopropanes might be generated through rhodacyclopentene intermediates. Future studies will focus on expanding the scope and elucidation of the precise mechanism.

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Supporting Information Available: Experimental procedures, compound characterization data, and X-ray crystallographic information files (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Yamamoto, Y.; Kitahara, H.; Ogawa, R.; Kawaguchi, H.; Tatsumi, K.; Itoh, K. *J. Am. Chem. Soc.* **2000**, *122*, 4310.