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Pd(II)- and Pd(0)-Cocatalyzed Reactions of Sulfonamides with MCPs

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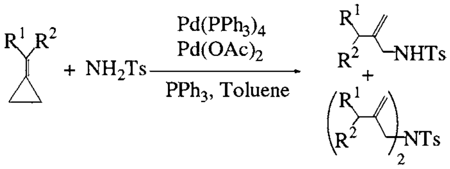
ABSTRACT



MCPs can efficiently react with sulfonamides in the presence of Pd(0) and Pd(II) catalysts to give the corresponding ring-opened products in high yields.

Methylenecyclopropanes (MCPs) **1** are highly strained but readily accessible molecules that have served as useful building blocks in organic synthesis. MCPs **1** undergo a variety of ring-opening reactions because the relief of ring strain provides a potent thermodynamic driving force.[1] Recently, reactions of MCPs with various reactants, catalyzed by transition metals such as Pd, Rh, Ru, and Pt, have attracted much attention.[2] Among them the Pd(0)- or Pd(II)-catalyzed reactions hold first place.[3] In this paper, we wish to report an unprecedented Pd(0)- and Pd(II)-cocatalyzed ring-opening reaction of MCPs **1** with sulfonamides.

During our own investigations on the ring-opening reaction of MCPs **1** (3.0 equiv) with sulfonamides **2** (1.0 equiv), we found that either Pd(0) catalyst (5 mol %) [Pd(PPh$_3$)$_4$, Pd$_2$(dba)$_3$] with PPh$_3$ (40 mol %) or Pd(II) catalyst (5 mol %) {Pd(OH)$_2$, Pd(OAc)$_2$, Pd(PPh$_3$)$_2$Cl$_2$, [(η^3-allyl)PdCl]$_2$} with PPh$_3$ (40 mol %) or dppp (12.5 mol %) cannot promote the reaction of MCP **1a** with sulfonamide **2a** in toluene or 1,2-dimethoxyethane (DME) under reflux within 24 h (Table 1, entries 2−7). A hydropalladation catalytic system [Pd$_2$(dba)$_3$, HCO$_2$H] developed by Trost for the cycloisomerization of enynes showed no activity for this reaction (Table 1, entries 8 and 9).[4] However, in the coexistence of Pd(0) and Pd(II) catalyst such as Pd(OH)$_2$/C (5 mol %) and Pd(PPh$_3$)$_4$ (10 mol %) with PPh$_3$ (40 mol %) or Pd(OAc)$_2$ (5 mol %) and Pd(PPh$_3$)$_4$ (10 mol %) with PPh$_3$ (40 mol %), the reaction proceeds smoothly to give the corresponding ring-opening

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(1) (a) Synthesis of MCPs: Brandi, A.; Goti, A. *Chem. Rev.* **1998**, *98*, 598. (b) *Carbocyclic Three-Membered Ring Compounds*; de Meijere, A., Ed.; Houben-Weyl: Thieme, Stuttgart, 1996;

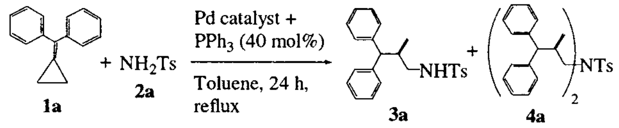
(2) For a recent review, see: Nakamura, I.; Yamamoto, Y. *Adv. Synth. Catal.* **2002**, *344*, 111.

(3) For Pd(0)- or Pd(II)-catalyzed ring-opening reactions, please see: (a) Nüske, H.; Notlemeyer, M.; de Meijere, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 3411. (b) Nakamura, I.; Oh, B.-H.; Saito, S.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 1298. (c) Oh, B.-H.; Nakamura, I.; Saito, S.; Yamamoto, Y. *Tetrahedron Lett.* **2001**, *42*, 6203. (d) Fournet, G.; Balme, G.; Goré, J. *Tetrahedron* **1988**, *44*, 5809. (e) Bräse, S.; de Meijere A. *Angew. Chem., Int, Ed. Engl.* **1995**, *34*, 2545. (f) Lautens, M.; Meyer, C.; Lorenz, A. *J. Am. Chem. Soc.* **1996**, *118*, 10676. (g) Tsukada, N.; Shibuya, A.; Nakamura, I.; Yamamoto, Y. *J. Am. Chem. Soc.* **1997**, *119*, 8123. (h) Tsukada, N.; Shibuya, A.; Nakamura, I.; Kitahara, H.; Yamamoto, Y. *Tetrahedron* **1999**, *55*, 8833. (i) Nakamura, I.; Saito, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **2000**, *122*, 2661. (j) Nakamura, I.; Itagaki, H.; Yamamoto, Y. *J. Org. Chem.* **1998**, *63*, 6458. (k) Camacho, D. H.; Nakamura, I.; Saito, S.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **1999**, *38*, 3365. (l) Suginome, M.; Matsuda, T.; Ito, Y. *J. Am. Chem. Soc.* **2000**, *122*, 11015. (m) Binger, P.; B ch, H. M. *Top. Curr. Chem.* **1987**, *135*, 77. (n) Ohta, T.; Takaya, H. In *Comprehensive Organic Chemistry*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon Press: Oxford, 1991; Vol 5, pp 1185−1205. (o) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49. (p) Zuber, R.; Carlens, G.; Haag, R.; de Meijere, A. *Synlett* **1996**, 542.

(4) (a) Trost, B. M.; Lee, D. C.; Rise, F. *Tetrahedron Lett.* **1989**, *30*, 651. (b) Trost, B. M.; Li, Y. *J. Am. Chem. Soc.* **1996**, *118*, 6625. (c) Trost, B. M.; Krische, M. J. *Synlett* **1998**, 1.

10.1021/ol034146p CCC: $25.00

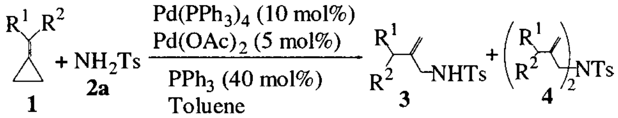
Table 1. Reaction of MCP **1a** with $TsNH_2$ Catalyzed by Various Pd Catalysts (5 mol %) with PPh_3 (40 mol %)

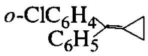
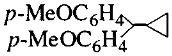
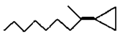
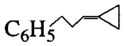
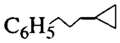
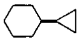
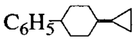


entry	catalyst	yield (%)[f]	
		3a	**4a**
1			
2	$Pd_2(dba)_3$		
3	$Pd(PPh_3)_4$		
4	$Pd(PPh_3)_2Cl_2$		
5	$Pd(OH)_2/C$		
6	$Pd(OAc)_2$		
7[a]	$[(\eta^3\text{-allyl})PdCl]_2$ (5 mol %) + dppp (12.5 mol %)		
8	$Pd_2(dba)_3$ (2.5 mol %) + HCO_2H (0.5 eq)		
9	$Pd_2(dba)_3$ (2.5 mol %) + HCO_2H (0.5 eq) + PPh_3 (5 mol %)		
10[b]	$Pd(OH)_2/C + Pd(PPh_3)_4$		100
11[c]	$Pd(OAc)_2 + Pd(PPh_3)_4$		100
12[d]	$Pd(OAc)_2 + Pd(PPh_3)_4$		100
13[d]	$Pd(OH)_2/C + Pd(PPh_3)_4$		100
14[e]	$Pd(OH)_2/C + Pd(PPh_3)_4$	28	71

[a] The reaction was carried out in DME under reflux in the presence of dppp. [b] The reaction was carried out for 5 h in toluene under reflux. [c] The reaction was carried out for 3 h in toluene under reflux. [d] 10 mol % of PPh_3 was employed, and the reaction was completed within 6 h. [e] The reaction was carried out for 8 h in the absence of PPh_3. [f] Isolated yields.

Table 2. Reaction of MCPs **1** with $TsNH_2$ Catalyzed by $Pd(PPh_3)_4$ and $Pd(OAc)_2$ Catalysts



entry	MCP		time [h]	temp. [°C]	yield [%][a)]	
					3	**4**
1		**1b**	17	110	**3b** (27)	**4b** (71)
2		**1c**	3	115	-	**4c** (100)
3		**1d**	8	110	-	**4d** (100)
4		**1e**	36	110	-	-
5		**1e**	10	90	**3e** (56)	trace
6		**1f**	24	110	trace	**4f** (85)
7		**1g**	19	110	**3g** (14)	**4g** (62)

[a] Isolated yields.

product **4a** quantitatively within 3 or 5 h (Table 1, entries 10 and 11). Considering the fact that a combination of $Pd(OAc)_2$ and PPh_3 is routinely used to generate a PPh_3-modified Pd(0) species for synthetic reactions, it is not clear that $Pd(OAc)_2$ remains as it is in the reaction mixture. Thus, we checked the amount of PPh_3 on this reaction. In this reaction system, the addition of PPh_3 is required in order to get **4a** in high yields within a shorter reaction time.[5] However, the amount of PPh_3 can be reduced to 10 mol % and give results similar to those with 40 mol % of PPh_3 (Table 1, entries 12 and 13). In the absence of PPh_3, **3a** and **4a** were obtained in 28% and 71%, respectively, after 8 h under the same conditions (Table 1, entry 14). In addition, there is no report to clarify that the combination of $Pd(OH)_2$ with PPh_3 can give a Pd(0) species. It was found that the ring-opening reaction of MCP **1a** with sulfonamide **2a** cocatalyzed by $Pd(OH)_2/C$ and $Pd(PPh_3)_4$ with PPh_3 gave results the same as those of $Pd(OAc)_2$ and $Pd(PPh_3)_4$ with PPh_3 (Table 1, entries 10 and 11; entries 12 and 13). On the basis of the above investigations, the catalytic ability of this mixed valence of the Pd catalytic system might be related with the Pd(II) catalyst [$Pd(OAc)_2$ or $Pd(OH)_2$].

By means of this Pd(0)- and Pd(II)-cocatalyzed reaction system, it was found that the other MCPs **1b**−**g** (3.0 equiv) also can react with **2a** (1.0 equiv) to afford the corresponding ring-opened products **3** and **4** in good yields within short reaction times (Table 2, entries 1−7). For MCP **1e**, the reaction should be carried out at lower temperature (90 °C) to get **3** in high yield (Table 2, entries 4 and 5). Except for **1e**, *N*,*N*-dialkylated product **4** was obtained as major product.

The structures of **3** and **4** were established by by the ^1H and ^{13}C NMR spectroscopic data (Supporting Information) and X-ray analysis. The X-ray crystal structure of **4a** is shown in Figure 1.[6]

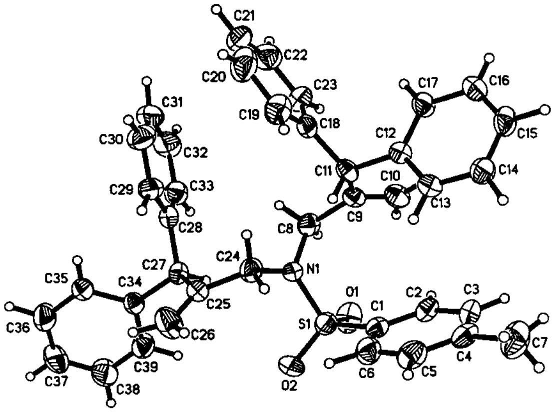


Figure 1. X-ray crystal structure of **4a**.

The product ratio of **3** and **4** cannot be adjusted by the reactant ratio because in the reaction of **1a** (1.0 equiv) with **2a** (1.0 equiv) under the same conditions, **4a** was obtained as a major product as well, whereas **3a** can be produced as the major product if the reaction time is shortened (Scheme 1).

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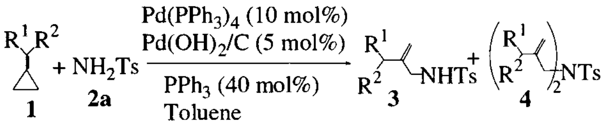
(5) In the absence of PPh_3, the precipitation of black Pd metal was observed during reaction.

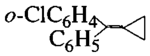
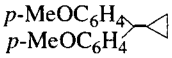
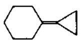
Scheme 1. Pd(0)- and Pd(II)-Cocatalyzed Ring-Opening Reaction of **1a** with **2a** at 90 °C

$$\mathbf{1a} + \mathbf{2a} \xrightarrow[\text{Toluene, 1 h, 90 °C}]{\text{Pd(0) and Pd(II) catalyst + PPh}_3} \underset{50\%}{\mathbf{3a}}$$

We further confirmed that in the combination of Pd(OH)$_2$/C and Pd(PPh$_3$)$_4$ with PPh$_3$ for other substrates, similar results were obtained (Table 3, entries 1−4).

Table 3. Reaction of MCPs **1** with TsNH$_2$ Catalyzed by Pd(PPh$_3$)$_4$ and Pd(OH)$_2$/C Catalyst

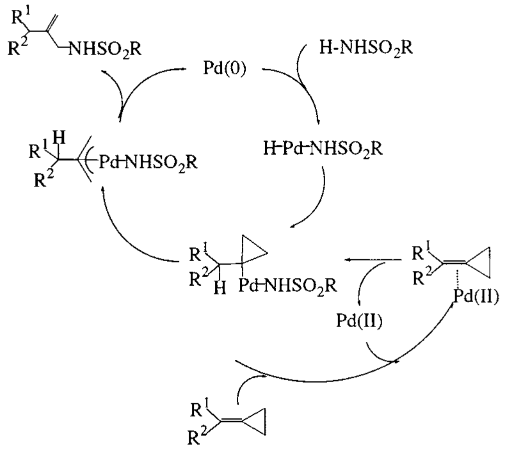


entry	MCP		time [h]	temp. [°C]	yield [%][a] 3	4
1		**1b**	14	110	**3b** (37)	**4b** (59)
2		**1c**	5	115	-	**4c** (100)
3		**1d**	8	110	-	**4d** (100)
4		**1f**	24	110	trace	**4f** (78)

[a] Isolated yields.

This is a very unusual phenomenon in Pd chemistry. To the best of our knowledge, no such mixed valence Pd-cocatalyzed system has been disclosed before. Recently Yamamoto's group revealed that a Pd(II) catalyst exhibits dual roles: it can act simultaneously as a Lewis acid and as a transition metal catalyst in the synthesis of cyclic alkenyl ethers from acetylenic aldehydes.[7] On the basis of this new concept, we can conclude that in this novel catalytic system, the Pd(II) complex acted as a Lewis acid and the Pd(0) complex as a transition metal catalyst. A conceivable mechanism of the present reaction is elucidated in Scheme 2. This is a simple Pd(0)-catalyzed reaction that has been disclosed in previous papers.[3i,j] Pd(II) [Pd(OAc)$_2$ or Pd(OH)$_2$] acted as a weak Lewis acid to help the ring opening of cyclopropane and subsequently accelerate the reaction.[8] We believe that Pd(II) species from Pd(0) with sulfonamides is different from Pd(II) catalyst [Pd(OAc)$_2$ or Pd(OH)$_2$] that previously existed in the reaction system. This in situ formed Pd(II) species is more active and reacts quickly with MCPs **1** activated by weak Lewis acid Pd(II) [Pd(OAc)$_2$ or Pd(OH)$_2$] catalyst to give the corresponding ring-opened products.

Scheme 2 Plausible Reaction Mechanism for Pd(II)- and Pd(0)-Cocatalyzed Reactions



The concept of using transition metal and Lewis acid cocatalysts has been reported before.[9] In this reaction system, we tried the Pd(PPh$_3$)$_4$ (10 mol %) and Sn(OTf)$_2$ or Sc(OTf)$_3$ (5 mol %) cocatalytic system,[10] but no reaction occurred in the presence of these bimetallic systems.

^{13}C NMR studies of a 1:1 mixture of **1a** and Pd(OAc)$_2$ in [d_6]benzene at room temperature were carried out. In the absence of Pd(OAc)$_2$, the olefinic carbon signals of **1a** appeared at δ 124.486 and 130.531, while the downfield shift of olefinic carbon within the cyclopropane at δ 124.509 and upfield shift of olefinic carbon connecting to the phenyl groups at δ 130.523 in **1a** were observed in the presence of Pd(OAc)$_2$. Because of the poor solubility of Pd(OAc)$_2$ in [d_6]benzene at room temperature, we also carried out the ^{13}C NMR studies of a 1:1 mixture of **1a** and Pd(OAc)$_2$ in [d_6]benzene at 70 °C. In the absence of Pd(OAc)$_2$, the olefinic carbon of **1a** appeared at δ 124.356 and 130.689, whereas the upfield shift of olefinic carbon connecting to cyclopropane at δ 124.195 and downfield shift of olefinic carbon connecting to phenyl group at δ 130.906 in **1a** were observed in the presence of Pd(OAc)$_2$. Using CDCl$_3$, which can easily

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(6) The crystal data of **4a** has been deposited in CCDC with number 178988. Empirical formula: $C_{39}H_{37}NO_2S$. Formula weight: 583.76. Crystal color, habit: colorless, prismatic. Crystal dimensions: 1.368 × 0.288 × 0.151 mm^3. Crystal system: monoclinic; lattice type: primitive. Lattice parameters: $a = 9.4257(8)$ Å, $b = 23.866(2)$ Å, $c = 14.1584(12)$ Å, $\alpha = 90°$, $\beta = 91.312(2)°$, $\gamma = 90°$, $V = 3184.1(5)$ Å^3. Space group: $P2(1)/c$; $Z = 4$; $D_{calc} = 1.218$ g/cm^3; $F_{000} = 1240$. Diffractometer: Rigaku AFC7R. Residuals: R, Rw: 0.0464, 0.0481.

(7) Asao, N.; Nogami, T.; Takahashi, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 764.

(8) Lewis acid catalyzed ring-opening reaction of MCPs has been disclosed by our group: (a) Shi, M.; Xu, B. *Org. Lett.* **2002**, *4*, 2145. (b) Shi, M.; Chen, Y.; Xu, B.; Tang, J. *Tetrahedron Lett.* **2002**, *43*, 8019. On the other hand, Kilburn reported Lewis acid mediated cascade reactions of silyl-substituted methylenecyclopropane with ketones and aldehydes: (c) Peron, G. L. N.; Kitteringham, J.; Kilburn, J. D. *Tetrahedron Lett.* **2000**, *41*, 1615. (d) Peron, G. L. N.; Norton, D.; Kitteringham, J.; Kilburn, J. D. *Tetrahedron Lett.* **2001**, *42*, 347. (e) Patient, L.; Berry, M. B.; Kilburn, J. D. *Tetrahedron Lett.* **2003**, *44*, 1015.

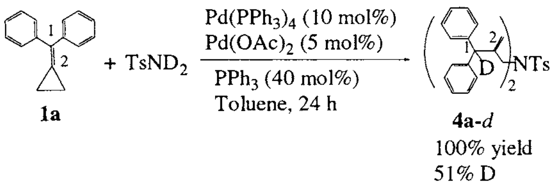
(9) (a) Sawamura, M.; Sudoh, M.; Ito, Y. *J. Am. Chem. Soc.* **1996**, *118*, 3309. (b) Kamijo, S.; Yamamoto, Y. *Angew. Chem., Int, Ed.* **2002**, *41*, 3230. (c) Ikeda, S.-i.; Mori, N.; Sato, Y. *J. Am. Chem. Soc.* **1997**, *119*, 4779.

(10) Sn(OTf)$_2$ is the best Lewis acid for ring-opening reactions of MCPs **1** with alcoholic and aromatic amino nucleophiles.[8a,b]

dissolve $Pd(OAc)_2$ at room temperature, as a solvent, a relatively obvious chemical shift was observed from δ 124.376 to 124.338 and δ 129.902 to 129.833. All the ^{13}C NMR charts have been elucidated in Supporting Information. These results may indicate that Pd(II) such as $Pd(OAc)_2$ can be potentially coordinated by olefinic moiety in MCPs, although the observed chemical shift differences are small.

To confirm the mechanism shown in Scheme 2, the ring-opening reaction of MCP **1a** with deuterated *p*-toluenesulfonamide $TsND_2$ (D content 75%) was performed.[11] The reaction of **1a** with $TsND_2$ under the same conditions as above afforded **4a**-*d* in 100% yield in which the deuterium content at the C-1 position was 51% yield (Scheme 3).

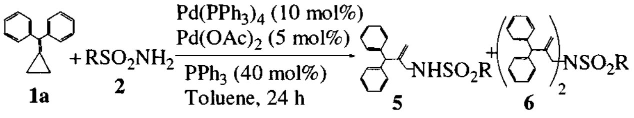
Scheme 3 Reaction of $TsND_2$ with **1a**



Deuterium incorporation did not occur at the other carbon of **4a**. The result supports the Markovnikov hydropalladation mechanism elucidated in Scheme 2.

In this catalytic system, these other sulfonamides **2b**−**d** also smoothly reacted with MCPs **1** to give the ring-opened products in very high yields (Table 4).

Table 4. The Reaction of MCP **1a** with RSO_2NH_2 Catalyzed by Pd(0) and Pd(II) Catalyst

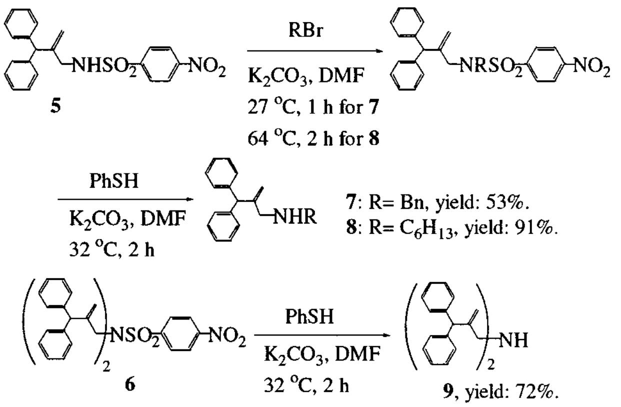


			yield (%)[a]	
entry	RSO_2NH_2	temp (°C)	5	6
1	$CH_3SO_2NH_2$ **2b**	110	**5b** (91)	
2	*p*-$NO_2C_6H_4SO_2NH_2$ **2c**	120		**6c** (100)
3	*m*-$NO_2C_6H_4SO_2NH_2$ **2b**	120[b]	**5d** (60)	

[a] Isolated yields. [b] The reaction time is 48 h.

By means of this ring-opening reaction, various allylic amines, which are useful as intermediates and have significant physiological properties,[12] can be exclusively produced via denitrobenzenesulfonylation using thiophenol under basic conditions (Scheme 4).[13] Thus, this novel catalytic reaction provides an alternative synthetic method for the preparation of allylic amines under mild conditions.

Scheme 4 Synthesis of Allylic Amines



In conclusion, during our investigation on the ring-opening reactions of MCPs **1**, we found that Pd(0) and Pd(II) can efficiently cocatalyze the reaction of MCPs **1** with sulfonamides **2** to give high yields of the corresponding ring-opened products **3** and **4**. Perhaps the catalytic system presented here may be applicable to a wide range of Pd-catalyzed transformations. Efforts are underway to elucidate the mechanistic details of this catalytic system and to identify systems enabling the acceleration of reaction rate under the same conditions and subsequent transformation thereof.

Acknowledgment. We thank the State Key Project of Basic Research (Project 973) (no. G2000048007), Shanghai Municipal Committee of Science and Technology, and the National Natural Science Foundation of China for financial support (20025206 and 20272069).

Supporting Information Available: Spectroscopic data (^1H and ^{13}C NMR) of the compounds in Tables 1−4 and Scheme 4 and detailed descriptions of experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

OL034146P

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(11) $TsND_2$ was prepared according to the literature: (a) Smith, J. K.; Bergbreiter, D. E.; Newcomb, M. *J. Org. Chem.* **1985**, *50*, 4549. (b) Inbar, S.; Linschitz, H.; Cohen, S. G. *J. Am. Chem. Soc.* **1981**, *103*, 1048. Please also see ref 3j.

(12) (a) Prashad, M. *J. Med. Chem.* **1993**, *36*, 631. (b) Stutz, A. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 320. (c) Vedejs, E.; Gingras, M. *J. Am. Chem. Soc.* **1994**, *116*, 579. (d) Kadota, I.; Kawada, M.; Muramatsu, Y.; Yamamoto, Y. *Tetrahedron: Asymmetry* **1997**, *8*, 3887.

(13) Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373.