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Insertion of cyclopropanes between a carbonyl carbon and an α-carbon of carbonyl compounds with cyclopropylmagnesium carbenoids

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ABSTRACT

The reaction of the lithium enolates of α-aryl carbonyl compounds with cyclopropylmagnesium carbenoids, derived from 1-chlorocyclopropyl *p*-tolyl sulfoxides with *i*-PrMgCl at low temperature, resulted in the formation of β-aryl carbonyl compounds bearing a cyclopropane ring at the α-position with one-carbon homologation in variable yields. The reaction was found to be highly stereospecific with respect to the stereochemistry of the cyclopropylmagnesium carbenoids. Mechanism and origin of the stereospecificity of the reaction are also discussed. This is the first example for the insertion of cyclopropanes in between a carbonyl carbon and an α-carbon of carbonyl compounds.

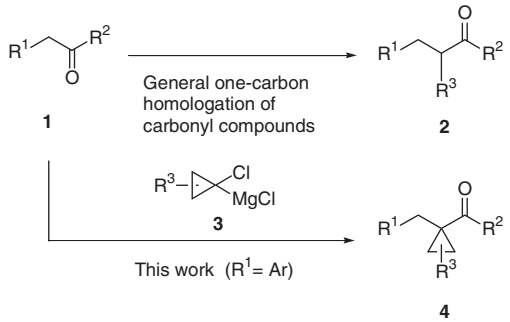
Introduction

Homologation of carbonyl compounds from lower carbonyl compounds by carbon–carbon coupling is a very useful procedure for obtaining the desired carbonyl compounds and innumerable procedures have already been reported.[1] If the homologation reactions would be applied to cyclic carbonyl compounds, ring-expanded carbonyl compounds could be obtained.[2] We have also long been interested in the homologation of carbonyl compounds based on our original chemistry; the chemistry of magnesium carbenoids or lithium carbenoids generated from α-chloroalkyl aryl sulfoxides with Grignard reagents or alkyllithiums, respectively.[3]

For the homologation of carbonyl compounds, as shown in Scheme 1, one-carbon homologation of carbonyl compounds **1** to carbonyl compounds **2** is quite general and a variety of methods have been reported.[1–3] On the other hand, homologation of **1** to cyclopropyl carbonyl compounds **4** is very unusual and, to the best of our knowledge, no report has appeared yet. We have recently studied the chemistry and uses of cyclopropylmagnesium carbenoids **3** and a variety of unprecedented reactions have appeared.[4] In continuation of our interest in the homologation of carbonyl compounds and in the chemistry of cyclopropylmagnesium carbenoids in organic synthesis, we found that the reaction of the lithium enolates of α-aryl carbonyl compounds (**1**, R^1 = Ar) with cyclopropylmagnesium carbenoids **3** resulted in the formation of cyclopropyl carbonyl compounds **4** in variable yields. In this Letter, details of this procedure and the stereochemistry of the reactions are described.

Results and discussion

In our previous studies, we reported the reactions of cyclopropylmagnesium carbenoids **3** with phenolates[4e] and *N*-lithio arylamines.[4h] Based on the experiences of these studies, we first treated cyclopropylmagnesium carbenoid **6**, generated from 1-chloro-2,2-dimethylcyclopropyl *p*-tolyl sulfoxide **5**[4h] with *i*-PrMgCl in THF at −78 °C, with 3 equiv of the lithium enolate of α-tetralone **7**, generated from α-tetralone with LDA in THF at −78 °C (Scheme 2). The temperature of the reaction mixture was slowly



Scheme 1.

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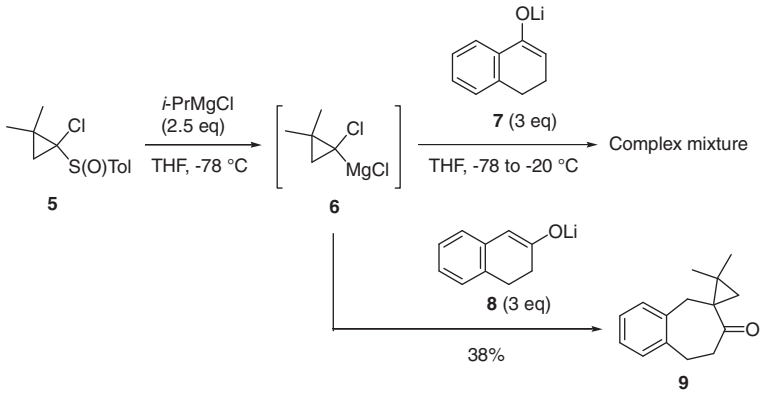


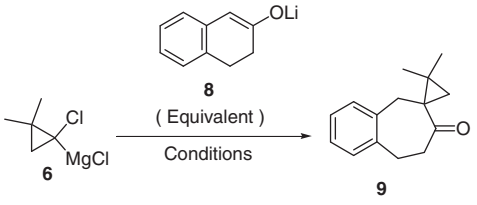
Scheme 2.

allowed to warm to −20 °C. The reaction, however, gave none of the promising products but a complex mixture.

Next, the same reaction was conducted with the lithium enolate of β-tetralone **8**. We obtained a product from the reaction mixture and, very interestingly, the product was proved to be one-carbon homologated cycloheptanone derivative bearing dimethylcyclopropyl group at the α-position of the carbonyl carbon **9** in 38% yield (the yield was calculated based on the starting material **5**). We recognized that this is an unprecedented one-carbon homologation of a ketone to a ketone bearing a cyclopropane ring at the α-position. Next, the investigation to find the best conditions for this reaction was carried out and the results are summarized in Table 1.

The result shown in entry 1 has already been mentioned above. When the amount of enolate **8** was increased to 5 equiv and the temperature of the reaction mixture was allowed to warm to −20 °C, the yield of **9** was improved to 68% (entry 2). Further increasing the amount of enolate **8** did not give a better yield (entry 3). When the reaction was carried out with 5 equiv of **8** and the temperature of the reaction mixture was allowed to warm to room temperature, the yield of **9** was increased up to 78% (entries 4 and 5).[5] Addition of HMPA as an additive (entry 6) or using toluene as the solvent gave much worse results (entries 6 and 7). We decided that the conditions described in entry 5 were the conditions of choice for this reaction and we used them throughout in this study.

Table 1
Study for the conditions of the reaction of cyclopropylmagnesium carbenoid **6** with lithium enolate of β-tetralone **8**



Entry	Conditions			**9**
	Solvent	Equiv of **8**	Temp/°C	Yield/%
1	THF	3	−78 to −20	38
2	THF	5	−78 to −20	68
3	THF	7	−78 to −20	61
4	THF	5	−78 to 0	76
5	THF	5	−78 to rt	78
6	THF/HMPA[a]	5	−78 to −20	7
7	Toluene	5	−78 to −20	11

[a] HMPA (5 equiv) was added as an additive.

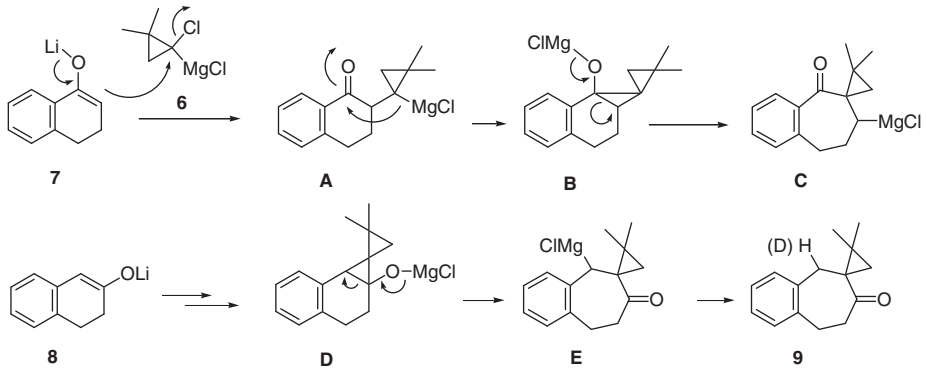
It is very important to understand the reason why the reaction of cyclopropylmagnesium carbenoid **6** with lithium enolate of β-tetralone gave one-carbon homologated cyclopropyl ketone **9**, however, the lithium enolate of α-tetralone did not. The plausible rationalization for the differences of the reactivity is shown in Scheme 3. Thus, lithium enolate of α-tetralone **7** reacts with magnesium carbenoid **6** to afford cyclopropylmagnesium chloride intermediate **A**. Intramolecular nucleophilic addition of the cyclopropylmagnesium chloride to the carbonyl carbon gave highly strained intermediate **B**, from which intermediate **C** is generated with C–C bond cleavage. However, the generated carbanion of intermediate **C** is not stabilized at all. As a result, the reaction of **7** and **6** did not give **C** but a complex mixture.

On the contrary, lithium enolate of β-tetralone **8** reacts with **6** to give highly strained intermediate **D**, from which intermediate **E** is generated with C–C bond cleavage. The generated carbanion of intermediate **E** is stabilized by the benzene ring and this reaction did indeed occur. In fact, quenching of this reaction with CH_3OD, deuterated product **9** (D) was obtained with about 70% D-content.

Next, generality of this reaction was investigated with cyclopropylmagnesium carbenoid **6** and a variety of carbonyl compounds, and the results are summarized in Table 2. The reaction of **6** with 7-methoxy β-tetralone gave a high yield of the desired product (entry 1). Seven-membered ketones gave the desired eight-membered α-cyclopropyl ketones; however, the yields were not satisfactory (entries 2 and 3). Dipropyl ketone gave only complex mixture as anticipated (entry 4). On the contrary, dibenzyl ketone gave good yield of the desired product as expected (entry 5). Although the yields were not satisfactory, α-aryl ketones gave the desired homologated α-cyclopropyl ketones (entries 6–8). Even phenylacetaldehyde gave the desired one-carbon homologated α-cyclopropyl aldehyde in 36% yield (entry 9).

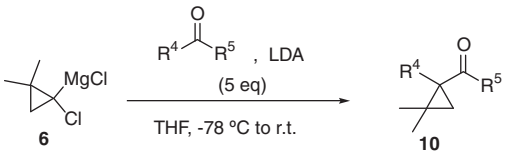
The reaction was studied by using other cyclopropylmagnesium carbenoids **12** derived from 1-chlorocyclopropyl aryl sulfoxides **11** with lithium enolate of β-tetralone **8** and the results are shown in Scheme 4. Thus, cyclopropylmagnesium carbenoid without any substituent on the cyclopropane ring **12a** reacted with **8** to give 83% yield of **13a**. In a similar manner, cyclopropylmagnesium carbenoid bearing a methyl substituent on the cyclopropane ring **12b** reacted with **8** to give 83% yield of **13b**. Even the cyclopropylmagnesium carbenoid bearing both a methyl and 2-trityloxymethyl substituents on the cyclopropane ring **12c** reacted with **8** to give good yield (71%) of the desired product **13c**.

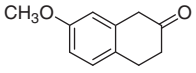
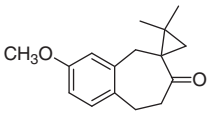
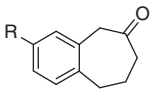
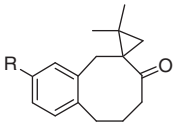
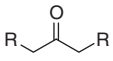
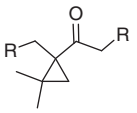
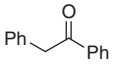
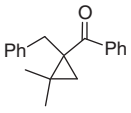
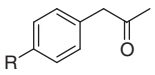
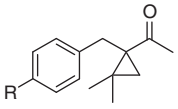
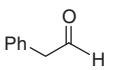
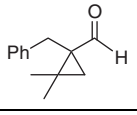
In this reaction, quite interesting stereospecificity was observed. Thus, as shown in Scheme 5, reaction of lithium enolate of β-tetralone **8** with cyclopropylmagnesium carbenoid **15**, derived from 1-chlorocyclopropyl *p*-tolyl sulfoxide **14**, gave the desired product **16** in 81% yield as a single product. In the same manner,



Scheme 3. A plausible rationalization for the reason why lithium enolate of β-tetralone gave one-carbon homologated α-cyclopropyl ketone **9** but lithium enolate of α-tetralone did not.

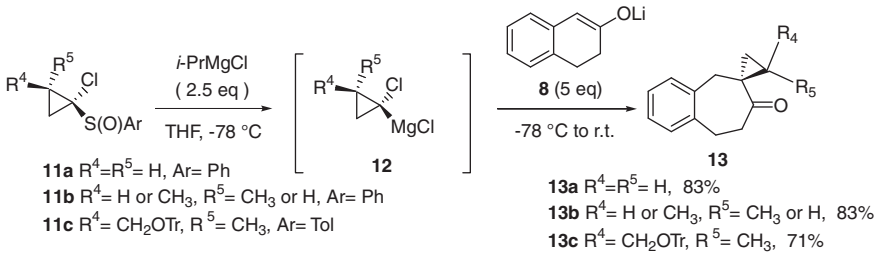
Table 2
One-carbon homologation of carbonyl compounds to cyclopropyl carbonyl compounds **10** with cyclopropylmagnesium carbenoid **6**



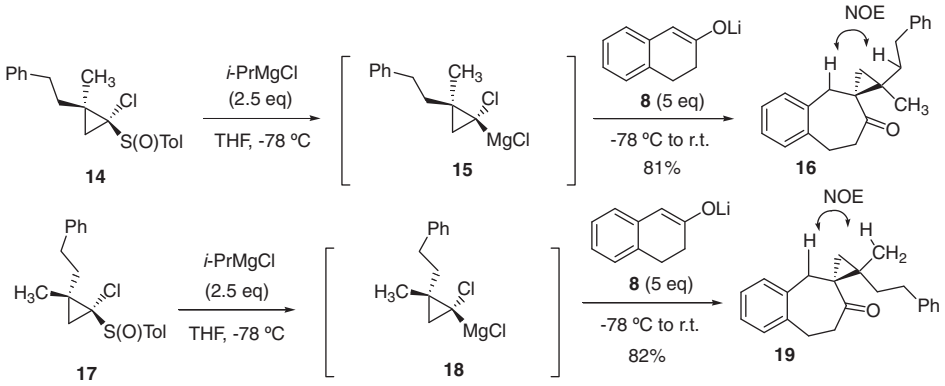
Entry	Carbonyl compound	**10**	Yield/%
1			86
2		 R = H	15
3		R = OCH_3	30
4		 R = Et	Complex mixture
5		R = Ph	73
6			41
7		 R = OMe	35
8		R = F	20
9			36

the reaction of **8** with cyclopropylmagnesium carbenoid **18**, derived from **17**, gave the desired product **19** in 82% yield, again as a single product. The products **16** and **19** were found to be diastereomers to each other. Stereochemistry of both products was determined by NOESY spectra as shown in Scheme 5.

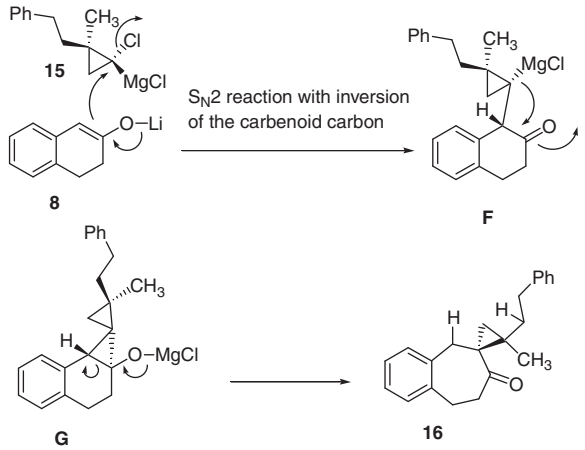
The rational explanation of the stereospecificity is as follows (Scheme 6). As the sulfoxide-magnesium exchange reaction[6] is proved to proceed with retention of the configuration of the carbon bearing the sulfoxide group,[7] sulfoxide **14** gave cyclopropylmagnesium carbenoid **15**. Nucleophilic substitution of the cyclopropyl-



Scheme 4. Reaction of cyclopropylmagnesium carbenoids **12**, derived from 1-chlorocyclopropyl aryl sulfoxides **11**, with lithium enolate of β-tetralone **8**.



Scheme 5. The stereospecific reaction of cyclopropylmagnesium carbenoids **15** and **18**, derived from 1-chlorocyclopropyl *p*-tolyl sulfoxides **14** and **17**, respectively, with lithium enolate of β-tetralone **8**.



Scheme 6. Stereochemistry of the reaction of **15** with lithium enolate of β-tetralone **8** to afford one-carbon homologated α-cyclopropyl ketone **16**.

magnesium carbenoids with carbanions was proved to take place with inversion of the carbenoid carbon.[4g] Thus, the reaction of carbenoid **15** with lithium enolate **8** afforded the cyclopropylmagnesium chloride intermediate **F**. Intramolecular nucleophilic addition of the carbanion to the carbonyl carbon gave intermediate **G**, which afforded the product **16** with C–C bond cleavage. In the same manner, the reaction of **18**, derived from **17**, with enolate **8** gave product **19** with high stereospecificity.

In conclusion, we found that the reaction of the lithium enolates of α-aryl carbonyl compounds with cyclopropylmagnesium carbenoids resulted in the formation of β-aryl carbonyl compounds bearing a cyclopropane ring at the α-position with one-carbon homologation. The reaction was found to be highly stereospecific with respect to the stereochemistry of the cyclopropylmagnesium carbenoids. This is the first example for the insertion of cyclopropanes in between a carbonyl carbon and an α-carbon of carbonyl compounds. Further investigation of this reaction, including asymmetric synthesis, is underway in our laboratory.

Acknowledgments

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References and notes

1. A monograph and some reviews concerning homologation of carbonyl compounds: (a) Hase, T. A. *Umpoled Synthons: A Survey of Sources and Uses in Synthesis*; John Wiley and Sons: New York, 1987; (b) Martin, S. F. *Synthesis* **1979**, 633; (c) Hase, T. A.; Koskimies, J. K. *Aldrichimica Acta* **1981**, *14*, 73; (d) Stowell, J. C. *Chem. Rev.* **1984**, *84*, 409; (e) Badham, N. F. *Tetrahedron* **2004**, *60*, 11; (f) Satoh, T. *J. Syn. Org. Chem. Jpn.* **2009**, *67*, 381.
2. A monograph and some reviews concerning ring-expansion reactions: (a) Hesse, M. *Ring Enlargement in Organic Synthesis*; VCH: Weinheim, 1991; (b) Hiyama, T.; Nozaki, H. *J. Syn. Org. Chem. Jpn.* **1977**, *35*, 979; (c) Krow, G. R. *Tetrahedron* **1987**, *43*, 3; (d) Dowd, P.; Zhang, W. *Chem. Rev.* **1993**, *93*, 2091; (e) Roxburgh, C. J. *Tetrahedron* **1993**, *49*, 10749; (f) Tochtermann, W.; Kraft, P. *Synlett* **1996**, 1029.
3. Some recent papers concerning the homologation of carbonyl compounds from our laboratories: (a) Satoh, T.; Mizu, Y.; Hayashi, Y.; Yamakawa, K. *Tetrahedron Lett.* **1994**, *35*, 133; (b) Satoh, T.; Hayashi, Y.; Mizu, Y.; Yamakawa, K. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 1412; (c) Satoh, T.; Itoh, N.; Gengyo, K.; Takada, S.; Asakawa, N.; Yamani, Y.; Yamakawa, K. *Tetrahedron* **1994**, *50*, 11839; (d) Satoh, T.; Mizu, Y.; Kawashima, T.; Yamakawa, K. *Tetrahedron* **1995**, *51*, 703; (e) Satoh, T.; Unno, H.; Mizu, Y.; Hayashi, Y. *Tetrahedron* **1997**, *53*, 7843; (f) Satoh, T.; Kurihara, T. *Tetrahedron Lett.* **1998**, *39*, 9215; (g) Satoh, T.; Imai, K. *Chem. Pharm. Bull.* **2003**, *51*, 602; (h) Satoh, T.; Miyashita, K. *Tetrahedron Lett.* **2004**, *45*, 4859; (i) Miyashita, K.; Satoh, T. *Tetrahedron* **2005**, *61*, 5067; (j) Satoh, T.; Tanaka, S.; Asakawa, N. *Tetrahedron Lett.* **2006**, *47*, 6769; (k) Tanaka, S.; Anai, T.; Tadokoro, M.; Satoh, T. *Tetrahedron* **2008**, *64*, 7199.
4. The papers concerning the chemistry and synthetic uses of cyclopropylmagnesium carbenoids: (a) Satoh, T.; Kurihara, T.; Fujita, K. *Tetrahedron* **2001**, *57*, 5369; (b) Satoh, T.; Saito, S. *Tetrahedron Lett.* **2004**, *45*, 347; (c) Satoh, T.; Miura, M.; Sakai, K.; Yokoyama, Y. *Tetrahedron* **2006**, *62*, 4253; (d) Yamada, Y.; Miura, M.; Satoh, T. *Tetrahedron Lett.* **2008**, *49*, 169; (e) Satoh, T.;

Nagamoto, S.; Yajima, M.; Yamada, Y.; Ohata, Y.; Tadokoro, M. *Tetrahedron Lett.* **2008**, *49*, 5431; (f) Satoh, T.; Noguchi, T.; Miyagawa, T. *Tetrahedron Lett.* **2008**, *49*, 5689; (g) Yajima, M.; Nonaka, R.; Yamashita, H.; Satoh, T. *Tetrahedron Lett.* **2009**, *50*, 4754; (h) Yamada, Y.; Mizuno, M.; Nagamoto, S.; Satoh, T. *Tetrahedron* **2009**, *65*, 10025; (i) Satoh, T.; Ikeda, S.; Miyagawa, T.; Noguchi, T. *Tetrahedron Lett.* **2010**, *51*, 1955; (j) Momochi, H.; Noguchi, T.; Miyagawa, T.; Ogawa, N.; Tadokoro, M.; Satoh, T. *Tetrahedron Lett.* **2011**, *52*, 3016.

5. To a solution of 1-chloro-2,2-dimethylcyclopropyl *p*-tolyl sulfoxide **5** (73 mg; 0.3 mmol) in 0.7 mL of dry THF in a flame-dried flask at −78 °C under argon atmosphere was added a solution of *i*-PrMgCl (2.0 mol/L in THF; 0.38 mL; 0.75 mmol) dropwise with stirring and the reaction mixture was stirred for 10 min to give cyclopropylmagnesium carbenoid **6**. In another flame-dried flask, β-tetralone (0.20 mL; 1.5 mmol) was added to a solution of LDA (1.5 mmol) in 0.8 mL of dry THF at −78 °C under argon atmosphere. This solution was added to the solution of **6** through a cannula. The temperature of the reaction mixture was allowed to warm slowly to room temperature. The reaction was quenched by satd aq NH_4Cl and the whole mixture was extracted with $CHCl_3$. The organic layer was washed once with water and dried over $MgSO_4$. After removal of the solvent, the product was purified by silica gel column chromatography to give **9** (50.2 mg, 78%) as light yellow oil. IR (neat); 2941, 1693 (CO), 1454, 1378, 1366, and 759 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.53 (1H, d, J = 4.4 Hz), 0.94 (3H, s), 1.12 (3H, s), 1.52 (1H, d, J = 4.4 Hz), 2.51–2.57 (1H, m), 2.76 (1H, d, J = 16.2 Hz), 2.98–3.08 (3H, m), 3.40 (1H, d, J = 16.2 Hz), 7.09–7.17 (4H, m); ^{13}C NMR (125.65 MHz, $CDCl_3$) δ 20.7 (CH_3), 22.2 (CH_3), 26.2 (CH_2), 27.4 (C), 29.9 (CH_2), 37.7 (CH_2), 40.8 (C), 43.4 (CH_2), 126.3 (CH), 126.5 (CH), 129.3 (CH), 130.3 (CH), 138.6 (C), 139.3 (C), 210.1 (CO). MS *m*/*z* (%): 214 (M^+, 100), 158 (36), 146 (40), 130 (58), 115 (30). Calcd for $C_{15}H_{18}O$: M, 214.1358. Found: *m*/*z* 214.1359.
6. (a) Satoh, T. *Chem. Rec.* **2004**, *3*, 329; (b) Satoh, T. *Chem. Soc. Rev.* **2007**, *36*, 1561; (c) Satoh, T. In *The Chemistry of Organomagnesium Compounds*; Rappoport, Z., Marek, I., Eds.; John Wiley and Sons: Chichester, 2008; pp 717–769; (d) Satoh, T. *Yakugaku Zasshi* **2009**, *129*, 1013.
7. (a) Satoh, T.; Kobayashi, S.; Nakanishi, S.; Horiguchi, K.; Irisa, S. *Tetrahedron* **1999**, *55*, 2515; (b) Hoffmann, R. W.; Holzer, B.; Knopff, O.; Harms, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 3072; (c) Satoh, T.; Matsue, R.; Fujii, T.; Morikawa, S. *Tetrahedron* **2001**, *57*, 3891; (d) Hoffmann, R. W. *Chem. Soc. Rev.* **2003**, *32*, 225; (e) Mitusnaga, S.; Ohbayashi, T.; Sugiyama, S.; Saitou, T.; Tadokoro, M.; Satoh, T. *Tetrahedron: Asymmetry* **2009**, *20*, 1697; (f) Satoh, T.; Kuramoto, T.; Ogata, S.; Watanabe, H.; Saitou, T.; Tadokoro, M. *Tetrahedron: Asymmetry* **2010**, *21*, 1.