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# A new synthesis, including asymmetric synthesis, of alkylidenecyclopropanes by 1,2-CC insertion of cyclobutylmagnesium carbenoides as the key reaction

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ABSTRACT

Treatment of 1-chlorovinyl *p*-tolyl sulfoxides, derived from ketones and chloromethyl *p*-tolyl sulfoxide, with lithium enolate of carboxylic acid *tert*-butyl esters gave adducts in high yields. The adducts were converted to 1-chlorocyclobutyl *p*-tolyl sulfoxides in four steps in high overall yields. Treatment of the 1-chlorocyclobutyl *p*-tolyl sulfoxides with cyclopentylmagnesium chloride in THF at −40 °C resulted in the formation of cyclobutylmagnesium carbenoids. The magnesium carbenoid 1,2-CC insertion reaction took place smoothly from the cyclobutylmagnesium carbenoids to afford alkylidenecyclopropanes in good to high yields. An asymmetric synthesis of optically active alkylidenecyclopropane was successfully achieved starting from optically active 1-chlorovinyl *p*-tolyl sulfoxide.



## 1. Introduction

Alkylidenecyclopropanes, including methylenecyclopropanes, are quite interesting compounds. They are structurally highly strained; however, usually present as stable compounds at room temperature. Because of their highly strained nature, alkylidenecyclopropanes show various reactivities and have long been used widely in organic synthesis.[1] Moreover, some biologically active compounds comprising an alkylidenecyclopropane moiety as a basic skeleton, such as G1499-2, amphimic acids, and 9-hydroxymethylcyclopropylidene-methylenyladenine,[2] have been known. Therefore, new methods for the synthesis of alkylidenecyclopropanes are very much desired.

A variety of the methods for synthesis of alkylidenecyclopropanes have been reported;[3] however, synthesis of optically active alkylidenecyclopropanes is limited.[4] We are also interested in the chemistry of alkylidenecyclopropanes and reported their synthesis based on the reaction of cyclopropylmagnesium carbenoids with lithium α-sulfonyl carbanions.[5] In continuation of our interest in the chemistry of magnesium carbenoids in organic synthesis,[6] recently, we developed a new method for a synthesis, including asymmetric synthesis, of alkylidenecyclopropanes by our original method as shown in Scheme 1.

Thus, 1-chlorovinyl *p*-tolyl sulfoxides **2**, synthesized from ketones **1**,[7] are treated with lithium enolate of *tert*-butyl carboxylates to give adducts **3** in high yields. The *tert*-butyl ester moiety is converted to an iodide group under conventional reactions to give iodides **4**, which are treated with a base to afford 1-chlorocyclobutyl *p*-tolyl sulfoxides **5** in high yields. Finally, sulfoxides **5** are treated with cyclopentylmagnesium chloride to give alkylidenecyclopropanes **6** in good yields. When optically active 1-chlorovinyl *p*-tolyl sulfoxide **2** was used in this procedure, an asymmetric synthesis of optically active alkylidenecyclopropane **6** was achieved. In this Letter we report the above-mentioned procedure.

## 2. Results and discussion

At first, representative example of this procedure is shown using 1-chlorovinyl *p*-tolyl sulfoxide **7**, which was derived from cyclohexanone, as the starting material (Scheme 2). Thus, 1-chlorovinyl *p*-tolyl sulfoxide **7**[7a] was treated with lithium enolate of *tert*-butyl 3-phenylpropionate to afford adduct **8** in a quantitative yield.[8] Stereochemistry of adduct **8** (*syn*-relationship between the chlorine atom and the benzyl group) was determined based on our previous study.[9] The adduct was treated with trifluoroacetic acid in dichloromethane to give a carboxylic acid, which was reduced with $BH_3$–THF in THF at 0 °C to give alcohol **9** in 91% overall yield from **8**. Attempt to direct reduction of ester **8** with DIBAL to alcohol **9** resulted in low yield (up to 60%). The hydroxyl group in **9** was converted to iodide group under the conventional reaction and the resultant iodide was treated with 2 equiv of KHMDS to give the desired 1-chlorocyclobutyl *p*-tolyl sulfoxide **10** in 94% overall yield from **9** as a single product.[10] Stereochemistry of **10** was determined by NOESY spectrum of the desulfinylated compound **13** (vide infra).

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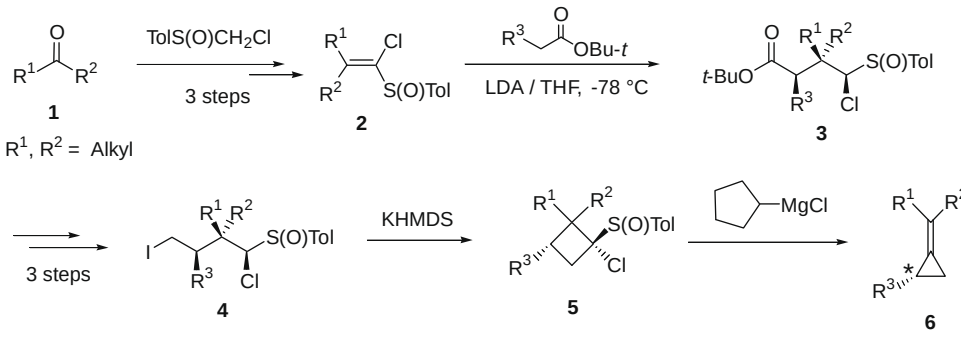
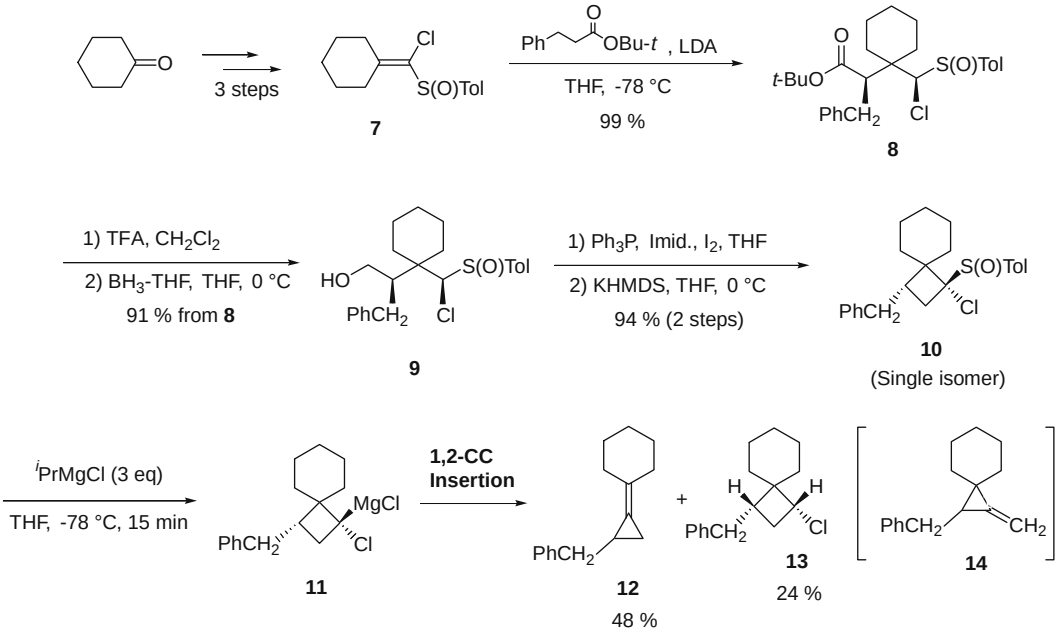



**Scheme 1.**




**Scheme 2.**

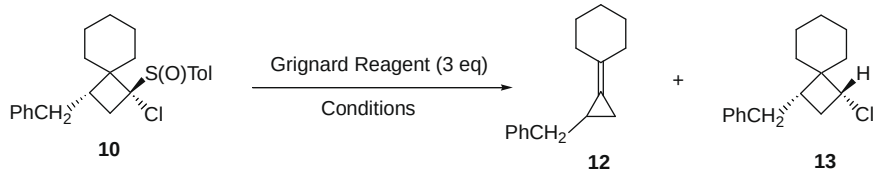
The key reaction was carried out as follows. A solution of *i*-PrMgCl in ether (3 equiv) was added to a solution of 1-chlorocyclobutyl *p*-tolyl sulfoxide **10** in THF at −78 °C under Ar atmosphere. After the reaction mixture was stirred for 15 min, the reaction was quenched with satd aq $NH_4Cl$. The reaction mixture was rather clean and two products were obtained. The main product was determined to be 2-benzyl(cyclopropylidene)cyclohexane **12** (48%) and the minor product was desulfinylated chlorocyclobutane **13** (24%). Alkylidenecyclopropane **12** is the expected product from 1,2-CC insertion reaction of the cyclobutylmagnesium carbenoid **11**, which was derived from **10** by the sulfoxide–magnesium exchange reaction, and **13** is the protonated product of **11**. Quite interestingly, methylenecyclopropane **14**, which is another expected product from the 1,2-CC insertion reaction of the magnesium carbenoid intermediate **11**, was not observed at all. Configuration of **13** was determined from its $^1H$ NMR spectrum, especially by NOESY spectrum (NOE was observed between the hydrogens on the carbons bearing the chlorine atom and the benzyl group). Configuration of the starting material **10** was determined to be as shown in Scheme 2 from the stereochemistry of **13**.[11]

As we recognized that the above-mentioned procedure would become quite interesting and new way for a synthesis of alkylidenecyclopropanes, the proper conditions to the key reaction were investigated and the results are summarized in Table 1. Entries 1–4 show the effects of four Grignard reagents other than *i*-PrMgCl at −78 °C for 15 min. The sulfoxide–magnesium exchange reaction did not take place with MeMgCl and PhMgCl. EtMgCl and cyclopentylmagnesium chloride gave **12** in better yields compared to that of *i*-PrMgCl (48%; see Scheme 2). We concluded that cyclopentylmagnesium chloride is the Grignard reagent of choice in this reaction.

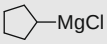
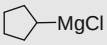
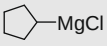
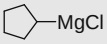
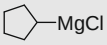
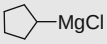
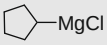
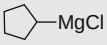
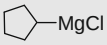
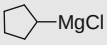
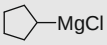
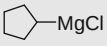
Entries 5–9 show the effect of the temperature of the reaction with cyclopentylmagnesium chloride in THF for 15 min. As shown, when the reaction was carried out at −40 °C, the best yield (87%) was obtained (entry 6). Entries 10–13 show the results for the reaction time in THF at −40 °C. Both shortening and prolonging of the reaction time did not give better results. Finally, we investigated the effect of the solvent (entries 14 and 15) and found that both ether and toluene were not effective to this reaction. We concluded that the conditions in entry 6 are the conditions of choice in this reaction.

Next, generality of this procedure was examined and the results are summarized in Table 2. As the starting material for the synthesis of 1-chlorocyclobutyl *p*-tolyl sulfoxides **15a**–**15g**, cyclopentanone, cycloheptanone, cyclopentadecanone, and cyclohexanone were used as cyclic ketones (entries 1–4). Acetone and 4-phenyl-2-butanone were used as acyclic ketones (entries 5–7). *tert*-Butyl

**Table 1**
Examination of the optimum conditions for the synthesis of alkylidenecyclopropane **12** through the magnesium carbenoid 1,2-CC insertion reaction




**10** **12** **13**

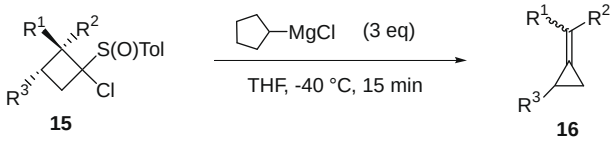
| Entry | Grignard reagent | Conditions | | | Yield (%) | |
|---|---|---|---|---|---|---|
| | | Temp (°C) | Time (min) | Solvent | **12** | **13** |
| 1 | MeMgCl | −78 | 15 | THF | —[a] | — |
| 2 | PhMgCl | −78 | 15 | THF | —[a] | — |
| 3 | EtMgCl | −78 | 15 | THF | 54 | 19 |
| 4 |  | −78 | 15 | THF | 56 | 29 |
| 5 |  | −60 | 15 | THF | 76 | 15 |
| 6 |  | −40 | 15 | THF | 87 | 1 |
| 7 |  | −20 | 15 | THF | 73 | 2 |
| 8 |  | 0 | 15 | THF | 71 | 2 |
| 9 |  | rt | 15 | THF | 73 | 1 |
| 10 |  | −40 | 5 | THF | 74 | 6 |
| 11 |  | −40 | 10 | THF | 85 | 3 |
| 12 |  | −40 | 30 | THF | 80 | 1 |
| 13 |  | −40 | 60 | THF | 75 | 2 |
| 14 |  | −40 | 15 | $Et_2O$ | 39[b] | Trace |
| 15 |  | −40 | 15 | Toluene | 27[c] | Trace |

[a] No reaction was observed and the starting material was quantitatively recovered.
[b] The starting material was recovered in 58%.
[c] The starting material was recovered in 69%.

3-phenylpropionate, *tert*-butyl 4-phenylbutyrate, and *tert*-butyl propionate were used as esters.

The sulfoxide–magnesium exchange reaction was carried out under the best conditions as mentioned above (Table 1, entry 6). As shown in Table 2, all 1-chlorocyclobutyl *p*-tolyl sulfoxides **15**, except one case (entry 2), gave the desired alkylidenecyclopropanes **16** in 62–86% yields. From these results, the procedure presented herein proved to be quite useful for obtaining various alkylidenecyclopropanes. When diastereomers **15f** and **15g** were treated with cyclopentylmagnesium chloride, a mixture of two geometrical isomers was obtained (entries 6 and 7). These results suggested that this 1,2-CC insertion would not be a concerted reaction but a stepwise reaction.

**Table 2**
Synthesis of alkylidenecyclopropanes **16** from 1-chlorocyclobutyl *p*-tolyl sulfoxides **15** through the magnesium carbenoid 1,2-CC insertion reaction



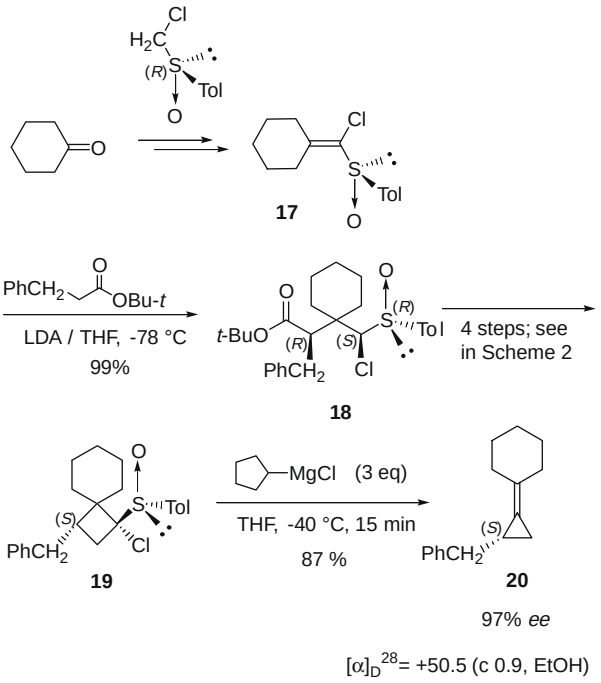

**15** **16**

| Entry | **15** | | | | **16** |
|---|---|---|---|---|---|
| | $R^1$ | $R^2$ | | $R^3$ | Yield (%) |
| 1 | **15a** | $-(CH_2)_4-$ | | $PhCH_2$ | 62 |
| 2 | **15b** | $-(CH_2)_6-$ | | $PhCH_2$ | 39[a] |
| 3 | **15c** | $-(CH_2)_{14}-$ | | $PhCH_2$ | 73 |
| 4 | **15d** | $-(CH_2)_5-$ | | $PhCH_2CH_2$ | 86 |
| 5 | **15e** | $CH_3$ | $CH_3$ | $PhCH_2$ | 77 |
| 6 | **15f** | $PhCH_2CH_2$ | $CH_3$ | $CH_3$ | 82[b] |
| 7 | **15g** | $CH_3$ | $PhCH_2CH_2$ | $CH_3$ | 75[c] |

[a] The structure of the other products could not be determined.
[b] A 2:1 mixture of two geometrical isomers was obtained.
[c] A 1:1 mixture of two geometrical isomers was obtained.

As an application of this procedure, an asymmetric synthesis of optically active alkylidenecyclopropanes was investigated (Scheme 3). Thus, optically active 1-chlorovinyl *p*-tolyl sulfoxide **17** was synthesized from cyclohexanone with (*R*)-chloromethyl *p*-tolyl sulfoxide.[12] Addition reaction of **17** with lithium enolate of *tert*-butyl 3-phenylpropionate gave adduct **18** and all the absolute stereochemistry were unambiguously determined as shown in Scheme 3 based on our previous work.[9,13] Optically active **18** was converted to optically active (1*R*,3*S*,$R_s$)-1-chloro-3-benzyl-1-(*p*-tolylsulfinyl)spiro[3.5]nonane **19** in the same reaction described above.

Finally, optically active **19** was treated with cyclopentylmagnesium chloride in THF at −40 °C to give optically active (*S*)-2-benzylcyclopropylidenecyclohexane **20** in 87% yield.[14] The optical purity of **20** was easily determined to be over 97% by using a chiral stationary column (CHIRALCEL OD (Daicel); hexane as a developing solvent). As the optical purity of the starting material, (*R*)-chloromethyl *p*-tolyl sulfoxide, was 97–99%,[12] the procedure shown in Scheme 3 is thought to proceed without racemization.




**Scheme 3.**

In conclusion, we have developed a new method for a synthesis of alkylidenecyclopropanes from 1-chlorovinyl *p*-tolyl sulfoxides. In addition, by using optically active 1-chlorovinyl *p*-tolyl sulfoxides asymmetric synthesis of them can be realized. Synthesis of alkylidenecyclopropanes from 1,1-dibromocyclobutanes with methyllithium has been known.[15] The presented procedure is the first example for the synthesis of alkylidenecyclopropanes through the 1,2-CC insertion of cyclobutylmagnesium carbenoids with one-carbon contraction.

## Acknowledgments

This work was supported by a Grant-in-Aid for Scientific Research No. 19590018 from the Ministry of Education, Culture, Sports, Science and Technology, Japan, and TUS Grant for Research Promotion from Tokyo University of Science, which are gratefully acknowledged. We thank Professor Shinichi Saito of this department for his helpful suggestion.

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5. Satoh, T.; Saito, S. *Tetrahedron Lett.* **2004**, *45*, 347.
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7. (a) Satoh, T.; Kawashima, T.; Takahashi, S.; Sakai, K. *Tetrahedron* **2003**, *59*, 9599; (b) Sugiyama, S.; Satoh, T. *Tetrahedron: Asymmetry* **2005**, *16*, 665.
8. Adduct **8** was obtained as a mixture of two diastereomers (the ratio 93:7) with respect to the stereogenic carbon bearing the chlorine atom.
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10. Experimental procedure for the synthesis of 3-benzyl-1-chloro-1-(*p*-tolylsulfinyl)spiro[3.5]nonane **10**. *tert*-Butyl 3-phenylpropionate (3.8 g; 18.6 mmol) was added to a solution of LDA (18.6 mmol) in 69 mL of dry THF at −78 °C with stirring under argon atmosphere. The solution was stirred for 15 min, and a solution of **7** (1.0 g; 3.7 mmol) in THF (5 mL) was added. The reaction mixture was stirred for 15 min, and the reaction was quenched by adding satd aq $NH_4Cl$. The whole was extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The product was purified by silica gel column chromatography to afford **8** (1.75 g; 99%) as colorless oil; IR (neat) 3028, 2976, 2931, 1722 (CO), 1597, 1494, 1456, 1367, 1254, 1221, 1144, 1083, 1056 (SO); $^1$H NMR $\delta$ 1.20 (9H, s), 1.23–1.45 (2H, m), 1.45–1.63 (2H, m), 1.66–1.86 (3H, m), 1.87–2.07 (1H, m), 2.09–2.21 (1H, m), 2.45 (3H, s), 2.66–2.79 (1H, m), 2.99–3.18 (1H, m), 3.28–3.46 (2H, m), 5.07 (1H, s), 7.14–7.29 (5H, m), 7.34 (2H, d, $J$ = 8.1 Hz), 7.77 (2H, d, $J$ = 8.1 Hz). MS *m/z* (%) 474 ($M^+$, trace), 457 (7), 401 (14), 281 (16), 279 (48), 243 (63), 242 (16), 197 (39), 161 (31), 141 (27), 140 (100), 141 (28), 91 (96). Calcd for $C_{27}H_{35}ClO_3S$: *M*, 474.1996. Found; *m/z* 474.1995.
TFA (0.92 mL; 12.4 mmol) was added to a solution of **8** (1.18 g; 2.5 mmol) in 25 mL of $CH_2Cl_2$ with stirring. The solution was stirred for 1 day and the reaction was quenched with satd aq $NaHCO_3$. The whole was extracted with $CH_2Cl_2$, and the organic layer was dried over $MgSO_4$. The solvent was evaporated to afford crude carboxylic acid. A solution of $BH_3$–THF complex (12.4 mmol) in 11.7 mL of THF was added dropwise to a solution of the crude carboxylic acid in 25 mL of THF under argon atmosphere with stirring. The solution was stirred for 1 day and the reaction was quenched with satd aq $NH_4Cl$. The whole was extracted with $CHCl_3$, and the organic layer was dried over $MgSO_4$. The solvent was evaporated and the residue was purified by silica gel column chromatography to afford alcohol **9** (918 mg; 91% from **8**) as colorless crystals. Mp 108–109 °C (AcOEt–hexane); IR (KBr) 3445 (OH), 3060, 3026, 2927, 1738, 1597, 1495, 1455, 1399, 1304, 1244, 1082, 1050 (SO) $cm^{-1}$; $^1$H NMR $\delta$ 1.37–1.56 (3H, m), 1.63–1.87 (4H, m), 1.91–2.05 (1H, m), 2.12–2.25 (1H, m), 2.34–2.48 (2H, m), 2.45 (3H, s), 2.86 (1H, dd, $J$ = 13.4, 11.5 Hz), 3.19 (1H, dd, $J$ = 13.4, 2.8 Hz), 3.68–3.81 (1H, m), 3.88–4.00 (1H, m), 4.95 (1H, s), 7.17–7.27 (1H, m), 7.28–7.39 (6H, m), 7.72–7.79 (2H, m). MS *m/z* (%) 405 ($[M+H]^+$, trace), 387(5), 230 (12), 229 (72), 211 (16), 199 (6), 155 (5), 140 (66), 141 (28), 117 (34), 90 (29), 91 (100). Calcd for $C_{23}H_{30}ClO_2S$: *M+H*, 405.1646.Found; *m/z* 405.1650.
$Ph_3P$ (2.97 g; 11.3 mmol) and $I_2$ (1.44 g; 11.3 mmol) were added to a solution of **9** (918 mg; 2.3 mmol) in 23 mL of THF with stirring. After the solution was stirred for 10 min, imidazole (771 mg; 11.3 mmol) was added to the reaction mixture. After 15 min of stirring, the reaction was quenched with satd aq $Na_2SO_3$. The whole was extracted with $CHCl_3$, and the organic layer was dried over $MgSO_4$. The solvent was evaporated and the residue was purified by silica gel column chromatography to give the desired iodide. A solution of KHMDS (4.5 mmol) in 9.1 mL of toluene was added dropwise to a solution of the iodide in 91 mL of THF at 0 °C under argon atmosphere with stirring. The reaction mixture was stirred for 15 min and the reaction was quenched with satd aq $NH_4Cl$. The whole was extracted with $CHCl_3$, and the organic layer was dried over $MgSO_4$. The solvent was evaporated and the residue was purified by silica gel column chromatography to afford **10** (822 mg; 94% in two steps) as colorless oil; IR (neat) 3026, 2928, 2856, 1598, 1495, 1454, 1086, 1059 (SO) $cm^{-1}$; $^1$H NMR $\delta$ 1.34–1.60 (4H, m), 1.66–1.95 (4H, m), 1.96–2.15 (2H, m), 2.18–2.31 (1H, m), 2.34–2.49 (2H, m), 2.39 (3H, s), 2.72–2.86 (1H, m), 3.05 (1H, dd, $J$ = 13.6, 4.1 Hz), 7.08–7.15 (2H, m), 7.15–7.31 (5H, m), 7.46–7.54 (2H, m). MS *m/z* (%) 386 ($M^+$, trace), 247 (10), 212 (12), 211 (61), 201 (5), 169 (5), 155 (6), 143 (15), 140 (54), 129 (17), 107 (32), 91 (100). Calcd for $C_{23}H_{27}ClOS$: *M*, 386.1471. Found; *m/z* 386.1478.
11. The sulfoxide–magnesium exchange reaction is known to take place with retention of configuration of the carbon bearing a sulfinyl group (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.
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14. A solution of cyclopentylmagnesium chloride (0.23 mmol) was added to a solution of **19** (30 mg; 0.08 mmol) in 0.78 mL of THF at −40 °C with stirring under Ar atmosphere. The solution was stirred for 15 min and the reaction was quenched with satd aq $NH_4Cl$. The whole was extracted with $CHCl_3$ and the organic layer was dried over $MgSO_4$. The solvent was evaporated and the residue was purified by silica gel column chromatography to afford **20** (14.3 mg; 87%) as colorless oil; IR (neat) 3028, 2929, 2853, 1604, 1496, 1447, 1260, 1238, 737, 698 $cm^{-1}$; $^1H$ NMR $\delta$ 0.73–0.81 (1H, m), 1.14–1.24 (1H, m), 1.45–1.59 (6H, m), 1.63–1.75 (1H, m), 2.05–2.16 (2H, m), 2.16–2.27 (2H, m), 2.55 (1H, dd, $J$ = 14.3, 7.7 Hz), 2.76 (1H, dd, $J$ = 14.3, 6.1 Hz), 7.13–7.33 (5H, m). MS *m/z* (%) 212 ($M^+$, 69), 197 (11), 183 (24), 169 (21), 155 (18), 143 (21), 130 (43), 129 (100), 128 (33), 121 (59), 115 (24), 104 (41), 93 (41), 91 (99). Calcd for $C_{16}H_{21}$: *M*, 212.1565. Found; *m/z* 212.1555. $[\alpha]_D^{28}$ +50.5 (*c* 0.9, EtOH).
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