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Tetrahedron Letters
Tetrahedron Letters 48 (2007) 5017–5021

The first example of regiospecific magnesium carbenoid 1,3-CH insertion: its mechanism and stereochemistry

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Received 1 May 2007; revised 15 May 2007; accepted 17 May 2007
Available online 23 May 2007

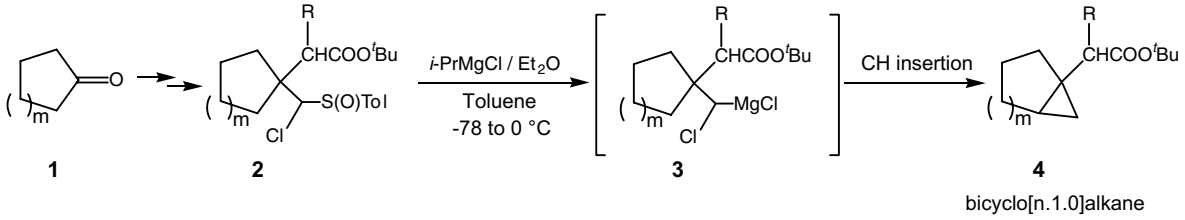
Abstract—Addition reaction of two geometrical isomers of 1-chlorovinyl *p*-tolyl sulfoxides, derived from unsymmetrical ketones and chloromethyl *p*-tolyl sulfoxide, with lithium enolate of *tert*-butyl acetate gave single isomers of the adduct, respectively. Treatment of each diastereomer with *i*-PrMgCl resulted in the formation of magnesium carbenoids. Highly regiospecific 1,3-CH insertion reaction was found to take place from the magnesium carbenoids to afford cyclopropanes in high yields. Stereochemistry of the adducts, reaction mechanism, and origin of the regiospecificity are discussed.

The carbon–hydrogen insertion (CH insertion) reaction is one of the most striking reactions of carbenes and carbenoids. The reaction is very interesting and quite useful for construction of molecules, because formation of a carbon–carbon bond between a carbene (or carbenoid) carbon and an inactivated carbon is achieved.

Especially, rhodium-catalyzed cyclization of α-diazocarbonyl compounds giving cyclopentanone derivatives and γ-lactones is well known. This is the most famous intramolecular 1,5-CH insertion of carbenoids derived from α-diazocarbonyl compounds.[1] Recently, intramolecular 1,5-CH insertion reaction of alkylidene carbene was widely investigated for construction of cyclopentene derivatives.[2] Although 1,5-CH insertion reactions giving cyclopentane derivatives are extensively studied, as mentioned above, 1,3-CH insertion reactions affording cyclopropane derivatives are quite limited.[3]

We recently reported a new method for the synthesis of bicyclo[*n*.1.0]alkanes **4** from cyclic ketones **1** via 1-chloroalkyl *p*-tolyl sulfoxides **2**.[4] The key reaction of this procedure is magnesium carbenoid 1,3-CH insertion reaction of carbenoid **3**, generated from **2** with *i*-PrMgCl by the sulfoxide–magnesium exchange reaction[5] (Scheme 1).

As the magnesium carbenoid 1,3-CH insertion is an unprecedented highly useful reaction for the synthesis of cyclopropanes, we further investigated this reaction



Scheme 1.

Keywords: Cyclopropane; CH insertion; Magnesium carbenoid; Sulfoxide–magnesium exchange reaction; Regiospecific reaction.
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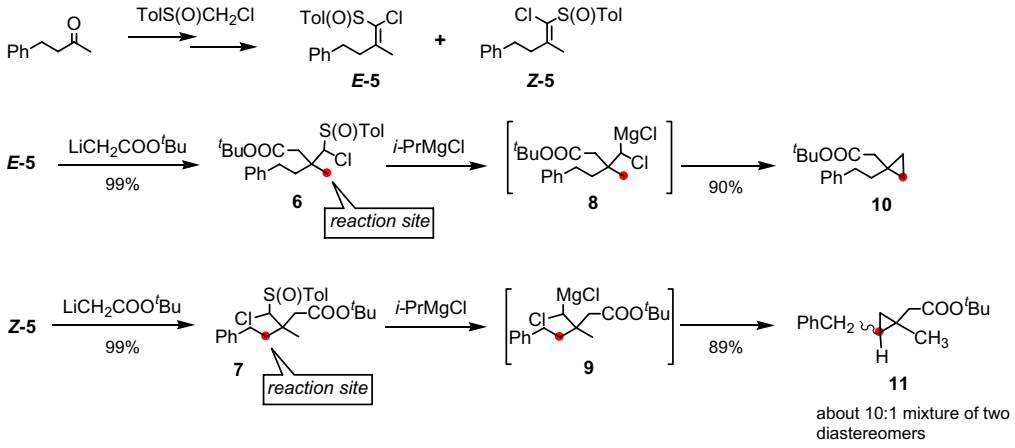
doi:10.1016/j.tetlet.2007.05.101

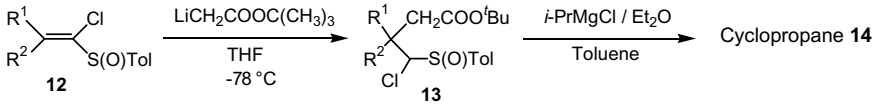
starting from acyclic unsymmetrical ketones and quite interesting results were obtained.

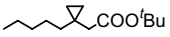
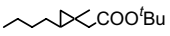
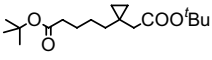
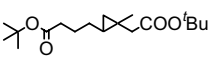
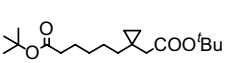
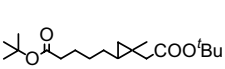
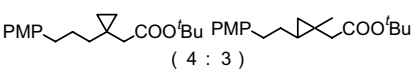
Thus, geometrical isomers of vinyl sulfoxides ***E*–5** and ***Z*–5** were synthesized from 4-phenyl-2-butanone in high overall yields.[6] Addition reaction of these vinyl sulfoxides with lithium enolate of *tert*-butyl acetate gave adducts **6** and **7**, respectively, in quantitative yields. Adducts **6** and **7** were both single isomers and diastereomers to each other. The adducts were treated with *i*-PrMgCl (ether solution) in toluene at −78 °C and the temperature of the reaction mixture was slowly allowed to warm to 0 °C.[7] Interestingly, the treatment of **6** with *i*-PrMgCl gave cyclopropane **10** in 90% yield without any contamination of cyclopropane **11**. On the contrary, the same treatment of **7** with *i*-PrMgCl afforded cyclopropane **11** in 89% yield without any trace of cyclopropane **10**. Namely, the 1,3-CH insertion of adduct **6**, derived from ***E*-5**, took place between the carbenoid carbon and the methyl carbon to give **10**. The 1,3-CH inser-



Scheme 2.

Table 1. Synthesis of cyclopropanes **14** from 1-chlorovinyl *p*-tolyl sulfoxide **12** through adduct **13** by regiospecific magnesium carbenoid 1,3-CH insertion



Entry	12			13	Cyclopropane **14**	
	R^1	R^2	Configuration	Yield %		Yield %
1	Me	*n*-Pentyl	*E*	99[a]		88
2	*n*-Pentyl	Me	*Z*	95[a]		91[b]
3	Me	$(CH_2)_4COO^tBu$	*E*	99[a]		94
4	$(CH_2)_4COO^tBu$	Me	*Z*	99[a]		97[c]
5	Me	$(CH_2)_5COO^tBu$	*E*	99[a]		87
6	$(CH_2)_5COO^tBu$	Me	*Z*	99[a]		81[d]
7	Me / $(CH_2)_2PMP$	$(CH_2)_2PMP$ / Me	*E*, *Z* mixture (*E*:*Z* = 4:3)	95	 (4 : 3)	89[e]

[a] Obtained as a single isomer.
[b] A 3:1 mixture of two diastereomers.
[c] A 4:1 mixture of two diastereomers.
[d] A 4:3 mixture of two diastereomers.
[e] Minor cyclopropane was obtained as a 6:1 mixture of two diastereomers.

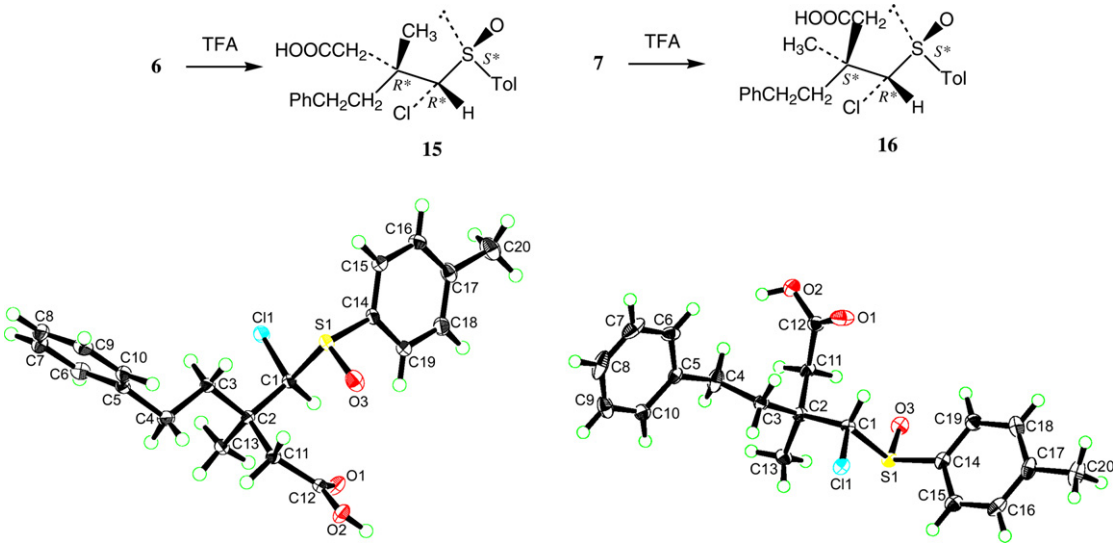
tion reaction of adduct **7**, derived from ***Z*-5**, took place between the carbenoid carbon and the methylene carbon to give **11** with perfect regiospecificity (Scheme 2).

In order to know the generality of this regiospecific magnesium carbenoid 1,3-CH insertion reaction, we next synthesized two geometrical isomers **12** from unsymmetrical ketones as shown in Table 1. As the unsymmetrical ketones, 2-heptanone (entries 1 and 2), *tert*-butyl 6-oxoheptanoate (entries 3 and 4), *tert*-butyl 7-oxooctanoate (entries 5 and 6), and 4-(4-methoxyphenyl)-2-butanone (entry 7) were selected. Each geometrical isomer was separated and reacted with lithium enolate of *tert*-butyl acetate to give adduct **13** in quantitative yield. In the case shown in entry 7, the geometrical isomers could not be separated and used as a mixture.

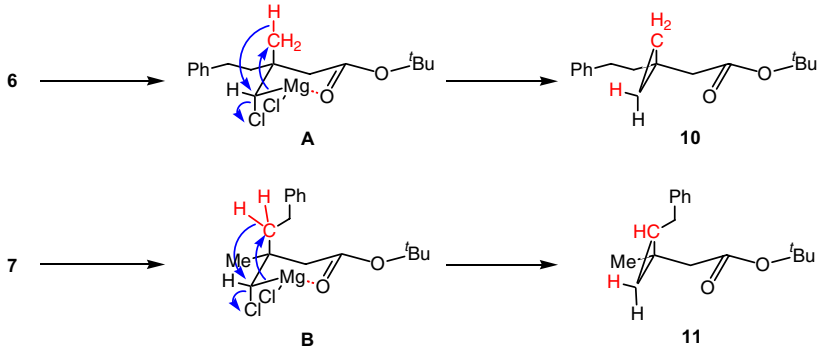
Each adduct **13** was treated with *i*-PrMgCl (ether solution) to give cyclopropane **14** with perfect regiospecificity in high yield. Very interestingly, adduct **13** derived from *E*-1-chlorovinyl *p*-tolyl sulfoxides gave the cyclopropanes from the 1,3-CH insertion reaction between the carbenoid carbon and the methyl carbon (entries 1, 3, 5, and 7). On the contrary, adduct **13** derived from *Z*-vinyl sulfoxides gave the cyclopropanes from the 1,3-CH insertion reaction between the carbenoid carbon and the methylene carbon (entries 2, 4, 6, and 7). It is worth noting that this is an unprecedented highly regiospecific carbenoid 1,3-CH insertion reaction.

Elucidation of the origin of this regiospecificity is quite important for development of the chemistry of magnesium carbenoid. We tried to determine the stereochemistry of adducts **6** and **7**. Unfortunately, as they are oily products, they were converted to well crystalline carboxylic acids **15** and **16**, and the stereochemistry was determined by X-ray analysis[8] (Scheme 3). As shown in Scheme 3, configurations of the carboxylic acids **15** and **16**, derived from **6** and **7**, were determined to be (3*R**,4*R**,s*S**) and (3*S**,4*R**,s*S**), respectively.

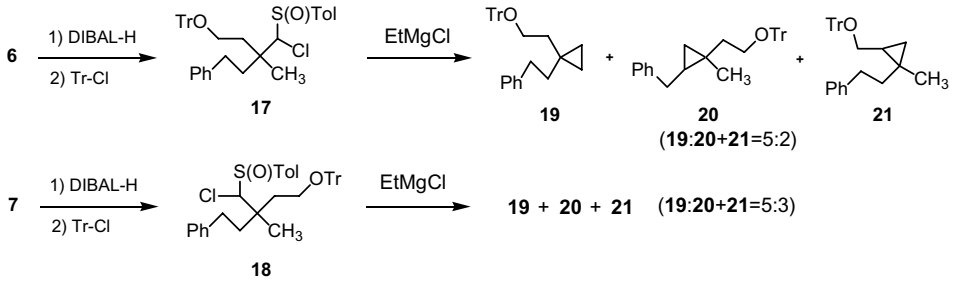
With configuration of adducts **6** and **7** in hand, the mechanism of this highly regiospecific carbenoid 1,3-CH insertion reaction is explained as follows (Scheme 4). Because the sulfoxide–metal exchange reaction is known to take place with retention of configuration of the carbon bearing the sulfinyl group,[9] treatment of **6** with *i*-PrMgCl gives magnesium carbenoid having



Scheme 3.



Scheme 4.



Scheme 5.

*R**-configuration. The magnesium and carbonyl oxygen atom of the ester group must make six-membered intermediate **A**, in which the bulkiest *tert*-butoxy group would occupy equatorial position. In this intermediate, C–H bond of the methyl group attacks back side of the chlorine atom to give cyclopropane **10**.

The situation of the reaction of **7** with *i*-PrMgCl is thought to be quite similar. Thus, the most stable six-membered transition state having the interaction between magnesium and carbonyl oxygen atom must give the chair-like intermediate **B**, from which the magnesium carbenoid 1,3-CH insertion reaction would give cyclopropane **11**.

In order to confirm the validity of this explanation, we converted **6** and **7** to trityl ether **17** and **18**, respectively, in two steps (Scheme 5). Treatment of **17** with EtMgCl[10] gave a mixture of cyclopropanes **19**, **20**, and **21** (90% yield; **19**:**20**+**21** = 5:2) with almost no regiospecificity. A similar result was obtained from the reaction of **18** with EtMgCl (38% yield with 41% of the recovery of **18**; **19**:**20**+**21** = 5:3). As expected, these reactions showed only low regioselectivity. Loss of the highly Lewis-basic carbonyl oxygen is thought to be the most important factor for the disappearance of the regiospecificity.

In conclusion, we found that the magnesium carbenoid 1,3-CH insertion reaction of the substrate having an ester group proceeded with complete regiospecificity. The origin of the regiospecificity was discussed on the bases of the fixed conformation of the magnesium carbenoid intermediate. The results described in this Letter contribute greatly to further development of the chemistry of magnesium carbenoids and also to regiospecific synthesis of cyclopropanes.

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7. *tert*-Butyl acetate (0.328 mL; 2.44 mmol) was added to a solution of LDA (2.35 mmol) in 8 mL of dry THF at −78 °C with stirring. After the solution was stirred for 10 min, a solution of ***E*-5** (150 mg; 0.47 mmol) in THF (1.4 mL) was added. The reaction mixture was stirred for 10 min and the reaction was quenched by adding satd aq NH_4Cl. The product was purified by silica gel column chromatography to afford **6** (204.3 mg; 99%) as a colorless oil; IR (neat) 2976, 2926, 1716 (CO), 1597, 1491, 1458, 1364, 1160, 1055 (SO), 812 cm^{-1}; ^1H NMR δ 1.42 (3H, s), 1.47 (9H, s), 2.19, 2.29 (each 1H, dt, $J = 9.6$, 5.4 Hz), 2.42 (3H, s), 2.67, 3.07 (each 1H, d, $J = 15.6$ Hz), 2.68, 2.75 (each 1H, dt, $J = 12.6$, 5.4 Hz), 5.21 (1H, s), 7.18 (1H, m),

7.23–7.26 (2H, m), 7.28–7.31 (4H, m), 7.72 (2H, d, $J = 8.4$ Hz). MS m/z (%) 434 (M^+, 0.5), 361 (13), 203 (20), 140 (100), 91 (69), Calcd for $C_{24}H_{31}ClO_3S$: M, 434.1682. Found: m/z 434.1689.

To a flame-dried flask was added dry toluene (2 mL) followed by *i*-PrMgCl (in ether; 0.37 mmol; 5.0 equiv) at −78 °C. A solution of **6** (40 mg; 0.092 mmol) in toluene (1 mL) was added to the solution of Grignard reagent dropwise with stirring and the reaction mixture was slowly allowed to warm to 0 °C for 2 h. The reaction was quenched with satd aq NH_4Cl and the whole was extracted with $CHCl_3$. The product was purified over silica gel column chromatography to afford 21.5 mg (90%) of cyclopropane **10** as a colorless oil. IR (neat) 2978, 2931, 1725 (CO), 1603, 1455, 1367, 1314, 1256, 1141, 1017, 966, 842, 746, 699 cm^{-1}; ^1H NMR δ 0.38 (2H, m), 0.47 (2H, m), 1.47 (9H, s), 1.63 (2H, m), 2.21 (2H, s), 2.70 (2H, m), 7.14–7.20 (3H, m), 7.24–7.28 (2H, m). MS m/z (%) 260 (M^+, 3), 204 (51), 159 (12), 144 (82), 104 (37), 91 (100), 57 (78). Calcd for $C_{17}H_{24}O_2$: M, 260.1772. Found: m/z 260.1777.

8. Crystal data for **15**: $C_{20}H_{23}ClO_3S$, $M = 378.89$, Triclinic, space group $P\bar{1}$ (#2), $a = 8.1705(11)$, $b = 10.3277(14)$, $c = 11.5251(15)$ Å, $\alpha = 89.8780(10)°$, $\beta = 75.3680(10)°$, $\gamma = 87.9130(10)°$, $V = 940.3(2)$ Å^3, $Z = 2$, $F(0\,0\,0) = 400$, $D_{calc} = 1.338$ g cm^{-3}, $\mu(Mo\,K_\alpha) = 3.30$ cm^{-1}, $T = 100$ K, radiation = 0.71073 Å, $R_1 = 0.0315$ for $I > 2.0\sigma(I)$, $wR_2 = 0.0845$ for all data (3949 reflections), GOF = 1.019 (229 parameters), crystal dimensions $0.20 \times 0.12 \times 0.10$ mm^3. A quality single crystal of **15** (colorless prisms; mp 154.5–155 °C (AcOEt–hexane)) was mounted on a glass fiber. Diffraction data were measured on a Bruker APEXII CCD-Detector X-ray diffractometer with monochromated Mo K_α radiation from a rotating anode source with a mirror focusing apparatus. The data reduction, structure solution and refinement, and all the necessary computational data processes were performed using APEX2, SAINT, SHELXTL, KENX, and TEXSAN programs. Data were deposited at the Cambridge Crystallographic Data Center; deposition number CCDC 643995.

Crystal data for **16**: $C_{20}H_{23}ClO_3S$, $M = 378.89$, Triclinic, space group $P\bar{1}$ (#2), $a = 8.788(3)$, $b = 10.880(4)$, $c = 20.409(7)$ Å, $\alpha = 77.374(4)°$, $\beta = 88.875(4)°$, $\gamma = 88.308(4)°$, $V = 1903.2(11)$ Å^3, $Z = 4$, $F(0\,0\,0) = 800$, $D_{calc} = 1.322$ g cm^{-3}, $\mu(Mo\,K_\alpha) = 3.26$ cm^{-1}, $T = 100$ K, radiation = 0.71073 Å, $R_1 = 0.0657$ for $I > 2.0\sigma(I)$, $wR_2 = 0.1570$ for all data (7683 reflections), GOF = 1.099 (457 parameters), crystal dimensions $0.12 \times 0.03 \times 0.02$ mm^3. A quality single crystal of **16** (colorless needles; mp 116–116.5 °C (AcOEt–hexane)) was mounted on a glass fiber. Diffraction data were measured on a Bruker APEXII CCD-Detector X-ray diffractometer with monochromated Mo K_α radiation from a rotating anode source with a mirror focusing apparatus. The data reduction, structure solution and refinement, and all the necessary computational data processes were performed using APEX2, SAINT, SHELXTL, KENX, and TEXSAN programs. Data were deposited at the Cambridge Crystallographic Data Center; deposition number CCDC 643996.

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10. Because the reaction of **17** and **18** with *i*-PrMgCl did not proceed, EtMgCl was used in this reaction.