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New synthesis of multi-substituted α-chlorocyclobutanones from 1-chloro-3-cyanoalkyl *p*-tolyl sulfoxides by 4-*Exo-Dig* nucleophilic ring closure of magnesium carbenoids to nitrile group as the key reaction

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ABSTRACT

1-Chloro-3-cyanoalkyl *p*-tolyl sulfoxides were easily prepared from 1-chlorovinyl *p*-tolyl sulfoxides, which were synthesized from carbonyl compounds and chloromethyl *p*-tolyl sulfoxide, with lithium α-cyano carbanion of acetonitrile derivatives in good yields. Treatment of these sulfoxides with *i*-PrMgCl resulted in the formation of multi-substituted α-chlorocyclobutanones in good to high yields via the 4-*Exo-Dig* nucleophilic ring closure of the generated magnesium carbenoid intermediates to the nitrile group. This procedure provides a new and good way for the synthesis of multi-substituted α-chlorocyclobutanones from carbonyl compounds and substituted acetonitriles with formation of three carbon–carbon bonds in relatively short steps.

Cyclopropanes and cyclobutanes, including cyclobutanones and their derivatives, have been widely recognized to be versatile intermediates in organic- and synthetic organic chemistry. The characteristic reactivity of cyclopropanes and cyclobutanes is attributable to their ring strain. A large number of studies for the chemistry, synthesis, and synthetic uses of cyclopropanes have been carried out; however, those for cyclobutanes and cyclobutanones are relatively limited.[1,2]

The most widely used method for the synthesis of cyclobutanes is intermolecular and intramolecular photochemical [2+2] cycloaddition reactions of olefins.[1] On the other hand, thermal [2+2] cycloaddition reactions of ketenes with olefins are widely used as the general method for the synthesis of cyclobutanones.[2,3] However, in view of the importance of cyclobutanones in organic synthesis, new methods for their synthesis are still very much desired.

We recently reported a new method for the synthesis of cyanocyclopropanes by the intramolecular alkylation of magnesium carbenoids generated from 1-chloro-3-cyanoproyl *p*-tolyl sulfoxides with *i*-PrMgCl (Scheme 1).[4] Thus, treatment of 1-chloro-3-cyanopropyl *p*-tolyl sulfoxide **2**, derived from 1-chlorovinyl *p*-tolyl sulfoxide **1** with cyanomethyllithium, with excess *i*-PrMgCl resulted in the formation of cyanocyclopropane **6** in good yield through magnesium carbenoid intermediate **3**.[5] This reaction was proved to proceed via intramolecular S_N2 reaction of α-cyano carbanion intermediate **4** generated from **3** by the excess *i*-PrMgCl.[4] Later, from the detailed inspection of this reaction, we found that a trace amount of 2-chlorocyclobutanone **8** was generated as a byproduct. This product was presumed to be obtained from the 4-*Exo-Dig* nucleophilic ring closure[6] of magnesium carbenoid intermediate **3**. It is interesting to note that 4-*Exo-Dig* ring closure was reported to be a disfavored process.[6]

As described above, cyclobutanones are quite interesting and important compounds in organic chemistry. We expected that if the reaction is carried out with 1-chloro-3-cyanoalkyl *p*-tolyl sulfoxides having no hydrogen on the carbon next to the cyano group, α-chlorocyclobutanones would be produced via the 4-*Exo-Dig* nucleophilic ring closure. In fact, this expectation was proved to be fruitful. In this Letter, we describe a new and unprecedented synthesis of multi-substituted α-chlorocyclobutanones from carbonyl compounds by 4-*Exo-Dig* nucleophilic ring closure of magnesium carbenoid intermediates to nitrile group as the key reaction, as shown in Scheme 2.

Thus, 1-chlorovinyl *p*-tolyl sulfoxides **10** were easily obtained from carbonyl compounds **9** with chloromethyl *p*-tolyl sulfoxide.[7] The reaction of **10** with lithium α-cyano carbanion of acetonitrile derivatives gave adducts, 1-chloro-3-cyanoalkyl *p*-tolyl sulfoxides **11**, in good to high yields.[8] Finally, treatment of **11** with excess *i*-PrMgCl resulted in the formation of multi-substituted α-chlorocyclobutanones **14** via the 4-*Exo-Dig* cyclization of the generated magnesium carbenoid intermediates **12** and resultant imine anions **13**.

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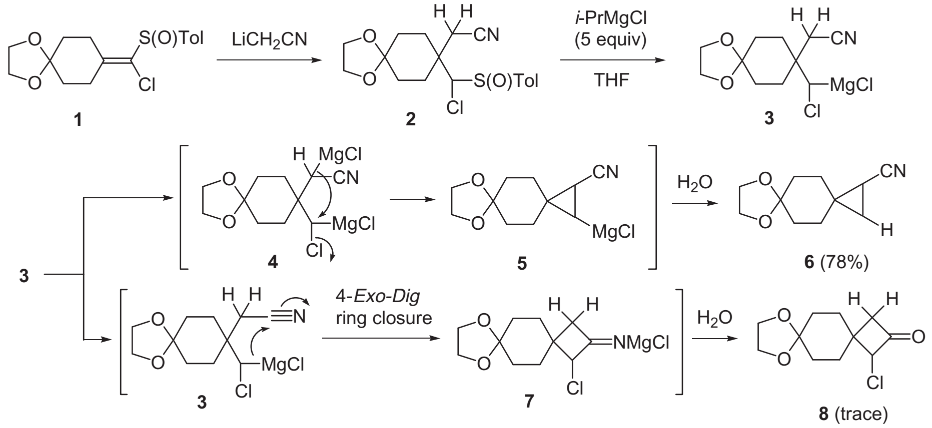
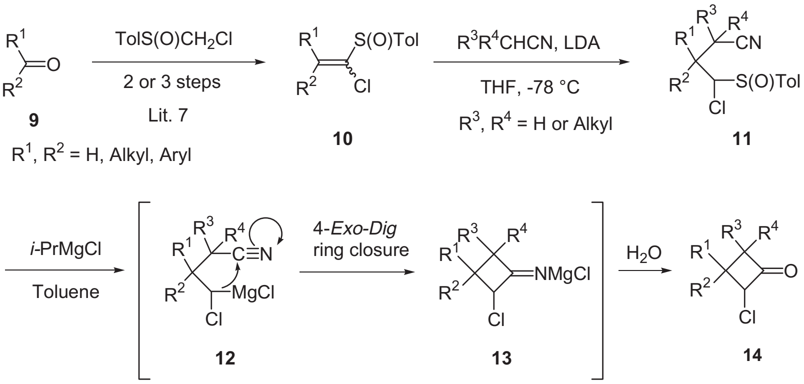


Scheme 1. Two pathways for the reaction of magnesium carbenoid **3** giving cyanocyclopropane **6** and 2-chlorocyclobutanone **8** by the intramolecular S_N2 reaction and 4-*Exo-Dig* nucleophilic ring closure, respectively.

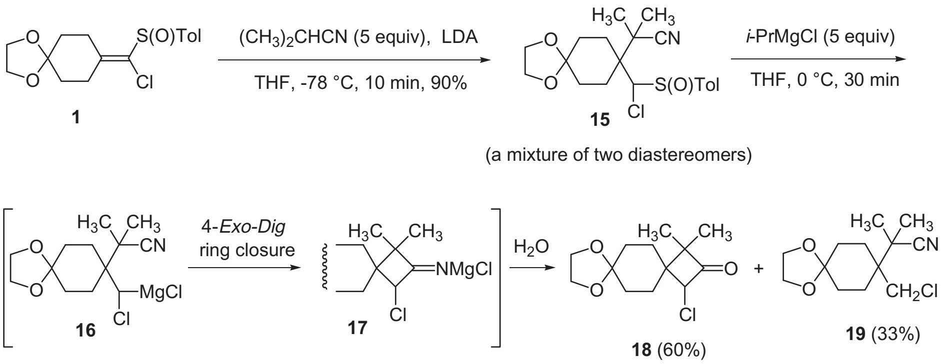


Scheme 2. General scheme for this work.

Synthesis of 4-chloro-2,2,3,3-tetrasubstituted and 2-chloro-3,3,4-trisubstituted cyclobutanones

Details of this procedure are reported using 1-chloro-3-cyanoalkyl *p*-tolyl sulfoxide bearing two methyl groups at the α-position of the cyano group **15** as a representative example for the precursor of magnesium carbenoid intermediates (Scheme 3). Thus, treatment of 1-chlorovinyl *p*-tolyl sulfoxide **1**[7] with lithium α-cyano carbanion of isobutyronitrile gave adduct **15** as a mixture of two diastereomers in 90% yield. A mixture of this adduct was treated with 5 equiv of *i*-PrMgCl (ether solution) in THF at 0 °C for 30 min. Gratifyingly, the desired α-chlorocyclobutanone **18** was obtained in 60% yield with chloroalkane **19** (33% yield). The mechanism of this reaction is presumed to be as follows. The treatment of **15** with *i*-PrMgCl resulted in the formation of magnesium carbenoid **16** by the sulfoxide–magnesium exchange reaction.[5] As magnesium carbenoids have both nucleophilic and electrophilic properties,[7a] 4-*Exo-Dig* nucleophilic ring closure must take place to give imine anion intermediate **17**, which was hydrolyzed in the work up process to give **18**. Chloroalkane **19** is the protonated product of magnesium carbenoid intermediate **16**.

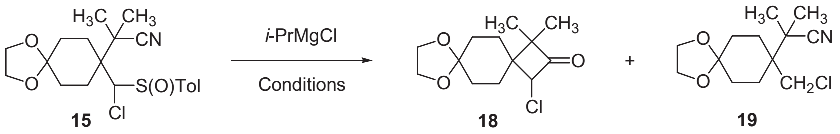
As we recognized that this will become a new and unprecedented procedure for the synthesis of α-chlorocyclobutanones, we investigated the conditions for reducing the yield of protonated



Scheme 3. Addition reaction of lithium α-cyano carbanion of isobutyronitrile to 1-chlorovinyl *p*-tolyl sulfoxide **1** and the treatment of adduct **15** with *i*-PrMgCl to give multi-substituted α-chlorocyclobutanone **18.**

Table 1

Investigation of the conditions for preparation of α-chlorocyclobutanone **18** from **15** with *i*-PrMgCl

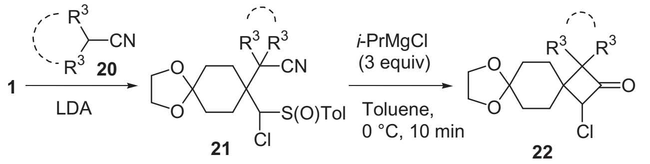


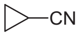
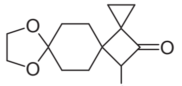
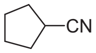
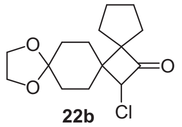
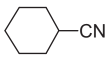
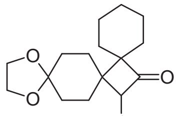
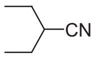
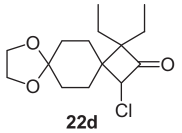
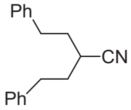
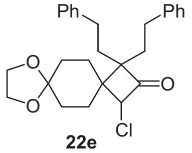
Entry	Conditions				**18**	**19**
	Temp (°C)	Time (min)	Solvent	Reagent (equiv)	Yield (%)	Yield (%)
1	0	30	THF	*i*-PrMgCl in Et_2O (5)	60	33
2	−78 to 0	60	THF	*i*-PrMgCl in Et_2O (5)	40	59
3	0	10	THF	*i*-PrMgCl in Et_2O (5)	59	31
4	0	60	THF	*i*-PrMgCl in Et_2O (5)	55	30
5	0	10	Toluene	*i*-PrMgCl in THF (5)	69	6
6	0	10	Toluene	*i*-PrMgCl in THF (5)	84	12
7	0	10	Toluene	*i*-PrMgBr in THF (5)	80	11
8	0	10	Toluene	*i*-PrMgCl in THF (3)	85	14
9	0	10	Toluene	*i*-PrMgCl in THF (2)	34 [a]	13

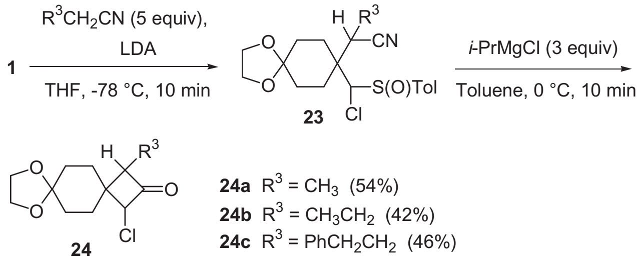
[a] Starting material **15** was recovered in 50% yield.

Table 2

Synthesis of 4-chloro-2,2,3,3-tetrasubstituted cyclobutanones **22** from **1** through nitrile adducts **21**



Entry	Nitrile **20**	**21**/Yield (%)	**22**/Yield (%)	
1		**21a** (99)	 **22a**	(82)
2		**21b** (85)	 **22b**	(88)
3		**21c** (94)	 **22c**	(76)
4		**21d** (99)	 **22d**	(74)
5		**21e** (67)	 **22e**	(62)



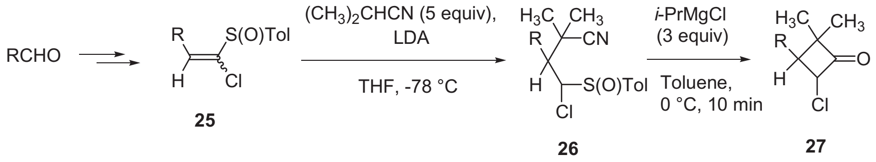
Scheme 4. Synthesis of 2-chloro-3,3,4-trisubstituted cyclobutanones **24** from nitrile adducts **23** derived from **1** and acetonitrile derivatives.

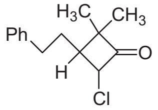
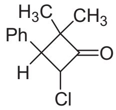
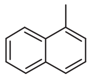
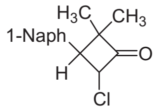
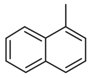
chloroalkane **19** and the results are summarized in Table 1. Entry 1 shows the result described above. As shown in entries 2–4, when the reaction was conducted in THF, a significant amount of **19** was obtained. Using toluene and *i*-PrMgCl in ether for 10 min was found to be much better condition (entry 5). When *i*-PrMgCl or *i*-PrMgBr in THF solution was used in this reaction, the desired **18** was obtained in up to 84% yield (entries 6 and 7). Finally, using 3 equiv of *i*-PrMgCl (in THF solution) in toluene at 0 °C for 10 min was found to be the condition of choice for this reaction (entry 8) and we used these conditions throughout in this study.[9]

The procedure starting with 1-chlorovinyl *p*-tolyl sulfoxide **1** described above was carried out with cyclopropanecarbonitrile, cyclopentanecarbonitrile, cyclohexanecarbonitrile, 3-cyanopentane, and 3-cyano-1,5-diphenylpentane and the results are summarized in Table 2. As shown in Table 2, addition reactions of lithium α-cyano carbanions to **1** afforded good to quantitative yields of adducts **21** as single isomers. The treatment of cyclic nitrile adducts **21a**–**21c** with *i*-PrMgCl under the conditions described above gave structurally very interesting dispirocompounds, 10-chlorodispiro[2.0.5.2]undecan-11-one **22a**, 12-chlorodispiro[4.0.5.2]tridecane-13-one **22b**, and 14-chlorodispiro[5.0.5.2]tetradecan-13-one **22c** in good to high yields (entries 1–3). The reactions with acyclic nitriles also gave adducts **21d** and **21e** in 99% and 67% yields, respectively. The key reaction of **21d** and **21e** with *i*-PrMgCl afforded 1,1-disubstituted 3-chlorospiro[3.5]nonan-2-ones **22d** and **22e** in somewhat lower yields compared with those of **22a**–**c**. These results implied that the procedure described above has general applicability.

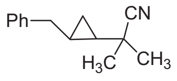
Next, we investigated this procedure with mono-substituted acetonitriles (Scheme 4). Thus, the addition reaction of **1** with excess lithium α-cyano carbanion of propionitrile ($R^3 = CH_3$), butyronitrile ($R^3 = CH_3CH_2$), and 4-phenylbutyronitrile ($R^3 = PhCH_2CH_2$) gave adducts **23** as a mixture of diastereomers in quantitative yields. Treatment of adducts **23** with *i*-PrMgCl in toluene gave the desired 2-chlorocyclobutanones **24a** to **24c** in up to 54% yield. The cyanocyclopropanes, which were worried about to be produced by the intramolecular S_N2 reaction as described in the introduction, were not observed. The reason why the yields of **24** were

Table 3
Synthesis of 4-chloro-2,2,3-trisubstituted cyclobutanones **27** from aldehydes



Entry	Aldehyde R	25	26/Yield (%)	27/Yield (%)	
1	$PhCH_2CH_2$	*Z*-**25a**	**26aA** (95)		**27a** (51)[a]
2	$PhCH_2CH_2$	*E*-**25a**	**26aB** (96)		**27a** (32)[b,c]
3	Ph	*Z*-**25b**	**26bA** (95)		**27b** (59)[a]
4	Ph	*E*-**25b**	**26bB** (81)		**27b** (trace)[d]
5		*Z*-**25c**	**26cA** (74)		**27c** (44)[a]
6		*E*-**25c**	**26cB** (80)		**27c** (trace)[e]

[a] Single isomer (configuration not determined).
[b] About 1:1 mixture of two diastereomers.
[c] Cyclopropane **28** (1,3-CH insertion product of the magnesium carbenoid intermediate) was obtained in 39% yield.
[d] Olefin **29** (1,2-CC insertion product of the magnesium carbenoid intermediate) was obtained in 74% yield.
[e] Olefin **30** (1,2-CC insertion product of the magnesium carbenoid intermediate) was obtained in 34% yield.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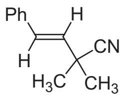
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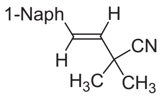

30

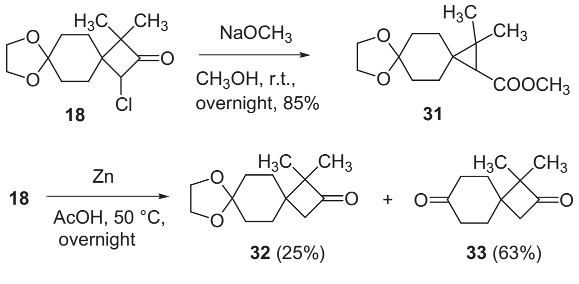
somewhat low is due to the formation of about 15% of protonated chloroalkanes and some structurally unknown byproducts.

Synthesis of 4-chloro-2,2,3-trisubstituted cyclobutanones from aldehydes

Finally, the procedure was carried out starting from aldehydes (Table 3). Thus, 1-chlorovinyl *p*-tolyl sulfoxides **25** were synthesized from 3-phenylpropanal, benzaldehyde, and 1-naphthaldehyde in two steps as a mixture of easily separable two geometrical isomers. Addition reaction of lithium α-cyano carbanion of isobutyronitrile to **25** gave high yields of adducts **26**.

Treatment of **26aA**, derived from *Z*-**25a**, with *i*-PrMgCl resulted in the formation of the desired 4-chloro-2,2-dimethyl-3-(2-phenylethyl)cyclobutanone **27a** in 51% yield as a single isomer (entry 1). Interestingly, the reaction of adduct **26aB**, derived from *E*-**25a**, gave **27a** as about 1:1 mixture of two diastereomers with a significant amount of cyclopropane **28**, derived via the 1,3-CH insertion of magnesium carbenoid intermediate.[10] Entries 3–6 show the results obtained from adducts **26** derived from aromatic aldehydes. Interestingly, the reaction of the adducts **26bA** and **26cA** (derived from *Z*-**25b** and *Z*-**25c**, respectively) gave the desired 3-aryl-4-chloro-2,2-dimethylcyclobutanones **27b** and **27c** in moderate yields as both single isomers (entries 3 and 5). However, the reaction of **26bB** and **26cB** gave olefins **29** and **30** as major products with trace amount of the desired products (entries 4 and 6). Olefins **29** and **30** are the 1,2-CC insertion products (aryl group migration product) of the magnesium carbenoid intermediates. The mechanism of this stereospecificity of the reactions is unclear at present.[11,12]

α-Chlorocyclobutanones are quite interesting intermediates in organic synthesis. Two known reactions of the α-chlorocyclobutanone were applied to **18** (Scheme 5). Thus, treatment of **18** with sodium methoxide in methanol gave cyclopropane bearing a methoxycarbonyl group **31** in 85% yield via the quasi Favorskii rearrangement.[13] Reduction of the chlorine atom of **18** with zinc



Scheme 5. Two reactions of α-chlorocyclobutanone **18**.

in acetic acid[14] gave a mixture of **32** and deacetal product **33** in good total yield.

In conclusion, we have developed a new procedure for a synthesis of multi-substituted α-chlorocyclobutanones from carbonyl compounds by 4-*Exo-Dig* nucleophilic ring closure of magnesium carbenoid intermediate to nitrile group as the key reaction in relatively short steps. We believe that the chemistry presented in this Letter contributes to the synthesis of various α-chlorocyclobutanones and also to the chemistry of magnesium carbenoids.

Acknowledgements

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Supplementary data

Supplementary data (X-ray crystallographic data of compound **26cB**′ and schematic explanation of the reaction courses) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.03.127.

References and notes

1. For reviews on the chemistry, synthesis, and synthetic uses of cyclobutanes: (a) Demuth, M.; Mikhail, G. *Synthesis* **1989**, 145; (b) Inoue, Y. *Chem. Rev.* **1992**, *92*, 741; (c) Keukeleire, D. D.; He, S-L. *Chem. Rev.* **1993**, *93*, 359; (d) Bach, T. *Synthesis* **1998**, 683; (e) Lee-Ruff, E.; Mladenova, G. *Chem. Rev.* **2003**, *103*, 1449; (f) Namyslo, J. C.; Kaufmann, D. E. *Chem. Rev.* **2003**, *103*, 1485; (g) Sadana, A. K.; Saini, R. K.; Billups, W. E. *Chem. Rev.* **2003**, *103*, 1539; (h) Leemans, E.; D'hooghe, M.; De Kimpe, N. *Chem. Rev.* **2011**, *111*, 3268.
2. For reviews on the chemistry, synthesis, and synthetic uses of cyclobutanones: (a) Belluš, D.; Ernst, B. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 797; (b) Madelaine, C.; Valerio, V.; Maulide, N. *Chem. Asian J.* **2011**, *6*, 2224.
3. (a) Tidwell, T. T. *Ketenes*; John Wiley and Sons: New York, 1995; (b) Brady, W. T. *Synthesis* **1971**, 415; (c) Nakyama, Y.; Nagase, M. *J. Org. Chem.* **1995**, *60*, 1878; (d) Matsuo, J.; Okuno, R.; Takeuchi, K.; Kawano, M.; Ishibashi, H. *Tetrahedron Lett.* **2010**, *51*, 3736.
4. Saitoh, H.; Satoh, T. *Tetrahedron Lett.* **2010**, *51*, 3380.
5. (a) Satoh, T. *Chem. Soc. Rev.* **2007**, *36*, 1561; (b) Satoh, T. In *The Chemistry of Organomagnesium Compounds*; Rappoport, Z., Marek, I., Eds.; John Wiley and Sons: Chichester, 2008; pp 717–769; (c) Satoh, T. *J. Synth. Org. Chem. Jpn.* **2009**, *67*, 381; (d) Satoh, T. *Yakugaku Zasshi* **2009**, *129*, 1013; (e) Satoh, T. *Heterocycles* **2012**, *85*, 1.
6. Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.
7. (a) Satoh, T.; Takano, K.; Ota, H.; Someya, H.; Matsuda, K.; Koyama, M. *Tetrahedron* **1998**, *54*, 5557; (b) Satoh, T.; Kawashima, T.; Takahashi, S.; Sakai, K. *Tetrahedron* **2003**, *59*, 9599.
8. Wakasugi, D.; Satoh, T. *Tetrahedron* **2005**, *61*, 1245.
9. A solution of **15** (mixture of two diastereomers, 40.0 mg; 0.10 mmol) in toluene (0.7 mL) was added dropwise to a solution of *i*-PrMgCl (2.0 mol/L solution in THF; 0.15 mL; 0.3 mmol) in toluene (1.3 mL) at 0 °C, and the mixture was stirred at 0 °C for 10 min. The reaction was quenched with satd aq NH_4Cl (1 mL), and the mixture was extracted with $CHCl_3$ (3×3 mL). The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel using hexane/AcOEt as the eluent to give 3-chloro-1,1-dimethyl-8,11-dioxadispiro[3.2.4.2]tridecan-2-one **18** (22.2 mg; 85%) as colorless oil and 2-(8-chloromethyl-1,4-dioxaspiro[4.5]dec-8-yl)-2-methylpropionitrile **19** (3.6 mg; 14%) as colorless crystals. Compound **18**: IR (neat) 2944, 2882, 1789 (CO), 1453, 1376, 1270, 1146, 1110, 1068, 1036 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.20 (s, 3H), 1.23 (s, 3H), 1.65–1.80 (m, 4H), 1.84–2.05 (m, 4H), 3.92–4.02 (m, 4H), 4.78 (s, 1H); MS (EI) *m*/*z* (%) 258 (M$^+$, 1), 243 (1), 223 (10), 182 (10), 153 (39), 114 (81), 99 (97), 86 (63), 70 (100); HRMS (EI) calcd for $C_{13}H_{19}ClO_3$: 258.1023, found: 258.1029. Compound **19**: mp 100.0–101.0 °C (hexane); IR (KBr) 2961, 2230 (CN), 1454, 1375, 1153, 1126, 1113, 1034, 885, 738 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.46 (s, 6H), 1.51–1.98 (m, 8H), 3.77 (s, 2H), 3.93–3.97 (m, 4H); MS (EI) *m*/*z* (%) 257 (M$^+$, 0.3), 189 (9), 99 (100), 86 (11), 28 (24); HRMS (EI) calcd for $C_{13}H_{20}ClNO_2$: 257.1183, found: 257.1188.
10. 1,3-CH insertion reaction of magnesium carbenoids giving cyclopropanes: (a) Satoh, T.; Musashi, J.; Kondo, A. *Tetrahedron Lett.* **2005**, *46*, 599; (b) Satoh, T.; Ogata, S.; Wakasugi, D. *Tetrahedron Lett.* **2006**, *47*, 7249; (c) Ogata, S.; Masaoka, S.; Sakai, K.; Satoh, T. *Tetrahedron Lett.* **2007**, *48*, 5017; (d) Ogata, S.; Saitoh, H.; Wakasugi, D.; Satoh, T. *Tetrahedron* **2008**, *64*, 5711; (e) Satoh, T.; Kuramoto, T.; Ogata, S.; Watanabe, H.; Saitou, T.; Tadokoro, M. *Tetrahedron: Asymmetry* **2010**, *21*, 1; (f) Watanabe, H.; Ogata, S.; Satoh, T. *Tetrahedron* **2010**, *66*, 5675.
11. The magnesium carbenoids have two chiral carbon centers. The reaction of magnesium carbenoids generated from **26A** provided cyclobutanones, whereas the reaction of those generated from **26B** afforded significant amounts of byproducts. The difference in reactivity indicates that these magnesium carbenoids are diastereomers to each other. The relative configuration of (3*R**,4*S**)-4-chloro-3-(naphthalen-1-yl)-4-((*R**)-*p*-tolylsulfinyl)butanenitrile (**26cB**′), which was prepared from *E*-**25c** and $LiCH_2CN$, was determined by X-ray molecular structure analysis (see Supplementary data). According to the above experimental results and the relative configuration of **26cB**′, the relative configuration of adducts **26cA** and **26cB** was assigned to be 3*R**,4*R** and 3*R**,4*S**, respectively. In the case of magnesium carbenoids generated from **26B**, an anti-conformer, in which *R* group is located at opposite end of Cl, appears to be the most stable conformational isomer (see Supplementary data). Therefore, the side reactions such as 1,2-CC insertion and 1,3-CH insertion seem to take place preferentially rather than the nucleophilic ring closure.
12. Crystallographic data (excluding structure factors) for **26cB**′ have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 870599. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, [fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.Uk].
13. Brady, W. T.; Norton, S. J.; Ko, J. *Synthesis* **1983**, 1002.
14. Gruhn, A. G.; Reusch, W. *Tetrahedron* **1993**, *49*, 8159.