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New synthesis of multisubstituted cyanocyclopropanes by the intramolecular S_N2 alkylation and 1,3-CC insertion reaction of magnesium carbenoids as the key reactions

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ABSTRACT

Addition reaction of 1-chlorovinyl *p*-tolyl sulfoxides derived from ketones and aldehydes with lithium α-cyano carbanions gave nitrile adducts in high to quantitative yields. Treatment of the nitrile adducts derived from acetonitrile with excess *i*-PrMgCl in THF resulted in the formation of cyanocyclopropanes via the intramolecular S_N2 alkylation of the generated magnesium carbenoids. The intermediate of this reaction was proved to be a cyclopropylmagnesium chloride and was reactive with electrophiles to give multisubstituted cyanocyclopropanes. On the other hand, the reaction of the nitrile adducts derived from arylacetonitriles with *i*-PrMgCl resulted in the formation of 2-arylcyanocyclopropanes by the 1,3-carbon–carbon (1,3-CC) insertion reaction of the generated magnesium carbenoid intermediates. This reaction was found to proceed in a highly stereospecific manner. The key reactions, intramolecular S_N2 alkylation and 1,3-CC insertion reaction of the magnesium carbenoids, are the first examples for the reaction of the magnesium carbenoids bearing a nitrile functional group.

1. Introduction

Cyclopropanes and their derivatives are definitely one of the most important and fundamental compounds in organic and synthetic organic chemistry. Cyclopropanes and their derivatives undergo a variety of ring-opening reactions under the influence of a variety of conditions in neutral, acidic, and basic medium with carbon–carbon and carbon–heteroatom bond-formation or rearrangement etc. Based on these properties, cyclopropane derivatives have been recognized to be versatile intermediates in organic synthesis.[1] We have been interested for a long time in the synthesis of cyclopropanes based on our original methods.[2] In our investigation for developments of new synthetic methods of cyclopropanes, we recently reported that the treatment of 1-chloroalkyl *p*-tolyl sulfoxides bearing a cyano group at the 3-position with *i*-PrMgCl resulted in the formation of multisubstituted cyanocyclopropanes in good yields.[3]

We further investigated into this reaction with 1-chlorovinyl *p*-tolyl sulfoxides derived from ketones and aldehydes, and alkyl- and aryl-substituted acetonitriles. Quite interesting results were obtained from the investigation (Scheme 1).

Thus, 1-chlorovinyl *p*-tolyl sulfoxides **1**, prepared from ketones and aldehydes, and chloromethyl *p*-tolyl sulfoxide,[4] were treated with cyanomethyllithium (R^3=H) to give adducts, 1-chloroalkyl *p*-tolyl sulfoxides bearing a cyano group at 3-position **2**, in high yields.[5] Treatment of **2** with excess *i*-PrMgCl resulted in the formation of cyanocyclopropanes **5** (E=H) in good to high yields. This reaction was proved to proceed via the intramolecular S_N2 alkylation of the generated magnesium carbenoid[6] bearing magnesium chloride at the α-position of the nitrile group **3** and the intermediate of this alkylation was found to be cyclopropylmagnesium chloride **4**. The cyclopropylmagnesium chloride intermediates **4** could be trapped with some electrophiles to give multisubstituted cyanocyclopropanes **5** (E=a moiety from an electrophile). On the other hand, the reaction of the adducts derived from arylacetonitriles **2** (R^3=Ar) with *i*-PrMgCl resulted in the formation of 2-arylcyanocyclopropanes **7** by the 1,3-CC insertion reaction of the generated magnesium carbenoid intermediates **6**. This reaction was proved to proceed in a highly stereospecific manner. Hereinafter, the procedure and the mechanism of the key reactions mentioned above are reported in detail.

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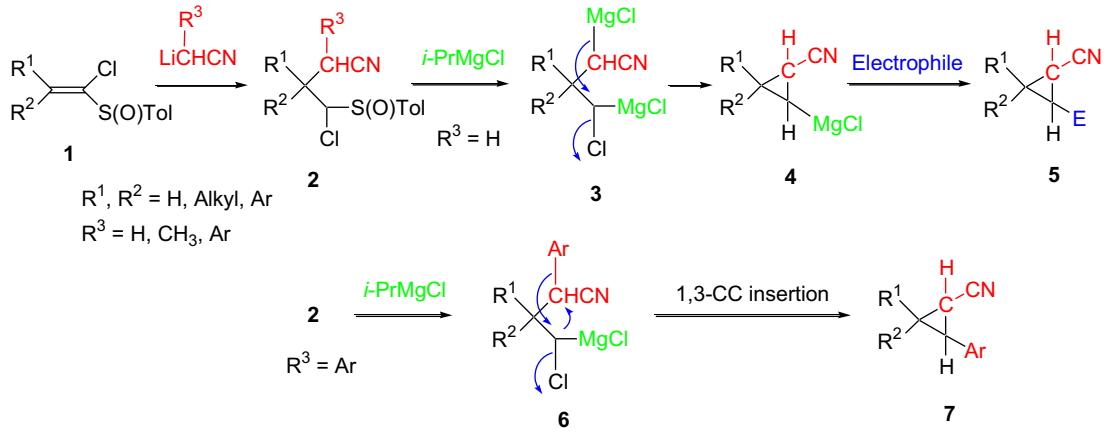


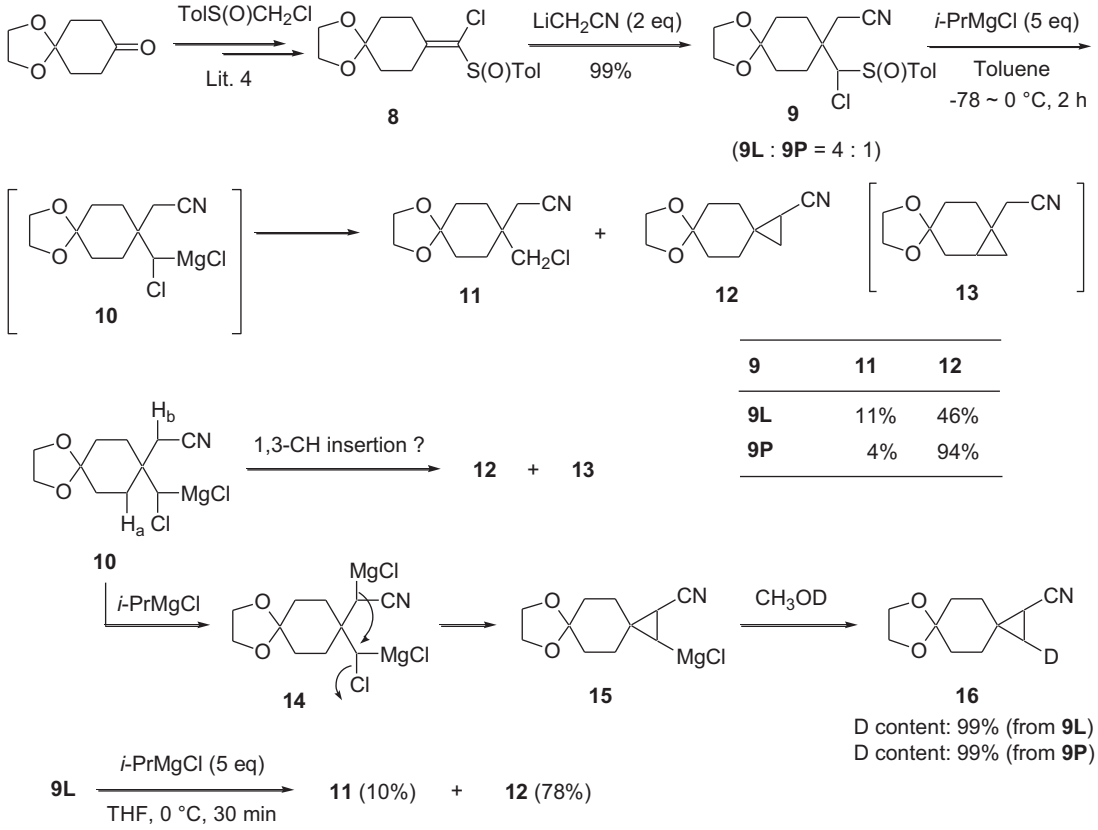
Scheme 1. General scheme for this work.

2. Results and discussion

2.1. Synthesis of multisubstituted cyanocyclopropanes from 1-chlorovinyl *p*-tolyl sulfoxides with acetonitrile by intramolecular S_N2 alkylation and trapping the intermediates with electrophiles

Representative example of this study starting from 1-chlorovinyl *p*-tolyl sulfoxide **8** derived from 1,4-cyclohexanedione monoethyleneketal and chloromethyl *p*-tolyl sulfoxide[4] is reported (Scheme 2). Thus, treatment of 1-chlorovinyl *p*-tolyl sulfoxide **8** with 2 equiv of cyanomethyllithium[7] gave adduct **9** in quantitative yield as a mixture of two diastereomers (these diastereomers are expressed as **9L** and **9P** (less polar product and more polar product on silica gel TLC, respectively), **9L**/**9P**=4:1).[5] The diastereomers could be easily separated by silica gel column chromatography. At first, major product **9L** was treated with 5 equiv of *i*-PrMgCl[8,9] in toluene at −78 °C and the temperature of the reaction mixture was slowly allowed to warm to 0 °C for 2 h. Two products were obtained from this reaction. One was chloroalkane **11** (11%) and the other was proved to be 1-cyanospiro[2.5]octane derivative **12** (46%). Somewhat surprisingly, expected bicyclo[4.1.0]heptane derivative **13**[10] was not observed. Interestingly, the same reaction of minor diastereomer **9P** gave **12** in 94% yield and again no **13** was observed (see table in Scheme 2).

Initially, we presumed that the product **12** would be produced by the 1,3-CH insertion reaction of the generated magnesium



9	11	12
9L	11%	46%
9P	4%	94%

Scheme 2. The reaction of acetonitrile adduct **9** with excess *i*-PrMgCl giving cyanocyclopropanes **12**, and the proposed reaction mechanism.

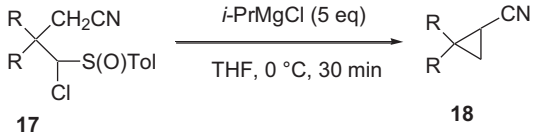
carbenoid intermediate **10** (Scheme 2).[10] Thus, when the 1,3-CH insertion reaction takes place between the magnesium carbenoid and the bond between carbon-H_a, bicyclo[4.1.0]heptane **13** must be produced. On the other hand, when the 1,3-CH insertion reaction takes place between the magnesium carbenoid and the carbon-H_b bond, spiro[2.5]octane **12** should be produced. However, based on our experiences, it was anticipated that the 1,3-CH insertion reaction between the carbenoid carbon and the carbon bearing an electron-withdrawing group was difficult.[10,11] In order to obtain some informations about the mechanism for the reaction giving **12**, the reaction of **9L** and **9P** with *i*-PrMgCl was quenched with CH_3OD, and somewhat surprisingly, we found that the cyclopropane ring of spiro-cyclic cyanocyclopropane was deuterated at 2-position to give **16** as a mixture of cis- and trans-isomers with over 99% deuterium incorporation.

From this result, the mechanism of the reaction giving **12** is proved as follows (Scheme 2). Thus, treatment of adduct **9** with *i*-PrMgCl results in the formation of magnesium carbenoid **10** by the sulfoxide–magnesium exchange reaction,[6] and then the acidic hydrogen (H_b) was eliminated by the excess *i*-PrMgCl to produce cyano-stabilized carbanion **14**. Intramolecular S_N2 alkylation of the magnesium carbenoid with the cyano-stabilized carbanion must occur to give cyclopropylmagnesium chloride intermediate bearing a cyano group **15**. Quenching of the intermediate **15** with deuterio methanol gives a cyanocyclopropane bearing deuterium at 2-position **16** with perfect deuterium incorporation. Inter- or intramolecular proton abstraction of magnesium carbenoid **10** and **14** afforded chloroalkane **11**.

Since the reaction described above is unprecedented and quite interesting for the synthesis of cyanocyclopropanes,[12] we investigated the best conditions for obtaining **12** from **9L**. Details of the investigation were reported in the preliminary letter[3] and the best conditions are described in Scheme 2. Thus, treatment of **9L** with 5 equiv of *i*-PrMgCl in THF at 0 °C for 30 min was found to be the conditions of choice to afford **12** in 78% yield with 10% of chloroalkane **11**. We used these conditions throughout in this study.

In order to investigate the generality of this reaction, we further studied this procedure starting with various symmetrical ketones via acetonitrile adducts **17** and the results are summarized in Table 1. The addition reaction of acetonitrile to the 1-chlorovinyl *p*-tolyl sulfoxides derived from 1,5-diphenylpentan-3-one, cyclododecanone, cyclopentadecanone, and benzophenone gave the corresponding adducts **17a** to **17d** in high to quantitative yields as a mixture of two diastereomers.[5] Less polar products (major diastereomers) were used in this study. The reaction of **17a**–**c** with *i*-PrMgCl in THF at 0 °C for 30 min gave the expected 2,2-disubstituted cyanocyclopropanes **18a** to **18c** in up to 79% yields (entries 1–3). When **17d** was treated with *i*-PrMgCl, the desired **18d** was obtained in 42% yield with rearrangement product **19** (25%). This product was produced via the 1,2-CC insertion reaction (rearrangement of phenyl group) of the corresponding magnesium carbenoid intermediate.

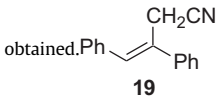
Table 1
Synthesis of cyanocyclopropanes **18** from symmetrical ketones via acetonitrile adducts **17**



17 **18**

Entry	17[a]		18	
		R		Yield/%
1	**17a**	$PhCH_2CH_2$	**18a**	79
2	**17b**	$-(CH_2)_{11}-$	**18b**	78
3	**17c**	$-(CH_2)_{14}-$	**18c**	73
4	**17d**	Ph	**18d**	42[b]

[a] Major acetonitrile adducts (less polar adducts) were used in this study.
[b] Significant amount (25%) of rearranged product **19** was obtained.



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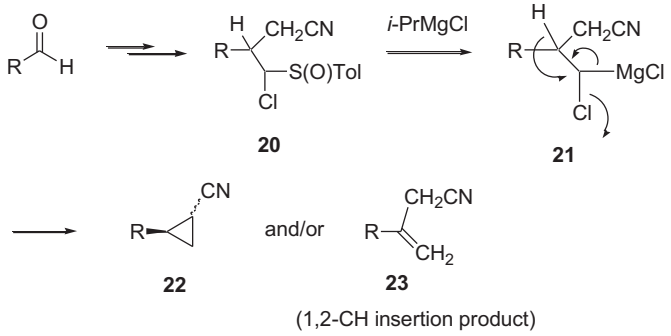
Next, we investigated this procedure starting from the acetonitrile adduct **20** derived from aldehydes (Scheme 3). Two reactions were anticipated to take place from the magnesium carbenoid intermediate **21** derived from **20** with *i*-PrMgCl, because **21** had hydrogen on the carbon next to the carbenoid carbon. One is the intramolecular S_N2 alkylation (giving **22**) as described above and the other is the 1,2-CH insertion reaction (giving olefin **23**) of magnesium carbenoid intermediate **21**.[13]



20 **21** **22** **23**

Scheme 3. Anticipated products **22** and/or **23** by treatment of acetonitrile adduct **20** derived from aldehydes with *i*-PrMgCl.

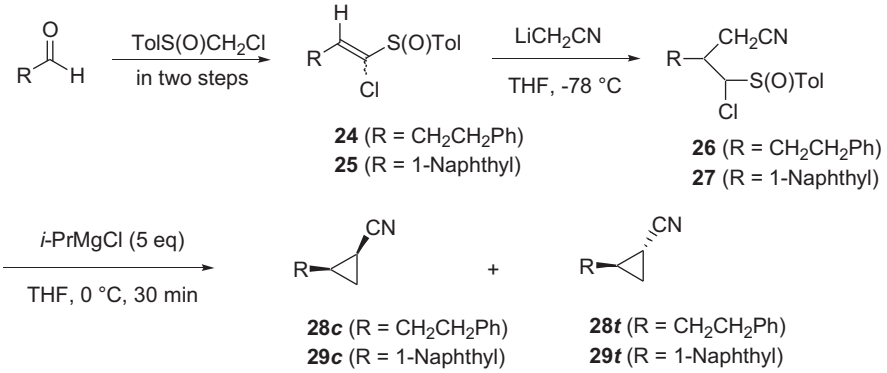
Anyway, we tried the reaction mentioned above with **20** and the results are summarized in Table 2. At first, 1-chlorovinyl *p*-tolyl sufoxides **24** and **25** were synthesized from 3-phenylpropanal and 1-naphthaldehyde, respectively, in high yields as a mixture of *E*- and *Z*-isomers.[4] Addition reaction of **24*E*** with cyanomethyllithium gave two adducts, **26*E*L** and **26*E*P** in 83% and 16% yields, respectively, as shown in entries 1 and 2.

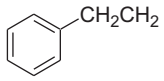
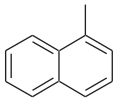
Treatment of **26*E*L** with 5 equiv of *i*-PrMgCl in THF at 0 °C afforded 2-(2-phenylethyl)cyanocyclopropane **28** as a 1:1 mixture of two diastereomers (**28***c* (cis isomer) and **28***t* (trans isomer)) in 69% yield without any olefinic product (entry 1). Similarly, **26*E*P** gave **28** as a mixture of two diastereomers (**28***c* and **28***t*) in 68% yield. Again, no olefinic product was observed in this reaction (entry 2). In the same way, **24*Z*** was reacted with cyanomethyllithium to afford adducts **26*Z*L** and **26*Z*P** in 88% and 11% yields, respectively. Treatment of these adducts with *i*-PrMgCl gave almost the same yields of cyanocyclopropanes **28***c* and **28***t* (entries 3 and 4). Interestingly, ratio of the two products, **28***c* and **28***t*, was quite different in two cases as shown in entries 2 and 3. The mechanism for this selectivity is obscure at present.

The results of this procedure starting from aryl aldehyde, 1-naphthaldehyde, were summarized in entries 5–7. The addition reaction of 1-chlorovinyl *p*-tolyl sulfoxides **25*E*** and **25*Z*** with cyanomethyllithium gave about 70% yields of adducts **27*E*** and **27*Z***, respectively. The key reaction of these adducts **27** gave the desired cyanocyclopropanes **29** in somewhat better yields compared with those of **28**. Interestingly, the ratio of cis and trans isomer was not so different in these cases.

As mentioned above, the intermediate of the reaction of **9L** with excess *i*-PrMgCl was proved to be cyclopropylmagnesium chloride bearing a cyano group **15** (Scheme 2). If this intermediate can be trapped with electrophiles other than proton, the whole procedure becomes a new method for the synthesis of multisubstituted cyanocyclopropanes. We investigated the feasibility of this plan and the results are shown in Scheme 4. Thus, adduct **9L** was treated

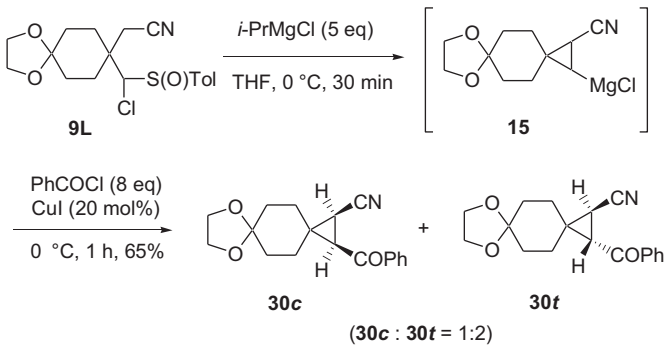
Table 2
Synthesis of mono-substituted cyanocyclopropanes **28** and **29** from aldehydes via acetonitrile adducts **26** and **27**



Entry	1-Chlorovinyl *p*-tolyl sulfoxides **24**, **25** R		**26** and **27** (Yield/%)	**28** and **29** Yield/% (*cis*/*trans*)
1		**24*E***	**26*E*L** (83)	**28***c*, **28***t* 69 (1:1)
2		**24*E***	**26*E*P** (16)	**28***c*, **28***t* 68 (12:1)
3		**24*Z***	**26*Z*L** (88)	**28***c*, **28***t* 69 (12:1)
4		**24*Z***	**26*Z*P** (11)	**28***c*, **28***t* 70 (1:1)
5		**25*E***	**27*E*** (71)[a]	**29***c*, **29***t* 84 (1:3)
6		**25*Z***	**27*Z*L** (60)	**29***c*, **29***t* 81 (2:1)
7		**25*Z***	**27*Z*P** (8)	**29***c*, **29***t* 90 (1:3)

[a] Adduct **27*E*** was obtained as a single isomer.

with 5 equiv of *i*-PrMgCl in THF at 0 °C and after 30 min, Cu(I) iodide (20 mol %) followed by benzoyl chloride (8 equiv) were added to the reaction mixture and the whole mixture was stirred at 0 °C for 1 h. This procedure gave the expected benzoylated products **30***c* and **30***t* (**30***c*/**30***t*=1:2) in 65% yield. The stereochemistry of the products was easily determined from the coupling constant of their ^{1}H NMR spectra (J_{H-H} of **30***c*, 7.7 Hz; J_{H-H} of **30***t*, 5.2 Hz).[14] When this reaction was conducted without Cu(I) iodide, only a complex mixture was obtained.



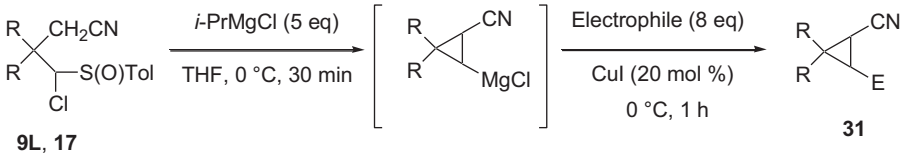
Scheme 4. Generation of cyclopropylmagnesium chloride intermediate **15** from **9L** and trapping the intermediate with benzoyl chloride.

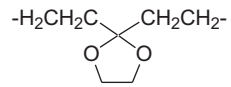
In order to investigate the generality of this procedure, acetonitrile adducts derived from symmetrical ketones were treated with *i*-PrMgCl under the aforementioned conditions followed by electrophiles and the results are summarized in Table 3. Although the reaction of **9L** with *i*-PrMgCl followed by benzoyl chloride gave benzoylated product **30***c* and **30***t* in moderate yields (see Scheme 4), the reaction with haloalkane did not give good result (entry 1). Even iodomethane did not react with the cyclopropylmagnesium chloride intermediate. The reaction of **17a**–**c** and **17e** with *i*-PrMgCl followed by benzoyl chloride gave cyanocyclopropanes bearing a benzoyl group at the 2-position in 42–70% yields (entries 2–5). Benzyl bromide worked in the reaction of **17e**; however, again the yield was moderate (entry 6). Unfortunately, other electrophiles, such as ketones, aldehydes, ethyl chloroformate only gave a complex mixture.

Above-mentioned chemistry was applied to 1-chlorovinyl *p*-tolyl sulfoxides derived from aldehydes. The reactions starting from (*Z*)-1-chloro-1-(*p*-tolylsulfinyl)-1-propene **32** derived from acetaldehyde are reported as a representative example (Scheme 5). Thus, the reaction of **32** with cyanomethyllithium gave adduct **33** in quantitative yield as a 4:1 mixture of two diastereomers **33L** and **33P**. Treatment of **33L** followed by benzoyl chloride under the same conditions described above gave two cyanocyclopropanes bearing a benzoyl group, **34** and **35**, in 48% and 22% yields, respectively. The reaction of **33P** gave **36** and **37** in 42% and 20% yields, respectively. It is interesting to note that the four products (**34**–**37**) were the theoretical all four diastereomers of 2-benzoyl-3-methylcyanocyclopropane.

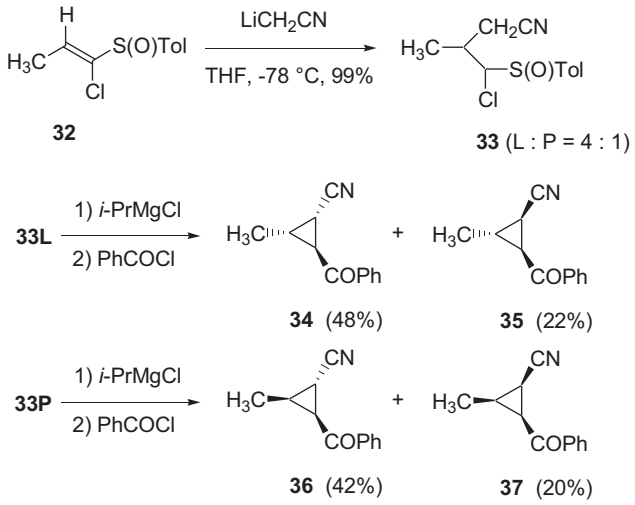
Above-mentioned reaction was further conducted with acetonitrile adducts **26** and **27**, and the results are summarized in Table 4. As shown in entries 1 and 2, the reaction of **26*E*L** and **26*Z*L** with *i*-PrMgCl followed by benzoyl chloride afforded the expected products **38a** to **38d**. Interestingly, stereochemistry of major products (**38a** and **38c**) was found to be trans with respect to the cyano group and the benzoyl group. In these two cases, the yields of the minor products **38b** and **38d** were about 5%. The reaction of **27*E*** gave **38e** in 54% yield as a sole product and any stereoisomers were

Table 3
Generation of cyclopropylmagnesium chloride intermediates and trapping them with electrophiles



Entry	**9L**, **17**		Electrophile	**31**
		R		Yield/% (*cis*/*trans*)
1	**9L**		$PhCH_2Br$	**31a** 14 (1:4)
2	**17a**[a]	$PhCH_2CH_2$	PhCOCl	**31b** 42 (0:1)
3	**17b**[a]	$-(CH_2)_{11}-$	PhCOCl	**31c** 64 (1:3)
4	**17c**[a]	$-(CH_2)_{14}-$	PhCOCl	**31d** 61 (1:3)
5	**17e**[a]	CH_3	PhCOCl	**31e** 70 (2:3)
6	**17e**[a]	CH_3	$PhCH_2Br$	**31f** 44 (0:1)

[a] Major acetonitrile adduct (less polar product) was used in this study.



Scheme 5. Treatment of acetonitrile adducts **33L** and **33P** derived from **32** with *i*-PrMgCl followed by benzoyl chloride giving 2-benzoyl-3-methylcyanocyclopropanes **34**–**37**.

observed. The reaction of **27*Z*L** gave again trans isomer (with respect to the cyano group and benzoyl group) as the major product (37%) with **38g** as a minor product in 11% yield. The stereochemistry of these products is quite interesting; however, clear explanation of the mechanism for the selectivity is difficult to present up to now. Anyway, 2,3-disubstituted cyanocyclopropanes bearing a benzoyl group at 2-position were obtained from 1-chlorovinyl *p*-tolyl sulfoxides through the acetonitrile adducts in three steps in two pot reaction in moderate to good yields by the reactions mentioned in this section.

2.2. Synthesis of multisubstituted cyanocyclopropanes from 1-chlorovinyl *p*-tolyl sulfoxides with propionitrile and arylacetonitriles by the S_N2 alkylation and 1,3-CC insertion reaction, respectively

In continuation of above-mentioned investigations, we next turned our attention to the reaction with α-substituted acetonitriles. At first, the reaction starting from 1-chlorovinyl *p*-tolyl sulfoxide **8** and lithium α-cyano carbanion of propionitrile was investigated and the results are shown in Scheme 6. Thus, the addition reaction of **8** with lithium α-cyano carbanion of propionitrile gave expected adduct **39** in 96% yield as a mixture of four diastereomers (**39a**–**d**). The diastereomers were separated and they were treated with *i*-PrMgCl. The reactions gave the desired cyanocyclopropane **40**; however, the yields were low to moderate (39–47%). The reason for these poor results could be explained from the lowering of the acidity of the hydrogen on the carbon next to the cyano group by the presence of a methyl group and steric hindrance of the carbon bearing the methyl group. We concluded that this reaction looked unpromising to the synthesis of multisubstituted cyanocyclopropanes bearing an alkyl group on the 1-position.

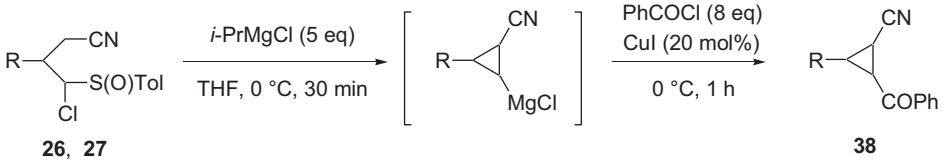
Finally, we investigated this procedure with arylacetonitriles. Representative example using phenylacetonitrile is shown in Scheme 7. Thus, addition reaction of 1-chlorovinyl *p*-tolyl sulfoxide **8** with lithium α-cyano carbanion of phenylacetonitrile at −78 °C gave adduct **41** as a mixture of two diastereomers (**41L** and **41P**; L/P=10:3) in 86% yield.[15]

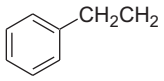
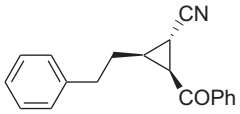
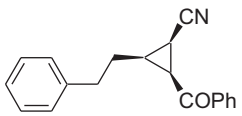
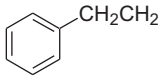
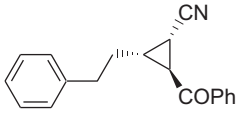
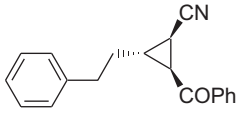
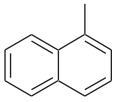
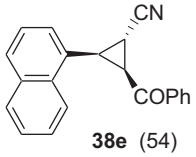
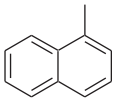
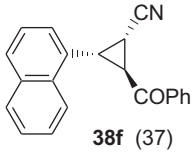
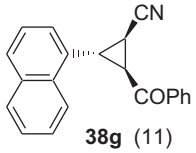
Very interestingly, the product from the treatment of **41L** with *i*-PrMgCl in THF at 0 °C was not the expected 1-phenylcyanocyclopropane **45** but *cis*-3-phenylcyanocyclopropane **43** (74% yield as a sole product). This result clearly indicated that magnesium carbenoid **42L** generated from **41L** underwent 1,3-CC insertion reaction (insertion of the carbenoid carbon into the carbon–carbon bond between α-carbon and the phenyl carbon).[16] The same reaction of **41P** gave *trans*-3-phenylcyanocyclopropane **44**. In this case trans-compound was obtained as a sole product in better yield. Namely, these reactions are highly stereospecific. Transferability of aryl group is known to be high compared with that of methyl group. Therefore, the 1,3-CC insertion reaction took place in the case of aryl-substituted substrates.

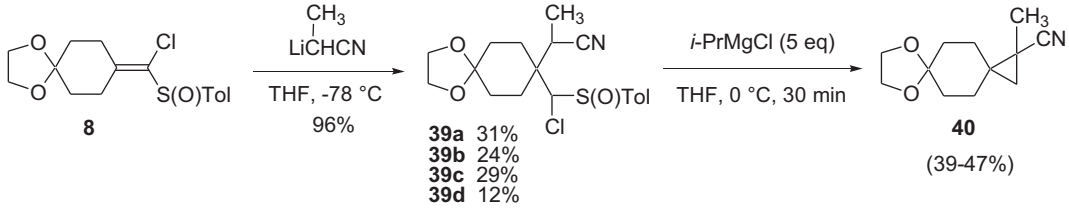
Elucidation of the mechanism of this stereospecificity is quite important for development of the presented procedure. At first, we tried to determine the relative configuration of adducts **41L** and **41P** by single crystal X-ray analysis and the result is shown in Fig. 1. These two products were proved to be the epimers to each other with respect to the configuration of the carbon bearing chlorine atom.

With relative configuration of adducts **41L** and **41P** in hand, the mechanism of this highly stereosepecific 1,3-CC insertion reaction is explained as follows (Scheme 8). As the sulfoxide–magnesium exchange reaction is known to take place with retention of

Table 4
Treatment of acetonitrile adducts **26** and **27** with *i*-PrMgCl followed by benzoyl chloride giving 2-benzoyl-3-substituted cyanocyclopropanes **38**



Entry	**26**, **27** R	**38** (Yield/%)	
1	**26*EL***		 **38a** (35)  **38b** (6)
2	**26ZL**		 **38c** (46)  **38d** (5)
3	**27*E***		 **38e** (54)
4	**27ZL**		 **38f** (37)  **38g** (11)



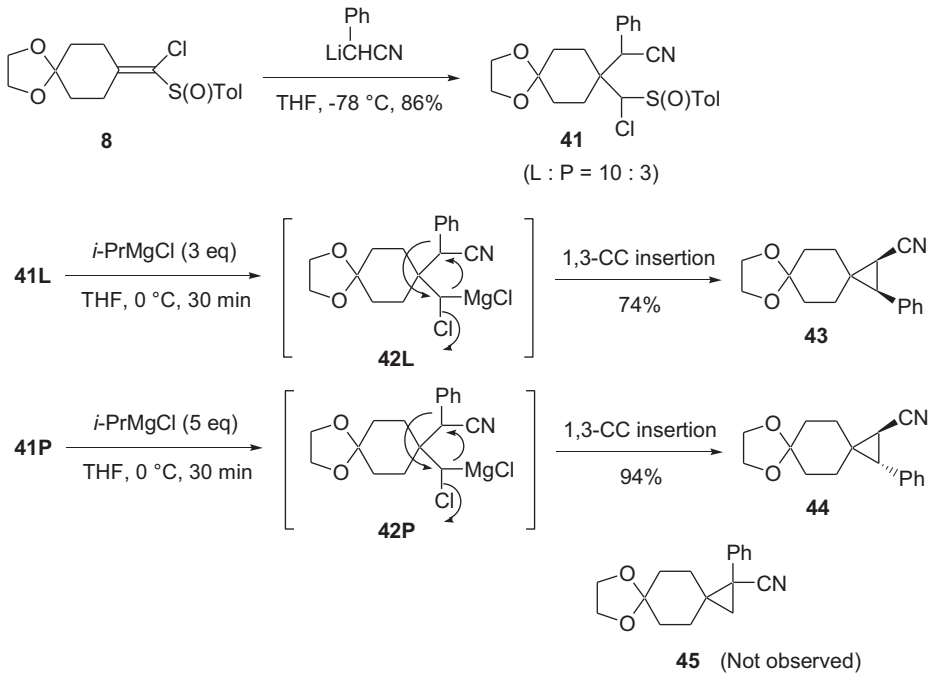
Scheme 6. Addition reaction of **8** with lithium α-cyano carbanion of propionitrile and the treatment of adducts **39a** to **39d** with excess *i*-PrMgCl.

configuration of the carbon bearing the sulfinyl group,[9,17] treatment of **41L** with *i*-PrMgCl gives magnesium carbenoid **A**. The 1,3-CC insertion reaction must take place from backside of the carbon–chlorine bond of the magnesium carbenoid intermediate **A** with inversion of the carbon bearing the chlorine atom[2d] to give *cis*-3-phenylcyanocyclopropane **43**. In the same way, the 1,3-CC insertion of magnesium carbenoid intermediate **B** derived from epimer **41P** gave *trans*-3-phenylcyanocyclopropane **44**.

As we recognized that this procedure is quite interesting unprecedented way for the synthesis of multisubstituted 3-arylcyanocyclopropanes, generality of the reaction was studied and the results are summarized in Table 5. Arylacetonitrile adducts **46a** to **46e** were synthesized from **8** with lithium α-cyano carbanions generated from various arylacetonitriles in high to quantitative yields. Adduct **46f** was synthesized starting with acetone.

In a single glance, L-isomer gave *cis*-cyclopropanes **47** and P-isomer gave *trans*-cyclopropanes **48** in high to complete stereospecificity. Generally, better yields were obtained from the reaction with P-isomer compared to those of L-isomer. Somewhat better yields were obtained from **46** bearing an aryl group having an electron-donating group at the *para*-position. In any event, this procedure was proved to be useful for the synthesis of multisubstituted 3-arylcyanocyclopropanes.

In conclusion, a method for the synthesis of multisubstituted cyanocyclopropanes was established starting from 1-chlorovinyl *p*-tolyl sulfoxides derived from ketones and aldehydes with acetonitrile derivatives and electrophiles. The key reaction of this procedure is the intramolecular alkylation of magnesium carbenoid with cyano-stabilized carbanion followed by trapping the cyclopropylmagnesium chloride intermediate with electrophiles. When



Scheme 7. Reaction of **8** with lithium α-cyano carbanion of phenylacetonitrile and the treatment of the adducts **41L** and **41P** with *i*-PrMgCl giving 3-phenylcyanocyclopropanes **43** and **44**.

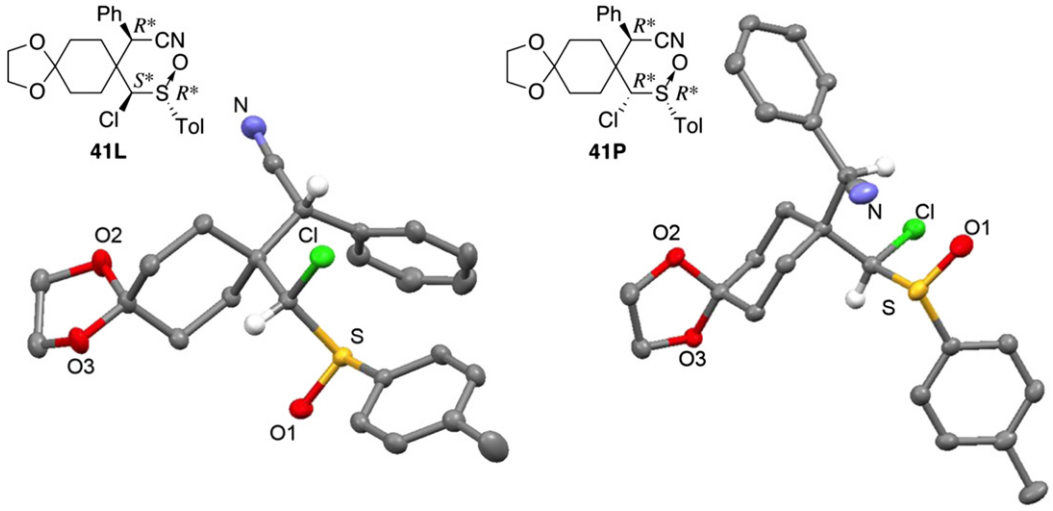


Fig. 1. ORTEP drawings of **41L** and **41P** with thermal ellipsoids at the 50% probability level. Hydrogen atoms except those on the chiral carbon atoms have been omitted for clarity.

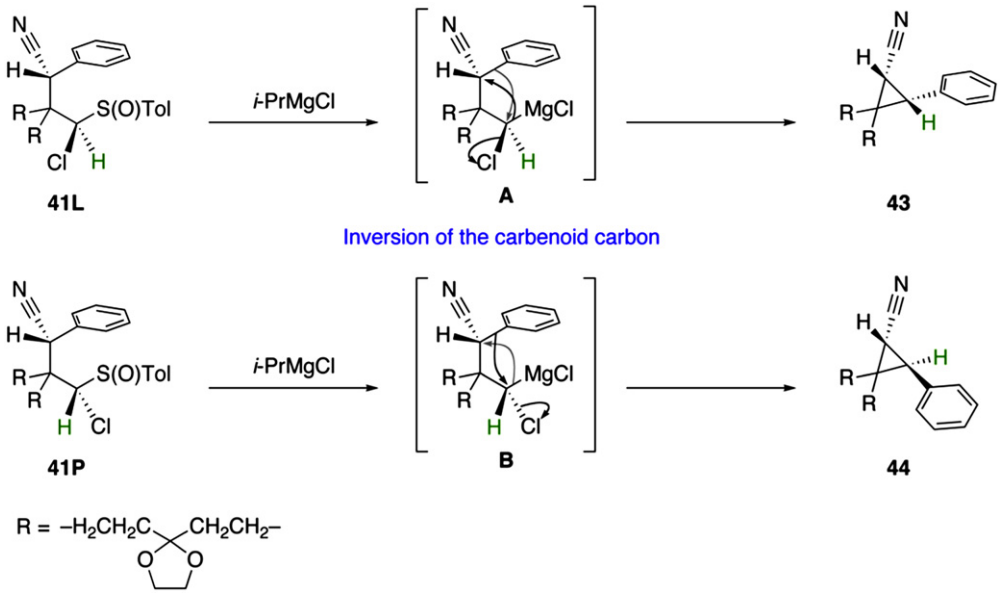
this procedure was carried out with arylacetonitriles, 3-arylcyanocyclopropanes were obtained in good to high yield through 1,3-CC insertion as the key reaction with high stereospecificity. We believe that the results described in this paper will contribute to the synthesis of multisubstituted cyanocyclopropanes and the chemistry of magnesium carbenoids.

3. Experimental

3.1. General

All melting points were measured on a Yanaco MP-S3 apparatus and are uncorrected. ^{1}H NMR spectra were measured in a $CDCl_3$ solution with JEOL JNM-LA 300, 500, Bruker DPX 400, and AV 600 spectrometer. Electron-impact mass spectra (MS) were obtained at 70 eV by direct insertion with HITACHI M-80B mass spectrometer. IR spectra were recorded on a Perkin–Elmer Spectrum One FTIR instrument. Silica gel 60 N (KANTO CHEMICAL) containing 0.5% fluorescence reagent 254 and a quartz column were used for column chromatography, and the products having UV absorption were detected by UV irradiation. In experiments requiring dry solvents and reagents, THF was distilled from diphenylketyl. Diisopropylamine, acetonitrile, and propionitrile were distilled from CaH_2. Phenylacetonitrile, 4-methoxyphenylacetonitrile, and 4-fluorophenylacetonitrile were distilled before use. All reactions involving air- or water-sensitive compounds were routinely conducted in glassware, which was flame-dried under a positive pressure of argon. 1-Chlorovinyl *p*-tolyl sulfoxides **8**,[4a] **24*E***,[18] **24*Z***,[18] **25*E***,[13b] and **25*Z***,[13b] adducts **9**,[5d] **17c**,[5d] and **17d**,[5d] are known compounds.

*3.1.1. {8-[Chloro-(p-tolylsulfinyl)methyl]-1,4-dioxaspiro[4.5]decan-8-yl}acetonitrile (**9**).* Adducts **9L** and **9P** were prepared according to the procedure described in the literature.[5d] A solution of BuLi in hexane (1.55 mol/L; 1.30 mL; 2.0 mmol) was added to a solution of diisopropylamine (209 mg; 2.10 mmol) in THF (16 mL) at 0 °C, and the mixture was stirred at 0 °C for 10 min. Acetonitrile (86 mg;



Scheme 8. A plausible mechanism for the stereospecific 1,3-CC insertion of magnesium carbenoids **A** and **B**.

2.0 mmol) was added dropwise to the resulting solution at −78 °C, and the mixture was stirred at that temperature for 10 min. A solution of **8** (327 mg; 1.00 mmol) in THF (4 mL) was added dropwise to the mixture at −78 °C, and the mixture was stirred at that temperature for 5 min. The reaction was quenched with satd aq NH_4Cl (10 mL), and the mixture was extracted with $CHCl_3$ (3×15 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 **9L** (less polar adduct; 291 mg; 0.79 mmol; 79%) as colorless crystals and **9P** (more polar adduct; 74 mg; 0.20 mmol; 20%) as colorless crystals.

*3.1.2. 7,10-Dioxadispiro[2.2.4.2]dodecane-1-carbonitrile (**12**).* A solution of **9L** (73.6 mg; 0.200 mmol) in THF (1.0 mL) was added dropwise to a solution of isopropylmagnesium chloride (2.0 mol/L solution in Et_2O; 0.50 mL; 1.0 mmol) in THF (9.0 mL) at 0 °C, and the mixture was stirred at that temperature for 30 min. The reaction was quenched with satd aq NH_4Cl (1 mL), and the mixture was extracted with $CHCl_3$ (3×6 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 [(8-chloromethyl)-1,4-dioxaspiro[4.5]decan-8-yl] acetonitrile **11** (4.6 mg; 0.020 mmol; 11%) as colorless crystals and **12** (29.5 mg; 0.156 mmol; 78%) as colorless oil. Compound **11**; mp 88.5–89.5 °C (hexane/AcOEt); IR (KBr) 2953, 2888, 2243 (CN), 1104, 906, 747 cm^{-1}; ^1H NMR δ 1.60–1.77 (m, 8H), 2.53 (s, 2H), 3.62 (s, 2H), 3.95–4.00 (m, 4H); Anal. Calcd for $C_{11}H_{16}ClNO_2$: C, 57.52; H, 7.02; Cl, 15.43; N, 6.10, found: C, 57.55; H, 6.97; Cl, 15.04; N, 6.00. Compound **12**: IR (neat) 2950, 2887, 2234 (CN), 1443, 1260, 1140, 1092, 1035, 913 cm^{-1}; ^1H NMR δ 1.01 (t, J=5.3 Hz, 1H), 1.04 (dd, J=5.3, 8.5 Hz, 1H), 1.24 (dd, J=5.3, 8.5 Hz, 1H), 1.34–1.42 (m, 1H), 1.60–1.85 (m, 7H), 3.95–3.99 (m, 4H); MS (EI) m/z (%) 193 (M^+, 59), 153 (15), 148 (25), 140 (27), 125 (48), 99 (77), 86 (100); HRMS (EI) calcd for $C_{11}H_{15}NO_2$: 193.1103, found: 193.1103.

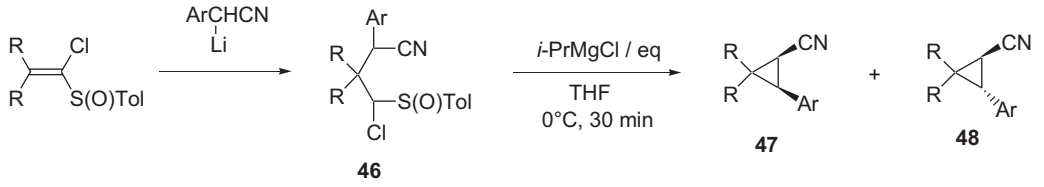
*3.1.3. 2-Deuterio-7,10-dioxadispiro[2.2.4.2]dodecane-1-carbonitrile (**16**).* ^1H NMR δ 0.99–1.05 (m, 1H), 1.21–1.26 (m, 1H), 1.34–1.42 (m, 1H), 1.60–1.85 (m, 7H), 3.95–3.99 (m, 4H).

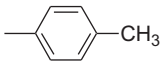
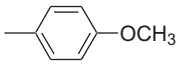
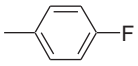
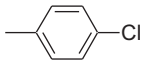
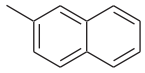
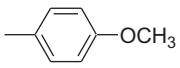
*3.1.4. 3-[Chloro(p-tolylsulfinyl)methyl]-3-(2-phenylethyl)-5-phenylpentanenitrile (**17a**).* Compound **17aL**: yield (55%); colorless oil; IR (neat) 3027, 2933, 2246 (CN), 1496, 1455, 1082, 1052, 910, 812, 733, 700 cm^{-1}; ^1H NMR δ 2.18–2.26 (m, 2H), 2.28–2.36 (m, 2H), 2.45 (s, 3H), 2.63–2.82 (m, 2H), 2.84–2.91 (m, 2H), 3.01 (d, J=17.1 Hz, 1H), 3.23 (d, J=17.1 Hz, 1H), 4.66 (s, 1H), 7.19–7.34 (m, 10H), 7.37 (d, J=8.2 Hz, 2H), 7.77 (d, J=8.2 Hz, 2H); MS (EI) m/z (%) 449 (M^+, 0.3), 432 (9), 274 (9), 140 (81), 105 (25), 91 (100); HRMS (EI) calcd for $C_{27}H_{28}ClNOS$: 449.1580, found: 449.1580. Compound **17aP**: yield (36%); colorless oil; IR (neat) 3027, 2930, 2245 (CN), 1496, 1455, 1089, 1062, 910, 811, 734, 700 cm^{-1}; ^1H NMR δ 2.16–2.46 (m, 4H), 2.44 (s, 3H), 2.70–3.00 (m, 4H), 2.91 (d, J=17.4 Hz, 1H), 2.98 (d, J=17.4 Hz, 1H), 4.43 (s, 1H), 7.20–7.39 (m, 12H), 7.50 (d, J=8.3 Hz, 2H); MS (EI) m/z (%) 449 (M^+, 0.4), 432 (12), 274 (10), 140 (73), 105 (28), 91 (100); HRMS (EI) calcd for $C_{27}H_{28}ClNOS$: 449.1580, found: 449.1580.

*3.1.5. {1-[Chloro(p-tolylsulfinyl)methyl]cyclododecyl}acetonitrile (**17b**).* Compound **17bL**: yield (93%); colorless oil; IR (neat) 2934, 2863, 2244 (CN), 1472, 1446, 1083, 1051, 912, 811, 733 cm^{-1}; ^1H NMR δ 1.20–1.79 (m, 20H), 1.89–2.01 (m, 2H), 2.44 (s, 3H), 2.54 (d, J=17.0 Hz, 1H), 3.32 (d, J=17.0 Hz, 1H), 4.54 (s, 1H), 7.34 (d, J=8.2 Hz, 2H), 7.74 (d, J=8.2 Hz, 2H); MS (EI) m/z (%) 393 (M^+, 0.5), 140 (100), 92 (13); HRMS (EI) calcd for $C_{22}H_{32}ClNOS$: 393.1893, found: 393.1892. Compound **17bP**: yield (6%); colorless crystal; mp 114.0–115.0 °C (hexane/AcOEt); IR (KBr) 2942, 2847, 2246 (CN), 1595, 1471, 1441, 1085, 1049, 1017, 806 cm^{-1}; ^1H NMR δ 1.20–1.70 (m, 19H), 1.79–1.93 (m, 2H), 2.01–2.13 (m, 1H), 2.43 (s, 3H), 2.79 (d, J=17.3 Hz, 1H), 2.86 (d, J=17.3 Hz, 1H), 4.19 (s, 1H), 7.35 (d, J=8.1 Hz, 2H), 7.47 (d, J=8.1 Hz, 2H); MS (EI) m/z (%) 393 (M^+, 0.5), 377 (1), 140 (100), 92 (13); HRMS (EI) calcd for $C_{22}H_{32}ClNOS$: 393.1893, found: 393.1896.

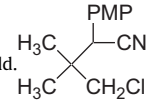
*3.1.6. 4-Chloro-3,3-dimethyl-4-(p-tolylsulfinyl)butanenitrile (**17e**).* Compound **17eL**: yield (79%); colorless crystal; mp 62.5–63.0 °C (hexane/AcOEt); IR (KBr) 2973, 2939, 2243 (CN), 1595, 1492, 1459, 1398, 1373, 1045, 808, 737 cm^{-1}; ^1H NMR δ 1.41 (s, 3H), 1.52 (s, 3H), 2.44 (s, 3H), 2.75 (d, J=16.6 Hz, 1H), 3.12 (d, J=16.6 Hz, 1H), 4.43 (s, 1H), 7.35 (d, J=8.2 Hz, 2H), 7.73 (d, J=8.2 Hz, 2H); MS (EI) m/z (%) 269 (M^+, 7), 140 (100), 92 (47); HRMS (EI) calcd for $C_{13}H_{16}ClNOS$: 269.0641, found: 269.0641. Compound **17eP**: yield (19%); yellow solid; mp 129.0–129.5 °C; IR (KBr) 2979, 2239 (CN),

Table 5
Reaction of arylacetonitrile adducts **46** with *i*-PrMgCl giving 3-arylcyanocyclopropanes **47** and **48**



Entry	**46**			*i*-PrMgCl/equiv	**47**	**48**
	R	Ar			(Yield/%)	(Yield/%)
1	**46aL**	—CH_2CH_2 CH_2CH_2— (O, O)		3	**47a** (67)	**48a** (trace)
2	**46aP**			5	**47a** (0)	**48a** (95)
3	**46bL**			3	**47b** (78)	**48b** (0)
4	**46bP**			5	**47b** (0)	**48b** (96)
5	**46cL**			3	**47c** (55)	**48c** (trace)
6	**46cP**			5	**47c** (6)	**48c** (82)
7	**46dL**			3	**47d** (49)	**48d** (trace)
8	**46dP**			5	**47d** (7)	**48d** (85)
9	**46eL**			3	**47e** (54)	**48e** (0)
10	**46eP**			5	**47e** (trace)	**48e** (82)
11	**46fL**	CH_3		5	**47f** (27)[a]	**48f** (0)
12	**46fP**	CH_3		5	**47f** (0)	**48f** (56)

[a] Protonated product **49** was obtained in 42% yield.



49

1469, 1399, 1087, 1054, 811 cm^{-1}; ^1H NMR δ 1.48 (s, 3H), 1.50 (s, 3H), 2.44 (s, 3H), 2.70 (d, J=17.0 Hz, 1H), 2.77 (d, J=17.0 Hz, 1H), 4.24 (s, 1H), 7.36 (d, J=8.4 Hz, 2H), 7.49 (d, J=8.4 Hz, 2H); MS (EI) m/z (%) 269 (M^+,12), 140 (100), 92 (43); HRMS (EI) calcd for $C_{13}H_{16}ClNOS$: 269.0641, found: 269.0638.

*3.1.7. 2,2-Bis(2-phenylethyl)cyclopropanecarbonitrile (**18a**).* Colorless oil; IR (neat) 3027, 2931, 2863, 2234 (CN), 1603, 1497, 1455, 752, 700 cm^{-1}; ^1H NMR δ 0.92 (t, J=5.3 Hz, 1H), 0.96 (dd, J=5.3, 8.5 Hz, 1H), 1.18 (dd, J=5.3, 8.5 Hz, 1H), 1.65–1.72 (m, 2H), 1.92 (t, J=8.0 Hz, 2H), 2.68–2.93 (m, 4H), 7.13–7.33 (m, 10H); MS (EI) m/z (%) 275 (M^+, 9), 184 (18), 91 (100); HRMS (EI) calcd for $C_{20}H_{21}N$: 275.1674, found: 275.1669.

*3.1.8. Spiro[2.11]tetradecane-1-carbonitrile (**18b**).* Colorless oil; IR (neat) 2938, 2863, 2234 (CN), 1471, 1446, 756 cm^{-1}; ^1H NMR δ 0.92 (t, J=5.2 Hz, 1H), 0.95 (dd, J=5.2, 8.3 Hz, 1H), 1.14 (dd, J=5.2, 8.3 Hz, 1H), 1.18–1.74 (m, 22H); MS (EI) m/z (%) 219 (M^+, 25), 166 (56), 109 (47), 96 (92), 82 (100), 67 (68), 55 (63), 41 (64); HRMS (EI) calcd for $C_{15}H_{25}N$: 219.1987, found: 219.1994.

*3.1.9. Spiro[2.14]heptadecane-1-carbonitrile (**18c**).* Colorless oil; IR (neat) 2930, 2858, 2235 (CN), 1460, 757 cm^{-1}; ^1H NMR δ 0.91 (t, J=5.2 Hz, 1H), 0.95 (dd, J=5.2, 8.4 Hz, 1H), 1.15 (dd, J=5.2, 8.4 Hz, 1H), 1.20–1.65 (m, 28H); MS (EI) m/z (%) 261 (M^+, 94), 232 (67), 218 (60), 108 (53), 96 (93), 82 (100), 67 (62), 55 (80), 41 (60); HRMS (EI) calcd for $C_{18}H_{31}N$: 261.2457, found: 261.2457.

*3.1.10. 3,4-Diphenylbut-3-enenitrile (**19**).* Yellow oil; IR (neat) 3058, 3026, 2248 (CN), 1600, 1496, 1447, 1420, 1078, 920, 760, 699 cm^{-1}; ^1H NMR δ 3.65 (s, 2H), 7.10 (s, 1H), 7.31–7.48 (m, 8H), 7.52–7.58 (m, 2H); MS (EI) m/z (%) 219 (M^+, 100), 179 (97); HRMS (EI) calcd for $C_{16}H_{13}N$: 219.1048, found: 219.1049.

*3.1.11. 3-[Chloro(p-tolylsulfinyl)methyl]-5-phenylpentanenitrile (**26**).* Compound **26EL**: colorless oil; IR (neat) 3028, 2927, 2864,

2249 (CN), 1597, 1495, 1455, 1420, 1084, 1052, 813 cm^{-1}; ^1H NMR δ 1.92–2.06 (m, 1H), 2.10–2.23 (m, 1H), 2.45 (s, 3H), 2.59–2.73 (m, 3H), 2.83–2.99 (m, 2H), 4.43 (d, J=2.2 Hz, 1H), 7.14–7.33 (m, 5H), 7.35 (d, J=8.1 Hz, 2H), 7.61 (d, J=8.1 Hz, 2H); MS (EI) m/z (%) 345 (M^+, 0.5), 140 (100), 129 (25), 105 (16), 91 (72); HRMS (EI) calcd for $C_{19}H_{20}ClNOS$: 345.0954, found: 345.0959. Compound **26*EP***: colorless oil; IR (neat) 3026, 2928, 2247 (CN), 1597, 1495, 1455, 1089, 1060, 754 cm^{-1}; ^1H NMR δ 1.99 (dtd, J=5.7, 8.9, 14.4 Hz, 1H), 2.30 (dddd, J=4.3, 7.6, 8.9, 14.4 Hz, 1H), 2.43 (s, 3H), 2.44–2.50 (m, 1H), 2.65 (td, J=8.0, 14.0 Hz, 1H), 2.75 (dd, J=6.5, 17.3 Hz, 1H), 2.82 (dd, J=6.3, 17.3 Hz, 1H), 2.84 (ddd, J=5.7, 8.9, 14.0 Hz, 1H), 4.52 (d, J=5.2 Hz, 1H), 7.18–7.21 (m, 2H), 7.23–7.27 (m, 1H), 7.31–7.35 (m, 4H), 7.41 (d, J=8.3 Hz, 2H); MS (EI) m/z (%) 345 (M^+, 1), 328 (6), 140 (100), 129 (24), 105 (18), 91 (88), 65 (11); HRMS (EI) calcd for $C_{19}H_{20}ClNOS$: 345.0954, found: 345.0954. Compound **26*ZL***: colorless oil; IR (neat) 3026, 2927, 2242 (CN), 1597, 1495, 1455, 1083, 1053, 812, 755 cm^{-1}; ^1H NMR δ 1.75–1.90 (m, 1H), 2.27–2.39 (m, 1H), 2.43 (s, 3H), 2.53 (dd, J=9.5, 17.0 Hz, 1H), 2.69 (dd, J=5.0, 17.0 Hz, 1H), 2.72–2.89 (m, 2H), 2.96–3.06 (m, 1H), 4.53 (d, J=2.5 Hz, 1H), 7.20–7.28 (m, 3H), 7.30–7.36 (m, 4H), 7.67 (d, J=8.1 Hz, 2H); MS (FAB^+) m/z (%) 346 ($[M+H]^+$, 100), 310 (4), 294 (5), 170 (10), 129 (27), 91 (33), 77 (6); HRMS (FAB^+) calcd for $C_{19}H_{21}ClNOS$: 346.1032, found: 346.1032. Compound **26*ZP***: colorless oil; IR (neat) 3027, 2929, 2248 (CN), 1596, 1495, 1455, 1088, 1059, 812, 753, 701 cm^{-1}; ^1H NMR δ 2.04–2.29 (m, 2H), 2.44 (s, 3H), 2.55–2.78 (m, 4H), 2.85 (dd, J=3.8, 16.5 Hz, 1H), 4.40 (d, J=5.2 Hz, 1H), 7.16–7.21 (m, 2H), 7.23–7.38 (m, 5H), 7.45 (d, J=8.3 Hz, 2H); MS (FAB^+) m/z (%) 346 ($[M+H]^+$, 100), 294 (6), 170 (13), 140 (23), 129 (32), 91 (37); HRMS (FAB^+) calcd for $C_{19}H_{21}ClNOS$: 346.1032, found: 346.1033.

*3.1.12. 4-Chloro-3-(1-naphthyl)-4-(p-tolylsulfinyl)butanenitrile (**27**).* Compound **27*E***: colorless crystal; mp 132.0–132.5 °C (hexane/AcOEt); IR (KBr) 2942, 2248 (CN), 1599, 1509, 1489, 1432, 1397, 1258, 1083, 1052, 1013, 816, 780 cm^{-1}; ^1H NMR δ 2.42 (s, 3H), 3.34 (d, J=8.5 Hz, 1H), 3.35 (d, J=6.8 Hz, 1H), 4.65 (d, J=2.1 Hz, 1H), 5.15 (ddd, J=2.1, 6.8, 8.5 Hz, 1H), 7.32 (d, J=8.2 Hz, 2H), 7.47–7.61 (m, 4H), 7.64 (d, J=8.2 Hz, 2H), 7.82–7.96 (m, 3H); MS (FAB^+) m/z (%) 368 ($[M+H]^+$, 100), 228 (82), 192 (25), 154 (28), 136 (23), 93 (15); HRMS (FAB^+) calcd for $C_{21}H_{19}ClNOS$: 368.0876, found: 368.0882. Compound **27*ZL***: colorless crystal; mp 109.0–110.0 °C (hexane/AcOEt); IR (KBr) 2947, 2245 (CN), 1737, 1596, 1512, 1118, 1084, 1057, 1048, 783 cm^{-1}; ^1H NMR δ 2.43 (s, 3H), 3.12 (dd, J=7.0, 16.9 Hz, 1H), 3.19 (dd, J=7.6, 16.9 Hz, 1H), 4.90 (d, J=4.7 Hz, 1H), 5.02–5.17 (m, 1H), 7.33 (d, J=8.0 Hz, 2H), 7.49–7.70 (m, 5H), 7.74 (d, J=7.0 Hz, 1H), 7.91 (d, J=8.0 Hz, 2H), 8.37 (d, J=8.7 Hz, 1H); MS (FAB^+) m/z (%) 368 ($[M+H]^+$, 100), 228 (68), 192 (32), 154 (31), 137 (26), 93 (42); HRMS (FAB^+) calcd for $C_{21}H_{19}ClNOS$: 368.0876, found: 368.0877. Compound **27*ZP***: colorless crystal; mp 155.5–156.0 °C (hexane/AcOEt); IR (KBr) 2947, 2250 (CN), 1598, 1514, 1493, 1418, 1397, 1086, 1052, 1016, 811, 785 cm^{-1}; ^1H NMR δ 2.43 (s, 3H), 3.03 (dd, J=3.3, 17.0 Hz, 1H), 3.24 (dd, J=8.6, 17.0 Hz, 1H), 4.62–4.80 (m, 1H), 4.89 (d, J=8.2 Hz, 1H), 7.34 (d, J=8.1 Hz, 2H), 7.46 (d, J=8.1 Hz, 2H), 7.54–7.67 (m, 4H), 7.90–8.01 (m, 3H); MS (FAB^+) m/z (%) 368 ($[M+H]^+$, 100), 228 (63), 192 (20), 154 (47), 136 (35), 93 (37); HRMS (FAB^+) calcd for $C_{21}H_{19}ClNOS$: 368.0876, found: 368.0876.

*3.1.13. 2-(2-Phenylethyl)cyclopropanecarbonitrile (**28**).* Compound **28*c***: colorless oil; IR (neat) 3027, 2927, 2235 (CN), 1603, 1497, 1455, 752, 701 cm^{-1}; ^1H NMR δ 0.79 (td, J=5.1, 6.9 Hz, 1H), 1.13 (dt, J=5.1, 8.3 Hz, 1H), 1.24 (qt, J=6.9, 8.3 Hz, 1H), 1.43 (dt, J=5.1, 8.3 Hz, 1H), 1.80–1.89 (m, 2H), 2.71–2.91 (m, 2H), 7.15–7.33 (m, 5H); MS (EI) m/z (%) 171 (M^+, 10), 117 (24), 105 (15), 91 (100), 65 (12); HRMS (EI) calcd for $C_{12}H_{13}N$: 171.1048, found: 171.1049. Compound **28*t***: colorless oil; IR (neat) 3027, 2926, 2236 (CN), 1604, 1497, 1455, 755, 700 cm^{-1}; ^1H NMR δ 0.78 (ddd, J=5.1, 6.4, 8.6 Hz, 1H), 0.99 (td, J=4.8, 8.8 Hz, 1H), 1.18 (td, J=5.0, 8.8 Hz, 1H), 1.40–1.47 (m, 1H), 1.54–1.68 (m, 2H), 2.74 (t, J=7.4 Hz, 2H), 7.15–7.23 (m, 3H), 7.28–7.32 (m, 2H); MS (EI) m/z (%) 171 (M^+, 6), 128 (14), 117 (25), 105 (20), 91 (100), 65 (11); HRMS (EI) calcd for $C_{12}H_{13}N$: 171.1048, found: 171.1050.

*3.1.14. 2-(1-Naphthyl)cyclopropanecarbonitrile (**29**).* Compound **29*c***: colorless crystal; mp 70.0–70.5 °C (hexane/AcOEt); IR (KBr) 3050, 2235 (CN), 1597, 1063, 779 cm^{-1}; ^1H NMR δ 1.68 (dt, J=5.4, 8.5 Hz, 1H), 1.75 (td, J=5.4, 7.2 Hz, 1H), 2.09 (dt, J=5.4, 8.3 Hz, 1H), 2.93 (q, J=7.8 Hz, 1H), 7.40–7.63 (m, 4H), 7.83 (d, J=7.6 Hz, 1H), 7.88–7.92 (m, 1H), 8.20 (d, J=8.5 Hz, 1H); MS (EI) m/z (%) 193 (M^+, 100), 178 (12), 165 (85), 153 (44), 139 (14); HRMS (EI) calcd for $C_{14}H_{11}N$: 193.0891, found: 193.0892. Compound **29*t***: colorless crystal; mp 63.0–63.5 °C (hexane/AcOEt); IR (KBr) 3059, 2236 (CN), 1508, 799, 775 cm^{-1}; ^1H NMR δ 1.51–1.63 (m, 2H), 1.77 (td, J=4.0, 8.9 Hz, 1H), 3.05 (td, J=6.1, 8.8 Hz, 1H), 7.24 (d, J=7.2 Hz, 1H), 7.39 (t, J=7.7 Hz, 1H), 7.52–7.66 (m, 2H), 7.80 (d, J=8.1 Hz, 1H), 7.88 (d, J=7.8 Hz, 1H), 8.25 (d, J=8.1 Hz, 1H); MS (EI) m/z (%) 193 (M^+, 90), 178 (12), 165 (100), 153 (45), 139 (16), 115 (10); HRMS (EI) calcd for $C_{14}H_{11}N$: 193.0891, found: 193.0889.

*3.1.15. 2-Benzoyl-7,10-dioxadispiro[2.2.4.2]dodecane-1-carbonitrile (**30**).* A solution of **9L** (73.6 mg; 0.200 mmol) in THF (1.0 mL) was added dropwise to a solution of isopropylmagnesium chloride (2.0 mol/L solution in Et_2O; 0.50 mL; 1.0 mmol) in THF (3.0 mL) at 0 °C, and the mixture was stirred at that temperature for 30 min. Copper(I) iodide (7.6 mg; 0.040 mmol) was added to the mixture at 0 °C, and the mixture was stirred at that temperature for 5 min. Benzoyl chloride (225 mg; 1.60 mmol) was then added dropwise to the mixture at 0 °C, and the mixture was stirred at that temperature for 60 min. The reaction was quenched with satd aq NH_4Cl (1 mL), and the mixture was extracted with $CHCl_3$ (3×6 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 **30*c*** as colorless crystals (12.6 mg; 0.042 mmol; 21%) and **30*t*** as colorless crystals (25.9 mg; 0.087 mmol; 44%). Compound **30*c***: mp 141.0–142.0 °C (hexane/AcOEt); IR (KBr) 2949, 2925, 2864, 2238 (CN), 1668 (CO), 1594, 1577, 1448, 1412, 1220, 1129, 1098, 1040, 716 cm^{-1}; ^1H NMR δ 1.48–1.59 (m, 1H), 1.64–1.85 (m, 4H), 1.86–1.99 (m, 4H), 2.89 (d, J=7.7 Hz, 1H), 3.88–4.01 (m, 4H), 7.46–7.54 (m, 2H), 7.57–7.65 (m, 1H), 7.92–7.99 (m, 2H); MS (EI) m/z (%) 297 (M^+, 10), 192 (46), 148 (11), 105 (100), 99 (19), 86 (30), 77 (34); HRMS (EI) calcd for $C_{18}H_{19}NO_3$: 297.1365, found: 297.1366. Compound **30*t***: mp 175.0–176.0 °C (hexane/AcOEt); IR (KBr) 3015, 2939, 2234 (CN), 1680 (CO), 1451, 1265, 1212, 1143, 1099, 1030, 903 cm^{-1}; ^1H NMR δ 1.40–1.66 (m, 4H), 1.80–2.16 (m, 4H), 2.46 (d, J=5.2 Hz, 1H), 3.09 (d, J=5.2 Hz, 1H), 3.88–3.99 (m, 4H), 7.47–7.55 (m, 2H), 7.59–7.66 (m, 1H), 7.93–7.99 (m, 2H); MS (EI) m/z (%) 297 (M^+, 9), 192 (65), 140 (10), 105 (100), 99 (30), 86 (31), 77 (33); HRMS (EI) calcd for $C_{18}H_{19}NO_3$: 297.1365, found: 297.1363.

*3.1.16. 2-Benzyl-7,10-dioxadispiro[2.2.4.2]dodecane-1-carbonitrile (**31a**).* Colorless oil (approximately 1:4 mixture of two diastereomers); IR (neat) 2952, 2886, 2231 (CN), 1497, 1455, 1259, 1140, 1104, 1035, 906, 750, 699 cm^{-1}; ^1H NMR δ 1.08 (d, J=5.1 Hz, 0.8H), 1.19–1.27 (m, 0.2H), 1.37 (d, J=8.2 Hz, 0.2H), 1.40–1.98 (m, 8.8H), 2.77 (d, J=7.4 Hz, 1.6H), 2.87 (d, J=7.4 Hz, 0.4H), 3.92–4.01 (m, 4H), 7.17–7.36 (m, 5H); MS (EI) m/z (%) 283 (M^+, 40), 192 (26), 148 (12), 99 (54), 86 (100); HRMS (EI) calcd for $C_{18}H_{21}NO_2$: 283.1572, found: 283.1571.

3.1.17. (1R,3R*)-3-Benzoyl-2,2-bis(2-phenylethyl)cyclopropanecarbonitrile (**31b**).* Colorless crystal; mp 83.0–84.0 °C (hexane/AcOEt); IR (KBr) 3025, 2238 (CN), 1662 (CO), 1596, 1453, 1218, 1020,

749 cm^{-1}; ^1H NMR δ 1.77 (ddd, J=5.1, 10.9, 14.5 Hz, 1H), 1.98 (ddd, J=6.1, 10.7, 14.5 Hz, 1H), 2.06 (ddd, J=5.1, 10.7, 14.5 Hz, 1H), 2.32 (ddd, J=6.3, 10.9, 14.5 Hz, 1H), 2.41 (d, J=5.4 Hz, 1H), 2.37–2.48 (m, 1H), 2.66 (ddd, J=6.1, 10.7, 13.3 Hz, 1H), 2.87 (ddd, J=6.3, 10.9, 13.3 Hz, 1H), 2.96 (ddd, J=5.1, 10.9, 13.3 Hz, 1H), 3.04 (d, J=5.4 Hz, 1H), 6.99–7.06 (m, 2H), 7.10–7.17 (m, 1H), 7.19–7.36 (m, 7H), 7.43–7.51 (m, 2H), 7.56–7.64 (m, 1H), 7.84–7.90 (m, 2H); MS (EI) m/z (%) 379 (M^+, 13), 209 (13), 117 (15), 105 (100), 91 (59), 77 (20); HRMS (EI) calcd for $C_{27}H_{25}NO$: 379.1936, found: 379.1935.

*3.1.18. 2-Benzoylspiro[2.11]tetradecane-1-carbonitrile (**31c**).* Compound *cis*-**31c**: colorless oil; IR (neat) 2930, 2851, 2236 (CN), 1673 (CO), 1470, 1448, 1230 cm^{-1}; ^1H NMR δ 1.08–1.91 (m, 22H), 1.86 (d, J=7.7 Hz, 1H), 2.83 (d, J=7.7 Hz, 1H), 7.46–7.54 (m, 2H), 7.56–7.64 (m, 1H), 7.93–8.00 (m, 2H); MS (EI) m/z (%) 323 (M^+, 3), 218 (4), 120 (8), 105 (100), 77 (14); HRMS (EI) calcd for $C_{22}H_{29}NO$: 323.2249, found: 323.2254. Compound *trans*-**31c**: colorless oil; IR (neat) 2930, 2858, 2239 (CN), 1674 (CO), 1460, 1449, 1232, 1037, 1020, 757 cm^{-1}; ^1H NMR δ 1.04–1.84 (m, 21H), 1.96–2.03 (m, 1H), 2.40 (d, J=5.2 Hz, 1H), 3.00 (d, J=5.2 Hz, 1H), 7.48–7.55 (m, 2H), 7.59–7.65 (m, 1H), 7.95–8.00 (m, 2H); MS (EI) m/z (%) 323 (M^+, 4), 105 (100), 77 (14); HRMS (EI) calcd for $C_{22}H_{29}NO$: 323.2249, found: 323.2249.

*3.1.19. 2-Benzoylspiro[2.14]heptadecane-1-carbonitrile (**31d**).* Compound *cis*-**31d**: colorless oil; IR (neat) 2926, 2857, 2239 (CN), 1674 (CO), 1449, 1223 cm^{-1}; ^1H NMR δ 1.08–1.84 (m, 28H), 1.85 (d, J=7.9 Hz, 1H), 2.82 (d, J=7.9 Hz, 1H), 7.47–7.54 (m, 2H), 7.57–7.64 (m, 1H), 7.93–7.99 (m, 2H); MS (EI) m/z (%) 365 (M^+, 3), 325 (32), 105 (100), 77 (14); HRMS (EI) calcd for $C_{25}H_{35}NO$: 365.2719, found: 365.2718. Compound *trans*-**31d**: colorless oil; IR (neat) 2934, 2863, 2239 (CN), 1673 (CO), 1471, 1449, 1227, 1022, 911 cm^{-1}; ^1H NMR δ 1.02–1.80 (m, 27H), 1.82–1.94 (m, 1H), 2.39 (d, J=5.3 Hz, 1H), 3.00 (d, J=5.3 Hz, 1H), 7.48–7.55 (m, 2H), 7.59–7.66 (m, 1H), 7.94–8.00 (m, 2H); MS m/z (%) 365 (M^+, 4), 105 (100), 77 (11); HRMS (EI) calcd for $C_{25}H_{35}NO$: 365.2719, found: 365.2718.

*3.1.20. 3-Benzoyl-2,2-dimethylcyclopropanecarbonitrile (**31e**).* Compound *cis*-**31e**: colorless crystal; mp 100.5–101.0 °C (hexane/AcOEt); IR (KBr) 3018, 2955, 2237 (CN), 1669 (CO), 1449, 1236, 727 cm^{-1}; ^1H NMR δ 1.34 (s, 3H), 1.46 (s, 3H), 1.87 (d, J=8.0 Hz, 1H), 2.80 (d, J=8.0 Hz, 1H), 7.48–7.53 (m, 2H), 7.58–7.64 (m, 1H), 7.92–7.95 (m, 2H); Anal. Calcd for $C_{13}H_{13}NO$: C, 78.36; H, 6.58; N, 7.03, found: C, 78.13; H, 6.60; N, 7.01. Compound *trans*-**31e**: colorless oil; IR (neat) 2963, 2240 (CN), 1680 (CO), 1450, 1237, 1021, 720 cm^{-1}; ^1H NMR δ 1.13 (s, 3H), 1.60 (s, 3H), 2.39 (d, J=5.3 Hz, 1H), 2.98 (d, J=5.3 Hz, 1H), 7.49–7.54 (m, 2H), 7.60–7.66 (m, 1H), 7.92–7.95 (m, 2H); MS (EI) m/z (%) 199 (M^+, 2), 105 (100), 77 (33), 51 (8); HRMS (EI) calcd for $C_{13}H_{13}NO$: 199.0997, found: 199.1001.

3.1.21. (1R,3R*)-3-Benzyl-2,2-dimethylcyclopropanecarbonitrile (**31f**).* Colorless oil; IR (neat) 2958, 2231 (CN), 1497, 1454, 1382, 1117, 1030, 745, 699 cm^{-1}; ^1H NMR δ 1.03 (d, J=5.3 Hz, 1H), 1.23 (s, 3H), 1.36 (s, 3H), 1.51 (dt, J=5.3, 7.3 Hz, 1H), 2.71 (dd, J=7.8, 15.0 Hz, 1H), 2.79 (dd, J=6.9, 15.0 Hz, 1H), 7.18–7.24 (m, 3H), 7.30–7.35 (m, 2H); MS (EI) m/z (%) 185 (M^+, 11), 170 (3), 143 (3), 91 (100), 77 (4); HRMS (EI) calcd for $C_{13}H_{15}N$: 185.1204, found: 185.1206.

*3.1.22. 4-Chloro-3-methyl-4-(p-tolylsulfinyl)butanenitrile (**33**).* Compound **33L**: colorless crystal; mp 64.5–65.0 °C (hexane/AcOEt); IR (KBr) 2975, 2241 (CN), 1594, 1400, 1085, 1048, 846, 813, 727 cm^{-1}; ^1H NMR δ 1.36 (d, J=6.6 Hz, 3H), 2.45 (s, 3H), 2.49 (dd, J=8.1, 16.8 Hz, 1H), 2.56 (dd, J=7.1, 16.8 Hz, 1H), 3.08–3.22 (m, 1H), 4.45 (d, J=2.4 Hz, 1H), 7.36 (d, J=8.1 Hz, 2H), 7.69 (d, J=8.1 Hz, 2H); Anal. Calcd for $C_{12}H_{14}ClNOS$: C, 56.35; H, 5.52; Cl, 13.86; N, 5.48; S, 12.54, found: C, 56.20; H, 5.52; Cl, 13.80; N, 5.44; S, 12.55. Compound **33P**: colorless crystal; mp 126.0–126.5 °C (hexane/AcOEt); IR (KBr) 2974, 2247 (CN), 1495, 1453, 1376, 1124, 1089, 1059, 813 cm^{-1}; ^1H NMR δ 1.50 (d, J=6.6 Hz, 3H), 2.44 (s, 3H), 2.63–2.82 (m, 3H), 4.31 (d, J=6.6 Hz, 1H), 7.37 (d, J=8.2 Hz, 2H), 7.51 (d, J=8.2 Hz, 2H); Anal. Calcd for $C_{12}H_{14}ClNOS$: C, 56.35; H, 5.52; Cl, 13.86; N, 5.48; S, 12.54, found: C, 56.15; H, 5.45; Cl, 13.73; N, 5.42; S, 12.52.

3.1.23. (1R,2R*,3S*)-2-Benzoyl-3-methylcyclopropanecarbonitrile (**34**).* Yellow oil; IR (neat) 3064, 3040, 2971, 2935, 2241 (CN), 1671 (CO), 1598, 1450, 1413, 1297, 1225, 1069, 1039, 1024, 762, 695 cm^{-1}; ^1H NMR δ 1.48 (d, J=6.3 Hz, 3H), 1.93 (dqd, J=4.9, 6.3, 8.6 Hz, 1H), 2.35 (dd, J=4.9, 8.6 Hz, 1H), 2.92 (t, J=4.9 Hz, 1H), 7.49–7.56 (m, 2H), 7.60–7.67 (m, 1H), 7.97–8.02 (m, 2H); MS (EI) m/z (%) 185 (M^+, 13), 141 (6), 105 (100), 77 (39), 51 (11); HRMS (EI) calcd for $C_{12}H_{11}NO$: 185.0841, found: 185.0843.

3.1.24. (1R,2S*,3R*)-2-Benzoyl-3-methylcyclopropanecarbonitrile (**35**).* Yellow solid; mp 69.5–70.0 °C; IR (KBr) 3070, 2969, 2236 (CN), 1667 (CO), 1450, 1236, 1079, 1055, 990, 952, 797, 706 cm^{-1}; ^1H NMR δ 1.31 (d, J=6.2 Hz, 3H), 1.80 (dd, J=6.2, 8.0 Hz, 1H), 2.25 (sextet, J=6.2 Hz, 1H), 2.89 (dd, J=6.2, 8.0 Hz, 1H), 7.47–7.55 (m, 2H), 7.59–7.66 (m, 1H), 8.00–8.05 (m, 2H); MS (EI) m/z (%) 185 (M^+, 15), 141 (7), 105 (100), 77 (44); HRMS (EI) calcd for $C_{12}H_{11}NO$: 185.0841, found: 185.0845.

3.1.25. (1R,2R*,3R*)-2-Benzoyl-3-methylcyclopropanecarbonitrile (**36**).* Yellow oil; IR (neat) 3062, 2936, 2241 (CN), 1672 (CO), 1597, 1450, 1364, 1282, 1224, 1061, 1017, 700 cm^{-1}; ^1H NMR δ 1.14 (d, J=6.0 Hz, 3H), 2.13 (d of quintets, J=6.0, 9.8 Hz, 1H), 2.23 (dd, J=5.1, 6.0 Hz, 1H), 3.30 (dd, J=5.1, 9.8 Hz, 1H), 7.48–7.56 (m, 2H), 7.60–7.67 (m, 1H), 7.97–8.02 (m, 2H); MS (EI) m/z (%) 185 (M^+, 13), 105 (100), 77 (41), 51 (11); HRMS (EI) calcd for $C_{12}H_{11}NO$: 185.0841, found: 185.0842.

3.1.26. (1R,2S*,3S*)-2-Benzoyl-3-methylcyclopropanecarbonitrile (**37**).* Yellow solid; mp 75.0–76.0 °C; IR (KBr) 3029, 2238 (CN), 1671 (CO), 1595, 1447, 1395, 1228, 1057, 995, 721, 690 cm^{-1}; ^1H NMR δ 1.36 (d, J=6.3 Hz, 3H), 2.01 (qdd, J=6.3, 8.1, 9.0 Hz, 1H), 2.12 (t, J=8.1 Hz, 1H), 3.04 (dd, J=8.1, 9.0 Hz, 1H), 7.47–7.54 (m, 2H), 7.57–7.65 (m, 1H), 7.96–8.02 (m, 2H); MS (EI) m/z (%) 185 (M^+, 11), 105 (100), 77 (45), 51 (12); HRMS (EI) calcd for $C_{12}H_{11}NO$: 185.0841, found: 185.0839.

3.1.27. (1R,2R*,3R*)-2-Benzoyl-3-(2-phenylethyl)cyclopropanecarbonitrile (**38a**).* Yellow oil; IR (neat) 3028, 2242 (CN), 1674 (CO), 1597, 1450, 1226, 1018, 755, 699 cm^{-1}; ^1H NMR δ 1.66–1.88 (m, 2H), 2.05 (dtd, J=6.1, 7.2, 9.7 Hz, 1H), 2.23 (dd, J=5.0, 6.1 Hz, 1H), 2.59 (t, J=7.4 Hz, 2H), 3.29 (dd, J=5.0, 9.7 Hz, 1H), 7.05–7.27 (m, 5H), 7.47–7.54 (m, 2H), 7.59–7.66 (m, 1H), 7.95–8.00 (m, 2H); MS (EI) m/z (%) 275 (M^+, 34), 209 (58), 171 (44), 144 (60), 120 (57), 105 (86), 91 (100), 77 (70); HRMS (EI) calcd for $C_{19}H_{17}NO$: 275.1310, found: 275.1313.

3.1.28. (1R,2S*,3S*)-2-Benzoyl-3-(2-phenylethyl)cyclopropanecarbonitrile (**38b**).* Yellow amorphous; IR (KBr) 3038, 2922, 2239 (CN), 1671 (CO), 1596, 1448, 1398, 1235, 1217, 980, 722 cm^{-1}; ^1H NMR δ 1.84–1.95 (m, 1H), 2.02–2.20 (m, 3H), 2.60–2.79 (m, 2H), 3.05 (dd, J=8.0, 9.2 Hz, 1H), 7.10–7.28 (m, 5H), 7.46–7.52 (m, 2H), 7.57–7.64 (m, 1H), 7.94–8.00 (m, 2H); MS (EI) m/z (%) 275 (M^+, 54), 209 (55), 171 (51), 155 (25), 144 (73), 120 (50), 105 (100), 91 (95), 77 (84), 65 (22); HRMS (EI) calcd for $C_{19}H_{17}NO$: 275.1310, found: 275.1310.

3.1.29. (1R,2R*,3S*)-2-Benzoyl-3-(2-phenylethyl)cyclopropanecarbonitrile (**38c**).* Colorless solid; mp 72.0–73.0 °C; IR (KBr) 3067,

3023, 2240 (CN), 1667 (CO), 1596, 1449, 1248, 1222, 1073, 1039, 1026, 1008, 741, 697 cm^{-1}; ^1H NMR δ 1.83–2.19 (m, 3H), 2.31 (dd, J=4.7, 8.5 Hz, 1H), 2.78 (td, J=7.7, 13.8 Hz, 1H), 2.85 (t, J=4.7 Hz, 1H), 2.93 (ddd, J=5.9, 7.7, 13.8 Hz, 1H), 7.10–7.27 (m, 5H), 7.44–7.52 (m, 2H), 7.59–7.66 (m, 1H), 7.81–7.86 (m, 2H); MS (EI) m/z (%) 275 (M^+, 26), 170 (18), 105 (100), 91 (75), 77 (44); HRMS (EI) calcd for $C_{19}H_{17}NO$: 275.1310, found: 275.1309.

3.1.30. (1R,2S*,3R*)-2-Benzoyl-3-(2-phenylethyl)cyclopropanecarbonitrile (**38d**).* Yellow amorphous; IR (KBr) 3031, 2920, 2237 (CN), 1662 (CO), 1597, 1450, 1232, 995, 718, 690 cm^{-1}; ^1H NMR δ 1.70 (dd, J=6.3, 8.0 Hz, 1H), 1.73–1.97 (m, 2H), 2.25 (quintet, J=6.3 Hz, 1H), 2.74 (dd, J=6.3, 8.0 Hz, 1H), 2.70–2.87 (m, 2H), 7.11–7.18 (m, 3H), 7.20–7.27 (m, 2H), 7.44–7.51 (m, 2H), 7.57–7.64 (m, 1H), 7.85–7.91 (m, 2H); MS (EI) m/z (%) 275 (M^+, 16), 209 (7), 170 (10), 120 (12), 105 (100), 91 (48), 77 (38), 65 (9); HRMS (EI) calcd for $C_{19}H_{17}NO$: 275.1310, found: 275.1315.

3.1.31. (1R,2R*,3R*)-2-Benzoyl-3-(1-naphthyl)cyclopropanecarbonitrile (**38e**).* Colorless crystal; mp 158.5–159.0 °C (hexane/AcOEt); IR (KBr) 3047, 2242 (CN), 1661 (CO), 1596, 1450, 1228, 1019, 802, 780, 702 cm^{-1}; ^1H NMR δ 3.13 (dd, J=4.9, 6.7 Hz, 1H), 3.72 (dd, J=6.7, 9.7 Hz, 1H), 3.95 (dd, J=4.9, 9.7 Hz, 1H), 7.30–7.45 (m, 6H), 7.52–7.58 (m, 1H), 7.73–7.81 (m, 2H), 7.86–7.90 (m, 2H), 7.99–8.03 (m, 1H); MS (EI) m/z (%) 297 (M^+, 7), 105 (100), 77 (25); HRMS (EI) calcd for $C_{21}H_{15}NO$: 297.1154, found: 297.1147.

3.1.32. (1R,2R*,3S*)-2-Benzoyl-3-(1-naphthyl)cyclopropanecarbonitrile (**38f**).* Colorless crystal; mp 177.0–178.0 °C (hexane/AcOEt); IR (KBr) 3044, 2242 (CN), 1669 (CO), 1596, 1450, 1295, 1229, 1017, 805, 780, 696 cm^{-1}; ^1H NMR δ 2.89 (dd, J=4.7, 8.8 Hz, 1H), 3.53 (dd, J=6.1, 8.8 Hz, 1H), 3.77 (dd, J=4.7, 6.1 Hz, 1H), 7.47–7.62 (m, 6H), 7.67–7.74 (m, 1H), 7.86–7.94 (m, 2H), 8.07–8.18 (m, 3H); MS (EI) m/z (%) 297 (M^+, 7), 190 (7), 165 (6), 105 (100), 77 (25); HRMS (EI) calcd for $C_{21}H_{15}NO$: 297.1154, found: 297.1153.

3.1.33. (1R,2S*,3R*)-2-Benzoyl-3-(1-naphthyl)cyclopropanecarbonitrile (**38g**).* Colorless crystal; mp 166.0–166.5 °C (hexane/AcOEt); IR (KBr) 3060, 2242 (CN), 1662 (CO), 1596, 1449, 1393, 1359, 1229, 1054, 999, 801, 780, 727, 681 cm^{-1}; ^1H NMR δ 2.48 (dd, J=6.4, 8.4 Hz, 1H), 3.43 (dd, J=6.4, 8.4 Hz, 1H), 3.88 (t, J=6.4 Hz, 1H), 7.32 (d, J=7.2 Hz, 1H), 7.44 (dd, J=7.2, 8.1 Hz, 1H), 7.51–7.60 (m, 4H), 7.63–7.70 (m, 1H), 7.85 (d, J=8.1 Hz, 1H), 7.88–7.92 (m, 1H), 8.04–8.14 (m, 3H); MS (EI) m/z (%) 297 (M^+, 6), 190 (7), 165 (7), 105 (100), 77 (25); HRMS (EI) calcd for $C_{21}H_{15}NO$: 297.1154, found: 297.1167.

*3.1.34. 2-{8-[Chloro-(p-tolylsulfinyl)methyl]-1,4-dioxaspiro[4.5]decan-8-yl}propanenitrile (**39**).* A solution of BuLi in hexane (1.66 mol/L; 7.20 mL; 12 mmol) was added to a solution of diisopropylamine (1.25 g; 12.3 mmol) in THF (50 mL) at 0 °C, and the mixture was stirred at 0 °C for 10 min. Propionitrile (0.730 g; 12.3 mmol) was added dropwise to the resulting solution at −78 °C, and the mixture was stirred at that temperature for 10 min. A solution of **8** (981 mg; 3.00 mmol) in THF (10 mL) was added dropwise to the mixture at −78 °C, and the reaction mixture was stirred at that temperature for 20 min. The reaction was quenched with satd aq NH_4Cl (20 mL), and the mixture was extracted with $CHCl_3$ (3×30 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 **39a** (360 mg; 0.94 mmol; 31%), **39b** (277 mg; 0.72 mmol; 24%), **39c** (337 mg; 0.88 mmol; 29%), and **39d** (142 mg; 0.37 mmol; 12%). Compound **39a**: colorless crystal; mp 111.5–112.0 °C (hexane/AcOEt); IR (KBr) 2958, 2888, 2241 (CN), 1595, 1106, 1051, 946, 883, 812 cm^{-1}; ^1H NMR δ 1.54 (dt, J=3.9, 13.4 Hz, 1H), 1.62 (d, J=7.3 Hz, 3H), 1.65–1.74 (m, 1H), 1.78–1.85 (m, 2H), 1.97 (dt, J=4.0, 13.4 Hz, 1H), 2.12–2.25 (m, 2H), 2.45 (s, 3H), 2.59–2.69 (m, 1H), 3.70 (q, J=7.3 Hz, 1H), 3.90–4.00 (m, 4H), 4.79 (s, 1H), 7.35 (d, J=8.1 Hz, 2H), 7.71 (d, J=8.1 Hz, 2H); Anal. Calcd for $C_{19}H_{24}ClNO_3S$: C, 59.75; H, 6.33; Cl, 9.28; N, 3.67; S, 8.40, found: C, 59.78; H, 6.21; Cl, 9.29; N, 3.60; S, 8.43. Compound **39b**: colorless crystal; mp 146.5–147.5 °C (hexane/AcOEt); IR (KBr) 2956, 2941, 2235 (CN), 1446, 1088, 1065, 1034, 810 cm^{-1}; ^1H NMR δ 1.53 (d, J=7.2 Hz, 3H), 1.56–1.82 (m, 4H), 1.97 (ddd, J=4.0, 11.3, 14.2 Hz, 1H), 2.23–2.35 (m, 3H), 2.44 (s, 3H), 3.44 (q, J=7.2 Hz, 1H), 3.93–3.98 (m, 4H), 4.58 (s, 1H), 7.36 (d, J=8.1 Hz, 2H), 7.46 (d, J=8.1 Hz, 2H); Anal. Calcd for $C_{19}H_{24}ClNO_3S$: C, 59.75; H, 6.33; Cl, 9.28; N, 3.67; S, 8.40, found: C, 59.68; H, 6.22; Cl, 9.26; N, 3.58; S, 8.39. Compound **39c**: colorless crystal; mp 169.0–170.0 °C (hexane/AcOEt); IR (KBr) 2949, 2866, 2239 (CN), 1450, 1104, 1083, 1049, 955, 810 cm^{-1}; ^1H NMR δ 1.54 (d, J=7.2 Hz, 3H), 1.63–1.84 (m, 3H), 1.85–1.97 (m, 2H), 2.09 (ddd, J=4.1, 10.7, 13.8 Hz, 1H), 2.27–2.36 (m, 1H), 2.45 (s, 3H), 2.56–2.65 (m, 1H), 3.46 (q, J=7.2 Hz, 1H), 3.94–3.99 (m, 4H), 4.69 (s, 1H), 7.35 (d, J=8.2 Hz, 2H), 7.71 (d, J=8.2 Hz, 2H); Anal. Calcd for $C_{19}H_{24}ClNO_3S$: C, 59.75; H, 6.33; Cl, 9.28; N, 3.67; S, 8.40, found: C, 59.69; H, 6.22; Cl, 9.23; N, 3.61; S, 8.32. Compound **39d**: colorless crystal; mp 205.0–205.5 °C (hexane/AcOEt); IR (KBr) 2956, 2881, 2239 (CN), 1449, 1110, 1088, 1060, 813 cm^{-1}; ^1H NMR δ 1.53 (d, J=7.3 Hz, 3H), 1.62–1.79 (m, 4H), 1.86–1.97 (m, 1H), 2.06–2.17 (m, 1H), 2.23–2.38 (m, 2H), 2.43 (s, 3H), 3.38 (q, J=7.3 Hz, 1H), 3.94–4.00 (m, 4H), 4.46 (s, 1H), 7.35 (d, J=8.2 Hz, 2H), 7.51 (d, J=8.2 Hz, 2H); Anal. Calcd for $C_{19}H_{24}ClNO_3S$: C, 59.75; H, 6.33; Cl, 9.28; N, 3.67; S, 8.40, found: C, 59.71; H, 6.45; Cl, 9.14; N, 3.62; S, 8.30.

*3.1.35. 1-Methyl-7,10-dioxadispiro[2.2.4.2]dodecane-1-carbonitrile (**40**).* Colorless oil; IR (neat) 2952, 2230 (CN), 1442, 1269, 1144, 1113, 1083, 1035, 906 cm^{-1}; ^1H NMR δ 0.67 (d, J=5.1 Hz, 1H), 1.12 (d, J=5.1 Hz, 1H), 1.43 (s, 3H), 1.60–1.84 (m, 8H), 3.94–4.00 (m, 4H); MS (EI) m/z (%) 207 (M^+, 67), 162 (22), 140 (55), 125 (58), 99 (49), 86 (100); HRMS (EI) calcd for $C_{12}H_{17}NO_2$: 207.1259, found: 207.1264.

*3.1.36. 2-{8-[Chloro(p-tolylsulfinyl)methyl]-1,4-dioxaspiro[4.5]decan-8-yl}-2-phenylacetonitrile (**41**).* A solution of BuLi in hexane (1.66 mol/L; 1.80 mL; 3.0 mmol) was added to a solution of diisopropylamine (314 mg; 3.10 mmol) in THF (16 mL) at 0 °C, and the mixture was stirred at that temperature for 10 min. Phenylacetonitrile (363 mg; 3.10 mmol) was added dropwise to the resulting solution at −78 °C, and the mixture was stirred at that temperature for 10 min. A solution of **8** (327 mg; 1.00 mmol) in THF (4 mL) was added to the mixture at −78 °C, and the mixture was stirred at that temperature for 30 min. The reaction was quenched with satd aq NH_4Cl (10 mL), and the mixture was extracted with $CHCl_3$ (3×20 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/1,4-dioxane as the eluent to give (2R*)-2-{8-[(S*)-chloro((R_S*)-p-tolylsulfinyl)methyl]-1,4-dioxaspiro[4.5]decan-8-yl}-2-phenylacetonitrile **41L** as colorless crystals (less polar adduct; 293 mg; 0.66 mmol; 66%) and (2R*)-2-{8-[(R*)-chloro((R_S*)-p-tolylsulfinyl)methyl]-1,4-dioxaspiro[4.5]decan-8-yl}-2-phenylacetonitrile **41P** as colorless crystals (more polar adduct; 89 mg; 0.20 mmol; 20%). Compound **41L**: mp 169.0–169.5 °C (hexane/AcOEt); IR (KBr) 2965, 2941, 2890, 2236 (CN), 1595, 1492, 1455, 1375, 1261, 1195, 1158, 1111, 1081, 1047, 953, 940 cm^{-1}; ^1H NMR δ 1.62–1.72 (m, 1H), 1.73–1.79 (m, 2H), 1.86–2.04 (m, 3H), 2.35–2.42 (m, 1H), 2.44 (s, 3H), 2.59–2.65 (m, 1H), 3.88–3.94 (m, 4H), 4.63 (s, 1H), 4.65 (br s, 1H), 7.32 (d, J=8.3 Hz, 2H), 7.40–7.50 (m, 5H), 7.61 (d, J=8.3 Hz, 2H); Anal. Calcd for $C_{24}H_{26}ClNO_3S$: C, 64.92; H, 5.90; Cl, 7.99; N, 3.15; S, 7.22, found: C, 64.95; H, 5.79; Cl, 8.03; N, 3.16; S, 7.15. Compound **41P**: mp 193.5–194.0 °C (hexane/AcOEt); IR (KBr) 2968, 2898, 2234 (CN), 1599, 1495, 1456, 1379, 1157, 1103, 1066, 886, 814 cm^{-1};

^{1}H NMR δ 1.53–1.61 (m, 3H), 1.74 (ddd, J=4.4, 11.2, 14.0 Hz, 1H), 1.85–1.96 (m, 2H), 2.31 (ddd, J=4.3, 11.2, 14.6 Hz, 1H), 2.43 (s, 3H), 2.67–2.70 (m, 1H), 3.87–3.95 (m, 4H), 4.53 (s, 1H), 4.61 (s, 1H), 7.33–7.46 (m, 9H); Anal. Calcd for $C_{24}H_{26}ClNO_3S$: C, 64.92; H, 5.90; Cl, 7.99; N, 3.15; S, 7.22, found: C, 64.81; H, 5.87; Cl, 7.91; N, 3.14; S, 7.15.

3.1.37. (1R,2R*)-2-Phenyl-7,10-dioxadispiro[2.2.4.2]dodecane-1-carbonitrile (**43**).* Colorless oil; IR (neat) 2952, 2886, 2232 (CN), 1499, 1447, 1138, 1092, 1035, 921, 739, 702 cm^{-1}; ^{1}H NMR δ 1.31–1.41 (m, 2H), 1.69 (d, J=8.6 Hz, 1H), 1.71–1.88 (m, 5H), 2.16 (ddd, J=4.6, 11.2, 13.0 Hz, 1H), 2.47 (d, J=8.6 Hz, 1H), 3.94–4.02 (m, 4H), 7.24–7.29 (m, 1H), 7.32–7.39 (m, 4H); MS (EI) m/z (%) 269 (M^+, 45), 241 (12), 140 (25), 125 (16), 115 (10), 99 (84), 86 (100); HRMS (EI) calcd for $C_{17}H_{19}NO_2$: 269.1416, found: 269.1415.

3.1.38. (1R,2S*)-2-Phenyl-7,10-dioxadispiro[2.2.4.2]dodecane-1-carbonitrile (**44**).* Colorless crystal; mp 114.0–114.5 °C (hexane/AcOEt); IR (KBr) 2952, 2231 (CN), 1441, 1262, 1126, 1088, 1034, 907, 705 cm^{-1}; ^{1}H NMR δ 1.17 (td, J=6.0, 12.6 Hz, 1H), 1.43 (td, J=6.8, 13.7 Hz, 1H), 1.49–1.56 (m, 2H), 1.73 (d, J=5.5 Hz, 1H), 1.82–1.94 (m, 3H), 1.99–2.05 (m, 1H), 2.62 (d, J=5.5 Hz, 1H), 3.89–3.99 (m, 4H), 7.16 (d, J=7.4 Hz, 2H), 7.24–7.34 (m, 3H); MS (EI) m/z (%) 269 (M^+, 42), 140 (27), 125 (18), 99 (78), 86 (100); HRMS (EI) calcd for $C_{17}H_{19}NO_2$: 269.1416, found: 269.1415.

3.1.39. (2R)-2-{8-[(S*)-Chloro((R$_S$*)-p-tolylsulfinyl)methyl]-1,4-dioxaspiro[4.5]decan-8-yl}-2-(p-tolyl)acetonitrile (**46aL**).* Yield (79%); colorless crystal; mp 162.5–163.0 °C (hexane/AcOEt); IR (KBr) 2934, 2868, 2231 (CN), 1514, 1455, 1375, 1155, 1105, 1081, 1058, 1036, 933, 813 cm^{-1}; ^{1}H NMR δ 1.62–1.70 (m, 1H), 1.72–1.80 (m, 2H), 1.85–2.02 (m, 3H), 2.30–2.50 (m, 1H), 2.38 (s, 3H), 2.44 (s, 3H), 2.56–2.66 (m, 1H), 3.85–3.97 (m, 4H), 4.59 (s, 1H), 4.64 (br s, 1H), 7.22 (d, J=8.0 Hz, 2H), 7.32 (d, J=7.9 Hz, 2H), 7.36 (d, J=7.9 Hz, 2H), 7.61 (d, J=8.0 Hz, 2H); Anal. Calcd for $C_{25}H_{28}ClNO_3S$: C, 65.56; H, 6.16; Cl, 7.74; N, 3.06; S, 7.00, found: C, 65.44; H, 6.08; Cl, 7.85; N, 3.05; S, 6.92.

3.1.40. (2R)-2-{8-[(R*)-Chloro((R$_S$*)-p-tolylsulfinyl)methyl]-1,4-dioxaspiro[4.5]decan-8-yl}-2-(p-tolyl)acetonitrile (**46aP**).* Yield (20%); colorless crystal; mp 174.5–175.0 °C (hexane/AcOEt); IR (KBr) 2953, 2936, 2884, 2234 (CN), 1453, 1161, 1086, 1058, 936, 811 cm^{-1}; ^{1}H NMR δ 1.50–1.63 (m, 3H), 1.74 (ddd, J=4.2, 10.9, 14.1 Hz, 1H), 1.84–1.96 (m, 2H), 2.27 (ddd, J=4.1, 11.2, 14.5 Hz, 1H), 2.37 (s, 3H), 2.43 (s, 3H), 2.62–2.70 (m, 1H), 3.85–3.98 (m, 4H), 4.52 (s, 1H), 4.57 (s, 1H), 7.19 (d, J=8.0 Hz, 2H), 7.31 (d, J=8.0 Hz, 2H), 7.34 (d, J=8.0 Hz, 2H), 7.46 (d, J=8.0 Hz, 2H); Anal. Calcd for $C_{25}H_{28}ClNO_3S$: C, 65.56; H, 6.16; Cl, 7.74; N, 3.06; S, 7.00, found: C, 65.20; H, 6.14; Cl, 7.82; N, 3.02; S, 6.86.

3.1.41. (2R)-2-{8-[(S*)-Chloro((R$_S$*)-p-tolylsulfinyl)methyl]-1,4-dioxaspiro[4.5]decan-8-yl}-2-(4-methoxyphenyl)acetonitrile (**46bL**).* Yield (64%); colorless crystal; mp 151.0–151.5 °C (hexane/AcOEt); IR (KBr) 2942, 2232 (CN), 1734, 1611, 1512, 1257, 1180, 1103, 1054, 932, 837, 815 cm^{-1}; ^{1}H NMR δ 1.66 (ddd, J=3.7, 11.2, 14.9 Hz, 1H), 1.72–1.79 (m, 2H), 1.90 (dt, J=3.8, 12.9 Hz, 1H), 1.98 (ddd, J=4.0, 12.0, 13.7 Hz, 2H), 2.30–2.40 (m, 1H), 2.43 (s, 3H), 2.60–2.66 (m, 1H), 3.84 (s, 3H), 3.89–3.95 (m, 4H), 4.56 (s, 1H), 4.65 (br s, 1H), 6.94 (d, J=8.7 Hz, 2H), 7.31 (d, J=8.2 Hz, 2H), 7.39 (d, J=8.7 Hz, 2H), 7.61 (d, J=8.2 Hz, 2H); Anal. Calcd for $C_{25}H_{28}ClNO_4S$: C, 63.35; H, 5.95; Cl, 7.48; N, 2.95; S, 6.76, found: C, 62.82; H, 5.87; Cl, 7.34; N, 2.96; S, 6.67.

3.1.42. (2R)-2-{8-[(R*)-Chloro((R$_S$*)-p-tolylsulfinyl)methyl]-1,4-dioxaspiro[4.5]decan-8-yl}-2-(4-methoxyphenyl)acetonitrile (**46bP**).* Yield (32%); colorless crystal; mp 162.0–162.5 °C (hexane/AcOEt); IR (KBr) 2917, 2234 (CN), 1610, 1513, 1255, 1098, 1085, 1057, 1031, 952, 843 cm^{-1}; ^{1}H NMR δ 1.50–1.64 (m, 3H), 1.73 (ddd, J=4.4, 11.2, 14.0 Hz, 1H), 1.82–1.96 (m, 2H), 2.28 (ddd, J=4.2, 11.0, 14.4 Hz, 1H), 2.43 (s, 3H), 2.60–2.70 (m, 1H), 3.82 (s, 3H), 3.87–3.96 (m, 4H), 4.52 (s, 1H), 4.56 (s, 1H), 6.90 (d, J=8.8 Hz, 2H), 7.34 (d, J=8.1 Hz, 2H), 7.35 (d, J=8.8 Hz, 2H), 7.46 (d, J=8.1 Hz, 2H); Anal. Calcd for $C_{25}H_{28}ClNO_4S$: C, 63.35; H, 5.95; Cl, 7.48; N, 2.95; S, 6.76, found: C, 62.94; H, 5.89; Cl, 7.40; N, 2.97; S, 6.72.

3.1.43. (2R)-2-{8-[(S*)-Chloro((R$_S$*)-p-tolylsulfinyl)methyl]-1,4-dioxaspiro[4.5]decan-8-yl}-2-(4-fluorophenyl)acetonitrile (**46cL**).* Yield (60%); colorless crystal; mp 160.5–161.0 °C (hexane/AcOEt); IR (KBr) 2935, 2237 (CN), 1600, 1509, 1240, 1158, 1079, 933, 841, 814 cm^{-1}; ^{1}H NMR δ 1.54–2.01 (m, 6H), 2.31–2.41 (m, 1H), 2.44 (s, 3H), 2.60–2.69 (m, 1H), 3.86–3.97 (m, 4H), 4.64 (s, 1H), 4.68 (br s, 1H), 7.13 (t, J=8.6 Hz, 2H), 7.33 (d, J=8.2 Hz, 2H), 7.47 (dd, J=5.1, 8.6 Hz, 2H), 7.62 (d, J=8.2 Hz, 2H); Anal. Calcd for $C_{24}H_{25}ClFNO_3S$: C, 62.40; H, 5.45; Cl, 7.67; F, 4.11; N, 3.03; S, 6.94, found: C, 62.24; H, 5.35; Cl, 7.67; F, 4.15; N, 3.00; S, 6.86.

3.1.44. (2R)-2-{8-[(R*)-Chloro((R$_S$*)-p-tolylsulfinyl)methyl]-1,4-dioxaspiro[4.5]decan-8-yl}-2-(4-fluorophenyl)acetonitrile (**46cP**).* Yield (20%); colorless crystal; mp 164.0–164.5 °C (hexane/AcOEt); IR (KBr) 2967, 2239 (CN), 1606, 1509, 1239, 1158, 1104, 1066, 1034, 942, 885, 832, 813 cm^{-1}; ^{1}H NMR δ 1.43–1.58 (m, 3H), 1.71 (ddd, J=4.3, 12.1, 14.1 Hz, 1H), 1.78–1.99 (m, 2H), 2.36 (ddd, J=4.4, 12.1, 14.5 Hz, 1H), 2.44 (s, 3H), 2.64–2.76 (m, 1H), 3.86–3.98 (m, 4H), 4.58 (s, 1H), 4.63 (s, 1H), 7.07 (t, J=8.6 Hz, 2H), 7.35 (d, J=8.3 Hz, 2H), 7.44 (dd, J=5.2, 8.6 Hz, 2H), 7.48 (d, J=8.3 Hz, 2H); Anal. Calcd for $C_{24}H_{25}ClFNO_3S$: C, 62.40; H, 5.45; Cl, 7.67; F, 4.11; N, 3.03; S, 6.94, found: C, 62.09; H, 5.41; Cl, 7.59; F, 4.16; N, 3.01; S, 6.86.

3.1.45. (2R)-2-{8-[(S*)-Chloro((R$_S$*)-p-tolylsulfinyl)methyl]-1,4-dioxaspiro[4.5]decan-8-yl}-2-(4-chlorophenyl)acetonitrile (**46dL**).* 4-Chloroacetonitrile (5 equiv) and LDA (5 equiv) were used. Yield (36%); colorless crystal; mp 122.0–122.5 °C (hexane/AcOEt); IR (KBr) 2938, 2233 (CN), 1742, 1596, 1489, 1375, 1242, 1155, 1095, 1056, 810 cm^{-1}; ^{1}H NMR δ 1.62–2.00 (m, 6H), 2.32–2.42 (m, 1H), 2.44 (s, 3H), 2.55–2.71 (m, 1H), 3.85–3.96 (m, 4H), 4.65 (s, 1H), 4.68 (br s, 1H), 7.34 (d, J=8.1 Hz, 2H), 7.38–7.46 (m, 4H), 7.63 (d, J=8.1 Hz, 2H); MS (FAB$^+$) m/z (%) 478 ([M+H]$^+$, 60), 338 (12), 246 (23), 154 (71), 93 (100); HRMS (FAB$^+$) calcd for $C_{24}H_{26}Cl_2NO_3S$: 478.1010, found: 478.1011.

3.1.46. (2R)-2-{8-[(R*)-Chloro((R$_S$*)-p-tolylsulfinyl)methyl]-1,4-dioxaspiro[4.5]decan-8-yl}-2-(4-chlorophenyl)acetonitrile (**46dP**).* Yield (12%); colorless crystal; mp 126.5–127.0 °C (hexane/AcOEt); IR (KBr) 2945, 2242 (CN), 1592, 1490, 1155, 1092, 1016, 836, 806 cm^{-1}; ^{1}H NMR δ 1.44–1.60 (m, 3H), 1.71 (ddd, J=4.3, 12.3, 14.1 Hz, 1H), 1.77–1.86 (m, 1H), 1.87–1.98 (m, 1H), 2.37 (ddd, J=4.4, 12.3, 14.6 Hz, 1H), 2.44 (s, 3H), 2.67–2.78 (m, 1H), 3.86–3.98 (m, 4H), 4.59 (s, 1H), 4.63 (s, 1H), 7.32–7.43 (m, 6H), 7.48 (d, J=8.2 Hz, 2H); MS (FAB$^+$) m/z (%) 478 ([M+H]$^+$, 100), 246 (11), 185 (33), 154 (36), 93 (50); HRMS (FAB$^+$) calcd for $C_{24}H_{26}Cl_2NO_3S$: 478.1010, found: 478.1010.

3.1.47. (2R)-2-{8-[(S*)-Chloro((R$_S$*)-p-tolylsulfinyl)methyl]-1,4-dioxaspiro[4.5]decan-8-yl}-2-(2-naphthyl)acetonitrile (**46eL**).* (2-Naphthyl)acetonitrile (5 equiv) and LDA (5 equiv) were used. Yield (45%); colorless crystal; mp 118.0–118.5 °C (hexane/AcOEt); IR (KBr) 2939, 2230 (CN), 1598, 1494, 1452, 1375, 1156, 1102, 1056, 814, 743 cm^{-1}; ^{1}H NMR δ 1.63–2.13 (m, 6H), 2.40–2.51 (m, 1H), 2.43 (s, 3H), 2.60–2.74 (m, 1H), 3.82–3.94 (m, 4H), 4.72 (br s, 1H), 4.84 (s, 1H), 7.30 (d, J=8.1 Hz, 2H), 7.52–7.57 (m, 3H), 7.59 (d, J=8.1 Hz, 2H), 7.86–7.96 (m, 4H); MS (FAB$^+$) m/z (%) 494 ([M+H]$^+$, 60), 354 (13),

318 (10), 219 (12), 185 (30), 160 (100), 137 (51), 93 (62); HRMS (FAB^+) calcd for $C_{28}H_{29}ClNO_3S$: 494.1557, found: 494.1556.

3.1.48. (2R)-2-{8-[(R*)-Chloro((R$_S$*)-p-tolylsulfinyl)methyl]-1,4-dioxaspiro[4.5]decan-8-yl}-2-(2-naphthyl)acetonitrile (**46eP**).* Yield (15%); colorless crystal; mp 103.5–104.0 °C (hexane/AcOEt); IR (KBr) 2954, 2235 (CN), 1742, 1597, 1448, 1217, 1153, 1090, 1063, 813, 757 cm^{-1}; ^1H NMR δ 1.49–1.62 (m, 3H), 1.76 (ddd, *J*=4.2, 11.2, 14.2 Hz, 1H), 1.85–2.03 (m, 2H), 2.32–2.46 (m, 1H), 2.42 (s, 3H), 2.70–2.83 (m, 1H), 3.80–3.96 (m, 4H), 4.59 (s, 1H), 4.80 (s, 1H), 7.32 (d, *J*=8.1 Hz, 2H), 7.47 (d, *J*=8.1 Hz, 2H), 7.49–7.57 (m, 3H), 7.82–7.95 (m, 4H); MS (FAB^+) *m*/*z* (%) 494 ($[M+H]^+$, 60), 354 (10), 318 (10), 166 (100), 154 (51), 99 (15), 93 (21); HRMS (FAB^+) calcd for $C_{28}H_{29}ClNO_3S$: 494.1557, found: 494.1558.

*3.1.49. 4-Chloro-2-(4-methoxyphenyl)-3,3-dimethyl-4-(p-tolylsulfinyl)butanenitrile (**46f**).* Compound **46fL**: Yield (88%); colorless crystal; mp 126.0–126.5 °C (hexane/AcOEt); IR (KBr) 2974, 2232 (CN), 1610, 1512, 1258, 1081, 1038, 844, 739 cm^{-1}; ^1H NMR δ 1.28 (s, 3H), 1.69 (s, 3H), 2.43 (s, 3H), 3.84 (s, 3H), 4.45 (s, 1H), 4.94 (s, 1H), 6.94 (d, *J*=8.6 Hz, 2H), 7.33 (d, *J*=8.0 Hz, 2H), 7.50 (d, *J*=8.6 Hz, 2H), 7.73 (d, *J*=8.0 Hz, 2H); MS (EI) *m*/*z* (%) 375 (M^+, 4), 200 (16), 146 (100), 140 (32); HRMS (EI) calcd for $C_{20}H_{22}ClNO_2S$: 375.1060, found: 375.1050. Compound **46fP**: Yield (11%); colorless crystal; mp 132.5–133.0 °C (hexane/AcOEt); IR (KBr) 2996, 2233 (CN), 1614, 1514, 1460, 1252, 1181, 1086, 1060, 820 cm^{-1}; ^1H NMR δ 1.43 (s, 3H), 1.47 (s, 3H), 2.42 (s, 3H), 3.83 (s, 3H), 4.06 (s, 1H), 4.30 (s, 1H), 6.90 (d, *J*=8.8 Hz, 2H), 7.27–7.34 (m, 4H), 7.37–7.42 (m, 2H); MS (EI) *m*/*z* (%) 375 (M^+, 4), 200 (16), 146 (100), 140 (12); HRMS (EI) calcd for $C_{20}H_{22}ClNO_2S$: 375.1060, found: 375.1064.

3.1.50. (1R,2R*)-2-(p-Tolyl)-7,10-dioxadispiro[2.2.4.2]dodecane-1-carbonitrile (**47a**).* Colorless oil; IR (neat) 2952, 2885, 2232 (CN), 1518, 1138, 1094, 1036, 921, 756 cm^{-1}; ^1H NMR δ 1.30–1.36 (m, 1H), 1.38 (dtd, *J*=1.9, 4.7, 13.9 Hz, 1H), 1.66 (d, *J*=8.5 Hz, 1H), 1.70–1.87 (m, 5H), 2.08 (ddd, *J*=4.5, 10.9, 13.4 Hz, 1H), 2.33 (s, 3H), 2.43 (d, *J*=8.5 Hz, 1H), 3.94–4.00 (m, 4H), 7.14 (d, *J*=8.0 Hz, 2H), 7.26 (d, *J*=8.0 Hz, 2H); MS (EI) *m*/*z* (%) 283 (M^+, 38), 255 (16), 189 (14), 140 (20), 99 (100), 86 (84); HRMS (EI) calcd for $C_{18}H_{21}NO_2$: 283.1572, found: 283.1577.

3.1.51. (1R,2S*)-2-(p-Tolyl)-7,10-dioxadispiro[2.2.4.2]dodecane-1-carbonitrile (**48a**).* Colorless crystal; mp 92.0–92.5 °C (hexane); IR (KBr) 2950, 2882, 2232 (CN), 1518, 1445, 1258, 1138, 1093, 1034, 901, 800, 755 cm^{-1}; ^1H NMR δ 1.17 (td, *J*=5.7, 13.4 Hz, 1H), 1.42 (td, *J*=6.6, 13.6 Hz, 1H), 1.50–1.58 (m, 2H), 1.69 (d, *J*=5.5 Hz, 1H), 1.80–2.05 (m, 4H), 2.32 (s, 3H), 2.57 (d, *J*=5.5 Hz, 1H), 3.90–4.01 (m, 4H), 7.05 (d, *J*=8.1 Hz, 2H), 7.11 (d, *J*=8.1 Hz, 2H); MS (EI) *m*/*z* (%) 283 (M^+, 38), 255 (15), 189 (17), 140 (20), 99 (100), 86 (83); HRMS (EI) calcd for $C_{18}H_{21}NO_2$: 283.1572, found: 283.1577.

3.1.52. (1R,2R*)-2-(4-Methoxyphenyl)-7,10-dioxadispiro[2.2.4.2]dodecane-1-carbonitrile (**47b**).* Colorless oil; IR (neat) 2953, 2232 (CN), 1612, 1516, 1250, 1138, 1094, 1035, 921, 754 cm^{-1}; ^1H NMR δ 1.29–1.34 (m, 1H), 1.38 (dtd, *J*=2.0, 4.7, 13.9 Hz, 1H), 1.65 (d, *J*=8.6 Hz, 1H), 1.71–1.87 (m, 5H), 2.08 (ddd, *J*=4.6, 10.9, 13.6 Hz, 1H), 2.41 (d, *J*=8.6 Hz, 1H), 3.79 (s, 3H), 3.93–4.00 (m, 4H), 6.87 (d, *J*=8.4 Hz, 2H), 7.28 (d, *J*=8.4 Hz, 2H); MS (EI) *m*/*z* (%) 299 (M^+, 50), 272 (12), 205 (28), 185 (37), 159 (28), 121 (16), 99 (100), 86 (28); HRMS (EI) calcd for $C_{18}H_{21}NO_3$: 299.1521, found: 299.1524.

3.1.53. (1R,2S*)-2-(4-Methoxyphenyl)-7,10-dioxadispiro[2.2.4.2]dodecane-1-carbonitrile (**48b**).* Colorless oil; IR (neat) 2952, 2233 (CN), 1612, 1516, 1444, 1250, 1181, 1138, 1092, 1035, 903, 838, 807, 759 cm^{-1}; ^1H NMR δ 1.13–1.20 (m, 1H), 1.39–1.46 (m, 1H), 1.49–1.59 (m, 2H), 1.65 (d, *J*=5.5 Hz, 1H), 1.80–1.93 (m, 3H), 1.95–2.02 (m, 1H), 2.55 (d, *J*=5.5 Hz, 1H), 3.79 (s, 3H), 3.90–4.00 (m, 4H), 6.84 (d, *J*=8.6 Hz, 2H), 7.08 (d, *J*=8.6 Hz, 2H); MS (EI) *m*/*z* (%) 299 (M^+, 44), 205 (25), 185 (35), 159 (26), 121 (15), 99 (100), 86 (28); HRMS (EI) calcd for $C_{18}H_{21}NO_3$: 299.1521, found: 299.1519.

3.1.54. (1R,2R*)-2-(4-Fluorophenyl)-7,10-dioxadispiro[2.2.4.2]dodecane-1-carbonitrile (**47c**).* Colorless oil; IR (neat) 2953, 2887, 2233 (CN), 1513, 1226, 1139, 1095, 1035, 756 cm^{-1}; ^1H NMR δ 1.24–1.40 (m, 2H), 1.69 (d, *J*=8.7 Hz, 1H), 1.71–1.90 (m, 5H), 2.11 (ddd, *J*=5.1, 10.4, 13.5 Hz, 1H), 2.43 (d, *J*=8.7 Hz, 1H), 3.92–4.02 (m, 4H), 7.03 (t, *J*=8.7 Hz, 2H), 7.34 (dd, *J*=5.5, 8.2 Hz, 2H); MS (EI) *m*/*z* (%) 287 (M^+, 50), 140 (28), 99 (72), 86 (100); HRMS (EI) calcd for $C_{17}H_{18}FNO_2$: 287.1322, found: 287.1323.

3.1.55. (1R,2S*)-2-(4-Fluorophenyl)-7,10-dioxadispiro[2.2.4.2]dodecane-1-carbonitrile (**48c**).* Colorless oil; IR (neat) 2952, 2887, 2234 (CN), 1514, 1444, 1226, 1139, 1092, 1035, 904, 764 cm^{-1}; ^1H NMR δ 1.09–1.17 (m, 1H), 1.44 (td, *J*=6.7, 14.0 Hz, 1H), 1.53–1.57 (m, 2H), 1.67 (d, *J*=5.5 Hz, 1H), 1.80–1.94 (m, 3H), 1.98–2.08 (m, 1H), 2.58 (d, *J*=5.5 Hz, 1H), 3.90–4.00 (m, 4H), 7.00 (t, *J*=8.6 Hz, 2H), 7.14 (dd, *J*=5.3, 8.6 Hz, 2H); MS (EI) *m*/*z* (%) 287 (M^+, 40), 193 (14), 147 (11), 140 (26), 125 (20), 109 (15), 99 (74), 86 (100); HRMS (EI) calcd for $C_{17}H_{18}FNO_2$: 287.1322, found: 287.1321.

3.1.56. (1R,2R*)-2-(4-Chlorophenyl)-7,10-dioxadispiro[2.2.4.2]dodecane-1-carbonitrile (**47d**).* Colorless oil; IR (neat) 2953, 2233 (CN), 1495, 1138, 1095, 1035, 921, 771 cm^{-1}; ^1H NMR δ 1.25–1.40 (m, 2H), 1.68–1.90 (m, 6H), 2.11 (ddd, *J*=5.0, 10.4, 13.7 Hz, 1H), 2.42 (d, *J*=8.5 Hz, 1H), 3.95–4.00 (m, 4H), 7.30–7.35 (m, 4H); MS (EI) *m*/*z* (%) 303 (M^+, 45), 209 (10), 140 (30), 125 (21), 99 (70), 86 (100); HRMS (EI) calcd for $C_{17}H_{18}ClNO_2$: 303.1026, found: *m*/*z* 303.1019.

3.1.57. (1R,2S*)-2-(4-Chlorophenyl)-7,10-dioxadispiro[2.2.4.2]dodecane-1-carbonitrile (**48d**).* Colorless oil; IR (neat) 2947, 2234 (CN), 1496, 1260, 1138, 1092, 1034, 902, 755 cm^{-1}; ^1H NMR δ 1.14 (td, *J*=5.3, 13.5 Hz, 1H), 1.37–1.48 (m, 1H), 1.51–1.57 (m, 2H), 1.69 (d, *J*=5.5 Hz, 1H), 1.80–2.08 (m, 4H), 2.57 (d, *J*=5.5 Hz, 1H), 3.89–4.01 (m, 4H), 7.10 (d, *J*=8.3 Hz, 2H), 7.29 (d, *J*=8.3 Hz, 2H); MS (EI) *m*/*z* (%) 303 (M^+, 32), 140 (28), 125 (21), 99 (64), 86 (100); HRMS (EI) calcd for $C_{17}H_{18}ClNO_2$: 303.1026, found: 303.1022.

3.1.58. (1R,2R*)-2-(2-Naphthyl)-7,10-dioxadispiro[2.2.4.2]dodecane-1-carbonitrile (**47e**).* Colorless oil; IR (neat) 2952, 2886, 2232 (CN), 1602, 1507, 1440, 1250, 1138, 1122, 1093, 1035, 905, 820, 755 cm^{-1}; ^1H NMR δ 1.37–1.46 (m, 2H), 1.71–1.75 (m, 2H), 1.77 (d, *J*=8.5 Hz, 1H), 1.80–1.95 (m, 3H), 2.16 (ddd, *J*=4.5, 11.0, 13.5 Hz, 1H), 2.62 (d, *J*=8.5 Hz, 1H), 3.94–4.03 (m, 4H), 7.44 (dd, *J*=1.8, 8.6 Hz, 1H), 7.46–7.49 (m, 2H), 7.78–7.85 (m, 3H), 7.90 (s, 1H); MS (EI) *m*/*z* (%) 319 (M^+, 85), 291 (15), 233 (16), 205 (36), 179 (35), 165 (13), 141 (18), 99 (100), 86 (50); HRMS (EI) calcd for $C_{21}H_{21}NO_2$: 319.1572, found: 319.1571.

3.1.59. (1R,2S*)-2-(2-Naphthyl)-7,10-dioxadispiro[2.2.4.2]dodecane-1-carbonitrile (**48e**).* Colorless crystal; mp 130.5–131.0 °C (hexane/AcOEt); IR (KBr) 2960, 2946, 2883, 2230 (CN), 1601, 1445, 1261, 1139, 1122, 1095, 1034, 946, 909, 821, 759 cm^{-1}; ^1H NMR δ 1.15–1.25 (m, 1H), 1.40–1.58 (m, 3H), 1.86–2.12 (m, 5H), 2.77 (d, *J*=5.5 Hz, 1H), 3.89–4.01 (m, 4H), 7.32 (dd, *J*=1.7, 8.5 Hz, 1H), 7.43–7.53 (m, 2H), 7.57 (s, 1H), 7.76–7.84 (m, 3H); MS (EI) *m*/*z* (%) 319 (M^+, 67), 291 (13), 233 (15), 205 (35), 179 (36), 141 (19), 99 (100), 86 (50); HRMS (EI) calcd for $C_{21}H_{21}NO_2$: 319.1572, found: 319.1571.

3.1.60. (1R,3R*)-3-(4-Methoxyphenyl)-2,2-dimethylcyclopropanecarbonitrile (**47f**).* Colorless oil; IR (neat) 2959, 2233 (CN), 1612,

1516, 1249, 1177, 1035, 840, 759 cm^{-1}; ^1H NMR δ 1.15 (s, 3H), 1.34 (s, 3H), 1.64 (d, J=8.7 Hz, 1H), 2.34 (d, J=8.7 Hz, 1H), 3.80 (s, 3H), 6.89 (d, J=8.8 Hz, 2H), 7.25 (d, J=8.8 Hz, 2H); MS (EI) m/z (%) 201 (M^+, 50), 186 (100), 159 (18), 144 (10), 121 (15); HRMS (EI) calcd for $C_{13}H_{15}NO$: 201.1154, found: 201.1155.

3.1.61. (1R,3S*)-3-(4-Methoxyphenyl)-2,2-dimethylcyclopropanecarbonitrile (**48f**).* Colorless oil; IR (neat) 2959, 2233 (CN), 1612, 1516, 1250, 1180, 1035, 837, 797 cm^{-1}; ^1H NMR δ 0.91 (s, 3H), 1.48 (s, 3H), 1.57 (d, J=5.6 Hz, 1H), 2.46 (d, J=5.6 Hz, 1H), 3.80 (s, 3H), 6.85 (d, J=8.7 Hz, 2H), 7.06 (d, J=8.7 Hz, 2H); MS (EI) m/z (%) 201 (M^+, 58), 186 (100), 159 (16), 121 (12); HRMS (EI) calcd for $C_{13}H_{15}NO$: 201.1154, found: 201.1154.

*3.1.62. 4-Chloro-2-(4-methoxyphenyl)-3,3-dimethylbutanenitrile (**49**).* Colorless oil; IR (neat) 2971, 2238 (CN), 1612, 1513, 1467, 1253, 1182, 1035, 835 cm^{-1}; ^1H NMR δ 1.01 (s, 3H), 1.26 (s, 3H), 3.26 (d, J=11.4 Hz, 1H), 3.44 (d, J=11.4 Hz, 1H), 3.82 (s, 3H), 4.03 (s, 1H), 6.90 (d, J=8.8 Hz, 2H), 7.29 (d, J=8.8 Hz, 2H); MS (EI) m/z (%) 237 (M^+, 8), 147 (100), 132 (15), 103 (5), 91 (5), 55 (6); HRMS (EI) calcd for $C_{13}H_{16}ClNO$: 237.0920, found: 237.0921.

3.2. X-ray crystallographic analysis of 41L and 41P

Single crystals of **41L** and **41P** suitable for an X-ray diffraction study were obtained by their recrystallization from hot ethyl acetate and hot hexane/ethyl acetate, respectively. The crystal was mounted on a glass fiber, and diffraction data were collected on a Bruker AXS SMART APEX CCD diffractometer at 173 K with graphite-monochromated Mo Kα radiation (λ=0.71073 Å).[19] The data reduction and integration were performed using the program SAINT.[20] An empirical absorption correction was applied using the program SADABS.[21] The structures were solved by direct methods with SHELXS-97[22] and refined by full-matrix least squares techniques against F^2 using SHELXL-97.[23] All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were placed in calculated positions and refined using the riding model. Crystal data for **41L**: a colorless block-shaped crystal, 0.20×0.30×0.35 mm, $C_{24}H_{26}ClNO_3S$, M=443.97, monoclinic, space group $P2(1)/n$, a=9.3441(4) Å, b=8.9794(4) Å, c=26.0925(11) Å, β=91.7520(10)°, V=2188.25(16) $Å^3$, Z=4, D_{calcd}=1.348 g cm^{-3}, μ(Mo Kα)=0.296 mm^{-1}, F(000)=936, 4993 reflections, 272 parameters, R_1=0.0315 [$I>2\sigma(I)$], R_w=0.0857 (all data), GOF=1.060. Crystal data for **41P**: a colorless block-shaped crystal, 0.10×0.10×0.20 mm, $C_{24}H_{26}ClNO_3S$, M=443.97, monoclinic, space group $P2(1)/n$, a=11.0600(12) Å, b=13.5162(15) Å, c=14.9278(17) Å, β=105.227(2)°, V=2153.2(4) $Å^3$, Z=4, D_{calcd}=1.370 g cm^{-3}, μ(Mo Kα)=0.301 mm^{-1}, F(000)=936, 4931 reflections, 272 parameters, R_1=0.0470 [$I>2\sigma(I)$], R_w=0.1351 (all data), GOF=1.144. Crystallographic data (excluding structure factors) for **41L** and **41P** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 857059 and CCDC 857060, respectively. 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].

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