ALKYL PYRIDINESULFONATES AND ALLYLIC PYRIDINECARBOXYLATES, NEW BOOSTERS FOR THE SUBSTITUTION AT SECONDARY CARBONS

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Abstract – Substitution at allylic secondary carbons using the pyridinecarboxylate (picolinoxy, PyCO₂, or Pic) leaving group is described in the first part of this review (Sections 2–4). Alkyl as well as less reactive alkenyl, heteroaryl, and aryl copper reagents are suitable for the substitution, giving anti $S_N2'$ products highly regio- and stereoselectively. In Section 2, finding and synthetic application of the allylic substitution giving tertiary carbon centers are presented. Extension of the substitution for the construction of quaternary carbon centers is described in Section 3 with its synthetic application. Section 4 deals with the construction of quaternary carbon centers on cyclohexane rings by the allylic substitution of cyclohexylidene picolinites. The stereochemistry is created by equatorial attack to the chair conformer with high diastereselectivity. The stereochemical prediction facilitated synthesis designs of biologically active compounds. The second part of the review (Section 5) presents recent advances in metal-catalyzed substitutions at secondary alkyl carbons, giving enantiomerically enriched products. Our findings of the pyridinesulfonyloxy leaving group and an associated copper catalyst are included. Substitutions with cuprates are mentioned briefly for reactivity discussion with the copper-catalyzed substitution.

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1. Overview of the Review

Substitution of secondary carbon–oxygen bonds with organometallic reagents is a fundamental tool for organic synthesis of complex molecules. Although several types of the substitution have been studied, we were interested in allylic substitution and found that the pyridinecarboxylate (picolinoxy, PyCO₂, or simply Pic) is a booster for allylic picolinates 1 with RMgBr/CuBr to afford anti S_N2' products 2 regio- and stereoselectively (Scheme 1, eq 1, R³ = H). Successful reagent types are alkyl (sp³-C), aryl and alkenyl (sp²-C), and alkynyl (sp-C) reagents. The latter two types were among slow or marginally reactive reagents when we started the investigation in 2007. We then disclosed that the substitution of allylic picolinates 3 of R³ = alkyl produces quaternary carbon compounds 4 (Scheme 1, eq 1, R³ = alkyl). Based on the fact that Mg²⁺ is generated in situ from RMgBr and CuBr·Me₂S, the substitution is likely to proceed via complex 5, in which the Pic group is synergistically activated by chelation to Mg²⁺ and electron withdrawing nature of the pyridyl group. Herein, we present a summary of this allylic substitution and the application in organic synthesis.
On the other hand, only a few combinations of leaving groups/reagents/catalysts have been developed for metal-catalyzed substitution at saturated secondary alkyl carbons (alkyl carbons). However, the substitutions were somewhat slow. To develop a method for faster substitution, we applied the activation mechanism of Pic to 2-pyridinesulfonates 6 and found the Cu(OTf)$_2$-catalyzed substitution of 6 with RMgCl. This substitution and that developed by other groups are presented in the latter part of the review.

Scheme 1. Substitution Reactions and a Plausible Mechanism of the Activation

2. Substitution of Secondary Allylic Picolinates, Producing Tertiary Carbon Centers

2.1. Background

Catalytic allylic substitution with soft and hard nucleophiles in catalytic allylic substitution has been well studied. Mechanistically, the former nucleophiles attack π-allyl intermediate generated from allylic substrate with transition metal catalysts, and hence the regioselectivity is influenced by substituents attached to the allylic system. In contrast, the well-studied hard nucleophiles are organocoppers, which have been prepared from organometallics and copper salts or generated catalytically.\textsuperscript{1-5} The substitution takes place at the olefinic carbon with inversion of the stereochemistry (anti $S_N2'$). However, large substituents affect the reaction, and induce the formation of π-allyl intermediate, thus reducing the regioselectivity.
Two types of allylic substrates 9 and 11 have been investigated for the allylic substitution with copper reagents (Scheme 2). Efficiency of these substitutions has been discussed with reactivity, regio- and stereoselectivity, a scope of reagents, and/or availability of the substrates. The usual size of substituent R in 9 marginally affected the reactivity (eq 3), and many chiral ligands for the asymmetric substitution of allylic halides and less reactive esters have been developed. 6–8 On the other hand, the reactivity of 11 in eq 4 was substantially reduced by substituents R and R’, and hence highly potent leaving groups such as C₆F₅CO₂, o-Ph₂P-C₆H₄CO₂ (o-DPPB), and o-Ph₂P(O)-C₆H₄CO₂ have necessary been developed (Scheme 3, eqs 5–7). 9–11 Furthermore, the substitution using o-DPPB (eq 6) has been applied to the synthesis of poly(1,3-dimethyl)alkanes. 12

On the other hand, release from the steric congestion was the driving force of the allylic substitution (eq 8). 13 The hydroxy group on the cyclopentene ring enhanced the reactivity and controlled regio- and stereoselectivity (eqs 9 and 10). 14

In addition, the nickel-catalyzed allylic substitution shown in eq 11 (Scheme 4) has been developed. The high regioselectivity was brought by the additives (NaI, t-BuCN). 15,16 Coordination of PPh₂ to a nickel catalyst in eq 12 enhanced the reactivity and regioselectivity. 17

Scheme 2. Allylic Substitutions at the Terminal and Internal Positions
In 2007, we planned a new research project to utilize allylic substitution of the eq 4-type to organic synthesis because of expected synthetic merits of: (1) more flexibility in designing an original substrate possessing substituents $R_1$ and $R_2$ than that for 9 possessing one substituent $R_1$; and (2) many possible transformations of product 12 to a target compound. However, successful copper reagents of eqs 5–7, concrete examples of eq 4, were limited to mostly alkyl reagents, which are generally more reactive than aryl and alkenyl reagents. Consequently, our initial investigation was set to find an efficient leaving group that is applied to a wide range of substrates and reagents. Results of this investigation are presented in following paragraphs, and application to the synthesis of biologically active compounds is mentioned in Section 2.6. Note that the allylic substitution using borane reagents in the presence of Cu$^{18}$ and Pd$^{19}$ catalysts has been developed by Sawamura.
2.2. Finding of the Picolinoxy Leaving Group (PyCO₂)

Based on the underlying mechanisms of the substitutions shown in eqs 5 and 6 and the copper-catalyzed addition of ArMgI to (2-pyridyl)silylalkyne 13 to give intermediate 14 (Scheme 5) we envisaged that a hybrid of these activations would be more effective than the single activation, and selected the picolinoxy group (Pic or PyCO₂) as a candidate. In practice, anti SN2' substitution of cis allylic picolates 1 took place with aryl and alkenyl reagents, which were less reactive than alkyl reagents (Scheme 6, eq 13). Under the modified conditions, reagents were extended to heteroaromatic and alkynyl copper reagents, which are less nucleophilic than aryl reagents. The substitution of picolates 3 furnished quaternary carbon centers of 4 (eq 14). A quaternary carbon center was also formed on the cyclohexane ring (eq 15), in which the stereochemistry of 16 was controlled by conformation of the cyclohexane ring.

2.3. Comparison of Reactivity between Picolates and Other Esters

Examination of leaving groups including the Pic group is summarized in Table 1. The substitution of racemic picolinate 1a (L = 2-PyCO₂) was studied with 2 or 3 equivalents (equiv) of Ph copper reagents derived from PhMgBr/CuBr₂·Me₂S in 1~4:1 ratios to produce 2a in good yields with high regioselectivity of 2a/21 (entries 1–3). The active species are probably PhCu·MgBr₂ from the 1:1 mixture and
Ph₂CuMg₂MgBr₂ from the 2:1 and 4:1 mixtures. Similar reactivity and/or regioselectivity was observed with CuCl, CuBr, CuI, and CuCN. On the other hand, 4-PyCO₂ was a slower leaving group than Pic (entry 4), and PhCO₂ had no reactivity (entry 5). These results clearly indicated that the substitution was accelerated by the electron withdrawing nature of the pyridyl group and the coordination of carbonyl oxygen and pyridyl nitrogen in Pic to the Mg cation. The C₆F₅CO₂ group was also ineffective (entry 6).

Phosphate 20 produced a mixture of 2a and the cis isomer (entry 7, footnote a). Among Ph₂Zn and PhZnBr, the former was more reactive (entries 8 and 9). In contrast to the cis allylic picolinates, trans isomers 23 and 24 gave regioisomeric mixtures (Scheme 7).

Scheme 6. Allylic Substitution of Picolinates with Copper Reagents

Scheme 7. Allylic Substitution of trans Allylic Picolinates Giving Regioisomeric Mixtures
Table 1. Substitution of Various Secondary Allylic Esters with Phenyl Copper Reagents

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>L</th>
<th>reagent</th>
<th>Mg/Cu</th>
<th>temp. (°C)</th>
<th>time (h)</th>
<th>2a : 21 : 22 : 1a</th>
<th>2a : 21</th>
<th>yield of 2a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>PyCO2</td>
<td>PhMgBr/CuBr⋅Me2S</td>
<td>1 : 1</td>
<td>0</td>
<td>1.5</td>
<td>98 : 2 : 0 : 0</td>
<td>98 : 2</td>
<td>84%</td>
</tr>
<tr>
<td>2</td>
<td>1a</td>
<td>PyCO2</td>
<td>as above</td>
<td>2 : 1</td>
<td>0</td>
<td>1</td>
<td>99 : 1 : 0 : 0</td>
<td>99 : 1</td>
<td>91%</td>
</tr>
<tr>
<td>3</td>
<td>1a</td>
<td>PyCO2</td>
<td>as above</td>
<td>4 : 1</td>
<td>0</td>
<td>1</td>
<td>99 : 1 : 0 : 0</td>
<td>99 : 1</td>
<td>85%</td>
</tr>
<tr>
<td>4</td>
<td>17</td>
<td>4-PyCO2</td>
<td>as above</td>
<td>2 : 1</td>
<td>0–rt</td>
<td>3</td>
<td>46 : 0 : 0 : 54</td>
<td>&gt;99 : 1</td>
<td>nd</td>
</tr>
<tr>
<td>5</td>
<td>18</td>
<td>PhCO2</td>
<td>as above</td>
<td>2 : 1</td>
<td>0–rt</td>
<td>20</td>
<td>0 : 0 : 0 : 100</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>6</td>
<td>19</td>
<td>C6F5CO2</td>
<td>as above</td>
<td>1 : 1</td>
<td>0–rt</td>
<td>18</td>
<td>60 : 0 : 40 : 0</td>
<td>&gt;99 : 1</td>
<td>nd</td>
</tr>
<tr>
<td>7</td>
<td>20</td>
<td>(EtO)2PO2</td>
<td>as above</td>
<td>3 : 1</td>
<td>0</td>
<td>3</td>
<td>99 : 1 : 0 : 0</td>
<td>99% : 1</td>
<td>90%*</td>
</tr>
<tr>
<td>8</td>
<td>1a</td>
<td>PyCO2</td>
<td>Ph2Zn⋅2MgBr2/CuBr⋅Me2S</td>
<td>2 : 1</td>
<td>−15–0</td>
<td>1</td>
<td>99 : 1 : 0 : 0</td>
<td>99 : 1</td>
<td>91%</td>
</tr>
<tr>
<td>9</td>
<td>1a</td>
<td>PyCO2</td>
<td>PhZnBr⋅2MgBr2/CuBr⋅Me2S</td>
<td>2 : 1</td>
<td>−15–0</td>
<td>1</td>
<td>85 : 2 : 0 : 13</td>
<td>98 : 2</td>
<td>nd*</td>
</tr>
</tbody>
</table>

*a* Contained 20% cis isomer of 2a. *b* Not determined.

The transition state theory for the allylic substitution of allyl acetate with lithium cuprates suggests that Li+ and Me2Cu− in the cuprate dimer interact with the acetate oxygen and the π-orbital. With this theory in mind, stereochemical view of the likely transition state 5 is illustrated in Scheme 8, Part A, in which the conformation of 1 is fixed as drawn by allylic strain. In addition to the self-activation by the pyridyl group, the Pic group is further activated by the coordination to MgBr2, which is generated in situ from RMgBr and CuBr⋅Me2S, and the copper reagent accesses to the π-orbital on the olefin. In contrast, the trans isomer of 1 consists of conformers with comparable energy levels, and thus both sides of the π-orbital are blocked from forming the complexation (Part B). As a consequence, another reaction path via π-allyl intermediate becomes competitive.
**Table 2. Allylic Substitution of Enantioenriched Picolinates**

<table>
<thead>
<tr>
<th>entry</th>
<th>R in RMgBr</th>
<th>R/Cu</th>
<th>product</th>
<th>yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>4:1</td>
<td>(R)-2a</td>
<td>83</td>
<td>98</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>2:1</td>
<td>(R)-2a</td>
<td>93</td>
<td>99</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>2:1</td>
<td>2c</td>
<td>81</td>
<td>99</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>2:1</td>
<td>2d</td>
<td>85</td>
<td>98</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>2:1</td>
<td>2e</td>
<td>81</td>
<td>98</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>2:1</td>
<td>2f</td>
<td>75</td>
<td>97</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>2:1</td>
<td>2g</td>
<td>85</td>
<td>97</td>
</tr>
<tr>
<td>8</td>
<td>Me</td>
<td>2:1</td>
<td>2h</td>
<td>90</td>
<td>96</td>
</tr>
<tr>
<td>9</td>
<td>n-Bu</td>
<td>2:1</td>
<td>2i</td>
<td>89</td>
<td>96</td>
</tr>
</tbody>
</table>

*Enantiospecificity: (% ee of product / % ee of substrate) x 100.
2.4. Stereochemical Outcome of the Allylic Substitution

The *anti* $\text{S}_\text{N}2'$ pathway was proven by the substitution of (S)-1a with PhMgBr/CuBr·Me$_2$S in 4:1 and 2:1 ratios to afford (R)-2a, and enantiospecificity (es) defined in Table 2, footnote a was sufficiently high (entries 1 and 2). Substituents at the *ortho* position of reagents did not interfere efficiency in the production of 2c and 2d (entries 3 and 4). Vinylic reagents were not exceptions (entries 5–7). Me and Bu reagents, typical alkyl reagents, afforded *anti* $\text{S}_\text{N}2'$ products 2h and 2i (entries 8 and 9).

More entries of the substitution using enantioenriched picolinates are displaced in Table 3, indicating high efficiency of the Pic substitution. Products 2j and 2a are the regioisomers each other. Products 2m and 2n were intermediates for the synthesis of sesquichamaenol$_{21b}$ and equol$_{25}$ respectively. The syntheses of these compounds were mentioned in later paragraphs.

Table 3. Examples of the Allylic Substitution of Enantioenriched Picolinates

<table>
<thead>
<tr>
<th>entry</th>
<th>picolinate</th>
<th>R/Cu</th>
<th>product</th>
<th>yield (%)</th>
<th>es (%)</th>
<th>ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>PhMgBr/CuBr·Me$_2$S (2 : 1)</td>
<td>93</td>
<td>97</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>PhMgBr/CuBr·Me$_2$S (2 : 1)</td>
<td>86</td>
<td>99</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>OPMB</td>
<td>PhMgBr/CuBr·Me$_2$S (2 : 1)</td>
<td>83</td>
<td>99</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>OCOPy</td>
<td>PhMgBr/CuBr·Me$_2$S (2 : 1)</td>
<td>61$^a$</td>
<td>99</td>
<td>21b</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>OCOPy</td>
<td>PhMgBr/CuBr·Me$_2$S (2 : 1)</td>
<td>75$^b$</td>
<td>97</td>
<td>25</td>
<td></td>
</tr>
</tbody>
</table>

$^a$After desilylation. $^b$After dihydroxylation.
2.5. Optimization for Lithium-Based Copper Reagents

While Grignard reagents are available only from halides and Mg, organolithiums are available by several methods such as Li-halogen exchange, ortho-lithiation, and direct lithiation. To enjoy these methods, we investigated the allylic substitution with organolithium-based copper reagents at 0 °C for 1 h. However, copper reagents derived from salt-free PhLi and CuBr·Me₂S in 1~4:1 ratios produced mixtures of 2a, alcohol 22, and unreacted picolinate 1a (Table 4, entries 1, 3, and 6). Fortunately, reactivity and product selectivity were improved by addition of MgBr₂ (entries 2, 5, and 7), and the successful ratio of MgBr₂/PhLi was elucidated to be MgBr₂>PhLi (entry 4). The substitution using enantiomerically enriched (S)-1a disclosed that PhLi/CuBr·Me₂S in 1:1 and 2:1 ratios afforded the *anti* S_N2*’* product with 98% es (entries 2 and 5), whereas low es of 84% was recorded with the 4:1 reagent (entry 7). The addition of MgBr₂ was also effective for the substitution of 1a with PhZnBr·LiBr and Ph₂Zn·2LiBr (prepared by mixing PhLi and ZnBr₂). These results prompted a study with functionalized zinc reagents. However, the stereochemical course with the zinc reagents was left unexplored.

Table 4. Preliminary Study on the Substitution with Salt-free PhLi-Based Copper Reagents

<table>
<thead>
<tr>
<th>entry</th>
<th>picolinate</th>
<th>Ph/Cu equiv of MgBr₂ yield (%)</th>
<th>2a : 22 : 1a es of 2a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>1:1</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>(S)-1a</td>
<td>1:1</td>
<td>3 92</td>
</tr>
<tr>
<td>3</td>
<td>1a</td>
<td>2:1</td>
<td>–</td>
</tr>
<tr>
<td>4</td>
<td>1a</td>
<td>2:1</td>
<td>2 84</td>
</tr>
<tr>
<td>5</td>
<td>(S)-1a</td>
<td>2:1</td>
<td>3 92</td>
</tr>
<tr>
<td>6</td>
<td>1a</td>
<td>4:1</td>
<td>–</td>
</tr>
<tr>
<td>7</td>
<td>(S)-1a</td>
<td>4:1</td>
<td>3 90</td>
</tr>
</tbody>
</table>

*Commercially available salt-free PhLi was used.

The above method was applied to other substrates such as 1j and to reagents prepared by Li-halogen exchange, ortho-lithiation, and direct lithiation (Table 5). Substitution of picolinate 1j (99% ee) proceeded smoothly (entry 1). PhLi prepared by Li-Br and Li-I exchanges of PhBr and PhI with t-BuLi were compatible (entries 2 and 4), whereas the use of n-BuLi for the Li-X exchange (X = Br, I) was unsuccessful, but instead produced n-Bu-Ph (entry 3 and footnote c). This side reaction was published as
Table 5. Allylic Substitution with RLi-Based Copper Reagents$^{a,b}$

\[
\begin{array}{cccccc}
\text{entry} & \text{picolinate} & \text{R-Li} & \text{preparation of RLi} & \text{R/Cu} & \text{yield (%)} & \text{es} \\
1 & \text{PyCOO} & \text{Ph-Li} & \text{commercial, salt free} & 2:1 & 87 & 99 \\
2 & \text{PyCOO} & \text{Ph-Li} & \text{Li-Br exchange with } t\text{-BuLi} & 2:1 & 93 & 98 \\
3 & (S)-1a & \text{Ph-Li} & \text{Li-Br exchange with } n\text{-BuLi} & 2:1 & 0^c & – \\
4 & (S)-1a & \text{Ph-Li} & \text{Li-I exchange with } t\text{-BuLi} & 2:1 & 90 & 98 \\
5 & (S)-1a & \text{Li-Br exchange} & 2:1 & 88 & 97 \\
6 & (S)-1a & \text{ortho lithiation} & 2:1 & 85 & 99 \\
7 & (S)-1a & \text{ortho lithiation} & 2:1 & 97 & >99 \\
8 & (S)-1a & \text{ortho lithiation} & 2:1 & 98 & >99 \\
9 & (S)-1a & \text{Li-I exchange} & 2:1 & 75 & 98 \\
10 & (S)-1a & \text{Li-I exchange} & 2:1 & 93 & 98 \\
11 & (S)-1a & \text{direct lithiation} & 2:1 & 93 & 99 \\
12 & (S)-1a & \text{direct lithiation} & 2:1 & 86 & 99 \\
13 & (S)-1a & \text{direct lithiation} & 2:1 & 89 & 99 \\
\end{array}
\]

$^a$Entries 1–12, ref. 22a; entry 13, ref. 22b. $^b$Regioselectivity (rs) was >97% in all cases. $^c$Li-I exchange with $n$-BuLi also gave $n$-Bu-Ph as well.
a substitution reaction at primary alkyl carbons.\textsuperscript{28} The sterically hindered lithium reagent prepared from 2,6-(Me)\textsubscript{2}C\textsubscript{6}H\textsubscript{3}Br by Li-Br exchange could be used for the substitution (entry 5). Similarly, sterically hindered lithium reagents derived by ortho-lithiation gave successful entries 6–8. The stereochemistry of alkenyl halides was completely retained during the allylic substitutions (entries 9 and 10). This result is one of the synthetic merits of the organolithium-based reagents over Grignard reagents since the preparation of Grignard reagents from stereodefined alkenyl halides generally suffers from a partial loss of the olefinic integrity. The reactions with heterocyclic reagents (entries 11–13)\textsuperscript{29b} demonstrated another advantage of the method since thienyl\textsuperscript{29a,b} and alkynyl\textsuperscript{29c} groups on copper reagents are marginally reactive and hence used as dummy ligands for the 1,4-addition reactions to enone 25 (Scheme 9, eqs 16–18).

Scheme 9. 1,4-Addition Reactions of Classical Copper Reagents to an Enone

Figure 1. Targets of the Allylic Substitution

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and 17). Similarly, low reactivity of the furylcopper reagent toward 1,4-addition to enone 25 was complemented by pre-activation of the enone with BF$_3$·OEt$_2$ (eq 18). Note that the derived borane enolate suffers from the low nucleophilic reactivity, and hence methods for 1,4-addition/enolate trap have been published.

2.6. Application of the Allylic Substitution

The above allylic substitution was applied to synthesis of biologically active compounds 28–31 (Figure 1) to demonstrate flexibility in designing allylic substrates of type 11 (Scheme 2, eq 4). Furthermore, synthesis of thermodynamically less stable cyclohexanones 33 and cyclic compounds 34 possessing chiral side chains has been developed.

**Sesquichamaenol (28)**, isolated from several kinds of wood. Allylic substitution of picolinate 1m with a copper reagent derived from 37 and CuBr·Me$_2$S was envisaged to afford a new key intermediate 38 (Scheme 10). Picolinate 1m was prepared from aldehyde 35 via the Wittig reaction and the subsequent Mitsunobu inversion with PyCO$_2$H. The allylic substitution with 37/CuBr·Me$_2$S (2:1) took place with 99% es, and the anti $S_N$2' product 38 was transformed to acid 40, which was subjected to demethylation (HBr in AcOH) and reaction with MeLi to produce the target 28 in a good yield.

![Scheme 10. Synthesis of Sesquichamaenol](image-url)
**Equol:** The (S)-form of equol (29) stimulates the estrogenic response by binding to estrogen receptor β (ERβ), whereas the (R)-isomer is moderately ERα selective. Allylic picolinate 1n was envisaged as a precursor of the (S)-isomer. The Wittig reaction of aldehyde 41 with 42/NaN(TMS)₂ was used to construct the framework of picolinate 1n (94% ee) (Scheme 11). The allylic substitution of 1n with the copper reagent derived from 4-(MeO)C₆H₄MgBr/CuBr·Me₂S in a 2:1 produced *anti* S₈N₂' product 2n, which was then converted to alcohol 43 with 91% ee. Bromination of 43, demethylation with BBr₃, and dihydropyran ring formation with K₂CO₃ furnished (S)-equol (29).

![Scheme 11. Synthesis of (S)-Equol](image)

**The ACAT inhibitor (30),** an acyl-coenzyme cholesterol acyltransferase (ACAT) inhibitor: An allylic picolinate 1o was designed for the synthesis, and prepared from acetylenic ketone 44 via the asymmetric transfer hydrogenation (Scheme 12). The Grignard reagent 45c derived from bromide 45a and Mg turnings showed poor solubility in THF, and the two phases were mixed with CuBr·Me₂S to obtain a supposed copper reagent of "45c/CuBr·Me₂S (2:1)". The allylic substitution of picolinate 1o with the reagent followed by hydrogenation gave 46 in rather inferior yield and es (57% yield, 64% es). The low solubility of 45c was responsible for the result because the substitution of 1o with the copper reagent derived from THF soluble PhMgBr and CuBr·Me₂S afforded the corresponding product in 73% yield with 99% es. Alternatively, Li reagent 45b prepared from bromide 45a by Li-Br exchange was soluble in THF and the reagent of 45b/CuBr·Me₂S/MgBr₂ (2:1:3) afforded 46 in 72% yield with 97% es. Subsequently, transformation of 46 to the target 30 via 47 was conducted without any problem.
Bioactive Form of Loxoprofen: Loxoprofen (32) presented in Figure 1 is an artificial anti-inflammatory drug, and marketed as loxonin in a racemic form, which, once administered, is converted to the active form 31. The synthesis of 31 was envisaged as summarized in Scheme 13, Part B, in which the allylic substitution was set in two steps, giving 53 and 57, respectively. Since different reactivity and selectivity were anticipated for the benzylic copper reagent derived from 52, model benzyl reagents, BnMgBr (49)/CuBr·Me2S in different 1~4:1 ratios, were preliminary subjected to the substitution with racemic picolinates 48a (R = TBS) and 48b (R = PMB) (Scheme 13, Part A). The reagent derived from 49/CuBr·Me2S in a 2:1 ratio was sufficiently reactive, but slightly less regioselective (90–95%) (runs 1 and 3). A similar level of the efficiency was obtained with the 4:1 reagent. In contrast, the 1:1 reagent was less reactive and less product-selective. Unexpectedly, the regioselectivity was increased by addition of 1–3 equivs of ZnBr2 (runs 2 and 4; footnote b).

The above method was applied to enantioenriched 48a and benzylic reagent 52 to produce 53 exclusively (Scheme 13, Part B). Subsequently, diimide reduction of 53 gave 54, which was converted to the copper reagent 55 by Li-Br exchange. The second allylic substitution of picolinate 55 (96% ee) with 55 proceeded smoothly, and the anti $S_N2'$ product 57 was converted to the target 31.
Scheme 13. Synthesis of the Bioactive Form of Loxoprofen

a Result with three (3) equiv of ZnBr$_2$. b Similar results were obtained with 1 and 2 equivs of ZnBr$_2$. c NBSH: o-(NO$_2$)C$_6$H$_4$SO$_2$NHNH$_2$.

**Thermodynamically Less Stable trans Isomers of 2,6-Disubstituted Cyclohexanones:** The synthesis of 2,6-disubstituted cyclohexanones 33 summarized in Scheme 14 included allylic substitution in two steps, and the products 33 were thermodynamically less stable *trans* stereoisomers than *cis* isomers.$^{39}$ For example, exposure of 33b (*trans* isomer) to $t$-BuOK produced the *cis* isomer with 81% *cis* purity over the *trans* (33b). Picolinate 59 for the first substitution was synthesized in racemic and enantioenriched forms via reduction of $\alpha$-bromocyclohexenone (58) with NaBH$_4$/CeCl$_3$·7H$_2$O or the CBS reagent. The substitution of 59 (98% ee) with PhMgBr/CuBr·Me$_2$S (1:1) was stereoselective (90% es) to produce 60 ($R^1 = $ Ph) with 88% ee, whereas the 2:1 reagent proceeded with racemization. Picolinate 61 for the second substitution was synthesized from 60 as 1:1 diastereomeric mixtures. Fortunately, both diastereomers underwent the MgBr$_2$-assisted substitution with copper reagents derived from $R^2$Li/Cu in a
1:1 ratio to give 62 in good yields with high regio- and diastereoselectivity. In contrast, the 2:1 reagents with Me and Ph as R$_2$ suffered from the low regioselectivity. The last step of the method was ozonolysis of 62, which produced the target ketones 33. Products thus synthesized were displaced in the bottom portion of Scheme 14. The trans stereochemical outcome indicated that R$_1$ (aromatic group) substantially prevented access of the R$_2$ reagents from $\alpha$ face and that the approach from unoccupied $\beta$ face was not affected by the Me group on the stereogenic carbon bearing the Pic group.

Cycloalkenes Possessing Chiral Side Chains: Allylic substitution was applied to cyclopentane derivative 63 and cyclohexane derivatives, which were prepared via aldol reactions (Scheme 15). Phenyl (Ph) and other aryl reagents derived from CuBr·Me$_2$S were reacted on the side chain to afford 34 with high regio- and stereoselectivity (run 1). Similar reagents derived from Cu(acac)$_2$ proceeded with higher selectivity (runs 2).
2.7. The Allylic Substitution with Alkynyl Copper Reagents

An alkynyl group bound to copper reagents has been a dummy ligand for the 1,4-addition reaction to enones because of marginally nucleophilicity (Scheme 9, eq 17).

In contrast, alkynyl copper reagents derived from alkynyllithiums and CuBr·Me₂S were sufficiently reactive toward allylic picolinates 1 in the presence of MgBr₂ to produce anti Sn2' products 2 with high efficiency in yield, es, and rs (Table 6).

Table 6. Allylic Substitution with Alkynyl Reagents

<table>
<thead>
<tr>
<th>entry</th>
<th>picolinate 1</th>
<th>product 2</th>
<th>yield (%)</th>
<th>es (%)</th>
<th>rs (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td>93</td>
<td>99</td>
<td>94</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td>70</td>
<td>96</td>
<td>95</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td>67</td>
<td>97</td>
<td>92</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td>88</td>
<td>98</td>
<td>95</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td>83</td>
<td>98</td>
<td>97</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td>89</td>
<td>98</td>
<td>94</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
<td>66</td>
<td>86</td>
<td>96</td>
</tr>
</tbody>
</table>
entries 1–6. However, yield and ee were slightly decreased by a bulky substituent (c-C_{6}H_{11}) on 1q (entry 7). Later, a copper catalyzed version was developed by Sawamura.\(^{41}\)

Different from the above acyclic picolinates (Table 6), cyclopentenyl picolinate 48a underwent slow substitution with the alkynyl copper reagent derived from 65 and CuBr·Me_{2}S (3:1) to afford 66 with low regioselectivity (Scheme 16, Part A, run 1). Fortunately, 65/Cu(acac)\(_{2}\) in a mixed solvent of CH\(_{2}\)Cl\(_{2}\)/THF (2:1) produced 66 with high regioselectivity (run 3).\(^{42}\) The cyclohexyl derivative was similarly reactive and selective. Previously, racemic prostaglandin F\(_{2}\alpha\) (71) was synthesized by Stork, who prepared intermediate 70 as a diastereomeric mixture via the epoxide ring opening of racemic cyclopentadiene monoepoxide with the corresponding lithium acetylide.\(^{43}\) In our synthesis, (1R,2S)-66 was synthesized from (1S,4R)-48a (structure not shown), and transformed to 70 in an optically active form (Scheme 16, Part B).

(Part A) Allylic Substitution of Picolinate 48a

(Part B) Synthesis of Intermediate 70

Scheme 16. Synthesis of the Prostaglandin Intermediate 70
3. Construction of Quaternary Carbon Centers by the Allylic Substitution

3.1. Optimization

Synthesis of quaternary carbon centers has been a subject of current organic chemistry. One of the methods is the S\textsuperscript{2}N\textsuperscript{2} allylic substitution of terminal allylic substrates, which has well-studied with alkyl, alkenyl, and aryl copper reagents. In contrast, a similar substitution of internal allylic esters was reported with alkyl reagents, when we started the substitution that was formulated as eq 14 in Scheme 6. As Table 7 indicates, the allylic substitution of 3a with PhMgBr/CuBr-Me\textsubscript{2}S (2:1), which was one of the regioselective reagents for the substitution of picolinate 1a (Table 1, entry 2), gave a mixture of 4a and the regioisomer 72 (entry 1). Attempted addition of ZnI\textsubscript{2} ended up in vain (entry 2). Surprisingly, copper reagent prepared from PhMgBr and Cu(acac)\textsubscript{2} produced 4a with high regioselectivity in a quantitative yield (entry 3). In contrast, a PhMgBr/Cu(acac)\textsubscript{2} in a 3:1 ratio with ZnI\textsubscript{2} produced the high selectivity (entry 6; cf. entry 5). Different from the above PhMgBr-based reagents, PhLi/CuBr-Me\textsubscript{2}S and PhLi/Cu(acac)\textsubscript{2} with MgBr\textsubscript{2} were inadequate (entries 7 and 8), whereas PhLi/CuTC (2:1) (TC: thiophene-2-carboxylate) was highly regioselective (entry 9). Furthermore, CuTC was found to be

<table>
<thead>
<tr>
<th>entry</th>
<th>reagent source</th>
<th>copper reagent (ratio)</th>
<th>Cu (equiv)</th>
<th>additive (equiv)</th>
<th>4/72</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhMgBr</td>
<td>PhMgBr/CuBr-Me\textsubscript{2}S (2 : 1)</td>
<td>1</td>
<td>–</td>
<td>76 : 24</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>PhMgBr</td>
<td>PhMgBr/CuBr-Me\textsubscript{2}S (2 : 1)</td>
<td>1.5</td>
<td>ZnI\textsubscript{2} (1.5)</td>
<td>86 : 14</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>PhMgBr</td>
<td>PhMgBr/Cu(acac)\textsubscript{2} (2 : 1)</td>
<td>1.5</td>
<td>–</td>
<td>&gt;99 : 1</td>
<td>100</td>
</tr>
<tr>
<td>4</td>
<td>PhMgBr</td>
<td>PhMgBr/Cu(acac)\textsubscript{2} (2 : 1)</td>
<td>1.5</td>
<td>ZnI\textsubscript{2} (1.5)</td>
<td>no reaction</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>PhMgBr</td>
<td>PhMgBr/Cu(acac)\textsubscript{2} (3 : 1)</td>
<td>1.5</td>
<td>–</td>
<td>52 : 48</td>
<td>–</td>
</tr>
<tr>
<td>6</td>
<td>PhMgBr</td>
<td>PhMgBr/Cu(acac)\textsubscript{2} (3 : 1)</td>
<td>1.5</td>
<td>ZnI\textsubscript{2} (1.5)</td>
<td>98 : 2</td>
<td>–</td>
</tr>
<tr>
<td>7</td>
<td>PhLi</td>
<td>PhLi/CuBr-Me\textsubscript{2}S (2 : 1)</td>
<td>1.5</td>
<td>MgBr\textsubscript{2} (4)</td>
<td>82 : 18</td>
<td>–</td>
</tr>
<tr>
<td>8</td>
<td>PhLi</td>
<td>PhLi/Cu(acac)\textsubscript{2} (2 : 1)</td>
<td>1.5</td>
<td>MgBr\textsubscript{2} (4)</td>
<td>complex</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>PhLi</td>
<td>PhLi/CuTC\textsuperscript{a} (2 : 1)</td>
<td>1.6</td>
<td>MgBr\textsubscript{2} (3)</td>
<td>98 : 2</td>
<td>88</td>
</tr>
<tr>
<td>10</td>
<td>n-BuMgBr</td>
<td>n-BuMgBr/CuBr-Me\textsubscript{2}S (2 : 1)</td>
<td>1.5</td>
<td>–</td>
<td>54 : 46</td>
<td>–</td>
</tr>
<tr>
<td>11</td>
<td>n-BuMgBr</td>
<td>n-BuMgBr/CuBr-Me\textsubscript{2}S (2 : 1)</td>
<td>1.5</td>
<td>ZnI\textsubscript{2} (1.5)</td>
<td>&gt;99 : 1</td>
<td>91</td>
</tr>
</tbody>
</table>

\textsuperscript{a}TC: thiophene-2-carboxylate.
compatible with aryllithiums prepared by Li-halogen exchange and ortho-lithiation. As for the $n$-BuMgBr-based reagent, a low regioisomeric ratio by $n$-BuMgBr/CuBr·Me$_2$S in a 2:1 ratio (entry 10) was remarkably improved by addition of ZnI$_2$ and 4b was obtained in a high yield (entry 11).

The above method was applied to the substitution of enantioenriched picolinates 3c–e with PhMgBr- and PhLi-based reagents to produce anti $\text{S}_{N}2'$ products selectively (Scheme 17). Me-, MeO-, and F-substituted phenyl groups were installed as well, and an ortho substituent affected the reaction little (data not presented).

Scheme 17. Formation of Enantioenriched Quaternary Carbon Centers with Ph Copper Reagents

3.2. Synthesis of Biologically Active Compounds Possessing Quaternary Carbon Centers

Natural products and artificial drugs delineated in Figure 2 were chosen as synthesis targets of the allylic substitution. The necessary picolinates were prepared stereoselectively by a strategy summarized in Scheme 18. The asymmetric transfer hydrogenation of ketone 77 in Step 1 afforded propargylic alcohol 78. In Step 2, three substituted olefin structures of alcohols 80 and 82 were constructed by two stereospecific methods. Thus, the hydroalumination of 78 with Red-Al (Na$^+$/[AlH$_2$(OCH$_2$CH$_2$OMe)$_2$]–) followed by iodination gave (Z)-ido alcohol 79, which upon metal-catalyzed coupling with R$_3$-met. produced 80, while the hydromagnesiation of 78 with $i$-BuMgCl followed by the same sequence of the steps afforded 82 via (E)-isomer 81. These alcohols 80 and 82 were converted to picolinates 3 of types 1 and 2.
Sporochnol: The (S)-form was isolated from the Caribbean marine alga *Sporochnus bolleanus* as an effective chemical defense against marine herbivores. The synthesis is presented in Scheme 19, in which the olefin moiety of 3d was constructed through hydroalumination/iodination followed by the Negishi coupling of the derived iodide with MeZnI (3 equiv). The allylic substitution of picolinate 3d with 4-MeOC₈H₄MgBr/Cu(acac)₂ proceeded with 95% es and 98% rs to afford 4f, which was transformed to the known methyl ether of sporochnol, i.e., (R)-88. In a similar way, (S)-88 with the natural configuration was synthesized.
LY426965 (74), a serotonin 1A receptor antagonist. The key allylic picolinate 3g designed for the synthesis of LY426965 (74) was structurally similar to 3d (Scheme 20), and thus the same set of the
reactions was applied to acetylenic ketone 89. The allylic substitution of 3g (93% ee) afforded 4g in 82% yield with 99% es and 99% rs. The olefin part of 4g was cleaved to hemiacetal 92, to which c-C₆H₁₁ and piperazine groups were attached to furnish the target 74.

Verapamil Intermediate (75): This compound is the intermediate in the synthesis of the (S)-isomer of verapamil (101), which is a more potent calcium ion channel blocker than the (R)-isomer. Picoline 3h or the olefinic isomer was a candidate for the substitution with the copper reagent derived from the Grignard reagent 99 and Cu(acac)₂ (Scheme 21). Initially, installation of the i-Pr group on a model iodide 102 was attempted with i-PrZnCl under the Negishi coupling conditions to afford a mixture of undesired products 104 and 105 (Scheme 22, Part A), indicating a faster process of the initially formed i-Pr-Pd 103A to propene complex of Pd-H 104A followed by reconstruction to n-Pr-Pd 105A than the reductive elimination of 103A to 103 (Part B). We then took allyl-MgBr with an expectation of marginal β-H elimination, if any. In practice, the Pd-catalyzed coupling of the real iodide 97 possessing the i-Pr substituent was successful and the resulting olefin 98 was converted to picoline 3h smoothly. The substitution of 3h with 1.5–3.0 equivs of 99/Cu(acac)₂ in the 2:1 ratio was slower than that of sterically less congested picolines 3d and 3g in Schemes 19 and 20, but completed by using six equiv of the

Scheme 21. Synthesis of the Verapamil Intermediate 75
reagent. Product 4h was oxidized to aldehyde 100, and subsequent conversion furnished the target 75 in 37% yield from picolinate 3h.

**Scheme 22. An Attempted Coupling of 102 with i-PrZnCl and a Plausible Mechanism**

**Mesembrine (76)**, one of the 3a-(aryl)octahydroindole family, and a potent inhibitor of 5-hydroxytryptamine (5-HT) uptake (IC\textsubscript{50} = 27 nM)\textsuperscript{55} by binding to the 5-HT transporter.\textsuperscript{56} Allylic picolinates of alcohols 107 and 109 were conceived to produce a necessary framework of mesembrine (76) by \textit{anti} S\textsubscript{N}2' allylic substitution (Scheme 23). Preliminarily, synthesis of these alcohols from (Z)-iodides 106 and (E)-iodide 108 by Pd-catalyzed coupling with a CH\textsubscript{2}=CH(CH\textsubscript{2})\textsubscript{2}ZnX was studied using racemic alcohols and n-BuZnX (Part B).\textsuperscript{57} The Pd-catalyzed coupling of rac-106a (R = PMB) with model n-BuZnCl suffered from the \(\beta\)-H elimination and/or slow reaction depending on Pd catalysts (Scheme 23, Part B). In contrast, (E)-isomer rac-108b (R = TBS) and n-BuZnCl afforded 112b as the major product (Part B). n-BuMgBr gave similar product selectivity. Ni(acac)\textsubscript{2} did not produce 112b, but the \textit{trans} isomer of 113b was product. Based on these results, the synthesis of mesembrine (76) was accomplished as presented in the next paragraph.

The hydromagnesiation of 115 (96% ee) according to Sato\textsuperscript{48} afforded 108b exclusively after iodination (Scheme 24). The Pd-catalyzed coupling of 108b with CH\textsubscript{2}=CH(CH\textsubscript{2})\textsubscript{2}MgBr proceeded as efficient as with n-BuMgCl, and subsequent esterification of 109b with PyCO\textsubscript{2}H afforded allylic picolinate 3i stereospecifically. The allylic substitution of 3i with 3,4-(MeO)\textsubscript{2}C\textsubscript{6}H\textsubscript{5}MgBr (99)/Cu(acac)\textsubscript{2} in a 2:1 ratio
Scheme 23. Preliminary Study for the Synthesis of Mesembrine

Scheme 24. Synthesis of Mesembrine
was stereo- and regioselective, and the resulting $S_N2'$ product 4i was transformed to keto aldehyde 117 through the Wacker oxidation to afford methyl ketone 116. Finally, aldol reaction of 117 and subsequent de-nosylation afforded mesembrine (76).

4. Synthesis of Quaternary Carbon Centers on Cyclohexane Rings

The next challenge was construction of a quaternary carbon center on a cyclohexane ring by allylic substitution. This reaction pattern is presented in the introduction (eq 15 in Scheme 6), which is also shown in Scheme 25 with the preparation of allylic substrates 15 from ketones 118. Since the Horner-Wadsworth-Emmons reaction of 118 was expected to produce 15 as an olefinic mixture, influence of the olefin geometry on the stereochemical outcome of the allylic substitution, i.e., diastereoselectivity (ds) relative to $R^1$, was a prime concern. Furthermore, low regioselectivity (rs) of 16 over 119 was worried since the $\alpha$ carbon of picolinates 15 is sterically much less congested. In this section, the allylic substitution of 15 and synthesis of biologically active cyclohexanes are described.

Scheme 25. Construction of Quaternary Carbon Centers on Cyclohexane Rings

4.1. Regioselectivity and Conformation-Controlled Stereochemistry

The $t$-Bu derivative 15a was the test picolinate to figure out regioselectivity (rs) (16a over 119a) and reactivity of reagents. Methyl copper reagents, MeMgBr/CuBr·Me2S (2:1), gave a mixture of 16a and 119a in a 22:78 ratio, which was 22% rs for 16a (Table 8, entry 1). The ratio was improved by addition of $ZnX_2$ ($X = Br, I$) (entries 2 and 3). In contrast, the 1:1 reagent was less regioselective and less reactive (entry 4). The diastereomeric selectivity (ds) (16a over 120a) was high enough irrespective of $ZnX_2$ (entries 1–3). Similar levels of the selectivity were also found for Et, $n$-Bu and $i$-Pr copper reagents (e.g., $n$-Bu: entry 6 vs. entry 5). Native rs of PhMgBr/CuBr·Me2S (2:1) was 46% (entry 7), which was improved with $ZnI_2$ to 80% (entry 8). Later, higher rs (87%) was realized with PhMgBr/Cu(acac)$_2$/ZnI$_2$ (entry 9). However, we think that the selectivity is not a practical level.

Allylic compounds 121 possessing other leaving groups were also subjected to the substitution with the $n$-Bu reagent to disclose that low rs (46%) for phosphate 121 ($L = (EtO)_2P(O)O$) was improved by $ZnI_2$ to
97%, which was an almost same level as that for picolinate 15a (entry 6). In contrast, \(o-(\text{Ph}_2\text{P})\text{C}_6\text{H}_4\text{CO}_2\) (\(o\text{-DPPB}\)), \(\text{C}_6\text{F}_5\text{CO}_2\), and \(\text{MeOCO}_2\) showed low to marginal reactivity and/or regioselectivity.

Table 8. Construction of a Quaternary Carbon Center

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>reagent (ratio)</th>
<th>additive (ZnX(_2))</th>
<th>rs(^b) (%)</th>
<th>ds(^c) (%)</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>(\text{MeMgBr}/\text{CuBr\cdot Me}_2\text{S} (2:1))</td>
<td>–</td>
<td>22</td>
<td>98</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>Me</td>
<td>(\text{MeMgBr}/\text{CuBr\cdot Me}_2\text{S} (2:1))</td>
<td>ZnBr(_2)</td>
<td>99</td>
<td>97</td>
<td>94</td>
</tr>
<tr>
<td>3</td>
<td>Me</td>
<td>(\text{MeMgBr}/\text{CuBr\cdot Me}_2\text{S} (2:1))</td>
<td>ZnI(_2)</td>
<td>100</td>
<td>100</td>
<td>85</td>
</tr>
<tr>
<td>4</td>
<td>Me</td>
<td>(\text{MeMgBr}/\text{CuBr\cdot Me}_2\text{S} (1:1))</td>
<td>ZnBr(_2)</td>
<td>85</td>
<td>94</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td>(n\text{-Bu})</td>
<td>(n\text{-BuMgBr}/\text{CuBr\cdot Me}_2\text{S} (2:1))</td>
<td>–</td>
<td>62</td>
<td>100</td>
<td>–</td>
</tr>
<tr>
<td>6</td>
<td>(n\text{-Bu})</td>
<td>(n\text{-BuMgBr}/\text{CuBr\cdot Me}_2\text{S} (2:1))</td>
<td>ZnI(_2)</td>
<td>99</td>
<td>100</td>
<td>94</td>
</tr>
<tr>
<td>7</td>
<td>Ph</td>
<td>(\text{PhMgBr}/\text{CuBr\cdot Me}_2\text{S} (2:1))</td>
<td>–</td>
<td>46</td>
<td>nd</td>
<td>–</td>
</tr>
<tr>
<td>8</td>
<td>Ph</td>
<td>(\text{PhMgBr}/\text{CuBr\cdot Me}_2\text{S} (2:1))</td>
<td>ZnI(_2)</td>
<td>80</td>
<td>&gt;99</td>
<td>–</td>
</tr>
<tr>
<td>9(^d)</td>
<td>Ph</td>
<td>(\text{PhMgBr}/\text{Cu(acac)}_2 (3:1))</td>
<td>ZnI(_2)</td>
<td>87</td>
<td>&gt;99</td>
<td>73</td>
</tr>
</tbody>
</table>

\(^a\) 1.5 equiv except for entry 6 (3 equiv). \(^b\) 16a over 119a. \(^c\) 16a over 120a. \(^d\) \(t\text{-Bu}\) in 15a was replaced by Ph.

The conformation of 15a and the likely repulsion between the incoming reagent and the axial hydrogens (Ha, Hb) are illustrated in Scheme 26. Since Hb overhangs above the olefin more significantly than Ha, the equatorial attack from the bottom (Ha-side) is sterically favored. This stereochemical analysis was
next applied to various picolinates to establish the generality of the conformation-controlled allylic substitution.

Allylic picolinates that were prepared as mixtures of $Z/E$ olefinic isomers by the method of Scheme 25 (118 → 15) were also good substrates to afford desired products with high diastereomeric selectivity (ds) and almost complete regioselectivity (rs) in good isolated yields (Scheme 27). High ds observed in eq 25 was noteworthy since the chair conformation of the starting picolinate is probably distorted. Picolinate derived from a steroid was not an exception, and high ds indicates marginal influence by 19-Me (eq 28). A piperidine derivative was also a good substrate (eq 26).

![Scheme 27. Conformation-Controlled Allylic Substitution](image)

4.2. Synthesis of Biologically Active Cyclohexanes Possessing Quaternary Carbon Centers

With the above diastereochemistry in mind, synthesis of cyclobakuchiol A (122), anastrephin (124), and axenol (125) delineated in Figure 3 has been accomplished as described in the following paragraphs. The
concept of the conformation-control was successfully applied to synthesis of cyclobakuchiol B (123). The synthesis of psoracorylifol B (126) by Tong is also presented.

Figure 3. Synthetic Targets Possessing Quaternary Carbon Centers on Rings

**Cyclobakuchiol A (122):** This compound and its diastereomer, cyclobakuchiol B (123), are antipyretic and anti-inflammatory compounds isolated as a mixture from *Psoralea glandulosa* L.\(^{58}\) Among the diastereoisomers, the stereochemistry of cyclobakuchiol A (122) was identical to that predicted by the conformation-controlled allylic substitution of 130 (Scheme 28).\(^{59}\) Enone 127 was derived from (+)-β-pinene, and 1,4-addition of 4-MeOC\(_6\)H\(_4\)MgBr to the enone afforded 128, which was then converted to ketone 129. This ketone was later synthesized from quinic acid.\(^{60}\) Horner-Wadsworth-Emmons reaction followed by reduction and esterification afforded allylic picolinate 130, which was a 1:1 \(E\) and \(Z\) mixture. The allylic substitution of picolinate 130 with MeMgBr/CuBr·Me\(_2\)S (2:1) in the presence of ZnI\(_2\) proceeded with 98% \(\text{ds}\). Without ZnI\(_2\), the regioisomer was produced with 97% \(\text{rs}\) in 98% yield.

Scheme 28. Synthesis of Cyclobakuchiol A via Conformation-Controlled Allylic Substitution
**Cyclobakuchiol B:** Based on the concept of the conformation-controlled diastereoselectivity, enolate trap of 134 with vinylsulfoxide 133 was expected to afford the framework of cyclobakuchiol B stereoselectively (Scheme 29). Ketone 129 was converted to ester 132 in three steps via the cyanide (TsCH₂NC, t-BuOK). The enolate trap at −105 °C (MeOH, liquid nitrogen) afforded 135 with 96% ds (cf. 86% ds at −78 °C). Then, the thermal decomposition of 135 afforded olefin 136, which was transformed to cyclobakuchiol B (123) in four steps.

**Scheme 29. Synthesis of Cyclobakuchiol B via Stereoselective Reaction of Enolate 134**

**Anastrephin** (124), a sex pheromone produced by Caribbean and Mexican fruit flies. The conformation-controlled allylic substitution of picolinate 142 through a likely conformer depicted in Scheme 30 was conceived to afford the all-carbon quaternary center present in anastrephin (124). As shown in Scheme 30, Part A, epoxidation of alcohol 137 (>99% ee) synthesized via the CBS reduction was stereoselective, and the resulting epoxy alcohol 138 was converted to epoxide 140, which was a 1:1 mixture of the (E)- and (Z)-olefins. The epoxide ring opening of the mixture with the Al enolate derived from MeCO₂-t-Bu afforded 141, which was then transformed to picolinate 142 (E/Z = 1:1) in 54% yield over three steps. The ZnI₂-assisted substitution of 142 with MeMgBr/CuBr·Me₂S (2:1) followed by hydrolysis of the TMS group afforded alcohol 144 with 92% ds in 51% yield. Finally, TsOH-promoted lactonization produced anastrephin (124) in a high yield. Since slightly low ds of 92% was observed for the allylic substitution, each of the (E)- and (Z)-isomers of picolinate 142 was subjected to the allylic substitution to find that the (E)-isomer afforded 143 with 99% ds in 85% yield (Scheme 30, Part B), whereas the (Z)-isomer was reluctant to the substitution and gave a mixture of 143 with 87% ds and unidentified products.
Axenol (125), a synthetic intermediate for gleenol and axisonitrile-3: Since gleenol, the diastereomer of 125 at the OH-carbon, has occasionally been called as "axenol", the structure in a publication should be confirmed before a research regarding to axenol/gleenol will start. A retrosynthesis of 125 by ring-closing metathesis produced 145, and the conformation-controlled allylic substitution of picolinate 146 with the reagent derived from 147 and CuBr·Me₂S was envisaged to produce 145 (Scheme 31). 63

The synthesis along this analysis is summarized in Scheme 32, in which (−)-menthol (148) was converted to ketone 149 in five steps via the dihydroxylation of the derived cyclohexene. 64 The Horner–Wadsworth–Emmons reaction of 149 under normal and Masamune conditions (NaH in THF; LiCl/DBU, respectively) was unsuccessful, probably by steric reasons. Instead, the reaction with the anion derived from TMSCH₂CO₂Et and LDA proceeded highly stereoselectively to afford (Z)-ester (Z)-150, which was
then converted to picolinate (Z)-146. The allylic substitution of the picolinate with 147/CuBr·Me₂S (2:1) was regio- and diastereoselective to furnish 145 in 85% yield after desilylation. Finally, the ring-closing metathesis furnished axenol (125).

Psoracorylifol B (126), a natural product isolated from the seeds of Psoralea corylifolia L. (a well-known traditional Chinese medicine): This compound was a synthetic target of Tong, who envisaged allylic substitution of picolinate 152 with MeCuMgBr reagent (Scheme 33). Since the α face (bottom side) in their stereochemical structure 152A was concave and hence formation of stereoisomers was expected. However, the allylic substitution of picolinate 152 (E/Z = 3:1) with Me₂CuMgBr/ZnCl₂ was stereoselective to afford 153 with 91% ds (153/isomer = 10.5:1). To understand the result, the stereostructure of 152 is depicted from a different angle to produce 152B (Scheme 33), and
following reasons (one or both) are suggested: (1) the α face is rather opened for the substitution and the equatorial attack is preferred as a consequence of smaller influence by Hc at C7 than that by Hb at C4 (Part A); (2) the Ar group (TIPSOC₆H₄⁻) is a steric bias to push the Pic group to the β-face and the anti SN₂ substitution takes place selectively (Part B).

< Synthesis and the proposed conformation of 152 >

Scheme 33. Synthesis of Psoracorylifol B by Tong

5. Substitution Reaction at Saturated Secondary Carbons by Us and Other Groups

Although many methods for metal-catalyzed substitution at primary alkyl carbons are available, only a few methods have been developed for the substitution at sterically more congested secondary alkyl carbons. In this section, the substitutions at secondary carbons producing enantioenriched compounds are summarized. Our recent finding of the copper-catalyzed substitution of alkyl pyridinesulfonates possessing the PySO₃ leaving group is also presented (Scheme 1, eq 2). However, reactions on cyclohexanes and -pentanes that probably proceed via radicals are omitted.
5.1. Reactivity of Substrates and Cuprates

The substitution of halides and sulfonates with cuprates has a long history, and the investigations summarized in eqs 29 and 30 in Scheme 34 are especially informative for discussion about reactivity and stereochemistry. The substitution of halides using a Gilman cuprate (Ph₂CuLi) proceeded with inversion (eq 29). Inversion was also observed for the substitution of bromide (X = Br) with higher order cuprates (R₂Cu(CN)Li₂), whereas a more reactive iodide (X = I) proceeded with racemization (eq 30). In contrast, tosylate (X = OTs) was less reactive, and required excess n-Bu₂Cu(CN)Li₂ (10 equiv) at rt to produce (R = n-Bu) in >80% yield. However, the stereochemical course was not elucidated.

Although tosylates of secondary alcohols were not good substrates as mentioned above (low reactivity and requirement of large quantity of cuprates), tosylates have been used in organic synthesis probably because of easy accesses. As delineated in eqs 31–33 in Scheme 35, the tosylate substitution proceeded with inversion of the stereogenic centers. Higher reactivity of R₂CuMgBr than R₂CuLi was reported (eqs 32 and 33).
A Lewis basic substituent such as MeSCH$_2$O, PhS, and MeOCH$_2$O at a proximal position from C-OTs accelerated the substitution. For example, the substitution of 157 and 159 completed in 15 h and 4.5 h for Me and n-Bu cuprates, respectively (Scheme 36). The reaction times indicated the lower reactivity of Me$_2$CuLi than other alkyl cuprates. A similar reactivity order was reported for the substitution of secondary halides with (R$_2$Cu(CN)Li)$_2$ (eq 30). The method (Scheme 36) was applied for the synthesis of ionomycin.

Scheme 35. Substitution of Secondary Tosylates with Cuprates

Scheme 36. Acceleration of the Substitution by a Proximal Substituent on Secondary Tosylates

5.2. Previous Copper-Catalyzed Substitutions of Tosylates

As mentioned above, the substitution of secondary tosylates generally required excess molar quantity of cuprates and long reaction times, and thus the next generation of the study was directed to find a catalytic version and/or a booster for the substitution. In connection with the synthesis study of metacyclophanes, Burns studied a copper-catalyzed substitution of primary tosylates with Grignard reagents in 1997, and discovered a catalytic system consisting of a THF-soluble CuBr·Me$_2$S·LiBr·LiSPh (6 mol%) and HMPA in THF (6% v/v) (Scheme 37, eq 34). This catalyst was superior to Li$_2$CuCl$_4$ and CuBr/HMPA. Aryl- and vinyl-MgBr were compatible with this catalyst. However, the substitution of secondary tosylates was
affected by bulkiness of substituents (eqs 35 and 36). In contrast, the corresponding mesylates gave higher yields than the tosylates.

Scheme 37. Cu-Catalyzed Substitution of Tosylates by Burns

In 2012, Liu published a CuI-catalyzed substitution of secondary tosylate 161 with c-C₆H₁₁MgBr in the presence of TMEDA (0.2 equiv) and LiOMe (1 equiv) to produce 162 in 86% yield (Scheme 38, eq 37). TMEDA functioned to reduce the formation of olefins. Other copper salts such as CuBr, CuTC, Cu(OTf)₂

Scheme 38. Cu-Catalyzed Substitution of Secondary Tosylates by Liu
lowered the yield. As shown in eqs 38 and 39 the substitution of enantiomerically enriched tosylates proceeded with inversion of the stereochemistry (es is not given). Furthermore, the authors emphasized the applicability of the method to secondary and tertiary Grignard reagents.

Later, Negishi applied the above substitution for the synthesis of phthioceranic acid (170).\textsuperscript{21} Initially, a model substitution of 163 with $i$-BuMgBr produced 164 in a moderate yield (40%), which was improved with bipyridyl (75%) (Scheme 39, Part A). This modification was applied to the substitution of 163 with 165 and that of 167 with 168 (Part B). The resulting product 169 was finally oxidized to the target 170. Note that reagents 165 and 168 were synthesized via Zr-catalyzed asymmetric carboalumination of alkenes (ZACA) followed by Pd-catalyzed vinylation.\textsuperscript{24} This tandem process is one of the Negishi's signature reactions.

\begin{align*}
\text{(Part A) Optimized Reaction Conditions} & \\
\text{163} & \xrightarrow{\text{MgBr (1.5 equiv)}} \text{164} \\
\text{Cul (0.2 equiv), amine (0.2–0.4 equiv)} & \text{LiOMe (1 equiv), THF, 0 °C, 24 h} \\
\text{amine yield} & \\
\text{TMEDA, 40%} & \text{Bipyridyl, 75%}
\end{align*}

\begin{align*}
\text{(Part B) Synthesis of Phthioceranic Acid} & \\
\text{163} & \xrightarrow{\text{Cul/bipyridyl/LiOMe}} \text{166, 58%} \\
\text{C}_{16}\text{H}_{33}\text{MgBr} & \xrightarrow{\text{165 (1.5 equiv)}} \text{C}_{16}\text{H}_{33}\text{O} \text{Ph} \\
\text{BrMg} & \xrightarrow{\text{Cul/bipyridyl/LiOMe}} \text{C}_{16}\text{H}_{33}\text{R} \\
\text{Ru (cat.)} & \xrightarrow{\text{NaIO}_4} \text{169, } R = \text{Ph, 48%} \\
\text{170, } R = \text{CO}_2\text{H (phthioceranic acid)}
\end{align*}

Scheme 39. Optimization of the Substitution and Synthesis of Phthioceranic Acid by Negishi

### 5.3. The Copper-Catalyzed Substitution of Pyridinesulfonates

The substitution at secondary carbons with MeMgX is a useful method for the synthesis of biologically active Me substituted compounds.\textsuperscript{23,24} However, methylation was not described in the above copper-catalyzed systems. Instead, the lower reactivity of Me cuprates than that of alkyl cuprates has been reported.\textsuperscript{69,73} Consequently, our goal was set to develop a new catalytic system and a booster not only for
RMgX but also for MeMgX. Since the carbonyl carbon of picolinate is susceptible to Grignard reagents, we selected the pyridinesulfonyloxy group (PySO$_3$) with expectations of compatibility with RMgX and an activation mechanism similar to that operated to the pyridinecarboxy group (Pic). Before the study of substitution using PySO$_3$, the substitutions of tosylate 171 with c-C$_6$H$_ {11}$MgBr and MeMgCl were examined according to the Liu's procedure to figure out the reactivity order of c-C$_6$H$_ {11}$MgBr > MeMgCl (Scheme 40, eqs 40 and 41).

![Scheme 40. Finding of the PySO$_3$ Group for Substitution by Us](image)

The substitution of pyridinesulfonate 173 with MeMgCl under similar conditions completed only in 15 min (data not presented), and further investigation disclosed that Cu(OTf)$_2$ catalyzed the substitution without the additives (LiOMe, TMEDA) to afford 172b in 77% yield (Scheme 40, eq 42). The substitution of 174 with various RMgBr also completed in 30 min (eq 43). The substitution examined with substrates shown in Scheme 41 proceeded with inversion of the stereochemistry. Thus, (S)-174 (96% ee) afforded enantioenriched (R)-175a with 98% es, while diastereomerically enriched racemic sulfonates 163, 176, and 178 gave inversion products 164, 177, and 179 in a stereospecific manner. These results support the mechanism illustrated in Scheme 1, eq 2.
5.4. The Zinc-Catalyzed Substitution at α-Carbons of Esters

Triflates 180 derived from α-hydroxy esters underwent ZnCl₂-catalyzed substitution with RMgX as developed by Breit (Scheme 42, eq 44). Easy availability of precursor alcohols, complete inversion, and high yields make this method particularly appealing.

Scheme 42. Substitution at α-Carbons of Esters and Synthesis of Iterative 1,3-Dimethyl Units by Breit
high yields are advantages of the substitution. The iterative process was developed later to produce the 1,3-dimethyl unit 183.

5.5. The Nickel-Catalyzed Asymmetric Substitution of Secondary Halides Possessing Functional Groups

The substitution of secondary racemic halides with boranes developed by Fu using Ni/diamine catalyst was later modified to an asymmetric version with the chiral diamine \((R,R)-194a\). For example, racemic secondary halides 184 underwent asymmetric substitution with borane 185a to produce highly enantioenriched product 186 (Scheme 43, eq 45). An aromatic substituent (Ar) in a proximal position is the structural requirement. Later, the asymmetric substitution was successfully expanded to racemic

\[
\text{Ar} \text{Br} + \text{BPhMeHNMe} \xrightarrow{\text{Ni(cod)}_2, \text{t-BuOK, t-BuOH}} \text{ArPh} \\
\text{Bn} \text{O} = \text{Ph} \text{Br} + \text{Bn} \text{O} = \text{Ph} \text{Br} \xrightarrow{\text{NiBr}_2, \text{t-BuOK, } n-C_8H_{17}OH} \text{Bn} \text{O} = \text{Ph} \\
\text{Ph} \text{Cl} + \text{Bn} \text{O} = \text{Ph} \xrightarrow{\text{NiBr}_2, \text{t-BuOK, } n-C_8H_{17}OH} \text{PhO} = \text{Bn} \\
\text{Bn} \text{O} = \text{Ph} \text{Br} + \text{BrZnPh} \xrightarrow{\text{NiBr}_2, \text{t-BuOK, } n-C_8H_{17}OH} \text{Bn} \text{O} = \text{Ph} 
\]

\begin{align*}
\text{Scheme 43. Nickel-Catalyzed Asymmetric Substitution by Fu}
\end{align*}
secondary halides such as 187 and 189 possessing oxygen- or nitrogen-containing functional groups as indicated by eqs 46 and 47, respectively.\textsuperscript{83,84} A similar coupling reaction has been reported using organozincs (eq 48).\textsuperscript{85} These substitutions are summarized in his review.\textsuperscript{66a}

6. Conclusion

This review summarized the high potency of the picolinoxy (PyCO\textsubscript{2}) and pyridinesulfonyloxy (PySO\textsubscript{3}) leaving groups for the allylic and alkyl substitution reactions at secondary carbons. The allylic substitution described in the first part covers alkyl, aryl, heteroaryl, alkenyl, and alkynyl copper reagents. These reagents are conveniently synthesized by mixing Grignard reagents and CuBr·Me\textsubscript{2}S or organolithiums, copper salt, and MgBr\textsubscript{2}. The reaction proceeds with \textit{anti} S\textsubscript{N}2' manner with high enantiospecificity (es), and creates tertiary and quaternary carbon centers. Cyclohexylidene picolinates afford cyclohexanes with quaternary carbon centers. Successful syntheses of biologically active compounds using the allylic substitution as key steps were presented, showing synthetic flexibility in designing the syntheses. In the second part of this review, alkyl substitution reaction at secondary carbons was presented. The copper-catalyzed reaction of secondary tosylates with Grignard reagents in literatures proceeds with inversion, but slowly. In contrast, PySO\textsubscript{3}, selected by us on the analogy of PyCO\textsubscript{2}, shows high leaving potency to complete the reaction in short times (usually 30 min) with RMgX and less nucleophilic MeMgCl. The substitution at the α-carbons and the asymmetric substitution of racemic secondary halides possessing functional groups were also described.

ACKNOWLEDGEMENTS

This work was supported by Grant-in-Aids for Scientific Research from MEXT (26410111, 23550119, 20031009, 19550102, 18045013) and in part by a Grant-in-Aid for Young Scientists from JSPS.

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65. (a) J. Ren, Y. Liu, L. Song, and R. Tong, *Org. Lett.*, 2014, 16, 2986; (b) Structure 17 in Scheme 3 of ref. 65a was redrawn.
Yuichi Kobayashi, an emeritus professor of Tokyo Institute of Technology, received his Ph. D. from Tokyo Institute of Technology in 1981. He worked for Professor Gilbert Stork at Columbia University, New York (1981 to 1982). He joined the Fumie Sato’s laboratory at Tokyo Institute of Technology in 1982 as an assistant professor. Since then he spent at the university 37 years long for teaching and research until his retirement in March, 2019. During the period, he promoted to associate professor in 1988, became an independent researcher in 1995, and advanced to full professor in Dec., 2010. He received Young Chemist Award of the Chemical Society of Japan in 1988. In April, 2019, he moved to Meiji University, Organization for the Strategic Coordination of Research and Intellectual Properties. His research interests include organic synthesis using transition metal catalysts and developments of chiral C–C bond formation. Targets include fatty acid metabolites known as resolvins and leukotrienes, isoprostanes, epi-jasmonates, tetrahydrocannabinoids, cinchona alkaloids, phoslactomycins, and compounds presented in this review.