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

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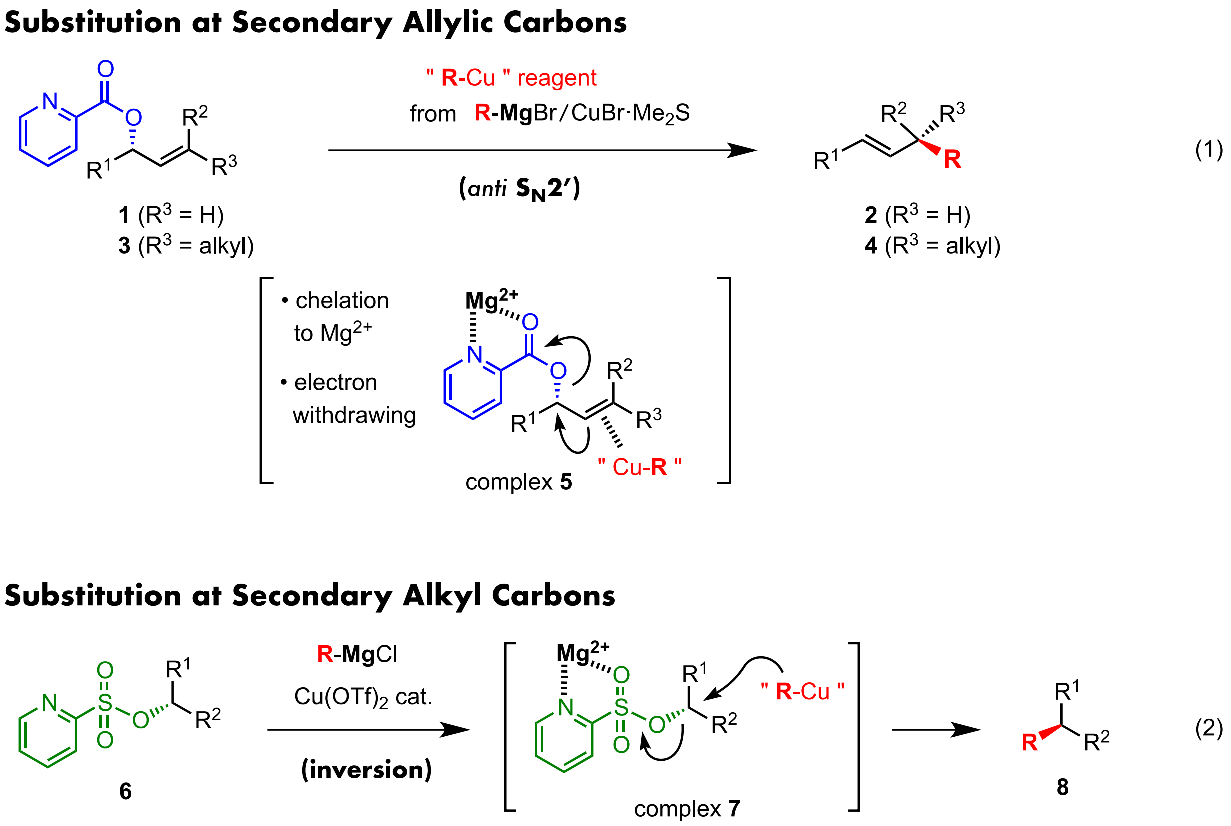
Abstract – Substitution at allylic secondary carbons using the pyridinecarboxylate (picolinoxy, $PyCO_2$, or Pic) leaving group is described in the first part of this review (Sections 2–4). Alkyl as well as less reactive alkenyl, heteroaryl, and aryl copper reagents are suitable for the substitution, 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 picolinates. 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.

CONTENTS

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, $PyCO_2$, 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, R^3 = H). Successful reagent types are alkyl (sp^3-C), aryl and alkenyl (sp^2-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 R^3 = alkyl produces quaternary carbon compounds **4** (Scheme 1, eq 1, R^3 = alkyl). Based on the fact that Mg^{2+} is generated in situ from RMgBr and $CuBr{\cdot}Me_2S$, the substitution is likely to proceed via complex **5**, in which the Pic group is synergistically activated by chelation to Mg^{2+} 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.

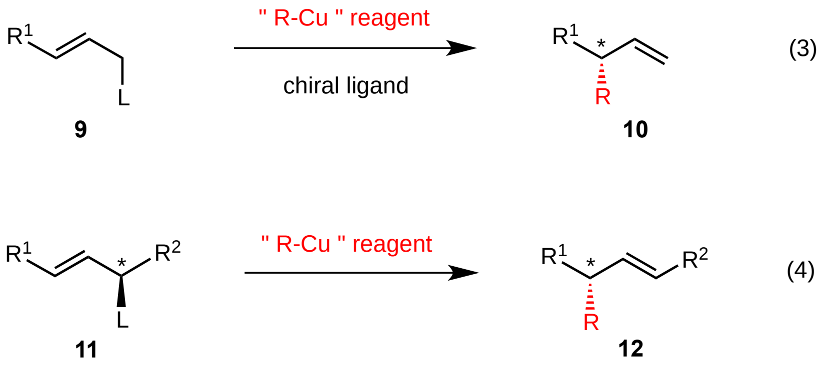


Scheme 1. Substitution Reactions and a Plausible Mechanism of the Activation

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.[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.



Items to be evaluated

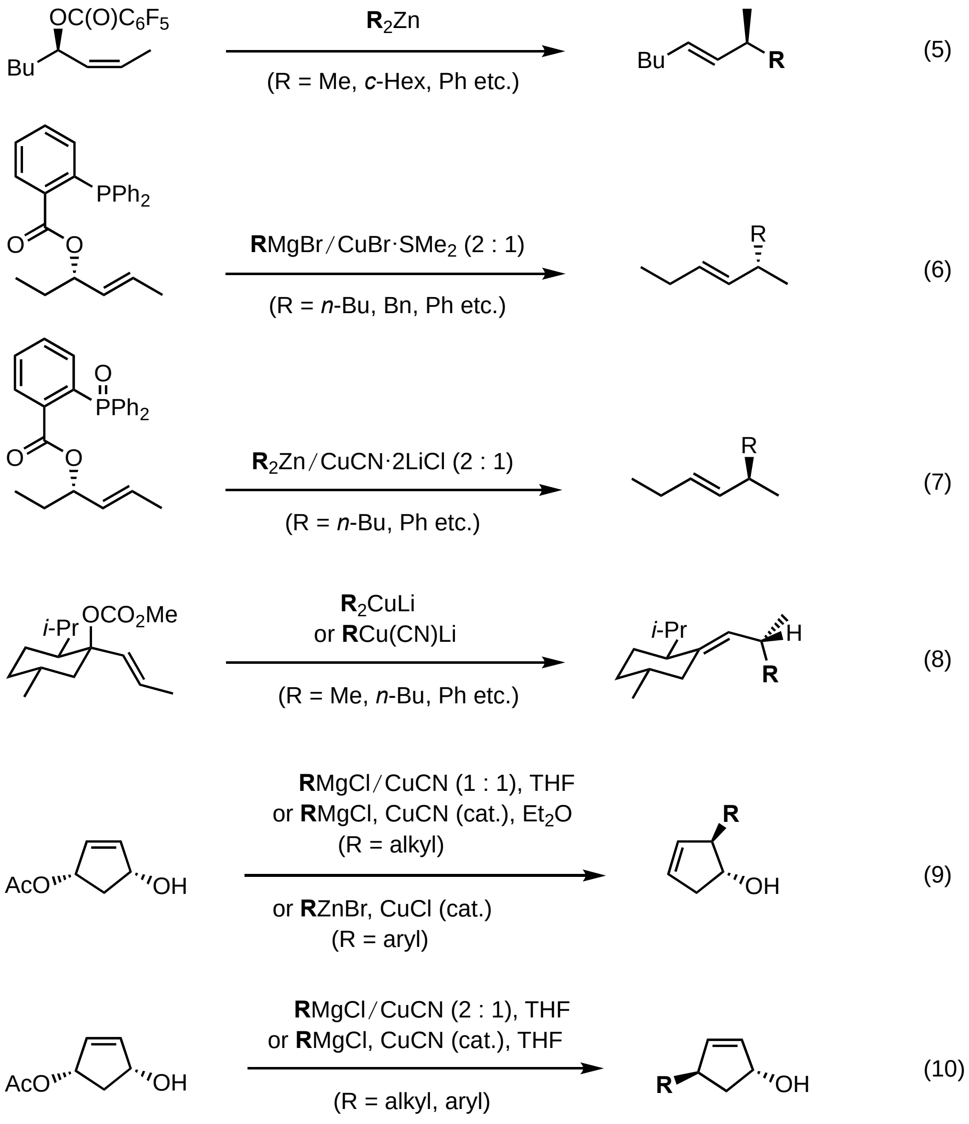
(a) reactivity
(b) regioselectivity
(c) stereoselectivity (chirality transfer)
(d) R in copper reagents: sp^3-C, sp^2-C, sp-C
(e) availability of substrates/reagents

Scheme 2. Allylic Substitutions at the Terminal and Internal Positions

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^1 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^1 and R^2, and hence highly potent leaving groups such as $C_6F_5CO_2$, *o*-Ph_2P-$C_6H_4CO_2$ (*o*-DPPB), and *o*-$Ph_2P(O)$-$C_6H_4CO_2$ 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]

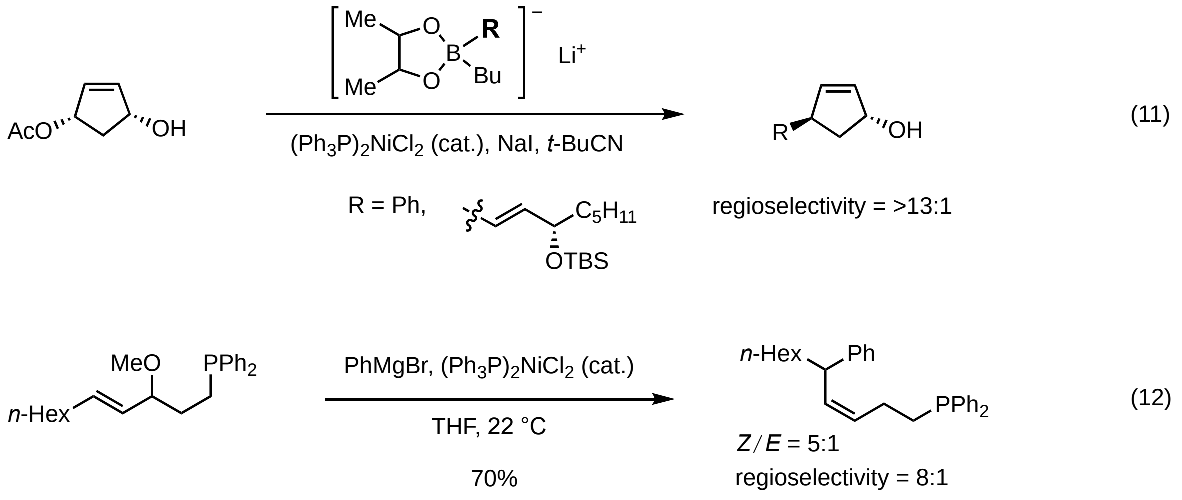
On the other hand, release from the steric congestion was the driving force of the allylic substitution (eq 8).[13] The hydroxy group on the cyclopentene ring enhanced the reactivity and controlled regio- and stereoselectivity (eqs 9 and 10).[14]

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 PPh_2 to a nickel catalyst in eq 12 enhanced the reactivity and regioselectivity.[17]



Scheme 3. Allylic Substitution of Secondary Allylic Esters with Copper Reagents Published by 2007

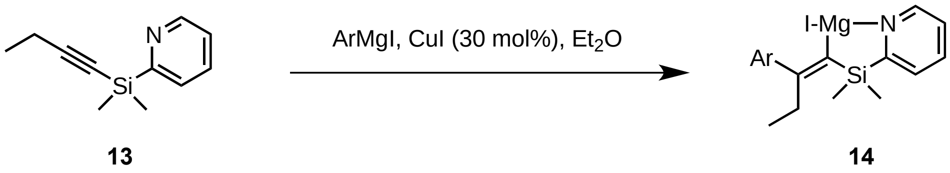
In 2007, we planned a new research project to utilize allylic substitution of the eq 4-type to organic synthesis because of expected synthetic merits of: (1) more flexibility in designing an original substrate **11** possessing substituents R^1 and R^2 than that for **9** possessing one substituent R^1; 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.



Scheme 4. Ni-Catalyzed Allylic Substitution

2.2. Finding of the Picolinoxy Leaving Group ($PyCO_2$)

Based on the underlying mechanisms of the substitutions shown in eqs 5[9] and 6[10] and the copper-catalyzed addition of ArMgI to (2-pyridyl)silylalkyne **13** to give intermediate **14** (Scheme 5)[20] we envisaged that a hybrid of these activations would be more effective than the single activation, and selected the picolinoxy group (Pic or $PyCO_2$) as a candidate. In practice, *anti* S_N2' substitution of *cis* allylic picolinates **1** took place with aryl and alkenyl reagents, which were less reactive than alkyl reagents (Scheme 6, eq 13).[21] Under the modified conditions, reagents were extended to heteroaromatic[22] and alkynyl copper reagents,[23] which are less nucleophilic than aryl reagents. The substitution of picolinates **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.[24]

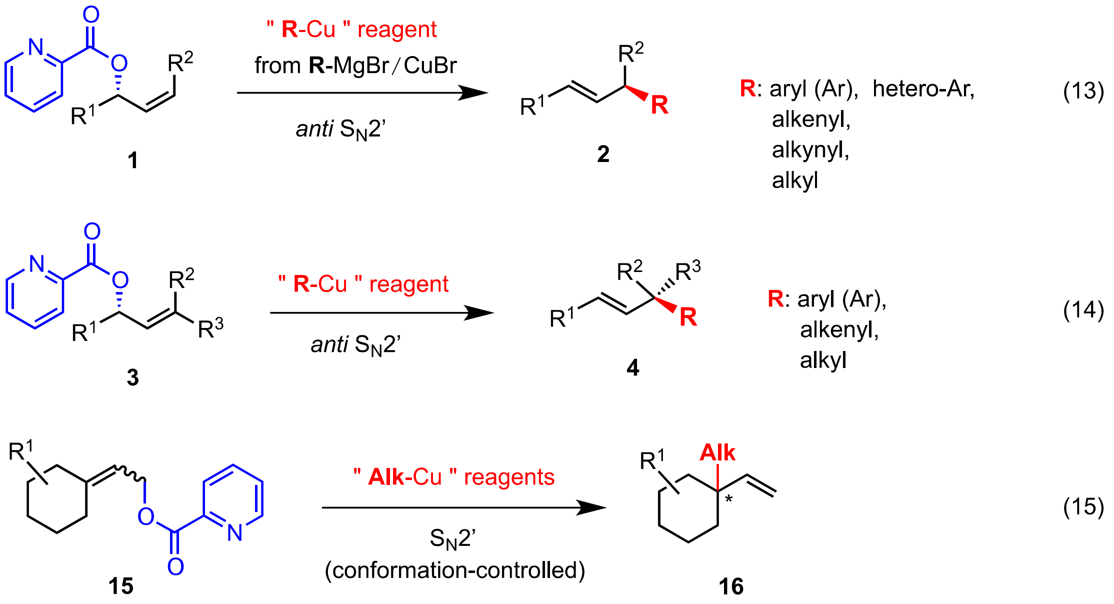


Scheme 5. Addition of ArMgI to 2-Pyridylsilylacetylene

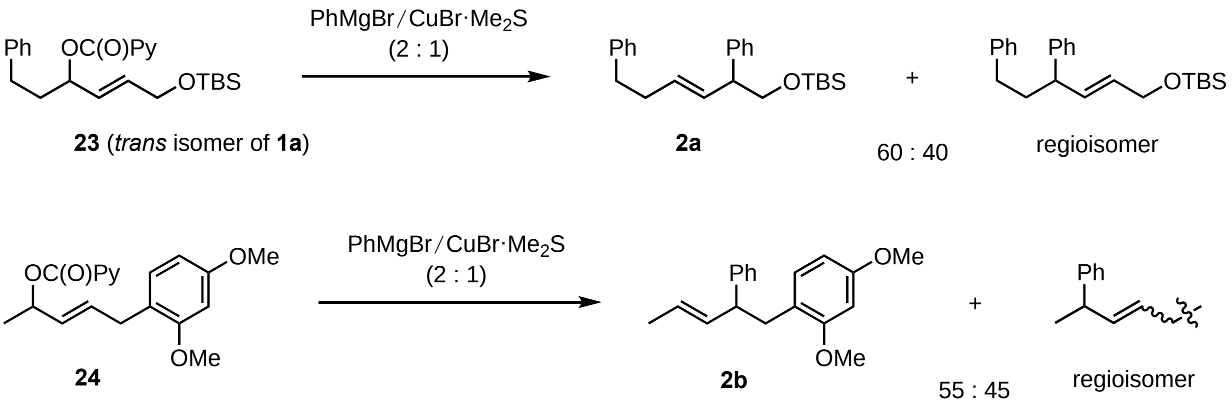
2.3. Comparison of Reactivity between Picolinates and Other Esters

Examination of leaving groups including the Pic group is summarized in Table 1.[21] The substitution of racemic picolinate **1a** (L = 2-$PyCO_2$) was studied with 2 or 3 equivalents (equiv) of Ph copper reagents derived from PhMgBr/CuBr·Me_2S 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·$MgBr_2$ from the 1:1 mixture and

$Ph_2CuMg\cdot MgBr_2$ 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-$PyCO_2$ was a slower leaving group than Pic (entry 4), and $PhCO_2$ 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 $C_6F_5CO_2$ group was also ineffective (entry 6). Phosphate **20** produced a mixture of **2a** and the *cis* isomer (entry 7, footnote a). Among Ph_2Zn 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).[21,25]

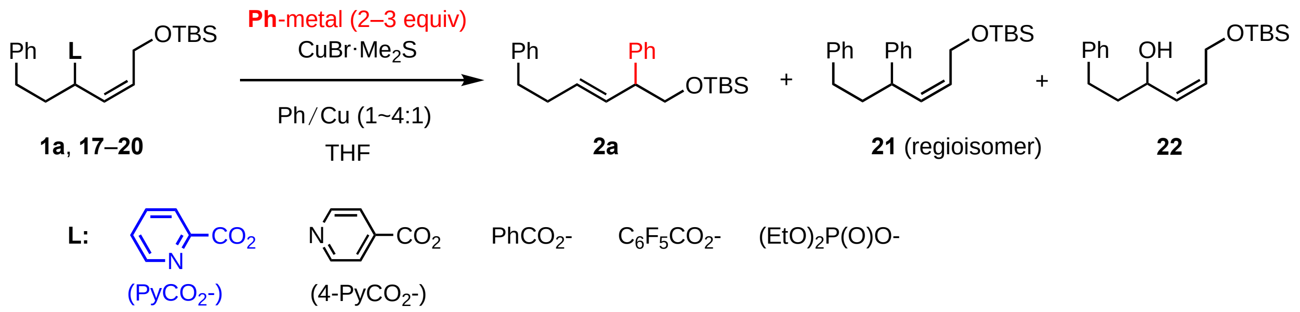


Scheme 6. Allylic Substitution of Picolinates with Copper Reagents



Scheme 7. Allylic Substitution of *trans* Allylic Picolinates Giving Regioisomeric Mixtures

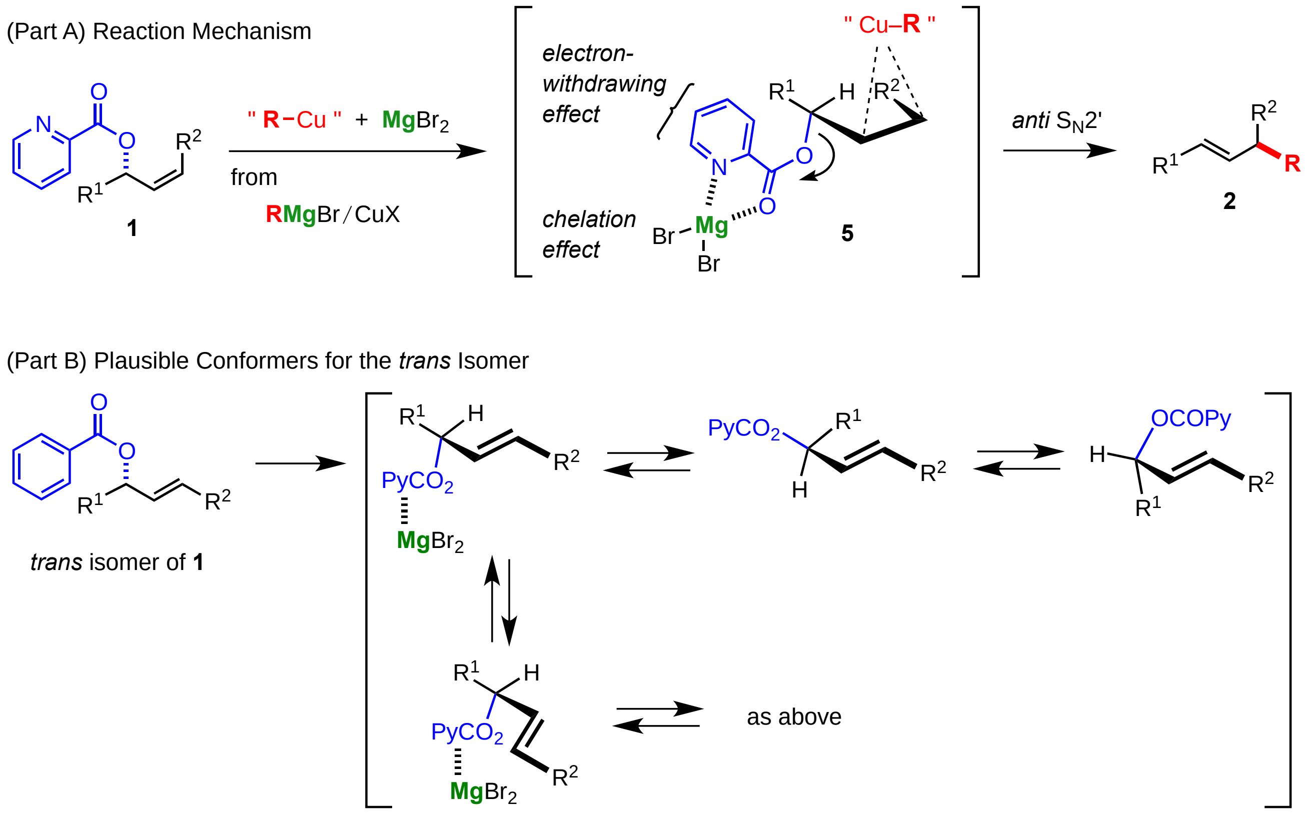
Table 1. Substitution of Various Secondary Allylic Esters with Phenyl Copper Reagents



entry	sub-strate	L	reagent	Mg/Cu	temp. (°C)	time (h)	**2a** : **21** : **22** : **1a**	**2a** : **21**	yield of **2a**
1	**1a**	**$PyCO_2$**	**$PhMgBr/$ $CuBr\cdot Me_2S$**	**1 : 1**	**0**	**1.5**	**98 : 2 : 0 : 0**	**98 : 2**	**84%**
2	**1a**	**$PyCO_2$**	**as above**	**2 : 1**	**0**	**1**	**99 : 1 : 0 : 0**	**99 : 1**	**91%**
3	**1a**	**$PyCO_2$**	**as above**	**4 : 1**	**0**	**1**	**99 : 1 : 0 : 0**	**99 : 1**	**85%**
4	**17**	4-$PyCO_2$	as above	2 : 1	0~rt	13	46 : 0 : 0 : 54	>99 : 1	nd
5	**18**	$PhCO_2$	as above	2 : 1	0~rt	20	0 : 0 : 0 : 100	–	–
6	**19**	$C_6F_5CO_2$	as above	1 : 1	0~rt	18	60 : 0 : 40 : 0	>99 : 1	nd
7	**20**	$(EtO)_2PO_2$	as above	3 : 1	0	3	99 : 1 : 0 : 0	99[a] : 1	90%[a]
8	**1a**	**$PyCO_2$**	**$Ph_2Zn\cdot 2MgBr_2/$ $CuBr\cdot Me_2S$**	**2 : 1**	**–15~0**	**1**	**99 : 1 : 0 : 0**	**99 : 1**	**91%**
9	**1a**	**$PyCO_2$**	**$PhZnBr\cdot 2MgBr_2/$ $CuBr\cdot Me_2S$**	**2 : 1**	**–15~0**	**1**	**85 : 2 : 0 : 13**	**98 : 2**	**nd**[b]

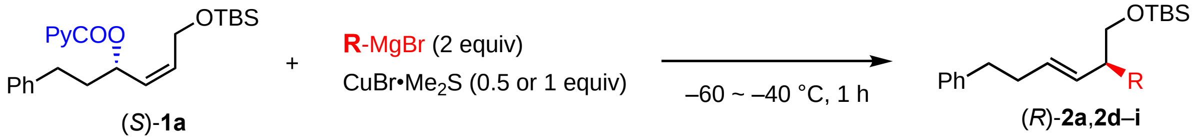
[a] Contained 20% *cis* isomer of **2a**. [b] Not determined.

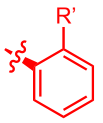
The transition state theory for the allylic substitution of allyl acetate with lithium cuprates suggests that Li^+ and Me_2Cu^- in the cuprate dimer interact with the acetate oxygen and the π-orbital.[26] With this theory in mind, stereochemical view of the likely transition state **5** is illustrated 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 $MgBr_2$, which is generated in situ from RMgBr and $CuBr\cdot Me_2S$, 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.



Scheme 8. Double Activation of the Pic Group

Table 2. Allylic Substitution of Enantioenriched Picolinates



entry	R in RMgBr	R / Cu	product		yield (%)	es^a (%)
1		4:1	(*R*)-**2a**	R' = H	83	98
2		2:1	(*R*)-**2a**	R' = H	93	99
3		2:1	**2c**	R' = Me	81	99
4		2:1	**2d**	R' = OMe	85	98
5		2:1	**2e**	R' = H	81	98
6		2:1	**2f**	R' = C_5H_{11}	75	97
7		2:1	**2g**	R' = Ph	85	97
8	Me	2:1	**2h**	R = Me	90	96
9	*n*-Bu	2:1	**2i**	R = *n*-Bu	89	96

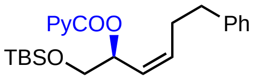
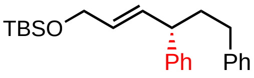
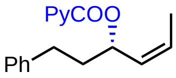
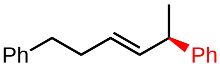
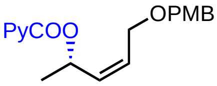
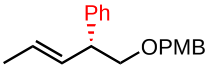
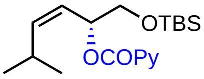
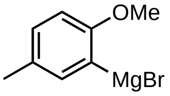
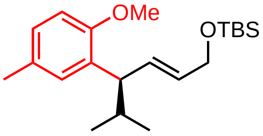
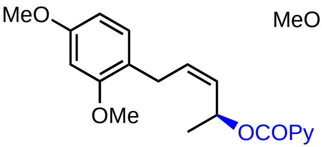
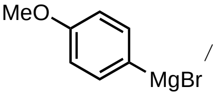
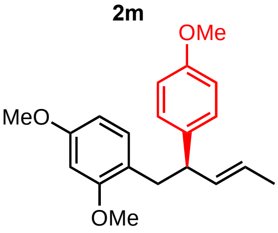
[a] Enantiospecificity: (% ee of product / % ee of substrate) x 100.

2.4. Stereochemical Outcome of the Allylic Substitution

The *anti* S_N2' 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* S_N2' 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

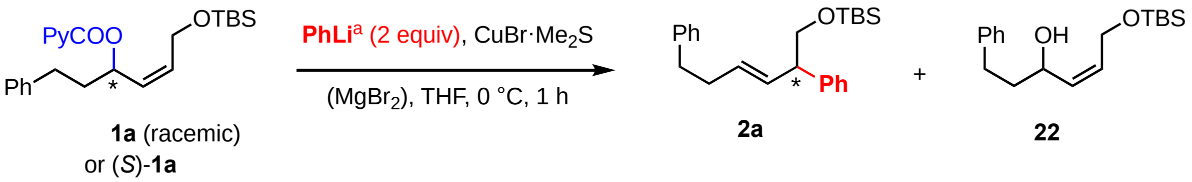
entry	picolinate	R / Cu	product	yield (%)	es (%)	ref.
1	 **1j**	PhMgBr / CuBr·Me$_2$S (2 : 1)	 **2j**	93	97	21
2	 **1k**	PhMgBr / CuBr·Me$_2$S (2 : 1)	 **2k**	86	99	21
3	 **1*l***	PhMgBr / CuBr·Me$_2$S (2 : 1)	 **2*l***	83	99	21
4	 **1m**	 / CuBr·Me$_2$S (2 : 1)	 **2m**	61[a]	99	21b
5	 **1n**	 / CuBr·Me$_2$S (2 : 1)	 **2n**	75[b]	97	25

[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·Me_2S in 1~4:1 ratios produced mixtures of **2a**, alcohol **22**, and unreacted picolinate **1a** (Table 4, entries 1, 3, and 6).[22a,27] Fortunately, reactivity and product selectivity were improved by addition of $MgBr_2$ (entries 2, 5, and 7), and the successful ratio of $MgBr_2$/PhLi was elucidated to be $MgBr_2$>PhLi (entry 4). The substitution using enantiomerically enriched (*S*)-**1a** disclosed that PhLi/CuBr·Me_2S 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 $MgBr_2$ was also effective for the substitution of **1a** with PhZnBr·LiBr and Ph_2Zn·2LiBr (prepared by mixing PhLi and $ZnBr_2$). 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

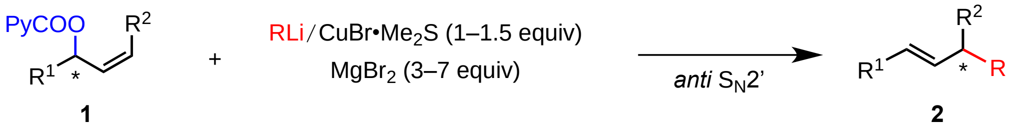


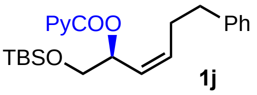
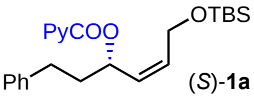
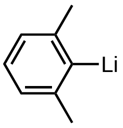
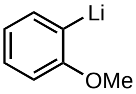
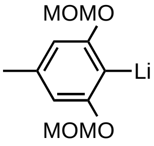
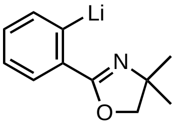
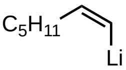
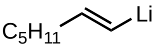
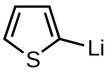
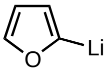
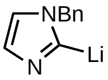
entry	picolinate	Ph/Cu	equiv of $MgBr_2$	yield (%)	**2a** : **22** : **1a**	es of **2a**
1	**1a**	1:1	–	–	9 : 69 : 22	–
2	(*S*)-**1a**	1:1	3	92	100 : 0 : 0	98
3	**1a**	2:1	–	–	11 : 47 : 42	–
4	**1a**	2:1	2	–	84 : 15 : 1	–
5	(*S*)-**1a**	2:1	3	92	100 : 0 : 0	98
6	**1a**	4:1	–	–	48 : 44 : 8	–
7	(*S*)-**1a**	4:1	3	90	100 : 0 : 0	84

[a] 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

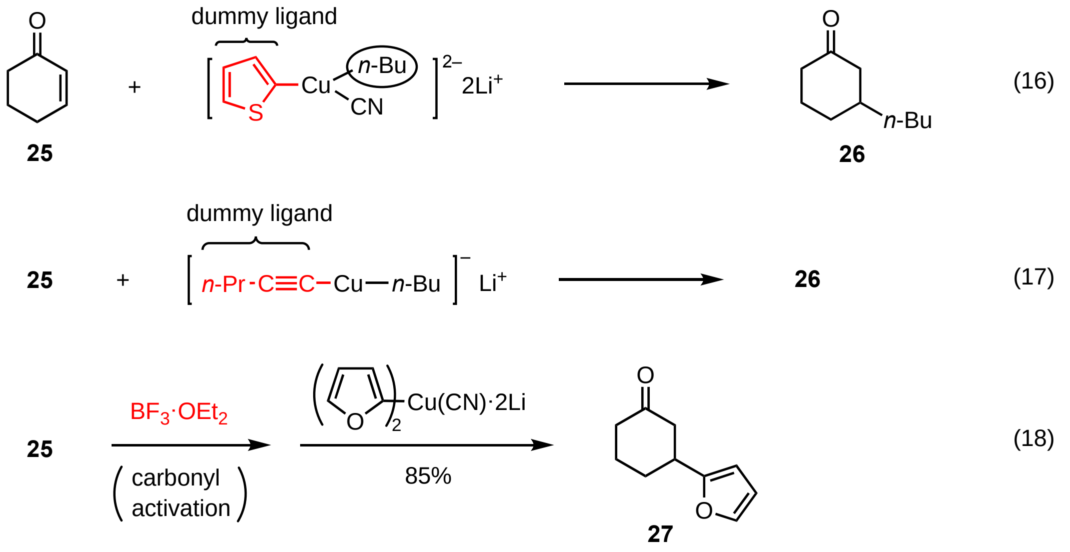
Table 5. Allylic Substitution with RLi-Based Copper Reagents[a,b]



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

[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.[28] The sterically hindered lithium reagent prepared from 2,6-(Me)$_2$C$_6$H$_3$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)[22b] demonstrated another advantage of the method since thienyl[29a,b] and alkynyl[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



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

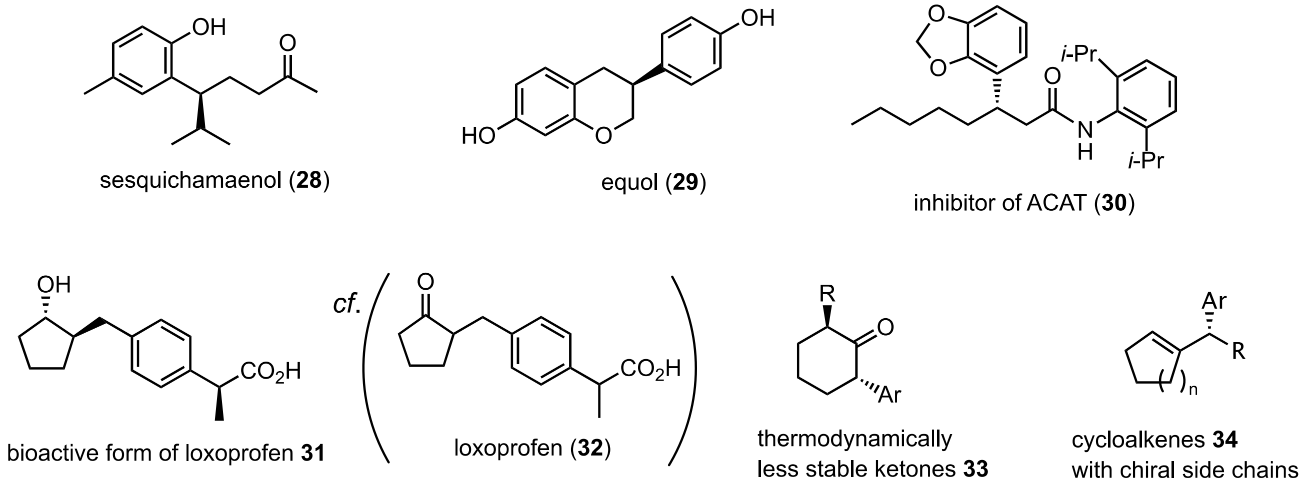


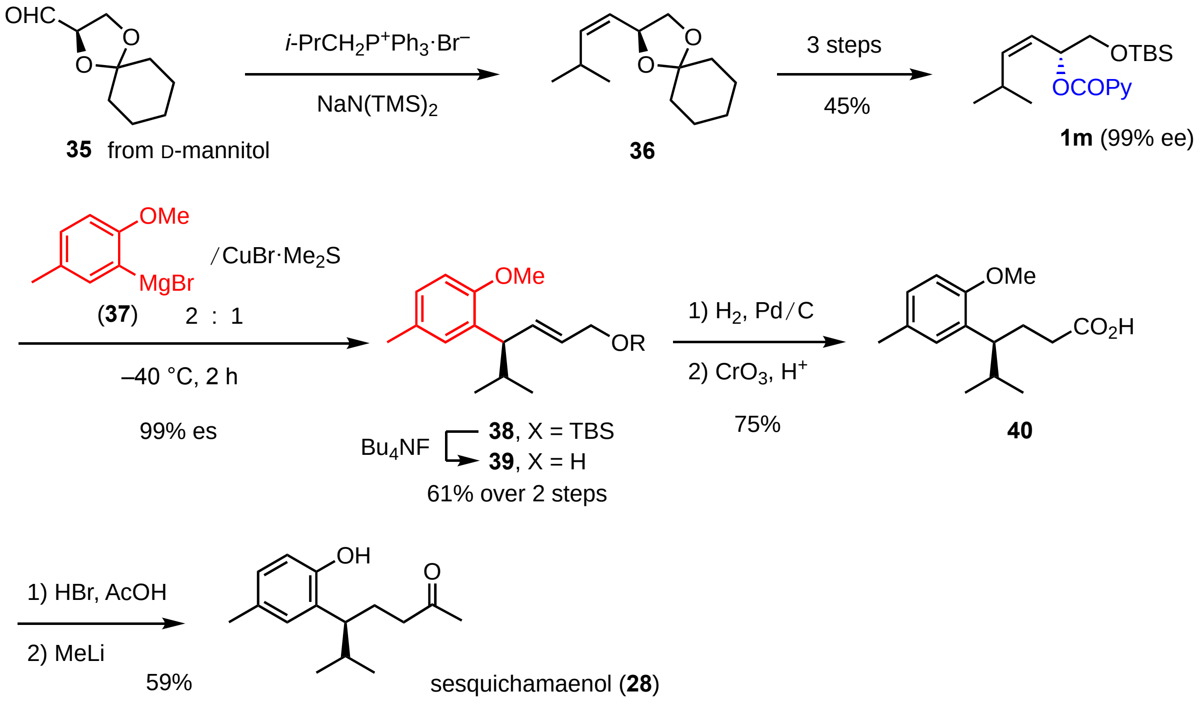
Figure 1. Targets of the Allylic Substitution

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 $BF_3 \cdot OEt_2$ (eq 18).[30] Note that the derived borane enolate suffers from the low nucleophilic reactivity, and hence methods for 1,4-addition/enolate trap have been published.[31]

2.6. Application of the Allylic Substitution

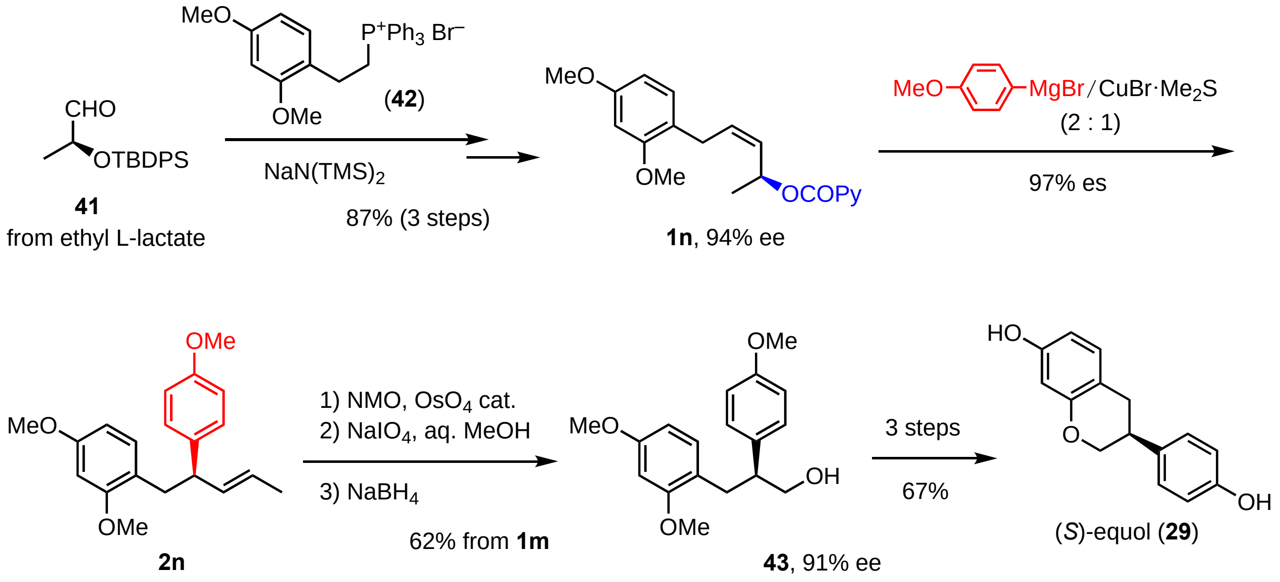
The above allylic substitution was applied to synthesis of biologically active compounds **28**–**31** (Figure 1) to demonstrate flexibility in designing allylic substrates of type **11** (Scheme 2, eq 4). Furthermore, synthesis of thermodynamically less stable cyclohexanones **33** and cyclic compounds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

Sesquichamaenol (**28**), isolated from several kinds of wood:[32] Allylic substitution of picolinate **1m** with a copper reagent derived from **37** and $CuBr \cdot Me_2S$ was envisaged to afford a new key intermediate **38** (Scheme 10).[21b] Picolinate **1m** was prepared from aldehyde **35** via the Wittig reaction and the subsequent Mitsunobu inversion with $PyCO_2H$. The allylic substitution with **37**/$CuBr \cdot Me_2S$ (2:1) took place with 99% es, and the *anti* S_N2' 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.



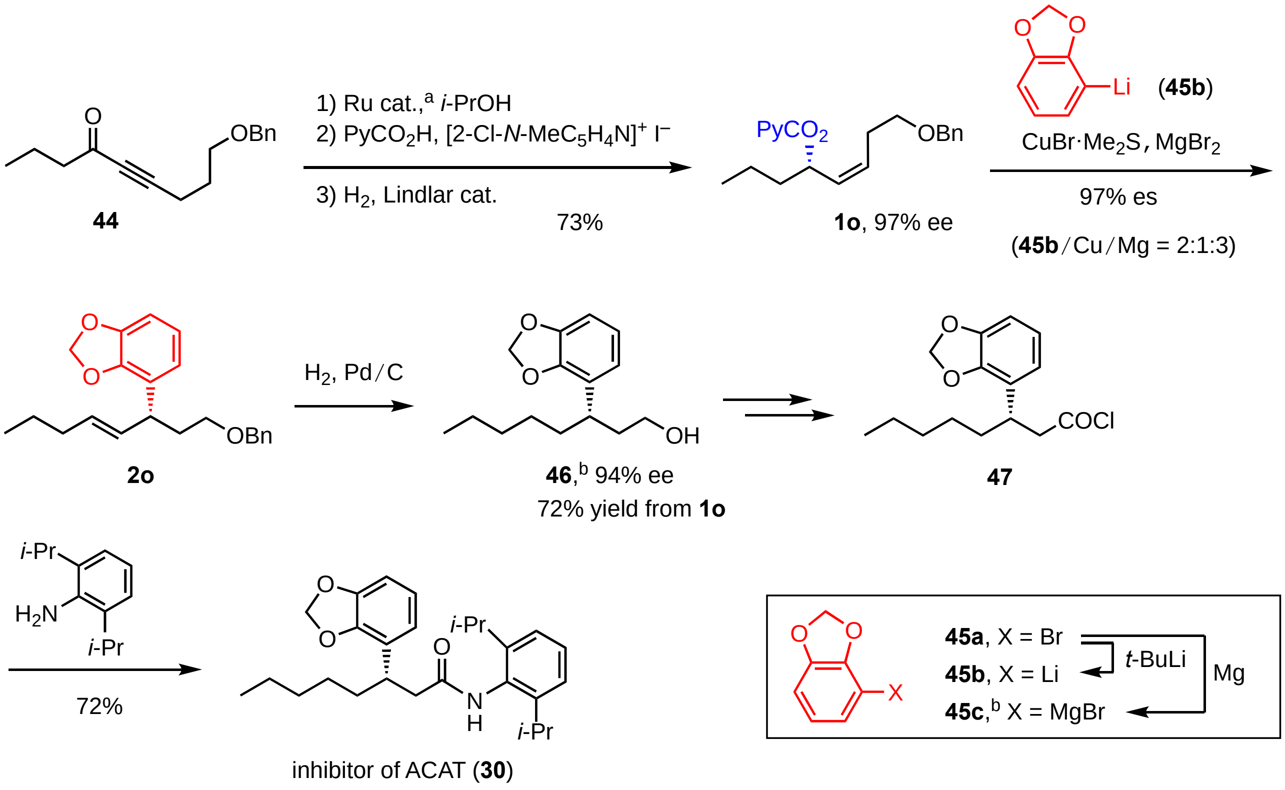
Scheme 10. Synthesis of Sesquichamaenol

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.[33] 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)C_6H_4MgBr/CuBr·Me$_2$S in a 2:1 produced *anti* S_N2' product **2n**, which was then converted to alcohol **43** with 91% ee. Bromination of **43**, demethylation with BBr$_3$, and dihydropyrane ring formation with K_2CO_3 furnished (*S*)-equol (**29**).



Scheme 11. Synthesis of (*S*)-Equol

The ACAT inhibitor (30), an acyl-coenzyme cholesterol acyltransferase (ACAT) inhibitor:[34] An allylic picolinate **1o** was designed for the synthesis, and prepared from acetylenic ketone **44** via the asymmetric transfer hydrogenation[35] (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·Me$_2$S to obtain a supposed copper reagent of "**45c**/CuBr·Me$_2$S (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·Me$_2$S 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·Me$_2$S/MgBr$_2$ (2:1:3) afforded **46** in 72% yield with 97% es.[36] Subsequently, transformation of **46** to the target **30** via **47** was conducted without any problem.



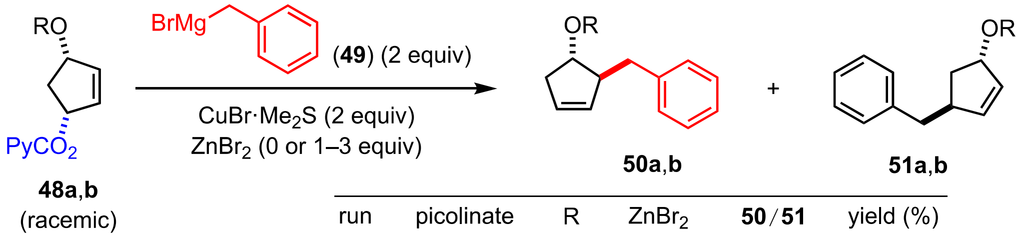
Scheme 12. Synthesis of the Inhibitor of ACAT

[a]Ru cat.: Ru[(*S*,*S*)-TsDPEN](*p*-cymene). [b]**45c**/CuBr·Me$_2$S (2:1) gave **46** in 57% yield with 62% ee.

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**.[37] The synthesis of **31** was envisaged as summarized in Scheme 13, Part B,[38] 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·Me$_2$S 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·Me$_2$S 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 ZnBr$_2$ (runs 2 and 4; footnote b).

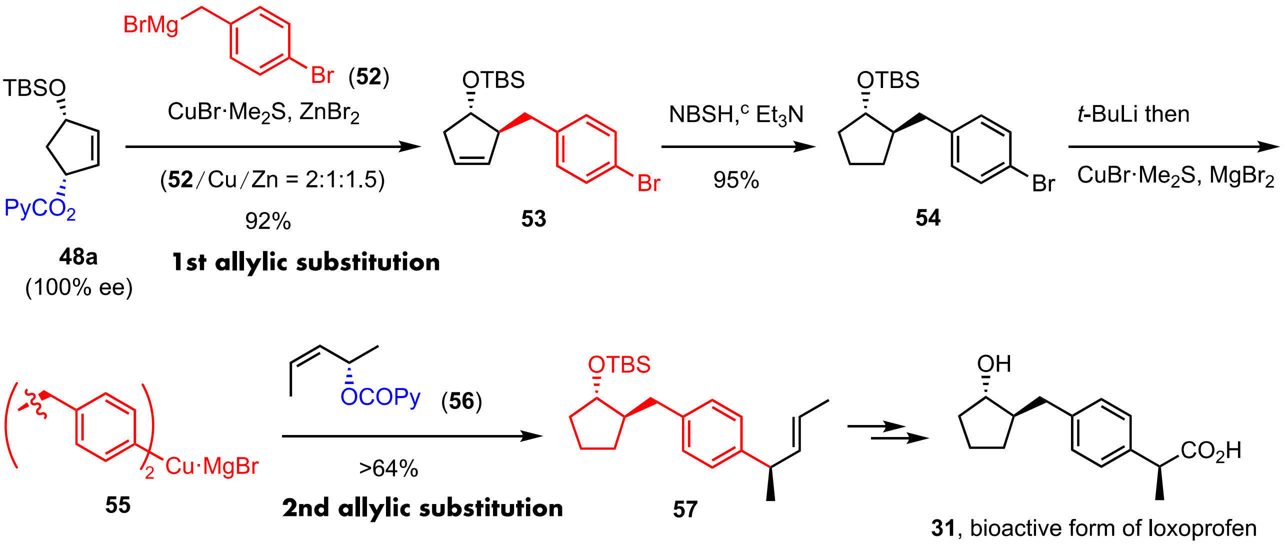
The above method was applied to enantioenriched **48a** and benzylic reagent **52** to produce **53** exclusively (Scheme 13, Part B). Subsequently, diimide reduction of **53** gave **54**, which was converted to the copper reagent **55** by Li-Br exchange. The second allylic substitution of picolinate **55** (96% ee) with **55** proceeded smoothly, and the *anti* S$_N$2' product **57** was converted to the target **31**.

(Part A) Preliminary Study for the First Substitution



run	picolinate	R	$ZnBr_2$	**50**/**51**	yield (%)
1	**48a**	TBS	0	90:10	82
2	**48a**	TBS	1–3	100:0	81[a,b]
3	**48b**	PMB	0	95:5	95
4	**48b**	PMB	3	100:0	83

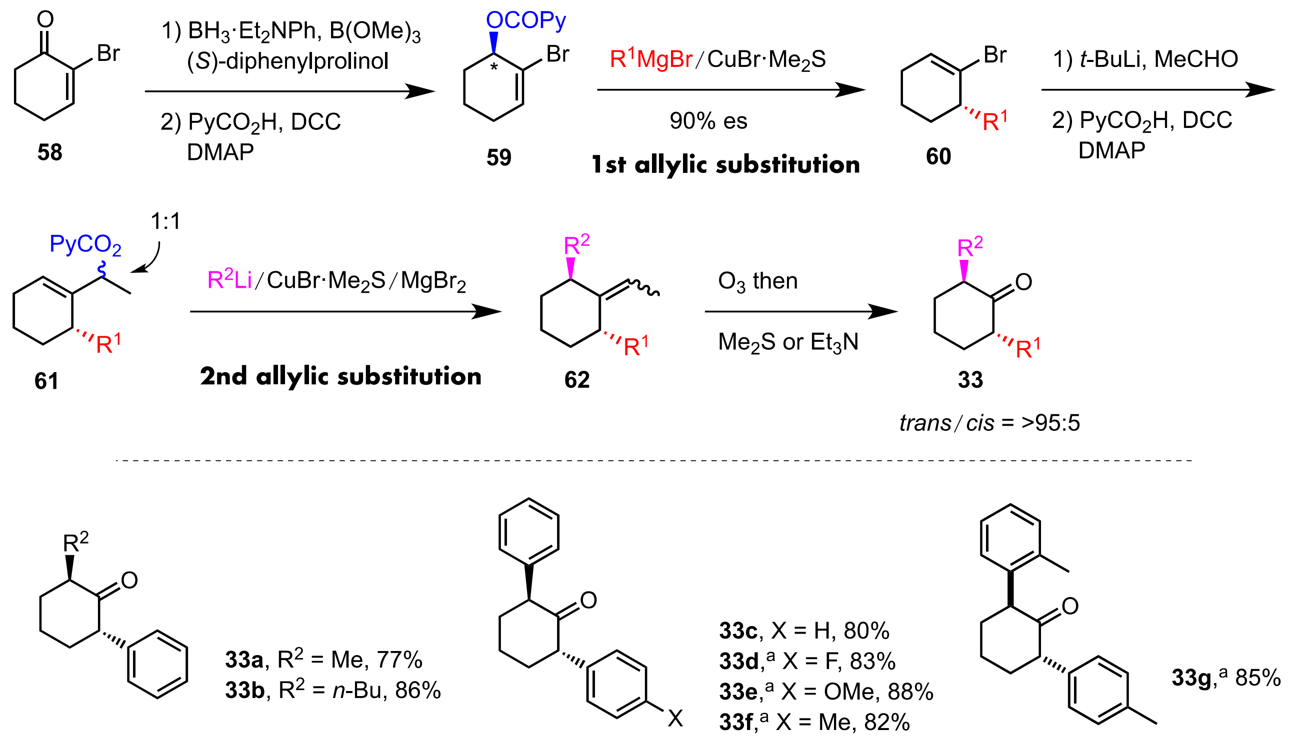
(Part B) Synthesis of the Target **31**



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*-$(NO_2)C_6H_4SO_2NHNH_2$.

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 α-bromocyclohexenone (**58**) with $NaBH_4/CeCl_3·7H_2O$ or the CBS reagent. The substitution of **59** (98% ee) with PhMgBr/CuBr·Me_2S (1:1) was stereoselective (90% es) to produce **60** (R^1 = Ph) with 88% ee, whereas the 2:1 reagent proceeded with racemization. Picolinates **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^2Li/Cu in a

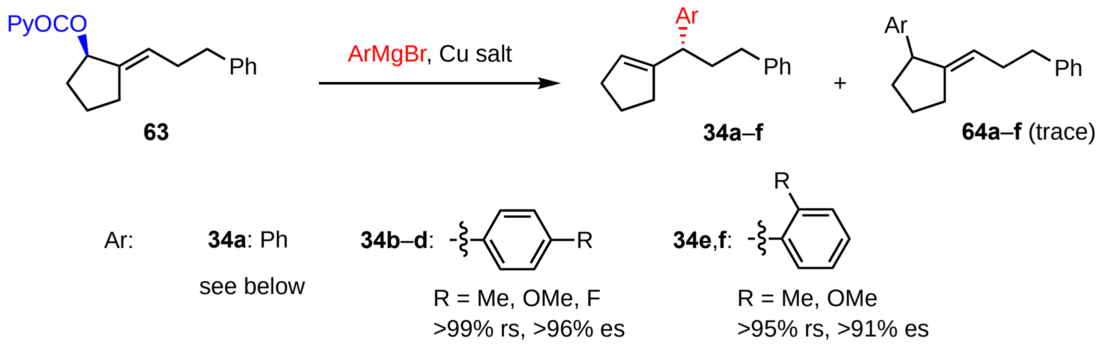


Scheme 14. Synthesis of *trans*-2,6-Disubstituted Cyclohexanones

[a] Racemic product.

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 α face and that the approach from unoccupied β 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 $CuBr\cdot Me_2S$ were reacted on the side chain to afford **34** with high regio- and stereoselectivity (run 1).[40] Similar reagents derived from $Cu(acac)_2$ proceeded with higher selectivity (runs 2).



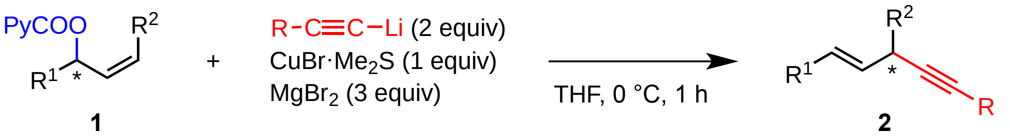
run	ArMgBr (equiv)	Cu salt (equiv)	Ar / Cu	**34a** / **64a**	es	yield (%)
1	PhMgBr (2)	$CuBr{\cdot}Me_2S$ (1)	2:1	98:2	98	89
2	PhMgBr (3)	$Cu(acac)_2$ (1.5)	2:1	>99:1	>99	80

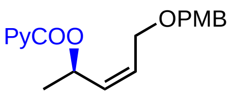
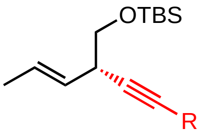
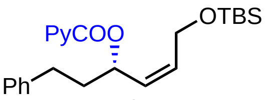
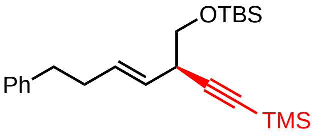
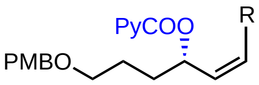
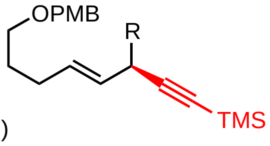
Scheme 15. Allylic Substitution of a Picolinate with the *exo*-Olefinic Ring System

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).[29] In contrast, alkynyl copper reagents derived from alkynyllithiums and $CuBr{\cdot}Me_2S$ were sufficiently reactive toward allylic picolinates **1** in the presence of $MgBr_2$ to produce *anti* S_N2' products **2** with high efficiency in yield, es, and rs (Table 6,

Table 6. Allylic Substitution with Alkynyl Reagents

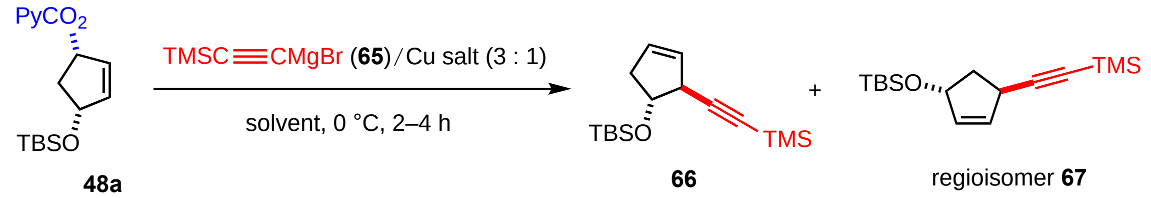


entry	picolinate **1**	product **2**		yield (%)	es (%)	rs (%)
1	 *ent*-**1*l***		R = TMS	93	99	94
2			R = Ph	70	96	95
3			R = 4-$MeOC_6H_4$	67	97	92
4			R = 4-FC_6H_4	88	98	95
5	 (*S*)-**1a**			83	98	97
6	 **1p** (R = C_5H_{11})			89	98	94
7	**1q** (R = *c*-C_6H_{11})			66	86	96

entries 1–6).[23] However, yield and es were slightly decreased by a bulky substituent (*c*-C_6H_{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_2S (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_2Cl_2/THF (2:1) produced **66** with high regioselectivity (run 3).[42] The cyclohexyl derivative was similarly reactive and selective. Previously, racemic prostaglandin $F_{2α}$ (**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, (1*R*,2*S*)-**66** was synthesized from (1*S*,4*R*)-**48a** (structure not shown), and transformed to **70** in an optically active form (Scheme 16, Part B).

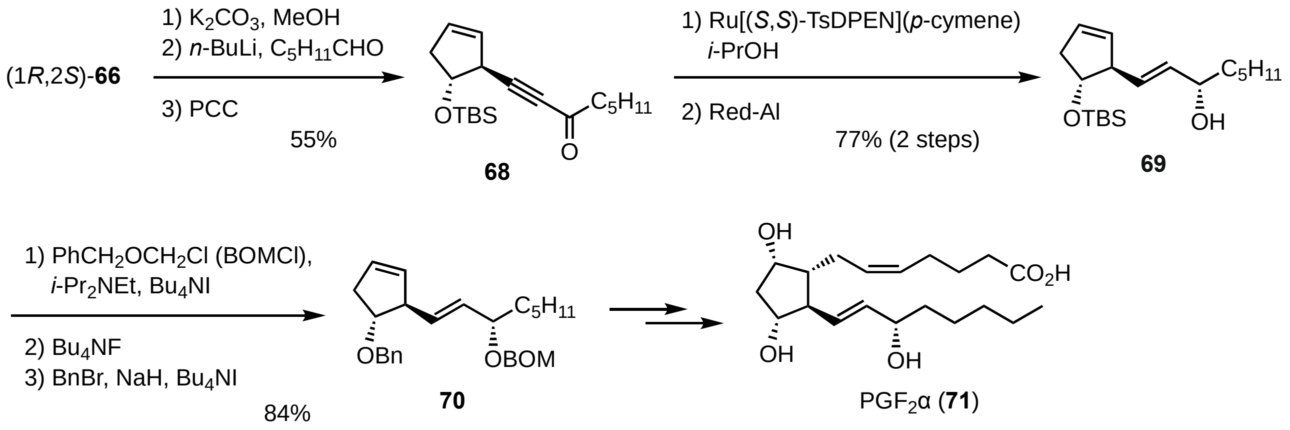
(Part A) Allylic Substitution of Picolinate **48a**



run	Cu salt	solvent	**66**/**67**
1	CuBr·Me_2S	THF[a]	79 : 21
2	CuBr·Me_2S	CH_2Cl_2/THF (2 : 1)	82 : 18
3	Cu$(acac)_2$	CH_2Cl_2/THF (2 : 1)	94 : 6 (91%)[b]

[a]Picolinate **48a** was reconverd in 14% yield. [b]Isolated yield.

(Part B) Synthesis of Intermediate **70**



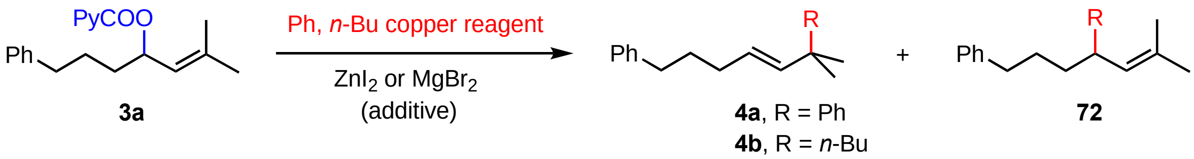
Scheme 16. Synthesis of the Prostaglandin Intermediate **70**

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.[44] One of the methods is the S_N2' allylic substitution of terminal allylic substrates, which has well-studied with alkyl, alkenyl, and aryl copper reagents.[6–8] In contrast, a similar substitution of internal allylic esters was reported with alkyl reagents,[4] when we started the substitution that was formulated as eq 14 in Scheme 6.[45–47] As Table 7 indicates, the allylic substitution of **3a** with $PhMgBr/CuBr\cdot Me_2S$ (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_2 ended up in vain (entry 2). Surprisingly, copper reagent prepared from PhMgBr and $Cu(acac)_2$ produced **4a** with high regioselectivity in a quantitative yield (entry 3).[45] In contrast, a $PhMgBr/Cu(acac)_2$ in a 3:1 ratio with ZnI_2 produced the high selectivity (entry 6; cf. entry 5). Different from the above PhMgBr-based reagents, $PhLi/CuBr\cdot Me_2S$ and $PhLi/Cu(acac)_2$ with $MgBr_2$ were inadequate (entries 7 and 8), whereas PhLi/CuTC (2:1) (TC: thiophene-2-carboxylate) was highly regioselective (entry 9).[46] Furthermore, CuTC was found to be

Table 7. Quaternary Carbon Center-Forming Allylic Substitution with Ph and *n*-Bu Copper Reagents

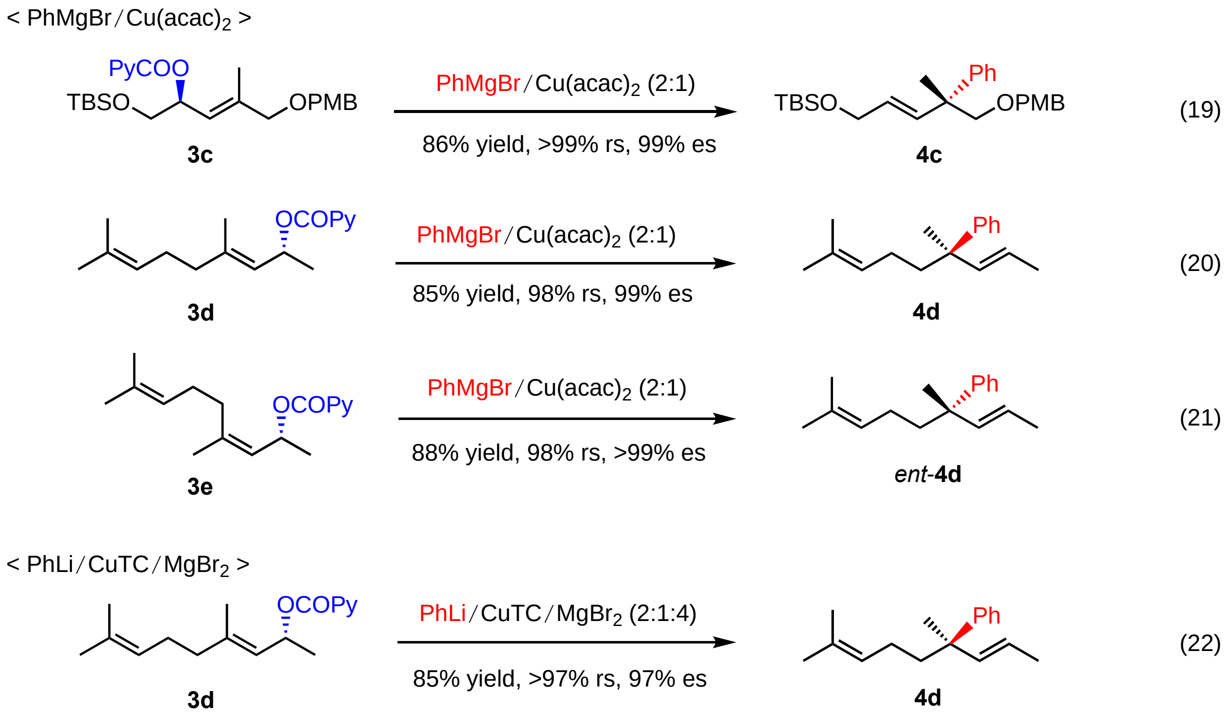


entry	reagent source	copper reagent (ratio)	Cu (equiv)	additive (equiv)	**4**/**72**	yield (%)
1	PhMgBr	$PhMgBr/CuBr\cdot Me_2S$ (2 : 1)	1	–	76 : 24	–
2	PhMgBr	$PhMgBr/CuBr\cdot Me_2S$ (2 : 1)	1.5	ZnI_2 (1.5)	86 : 14	–
3	**PhMgBr**	**$PhMgBr/Cu(acac)_2$ (2 : 1)**	**1.5**	**–**	**>99 : 1**	**100**
4	PhMgBr	$PhMgBr/Cu(acac)_2$ (2 : 1)	1.5	ZnI_2 (1.5)	no reaction	
5	PhMgBr	$PhMgBr/Cu(acac)_2$ (3 : 1)	1.5	–	52 : 48	–
6	PhMgBr	$PhMgBr/Cu(acac)_2$ (3 : 1)	1.5	ZnI_2 (1.5)	98 : 2	–
7	PhLi	$PhLi/CuBr\cdot Me_2S$ (2 : 1)	1.5	$MgBr_2$ (4)	82 : 18	–
8	PhLi	$PhLi/Cu(acac)_2$ (2 : 1)	1.5	$MgBr_2$ (4)	complex	
9	**PhLi**	**PhLi/CuTC[a] (2 : 1)**	**1.6**	**$MgBr_2$ (3)**	**98 : 2**	**88**
10	*n*-BuMgBr	*n*-$BuMgBr/CuBr\cdot Me_2S$ (2 : 1)	1.5	–	54 : 46	–
11	***n*-BuMgBr**	***n*-$BuMgBr/CuBr\cdot Me_2S$ (2 : 1)**	**1.5**	**ZnI_2 (1.5)**	**>99 : 1**	**91**

[a] TC: thiophene-2-carboxylate.

compatible with aryllithiums prepared by Li-halogen exchange and ortho-lithiation.[46] 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).[47]

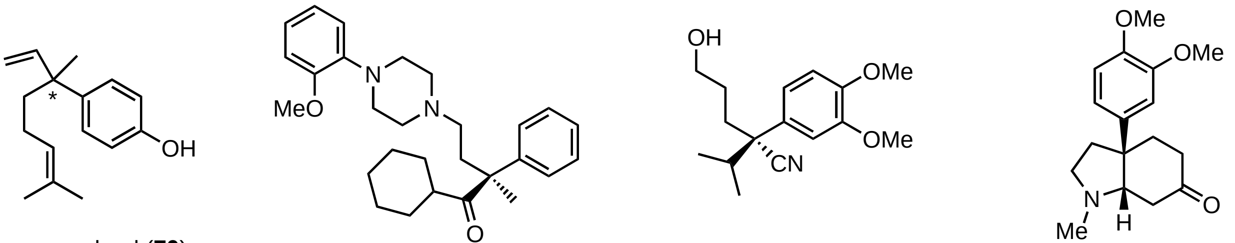
The above method was applied to the substitution of enantioenriched picolinates **3c**–**e** with PhMgBr- and PhLi-based reagents to produce *anti* S$_N$2' products selectively (Scheme 17).[45,46] Me-, MeO-, and F-substituted phenyl groups were installed as well, and an *ortho* substituent affected the 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[35] 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)-iodo alcohol **79**, which upon metal-catalyzed coupling with R^3-met. produced **80**, while the hydromagnesiation of **78** with i-BuMgCl[48] 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.



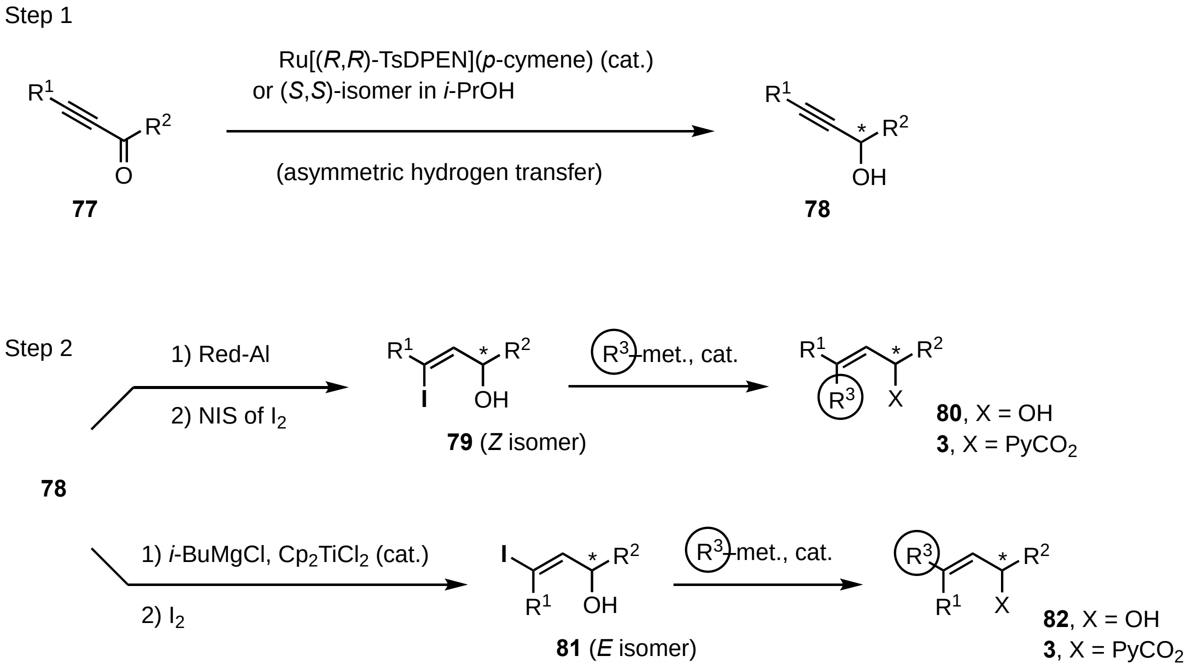
sporochnol (**73**)
(natural: (*S*)-form)

LY426965 (**74**)

key intermediate (**75**) for the
synthesis of verapamil

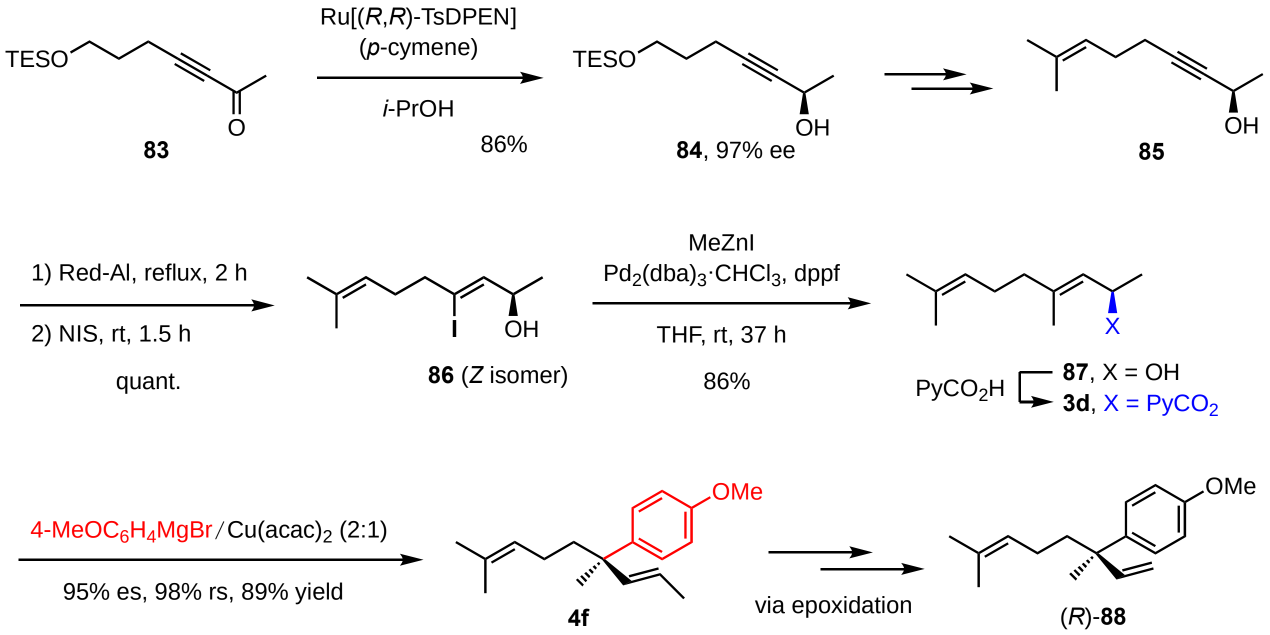
mesembrine (**76**)

Figure 2. Synthetic Targets Possessing Quaternary Carbon Centers



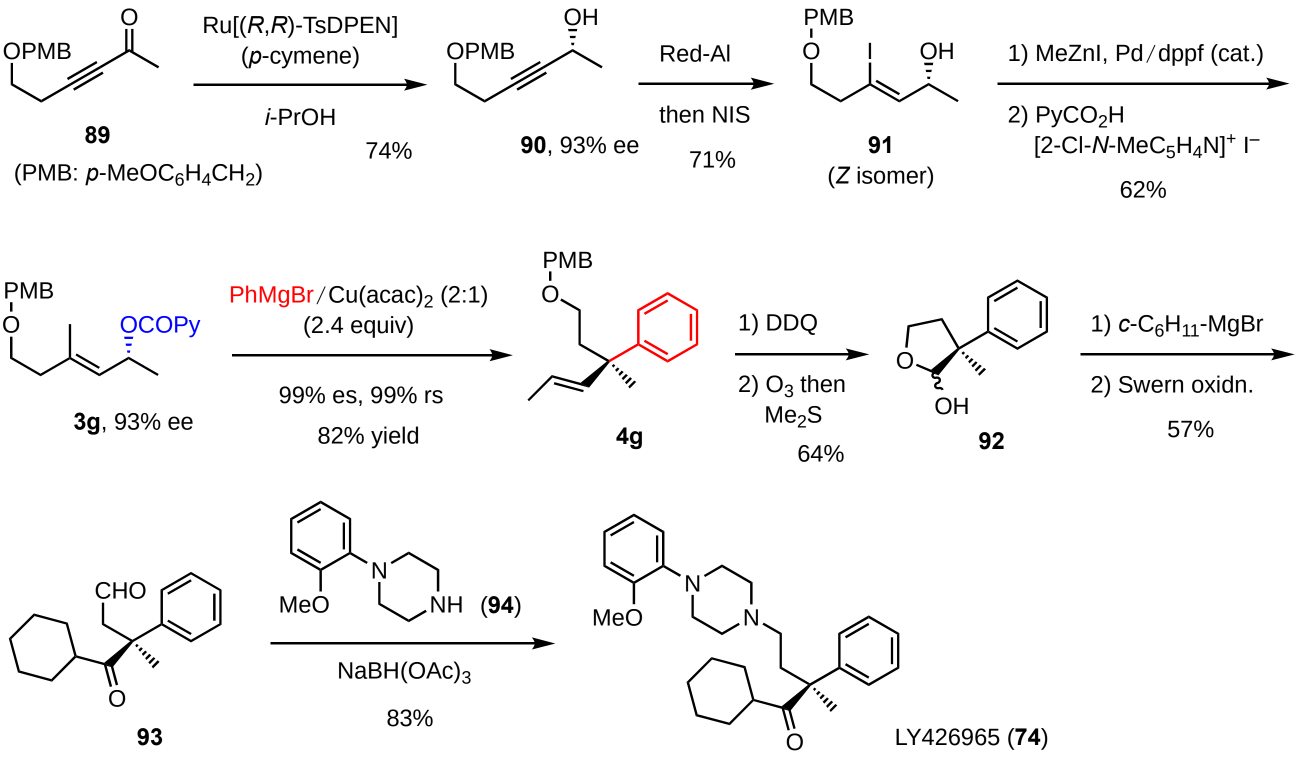
Scheme 18. Stereoselective Access to Three-Substituted Allylic Picolinates

Sporochnol: The (*S*)-form was isolated from the Caribbean marine alga *Sporochnus bolleanus* as an effective chemical defense against marine herbivores.[49] The synthesis[50] 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 **86** with MeZnI (3 equiv). The allylic substitution of picolinate **3d** with 4-$MeOC_6H_4MgBr/Cu(acac)_2$ 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.



note: (*S*)-**88** was similarly synthesized.

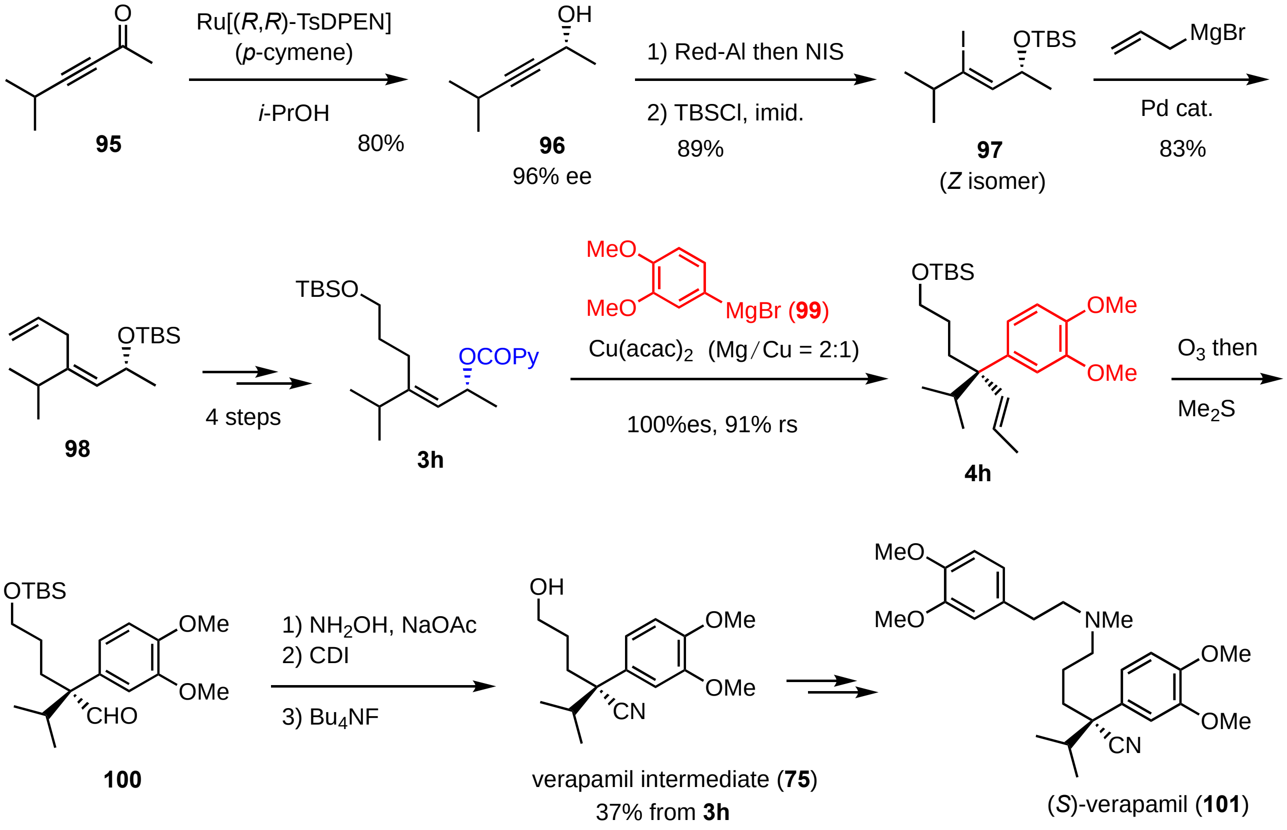
Scheme 19. Synthesis of the Methyl Ether of Sporochnol **88**



Scheme 20. Synthesis of LY426965

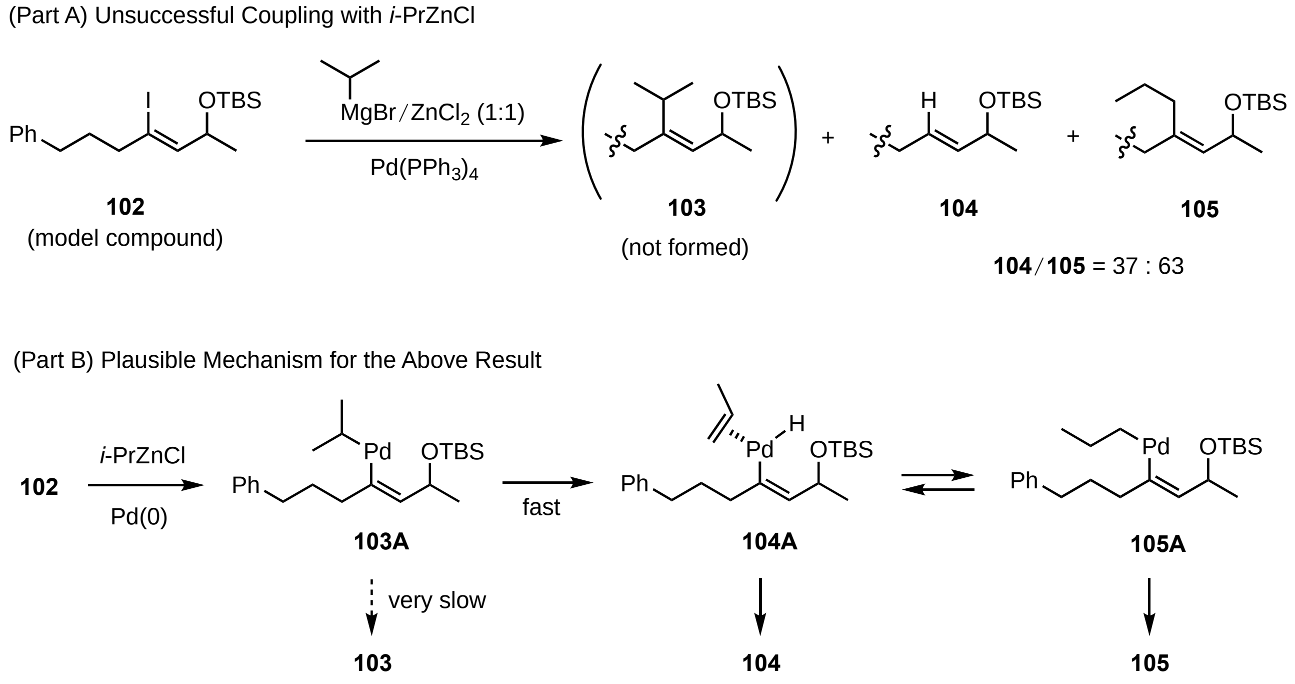
LY426965 (74), a serotonin 1A receptor antagonist:[51] The key allylic picolinate **3g** designed for the synthesis of LY426965 (**74**) was structurally similar to **3d** (Scheme 20), and thus the same set of the reactions was applied to acetylenic ketone **89**.[52] The allylic substitution of **3g** (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*-C_6H_{11} 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.[53] Picolinate **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).[54] 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 picolinate **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 picolinates **3d** and **3g** in Schemes 19 and 20, but completed by using six equiv of the



Scheme 21. Synthesis of the Verapamil Intermediate **75**

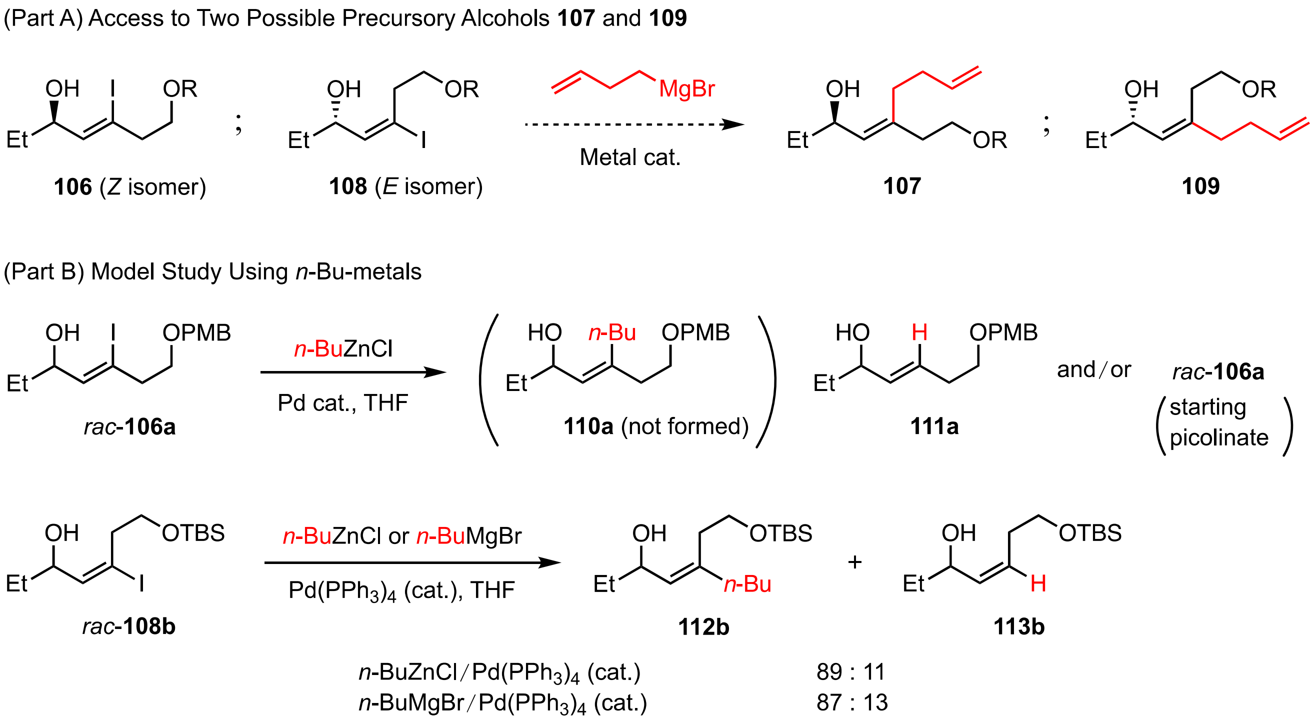
reagent. Product **4h** was oxidized to aldehyde **100**, and subsequent conversion furnished the target **75** in 37% yield from picolinate **3h**.



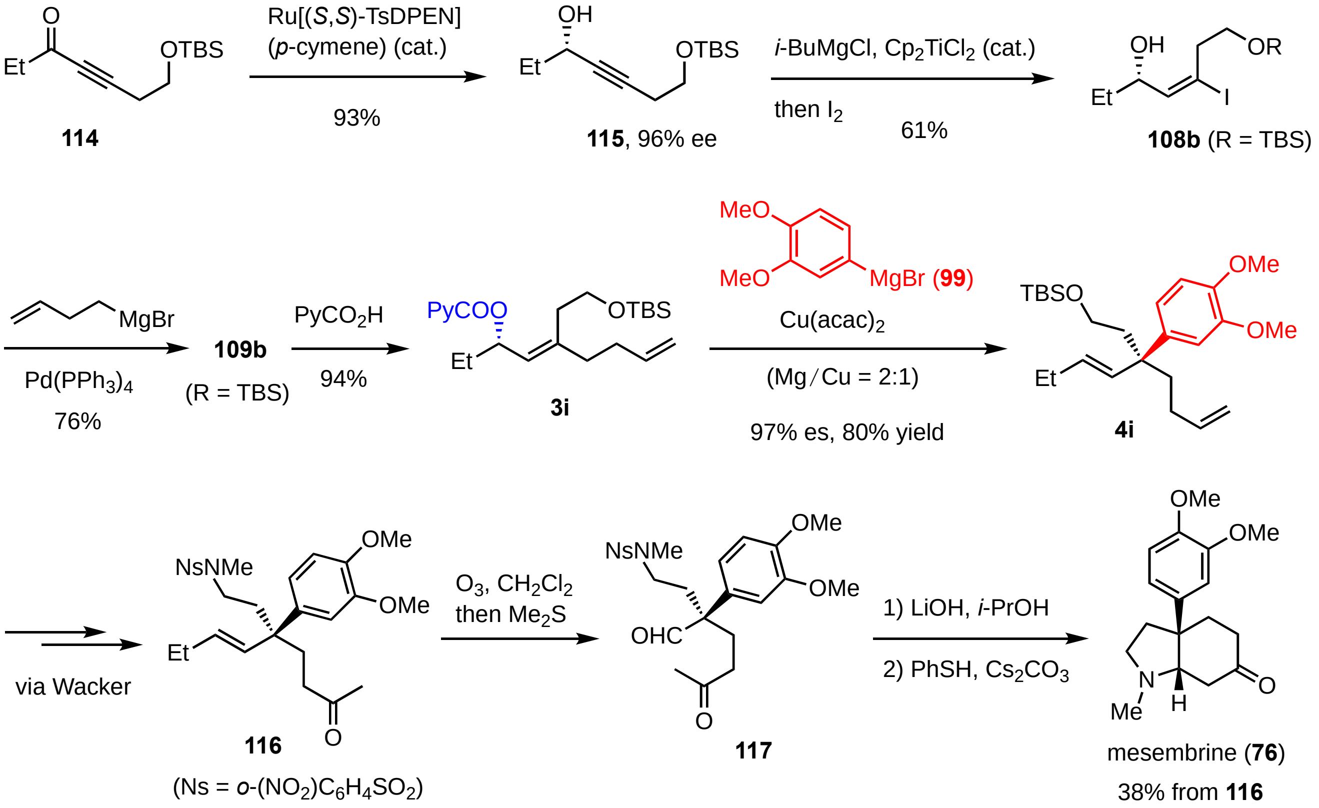
Scheme 22. An Attempted Coupling of **102** with *i*-PrZnCl and a Plausible Mechanism

Mesembrine (76), one of the 3a-(aryl)octahydroindole family, and a potent inhibitor of 5-hydroxytryptamine (5-HT) uptake (IC_{50} = 27 nM)[55] by binding to the 5-HT transporter.[56] Allylic picolinates of alcohols **107** and **109** were conceived to produce a necessary framework of mesembrine (**76**) by *anti* S_N2' allylic substitution (Scheme 23). Preliminarily, synthesis of these alcohols from (*Z*)-iodides **106** and (*E*)-iodide **108** by Pd-catalyzed coupling with a $CH_2{=}CH(CH_2)_2ZnX$ was studied using racemic alcohols and *n*-BuZnX (Part B).[57] The Pd-catalyzed coupling of *rac*-**106a** (R = PMB) with model *n*-BuZnCl suffered from the β-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. $Ni(acac)_2$ did not produce **112b**, but the *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[48] afforded **108b** exclusively after iodination (Scheme 24). The Pd-catalyzed coupling of **108b** with $CH_2{=}CH(CH_2)_2MgBr$ proceeded as efficient as with *n*-BuMgCl, and subsequent esterification of **109b** with $PyCO_2H$ afforded allylic picolinate **3i** stereospecifically. The allylic substitution of **3i** with $3,4\text{-}(MeO)_2C_6H_3MgBr$ (**99**)/$Cu(acac)_2$ in a 2:1 ratio



Scheme 23. Preliminary Study for the Synthesis of Mesembrine

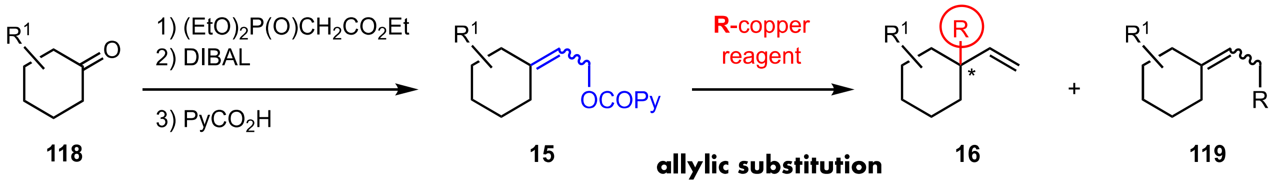


Scheme 24. Synthesis of Mesembrine

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.[24] 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 α 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

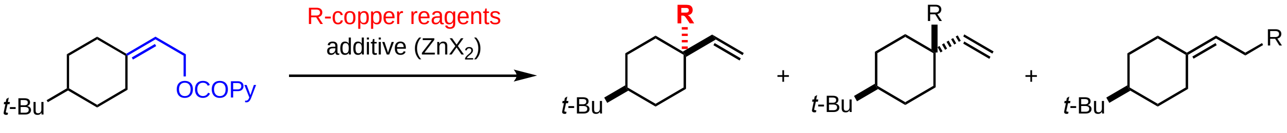
4.1. Regioselectivity and Conformation-Controlled Stereochemistry

The *t*-Bu derivative **15a** was the test picolinate to figure out regioselectivity (rs) (**16a** over **119a**) and reactivity of reagents.[24] Methyl copper reagents, MeMgBr/CuBr·Me_2S (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·Me_2S (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).[45] 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*-$(Ph_2P)C_6H_4CO_2$ (*o*-DPPB), $C_6F_5CO_2$, and $MeOCO_2$ showed low to marginal reactivity and/or regioselectivity.

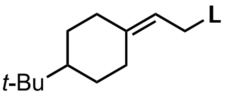
Table 8. Construction of a Quaternary Carbon Center



15a R = Me, *n*-Bu, *i*-Pr, Ph **16a** **120a** **119a**

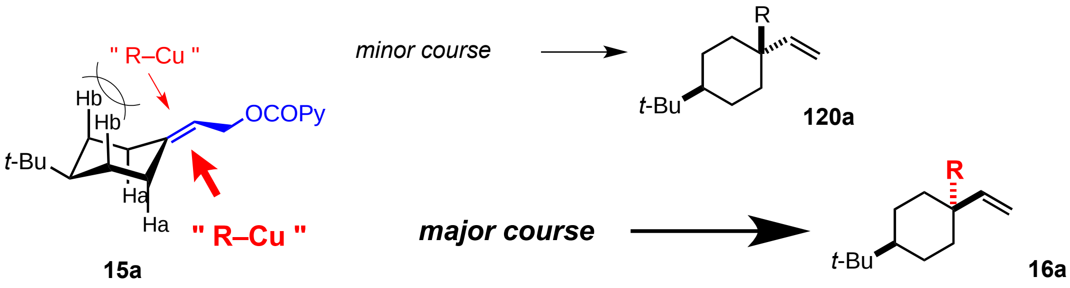
entry	R	reagent (ratio)[a]	additive	rs[b] (%)	ds[c] (%)	yield (%)
1	Me	MeMgBr/CuBr·Me_2S (2:1)	–	22	98	–
2	**Me**	**MeMgBr/CuBr·Me_2S (2:1)**	**$ZnBr_2$**	**99**	**97**	**94**
3	**Me**	**MeMgBr/CuBr·Me_2S (2:1)**	**ZnI_2**	**100**	**100**	**85**
4	Me	MeMgBr/CuBr·Me_2S (1:1)	$ZnBr_2$	85	94	–
5	*n*-Bu	*n*-BuMgBr/CuBr·Me_2S (2:1)	–	62	100	–
6	***n*-Bu**	***n*-BuMgBr/CuBr·Me_2S (2:1)**	**ZnI_2**	**99**	**100**	**94**
7	Ph	PhMgBr/CuBr·Me_2S (2:1)	–	46	nd	–
8	Ph	PhMgBr/CuBr·Me_2S (2:1)	ZnI_2	80	>99	–
9[d]	Ph	PhMgBr/Cu(acac)$_2$ (3:1)	ZnI_2	87	>99	73

[a] 1.5 equiv except for entry 6 (3 equiv). [b] **16a** over **119a**. [c] **16a** over **120a**. [d] *t*-Bu in **15a** was replaced by Ph.



121, **L**: $(EtO)_2PO_2$, *o*-$(Ph_2P)C_6H_4CO_2$, $C_6F_5CO_2$, $MeOCO_2$

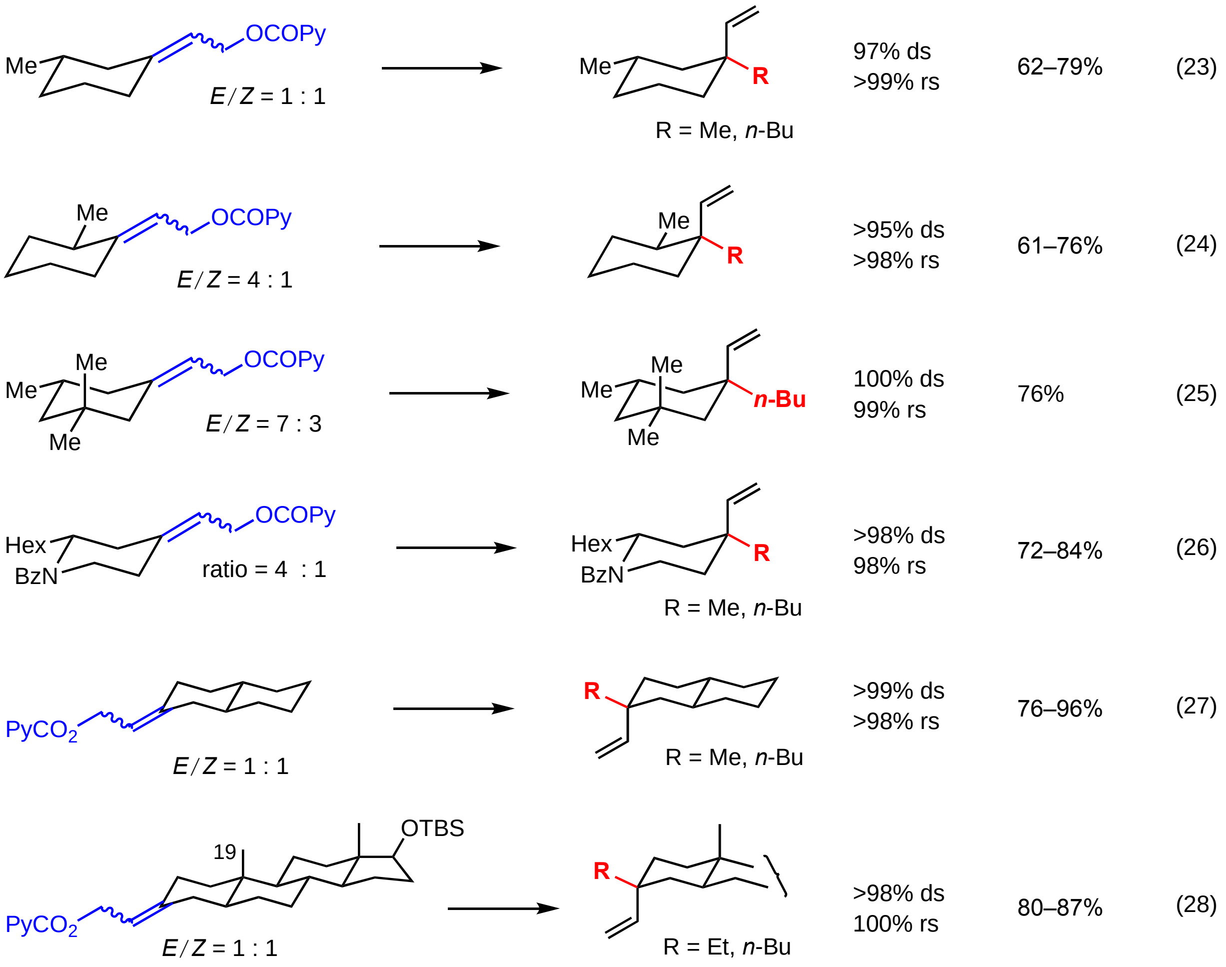
The conformation of **15a** and the likely repulsion between the incoming reagent and the axial hydrogens (Ha, Hb) are illustrated in Scheme 26. Since Hb overhangs above the olefin more significantly than Ha, the equatorial attack from the bottom (Ha-side) is sterically favored. This stereochemical analysis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



Scheme 26. Stereochemical Course Controlled by the Conformation

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[a]

[a]Diastereoselectivity (ds), regioselectivity (rs).

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.

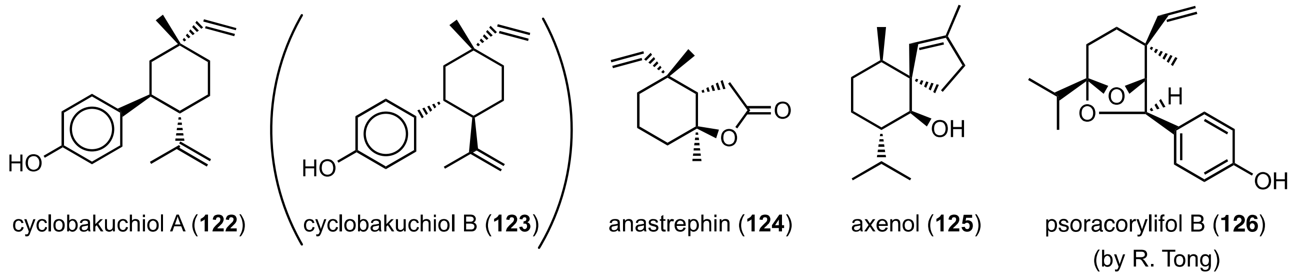
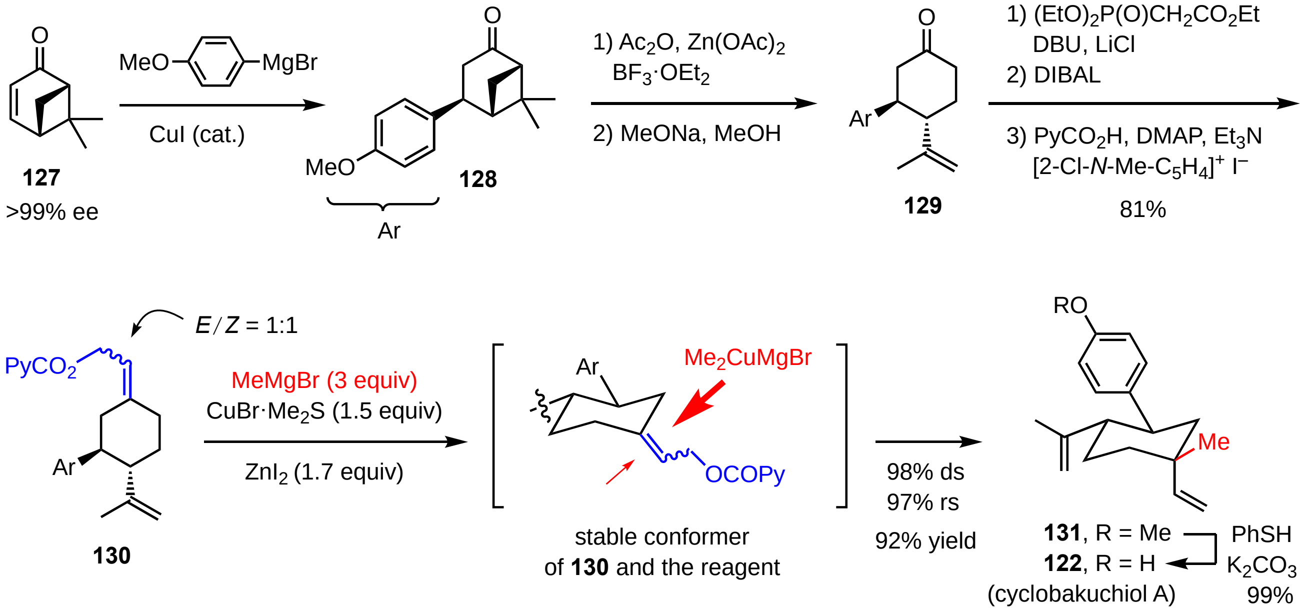


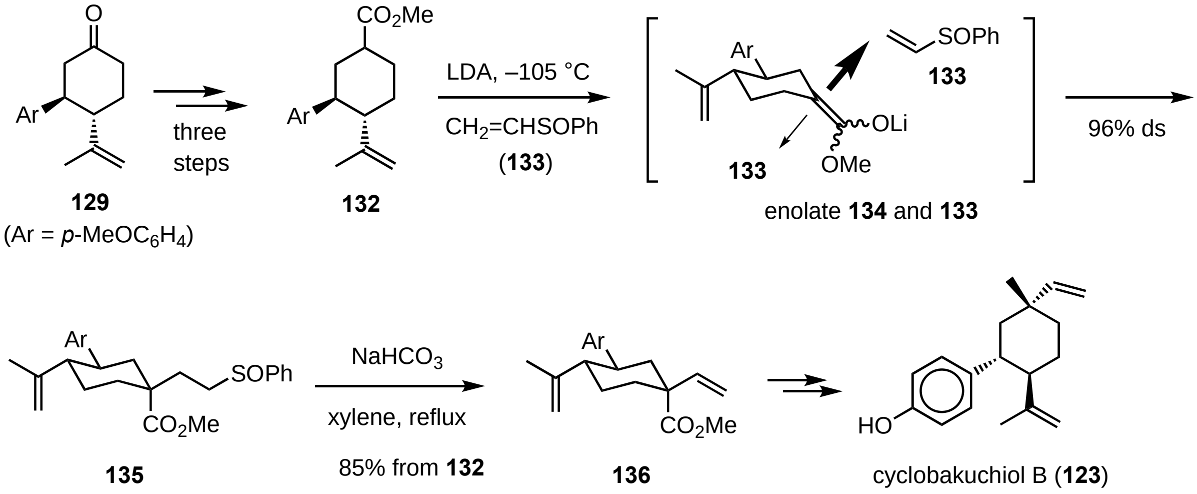
Figure 3. Synthetic Targets Possessing Quaternary Carbon Centers on Rings

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% ds. Without ZnI$_2$, the regioisomer was produced with 97% rs in 98% yield.



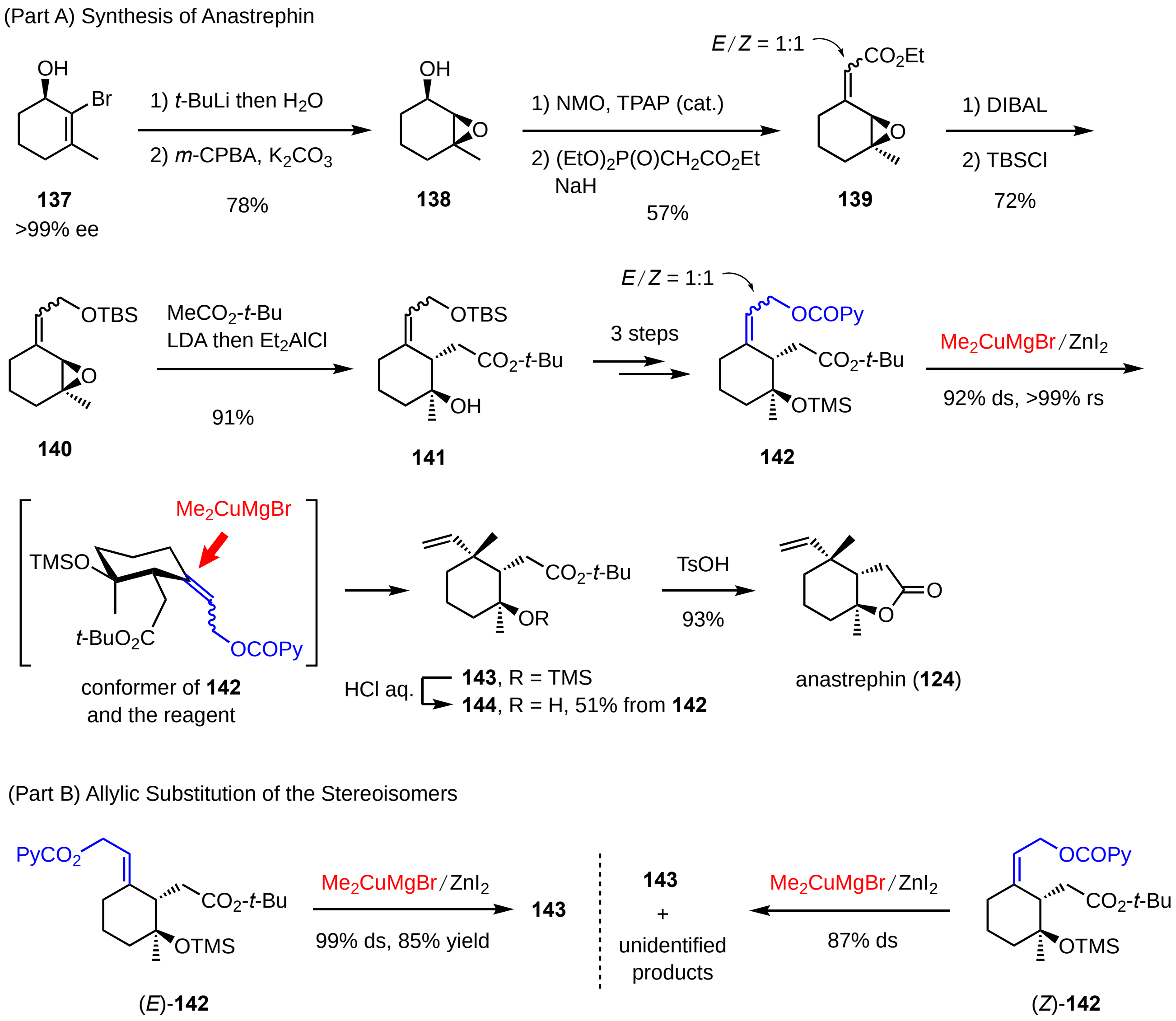
Scheme 28. Synthesis of Cyclobakuchiol A via Conformation-Controlled Allylic Substitution

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).[59] Ketone **129** was converted to ester **132** in three steps via the cyanide ($TsCH_2NC$, *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**

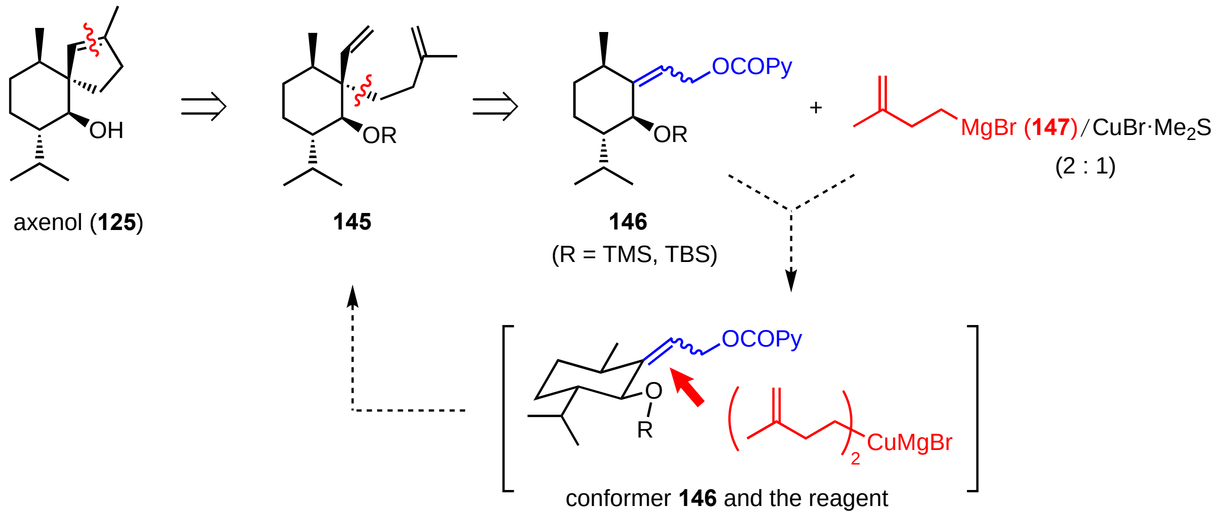
Anastrephin (124), a sex pheromone produced by Caribbean and Mexican fruit flies:[61] The conformation-controlled allylic substitution of picolinate **142** through a likely conformer depicted in Scheme 30 was conceived to afford the all-carbon quaternary center present in anastrephin (**124**).[62] 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 $MeCO_2$-*t*-Bu afforded **141**, which was then transformed to picolinate **142** (*E*/*Z* = 1:1) in 54% yield over three steps. The ZnI_2-assisted substitution of **142** with MeMgBr/CuBr·Me_2S (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.



Scheme 30. Synthesis of Anastrephin via Allylic Substitution

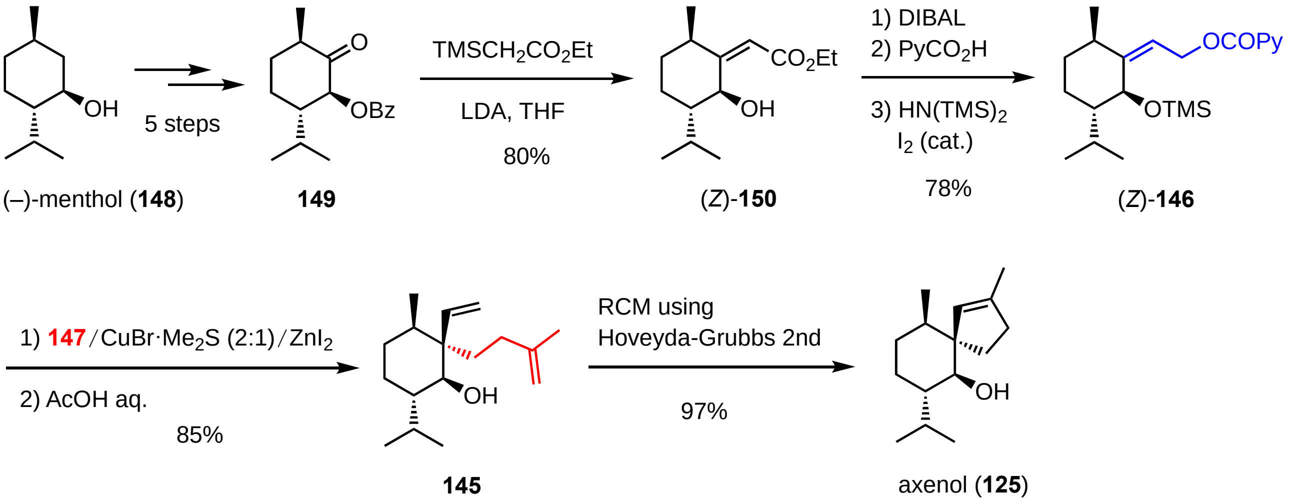
Axenol (125), a synthetic intermediate for gleenol and axisonitrile-3: Since gleenol, the diastereomer of **125** at the OH-carbon, has occasionally been called as "axenol", the structure in a publication should be confirmed before a research regarding to axenol/gleenol will start. A retrosynthesis of **125** by ring-closing metathesis produced **145**, and the conformation-controlled allylic substitution of picolinate **146** with the reagent derived from **147** and CuBr·Me$_2$S 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 TMSCH$_2$CO$_2$Et and LDA proceeded highly stereoselectively to afford (*Z*)-ester (*Z*)-**150**, which was



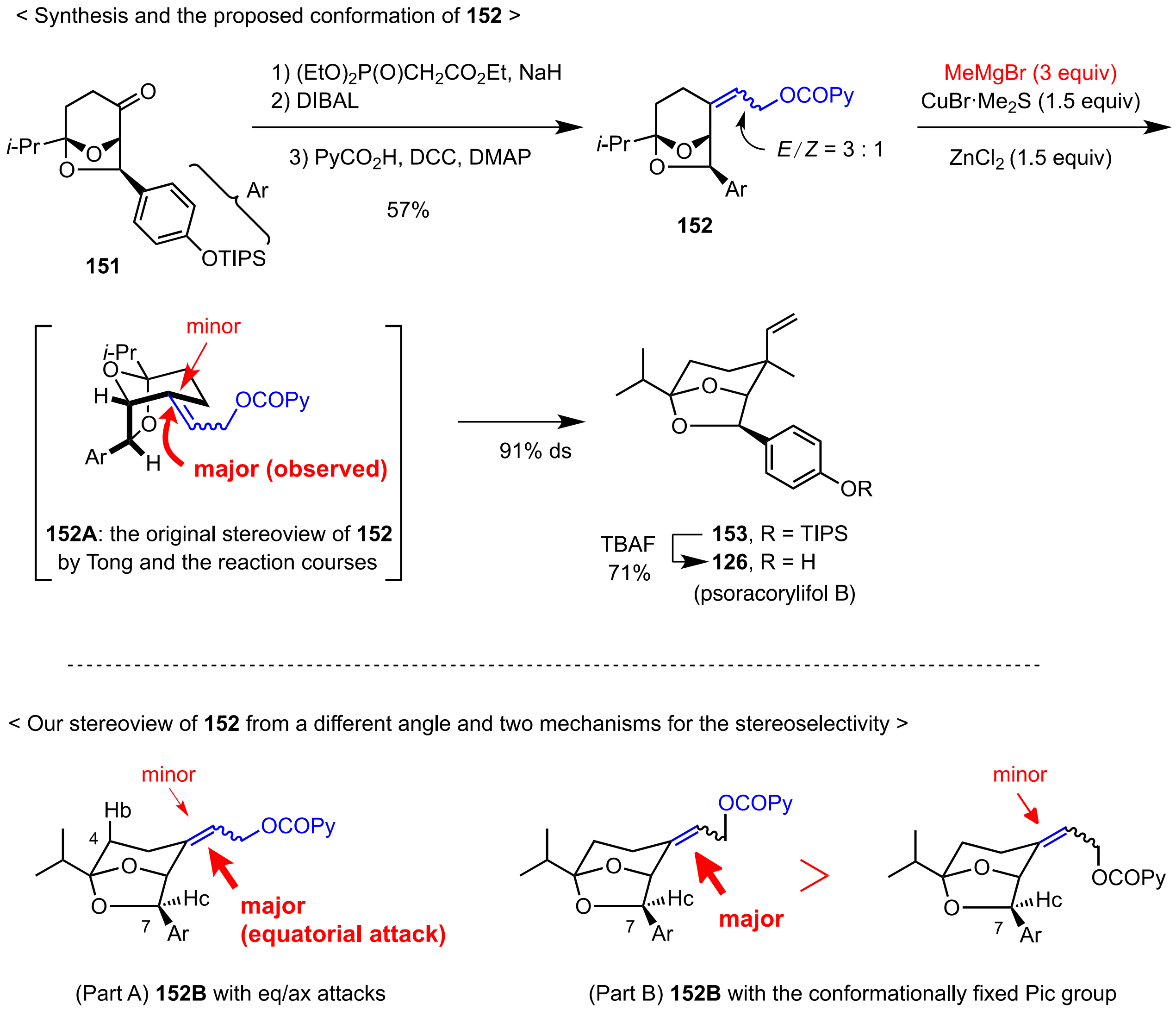
Scheme 31. Retrosynthesis of Axenol

then converted to picolinate (*Z*)-**146**. The allylic substitution of the picolinate with **147**/CuBr·Me_2S (2:1) was regio- and diastereoselective to furnish **145** in 85% yield after desilylation. Finally, the ring-closing metathesis furnished axenol (**125**).



Scheme 32. Synthesis of Axenol

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,[65a] who envisaged allylic substitution of picolinate **152** with Me copper reagent (Scheme 33). Since the α face (bottom side) in their stereochemical structure **152A**[65b] was concave and hence formation of stereoisomers was expected. However, the allylic substitution of picolinate **152** (*E*/*Z* = 3:1) with $Me_2CuMgBr$/$ZnCl_2$ 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 (TIPSOC$_6$H$_4$-) is a steric bias to push the Pic group to the β-face and the *anti* S$_N$2' substitution takes place selectively (Part B).



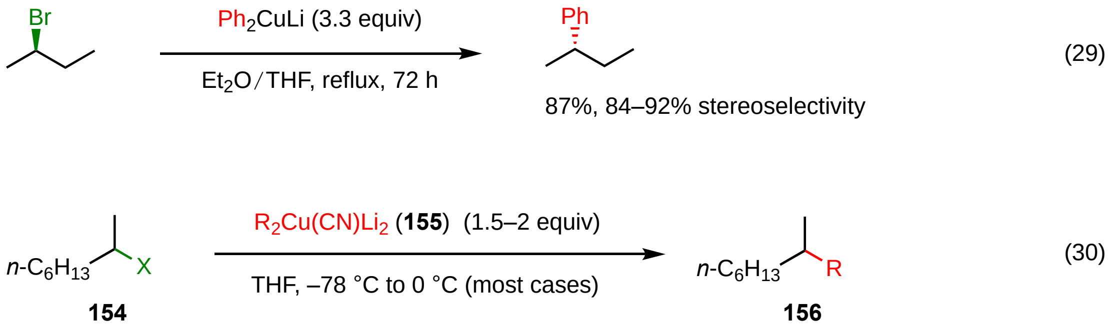
Scheme 33. Synthesis of Psoracorylifol B by Tong

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.[66] 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 PySO$_3$ leaving group is also presented (Scheme 1, eq 2).[67] 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 eqs 29 and 30 in Scheme 34 are especially informative for discussion about reactivity and stereochemistry. The substitution of halides using a Gilman cuprate (Ph_2CuLi) proceeded with inversion (eq 29).[68] Inversion was also observed for the substitution of bromide **154** (X = Br) with higher order cuprates ($R_2Cu(CN)Li_2$), whereas a more reactive iodide **154** (X = I) proceeded with racemization (eq 30).[69] In contrast, tosylate **154** (X = OTs) was less reactive, and required excess *n*-$Bu_2Cu(CN)Li_2$ (10 equiv) at rt to produce **156** (R = *n*-Bu) in >80% yield. However, the stereochemical course was not elucidated.

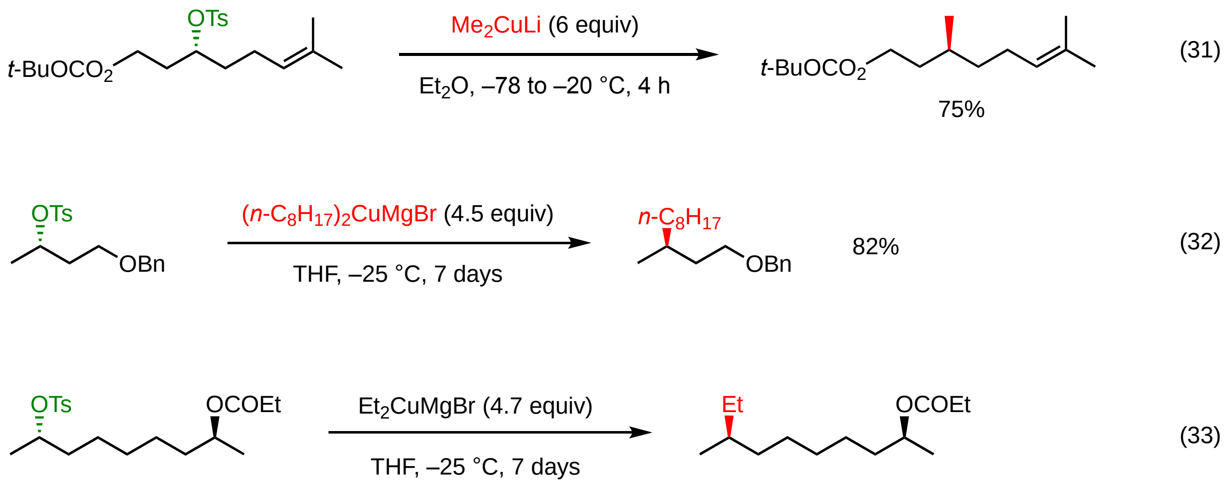


reactivity: X in substrates **154**: I > Br > TsO
R in reagent **155**: *n*-Bu, Et > Me > Ph

stereochem.: X = I: racemization
X = Br: inversion

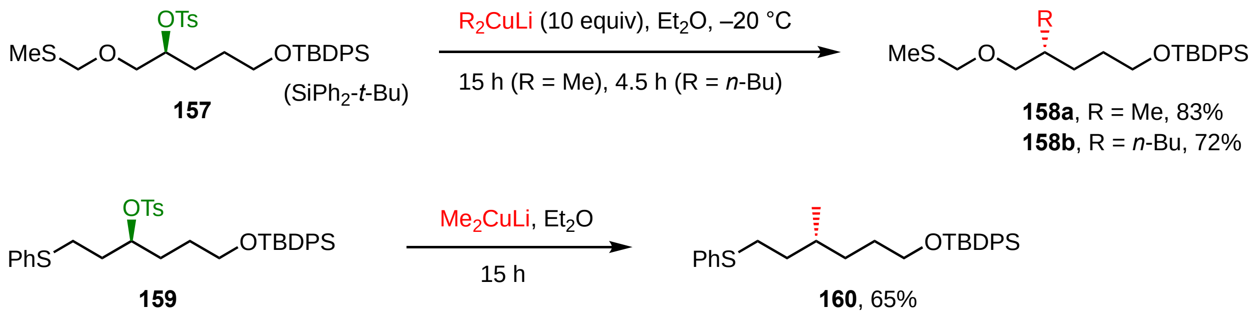
Scheme 34. Substitution of Secondary Halides with Cuprates

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.[70–72] Higher reactivity of $R_2CuMgBr$ than R_2CuLi was reported (eqs 32 and 33).



Scheme 35. Substitution of Secondary Tosylates with Cuprates

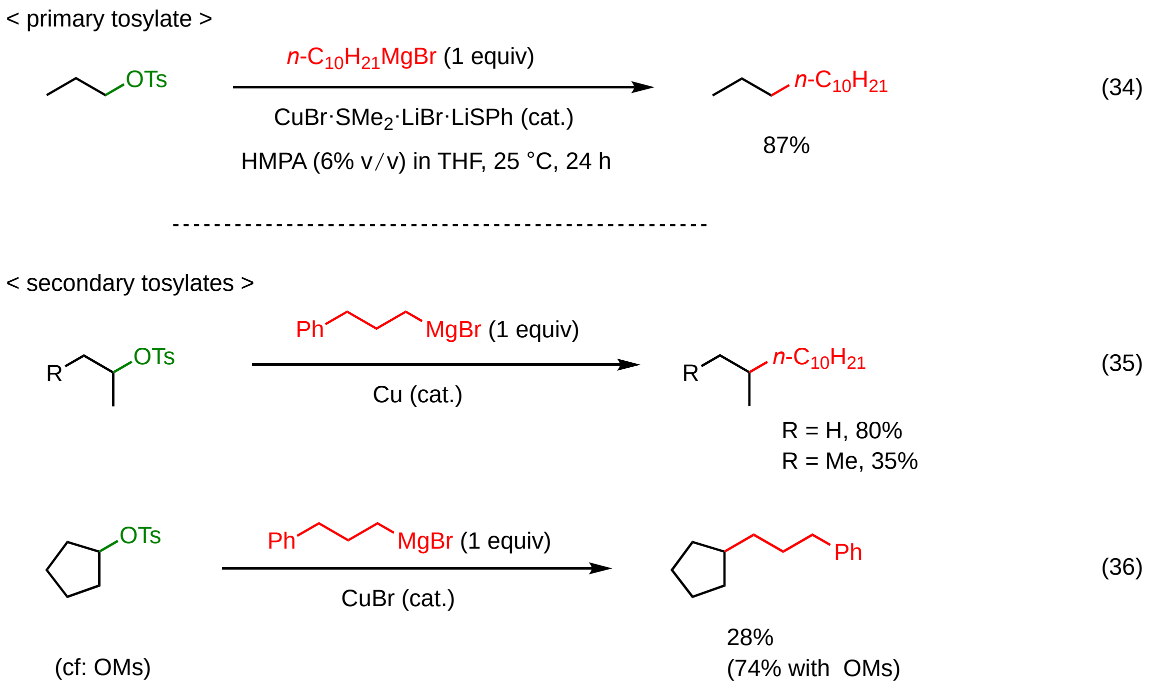
A Lewis basic substituent such as $MeSCH_2O$, PhS, and $MeOCH_2O$ at a proximal position from ***C***-OTs accelerated the substitution. For example, the substitution of **157** and **159** completed in 15 h and 4.5 h for Me and *n*-Bu cuprates, respectively (Scheme 36).[73] The reaction times indicated the lower reactivity of Me_2CuLi than other alkyl cuprates. A similar reactivity order was reported for the substitution of secondary halides with ($R_2Cu(CN)Li_2$) (eq 30).[69] The method (Scheme 36) was applied for the synthesis of ionomycin.[74]



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

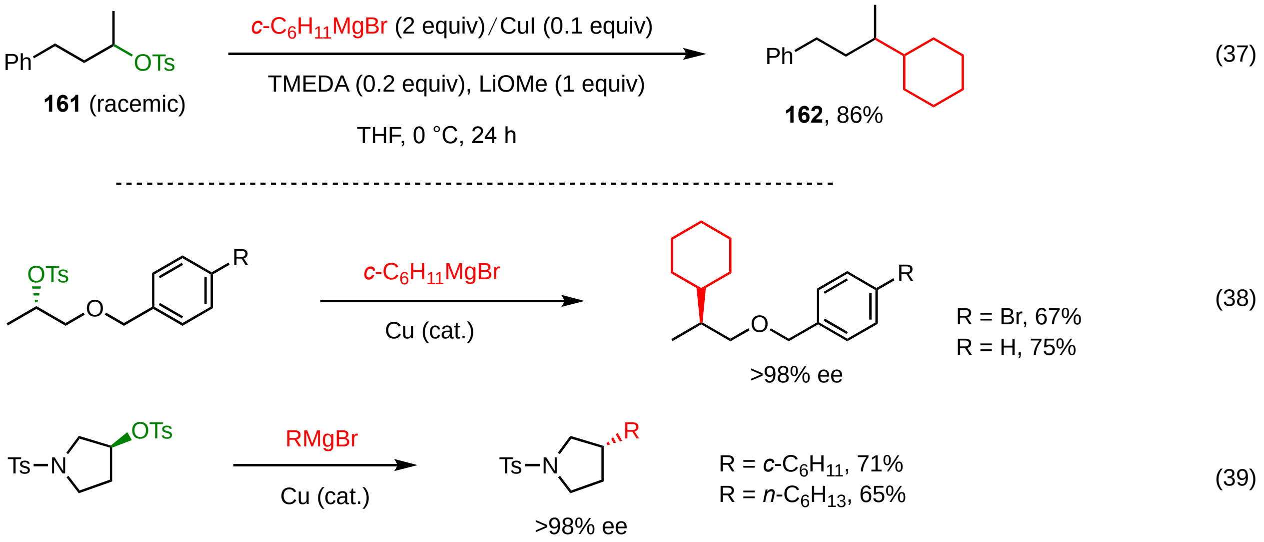
5.2. Previous Copper-Catalyzed Substitutions of Tosylates

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 $CuBr·Me_2S·LiBr·LiSPh$ (6 mol%) and HMPA in THF (6% v/v) (Scheme 37, eq 34).[75] This catalyst was superior to Li_2CuCl_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

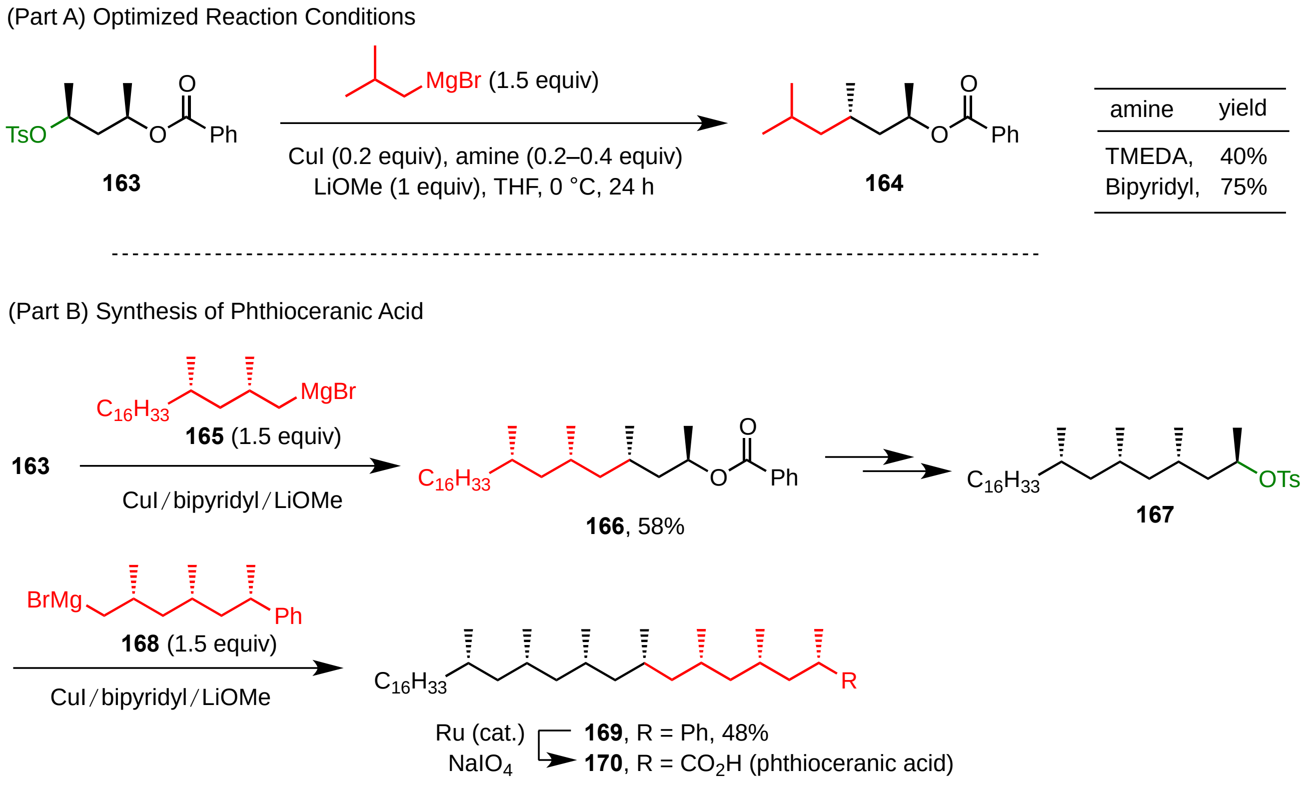
In 2012, Liu published a CuI-catalyzed substitution of secondary tosylate **161** with *c*-$C_6H_{11}MgBr$ in the presence of TMEDA (0.2 equiv) and LiOMe (1 equiv) to produce **162** in 86% yield (Scheme 38, eq 37).[76] TMEDA functioned to reduce the formation of olefins. Other copper salts such as CuBr, 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**).[77] 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.[78] This tandem process is one of the Negishi's signature reactions.



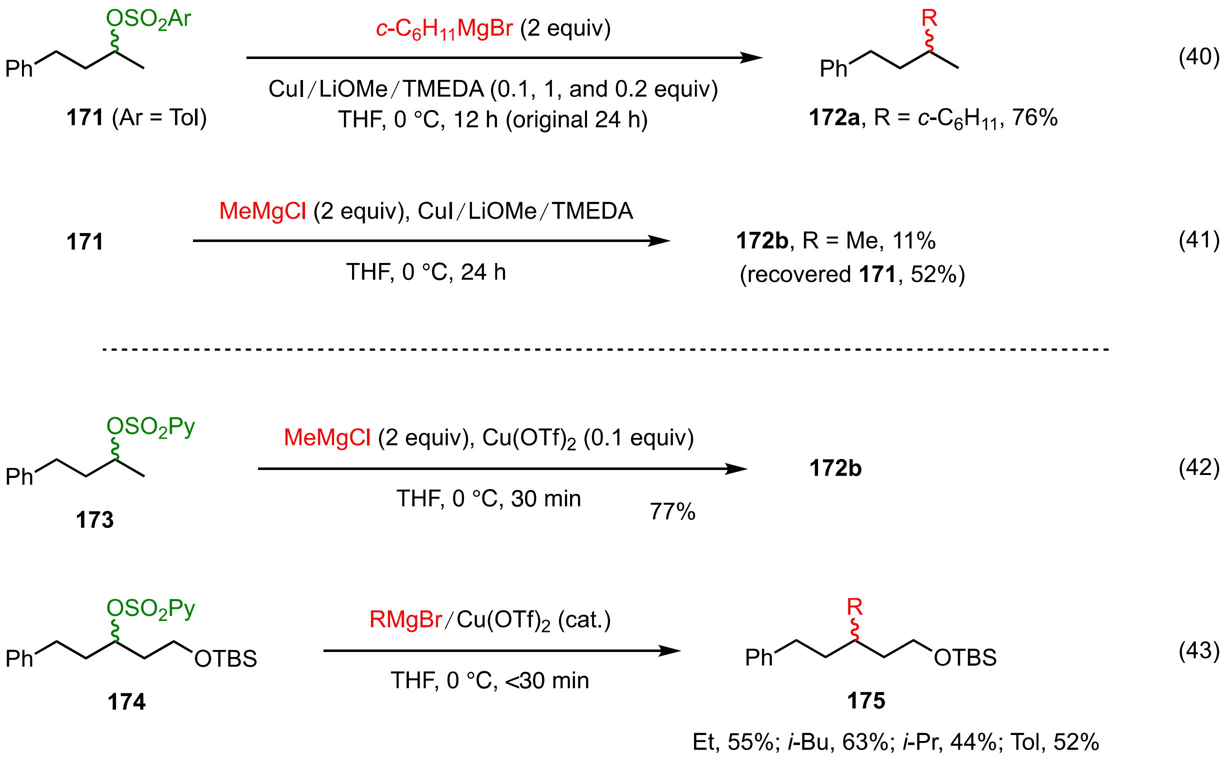
amine	yield
TMEDA,	40%
Bipyridyl,	75%

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

5.3. The Copper-Catalyzed Substitution of Pyridinesulfonates

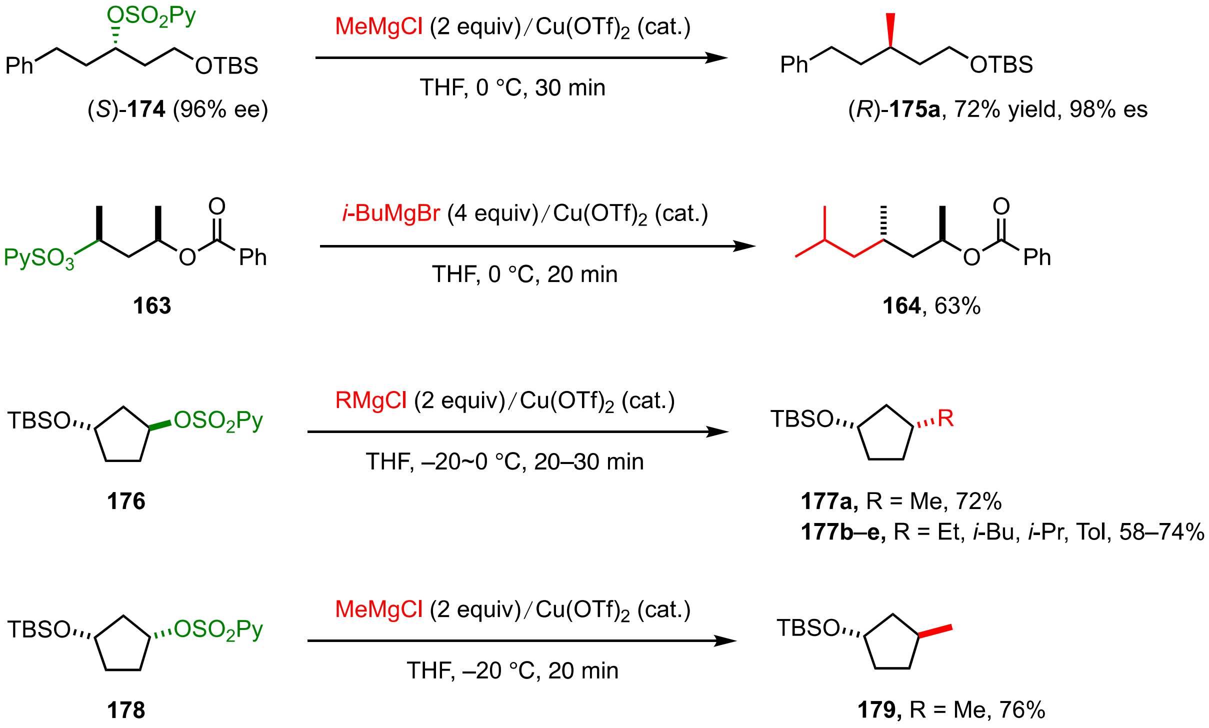
The substitution at secondary carbons with MeMgX is a useful method for the synthesis of biologically active Me substituted compounds.[73,74] However, methylation was not described in the above copper-catalyzed systems. Instead, the lower reactivity of Me cuprates than that of alkyl cuprates has been reported.[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*-$C_6H_{11}MgBr$ and MeMgCl were examined according to the Liu's procedure to figure out the reactivity order of *c*-$C_6H_{11}MgBr$ > MeMgCl (Scheme 40, eqs 40 and 41).[67]



Scheme 40. Finding of the $PySO_3$ Group for Substitution by Us

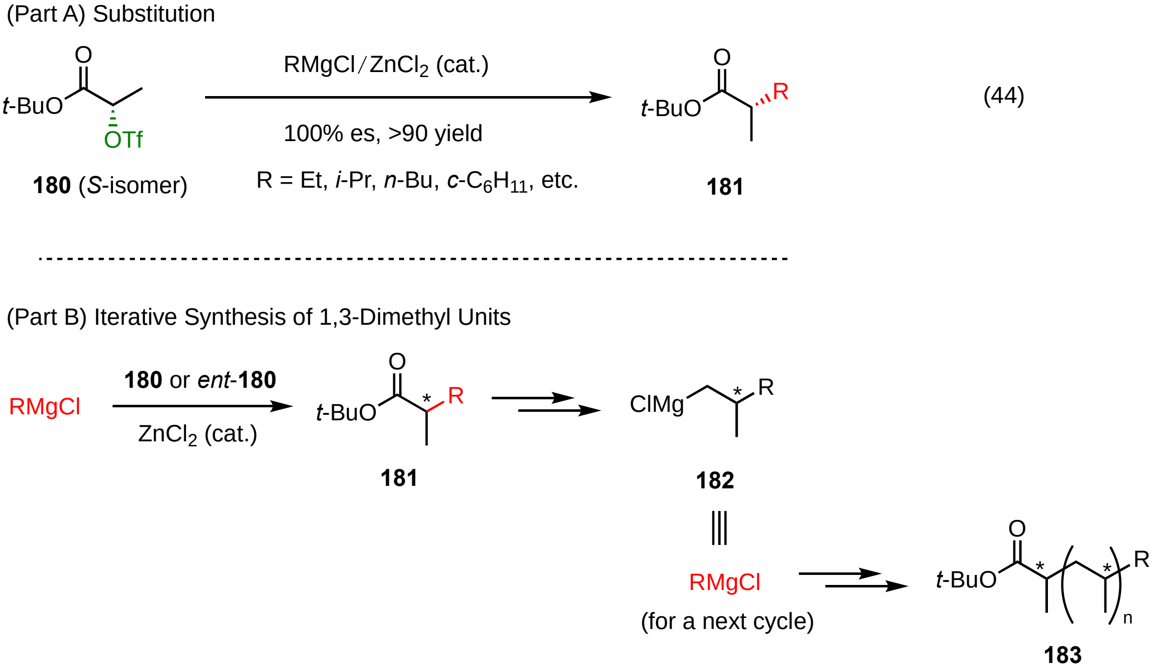
The substitution of pyridinesulfonate **173** with MeMgCl under similar conditions completed only in 15 min (data not presented), and further investigation disclosed that $Cu(OTf)_2$ catalyzed the substitution without the additives (LiOMe, TMEDA) to afford **172b** in 77% yield (Scheme 40, eq 42).[67] 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.



Scheme 41. Stereochemical Outcome of the Substitution Using the $PySO_3$ Leaving Group

5.4. The Zinc-Catalyzed Substitution at α-Carbons of Esters

Triflates **180** derived from α-hydroxy esters underwent $ZnCl_2$-catalyzed substitution with RMgX as developed by Breit (Scheme 42, eq 44).[79] Easy availability of precursor alcohols, complete inversion, and

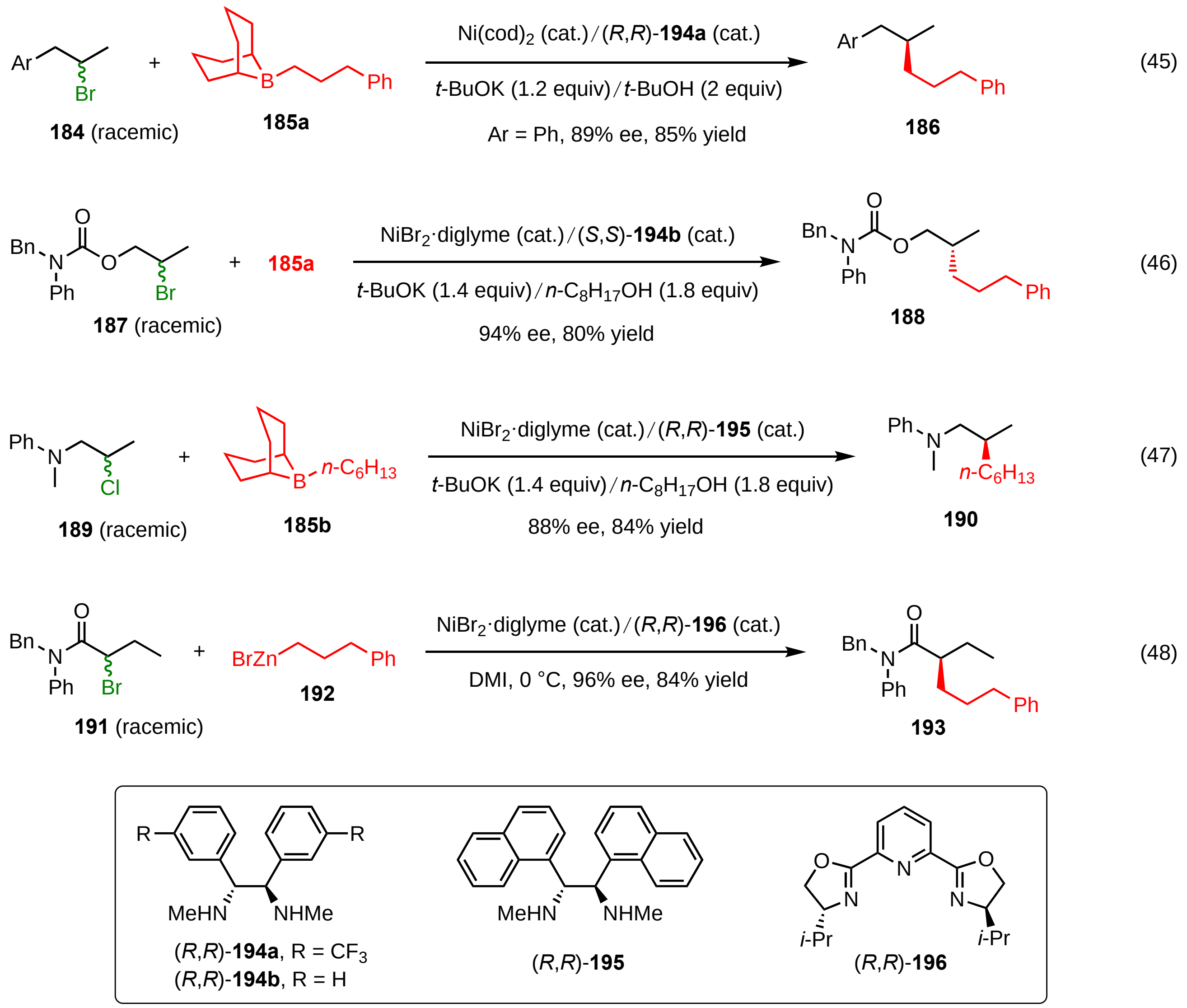


Scheme 42. Substitution at α-Carbons of Esters and Synthesis of Iterative 1,3-Dimethyl Units by Breit

high yields are advantages of the substitution. The iterative process was developed later to produce the 1,3-dimethyl unit **183**.[80]

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[81] 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).[82] An aromatic substituent (Ar) in a proximal position is the structural requirement. Later, the asymmetric substitution was successfully expanded to racemic



Scheme 43. Nickel-Catalyzed Asymmetric Substitution by Fu

secondary halides such as **187** and **189** possessing oxygen- or nitrogen-containing functional groups as indicated by eqs 46 and 47, respectively.[83,84] A similar coupling reaction has been reported using organozincs (eq 48).[85] These substitutions are summarized in his review.[66a]

6. Conclusion

This review summarized the high potency of the picolinoxy ($PyCO_2$) and pyridinesulfonyloxy ($PySO_3$) 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 $CuBr{\cdot}Me_2S$ or organolithiums, copper salt, and $MgBr_2$. The reaction proceeds with *anti* S_N2' 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, $PySO_3$, selected by us on the analogy of $PyCO_2$, shows high leaving potency to complete the reaction in short times (usually 30 min) with RMgX and less nuclephilic MeMgCl. The substitution at the α-carbons and the asymmetric substitution of racemic secondary halides possessing functional groups were also described.

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