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ASYMMETRIC SYNTHESIS OF CYCLOPROPYLAMINE DERIVATIVES

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Abstract – Cyclopropylamines are important synthetic intermediates and their enantiopure forms are also useful as chiral resolving agents. The present review outlines the recent developments on the asymmetric synthesis of cyclopropylamine derivatives. The transformations based on carbene or carbenoid species, asymmetric catalysis, ylide formation, Simmons-Smith, Kulinkovich and Mitsunobu reaction, conjugate addition, Favorskii-type rearrangement and intramolecular cyclopropanations are elaborated.

CONTENTS

1. INTRODUCTION

Amine functionalities are widely present in a large number of drugs and drug candidates. Asymmetric synthesis of amine derivatives has been an extremely challenging task for the design of potent drugs and their precursors. The widespread occurrence of highly strained cyclopropylamines as pharmaceutical or agrochemical subunits has stimulated their studies in recent years as potential chiral resolving agents or as synthetic intermediates for further reactions.[1]

Cyclopropylamine (CPA) is the key intermediate for the preparation of antibacterial drugs such as ciprofloxacin (**1**), sparfloxacin (**2**), balofloxacin (**3**) and grepafloxacin (**4**) (Figure 1).[2] CPA is also used in the synthesis of herbicides such as 2-*N*-cyclopropylamine-4,6-dichlorotriazine (**5**) and cyprazine (**6**), insecticides cyromazine (**7**) (Figure 1) as well as many other plant protection agents and feed additives.[3] 1-Aminocyclopropane carboxylic acid (ACC, **8**) is present in many plants as the immediate precursor to the plant hormone ethylene.[4] The diazepinone derivative Nevirapine (**9**) is an anti-HIV drug candidate.[5]

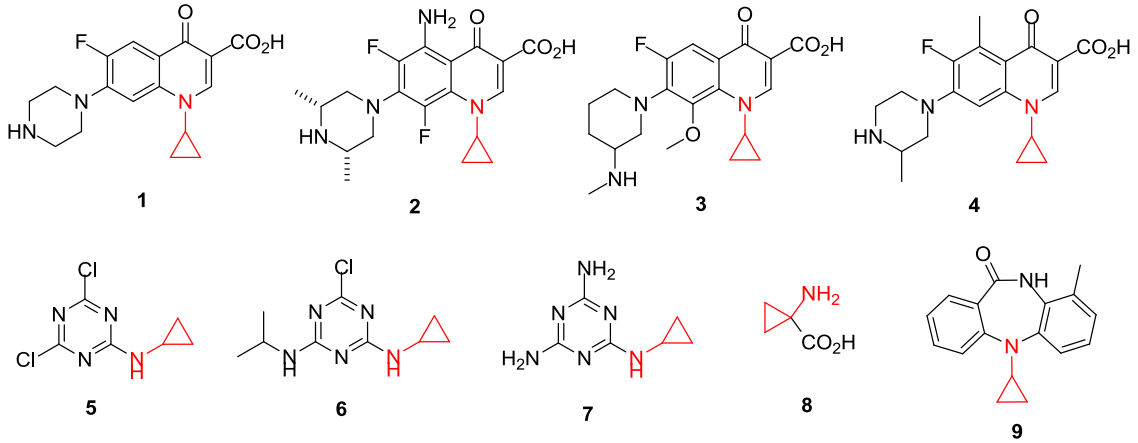


Figure 1. Chemical Structures of Compounds **1**–**9**

Chiral cyclopropylamine derivatives are also used in many drug molecules, such as an anticoagulant ticagrelor (**10**) (Figure 2) approved by FDA in 2011.[6] 2,5-Dimethoxyamphetamine derivatives **11** and **12** (Figure 2) are lead compounds with high affinity for 5-hydroxytryptamine 2 (5-HT_2) receptor with an EC_{50} = 2.0–6.3 nM, the more potent stereoisomer of the cyclopropane analogs has the expected (–)-(1*R*,2*S*)- configuration.[7] *trans*-2-Phenylcyclopropylamine (2-PCPA) (**13**) also exhibits lysine specific demethylase 1 (LSD1) and monoamine oxidase (MAO) inhibitory activities. Some other derivatives, such

as compounds **14** and **15** (Figure 2) have inhibitory activities both on LSD1 (IC_{50} = 1.3–1.9 μM) and MAO-A (IC_{50} = 0.5–1.2 μM). In particular, the compound **16** displays better inhibition selectivity over LSD1 (IC_{50} = 1.9 μM) and MAO-A and B (IC_{50} = 230 μM).[8–10] The *Streptomyces* sp. UCK 14 metabolite Belactosin A (**17**) and its derivatives, which contain the unusual 2-*trans*-(2-aminocyclopropyl)alanine residue, exhibit remarkable proteasome inhibitory activities.[11]

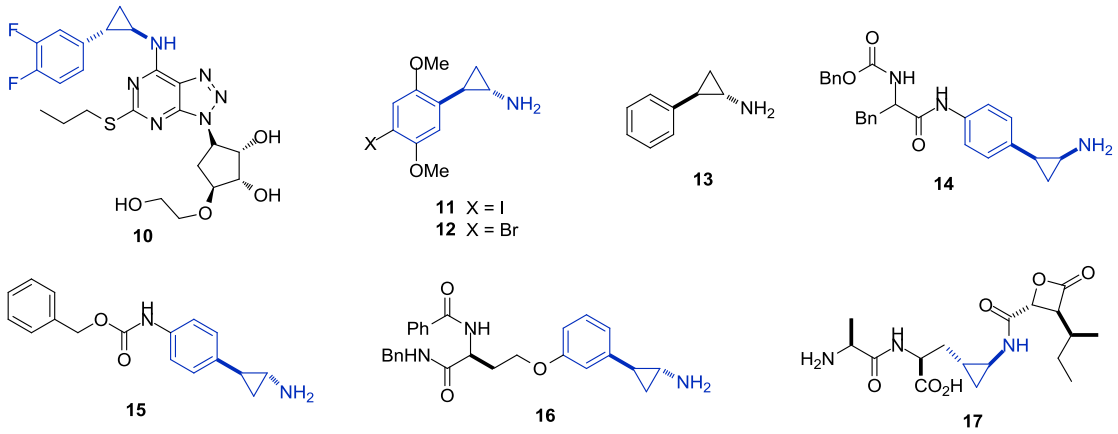


Figure 2. Chemical Structures of Compounds **10**–**17**

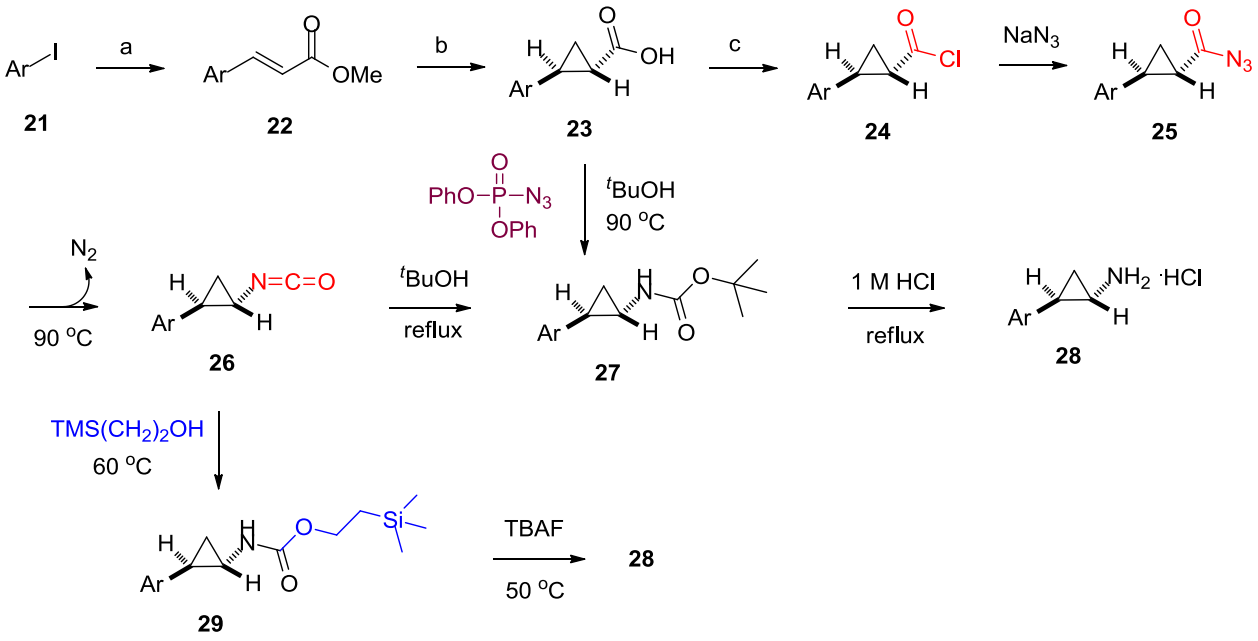
Similar to the synthesis of CPA, most common methods for the preparation of the chiral cyclopropylamine derivatives are based on asymmetric addition of a carbene or carbenoid species (such as diazomethane and its derivative, sulfur ylides, Simmons-Smiths reagents, etc.) to an olefin promoted by a chiral catalyst or through the introduction of a chiral auxiliary group to the olefin to control the sterochemical configuration of the product.[12] Generally α,β-unsaturated carboxylic esters are used as the olefin substrate. The cyclopropylamine products are obtained from the cyclopropanecarboxylate intermediates through the traditional ester hydrolysis, Hofmann degradation or Curtius rearrangement reactions. Other methods to produce chiral cyclopropylamine derivatives include Kulinkovich reactions, intramolecular Mitsunobu reaction, Favorskii rearrangement, and so on.[13]

2. USING CARBENE AND CARBENOID TO BUILD THE CYCLOPROPANE

2.1 Diazomethane as Carbene

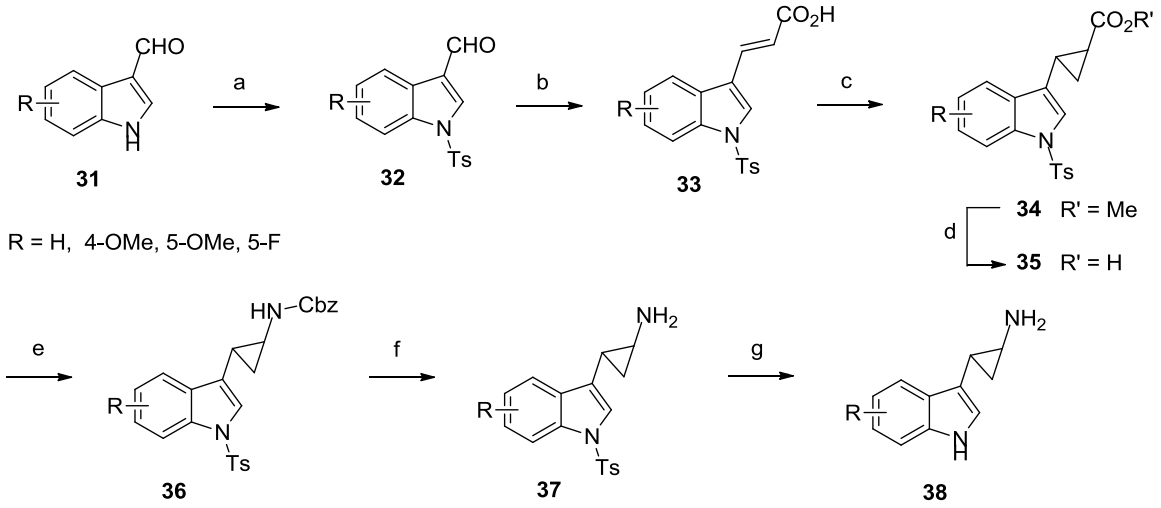
The arylated methyl acrylate derivatives were cyclopropanated with diazomethane in the presence of 0.5 mol% of palladium-(II) acetate. Higher concentrations of the catalyst often led to precipitation of palladium-(0) with accompanying termination of the reaction. Alkaline hydrolysis gave the desired *trans*-arylcyclopropanecarboxylic acids **23** (Scheme 1).[14] These acids were transformed to the corresponding primary amines by Curtius rearrangements. The one-pot procedure with diphenyl phosphorazidate (DPPA)[15] worked well in many cases. An alternative method used involved preparation of acyl chloride **24** which was subsequently treated with sodium azide to obtain acyl azides **25**. These

were transformed into *tert*-butyl carbamates via the corresponding isocyanates **26**. The resulting carbamates were finally hydrolyzed with 1 M hydrochloric acid to give the desired cyclopropanamine **28**. When the aryl moiety was acid sensitive, the 2-(trimethylsilyl)ethyl carbamate **29** was prepared, which was hydrolyzed with tetrabutylammonium fluoride (TBAF).[16]



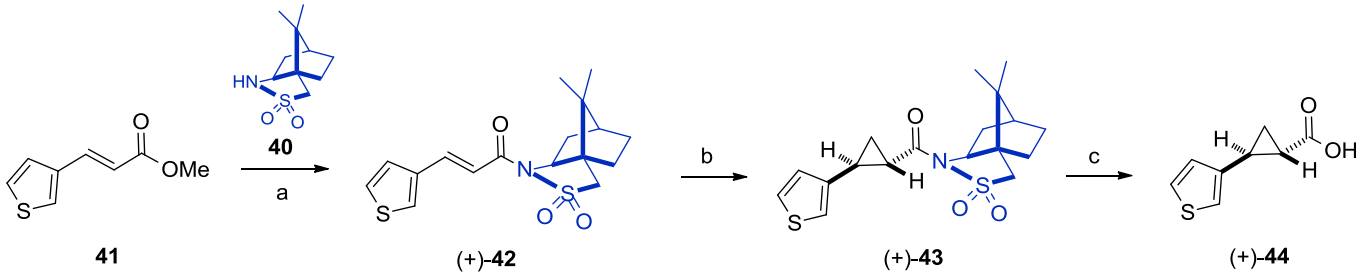
Scheme 1. Reagents: (a) methyl acrylate, $Pd(OAc)_2$, Bu_4NCl, K_2CO_3, DMF; (b) i) CH_2N_2, $Pd(OAc)_2$, ii) NaOH, H_2O, MeOH; (c) Et_3N, EtOCOCl, acetone.

Besides *tert*-butanol, the intermediate isocyanates can be trapped with benzyl alcohol in the Curtius rearrangement, as reported by Vangveravong[17] and Erhardt.[18] As shown in Scheme 2, indole-3-carboxaldehydes **31** were first protected as the *N*-*p*-toluenesulfonyl derivatives **32**. This protection was *key* to the success of the synthesis, not only because it enhanced reactivity of the carboxaldehyde but also because attempts to deprotect prior to the final step led to unstable intermediates that could not be isolated and purified. The protected indolecarboxaldehydes were condensed with malonic acid to afford the *trans*-β-indol-3-yl-acrylic acids **33**. The acids were converted to their methyl esters, and cyclopropanation with retention of *trans* stereochemistry was then accomplished using ethereal diazomethane in the presence of catalytic palladium diacetate.[19] Hydrolysis of the cyclopropyl methyl esters provided acids **35**, which were reacted under the conditions of Curtius rearrangement, trapped with benzyl alcohol and then subjected to catalytic hydrogenation to give the amines **37**. *N*-Detosylation as the final step was accomplished using sodium amalgam under buffered conditions to afford the desired indolecyclopropylamines **38**.



Scheme 2. Reagents: (a) *p*-toluenesulfonyl chloride, Et_3N; (b) malonic acid, pyridine, piperidine; (c) i) CH_2N_2, ii) CH_2N_2/$Pd(OAc)_2$; (d) NaOH/MeOH, then HCl; (e) i) Et_3N, $ClCO_2Et$, NaN_3, ii) BnOH, heat; (f) H_2, Pd-C, EtOH; (g) Na-Hg, Na_2HPO_4, MeOH.

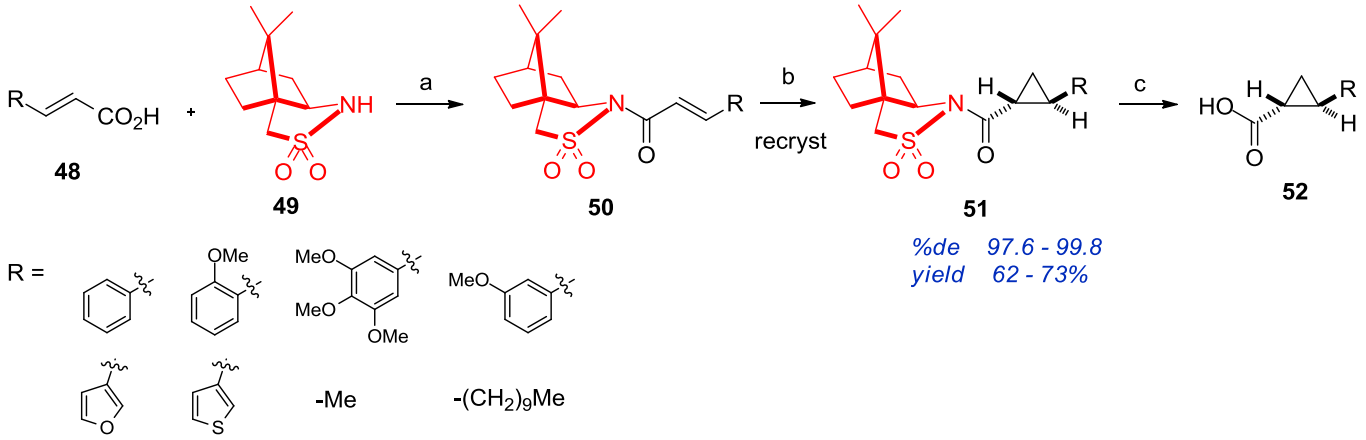
In order to obtain (1*S*,2*R*)-2-(thiophen-3-yl)cyclopropanamine, the (+)-enoyl sultams were prepared from L-(+)-camphorsultam (**40**) and the methyl acrylate derivatives **41** (Scheme 3).[14] The enoyl sultams were cyclopropanated, and the products were recrystallized to provide the corresponding cyclopropanoyl derivatives (+)-**43** with high diastereomeric purities. The camphorsultam moiety of the diastereoisomers was removed by a two-step procedure involving (a) treatment with titanium-(IV) isopropoxide in benzyl alcohol and (b) base promoted hydrolysis of the resulting benzyl ester, thus providing the desired (+)-**44**.



Scheme 3. Reagents: (a) i) NaOH, MeOH, H_2O, ii) $(COCl)_2$; (b) CH_2N_2, $Pd(OAc)_2$; (c) i) $Ti(^iPrO)_4$, BnOH, ii) 2 M NaOH, MeOH, THF.

D-(–)-Camphorsultam (Oppolzer's Sultam, **49**) was also adopted in the asymmetric synthesis of cyclopropylamine, which functions as an easily removable, inexpensive, and efficient chiral auxiliary, as reported by Vallgarda[20,21] and Vangveravong[22] (Scheme 4). Adopting the similar methods as described before, **51** were obtained in good yield, and the stereochemical purity can be easily increased by recrystallization. The cyclopropanation was quantitative at temperatures between –30 °C and 28 °C. At

temperatures below –30 °C the reaction became very sluggish and above 30 °C the volatility of diazomethane caused problems. The stereoselectivity of the reaction increased with the reaction temperature, the diastereomeric excess (de %) of the product increased from about 53 to 87% as a result of an increase in reaction temperature from –30 °C to 0 °C. Thus, it appears that reaction conditions favored formation of thermodynamically controlled product with enhanced stereoselectivity.

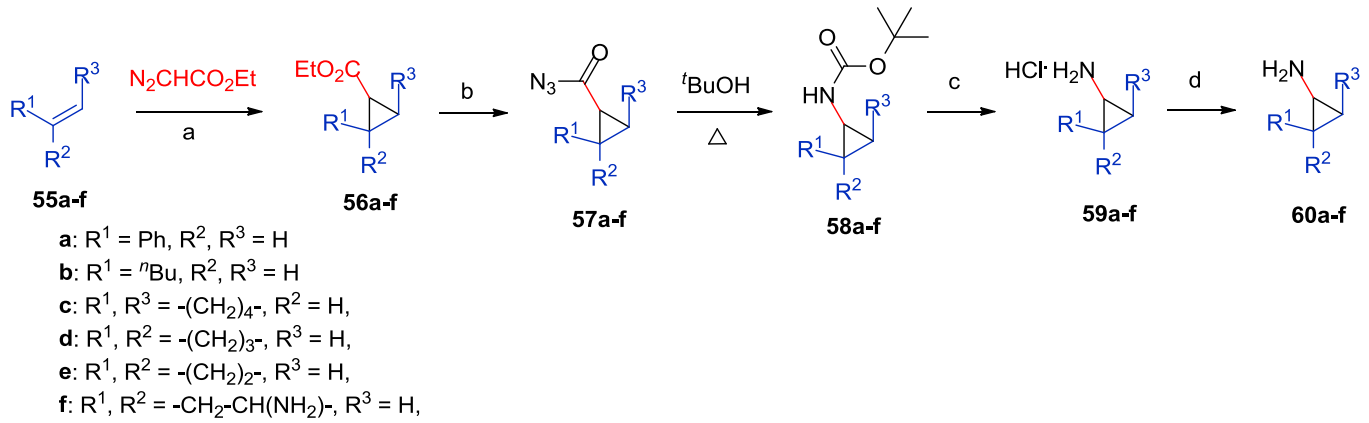


Scheme 4. Reagents: (a) i) $(COCl)_2$, toluene, ii) NaH; (b) CH_2N_2, $Pd(OAc)_2$; (c) i) $Ti(^iPrO)_4$, BnOH, ii) 2 M NaOH, MeOH, THF.

2.2 Diazo Esters as the Carbenoid

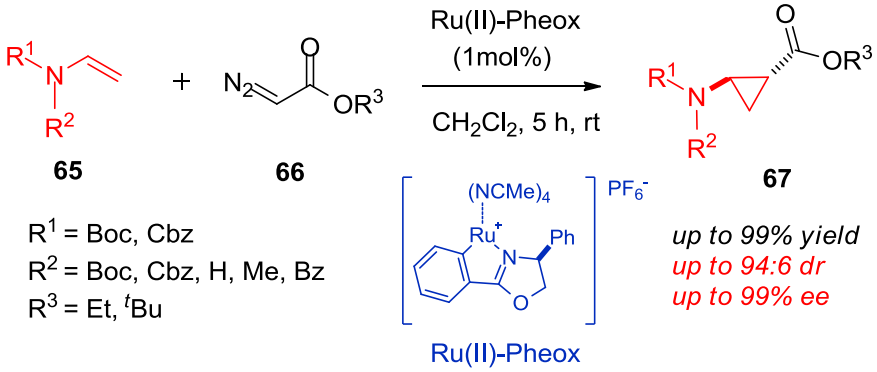
To date developments in cyclopropanation have been restricted to diazo esters and α-substituted analogues for two reasons: (i) diazo esters are more stable (ethyl diazoacetate is commercially available) and therefore easier to handle than aryl-, alkenyl-, or alkynyldiazomethanes, which are unstable and potentially explosive,[23–25] and (ii) diazo esters are much less prone to metal-catalyzed diazo dimerization than the above diazo compounds.

As shown in Scheme 5, ethyl diazoacetate reacted with olefins **55a–f** in the presence of catalyst rhodium acetate to give the cyclopropanecarboxylate **56a–f**.[26,27] The transformations of **56a–f** into **59a–f** were carried out without isolation of the intermediate azides **57a–f** and the products of Curtius rearrangement **58a–f**. The hydrochlorides **59a–f** were purified by recrystallization from chloroform or methanol before conversion into the corresponding amines **60a–f**. The cyclopropane products were mixture of four isomers, for example, 1,4-diazidospiro[2.2]pentane (**57f**)**:A:B:C:D** = 50:20:20:10, and Spiro[2.2]-pentane-1,4-diamine dihydrochloride (**59f**)**:A:B:C:D** = 35:30:25:10.



Scheme 5. Reagents: (a) $Rh_2(OAc)_4$; (b) i) $N_2H_4 \cdot H_2O$, ii) HCl, iii) $NaNO_3$; (c) i) HCl, ii) NaOH.

Recently, Chanthamath[28] developed a highly enantioselective cyclopropanation of vinyl carbamate derivatives with diazoesters, using the Ru(II)-Pheox complex as a catalyst, as shown in Scheme 6. The reaction proceeds smoothly under mild conditions, giving the corresponding protected cyclopropylamine products **67** in high yield, with excellent diastereoselectivity (up to 96:4) and enantioselectivity (up to 99% ee).

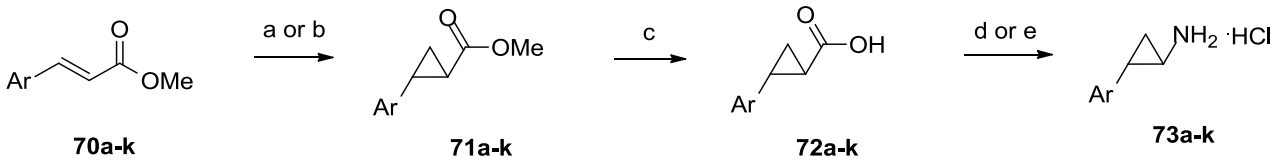


Scheme 6. General Synthesis of Compound **67**

2.3 Using Ylides to Build the Cyclopropane

(1) Sulfur Ylide

Gooden[29] reported a facile route to synthesize *trans*-2-arylcyclopropylamines **73a–k** (Scheme 7). Two cyclopropanation methods were employed for the preparation of compounds **71a–k** (Table 1). Reaction of α,β-unsaturated esters **70a–k** with the Corey-Chaykovsky reagent (dimethylsulfosonium methylide) in DMSO (Method A) generally gave poor yields of the desired cyclopropanated products than the traditional diazomethane approach (Method B).[30] Detosylation of the indole nitrogen in **70k** was anticipated under the strongly basic conditions of Method A, thus cyclopropanation by this method was not attempted. On the other hand, use of diazomethane with palladium (II) acetate (Method B) afforded the corresponding cyclopropanated products in excellent yields.



70a-k **71a-k** **72a-k** **73a-k**

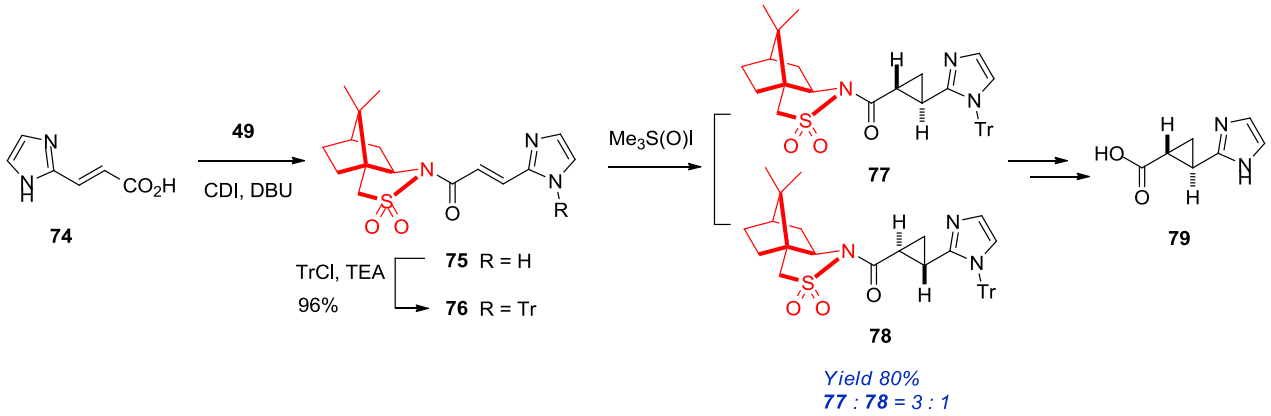
Scheme 7. Reagents: (a) 1.6 mol% $Pd(OAc)_2$, CH_2N_2, THF (Method A); (b) $Me_3S(O)I$ / NaH, DMSO (Method B); (c) i) aq NaOH, MeOH; ii) aq HCl; (c) i) diphenylphosphoryl azide, Et_3N, ^tBuOH; ii) aq HCl, THF; (e) i) $ClCO_2Et$, Et_3N, acetone; ii) aq NaN_3; iii) $Me_3Si(CH_2)_2OH$; iv) Bu_4NF, THF.

Table 1. Cyclopropanation Methods for the Preparation of Esters **71a–k** from **70a–k**

Entry	Compound	Ar	% yield (Method A)	% yield (Method B)
1	**71a**	4-$CF_3C_6H_4$	27	96
2	**71b**	4-BrC_6H_4	50	94
3	**71c**	4-$MeOC_6H_4$	50	98
4	**71d**	4-$NO_2C_6H_4$	5	65
5	**71e**	2-thienyl	40	97
6	**71f**	3-thienyl	59	99
7	**71g**	2-furyl	27	94
8	**71h**	3-furyl	21	99
9	**71i**	3-pyridyl	34	–
10	**71j**	1-naphthyl	65	–
11	**71k**	*N*(Ts)-5-indoyl	–	97

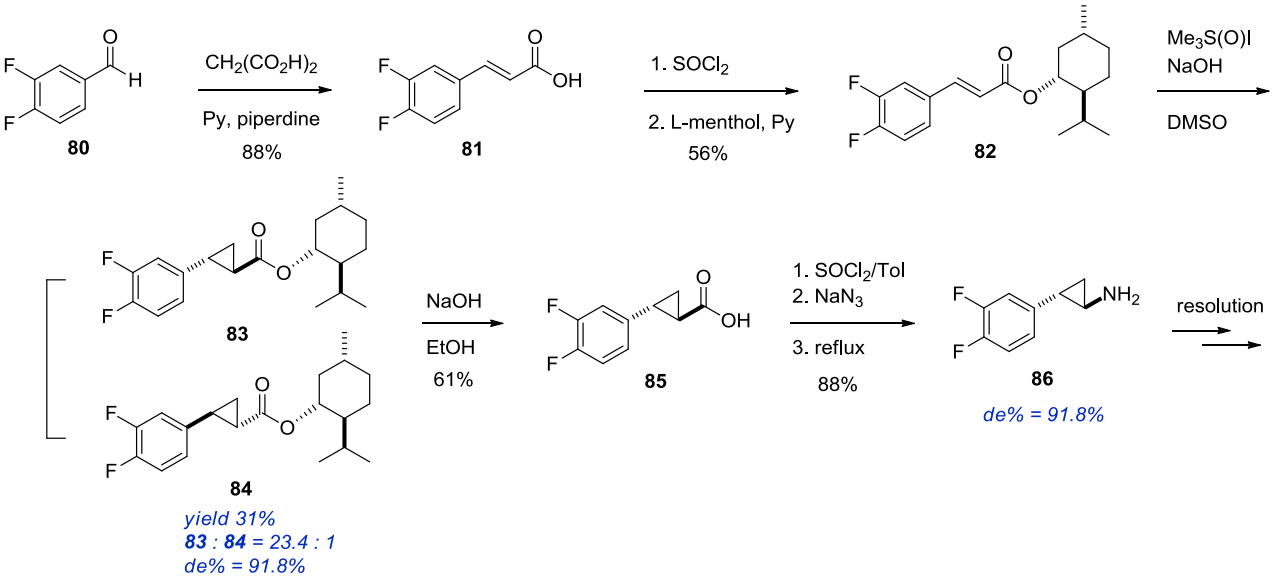
For the two substrates (entries 9 and 10), cyclopropanation by Method B gave complex reaction mixtures whereas all other substrates reacted under these conditions yielding the cyclopropyl adduct as the sole reaction product. However, cyclopropanation by Method A provided **71i** and **71j** in acceptable yield as the sole reaction products without the need for further purification.

Using Oppolzer's sultam (**49**) as the auxillary group, Khan[31] synthesized the *trans*-cyclopropanecarboxylic acid **79** diastereoselectively based on the sulfur ylide cyclopropanations (Scheme 8). The cyclopropanation of *N*-acryloyl derivative **76** with trimethylsulfoxonium iodide proceeded in DMSO:THF (1:1) to give on the average of three runs a 3:1 mixture of (1*S*,2*S*)-cyclopropane-sultam **77** and (1*R*,2*R*)-cyclopropane-sultam **78** respectively, with 80% isolated yield of the diastereomeric mixture.



Scheme 8. General synthesis of Compound **79**

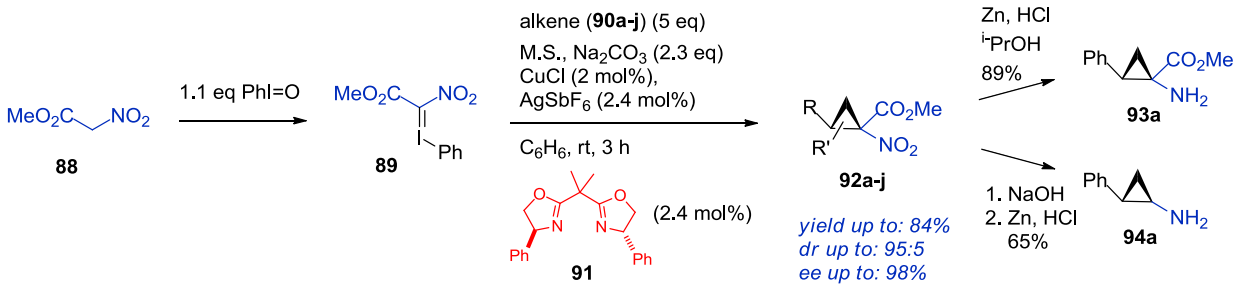
Clark[32] reported a kilogram-scale method to prepare *trans*-(1*R*,2*S*)-2-(3,4-difluorophenyl)-cyclopropylamine (**86**), the key intermediate of ticagrelor (**9**), using L-menthol as the auxiliary group (Scheme 9). The key sulfur ylide cyclopropanation step from **82** gave a 31% isolated yield and 91.8% de of **83** and **84**. After the ester hydrolysis, Curtius rearrangement process, the product **86** was obtained with 91.8% de, which can be purified by resolution with *R*-(–)-mandelic acid in ethyl acetate.



Scheme 9. General Synthesis of Compound **86**

(2) Iodonium Ylides

Moreau[33] reported a method for synthesis of cyclopropane α-amino acids by a catalytic asymmetric cyclopropanation of alkenes using iodonium ylides derived from methyl nitroacetate (Scheme 10). A three-step synthesis of enantiomerically enriched products was developed using the Cu(I)-catalyzed asymmetric cyclopropanation reaction of phenyliodonium ylides with alkenes. Commercially available isopropylidene-bis(4-phenyl-2-oxazoline) (**91**) and $AgSbF_6$ were used as catalyst precursors.



Scheme 10. General synthesis of Compounds **93**, **94**

Several alkenes (**90a–j**) were employed and the results are depicted in Table 2. Substitution of the aromatic ring could be accomplished with success, as the cyclopropanation of sterically hindered 2,4,6-trimethylstyrene **90g** led to the desired product in 54% yield and 93% ee (entry 7). Indene (**90i**) also furnished excellent yield, diastereoselectivity, and enantioselectivity of the corresponding cyclopropane (entry 9).

Table 2. Scope for the Cyclopropanation of Alkenes (**90a–j**)

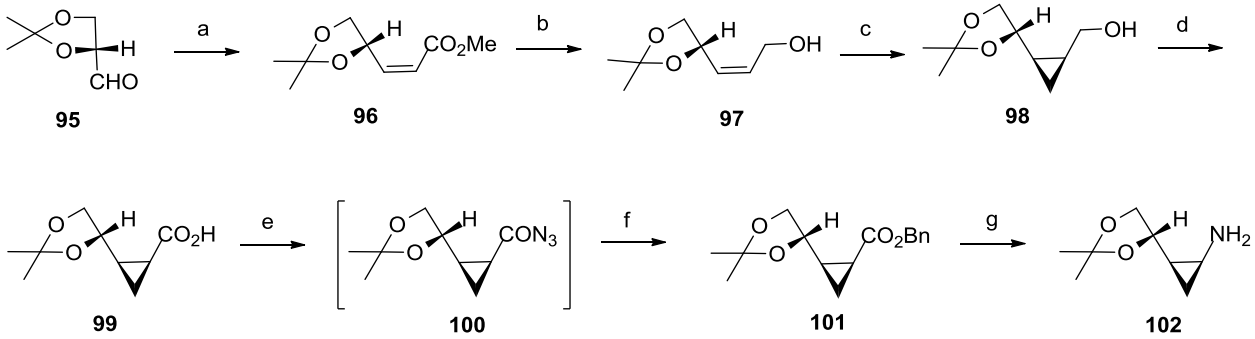
Entry	Compound	alkene	% yield	dr	%ee
1	**90a**	PhCH=CH_2	82	94:6	91
2	**90b**	4-Cl-PhCH=CH_2	45	92:8	91
3	**90c**	4-MeO-PhCH=CH_2	71	93:7	68
4	**90d**	4-Me-PhCH=CH_2	76	93:7	92
5	**90e**	1-NaphthCH=CH_2	53	93:7	91
6	**90f**	2-NaphthCH=CH_2	74	91:9	91
7	**90g**	2,4,6-$Me_3C_6H_2$CH=CH_2	54	95:5	93
8	**90h**	4-^{t}Bu-PhCH=CH_2	80	93:7	90
9	**90i**	indene	72	95:5	98
10	**90j**	1,3-butadiene	84	82:18	90

The cyclopropylamine ester **93a** was obtained in high yield from the nitroester **92a** by a simple Zn-mediated reduction. Similarly, a simple two-step process was used to decarboxylate and reduce **92a** into the amine **94a**. The high enantioselectivity was preserved in both cases.

2.4 Building the Cyclopropane Ring by Simmons-Smith Reaction

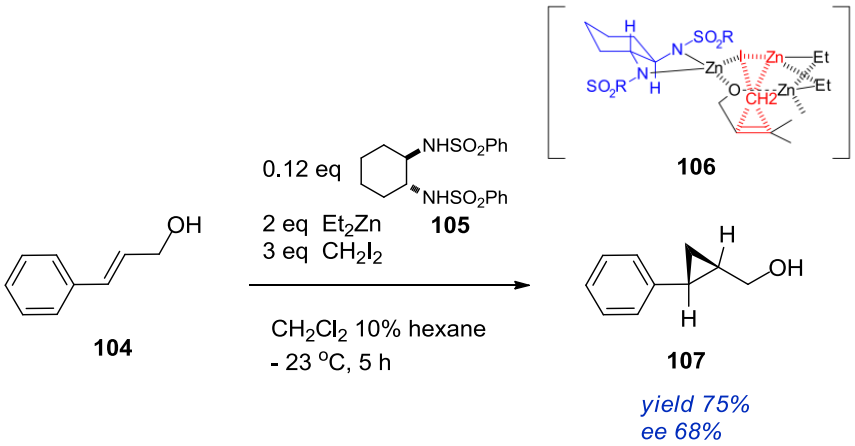
The Simmons-Smith reaction is an organic cheletropic reaction in which a carbenoid reacts with an alkene (or alkyne) to form a cyclopropane.[34] Zhao[35] reported an asymmetric synthesis of (l'*S*,2'*R*)-cyclopropyl carbocyclic nucleoside based on this reaction. Their initial attempts to directly convert β-unsaturated ester **96** to the cyclopropyl derivative, using dimethyloxosulfonium methylide,

gave a low yield (~10%) without stereoselectivity. Thus, the ester **96**, which was prepared by the Wittig reaction of **95**, was reduced by DIBALH at –78 °C to **97** in 84% yield (Scheme 11). Treatment with Et_2Zn and CH_2I_2 at 0 °C gave optically pure cyclopropylmethyl alcohol **98** as the major isomer, which was oxidized with $NaIO_4$ in the presence of RuO_2 to obtain acid **99**. The cyclopropylamine **102** was obtained after the Curtius process.



Scheme 11. Reagents: (a) $Ph_3P{=}CHCO_2Me$, 81%; (b) DIBALH, –78 °C, 84%; (c) $ZnEt_2$, CH_2I_2, 70%; (d) $RuO_2/NaIO_4$; (e) i) $ClCO_2Et$, ii) NaN_3; (f) BnOH, 87%; (g) H_2, Pd/C, 95%.

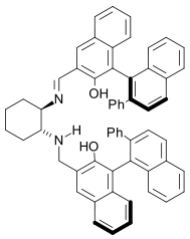
The asymmetric Simmons-Smith cyclopropanation reaction was introduced in 1992[36] by employing a reaction of cinnamyl alcohol (**104**) with diethylzinc, diiodomethane and a chiral disulfonamide **105** in dichloromethane (Scheme 12). The hydroxyl group is a prerequisite serving as an anchor for zinc.



Scheme 12. General Synthesis of Compound **107**

In another version of this reaction[37] the ligand was based on the Salalen reagent **119** and an Al Lewis acid / N-Lewis base bifunctional catalyst (Table 3). The experimental results suggested that the bifunctional catalysis of the Al (salalen) complex (**120**) is essential for obtaining high enantioselectivities.

Table 3. Asymmetric Simmons-Smith Reaction of Allylic Alcohols with **119**



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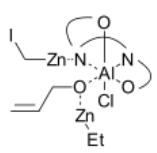

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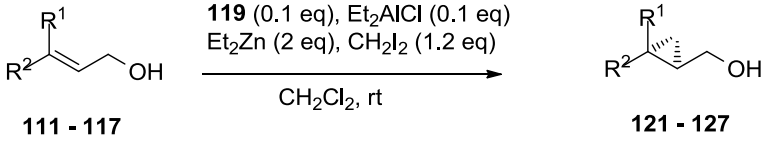
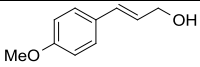
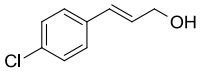
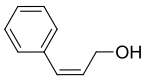
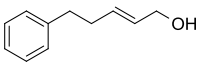
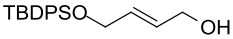
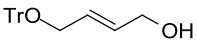
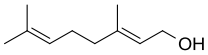
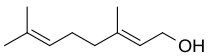
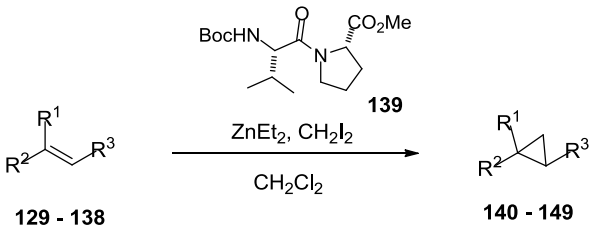


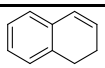
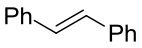
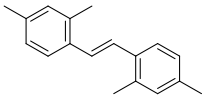
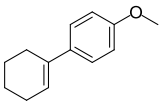
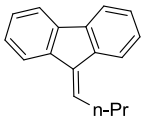
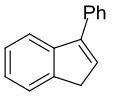
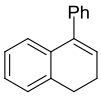
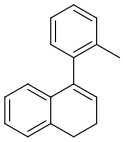
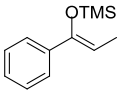
Entry	Substrate (**111–117**)	t [h]	% yield[a]	% ee[b]	Config.[c] (**121–127**)
1		3	93	94	1*S*, 2*S*
2		1	94	94	1*S*, 2*S*
3		1	99	58	1*R*, 2*S*
4		3	95	86	1*S*, 2*S*
5		3	99	90	n.d.
6		3	98	87	1*S*, 2*S*
7		4	98	63	1*S*, 2*S*
8[d]		10	92	70	1*S*, 2*S*

[a] Calculated from ^{1}H NMR analysis by using 1-bromonaphthalene as an internal standard. The values in the parentheses show the yields of the isolated products. [b]Determined by HPLC analysis by using chiral stationary phase column. [c]Determined by chiroptical comparison. [d]Reaction was carried out at 0 ^{o}C.

Long[38] found that the readily available dipeptide *N*-Boc-L-Val-L-Pro-OMe (**139**) (Table 4) is an effective ligand for asymmetric cyclopropanation of unfunctionalized olefins. Using this methodology, up to 91% ee was attained. These results suggest that the development of a highly enantioselective Simmons-Smith type cyclopropanation of unfunctionalized olefins via transfer of a simple methylene group is a real possibility.

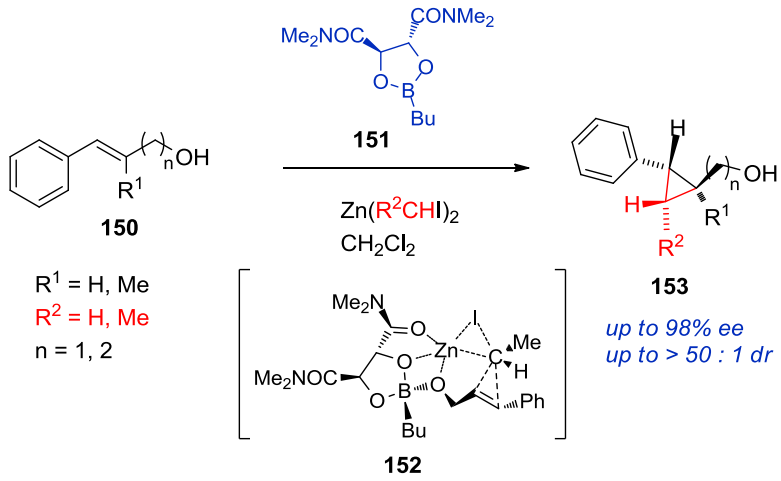
Table 4. Asymmetric Cyclopropanation of Olefins with **139**



Entry	Substrate (**129–138**)	% yield	% ee
1		71	72
2		83	75
3		43	89
4		71	75
5		78	90
6		84	78(98[a])
7		83	90(99[a])
8		71	91(99[a])
9		71	79(98[a])
10		68	85

[a]The ee's after recrystallization from hexanes.

Wang[39] reported an asymmetric Simmons-Smith reaction using Charette chiral dioxaborolane ligand (**151**) for the construction of enantiomerically enriched cyclopropane ring (Scheme 13). Substituted iodomethylzinc reagents proved ideal for the Charette asymmetric *SS* reaction to obtain excellent enantioselectivities (90–98% ee) and high diastereoselectivities (from 10:1 to > 50:1 dr).[40]

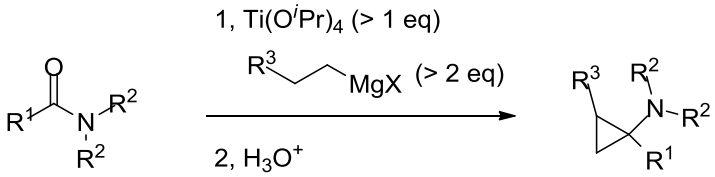


Scheme 13. General Synthesis of Compd. **153**

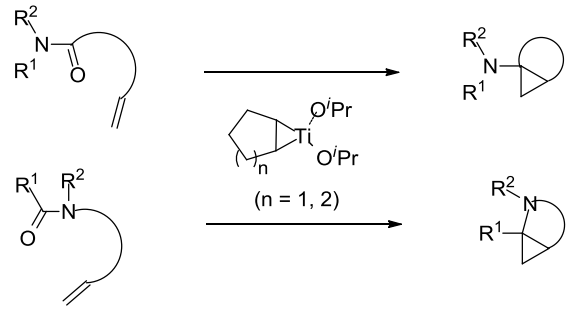
It is interesting to note that the cyclopropanation reactions of 2-substituted allylic alcohols and homoallylic alcohols gave relatively lower levels of enantioselectivities (around 80% ee). Computational studies suggest that when Charette chiral ligand **151** is employed, monomeric iodomethylzinc allyloxide is converted into an energetically more stable four-coordinated chiral zinc/ligand complex **152**. The chiral complex with the zinc metal bonded to the CH_2I group and linked to three oxygen atoms through coordinate linkage (from the allylic alcohol, carbonyl oxygen and the dioxaborolane ligand) can readily undergo the desired cyclopropanation.

3. BUILDING THE CYCLOPROPANE RING BY KULINKOVICH REACTIONS

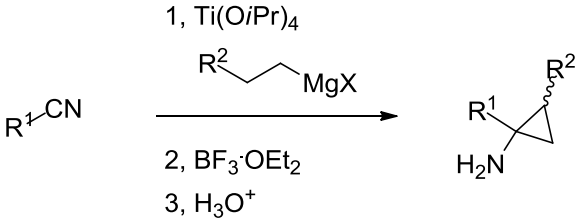
The Kulinkovich reaction describes the synthesis of cyclopropanols via reaction of esters with dialkyldialkoxytitanium reagents, generated in situ from Grignard reagents bearing hydrogen in beta-position and titanium(IV) alkoxides such as titanium isopropoxide.[41] Titanium catalysts employed for this purpose are $ClTi(O^iPr)_3$ or $Ti(O^iPr)_4$, $ClTi(O^tBu)_3$ or $Ti(O^tBu)_4$, whereas Grignard reagents are EtMgX, PrMgX or BuMgX. With amides instead of esters, the reaction product is an aminocyclopropane in the de Meijere variation (Scheme 14).[42] The intramolecular version of the reaction is also known (Scheme 15),[43] while in the Szymoniak variation the substrate is a nitrile and the reaction product a cyclopropane with a primary amine group (Scheme 16).[44]



Scheme 14. General Process of Kulinkovich Reaction

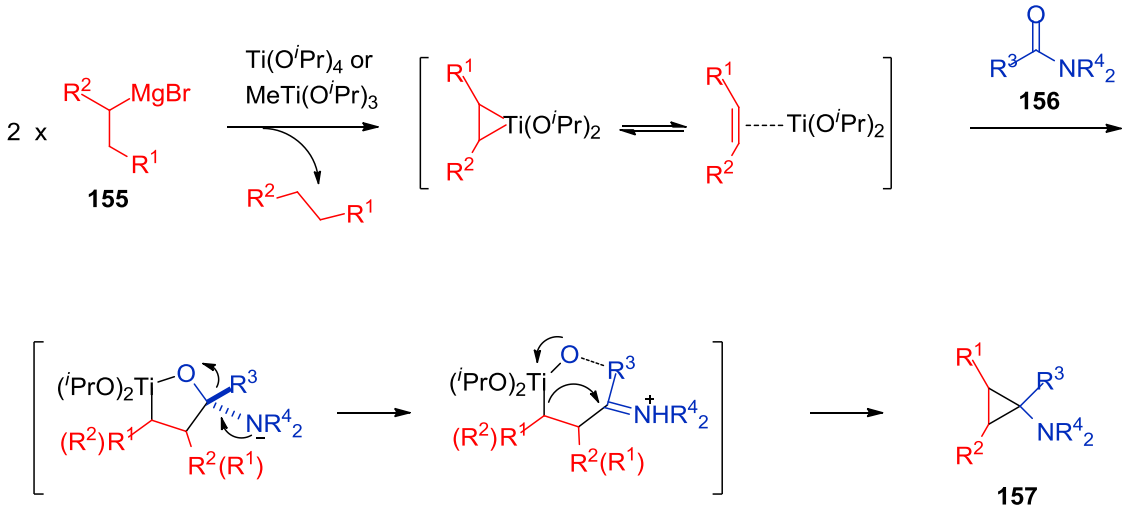


Scheme 15. The Intramolecular Kulinkovich Reaction



Scheme 16. General Process of Szymoniak Variation

de Meijere[45] conducted an excellent study based on the Kulinkovich reaction by treating *N*,*N*-dialkyl- and *N*-alkyl-*N*-phosphorylalkyl-substituted carboxamides (**156**) with unsubstituted as well as with 2-alkyl-, 2,2-dialkyl-, and 3-alkenyl-substituted ethylmagnesium bromides (**155**) in the presence of stoichiometric amounts of titanium tetraisopropoxide or methyltitanium triisopropoxide to furnish substituted cyclopropylamines (**157**) in 20–98% yield. Depending on the substituents, the reaction afforded from practically negligible (1:1) to excellent (>25:1) diastereoselectivities (Scheme 17). With substituted ethylmagnesium bromides, two chiral centers are produced in the cyclopropylamine ring; the results are depicted in Table 5.



Scheme 17. General Reaction Process of de Meijere's Method

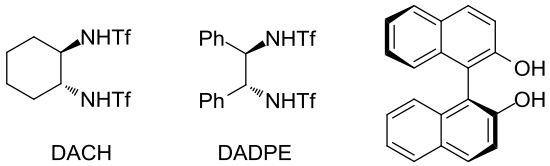
Table 5. Cyclopropylamines **157** from Carboxamides **156** and Grignard Reagents **155**

Entry	**155**	R^1	R^2	**156**	R^3	R^4		Products	%Yield (*E*/*Z* ratio)
1	**a**	Me	H	**a**	Me	Bn_2	$Ti(O^iPr)_4$	**157aa**	50[a]
2	**a**	Me	H	**b**	Et	Bn_2	$Ti(O^iPr)_4$	**157ab**	38[a]
3	**b**	^{n}Bu	H	**c**	^{n}Pr	Bn_2	$Ti(O^iPr)_4$	**157bc**	35[a]
4	**a**	Me	H	**d**	H	Bn_2	$Ti(O^iPr)_4$	**157ad**	63 (1:1)
5	**b**	^{n}Bu	H	**d**	H	Bn_2	$Ti(O^iPr)_4$	**157bd**	52 (1:2.3)
6	**b**	^{n}Bu	H	**a**	Me	Me_2	$Ti(O^iPr)_4$	**157ba**	37[a]
7	**c**	Et	H	**a**	Me	Bn_2	$Ti(O^iPr)_4$	**157ca**	47[a]
8	**d**	CH_2=CH-	H	**d**	H	Bn_2	$Ti(O^iPr)_4$	**157dd**	42 (>25:1)
9	**a**	Me	H	**e**	$(MeO)PhP(O)(CH_2)_2$	Me_2	$Ti(O^iPr)_4$	**157ae**	39 (8.5:1)
10	**c**	Et	H	**e**	$(MeO)PhP(O)(CH_2)_2$	Me_2	$Ti(O^iPr)_4$	**157ce**	42 (10:1)
11	**f**	-$(CH_2)_3$-		**d**	H	Bn_2	$Ti(O^iPr)_4$	**157fd**	63–92[b]
12	**g**	-$(CH_2)_4$-		**d**	H	Bn_2	$Ti(O^iPr)_4$	**157gd**	34[b]
13	**b**	^{n}Bu	H	**a**	Me	Me_2	$MeTi(O^iPr)_3$	**157ba**	51[a]
14	**b**	^{n}Bu	H	**c**	^{n}Pr	Bn_2	$MeTi(O^iPr)_3$	**157bc**	47 (10:1)
15	**a**	Me	H	**f**	$BnO(CH_2)_2$	Bn_2	$MeTi(O^iPr)_3$	**157af**	33 (1:3)
16	**d**	CH_2=CH-	H	**g**	H	Me_2	$MeTi(O^iPr)_3$	**157dg**	52 (10:1)
17	**a**	Me	H	**d**	H	Bn_2	$MeTi(O^iPr)_3$	**157ad**	89 (1.2:1)
18	**h**	^{n}Pr	H	**d**	H	Bn_2	$MeTi(O^iPr)_3$	**157hd**	85 (2.1:1)
19	**b**	^{n}Bu	H	**d**	H	Bn_2	$MeTi(O^iPr)_3$	**157bd**	87 (2.1:1)
20	**i**	$CH_2{}^c$Pr	H	**d**	H	Bn_2	$MeTi(O^iPr)_3$	**157id**	85 (2.2:1)
21	**d**	CH_2=CH-	H	**d**	H	Bn_2	$MeTi(O^iPr)_3$	**157dd**	98 (7:1)
22	**j**	Ph	H	**d**	H	Bn_2	$MeTi(O^iPr)_3$	**157jd**	98 (2.3:1)
23	**j**	Ph	H	**h**	H	-$(CH_2)_5$-	$MeTi(O^iPr)_3$	**157jh**	92 (1.5:1)
24	**d**	CH_2=CH-	H	**i**	H	PhMe	$MeTi(O^iPr)_3$	**157di**	44 (7:1)
25	**a**	Me	H	**k**	$Ph_2P(O)(CH_2)_2$	Me_2	$MeTi(O^iPr)_3$	**157ak**	80 (1:3.5)
26	**d**	CH_2=CH-	H	**k**	$Ph_2P(O)(CH_2)_2$	Me_2	$MeTi(O^iPr)_3$	**157dk**	83 (1:3)
27	**j**	Ph	H	**k**	$Ph_2P(O)(CH_2)_2$	Me_2	$MeTi(O^iPr)_3$	**157jk**	67 (1:1.6)
28	**a**	Me	H	**l**	$(MeO)_2P(O)(CH_2)_2$	Me_2	$MeTi(O^iPr)_3$	**157al**	81 (1:6)
29	**d**	CH_2=CH-	H	**l**	$(MeO)_2P(O)(CH_2)_2$	Me_2	$MeTi(O^iPr)_3$	**157dl**	86 (1:1.6)
30	**j**	Ph	H	**l**	$(MeO)_2P(O)(CH_2)_2$	Me_2	$MeTi(O^iPr)_3$	**157jl**	82 (1:1.4)

[a] Only one diastereomer was isolated, presumably with an *E* configuration. [b] Only the exo isomer was isolated.

The *N*,*N*-dibenzylformamide **156d** with *n*-hexylmagnesium bromide **155b** (Table 5, entry 5) was chosen for further experiments to prepare 2-butyl-*N*,*N*-dibenzylcyclopropylamine **157bd** (Table 6). It was found that chiral titanium ligands generated from one equivalent of $Ti(O^iPr)_4$ and one equivalent of diamine/diol such as DACH (**158**) and DADPE (**159**), or BINOL (**160**) did only furnish racemic products (Table 6, entries 1–3) with concomitant loss of yield (52–65% vs 87% for the variant with a chiral $MeTi(O^iPr)_3$ (Table 5, entry 19). In contrast, application of tetraphenyldioxolanedimethanol (TADDOL) **161** led to **157bd** in 59% yield with moderate enantiomeric excesses of 41% for the *Z* and 35% for the *E* isomer (Table 6, entry 4). Further improvement of the enantiomeric excesses to 66% for the *Z* and 42% for the *E* isomer could be achieved by generating the chiral titanium from two instead of one equivalent of **161** (Table 6, entry 5).

Table 6. Enantioselective Reductive Cyclopropanation of Carboxamide **156d** with **155b** (see Table 5)



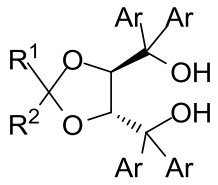
DACH **158** DADPE **159** BINOL **160** TADDOL **161**

Entry	"Ti"	Ligand	Yield% **157bd**	*Z*/*E*	ee% *Z* isomer	ee% *E* isomer
1	$Ti(O^iPr)_2L$	**158**	52	1:3.2	2	1
2	$Ti(O^iPr)_2L$	**159**	50	1:2.3	1	2
3	$Ti(O^iPr)_2L$	**160**	65	1:1.7	2	5
4	$Ti(O^iPr)_2L$	**161**	59	1:2.0	41	35
5	TiL_2	**161**	57	1:5.0	66	42

These results induced an attempt to optimize the enantioselectivity by systematic modification of the TADDOL ligand (Table 7). Switching from the two methyl substituents R^1 and R^2 on the dioxolane ring to the more bulky groups improved the enantiomeric excess to 70–84% for the *Z* and 55–77% for the *E* isomer. When the aryl substituents on the diol moiety were changed from phenyl to 3,5-dimethylphenyl or 3,5-trifluoromethylphenyl substituents, yields as well as enantioselectivities were lowered.

Table 7. Enantioselective Reductive Cyclopropanation of **156d** with **155b** in the Presence of Chirally Modified $Ti(L^2)_2$ **162**

L² =

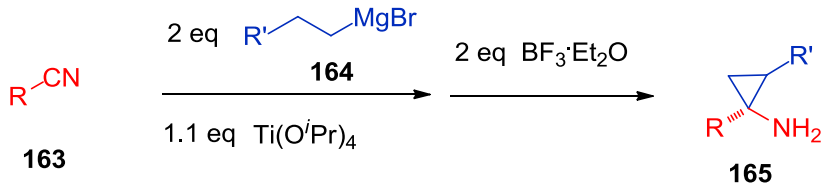


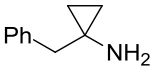
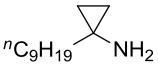
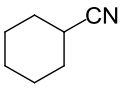
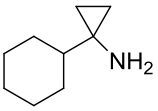
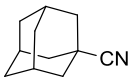
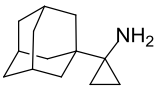
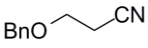
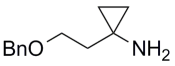
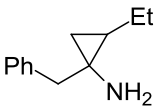
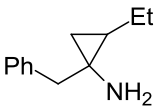
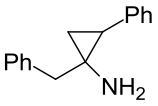
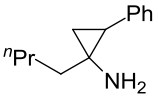
162

Entry	R^1	R^2	Ar	Yield% **157bd**	*Z/E*	ee% *Z* isomer	ee% *E* isomer
1	Me	Me	Ph	57	1:5.0	66	42
2	Et	Et	Ph	61	1:3.5	70	55
3	-(CH_2)-		Ph	64	1:2.8	65	50
4	Ph	H	Ph	55	1:3.0	73	62
5	Mes	H	Ph	55	1:2.7	71	65
6	^{t}Bu	H	Ph	47	1:3.0	84	77
7	Me	Me	1-naphthyl	38	1:3.1	80	75
8	Me	Me	3,5-Me_2Ph	40	1:2.5	60	49
9	Me	Me	3,5-$(CF_3)_2$Ph	73	1:2.5	25	11

The established Kulinkovich-Szymoniak procedure is simple and the reaction appears to be quite general. A wide range of nitriles and organomagnesium reagents can react to afford diversely substituted cyclopropylamines. Furthermore, bicyclic cyclopropylamines can be obtained via an intramolecular coupling from unsaturated nitriles.[46] Bertus[47] performed detailed studies on this and presented a new method for the preparation of primary cyclopropylamines **165** (Table 8) involving a cooperative Ti(II) and Lewis acid-mediated coupling of nitriles **163** with Grignard reagents **164**. With other substituted EtMgBr Grignard reagents, 1,2-disubstituted cyclopropylamines could be obtained as shown in entries 6–9. In all cases, a moderate diastereoselectivity of about 2:1 was observed.

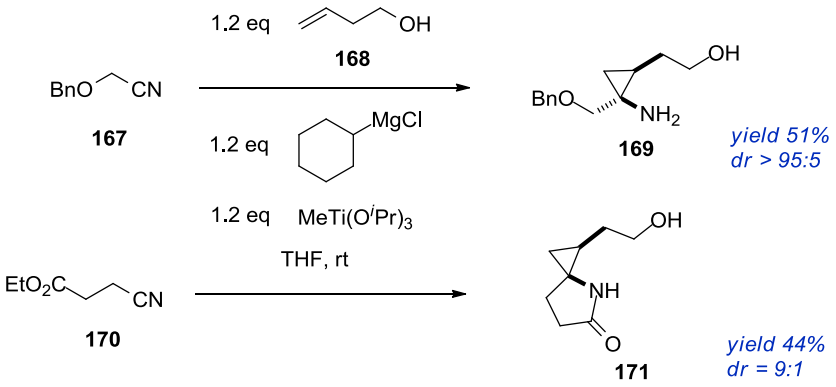
Table 8. Reaction of Nitriles with Grignard Reagents Promoted by $Ti(O^iPr)_4$ and $BF_3{\cdot}Et_2O$



Entry	**163**	**164**	**165**	% yield[a]
1	$PhCH_2CN$	EtMgBr		70
2	$^nC_9H_{19}CN$	EtMgBr		70
3		EtMgBr		52
4		EtMgBr		53
5		EtMgBr		54
6	$PhCH_2CN$	^{n}BuMgBr		57 (64:36)[b]
7	$PhCH_2CN$	^{s}BuMgBr		54 (55:45)[b]
8	$PhCH_2CN$	$Ph(CH_2)_2MgBr$		51 (68:32)[b]
9	^{n}PrCN	$Ph(CH_2)_2MgBr$		54 (68:32)[b]

[a] Yields of isolated products. [b]Mixture of diastereomers.

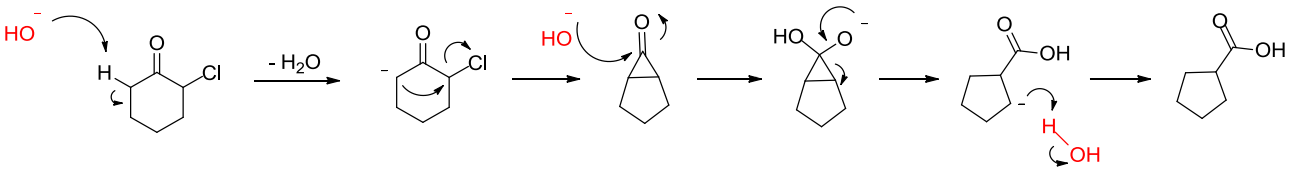
Pradhan[48] reported a simple and stereoselective method for the preparation of (*Z*)-2-substituted 1-aminocyclopropane (**169**) and (*Z*)-1-(2-hydroxyethyl)[2.4]4-azaspiroheptan-5-one (**171**). The common key step for these reaction sequences involves the stereoselective Ti-mediated coupling of nitrile **167** or **170** and homoallylic alcohol **168** (Scheme 18). The major advantages of this method are the simplicity and high diastereoselectivity of the cyclopropanation key step and low cost as well as ready availability of the starting materials for scale-up.



Scheme 18. General Synthesis of Compounds **169**, **171**

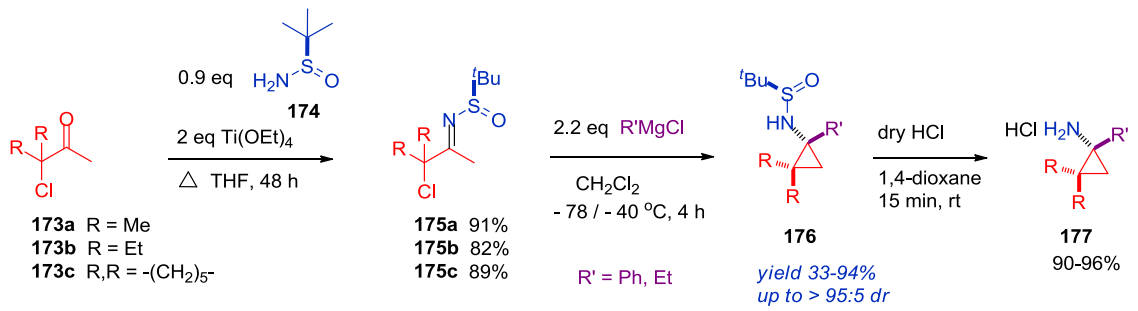
4. BUILDING THE CYCLOPROPANE RING BY FAVORSKII-TYPE REARRANGEMENT

In principle, the Favorskii rearrangement is a rearrangement of cyclopropanones and α-halo ketones which leads to carboxylic acid derivatives.[49] In the case of cyclic α-halo ketones, the rearrangement constitutes a ring contraction, as shown in Scheme 19.



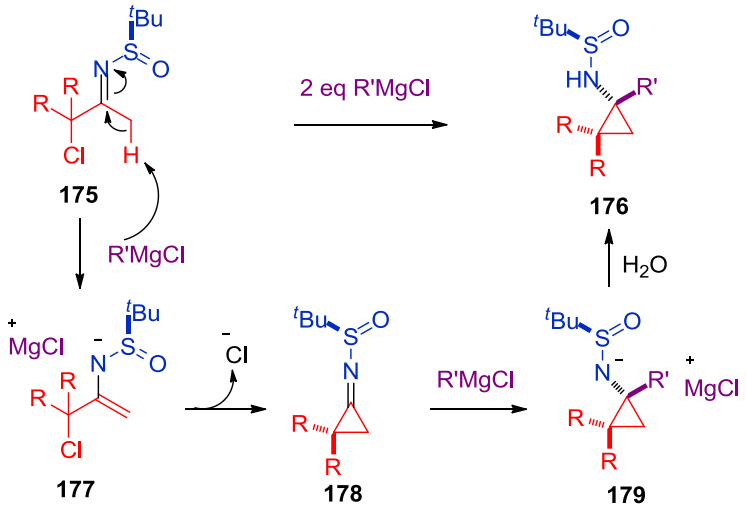
Scheme 19. The process of Favorskii rearrangement

This kind of reaction can be used for the stereoselective synthesis of cyclopropylamines, as reported by Denolf.[50] *N*-Sulfinyl *α*-chloro ketimines (R_S)-**175**, a new class of functionalized *N*-sulfinylimines, were synthesized via condensation of *α*-chloro ketones **173** with (R_S)-*tert*-butanesulfinamide **174** in the presence of 2 equiv of $Ti(OEt)_4$ (Scheme 20) and subsequently tested for their reactivity upon treatment with Grignard reagents. The best results were obtained when 2.2 equiv of PhMgCl was added to ketimine (R_S)-**175a** in dichloromethane at –78 °C. Subsequent stirring for 2 h at –78 °C and 4 h at –40 °C afforded 1-phenylcyclopropylamine (R_S,*R*)-**176a** after aqueous NH_4Cl workup in high yield (70%) and excellent diastereoselectivity (95:5 dr). Stirring for 15 min at room temperature afforded the HCl salts of the cyclopropylamines **177** in high yield (> 90%) and purity (85–95%) (Scheme 20).



Scheme 20. General Synthesis of Compound **177**

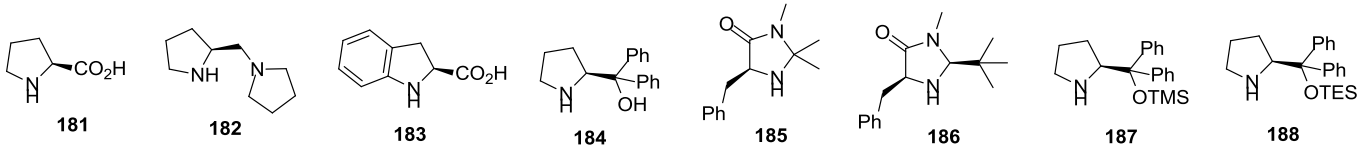
It is proposed that the cyclopropanation reaction proceeds via a Favorskii-type reaction mechanism (Scheme 21). Hence, the first equivalent of Grignard reagent acts as a base, an unprecedented reaction in this field. A proton at the *α*-position of the imino function of ketimines (R_S)-**175** is abstracted, the resulting 1-azaallylic anion **177** undergoes chloride expulsion to produce the intermediate *N*-(cyclopropylidene)-*tert*-butanesulfinamide **178**, which is attacked by the second equivalent of Grignard reagent at the reactive imino function of **178** giving rise to cyclopropylamine **176** after aqueous NH_4Cl workup. The highly strained Favorskiitype intermediate **178**, in combination with the bulky *tert*-butanesulfinyl group, results in the formation of an enantioenriched cyclopropylamine **176**.



Scheme 21. Proposed Favorskii-Type Reaction Mechanism

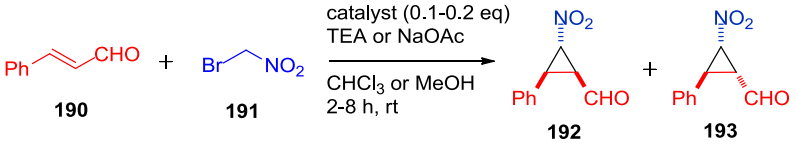
5. ADDITION OF BROMONITROALKANES TO A,B-UNSATURATED ALDEHYDES TO FORM CHIRAL NITROCYCLOPROPANES

Vesely[51r] and Zhang[52] reported their respective results on asymmetric conjugate addition of bromonitromethane to α,β-unsaturated aldehydes. Several chiral secondary amines (**181–188**) (Scheme 22) were chosen to catalyze the reaction and diphenylprolinol triethylsilyl ether (**188**) was identified as the best catalyst for the reaction (Table 9). Excellent enantioselectivities and good yields were achieved for a number of β-arylacroleins under MeOH/AcONa system (Table 10). Substituted 1-bromonitromethanes, such as 1-bromonitroethane and 1-phenyl-1-bromonitromethane, also provided excellent enantioselectivities and improved diastereoselectivities. The reaction is efficient for preparing highly substituted chiral nitrocyclopropanes, which can be used as the precursor of cyclopropylamines.



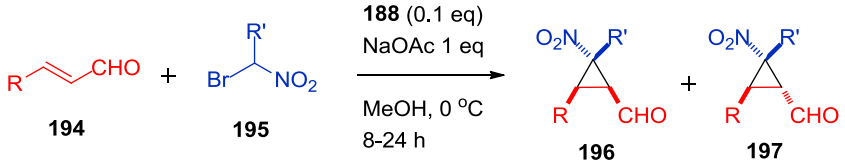
Scheme 22. Chemical Structures of **181–188**

Table 9. Catalyst Screening for the Reaction of **190** and **191**



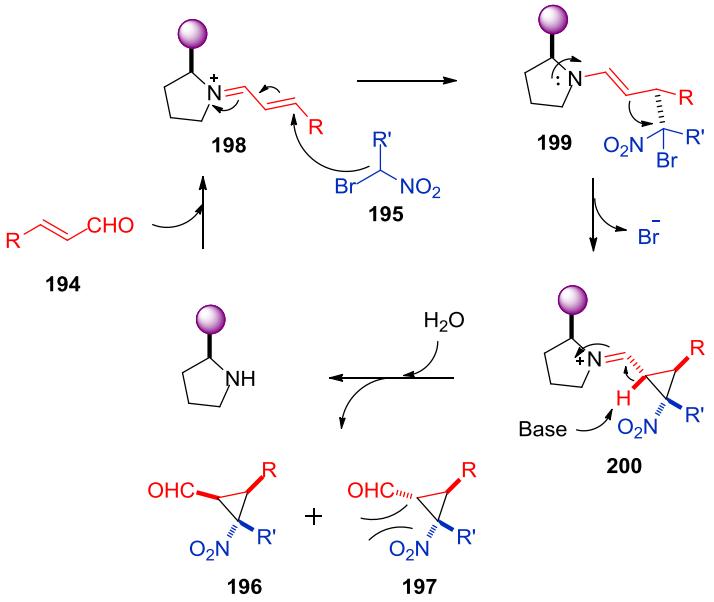
Entry	catalyst	% yield	**192**:**193**	%ee (**192**/**193**)
1	**181**	59	50:50	25/25
2	**182**	69	75:25	25/25
3	**183**	52	50:50	–91/ –86
4	**184**	48	57:43	80/70
5	**185**	7	23:77	48/32
6	**186**	6	23:77	11/14
7	**187**	76	60:40	90/94
8	**188**	79	44:56	96/96

Table 10. Reaction of α,β-Unsaturated Aldehydes **194** with Bromonitromethanes **195** Catalyzed by **188**



Entry	R	R’	% yield	**196**:**197**	%ee (**196**/**197**)
1	4-NO_2Ph	H	63	50:50	98/92
2	4-ClPh	H	63	66:34	91/95
3	4-MePh	H	67	63:37	94/94
4	4-MeOPh	H	61	68:32	89/96
5	3-ClPh	H	65	65:35	96/96
6	2-ClPh	H	68	67:33	88/96
7	2-MeOPh	H	61	71:29	95/89
8	2-furyl	H	48	67:33	89/92
9	3-pyridyl	H	46	67:33	88/86
10	Ph	Me	65	14:86	95/98
11	Ph	Et	28	4:96	n.d.
12	Ph	Ph	63	< 1:99	n.d./99
13	Ph	CO_2Et	no	n.d.	n.d.

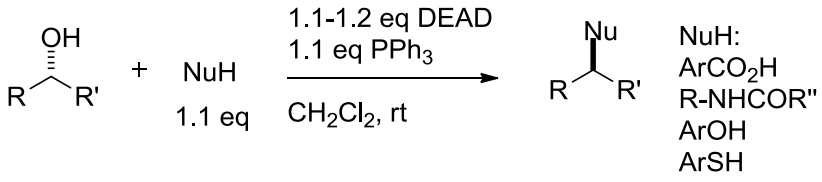
Accordingly, efficient shielding of the *Si*-face of the chiral iminium intermediate **198** by the bulky aryl groups of chiral pyrrolidine **188** leads to stereoselective *Re*-facial nucleophilic conjugate addition by the bromonitromethane**195** (Scheme 23). Next, the generated chiral enamine intermediate **199** undergoes intramolecular 3-*exo*-*tert* nucleophilic attack to form the cyclopropane ring of **200**. The intramolecular ring-closure pushes the equilibrium forward and makes this step irreversible. Hydrolysis of iminium intermediate **200** releases the catalyst and gives the corresponding 2-formylcyclopropane **196** and **197**. Due to steric repulsion between the nitro-group and the catalyst of iminium complex **200** or the nitro- and 2-formyl-groups of **197**, diastereoisomer **196** is formed.



Scheme 23. Proposed Reaction Mechanism

6. BUILDING THE CHIRAL NITROCYCLOPROPANE RING BY MITSUNOBU REACTION

The Mitsunobu Reaction allows the conversion of primary and secondary alcohols to esters, phenyl ethers, thioethers and various other compounds.[53] Triphenylphosphine and an azodicarboxylate such as diethyl azodicarboxylate (DEAD) or diisopropyl azodicarboxylate (DIAD) are used. The alcohol undergoes an inversion of stereochemistry as depicted in Scheme 24.

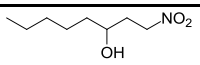
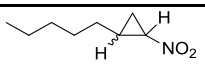
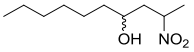
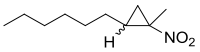
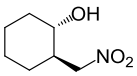
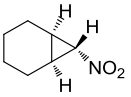
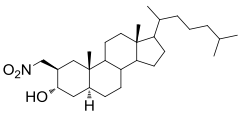
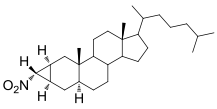
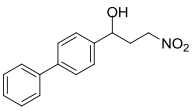
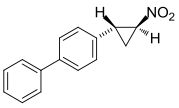
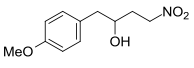
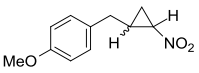
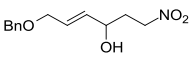
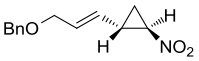
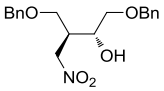
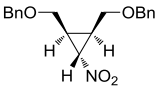


Scheme 24. General Process of Mitsunobu Reaction

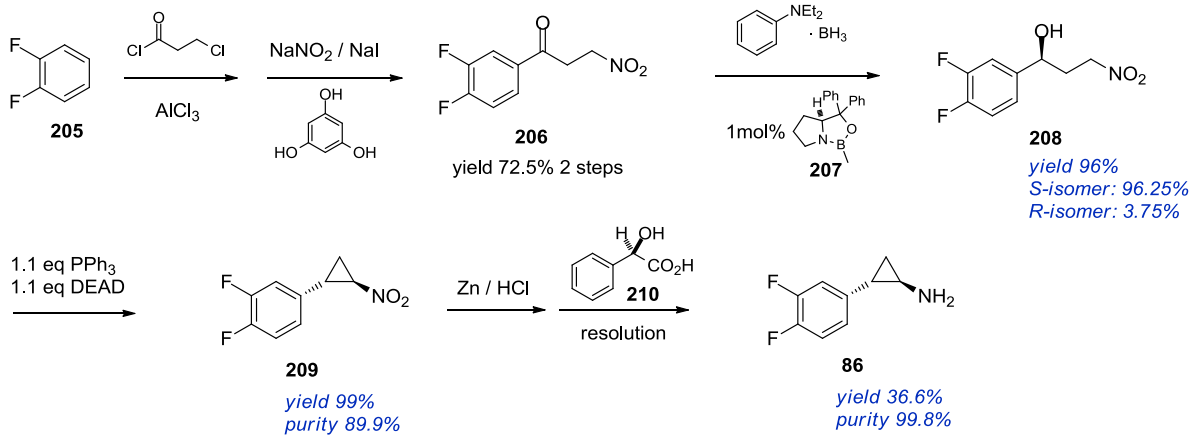
Yu[54] reported a method to afford α-nitrocyclopropanes by treatment of a wide variety of γ-nitroalkanols with a preformed complex of DEAD and Ph_3P in good to excellent yields (Table 11). The reaction

proceeds rapidly at ambient temperature under essentially neutral conditions in benzene or THF. This represents a highly efficient intramolecular variant of the Mitsunobu displacement procedure in which a nitronate anion acts as a carbon nucleophile resulting in a new carbon-carbon bond.

Table 11. Synthesis of Nitrocyclopropanes

Entry	nitro alcohol	product	*trans*:*cis*	% yield
1			10:1	82
2			10:1	87
3			*trans* only	92
4			*trans* only	76
5			*trans* only	75
6			7:1	92
7			*trans* only	64
8			*trans* only	94

Khile *et al.*[55] prepared the *trans*-(1*R*,2*S*)-cyclopropylamine **86** (intermediate of ticagrelor) on a hundred-gram scale based on the intramolecular Mitsunobu reaction (Scheme 25). 1-(3,4-Difluorophenyl)-3-nitropropan-1-one (**206**) was obtained from difluorobenzene **205** in acceptable yield, which was then converted to the (*S*)-benzyl alcohol **208** by treating with borane-*N*,*N*-diethylaniline and 1 mol% (*S*)-(–)-2-methyl-CBS-oxazaborolidine (**207**) through an asymmetric process with high selectivity. Then it underwent the Mitsunobu reaction to give the *trans*-(1*R*,2*S*)-nitrocyclopropane **209** with good yield and selectivity. The cyclopropylamine product **86** was afforded through reduction and subsequent resolution with (*R*)-(–)-mandelic acid in high purity and medium overall yield.

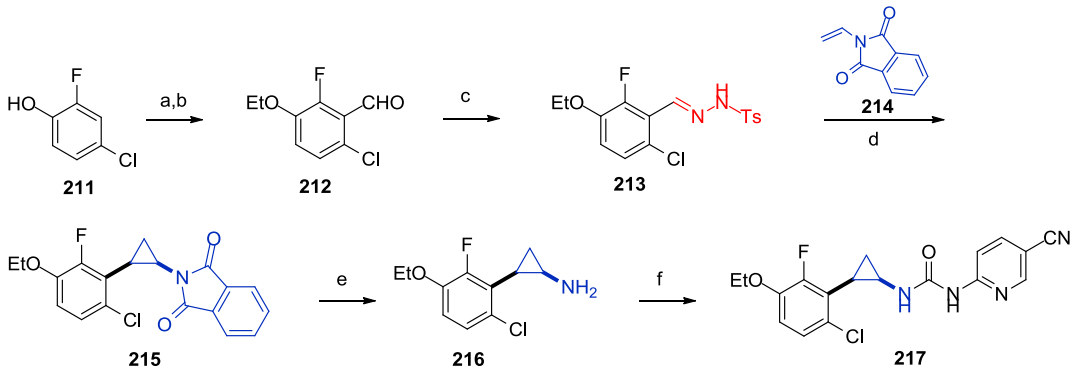


Scheme 25. Synthesis of Compound **86** by the Mitsunobu Reaction

7. OTHER ASYMMETRIC SYNTHESIS METHOD OF CYCLOPROPYLAMINES

7.1 Using Tosylhydrazones to Build the Cyclopropylamine Ring

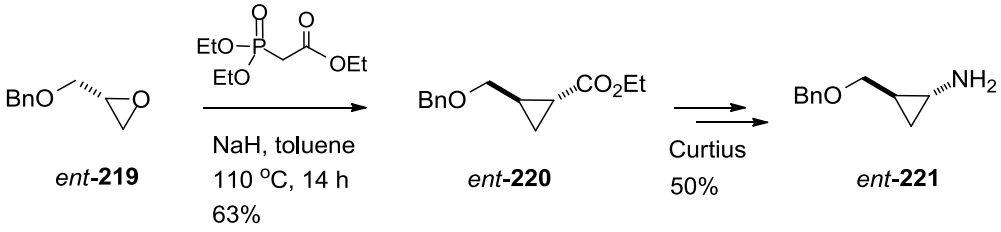
Aggarwal[56] reported a user-friendly, one-pot process for catalytic cyclopropanation of alkenes from tosylhydrazones. The cyclopropanation of *N*-vinylphthalimide (**214**) provides a new route to 2-arylcyclopropylamines. This process provided a route to the less easily accessible *cis* isomer with high diastereoselectivity, which was exemplified in the efficient synthesis of the HIV-1 reverse transcriptase inhibitor **217** (Scheme 26). Aldehyde **212** was converted into the tosylhydrazone **213**. Deprotonation with LiHMDS and treatment with **214**, PTC, and rhodium acetate gave the cyclopropane **215** in 76% yield and as an 85:15 mixture in favor of the required *cis* isomer. It was interesting to note that even though a hindered 2,3,6-trisubstituted arylhydrazone was employed, high yield and high cis selectivity was still achieved. Following hydrazinolysis, the amine was coupled with 2-amino-5-cyanopyridine in the presence of triphosgene to give the urea **217**.



Scheme 26. Reagents: (a) CH_2I_2, acetone, K_2CO_3, 55 °C, 100%; (b) ^{n}BuLi, THF, –65 °C to rt, 87%; (c) $TsNHNH_2$, MeOH, rt, 72%; (d) LiHMDS, THF, –78 °C to rt, then *N*-vinylphthalimide (**214**), $Rh_2(OAc)_4$, 10% PTC, 1,4-dioxane, rt, *trans*:*cis* 15:85, 76%; (e) $N_2H_4 \cdot H_2O$, EtOH, 40 °C, then 1 M HCl, EtOH, 78%; (f) 2-amino-5-cyanopyridine, triphosgene, THF, –78 °C to rt, 56%.

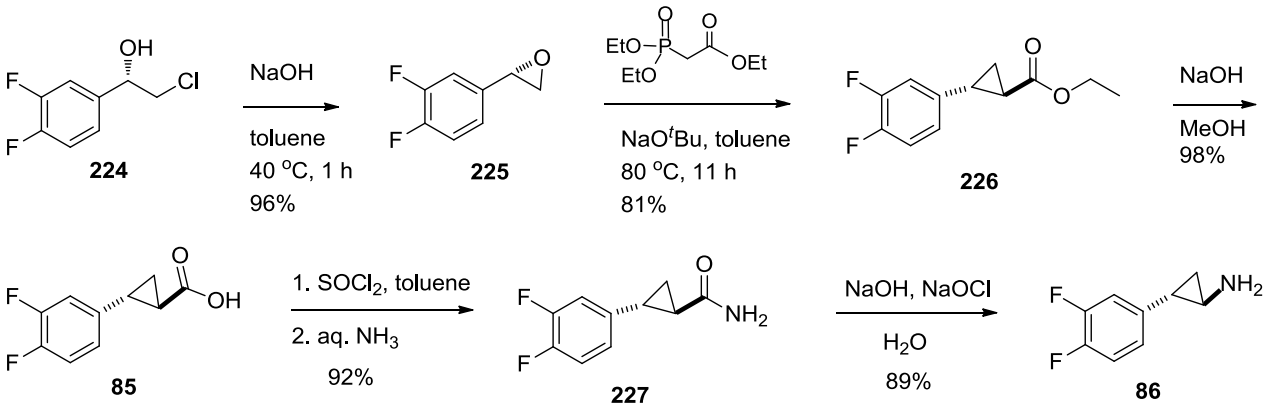
7.2 Wadsworth-Emmons Cyclopropanation

Armstrong[57] reported a concise synthesis of 3-(*trans*-2-aminocyclopropyl) alanine, a component of belactosin A, using asymmetric alkylation of a glycine enolate in the presence of chiral phase-transfer catalysts to control the configuration at C2. Reaction of protected glycidol with triethyl phosphonoacetate (Wadsworth-Emmons cyclopropanation) is used for enantiospecific preparation of an intermediate cyclopropanecarboxylate that is converted to a cyclopropylamine via Curtius rearrangement (Scheme 27).



Scheme 27. The Process of Wadsworth-Emmons Cyclopropanation

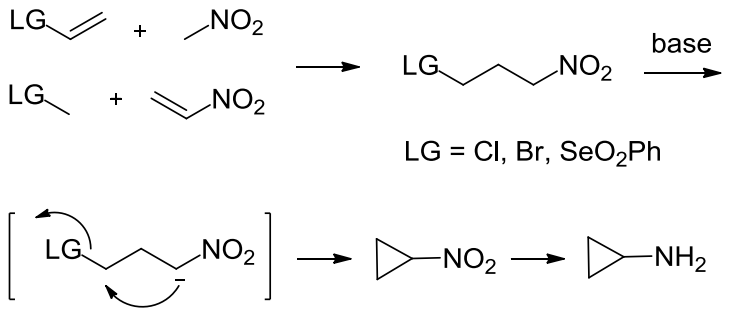
Based on the above cyclopropanation procedure, Mitsuda[58] prepared the *trans*-(1*R*,2*S*)-cyclopropylamine **86** (intermediate of ticagrelor) on a grams scale (Scheme 28). (2*S*)-2-(3,4-Difluorophenyl)oxirane (**225**) was synthesized from (2*S*)-2-chlorobenzyl alcohol **224** in basic condition. Then it was treated in accordance with the Wadsworth-Emmons cyclopropanation method to give the (1*R*,2*R*)-cyclopropanecarboxylate **226** in good yield. After the ester hydrolysis and amidation, the (1*R*,2*R*)-cyclopropanecarboxamide **227** was obtained, which was reacted with NaOH / NaOCl to give the *trans*-(1*R*,2*S*) product **86** through a Hofmann rearrangement process.



Scheme 28. Synthesis of Compound **86** by the Wadsworth-Emmons Cyclopropanation

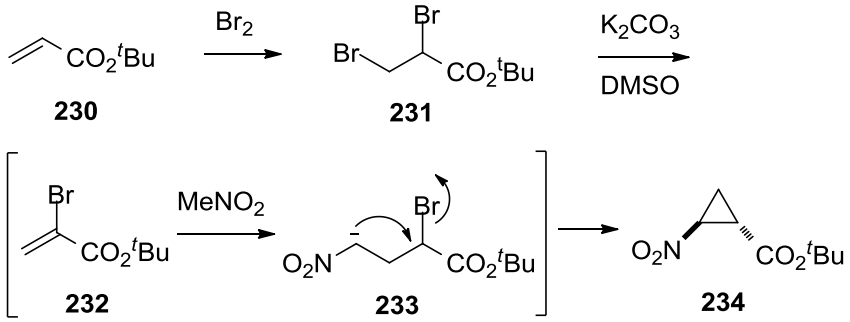
7.3 Intramolecular Cyclopropanation of 1-Nitropropane Derivatives

Averina[59] summarized the present knowledge on the methods of synthesis and transformations of nitrocyclopropanes systematically, mainly including the methods of stereoselective cyclopropanation, which can be used as the precursors to synthesize chiral cyclopropylamines. The synthetic routes involve an intramolecular 1,3-elimination to afford the desired nitrocyclopropanes (Scheme 29).



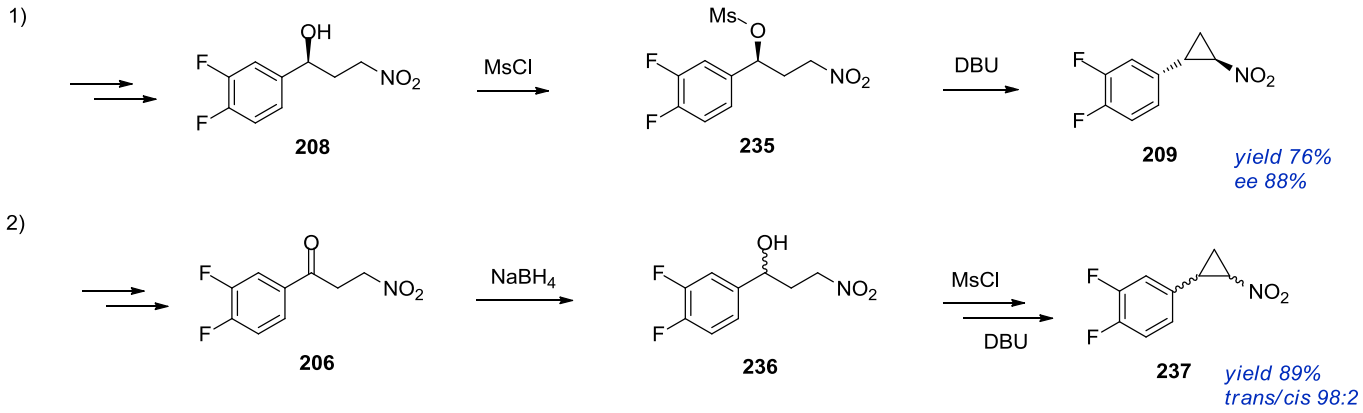
Scheme 29. General Intramolecular Cyclopropanation Process of 1-Nitropropane Derivatives

The dibromopropanoate **231** eliminated an HBr molecule by treating with K_2CO_3 to give the **232**. Subsequent addition by $MeNO_2$ followed by cyclopropanation afforded the desired product **234** (Scheme 30).[60]



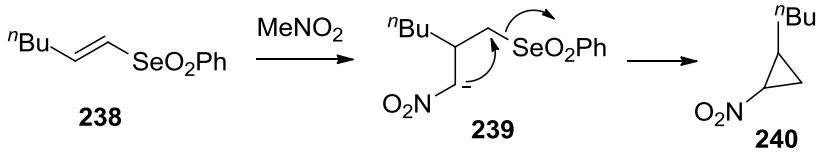
Scheme 30. Intramolecular Cyclopropanation Process of Nitropropane **233**

During the process research of *trans*-(1*R*,2*S*)-cyclopropylamine **86**, Rasparini *et al.*[61] developed an effective method based on introducing a γ-leaving group to the nitropropane, as shown in Scheme 31. Mesylate, tosylate, triflate, or just -Br can be the γ-leaving group, while the mesylate example was described in detail. There were two route to give the (1*S*,2*R*)-2-nitrocyclopropylbenzene **209**. One is treating the (*S*)-benzyl alcohol **208** with mesyl chloride in pyridine to give **235**, which was cyclized in DBU to obtain **209** with good yield and *ee* value. The other is using enantiomer benzyl alcohol **236** as the reactant to afford the enantiomer product **237**, which has a high stereoselectivity.



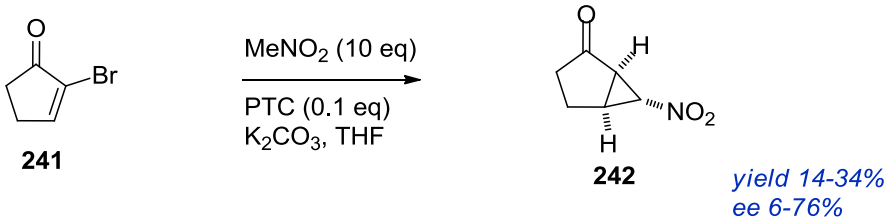
Scheme 31. Intramolecular Cyclopropanation of γ-MsO-nitropropane

Besides sulphonate and halogen, other leaving group such as -SeO_2Ph can also be employed for cyclopropanation. Thus, (hex-1-en-1-ylselenonyl)benzene **238** was treated with $MeNO_2$ to afford the product **240** (Scheme 32).[62]



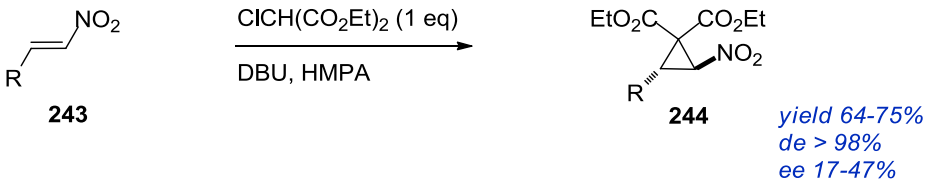
Scheme 32. Intramolecular Cyclopropanation Process of Nitropropane **239**

When a rigid substrate **241** was adopted, the reaction exhibited some stereoselectivety to give the product **242** with a medium to good *ee* value (Scheme 33).[63]



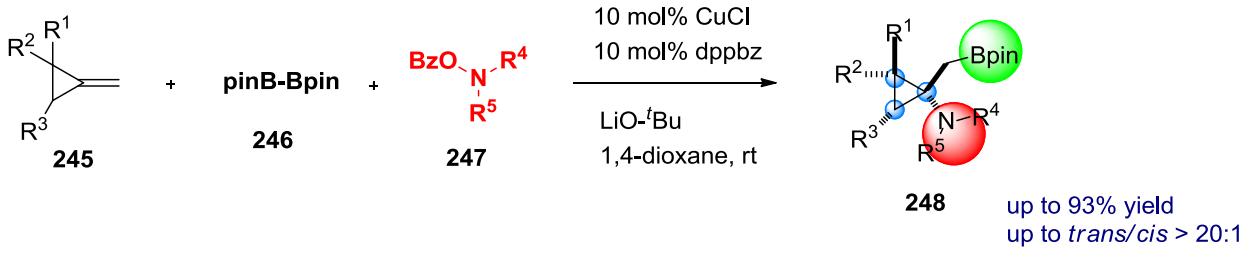
Scheme 33. The Synthesis of Compound **242**

Reaction of a halohydrocarbon with a nitro olefin is another method that leads to cyclopropanation. The nitroethene **243** reacted with diethyl 2-chloromalonate under basic condition to give the nitrocyclopropane **244** with good yield and high *de* and medium *ee* value (Scheme 34).[64]



Scheme 34. General Synthesis of Compound **244**

Recently, Sakae reported a Cu-catalyzed aminoboration of 1-methylenecyclopropanes (**245**) with bis(pinacolato)diboron (**246**) and *O*-benzoyl-*N*,*N*-dialkylhydroxylamines (**247**), which provides a rapid and concise access to (borylmethyl)cyclopropylamines (**248**) in a highly regio- and diastereoselective manner (Scheme 35).[65]



Scheme 35. General Synthesis of Compound **248**

8. CONCLUSION

Since optically active cyclopropylamines have been recognized as useful building blocks for biologically active compounds, several methodologies are encountered in the literature for their synthesis. The preparation of cyclopropylamines or the introduction of a cyclopropyl residue to nitrogen containing functional group has only begun to commence in true sense since the last two decades. The most common approach involves reaction of α,β-unsaturated carboxylic esters with carbene sources such as diazomethane and 1-methyl-1-nitrosourea or carbenoid species which include diazo esters, sulfur ylide, iodonium ylide or Simmons-Smith reagents. Generally the stereoselectivity of the reaction is achieved through the introduction of a chiral auxiliary (such as camphorsultam, L-menthol) into an α,β-unsaturated carboxylic ester to afford another chiral α,β-unsaturated carboxylic ester or amide. Subsequent alkaline hydrolysis generates a chiral cyclopropanecarboxylic acid which then undergoes a Curtius or Hofmann rearrangement to give the desired cyclopropylamine. Although there are many successful examples of carbene or carbenoid based synthesis of cyclopropylamines, lack of operational safety, high cost and difficulties associated to recycle the chiral auxiliary often impose a restriction to the general applicability of the process. In recent years, synthesis of chiral cyclopropylamines based on asymmetric catalysis, ylide generation and Simmons-Smith reaction have gained wide attention due to their simple operation, high stereoselectivity and goodatom economy. Whereas Simmons-Smith reactions afford satisfactory results only with prop-2-en-1-ol derivatives, the lower yield associated with sulfur ylide based reactions needs to be addressed in future.

Kulinkovich reaction has been developed in-depth by de Meijere and other scholars for the asymmetric synthesis of substituted cyclopropylamines. TADDOL (**161**) and its derivatives were proved to be effective catalysts, which gave medium to good stereoselectivity in many cases. (R_S)-*tert*-Butanesulfinamide could be introduced to *α*-chloro ketones as the chiral auxiliary as well as the active ketimine intermediate. The chiral cyclopropylamines are obtained through a Favorskii-type rearrangement and subsequent acid hydrolysis. In addition, since the Kulinkovich reaction and Favorskii-type rearrangement introduce the amino functionality directly onto a cyclopropane ring, both of them offer better atom economy in the absence of traditional Curtius rearrangement process.

Addition of bromonitroalkanes to α,β-unsaturated aldehydes provides yet another route to nitrocyclopropane, a potent precursor to cyclopropylamine. Several chiral secondary amines were chosen to catalyze the reaction, some of which displayed excellent stereoselectivity. Besides nitro group, a formyl group can also be introduced onto the cyclopropane ring but the method has not been found useful for the synthesis of cyclopropylamines.

The intramolecular Mitsunobu reaction can be used for the synthesis of chiral cyclopropylamines for its high chemical selectivity. The main drawback of this method is the requirement of prior preparation of the optically pure substrate through asymmetric synthesis. The same problem is also encountered in Wadsworth-Emmons cyclopropanation, which employs enantiopure epoxypropane derivatives. Intramolecular cyclopropanation of 1-nitropropane derivatives also affords nitrocyclopropanes with moderate chemical selectivity. Nevertheless, further studies are still required to optimize reaction parameters for preparing asymmetric cyclopropylamines through easily accessible and inexpensive techniques.

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REFERENCES AND NOTES

1. a) H. Lebel, J. F. Marcoux, C. Molinaro, and A. B. Charette, *Chem. Rev.*, 2003, **103**, 977; b) L. A. Wessjohann, W. Brandt, and T. Thiemann, *Chem. Rev.*, 2003, **103**, 1625.
2. a) F. Gnad and O. Reiser, *Chem. Rev.*, 2003, **103**, 1603; b) W. R. Dolbier and M. A. Battiste, *Chem. Rev.*, 2003, **103**, 1071.
3. P. Remuzon, D. Bouzard, P. Di Cesare, M. Essiz, J. Jacquet, J. Kiechel, B. Ledoussal, R. Kessler, and J. Fung-Tomc, *J. Med. Chem.*, 1991, **34**, 29.
4. a) A. Reichelt and S. F. Martin, *Acc. Chem. Res.*, 2006, **39**, 433; b) J. Pietruszka, *Chem. Rev.*, 2003, **103**, 1051.
5. a) S. F. Yang and N. E. Hoffman, *Ann. Rev. Plant Physiol.*, 1984, **35**, 155; b) H. Kende, *Ann. Rev. Plant Physiol.*, 1993, **44**, 283.
6. a) K. D. Hargrave, J. R. Proudfoot, K. G. Grozinger, E. Cullen, S. R. Kapadia, U. R. Patel, V. U. Fuchs, S. C. Mauldin, J. Vitous, and M. L. Behnke, *J. Med. Chem.*, 1991, **34**, 2231; b) T. A. Kelly and U. R. Patel, *J. Org. Chem.*, 1995, **60**, 1875.
7. M. A. Gaglia, Jr. and R. Waksman, *Circulation*, 2011, **123**, 451.
8. A. Pigott, S. Frescas, J. D. McCorvy, X. P. Huang, B. L. Roth, and D. E. Nichols, *Beilstein J. Org. Chem.*, 2012, **8**, 1705.
9. a) D. M. Schmidt and D. G. McCafferty, *Biochemistry*, 2007, **46**, 4408; b) R. Ueda, T. Suzuki, K. Mino, H. Tsumoto, H. Nakagawa, M. Hasegawa, R. Sasaki, T. Mizukami, and N. Miyata, *J. Am. Chem. Soc.*, 2009, **131**, 17536; c) C. Binda, S. Valente, M. Romanenghi, S. Pilotto, R. Cirilli, A.

Karytinos, G. Ciossani, O. A. Botrugno, F. Forneris, and M. Tardugno, *J. Am. Chem. Soc.*, 2010, **132**, 6827; d) J. C. Culhane, D. Wang, P. M. Yen, and P. A. Cole, *J. Am. Chem. Soc.*, 2010, **132**, 3164.

10. a) M. C. T. Fyfe, A. M. Ortega, J. C. P. Laria, M. M. Pedemonte, M. L. A. Estiarte-Martinez, and N. M. Valls, PCT Int. Appl. WO 2012013727, Feb 2, 2012; b) L. J. Castro-Palomino, M. C. T. Fyfe, P. M. Martinell, M. A. Ortega, and V. N. Valls, PCT Int. Appl. WO 2012045883, Apr 12, 2012.
11. a) V. S. Georgiev, R. A. Mack, D. J. Walter, L. A. Radov, and J. E. Baer, *Helv. Chim. Acta*, 1987, **70**, 1526; b) D. Caille, O. E. Bergis, C. Fankhauser, A. Gardes, R. Adam, T. Charieras, A. Grosset, V. Rovei, and F. X. Jarreau, *J. Pharmacol. Exp. Ther.*, 1996, **277**, 265; c) Y. He, S. Liu, A. Menon, S. Stanford, E. Oppong, A. M. Gunawan, L. Wu, D. J. Wu, A. M. Barrios, N. Bottini, A. C. Cato, and Z. Y. Zhang, *J. Med. Chem.*, 2013, **56**, 4990.
12. A. Soldevilla and D. Sampedro, *Org. Prep. Proced. Int.*, 2007, **39**, 561.
13. a) C. Tanguy, P. Bertus, J. Szymoniak, O. V. Larionov, and A. de Meijere, *Synlett*, 2006, 3164; b) J. Pietruszka and G. Solduga, *Synlett*, 2008, 1349.
14. a) G. Maas, M. Alt, D. Mayer, U. Bergstrasser, S. Sklenak, P. Xavier, and Y. Apeloig, *Organometallics*, 2001, **20**, 4607; b) G. Maas, *Chem. Soc. Rev.*, 2004, **33**, 183; c) V. K. Aggarwal, J. de Vicente, and R. V. Bonnert, *J. Org. Chem.*, 2003, **68**, 5381.
15. J. Vallgarda, U. Appelberg, L. E. Arvidsson, S. Hjorth, B. E. Svensson, and U. Hacksell, *J. Med. Chem.*, 1996, **39**, 1485.
16. a) T. Shioiri, K. Ninomiya, and S. Yamada, *J. Am. Chem. Soc.*, 1972, **94**, 6203; b) L. A. Carpino and A. C. Tsao, *J. Chem. Soc., Chem. Commun.*, 1979, 514; c) T. L. Capson, M. D. Thompson, V. M. Dixit, R. G. Gaughan, and C. D. Poulte, *J. Org. Chem.*, 1988, **53**, 5903.
17. S. Vangveravong, A. Kanthasamy, V. L. Lucaites, D. L. Nelson, and D. E. Nichols, *J. Med. Chem.*, 1998, **41**, 4995.
18. P. W. Erhardt, R. J. Gorczynski, and W. G. Anderson, *J. Med. Chem.*, 1979, **22**, 907.
19. L. E. Arvidsson, A. M. Johansson, U. Hacksell, J. L. G. Nilsson, K. Svensson, S. Hjorth, T. Magnusson, A. Carlsson, P. Lindberg, B. Andersson, D. Sanchez, H. Wikstrom, and S. Sundell, *J. Med. Chem.*, 1988, **31**, 92.
20. J. Vallgarda and U. Hacksell, *Tetrahedron Lett.*, 1991, **32**, 5625.
21. J. Vallgarda, U. Appelberg, I. Csoregh, and U. Hacksell, *J. Chem. Soc., Perkin Trans. 1*, 1994, 461.
22. S. Vangveravong and D. E. Nichols, *J. Org. Chem.*, 1995, **60**, 3409.
23. M. P. Doyle, M. A. McKervey, and T. Ye, 'Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides', Wiley-Interscience: New York, 1998.
24. M. Regitz and G. Maas, 'Diazo Compounds: Properties and Synthesis', Academic Press: London, 1996.

25. M. P. Doyle, K. G. High, S. M. Oon, and A. K. Osborn, *Tetrahedron Lett.*, 1989, **30**, 3049.
26. Y. A. Volkova, O. A. Ivanova, E. M. Budynina, E. V. Revunov, and E. B. Averina, *Tetrahedron Lett.*, 2009, **50**, 2793.
27. a) G. Q. Feng, D. X. Wang, Q. Y. Zheng, and M. X. Wang, *Tetrahedron: Asymmetry*, 2006, **17**, 2775; b) S. Mangelinckx and N. De Kimpe, *Tetrahedron Lett.*, 2003, **44**, 1771; c) A. Salgado, T. Huybrechts, A. Eeckhaut, J. Van der Eycken, Z. Szakonyi, F. Fulop, A. Tkachev, and N. De Kimpe, *Tetrahedron*, 2001, **57**, 2781.
28. S. Chanthamath, D. T. Nguyen, K. Shibatomi, and S. Iwasa, *Org. Lett.*, 2013, **15**, 772.
29. D. M. Gooden, D. M. Z. Schmidt, J. A. Pollock, A. M. Kabadi, and D. G. McCafferty, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 3047.
30. V. S. Yarmolchuk, A. V. Bezdudny, N. A. Tolmacheva, O. Lukin, A. N. Boyko, A. Chekotylo, A. A. Tolmachev, and P. K. Mykhailiuk, *Synthesis*, 2012, 1152.
31. M. A. Khan, S. L. Yates, C. E. Tedford, K. Kirschbaum, and J. G. Phillips, *Bioorg. Med. Chem. Lett.*, 1997, **7**, 3017.
32. A. Clark, E. Jones, U. Larsson, and A. Minidis, US7122695, Oct 17, 2006.
33. B. Moreau and A. B. Charette, *J. Am. Chem. Soc.*, 2005, **127**, 18014.
34. a) H. E. Simmons and R. D. Smith, *J. Am. Chem. Soc.*, 1958, **80**, 5323; b) H. E. Simmons and R. D. Smith, *J. Am. Chem. Soc.*, 1959, **81**, 4256; c) J. Denis, C. Girard, and J. Conia, *Synthesis*, 1972, 549; d) A. B. Charette and A. Beauchemin, *Org. React.*, 2001, **58**, 1.
35. Y. Zhao, T. Yang, M. Lee, D. Lee, M. G. Newton, and C. K. Chu, *J. Org. Chem.*, 1995, **60**, 5236.
36. H. Takahashi, M. Yoshioka, M. Ohno, and S. Kobayashi, *Tetrahedron Lett.*, 1992, **33**, 2575.
37. H. Shitama and T. Katsuki, *Angew. Chem., Int. Ed. Engl.*, 2008, **47**, 2450.
38. J. Long, Y. Yuan, and Y. Shi, *J. Am. Chem. Soc.*, 2003, **125**, 13632.
39. T. Wang, Y. Liang, and Z. X. Yu, *J. Am. Chem. Soc.*, 2011, **133**, 9343.
40. a) A. B. Charette and J. Lemay, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 1090; b) A. B. Charette, H. Juteau, H. Lebel, and C. Molinaro, *J. Am. Chem. Soc.*, 1998, **120**, 11943.
41. a) O. G. Kulinkovich and A. de Meijere, *Chem. Rev.*, 2000, **100**, 2789; b) F. Sato, H. Urabe, and S. Okamoto, *Chem. Rev.*, 2000, **100**, 2835; c) Y. D. Wu and Z. X. Yu, *J. Am. Chem. Soc.*, 2001, **123**, 5777.
42. a) V. Chaplinski and A. A de Meijere, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 413; b) A. de Meijere, H. Winsel, and B. Stecker, *Org. Synth.*, 2005, **81**, 14.
43. a) H. B. Lee, M. J. Sung, S. C. Blackstock, and J. K. Cha, *J. Am. Chem. Soc.*, 2001, **123**, 11322; b) M. Gensini, S. I. Kozhushkov, D. S. Yufit, J. A. Howard, M. Es-Sayed, and A. de Meijere, *Eur. J. Org. Chem.*, 2002, 2499; c) G. D. Tebben, K. Rauch, C. Stratmann, C. M. Williams, and A. de Meijere,

Org. Lett., 2003, **5**, 483; d) L. Larquetoux, J. A. Kowalska, and Y. Six, *Eur. J. Org. Chem.*, 2004, 3517; e) L. Larquetoux, N. Ouhamou, A. Chiaroni, and Y. Six, *Eur. J. Org. Chem.*, 2005, 4654.

44. a) P. Bertus and J. Szymoniak, *Chem. Commun.*, 2001, 1792; b) D. Gauvreau, S. J. Dolman, G. Hughes, P. D. O'Shea, and I. W. Davies, *J. Org. Chem.*, 2010, **75**, 4078.
45. A. de Meijere, V. Chaplinski, H. Winsel, M. Kordes, B. Stecker, V. Gazizova, A. I. Savchenko, R. Boese, and F. Schill, *Chem. Eur. J.*, 2010, **16**, 13862.
46. P. Bertus and J. Szymoniak, *Synlett*, 2007, 1346.
47. a) P. Bertus, C. Menant, C. Tanguy, and J. Szymoniak, *Org. Lett.*, 2008, **10**, 777; b) A. Joosten, J. L. Vasse, P. Bertus, and J. Szymoniak, *Synlett*, 2008, 2455.
48. T. K. Pradhan, A. Joosten, J. L. Vasse, P. Bertus, P. Karoyan, and J. Szymoniak, *Eur. J. Org. Chem.*, 2009, 5072.
49. a) A. S. Kende, *Org. React.*, 1960, **11**, 261; b) J. Wohllebe and E. W. Garbisch, *Org. Synth.*, 1977, **56**, 107; c) Y. Hamada and T. Shioiri, *Org. Synth.*, 1984, **62**, 191.
50. B. Denolf, S. Mangelinckx, K. W. Tornroos, and N. De Kimpe, *Org. Lett.*, 2007, **9**, 187.
51. J. Vesely, G. L. Zhao, A. Bartoszewicz, and A. Cordova, *Tetrahedron Lett.*, 2008, **49**, 4209.
52. a) J. M. Zhang, Z. P. Hu, S. Q. Zhao, and M. Yan, *Tetrahedron*, 2009, **65**, 802; b) J. M. Zhang, Z. P. Hu, L. T. Dong, Y. N. Xuan, C. L. Lou, and M. Yan, *Tetrahedron: Asymmetry*, 2009, **20**, 355.
53. O. Mitsunobu, *Synthesis*, 1981, 1.
54. J. Yu, J. Falck, and C. Mioskowski, *J. Org. Chem.*, 1992, **57**, 3757.
55. a) A. S. Khile, J. Patel, N. Trivedin, and N. S. Pradhan, WO 2011132083, Jan 5, 2011; b) B. Zupancic, P. K. Luthra, R. Khan, R. Nair, T. Das, S. Gudekar, and A. Syed, WO 2013144295, Oct 3, 2013; c) M. Rasparini, M. Taddei, E. Cini, C. Minelli, N. Turner, and K. G. Hugentobler, EP 2589587, May 8, 2013.
56. V. K. Aggarwal, J. de Vicente, and R. V. Bonnert, *Org. Lett.*, 2001, **3**, 2785.
57. A. Armstrong and J. N. Scutt, *Org. Lett.*, 2003, **5**, 2331.
58. M. Mitsuda, T. Moroshima, K. Tsukuya, K. Watabe, and M. Yamada, WO2008018823, Feb 14, 2008.
59. E. B. Averina, N. V. Yashin, T. S. Kuznetsova, and N. S. Zefirov, *Russ. Chem. Rev.*, 2009, **78**, 887.
60. J. Zindel and A. de Meijere, *J. Org. Chem.*, 1995, **60**, 2968.
61. M. Rasparini, M. Taddei, E. Cini, C. Minelli, N. Turner, and K. G. Hugentobler, EP 2589587, May 8, 2013.
62. Y. A. Volkova, O. A. Ivanova, E. M. Budynina, E. V. Revunov, and E. B. Averina, *Tetrahedron Lett.*, 2009, **50**, 2793.
63. S. Arai, K. Nakayama, K. Hatano, and T. Shioiri, *J. Org. Chem.*, 1998, **63**, 9572.
64. a) H. J. Lee, S. M. Kim, and D. Y. Kim, *Tetrahedron Lett.*, 2012, **53**, 3437; b) S. Y. Cai, S. L. Zhang,

Y. H. Zhao, and D. Z. Wang, *Org. Lett.*, 2013, **15**, 2660.

65. R. Sakae, N. Matsuda, K. Hirano, T. Satoh, and M. Miura, *Org. Lett.*, 2014, **16**, 1228.

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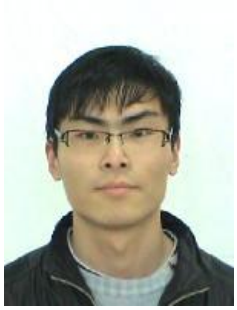

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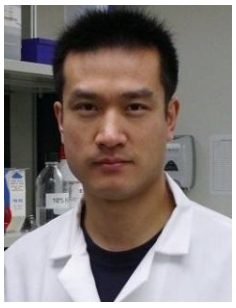

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