DISSERTATION

Development of Carbocycle-forming Methods via Cyclization of Nitriles

（ニトリル誘導体の環化反応による炭素環構築法の開発）

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Contents

Introduction

Development of new efficient methodologies for synthesizing organic compounds is one of the most important tasks in organic chemistry, because organic compounds such as bioactive natural products, medicines, agrochemicals, and dyes are essential for daily life of humanity (Figure I-1). Since most of these compounds possess aromatic and/or alicyclic carbocycles, development of efficient C–C bond forming reactions which provide carbocycles are of critical importance in organic synthesis.

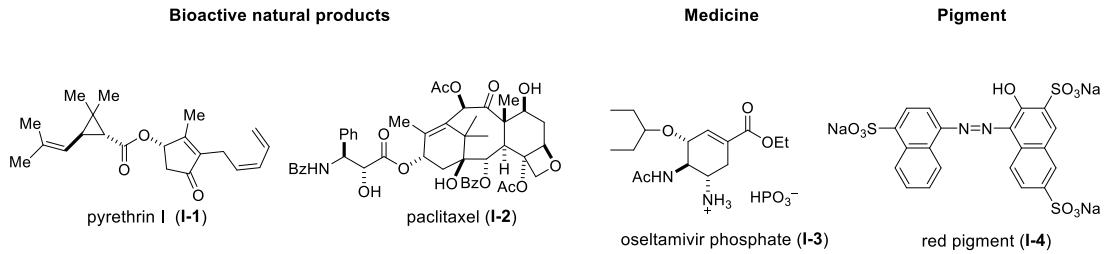
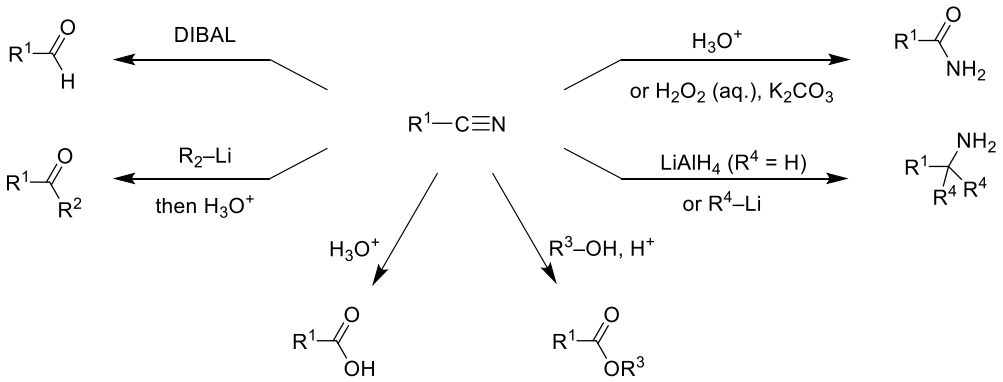


Figure I-1. Carbocycles found in important organic molecules

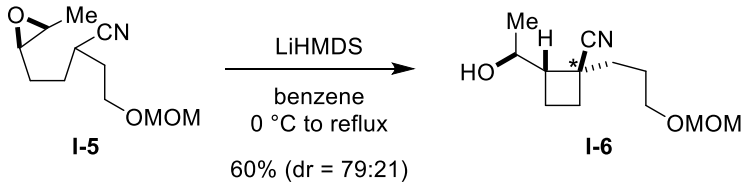
A number of methodologies for constructing carbocycles via C–C bond formation have been reported. These methods can be classified into cycloadditions which are typified by the Diels–Alder reaction[1] and annulations which include intramolecular alkylation, intramolecular nucleophilic addition, ring-closing metathesis,[2] and Robinson annulation.[3]

On the other hand, cyano group has found widespread use in organic synthesis because of the properties that include: (1) nitriles are readily obtainable from other organic compounds through functional group interconversion or one-carbon elongation using cyanide anion, (2) nitriles can be transformed into various kinds of organic compounds via hydration, reduction, and addition reactions (Scheme I-1), (3) an α-cyano carbanion species which can be generated from the corresponding alkane nitrile acts as a good nucleophile, (4) from a structural perspective, cyano group is extremely compact in comparison with ester, amide, and keto groups. For example, the *A*-value of cyano group is 0.2 kcal/mol, whereas that of methyl ester is 1.2–1.3 kcal/mol.[4]



Scheme I-1. Various transformations of nitriles

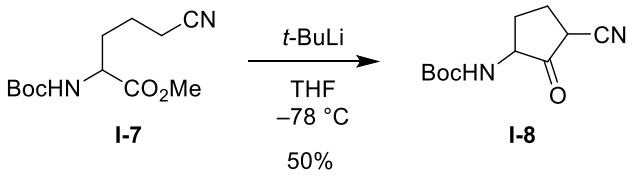
These properties of cyano group make it a useful tool for constructing carbocycles, and there have been reported a number of approaches. Among them, intramolecular nucleophilic substitutions or additions of α-cyano carbanions generated from the corresponding alkanenitriles are most frequently used for the synthesis of carbocyles.[5] These methods are useful for C–C bond forming reactions at sterically congested positions because of the extremely small size of the cyano group. Additionally, α-cyano carbanions exhibit high nucleophilicity compared with enolates of ketones or esters due to the relatively localized, high charge density. Furthermore, thermally stable nature of α-cyano carbanions allows the use of them even upon heating. For example, Guerrero and co-workers synthesized cyclobutane derivative **I-6** by intramolecular nucleophilic substitution of the α-cyano carbanion generated in situ from alkanenitrile **I-5** having epoxide moiety (Scheme I-2).[6] In this reaction, the quaternary carbon atom at the α-position of the cyano group was constructed.



I-5 **I-6**

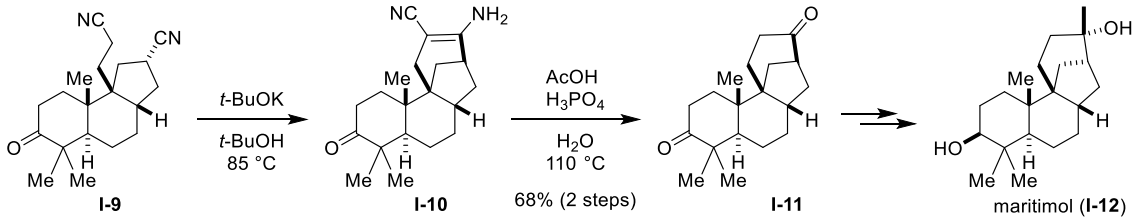
Scheme I-2. Intramolecular nucleophilic addition of α-cyano carbanion

Kemp and co-workers reported the synthesis of cyclopentanone derivative **I-8** bearing a Boc-protected amino group by intramolecular acylation of the α-cyano carbanion generated from **I-7** with *t*-BuLi (Scheme I-3).[7]



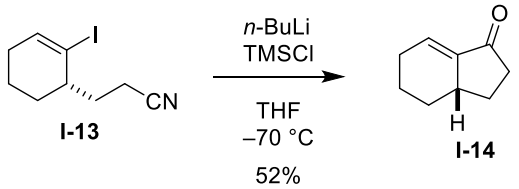
Scheme I-3. Intramolecular acylation of α-cyano carbanion

The intramolecular condensation of dinitriles is known as the Thorpe-Ziegler reaction.[8] As shown in Scheme I-4, Deslongchamps and co-workers utilized this type of reaction in the total synthesis of maritimol (**I-12**).[9] When dinitrile **I-9** was treated with *t*-BuOK, intramolecular nucleophilic addition of the α-cyano carbanion generated from the primary nitrile to the secondary nitrile proceeded to give enaminonitrile **I-10** by the formation of a six-membered ring. Subsequent treatment of **I-10** with aqueous AcOH–H_3PO_4 solution afforded diketone **I-11**, which was successfully converted into maritimol (**I-12**).



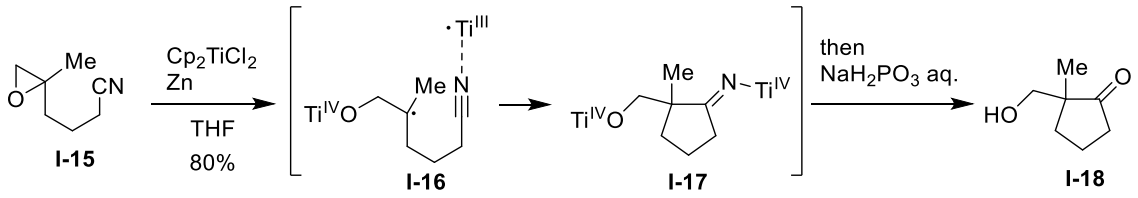
Scheme I-4. Thorpe-Ziegler reaction

A cyano group is also used as an electrophile in an intramolecular nucleophilic addition reaction of carbon nucleophiles. For example, Knochel and co-workers synthesized bicyclic ketone **I-14** by the intramolecular nucleophilic addition of the alkenyl lithium generated in situ by halogen-metal exchange between *n*-BuLi and alkenyl iodide **I-13** (Scheme I-5).[10]



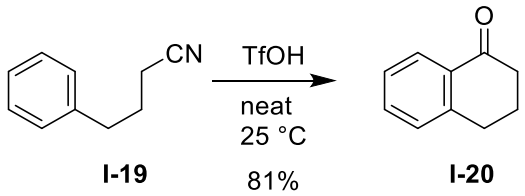
Scheme I-5. Intramolecular addition of alkenyl lithium

A cyano group also behaves as a radical acceptor (Scheme I-6).[11] Fernández-Mateos and co-workers reported that the cyclopentanone derivative **I-18** was obtained by the treatment of epoxy nitrile **I-15** with a Ti(III) reagent. In this reaction, reductive cleavage of the epoxide afforded tertiary carbon radical **I-16** which underwent addition with the nitrile moiety, and the resulting imine derivative was converted to ketone **I-18** under acidic conditions.



Scheme I-6. Radical cyclization of nitrile

The intramolecular Houben-Hoesch reaction (i.e. acid promoted acylation of an aromatic compound with a nitrile) has been reported for the formation of carbocycles (Scheme I-7).[12] For example, Ohwada and co-workers reported that α-tetralone (**I-20**) was formed from 4-phenylbytyronitrile (**I-19**) through the intramolecular Houben-Hoesch reaction mediated by trifluoromethanesulfonic acid followed by aqueous work-up effecting the hydrolysis of the resulting imine.



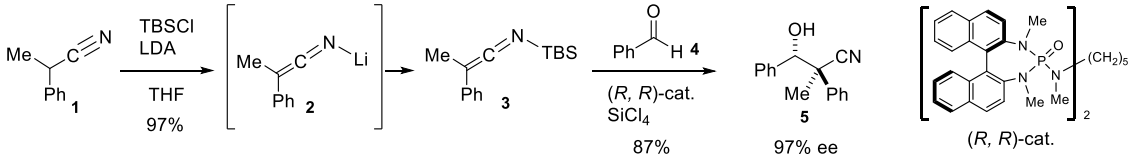
Scheme I-7. Intramolecular Houben-Hoesch reaction

From the above background, the author undertook studies to develop novel and synthetically useful carbocycle-forming methods based on cyclizations of nitriles. In this dissertation, the author will describe two subjects aiming at the development of novel methodology for the construction of carbocycles by utilizing nitriles. In chapter 1, synthesis of aryl amine derivatives via electrocyclization of the *N*-silyl ketene imines generated in situ is described. In chapter 2, synthetic study of andrastin C via cyclizations of alkanenitriles is described.

Chapter 1

Synthesis of Aryl Amine derivatives via Electrocyclization of *N*-Silyl Ketene Imines

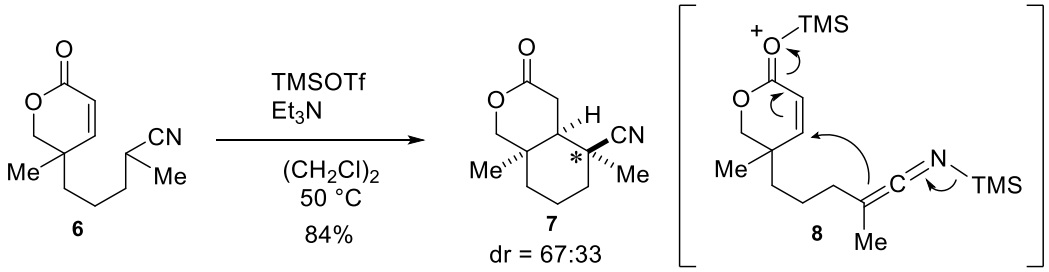
N-Silyl ketene imines, which have cumulative double bond as **3**, have recently received much attention as a competent α-cyano carbanion equivalent.[13] Because of sterically less demanding nature arising from its liner structure, *N*-silyl ketene imines are expected to be effectively reactive species for constructing a quaternary carbon center. For example, Denmark and co-workers reported enantioselective nucleophilic addition of *N*-silyl ketene imines to aldehydes catalyzed by the combination of $SiCl_4$ and the chiral Lewis base (Scheme 1).[14]



Scheme 1. Nucleophilic addition of *N*-silyl ketene imine **3**

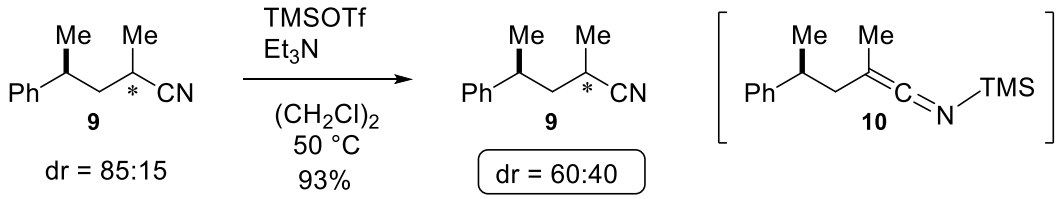
Despite its synthetic potential as identified above, the use of *N*-silyl ketene imines is limited, whereas ketene silyl acetals, ester analogues of *N*-silyl ketene imines, have had wide application in organic synthesis. The major problem belong to the use of *N*-silyl ketene imines is the difficulty in their handling and storing instability arising from its high tendency toward hydrolysis. In addition, harsh reaction condition in its preparation is also a problem. Namely, *N*-silyl ketene imines are typically prepared via *N*-silylation of α-cyano carbanions generated from alkanenitriles under the influence of strong bases such as LDA (cf. **1**→**3**).[15]

In this context, Mori and Torizuka in the author's laboratory found that *N*-silyl ketene imines could be generated under non-basic mild reaction conditions.[16] Under the influence of TMSOTf and Et_3N, α,β-unsaturated lactone **6** that bears an alkanenitrile sidechain underwent intramolecular conjugate addition to afford bicyclic compound **7**. The cyclization seemed to proceed via the nucleophilic addition of in situ-generated *N*-silyl ketene imine **8** to the α,β-unsaturated lactone activated by TMSOTf.



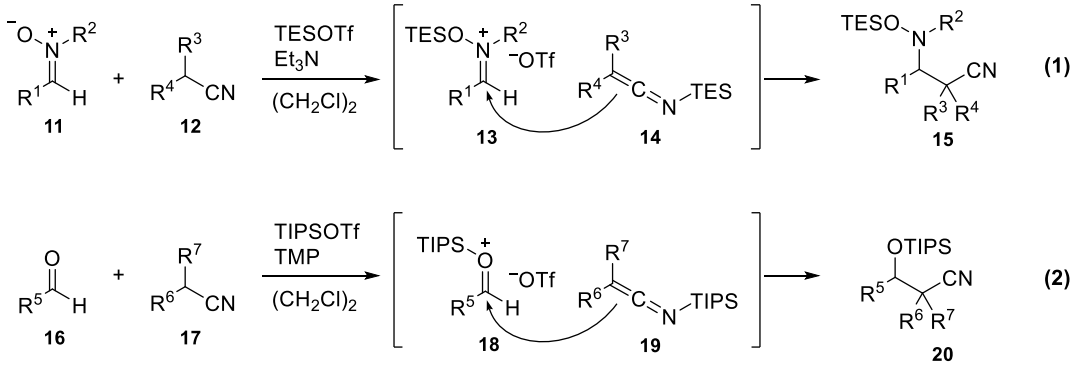
Scheme 2. Intramolecular conjugate addition of alkanenitrile under TMSOTf–Et_3N system

Because the *N*-silyl ketene imine intermediate **8** could not be observed by ^{1}H NMR or ^{13}C NMR, Torizuka performed the following experiment. Thus, diastereomeric ratio of nitrile **9** was changed from 85:15 to 60:40 upon the treatment of the silylation condition same as the above cyclization (Scheme 3). This observation of isomerization strongly supports the generation of the *N*-silyl ketene imine intermediate **10** under non-basic mild conditions.[17]



Scheme 3. Isomerization of nitrile **9** under TMSOTf–Et_3N system

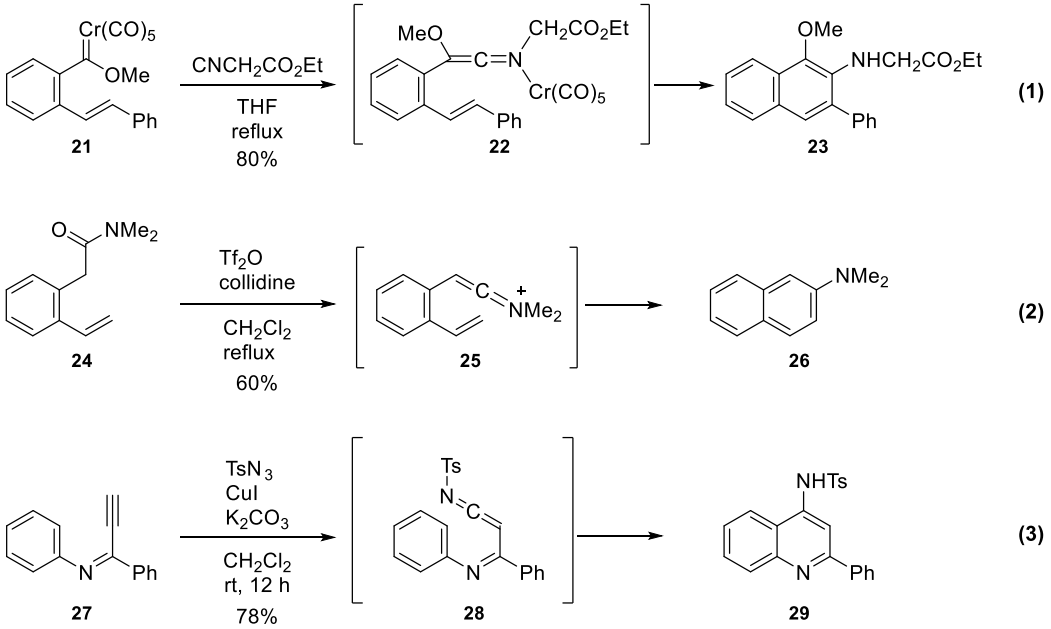
Based on these findings, two intermolecular nucleophilic addition reactions of alkanenitriles under non-basic silylation conditions were developed in the author's laboratory.[18] Thus, upon treatment with TESOTf and Et_3N, the addition reaction of nitrones **11** and nitriles **12** proceeds to give β-(hydroxyamino)nitrile derivatives **15**, which was included in the author's M.S. thesis. Additionally, the aldol type reaction of aldehydes **16** and nitriles **17** was enabled by treatment with TIPSOTf and TMP. These reactions seem to proceed through generation of *N*-silyl ketene imine intermediates followed by nucleophilic addition to nitrones (eq. 1) or aldehydes (eq. 2) activated by silyl triflate. The advantage of these reactions is not only mild reaction conditions but also unnecessity of isolation of the labile *N*-silyl ketene imine intermediates.



Scheme 4. Intermolecular nucleophilic addition of nitriles under non-basic silylation conditions

From the above background, the author undertook research to explore the novel reactivity of *N*-silyl ketene imines generated under silyl triflate and amine base system. Previously, the use of *N*-silyl ketene imines have been mainly focused on nucleophilic addition reactions. Pericyclic reactions of *N*-silyl ketene imines have not been explored except for one report of Diels-Alder reaction.[19] Therefore, the author focused on the electrocyclization reactions of *N*-silyl ketene imines.

Electrocyclization of ketene imine derivatives is one of the important methods to synthesize aryl amine derivatives. Several electrocyclizations of the related in situ-generated ketene imine derivatives have been disclosed (Scheme 4). Merlic and co-workers reported the electrocyclization of chromium ketene imine complex **22** generated from chromium carbene complex **21** and isonitriles.[20] De Masmaeker and co-workers synthesized aryl amine **26** by the electrocyclization of ketene iminium **25** generated from phenylacetamide **24** bearing vinyl group at the *ortho* position via the treatment with Tf_2O.[21] Cui and co-workers reported that 4-aminosulfonamidequinoline **29** was obtained by the copper-catalyzed formation of *N*-sulfonyl keteneimine **28** followed by electrocyclization.[22]



Scheme 4. Electrocyclizations of ketene imine derivatives

Aryl amines are ubiquitous structure found in many biologically active compounds[23] including natural products and a variety of functional molecules such as dyes and anion sensors[24] (Figure 1). The author expected that the development of electrocyclization of *N*-silyl ketene imines would provide new access to aryl amine derivatives under mild reaction conditions.

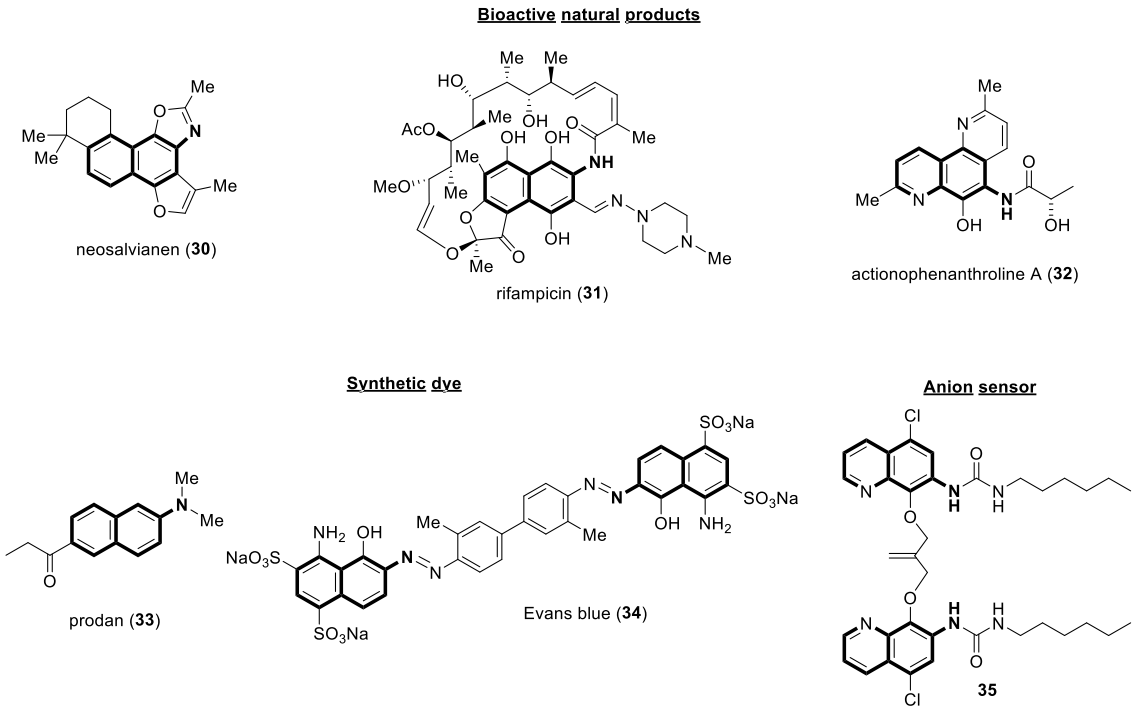
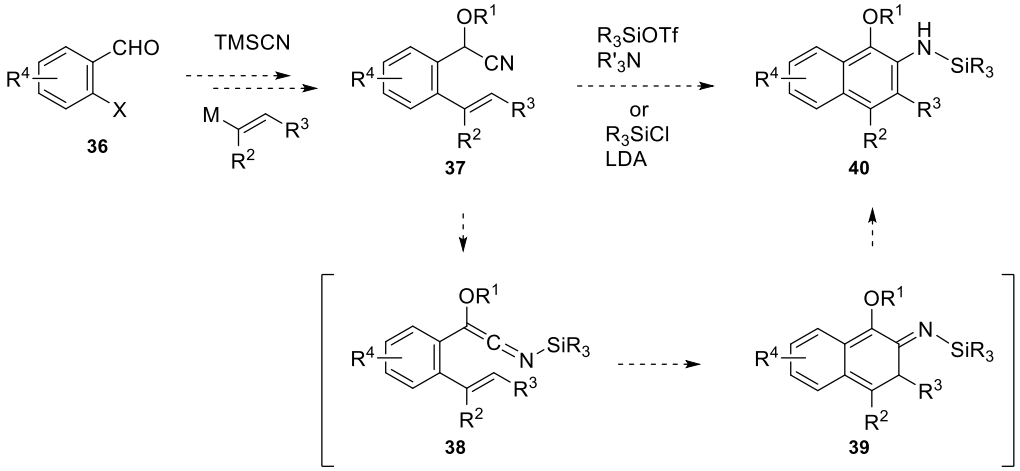


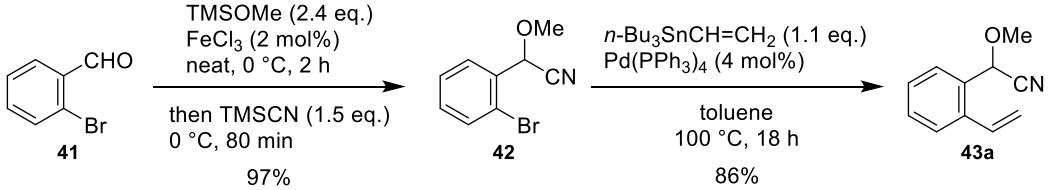
Figure 1. Important compounds found in aryl amine derivatives

The strategy for the synthesis of aryl amines via electrocyclization is shown in Scheme 5. The author expected that aryl amines **40** would be obtained from benzyl cyanides **37** bearing an alkenyl or an aryl group at the *ortho* position through the spontaneous electrocyclization of in situ-generated *N*-silyl ketene imine intermediate **38** followed by aromatization. The *N*-silyl ketene imine intermediate **38** would be generated under the previous non-basic conditions (trialkylsilyl triflate–tertiary amine system) or conventional basic conditions (trialkylsilyl chloride–amide base system). The substrates **37** would be readily accessible through the sequential three-component coupling reactions of *o*-halogenated benzaldehydes **36**, TMSCN, and alkenyl or aryl metal species. This process would provide an efficient methodology for preparing various substituted aryl amines by choosing the appropriate coupling partners (i.e. **36** and alkenyl or aryl metal species), because a variety of these components are readily available to prepare the substrates **37**.



Scheme 5. Strategy to synthesize aryl amines

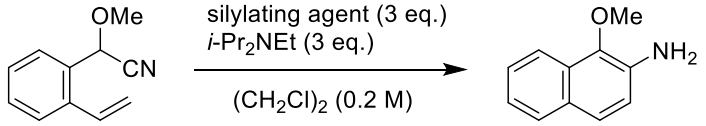
The *o*-vinyl benzyl cyanide derivative **43a** was synthesized as a model substrate to examine the above strategy (Scheme 6). Thus, *o*-bromobenzaldehyde (**41**) was converted to cyanohydrin methyl ether **42** through a formation of dimethyl acetal and subsequent treatment with TMSCN in one pot according to the Oriyama's procedure.[25] The vinyl group was introduced by the Stille coupling reaction with tri-*n*-butyl(vinyl)tin affording the model substrate **43a**.



Scheme 6. Synthesis of model substrate **43a**

With *o*-vinyl benzyl cyanide **43a** in hand, optimization of the reaction conditions was carried out (Table 1). Initially, non-basic silylation conditions by using trialkylsilyl triflate–tertiary amine system were examined. Under the influence of TESOTf (3 eq.) and *i*-Pr_2NEt (3 eq.) in $(CH_2Cl)_2$, the desired aryl amine **44a** was obtained albeit in low yield (1%), and the starting material was recovered (79% yield) (entry 1). The use of TMSOTf did not promote the reaction (entry 2). On the contrary, $TMSNTf_2$,[26] a silylating agent more reactive than TMSOTf, found to be effective for this cyclization, and aryl amine **44a** was obtained in 88% yield without any recovery of the starting material (entry 3). The use of Et_3N instead of *i*-Pr_2NEt led to the low yield of aryl amine **44a** (entry 4). The use of an excess amount of the silylating agent is critical for full conversion of the reaction, presumably due to the competing silylation of the resulting amino group of the product. Thus, when each 1 or 2 equivalents of $TMSNTf_2$ and *i*-Pr_2NEt were used, the yield of the product was reduced (entries 5 and 6). The reaction did not proceed in the absence of $TMSNTf_2$ at all (entry 7). On the other hand, the reaction proceeded in the absence of *i*-Pr_2NEt, giving aryl amine **44a** in 81% yield, whereas the reaction required heating at 85 °C (entry 8).[27] From the above optimization, entry 3 was selected as the best reaction conditions for this cyclization.

Table 1. Optimization of reaction conditions

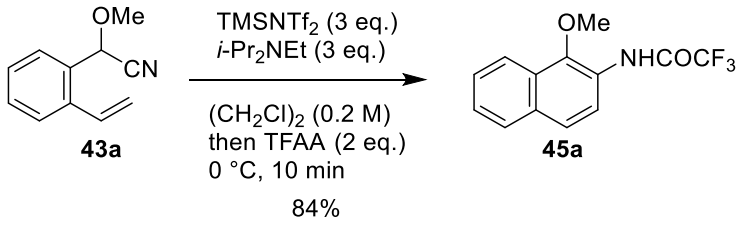


43a **44a**

entry	silylating agent	temp.	time	NMR yield[1)]	
				43a	**44a**
1	TESOTf	85 °C	9.5 h	79%	1%
2	TMSOTf	85 °C	9.5 h	97%	1%
3	$TMSNTf_2$	rt	1.5 h	0%	88%
4	$TMSNTf_2$ [2)]	rt	1.5 h	57%	7%
5	$TMSNTf_2$ [3)]	rt to 85 °C	1.5 h	58%	8%
6	$TMSNTf_2$ [4)]	rt to 85 °C	2 h	50%	22%
7	none	85 °C	7 h	98%	0%
8	$TMSNTf_2$ [5)]	rt to 85 °C	2 h	0%	81%

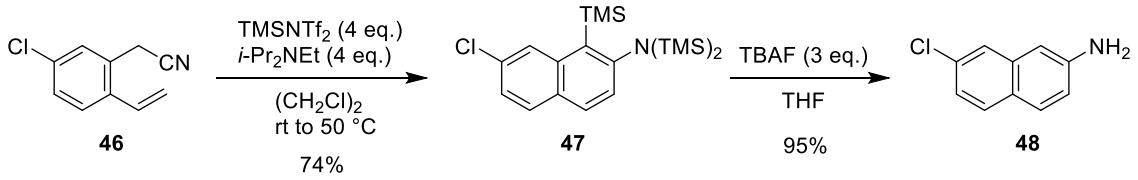
1) The NMR yields were determined by ^1H NMR analysis of the crude products using pyrazine as an internal standard.
2) Et_3N was used instead of *i*-Pr_2NEt.
3) $TMSNTf_2$ (1 eq.) and *i*-Pr_2NEt (1 eq.) were used.
4) $TMSNTf_2$ (2 eq.) and *i*-Pr_2NEt (2 eq.) were used.
5) in the absence of *i*-Pr_2NEt

Although the optimal conditions for the cyclization have been established, it was found that the unprotected aryl amine products were slightly unstable to silica gel column chromatography, storage, or air. Therefore, the product was isolated as its trifluoroacetamide. After cyclization under the optimized conditions, the product was trifluoroacetylated via an addition of TFAA (2 eq.) in one-pot (Scheme 7). This protocol gave the product as stable trifluoroacetamide **45a** in 84% yield.



Scheme 7. Optimal protocol for $TMSNTf_2$-*i*-Pr_2NEt system

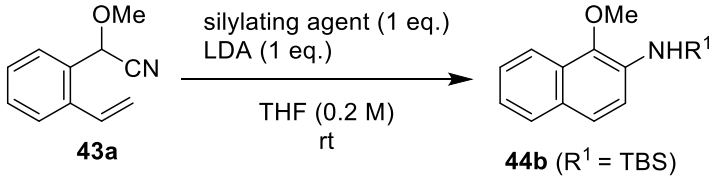
The oxygen functionality at benzyl position is not essential for the cyclization. The cyclization of benzyl cyanide **46** afforded the silylated aryl amine **47** through *C*-silylation at the benzyl position, *N*-silyl ketene imine formation, and the subsequent electrocyclization (Scheme 8). Desilylation of **47** gave free 2-naphlylamine **48**.



Scheme 8. Cyclization of benzyl cyanide **46**

Next, cyclization under conventional basic conditions for *N*-silyl ketene imine formation (trialkylsilyl chloride–LDA system) was conducted (Table 2). Initially, α-cyano carbanion prepared from benzyl cyanide **43a** and LDA in THF was silylated by TBSCl.[28] The cyclization proceeded at room temperature and aryl amine **44b** was obtained in 59% yield (entry 1). However, the reaction did not complete and the starting material was recovered in 40% yield. The use of liquid TIPSCl improved the conversion of the reaction, giving aryl amine **44c** in 87% yield (entry 2). Note that aryl amine **44c** was not obtained in the absence of either LDA or TIPSCl (entries 3 and 4). Accordingly, this cyclization did not involve the electrocyclization of the *N*-lithiated ketene imine derived from **43a** (entry 4). From the above optimization, entry 2 was selected as the best condition.

Table 2. Optimization of reaction conditions

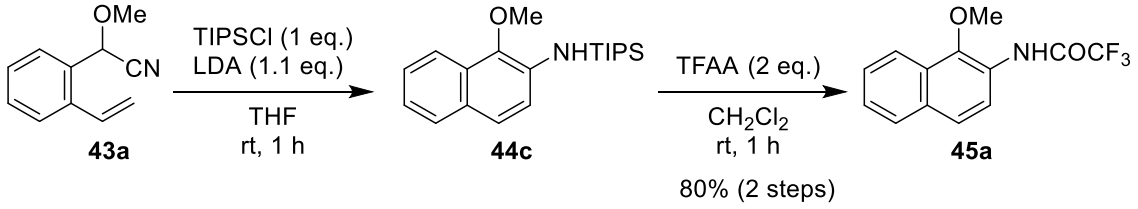


44b (R^1 = TBS)
44c (R^1 = TIPS)

entry	silylating agent	time	NMR yield[1)]	
			43a	**44**
1	TBSCl	1 h	40%	**44b**; 59%
2	TIPSCl	1 h	0%	**44c**; 87%
3	TIPSCl[2)]	1.5 h	82%	0%
4[3)]	none	2 h	9%	0%

1) The NMR yields were determined by ^{1}H NMR analysis of the crude products using pyrazine as an internal standard.
2) in the absence of LDA
3) Unidentified products were obtained.

Similar to the cyclization mediated by the $TMSNTf_2$–*i*-Pr_2NEt system, aryl amine **44c** was isolated as its TFA amide by the following protocol (Scheme 9). Thus, after *o*-vinyl benzyl cyanide **43a** was cyclized under the above optimized condition, the crude *N*-TIPS aryl amine **44c** was trifluoroacetylated via treatment with TFAA in CH_2Cl_2 at room temperature, giving rise to trifluoroacetamide **45a** in 80% yield. Slightly excess amount of LDA (1.1 eq.) was required to achieve completion of this cyclization with reproducibility.

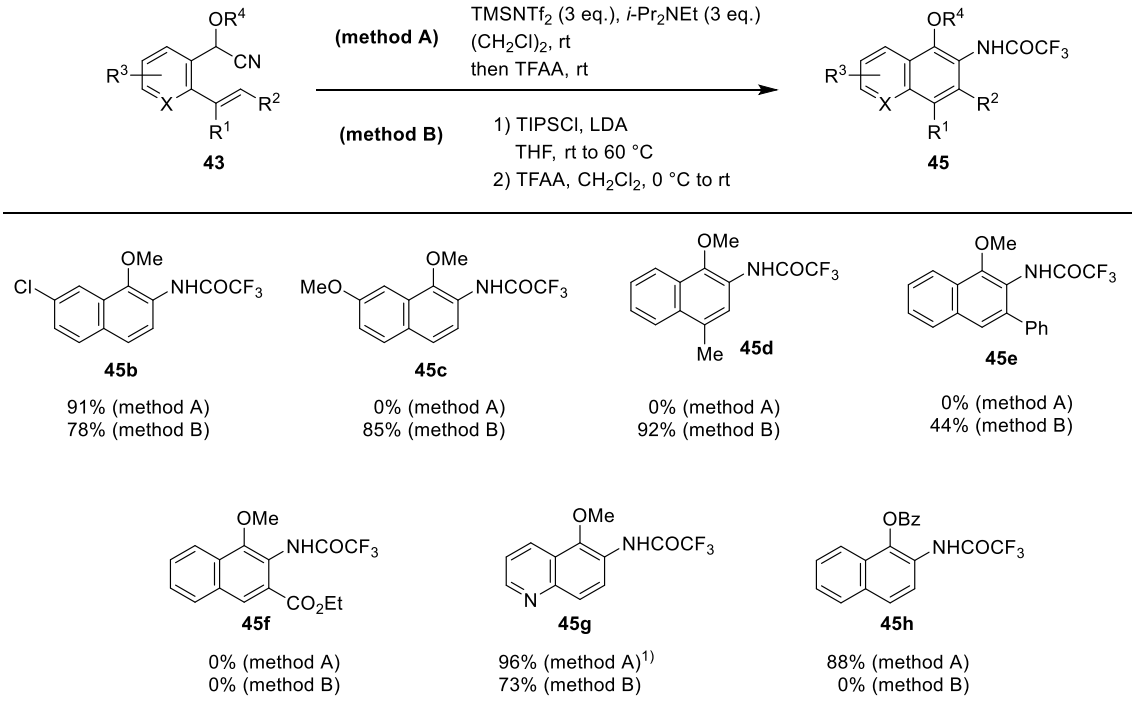


Scheme 9. Optimal protocol for basic TIPSCl–LDA system

It is noteworthy that the reported syntheses of 2-naphthylamine derivatives via electrocyclization of *N*-substituted ketene imine derivatives required high temperature (cf. Scheme 4). On the contrary, the above electrocyclization of *N*-silyl ketene imines proceeds smoothly at room temperature, which clearly indicates the high reactivity of *N*-silyl ketene

imines for 6π-electrocyclization.

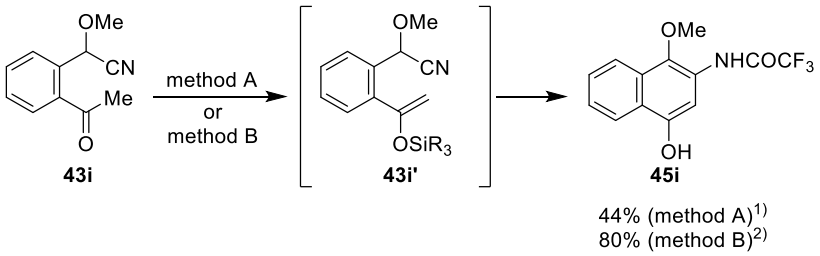
With two optimal conditions in hand, the scope and limitations of substrates were explored (Scheme 10). The two protocols, $TMSNTf_2$–*i*-Pr_2NEt system and TIPSCl–LDA system, were named method A and method B, respectively. Both methods were applied to a series of *o*-alkenyl benzyl cyanides,[29] which were prepared from commercially available *o*-halogenated benzaldehydes through cyanohydrin methyl ether or benzoate formations and the subsequent cross coupling reactions with the corresponding alkenyl metal species. Electron-withdrawing group on the benzene ring did not affect the reaction, and both methods resulted in the formation of aryl amine **45b** in good yields. Substrates having electron-donating group on the benzene ring or tri-substituted alkenyl group resulted in the formation of complex mixtures and the desired aryl amines **45c**–**45e** were not obtained by method A.[30] On the contrary, cyclizations of **43c–43e** gave aryl amines **45c**–**45e** in high yield by method B. On the other hand, a substrate bearing an α,β-unsaturated ester did not afford the desired aryl amine **45f** in both method A and B. A substrate having pyridine ring such as **43g** gave the quinoline amine product **45g** in good yield. Base sensitive *O*-benzoyl cyanohydrin gave 1-benzoyloxy-2-naphthylamine derivative **45h** only by non-basic method A whereas basic and anionic method B did not afford **45h**.



1) Two step yield for cyclization and trifluoroacetylation

Scheme 10. Substrate scope

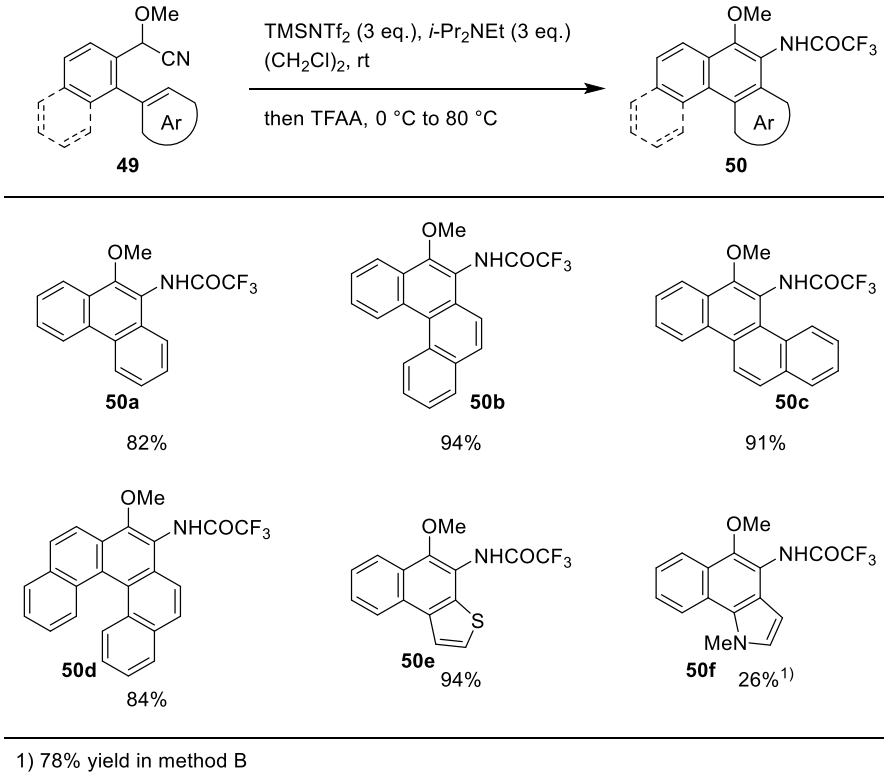
In addition, silyl enol ether could be used as a π-component in this cyclization. Thus, the cyclization of benzyl cyanide **43i** bearing methyl ketone moiety at the *ortho* position gave 1,2,4-tri-heteroatom substituted naphthalene derivative **45i** through the electrocyclization of the in situ-formed silyl enol ether **43i'** (Scheme 11).



1) Four equivalents of both $TMSNTf_2$ and *i*-Pr_2NEt were used.
2) Two equivalents of TIPSCl and 2.1 equivalents of LDA were used.

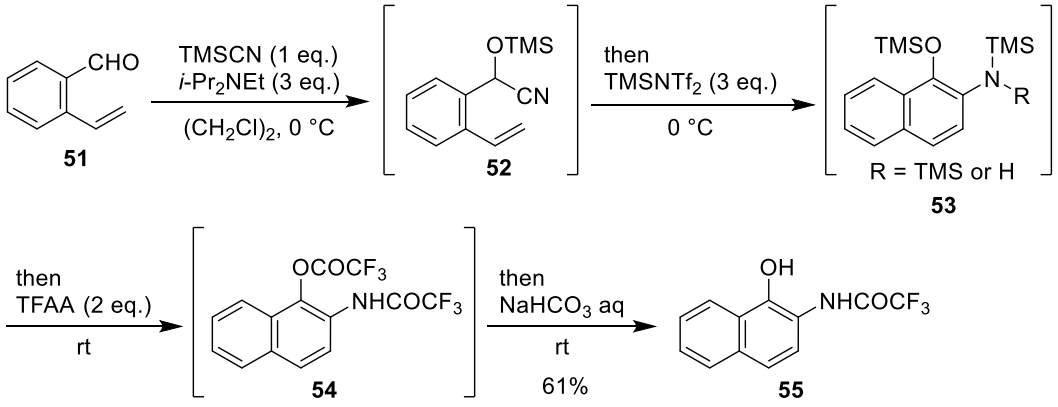
Scheme 11. Cyclization of methyl ketone **43i**

In addition to alkenyl groups, aryl groups could be also used as a π-component in the 6π electrocyclization, and a variety of polycyclic aromatic amines are accessible from biaryl nitriles **49** by non-basic cyclization conditions, namely, method A. Thus, biphenyl derivative smoothly cyclized to give phenanthrene amine **50a** in high yield. Benzo[*a*]phenanthrene amine **50b** and benzo[*c*]phenanthrene amine **50c** were synthesized from benzyl cyanides bearing 1-naphthyl or 2-naphthyl group, respectively. When using 1,1'-binaphthyl derivative, dibenzophenanthrene skeleton, i.e. helicene skeleton, was constructed (cf. **50d**). Substrates bearing hetero aromatic ring also gave the cyclized products **50e** and **50f**. Although the benzo[*g*]indolamine derivative **50f** was obtained in low yield by method A, cyclization under basic TIPSCl-LDA system (method B) gave **50f** in 78% yield. This protocol would provide a new synthetic route to important polycyclic aromatic/heteroaromatic skeletons, which are widely found in organic materials science.[31]



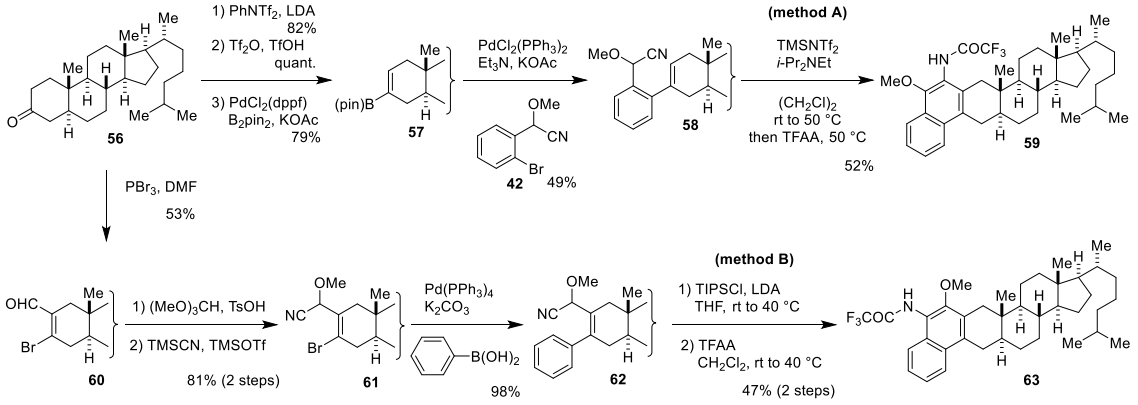
Scheme 12. Synthesis of polycyclic aryl amines

Hydroxy naphthylamine could be directly synthesized from *o*-vinyl benzaldehyde through the cyclization of the in situ-formed cyanohydrin TMS-ether by method A. Thus, by treating *o*-vinylbenzaldehyde (**51**) with TMSCN and *i*-Pr_2NEt, cyanohydrin silyl ether **52** was formed at first. Then, electrocyclization proceeded by the addition of $TMSNTf_2$ (**52→53**). Subsequent *N*,*O*-bis-trifluoroacetylation occurred by the addition of TFAA (**53→54**). Finally, $NaHCO_3$ aq. was added for the selective hydrolysis of trifluoroacetate in the presence of trifluoroacetamide (**54→55**). Notably, in this protocol, four reactions were conducted in one-pot operation.



Scheme 13. One-pot synthesis of hydroxynaphthylamine from *o*-vinylbenzaldehyde

The cyclization methodology could be applied to regiodivergent synthesis of naphthylamine-fused cycloalkanes from a common cycloalkanone. A benzyl cyanide having cyclohexene ring at the *otrho* position **58** was synthesized from steroidal cyclohexanone **56** in 4 steps including enol triflate formation, borylation, and Suzuki-Miyaura cross coupling reaction with aryl bromide **42**. Cyclization of benzyl cyanide **58** by method A gave 2-naphthylamine-fused steroid **59** in 52% yield. On the other hand, 1-naphthylamine fused cyclohexane **63** was synthesized by the cyclization of allyl cyanide **62**, which was synthesized from the same cyclohexanone **56** in 4 steps including Vilsmeier-Haack reaction, acetalization, cyanohydrin methyl ether formation, and Suzuki-Miyaura cross coupling reaction with phenyboronic acid. Cyclization of allyl cyanide **62** by method B afforded 1-naphthylamine-fuzed cyclohexene **63** in 47% yield. Note that in this cyclization, not only benzyl cyanides, but also ally cyanides could be used as a cyclization precursor.



Scheme 14. Regiodivergent strategy to fuse naphthylamine moiety to cyclic ketone

In this chapter, the author described the development of electrocyclization of in situ-generated *N*-silyl ketene imines. The author found that under two reaction conditions, i.e., non-basic condition ($TMSNTf_2$–*i*-Pr_2NEt system) or conventional basic condition (TIPSCl–LDA system), electrocyclization of *N*-silyl ketene imines smoothly proceed to give aryl amines. The advantage in this protocol is that a variety of substrates are readily accessible from commercially available starting materials. This methodology would provide new access to aryl amine derivatives, which are found in important molecules such as biologically active compounds and functional molecules. To the best of our knowledge, this is the first application of an *N*-silyl ketene imine to 6π-electrocyclization.

Experimental Section of Chapter 1

General Methods

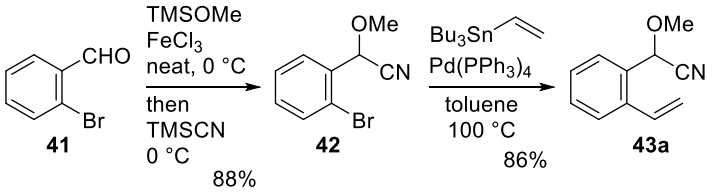
The reactions were performed using flame-dried glasswares under a positive pressure of argon. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl. Anhydrous 1,2-dichloroethane, 1,2-dimethoxyethane, toluene, methanol, ethanol, and dichloromethane were purchased from Sigma-Aldrich Co. Ltd or Kanto Chemical Co. Diisopropylamine, diisopropylethylamine and triethylamine was distilled from CaH_2 under argon and stored in the presence of NaOH (pellets). All other reagents and solvents were used as received from commercial sources without further purification.

^{1}H NMR spectra were measured using a JEOL ECA-500 (500 MHz) in $CDCl_3$ (δ_H 7.26), CD_3OD (δ_H 3.30), CD_3CN (δ_H 1.93), $(CD_3)_2SO$ (δ_H 2.49), and $(CD_3)_2CO$ (δ_H 2.04) with tetramethylsilane as an internal standard. Chemical shifts are reported in parts per million (ppm) from internal tetramethylsilane, and signal are expressed as singlet (s), doublet (d), triplet (t), quartet (q), septet (sept), and multiplet (m). Coupling constants are reported in Hz. ^{13}C NMR spectra were measured using a JEOL ECA-500 (125 MHz) in $CDCl_3$ (δ_C 77.0), CD_3CN (δ_C 118.2), $(CD_3)_2SO$ (δ_C 39.7), $(CD_3)_2CO$ (δ_C 29.8), CD_3OD (δ_C 49.0) and C_6D_6 (δ_C 128.0) with tetramethylsilane as an internal standard. High-resolution mass spectra (HRMS) were recorded on a JEOL JMS-T100GCV or a JEOL JMS-SX102A at the GC-MS & NMR Laboratory, Faculty of Agriculture, Hokkaido University. Infrared (IR) spectra were recorded on a JASCO FT/IR-4100 spectrophotometer.

Analytical thin layer chromatography (TLC) was performed using 0.25 mm E. Merck Silica gel (60F-254) plates. Reaction components were visualized by illumination with ultraviolet light (254 nm) and by staining with 6% ethanolic p-anisaldehyde (includes 6% conc. sulfuric acid and 1% acetic acid), 8% ethanolic phosphomolybdic acid, ceric ammonium molybdate in 10% sulfuric acid, or basic potassium permanganate solution. Kanto Chem. Co. Silica Gel 60N (particle size 0.040–0.050 mm) was used for flash column chromatography. To remove organotin impurities, 10wt% K_2CO_3/SiO_2 was used for flash column chromatography of the Stille coupling products.[1]

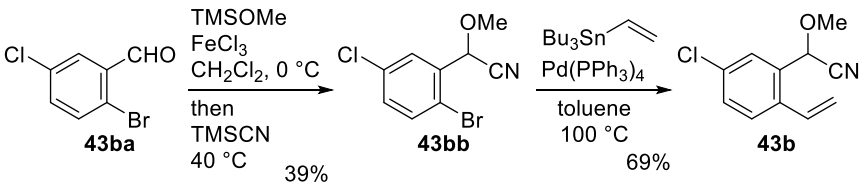
(1) Harrowven, D. C.; Curran, D. P.; Kostiuk, S. L.; Wallis-Guy, I. L.; Whiting, S.; Stenning, K. J.; Tang, B.; Packard, E.; Nanson, L. *Chem. Commun*. **2010**, *46*, 6335–6337.

Experimental Procedure for Chapter 1



2-(2-Bromophenyl)-2-methoxyacetonitrile (42): To a mixture of methoxytrimethylsilane (1.3 mL, 9.6 mmol) and $FeCl_3$ (13.0 mg, 0.080 mmol) was added 2-bromobenzaldehyde (**41**) (467 μL, 4.0 mmol) and the mixture was stirred at 0 °C for 2 h. Trimethylsilyl cyanide (751 μL, 6.0 mmol) was added to the mixture, and the resulting mixture was stirred at 0 °C for 80 min. Saturated aqueous sodium bicarbonate (ca. 3 mL) was added to the mixture and the products were extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, hexane–Et_2O = 5:1) afforded cyanohydrin methyl ether **42** (795.8 mg, 3.52 mmol, 88%).
Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (1H, dd, *J* = 8.0, 1.7 Hz), 7.62 (1H, d, *J* = 8.1 Hz), 7.44–7.38 (1H, m), 7.32–7.27 (1H, m), 5.44 (1H, s), 3.62 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.11, 132.71, 131.23, 128.92, 127.99, 122.83, 116.31, 71.63, 57.96; IR (ATR) ν 2394, 2830, 1572, 1470, 1437, 1323, 1277, 1198, 1083, 1026, 972, 947, 751, 632 cm^{-1}; HRMS (FD) calcd for C_9H_8BrNO (M^+): 224.9789, found: 224.9776.

2-Methoxy-2-(2-vinylphenyl)acetonitrile (43a): To a mixture of cyanohydrin methyl ether **42** (866 mg, 774 μL, 5.0 mmol) and tributyl(vinyl)stannane (1.8 mL, 6.0 mmol) in toluene (12.5 mL) was added $Pd(PPh_3)_4$ (231.1 mg, 0.20 mmol) and the mixture was stirred at 100 °C for 18 h. The mixture was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (10wt% K_2CO_3/SiO_2, hexane–Et_2O = 15:1) afforded nitrile **43a** (746.8 mg, 4.31 mmol, 86%).
Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (1H, d, *J* = 7.6 Hz), 7.54 (1H, d, *J* = 8.0 Hz), 7.42 (1H, t, *J* = 7.5 Hz), 7.35 (1H, t, *J* = 7.5 Hz), 6.97 (1H, dd, *J* = 17.2, 10.9 Hz), 5.71 (1H, dd, *J* = 17.2, 1.2 Hz), 5.46 (1H, d, *J* = 10.9 Hz), 5.38 (1H, s), 3.54 (3H, s); ^{13}C NMR (125 MHz, CD_3OD) δ 138.56, 134.23, 131.91, 131.13, 129.16, 129.10, 127.73, 118.29, 118.25, 71.28, 57.53; IR (ATR) ν 3264, 2161, 1710, 1538, 1389, 1318, 1260, 1160, 1081, 1054, 813, 749 cm^{-1}; HRMS (FD) calcd for $C_{11}H_{11}NO$ (M^+): 173.0841, found: 173.0848.

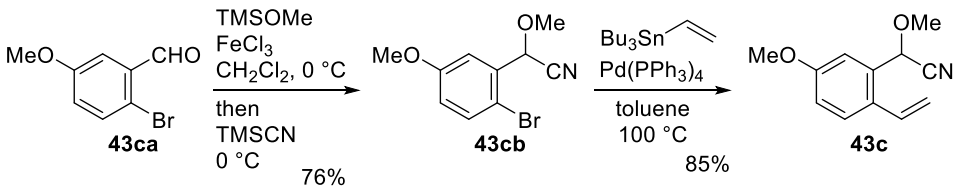


2-(2-Bromo-5-chlorophenyl)-2-methoxyacetonitrile (43bb): A mixture of methoxytrimethylsilane (3.3 mL, 24 mmol), 2-bromo-5-chlorobenzaldehyde (**43ba**) (2.19 g, 10 mmol), and $FeCl_3$ (32.4 mg, 0.20 mmol) in CH_2Cl_2 (5 mL) was stirred at 0 °C for 3 h. Trimethylsilyl cyanide (1.9 mL, 15 mmol) was then added and the mixture was stirred at 40 °C for 18 h. Saturated aqueous sodium bicarbonate (ca. 10 mL) was added to the mixture and the products were extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, hexane–Et_2O = 20:1) afforded cyanohydrin methyl ether **43bb** (1.02 g, 3.92 mmol, 39%).

White solid; M.p. 108–109 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (1H, d, *J* = 2.3 Hz), 7.54 (1H, d, *J* = 8.1 Hz), 7.28 (1H, dd, *J* = 8.6, 2.9 Hz), 5.35 (1H, s), 3.64 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.50, 134.40, 134.21, 131.30, 128.98, 120.31, 115.78, 71.21, 58.29; IR (ATR) ν 3095, 2952, 2833, 2065, 1455, 1194, 1091, 970, 866, 818 cm^{-1}; HRMS (FD) calcd for $C_9H_7BrClNO$ (M^+): 258.9400, found: 258.9396.

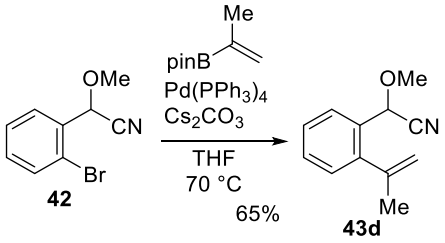
2-(5-Chloro-2-vinylphenyl)-2-methoxyacetonitrile (43b): To a mixture of cyanohydrin methyl ether **43bb** (781.5 mg, 3 mmol) and tributyl(vinyl)stannane (994 μL, 3.3 mmol) in toluene (7.5 mL) was added $Pd(PPh_3)_4$ (138.7 mg, 0.12 mmol) and the mixture was stirred at 100 °C for 16 h. The mixture was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (10wt% K_2CO_3/SiO_2, hexane–EtOAc = 10:1) afforded nitrile **43b** (428.5 mg, 2.06 mmol, 69%).

Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (1H, d, *J* = 2.3 Hz), 7.47 (1H, d, *J* = 8.6 Hz), 7.38 (1H, dd, *J* = 8.6, 1.8 Hz), 6.89 (1H, dd, *J* = 17.2, 10.9 Hz), 5.70 (1H, d, *J* = 17.2 Hz), 5.48 (1H, d, *J* = 10.9 Hz), 5.30 (1H, s), 3.56 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.51, 133.93, 131.66, 131.53, 130.16, 128.30, 127.89, 119.23, 116.22, 69.59, 57.41; IR (ATR) ν 2934, 2830, 1960, 1595, 1481, 1190, 973, 932, 832 cm^{-1}; HRMS (FD) calcd for $C_9H_7BrClNO$ (M^+): 258.9400, found: 258.9396.



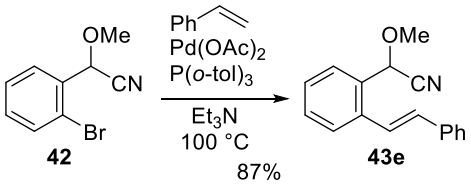
2-(2-Bromo-5-methoxyphenyl)-2-methoxyacetonitrile (43cb): A mixture of 2-bromo-5-methoxybenzaldehyde (**43ca**) (856.6 mg, 4.0 mmol), methoxytrimethylsilane (1.3 mL, 9.6 mmol) and $FeCl_3$ (13.0 mg, 0.08 mmol) in CH_2Cl_2 (2 mL) was stirred at 0 °C for 3 h. Trimethylsilyl cyanide (751 μL, 6.0 mmol) was then added and the mixture was stirred at 0 °C for 1 h. Saturated aqueous sodium bicarbonate (ca. 3 mL) was added to the mixture and the products were extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, hexane–EtOAc = 15:1) afforded cyanohydrin methyl ether **43cb** (774.9 mg, 3.03 mmol, 76%).
White solid; M.p. 67–68 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (1H, d, *J* = 9.2 Hz), 7.22 (1H, d, *J* = 2.9 Hz), 6.84 (1H, dd, *J* = 9.2, 2.9 Hz), 5.38 (1H, s), 3.83 (3H, s), 3.62 (3H, s); ^{13}C NMR (125 MHz, CD_3OD) δ 159.35, 133.75, 133.56, 117.34, 116.32, 114.10, 112.76, 71.63, 58.07, 55.61; IR (ATR) ν 2950, 2830, 2161, 1577, 1471, 1295, 1229, 1089, 1052, 968, 861, 771, 598 cm^{-1}; HRMS (FD) calcd for $C_{11}H_{10}ClNO$ (M^+): 207.0451, found: 207.0462.

2-Methoxy-2-(5-methoxy-2-vinylphenyl)acetonitrile (43c): To a solution of cyanohydrin methyl ether **43cb** (774.9 mg, 3.03 mmol) and tributyl(vinyl)stannane (1.0 mL, 3.3 mmol) in toluene (7.5 mL) was added $Pd(PPh_3)_4$ (139.8 mg, 0.12 mmol) and the mixture was stirred at 100 °C for 30 h. The mixture was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (10wt% K_2CO_3/SiO_2, hexane–EtOAc = 10:1) afforded nitrile **43c** (524.6 mg, 2.58 mmol, 85%).
White solid; M.p. 44–45 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (1H, d, *J* = 8.6 Hz), 7.13 (1H, d, *J* = 2.9 Hz), 6.94 (1H, dd, *J* = 8.6, 2.9 Hz), 6.89 (1H, dd, *J* = 17.2, 10.9 Hz), 5.60 (1H, dd, *J* = 17.2, 1.1 Hz), 5.35 (1H, d, *J* = 10.4 Hz), 5.34 (1H, s), 3.85 (3H, s), 3.55 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.95, 133.63, 133.17, 130.79, 129.05, 118.27, 116.43, 116.11, 114.30, 71.13, 57.60, 55.90; IR (ATR) ν 2952, 2163, 1610, 1494, 1297, 1239, 1073, 968, 862 cm^{-1}; HRMS (FD) calcd for $C_{12}H_{13}NO_2$ (M^+): 203.0946, found: 203.0957.



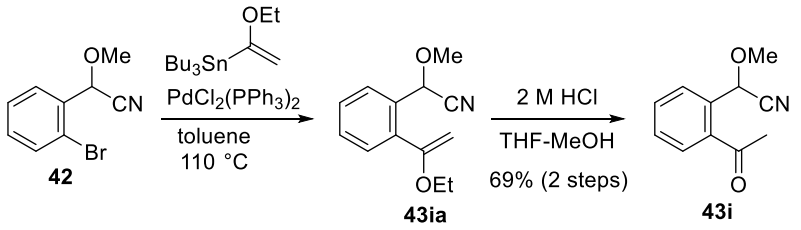
2-Methoxy-2-(2-(prop-1-en-2-yl)phenyl)acetonitrile (43d): To a mixture of cyanohydrin methyl ether **42** (346 mg, 310 μL, 2 mmol)**,** 2-isopropenyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (752 μL, 4 mmol), and Cs_2CO_3 (1.95 g, 6 mmol) in THF (20 mL) was added $Pd(PPh_3)_4$ (693.3 mg, 0.6 mmol) and the reaction mixture was stirred at 70 °C for 27 h. The mixture was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, hexane–Et_2O = 10:1) afforded nitrile **43d** (243.0 mg, 1.30 mmol, 65%).

Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (1H, dd, *J* = 7.5, 1.7 Hz), 7.39 (1H, td, *J* = 7.5, 1.7 Hz), 7.36 (1H, td, *J* = 7.5, 1.7 Hz), 7.24 (1H, dd, *J* = 9.7, 2.1 Hz), 5.34 (1H, s), 5.33–5.31 (1H, m), 4.94 (1H, s), 3.53 (3H, s), 2.09 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.44, 143.17, 130.30, 129.61, 128.14, 128.06, 127.68, 117.68, 116.72, 69.70, 57.39, 25.13; IR (ATR) ν 3073, 2944, 2828, 2333, 1639, 1489, 1448, 1190, 1077, 970, 910, 756 cm^{-1}; HRMS (FD) calcd for $C_{12}H_{13}NO$ (M^+): 187.0997, found: 187.1009.



(*E*)-2-Methoxy-2-(2-styrylphenyl)acetonitrile (43e): A mixture of cyanohydrin methyl ether **42** (866 mg, 774 μL, 5 mmol), stylene (723 μL, 6.3 mmol), tri(*o*-tolyl)phosphine (60.9 mg, 0.2 mmol), and $Pd(OAc)_2$ (693.3 mg, 0.6 mmol) in Et_3N (2.5 mL) was stirred at 100 °C for 24 h in a sealed tube. The mixture was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, hexane–Et_2O = 5:1) afforded nitrile **43e** (1.09 g, 4.37 mmol, 87%).

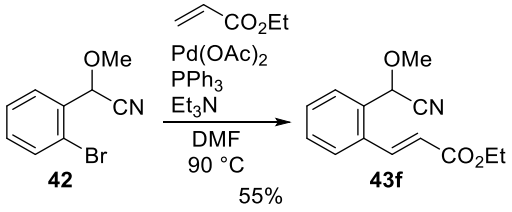
Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (1H, d, *J* = 7.5 Hz), 7.63 (1H, d, *J* = 7.5 Hz), 7.53 (2H, d, *J* = 7.5 Hz), 7.45 (1H, t, *J* = 7.2 Hz), 7.42–7.29 (5H, m), 7.04 (1H, d, *J* = 16.1 Hz), 5.46 (1H, s), 3.57 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.02, 136.83, 133.15, 130.23, 130.06, 128.78, 128.42, 128.25, 127.88, 126.98, 126.79, 124.06, 116.80, 70.56, 57.09; IR (ATR) ν 3028, 2932, 2827, 2122, 1496, 1450, 1189, 1079, 965, 761, 691 cm^{-1}; HRMS (FD) calcd for $C_{17}H_{15}NO$ (M^+): 249.1154, found: 249.1146.



2-(2-Acetylphenyl)-2-methoxyacetonitrile (12e): To a solution of cyanohydrin methyl ether **42** (339 mg, 232 μL, 1.50 mmol) and tributyl(1-ethoxyvinyl)stannane (547 μL, 1.65 mmol) in toluene (0.6 mL) was added $PdCl_2(PPh_3)_2$ (10.5 mg, 0.015 mmol), and the mixture was stirred at 110 °C for 3 h. The mixture was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure to give vinyl ether **43ia** (923.2 mg). This product was used for the next step without further purification.

To a solution of the above vinyl ether **43ia** (923.2 mg, as 1.50 mmol) in THF (2 mL) and MeOH (0.5 mL) was added 2 M aqueous HCl (1 mL) and the mixture was stirred at room temperature for 1 h. Saturated sodium bicarbonate (2 mL) was added to the mixture and the products were extracted with Et_2O. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chlomatography (SiO_2, hexane–EtOAc = 1:1) followed by recrystallization from hexane–Et_2O afforded nitrile **43i** (194.8 mg, 1.03 mmol, 69% for 2 steps).

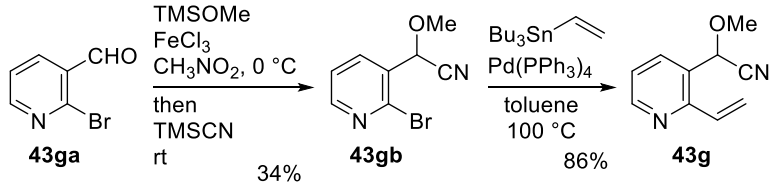
Yellow solid; M.p. 70–73 °C (hexane–Et_2O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91–7.84 (2H, m), 7.65–7.59 (1H, m), 7.55–7.50 (1H, m), 5.95 (1H, s), 3.63 (3H, s), 2.65 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.65, 135.11, 133.97, 132.81, 130.20, 129.37, 127.87, 117.26, 69.48. 58.27, 28.79; IR (ATR) ν 2939, 2833, 2174, 1672, 1576, 1360, 1260, 1092, 973, 770, 588 cm^{-1}; HRMS (FD) calcd for $C_{11}H_{11}NO_2$ (M^+): 189.0790, found: 189.0794.



Ethyl (*E*)-3-(2-(cyano(methoxy)methyl)phenyl)acrylate (43f): To a solution of $Pd(OAc)_2$ (11.2 mg, 0.050 mmol) and triphenylphosphine (26.2 mg, 0.10 mmol) in DMF (14 mL) were added cyanohydrin methyl ether **42** (866 mg, 774 μL, 5 mmol), ethyl acrylate (1.6 mL, 15 mmol), and Et_3N (0.98 mL, 7.0 mmol). The mixture was stirred at 90 °C for 15 h. The reaction mixture was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, hexane–EtOAc = 3:1) afforded

nitrile **43f** (680.0 mg, 2.77 mmol, 55%).

Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (1H, d, *J* = 16.1 Hz), 7.72–7.66 (1H, m), 7.65–7.60 (1H, m), 7.49–7.43 (2H, m), 6.40 (1H, d, *J* = 16.1 Hz), 5.44 (1H, s), 4.29 (2H, q, *J* = 6.9 Hz), 3.58 (3H, s), 1.35 (3H, t, *J* = 6.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.15, 139.72, 133.77, 131.46, 130.31, 130.13, 128.49, 127.52, 122.22, 116.32, 70.10, 60.70, 57.27, 14.19; IR (ATR) ν 2988, 2902, 2041, 1715, 1483, 1366, 1267, 1074, 969, 763 cm^{-1}; HRMS (FD) calcd for $C_{14}H_{15}NO_3$ (M^+): 245.1052, found: 245.1064.



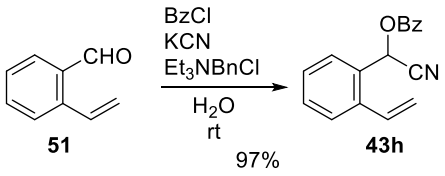
2-(2-Bromopyridin-3-yl)-2-methoxyacetonitrile (43gb): A mixture of methoxytrimethylsilane (1.82 mL, 13.2 mmol), $FeCl_3$ (17.8 mg, 0.11 mmol), and 2-bromonicotinaldehyde (**43ga**) (1.02 g, 5.5 mmol) in nitromethane (2.8 mL) was stirred at 0 °C for 3 h. Trimethylsilyl cyanide (1.82 mL, 13.2 mmol) was then added and the mixture was stirred at room temperature for 24 h. Saturated aqueous sodium bicarbonate (ca. 3 mL) was added to the mixture and the products were extracted with Et_2O. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, hexane–Et_2O = 3:1) afforded cyanohydrin methyl ether **43gb** (424.6 mg, 1.87 mmol, 34%).

Yellow solid; M.p. 55–57°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.44 (1H, d, *J* = 3.5 Hz), 7.99 (1H, d, *J* = 7.5 Hz), 7.40 (1H, dd, *J* = 7.5, 4.6 Hz), 5.36 (1H, s), 3.67 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.96, 141.97, 137.18, 130.67, 123.27, 115.52, 70.82, 58.44; IR (ATR) ν 3006, 2936, 2832, 2158, 1562, 1406, 1301, 1051, 968, 804, 715 cm^{-1}; HRMS (FD) calcd for $C_8H_7BrN_2O$ (M^+): 225.9742, found: 225.9758.

2-Methoxy-2-(2-vinylpyridin-3-yl)acetonitrile (43g): To a mixture of cyanohydrin methyl ether **43gb** (424.6 mg, 1.87 mmol) and tributyl(vinyl)stannane (783 μL, 2.6 mmol) in toluene (5.4 mL) was added $Pd(PPh_3)_4$ (100.5 mg, 0.087 mmol) and the mixture was stirred at 100 °C for 4 h. The mixture was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (10wt% K_2CO_3/SiO_2, hexane–Et_2O = 3:1) afforded nitrile **43g** (280.8 mg, 1.61 mmol, 86%).

Green oil; ^{1}H NMR (500 MHz, $CDCl_3$) 8.65 (1H, dd, *J* = 5.2, 1.8 Hz), 7.92 (1H, dd, *J* = 8.0, 1.7 Hz), 7.28 (1H, dd, *J* = 8.0, 4.6 Hz), 6.97 (1H, dd, *J* = 16.6, 10.9 Hz), 6.46 (1H, dd, *J* = 17.2, 1.8

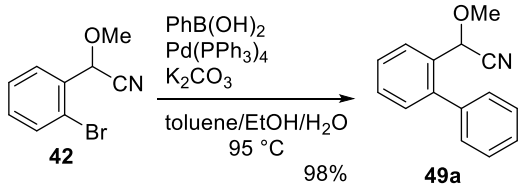
Hz), 5.67 (1H, dd, *J* = 10.9, 1.8 Hz), 5.40 (1H, s), 3.58 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.43, 150.55, 136.03, 131.22, 125.73, 122.60, 122.54, 116.04, 69.46, 57.50; IR (ATR) ν 2932, 2831, 2191, 1561, 1311, 1188, 1065, 970, 926, 798 cm^{-1}; HRMS (FD) calcd for $C_{10}H_{10}N_2O$ (M^+): 174.0793, found: 174.0801.



Cyano(2-vinylphenyl)methyl benzoate (43h): To a mixture of *o*-vinylbenzaldehyde (**51**)[2] (660.8 mg, 5.0 mmol), benzoyl chloride (749 μL, 6.5 mmol), and KCN (488.4 mg, 7.5 mmol) in H_2O (1.5 mL) was added benzyltriethylammonium chloride (34.0 mg, 0.15 mmol) and the reaction mixture was stirred at room temperature for 26 h. Saturated aqueous sodium bicarbonate (ca. 10 mL) was added to the mixture and the products were extracted with Et_2O. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, hexane–EtOAc = 8:1) afforded *O*-benzoyl cyanohydrin **43h** (1.28 g, 4.86 mmol, 97%).

Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (2H, d, *J* = 7.5 Hz), 7.71 (1H, dd, *J* = 7.4, 1.2 Hz), 7.62 (1H, t, *J* = 7.5 Hz), 7.58 (1H, d, *J* = 7.4 Hz), 7.49–7.44 (3H, m), 7.41 (1H, td, *J* = 7.5, 1.2 Hz), 7.07 (1H, dd, *J* = 17.2, 10.9 Hz), 6.82 (1H, s), 5.73 (1H, d, *J* = 17.2 Hz), 5.50 (1H, dd, *J* = 10.9, 1.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.42, 137.53, 134.04, 132.44, 130.68, 129.99, 128.76, 128.58, 128.53, 128.36, 127.94, 127.24, 119.26, 115.99, 61.32; IR (ATR) ν 3066, 2955, 2361, 1728, 1601, 1452, 1240, 1065, 992, 939, 771, 706 cm^{-1}; HRMS (FD) calcd for $C_{17}H_{13}NO_2$ (M^+): 263.0946, found: 263.0949.

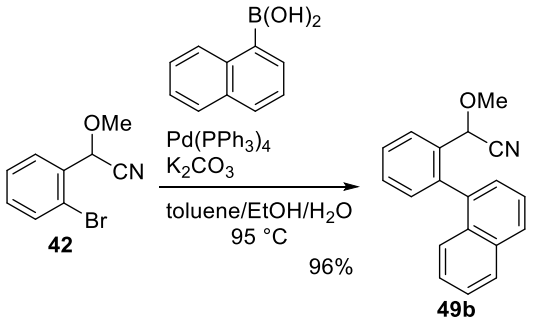
(2) Jagdale, A. R.; Youn, S. W. *Eur. J. Org. Chem.* **2011**, 3904–3910.



2-([1,1'-Biphenyl]-2-yl)-2-methoxyacetonitrile (49a): To a mixture of cyanohydrin methyl ether **42** (1.21 g, 1.08 mL, 7.0 mmol), phenyl boronic acid (938.9 mg, 7.7 mmol), and K_2CO_3

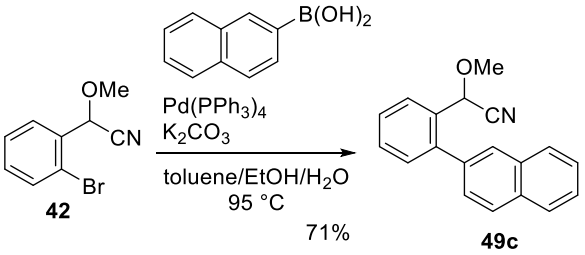
(1.93 g, 14.0 mmol) in toluene–EtOH–H_2O (3:3:1, 23 mL) was added $Pd(PPh_3)_4$ (242.7 mg, 0.21 mmol) and the reaction mixture was stirred at 95 °C for 4 h. Water (15 mL) was added to the mixture and the products were extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, hexane–Et_2O = 10:1) afforded nitrile **49a** (1.54 g, 6.88 mmol, 98%).

White solid; M.p. 43–46 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82–7.76 (1H, m), 7.52–7.40 (5H, m), 7.38–7.31 (3H, m), 5.00 (1H, s), 3.44 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.96, 139.23, 131.27, 130.38, 129.80, 129.13, 128.48, 128.27, 128.21, 127.93, 117.55, 69.87, 57.38; IR (ATR) ν 3057, 2927, 2824, 2337, 1478, 1186, 1073, 930, 762, 701, 507 cm^{-1}; HRMS (FD) calcd for $C_{15}H_{13}NO$ (M^+): 223.0997, found: 223.1005.

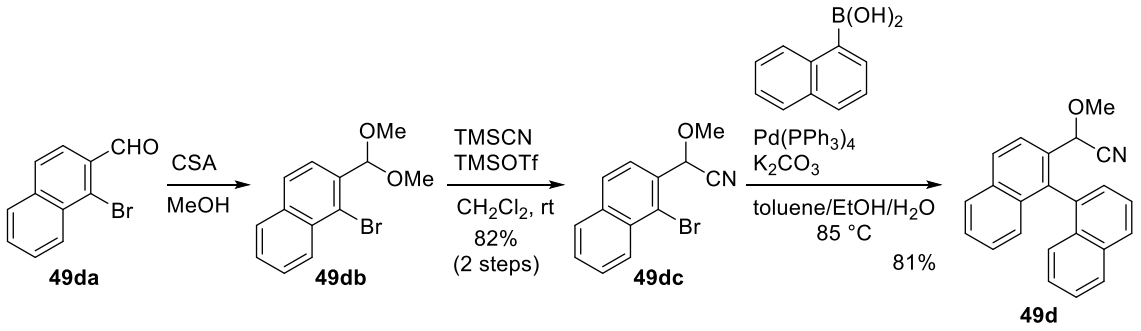


2-Methoxy-2-(2-(naphthalen-1-yl)phenyl)acetonitrile (49b): To a mixture of cyanohydrin methyl ether **42** (346 mg, 310 μL, 2.0 mmol), 1-naphthalene boronic acid (378.4 mg, 2.2 mmol), and K_2CO_3 (552.8 mg, 4.0 mmol) in toluene–EtOH–H_2O (3:3:1, 6.7 mL) was added $Pd(PPh_3)_4$ (69.3 mg, 0.060 mmol) and the reaction mixture was stirred at 95 °C for 5 h. Brine (5 mL) was added to the mixture and the products were extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, hexane–Et_2O = 10:1) afforded nitrile **49b** (524.1 mg, 1.92 mmol, 96%) as a 50:50 mixture of atropisomers.

Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96–7.91 (2H, m), 7.87 (0.5H, d, *J* = 7.5 Hz), 7.83 (0.5H, d, *J* = 8.0 Hz), 7.61–7.48 (4H, m), 7.47–7.33 (4H, m), 4.68 (0.5H, s), 4.66 (0.5H, s), 3.25 (1.5H, s), 3.10 (1.5H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.01, 139.44, 136.40, 136.22, 133.50, 133.43, 132.95, 132.60, 132.04, 131.88, 131.15, 131.02, 129.79, 129.52, 128.66, 128.53, 128.33, 128.25, 127.17, 127.52, 127.45, 127.43, 126.83, 126.29, 126.24, 126.14, 125.73, 125.48, 125.29, 125.00, 117.53, 117.44, 69.87, 69.63, 57,75, 57.44; IR (ATR) ν 3058, 2928, 2826, 2027, 1448, 1394, 1329, 1271, 1192, 1081, 967, 779 cm^{-1}; HRMS (FD) calcd for $C_{19}H_{15}NO$ (M^+): 273.1154, found: 273.1160.



2-Methoxy-2-(2-(naphthalen-2-yl)phenyl)acetonitrile (49c): To a mixture of cyanohydrin methyl ether **42** (310 μL, 2.0 mmol), 2-naphthalene boronic acid (378.4 mg, 2.2 mmol), and K_2CO_3 (552.8 mg, 4.00 mmol) in toluene–EtOH–H_2O (3:3:1, 6.7 mL) was added $Pd(PPh_3)_4$ (69.3 mg, 0.0600 mmol) and the reaction mixture was stirred at 95 °C for 6 h. Brine (5 mL) was added to the mixture and the products were extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, hexane–Et_2O = 20:1) afforded nitrile **49c** (388.8 mg, 1.42 mmol, 71%). White solid; M.p. 43–45 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93–7.86 (3H, m), 7.83 (2H, s), 7.60–7.50 (4H, m), 7.49 (1H, d, *J* = 8.0 Hz), 7.46–7.41 (1H, m), 5.04 (1H, s), 3.45 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.88, 136.60, 133.03, 132.63, 131.50, 130.57, 129.83, 128.35, 128.29, 128.20, 128.18, 128.06, 127.72, 127.05, 126.70, 126.51, 117.56, 69.96, 57.47; IR (ATR) ν 3053, 2931, 2829, 2340, 1448, 1327, 1185, 1072, 957, 763, 478 cm^{-1}; HRMS (FD) calcd for $C_{19}H_{15}NO$ (M^+): 273.1154, found: 273.1147.



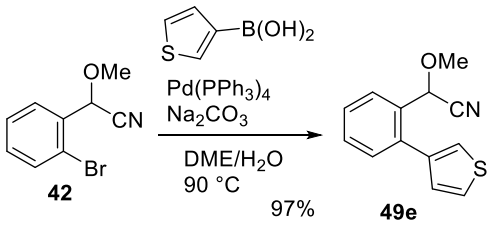
2-(1-Bromonaphthalen-2-yl)-2-methoxyacetonitrile (49db): To a solution of 1-bromo-2-naphthaldehyde (**49da**) (278.0 mg, 1.18 mmol) in MeOH (4 mL) was added (+)-10-camphorsulfonic acid (27.4 mg, 0.118 mmol) and the reaction mixture was stirred at room temperature for 3 h. Saturated aqueous sodium bicarbonate (2 mL) was added to the mixture and the products were extracted with Et_2O. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude dimethyl acetal **49db** (335.2 mg) was used for the next step without further purification.

To a mixture of the above crude dimethyl acetal **49db** (335.2 mg, as 1.18 mmol) and TMSCN (221 μL, 1.77 mmol) in CH_2Cl_2 (6 mL) was added TMSOTf (21 μL, 0.118 mmol) and the reaction mixture was stirred at room temperature for 18 h. Saturated aqueous sodium bicarbonate (2 mL) was added to the mixture and the products were extracted with Et_2O. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, hexane–EtOAc = 4:1) afforded cyanohydrin methyl ether **46dc** (268.1 mg, 0.971 mmol, 82% for 2 steps).

Brown solid; M.p. 55–57 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.33 (1H, d, *J* = 8.6 Hz), 7.90 (1H, d, *J* = 8.6 Hz), 7.86 (1H, d, *J* = 8.1 Hz), 7.76 (1H, d, *J* = 8.6 Hz), 7.65 (1H, t, *J* = 6.9 Hz), 7.61–7.57 (1H, m), 5.77 (1H, s), 3.67 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.44, 131.64, 130.59, 128.47, 128.03, 127.88, 127.52, 127.27, 124.21, 123.61, 116.48, 72.26, 57.92; IR (ATR) ν 2929, 2832, 2336, 1503, 1458, 1326, 1104, 967, 815, 764, 660 cm^{-1}; HRMS (FD) calcd for $C_{13}H_{10}BrNO$ (M^+): 274.9946, found: 274.9927.

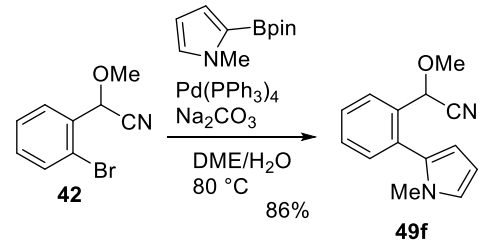
2-([1,1'-Binaphthalen]-2-yl)-2-methoxyacetonitrile (49d): To a mixture of cyanohydrin methyl ether **49dc** (263.2 mg, 0.953 mmol), 1-naphthalene boronic acid (180.6 mg, 1.05 mmol), and K_2CO_3 (264.0 mg, 1.91 mmol) in toluene–EtOH–H_2O (3:3:1, 3.2 mL) was added $Pd(PPh_3)_4$ (33.5 mg, 0.0290 mmol) and the reaction mixture was stirred at 85 °C for 5 h. Brine (5 mL) was added to the mixture and the products were extracted with Et_2O. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, hexane–EtOAc = 10:1) afforded nitrile **49d** (248.4 mg, 0.768 mmol, 81%) as a 63:37 mixture of atropisomers.

Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (1H, d, *J* = 8.6 Hz), 8.03 (1H, d, *J* = 8.6 Hz), 8.01–7.88 (3H, m), 7.69–7.60 (1H, m), 7.56–7.41 (3H, m), 7.37–7.26 (2H, m), 7.18 (2H, t, *J* = 7.5 Hz), 4.70 (1H, s), 3.30 (2H, s), 3.12 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.79, 137.15, 134.01, 133.97, 133.76, 133.67, 133.51, 133.42, 132.79, 132.67, 132.29, 130.35, 129.99, 129.25, 129.20, 128.81, 128.79, 128.62, 128.31, 128.20, 127.97, 127.20, 127.04, 127.00, 126.95, 126.91, 126.75, 126.73, 126.44, 126.41, 126.27, 125.81, 125.68, 125.50, 125.10, 124.26, 123.59, 117.54, 117.44, 70.00, 69.97, 57.72, 57.53; IR (ATR) ν 3058, 2929, 2826, 1593, 1507, 1457, 1370, 1337, 1264, 1189, 1081, 957, 907, 782, 729 cm^{-1}; HRMS (FD) calcd for $C_{23}H_{17}NO$ (M^+): 323.1310, found: 323.1317.



2-Methoxy-2-(2-(thiophen-3-yl)phenyl)acetonitrile (49e): To a mixture of cyanohydrin methyl ether **42** (173 mg, 155 μL, 1.00 mmol), 3-thiophene boronic acid (160.0 mg, 1.25 mmol), and Na_2CO_3 (256.5 mg, 2.42 mmol) in DME–H_2O (3:2, 3 mL) was added $Pd(PPh_3)_4$ (57.8 mg, 0.050 mmol) and the reaction mixture was stirred at 90 °C for 3 h. H_2O (2 mL) was added to the mixture and the products were extracted with Et_2O. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, hexane–EtOAc = 8:1) afforded nitrile **49e** (223.1 mg, 0.973 mmol, 97%).

Yellow solid; M.p. 63–64 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81–7.76 (1H, m), 7.48–7.43 (3H, m), 7.42–7.36 (1H, m), 7.39–7.32 (1H, m), 7.16 (1H, dd, *J* = 5.2, 1.1 Hz), 5.12 (1H, s), 3.50 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.35, 136.77, 131.23, 130.39, 129.88, 128.73, 128.48, 128.15, 126.14, 123.86, 117.37, 70.00, 57.14; IR (ATR) ν 3103, 2950, 2827, 2337, 1450, 1181, 1068, 969, 806, 763 cm^{-1}; HRMS (FD) calcd for $C_{13}H_{11}NOS$ (M^+): 229.0561, found: 229.0550.

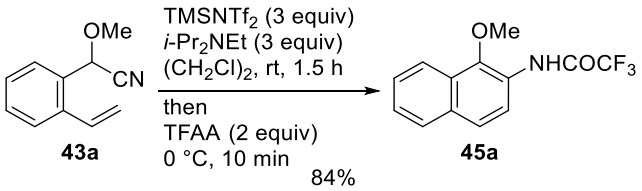


2-Methoxy-2-(2-(1-methyl-1H-pyrrol-2-yl)phenyl)acetonitrile (49f): To a mixture of cyanohydrin methyl ether **42** (866 mg, 774 μL, 5.00 mmol), 1-methyl-2-pyrroleboronic acid pinacol ester (1.35 g, 6.5 mmol), and Na_2CO_3 (1.06 g, 10 mmol) in DME–H_2O (3:2, 47 mL) was added $Pd(PPh_3)_4$ (346.7 mg, 0.300 mmol) and the reaction mixture was stirred at 80 °C for 24 h. H_2O (2 mL) was added to the mixture and the products were extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, hexane–EtOAc = 8:1) afforded nitrile **49f** (972.1 mg, 4.30 mmol, 86%).

Red oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80–7.75 (1H, m), 7.52–7.44 (2H, m), 7.35–7.30 (1H, m), 7.68–7.64 (1H, m), 6.24–6.21 (1H, m), 6.17–6.14 (1H, m), 5.13 (1H, s), 3.45 (3H, s), 3.44

(3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.86, 132.70, 131.44, 129.39, 129.34, 128.67, 127.95, 123.13, 110.08, 107.63, 69.90, 57.57, 34.31; IR (ATR) ν 2934, 2826, 2356, 1734, 1480, 1309, 1242, 1188, 1078, 970, 927, 764, 714 cm^{-1}; HRMS (FD) calcd for $C_{14}H_{14}N_2O$ (M^+): 226.1106, found: 226.1114.

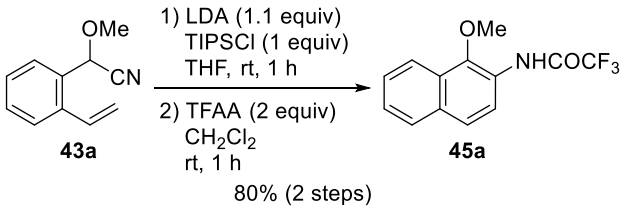
General Procedure for the Cyclization with $TMSNTf_2$–*i*-Pr_2NEt System (method A)



$TMSNTf_2$ (206 μL, 0.9 mmol, 3 equiv) was added to a solution of nitrile **43a** (52.0 mg, 50 μL, 0.300 mmol, 1 equiv) and *i*-Pr_2NEt (147 μL, 0.900 mmol, 3 equiv) in $(CH_2Cl)_2$ (1.5 mL), and the mixture was stirred at room temperature for 1.5 h, at which point the consumption of starting material **43a** was complete (as determined by TLC analysis, hexane–EtOAc = 4:1). After cooled to 0 °C, TFAA (85 μL, 0.600 mmol, 2 equiv) was added, and the mixture was stirred at 0 °C for 10 min. The reaction was quenched by slow addition of saturated aqueous $NaHCO_3$ (3 mL), and the resulting mixture was extracted with Et_2O (2 mL×2). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, hexane–EtOAc = 6:1) to give aryl amine **45a** (67.8 mg, 0.252 mmol, 84%).

2,2,2-Trifluoro-*N*-(1-methoxynaphthalen-2-yl)acetamide1-Methoxynaphthalen-2-amine (45a): White solid; M.p. 119–122 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.66 (1H, br-s), 8.41 (1H, d, *J* = 9.2 Hz), 8.04 (1H, d, *J* = 8.1 Hz), 7.87 (1H, d, *J* = 8.0 Hz), 7.70 (1H, d, *J* = 9.2 Hz), 7.59–7.54 (1H, m), 7.53–7.48 (1H, m), 4.00 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.66 [q, ^2J(C,F) = 37.0 Hz], 144.46, 132.42, 128.32, 126.83, 126.76, 126.03, 125.24, 125.02, 121.40, 119.03, 115.77 [q, ^1J(C,F) = 287.3 Hz], 62.00; IR (ATR) ν 3271, 2355, 1709, 1541, 1375, 1340, 1257, 1153, 1087, 991, 915, 814 cm^{-1}; HRMS (FD) calcd for $C_{13}H_{10}F_3NO_2$ (M^+): 269.0664, found: 269.0654.

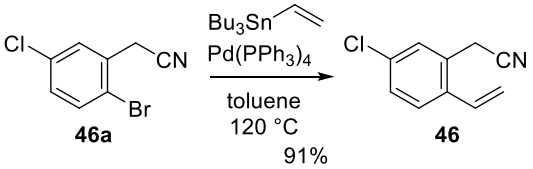
General Procedure for the Cyclization with TIPSCl–LDA System (method B)



43a **45a**

To a solution of *i*-Pr_2NH (49 μL, 0.348 mmol, 1.16 equiv) in THF (1.5 mL) was added *n*-BuLi (2.65 M in hexane, 125 μL, 0.330 mmol, 1.10 equiv) at –78 °C, and the mixture was stirred at this temperature for 15 min. To the mixture was added nitrile **43a** (52.0 mg, 50 μL, 0.30 mmol, 1 equiv) at –78 °C, and the reaction mixture was stirred at this temperature for 1 h. TIPSCl (64 μL, 0.300 mmol, 1 equiv) was then added and the mixture was stirred at –78 °C for 5 min. After warmed to room temperature, the mixture was stirred at this temperature for 1 h. The reaction was quenched by addition of saturated aqueous NH_4Cl (3 mL), and the resulting mixture was extracted with Et_2O (2 mL×2). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The crude aromatic amine (116.2 mg) was used for the next step without further purification.

To a mixture of the above crude aromatic amine (116.2 mg, as 0.300 mmol) in CH_2Cl_2 (1.5 mL) was added TFAA (85 μL, 0.600 mmol, 2 equiv) at 0 °C and the reaction mixture was stirred at room temperature for 1 h. The reaction was quenched by slow addition of saturated aqueous $NaHCO_3$ (3 mL), and the resultant solution was extracted with Et_2O (2 mL×2). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, hexane–EtOAc = 6:1) to give aryl amine **45a** (64.3 mg, 0.239 mmol, 80% for 2 steps). ^1H and ^{13}C NMR spectra of this product were identical with those prepared by method A as mentioned above.



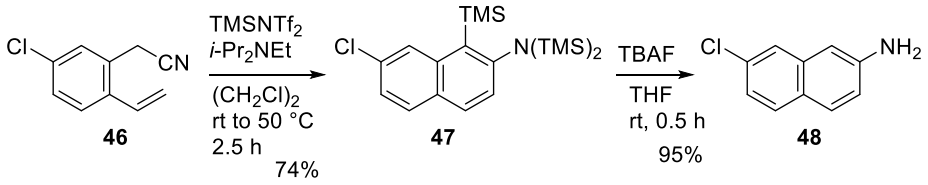
46a **46**

2-(5-Chloro-2-vinylphenyl)acetonitrile (46): To a mixture of aryl bromide **46a** (491.5 mg, 2.13 mmol)[3] and tributyl(vinyl)stannane (748 μL, 2.56 mmol) in toluene (5.3 mL) was added $Pd(PPh_3)_4$ (98.4 mg, 0.0852 mmol) and the mixture was stirred at 120 °C for 3 h. The reaction mixture was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (10wt% K_2CO_3/SiO_2, hexane–Et_2O = 4:1) afforded nitrile **46** (345.8 mg, 1.95 mmol, 91%).

Colorless oil; ^1H NMR (500 MHz, $CDCl_3$) δ 7.49 (1H, d, *J* = 8.0 Hz), 7.40 (1H, d, *J* = 1.8 Hz),

7.31 (1H, dd, *J* = 8.6, 1.8 Hz), 6.78 (1H, dd, *J* = 17.2, 10.9 Hz), 5.69 (1H, d, *J* = 17.2 Hz), 5.47 (1H, d, *J* = 11.5 Hz), 3.73 (2H, s); ^{13}C NMR (125 MHz, CD_3OD) δ 136.92, 134.87, 133.36, 131.45, 129.92, 129.61, 128.97, 118.73, 118.69, 21.51; IR (ATR) ν 2933, 2363, 2253, 1734, 1594, 1482, 1415, 1220, 1117, 984, 924, 865, 827, 882 cm^{-1}; HRMS (FD) calcd for $C_{10}H_8ClN$ (M^+): 177.0345, found: 177.0339.

(3) Hsieh, J.; Cheng, A.; Fu, J.; Kang, T. *Org. Biol. Chem.* **2012**, *10*, 6404–6409.



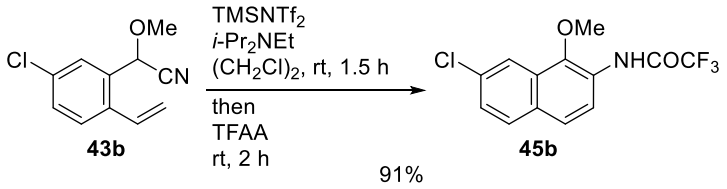
***N*-(7-Chloro-1-(trimethylsilyl)naphthalen-2-yl)-1,1,1-trimethyl-*N*-(trimethylsilyl)silanamine (47):** To a mixture of nitrile **46** (22.4 mg, 0.126 mmol) and *i*-Pr_2NEt (82 μL, 0.504 mmol) in $(CH_2Cl)_2$ (0.63 mL) was added $TMSNTf_2$ (116 μL, 0.504 mmol) and the reaction mixture was stirred at room temperature for 1 h and then stirred at 50 °C for 1.5 h. Saturated aqueous sodium bicarbonate (0.1 mL) was added to the mixture and the products were extracted with Et_2O. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, hexane–Et_2O = 15:1) afforded silyl amine **47** (36.7 mg, 0.0931 mmol, 74%).

Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (1H, s), 7.71 (1H, d, *J* = 9.2 Hz), 7.66 (1H, d, *J* = 8.6 Hz), 7.32 (1H, d, *J* = 8.6 Hz), 7.07 (1H, d, *J* = 8.6 Hz), 0.53 (9H, s), 0.10 (18H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.93, 138.98, 133.84, 131.15, 130.91, 130.07, 129.59, 129.40, 127.24, 124.66, 4.15, 2.30; IR (ATR) ν 2956, 1608, 1495, 1341, 1249, 1206, 1171, 1143, 1091, 1001, 928, 819, 754, 668 cm^{-1}; HRMS (FD) calcd for $C_{19}H_{32}ClNSi_3$ (M^+): 393.1531, found: 393.1543.

7-Chloronaphthalen-2-amine (48): To a solution of silyl amine **47** (36.7 mg, 0.0931 mmol) in THF (0.47 mL) was added TBAF (1.0 M in THF, 279 μL, 0.279 mmol), and the reaction mixture was stirred at room temperature for 30 min. H_2O (0.5 mL) was added to the mixture and the products were extracted with Et_2O. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, hexane–EtOAc = 4:1) afforded free amine **48** (15.7 mg, 0.0884 mmol, 95%).

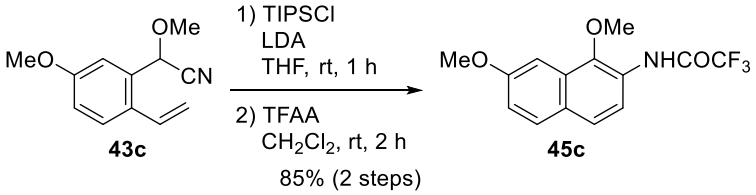
White solid; M.p. 116–120 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (1H, d, *J* = 8.0 Hz), 7.61

(1H, d, *J* = 8.1 Hz), 7.56 (1H, d, *J* = 1.7 Hz), 7.15 (1H, dd, *J* = 8.6, 2.3 Hz), 6.92 (1H, dd, *J* = 8.6, 2.3 Hz), 6.88 (1H, d, *J* = 1.7 Hz), 3.91 (2H, br-s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.04, 135.65, 132.12, 129.23, 129.14, 126.03, 124.39, 123.18, 118.29, 107.46; IR (ATR) ν 3445, 3335, 2925, 1631, 1505, 1387, 1257, 1073, 892, 831 cm^{-1}; HRMS (FD) calcd for $C_{10}H_8ClN$ (M^+): 177.0345, found: 177.0337.



***N*-(7-Chloro-1-methoxynaphthalen-2-yl)-2,2,2-trifluoroacetamide (45b):** Prepared by using the general procedure above (method A) from 2-(5-chloro-2-vinylphenyl)-2-methoxyacetonitrile (**43b**) (62.3 mg, 0.300 mmol) except for the reaction conditions of amidation (room temperature for 2 h). Purification by flash column chromatography (SiO_2, hexane–Et_2O = 15:1) afforded aryl amine **45b** (82.8 mg, 0.273 mmol, 91%).

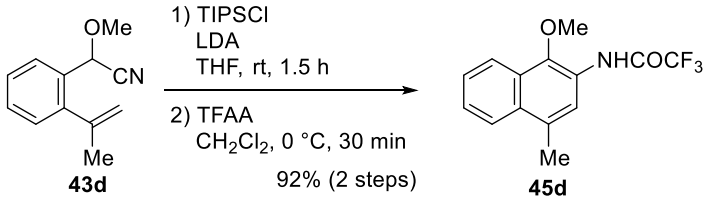
White powder; M.p. 130–135 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.63 (1H, br-s), 8.42 (1H, d, *J* = 9.2 Hz), 8.00 (1H, d, *J* = 2.3 Hz), 7.80 (1H, d, *J* = 9.2 Hz), 7.68 (1H, d, *J* = 9.2 Hz), 7.43 (1H, dd, *J* = 9.2, 1.7 Hz), 3.99 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.73 [q, ^2J(C,F) = 37.0 Hz], 143.57, 133.08, 130.48, 129.98, 127.59, 127.02, 126.28, 124.95, 120.43, 119.25, 115.66 [q, ^1J(C,F) = 287.4 Hz], 62.15; IR (ATR) ν 3409, 2941, 1722, 1529, 1504, 1270, 1148, 970, 830, 653 cm^{-1}; HRMS (FD) calcd for $C_{13}H_9ClF_3NO_2$ (M^+): 303.0274, found: 303.0269.



***N*-(1,7-Dimethoxynaphthalen-2-yl)-2,2,2-trifluoroacetamide (45c):** Prepared by using the general procedure above (method B) from 2-methoxy-2-(5-methoxy-2-vinylphenyl)acetonitrile (**43c**) (40.6 mg, 0.200 mmol) except for the reaction conditions for amidation (TFAA (28 μL, 0.20 mmol, 1 equiv), room temperature for 2 h). Purification by flash column chromatography (SiO_2, hexane–Et_2O = 10:1) afforded aryl amine **45c** (51.5 mg, 0.171 mmol, 85% for 2 steps).

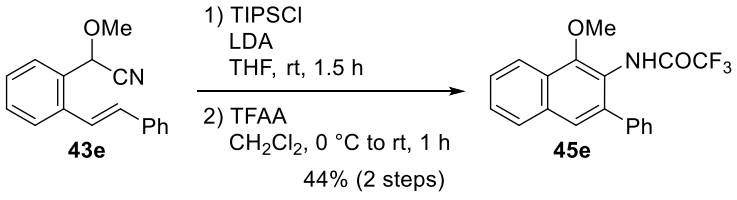
White solid; M.p. 71–73 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.64 (1H, br-s), 8.25 (1H, d, *J* = 8.6

Hz), 7.75 (1H, d, *J* = 8.2 Hz), 7.61 (1H, d, *J* = 8.6 Hz), 7.27 (1H, d, *J* = 2.3 Hz), 7.15 (1H, dd, *J* = 9.2, 2.3 Hz), 3.98 (3H, s), 3.97 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.54, 154.61 [q, ^2J(C,F) = 37.0 Hz], 143.50, 130.00, 128.02, 127.96, 125.84, 124.80, 118.89, 116.49, 115.77 [q, ^1J(C,F) = 287.3 Hz], 99.49 61.40, 55.38; IR (ATR) ν 3284, 1710, 1541, 1074, 1031, 979, 833, 771, 683 cm^{-1}; HRMS (FD) calcd for $C_{14}H_{12}F_3NO_3$ (M^+): 299.0769, found: 299.0776.



2,2,2-Trifluoro-*N*-(1-methoxy-4-methylnaphthalen-2-yl)acetamide (45d): Prepared by using the general procedure above (method B) from 2-methoxy-2-(2-(prop-1-en-2-yl)phenyl)acetonitrile (**43d**) (44.9 mg, 0.240 mmol) except for the reaction time of cyclization (1.5 h) and the reaction conditions of amidation (0 °C for 30 min). Purification by flash column chromatography (SiO_2, hexane–Et_2O = 10:1) afforded aryl amine **45d** (62.5 mg, 0.221 mmol, 92% for 2 steps).

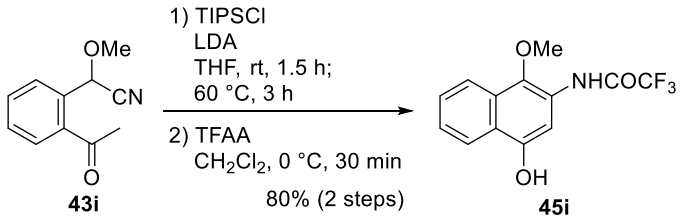
White solid; M.p. 102–104 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.60 (1H, br-s), 8.25 (1H, s), 8.05 (1H, d, *J* = 8.0 Hz), 7.99 (1H, d, *J* = 8.6 Hz), 7.60–7.51 (2H, m), 3.97 (3H, s), 2.69 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.12 [q, ^2J(C,F) = 37.0 Hz], 143.02, 131.91, 131.42, 126.89, 126.47, 125.86, 124.83, 124.61, 121.91, 119.38, 115.80 [q, ^1J(C,F) = 286.2 Hz], 62.05, 19.24; IR (ATR) ν 3202, 1537, 1335, 1244, 1155, 1102, 926, 768 cm^{-1}; HRMS (FD) calcd for $C_{14}H_{12}F_3NO_2$ (M^+):283.0820, found: 283.0824.



2,2,2-Trifluoro-*N*-(1-methoxy-3-phenylnaphthalen-2-yl)acetamide (45e): Prepared by using the general procedure above (method B) from (*E*)-2-methoxy-2-(2-styrylphenyl)acetonitrile (**43e**) (93.6 mg, 0.375 mmol) except for the reaction time of cyclization (1.5 h) and the reaction conditions of amidation (0 °C for 30 min then room temperature for 30 min). Purification by flash column chromatography (SiO_2, hexane–EtOAc = 15:1) afforded aryl amine **45e** (56.8 mg,

0.164 mmol, 44% for 2 steps).

White solid; M.p. 160–175 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17–8.12 (1H, m), 7.90–7.85 (1H, m), 7.79 (1H, s), 7.66 (1H, s), 7.61–7.55 (2H, m), 7.44–7.34 (5H, m), 3.96 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.90 [q, ^{2}J(C,F) = 37.0 Hz], 151.91, 138.10, 137.86, 134.06, 128.55, 128.44, 128.25, 127.84, 127.41, 127.15, 126.60, 125.53, 122.30, 121.16, 115.81 [q, ^{1}J(C,F) = 287.3 Hz], 62.12; IR (ATR) ν 3229, 3057, 2980, 1708, 1547, 1375, 1262, 752, 696 cm^{-1}; HRMS (FD) calcd for $C_{19}H_{14}F_3NO_2$ (M^+): 345.0977, found: 345.0985.

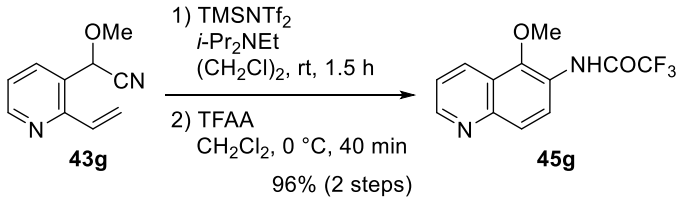


2,2,2-Trifluoro-*N*-(4-hydroxy-1-methoxynaphthalen-2-yl)acetamide (45i): To a solution of *i*-Pr_2NH (93 μL, 0.66 mmol, 2.2 equiv) in THF (1.5 mL) was added *n*-BuLi (2.65 M in hexane, 238 μL, 0.63 mmol, 2.1 equiv) at –78 °C, and the mixture was stirred at this temperature for 15 min. Nitrile **43i** (56.8 mg, 0.300 mmol) in THF (0.5 mL) was then added, and the mixture was stirred at –78 °C for 1 h. After addition of TIPSCl (127 μL, 0.90 mmol, 2 equiv) and stirred at –78 °C for 5 min, the mixture was allowed to warm to room temperature. The mixture was stirred at room temperature for 1.5 h and then at 60 °C for 3 h. The reaction was quenched by addition of saturated aqueous NH_4Cl (3 mL), and the resulting mixture was extracted with Et_2O (2 mL×2). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The crude aromatic amine (132.8 mg) was used for the next step without further purification.

To a mixture of the above crude aromatic amine (132.8 mg, as 0.300 mmol) in CH_2Cl_2 (1.5 mL) was added TFAA (127 μL, 0.900 mmol, 3 equiv), and the reaction mixture was stirred at room temperature for 30 min. The reaction was quenched by slow addition of saturated aqueous $NaHCO_3$ (3 mL), and the resulting mixture was extracted with Et_2O (2 mL×2). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, hexane–Et_2O = 5:1) to give aryl amine **45i** (68.4 mg, 0.240 mmol, 80% for 2 steps).

White solid; M.p. 164–167 °C; ^{1}H NMR (500 MHz, CD_3CN) δ 8.99 (1H, br-s), 8.14 (1H, d, *J* = 8.6 Hz), 8.01 (1H, d, *J* = 8.0 Hz), 7.80 (1H, br-s), 7.59–7.93 (1H, m), 7.54 (1H, s), 7.51–7.45 (1H, m), 3.86 (3H, s); ^{13}C NMR (125 MHz, CD_3CN) δ 155.98 [q, ^{2}J(C,F) = 37.0 Hz], 150.23, 140.54, 128.88, 128.21, 126.25, 125.57, 124.67, 123.46, 122.48, 117.97 [q, ^{1}J(C,F) = 285.0 Hz],

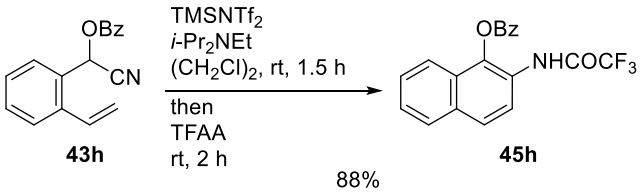
103.88, 62.71; IR (ATR) ν 3332, 2957, 1707, 1594, 1542, 1441, 1388, 1312, 1260, 1146, 1075, 990, 960, 909, 848, 763, 650 cm^{-1}; HRMS (FD) calcd for $C_{13}H_{10}F_3NO_3$ (M^+): 285.0613, found: 285.0621.



2,2,2-Trifluoro-*N*-(5-methoxyquinolin-6-yl)acetamide (45g): $TMSNTf_2$ (206 μL, 0.9 mmol, 3equiv) was added to a solution of nitrile **43g** (52.3 mg, 0.300 mmol, 1 equiv) and *i*-Pr_2NEt (147 μL, 0.900 mmol, 3 equiv) in $(CH_2Cl)_2$ (1.5 mL), and the mixture was stirred at room temperature for 1.5 h, at which point the consumption of starting material **43g** was complete (as determined by TLC analysis, hexane–EtOAc = 1:1). The reaction was quenched by slow addition of saturated aqueous $NaHCO_3$ (3 mL), and the resulting mixture was extracted with EtOAc (2 mL×2). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The crude aromatic amine (325.4 mg) was used for the next step without further purification.

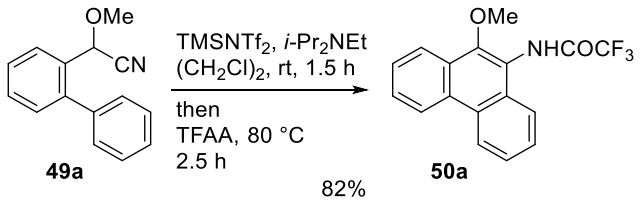
TFAA (42 μL, 0.300 mmol, 1 equiv) was added to a solution of the above crude aromatic amine (325.4 mg, as 0.300 mmol) in CH_2Cl_2 (1.5 mL), and the mixture was stirred at 0 °C for 40 min. The reaction was quenched by slow addition of saturated aqueous $NaHCO_3$ (3 mL), and the resulting mixture was extracted with Et_2O (2 mL×2). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, hexane–EtOAc = 1:1) to give aryl amine **45g** (78.0 mg, 0.289 mmol, 96% for 2 steps).

Green solid; M.p. 164–177 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.94 (1H, dd, *J* = 4.3, 1.4 Hz), 8.68 (1H, dd, *J* = 9.2, 2.9 Hz), 8.60 (1H, br-s), 8.41 (1H, d, *J* = 8.6 Hz), 8.02 (1H, d, *J* = 9.8 Hz), 7.51 (1H, dd, *J* = 8.3, 4.3 Hz), 4.01 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.85 [q, ^2J(C,F) = 38.2 Hz], 150.14, 146.27, 144.21, 130.32, 126.21, 125.74, 122.86, 122.32, 121.54, 115.61 [q, ^1J(C,F) = 287.4 Hz]; IR (ATR) ν 3315, 2925, 1711, 1542, 1323, 1265, 1153, 1075, 831, 812, 663 cm^{-1}; HRMS (FD) calcd for $C_{12}H_9F_3N_2O_2$ (M^+): 270.0616, found: 270.0595.



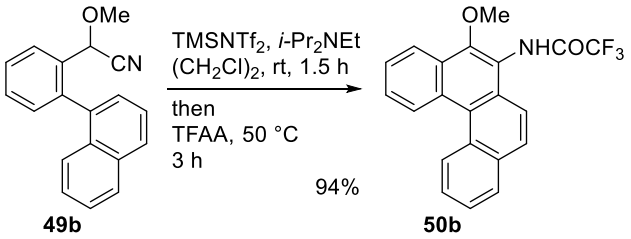
2-(2,2,2-Trifluoroacetamido)naphthalen-1-yl benzoate (45h): Prepared by using the general procedure above (method A) from cyano(2-vinylphenyl)methyl benzoate (**43h**) (79.0 mg, 0.300 mmol) except for the reaction time of amidation (2 h). Purification by flash column chromatography (SiO_2, hexane–EtOAc = 4:1) afforded aryl amine **45h** (94.9 mg, 0.264 mmol, 88%).

White solid; M.p. 182–185 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.36 (2H, d, *J* = 6.9 Hz), 8.20 (1H, br-s), 8.10 (1H, d, *J* = 9.2 Hz), 7.94–7.90 (1H, m), 7.88 (2H, d, *J* = 9.2 Hz), 7.77 (1H, t, *J* = 7.7 Hz), 7.63 (2H, t, *J* = 7.7 Hz), 7.68–7.53 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.50, 155.21 [q, ^2J(C,F) = 38.2 Hz], 137.85, 134.71, 132.77, 130.55, 129.09, 128.11, 127.67, 127.43, 127.10, 126.92, 126.81, 124.21, 121.45, 121.28, 115.62 [q, ^1J(C,F) = 287.3 Hz]; IR (ATR) ν 3237, 1739, 1710, 1544, 1245, 1158, 1085, 1047, 1021, 908, 806, 706 cm^{-1}; HRMS (FD) calcd for $C_{19}H_{12}F_3NO_3$ (M^+): 359.0769, found: 359.0785.



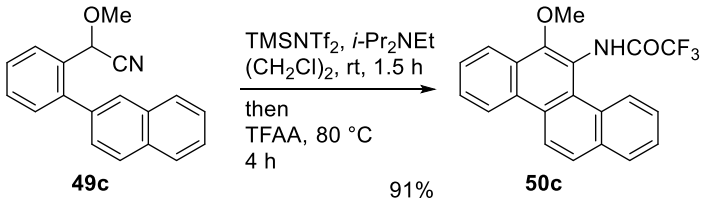
2,2,2-Trifluoro-*N*-(10-methoxyphenanthren-9-yl)acetamide (50a): Prepared by using the general procedure above (method A) from 2-([1,1'-biphenyl]-2-yl)-2-methoxyacetonitrile (**49a**) (67.0 mg, 0.300 mmol) except for the reaction conditions of amidation (80 °C for 2.5 h). Purification by flash column chromatography (SiO_2, hexane–EtOAc = 6:1) afforded aryl amine **50a** (78.9 mg, 0.247 mmol, 82%).

White solid; M.p. 185–187 °C; ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ 10.33 (1H, br-s), 8.88 (1H, d, *J* = 8.0 Hz), 8.88–8.82 (1H, m), 8.27 (1H, d, *J* = 8.1 Hz), 7.98–7.93 (1H, m), 7.82–7.77 (1H, m), 7.77–7.72 (1H, m), 7.72–7.67 (2H, m), 4.01 (3H, s); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 156.47 [q, ^2J(C,F) = 37.0 Hz], 15.054, 130.96, 129.25, 128.31, 128.03, 127.94, 127.75, 127.11, 126.73, 123.69, 123.57, 123.10, 119.67, 116.48 [q, ^1J(C,F) = 287.3 Hz], 61.79; IR (ATR) ν 3240, 1543, 1450, 1325, 1204, 1156, 1105, 1029, 969, 936, 756 cm^{-1}; HRMS (FD) calcd for $C_{17}H_{12}F_3NO_2$ (M^+): 319.0820, found: 319.0820.



2,2,2-Trifluoro-*N*-(5-methoxybenzo[*c*]phenanthren-6-yl)acetamide (50b): Prepared by using the general procedure above (method A) from 2-methoxy-2-(2-(naphthalen-1-yl)phenyl)acetonitrile (**49b**) (68.0 mg, 0.249 mmol) except for the reaction conditions of amidation (TFAA (140 μL, 0.996 mmol, 4 equiv), 50 °C for 3 h). Purification by flash column chromatography (SiO_2, hexane–EtOAc = 6:1) afforded aryl amine **50b** (86.3 mg, 0.234 mmol, 94%).

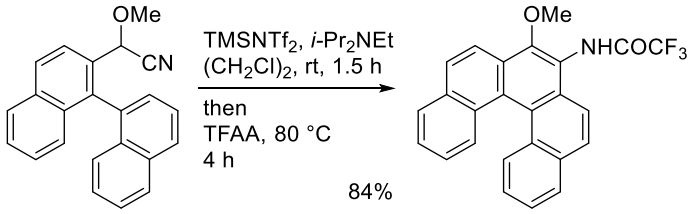
White solid; M.p. 160–173 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.10 (1H, d, *J* = 8.6 Hz), 9.02 (1H, d, *J* = 8.6 Hz), 8.34 (1H, d, *J* = 8.1 Hz), 8.07 (1H, br-s), 8.03 (1H, d, *J* = 7.4 Hz), 7.95 (1H, d, *J* = 9.2 Hz), 7.78–7.67 (4H, m), 7.66–7.62 (1H, m), 4.02 (3H, s); ^{13}C NMR (125 MHz, $(CD_3)_2CO$) δ 157.62 [q, ^2J(C,F) = 37.0 Hz], 152.06, 133.82, 131.75, 130.56, 129.38, 129.33, 129.18, 129.00, 128.86, 128.43, 128.18, 127.54, 127.43, 126.96, 125.83, 123.72, 121.27, 120.57, 117.45 [q, ^1J(C,F) = 286.2 Hz], 62.27; IR (ATR) ν 3257, 2933, 1713, 1539, 1219, 1151, 1122, 1103, 1072 cm^{-1}; HRMS (FD) calcd for $C_{21}H_{14}F_3NO_2$ (M^+): 369.0977, found: 369.0994.



2,2,2-Trifluoro-*N*-(6-methoxychrysen-5-yl)acetamide (50c): Prepared by using the general procedure above (method A) from 2-methoxy-2-(2-(naphthalen-2-yl)phenyl)acetonitrile (**49c**) (82.0 mg, 0.300 mmol) except for the reaction conditions of amidation (80 °C for 4 h). Purification by flash column chromatography (SiO_2, hexane–Et_2O = 1:1) afforded aryl amine **50c** (100.6 mg, 0.272 mmol, 91%).

White solid; M.p. 193–202 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.90 (1H, d, *J* = 8.6 Hz), 8.76 (1H, d, *J* = 8.6 Hz), 8.63 (1H, d, *J* = 9.2 Hz), 8.23 (1H, d, *J* = 8.6 Hz), 7.98–7.92 (2H, m), 7.80–7.74 (1H, m), 7.74–7.68 (1H, m), 7.63–7.53 (2H, m), 3.91 (3H, s); ^{13}C NMR (125 MHz, $(CD_3)_2CO$) δ 156.97 [q, ^2J(C,F) = 37.0 Hz], 153.51, 134.26, 132.33, 130.53, 129.74, 129.00,

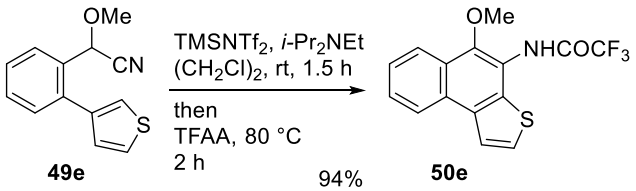
128.65, 128.25, 128.19, 127.68, 127.54, 127.04, 126.88, 126.34, 124.92, 123.85, 122.78, 122.05, 117.47 [q, ^{1}J(C,F) = 287.4 Hz], 62.34; IR (ATR) ν 3258, 2162, 1705, 1684, 1591, 1533, 1429, 1339, 1219, 1155, 772 cm^{-1}; HRMS (FD) calcd for $C_{21}H_{14}F_3NO_2$ (M^+): 369.0977, found: 369.0979.



49d **50d**

2,2,2-Trifluoro-*N*-(4-methoxydibenzo[*c*,*g*]phenanthren-3-yl)acetamide (47d): Prepared by using the general procedure above (method A) from 2-([1,1'-binaphthalen]-2-yl)-2-methoxyacetonitrile (**49d**) (176.5 mg, 0.546 mmol) except for the reaction conditions of amidation (TFAA (231 μL, 1.64 mmol, 3 equiv), 80 °C for 4 h). Purification by flash column chromatography (SiO_2, hexane–EtOAc = 4:1) afforded aryl amine **50d** (192.1 mg, 0.458 mmol, 84%).

Brown solid; M.p. 237–240 °C; ^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ 11.60 (1H, s), 8.29–8.21 (3H, m), 8.21–8.12 (3H, m), 8.09 (1H, d, *J* = 8.0 Hz), 7.91 (1H, d, *J* = 8.1 Hz), 7.63 (1H, t, *J* = 7.5 Hz), 7.59 (1H, t, *J* = 7.5 Hz), 7.38–7.32 (2H, m), 3.98 (3H, s); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 156.45 [q, ^{2}J(C,F) = 35.8 Hz], 150.96, 132.36, 131.57, 129.89, 129.79, 129.10, 128.60, 128.37, 128.19, 128.13, 128.02, 127.23, 127.15, 126.68, 126.60, 125.07, 125.02, 123.60, 120.73, 120.14, 119.71, 116.34 [q, ^{1}J(C,F) = 287.3 Hz], 62.00; IR (ATR) ν 3264, 1710, 1538, 1318, 1260, 1160, 1054, 813, 749 cm^{-1}; HRMS (FD) calcd for $C_{25}H_{16}F_3NO_2$ (M^+): 419.1133, found: 419.1142.

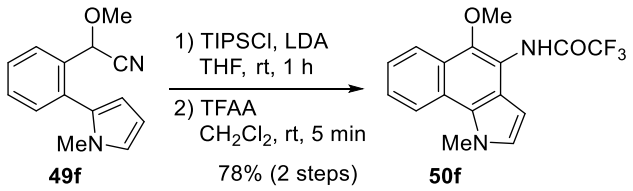


49e **50e**

2,2,2-Trifluoro-*N*-(5-methoxynaphtho[2,1-*b*]thiophen-4-yl)acetamide (50e): Prepared by using the general procedure above (method A) from 2-methoxy-2-(2-(thiophen-3-yl)phenyl)acetonitrile (**49e**) (68.8 mg, 0.300 mmol) except for the reaction conditions of amidation (TFAA (254 μL, 1.80 mmol, 6 equiv), 80 °C for 2 h).

Purification by flash column chromatography (SiO_2, hexane–EtOAc = 6:1) afforded aryl amine **50e** (91.4 mg, 0.281 mmol, 94%).

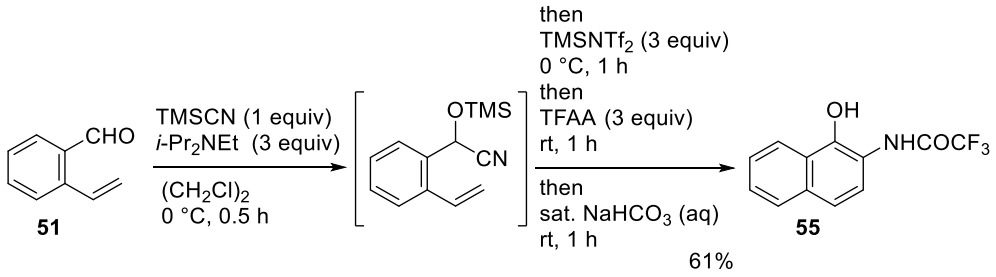
Green solid; M.p. 164–177 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35 (1H, d, *J* = 8.0 Hz), 8.30–8.04 (1H, br-s), 8.20 (1H, d, *J* = 8.6 Hz), 7.97 (1H, d, *J* = 5.2 Hz), 7.71–7.65 (1H, m), 7.65–7.57 (2H, m), 4.01 (3H, s); ^{13}C NMR (125 MHz, CD_3OD) δ 158.11 [q, ^2J(C,F) = 37.0 Hz], 150.96, 137.14, 134.97, 130.88, 128.62, 127.89, 126.93, 126.72, 125.17, 124.31, 123.50, 119.77, 117.73 [q, ^1J(C,F) = 286.2 Hz], 62.73; IR (ATR) ν 3231, 3072, 2390, 1715, 1547, 1456, 1345, 1260, 1151, 1037, 715 cm^{-1}; HRMS (FD) calcd for $C_{15}H_{10}F_3NO_2S$ (M^+): 325.0384, found: 325.0397.



49f **50f**

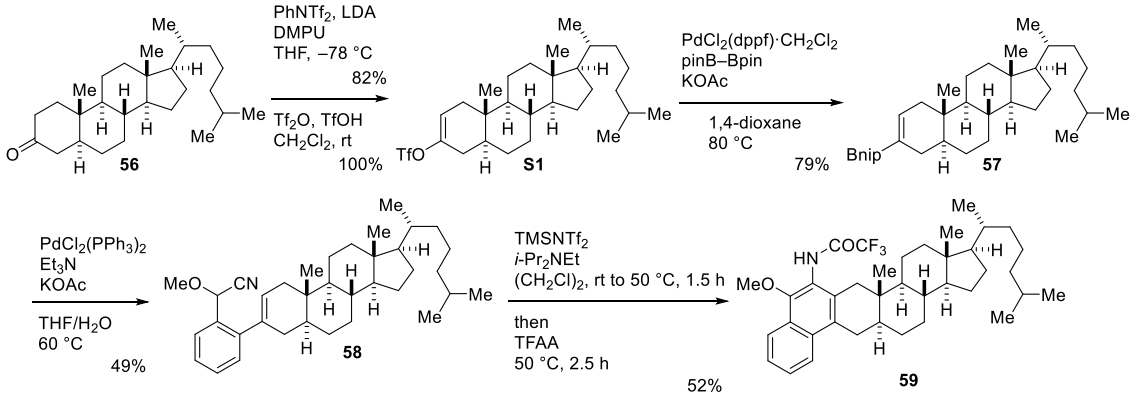
2,2,2-Trifluoro-*N*-(5-methoxy-1-methyl-1H-benzo[*g*]indol-4-yl)acetamide (50f): Prepared by using the general procedure above (method B) from 2-methoxy-2-(2-(1-methyl-1H-pyrrol-2-yl)phenyl)acetonitrile (**49f**) (67.8 mg, 0.300 mmol) except for the reaction conditions of amidation (TFAA (42.3 μL, 0.300 mmol, 1 equiv), room temperature for 5 min). Purification by flash column chromatography (SiO_2, hexane–Et_2O = 2:1) afforded aryl amine **50f** (75.1 mg, 0.233 mmol, 78% for 2 steps).

White solid; M.p. 127–129 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.46 (1H, d, *J* = 8.6 Hz), 8.30 (1H, br-s), 8.20 (1H, d, *J* = 8.6 Hz), 7.61–7.56 (1H, m), 7.54–7.49 (1H, m), 7.08 (1H, d, *J* = 2.9 Hz), 6.50 (1H, d, *J* = 2.9 Hz), 4.27 (3H, s), 3.93 (3H, s); ^{13}C NMR (125 MHz, CD_3OD) δ 158.07 [q, ^2J(C,F) = 37.0 Hz], 146.36, 131.08, 128.73, 127.24, 126.73, 124.90, 124.71, 124.48, 123.75, 122.10, 118.56, 117.93 [q, ^1J(C,F) = 285.0 Hz], 101.61, 62.28, 38.60; IR (ATR) ν 3246, 2592, 1712, 1446, 1348, 1303, 1153, 1086, 981, 918, 849, 757, 728, 700, 688 cm^{-1}; HRMS (FD) calcd for $C_{16}H_{13}F_3N_2O_2$ (M^+): 322.0929, found: 322.1914.



2,2,2-Trifluoro-*N*-(1-hydroxynaphthalen-2-yl)acetamide (55): To a mixture of *o*-vilylbenzaldehyde (**51**) (52.9 mg, 0.400 mmol) and *i*-Pr_2NEt (196 μL, 1.20 mmol, 3 equiv) in $(CH_2Cl)_2$ (2.00 mL) was added TMSCN (50 μL, 0.400mmol, 1 equiv) at 0 °C, and the reaction mixture was stirred at this temperature for 30 min. To the mixture was added $TMSNTf_2$ (275 μL, 1.20 mmol, 3 equiv), and the resulting mixture was stirred at 0 °C for 1 h. TFAA (113 μL, 0.800 mmol, 2 equiv) was then added to the reaction mixture, and the mixture was stirred at room temperature for 1 h. The reaction mixture was basified by slow addition of $NaHCO_3$ (pH of organic layer was ca. 8, as monitored by pH paper), and the mixture was vigorously stirred at room temperature for 1 h. The resultant *O*-trifluoroacetate was hydrolyzed at this stage. The products were extracted with Et_2O (1 mL×3), dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash column chromatography [Merck KGaA, Silica Gel 60 (particle size 0.040–0.063 mm), hexane–EtOAc = 6:1] afforded hydroxy naphthylamine derivative **55** (62.7 mg, 0.246 mmol, 61%).

Gray solid; M.p. 140–143 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35 (1H, br-s), 8.29 (1H, d, J = 7.4 Hz), 7.83–7.77 (1H, m), 7.59–7.50 (3H, m), 7.48 (1H, d, J = 9.2 Hz), 7.34 (1H, d, J = 8.6 Hz); ^{13}C NMR (125 MHz, CD_3CN) δ 157.03 [q, ^2J(C,F) = 40.0 Hz], 146.19, 134.28, 128.45, 127.66, 126.80, 126.53, 124.02, 122.93, 121.27, 117.65, 116.85 [q, ^1J(C,F) = 285.0 Hz]; IR (ATR) ν 3395, 1702, 1606, 1544, 1516, 1357, 1267, 1152, 950, 900, 801, 647 cm^{-1}; HRMS (FD) calcd for $C_{12}H_8F_3NO_2$ (M^+): 255.0507, found: 255.0502.



(5*S*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-10,13-Dimethyl-17-(6-methylheptan-2-yl)-4,5,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[*a*]phenanthren-3-yl trifluoromethanesulfonate (S1): Vinyl triflate **S1** was prepared according to the reported procedure.[4,5] To a solution of *i*-Pr_2NH (727 μL, 5.16 mmol) in THF (10 mL) was added *n*-BuLi (2.65 M in hexane, 1.85 mL, 4.9 mmol) at 0 °C and the mixture was stirred at this temperature for 30 min. After cooled to –78 °C, a solution of ketone **56** (1.73g 4.45 mmol) and DMPU (1.61 mL, 13.4 mmol) in THF (8 mL) was added to the resulting LDA solution and the reaction mixture was stirred at –78 °C for 2 h. A solution of $PhNTf_2$ (1.84 g, 5.16 mmol) in THF (8 mL) was then added to the reaction mixture and the mixture was stirred at –78 °C for 1.5 h. To the mixture was added saturated aqueous NH_4Cl (10 mL) and the products were extracted with hexane. The combined organic layers were died over $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, hexane only) afforded vinyl triflate **S1** (1.90 g, 3.66 mmol, 82%) as a 71:29 mixture of diastereomers.

To a solution of the above 71:29 diastereomeric mixture of vinyl triflate **S1** (1.85 g, 3.57 mmol) and Tf_2O (0.36 mL, 2.19 mmol) in CH_2Cl_2 (18 mL) was added TfOH (100 μL, 1.13 mmol) and reaction mixture was stirred at room temperature for 24 h. Saturated sodium bicarbonate (10 mL) was added to the mixture and the products were extracted with hexane. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to give the isomerized vinyl triflate **S1** (1.85 g, 3.57 mmol, 100%) as a 89:11 mixture of diastereomers.

White solid; M.p. 87–90°C; $[\alpha]_D^{23}$ 5.95 (c 3.09, $CHCl_3$); ^{1}H NMR of major isomer: (500 MHz, $CDCl_3$) δ 5.67–5.62 (1H, m), 2.19–2.02 (3H, m), 2.02–1.95 (1H, m), 1.92–1.77 (2H, m), 1.72–1.65 (1H, m), 1.62–1.19 (14H, m), 1.19–0.93 (8H, m), 0.90 (3H, d, *J* = 6.3 Hz), 0.865 (3H, d, *J* = 6.3 Hz), 0.860 (3H, d, *J* = 6.3 Hz), 0.79 (3H, s), 0.66 (3H, s); ^{13}C NMR of major isomer: (125 MHz, C_6D_6) δ 147.82, 119.22 [q, ^1J(C,F) = 318.4 Hz], 117.33, 56.66, 56.45, 53.36, 42.69, 42.06, 40.18, 39.92, 38.36, 36.63, 36.19, 35.50, 34.32, 32.20, 31.62, 28.56, 28.41, 28.19, 24.45, 24.36, 23.02, 22.76, 21.40, 18.97, 12.17, 11.44; IR (ATR) ν 2927, 1415, 1247, 1219, 1200, 1141, 1038, 872, 772, 613, 454 cm^{-1}; HRMS (FD) calcd for $C_{28}H_{45}F_3O_3S$ (M^+): 518.3042, found: 518.3054.

2-((5*S*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-10,13-dimethyl-17-(6-methylheptan-2-yl)-4,5,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[*a*]phenanthren-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (57): Boronate ester **57** was prepared according to the reported procedure.[6] To a solution of the above vinyl triflate **S1** (1.55 g, 3.0 mmol), KOAc (883.4 mg, 9.0 mmol), and bis(pinacolato)diboron (761.8 mg, 3.0 mmol) in 1,4-dioxane (15 mL) was added $PdCl_2(dppf)\cdot CH_2Cl_2$ (122.5 mg, 0.15 mmol) and the reaction mixture was stirred at 80 °C for 3 h. The mixture was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, hexane–EtOAc = 10:1) afforded boronate ester **57** (1.17 g, 2.36 mmol, 79%) as a 91:9 mixture of diastereomers.

White solid; M.p. 177–179 °C; $[\alpha]_D^{23}$ 58.8 (c 1.09, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.48 (1H, d, *J* = 4.0 Hz), 2.09–1.93 (3H, m), 1.86–0.93 (38 H, m), 0.90 (3H, d, *J* = 6.3 Hz), 0.860 (3H, d, *J* = 6.3 Hz), 0.856 (3H, d, *J* = 6.3 Hz), 0.71 (3H, s), 0.65 (3H, s); ^{13}C NMR (125 MHz, C_6D_6) δ 142.37, 82.91, 56.67, 56.63, 54.19, 42.74, 41.82, 41.78, 40.32, 39.90, 36.65, 36.23, 35.83, 34.51, 32.14, 29.09, 28.62, 28.39, 25.03, 24.49, 24.37, 23.04, 22.78, 21.26, 19.02, 12.24, 12.17; IR (ATR) ν 2927, 2339, 2165, 1974, 1635, 1390, 1337, 1310 cm^{-1}; HRMS (FD) calcd for $C_{33}H_{57}BO_2$ (M^+): 496.4452, found: 496.4458.

2-(2-((5*S*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-10,13-dimethyl-17-(6-methylheptan-2-yl)-4,5,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[*a*]phenanthren-3-yl)phenyl)-2-methoxyacetonitrile (58): To a mixture of boronate ester **57** (565.0 mg, 1.14 mmol), KOAc (167.8 mg, 1.71 mmol), and $PdCl_2(PPh_3)_2$ (35.1 mg, 0.0500 mmol) in THF−H_2O (6:1, 3.8 mL) were added Et_3N (120 μL, 0.86 mmol) and 2-(2-bromophenyl)-2-methoxyacetonitrile (353 μL, 2.28 mmol) and the reaction mixture was stirred at 60 °C for 12 h. The mixture was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, hexane–Et_2O = 30:1) afforded nitrile **58** (291.0 mg, 0.564 mmol, 49%) as a 50:50 mixture of diastereomers.

White solid; M.p. 106–118 °C; $[\alpha]_D^{23}$ 52.8 (c 0.570, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68–7.62 (1H, m), 7.38–7.29 (2H, m), 7.44 (1H, d, *J* = 7.5 Hz), 5.57 (1H, s), 5.30 (0.5H, s), 5.24 (0.5H, s), 3.51 (1.5H, s), 3.50 (1.5H, s), 2.22–1.76 (6H, m), 1.75–0.96 (22H, m), 0.92 (3H, d, *J* = 5.0 Hz), 0.89–0.83 (9H, m), 0.81–0.72 (1H, m), 0.69 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.93, 143.88, 134.96, 134.95, 130.77, 130.68, 129.55, 129.52, 128.74, 128.62, 128.02, 127.95, 127.27, 127.19, 117.87, 69.97, 69.78, 57.57, 57.44, 56.44, 56.25, 53.85, 42.48, 41.94, 41.89, 40.23, 40.17, 39.97, 39.50, 36.17, 35.78, 35.77, 35.71, 35.63, 35.61, 34.13, 34.10, 31.67, 28.51, 28.48, 28.21, 28.00, 24.20, 23.82, 22.81, 22.56, 21.09, 18.69, 12.20, 12.09, 12.01; IR (ATR) ν 3734, 2929, 2868, 2360, 2336, 1458, 1445, 1382, 1083, 757 cm^{-1}; HRMS (FD)

calcd for $C_{36}H_{53}NO$ (M^+): 515.4127, found: 515.4130.

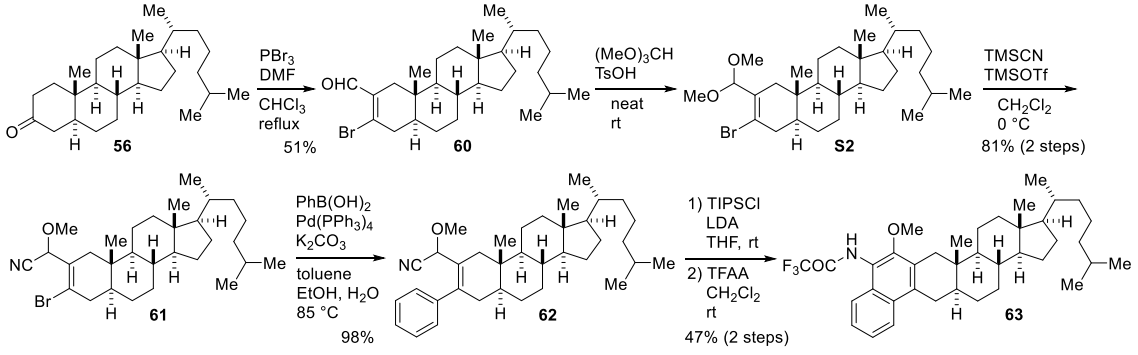
2,2,2-Trifluoro-*N*-((1*R*,3a*S*,3b*R*,5a*S*,13a*S*,13b*S*,15a*R*)-11-methoxy-13a,15a-dimethyl-1-((*R*)-6-methylheptan-2-yl)-2,3,3a,3b,4,5,5a,6,13,13a,13b,14,15,15a-tetradecahydro-1H-benzo[*k*]cyclopenta[*c*]tetraphen-12-yl)acetamide (59): Prepared by using the general procedure above (method A) from nitrile **58** (61.8 mg, 0.120 mmol) except for the reaction conditions of cyclization (room temperature for 30 min then 50 °C for 1 h) and the reaction conditions of amidation (50 °C for 2.5 h). Purification by flash column chromatography (SiO_2, hexane–EtOAc = 10:1) afforded aryl amine **59** (38.2 mg, 0.0624 mmol, 52%).

Colorless oil; $[\alpha]_D^{23}$ 4.33 (c 4.32, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.49 (1H, d, *J* = 8.6 Hz), 8.00 (1H, d, *J* = 8.0 Hz), 7.95 (1H, s), 7.58–7.47 (2H, m), 3.90 (3H, s), 3.06 (1H, dd, *J* = 17.2, 5.2 Hz), 2.66–2.54 (2H, m), 2.29 (1H, d, *J* = 16.7 Hz), 2.03 (1H, d, *J* = 12.6 Hz), 1.89–1.79 (1H, m), 1.75 (1H, d, *J* = 12.6 Hz), 1.68 (1H, *J* = 13.2 Hz), 1.64–1.44 (6H, m), 1.44–0.95 (13H, m), 0.93 (3H, d, *J* = 6.3 Hz), 0.90–0.78 (8H, m), 0.67 (3H, s), 0.64 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.44 [q, ^2J(C,F) = 37.0 Hz], 149.48, 132.69, 131.41, 128.73, 126.89, 125.95, 125.54, 123.58, 122.76, 122.36, 116.14 [q, ^1J(C,F) = 286.2 Hz], 62.28, 56.25, 53.45, 42.39, 40.95, 39.90, 39.51, 39.28, 36.17, 35.80, 35.49, 34.32, 31.61, 30.88, 28.82, 28.22, 28.02, 24.24, 23.85, 22.83, 22.57, 20.96, 18.68, 11.92, 11.36; IR (ATR) ν 2929, 1707, 1559, 1456, 1377, 1339, 1219, 1186, 772 cm^{-1}; HRMS (FD) calcd for $C_{38}H_{52}F_3NO_2$ (M^+): 611.3950, found: 611.3950.

(4) Scheiper, B.; Bonnekessel, M.; Krause, H.; Fürstner, A. *J. Org. Chem.* **2004**, *69*, 3943–3949.

(5) Cacchi, S.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1984**, *25*, 2271–2274.

(6) Burger, M. T.; Han, W.; Lan, J.; Nishiguchi, G. U.S. Patent US2010/0056576 A1, **2010**.



(5*S*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-3-Bromo-10,13-dimethyl-17-((*R*)-6-methylheptan-2-yl)-4,5,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthrene-2-carbaldehyde (60): Aldehyde **60** was prepared according to the reported procedure.[7] A mixture of PBr_3 (2.63 mL, 28.0 mmol) and DMF (4.34 mL, 56.0 mL) in $CHCl_3$ (20 mL) was stirred at room

temperature for 15 min. Then a solution of ketone **56** (2.71 g, 7.00 mmol) in $CHCl_3$ (15 mL) was added and the mixture was heated to reflux for 2 h. The reaction mixture was slowly poured into ice-cold water (200 mL) and basified with saturated aqueous sodium bicarbonate, and the products were extracted with Et_2O. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, hexane–Et_2O = 8:1) afforded aldehyde **60** (1.71 g, 3.58 mmol, 51%). The spectral data (^1H NMR) was identical to that was previously reported.[6]

(5*S*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-3-Bromo-2-(dimethoxymethyl)-10,13-dimethyl-17-((*R*)-6-methylheptan-2-yl)-4,5,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthrene (S2): To a mixture of aldehyde **60** (1.61 g, 3.37 mmol) and $(MeO)_3CH$ (11.0 mL, 10.1 mmol) was added $TsOH·H_2O$ (29.1 mg, 0.169 mmol) and the mixture was stirred at room temperature for 1.5 h. The reaction mixture was diluted with Et_2O (50 mL) and washed with saturated aqueous sodium bicarbonate. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to give dimethyl acetal **S2** (2.31 g). This material was used for the next step without further purification.

2-((5*S*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-3-Bromo-10,13-dimethyl-17-(6-methylheptan-2-yl)-4,5,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[*a*]phenanthren-2-yl)-2-methoxyacetonitrile (61): To a solution of the above dimethyl acetal **S2** (2.31 g, as 3.37 mmol) and TMSCN (627 μL, 5.01 mmol) in CH_2Cl_2 (17 mL) was added TMSOTf (61 μL, 0.337 mmol) and the mixture was stirred at 0 °C for 1 h. Saturated aqueous sodium bicarbonate (10 mL) was added and the products were extracted with Et_2O. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, hexane–Et_2O = 10:1) to give cyanohydrin methyl ether **61** (1.41 g, 2.72 mmol, 81% for 2 steps) as a 67:33 mixture of diastereomers.

Colorless oil; $[\alpha]_D^{23}$ 57.7 (c 1.12, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 5.20 (1H, s), 3.47 (0.7H, s), 3.44 (0.3H, s), 2.47–2.19 (3H, m), 2.04–1.64 (5H, m), 1.60–0.93 (21H, m), 0.90 (3H, d, *J* = 6.3 Hz), 0.98–0.94 (6H, m), 0.81–0.70 (4H, m), 0.68–0.64 (4H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 128.42, 128.22, 124.93, 123.89, 116.36, 116.24, 73.98, 72.39, 57.68, 57.41, 56.23, 56.20, 56.15, 56.13, 53.35, 53.24, 43.55, 43.31, 42.41, 41.30, 41.26, 40.83, 40.15, 39.71, 39.68, 39.48, 36.12, 35.75, 35.73, 35.38, 35.30, 34.79, 34.54, 31.34, 31.31, 28.14, 27.96, 27.72, 27.67, 24.16, 23.79, 22.80, 22.54, 21.10, 18.65, 11.95, 11.78, 11.42; IR (ATR) ν 2929, 2324, 1661, 1465, 1383, 1337, 1184, 1092, 959 cm^{-1}; HRMS (FD) calcd for $C_{30}H_{48}BrNO$ (M^+): 517.2919, found: 517.2938.

2-((5*S*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-10,13-Dimethyl-17-(6-methylheptan-2-yl)-3-phenyl-4,5,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[*a*]phenanthren-2-yl)-2-methoxy acetonitrile (62): To a mixture of cyanohydrin methyl ether **61** (1.02 g, 1.97 mmol), $PhB(OH)_2$ (263.4 mg, 2.16 mmol), and K_2CO_3 (544.5 mg, 3.94 mmol) in toluene–EtOH–H_2O (3:3:1, 6.2 mL) was added $Pd(PPh_3)_4$ (68.3 mg, 0.0591 mmol) and the reaction mixture was stirred at 85 °C for 10 h. The mixture was filtered through a pad of Celite. To the filtrate was added water (3 mL) and the products were extracted with Et_2O. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, hexane–Et_2O = 10:1) afforded nitrile **62** (991.2 mg, 1.92 mmol, 98%) as a 68:32 mixture of diastereomers.

White solid; M.p. 106–110 °C; $[\alpha]_D^{22}$ 90.5 (c 1.10, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39–7.27 (3H, m), 7.12 (2H, d, *J* = 6.9 Hz), 4.57 (0.7H, s), 4.52 (0.3H, s), 3.30–3.27 (3H, m), 2.40–2.17 (2H, m), 2.10–1.74 (4H, m), 1.73–1.67 (1H, m), 1.64–0.95 (20H, m), 0.95–0.75 (14H, m), 0.70–0.66 (3H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.14, 140.96, 140.78, 140.76, 140.57, 128.67, 128.56, 128.45, 127.60, 127.57, 127.48, 127.43, 127.07, 125.71, 117.49, 117.39, 71.83, 70.24, 57.10, 56.79, 56.38, 56.32, 56.21, 56.16, 53.79, 53.67, 42.43, 41.65, 41.35, 39.84, 39.82, 39.48, 38.73, 37.95, 37.54, 37.36, 36.14, 35.77, 35.75, 35.56, 35.48, 34.54, 34.29, 31.55, 28.16, 28.11, 28.05, 27.95, 24.17, 23.80, 22.78, 22.54, 21.17, 18.67, 11.98, 11.71, 11.37; IR (ATR) ν 2929, 2153, 1442, 1382, 1219, 1089, 773, 701 cm^{-1}; HRMS (FD) calcd for $C_{36}H_{53}NO$ (M^+): 515.4127, found: 515.4129.

2,2,2-Trifluoro-*N*-((1*R*,3a*S*,3b*R*,5a*S*,13a*S*,13b*S*,15a*R*)-12-methoxy-13a,15a-dimethyl-1-(6-methylheptan-2-yl)-2,3,3a,3b,4,5,5a,6,13,13a,13b,14,15,15a-tetradecahydro-1H-benzo[*k*]cyclopenta[c]tetraphen-11-yl)acetamide (63): Prepared by using the general procedure above (method B) from nitrile **63** (51.6 mg, 0.100 mmol) except for the reaction time of cyclization (2 h) and the reaction time of amidation (2 h). Purification by flash column chromatography (SiO_2, hexane–Et_2O = 10:1) afforded aryl amine **63** (28.7 mg, 0.0469 mmol, 47%).

Colorless oil; $[\alpha]_D^{23}$ 3.04 (c 7.34, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (1H, d, *J* = 8.6 Hz), 7.95 (1H, s), 7.65 (1H, d, *J* = 7.5 Hz), 7.53–7.44 (2H, m), 3.78 (3H, s), 3.10 (1H, dd, *J* = 17.2, 4.9 Hz), 3.01 (1H, d, *J* = 16.6 Hz), 2.71–2.59 (1H, m), 2.26 (1H, d, *J* = 16.6 Hz), 2.07 (1H, d, *J* = 12.6 Hz), 1.91–1.75 (2H, m), 1.74–0.97 (21H, m), 0.94 (3H, d, *J* = 6.3 Hz), 0.91–0.84 (7H, m), 0.70 (3H, s), 0.68 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.84 [q, ^2J(C,F) = 35.8 Hz], 152.66, 134.38, 129.62, 129.33, 128.22, 126.25, 125.47, 123.53, 122.22, 118.89, 116.19 [q, ^1J(C,F) = 287.4 Hz], 60.81, 56.44, 56.32, 53.79, 42.48, 41.17, 39.98, 39.50, 38.14, 36.17, 35.79, 35.60, 34.22, 31.65, 31.09, 28.84, 28.22, 28.00, 24.23, 23.85, 22.81, 22.56, 21.18, 18.69, 12.00, 11.35; IR (ATR) ν 3276, 2932, 1728, 1524, 1456, 1383, 1316, 1212, 1168, 1028, 944, 755 cm^{-1};

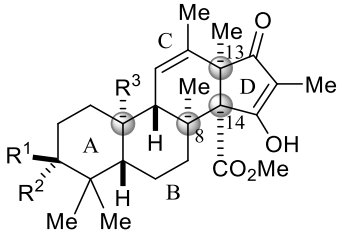
HRMS (FD) calcd for $C_{38}H_{52}F_3NO_2$ (M^+): 611.3950, found: 611.3952.

(7) Gogoi, S.; Shekarrao, K.; Duarah, A.; Bora, T. C.; Gogoi, S.; Boruah, R. C. *Steroids* **2012**, *77*, 1438–1445.

Chapter 2
Synthetic Study of Andrastin C

There are a number of natural products possessing multiple quaternary stereogenic carbon atoms on their carbocyclic skeletons. While many natural products exhibit distinctive biological activities, the studies for exploring the mechanism of the activities of them often suffer from the poor availability from the natural sources. Chemical synthesis of the natural products would solve the problem, but it is difficult to construct the carbocyclic skeleton with quaternary stereogenic centers. The major challenges to achieve the total synthesis of these compounds are the following: (1) construction of quaternary stereogenic carbon atoms which requires stereoselective C–C bond formation at highly sterically demanding positions; (2) functionalization of the sterically hindered neighboring positions of the resulting quaternary asymmetric carbon atoms. Especially, the challenge is further exacerbated when two or more quaternary asymmetric carbon atoms are consecutive to one another.[32]

Andrastin C (**68**) is a fungal meroterpenoid isolated from cultured broth of *Penicillium* sp. FO-3929 with three analogues (i.e., andrastins A, B, and D) by Ōmura and co-workers in 1996 (Figure 2).[33] This compound has four quaternary stereogenic carbon atoms, in which three of them are in consecutive positions, on its steroidal 6-6-6-5 tetracyclic skeleton. Biosynthetic pathway of andrastins have also been extensively studied in the last decade.[34] Andrastins exhibit inhibitory activity toward protein farnesyl transferase (PFTase), and the IC_{50} value of andrastin C, which is the most active compound among them, is 13.3 μM.[33a] Because PFTase is essential for maturation of Ras oncogene protein,[35] andrastins are expected to become lead compounds for anti-cancer drugs.



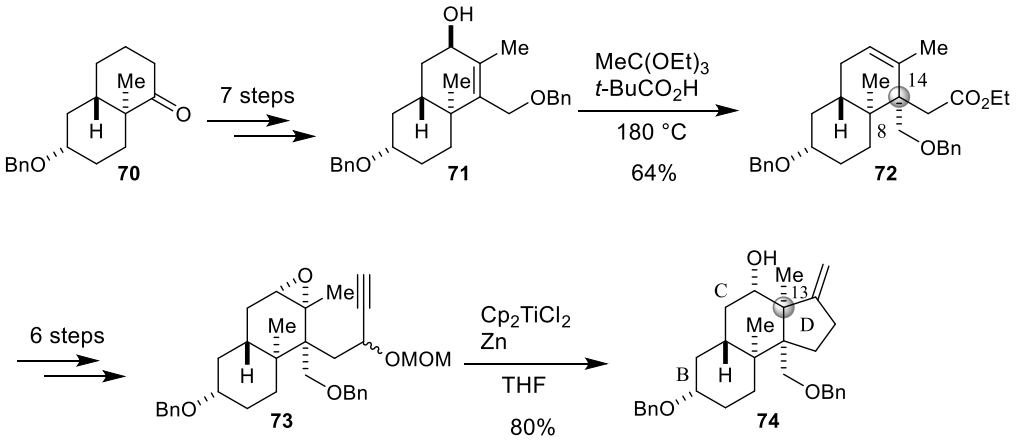
andrastin A (**66**) (R^1=OAc, R^2=H, R^3=CHO)
andrastin B (**67**) (R^1=OAc, R^2=H, R^3=CH_2OH)
andrastin C (**68**) (R^1=OAc, R^2=H, R^3=Me)
andrastin D (**69**) (R^1, R^2=O, R^3=Me)

Figure 2. Structures of andrastins

Both their biological activities and complex chemical structures have made andrastins as attractive targets for total synthesis, and a number of research groups have been involved in the development of synthetic strategies directed towards andrastins.[36] From a synthetic viewpoint, the greatest challenges posed by the total synthesis of andrastins is the construction of the C-ring possessing three contiguous quaternary stereogenic carbon atoms at C_8, C_{14}, and C_{13} that is fused with the highly oxidized D-ring. In 2017, after twenty years of isolation, the first total

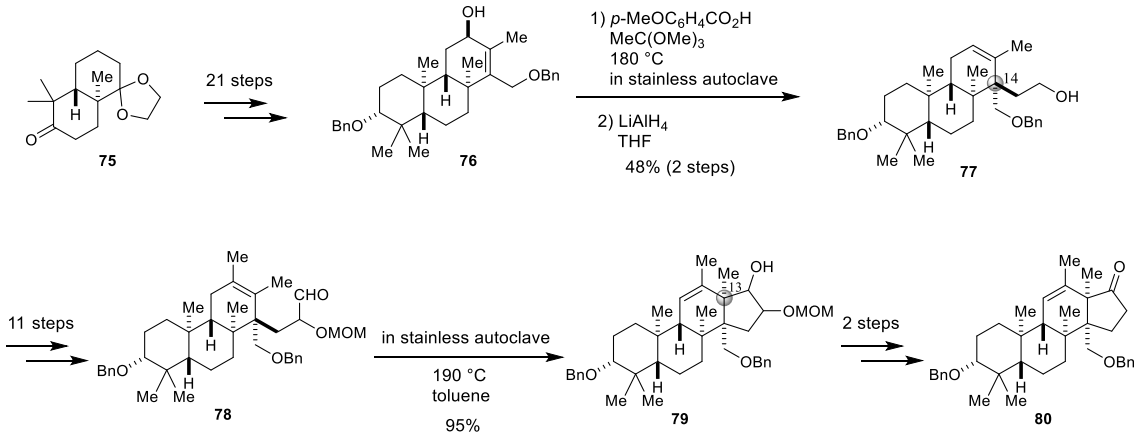
synthesis of andrastin D (**69**) was accomplished by Newhowse, Maimone and co-workers.[36e] These reported synthetic studies of andrastins are summarized in chronological order in the following paragraphs.

Ihara, Toyota, and co-workers constructed the BCD-ring system of andrastins with three contiguous quaternary carbon centers (Scheme 15).[36a] Stating from the bicyclic ketone **70**, the C_{14} quaternary stereogenic center was constructed by the Johnson-Claisen rearrangement of allyl alcohol **71**. The configuration of the newly created quaternary carbon center was controlled by the 1,3-chirality transfer of the secondary alcohol. After conversion to epoxide **73**, the D-ring with the C_{13} quaternary carbon was constructed by Ti(III)-induced reductive radical cyclization.



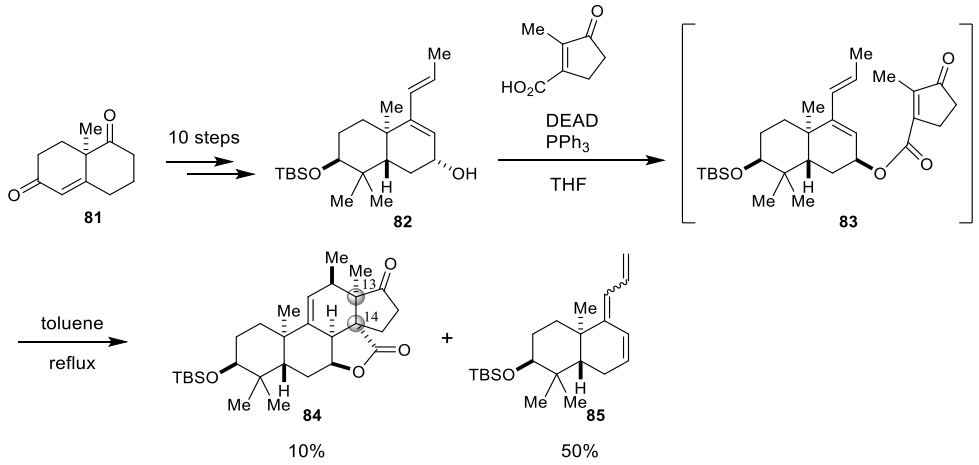
Scheme 15. Ihara and Toyota's strategy for construction of the BCD-ring system

In their following full paper, Ihara, Toyota and co-workers reported the advanced method for constructing the functionalized ABCD-skeleton of andrastin C (**68**) (Scheme 16).[36b] Similar to the synthesis of ester **72**, construction of the C_{14} quaternary carbon center was carried out by the Johnson-Claisen rearrangement of tricyclic allyl alcohol **76**. After reduction of the resulting ester, alcohol **77** was transformed into aldehyde **78**. Then, the D-ring formation was achieved by the intramolecular carbonyl-ene reaction which effected the stereoselective construction of the C_{13} quaternary stereogenic center. Further oxidation of the D-ring moiety remains a challenge for the totally synthesis of andrastins.



Scheme 16. Ihara and Toyota's strategy to the functionalized ABCD-skeleton

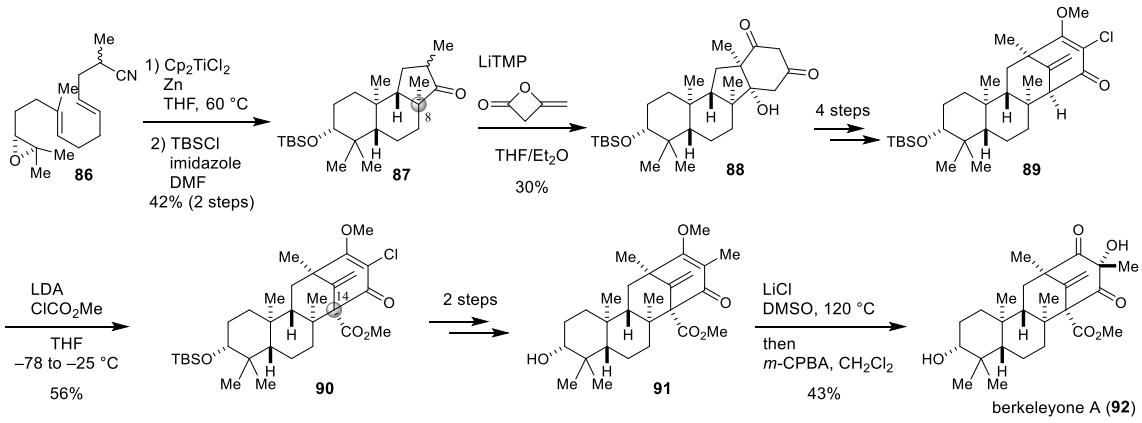
Matsuya and co-workers disclosed the construction of the *cis*-fused CD-ring of andrastins with two contiguous quaternary carbon atoms by an intramolecular Diels-Alder reaction (Scheme 17).[36d] Thus, the dienyl alcohol **82**, which was derived from Wieland-Miescher ketone **81**, was coupled with the D-ring unit via Mitsunobu reaction. Upon refluxing in toluene, triene **83** underwent the intramolecular Diels-Alder reaction to form tetracyclic ABCD-ring framework, giving rise to lactone **84**. Unfortunately, the reaction suffered from the competitive formation of triene **85** via a conjugative elimination reaction of the ester group.



Scheme 17. Matsuya's strategy to construct the ABCD-skeleton

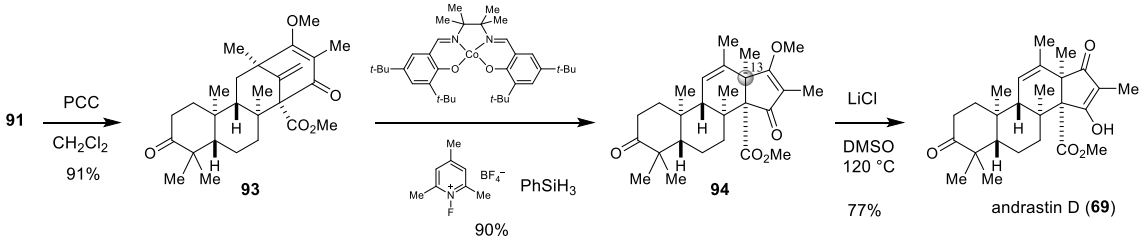
On the other hand, Newhouse, Maimone, and co-workers completed the total synthesis of (±)-andrastin D (**69**) by the bioinspired polyene cyclization and radical rearrangement as the key steps.[36e] They designed the tetracyclic compound **91** as the late-stage common synthetic intermediate for the synthesis of andrastin and terretonin meroterpenes (Scheme 18). This

compound was synthesized as follows.[37] The Ti(III)-mediated radical cyclization of polyene **86** afforded tricyclic compound **87**, and the subsequent annulation of **87** with diketene gave tetracyclic diketone **88**. After several functional group transformations, the remaining quaternary stereogenic carbon center was constructed by *C*-acylation of vinylogous ester **89** to afford tetracyclic compound **91**. This compound was successfully converted to berkeleyone A (**92**) upon Krapcho-type demethylation followed by oxidation with *m*-CPBA.



Scheme 18. Maimone's synthesis of the key tetracyclic intermediate **91**

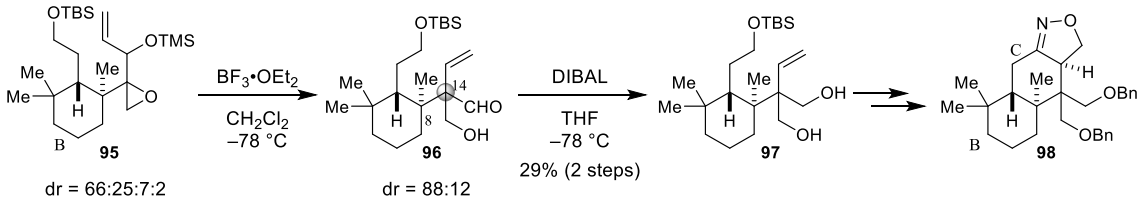
Andrastin D (**69**) could be synthesized from the common intermediate **91** (Scheme 19).[36e] Alcohol **91** was oxidized to the corresponding ketone **93** which was subjected to the skeletal radical rearrangement mediated by Co-salen catalyst. Finally, the resulting andrastin-type tetracyclic compound **94** was heated with LiCl to afford (±)-andrastin D (**69**) via demethylation.



Scheme 19. Total synthesis of andrastin D by Newhouse and Maimone

In this connection, Mr. Ishioka in the author's laboratory also conducted the studies directed toward the total synthesis of andratstin C (**68**).[38] He designed the strategy for constructing contiguous quaternary carbon atoms by using semi-pinacol rearrangement (Scheme 20). To explore model studies of the above rearrangement, epoxy silyl ether **95** possessing a cyclohexane ring, which corresponds to the B-ring of andrastins, was prepared. When **95** was

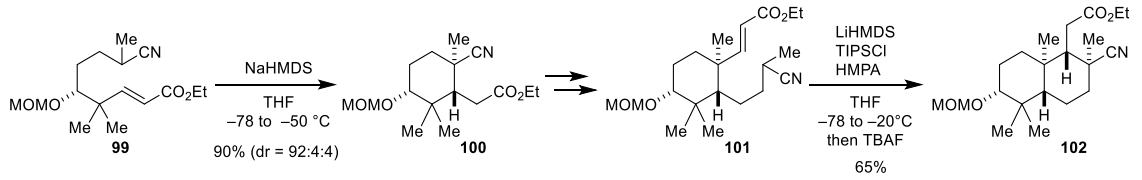
treated with BF_3•OEt_2 at –78 °C in CH_2Cl_2, 1,2-rearrangement of the vinyl group occurred to give β-hydroxyaldehyde **96** having two contiguous quaternary carbon atoms. Since aldehyde **96** was found to be unstable, **96** was immediately reduced to diol **97**. Then, the C-ring was constructed by the subsequent transformations including the intramolecular [3+2] cycloaddition reaction of nitrile oxide. Although the approach could led to the model compound **98**, the poor yield (29%) of the semi-pinacol rearrangement indicated the difficulty in constructing the two contiguous quaternary carbon atoms.



Scheme 20. Ishioka's strategy to construct the BC-ring system

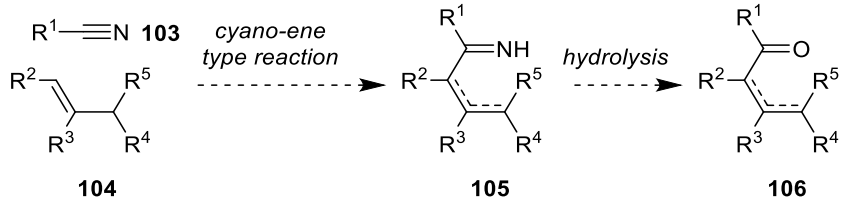
These backgrounds led the author to undertake a synthetic study of andrastin C (**68**) through the development of an efficient methodology for constructing the CD-ring. The author designed a synthetic strategy of **68** focusing on two C–C bond forming reactions, namely, the intramolecular conjugate addition of alkanenitriles and the intramolecular cyano-ene type reactions. These ideas came from the efficient properties of the cyano group, which was discussed in the introduction part.

In this context, Torizuka and Mori in the author's laboratory have developed a novel method for constructing carbocycles via intramolecular conjugate addition of alkanenitriles to α,β-unsaturated esters. Thus, upon treatment with NaHMDS, α,β-unsaturated ester **99** bearing an alkanenitrile sidechain underwent the conjugate addition of the in situ generated α-cyano carbanion to the α,β-unsaturated ester moiety, and cyclohexane derivative **100** was obtained in high yield with high diastereoselectivity (Scheme 21). The cyclization reaction provides a powerful tool for constructing a quaternary carbon atom on a carbocycle in a stereoselective fashion. Torizuka successfully synthesized *trans*-decalin **102** possessing two quaternary stereogenic carbon atoms through intramolecular conjugate additions of alkanenitriles **99** and **101** in his synthetic study of brasilicardin A.[39]



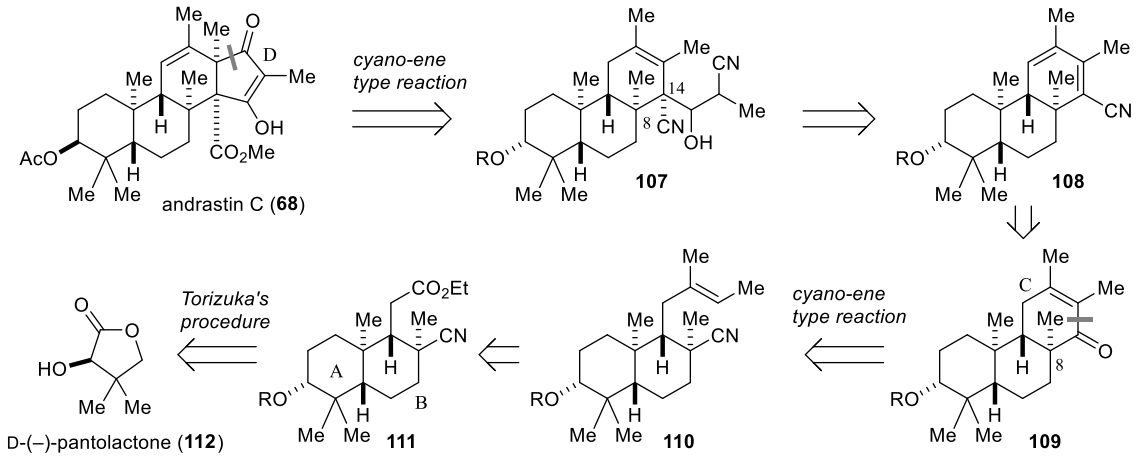
Scheme 21. Synthesis of *trans*-decalin skeleton via intramolecular conjugate addition reactions

Conversely, there have been a limited number of reports for C–C bond forming reactions between olefins and nitriles, i.e. cyano-ene type reactions,[40,41] whereas carbonyl-ene reactions (Prins reaction) have been widely used in synthetic chemistry.[42] Cyano-ene reactions are expected to be suitable for the C–C bond formation at sterically congested positions due to the minimal steric demand of small cyano group (Scheme 22). Additionally, the products would be obtained as unsaturated imine **105** or unsaturated ketone **106** through hydrolysis, which would be advantageous for further transformations. Furthermore, imine **105** could be a useful synthetic precursor of nitrogen-containing compounds. Despite their synthetic potential, the use of cyano-ene type reactions is limited presumably due to the low reactivity of cyano group as an enophile. Therefore, the author designed an intramolecular version of the cyano-ene type reaction, which would provide a useful method for the synthesis of carbocycles with high oxidation state.



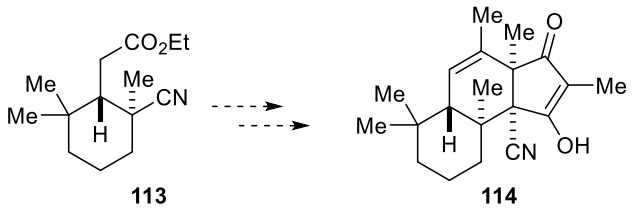
Scheme 22. Cyano-ene type reaction

With a view to provide variants for exploring the structure-biological activity-relationship in future, the author designed the synthetic route toward andrastin C including stepwise construction of each rings. Retrosynthetic analysis for andrastin C (**68**) is shown in Scheme 23. In Ishioka's synthetic strategy, the C_8–C_{14} contiguous quaternary stereogenic carbon atoms were constructed prior to the formation of the C-ring (cf. Scheme 20). On the contrary, the author planned to construct the C_{14} quaternary carbon after the formation of the C-ring. Thus, the D-ring of andrastin C (**68**) would be constructed by an intramolecular cyano-ene type reaction of nitrile **107** with the stereocontrolled formation of the angular quaternary carbon atom. The alkanenitrile moiety in **107** would be introduced through alkylation of the α-cyano carbanion generated from unsaturated nitrile **108**. The C-ring would be constructed by an intramolecular cyano-ene type reaction of **110**. The sterically less demanding cyano group would be suitable for the C–C bond formation at the sterically hindered neopentyl position. The cyclization precursor **110** would be derived from bicyclic compound **111** which would be synthesized from commercially available D-(–)-pantolactone (**112**) as an optically pure form according to the Torizuka's procedure[40].



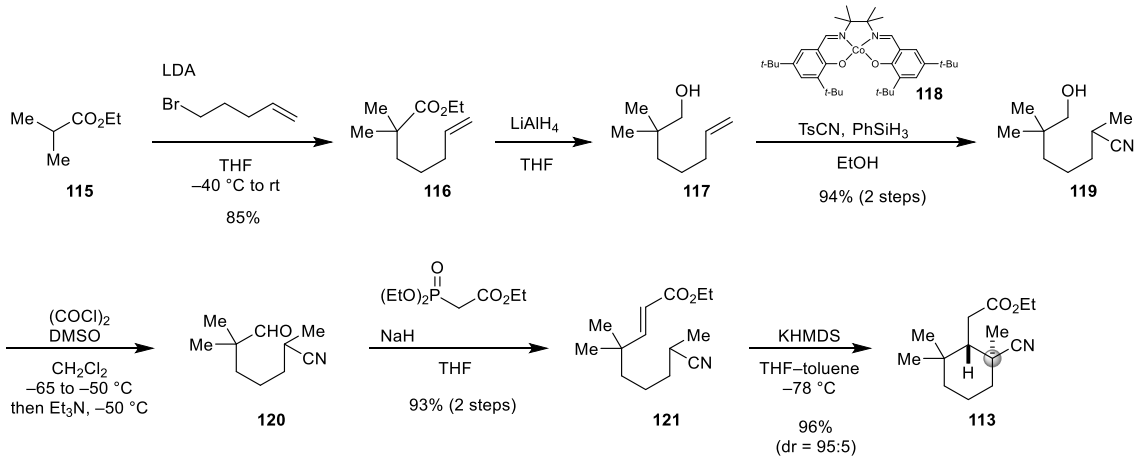
Scheme 23. Retrosynthetic analysis for andrastin C (**68**)

To examine the viability of the above strategy, especially construction of highly oxidized CD-ring with three consecutive quaternary carbon atoms, the author planned to conduct a model study, namely, the synthesis of tricyclic compound **114** from cyclic nitrile **113** (Scheme 24).



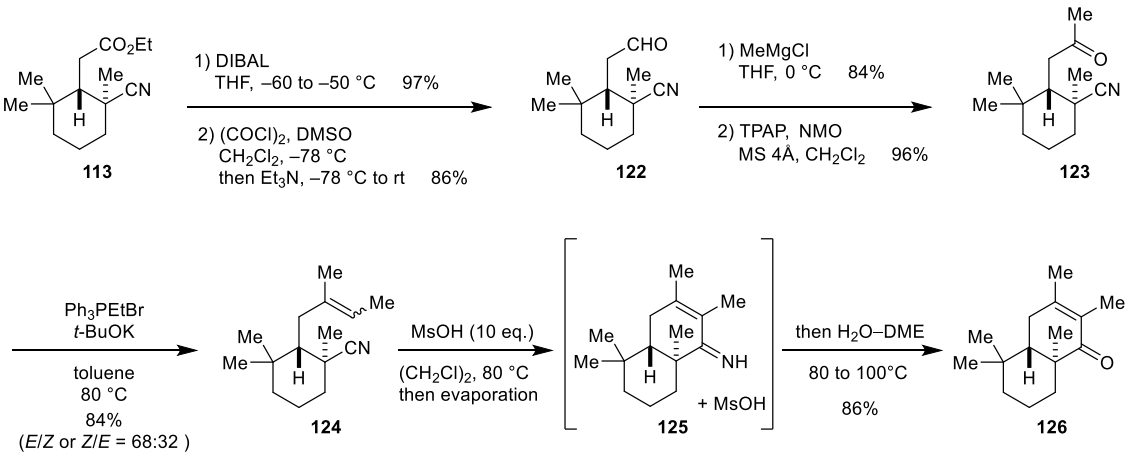
Scheme 24. Plan for model study

The synthetic study was begun with the synthesis of the B-ring model compound **113** according to Ishioka's procedure[38] (Scheme 25). The enolate generated from ethyl isobutyrate (**115**) and LDA was reacted with 5-bromo-1-pentene, and the resulting ester **116** was then reduced to primary alcohol **117**. After cobalt-catalyzed hydrocyanation which was reported by Carreira and Gasper,[43] alcohol **119** was oxidized to aldehyde **120**, and the subsequent Horner-Wadsworth-Emmons reaction afforded α,β-unsaturated ester **121** having an alkanenitrile side chain. Treatment of **121** with KHMDS induced the intramolecular conjugate addition reaction to give the B-ring model compound **113** in a highly diastereoselective manner.



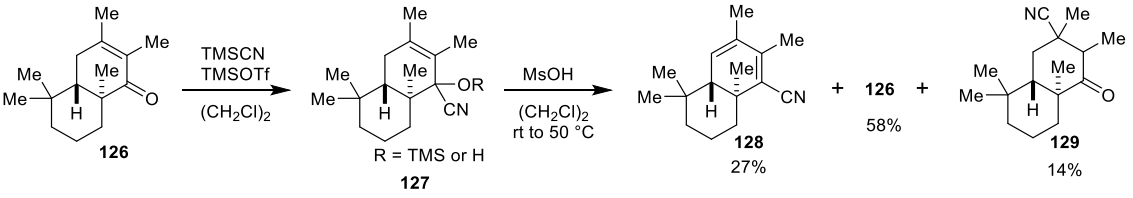
Scheme 25. Synthesis of the B-ring model compound **113**

With **113** in hand, construction of the C-ring was examined (Scheme 26). Ester **113** was converted to aldehyde **122** through DIBAL reduction followed by Swern oxidation. At this point, **122** was obtained as a single isomer after recrystallization. Then, cyclization precursor **124** was obtained in three steps, including nucleophilic addition of MeMgCl, oxidation of the resulting secondary alcohol to ketone **123**, and Wittig olefination. Treatment of **124** with an excess amount of MsOH in 1,2-dichloroethane at 80 °C effected the intramolecular cyano-ene type reaction (i.e. nitrile analogue of Prins reaction) and the subsequent isomerization of the olefin moiety.[44] After confirming the disappearance of the starting material by TLC monitoring, the solvent was removed by evaporation, and the resulting mixture containing the α,β-unsaturated ketimine and MsOH was hydrolyzed by heating with water at 80–100 °C, giving rise to enone **126** in 86% yield. Thus, cyano-ene type reaction proved to be effective for the construction of cyclohexenone moiety at a sterically hindered neopentyl position.



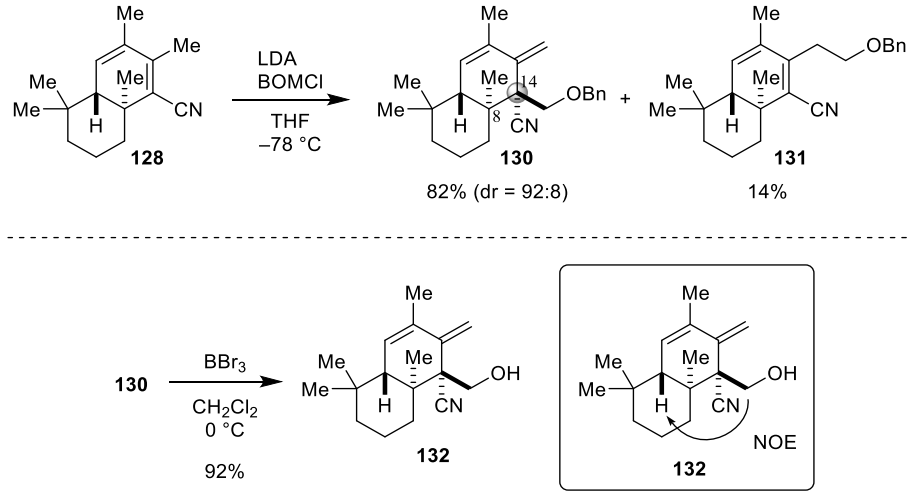
Scheme 26. Formation of the C-ring

A cyano group that was required for elongation of the sidechain was introduced as shown in Scheme 27. Thus, treatment of **126** with TMSCN in the presence of a catalytic amount of TMSOTf afforded a diastereomeric mixture of cyanohydrins and its silyl ethers. Treatment of the crude mixture of **127** with MsOH in $(CH_2Cl)_2$ afforded unsaturated nitrile **128** in 27% yield via dehydration accompanied by the recovery of the starting material **126** and β-keto nitrile **129** which was derived from 1,4-addittion of a cyanide.



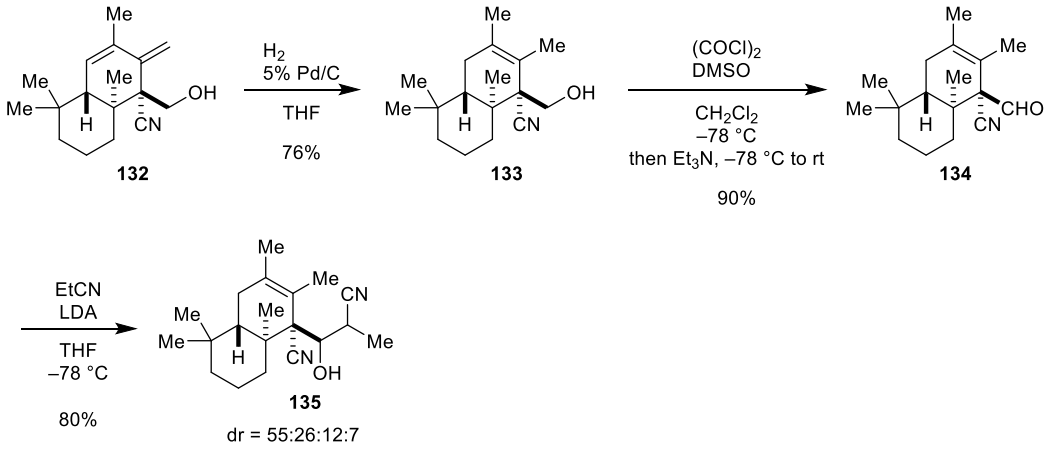
Scheme 27. Synthesis of the unsaturated nitrile **128**

With nitrile **128** in hand, the author next examined construction of the stereogenic quaternary carbon at the C_{14} position (Scheme 28). Thus, deprotonation at the γ-position of unsaturated nitrile **128** by LDA followed by trapping of the resulting α-cyano carbanion with BOMCl gave the desired α-alkylated product **130** which has C_8–C_{14} contiguous quaternary carbon atoms (82% yield) along with the γ-alkylated product **131** (14% yield). It is noteworthy that the use of other electrophiles such as aldehydes or ethyl cyanoformate led to poor α-selectivities. The α-alkylation occurred exclusively from the opposite face of the angular C_{14} methyl group so as to avoid the steric repulsion with it. The stereostructure of **130** was unambiguously determined by the NOE experiment of alcohol **132** after removal of the benzyl group of **130** by BBr_3.



Scheme 28. Construction of the C_{14} quaternary asymmetric carbon

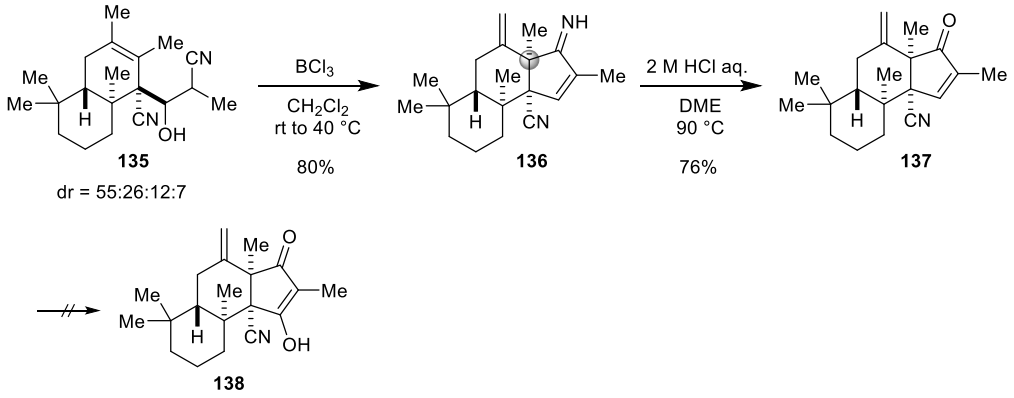
Having a compound possessing two contiguous C_8–C_{14} quaternary carbon atoms with correct configuration, construction of the D-ring was investigated. To this end, diene **132** was initially converted to tetrasubstituted olefin **133** by partial hydrogenation with Pd/C (Scheme 29). The alkanenitrile sidechain was installed to **133** through oxidation of alcohol **133** to aldehyde **134** followed by the reaction with the α-cyano carbanion generated from EtCN, and the desired β-hydroxynitrile **135** was obtained as a mixture of four diastereomers.



Scheme 29. Installation of alkanenitrile sidechain

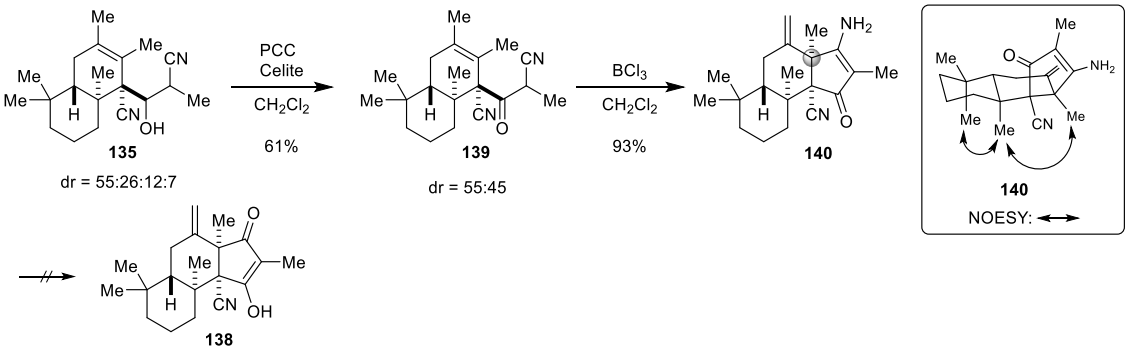
Construction of the D-ring was again achieved by a cyano-ene type reaction (Scheme 30). In contrast to the cyclization of **124**, Brønsted acid such as MsOH failed to promote the cyano-ene type cyclization of nitrile **135**. The author found that BCl_3 was a choice of a Lewis acid, and **135** smoothly underwent a cyclization followed by dehydration to afford α,β-unsaturated ketimine **136** in 80% yield. The olefin moiety of the C-ring of **136** was

exclusively *exo*, suggesting that the cyclization proceeded through a concerted cyano-ene reaction. After hydrolysis of imine **136** with aqueous HCl, enone **137** was obtained. Thus, the BCD-ring possessing three contiguous quaternary stereogenic carbon atoms was successfully constructed. Although the next task was the oxidation of cyclopentenone **137** to 1,3-diketone **138**, all efforts for introducing an oxygen functional group at the β-position of the enone were fruitless.



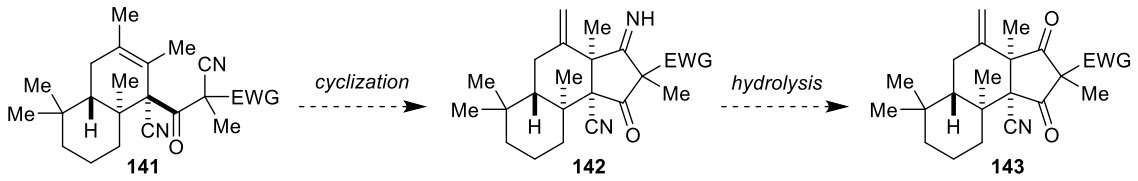
Scheme 30. Construction of the D-ring via cyclization of β-hydroxynitrile **135**

Since the late-stage oxidation of the D-ring was quite difficult, the alkanenitrile moiety of **135** was oxidized with PCC prior to the D-ring formation (Scheme 31). The resulting β-ketonitrile **139** underwent the cyclization reaction under the influence of BCl_3, providing enaminone **140** which is in the same oxidation level as 1,3-diketone **138**. The stereochemistry of **140** was determined by the NOESY experiment, in which correlations between the methyl groups were observed. The efforts to effect hydrolysis of enaminone **140**, however, resulted in the recovery of the substrate under acidic or basic conditions.



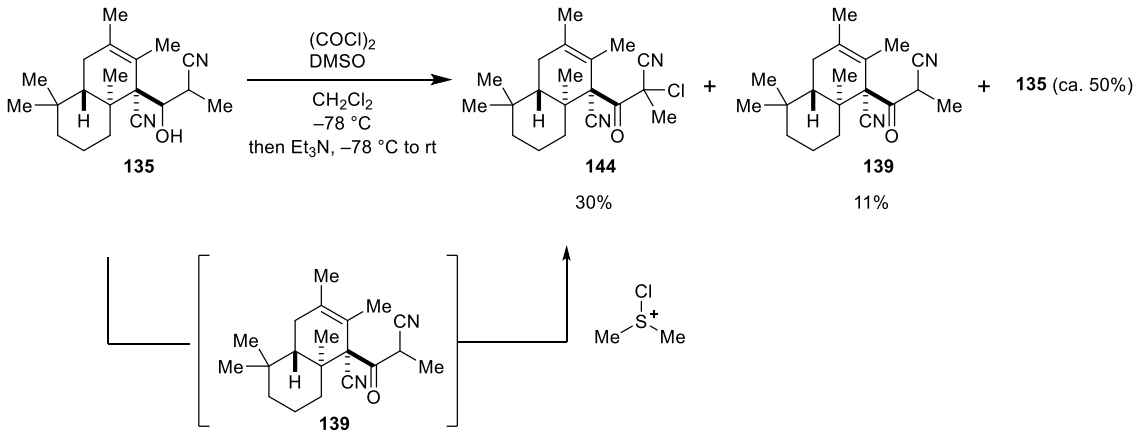
Scheme 31. Cyclization of β-ketonitrile **139**

With a view to enhancing the reactivity toward hydrolysis, the author planned to introduce an electron-withdrawing group at the α-position of the cyano group on the sidechain (Scheme 32). Thus, cyclization of ketonitrile **141** would afford imine **142** which cannot isomerize to an enamide form, and the subsequent hydrolysis would produce 1,3-diketone **143** with little difficulty.



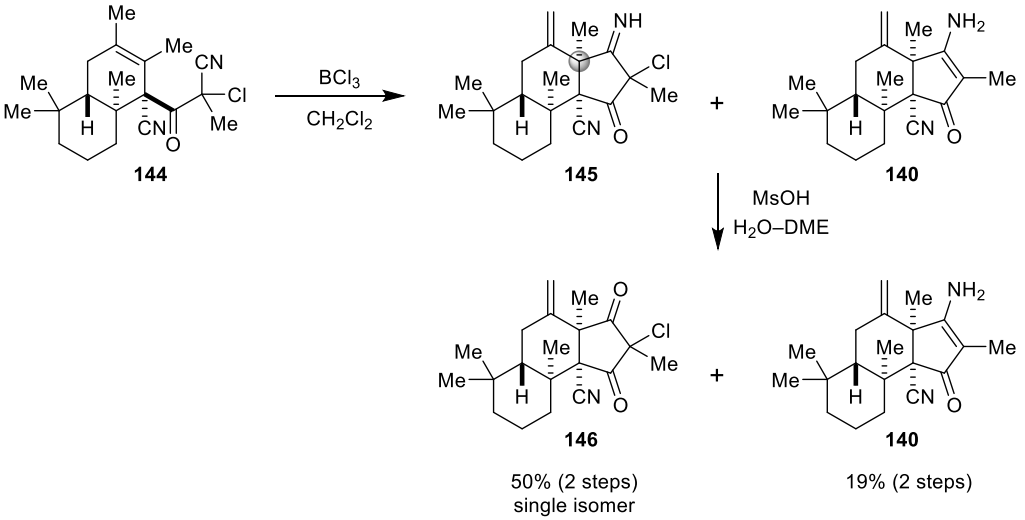
Scheme 32. New synthetic plan

As shown in Scheme 33, it was found that Swern oxidation of β-hydroxynitrile **135** led to formation of α-chloro-β-ketonitrile **144**, albeit in low yield (i.e. 30%), accompanied with **139** (11% yield).[45] The unexpected product **144** would be formed through chlorination of the primary product **139** with chlorodimethylsulfonium ion. The author was delighted, because the chlorine atom of **144** may work as an electron-withdrawing group that was depicted in Scheme 32.



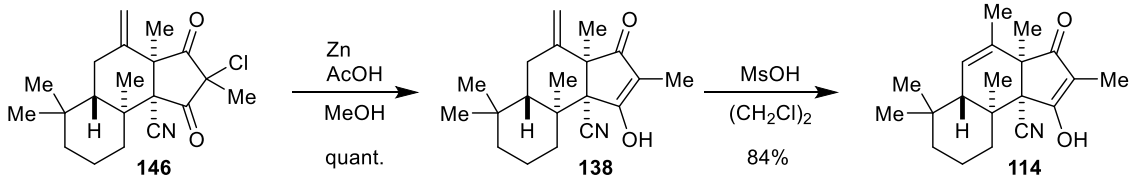
Scheme 33. Synthesis of α-chloro-β-ketonitrile **144**

The cyclization of **144** proceeded by the treatment with BCl_3 (Scheme 34), and the resulting imine **145** underwent hydrolysis in aqueous MsOH, giving rise to the desired diketone **146** in 50% yield as a single diastereomer. The two-step transformation was accompanied with partial dechlorination to give enamine **140** in 19% yield.



Scheme 34. Cyclization of α-chloro-β-ketonitrile **137**

Diketone **146** was then converted to the tricyclic model compound **114** (Scheme 35). Thus, the chlorine atom of **146** was cleanly removed by the reaction with zinc powder and acetic acid in methanol. The resulting 1,3-diketone **138** in enol form was treated with MsOH in $(CH_2Cl)_2$, and the *exo* olefin moiety was successfully isomerized to the *endo* olefin. Consequently, the BCD-skeleton of andrastin C containing three contiguous quaternary stereogenic carbon atoms and the 1,3-diketone moiety was successfully constructed.

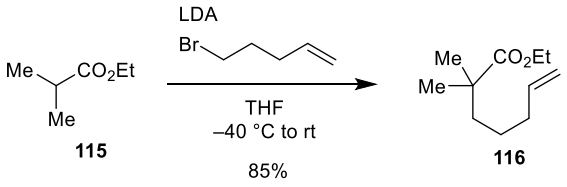


Scheme 35. Completion of the synthesis of tricyclic compound **114**

In summary, the author developed the new method for the construction of the BCD-skeleton of andrastin C on the basis of the cyclization reactions of alkanenitrile derivatives. The B ring was constructed by an intramolecular conjugate addition of alkanenitrile to α,β-unsaturated ester, with the stereocontrol of an angular quaternary carbon atom. Intramolecular cyano-ene type reactions were applied for the cyclization of the C ring and the D ring. The property of a cyano group, namely, sterically compact linear shape, showed advantage for constructing the BCD-skeleton of andrastin C possessing three contiguous quaternary carbon atoms. These methods would provide new synthetic route to andrastins and other natural products possessing polycyclic carbon framework.

Experimental Section of Chapter 2

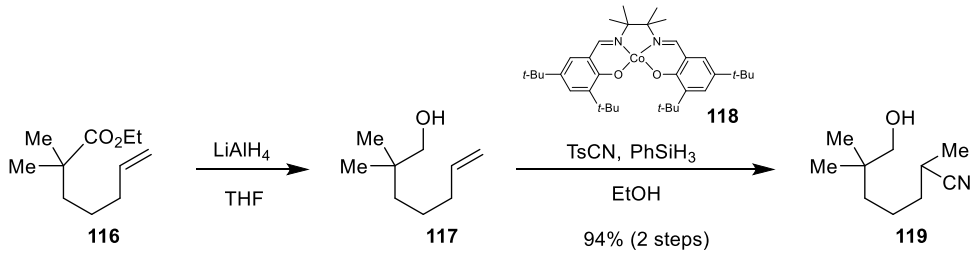
Experimental Procedure for Chapter 2



Ethyl 2,2-dimethylhept-6-enoate (116): To a stirred solution of diisopropylamine (15.5 mL, 110 mmol) in THF (333 mL) was added 2.69 M solution of *n*-butyllithium in hexane (39.0 mL, 105 mmol) at 0 °C, and the solution was stirred at 0 °C for 30 min. After the resulting LDA solution was cooled to –50 °C, ethyl isobutylate (**115**) (13.4 mL, 100 mmol) was added slowly. After being stirred at –50 to –40 °C for 1 h, 5-bromo-1-pentene (15.4 mL, 130 mmol) was added and stirred at –40°C for 10 min and then at room temperature for 6 h. Saturated aqueous NH_4Cl (50 mL) was added into the mixture and the product was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure.

Purification of the residue by distillation (3 mmHg, 48 °C) afforded ester **116** (15.7 g, 85.3 mmol, 85%)

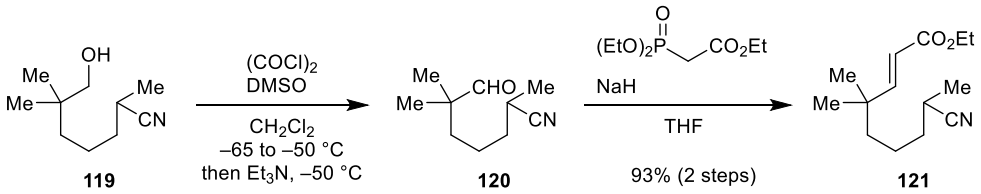
Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) 5.83–5.73 (1H, m), 5.00 (1H, d, *J* = 17.2 Hz), 4.94 (1H, d, *J* = 10.3 Hz), 4.11 (2H, q, *J* = 6.9 Hz), 2.02 (2H, q, *J* = 6.9 Hz), 1.37–1.27 (2H, m), 1.55–1.48 (2H, m), 1.24 (3H, t, *J* = 6.9 Hz), 1.16 (2×3H, s)



7-Hydroxy-2,6,6-trimethylheptanenitrile (119): To a stirred suspension of lithium alminium hydride (21.0 mmol, 797.0 mg) in THF (45mL) was added a solution of ester **116** (5.53 g, 30.0 mmol) in THF (15mL) slowly at 0 °C. The reaction mixture was stirred at room temperature for 35 min, and quenched by successive addition of water (0.8 mL), 15% aqueous NaOH (0.8 mL), and water (2.4 mL) at 0 °C. After being stirred for 30 min at room temperature, the mixture was dried over $MgSO_4$ and concentrated under reduced pressure. The crude alcohol **117** (4.47 g) was used for the next step without further purification.

To a stirred solution of the above crude alcohol **117** in EtOH (141 mL) was added cobalt-salen catalyst **118** (169.7 mg, 0.281 mmol), *p*-toluene sulfonyl cyanide (5.60 g, 30.9 mmol), and phenylsilane (3.46 mL, 28.1 mmol) at room temperature. The solution was stirred at room temperature for 17.5 h and then the solvent was removed under reduced pressure. To the residue was added saturated aqueous sodium bicarbonate (150 mL) and the product was extracted with Et_2O. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, hexane–EtOAc = 1:1) gave hydroxynitrile **119** (4.79 g, 28.3 mmol, 94%)

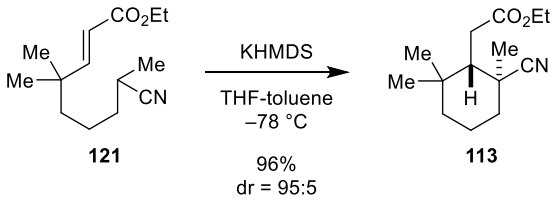
Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) 3.33 (2H, d, *J* = 5.7 Hz), 2.67–2.57 (1H, m), 1.66–1.57 (1H, m), 1.54–1.45 (1H, m), 1.44–1.35 (1H, m), 1.32 (3H, d, *J* = 6.9 Hz), 1.32–1.23 (3H, m), 0.88 (2×3H, s)



Ethyl (*E*)-8-cyano-4,4-dimethylnon-2-enoate (121): To a stirred solution of oxalyl chloride (3.96 mL, 46.2 mmol) in CH_2Cl_2 (130 mL) was added a solution of dimethyl sulfoxide (6.56 mL, 92.4 mmol) in CH_2Cl_2 (30 mL) at –78 °C. After being stirred at –78 °C for 10 min, a solution of alcohol **119** in CH_2Cl_2 (30 mL) was added at –65 °C and then the resulting mixture was gradually warmed to –50 °C within 80 min. Triethylamine (26.8 mL, 193 mmol) was added into the mixture and stirred at –50 °C for 30 min. The reaction was quenched by the addition of saturated aqueous NH_4Cl and the product was extracted with EtOAc. The combined organic layeres were washed successively with water and brine and then dried over $MgSO_4$ and concentrated under reduced pressure. The residue was dissolved in Et_2O and filered through a cotton plug and then concentrated under reduced pressure. The crude aldehyde **120** (6.57 g) was used for the next step without further purification.

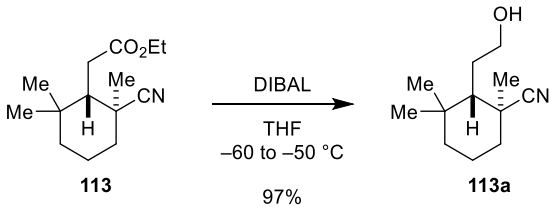
To a stirred suspension of NaH (55%, 2.10 g, 48.1 mmol) in THF (78 mL) was added Ethyl diethylphosphonoacetate (9.94 mL, 50.1 mmol) at 0 °C. After being stirred at 0 °C for 30 min, a solution of the crude aldehyde **120** in THF (50 mL) was added. The mixture was stirred at room temperature for 1 h, and then saturated aqueous NH_4Cl was added. The product was extracted with EtOAc and combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, hexahe–EtOAc = 4:1) afforded unsaturated ester **121** (8.50g, 35.8 mmol, 93% for 2 steps)

Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) 6.89 (1H, d, *J* = 16.0 Hz), 5.73 (1H, d, *J* = 16.0 Hz), 4.19 (2H, q, *J* = 7.5 Hz), 2.63–2.54 (1H, m), 1.62–1.25 (9H, m), 1.30 (3H, t, *J* = 6.9 Hz), 1.06 (2×3H, s)



Ethyl 2-((1*S,2*S**)-2-cyano-2,6,6-trimethylcyclohexyl)acetate (113):** To a stirred solution of unsaturated ester **121** (4.75 g, 20.0 mmol) in THF (100 mL) was added KHMDS (0.5 M in toluene, 60.0 mL, 30.0 mmol) at –78 °C and the solution was stirred at –78 °C for 2 h. Saturated aqueous NH_4Cl was added into the mixture and the product was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, hexahe–EtOAc = 5:1) afforded unsaturated ester **113** (4.56 g, 19.2 mmol, 96%) as a 95:5 mixture of diastereomers.

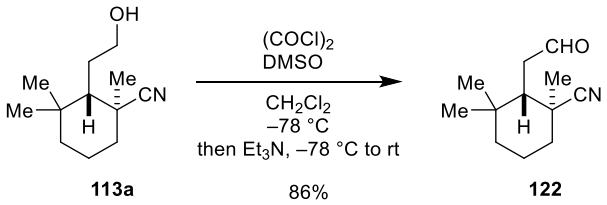
Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) 4.22–4.13 (2H, m), 2.49 (1H, dd, *J* = 16.1, 6.3 Hz), 2.41 (1H, dd, *J* = 16.1, 4.6 Hz), 2.34–2.30 (1H, m), 1.91–1.86 (2H, m), 1.64–1.53 (2H, m), 1.47–1.40 (1H, m), 1.35 (3H, s), 1.36–1.30 (1H, m), 1.28 (3H, t, *J* = 7.5 Hz), 0.94 (3H, s), 0.88 (3H, s)



(1*S,2*S**)-2-(2-Hydroxyethyl)-1,3,3-trimethylcyclohexane-1-carbonitrile (113a):** To a stirred solution of ester **113** (3.61 mmol, 15.2 mmol) in THF (76 mL) was added DIBAL (1.03 M in hexane, 31.0 mL, 31.9 mmol) at –78°C and the reaction mixture was stirred at –60 °C for 2.5 h. Additional DIBAL (1.03 M in hexane, 3.10 mL, 3.19 mmol) was added into the reaction mixture and stirred at –60 °C for 30 min. The reaction was quenched by the addition of saturated aqueous NH_4Cl. After dilution with EtOAc, Roschell's salt was added and the resulting mixture was stirred vigorously at room temperature. The product was extracted with EtOAc and the combined organic layers were dried over $MgSO_4$ and concentrated under

reduced pressure. Purification by flash column chromatography (SiO_2, hexahe–EtOAc = 1:1) afforded alcohol **113a** (2.87 g, 14.7 mmol, 97%) as a 93:7 mixture of diastereomers.

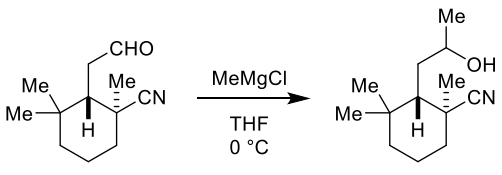
Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) 3.86–3.76 (2H, m), 1.96–1.89 (1H, m), 1.88–1.77 (2H, m), 1.72–1.60 (1H, m), 1.59–1.49 (2H, m), 1.48–1.42 (1H, m), 1.37 (3H, s), 1.34–1.19 (2H, m), 0.96 (3H, s), 0.88 (3H, s)



113a 122

(1*S,2*S**)-1,3,3-Trimethyl-2-(2-oxoethyl)cyclohexane-1-carbonitrile (122):** To a stirred solution of oxalyl chloride (1.35 mL, 15.7 mmol) in CH_2Cl_2 (35 mL) was added a solution of dimethyl sulfoxide (2.23 mL, 31.4 mmol) in CH_2Cl_2 (15 mL) at –78 °C. After being stirred at –78 °C for 10 min, a solution of alcohol **113a** (2.55 g, 13.1 mmol) in CH_2Cl_2 (15 mL) was added and the resulting mixture was stirred at –78 °C for 1 h. Triethylamine (9.13 mL, 65.5 mmol) was added into the mixture and stirred at –78 °C for 40 min and then at room temperature for 15 min. Saturated aqueous NH_4Cl was added into the mixture and the product was extracted with Et_2O. The combined organic layers were washed successively with water, brine and then dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, hexahe–EtOAc = 2:1) afforded aldehyde **122** (2.37 g, 12.3 mmol, 94%) as a 97:3 mixture of diastereomers. Further purification by ecrystallization (hexane-Et_2O = 5:1) afforded aldehyde **122** (2.18g, 11.3mmol, 86%) as a single diastereomer.

Colorless solid; ^{1}H NMR (500 MHz, $CDCl_3$) 9.83–9.80 (1H, m), 2.63 (1H, ddd, *J* = 17.8, 6.9, 2.3 Hz), 2.54 (1H, dd, *J* = 17.8, 4.0 Hz), 2.38 (1H, dd, *J* = 6.9, 4.1 Hz), 1.94–1.86 (2H, m), 1.65–1.45 (5H, m), 1.36–1.28 (1H, m), 1.35 (3H, s), 0.88 (2×3H, s)

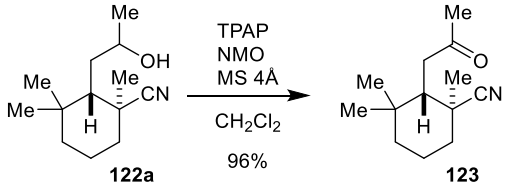


122 122a

(1*S,2*S**)-2-(2-Hydroxypropyl)-1,3,3-trimethylcyclohexane-1-carbonitrile (122a):** To a stirred solution of aldehyde **122** (5.03 g, 26.0 mmol) in THF (130 mL) was added MeMgBr (3M

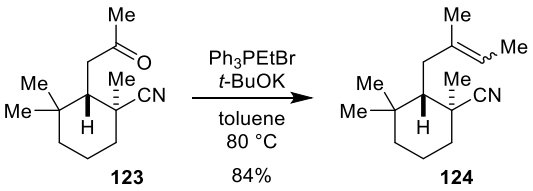
in THF, 11.0 mL, 33 mmol) at 0 °C and the reaction mixture was stirred at 0 °C for 10 min. Saturated aqueous NH_4Cl was added into the mixture and the product was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, hexahe–EtOAc = 2:1 to 1:1) afforded aldehyde **122a** (4.59 g, 21.9 mmol, 84%) as a 52:48 mixture of diastereomers.

Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) 4.22 (0.52H, br-s), 3.92 (0.48H, br-s), 1.98–1.61 (4H, m), 1.58–1.41 (4H, m), 1.37 (1.6H, s), 1.35 (1.4H, s), 1.32–1.23 (4H, m), 0.98 (1.6H, s), 0.96 (1.4 H, s), 0.88 (1.4H, s), 0.86 (1.6H, s)



(1*S,2*S**)-1,3,3-Trimethyl-2-(2-oxopropyl)cyclohexane-1-carbonitrile (123):** To a stirred mixture of alcohol **122a** (1.52 g, 7.26 mmol), *N*-methyl morpholine *N*-oxide (1.70 g, 14.5 mmol) and MS 4Å (2.00 g) in CH_2Cl_2 (36 mL) was added TPAP (255.1 mg, 0.726 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 6.3 h and then filtered through a Celite pad and then concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, hexahe–EtOAc = 3:1) afforded ketone **123** (1.40 g, 6.74 mmol, 93%).

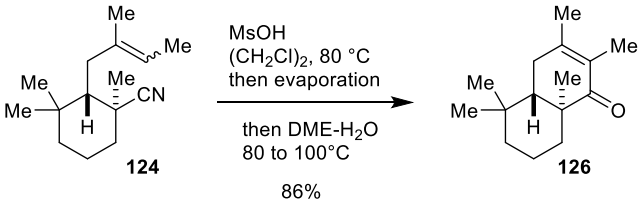
Colorless solid; ^{1}H NMR (500 MHz, $CDCl_3$) 2.62–2.57 (1H, m), 2.52–2.44 (2H, m), 2.24 (3H, s), 1.90–1.86 (2H, m), 1.65–1.55 (2H, m), 1.46–1.40 (1H, m), 1.37–1.29 (1H, m), 1.35 (3H, s), 0.86 (3H, s), 0.85 (3H, s)



(1*S,2*S**)-1,3,3-Trimethyl-2-(2-methylbut-2-en-1-yl)cyclohexane-1-carbonitrile (124):** A mixture of *t*-BuOK (673.3 mg, 6.00 mmol) and Ph_3PEtBr (2.38 g, 6.41 mmol) was stirred under vaccum at 80 °C for 2 h. To the mixture was added toluene (15 mL) and stirrrd at 80 °C for 30 min. To the mixture was added ketone **123** (921.4 mg, 4.44 mmol) in toluene (5 mL) and the reaction mixture was stirred at 80 °C for 30 min. The reaction was quenched by the addition of

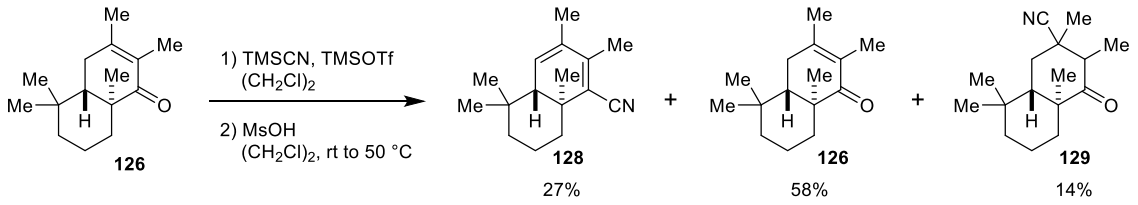
saturated aqueous NH_4Cl and the product was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, hexane–Et_2O = 10:1) afforded olefin **124** (814.9 mg, 3.71 mmol, 84%) as a 68:32 mixture of diastereomers.

Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) 5.38 (0.7H, q, *J* = 6.3 Hz), 5.23 (0.3H, q, *J* = 6.9 Hz), 2.50 (0.3H, dd, *J* = 14.9, 7.4 Hz), 2.31 (0.7H, dd, *J* = 14.9, 6.3 Hz), 2.20 (0.7H, dd, *J* = 14.9, 6.9 Hz), 2.15–2.09 (0.3H, m), 1.99–1.91 (1H, m), 1.89–1.77 (3H, m), 1.69–1.66 (3H, m), 1.59–1.56 (2H, m), 1.53–1.48 (2H, m), 1.44–1.39 (1H, m), 1.37 (1H, s), 1.34 (2H, s), 0.97–0.93 (4H, m), 0.89 (3H, s)



(4a*S,8a*S**)-2,3,5,5,8a-Pentamethyl-4a,5,6,7,8,8a-hexahydronaphthalen-1(4H)-one (126):** To a stirred solution of nitrile **124** (1.64g, 7.46 mmol) in $(CH_2Cl)_2$ (37.0 mL) was added MsOH (4.80 mL, 74.6 mmol) and stirred at 80 °C for 2 h. After the solution was cooled to room temperature, solvent was removed under reduced pressure. The residue was dissolved in 1:1 mixture of DME-H_2O (380 mL) and the solution was stirred at 80 °C for 20.5 h and then at 100 °C for 7.5 h. After cooling to room temperature, DME was removed under reduced pressure and saturated aqueous sodium bicarbonate was added to the mixture. The product was extracted with EtOAc and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, hexane–EtOAc = 3:1) afforded enone **126** (1.42 g, 6.44 mmol, 86%)

Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) 2.37–2.16 (2H, m), 1.91 (3H, s), 1.91–1.85 (1H, m), 1.73 (3H, s), 1.59–1.52 (3H, m), 1.46–1.39 (1H, m), 1.34–1.24 (1H, m), 1.20–1.12 (1H, m), 1.00 (3H, s), 0.97 (3H, s), 0.90 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.20, 152.35, 128.20, 48.19, 44.02, 41.58, 33.57, 33.38, 32.23, 30.95, 22.09, 21.18, 18.21, 17.29, 11.43; IR (ATR) ν 2925, 1663, 1460, 1373, 1301, 1016 cm^{-1}; HRMS (FD) calcd for $C_{15}H_{24}O$ (M^+): 220.1827, found: 220.1819.

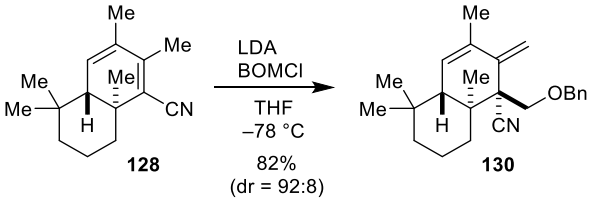


To a stirred solution of enone **126** (5.48 g, 24.9 mmol) in $(CH_2Cl)_2$ (125 mL) were added TMSCN (21.6 mL, 174 mmol) and TMSOTf (5.10 mL, 12.5 mmol) at 0 °C and the reaction mixture was stirred at room temperature for 3 h. The mixture was poured into saturated aqueous sodium bicarbonate (300 mL) and the product was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product (7.62 g) was used for the next step without further purification.

To a stirred mixture of the crude product in $(CH_2Cl)_2$ was added MsOH (8.10 mL, 125 mmol) and stirred at room temperature for 15 min and then at 50 °C for 1.5 h. The reaction was quenched by the addition of saturated aqueous sodium bicarbonate and the product was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, hexane–CH_2Cl_2 = 5:1–3:1 for **128**, hexane‑EtOAc = 1:1 for **126** and **129**) afforded nitrile **128** (1.53 g, 6.66 mmol, 27%) , and mixture of enone **129** (3.18 g, 14.4 mmol, 58%), and β-ketonitrile **129** (0.90 g, 3.64 mmol, 14%).

(4a*S,8a*S**)-2,3,5,5,8a-Pentamethyl-4a,5,6,7,8,8a-hexahydronaphthalene-1-carbonitrile (128):** Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) 5.84 (1H, s), 2.05 (3H, s), 2.02–1.98 (1H, m), 1.87 (3H, s), 1.85–1.83 (1H, m), 1.69–1.57 (2H, m), 1.52–1.44 (2H, m), 1.24–1.16 (1H, m), 0.953 (3H, s), 0.945 (3H, s), 0.94 (3H, s)

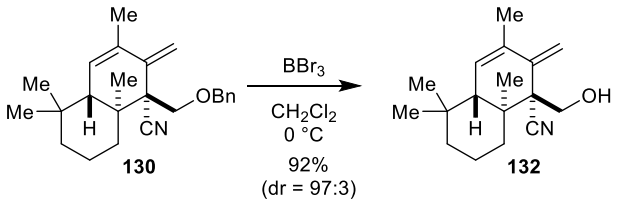
(4a*S,8a*S**)-2,3,4a,8,8-pentamethyl-4-oxodecahydronaphthalene-2-carbonitrile (129):**colorless solid; ^{1}H NMR (500 MHz, $CDCl_3$) 2.56 (1H, q, *J* = 6.3 Hz), 2.07 (1H, dd, *J* = 11.3, 2.3 Hz), 1.85 (1H, t, *J* = 13.2 Hz), 1.61–1.53 (5H, m), 1.54 (3H, s), 1.47–1.40 (1H, s), 1.27–1.20 (1H, m), 1.19 (3H, d, *J* = 6.3 Hz), 1.14 (3H, s), 0.96 (3H, s), 0.93 (3H, s)



(1*S,4a*S**,8a*S**)-1-((Benzyloxy)methyl)-3,5,5,8a-tetramethyl-2-methylene-1,2,4a,5,6,7,8,8a-octahydronaphthalene-1-carbonitrile (130):** To a stirred solution of *i*-Pr_2NH (853 μL, 6.06

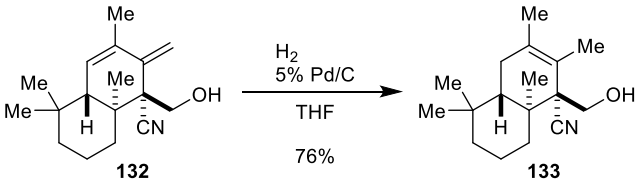
mmol) in THF (30 mL) was added *n*-BuLi (2.65 M in hexane, 2.15 mL, 5.69 mmol) at 0 °C and the solution was stirred at 0 °C for 30 min. To the resulting LDA solution was added a solution of unsaturated nitile **128** (868.7 mg, 3.79 mmol) in THF (8 mL) at –78 °C and the reaction mixture was stirred at –78 °C for 30 min. BOMCl was added into the reaction mixture and stirred at –78 °C for 1 h. Saturated aqueous NH_4Cl was added into the mixture and the product was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, hexahe–EtOAc =10:1) afforded benzyl ether **130** (1.09 g, 3.12 mmol, 82%, dr = 92:8) as a 82:18 mixture with di(benzyloxy)methane.

Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) 7.37–7.30 (5H, m), 5.41 (1H, s), 5.52 (1H, s), 5.31 (1H, s), 4.06 (1H, d, *J* = 12.6 Hz), 4.55 (1H, d, *J* = 12.6 Hz), 3.80 (1H, d, *J* = 9.8 Hz), 3.40 (1H, d, *J* = 9.2 Hz), 1.87 (3H, s), 1.80 (1H, s), 1.77–1.68 (3H, m), 1.59–1.55 (1H, m), 1.49–1.43 (1H, m), 1.22–1.12 (1H, m), 1.03 (3H, s), 0.94 (3H, s), 0.85 (3H, s)

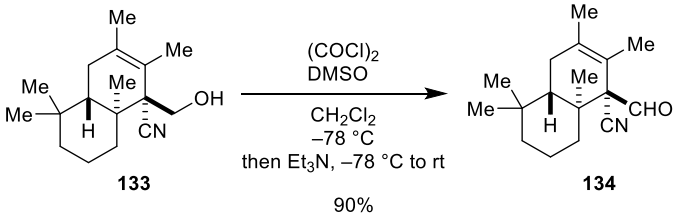


(1*S,4a*S**,8a*S**)-1-(Hydroxymethyl)-3,5,5,8a-tetramethyl-2-methylene-1,2,4a,5,6,7,8,8a-octahydronaphthalene-1-carbonitrile (132):** To a stirred solution of benzyl ether **130** (1.09 g, 3.12 mmol) in CH_2Cl_2 (16 mL) was added BBr_3 (1M in CH_2Cl_2, 9.36 mL, 9.36 mmol) at 0 °C. After being stirred at 0 °C for 1 h, the reaction mixture was poured into saturated aqueous sodium bicarbonate via cannula. The product was extracted with EtOAc and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, hexane–EtOAc = 1:1) afforded alcohol **132** (747.2 mg, 2.88 mmol, 92%) as a 97:3 mixture of diastereomers.

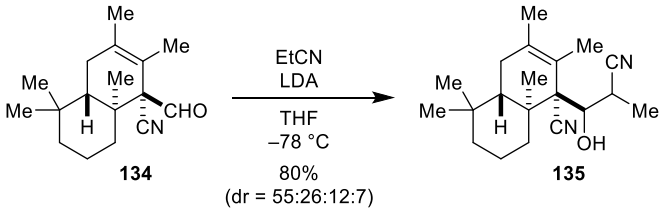
Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) 5.64 (1H, s), 5.48 (1H, s), 5.37 (1H, s), 3.96 (1H, t, *J* = 9.7 Hz), 3.58 (1H, dd, *J* = 10.9, 5.2 Hz), 1.91 (3H, s), 1.87 (1H, s), 1.83–1.68 (3H, m), 1.65–1.57 (1H, m), 1.52–1.47 (1H, m), 1.24–1.15 (1H, m), 1.06 (3H, s), 0.99 (3H, s), 0.87 (3H, s)



(1*S,4a*S**,8a*S**)-1-(Hydroxymethyl)-2,3,5,5,8a-pentamethyl-1,4,4a,5,6,7,8,8a-octahydronaphthalene-1-carbonitrile (133):** A mixture of diene **132** (747.2 mg, 2.88 mmol) and 5% palladium on charcoal (747.2 mg) in THF (14.4 mL) was stirred under hydrogen atmosphere (balloon) at room temperature for 45 min. The reaction mixture was filtered through a Celite pad and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, hexane–EtOAc = 10:1) afforded tetrasubstituted olefin **133** (573.5 mg, 2.19 mmol, 76%).
Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) 3.90 (1H, dd, *J* = 12.1, 6.9 Hz), 3.75 (1H, dd, *J* = 12.0, 7.5 Hz), 1.99–1.88 (1H, m), 1.86 (3H, s), 1.79–1.73 (2H, m), 1.73 (3H, s), 1.66–1.60 (2H, m), 1.51–1.50 (1H, m), 1.49–1.43 (1H, m), 1.31–1.17 (2H, m), 1.12 (3H, s), 0.94 (3H, s), 0.89 (3H, s)

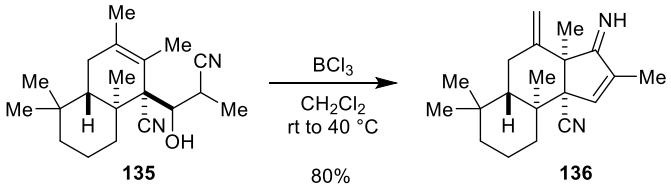


(1*S,4a*S**,8a*S**)-1-Formyl-2,3,5,5,8a-pentamethyl-1,4,4a,5,6,7,8,8a-octahydronaphthalene-1-carbonitrile (134):** To a stirred solution of oxalyl chloride (80.6 μL, 0.938 mmol) in CH_2Cl_2 (3.0 mL) was added a solution of dimethyl sulfoxide (133 μL, 1.88 mmol) in CH_2Cl_2 (0.70 mL) at –78 °C. After being stirred at –78 °C for 15 min, a solution of alcohol **133** (122.6 mg, 0.469 mmol) in CH_2Cl_2 (1.0 mL) was added and the resulting mixture was stirred at –78 °C for 30 min. Triethylamine (524 μL, 3.76 mmol) was added into the mixture and stirred at –78 °C for 10 min and then at room temperature for 40 min. Saturated aqueous NH_4Cl was added into the mixture and the product was extracted with Et_2O. The combined organic layers were washed successively with water, brine and then dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, hexahe–EtOAc = 10:1) afforded aldehyde **134** (110.0 mg, 0.425 mmol, 90%).
Colorless solid; ^{1}H NMR (500 MHz, $CDCl_3$) 9.47 (1H, s), 2.20–2.12 (1H, m), 2.10–1.98 (1H, m), 1.92–1.84 (2H, m), 1.81 (3H, s), 1.77–1.71 (1H, m), 1.68 (3H, s), 1.65–1.44 (3H, m), 1.22–1.14 (1H, m), 1.17 (3H, s), 0.97 (3H, s), 0.94 (3H, s)



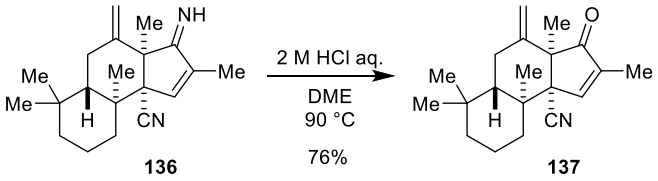
(1*S,4a*S**,8a*S**)-1-((1*R*)-2-Cyano-1-hydroxypropyl)-2,3,5,5,8a-pentamethyl-1,4,4a,5,6,7,8,8a-octahydronaphthalene-1-carbonitrile (135):** To a stirred solution of *i*-Pr_2NH (26.0 μL, 0.186 mmol) in THF (1.00 mL) was added *n*-BuLi (2.65 M in hexane, 68.0 μL, 0.179 mmol) at 0 °C and the mixture was stirred at 0 °C for 30 min. To the resulting LDA solution was added propionitrile (14.0 μL, 0.194 mmol) at –78 °C and the reaction mixture was stirred at –78 °C for 30 min. A solution of aldehyde **134** (38.7 mg, 0.149 mmol) in THF (0.49 mL) was added and the reaction mixture was stirred at –78 °C for 15 min. Saturated aqueous NH_4Cl was added into the mixture and the product was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, hexahe–EtOAc = 1:1) afforded hyroxynitrile **135** (37.5 mg, 0.119 mmol, 80%) as a 55:26:12:7 mixture of four diastereomers.

Colorless solid; ^{1}H NMR (500 MHz, $CDCl_3$) 4.20–4.15 (0.26H, m), 4.09–4.04 (0.12H, m), 3.83 (0.07H, d, *J* = 6.3 Hz), 3.79 (0.55H, d, *J* = 10.3 Hz), 3.22–3.05 (0.26H, m), 2.87–2.74 (0.74H, m), 2.56–2.20 (1H, m), 2.10–1.98 (4H, m), 1.96–1.73 (2H, m), 1.72–1.53 (6H, m), 1.52–1.35 (3H, m), 1.34–1.12 (3H, m), 1.11–1.07 (2H, m), 0.97–0.85 (6H, m),



(3a*R,5a*S**,9a*S**,9b*R**)-3-Imino-2,3a,6,6,9a-pentamethyl-4-methylene-3,3a,4,5,5a,6,7,8,9,9a-decahydro-9bH-cyclopenta[*a*]naphthalene-9b-carbonitrile (136):** To a stirred solution of hydroxynitrile **135** (66.8 mg, 0.212 mmol) in CH_2Cl_2 (1.06 mL) was added BCl_3 (1 M in CH_2Cl_2, 1.23 mL, 1.23 mmol) and the reaction mixture was stirred at room temperature for 15 h and then stirred at 40 °C for 6.3 h. Saturated aqueous sodium bicarbonate was added into the mixture and the product was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, hexahe–EtOAc = 1:1) afforded unsaturated imine **136** (50.0 mg, 0.169 mmol, 80%).

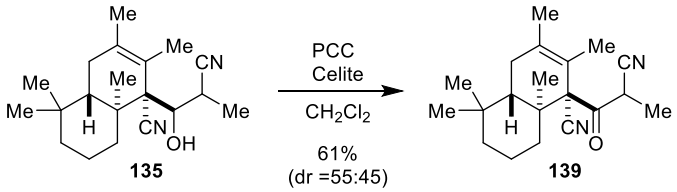
Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) 6.55 (1H, s), 5.19–5.15 (2H, m), 2.29–2.13 (2H, m), 2.00 (3H, s), 1.80–1.72 (1H, m), 1.63–1.46 (3H, m), 1.44–1.35 (1H, m), 1.39 (3H, s), 1.23 (3H, s), 1.11–1.07 (1H, m), 1.14–0.97 (1H, m), 0.92 (3H, s), 0.76 (3H, s)



136 137

(3a*R*,5a*S***,9a*S***,9b*R***)-2,3a,6,6,9a-Pentamethyl-4-methylene-3-oxo-3,3a,4,5,5a,6,7,8,9,9a-decahydro-9bH-cyclopenta[*a*]naphthalene-9b-carbonitrile (137):** To a stirred solution of unsaturated imine **136** (50.0 mg, 0.169 mmol) in DME (2.00 mL) was added 2M aqueous HCl (2.00 mL) and the reaction mixture was stirred at 90 °C for 25 h. Saturated aqueous sodium bicarbonate was added into the mixture and the product was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, hexahe–EtOAc = 10:1) afforded unsaturated ketone **137** (38.3 mg, 0.129 mmol, 76%).

Colorless solid; ^{1}H NMR (500 MHz, $CDCl_3$) 7.25 (1H, s), 5.13 (2H, s), 2.26–2.20 (2H, m), 1.91 (3H, s), 1.89–1.77 (1H, m), 1.54–1.50 (1H, m), 1.46 (3H, s), 1.46–1.38 (2H, m), 1.28 (3H, s), 1.27–1.23 (1H, m), 1.14–1.00 (2H, m), 0.93 (3H, s), 0.78 (3H, s)

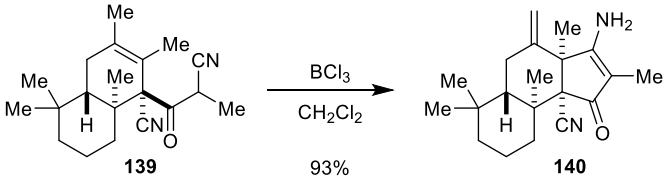


135 139

(1*S*,4a*S***,8a*S***)-1-(2-Cyanopropanoyl)-2,3,5,5,8a-pentamethyl-1,4,4a,5,6,7,8,8a-octahydro naphthalene-1-carbonitrile (139):** To a stirred mixture of hydroxylnitrile **135** (23.3 mg, 0.0740 mmol) and Celite (0.23 g) in CH_2Cl_2 (0.74 mL) was added PCC (79.8 mg, 0.37 mmol) and the reaction mixture was stirred at room temperature for 19 h. The reaction mixture was diluted with Et_2O and filtered through Celite pad and then concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, hexahe–EtOAc = 10:1) afforded ketonitrile **139** (14.1 mg, 0.0451 mmol, 61%) as a 55:45 mixture of diastereomers.

Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) 4.35 (0.6H, q, J = 7.5 Hz), 4.23 (0.4H, q, J = 6.9 Hz), 2.13–1.86 (3H, m), 1.82–1.74 (3H, m), 1.70–1.64 (3H, m), 1.62–1.51 (3H, m), 1.47–1.41 (1H,

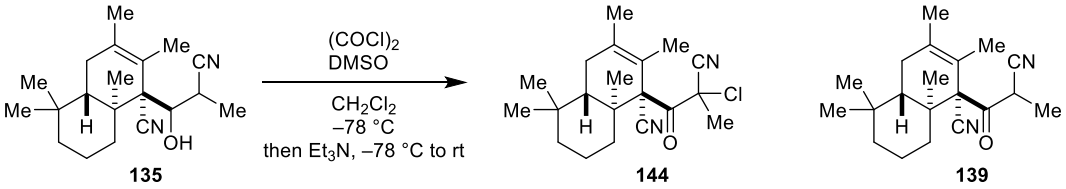
m), 1.34–1.24 (5H, m), 1.13–1.00 (2H, m), 0.97–0.86 (7H, m)



139 140

(3a*R,5a*S**,9a*S**,9b*S**)-3-Amino-2,3a,6,6,9a-pentamethyl-4-methylene-1-oxo-1,3a,4,5,5a,6,7,8,9,9a-decahydro-9bH-cyclopenta[*a*]naphthalene-9b-carbonitrile (140):** To a stirred solution of ketonitrile **139** (14.1 mg, 0.0451 mmol) in CH_2Cl_2 (0.90 mL) was added BCl_3 (1 M in CH_2Cl_2, 270 μL, 0.270 mmol) and the reaction mixture was stirred at room temperature for 8.1 h. Saturated aqueous sodium bicarbonate was added into the mixture and the product was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, hexahe–EtOAc = 1:1) afforded enaminone **140** (13.1 mg, 0.0419 mmol, 93%).

Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) 5.20 (2H, s), 4.71 (2H, br-s), 2.39–2.25 (3H, m), 1.67 (3H, s), 1.62 (3H, s), 1.56–1.48 (2H, m), 1.32–1.23 (3H, m), 1.22 (3H, s), 1.12–1.04 (1H, m), 0.92 (3H, s), 0.75 (3H, s)

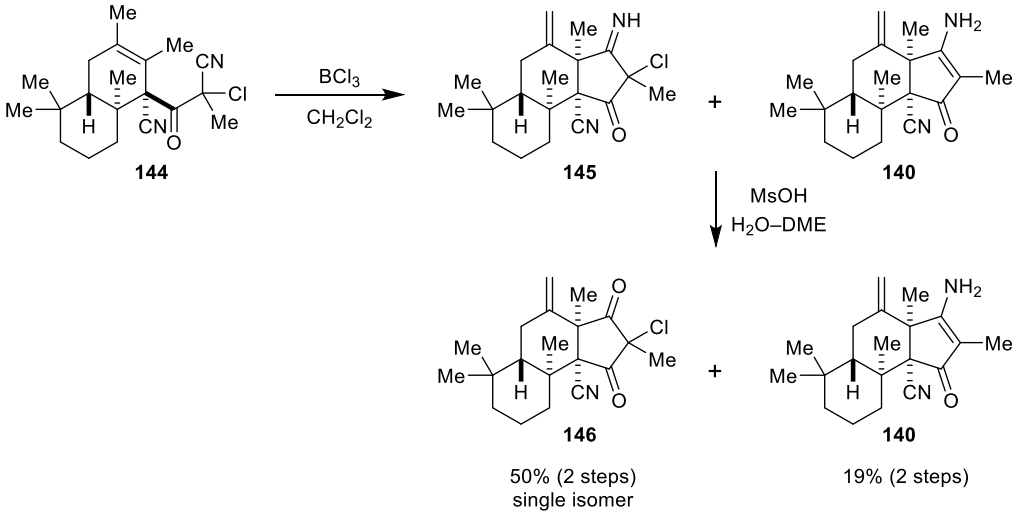


135 144 139

30% 11%

(1*S,4a*S**,8a*S**)-1-(2-Chloro-2-cyanopropanoyl)-2,3,5,5,8a-pentamethyl-1,4,4a,5,6,7,8,8a-octahydronaphthalene-1-carbonitrile (144):** To a stirred solution of oxalyl chloride (30.9 μL, 0.360 mmol) in CH_2Cl_2 (0.6 mL) was added a solution of dimethyl sulfoxide (51.1 μL, 0.720 mmol) in CH_2Cl_2 (0.3 mL) at –78 °C. After being stirred at –78 °C for 15 min, a solution of alcohol **135** (37.5 mg, 0.119 mmol) in CH_2Cl_2 (0.3 mL) was added and the resulting mixture was stirred at –78 °C for 1 h. Triethylamine (251 μL, 1.80 mmol) was added into the mixture and stirred at –78 °C for 30 min and the at room temperature for 2 h. Saturated aqueous NH_4Cl was added into the mixture and the product was extracted with Et_2O. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, hexahe–EtOAc = 15:1) afforded ketone **144** (12.3 mg, 0.0355 mmol, 30%) and enaminone **139** (4.2 mg, 0.013mmol, 11%).

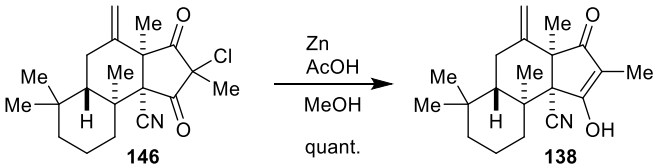
Colorless oil; (500 MHz, $CDCl_3$) 2.40–2.34 (1H, m), 2.27–2.20 (1H, m), 2.17–2.02 (2H, m), 1.98–1.90 (1H, m), 1.84–1.78 (4H, m), 1.76 (3H, s), 1.60–1.53 (1H, m), 1.46–1.40 (1H, m), 1.32–1.23 (5H, m), 0.98–0.87 (8H, m)



(3a*R,5a*S**,9a*S**,9b*S**)-2-Chloro-2,3a,6,6,9a-pentamethyl-4-methylene-1,3-dioxododecahydro-9bH-cyclopenta[*a*]naphthalene-9b-carbonitrile (146):** To a stirred solution of ketonirile **144** (18.7 mg, 0.0539 mmol) in CH_2Cl_2 (0.50 mL) was added BCl_3 (1 M in CH_2Cl_2, 320 μL, 0.320 mmol) and the reaction mixture was stirred at room temperature for 2 h. Saturated aqueous sodium bicarbonate was added into the mixture and the product was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The resulting crude imine was used for the next step without further purification.

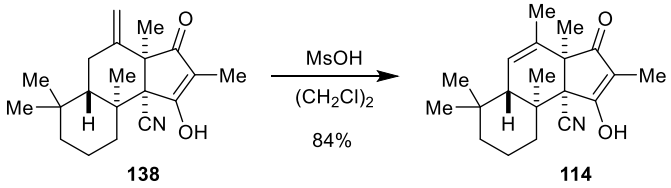
To a solution of the above crude imine in DME (0.27 mL) and H_2O (0.27 mL) was added MsOH (35.0 μL, 0.364 mmol) and the reaction mixture was stirred at room temperature for 3.7 h. Saturated aqueous sodium bicarbonate was added into the mixture and the product was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, hexahe–EtOAc = 10:1 for **146** and 1:1 for **140**) afforded diketone **146** (9.3 mg, 0.027 mmol, 50% for 2 steps) and enominone **140** (3.2 mg, 0.010 mmol, 19% for 2 steps).

Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) 5.16 (1H, s), 4.89 (1H, s), 2.46–2.36 (2H, m), 2.35–2.26 (1H, m), 1.88 (3H, s), 1.67 (3H, s), 1.66–1.43 (3H, m), 1.31 (3H, s), 1.28–1.21 (1H, m), 0.96–0.83 (8H, m)



(3a*R,5a*S**,9a*S**,9b*S**)-1-Hydroxy-2,3a,6,6,9a-pentamethyl-4-methylene-3-oxo-3,3a,4,5,5a,6,7,8,9,9a-decahydro-9bH-cyclopenta[*a*]naphthalene-9b-carbonitrile (138):** To a solution of diketone **146** (9.3 mg, 0.027 mmol) in MeOH (0.5 mL) were successively added AcOH (15.4 μL, 0.270 mmol) and zinc powder (17.6 mg, 0.270 mmol). After being stirred at room temperature for 40 min, the reaction mixture was filtered through a Celite pad and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, $CHCl_3$–MeOH = 5:1) afforded diketone **138** (8.5 mg, 0.027 mmol, 100%).

Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) 5.27 (1H, s), 5.25 (1H, s), 2.40–2.28 (2H, m), 1.83–1.74 (1H, m), 1.72 (3H, s), 1.71–1.65 (1H, m), 1.43–1.37 (1H, m), 1.32–1.23 (2H, m), 1.22 (3H, s), 1.12–1.02 (1H, m), 0.93 (3H, s), 0.95–0.86 (4H, m), 0.77 (3H, s)



(3a*R,5a*S**,9a*S**,9b*S**)-1-Hydroxy-2,3a,4,6,6,9a-hexamethyl-3-oxo-3,3a,5a,6,7,8,9,9a-octahydro-9bH-cyclopenta[*a*]naphthalene-9b-carbonitrile (114):** To a stirred solution of **138** (8.5 mg, 0.027 mmol) in $(CH_2Cl)_2$ (0.5 mL) was added MsOH (3.5 μL, 0.054 mmol) and the reaction mixture was stirred at room temperature for 1 h. Water (0.5 mL) was added into the reaction mixture and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, $CHCl_3$–MeOH = 5:1) afforded diketone **114** (7.1 mg, 0.023 mmol, 84%).

Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) 5.44 (1H, s), 2.64 (1H, br-s), 1.91 (3H, s), 1.82 (1H, d, J = 12.6 Hz), 1.78–1.40 (4H, m), 1.66 (3H, s), 1.47–1.40 (1H, m), 1.25 (3H, s), 1.23–1.15 (1H, m), 1.22 (3H, s), 0.89 (3H, s), 0.86 (3H, s)

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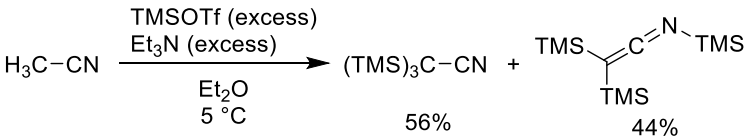

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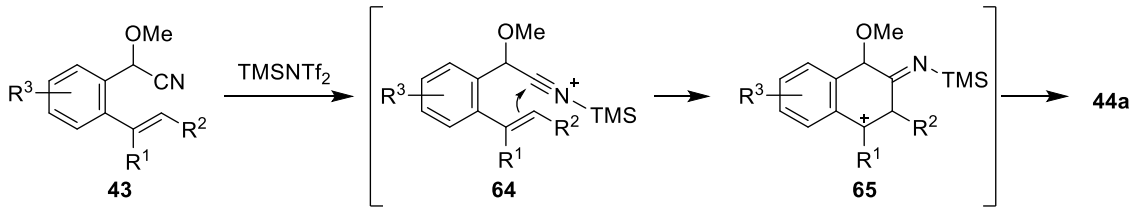
27) Considering the result of entry 8, the possibility of cationic mechanism as depicted below could not be excluded.



28) Low conversion by TBSCl was probably due to contamination of water when weighing hygroscopic solid TBSCl.

29) Because Japanese industrial safety and health law prohibits the production of 2-naphthylamine, the author did not examine the cyclization of unsubstituted 2-vinyl benzylcyanide.

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