Synthesis of Heterocycles Based on Transition Metal-catalyzed Cycloisomerization Reactions of Nitriles Having Multifunctionalities

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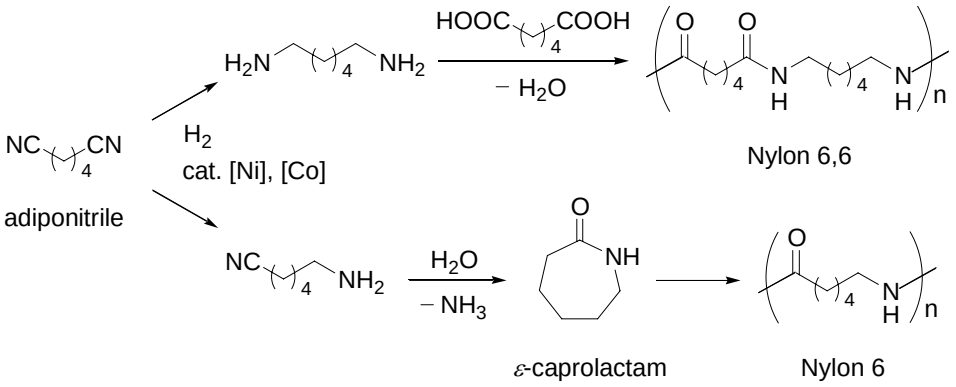
Contents

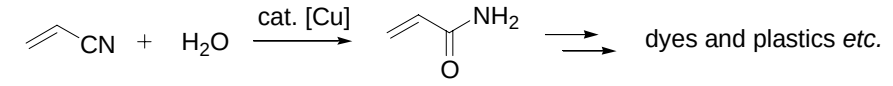
General Introduction

The occurrence of nitrogen-containing organic compounds in nature is widespread, and a vast number of them have found applications as pharmaceutical and functional material chemistry. In this respect, transition metal-catalyzed addition reactions to nitriles have received considerable attention as facile methods for the preparation of various amines and amides.[1] Nickel- or cobalt-catalyzed hydrogenation of adiponitrile is an important industrial process to obtain hexamethylenediamine or ε-caprolactam, which are precursors of Nylon 6,6 and Nylon 6, respectively (Scheme 1).[2] Hydration of acrylonitirle is also an important process in the industrial manufacture of acrylamide (Scheme 2).[2-4]

Scheme 1

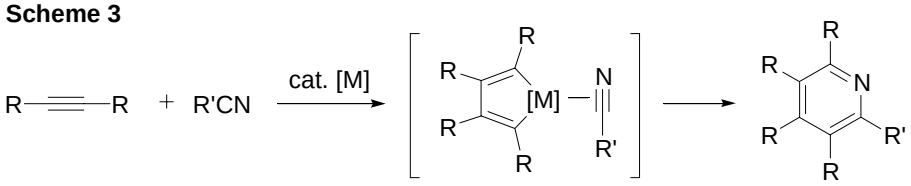


Scheme 2



Catalytic synthesis of pyridine derivatives via [2+2+2] cycloaddition reactions of two alkynes (or a tethered diyne) with a nitrile using various transition metal complexes including cobalt, ruthenium, rhodium, and nickel has also been well investigated (Scheme 3).[5] Although catalytic addition reactions to nitriles are one of the most important and highly

Scheme 3

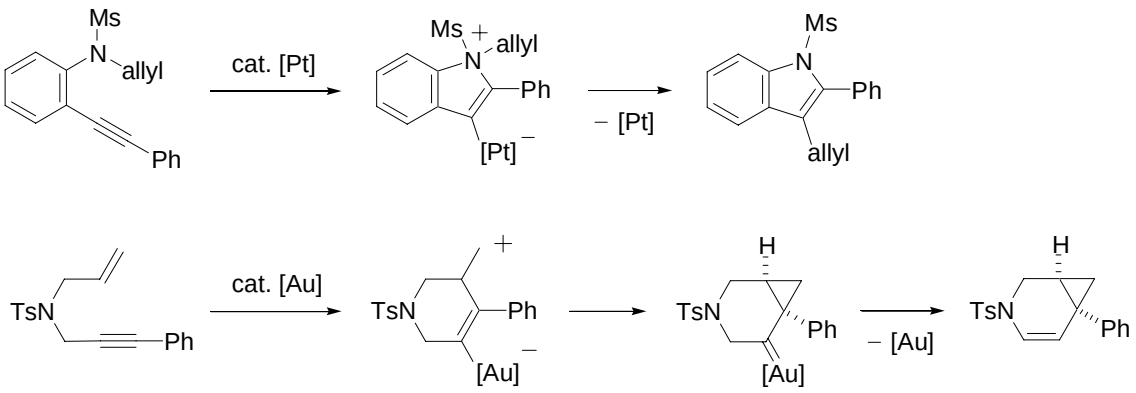


atom-efficient transformation methods, stoichiometric amounts of transition metal complexes are often required for the activation of nitriles to achieve their transformations except for extensively studied above examples.[6]

In general, nitriles are prone to coordinate with transition metal complexes. In fact, acetonitrile and benzonitrile are one of the most commonly used solvents in a range of catalytic reactions, and various metal complexes having nitrile ligands, i.e., $PdCl_2(RCN)_2$, are widely used as precatalysts in the transition metal-catalyzed reactions.[1] Considering the fact that development of pharmaceuticals and functional materials requires ready access to a diverse range of heterocycles, the discovery of transition metal-catalyzed methods to construct them with high efficiency using readily accessible building blocks are still needed.

Recently, transition metal-catalyzed cycloisomerization reactions have emerged as extremely efficient and powerful tools for the synthesis of various types of heterocycles. They now provide various heterocycles atom-efficiently with excellent functional group compatibility.[7] While cycloisomerization of alkynes, alkenes, and allenes have been extensively studied (Scheme 4), cycloisomerization of nitriles analogous have been received

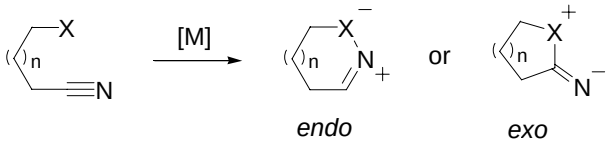
Scheme 4



much less attention.

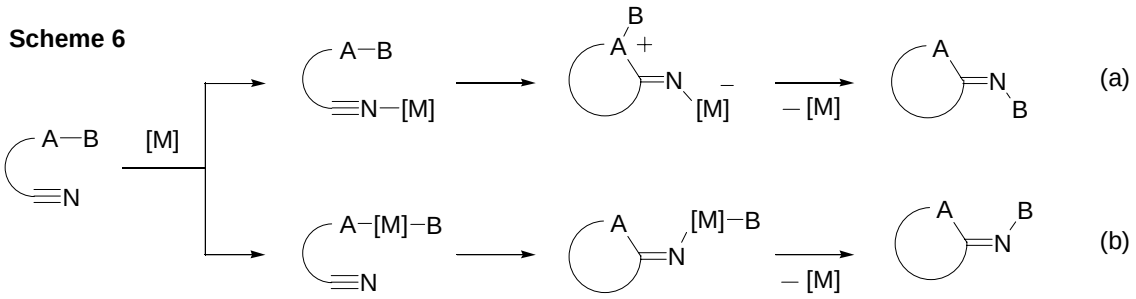
The cycloisomerization of nitriles can be classified into two types as shown in Scheme 5, i.e., (a) *Endo* cyclization by the nucleophilic attack of a nitrile nitrogen and (b) *Exo* cyclization by the electrophilic attack of a nitrile carbon.

Scheme 5



The latter *exo* cyclization mode can be classified into further two types as shown in Scheme 6; (a) Cycloisomerization via the activation of the cyano moiety by the transition metal complex and (b) Cycloisomerization via the activation of functional group that adds to cyano moiety by the transition metal complex.

Scheme 6



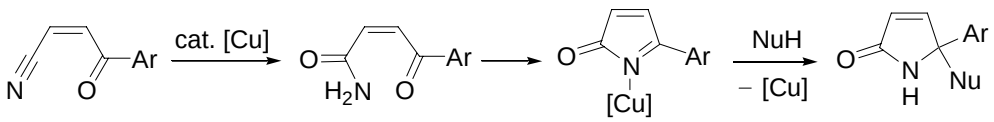
Since reaction modes of Scheme 5 and 6 give different cyclization products, it is important to control these modes precisely on the basis of both starting substrate structures and reaction conditions. Taking these considerations into account, the author started his study, aiming at establishing novel synthetic routes toward heterocycles through the cycloisomerization of nitriles. In this thesis, several new reactions were disclosed to demonstrate the synthetic value of cycloisomerization of nitriles. The benefit of these reaction systems is that highly useful heterocycles are obtained directly from readily

accessible starting materials in a single chemical operation with complete atom-efficiency under neutral reaction conditions.

In Chapters 1, 2, and 3, cycloisomerization of carbonyl-ene-nitrile compounds, i.e., nitriles having conjugated enone moieties, are described. Choosing appropriate reaction conditions, the author succeeded in controlling two different types of cyclization modes as shown in Scheme 5. Chapter 4 deals with new synthetic methods of carbonyl-ene-nitrile compounds through catalytic bromocyanation of alkynes. Using gallium chloride as a catalyst, regio- and stereoselective introduction of both bromo and cyano groups was achieved. In Chapters 5 and 6, palladium-catalyzed formation of 3-acyl-2-amino-benzofurans via the cycloisomerization of 2-(cyanomethyl)phenyl esters are described. Activating the ester group that adds to a cyano group by palladium catalysts, the author demonstrated unprecedented cycloisomerization of nitriles (Scheme 6b). Summary of this thesis is given below.

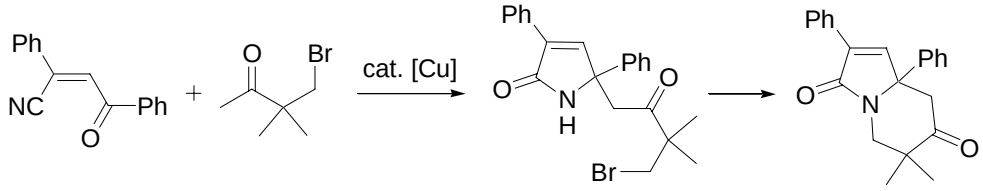
Overview of This Thesis

In Chapter 1, the author describes cycloisomerization of carbonyl-ene-nitrile compounds to 2-aza-2,4-cyclopentadienones using $Cu(OTf)_2$ as a catalyst (eq 1). The reaction proceeds via hydration of cyano group activated by the copper complex followed by dehydrative cyclization,[4] which is formally classified into the *endo* type cycloisomerization (Scheme 5). The resulting 2-aza-2,4-cyclopentadienones undergo the electrophilic attack of various compounds such as alkenes, aromatics, arylacetylenes, and alcohols to afford the corresponding pyrrolin-2-ones (γ-lactam) in the presence of the copper catalyst.



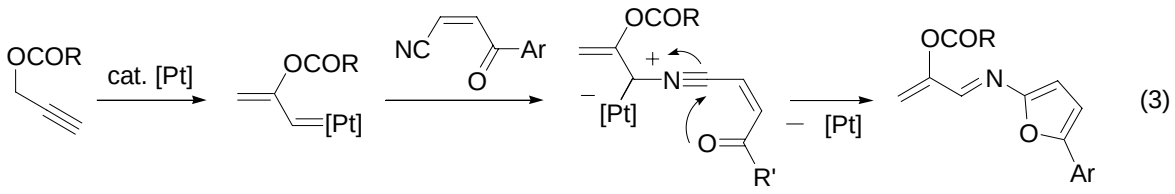
(1)

Chapter 2 deals with copper-catalyzed Mannich-type reactions of ketimine moiety of 2-aza-2,4-cyclopentadienone generated from cycloisomerization of carbonyl-ene-nitrile compound with ketones, leading to pyrrolin-2-one derivatives having acetonyl groups. Synthetic utility of this method is demonstrated by a rapid synthesis of azabicyclo-[4.3.0]nonanone (indolizidine), which has received considerable attention in view of its wide range of biological activities (eq 2).[8]



(2)

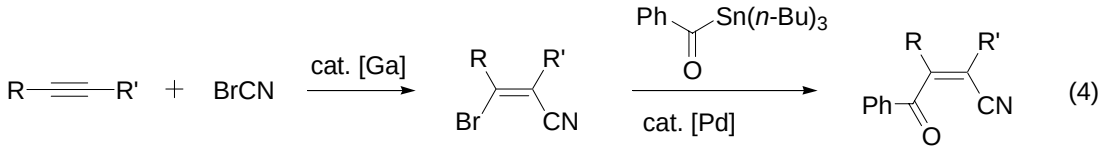
In Chapter 3, the author discloses platinum-catalyzed coupling reactions of carbonyl-ene-nitrile compounds with vinylcarbene complexes generated in situ from propargyl carboxylates (eq 3).[9] By simply changing reaction partners and catalysts, the formal *exo* type cyclization mode can be controlled (Scheme 5), and α-alkylidene-*N*-furylimines are obtained in moderate to good yields.



(3)

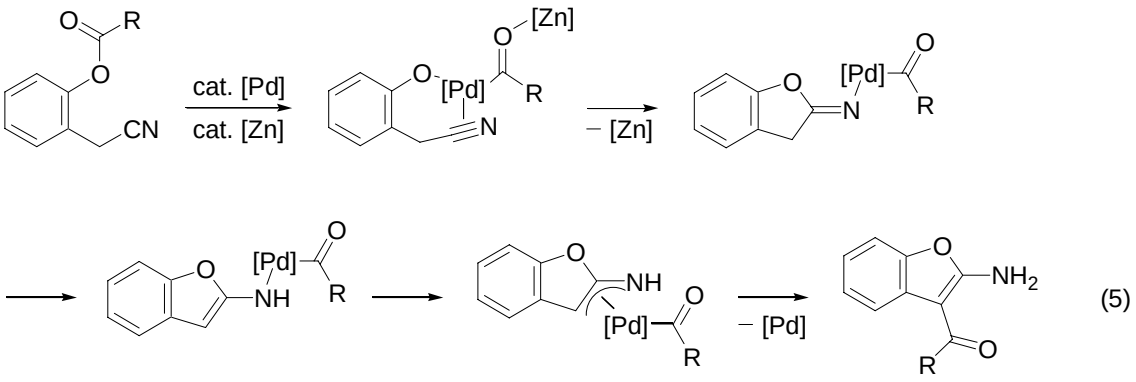
As demonstrated in Chapters 1, 2, and 3, carbonyl-ene-nitrile compounds are highly useful precursors for the cycloisomerization reactions. However, there have been only a few general methods to prepare their backbones stereoselectively.[10] Therefore, the author examined the synthesis of properly functionalized nitrile compounds, and found gallium-catalyzed regio- and stereoselective bromocyanation of alkynes with cyanogen bromide (Chapter 4). Since the carbon-bromine bonds can be further converted into various

carbon-carbon bonds stereospecifically by cross-coupling reactions, these two-step transformations serve as a useful method for regio-, stereo-, and chemoselective introduction of two different functional groups to a carbon-carbon triple bond (eq 4). Cycloisomerization of a carbonyl-ene-nitrile compound, which was obtained from the palladium-catalyzed cross-coupling reaction of a (*Z*)-*β*-bromoacrylonitrile with benzoyltributhylstannane, was also examined.



> 90% stereoselectivity

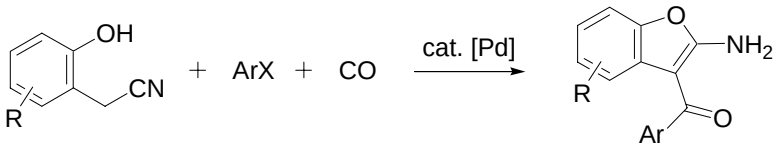
As described above, the author succeeded in the development of cycloisomerization reactions using carbonyl-ene-nitrile compounds. These results stimulated him to investigate new types of cyclization reactions of properly functionalized nitriles. In Chapter 5, the author discloses palladium-catalyzed cycloisomerization reactions of 2-(cyanomethyl)phenyl esters leading to 3-acyl-2-aminobenzofuran (eq 5). The reactions were dramatically accelerated by using the combination of $Pd(PCy_3)_2$ and $Zn(OAc)_2$ as catalysts. The reaction proceeded via cleavage of an acyl-oxygen bond with palladium catalyst and oxy-palladation of a cyano moiety followed by isomerization and reductive elimination. In this reaction, cycloisomerization proceeded through the activation of the ester group that adds to the cyano



(5)

group by the palladium catalyst (Scheme 6b). Usefulness of the reaction was demonstrated by the synthesis of Elbfluorene, which is known as CDK inhibitor.[11]

Since the resulting benzofurans have both an amino and a carbonyl group, they are useful building blocks for the synthesis of various benzofuran-fused heterocycles. To show the further utilities, Chapter 6 deals with palladium-catalyzed synthesis of 3-acyl-2-amino-benzofurans via three-component coupling reactions of 2-(cyanomethyl)phenol, aryl halides, and CO (eq 6).[12,13] The combination of $Pd(PCy_3)_2$ and $Pd(PPh_3)_4$ was found to be effective for the reaction, and various 3-acyl-2-aminobenzofurans were obtained.[14]



(6)

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Chapter 1

Copper-catalyzed Synthesis of 1*H*–Pyrrolin-2(5*H*)-ones from Carbonyl-ene-nitrile Compounds with Various Nucleophiles

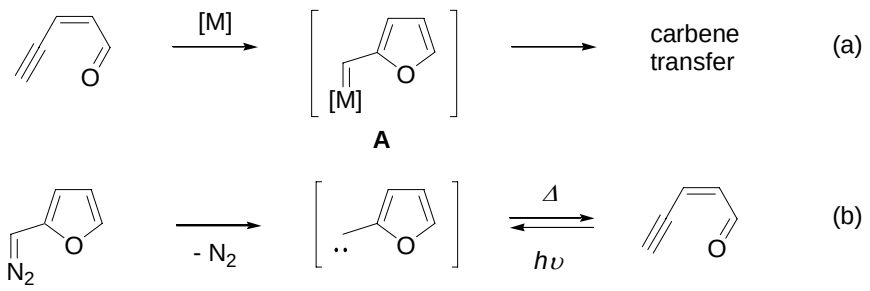
Abstract

The reaction of carbonyl-ene-nitrile compounds with nucleophiles in the presence of a catalytic amount of $Cu(OTf)_2$ gave pyrrolin-2-ones (γ-lactams). The result of ^{18}O-labeling experiment indicates that the reactive intermediates 2-aza-2,4-cyclopentadienones might be generated from carbonyl-ene-nitrile compounds via cycloisomerization including hydration at a cyano moiety activated by a copper catalyst followed by dehydrative cyclization between the resulting amide and the original carbonyl moieties. Not only carbon-nucleophiles such as alkenes, aromatics, arylacetylenes, and allylsilanes but also oxygen-nucleophiles such as alcohols can participate in the reaction, affording pyrrolin-2-ones in good to excellent yields.

Introduction

The in situ generation of transient electrophilic carbenoids from α-diazocarbonyl compounds with various transition metal complexes have been well investigated to apply for various inter- or intramolecular carbene transfer reactions.[1,2] The author's group has continuously investigated several catalytic carbene transfer reactions via (2-furyl)carbene complexes in situ generated from carbonyl-ene-yne compounds leading to the formation of functionalized furan derivatives (Scheme 1a).[3]

Scheme 1

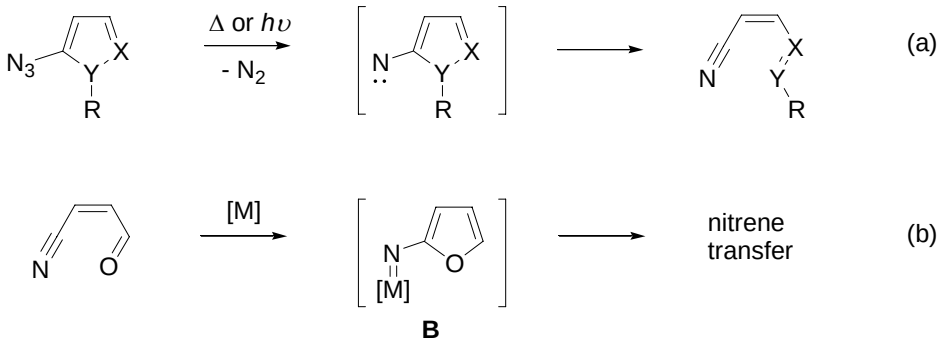


The transition metal-triggered intramolecular *5-exo-dig* cycloisomerization of carbonyl-ene-yne compounds is proposed as the key step to form (2-furyl)carbene intermediates **A**.[4] In general, 2-furfurylidenes generated from diazoalkanes by thermolysis or photolysis are well known to be converted to give carbonyl-ene-yne compounds via rapid rearrangement (Scheme 1b).[5-8] Transition metal compounds as catalysts for (2-furyl)carbene transfer reactions are considered to act as a soft Lewis acid for activation of the alkyne moiety leading to stabilized (2-furyl)carbene complexes.

Recent studies have focused on nitrene intermediates in situ generated from azide derivatives by flash vacuum thermolysis or photolysis (Scheme 2a).[9] The in situ generated nitrene intermediates are found to convert to more stable isomeric nitriles even though under

mild conditions.[9b] Considering the similarity of nitrene species with (2-furyl)carbene complexes, the author envisioned the nitrene transfer reactions of (2-furyl)nitrene complex **B** which is generated via cycloisomerization of carbonyl-ene-nitrile compounds (Scheme 2b).

Scheme 2



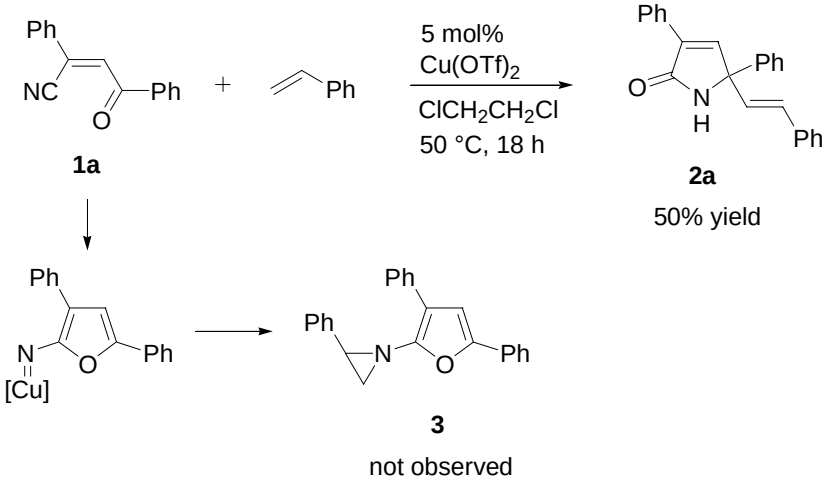
Although the intermediary of the nitrene species have not yet been observed, the author found the unique copper-catalyzed formation of 1*H*-pyrrolin-2(5*H*)-ones via cycloisomerization of carbonyl-ene-nitrile compounds followed by addition reactions of various nucleophiles.[10,11]

Results and Discussion

First, the reaction of carbonyl-ene-nitrile compound **1a** with styrene as a nitrene acceptor was carried out in the presence of 5 mol% of $Cu(OTf)_2$ in $ClCH_2CH_2Cl$ at 50 °C. Although the expected aziridine **3** was not observed, unexpected 1*H*-pyrrolin-2(5*H*)-one **2a** was obtained in 50% yield (59% conversion of **1a**) (Scheme 3). When carbonyl-ene-nitrile compound **1a** was treated with a catalytic amount of $[Rh(OAc)_2]_2$, which is one of the most efficient catalysts for carbene transfer reactions, no reaction took place, and the starting

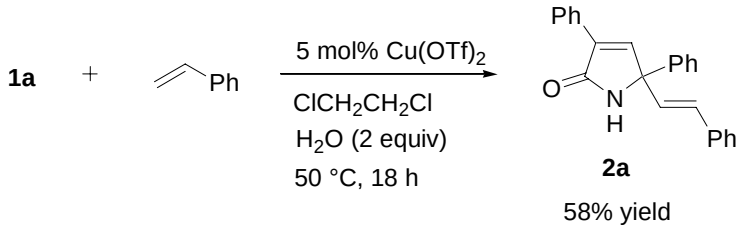
material was recovered intact. The reactions of **1a** with other several transition metal complexes, such as $[RuCl_2(CO)_3]_2$, $PtCl_2$, $AuCl_3$, $PdCl_2$, $GaCl_3$, Cu(OTf)-benzene, CuCl, and $CuCl_2$, did not afford the pyrrolin-2-one **2a** at all.

Scheme 3



The structure of pyrrolin-2-one **2a** suggests that the reaction mechanism involving dehydrative cyclization as well as hydration of cyano moiety of **1a**. As expected, the reaction in the presence of water slightly increased the yield of **2a** up to 58% (Scheme 4).

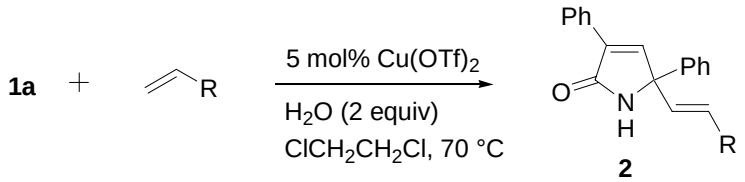
Scheme 4



The author next examined the vinylation reaction with various styrene derivatives. Selected results are summarized in Table 1. The reaction of **1a** with 4-methylstyrene gave the corresponding pyrrolin-2-one **2b** in 50% yield (entry 1), while the reactions with 4-chlorostyrene or 4-bromostyrene gave **2c** and **2d** in slightly lower yields, respectively (entries 2 and 3). No vinylated product was observed from the reaction with

4-methoxystyrene, because polymerization of 4-methoxystyrene occurred quickly under the identical conditions (entry 4).[12] The reaction of **1a** with 2-vinylnaphthalene also gave the corresponding product **2e** in 53% yield (entry 5). It is noteworthy that the reaction proceeded regioselectively to afford single isomer in all cases. On the other hand, when reactions with 2,3-dihydrofuran, 3,4-dihydro-2*H*-pyran, and methyl vinyl ketone were carried out, the corresponding pyrrolin-2-ones were not obtained.

Table 1. Cu-catalyzed vinylation of **1a** with styrene derivatives[a]



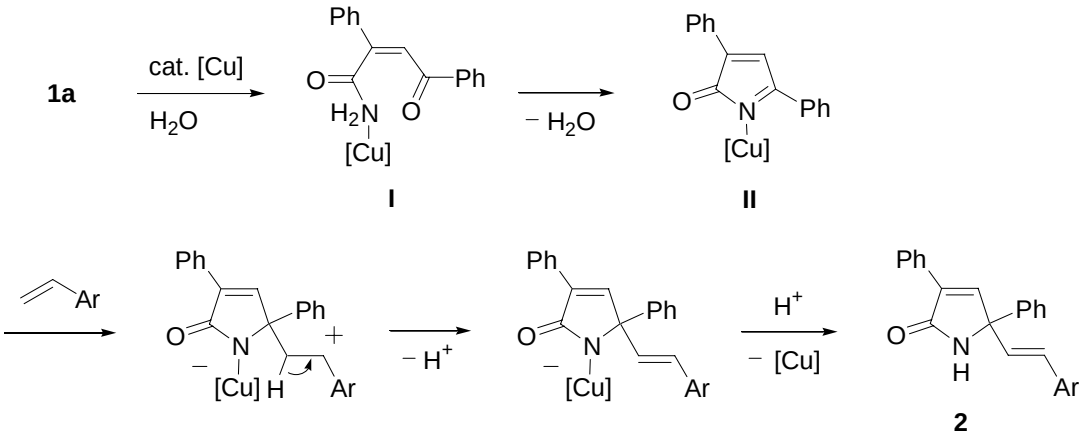
entry	R	time (h)	product	yield (%)[b]
1	4-MeC_6H_4	9	**2b**	50
2	4-ClC_6H_4	9	**2c**	41
3[c]	4-BrC_6H_4	24	**2d**	40
4	4-$MeOC_6H_4$	24	—[d]	—[d]
5	2-Naph	15	**2e**	53

[a] Reaction conditions: **1a** (0.40 mmol), alkene (2.0 mmol), $Cu(OTf)_2$ (0.020 mmol), H_2O (0.80 mmol) in $ClCH_2CH_2Cl$ (1.6 mL) at 70 °C. [b] Isolated yields. [c] 80 °C. [d] Complex mixture.

Most plausible reaction mechanism of the pyrrolin-2-ones formation from carbonyl-ene-nitrile compounds is shown in Scheme 5. First, hydration of a cyano moiety activated by a copper catalyst affords a carbonyl-ene-amide intermediate **I**. The subsequent dehydrative cyclization between a carbonyl and an amide moiety in the intermediate **I** takes place to afford the more reactive intermediate, 2-aza-2,4-cyclopentadienone **II**. While non-substituted 2-aza-2,4-cyclopentadienone reacts with both an enophile and a dienophile to give Diels-Alder adducts,[13] the ketimine moiety in 2-aza-2,4-cyclopentadienone **II** undergoes

electrophilic addition of alkenes followed by deprotonation and protodemetalation to form pyrrolin-2-ones **2**.

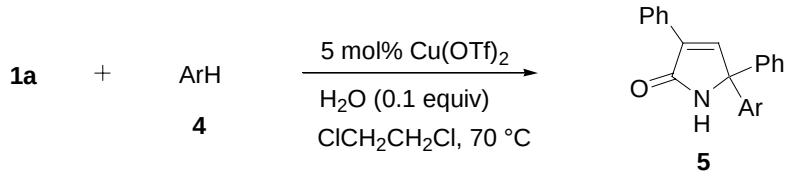
Scheme 5



Since the reaction with styrene derivatives took place smoothly, the author next examined the reaction of **1a** with various aromatics as nucleophiles (Table 2).[14] As expected, the arylated pyrrolin-2-ones **5** were obtained in all cases. Electron-rich aromatics such as anisole (**4a**), phenol (**4b**), and 1,3-dimethoxybenzene (**4c**) reacted smoothly with **1a** to afford the corresponding pyrrolin-2-ones **5a**, **5b**, and **5c** in good to excellent yields (entries 1-3). In the case of *N*,*N*-dimethylaniline (**4d**), the corresponding arylated product **5d** was obtained in 77% yield, although a prolonged reaction time and higher reaction temperature were required (entry 4). It is noteworthy that reactions occurred selectively at *para*-positions of these electron-rich aromatics, although a mixture of **5a** and **5a'** was obtained from the reaction with anisole in a ratio of 16:1 (entry 1). When reactions of **1a** with several heteroaromatics such as furan (**4e**), 2-methylfuran (**4f**), thiophene (**4g**), 2-methylthiophene (**4h**), and benzofuran (**4i**) were carried out, the corresponding products **5e-5i** were obtained in excellent yields with high regioselectivities (entries 5-10). In all cases, reactions occurred selectively at the carbon next to hetero atoms, except for the reaction with benzofuran. In addition, the reaction with furan successfully proceeded even when the catalyst loading was decreased to 1

mol% (entry 6). When reactions with other aromatics such as acetanilide, toluene, 2-methoxyfuran, pyrrole, *N*-methylpyrrole, *N*-tosylpyrrole, and indol were carried out, the corresponding arylated products were not observed due to the weak nucleophilicity of these aromatics or low stability of the products under the reaction conditions.

Table 2. Cu-catalyzed arylation of **1a** with aromatic compounds[a]



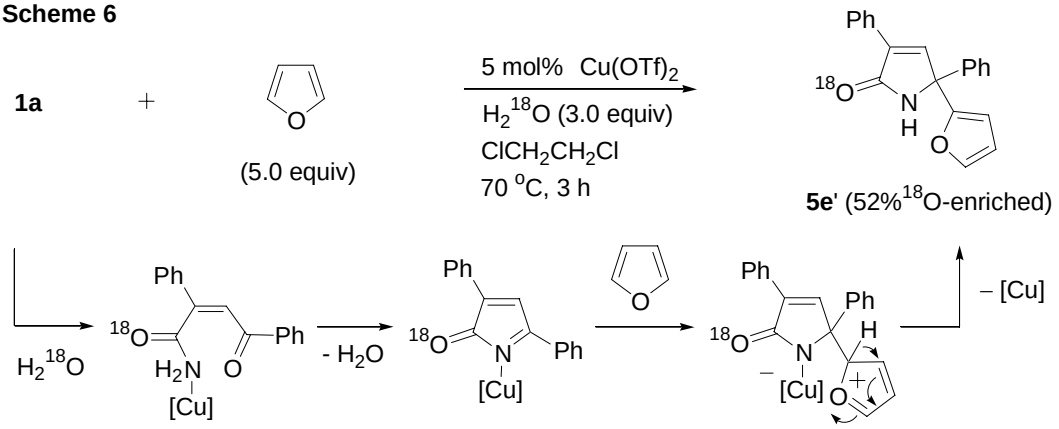
entry	ArH	time (h)	product	yield (%)[b]
1	**4a** (X = OMe, Y = H)	18	**5a + 5a'** [c]	84
2	**4b** (X = OH, Y = H)	3	**5b**	90
3	**4c** (X = OMe, Y = OMe)	8	**5c**	98
4[d]	**4d** (X = NMe_2, Y = H)	24	**5d**	77
5	**4e** (X = O, R = H)	3	**5e**	93
6[e]	**4e**	6	**5e**	90
7	**4f** (X = O, R = Me)	3	**5f**	94
8	**4g** (X = S, R = H)	12	**5g**	88
9	**4h** (X = S, R = Me)	3	**5h**	91
10	**4i**	3	**5i + 5i'** [f]	90

[a] Reaction conditions: **1a** (0.40 mmol), ArH (2.0 mmol), $Cu(OTf)_2$ (0.020 mmol), H_2O (0.040 mmol) in $ClCH_2CH_2Cl$ (1.6 mL) at 70 °C. [b] Isolated yields. [c] **5a** (X = OMe, Y = H) : **5a'** (X = H, Y = OMe) = 16 : 1. [d] In toluene at 110 °C. [e] 1 mol% of $Cu(OTf)_2$ was used. [f] **5i** (3-) : **5i'** (2-) = 29 : 1.

To gain insight into the reaction mechanism, isotopic labeling experiment using the ^{18}O-labeled water (98% ^{18}O) was carried out (Scheme 6). Treatment of **1a** with furan in the presence of 3 equiv of the ^{18}O-labeled water under similar reaction condition afforded the ^{18}O-enriched product **5e'**. The high-resolution mass spectrum of the product **5e'** showed two

sharp peaks at m/z = 304.1244 (100% intensity) and at m/z = 302.1168 (94% intensity), indicating 52% ^{18}O incorporation in the product.[15] This isotopic labeling experiment supports the hypothesis that the reaction proceeds via hydration of a cyano moiety and subsequent dehydrative cyclization between the resulting amide and the original carbonyl group. However, attempts to isolate 2-aza-2,4-cyclopentadienone intermediate failed, probably due to its high reactivity.

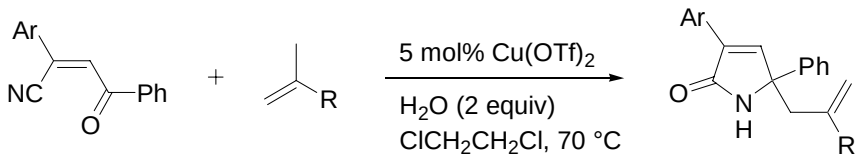
Scheme 6



As shown above, the author proved the reaction mechanism involves addition reactions with ketimine moiety of the 2-aza-2,4-cyclopentadienone intermediate, which is formed via hydration of a cyano moiety followed by dehydrative cyclization. In contrast to the well studied addition reactions of carbon nucleophiles with aldimines, reactions with ketimines are limited because of their poor electrophilicity and steric hindrance.[16,17] Therefore, most reported methods require strong nucleophiles such as organometallic reagents[16] and trimethylsilyl cyanide.[17] The direct addition reactions of C–H bonds of carbon nucleophiles appear to be even more difficult.[18,19] To the best of his knowledge, the existing examples are limited to the reactions of electronically activated ketimines that have electron-withdrawing groups on the imine carbon,[19b,d,e] reactions mediated by stoichiometric Brønsted or Lewis acids,[19b,c,e] or intramolecular reactions.[19a,b]

Taking these facts into consideration, the author investigated the imino-ene reaction of intermediary 2-aza-2,4-cyclopentadienone leading to allylated pyrrolin-2-ones.[20-22] Typical results are summarized in Table 3. When the reaction of **1a** with α-methylstyrene was carried out under the identical reaction condition, allylated pyrrolin-2-one **6a** was obtained in 67% yield (entry 1). 4-Methyl-, 4-chloro-, and 4-bromo-α-methylstyrene also reacted with **1a** to afford the corresponding products **6b**, **6c**, and **6d** in modest yields (entries 2-4). The structure of **6b** was unambiguously determined by X-ray crystallography analysis (See Experimental section). 2-(2-Propenyl)naphthalene was reacted with **1a** to give the corresponding product **6e** in 57% yield (entry 5). Carbonyl-ene-nitrile compound **1b** (Ar = 4-MeC_6H_4) was also reacted with both of α-methylstyrene and 2-(2-propenyl)naphthalene to give the corresponding products **7a** and **7e** in 70% and 57% yields, respectively, although slight decreases of the reaction rates were observed (entries 6 and 7).

Table 3. Cu-catalyzed allylation of **1** with α-methylstyrene derivatives[a]



1a (Ar = Ph)
1b (Ar = 4-MeC_6H_4)

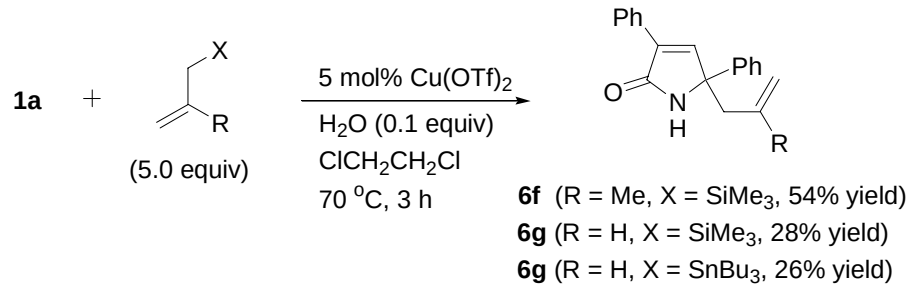
6 or **7**

entry	Ar	R	time (h)	product	yield (%)[b]
1	Ph	Ph	4	**6a**	67
2	Ph	4-MeC_6H_4	3	**6b**	44
3	Ph	4-ClC_6H_4	4	**6c**	39
4	Ph	4-BrC_6H_4	4	**6d**	47
5	Ph	2-Naphthyl	10	**6e**	57
6	4-MeC_6H_4	Ph	24	**7a**	70
7	4-MeC_6H_4	2-Naphthyl	40	**7e**	57

[a] Reaction conditions: **1a** or **1b** (0.40 mmol), alkene (2.0 mmol), $Cu(OTf)_2$ (0.020 mmol), H_2O (0.80 mmol) in $ClCH_2CH_2Cl$ (1.6 mL) at 70 ^oC. [b] Isolated yields.

Allylation was also achieved using allylsilanes as nucleophiles (Scheme 7).[22] When the reaction of **1a** with methallyltrimethylsilane was carried out, the allylated pyrrolin-2-one **6f** was obtained in 54% yield, whereas the reaction with either allyltrimethylsilane or allyltributylstannane gave the corresponding product **6g** in low yields.

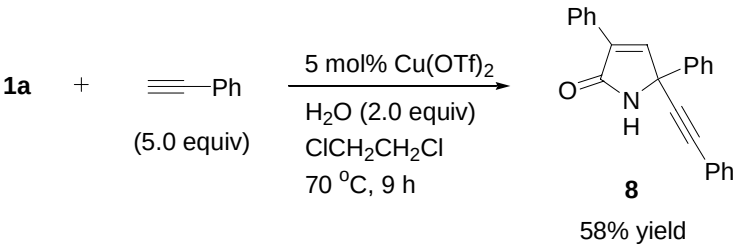
Scheme 7



6f (R = Me, X = $SiMe_3$, 54% yield)
6g (R = H, X = $SiMe_3$, 28% yield)
6g (R = H, X = $SnBu_3$, 26% yield)

The present catalyst was also suitable for the alkynylation reaction of 2-aza-2,4-cyclopentadienone intermediate generated from **1a**.[18,23] When the reaction of **1a** with phenylacetylene was carried out, 5-alkynylpyrrolin-2-one **8** was obtained in 58% yield (Scheme 8). However, reactions of **1a** with other alkynes such as trimethylsilylacetylene, 1-hexyne, 4-octyne, and bis(trimethylsilyl)acetylene failed.

Scheme 8

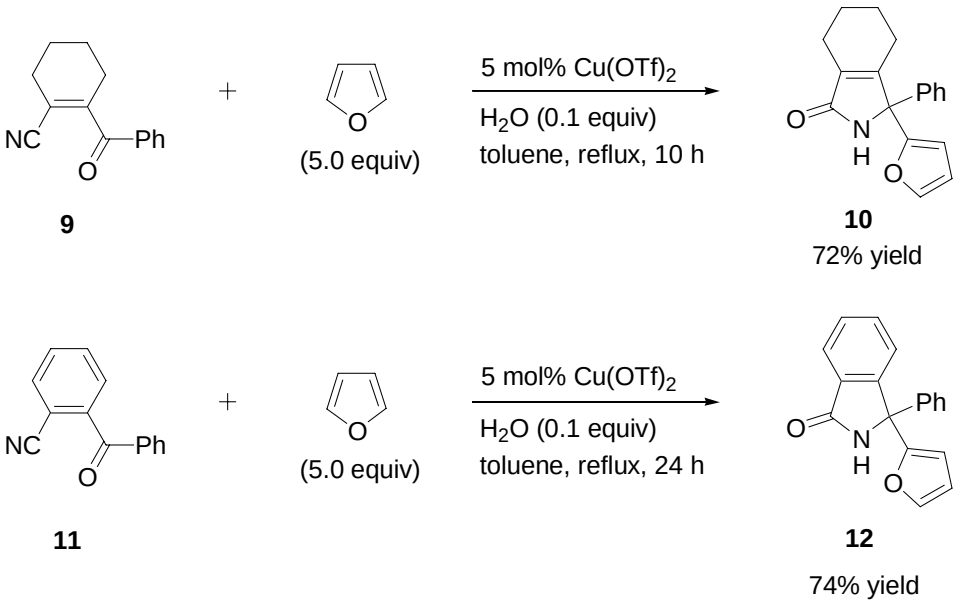


8
58% yield

The reactions of several nitrile compounds containing carbonyl moieties with furan were next examined (Scheme 9). Cyclohexene-fused carbonyl-ene-nitrile compound **9** reacted with furan in toluene at reflux temperature to give the corresponding pyrrolin-2-one **10** in 72% yield. Furthermore, the present protocol was also extended to the reaction with 2-cyanobenzophenone **11**, (2-furyl)isoindolin-1-one derivative **12** being obtained in 74%

yield.

Scheme 9



On the other hand, the reaction of **13**, which has no conjugation between the cyano and carbonyl moieties, did not proceed at all (Figure 1). Moreover, formyl-ene-nitrile compounds **14** and **15**, alkoxycarbonyl-ene-nitrile compound **16**, and carbamoyl-ene-nitrile compound **17** failed to afford the corresponding pyrrolin-2-ones. These results indicate that acyl moieties are essential in the reaction.

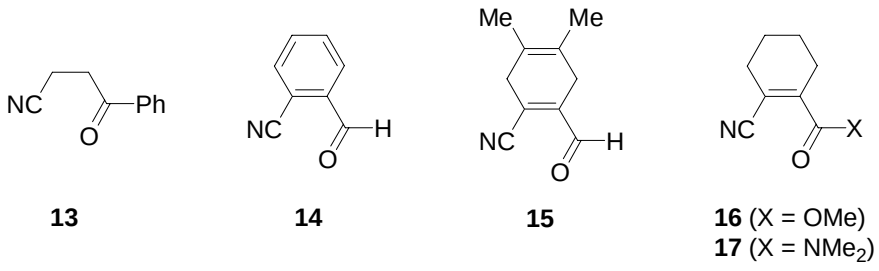
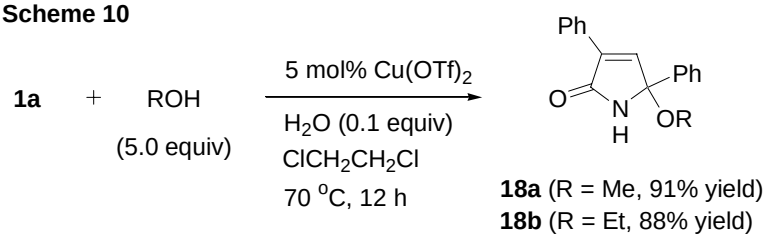


Figure 1. Various nitrile compounds examined for Cu-catalyzed reactions.

In addition to carbon-nucleophiles, oxygen-nucleophiles such as alcohols reacted with **1a** to give 5-alkoxylpyrrolin-2-ones **18** (Scheme 10). The reactions of **1a** with methanol and ethanol proceeded smoothly to give 5-alkoxypyrrolin-2-ones **18a** and **18b** in 91% and 88%

yields, respectively. However, 2-propanol, propargyl alcohol, and allyl alcohol, as well as nitrogen-nucleophiles such as diethylamine did not afford the alkoxy- or aminopyrrolin-2-ones at all.

Scheme 10



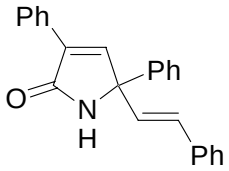
In summary, the author has demonstrated the copper-catalyzed cycloisomerization of carbonyl-ene-nitrile compounds leading to 2-aza-2,4-cyclopentadienone intermediates. The ketimine moieties of the resulting 2-aza-2,4-cyclopentadienones efficiently underwent addition reactions with various nucleophiles including alkenes, aromatics, arylacetylenes, allylsilanes, and alcohols leading to a range of 5-substituted pyrrolin-2-ones. Multistep reactions, including hydration of a cyano moiety, dehydrative cyclization, and the carbon-carbon or carbon-oxygen bond formation with various nucleophiles were achieved by only single copper catalyst at once. Since the reaction proceeded under mild conditions with high atom-efficiency, the present reaction offers new accesses to synthetically useful pyrrolin-2-ones.[24]

Experimental

General Method. Unless otherwise noted, chemicals obtained from commercial suppliers were used without further purification. Solvents were dried by the usual methods and distilled before use. Carbonyl-ene-nitrile compounds **1a,**[11] **1b**,[11] **11**,[25] and **13**[26] were

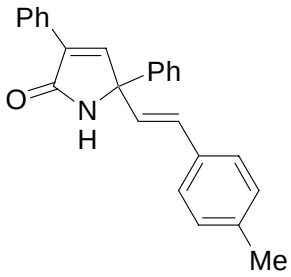
prepared according to the reported procedure. ^{18}O-labeled water (98 atom% excess ^{18}O) was purchased from TAIYO NIPPON SANSO Corporation. All reactions were carried out under nitrogen atmosphere. NMR spectra were measured for solutions in $CDCl_3$ or acetone-d_6 with tetramethylsilane as an internal standard (^{1}H and ^{13}C): the following abbreviations are used; br s: broad singlet, s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet. IR spectra were recorded with an FT-IR spectrometer. Melting points (mp) are uncorrected. Element analyses were performed at Microanalytical Center of Kyoto University. High-resolution mass spectra (HRMS) was measured with JEOL JMX-SX 102A spectrometer.

General Procedure for Copper-catalyzed Transformation of Carbonyl-ene-nitrile Compounds. A flame dried Schlenk flask was charged with $Cu(OTf)_2$ (7.2 mg, 0.020 mmol), carbonyl-ene-nitrile compound **1** (0.40 mmol), and nucleophile (2.0 mmol) in $ClCH_2CH_2Cl$ (2.0 mL). The solution was stirred at room temperature for 5 min and then water (0.040 or 0.80 mmol) was added dropwise. After stirring under the reaction conditions specified in Scheme 3-4, 6-10, and Tables 1-4, the reaction mixture was diluted with Et_2O and filtered through a short silica gel pad. Filtrate was concentrated under reduced pressure and the residue was subjected to flash column chromatography on silica gel with hexane/AcOEt (v/v = 7/1-4/1) as eluents to afford the corresponding pyrrolin-2-ones. Regioisomers of **5a**, and **5i** were separated by column chromatography.

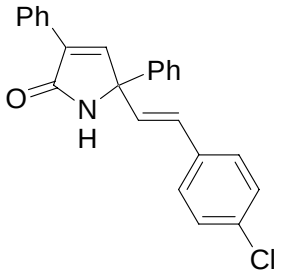


3,5-Diphenyl-5-[(1*E*)-2-phenylethenyl]-3-pyrrolin-2-one (2a): A white solid; mp 78.8-79.8 °C. IR (KBr): 693, 746, 794, 966, 1447, 1491, 1690 (C=O), 3027, 3060, 3203 (N-H) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.51 (d, J = 16.0 Hz, 1H), 6.66 (d, J = 16.0 Hz, 1H), 7.23-7.48 (m, 14H), 7.55 (br s, 1H), 7.90 (d, J = 6.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 67.2, 126.3, 126.6, 127.2,

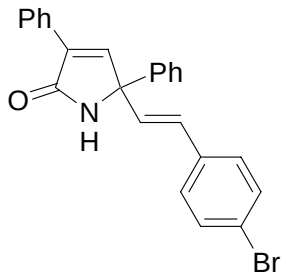
128.0, 128.1, 128.4, 128.6, 128.7, 128.8, 128.9, 130.7, 130.9, 133.6, 135.9, 139.5, 145.3, 172.0. Anal. calcd for $C_{24}H_{19}NO$: C, 85.43; H, 5.68; N, 4.15. found: C, 85.44; H, 5.89; N, 3.85.



3,5-Diphenyl-5-[(1*E*)-2-(4-methylphenyl)ethenyl]-3-pyrrolin-2-one (2b): A white solid; mp 75.1-76.8 ^{o}C. IR (KBr): 695, 746, 795, 968, 1447, 1490, 1691 (C=O), 2920, 3024, 3057, 3211 (N-H) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ2.33 (s, 3H), 6.46 (d, J = 16.0 Hz, 1H), 6.62 (d, J = 16.0 Hz, 1H), 6.95 (br s, 1H), 7.12 (d, J = 7.6 Hz, 2H), 7.34-7.48 (m, 9H), 7.46 (d, J = 7.6 Hz, 2H), 7.90 (d, J = 6.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ21.3, 67.1, 126.3, 126.5, 127.2, 127.7, 128.1, 128.4, 128.6, 128.7, 128.8, 129.3, 130.7, 130.9, 133.1, 138.1, 139.6, 145.5, 171.8. HRMS (FAB) calcd for M+H^{+} of $C_{25}H_{21}NO$ 352.1701, found 352.1707.

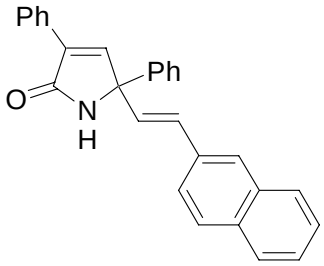


3,5-Diphenyl-5-[(1*E*)-2-(4-chlorophenyl)ethenyl]-3-pyrrolin-2-one (2c): A white solid; mp 180.3-181.9 ^{o}C. IR (KBr): 693, 745, 972, 1490, 1687 (C=O), 3031, 3060, 3214 (N-H) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ6.49 (d, J = 16.0 Hz, 1H), 6.62 (d, J = 16.0 Hz, 1H), 6.84 (s, 1H), 7.26-7.46 (m, 13H), 7.91 (d, J = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ68.0, 126.2, 127.2, 127.8, 128.2, 128.4, 128.8, 128.9, 129.0, 129.5, 129.6, 130.8, 133.7, 133.8, 134.4, 139.2, 145.1, 171.7. HRMS (FAB) calcd for M+H^{+} of $C_{24}H_{18}ClNO$ 372.1155, found 372.1151.

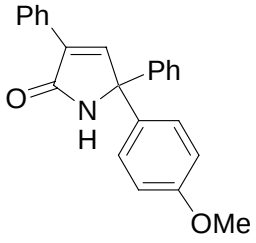


3,5-Diphenyl-5-[(1*E*)-2-(4-bromophenyl)ethenyl]-3-pyrrolin-2-one (2d): A white solid; mp 186.2-187.6 ^{o}C. IR (KBr): 695, 793, 1008, 1446, 1490, 1690 (C=O), 2926, 3027, 3060, 3209 (N-H) cm^{-1}.

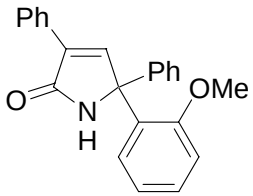
^{1}H NMR (400 MHz, $CDCl_3$): δ6.50 (d, J = 16.0 Hz, 1H), 6.60 (d, J = 16.0 Hz, 1H), 7.22 (d, J = 8.0 Hz, 2H), 7.35-7.46 (m, 12H), 7.91 (d, J = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ67.1, 122.0, 126.3, 127.2, 128.1, 128.2, 128.4, 128.8, 128.9, 129.6, 129.7, 130.8, 131.7, 133.7, 134.8, 139.2, 145.0, 171.9. HRMS (FAB) calcd for M+H$^+$ of $C_{24}H_{18}BrNO$ 418.0633, found 418.0639.



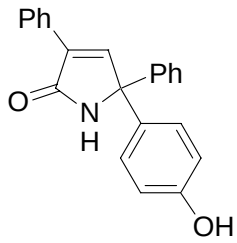
3,5-Diphenyl-5-[(1*E*)-2-naphthalenylethenyl]-3-pyrrolin-2-one (2e): A white solid; mp 88.9-90.3 ^{o}C. IR (KBr): 695, 745, 965, 1447, 1490, 1688 (C=O), 2872, 3055, 3211 (N-H) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ6.64 (d, J = 16.0 Hz, 1H), 6.72 (br s, 1H), 6.82 (d, J = 16.0 Hz, 1H), 7.36-7.51 (m, 11H), 7.59 (m, 1H), 7.73 (s, 1H), 7.79 (m, 3H), 7.93 (d, J = 6.8 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ67.1, 123.4, 126.2, 126.4, 126.5, 127.0, 127.3, 127.7, 128.1, 128.3, 128.4, 128.5, 128.6, 128.9, 129.0, 129.1, 130.9, 131.1, 133.2, 133.4, 133.5, 139.5, 145.6, 171.8. HRMS (FAB) calcd for M+H$^+$ of $C_{28}H_{21}NO$ 388.1701, found 388.1708.



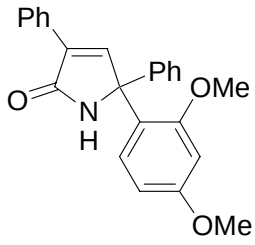
3,5-Diphenyl-5-(4-methoxyphenyl)-3-pyrrolin-2-one (5a): A white solid; mp 171.3-172.4 ^{o}C. IR (KBr): 696, 743, 795, 830, 1034, 1177, 1250, 1306, 1362, 1448, 1509, 1606, 1686 (C=O), 2834, 3056, 3154 (N-H) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ3.76 (s, 3H), 6.83 (d, J = 8.8 Hz, 2H), 7.22 (d, J = 8.8 Hz, 2H), 7.28-7.40 (m, 8H), 7.54 (s, 1H), 7.75 (br s, 1H), 7.90 (d, J = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ55.3, 68.8, 113.9, 126.8, 127.2, 127.7, 128.0, 128.1, 128.3, 128.5, 128.6, 131.0, 133.2, 141.4, 146.8, 159.0, 171.9. HRMS (FAB) calcd for M+H$^+$ of $C_{23}H_{19}NO_2$ 342.1494, found 342.1494.



3,5-Diphenyl-5-(2-methoxyphenyl)-3-pyrrolin-2-one (5a'): A white solid; mp 167.2-168.4 °C. IR (KBr): 697, 747, 790, 829, 1029, 1178, 1252, 1293, 1331, 1450, 1509, 1606, 1701 (C=O), 2834, 3061, 3189 (N-H) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.78 (s, 3H), 6.10 (d, J = 2.0 Hz, 1H), 6.85 (d, J = 8.8 Hz, 2H), 7.25-7.45 (m, 10H), 7.51 (d, J = 8.0 Hz, 2H), 8.20 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.3, 63.1, 110.7, 113.9, 124.7, 127.1, 127.9, 128.5, 128.8, 128.9, 129.0, 129.1, 129.2, 129.6, 133.1, 139.1, 141.3, 158.6, 181.1.

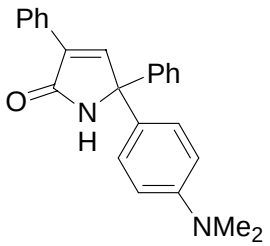


3,5-Diphenyl-5-(4-hydroxyphenyl)-3-pyrrolin-2-one (5b): A white solid; mp 138.2-139.4 °C. IR (KBr): 696, 748, 794, 830, 1167, 1223, 1362, 1446, 1490, 1514, 1597, 1611, 1672 (C=O), 2848, 3057, 3199 (N-H), 3354 (O-H) cm^{-1}. ^1H NMR (400 MHz, $(CD_3)_2CO$): δ 6.79 (s, 2H), 7.18-7.42 (m, 10H), 8.03 (s, 3H), 8.52 (br s, 1H), 8.85 (s, 1H). ^{13}C NMR (100 MHz, $(CD_3)_2CO$): δ 69.0, 115.7, 127.4, 127.7, 127.9, 128.6, 128.7, 128.8, 128.9, 132.3, 133.1, 133.5, 143.2, 147.8, 157.3, 171.6. HRMS (FAB) calcd for M+H^+ of $C_{22}H_{17}NO_2$ 328.1343, found 328.1338.

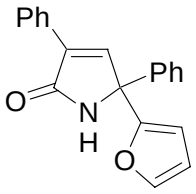


3,5-Diphenyl-5-(2,4-dimethoxyphenyl)-3-pyrrolin-2-one (5c): A white solid; mp 218.4-219.9 °C. IR (KBr): 690, 696, 746, 765, 793, 832, 862, 919, 923, 939, 1035, 1147, 1211, 1259, 1315, 1350, 1376, 1420, 1447, 1504, 1585, 1611, 1692 (C=O), 2838, 2935, 2961, 3021, 3054, 3276 (N-H) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.57 (s, 3H), 3.80 (s, 3H), 6.48 (m, 2H), 7.18-7.25 (m, 5H), 7.32 (d, J = 8.0 Hz, 2H), 7.34-7.39 (m, 2H), 7.56 (br s, 1H), 7.59 (s, 1H), 7.89 (d, J = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.3, 55.4, 67.2, 100.0, 103.7, 122.3, 125.2, 127.0, 127.2, 128.1, 128.2, 128.3, 128.5, 131.2, 133.2, 141.5, 146.1, 158.0,

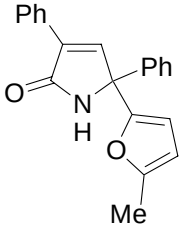
160.7, 171.2. HRMS (FAB) calcd for M+H$^+$ of $C_{24}H_{21}NO_3$ 372.1602, found 372.1600.



3,5-Diphenyl-5-(4-(*N*,*N*-dimethylamino)-phenyl)-3-pyrrolin-2-one (5d): A white solid; mp 189.8-191.2 ^oC. IR (KBr): 691, 740, 794, 817, 1163, 1233, 1352, 1446, 1520, 1609, 1687 (C=O), 2849, 3063, 3183 (N-H) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.94 (s, 6H), 6.66 (d, J = 8.8 Hz, 3H), 7.25 (d, J = 8.8 Hz, 2H), 7.30-7.42 (m, 8H), 7.53 (d, J = 2.0 Hz, 1H), 7.90 (d, J = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 40.4, 68.7, 112.2, 126.9, 127.2, 127.7, 127.8, 128.2, 128.3, 128.4, 128.5, 131.1, 132.9, 141.6, 147.3, 150.0, 171.7. HRMS (FAB) calcd for M+H$^+$ $C_{24}H_{21}N_2O$ 355.1812, found 355.1810.

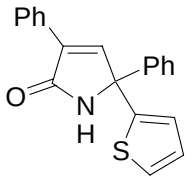


3,5-Diphenyl-5-(2-furyl)-3-pyrrolin-2-one (5e): A white solid; mp 141.3-142.5 ^oC. IR (KBr): 694, 746, 794, 894, 1076, 1153, 1236, 1361, 1446, 1491, 1599, 1687 (C=O), 2852, 3066, 3167 (N-H) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.33 (s, 1H), 6.35 (s, 1H), 7.29-7.42 (m, 9H), 7.48 (s, 1H), 7.62 (br s, 1H), 7.90 (d, J = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 65.1, 107.7, 110.2, 126.1, 127.3, 128.2, 128.4, 128.7, 128.8, 130.7, 134.2, 138.8, 142.9, 143.7, 152.6, 171.8. HRMS (FAB) calcd for M+H$^+$ of $C_{20}H_{16}NO_2$ 302.1181, found 302.1181. Anal. calcd for $C_{20}H_{15}NO_2$: C, 79.72; H, 5.02. found: C, 80.00; H, 5.02.

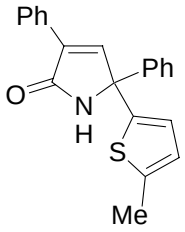


3,5-Diphenyl-5-[2-(5-methylfuryl)]-3-pyrrolin-2-one (5f): A white solid; mp 146.0-147.8 ^oC. IR (KBr): 695, 746, 794, 896, 1032, 1157, 1218, 1238, 1365, 1447, 1492, 1548, 1685 (C=O), 2845, 3065, 3195 (N-H) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.24 (s, 3H), 5.92 (s, 1H), 6.16 (d, J = 3.2 Hz, 1H), 7.28-7.46 (m, 10H), 7.89 (d, J = 6.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.6,

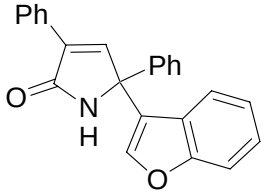
65.1, 106.1, 108.6, 126.1, 127.2, 128.1, 128.3, 128.6, 128.7, 130.8, 134.0, 139.0, 144.0, 150.5, 152.7, 171.8. HRMS (FAB) calcd for M+H$^+$ of $C_{21}H_{17}NO_2$ 316.1338, found 316.1338.



3,5-Diphenyl-5-(2-thienyl)-3-pyrrolin-2-one (5g): A white solid; mp 135.7-136.9 ^{o}C. IR (KBr): 694, 746, 794, 892, 1075, 1155, 1235, 1361, 1447, 1491, 1592, 1687 (C=O), 2850, 3065, 3179 (N-H) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ6.90 (s, 1H), 6.94 (t, J = 4.0 Hz, 1H), 7.23 (d, J = 4.8 Hz, 1H), 7.30-7.41 (m, 6H), 7.45 (d, J = 7.2 Hz, 2H), 7.53 (s, 1H), 7.69 (br s, 1H), 7.89 (d, J = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ66.5, 125.4, 126.2, 126.4, 126.9, 127.3, 128.2, 128.4, 128.6, 128.8, 130.6, 133.4, 140.5, 145.4, 146.0, 171.5. HRMS (FAB) calcd for M+H$^+$ of $C_{20}H_{15}NOS$ 318.0944, found 318.0953.

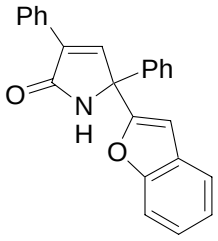


3,5-Diphenyl-5-[2-(5-methylthienyl)]-3-pyrrolin-2-one (5h): A white solid; mp 158.2-159.1 ^{o}C. IR (KBr): 695, 747, 794, 890, 1185, 1235, 1361, 1447, 1490, 1619, 1687 (C=O), 2855, 3064, 3184 (N-H) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ2.39 (s, 3H), 6.56 (d, J = 3.2 Hz, 1H), 6.66 (d, J = 3.2 Hz, 1H), 7.29-7.39 (m, 6H), 7.46 (d, J = 7.2 Hz, 2H), 7.50 (s, 1H), 7.88 (d, J = 7.2 Hz, 2H), 7.94 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ15.3, 66.6, 124.9, 125.9, 126.4, 127.3, 128.0, 128.3, 128.5, 128.7, 130.7, 133.2, 140.1, 140.4, 142.7, 146.1, 171.5. HRMS (FAB) calcd for M+H$^+$ of $C_{21}H_{17}NOS$ 332.1114, found 332.1109.

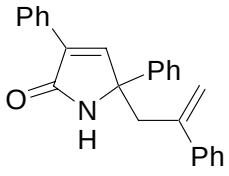


3,5-Diphenyl-5-(3-benzofuryl)-3-pyrrolin-2-one (5i): A white solid; mp 196.2-197.4 ^{o}C. IR (KBr): 699, 753, 795, 901, 1177, 1251, 1345, 1451, 1490, 1635, 1698 (C=O), 2838, 3065, 3160 (N-H) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ6.74 (s, 1H), 7.20-7.29 (m, 2H), 7.31-7.42

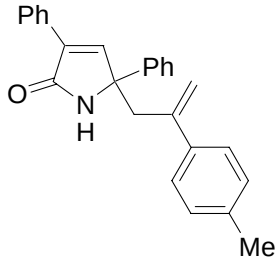
(m, 9H), 7.54 (d, J = 6.8 Hz, 1H), 7.59 (s, 1H), 7.60 (br s, 1H), 7.91 (d, J = 6.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ65.5, 104.6, 111.3, 121.2, 123.1, 124.6, 126.2, 126.3, 127.3, 127.5, 128.4, 128.9, 129.0, 130.5, 134.7, 138.2, 143.3, 155.0, 155.3, 171.7. HRMS (FAB) calcd for M+H$^+$ of $C_{24}H_{17}NO_2$ 352.1330, found 352.1338.



3,5-Diphenyl-5-(2-benzofuryl)-3-pyrrolin-2-one (5i'): A white solid; mp 181.2-182.6 ^{o}C. IR (KBr): 693, 755, 791, 900, 1175, 1221, 1251, 1340, 1451, 1493, 1635, 1710 (C=O), 2858, 3061, 3182 (N-H) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ6.23 (s, 1H), 6.81 (s, 1H), 7.59 (m, 14H), 8.41 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ59.9, 104.8, 107.1, 111.2, 121.0, 122.8, 124.1, 124.9, 127.2, 127.9, 128.0, 128.7, 128.9, 129.3, 129.5, 137.6, 141.0, 155.0, 155.1, 178.4.

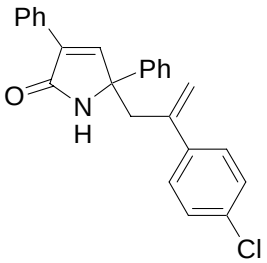


3,5-Diphenyl-5-(2-phenyl-2-propenyl)-3-pyrrolin-2-one (6a): A white solid; mp 182.2-184.1 ^{o}C. IR (KBr): 699, 754, 793, 977, 1447, 1492, 1599, 1635, 1691 (C=O), 2872, 3028, 3061, 3142, 3181 (N-H) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ3.29 (d, J = 13.6 Hz, 1H) 3.40 (d, J = 13.6 Hz, 1H), 5.05 (s, 1H), 5.26 (s, 1H), 7.00 (br s, 1H), 7.21-7.35 (m, 12H), 7.39 (d, J = 7.2 Hz, 2H), 7.53 (d, J = 7.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ45.9, 66.3, 118.9, 125.5, 126.4, 127.1, 127.4, 127.5, 128.1, 128.3, 128.5, 128.6, 131.0, 133.5, 140.4, 141.7, 143.1, 146.6, 171.8. HRMS (FAB) calcd for M+H$^+$ of $C_{25}H_{21}NO$ 352.1701, found 352.1710.

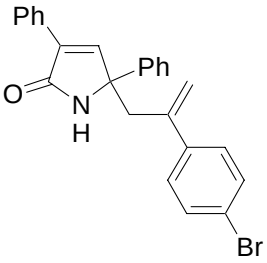


3,5-Diphenyl-5-[2-(4-methylphenyl)-2-propenyl]-3-pyrrolin-2-one (6b): A colorless crystal; mp 146.5-147.9 ^{o}C. IR (KBr): 697, 749, 794, 915, 1447, 1492, 1514, 1623, 1692 (C=O), 2863, 2920, 3027, 3061, 3147, 3197 (N-H) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ2.30

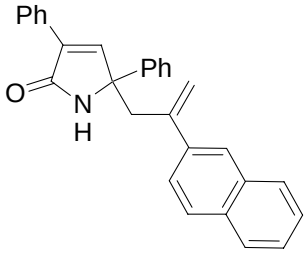
(s, 3H), 3.25 (d, *J* = 13.6 Hz, 1H), 3.38 (d, *J* = 13.6 Hz, 1H), 4.99 (s, 1H), 5.21 (s, 1H), 7.00 (s, 1H), 7.05 (d, *J* = 7.2 Hz, 2H), 7.13 (d, *J* = 7.2 Hz, 2H), 7.23-7.34 (m, 6H), 7.40 (d, *J* = 7.6 Hz, 2H), 7.53-7.60 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ21.1, 46.0, 66.4, 118.1, 125.6, 126.2, 127.1, 127.4, 128.0, 128.3, 128.6, 128.8, 129.1, 131.0, 137.2, 138.8, 140.5, 142.8, 146.7, 172.0. HRMS (FAB) calcd for M+H$^+$ of $C_{26}H_{23}NO$ 366.1858, found 366.1846.



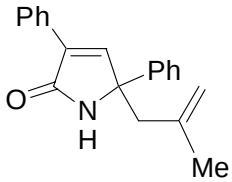
3,5-Diphenyl-5-[2-(4-chlorophenyl)-2-propenyl]-3-pyrrolin-2-one (6c): A white solid; mp 127.3-128.8 ^{o}C. IR (KBr): 694, 748, 794, 919, 1447, 1491, 1597, 1625, 1689 (C=O), 2857, 2920, 3027, 3062, 3147, 3179 (N-H) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ3.26 (d, *J* = 14.0 Hz, 1H), 3.35 (d, *J* = 14.0 Hz, 1H), 5.09 (s, 1H), 5.24 (s, 1H), 7.00 (s, 1H), 7.14 (d, *J* = 8.0 Hz, 2H), 7.18 (d, *J* = 8.0 Hz, 2H), 7.23-7.27 (m, 2H), 7.30-7.34 (m, 4H), 7.39 (d, *J* = 8.0 Hz, 2H), 7.54-7.57 (m, 2H), 7.89 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ45.9, 66.3, 119.5, 125.5, 127.0, 127.5, 127.7, 128.2, 128.5, 128.7, 129.7, 130.9, 133.2, 133.7, 134.9, 140.3, 142.1, 146.2, 172.0. HRMS (FAB) calcd for M+H$^+$ of $C_{25}H_{20}ClNO$ 386.1312, found 386.1313.



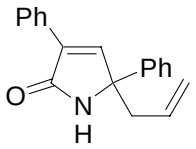
3,5-Diphenyl-5-[2-(4-bromophenyl)-2-propenyl]-3-pyrrolin-2-one (6d): A white solid; mp 66.3-67.2 ^{o}C. IR (KBr): 695, 794, 909, 1489, 1625, 1691 (C=O), 2919, 3062, 3185 (N-H) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ3.25 (d, *J* = 13.8 Hz, 1H), 3.35 (d, *J* = 13.8 Hz, 1H), 5.09 (s, 1H), 5.24 (s, 1H), 6.98 (s, 1H), 7.07 (d, *J* = 8.1 Hz, 2H), 7.23-7.42 (m, 10H), 7.52-7.56 (m, 2H), 8.04 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ45.8, 66.4, 119.6, 121.4, 125.6, 127.1, 127.6, 128.0 128.2, 128.5, 128.7, 130.9, 131.5, 133.8, 140.4, 140.9, 142.2, 146.3, 172.2. HRMS (FAB) calcd for M+H$^+$ of $C_{25}H_{20}BrNO$ 432.0790, found 432.0786.



3,5-Diphenyl-5-[2-naphthalenyl-2-propenyl]-3-pyrrolin-2-one (6e): A white solid; mp 51.2-52.9 ^{o}C. IR (KBr): 695, 748, 794, 1220, 1446, 1491, 1597, 1626, 1691 (C=O), 2856, 3026, 3057, 3210 (N-H) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.37 (d, J = 13.6 Hz, 1H), 3.51 (d, J = 13.6 Hz, 1H), 5.16 (s, 1H), 5.37 (s, 1H), 6.95 (s, 1H), 7.15-7.25 (m, 4H), 7.28-7.34 (m, 2H), 7.36-7.47 (m, 7H), 7.66 (br s, 1H), 7.68-7.95 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 46.0, 66.5, 119.4, 124.8, 125.1, 125.6, 125.9, 126.2, 127.1, 127.4, 127.5, 127.9, 128.0, 128.1, 128.3, 128.6, 130. 9, 132.6, 133.2, 133.6, 139.2, 140.5, 143.0, 146.4, 172.0. HRMS (FAB) calcd for M+H^{+} of $C_{29}H_{23}NO$ 402.1858, found 402.1852.

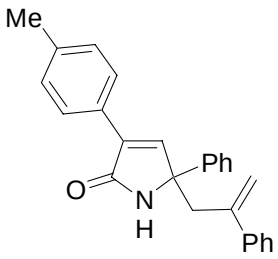


3-Phenyl-5-(2-methyl-2-propenyl)-5-phenyl-3-pyrrolin-2-one (6f): A white solid; mp 114.3-115.5 ^{o}C. IR (KBr): 697, 796, 900, 1225, 1364, 1448, 1492, 1599, 1685 (C=O), 2897, 2975, 3026, 3063, 3213 (N-H) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.52 (s, 3H), 2.71 (d, J = 13.6 Hz, 1H), 2.93 (d, J = 13.6 Hz, 1H), 4.75 (s, 1H), 4.88 (s, 1H), 7.24-7.39 (m, 7H), 7.46 (d, J = 7.6 Hz, 2H), 7.69 (br s, 1H), 7.84 (d, J = 7.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.3, 47.5, 65.9, 116.5, 125.5, 127.1, 127.5, 128.3, 128.5, 128.7, 128.8, 131.0, 133.4, 140.1, 147.0, 172.1. HRMS (FAB) calcd for M+H^{+} of $C_{20}H_{19}NO$ 290.1548, found 290.1545.

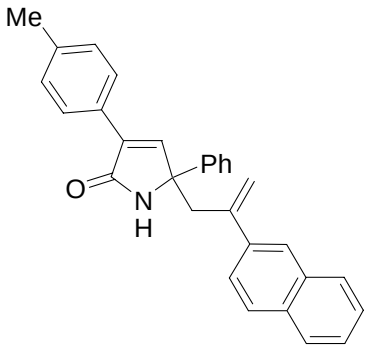


3-phenyl-5-(2-propenyl)-5-phenyl-3-pyrrolin-2-one (6g): A white solid; mp 35.1-36.2 ^{o}C. IR (KBr): 694, 747, 795, 923, 1447, 1491, 1688 (C=O), 2923, 2979, 3060, 3197 (N-H) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.71 (dd, J = 6.4, 13.6 Hz, 1H), 2.99 (dd, J = 7.6, 13.6 Hz, 1H), 5.10 (d, J = 10.4 Hz, 1H), 5.15 (d, J = 16.8 Hz, 1H), 5.57-5.67 (m, 1H), 7.25-7.38 (m, 8H), 7.44 (d, J = 8.0 Hz, 2H), 7.85 (d, J = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 43.6, 65.7, 120.0, 125.5, 127.1, 127.6, 128.3,

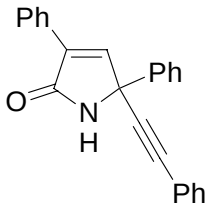
128.6, 128.8, 131.0, 131.8, 133.9, 139.7, 146.9, 172.0. HRMS (FAB) calcd for M+H$^+$ of $C_{19}H_{17}NO$ 276.1389, found 276.1388.



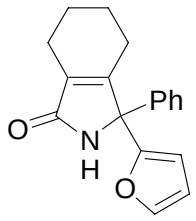
3-(4-Methylphenyl)-5-phenyl-5-(2-phenyl-2-propenyl)-3-pyrrolin-2-one (7a): A white solid; mp 146.0-147.8 ^oC. IR (KBr): 698, 779, 911, 1446, 1495, 1509, 1625, 1687 (C=O), 2864, 2920, 3025, 3060, 3179 (N-H) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ2.32 (s, 3H), 3.26 (d, J = 13.6 Hz, 1H), 3.38 (d, J = 13.6 Hz, 1H), 5.04 (s, 1H), 5.23 (s, 1H), 6.93 (s, 1H), 7.15 (d, J = 7.6 Hz, 2H), 7.21-7.25 (m, 5H), 7.31 (t, J = 7.6 Hz, 3H), 7.39 (d, J = 8.0 Hz, 2H), 7.44 (d, J = 8.0 Hz, 2H), 7.74 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ21.4, 46.0, 66.3, 118.8, 125.6, 126.4, 127.0, 127.3, 128.2, 128.4, 128.5, 128.8, 133.4, 138.2, 140.5, 140.6, 141.8, 143.1, 145.5, 172.1. HRMS (FAB) calcd for M+H$^+$ of $C_{26}H_{23}NO$ 366.1858, found 366.1857.



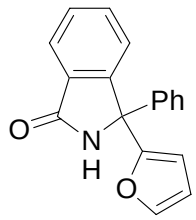
3-(4-Methylphenyl)-5-phenyl-5-(2-naphthalenyl-2-propenyl)-3-pyrrolin-2-one (7e): A white solid; mp 164.2-165.8 ^oC. IR (KBr): 697, 751, 822, 1507, 1689 (C=O), 2860, 2924, 3049, 3056, 3193 (N-H) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ2.29 (s, 3H), 3.36 (d, J = 13.6 Hz, 1H), 3.42 (d, J = 13.6 Hz, 1H), 5.14 (s, 1H), 5.36 (s, 1H), 6.91 (s, 1H), 7.00 (d, J = 8.0 Hz, 2H), 7.20-7.46 (m, 10H), 7.64 (d, J = 9.6 Hz, 2H), 7.71 (d, J = 8.0 Hz, 2H), 7.76-7.79 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ21.3, 46.0, 66.4, 119.3, 124.8, 125.1, 125.6, 125.8, 126.1, 126.9, 127.4, 128.0, 128.1, 128.6, 128.7, 132.6, 133.2, 133.5, 138.1, 139.2, 140.6, 143.0, 145.5, 172.1. HRMS (FAB) calcd for M+H$^+$ of $C_{30}H_{25}NO$ 416.2014, found 416.2017.



3,5-Diphenyl-5-phenylethynyl-3-pyrrolin-2-one (8): A yellow solid; mp 98.4-99.9 °C. IR (KBr): 691, 761, 793, 957, 1063, 1223, 1254, 1354, 1446, 1490, 1596, 1696 (C=O), 2842, 3061, 3168 (N-H) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.96 (s, 1H), 7.20 (d, J = 1.6 Hz, 1H), 7.32-7.42 (m, 9H), 7.49-7.52 (m, 2H), 7.65-7.68 (m, 2H), 7.88-7.91 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 60.6, 84.8, 86.2, 121.8, 125.8, 127.3, 128.3, 128.4, 128.6, 128.8, 128.9, 129.0, 130.4, 131.7, 132.9, 137.7, 144.7, 171.8. HRMS (FAB) calcd for $M+H^+$ of $C_{24}H_{17}NO$ 336.1388, found 336.1381.

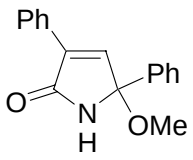


3-(2-Furyl)-3-phenyl-2,4,5,6,7-pentahydroisoindol-1-one (10): A white solid; mp 140.8-141.9 °C. IR (KBr): 701, 753, 865, 1015, 1154, 1232, 1310, 1448, 1504, 1688 (C=O), 2942, 3058, 3198 (N-H) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.61-1.70 (m, 4H), 1.99-2.02 (m, 1H), 2.28-2.36 (m, 3H), 6.28 (d, J = 2.4 Hz, 1H), 6.38 (dd, J = 1.6, 2.4 Hz, 1H), 6.42 (br s, 1H), 7.15 (d, J = 6.8 Hz, 2H), 7.31-7.33 (m, 3H), 7.41 (d, J = 1.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.2, 21.6, 22.2, 23.1, 68.1, 107.9, 110.2, 126.4, 128.2, 128.7, 131.1, 139.0, 142.8, 153.0, 158.0, 173.4. HRMS (FAB) calcd for $M+H^+$ of $C_{18}H_{17}NO_2$ 280.1338, found 280.1332.

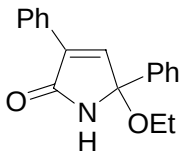


3-(2-Furyl)-3-phenylisoindolin-1-one (12): A white solid; mp 163.2-165.4 °C. IR (KBr): 699, 752, 801, 885, 1015, 1151, 1224, 1315, 1342, 1449, 1469, 1495, 1612, 1694 (C=O), 2834, 3066, 3188 (N-H) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.26 (d, J = 2.8 Hz, 1H), 6.33 (dd, J = 1.6, 2.8 Hz, 1H), 7.20-7.25 (m, 2H), 7.26-7.33 (m, 3H), 7.42 (d, J = 1.6 Hz, 1H), 7.52-7.58 (m, 3H), 7.64 (br s, 1H), 7.88 (d, J = 7.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 66. 4, 108.2, 110.0, 123.9, 124.1, 126.1, 128.2, 128.7, 128.8, 130.4, 132.3, 140.3, 143.2, 148.5, 153.4, 169.9.

HRMS (FAB) calcd for M+H$^+$ of $C_{18}H_{13}NO_2$ 276.1016, found 276.1025.



3,5-Diphenyl-5-methoxy-3-pyrrolin-2-one (18a): A colorless crystal; mp 78.2-79.4 ^oC. IR (KBr): 650, 693, 746, 764, 797, 885, 965, 1092, 1216, 1237, 1261, 1353, 1448, 1491, 1573, 1623, 1705 (C=O), 1814, 1891, 1960, 2826, 2931, 2950, 3067, 3211 (N-H) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.34 (s, 3H), 6.96 (s, 1H), 7.29-7.35 (m, 6H), 7.46 (br s, 1H), 7.55 (d, J = 8.0 Hz, 2H), 7.85 (d, J = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 50.6, 90.8, 125.6, 127.3, 128.3, 128.5, 128.6, 129.0, 130.0, 135.3, 138.2, 142.6, 171.7. HRMS (FAB) calcd for M+H$^+$ of $C_{17}H_{15}NO_2$ 266.1176, found 266.1181.

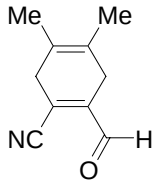


3,5-Diphenyl-5-ethoxy-3-pyrrolin-2-one (18b): A colorless crystal; mp 39.8-40.8 ^oC. IR (KBr): 653, 693, 744, 769, 795, 880, 981, 1066, 1215, 1236, 1261, 1352, 1390, 1448, 1491, 1575, 1623, 1699 (C=O), 1806, 1897, 1958, 2886, 2929, 2976, 3065, 3223 (N-H) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.26 (t, J = 7.2 Hz, 3H), 3.54 (dq, J = 7.2, 9.2 Hz, 1H), 3.65 (dq, J = 7.2, 9.2 Hz, 1H), 6.95 (br s, 1H), 7.00 (s, 1H), 7.32-7.40 (m, 6H), 7.57 (dd, J = 1.6, 7.6 Hz, 2H), 7.86 (dd, J = 1.6, 7.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.6, 58. 8, 90.4, 125.6, 127.4, 128.4, 128.5, 128.6, 129.0, 130.2, 135.0, 138.6, 143.2, 171.5. HRMS (FAB) calcd for M+H$^+$ of $C_{18}H_{17}NO_2$ 280.1342, found 280.1338.

Isotope Labeling Experiment

A flame dried Schlenk flask was charged with $Cu(OTf)_2$ (18 mg, 0.050 mmol), carbonyl-ene-nitrile **1a** (233 mg, 1.0 mmol), ^{18}O-labeled water (98% ^{18}O) (60 μL, 3.0 mmol) and furan (340 mg, 5.0 mmol) in $ClCH_2CH_2Cl$ (5.0 mL) and resulting reaction mixture was

stirred at 70 °C for 3 h. The mixture was diluted with Et_2O and filtered through a short silica gel pad. The organic solvent was removed under reduced pressure and the residue was subjected to flash column chromatography on silica gel with hexane/AcOEt (v/v = 7/1-4/1) as eluents to afford 3,5-diphenyl-5-(2-furyl)-3- pyrrolin-2-one **5e'** as a white solid (196 mg, 0.65 mmol; 65% yield). ^{18}O-incorporation was monitored by high resolution mass spectroscopy. HRMS (FAB) m/z: 302.1168 (94% intensity, $C_{20}H_{15}N^{16}O_2$), 304.1244 (100% intensity. $C_{20}H_{15}N^{16}O^{18}O$). The incorporation of ^{18}O into the product **5e** was not observed, when the isolated **5e** was stirred under the reaction conditions involving ^{18}O-labeled water, and $Cu(OTf)_2$ in $ClCH_2CH_2Cl$.



Synthesis of 2-cyano-4,5-dimethyl-1,4-cyclohexadiene-1-carboxaldehyde (15). To a solution of 1-hydroxy-3-cyano-2-propyne[27] (405 mg, 5.0 mmol) in CH_2Cl_2 (10 mL) was added Dess-Martin periodinane (2.12 g, 5.0 mmol) at 0 °C and the mixture was stirred for 30 min. Then 2,3-dimethyl-1,3-buatadiene (4.11 g, 50 mmol) was added and the mixture was stirred at 0 °C for additional 30 min. After stirring at room temperature overnight, the solvent was removed under reduced pressure. The residue was subjected to flash column chromatography on silica gel with hexane/AcOEt (v/v = 7/1-4/1) as eluents to afford 2-cyano-4,5-dimethyl-1,4-cyclohexadiene-1-carbox-aldehyde **15** as a pale yellow solid (459 mg, 2.85 mmol, 57% yield). mp 115.2-115.8 °C. IR (KBr): 633, 790, 1136, 1205, 1269, 1422, 1633, 1684 (C=O), 2216 (CN), 2864 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.71 (s, 6H), 2.90 (t, J = 8.0 Hz, 2H), 3.10 (t, J = 8.0 Hz, 2H), 10.1 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.0, 18.3, 30.1, 36.3, 115.3, 120.1, 122.2, 124.7, 147.0, 189.2. Anal. calcd for $C_{10}H_{11}NO$: C, 74.51; H, 6.88; N, 8.69. found C, 74.21; H, 6.90; N, 8.52.

X-ray Crystallographic Studies of 6b. Colorless crystals of **6b** suitable for X-ray analysis were obtained by recrystallization from CH_2Cl_2/*n*-pentane. The single crystal was sealed in a Pyrex glass capillary under N_2 atmosphere and used for data collection. All measurements were made on a Rigaku RAXIS imaging plate area detector with graphite monochromated Mo-Kα radiation. Details of crystal and data collection parameters are summarized in Table 4. The positions of non-hydrogen atoms were determined by direct methods (SIR92) and subsequent Fourier syntheses (DIRDIF PATTY). An ORTEP drawing of **6b** is shown in Figure 2.

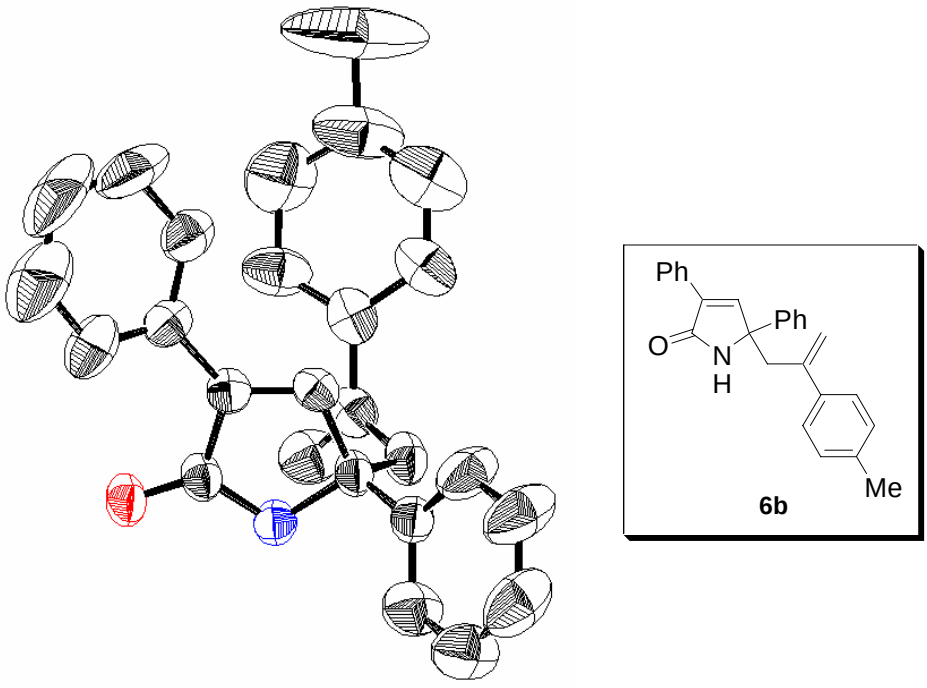


Figure 2. ORTEP drawing of **6b**. Hydrogen atoms are omitted for clarity.

Table 4. Summary of crystallographic data of **6b**

Empirical formula: $C_{26}H_{23}NO$

Formula weight: 365.47

Crystal system: monoclinic

Space group: P21/c (#14)

Crystal color: colorless

Lattice parameters:

a (Å) = 10.669(7), b (Å) = 10.059(7), c (Å) = 19.738(14),

V (Å^3) = 2110(3), β = 94.978(6)^o

Z = 4

D_{calc} (g cm^{-3}): 1.150

μ (Mo K α) (cm^{-1}): 0.692

Goodness of fit (GOF) = 1.039

F(000): 776

Diffractometer: Rigaku RAXIS-RAPID

Radiation: MoK α (λ = 0.71070 Å), Graphite Monochromated

Temp (^{o}C): -150

Scan type: ω–2 θ

Max. 2 θ (^{o}): 55.0

No. of reflections measured total: 16059

No. of observations (I > 2.00 σ (I)): 7888

Structure solution: Direct Methods (SIR92)

Refinement: Full-Matrix Least-Squares on F

No. of variables: 324

Reflection/parameter ratio: 24.35

Residuals: R = 0.0921, R_{int} = 0.052, R_w = 0.0853

Max Shift/Error in Final Cycle: 0.00

Maximum peak in Final Diff Map (e (Å^{-3}): 1.64

Minimum peak in Final Diff Map (e (Å^{-3}): -1.10

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Chapter 2

Copper-catalyzed Mannich-type Reactions of 2-Aza-2,4-cyclopentadienone Generated from Cycloisomerization of Carbonyl-ene-nitrile Compound with Ketones

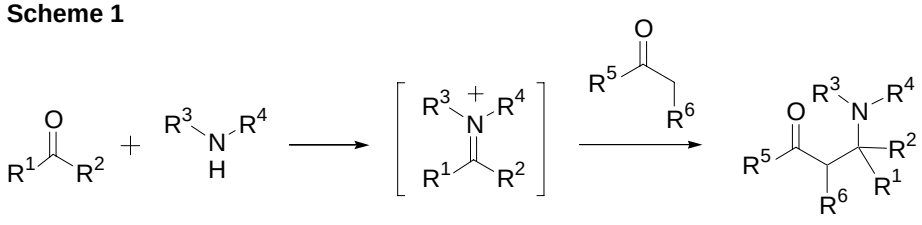
Abstract

Copper-catalyzed Mannich-type reactions of a carbonyl-ene-nitrile compound with ketones gave corresponding acetonylated pyrrolin-2-one derivatives in excellent yields. The reaction involves addition reactions of enolates or enols of ketones with a ketimine moiety of the 2-aza-2,4-cyclopentadienone intermediate which is formed via cycloisomerization of a carbonyl-ene-nitrile compound. The reaction proceeds under mild conditions and provides efficient access to synthetically useful pyrrolin-2-ones, which can be applied to the synthesis of azabicyclo[4.3.0]nonanone (indolizidine) derivatives.

Introduction

Due to the importance of amino acid derivatives in pharmaceuticals and functional materials, much effort has been devoted to the development of new and effective methods to access these compounds. Among them, Mannich-type reactions represent one of the most powerful and direct methods for the synthesis of various *β*-amino carbonyl compounds through the formation of new carbon-carbon bonds.[1] The reaction proceeds via addition reactions of the enolates generated from ketones to iminium ions which are formed by condensation of carbonyl compounds with amines (Scheme 1).[2] Although addition reactions of enolates with aldimines have been well studied, there have been much less reports on the reactions with ketimines, leading to *β*,*β*-disubstituted amino carbonyl compounds directly.[3]

Scheme 1

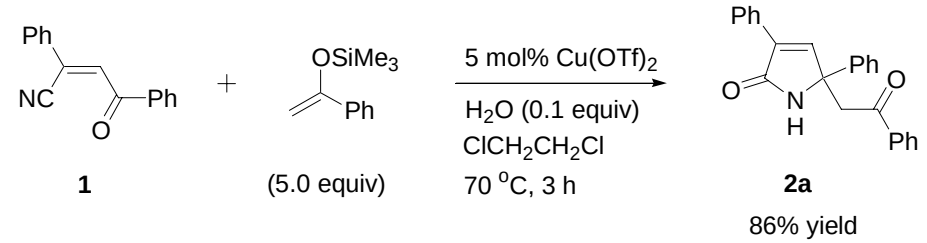


In Chapter 1, the author has demonstrated that copper-catalyzed reactions of carbonyl-ene-nitrile compounds with various nucleophiles including alkenes, aromatics, an alkyne, and alcohols afforded the corresponding 5-substituted pyrrolin-2-ones (*γ*-lactams).[4] The reaction proceeds via addition reactions with ketimine moiety of the 2-aza-2,4-cyclopentadienone intermediate, which is formed via cycloisomerization of carbonyl-ene-nitrile compounds including hydration of a cyano moiety followed by dehydrative cyclization between the resulting amide and an original carbonyl moiety.[5] These results stimulated him to make further efforts to investigate catalytic Mannich-type reactions of the ketimine moiety of 2-aza-2,4-cyclopentadinone.

Results and Discussion

First, the author attempted Mannich-type reactions of carbonyl-ene-nitrile compound **1** with silyl enol ethers (Scheme 2).[6] When the reaction of **1** with 1-phenyl-1-trimethylsilyloxyethylene was examined in the presence of a catalytic amount of $Cu(OTf)_2$ and water, the Mannich-type product **2a** was obtained in 86% yield. In contrast, the reaction with 2-trimethylsiloxy-1-propene did not afford the corresponding product at all due to the low stability of the product in the presence of the reactive silyl enol ether.

Scheme 2



1 (5.0 equiv) **2a** 86% yield

During the course of these studies, the author was pleased to find direct Mannich-type reactions of **1** with ketones (Scheme 3). Selected results are summarized in Table 1. When the reaction of **1** with acetophenone was carried out, **2a** was obtained in 95% yield (entry 1). Both 4-methoxy and 4-trifluoromethylacetophenone reacted with **1** to afford the corresponding products **2b** and **2c** in excellent yields, respectively (entries 2 and 3). Surprisingly, the aliphatic ketones such as acetone and *tert*-butyl methyl ketone also gave the Mannich-type products **2d** and **2e** in 92% and 93% yields, respectively (entries 4 and 5).

Scheme 3

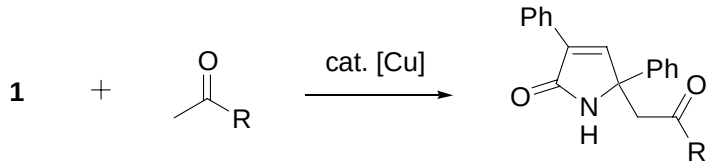
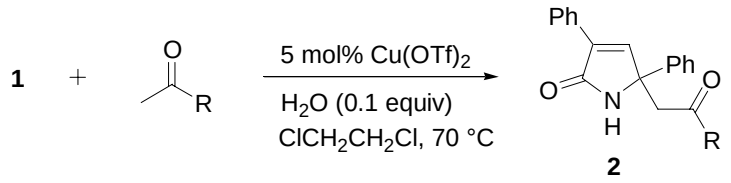


Table 1. Cu-catalyzed Mannich-type reactions with ketones[a]

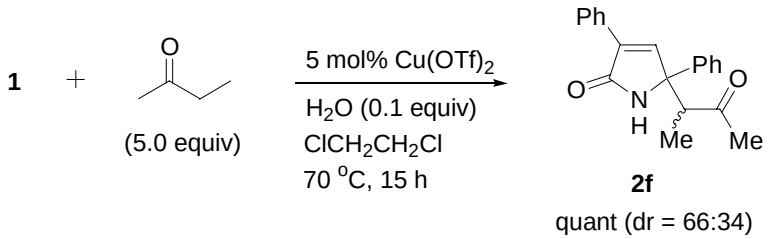


entry	R	time (h)	product	yield (%)[b]
1	Ph	24	**2a**	95
2	4-$MeOC_6H_4$	3	**2b**	quant
3[c]	4-$CF_3C_6H_4$	8	**2c**	97
4	Me	6	**2d**	92
5	^{t}Bu	6	**2e**	93

[a] Reaction conditions: **1** (0.40 mmol), ketone (2.0 mmol), $Cu(OTf)_2$ (0.020 mmol), H_2O (0.04 mmol) in $ClCH_2CH_2Cl$ (1.6 mL) at 70 °C. [b] Isolated yields. [c] 80 °C.

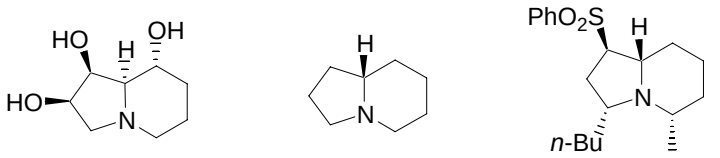
Carbonyl-ene-nitrile compound **1** also reacted with 2-butanone to give single constitutional isomer **2f** quantitatively as a mixture of two diastereomers (dr = 66:34) (Scheme 4). The structure of **2f** suggested that 2-aza-2,4-cyclopentadienone generated from **1** reacted selectively with a thermodynamically stable enol generated from 2-butanone.

Scheme 4



As described above, the author established the Mannich-type reactions of a carbonyl-ene-nitrile compound with various ketones leading to corresponding 5-(2'-oxoalkyl)pyrrolin-2-ones. By utilizing this one step pyrrolin-2-one synthesis, he next decided to demonstrate the synthetic application to indolizidine alkaloids, which have received considerable attention due to their wide range of biological activities.[7] A variety of applications in pharmaceutical uses have been reported to date. For an example, it has been

reported that (–)-swainsonine shows inhibitory characteristics with respect to tumor growth and metastasis (Figure 1).[8]

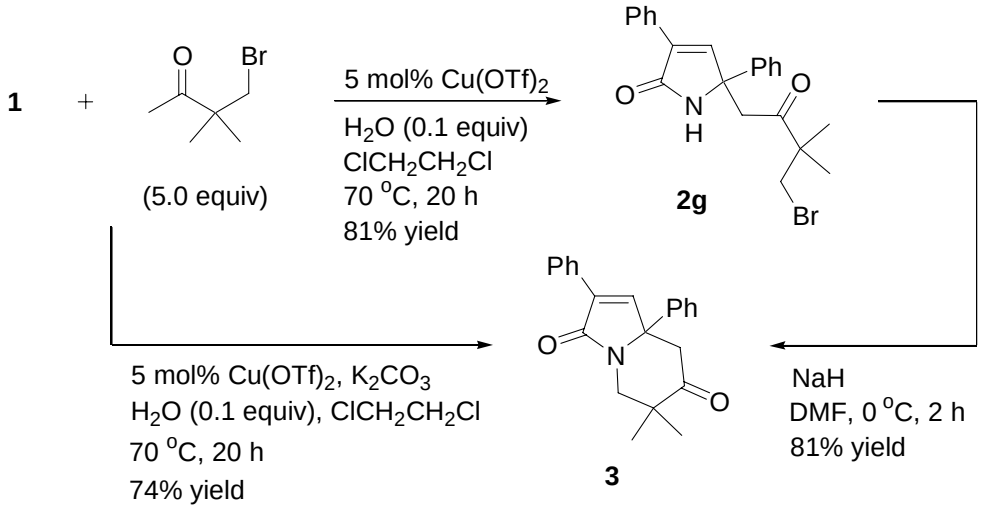


(-)-Swainsonine (-)-δ-Coniceine (+)-Monomorine

Figure 1. Various indolizidine alkaloids.

When the reaction of **1** with *β*-bromoketone in the presence of $Cu(OTf)_2$ was carried out, the corresponding pyrrolin-2-one was obtained in 81% yield (Scheme 5). The subsequent intramolecular cyclization of **2g** using sodium hydride afforded azabicyclo[4.3.0]nonanone **3** (indolizidinone) in 81% yield. Furthermore, one-pot synthesis of **3** from **1** and *β*-bromoketone was examined in the presence of potassium carbonate as a base. The author was delighted to find that **3** was obtained in 74% yield from **1** and *β*-bromoketone in one pot.

Scheme 5



In conclusion, the author has described copper-catalyzed Mannich-type reactions of a carbonyl-ene-nitrile compound with ketones leading to acetonylated pyrrolin-2-ones on the basis of the in situ generation of reactive 2-aza-2,4-cyclopentadienone intermediates.

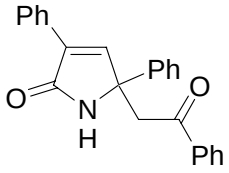
Ketones as well as a silyl enol ether are applicable to the reaction to afford the corresponding Mannich-type products in excellent yields via addition reactions with a ketimine moiety of the 2-aza-2,4-cyclopentadienone. Furthermore, cascade reaction of copper-catalyzed pyrrolin-2-one formation with a β-bromoketone followed by intramolecular cyclization allows the one-pot synthesis of an indolizidinone. As demonstrated by this application, the present transformation of a carbonyl-ene-nitrile compound may open up new possibility for rapid synthesis of natural products containing indolizinone skeletons.

Experimental

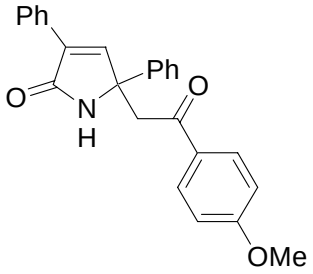
General Method. Unless otherwise noted, chemicals obtained from commercial suppliers were used without further purification. Solvents were dried by the usual methods and distilled before use. All reactions were carried out under nitrogen atmosphere. NMR spectra were measured for solutions in $CDCl_3$ or acetone-d_6 with tetramethylsilane as an internal standard (^1H and ^{13}C): the following abbreviations are used; br s: broad singlet, s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet. IR spectra were recorded with an FT-IR spectrometer. Melting points (mp) are uncorrected. Element analyses were performed at Microanalytical Center of Kyoto University. High-resolution mass spectra (HRMS) was measured with JEOL JMX-SX 102A spectrometer.

General Procedure for Copper-catalyzed Mannich-type Reactions of Carbonyl-ene-nitrile Compound with Ketones. A flame dried Schlenk flask was charged with $Cu(OTf)_2$ (7.2 mg, 0.020 mmol), carbonyl-ene-nitrile compound **1** (0.40 mmol), and ketone (2.0 mmol) in $ClCH_2CH_2Cl$ (2.0 mL). The solution was stirred at room temperature

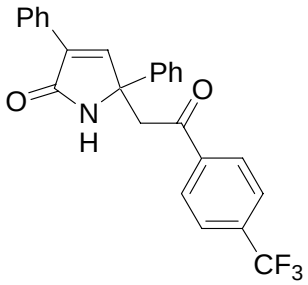
for 5 min and then water (0.040 mmol) was added dropwise. After stirring under the reaction conditions specified in Scheme 2-5 and Tables 1, the reaction mixture was diluted with Et_2O and filtered through a short silica gel pad. Filtrate was concentrated under reduced pressure and the residue was subjected to flash column chromatography on silica gel with hexane/AcOEt (v/v = 7/1-4/1) as eluents to afford the corresponding acetonylated pyrrolin-2-ones **2**. Diastereoisomers of **2f** were separated by column chromatography.



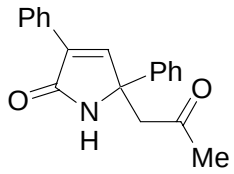
3,5-Diphenyl-5-(2-oxo-2-phenylethyl)-3-pyrrolin-2-one (2a): A colorless solid; mp 141.3-142.5 ^oC. IR (KBr): 692, 763, 795, 867, 1184, 1217, 1360, 1398, 1448, 1491, 1595, 1684 (C=O), 3025, 3060, 3241 (N-H) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.29 (d, J = 18.4 Hz, 1H), 4.38 (d, J = 18.4 Hz, 1H), 7.21-7.26 (m, 1H), 7.29-7.49 (m, 10H), 7.56-7.64 (m, 2H), 7.84-7.92 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 45.9, 63.7, 125.1, 127.2, 127.6, 128.0, 128.4, 128.7, 128.8, 128.9, 130.8, 133.7, 133.8, 136.4, 138.9, 146.5, 171.0, 196.6. HRMS (FAB) calcd for $M+H^+$ of $C_{24}H_{19}NO_2$ 354.1495, found 354.1494.



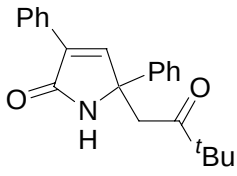
3,5-Diphenyl-5-[2-(4-methoxyphenyl)-2-oxoethyl]-3-pyrrolin-2-one (2b): A pale yellow solid; mp 63.8-64.9 ^oC. IR (KBr): 695, 745, 793, 840, 1030, 1170, 1232, 1262, 1349, 1380, 1447, 1492, 1510, 1574, 1599, 1696 (C=O), 2932, 3059, 3429 (N-H) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.20 (d, J = 18.0 Hz, 1H), 3.81 (s, 1H), 4.28 (d, J = 18.0 Hz, 1H), 6.89 (d, J = 9.0 Hz, 2H), 7.15-7.42 (m, 10H), 7.78 (br s, 1H), 7.85 (s, 2H), 7.88 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 45.4, 55.4, 63.8, 113.8, 125.1, 127.1, 127.4, 128.3, 128.6, 128.7, 129.4, 130.3, 130.9, 133.6, 139.2, 146.7, 163.9, 171.1, 195.1. HRMS (FAB) calcd for $M+H^+$ of $C_{25}H_{21}NO_3$ 384.1599, found 384.1600.



3,5-Diphenyl-5-[2-oxo-2-(4-trifluoromethylphenyl)ethyl]-3-pyrrolin-2-one (2c): A white solid; mp 163.2-165.4 ^{o}C. IR (KBr): 697, 747, 791, 844, 877, 1065, 1110, 1126, 1168, 1213, 1328, 1410, 1447, 1493, 1599, 1692 (C=O), 3058, 3266 (N-H) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.37 (d, J = 17.4 Hz, 1H), 4.32 (d, J = 17.4 Hz, 1H), 7.25-7.42 (m, 9H), 7.71 (m, 3H), 7.85 (d, J = 8.0 Hz, 2H), 7.98 (d, J = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 46.5, 63.7, 123.3 (q, J = 273.1 Hz), 125.1, 125.8 (q, J = 4.0 Hz), 127.1, 127.7, 128.3, 128.4, 128.8, 128.9, 130.7, 133.9, 134.9 (q, J = 33.1 Hz), 138.7, 138.9, 146.1, 171.1, 195.8. HRMS (FAB) calcd for M+H^{+} of $C_{25}H_{18}F_3NO_2$ 422.1369, found 422.1368.

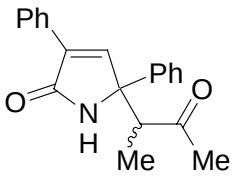


3,5-Diphenyl-5-(2-oxopropyl)-3-pyrrolin-2-one (2d): A white solid; mp 30.2-31.3 ^{o}C. IR (KBr): 696, 746, 794, 879, 1067, 1179, 1236, 1360, 1388, 1447, 1492, 1599, 1699 (C=O), 2975, 3062, 3243 (N-H) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.07 (s, 1H), 2.81 (d, J = 17.4 Hz, 1H), 3.62 (d, J = 17.4 Hz, 1H), 7.25-7.39 (m, 10H), 7.73 (br s, 1H), 7.84 (d, J = 7.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 31.0, 50.6, 63.5, 125.1, 127.1, 127.8, 128.3, 128.7, 128.8, 130.8, 133.7, 138.9, 146.1, 171.2, 205.5. HRMS (FAB) calcd for M+H^{+} of $C_{19}H_{17}NO_2$ 292.1338, found 292.1338.

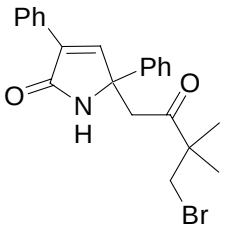


3,5-Diphenyl-5-(3,3-dimethyl-2-oxobutyl)-3-pyrrolin-2-one (2e): A white solid; mp 47.5-48.8 ^{o}C. IR (KBr): 696, 746, 794, 874, 905, 1005, 1067, 1176, 1222, 1365, 1448, 1478, 1492, 1599, 1682 (C=O), 2871, 2968, 3063, 3274 (N-H) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.95 (s, 9H), 2.65 (d, J = 16.8 Hz, 1H), 3.76 (d, J = 16.8 Hz, 1H), 7.12-7.32 (m, 9H), 7.65 (br s, 1H), 7.84 (d, J = 7.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.0, 44.3, 44.7, 63.6, 125.0, 127.0, 127.4, 128.2,

128.6, 130.8, 133.6, 139.0, 146.4, 170.9, 212.6. HRMS (FAB) calcd for M+H$^+$ of $C_{22}H_{23}NO_2$ 334.1812 found 334.1807.

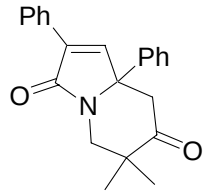


3,5-Diphenyl-5-(1-methyl-2-oxopropyl)-3-pyrrolin-2-one (2f): After the reaction was complete, **2f** was obtained as a mixture of diastereoisomers (dr = 66:34) which could be separated by column chromatography on silica gel. The major isomer was eluted with hexane/AcOEt (v/v = 7/1), and the minor one was eluted with hexane/AcOEt (v/v = 3/1), respectively. Major diastereomer: A white solid; mp 138.9-139.8 ^oC. IR (KBr): 698, 748, 795, 883, 1033, 1112, 1178, 1227, 1357, 1414, 1447, 1491, 1597, 1683 (C=O), 2875, 2932, 2972, 3059, 3351 (N-H) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.13 (d, J = 7.6 Hz, 3H), 1.96 (s, 3H), 3.67 (q, J = 7.6 Hz, 1H), 7.13 (d, J = 2.0 Hz, 1H), 7.24-7.28 (m, 1H), 7.31-7.42 (m, 7H), 7.43 (br s, 1H), 7.84 (dd, J = 2.0, 8.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.7, 31.1, 51.9, 67.0, 125.2, 127.1, 127.6, 128.3, 128. 7, 128.8, 130.8, 134.7, 139.7, 144.6, 171.6, 211.1. HRMS (FAB, M+H$^+$): calcd for $C_{20}H_{20}NO_2$ 306.1487, found 306.1494. Minor diastereomer: A white solid; mp 176.8-177.3 ^oC. IR (KBr): 698, 748, 795, 878, 1032, 1144, 1185, 1238, 1357, 1417, 1449, 1492, 1597, 1681 (C=O), 2873, 2932, 2974, 3067, 3210 (N-H) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.14 (d, J = 6.8 Hz, 3H), 1.91 (s, 3H), 3.45 (q, J = 6.8 Hz, 1H), 7.29 (d, J = 6.8 Hz, 1H), 7.36 (q, J = 6.8 Hz, 2H), 7.40-7.45 (m, 4H), 7.82 (d, J = 1.6 Hz, 1H), 7.92 (dd, J = 1.6, 8.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.4, 30.8, 55.2, 67.3, 126.2, 127.3, 127.8, 128.4, 128.7, 128.8, 131.0, 135.7, 139.6, 144.1, 171.9, 209.7. HRMS (FAB, M+H$^+$): calcd for $C_{20}H_{19}NO_2$ 306.1487, found 306.1489.



3,5-Diphenyl-5-(4-bromo-3,3-dimethyl-2-oxobutyl)-3-pyrrolin-2-one (2g): A white solid; mp 42.8-43.2 °C. IR (KBr): 696, 745, 794, 870, 1032, 1178, 1241, 1365, 1386, 1447, 1468, 1492, 1599, 1696 (C=O), 2970, 3060, 3257 (N-H), 3395 (N-H) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.14 (s, 3H), 1.17 (s, 3H), 2.85 (d, J = 18.0 Hz, 1H), 3.37 (s, 2H), 3.85 (d, J = 18.0 Hz, 1H), 7.21-7.40 (m, 9H), 7.66 (br s, 1H), 7.85 (d, J = 6.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.4, 23.5, 40.2, 45.7, 48.7, 63.5, 125.1, 127.0, 127.5, 128.3, 128.6, 128.6, 130.7, 133.7, 138.7, 146.0, 170.9, 209.3. HRMS (FAB) calcd for $M+H^+$ of $C_{22}H_{22}BrNO_2$ 412.0912, found 412.0912.

Synthesis of Azabicyclo[4,3,0]nonanone (6,6-Dimethyl-2,8a-diphenyl-5,6,7,8-tetrahydro-indolizin-3,7-dione) (3): A solution of 3,5-diphenyl-5-(4-bromo-3,3-dimethyl-2-oxo-butyl)-3-pyrrolin-2-one **2g** (41.2 mg, 0.10 mmol) in DMF (10 mL) was added to sodium hydride (4.8 mg, 0.20 mmol, 60% in mineral oil) at 0 °C, and the resulting mixture was stirred for 2 h. The obtained yellow solution was carefully poured into water (10 mL), and extracted with Et_2O (20 mL × 3). The combined organic layer was dried over $MgSO_4$. The organic solvent was removed under reduced pressure and the residue was subjected to flash column chromatography on silica gel with hexane/AcOEt (v/v = 7/1-4/1) as eluents to afford 6,6-dimethyl-2,8a-diphenyl-5,6,7,8-tetrahydroindolizin-3,7-dione **3** as a pale yellow viscous oil (26.8 mg, 0.080 mmol, 81% yield). IR (neat): 695, 789, 874, 1139, 1166, 1311, 1401, 1447, 1493, 1691 (C=O), 2867, 2929, 2969 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.02 (s, 3H), 1.22 (s, 3H), 2.71 (d, J = 13.6 Hz, 1H), 2.83 (d, J = 14.8 Hz, 1H), 3.40 (d, J = 14.8 Hz, 1H), 4.28 (d, J = 13.6 Hz, 1H), 7.21-7.28 (m, 3H), 7.30-7.44 (m, 7H), 7.98 (d, J = 6.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.8, 25.1, 44.1, 44.5, 46.9, 67.9, 126.3, 127.2, 128.5, 128.8, 129.0, 129.3, 130.9,



133.8, 135. 7, 145.2, 168.7, 210.2. HRMS (FAB) calcd for M+H$^+$ of $C_{22}H_{21}NO_2$ 332.1651, found 332.1657.

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3699. (m) Notte, G. T.; Leighton, J. L. *J. Am. Chem. Soc.* **2008**, *130*, 6676.

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(5) 2-Aza-2,4-cyclopentadienone intermediates were proposed in nickel- and iron-catalyzed tandem cyanation, cyclization, and carboxylation of alkynylketones leading to pyrrolinone derivatives. See: (a) Arzoumanian, H.; Jean, M.; Nuel, D.; Garcia, J. L.; Rosas, N. *Organometallics* **1997**, *16*, 2726. (b) Rosas, N.; Sharma, P.; Arellano, I.; Ramírez, M.; Pérez, D.; Hernández, S.; Cabrera, A. *Organometallics* **2005**, *24*, 4893.

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(8) (a) Fernandes, B.; Baker, M.; Dennis, J. W. *Cancer Res.* **1994**, *54*, 145. (b) Asano, N.; Kato, A.; Watson, A. A. *Mini Rev. Med. Chem.* **2001**, *1*, 145. (c) Carmona, A. T.; Fuentes, J.; Robina, I.; Rodriguez Garcia, E.; Demange, R.; Vogel, P.; Winters, A. L. *J. Org. Chem.* **2003**, *68*, 3874.

Chapter 3

Platinum-catalyzed Synthesis of α-Alkylidene-*N*-furylimines via Catalytic Vinylcarbene-transfer Reactions to Carbonyl-ene-nitrile Compounds

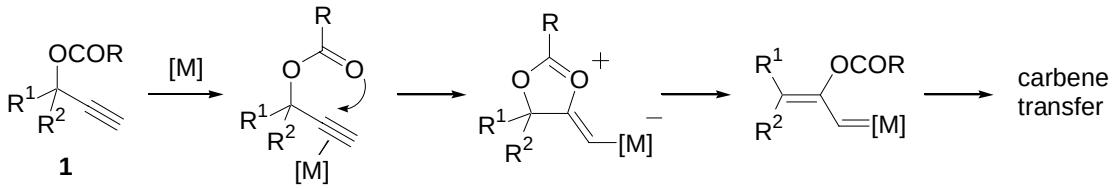
Abstract

The reaction of carbonyl-ene-nitrile compounds with propargyl carboxylates in the presence of a catalytic amount of $PtCl_2$ afforded the α-alkylidene-*N*-furylimine derivatives with high stereoselectivities. Propargyl carboxylates and carbonyl-ene-nitrile compounds are considered to serve as equivalents of vinylcarbenes and 2-furylnitrenes, respectively. The reaction proceeds in a complete atom-economical fashion and provides straightforward access to α-alkylidene-*N*-furylimines, which can be employed as building blocks for the synthesis of nitrogen-containing heterocycles.

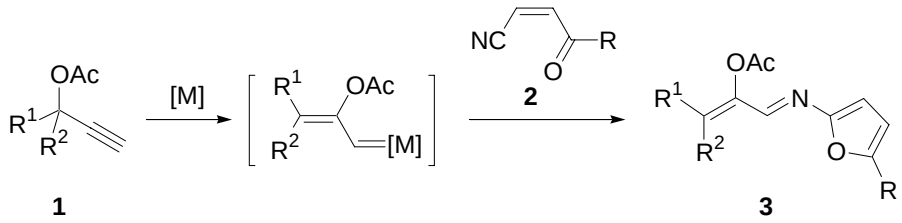
Introduction

Catalytic carbene-transfer reactions have been well investigated, aimed at developing facile and efficient access to structurally complex molecules.[1] Recently, the reaction between propargyl carboxylates **1** and transition metals has received considerable attention as a diazoalkane-free atom-efficient generation method of vinylcarbene complexes (Scheme 1).[2] The author's group has previously developed a wide range of catalytic vinylcarbene-transfer reactions including cyclopropanation reactions of alkenes, ring opening reactions of heterocycles, and carbene migration reactions using propargyl carboxylates.[3] Based on these works, the author set out his investigation using propargyl carboxylates as carbene precursors and nitriles as carbene acceptors to seek for new reactions.[4-6] He found that carbonyl-ene-nitrile compounds **2**[7] reacted with propargyl carboxylates **1** to afford α-alkylidene-*N*-furylimines **3** in the presence of a catalytic amount of platinum complexes atom-efficiently (Scheme 2).

Scheme 1



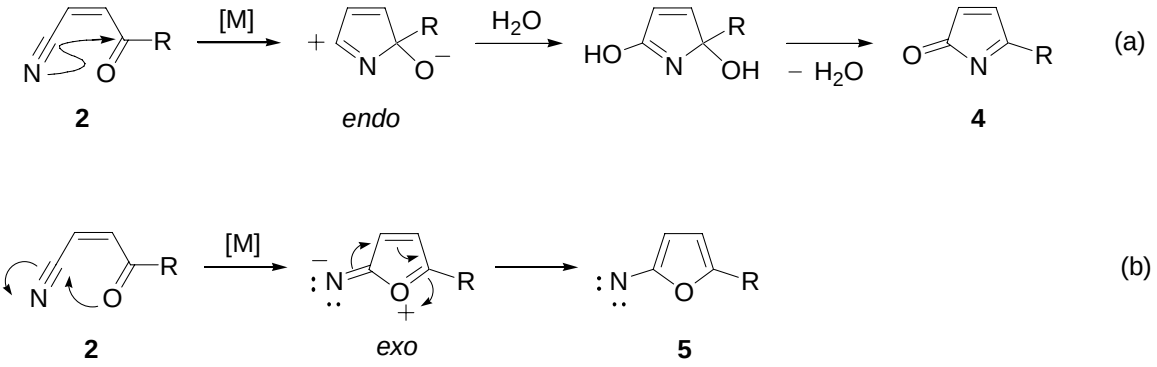
Scheme 2



While formal *endo* type cycloisomerization of carbonyl-ene-nitrile compounds **2** leading to 2-aza-2,4-cyclopentadienone **4** was described in Chapters 1 and 2 (Scheme 3a), the proper

choice of the reaction conditions changed the cycloisomerization mode. In this chapter, carbonyl-ene-nitrile compounds **2** act as 2-furylnitrene equivalents **5** via formal *exo* type cyclization to afford α-alkylidene-*N*-furylimines **3** (Scheme 3b, and see also General Introduction).[8]

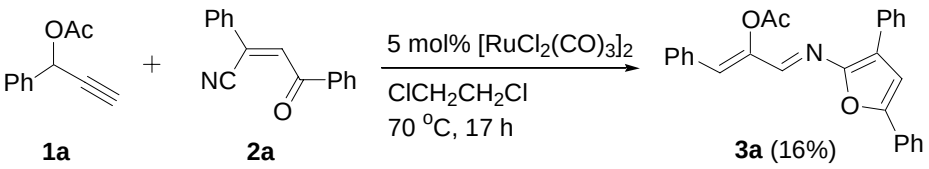
Scheme 3



Results and Discussion

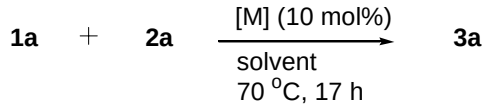
When the reaction of 1-phenyl-2-propynyl acetate **1a** as a carbene precursor with carbonyl-ene-nitrile compound **2a** was carried out in the presence of a catalytic amount of $[RuCl_2(CO)_3]_2$ (5 mol%) in $ClCH_2CH_2Cl$ at 70 ^oC, α-alkylidene-*N*-furylimine **3a** was obtained in 16% yield as a single stereoisomer (Scheme 4).

Scheme 4



This unusual reaction of a nitrile encouraged the author to optimize the reaction conditions. First, reactions of **1a** and **2a** in the presence of several transition metal catalysts were examined. The results are summarized in Table 1. Among the catalysts screened, he found that $PtCl_2$ was superior to $[RuCl_2(CO)_3]_2$, giving **3a** in 27% yield (entry 1). Although other platinum catalysts, such as $PtCl_2(PPh_3)_2$ and $PtCl_4$, exhibited marginal catalytic activity (entries 5 and 6), $[Rh(OAc)_2]_2$, $GaCl_3$, $AuCl_3$, $AuCl(PPh_3)$, $[RuCl_2(p\text{-cymene})]_2$, and $PdCl_2(CH_3CN)_2$ were almost ineffective for the present reaction, **2a** being recovered intact (entries 7-9). This reaction was strongly influenced by the solvent used. Among the solvents examined, toluene was superior to $ClCH_2CH_2Cl$ and THF, and **3a** was obtained in 52% yield (entries 2 and 3). In all cases, **2a** was not completely converted to **3a** even with extended reaction time and a stoichiometric amount of platinum compounds (entry 4).

Table 1. Optimization of reaction conditions[a]



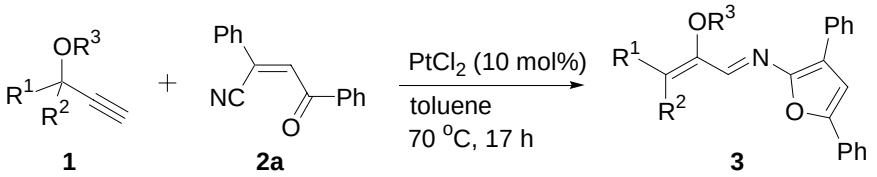
entry	[M]	solvent	conv. of **2a** (%)	yield of **3a** (%)[b]
1	$PtCl_2$	$ClCH_2CH_2Cl$	32	27
2	$PtCl_2$	THF	8	3
3	$PtCl_2$	toluene	66	52
4[c]	$PtCl_2$	toluene	69	50
5	$PtCl_2(PPh_3)_2$	$ClCH_2CH_2Cl$	3	1
6	$PtCl_4$	$ClCH_2CH_2Cl$	28	21
7[d]	$[Rh(OAc)_2]_2$	$ClCH_2CH_2Cl$	0	0
8	$GaCl_3$	$ClCH_2CH_2Cl$	0	0
9	$AuCl_3$	$ClCH_2CH_2Cl$	0	0

[a]Reaction conditions: **1a** (0.90 mmol), **2a** (0.30 mmol), [M] (0.030 mmol) in solvent (1.2 mL). [b]Isolated yields. [c]For 48 h. [d] $[Rh(OAc)_2]_2$ (5 mol%).

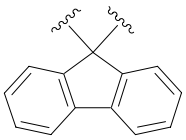
Next, the author examined the substrate scope of the reaction using a variety of 1-aryl-2-propynyl carboxylates **1** as carbene precursors in the presence of $PtCl_2$ (Table 2). Reactions of propargyl pivalate **1b** and benzoate **1c** with **2a** gave α-alkylidene-*N*-furylimines

3b and **3c**, respectively, with slightly lower yields in comparison with propargyl acetate **1a** (entries 1 and 2). The reaction was sensitive to the electronic features of the aryl group of **1**. Propargyl acetates **1d**, **1e**, and **1f**, which possess electron-withdrawing groups, reacted with **2a** to give the corresponding α-alkylidene-*N*-furylimines **3d**, **3e**, and **3f**, respectively, in good yields (entries 3-5). On the other hand, propargyl acetates **1g** and **1h** having electron-donating groups at the para-position of the aryl group produced α-alkylidene-*N*-furylimines in lower yields (entries 6 and 7). These results can be explained by assuming the resonance structures of vinylcarbene complex intermediates (Figure 1).[3] The substrate scope could be expanded to *tert*-propargyl acetates. The reaction of **1i**[3e] with **2a** gave α-fluoren-9-ylidene-*N*-furylimine **3i** in 80% yield (entry 8). The formation of *Z*- and *anti*-stereo regulated products reflects the intervention of *Z*-vinylcarbene complexes (Figure 1).

Table 2. Pt-catalyzed reactions of carbonyl-ene-nitrile compound **2a** with 1-aryl-2-propynyl carboxylates **1**[a]



1 **2a** **3**

entry	R^1	R^2	R^3		conv. of **2a** (%)	product	yield (%)[b]
1	Ph	H	Piv	**1b**	61	**3b**	47
2	Ph	H	Bz	**1c**	65	**3c**	57
3	4-BrC_6H_4	H	Ac	**1d**	64	**3d**	64
4	4-$CF_3C_6H_4$	H	Ac	**1e**	82	**3e**	66
5	C_6F_5	H	Ac	**1f**	81	**3f**	74
6	4-MeC_6H_4	H	Ac	**1g**	42	**3g**	38
7	4-MeOC_6H_4	H	Ac	**1h**	38	**3h**	24
8			Ac	**1i**	80	**3i**	80

[a]Reaction conditions: **1** (1.2 mmol), **2a** (0.40 mmol), $PtCl_2$ (0.040 mmol) in toluene (1.2 mL). [b]Isolated yields.

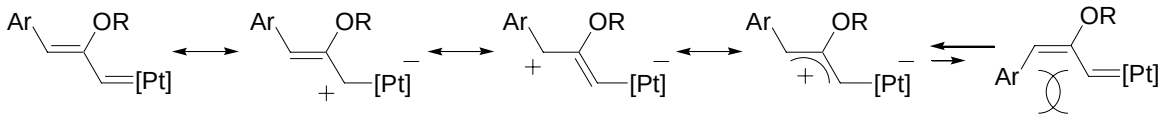
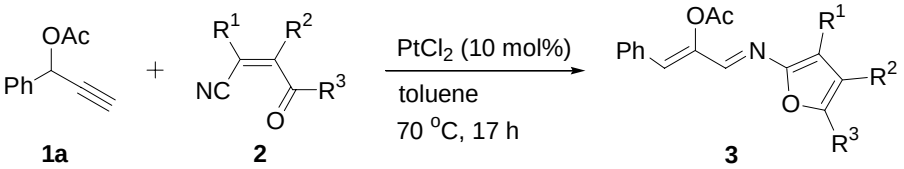


Figure 1. Resonance structures of Pt-vinylcarbenoids.

The structure of the product was confirmed by X-ray crystallographic analysis. An ORTEP drawing of the pentafluorobenzene derivative **3f** unambiguously shows the *anti* configuration of the imine and *Z*-geometry of the alkenyl moiety (See Figure 2 in Experimental section).

N-Furylimines were produced by reactions with various carbonyl-ene-nitrile compounds **2** (Table 3). The reaction of **2b** with propargyl acetate **1a** gave the corresponding α-alkylidene-*N*-furylimine **3j** in 48% yield. Interestingly, a cyano group and an ester group as an R^1 in **2c** and **2d** can be tolerated under these reaction conditions, the corresponding α-alkylidene-*N*-furylimines **3k** and **3l** being obtained in good yields. Moreover, cyclohexene-fused carbonyl-ene-nitrile compounds **2e** and **2f** reacted with **1a** to give **3m** and **3n** in 66% and 72% yields, respectively.

Table 3. Pt-catalyzed reactions of carbonyl-ene-nitrile compounds **2** with 1-phenyl-2-propynyl acetate **1a**[a]

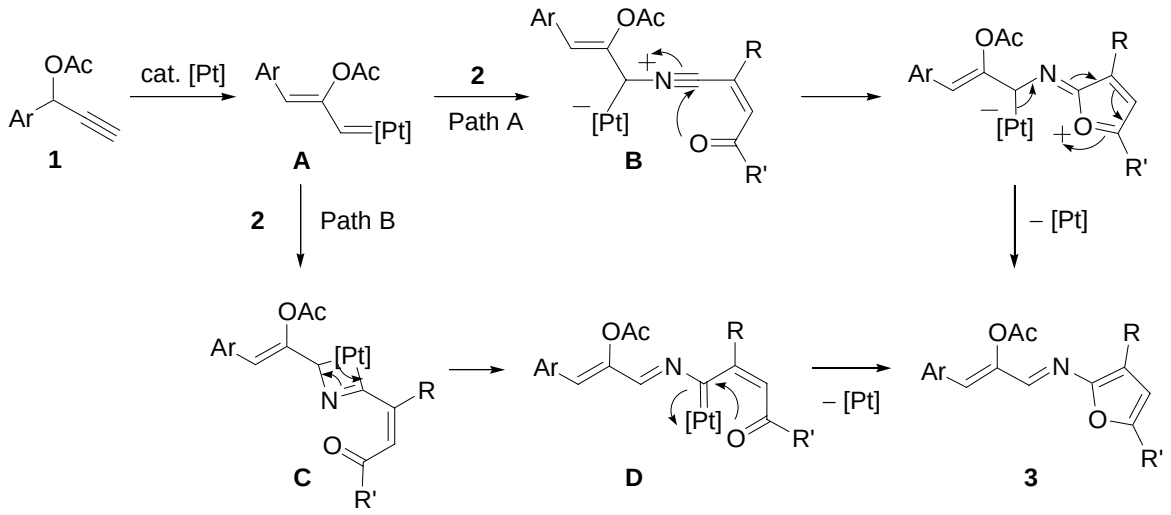


entry	R^1	R^2	R^3	**2**	product	yield (%)[b]
1	4-MeC_6H_4	H	Ph	**2b**	**3j**	48
2	CN	H	Ph	**2c**	**3k**	68
3	CO_2Et	H	Ph	**2d**	**3l**	58
4	$-(CH_2)_4-$		Ph	**2e**	**3m**	66
5	$-(CH_2)_4-$		4-$CF_3C_6H_4$	**2f**	**3n**	72

[a]Reaction conditions: **1a** (0.90 mmol), **2** (0.30 mmol), [M] (0.030 mmol) in toluene (1.2 mL). [b]Isolated yields.

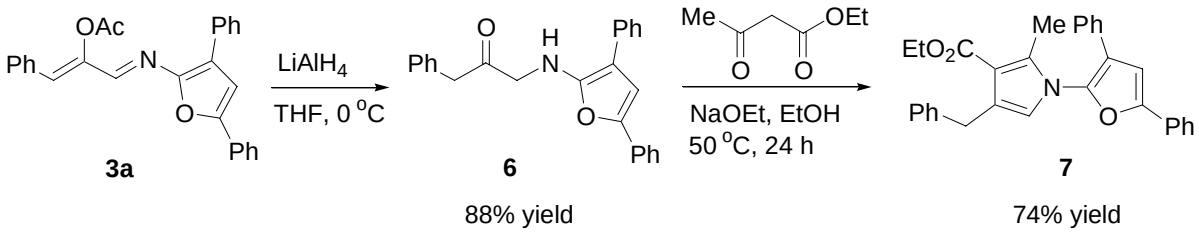
The most plausible mechanism for the present reaction is illustrated in Scheme 5. First, platinum-vinylcarbene complex **A** is formed via the 1,2-migration of the acetate to an internal carbon atom of the alkyne.[2] Platinum-vinylcarbene complex **A** then reacts with **2** through two possible pathways (path A or B). In path A, nucleophilic attack of a cyano moiety of **2** on the carbenoid carbon would afford metal-containing nitrile ylide intermediate **B**, which then converts to α-alkylidene-*N*-furylimine via intramolecular cyclization followed by regeneration of the catalyst. In path B, [2+2] cycloaddition between **A** and **2** followed by ring cleavage generates iminocarbene complex **D**,[9] which undergoes insertion of a carbonyl group to give the α-alkylidene-*N*-furylimine **3** along with regeneration of the catalyst.[10]

Scheme 5



Since the α-alkylidene-*N*-furylimines was obtained from the one-pot reaction, the author next demonstrated the synthetic application of them to *N*-furyl substituted nitrogen-containing heterocycles. When the reduction of **3a** with $LiAlH_4$ was carried out, *N*-(2-furyl)-α-amino ketone **6** was obtained in 88% yield.[11] The subsequent condensation and annulation with ethyl acetoacetate afforded *N*-(2-furyl)pyrrole **7** in 74% yield (Scheme 4). *N*-(2-Furyl)pyrroles are of biological interest as inhibitor of xanthine oxidase, antagonist on thromboxane A_2, and prostaglandin D_2 receptors.[12]

Scheme 4



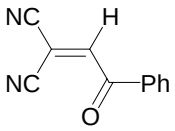
In conclusion, the author has demonstrated catalytic carbene transfer reactions to carbonyl-ene-nitrile compounds on the basis of the in situ generation of vinylcarbene complexes from propargyl carboxylates leading to α-alkylidene-*N*-furylimines. α-Alkylidene-*N*-furylimines can be considered as coupling products of vinylcarbenes, which were generated from propargyl carboxylates, with carbonyl-ene-nitrile compounds as 2-furylnitrene equivalents.[8,13] The reaction proceeds in a complete atom-economical fashion and provides straightforward access to α-alkylidene-*N*-furylimines, which can be employed as building blocks for the synthesis of nitrogen-containing heterocycles.

Experimental

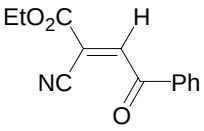
General Method. Unless otherwise noted, chemicals obtained from commercial suppliers were used without further purification. Solvents were dried by the usual methods and distilled before use. Propargyl carboxylates **1** and carbonyl-ene-nitrile compounds **2a** and **2b** were prepared according to the reported procedure.[14,15] All reactions were carried out under nitrogen atmosphere. NMR spectra were measured for solutions in $CDCl_3$ with tetramethylsilane as an internal standard (^1H and ^{13}C): the following abbreviations are used; s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet. IR spectra were recorded with an FT-IR spectrometer. Melting points (mp) are uncorrected. Element analyses were performed at

Microanalytical Center of Kyoto University. High-resolution mass spectra (HRMS) was measured with JEOL JMX-SX 102A spectrometer.

Preparation of Carbonyl-ene-nitrile Compounds 2c and 2d. To a solution of phenylglyoxal monohydrate[16] (1.38 g, 10 mmol) and MS4A (2.0 g) in MeCN (20 mL) was added malononitrile (for **2c**) or ethyl cyanoacetate (for **2d**) (10 mmol), and the mixture was stirred overnight at 80 ^{o}C. The resulting mixture was filtered through short silica gel pad, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel with hexane/AcOEt (v/v = 7/1-4/1) as eluents to afford corresponding carbonyl-ene-nitrile compounds **2c** or **2d** as yellow solids, respectively. **2d** was obtained as a single stereoisomer.



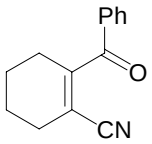
3,3-Dicyano-1-phenyl-2-propen-1-one (2c): A pale yellow solid; mp 115.1-115.6 ^{o}C. IR (KBr): 687, 778, 896, 1011, 1182, 1254, 1364, 1446, 1598, 1662 (C=O), 2211, 3428 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (t, J = 7.7 Hz, 2H), 7.74 (t, J = 7.7 Hz, 1H), 7.98 (d, J = 7.7 Hz, 2H), 8.20 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 96.7, 110.3, 111.9, 129.1, 129.5, 134.3, 135.7, 151.2, 184.0. HRMS (FAB) calcd for M+H^{+} of $C_{11}H_6N_2O$ 183.0558, found 183.0555.



Ethyl (*Z*)-1-benzoyl-2-cyanoacrylate (2d): A yellow solid; mp 63.6-64.2 ^{o}C. IR (KBr): 693, 756, 1002, 1094, 1265, 1448, 1595, 1671 (C=O), 1740 (C=O), 2214, 3460 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.42 (t, J = 7.3 Hz, 3H), 4.44 (q, J = 6.8 Hz, 2H), 7.56 (t, J = 7.3 Hz, 2H), 7.69 (tt, J = 1.5, 7.3 Hz, 1H), 8.00 (dd, J = 1.5, 7.3 Hz, 2H), 8.44 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9, 63.7, 112.8, 115.5, 129.0, 129.2, 135.0, 135.1, 147.5, 160.4, 186.9. HRMS (FAB) calcd for M+H^{+} of $C_{13}H_{11}NO_3$ 230.0817,

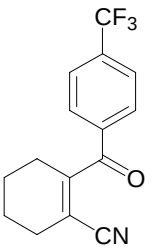
found 230.0822.

Preparation of Carbonyl-ene-nitrile Compounds 2e and 2f.



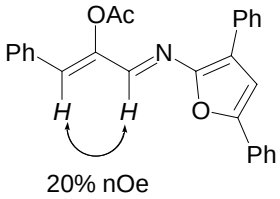
1-Benzoyl-2-cyanocyclohexene (2e): To a solution of 2-bromo-1-cyclohexene-carbaldehyde (1.69 g, 9.0 mmol) in THF (10 mL) was added a solution of phenylmagnesium bromide (10 mmol) in THF (10 mL) at -78 ^{o}C under N_2. The mixture was stirred at -78 ^{o}C for 1 h, and then poured into saturated aqueous NH_4Cl solution (20 mL). The resulting mixture was extracted with AcOEt (20 mL×3), and the organic layer was dried over $MgSO_4$. The organic solvent was removed under reduced pressure to afford α-(2-bromocyclohexen-1-yl)benzyl alcohol (2.29 g, 9.0 mmol, quant.) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.55-1.76 (m, 4H), 2.07-2.09 (m, 1H), 2.23-2.32 (m, 1H), 2.55-2.60 (m, 2H), 6.04 (d, J = 3.4 Hz, 1H), 7.26 (t, J = 7.4 Hz, 1H), 7.34 (t, J = 7.4 Hz, 2H), 7.43 (d, J = 7.4 Hz, 2H). To a solution of α-(2-bromocyclohexen-1-yl)benzyl alcohol (2.29 g, 9.0 mmol) in CH_2Cl_2 (20 mL) was added Dess-Martin periodinane (3.82 g, 9.0 mmol) at 0 ^{o}C, and the resulting mixture was stirred at room temperature for 10 min. The organic solvent was removed under reduced pressure and the resulting white solid was filtered through short silica gel pad with Et_2O as an eluent. The residue was subjected to flash column chromatography on silica gel with hexane/AcOEt (v/v = 20/1) as eluents to afford 1-benzoyl-2-bromocyclohexene (2.30 g, 8.7 mmol, 97%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.77-1.89 (m, 4H), 2.34-2.36 (m, 2H), 2.61-2.64 (m, 2H), 7.49 (t, J = 7.3 Hz, 2H), 7.60 (t, J = 7.3 Hz, 1H), 7.95 (d, J = 7.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.4, 24.2, 29.6, 35.6, 120.2, 128.8, 129.6, 133.6, 134.5, 137.8, 197.6. To a solution of 1-benzoyl-2-bromocyclohexene (2.30 g, 8.7 mmol) in DMF (20 mL) was added CuCN (860 mg, 9.6 mmol), and the resulting mixture was stirred at 110 ^{o}C for 3 h. The reaction mixture was poured into water, and then the aqueous layer was extracted with AcOEt

(50 mL×3). The combined organic layer was washed with brine and dried over $MgSO_4$. The organic solvent was removed under reduced pressure and the residue was subjected to flash column chromatography on silica gel with hexane/AcOEt (v/v = 4/1) as eluents to afford 1-benzoyl-2-cyanocyclohexene **2e** (1.66 g, 7.8 mmol, 90% yield) as a colorless solid. mp 41.0-42.0 °C. IR (KBr): 690, 758, 1205, 1446, 1499, 1740 (C=O), 2912, 3420 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.75-1.79 (m, 4H), 2.39-2.42 (m, 2H), 2.42-2.47 (m, 2H), 7.49 (t, J = 7.8 Hz, 2H), 7.62 (t, J = 7.8 Hz, 1H), 7.87 (d, J = 7.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.5, 20.8, 27.2, 27.6, 111.2, 117.0, 128.8, 129.4, 134.1, 134.5, 154.4, 196.0. HRMS (FAB) calcd for $M+H^+$ of $C_{14}H_{13}NO$ 212.1075, found 212.1088.

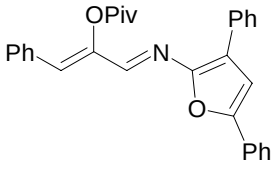


2-Cyano-1-cyclohexenyl (4-trifluoromethyl)phenyl ketone (2f): A pale yellow solid; mp 63.2-64.1 °C. IR (KBr): 687, 752, 1203, 1364, 1612, 1728 (C=O), 2910, 3428 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.80-1.82 (m, 4H), 2.45-2.48 (m, 4H), 7.77 (d, J = 7.8 Hz, 2H), 7.98 (d, J = 7.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.6, 20.9, 27.5, 27.6, 112.7, 116.8, 123.3 (q, J = 273 Hz), 126.0 (q, J = 3.3 Hz), 129.8, 135.3 (q, J = 32.2 Hz), 137.5, 153.5, 195.0. HRMS (FAB) calcd for $M+H^+$ of $C_{15}H_{12}F_3NO$ 280.0949, found 280.0947.

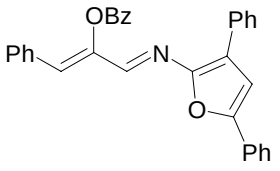
General Procedure for Platinum-catalyzed Reactions of Propargyl Carboxylates with Carbonyl-ene-nitrile Compounds. A solution of propargyl carboxylate **1** (1.2 mmol) and $PtCl_2$ (8.0 mg, 0.030 mmol) in toluene (1.2 mL) was added to carbonyl-ene-nitrile compound **2** (0.30 mmol), and the resulting mixture was stirred at 70 °C for 17 h. The resulting mixture was directly subjected to flash column chromatography on silica gel with hexane/AcOEt/ CH_2Cl_2 (v/v = 15/1/1) as eluents to afford the corresponding *N*-furylimine. The structures of products were determined by nOe experiments.



***N*-(2-Acetoxy-3-phenyl-2-propen-1-ylidene)-3,5-diphenyl-2-furanamine (3a)**: A yellow solid; mp 168.1-169.3 ^{o}C. IR (KBr): 689, 756, 929, 1129, 1206, 1449, 1493, 1753 (C=O), 3422 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.42 (s, 3H), 6.72 (s, 1H), 6.99 (s, 1H), 7.27-7.43 (m, 9H), 7.61 (d, J = 7.2 Hz, 2H), 7.72 (d, J = 7.2 Hz, 2H), 7.83 (d, J = 7.2 Hz, 2H), 8.32 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.0, 107.4, 122.9, 123.9, 126.7, 127.2, 127.9, 128.0, 128.2, 128.7, 128.9, 129.1, 129.5, 129.9, 132.3, 133.4, 146.1, 146.4, 149.0, 150.3, 168.1. Anal. calcd for $C_{27}H_{21}NO_3$: C, 79.59; H, 5.19. Found: C, 79.41; H, 5.21.

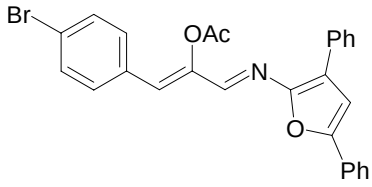


***N*-(2-Pivaloyloxy-3-phenyl-2-propen-1-ylidene)-3,5-diphenyl-2-furanamine (3b)**: A yellow solid; mp 175.2-176.0 ^{o}C. IR (KBr): 694, 761, 1114, 1270, 1480, 1744 (C=O), 3460 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.30 (s, 9H), 6.69 (s, 1H), 6.90 (s, 1H), 7.21-7.33 (m, 9H), 7.52 (d, J = 6.8 Hz, 2H), 7.64 (d, J = 7.3 Hz, 2H), 7.72 (d, J = 7.3 Hz, 2H), 8.31 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.4, 39.0, 107.7, 122.6, 124.0, 127.1, 128.0, 128.2, 128.2, 128.5, 128.7, 129.0, 129.5, 129.8, 130.0, 132.4, 133.5, 146.7, 148.2, 149.6, 150.1, 175.4. HRMS (FAB) calcd for M^+ of $C_{30}H_{27}NO_3$ 449.1991, found 449.1991.

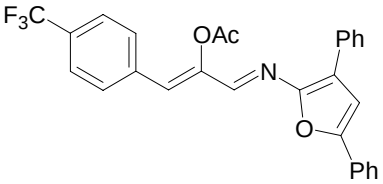


***N*-(2-Benzoyloxy-3-phenyl-2-propen-1-ylidene)-3,5-diphenyl-2-furanamine (3c)**: A yellow solid; mp 224.2-225.0 ^{o}C. IR (KBr): 690, 759, 1061, 1244, 1450, 1492, 1733 (C=O), 3426 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.78 (t, J = 7.6 Hz, 2H), 6.87 (s, 1H), 7.00 (t, J = 7.3 Hz, 2H), 7.30-7.36 (m, 4H), 7.41 (t, J = 7.6 Hz, 2H), 7.58-7.68 (m, 6H), 7.73-7.75 (m, 3H), 8.34 (d, J = 7.3 Hz, 2H), 8.45 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 107.1, 122.6, 124.1, 126.9, 127.6, 127.9, 128.1, 128.7, 128.8, 129.1, 129.2, 129.5, 129.7, 130.0, 130.6, 130.6, 131.8, 133.6, 133.7,

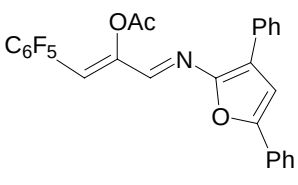
145.8, 146.8, 149.1, 150.4, 164.0. Anal. calcd for $C_{32}H_{23}NO_3$: C, 81.86; H, 4.94. Found: C, 81.89; H, 4.82.



***N*-[2-Acetoxy-3-(4-bromophenyl)-2-propen-1-ylidene]-3,5-diphenyl-2-furanamine (3d)**: A yellow solid; mp 222.0-223.4 °C. IR (KBr): 686, 755, 1215, 1488, 1636, 1750 (C=O), 3421 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.41 (s, 3H), 6.66 (s, 1H), 7.01 (s, 1H), 7.30-7.50 (m, 10H), 7.73 (d, J = 7.2 Hz, 2H), 7.82 (d, J = 7.2 Hz, 2H), 8.31 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.0, 107.5, 123.2, 123.4, 124.0, 127.3, 127.4, 128.0, 128.1, 128.2, 128.7, 128.8, 130.8, 131.9, 132.3, 132.4, 145.7, 147.0, 148.9, 150.5, 167.9. HRMS (FAB) calcd for M^+ of $C_{27}H_{20}BrNO_3$ 487.0610, found 487.0629.

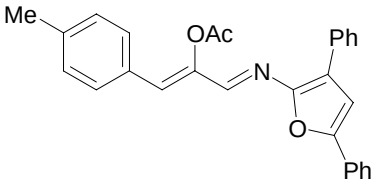


***N*-[2-Acetoxy-3-(4-trifluoromethylphenyl)-2-propen-1-ylidene]-3,5-diphenyl-2-furanamine (3e)**: A yellow solid; mp 174.5-175.5 °C. IR (KBr): 686, 755, 1069, 1113, 1165, 1328, 1612, 1751 (C=O), 3448 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.41 (s, 3H), 6.71 (s, 1H), 6.99 (s, 1H), 7.30-7.31 (m, 2H), 7.37-7.43 (m, 4H), 7.60 (d, J = 8.4 Hz, 2H), 7.64-7.71 (m, 4H), 7.82 (d, J = 7.2 Hz, 2H), 8.29 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.0, 107.5, 123.9, 125.6 (q, J = 3.7 Hz), 125.8 (q, J = 272.5 Hz), 126.7, 127.9, 128.2, 128.4, 128.7, 128.9, 129.5, 129.8, 130.1, 130.4 (q, J = 32.9 Hz), 132.2, 136.8, 145.4, 148.2, 148.8, 150.8, 168.0. HRMS (FAB) calcd for M^+ of $C_{28}H_{20}F_3NO_3$ 475.1395, found 475.1389.

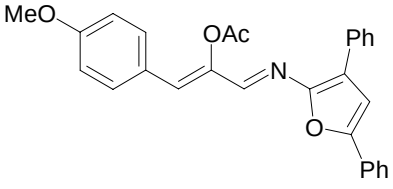


***N*-[2-Acetoxy-3-(1,2,3,4,5-pentafluorophenyl)-2-propen-1-ylidene]3,5-diphenyl-2-furanamine (3f)**: A yellow solid; mp 222.8-223.9 °C. IR (KBr): 690, 758, 998, 1180, 1496, 1517, 1778

(C=O), 3448 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.31 (s, 3H), 6.61 (s, 1H), 7.04 (s, 1H), 7.30-7.46 (m, 6H), 7.75 (d, J = 7.2 Hz, 2H), 7.82 (d, J = 7.2 Hz, 2H), 8.37 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.7, 107.7, 108.4-108.9 (m), 111.4, 124.2, 125.2, 127.7, 128.2, 128.5, 128.7, 128.9, 129.7, 132.1, 137.8 (dm, J = 251.8 Hz), 141.1 (dm, J = 250.0 Hz), 144.0, 144.4 (dm, J = 246.2 Hz), 148.3, 150.9, 151.4, 167.9. HRMS (FAB) calcd for M^+ of $C_{27}H_{16}F_5NO_3$ 497.1050, found 497.1043.

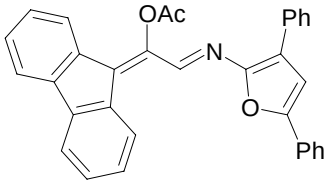


***N*-[2-Acetoxy-3-(4-methylphenyl)-2-propen-1-ylidene]-3,5-diphenyl-2-furanamine (3g)**: A yellow solid; mp 186.0-186.8 ^oC. IR (KBr): 692, 756, 861, 925, 1211, 1493, 1756 (C=O), 3448 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.38 (s, 3H), 2.42 (s, 3H), 6.73 (s, 1H), 7.02 (s, 1H), 7.19-7.32 (m, 4H), 7.39 (d, J = 8.1 Hz, 2H), 753 (d, J = 8.1 Hz, 2H), 7.52 (d, J = 8.0 Hz, 2H), 7.73 (d, J = 7.3 Hz, 2H), 7.85 (d, J = 7.3 Hz, 2H), 8.36 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.0, 21.5, 107.4, 122.6, 124.0, 127.2, 128.0, 128.2, 128.7, 128.9, 129.1, 129.5, 129.6, 130.0, 130.8, 132.5, 139.5, 146.0, 146.4, 149.2, 150.3, 168.2. HRMS (FAB) calcd for M^+ of $C_{28}H_{23}NO_3$ 421.1678, found 421.1674.

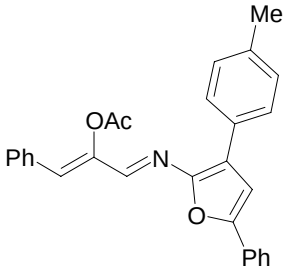


***N*-[2-Acetoxy-3-(4-methoxyphenyl)-2-propen-1-ylidene]-3,5-diphenyl-2-furanamine (3h)**: A yellow solid; mp 144.2-145.0 ^oC. IR (KBr): 692, 757, 1028, 1208, 1256, 1508, 1601, 1752 (C=O), 3422 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.43 (s, 3H), 3.85 (s, 3H), 6.70 (s, 1H), 6.92 (d, J = 8.7 Hz, 2H), 7.01 (s, 1H), 7.28-7.45 (m, 6H), 7.59 (d, J = 8.7 Hz, 2H), 7.73 (d, J = 7.8 Hz, 2H), 7.85 (d, J = 7.8 Hz, 2H), 8.34 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.1, 55.4, 107.4, 114.3, 122.3, 123.9, 126.3, 127.1, 127.9, 127.9, 128.2, 128.7, 128.8, 130.0, 131.2, 132.5, 145.0, 146.4, 149.2, 150.1, 160.3, 168.2. HRMS (FAB)

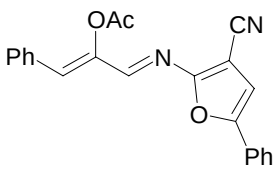
calcd for M^+ of $C_{28}H_{23}NO_4$ 437.1627, found 437.1625.



***N*-[2-Acetoxy-2-(9H-fluoren-9-ylidene)ethylidene]-3,5-di-phenyl-2-furanamine (3i):** A red solid; 266.7-267.2 °C. λ_{abs} = 476 nm ($\varepsilon = 2.6\times10^{-6}$ L mol^{-1} cm^{-1}, 5.0×10^{-6} M in CH_2Cl_2), λ_{em} = 557 nm (λ_{ex} = 476 nm, 5.0×10^{-7} M in CH_2Cl_2). IR: (KBr) 688, 727, 758, 1017, 1200, 1369, 1444, 1474, 1490, 1759 (C=O), 3448 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.53 (s, 3H), 7.10 (s, 1H), 7.26-7.50 (m, 10H), 7.70-7.75 (m, 2H), 7.79 (d, J = 7.6 Hz, 2H), 7.89-7.97 (m, 4H), 9.33 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0, 108.2, 119.8, 120.3, 124.3, 125.5, 125.8, 126.2, 127.4, 127.7, 127.8, 128.2, 128.3, 128.5, 128.9, 129.0, 129.5, 129.7, 132.2, 134.1, 135.4, 137.0, 140.3, 141.2, 142.1, 146.0, 149.7, 151.6, 168.4. HRMS (FAB) calcd for M^+ of $C_{33}H_{23}NO_3$, 481.1678, found 487.1673.

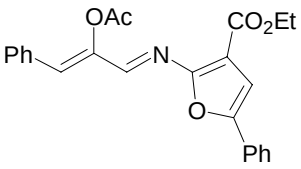


***N*-(2-Acetoxy-3-phenyl-2-propen-1-ylidene)-3-(4-methylphenyl)-5-phenyl-2-furanamine (3j)**: A yellow solid; mp 202.0-203.5 °C. IR (KBr): 689, 760, 809, 928, 1197, 1447, 1758 (C=O), 3448 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.39 (s, 3H), 2.44 (s, 3H), 6.74 (s, 1H), 7.00 (s, 1H), 7.20-7.43 (m, 8H), 7.63 (d, J = 6.6 Hz, 2H), 7.73-7.76 (m, 4H), 8.34 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1, 21.4, 107.4, 123.0, 124.0, 127.8, 128.0, 128.6, 128.6, 128.7, 128.8, 128.9, 129.0, 129.4, 130.0, 133.5, 137.1, 145.7, 146.6, 148.8, 150.3, 168.1. HRMS (FAB) calcd for M^+ of $C_{28}H_{23}NO_3$, 421.1678, found 421.1683.

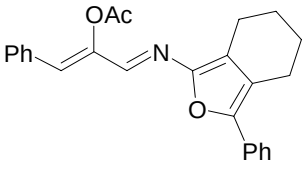


2-(2-Acetoxy-3-phenyl-2-propen-1-ylidene)amino-5-phenyl-3-furancarbonitrile (3k): A yellow solid; mp 156.2-157.1 °C. IR (KBr): 688, 755, 1205, 1449, 1599, 1752 (C=O), 3422 cm^{-1}. ^{1}H

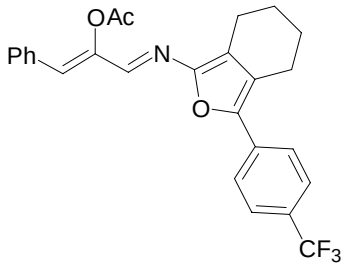
NMR (400 MHz, $CDCl_3$): δ 2.47 (s, 3H), 6.82 (s, 1H), 6.89 (s, 1H), 7.35-7.46 (m, 6H), 7.64-7.68 (m, 4H), 8.39 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.9, 94.1, 107.8, 113.2, 118.2, 124.3, 128.9, 129.0, 129.2, 130.1, 130.2, 132.9, 133.3, 145.7, 151.5, 152.7, 158.5, 168.4. HRMS (FAB) calcd for M^+ of $C_{22}H_{16}N_2O_3$ 357.1161, found 357.1169.



Ethyl 2-(2-acetoxy-3-phenyl-2-propen-1-ylidene)amino-5-phenyl-3-furancarboxylate (3l): A yellow solid; mp 122.1-123.1 ^oC. IR (KBr): 689, 758, 1200, 1484, 1589, 1692, 1758 (C=O), 3430 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.39 (t, J = 6.8 Hz, 3H), 2.50 (s, 3H), 4.35 (q, J = 6.8 Hz, 2H), 6.86 (s, 1H), 7.05 (s, 1H), 7.30-7.44 (m, 6H), 7.64-7.70 (m, 4H), 8.53 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.4, 21.0, 60.6, 108.5, 112.9, 124.0, 128.4, 128.8, 128.9, 129.4, 129.8, 129.9, 132.0, 133.1, 146.2, 149.8, 152.9, 154.7, 162.5, 168.5. HRMS (FAB) calcd for M^+ of $C_{24}H_{21}NO_5$ 403.1420, found 403.1428.

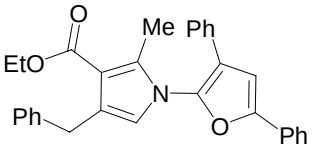


***N*-(2-Acetoxy-3-phenyl-2-propen-1-ylidene)-3-phenyl-4,5,6,7-tetrahydroisobenzofuran-1-amine (3m)**: A yellow solid; mp 84.2-85.1 ^oC. IR (KBr): 697, 758, 1202, 1449, 1493, 1691, 1754 (C=O), 2859, 2936, 3382 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.71-1.79 (m, 4H), 2.41 (s, 3H), 2.64 (t, J = 6.3 Hz, 2H), 2.76 (t, J = 6.3 Hz, 2H), 6.65 (s, 1H), 7.21-7.41 (m, 6H), 7.59 (d, J = 7.3 Hz, 2H), 7.64 (d, J = 7.3 Hz, 2H), 8.15 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.8, 20.9, 22.3, 22.9, 23.3, 122.0, 122.4, 124.7, 126.7, 127.2, 128.6, 128.7, 128.8, 129.4, 131.4, 133.7, 143.6, 144.1, 146.8, 148.0, 168.4. HRMS (FAB) calcd for M^+ of $C_{25}H_{23}NO_3$ 385.1678, found 385.1678.



***N*-(2-Acetoxy-3-phenyl-2-propen-1-ylidene)-3-(4-trifluoro-methylphenyl)-4,5,6,7-tetrahydroisobenzofuran-1-amine (3n)**: A yellow solid; mp 150.2-150.9 °C. IR (KBr): 688, 754, 1205, 1325, 1609, 1760 (C=O), 2862, 2935, 3404 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.73-1.81 (m, 4H), 2.41 (s, 3H), 2.64 (t, J = 5.9 Hz, 2H), 2.76 (t, J = 5.9 Hz, 2H), 6.69 (s, 1H), 7.27-7.43 (m, 3H), 7.59-7.64 (m, 4H), 7.71 (d, J = 8.3 Hz, 2H), 8.18 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.7, 20.9, 22.2, 23.0, 23.1, 122.3, 124.1, 124.2 (q, J = 271 Hz), 124.4, 125.5 (q, J = 4.1 Hz), 128.1, 128.7, 128.8 (q, J = 67.0 Hz), 129.0, 129.5, 133.5, 134.6, 142.6, 145.0, 146.6, 148.8, 168.4. HRMS (FAB) calcd for M^+ of $C_{26}H_{22}F_3NO_3$ 453.1552, found 453.1560.

Synthetic of Ethyl *N*-[2-(3,5-Diphenylfuryl)]-2-methyl-4-benzylpyrrole-3-carboxylate (7).



A solution of *N*-(2-acetoxy-3-phenyl-2-propen-1-ylidene)-3,5-diphenyl-2-furan- amine **3a** (40.7 mg, 0.10 mmol) in THF (2 mL) was added to $LiAlH_4$ (11.4 mg, 0.30 mmol) at 0 °C, and the resulting mixture was stirred for 2 h at rt. The obtained dark green solution was carefully poured into water (10 mL), and extracted with Et_2O (10 mL × 3). The combined organic layer was dried over Na_2SO_4, then the organic solvent was removed under reduced pressure. The residue was passed through short silica gel pad, and concentrated in vacuo to give *N*-(3-phenyl-2-oxopropyl)-3,5-diphenyl-2-furanamine **6** (32.2 mg, 0.088 mmol, 88% yield) as a yellow viscous oil. IR (neat): 698, 765, 947, 1177, 1212, 1449, 1495, 1700, 1732 (C=O), 2851, 2923, 3025, 3062 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.78 (s, 2H), 4.28 (d, J = 5.2 Hz, 2H), 5.02 (t, J = 5.2 Hz, 1H), 6.78 (s, 1H), 7.13-7.50 (m, 15H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 47.4, 53.1, 102.3, 107.1, 122.2, 125.4, 125.9, 127.4, 128.6, 128.9, 129.0, 129.3, 129.4, 130.8, 133.1, 133.7, 144.9, 150.8, 204.0. HRMS (FAB) calcd for $M+H^+$ of

$C_{25}H_{20}NO_2$ 368.1651, found 368.1659. To a solution of **6** (29.3 mg, 0.080 mmol), ethyl acetoacetate (21.0 mg, 0.16 mmol) in EtOH (2 mL) was added to sodium ethoxide (10.9 mg, 0.16 mmol), and the resulting mixture was stirred at 50 ^{o}C for 24 h. The reaction mixture was quenched by adding excess of 10% NH_4Cl aqueous solution, and the aqueous layer was extracted with Et_2O (10 mL × 3). The combined organic layer was washed with brine and dried over $MgSO_4$. The organic solvent was removed under reduced pressure and the residue was subjected to flash column chromatography on silica gel with hexane/AcOEt (v/v = 20/1) as eluents to afford *N*-[2-(3,5-diphenylfuryl)]-2-methyl-4-benzylpyrrole-3-carboxylate **7** (27.0 mg, 0.060 mmol, 74% yield) as a yellow viscous oil. IR (neat): 694, 760, 801, 1027, 1095, 1261, 1420, 1637, 1700, 2925, 2963, 3027, 3060, 3384 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.27 (t, J = 7.3 H z, 3H), 2.34 (s, 3H), 4.10 (s, 2H), 4.25 (q, J = 7.3 Hz, 2H), 6.33 (s, 1H), 7.01 (s, 1H), 7.11-7.14 (m, 2H), 7.24-7.30 (m, 5H), 7.39-7.34 (m, 4H), 7.41 (t, J = 7.3 Hz, 2H), 7.69 (d, J = 7.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.1, 14.3, 33.1, 59.5, 105.3, 112.8, 120.7, 120.8, 123.9, 125.7, 126.1, 126.2, 127.6, 128.1, 128.2, 128.7, 128.8, 128.9, 129.7, 130.5, 139.0, 139.1, 141.2, 151.3, 165.6. HRMS (FAB) calcd for $M+H^+$ of $C_{31}H_{27}NO_3$ 462.2069, found 462.2067.

X-ray Crystallographic Studies of 3f. Orange crystals of **3f** suitable for X-ray analysis were obtained by recrystallization from $CHCl_3$/hexane. The single crystal was sealed in a Pyrex glass capillary under N_2 atmosphere and used for data collection. All measurements were made on a Rigaku RAXIS imaging plate area detector with graphite monochromated Mo-Kα radiation. Details of crystal and data collection parameters are summarized in Table 4. The positions of non-hydrogen atoms were determined by direct methods (SIR92) and subsequent Fourier syntheses (DIRDIF PATTY). An ORTEP drawing of **3f** is shown in Figure 2.

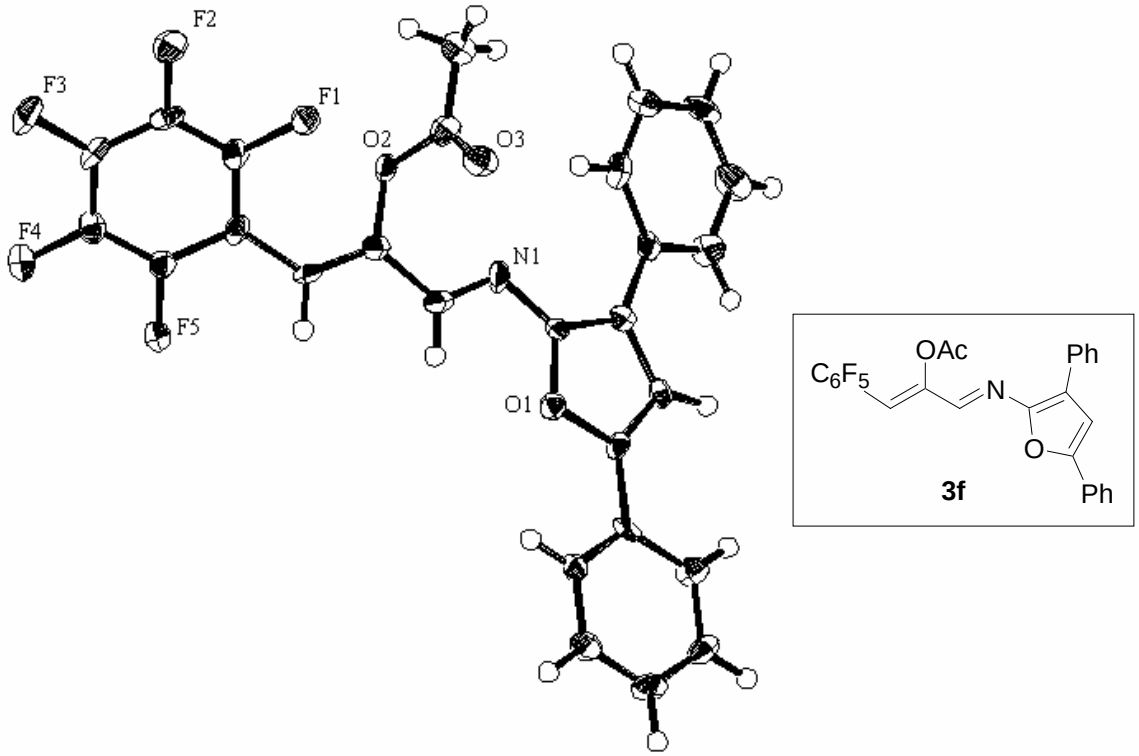


Figure 2. ORTEP drawing of **3f**.

Table 4. Summary of crystallographic data of **3f**

Empirical formula: $C_{27}H_{16}F_5NO_3$
Formula weight: 497.42
Crystal system: monoclinic
Space group: P21/c (#14)
Crystal color: orange
Lattice parameters:
a (Å) = 14.794(6), *b* (Å) = 7.433(3), *c* (Å) = 20.806(8),
V (Å^3) = 2189.0(15), β = 106.905(2)^o,
Z = 4
D_{calc} (g cm^{-3}): 1.509
μ (Mo K α) (cm^{-1}): 1.268
Goodness of fit (GOF) = 1.000
F(000): 1016
Diffractometer: Rigaku RAXIS-RAPID
Radiation: MoK α (λ = 0.71070 Å), Graphite Monochromated
Temp (^{o}C): -150
Scan type: ω–2 θ
Max. 2 θ (^{o}): 55.0
No. of reflections measured total: 4910
No. of observations (*I* > 3.00 σ (*I*)): 14606
Structure solution: Direct Methods (SIR92)
Refinement: Full-Matrix Least-Squares on F
No. of variables: 341
Reflection/parameter ratio: 14.4
Residuals: R = 0.0534, R_{int} = 0.067, R_w = 0.1412
Max Shift/Error in Final Cycle: 0.00
Maximum peak in Final Diff Map (e (Å^{-3}): 0.92
Maximum peak in Final Diff Map (e (Å^{-3}): -0.84

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(2) For recent reviews, see: (a) Miki, K.; Uemura, S.; Ohe, K. *Chem. Lett.* **2005**, *34*, 1068. (b) Crone B.; Kirsch, S. F. *Angew. Chem. Int. Ed.* **2008**, *14,* 3514. (c) Li, Z.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239. (d) Ohe K.; Miki, K. *J. Synth. Org. Chem., Jpn.* **2009**, *67*, 1161.

(3) (a) Miki, K.; Ohe, K.; Uemura, S. *Tetrahedron Lett.* **2003**, *44*, 2019. (b) Miki, K.; Ohe, K.; Uemura, S. *J. Org. Chem.* **2003**, *68,* 8505. (c) Miki, K.; Fujita, M.; Uemura, S.; Ohe, K. *Org. Lett.* **2006**, *8*, 1741. (d) Ohe, K.; Fujita, M.; Matsumoto, H.; Tai, Y.; Miki, K. *J. Am. Chem. Soc.* **2006**, *128*, 9270. (e) Ikeda, Y.; Murai, M.; Abo, T.; Miki, K.; Ohe, K. *Tetrahedron Lett*. **2007**, *48,* 6651. (f) Miki, K.; Senda, Y.; Kowada, T.; Ohe, K. *Synlett* **2009**, 1937.

(4) For recent reviews on the synthesis of 1,3-oxazoles from addition reactions of rhodium-carbene complexes generated from α-diazocarbonyl compounds to nitriles, see: (a) Padwa, A.; Hornbuckle, S. F. *Chem. Rev.* **1991**, *91*, 263. (b) Escolano, C.; Duque, M. D.; Vázquez, A. *Curr. Org. Chem.* **2007**, *11*, 741.

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(6) Non-catalytic 1,3-dipolar cycloadditions of nitrile ylides, which are formed by reactions of nitriles with carbenes generated from thermal or photochemical decomposition of diazoalkanes, are of special interest. See: (a) Sheppard, W. A.; Gokel, G. W.; Webster, W.; Betterton, K.; Timberlake, J. W. *J. Org. Chem.* **1979**, *44*, 1717. (b) Kende, A. S.; Hebeisen, P.; Sanfilippo, P. J.; Toder, B. H. *J. Am. Chem. Soc*. **1982**, *104*, 4244. (c) Turro, N. J.; Cha, Y.; Gould, I. R.; Padwa, A.; Gasdaska, J. R.; Tomas, M. *J. Org. Chem.* **1985**, *50*, 4415. (d) Padwa, A.; Gasdaska, J. R.; Tomas, M.; Turro, N. J.; Cha, Y.; Gould, I. R. *J. Am. Chem. Soc*. **1986**, *108*, 6739.

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(8) (*Z*)-Carbonyl-ene-nitrile compounds **2** are ring-opened isomers of (2-furyl)nitrenes. Ring-opening of its analogous, (2-pyrazolyl)nitrenes and (1,2,3-triazolyl)nitrenes to acyclic conjugated nitriles have been investigated. See: (a) Smith, P. A. S.; Resemann, W.; Krbechek, L. O. *J. Am. Chem. Soc.* **1964**, *86*, 2025. (b) Smith, P. A. S.; Breen, G. J. W.; Hajek, M. K.; Awang, D. V. C. *J. Org. Chem.* **1970**, *35*, 2215. (c) Smith, P. A. S.; Founchis, H. *J. Org. Chem.* **1973**, *38,* 2958. (d) Suárez, D.; Sordo, T. L. *J. Am. Chem. Soc.* **1997**, *119,* 10291. (e) Svenstrup, N.; Simonsen, K. B.; Thorup, N.; Brodersen, J.; Dehaen, W.; Becher, J. *J. Org. Chem.* **1999**, *64*, 2814.

(9) For stoichiometric reactions of Fischer carbene complexes of the group 6 metals with nitriles leading to iminocarbene complexes, see: (a) Fischer, H.; Zeuner, S. *J. Organomet. Chem.* **1987**, *327*, 63. (b) Yang, D. C.; Dragisich, V.; Wulff, W. D.; Huffman, J. C. *J. Am. Chem. Soc.* **1988**, *110*, 307.

(10) The azametallacyclobutene intermediates were reported by Gevorgyan *et al.* See ref 5a.

(11) Reduction of vinylcarboxylates into corresponding ketones with $LiAlH_4$ has been reported.

See: (a) Matsumoto, K.; Suzuki, N.; Ohta, H. *Tetrahedron Lett.* **1990**, *31*, 7159. (b) Mauleon, P.; Krinsky, J. L.; Toste, F. D. *J. Am. Chem. Soc.* **2009**, *131*, 4513.

(12) (a) Honma, T.; Hiramatsu, Y.; Arimura, A. *PCT Int. Appl.* WO 2000053573, **2000**. [Chem. Abstr. **2000**, *133*, 222579.] (b) Yagami, T.; Honma, T.; Katsuura, G. *PCT Int. Appl.* WO2000030683, **2000**. [Chem. Abstr. **2000**, *133*, 12765.] (c) Tanimoto, N.; Arimura, A. *PCT Int. Appl.* WO 2001094309, **2001**. [Chem. Abstr. **2001**, *136*, 37614.] (d) Shimizu, K.; Takigawa, Y.; Fujikura, H.; IIzuka, M.; Hiratochi, M.; Kikuchi, N. *PCT Int. Appl.* WO 2008126899, **2008**. [Chem. Abstr. **2008**, *149*, 493522.]

(13) Recently, cross-coupling reaction of vinylcarbenes generated from propargyl carboxylates with diazoalkanes has been reported. See: Vovard-Le Bray, C.; Dérien, S.; Dixneuf, P. H. *Angew. Chem. Int. Ed.* **2009**, *48*, 1439.

(14) Nozaki, K.; Sato, N.; Takaya, H. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 1629.

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Chapter 4

Gallium-catalyzed Bromocyanation of Alkynes with Cyanogen Bromide: Regio- and Stereoselective Synthesis of Functionalized Nitriles

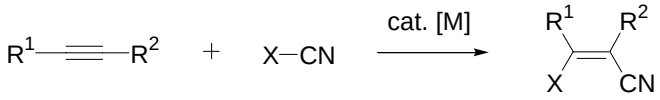
Abstract

Gallium-catalyzed reactions of arylacetylenes with cyanogen bromide gave (*Z*)-*β*-bromoacrylonitriles with high regio- and stereoselectivity. Since the carbon-bromine bonds can be further converted stereospecifically into various carbon-carbon bonds by cross-coupling reactions, two-step conversion of carbon-carbon triple bonds represents the regio-, stereo-, and chemoselective synthesis of a wide range of *α,β*-unsaturated nitriles. (*Z*)-*β*-Bromoacrylonitriles serve as useful precursors for the synthesis of biologically active nitrogen-containing heterocycles.

Introduction

Catalytic addition reactions of X-CN bonds to carbon-carbon unsaturated bonds are currently an active area of research, because such reactions can provide a simultaneous installation of two functional groups from simple starting materials with complete atom-efficiency (Scheme 1). To date, several addition reactions of X-CN bonds including transition metal-catalyzed carbocyanation (C-CN),[1,2] cyanosilylation (Si-CN),[3] germylcyanation (Ge-CN),[4] cyanoboration (B-CN),[5] cyanothiolation (S-CN),[6] and cyanostannylation (Sn-CN)[7] have been reported. On the other hand, much less attention has been paid to halocyanation of alkynes, in which the halogen and cyano functionalities are introduced simultaneously to unsaturated substrates.[8-10]

Scheme 1



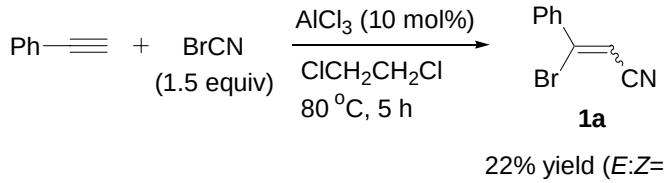
As described in Chapters 1, 2, and 3, properly functionalized nitriles, such as carbonyl-ene-nitrile compounds are highly useful precursors for the synthesis of heterocycles.[11] However, there have been few general methods for stereoselective preparation of carbonyl-ene-nitrile compounds.[12] We envisioned that (*Z*)-*β*-bromo-acrylonitriles obtained from stereoselective addition reactions of cyanogen bromide to alkynes were useful intermediates for the synthesis of carbonyl-ene-nitrile compounds. Although the addition of cyanogen bromide[13] to ynamines to afford *β*-bromo-*α*- cyanoenamines was reported to proceed without catalyst, the substrate scope is limited to only two examples.[8] In this chapter, the author describes the gallium-catalyzed bromocyanation of alkynes with cyanogen bromide, providing an efficient route to (*Z*)-*β*-bromoacrylonitriles with high regio- and stereoselectivity. Taking advantage of (*Z*)-*β*-bromoacrylonitrile as a key intermediate,

the author has established an efficient route to prepare a wide range of α,β-unsaturated nitriles, which are synthetically applicable to heterocycles formation.

Results and Discussion

As the first attempt, the author examined the reaction of phenylacetylene with cyanogen bromide in the presence of a catalytic amount of typical Lewis acids. The addition reaction in the presence of $AlCl_3$ (10 mol%), which have been reported as an effective promoter for the cyanation of aromatics using cyanogen bromide as electrophilic cyanating reagent,[14] proceeded to provide 3-bromo-3-phenylprop-2-enenitrile **1a** in 22% yield as mixtures of two stereoisomers (*E*:*Z* = 10:90) (Scheme 2). The regio- and stereochemistry of the major product was identified on the basis of the spectral data of derivatives reported previously. It should be noted that the cyano group was introduced at the terminal carbon atom with high stereoselectivity, and regioisomers of **1a** were not detected. This is in sharp contrast with observations from the previously reported non-catalyzed bromocyanation of ynamine, in which the cyano group was introduced at the internal carbon atom with low stereoselectiviry (*E*:*Z* = 50:50 ~ 40:60).[8]

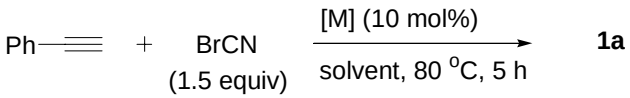
Scheme 2



The results from reactions of phenylacetylene and cyanogen bromide in the presence of several metal catalysts are summarized in Table 1. After intensive screening, he found that **1a** was obtained in 57 % yield (*E*:*Z* = 8:92) by employing 10 mol% of $GaCl_3$ (entry 6).

Although other catalysts, such as $InCl_3$, $InBr_3$, and $GaBr_3$ gave **1a** in low to moderate yields (entries 1, 2, and 7), $FeBr_3$, $CuBr_2$, and $ZnBr_2$ were thoroughly ineffective giving no desired product **1a** (entries 3-5). It is noted that the formation of chlorocyanation product was not observed at all, even when metal chloride complexes were used as catalysts. Oligomers of phenylacetylene were formed, whenever reactions did not afford **1a**. In the absence of catalysts, **1a** was not observed at all. The author next investigated the effect of different reaction parameters, such as temperature and solvents. Reactions were found to proceed more efficiently at high temperature (entries 6 and 8). The reaction also proceeded in non-polar solvents such as toluene and heptane, while in polar solvents such as MeCN, dioxane, THF, and DMF, the reaction resulted in complete recovery of phenylacetylene

Table 1. Lewis acid-catalyzed bromocyanation reaction of phenylacetylene with BrCN[a]



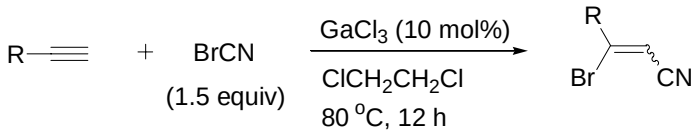
entry	[M]	solvent	yield[b]	*E*:*Z*[c]
1	$InCl_3$	$ClCH_2CH_2Cl$	23%	10:90
2	$InBr_3$	$ClCH_2CH_2Cl$	31%	12:88
3	$FeBr_3$	$ClCH_2CH_2Cl$	0%	——
4	$CuBr_2$	$ClCH_2CH_2Cl$	0%	——
5	$ZnBr_2$	$ClCH_2CH_2Cl$	0%	——
6	$GaCl_3$	$ClCH_2CH_2Cl$	57%	8:92
7	$GaBr_3$	$ClCH_2CH_2Cl$	47%	9:91
8[d]	$GaCl_3$	$ClCH_2CH_2Cl$	42%	8:92
9	$GaCl_3$	toluene	41%	4:96
10	$GaCl_3$	heptane	12%	15:85
11	$GaCl_3$	MeCN	0%	——
12	$GaCl_3$	dioxane	0%	——
13[e]	$GaCl_3$	$ClCH_2CH_2Cl$	68%	8:92

[a]Reaction conditions: phenylacetylene (0.40 mmol), BrCN (0.60 mmol), [M] (0.040 mmol) in solvent (1.6 mL). [b]Isolated yield. [c]Determined by ^{1}H NMR. [d]At 70 °C. [e]For 12 h.

(entries 9-12). Under the optimized reaction conditions (10 mol% of $GaCl_3$ in $ClCH_2CH_2Cl$ at 80 ^oC), **1a** was obtained in 68% yield when the reaction time was prolonged to 12 h (entry 13).

With the optimized reaction conditions in hand, the author next examined substrate scope of terminal alkynes. The results are summarized in Table 2. The reactions of 4-tolylacetylene and 2-ethynylnaphthalene proceeded smoothly to give **1b** and **1c** in 58% and 61% yields with high regio- and stereoselectivity, respectively (entries 1 and 2). Sterically hindered 2-tolylacetylene was also converted into the corresponding (*Z*)-adduct **1d** predominantly with slightly lower yield compared with 4-tolylacetylene (entry 3). The reactions were sensitive to the electronic features of the aryl groups of alkynes. The bromocyanation of arylacetylenes bearing an electron-withdrawing group such as fluoro, chloro, and bromo groups at the *para* position afforded the corresponding *β*-bromo-

Table 2. $GaCl_3$-catalyzed bromocyanation of terminal alkynes[a]



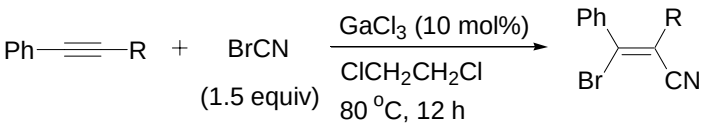
entry	R	product	yield[b]	*E*:*Z* [c]
1	4-MeC_6H_4	**1b**	61%	4:96
2	2-Naph	**1c**	58%	5:95
3	2-MeC_6H_4	**1d**	50%	2:98
4	4-FC_6H_4	**1e**	72%	10:90
5	4-ClC_6H_4	**1f**	64%	10:90
6	4-BrC_6H_4	**1g**	68%	9:91
7	4-$MeOC_6H_4$		0%	——
8	*n*-Hex		0%	——
9	TMS		0%	——

[a]Reaction conditions: Alkyne (0.40 mmol), BrCN (0.60 mmol), $GaCl_3$ (0.040 mmol) in $ClCH_2CH_2Cl$ (1.6 mL). [b]Isolated yield. [c]Determined by ^1H NMR.

acrylonitriles **1e**,[15] **1f**, **1g** in good yields, respectively (entries 4-6). Bromocyanation reaction of electron-donating 4-methoxyphenylacetylene and aliphatic alkynes, such as 1-octyne, trimethylsilylacetylene resulted in failure.

The substrate scope was further expanded to internal alkynes (Table 3). Reaction of unsymmetrical internal acetylenes such as 1-phenyl-1-propyne and 1-phenyl-1-hexyne with cyanogen bromide proceeded smoothly to afford **1h** and **1i** in good yields with high regio- and stereoselectivities (entries 1, 2). The stereochemistry of **1h** was determined by nOe analysis of the corresponding 3-bromo-2-propen-1-ol **3**, which was derived from subsequent reduction of **1h** with DIBAL-H and $NaBH_4$ (Scheme 3). Although the reaction of sterically hindered diphenylacetylene gave rise to the corresponding adduct **1j** in low yield, use of an excess amount of cyanogen bromide (3.0 equiv) improved the yield up to 64% (entries 3 and 4). All the alkynes examined possess at least one aromatic substituent, and a bromide of cyanogen bromide always attacks the carbon attached to the aromatic rings in each alkyne. Attempts to react aliphatic and silylated alkynes such as 4-octyne and bistrimethylsilyl-

Table 3. $GaCl_3$-catalyzed bromocyanation of internal alkynes[a]

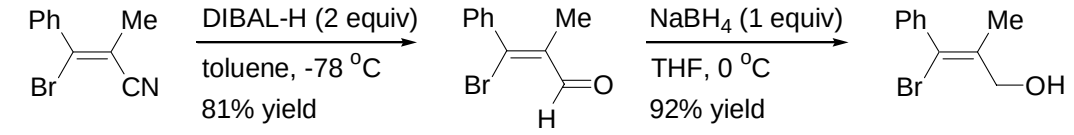


entry	R	product	yield[b]	*E*:*Z*[c]
1	Me	**1h**	69%	5:95
2	*n*-Bu	**1i**	81%	9:91
3	Ph	**1j**	19%	——[e]
4[d]	Ph	**1j**	64%	——[e]

[a]Reaction conditions: Alkyne (0.40 mmol), BrCN (0.60 mmol), $GaCl_3$ (0.040 mmol) in $ClCH_2CH_2Cl$ (1.6 mL). [b]Isolated yield. [c]Determined by ^1H NMR. [d]BrCN (3.0 equiv) was used. [e]Ratio of stereoisomers were not determined.

acetylene with cyanogen bromide failed to give the corresponding *β*-bromoacrylonitriles under the reaction conditions. Furthermore, alkynes having coordinating functional groups such as phenyl propiolate and 3-phenyl-2-propyn-1-ol also deterred the reaction.

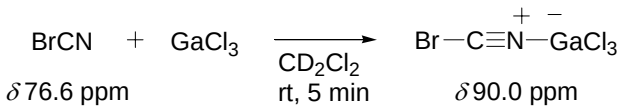
Scheme 3



1h (*E*:*Z* = 5:95) **2** (*E*:*Z* = 5:95) **3** (*E*:*Z* = 4:96)

To gain insight into the reaction mechanism, a stoichiometric reaction of cyanogen bromide with gallium trichloride was examined. After stirring these two reagents in CD_2Cl_2 at room temperature for 5 min, the carbon signal of cyanogen bromide (δ 76.6 ppm) completely disappeared, and a new peak of carbon atom appeared at 90.0 ppm (Scheme 4). Since the downfield shift of the carbon signal revealed that the carbon atom of cyanogen is electronically positive by the interaction with gallium trichloride, the author anticipated the formation of intermediate **A**.[16] The ratio of the two stereoisomers of *β*-bromoacrylonitriles was not changed even when they were subjected in the presence of cyanogen bromide and $GaCl_3$ at 80 °C for 24 h. This fact clearly indicates no interconversion of *β*-bromoacrylonitriles between (*Z*)- and (*E*)-adducts throughout the reaction.

Scheme 4

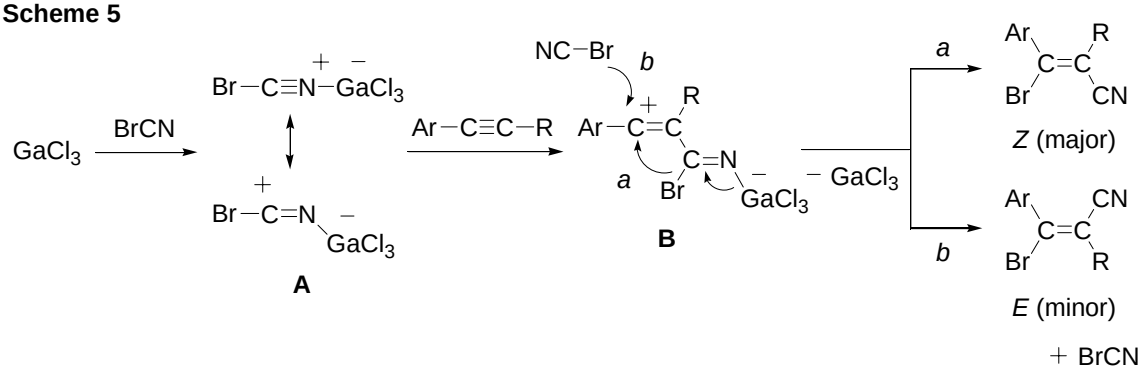


A

Based on these observations, the author proposed the reaction mechanism as shown in Scheme 5. Cyanogen bromide initially coordinates with $GaCl_3$ to form a complex **A**. The complex **A** then reacts with alkynes to generate zwitter ionic intermediate **B**. The generation

of a vinyl cation intermediate **B** stabilized with an aryl group probably plays a crucial role in the addition reaction, as supported by the failure of bromocyanation with aliphatic alkynes. The stereochemistry of the products might support that the reaction proceeded via the formation of intermediate **B**. The Br-CN bond of an intermediate **B** can be activated to promote nucleophilic attack to a cationic center giving (*Z*)-bromocyanation product along with the regeneration of $GaCl_3$ (path a).[16] (*E*)-Bromocyanation adduct might be produced via the formation of intermediate **B** followed by external nucleophilic attack of another cyanogen bromide from opposite side of gallium complex (path b).

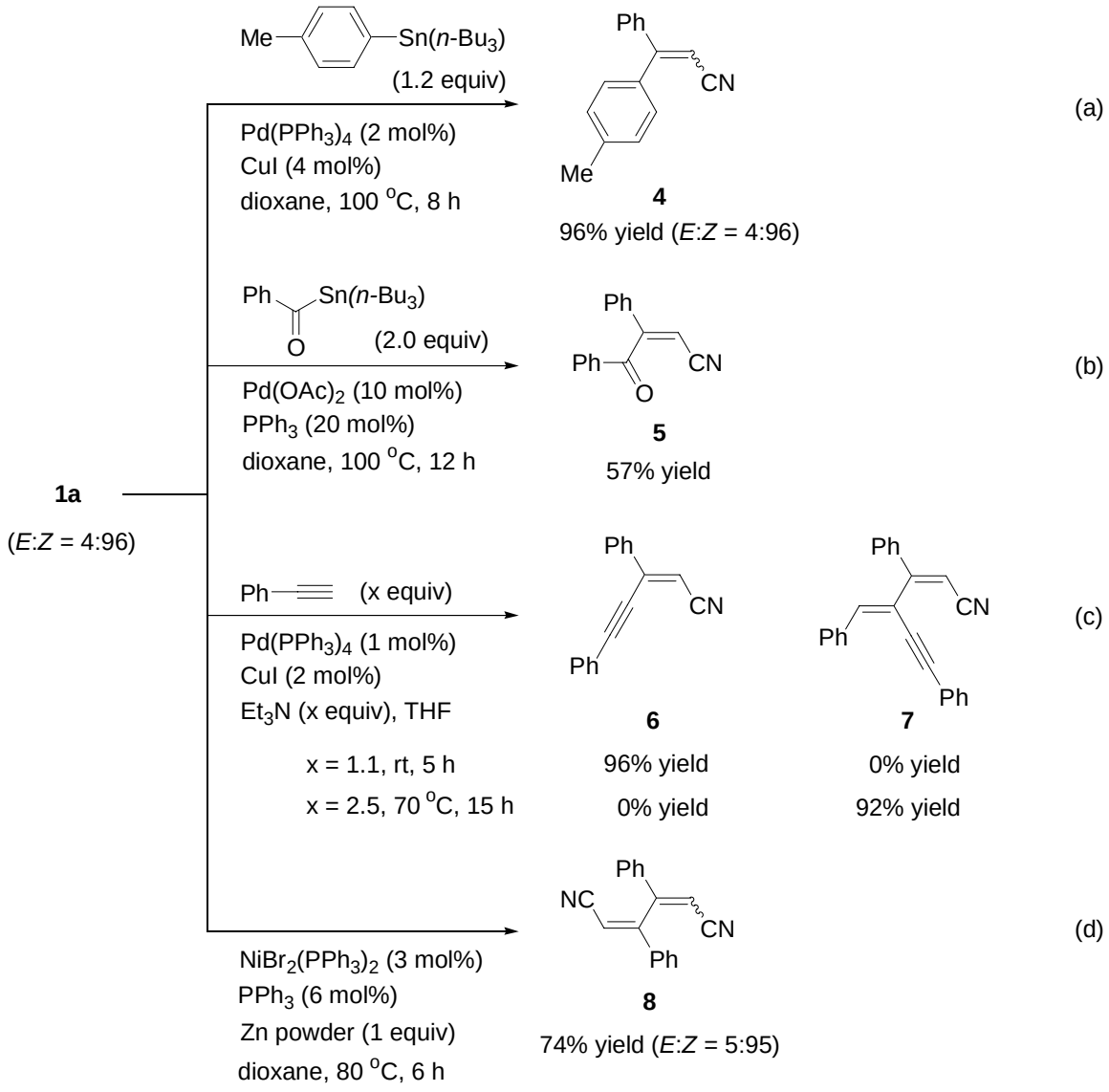
Scheme 5



Combined with the cross-coupling reaction, the present bromocyanation reaction would allow easy access to various *β*-functionalized acrylonitriles. For example, palladium-catalyzed cross-coupling reaction of **1a** with tributhyl-4-tolylstannane gave **4** in 96% yield with high stereoselectivity (Scheme 6a). Palladium-catalyzed cross-coupling reaction of **1a** with benzoyltributhylstannane produced (*Z*)-carbonyl-ene-nitrile compound **5** in 57% yield (Scheme 6b). Treatment of **1a** with phenylacetylene in the presence of palladium and copper catalysts, and Et_3N afforded (*Z*)-3-alkynylacrylonitrile **6** in 96% yield as a single stereoisomer (Scheme 6c). When the amounts of both phenyl acetylene and Et_3N were increased to 2.5 equivalent and heated at 70 ^oC for 15 h, a conjugated nitrile **7** was obtained in 92% yield as a single stereoisomer.[17,18] The reaction of **1a** in the presence of

catalytic amount of $NiBr_2(PPh_3)_2$ and a stoichiometric amount of Zn powder afforded homo-coupling product **8**, which is a precursor of hexamethylenediamine derivative known as one of the monomers used in the production of Nylon 6,6 in 74% yield (Scheme 6d).[19,20]

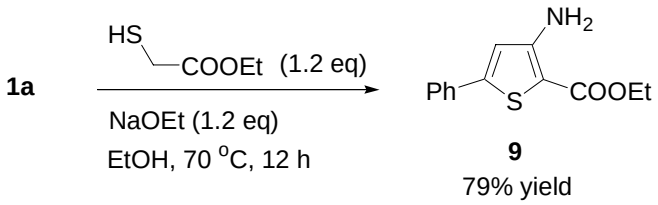
Scheme 6



The transformation of β-bromoacrylonitriles into heterocycles further demonstrated the synthetic utility of the bromocyanation reaction. For example, 3-amino-2-acylthiophene **9**, which was a useful intermediate for the synthesis of various biologically active compounds,[21] was obtained in 86% yield by simply heating with ethyl thioglycolate in the presence of

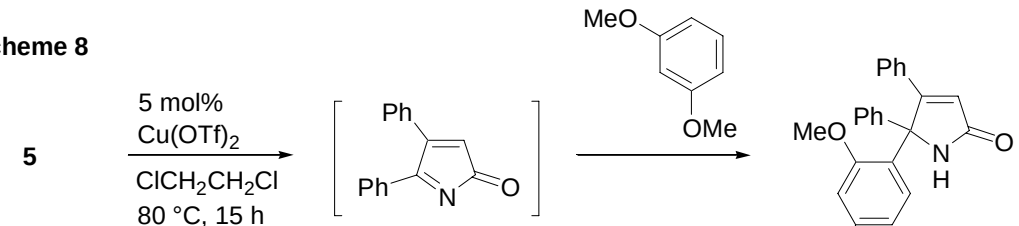
NaOEt (Scheme 7). Furthermore, copper-catalyzed reaction of carbonyl-ene-nitrile compound **5** with 1,3-dimethoxybenzene gave arylated pyrrolin-2-one **10** in 70% yield via cycloisomerization of **5** leading to 2-aza-2,4-cyclopentadienone as described in Chapter 1(Scheme 8).[11]

Scheme 7



9
79% yield

Scheme 8



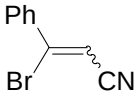
10
70% yield

In conclusion, a novel gallium-catalyzed bromocyanation of arylacetylenes leading to *β*-bromoacrylonitriles has been demonstrated. Using commercially available cyanogen bromide, synthetically useful bromo and cyano groups were simultaneously introduced with high chemo-, regio-, and stereoselectivities. The resulting bromocyanation products are shown to serve as synthetically useful building blocks for not only various *β*-substituted acrylonitirle derivatives through palladium-catalyzed cross-coupling reactions but also nitrogen-containing heterocycles as described in the previous chapters.

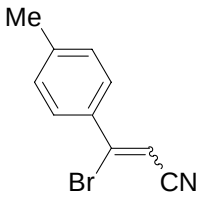
Experimental

General Method. Unless otherwise noted, chemicals obtained from commercial suppliers were used without further purification. $ClCH_2CH_2Cl$ was dried by the usual methods, distilled, and bubbled vigorously with a nitrogen gas for 20 min before use. All reactions were carried out under nitrogen atmosphere. NMR spectra were measured for solutions in $CDCl_3$ or CD_2Cl_2 with tetramethylsilane as an internal standard (^1H and ^{13}C): the following abbreviations are used; br s: broad singlet, s: singlet, d: doublet, t: triplet, q: quartet, quint: quintet, sext: sextet, m: multiplet. IR spectra were recorded with an FT-IR spectrometer. Melting points (mp) are uncorrected. High-resolution mass spectra (HRMS) was measured with JEOL JMX-SX 102A spectrometer.

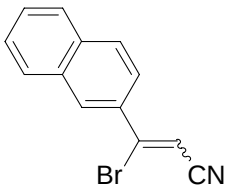
General Procedure of Gallium-catalyzed Bromocyanation of Alkynes. A flame dried Schlenk flask was charged with $GaCl_3$ (7.0 mg, 0.040 mmol) and $ClCH_2CH_2Cl$ (1.6 mL), then BrCN (63.6 mg, 0.60 mmol) was added. After stirring at room temperature for 5 min, alkyne (0.40 mmol) was added, and the resulting mixture was stirred at 80 ^oC. After the time specified in Tables 1-2, the mixture was concentrated in vacuo. The residue was subjected to flash column chromatography on silica gel with hexane/AcOEt (v/v = 10/1-4/1) as eluents to afford the corresponding β-bromoacrylonitriles.



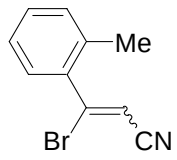
3-Bromo-3-phenylprop-2-enenitrile (1a): A brown oil (*E*:*Z* = 8:92); ^1H NMR (400 MHz, $CDCl_3$): δ 6.02 (s, 0.08×1H, (*E*)-**1a**), 6.30 (s, 0.92×1H, (*Z*)-**1a**), 7.40-7.50 (m, 3H), 7.60-7.63 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): (*Z*)-**1a** δ 100.6, 116.6, 127.8, 128.9, 131.7, 136.1, 145.6; (*E*)-**1a** δ 96.0, 115.3, 126.6, 128.7, 131.7, 133.7, 152.8. The spectral data match those reported in the literature (*J. Med. Chem.* **2000**, *43*, 4288.).



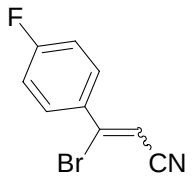
3-Bromo-3-(4-tolyl)prop-2-enenitrile (1b): A brown oil (*E*:*Z* = 4:96); IR (neat): 822, 890, 1250, 1277, 1363, 1456, 1612, 1678, 2219 (CN), 3042 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ2.40 (s, 6H), 5.98 (s, 0.04×1H, (*E*)-**1b**), 6.26 (s, 0.96×1H, (*Z*)-**1b**), 7.23 (d, 0.96×2H, *J* = 8.8 Hz, (*Z*)-**1b**), 7.24 (d, 0.04×2H, *J* = 8.8 Hz, (*E*)-**1b**), 7.51 (d, 0.96×2H, *J* = 8.8 Hz, (*Z*)-**1b**), 7.55 (d, 0.96 ×2H, *J* = 8.8 Hz, (*E*)-**1b**). ^{13}C NMR (100 MHz, $CDCl_3$): (*Z*)-**1b** δ21.3, 99.5, 116.8, 127.7, 129.5, 133.2, 142.5, 145.7; (*E*)-**1b** δ21.4, 95.0, 115.6, 126.8, 129.6, 133.4, 142.7, 153.3. HRMS (FAB) calcd for M+H^+ of $C_{10}H_8BrN$ 221.9918, found 221.9928.



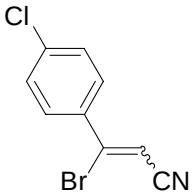
3-Bromo-3-(2-naphtyl)prop-2-enenitrile (1c): A white solid (*E*:*Z* = 5:95); mp 39.5-40.2 ^{o}C (from $CHCl_3$/hexane). IR (KBr): 859, 889, 1182, 1273, 1351, 1466, 1505, 1584, 2214 (CN), 3056 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ6.15 (s, 0.05×1H, (*E*)-**1c**), 6.43 (s, 0.95×1H, (*Z*)-**1c**), 7.55-7.65 (m, 4H), 7.84-7.95 (m, 2H), 8.16 (s, 0.95×1H, (*Z*)-**1c**), 8.21 (s, 0.05×1H, (*E*)-**1c**). ^{13}C NMR (100 MHz, $CDCl_3$): (*Z*)-**1c** δ100.6, 116.8, 123.3, 127.4, 127.7, 128.3, 128.7, 129.0, 129.4, 132.6, 133.0, 134.5, 145.6. HRMS (FAB) calcd for M+H^+ of $C_{13}H_8BrN$ 257.9918, found 257.9926.



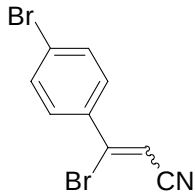
3-Bromo-3-(2-tolyl)prop-2-enenitrile (1d): A pale yellow oil (*E*:*Z* = 2:98); IR (neat): 818, 890, 1225, 1252, 1288, 1383, 1456, 1485, 1612, 1684,2224 (CN), 3039 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ2.37 (s, 0.98×3H, (*Z*)-**1d**), 2.40 (s, 0.02×3H, (*E*)-**1d**), 5.67 (s, 0.02×1H, (*E*)-**1d**), 5.99 (s, 0.98×1H, (*Z*)-**1d**), 7.21-7.34 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): (*Z*)-**1d** δ19.8, 105.1, 115.8, 126.1, 128.3, 130.5, 130.9, 132.0, 137.7, 145.0. HRMS (FAB) calcd for M+H^+ of $C_{10}H_8BrN$ 221.9918, found 221.9920.



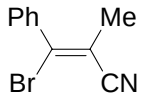
3-Bromo-3-(4-fluorophenyl)prop-2-enenitrile (1e): A white solid (*E*:*Z* = 10:90); mp 80.0-80.5 °C (from $CHCl_3$/hexane). IR (KBr): 818, 893, 1164, 1229, 1306, 1409, 1505, 1584, 1599, 2219 (CN), 3042 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.98 (s, 0.10×1H, (*E*)-**1e**), 6.26 (s, 0.90×1H, (*Z*)-**1e**), 7.09-7.15 (m, 2H), 7.61-7.69 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): (*Z*)-**1e** δ 100.6, 116.1 (d, *J* = 21.5 Hz), 116.3, 130.0 (d, *J* = 9.1 Hz), 132.3 (d, *J* = 3.3 Hz), 144.2, 164.7 (d, *J* = 253.8 Hz); (*E*)-**1e** δ 96.1, 116.2 (d, *J* = 22.3 Hz), 116.5, 129.1 (d, *J* = 9.1 Hz), 129.9 (d, *J* = 2.5 Hz), 152.0, 164.8 (d, *J* = 254.9 Hz). HRMS (FAB) calcd for M+H^+ of C_9H_5BrFN 225.9668, found 225.9663.



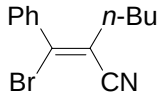
3-Bromo-3-(4-chlorophenyl)prop-2-enenitrile (1f): A white solid (*E*:*Z* = 16:84); mp 66.8-67.2 °C (from $CHCl_3$/hexane). IR (KBr): 804, 887, 1012, 1096, 1221, 1401, 1486, 1562, 1586, 2218 (CN), 3041 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.05 (s, 0.16×1H, (*E*)-**1f**), 6.33 (s, 0.84×1H, (*Z*)-**1f**), 7.37-7.43 (m, 2H), 7.54-7.62 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): (*Z*)-**1f** δ 101.0, 116.4, 128.9, 129.0, 134.3, 137.9, 144.0; (*E*)-**1f** δ 96.6, 115.1, 128.0, 129.1, 132.4, 138.1, 151.7. HRMS (FAB) calcd for M+H^+ of C_9H_5BrClN 241.9372, found 241.9370.



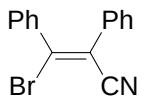
3-Bromo-3-(4-bromophenyl)prop-2-enenitrile (1g): A white solid (*E*:*Z* = 9:91); mp 66.8-67.2 °C (from $CHCl_3$/hexane). IR (KBr): 828, 886, 1008, 1076, 1223, 1396, 1482, 1582, 2216 (CN), 3035 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.04 (s, 0.09×1H, (*E*)-**1g**), 6.32 (s, 0.91×1H, (*Z*)-**1g**), 7.46-7.52 (m, 2H), 7.53-7.61 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): (*Z*)-**1g** δ 101.1, 116.4, 126.5, 129.1, 132.1, 134.9, 144.2; (*E*)-**1g** δ 96.7, 115.1, 126.8, 128.3, 132.2, 136.0, 152.1. HRMS (FAB) calcd for M+H^+ of $C_9H_5Br_2N$ 285.8867, found 285.8855.



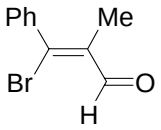
3-Bromo-2-methyl-3-phenylprop-2-enenitrile (1h): A pale yellow crystal (*E*:*Z* = 5:95); mp 37.5-37.8 °C (from $CHCl_3$/hexane). IR (KBr): 883, 1019, 1235, 1443, 1489, 1614, 1686, 2218 (CN), 3060 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.94 (s, 0.95×3H, (*Z*)-**1h**), 2.01 (s, 0.05×3H, (*E*)-**1h**), 7.31-7.34 (m, 2H), 7.39-7.42 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): (*Z*)-**1h** δ 19.4, 112.6, 118.9, 128.4, 128.5, 130.0, 135.9, 136.7. HRMS (FAB) calcd for M+H^+ of $C_{10}H_8BrN$ 221.9918, found 221.9916.



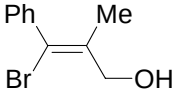
3-Bromo-2-buthyl-3-phenylprop-2-enenitrile (1i): A colorless oil (*E*:*Z* = 13:87); IR (KBr): 883, 1231, 1444, 1489, 1594, 1685, 2217 (CN), 2862, 2930, 2959, 3060 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.83 (t, *J* = 7.3 Hz, 0.87×3H, (*Z*)-**1i**), 0.91 (t, *J* = 7.3 Hz, 0.13×3H, (*E*)-**1i**), 1.26 (sext, *J* = 7.3 Hz, 0.87×2H, (*Z*)-**1i**), 1.37 (sext, *J* = 7.3 Hz, 0.13×2H, (*E*)-**1i**), 1.57 (quint, *J* = 7.3 Hz, 0.87×2H, (*Z*)-**1i**), 1.74 (quint, *J* = 7.3 Hz, 0.13×2H, (*E*)-**1i**), 2.22 (t, *J* = 7.3 Hz, 0.87×2H, (*Z*)-**1i**), 2.96 (t, *J* = 7.3 Hz, 0.13×2H, (*E*)-**1i**), 7.28-7.31 (m, 2H), 7.40-7.42 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): (*Z*)-**1i** δ 13.5, 21.8, 30.3, 32.4, 118.2, 118.8, 128.2, 128.6, 130.0, 135.6, 137.2; (*E*)-**1i** δ 13.9, 22.5, 31.5, 38.6, 118.1, 118.7, 128.0, 128.5, 132.8, 133.6, 137.1. HRMS (FAB) calcd for M+H^+ of $C_{13}H_{14}BrN$ 264.0388, found 264.0394.



3-Bromo-2,3-diphenylprop-2-enenitrile (1j): A pale yellow solid; mp 77.2-77.9 °C (from $CHCl_3$/hexane). IR (KBr): 883, 919, 1081, 1266, 1444, 1488, 1584, 1597, 2214 (CN), 3062 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.14-7.31 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 117.9, 118.7, 128.5, 128.7, 129.0, 129.1, 129.5, 130.2, 133.2, 137.2, 138.4. HRMS (FAB) calcd for M+H^+ of $C_{15}H_{10}BrN$ 284.0075, found 284.0071.

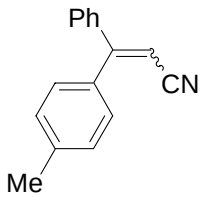


Reduction of 1h with DIBAL-H. To a solution of **1h** (222 mg, 1.0 mmol) in toluene (4 mL) was added a 1.5 M solution of DIBAL-H in toluene (1.0 mL, 1.5 mmol) at -78 °C, and the resulting mixture was stirred at the same temperature for 1 h. The reaction was quenched with MeOH (0.5 mL) at -78 °C and was warmed at room temperature. The mixture was filtered through a short silica gel pad with Et_2O as an eluent, and concentrated in vacuo. The residue was subjected to flash column chromatography on silica gel with hexane/AcOEt (v/v = 10/1) as eluents to give 3-bromo-2-methyl-3-phenylprop-2-enen-1-al **2** (112 mg, 0.81 mmol, 81% yield) as a colorless oil (*E*:*Z* = 5:95). IR (neat): 865, 1022, 1261, 1443, 1490, 1591, 1604, 1681 (C=O), 1717, 2863, 3057 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.79 (s, 0.95×3H, (*Z*)-**2**), 1.85 (s, 0.05×3H, (*E*)-**2**), 7.25-7.45 (m, 5H), 10.2 (s, 0.95×1H, (*Z*)-**2**), 10.4 (s, 0.05×1H, (*E*)-**2**). ^{13}C NMR (100 MHz, $CDCl_3$): (*Z*)-**2** δ 14.8, 128.4, 128.5, 129.7, 134.6, 139.3, 139.4, 194.3. HRMS (FAB) calcd for $M+H^+$ of $C_{10}H_9BrO$ 224.9915, found 224.9912.

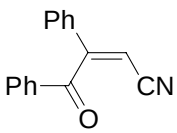


Reduction of 2 by $NaBH_4$. To a suspension of $NaBH_4$ (15.1 mg, 0.40 mmol) in THF (2.0 mL) was added a solution of **2** (90 mg, 0.40 mmol) in THF (1.0 mL) at 0 °C, and the resulting mixture was stirred for 30 min. The reaction was quenched with 10% HCl aqueous solution at 0 °C, and the resulting mixture was extracted with Et_2O (10 mL×3). The combined organic layers were washed with a sat. $NaHCO_3$ aqueous solution and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was subjected to flash column chromatography on silica gel with hexane/AcOEt (v/v = 3/1) as eluents to give 3-bromo-2-methyl-3-phenyl- 2-propen-1-ol **3** (83.5 mg, 0.37 mmol, 92% yield) as a colorless oil (*E*:*Z* = 4:96). IR (neat): 867, 1012, 1263, 1442, 1490, 1704, 2857, 2917, 3336 (OH) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.81 (s, 0.96×1H, (*Z*)-**3**), 1.85 (s, 0.04×2H, (*E*)-**3**), 4.45 (s, 0.96×3H, (*Z*)-**3**), 4.47 (s, 0.04×2H, (*E*)-**3**), 7.25-7.32 (m, 2H),

7.33-7.38 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): (*Z*)-**3** δ18.3, 67.4, 118.4, 128.1, 128.2, 129.1, 136.2, 140.3. HRMS (FAB) calcd for M+H$^+$ of $C_{10}H_{11}BrO$ 227.0072, found 227.0072.

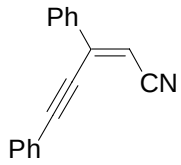


Palladium-catalyzed Cross-coupling Reaction of 1a with Tributhyl-4-tolylstannane. A flame dried Schlenk flask was charged with $Pd(PPh_3)_4$ (9.2 mg, 0.0080 mmol), CuI (3.0 mg, 0.016 mmol), **1a** (82.9 mg, 0.40 mmol), tributhyl-4-tolylstannane (183 mg, 0.48 mmol)**,** and dioxane (1.6 mL). The mixture was stirred at 100 ^{o}C for 8 h, and then diluted with Et_2O (5 mL). The resulting mixture was treated with a 10 mol% KF aqueous solution (2 mL) for 30 min, and the insoluble materials were filtered through a Celite pad. The organic layer was washed with water and brine, and then dried over $MgSO_4$. The organic solvent was removed under reduced pressure and the residue was subjected to flash column chromatography on silica gel with hexane/AcOEt (v/v = 7/1) as eluents to afford 3-(4-methylphenyl)-3-phenyl-2-propenenitrile **4** (83.0 mg, 0.38 mmol) as a white solid (*E*:*Z* = 6:94). ^{1}H NMR (400 MHz, $CDCl_3$): δ2.40 (s, 0.96×3H, (*Z*)-**4**), 2.36 (s, 0.04×1H, (*E*)-**4**), 5.67 (s, 0.96×1H, (*Z*)-**4**), 5.70 (s, 0.04×1H, (*E*)-**3**), 7.23-7.44 (m, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): (*Z*)-**4** δ21.4, 94.2, 118.1, 128.4, 128.5, 129.2, 129.5, 130.3, 134.1, 139.2, 140.3, 163.1; (*E*)-**4** δ21.2, 94.0, 117.8, 128.4, 128.5, 129.0, 129.3, 129.8, 135.5, 137.2, 140.7, 162.9. The spectral data match those reported in the literature (*Synthesis* **2002**, 1903.).



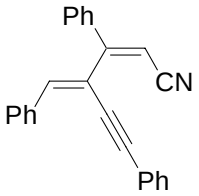
Palladium-catalyzed Cross-coupling Reaction of 1a with Benzoyl-tributhylstannane. A flame dried Schlenk flask was charged with $Pd(OAc)_2$ (9.2 mg, 0.040 mmol), PPh_3 (21.0 mg, 0.080 mmol), **1a** (82.9 mg, 0.40 mmol), benzoyltributhylstannane (316 mg, 0.80 mmol), and dioxane (1.6 mL). The mixture was

stirred at 100 °C for 12 h, and then diluted with Et_2O (5 mL). The resulting mixture was treated with a 10 mol% KF aqueous solution (2 mL) for 30 min, and the insoluble materials were filtered through a short silica gel pad with Et_2O as an eluent. The organic layer was washed with water and brine, and then dried over $MgSO_4$. The organic solvent was removed under reduced pressure and the residue was subjected to flash column chromatography on silica gel with hexane/AcOEt (v/v = 4/1) as eluents to afford (2*Z*)-4-oxo-3,4-diphenylbut-2-en-carbonitrile **5** (53.6 mg, 0.23 mmol, 57% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.03 (s, 1H), 7.39-7.50 (m, 7H), 7.63 (t, J = 6.8 Hz, 1H), 7.94 (d, J = 7.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 96.1, 115.5, 126.6, 129.1, 129.4, 129.9, 131.4, 133.2, 134.7, 134.8, 161.0, 194.0. The spectral data match those reported in the literature (*J*. *Org*. *Chem*. **2008**, *73*, 2396.).

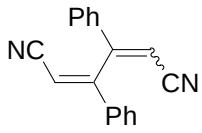


Palladium-catalyzed Cross-coupling Reaction of 1a with Phenylacetylene. A flame dried Schlenk flask was charged with **1a** (82.9 mg, 0.40 mmol) and phenylacetylene (44.9 mg, 0.44 mmol) in THF (1.6 mL) was degassed by three freeze-thaw cycles. To this were added $Pd(PPh_3)_4$ (4.6 mg, 0.0040 mmol), CuI (1.5 mg, 0.0080 mmol), and Et_3N (44.5 mg, 0.44 mmol), and then the mixture was stirred at rt for 5 h. The reaction mixture was washed with water and brine, and then dried over $MgSO_4$. The organic solvent was removed under reduced pressure and the residue was subjected to flash column chromatography on silica gel with hexane/AcOEt (v/v = 10/1) as eluents to afford (2*Z*)-3,5-diphenylpent-2-en- 4-ynenitrile **6** as a pale yellow oil (88.0 mg, 0.38 mmol, 96% yield). IR (neat): 919, 1069, 1213, 1257, 1362, 1444, 1489, 1556, 2191, 2217 (CN), 2362, 3060 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.98 (s, 1H), 7.33-7.45 (m, 6H), 7.63 (dd, J = 2.0, 7.8 Hz, 2H), 7.71 (dd, J = 2.0, 7.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 85.2, 100.0, 101.9, 117.4, 121.3, 126.6, 128.4, 128.8, 129.8, 130.9, 132.2, 134.2, 142.9. HRMS (FAB)

calcd for M+H$^+$ of $C_{17}H_{11}N$ 230.0970, found 230.0977.

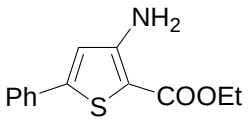


According to the procedure for the synthesis of **6**, **1a** (82.9 mg, 0.40 mmol)) and phenylacetylene (102 mg, 1.0 mmol) in THF (1.6 mL) was added $Pd(PPh_3)_4$ (4.6 mg, 0.004 mmol), CuI (1.5 mg, 0.008 mmol), and Et_3N (101 mg, 1.0 mmol), and then the mixture was stirred at 70 ^oC for 15 h. The reaction mixture was washed with water and brine, and then dried over $MgSO_4$. The organic solvent was removed under reduced pressure and the residue was subjected to flash column chromatography on silica gel with hexane/AcOEt (v/v = 10/1) as eluents to afford (2*Z*,4*Z*)-3,5,7-triphenylhepta-2,4-dien-6-ynenitrile **7** as a pale yellow oil (88.0 mg, 0.38 mmol, 96% yield); A pale yellow crystal; mp 97.2-97.8 ^oC. IR (KBr): 1029, 1343, 1445, 1490, 1571, 2210 (CN), 2359, 2923, 3057 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.65 (s, 1H), 7.05 (s, 1H), 7.28-7.30 (m, 2H), 7.37-7.45 (m, 9H), 7.50-7.54 (m, 2H), 8.02 (d, *J* = 6.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 86.9, 95.5, 98.7, 117.1 118.2, 122.7, 128.3, 128.4, 128.5, 128.7, 128.8, 129.6, 129.7, 130.4, 131.5, 135.2, 137.4, 142.1, 161.7. HRMS (FAB) calcd for M+H$^+$ of $C_{25}H_{17}N$ 332.1439, found 332.1436.



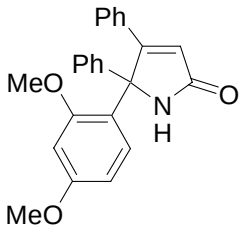
Palladium-catalyzed Homo-coupling Reaction of 1a. A flame dried Schlenk flask was charged with $NiBr_2(PPh_3)_2$ (6.7 mg, 0.0090 mmol), PPh_3 (4.7 mg, 0.018 mmol), zinc powder (19.6 mg, 0.30 mmol), and dioxane (1.2 mL). The solution was stirred at room temperature for 10 min, and then **1a** (62.2 mg, 0.30 mmol) was added dropwise. The mixture was stirred at 80 ^oC for 6 h, and then diluted with Et_2O (5 mL). The reaction mixture was washed with water and brine, and then dried over $MgSO_4$. The organic solvent was removed under reduced pressure and the residue was subjected to flash column chromatography on silica gel with hexane/AcOEt (v/v = 10/1) as

eluents to afford 3,4-diphenylhexa-2,4-hexadiene-1,6-dinitrile **8** (28.5 mg, 0.11 mmol, 74% yield) as a white solid (*E*:*Z* = 4:96). mp 183.8-184.6 °C (from $CHCl_3$/hexane). IR (KBr): 1031, 1372, 1445, 1493, 1604, 2215 (CN), 2922, 3057 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.77 (s, 0.04×1H, (4*E*)-**8**), 5.95 (s, 0.04×1H, (4*E*)-**8**), 6.20 (s, 0.96×2H, (4*Z*)-**8**), 7.36-7.46 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$): (4*Z*)-**8** δ 99.2, 115.9, 126.8, 129.4, 131.4, 134.0, 157.8. HRMS (FAB) calcd for M+H^+ of $C_{18}H_{12}N_2$ 257.1079, found 257.1078.



Synthesis of Ethyl 3-Amino-5-phenylthiophene-2-carboxylate 9. To a stirred solution of **1a** (82.9 mg, 0.40 mmol) and ethyl thioglycolate (57.7 mg, 0.48 mmol) in EtOH (2 mL) was added sodium ethoxide (32.7 mg, 0.48 mmol) at rt. After stirring at 70 °C for 12 h, the solvent was removed. The residue was dissolved in Et_2O, washed with water, and then dried over $MgSO_4$. The organic solvent was removed under reduced pressure and the residue was subjected to flash column chromatography on silica gel with hexane/AcOEt (v/v = 4/1) as eluents to afford ethyl 3-amino-5-phenylthiophene-2-carboxylate **9** as a white solid (84.0 mg, 0.34 mmol, 86% yield). mp 92.1-92.7 °C. IR (KBr): 768, 1039, 1094, 1129, 1294, 1368, 1467, 1553, 1607, 1673, 3309, 3389 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.36 (t, *J* = 7.3 Hz, 3H), 4.30 (q, *J* = 7.3 Hz, 2H), 5.47 (br, 2H), 6.75 (s, 1H), 7.30-7.40 (m, 3H), 7.55-7.59 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.5, 58.2, 115.5, 125.9, 128.8, 128.9, 133.3, 148.9, 154.1, 164.6. HRMS (FAB) calcd for M+H^+ of $C_{13}H_{13}NO_2S$ 248.0745, found 248.0744.

Copper-catalyzed Reaction of Carbonyl-ene-nitrile Compound 5. A flame dried Schlenk flask was charged with $Cu(OTf)_2$ (7.2 mg, 0.020 mmol), **5** (46.6 mg, 0.20 mmol), 1,3-dimethoxybenzene (138.2 mg, 1.0 mmol), and $ClCH_2CH_2Cl$ (2.0 mL). After stirring at 80 °C for 15 h, the mixture was diluted with Et_2O and filtered through a short silica gel pad.



Filtrate was concentrated under reduced pressure and the residue was subjected to flash column chromatography on with hexane/AcOEt (v/v = 7/1-3/1) as eluents to afford 4,5-diphenyl-5-(2,4-dimethoxyphenyl)-3-pyrrolin-2-one **10** (52.1 mg, 0.14 mmol, 70% yield) as a white solid. mp 210.3-210.8 ^{o}C. IR (KBr): 794, 832, 868, 922, 1038, 1211, 1262, 1353, 1378, 1418, 1447, 1586, 1612, 1693 (C=O), 2838, 2942, 3017, 3276 (N-H) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.57 (s, 3H), 3.80 (s, 3H), 6.22 (s, 1H), 6.48 (s, 1H), 6.48-6.49 (m, 1H), 7.07-7.23 (m, 5H), 7.31 (d, J = 7.8 Hz, 2H), 7.32-7.39 (m, 2H), 7.41 (br s, 1H) , 7.83 (d, J = 7.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.3, 55.4, 67.8, 100.8, 104.27, 122.4, 125.6, 127.1, 127.2, 128.1, 128.2, 128.3, 128.5, 131.0, 132.8, 141.0, 146.1, 158.0, 162.8, 171.8. HRMS (FAB) calcd for M+H^{+} of $C_{24}H_{21}NO_3$ 372.1602, found 372.1600.

Determination of Products Structures. The structures of known compounds **1a**, **3**, and **4** were determined on the basis of NMR spectrum in literatures. The regio- and stereochemistry of other bromocyanation adducts derived from terminal acetylenes, such as **1b**-**1g** were determined by comparing their chemical shift values of analogous vinyl protons with that of **1a**. The stereochemistry were also confirmed by nOe experiments of ^{1}H NMR. Selected results are shown below (Figure 1). The structure of major product of **1e** and **7** was unambiguously determined by X-ray crystallographic analysis (Figures 2 and 3).

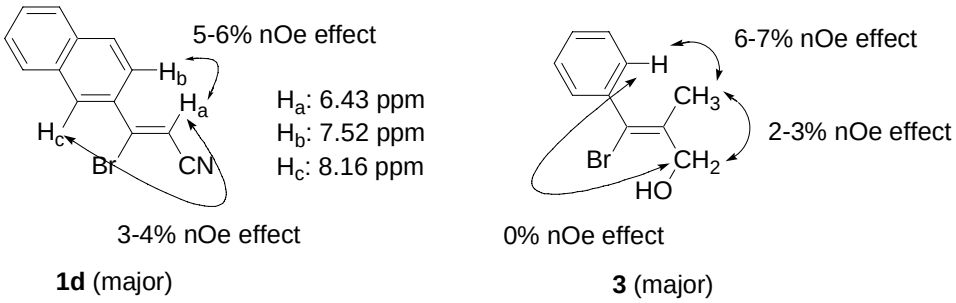


Figure 1. Determination of stereochemistry of the products.

X-ray Crystallographic Studies of 1e. Colorless crystals of (*Z*)-**1e** suitable for X-ray analysis were obtained by recrystallization from $CHCl_3$ /hexane. The single crystal was sealed in a Pyrex glass capillary under N_2 atmosphere and used for data collection. All measurements were made on a Rigaku RAXIS imaging plate area detector with graphite monochromated Mo-Kα radiation. Details of crystal and data collection parameters are summarized in Table 4. The positions of non-hydrogen atoms were determined by direct methods (SIR92) and subsequent Fourier syntheses (DIRDIF PATTY). An ORTEP drawing of (*Z*)-**1e** is shown in Figure 2.

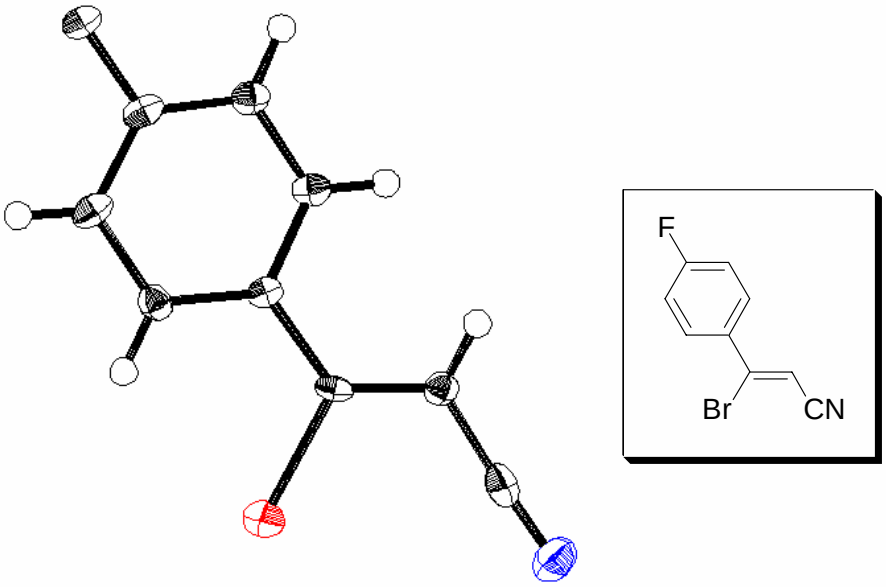


Figure 2. ORTEP drawing of (*Z*)-**1e**.

Table 4. Summary of Crystallographic Data of (*Z*)-**1e**

Empirical formula: C_9H_6BrFN

Formula weight: 227.06

Crystal system: triclinic

Space group: P-1 (#2)

Crystal color: colorless

Lattice parameters:

a (Å) = 7.460(4), *b* (Å) = 9.197(5), *c* (Å) = 12.279(7)

V (Å^3) = 822.2(8), α = 83.7518(18)^o, β = 86.002(16)^o

γ = 79.445(15)^o

Z = 4

D_{calc} (g cm^{-3}): 1.834

μ (Mo K α) (cm^{-1}): 49.662

Goodness of fit (GOF) = 1.002

F(000): 444

Diffractometer: Rigaku RAXIS-RAPID

Radiation: MoK α (λ = 0.71070 Å), Graphite Monochromated

Temp (^{o}C): 23.0

Scan type: ω–2 θ

Max. 2 θ (^{o}): 54.9

No. of reflections measured total: 5520

No. of observns ($I > 3.00\ \sigma(I)$): 3075

Structure solution: Direct Methods (SIR92)

Refinement: Full-Matrix Least-Squares on F

No. of variables: 217

Reflection/parameter ratio: 14.17

Residuals: R = 0.0634, R_w = 0.0630

Max Shift/Error in Final Cycle: 0.00

Maximum peak in Final Diff Map (e (Å^{-3}): 0.99

Minimum peak in Final Diff Map (e (Å^{-3}): -0.71

X-ray Crystallographic Studies of 7. Pale yellow crystals of **7** suitable for X-ray analysis were obtained by recrystallization from $CHCl_3$/hexane. The single crystal was sealed in a Pyrex glass capillary under N_2 atmosphere and used for data collection. All measurements were made on a Rigaku RAXIS imaging plate area detector with graphite monochromated Mo-Kα radiation. Details of crystal and data collection parameters are summarized in Table 5. The positions of non-hydrogen atoms were determined by direct methods (SIR92) and subsequent Fourier syntheses (DIRDIF PATTY). An ORTEP drawing of **7** is shown in Figure 3.

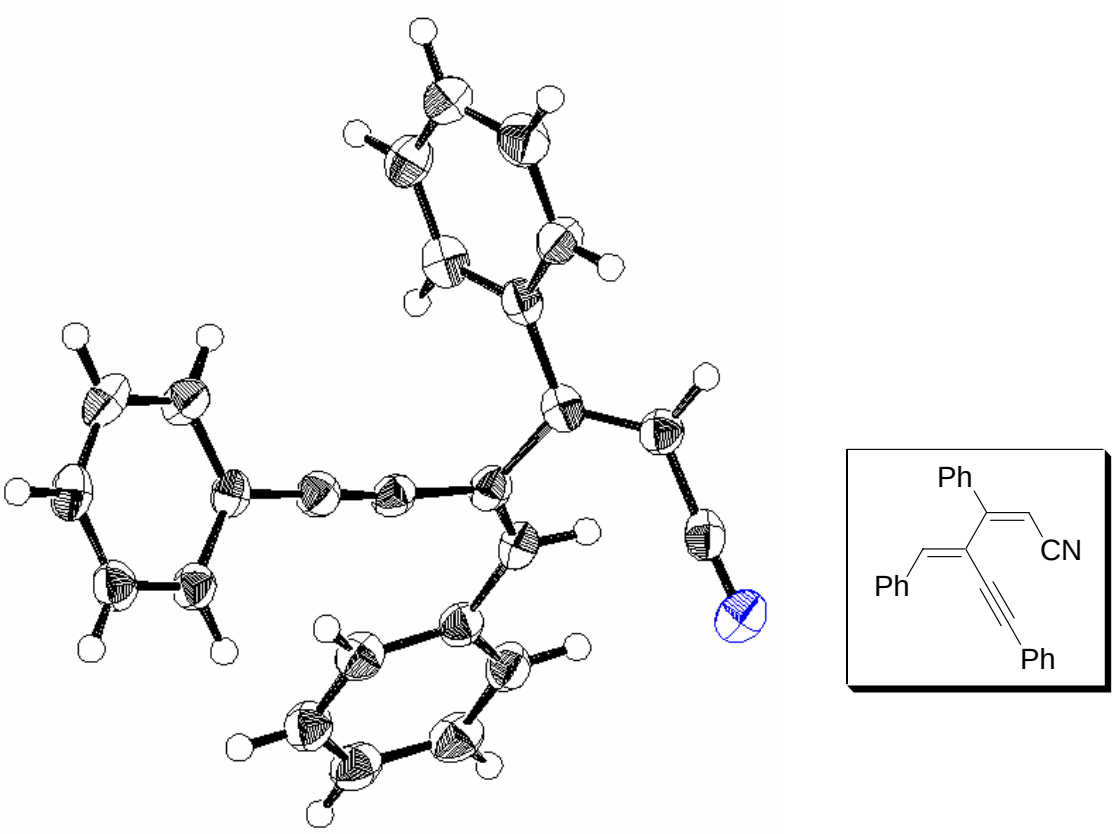


Figure 3. ORTEP drawing of **7**.

Table 5. Summary of Crystallographic Data of **7**

Empirical formula: $C_{25}H_{17}N$
Formula weight: 331.42
Crystal system: triclinic
Space group: P-1 (#2)
Crystal color: yellow
Lattice parameters:
a (Å) = 9.162(7), *b* (Å) = 10.020(7), *c* (Å) = 10.939(9)
V (Å^3) = 919.7(12), α = 87.93(2)^o, β = 88.96(2)^o
γ = 66.424(14)^o
Z = 4
D_{calc} (g cm^{-3}): 2.393
μ (Mo K α) (cm^{-1}): 1.381
Goodness of fit (GOF) = 1.002
F(000): 696
Diffractometer: Rigaku RAXIS-RAPID
Radiation: MoK α (λ = 0.71070 Å), Graphite Monochromated
Temp (^{o}C): 23.0
Scan type: ω–2 θ
Max. 2 θ (^{o}): 54.9
No. of reflections measured total: 5114
No. of observns ($I > 3.00\ \sigma(I)$): 3192
Structure solution: Direct Methods (SIR92)
Refinement: Full-Matrix Least-Squares on F
No. of variables: 252
Reflection/parameter ratio: 12.67
Residuals: R = 0.1296, R_w = 0.0912
Max Shift/Error in Final Cycle: 0.00
Maximum peak in Final Diff Map (e (Å^{-3}): 0.40
Minimum peak in Final Diff Map (e (Å^{-3}): -0.41

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Chapter 5

Palladium-catalyzed Cycloisomerization of 2-(Cyanomethyl)phenyl Esters: A New Route to 3-Acyl-2-aminobenzofurans

Abstract

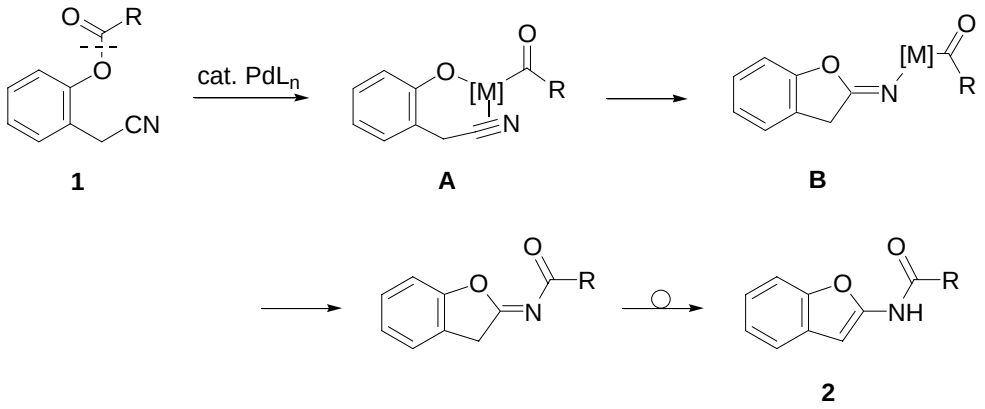
Palladium-catalyzed cycloisomerization of 2-(cyanomethyl)phenyl esters leading to 3-acyl-2-aminobenzofurans are described. The reaction proceeded via cleavage of an acyl-oxygen bond with palladium catalyst and oxypalladation of a cyano moiety followed by isomerization and reductive elimination. The reaction was dramatically accelerated by using the combination of $Pd(PCy_3)_2$ and $Zn(OAc)_2$ as catalysts. The substrate scope could also be expanded to formate and carbonate, giving corresponding 2-aminobenzofurans in good to excellent yields. Since the resulting benzofurans have both an amino and a carbonyl group, they are useful building blocks for the synthesis of various benzofuran-fused heterocycles, such as Elbfluorene.

Introduction

Recently, transition metal-catalyzed cycloisomerization reactions have received considerable attention as useful tools for the synthesis of various carbo- and heterocycles.[1] Although cycloisomerization of alkynes, alkenes, and allenes has been well investigated, counterparts of nitriles are limited and still remain challenging.[2] In Chapters 1 and 2, the author describes copper-catalyzed cycloisomerization of carbonyl-ene-nitrile compounds leading to 2-aza-2,4-cyclopentadienones, which are useful intermediates for the synthesis of variously functionalized pyrrolin-2-ones.[3] Furthermore, using the same carbonyl-ene-nitrile compounds, platinum-catalyzed coupling reaction of carbonyl-ene-nitrile compounds with vinylcarbene complexes generated in situ from propargyl carboxylates were demonstrated, in Chapter 3. These results stimulated him to investigate new types of cycloisomerization of properly functionalized nitriles.

In this chapter, the author describes a novel palladium-catalyzed cycloisomerization of 2-(cyanomethyl)phenyl esters **1** leading to 2-aminobenzofurans. Although 2-aminobenzofurans are an important class of heterocyclic compounds, they are difficult to work with because of the instability.[4] However, it is well known that substitution at the 3-position as well as *N*-acylation remarkably increases the stability of otherwise unstable 2-aminobenzofurans.[5,6] The author hypothesized that intramolecular oxyacylation of **1** via cleavage of the acyl-oxygen bond followed by prototropic isomerization of a cyclic *N*-acylimino ether would give rise to a series of stable *N*-acyl-2-aminobenzofurans **2**[7] (Scheme 1).

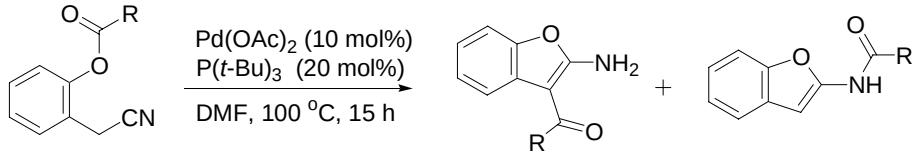
Scheme 1



Results and Discussion

The author examined the reaction of 2-(cyanomethyl)phenyl 4-trifluoromethylbenzoate **1a**, which contains an acyl-oxygen bond prone to cleavage by low-valent transition metals because of activation by the electron-withdrawal of a trifluoromethyl group.[8] When the reaction of **1a** in the presence of $Pd(OAc)_2$ (10 mol%) and P(*t*-Bu)$_3$ (20 mol%) in DMF at 100 °C was carried out, 3-acyl-2-aminobenzofuran **3a** was obtained in 27% yield instead of the expected *N*-acyl-2-aminobenzofuran **2a** (Scheme 2).[9]

Scheme 2

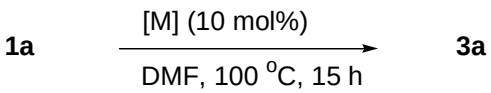


1a (R = 4-$CF_3C_6H_4$) **3a** 27% yield **2a** not observed

This interesting result stimulated him to optimize conditions for the cycloisomerization of **1a** (Table 1). Several phosphines including PCy_3, PCy_2Ph, and diphenylphosphinoferrocene

(dppf) were also effective (entries 1-3), whereas PPh_3 was found to be ineffective for the reaction (entry 4). Other palladium compounds including $PdCl_2$ and $Pd_2(dba)_3$ did not catalyze the reaction, even when PCy_3 was used as a ligand. On the other hand, the use of $Ni(cod)_2$ (10 mol%) and PCy_3 (20 mol%) produced **3a** in a yield comparable to that of the combination of $Pd(OAc)_2$ and PCy_3 (entry 5). Since $Pd(PCy_3)_2$ is assumed as an active catalyst for the present reaction, the author next examined the reaction in the presence of $Pd(PCy_3)_2$. To his delight, the yield of **3a** increased up to 62% yield (entry 6). Furthermore, it was revealed that the addition of $Zn(OAc)_2$ to $Pd(PCy_3)_2$ system was effective to facilitate the reaction to give **3a** in 96% yield (entry 7). The author also found the reaction proceeded smoothly using combined catalyst of cheap $Pd(OAc)_2/PCy_3/Zn$ to furnish **3a** in 98% yield (entry 8).[10] As a solvent, DMF was found to give the best result, whereas DMSO, toluene, and dioxane decreased the yield of **3a**.

Table 1. Optimization of cycloisomerization of **1a**[a]

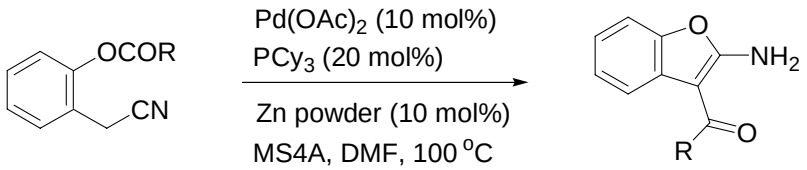


entry	[M] / ligand / additive	conv. (%)	yield (%)[b]
1	$Pd(OAc)_2$ / PCy_3	54	36
2	$Pd(OAc)_2$ / PCy_2Ph	53	31
3[c]	$Pd(OAc)_2$ / dppf	78	32
4	$Pd(OAc)_2$ / PPh_3	79	0
5	$Ni(cod)_2$ / PCy_3	68	32
6	$Pd(PCy_3)_2$	68	62
7[d]	$Pd(PCy_3)_2$ / $Zn(OAc)_2$	100	96
8[e]	$Pd(OAc)_2$ / PCy_3 / Zn	100	98

[a]Reaction conditions: **1a** (0.40 mmol), [M] (0.040 mmol), ligand (0.080 mmol) (0.040 mmol) in DMF (2.0 mL). [b]Isolated yields. [c]dppf (10 mol%) was used. [d]$Zn(OAc)_2$ (0.040 mmol) was used. [e]$Pd(OAc)_2$ (0.040 mmol), PCy_3 (0.080 mmol), Zn powder (0.040 mmol).

With the optimal reaction conditions ($Pd(OAc)_2$, PCy_3, and Zn powder) established, the author next examined reactions of 2-(cyanomethyl)phenyl esters **1** containing various carboxylates. The results are summarized in Table 2. All reactions were conducted in the presence of MS4A to avoid competitive hydrolysis of **1** to 2-(cyanomethyl)phenol. Reactions of **1b-d** with halogen at the ortho or para position occurred smoothly and gave 3-acyl-2-amino-benzofurans **3b-d** in good yields, respectively (entries 1-3). The cycloisomerization described here is applicable to esters having either moderately electron-withdrawing or electron-donating substituents (entries 4-8). Surprisingly, 2-(cyanomethyl)phenyl acetate **1j** also afforded

Table 2. Palladium-catalyzed cycloisomerization of 2-(cyanomethyl)phenyl esters **1**



1 **3**

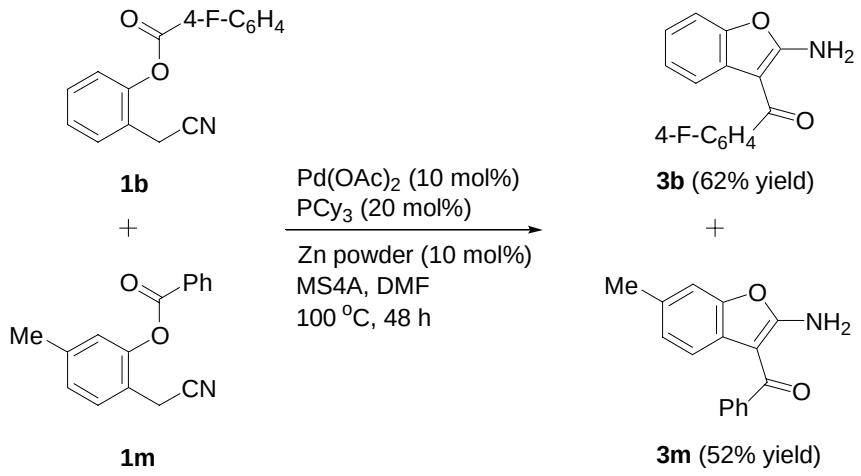
entry	R	**1**	time (h)	product	yield (%)[b]
1	4-FC_6H_4	**1b**	24	**3b**	74
2	4-ClC_6H_4	**1c**	24	**3c**	79
3	2-ClC_6H_4	**1d**	24	**3d**	91
4	2-Naph	**1e**	24	**3e**	89
5	Ph	**1f**	72	**3f**	68
6	4-MeC_6H_4	**1g**	72	**3g**	71
7	4-$MeOC_6H_4$	**1h**	72	**3h**	64
8	4-$Me_2NC_6H_4$	**1i**	96	**3i**	68
9	Me	**1j**	72	**3j**	57
10	H	**1k**	60	**3k**	50
11	OEt	**1l**	24	**3l**	68

[a]Reaction conditions: **1** (0.40 mmol), $Pd(OAc)_2$ (0.040 mmol), PCy_3 (0.080 mmol), Zn powder (0.040 mmol) and molecular sieves 4A (40 mg) in DMF (2.0 mL) at 100 °C. [b]Isolated yields.

3-acetyl-2-aminobenzofuran **3j** in 57% yield (entry 9). Furthermore, the substrate scope could be expanded to formate **1k** and carbonate **1l**, giving 2-amino-3-formylbenzofuran **3k** and 2-amino-3-ethoxycarbonylbenzofuran **3l** in 50% and 68% yields, respectively (entries 10 and 11).

To gain insight into the reaction mechanism, a crossover experiment was carried out (Scheme 3). Palladium-catalyzed cycloisomerization of a mixture of equimolar amounts of esters **1b** and **1m** yielded only two types of 3-acyl-2-aminobenzofurans, **3b** and **3m** without any crossover products. This result clearly shows that the present cycloisomerization reaction proceeds in an intramolecular fashion.

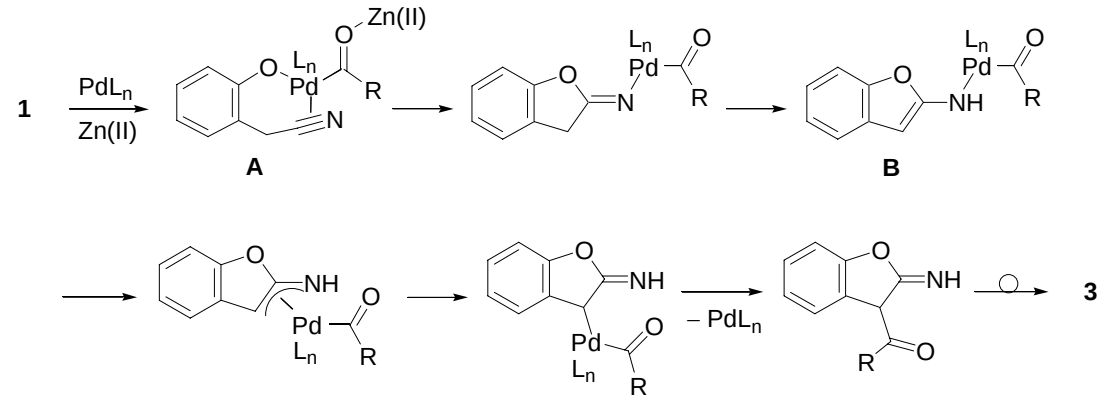
Scheme 3



Although the details of the process remains to be elucidated, the author proposes the following mechanism for the reaction involving oxidative cleavage of an acyl-oxygen bond with the low valent palladium species (Scheme 4).[8,11] The oxidative cleavage of an acyl-oxygen bond with transition metals is known to be difficult to achieve, except in the case of esters activated with electron-withdrawing groups[8] and esters having 2-pyridylmethyl as a directing group.[12] In the present reaction $Zn(OAc)_2$ which is generated from the reaction of $Pd(OAc)_2$ with zinc might accelerate the oxidative cleavage of an acyl-oxygen bond forming an

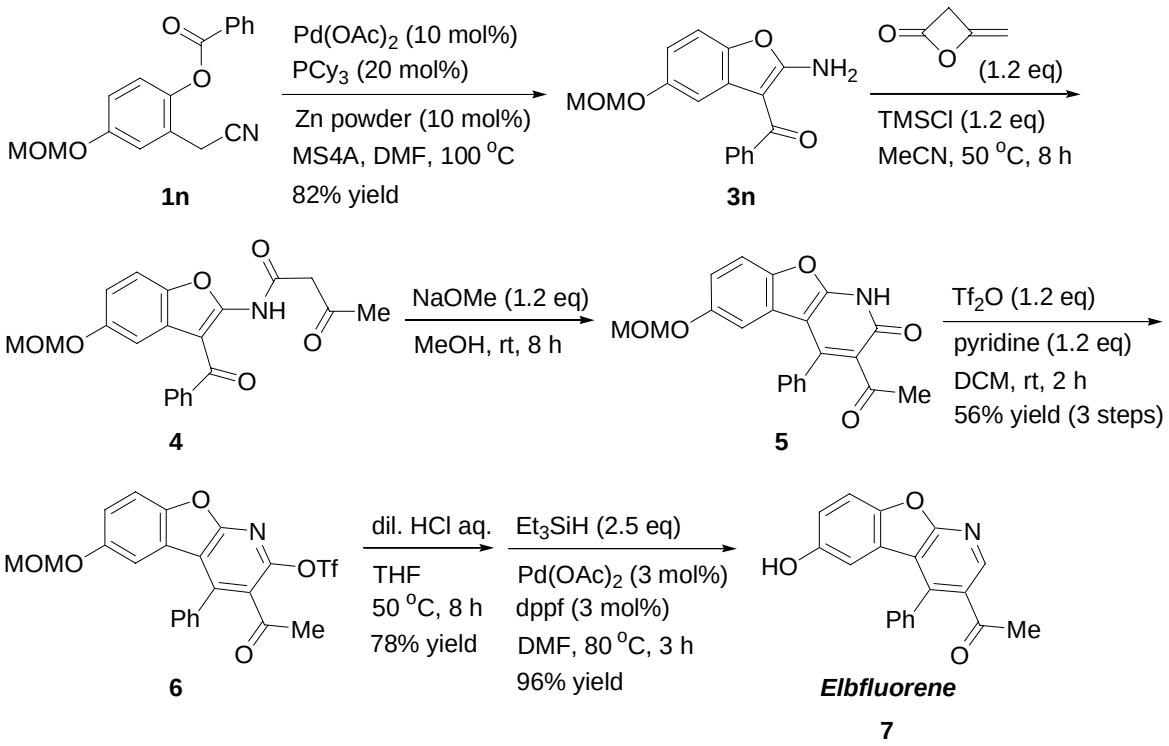
intermediate **A** by coordination to the carbonyl group.[13] In the next step, oxypalladation of a cyano moiety followed by prototropic isomerization gives the intermediate **B**. Subsequent σ-π isomerization of an azaallyl-palladium and reductive elimination at the 3-position of the benzofuran yield 3-acyl-2-aminobenzofuran **3**, and regenerate the catalyst.[14,15]

Scheme 4



Since 3-acyl-2-aminobenzofurans have both an amino and a carbonyl group, they are implemented as the key useful building blocks for the synthesis of benzofuran fused heterocycles. Elbfluorene **7**, which is a CDK (cyclin-dependent-kinase) inhibitor is a logical target for the application of 3-acyl-2-aminobenzofuran (Scheme 5).[16] Palladium-catalyzed cycloisomerization of 2-(cyanomethyl)phenyl ester **1n** afforded corresponding 3-acyl-2-amino-benzofuran **3n** in 82% yield. Reaction of **3n** with ketene followed by dehydrative cyclization lead to the formation of pyridone skeleton to give **5**. After the amide carbonyl moiety of **5** was converted to the trifrate, methoxymethoxy group was deprotected. Finally, palladium-catalyzed reduction with silane gave Elbfluorene **7**.

Scheme 5



In conclusion, unique palladium-catalyzed cycloisomerization of 2-(cyanomethyl)phenyl esters has been developed. The reaction provides a new route to 3-acyl-2-aminobenzofurans, which are rather inaccessible substituted heterocyclic structures. Furthermore, 3-acyl-2-aminobenzofurans are applicable to the synthesis of biologically active nitrogen-containing heterocycles as demonstrated by the synthesis of Elbfluorene.

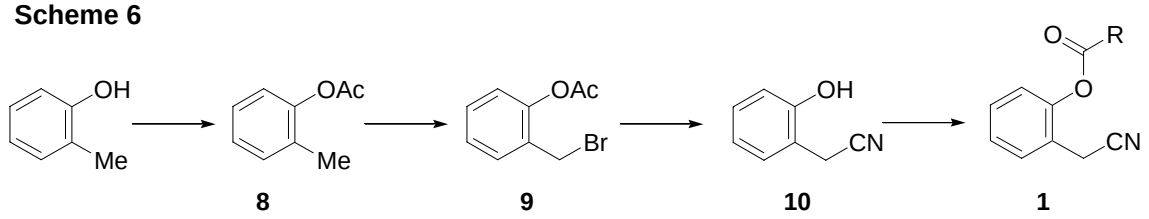
Experimental

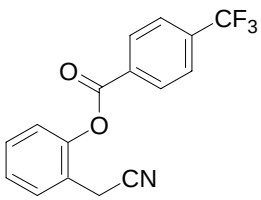
General Method. Unless otherwise noted, chemicals obtained from commercial suppliers were used without further purification. Solvents were dried by the usual methods and distilled before use. Zinc powder was washed successively with dil. HCl aqueous solution, water, ethanol, acetone, and diethyl ether, and dried under reduced pressure prior to use.[17]

All reactions were carried out under nitrogen atmosphere. NMR spectra were measured for solutions in $CDCl_3$ or acetone-d_6 with tetramethylsilane as an internal standard (^1H and ^{13}C): the following abbreviations are used; br s: broad singlet, s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet. IR spectra were recorded with an FT-IR spectrometer. Melting points (mp) are uncorrected. Element analyses were performed at Microanalytical Center of Kyoto University. High-resolution mass spectra (HRMS) was measured with JEOL JMX-SX 102A spectrometer.

Preparation of 2-(Cyanomethyl)phenyl Esters 1 (Scheme 6)

Scheme 6

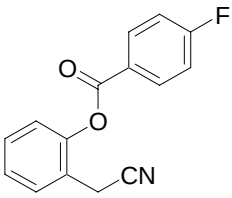




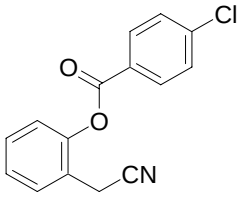
2-(Cyanomethyl)phenyl 4'-trifluoromethylbenzoate (1a): To a solution of *o*-cresol (5.41 g, 50 mmol), triethylamine (10.4 mL, 75 mmol), and 4-*N*,*N*-dimethylaminopyridine (611 mg, 5.0 mmol) in CH_2Cl_2 (75 mL) was slowly added acetic anhydride (7.2 mL, 75 mmol) at 0 ^oC and the mixture was stirred at room temperature for 1 h. The reaction mixture was poured into sat. $NaHCO_3$ aqueous solution. The aqueous layer was extracted with Et_2O (50 mL×3). The combined organic layer was washed with brine and dried over $MgSO_4$. The organic solvent was removed under reduced pressure and the residue was subjected to flash column chromatography on silica gel with hexane/AcOEt (v/v = 100/0-20/1) as eluents to afford 2-methylphenyl acetate **8** (7.43 g, 49.5 mmol, 99% yield) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ2.18 (s, 3H), 2.31 (s, 3H), 7.00 (d, J = 7.7 Hz, 1H), 7.11-7.25 (m, 3H).

To a suspension of *N*-bromosuccinimide (8.92 g, 50 mmol) and benzoyl peroxide (121 mg, 0.50 mmol) in CCl_4 (50 mL) was added 2-methyl phenylacetate **8** (7.43 g, 49.5 mmol) in CCl_4 (10 mL) at 0 ^oC, and the resulting mixture was heated at 80 ^oC for 1 h. The reaction mixture was filtered through a short silica gel pad. Filtrate was concentrated under reduced pressure and the residue was subjected to flash column chromatography on silica gel with hexane/AcOEt (v/v = 100/0-20/1) as eluents to afford 2-(bromomethyl)phenylacetate **9** (10.4 g, 45.5 mmol, 92% yield) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 2.33 (s, 3H), 4.40 (s, 2H), 7.10 (d, J = 7.9 Hz. 1H), 7.17 (t, J = 7.9 Hz, 1H), 7.32 (t, J = 7.9 Hz, 1H), 7.38 (d, J = 7.9 Hz, 1H). A solution of 2-(bromomethyl)phenylacetate **9** (6.86 g, 30 mmol) in DMF (30 mL) was added to sodium cyanide (3.71 g, 75 mmol), and the resulting mixture was stirred for at 80 ^oC for 3 h. After the resulting solution was cooled to room temperature, it was poured into 10% HCl aqueous solution (30 mL), and extracted with Et_2O (30 mL$\times$3). The combined organic layer was dried over $MgSO_4$, and the organic solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel with hexane/AcOEt (v/v = 20/1-5/1) as eluents followed by recrystallization from hexane/$CHCl_3$ gave 2-(cyanomethyl)phenol **10** (1.52 g, 11.4 mmol, 38% yield) as a pale yellow solid. ^1H NMR (400 MHz, $CDCl_3$): δ 3.72 (s, 2H), 5.05 (br s, 1H), 6.80 (d, J = 7.9 Hz. 1H), 6.95 (t, J = 7.9 Hz, 1H), 7.20 (t, J = 7.9 Hz, 1H), 7.33 (d, J = 7.9 Hz, 1H). The spectral data match those reported in the literature.[18] To a solution of 2-(cyanomethyl)-phenol **10** (666 mg, 5.0 mmol), triethylamine (1.04 mL, 7.5 mmol), and 4-*N*,*N*-dimethylaminopyridine (61.1 mg, 0.50 mmol) in CH_2Cl_2 (20 mL) was added 4-trifluoromethylbenzoyl chloride (1.56 g, 7.5 mmol) at 0 ^oC and the mixture was stirred at room temperature for 3 h. The reaction mixture was poured into water (20 mL), and extracted with Et_2O (20 mL$\times$3). The combined organic layer was dried over $MgSO_4$. The organic solvent was removed under reduced pressure and the residue was subjected to flash

column chromatography on silica gel with hexane/AcOEt (v/v = 20/1-7/1) as eluents to afford 2-(cyanomethyl)phenyl 4'-trifluoromethylbenzoate **1a** (1.22 g, 4.0 mmol, 80% yield) as a white solid. mp 62.1-62.8 ^{o}C. IR (KBr): 751, 758, 771, 862, 1016, 1074, 1126, 1171, 1219, 1269, 1328, 1415, 1493, 1736 (C=O), 2259 (CN), 2945, 2981, 3062 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.66 (s, 2H), 7.28 (d, J = 7.6 Hz, 1H), 7.30 (t, J = 7.6 Hz, 1H), 7.41 (t, J = 7.6 Hz, 1H), 7.47 (d, J = 7.6 Hz, 1H), 7.77 (d, J = 8.0 Hz, 2H), 8.32 (d, J = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.1, 116.7, 122.4, 122.5, 123.3 (q, J = 272.5 Hz), 125.6 (q, J = 3.3 Hz), 126.8, 129.5, 129.6, 130.5, 131.7, 135.1 (q, J = 32.3 Hz), 148.3, 163.0. Anal. calcd for $C_{16}H_{10}F_3NO_2$: C, 62.96; H, 3.30. found: C, 62.82; H, 3.41.

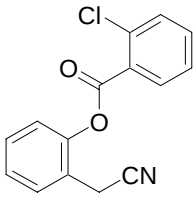


2-(Cyanomethyl)phenyl 4'-fluorobenzoate (1b): A white solid; mp 31.8-32.2 ^{o}C. IR (KBr): 756, 779, 853, 1011, 1061, 1096, 1150, 1170, 1198, 1217, 1267, 1413, 1456, 1504, 1603, 1733 (C=O), 2262 (CN), 2943, 2973 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.65 (s, 2H), 7.17 (d, J = 8.8 Hz, 2H), 7.26 (d, J = 7.6 Hz, 1H), 7.28 (t, J = 7.6 Hz, 1H), 7.40 (t, J = 7.6 Hz, 1H), 7.46 (d, J = 7.6 Hz, 1H), 8.22 (d, J = 8.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.0, 115.7, 115.9, 116.7, 122.5, 122.6, 124.7 (d, J = 3.3 Hz), 126.5, 129.4 (d, J = 8.2 Hz), 132.8 (d, J = 9.9 Hz), 148.4, 163.1, 166.1 (d, J = 255.9 Hz). Anal. calcd for $C_{15}H_{10}FNO_2$: C, 70.58; H, 3.95. found: C, 70.60; H, 3.99.

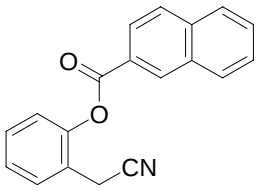


2-(Cyanomethyl)phenyl 4'-chlorobenzoate (1c): A white solid; mp 67.8-68.0 ^{o}C. IR (KBr): 759, 849, 955, 1012, 1095, 1170, 1220, 1275, 1401, 1456, 1492, 1594, 1722 (C=O), 2251 (CN), 2906, 2932 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.64 (s, 2H), 7.24 (d, J = 7.8 Hz, 1H), 7.28 (t, J = 7.3 Hz, 1H), 7.40 (t, J = 7.3 Hz, 1H), 7.46 (d, J = 7.8 Hz, 1H), 7.47 (d, J = 8.3 Hz, 2H),

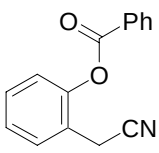
8.13 (d, J = 8.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.0, 116.7, 122.5, 122.6, 126.6, 126.9, 129.0, 129.5, 129.6, 131.5, 140.4, 148.4, 163.4. Anal. calcd for $C_{15}H_{10}ClNO_2$: C, 66.31; H, 3.71. found: C, 66.11; H, 3.83.



2-(Cyanomethyl)phenyl 2'-chlorobenzoate (1d): A white solid; mp 65.8-66.2 ^{o}C. IR (KBr): 756, 868, 947, 1032, 1099, 1172, 1220, 1243, 1401, 1456, 1492, 1594, 1722 (C=O), 2251 (CN), 2906, 2932 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.74 (s, 2H), 7.26-7.36 (m, 2H), 7.38-7.46 (m, 2H), 7.50-7.57 (m, 3H), 8.09 (d, J = 7.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.3, 116.9, 122.6, 122.7, 126.8, 126.9, 128.4, 129.6, 129.7, 131.5, 132.1, 133.7, 134.5, 148.5, 163.3. Anal. calcd for $C_{15}H_{10}ClNO_2$: C, 66.31; H, 3.71. found: C, 66.29; H, 3.58.

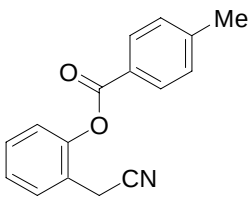


2-(Cyanomethyl)phenyl 2'-naphthoate (1e): A colorless oil; IR (neat): 761, 775, 825, 951, 1059, 1098, 1128, 1172, 1190, 1218, 1281, 1415, 1456, 1492, 1630, 1735 (C=O), 2251 (CN), 2942, 2968 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.70 (s, 2H), 7.28-7.32 (m, 2H), 7.42 (d, J = 7.6 Hz, 1H), 7.50 (d, J = 7.6 Hz, 1H), 7.56 (t, J = 7.6 Hz, 1H), 7.62 (t, J = 7.6 Hz, 1H), 7.89 (d, J = 8.4 Hz, 1H), 7.93 (d, J = 8.4 Hz, 1H), 7.98 (d, J = 8.4 Hz, 1H), 8.18 (d, J = 8.4 Hz, 1H), 8.81 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.1, 116.9, 122.7, 122.8, 125.2, 125.7, 126.6, 126.9, 127.8, 128.6, 128.9, 129.4, 129.5, 129.6, 132.2, 132.4, 135.9, 148.7, 164.5. Anal. calcd for $C_{19}H_{13}NO_2$: C, 79.28; H, 4.67. found: C, 79.43; H, 4.56.

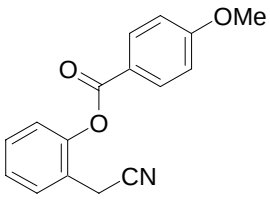


2-(Cyanomethyl)phenyl benzoate (1f): A white solid; mp 39.8-40.1 ^{o}C. IR (KBr): 751, 842, 1024, 1064, 1078, 1105, 1172, 1223, 1268, 1417, 1452, 1494, 1600, 1733 (C=O), 2255 (CN), 2963, 2975, 3061 cm^{-1}. ^{1}H NMR (400 MHz,

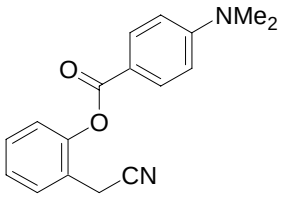
$CDCl_3$): δ3.65 (s, 2H), 7.23 (d, J = 8.0 Hz, 1H), 7.28 (t, J = 7.2 Hz, 1H), 7.39 (t, J = 8.0 Hz, 1H), 7.49 (t, J = 8.0 Hz, 2H), 7.52 (d, J = 8.0 Hz, 1H), 7.64 (t, J = 8.0 Hz, 1H), 8.21 (d, J = 7.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ19.1, 116.8, 122.6, 122.7, 126.5, 128.4, 128.6, 129.3, 129.4, 130.4, 133.9, 148.5, 164.1. Anal. calcd for $C_{15}H_{11}NO_2$: C, 75.94; H, 4.67. found: C, 76.18; H, 4.71.



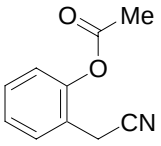
2-(Cyanomethyl)phenyl 4'-methylbenzoate (1g): A white solid; mp 44.8-45.3 ^{o}C. IR (KBr): 744, 837, 1019, 1072, 1103, 1170, 1221, 1269, 1417, 1457, 1493, 1610, 1735 (C=O), 2255 (CN), 2926, 2938 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ2.44 (s, 3H), 3.65 (s, 2H), 7.22-7.28 (m, 2H), 7.31 (d, J = 8.0 Hz, 2H), 7.41 (t, J = 7.6 Hz, 1H), 7.48 (t, J = 7.6 Hz, 1H), 8.10 (d, J = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ19.0, 21.6, 116.9, 122.7, 122.8, 125.7, 126.4, 129.2, 129.3, 129.4, 130.2, 144.9, 148.7, 164.3. Anal. calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21. found: C, 76.76; H, 5.21.



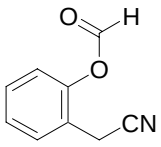
2-(Cyanomethyl)phenyl 4'-methoxybenzoate (1h): A white solid; mp 79.0-80.2 ^{o}C. IR (KBr): 753, 842, 1028, 1065, 1103, 1169, 1223, 1263, 1425, 1456, 1493, 1513, 1607, 1722 (C=O), 2245 (CN), 2842, 2929, 2959 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ3.67 (s, 2H), 3.89 (s, 3H), 7.00 (d, J = 8.4 Hz, 2H), 7.25 (d, J = 7.6 Hz, 1H), 7.29 (t, J = 7.6 Hz, 1H), 7.41 (t, J = 7.6 Hz, 1H), 7.49 (d, J = 7.6 Hz, 1H), 8.17 (d, J = 8.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ19.1, 55.5, 114.0, 117.0, 120.7, 122.8, 122.9, 126.5, 129.4, 129.5, 132.4, 148.8, 164.0, 164.2. Anal. calcd for $C_{16}H_{13}NO_2$: C, 71.90; H, 4.90. found: C, 71.63; H, 4.89.



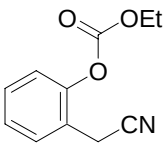
2-(Cyanomethyl)phenyl 4'-(*N*,*N*-dimethylamino)benzoate (1i): A pale yellow solid; mp 139.2-140.6 ^{o}C. IR (KBr): 761, 824, 1053, 1096, 1165, 1184, 1223, 1282, 1383, 1454, 1487, 1537, 1604, 1701 (C=O), 2247 (CN), 2826, 2925, 2960 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ3.06 (s, 6H), 3.66 (s, 2H), 6.69 (d, J = 9.2 Hz, 2H), 7.23 (d, J = 8.0 Hz, 1H), 7.26 (t, J = 8.0 Hz, 1H), 7.38 (t, J = 8.0 Hz, 1H), 7.48 (d, J = 8.0 Hz, 1H), 8.06 (d, J = 9.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ19.1, 39.9, 110.7, 114.5, 117.1, 122.8, 122.9, 126.0, 129.1, 129.2, 132.0, 148.9, 153.8, 164.4. Anal. calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75. found: C, 72.54; H, 5.86.



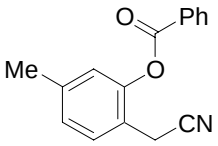
2-(Cyanomethyl)phenyl acetate (1j): A colorless oil; IR (neat): 753, 792, 830, 1011, 1095, 1171, 1202, 1370, 1417, 1456, 1492, 1588, 1768 (C=O), 2250 (CN), 2928, 2980, 3067 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ2.32 (s, 3H), 3.61 (s, 2H), 7.11 (d, J = 7.9 Hz, 1H), 7.25 (t, J = 7.9 Hz, 1H), 7.34 (t, J = 7.9 Hz, 1H), 7.40 (d, J = 7.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ18. 9, 20.6, 116.7, 122.2, 122.5, 126.2, 129.2, 129.3, 148.2, 168.4. Anal. calcd for $C_{13}H_9NO_2$: C, 68.56; H, 5.18. found: C, 68.39; H, 5.19.



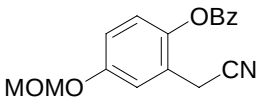
2-(Cyanomethyl)phenyl formate (1k): A colorless oil; IR (neat): 760, 830, 1085, 1116, 1172, 1215, 1415, 1457, 1493, 1589, 1740 (C=O), 2252 (CN), 2968, 3068 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ3.66 (s, 2H), 7.18 (d, J = 7.8 Hz, 1H), 7.29 (t, J = 7.8 Hz, 1H), 7.38 (t, J = 7.8 Hz, 1H), 7.47 (d, J = 7.8 Hz, 1H), 8.31 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ18.8, 116.7, 122.0, 122.1, 126.9, 129.5, 129.7, 147.4, 158.2. Anal. calcd for $C_9H_7NO_2$: C, 67.07; H, 4.38. found: C, 67.32; H, 4.64.



2-(Cyanomethyl)phenyl ethyl carbonate (1l): A colorless oil; IR (neat): 775, 897, 996, 1056, 1176, 1226, 1258, 1457, 1494, 1589, 1767 (C=O), 2251 (CN), 2986, 3068 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.38 (t, J = 7.3 Hz, 3H), 3.70 (s, 2H), 4.32 (q, J = 7.3 Hz, 2H), 7.28-7.30 (m, 2H), 7.36 (t, J = 7.8 Hz, 1H), 7.45 (d, J = 7.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 18.6, 65.2, 116.7, 122.1, 122.2, 126.6, 129.3, 129.4, 148.6, 152.7. Anal. calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40. found: C, 64.34; H, 5.43.

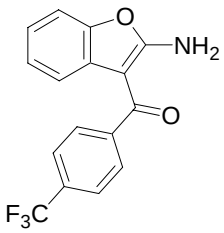


2-Cyanomethyl-5-methylphenyl benzoate (1m): A white solid; mp 74.0-74.6 ^oC. IR (neat): 712, 815, 892, 946, 1023, 1065, 1104, 1153, 1174, 1238, 1256, 1315, 1413, 1451, 1508, 1581, 1600, 1622, 1725 (C=O), 2247 (CN), 2857, 2920, 2970, 3032 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.33 (s, 3H), 3.56 (s, 2H), 7.04 (s, 1H), 7.05 (d, J = 7.3 Hz, 1H), 7.30 (d, J = 7.3 Hz, 1H), 7.47 (t, J = 7.3 Hz, 2H), 7.60 (t, J = 7.3 Hz, 1H), 8.19 (d, J = 7.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.4, 20.7, 116.9, 119.4, 123.0, 127.1, 128.5, 129.0, 129.9, 130.0, 133.7, 139.6, 148.3, 164.1. Anal. calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21. found: C, 76.52; H, 5.32.

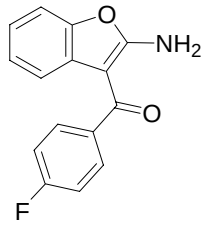


2-Cyanomethyl-4-(methoxymethoxy)phenyl benzoate (1n): A pale yellow oil; IR (neat): 709, 804, 872, 923, 1010, 1059, 1077, 1102, 1153, 1188, 1265, 1315, 1452, 1499, 1602, 1739 (C=O), 2251 (CN), 2828, 2957, 3070 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.49 (s, 3H), 3.64 (s, 2H), 5.18 (s, 2H), 7.08 (d, J = 8.3 Hz, 1H), 7.17 (s, 1H), 7.18 (d, J = 8.3 Hz, 1H), 7.53 (t, J = 7.3 Hz, 2H), 7.66 (t, J = 7.3 Hz, 1H), 8.21 (d, J = 7.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.3, 56.0, 94.7, 116.7, 117.0, 117.3, 123.6, 128.6, 128.7, 130.2, 130.3, 134.0, 143.0, 155.3, 164.7. Anal. calcd for $C_{17}H_{15}NO_4$: C, 68.68; H, 5.09. found: C, 68.52; H, 5.16.

General Procedure of Palladium-Catalyzed Cycloisomerization Reactions. A flame dried Schlenk flask was charged with $Pd(OAc)_2$ (6.7 mg, 0.030 mmol), PCy_3 (16.9 mg, 0.060 mmol), zinc powder (19.6 mg, 0.30 mmol), MS4A (30 mg), and DMF (1.2 mL). After stirring at room temperature for 20 min, 2-(cyanomethyl)phenyl ester **1** (0.30 mmol) was added and the resulting mixture was stirred at 100 ^{o}C. After the time specified in Tables 1-2, the mixture was diluted with Et_2O and filtered through a short silica gel pad. The filtrate was washed with brine, and the aqueous layer was extracted with Et_2O (10 mL × 3). The combined organic layer was dried over $MgSO_4$, and then filtered. The organic solvent was removed under reduced pressure and the residue was subjected to flash column chromatography on silica gel with hexane/AcOEt (v/v = 7/1-2/1) as eluents to afford the corresponding 3-acyl-2-aminobenzofuran **3**.

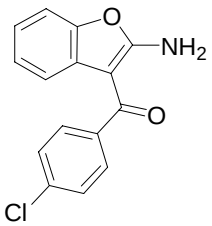


2-Amino-3-(4'-trifluoromethylbenzoyl)benzo[*b*]furan (3a): A yellow solid; mp 117.8-119.5 ^{o}C. IR (KBr): 745, 784, 854, 918, 978, 1018, 1067, 1123, 1177, 1240, 1298, 1327, 1480, 1515, 1593, 1650 (C=O), 2940, 3120, 3161, 3369 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.76 (d, J = 7.2 Hz, 1H), 7.00 (t, J = 7.6 Hz, 1H), 7.05 (t, J = 7.6 Hz, 1H), 7.20 (d, J = 7.2 Hz, 1H), 7.38 (br s, 2H), 7.74 (d, J = 8.4 Hz, 2H), 7.80 (d, J = 8.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 94.2, 110.1, 118.5, 122.2, 123.8 (q, J = 271.7 Hz), 123.9, 125.4 (q, J = 3.3 Hz), 125.6, 127.7, 132.2 (q, J = 32.2 Hz), 144.0, 149.2, 166.9, 188.8. Anal. calcd for $C_{16}H_{10}F_3NO_2$: C, 62.96; H, 3.30. found: C, 63.09; H, 3.22.

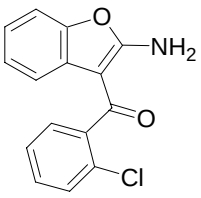


2-Amino-3-(4'-fluorobenzoyl)benzo[*b*]furan (3b): A pale yellow solid; mp 107.2-108.4 ^{o}C. IR (KBr): 745, 781, 849, 916, 977, 1021, 1095, 1153, 1177, 1240, 1298, 1336, 1478, 1509, 1599, 1644 (C=O), 2930, 3119, 3164,

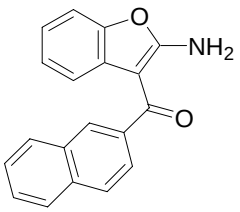
3368 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ6.91 (d, J = 6.8 Hz, 1H), 7.00-7.07 (m, 2H), 7.11-7.19 (m, 4H), 7.23 (d, J = 6.8 Hz, 1H), 7.73 (d, J = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ94.2, 110.1, 115.3 (d, J = 22.4 Hz), 118.7, 121.9, 123.7, 126.1, 129.9 (d, J = 8.3 Hz), 136.9 (d, J = 3.3 Hz), 149.1, 164.2 (d, J = 250.1 Hz), 166.5, 189.3. Anal. calcd for $C_{15}H_{10}FNO_2$: C, 70.58; H, 3.95. found: C, 70.67; H, 3.91.



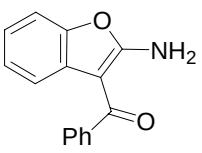
2-Amino-3-(4'-chlorobenzoyl)benzo[*b*]furan (3c): A yellow solid; mp 122.1-122.7 ^oC. IR (KBr): 750, 777, 840, 917, 975, 1016, 1095, 1173, 1241, 1337, 1437, 1477, 1591, 1614, 1642 (C=O), 3169, 3393 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ6.90 (d, J = 7.3 Hz, 1H), 7.03 (t, J = 7.8 Hz, 1H), 7.04 (t, J = 7.8 Hz, 1H), 7.09 (br s, 2H), 7.23 (d, J = 7.3 Hz, 1H), 7.46 (d, J = 8.3 Hz, 2H), 7.66 (d, J = 8.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ94.2, 110.2, 118.8, 122.1, 123.9, 128.6, 129.1, 130.9, 137.0, 139.2, 149.2, 166.7, 189.2. Anal. calcd for $C_{15}H_{10}ClNO_2$: C, 66.31; H, 3.71. found: C, 66.34; H, 3.53.



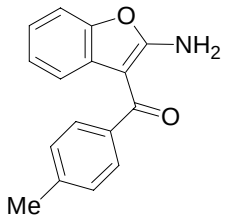
2-Amino-3-(2'-chlorobenzoyl)benzo[*b*]furan (3d): A yellow solid; mp 120.7-121.8 ^oC. IR (KBr): 741, 761, 851, 920, 979, 1018, 1098, 1181, 1238, 1338, 1442, 1495, 1594, 1614, 1656 (C=O), 3114, 3246, 3380 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ6.26 (d, J = 7.3 Hz, 1H), 6.94 (t, J = 7.3 Hz, 1H), 7.01 (t, J = 7.3 Hz, 1H), 7.20 (d, J = 7.3 Hz, 2H), 7.37 (br s, 2H), 7.42 (m, 2H), 7.50 (d, J = 7.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ95.3, 110.0, 117.9, 122.0, 124.1, 125.8, 127.1, 127.7, 130.0, 130.3, 130.5, 140.5, 149.3, 166.3, 188.0. Anal. calcd for $C_{15}H_{10}ClNO_2$: C, 66.31; H, 3.71. found: C, 66.38; H, 3.60.



2-Amino-3-(2'-naphtoyl)benzo[*b*]furan (3e): A yellow solid; mp 47.8-49.2 °C. IR (KBr): 744, 783, 812, 915, 976, 1018, 1099 1177, 1229, 1298, 1334, 1481, 1507, 1597, 1614 1647 (C=O), 2951, 3054, 3194, 3360 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ6.85-6.94 (m, 2H), 6.95 (t, *J* = 6.8 Hz, 1H), 7.11 (d, *J* = 7.6 Hz, 1H), 7.43 (br s, 2H), 7.45-7.55 (m, 2H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.86 (t, *J* = 6.8 Hz, 2H), 7.92 (d, *J* = 8.0 Hz, 1H), 8.22 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ94.4, 109.9, 118.8, 121.7, 123.6, 124.5, 126.2, 126.4, 127.2, 127.6, 127.7, 128.1, 128.7, 132.4, 134.4, 137.9, 149.0, 166.7, 190.3 Anal. calcd for $C_{19}H_{13}NO_2$: C, 79.43; H, 4.56. found: C, 79.44; H, 4.64.

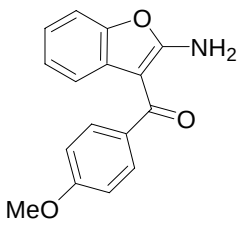


2-Amino-3-benzoylbenzo[*b*]furan (3f): A yellow solid; mp 138.9-140.3 °C. IR (KBr): 749, 762, 794, 906, 930, 974, 1017, 1104, 1173, 1185, 1243, 1300, 1338, 1437, 1481, 1596, 1618, 1645 (C=O), 2938, 3054, 3153, 3207, 3410 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ6.85 (d, *J* = 7.2 Hz, 1H), 6.95-7.02 (m, 2H), 7.18 (d, *J* = 7.2 Hz, 1H), 7.33 (br s, 2H), 7.45-7.53 (m, 3H), 7.75 (d, *J* = 6.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ94.6, 109.8, 118.7, 121.7, 123.5, 126.1, 127.2, 128.2, 130.6, 140.8, 149.0, 166.5, 191.0. Anal. calcd for $C_{15}H_{11}NO_2$: C, 75.94; H, 4.67. found: C, 76.11; H, 4.66.

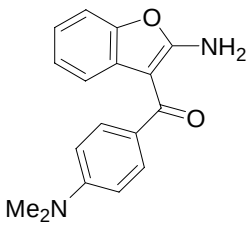


2-Amino-3-(4'-methylbenzoyl)benzo[*b*]furan (3g): A yellow solid; mp 108.6-109.2 °C. IR (KBr): 746, 776, 833, 914, 971, 1018, 1100, 1175, 1242, 1298, 1332, 1439, 1479, 1596, 1610, 1646 (C=O), 2946, 3190, 3205, 3364 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ2.42 (s, 3H), 6.98 (d, *J* = 8.0 Hz, 1H), 6.97-7.03 (m, 2H), 7.17-7.19 (m, 1H), 7.21 (br s, 2H), 7.26 (d, *J* = 7.6 Hz, 2H), 7.62 (d, *J* = 7.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ21.5, 94.2, 109.9, 119.0, 121.7, 123.6, 126.4, 127.6, 128.9, 138.0, 141.2, 149.1, 166.6, 190.7. Anal. calcd for $C_{16}H_{13}NO_2$: C, 76.48;

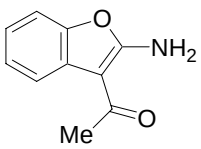
H, 5.21. found: C, 76.64; H, 5.20.



2-Amino-3-(4'-methoxybenzoyl)benzo[*b*]furan (3h): A yellow solid; mp 115.8-116.5 ^{o}C. IR (KBr): 743, 780, 844, 915, 975, 1025, 1103, 1170, 1185, 1245, 1299, 1337, 1437, 1482, 1589, 1605, 1647 (C=O), 2940, 3046, 3192, 3247, 3379 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.84 (s, 3H), 6.97 (d, J = 7.2 Hz, 1H), 6.95-7.02 (m, 4H), 7.18-7.21 (m, 1H), 7.27 (br s, 2H), 7.74 (d, J = 7.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.3, 94.5, 109.8, 113.3, 118.8, 121.5, 123.4, 126.4, 129.6, 133.3, 149.0, 161.6, 166.4, 190.1. Anal. calcd for $C_{16}H_{13}NO_3$: C, 71.90; H, 4.90. found: C, 71.67; H, 4.90.

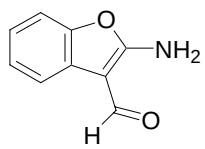


2-Amino-3-(4'-*N*,*N*-dimehylaminobenzoyl)benzo[*b*]furan (3i): A yellow solid; mp 54.2-55.8 ^{o}C. IR (KBr): 744, 780, 825, 914, 970, 1018, 1100, 1174, 1186, 1248, 1298, 1337, 1430, 1476, 1601, 1646 (C=O), 2952, 3195, 3218, 3385 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.05 (s, 6H), 6.71 (d, J = 7.2 Hz, 2H), 6.89 (br s, 2H), 7.00-7.08 (m, 2H), 7.23-7.25 (m, 2H), 7.75 (d, J = 7.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 40.1, 94.4, 109.8, 110.7, 119.3, 121.3, 123.4, 127.0, 128.0, 130.0, 149.1, 152.5, 166.0, 190.1. Anal. calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75. found: C, 72.54; H, 5.75.

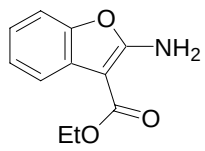


3-Acetyl-2-aminobenzo[*b*]furan (3j): A yellow solid; mp 171.2-172.3 ^{o}C. IR (KBr): 739, 753, 940, 1024, 1103, 1179, 1236, 1299, 1326, 1362, 1422, 1442, 1494, 1605, 1656 1676 (C=O), 2946, 3072, 3168, 3222, 3384 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.55 (s, 3H), 6.84 (br s, 2H), 7.10 (t, J = 7.6 Hz, 1H), 7.25 (t, J = 7.6 Hz, 1H), 7.26 (d, J = 7.6 Hz, 1H), 7.48 (d, J = 7.6 Hz, 1H). ^{13}C NMR (100 MHz,

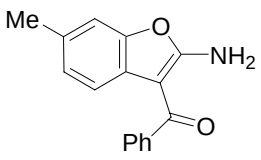
$CDCl_3$): δ29.5, 95.2, 110.2, 118.3, 121.6, 124.1, 126.4, 149.1, 164.8, 192.7. Anal. calcd for $C_{10}H_9NO_2$: C, 68.56; H, 5.18. found: C, 68.29; H, 5.02.



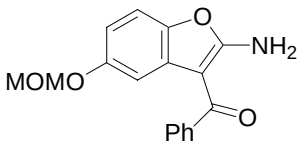
2-Amino-3-formylbenzo[*b*]furan (3k): A white solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ6.78 (br s, 2H), 6.93-7.33 (m, 3H), 7.68-7.71 (m, 1H), 9.91 (s, 1H). The spectral data match those reported in the literature.[19]



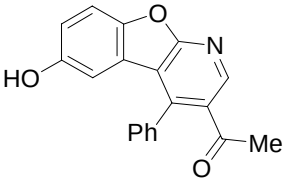
2-Amino-3-ethoxycarbonylbenzo[*b*]furan (3l): A white solid; mp 69.2-69.8 ^{o}C. IR (KBr): 746, 785, 969, 1039, 1123, 1173, 1240, 1298, 1321, 1368, 1434, 1487, 1535, 1628, 1664 (C=O), 2931, 2984, 3149, 3274, 3414 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ1.42 (t, J = 7.3 Hz, 3H), 4.37 (q, J = 7.3 Hz, 2H), 6.03 (br s, 2H), 7.05 (t, J = 7.8 Hz, 1H), 7.16-7.26 (m, 2H), 7.65 (d, J = 7.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ14.5, 59.7, 84.6, 109.6, 119.3, 121.4, 124.0, 126.8, 149.1, 164.5, 166.2. Anal. calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40. found: C, 64.37; H, 5.49.



2-Amino-3-benzoyl-6-methylbenzo[*b*]furan (3m): A yellow solid; mp 123.1-123.9 ^{o}C. IR (KBr): 762, 807, 899, 937, 983, 1033, 1111, 1156, 1209, 1254, 1336, 1364, 1477, 1504, 1590, 1629, 1659 (C=O), 2859, 3177 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ2.33 (s, 3H), 6.75 (d, J = 7.8 Hz, 1H), 6.80 (d, J = 7.8 Hz, 1H), 7.01 (s, 1H), 7.18 (br s, 2H), 7.42-7.56 (m, 3H), 7.69 (d, J = 7.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ21.2, 94.2, 110.5, 118.5, 123.5, 124.5, 127.4, 128.2, 130.7, 131.9, 140.9, 149.5, 166.5, 190.5. Anal. calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21. found: C, 76.52; H, 5.32.

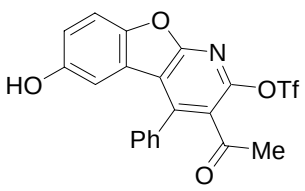


2-Amino-3-benzoyl-4-(methoxymethoxy)benzo[*b*]furan (3n): A yellow solid; mp 118.9-119.7 °C. IR (KBr): 756, 797, 920, 1023, 1079, 1152, 1175, 1246, 1342, 1480, 1593, 1651(C=O), 2942, 3111, 3325 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ3.40 (s, 3H), 4.98 (s, 2H), 6.55 (d, J = 2.5 Hz, 1H), 6.74 (dd, J = 2.5, 8.8 Hz, 1H), 7.06 (br s, 2H), 7.11 (d, J = 8.8 Hz, 1H), 7.49 (d, J = 6.8 Hz, 1H), 7.49-7.55 (m, 1H), 7.69 (d, J = 6.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ55.8, 94.7, 95.4, 107.6, 110.2, 110.7, 127.2, 127.4, 128.3, 130.9, 140.7, 144.8, 154.0, 167.1, 190.7. Anal. calcd for $C_{17}H_{15}NO_4$: C, 68.68; H, 5.09. found: C, 68.61; H, 5.11.



Synthesis of Elbfluorene (7): To a solution of 2-amino-3-benzoyl-4-(methoxymethoxy)benzo[*b*]furan **3n** (595 mg, 2.0 mmol), diketene (0.19 mL, 2.4 mmol) in CH_3CN (6.0 mL) were added dropwise a solution of trimethylchlorosilane (0.30 mL, 2.4 mmol) in CH_3CN (6 mL) at 50 °C over 12 h. After being stirred additionally for 2 h, the reaction mixture was poured into sat. $NaHCO_3$ aqueous solution. The aqueous layer was extracted with Et_2O (20 mL x 3). The combined organic layer was washed with brine and dried over $MgSO_4$. The organic solvent was removed under reduced pressure to afford **4** (2:1 mixture of two tautomers) as a brown oil. ^1H NMR (400 MHz, $CDCl_3$): δ2.06 (s, 3H), 2.35 (s, 3H), 3.39 (s, 6H), 3.76 (s, 2H), 5.00 (s, 4H), 5.37 (s, 1H), 6.67-6.71 (m, 2H), 6.91-6.94 (m, 2H), 7.39-7.44 (m, 2H), 7.48-7.60 (m, 8H), 7.72-7.78 (m, 4H), 10.9 (s, 1H), 11.7 (s, 1H), 13.3 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ21.8, 30.8, 50.9, 55.8, 62.5, 91.7, 94.6, 95.2, 99.8, 101.0, 107.9, 108.0, 111.8, 111.9, 113.2, 113.5, 124.8, 124.9, 127.9, 128.2, 128.3, 128.4, 128.5, 130.0, 132.0, 132.2, 133.6, 139.0, 139.3, 146.0, 146.1, 154.3, 154.4, 156.9, 158.6, 162.9, 168.5, 178.8, 191.9, 192.2, 202.0. To a solution of **4** in MeOH (4 mL) was added sodium methoxide (130 mg, 2.4 mmol), and the resulting mixture was stirred at room temperature for 8 h, then the reaction

was quenched by adding excess of 10% NH_4Cl aqueous solution. The aqueous layer was extracted with Et_2O (20 mL×3). The combined organic layer was washed with brine and dried over $MgSO_4$. After the organic solvent was removed under reduced pressure, the resulting mixture diluted with CH_2Cl_2 (8 mL) was slowly added to pyridine (0.19 mL, 2.4 mmol) and trifluoromethanesulfonic anhydride (0.40 mL, 2.4 mmol) at -78 °C. After stirring for 1 h at -78 °C, the resulting solution was gradually warmed up to room temperature and then stirred additionally for 1 h. The solution was washed with sat. NH_4Cl aqueous solution, and the aqueous layer was extracted with Et_2O (10 mL×3). The combined organic layer was washed with brine and dried over $MgSO_4$. The organic solvent was removed under reduced pressure and the residue was subjected to flash column chromatography on silica gel with hexane/AcOEt (v/v = 50/1) as eluents to afford **6** (555 mg, 1.12 mmol, 56% (three steps from 2n)) as a pale yellow oil. IR (KBr): 704, 756, 916, 1002, 1074, 1149, 1194, 1251, 1378, 1474, 1557, 1585, 1700 (C=O), 2853, 2925, 3090 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.15 (s, 3H), 3.41 (s, 3H), 5.02 (s, 2H), 6.86 (d, J = 2.4 Hz, 1H), 7.22-7.23 (m, 1H), 7.48-7.51 (m, 2H), 7.56 (d, J = 8.8 Hz, 1H), 7.61-7.63 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 32.0, 55.9, 95.4, 109.8, 112.9, 115.9, 118.5 (q, J = 320.7 Hz), 119.0, 121.7, 124.4, 128.5, 129.4, 130.3, 133.6, 147.1, 148.5, 151.0, 153.9, 160.3, 198.4. HRMS (FAB) calcd for $M+H^+$ of $C_{22}H_{16}F_3NO_7S$ 496.0678, found 496.0677. To a solution of **6** (248 mg, 0.50 mmol) in THF (2 mL) was added 10% HCl aqueous solution, and the mixture was stirred at 50 °C for 8 h. The reaction mixture was poured into sat. $NaHCO_3$ aqueous solution, and then the aqueous layer was extracted with Et_2O (50 mL×3). The combined organic layer was washed with brine and dried over $MgSO_4$. The organic solvent was removed under reduced pressure and the residue was subjected to flash column chromatography on silica gel with hexane/AcOEt (v/v = 10/1) as eluents to afford triflate **11** (176 mg, 0.39 mmol, 78%) as a



11

pale yellow solid. mp 203.4-204.8 °C. IR (KBr): 796, 812, 839, 903, 1023, 1134, 1168, 1218, 1293, 1375, 1421, 1497, 1588, 1699 (C=O), 3056, 3558 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.13 (s, 3H), 5.00 (br s, 1H), 6.60 (d, J = 2.4 Hz, 1H), 7.01 (dd, J = 2.4, 8.8 Hz, 1H), 7.45-7.52 (m, 3H), 7.59-7.62 (m, 3H). ^{13}C NMR (100 MHz, d_6-acetone): δ 32.1, 108.3, 113.7, 117.1, 119.4 (q, J = 320.7 Hz), 118.8, 122.6, 125.3, 129.5, 130.3, 131.0, 134.8, 148.3, 149.0, 150.4, 155.1, 161.0, 198.7. HRMS (FAB) calcd for $M+H^+$ of $C_{20}H_{12}F_3NO_6S$ 452.0416, found 452.0412. A flame dried Schlenk flask was charged with $Pd(OAc)_2$ (2.0 mg, 0.0090 mmol), dppf (5.0 mg, 0.0090 mmol), **11** (135 mg, 0.30 mmol), triethylsilane (0.070 ml, 0.45 mmol), and DMF (1.2 mL). After stirring at 70 °C for 3 h, the mixture was diluted with Et_2O and filtered through a short silica gel pad. The filtrate was washed with brine, and the aqueous layer was extracted with Et_2O (10 mL × 3). The combined organic layer was dried over $MgSO_4$, and then filtered. The organic solvent was removed under reduced pressure and the residue was subjected to flash column chromatography on silica gel with hexane/acetone (v/v = 10/1) as eluents to afford Elbfluorene **7** (87.0 mg, 0.29 mmol, 96%) as a white solid. mp 234.8-235.6 °C. IR (KBr): 706, 738, 835, 910, 978, 1037, 1106, 1146, 1184, 1228, 1248, 1282, 1355, 1410, 1471, 1586, 1692 (C=O), 2873, 3146 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.12 (s, 3H), 4.98 (br s, 1H), 6.48 (d, J = 2.4 Hz, 1H), 7.00 (dd, J = 2.4, 8.8 Hz, 1H), 7.43-7.47 (m, 2H), 7.50 (d, J = 8.8 Hz, 1H), 7.58-7.62 (m, 3H), 8.75 (s, 1H). ^{13}C NMR (100 MHz, d_6-acetone): δ 30.7, 108.7, 113.2, 116.1, 118.0, 123.5, 129.3, 129.9, 130.0, 132.6, 137.1, 145.9, 147.8, 149.8, 154.6, 165.1, 200.0. HRMS (FAB) calcd for $M+H^+$ of $C_{19}H_{13}NO_3$ 304.0974, found 304.0966.

X-ray Crystallographic Studies of 3a. Yellow crystals of 3a suitable for X-ray analysis were obtained by recrystallization from $CHCl_3$/hexane. The single crystal was sealed in a Pyrex glass capillary under N_2 atmosphere and used for data collection. All measurements were made on a Rigaku RAXIS imaging plate area detector with graphite monochromated Mo-Kα radiation. Details of crystal and data collection parameters are summarized in Table 3. The positions of non-hydrogen atoms were determined by direct methods (SIR97) and subsequent Fourier syntheses (DIRDIF PATTY). An ORTEP drawing of **3a** is shown in Figure 1.

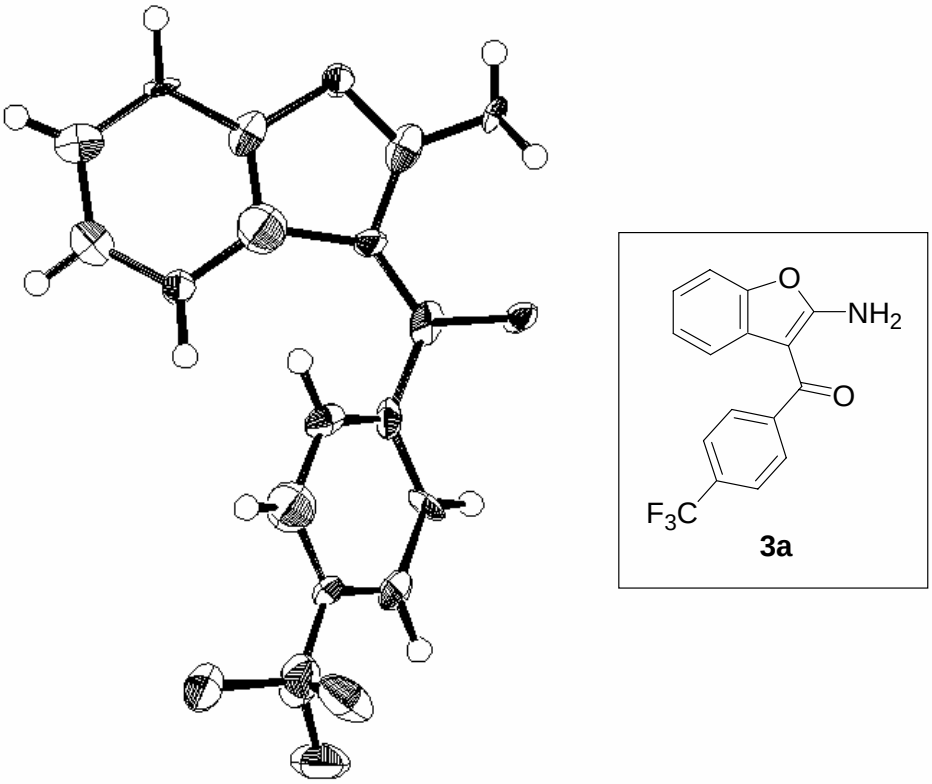


Figure 1. ORTEP drawing of **3a**.

Table 3. Summary of Crystallographic Data of **3a**

Empirical formula: $C_{16}H_{10}F_3NO_2$

Formula weight: 305.26

Crystal system: monoclinic

Space group: P21/n (#14)

Crystal color: yellow

Lattice parameters:

a (Å) = 9.129(6), b (Å) = 29.139(19), c (Å) = 20.733(14),

V (Å^3) = 5494(6), $\alpha = \beta = 90^o$, $\gamma = 95.000(3)^o$

Z = 16

D_{calc} (g cm^{-3}): 1.476

μ (Mo K α) (cm^{-1}): 1.249

Goodness of fit (GOF) = 1.001

F(000): 632

Diffractometer: Rigaku RAXIS-RAPID

Radiation: MoK α (λ = 0.71070 Å), Graphite Monochromated

Temp (^{o}C): -150

Scan type: ω–2 θ

Max. 2 θ (^{o}): 55.0

No. of reflections measured total: 21191

No. of observns ($I > 3.00\ \sigma(I)$): 9597

Structure solution: Direct Methods (SIR92)

Refinement: Full-Matrix Least-Squares on F

No. of variables: 829

Reflection/parameter ratio: 11.58

Residuals: R = 0.0786, R_{int} = 0.059, R_w = 0.1390

Max Shift/Error in Final Cycle: 0.00

Maximum peak in Final Diff Map (e (Å^{-3}): 1.39

Minimum peak in Final Diff Map (e (Å^{-3}): -1.44

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Chapter 6

Palladium-catalyzed Three-component Coupling Reactions of 2-(Cyanomethyl)phenol, Aryl Halides, and CO

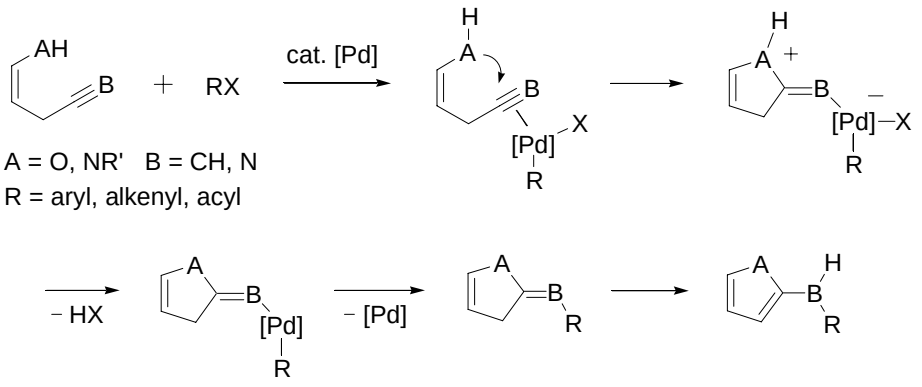
Abstract

Palladium-catalyzed three-component coupling reactions of 2-(cyanomethyl)phenol, aryl halides, and CO gave 3-acyl-2-aminobenzofurans. In this reaction, 2-(cyanomethyl)phenyl esters, which are produced via the $Pd(PPh_3)_4$-catalyzed alkoxycarbonylation of aryl halides with 2-(cyanomethyl)phenol, undergo in situ cycloisomerization reaction catalyzed by $Pd(PCy_3)_2$ as a co-catalyst to give 3-acyl-2-aminobenzofurans. Bases play an important role in this catalytic reaction, and two types of products were obtained. In the presence of Et_3N as a base, 3-acyl-2-aminobenzofurans were obtained through the three-component coupling reactions, while in the presence of K_2CO_3, 3-acyl-2-(*N*-acylamino)benzofurans were obtained as a major product. Because 2-(cyanomethyl)phenols can be synthesized from commercially available salicylic acids in two steps, the present method provides a facile access to synthetically useful 3-acyl-2-aminobenzofurans, which are useful building blocks for the synthesis of benzofuran-fused *N*-heterocycles.

Introduction

Cascade reactions provide an efficient access to structurally complex molecules from simple and readily available starting materials.[1] These reactions often involve inter- and intramolecular multibond-forming processes with simple operation, and thus minimize requisite reagents, cost, byproducts, time, and separation processes for the desired transformation. Among them, transition metal-catalyzed cascade reactions involving cyclization of alkynes have proven to be one of the most powerful methods to construct a wide variety of carbo- and heterocycles.[1,2] In particular, there have been many reports on palladium-catalyzed synthesis of heterocycles via cyclization of alkynes, which possess nucleophilic oxygen or nitrogen moieties in close proximity to the carbon-carbon triple bonds, followed by coupling reaction with aryl, alkenyl, and acid halides (Scheme 1; B = CH).[3] In contrast to reactions of alkynes, only a few examples on analogous reactions of nitriles have been reported (Scheme 1; B = N).[4] To the best of his knowledge, the reported examples are limited to transition metal-catalyzed cascade reactions involving two-component coupling

Scheme 1

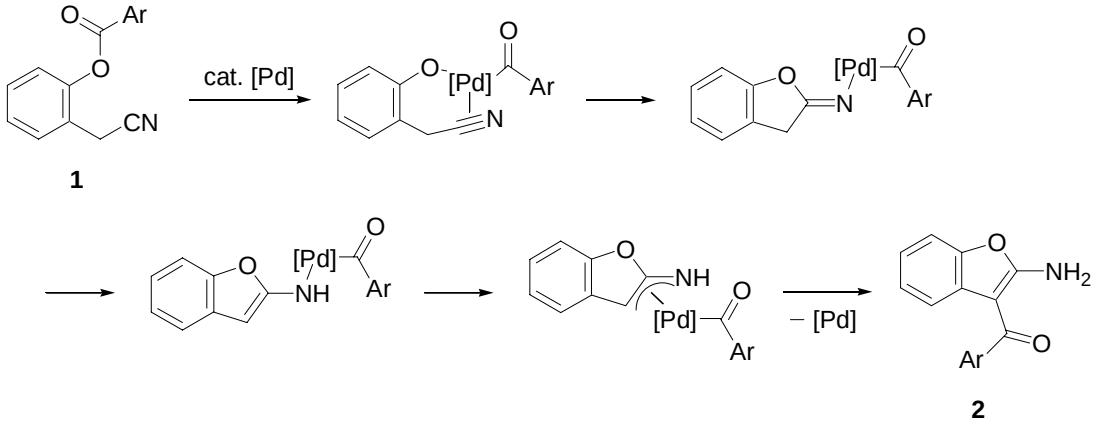


reactions of nitriles,[5,6] while there is no example of three-component coupling reactions leading to heterocycles.[7,8] Therefore, the development of such a cascade reaction of nitriles might be a significant contribution to organic synthesis, as it allows a rapid construction of

complicated molecules having carbon-carbon and carbon-heteroatom bonds.[9]

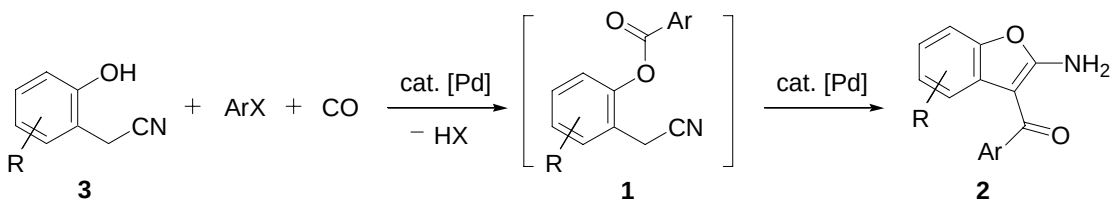
As described in Chapter 5, the author found a novel palladium-catalyzed cycloisomerization of 2-(cyanomethyl)phenyl esters **1** leading to the formation of 3-acyl-2-aminobenzofurans **2**.[10] The reaction involves oxidative cleavage of an acyl-oxygen bond of esters by a low-valent palladium complex, and subsequent intramolecular oxypalladation of a cyano moiety followed by isomerization via aza-π-allyl palladium complex (Scheme 2).

Scheme 2



Since 3-acyl-2-aminobenzofurans **2** have both an amino and a carbonyl group, they are useful building blocks for the synthesis of various benzofuran-fused heterocycles. The author envisioned that three-component coupling reactions of 2-(cyanomethyl)phenol **3**, aryl halides, and CO can be an efficient and straightforward synthetic method for **2** (Scheme 3).[11,12] In the course of investigation, the author found a unique cooperative catalytic system consisting of two different palladium complexes, which promoted the three-component

Scheme 3

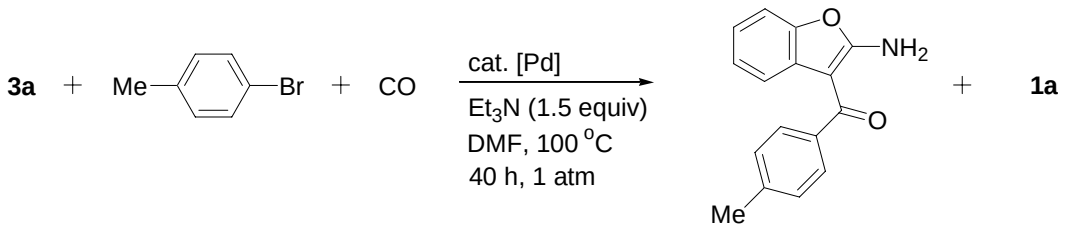


coupling reactions of nitriles, aryl halides, and CO.[13,14]

Results and Discussion

First, the palladium-catalyzed three-component coupling reaction of 2-(cyanomethyl)phenol **3a** and 1.5 equiv of 4-bromotoluene in the presence of 1.5 equiv of Et_3N in DMF at 100 ^oC under a CO atmosphere for 40 h was examined. Although $Pd(PCy_3)_2$ was effective for the cycloisomerization of 2-(cyanomethyl)phenyl ester **1a** into **2a** as described in Chapter 5, it was totally ineffective in the three-component coupling reaction even when $Zn(OAc)_2$ was used as an additive (Scheme 4).[10] However, when the reaction was carried out in the presence of 5 mol% of $Pd(PCy_3)_2$ and 5 mol% of $Pd(PPh_3)_4$, **2a** was formed in 28% yield along with **1a** in 42% yield.[13]

Scheme 4

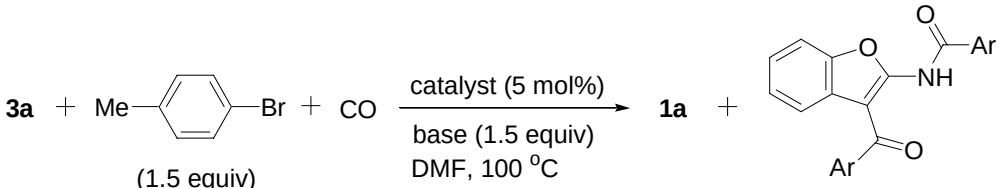


2a

$Pd(PCy_3)_2$ (10 mol%), $Zn(OAc)_2$	0%	0%
$Pd(PCy_3)_2$ (5 mol%), $Pd(PPh_3)_4$ (5 mol%)	28%	42%

Since the author has already found that $Pd(PCy_3)_2$ was the most effective catalyst for the cycloisomerization of **1a** to **2a**,[10] he next optimized the reaction condition for alkoxy-carbonylation of 4-bromotoluene with **3a** and CO. Results are summarized in Table 1.

Table 1. Pd-catalyzed alkoxycarbonylation of 4-bromotoluene with **3a** and CO[a]



4a (Ar = 4-MeC_6H_4)

entry	catalyst	base	conv. (%)	yield (%)[b]	
				1a	**4a**
1	$Pd(OAc)_2/PPh_3$ (1:2)	Et_3N	100	91	0
2	$Pd(OAc)_2/P(o\text{-}Tol)_3$ (1:2)	Et_3N	68	34	0
3	$Pd(OAc)_2/P(t\text{-}Bu)_3$ (1:2)	Et_3N	6	0	0
4	$Pd(OAc)_2$/dppf (1:1)	Et_3N	100	82	0
5	$Pd(OAc)_2$/DPEphos (1:1)	Et_3N	100	92	0
6	$Pd(PPh_3)_4$	Et_3N	100	94	0
7	$Pd(PPh_3)_4$	$i\text{-}Pr_2EtN$	100	94	0
8	$Pd(PPh_3)_4$	pyridine	89	63	0
9	$Pd(PPh_3)_4$	K_2CO_3	83	68	9
10	$Pd(PPh_3)_4$	NaOEt	100	79	4
11[c]	$Pd(PPh_3)_4$	Et_3N	100	94	0

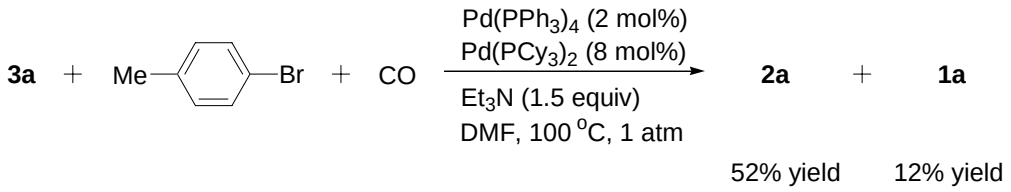
[a]Reaction conditions: **3a** (0.20 mmol), ArBr (0.30 mmol), Et_3N (0.30 mmol), catalyst (0.01 mmol) in DMF (0.8 mL) under CO (1atm). [b]Isolated yields. [c]$Pd(PPh_3)_4$ (2 mol%).

When three-component coupling reaction of **3a**, 4-bromotoluene, and CO was carried out using the combination of 5 mol% of $Pd(OAc)_2$ and 10 mol% of PPh_3 as a catalyst, **1a** was obtained in 91% yield (entry 1). Although changing PPh_3 to more sterically hindered $P(o\text{-}Tol)_3$ and basic $P(t\text{-}Bu)_3$ deterred the carbonylation reaction, bidentate ligands such as dppf and DPEphos gave **1a** in 82% and 92% yields, respectively (entries 2-5). Among the catalysts screened, $Pd(PPh_3)_4$ showed the best catalytic activity for the alkoxycarbonylation to afford **1a** in 94% yield (entry 6). Next, various bases were examined when $Pd(PPh_3)_4$ was used as a catalyst. $i\text{-}Pr_2EtN$ was comparably effective to afford **1a** in 94% yield, while pyridine, K_2CO_3, and NaOEt were less effective, affording **1a** in moderate yields (entries 7-10). It should be noted that a small amount of 3-acyl-2-(*N*-acylamino)benzofuran **4a** was

obtained together with **1a**, when inorganic bases such as K_2CO_3 and NaOEt were used (entries 9 and 10). However, the formation of 3-acyl-2-aminobenzofuran **2a** was not observed at all in all the conditions listed in Table 1. These results show that the combination of $Pd(PPh_3)_4$ as a catalyst and Et_3N as a base was most effective for the alkoxycarbonylation of 4-bromotoluene with **3a** and CO. In addition, the alkoxycarbonylation proceeded successfully even when the loading of $Pd(PPh_3)_4$ was decreased to 2 mol% (entry 11).

Finally, when the author carried out the three-component coupling reaction of **3a**, 4-bromotoluene, and CO using $Pd(PPh_3)_4$ (2 mol%) and $Pd(PCy_3)_2$ (8 mol%), he obtained **2a** in 52% yield (Scheme 5).

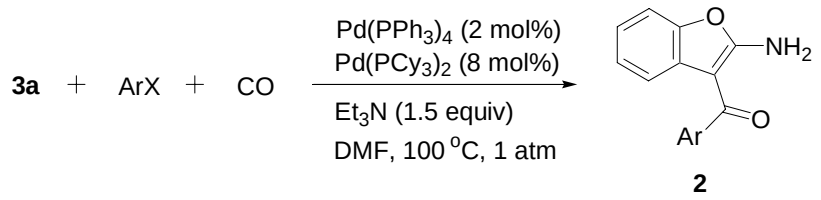
Scheme 5



Under the optimized reaction conditions (1.5 equiv of aryl bromide, 2 mol % of $Pd(PPh_3)_2$, 8 mol % of $Pd(PCy_3)_2$, and 1.5 equiv of Et_3N in DMF at 100 °C under 1 atm of CO), the substrate scope was examined using several aryl halides. The results are summarized in Table 2. The reactions with aryl bromides having electron-withdrawing groups such as trifluoromethyl and chloro groups at the para positions afforded the corresponding 3-acyl-2-aminobenzofurans **2b** and **2c** in 84% and 74% yields, respectively (entries 1-2). A substituent at an ortho position such as a chloro group did not deter the reaction (entry 3). Three-component coupling reaction described here was also applicable to aryl halides having either moderately electron-withdrawing or electron-donating substituents, although a relatively longer reaction time was required for the completion of reactions (entries 4-6).

Although a coupling reaction with 4-bromoanisole was sluggish to give a small amount of 3-acyl-2-aminobenzofuran **2h**, the yield was improved up to 42% yield using 4-iodoanisole instead of 4-bromoanisole (entries 7 and 8).

Table 2. Pd-catalyzed three-component coupling reactions using aryl halides, **3a**, and CO leading to 3-acyl-2-aminobenzofurans[a]



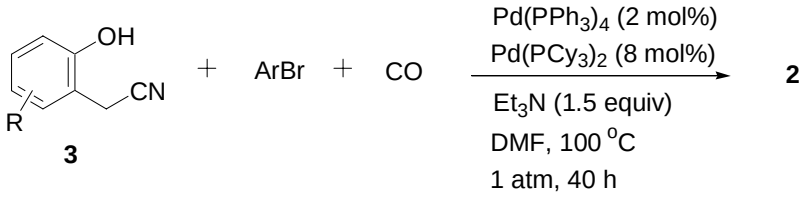
2

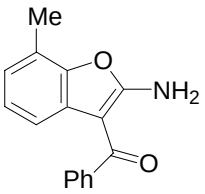
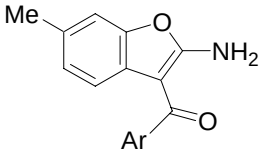
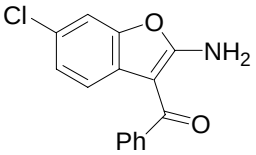
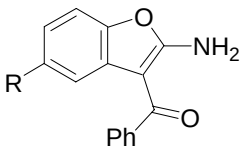
entry	Ar	X	time (h)	product	yield (%)[b]
1	4-$CF_3C_6H_4$	Br	20	**2b**	84
2	4-ClC_6H_4	Br	30	**2c**	74
3	2-ClC_6H_4	Br	30	**2d**	71
4	4-FC_6H_4	Br	40	**2e**	60
5	2-Naph	Br	40	**2f**	71
6	Ph	Br	40	**2g**	57
7	4-$MeOC_6H_4$	Br	40	**2h**	7
8	4-$MeOC_6H_4$	I	40	**2h**	42

[a]Reaction conditions: **3a** (0.30 mmol), ArX (0.45 mmol), Et_3N (0.45 mmol), $Pd(PPh_3)_4$ (0.0060 mmol), and $Pd(PCy_3)_2$ in DMF (1.2 mL) under CO (1 atm).
[b]Isolated yields.

Furthermore, the substrate scope in variation of 2-(cyanomethyl)phenol was examined. As shown in Table 3, 2-(cyanomethyl)phenols possessing various substituents undergo the cascade reactions to give the corresponding 3-acyl-2-aminobenzofuran **2i-2l** in moderate to good yield (entries 1-4). It should be noted that a remote ester group of **2m** remained intact under the reaction conditions (entry 5). Silyloxy and methoxymethoxy groups were compatible with the reaction conditions to afford **2n** and **2o** in 70% and 72% yields, respectively (entries 6 and 7).

Table 3. Pd-catalyzed three-component coupling reactions leading to 3-acyl-2-aminobenzofurans[a]



entry	product		yield (%)[b]
1		**2i**	55
2		**2j** (Ar = 4-$CF_3C_6H_4$)	86
3		**2k** (Ar = Ph)	71
4		**2l**	66
5		**2m** (R = OBz)	54
6		**2n** (R = OTBDMS)	70
7		**2o** (OMOM)	72

[a]Reaction conditions: **3** (0.30 mmol), ArBr (0.45 mmol), Et_3N (0.45 mmol), $Pd(PPh_3)_4$ (0.006 mmol), and $Pd(PCy_3)_2$ (0.024 mmol) in DMF (1.2 mL) under CO (1 atm). [b]Isolated yields.

The most plausible catalytic cycle leading to 3-acyl-2-aminobenzofurans **2** is shown in Figure 1. The $Pd(PPh_3)_4$-catalyzed alkoxycarbonylation of aryl halides, CO, and phenols **3** produces 2-(cyanomethyl)phenyl esters **1** (cycle A).[15] Esters **1** then participates in the second catalytic cycle, and are converted to 3-acyl-2-aminobenzofurans **2** via cycloisomerization catalyzed by $Pd(PCy_3)_2$, which was described in Chapter 5 (cycle B).[10]

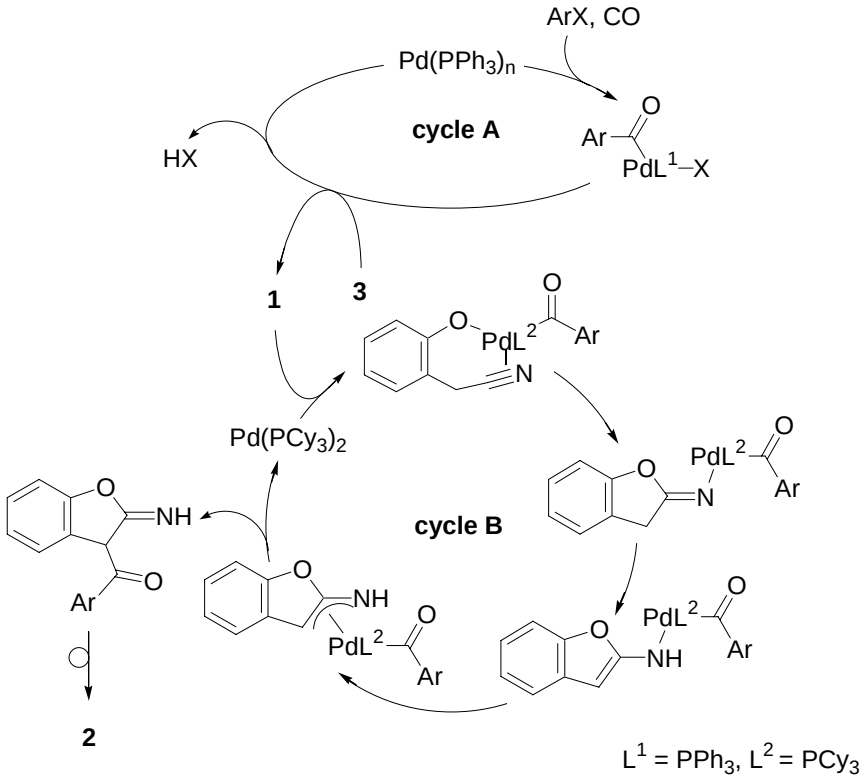
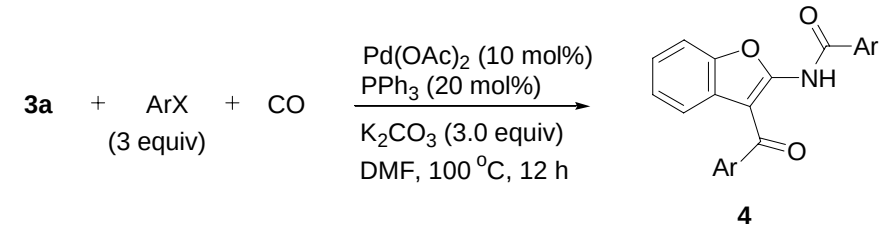


Figure 1. Plausible reaction mechanism for the three-component coupling reaction.

When the reaction was carried out using K_2CO_3 or NaOEt as a base and $Pd(PPh_3)_4$ as a catalyst, 3-acyl-2-(*N*-acylamino)benzofuran **4a** was obtained in 9% and 4% yields together with ester **1a** (Table 1, entries 9 and 10). The yield of **4a** was increased to 73%, when $Pd(OAc)_2$, PPh_3 (Pd:P = 1:2), 3 equiv of 4-bromotoluene, and K_2CO_3 were used (Table 4, entry 1). Under the reaction conditions, a variety of aryl halides afford the corresponding 3-acyl-2-(*N*-acylamino)benzofurans **4b-4g** in moderate to good yields (entries 2-7). In all cases, 3-acyl-2-aminobenzofurans **2** were not obtained at all. These results show that each reaction leading to **2** or **4** proceeds via different pathways controlled by a base used.

Table 4. Pd-catalyzed three-component coupling reactions in the presence of K_2CO_3 leading to 3-acyl-2-(*N*-acylamino)benzofurans **4**[a]



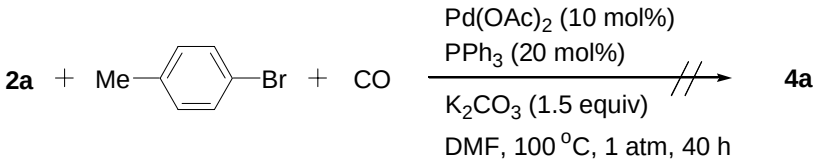
4

entry	Ar	X	product	yield (%)[b]
1	4-MeC_6H_4	Br	**4a**	73
2	4-$CF_3C_6H_4$	Br	**4b**	91
3	4-ClC_6H_4	Br	**4c**	63
4	Ph	Br	**4d**	82
5	2-Naph	Br	**4e**	88
6	4-$MeOC_6H_4$	I	**4f**	41
7	2-MeC_6H_4	I	**4g**	68

[a]Reaction conditions: **3a** (0.30 mmol), ArBr (0.90 mmol), K_2CO_3 (0.90 mmol), $Pd(OAc)_2$ (0.030 mmol), and PPh_3 (0.060 mmol) in DMF (1.2 mL) under CO (1 atm). [b]Isolated yields.

To gain insight into the reaction mechanism, **2a** was heated with 4-bromotoluene and K_2CO_3 in the presence of a palladium catalyst. However, **4a** was not obtained even in the presence of excess amount of 4-bromotoluene. This result clearly shows that the conversion of **3a** to **4a** did not proceed via **2a** (Scheme 6).

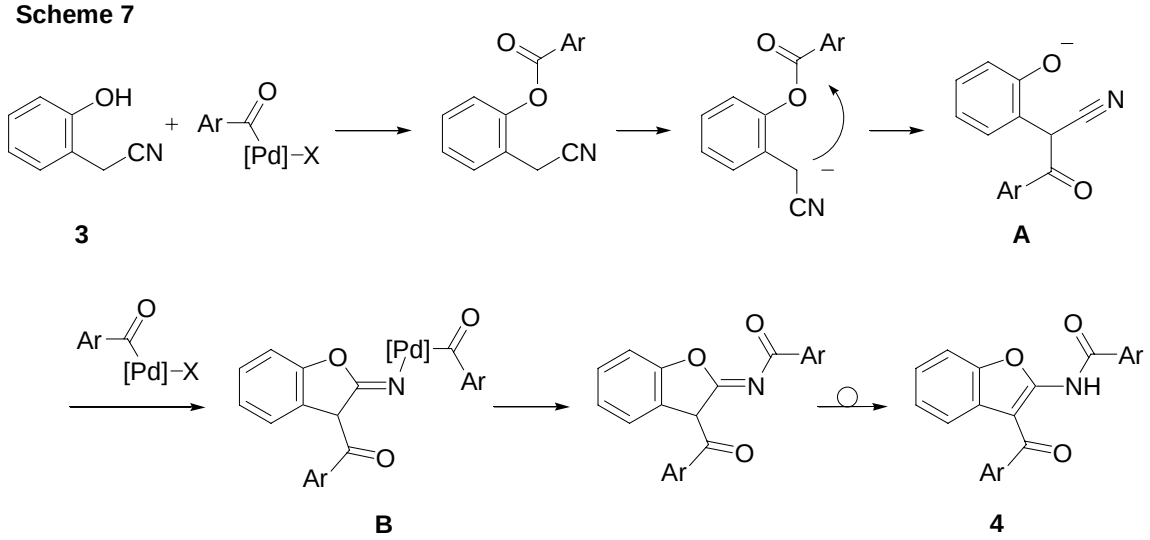
Scheme 6



Based on these results, the author proposes the reaction mechanism leading to **4** as shown in Scheme 7. The reaction proceeds via the aroylation of **3** followed by 1,4-benzoyl shift to afford intermediate **A**. The direct attack of a phenolate anion of **A** to a nitrile moiety

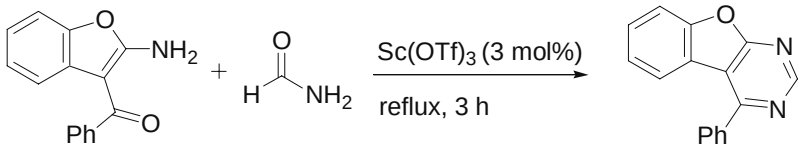
activated by aroylpalladium complexes gave a cyclic intermediate **B**, which results in the formation of the *N*-acyl-2-aminobenzofuran **4** by reductive elimination of palladium complex followed by aromatization.

Scheme 7



Since benzofurans obtained from the present palladium-catalyzed three-component coupling reactions possess both an amino and a carbonyl group, they serve as key intermediates for the synthesis of benzofuran-fused nitrogen-containing heterocycles.[16] For example, 3-acyl-2-aminobenzofuran **2g** was converted into corresponding benzofuro[2,3-*d*]-pyrimidine derivative **8** in 97% yield by simply heating with formamide in the presence of 3 mol% of $Sc(OTf)_3$ (Scheme 8).

Scheme 8



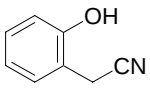
In conclusion, the author has demonstrated a palladium-catalyzed three-component coupling reaction of 2-(cyanomethyl)phenols, aryl halides, and CO leading to 3-acyl-2-amino-

benzofuran derivatives. The present transformation is composed of two types of reactions catalyzed by independent palladium complexes, respectively, i.e., (i) $Pd(PPh_3)_4$-catalyzed alkoxycarbonylation of aryl halides with 2-(cyanomethyl)phenols and (ii) $Pd(PCy_3)_2$-catalyzed cycloisomerization leading to 3-acyl-2-aminobenzofurans. Under the reaction conditions, a diverse array of functional groups, including chloro, silyloxy, methoxymethoxy as well as an ester are tolerated. Furthermore, choosing the base and palladium catalyst properly, two types of different 3-acyl-2-aminobenzofurans were obtained selectively. Since 2-(cyanomethyl)phenols can be easily prepared from commercially available salicylic acids in two steps, the present method provides a facile access to 3-acyl-2-aminobenzofurans.

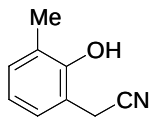
Experimental

General Method. Unless otherwise noted, chemicals obtained from commercial suppliers were used without further purification. CO gas (purity 99.97%) was purchased from Sumitomo Seika Co. Solvents were dried by the usual methods and distilled before use. All reactions were carried out under nitrogen atmosphere. NMR spectra were measured for solutions in $CDCl_3$ or acetone-d_6 with tetramethylsilane as an internal standard (^1H and ^{13}C): the following abbreviations are used; br s: broad singlet, s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet. IR spectra were recorded with an FT-IR spectrometer. Melting points (mp) are uncorrected. Element analyses were performed at Microanalytical Center of Kyoto University. High-resolution mass spectra (HRMS) was measured with JEOL JMX-SX 102A spectrometer.

Preparation of 2-(Cyanomethyl)phenols 3

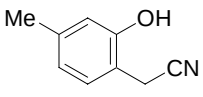


2-(Cyanomethyl)phenol (3a): To a solution of $LiAlH_4$ (2.1 g, 55 mmol) in THF (100 mL) was added salicylic acid (6.9 g, 50 mmol) at 0 ^oC, and stirred at 60 ^oC overnight. The reaction mixture was cooled to 0 ^oC, and then degassed water (2 mL), 15 wt% NaOH aqueous solution (2 mL), and water (6 mL) were successively added. After stirring at room temperature for 1 h, the mixture was filtered and washed with Et_2O (50 mL $\times$3). The combined organic layer was washed with brine and dried over $MgSO_4$. The organic solvent was removed under reduced pressure to afford 2-hydroxymethyl phenol (4.5 g, 33.5 mmol, 67% yield) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ2.26 (br, 1H), 4.86 (s, 2H), 6.84 (t, J = 7.3 Hz), 6.88 (d, J = 6.8 Hz, 1H), 7.04 (d, J = 6.8 Hz, 1H), 7.21 (t, J = 7.3 Hz, 1H). A solution of 2-hydroxymethyl phenol (3.9 g, 30 mmol) in DMF (30 mL) was added to sodium cyanide (2.9 g, 60 mmol), and the resulting mixture was stirred at 100 ^oC for 12 h. After the resulting solution was cooled to room temperature, it was poured into 10% HCl aqueous solution (30 mL), and extracted with Et_2O (30 mL$\times$3). The combined organic layer was dried over $MgSO_4$, and the organic solvent was removed under reduced pressure. The residue was filtered through a short silica gel pad followed by recrystallization from hexane/$CHCl_3$ gave 2-(cyanomethyl)phenol **3a** (3.2 g, 24 mmol, 80% yield) as a pale yellow solid. ^1H NMR (400 MHz, $CDCl_3$): δ3.72 (s, 2H), 5.05 (br s, 1H), 6.80 (d, J = 7.9 Hz. 1H), 6.95 (t, J = 7.9 Hz, 1H), 7.20 (t, J = 7.9Hz, 1H), 7.33 (d, J = 7.9 Hz, 1H).

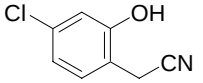


2-Cyanomethyl-6-methylphenol (3i): A yellow solid; mp 103.5-104.3 ^oC. IR (KBr): 762, 883, 958, 1097, 1160, 1193, 1216, 1333, 1411, 1472, 1595, 2255 (CN), 2926, 3422 (OH) cm^{-1}. ^1H NMR (400 MHz, acetone-d_6): δ2.15 (s, 3H), 3.67 (s, 2H), 6.69 (t, J = 7.3 Hz, 1H), 6.98 (d, J = 7.3 Hz, 1H), 7.05 (d, J = 7.3 Hz, 1H). ^{13}C NMR (100 MHz, acetone-d_6): δ16.4, 18.8, 118.9, 119.0, 120.9, 125.3, 127.8, 131.4, 153.4. HRMS

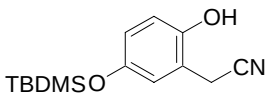
(FAB) calcd for M+H$^+$ of C_9H_9NO 148.0762, found 148.0758.



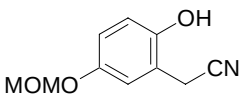
2-Cyanomethyl-5-methylphenol (3j): A yellow solid; mp 107.2-108.3 ^{o}C. IR (KBr): 734, 813, 858, 957, 1114, 1157, 1195, 1233, 1287, 1353, 1425, 1523, 1593, 1618, 2262 (CN), 2907, 2957, 3332 (OH) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.28 (s, 3H), 3.68 (s, 2H), 5.40 (br s, 1H), 6.60 (s, 1H), 6.75 (d, J = 7.8 Hz, 1H), 7.19 (d, J = 7.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.1, 21.1, 113.8, 116.1, 118.2, 121.9, 129.4, 139.8, 153.0. HRMS (FAB) calcd for M+H$^+$ of C_9H_9NO 148.0762, found 148.0760.



5-Chloro-2-(cyanomethyl)phenol (3l): A orange solid; mp 108.7-109.5 ^{o}C. IR (KBr): 724, 822, 870, 910, 1086, 1119, 1228, 1284, 1351, 1426, 1505, 1607, 2268 (CN), 2914, 2974, 3328 (OH) cm^{-1}. ^{1}H NMR (400 MHz, acetone-d_6): δ 3.76 (s, 2H), 6.90 (d, J = 8.8 Hz, 1H), 7.14 (d, J = 8.8 Hz, 1H), 7.31 (s, 1H). ^{13}C NMR (100 MHz, acetone-d_6): δ 18.4, 117.4, 118.4, 120.8, 124.7, 129.7, 129.9, 154.6. HRMS (FAB) calcd for M+H$^+$ of C_8H_6ClNO 168.0216, found 168.0210.

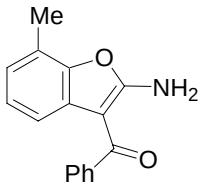


2-Cyanomethyl-4-(*tert*-butyldimethylsilyloxy)phenol (3n): A yellow solid; mp 69.7-70.4 ^{o}C. IR (KBr): 780, 813, 912, 985, 1093, 1151, 1206, 1270, 1362, 1438, 1511, 1614, 2277 (CN), 2856, 2892, 2927, 2957, 3325 (OH) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.17 (s, 6H), 0.97 (s, 9H), 3.67 (s, 2H), 5.73 (br s, 1H), 6.66 (m, 2H), 6.82 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ -4.54, 18.1, 18.5, 25.6, 116.1, 117.5, 118.0, 120.4, 147.6, 149.3. HRMS (FAB) calcd for M+H$^+$ of $C_{14}H_{21}NO_2Si$ 264.1420, found 264.1428.



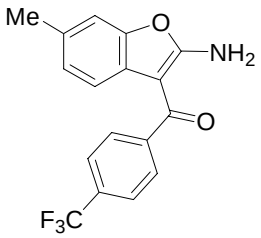
2-Cyanomethyl-4-(methoxymethoxy)phenol (3o): A yellow oil; IR (neat): 733, 810, 872, 1112, 1188, 1262, 1351, 1452, 1612, 2259 (CN), 2824, 2957, 3328 (OH) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.48 (s, 3H), 3.66 (s, 2H), 5.10 (br s, 1H), 6.69 (d, J = 8.8 Hz, 1H), 6.85 (d, J = 8.8 Hz, 1H), 7.00 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.5, 55.8, 95.2, 116.0, 117.5, 117.6, 117.9, 118.0, 148.7, 150.7. HRMS (FAB) calcd for M+H^+ of $C_{10}H_{11}NO_3$ 194.0817, found 194.0812.

General Procedure of Palladium-Catalyzed Three-component Coupling Reactions Leading to 3-Acyl-2-aminobenzofurans. A flame dried Schlenk flask was charged with $Pd(PCy_3)_2$ (10.7 mg, 0.016 mmol), $Pd(PPh_3)_4$ (4.6 mg, 0.0040 mmol), 2-(cyanomethyl)phenols **3** (0.20 mmol), aryl halides (0.30 mmol), Et_3N (0.042 mL, 0.30 mmol), and DMF (0.80 mL). The flask was then flushed with CO, and the system was closed. After the reaction mixture was stirred at 100 ^oC for the time specified in Scheme 4, 5 and Tables 1-3, it was diluted with Et_2O and filtered through a short silica gel pad. The filtrate was washed with brine, and the aqueous layer was extracted with Et_2O (10 mL × 3). The combined organic layer was dried over $MgSO_4$, and then filtered. The organic solvent was removed under reduced pressure and the residue was subjected to flash column chromatography on silica gel with hexane/AcOEt (v/v = 7/1-2/1) as eluents to afford the corresponding 3-acyl-2-aminobenzofurans **2**.

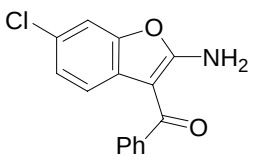


2-Amino-3-benzoyl-7-methylbenzo[*b*]furan (2i): A yellow solid; mp 153.8-154.7 ^oC. IR (KBr): 749, 772, 849, 920, 1062, 1170, 1281, 1340, 1477, 1645 (C=O), 3198, 3366 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.40 (s, 3H), 6.70 (d, J = 7.3 Hz, 1H), 6.84 (d, J = 6.8 Hz, 1H), 6.89 (t, J = 7.3 Hz, 1H), 7.11 (br s, 2H), 7.44-7.54 (m, 3H), 7.70 (d, J = 6.8 Hz, 2H). ^{13}C NMR (100 MHz,

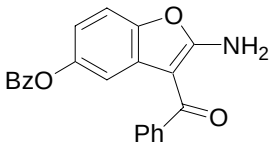
$CDCl_3$): δ14.7, 94.7, 116.5, 120.1, 123.3, 123.6, 125.8, 127.4, 128.3, 130.8, 140.9, 147.9, 166.4, 190.9. Anal. calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21. found: C, 76.38; H, 5.50.



2-Amino-6-methyl-3-(4'-trifluoromethylbenzoyl)benzo[*b*]furan (2j): A yellow solid; mp 126.8-127.3 ^{o}C. IR (KBr): 782, 810, 859, 904, 980, 1018, 1067, 1109, 1125, 1173, 1250, 1323, 1475, 1589, 1656 (C=O), 3165, 3351 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ2.35 (s, 3H), 6.64 (d, J = 8.3 Hz, 1H), 6.83 (d, J = 8.3 Hz, 1H), 7.03 (s, 1H), 7.25 (br s, 2H), 7.74 (d, J = 8.3 Hz, 2H), 7.79 (d, J = 8.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ21.2, 94.2, 110.7, 118.2, 123.0, 123.8 (q, J = 271.9 Hz), 124.8, 125.4 (q, J = 3.3 Hz), 127.8, 132.4 (q, J = 32.2 Hz), 132.5, 144.1, 149.6, 166.9, 188.7. HRMS (FAB) calcd for M+H^{+} of $C_{17}H_{12}F_3NO_2$ 320.0898, found 320.0891.

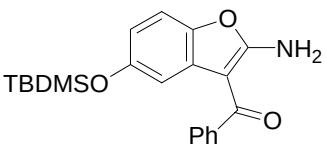


2-Amino3-benzoyl-6-chlorobenzo[*b*]furan (2l): A pale yellow solid; mp 121.3-122.5 ^{o}C. IR (KBr): 759, 799, 858, 920, 993, 1073, 1177, 1242, 1347, 1435, 1478, 1589, 1658 (C=O), 3110, 3325 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ6.84 (d, J = 2.0 Hz, 1H), 6.99 (dd, J = 2.0, 8.8 Hz, 1H), 7.09 (br s, 2H), 7.13 (d, J = 8.8 Hz, 1H), 7.52 (d, J = 7.3 Hz, 2H), 7.49-7.59 (m, 1H), 7.67 (d, J = 7.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ94.0, 110.9, 118.8, 121.7, 127.3, 127.9, 128.5, 129.4, 131.3, 140.4, 147.5, 167.0, 190.7. Anal. calcd for $C_{15}H_{10}ClNO_2$: C, 66.31; H, 3.71. found: C, 66.34; H, 3.53.



5-(2-Amino-3-benzoylbenzo[*b*]furyl)benzoate (2m): A yellow solid; mp 145.4- 146.3 ^{o}C. IR (KBr): 757, 800, 873, 923, 1004, 1065 1165, 1266, 1450, 1479, 1593, 1656 (C=O), 1722 (C=O), 3096, 3329 cm^{-1}.

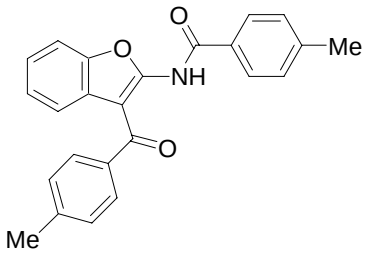
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.72 (d, J = 2.0 Hz, 1H), 6.86 (dd, J = 2.0, 8.3 Hz, 1H), 7.17 (br s, 2H), 7.22 (d, J = 8.8 Hz, 1H), 7.46-7.50 (m, 5H), 7.61 (t, J = 7.3 Hz, 1H), 7.71 (d, J = 7.3 Hz, 2H), 8.14 (d, J = 8.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 94.4, 110.4, 112.3, 115.2, 127.4, 127.5, 128.4, 128.5, 129.5, 130.1, 131.1, 133.5, 140.5, 146.7, 147.3, 165.5, 167.3, 190.5. Anal. calcd for $C_{22}H_{15}NO_4$: C, 73.94; H, 4.23. found: C, 73.77; H, 4.18.



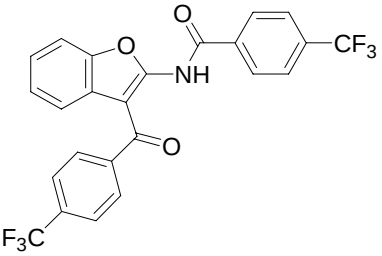
2-Amino-3-benzoyl-5-(*tert*-butyldimethylsilyl)oxybenzo[*b*]-furan (2n): A yellow solid; mp 147.8-148.8 ^{o}C. IR (KBr): 752, 852, 920, 1073, 1156, 1232, 1364, 1438, 1479, 1590, 1655 (C=O), 3112, 3326 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.06 (s, 6H), 0.91 (s, 9H), 6.29 (d, J = 2.9 Hz, 1H), 6.52 (d, J = 2.9, 8.8 Hz, 1H), 7.04 (d, J = 8.4 Hz, 1H), 7.19 (br s, 2H), 7.45-7.55 (m, 3H), 7.67 (d, J = 6.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ -4.64, 18.1, 25.6, 94.6, 110.0, 110.1, 113.9, 127.0, 127.1, 128.3, 130.6, 140.9, 144.2, 152.1, 167.2, 190.7. HRMS (FAB) calcd for M+H$^+$ of $C_{21}H_{25}NO_3Si$ 368.1682, found 368.1682.

General Procedure of Palladium-Catalyzed Three-component Coupling Reactions Leading to 3-Acyl-2-(*N*-acylamino)benzofurans. A flame dried Schlenk flask was charged with $Pd(OAc)_2$ (6.7 mg, 0.030 mmol), PPh_3 (15.7 mg, 0.060 mmol), 2-(cyanomethyl)phenol **3a** (39.9 mg, 0.30 mmol), aryl halides (0.9 mmol), K_2CO_3 (124 mg, 0.9 mmol), and DMF (1.2 mL). The flask was then flushed with CO, and the system was closed. After the reaction mixture was stirred at 100 ^{o}C for the time specified in Table 4, it was diluted with Et_2O and filtered through a short silica gel pad. The filtrate was washed with brine, and the aqueous layer was extracted with Et_2O (10 mL × 3). The combined organic layer was dried over $MgSO_4$, and then filtered. The organic solvent was removed under reduced pressure and the residue was subjected to flash column chromatography on silica gel with hexane/AcOEt =

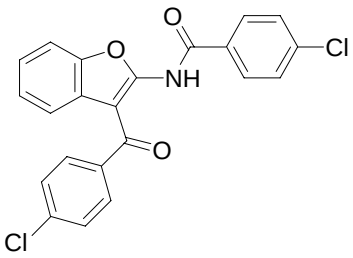
7/1-2/1 as eluents to afford the corresponding 3-acyl-2-(*N*-acylamino)benzofurans **6**.



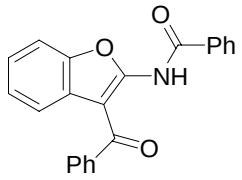
***N*-[3-(4'-Methylbenzoyl)-2-benzo[*b*]furyl]-4'-methylbenzamide (6a)**: A yellow solid; mp 157.1-157.7 ^{o}C. IR (KBr): 745, 773, 828, 932, 1016, 1061, 1285, 1324, 1461, 1557, 1614 (C=O), 1712 (C=O), 2921, 3027 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.43 (s, 3H), 2.46 (s, 3H), 7.11-7.15 (m, 2H), 7.20-7.25 (m, 1H), 7.32 (d, J = 2.4 Hz 2H), 7.33 (d, J = 2.4 Hz, 2H), 7.58 (d, J = 8.3 Hz, 1H), 7.71 (d, J = 7.8 Hz, 2H), 8.01 (d, J = 8.3 Hz, 2H) 12.2 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.5, 21.6, 100.0, 111.6, 120.2, 123.7, 123.8, 124.0, 124.2, 127.9, 128.2, 129.1, 129.6, 136.8, 142.8, 143.9, 150.7, 158.9, 163.1, 192.6. HRMS (FAB) calcd for M+H^{+} of $C_{24}H_{19}NO_3$ 370.1443, found 370.1449.



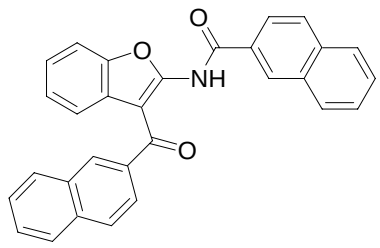
***N*-[3-(4'-Trifluoromethylbenzoyl)-2-benzo[*b*]furyl]-4'-trifluoromethylbenzamide (6b)**: A yellow solid; mp 176.2-176.9 ^{o}C. IR (KBr): 677, 751, 785, 855, 1014, 1068, 1124, 1170, 1287, 1326, 1462, 1558, 1617, 1718, 2361, 3077 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.01 (d, J = 7.8 Hz, 1H), 7.19 (t, J = 7.8 Hz, 1H), 7.29 (t, J = 7.3 Hz 1H), 7.61 (d, J = 8.3 Hz, 1H), 7.83 (d, J = 8.3 Hz, 4H), 7.91(d, J = 8.3 Hz, 2H), 8.21 (d, J = 7.8 Hz, 2H), 12.3 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 100.3, 111.9, 119.9, 123.1, 123.4 (q, J = 272.3 Hz), 123.6 (q, J = 272.3 Hz), 124.6, 124.8, 125.7 (q, J = 3.3 Hz), 126.2 (q, J = 3.3 Hz), 128.3, 128.4, 133.8 (q, J = 32.3 Hz), 134.8 (q, J = 32.3 Hz), 135.4, 142.4, 150.8, 159.0, 161.9, 191.6. HRMS (FAB) calcd for M+H^{+} of $C_{24}H_{13}F_6NO_3$ 478.0878, found: 478.0884.



***N*-[3-(4'-Chlorobenzoyl)-2-benzo[*b*]furyl]-4'-chlorobenz amide (6c)**: A yellow solid; mp 181.2-181.9 °C. IR (KBr): 668, 742, 774, 845, 934, 1011, 1060, 1091, 1285, 1323, 1430, 1458, 1558, 1615, 1714, 2342, 2359. 3032. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.11 (d, J = 7.6 Hz, 1H), 7.18 (t, J = 7.6 Hz, 1H), 7.27 (t, J = 7.6 Hz 1H), 7.52 (d, J = 8.3 Hz 4H), 7.60 (d, J = 8.3 Hz, 1H), 7.75 (d, J = 8.3 Hz, 2H), 8.04 (d, J = 8.3 Hz, 1H), 12.2 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 100.1, 111.9, 120.1, 123.5, 124.3, 124.6, 128.9, 129.3, 129.4, 129.6, 130.7, 137.6, 138.6, 139.8, 150.8, 159.0, 162.1, 191.6. HRMS (FAB) calcd for M+H$^+$ of $C_{22}H_{13}Cl_2NO_3$ 410.0351, found 410.0344.

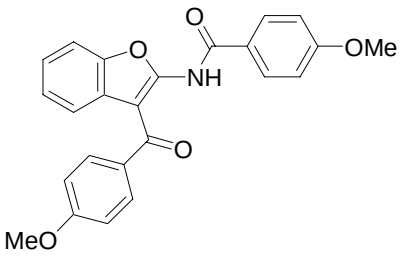


***N*-(3-Benzoyl-2-benzo[*b*]furyl)benzamide (6d)**: A yellow solid; mp 162.4-163.0 °C. IR (KBr): 622, 698, 749, 860, 982, 1178, 1282, 1451, 1487, 1504, 1523, 1610, 1625, 1662, 2953, 3036, 3285 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.11 (t, J = 7.8 Hz, 1H), 7.15 (t, J = 7.8 Hz, 1H), 7.26 (t, J = 8.8 Hz 1H), 7.52-7.65 (m, 7H), 7.81 (d, J = 6.8 Hz, 2H), 8.13 (d, J = 7.3 Hz, 2H), 12.3 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 100.2, 111.8, 120.2, 123.9, 124.0, 124.4, 128.0, 128.1, 128.5, 129.1, 132.2, 132.4, 133.2, 139.5, 150.8, 159.0, 163.3, 193.0. HRMS (FAB) calcd for M+H$^+$ of $C_{22}H_{15}NO_3$ 342.1130, found 342.1131.

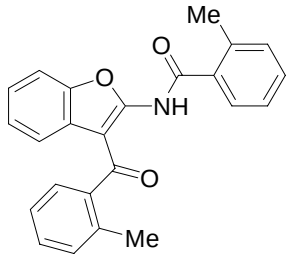


***N*-[3-(2'-Naphtoyl)-2-benzo[*b*]furyl]-2'-naphthalene-carboxamide (6e)**: A yellow solid; mp 184.0-184.5 °C. IR (KBr): 698, 749, 806, 932, 1060, 1125, 1198, 1224, 1286, 1318, 1435, 1457, 1473, 1558, 1607, 1704, 2258, 3027 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.12-7.13 (m, 2H), 7.25-7.29 (m, 1H), 7.57-7.67 (m, 5H), 7.88-7.91 (dd, J = 1.5, 8.3 Hz, 1H), 7.93-7.97 (m, J = 3.4 Hz, 2H), 8.00 (d, J = 8.8 Hz, 1H),

8.02 (d, *J* = 8.8 Hz, 1H), 8.07 (d, *J* = 7.8 Hz, 1H), 8.17 (dd, *J* = 1.5, 8.3 Hz, 1H), 8.38 (s, 1H), 8.67 (s, 1H), 12.5 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 100.4, 111.8, 120.3, 123.6, 123.9, 124.0, 124.4, 126.9, 127.0, 127.8, 127.9, 128.1, 128.5, 128.6, 129.0, 129.1, 129.2, 129.3, 129.4, 129.5, 129.6, 132.4, 132.5, 135.1, 135.4, 136.7, 150.8, 159.0, 163.3, 192.8. HRMS (FAB) calcd for M+H$^+$ of $C_{30}H_{19}NO_3$ 442.1443, found 442.1440.

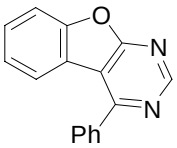


***N*-[3-(4'-Methoxybenzoyl)-2-benzo[*b*]furyl]-4'-methoxy benzamide (6f)**: A yellow solid; mp 202.9-203.7 ^{o}C. IR (KBr): 749, 780, 840, 933, 1032, 1063, 1174, 1192, 1246, 1286, 1328, 1430, 1463, 1558, 1576, 1615, 1698, 3040. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.90 (s, 3H), 3.93 (s, 3H), 7.03 (dd, *J* = 1.5, 8.8 Hz, 4H), 7.18 (d, *J* = 7.3 Hz, 1H), 7.24 (d, *J* =7.3 Hz, 1H), 7.26-7.27 (m, 1H), 7.61 (d, *J* = 7.8 Hz, 1H), 7.84 (d, *J* = 6.8 Hz, 2H), 8.09 (d, *J* = 8.8 Hz, 2H), 12.2 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.4, 55.5, 100.0, 111.8, 113.7, 114.3, 120.3, 123.7, 124.1, 124.2, 124.8, 130.1, 130.6, 132.0, 150.8, 159.0, 162.8, 163.0, 163.6, 191.7. HRMS (FAB) calcd for M+H$^+$ of $C_{24}H_{19}NO_5$ 402.1341, found 402.1344.



***N*-[3-(2'-Methylbenzoyl)-2-benzo[*b*]furyl]-2'-methylbenz-amide (6g)**: A yellow solid; mp 169.7-170.3 ^{o}C. IR (KBr): 738, 763, 929, 1054, 1174, 1221, 1284, 1322, 1434, 1461, 1558, 1592, 1621, 1708, 3063. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.33 (s, 3H), 2.67 (s, 3H), 6.47 (d, *J* = 7.8 Hz, 1H) 7.06 (t, *J* = 8.3 Hz, 1H), 7.21 (t, *J* = 8.3 Hz, 1H), 7.30-7.37 (m, 5H), 7.42-7.47 (m, 2H), 7.58 (d, *J* = 7.8 Hz, 1H), 7.81 (d, *J* = 7.8 Hz, 1H), 11.8 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.1, 20.7, 100.8, 111.6, 119.4, 123.7, 123.9, 124.6, 126.0, 126.3, 126.4, 127.7, 130.2, 130.9, 131.7, 132.0, 133.2, 134.7, 138.7, 140.1, 150.7, 158.3,

165.5, 194.7. HRMS (FAB) calcd for M+H$^+$ of $C_{24}H_{19}NO_3$ 370. 1443, found 370.1444.



Synthesis of 4-Phenylbenzofuro[2,3-*d*]pyrimidine (8). To a solution of 2-amino-3-benzoylbenzo[*b*]furan **2g** (94.9 mg, 0.40 mmol) in formamide (0.8 mL) was added $Sc(OTf)_3$ (5.9 mg, 0.012 mmol), and the resulting mixture was stirred at 140 ^oC for 3 h. The reaction mixture was washed with water and brine, and then dried over $MgSO_4$. The organic solvent was removed under reduced pressure and the residue was subjected to flash column chromatography on silica gel with hexane/AcOEt = 4/1 as eluents to afford 4-phenylbenzofuro[2,3-*d*]pyrimidine **8** as a white solid (95.5 mg, 0.39 mmol, 97% yield) as a white solid. mp 120.2-120.8 ^oC. IR (KBr): 750, 765, 816, 849, 930, 941, 1128, 1201, 1248, 1315, 1368, 1431, 1462, 1478, 1552, 1585, 3023, 3071 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.30 (t, J = 7.3 Hz, 1H), 7.53 (t, J = 8.3 Hz, 1H), 7.60-7.68 (m, 4H), 7.91 (d, J = 7.8 Hz, 1H), 7.96-8.00 (m, 2H), 9.10 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 112.2, 112.3, 120.2, 122.8, 124.0, 128.7, 128.8, 129.2, 130.7, 137.1, 153.7, 155.4, 161.6, 168.9. Anal. calcd for $C_{11}H_8N_2O$: C, 78.03; H, 4.09. found: C, 78.05; H, 4.37.

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List of Publications

Chapter 1 **"**Copper-catalyzed Transformation of Carbonyl-en-nitrile Compounds: Vinylation, Imino Ene Reaction, and Alkynylation of 2-Aza-2,4-cyclopentadienone Intermediates Generated via Ritter-type Hydration and Dehydrative Cyclization Reactions"

Masahito Murai, Shigekazu Kawai, Koji Miki, Kouichi Ohe

J. Organomet. Chem. **2007**, *692*, 579.

Chapter 2 **"**Copper-catalyzed Addition Reactions of Aromatics and Ketones to 2-Aza-2,4-cyclopentadienone: Facile and Efficient Transformation of Carbonyl-ene-nitriles to 1*H*-Pyrrolin-2(5*H*)-ones"

Masahito Murai, Koji Miki, Kouichi Ohe

J. Org. Chem. **2008**, *73*, 9174.

Chapter 3 **"**Atom-efficient Synthesis of α-Alkylidene-*N*-furylimines via Catalytic Vinylcarbene-transfer Reactions to Carbonyl-ene-nitrile Compounds"

Masahito Murai, Shotaro Yoshida, Koji Miki, Kouichi Ohe

Chem. Commun. in press.

Chapter 4 "Gallium-catalyzed Bromocyanation of Alkynes with Cyanogen Bromide: Regio- and Stereoselective Synthesis of Functionalized Nitriles"

Masahito Murai, Ryo Hatano, Kouichi Ohe

Submitted to *J. Am. Chem. Soc.*

.

Chapter 5 "A New Route to 3-Acyl-2-aminobenzofurans: Palladium-catalyzed Cycloisomerisation of 2-(Cyanomethyl)phenyl esters"
Masahito Murai, Koji Miki, Kouichi Ohe
Chem. *Commun*. **2009**, 3466.

Chapter 6 "Palladium-catalyzed Three-component Coupling Reactions of 1-(Cyanomethyl)phenol, Aryl Halides and CO"
Masahito Murai, Kentaro Koumura, Kouichi Ohe
In preparation.

Other Publications

"Facile Synthesis of Trifluoromethyl-substituted Enynes: Remarkable Reactivity and Stereoselectivity of Tributyl(3,3,3-trifluoropropynyl)stannane in Carbostannylation of Alkynes"

Masaki Shimizu, Guofang Jiang, Masahito Murai, Youhei Takeda, Yoshiaki Nakao, Eiji Shirakawa, Tamejiro Hiyama

Chem. *Lett*. **2005**, *34*, 1701.

"Transition Metal-Catalyzed Ring-opening, Substitution, and Cyclopropanation Reactions via Vinylcarbene Complexes Generated from *O*-Propargyl Thiocarbamates"

Yuji Ikeda, Masahito Murai, Tomohiro Abo, Koji Miki, Kouichi Ohe

Tetrahedron Lett. **2007**, *48*, 6651.

"Novel Generation of 3,3,3-Trifluoropropynyllithium and Transformation of the Carbonyl Adducts to Trifluoromethyl-substituted Allenes"

Masaki Shimizu, Masahiro Higashi, Youhei Takeda, Guofang Jiang, Masahito Murai, Tamejiro Hiyama

Synlett **2007**, *7*, 1163.

"New Preparation and Synthetic Reactions of 3,3,3-Trifluoropropynyllithium, -borate and -stannane: Facile Synthesis of Trifluoromethylated Allenes, Arylacetylenes and Enynes"

Masaki Shimizu, Masahiro Higashi, Youhei Takeda, Masahito Murai, Guofang Jiang, Yuiga Asai, Yoshiaki Nakao, Eiji Shirakawa, Tamejiro Hiyama

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