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SYNTHESIS OF NITROGEN HETEROCYCLES THROUGH CYANATIVE CYCLIZATION AND CYCLOADDITION REACTIONS UNDER TRANSITION METAL CATALYSIS

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Abstract – Synthesis of cyano-functionalized nitrogen heterocycles under palladium, nickel, and cobalt catalysis is described. These transformations include the activation of C-C multiple bonds to give the functionalized pyrrolidines and their related compounds. The palladium-catalyzed reactions promote nucleophilic cyanation to non-activated terminal alkynes. Nickel catalysis enables to install H and CN functionalities into allenes with regio- and stereoselective manner. In the case of cobalt-catalyzed hydrocyanation, hydroacylation and hydroarylation, simple olefins as well as enamines are suitable substrates to construct highly functionalized hetero- and carbocycles. The applications of the above methodologies for the synthesis of alkaloids and related compounds are also described.

CONTENTS

1. INTRODUCTION

A cyano group is a synthetic equivalent of formyl, amino- and hydroxymethyl groups as well as a key component for nitrogen heterocycles, and also gives a significant influence on the biological activity of pharmaceuticals and drug candidates (Figure 1).[1] Therefore, its introduction has been regarded as one of the most significant and fundamental synthetic transformations.[2-4] Notably, the development of catalytic regio- and stereoselective cyanation has been a significant challenge in synthetic organic chemistry, and various cyanation protocols have been reported (Scheme 1).

Classical methods use polarized multiple bonds such as a carbonyl group as an electrophile, and nucleophilic cyanide effectively attacks to form a new C-C bond (Scheme 1-1). On the other hand, non-polarized C-C multiple bonds require to use transition metal complexes for their activation. C-C triple bonds are reliable functionality for metal-catalyzed cyanation, and many types using various cyanating agents (X-CN:[5,6] X = Si,[7,8] Ge,[9] Sn,[10] S,[11] Se,[12] B,[13] halogen[14-16] O,[17] C,[18,19]) have been developed since the pioneer work of nickel-catalyzed hydrocyanation has been reported in 1980's[20,21] (Scheme 1-2). These backgrounds show that cyanation chemistry is still an attractive area in the synthetic community, and the authors have focused on the versatility of a cyano group to be transformed to various useful molecules. In this review, new cyanation protocols under Pd, Ni, and Co catalysis and their applications for the synthesis of highly functionalized nitrogen heterocycles developed by the authors are summarized.

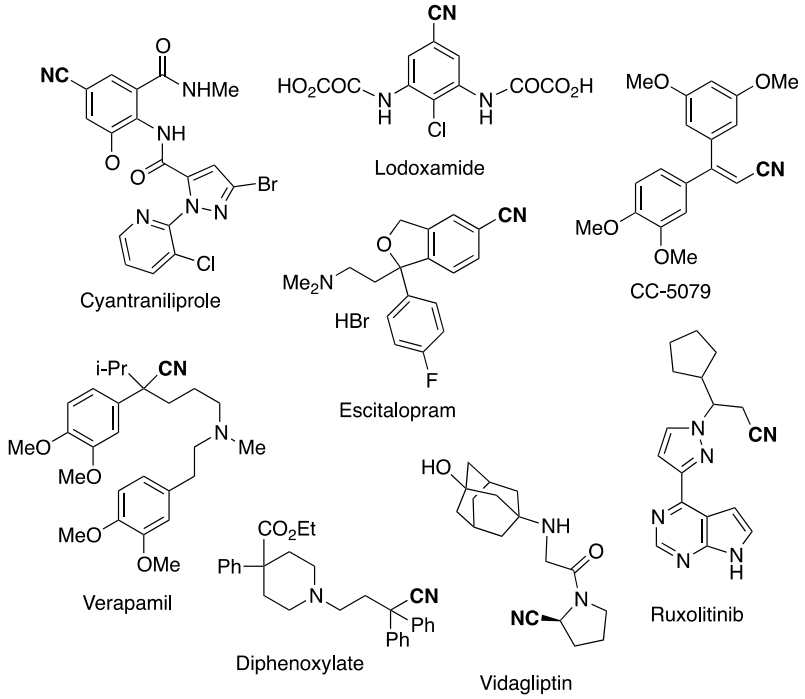


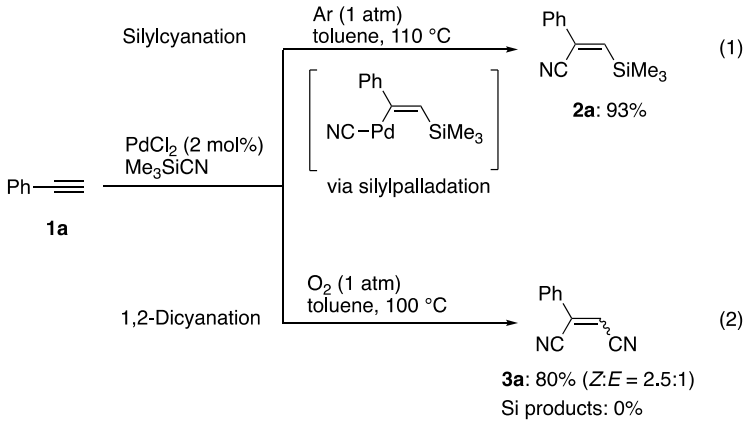
Figure 1. Biologically Important Molecules That Include a Cyano Group

Scheme 1. Nucleophilic Cyanation and Metal-Catalyzed Cyanation

2. PALLADIUM-CATALYZED 1,2-DICYANAION

2-1. Silyl Cyanation vs. 1,2-Dicyanation Using Terminal Alkynes

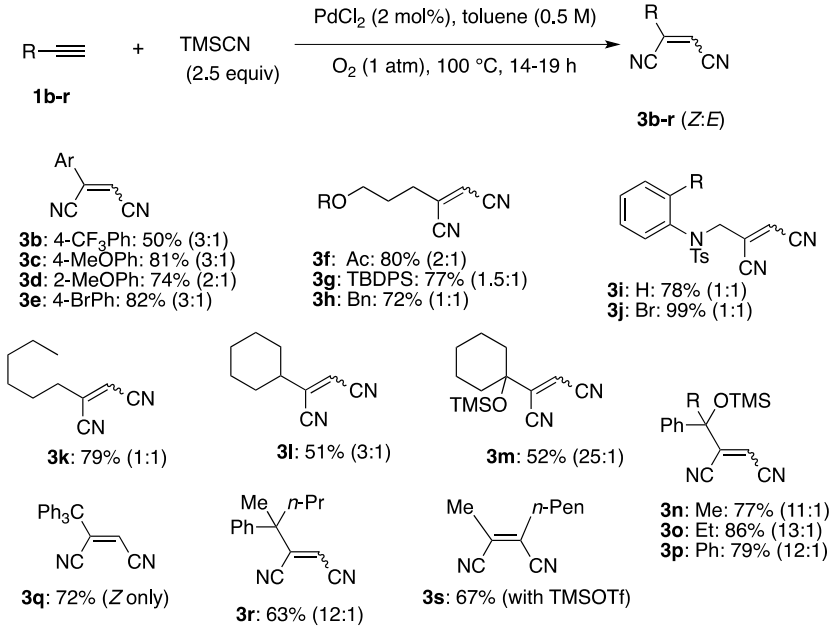
One of the most efficient and reliable cyanation using non-activated terminal alkynes has been Chatani's silylcyanation reported in 1980.[7] This protocol uses a palladium(II) species as a catalyst and a single product including both Me_3Si (trimethylsilyl: TMS) and CN groups can be obtained with regio- and stereoselective manner (Scheme 2-1). The observed *syn*-selectivity in **2a** suggests that the regio- and stereocontrolled organopalladium intermediate provided by *syn*-silylpalladation of **1a** could be involved. Its regiochemistry would be dependent on the steric bulk of a TMS group which prefers to add the terminal sp carbon. On the other hand, the authors observed that the reaction behavior completely changed to give **3a** without any trace of silylated products when the reaction was performed under oxygen atmosphere instead of argon (Scheme 2-2).[22] This finding prompted us to develop new cyanation protocols under metal catalysis and their related applications including natural product syntheses.



Scheme 2. Pd-Catalyzed Cyanation Using **1**

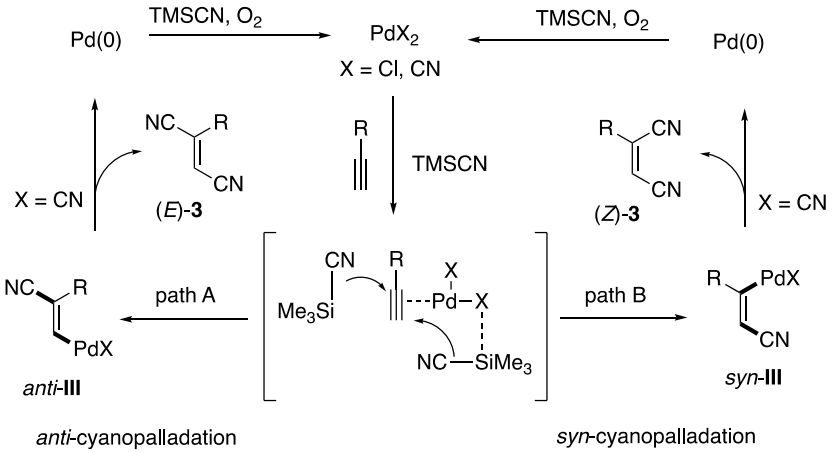
2-2. Reaction Scope and Mechanistic Insights

Stereoselectivity observed in **3a** was not dependent on the reaction temperature, solvent, Pd source, or ligands; however, the substrate scope revealed that this catalytic 1,2-dicyanation was strongly influenced by the substituents on substrates, as shown in Scheme 3. Various aliphatic and aromatic alkynes (**1b-l**) were all applicable to be transformed into the corresponding adducts in good yields with lower stereoselectivity (up to 3:1). The use of **1m** was a key to predict the origin of stereoselectivity and explain the significant influence of propargylic substituents, for example, a dramatical increase of stereoselectivity (*Z*/*E*) of **3m** was observed when **1m** was employed (**1l** vs. **1m**). A similar trend was observed in **1n-r** having quaternary carbons to give >10:1 selectivity, and **3q** was given in 72% yield with perfect stereoselectivity. In the case of an internal alkyne, the addition of TMSOTf was essential for the efficient activation of a triple bond, and the corresponding *syn*-**3s** was exclusively obtained in 67% yield.[22,23]



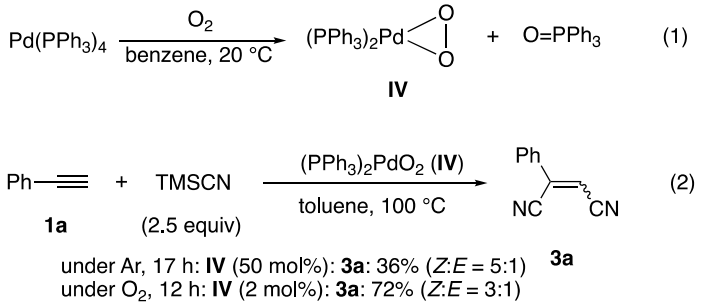
Scheme 3. Scope of Pd-Catalyzed 1,2-Dicyanation

The observed stereoselectivity leads to propose the alternative cyanation pathways relative to Chatani's cyanation, as outlined in Scheme 4. The initial step is nucleophilic cyanation to the activated C-C triple bond by Pd(II) species. This process seems to be switchable due to the steric bulk around triple bonds: less bulky substituents (R) on triple bonds in **1b-r** would promote nucleophilic cyanation at both internal and terminal sp carbons. The former cyanation (path A: *anti*-cyanopalladation) would be operative at more substituted internal sp carbon from the back side of Pd(II) to form *anti*-**III**. Another cyanation (path B: *syn*-cyanopalladation) would be favorably occurred at a less-bulky terminal sp carbon through the interaction between X and Si atoms[24] to give *syn*-**III**. The sequential reductive elimination provides the corresponding products via C-CN bond formation, and the resulting Pd(0) species would be quickly oxidized to Pd(II) species by molecular oxygen (Scheme 4). The selectivity determining steps are both cyanopalladation, which could be influenced by R group, and Path B would be more operative in bulky substrates such as **1m-r**. In the case of an internal alkyne, in-situ generated $Pd(OTf)_2$[25] would activate the hindered C-C triple bond and **3s** was exclusively obtained via *syn*-cyanopalladation.



Scheme 4. Plausible Reaction Mechanism for Pd-Catalyzed 1,2-Dicyanation

To reveal the role of oxygen, the known Pd(II) complex (**IV**)[26] prepared from $Pd(PPh_3)_4$ with oxygen was next investigated as a promoter. The 1,2-dicyanation reaction using **1a** with TMSCN in the presence of **IV** (50 mol%) under argon proceeded however its conversion was resulted in only 36% yield, suggesting that re-oxidation of Pd(0) to Pd(II) would be an essential process for the catalytic turn over. On the other hand, the catalytic activity of **IV** was clearly observed when the reaction was employed under oxygen atmosphere, and the expected dicyanoadduct of **3a** was obtained in 72% yield. In both cases, any silylated products were not observed at all, indicating that the active species for this reaction would be Pd(II) (Scheme 5).[27]



Scheme 5. Effect of Molecular Oxygen for 1,2-Dicyanation

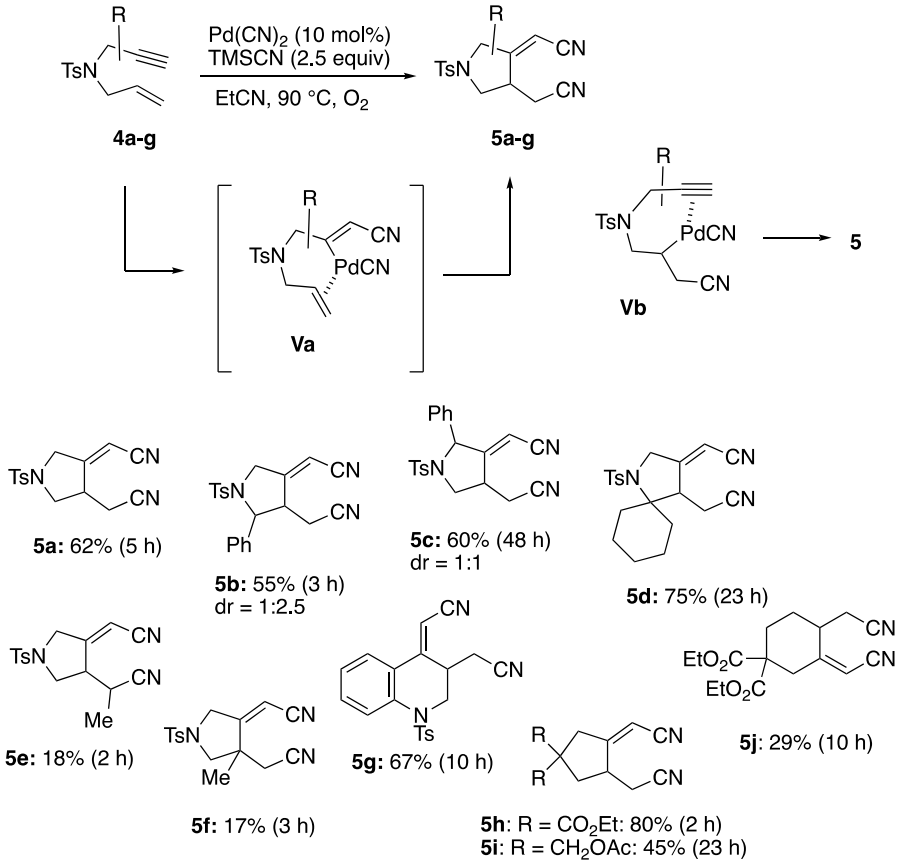
The above experimental informations reasonably explain 1) the role of oxygen, 2) the mechanistic behavior of Pd(II) species, 3) no formation of the silylated products, and 4) predominant formation of *Z*-adduct. These considerations suggest that the alkenylpalladium intermediates such as *syn*- and/or *anti*-**III** could be suitable precursors to design alternative catalytic pathways, as described in the next section.

3. PALLADIUM-CATALYZED DICYANATIVE CYCLIZATION AND CYCLOADDITION

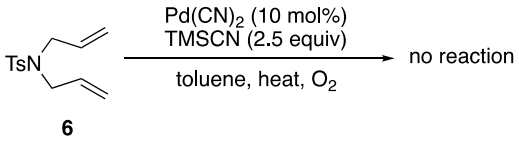
3-1. 5-*exo* Cyclization Using Enynes and Diynes

If the organopalladium species such as *syn*-**III** would be reactive toward the additional unsaturated bonds, a sequential C-C bond formation would accomplish the ring closure reaction (Scheme 6). In the case of simple enyne (**4a**), the corresponding dicyanoadduct (**5a**) as a functionalized heterocycle was obtained in 62% yield. The formation of both C-CN bonds at the terminal unsaturated carbons in **4a** proposed that the cyanopalladation to a triple bond in **4** would be a trigger and the following *exo* cyclization-reductive elimination sequence gave **5** through **Va**. Other substrates bearing a phenyl group and quaternary carbons on α-position or a methyl group on olefin gave the corresponding adducts of **5b-f**. A quinoline derivative (**5g**), as well as carbocycles (**5h-j**), were also obtained with stereoselective manner. All the trisubstituted olefins observed in products were fully controlled to be syn, which indicates that *syn*-cyanopalladation was more operative.[22,23]

Another mechanistic proposal to give **5** is an alternative intermediate (**Vb**), which could be provided by nucleophilic cyanation to an olefin terminus instead. To evaluate this possibility, diene (**6**) was next employed under the similar conditions, and no reaction occurred at all (Scheme 7). These results concluded that 1) the cyanopalladation would predominantly occur in C-C triple bonds and 2) terminal sp carbons are more suitable to form C-CN bonds for *syn*-cyanopalladation in enyne substrates.

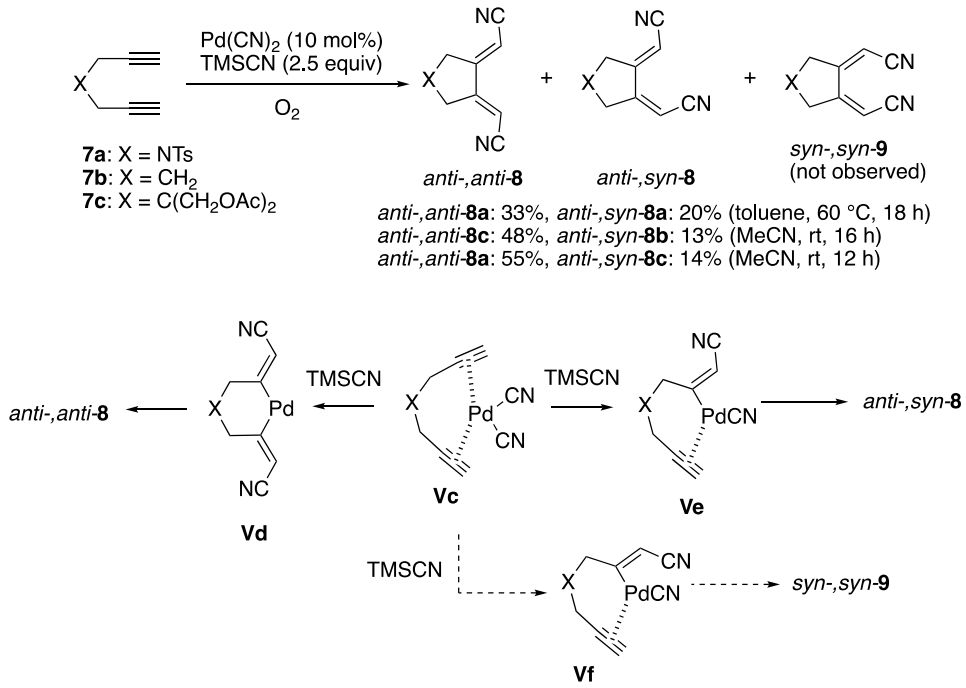


Scheme 6. Dicyanative Cyclization Using **4**



Scheme 7. Attempted Cyclization Using **6**

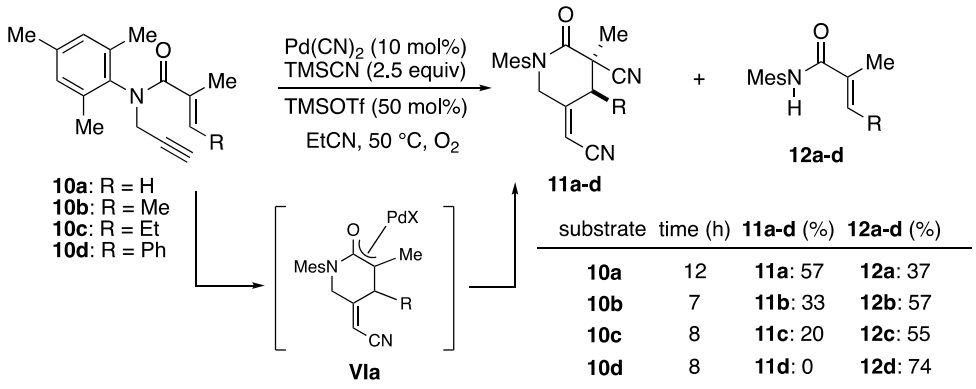
In the case of diynes (**7a-c**), the dicyanative cyclization proceeded to form 5-membered carbo- and heterocycles and their stereoisomers were assigned to be *anti*-,*anti*-**8** and *anti*-,*syn*-**8**, respectively. The major products *anti*-,*anti*-**8** could be provided by bis *anti*-cyanopalladation to form **Vd** from **Vc**. The minor isomers of non-symmetric *anti*-,*syn*-**8** could be originated from *anti*-cyanopalladation-5-*exo* cyclization sequence through **Ve**. No observation of *syn*-,*syn*-**9** could explained that *syn*-cyanopalladation to **Vc** would be less operative.



Scheme 8. Diyne Cyclization Using **7** and Plausible Reaction Pathway

3-2. 6-*endo* Cyclization Using 1,6-Enynes

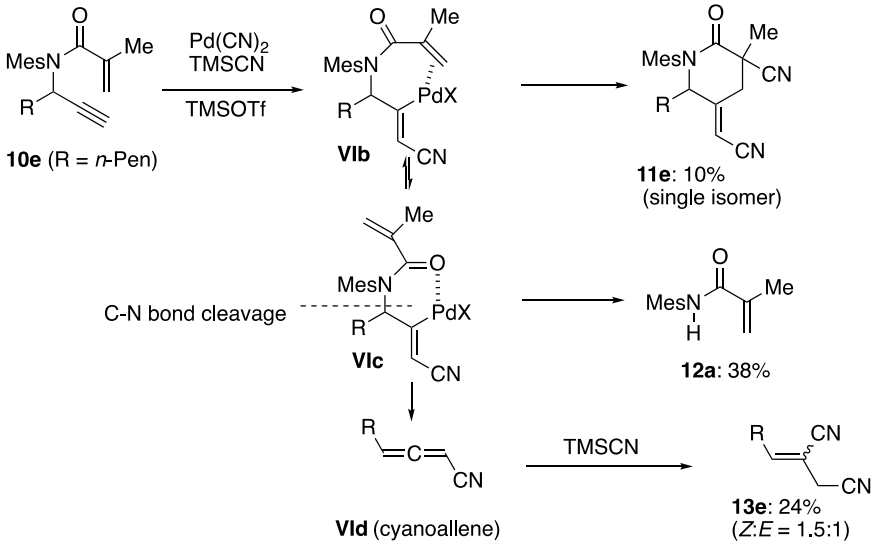
1,6-Enynes that include electron deficient olefins gave the stereocontrolled 6-*endo* cyclization products (**11**) (Scheme 9). This reaction would also be triggered by *syn*-cyanopalladation, and the sequential 6-*endo* cyclization via conjugated addition favorably proceeds to give the corresponding oxo-π-allyl Pd(II) intermediates (**VIa**), which could be transformed to **11** as a single cyclized product with the formation of quaternary carbons. The most reactive precursor was **10a**, which gave **11a** in 57% yield with the formation of **12a** in 37% yield, respectively. A bulky mesityl group on nitrogen and TMSOTf to activate a carbonyl group were both essential to increase the cyclization efficiency however, β-substituents on unsaturated amides (**10b-d**) gave serious problems; the formation of **12b-d** caused by C-N bond cleavage prevented the transformation to **11b-d** even though the total conversion did not change. For example, the corresponding dicyanoadduct (**11b**) was obtained only in 33% together with **12b** in 57% yield when hydrogen was replaced to a methyl group. In the case of **10d**, no cycloadducts were observed at all, whereas the exclusive formation of **12d** was observed in 74% yield.[28]



substrate	time (h)	**11a-d** (%)	**12a-d** (%)
10a	12	**11a**: 57	**12a**: 37
10b	7	**11b**: 33	**12b**: 57
10c	8	**11c**: 20	**12c**: 55
10d	8	**11d**: 0	**12d**: 74

Scheme 9. Dicyanative 6-*endo* Cyclization Using **10**

To understand these behaviors of the propargyl moiety in C-N bond cleavage, another precursor (**10e**) was next examined (Scheme 10). A similar treatment using TMSCN and TMSOTf with $Pd(CN)_2$ under molecular oxygen gave the isolable products of **11e**, **12a**, and **13e** in respective yields of 10%, 38%, and 24%. The structure of **13e** was fortunately determined to be 1,2-dicyanaoalkene, which could be provided by conjugated cyanation of **VId**. Its precursor could be proposed as **VIc**, which gives **12a** via β-nitrogen elimination as a non-cyclization pathway, whereas the corresponding rotamer (**VIb**) could be favorable for cyclization to **11e**. The above results suggest that the cyanoallene such as **VId** could be a key intermediate to design and predict alternative catalytic cycles and/or new reaction pathways, as described in the following section.

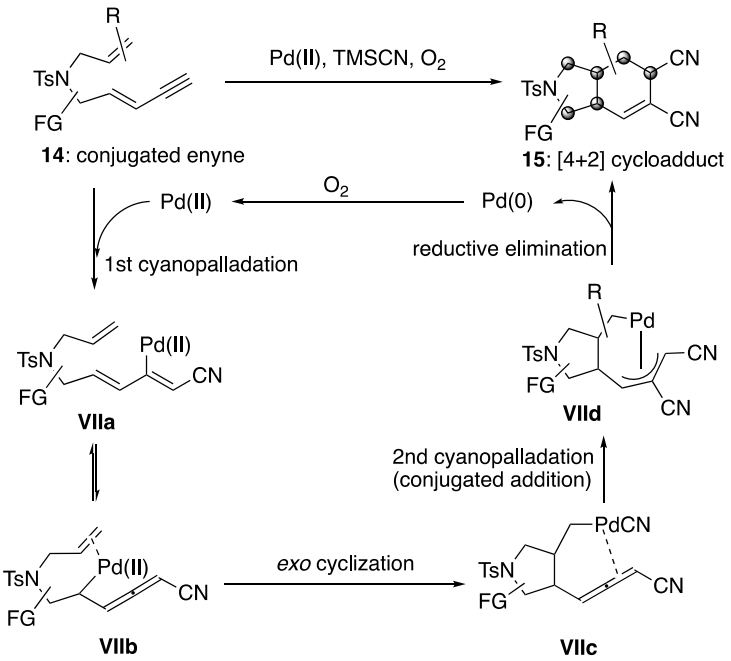


Scheme 10. A C-N Bond Cleavage in **10e**

3-3. [4+2] Cycloaddition Using Conjugated Enynes

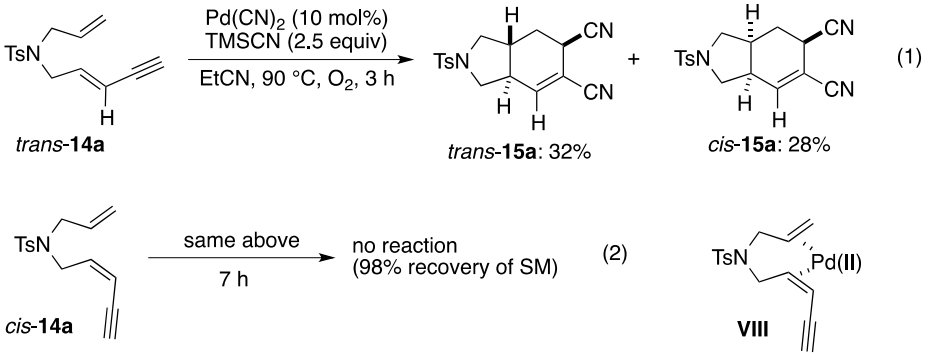
Based on the chemo-, regio- and stereoselectivity observed in enyne cyclizations, a new substrate for alternative dicyanative cycloaddition reaction could be proposed as follows (Scheme 11). The initial

cyanation would regioselectively occur at a terminal sp carbon even the presence of three C-C multiple bonds in **14** and gives **VIIa** that quickly isomerizes to **VIIb** to interact with terminal olefin. The following *exo*-cyclization would give **VIIc**, and then the external TMSCN promotes the second cyanopalladation (conjugated addition) to the allenyl sp carbon. The resulting π-allyl Pd(II) species (**VIId**) would prefer to cyclize to less-strained 6-membered ring (not 4-membered ring) via regioselective reductive elimination to give **15** with a release of Pd(0), that would be re-oxidized to Pd(II) by O_2. This plausible catalytic pathway would construct the bicyclic skeleton with maximum of six stereogenic centers through four C-C bond formations in one operation.



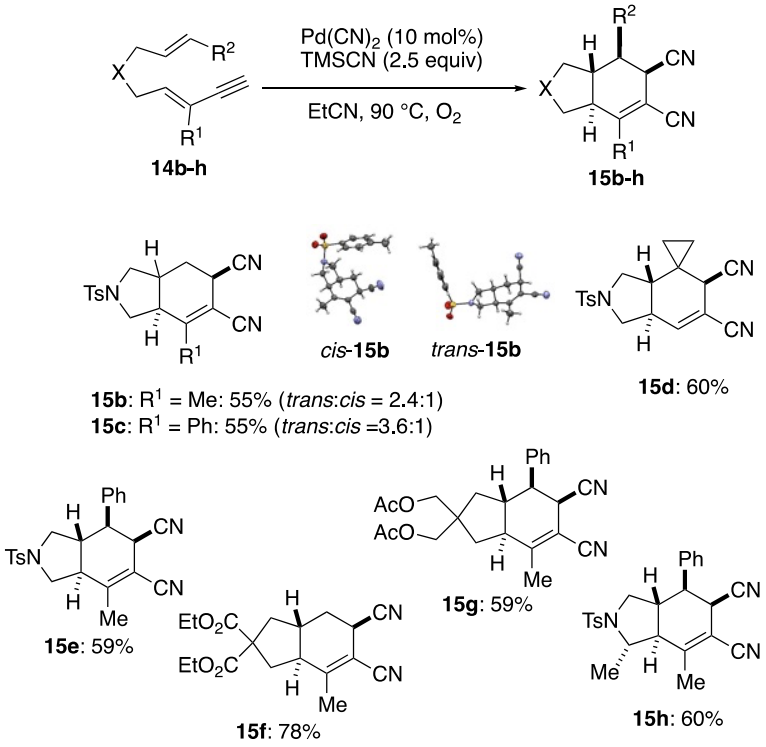
Scheme 11. Newly Designed Reaction Pathway for Dicyanative Cycloaddition

To confirm the above proposal, the influence of stereochemistry of the conjugated enyne was initially investigated by the use of *trans*- and *cis*-**14a** as the precursors. The former (*trans*-**14a)** was a suitable to proceed the dicyanative [4+2] cycloaddition smoothly and *cis*- and *trans*-**15a** were both given in respective yields of 28% and 32% (Scheme 12-1), whereas *cis*-**14a** was entirely inert for giving no reaction at all under similar conditions (Scheme 12-2). These results indicate that the reactivity for [4+2] cycloaddition reaction was highly dependent on the olefin geometry of **14**. The 1,6-diene moiety in *cis*-**14a** would be more favored to stabilize Pd(II) as a bidentate ligand to form **VIII**, and the activation of terminal alkyne would be unsuitable. In the case of *trans*-**14a**, the coordination of a C-C triple bond as well as double bonds to a Pd(II) center could be both operative to proceed cyanopalladation effectively. These would be the origin of the reaction behavior observed in between *trans*- and *cis*-**14a**.

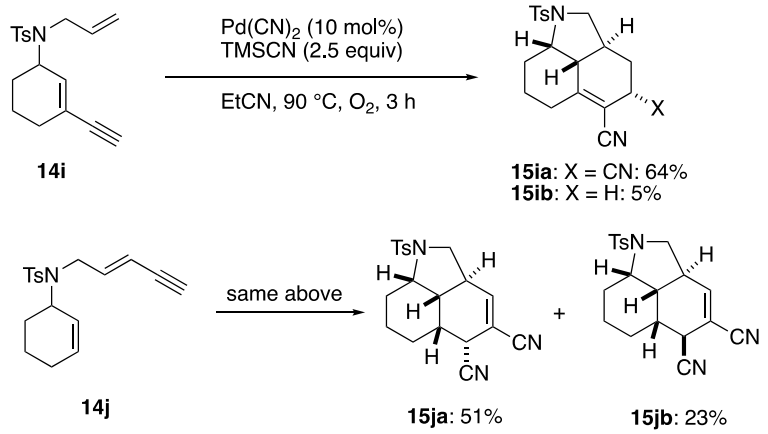


Scheme 12. Dicyanative [4+2] Cycloaddition Using **14a**

The substrate scope of the dicyanative [4+2] cycloaddition is summarized in Scheme 13. This cycloaddition enables to use various substituents on olefins such as hydrogen, methyl, cyclopropyl, and phenyl groups to give **15b-e** in the range of 55-60% yield. Stereoselectivity was fully controlled when R^2 is not hydrogen. Malonate derivatives such as **14f**,**g** were also suitable to construct carbocycles as single products (**15f**,**g**) in respective yields of 78% and 59%. Particularly, five contiguous stereogenic centers were fully controlled in one operation to give **15h** as a single isomer. In the case of cyclic dienyne precursors such as **14i**,**j**, the corresponding tricyclic structure was successfully constructed. In the case of **14i**, **15ia** was obtained in 64% together with **15ib** in 5% yield. The substrate bearing linear conjugated enyne (**14j**) was also effective to be transformed into the corresponding cycloadducts of **15ja** and **15jb** in respective yields of 51% and 23% (Scheme 14).[29-31]



Scheme 13. Scope of Dicyanative [4+2] Cycloaddition

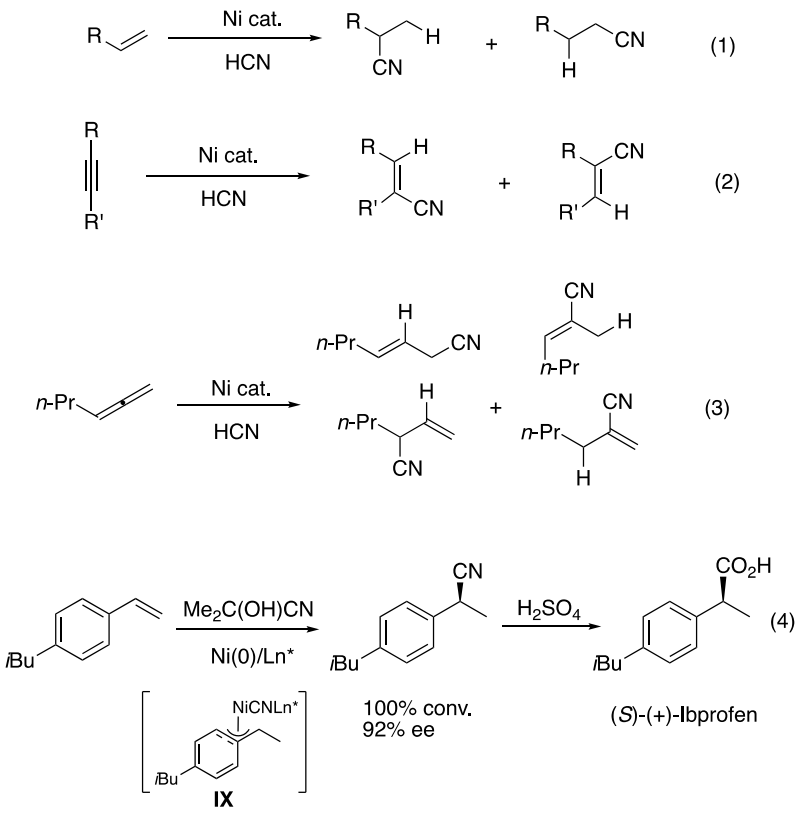


Scheme 14. Construction of Tricyclic System Using **14i**,**j**

4. NICKEL-CATALYZED HYDROCYANATIVE CYCLIZATION

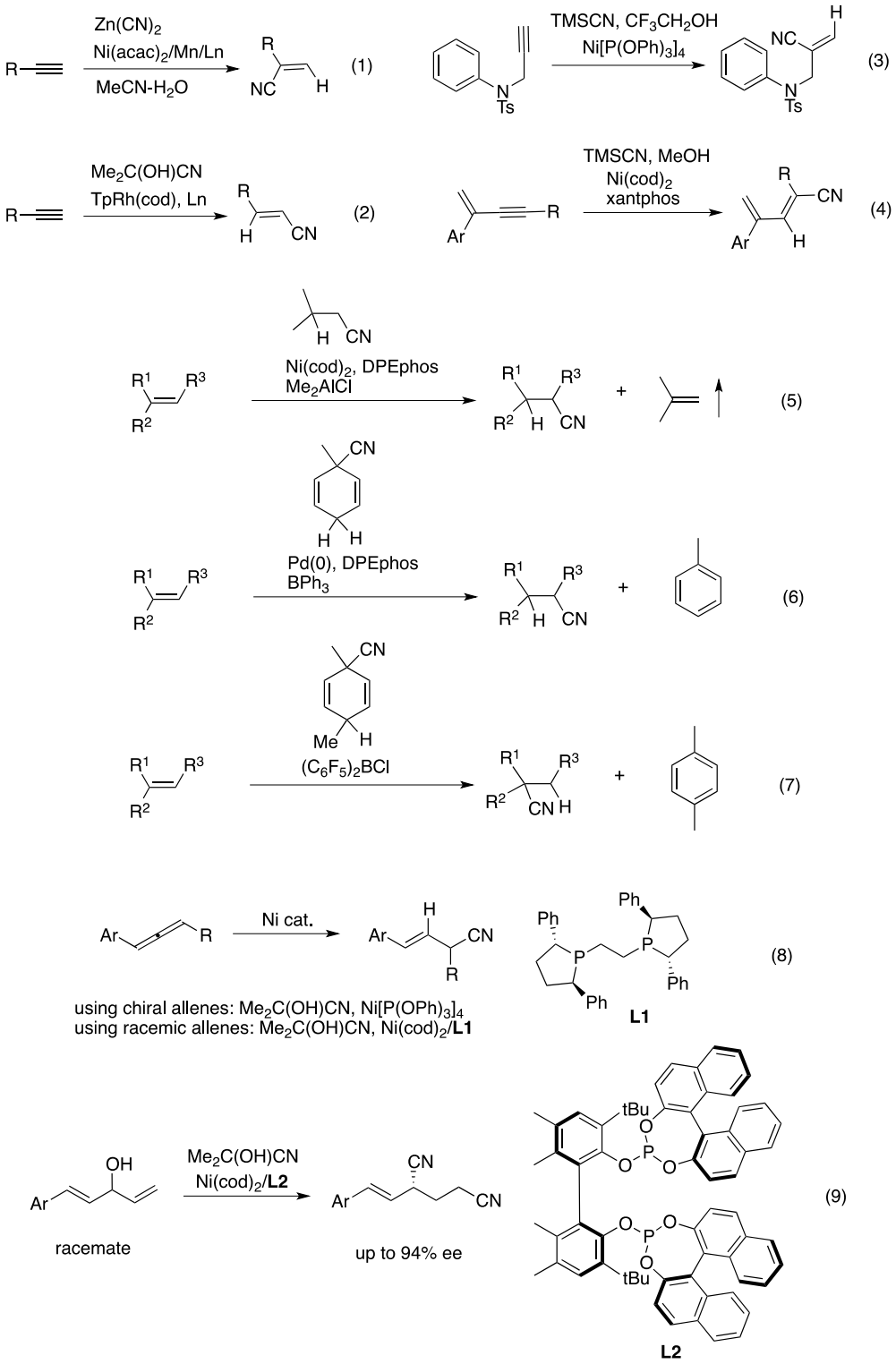
4-1. Hydrocyanation

Hydrocyanation of C-C multiple bonds has been one of the most historical, reliable and facile synthetic tools to obtain functionalized carbonitriles, and particularly nickel catalysis using various C-C unsaturated bonds such as alkenes, alkynes, and allenes has been a general and representative method (Scheme 15).[32] However their catalytic efficiency in above reactions are acceptable, the lower regio- and stereoselectivity in the products have been serious problems to be solved (Scheme 15-1). In the case of internal alkynes, lower regioselectivity is generally observed, except the sterically huge substituents are involved in substrates (Scheme 15-2).[20,21] Simple allene gives more complicated results because the differentiation of two C-C double bonds in the starting allene has been less controllable (Scheme 15-3).[33] On the other hand, the styrene derivatives ($ArCH=CH_2$) are the most reliable and well-investigated precursors because regiochemistry of the products is highly predictable. Aromatic functionalities contribute the predominant formation of a C-Ni bond at benzylic position to stabilize the resulting organonickel intermediate (**IX**).[34,35] This would be the origin for higher regioselectivity, and further application using a chiral ligand enables the enantioselective hydrocyanation for the synthesis of (*S*)-ibprofen (Scheme 15-4).[34]



Scheme 15. Ni-Catalyzed Hydrocyanation Using Various C-C Multiple Bonds

Hydrocyanation chemistry is still an attractive transformation among many synthetic chemists, and useful applications that achieve more practical conditions and higher regioselectivity have been recently reported (Scheme 16). Nemoto and co-workers use inexpensive nickel source as a catalyst with $Me_2C(OH)CN$ to demonstrate regioselective olefin hydrocyanation.[36] Liu and co-workers succeeded in alkyne hydrocyanation utilizing $Zn(CN)_2$ with H_2O as a HCN surrogate.[37] Rhodium-catalyzed hydrocyanation of terminal alkynes reported by Ritter group achieves higher *anti*-Markovnikov stereoselectivity (Scheme 16-2).[38] Sulfonyl group-assisted regioselective hydrocyanation of terminal alkynes[39] and regio- and stereocontrolled hydrocyanation of conjugated enynes[40] have been both achieved by use of TMSCN with alcohol under Ni catalysis (Scheme 16-3,4). Organonitriles also act as HCN surrogates to achieve *anti*-Markovnikov hydrocyanation of simple olefins under Ni and Pd catalysis (Scheme 16-5,6).[41,42] These practical transfer hydrocyanations enable to use cheap and non-toxic HCN source and side products are easily removable. In the case of boron catalysis, Markovnikov selectivity is observed in olefin hydrocyanation (Scheme 16-7).[43] Simple allenes that contains aryl groups are suitable for regio- and stereoselective transformation to give the corresponding allyl cyanide.[44] Axial chirality of optically active allenes are effectively transformed via diastereoselective hydrocyanation,[45] and racemic allenes are key precursors for catalytic asymmetric synthesis of allylcyanides using $Ni(cod)_2$-**L1** system (Scheme 16-8).[46] Racemic non-conjugated dienes with $Ni(cod)_2$/**L2** is smoothly transformed to the optically active 1,3-dicyanoalkenes with high enantioselectivity (Scheme 16-9).[47]

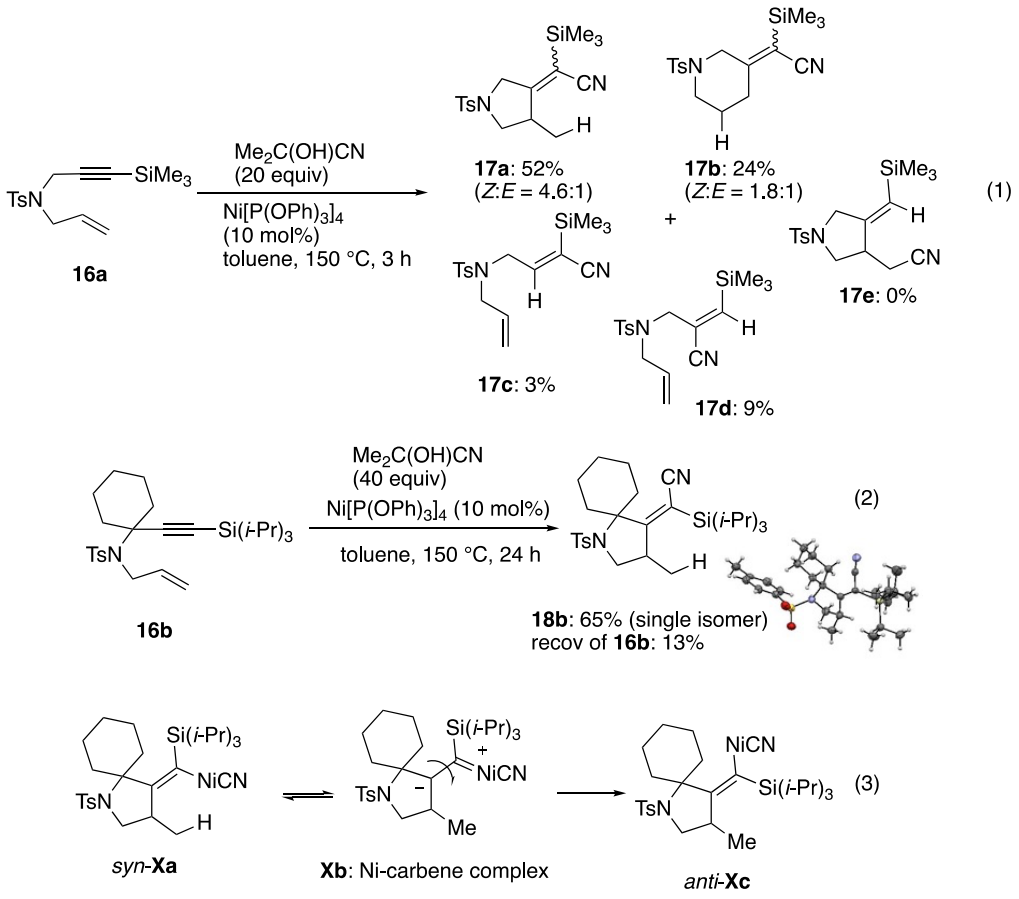


Scheme 16. Recent Hydrocyanation Under Metal Catalysis

4-2. Hydrocyanative Cyclization Using Enynes

Before starting this project by the authors, a detailed investigation focusing on the relative reactivity between C-C double and triple bonds on hydrocyanation have not been reported at all. Therefore, the evaluation of these functionalities using **16a** was initially examined under typical hydrocyanation

conditions using commercially available $Ni[P(OPh)_3]_4$ with $Me_2C(OH)CN$ (Scheme 17-1). The observed cyclic and non-cyclic products (**17a-d**) suggest that the initial hydronickelation to a multiple bond were not well-controlled in chemo-, regio- and stereoselectivity. Therefore, the structural modification by installing bulky triisopropylsilyl and cyclohexyl groups around a triple bond (**16b**) was next examined. However, the serious decrease of the reactivity was observed (150 °C, 24 h), a C-C double bond in **16b** selectively reacted to form a C-H bond and **18b** was given in 65% yield, exclusively (Scheme 17-2).[48] Its structural determination revealed that newly formed C-C bonds in **18b** were installed in the *anti*-orientation (*anti*-carbocyanation). The possible pathway could be described as follows; the initially formed *syn*-**Xa** provided by hydronickelative 5-*exo* cyclization would be transformed to *anti*-**Xc** via carbene intermediate (**Xb**),[49] which promotes a C-C single bond rotation for minimizing the steric repulsion between $Si(i\text{-}Pr)_3$ and cyclohexyl groups (Scheme 17-3).

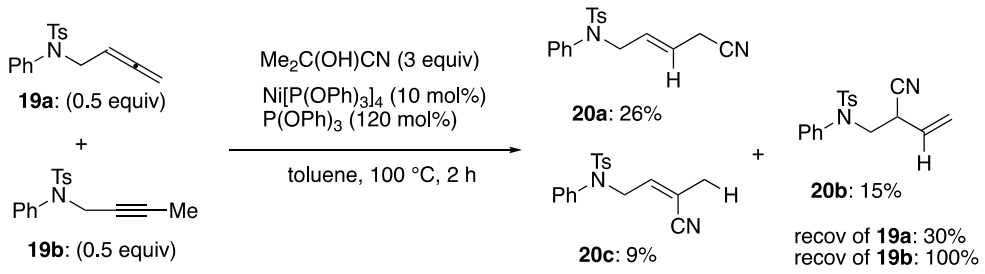


Scheme 17. Hydrocyanative Cyclization Using **16a,b**

4-3. Hydrocyanative Cyclization Using Allene-Ynes

For further improvement without the use of specific bulky substituents, allenes (C=C=C) as the alternative H acceptors were next examined instead of olefins. To understand the different reactivity between allenyl and alkynyl C-C multiple bonds, the competitive experiment using a mixture of **19a** and

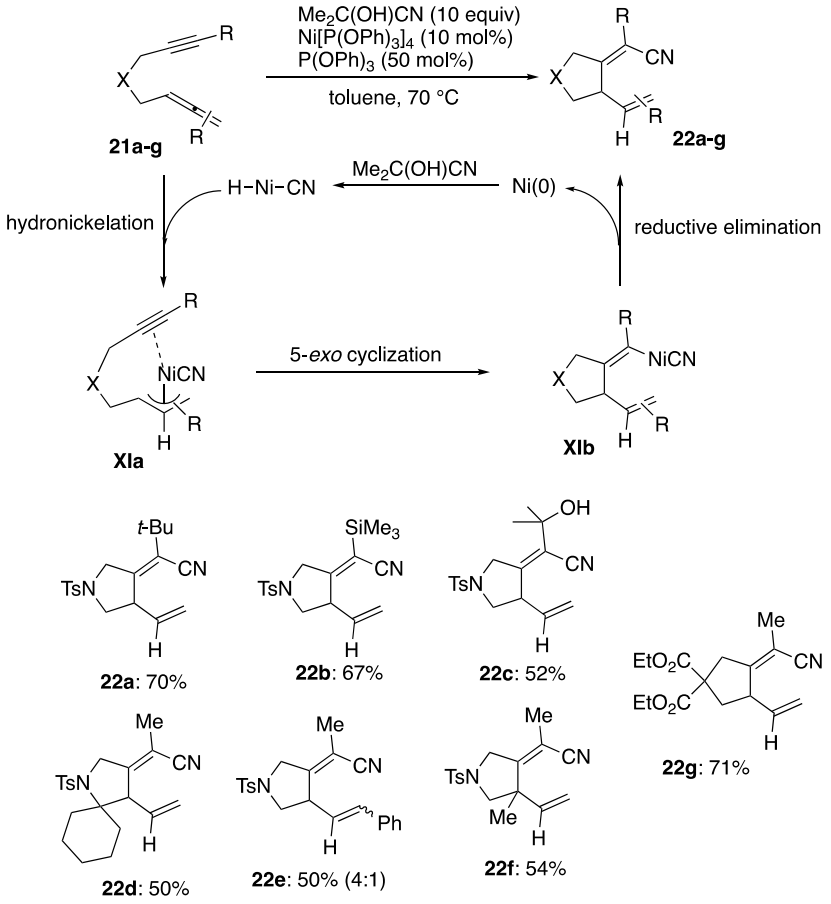
19b was employed under Ni catalysis (Scheme 18). Obviously, their relative reactivity between them was quite different and all the three products (**20a-c**) were originated from **19a** with a full recovery of **19b**. This result suggests that the allene is much more reactive than alkynes and more suitable for a hydrogen acceptor due to its electrophilicity of sp carbon. Therefore, these multiple bonds could be easily discriminated and the allene-ynes are expected to be reliable and useful precursors for the preparation of the cyano-functionalized heterocycles via a single reaction pathway.[50,51]



Scheme 18. Competitive Experiment Using **19a,b**

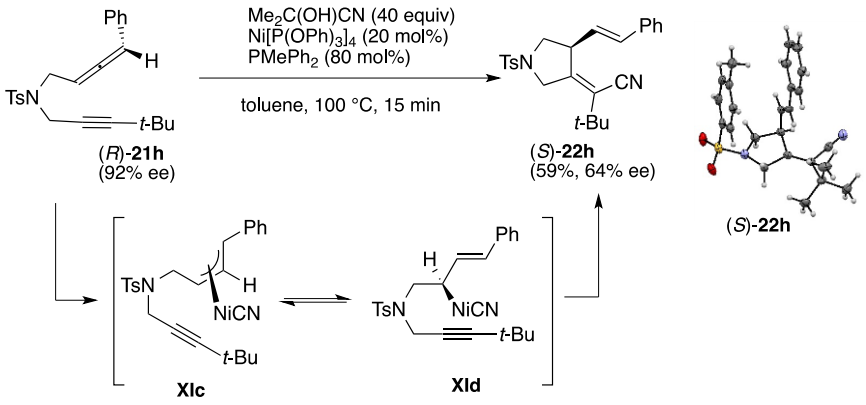
The plausible catalytic cycle is described in Scheme 19. The initial step would be hydronickelation to form a C-H bond at sp carbon of **21**. The resulting π-allyl Ni(II) intermediate (**XIa**) is suitable for the sequential *syn*-carbometalative cyclization to give alkenyl Ni(II) (**XIb**). Finally, tetrasubstituted olefin in **22** is formed with a release of Ni(0) via reductive elimination. The above mechanism clearly explains the regio- and stereochemistry in the cyclization products, and the following substrate scope gave a rational understanding of the behavior of the catalyst and substrates.

In fact, nitrogen- and carbon-tethered cyclization precursors were both effectively transformed via 5-*exo* mode to give the corresponding cyclic compounds through one operation. Bulky substituents such as *tert*-butyl and trimethylsilyl as well as free OH groups were all applicable for this cyclization to give **22a-c** with highly regio- and stereoselective manner. Quaternary carbons were installed in the pyrrolidine ring (**22d**,**f**), and 1,1- and 1,3-disubstituted allenes (**21e**,**f**) were also applicable. A highly functionalized cyclopentene ring (**22g**) was also constructed by using a malonate derivative (Scheme 19).[52-55]



Scheme 19. Hydrocyanative Cyclization: Plausible Mechanism and Substrate Scope

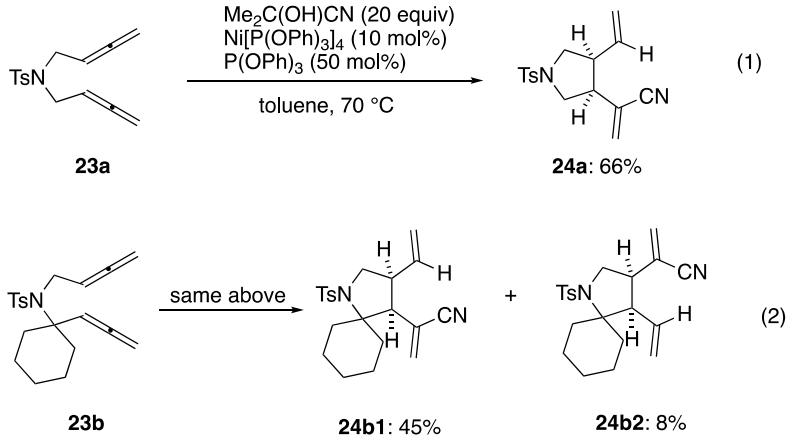
This method could be applied for the chirality transfer process using (*R*)-**21h**. The cyanative cyclization using Ni(0) with $MePPh_2$ smoothly proceeded to give (*S*)-**22h** with 64% ee, which absolute configuration was estimated by X-ray crystallographic analysis (Scheme 20). This result suggests that the axial chirality of allene can be transferred to both π- and σ-allyl Ni(II) intermediates (**XIc**,**d**) (Scheme 20). The decrease of enantiomeric excess during the reaction could be caused by the racemization of the axial chirality of **21h**.[50]



Scheme 20. Enantioselective Cyclization Using (*R*)-**21**

4-4. Hydrocyanative Cyclization Using Bisallenes

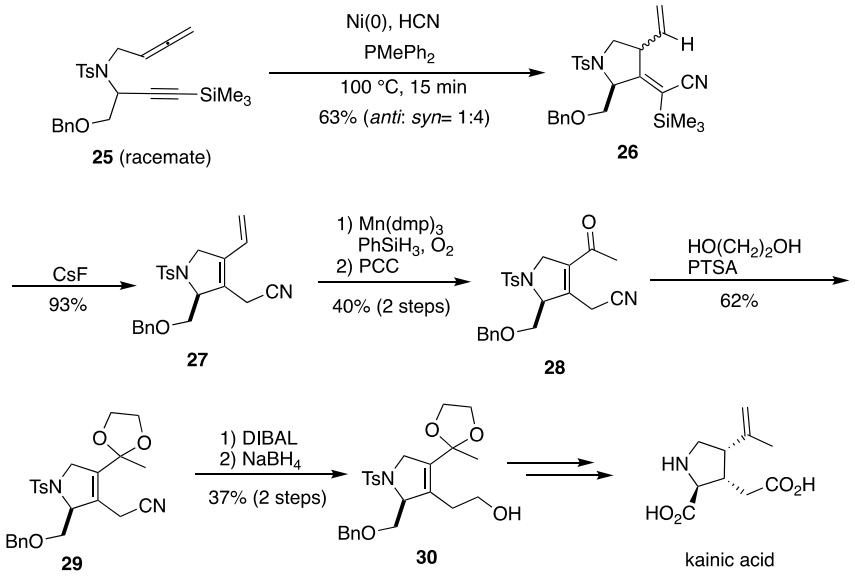
Bisallenes were also reactive components to proceed hydrocyanative cyclization with regio- and stereoselective manner.[53] Symmetric bisallene (**23a**) was suitable for the exclusive formation of **24a** via *cis*-selective 5-*exo* cyclization (Scheme 23-1). Steric environment around allenyl C-C double bonds was sensitive to determine the selectivity, for example, **24b1** was given as a major product from **23b** because the initial hydronickelation would prefer the less hindered allenyl sp carbon.



Scheme 21. Hydrocyanative Cyclization **23**

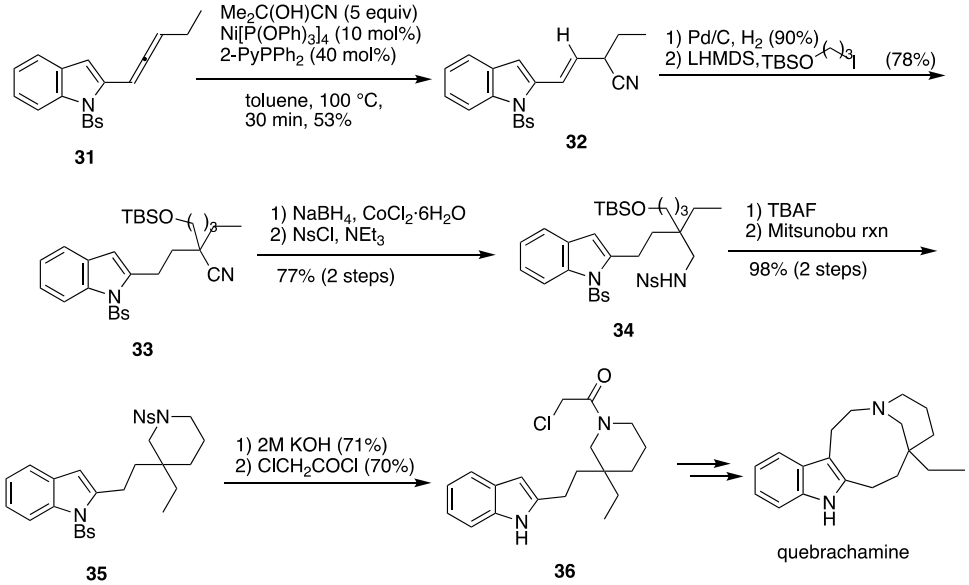
4-5. Application to the Synthesis of Alkaloids

Cyano-functionalized pyrrolidine derivatives were useful structural motifs for the synthesis of biologically important molecules, and the authors aimed to apply for the formal synthesis of kainic acid (Scheme 22).[50] The key reaction was hydrocyanative cyclization using **25** to give a mixture of the desired 5-membered ring (**26**). Both diastereomers were applicable for further transformation. The removal of a trimethylsilyl group with CsF gave the conjugated diene (**27**), which was transformed to **28** via Mukaiyama hydration[56] followed by PCC oxidation in 40% yield (2 steps). The resulting methyl ketone (**28**) was employed under acidic conditions to accomplish acetalization and **29** was obtained in 62% yield. Finally, sequential reduction of nitrile to a primary hydroxy group via aldehyde successfully gave Trost's key intermediate (**30**)[57] for kainic acid synthesis.



Scheme 22. Formal Synthesis of Kainic Acid

Simple allenes were also applicable for regio- and stereoselective hydrocyanation when aryl substituents are introduced to allenes.[44,45] The authors utilized the indole derivatives (**31**) for the formal synthesis of quebrachamine.[50,58] Two double bonds in **31** were critically differentiated in Ni-catalyzed hydrocyanation to give **32** as a single product. The stereochemistry of the double bond in **32** was controlled to be trans with the conjugation of the indole moiety. Sequential hydrogenation followed by alkylation using LHMDS with $TBSO(CH_2)_3I$ gave **33** in 78% yield (2 steps). A cyano group was successfully converted to the corresponding amide (**34**) via a reduction-sulfonylation sequence. Then, the removal of a TBS group by TBAF and Mitsunobu reaction promoted intramolecular alkylation to give **35** in 98% yield.[59] Finally, the known intermediate (**36**)[60] of quebrachamine was synthesized by the removal of a nosyl group followed by chloroacetylation (Scheme 23).

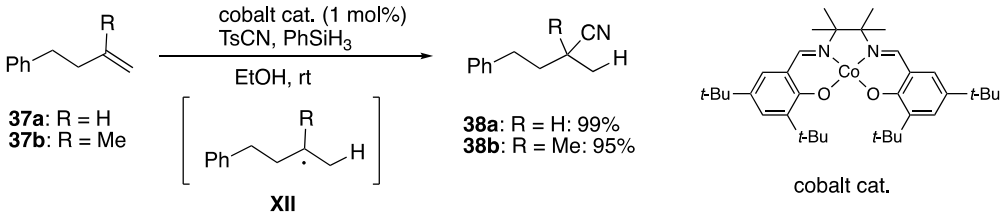


Scheme 23. Formal Synthesis of Quebrachamine

5. COBALT-CATALYZED HYDROCYANATIVE CYCLIZATION AND RELATED REACTIONS

5-1. Background

Since Carreira and a co-worker have succeeded in cobalt-catalyzed hydrocyanation, radical-mediated hydrocyanation to non-activated C-C multiple bonds has been an attractive synthetic tool because of practical benigns (Scheme 24). They demonstrated to use terminal olefins such as **37a**,**b** with a Co(salen) complex in the presence of TsCN and $PhSiH_3$, and obtained highly regiocontrolled secondary and tertiary carbonitriles at room temperature.[61] They proved lower catalyst loading (1 mol%) was enough to achieve high conversion and regioselectivity, which was provided by the generation of **XII** through regioselective hydrogen atom transfer process. These achievements could offer the applications using dienes as precursors for the synthesis of cyano-functionalized heterocycles.

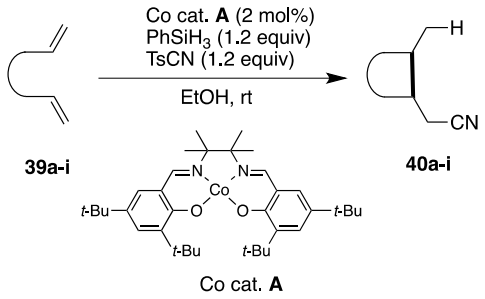


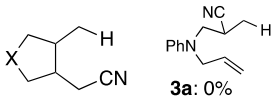
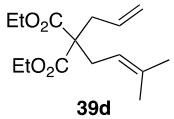
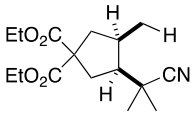
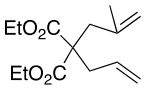
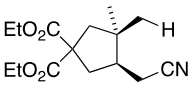
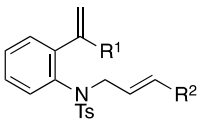
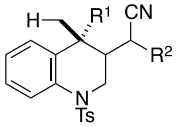
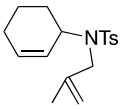
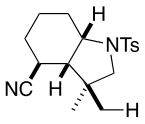
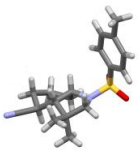
Scheme 24. Carreira's Hydrocyanation Using Simple Olefins Under Co catalysis

5-2. Hydrocyanative Cyclization of Dienes

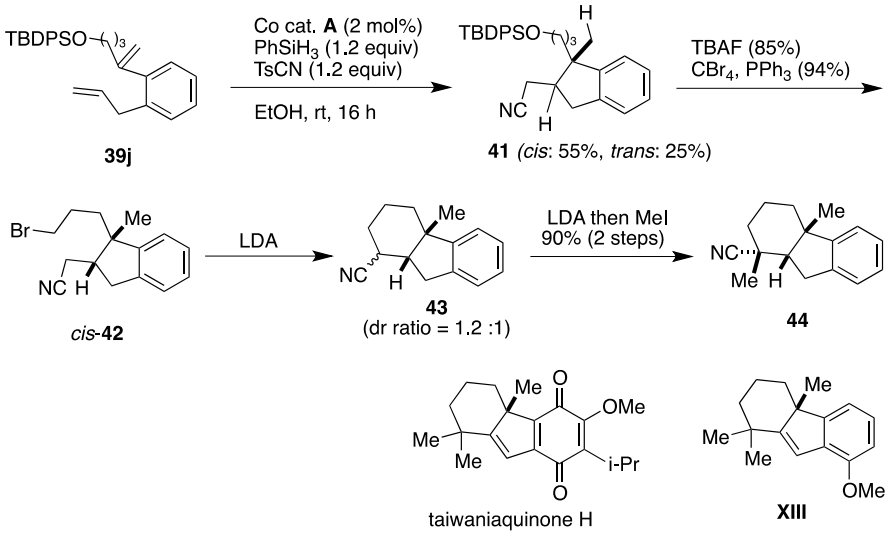
As expected, dienes (**39a-i**) were suitable precursors for the synthesis of carbo- and heterocycles under cobalt catalysis (Table 1). In the case of symmetric diene (**39a-c**), internal sp^2 carbons were effectively connected to form 5-membered ring (entry 1-3). Lower selectivity and conversion were observed in the reaction using **39a**,**b**. Notably, a malonate derivative (**39c**) gave a single diastereomer of *cis*-**40c** in 82% yield. Mono- and trisubstituted olefins in **39d** were easily discriminable, and the former was found to be a suitable hydrogen acceptor to give *cis*-**40d**, exclusively (entry 4). The reactivity between mono- and 1,1-disubstituted olefin in **39e** was also controllable by installing a CN group into mono-substituted olefin with construction of a quaternary carbon. The initial hydrogen transfer favorably occurs at more substituted olefin to generate tertiary carboradical species, which smoothly cyclize via *exo* mode to give **40e** in 72% yield. Among the aniline derivatives, the conjugated olefins were more reactive and suitable for hydrogen transfer process, and the corresponding 6-membered ring products (**40f-h**) were given in 58-90% yield (entry 6-8). When the cycloalkene such as **39i** was employed under similar conditions, three contiguous stereogenic centers in **40i** were fully controlled to construct bicyclic system and its structure was confirmed by X-ray crystallographic analysis (entry 9).[62]

Table 1. Substrate Scope for Hydrocyanative Cyclization Using **39**



entry	substrates	time (h)	products
			 **3a**: 0%
1	**39a**: X = NPh	24	**40a**: 47% (*cis:trans* = 2.4:1)
2	**39b**: X = NTs	6	**40b**: 68% (*cis:trans* = 2.6:1)
3	**39c**: X = $C(CO_2Et)_2$	4	*cis*-**40c**: 82%
4	 **39d**	9	 *cis*-**40d**: 62%
5	 **39e**	9	 **40e**: 72%
			
6	**39f**: R^1 = Me, R^2 = H	2	**40f**: 71%
7	**39g**: R^1 = R^2 = Me	2	**40g**: 90% (dr = 1.9:1)
8	**39h**: R^1 = Et, R^2 = H	2	**40h**: 58% (dr = 1.3:1)
9	 **39i**	3	 **40i**: 70% (single isomer) 

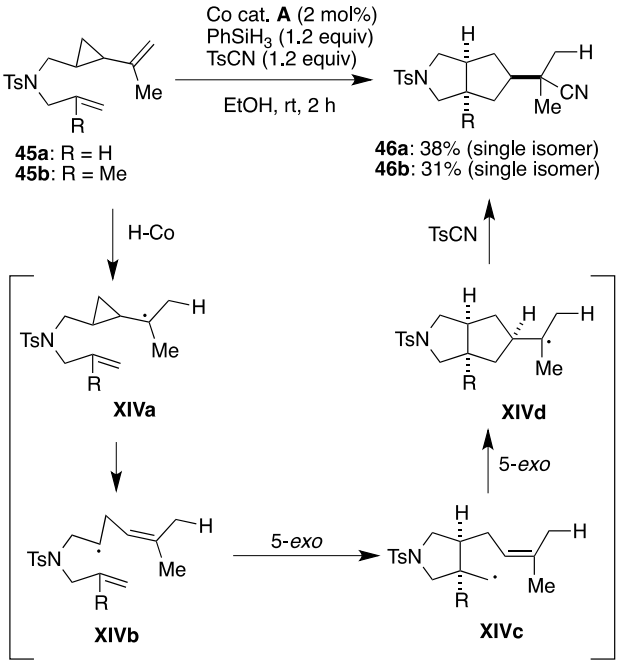
Synthetic application to an indene derivative (**44**) was next investigated. Taiwaniaquinone and its synthetic intermediates (**XIII**)[63,64] have two quaternary carbons, and their basic flamework could be synthesized by two cyclization sequence introducing a cyano group (Scheme 25). The key hydrocyanative cyclization using **39j** gave **41** as a mixture of stereoisomers (*cis*-**41**: 55%, *trans*-**41**: 25%). After isolation of *cis*-**41**, the deprotection of a TBDPS group followed by bromination gave *cis*-**42**. And then, the intramolecular alkylation gave tricyclic system (**43**), and the resulting diastereomers were both transformed to **44** via stereoselective methylation in 90% yield (2 steps).



Scheme 25. Synthetic Application to Tricyclic Core

5-3. Cyclopropane Cleavage

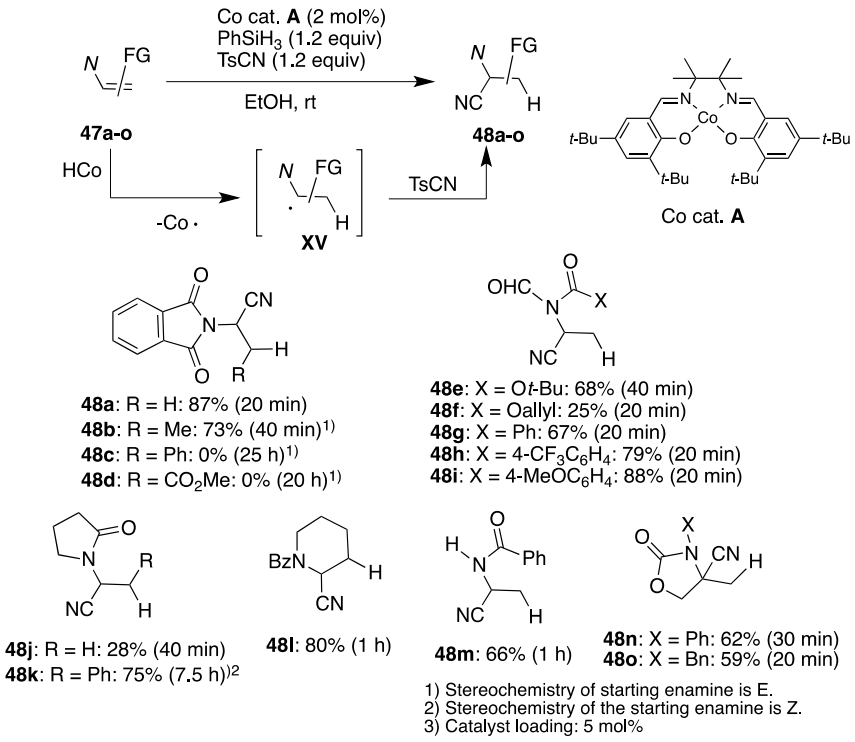
Alkenylcyclopropanes were also suitable functionalities for the regioselective generation of carboradical species. Dienes in **45a**,**b** were easily discriminable to promote hydrocyanative [3+2] cycloaddition by forming bicyclo[3.3.0]skeleton in one operation (Scheme 26). The terminal olefin bearing a cyclopropyl group were more feasible to accept hydrogen to give **XIVa**, which were quickly transformed to **XIVb** via cyclopropane cleavage. Sequential 5-*exo* cyclizations took place to give tertiary carboradical (**XIVd**) via **XIVc** with stereoselective manner. Finally, the catalytic cycle would be terminated by radical cyanation with TsCN to give **46a**,**b**, as a single isomer.[62]



Scheme 26. Hydrocyanative [3+2] Cycloaddition Using **45**

5-4. Hydrocyanation of Enamines

One of the most significant synthetic advantages using cobalt catalysis is a neutral condition that enables to use of acid-sensitive substrates such as enamines, the key precursors for the synthesis of amino acids and their derivatives. The authors realized that this radical cyanation could be a key practical process to prepare functionalized aminonitriles (Scheme 27). The reaction initially generates H-Co species from $PhSiH_3$ with a Co complex, and the regioselective hydrogen transfer would give **XV** that reacts with TsCN to terminate the catalytic cycle providing with α-aminonitriles (**48**). When the phthalimide derivatives (**47a-d**) were examined, the β-substituents were found to be quite sensitive for the reaction efficacy; for example, hydrogen and methyl groups completed the reaction within 20 and 40 min to give **48a**,**b**, respectively however, phenyl and ester functionalities did not give any products atall (**48c**,**d**). The predicted β-CN adducts were not observed at all in these reactions. In the case of formamides, the reactions were completed in 40 min to provide the corresponding aminonitriles in 25-88% yield (**48e-i**). Lactams and the cyclic enamine were all suitable to give **48j-l** in 28-80% yield. An NH free, as well as oxazolidone derivatives also proceeded regioselective hydrocyanation to give **48m-o** in 59-66% yield.[65]

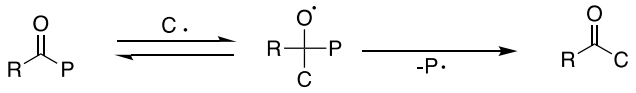


Scheme 27. Scope for Co-Catalyzed Hydrocyanation Using **47**

5-5. Hydroacylative Cyclization Using Acylphosphates

The above cyanation protocol was also applicable for alternative radical-mediated C-C bond formation. The authors focused on easily cleavable C-P bonds with nucleophilic radical species. The activated C-P

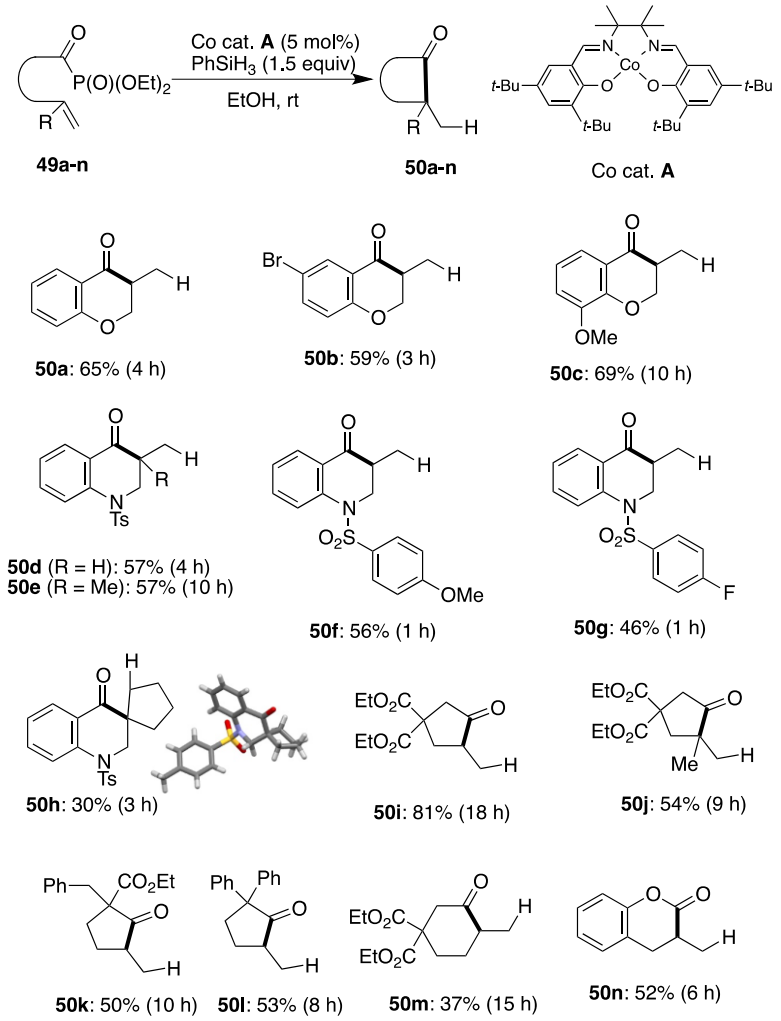
bonds in acylphosphates seem to be suitable candidates for radical carbonylation under cobalt catalysis (Scheme 28) however, their synthetic application has been limited in photochemical transformations that require hash conditions.[66-68] Therefore, the authors investigated the intramolecular acylation of **49** to evaluate their utility as synthetic transformation.



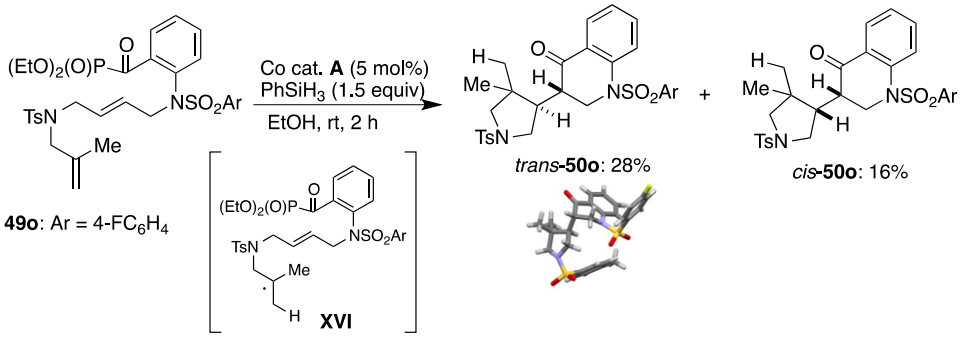
Scheme 28. Radical Addition to Acylphosphates

Cobalt catalysis using **49a** with phenylsilane ($PhSiH_3$) was effective to proceed intramolecular acylation reaction at room temperature and the cycloalkenone (**50a**) was given in 65% yield without any formation of the regioisomers. Various functionalities on aromatic rings such as bromo, fluoro, methoxy and sulfonamide were all suitable for the smooth cyclization giving **50b-g** in 46-69% yield. Various carbocycles including quaternary carbons or spiro structure as well as lactone, were all synthesized from the corresponding precursors by this protocol (Scheme 29).

The application to the tandem cyclization using dienyl acylphosphates (**49o**) was next investigated (Scheme 30). To minimize the possible reaction pathways, a choice of olefins was a key and easily differentiable C-C double bonds through hydrogen transfer process were installed in a substrate. As a result, the sequential cyclization smoothly proceeded to give a mixture of stereoisomers (**50o**) in 44% yield. The initial H transfer would prefer at 1,1-disubstituted olefin to give tertiary carboradical (**XVI**), and the following 5-*exo* and acylative cyclizations give **50o** as a mixture of stereoisomers. A structural assignment of a major product was established to be trans by X-ray crystallographic analysis.[62]



Scheme 29. Scope for Hydroacylative Cyclization Using **49**

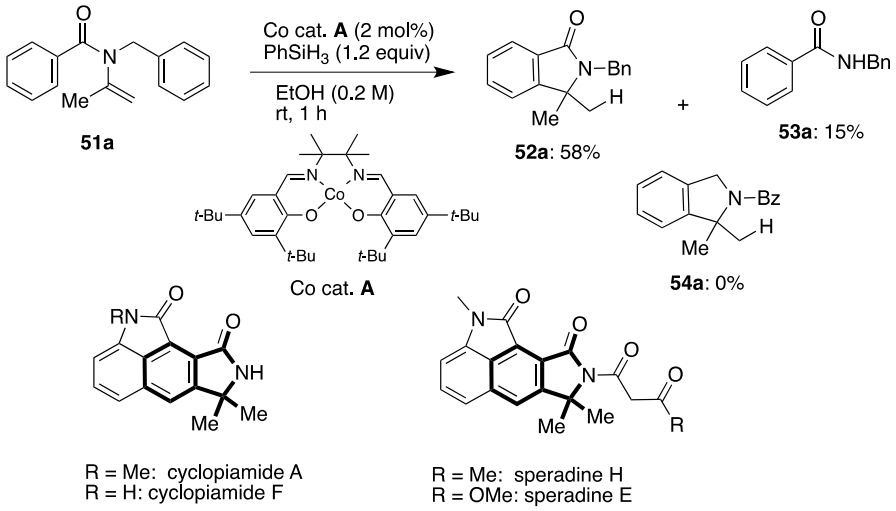


Scheme 30. Tandem Cyclization Using **49o**

5-6. Hydroarylative Cyclization Using Enamines

The carboradical species generated from enamines were also reactive with the electron poor aromatic rings. For example, a benzoyl aromatic ring acts as a radical acceptor to form a new C-C bond under cobalt-catalysis. Significant point is that **51a** was exclusively transformed to **52a** through complete

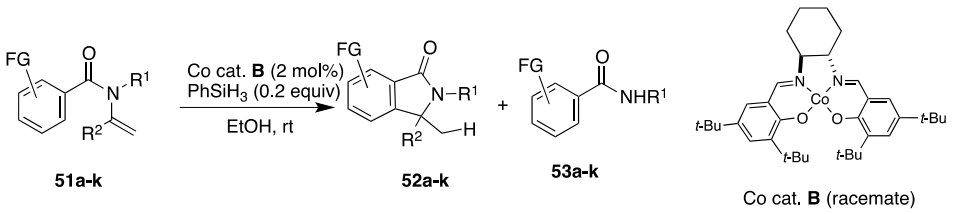
discrimination between benzoyl and benzyl aromatic rings (Scheme 31). This reaction made it possible for facile construction of a quaternary carbon including biologically important flamework in one operation.[70,71]



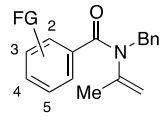
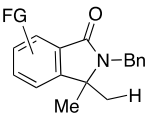
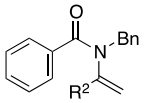
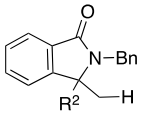
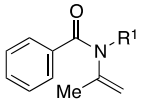
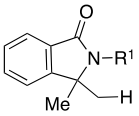
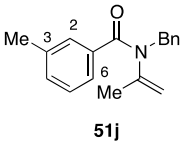
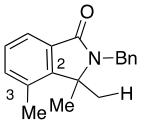
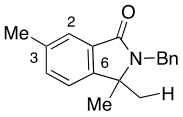
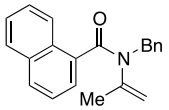
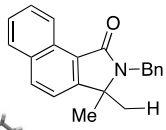
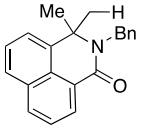
Scheme 31. Initial Attempt for Hydroarylation

Detailed investigation revealed that Co. cat **B** was more effective, and the typical conditions (**51** with $PhSiH_3$ in EtOH at rt) was employed to investigate the substrate scope for this hydroarylative cyclization (Table 2). Various substituents of bromo, fluoro, alkyl and CF_3 groups on benzene ring are all applicable for this cyclization giving a sole product in good to excellent yield (entry 1-5). Phenethyl, allyl and ester instead of a benzyl group are all suitable to provide the corresponding lactams (**52f-i**) (entry 6-9). Non-symmetric aromatic rings in **51j**,**k** gave a mixture of regioisomeric products (**52j**,**k**) in both cases. The former substrate favorably cyclized at C2 over C6 position due to the radical stabilization effect by a methyl group at C3 in the resulting intermediate, and **52j-1** would be given as a major product (entry 10).[72] In the case of an α-naphthyl group (**51k**), both 5- and 6-membered ring formation are observed without any selectivity to give **52k-1** and **52k-2**. The structural determination of the former isomer was established by X-ray crystallographic analysis (entry 10).[65]

Table 2. Scope for Cobalt-Catalyzed Hydroarylative Cyclization Using **51**



51a-k **52a-k** **53a-k** Co cat. **B** (racemate)

entry	substrates	time (h)	products		
1 2 3 4 5		**51a**: FG = H **51b**: FG = 4-CF_3 **51c**: FG = 2-Br **51d**: FG = 3,5-Me_2 **51e**: FG = 3,5-F_2	0.5 0.5 0.5 0.5 0.5		**52a**: 90% **52b**: 83% **52c**: 73%[1] **52d**: 93% **52e**: 94%	**53b**: 6%
6 7		**51f**: R^2 = $(CH_2)_2Ph$ **51g**: R^2 = CO_2Me	2 5		**52f**: 68%[2] **52g**: 74%	**53f**: 8%
8 9		**51h**: R^1 = $(CH_2)_2Ph$ **51i**: R^1 = allyl	0.5 4		**52h**: 90% **52i**: 41%[2,3]	**53h**: 2%
10	 **51j**		0.5	 **52j-1**: 64%	 **52j-2**: 25%	**53j**: 5%
11	 **51k**		0.5	 **52k-1**: 36%	 **52k-2**: 39%	

1) $PhSiH_3$ (0.4 eq) was used.
2) $PhSiH_3$ (3 eq) was used.
3) Catalyst loading: 7 mol%

6. CONCLUSIONS

All the protocols shown above provide broad synthetic applications for the synthesis of cyano-, acyl- and aryl functionalized hetero- and carbocycles under transition metal catalysis. Various precursors such as enynes, diynes, dienynes, allene-ynes, simple allenes, bisallenes, dienes, enamines as well as cyclopropane derivatives are all efficiently transformed to the corresponding adducts with chemo-, regio- and stereoselective manner. These achievements are key findings to prove their potential of metal-catalyzed cyanation and related reactions in synthetic organic chemistry and further progress will enhance the efficiency for creating useful molecules and transformations.

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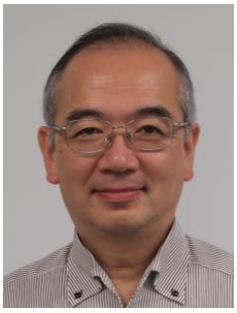

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