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Highlight Review

Renaissance of Organic Synthesis Using Isocyanides

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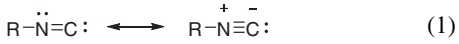
Abstract

New reactions using old functionality, isocyanides, are described. By using isocyanides in place of carbon monoxide, transformations otherwise difficult to achieve, such as $GaCl_3$-catalyzed [4 + 1] cycloaddition and TfOH-catalyzed insertion into a C–O bond of acetals, are realized. In addition, isocyanides are exploited as a key component in transition-metal-catalyzed C–H bond activation and borylation reactions.

♦ Introduction

Originally discovered as isomers of cyanides in the late 1860's,[1] isocyanides are now recognized as unique building blocks for use in organic synthesis.[2] The uniqueness of isocyanides stems from a structural feature wherein the terminal carbon atom is formally divalent (eq 1), which enables these molecules to react with electrophiles, nucleophiles, and radicals. In addition, isocyanides are frequently employed as two-electron-donating ligands in organometallic chemistry.[3] Rather than simply serving as a spectator, isocyanides are also activated on organometallic complexes to be utilized as substrates for new catalytic transformations.

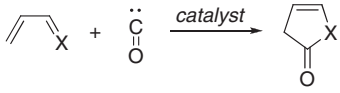


(1)

Based on the diverse modes of reactivity exhibited by isocyanides, numerous reactions have been developed. Multicomponent Passerini and Ugi reactions are arguably among the most popular processes in isocyanide chemistry.[4] Isocyanides also serve as versatile starting materials for the synthesis of nitrogen heterocycles.[5] Despite advances in the reactions of isocyanides, there remains much need to expand the scope, particularly in the context of a formal reaction pattern, to fully exploit the potential utility of isocyanides. We recently developed a series of new transformations using isocyanides as a key component with the aid of acid or transition-metal complexes. In some cases, we revisited some of the classical stoichiometric reactions and developed them into catalytic variants with a significantly expanded scope by adopting new catalysts.[6] In other cases, we introduced contemporary concepts, such as C–H activation, in the reaction development using isocyanides. This Highlight Review describes our recent endeavors in developing new transformations using isocyanides, with special emphasis on the reasoning behind the design of the reactions.

♦ Initial Finding: [4 + 1] Cycloaddition

In the late 1990s, our interests were directed to the development of catalytic carbonylative cycloaddition, wherein carbon monoxide (CO) was used as a C1 component in cycloaddition reactions.[7] Such ring-forming reactions represent a powerful and atom-economical strategy for the synthesis of cyclic carbonyl compounds, as exemplified by cyclopentenone synthesis via the Pauson–Khand reaction. In the course of our study along this line, we discovered a ruthenium-catalyzed [4 + 1] cycloaddition of α,β-unsaturated imine and CO, which leads to the construction of an unsaturated γ-lactam framework (Scheme 1c).[8] Naturally, we subsequently pursued the possibility of applying this [4 + 1] strategy to the corresponding α,β-unsaturated carbonyl compounds in the hope of assembling γ-lactones (Scheme 1b). However, all attempts to this end were unsuccessful.



(a) X = C no example but stoichiometric (Fe: 1992)
(b) X = O no example
(c) X = N *catalytic* (Ru: 1999)

Scheme 1. [4 + 1] Carbonylative cycloadditions.

The isoelectronic relationship between CO and isocyanides led us to examine [4 + 1] cycloaddition of α,β-unsaturated carbonyl compounds and isocyanides. We expected the reaction to be realized since the reactivity of isocyanides is tunable both electronically and sterically, which represents an eminent nature that CO does not possess. Thus, a variety of transition-metal complexes were examined for their ability to catalyze the desired [4 + 1] cycloaddition using several electronically and sterically different isocyanides. However, again, no γ-lactone derivatives were obtained in any case. Finally, we envisioned that a Lewis acid would promote the target reaction in view of the well-precedented nucleophilic reactivity of isocyanides combined with electrophilic activation of α,β-unsaturated carbonyls by Lewis acids. Our experience in alkyne activation by a $GaCl_3$ catalyst[9,10] prompted us to initially examine this Lewis acid, since it was hoped that the softness of $GaCl_3$ would allow for an efficient catalyst turnover in the presence of the polar functional groups. To our delight, the [4 + 1] cycloaddition of enone and isocyanide indeed occurred in the presence of a $GaCl_3$ catalyst (eq 2).[11]

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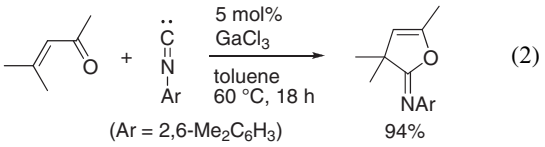
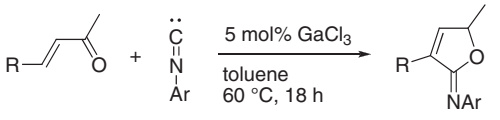


(2)

Soon after we obtained these intriguing results in 2000, we noticed that Ito and Saegusa had reported that virtually the same reaction (using methyl isocyanide) could be promoted by a stoichiometric amount of Et_2AlCl in 1982.[12] Despite this pioneering work, we decided to pursue our gallium-catalyzed reaction, because the reaction demonstrates the first example of the *catalytic* [4 + 1] cycloaddition of enones and isocyanides, and also because we expected the reaction to serve as a basis for further development of soft Lewis acid-catalyzed processes using isocyanides.

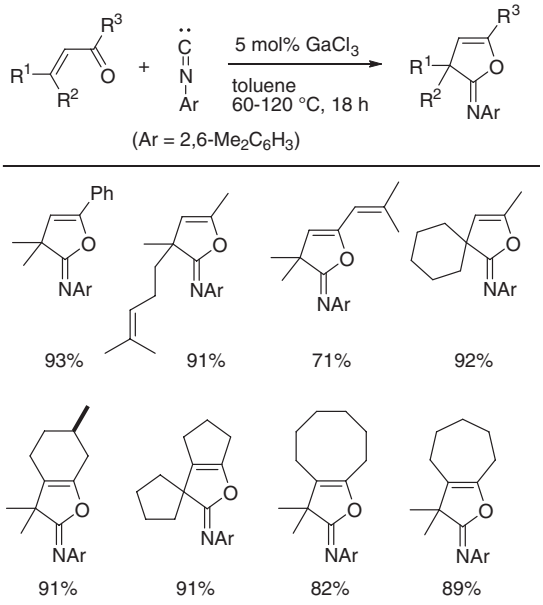
Catalyst screening revealed that, apart from $GaCl_3$, several Lewis acids, including $ZrCl_4$ (71%), $Yb(OTf)_3$ (60%), and $In(OTf)_3$ (44%), catalyzed the reaction shown in eq 2. To our surprise, 5 mol % of Et_2AlCl also afforded the product in 87% yield when 2,6-$Me_2C_6H_3NC$ was used. Further studies established that $GaCl_3$ is the optimal catalyst in terms of both catalytic activity and substrate generality. Regarding the structure of isocyanides, aromatic substituents, especially those bearing sterically demanding or electron-withdrawing groups, were suitable and aliphatic isocyanides were not: 2,6-*i*-$Pr_2C_6H_3NC$ (94%), 2-MeC_6H_4NC (65%), 2,6-$(CF_3)_2C_6H_3NC$ (92%), 2-$CF_3C_6H_4NC$ (85%), *t*-BuNC (24%), and cyclohexyl-NC (trace).

A diverse array of acyclic and cyclic enones can participate in this $GaCl_3$-catalyzed cycloaddition with isocyanides to efficiently furnish the corresponding iminolactones. Selected examples are shown in Scheme 2. While β,β-disubstituted enones smoothly underwent [4 + 1] cycloaddition with isocyanides, significantly decreased reactivity was observed with β-monosubstituted enones. For instance, (*E*)-oct-3-en-2-one afforded the [4 + 1] cycloadduct in only 20% under the standard conditions (eq 3, R = Bu). It should be noted that, in the case of β-monosubstituted substrates, an initially formed β,γ-unsaturated product was isomerized into a more stable α,β-unsaturated isomer under these conditions. The low yield can be attributed, in part, to the further reaction of the product with the starting enone.[13] Interestingly, the steric bulk imposed by the β-substituent of enones dramatically increased the yield of the product: R = *i*-Pr (43%) and R = *t*-Bu (71%). More importantly, the low reactivity of β-monosubstituted substrates was overcome by using an electron-deficient aryl isocyanide, by which the yield of the cycloadduct was improved from 20 to 65%.

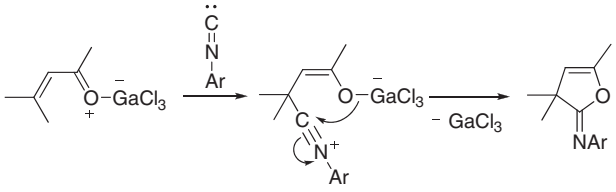


(3)

As we envisioned, nucleophilic attack of isocyanides onto the β-carbon of enones that is electrophilically activated by $GaCl_3$ followed by intramolecular cyclization can account for this [4 + 1] cycloaddition process (Scheme 3). The presence of bulky substituent(s) at the β-position of enones should facilitate the intramolecular cyclization step by the Thorpe–Ingold effect,[14] which was indeed observed experimentally. The viability of this mechanism was supported in a computational study by Xie.[15]

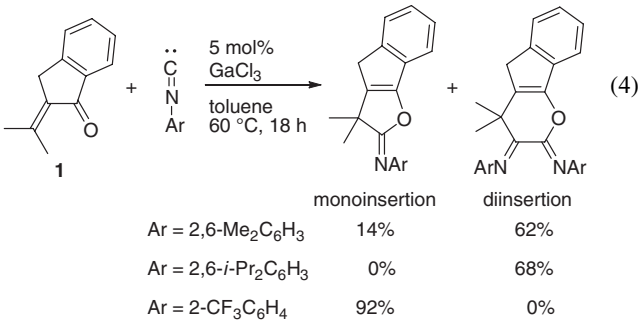


Scheme 2. $GaCl_3$-catalyzed [4 + 1] cycloaddition of enones and isocyanides.



Scheme 3. A plausible mechanism for the $GaCl_3$-catalyzed [4 + 1] cycloaddition of enones with isocyanides.

Isocyanides are capable of multiple insertion, which is a prominent difference between them and CO. With nearly all of the substrates we tested, only one molecule of isocyanide was incorporated to furnish a five-membered framework. However, formal [4 + 1 + 1] cycloaddition, wherein two molecules of isocyanide were inserted, proceeded when indenone derivative **1** was subjected to gallium-catalyzed conditions (eq 4). The formation of the double insertion product with this specific substrate **1** may be ascribed to the relatively high ring strain in the tricyclic skeleton of the monoinserted product, which was relieved by the increased ring size of the diinsertion product. The product distribution can be precisely controlled by the nature of the substituents on the isocyanides used. Exclusive formation of the [4 + 1 + 1] cycloaddition product was accomplished by using sterically hindered 2,6-*i*-$Pr_2C_6H_3NC$, while a complete switch to the [4 + 1] mode was observed with electron-deficient 2-$CF_3C_6H_4NC$, the increased electrophilicity of which effectively promoted a difficult intramolecular cyclization to form a strained fused five-membered ring system.

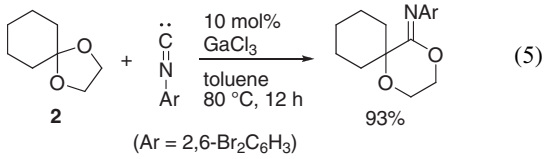


(4)

It should be noted that several related [4 + 1] cycloaddition reactions using isocyanides appeared after our publication.[10e,16]

♦ *Insertion into C–O Bonds of Acetals*

The successful development of the $GaCl_3$-catalyzed [4 + 1] cycloaddition led us to an application of the unique catalytic activity of $GaCl_3$ to other catalytic processes using isocyanides. A brief description reported in a paper by Ito and Saegusa in 1984 attracted our attention. In the paper, the insertion of isocyanides into the C–O bond of cyclic acetal **2** was accomplished with the aid of a stoichiometric amount of $TiCl_4$, although the scope of the reaction was not investigated further.[17] Guided by this intriguing report, we examined the catalytic activity of $GaCl_3$ in this insertion reaction. As expected, the reaction proceeded to furnish the insertion product in an excellent yield (eq 5).[18] The use of aryl isocyanides bearing electron-withdrawing groups, such as Cl and Br, was essential for an efficient reaction.

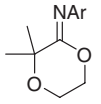
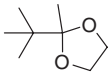
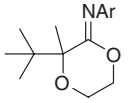
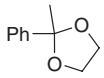
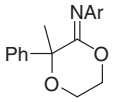
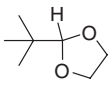
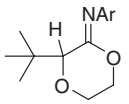
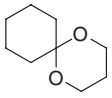
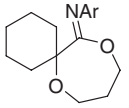


(5)

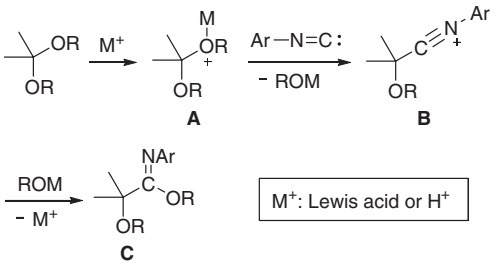
As shown in Table 1, acetals derived from aliphatic ketones gave rise to the corresponding insertion products in good yields (Entries 1 and 2). However, only moderate yields were obtained with acetals derived from aromatic ketones and aldehydes (Entries 3 and 4). In addition to a five-membered ring system, i.e., 1,3-dioxolane, six-membered 1,3-dioxanes can also participate in this $GaCl_3$-catalyzed insertion of isocyanides, although the efficiency was significantly lowered (Entry 5).

Although we were confident with the first demonstration of this catalytic variant of isocyanide insertion into acetals, several limitations, particularly inapplicability to acyclic acetals, prompted us to re-explore the catalyst that can promote wider range of acetals. Despite the apparent similarities, cyclic and acyclic acetals pose significantly different challenges when applied in this type of reaction. The difficulty associated with acyclic acetals is not surprising considering the mechanism illustrated in Scheme 4. For cyclic acetals, a once-cleaved alkoxy group (ROM) is tethered by the substrate. As a result, the recombination (**B** → **C**) proceeds via a relatively facile intramolecular process. In contrast, in the case of acyclic acetals, the recombination of ROM competes with other undesired intermolecular processes, such as nucleophilic attack by the second

Table 1. $GaCl_3$-catalyzed insertion of isocyanides into a C–O bond of cyclic acetals[a]

Entry	Acetal	Product[b]	Yield/%[c]
1			81
2			92
3			51
4			55
5			34

[a]Reaction conditions: acetal (0.4 mmol), 2,6-dibromophenylisocyanide (0.44 mmol), $GaCl_3$ (0.04 mmol, 1 M in methylcyclohexane) in toluene (1.5 mL) at 80 °C, 12 h. [b]Ar = 2,6-dibromophenyl. [c]Isolated yields.



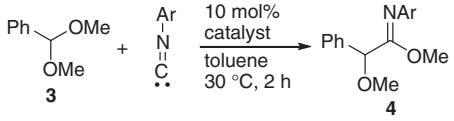
Scheme 4. Mechanistic consideration for acid-catalyzed insertion of isocyanides into a C–O bond in acetals.

molecule of isocyanide or by residual water. Indeed, almost all of the acid-mediated reactions of acyclic acetals result in the formation of a substitution product, where one of the two alkoxy groups is lost, rather than in an insertion product.[19]

With the aforementioned difficulty in mind, we initiated our study by investigating various Lewis acids that could promote the reaction of acyclic acetal **3** with 2,6-$Cl_2C_6H_3NC$. After screening a variety of catalysts, we were pleased to find that triflate salts exhibited promising catalytic activity, furnishing the desired insertion product **4** (Table 2). These results led us to an examination of TfOH, which often serves as a true catalyst in several triflate salt-mediated processes.[20] Indeed, TfOH proved to be an excellent catalyst for this reaction, affording **4** in 89% isolated yield at ambient temperature within 2 h (Entry 6).[21]

The nature of an *N*-substituent on isocyanide has a significant impact on the course of the reaction (Scheme 5).

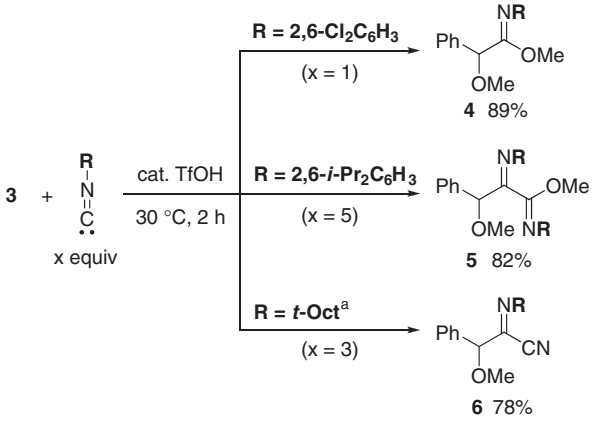
Table 2. Catalytic activity of selected acids in the insertion of isocyanides into acyclic acetal **3**



(Ar = 2,6-$Cl_2C_6H_3$)

Entry	Catalyst	Yield/%	Entry	Catalyst	Yield/%
1	$GaCl_3$	<10	5	Me_3SiOTf	80
2	$InCl_3$	trace	6	**TfOH**	**89**
3	$Cu(OTf)_2$	38	7	Tf_2NH	58[a]
4	$Sc(OTf)_3$	48[a]	8	TFA	3

[a]8–10% of the diinsertion product was also obtained.



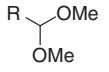
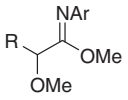
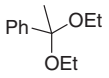
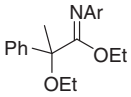
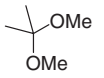
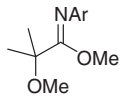
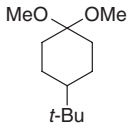
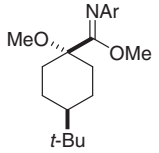
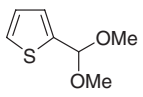
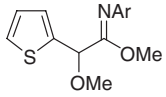
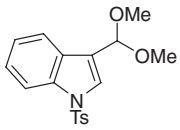
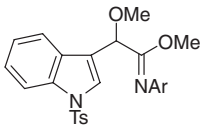
Scheme 5. Dependence of the reaction course on the *N*-substituent of isocyanides employed in TfOH-catalyzed reaction of acyclic acetal **3**. [a]1,1,3,3-tetramethylbutyl.

As mentioned above, monoinsertion product **4** was obtained exclusively when electron-deficient aryl isocyanide (2,6-$Cl_2C_6H_3NC$) was used. On the other hand, when sterically hindered aryl isocyanide (2,6-*i*-$Pr_2C_6H_3NC$) was applied to the same TfOH-catalyzed reaction of **3**, the diinsertion product **5** was obtained in 82% yield. Moreover, an exclusive formation of imidoyl cyanide **6** was observed in the case of *tert*-alkyl isocyanide.[22] The structure of isocyanide dictates which of the three different paths will proceed.

The isocyanide and catalyst that were suitable for a selective monoinsertion into acyclic acetal **3** proved to be applicable to a diverse array of substrates (Table 3). In contrast to the $GaCl_3$-catalyzed reaction (i.e., Table 1), acetals derived from both aldehydes and ketones bearing aliphatic and aromatic substituents all afforded the corresponding insertion products in good yields. In addition, compatibility of polar functional groups, including CN and NO_2, is another notable advantage of this TfOH-catalyzed process. It should be noted that TfOH also catalyzes the insertion into cyclic acetals in yields that are comparable to those obtained with the $GaCl_3$ catalyst.

Under these conditions, isocyanide also inserts into mixed acetals (Table 4). The TfOH-catalyzed reactions of tetrahydrofuranyl (Entry 1) and -pyranyl (Entry 2) ethers with isocyanides resulted in an exclusive insertion into exo-cyclic C–O bonds.

Table 3. TfOH-catalyzed insertion of isocyanide into acyclic acetals[a]

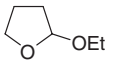
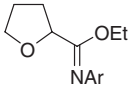
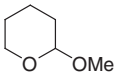
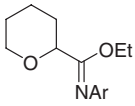
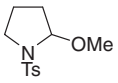
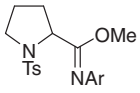
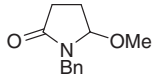
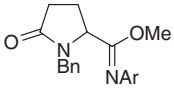
Entry	Acetal	Insertion product[b]	Yield/%[c]
			
1		R = Ph	89
2		(4-OMe)C_6H_4	81
3		(4-CO_2Me)C_6H_4	82
4		(4-CF_3)C_6H_4	70
5		(4-NO_2)C_6H_4	72
6		(4-CN)C_6H_4	75
7		(4-F)C_6H_4	86
8		(4-Br)C_6H_4	89
9		(2-Me)C_6H_4	91
10		1-naphthyl	86
11		2-naphthyl	86
12		$PhCH_2$	81
13		(*E*)-PrCH=CH	80
14			70
15			77
16			83[d]
17			80
18			90

[a]Reaction conditions: acetal (1.0 mmol), 2,6-dichlorophenyl isocyanide (1.0 mmol), TfOH (0.1 mmol) in toluene (6 mL) at 30 °C, 2 h. [b]Ar = 2,6-dichlorophenyl. [c]Isolated yields. [d]Stereoisomeric ratio = 20:1.

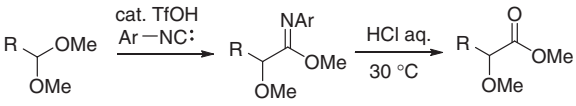
N,*O*-Acetals also served as suitable substrates to furnish the C–O insertion products, which are useful precursors for amino acid derivatives (Entries 3 and 4).

The imidate functionality of the products obtained in this insertion reaction can be converted to an ester group by simple acid hydrolysis (eq 6). Thus, the overall sequence demonstrates a formal carbonylation of acetals: a transformation that has never been accomplished. More importantly, α-oxygenated esters could be synthesized from aldehydes via one-carbon homologation by executing three reactions, acetal formation/isocyanide insertion/acid hydrolysis, in one pot (eq 7).

Table 4. TfOH-catalyzed insertion of isocyanide into mixed acetals[a]

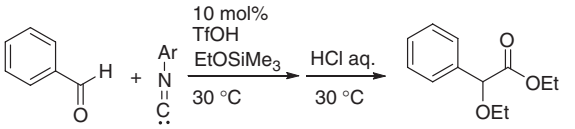
Entry	Acetal	Insertion product[b]	Yield/%[c]
1			60
2			76
3			80[d]
4			95

[a]Reaction conditions: acetal (1.0 mmol), 2,6-dichlorophenyl isocyanide (1.0 mmol), TfOH (0.1 mmol) in toluene (6 mL) at 30 °C, 2 h. [b]Ar = 2,6-dichlorophenyl. [c]Isolated yields. [d]Run for 1 h.



(6)

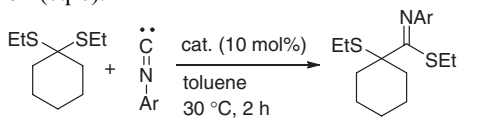
R = 2-naphthyl 85%
R = benzyl 73%



(7)

overall yield 67%

We also applied isocyanide insertion to C–S bonds in dithioacetals, in which $GaCl_3$ and $TiCl_4$ both effectively catalyze the reaction (eq 8).[23]

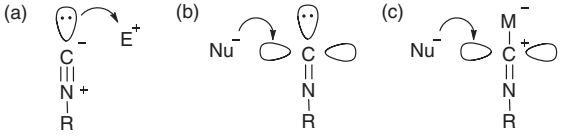


(8)

(Ar = 2,6-dichlorophenyl) with $GaCl_3$ 80%
with $TiCl_4$ 74%

♦ *Insertion into C–H Bonds*

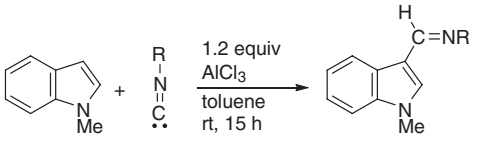
The acid-mediated reactions we have discussed thus far are based on the nucleophilic reactivity of isocyanides, which results from the interaction of the vacant p_π orbital of the terminal carbon with the lone pair electrons on the nitrogen (Scheme 6a). Isocyanides can also serve as an electrophile, in which the π^* orbital accepts an electron from a nucleophile (Scheme 6b). However, this type of reactivity has only been observed when strong nucleophiles, such as organolithium,[24a] -magnesium,[24a] and -zinc[24b] reagents, are used.[25] Obviously, broadening the scope of nucleophiles used in this α-addition reaction could lead to further increases in the synthetic utility of isocyanides.



Scheme 6. Ambiphilic reactivity of isocyanide serving (a) as nucleophile, (b) as electrophile, and (c) as electrophile in which isocyanide is activated by a Lewis acid (M).

In our mechanistic studies of the reactions mentioned in the previous sections, the interactions between $GaCl_3$ and isocyanides have been observed by NMR, although such a isocyanide/$GaCl_3$ complex does not participate in a productive pathway.[11b] These observations led us to examine a simple hypothesis that electrophilic reactivity of isocyanides should be enhanced by a Lewis acid complexation, as in the chemistry of carbonyl groups, thus allowing for the development of new α-additions to isocyanides (Scheme 6c). To our surprise, despite several reports on Lewis acid/isocyanide complexes,[26] such species have rarely been exploited in organic synthesis, with the exception of polymerization.[27]

On exploring the possible nucleophiles that can add to the isocyanide activated by a Lewis acid, we found that indoles serve as appropriate substrates to afford 3-iminoindoles (eq 9).[28] Lewis acids containing group 13 elements proved to be excellent promoters for this formal C–H insertion reaction: $BF_3 \cdot OEt_2$ (68%), $AlCl_3$ (88%), $GaCl_3$ (86%), and $In(OTf)_3$ (90%). The reaction is relatively insensitive to the electronic and steric nature of isocyanides. An array of isocyanides uniformly furnished the products in good yields.



(9)

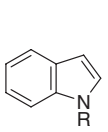
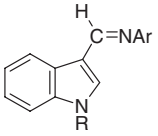
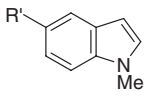
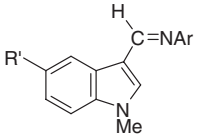
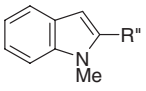
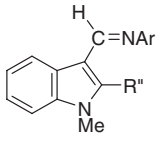
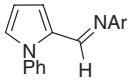
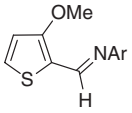
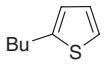
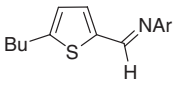
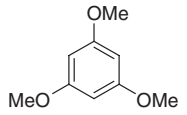
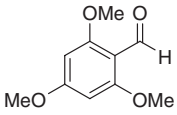
R = 2,6-$Me_2C_6H_3$	88%
3,5-$Me_2C_6H_3$	68%
4-$MeOC_6H_4$	79%
4-ClC_6H_4	64%
benzyl	82%

The scope of this isocyanide insertion reaction into aromatic C–H bonds using inexpensive $AlCl_3$ as a promoter is depicted in Table 5. A broad range of indoles bearing various *N*-protective groups (Entries 1–4), and different electronic (Entries 5–9) and steric (Entries 10 and 11) properties were applicable to this reaction. Other electron-rich heteroaromatic compounds, such as pyrroles (Entry 12) and thiophenes (Entries 13 and 14), also underwent the insertion with high regioselectivity. Moreover, highly electron-rich 2,4,6-trimethoxybenzene can serve as a good nucleophile to furnish the corresponding insertion product (Entry 15).

♦ *Isocyanides for Transition-metal-catalyzed C–H Bond Activation*

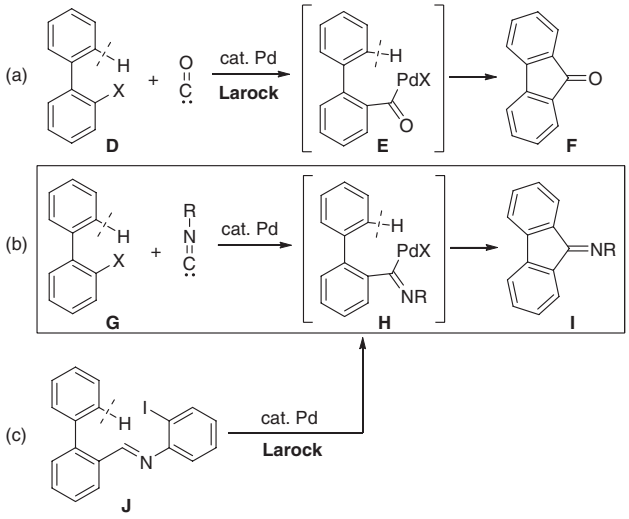
In our $AlCl_3$-promoted reaction mentioned above, C–H bonds in electron-rich aromatic compounds are functionalized via a classical electrophilic substitution process. If this type of

Table 5. $AlCl_3$-mediated insertion of isocyanide into C–H bonds in aromatic compounds[a]

Entry	Aromatics	Product[b]		Yield/%[c]
1			R = Me	88
2			R = CH_2Ph	81
3			R = 4-MeC_6H_4	93
4			R = H	78
5			R′ = Me	76
6			R′ = Ph	73
7			R′ = OMe	80
8			R′ = Br	89
9			R′ = CO_2Me	83
10[d]			R″ = Me	85
11			R″ = Ph	92
12				84[e]
13				78
14[d]				82
15				77[f]

[a]Reaction conditions: aromatic compound (1.0 mmol), 2,6-dimethylphenyl isocyanide (1.1 mmol), $AlCl_3$ (1.2 mmol) in toluene (2 mL) at rt, 15 h. [b]Ar = 2,6-dimethylphenyl. [c]NMR yields. [d]Run at 60 °C. [e]The 3-substituted isomer was also observed as a minor product (6%). [f]Only a hydrolyzed product was observed.

transformation can be realized through transition-metal catalysis, that would lead not simply to the improvement of the synthetic utility of this specific transformation but also to an advancement in C–H bond activation chemistry, a currently vibrant research area.[29] We have been involved in a research program directed toward catalytic C–H bond carbonylation using CO as a carbonyl source since 1996.[30] This encouraged us to examine the possible use of isocyanides as a C1 component in catalytic C–H bond transformation reactions. Only a limited portion of work in this context has been reported. Jones reported that the isomerization of 2,6-$Me_2C_6H_3NC$ to 7-methyl-1*H*-indole is catalyzed by a ruthenium complex via the insertion of an isocyano group into benzylic C–H bonds.[31] Tanaka[32a] and Jones[32b,32c] independently reported the rhodium-catalyzed insertion reaction of isocyanide into a C–H bond of benzene under irradiation conditions. The palladium-catalyzed cascade coupling of isocyanides with 6-iodo-*N*-(2-propynyl)pyridones was reported by Curran.[33] Despite these precedents, we felt a need remained to develop more

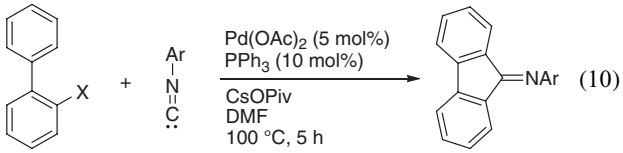


Scheme 7. Catalytic C–H bond functionalization through acyl– and imidoyl–metal species.

general catalytic reactions to assess the utility of isocyanides in C–H bond functionalization reactions.

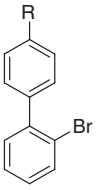
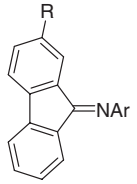
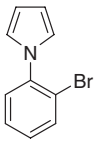
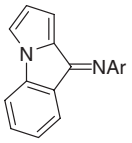
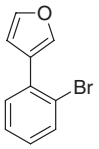
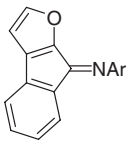
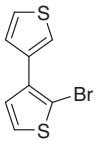
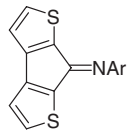
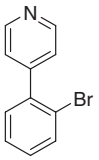
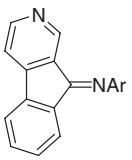
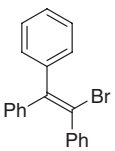
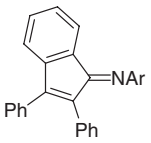
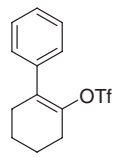
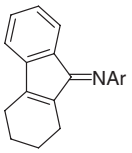
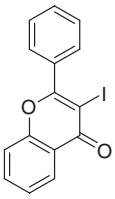
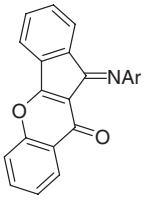
At the outset of our investigation, we chose as a model reaction Larock's palladium-catalyzed cyclocarbonylation of 2-halobiaryls **D**, wherein fluoren-9-one derivatives **F** are formed through C–H bond activation (Scheme 7a).[34] The hypothesis is that replacing CO with isocyanides in this reaction would lead to the formation of the corresponding imine derivatives **I** if an imidoyl–palladium intermediate **H** possesses a reactivity comparable to acyl–palladium **E** toward the proximal C–H bonds (Scheme 7b). The feasibility of the hypothesis was supported, in part, by Larock's report that imidoyl palladium that is generated from iodide **J** by unique aryl-to-imidoyl palladium migration can undergo similar cyclization to afford imine **I** (Scheme 7c).[35]

To our delight, the desired cyclocoupling of 2-halobiphenyl and isocyanide proceeded under conditions almost identical to those of Larock's cyclocarbonylation (eq 10).[36] A minor difference from Larock's conditions was the effect of the ligand: PPh_3, in place of bulky electron-rich PCy_3, promoted the reaction effectively. The use of 2,6-disubstituted aryl isocyanides was essential for an efficient reaction. Unsubstituted phenyl and alkyl isocyanides did not afford the corresponding products, presumably due to their instability under these catalytic conditions and/or catalyst deactivation by their multiple coordination to a palladium center.[37] While bromides, iodides, and triflates all afforded the cyclocoupling product in excellent yields, the corresponding chlorides remained intact even in the presence of a PCy_3 ligand.[38]

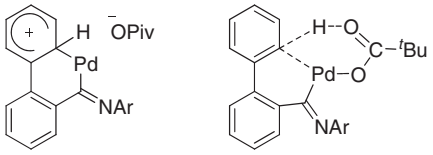


(10)

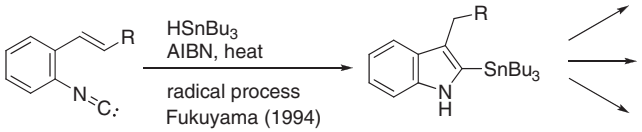
Table 6. Pd-catalyzed cyclocoupling of haloarenes with isocyanide[a]

Entry	Substrate		Product[b]	Yield/%[c]
1		R = Me		87
2[d]		R = OMe		90
3		R = CF_3		95
4		R = CO_2Me		82
5		R = CHO		85
6		R = CN		92
7				99
8				93
9				95
10				53
11				80
12				62
13				40

[a]Reaction conditions: haloarene (0.25 mmol), 2,6-*i*-$Pr_2C_6H_3NC$ (0.30 mmol), $Pd(OAc)_2$ (0.0125 mmol), PPh_3 (0.025 mmol), and CsOPiv (0.30 mmol) in DMF (2.0 mL) at 100 °C for 5 h. [b]Ar = 2,6-*i*-$Pr_2C_6H_3$. [c]Isolated yield based on haloarene. [d]Run for 20 h.



Scheme 8. C–H activation by an imidoyl–palladium species.



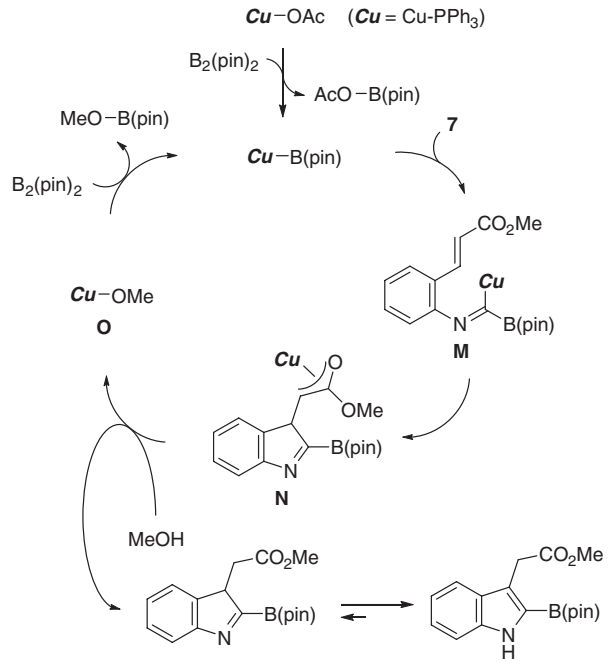
Scheme 9. Fukuyama indole synthesis.

As illustrated in Table 6, the scope of this palladium-catalyzed cyclocoupling is quite broad with respect to the biaryl substrates. A range of functional groups, including a reactive aldehyde moiety, are tolerated (Entries 1–6). C–H bonds in heteroaromatic rings, including pyrroles, furans, thiophenes, and pyridines, can also participate in this catalytic cyclocoupling to furnish a diverse array of tricyclic architecture (Entries 7–10). Moreover, alkenyl halides function as appropriate substrates, further expanding the scope of the reaction (Entries 11–13).

As we envisaged, imidoyl–palladium species, generated by insertion of isocyanide into an aryl–palladium complex, proved to be adequate for C–H bond activation, comparable to the acyl–palladium species. Intramolecular kinetic isotope study has revealed that the cleavage of a C–H bond is turnover-limiting in this catalysis ($k_H/k_D = 5.3$). Although the precise mechanism for the C–H activation in our system is not clear at the present time, either an electrophilic palladation (via **K** in Scheme 8) or a concerted metallation/deprotonation (via **L**) path is plausible based on the plethora of mechanistic discussion on C–H activation by an aryl–palladium species.[39]

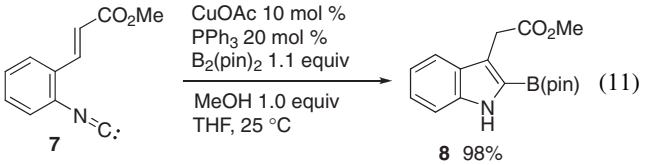
♦ *Catalytic Indole Synthesis*

In all of the reactions we have mentioned above, isocyanides are incorporated into the products as an imino group. Another possible form that isocyanides can be transformed into is a C–N bond in *N*-heterocycles.[5] Among the various *N*-heterocycles that can be synthesized from isocyanides, indoles are particularly attractive targets in view of their widespread occurrence in natural and unnatural products.[40] In this context, Fukuyama disclosed that the reaction of 2-alkenylphenyl isocyanide with tin hydride under radical conditions affords 2-stannylindoles, which are amenable to further elaboration, for example, via the Migita–Kosugi–Stille coupling (Scheme 9).[41] We felt that if this reaction could be extended to the synthesis of the corresponding boron analogs, it would lead to a nontoxic and more versatile platform for indole-based compounds on the basis of recent outstanding progress in organic synthesis using organoboron reagents.[42] Borylated indoles can be prepared either by the protocol of lithiation/trap with boron electrophiles[43] or by catalytic C–H borylation.[44] However, the former method cannot be applied to indoles bearing base-sensitive groups, and the latter is susceptible to steric demand.



Scheme 10. A possible mechanism for the copper-catalyzed borylative cyclization of 2-alkenylphenyl isocyanide **7**.

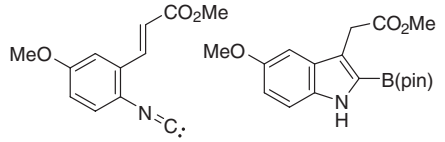
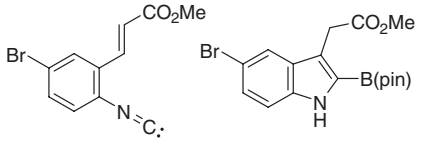
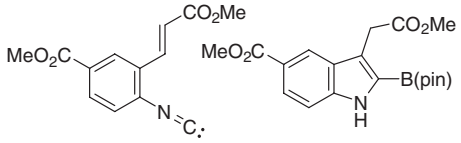
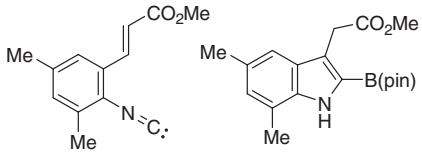
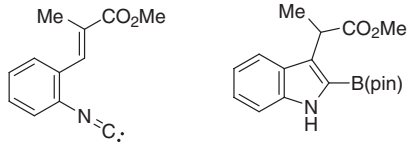
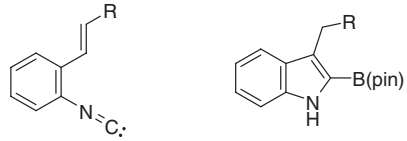
Independently pioneered by Hosomi[45a] and Miyaura,[45b] a boryl–copper species generated by a copper catalyst and diboron mediates nucleophilic borylation of carbon electrophiles such as α,β-unsaturated carbonyl compounds.[45] Those reports led us to hypothesize that a nucleophilic borylation of 2-alkenylphenyl isocyanide would initiate cyclization to furnish 2-borylindole in the presence of a copper catalyst and diboron, if the electrophilicity of an isocyano moiety was sufficient to be attacked by a boryl–copper species. Fortunately, as we had hoped, the borylative cyclization of isocyanide **7** proceeded to afford 2-borylindole **8** efficiently at room temperature (eq 11).[46] The addition of 1 equivalent of MeOH significantly improved the yield of the product. This is probably because the relatively slow catalyst regeneration through the reaction of copper enolate **N** with diboron is accelerated by the intermediacy of copper methoxide **O** generated by the methanolysis of **N** (Scheme 10).[45c]



(11)

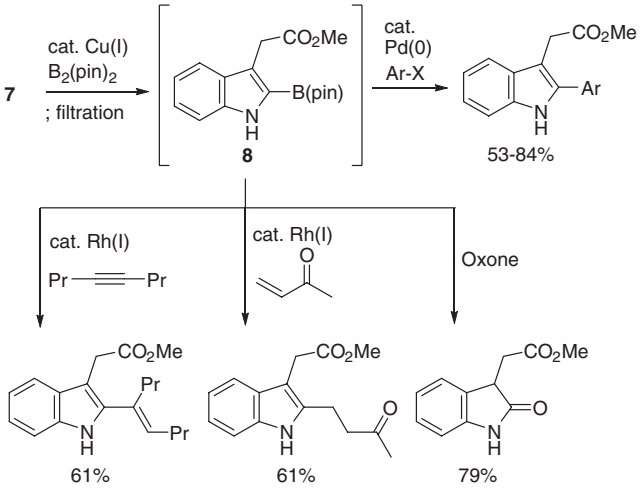
The present copper-catalyzed borylative cyclization can be applied to various aryl isocyanides bearing an unsaturated ester moiety at the 2-position (Table 7). Ethers, bromides, and esters are tolerated, and a sterically hindered 2,6-disubstituted substrate is also applicable (Entries 2–5). In agreement with the mechanistic proposal (Scheme 10), several pendant Michael acceptors, such as methacrylate and unsaturated ketone, amide, and nitrile could also participate in this borylative cyclization (Entries 6–9). It should be noted that the 2-borylindoles shown in Table 7 are inaccessible by conventional borylation methods.

Table 7. Cu-catalyzed borylative cyclization of 2-alkenylaryl isocyanides[a]

Entry	Isocyanide	Product	Yield/%[b]
1			84
2			74
3			58
4			62
5			95
6	R = COMe		57
7	R = $CONMe_2$		94
8	R = CN		63

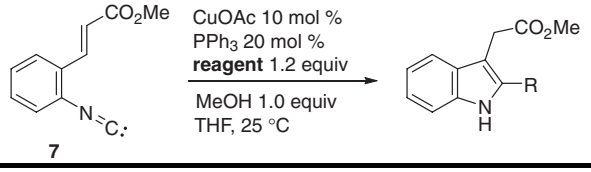
[a]Reaction conditions: isocyanide (0.5 mmol), $B_2(pin)_2$ (0.55 mmol), CuOAc (0.05 mmol), PPh_3 (0.10 mmol), MeOH (0.5 mmol), THF (4 mL) in a two-necked flask under N_2. [b]NMR yields based on isocyanide.

Although the borylindoles synthesized by this method are relatively prone to protodeboronation on chromatographic purification, they are directly used for the Suzuki–Miyaura coupling after removing copper residue by simple filtration (Scheme 11). This simple procedure was successfully applied to a rapid assembly of paullone, which is known as a potent inhibitor of cyclin-dependent kinases. The Rh(I)-catalyzed addition to alkynes and enones also is applicable to the 2-borylindoles obtained by our catalytic reaction. Moreover, oxidation using Oxone afforded oxindoles, which constitutes an important subclass of indole-based compounds. As demonstrated, 2-borylindoles are versatile building blocks for the synthesis of a variety of indole derivatives, thus highlighting the utility of this borylative cyclization in diversity-oriented synthesis.



Scheme 11. 2-Borylindole **8** serves as a versatile building block.

Table 8. Cu-catalyzed cyclization of 2-alkenylaryl isocyanides using various reagents[a]

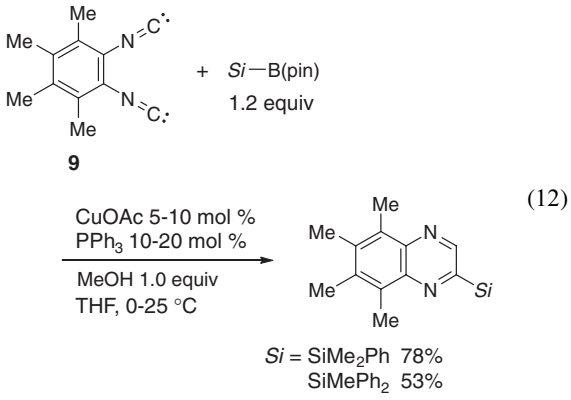


Entry	Reagents	Time/h	R	Yield/%[b]
1	HB(pin)[c]	1	H	78
2	$HSiPhMe_2$	5	H	81
3[d]	(pin)B-$SiMe_2Ph$	3	$SiMe_2Ph$	87
4[d]	(pin)B-$SiMePh_2$	3	$SiMePh_2$	77
5	$PhB(OH)_2$	24	Ph	0

[a]Reaction conditions: **7** (0.5 mmol), reagent (0.6 mmol), CuOAc (0.05 mmol), PPh_3 (0.10 mmol), MeOH (0.5 mmol), THF (4.0 mL) in a two-necked flask under N_2 at 25 °C. [b]Isolated yield based on **7**. [c]HB(pin) (1.0 mmol) was used. [d]Run with CuOAc (0.025 mmol) and PPh_3 (0.05 mmol) at 0 °C.

In the present borylative cyclization, nucleophilic borylation of isocyanides by a boryl–copper species is a key step in the catalytic cycle. As mentioned in the previous section, such electrophilic reactivity of isocyanides is relatively unexplored, compared with their widespread utility as nucleophiles. Thus, we were interested in applying this catalytic addition/cyclization using isocyanide **7** to other transformations. To obtain qualitative insight into the electrophilic reactivity of isocyanide **7**, copper-catalyzed reactions of **7** with potentially nucleophilic reagents were examined (Table 8). Copper(I) hydride generated in situ by the reaction with HB(pin)[47] or $HSiPhMe_2$[48] was also capable of initiating the cyclization to afford indole, in which hydride is incorporated at the 2-position (Entries 1 and 2). Interestingly, 2-silylindoles were obtained when silylboranes were employed in a copper-catalyzed reaction of **7**, in which silyl–copper species is likely to be involved as a key intermediate (Entries 3 and 4).[49] However, the direct synthesis of 2-phenylindoles by a phenyl–copper species generated from phenylboronic acid[50] was unsuccessful (Entry 5). The reactivity trend observed in Table 8 is in good correlation with the magnitude of trans influence of a series of ligands. Lin and Marder reported that the order of the magnitude of trans influence is as follows: $SiMe_3$ > B(pin) > H > Ph.[51] On the basis of these data, a σ-donating ability stronger than hydride is presumably required for the copper species to nucleophilically add to isocyanides.

As illustrated in Scheme 10, the present reaction is initiated by nucleophilic borylation (or silylation) of isocyanide, followed by the intramolecular 1,4-addition of imidoyl–copper species **M** to an α,β-unsaturated ester. We found that the imidoyl–copper species can also be intercepted by another isocyanide group. Thus, the reaction of 1,2-diisocyanobenzene **9** with silylborane in the presence of a copper catalyst furnished 2-silylquinoxalines (eq 12).[52] The use of diboron in place of silylborane in the reaction shown in eq 11 did not afford the corresponding 2-borylquinoxaline, but, instead, a protodeborylated product was obtained in low yield. Superior σ-donating ability of a silyl to a boryl group might be a key factor for efficient cyclization.



(12)

♦ Summary

This Highlight Review describes our continuous efforts to develop new transformations using isocyanides as key components. We launched this project on the basis of the idea that isocyanides can be exploited as a CO surrogate. However, electronic and steric modularity of isocyanides makes them more than a CO surrogate, allowing for the development of the reactions that are unattainable with CO. In addition, isocyanides proved to play an eminent role in transition-metal-catalyzed C–H bond activation and borylation reactions.

Considering the fact that even a simple reaction of isocyanides with carboxylic acids remained undiscovered until 2008,[53] isocyanides would undoubtedly offer numerous opportunities for methodology development when combined with contemporary concepts, such as C–H bond activation or organocatalysis. We believe that this venerable class of compounds will continue to serve as a unique element for the design of new reactions.

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