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Tandem Insertion–Cyclization Reaction of Isocyanides in the Synthesis of 1,4-Diaryl-1*H*-imidazoles: Presence of *N*-Arylformimidate Intermediate

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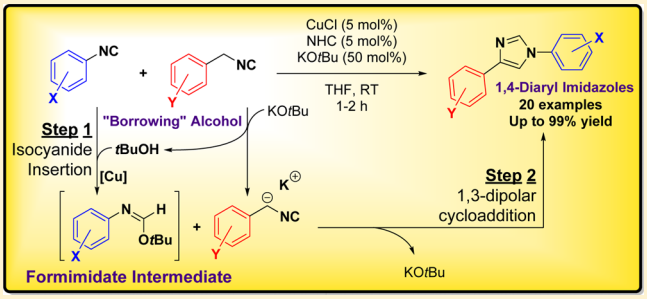
Supporting Information

ABSTRACT: A straightforward and high-yielding synthesis of 1,4-diaryl-1*H*-imidazoles is reported. 1,4-Diaryl-1*H*-imidazoles have been difficult to access in ambient conditions, but our method utilizes two different facets of isocyanide reactivity to achieve it. The reaction is believed to involve (1) NHC–copper-catalyzed isocyanide insertion into alcohol to form an *N*-arylformimidate intermediate and (2) subsequent base-promoted cycloaddition with benzyl isocyanide derivatives. There is cooperation between these two processes through the deprotonation of benzyl isocyanide by KO*t*Bu. The deprotonation gives *tert*-butyl alcohol and the benzyl isocyanide anion, which are used for the first and second steps of the reaction, respectively. Various control and kinetic experiments were carried out to gain an in-depth understanding of the reaction mechanism and isocyanide reactivity. The reaction mechanism determined by density functional theory calculations was consistent with the experimental data and provided detailed explanations for the reactivity trends.



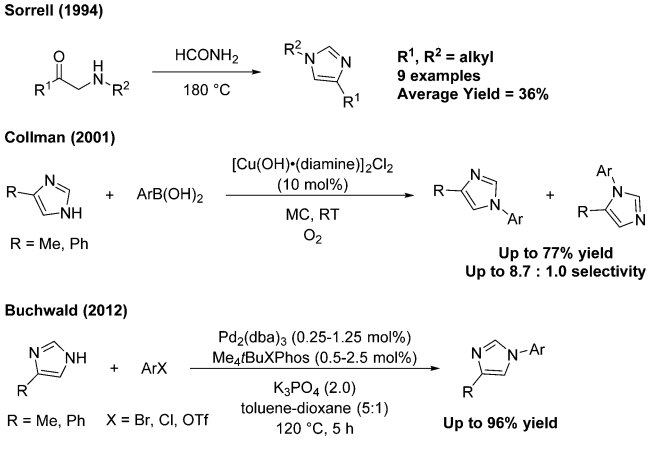
1. INTRODUCTION

Development of synthetic routes to functionalized imidazoles is highly regarded in both the chemical industry and academia. Present in the essential amino acid histidine, imidazoles are found in many enzymes and metallo-enzymes in biological systems.[1] Thus, many synthetic molecules containing an imidazole functionality possess biological activity and are valuable drug candidates.[2] Taking the cue from nature, imidazoles are also used as ligands in transition metal complexes.[3] The synthesis of closely related imidazolium salt has also gained importance recently because of the recognition that N-heterocyclic carbenes (NHCs) act as useful ligands in organometallic chemistry as well as organocatalysis.[4] Imidazoles also play important roles in materials chemistry and are present in many organic functional materials[5] and ionic liquids.[6]

In every different application of an imidazole molecule, the substitution pattern of the ring is important because it has an immense impact on both physical and chemical properties of the resultant molecule. Hence selective synthesis of imidazoles with specific substitution patterns is highly valuable. Functionalized imidazoles are usually synthesized via further functionalization of imidazoles, which are first constructed via cycloaddition. However, synthesizing an imidazole having a specific substitution pattern can be challenging because its C-2 position is highly acidic.[7] The synthesis of 1,4-disubstituted imidazoles is particularly difficult, and the direct synthesis via cycloaddition is limited in scope and requires harsh conditions (Scheme 1).[8] Until recently, N-functionalization of preformed 4-substituted imidazoles[9] had also been plagued with regioselectivity issues.[10]

Cycloaddition reactions of activated methylene isocyanides, such as tosylmethyl isocyanides and isocyanoacetates, across

Scheme 1. Examples of the Synthesis of 1,4-Disubstituted Imidazoles



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unsaturated bonds are attractive alternative synthetic routes to useful heterocyclic compounds such as imidazoles, oxazoles, pyrroles, and their saturated analogues.[11] van Leusen et al. reported the cycloaddition reaction between tosylmethyl isocyanides and imines, which yields 1,5-disubstituted imidazoles,[12] while Grigg's group and Yamamoto's group independently reported the synthesis of 1,4-disubstituted imidazoles via the cycloaddition of isocyanoacetates and another isocyanide under silver and copper catalytic conditions, respectively.[13] However, the latter group reported that benzyl isocyanide was not reactive under their experimental conditions, which implied that aryl variations on the 4-position remained difficult.

This is not uncommon because cycloaddition reactions of activated methylene isocyanides, with the exception of a few cases,[14] are generally limited to methylene isocyanides that are activated by highly electron-withdrawing groups such as esters, amides, or tosyl groups.[12,13,15] The formation of heteroaryl−aryl bonds is of high importance in chemical synthesis.[16] In view of its widespread application in the pharmaceutical industry, biochemistry, and materials science,[17] there is certainly a need to "unlock" the potential of aryl-substituted methylene isocyanides in order to allow for the general application of methylene isocyanides in the efficient synthesis of heterocycles.

We took a particular interest in the cycloaddition reaction between two different isocyanides developed by Yamamoto's group. They proposed that Cu_2O first acts as a base to deprotonate the activated methylene isocyanide (**A**), after which aryl isocyanide (**1**) inserts into the copper−carbon bond to form intermediate **B** (Figure 1). This was a highly interesting

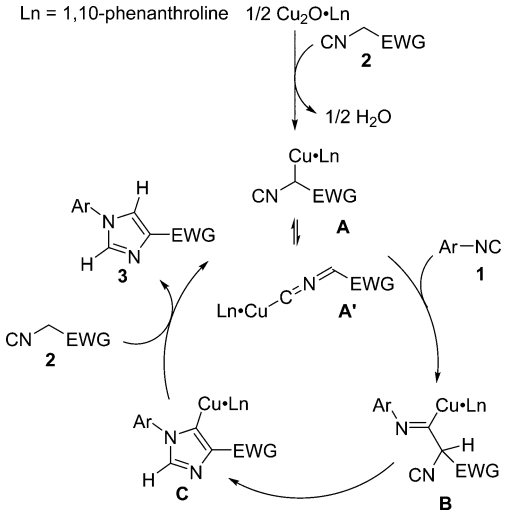


Figure 1. Yamamoto's proposed mechanism.

proposal because, unlike the cases of their palladium, ruthenium, or rhodium counterparts, isocyanide insertion into copper−carbon bonds had not been studied.[18] Structures **A** and **A′** were initially proposed by Saegusa et al. in their report on the cycloaddition reaction of isocyanides with ketones and activated olefins, which yields pyrroline and oxazoline.[19] In their paper, Saegusa et al. proposed that the organocopper intermediate consists of the α-metalated methylene isocyanide with the copper metal supported by other isocyanide ligands (Figure 2). In contrast to Yamamoto's work, Saegusa et al.'s report showed that benzyl isocyanides as well as isocyanoacetates gave the desired product.

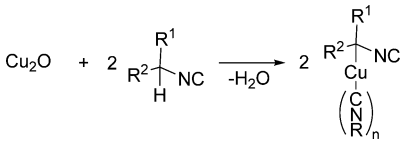
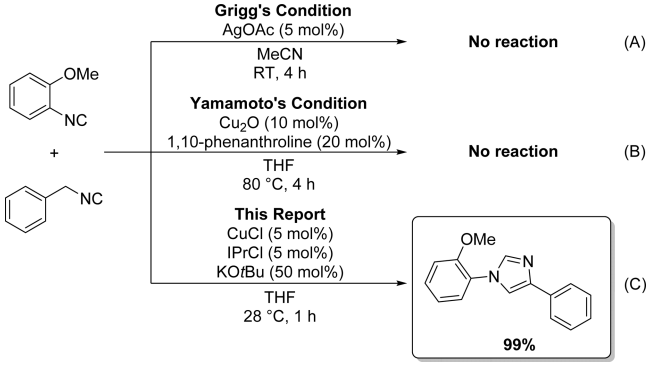


Figure 2. Saegusa's proposed organocopper intermediate.

Given the proposed mechanisms, it was not clear to us why benzyl isocyanide was unreactive. Since α-metalation of benzyl isocyanide with Cu_2O has been reported to be facile, it could be that the insertion of aryl isocyanides into the copper−carbon bond of the copper−isocyanide complex is sluggish. We surmised that an increase in electron density on the metal center upon changing the supporting ligand might accelerate the insertion of isocyanide. Copper-NHC complexes have been reported to enable the catalysis of difficult C−H functionalization reactions.[20] In particular, Hou and co-workers utilized a CuCl/IPrCl/KO*t*Bu catalytic system (IPrCl = 1,3-bis(2,6-diisopropylphenyl)-1*H*-imidazol-3-ium chloride) to activate the benzoxazole C−H bond having a pK_a of 24.8.[21] We were hopeful that such a catalytic system will allow us to generate a benzyl isocyanide anion, which has a pK_a of 27.4,[22] while simultaneously accelerating the isocyanide insertion process, which may be caused by the markedly high σ-donating property of the NHC ligand.

Herein, we report the facile formation of 1,4-disubstituted imidazoles via the cycloaddition reaction between two isocyanides catalyzed by a copper−NHC complex under ambient conditions and temperature. By changing the catalytic system from Cu_2O/1,10-phenanthroline to CuCl/IPrCl/KO*t*Bu, we were able to lower the reaction temperature, shorten reaction time, and access a wide range of diaryl-substituted imidazoles which were not formed by previous methods for imidazole synthesis reported by Yamamoto's and Grigg's groups (Scheme 2).[13]

Scheme 2. Synthesis of 1,4-Diaryl-1*H*-imidazoles



Control experiments revealed that the reaction proceeded through a two-step process in which an *N*-arylformimidate intermediate was formed, which is different from the mechanism proposed by Yamamoto's group. An in-depth mechanistic study was also performed computationally using density functional theory (DFT) calculations.

2. RESULTS AND DISCUSSION

2.1. Reaction Optimization. We first carried out the reaction of 2-methoxyphenyl isocyanide (**1a**) with benzyl isocyanide (**2a**) employing an NHC−copper catalyst system. To our delight, the target compound **3a** was formed in 83% yield

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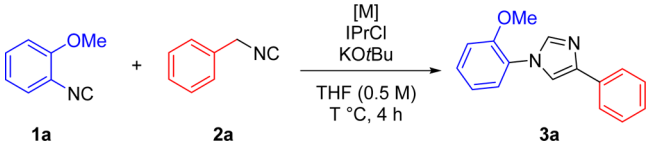
Table 1. Optimization of the Reaction Condition[a]



1a 2a 3a

entry	[M] (mol %)	base (mol %)	T (°C)	3a (%)[b]
1	CuCl (20)	KO*t*Bu (100)	80	83
2	$CuCl_2$ (20)	KO*t*Bu (100)	80	76
3	CuBr (20)	KO*t*Bu (100)	80	86
4	Cu_2O (20)	KO*t*Bu (100)	80	88
5	CuCl (20)	KO*t*Bu (50)	80	71
6	CuBr (20)	KO*t*Bu (50)	80	68
7	Cu_2O (20)	KO*t*Bu (50)	80	22
8	CuCl (10)	KO*t*Bu (50)	80	80
9	CuCl (5)	KO*t*Bu (50)	80	85
10	CuCl (5)	KO*t*Bu (50)	28	76
11	CuCl (5)	KO*t*Bu (40)	28	49
12	CuCl (5)	KO*t*Bu (30)	28	36
13[c]	***CuCl (5)***	***KO*t*Bu (50)***	***28***	***99***

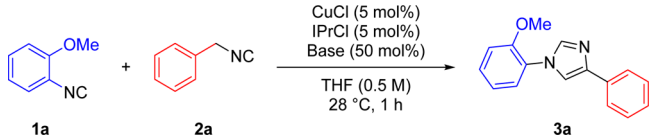
[a]Reaction of 2-methoxyphenyl isocyanide **1a** (0.1 mmol) with benzyl isocyanide **2a** (0.14 mmol) using a metal catalyst, IPrCl = 1,3-bis(2,6-diisopropylphenyl)-1*H*-imidazol-3-ium chloride and base in tetrahydrofuran (0.5 M). [b]Yields determined by ^{1}H NMR using anisole as internal standard. [c]A 5 min catalyst induction time followed by 1 h reaction time.

(Table 1, entry 1). We began to optimize the reaction conditions by changing the metal catalyst, and after screening a variety of metal catalysts, copper(I) halides were found to perform best at a lower base loading (Table 1, entries 1–7). Interestingly, lowering the catalyst loading increased the yield (Table 1, entries 8 and 9); however, lowering the base loading drastically decreased the yield (Table 1, entries 10–12). Because our aim was to find milder conditions for the reaction, we were pleased to find that lowering the temperature to 28 °C did not decrease the yield significantly (Table 1, entry 10). Finally, it was gratifying to us to find that a short catalyst induction time of 5 min afforded **3a** in quantitative yield (Table 1, entry 13).

During the screening process, we gained some mechanistic insight. We discovered that the reaction works only when KO*t*Bu is used as the base. Changing the countercation to sodium decreased the yield to 47%, whereas using other alkoxide-type bases gave trace amounts of the product (Table 2, entries 2–4). Surprisingly, the use of more basic NaH and KH was not effective (Table 2, entries 5 and 6). We speculated that KO*t*Bu does not merely serve as a base, but both K^+ and tBuO$^-$ may play essential roles in the reaction.

2.2. Substrate Scope and Limitation. With the optimized reaction conditions in hand, we examined the substrate scope of the developed method (Chart 1). To check the feasibility of this method with other benzyl isocyanide derivatives, we first varied the second component (substituted benzyl isocyanide) of the reaction. Either *para*-methoxy or *para*-methyl functionality on the phenyl ring of benzyl isocyanide will render the α-proton less acidic; however, contrary to our assumption, we were pleasantly surprised to find that **3b** and **3c** were formed in excellent yields. More acidic 4-chlorobenzyl isocyanide gave the product in excellent yield (**3d**), although 4-trifluoromethylbenzyl isocyanide afforded the product only in slightly reduced yield (**3e**) despite having a more acidic α-proton. 2-(Isocyanomethyl)-thiophene afforded **3f** in good yield, whereas 3-(isocyanomethyl)-pyridine afforded **3g** in poor yield even after extending the reaction

Table 2. Base Effect[a]



1a 2a 3a

entry	base	3a (%)[b]
1	KO*t*Bu	99
2	NaO*t*Bu	47
3	potassium *tert*-pentoxide	trace
4	KOMe	trace
5	KH	7
6	NaH	6
7	NaOAc	trace
8	Cs_2CO_3	trace

[a]Copper chloride, NHC precursor, and base were allowed to react in THF for 5 min at room temperature before the addition of **1a** and **2a**. [b]Yields determined by ^{1}H NMR using anisole as internal standard.

time to 2 h, probably as a result of the poisoning of the copper catalyst. Even more surprising was that commonly used activated methylene isocyanides, which are more acidic than benzyl isocyanide, afforded a poor amount or a trace of the corresponding imidazoles (**3h** and **3i**).

Next, we varied the first component (substituted phenyl isocyanide) of the reaction. Irrespective of whether the phenyl isocyanide had an electron-withdrawing or an electron-donating group, the reactions afforded the corresponding imidazoles in excellent yields (**3j–o**). Gratifyingly, halide substituents were compatible with the developed reaction conditions, providing handles for further functionalization. The reactions of the phenyl isocyanides bearing bulkier substituents required slightly longer reaction times (2 h) yet afforded the corresponding imidazoles smoothly (**3p–s**). Interestingly, 1-naphthyl isocyanide afforded **3s** in excellent yield, whereas 2-biphenyl isocyanide afforded **3r** in moderate yield. As bis-heteroaryl compounds are important in the drug industry, we were pleased to see that 3-pyridinyl isocyanide afforded **3t** in moderate yield. Alkyl isocyanides, however, did not give the desired imidazole. When cyclohexyl isocyanide reacted with benzyl isocyanide, an imidazole **3u** from the self-cycloaddition between two benzyl isocyanide molecules was formed rather than the predicted **3v**. The reaction between two benzyl isocyanide molecules gave **3u** in good yields.

2.3. Mechanistic Investigation. *2.3.1. Formation of Formimidate Intermediate.* To probe deeper into the cyclization process, α-methyl benzyl isocyanide **2b** was synthesized and subjected to two reaction conditions (Scheme 3). As both α-protons of benzyl isocyanide are expected to migrate to the 2- and 5-positions of the final imidazole, we attempted to trap a possible intermediate by attaching a methyl substituent on the α-position. To our surprise, the trapped imidazoline intermediate **4a** contained a *tert*-butoxy group on the 5-position in a mixture of stereoisomers with a *cis*/*trans* ratio of 1.5:1 (Scheme 3a). In order to isolate a larger amount of the sample for analysis, we increased the KO*t*Bu loading to 100 mol %, which, however, resulted in a decreased yield of **4a** and the formation of isolated formimidate **4b** and amide **4c** (Scheme 3b).

These results strongly indicate that formimidate intermediate **5a** was formed within the reaction, probably through insertion of isocyanide into *tert*-butyl alcohol. Upon deprotonation of benzyl isocyanide **2b**, a 1,3-dipolar compound is formed, which then undergoes a nonconcerted cycloaddition reaction with **5a** to

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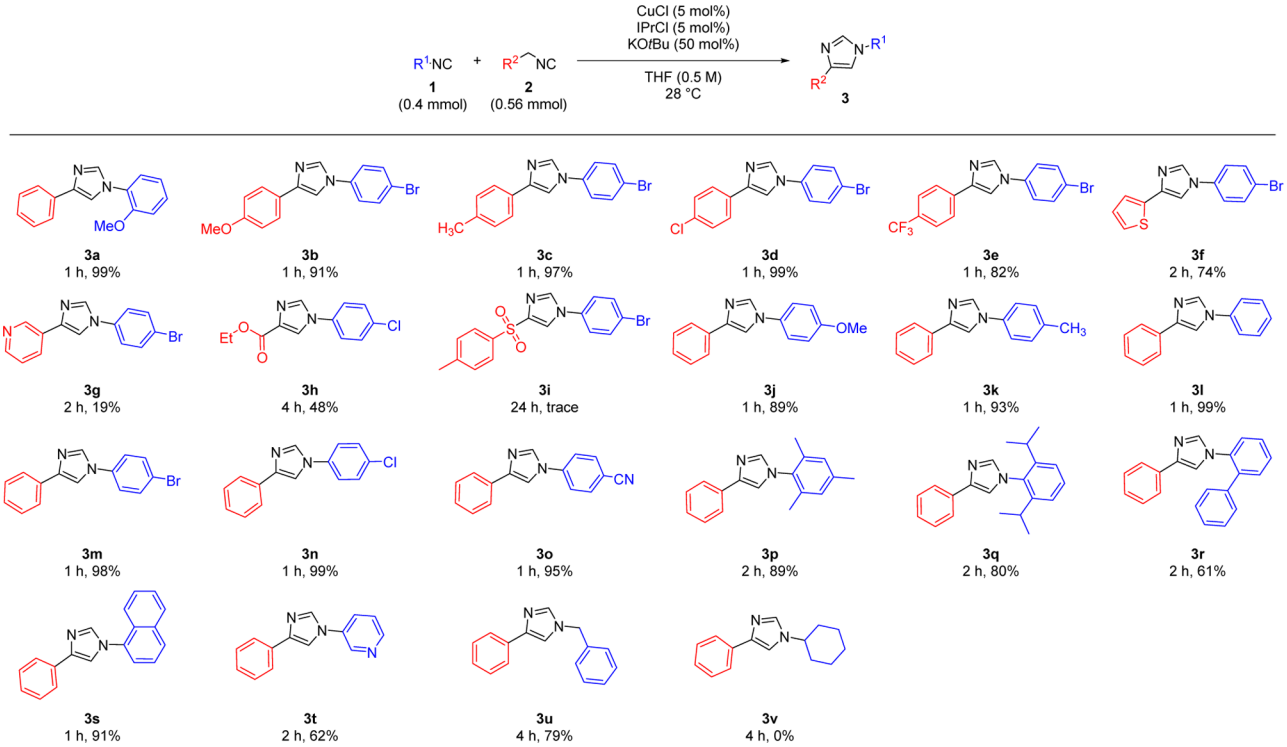
Chart 1. Substrate Scope and Limitation[a,b]



[a]Reaction of aryl isocyanides **1** (0.4 mmol) with benzyl isocyanides **2** (0.56 mmol) using CuCl (0.02 mmol), IPrCl (0.02 mmol), and KO*t*Bu (0.2 mmol) in tetrahydrofuran (0.5 M) at 28 °C with a catalyst induction time of 5 min. [b]Yields represent isolated yields.

yield our imidazoline product **4a**. To the best of our knowledge, this is a rare example in which the isocyanide functionality behaves as a formal dipolarophile in a cycloaddition reaction. When an excess amount of KO*t*Bu is used, unwanted side reactions occur, yielding formimidate **4b** that can further undergo Chapman rearrangement[23] to yield amide **4c** (Scheme 3c).

Experiments carried out with purchased (*Z*-)ethyl *N*-phenylformimidate validated the hypothesis that formimidate is a possible reaction intermediate (Scheme 4). The ratio of *cis* and *trans* products was 3:1, which was different from the previous reaction (Scheme 3a,b), suggesting that either formimidate formation from isocyanide forms a mixture of formimidate stereoisomers or the steric bulk of the *tert*-butoxy group influences the conformation of the transition state. As there was only exclusive formation of **4d** without the formation of *tert*-butoxy-containing imidazolines, it could then be postulated that the formimidate formation from isocyanide is not a reversible reaction. It was found that cyclization could also occur in the absence of copper without significant decrease in yields (Scheme 4b,c). A copper catalyst is probably required only for the formimidate formation that occurs before cyclization. Reaction of **5b** with deuterated benzyl isocyanide (99% D) also gave exclusive deuteration on the 2-position of imidazole and no deuteration on 5-position, providing further evidence that formimidate **5b** is not in equilibrium with phenyl isocyanide and ethanol. Hence, we believe that we have compelling evidence for the participation of formimidate as a crucial reactive intermediate within the reaction mechanism.

2.3.2. Chemistry of Isocyanide and Imidates. Much of the isocyanide chemistry in the 20th century was concerned with the development of the Ugi, Passerini, and other multicomponent reactions.[24] However, since the beginning of the century, isocyanide chemistry has been experiencing a renaissance with many new developments achieved in the synthesis of heterocycles,[11b,c] metal-catalyzed insertion reactions,[18,25] and "two-component coupling" to form amide bonds.[26] Our study involves the copper-catalyzed insertion of aryl isocyanide into alcohol, which yields a more electrophilic *N*-arylformimidate intermediate that undergoes further cycloaddition with 1,3-dipolar compounds. Although it is a combination of two known reactivity patterns of isocyanide, this is the first time that the two unique facets of isocyanide chemistry have been combined for use within a single reaction. It is also interesting to note that both carbon and nitrogen atoms of the isocyanide and formimidate are present within the ring of the heterocycle.

The chemistry of imidates has been well studied since the late 19th century,[27] and recently, there have been several reports on the high utility of imidates and formimidates as starting materials[28] or reactive intermediates[29] for the formation of indoles, imidazoles, and other important heterocyclic compounds. Most of the reactions utilize the highly electrophilic imidate carbon for facile inter- or intramolecular addition of a nucleophile, while there has only been a rare recent example of the use of formimidates as a dipolarophile for cycloaddition.[28c]

Although isocyanides show limited reactivity to alcohols and other nucleophiles in the absence of any catalyst,[30] Saegusa et al. and Knol et al. reported independently that, in the presence of a copper catalyst, *N*-alkylformimidates and *N*-arylformimidates could be synthesized via the insertion reaction of isocyanides into alcohols (Scheme 5).[31] It is interesting to note that Knol's electron-rich $Cu(PhNC)_4BF_4$ and Saegusa's relatively electron-poor Cu_2O catalytic system show opposite reactivity patterns in the reactions of phenyl isocyanide and cyclohexyl isocyanide. This could possibly be explained by the different nucleophilicity

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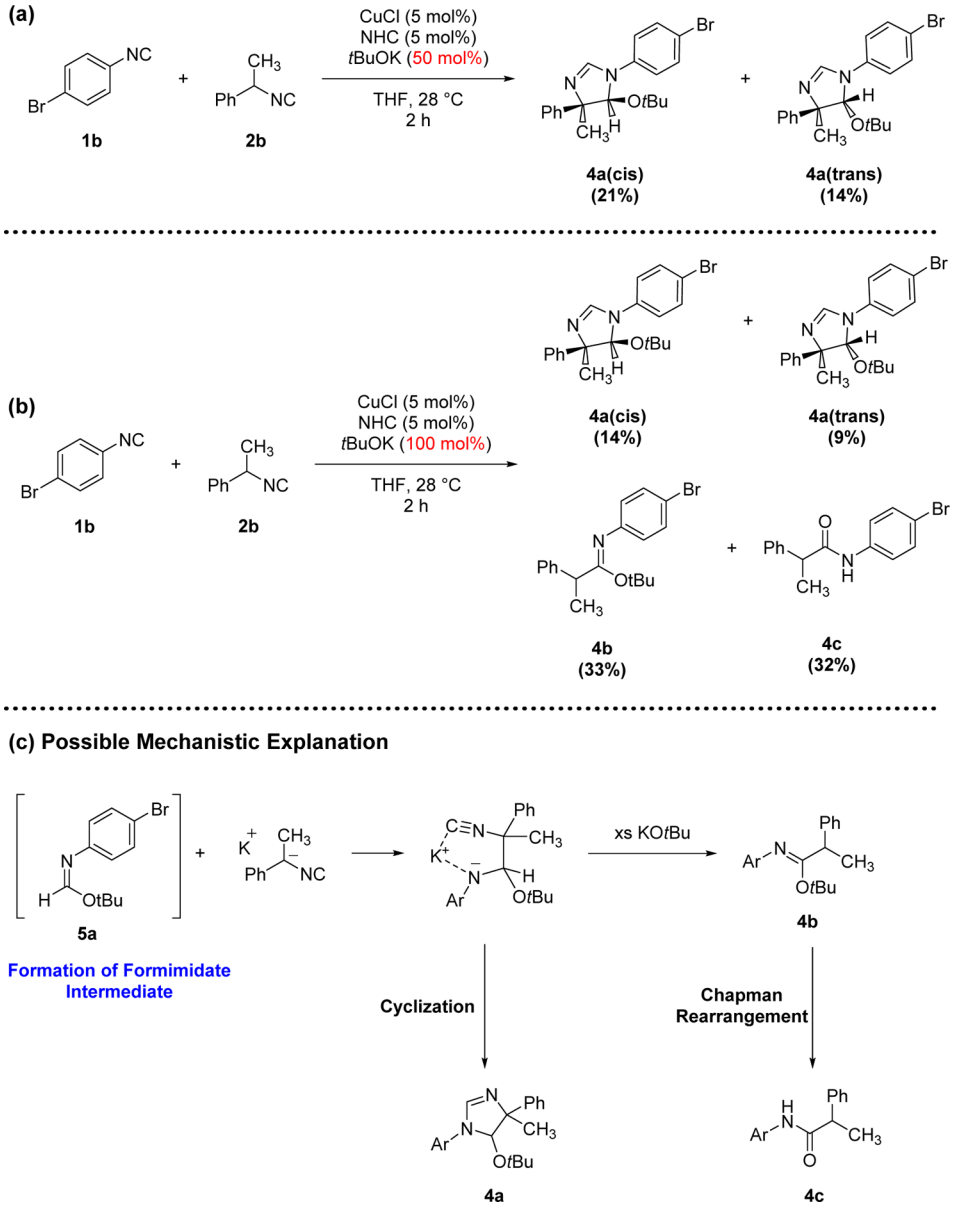
Scheme 3. Reaction of 4-Bromophenyl Isocyanide and α-Methyl Benzyl Isocyanide and Plausible Explanation for Formation of Products



of alkyl and aryl isocyanides. It has been reported that alkyl isocyanides are more nucleophilic than their aryl counterparts,[32] and infrared (IR) stretching frequencies of isocyanide groups suggest that the zwitterionic form is more prevalent in alkyl isocyanides than in their aryl counterparts (Figure 3).[33] It will then appear that the more electron-rich $Cu(PhNC)_4BF_4$ catalyzes the addition of less nucleophilic phenyl isocyanide to alcohol while the relatively electron-poor Cu_2O catalyzes the addition of more nucleophilic cyclohexyl isocyanide.

2.3.3. Relationship between Nucleophilicity and Formimidate Formation. NHC−copper(I) species are highly electron-rich because of the strong σ-donating ability of the NHC ligand; thus by applying the reactivity trends described in Saegusa's and Knol's reports, we will then expect our copper catalyst to behave in a similar manner to Knol's. Kinetic studies done by Knol et al. revealed that less nucleophilic isocyanides showed much higher rates for the formation of formimidate.[31a] Similarly, more facile formimidate formation will probably lead to higher yields of imidazole in our reaction system. This argument will explain the reactivity trend observed in our substrate scope (Chart 1) for compounds **3j−o**. As the substituent on the phenyl ring becomes more electron-withdrawing (4-methoxyphenyl compared with 4-chlorophenyl), the nucleophilicity of isocyanide carbon will decrease and therefore lead to more facile formimidate formation. This consequence is thus reflected in the higher yields of imidazoles formed from aryl isocyanides with electron-withdrawing substituents (**3m−o**) as compared to that of aryl isocyanides with electron-donating substituents (**3j−k**).

The effect of isocyanide nucleophilicity and imidazole formation is further pronounced in the reaction between tosylmethyl isocyanide and 4-bromophenyl isocyanide (**3i**). Tosylmethyl isocyanide, which is less nucleophilic than 4-bromophenyl isocyanide, will preferentially undergo insertion into alcohol to form the formimidate intermediate. However, 4-bromophenyl isocyanide, which does not have an acidic proton, is unable to generate a 1,3-dipole, and therefore, cyclization does not occur,

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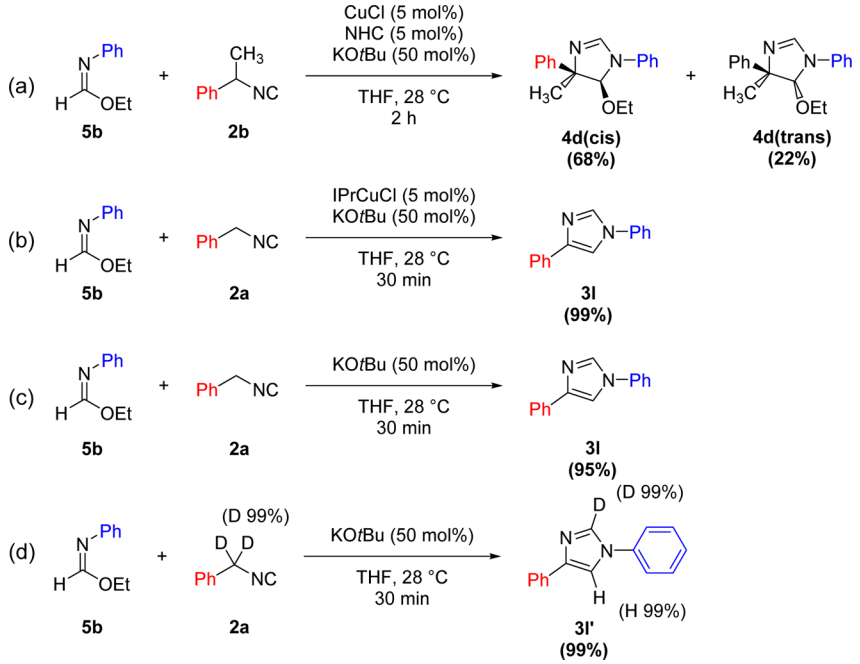
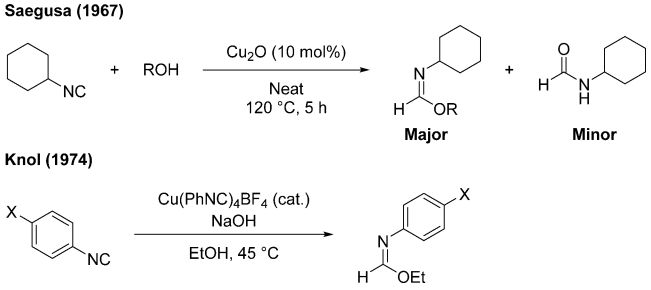
Scheme 4. Imidazole Formation from Ethyl *N*-Phenylformimidate and Benzyl Isocyanides



Scheme 5. Previous Examples of Isocyanide Insertion into a C−O Bond of Alcohols



resulting in formation of a trace amount of **3i** (Figure 4b). This hypothesis can be further supported by the formation of **3u** in the reaction of cyclohexyl isocyanide and benzyl isocyanide. Benzyl isocyanide will preferentially undergo insertion into alcohol, and since cyclohexyl isocyanide is unable to generate a 1,3-dipole, the formimidate formed from benzyl isocyanide reacts with another molecule of benzyl isocyanide to form **3u** (Figure 4c).

2.3.4. Elucidation of Reaction Mechanism with Theoretical Calculations and Experimental Data. Additional experimental and DFT computational studies were conducted to gain insight into the mechanistic details of our 1,4-diaryl-1*H*-imidazole formation reaction. DFT calculations were initially performed at the B3LYP/[SDD(Cu),6-31G*(others)] level using Gaussian 09.[34−36] This method was used to optimize individual stationary point structures, and subsequent frequency calculations at the same level yielded thermal corrections to free energy at 298.15 K and 1 atm (G_{corr}). To further improve the energetics, B3LYP/6-311+G(d,p) energy calculations were performed for the optimized structures. When doing the latter energy calculations, the solvent effect of tetrahydrofuran was included using the IEFPCM method.[37] The resultant energy is designated as E(B2-solv). Furthermore, empirical dispersion correction (E_{disp}) was evaluated for each species, using the DFT-D3(BJ) method.[38]

The following quantity G was used to assess the relative stability of species on reaction pathways:

$$G = E(\text{B2-solv}) + G_{corr} + E_{disp} \quad (1)$$

2.3.5. [IPrCu(OtBu)] Catalyzes the Formation of Formimidate from Aryl Isocyanides and tert-Butyl Alcohol. Experiments were undertaken with possible NHC−copper(I) intermediates [IPrCuCl] and [IPrCu(O*t*Bu)] (IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene) in order to determine the active catalytic species within our reaction (Scheme 6). The yields for the reactions catalyzed by [IPrCuCl] and [IPrCu(O*t*Bu)] show no significant difference, indicating that either complex could be a possible active catalyst for this reaction.

Using DFT calculations, we compared three possible mechanisms (Scheme 7, Figures 5−7). In the first mechanism (mechanism A), [IPrCuCl] reacts with KO*t*Bu to form [IPrCu(O*t*Bu)] before reacting with PhNC. In the second mechanism (mechanism B), [IPrCuCl] reacts directly with PhNC to form a coordination complex. Mechanism C begins with deprotonation of benzyl isocyanide, and the resultant deptotonated species coordinates to [IPrCuCl]. The computationally determined energy diagrams are shown in Figures 5−7. A comparison of the initial steps of mechanisms A−C shows that the barrier for the reaction between [IPrCuCl] and KO*t*Bu (mechanism A) is slightly lower than that for the other two cases. Therefore, the [IPrCu(O*t*Bu)] intermediate, **Int1**$_a$, will be favorably formed in the early stage of the reaction. The mechanism involving the [IPrCu(O*t*Bu)] formation is consistent with the experimental observation that [IPrCuCl] and [IPrCu(O*t*Bu)] provided the same product yield (Scheme 6).

In mechanism A, PhNC coordinates to the copper atom in [IPrCu(O*t*Bu)], and there is a subsequent migration of the *t*BuO$^-$ moiety to the isocyanide carbon. The transition state for this alkoxy migration (**TS3**$_a$) has a relative energy of 7.5 kcal/mol, and the energy gap between **Int1**$_a$ and **TS3**$_a$ constitutes the highest energy barrier (19.6 kcal/mol) within the entire reaction. Calculations suggest that supply of KO*t*Bu and *t*BuOH gives an

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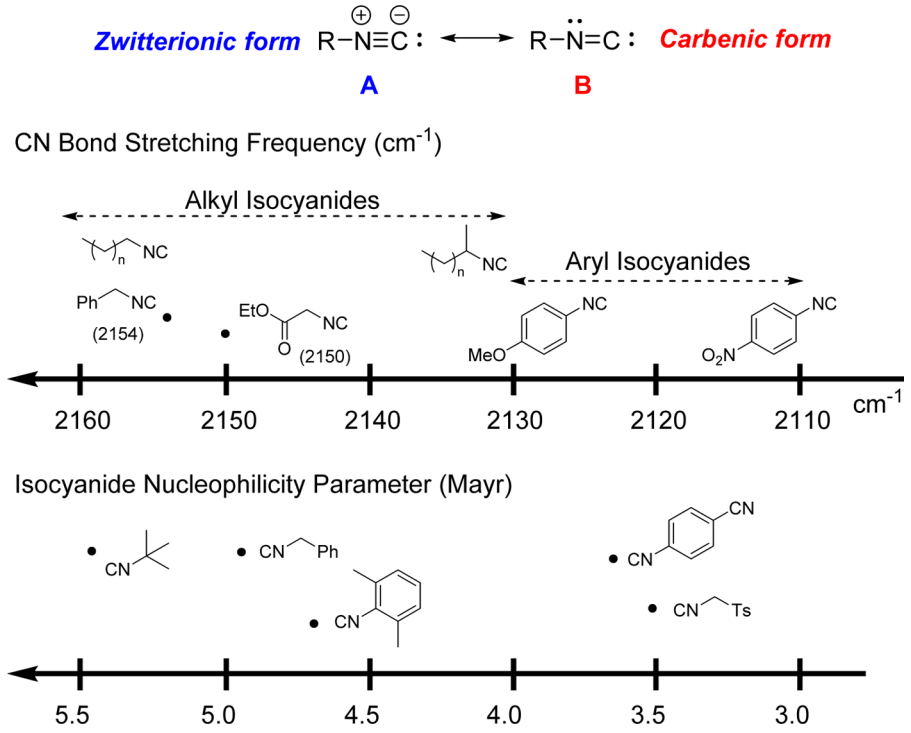

Figure 3. Resonance structure of isocyanides. More pronounced nucleophilicity is reported in the zwitterionic form **A** as compared to the carbenic form **B**. Relative CN bond stretching frequencies of isocyanides as well as the nucleophilicity parameter of isocyanides measured by Drenth and Mayr, respectively.

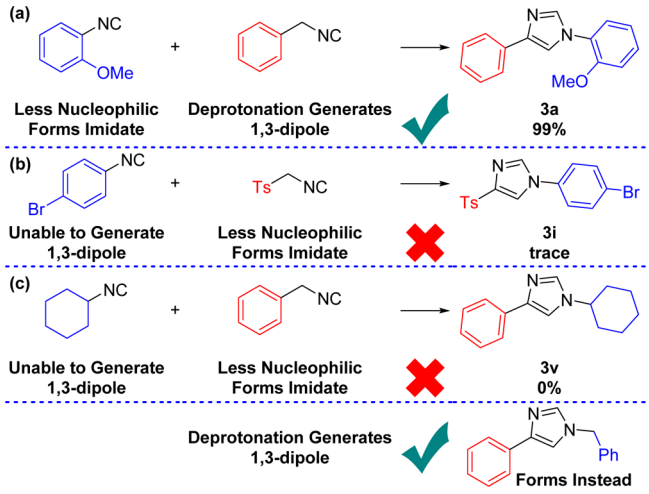

Figure 4. Using the relative nucleophilicity of the isocyanides, we are able to predict if the formimidate and 1,3-dipole formation occurs. This is eventually reflected in the yield of imidazole.

N-phenylformimidate intermediate (**Int6**$_a$) without a significant energy barrier. The *t*BuOH here is produced by the deprotonation of benzyl isocyanide by KO*t*Bu (Figure 5a). Experimental results support this mechanism because the quantitative formation of formimidate from aryl isocyanide and *tert*-butyl alcohol occurred with 1 equiv of KO*t*Bu and catalytic [IPrCu(O*t*Bu)] (Table 3, entry 1). Decreasing the amount of base led to a quick decrease in formimidate yield (Table 3, entries 2 and 3). Another interesting experimental finding was that the formimidate formation was not stereoselective; however, the *Z* isomer was always formed as the major isomer. The DFT calculations suggest that the formimidate is formed after Cu−C bond cleavage via transition state **TS5**$_a$, which has a *Z* diastereometric five-membered cyclic structure. This geometric restraint explains why the resultant formimidate intermediate **Int6**$_a$ tends to have a *Z* geometry.

If the reaction happens to follow mechanism B instead (Scheme 7b and Figure 6), an intermediate (**Int2′**$_b$) is formed which is equivalent to **Int3**$_a$ in mechanism A (Supporting Information Figure S1). Hence, after **TS2**$_b$, mechanism B is merged to mechanism A, and the formimidate intermediate **Int6**$_a$ should eventually be formed.

Another possible mechanism (mechanism C) involves the direct coordination of benzyl isocyanide anion to [IPrCuCl] (Scheme 7c and Figure 7) but does not involve any formimidate formation. In this case, the ring closure step from **Int4**$_c$ to **Int5**$_c$ has the highest energy barrier (15.9 kcal/mol), and 1,4-diaryl-1*H*-imidazole is formed relatively easily. Nevertheless, the initial steps have somewhat higher barriers than those in mechanism A, and thus the reaction will rather choose mechanism A for the imidazole formation. Furthermore, as a much larger amount of KO*t*Bu than that of [IPrCuCl] is present, formation of thermodynamically more stable [IPrCu(O*t*Bu)] species will occur predominantly, which renders mechanism A more plausible.

2.3.6. Base and Cationic Effects of KOtBu and Participation of tert-Butyl Alcohol in the Cyclization Process. Deprotonation of benzyl isocyanide **2a** is rather facile; the energy difference between the protonated and deprotonated forms of benzyl isocyanide is small, and thus both forms will exist in equilibrium with each other. This equilibrium is an essential part of our reaction. The proton abstracted from benzyl isocyanide (Figure 5a) temporarily resides in *tert*-butyl alcohol, but it is later used in formimidate formation. The deprotonation step also produces benzyl isocyanide anion, but it participates in the reaction in the cyclization reaction instead (Figure 5b). Thus, there is cooperation between formimidate formation and cyclization

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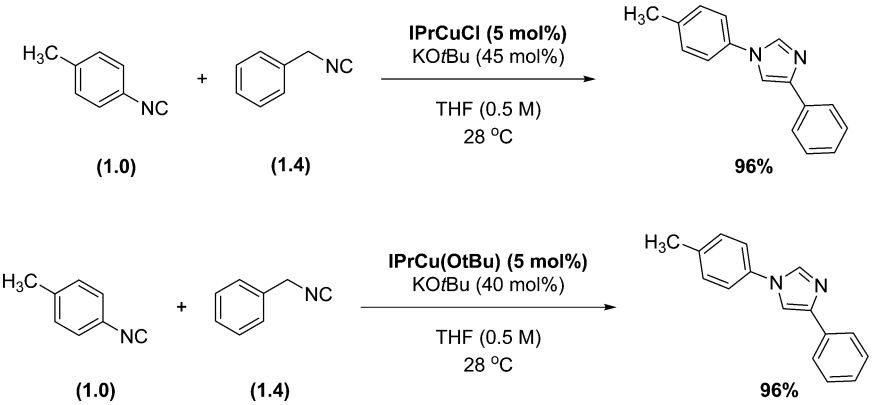
Scheme 6. Reactions Catalyzed by Possible Active Copper Species



Scheme 7. Initial Intermediates Produced in Computationally Examined Mechanisms A (a), B (b), and C (c)

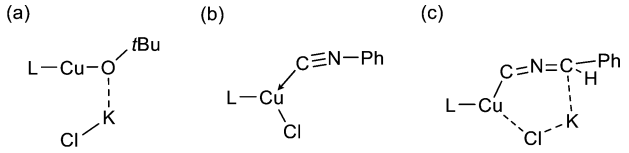
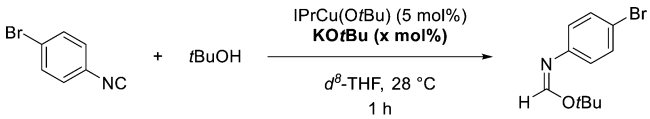


Table 3. Copper-Catalyzed Formimidate Formation[a]



1b **5a**

entry	base loading (mol %)	**5a** (%)[b]
1	100	99[c]
2	50	68
3	10	27
4	5	14

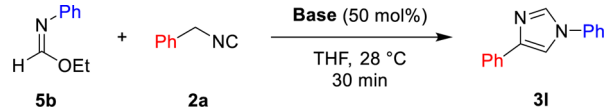
[a]Reaction of 4-bromophenyl isocyanide **1b** (0.1 mmol) with *tert*-butyl alcohol (0.1 mmol) using [IPrCu(O*t*Bu)] (5 mol %) and KO*t*Bu in tetrahydrofuran (0.5 M). [b]Yields determined by ^{1}H NMR using mesitylene as internal standard. [c]*Z*/*E* ratio = 5:1.

through the deprotonation of benzyl isocyanide, and neither reaction is able to occur without the deprotonation.

The isocyanide moiety and the formimidate are brought within close proximity with the aid of a K^+ cation (**RC**$_{a2}$ in Figure 5b). The anionic carbon of deprotonated benzyl isocyanide then attacks the carbon of formimidate to form a new C−C bond. The *tert*-butoxide in the resultant intermediate can easily dissociate because the dissociating *tert*-butoxide anion is stabilized by the potassium ion of KO*t*Bu. Before the dissociation is completed, *tert*-butoxide is able to abstract the proton from the adjacent carbon atom without an energy barrier, to form **Int2**$_{a2}$. Thus, the dissociation of *tert*-butoxide and the formation of *t*BuOH occur in a single step via transition state **TS2**$_{a2}$. The subsequent ring closure via **TS2**$_{a2}$ turns out to be facile, and the 1,4-diaryl-1*H*-imidazole product (**PC**$_{a2}$) is finally formed.

The final step of our proposed reaction mechanism involves the protonation of imidazole carbanion, formed after cyclization, by *tert*-butyl alcohol. This *tert*-butyl alcohol is produced in the preceding *tert*-butoxide dissociation. This is in contrast to the mechanism involving a 1,3-hydrogen shift, which was proposed by Yamamoto and co-workers. Cyclization experiments carried

Table 4. Base Effect in Cyclization of Formimidate and Benzyl Isocyanide[a]



5b **2a** **3l**

entry	base	**3l** (%)[b]
1	NaO*t*Bu	52
2	potassium *tert*-pentoxide	99
3	sodium *tert*-pentoxide	56
4	KOEt	trace
5	NaOMe	10
6	Cs_2CO_3	trace
7	NaOAc	trace
8	NaH	30

[a]Reaction of ethyl *N*-phenylformimidate **5b** (0.1 mmol) with benzyl isocyanide **2a** (0.14 mmol) using base in tetrahydrofuran (0.5 M). [b]Yields determined by GC using dodecane as internal standard.

out with various bases provided further experimental evidence for the roles of *tert*-butyl alcohol and potassium cation in the cyclization mechanism (Table 4). Replacing the base with NaO*t*Bu or sodium *tert*-pentoxide led to a significant decrease in yields as compared to the case of their potassium equivalent (Table 4, entries 1−3), strongly indicating the participation of K^+ ion in the cyclization process. It should be noted that, although potassium *tert*-pentoxide gave trace amounts of products in the reaction between two isocyanides (Table 2, entry 3), high yields were achieved when it was used in the cyclization of formimidate and benzyl isocyanide (Table 4, entry 2). This result further supports the calculated mechanism A (Figure 5) in which the formation of [IPrCu(O*t*Bu)] is essential for formimidate and eventual imidazole formation. If the reaction was to follow mechanism C instead (Figure 7), KO*t*Bu or potassium *tert*-pentoxide will serve only as a base and therefore should give similar yields in the reaction between two isocyanides. Hence, we believe that we have conclusive evidence for mechanism A being the dominant mechanism in our reaction.

Bases weaker than KO*t*Bu gave trace amounts of yields probably because these bases were unable to generate the benzyl isocyanide anion (Table 4, entries 4−7). The use of more basic NaH resulted in 30% yield of imidazole (Table 4, entry 8). Deprotonation by NaH is irreversible as H_2 is liberated, which will result in the inability of the system to use alcohol as a proton source in the cyclization. The 1,3-hydrogen shift, proposed by Yamamoto, is unlikely to occur in our reaction, as the reaction

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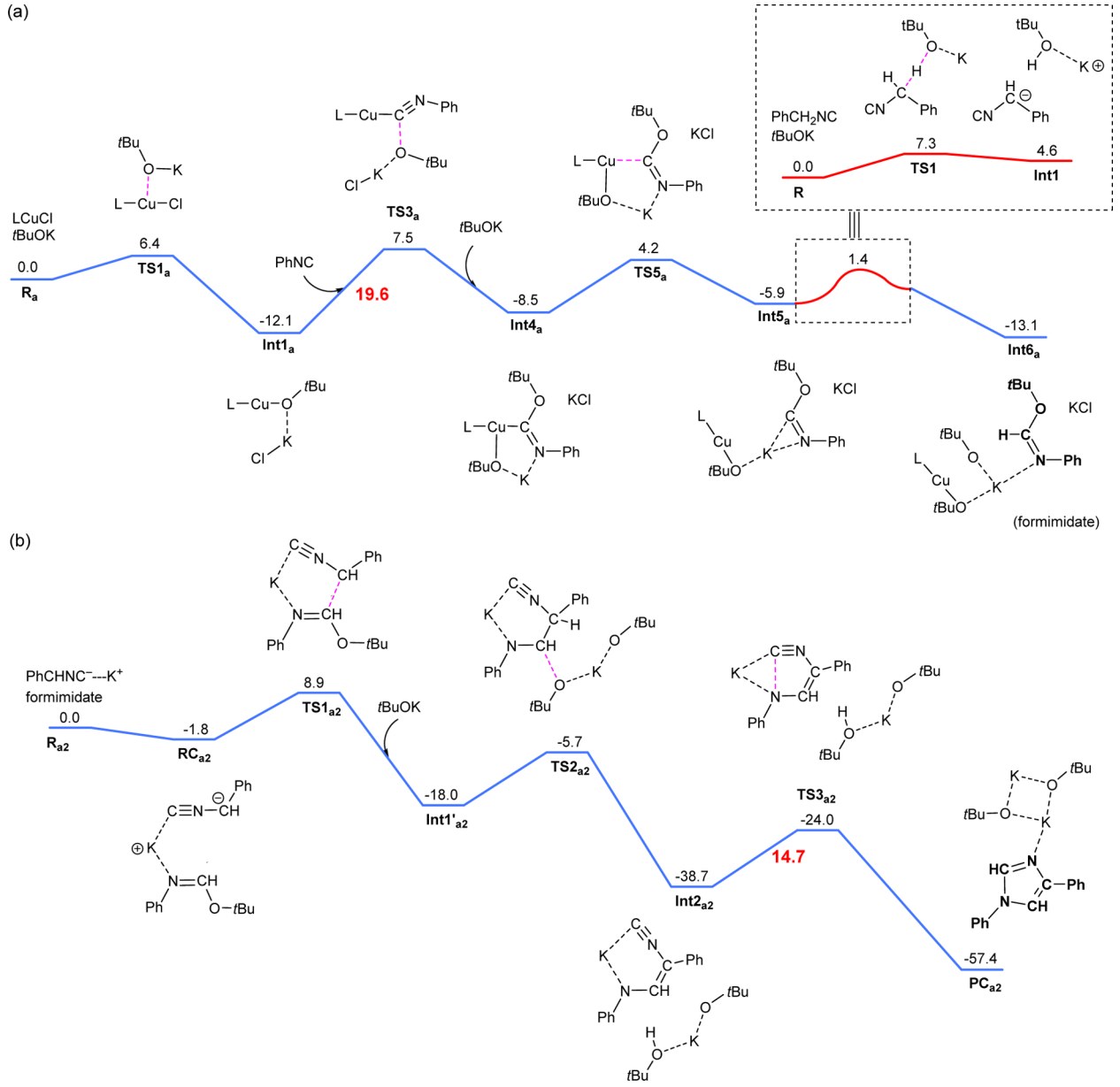

Figure 5. Reaction energy profiles for mechanism A (in kcal/mol) determined by DFT calculations: (a) the first step; (b) the second step. Minor intermediates and transition states were omitted for clarity. For full data, see Figure S1 in the Supporting Information.

with NaH shows that the presence of alcohol that protonates the imidazole carbanion is essential.

Finally, a one-pot two-step reaction was carried out (Scheme 8). Isocyanide **1b** was first reacted with *tert*-butyl alcohol in the presence of [IPrCu(O*t*Bu)] and KO*t*Bu for 30 min at ambient conditions. An equivalent of benzyl isocyanide **2a** was then added into the reaction mixture, which was stirred for an additional 30 min. The desired imidazole **3m** was formed quantitatively, further supporting the reaction mechanism predicted by theoretical calculations.

2.4. Proposed Mechanism. On the basis of the above-described experimental and theoretical data, we propose that the reported transformation occurs in two separate cycles (Figure 8). Cycle I is *tert*-butyl *N*-arylformimidate formation from aryl isocyanide and *tert*-butyl alcohol, which is catalyzed by [IPrCu(O*t*Bu)]. Cycle II is the base-facilitated cycloaddition reaction between benzyl isocyanide anion and formimidate formed in cycle I. An essential part of the proposed mechanism is the deprotonation of benzyl isocyanide by KO*t*Bu to give *tert*-butyl alcohol and benzyl isocyanide anion, which are used for cycles I and II, respectively.

As proposed by Hou[21] and supported by our calculations, [IPrCu(O*t*Bu)] **Int1**$_a$ is formed easily during the 5 min induction time. Aryl isocyanide will approach **Int1**$_a$ to form the NHC−copper(I)−*tert*-butoxide isocyanide ternary complex **Int2**$_a$. *tert*-Butoxide in **Int2**$_a$ will intramolecularly attack the electrophilic isocyanide carbon, forming the copper−imidate complex **Int3**$_a$. Upon addition of a molecule of *tert*-butyl alcohol and KO*t*Bu, formimidate **Int6**$_a$ is formed and [IPrCu(O*t*Bu)] is regenerated. The formimidate **Int6**$_a$ then enters cycle II and undergoes nucleophilic substitution with the benzyl isocyanide anion at the electrophilic imidate carbon. The addition product **Int1**$_{a2}$ is stabilized by the coordination of the K^+ ion to both amido anion and isocyanide. KO*t*Bu will promote the dissociation of *tert*-butoxide and the subsequent spontaneous deprotonation of the α-proton to form intermediate **Int2**$_{a2}$. The isocyanide

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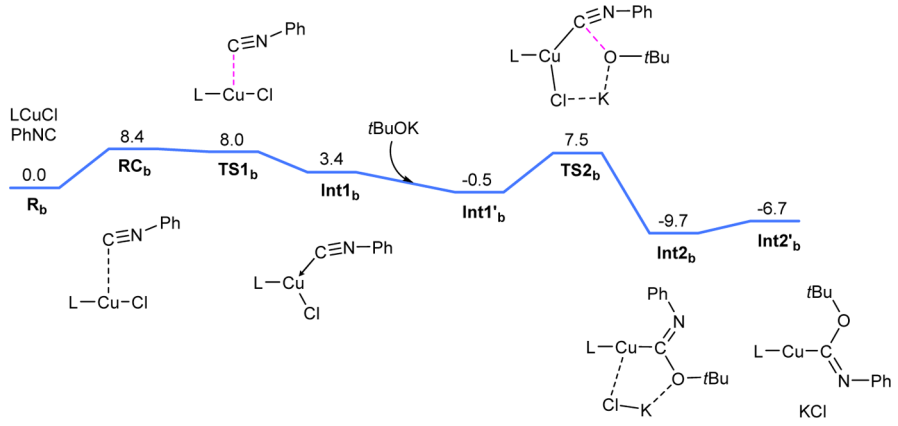

Figure 6. Reaction energy profiles for mechanism B (in kcal/mol) determined by DFT calculations.

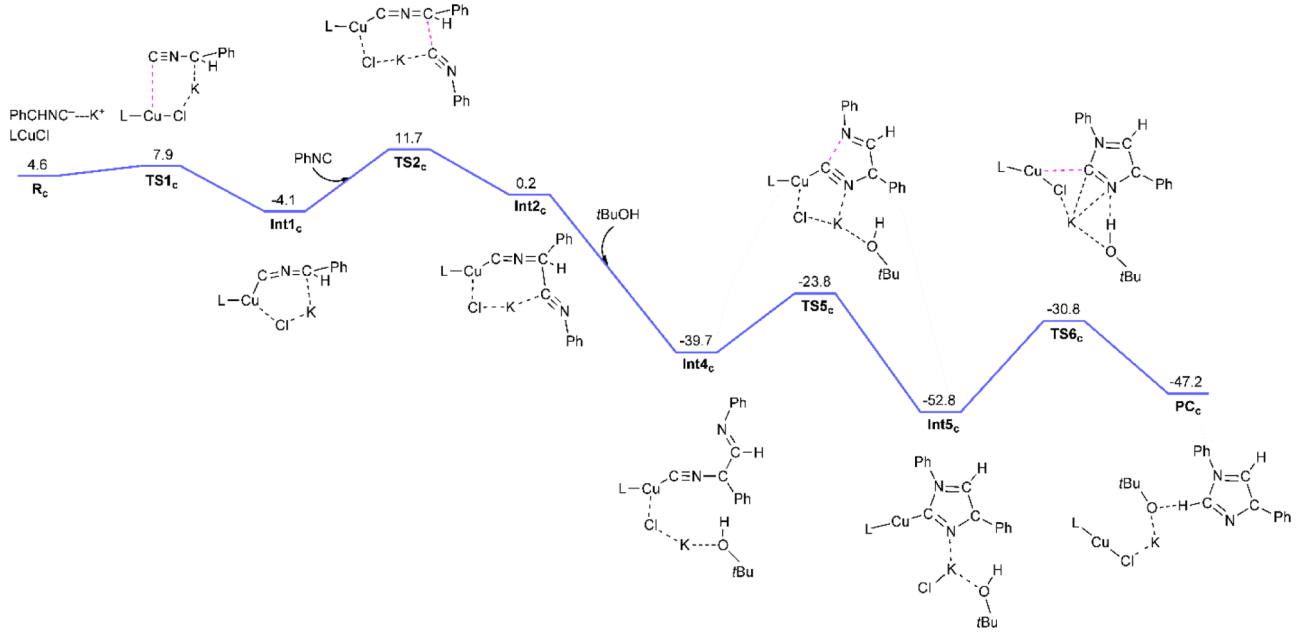

Figure 7. Reaction energy profiles for mechanism C (in kcal/mol) determined by DFT calculations. The initial step of deprotonation from benzyl isocyanide (see Figure 5a, inset) is omitted. Minor intermediates and transition states were omitted for clarity. For full data, see Figure S2 in the Supporting Information.

functionality is converted from a benzyl isocyanide in $\mathbf{Int1}_{a2}$ to a vinyl isocyanide in $\mathbf{Int2}_{a2}$, making the isocyanide carbon more electrophilic. This facilitates the cyclization involving the nucleophilic attack of amido anion on isocyanide, leading to the formation of imidazole carbanion $\mathbf{Int3}_{a2}$. This ring-closure step has the highest barrier (14.7 kcal/mol) in cycle II. Proton donation from *tert*-butyl alcohol to $\mathbf{Int3}_{a2}$ results in the formation of product complex $\mathbf{PC}_{a2}$, while KO*t*Bu is regenerated.

2.5. Rate-Determining Step Is the Nucleophilic Attack on Coordinated Isocyanide To Form NHC−Copper−Imidate Complex. As there was no buildup of formimidate during the reaction, which would have led to its in situ detection by spectroscopic means, cycle II is believed to be much faster than cycle I. The rate-determining step will therefore exist in cycle I. This argument is supported by the DFT calculations, which predicted that the highest barriers in cycles I and II are 19.6 and 14.7 kcal/mol, respectively (Figure 5a,b). Experiments carried out to measure the kinetic isotope effect (KIE) revealed a small KIE of 1.43 ± 0.03 (Figure 9a). In fact, our theoretical calculations suggest that the nucleophilic attack on coordinated isocyanide carbon is the rate-determining step of the reaction (Figures 5a and S1, $\mathbf{Int1}_a$ to $\mathbf{Int3}_a$). At this stage, benzyl isocyanide has not participated in the reaction yet, and therefore, the theoretical KIE according to transition state theory is 1. Thus, experiment and theory agree reasonably well with each other, although the reason for the small deviation remains unclear at this point. This mechanism is further supported by the report from Knol's group in which the high positive Hammett ρ value suggests a nucleophilic attack in the rate-determining step.[31a] The rate-determining step during the cyclization is predicted to be the ring-closing process (Figures 5b and S1, $\mathbf{Int2}_{a2}$ to $\mathbf{Int3}_{a2}$). The good agreement between the experimental (1.00 ± 0.06, Figure 9b) and theoretical (1.05) KIE values for the cycloaddition step backs up this point.

3. CONCLUSION

Our studies have demonstrated that the NHC−copper(I)-catalyzed cycloaddition reaction between an aryl isocyanide and a benzyl isocyanide derivative is an effective method for the

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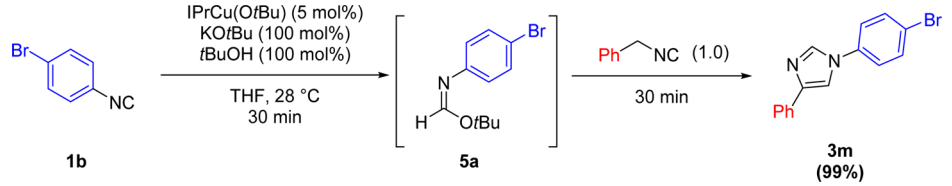
Scheme 8. One-Pot Two-Step Sequence for Imidazole Formation



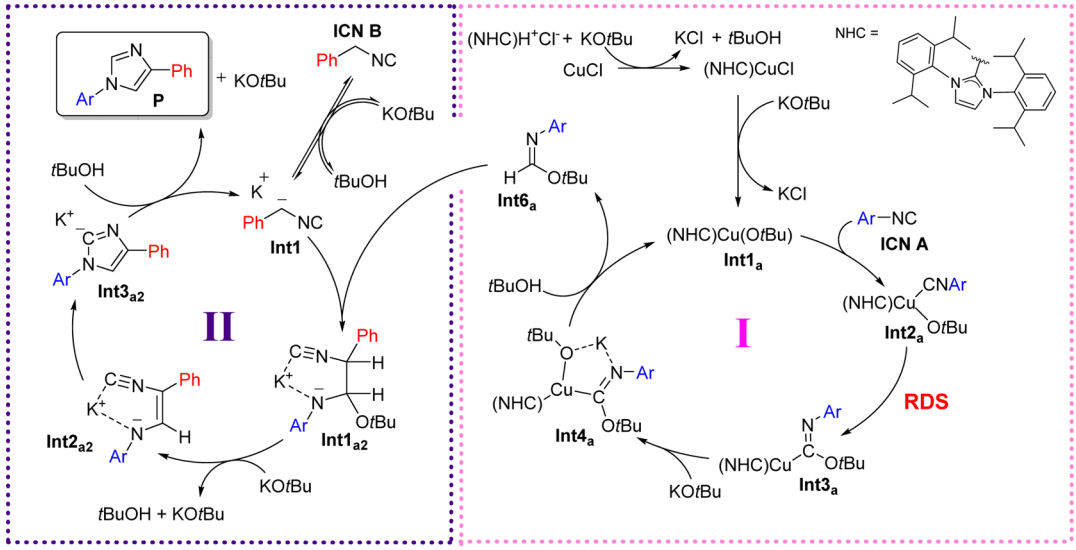


Figure 8. Plausible mechanism based on experimental data and theoretical calculations.

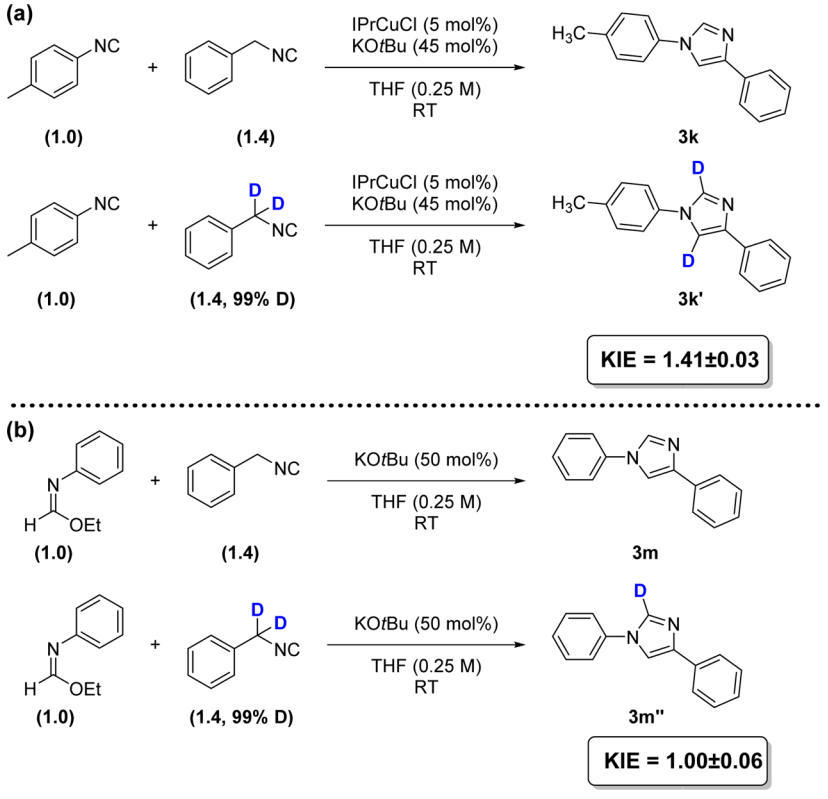


Figure 9. Kinetic isotope effect experiments carried out with deuterated and nondeuterated benzyl isocyanides.

synthesis of a wide range of 1,4-diaryl-1*H*-imidazoles at ambient conditions, including imidazoles with heteroaryl groups on the N-1 or C-4 position. Halide substituents were compatible with developed reaction conditions, thus providing convenient handles for further functionalization. Our experimental and theoretical data led us to make several important conclusions

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about the reactivity as well as the unique properties of the reaction mechanism.

(1) The reaction occurred via a tandem two-step process that included NHC−copper-catalyzed insertion of aryl isocyanide into alcohol to form formimidate followed by the base-promoted cycloaddition of formimidate with benzyl isocyanide.

(2) The reactivity of isocyanides to formimidate formation is closely related to its nucleophilicity. The lower the nucleophilicity, the faster the rate for formimidate formation. Our computational data as well as reported highly positive Hammett ρ values suggested that the rate-determining step for formimidate formation and the entire process is the nucleophilic attack on coordinated isocyanide to form the copper−imidate intermediate.

(3) Nonconcerted cycloaddition of formimidate and the benzyl isocyanide anion occurs without the presence of copper. However, the involvement of K^+ ion from KO*t*Bu is essential for the cyclization process, with the Na^+ ion giving lower yields. Our computational and experimental observation of the lack of KIE suggests that the ring-closing step is the rate-determining step of cycle II.

(4) The final step of imidazole formation is the protonation of an imidazole carbanion, for which *tert*-butyl alcohol is used. The *tert*-butyl alcohol is generated when *tert*-butoxide undergoes dissociation. This is in contrast to the 1,3-hydrogen shift suggested by Yamamoto and co-workers previously.

(5) The proton in *tert*-butyl alcohol for the formimidate originates from benzyl isocyanide and is returned during the cyclization process. This mechanism suggests that there is cooperation between the two cycles, which is mediated by the essential proton abstraction of benzyl isocyanide by KO*t*Bu.

The discovery of new types of reactivity as well as novel applications in chemical transformations is constantly expanding the utility of isocyanides in chemical synthesis. We believe that our novel combination of two unique facets of isocyanide reactivity, metal-catalyzed insertion and generation of 1,3-dipoles from methylene isocyanides, in a single reaction will inspire the development of more unique reactions involving isocyanides. With this new and much simpler route to 1,4-diaryl-1*H*-imidazoles, we also hope that a larger library of imidazoles will become available for biological and pharmaceutical testing. Further studies aiming to extend our reaction to use other cycloaddition partners are currently underway in our laboratory.

4. EXPERIMENTAL SECTION

4.1. General Information. Unless otherwise noted, all reactions were performed with standard Schlenk technique or in an argon-filled glovebox. NMR spectra were recorded in $CDCl_3$ or THF-d_8, and residue solvent signals were used as a reference. Chemical shifts were reported in parts per million and coupling constants in hertz. Multiplicity is indicated by one or more of the following: s (singlet); d (doublet); t (triplet); q (quartet); spt (septet); m (multiplet). Mass spectrometry was performed by a magnetic sector mass analyzer using fast atom bombardment (FAB) ionization mode at the National Center for Inter-University Research Facilities of Seoul National University (NCIRF). All reagents and solvents, unless otherwise noted, were purchased from commercial suppliers and used as received without further purification. Benzyl isocyanide, 4-methoxyphenyl isocyanide, ethyl isocyanoacetate, *p*-toluenesulfonylmethyl isocyanide, and cyclohexyl isocyanide were purchased from commercial sources and used without further purification. Other isocyanides were prepared from their corresponding amines by methods reported in literature, and the identity was confirmed by comparing with reported data. All 1,4-diarylimidazole products were purified by flash column chromatography (hexane/EtOAc = 9:1).

4.2. General Procedure for Synthesis of Imidazole (3) and 1-(2,6-Diisopropylphenyl)-4-phenyl-1*H*-imidazole (3q). CuCl (1.98 mg, 0.02 mmol), 1,3-bis(2,6-diisopropylphenyl)-1*H*-imidazol-3-ium chloride (8.5 mg, 0.02 mmol), and potassium *tert*-butoxide (22.4 mg, 0.2 mmol) were added to THF (0.8 mL) under argon atmosphere in a 4 mL vial. The vial was then sealed with a Teflon-lined septum, and the solution was allowed to stir for 5 min at 28 °C. The resulting mixture was a light tan color. The stirring was stopped momentarily while 2-isocyano-1,3-diisopropylbenzene (78.7 μL, 0.4 mmol) and (isocyanomethyl)benzene (66.9 μL, 0.56 mmol) was added quickly via a gastight syringe. The solution darkened immediately and was allowed to stir for a further 2 h at 28 °C. Solvent was then removed in vacuo and the remaining residue purified by flash column chromatography (hexane/EtOAc = 9:1) to afford pure 1-(2,6-diisopropylphenyl)-4-phenyl-1*H*-imidazole (80% yield): ^{1}H NMR ($CDCl_3$, 499 MHz) δ = 7.87−7.92 (m, 2 H), 7.53 (d, J = 1.0 Hz, 1 H), 7.41−7.49 (m, 3 H), 7.26−7.32 (m, 4 H), 2.56 (spt, J = 6.8 Hz, 2 H), 1.17 (d, J = 6.8 Hz, 6 H), 1.18 ppm (d, J = 6.8 Hz, 6 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 146.5, 142.1, 138.7, 133.9, 132.7, 129.9, 128.7, 127.0, 124.8, 123.8, 117.1, 28.1, 24.5, 24.3 ppm; HRMS−FAB (m/z) [M + H]$^+$ calcd for $C_{21}H_{25}N_2$, 305.2018; found, 305.2012.

*4.2.1. 1-(2-Methoxyphenyl)-4-phenyl-1H-imidazole (**3a**):* 99.4 mg, 99%; ^{1}H NMR ($CDCl_3$, 499 MHz) δ = 7.84−7.92 (m, 3 H), 7.51 (s, 1 H), 7.32−7.45 (m, 4 H), 7.24−7.31 (m, 1 H), 7.03−7.11 (m, 2 H), 3.86 ppm (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 152.5, 141.3, 137.9, 133.7, 129.0, 128.5, 126.8, 126.2, 125.3, 124.8, 121.0, 115.9, 112.3, 55.8 ppm; HRMS−FAB (m/z) [M + H]$^+$ calcd for $C_{16}H_{15}N_2O$, 251.1184; found, 251.1181.

*4.2.2. 1-(4-Bromophenyl)-4-(4-methoxyphenyl)-1H-imidazole (**3b**):* 119.8 mg, 91%; ^{1}H NMR ($CDCl_3$, 499 MHz) δ = 7.83 (s, 1 H), 7.74 (d, J = 8.3 Hz, 2 H), 7.58 (d, J = 8.3 Hz, 2 H), 7.41 (s, 1 H), 7.29 (s, 2 H), 6.94 (d, J = 8.3 Hz, 2 H), 3.83 ppm (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 158.9, 143.3, 136.1, 135.2, 132.9, 126.2, 126.1, 122.5, 120.6, 114.0, 112.3, 55.2 ppm; HRMS−FAB (m/z) [M + H]$^+$ calcd for $C_{16}H_{14}BrN_2O$, 329.0289; found, 329.0286.

*4.2.3. 1-(4-Bromophenyl)-4-(p-tolyl)-1H-imidazole (**3c**):* 121.5 mg, 97%; ^{1}H NMR ($CDCl_3$, 499 MHz) δ = 7.87 (s, 1 H), 7.73 (d, J = 7.8 Hz, 2 H), 7.63 (d, J = 8.8 Hz, 2 H), 7.49 (s, 1 H), 7.34 (m, J = 8.8 Hz, 2 H), 7.23 (m, J = 7.3 Hz, 2 H), 2.38 ppm (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 143.6, 137.0, 136.2, 135.3, 133.0, 130.6, 129.4, 124.9, 122.7, 120.9, 113.0, 21.2 ppm; HRMS−FAB (m/z) [M + H]$^+$ calcd for $C_{16}H_{14}BrN_2$, 313.0340; found, 313.0332.

*4.2.4. 1-(4-Bromophenyl)-4-(4-chlorophenyl)-1H-imidazole (**3d**):* 131.9 mg, 99%; ^{1}H NMR ($CDCl_3$, 499 MHz) δ = 7.85 (s, 1 H), 7.75 (d, J = 8.3 Hz, 2 H), 7.62 (d, J = 8.8 Hz, 2 H), 7.50 (s, 1 H), 7.37 (d, J = 8.3 Hz, 2 H), 7.31 ppm (d, J = 8.8 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 142.4, 136.0, 135.6, 133.0, 132.8, 132.0, 128.8, 126.1, 122.7, 121.0, 113.6 ppm; HRMS−FAB (m/z) [M + H]$^+$ calcd for $C_{15}H_{11}BrClN_2$, 332.9794; found, 332.9790.

*4.2.5. 1-(4-Bromophenyl)-4-(4-(trifluoromethyl)phenyl)-1H-imidazole (**3e**):* 120.4 mg, 82%; ^{1}H NMR ($CDCl_3$, 499 MHz) δ = 7.87−7.98 (m, 3 H), 7.59−7.70 (m, 5 H), 7.31−7.38 ppm (m, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 142.11, 136.87 (d, J = 1.6 Hz), 135.92, 133.11, 128.96 (q, J = 32.3 Hz), 125.64 (q, J = 3.2 Hz), 124.96, 122.83, 121.32, 122.46 (q, J = 272.1 Hz), 114.68 ppm; ^{19}F NMR ($CDCl_3$, 376 MHz) δ = −63.58 ppm; HRMS−FAB (m/z) [M + H]$^+$ calcd for $C_{16}H_{11}BrF_3N_2$, 367.0058; found, 367.0054.

*4.2.6. 1-(4-Bromophenyl)-4-(thiophen-2-yl)-1H-imidazole (**3f**):* 90.3 mg, 74%; ^{1}H NMR ($CDCl_3$, 499 MHz) δ = 7.80 (s, 1 H), 7.59 (d, J = 8.8 Hz, 2 H), 7.41 (s, 1 H), 7.31−7.35 (m, 1 H), 7.29 (d, J = 8.8 Hz, 2 H), 7.22 (d, J = 4.9 Hz, 1 H), 7.05 ppm (dd, J = 4.6, 3.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 138.6, 137.1, 135.9, 135.3, 133.0, 127.6, 123.8, 122.6, 122.3, 121.0, 112.7 ppm; HRMS−FAB (m/z) [M + H]$^+$ calcd for $C_{13}H_{10}BrN_2S$, 304.9748; found, 304.9746.

*4.2.7. 3-(1-(4-Bromophenyl)-1H-imidazol-4-yl)pyridine (**3g**):* 22.8 mg, 19%; ^{1}H NMR ($CDCl_3$, 499 MHz) δ = 9.03−9.04 (m, 1 H), 8.52 (dd, J = 4.6, 1.7 Hz, 1 H), 8.14 (dt, J = 8.1, 2.1 Hz, 1 H), 7.89 (d, J = 1.5 Hz, 1 H), 7.64 (d, J = 8.8 Hz, 2 H), 7.60 (d, J = 1.5 Hz, 1 H), 7.33 ppm (d, J = 8.8 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 148.3, 146.6, 140.5, 136.0, 135.9, 133.1, 132.2, 129.4, 123.6, 122.9, 121.3, 114.2 ppm;

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HRMS−FAB (m/z) $[M + H]^+$ calcd for $C_{14}H_{11}BrN_3$, 300.0136; found, 300.0138.

*4.2.8. Ethyl-1-(4-chlorophenyl)-1H-imidazole-4-carboxylate (**3h**):*[13a] 48.1 mg, 48%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.92 (d, J = 1.2 Hz, 1 H), 7.83 (d, J = 1.2 Hz, 1 H), 7.49 (d, J = 8.6 Hz, 2 H), 7.37 (d, J = 8.6 Hz, 2 H), 4.40 (q, J = 7.3 Hz, 2 H), 1.40 ppm (t, J = 7.2 Hz, 3 H).

*4.2.9. 1-(4-Methoxyphenyl)-4-phenyl-1H-imidazole (**3j**):*[39] 89.1 mg, 89%; ^{1}H NMR ($CDCl_3$, 499 MHz) δ = 7.94 (d, J = 7.3 Hz, 2 H), 7.62 (s., 1 H), 7.54 (d, J = 8.8 Hz, 2 H), 7.42−7.50 (m, 2 H), 7.33−7.42 (m, 2 H), 7.02−7.12 (d, J = 8.8 Hz, 2 H), 3.88 ppm (s, 3 H).

*4.2.10. 4-Phenyl-1-(p-tolyl)-1H-imidazole (**3k**):*[39] 87.2 mg, 93%; ^{1}H NMR ($CDCl_3$, 499 MHz) δ = 7.82−7.90 (m, 3 H), 7.54 (s, 1 H), 7.42 (dd, J = 7.6 Hz, 2 H), 7.24−7.36 (m, 5 H), 2.42 ppm (s, 3 H).

*4.2.11. 1,4-Diphenyl-1H-imidazole (**3l**):*[39] 87.2 mg, 99%; ^{1}H NMR ($CDCl_3$, 499 MHz) δ = 7.87 (d, J = 1.5 Hz, 1 H), 7.81−7.85 (m, 2 H), 7.54 (d, J = 1.5 Hz, 1 H), 7.44−7.49 (m, 2 H), 7.33−7.42 (m, 5 H), 7.23−7.28 ppm (m, 1 H).

*4.2.12. 1-(4-Bromophenyl)-4-phenyl-1H-imidazole (**3m**):*[39] 117.3 mg, 98%; ^{1}H NMR ($CDCl_3$, 499 MHz) δ = 7.81−7.89 (m, 3 H), 7.60−7.65 (m, 2 H), 7.53 (d, J = 1.5 Hz, 1 H), 7.39−7.45 (m, 2 H), 7.27−7.35 ppm (m, 3 H).

*4.2.13. 1-(4-Chlorophenyl)-4-phenyl-1H-imidazole (**3n**):*[39] 100.9 mg, 99%; ^{1}H NMR ($CDCl_3$, 499 MHz) δ = 7.81−7.87 (m, 3 H), 7.52 (d, J = 1.5 Hz, 1 H), 7.46 (d, J = 8.8 Hz, 2 H), 7.42 (t, J = 7.3 Hz, 2 H), 7.37 (d, J = 8.8 Hz, 2 H), 7.29 ppm (tt, J = 7.3, 1.0 Hz, 1 H).

*4.2.14. 4-(4-Phenyl-1H-imidazol-1-yl)benzonitrile (**3o**):* 93.5 mg, 95%; ^{1}H NMR ($CDCl_3$, 499 MHz) δ = 8.01 (s, 1 H), 7.81−7.86 (m, 4 H), 7.57−7.63 (m, 3 H), 7.41−7.46 (m, 2 H), 7.30−7.35 ppm (m, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 144.1, 140.2, 135.3, 134.1, 132.9, 128.7, 127.6, 125.0, 121.0, 117.8, 112.6, 110.9 ppm; HRMS−FAB (m/z) $[M + H]^+$ calcd for $C_{16}H_{12}N_3$, 246.1031; found, 246.1033.

*4.2.15. 1-Mesityl-4-phenyl-1H-imidazole (**3p**):* 93.7 mg, 89%; ^{1}H NMR ($CDCl_3$, 499 MHz) δ = 7.85 (dd, J = 8.1, 1.2 Hz, 2 H), 7.48 (d, J = 1.5 Hz, 1 H), 7.37−7.43 (m, 2 H), 7.23−7.29 (m, 1 H), 7.20 (d, J = 1.5 Hz, 1 H), 6.99 (s, 2 H), 2.35 (s, 3 H), 2.06 ppm (s, 6 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 142.3, 138.9, 137.7, 135.3, 134.0, 133.3, 129.0, 128.6, 126.8, 124.7, 115.8, 21.0, 17.4 ppm; HRMS−FAB (m/z) $[M + H]^+$ calcd for $C_{18}H_{19}N_2$, 263.1548; found, 263.1547.

*4.2.16. 1-([1,1′-Biphenyl]-2-yl)-4-phenyl-1H-imidazole (**3r**):* 72.5 mg, 61%; ^{1}H NMR ($CDCl_3$, 499 MHz) δ = 7.74 (d, J = 8.3 Hz, 2 H), 7.47−7.58 (m, 3 H), 7.41−7.47 (m, 2 H), 7.38 (t, J = 7.6 Hz, 2 H), 7.30−7.35 (m, 3 H), 7.23−7.29 (m, 1 H), 7.16−7.22 ppm (m, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 142.0, 137.6, 137.3, 134.9, 133.7, 131.4, 128.7, 128.5, 128.3, 127.8, 126.8, 126.0, 124.8, 116.0 ppm; HRMS−FAB (m/z) $[M + H]^+$ calcd for $C_{21}H_{17}N_2$, 297.1392; found, 297.1388.

*4.2.17. 1-(Naphthalen-1-yl)-4-phenyl-1H-imidazole (**3s**):* 98.7 mg, 91%; ^{1}H NMR ($CDCl_3$, 499 MHz) δ = 7.96 (dd, J = 7.8, 4.4 Hz, 2 H), 7.90 (d, J = 6.8 Hz, 2 H), 7.81 (s, 1 H), 7.72 (d, J = 7.8 Hz, 1 H), 7.53−7.60 (m, 4 H), 7.49−7.52 (m, 1 H), 7.43 (t, J = 7.8 Hz, 2 H), 7.29 ppm (t, J = 7.3 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 142.3, 138.5, 134.1, 133.8, 133.8, 129.3, 129.2, 128.6, 128.3, 127.6, 127.0, 126.9, 125.1, 124.9, 123.5, 122.3, 117.3 ppm; HRMS−FAB (m/z) $[M + H]^+$ calcd for $C_{19}H_{15}N_2$, 271.1235; found, 271.1235.

*4.2.18. 3-(4-Phenyl-1H-imidazol-1-yl)pyridine (**3t**):*[40] 54.9 mg, 62%; ^{1}H NMR ($CDCl_3$, 499 MHz) δ = 8.80 (s, 1 H), 8.62−8.68 (m, 1 H), 7.91 (s, 1 H), 7.84 (d, J = 7.8 Hz, 2 H), 7.77 (d, J = 8.3 Hz, 1 H), 7.57 (s, 1 H), 7.46 (dd, J = 7.8, 4.9 Hz, 1 H), 7.41 (t, J = 7.6 Hz, 2 H), 7.29 ppm (t, J = 7.3 Hz, 1 H).

*4.2.19. 1-Benzyl-4-phenyl-1H-imidazole (**3u**):*[41] 74.0 mg, 79%; ^{1}H NMR ($CDCl_3$, 499 MHz) δ = 7.77 (d, J = 7.8 Hz, 2 H), 7.59 (s, 1 H), 7.31−7.42 (m, 5 H), 7.14−7.26 (m, 4 H), 5.12 ppm (s, 2 H).

*4.2.20. 1-(4-Bromophenyl)-5-(tert-butoxy)-4-methyl-4-phenyl-4,5-dihydro-1H-imidazole (**4a**):* 35.6 mg, 23%; ^{1}H NMR ($CDCl_3$, 499 MHz) δ = 7.47−7.52 (m, J = 8.3 Hz, 2 H) (major-*cis*), 7.23−7.47 (m, 14 H) (mixture), 7.09−7.15 (m, J = 8.3 Hz, 2 H) (major), 7.00 (d, J = 8.3 Hz, 2 H) (minor-*trans*), 5.24 (s, 1 H) (minor), 5.10 (s, 1 H) (major), 1.70 (s, 3 H) (minor), 1.69 (s, 3 H) (major), 1.00 (s, 9 H) (minor), 0.55 ppm (s, 9 H) (major); ^{13}C NMR ($CDCl_3$, 126 MHz) δ = 151.2, 150.7, 145.8, 140.8, 138.1, 137.9, 132.1, 132.0, 128.5, 128.5, 127.3, 127.1, 126.9, 126.9, 126.2, 125.4, 119.4, 118.7, 93.0, 92.0, 76.1, 75.7, 74.5, 74.1, 28.9, 28.4, 24.4, 22.6 ppm; HRMS−FAB (m/z) $[M + H]^+$ calcd for $C_{20}H_{23}BrN_2O$, 387.1072; found, 387.1068.

*4.2.21. tert-Butyl (Z)-N-(4-Bromophenyl)-2-phenylpropanimidate (**4b**):* 47.4 mg, 33%; ^{1}H NMR ($CDCl_3$, 499 MHz) δ = 7.39 (d, J = 8.3 Hz, 2 H), 7.19−7.33 (m, 5 H), 6.58 (d, J = 8.3 Hz, 2 H), 3.73 (q, J = 6.8 Hz, 1 H), 1.55 (s, 9 H), 1.42 ppm (d, J = 6.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ = 162.2, 148.0, 142.1, 131.8, 128.2, 127.5, 126.5, 122.9, 114.9, 80.0, 40.9, 27.9, 19.5 ppm; HRMS−FAB (m/z) $[M + H]^+$ calcd for $C_{19}H_{22}BrNO$, 359.0885; found, 359.0882.

*4.2.22. N-(4-Bromophenyl)-2-phenylpropanamide (**4c**):*[42] 39.1 mg, 32%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 7.24−7.47 (m, 9 H), 7.18 (br s, 1 H), 3.72 (q, J = 7.2 Hz, 1 H), 1.59 ppm (d, J = 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 172.3, 140.6, 136.9, 131.8, 129.2, 127.7, 127.6, 121.2, 116.7, 48.0, 18.5 ppm.

*4.2.23. cis-5-Ethoxy-4-methyl-1,4-diphenyl-4,5-dihydro-1H-imidazole (**4d**(cis)):* 76.5 mg, 68%; ^{1}H NMR ($CDCl_3$, 499 MHz) δ = 7.75 (s, 1 H), 7.60−7.65 (d, J = 7.3 Hz, 2 H), 7.33−7.40 (m, 4 H), 7.26−7.31 (m, 1 H), 7.18−7.22 (d, J = 7.8 Hz, 2 H), 7.07 (t, J = 7.3 Hz, 1 H), 5.35 (s, 1 H), 2.76−2.95 (m, 2 H), 1.55 (s, 3 H), 0.55 ppm (t, J = 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 147.2, 140.9, 139.3, 129.6, 127.5, 127.3, 126.7, 122.7, 115.8, 94.5, 75.7, 59.8, 29.6, 14.2 ppm; HRMS−FAB (m/z) $[M + H]^+$ calcd for $C_{18}H_{20}N_2O$, 281.1654; found, 281.1652.

*4.2.24. trans-5-Ethoxy-4-methyl-1,4-diphenyl-4,5-dihydro-1H-imidazole (**4d**(trans)):* 24.7 mg, 22%; ^{1}H NMR ($CDCl_3$, 499 MHz) δ = 7.75 (s, 1 H), 7.43 (d, J = 7.8 Hz, 2 H), 7.28−7.39 (m, 5 H), 7.01−7.06 (m, 3 H), 5.24 (s, 1 H), 3.66−3.79 (m, 2 H), 1.74 (s, 3 H), 1.28 ppm (t, J = 6.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 147.8, 146.4, 139.0, 129.5, 128.5, 127.0, 125.3, 122.9, 116.5, 96.9, 77.2, 64.5, 22.3, 15.2 ppm; HRMS−FAB (m/z) $[M + H]^+$ calcd for $C_{18}H_{20}N_2O$, 281.1654; found, 281.1652.

*4.2.25. N-tert-Butyl (4-bromophenyl)formimidate (**5a**):* ^{1}H NMR (THF-d_8, 499 MHz) δ = 7.74 (s, 1 H) (major), 7.39 (br s, 1 H) (minor), 7.38 (d, J = 8.8 Hz, 2 H) (major), 7.32 (d, J = 8.3 Hz, 2 H) (minor), 6.91 (d, J = 8.3 Hz, 2 H) (minor), 6.84 (d, J = 8.3 Hz, 2 H) (major), 1.52 (s, 9 H) (major), 1.38 ppm (s, 3 H) (minor); ^{13}C NMR (THF-d_8, 75 MHz) δ = 155.7, 149.5, 132.8, 124.2, 117.6, 81.2, 28.7 ppm (spectra contains peaks from *E* isomer).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Details of computational results and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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