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Dual Activation of Nucleophiles and Electrophiles by N-Heterocyclic Carbene Organocatalysis: Chemoselective N-Imination of Indoles with Isocyanides

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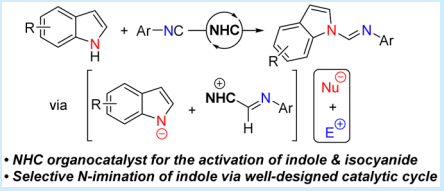
Supporting Information

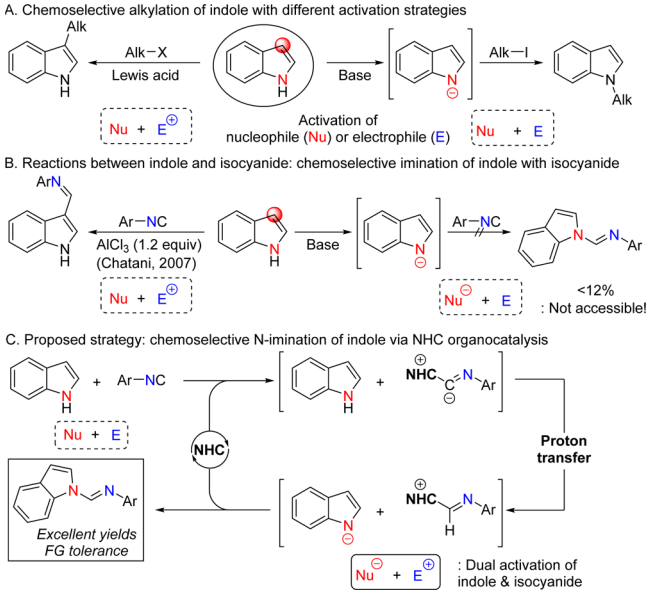
ABSTRACT: The first chemoselective N-imination of indoles with isocyanides by using an N-heterocyclic carbene (NHC) as an organocatalyst was achieved. A concurrent activation of nucleophile (indole) and electrophile (isocyanide) took place facilitated by the novel NHC organocatalysis via initial activation of isocyanide. The in situ generated indole anion and imine-azolium species performed a coupling reaction, producing several new indole-based formamidines in high yields under mild conditions, which was not feasible via previously reported strategies.



Selective functionalization of indoles is one of the most actively pursued research areas in organic synthesis, due to its privileged structure in natural products, drugs, agrochemicals, and materials.[1] Especially, chemoselective control between C3- and N-positions of indole is a very important issue in the synthesis of functionalized indoles. Generally, either the starting indole or its coupling partner requires an activation step, which determines the chemoselectivity of the overall transformation. For example, direct alkylation of indole at the C3-position can be achieved by using alkyl halides or alcohols activated by Lewis acids (Friedel−Crafts alkylation),[2] whereas direct N-alkylation can be performed with the deprotonated indole anion, such as an indole sodium salt, which has an enhanced nucleophilicity at the nitrogen position (Scheme 1A).[3] Apart from alkylation, several other types of reactions such as vinylation,[3c,4] allylation,[5] acylation,[6] and carboxylation[7] have also been developed to achieve selective introduction of functionality at the indole moiety, enhancing the diversity of synthetic pathways.

The isocyanide functional group is versatile and has been utilized for the synthesis of many useful molecules.[8] Generally, isocyanides have been employed in metal-based activation strategies as an iminating reagent for coupling reactions with different types of nucleophiles.[9,10] Chatani et al. have demonstrated the first C3-imination of indoles by using a stoichiometric amount of $AlCl_3$ for activation of the isocyanide (Scheme 1B).[11] To the best of our knowledge, no practical approach toward the direct N-imination of indoles for the synthesis of indole-formamidines has been reported to date.[12] Initial trial reactions for N-imination of indole using an indole anion species gave very low yields, which may be due to the low electrophilicity of isocyanide itself (Scheme 1B). Therefore, a new strategy for concurrent activation of the indole and the isocyanide is required. We envisioned that the use of N-heterocyclic carbene (NHC) as an organocatalyst would have a chance to induce a new reaction pathway for the selective N-imination reaction of indole. NHC has been widely applied in several types of organocatalysis, including nucleophilic catalysis for the activation of carbonyl compounds and base catalysis for the activation of nucleophiles.[13] Recently, an activation strategy to enhance the basicity of the terminal carbon of isocyanides was developed by introducing NHC organocatalysis.[14] On the basis of the result, it was envisioned that the NHC organocatalyst can generate the basic imidoyl intermediate, which can further activate the indole substrate via deprotonation. Thus, an activated nucleophile (indole anion) and an

Scheme 1. Chemoselective Functionalization of Indole



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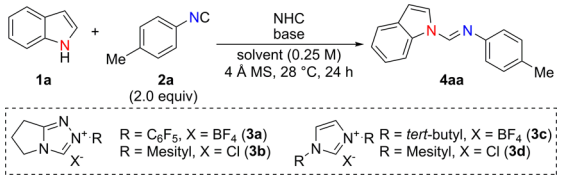
activated electrophile (imine-azolium) can be produced together, which can be coupled to produce indole-based formamidines (Scheme 1C).[15]

To check the viability of our proposed approach for N-imination of indoles, the reaction of indole (**1a**) with 4-methylphenyl isocyanide (**2a**) was investigated. After an extensive screening process with the model substrates, we found the reaction conditions which gave the desired product in 85% yields (Tables S2–S5). With this result, further variations of reaction conditions from the standard conditions were evaluated to check the effect of each component of the reaction (Table 1). Among several NHC precursors tested, a

Table 1. Variations of Reaction Conditions[a]



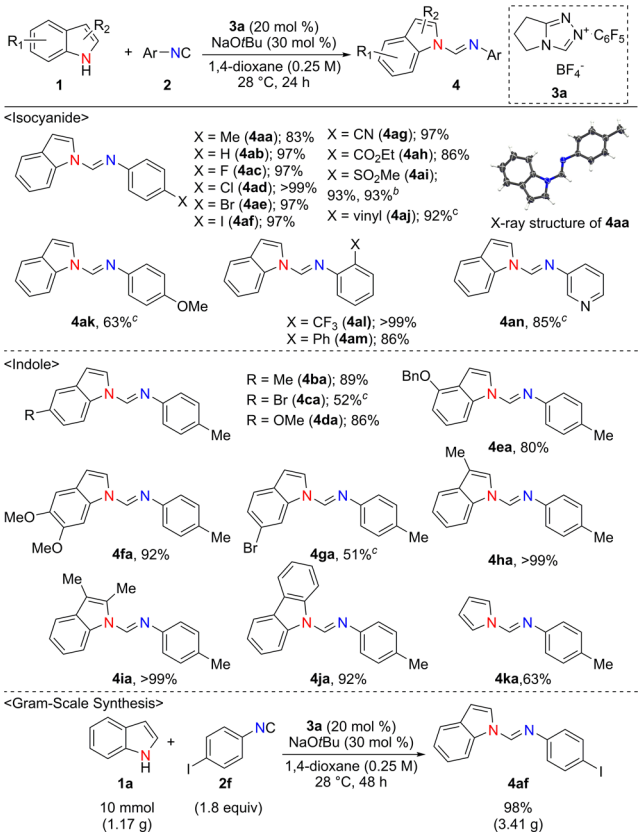
entry	NHC (mol %)	base (mol %)	solvent	yield (%)[b]
1	**3a** (20)	NaO*t*Bu (130)	1,4-dioxane	85
2	**3b** (20)	NaO*t*Bu (130)	1,4-dioxane	48
3	**3c** (20)	NaO*t*Bu (130)	1,4-dioxane	43
4	**3d** (20)	NaO*t*Bu (130)	1,4-dioxane	31
5	**3a** (20)	KO*t*Bu (130)	1,4-dioxane	45
6	**3a** (20)	NaH (130)	1,4-dioxane	43
7	**3a** (20)	DIPEA (130)	1,4-dioxane	trace
8	**3a** (20)	NaO*t*Bu (130)	THF	61
9	**3a** (20)	NaO*t*Bu (130)	Toluene	10
10	**3a** (20)	NaO*t*Bu (130)	MeCN	26
11	None	NaO*t*Bu (130)	1,4-dioxane	20
12[c]	**3a** (20)	NaO*t*Bu (30)	1,4-dioxane	83

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), NHC salt, 4 Å MS, base and solvent (0.8 mL) for 24 h at 28 °C, including 5 min induction period. [b]Yields were determined by GC using mesitylene as internal standard. [c]Without 4 Å MS.

triazolium salt **3a** containing an electron-deficient aryl group gave the highest yield (entries 1–4). The choice of base and solvent was also crucial to obtain high yields of the desired product (entries 5–10). Omission of an NHC salt from reaction conditions showed a dramatic decrease of yield (20%), suggesting the role of **3a** as an organocatalyst (entry 11). The use of a catalytic amount of a base for the generation of free NHC did not significantly drop the reactivity (entry 12). This clearly supports that deprotonation of indole could be performed by in situ generated imidoyl anion via proton abstraction process in a catalytic manner. Notably, no C3-iminated product was observed for all entries. Thus, NHC-based organocatalytic dual activation of neutral indole (**1a**) and isocyanide (**2a**) enabled the coupling process under mild reaction conditions (at 28 °C) without the use of a stoichiometric amount of an activator.

Under the optimized conditions, the substrate scope for the reaction was evaluated (Scheme 2). Phenyl isocyanide (**2b**) gave an excellent yield of the corresponding formamidine (**4ab**). Gratifyingly, the halide-containing isocyanides (**2c–2f**, **2l**) were all tolerated and produced halogenated formamidines in excellent yields (**4ac–4af**, **4al**). Other electron-withdrawing groups, such as cyanide (**4ag**), ester (**4ah**), and sulfone (**4ai**), present in isocyanides also showed excellent yields, illustrating

Scheme 2. Substrate Scope[a]



[a]Reaction conditions: **1** (0.2 mmol), **2** (2.0 equiv), **3a** (20 mol %), NaO*t*Bu (30 mol %), and 1,4-dioxane (0.8 mL) for 24 h at 28 °C, including 5 min induction period. All yields are isolated yields. [b]0.6 mmol of **1a** in 2.4 mL of 1,4-dioxane. [c]1.3 equiv of NaO*t*Bu and 4 Å MS.

the advantages of the mild reaction conditions. Furthermore, scale-up of the reaction with isocyanide **2i** proceeded smoothly, showing the scalability of the developed reaction conditions. In contrast, introduction of an electron-donating group on the isocyanide resulted in a decreased yield even when an excess amount of a base was used (**4ak**). *Ortho*-substituted isocyanides also showed good to excellent reactivity, despite their increased steric hindrance (**4al**, **4am**). 4-Styryl isocyanide (**2j**) and 3-pyridyl isocyanide (**2n**) gave corresponding formamidines (**4aj**, **4an**) in high yields. However, several reaction attempts with alkyl isocyanides were not successful for the synthesis of corresponding formamidines, presumably due to the low electrophilicity of alkyl isocyanides.[14] Reactions with substituted indoles proceeded smoothly under the mild reaction conditions, regardless of the position of substituents. Indoles containing electron-donating groups, such as methyl (**1b**) and alkoxy (**1d–1f**), gave excellent yields of corresponding formamidines, whereas relatively electron-deficient indoles (**1c**, **1g**) required an excess amount of the base to afford moderate yields of formamidines (**4ca**, **4ga**). The use of more electron-deficient indole, such as 5-nitroindole, was not successful, showing no reactivity under the optimized conditions. Substitution on the C2-/C3-positions of indole, which can affect the steric environment of the reactive center, was also tolerated and corresponding products (**4ha**, **4ia**) were obtained. Other nitrogen-heterocycles, such as carbazole (**1j**) and pyrrole (**1k**), gave the desired products in good to excellent

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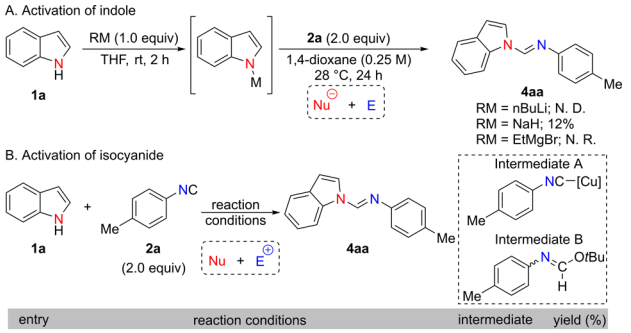
yields (**4ja**, **4ka**). The scalability of the reaction was further confirmed with a gram-scale reaction with isocyanide **2f**, and formamidine **4af** was obtained in 98% yield.

To get detailed insight into the reaction, comparisons with previously reported strategies were conducted (Scheme 3).

Scheme 3. Previous Activation Strategies

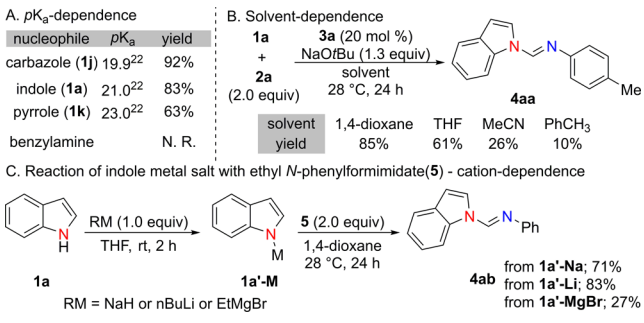


entry	reaction conditions	intermediate	yield (%)
1	CuCl (10 mol %), THF (0.5 M), reflux, 24 h	A	Trace
2	CuCl (20 mol %), NaH (1.0 equiv) 1,4-dioxane (0.25 M), 28 °C, 24 h	A	42
3	CuI (5 mol %), KO*t*Bu (1.2 equiv), DME (0.5 M), 55 °C, 24 h	B	10
4	CuI (20 mol %), KO*t*Bu (1.2 equiv), DME (0.5 M), 28 °C, 24 h	B	44

First, reactions of isocyanide with deprotonated indole species using a strong base were tested (Scheme 3A). Among several attempts, a stepwise reaction with sodium hydride (NaH) afforded formamidine **4aa** in less than 12% yield, which proves that the use of unactivated isocyanide as an electrophile is not effective for the imination of indole. Next, several reported strategies for the activation of isocyanides into electrophilic intermediates were investigated (Scheme 3B). Cu-based catalytic systems which can generate an electrophilic isocyanide analogue such as Cu-bound isocyanide (intermediate A)[10a] or formimidate (intermediate B)[16] have been previously developed. However, the reported reaction conditions for the synthesis of formamidine from indole were not as efficient as those discussed in this work. Based on the knowledge that a nonactivated isocyanide cannot react with the indole anion efficiently (Scheme 3A), these observations clearly suggest that the dual activation of indole and isocyanide substrates via NHC organocatalysis is essential for the coupling reaction.

The involvement of indole anion is further supported by the correlation between reaction parameters and the yield of formamidines (Scheme 4). First, it was observed that the yields of the formamidines obtained from indole (**1a**), carbazole (**1j**), and pyrrole (**1k**) are found to increase as the acidity of NH-proton increases, and benzylamine did not show any reactivity at all (Scheme 4A). Those observations indicate that the proton transfer process from nucleophile to isocyanide is necessary to

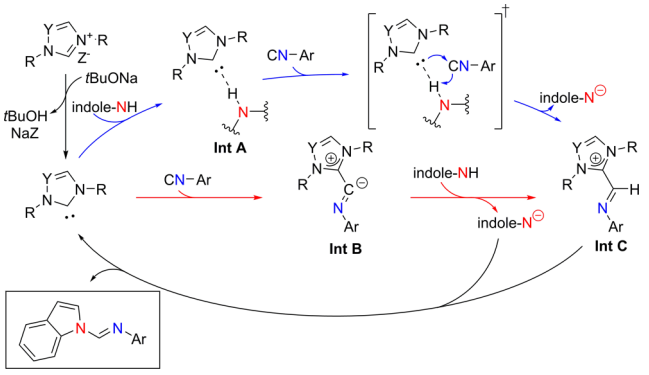
Scheme 4. Evidence of the Involvement of Indole Anion



generate the deprotonated nucleophilic species and electrophilic imine-azolium intermediate.[17] Moreover, a higher yield was observed when oxygen-containing solvents were used during the optimization of the reaction conditions (Scheme 4B). This could be related to solvation of an indole anion with dissociation of a countercation (Na^+). The generation of the naked anionic species might be necessary to perform the desired transformation of indoles under our reaction conditions.[3a,b,18] To further test this hypothesis, several indole anion salts were prepared and used for the synthesis of formamidine **4ab**. It was previously known that the use of indole anion salts (potassium or sodium salts of indole) that dissociate easily result in N-selectivity, whereas the use of magnesium[19] or zinc[20] salts exhibits C3-selectivity, due to the high degree of covalent character in the N−M bond.[18a,21] In the reaction of the indole anion salt with readily available ethyl *N*-phenylformimidate (**5**), an activated analogue of isocyanide, different reaction yields were obtained depending on the countercations of the indole salts (Scheme 4C). In the case of reactions with a more ionic salt (**1a′-Na** or **1a′-Li**), a higher degree of reactivity was observed. In contrast, the reaction with a more covalent salt (**1a′-MgBr**) exhibited significantly decreased yield. These results strongly indicate the involvement of a naked indole anion in the reaction system.

Based on the aforementioned experimental results, a plausible mechanism was proposed (Scheme 5). After

Scheme 5. Proposed Mechanism



production of the imidoyl intermediate (**Int B**) from the NHC catalyst and isocyanide and deprotonation of the acidic proton of indole, the activated nucleophile (indole-N^-) and electrophile (**Int C**) can be generated simultaneously, and the subsequent coupling reaction produces the desired formamidine.[14,17] Besides the stepwise process (red arrow), a concerted mechanism (blue arrow), based on the reported interaction between the acidic proton and NHC, is also possible.[23] However, the direct insertion of isocyanide into the N−H bond would not be favorable due to the innate low electrophilicity of isocyanide (Scheme 3A). Therefore, the concerted addition/deprotonation for generation of **Int C** is proposed to be more plausible under our reaction conditions. The involvement of in situ generated *t*BuOH as a proton source[23c] is also less likely, due to relatively big difference in pK_a values between *t*BuOH (32.2 in DMSO)[24] and indole (21.0 in DMSO).[22] Additionally, reactions with *t*BuOD as an additive showed a rather low yield and limited deuterium incorporation ratio, even in the existence of excess *t*BuOD, supporting the exclusion of *t*BuOH as the proton source (Schemes S6−S8). Participation of formimidate

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as an alternative electrophile is also not plausible, based on the trials for the detection of formimidate intermediates (Schemes S9–S10). As previously reported,[14] attempts to observe **Int B** or **Int C** with various experimental approaches were unsuccessful, presumably due to the transient nature of the proposed intermediates.[17,25] Although those results provided the challenges for the detailed elucidation of the catalytic cycle, the involvement of the imidoyl intermediate (**Int B**)[25] and imine-azolium intermediate (**Int C**)[17] would be the most plausible scenario in our catalytic cycle, based on the previous literature studies[10,14,17,23,25] and discussed mechanistic aspects of the reaction.

To conclude, the first chemoselective N-imination of indoles with aryl isocyanides for the synthesis of formamidines was successfully achieved via NHC-catalyzed concurrent activation of both nucleophile and electrophile substrates. Several new indole-based formamidines were obtained in a high degree of reactivity and wide substrate scope under mild reaction conditions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01377.

Experimental procedures and full spectroscopic data for all new compounds (PDF)

X-ray crystallographic data for **4aa** (CIF)

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Notes

The authors declare no competing financial interest.

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