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Synthesis of Unprotected and Highly Substituted Indoles by the Ruthenium(II)-Catalyzed Reaction of Phenyl Isocyanates with Diaryl/Diheteroaryl Alkynes/Ethyl-3-phenyl Propiolates

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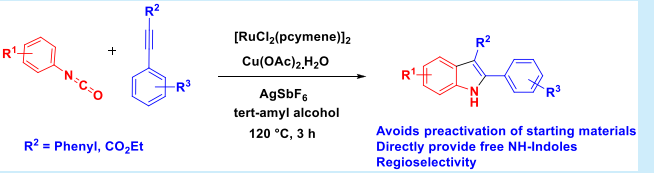
ABSTRACT: A one-pot transformation has been developed for the synthesis of unprotected and highly substituted indoles by an *in situ* installed carbamide-directed Ru(II)-catalyzed intermolecular oxidative annulation of phenyl isocyanates with diaryl/diheteroaryl alkynes/ethyl phenyl propiolates in the presence of $Cu(OAc)_2 \cdot H_2O$ as an oxidant and $AgSbF_6$ as an additive at 120 °C within 3 h.



Indoles can be found in nature, in various commercial drugs, as well as in molecules currently under clinical trials[1] (Figure 1). The prevalence of the indole skeleton in bioactive

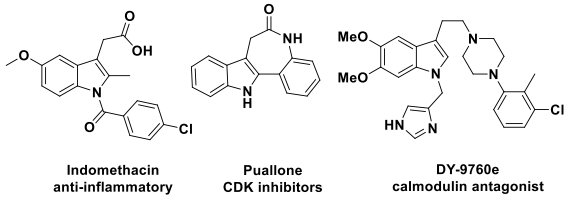
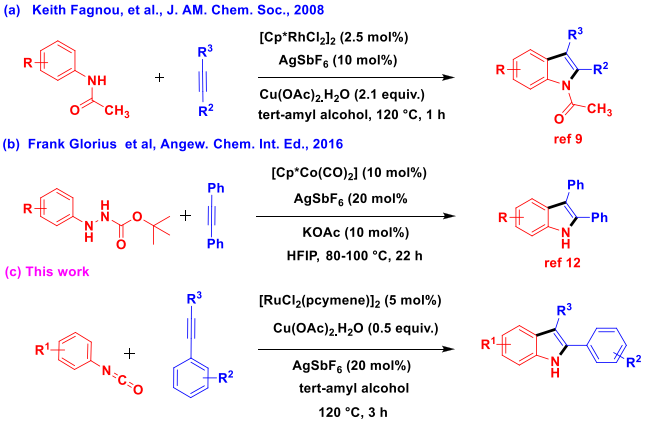


Figure 1. Indole skeleton containing commercial drugs/compounds currently in clinical trials.

natural products has prompted organic and medicinal chemists to develop new methods for their preparation.[2] Various transition-metal complexes involving Ru,[3] Rh,[4] Pd,[5] Ir,[6] and Co[7] have been effectively applied to indole synthesis by the *ortho*-C−H functionalization of anilides. Despite advances, most of these methods heavily rely on preactivated aniline substrates, which can give N-substituted indoles.[8] For example, recently, Fagnou and coworkers developed NH-Ac-assisted dehydrogenative cyclization between internal alkynes and arenes using a Rh(III) catalyst to give *N*-acetylated indoles (Scheme 1a).[9] Zhu and coworkers explored the Rh(III)-catalyzed cyclization of *N*-nitroso anilines with alkynes for the synthesis of N-alkylated indoles.[10] Su and coworkers disclosed the Rh-catalyzed reaction between the *N*-nitroso group of *N*-alkyl anilines and internal alkynes.[11] Very limited methods are reported in the literature, in which preactivated aniline substrates directly provide unprotected (free NH) indoles. The research group of Glorius and coworkers described the cobalt-catalyzed unprotected indole synthesis from Boc-phenylhydrazines (Scheme 1b).[12] Similarly, Huang and coworkers disclosed a Rh(III)-catalyzed unprotected indole synthesis via triazene-directed annulation with alkynes.[13]

Scheme 1. Previous Synthetic Protocols and Our Work on the Substituted Indole Synthesis



We desired to prepare unprotected and highly substituted indoles without using preactivated substrates. We therefore used commercial phenyl isocyanates, which can generate carbamide *in situ* and subsequently act as a directing group. Herein we disclose the synthesis of unprotected and highly substituted indoles from phenyl isocyanates and diaryl/diheteroaryl alkynes/ethyl-3-phenyl propiolates (Scheme 1c) for the first time.

Initially, we carried out a test reaction between *p*-tolyl isocyanate (**1a**, 1 mmol) and diaryl acetylene (**2a**, 1 mmol) with 5 mol % of catalysts $Pd(OAc)_2/PtBr_2/RuO_2$, additive

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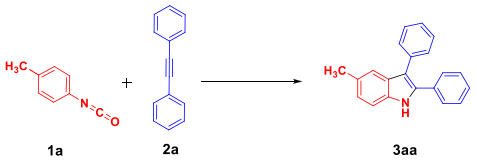
Table 1. Screening of Reaction Conditions[a]



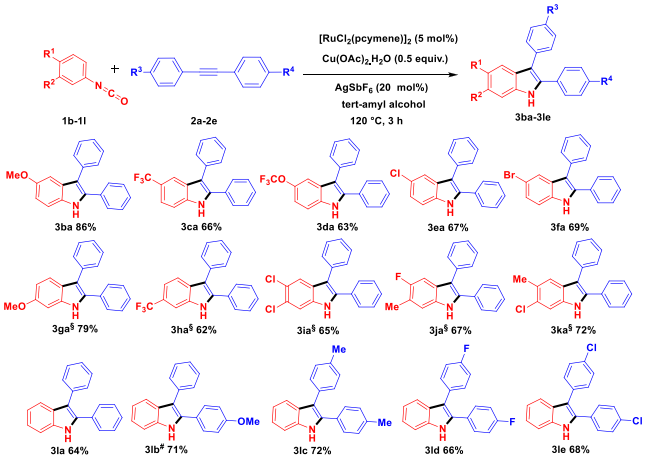
entry	catalyst (5 mol %)	oxidant (0.5 mmol)	additive (20 mol %)	solvent	yield (%)[e]
1[b]	$Pd(OAc)_2$	$Cu(OAc)_2{\cdot}H_2O$	$AgSbF_6$	ROH	NR
2[b]	$PtBr_2$	$Cu(OAc)_2{\cdot}H_2O$	$AgSbF_6$	ROH	NR
3[b]	RuO_2	$Cu(OAc)_2{\cdot}H_2O$	$AgSbF_6$	ROH	NR
4[c]	$[RuCl_2(pcymene)]_2$	$Cu(OAc)_2{\cdot}H_2O$	$AgSbF_6$	MeOH	49
5[c]	$[RuCl_2(pcymene)]_2$	$Cu(OAc)_2{\cdot}H_2O$	$AgSbF_6$	EtOH	53
6[c]	$[RuCl_2(pcymene)]_2$	$Cu(OAc)_2{\cdot}H_2O$	$AgSbF_6$	*n*-PrOH	57
7[c]	$[RuCl_2(pcymene)]_2$	$Cu(OAc)_2{\cdot}H_2O$	$AgSbF_6$	*t*-BuOH	67
8[c]	$[RuCl_2(pcymene)]_2$	$Cu(OAc)_2{\cdot}H_2O$	$AgSbF_6$	*t*-AmOH	91
9[d]	$[RuCl_2(pcymene)]_2$	$Cu(OAc)_2{\cdot}H_2O$	$AgSbF_6$	DCE	NR
10[c]	$[RuCl_2(pcymene)]_2$	$Cu(OAc)_2{\cdot}H_2O$	$AgSbF_6$	DMF	NR
11[c]	$[RuCl_2(pcymene)]_2$	$Cu(OAc)_2{\cdot}H_2O$	$AgSbF_6$	DMSO	NR
12[c]	$[RuCl_2(pcymene)]_2$	$Cu(OAc)_2{\cdot}H_2O$	$AgSbF_6$	toluene	NR
13[b]	$[RuCl_2(pcymene)]_2$	Cu_2O	$AgSbF_6$	*t*-AmOH	NR
14[b]	$[RuCl_2(pcymene)]_2$	AgOAc	$AgSbF_6$	*t*-AmOH	NR
15[c]	$[RuCl_2(pcymene)]_2$	$Cu(OAc)_2{\cdot}H_2O$	Ag_2CO_3	*t*-AmOH	NR
16[c]	$[RuCl_2(pcymene)]_2$	$Cu(OAc)_2{\cdot}H_2O$	$AgSO_3CF_3$	*t*-AmOH	59
17[c]	$[RuCl_2(pcymene)]_2$	$Cu(OAc)_2{\cdot}H_2O$	$AgBF_4$	*t*-AmOH	63
18[c]	$[RuCl_2(pcymene)]_2$	$Cu(OAc)_2{\cdot}H_2O$	Ag_2O	*t*-AmOH	41
19[c]	$[RuCl_2(pcymene)]_2$	$Cu(OAc)_2{\cdot}H_2O$	$AgNO_3$	*t*-AmOH	15

[a]Reaction conditions: **1a** (1 mmol), **2a** (1 mmol), at 120 °C. ROH = methyl/ethyl/isopropyl/*t*-butyl/*t*-amyl alcohol. [b]6 h. [c]3 h. [d]5 h. [e]Isolated yields. NR = no reaction.

$AgSbF_6$ (20 mol %), and oxidant $Cu(OAc)_2{\cdot}H_2O$ (0.5 mmol) at 120 °C for 6 h in various alcohols, which did not give the anticipated product (Table 1, entries 1−3). Fortunately, attempts with 5 mol % of the $[(RuCl_2(p\text{-cymene})_2]$ catalyst in the place of other catalysts along with the above-described reaction conditions resulted in the anticipated product **3aa** in 49, 53, 57, 67, and 91% yield, respectively (Table 1, entries 4−8). The formation of **3aa** was determined by 2D-NMR spectral data. Our attempts with other solvents such as DCE, DMF, DMSO, and toluene in place of alcohols, however, failed to give **3aa** (Table 1, entries 9−12). The reaction with 5 mol % of $[RuCl_2(p\text{-cymene})]_2$ catalyst, Cu_2O (0.5 mmol), or AgOAc (0.5 mmol) as an oxidant at 120 °C for 6 h also did not give the product **3aa** (Table 1 entries 13 and 14). We then tested the role of various additives. For this purpose, we screened a few additives such as Ag_2CO_3 (0%), $AgSO_3CF_3$ (59%), $AgBF_4$ (63%), Ag_2O (41%), and $AgNO_3$ (15%) (Table 1, entries 15−19) and found that $AgSbF_6$ (91%) gave the best results (Table 1, entry 8).

After developing the optimized conditions, we studied the substrate scope of our method to find out the generality of the reaction and the influence of substitution on the yield (Scheme 2). Various substituted phenyl isocyanates **1b−k** were investigated with the unsubstituted diaryl alkyne **2** and the synthesized respective indoles **3ba−ka** with yields ranging from 62 to 86%. The phenyl isocyanate with electron-releasing substituents such as *p*-OMe (**1b**, 86%) and *m*-OMe (**1g**, 79%) gave good yields, whereas the electron-withdrawing groups containing phenyl isocyanates such as *p*-CF_3 (**1c**, 66%), *p*-OCF_3 (**1d**, 63%), *p*-chloro (**1e**, 67%), *p*-bromo (**1f**, 69%), *m*-CF_3 (**1h**, 62%), 3,4-dichloro (**1i**, 65%), 4-fluoro,3-methyl (**1j**, 67%), and 3-chloro, 4-methyl (**1k**, 72%) resulted in moderate

Scheme 2. Reaction between Substituted Phenyl Isocyanates/Unsubstituted Phenyl Isocyanate 1b−k/1l and Diaryl Acetylene/Substituted Diaryl Acetylenes 2a/2a−e and Isolated Yields of Substituted Indoles 3ba−le[a]



[a]§, Regioisomer due to the influence of the steric factor. #, Regioisomeric mixture formation determined by HPLC.

yields. The steric factors might be influencing the exclusive formation of regioisomers **3ga−ka** with symmetrical diaryl alkynes. We next examined various substituted diaryl acetylenes **2a−e** with unsubstituted phenyl isocyanate **1l** under the optimized conditions, which also successfully furnished the desired products **3la−le** (Scheme 2) in moderate to good yields (64−72%). Diaryl alkyne **2a** without substitution gave a moderate yield of **3la** (64%). Symmetrical diaryl alkynes **2b** and **2c**, which have electron-donating groups

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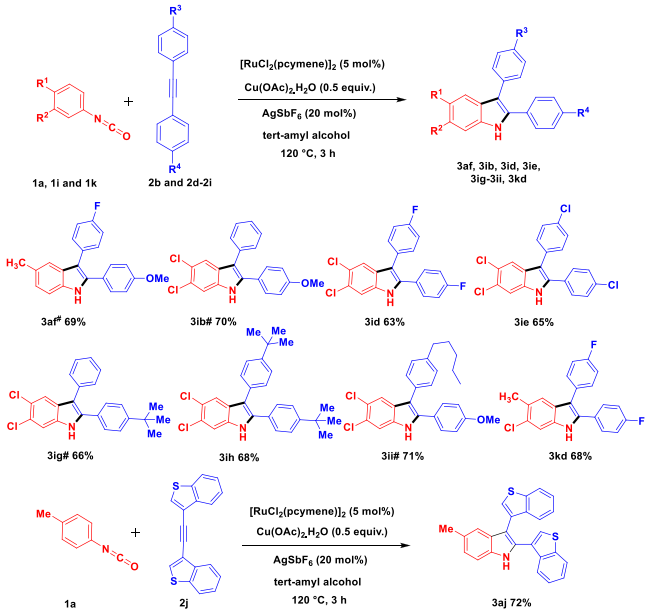
on the aromatic ring, gave improved yields (**3lb**, 71%; **3lc**, 72%). In contrast, electron-withdrawing substituents containing symmetrical diary alkynes **2d** and **2e** furnished the products **3ld** (66%) and **3le** (68%) in marginally low yields. However, the reaction of **1l** with the monosubstituted diaryl alkyne **2b** (unsymmetrical) resulted in the formation of a 6:4 mixture of regioisomers **3lb** and **3lb′** (determined by HPLC).

In further testing, we carried out a few reactions with both substituted phenyl isocyanates **1a**, **1i**, and **1k** and substituted diaryl alkynes **2b** and **2d−i** using our standardized reaction conditions, which resulted in 63−71% of yields of highly substituted indoles **3af**, **3ib**, **3id**,**ie**, **3ig−ii**, and **3kd**, which supports the generality and wide applicability of the reaction (Scheme 3). Here regiomeric mixtures **3af** (62:38), **3ib** (51:49), **3ig** (74:26), and **3ii** were also formed from the respective unsymmetrical diaryl alkynes **2a**, **2b**, **2g**, and **2i** due to electronic factors (ratio determined by HPLC; see the SI). Interestingly, attempts with heteroaryl alkyne **2j** also successfully gave the respective indole **3aj** under the standardized reaction conditions.

Scheme 3. Reaction between Substituted Phenyl Isocyanates 1a, 1k, and 1i and Substituted Diaryl/Diheteroaryl Acetylenes 2b, 2d−i, and 2j and Isolated Yields of Substituted Indoles 3af, 3ib, 3id,ie, 3ig−ii, 3kd, and 3aj[a]

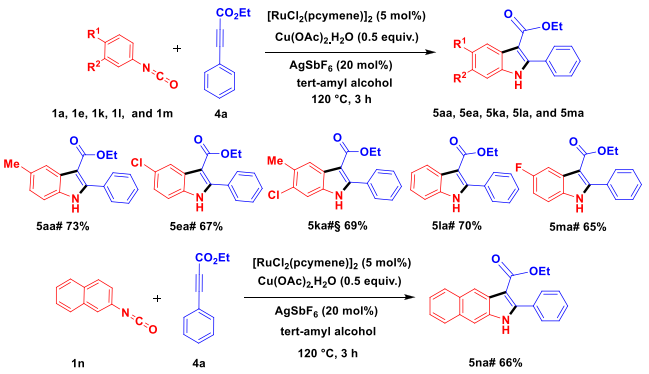


[a]§, Regioisomer due to steric factors. #, Regioisomeric mixture formation determined by HPLC.

To test the further application of the method, we carried out a reaction between phenyl propiolate **4a**, instead of diaryl acetylene **2a**, and various substituted phenyl isocyanates **1a**, **1e**, and **1k−n**, which also successfully resulted in the formation of ester-containing indoles **5aa**, **5ea**, and **5ka−na** regioselectively (>90%) in 65−73% yield (Scheme 4) due to the conjugated electronic system.

However, an attempt at a reaction between aliphatic internal alkyne/phenyl acetylene/3-phenylprop-2-yn-1ol/trimethyl-(phenylethynyl)silane/4-phenyl-3-butyn-2-one and phenyl isocyanate **1a** did not give the respective indole product under the optimized conditions (Scheme S1 of the Supporting Information), which indicates the requirement of the diaryl alkyne or phenyl propiolate system to obtain the indole products.

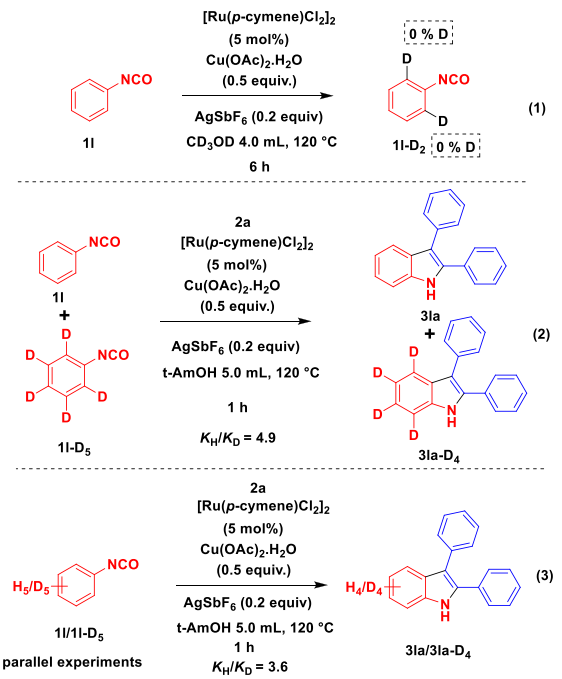
Scheme 4. Reaction between Substituted Phenyl Isocyanates 1a, 1e, and 1k−n and Phenyl Propiolate 4a and Isolated Yields of Substituted Indoles 5aa, 5ea, and 5ka−na[a]



[a]§, Regioisomer due to the substitution pattern of phenylisocyanate. #, Regioisomer due to electronic factors.

To find out the rate-determining step, a few deuterium labeling experiments were carried out. A reaction with phenyl isocyanate **1l** in CD_3OD in the absence of alkyne **2a** under the optimized conditions did not give the deuterium−hydrogen exchanged compound **1l-D$_2$** (Scheme 5, eq 1). The competitive (Scheme 5, eq 2) and intermolecular (Scheme 5, eq 3) kinetic isotope effect experiments resulted in a k_H/k_D of 4.9 and 3.6, respectively. These experiments indicated that the rate-limiting step could be the metal-catalyzed C(sp^2)−H bond activation.

Scheme 5. Isotopically Labeled Experiments



Some control experiments were also carried out to understand the reaction mechanism (Scheme S2 of the Supporting Information). A reaction with *p*-tolyl isocyanate **1a** in *t*-amyl alcohol in the absence of a catalyst gave the isolable intermediate **B**, which was confirmed by the spectral

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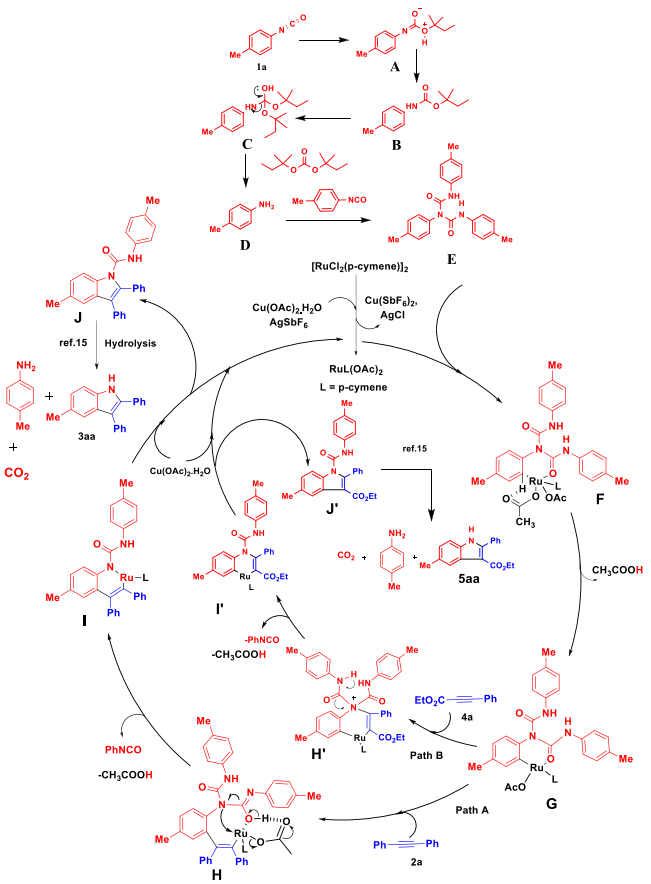
data (Supporting Information). The reaction of *p*-tolyl isocyanate **1a** with $Cu(OAc)_2·H_2O$ or $AgSbF_6$ in *t*-amyl alcohol in the absence of **2a** and a catalyst [$(RuCl_2(p\text{-cymene})_2$] gave intermediate **E** in 96% yield.[14] A reaction of **E** (1 mmol) with **2a** (1 mmol) using the optimized reaction conditions resulted in intermediate **J**, and a further extension of the reaction time gave **3aa** in 93% isolated yield. The isolated intermediate **J** was subjected to the optimized reaction conditions, which also gave the final product **3aa**.[15]

On the basis of control experiments and isolated intermediates (see the Supporting Information), a plausible reaction mechanism for the indole synthesis is proposed as an oxidative annulation of *p*-tolyl isocyanate **1a** with diaryl alkyne **2a**/phenyl propiolates **4a**. First, the carbamate B might have formed due to the nucleophilic attack of *t*-AmOH on the carbonyl group followed by aniline intermediate **D** due to the elimination of di-*tert*-pentyl carbamate **C**. Carbamide intermediate **E** might have been generated due to a reaction between intermediate **D** and *p*-tolyl isocyanate.[14] Both the intermediates **B** and **E** were isolated from the reaction mixture, and they were characterized by 2D-NMR spectral data (Supporting Information). The intermediate **E** might have transformed to **F** due to the Ru(II)-catalyzed C−H activation via an MD mechanism with acetate ion assistance and subsequently transformed to **G** (Scheme 6) by the loss of acetic acid. Diaryl-alkyne **2a**'s coordinative insertion into the Ru−carbon bond of **G** might have given species **H**, and the subsequent removal of *p*-tolyl isocyanate with the assistance of an acetate ion might have led to species **I**.[16] The intermediate **J** might have been afforded due to the reductive elimination in the presence of $Cu(OAc)_2·H_2O$ and regenerated the active Ru species for the next catalytic cycle. The intermediate **J** was also purified from the reaction mixture and characterized by 2D-NMR spectral data. Furthermore, the cleavage of the C−N bond of indole-1-carboxamide intermediate **J** in the presence of the optimized reaction conditions might have resulted in the desired unprotected and highly substituted indole **3aa**.[15] The electron-releasing groups on **2b**, **2f**, **2g**, and **2i** might have influenced the alkyne insertion into the Ru−N bond in producing major regioisomers **3af**, **3ib**, **3ig**, and **3ii**. The regioselective formation of ester-containing indoles **5aa**, **5ea**, **5ka**−**na** from phenyl propiolate **4a** also accounted for the electronic factors of the extended conjugation system upon the alkyne insertion into the Ru−N bond (Schemes 4 and 6, path B).[17] Further studies, however, are essential to support the exact reaction mechanism.

Scheme 6. Plausible Reaction Mechanism for the Synthesis of Unprotected Substituted Indoles



In summary, we have developed a new method for the synthesis of unprotected indoles by a Ru(II)-catalyzed and *in situ* generated carbamide (urea derivative)-directed oxidative annulation reaction between phenyl isocyanates and diaryl/diheteroaryl alkynes/phenyl propiolates for the first time in the presence of $Cu(OAc)_2·H_2O$ and additive $AgSbF_6$ and have demonstrated its wide application. This method can avoid the synthesis of preactivated aniline surrogates and the deprotection of *N*-alkyl or *N*-acyl groups of final products. Further work is in progress to use the *in situ* installed carbamide group from isocyanate and its directing chemistry to make privileged structures of biological importance at our lab.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02793.

General information, general procedure for the synthesis of substituted indoles, general procedure for the preparation of alkynes, control experiments, isotopically labelled experiments, spectral data of internal alkynes, references, spectral data of isolated intermediates B, E, and J, spectral data of the obtained compounds, copies of NMR spectra, and HPLC data (PDF)

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Notes

The authors declare no competing financial interest.

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