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COMMUNICATION

Ruthenium(II)-Catalyzed Synthesis of Indolo[2,1-a]isoquinolines through Double Oxidative Annulation Reaction of Phenyl Isocyanates with Di(hetero)aryl Alkynes

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Abstract Indole-containing polycyclic hetero aromatic compounds are synthesized by multistep process, which have wide application in biological activities and organic semi-conductor materials. Herein we report the one-pot method for the synthesis of polysubstituted indolo[2,1-a]isoquinolines by Ru(II) catalyzed double aryl/hetero aryl C(sp^2)-H activation through *in-situ* installed carbamide of phenyl isocyanate and di(hetero)aryl substituted alkynes in the presence of $Cu(OAc)_2.H_2O$ as an oxidant and CsOAc as an additive at 120 °C for 3 h in good to excellent yields.

Keywords: Phenyl isocyanate; Double C-H oxidative cyclization; Ru(II) catalyst; Indolo[2,1-a]isoquinolines

The fused polycyclic heteroaromatic skeletons present in various range of natural and biological molecules.[1] Indolo[2,1-a]isoquinolines and their derivatives show various biological activities such as tubulin-binding,[2] acting as estrogen receptor modulators[3] (Figure 1).

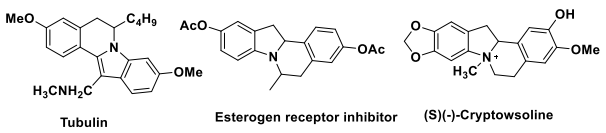
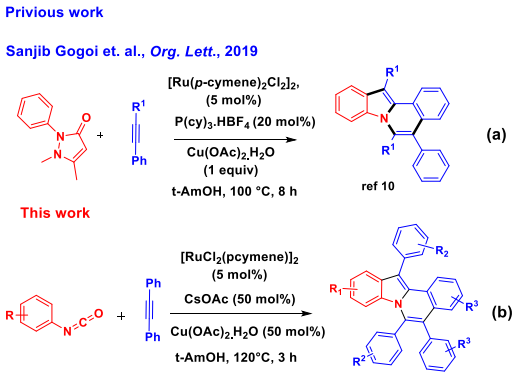


Figure 1. Indolo[2,1-a]isoquinoline containing Bioactive and Luminescence compounds.

Indolo isoquinoline motif also has great importance as semiconductor compounds because of their unique property of π-conjugation.[4] The construction of highly arylated indolo[2,1-a]isoquinolines involves multistep synthesis and adverse reaction conditions by conventional methods.[5] Transition metal-catalyzed double C(sp^2)-H activation of the aryl C(sp^2)-H bond followed by alkyne annulation reactions is very helpful for synthesizing heteroaromatic compounds.[6] Although few double C-H bond activation and subsequently C-C and C-N/O-H bond formation reactions are reported by using diverse transition metals, such as using Rhodium for the syntheses of benzo[de](isoquinolino[2,1-a])[1,8]naphthyridines,[7] using cobalt for the syntheses of dihydropyrroloindoles[8] and using palladium for the syntheses of 11-methyl-5,6-diphenyl-11H-benzo[a]carbazole,[9] very limited methods are available in the literature for the synthesis of arylated indolo[2,1-a]isoquinolines.[10]



Scheme 1. Examples of double C(sp^2)-H activation and alkyne annulation reactions for the synthesis of polysubstituted indolo[2,1-a]isoquinolines

Very recently Gogoi and co-workers reported a straightforward method for the synthesis of indolo[2,1-a]isoquinolines by Ru(II) catalyzed double activation of $C_{(sp^2)}$-H bonds of preactivated antipyrine and alkyne annulation reaction in the presence of 20% phosphine ligand tricyclohexyl phospine tetrafluoroborate (**Scheme 1a**).[11] Our continuous interest in metal-catalyzed C-H activation reactions for the synthesis of polycylic hetero aromatic compounds, we explored

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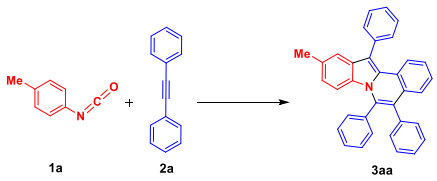
commercially available phenyl isocyanates with an anticipation that the *in-situ* generated carbamide (urea derivative) from isocyanate group may act as a directing group to provide desired polysubstituted indolo[2,1-a]isoquinolines, which can avoid the substrate preactivation. We herein report polysubstituted indolo[2,1-a]isoquinolines synthesis by Ru(II) catalyzed double $C_{(sp^2)}$-H bond activation of commercially available phenyl isocyanates and diaryl alkyne/dihetero aryl alkynes (**Scheme 1b**).

Table 1. Optimization of reaction conditions



1a 2a 3aa

Entry	Oxidant (50 mol %)	Additive (50 mol %)	Solvent	Yield(%)[e]
1[a]	$Cu(OAc)_2.H_2O$	CsOAc	ROH	NR
2[b]	$Cu(OAc)_2.H_2O$	CsOAc	ROH	NR
3[c]	$Cu(OAc)_2.H_2O$	CsOAc	ROH	NR
4[d]	$Cu(OAc)_2.H_2O$	CsOAc	MeOH	33
5[d]	$Cu(OAc)_2.H_2O$	CsOAc	EtOH	51
6[d]	$Cu(OAc)_2.H_2O$	CsOAc	Iso-propanol	68
7[d]	$Cu(OAc)_2.H_2O$	CsOAc	t-Butanol	73
8[d]	$Cu(OAc)_2.H_2O$	CsOAc)	t-AmOH	92
9[d]	$Cu(OAc)_2.H_2O$	CsOAc	DMF	NR
10[d]	$Cu(OAc)_2.H_2O$	CsOAc	DMSO	NR
11[d]	$Cu(OAc)_2.H_2O$	CsOAc)	CH_3CN	NR
12[d]	$Cu(OAc)_2.H_2O$	CsOAc	DCE	NR
13[d]	$Cu(OAc)_2.H_2O$	CsOAc	Toluene	NR
14[d]	$Cu(OTf)_2$	CsOAc	t-AmOH	NR
15[d]	AgOAc	CsOAc	t-AmOH	NR
16[d]	$Zn(OAc)_2$	CsOAc	t-AmOH	NR
17[d]	$Cu(OAc)_2.H_2O$	NaOAc	t-AmOH	NR
18[d]	$Cu(OAc)_2.H_2O$	KOAc	t-AmOH	NR

Reaction Conditions: **1a** (1.0 equiv), **2a** (1.0 equiv.) in 2 ml of ROH at 120 °C for 3 h. R = ethyl, isopropyl, tert-butyl and tert-amyl alcohol, NR = no reaction.
[a] $Pd(OAc)_2$,
[b] $PtBr_2$,
[c] RuO_2,
[d] $[RuCl_2(pcymene)]_2$,
[e] Isolated yields.

At the beginning, we tested the reaction between phenyl isocyanate (**1a**, 1.0 equiv.) and diphenyl acetylene (**2a**, 1.0 equiv.) in the presence of 5 mol% of $Pd(OAc)_2$, $PtBr_2$ and RuO_2 at 120 ºC for 7 h (Table 1, entries 1-3), CsOAc (0.5 equiv.) as additive and $Cu(OAc).H_2O$ (50 mol%) as oxidant in solvents such as methanol, ethanol, isopropanol, t-butanol and t-amyl alcohol, however, no desired product was obtained. Fortunately, when we examined the reaction with 5 mol% of $[(RuCl_2(p\text{-cymene})]_2$ catalyst, CsOAc (50 mol%) as additive and $Cu(OAc).H_2O$ (50 mol%) as an oxidant in methanol, ethanol, isopropanol, t-butanol and t-amyl alcohol resulted in the formation of the desired product **3aa** in 33%, 51%, 68%, 73% and 92% yield respectively (Table 1, entries 4-7). The chemical structure of **3aa** has been confirmed by spectral data and single crystal X-ray data of **3ga** (CCDC No. 1943183). Encouraged by these results, we have screened with other solvents such as DMF, DMSO, CH_3CN, DCE and toluene, however, no product was obtained (Table 1, entries 9-13). Next we focused on to test few oxidants in t-amyl alcohol as a solvent. The reaction with 5 mol% of $[(RuCl_2(p\text{-cymene})]_2$ as catalyst, CsOAc (0.5 equiv.) as an additive and $Cu(OTf)_2$, AgOAc and $Zn(OAc)_2$ (50 mol%) as oxidant in t-amyl alcohol at 120 ^{0}C for 3 hours did not give desired product **3aa** (Table 1 entries 14-16). Investigation with few bases such as NaOAc and KOAc were also failed to give the desired product **3aa** under similar reaction condition (Table 1, entries 17 and 18).

With optimized reaction conditions in our hand, we explored the substrate scope of various substituted phenyl isocyanates **1b-1h** with diphenyl acetylene **2a**, which resulted in the formation of the desired product of indolo[2,1- a]isoquinoline derivatives **3ba-3ha** with yields ranging from 74 to 89% (**Scheme 2**). The phenyl isocyanates, which have electron withdrawing group such as F (**3ca**:79%), Cl (**3da**:82%) and Br (**3ea**:86%) at para position gave slightly less yield than the phenyl isocyanates which have electron releasing groups (**3aa**:92%; **3ba**:89%). The substitution pattern has also some influence in the yields. For example *m*-methyl phenyl isocyanate **1f** gave 86% yield of **3fa**, whereas *p*-methyl phenyl isocyante **1a** gave respective product **3aa** in 92% yield. The reaction with disubstituted phenyl isocyantes such as **1g** and 1**h** also resulted in lower yields of the respective products **3ga** (74%) and **3ha** (78%) with standardized reaction conditions.

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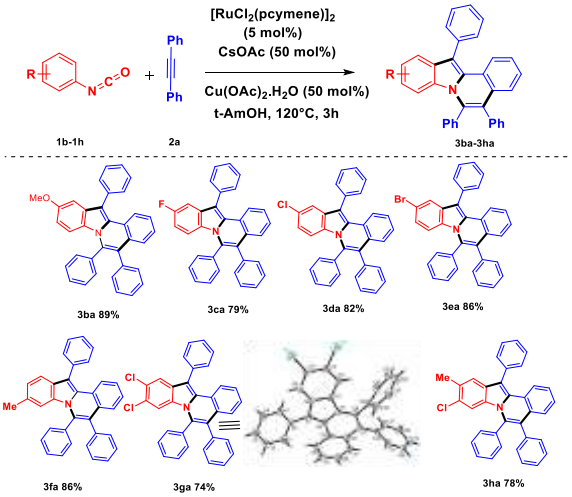
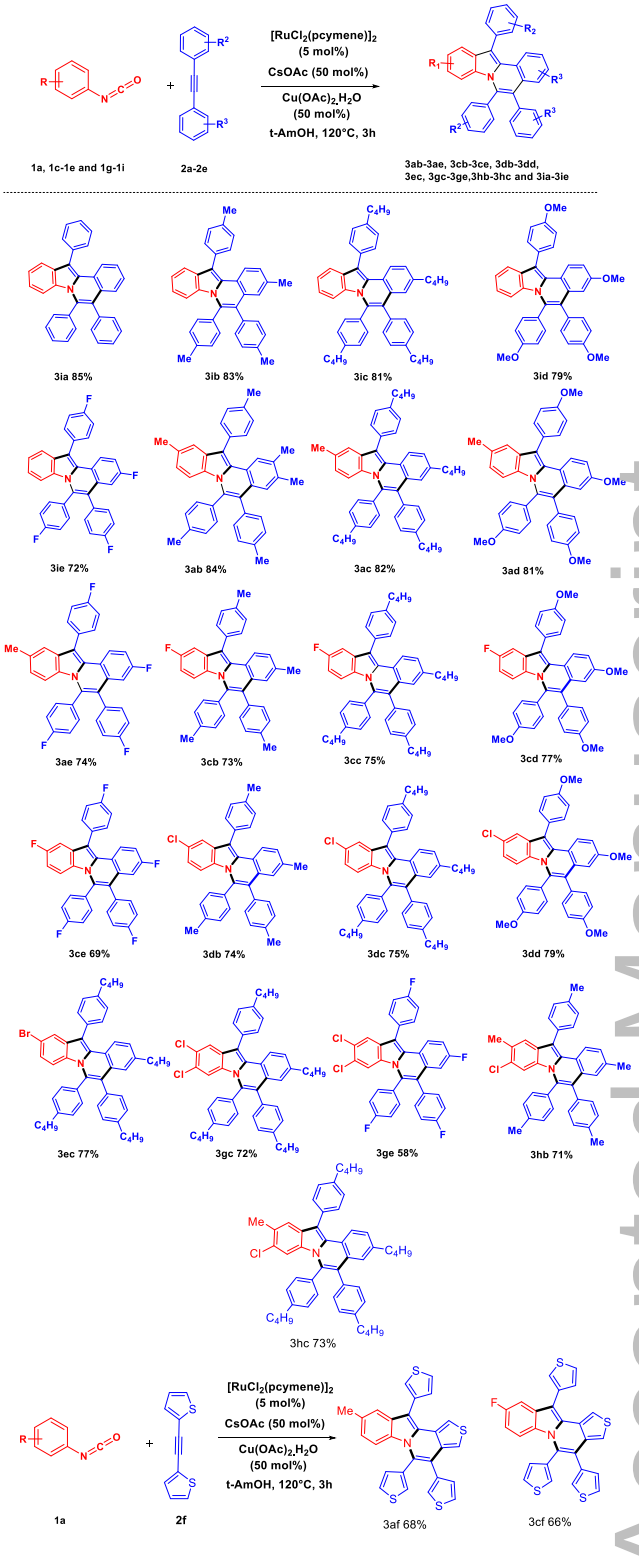


Scheme 2. Substrate scope of the reaction between Substituted Phenyl isocyanates (**1b-1h**) and Unsubstituted diaryl alkyne (**2a**).

We then shifted our focus on to investigate with various symmetrically substituted diaryl alkynes. Initially, a reaction was carried out between unsubstituted phenyl isocyanate **1i** and substituted alkynes such as **2a-2e** with standardized reaction conditions, which also gave their respective products **3ia-3ie** in yields ranging from 72-85% (**Scheme 3**). Further investigations with various substituted phenyl isocyanates (**1a**, **1c-1e** and **1g**) and substituted alkynes (**2a-2e**) also resulted in highly substituted indolo[2,1- a]isoquinolines in the yield range of 58 to 84%. Electron releasing groups on diaryl alkynes playing important role in enhancement of the product yields (**3cb**:73%, **3cc**:75%, **3cd**:77% and **3db**:74%; **3dc**:75%; **3dd**:79%), whereas electron withdrawing groups on phenyl isocyanate gave marginally decreased yields (**3cb**:73% vs **3db**:74%; **3cc** 71% vs **3dc**:75% vs **3ec**:77%; **3cd**:77% vs **3dd**:79%). The electron withdrawing groups on both phenyl isocyanates and alkynes have further impact on the yields (**3ce**:69% and **3ge**:58%). The reaction between disubstituted phenyl isocyanates and para substituted diaryl alkynes gave product with the yields in the range of 71-73% (**3gc**:72%; **3hb**:71% and **3hc**:73%). We then tried to carry out few reactions with heteroaryl alkynes in place of diaryl alkynes to verify the scope of the reaction.

We tested a reaction between phenyl isocyanate **1a**/**1b** and 1,2-di(thiophen-3-yl)ethyne (**2f**) with the standardized reaction conditions, which also, fortunately, gave respective thiophene substituted indolo[2,1-a]isoquinolines (**3af** and **3cf**) in moderate yields (68% and 66%) (**Scheme 3**).

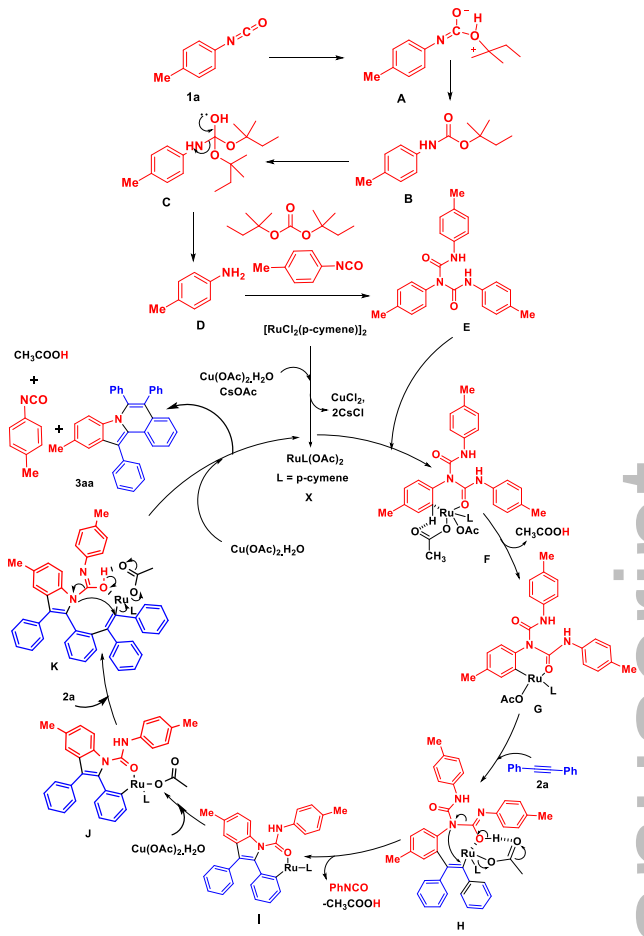


Scheme 3. Substrate scope of the reaction between Unsubstituted and Substituted Phenyl isocyanates (**1a-1c**, **1e** and **1g-1i**) and Substituted Symmetrical Diaryls (**2a-2e**) and Dihetero aryl acetylene (**2f**).

We further investigated the reaction between phenylisocyanate **1a** with unsymmetrical diaryl alkyne **2g** and phenyl isocyanates **1d** and **1h** with unsymmetrical

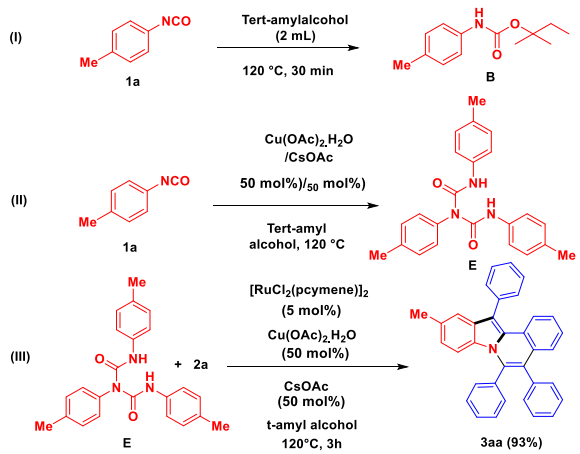
alkynes **2g** and **2h**. The reactions resulted an unresolvable mixture of regioisomers (see SI for spectra).

On the basis of our results, possible reaction mechanism for the indoles synthesis via oxidative annulations of phenylisocyanate **1a** with diarylalkyne **2a** is proposed in (**Scheme 4**). Initially, the nucleophilic attack of t-AmOH on the carbonyl group of **1a** generates a carbamate intermediate **B** followed by benzyl amine species **D** by elimination of di-tert-pentyl carbomate **C**. Reaction between benzyl amine species **D** and phenyl isocyanate might have led to formation of urea derivative **E**.[12] Fortunately, we could isolate the intermediate **B** and **E** and characterize them by 1 and 2 D-NMR spectral data respectively. The *in-situ* generated intermediate **E** might have converted into **F** by Ru(II) catalyzed C–H activation via a concerted metalation-deprotonation (CMD) mechanism assisted by the acetate ion and subsequent removal of acetic acid might led to **G**. Then coordinative insertion of diarylalkyne **2a** into the Ru-carbon bond of intermediate **G** in tandem with elimination of phenyl isocyanate might provide **H** and **I** respectively.[13] In the next step, **J** might have generated from **I** by reacting with $Cu(OAc_2)$. The second molecule of diaryl alkyne insertion between Ru-Carbon bond by Ru(II) catalyzed C–H activation of **J** might have led to **K** and further reductive elimination of the Ru resulted **3aa**.



Scheme 4. Plausible Reaction Mechanism for formation of Indolo[2,1-a]isoquinolines

To gain insight into the reaction mechanism, some control experiments were conducted as shown in (**Scheme 5)**. A reaction between 5-methyl-2,3-diphenyl-1H-indole (**1**) in t-amyl alcohol without catalyst resulted in the formation of intermediate **B** in 96% of yield, which was isolated and characterized by spectral data. Intermediate **E** was also isolated from the reaction mixture while carrying out a reaction with phenyl isocyanate and $Cu(OAc)_2.H_2O$/CsOAc in t-amyl alcohol without adding diaryl alkyne **2a** in 96% of yield (**Scheme 5**, **II**). Treatment of isolated intermediate **E** (1.0 equiv.) with **2a** (1.0 equiv) in the presence of standardized reaction conditions $[RuCl_2(p\text{-cymene})]_2$ (5 mol%), CsOAc (50 mol%) and $Cu(OAc)_2.H_2O$ (0.5 equiv) in t-AmOH at 120 °C for 3 h provided substituted indole **3aa** in 93% of isolated yield (**Scheme 5**, **III**). All these control experiments strongly support the proposed reaction mechanism.



Scheme 5. Control experiments

In conclusion, we have developed a new one-pot method for the synthesis of polysubstituted indolo[2,1-a]isoquinolines by Ru(II) catalyzed and *in-situ* installed carbamide directed double aryl $C_{(sp^2)}$-H activation between various phenyl isocyanates and internal aryl alkynes/hetero aryl alkynes in the presence of $[RuCl_2(p\text{-cymene})]_2$ (5 mol%), $Cu(OAc)_2.H_2O$ (50 mol%) and additive CsOAc (50 mol%) at 120 °C. To our knowledge, this is the first report on the use of *in-situ* generated carbamide (urea derivative) from isocyanate group as a directing group in C-H activation of the $C_{(sp^2)}$-H bond. Further exploration on the synthetic utilities of this *in-situ* installed carbamide group from isocyanate and its directing chemistry is currently progress in our lab and the results will be reported in due course of time.

Experimental Section

General procedure for synthesis of substituted indolo[2,1-a]isoquinolines: In an oven dried 50 ml R.B flask charged with stir bar, phenylisocyanate (1.0 equiv.), diarylalkyne (1.0 equiv.), $[RuCl_2(pcymene)]_2$ (5 mol%), $Cu(OAc)_2.H_2O$ (0.5 equiv) and CsOAc (0.5 equiv) in 2 ml of t-AmOH resulting mixture was stirred at 120 °C for 3h. Completion of reaction was monitored by TLC (1:7 Ethyl acetate and Hexane). Reaction mixture was cooled down to room temperature and diluted with 10 mL of H_2O. The resultant mixture was extracted with ethyl acetate (3 × 15 mL). The combined organic phase was dried over anhydrous Na_2SO_4. After removal of the solvent under reduced pressure, the crude product was purified by column chromatography on silica gel (60-120 mesh) by using hexane/ethylacetate solvent system to give desired poly substituted indolo[2,1-a]isoquinolines compounds.

CCDC-1943183 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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