Tetrahedron Letters 50 (2009) 6576–6579

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

# Thorpe–Ingold effect in copper(II)-catalyzed formal hydroalkoxylation–hydroarylation reaction of alkynols with indoles

Nitin T. Patil *, Vivek S. Raut, Rahul D. Kavthe, Vaddu V. N. Reddy, P. V. K. Raju

*Organic Chemistry Division-II, Indian Institute of Chemical Technology, Hyderabad 500 607, India*

A R T I C L E  I N F O

*Article history:*
Received 30 July 2009
Revised 8 September 2009
Accepted 10 September 2009
Available online 15 September 2009

*Keywords:*
Alkynes
Indoles
Copper catalyst
Hydroalkoxylation
Hydroarylation

A B S T R A C T

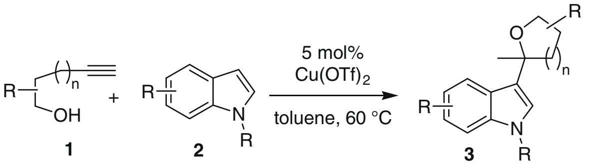
The use of $Cu(OTf)_2$ as a catalyst for tandem hydroalkoxylation–hydroarylation reaction of alkynes tethered with hydroxyl group is reported. The reaction proceeds at 60 °C or even at room temperature with 5 mol % catalyst loading and produces C-3-substituted indoles in good to high yields. The method was shown to be applicable to a broad range of indoles, containing electron-withdrawing and electron-donating substituents, and alkynol substrates bearing sterically demanding substituents in the tether. Interestingly, it was found that Thorpe–Ingold effect is operating for this cyclization reaction. Easy availability and low cost of $Cu(OTf)_2$ make this method attractive and amenable for large-scale synthesis compared to known literature methods.

In the past ten years, significant research has been directed toward the development of metal-catalyzed reactions for the addition of C–H bonds on to alkynes (hydroarylation).[1] Similarly, addition of oxygen nucleophiles across C–C triple bonds (hydroalkoxylation)[2] represents valuable tool for making oxygen-containing compounds. The combination of both the procedures (hydroalkoxylation–hydroarylation)[3] under the catalysis of a single metal salt may enable new transformation for maximum molecular complexity with minimum organic wastes.[4]

Indoles are versatile and useful heterocycles for the synthesis of a wide range of biologically active important molecules and natural products.[5] The synthesis and functionalization of indoles have been the object of research for over a century, and a variety of well-established classical methods and metal-catalyzed processes are now available.[6] The most commonly known method for the functionalization of indoles involves their treatment with electrophiles such as aldehydes, ketones, imines, Michael acceptors, and allylic substrates. Echavarren and co-workers[7] and Cheng and co-workers[8] independently reported an elegant process for the synthesis of C-3-functionalized indoles, by gold- and platinum-catalyzed reactions between alkynols and indoles. Recently, Barluenga and co-workers reported the use of cationic gold complexes for similar reactions.[9] However, all these methods suffer from the use of expensive catalysts. Moreover, the scope of this reaction with respect to alkynols is limited. Therefore, the introduction of new and robust methods for this transformation is highly desired.

As a part of our ongoing interest on alkyne activation,[10] we report herein an efficient $Cu(OTf)_2$-catalyzed tandem hydroalkoxylation–hydroarylation reaction between indoles and alkynols bearing sterically demanding substituents in the tether (Scheme 1).

Our study began with the reaction between alkynol **1a** and *N*-methyl indole **2a** in the presence of copper salts[11] in THF (Table 1). The use of 5 mol % CuI and CuBr in THF did not give the desired product (entries 1 and 2). The results can be attributed to the fact that Cu(I) salts have poor Lewis acidic properties which are necessary as shown in Figure 1 (catalytic cycle II, vide infra). Next, we screened Lewis acidic copper(II) catalysts. The use of 5 mol % $Cu(OAc)_2$ gave only a trace amount of **3a** along with recovery of **1a** (entry 3). The yield was significantly improved when $CuCl_2{\cdot}2H_2O$, $CuBr_2$, and $Cu(OTf)_2$ were employed and out of them the latter catalyst[12] showed excellent catalytic activity (entries 4–6). Next, the activity of $Cu(OTf)_2$ was examined in different solvents such as toluene, acetonitrile, methanol, and 1,4-dioxane (entries 7–10). Among them, toluene was proved to be more effective (entry 7). As can be judged from entry 11 that the reaction can be



**Scheme 1.** Copper(II)-catalyzed reaction between **1** and **2**.

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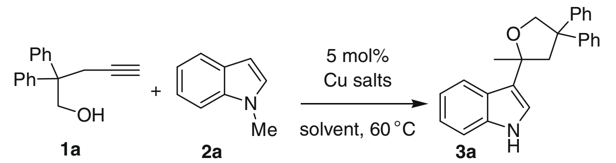
* Corresponding author. Tel.: +91 40 27191471; fax: +91 40 27193382.
*E-mail address:* nitin@iict.res.in (N.T. Patil).

0040-4039/$ - see front matter © 2009 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2009.09.057

**Table 1**
Optimization studies[a]



| Entry | Catalyst[a] | Solvent | Yield[b] (%) |
|---|---|---|---|
| 1 | CuI | THF | –[c] |
| 2 | CuBr | THF | –[c] |
| 3 | Cu(OAC)$_2$ | THF | –[c] |
| 4 | $CuCl_2{\cdot}H_2O$ | THF | 70 |
| 5 | CuBr$_2$ | THF | 78 |
| 6 | Cu(OTf)$_2$ | THF | 95 |
| 7 | Cu(OTf)$_2$ | Toluene | 98 |
| 8 | Cu(OTf)$_2$ | $CH_3CN$ | 50 |
| 9 | Cu(OTf)$_2$ | MeOH | –[c] |
| 10 | Cu(OTf)$_2$ | 1,4-Dioxane | –[c] |
| 11 | Cu(OTf)$_2$ | Toluene | 95[d] |

[a] Reaction conditions: 0.46 mmol **1a**, 0.38 mmol **2a**, 5 mol % copper salts, solvent (0.25 M), 60 °C, 3 h.
[b] Isolated yields based on **2a**.
[c] Indole **2a** was recovered in almost quantitative yields.
[d] Reaction was run at rt for 12 h.

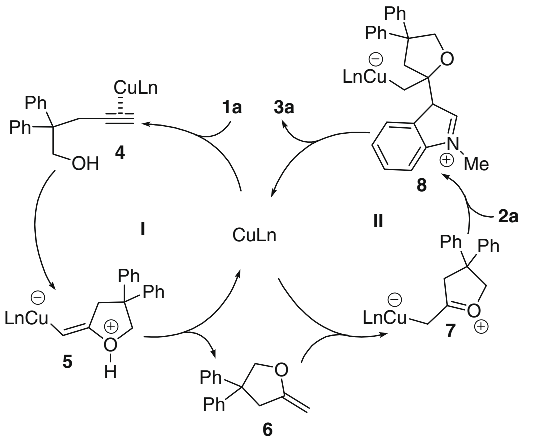
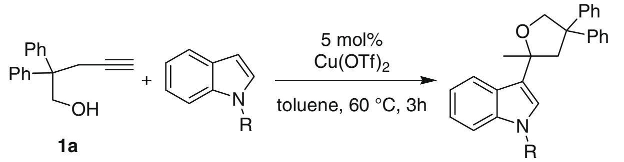


**Figure 1.** Plausible mechanism.

conducted at room temperature without significant decrease in yield, however, long time was required.

After establishing the proper reaction conditions (5 mol % Cu(OTf)$_2$, toluene, 60 °C, 3 h),[13] the effect of various groups on indole nitrogen was examined. A series of indoles **2a**–**e**, bearing –H, alkyl, aryl, and sulfonyl group were subjected to copper catalysis under these newly established conditions (Scheme 2). The indoles **2a**–**d** were reacted well with **1a** to afford **3a**–**d**,[14] in good to excellent yields. However, **2e** containing electron-withdrawing –Ts group proved to be inert and **3e** was not formed at all.



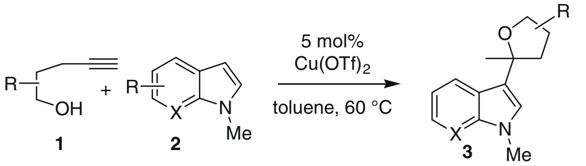
**2a** R = Me
**2b** R = H
**2c** R = Bn
**2d** R = Ph
**2e** R = Ts

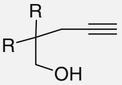
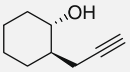
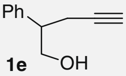
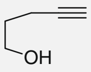
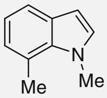
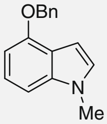
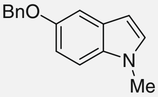
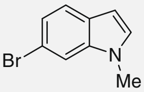
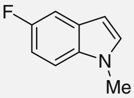
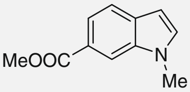
**3a** R = Me, 98% (table 1)
**3b** R = H, 68%
**3c** R = Bn, 69%
**3d** R = Ph, 93%
**3e** R = Ts, no reaction

**Scheme 2.** Effect of various groups on indole nitrogen.

Next, we studied the scope and limitations with respect to indoles and alkynols (Table 2). The alkynols bearing sterically demanding substituents in the tether such as **1b** and **1c** reacted well giving the corresponding products **3f** and **3g** in high yields (entries 1 and 2). A mixture of diastereomers **3h** + **3h**′ and **3i** + **3i**′

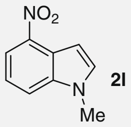
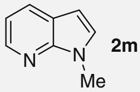
**Table 2**
Cu(OTf)$_2$-catalyzed hydroalkoxylation–hydroarylation of alkynes[a]



| Entry | 1 | 2 | 3, Yield[b] (%) |
|---|---|---|---|
| 1 | <br>**1b** R = –(CH$_2$)$_5$– | **2a** | **3f**, 97 |
| 2 | **1c** R = –(CH$_2$)$_4$– | **2a** | **3g**, 70 |
| 3 | <br>**1d** | **2a** | **3h** + **3h**′, 72[c] |
| 4 | <br>**1e** | **2a** | **3i** + **3i**′, 62[d] |
| 5 | <br>**1f** | **2a** | **3j**, 20[e] |
| 6 | **1a** |  **2f** | **3k**, 96 |
| 7 | **1a** |  **2g** | **3l**, 85 |
| 8 | **1a** |  **2h** | **3m**, 90 |
| 9 | **1a** |  **2i** | **3n**, 95 |
| 10 | **1a** |  **2j** | **3o**, 94 |
| 11 | **1a** |  **2k** | **3p**, 91 |

(*continued on next page*)

**Table 2** (*continued*)

| Entry | 1 | 2 | 3, Yield[b] (%) |
|---|---|---|---|
| 12 | **1a** |  **2l** | **3q**, 78[f] |
| 13 | **1a** |  **2m** | **3r**[g] |

[a] Reaction conditions: **1** (0.46 mmol), **2** (0.38 mmol), 5 mol %, Cu(OTf)$_2$, toluene (0.25 M), 60 °C, 3 h.

[b] Isolated yields based on indoles.

[c] Inseparable mixture of diastereomers in the ratio of 1:1 was obtained.

[d] Inseparable mixture of diastereomers in the ratio of 2:1 was obtained.

[e] Indole **2a** was recovered in 70% yield. Average of two runs.

[f] Reaction mixture was stirred for 12 h.

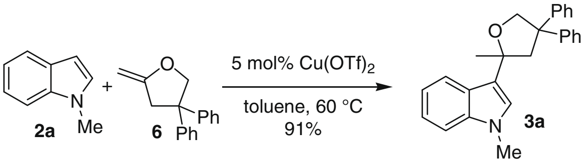
[g] Only trace amount of product was detected by $^1$H NMR spectroscopy.

was obtained from **1d** and **1e**, respectively (entries 3 and 4). To our surprise, alkynol **1f** after reacting with **2a** gave **3j** only in 20% yield; **2a** was recovered in 70% yield (entry 5). This observation is in contrast to the previously known reactions wherein the authors have reported the reaction of **1f** with *N*-methyl indole **2a** in high yields.[7,8] The reason for this lack of reactivity is not clear at present; however, it became obvious that the Thorpe–Ingold effect[15] is necessary for this formal hydroalkoxylation–hydroarylation reaction.[16] Next, we investigated the reactions of various indoles with **1a**. The reaction of **1a** with indoles **2f**, **2g,** and **2h** gave products **3k**, **3l**, and **3m**, respectively, in excellent yields (entries 6–8). As shown in entries 9 and 10, halo-substituted indoles **2i** and **2j** also reacted well with **1a** giving rise to the products **3n** and **3o**, respectively. The reaction of **2k**, bearing –COOMe group at C-6, with **1a** gave **3p** in high yield (entry 11), while that of **2l** having strong electron-withdrawing –NO$_2$ group at C-4 required longer reaction time to obtain **3q** in 78% yield (entry 12). However, methylated 7-azaindole **2m** reacted sluggishly with **1a** to give **3r** only in trace amount even after stirring for 12 h (entry 13). This could be probably due to the deactivation of Cu(OTf)$_2$ catalyst by the coordination with pyridine nitrogen in **2n**. It should be noted that the reaction is applicable to alkynols containing terminal alkynes.[17] 3-Decyne-1-ol did not give the desired product when reacted with **2a** under the present reaction conditions.

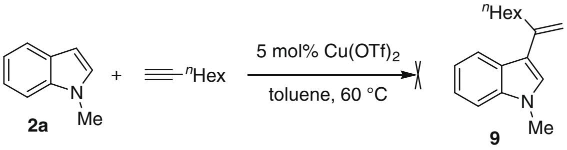
Concerning mechanism, the first step would be the complexation of Cu(II) catalysts to the alkyne function in **1a** which leads to intermediate **4** (Fig. 1, cycle **I**). The cyclization step may then occur directly by the attack of proximal hydroxyl group leading to vinylcopper intermediate **5**. The next step would be the protodemetalation to generate exocyclic enol ether **6** with release of catalyst. Once **6** is formed, it enters another catalytic cycle where Cu(OTf)$_2$ is supposed to act as a Lewis acid (cycle **II**). Thus, the Lewis acid catalyzes the formation of oxonium ion **7** from enol ether **6**. Intermolecular nucleophilic addition of the indole **2a** to **7** (cf. **8**) followed by re-aromatization and proto-demetalation leads to the final product **3a** with liberation of catalyst. Thus, in short, Cu(OTf)$_2$ acts as transition metal catalyst in cycle **I** and Lewis acid catalyst in cycle **II.**[18] Such kind of dual role exhibited by a single metal catalyst has been documented in the literature.[19]

To confirm unequivocally the intermediacy of exocyclic enol ether, we have conducted an experiment as shown in Scheme 3. Treatment of *N*-methyl indole **2a** with 2-methylene-4,4-diphenyltetrahydrofuran **6**[20] under standard condition gave C-3 functionalized indole **3a** in 91% yield (Scheme 3).

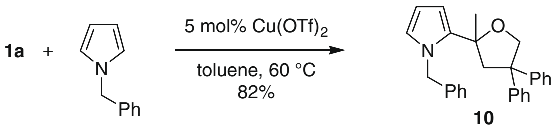
To completely rule out the mechanism involving direct addition of C3–H bond of indoles to alkynes, we treated **2a** with 1-octyne under the standard copper catalysis conditions (Scheme 4). The product **9** was not formed; **2a** was recovered in quantitative yield.



**Scheme 3.** Cu(OTf)$_2$-catalyzed reaction between **2a** with **6**.



**Scheme 4.** Cu(OTf)$_2$-catalyzed reaction between **2a** with 1-octyne.



**Scheme 5.** Cu(OTf)$_2$-catalyzed reaction between **1a** with *N*-benzyl pyrrole.

The catalyst Cu(OTf)$_2$ was also shown to be appropriate for C-2 functionalization of pyrroles. Thus, when a toluene solution of *N*-benzyl pyrrole reacted with **1a** in the presence of 5 mol % catalyst, the C-2 functionalized pyrrole **10** was obtained in 82% yield (Scheme 5).

In conclusion, we have shown that inexpensive and easily available Cu(II) salts catalyze the formal hydroalkoxylation–hydroarylation of alkynes. Interestingly, it was found that the Thorpe–Ingold effect is operating for this cyclization reaction. An applicability of this catalytic system has also been shown for the C-2 functionalization of *N*-benzylpyrroles. The reaction can also be run at room temperature at the expense of time. The tolerance of indoles containing electron-withdrawing and electron-donating substituents, and alkynol substrates bearing sterically-demanding substituents in the tether are the important features of this copper(II)-catalyzed transformation.

## Acknowledgments

We gratefully acknowledge financial support by the Council of Scientific and Industrial Research, India. NTP is grateful to Dr. J. S. Yadav, Director, IICT, and Dr. T. K. Chakraborty, Director, CDRI, for their support and encouragement.

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12. One of the reviewers suggested that trace amount of TfOH generated in the reaction mixture may be responsible for catalyzing the reaction. However, the reaction between **1a** and **2a** with 5 mol % TfOH under standard conditions did not give **3a,** clearly indicating that copper salts are necessary to catalyze the present transformation.
13. To a toluene (1.5 ml, 0.25 M) solution of **1a** (108 mg, 0.46 mmol) and **2a** (50 mg, 0.38 mmol) in 2 ml vial was added Cu(OTf)$_2$ (8 mg, 5 mol %) under nitrogen atmosphere. The mixture was stirred at 60 °C for 3 h. Then, the reaction mixture was filtered through a pad of silica gel with ethyl acetate as an eluent and the solvent was removed under reduced pressure. The residue was purified by flash silica gel column chromatography using ethyl acetate/hexane (10:90) as eluent to obtain **3a** (137 mg, 98%, based on indole).
14. *Characterization data for* **3a**: Thick liquid, $R_f$ 0.6 (hexane/EtOAc = 80/20); $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.6 (d, $J$ = 7.7 Hz, 1H), 7.38 (d, $J$ = 8.0 Hz, 2H), 7.28 (t, $J$ = 7.7 Hz, 2H), 7.21–7.01 (m, 9H), 6.83 (s, 1H), 4.76 (d, $J$ = 9.0 Hz, 1H), 4.24 (d, $J$ = 9.0 Hz, 1H), 3.70 (s, 3H), 3.27 (d, $J$ = 12.5 Hz, 1H) 2.95 (d, $J$ = 12.5 Hz, 1H), 1.50 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 147.2, 146.1, 137.5, 128.2, 127.9, 127.2, 127.1, 125.9, 125.8, 125.2, 124.4, 122.8, 121.2, 120.0, 118.7, 109.2, 82.7, 75.9, 56.9, 51.8, 32.6, 30.1; IR (film): $\nu_{\max}$ 3019, 2976, 1521, 1476, 1423, 1210, 1046, 928, 769 cm$^{-1}$; HRMS calcd for C$_{26}$H$_{25}$NO (M$^+$+H) 368.2020, found 368.2014.
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18. The catalyst is essential for both catalytic cycles and this has been confirmed by the following facts; Alkynol **1a** did not form **6** without Cu(OTf)$_2$ in toluene at 60 °C when being heated for 3 h. Similarly under the same reaction conditions **6** did not react with **2a** without Cu(OTf)$_2$ catalyst.
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20. The exocyclic enol ether **6** was prepared by the following procedure: To a toluene (1.5 ml, 0.28 M) solution of **1a** (100 mg, 0.42 mmol) in a 2 ml vial was added Cu(OTf)$_2$ (7 mg, 5 mol %) under nitrogen atmosphere. The mixture was stirred at 60 °C for 3 h. Then, the reaction mixture was filtered through a pad of silica gel with ethyl acetate as an eluent and the solvent was removed under reduced pressure. The residue was directly used without further purification.