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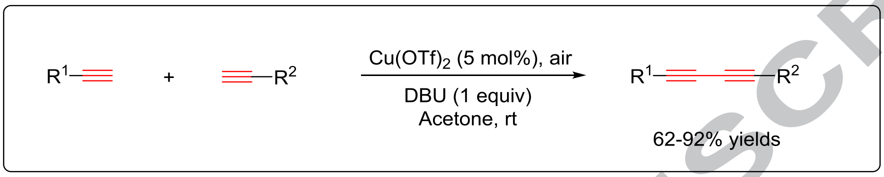

- Mild conditions
- Open to air
- Excellent functional group compatibility

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Copper (II) Catalyzed Homocoupling and Heterocoupling of Terminal Alkynes

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ABSTRACT

$Cu(OTf)_2$ catalyzed homo- and heterocoupling of aromatic and aliphatic terminal alkynes has been developed. Symmetric and unsymmetric 1,3-diynes have been synthesized in good yields under an aerobic condition in the presence of an organic base DBU. This reaction features mild conditions, a wide substrate scope, and excellent functional group compatibility.

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1. Introduction

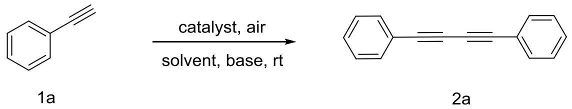
Petroleum-derived alkynes are readily available starting materials and building blocks for organic synthesis. Conjugated 1,3-diynes are essential structural motifs found in many natural products[1], bio-active compounds[2], and functional materials [3]. Therefore, coupling of terminal alkynes to access 1,3-diynes is of great significance to the synthetic community. Classic methods for terminal alkyne coupling include Glaser[4], Eglington [5], and Hay protocols [6]. Significant efforts have been made to develop more efficient and sustainable approaches to improve the originally used palladium/copper bi-catalyst system for oxidative coupling of terminal alkynes. Single transition metal catalysts such as Pd[7], Cu[8], Ni[9], Co[10], and Ti[11] have been employed in alkyne coupling. However, there are still challenges in this field such as the use of expensive and toxic palladium catalysts, requirement of complex ligands, external oxidants, and harsh reaction conditions.

Our research group has been interested in the development of green and sustainable synthetic methods for useful transformations of alkynes[12]. Herein, we wish to report our recent study on the synthesis of symmetric and unsymmetric 1,3-diynes by $Cu(OTf)_2$ catalyzed homo- and heterocoupling of terminal alkynes in the presence of DBU under ambient conditions. As a comparatively cheaper and easily accessible metal, Cu (I) and (II) salts attracted considerable attentions due to their high catalytic efficiency.[13] Balaraman and Kesavan reported a homo- and hetero-coupling of terminal alkynes utilizing 10 mol% of $Cu(OAc)_2{\cdot}H_2O$ as the catalyst, stoichiometric amount of piperidine as the base, and CH_2Cl_2 as the sovlent.[13a] In comparison, our work was able to improve the efficiency and sustainability of the coupling by lowering the catalyst loading of the Cu(II) salts to 5 mol% and using a halogen-free solvent.

2. Results

Initially, phenyl acetylene was chosen to serve as a model substrate for the study of the homocoupling of terminal alkynes (Table 1). We first screened several copper catalysts including $CuBr_2$, CuBr, CuI, $Cu(OAc)_2$, and $Cu(OTf)_2$ in the presence of 1 equiv. of a base DBU at room temperature. The reaction was exposed to air and acetone was employed as the solvent. To our delight, the desired homocoupling product was obtained in 92% yield when $Cu(OTf)_2$ was used as the catalyst (entry 5). The oxygen present in the air was proved to be an effective oxidant for this coupling reaction. Different bases were then utilized to further optimize the reaction yield (entry 6-8). However, Et_3N and pyridine gave lower yields (78% and 80%) of the coupling product and inorganic base K_2CO_3 did not produce any desired product. Next, we decided to investigate the solvent effect of this transformation. THF, 1,4-dioxane, dichloromethane, and acetonitrile were employed as the solvent in the presence of the optimal copper catalyst and base (entry 9-12). It was found that acetone was the best solvent among all the solvents we tested for this transformation.

Table 1. Optimization of copper catalyzed homocoupling of phenylacetylene.[a]



Entry	Solvent	Catalyst	Base	Isolated yield
1	Acetone	$CuBr_2$	DBU	35%
2	Acetone	CuBr	DBU	9%
3	Acetone	CuI	DBU	10%

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4	Acetone	$Cu(OAc)_2$	DBU	trace
5	Acetone	$Cu(OTf)_2$	DBU	92%
6	Acetone	$Cu(OTf)_2$	Et_3N	78%
7	Acetone	$Cu(OTf)_2$	K_2CO_3	0%
8	Acetone	$Cu(OTf)_2$	pyridine	80%
9	THF	$Cu(OTf)_2$	DBU	53%
10	1,4-Dioxane	$Cu(OTf)_2$	DBU	Trace
11	CH_2Cl_2	$Cu(OTf)_2$	DBU	70%
12	CH_3CN	$Cu(OTf)_2$	DBU	75%

[a] Reaction conditions: phenylacetylene **1a** (1 equiv.), catalyst (5 mol%), base (1 equiv.), room temperature, open flask, 2-5 hours.

With the optimal reaction conditions in hands, the homocoupling and heterocoupling reactions of a variety of substrates were conducted to investigate the substrate scope and limitations as well as the functional group compatibility of this reaction (Table 2). All the reactions were conducted at room temperature within a short period of time (2-5 hours). First, the homocoupling of terminal alkynes bearing different functional groups was conducted using our optimal reaction conditions. Aromatic terminal alkynes (2a-2l) and aliphatic terminal alkynes (2m-2n) both resulted in good to excellent yields (63% – 92%). To our delight, it was observed that both electron withdrawing and donating groups were compatible with the reaction conditions. For instance, electron withdrawing groups on the phenyl rings such as Br (2b), Cl (2c-2e), F (2f-2h), and ester (2j) were tolerated well and resulted in good yields. Terminal alkyne substrates containing electron donating groups (2i, 2k, and 2l) also produced the coupling products in good yields. Substituents at para-position of the phenyl ring (2d and 2h) provide the coupling products in slightly higher yields than that of meta- (2c and 2g) and ortho-positions. It was also found that aliphatic terminal alkynes (2m-2n) resulted in lower yields in comparison to the aromatic alkynes.

Table 2. Substrate scope of homocoupling of terminal alkynes

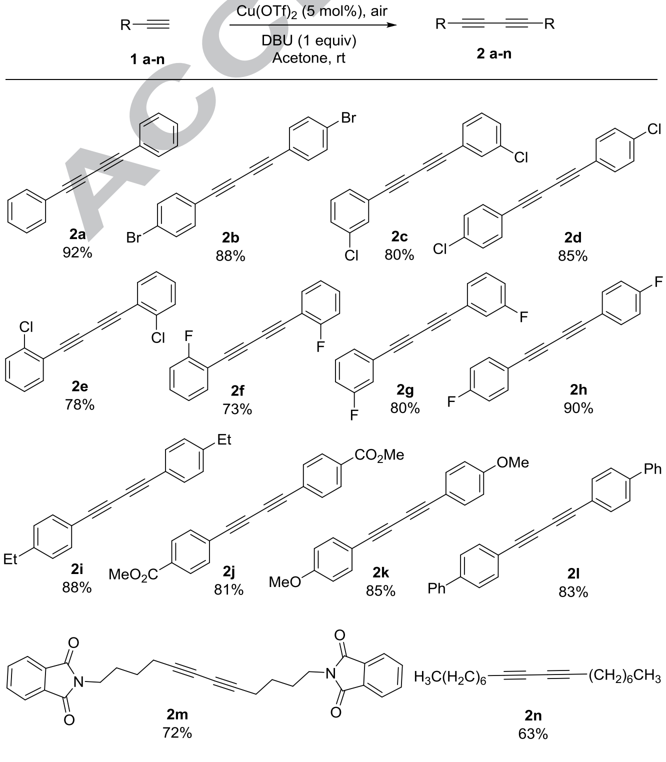
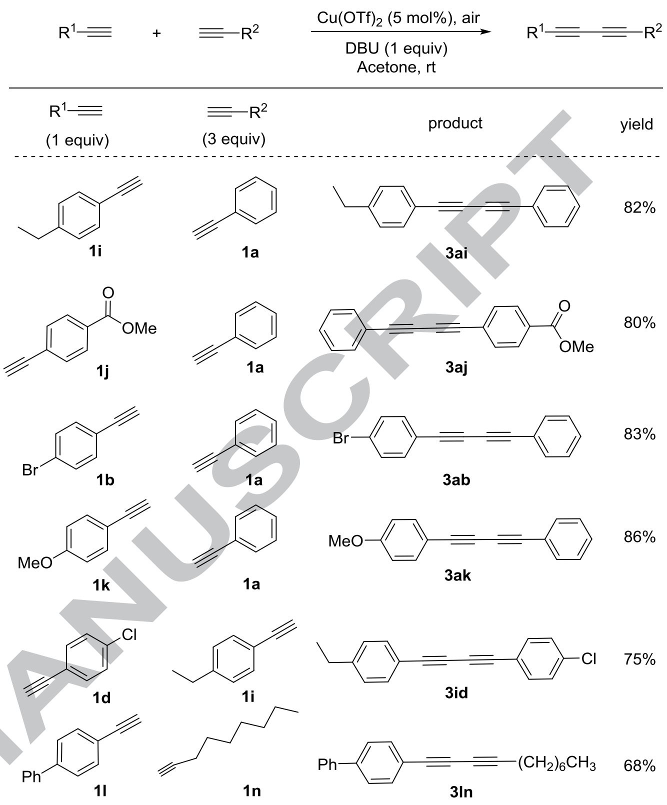


Table 3. Substrate scope of heterocoupling of terminal alkynes



After observing excellent yields in the homocoupling reactions of a variety of terminal alkyne substrates, the reaction conditions were applied to the heterocoupling reaction of several terminal alkynes. As shown in Table 3, unsymmetric 1,3-diynes were synthesized in 68-86% percent yields. Phenylacetylene was cross-coupled with several other aromatic terminal alkynes bearing both electron-withdrawing and electron-donating groups in good yields (3ai, 3aj, 3ab, and 3ak). Good yield was also achieved in the coupling of an aromatic substrate containing an electron withdrawing group to an aromatic substrate containing an electron donating group (3id). Additionally, the heterocoupling of an aromatic terminal alkyne and an aliphatic terminal alkyne (3ln) was tested and a lower yield (68%) was observed, as expected.

4. Conclusion

In summary, we have developed an efficient homo- and heterocoupling of terminal aromatic and aliphatic alkynes under open-air conditions. Readily available and inexpensive copper (II) salt $Cu(OTf)_2$ was found to smoothly catalyze the coupling reaction in the presence of an organic base DBU. Symmetric and unsymmetric 1,3-diynes with a wide substrate scope were prepared in good to excellent yields and within a short reaction time. Mild conditions, easy accessibility of the catalyst, and excellent functional group compatibility make this method an attractive protocol for the synthesis of complex 1,3-diynes.

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University and the Center for Research, College of Science and Health, William Paterson University of New Jersey.

Supplementary Material

Supplementary material that may be helpful in the review process should be prepared and provided as a separate electronic file. That file can then be transformed into PDF format and submitted along with the manuscript and graphic files to the appropriate editorial office.

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References and notes

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