

Letter

Cu(I)-Catalyzed Coupling and Cycloisomerization of Diazo Compounds with Terminal Yne-Alkylidenecyclopropanes: Synthesis of Functionalized Cyclopenta[b]naphthalene Derivatives

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(5) Supporting Information

ABSTRACT: A Cu(I)-catalyzed coupling and cycloisomerization of diazo compounds with terminal yne-alkylidenecyclopropanes (ACPs) has been presented. This reaction starts from the formation of an allenic intermediate in the Cu(I)-catalyzed cross-coupling reaction of a diazo compound with terminal alkyne in yne-tethered ACP and then undergoes a domino cycloisomerization of a 6π -electrocyclization and



cyclopropane ring-opening rearrangement to give functionalized cyclopenta[b] naphthalene derivatives in moderate to excellent yields under mild conditions.

M etal carbenes represent useful and versatile intermediates in modern organic synthesis.¹ Particularly, diazo compounds have emerged as useful synthetic intermediates, which have been widely utilized as carbene precursors, in synthetic organic chemistry over many decades.² Thus far, a great amount of unique transformations based on the reactions of metal carbenes derived from diazo compounds have been developed.

Classically, the metal carbene intermediates generated from diazo compounds in the presence of transition metal catalysts (Rh, Cu, Pd, Au, etc.) can subsequently undergo a series of X–H (X = C, O, S, N, etc.) insertion transformations (Scheme 1,





eq 1).^{2–6} Along with developments in this field, in recent years, a new type of metal carbene transformation that involves a cross-coupling process, characterized by a carbene migratory insertion with diazo compounds, has emerged in the chemical transformations of metal carbenes. Based on these studies, a series of novel Cu(I)-catalyzed cross-coupling reactions of *N*-tosylhydrazones or other diazo derivatives with terminal alkynes have been developed by Wang's group and others,⁷ affording various substituted allenes or enantiomerically enriched allenes with broad substrate scope and moderate to high yields under mild conditions (Scheme 1, eq 2).

Alkylidenecyclopropanes (ACPs), a class of highly strained but readily accessible compounds, are useful building blocks in organic synthesis, and numerous cyclizations have been explored to rapidly generate complex polycyclic frameworks via a simple manipulation.⁸ Therefore, based on the previous works of Cu(I)-catalyzed cross-coupling reactions of Ntosylhydrazones/diazoalkanes with terminal alkynes and our previous work on metal-catalyzed cyclizations of ACPs,⁹ we envisaged that the reaction of terminal yne-AlkylideneCyclo-Propanes (ACPs) with diazo compounds in the presence of Cu(I) catalyst might generate an allene species through a Cu(I)-carbene migratory insertion, and subsequently, the allenes might undergo a cycloisomerization with ACPs to give the multiple ring-fused products (Scheme 1, eq 3). These polycyclic products might be useful in the synthesis of biologically active compounds and in material science since

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they have a similar skeleton with several nature products and fluorophores (Figure 1).¹⁰



Figure 1. Selected examples of nature products and fluorophores with similar skeletons.

The investigation commenced with an evaluation of the reaction between terminal yne-tethered ACP 1a and methyl 2diazo-2-phenylacetate 2a by using different Cu/Rh catalysts (Table 1). First, with CuI and $[Cp*RhCl_2]_2$ as a cocatalyst,^{3f}

Table 1. Optimization of Reaction Conditions for theCoupling Cycloisomerization



^{*a*}Reactions were run under the following conditions: a solution of **1a** (0.1 mmol), **2a** (0.2 mmol), base (0.1 mmol), and catalysts (10 mol %) in dry solvent (2.0 mL) was stirred at 25 °C under nitrogen atmosphere for 20 h. ^{*b*}Isolated yields. ^{*c*}The diazo compound **2a** was added directly. ^{*d*}3.0 equiv of **2a** was added. ^{*e*}4.0 equiv of **2a** was added. ^{*f*}0.2 equiv of Et₃N was used.

the reaction of 1a with 2a in CHCl₃ afforded the desired product 3aa in 47% isolated yield using triethylamine (Et₃N) as a base (Table 1, entry 1). Using CuI and $[Rh(OAc)_2]_2$ as a cocatalyst, 3aa was obtained in less than 5% yield (Table 1, entry 2). Next, we optimized the reaction conditions by screening various copper catalysts and found that the use of Cu(MeCN)₄BF₄ as a single catalyst could produce 3aa in 59% yield, although Cu(OAc)₂, Cu(OTf)₂, and Cu(MeCN)₄PF₆ are not efficient ones in this transformation (Table 1, entries 3-6). Since $Cu(MeCN)_4PF_6$ has higher Lewis acidity, it caused the decomposition of the starting materials and the occurrence of a side reaction. Encouraged by this finding, the investigation was continued by using Cu(MeCN)₄BF₄ as the catalyst. The direct addition of diazo compound 2a without the use of a syringe pump gave the desired product 3aa in only 30% yield (Table 1, entry 7). Increasing the amount of diazo compound to 3.0 or 4.0 equiv, the reaction proceeded smoothly, giving the desired product 3aa in 71% and 81% yields, respectively, under otherwise identical conditions (Table 1, entries 8 and 9). Subsequently, various bases were investigated, and we found that using iPr₂NH as base afforded **3aa** in 78% yield under the standard conditions (Table 1, entry 10). The use of other organic bases such as iPr₂NEt and DMAP as well as inorganic bases such as K₂CO₃, Cs₂CO₃, and t-BuOK did not improve the reaction outcomes (Table 1, entries 11-15). Finally, we also evaluated the effect of solvents. It was found that carrying out the reactions in THF, CH₂Cl₂, and DCE afforded 3aa in good yields ranging from 65% to 77% (Table 1, entries 16-18); however, when MeCN and 1,4dioxane were used as the solvents, 3aa was given in lower yields (Table 1, entries 19 and 20). In addition, the reaction did not proceed very well in the absence of base or using catalytic amount of base (Table 1, entries 21 and 22).

Having determined the optimal reaction conditions for this Cu-catalyzed coupling and cycloisomerization reaction, we next turned our attention to the scope and limitations with respect to yne-ACP derivatives 1 in the reaction with methyl phenyldiazoacetate 2a, and the results are summarized in Scheme 2. When 4'-chloro-substituted 1b was used as substrate, the corresponding product 3ba was obtained in 72% yield, and its structure was further confirmed by X-ray diffraction. For substrates 1c and 1d with two halogen atoms as substituents in both phenyl rings, the reactions also proceeded efficiently, giving the corresponding products 3ca and 3da in





^{*a*}Unless otherwise specified, all reactions were carried out using **1** (0.1 mmol), **2a** (0.4 mmol), Cu(MeCN)₄BF₄ (10 mol %), and Et₃N (0.1 mmol) in CHCl₃ (2.0 mL) at 25 °C. ^{*b*}Isolated yields. ^{*c*}[Cp*RhCl₂]₂ (2 mol %) was added, and the reaction was performed at 40 °C. N.R. = No Reaction.

70% and 74% yields, respectively. Then, we synthesized a series of 4'-substituted substrates to investigate the electronic effect at the para-position of the benzene ring. For substrates 1e-1j, regardless of whether they had an electron-rich or electron-poor aromatic ring, the reactions all proceeded efficiently to afford the corresponding products 3ea-3ja in good yields ranging from 61% to 83%. To further evaluate the generality of this method, substrate 1k, in which the aromatic ring was replaced by a heteroaromatic thiophene, also gave the desired product 3ka in 77% yield under the standard reaction conditions. Moreover, the desired product 3la could also be isolated in 73% yield when the benzene ring was changed by a hydrogen atom. However, when cycloalkane-containing terminal yne-ACP 1m was used to react with 2a under the standard reaction conditions, only a trace of the desired product 3ma was detected. Furthermore, substrate 1n, in which an alkylidenecyclobutane moiety was tethered instead of alkylidenecyclopropane, did not react with 2a to give the desired product, thus indicating that the strained threemembered ring is essential in this copper(I)-catalyzed transformation.

Next, using unsubstituted yne-ACP 1a as the substrate, a variety of diazo compounds 2 were examined to expand the scope of the substrates under the optimal reaction conditions (Scheme 3). First, we utilized a variety of benzene ring

Scheme 3. Substrate Scope of Diazo Compounds^{*a,b*}



^{*a*}Unless otherwise specified, all reactions were carried out using **1a** (0.1 mmol), **2** (0.4 mmol), Cu(MeCN)₄BF₄ (10 mol %), and Et₃N (0.1 mmol) in CHCl₃ (2.0 mL) at 25 °C. ^{*b*}Isolated yields. ^{*c*}[Cp*RhCl₂]₂ (2 mol %) was added, and the reaction was carried out at 50 °C.

substituted diazo compounds to react with 1a and found that the corresponding cyclopenta[b]naphthalene derivatives 3ab– 3ae and 3ag–3aj were produced in moderate to good yields ranging from 66 to 83%, regardless of the electronic property of the substituent and the substituted position on the benzene ring. However, when methyl 2-(4-cyanophenyl)-2-diazoacetate 2f was used as the dizao compound, a trace of the desired product was detected under the standard reaction conditions. Changing the methyl group in the ester moiety to ethyl- and isopropyl acetates, the reactions also proceeded smoothly to give the corresponding products 3ak in 83% yield and 3al in 77% yield, respectively. However, in the case of diazo compound 2m containing a benzyl ester moiety, only a trace of the desired product 3am was detected. Moreover, ethyl 2diazo-2-(4-iodophenyl)acetate **2n** was also compatible in the reaction with **1a**, affording the desired product **3an** in 66% yield. The scope of the other type of diazo compounds was next examined. 2-Diazo-1-phenylethanone **2o** is tolerated in this transformation, giving the corresponding product **3ao** in 48% yield if using 2 mol % of $[Cp*RhCl_2]_2$ as the cocatalyst. However, when diethyl 2-diazomalonate **2p** and (diazomethylene)dibenzene **2q** were used to react with **1a**, we found that no reaction occurred in both cases even in the presence of rhodium catalyst or at the elevated temperature.

Moreover, when ethyl 2-diazopropanoate 2r was used to react with 1a, the compound 3ar' was obtained in 62% yield rather than the desired product (Scheme 4, eq 1). To further

Scheme 4. Further Investigations



demonstrate the synthetic usefulness of this reaction, a scale-up experiment was realized with 2.0 mmol of substrate 1a in the reaction with 2a under the standard conditions, affording 3aa in 74% isolated yield (559.7 mg) (Scheme 4, eq 2). Reduction of product 3aa with LiAlH₄ in THF gave the corresponding product 4aa in 94% yield (Scheme 4, eq 3). Furthermore, the asymmetric variant of this reaction was also examined using various chiral ligands, but all gave the desired product 3aa as racemates in 68%–92% yields (see Scheme S4 in the Supporting Information).

According to the previously reported literature^{7,9} and our experimental result, a plausible mechanism for this Cucatalyzed coupling and cycloisomerization reaction has been outlined in Scheme 5. In the presence of a base and a

Scheme 5. Plausible Mechanism for the Formation of 3aa



copper(I) salt, the intermediate of copper acetylide I was first formed from yne-ACP 1a. Next, the reaction of intermediate I with diazo compound 2a would lead to the formation of Cucarbene species II, which underwent a migratory insertion of the alkynyl group into the carbenic carbon atom to give the propargyl copper intermediate III. The allenic intermediate IV was then formed by protonation of intermediate III, accompanied by the regeneration of Cu(I) catalyst. The intermediate IV, which had a highly strained ACP moiety and highly active allenic structure, could easily generate the intermediate V through a 6π -electrocyclization at room temperature. This intermediate subsequently underwent a vinylcyclopropane rearrangement facilitated by generation of an aromatic ring to produce the corresponding product 3aa.

In summary, we have disclosed a novel protocol of Cu(I)catalyzed coupling and cycloisomerization of diazo compounds with terminal yne-alkylidenecyclopropanes (ACPs), giving the functionalized cyclopenta[b]naphthalene derivatives in moderate to good yields under mild conditions. A plausible mechanism has been proposed on the basis of previous literature and our own examination along with a further derivatization. We expect that this finding will provide a practical application for the synthesis of diversified cyclopenta-[b]naphthalene derivatives. The potential utilization and extension of this new synthetic methodology are currently under investigation in our laboratory.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.8b01812.

Experimental procedures and characterization data for all compounds (PDF)

Accession Codes

CCDC 1569645 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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