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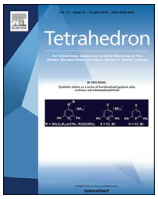

Copper(II)/Palladium(II) catalysed highly selective cross-coupling of terminal alkynes in supercritical carbon dioxide

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ABSTRACT

An efficient protocol for the synthesis of unsymmetrical 1,3-diynes was developed using supercritical carbon dioxide ($ScCO_2$) as the solvent. The direct coupling of two different terminal alkynes is catalysed by a bimetallic catalyst, $CuCl_2 \cdot 2H_2O/Pd(NH_3)_4Cl_2 \cdot H_2O$, in the presence of the base tetramethylethylenediamine (TMEDA) and O_2. In pure $ScCO_2$, our bimetallic catalytic system maintains high activity over a wide substrate scope to provide unsymmetrical 1,3-diynes in good to excellent yields. In the proposed reaction mechanism, the synergistic cooperation between copper(II) and palladium(II) centres is responsible for the superior selectivity of the cross-coupling.

1. Introduction

Conjugated alkynes are fundamental structural motifs in a variety of natural products and bioactive compounds.[1] Symmetrical and unsymmetrical 1,3-diyne scaffolds are also important building blocks for constructing functional materials with unique optical and conductive properties, such as functional polymers, liquid crystals, non-linear materials, molecular wires and supramolecular materials.[2–5] Therefore, the efficient and concise syntheses of 1,3-diynes have attracted considerable attention from chemists for decades.

Glaser-Hay coupling is a classic method used in the synthesis of 1,3-diynes and is extensively used to create symmetrical 1,3-diynes through the Cu-catalysed oxidative homocoupling of terminal alkynes in the presence of a base and an oxidant.[6] Along with the increased demand for unsymmetrical 1,3-diynes, the cross-coupling of alkynes has also been a focus in research. When two different terminal alkynes were coupled using the Glaser-Hay conditions, the yield suffered from an undesirable, competitive homocoupling reaction and, as a result, yielded a mixture of three coupling products (a heterodimer and two homodimers), which were difficult to separate.[7–10] Therefore, the improved selectivity of this cross-coupling has become a critical and challenging issue in the synthesis of unsymmetrical diynes when terminal alkynes are used as starting materials. A pioneering solution to this problem is the Cu(I)-catalysed cross-coupling between a 1-haloalkyne and a terminal alkyne published by Cadiot and Chodkiewicz.[11] In addition to the Cadiot-Chodkiewicz coupling, which is currently the most commonly used method, a number of alternative approaches have been developed, and the reaction partners of the haloalkyne have been expanded to metalated alkynes and other related substrates, such as magnesium acetylides, lithium acetylides, alkynylzincs, alkynylstannanes, alkynylborates and alkynylsilanes.[6,12] These precursors promoted the selective formation of unsymmetrical 1,3-diynes. However, because of the labour-intensive pre-functionalization of the alkyne, as well as the toxicity and low stability of 1-haloalkynes and organometallic reagents, direct oxidative coupling of two different terminal alkynes is widely believed to be the most straightforward and economic route for synthesizing unsymmetrical 1,3-diyne molecules. For years, considerable research has been performed to improve the efficiency of this direct synthetic methodology, such as modifying the catalytic systems (Cu, Pd, Ni),[7,13] bases,[14] oxidants[8] and other factors[15–18] based on the original Glaser-Hay conditions. Recently, significant progress has been made in the Au[19] or Cu-catalysed[18,20] highly selective cross-coupling of terminal alkynes. Despite these important advances, the competitive homocoupling reaction and the use of environmentally harmful organic solvents remain great challenges.

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Because of the increasing focus on applying green chemistry in organic synthesis, applicable methods are required to be not only high-yielding but also environmentally friendly.[21] Consequently, beyond developing highly selective catalysts, another frontier of the modern Glaser-Hay-type reaction is the introduction of "green" reaction media.[22] Several environmentally benign reaction media, such as supercritical carbon dioxide ($ScCO_2$),[23–25] ionic liquids,[26] water,[27] polyethylene glycol (PEG)[28] and even solvent-free conditions,[29] have been applied to both Glaser-Hay homocoupling and Cadiot-Chodkiewicz coupling, but the application of green media in the cross-coupling of two terminal alkynes is still underexplored. Therefore, it is essential to develop highly selective and environmentally friendly methods for preparing unsymmetrical 1,3-diynes via a Glaser-Hay-type heterocoupling pathway.

Supercritical carbon dioxide ($ScCO_2$) is an inexpensive and nontoxic solvent with notable properties, such as tunable solubility, an easily accessible critical point, and chemical and thermal stability.[30,31] To the best of our knowledge, there is no report in the literature regarding the cross-coupling of terminal alkynes using $ScCO_2$ as the reaction medium. In our previous work, a DBU-triggered and CuCl-catalysed oxidative homocoupling of terminal alkynes was performed to produce symmetrical 1,3-diynes with co-solvent free $ScCO_2$ as the environmentally friendly medium.[32] Encouraged by these results, we hypothesized that the cross-coupling of terminal alkynes might also be performed in $ScCO_2$.

In general, to achieve the direct cross-coupling of two alkynes, the selective formation of a specific metal acetylide is crucial. In other words, the two different alkynes must be "differentiated" by the active metal centres of the catalyst.[19,20] A synergistic activation using two metal centres with distinct properties is often required to achieve high selectivity.[33–35] We can expect that a cooperative bimetallic catalyst might be more suitable for the cross-coupling of two terminal alkynes. Cu(I) salts are the most commonly used catalysts, and they play a key role in the coupling of alkynes. Cu(II) salts also work well if the oxidants are present in order to build the Cu(I)/Cu(II) catalytic cycle.[22] Palladium catalysts, including Pd(0) complexes and Pd(II) salts in the presence of phosphines, are the other suitable catalysts for the coupling of alkynes. In these systems, an alkynylpalladium(II) intermediate and Pd(0)/Pd(II) catalytic cycle are the key steps for the coupling reactions to occur.[36] With the above analyses in mind, we focused on using a commercial Cu(II) salt and Pd(II) compound with crystal water to develop a highly selective Cu(II)/Pd(II) bimetallic catalytic system for the cross-coupling of terminal alkynes, and $ScCO_2$ was selected as a green reaction solvent.

In this paper, we report an efficient protocol towards unsymmetrical 1,3-diynes through the $CuCl_2 \cdot 2H_2O/Pd(NH_3)_4Cl_2 \cdot H_2O$ catalysed cross-couplings of terminal alkynes in green $ScCO_2$. We also describe a proposed bimetallic catalytic cross-coupling mechanism.

2. Results and discussion

2.1. Optimization of the cross-coupling conditions

Initially, the cross-coupling reaction of phenylacetylene (**1a**) with 1-ethynyl-4-methoxybenzene (**2a**) was conducted as a model using our homocoupling conditions (catalyst, CuCl; base, DBU; oxidant, O_2; solvent, $ScCO_2$).[32] All three of the possible coupled products **3a**, **4a**, and **5a** were obtained, and the heterocoupled product, **3a**, was given in 41% yield (Table 1, entry 1). Next, we screened reaction conditions to further enhance the yield of heterocoupled product. The results are summarized in Tables 1–3.

The study of various catalysts was included in Table 1. When copper, palladium and nickel salts were used as the sole catalyst (Table 1, entries 1–9), $CuCl_2 \cdot 2H_2O$ with DBU as a base additive gave the highest yield (**3a** yield: 56%). Interestingly, the yield of **3a** dropped dramatically to 18% when anhydrous $CuCl_2$ was used as a catalyst, which suggested that the crystal water of $CuCl_2 \cdot 2H_2O$ should be advantageous for the catalytic process (Table 1, entries 3 and 4). Because single-metal catalysts provided only moderate efficiency, we employed $CuCl_2 \cdot 2H_2O$ based bimetallic catalysts to enhance the performance of the reaction (Table 1, entries 11–13). When $CuCl_2 \cdot 2H_2O$ was combined with $PdCl_2$, $NiCl_2 \cdot 6H_2O$ or $Pd(NH_3)_4Cl_2 \cdot H_2O$, the yields of **3a** were noticeably raised to 66%, 74% and 86%, respectively. The reaction without $CuCl_2 \cdot 2H_2O$ only yielded 22% of the heterocoupled diyne **3a** (Table 1, entry 10), which demonstrated the crucial role of the $CuCl_2 \cdot 2H_2O$ catalyst in the formation of the heterocoupled diyne. The bimetallic catalyst $CuCl_2 \cdot 2H_2O/Pd(NH_3)_4Cl_2 \cdot H_2O$ was more effective than either $CuCl_2 \cdot 2H_2O$ or $Pd(NH_3)_4Cl_2 \cdot H_2O$ as the sole catalyst, which indicated that $CuCl_2 \cdot 2H_2O$ and $Pd(NH_3)_4Cl_2 \cdot H_2O$ synergistically promoted the reaction. The catalytic activity of $Pd(NH_3)_4Cl_2 \cdot H_2O$ was superior to $PdCl_2$ in the Cu/Pd bimetallic catalyst system, which suggested that the ammonia ligands and crystal water of $Pd(NH_3)_4Cl_2 \cdot H_2O$ might be helpful for the reaction. Notably, the amount and stoichiometric ratio of $CuCl_2 \cdot 2H_2O$ and $Pd(NH_3)_4Cl_2 \cdot H_2O$ in the combined catalyst also influenced the catalytic activity (Table 1, entries 13–17). An equimolar mixture of $CuCl_2 \cdot 2H_2O$ and $Pd(NH_3)_4Cl_2 \cdot H_2O$ (10:10, mol%) produced **3a** in a satisfactory yield and was therefore selected as a promising bimetallic catalyst for the cross-coupling of terminal alkynes in $ScCO_2$.

We attempted to further improve the yield of **3a** by changing both the bases and the ratios of the terminal alkynes. As shown in Table 2, the cross-coupling reaction could not occur in the absence of base (Table 2, entry 1). Although inorganic bases NaOAc and K_2CO_3 were effective for the reaction, the heterocoupled product was obtained in moderate yield (Table 2, entries 2 and 3). The use of other organic bases, including NEt_3, pyridine, TBD and TMEDA, also resulted in good yields (Table 2, entries 6–9), and TMEDA was the optimum base, producing **3a** in 91% yield with excellent hetero-/homoselectivity (**3a** vs **4a**, **3a**/**4a** = 91%/2%, entry 9). The variance in the yield might be attributed to the better solubility of organic bases in $ScCO_2$.[24,25] Incrementally increasing the amount of TMEDA from 100 mol% to 200 mol% (Table 2, entries 9–13) showed that 120 mol% produced the highest yield and selectivity. The cross-coupling reaction also strongly depended on the ratio of two terminal alkynes (Table 2, entries 13–17). An equimolar mixture of two alkynes gave a moderate yield of **3a** (65%, entry 15). Increasing the ratio of **1a** to **2a** from 1:1 to 1:2 significantly increased the yield of **3a** from 65% to 92% (Table 2, entry 14). When **2a** was increased further to a three-fold excess with respect to **1a**, a comparable yield for **3a** (92%) was observed (Table 2, entry 13). In contrast, the yields decreased when the ratio of **1a** to **2a** was inverted (2:1, 76%; 3:1, 84%; entries 16 and 17) because the redundant **1a** is more easily homocoupled. Thus, a two-fold excess of **2a** was employed in the following experiments. This bimetallic catalyst was also tested for the homocoupling of **1a** and the homocoupling of **2a**, and the corresponding homocoupled products were produced in relatively low yields (**4a**: 53%, **5a**: 40%; Table 2, entries 18 and 19), which indicated that our catalytic system in $ScCO_2$ was more efficient for cross-coupling.

The effect of other reaction conditions, such as temperature, O_2, CO_2 pressure and time, were also investigated (Table 3). The reaction proceeded smoothly when the temperature ranged from 40 °C–60 °C and provided the best result at 50 °C (Table 3, entries 1–3). O_2 was necessary for the cross-coupling to occur, and 1 MPa O_2 pressure was sufficient to support the reaction (Table 3, entries 4–7). When air was used in place of O_2, the yield of **3a** decreased