Homogeneous Catalysis

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Zinc-Catalyzed Dehydrogenative Cross-Coupling of Terminal Alkynes with Aldehydes: Access to Ynones

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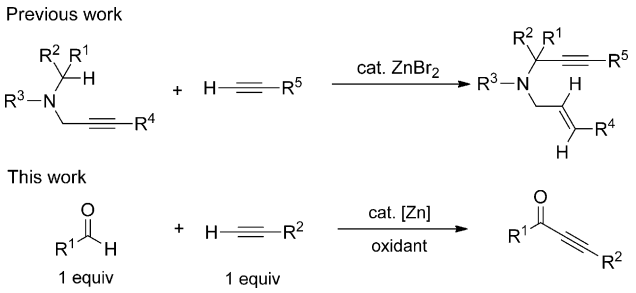
Abstract: *Because of the lack of redox ability, zinc has seldom been used as a catalyst in dehydrogenative cross-coupling reactions. Herein, a novel zinc-catalyzed dehydrogenative C(sp^2)–H/C(sp)–H cross-coupling of terminal alkynes with aldehydes was developed, and provides a simple way to access ynones from readily available materials under mild reaction conditions. Good reaction selectivity can be achieved with a 1:1 ratio of terminal alkyne and aldehyde. Various terminal alkynes and aldehydes are suitable in this transformation.*

Direct dehydrogenative cross-coupling between two hydrocarbons is an environmentally friendly and atom-economic strategy for C–C bond formation since it does not require prefunctionalization of the substrate.[1] However, most of these reactions rely on the use of redox transition metals. Transition metals with poor redox ability have seldom been applied in these transformations. Zinc salts are abundant, cheap, nontoxic, and exhibit environmentally benign properties. These features have attracted organic chemists to use zinc salts as catalysts in many organic transformations.[2] However, the interest in zinc as a catalyst core in cross-coupling is underdeveloped when compared with other transition metals.[3] Because of the lack of redox ability, dehydrogenative cross-coupling through zinc catalysis has received even less attention.[4] In 2012, an elegant zinc-catalyzed C(sp^3)–H/C(sp)–H dehydrogenative cross-coupling of propargylic amines and terminal alkynes was demonstrated by Nakamura and Sugiishi.[5] The C≡C bond of the propargylic amine acted as an internal oxidant, and was reduced to C=C after a zinc-promoted hydrogen-transfer process. This report proved that zinc salts were able to act as catalysts in dehydrogenative cross-coupling reactions. Admittedly, the application of zinc catalysis in dehydrogenative C–C bond formation reactions remains challenging. Herein, we report our progress on a zinc-catalyzed dehydrogenative cross-coupling of terminal alkynes with aldehydes to access ynones (Scheme 1).



Scheme 1. Zinc-catalyzed dehydrgenative cross-coupling for C–C bond formation.

Ynones are important structural motifs in organic chemistry because of their biomedical and material significance, and their widespread use in the synthesis of bioactive products.[6] Over the past decade, numerous efforts have been devoted to this reaction and impressive progress has been achieved.[7] However, most reactions require the use of functionalized materials such as alkynyl metal reagents, alkynyl halides, acyl halides, and α-keto acids. Direct utilization of readily available materials, aldehydes and terminal alkynes, to access ynones would be a much more appealing approach. Actually, zinc salts have been reported to act as catalysts for promoting the coupling of terminal alkynes with aldehydes.[8] However, these reactions are only able to access propargylic alcohols. An extra oxidation step is required for accessing ynones. Recently, our group found that excess amounts of zinc iodide could mediate the dehydrogenation reaction of the in situ generated propargylic alcohols with an additional amount of aldehyde.[9] However, the use of a large excess of zinc salts and aldehydes hindered this protocol from general application. Herein, utilizing a zinc salt as the catalyst in the selective dehydrogenative cross-coupling between terminal alkynes and aldehydes has great significance in terms of both concept innovation and practical application.

We started our research by using benzaldehyde (**1a**) and *p*-tolylacetylene (**2a**) in a model reaction to test the reaction conditions. Optimization of the reaction is shown in Table S1 in the Supporting Information. In the absence of hydrogen accepter oxidants, only small amounts of the desired product **3aa** (for structure see Table 1) could be obtained (Table S1, entry 1). Different ketones were then added into the reaction system and α,α,α-trifluoroacetophenone (**4**) gave a satisfactory yield for this dehydrogenative cross-coupling reaction (Table S1, entries 2–5). Notably, other zinc salts were unreactive for achieving this transformation (Table S1, entries 6–10). $Zn(OTf)_2$ was crucial in this transformation, and was key for achieving this catalytic reaction. Efforts were also taken to

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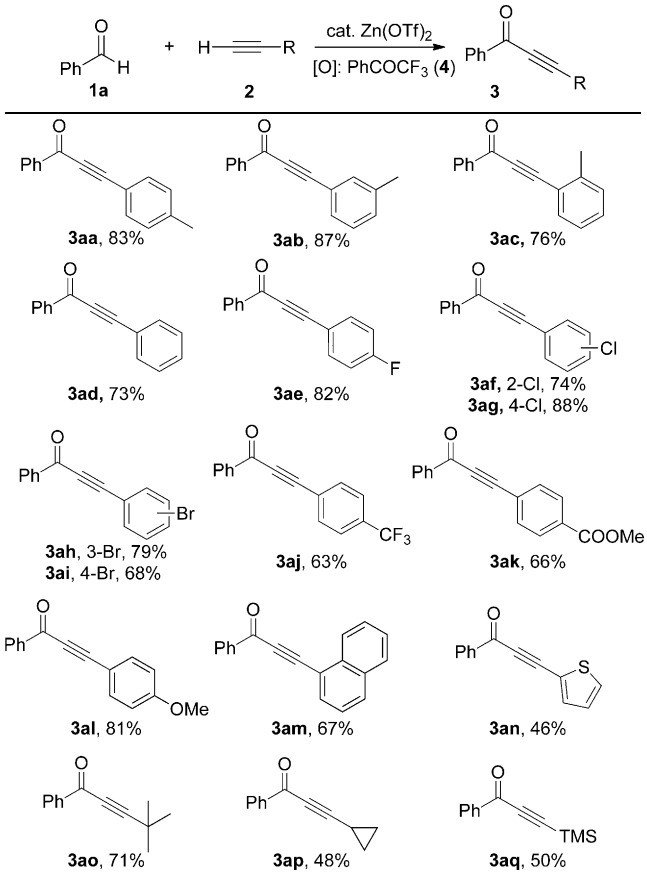
decrease the loading of the zinc catalyst. Use of 15 mol% of $Zn(OTf)_2$ was more effective for this transformation, whereas 10 mol% of $Zn(OTf)_2$ gave a decreased yield (Table S1, entries 11 and 12). Furthermore, several strong Lewis acids were used as co-catalysts to enhance the reaction efficiency (Table S1, entries 13–15). Delightfully, adding an additional 5 mol% of $In(OTf)_3$ led to an excellent yield (Table S1, entry 13). A control experiment showed that $Zn(OTf)_2$ was crucial for the dehydrogenative cross-coupling (Table S1, entry 16). Thus, the optimized reaction conditions include 15 mol% $Zn(OTf)_2$ as the catalyst, 5 mol% $In(OTf)_3$ as a co-catalyst, and 1.2 equivalents **4** as the oxidant.

With the optimized reaction conditions established, we turned to explore the functional-group tolerance of this zinc-catalyzed dehydrogenative cross-coupling. Firstly, different terminal alkynes were applied as substrates to react with **1a**. The reaction of *para*-, *meta*-, and *ortho*-methyl-substituted phenylacetylene all proceeded well and afforded the corresponding ynones in good yields (**3aa**–**ac**; Table 1). Simple phenylacetylene showed similar reactivity in this reaction (**3ad**). Notably, halide substituents such as F, Cl, and Br were all tolerated in this transformation, thus providing a possibility for further functionalization (**3ae**–**ai**). A slightly decreased reactivity was observed for the reaction with electron-deficient phenylacetylenes (**3aj** and **3ak**). The desired product was obtained in 81% yield when electron-rich *p*-methoxylphenylacetylene was used (**3al**). Other aromatic alkynes were also applied as substrates. 1-Ethynylnaphthalene was efficient for the construction of ynones (**3am**), and 2-ethynylthiophene was also applied in this transformation but only a 46% yield could be obtained (**3an**). Aliphatic alkynes were also tried in this dehydrogenative cross-coupling reaction and moderate to good yields were observed under the standard reaction conditions (**3ao** and **3ap**). It is worthy of noting that trimethyl silyl acetylene did generate the desired product with a satisfactory yield under the standard reaction conditions (**3aq**).

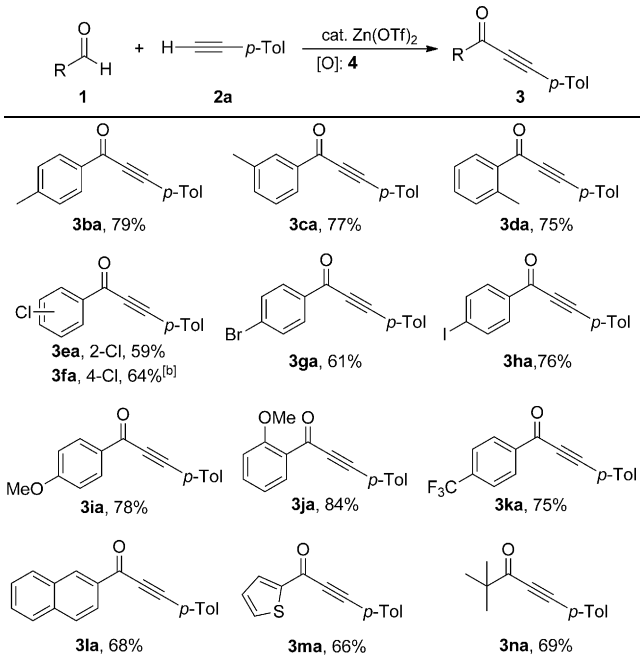
The reactions of *p*-tolylacetylene with various aldehydes were also conducted. The *para*-, *meta*-, and *ortho*-methyl-substituted benzaldehydes were all suitable in this transformation and furnished the desired product in good yields (**3ba**–**da**; Table 2). Benzaldehydes bearing halide substituents were also tolerated in this transformation and good reactivity was observed (**3ea**–**ha**). Both strongly electron-deficient and strongly electron-rich benzaldehydes were suitable in this transformation. The *para*- and *ortho*-methoxy-substituted benzaldehydes gave the corresponding ynones in high yields (**3ia** and **3ja**), and 4-(trifluoromethyl)benzaldehyde furnished the desired product in 75% yield (**3ka**). Other aromatic aldehydes such as 2-naphthaldehyde and thiophene-2-carb-

Table 1: Substrates scope for the zinc-catalyzed dehydrogenative cross-coupling of **1a** with terminal alkynes.[a]



[a] Reaction conditions: **1a** (1.0 equiv, 0.50 mmol), **2** (1.0 equiv, 0.50 mmol), $Zn(OTf)_2$ (15 mol%, 0.075 mmol), $In(OTf)_3$ (5 mol%, 0.025 mmol), α,α,α-trifluoroacetophenone (**4**; 1.2 equiv, 0.60 mmol), NEt_3 (2.4 equiv, 1.2 mmol) in toluene (0.50 mL) at 80°C for 27 h. Tf = trifluoromethanesulfonyl, TMS = trimethylsilyl.

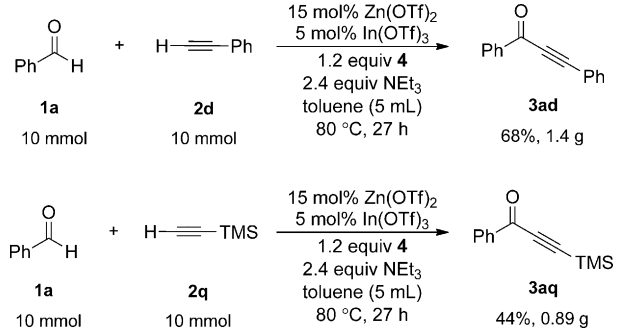
Table 2: Substrates scope for the zinc-catalyzed dehydrogenative cross-coupling of aldehydes with **2a**.[a]



[a] Reaction conditions: **1** (1.0 equiv, 0.50 mmol), **2a** (1.0 equiv, 0.50 mmol), $Zn(OTf)_2$ (15 mol%, 0.075 mmol), $In(OTf)_3$ (5 mol%, 0.025 mmol), **4** (1.2 equiv, 0.60 mmol), NEt_3 (2.4 equiv, 1.2 mmol) in toluene (0.50 mL) at 80°C for 27 h. [b] 20 mol% $Zn(OTf)_2$ was used.

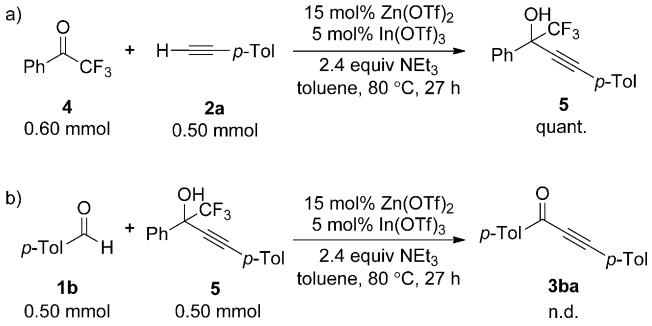
aldehyde showed good reactivity in this transformation (**3la** and **3ma**). Aliphatic aldehydes, such as pivalaldehyde, bearing no α-hydrogen atom, showed a good reactivity in this transformation (**3na**). However, aliphatic aldehydes bearing α-hydrogen atoms were not suitable in this transformation because they are susceptible to forming aldol byproducts.

The scalability of this novel ynone synthesis was evaluated by performing the zinc-catalyzed dehydrogenative cross-coupling in a 10 mmol scale. Coupling of **1a** with **2d** smoothly furnished the desired product in 68% yield (Scheme 2; **3ad**). Similarly, the gram-scale reaction between **1a** and **2q** afforded the desired product in 44% yield (**3aq**). These results highlight the potential of this dehydrogenative cross-coupling in practical applications.



Scheme 2. Gram-scale reactions.

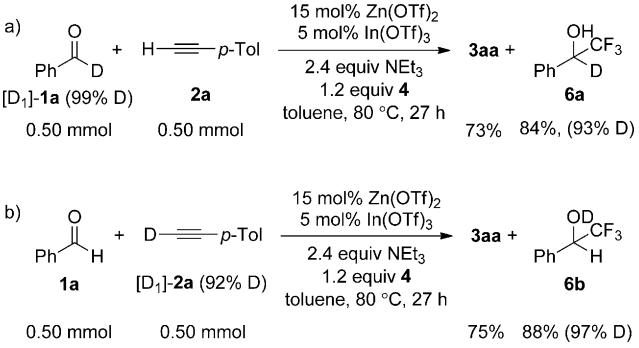
To gain some insight into the reaction intermediate, some control experiments with **4** were carried out. Under the standard reaction conditions, **2a** could directly react with **4** in the absence of aldehydes. The reaction gave the trifluoromethyl-substituted propargylic alcohol **5** in quantitative yield (Scheme 3a). We then checked whether **5** was an active reaction intermediate in this transformation. However, no



Scheme 3. Study of the reaction intermediates.

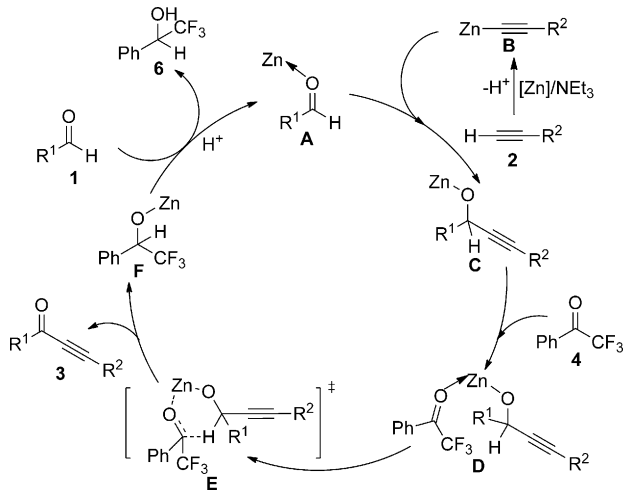
reaction between the aldehyde **1b** and **5** took place under the standard reaction conditions (Scheme 3b). These results indicated that addition of a terminal alkyne to **4** was not involved in the dehydrogenation process.

For understanding the mechanism of the dehydrogenation process, reactions with deuterated substrates were carried out. The deuterium of [D_1]-**1a** added to the carbon atom of the C=O group of **4** to give [D_1]2,2,2-trifluoro-1-phenylethan-1-ol (**6a**; Scheme 4a). At the same time, the deuterium of [D_1]-**2a** added to oxygen atom of the C=O group of **4** to give **6b** (Scheme 4b). These two reactions provided a clear view of the hydrogen-transfer pathway during the dehydrogenative cross-coupling reaction.



Scheme 4. Isotope-labeling experiments.

Based on the experimental results and previous mechanistic studies,[9,10] a tentative reaction mechanism is proposed for the dehydrogenative cross-coupling process (Scheme 5). It



Scheme 5. Proposed mechanism.

is well known that C(sp)–H bond activation of terminal alkynes could be achieved with the combination of a certain zinc salt and an organic base.[10] This C–H activation would lead to the formation of an alkynyl zinc species (**B**). Nucleophilic addition of the alkynyl zinc to the zinc coordinated aldehyde **A** would lead to the formation of the propargylic alcohol complex **C**. The hydrogen-acceptor oxidant **4**,[11] could then coordinate to **C**, and a hydrogen-transfer process would take place, through a then six-membered transition-state **E**, to furnish the final product and a zinc alcohol (**F**). Finally, the catalytic cycle is completed with the protonation of **F** to give 2,2,2-trifluoro-1-phenylethan-1-ol. There are three roles for zinc in this reaction:

1) C–H activation of the terminal alkyne; 2) activing the carbonyl group of aldehyde; 3) bridging the hydrogen transfer of the propargylic alcohol intermediate with **4**. Additionally, $In(OTf)_3$ is also likely to play a role in the activation of the terminal alkyne and aldehyde,[12] and is thus beneficial for achieving good reaction efficiency.

In conclusion, we have disclosed a novel zinc-catalyzed reaction system for the dehydrogenative cross-coupling between aldehydes and terminal alkynes. This reaction protocol provides an atom economic way for the synthesis of ynones. The use of $Zn(OTf)_2$ as catalyst and α,α,α-trifluoroacetophenone as oxidant was key for achieving this catalytic transformation. Notably, neither terminal alkyne nor aldehyde needed to be used in an excess amount. A good reaction selectivity was achieved, even with 1:1 ratio of terminal alkyne and aldehyde. The study of the substrate scope showed that various terminal alkynes and aldehydes were selectively converted into the corresponding ynones in high selectivity and good yields. Delightfully, this reaction could also be conducted on gram scale, which is important for future application.

Acknowledgments

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