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Nickel-Catalyzed Oxidative Coupling Reactions of Two Different Terminal Alkynes Using O_2 as the Oxidant at Room Temperature: Facile Syntheses of Unsymmetric 1,3-Diynes

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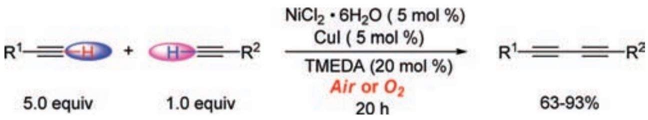
ABSTRACT



Two different terminal alkynes now can be coupled together in the presence of $NiCl_2{\cdot}6H_2O$/CuI by using an excess of one of the terminal alkyne substrates. The new method employed 20 mol % TMEDA as the ligand and environmentally benign O_2 or air as the oxidant. It is the first example using Ni-salt as catalyst by employing air or O_2 as oxidant, which led to efficient heterocoupling of two different alkynes.

Conjugated diynes are recurring building blocks in natural products, industrial and pharmaceutical intermediates, electronic and optical materials, etc.[1−3] Homocoupling of terminal alkynes was pioneered by Glaser[4,5] in 1869, and nowadays, Cu-salt mediated Glaser coupling and related modified methods[6−13] are still widely applied in the synthesis of conjugated diynes.[14] Recently, Pd-catalyzed oxidative homocouplings of alkynes with a stoichiometric amount of oxidant such as O_2,[15−18] α-halocarbonyl compounds,[19−21] I_2,[22,23] and others[24−30] have emerged as efficient means. Currently, the major methods for constructing unsymmetric conjugated diynes are Cadiot−Chodkiewicz coupling and its modifications,[31−34] which are Cu-catalyzed couplings between a haloalkyne and a terminal alkyne. Heterocoupling of a haloalkyne and a terminal alkyne using palladium catalysis are also known.[35−37] Haloalkynes are usually prepared from terminal alkynes by halogenation. Thus from an environmental and economical viewpoint, this protocol is inferior to a method directly coupling two different terminal alkynes.

Recently, this group was interested in the oxidative coupling to construct carbon−carbon bonds assisted by transition metals, such as Pd, Ni, Fe, etc.[38−41] O_2 as the oxidant is environmentally and economically benign and has

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attracted much attention during the past century.[42,43] Oxidation of low valent transition metals by readily available O_2, as a fundamental reaction in chemistry, plays an important role in many oxygenase enzyme functions and catalytic processes.[44−46] For example, catalytic chemistry of Pd with O_2 as an oxidant has made great strides recently,[47−54] and several new processes have been introduced to organic syntheses.[55−61] Oxidation of Ni(0)-complexes by O_2 similar to that of Pd and Pt has been investigated in stoichiometric and catalytic reactions, and side-on NiO_2 was identified or invoked as the outcome of the oxidation in several cases.[46,62−64] Although the inexpensive Ni possesses the potential of being an effective catalyst, applications of Ni catalyst with O_2 as oxidant in organic syntheses are still limited compared to the well-established Pd/O_2 chemistry and have yet to be explored.[65,66] Herein, we report our observation of a Ni-catalyzed oxidative coupling reaction of terminal alkynes to form unsymmetric conjugated diynes under aerobic conditions.

With strong interest in 1,3-diyne type compounds, we tested the homocoupling of phenylacetylene using the Hay modification [CuI (5 mol %), TMEDA (10 mol %)] under aerobic conditions. The reaction gave 25% product after 1 h (Figure 1). Unexpectedly, addition of 5 mol % of $NiCl_2{\cdot}6H_2O$ greatly enhanced the reaction, and the homocoupling was completed within 1 h in 93% yield (Figure 1). The phenomena indicated that $NiCl_2{\cdot}6H_2O$ and CuI promoted the reaction in a synergistic way.

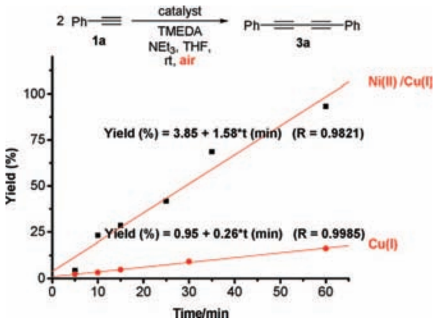

Figure 1. Time profiles of homocoupling of **1a** in the presence of NEt_3 and TMEDA in the air. Ni(II)/Cu(I) system: $NiCl_2{\cdot}6H_2O$ (0.05 mmol), CuI (0.05 mmol). Cu(I) system: CuI (0.05 mmol).

The reaction between phenylacetylene **1a** and prop-2-ynyl acetate **1b** was chosen as the model, and the reactions were carried out in the presence of $NiCl_2{\cdot}6H_2O$ (5 mol %), CuI (5 mol %), and TMEDA (20 mol %) in THF at room temperature under aerobic conditions for 20 h. When the ratio of **1a** to **1b** was 1:1 (Table 1, entry 1), 46% cross-

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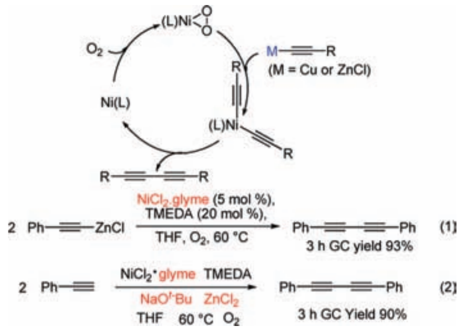
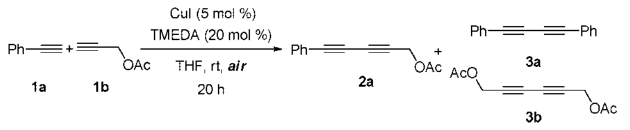
coupled conjugated diyne **2a** was obtained. When the ratio changed to 1:5 (Table 1, entry 2), 50% **2a** was obtained while **3a** was only 8%. When the ratio of **1a**:**1b** was changed to 5:1 (Table 1, entry 3), the yield of **2a** was 86%. The reaction proceeded smoothly without NEt_3 and gave **2a** in 82% yield (Table 1, entry 5). If the statistical distribution controlled the formation of cross-coupled and homocoupled diynes, the ratio of 1:5 will lead to 83% of the cross-coupled diyne. However, under the same reaction conditions, the reaction without the nickel catalyst only yielded 30% cross-coupled diyne (Table 1, entry 4), which exhibited the crucial role of the nickel catalyst during the formation of cross-coupled diynes.

Scheme 1. Speculated Reaction Pathways of Alkyne Couplings



The substrate scope of the syntheses of unsymmetric diynes was further examined, and the results are compiled in Table 2. All reactions proceeded smoothly at room temperature under aerobic conditions. By utilizing the different polarity between these alkyne substrates, we could overcome the problem of separation. Phenylacetylene **1a** successfully cross-coupled with a variety of alkynes based on propargylic alcohols and amines, and functional groups such as OR, OH, NHR, TBS, etc. were tolerated well (Table 2, entries 1−6, 8, 10, 11). The reaction between **1c** and **1h** resulted in product **2g** in 85% isolated yield, and that between **1b** and **1i** furnished 81% of the product (Table 2, entries 7 and 9).

Table 1. Heterocoupling of Alkynes Catalyzed by Ni/Cu



entry	1a (mmol)	1b (mmol)	$NiCl_2 6H_2O$	NEt_3	2a yield (%)[a]	3a yield (%)[b]	3b yield (%)[c]
1	1.0	1.0	5 mol %	3.0 equiv	46 (0.46)	41 (0.21)	54 (027)
2[d]	1.0	5.0	5 mol %	3.0 equiv	50 (0.50)	8 (0.04)	63 (1.6)
3	5.0	1.0	5 mol %	3.0 equiv	86 (0.86)	64 (1.6)	5 (0.025)
4[e]	5.0	1.0	none	3.0 equiv	30 (0.30)	20 (0.5)	7 (0.035)
5	5.0	1.0	5 mol %	none	82 (0.82)	64 (1.6)	7 (0.035)

[a] GC yields based on 1.0 mmol of reactant (naphthalene as the internal standard); the numbers in the parentheses are amounts of **2a** (mmol). [b] Yields based on **1a**; the numbers in the parentheses are amounts of **3a** (mmol). [c] Yields based on **1b**; the numbers in the parentheses are amounts of **3b** (mmol). [d] 42% of **1a** was not converted. [e] 60% of **1b** remained.

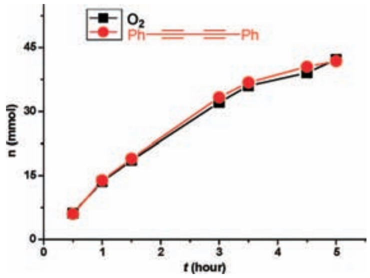


Figure 2. Time profiles of homocoupling of **1a** (100 mmol) catalyzed by Ni(II)/Cu(I) with TMEDA in THF in 500-mL Schlenk flask. Red line represents the amount of **3a** versus time; black line represents the consumed O_2 versus time.

Further investigations revealed that aryl bromides could be tolerated under the reaction conditions, and the couplings between **1k** and **1e** or **1f** furnished the corresponding products in good yields (Table 3, entries 1 and 2). It is noteworthy that even aryl iodides could be retained, and the substrates bearing a 2-iodophenyl group or a 4-iodophenyl group readily cross-coupled with another terminal alkyne in good yields (Table 3, entries 3−6). The results were significant because aryl bromides and iodides are reactive building blocks in many transition metal catalytic systems and thus are usually difficult to be tolerated; moreover, the halo groups retained in the products provided opportunities for further transformation.

Homocoupling of terminal alkynes under the above conditions had been examined, and good to excellent yields were obtained under mild conditions (for details, see Supporting Information, pp 9 and 10).

Nickel alkynyl complexes have been reported to be prepared by CuI-catalyzed reaction of Ni(0) with terminal alkynes,[67−74] implying that Cu(I) was more reactive toward terminal alkynes than the Ni(0) species. Therefore, the reaction is proposed to initiate from oxidation of the Ni-complex by O_2 to generate a $Ni(O_2)$ intermediate,[46,62] which is transmetalated stepwise with an copper alkynyl species to generate a dialkynyl-Ni intermediate. The final reductive

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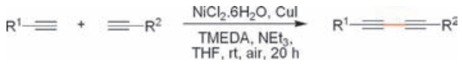
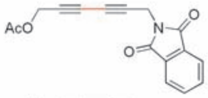
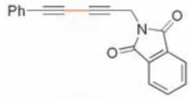
Table 2. Syntheses of Unsymmetric Conjugated Diynes[a]



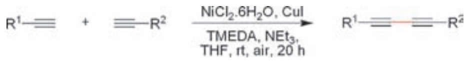
entry	R^1—≡	≡—R^2	R^1—≡—≡—R^2		yield (%)
1	1a	1b		2a	86
2	1a	1c		2b	90
3	1a	1d		2c	93
4	1a	1e		2d	80
5	1a	1f		2e	86
6	1a	1g		2f	72
7	1c	1h		2g	85
8	1a	1h		2h	84
9	1b	1i		2i	81
10	1a	1i		2j	84
11	1a	1j		2k	60

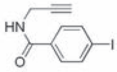
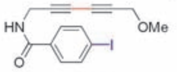
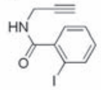
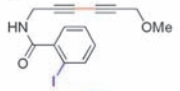
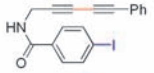
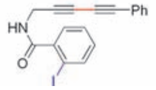
[a] Reaction conditions: $NiCl_2$•$6H_2O$ (5.0 mol %), CuI (5.0 mol %), TMEDA (20 mol %) in THF at room temperature under aerobic conditions. The ratio of R^1CCH:R^2CCH was 5:1. Isolated yields.

elimination would release the coupling product and regenerate the Ni(0) complex[75,76] (Scheme 1). The proposed reaction mechanism in Scheme 1 indicated that the role of CuX was to form the copper acetylide, which further transmetalated as the nucleophile with a Ni(O_2) complex. When zinc acetylide ((phenylethynyl)zinc(II) chloride) was employed as the nucleophile, without the CuI additive, the reaction in the presence of $NiCl_2$•glyme produced 93% homocoupled product (eq 1). Furthermore, the homocoupling of phenylacetylene could occur smoothly in the presence of NaO^tBu and $ZnCl_2$, and 90% homocoupled diyne was obtained (eq 2). This result supported the role of nickel catalyst, proposed in Scheme 1, in the oxidative coupling of alkynes.

In the above mechanism, the formation of 1 mol of coupling product would consume 1 mol of O_2. On the other hand, in Cu-catalyzed homocoupling of alkynes, consumption of 1 mol of O_2 was reported to result in 2 mol of coupling product.[6,14] To gain some preliminary understanding of the reaction, a 100 mmol scale homocoupling of **1a** was carried out. The kinetic profiles of the reaction clearly revealed that the formation of **3a** was accompanied by the consumption of an equal molar amount of O_2 (Figure 2).[77] Therefore, the observation supported the hypothesis shown in Scheme 1.

Table 3. Syntheses of Unsymmetric Conjugated Diynes[a]



entry	R^1—≡	≡—R^2	R^1—≡—≡—R^2		yield (%)
1	1k	1e		2l	75
2	1k	1f		2m	79
3	 1l	1c		2n	73
4	 1m	1c		2o	88
5	1l	1a		2p	74
6	1m	1a		2q	89

[a] Reaction conditions: $NiCl_2$•$6H_2O$ (5.0 mol %), CuI (5.0 mol %), TMEDA (20 mol %) in THF at room temperature under aerobic conditions. The ratio of R^1CCH:R^2CCH was 1:5. Isolated yields.

In summary, we have developed a Ni/Cu-cocatalyzed aerobic oxidative coupling reaction that efficiently promoted heterocouplings between two different terminal alkynes and provided a variety of unsymmetric conjugated diynes under mild conditions. Although the limitation for heterocouplings was evident, the obtained yields might be under statistical control. However, this method for constructing unsymmetric conjugated diynes though two different terminal alkynes, which were usually readily available, were environmentally benign. In addition, it is the first example using a Ni-salt as a catalyst by employing air or O_2 as oxidant, which led to efficient heterocoupling of two different alkynes. Further mechanistic studies are currently undergoing in our laboratory and will be reported in due course.

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Note Added after ASAP Publication. Red bonds were missing in Tables 2 and 3 in the version published ASAP December 24, 2008; the corrected version was published ASAP January 7, 2009.

Supporting Information Available: Detailed experimental procedure and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(77) This reaction time was longer than the one in the Figure 1, in which the size and shape of reactors for these two reactions were different. We speculated that the different reaction rate might be due to the reactors, which could affect the uptaking of O_2.