HOMO-COUPLING OF TERMINAL ALKYNES USING A SIMPLE, CHEAP Ni(dppe)Cl2/Ag2O CATALYST SYSTEM

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GRAPHICAL ABSTRACT

Abstract A simple Ni(dppe)Cl2/Ag2O combination has been established as an efficient catalyst system for the homo-coupling of aromatic terminal alkynes. This reaction proceeds under mild conditions and can be applied to alkynone substrates. Various aromatic 1,3-diynes were obtained in good to excellent yields.

Keywords 1,3-Diynes; homo-coupling; nickel; terminal alkynes

INTRODUCTION

1,3-Diynes are important motifs or synthetic intermediates in natural products,[1] pharmaceuticals,[2] supramolecular chemistry,[3] and π-conjugated acetylenic oligomers.[4] Undoubtedly, catalytically oxidative homo-couplings of terminal alkynes are the most commonly utilized approach to 1,3-diynes. Since the pioneering work of Glaser in 1869,[5] numerous catalysts including copper,[6] palladium,[7] nickel,[8] cobalt,[9] gold,[10] and titanium[11] have been developed. However, most of the existing methods require the use of excess amines, with characteristic foul smell and pungent flavor. In a recent publication,[7h] Bao and coworkers disclosed an improved method using an amine- and copper-salt-free palladium-catalyzed homo-coupling reaction. Accordingly, we were interested in developing a variant protocol where far cheaper
nickel would be utilized as catalyst in place of precious metal palladium. Herein, we report our finding involving the nickel-catalyzed homo-coupling of terminal alkynes.

RESULTS AND DISCUSSION

Phenylacetylene was chosen as a standard substrate for the screening of reaction conditions; Ag₂O was employed as additive in the model reaction considering the special role of silver salts in promoting the cross-coupling of terminal alkynes. The results are summarized in Table 1. Initially, several commonly used Ni(II) compounds were tested as catalysts (Table 1, entries 1–5). Ni(dppe)Cl₂ was found to be the most efficient catalyst among the Ni(II) precursors used, providing the desired product in 97% yield (Table 1, entry 5). Ni(PC₅₃)₂Cl₂ or Ni(PPh₃)₂Cl₂ gave a reasonable yield (Table 1, entries 3 and 4). An attempt to carry out the reaction in air afforded a disappointing result (Table 1, entry 5). This might be attributed to the negative influence of O₂ on the catalytic cycle. The use of nonbasic silver salts was ineffective (Table 1, entries 6 and 7). Copper oxides or salts are the most generally utilized activators in the homo-coupling of terminal alkynes. However, Cu₂O and CuO, analogs of Ag₂O, were also found not to work in this reaction (Table 1, entries 8 and 9). Among the solvents screened, both 1,2-dichloroethane (DCE) and toluene turned out to be the solvents of choice (Table 1, entries 5 and 10–12). DCE was

| Entry | Catalyst (mol%) | Additive (equiv) | Solvent   | Yield (%)  |
|-------|----------------|-----------------|-----------|------------|
| 1     | NiCl₂ ·6H₂O (5) | Ag₂O (1.0)      | DCE       | NR         |
| 2     | Ni(acac)₂ (5)   | Ag₂O (1.0)      | DCE       | 10         |
| 3     | Ni(PC₅₃)₂Cl₂ (5)| Ag₂O (1.0)      | DCE       | 71         |
| 4     | Ni(PPh₃)₂Cl₂ (5)| Ag₂O (1.0)      | DCE       | 79         |
| 5     | Ni(dppe)Cl₂ (5) | Ag₂O (1.0)      | DCE       | 97 (16°)   |
| 6     | Ni(dppe)Cl₂ (5) | AgNO₃ (1.0)     | DCE       | Trace      |
| 7     | Ni(dppe)Cl₂ (5) | AgOAc (1.0)     | DCE       | NR         |
| 8     | Ni(dppe)Cl₂ (5) | Cu₂O (1.0)      | DCE       | Trace      |
| 9     | Ni(dppe)Cl₂ (5) | CuO (1.0)       | DCE       | NR         |
| 10    | Ni(dppe)Cl₂ (5) | Ag₂O (1.0)      | Dioxane   | Trace      |
| 11    | Ni(dppe)Cl₂ (5) | Ag₂O (1.0)      | THF       | 81         |
| 12    | Ni(dppe)Cl₂ (5) | Ag₂O (1.0)      | Toluene   | 98         |
| 13    | Ni(dppe)Cl₂ (2.5)| Ag₂O (1.0)    | DCE       | 39         |
| 14    | Ni(dppe)Cl₂ (5) | Ag₂O (0.75)     | DCE       | 65         |
| 15    | Ni(dppe)Cl₂ (5) | Ag₂O (0)        | DCE       | NR         |
| 16    | Ni(dppe)Cl₂ (0) | Ag₂O (1.0)      | DCE       | NR         |

*aConditions: phenylacetylene (1 mmol), 5.0 mL of solvent, room temperature, N₂, 4 h.

*bIsolated yields.

*cDCE, 1,2-dichloroethane.

*dNR, no reaction.

*eUnder air.
Table 2. Oxidative homo-coupling of terminal alkynes\textsuperscript{a}

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\begin{array}{cccc}
\text{Entry} & \text{Substrate} & \text{Time (h)} & \text{Product} & \text{Yield (%)}\textsuperscript{b} \\
1 & & 4 & \text{ } & 97 \\
2 & & 4 & \text{ } & 93 \\
3 & & 4 & \text{ } & 95 \\
4 & \text{H}_2\text{N} & 12 & \text{ } & 25 (32\textsuperscript{c}) \\
5 & \text{O} & 12 & \text{ } & 91 \\
6 & \text{O} & 12 & \text{ } & 80 \\
7 & \text{F} & 4 & \text{ } & 93 \\
8 & \text{HO} & 8 & \text{ } & 86 \\
9 & \text{O} & 8 & \text{ } & 68 \\
10 & \text{O} & 18 & \text{ } & \text{Trace (11,}\textsuperscript{d} 84\textsuperscript{e}) \\
11 & \text{O} & 24 & \text{ } & \text{Trace (4,}\textsuperscript{d} 80\textsuperscript{f}) \\
12 & \text{O} & 18 & \text{ } & \text{Trace (9,}\textsuperscript{d} 89\textsuperscript{g}) \\
\end{array}
\]

(Continued)
preferably used in view of its solubility toward some 1,3-diynes. Attempts to decrease the catalyst loading and the amount of Ag$_2$O led to a sluggish reaction (Table 1, entry 5 vs entries 13 and 14). Additionally, no desired product would be observed without Ag$_2$O or Ni(dppe)Cl$_2$ (Table 1, entry 15 and 16). Therefore, our standard conditions were set up as entry 5 in Table 1.

Next, the scope and limitations of the reaction were investigated and the results are summarized in Table 2. Generally, the Ni(dppe)Cl$_2$/Ag$_2$O system is very effective for aromatic alkyne substrates, and the reaction tolerates a wider range of functional group. Tolylacetylenes were homo-coupled with excellent yields (Table 2, entries 2 and 3). The reaction of the substrate containing the free amino group was significantly sluggish even with the twofold catalyst loadings (Table 2, entry 4), but the reaction proceeded extremely smoothly after the free amino was protected by acylation (Table 2, entries 5 and 6). Based on these observations, we speculated that the poor reactivity of 3-aminophenylacetylene might result from the strong coordination of the amino group to Ni center. The strong electron-withdrawing fluorine substituent did not affect the reaction (Table 2, entry 7), despite the existence of the steric hindrance from the ortho-position substituent. Furthermore, the substrates bearing hydroxyl and ester group were also tolerated in the reaction (Table 2, entries 8–10).

Particular attention was paid to the terminal alkynes containing the carbonyl group substrates because they are normally difficult to homo-couple under the Glaser-type reaction conditions. To date, fewer methods have dealt with the homo-coupling of containing the carbonyl group terminal alkynes, and those gave only a moderate yield of the products.[6c,7h,13] Therefore, the highly efficient synthesis of (keto-aryl)diynes from the terminal alkynes containing the carbonyl group remains desirable. To our delight, the terminal alkynes containing the carbonyl group provided good yields of the homo-coupled products under our slightly modified standard conditions (Table 2, entries 10–12).

### Table 2. Continued

| Entry | Substrate | Time (h) | Product | Yield (%)$^b$ |
|-------|-----------|----------|---------|--------------|
| 13    | ![Substrate](image1.png) | 24       | ![Product](image2.png) | 9            |
| 14    | ![Substrate](image3.png) | 24       | ![Product](image4.png) | 11           |
| 15    | ![Substrate](image5.png) | 24       | ![Product](image6.png) | 15           |

$^a$Reaction conditions: terminal alkyne (1 mmol), Ni(dppe)Cl$_2$ (5 mol%), Ag$_2$O (1.0 mmol), DCE (5.0 mL), room temperature, N$_2$, 4 h.

$^b$Isolated yields.

$^c$20 mol% of Ni(dppe)Cl$_2$.

$^d$1.5 mmol of Ag$_2$O.

$^e$1.5 mmol of Ag$_2$O, 60 °C.
In striking contrast to the aromatic counterparts, aliphatic terminal alkynes did not seem to be suitable for the reaction (Table 2, entries 13–15). The reason is presumably that the acidity of aliphatic terminal alkynes is too weak to be deprotonated under our reaction conditions.

A plausible mechanism was proposed based on previous reports involving the use of silver salts (Scheme 1).\textsuperscript{[12]} Ag\textsubscript{2}O as a base affords the active alkynylsilver in situ. Then, Ni(dppe)Cl\textsubscript{2} reacts with alkynylsilver to generate the dialkynyl nickel intermediate, followed by reductive elimination. The desired product as well as Ni(0) are obtained. The nickel(0) species is then oxidized to regenerate the nickel(II) catalyst by Ag\textsubscript{2}O to close the catalytic cycle.

CONCLUSIONS

In summary, a simple, cheap Ni(dppe)Cl\textsubscript{2}/Ag\textsubscript{2}O system has been found to efficiently catalyze the homo-coupling of aromatic terminal alkynes. The reaction has mild conditions, tolerates a wider range of functional groups, and avoids the use of amines with foul and pungent smell. This protocol provides one more selection for the synthesis of 1,3-diyne compounds. Further work to elucidate the mechanistic details and extend the scope of substrates is currently under way in our laboratory.

EXPERIMENTAL

**General Procedure for the Homo-Coupling of Terminal Alkynes**

An oven-dried, 25-mL, three-necked flask was charged with Ni(dppe)Cl\textsubscript{2} (0.05 mmol) and Ag\textsubscript{2}O (1.0 mmol). Then the terminal alkyne (1 mmol) (if solid)
was added. The flask was evacuated and backfilled with nitrogen, with the operation being repeated twice. The terminal alkyne (if liquid) and DCE (5 mL) were added via syringe at this time. The reaction mixture was stirred at room temperature and the progress of the reaction was monitored by thin-layer chromatography (TLC). After completion of the reaction, the reaction mixture was then filtered through a silica-gel pad that was washed with ethyl acetate. The combined organic phases were evaporated under reduced pressure and the residue was purified by silica-gel column chromatography to give the desired products.

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SUPPORTING INFORMATION

Supplemental data for this article can be accessed on the publisher’s website.

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