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Iron/copper promoted oxidative homo-coupling reaction of terminal alkynes using air as the oxidant

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ABSTRACT

An inexpensive catalytic system, which used a readily available $Fe(acac)_3$ and trace quantity of $Cu(acac)_2$ as the co-catalyst and air as the oxidant for the homo-coupling of terminal alkynes, has been developed. The catalytic system could also apply to the cross-coupling reaction of two different terminal alkynes.

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1. Introduction

Diynes are very useful compounds building blocks in organic synthesis and a recurring functional group in linearly π-conjugated acetylenic oligomers and polymers,[1] nature products,[2] bioactive compounds,[2a,3] molecular recognition processes,[4] and nonlinear optical materials.[5] One of the main methods to create this type of bond is Glaser oxidative homo-coupling reaction of terminal alkynes.[6,7a] Among C–C bond-forming processes, palladium catalysis has played a key role because of its mild, efficient, and selective properties.[7] This well-known method, however, suffers from several drawbacks such as the use of expensive palladium reagents, phosphorus or amine ligands, and the lack of environmental friendliness. So there is a need for new methods that involve cheap and environmentally friendly catalytic systems to create 1,3-diynes. In the past years, several groups have developed homo-coupling reactions of terminal alkynes using Pd-free catalytic systems.[8] Jia and co-workers described the homo-coupling reaction of terminal alkynes in the presence of CuI/I_2.[9] Although the result was encouraging, a major drawback was the required presence of stoichiometric amounts of CuI and I_2. Recently, our group reported the homo-coupling reaction of terminal alkynes in the presence of $CuCl_2$ under solvent-free condition, but the drawback was required to use amine reagent necessarily.[10] It is generally acknowledged that iron complexes, which are cheap and environmentally friendly comparatively, associated with other metals, have not catalyzed this type of reactions.[11] Herein, we report an efficient and economically competitive Fe/Cu (trace quantity of copper) co-catalytic system for homo-coupling reaction of terminal alkynes.

2. Results and discussion

For initial optimization of the reaction conditions, phenylacetylene was chosen as a model substrate. This preliminary survey, carried out in DMF at 50 °C under air, allowed us to evaluate and optimize the most efficient catalytic system (Table 1). The initial results showed that only using catalytic amounts of Fe, $FeCl_2$, $FeCl_3$ or $Fe(acac)_3$ were not able to promote the reaction (entries 1–4). The other blank experiments in the absence of an iron additive but in the presence of a trace amount of copper catalyst revealed no conversion of phenylacetylene to diyne efficiently (entries 5–7).

Recently, It was noticed that Buchwald and Bolm found that trace quantity of copper impurities would influence several types of Fe/ligand-catalyzed cross-coupling reactions obviously.[11e] Therefore, when using 10 mol % Fe and trace quantity of Cu salts (0.1 mol %) as a co-catalyst, the yields of the desired product enhanced slightly (entries 8–10). According to alter the kind of Fe sources, it was surprisingly found that the homo-coupling of phenylacetylene was successful with good yields in the presence of catalytic amounts of Fe and trace amounts of Cu salts (entries 10 and 11).

Note that O_2 played a significant role in the Fe/Cu co-catalyzed homo-coupling reaction (entry 11). When carrying out the experiment under O_2 rather than N_2, the high yield of diyne was obtained. It was noted that an almost same yield of diyne could be obtained when using free air instead of O_2, because O_2 of air plays a role of oxidan.[12]

Other copper sources with different oxidation state (I, II) were examined but the outcomes were not so satisfactory (entries 12–15). Then the influence of altering the base on the homo-coupling reaction was examined. This confirmed that the homo-coupling reactions were not able to occur without a base (entry 16). It was found that K_2CO_3 and Cs_2CO_3 were both more efficient than other bases (entries 11, 16–20). It is reasonable to employ the later as the base in the reaction, because Cs_2CO_3 is much more expensive

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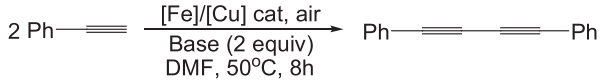
Table 1
Preliminary survey of the iron/copper catalytic system for the homo-coupling reaction of phenylacetylene



Entry	[Fe] cat (0.1 equiv)	[Cu] cat (0.001 equiv)	Base	Yield[a] (%)
1	Fe	—	K_2CO_3	0
2	$FeCl_2$	—	K_2CO_3	0
3	$FeCl_3$	—	K_2CO_3	0
4	$Fe(acac)_3$[b]	—	K_2CO_3	0
5	—	Cu	K_2CO_3	0
6	—	Cu_2O	K_2CO_3	15
7	—	$Cu(acac)_2$	K_2CO_3	25
8	$FeCl_3$	CuI	K_2CO_3	27
9	$FeCl_2$	$Cu(acac)_2$	K_2CO_3	40
10	$FeCl_3$	$Cu(acac)_2$	K_2CO_3	75
11	*$Fe(acac)_3$*	*$Cu(acac)_2$*	*K_2CO_3*	*94* (95,[c] trace[d])
12	$Fe(acac)_3$	Cu_2O	K_2CO_3	66
13	$Fe(acac)_3$	CuI	K_2CO_3	89
14	$Fe(acac)_3$	$CuCl_2$	K_2CO_3	83
15	$Fe(acac)_3$	$Cu(OAc)_2$	K_2CO_3	90
16	$Fe(acac)_3$	$Cu(acac)_2$	EtN_3	34 (0[e])
17	$Fe(acac)_3$	$Cu(acac)_2$	Pyridine	89
18	$Fe(acac)_3$	$Cu(acac)_2$	KOBu[t]	81
19	$Fe(acac)_3$	$Cu(acac)_2$	Cs_2CO_3	96
20	$Fe(acac)_3$	$Cu(acac)_2$	NaOH	72
21	$Fe(acac)_3$	$Cu(acac)_2$	K_2CO_3	55[f] (63,[g] 95,[h] 75[i])
22	$Fe(acac)_3$	$Cu(acac)_2$	K_2CO_3	89[j] (37[k])

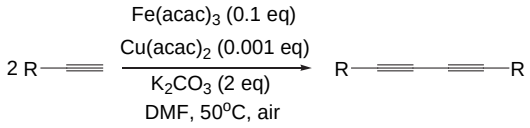
[a] Isolated yield.
[b] Acac=acetylacetone.
[c] Under O_2.
[d] Under N_2.
[e] Without base.
[f] Use of 0.001 equiv $Fe(acac)_3$ and 0.001 equiv $Cu(acac)_2$.
[g] Use of 0.01 equiv $Fe(acac)_3$ and 0.001 equiv $Cu(acac)_2$.
[h] Use of 0.2 equiv $Fe(acac)_3$ and 0.001 equiv $Cu(acac)_2$.
[i] Use of 1 equiv $Fe(acac)_3$ and 0.001 equiv $Cu(acac)_2$.
[j] 90 °C for 8 h.
[k] Room temperature for 24 h.

than K_2CO_3. Among various solvents examined, DMF turned out to be the best, whereas use of nonpolar (such as CH_2Cl_2 and THF) or nonprotic (such as acetone and benzene) resulted in more disappointing conversion. The reaction temperature and the load of catalyst were tested, the results showed using 10 mol % Fe $(acac)_3$+0.1 mol % $Cu(acac)_2$ as the co-catalyst at 50 °C was the best condition (entries 21 and 22).

Under the optimized condition, a wide range of terminal alkynes were successfully homo-coupled to afford the corresponding diynes (Table 2). As shown in Table 2, the catalytic system efficiently catalyzed homo-coupling reaction of terminal alkynes including aromatic and aliphatic acetylenes. The coupling reaction of terminal alkynes with electron-donating groups provided products in better yields than with electron-withdrawing groups (entries 1–9). Although taking longer reaction time, the homo-coupling reactions of various aliphatic acetylenes provided products in good yields (entries 10–14). Interestingly, expanding the procedure to heterocyclic acetylenes such as 3-thienylacetylene (entry 15) and ferrocenylacetylene (entry 16), the desired products were isolated in 87% and 64% yields, respectively.

In order to expend the application of this methodology, the Fe/Cu catalytic system was applied to the cross-coupling reaction of two different terminal alkynes.[10,12c] Initially, using equal amount of two different alkynes led to a lot of homo-coupling products of two alkynes rather than the cross-coupling product. When the excessive another alkyne (5.0 equiv) was used, the cross-coupling product was obtained. As shown in Table 3, under the optimized condition, several good yields of unsymmetric 1,3-diynes were obtained from the coupling two different aromatic terminal alkynes, while the corresponding homo-coupling products were

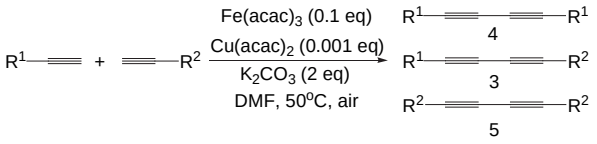
Table 2
Iron/copper co-catalyzed homo-coupling reaction of terminal alkynes[a]



Entry	R=	Time (h)	Yield[b] (%)
1	Ph	8	94
2	4-$CH_3C_6H_4$	8	86
3	4-$CH_3OC_6H_4$	8	88
4	4-*n*-$C_5H_{11}OC_6H_4$	8	91
5	3-$NH_2C_6H_4$	8	87
6	4-FC_6H_4	8	66
7	4-ClC_6H_4	8	67
8	2-ClC_6H_4	8	62
9	α-Naphthyl	8	90
10	*n*-C_4H_9	12	86
11	*n*-C_5H_{11}	12	89
12	2-OH-propyl	12	91
13	$ClCH_2$	12	49
14	$BrCH_2$	12	57
15	3-Thienyl	12	87
16	Ferrocenyl	12	64

[a] Reaction conditions: alkyne (1.0 mmol), $Fe(acac)_3$ (0.1 mmol), $Cu(acac)_2$ (0.001 mmol), K_2CO_3 (2.0 mmol), DMF (1 mL), 50 °C, under air.
[b] Isolated yield.

Table 3
Iron/copper co-catalyzed cross-coupling reaction of two different terminal alkynes[a]



Entry	R^1=	R^2=	Time (h)	Yield[b] for **3** (**4**/**5**) (%)
1	Ph	4-MeO-Ph	12	68 (87/8)
2	Ph	4-*n*-$C_5H_{11}O$-Ph	12	74 (85/5)
3	Ph	$OHCH_2$	12	45 (70/10)
4	Ph	2-OH-propyl	12	55 (65/8)
5	4-MeO-Ph	3-Thienyl	12	53 (72/8)
6	4-MeO-Ph	3-Me-Ph	12	70 (81/7)
7	*n*-C_4H_9	*n*-C_5H_{11}	24	Trace (84/80)
8	*n*-C_4H_9	2-OH-propyl	24	Trace (88/75)

[a] Reaction condition: R^1CCH (5.0 mmol), R^2CCH (1.0 mmol), $Fe(acac)_3$ (0.1 mmol), $Cu(acac)_2$ (0.001 mmol), K_2CO_3 (2.0 mmol), DMF (1 mL), 50 °C, under air.
[b] Isolated yield.

obtained unavoidably (Table 3, entries 1–6). Only using a trace amount of copper catalyst, trace yields of cross-coupling products were got. When using two different aliphatic terminal alkynes as the substrates, the outcomes were disappointing.

Noteworthy is that using phenyl iodide and phenylacetylene as the substrates under Fe/Cu catalytic system under N_2 rather than air, a largely cross-coupling product and trace homo-coupling product were obtained at this time (Fig. 1). Combining the experimental data above (Table 1, entry 11), it was found that O_2 influenced the reaction strongly and the iron catalyst could suppress the

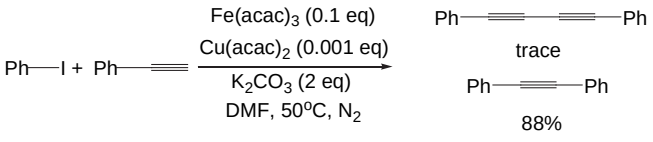


Figure 1. The Sonogashira-type reaction under N_2.

homo-coupling by-product in the Sonogashira-type reaction under N_2 and also could enhance the homo-coupling product in the homo-coupling reaction of terminal alkynes under air.[11c]

According to our results and a number of related literatures,[7,12,13] a possible mechanism for Fe/Cu co-catalyzed homo-coupling reaction of terminal acetylenes was proposed. With the aid of a base, the reaction of terminal acetylene with Cu $(acac)_2$ could afford intermediate copper acetylide readily.[6,7a] The next reductive elimination would release the homo-coupling product and generate Cu(I). Then Fe(III) could oxidize Cu (I) to generate Cu(II) and Fe(II). Iron catalyst might play a role of oxidant at this aspect. Finally, reduced Fe(II) was oxidized by terminal oxidant O_2 to regenerate the Fe(III) leading to a new catalytic cycle.

3. Conclusions

In conclusion, we have discovered an efficient, environmentally friendly and economical method for transforming same terminal acetylenes into 1,3-diynes and two different terminal alkynes into unsymmetric diynes in moderated to good yields and found that a trace amount of copper salt could influence the homo-coupling reactions obviously. The present procedure is mild, general, and tolerate of a variety of functional groups.

4. Experimental

4.1. General

All reactions were carried out under air. Solvents were dried and degassed by the standard methods and all alkynes are readily available. Fe and Cu salts were purchased from commercial suppliers and the purities >99.99%. Flash column chromatography was performed using silica gel (300–400 mesh). Analytical thin-layer chromatography was performed using glass plates pre-coated with 200–400 mesh silica gel impregnated with a fluorescent indicator (254 nm). NMR spectra were recorded in $CDCl_3$ on a Varian Inova-300 or 400 MHz NMR spectrometer with TMS as an internal reference. Products were characterized by comparison of ^1H NMR and ^{13}C NMR data with those in the literature.

4.2. Typical experimental procedure for the Fe/Cu co-catalyzed homo-coupling reaction (Table 2, entry 1)

To a stirred solution of phenylacetylene (4 mmol) in DMF (4 mL), $Fe(acac)_3$ (purity>99.99%) (0.4 mmol), $Cu(acac)_2$ (0.004 mmol), and K_2CO_3 (8 mmol) were added successively. The mixture was heated to 50 °C in air and stirred for indicated time. After cooling to room temperature, the mixture was diluted with ethyl acetate and filtered. The filtrate was removed under reduced pressure to get the crude product, which was further purified by silica gel chromatography (petroleum/ethyl acetate as eluent) to yield 1,4-diphenylbuta-1,3-diyne; white solid. ^1H NMR (300 MHz, $CDCl_3$): δ=7.53–7.51(d, J=7.4 Hz, 4H), 7.38–7.33(m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=132.4, 129.1, 128.4, 121.7, 81.5, 74.2.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2010.04.017.

References and notes

1. (a) Tour, J. M. *Chem. Rev.* **1996**, *96*, 537; (b) Martin, R. E.; Diederich, F. *Angew. Chem., Int. Ed.* **1999**, *38*, 1350.
2. (a) Bohlmann, F.; Burkhardt, T.; Zdero, C. In *Naturally Occurring Acetylenes*; Academic: New York, NY, 1973; (b) Jones, E. H. R.; Thaller, V. In *Handbook of Microbiology*; Laskin, A. I., Lechevalier, H. A., Eds.; CRC: Cleveland, 1973; Vol. 3, p 63; (c) Yamaguchi, M.; Park, H.-J.; Hirame, M.; Torisu, K.; Nakamura, S.; Minami, T.; Nishihara, H.; Hiraoka, T. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 1717.
3. (a) Viehe, H. G. *Chemistry of Acetylene*; Marcel Dekker: New York, NY, 1969; p 597; (b) Trahanovsky, W. S. *Oxidation in Organic Chemistry*; Academic: New York, NY, 1973; Vol. 5-B; (c) Hansen, L.; Boll, P. M. *Phytochemistry* **1986**, *25*, 285; (d) Kim, Y. S.; Jin, S. H.; Kim, S. L.; Hahn, D. R. *Arch. Pharm. Res.* **1989**, *12*, 207; (e) Matsunaga, H.; Katano, M.; Yamamoto, H.; Fujito, H.; Mori, M.; Tukata, K. *Chem. Pharm. Bull.* **1990**, *38*, 3480; (f) Hudlicky, M. *Oxidation in Organic Chemistry*. ACS Monograph 186; American Chemical Society: Washington, DC, 1990; p 58; (g) Sonogashira, k In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, UK, 1991; Vol. 3, p 551; (h) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079.
4. (a) Breitenbach, J.; Boosfeld, J.; Vögtle, F. In *Comprehensive Supramolecular Chemistry*; Vögtle, V., Ed.; Pergamon: Oxford, UK, 1996; Vol. 2; Chapter 2, pp 29–67; (b) Lehn, J.-M. In *Supramolecular Chemistry: Concepts and Perspectives*; VCH: Weinheim, 1995.
5. Hunstman, V. D. In *The Chemistry of the Carbon–Carbon Triple Bond*; Patai, S., Ed.; Wiley-Interscience: London, 1978; pp 553–620.
6. (a) Taylor, R. J. K. In *Organocopper Reagents: A Practical Approach*; Oxford University Press: New York, NY, 1994; (b) Glaser, C. *Ber. Dtsch. Chem. Ges.* **1869**, *2*, 422.
7. (a) Siemsen, P.; Livingston, R. C.; Diederich, F. *Angew. Chem., Int. Ed.* **2000**, *39*, 2632; (b) Batsanov, A. S.; Collings, J. C.; Fairlamb, I. J. S.; Holland, J. P.; Howard, J. A. K.; Lin, Z.; Marder, T. B.; Parsons, A. C.; Ward, R. M.; Zhu, J. *J. Org. Chem.* **2005**, *70*, 703; (c) Li, J.-H.; Liang, Y.; Xie, Y.-X. *J. Org. Chem.* **2005**, *70*, 4393; (d) Lei, A.; Srivastava, M.; Zhang, X. *J. Org. Chem.* **2002**, *67*, 1969; (e) Yang, F.; Cui, X.; Li, Y.-N.; Zhang, J.; Ren, G.-R.; Wu, Y. *Tetrahedron* **2007**, *63*, 1963; (f) Yang, J.; Wu, J.; Jin, H. *J. Organomet. Chem.* **2007**, *692*, 3636; (g) Li, J.-H.; Liang, Y.; Zhang, X.-D. *Tetrahedron* **2005**, *61*, 1903; (h) Fairlamb, I. J. S.; Bäuerlein, P. S.; Marrison, L. R.; Dickinson, J. M. *Chem. Commun.* **2003**, 632; (i) Damle, S. V.; Seomoon, D.; Lee, P. H. *J. Org. Chem.* **2003**, *68*, 7085; (j) Sin, M.; Qian, H.-X. *Appl. Organomet. Chem.* **2006**, *20*, 771; (k) Chalifoux, W. A.; Ferguson, M. J.; Tykwinski, R. R. *Eur. J. Org. Chem.* **2007**, 1001.
8. (a) Xian, H.; Wang, J.-H. *Synth. Commun.* **2000**, *30*, 9; (b) Kabalka, G. W.; Wang, L.; Pagin, R. M. *Synlett* **2001**, 108; (c) Zhu, B. C.; Jiang, X. Z. *Appl. Organomet. Chem.* **2007**, *21*, 345; (d) Kamata, K.; Yamaguchi, S.; Kotani, M.; Yamaguchi, K.; Mizuno, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 2407; (e) Yadav, J. S.; Reddy, B. V. S.; Reddy, K. B.; Gayathri, K. U.; Prasad, A. R. *Tetrahedron Lett.* **2003**, *44*, 6493; (f) Jiang, H.-F.; Tang, J.-Y.; Wang, A.-Z.; Deng, G.-H.; Yang, S.-R. *Synthesis* **2006**, 1155.
9. Li, D.; Yin, K.; Li, J.; Jia, X. *Tetrahedron Lett.* **2008**, *49*, 5918.
10. Wang, D.; Li, J.; Li, N.; Gao, T.; Hou, S.; Chen, B. *Green Chem.* **2010**, *12*, 45.
11. For recent works dealing with iron/copper-mediated coupling reaction, see: (a) Taillefer, M.; Xia, N.; Quali, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 934; (b) Volla, C. M. R.; Vogle, P. *Tetrahedron Lett.* **2008**, *49*, 5961; (c) Mao, J.; Xie, G.; Wu, M.; Guo, J.; Ji, S. *Adv. Synth. Catal.* **2008**, *305*, 2477; (d) Guo, D.; Huang, H.; Zhou, Y.; Xu, J.; Jiang, H.; Chen, K.; Liu, H. *Green. Chem.*, in press; (e) Buchwald, S. L.; Bolm, C. *Angew. Chem., Int. Ed.* **2009**, *48*, 5586.
12. (a) Punniyamurthy, T.; Velusamy, S.; Iqbal, J. *Chem. Rev.* **2005**, *105*, 2329; (b) Costas, M.; Mehn, M. P.; Jensen, M. P.; Que, L. *Chem. Rev.* **2004**, *104*, 939; (c) Yin, W.; He, C.; Chen, M.; Zhang, H.; Lei, A. *Org. Lett.* **2009**, *11*, 709.
13. Bohlmann, F.; Schoenowsky, H.; Inhoffen, E.; Grau, G. *Chem. Ber.* **1964**, *97*, 794.