

See discussions, stats, and author profiles for this publication at: <https://www.researchgate.net/publication/26284249>

ChemInform Abstract: Influence of Bases and Ligands on the Outcome of the Cu(I)-Catalyzed Oxidative Homocoupling of Terminal Alkynes to 1,4-Disubstituted 1,3-Diynes Using Oxygen as...

ARTICLE in THE JOURNAL OF ORGANIC CHEMISTRY · JULY 2009

Impact Factor: 4.72 · DOI: 10.1021/jo900246z · Source: PubMed

CITATIONS

83

READS

57

3 AUTHORS:



Adimurthy Subbarayappa

Central Salt and Marine Chemicals Research ...

74 PUBLICATIONS 946 CITATIONS

SEE PROFILE



Chandi C Malakar

National Institute of Technology, Manipur

25 PUBLICATIONS 278 CITATIONS

SEE PROFILE



Uwe Beifuss

Hohenheim University

230 PUBLICATIONS 3,754 CITATIONS

SEE PROFILE

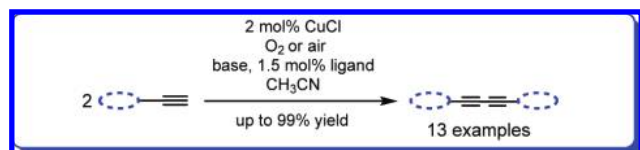
Influence of Bases and Ligands on the Outcome of the Cu(I)-Catalyzed Oxidative Homocoupling of Terminal Alkynes to 1,4-Disubstituted 1,3-Diynes Using Oxygen as an Oxidant

Subbarayappa Adimurthy,[†] Chandi C. Malakar,[‡] and Uwe Beifuss^{*‡}

[†]Central Salt & Marine Chemicals Research Institute, Gijubhai Badheka Marg, Bhavnagar 364 002, Gujrat, India, and [‡]Bioorganische Chemie, Institut für Chemie, Universität Hohenheim, Garbenstr. 30, D-70599 Stuttgart, Germany

ubeifuss@uni-hohenheim.de

Received February 10, 2009



The efficient Cu(I)-catalyzed oxidative homocoupling of terminal alkynes in the presence of a base using an amine as a ligand and oxygen as an oxidant yields the symmetrical 1,3-diynes with yields of up to 99%. The outcome of the couplings critically depends on the proper choice of base and ligand as well as reaction conditions. Best results were observed with 2.0 mol % CuCl, 1.5 mol % TMEDA or DBEDA, and DBU or DABCO in acetonitrile.

The dimerization of terminal alkynes through oxidative homocoupling to give 1,3-diynes is an important C–C bond-formation reaction.¹ It has been employed for a number of applications, including the construction of linear π -conjugated acetylenic oligomers and polymers,² the synthesis of natural products,³ and molecular recognition processes.⁴ The reaction dates back to 1869 when C. Glaser observed the formation of a precipitate upon the reaction of a terminal alkyne with a Cu(I) salt in the presence of aqueous ammonia; after air oxidation the oxidative homocoupling product was isolated.⁵ A number of improvements of the original method have emerged, including the Eglinton procedure (which

allows the reaction to be run under homogeneous conditions)⁶ and Hay's procedure, which relies on the use of catalytic amounts of Cu(I) salt as a catalyst, tertiary amines such as pyridine or *N,N,N',N'*-tetramethylethylenediamine (TMEDA) as complexing agents, and O₂ as an oxidant.⁷ Other methods for the synthesis of 1,4-disubstituted 1,3-diynes include the Cadiot–Chodkiewicz⁸ and the Sonogashira⁹ couplings. Recently, it has been shown that the oxidative homocoupling of terminal alkynes can be accomplished by a combination of a Pd catalyst and a Cu(I) salt.¹⁰ Even if the Pd-catalyzed reactions are highly efficient and proceed under mild reaction conditions, the Pd catalysts are far more expensive than the cheap and easily available Cu(I) salts. Another disadvantage of many of these protocols is that oxidants other than O₂ need to be used for the reoxidation of Pd(0) to Pd(II).^{10a–10c,10f} Finally, with some of the Pd-catalyzed systems the formation of the desired homocoupling products is accompanied by the formation of side products such as enynes. In addition, the Cu(II)-catalyzed homocoupling reaction of terminal alkynes in supercritical CO₂ has been reported.¹¹ This protocol requires special equipment and high CO₂ pressure at elevated temperatures. Using CuAl-hydrotalcite as a catalyst, an additional step for the preparation of the reagent is needed.¹²

The further development of the Cu(I) salt catalyzed coupling using O₂ as an oxidant appeared to be the most attractive approach in order to meet the demand for high yields and high selectivities, simple experimental procedures under mild reaction conditions, avoidance of expensive and/or harmful reagents, and use of O₂ as an environmentally benign oxidant. Quite unexpectedly we found that only a few experiments have so far been published on the influence of ligands, bases, and reaction conditions on the outcome of this type of coupling. Brandsma mentioned that the yields of the homocoupling of terminal alkynes can be increased by adding small amounts of 1,8-diazabicycloundec-7-ene (DBU).¹³ However, a detailed study of the influence of bases is missing. The same holds true for the influence of ligands.

(7) Hay, A. S. *J. Org. Chem.* **1960**, *25*, 1275. Hay, A. S. *J. Org. Chem.* **1962**, *27*, 3320.

(8) Cadiot, P.; Chodkiewicz, W. In *Chemistry of Acetylenes*; Viehe, H. G., Ed.; Marcel Dekker: New York, 1969; p 597.

(9) (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467. (b) For a review, see: Sonogashira, K. Coupling reactions between sp carbon centers. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1990; Vol. 3, p 521.

(10) (a) Rossi, R.; Carpita, A.; Bigelli, C. *Tetrahedron Lett.* **1985**, *26*, 523. (b) Liu, Q.; Burton, D. J. *Tetrahedron Lett.* **1997**, *38*, 4371. (c) Lei, A.; Srivastava, M.; Zhang, X. *J. Org. Chem.* **2002**, *67*, 1969. (d) Fairlamb, I. J. S.; Bäuerlein, P. S.; Marrison, L. R.; Dickinson, J. M. *Chem. Commun.* **2003**, 632. (e) 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. (f) Li, J.-H.; Liang, Y.; Zhang, X.-D. *Tetrahedron* **2005**, *61*, 1903. (g) Li, J. H.; Liang, Y.; Xie, Y.-X. *J. Org. Chem.* **2005**, *70*, 4393. (h) Shi, M.; Qian, H. X. *Appl. Organomet. Chem.* **2006**, *20*, 771. (i) Yang, F.; Cui, X.; Li, Y.; Zhang, J.; Ren, G.; Wu, Y. *Tetrahedron* **2007**, *63*, 1963.

(11) Li, J.; Jiang, H. *Chem. Commun.* **1999**, 2369. Jiang, H.-F.; Tang, J.-Y.; Wang, A.-Z.; Deng, G.-H.; Yang, S.-R. *Synthesis* **2006**, 1155.

(12) Zhu, B. C.; Jiang, X. Z. *Appl. Organomet. Chem.* **2007**, *21*, 345.

(13) Brandsma, L. *Preparative Acetylenic Chemistry*; Elsevier: Amsterdam, 1988; Chapter 10.

(1) For a review, see: Siemsen, P.; Livingston, R. C.; Diederich, F. *Angew. Chem., Int. Ed.* **2000**, *39*, 2632.

(2) Tour, J. M. *Chem. Rev.* **1996**, *96*, 537. Martin, R. E.; Diederich, F. *Angew. Chem., Int. Ed.* **1999**, *38*, 1350.

(3) For reviews, see: Shi Shun, A. L. K.; Tykwinski, R. R. *Angew. Chem., Int. Ed.* **2006**, *45*, 1034. Bohlmann, F.; Burkhardt, T.; Zdero, C. *Naturally Occurring Acetylenes*; Academic Press: New York, 1973.

(4) Lehn, J. M. *Supramolecular Chemistry: Concepts and Perspectives*; VCH: Weinheim, 1995.

(5) Glaser, C. *Ber. Dtsch. Chem. Ges.* **1869**, *2*, 422.

(6) Eglinton, G.; Galbraith, R. *J. Chem. Soc.* **1959**, 889.

This is why we decided to perform experiments toward this end.

Here we report on the effect of different bases and amines on the yields of the CuCl-catalyzed homocouplings of terminal alkynes with O₂ as an oxidant. The careful choice of base, ligand, solvent, and reaction conditions enabled us to develop convenient protocols that allow for the efficient reaction of both aryl- and alkyl-substituted terminal alkynes to give the corresponding 1,4-disubstituted 1,3-diyne with high yields.

Our initial studies focused on the development of an optimum set of reaction conditions for the homocoupling reaction of phenylacetylene (**1a**) using CuCl as a catalyst and TMEDA as a ligand. Some preliminary studies revealed that best results were obtained when the couplings were run with 2 mol % CuCl, 1.5 mol % TMEDA, and CH₃CN as the solvent at rt. Using this CuCl/TMEDA system, the effect of bases was studied. The results with different bases in different concentrations are summarized in Table 1. First, a control experiment without any additional base was performed. Under these conditions **2a** was obtained with a yield of merely 37% (Table 1, entry 1). After some disappointing experiments with inorganic bases such as K₂CO₃, and Cs₂CO₃ (Table 1, entries 2, 3) and diisopropylamine (DIPA) (Table 1, entry 4), the reaction was carried out with triethylamine (TEA) (Table 1, entry 5), diisopropylethylamine (DIPEA) (Table 1, entries 6, 7), *N*-methylpyrrolidine (NMP) (Table 1, entries 8, 9), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (Table 1, entries 10–14), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) (Table 1, entries 15, 16), 1,4-diazabicyclo[2.2.2]octane (DABCO) (Table 1, entries 17, 18), and 1,5-naphthylidine (Table 1, entries 19–21).

The results clearly show that the CuCl/TMEDA system can successfully be used in combination with many bases. The best results, however, were obtained with sterically hindered amine bases such as DBU and DABCO. Using these bases **2a** was isolated in yields of 99% and 97%, respectively (Table 1, entries 14, 18). To study the influence of the base concentration, the reaction with DBU was chosen as an example. The results indicate that the reaction can be performed in the presence of as little as 6.25 mol % and still yields 79% of **2a** (Table 1, entry 10). A gradual increase in the amount of DBU from 6.25 to 33 mol % leads to an increase in yields from 79% to 91% (Table 1, entries 10–13). From our experience the best compromise between base concentration and yield could be achieved with 12.5 mol % of DBU; this is why additional couplings with some of the other bases were performed at a concentration of 12.5 mol %. The results clearly indicate that DBU is superior to the other bases. Therefore most of the following experiments were carried out with DBU.

In all experiments described so far O₂ was bubbled through the reaction mixture. It was also possible to perform the reactions in static O₂ atmosphere. If the coupling of **1a** with 2 mol % CuCl, 1.5 mol % TMEDA, 100 mol % DBU, and 2 mL of CH₃CN was performed using a balloon filled with O₂ at rt for 18 h, the yield of **2a** amounted to 98%. It is worth mentioning that the amount of CH₃CN could be reduced from 10 to 2 mL under these conditions. A comparable yield of **2a** (97%) was observed when the balloon was filled with air (2 mol % CuCl, 1.5 mol % TMEDA, 100 mol % DBU, 2 mL of CH₃CN, rt, 24 h) instead of O₂.

TABLE 1. Effect of Bases on Oxidative Dimerization of **1a** Using a CuCl/TMEDA Catalytic System and O₂ as Oxidant^a

entry	base (mol %)	time (h)	yield (%) ^b
1		24	37
2	K ₂ CO ₃ (300)	6	46
3	Cs ₂ CO ₃ (120)	12	20
4	DIPA (210)	6	53
5	TEA (100)	12	74
6	DIPEA (100)	24	90
7	DIPEA (12.5)	24	80
8	NMP (12.5)	18	79
9	NMP (100)	24	84
10	DBU (6.25)	36	79
11	DBU (12.5)	24	87
12	DBU (25)	20	89
13	DBU (33)	18	91
14	DBU (100)	18	99
15	DBN (12.5)	24	66
16	DBN (100)	24	88
17	DABCO (12.5)	16	77
18	DABCO (100)	24	97
19	1,5-naphthylidine (12.5)	24	36
20	1,5-naphthylidine (50)	24	60
21	1,5-naphthylidine (100)	24	73

^aReaction conditions: **1a** (2.0 mmol), CuCl (2.0 mol %), O₂, base, TMEDA (1.5 mol %), CH₃CN (10 mL), r.t. ^bYields are not optimized.

TABLE 2. Ligand Screening for the Oxidative Dimerization of **1a**^a

entry	ligand	DBU (mol %)	time (h)	yield (%) ^b
1		100	24	55
2	TMEDA	12.5	24	87
3	1,5- <i>cis</i> -diazadecalin	12.5	24	74
4	DCU	12.5	24	65
5	DBEDA	12.5	15	91
6	Salen	12.5	24	72

^aReaction conditions: **1a** (2.0 mmol), CuCl (2.0 mol %), O₂, base, ligand (1.5 mol %), CH₃CN (10 mL), r.t. ^bYields are not optimized.

The yield of **2a** dropped to 87% when only 1 mL of CH₃CN was used (2 mol % CuCl, 1.5 mol % TMEDA, 100 mol % DBU, O₂ balloon, rt, 20 h).

The effect of the ligand could clearly be demonstrated when the coupling of **1a** was run with 1 equiv of DBU in the absence of a ligand; under these conditions the yield of **2a** dropped to 55% (Table 2, entry 1). To identify the most effective ligand, the dimerization of **1a** was run in the presence of 12.5 mol % DBU and 1.5 mol % of different ligands, including TMEDA, 1,5-*cis*-diazadecalin, *N,N'*-dicyclohexylurea (DCU), *N,N'*-dibenzylethylenediamine (DBEDA), and *N,N'*-bis(salicylidene)ethylenediamine (Salen); the results are summarized in Table 2. It turned out that DBEDA (91% yield of **2a**) was the best choice (Table 2, entry 5), followed by TMEDA (87% yield of **2a**) (Table 2, entry 2). Lower yields of **2a** were obtained with

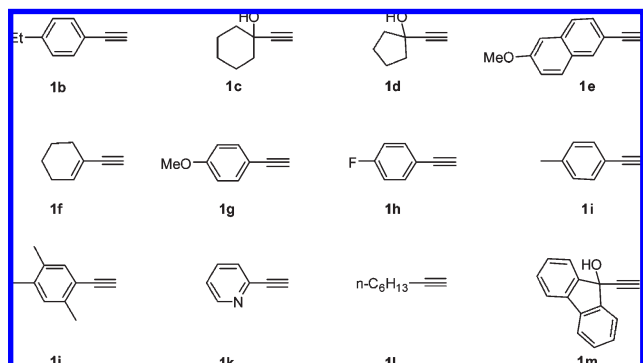


FIGURE 1. Terminal alkynes **1b–m** used for the oxidative homocoupling.

1,5-*cis*-diazadecalin, DCU, and Salen (Table 2, entries 3, 4, 6). Despite the higher yields obtained with DBEDA, the cheaper TMEDA was chosen for the following experiments.

To demonstrate the efficiency and to explore the scope of the CuCl/DBU/TMEDA catalytic system for the synthesis of symmetrical 1,3-diynes, a number of terminal alkynes (Figure 1) were homocoupled using 2 mol % CuCl, 1.5 mol % TMEDA, 1 equiv of DBU, and O₂ as an oxidant. In addition, the transformations were also studied with 12.5 mol % DBU. The results are given in Table 3.

Under the conditions mentioned the reactions proceeded smoothly and delivered the diynes with yields ranging from 55% to 99% when 1 equiv of DBU was used. In 8 out of 10 cases the yields exceeded 90%. When only 12.5 mol % of DBU was employed, the yields ranged between 34% and 97%. It is obvious that alkenyl, hydroxyl, fluoride, and ether groups are not affected under the reaction conditions. The transformations proceeded without any side product formation, except with 9-ethynyl-9-fluorenone (**1m**) (Table 3, entries 23–25), where considerable amounts of fluorene-9-one were isolated. This may be due to cleavage of the sp³–sp C–C bond in the starting material followed by oxidation to give fluorenone. The amount of fluorene-9-one could be reduced from 33% to 11% when the reaction temperature was decreased from rt to 0 °C.

The advantages of our protocol include the use of commercially available and cheap CuCl (2 mol %), bases (1 equiv), and amines (1.5 mol %), the exclusive use of O₂ as an oxidant, a simple experimental setup, mild reaction conditions, a simple workup, high yields, and no contamination of the product with enynes. In our protocol there is no need for the extra preparation of special Cu catalysts such as CuAl-hydrotalcites;¹² for an additional Pd catalyst such as Pd(PPh₃)₄,^{10a} PdCl₂(PPh₃)₂,^{10b–10e} PdCl₂,^{10f} Pd(OAc)₂,^{10g} an *N*-heterocyclic carbene-Pd(II) complex^{10h} or cyclopalladated ferrocenylimine;¹⁰ⁱ for additional stoichiometric oxidants such as ClCH₂COCH₃,^{10a} I₂,^{10b} BrCH₂CO₂Et^{10c} or Me₃NO·2H₂O;^{10f} for a large excess of bases;^{10b,10d–10g} or for additional phosphines such as PPh₃.^{10d,10e}

The results of the coupling of the alkyl-substituted alkyne **1l** were unsatisfactory since **2l** was obtained in yields of no more than 55% or 37% (Table 3, entries 21, 22). The low reactivity of **1l** is probably due to its weak acidity; this phenomenon is well-known for homocouplings of alkyl-substituted alkynes.¹³ To increase the yield of **2l** the homocoupling of **1l** was carried out with several base/ligand

TABLE 3. Oxidative Homocoupling of Terminal Alkynes^a

$2 \text{ R-C}\equiv\text{C-H} \xrightarrow[\text{CH}_3\text{CN}]{\text{2 mol\% CuCl, O}_2, \text{DBU, 1.5 mol\% TMEDA}} \text{R-C}\equiv\text{C-C}\equiv\text{C-R}$						
entry	1	base (mol %)	temp (°C)	time (h)	2	yield (%) ^b
1	b	DBU (100)	24	24	b	99
2		DBU (12.5)	24	36		97
3	c	DBU (100)	24	24	c	99
4		DBU (12.5)	24	36		87
5	d	DBU (100)	24	24	d	97
6		DBU (12.5)	24	36		83
7	e	DBU (100)	24	36	e	90
8		DBU (12.5)	24	36		61
9	f	DBU (100)	24	24	f	72
10		DBU (12.5)	24	36		34
11	g	DBU (100)	24	28	g	93
12		DBU (12.5)	24	36		69
13	h	DBU (100)	24	6	h	97
14		DBU (12.5)	24	36		89
15	i	DBU (100)	24	12	i	94
16		DBU (12.5)	24	36		87
17	j	DBU (100)	24	24	j	92
18		DBU (12.5)	24	36		66
19	k	DBU (12.5)	5	36	k	54
20		DBU (12.5)	0	24		75
21	l	DBU (100)	24	6	l	55
22		DBU (12.5)	24	36		37
23	m	DBU (12.5)	24	24	m	58 ^c
24		DBU (12.5)	5	30		70 ^d
25		DBU (12.5)	0	36		70 ^e

^a Reaction conditions: **1b–m** (2.0 mmol), CuCl (2.0 mol %), O₂, base, TMEDA (1.5 mol %), CH₃CN (10 mL). ^b Yields are not optimized. ^c 33% fluorenone was obtained. ^d 14% fluorenone was obtained. ^e 11% fluorenone was obtained.

TABLE 4. Base and Ligand Screening for the Homocoupling of *n*-Octyne (**1l**)^a

$2 \text{ n-C}_6\text{H}_{13}\text{-C}\equiv\text{C-H} \xrightarrow[\text{CH}_3\text{CN, r.t.}]{\text{2 mol\% CuCl, O}_2, \text{base, ligand}} \text{n-C}_6\text{H}_{13}\text{-C}\equiv\text{C-C}\equiv\text{C-n-C}_6\text{H}_{13}$				
entry	base (mol %)	ligand (mol %)	time (h)	yield (%) ^b
1	DBU (100)	TMEDA (1.5)	6	55
2	DBU (12.5)	TMEDA (1.5)	36	37
3	DBU (100)	DBEDA (1.5)	18	44
4	DBU (12.5)	DBEDA (1.5)	18	20
5	DBU (12.5)	DBEDA (5.0)	16	58
6	DABCO (12.5)	TMEDA (1.5)	16	46
7	DABCO (100)	TMEDA (1.5)	18	71
8	DABCO (12.5)	DBEDA (1.5)	18	51
9	DABCO (100)	DBEDA (1.5)	18	61

^a Reaction conditions: **1l** (5.0 mmol), CuCl (2.0 mol %), O₂, base, ligand, CH₃CN (15 mL). ^b Yields are not optimized.

combinations (Table 4). It turned out that the yield of **2l** could be raised to 71% when the coupling was performed with a combination of DABCO (100 mol %) and TMEDA (1.5 mol %) (Table 4, entry 7).

In conclusion, we have developed a mild and efficient synthetic protocol for the catalytic oxidative homocoupling of terminal alkynes by optimizing reagents and reaction conditions. For most alkynes the CuCl/DBU/TMEDA catalytic system proved to be successful; for less acidic alkynes

the CuCl/DABCO/TMEDA catalytic system was found to be the most suitable combination. Our protocols differ from others in that the reactions can be easily performed, all reagents are commercially available, cheap O₂ can be used as an oxidant, and in most cases a single product can be isolated in very high yields without any side product formation.

Experimental Section

General Procedure for Homocoupling of Alkynes 2 (2j as Example). DBU (304 mg, 2.0 mmol), TMEDA (3.5 mg, 0.03 mmol, 1.5 mol %), and CuCl (4 mg, 0.04 mmol, 2.0 mol %) were added at 24 °C under stirring to 10 mL of acetonitrile while oxygen was bubbled through the solution. After 10 min 286 mg (2.0 mmol) of 2,4,5-trimethyl phenylacetylene (**1j**) was added. The reaction mixture was stirred at 24 °C while oxygen was bubbled through the solution for 24 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was removed under reduced pressure and the crude product obtained was purified by column

chromatography over silica gel (ethyl acetate/hexane = 1: 9) to afford **2j** (263 mg, 92% yield) as a white solid.

1,4-Bis(2,4,5-trimethylphenyl)buta-1,3-diyne (2j). Mp 232–233 °C. IR (ATR): ν 2918 cm⁻¹, 2140, 1485, 1452, 1377, 1256, 1022, 1000, 879. ¹H NMR (CDCl₃): δ (ppm) 7.30 (brs, 2H), 7.01 (brs, 2H), 2.45 (s, 6H), 2.27 (s, 6H), 2.23 (s, 6H). ¹³C NMR (CDCl₃): δ (ppm) 139.2, 138.3, 134.1, 134.0, 131.2, 119.2, 81.4, 77.0, 20.4, 20.0, 19.3. MS (EI, 70 eV): m/z (%) 286 (100) [M⁺], 271 (23), 256 (43), 239 (14), 143 (15), 128 (14). HRMS (EI, M⁺) calcd for C₂₂H₂₂: 286.1722, found 286.1757.

Acknowledgment. S.A. is grateful to the Department of Science & Technology, Govt. of India, New Delhi, for the award of a BOYSCAST fellowship (SR/BY/C-05/06) for the year 2006-07. We thank Ms. S. Mika and Dr. J. Conrad for NMR spectra and Dipl.-Chem. F. Mert-Balci and Dr. H. Leutbecher for mass spectra.

Supporting Information Available: Detailed spectroscopic data for diynes **2**. This material is available free of charge via the Internet at <http://pubs.acs.org>.