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Copper-Catalyzed Oxidative Transformation of Aryl Propargylic Azides to Aryl Propiolonitriles

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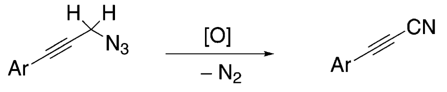
Abstract: A concise copper(I)-catalyzed oxidative transformation of aryl propargyl azides to aryl propiolonitriles has been developed. Aryl propiolonitrile derivatives can be obtained in moderate to good yields by this strategy. An oxidative Schmidt rearrangement is involved in this transformation.

Keywords: azides; copper; dehydrogenation; nitriles; oxidation; Schmidt rearrangement

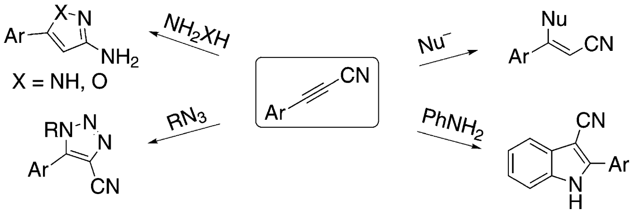
Aryl propiolonitriles have been identified in many cases as versatile building blocks (Scheme 1).[1] Many functionalized derivatives based on them have intriguing chemical and biological activities. Their importance in synthesis has encouraged organic chemists to develop new synthetic methods to prepare these compounds.[2] In general, many elegant protocols for producing nitriles have been established to date,[3] in which toxic cyanide salts or harsh conditions are often required. Although much progess has been made in the exploration of nitrogen resources,[4–7] it is still highly desirable to develop new approaches to aryl propiolonitriles from simple starting materials.

Recently, a series of concise and economical transformations for the synthesis of nitriles utilizing azide compounds as nitrogen resources *via* a benzyl or allyl azide intermediate has been achieved.[8] However, to the best of our knowledge, the direct approach to aryl propiolonitriles has not been realized yet. According to these reported processes, primary azides as the key intermediates underwent an analogous oxidative rearrangement to produce nitriles. Thus, the central issue is the selection of the proper oxidative system with azide precursors. Herein we demonstrate a novel approach to aryl propiolonitriles from aryl propargyl azides [Eq. (1)].



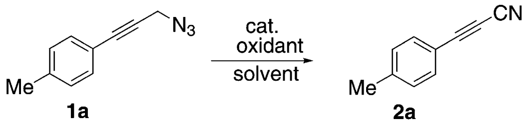
(1)

Our research was commenced with the oxidative rearrangement of the easily prepared 1-(3-azidoprop-1-ynyl)-4-methylbenzene **1a** (Table 1). When the reaction was carried out with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in the presence of $FeCl_2$, the desired 3-*p*-tolylpropiolonitrile **2a** was obtained in 22% yield (entry 1).[9] Subsequently, a variety of oxidants such as ceric ammonium nitrate (CAN), phenyliodonium diacetate (PIDA), potassium peroxomonosulfate (Oxone) and molecular oxygen, were investigated (entries 2 to 5). However, no product was detected. To our delight, **2a** was obtained in 71% yield in the presence of 5 mol% $(CuOTf)_2{\cdot}PhMe$ using *tert*-butyl hydroperoxide (TBHP) as an oxidant (entry 6). Other copper and iron salts exhibited lower efficiency than $(CuOTf)_2{\cdot}PhMe$ as the catalyst (entries 8 to 13).[10] Only a trace amount of **2a** was detected by GC in the absence of catalyst (entry 14), illustrating that the copper salt plays an important role in the catalytic oxidative rearrangement.



Scheme 1. Applications of aryl propiolonitriles.

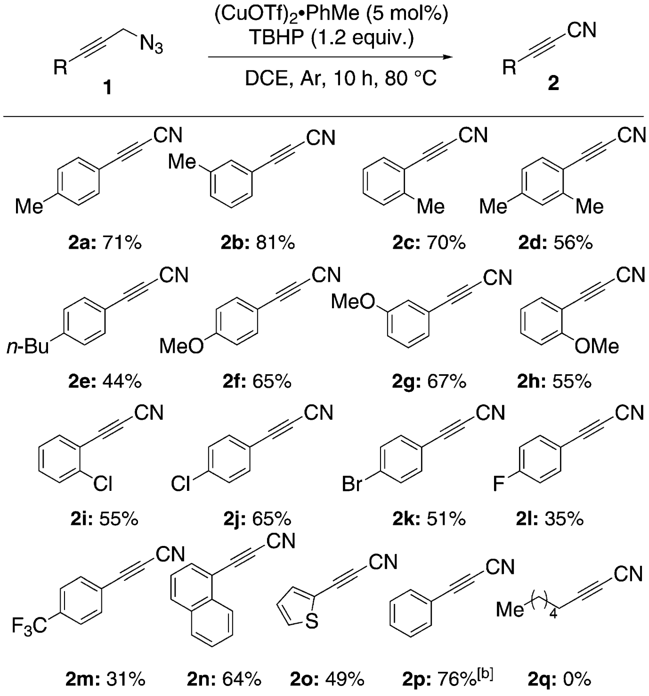
Table 1. Optimation of the transformation of aryl propargylic azides **1a** to aryl propiolonitriles **2a**.[a]



Entry	Catalyst (mol%)	Oxidant (equiv.)	Solvent (Temperature [ϒC])	Time [h]	Yield of **2a** [%][b]
1	$FeCl_2$ (10)	DDQ (2.0)	DCE (60)	8	22
2	--	CAN (2.0)	MeCN (60)	8	N.R.
3	--	PIDA (2.0)	MeCN (60)	8	N.R.
4	--	Oxone (2.0)	DCE (60)	8	N.R.
5[c]	$(CuOTf)_2$ (5)	O_2 balloon	DCE (80)	12	N.R.
6[c]	**$(CuOTf)_2$ (5)**	**TBHP (1.2)**	**DCE (80)**	**10**	**71**
7[c]	$(CuOTf)_2$ (5)	TBHP (1.2)	PhCl (80)	10	61
8	CuI (5)	TBHP (1.2)	DCE (80)	12	29
9	CuI (5)	TBHP (2.5)	H_2O (100)	2	31
10	CuCl (20)	TBHP (1.2)	DCE (80)	12	41
11	CuBr (10)	TBHP (1.2)	DCE (80)	12	41
12	CuCN (10)	TBHP (1.2)	DCE (80)	12	43
13	$FeCl_2$ (10)	TBHP (1.2)	DCE (80)	8	42
14	--	TBHP (1.2)	DCE (80)	12	trace

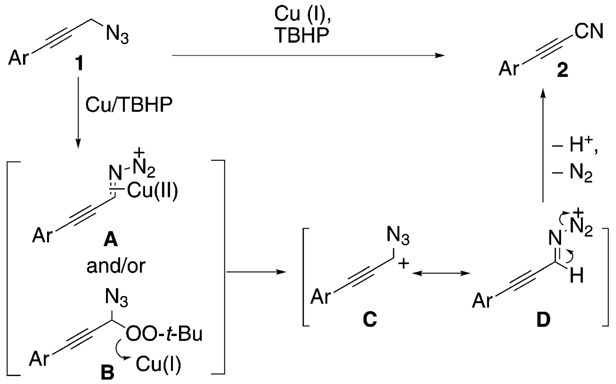
[a] *Reaction conditions:* **1a** (0.2 mmol), catalyst and oxidant in dry solvent (2 mL), stirred under Ar for 10 h.
[b] Isolated yield.
[c] $(CuOTf)_2$ stands for $(CuOTf)_2 \cdot PhMe$.

Table 2. The conversion from aryl propargylic azides **1** to aryl propiolonitriles **2**.[a]



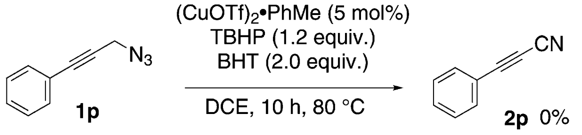
[a] *Reaction conditions:* **1** (0.2 mmol), $(CuOTf)_2 \cdot PhMe$ (0.01 mmol) and TBHP (0.24 mmol) in DCE (2 mL) at 80 °C under argon, 10 h. Yields are of the isolated products.
[b] The reaction was carried out on a 1 mmol scale.

With the optimized conditions in hand, the scope of substrates was investigated (Table 2). Aryl propargyl azides containing electron-donating groups at the aryl ring worked well under these conditions, producing the corresponding propiolonitriles **2** in moderate to good yields (**2a** to **2h**, Scheme 2). Aryl propiolonitriles bearing electron-withdrawing groups could also be obtained (**2l** and **2m**). The position of the substituents (*para*-, *meta*-, and *ortho*-positions) did not affect the efficiencies (**2a** to **2c**). Substrates containing halogenated arenes also are tolerated in this transformation under the standard conditions (**2i** to **2l**), which provided the possibility to carry out subsequent transformations. Notably, 1-(3-azidoprop-1-ynyl)-naphthalene **1n** gave **2n** in 64% yield. Heterocyclic substrates like **1o** exhibited reactivity in this transformation (49%, **2o**). A scale up run at 1 mmol was carried out to produce **2p** in 76% yield. Unfortunately, alkyl propiolonitriles could not be obtained under these conditions (**2q**).

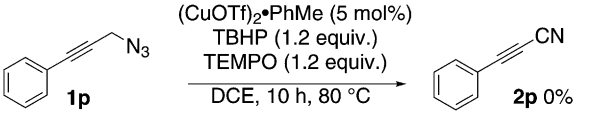


Scheme 2. Proposed mechanism for the transformation.

To probe the mechanism of this oxidative rearrangement, several control reactions were investigated. The reaction in the presence of 2.0 equivalents of 2,6-di-*tert*-butyl-4-methylphenol (BHT) as the radical scavenger, did not afford the desired product **2a**, although the starting material was consumed completely [Eq. (2)].[11] Moreover, the attempt to trap the possible radical intermediates with 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) failed [Eq. (3)]. Neither the desired product **2p** nor the TEMPO adduct was observed as expected. These results demonstrate that



(2)



(3)

the formation of products **2** can be inhibited by radical species under these oxidative conditions. Therefore, a single-electron transfer (SET) process may be involved in the transformation.[12]

Although the mechanism is not completely clear yet, a plausible pathway is proposed (Scheme 2) on the basis of the literature and the above mechanistic studies. A single electron transfer (SET) process is involved in this transformation through the Cu/TBHP catalytic system with the generation of *tert*-butoxyl radicals.[13] Two types of possible intermediates are likely generated by this Cu/TBHP catalysis.[14] Neither the copper coordinated imines **A** nor the peroxides **B** can be excluded.[13,14] Both of the intermediates can be converted into propargylic cations **C**,[15] which could be resonated with intermediates **D**. Finally, **D** undergoes a Schmidt rearrangement,[8,16] to give desired product **2** driven by losing a proton and releasing molecular nitrogen.

In conclusion, a transformation from aryl propargyl azides to aryl propiolonitriles catalyzed by copper(I) salts has been developed. A series of substrates was investigated and gave the desired products in moderate to good yields. The control reactions demonstrate that the copper catalyst is essential to the transformation *via* a SET process. Further studies on the mechanism and applications of this reaction are ongoing in our laboratory.

Experimental Section

Typical Procedure: 3-(*p*-Tolyl) Propiolonitrile (2a)

The solution of 1-(3-azidoprop-1-yn-1-yl)-4-methylbenzene **1a** (34.3 mg, 0.2 mmol) in DCE (2.0 mL) was added to a 25-mL Schlenk tube containing $(CuOTf)_2 \cdot PhMe$ (5.2 mg, 0.01 mmol) under argon. Then TBHP in decane (5.5 M, 43.6 μL, 0.24 mmol) was added to the stirred mixture. The reaction was conducted at 80 °C for 10 h. The crude product was purified by flash column chromatography on silica gel (eluent: petroleum ether/dichloromethane = 10:1) to afford **2a** as a solid; yield: 20.1 mg (71%). ^{1}H NMR: ($CDCl_3$, 400 MHz): $\delta = 7.50$ (d, $J = 8.1$ Hz, 2H), 7.21 (d, $J = 8.1$ Hz, 2H), 2.40 (s, 3H); ^{13}C NMR: (100 MHz, $CDCl_3$) $\delta = 142.8$, 133.4, 129.6, 114.4, 105.6, 83.5, 62.7, 21.8; IR (KBr): $\nu_{max} =$ 2926, 2266, 786, 686 cm^{-1}; MS (70 eV): $m/z = 141.1$ [M]$^+$.

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References

[1] a) M. Lazennec, *Bull. Soc. Chim. Fr.* **1906**, *3*, 526; b) I. Iwai, N. Nakamura, *Chem. Pharm. Bull.* **1966**, *14*, 1277; c) Z. Tanee Fomum, P. Forsche Asobo, S. R. Landor, P. D. Landor, *J. Chem. Soc. Perkin Trans. 1* **1984**, *5*, 1079; d) N. E. Heard, J. Turner, *J. Org. Chem.* **1995**, *60*, 4302; e) V. V. V. N. S. Rama Rao, B. P. V. Lingaiah, G. Ezikiel, R. Yadla, P. S. Rao, *Heterocycl. Commun.* **2006**, *12*, 275; f) Z.-Y. Cheng, W.-J. Li, F. He, J.-M. Zhou, X.-F. Zhu, *Bioorg. Med. Chem.* **2007**, *15*, 1533; g) Z. Shi, C. Zhang, S. Li, D. Pan, S. Ding, Y. Cui, N. Jiao, *Angew. Chem.* **2009**, *121*, 4642; *Angew. Chem. Int. Ed.* **2009**, *48*, 4572.

[2] For selected examples, see: a) R. E. Murray, G. Zweifel, *Synthesis* **1980**, 150; b) B. Merah, F. Texier, *Bull. Soc. Chim. Fr.* **1980**, 552; c) E. M. Beccalli, A. Manfredi, A. Marchesini, *J. Org. Chem.* **1985**, *50*, 2372; d) F.-T. Luo, R.-T. Wang, *Tetrahedron Lett.* **1993**, *34*, 5911; e) Y.-Q. Wu, D. C. Limburg, D. E. Wilkinson, G. S. Hamilton, *Org. Lett.* **2000**, *2*, 795.

[3] Synthesis of nitriles by Sandmeyer and transition-metal-mediated cyanation. For reviews, see: a) G. A. Ellis, T. M. Romney-Alexander, *Chem. Rev.* **1987**, *87*, 779; b) V. V. Grushin, H. Alper, *Chem. Rev.* **1994**, *94*, 1047; c) C. Galli, *Chem. Rev.* **1988**, *88*, 765; for some recent examples, see: d) T. Schareina, A. Zapf, M. Beller, *Chem. Commun.* **2004**, 1388; e) C. Yang, J. M. Williams, *Org. Lett.* **2004**, *6*, 2837; f) G. Chen, J. Weng, Z. Zheng, X. Zhu, Y. Cai, J. Cai, Y. Wan, *Eur. J. Org. Chem.* **2008**, 3524; g) T. Schareina, A. Zapf, W. Maegerlein, N. Müeller, M. Beller, *Chem. Eur. J.* **2007**, *13*, 6249; h) Y.-Z. Zhu, C. Cai, *Eur. J. Org. Chem.* **2007**, 2401; i) O. Grossman, D. Gelman, *Org. Lett.* **2006**, *8*, 1189; j) M. Sundermeier, A. Zapf, S. Mutyala, W. Baumann, J. Sans, S. Weiss, M. Beller, *Chem. Eur. J.* **2003**, *9*, 1828; k) Y. Ren, W. Wang, S. Zhao, X. Tian, J. Wang, W. Yin, L. Cheng, *Tetrahedron Lett.* **2009**, *50*, 4595; l) M. Alterman, A. Hallberg, *J. Org. Chem.* **2000**, *65*, 7984; m) J. Zanon, A. Klapars, S. L. Buchwald, *J. Am. Chem. Soc.* **2003**, *125*, 2890; n) H.-J. Cristau, A. Ouali, J.-F. Spindler, M. Taillefer, *Chem. Eur. J.* **2005**, *11*, 2483; o) M. Sundermeier, A. Zapf, M. Beller, *Angew. Chem.* **2003**, *115*, 1700; *Angew. Chem. Int. Ed.* **2003**, *42*, 1661.

[4] Recent examples for synthesis of nitriles from amines or alcohols: a) S. Iida, H. Togo, *Tetrahedron* **2007**, *63*, 8274; b) T. Oischi, K. Yamaguchi, N. Mizuno, *Angew. Chem.* **2009**, *121*, 6404; *Angew. Chem. Int. Ed.* **2009**, *48*, 6286; c) F.-E. Chen, Y.-Y. Kuang, H.-F. Dai, L. Lu, M. Huo, *Synthesis* **2003**, *17*, 2629; d) K. R. Reddy, C. U. Maheswari, M. Venkateshwar, S. Prashanthi, M. L. Kantam, *Tetrahedron Lett.* **2009**, *50*, 2050; e) F.-E. Chen, Y.-Y. Li, M. Xu, H.-Q. Jia, *Synthesis* **2002**, 1804; f) G. D. McAllister, C. D. Wilfred, R. J. K. Taylor, *Synlett* **2002**, 1291.

[5] Recent examples for synthesis of nitriles from amides or oximes: a) K. Ishihara, Y. Furuya, H. Yamamoto, *Angew. Chem.* **2002**, *114*, 3109; *Angew. Chem. Int. Ed.* **2002**, *41*, 2983; b) C.-W. Kuo, J.-L. Zhu, J.-D. Wu, C.-M. Chu, C.-F. Yao, K.-S. Shia, *Chem. Commun.* **2007**, 301; c) E. Choi, C. Lee, Y. Na, S. Chang, *Org. Lett.* **2002**, *4*,

2369; d) K. Yamaguchi, H. Fujiwara, Y. Ogasawara, M. Kotani, N. Mizuno, *Angew. Chem.* **2007**, *119*, 3996; *Angew. Chem. Int. Ed.* **2007**, *46*, 3922; e) S. Zhou, D. Addis, S. Das, K. Junge, M. Beller, *Chem. Commun.* **2009**, 4883; f) L. D. S. Yadav, V. P. Srivastava, R. Patel, *Tetrahedron Lett.* **2009**, *50*, 5532; g) M. K. Singh, M. K. Lakshman, *J. Org. Chem.* **2009**, *74*, 3079; h) D. Saha, A. Saha, B. C. Ranu, *Tetrahedron Lett.* **2009**, *50*, 6088; i) S. Zhou, K. Junge, D. Addis, S. Das, M. Beller, *Org. Lett.* **2009**, *11*, 2461.

[6] Recent examples for direct cyanation through C–H bond functionalization: a) X. Chen, X.-S. Hao, C. E. Goodhue, J.-Q. Yu, *J. Am. Chem. Soc.* **2006**, *128*, 6790; b) B. Mariampillai, J. Alliot, M. Li, M. Lautens, *J. Am. Chem. Soc.* **2007**, *129*, 15372; c) T. Dohi, K. Morimoto, Y. Kiyono, H. Tohma, Y. Kita, *Org. Lett.* **2005**, *7*, 537; d) G. Yan, C. Kuang, Y. Zhang, J. Wang, *Org. Lett.* **2010**, *12*, 1052; e) X. Jia, D. Yang, S. Zhang, J. Cheng, *Org. Lett.* **2009**, *11*, 4716; f) T. Dohi, K. Morimoto, N. Takenaga, A. Goto, A. Maruyama, Y. Kiyono, H. Tohma, Y. Kita, *J. Org. Chem.* **2007**, *72*, 109; g) X. Jia, D. Yang, W. Wang, F. Luo, J. Cheng, *J. Org. Chem.* **2009**, *74*, 9470; h) Z. Lu, C. Hu, J. Guo, J. Li, Y. Cui, Y. Jia, *Org. Lett.* **2010**, *12*, 480; i) H.-Q. Do, O. Daugulis, *Org. Lett.* **2010**, *12*, 2517.

[7] Other methods: a) B. Lücke, K. V. Narayana, A. Martin, K. Jähnisch, *Adv. Synth. Catal.* **2004**, *346*, 1407; b) V. N. Telvekar, K. N. Patel, H. S. Kundaikar, H. K. Chaudhari, *Tetrahedron Lett.* **2008**, *49*, 2213; c) N. D. Arote, D. S. Bhalerao, K. G. Akamanchi, *Tetrahedron Lett.* **2007**, *48*, 3651; d) R. Sasson, S. Rozen, *Org. Lett.* **2005**, *7*, 2177; e) H. Rudler, B. Denis, *Chem. Commun.* **1998**, 2145; f) A. Altamura, L. Daccolti, A. Detomaso, A. Dinoi, M. Fiorentino, C. Fusco, R. Curci, *Tetrahedron Lett.* **1998**, *39*, 2009; g) R. Fernandez, C. Gasch, J. M. Lassaletta, J. M. Llera, J. Vazquez, *Tetrahedron Lett.* **1993**, *34*, 141; h) Y. Nakao, S. Oda, T. Hiyama, *J. Am. Chem. Soc.* **2004**, *126*, 13904; i) Y. Nakao, T. Yukawa, Y. Hirata, S. Oda, J. Satoh, T. Hiyama, *J. Am. Chem. Soc.* **2006**, *128*, 7116; j) Y. Nakao, A. Yada, S. Ebata, T. Hiyama, *J. Am. Chem. Soc.* **2007**, *129*, 2428; k) S. Kojima, T. Fukuzaki, A. Yamakawa, Y. Murai, *Org. Lett.* **2004**, *6*, 3917; l) C. Peppe, P. A. Mello, R. P. das Chagas, *J. Organomet. Chem.* **2006**, *691*, 2335; m) T. Tomioka, Y. Takahashi, T. G. Vaughan, T. Yanase, *Org. Lett.* **2010**, *12*, 2171; n) S. Chiba, L. Zhang, G. Y. Ang, B. W.-Q. Hui, *Org. Lett.* **2010**, *12*, 2052; o) J. Kim, S. Chang, *J. Am. Chem. Soc.* **2010**, *132*, 10272; p) X. Ren, J. Chen, F. Chen, J. Cheng, *Chem. Commun.* **2011**, *47*, 6725; q) S. Ding, N. Jiao, *J. Am. Chem. Soc.* **2011**, *133*, 12374; r) S. Ushijima, K. Moriyama, H. Togo, *Tetrahedron* **2011**, *67*, 958; s) S. Kim, J. Choi, K. Shin, S. Chang, *J. Am. Chem. Soc.* **2012**, *134*, 2528; t) J. Kim, J. Chio, K. Shin, S. Chang, *Org. Lett.* **2012**, *14*, 3924.

[8] a) W. Zhou, L. Zhang, N. Jiao, *Angew. Chem.* **2009**, *121*, 7228; *Angew. Chem. Int. Ed.* **2009**, *48*, 7094; b) C. Qin, N. Jiao, *J. Am. Chem. Soc.* **2010**, *132*, 15893; c) W. Zhou, J. Xu, L. Zhang, N. Jiao, *Org. Lett.* **2010**, *12*, 2888; d) M. Lamani, K. R. Prabhu, *Angew. Chem.* **2010**, *122*, 6772; *Angew. Chem. Int. Ed.* **2010**, *49*, 6622; e) J. He, K. Yamaguchi, N. Mizuno, *J. Org. Chem.* **2011**, *76*, 4606.

[9] The desired products may be consumed by [2+2] cycloadditions with DDQ, see: S.-I. Kato, M. T. R. Beels, P. La Porta, W. B. Schweizer, C. Boudon, J.-P. Gisselbrecht, I. Biaggio, F. Diederich, *Angew. Chem.* **2010**, *122*, 6343; *Angew. Chem. Int. Ed.* **2010**, *49*, 6207.

[10] The reaction under Prabhu's conditions (ref.[8d]) only produced **2a** in 31% yield (entry 9, Table 1).

[11] a) A. Sud, D. Sureshkumar, M. Klussmann, *Chem. Commun.* **2009**, *22*, 3169; b) J.-H. Lee, M.-Y. Jung, *J. Food Sci.* **2010**, *75*, 506; c) J. Xie, H.-L. Jiang, Y.-X. Cheng, C.-Z. Zhu, *Chem. Commun.* **2012**, *48*, 979.

[12] a) Z.-P. Li, C.-J. Li, *J. Am. Chem. Soc.* **2004**, *126*, 11810; b) Z.-P. Li, D. S. Bohle, C.-J. Li, *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 8928; c) C.-J. Li, *Acc. Chem. Res.* **2009**, *42*, 335; d) J. Xie, Z.-Z. Huang, *Angew. Chem.* **2010**, *122*, 10379; *Angew. Chem. Int. Ed.* **2010**, *49*, 10181; e) F. Yang, J. Li, J. Xie, Z.-Z. Huang, *Org. Lett.* **2010**, *12*, 5214.

[13] a) L.-B. Gan, S.-H. Huang, X. Zhang, A.-X. Zhang, B.-C. Cheng, H. Cheng, X.-L. Li, G. Shang, *J. Am. Chem. Soc.* **2002**, *124*, 13384; b) C. M. Jones, M. J. Burkitt, *J. Am. Chem. Soc.* **2003**, *125*, 6946; c) Z.-J. Liu, J. Zhang, S.-L. Chen, E.-B. Shi, Y. Xu, X.-B. Wan, *Angew. Chem.* **2012**, *124*, 3285; *Angew. Chem. Int. Ed.* **2012**, *51*, 3231.

[14] a) S.-I. Murahashi, T. Naota, K. Yonemura, *J. Am. Chem. Soc.* **1988**, *110*, 8256; b) S.-I. Murahashi, T. Naota, T. Kuwabara, T. Saito, H. Kumobayashi, S. Akutagawa, *J. Am. Chem. Soc.* **1990**, *112*, 7820; c) Z.-P. Li, C.-J. Li, *J. Am. Chem. Soc.* **2005**, *127*, 3672.

[15] On the basis of the mechanistic studies on oxidative coupling reactions using copper(I)/TBHP system, a rapid equilibrium may exist, see: E. Boess, C. Schmitz, M. Klussmann, *J. Am. Chem. Soc.* **2012**, *134*, 5317.

[16] H. Wolff, *Org. React.* **1946**, 307.