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Copper-Catalyzed Aerobic Spirocyclization of Biaryl-*N*-H-imines via 1,4-Aminooxygenation of Benzene Rings

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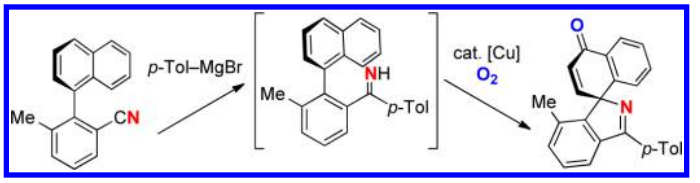
ABSTRACT



A synthetic method of azaspirocyclohexadienones has been developed through copper-catalyzed aerobic spirocyclization of biaryl-*N*-H-imines prepared by the reaction of biarylcarbonitriles and Grignard reagents.

The spirocyclic structures are prevalent in various kinds of biologically active natural products.[1] While the typical method to construct the spirocyclic cores involves oxidative spirocyclization of phenol derivatives, commonly with a stoichiometric amount of hypervalent iodine reagents that could deliver spirocyclohexadienones (Scheme 1a),[2,3] it would be beneficial to develop conceptually novel, practical, and environmentally benign processes for spirocyclization from readily available building blocks. We have recently been interested in copper-mediated oxidative functionalization of C−C unsaturated bonds under aerobic reaction conditions.[4−6] During the course of these studies, we disclosed a copper-catalyzed aerobic synthesis of diazaspirocyclohexadienones from α-azido-*N*-arylamides, which was carried out by a sequence of denitrogenative formation of iminyl copper species from α-azido-*N*-arylamides and their 1,4-amino-cupration with an intramolecular benzene ring on the amido nitrogen followed by consecutive formation of C=O bonds (1,4-aminooxygenation of the benzene ring) (Scheme 1b).[4d] Inspired by this unprecedented Cu-catalyzed aerobic spirocyclization, we have further strived to explore more opportunities to construct spirocycles with other types of substrates.

We have recently utilized readily available carbonitriles as a precursor of *N*-H imines by reaction with Grignard

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(4) (a) Wang, Y.-F.; Zhu, X.; Chiba, S. *J. Am. Chem. Soc.* **2012**, *134*, 3679. (b) Toh, K. K.; Wang, Y.-F.; Ng, E. P. J.; Chiba, S. *J. Am. Chem. Soc.* **2011**, *133*, 13942. (c) Zhang, L.; Ang, G. Y.; Chiba, S. *Org. Lett.* **2010**, *12*, 3682. (d) Chiba, S.; Zhang, L.; Lee, J.-Y. *J. Am. Chem. Soc.* **2010**, *132*, 7266.

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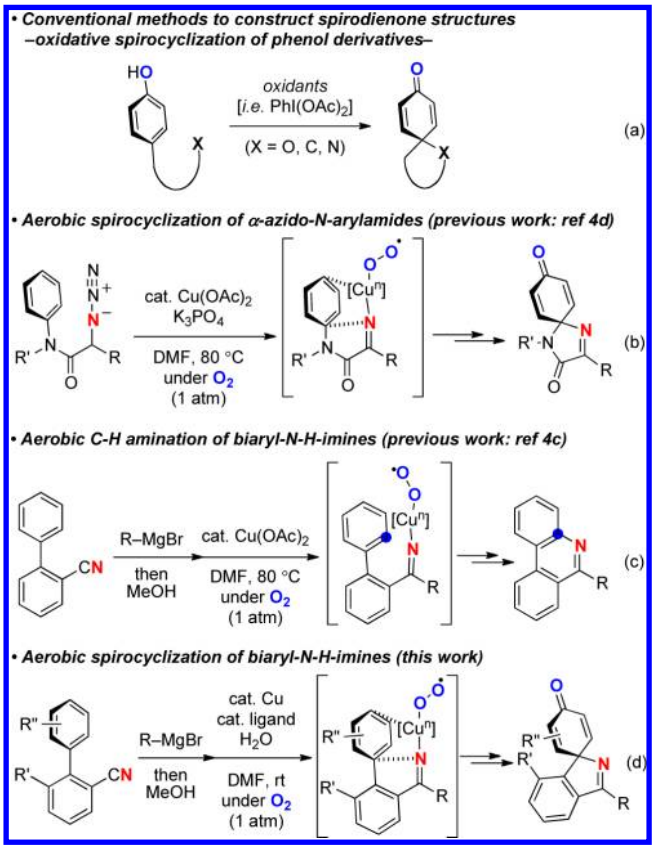
Scheme 1



reagents followed by proper protonation.[7] For example, we found that the biaryl-*N*-H imines generated from biaryl-2-carbonitriles possess an intriguing chemical reactivity toward Cu-catalyzed aerobic C−N bond formation on an intramolecular aryl C−H bond (aromatic C−H amination), affording phenanthridine derivatives (Scheme 1c).[4c] In the context of our continuous interests in the chemical reactivity of biaryl *N*-H imines under Cu-catalyzed aerobic conditions, we were attracted by the *ortho*-substituent effects which can maintain the helical sense of the biaryl motifs through hindered rotation about the biaryl axis. It was expected that the putative iminyl copper species could interact with the π-face of the benzene ring rather than with aromatic C−H bonds in such a nonplanar structure, leading to azaspirocyclohexadienones via intramolecular 1,4-aminooxygenation. Herein, we wish to report the Cu-catalyzed aerobic spirocyclization of biaryl *N*-H imine intermediates generated from biaryl-2-carbonitriles and Grignard reagents (Scheme 1d).

With this hypothesis, our investigation commenced with the reactions of 3-methyl-2-(1-naphthyl)benzonitrile (±)-(**1a**) and *p*-tolylmagnesium bromide (**2a**) (Table 1). The reaction of Grignard reagent **2a** to benzonitrile **1a** occurred smoothly in Et_2O at 80 °C (in sealed tube). After protonation with MeOH,[8] DMF (diluted to 0.1 M) and $Cu(OAc)_2$ (20 mol %) were subsequently added, and the reaction mixture was stirred at 80 °C under an O_2 atmosphere (1 atm) for 20 h, affording the 1,4-aminooxygenation product, azaspirocyclohexadienone (±)-**3aa**[9] in 34% yield as the sole product (entry 1). The addition of nitrogen ligands such as 1,10-phenanthroline (phen), 1,4-diazabicyclo[2.2.2]octane (DABCO), and 2,2′-bipyridine (bpy) improved the yield of **3aa** to 52−61% (entries 2−4). With 1,10-phenanthroline as a ligand, not only $Cu(OAc)_2$ but also $CuBr_2$ and $CuBr{\bullet}SMe_2$ showed similar catalytic activity (entries 5 and 6). Interestingly, the reaction with $Cu(OAc)_2$ and 1,10-phenanthroline (20 mol %) proceeded even at rt (entry 7), and further addition of H_2O (10 equiv) dramatically improved the yield of **3aa** to 81% (entry 8). Utilization of $^{18}O_2$ showed that one of the oxygen atoms from O_2 was incorporated into a resulting carbonyl group of the azaspirodienone (see Supporting Information for more details). Furthermore, reduction of the oxygen partial pressure using air (0.21 atm of O_2) accelerated the reaction (entry 9). Reduction of the catalyst loading to 10 mol % did not affect the chemical yield (entry 10), while 5 mol % of the catalysts render the process sluggish (entry 11). The structure of copper(II) acetate is binuclear with four carboxylate bridges.[10] We became keen to know the effect of a bimetallic structure of Cu species for the present spirocyclization. By using the modified Du Bois's procedure,[11] we succeeded in preparing $Cu^{II}_2(esp)_2{\bullet}2H_2O$,[12] which is supposed to have a more rigid and stable bimetallic structure with the dicarboxylic acid ligands. Interestingly, the reaction with 5 mol % of $Cu^{II}_2(esp)_2{\bullet}2H_2O$ proceeded smoothly without the aid of any additive such as 1,10-phen and H_2O, affording **3aa** in 70% yield under air (72% yield under an O_2 atmosphere) (entry 12). It is noted that the reaction under an Ar atmosphere (even with a stoichiometric amount of $Cu(OAc)_2$-phen) did not proceed at all (entry 13).

With the optimized reaction conditions in hand (Table 1, entry 10), we next investigated the scope of Grignard reagents **2** for the synthesis of azaspirocyclohexadienones **3** from carbonitrile **1a** (Table 2). Aryl Grignard reagents bearing both electron-donating (entries 1−3) and -withdrawing groups (entry 4) as well as a C−Cl bond (entries 5 and 6) could be utilized to give the corresponding spirodienones **3** in good yields. Sterically bulky substituents such as 1-naphthyl and mesityl groups could also be installed as R^1 (entries 7 and 8). The reaction of alkylketimine generated from primary alkyl Grignard reagent **2j** proceeded smoothly, while that of secondary **2k** was sluggish (entries 9 and 10).

(8) Protonation with MeOH could prevent the partial hydrolysis of *N*-H imines to the corresponding ketone; see: Pickard, P. L.; Tolbert, T. L. *J. Org. Chem.* **1961**, *26*, 4886.

(9) The structure of **3aa** was secured by X-ray crystallographic analysis (CCDC-874162); see Supporting Information.

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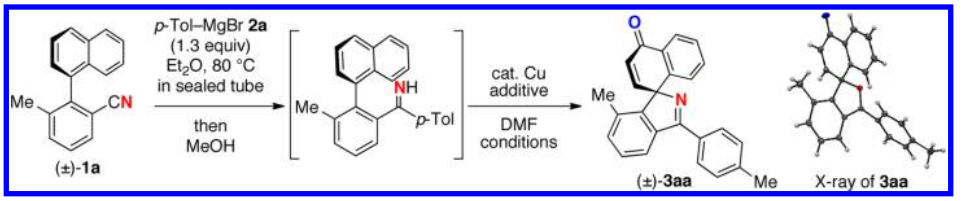
(11) Espino, C. G.; Fiori, K. W.; Kim, M.; Du Bois, J. *J. Am. Chem. Soc.* **2004**, *126*, 15378.

(12) The structure of $Cu^{II}_2(esp)_2{\bullet}2H_2O$ was secured by X-ray crystallographic analysis (CCDC-874165); see Supporting Information for more details.

Table 1. Optimization of Reaction Conditions[a]

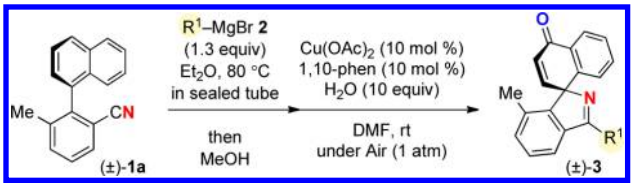


entry	Cu salts (mol %)	additive-1 (mol %)	additive-2 (equiv)	atmosphere	temp (°C)	time (h)	yield (%)[b]
1	$Cu(OAc)_2$ (20)	–	–	O_2	80	20	34
2	$Cu(OAc)_2$ (20)	1,10-phen (20)	–	O_2	80	3	61
3	$Cu(OAc)_2$ (20)	DABCO (20)	–	O_2	80	3	59
4	$Cu(OAc)_2$ (20)	bpy (20)	–	O_2	80	5	52
5	$CuBr_2$ (20)	1,10-phen (20)	–	O_2	80	5	50
6	$CuBr•SMe_2$ (20)	1,10-phen (20)	–	O_2	80	4	61
7	$Cu(OAc)_2$ (20)	1,10-phen (20)	–	O_2	rt	3	55
8	$Cu(OAc)_2$ (20)	1,10-phen (20)	H_2O (10)	O_2 ($^{18}O_2$)	rt	3	81 (82)[c]
9	$Cu(OAc)_2$ (20)	1,10-phen (20)	H_2O (10)	air	rt	2	82
10	$Cu(OAc)_2$ (10)	1,10-phen (10)	H_2O (10)	air	rt	3	80
11	$Cu(OAc)_2$ (5)	1,10-phen (5)	H_2O (10)	air	rt	17	76
12	$Cu_2(esp)_2•2H_2O$ (5)	–	–	air	rt	6	70 (72)[d]
13	$Cu(OAc)_2$ (100)	1,10-phen (100)	H_2O (10)	Ar	rt	48	0

[a] All reactions were conducted using 0.5 mmol of carbonitrile **1a** (racemic) with 1.3 equiv of Grignard reagents **2a** in Et_2O (0.5 mL) at 80 °C (sealed tube) for 2 h followed by addition of MeOH (60 μL), DMF (5 mL), Cu catalysts, and additives. [b] Isolated yields. [c] Isolated yield when the reaction was conducted under an $^{18}O_2$ atmosphere. [d] Isolated yield when the reaction was conducted under an O_2 atmosphere. 1,10-phen = 1,10-phenanthroline; DABCO = 1,4-diazabicyclo[2.2.2]octane; bpy = 2,2′-bipyridine; esp = α,α,α′,α′-tetramethyl-1,3-benzenedipropionate.

Next by varying the substituents on biaryl carbonitriles **1**, we further explored the substrate scope using *p*-tolyl Grignard reagent **2a** (Chart 1). In general, as the configurational (rotational) stability of the biaryl motifs become more rigid by installing more than two substituents in R^2 and R^3, the present oxygenative spirocyclization proceeded smoothly, affording the corresponding azaspirodienones **3** in good yields (for **3ca**–**3ja**, **3pa** except for **3ha** and **3oa**). The reactions of the substrates bearing only one substituent in either R^2 or R^3, however, became sluggish, giving azaspirodienones **3** in moderate yields (for **3ba**, **3ka**–**3na**). The reactions of [1,1′-binaphthalene]-2-carbonitrile (**1q**) and 2-(anthracen-9-yl)benzonitrile (**1r**) as well as 2-(dibenzofuran-4-yl)benzonitrile (**1s**) proceeded smoothly to give **3qa**, **3ra**, and **3sa**, respectively, in good yields. It is worth noting that the present oxygenation (the C=O bond formation) was observed exclusively at the *para*-position of the resulting aminated carbon (1,4-aminooxygenation).

Table 2. Scope of Grignard Reagents[a,b]



entry	R^1-MgBr **2**	time (h)	yield (%)[b]
1	**2b**: 4-MeO-C_6H_4-MgBr	20	**3ab**: 80
2	**2c**: 2-MeO-C_6H_4-MgBr	20	**3ac**: 72
3	**2d**: 4-PhO-C_6H_4-MgBr	72	**3ad**: 76
4	**2e**: 4-CF_3-C_6H_4-MgBr	19	**3ae**: 80
5	**2f**: 4-Cl-C_6H_4-MgBr	48	**3af**: 70
6	**2g**: 3-Cl-C_6H_4-MgBr	5	**3ag**: 70
7	**2h**: 1-naphthyl-MgBr	4	**3ah**: 85
8	**2i**: 2,4,6-$(Me)_3$-C_6H_2-MgBr	3.5	**3ai**: 65
9[c]	**2j**: *n*-C_8H_{17}-MgBr	3	**3aj**: 70
10[c]	**2k**: *i*-C_3H_7-MgBr	3	**3ak**: 29

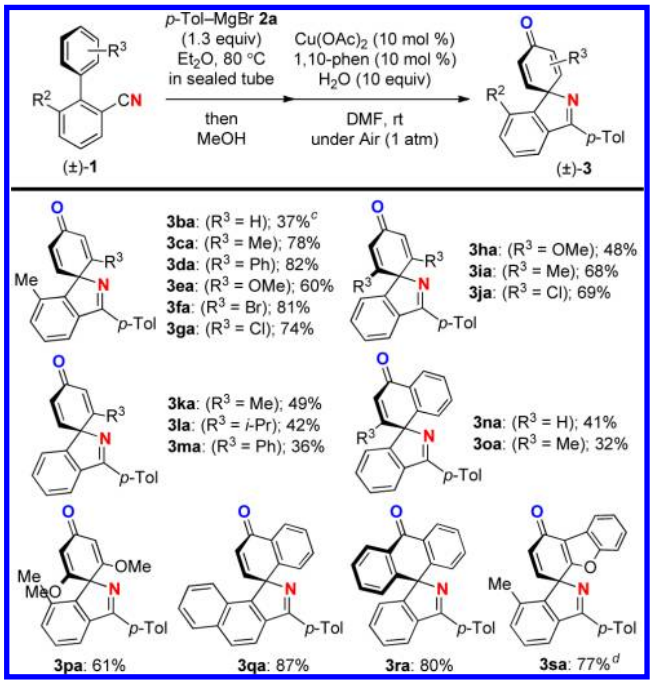
[a] All reactions were conducted using 0.5 mmol of carbonitrile **1a** (racemic) with 1.3 equiv of Grignard reagents **2** in Et_2O (0.5 mL) at 80 °C (sealed tube) for 2 h followed by addition of MeOH (60 μL), DMF (5 mL), $Cu(OAc)_2$–1,10-phenanthroline (10 mol %), H_2O (10 equiv), and stirring at rt under an air atmosphere. [b] Isolated yields. [c] The reactions with Grignard reagents **2j** and **2k** were stirred for 24 h.

Having developed the Cu-catalyzed aerobic spirocyclization of biaryl *N*-H-imine derivatives, we were interested in the possibility of transmitting the axial chirality of the

(13) For reviews on synthesis of axially chiral biaryl compounds, see: (a) Shibata, Y.; Tanaka, K. *Synthesis* **2012**, *44*, 323. (b) Bringmann, G.; Gulder, T.; Gulder, T. A. M.; Breuning, M. *Chem. Rev.* **2011**, *111*, 563. (c) Tanaka, K. *Chem.—Asian J.* **2009**, *4*, 508. (d) Bringmann, G.; Price Mortimer, A. J.; Keller, P. A.; Gresser, M. J.; Garner, J.; Breuning, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 5384. (e) Bringmann, G.; Breuning, M.; Tasler, S. *Synthesis* **1999**, 525.

(14) For reports on transmission of the biaryl axial chirality to the central chirality in the other processes, see: (a) Yasui, Y.; Suzuki, K.; Matsumoto, T. *Synlett* **2004**, 619. (b) Ohmori, K.; Kitamura, M.; Suzuki, K. *Angew. Chem., Int. Ed.* **1999**, *38*, 1226.

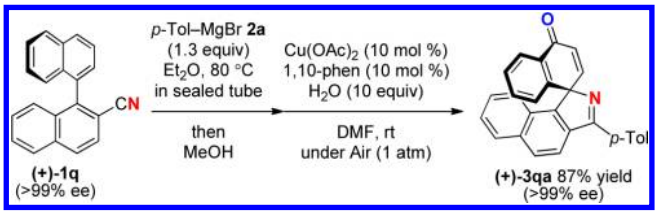
Chart 1. Scope of Biaryl Carbonitriles **1**[a,b]



[a] Unless otherwise noted, reactions were conducted using 0.5 mmol of carbonitrile **1** (racemic) with 1.3 equiv of Grignard reagents **2a** in Et_2O (0.5 mL) at 80 °C (sealed tube) for 2 h followed by addition of MeOH (60 μL), DMF (5 mL), $Cu(OAc)_2$–1,10-phenanthroline (10 mol %), H_2O (10 equiv), and stirring at rt under an Air atmosphere. [b] Isolated yields were recorded and are shown. [c] The reaction was conducted without the addition of H_2O. [d] The reaction was carried out at 60 °C.

biaryl-2-carbonitriles **1**[13] to the spiro central chirality of **3** in the present process.[14] Starting from optically active [1,1′-binaphthalene]-2-carbonitrile (+)-(**1q**) (>99% ee) prepared from known enantiomerically pure (*R*)-[1,1′-binaphthalene]-2-carbaldehyde,[15,16] the aerobic spirocyclization with *p*-tolylmagnesium bromide (**2a**) provided azaspiridienone (+)-**3qa** as an enantiomerically pure form (>99% ee), which suggested that the present process is most likely free from racemization (Scheme 2).[17,18]

Scheme 2. Transmission of Axial Chirality to Central One



In summary, we have developed a method for Cu-catalyzed aerobic spirocyclization of biaryl *N*-H imines which could be prepared concisely from readily available biaryl-2-carbonitriles and Grignard reagents. Molecular oxygen (O_2) is a prerequisite for achieving the present catalytic spirocyclization, where one of the oxygen atoms of O_2 is regioselectively incorporated into the benzene ring with dearomatization through 1,4-aminooxygenation. Further investigation of the scope, detailed mechanism, and synthetic applications of the present strategy to other spirocycles as well as development of the intermolecular processes for the benzene oxygenation is currently underway.

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Supporting Information Available. Experimental procedures, characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org

The authors declare no competing financial interest.

(15) Shindo, M.; Koga, K.; Tomioka, K. *J. Am. Chem. Soc.* **1992**, *114*, 8732.

(16) Based on the transformation utilized to prepare (+)-**1q** from enantiomerically pure (*R*)-[1,1′-binaphthalene]-2-carbaldehyde, the absolute configuration of (+)-**1q** is estimated to be (*R*). See Supporting Information for more details.

(17) The structures of both **1q** and **3qa** were determined by X-ray crystallographic analysis (CCDC-875163 and CCDC-874164, respectively); see Supporting Information.

(18) Based on the proposed mechanism of the present spirocyclization (see ref 4d), the absolute configuration of (+)-**3qa** is estimated to be (*R*).