Tetrahedron 74 (2018) 2121–2129

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Cu-catalyzed reduction of azaarenes and nitroaromatics with diboronic acid as reductant

Danwei Pi [a], Haifeng Zhou [a, *], Yanmei Zhou [a], Qixing Liu [a], Renke He [a], Guanshuo Shen [a, b], Yasuhiro Uozumi [a, b, **]

[a] *Research Center of Green Pharmaceutical Technology and Process, Hubei Key Laboratory of Natural Products Research and Development, College of Biological and Pharmaceutical Sciences, China Three Gorges University, Yichang 443002, China*
[b] *Institute for Molecular Science, Myodaiji, Okazaki 444-8787, Japan*

ARTICLE INFO

Article history:
Received 28 December 2017
Received in revised form
26 February 2018
Accepted 5 March 2018
Available online 10 March 2018

Keywords:
Reduction
Homogeneous catalysis
Nitrogen heterocycles
Quinolines
Amination
Aldehydes
Diboronic acid
Copper

ABSTRACT

A ligand-free copper-catalyzed reduction of azaarenes with diboronic acid as reductant in an aprotic solvent under mild conditions has been developed. Most interestingly, the nitroazaarenes could be reduced exclusively to give the corresponding amines without touching the azaarene moieties. Furthermore, the reductive amination of aromatic nitro compounds and aromatic aldehydes has also been realized. A series of hydrogenated azaarenes and secondary amines were obtained with good functional group tolerance.

1. Introduction

1,2,3,4-Tetrahydroquinolines and related *N*-heterocycles are important moieties in fine chemicals, pharmaceuticals, agrochemicals, dyes, fragrances, and hydrogen-storage materials.[1] The reduction of readily available quinolines using stoichiometric metal hydrides or reactive metals as classic reductants is a straightforward method for preparing such compounds.[2] In recent decades, various catalytic hydrogenations and transfer hydrogenations under homogeneous or heterogeneous conditions have also been developed.[3–5] Aromatic amines are important intermediates in the synthesis of many nitrogen-containing pharmaceuticals, agrochemicals, bioactive compounds, dyes, and polymers.[6] The reduction of nitro compounds is one of the common and simple routes to prepare amines. Since the discovery of Béchamp reduction, a classic process that generates much metallic waste,[7] numerous efforts have been focused on exploring new and efficient catalysts and reductants, as well as on developing simple and green procedures.[8] However, the reported methods have several drawbacks, such as a lack of chemoselectivity, the need to handle flammable hydrogen gas, the use of relatively expensive metal catalysts, harsh conditions. Given these facts, it is highly desirable to develop novel, efficient, and practical methods for preparing 1,2,3,4-tetrahydroquinolines and related compounds.

Diboron reagents were initially used as borylation agents for preparing organoboron compounds.[9] In 2016, the diboronic acid [$B_2(OH)_4$]-mediated, Pd-catalyzed, transfer hydrogenation of unsaturated carbon–carbon bonds with water as a hydrogen donor was realized.[10] Subsequently, the Cu–dipinacolborane (B_2pin_2)-catalyzed chemoselective reduction of carbon–carbon double or triple bonds to C–C single bonds in α,β-unsaturated ketones was developed.[11] More recently, the reduction of aromatic nitro compounds to aromatic amines mediated by diboron reagents has also been reported.[12] Subsequently, Xuan and Song developed a Pd/B_2pin_2-catalyzed reduction of *N*-heteroaromatics with water as a

---

* Corresponding author.
** Corresponding author. Research Center of Green Pharmaceutical Technology and Process, Hubei Key Laboratory of Natural Products Research and Development, College of Biological and Pharmaceutical Sciences, China Three Gorges University, Yichang 443002, China.
E-mail addresses: zhouhf@ctgu.edu.cn (H. Zhou), uo@ims.ac.jp (Y. Uozumi).

https://doi.org/10.1016/j.tet.2018.03.014

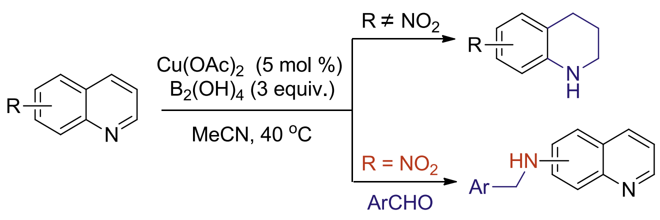
hydrogen donor.[13] Moreover, a $B_2(OH)_4$-promoted reduction of *N*-heteroaromatics with water as both solvent and hydrogen donor under metal-free conditions has also achieved.[14] In addition, several reductive tandem reactions with diboron reagents have also been reported.[15] Lately, we reported a palladium-catalyzed chemoselective reduction and reductive amination of nitroarenes with water as a hydrogen source mediated by diboronic acid.[12b] A one-pot synthesis of tetrahydroquinoxalines from readily available 2-amino(nitro)anilines and 1,2-dicarbonyl compounds mediated by diboronic acid with water as both a solvent and a hydrogen donor has also been reported by us.[14b] However, the noble metal palladium and excess amount of diboronic acid (8 equiv) were necessary in the above two cases. To continue our interest in using diboron reagents as a mediator for transfer hydrogen, we developed a Cu-catalyzed reduction of azaarenes and nitro aromatic compounds with $B_2(OH)_4$ as a reductant under mild conditions. Most interestingly, the nitroazaarenes can be reduced exclusively to the corresponding amine, with the azaarene remaining intact (Scheme 1).

2. Results and discussion

Initially, we selected the reduction of quinoline (**1a**) as a model reaction to optimize the reaction parameters. First, the reaction was performed with 3.0 equivalents of $B_2(OH)_4$ as reductant in acetonitrile at 40 °C for 24 h, but no reaction was observed (Table 1, entry 1).

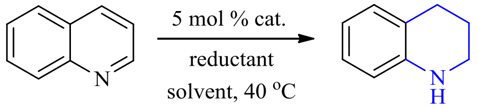
And then we tested various metal catalysts [Pd/C, $Pd(OAc)_2$, $Fe(OAc)_2$, $Zn(OAc)_2$, AgOAc, and $Cu(OAc)_2$] (entries 2–7), and we found that $Cu(OAc)_2$ gave 1,2,3,4-tetrahydroquinoline (**2a**) in 98% yield (entry 7). Other copper salts [$Cu(OTf)_2$, CuF_2, $CuCl_2$, $CuBr_2$, CuCl, and CuI] were also screened, but relatively lower yields were obtained (entries 8–13). Next, we examined the effects of the catalyst loading and the amount of reductant. The yield of **2a** decreased to 61% when 2 mol % of $Cu(OAc)_2$ was used (entry 14). When the amount of $B_2(OH)_4$ was reduced to 2.5 equivalents, a 92% yield of **2a** was obtained (entry 15). Other boron reagents [$NaBH_4$, $B(OH)_3$, B_2pin_2, and $B_2(cat)_2$] were examined, but no reaction took place (entries 16–19). The yield of **2a** remained unchanged when the reaction time was reduced to 8 h (entry 20). Other aprotic solvents [toluene, EtOAc, tetrahydrofuran (THF), CH_2Cl_2, and *N*,*N*-dimethylformamide (DMF)] were screened, but moderate yields were obtained in each case (entries 22–26). The reaction also proceeded smoothly in methanol, giving an 82% yield (entry 27), whereas a lower yield was obtained in water (entry 28). Finally, 5 mol % $Cu(OAc)_2$, 3 equivalents of $B_2(OH)_4$, 2 mL of MeCN, 40 °C, and 8 h were selected as the optimal reaction conditions.Scheme 2

With the optimal reaction conditions in hand, we investigated the scope of azaarene (Scheme 3). The reduction of electron-rich methyl-substituted quinolines **1b**–**g** and methoxy-substituted quinolines **1h**–**i** proceeded smoothly to give the corresponding products **2b**–**i** in 88–97% yield, whereas electron-deficient quinolines gave relatively lower yields. For example, 6-chloro-1,2,3,4-tetrahydroquinoline (**2j**) was isolated in 84% yield. None of the desired product was obtained from 8-nitroquinoline (**1k**). The 2-arylquinolines **1l**–**p** also underwent this transformation, affording the corresponding products **2l**–**p** in 84–92% yield at 80 °C for 12 h 2-(2-Thienyl)quinoline (**1q**) was converted into the corresponding tetrahydroquinoline **2q** in 82% yield. Polycyclic heteroaromatics acridine (**1r**) and benzo[h]quinoline (**1s**) similarly gave the corresponding products **2r** and **2s** in 78% and 72% yield, respectively. In addition, both the pyridine rings of 1,10-phenanthroline (**1t**) were reduced to give 1,2,3,4,7,8,9,10-octahydro-1,10-phenanthroline (**2t**) in 85% yield. However, no reaction occurred when pyridine was used as a substrate. Furthermore, the quinoxalines **1u** and **1v** also underwent the reduction to give the corresponding tetrahydroquinoxalines **2u** and **2v** in 90% and 93% yield, respectively.



Scheme 1. Cu-Catalyzed Chemoselective Reduction of Azaarenes and Nitro Groups.

Table 1
Optimization of the reaction conditions [a]



1a **2a**

Entry	Catalyst	Reductant (equiv)	Solvent	Time (h)	Yield (%)[b]
1	–	$B_2(OH)_4$ (3)	MeCN	24	0
2	Pd/C	$B_2(OH)_4$ (3)	MeCN	24	27
3	$Pd(OAc)_2$	$B_2(OH)_4$ (3)	MeCN	24	32
4	$Fe(OAc)_2$	$B_2(OH)_4$ (3)	MeCN	24	0
5	$Zn(OAc)_2$	$B_2(OH)_4$ (3)	MeCN	24	0
6	AgOAc	$B_2(OH)_4$ (3)	MeCN	24	0
7	$Cu(OAc)_2$	$B_2(OH)_4$ (3)	MeCN	24	98
8	$Cu(OTf)_2$	$B_2(OH)_4$ (3)	MeCN	24	71
9	CuF_2	$B_2(OH)_4$ (3)	MeCN	24	9
10	$CuCl_2$	$B_2(OH)_4$ (3)	MeCN	24	33
11	$CuBr_2$	$B_2(OH)_4$ (3)	MeCN	24	29
12	CuCl	$B_2(OH)_4$ (3)	MeCN	24	75
13	CuI	$B_2(OH)_4$ (3)	MeCN	24	67
14[c]	$Cu(OAc)_2$	$B_2(OH)_4$ (3)	MeCN	24	61
15	$Cu(OAc)_2$	$B_2(OH)_4$ (2.5)	MeCN	24	92
16	$Cu(OAc)_2$	$NaBH_4$ (3)	MeCN	24	0
17	$Cu(OAc)_2$	$B(OH)_3$ (3)	MeCN	24	0
18	$Cu(OAc)_2$	B_2pin_2 (3)	MeCN	24	0
19	$Cu(OAc)_2$	$B_2(cat)_2$ (3)	MeCN	24	0
20	$Cu(OAc)_2$	$B_2(OH)_4$ (3)	MeCN	8	98
21	$Cu(OAc)_2$	$B_2(OH)_4$ (3)	MeCN	6	78
22	$Cu(OAc)_2$	$B_2(OH)_4$ (3)	toluene	8	13
23	$Cu(OAc)_2$	$B_2(OH)_4$ (3)	EtOAc	8	12
24	$Cu(OAc)_2$	$B_2(OH)_4$ (3)	THF	8	45
25	$Cu(OAc)_2$	$B_2(OH)_4$ (3)	CH_2Cl_2	8	7
26	$Cu(OAc)_2$	$B_2(OH)_4$ (3)	DMF	8	60
27	$Cu(OAc)_2$	$B_2(OH)_4$ (3)	MeOH	8	82
28	$Cu(OAc)_2$	$B_2(OH)_4$ (3)	H_2O	8	23

[a] *Reaction conditions*: quinoline (**1a**; 0.5 mmol), catalyst (5 mol %), reductant (3.0 equiv), solvent (2 mL), 40 °C

[b] Determined by GC analysis with an internal standard (mesitylene).

[c] 2 mol % $Cu(OAc)_2$ was used.

To our surprise, when we conducted the reduction of 8-nitroquinoline (**1k**) in the presence of 5 mol % of $Cu(OAc)_2$ with three equivalents of $B_2(OH)_4$ as reductant in MeCN at 40 °C for 24 h, the product **2k** and **5** were not detected. Instead, the nitro group of **1k** was reduced exclusively to give quinolin-8-amine (**4a**) in 60% yield (Table 2, entry 1). The product **2k** and **5** were still not observed even if raising the temperature and increasing the amount of $B_2(OH)_4$ (entries 2–5). Very interestingly, **1k** could be reduced to compound **5** in 78% yield in the absence of $Cu(OAc)_2$, without detecting selective hydrogenated products **4a** and **2k** (entry 6).

As shown in Scheme 3, several control experiments were