Synthetic Methods

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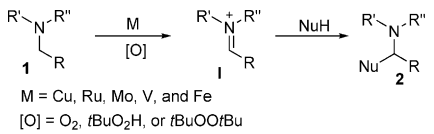
Copper-Catalyzed Oxidative Dimerizations of 3-*N*-Hydroxy-aminoprop-1-enes to form 1,4-Dihydroxy-2,3-diaminocyclohexanes with C_2 Symmetry**

*Satish Ghorpade and Rai-Shung Liu**

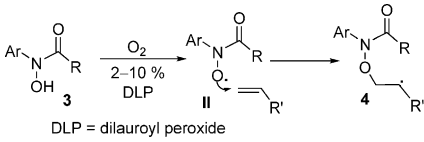
Abstract: *This work describes the one-step construction of complex and important molecular frameworks through copper-catalyzed oxidations of cheap tertiary amines. Copper-catalyzed aerobic oxidations of N-hydroxyaminopropenes to form C_2-symmetric N- and O-functionalized cyclohexanes are described. Such catalytic oxidations proceed with remarkable stereocontrol and high efficiency. Reductive cleavage of the two N–O bonds of these products delivers 1,4-dihydroxy-2,3-diaminocyclohexanes, which are important skeletons of several bioactive molecules.*

Metal-catalyzed oxidative C–H functionalizations of aminoalkane moieties have been a subject of intense interest because of their practical significance.[1] Reported examples focus mainly on the formation of iminium ions (**I**) which are subsequently attacked by suitable nucleophiles [Eq. (1)].[2–6]

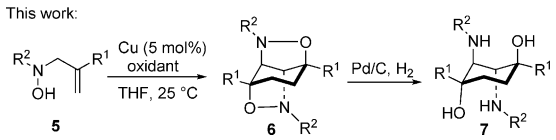


(1)

These reactions are appealing surrogates for the well-known Mannich reaction[7] because tertiary amines (**1**) are readily available and cheap reagents. *N*-Hydroxyaminoalkanes (**1**, R′ = OH) are an important class of organic compounds,[8] and their C–H oxidative functionalization generate nitrone species (**I**; R′ = O⁻) as depicted in Equation (1).[9] Alternatively, α-carbonyl N-hydroxyamino species (**3**) undergo metal-free oxidations to generate reactive amidoxyl radicals (**II**), which then attack an alkene to form a new C–O bond [Eq. (2)].[10] Despite numerous publications, the present N–CH oxidative functionalizations focus mainly on the Mannich-type reactions, rather than on the construction of complicated frameworks. Herein, we report the copper-catalyzed oxidative dimerizations of 3-*N*-hydroxy-aminoprop-1-enes (**5**) to produce highly O- and N-functionalized cyclohexanes (**6**) with excellent stereoselectivity (d.r. > 20:1) [Eq. (3)]. Subsequent reductive cleavage of their N–O bonds affords 1,4-dihydroxy-2,3-diaminocyclohexanes (**7**) efficiently. Notably, these substances do not follow current process to generate alkenylnitrone intermediates [Eq. (1)], despite the presence of a NCH_2 moiety.



(2)



(3)

These resulting O- and N-containing cyclohexane frameworks are found in bioactive molecules of various families as exemplified by the species **III**–**VI** (Figure 1), and their stereoselective synthesis inevitably requires long procedures.[11–15] Some 1,2-diaminocyclitols (**III**)[12] are potent glucocerebrosidase activators and promising pharmacological chaperones for Gaucher disease. In contrast, several conduritols (**IV**) showed biological activity as glycosidase inhibitors.[13] The compounds (**V**) are alcohol derivatives of *trans*-diaminocyclohexane dichloroplatinum (DACH-$PtCl_2$), which exhibits potent antitumor activity against P388 leukemia.[14] Oseltamivir phosphate (**VI**; Tamiflu) is currently used for the treatment of influenza.[15]

Table 1 presents optimization of the reaction conditions for the oxidative dimerizations of the 3-*N*-hydroxy-1-propene **5a** using various catalysts, oxidants, and solvents. We first

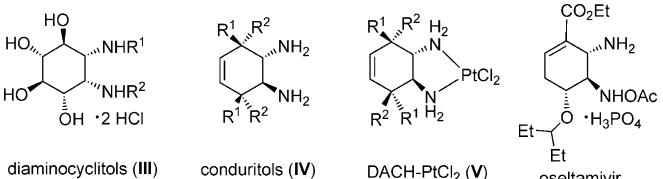


Figure 1. Representative bioactive molecules.

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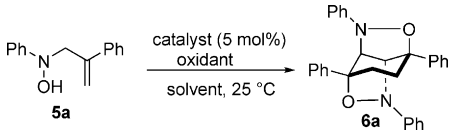
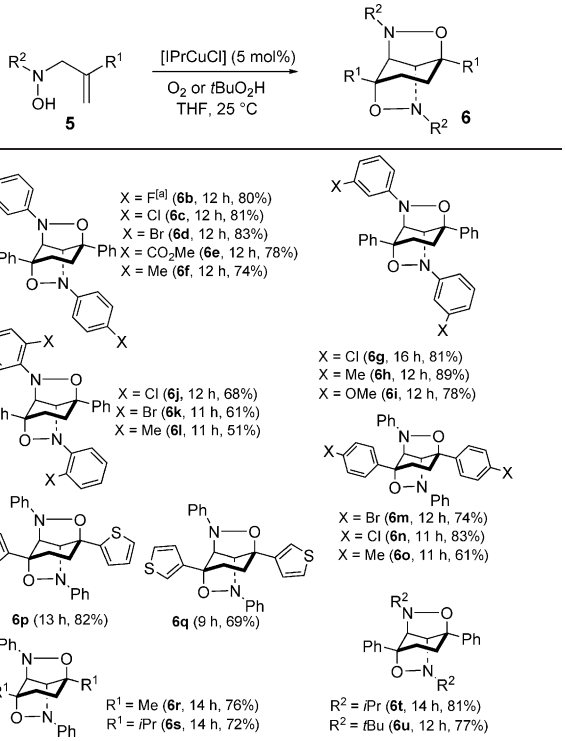
Table 1: Conditions for the oxidative dimerizations of **5a**.



Entry	Catalyst	Oxidant	Solvent[a]	Additive	*t* [h]	Yield[b] [%]
1	CuCl	O_2	THF	–	9	63
2	CuBr	O_2	THF	–	9	70
3	[IPrCuCl]	O_2	THF	–	9	84
4	$CuCl_2$	O_2	THF	–	9	25
5	$FeCl_3$	O_2	THF	–	9	67
6	$Co(OAc)_2$	O_2	THF	–	10	76
7	[IPrCuCl]	O_2	toluene	–	9	69
8	[IPrCuCl]	O_2	DCE	–	9	55
9	[IPrCuCl]	H_2O_2	THF	4 Å M.S.	9	71
10	[IPrCuCl]	*t*BuOOH	THF	4 Å M.S.	12	75
11	[IPrCuCl]	DTBP	THF	–	12	68
12	[IPrCuCl]	–	THF	–	12[c]	–
13	–	O_2	THF	–	12	–

[a] [**5a**] = 0.20 M. [b] Product yields are reported after purification from a silica gel column. [c] The recovery yield of **5a** was 67 and 71% for entries 12 and 13, respectively. M.S. = molecular sieves, THF = tetrahydrofuran.

Table 2: Scope for the oxidative dimerizations.



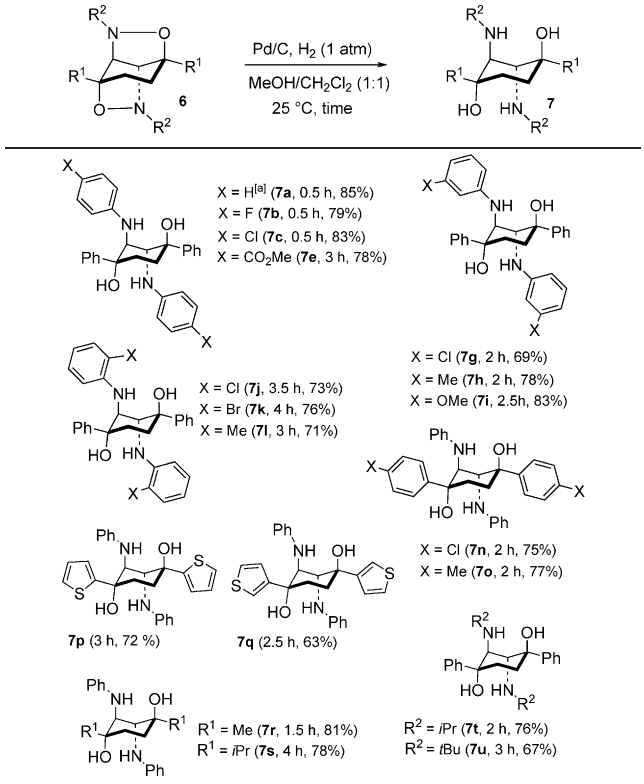
[a] [**6b**] = 0.20 M. Product yields are reported after purification from a silica gel column.

tested the reaction with a CuCl catalyst (5 mol%) and O_2 (1 atm) in THF under ambient conditions (25 °C, 9 h), which led to 1,4-dihydroxy-2,3-diaminocyclohexane **6a** as a single diastereomeric product (d.r. > 20:1) with a yield of 63% (entry 1). Among other copper catalysts tested, [IPrCuCl] (IPr = 1,3-bis(diisopropylphenyl)imidazol-2-ylidene) gave the best yield (84%) of **6a** (entry 3), whereas CuBr and $CuCl_2$ provided the same product in 70 and 25%, respectively (entries 2 and 4). In the presence of O_2, both $FeCl_3$ and $Co(OAc)_2$ were also effective catalysts, thus yielding **6a** in 67 and 76% yield, respectively (entries 5 and 6). The use of [IPrCuCl] in toluene and 1,2-dichloroethane (DCE) gave **6a** in 69 and 55% yield, respectively (entries 7 and 8). With [IPrCuCl], other oxidants such as H_2O_2, *tert*-butyl peroxide (TBPO), and di-*tert*-butyl peroxide (DTBP) also give the desired **6a** in 68–75% yields (entries 9–11). In the absence of an oxidant and metal catalyst, no reaction occurred over a protracted period (12 h) with 67 and 71% recovery, respectively, of the staring **5a** (entries 12 and 13). The structural characterization of **6a** relies on X-ray diffraction.[16] The ORTEP drawing (see the Supporting Information) indicates the presence of C_2 symmetry for the molecular framework.

We prepared additional 2-substituted 3-*N*-hydroxy-1-propenes (**5b–u**) to examine the generalization of such oxidative dimerizations (Table 2). Most reactions were performed with 5 mol% [IPrCuCl]/O_2 in THF (25 °C, 11–16 h) except for those involving **5j–l**, for which the reactions were run with [IPrCuCl]/*t*BuO_2H (3 equiv) in THF (4 Å M.S., 25 °C, 11–12 h). In all cases, the resulting O- and N-functionalized cyclohexanes **6b–u** were obtained as a single diastereomer (d.r. > 20:1). We tested the oxidations with the initial substrates **5b–f**, bearing variable aniline groups (R^2 = 4-XC_6H_4, X = F, Cl, Br, CO_2Me and Me), and the resulting products **6b–f** were obtained in 74–83% yields. We also prepared their *meta*-substituted analogues **5g–i** (R^2 = 3-XC_6H_4, X = Cl, Me, and OMe), which gave the desired products **6g–i** in 78–89%. The dimerizations of the *ortho*-substituted analogues **5j–l** (R^2 = 2-X C_6H_4, X = Cl, Br, and Me) were unsuccessful with [IPrCuCl] and O_2, but the use of [IPrCuCl] and *t*BuO_2H (3 equiv) enabled the production of desired compounds **6j–l** in reasonable yields (51–68%). We envisage that these *ortho* substituents are not favorable for the coordination of copper with their hydroxyamino groups, thus rendering the oxidation difficult. We also prepared the 3-*N*-hydroxy-1-propenes **5m–o** bearing various alkenyl substituents (R^1 = 4-XC_6H_4, X = Br, Cl, and Me), and their oxidative dimerizations proceeded smoothly with [IPrCuCl]/O_2 to give the desired **6m–o** in 61-83% yields. For the substrates **5p** and **5q** bearing a 2- and 3-thienyl group, respectively, at the alkenyl moiety, their corresponding products **6p** (82%) and **6q** (69%) were obtained. To our delight, these catalytic oxidations were compatible with the substrates **5r–u**, bearing various alkyl groups at their amino or alkenyl positions (R^1 = Me, *i*Pr or R^2 = *i*Pr or *t*Bu), and their desired dimerization products **6r–u** were obtained in 72–81% yields. These oxidative dimerizations failed to work with those substrates bearing R^1 = CO_2Me and H, and thus resulted in a complex mixture of products.

We also examined the access to the O- and N-containing cyclohexanes **7** by employing reductive cleave of the N–O bonds of the products **6**. The procedures[17] involved Pd/C and H_2 (1 atm) in MeOH/CH_2Cl_2 (1:1) near 25 °C. The results are summarized in Table 3. As shown, this N–O cleavage works

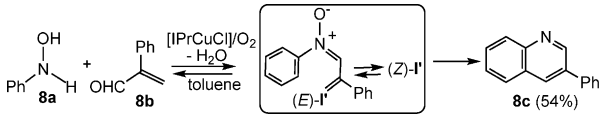
Table 3: Reductive cleavage of the N–O bonds.



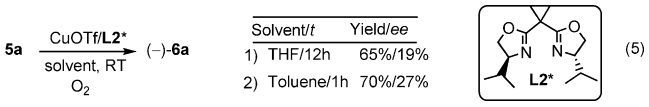
[a] [**6a**] = 0.04 M. Product yields are reported after purification from a silica gel column.

well for **6a–c** and **6e**, bearing various aniline groups (R^2 = 4-XC_6H_4, X = H, F, Cl, and CO_2Me), thus yielding the desired **7a–c** and **7e** in satisfactory yields (78–85%). This N–O cleavage is applicable to their *meta*- or *ortho*-substituted aniline analogues (**6g–i** and **6j–l**), thus giving the highly functionalized cyclohexanes **7g–i** and **7j–l** in 69–83% yields. The cleavage also proceeded well with substrates **6n** and **6o** comprising different R^1 substituents (R^1 = 4-XC_6H_4, X = Cl and Me), and giving the compounds **7n** and **7o**, respectively, in good yields. These reactions were compatible with the 2- and 3-thienyl-containing species **6p** and **6q**, respectively, thus yielding the corresponding products **7p** (72%) and **7q** (63%). For the alkyl-substituted derivatives **6r–u**, the reductive cleavage delivered the compounds **7r–u** in 67–81% yields. Of these products, X-ray diffraction[16] of a representative compound, **7b**, was performed to confirm its structure as having all hydroxy and amino groups in axial positions.

Shown in Equations (4) and (5) (Tf = trifluoromethanesulfonyl) are control experiments to assist the understanding of the mechanism of the dimerization. Treatment of *N*-hydroxyaniline (**8a**) with 2-phenyl-2-en-1-al (**8b**) with [IPrCuCl]/O_2 in toluene (25 °C, 12 h) produced the quinoline



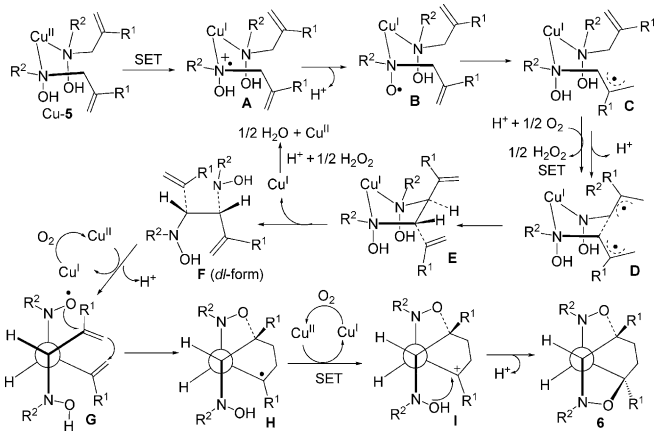
(4)



(5)

derivative **8c** in 54% yield through an intramolecular cyclization of the *E*-configured nitrone intermediate (*E*)-**I′**. We thus exclude the role of nitrone intermediates (**I′**) in the dimerization reactions because of their distinct chemoselectivity. We tested further the dimerization of **5a** with chiral CuOTf/**L2*** [**L2*** = 2,2-bis{(4S)-(−)-4-isopropyloxazoline}-propane], which enabled the production of (−)-**6a** in 19 and 27% *ee* in THF and toluene, respectively.[18] The observed asymmetric induction of (−)-**6a** suggests that copper complexes participate in the formation of the first asymmetric C–C bond during the course of the dimerization.

We postulate a mechanism in Scheme 1. Under O_2, Cu^{II} species are generated to coordinate with two molecules of the *N*-hydroxy aminopropenes **5** to form Cu-**5**, which undergoes a single-electron transfer (SET) to generate the radical cation **A**, and subsequently yields the amidoxyl radical **B**.[10] We



Scheme 1. Postulated mechanism and stereochemical course.

envisage that **B** becomes a stable allyl radical **C** by hydrogen transfer. Concurrently, air oxidation of Cu^I to Cu^{II}, as with **C**, enables the same SET to form the bis(allyl) radical **D**, further inducing a dimerization to generate species **E**. Notably, **E** should preferably have a *trans* configuration for two bulky alkenyl groups to minimize steric hindrance. We envisage that **E** tends to release Cu^I because of its highly substituted and congested geometry, thus yielding the dimers **F** only in *dl*-forms. This process rationalizes well the asymmetric induction of the chiral copper catalyst [Eq. (5)]. As shown by the ground-state staggered conformations, **F** undergoes SET to generate the amidoxyl radical **G** to activate double radical/alkene cyclizations,[10] thus yielding the tertiary carbon radical **H** efficiently. Cu^{II} oxidation of these carbon radicals form to activate double radical/alkene cyclizations,[10] thus yielding the stable tertiary cation **I**, and ultimately giving the desired compounds **6** upon ring closure. Such cascade radical cyclizations are consistent with the stereochemical course of these dimerizations.

In this mechanism, we did not observe a 5-*endo*-trig radical cyclization for the monomeric species **B** because this process is not feasible according to the Baldwin's rule.[19] In contrast, the 5-*exo*-trig cyclization of **G** is operable in accord with this rule. We postulated that its rigid staggered conformation allows the amidoxy radical close to its alkenyl group to facilitate this process.

In summary, we report the copper-catalyzed aerobic oxidation of *N*-hydroxyaminopropenes to form N- and O-containing cyclohexane derivatives. Such oxidations proceed with surprising stereocontrol and high efficiency. Reductive cleavage of the N–O bonds of these functionalized cyclohexanes affords 1,4-dihydroxy-2,3-diaminocyclohexanes which are the structural skeletons of several bioactive molecules. Our control experiments exclude the formation of nitrone intermediates, whereas chiral copper catalysts can induce asymmetric induction. We postulate a mechanism in which the key step involves the coordination of Cu^{II} with two allyl radicals to achieve a stereoselective C–C bond formation. These *dl*-configured dimeric intermediates presumably form amidoxyl radicals to undergo tandem radical/alkene cyclizations with high stereocontrol, thus giving observed products efficiently.

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