Synlett L. Wang, Z. Yan Letter

Visible-Light-Mediated Facile Reductive Aromatization of Quinols

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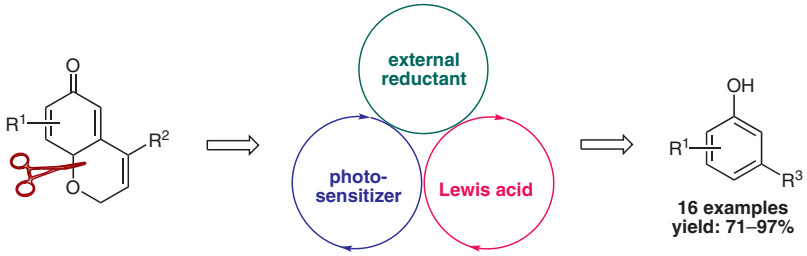


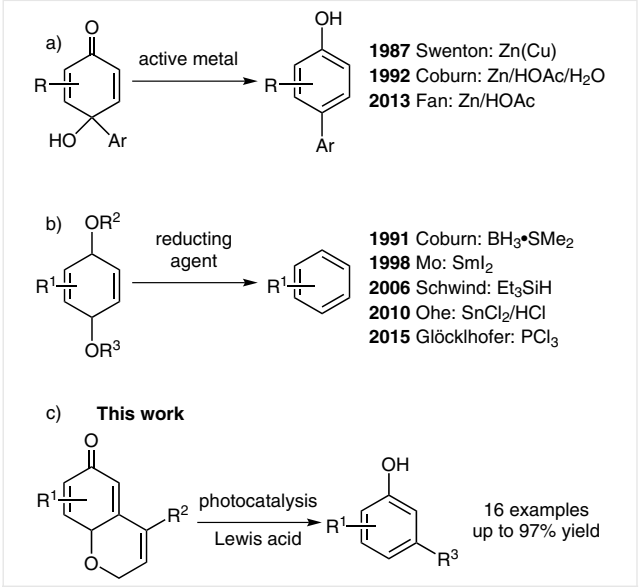
Received: 30.12.2015
Accepted after revision: 08.02.2016
Published online: 09.03.2016
DOI: 10.1055/s-0035-1561404; Art ID: st-2015-w1006-l

Abstract A range of phenols bearing multiple useful functionalities at their *meta* positions were prepared from the corresponding quinols under the cooperative effects of visible light irradiation, $Ru(bpy)_3Cl_2$ photosensitizer, Hünig's base, $LiBF_4$, and MeCN solvent. The process involves visible-light-enabled photocatalytic cleavage of C–O bond as the strategic event.

Key words visible light, photocatalysis, amine, C–O bond cleavage, aromatization

As a highly versatile class of substances, quinols are known to serve as useful precursors to various compounds in organic synthesis. Great efforts have been made to achieve vital transformations of quinols, such as cycloaddition,[1] Michael addition[2] and reductive aromatization.[3] As we know, reductive aromatization of quinols was first accomplished with zinc and its alloys. Various reducing agents were next well investigated involving $LiAlH_4$, Et_3SiH, $BH_3{\cdot}SMe_2$, SmI_2 and $SnCl_2$ (Scheme 1). Despite these significant advances, there remains a strong need for discovering mild and convenient methods for reductive aromatization of quinols.

In recent years, remarkable progress in photocatalytic cleavages of C–C and C–X bonds has been achieved in uncovering both new catalysis concepts and robust synthetic applications.[4–6] In turn, such advances serve as the key motivation for us to tackle a visible-light-mediated protocol for the direct and mild reductive aromatization. Within this context, we have reported the preparation of a range of phenols bearing multiple useful functionalities at their *meta* positions.



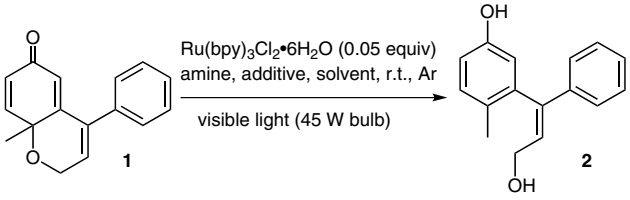
Scheme 1 Reductive aromatization of quinols and equivalents

To the best of our knowledge, C–O bonds cleavage of special substrates could be achieved in the presence of commercially available photosensitizer as the catalyst and amine as the real reducing agent. Therefore, *meta*-substituted phenols would be synthesized by photocatalytic reductive aromatization of quinols.

Motivated by this possibility, we initially explored a set of reaction conditions using $Ru(bpy)_3Cl_2$ as the photosensitizer. Eventual success was achieved after an elaborate screening (Table 1), proving that the formation of phenols in synthetically useful efficiency depends on the synergy of several factors critically. With quinol **1** as the model substrate and a 45 W household bulb as the light source, we employed the $Ru(bpy)_3Cl_2$ (0.05 equiv) as the photosensitiz-

er, amine *i*-Pr_2NEt (Hünig's base) (5.00 equiv) as the reducing agent and MeCN (0.05 M) as the solvent. Unfortunately, only trace of the desired product was detected (entry 1, Table 1). A significant observation was noted when mild Lewis acid ($LiClO_4$, 1.00 equiv) was added into the reaction system (42%, entry 2). In contrast, strong Lewis acid, such as $ZnCl_2$ (1.00 equiv), made substrate **1** decompose (entry 4). Interestingly, a simple switch of the Lewis Acid $La(OTf)_3$ to $LiBF_4$ was found to dramatically improve the reactivity (entries 5 and 6). To our delight, a doubled loading of $LiBF_4$ delivered the product in nearly quantitative yield (97% isolated yield). Compared with Lewis acid, the solvent effect was shown to be fairly significant during this transformation. Under otherwise identical reaction conditions, the product was all furnished in lower yields when MeCN was replaced by THF, 1,4-dioxane, MeOH, Et_2O, CH_2Cl_2 or DMF (entries 8–13). Furthermore, reaction parameters from the experiments shown in entries 14–18 revealed the critical importance of amine, as the use of Et_3N, Et_2NH, pyrrolidine, aniline or monomethylaniline led to significant reductions or even complete inhibitions in reactivities. The different reactivities would, thus, suggest that single electron transfer from amine to the photoexcited catalyst should be crucial in this transformation.[4d,7] $Ir(ppy)_3$ (5% mol) and eosin Y (5% mol) were examined while the Ru catalyst was absent, both leading to rather low yields (entries 19 and 20). Finally, complete inhibition of the reactivity could be identified from control experiments conducted under the absence of

Table 1 Optimization of Reaction Conditions



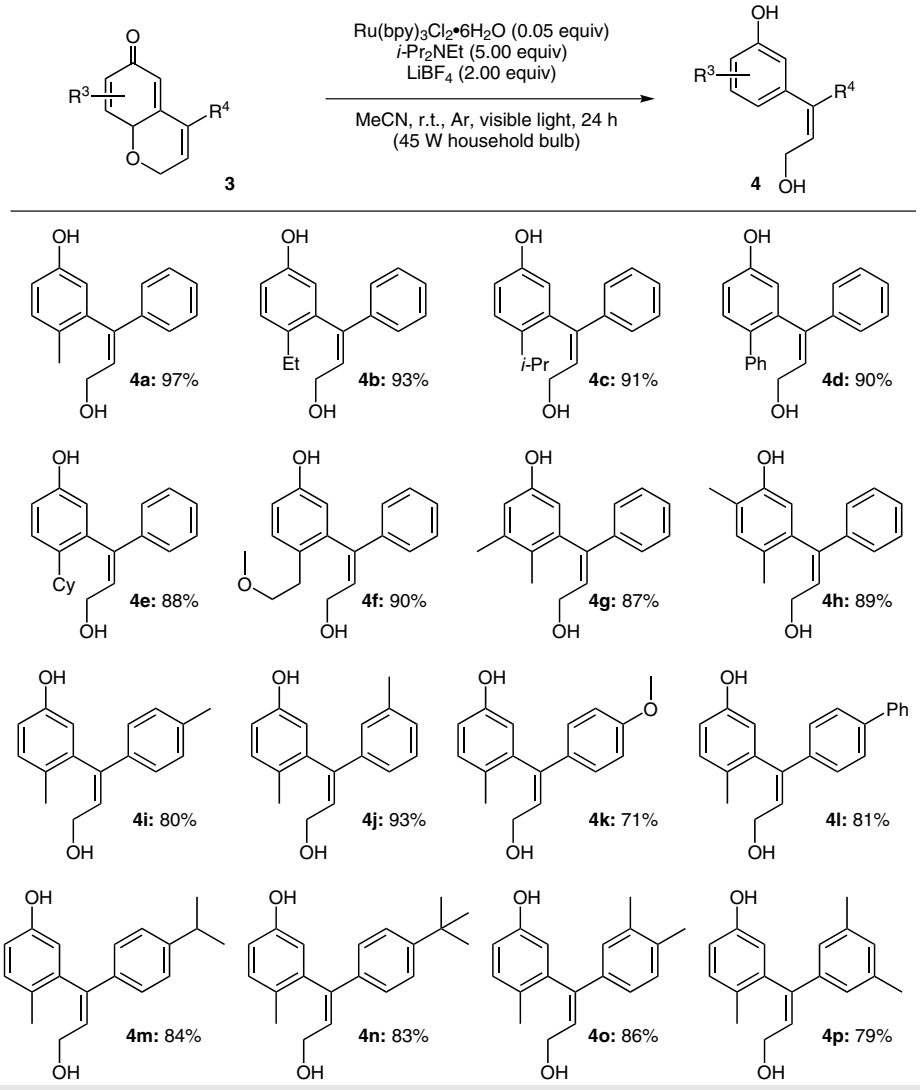
Entry	Catalyst (0.05 equiv)	Amine (5.00 equiv)	Solvent	Additive (equiv)	Yield (%)[a]
1	$Ru(bpy)_3Cl_2·6H_2O$	*i*-Pr_2Net	MeCN	–	trace
2	$Ru(bpy)_3Cl_2·6H_2O$	*i*-Pr_2Net	MeCN	$LiClO_4$ (1.00)	42
3	$Ru(bpy)_3Cl_2·6H_2O$	*i*-Pr_2NEt	MeCN	$Mg(ClO_4)_2$ (1.00)	31
4	$Ru(bpy)_3Cl_2·6H_2O$	*i*-Pr_2NEt	MeCN	$ZnCl_2$ (1.00)	dec.
5	$Ru(bpy)_3Cl_2·6H_2O$	*i*-Pr_2NEt	MeCN	$La(OTf)_3$ (1.00)	18
6	$Ru(bpy)_3Cl_2·6H_2O$	*i*-Pr_2NEt	MeCN	$LiBF_4$ (1.00)	70
7	$Ru(bpy)_3Cl_2·6H_2O$	*i*-Pr_2NEt	MeCN	$LiBF_4$ (2.00)	97[b]
8	$Ru(bpy)_3Cl_2·6H_2O$	*i*-Pr_2NEt	THF	$LiBF_4$ (2.00)	58
9	$Ru(bpy)_3Cl_2·6H_2O$	*i*-Pr_2NEt	1,4-dioxane	$LiBF_4$ (2.00)	61
10	$Ru(bpy)_3Cl_2·6H_2O$	*i*-Pr_2NEt	MeOH	$LiBF_4$ (2.00)	59
11	$Ru(bpy)_3Cl_2·6H_2O$	*i*-Pr_2NEt	Et_2O	$LiBF_4$ (2.00)	trace
12	$Ru(bpy)_3Cl_2·6H_2O$	*i*-Pr_2NEt	CH_2Cl_2	$LiBF_4$ (2.00)	35
13	$Ru(bpy)_3Cl_2·6H_2O$	*i*-Pr_2NEt	DMF	$LiBF_4$ (2.00)	51
14	$Ru(bpy)_3Cl_2·6H_2O$	Et_3N	MeCN	$LiBF_4$ (2.00)	31
15	$Ru(bpy)_3Cl_2·6H_2O$	Et_2NH	MeCN	$LiBF_4$ (2.00)	15
16	$Ru(bpy)_3Cl_2·6H_2O$	pyrrolidine	MeCN	$LiBF_4$ (2.00)	trace
17	$Ru(bpy)_3Cl_2·6H_2O$	aniline	MeCN	$LiBF_4$ (2.00)	trace
18	$Ru(bpy)_3Cl_2·6H_2O$	monomethylaniline	MeCN	$LiBF_4$ (2.00)	trace
19	Eosin-Y	*i*-Pr_2NEt	MeCN	$LiBF_4$ (2.00)	35
20	$Ir(ppy)_3$	*i*-Pr_2NEt	MeCN	$LiBF_4$ (2.00)	26
21	/	*i*-Pr_2NEt	MeCN	$LiBF_4$ (2.00)	NR
22	$Ru(bpy)_3Cl_2·6H_2O$	*i*-Pr_2NEt	MeCN	$LiBF_4$ (2.00)	NR
23	$Ru(bpy)_3Cl_2·6H_2O$	*i*-Pr_2NEt	MeCN	$LiBF_4$ (2.00)	NR

[a] Determined by ^1H NMR analysis using 1,3,5-trimethoxybenzene as internal standard.
[b] Isolated yield.

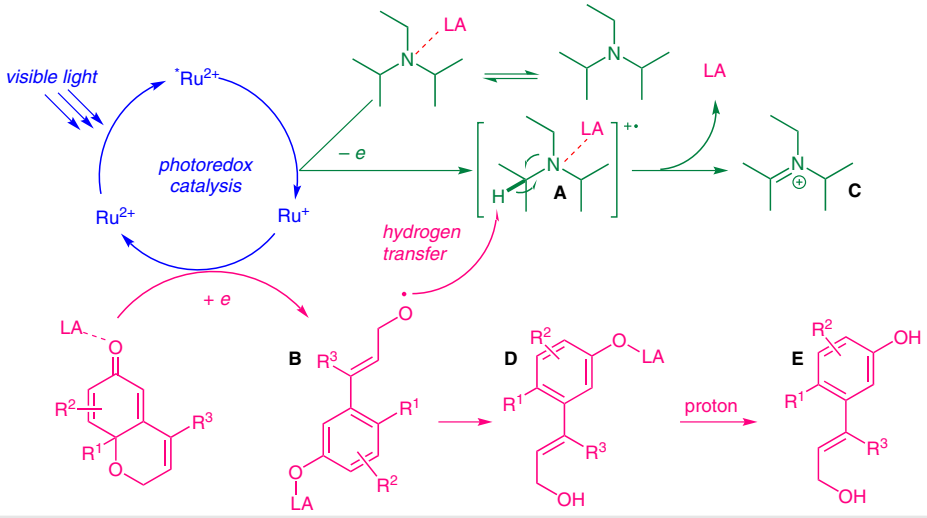
either a photocatalyst, visible light, or amine (entries 21–23). Collectively, these screening results established the optimal reaction conditions: 5% mol of $Ru(bpy)_3Cl_2$ photocatalyst, 5.00 equiv of Hünig's base, 2.00 equiv of $LiBF_4$ additive and MeCN as the solvent under a balloon-argon atmosphere at room temperature.

With the above optimal conditions in hand, we next probed the scope of the facile reductive aromatization of quinols. A range of quinols were prepared from simple phenols bearing electron-donating functional groups rather than electron-withdrawing functional groups[8] (see the Supporting Information). As compiled in Scheme 2, in each case the reaction proceeded smoothly to furnish the desired phenols in moderate-to-high isolated yields (71–97%). In the cases **4a**–**c**, steric effect of the aliphatic substitution patterns (R^3) on the quinol rings seemed to pose a slight influence on the reaction efficiencies; the presence of a bulky substituent retarded the reduction to some extent. Aromatic (**4d**), naphthenic (**4e**) and oxygen-containing substitutions (**4f**) were also well tolerated. 3,4,5-Trisubstituted and 2,4,5-trisubstituted phenols (**4g** and **4h**) were also successfully prepared by this facile reductive process with high efficiencies.

To further examine the substrate scope of the methodology, the effect of the aromatic residues (R^4) was next investigated. As summarized in Scheme 2 (**4i**–**p**), the corresponding phenols were generally delivered in moderate-to-high isolated yields. These results revealed the fact that the substitution patterns (*meta*, *para*) on the aryl rings seemed to pose no obvious influence on the reaction efficiency except in **4k**. Although methoxy-substituted aryl ring inhibited the reaction activity dramatically compared with other



Scheme 2 Survey of reaction scope



Scheme 3 Proposed mechanism

cases, the isolated yield was acceptable. An aryl ring with more conjugation (**4l**) was also a comparably competent substrate. Bulky substitution patterns (**4m**–**n**) and disubstituted (**4o**–**p**) aryl rings were well tolerated.

Enabled by these observations, a plausible mechanistic network is briefly depicted in Scheme 3. We believe that three intimately coupled pathways could play critical roles in this unusual photocatalytic reduction: Ru(I)/Ru(II)-photoredox cycle (in blue), amine dehydrogenative oxidation (in green), and quinol substrate reduction (in red). Under visible light irradiation, the excited state species *Ru(II) initially captures an electron from amine–Lewis acid complex,[6a,7b,c] giving rise to Ru(I) and the corresponding radical cation **A**. Activated by free Lewis acid, the electron deficiency of quinol could thus grant its oxidation capacity that abstracts an electron from the Ru(I) intermediate, closing the photoredox catalytic cycle. The concomitantly generated oxygen radical **B** could be immediately quenched by the radical cation **A** through a hydrogen transfer process, furnishing oxygen anion **D** and amine cation **C**. Finally, protonation of oxygen anion **D** leads to the phenol product **F**.

In summary, visible-light-mediated facile reductive aromatization of quinols was well developed.[9] A series of phenols bearing multiple useful functionalities at their *meta* positions were prepared based on the optimized conditions which may serve as new intermediates for natural products syntheses and pharmaceutical research. Furthermore, many useful synthetic utilities could be well exploited on a wider platform of photoredox catalysis.

Acknowledgment

We thank the Shenzhen Bureau of Science and Technology for financial support.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1561404.

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(8) Oxidative dearomatization of phenols bearing electron-withdrawing functional groups failed to occur.

(9) **General Procedure for Visible-Light-Mediated Facile Reductive Aromatization of Quinols**: A flame-dried round-bottom flask (10 mL) was equipped with magnetic stirring bar and charged with quinol compound (0.1 mmol, 1.0 equiv), tris(2,2′-bipyridyl)ruthenium(II) chloride hexahydrate (0.005 mmol, 0.05 equiv), $LiBF_4$ (0.2 mmol, 2.0 equiv) and MeCN (2.0 mL). To the mixture was then added amine (0.5 mmol, 5.0 equiv), and it was irradiated by a household bulb (45 W) under a balloon argon atmosphere at r.t. until the starting material disappeared from the TLC. The reaction mixture was filtrated through celite and washed with Et_2O. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography to afford the pure product.

(*Z*)-3-(3-Hydroxy-1-phenylprop-1-en-1-yl)-4-methylphenol (4a): colorless liquid; yield: 23.3 mg (97%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.13–7.30 (m, 5 H), 7.02 (d, *J* = 8.2 Hz, 1 H), 6.75 (dd, *J* = 8.2, 2.7 Hz, 1 H), 6.62 (d, *J* = 2.7 Hz, 1 H), 6.29 (t, *J* = 6.9 Hz, 1 H), 4.27 (s, 2 H), 4.02 (d, *J* = 5.9 Hz, 2 H), 1.89 (s, 3 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 153.76 (s), 143.13 (s), 139.95 (s), 139.30 (s), 131.35 (s), 128.35 (s), 128.18 (s), 127.59 (s), 126.70 (s), 126.46 (s), 116.64 (s), 114.83 (s), 60.84 (s), 18.59 (s). HRMS: *m*/*z* [M + Na^+] calcd for $C_{16}H_{16}NaO_2$: 263.1048; found: 263.1041.

(*Z*)-2-(3-Hydroxy-1-phenylprop-1-en-1-yl)-[1,1′-biphenyl]-4-ol (4d): white solid; yield: 27.2 mg (90%). ^{1}H NMR (500 MHz, MeOD): δ = 7.21 (d, *J* = 8.4 Hz, 1 H), 7.06–7.17 (m, 10 H), 6.89 (dd, *J* = 8.4, 2.6 Hz, 1 H), 6.69 (d, *J* = 2.6 Hz, 1 H), 6.06 (t, *J* = 6.4 Hz, 1 H), 4.00–4.14 (m, 1 H), 3.80 (dd, *J* = 13.2, 5.3 Hz, 1 H). ^{13}C NMR (126 MHz, acetone): δ = 156.51 (s), 141.53 (s), 141.29 (s), 140.95 (s), 138.76 (s), 133.35 (s), 131.26 (s), 129.30 (s), 128.78 (s), 127.92 (s), 127.56 (s), 126.89 (s), 126.66 (s), 126.12 (s), 117.41 (s), 115.05 (s), 60.17 (s). HRMS: *m*/*z* [M + Na^+] calcd for $C_{21}H_{18}NaO_2$: 325.1204; found: 325.1200.

(*Z*)-3-{1-([1,1′-Biphenyl]-4-yl)-3-hydroxyprop-1-en-1-yl}-4-methylphenol (4l): white solid; yield: 25.6 mg (81%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.53 (d, *J* = 7.4 Hz, 2 H), 7.44 (d, *J* = 8.3 Hz, 2 H), 7.39 (t, *J* = 7.6 Hz, 2 H), 7.32 (t, *J* = 7.3 Hz, 1 H), 7.25 (d, *J* = 8.3 Hz, 2 H), 7.05 (d, *J* = 8.3 Hz, 1 H), 6.78 (dd, *J* = 8.2, 2.6 Hz, 1 H), 6.67 (d, *J* = 2.6 Hz, 1 H), 6.36 (t, *J* = 6.9 Hz, 1 H), 3.98–4.10 (m, 2 H), 1.92 (s, 3 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 153.85 (s), 143.02 (s), 140.50 (s), 140.33 (s), 139.09 (s), 138.79 (s), 131.44 (s), 128.79 (s), 128.14 (s), 127.35 (s), 127.03 (s), 126.92 (s), 126.87 (s), 126.27 (s), 116.58 (s), 114.98 (s), 60.78 (s), 18.68 (s). HRMS: *m*/*z* [M + Na^+] calcd for $C_{22}H_{20}NaO_2$: 339.1361; found: 339.1357.

(*Z*)-3-[1-(3,4-Dimethylphenyl)-3-hydroxyprop-1-en-1-yl]-4-methylphenol (4o): colorless liquid; yield: 23.0 mg (86%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.99–7.13 (m, 3 H), 6.94 (d, *J* = 7.9 Hz, 1 H), 6.75 (dd, *J* = 8.2, 2.7 Hz, 1 H), 6.59 (d, *J* = 2.6 Hz, 1 H), 6.31 (t, *J* = 6.8 Hz, 1 H), 4.04 (d, *J* = 6.8 Hz, 2 H), 2.23 (s, 3 H), 2.21 (s, 3 H), 1.97 (s, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 153.5 (s), 142.9 (s), 138.9–139.5 (m), 137.5 (s), 136.4 (s), 136.2 (s), 131.2 (s), 129.6 (s), 128.2 (s), 127.5 (s), 125.7 (s), 124.0 (s), 116.5 (s), 114.5 (s), 60.9 (s), 19.8 (s), 19.4 (s), 18.6 (s). HRMS: *m*/*z* [M + Na^+] calcd for $C_{18}H_{20}NaO_2$: 291.1361; found: 291.1354.