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Asymmetric Dearomatization of Phenols via Ligand-Enabled Cooperative Gold Catalysis

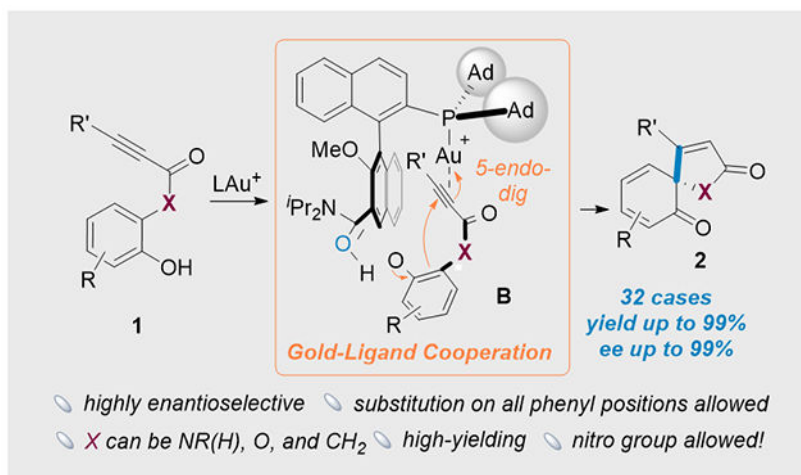
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Abstract

By employing a chiral bifunctional phosphine ligand, a gold(I)-catalyzed efficient and highly enantioselective dearomatization of phenols is achieved via versatile metal-ligand cooperation. The reaction is proven to be remarkably general in scope, permitting substitutions at all four remaining benzene positions, accommodating electron-withdrawing groups including strongly deactivating nitro, and allowing carbon-based groups of varying steric bulk including *tert*-butyl at the alkyne terminus. Moreover, besides *N*-(*o*-hydroxyphenyl)alkynylamides, the corresponding ynoates and ynones are all suitable substrates. Spirocyclohexadienone-pyrrol-2-ones, spirocyclohexadienone-butenolides, and spirocyclohexadienone-cyclopentenones are formed in yields up to 99% and with ee up to 99%.

Graphical Abstract



Asymmetric dearomatization of phenols was achieved by employing chiral bifunctional phosphine ligands in cooperative gold catalysis. This transformation demonstrated a remarkable generality, affording the desired product with high yields (up to 99%) and excellent enantioselectivities (ee up to 99%).

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Supporting information for this article is given via a link at the end of the document.

Keywords

Dearomatization; gold catalysis; metal-ligand cooperation; enantioselectivity; cyclization

Catalytic asymmetric dearomatization (CADA)^[1–2] is an efficient method for converting abundant planar aromatic compounds into chiral three-dimension structures featuring challenging quaternary carbon centers, enabling rapid synthesis of natural products^[3–5] and offering an expedient venue to escape the ‘flatland’.^[6] Over the past two decades, significant developments have been made in the catalytic asymmetric dearomatization of electron-rich aromatic compounds and in particular naphthols, furans, pyrroles, and indoles.^[1–2] However, the asymmetric dearomatization of ubiquitous phenols affording chiral quaternary centers remains largely underdeveloped and challenging partly due to their higher aromatic stabilization,^[7–9] and most literature reports in this area exhibit moderate enantioselectivity.^[10–14] For the ones reporting excellent ee values,^[15–24] the substrate scopes are limited (Scheme 1A). For example, in the enantioselective oxidative spiro-lactonization of phenol derivatives reported by Ishihara,^[16] an *ortho* substitution is required to achieve 90% ee; in the enantioselective fluorinative dearomatization of phenols reported by Toste, both the R group and the C6 substituents need to be H to achieve 87% ee;^[15] in the asymmetric hydroxylative phenol dearomatization reported by Pouységu and Quideau,^[17] the R group *ortho* to the phenolic OH group needs to be sterically demanding for high enantioselectivity; several studies focus on specific substrate types including resorcinol-based aryl ketones/ aldehydes^[18–19] and alkyl-/RO substituted phenols of certain patterns.^[20–24] Most of the substituents in these studies are limited to electron-donating alkyl/alkoxy/hydroxy, and no strongly electron-withdrawing groups are tolerated except in the case of resorcinol substrates^[18–19] where the additional phenolic OH group counters the deactivating carbonyl group. Only one case possessing a nitro group is reported, albeit exhibiting a low yield (24%).^[18] Notwithstanding, we describe in this work a highly enantioselective and high-yielding cyclative dearomatization of phenols that for the first time exhibits an extremely broad substrate scope including the accommodation of substitution at every remaining benzene ring position and the tolerance of ester and even nitro substituents and affords synthetically valuable chiral spirocyclic trienone products or their dimeric products.

In the past several years, we introduced the concept of gold-ligand cooperation to homogeneous gold catalysis via the development of biaryl-2-ylphosphine ligands featuring a remote basic group.^[25] This metal-ligand cooperation can achieve dramatic rate acceleration^[26] and offers a unique and novel approach to realizing asymmetric gold-catalyzed cyclization.^[27–28] For example, we achieved an enantioselective dearomatization of alkynyl naphthols via a 5-*exo-dig* cyclization (Scheme 1B).^[28] The H-bonding interaction between the ligand basic substituent and the phenolic hydrogen shown in structure **A** is key for the observed chiral induction. However, for more challenging phenol derivatives, the few reported substrates are limited to electron-rich ones and the enantioselectivity is moderate to good. We reasoned this type of metal-ligand cooperation, due to the rigid ligand framework and the potentially optimal special positioning of the metal center and the ligand H-bond acceptor group, would be uniquely equipped to deliver dearomatization with a general tolerance of various substitutions. In this context, we considered the phenolic compound of

type **1** (Scheme 1C) as suitable substrates for this endeavor as its alkynylcarbonyl moiety would render a) the C-C triple bond more electrophilic and hence reactive towards variously-substituted phenols including electronically deactivated ones and b) the more rigid nature of the connection between the C-C triple bond and the phenol moiety – due mostly to the carbonyl group – more conducive to enantiocontrol by the gold complex, as hypothesized in the structure **B**. Notably, the cyclization would be *5-endo-dig*, which is unique as our prior works on asymmetric cooperative gold catalysis all involve *exo* cyclization.^[27–28]

We initiated our study using *N*-benzyl-*N*-(2-hydroxyphenyl)hept-2-ynamide **1a** as the substrate (Table 1). It is readily prepared in two steps from 2-benzoxazolinone. The dearomative spirocyclization of this type of 2-alkynamide-functionalized phenols or protected phenols has been realized via gold catalysis^[29–31] or the activation of stoichiometric electrophilic halogen or chalcogen species.^[32–35] But, no enantioselective variants have been documented. With WangPhosAuCl (5 mol%) as the precatalyst, the reaction went to completion in less than 15 minutes at room temperature in DCM, affording the spirobicycle **2a** in 90% yield (Table 1, entry 1). **2a** contains one cyclohexa-2,4-dien-1-one ring and one γ -lactam ring, which are fused through a chiral quaternary carbon center. The fast reaction is consistent with the rate acceleration phenomena observed in our previous gold-ligand cooperative catalysis.^[26, 28] Encouraged by this racemic result, we explored several chiral bifunctional ligands prepared from (*S*)-binol^[28] for chiral induction. While the phosphonate ligand **L1** (entry 2) performed poorly, the amide-functionalized ligands **L2–L4** (entries 3–5) led to rapid reactions (<15 min) and excellent enantioselectivities, with (*S*)-**L4** featuring a *N,N*-diisopropylamide group being the best and affording **2a** with 98% ee (entry 5). In contrast, when the ligand (*S*)-**L5** missing the remote amide functional group was employed, the reaction was notably slower and resulted in a moderate ee with the opposite sense (entry 6). ¹H NMR monitoring of the reactions using **L4** and **L5** (0.5 mol %) separately as the ligand establishes >30 times of rate acceleration by the former. (see Supporting Information for more details). These results highlight the essential role of the amide functionality as a rate-accelerating directing group that inverts the inherent stereoinduction by the chiral ligand framework. Among the solvents tested, DCM and DCE gave the best result (entry 5, entries 7–10). Moreover, replacing the halogen scavenger NaBARF (10 mol%) with AgNTf₂ (5 mol%) or AgSbF₅ (5 mol%) did not affect the enantioselectivity (entries 11 and 12).

With the optimized reaction condition in hand (Table 1, entry 5), we carried out the scope study (Table 2). The reaction readily tolerates various alkyne substituents including ^tPr, ^tBu, different ring structures, and unsaturated groups. The spirocyclization products **2a–2g** were isolated in good to excellent yields and exhibited excellent enantiomeric excesses – in most cases 98%. The reaction forming **2c** required a longer reaction time due to steric hindrance caused by the ^tBu substituent. Despite this, the product was formed with near enantiopurity (i.e., ee = 99%). The propiolamide substrate (i.e., R¹ = H) also reacted smoothly, affording **2h** in 95% yield and with 90% ee. The reaction also showed excellent tolerance of different substituents on the phenol ring including Me, ^tBu, F, Br, CO₂Me, and strongly electron-withdrawing NO₂. The nitro case is remarkable in asymmetric phenol dearomatization and confirms the versatility of the cooperative catalysis. All of the corresponding dearomatized

cyclization products (**2i-2o**) were obtained in good yields and high enantioselectivities (97%-99% ee). Interestingly, the reaction forming **2p**, which has a methyl *ortho* to the amide group, was not enantioselective at all. This is likely due to the existence of racemic non-interconvertible atropisomers of the substrate **1p** at the ambient reaction temperature, which eventually led to the equal ratio of opposite enantiomeric products. The restricted rotation of the phenyl-N bond in this case is avoided by replacing the *N*-benzyl group with a hydrogen atom. As such, the spirocyclization led to the desired **2r** in 93% ee. Moreover, removing the *ortho*-methyl group led to **2s** with an NH group with a 97% ee. The *N*-benzyl group was also readily replaced by a *N*-Me group without consequence in the case of **2q**. When an *N*-allyl group was present in the reaction, the reaction proceeded to completion in 15 minutes under the standard reaction conditions, and the expected spirobicyclic product was observed by NMR measurement (see the Supporting Information for details). However, attempts to obtain the pure product were unsuccessful. As it undergoes the intramolecular Diels-Alder reaction (IMDA) [31] during workup and purification to form the adduct **2t** featuring a tetracyclic bridged skeleton. To this end, we performed the reaction at 40 °C for 12 hours. The starting material was fully converted to **2t**, which was isolated in 99% yield with 93% ee. Additionally, the tetracyclic product **2u** was obtained in 96% ee after the substrate containing a *N*-cinnamyl group was subjected to gold catalysis. In this case, the IMDA was faster as the reaction was performed at ambient temperature. In light of the afore-discussed scope limitations in the literature reports, it is remarkable that this chemistry tolerates various substituents at all four available positions on the benzene ring and of highly electron-withdrawing characteristics.

We were delighted to discover that the substrate scope can be expanded to 2-hydroxyphenyl ynoates (X = O). For example, the reaction of 2-hydroxyphenyl hex-2-ynoate (**1v**) resulted in the formation of the dimeric product **2v** in 81% yield and with 97% ee. The facile dimerization of the initially-formed spirocyclohexadienone-butenolide via the D-A reaction is consistent with the literature report.[36-38] The structure of **2v** was confirmed by X-ray diffraction studies.[39] Changing the alkyne terminal *n*Pr group to sterically bulkier cyclohexyl group also resulted in the formation of the dimer product **2w**. However, a *t*Bu group does suppress the D-A reaction, and the spirodienone-butenolide **2x** was isolated in a 79% yield. In all these cases, the reactions were highly enantioselective, with ee values ranging from 97% to 99%. The facile D-A dimerization can be prevented by the presence of 4,5-dibromo substitutions on the substrate phenol ring, and several spirocyclohexadienone-butenolides, i.e., **2y-2ab**, were obtained in good to excellent yields (85%-94%) and with excellent enantioselectivities (95%-98%). In the case of the propiolate substrate containing a terminal alkyne, the enantioselectivity is moderate (ee = 84%). The absolute configuration of the chiral quaternary carbon center of the dearomatization product was determined to be *R* by analyzing the X-ray structure of **2y**. [39]

Moreover, *o*-hydroxybenzyl ynone (i.e., X = CH₂) are also suitable substrates for this asymmetric dearomatization chemistry.[40-43] In the case of **2ad** possessing a bulky *t*-butyl group at the alkyne terminus, the gold catalysis is efficient and highly enantioselective, affording the spirodienone-cyclopentenone structure in 80% yield and with 98% ee. For the cases with a methyl (**2ae**) and an *n*-butyl (**2af**) group instead, the reactions were run at

cryogenic conditions, and good to excellent enantioselectivities (90% and 86%, respectively) were achieved.

This asymmetric gold catalysis can be readily scaled up (Scheme 2). For example, **2m** was prepared in 1.40 g (91% isolated yield and 99% ee) by using only 1 mol % catalyst loading. We investigated the preliminary synthetic utilities of these chiral spiro structures. For example, **2m** underwent the Suzuki coupling to afford the phenylated product **3** in 93% yield and 98% ee. The dimer **2v** can undergo retro-D-A reaction to generate the spirobicyclic cyclohexadienone-butenolide in situ upon heating at 180 °C in mesitylene in a sealed tube, which was trapped in situ by norbornene to afford the adduct **4** in 60% yield. The ee of **4** dropped to 75%, which might be due to a racemization process at a high temperature. In a similar vein, **2y** reacts smoothly with norbornene at room temperature, generating **5** in 87% yield and 99% ee, the structures of which were confirmed by X-ray crystallographic.^[39] Likewise, its D-A reaction with styrene was uneventful, affording **6** in 91% yield and 98% ee and with an *endo/exo* ratio of 13:1.

In summary, we report an efficient and highly enantioselective gold(I)-catalyzed dearomatization of phenols. The chiral binaphthylphosphine ligand featuring a 3'-*N,N*-diisopropylcarbamoyl group enables asymmetric gold-ligand cooperation in a 5-*endo-dig* cyclization via the formation of H-bonding interaction with the phenolic proton. The ligand rigidity and the optimal positioning of ligand basic group and Au enable this asymmetric phenol dearomatization to exhibit unprecedented generality in reaction scope. In contrast to prior arts, this chemistry tolerates substitution at all four remaining benzene positions and can accommodate the strongly electron-withdrawing nitro group, which is rare. It allows carbon-based groups of varying steric bulk including *tert*-butyl at the alkyne terminus. Moreover, the connecting group between the phenol moiety and the alkynylacyl group can be variously substituted amino group, oxygen, and methylene.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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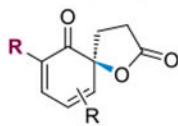
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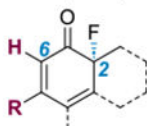
A) Literature with limited substitution patterns on phenol

Ishihara (2013)

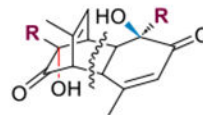


$R = H$, 87% ee
(one case)
 $R \neq H$, $\geq 90\%$ ee

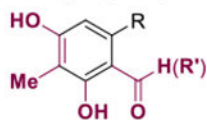
Toste (2013)



$R = H$ for $\geq 87\%$ ee
 $R = Me$, 79% ee
in one case

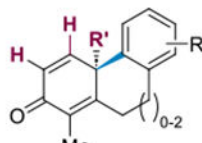
Pouységu and
Quideau (2014)

$R = Me$, 84% ee
 $R = iPr$, $\geq 92\%$ ee

Porco (2005)
Narayan (2018)

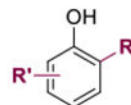
substrates
limited to this
specific type

Tang (2015)



Me
 R' limited to
primary alkyl

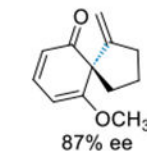
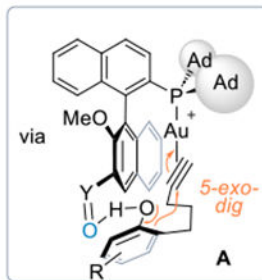
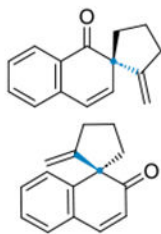
Buckley (2022)



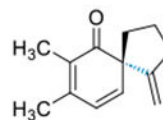
substrates limited to:
 R, R' = alkyl groups
2,4-substitution
pattern not suitable

B) Gold-catalyzed enantioselective dearomatization of alkynyl naphthols

Zhang (2022)

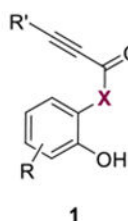


87% ee

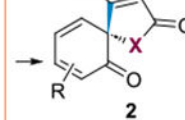
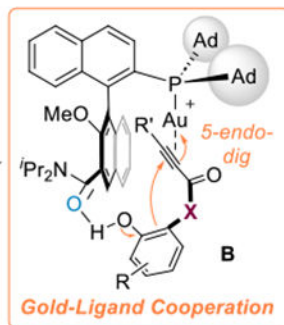


80% ee

C) This work



1



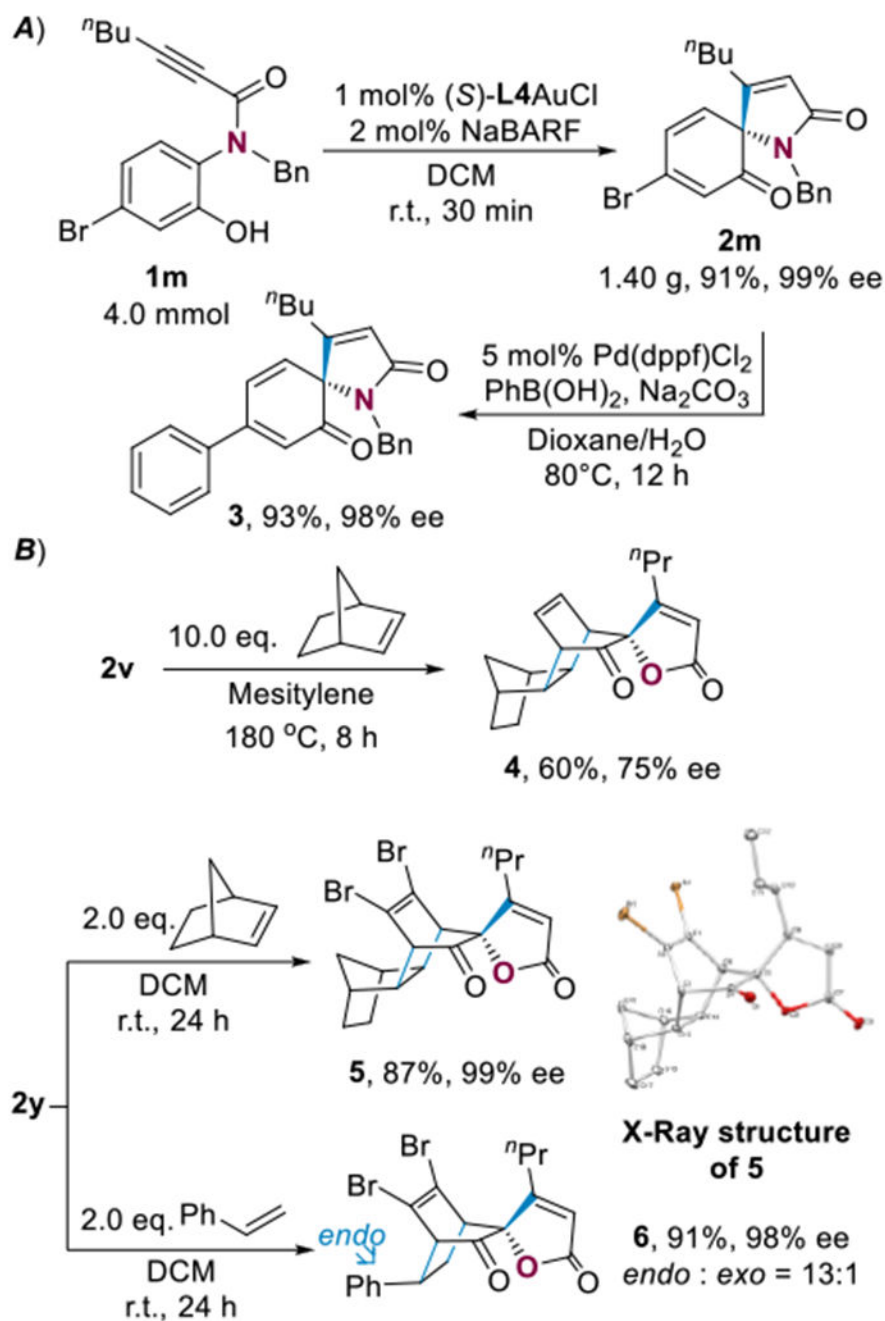
2

32 cases
yield up to 99%
ee up to 99%

- highly enantioselective
- substitution on all phenyl positions allowed
- X can be $NR(H)$, O , and CH_2
- high-yielding
- nitro group allowed!

Scheme 1.

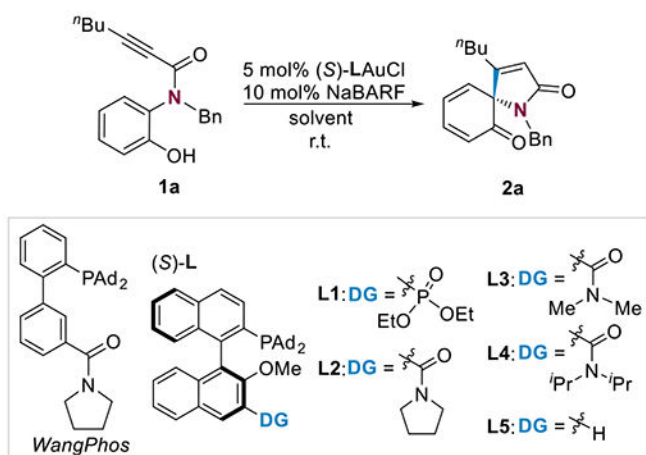
Prior studies of asymmetric dearomatization of phenols and this work.



Scheme 2.
Gram-scale synthesis and preliminary synthetic applications.

Table 1.

Reaction Conditions Optimization.



Entry	Ligand	Solvent	Time	Yield ^[a]	ee ^[b]
1	WangPhos	DCM	<15 min	90%	NA
2	(S)-L1	DCM	2 h	91%	-26%
3	(S)-L2	DCM	<15 min	95%	94%
4	(S)-L3	DCM	<15 min	86%	94%
5	(S)-L4	DCM	<15 min	90%	98%
6	(S)-L5	DCM	30 min	87%	-64%
7	(S)-L4	THF	24 h	14%	NA
8	(S)-L4	PhCF ₃	<15min	83%	97%
9	(S)-L4	toluene	30 min	95%	92%
10	(S)-L4	DCE	<15 min	89%	98%
11	(S)-L4 ^[c]	DCM	<15 min	88%	98%
12	(S)-L4 ^[d]	DCM	<15 min	89%	98%

^[a]Determined by ¹H NMR using diethyl phthalate as the internal standard.

^[b]Determined by chiral HPLC.

^[c]5 mol% AgNTf₂ was used instead of 10 mol% NaBARF.

^[d]5 mol% AgSbF₆ was used instead of 10 mol% NaBARF.

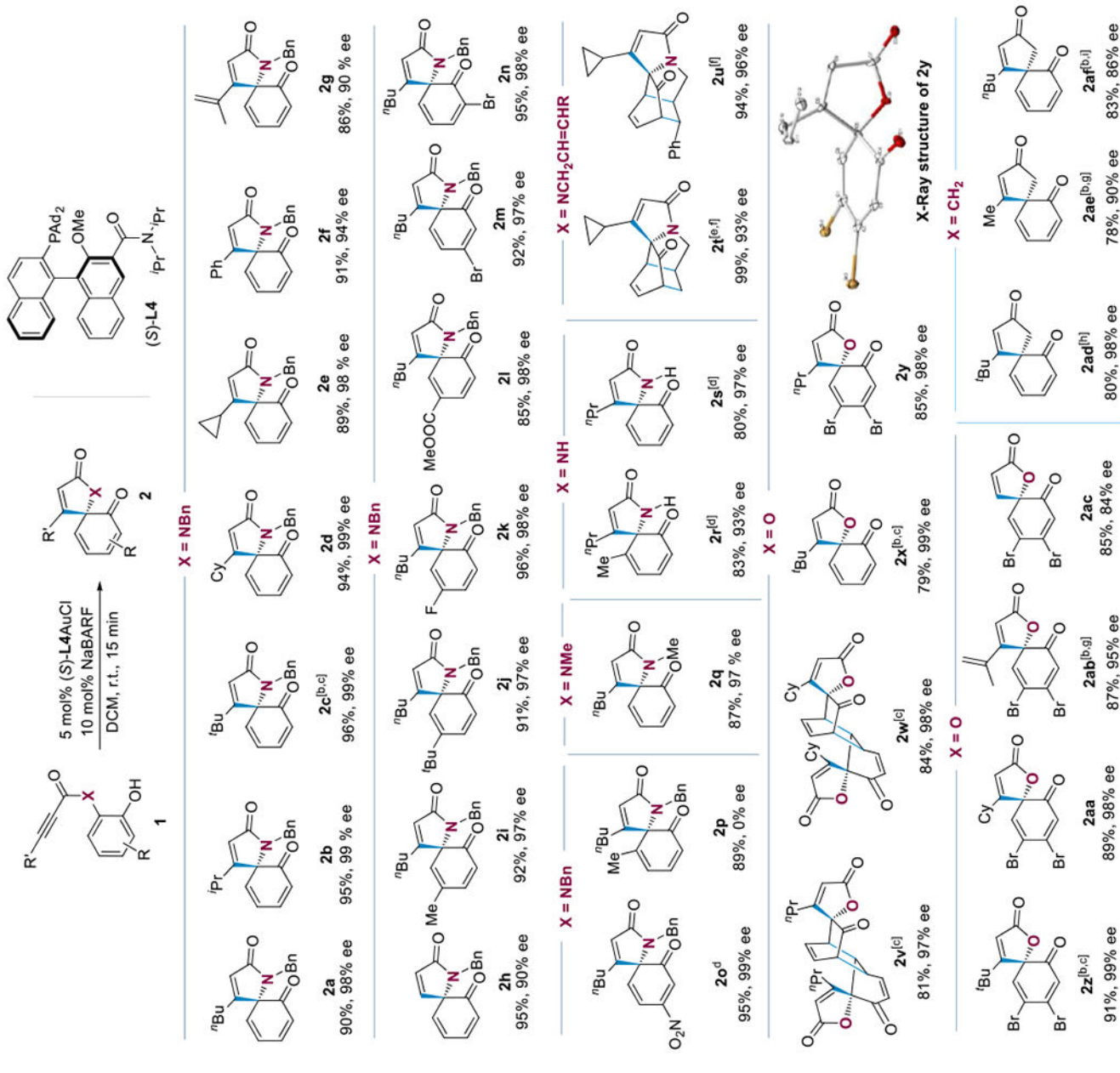
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Table 2.

Reaction Scope^[a]

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[a] Standard reaction conditions: 5 mol% (S)-L4AuCl, 10 mol% NaBARF, DCM (0.05 M), room temperature, 1.5 min.

[b] 5 mol% AgNTf₂ was used instead of 10 mol % NaBARF.

[c] 24 h.

[d] 2 h.

[e] 40 °C.

[f] 12 h.

[g] 40 °C.

[h] 10 mol % (S)-L4AuCl and 10 mol % AgNTf₂ was used, 24 h.

[i] -78 °C, 48 h.