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Chiral Bifunctional Phosphine Ligand Enables Asymmetric Trapping of Catalytic Vinyl Gold Carbene Species

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Abstract

Bifunctional ligand-enabled cooperative gold catalysis accelerates nucleophilic attacks and offers a versatile strategy to achieve asymmetric gold catalysis. Distinct from the prior studies employing alkyne/allene as the electrophilic site, this work engages an in situ-generated alkenyl/acyl gold carbene in a ligand-facilitated attack by an alcoholic nucleophile. With an amide-functionalized chiral binaphthylphosphine ligand, γ-alkoxy-α,β-unsaturated imides are formed with excellent enantiomeric excesses. The intermediacy of a carbene species is supported by its alternative access via dediazotization. The reaction tolerates a broad range of alcohols and can accommodate dienynamide substrates, in addition to arylenynamides. This work avails a versatile strategy to enrich gold chemistry and achieve challenging enantioselective gold catalysis via ligand-facilitated enantioselective trapping of reactive intermediates.

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ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.3c10865.

Experimental procedures, compound characterization data, X-ray diffraction data, and NMR spectra (PDF)

Accession Codes

CCDC 2287125 and 2287128 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

Complete contact information is available at: https://pubs.acs.org/10.1021/jacs.3c10865

The authors declare no competing financial interest.

For the past several years, our lab[1] has devoted efforts to realizing metal−ligand cooperation[2] in homogeneous gold catalysis.[3] The bifunctional ligands[4] tailored for achieving this type of cooperative catalysis are based on the privileged biaryl-2-ylphosphine framework[5] but feature a remote basic group on the pendant aryl ring. As outlined in Scheme 1A, such a basic group, when appropriately positioned, can interact with incoming nucleophiles to accelerate nucleophilic attack. For example, the addition of carboxylic acid to alkyne with the amide-functionalized WangPhos as the gold ligand is accelerated by >800 times over the reaction employing JohnPhos, in which there is no remote basic group.[6] With these types of bifunctional ligands prepared from chiral binols (e.g., (*S*)-**L1**), we have harnessed the accelerating phenomenon to achieve asymmetric allenol cyclization[7] and dearomatization reactions[8] with high levels of stereoselectivities. In all cases, the electrophilic site that is subjected to an accelerated nucleophilic attack is limited to gold-activated alkyne or allene moieties of substrates. To date, no reactive gold intermediate has been subjected to directed or accelerated nucleophilic attack via cooperative gold catalysis.

The exponential development of gold catalysis for the past 20 years or so has revealed or led to the proposal of a diverse array of reactive gold intermediates.[9] Many of them are electrophilic and could be subjected to ligand-facilitated nucleophilic attack, thereby substantially enriching cooperative gold catalysis and hence permitting further development of synthetically valuable asymmetric transformations.[3d,10] In this context, we envisioned gold-catalyzed oxidation of enynamide by a nucleophilic oxidant to form an acyl/alkenyl gold carbene species, i.e., **A** (Scheme 1B).[11] In the presence of a chiral ligand possessing a remote basic functional group, an incoming alcohol could form an H-bonding interaction with the ligand and hence be directed/facilitated in its nucleophilic attack at the vinylcarbene moiety, as outlined in structure **B.** The ligand chirality would permit valuable chiral induction in this process. It is noteworthy that Shin and co-workers previously reported a proton-catalyzed racemic version of this transformation,[12] in which DMSO is the nucleophilic oxidant and sulfonamide substrates are employed.

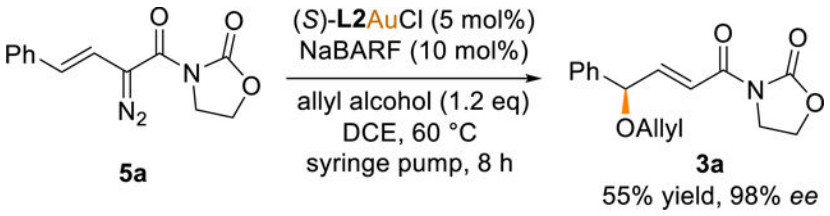
At the outset, (*E*)-3-(4-phenylbut-3-en-1-yn-1-yl)oxazolidin-2-one (**1a**) was employed as a model substrate and allyl alcohol as the trapping agent. As shown in Table 1, the optimal conditions are (*S*)-**L2**AuCl (5 mol %), NaBARF (10 mol %), diphenyl sulfoxide (**2c**, 1.05 equiv), allyl alcohol (1.2 equiv), 5 Å MS, DCE (0.05 M), 60 °C, and 6 h. Under these conditions, the desired (*E*)-γ-allyloxyenoyl oxazolidione product **3a** was formed in 90% yield with an outstanding 97% ee (entry 1). Its absolute configuration is assigned as (*R*) based on X-ray diffraction studies of two related products (*vide infra*). This configuration is consistent with the gold-ligand cooperation outlined in **B**, in which an (*S*)-ligand is shown. The side products including its (*Z*)-isomer **3a′** and the double oxidation product α-ketoimide **3a″** were formed in miniscule amounts, and the disubstituted furan **3a‴**, available via a proposed oxa-Nazarov cyclization,[13] was not detected. When the oxidant **2c** was replaced by 4-nitropyridine *N*-oxide (**2a**, entry 2), 8-methylquinoline *N*-oxide (**2b**, entry 3), or methyl phenyl sulfoxide (**2d**, entry 4), the yield of 3a suffered, but its enantiopurity remained largely the same. This phenomenon supports the intermediacy of a gold carbene of type **A**, in which the oxidant or its reduced part is not present. Replacing the *N*,*N*-diisopropylamino group in (*S*)-**L2** with a pyrrolidine-1-yl in (*S*)-**L1** resulted in a much

lower yield of **3a**, although its enantiopurity remained the same (entry 5). However, the phosphonate-based ligand (*S*)-**L3** performed poorly in the reaction (entry 6). **3a** was formed in only 13% yield, and the double oxidation forming **3a″** was a notable side reaction. With (*S*)-**L0** lacking any remote basic group as the gold ligand, all four products were formed in significant amounts (entry 7). This outcome is consistent with the amide group in (*S*)-**L2** facilitating/accelerating an alcohol attack at **A** and hence minimizing the side reactions. Lastly, when $AgNTf_2$ instead of NaBARF is used as a halogen scavenger, the reaction yield was notably lower, despite exhibiting an identical 97% ee. (entry 8).

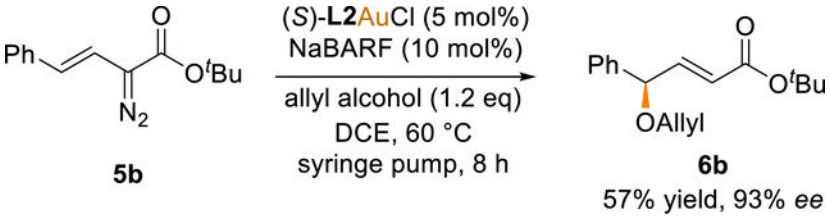
We then proceeded to examine the scope of this asymmetric gold catalysis. As depicted in Table 2A, we first examined various alcohols as trapping nucleophiles. A range of primary alcohols was readily accommodated, forming the enoyl oxazolidinones **3b−3h** in good to excellent yields and with ≥93% ee. In the case of methanol (**3b**), the ee is 99%. In this series, functional groups, such as furan, thiophene, and halides (Cl/Br/I), are well tolerated. The (*R*)-configuration of the iodinated product **3h** is established by X-ray diffraction studies (CCDC 2287125). Sterically demanding isopropyl alcohol also reacted smoothly to afford **3i** in 95% ee. We subsequently employed the enantiomers of 1-phenylethanol, and in both cases, **3j** and **3k**, high diastereomeric ratios were achieved, showing few matched/mismatched phenomena. In addition, phenol is a suitable nucleophile, and phenyl ether **3l** was formed with 96% ee. Moreover, the XRD studies confirmed that this compound also possesses the (*R*)-configuration (CCDC 2287128). Finally, water can also serve as the nucleophile, and the alcohol product **3m** was formed in 55% yield and with 91% ee. The relatively moderate yield is attributed to insufficient solubility of water in DCE. Additional nucleophiles including thiols, amides and indole were tested, resulting in messy reactions or a moderate enantioselectivity (60% ee with indole).

We next evaluated the scope of the enynamide substrates. Initially, we examined different substituents on the phenyl ring of **3a**. As shown in Table 2B, synthetically valuable halogens (**4c** and **4f**), electron-donating *p*-MeO (**4e**) and electron-with-drawing p-CF_3 (**4d**), and sterically congesting *o*-Me (**4b**) are all readily accommodated, affording the corresponding products with excellent enantioselectivities. The phenyl group of **3a** was replaced with 2-naphthyl (**4g**) or 2-thiophenyl (**4h**) with no issues. The replacement of the oxazolidione moiety by a TsNMe group in the case of **4i** led to a lower yield and a lower ee (92%). We also examined the influence of oxazolidinone chirality on asymmetric induction using substrates derived from enantiomers of 4-isopropyloxazolidin-2-one. When the (*R*)-enantiomer was employed, the reaction proceeded at a much slower rate, requiring 2 days to reach completion, but afforded **4j** with 25/1 diastereoselectivity. On the other hand, **4k** with the (S)-configured chiral auxiliary was isolated in 92% yield and with a lower but serviceable 10/1 diastereomeric ratio, representing a mismatched scenario. Our attempts to replace the phenyl group of **3a** with one or two alkyl groups led to little desired product. These outcomes could be partially attributed to the lack of sufficient stabilization of the gold carbene intermediate of type **A.** However, alkenyl groups are suitable replacements. In these cases (**4l−4m**), there can be a competitive nucleophilic attack at the ε position. To our delight, these reactions exhibited good γ-regioselectivities and 96% enantiomeric excess.

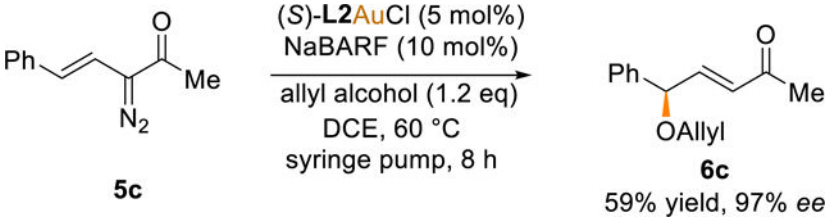
The presence of an oxazolidinone moiety[14] in the reaction can be scope-limiting, despite its demonstrated synthetic utility as an auxiliary. Since the reaction most likely traverses through a alkenyl/acyl gold carbene intermediate, alternative access to the same type of reactive intermediates would potentially broaden the reaction scope. To this end, we prepared *α*-diazoimide **5a** and anticipated that its gold-promoted dediazotization should afford the same carbene intermediate as in the reaction of **1a**. To our delight, **5a** reacted smoothly with allyl alcohol in the presence of catalytic (*S*)-**L2**Au$^+$, affording **3a** in 98% ee, which is essentially identical to that observed using **1a** as the substrate, albeit in a lower yield (eq 1). With the diazo approach established, we employed the *t*-butyl diazoester **5b** as the substrate. It reacted smoothly to deliver the *γ*-allyloxyenoate **6b** in a moderate yield and with 93% ee (eq 2).[15] The substrate scope was further expanded to the diazo ketone **5c**, and the *γ*-allyloxyenone **6c** was formed with 97% ee (eq 3).



Eq. 1



Eq. 2



Eq. 3

The richly functionalized nature of the products of this chemistry makes them synthetically versatile. For example, with **4j** featuring a (*R*)-oxazolidinone auxiliary, a Cu-mediated Michael addition afforded the *β*-methylated *N*-acyloxazolidinone **7** as the only diastereomer

in 85% yield (Scheme 2a). The use of **3a** with the parent oxazolidinone led to a 3:2 diastereoselectivity, suggesting that the γ-chiral center of **4j** does not dictate the observed diastereoselectivity. As such, the configuration of **7** was assigned by invoking the reported chelated conformation.[16] **7** was then subjected to α-methylation to afford **8** featuring a contiguous stereochemical triad in 91% yield.[17] 3g features a terminal bromide and undergoes radical cyclization to form the *trans*-disubstituted tetrahydrofuran product **9** in 92% yield (Scheme 2b). The corresponding iodide **3h** undergoes annulation with benzylamine via sequential alkylation and the Michael addition, the order of which is not certain, to deliver chiral disubstituted morpholine **10** in 75% and with a >20:1 *trans*/*cis* ratio. Finally, when (2*E*,4*E*)-hexa-2,4-dien-1-ol was used as the trapping alcohol, the gold catalysis was followed by a spontaneous D−A reaction to deliver the cyclohexene adduct **11** in 63% NMR yield and with ~10/1 diastereoselectivity (Scheme 2c).

In conclusion, a highly enantioselective trapping of an in situ generated alkenyl/acyl gold carbene by an alcoholic nucleophile is enabled by an amide-functionalized chiral binaphthylphosphine ligand via cooperative gold catalysis. The intermediacy of the carbene species is supported by its alternative access via dediazotization. The reaction tolerates a broad range of alcohols and can accommodate dienynamide substrates in addition to arylenynamides. This work is the first instance of cooperative gold catalysis featuring ligand-facilitated trapping of reactive catalytic intermediates. Considering the plethora of electrophilic gold intermediates documented in the literature, this chemistry avails a versatile strategy to enrich gold chemistry and in particular asymmetric gold catalysis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

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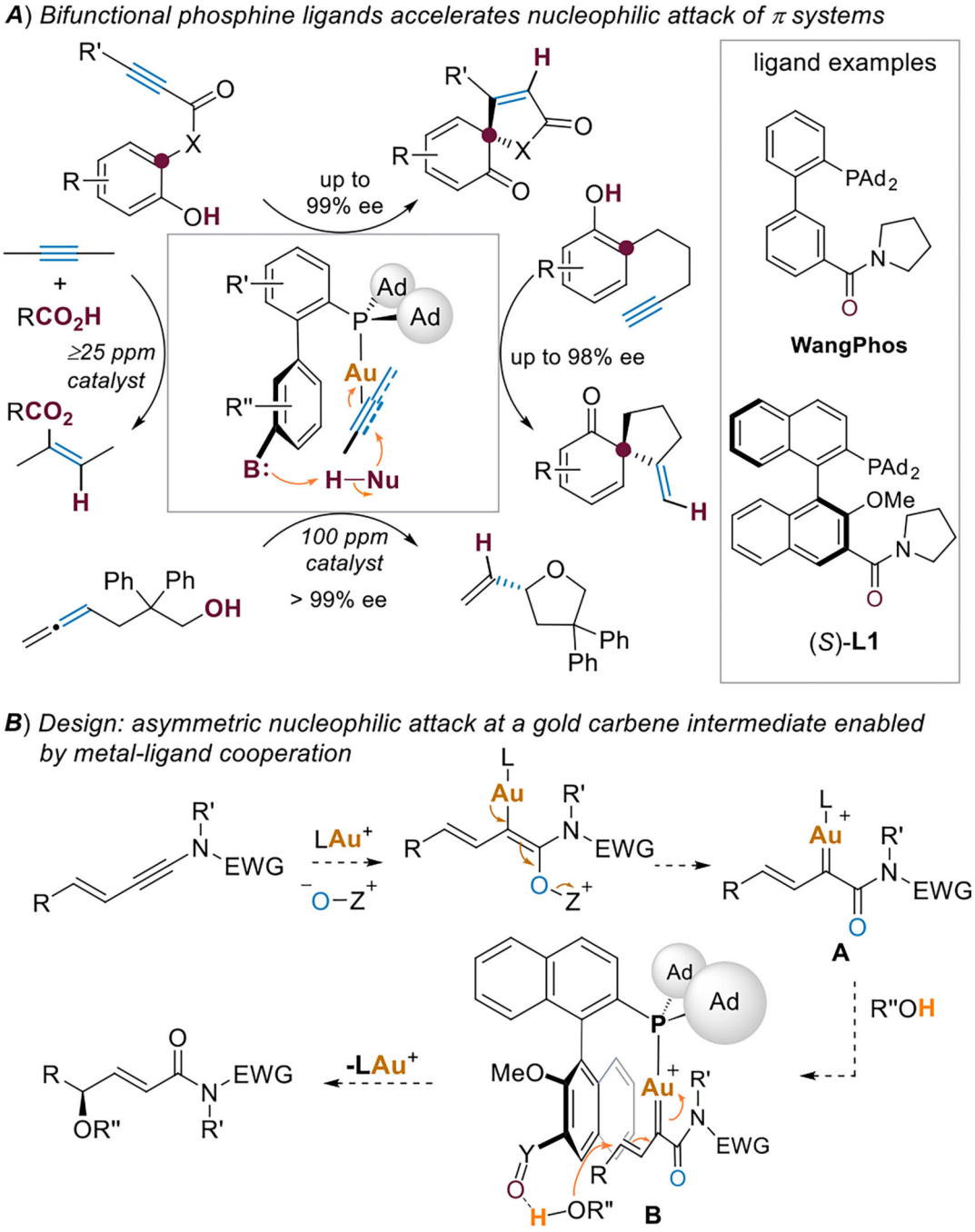
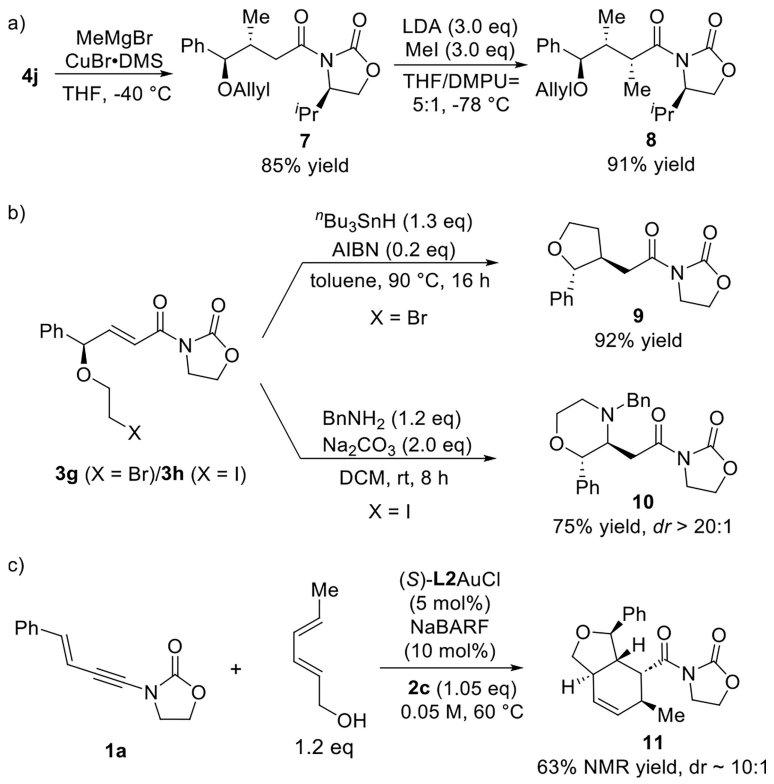


Scheme 1.

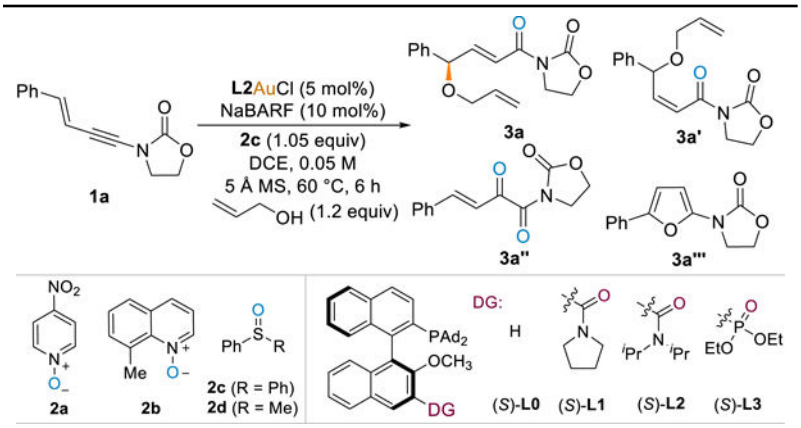
Cooperative Gold Catalysis with Accelerated/Facilitated Nucleophilic Attack and the Design of This Work



Scheme 2.
Synthetic Application

Table 1.

Optimization of the Reaction Conditions



entry	deviation from the optimal conditions	yield (%)[a] 3a/3a′/3a″/3a‴	ee of 3a[b]
1	–	**90/2/3/−**	**97%**
2	**2a** as the oxidant	70/4/3/<2	97%
3	**2b** as the oxidant	55/4/6/<2	95%
4	**2d** as the oxidant	63/2/5/−	96%
5	(*S*)-**L1** as the ligand	54/3/5/<2	97%
6	(*S*)-**L3** as the ligand	13/4/22/<3	–
7	(*S*)-**L0** as the ligand	17/27/16/21	–
8	$AgNTf_2$ (5 mol %) instead of NaBARF	63/3/3/−	97%

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

[b] Determined by chiral HPLC.

Table 2.

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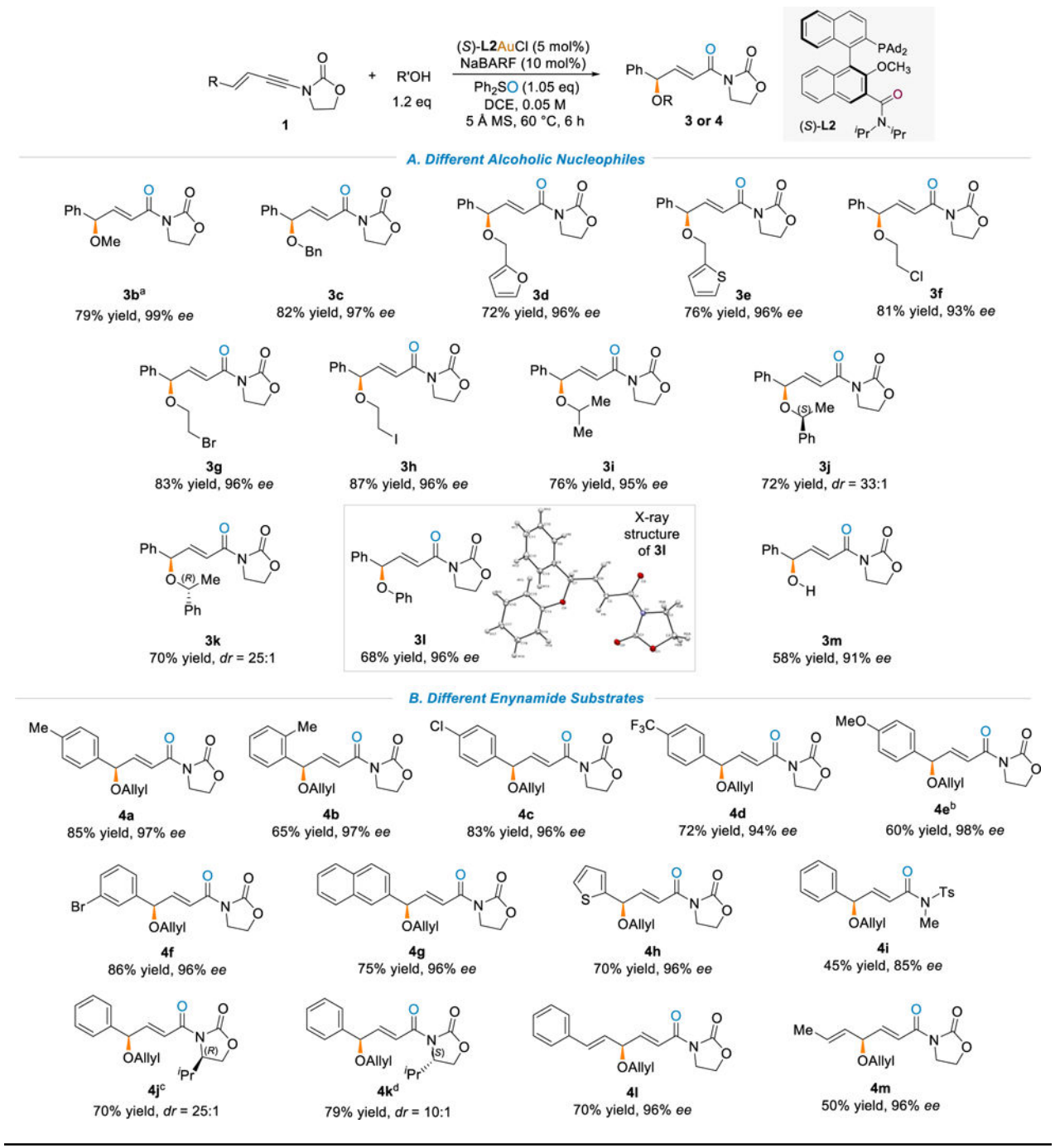
Reaction Scope



[a] 3 Å MS.

[b] NMR yield, the furan product of type **3a‴** could not be separated.

[c] 48 h.

[d] 15 h.