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Bifunctional Phosphine-Enabled Regioselective Cycloisomerization of Enynyl Esters En Route to Bicyclo[2.2.1]heptenes

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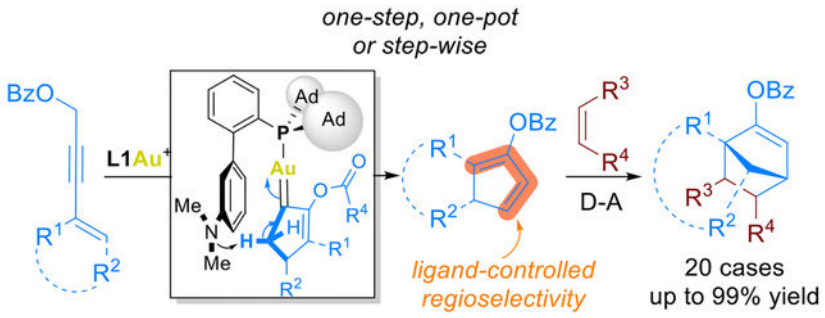
Abstract

Expedient access to bridged enol benzoates is realized via a tandem gold-catalyzed cycloisomerization of enynyl esters and the Diels–Alder reaction. The gold catalysis permits the use of enynyl substrates without additional propargylic substitution and achieves the highly regioselective formation of less stable cyclopentadienyl esters. The regioselectivity is enabled by a bifunctional phosphine ligand, the remote aniline group of which facilitates α-deprotonation of a gold carbene intermediate. The reaction works with different alkene substitution patterns and various dienophiles.

Graphical Abstract



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Author Contributions
The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Supporting Information
The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.3c00161.
Experimental procedure, structural characterization data, and ^{1}H and ^{13}C NMR spectra (PDF)

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.3c00161

The authors declare no competing financial interest.

Over the past several years, we have exploited metal–ligand cooperation[1] in homogeneous gold catalysis by employing biaryl-2-ylphosphine ligands such as WangPhos, **L1**, and **L2** featuring a Lewis/Brønsted basic functional group at the bottom half of the nonphosphine aryl ring (Scheme 1A).[2,3] The remote basic group can engage in accelerative interactions with nucleophiles via H-bonds[4] or permit challenging deprotonation.[5] In the latter scenario, we have so far demonstrated that with either an aniline[5] or a tertiary amino group[6] in this type of ligand, exceedingly mild and catalytic propargylic deprotonation, which otherwise would require $NaNH_2$ or ^{n}BuLi (Scheme 1B), can be realized, allowing isomerization of 1-aryl-1-alkynes into 1-aryl-1,3-dienes[5] and the asymmetric cycloisomerization of propargylic alcohols into 2,5-dihydrofurans as well as inter- and intramolecular propargylations.[2] To further exploit this cooperative gold catalysis, we surmised that these aniline-/amino-functionalized ligands could facilitate regioselective deprotonation due to their intramolecular nature and the relatively rigid ligand framework. Herein, we disclose that an aniline-based ligand indeed permits deprotonation of in situ generated gold carbenes with complete regiochemistry control, eventually affording bicyclo[2.2.1]heptenes upon subsequent D-A reactions.

In 2008, we reported the gold(I)-catalyzed cycloisomerization of enynyl ester **1** to cyclopentenone **2** in wet DCM (Scheme 1C).[7] Subsequent DFT studies[8] supported a mechanism involving gold-catalyzed 3,3-sigmatropic rearrangement of the substrate propargylic ester moiety, a goldpromoted Nazarov cyclization to form the cyclic vinylgold carbene species **A**, subsequent water-facilitated, rate-determining carbene α-deprotonation to form the cyclopentadienyl ester **3**, and the hydrolysis of **3** to deliver the final product. Though the scope and a variety of perturbations of the reactions[9] have been documented, there is no report of cases with R^3 being H. One anticipated issue is the formation of the more stable cyclopentadienyl ester isomer **3′** stemming from competitive γ-deprotonation of **A** or 1,5-hydride migration of **3** and, upon hydrolysis, the isomeric cyclopentenone **2′**. We surmised that by using our designed bifunctional ligands featuring a remote amino group, α-selective deprotonation of **A** with R^3 = H (i.e., **A-H**) could be achieved upon strategic positioning of a basic group in close proximity to the α-hydrogens (Scheme 1D); moreover, such an intramolecular deprotonation could be facile, thereby leading to accelerated. As such, the less stable cyclopentadienyl ester **3-H** would be formed selectively and efficiently, and the substrate scope of this valuable gold catalysis could be substantially expanded.

We began by subjecting the enynyl benzoate 1a to gold catalysis with different ligands. As shown in Table 1, the reaction conditions were toluene as the solvent, NaBARF as the chloride abstractor, ambient temperature, and 3 h. Except for the aniline ligand **L1** (entry 1) and WangPhos (entry 2), all the other ligands, including JohnPhos (entry 3) and the tertiary amine ligand **L2** (entry 4) performed poorly in terms of yields of **2a** and **3a′** based on conversion. In the case of the prototypical ligand Ph_3P (entry 6), no desired reaction was detected. In comparison to WangPhos, **L1** led to a much faster reaction, and **1a** was completely consumed in 3 h. This rate acceleration phenomenon is consistent with the hypothesis that the ligand aniline group may facilitate the rate-determining deprotonation in gold catalysis. Even though no water was purposely introduced to the reaction, the residual water permitted the hydrolytic formation of the more stable cyclopentenone product **2a′**,

which should be formed at least partly from the corresponding isomeric cyclopentadienyl benzoate **3a′**, even though it was not detected. Our attempt to access the less substituted cyclopentenone **2a**[10] by hydrolyzing purified **3a** under both acidic and basic conditions was foiled by the formation of the more stable **2a′** and the instability of **2a**.

Since it was unclear whether **L1** dictates the complete regioselective formation of **3a** over its regioisomer **3a′** by the above results, we then decided to trap the cyclopentadienyl benzoate product by *N*-phenylmaleimide in a tandem Diels–Alder reaction. The results are listed in Table 2. Among the five ligands examined, only **L1** resulted in complete selectivity for the formation of cycloadduct **4a** over **4a′**, which is the D–A product of the previously unobserved **3a′**. Moreover, **L1** led to an excellent yield (89%). Toluene was found to be a slightly better solvent (entry 1 vs entries 6 and 7), and the addition of drierite and the use of excess *N*-phenylmaleimide led to nearly quantitative yields of the tetracyclic imide adduct **4a** (entries 11 and 12). These results confirmed that the aniline ligand **L1** indeed achieves a highly regioselective deprotonation of the carbene intermediate of type **A**, while JohnPhos (entry 2) lacking the remote basic aniline group led to poor regioselectivity and substantial degradation to the **2a′** enone side product. Of note is the expedient access to the tetracyclic bridged structure of **4a** with excellent diastereoselectivity. Its relative stereochemistry was established by 2D NMR, and the face and endo selectivity is consistent with literature reports.[11]

With the optimized conditions shown in Table 2, entry 11, in hand, we set out to investigate the reaction scope. We first explored various enynyl benzoate substrates, and the results are shown in Figure 1. Substrates possessing 5- to 7-membered cyclic alkenes were readily allowed, affording **4a–4g** in mostly excellent yields. Among the cyclohexene cases, substituents on the ring are allowed, resulting in high product yields and mostly moderate diastereoselectivities (**4d–4g**). In these cases, the same or similar diastereomeric ratios are observed in the crude NMR of the cyclopentadienyl benzoate intermediates, thus revealing that the D–A reaction is highly face and endo selective. In the cases of **4d–4f**, the reactions are much slower, which may be attributed to the inductive deactivation caused by the oxygen-based substituents. In addition, the reaction tolerated *O*- (**4h**) and *N*-heterocycles (**4i**) and accommodated substrates featuring acyclic alkyl-substituted alkenes, affording **4j–4m** in excellent yields. However, with R^2 = Ph, the reaction was low-yielding and **4n** was contaminated with inseparable impurities. In all of these cases, we did not detect the formation of the corresponding regioisomeric products (**4′**). The D–A reactions were highly *endo*-selective, as confirmed by the NOESY experiments.

Next, we examined various dienophiles for the reaction, and the results are shown in Figure 2. For highly reactive dienophiles such as dimethyl acetylenedicarboxylate and 6,7-dibromo-1,4-naphthoquinone, the gold catalysis and the D–A reaction were performed in a single step, and the adducts **4o** and **4p** were formed in good yields. Of note is **4p**, the ^{13}C spectrum of which revealed its diketone form instead of the anticipated hydroquinone structure. On the other hand, less reactive dienophiles such as methyl acrylate and methyl vinyl ketone required a two-pot sequence, i.e., gold catalysis followed by Me_2AlCl-promoted D–A with crude cyclopentadienyl benzoate **4a** at −40 °C, giving

products **4q** and **4r** in good overall yield. The D–A reaction with MVK in the case of **4r** also afforded its minor regioisomer, while the reaction of methyl acrylate led to highly regioselective formation of **4q** (>30:1). For dienophiles of intermediate reactivities such as diisopropyl azodicarboxylate (**4s**) and nitrosobenzene (**4t**), a one-pot, two-step operation was required, where the gold-catalyzed step was allowed to complete prior to the addition of the dieneophile. It was observed that slightly improved yields could be achieved by shielding the reaction from light.

Finally, to demonstrate the synthetic utility of this chemistry, we carried out a gram-scale synthesis of **4a** and achieved 97% isolated yield with a catalyst loading of only 1 mol % (Scheme 2). Similarly, we scaled up the synthesis of **4t**. Due to the difficulty in separating the product from nitrosobenzene, the isolated yield was moderate (Scheme 2). The fused tricycle of **4t** readily underwent hydrogenolysis/hydrogenation with H_2 and Pd/C to cleave the N–O bond and reduce the enol ester to deliver the richly functionalized 5,6-fused carbocycle **6** in 87% yield.

In conclusion, we have developed an efficient route to obtaining bridged polycyclic enol esters in excellent yields from readily accessible enynyl ester substrates. Enynyl benzoates without additional substitution at the propargylic position can be converted to the less stable cyclopentadienyl esters with excellent regioselectivity, which is enabled by a biphenyl-2-ylphosphine ligand featuring a remote, weakly basic dimethyl aniline moiety. This gold-ligand cooperative catalysis tolerates a variety of substitution patterns, and the cyclopentadienyl benzoate products were captured by a range of dienophiles in subsequent D–A reactions, thereby allowing a rapid increase of structural complexity and providing an expedient access to bicyclo[2.2.1]cycloheptenes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

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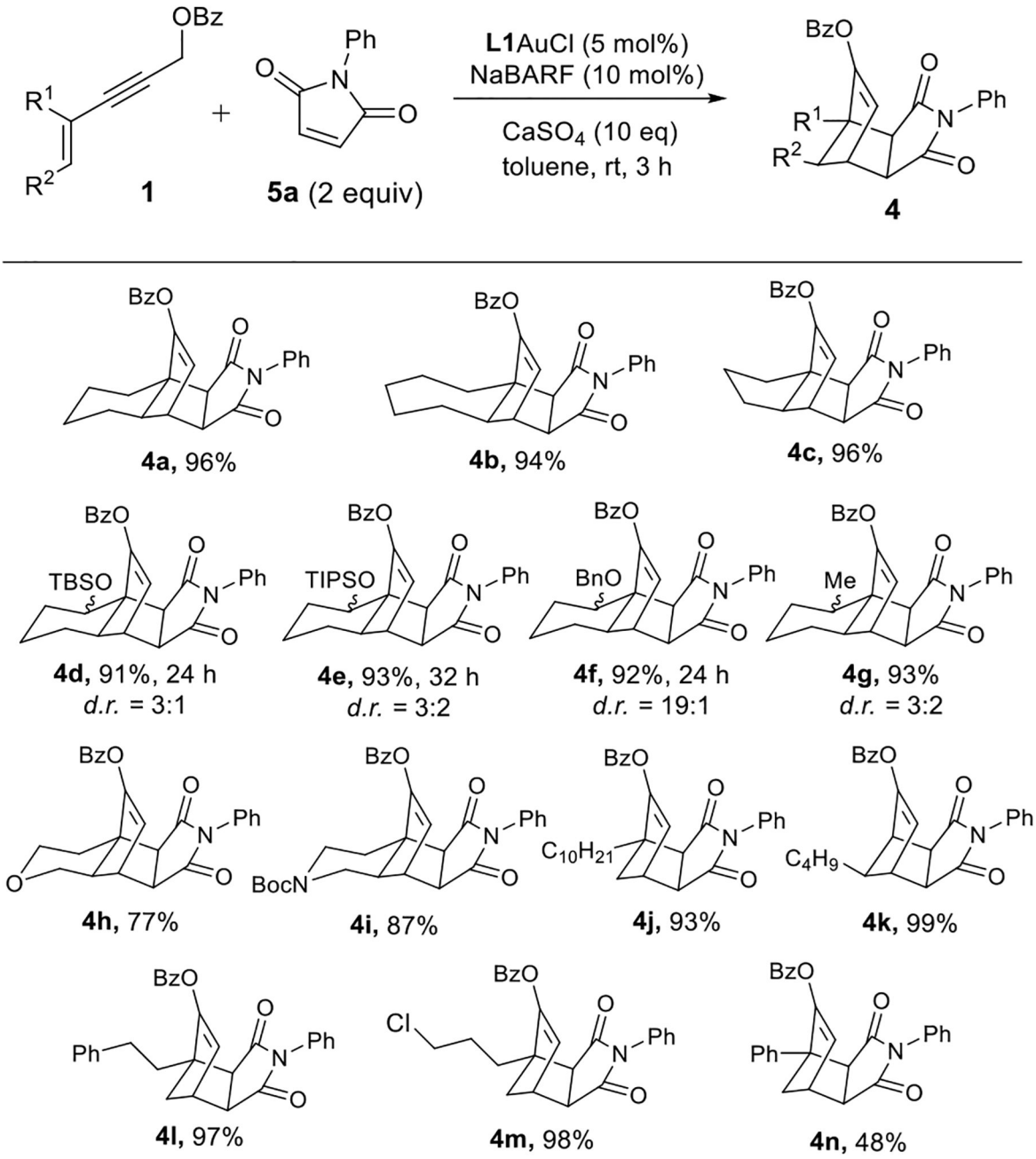


Figure 1.
Scope of enynyl benzoate substrate.

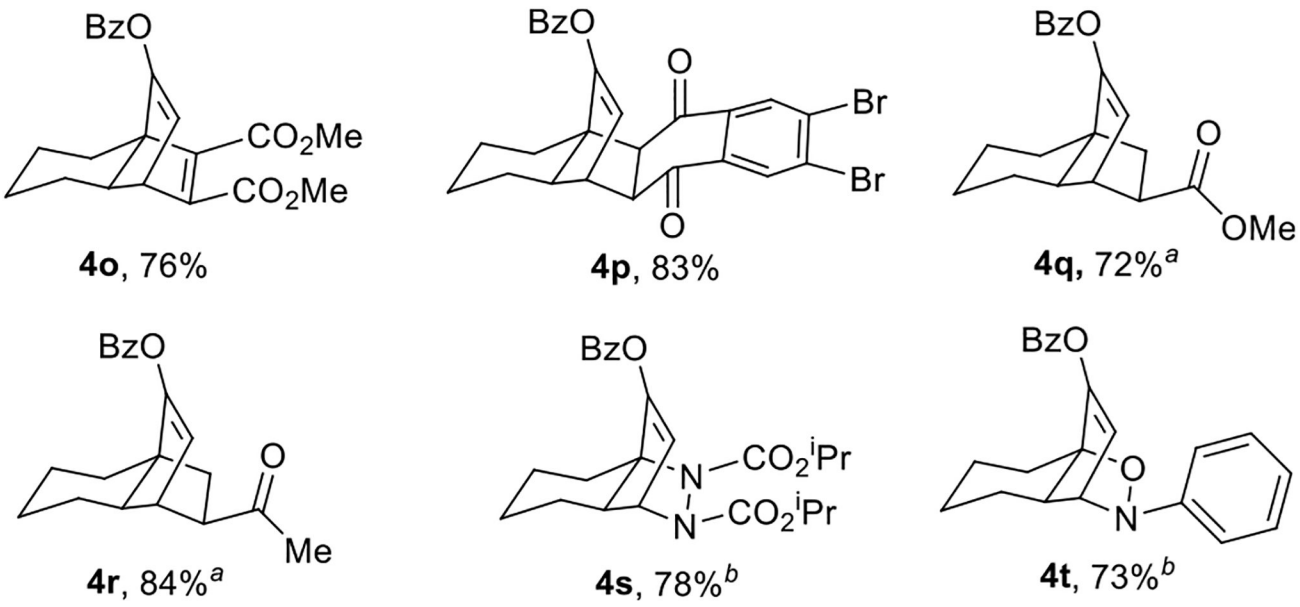
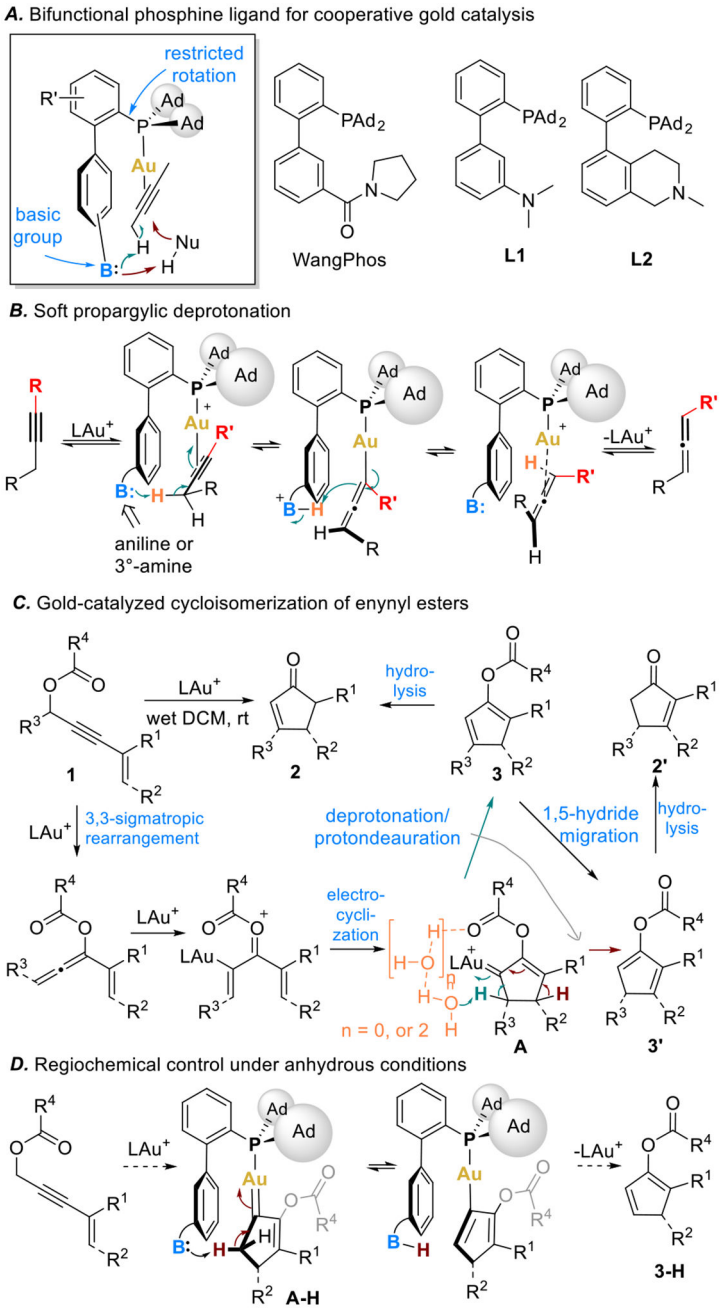


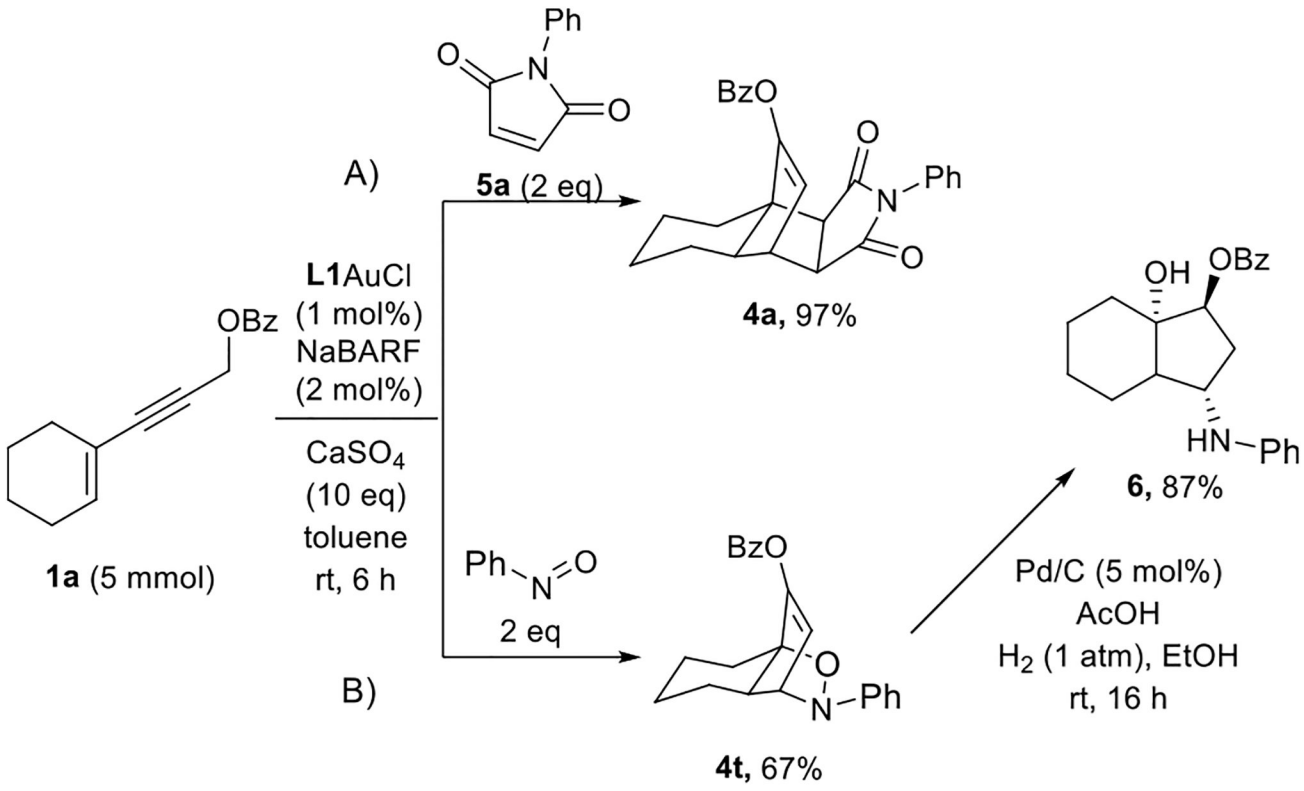
Figure 2.

Scope of dienophiles. Reaction conditions: **L1**AuCl (5 mol %), NaBARF (10 mol %), CaSO4 (10 eq), toluene, rt, 16 h. [a]The dieneophile was preactivated with Me_2AlCl in DCM at −40 °C and then treated with the crude product mixture from the first step dropwise. [b]The addition of a dieneophile followed the completion of the gold catalysis.



Scheme 1.

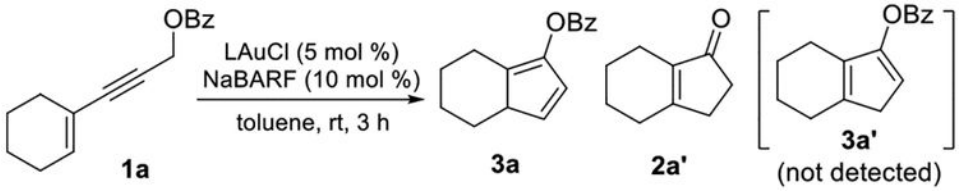
Bifunctional Phosphine Ligands and Application in Cooperative Gold Catalysis



Scheme 2.
Gram-Scale Synthesis and Synthetic Transformation

Table 1.

Initial Ligand Screening[a]

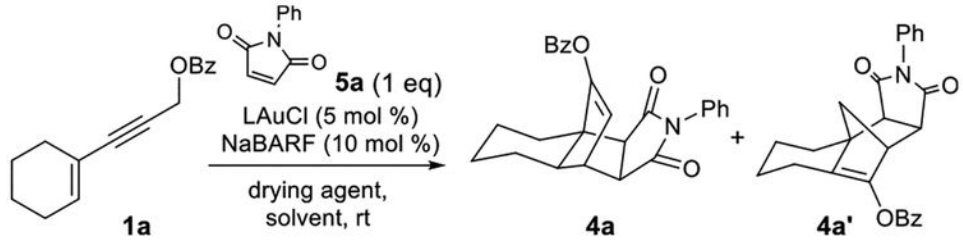


entry	ligand	conversion	% yield of 3a	% yield of 2a′
1	**L1**	100	46	54
2	WangPhos	53	20	26
3	JohnPhos	60	7	16
4	**L2**	50	3	7
5	IPr	48	1	1
6	PPh_3	16	0	0

[a]Reactions were run for 3 h at room temperature and then quenched with $^{n}Bu_4NCl$. Yields were calculated via ^{1}H NMR using diethyl phthalate as the internal standard.

Table 2.

Reaction Conditions Optimization with *N*-Phenylmaleimide (5a)[a]



entry	ligand	solvent	drying gent	% yield of 4*a*/4a′/2a′[b]
1	**L1**	toluene		89/–/–
2	JohnPhos	toluene		34/16/36
3[c]	WangPhos	toluene		46/12/5
4	**L2**	toluene		24/15/–
5	PPh_3	toluene		–/–/–
6	**L1**	DCM		85/–/4
7	**L1**	$PhCF_3$		83/–/–
8[e]	**L1**	toluene		9/–/–[d]
9	**L1**	toluene	drierite	91/–/–
10	**L1**	toluene	3 Å MS	84/–/–
11	**L1**	toluene	drierite	97/–/–[f]
12	**L1**	toluene	drierite	97/–/–[g]

[a]Yields were calculated via ^1H NMR using diethyl phthalate as the internal standard. Reactions were run for 16 h at room temperature and then quenched with $^nBu_4NCl$.

[b]Regioisomers were determined by an OBz aromatic signal at 8.09 ppm.

[c]88% conversion.

[d]Mostly starting material left.

[e]$AgNTf_2$ (5 mol %) instead of NaBARF (10 mol %) used as the halide abstractor.

[f]2 equiv of **5a** used.

[g]3 equiv of **5a** used.