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Ni-Catalyzed Reductive Antiarylative Cyclization of Alkynones

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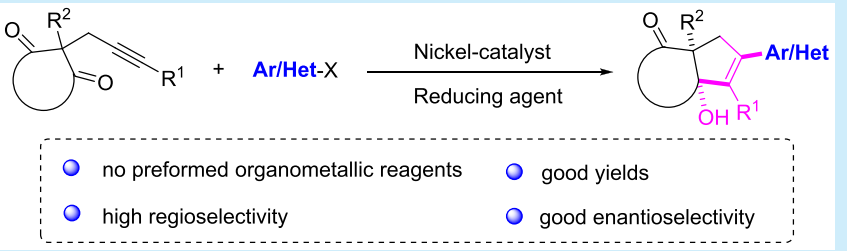


ABSTRACT: A new catalyst system for the antiarylative cyclization of alkynones and aryl halides through a reductive cross-coupling strategy is developed. The transformation proceeds smoothly in the absence of organometallic reagents and features high functional group tolerance. This method provides an effective platform to access a wide variety of synthetically useful endocyclic tetrasubstituted allylic alcohols in a stereoselective manner.

The cyclic tetrasubstituted allylic alcohol motif is commonly found in numerous biologically important compounds and natural products, including brasilenol, illudol, guadalupol, and conocephalenol (Figure 1).[1]

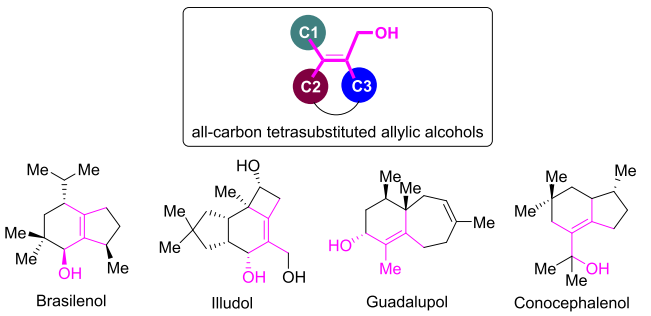
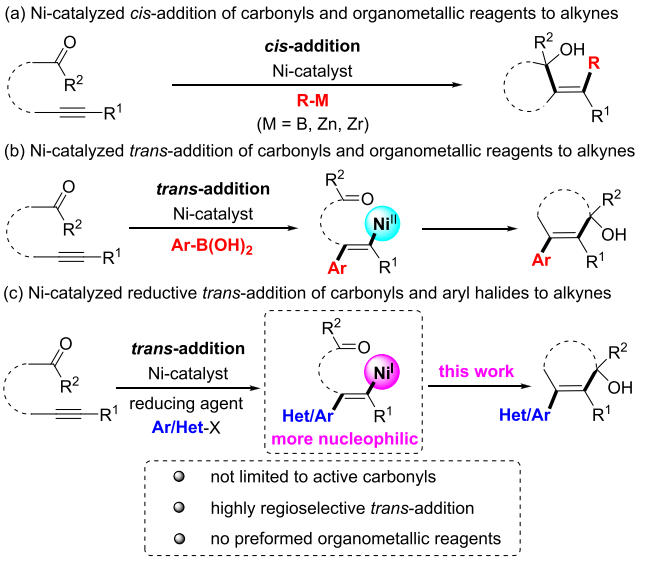


Figure 1. Representative natural products containing an endocyclic tetrasubstituted allylic alcohol moiety.

However, approaches for synthesizing these structures are still limited and still pose a significant synthetic challenge, especially in a regio- and stereocontrolled manner. Among various methods, Ni-catalyzed *cis*-1,2-addition cyclization of organometallic reagents and aldehydes or ketones onto alkynes has been well-developed and has become one of the most straightforward and attractive methods for the preparation of exocyclic tetrasubstituted allylic alcohols (Scheme 1a).[2−4] Alternatively, Lam et al. recently reported the Ni-catalyzed formal *trans*-1,2-addition of arylboronic acids and ketones to alkynes via an alkenyl−$Ni^{(II)}$ intermediate, providing an elegant protocol for endocyclic tetrasubstituted allylic alcohols (Scheme 1b).[5,6] Nevertheless, these methods are not without drawbacks.

Scheme 1. Ni-Catalyzed Coupling Reaction of Alkynes and Carbonyls for the Synthesis of Tetrasubstituted Allylic Alcohol



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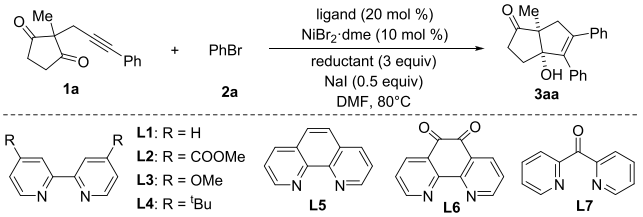
They are usually limited in substrate scope and require the use of stoichiometric organometallic reagents.

In recent years, the Ni-catalyzed cross-couplings of two carbon electrophiles under reducing conditions have attracted considerable attention from synthetic chemists.[7] Compared with the classic redox-neutral cross-couplings, the main advantage of this strategy is that it does not require the use of organometallic reagents and exhibits excellent functional group compatibility. Despite the tremendous progress made, difunctionalization of alkynes by *trans*-addition of two carbon electrophiles across the triple bond remains unexploited.[8] Martin's group described reductive *anti*-dicarbofunctionalization of alkynes via Ni-catalyzed cyclization/carboxylation of alkyne-tethered alkyl halides with CO_2.[8a] Montgomery et al. reported reductive *syn*-dicarbofunctionalization of alkynes through Ni-catalyzed oxidative cyclization of alkynals and coupling with alkyl halides.[8b] In continuation of our studies on Ni-catalyzed reductive arylfunctionalization of unsaturated carbon−carbon bonds,[9] we envisioned that with the proper combination of nickel catalyst, ligand, and reducing agent, the reductive arylative cyclization of alkynone and aryl halide may produce a more nucleophilic alkenyl−nickel$^{(I)}$ intermediate, which would provide a new and effective platform for the synthesis of endocyclic tetrasubstituted allylic alcohols (Scheme 1c).

Based on our previous studies on the Ni-catalyzed reductive difunctionalization of alkenes,[10] we chose alkynone **1a** and phenyl bromide **2a** as model substrates to test our reaction design. We were very delighted to find that, by employing a combination of $NiBr_2$·dme (10 mol %) as catalyst, bpy (**L1**, 20 mol %) as ligand, Zn^0 (3 equiv) as reducing agent, and NaI (50 mol %) as additive in DMF, the reaction did indeed take place, leading to the desired 5,5-bicyclic **3aa** in 28% yield (Table 1, entry 1). Among the different reducing agents investigated, Mn^0 powder gave the highest yield, whereas B_2Pin_2 gave only a trace amount of **3aa** (entries 2 and 3). Subsequently, a survey of bidentate nitrogen ligands was performed (entries 4−9), and 1,10-phenanthroline **L5** proved to be the most effective (56%, entry 7). The formation of target product **3aa** was not detected when the nitrogen ligands were replaced with phosphine ligands such as PPh_3 or dppe (entries 10 and 11). Finally, we found that an excess of PhBr was needed to isolate the desired **3aa** in 69% yield (entry 12). Nevertheless, most of the PhBr can be recovered after the reaction, and only a trace of homocoupling byproduct biphenyl was observed. Unsurprisingly, the reaction did not proceed in the absence of $NiBr_2$·dme or Mn^0 (entries 13 and 14).

Using the optimal reaction conditions described in Table 1, entry 12, we first evaluated the effects of various aryl halides **2** (Scheme 2). Bicyclic product **3aa** was obtained in 83% yield from phenyl iodide, whereas phenyl chloride was not reactive at all. Although a higher yield can be obtained using phenyl iodide, considering that aryl bromides are typically cheaper and more widely available, we decided to explore the substrate scope using aryl bromides. Aryl bromides adorned with electron-donating groups such as methoxy and amino group at the *para*-position proceeded smoothly to produce the corresponding products **3ab** and **3ac** in 84 and 73% yield, respectively. Whereas an electron-withdrawing group on the aromatic ring, such as a fluorine group, reduced the reaction efficiency, product **3ad** was obtained in 33% yield. It is worth noting that the reductive cyclization reaction could be carried out without affecting the aryl borate entity, thereby providing opportunities for further

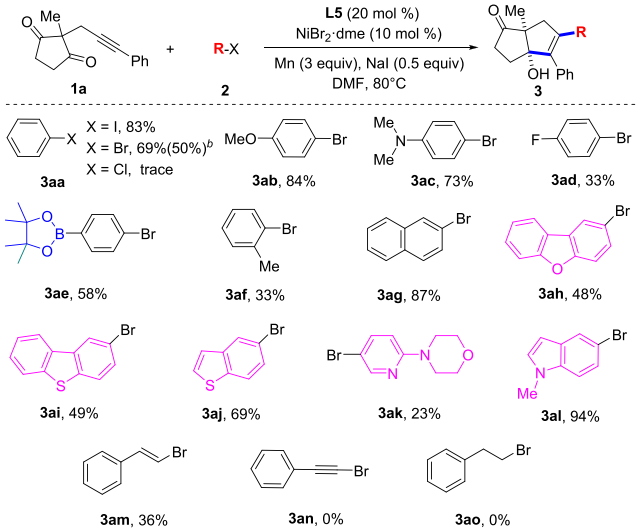
Table 1. Optimization of the Reaction Conditions[a]



entry	ligand	reducing agent	yield of **3aa** (%)[b]
1	**L1**	Zn	28
2	**L1**	Mn	43
3	**L1**	B_2Pin_2	trace
4	**L2**	Mn	17
5	**L3**	Mn	trace
6	**L4**	Mn	32
7	**L5**	Mn	56
8	**L6**	Mn	trace
9	**L7**	Mn	trace
10	dppe	Mn	trace
11	PPh_3	Mn	trace
12[c]	**L5**	Mn	79 (69)
13[d]	**L5**	Mn	0
14[e]	**L5**	Mn	0

[a]Unless noted otherwise, reactions were carried out in 2 mL of DMF at 80 °C for 24 h on a 0.1 mmol scale using 1 equiv of **1a**, 2 equiv of **2a**, 10 mol % of $NiBr_2$·dme, 20 mol % of ligand, and 3 equiv of reductant. [b]GC yield using adamantane as the internal standard. The value in brackets is the yield of isolated **3aa** after column chromatography purification on silica gel. [c]4 equiv of **2a** was used. [d]No $NiBr_2$·dme. [e]No Mn^0.

Scheme 2. Substrate Scope of Organic Halides[a]



[a]Reactions were conducted using 0.2 mmol of **1a**; 4 equiv of **2** was used. Yields are of isolated products. [b]The reaction was conducted on a 1 mmol scale using 5 mol % of $NiBr_2$·dme and 10 mol % of **L5**.

derivatization through the Suzuki coupling technique (**3ae**). 2-Naphthyl bromide was also tolerated to deliver **3ag** in 87% yield. In addition, various (hetero)aryl bromides were also tested. Dibenzofuran, dibenzothiophene, benzothiophene, pyridine, and indole were all successfully incorporated into the corresponding products **3ah**−**3al** in 23−94% yields. Excitingly, vinyl bromide **2m** was also a viable substrate to afford the

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corresponding 1,3-diene **3am** in 36% yield. However, for propargyl bromide **2n** and alkyl bromide **2o**, the desired products were not obtained.

Next, we studied the substrate scope of alkynone **1** (Scheme 3). The influence of the substituents (R^1) at the terminus of the alkyne was first investigated. Under the standard reaction conditions, the reactions tolerate the presence of various functional groups such as ether (**3ca**), chloride (**3da**), fluoride (**3ea**), trifluoromethyl (**3fa**), ester (**3ga**), borate (**3ha**), and cyano (**3ia**). 2-Naphthyl substrate reacted smoothly to give **3ja** in 70% yield. This methodology was compatible with a wide array of heteroarenes, such as 3,4-benzodioxole (**3ka**), 3,4-dihydrobenzodioxine (**3la**), indole (**3ma**), dibenzothiophene (**3na**), dibenzofuran (**3oa**), and pyridine (**3pa**) at the terminal end of the triple bond. More excitingly, estrone could also be successfully incorporated into product **3qa** in 79% yield (1/1 dr), indicating that our mild reaction conditions allow late-stage modification of complex molecules. In addition, the reaction is not restricted to the aryl group at the terminal of the triple bond, and an alkyne bearing a sterically hindered trimethysilyl group was also compatible with this transformation, albeit in a low yield (**3ra**). However, no desired product (**3sa**) was observed when methyl substituted alkynone substrate was used. Terminal alkyne **1t** produced complex mixtures. The introduction of a benzyl group (R^2) to the 2-position of the indan-1,3-dione-containing substrate was also amenable to this transformation, and the tricyclic product **3ua** was isolated in 94% yield.

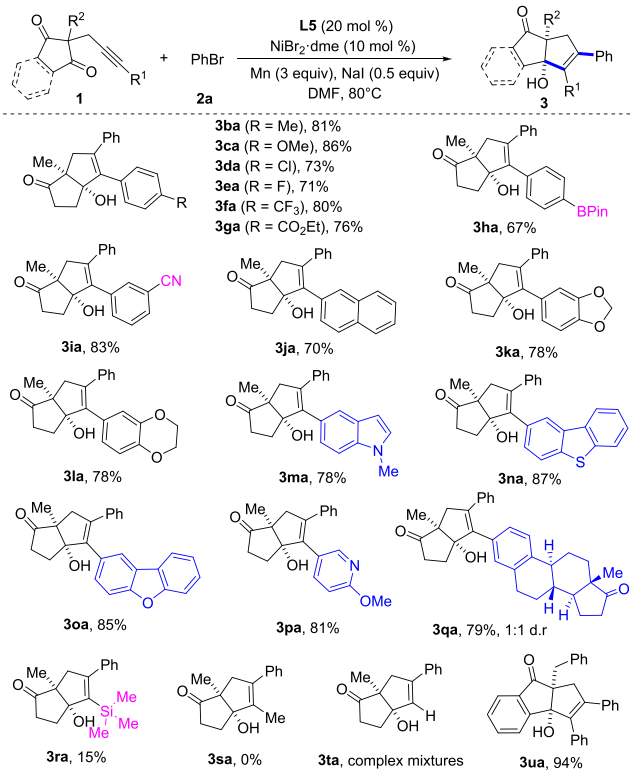
We decided to further explore other alkynone skeletons (Figure 2). Under the standard reaction conditions, the reaction of cyclohexane-1,3-dione **1v** with **2a** afforded the expected 5,6-bicyclic product **3va** in 40% yield (Figure 2a). The reaction does not rely on the 1,3-diketone backbone, and the monoketone substrate **1w** could also undergo reductive arylative cyclization to produce the cyclopentanol **3wa** in 70% yield (Figure 2b). In addition, the one-carbon homologous monoketone substrate **1x** was also tested, and the *trans*-6-*endo* arylative cyclization product **3xb** was obtained in 80%. Remarkably, the possible *cis*-5-*exo* arylative cyclization was not detected (Figure 2c).

More interestingly, the substrate bearing a phthalimide moiety could also smoothly undergo reductive cyclization reaction, and the target tricyclic pyrrolizinone **3ya** was afforded in 36% yield through the dehydration and isomerization of the initial cyclization product. It is worth mentioning that the pyrrolizinone skeleton containing a bridgehead nitrogen is a common structural unit in many naturally occurring alkaloids with various degrees of biological activities (Scheme 4).[11] The reaction of **1y** with phenylboronic acid under the previously reported redox-neutral reaction conditions was attempted;[5a] however, no target product was detected.

A series of chiral ligands was screened for achieving asymmetric induction in this tandem reaction (for details, see Tables S1 and S2 in the Supporting Information). It was found that (*S*)-Ph-Phox (**L8**) was the most effective ligand to afford **3aa** in 65% yield with 81% ee (Figure 3), which is comparable to the results previously reported by Lam et al. (86% ee).[5a]

To further clarify the possible catalytically active intermediates in the reaction, we synthesized 2-tolyl-$Ni^{(II)}$ complex **4** according to the previously reported method.[9a] Under our standard conditions, treatment of complex **4** with alkynone **1a**

Scheme 3. Substrate Scope of Alkynones 1[a]



[a]Reactions were conducted using 0.2 mmol of **1**; 4 equiv of **2a** was used. Yields are of isolated products.

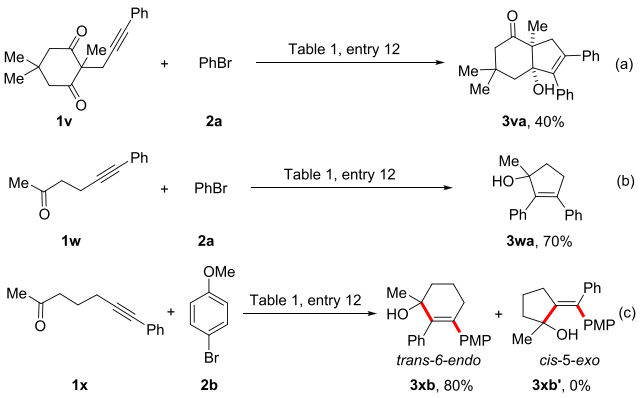
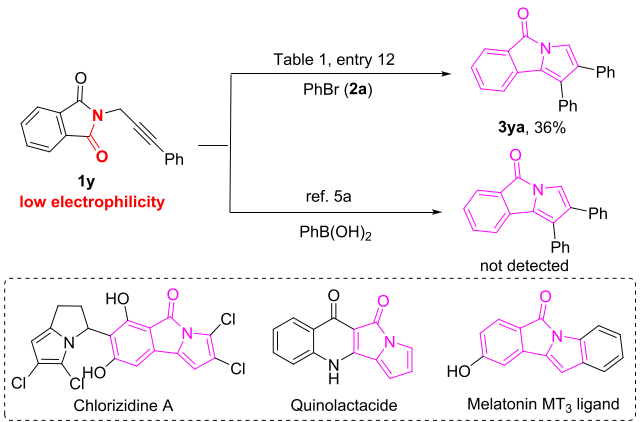


Figure 2. Results with substrates possessing different carbon skeletons.

Scheme 4. Construction of Tricyclic Pyrrolizinone Skeleton



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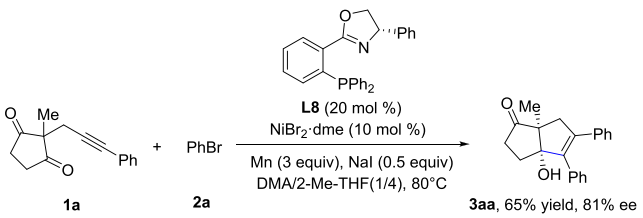


Figure 3. Asymmetric reductive antiarylative cyclization of alkynone.

furnished the desired **3af** in 17% yield. However, in the absence of Mn^0, the reaction of complex **4** with **1a** afforded **3af** in 20% yield (Figure 4). The above results indicate that both alkenyl−$Ni^{(I)}$ and alkenyl−$Ni^{(II)}$ intermediates may be the active species in the catalytic cycle.

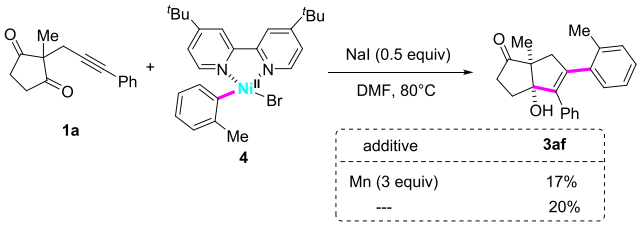
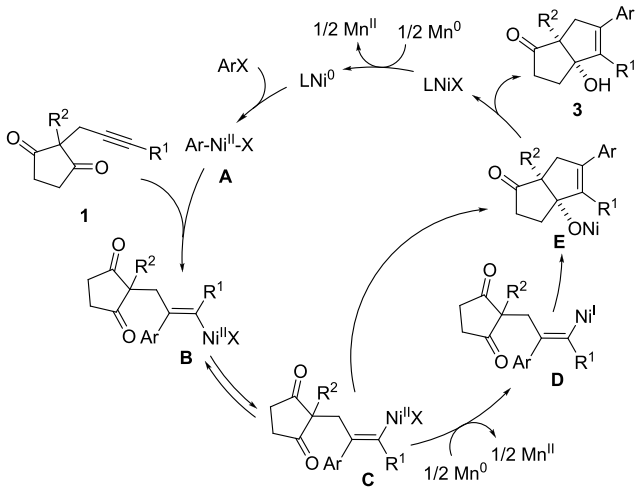


Figure 4. Mechanistic study.

Although many types of electrophiles have been found to capture alkenyl−$Ni^{(II)}$ species, the amide carbonyl group is rarely investigated,[12] and this is not surprising due to its poor electrophilicity. A direct evidence is that, under redox-neutral conditions, the reaction of phenylboronic acid with phthalimide **1y** cannot produce the expected tricyclic pyrrolizinone **3ya** (Scheme 4). This result seems to support the hypothesis that a more nucleophilic alkenyl−$Ni^{(I)}$ intermediate is involved under reducing conditions.

As displayed in Scheme 5, a possible reaction mechanism for the reductive arylative cyclization of alkynone was proposed.

Scheme 5. Proposed Reaction Mechanism



Alkenyl−$Ni^{(II)}$ intermediate **B** was afforded via the migratory insertion of aryl nickel species **A** into the triple bond of alkynone **1**. A reversible *E*/*Z* isomerization process[5] took place to produce a new alkenyl−$Ni^{(II)}$ intermediate **C**, which could be reduced by Mn^0 to give the more nucleophilic alkenyl−$Ni^{(I)}$ species **D**. The target endocyclic tetrasubstituted allylic alcohol **3** was formed by the nucleophilic attack of **D** to the carbonyl and subsequent protonolysis with water. The catalytically active $Ni^{(0)}$ species was then regenerated upon Mn^0 reduction. However, the pathway for the direct cyclization of $Ni^{(II)}$ intermediate **C** to form nickel alkoxide **E** cannot be ruled out at the current stage.

In summary, we have successfully developed a new catalyst system for the antiarylative cyclization of alkynones and organohalides. This transformation does not require the use of organometallic reagents and exhibits excellent functional group tolerance. Various highly functionalized endocyclic tetrasubstituted allylic alcohols were prepared in good yields with high regio- and enantioselectivity. Preliminary mechanistic investigation indicates that either alkenyl−$Ni^{(I)}$ or alkenyl−$Ni^{(II)}$ species may be the key intermediate of the reaction.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02534.

Experimental procedures and spectra data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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