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Highly Enantioselective Rhodium-Catalyzed Cross-Addition of Silylacetylenes to Cyclohexadienone-Tethered Internal Alkynes

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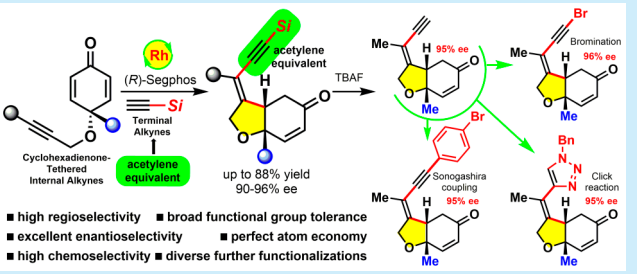
Supporting Information

ABSTRACT: The first highly enantioselective rhodium-catalyzed cross-addition of silylacetylenes to cyclohexadienone-tethered internal alkynes has been achieved via a tandem process: regioselective alkynylation of the internal alkynes and subsequent intramolecular conjugate addition to the cyclohexadienones, affording the *cis*-hydrobenzofuran frameworks with good yields (up to 88% yield) and excellent enantioselectivities (90%−96% ee). This mild reaction showed perfect atom economy and broad functional group tolerance. Furthermore, a gram-scale experiment and diverse further conversions of the cyclization products were also presented.



The carbon−carbon triple bond is an important and practical structure unit in modern organic synthesis because it could be functionalized using various methods.[1] The transition-metal-catalyzed direct alkynylation of unsaturated compounds with a terminal alkyne has been widely investigated and become an efficient, attractive, and atom-economical tool to introduce an alkyne moiety.[2−6] Among these, the regio- and stereoselective cross-addition of terminal alkynes to internal alkynes has been extensively developed using palladium,[6a,b,f,a,b,f,i−k] iridium,[6c] rhodium,[6d,e,g] nickel,[6g] and cobalt[6h] catalysts (Scheme 1a). However, such hydroalkynylation of internal alkynes could only construct a single carbon−carbon bond. The simultaneous formation of two carbon−carbon bonds, i.e., the alkynylative tandem reactions of internal alkynes with terminal alkynes, are relatively uncommon.[7] In 1997, Trost and co-workers reported the cross-trimerization of 1-phenylsulfonyl-1-propyne with either propargyl alcohol or phenylacetylene in the presence of a palladium catalyst.[7a] In this case, the initial cross-coupling adduct further reacted with the excessive 1-phenylsulfonyl-1-propyne. Then, Ogata, Fukuzawa, and co-workers demonstrated nickel-catalyzed highly regio-, chemo-, and stereoselective cross-trimerization, in which bulky triisopropylsilylacetylene could react with two internal alkynes (either the same or different).[7b,c] Recently, Tanaka and co-workers realized an extraordinary rhodium-catalyzed highly chemoselective three-component cross-addition of terminal silylacetylenes, activated internal alkynes bearing an electron-withdrawing group, and electron-deficient alkenes or isocyanates (Scheme 1b).[7e] Notably, none of these alkynylative tandem reactions of internal alkynes generated chiral products. To the best of our knowledge, the enantioselective alkynylative tandem reactions of internal alkynes have not been reported yet. Herein, we disclose the first chemo-, regio-, and enantioselective rhodium-catalyzed alkynylation/intramolecular-conjugate-addition tandem reaction between silylacetylenes and cyclohexadienone-tethered internal alkynes (Scheme 1c).

As part of our continuous efforts on transition-metal-catalyzed tandem desymmetrization reactions of cyclohexadienones,[8,9] we envision that this rhodium-catalyzed alkynylative tandem reaction would face three major challenges. The first is the chemoselectivity: the rhodium acetylide should undergo cross-addition with internal alkynes rather than conjugate addition to enones. The second is the regioselectivity: such addition should take place at outer sites of internal alkynes rather than inner ones. The last is the enantioselectivity: a suitable catalytic system should be found to effectively distinguish the prochiral cyclohexadienones during the intramolecular 1,4-addition (Scheme 1c).

With these considerations in mind, a series of privileged chiral ligands and rhodium precatalysts were screened for the rhodium-catalyzed cross-addition of terminal silylacetylene **2a**

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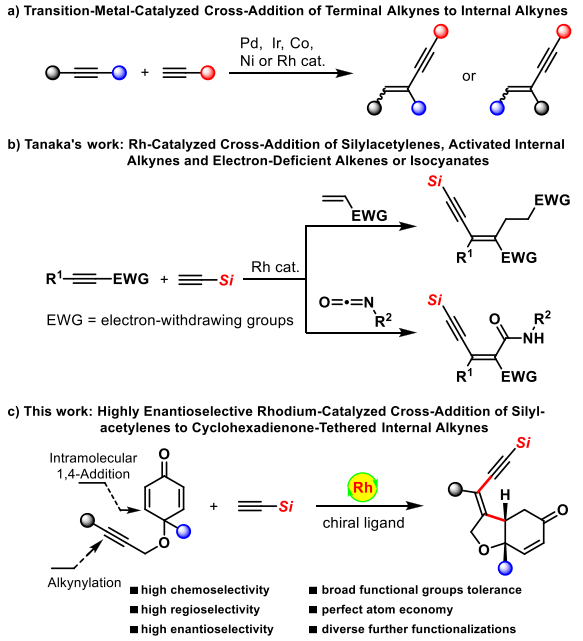
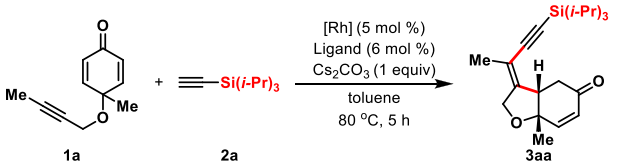
Scheme 1. Strategic Design



to cyclohexadienone-tethered internal alkyne **1a**, and selected results were summarized in Table 1.[10] The use of (*S*)-Binap (**L1**) as a ligand and $[Rh(coe)_2Cl]_2$ as a precatalyst afforded the desired alkynylative cyclization product **3aa** with good yield and high enantioselectivity (Table 1, entry 1). Next, several bisphosphine ligands including (*R*)-Segphos (**L2**), (*S*)-DTBM-Segphos (**L3**), (*R*,*R*)-Ph-BPE (**L4**), and (*R*,S_p)-Josiphos (**L5**) were tested. Only **L2** could offer a satisfactory result with an enantioselectivity up to 96% ee (Table 1, entries 2−5). Moreover, the chiral diene ligand **L6** failed to give the desired product,[11] which is probably because the Rh/diene catalyst has a shorter lifetime and quickly loses its catalytic activity during the reaction (Table 1, entry 6).[2p] Then, the reaction yield could be further improved to 70% when the rhodium precatalyst was switched to $Rh(nbd)_2BF_4$ (Table 1, entries 7−8). Increasing or decreasing the loading of **2a** had no obvious effect on the yield and enantioselectivity (Table 1, entries 9−10). In addition, lowering the reaction temperature resulted in a big erosion of the yield (Table 1, entry 11). More importantly, the desired alkynylative cyclization product **3aa** could not be detected in the absence of Cs_2CO_3, indicating the essential role of the base additives in this catalytic system (Table 1, entry 12).

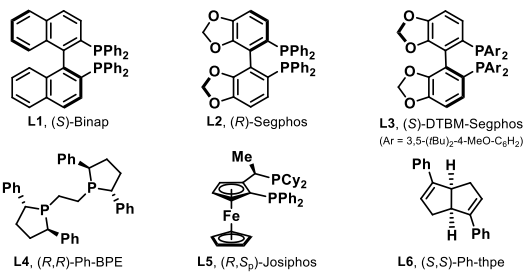
With the optimized reaction conditions in hand, the scope of the cyclohexadienone-tethered internal alkynes **1** was examined. Various R^1 substituents in the cyclohexadienone-tethered internal alkynes **1**, such as a simple alkyl, cyclohexyl, sterically hindered adamantyl, benzyl, vinyl, allyl, and phenyl group, could be well tolerated, and the reactions proceeded smoothly with good to high yields (60%−88%) and excellent enantioselectivities (Scheme 2, **3aa**−**3ka**, 90%−96% ee). Furthermore, diverse functional groups, such as ester, silyl ether, sulfonyl ester, and halogens (Cl, Br, I), were well tolerant, and the corresponding alkynylative cyclization products could be obtained with great enantioselectivities (Scheme 2, **3la**−**3ra**, 90%−94% ee). As for substrate **1s** derived from estrone, **L2** and *ent*-**L2** ligands led to similar yields, but with opposite diastereoselectivities, revealing that the formation of diastereomers in this case was completely controlled by the chiral ligand. To our delight, alkyl- and phenyl-

Table 1. Selected Optimization Studies[a]



1a 2a 3aa

entry	2a:1a	[Rh]	L	yield (%)[b]	ee (%)[c]
1	3.0	$[Rh(coe)_2Cl]_2$	**L1**	60	-94
2	3.0	$[Rh(coe)_2Cl]_2$	**L2**	62	96
3	3.0	$[Rh(coe)_2Cl]_2$	**L3**	47	-42
4	3.0	$[Rh(coe)_2Cl]_2$	**L4**	70	-73
5	3.0	$[Rh(coe)_2Cl]_2$	**L5**	15	13
6	3.0	$[Rh(coe)_2Cl]_2$	**L6**	0	-
7	3.0	$[Rh(cod)OH]_2$	**L2**	62	95
8	3.0	$Rh(nbd)_2BF_4$	**L2**	70	96
9	5.0	$Rh(nbd)_2BF_4$	**L2**	72	96
10	1.5	$Rh(nbd)_2BF_4$	**L2**	71	96
11[d]	1.5	$Rh(nbd)_2BF_4$	**L2**	32	91
12[e]	1.5	$Rh(nbd)_2BF_4$	**L2**	0	-



[a]Reactions were performed under an Ar atmosphere. [b]Determined by ^1H NMR analysis of unpurified mixtures. [c]Determined by HPLC analysis. [d]At 60 °C. [e]In the absence of Cs_2CO_3.

substituted internal alkynes were also feasible, and only the phenyl-substituted substrate resulted in a slight decrease of the yield (Scheme 2, **3ua**). More surprisingly, the R^2 substituents containing alkyl ether, ester, and silyl ether were also compatible in this reaction, affording the corresponding alkynylative cyclization products with good yields and favorable enantioselectivities (Scheme 2, **3va**−**3ya**, 63%−73% yields, 92%−94% ee). As for terminal alkyne substrate **1z**, the desired cyclization product was also obtained, albeit with a 22% yield and 70% ee (Scheme 2, **3za**).

Next, several terminal alkynes **2** were evaluated (Scheme 3). When trimethylsilylacetylene (**2b**), *tert*-butyl acetylene (**2e**), and methyl propiolate (**2f**) were individually applied to this reaction, no desired products were detected due to the homodimerization as the main side reaction for these less bulky terminal alkynes.[2b] The larger substituents including $SiEt_3$ and $Si(t\text{-}Bu)Me_2$ at silylacetylenes could still generate the desired products with moderate yields and excellent enantioselectivities (Scheme 3, **3ac**−**3ad**, 59%−68% yields, 90%−92% ee).

To demonstrate the synthetic utility of this rhodium-catalyzed alkynylative cyclization reaction, a gram-scale experiment was carried out, and the corresponding cyclization product **3aa** was isolated with good yield and constant enantioselectivity (Scheme 4). Then, several transformations of **3aa** were conducted to display the applications of the alkynyl unit.

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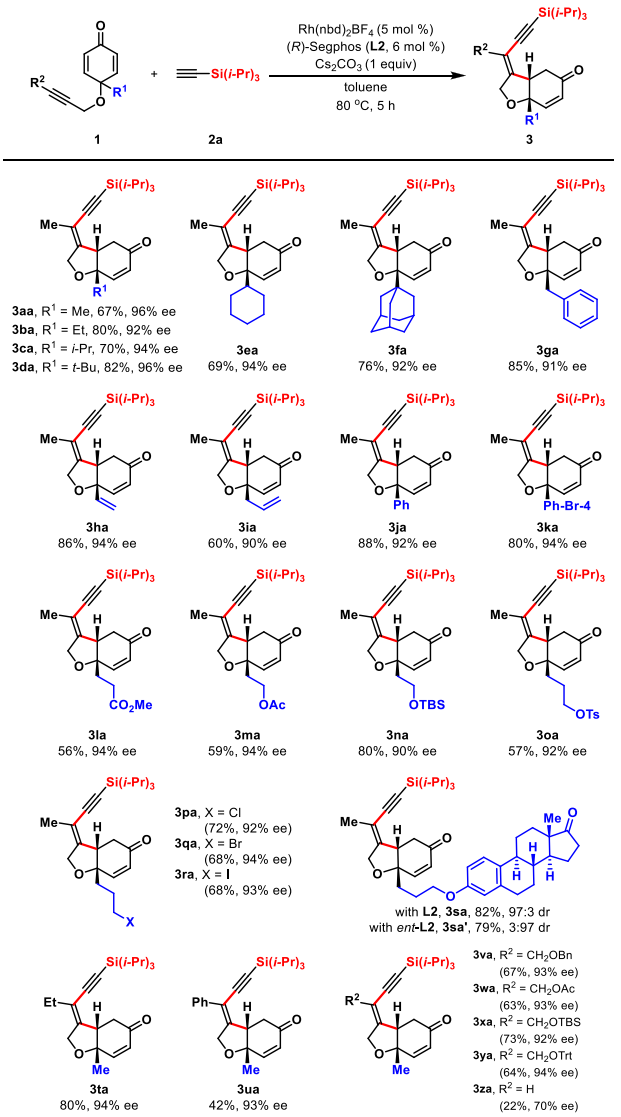
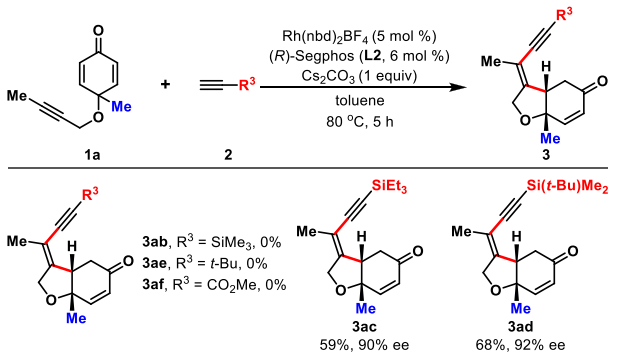
Scheme 2. Scope of 1,6-Enynes[a]



[a]Reactions were performed under an Ar atmosphere. [b]Yield of isolated product **3**. [c]Determined by HPLC analysis.

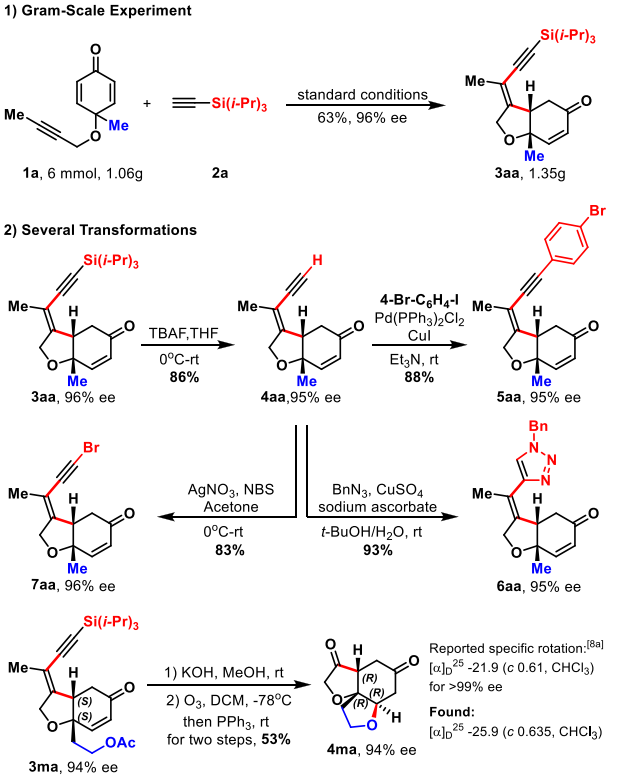
Scheme 3. Scope of Silylacetylenes[a]



[a]Reactions were performed under an Ar atmosphere. [b]Yield of isolated product **3**. [c]Determined by HPLC analysis.

Protodesiliconation of **3aa** with TBAF afforded the terminal alkyne **4aa**, which could undergo diverse transformations. For example, Sonogashira coupling of the terminal alkyne **4aa** with 1-bromo-4-iodobenzene proceeded smoothly to form the aryl-substituted internal alkyne.[12] The triazole product **6aa** could be easily obtained through a copper-catalyzed click reaction between **4aa** and benzyl azide.[13] Moreover, the terminal alkyne **4aa** could undergo silver-mediated bromination to afford **7aa** in high yield.[14] Finally, in order to determine the absolute configurations of the cyclization products, **3ma** was converted to a known chiral tricyclic product (*R,R,R*)-**4ma** through a two-step sequence including removal of the acetyl group in **3ma** and a simultaneous oxa-Michael addition under basic conditions and a subsequent ozonation reaction.[8a,15]

Scheme 4. Gram-Scale Experiment and Several Transformations



In conclusion, we have developed the first highly chemo-, regio-, and enantioselective rhodium-catalyzed alkynylation/intramolecular conjugate addition tandem reaction between terminal silylacetylenes and cyclohexadienone-tethered internal alkynes. This tandem process showed perfect atom economy and broad functional group tolerance and could conveniently afford optically pure *cis*-hydrobenzofuran skeletons containing a versatile silylacetylene fragment. Additionally, the cyclization products could be readily applied to diverse further functionalizations. Further studies on the transition-metal-catalyzed tandem desymmetrization reactions of cyclohexadienone-tethered alkynes are underway and will be disclosed in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00249.

Experimental procedures, spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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