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# Rhodium-Catalyzed Asymmetric Tandem Cyclization for Efficient and Rapid Access to Underexplored Heterocyclic Tertiary Allylic Alcohols Containing a Tetrasubstituted Olefin

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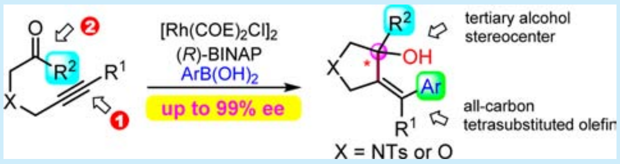
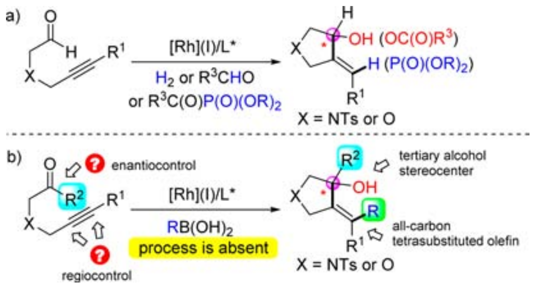
Ⓢ *Supporting Information*

**ABSTRACT:** The first Rh-catalyzed asymmetric tandem cyclization of nitrogen- or oxygen-bridged 5-alkynones with arylboronic acids was achieved. The simple catalytic system involving a rhodium(I) complex with readily available chiral BINAP ligand promotes the reaction to proceed in a highly stereocontrolled manner. This protocol provides a very reliable and practical access to a variety of chiral heterocyclic tertiary allylic alcohols possessing a tetrasubstituted carbon stereocenter and an all-carbon tetrasubstituted olefin functionality in good yields with great enantioselectivities up to 99% ee.



The transition-metal-catalyzed tandem cyclization reactions of 5-alkyne-1-carbonyl derivatives provide a powerful, straightforward, and atom-economical approach to diverse five-membered cyclic allyl alcohols with an exocyclic olefin, which are employed widely in organic and medicinal chemistry.[1] Among them, nitrogen- or oxygen-linked 5-alkyne-1-carbonyl compounds are particularly important starting materials for the construction of corresponding heterocyclic building blocks, such as tetrahydrofuran or tetrahydropyrrole derivatives. Despite the great progress made in developing efficient transition-metal catalysts including nickel,[2] rhodium,[3] palladium,[4] titanium,[5] or ruthenium[6] complexes, surprisingly, related asymmetric processes to give more valuable enantiomerically enriched products remain an understudied and elusive topic in the literature.[7−9] Rhodium-catalyzed asymmetric hydrogenation of heteroatom-linked acetylenic aldehydes disclosed by Krische in 2006 represents the first successful example of enantioselective cyclization (Scheme 1a).[7a,b] Furthermore, there are two reports of rhodium-catalyzed asymmetric reductive cyclization of similar 5-alkynals with the chelating heteroatom-substituted acetaldehydes or acyl phosphonates by Tanaka, nicely complementing that obtained by using hydrogen as reducing agent (Scheme 1a).[7c,d]

**Scheme 1. Tandem Cyclization Protocol To Access Chiral Heterocyclic Allylic Alcohols**



As for enantioselective cyclization employing nitrogen- or oxygen-linked 5-alkynyl ketones to afford chiral cyclic tertiary allylic alcohols, it is less explored mainly due to the decreased carbonyl electrophilicity and difficulty of stereocontrol (regio- and enantiocontrol). To our knowledge, only a single example of using trimethylsilyl-substituted NTs-tethered 5-alkynone as substrate was reported under palladium catalysis, giving moderate enantiocontrol (82% ee).[7e,8] Alternatively, Hayashi and Murakami have demonstrated that rhodium-catalyzed asymmetric arylative cyclization of 5-alkyne-1-carbonyls (X = $C(CH_2OBn)_2$, $C(CO_2Me)_2$ for substrate in Scheme 1a) with stable, commercially available arylboronic acids is an attractive route to carbocyclic allylic alcohols.[9] However, these processes are not equally applicable to nitrogen- or oxygen-linked substrates,[10] and it was assumed that the malonate tether contributes to the high regioselectivity of initial 1,2-addition across alkyne. Therefore, the development of an efficient catalytic system is desirable. We describe herein a highly enantioselective synthesis of heterocyclic tertiary allylic alcohols with an all-carbon tetrasubstituted olefin[11] functionality via arylative cyclization promoted by a Rh(I)/BINAP complex (Scheme 1b).

Our initial survey commenced with evaluation of representative chiral phosphoramidite ligand **L1** and phosphine ligands **L2**−**L3** in arylative cyclization of ether-linked 5-alkynone **1a** with (4-methoxyphenyl)boronic acid **2a** in the presence of 2.5 mol % of $[Rh(COE)_2Cl]_2$ and KOH (30 mol %) in toluene/$H_2O$ (10:1) at 60 °C. Intriguingly, the reactions proceeded smoothly to afford the expected cyclized product **3a** (Table 1, entries 1−3). Of these examined, the commercially available

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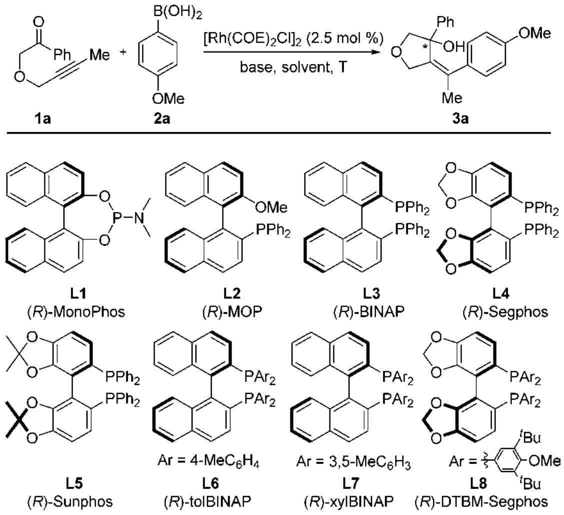
**Table 1. Optimization of Reaction Conditions for Rhodium-Catalyzed Asymmetric Arylative Cyclization of 1a with 2a**[a]



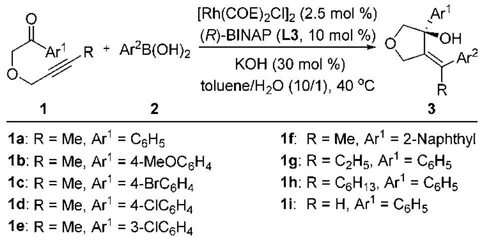
| entry | L | base | temp (°C) | solvent | yield[b] (%) | ee[c] (%) |
|---|---|---|---|---|---|---|
| 1 | **L1** | KOH | 60 | toluene | 83 | 58 |
| 2 | **L2** | KOH | 60 | toluene | 70 | 51 |
| 3 | **L3** | KOH | 60 | toluene | 86 | 94 |
| 4 | **L4** | KOH | 60 | toluene | 75 | 92 |
| 5 | **L5** | KOH | 60 | toluene | 74 | 93 |
| 6 | **L6** | KOH | 60 | toluene | 61 | 88 |
| 7 | **L7** | KOH | 60 | toluene | 41 | 11 |
| 8 | **L8** | KOH | 60 | toluene | <5 | |
| 9 | **L3** | KOH | 40 | toluene | 87 | 97 |
| 10 | **L3** | KOH | RT | toluene | 78 | 97 |
| 11 | **L3** | KOH | 40 | dioxane | 37 | 88 |
| 12 | **L3** | KOH | 40 | $CH_2Cl_2$ | 77 | 91 |
| 13 | **L3** | KOH | 40 | MeOH | 60 | 64 |
| 14 | **L3** | $K_2CO_3$ | 40 | toluene | 74 | 97 |
| 15 | **L3** | KF | 40 | toluene | 77 | 96 |

[a] The reaction was performed with **1a** (0.1 mmol), **2a** (0.3 mmol), $[Rh(COE)_2Cl]_2$ (2.5 mol %), **L** (10 mol %), and base (30 mol %) in 2 mL of solvent/$H_2O$ (10:1). COE = cyclooctene. [b] Isolated yields. [c] Determined by HPLC analysis using a chiral stationary phase.

(*R*)-BINAP **L3** (10 mol %) exhibited the greatest preference both in terms of catalytic activity and enantiocontrol (86% yield and 94% ee) (entry 3). To attain higher reactivity and enantioselectivity, a series of biaryl-type bisphosphine ligands **L4–L8** that contain different chiral backbones or sterically hindered aromatic substituents on the phosphorus were subsequently tested (entries 4–8). Unfortunately, no superior results were obtained. In all cases, the bisphosphine ligands were either less effective or altogether inactive. Following up on the encouraging results obtained with (*R*)-BINAP, effects related to the reaction temperature, solvent, and base were carefully examined. As revealed, it was found that lowering the reaction temperature to 40 °C was beneficial for the improvement of enantioselectivity (97% ee) without loss of reactivity (entry 9). However, at room temperature, a small erosion of yield was observed (entry 10). In addition, the investigation of various solvents including dioxane, $CH_2Cl_2$, and MeOH suggested that the use of toluene was the best choice (entries 9 and 11–13). Further efforts to improve the reaction yield and ee by tuning the effect of base turned out to be unhelpful (entries 14 and 15).

With the optimal reaction conditions in hand, we sought to evaluate the scope and generality of the reaction. As summarized in Table 2, a wide variety of ether-linked 5-alkynones **1** bearing different substituents on the aromatic ring attached to carbonyl group and/or at the alkyne terminus were successfully reacted with various arylboronic acids **2**, providing the corresponding chiral tertiary allylic alcohols containing a tri- or tetrasubstituted olefin and tetrahydrofuran skeleton **3a–x** mostly in good to high yields and excellent enantioselectivities (up to 99% ee). In general, with respect to *para*-substituted and *meta*-substituted arylboronic acids, the electronic properties of the phenyl ring of boronic acids did not appear to affect the reaction yield and enantiomeric excess values (entries 1–10). However, with the more hindered 2-methylphenylboronic acid or 1-naphthylboronic acid, almost no reaction occurred (data not shown). Moreover, ether-linked 5-alkynones **1b–f** with either electron-donating or electron-withdrawing groups on the aromatic ring attached to carbonyl group were found to be suitable substrates, as they exhibited high reactivity (70–85%

**Table 2. Rh/(*R*)-BINAP-Catalyzed Asymmetric Arylative Cyclization of 1**[a]



| entry | 1 | $Ar^2$ | 3 | yield[b] (%) | ee[c] (%) |
|---|---|---|---|---|---|
| 1 | **1a** | 4-$OMeC_6H_4$ | **3a** | 87 | 97 |
| 2[d] | **1a** | 4-$MeC_6H_4$ | **3b** | 73 | 92 |
| 3 | **1a** | 4-$^tBuC_6H_4$ | **3c** | 70 | 97 |
| 4[d] | **1a** | $C_6H_5$ | **3d** | 75 | 91 |
| 5 | **1a** | 4-$ClC_6H_4$ | **3e** | 72 | 94 |
| 6 | **1a** | 4-$FC_6H_4$ | **3f** | 76 | 96 |
| 7 | **1a** | 4-$BrC_6H_4$ | **3g** | 78 | 94 |
| 8 | **1a** | 2-naphthyl | **3h** | 88 | 96 |
| 9[d] | **1a** | 3-$MeC_6H_4$ | **3i** | 78 | 90 |
| 10[d] | **1a** | 3-$FC_6H_4$ | **3j** | 70 | 91 |
| 11 | **1b** | 4-$OMeC_6H_4$ | **3k** | 82 | 96 |
| 12 | **1b** | 4-$FC_6H_4$ | **3l** | 70 | 94 |
| 13 | **1c** | 4-$OMeC_6H_4$ | **3m** | 80 | 99 |
| 14 | **1c** | 4-$FC_6H_4$ | **3n** | 79 | 97 |
| 15 | **1d** | 4-$OMeC_6H_4$ | **3o** | 85 | 97 |
| 16 | **1d** | 4-$FC_6H_4$ | **3p** | 83 | 97 |
| 17 | **1e** | 4-$OMeC_6H_4$ | **3q** | 80 | 98 |
| 18 | **1e** | 4-$FC_6H_4$ | **3r** | 78 | 98 |
| 19 | **1f** | 4-$OMeC_6H_4$ | **3s** | 72 | 98 |
| 20 | **1f** | 4-$FC_6H_4$ | **3t** | 72 | 98 |
| 21 | **1g** | 4-$OMeC_6H_4$ | **3u** | 84 | 70 |
| 22 | **1h** | 4-$OMeC_6H_4$ | **3v** | 77 | 65 |
| 23 | **1i** | 4-$OMeC_6H_4$ | **3w** | 68 | 96 |
| 24 | **1i** | 4-$FC_6H_4$ | **3x** | 49 | 94 |

[a] The reaction was performed with **1** (0.1 mmol), **2** (0.3 mmol), $[Rh(COE)_2Cl]_2$ (2.5 mol %), (*R*)-BINAP (**L3**, 10 mol %), and KOH (30 mol %) in 2 mL of toluene/$H_2O$ (10:1) at 40 °C. [b] Isolated yields. [c] Determined by HPLC analysis using a chiral stationary phase; see the Supporting Information for details. [d] The reaction was performed at 60 °C.

yield) and led to the formation of highly optically active products **3k–t** (94–99% ee) (entries 11–20). In the cases of 5-alkynones **1g–h** bearing sterically demanding ethyl or *n*-hexyl, respectively, at the alkyne terminus, a distinct decrease in enantioselectivity was observed (entries 21 and 22). When R = Ph, unfortunately, no cyclized product was obtained. Notably, when more challenging 5-alkynone **1i**, possessing acidic hydrogen at the alkyne terminus, was used as the substrate, the tandem reactions proceeded equally smoothly and generated cyclized products with an exocyclic trisubstituted olefin in very high levels of stereocontrol (94–96% ee) (entries 23 and 24).

Fortunately, the structure of the product **3r** was confirmed unambiguously by single-crystal X-ray analysis, and the newly formed chiral center was determined to have the *S* configuration (Figure 1). Assuming an analogous reaction mechanism, the same absolute configurations of the obtained cyclic tertiary allylic alcohol derivatives were assigned.

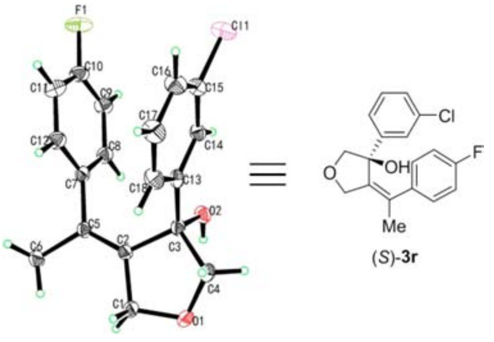
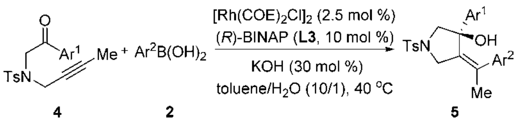


**Figure 1.** X-ray crystal structure of (*S*)-**3r**.

Given the remarkable performance of the present catalyst system in asymmetric arylative cyclization of ether-linked 5-alkynones **1** with arylboronic acids **2**, its further applicability was also examined with tosylamide-linked 5-alkynones **4** (Table 3, entries 1–4). To our delight, under the same reaction conditions, reaction involving tosylamide-linked 5-alkynones **4a,b** with several electronically different *para*-substituted arylboronic acids were all found to be successful to afford the corresponding chiral tertiary allylic alcohols **5a–d** containing tetrahydropyrrole skeleton in up to 71% yield with outstanding enantioselectivity (96–99% ee).

**Table 3. Rh/(*R*)-BINAP-Catalyzed Asymmetric Arylative Cyclization of 4**[a]

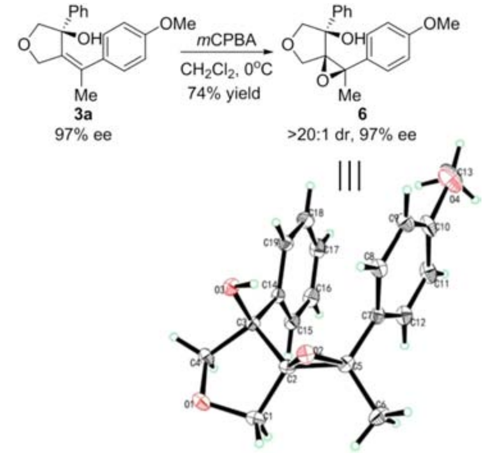


| entry | $Ar^1$ | $Ar^2$ | 5 | yield[b] (%) | ee[c] (%) |
|---|---|---|---|---|---|
| 1 | $C_6H_5$ | $4\text{-}OMeC_6H_4$ | **5a** | 61 | 96 |
| 2 | $C_6H_5$ | $4\text{-}FC_6H_4$ | **5b** | 71 | 98 |
| 3 | $4\text{-}ClC_6H_4$ | $4\text{-}OMeC_6H_4$ | **5c** | 62 | 99 |
| 4 | $4\text{-}ClC_6H_4$ | $4\text{-}FC_6H_4$ | **5d** | 70 | 97 |

[a] The reaction was performed with **4** (0.1 mmol), **2** (0.3 mmol), $[Rh(COE)_2Cl]_2$ (2.5 mol %), (*R*)-BINAP (**L3**, 10 mol %), and KOH (30 mol %) in 2 mL of toluene/$H_2O$ (10:1) at 40 °C. [b] Isolated yields. [c] Determined by HPLC analysis using a chiral stationary phase; see the Supporting Information for details.

Considering that glycidol containing a tetrahydrofuran skeleton is a unique motif existing in some biologically active compounds, such as peribysin B[12] and milbemycin derivatives,[13] epoxidation of the above obtained chiral tertiary allylic alcohol was attempted. As illustrated in Scheme 2, treatment of **3a** with *m*-CPBA in $CH_2Cl_2$ at 0 °C for 12 h led to efficient access to the desired product **6** in 74% yield with >20:1 diastereomeric ratio while maintaining high enantioselectivity. The molecular structure as well as the absolute configuration of the oxirine stereocenters were confirmed by single-crystal X-ray crystallography. Thus, a particularly interesting spirocyclic architecture bearing three consecutive quaternary stereocenters that is otherwise difficult-to-access was established in a highly stereoselective fashion.

**Scheme 2. Synthesis of the Spirocyclic Compound 6**



On the basis of the reaction stereochemical outcome, a plausible catalytic cycle and enantio-differentiation models are proposed in Figure 2. Initiation of the reaction through the transmetalation of hydroxyrhodium(I) **A** with arylboronic acid **2** generates the arylrhodium(I) **B**, which subsequently

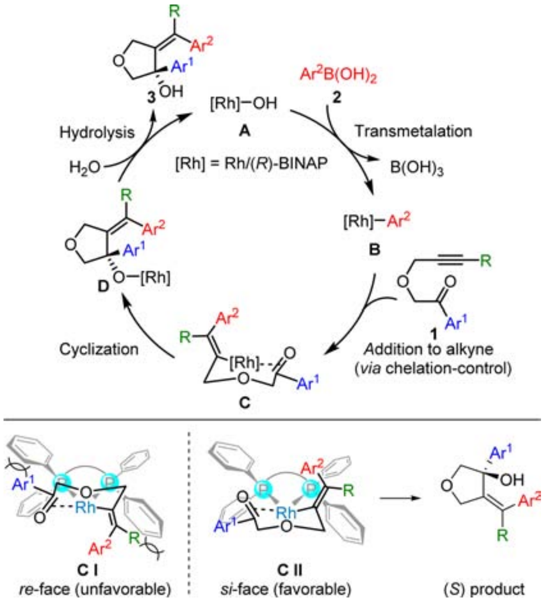


**Figure 2.** Proposed catalytic cycle and models for reaction enantioselectivity.

undergoes regioselective *syn* addition to the carbon−carbon triple bond in **1** to afford the vinylrhodium(I) intermediate **C**. The observed high regioselectivity of addition across alkyne might be attributed to chelation control[14] through the coordination of rhodium to the carbonyl group.[3b,9b] The resulting vinylrhodium(I) intermediate **C** undergoes intramolecular enantioselective nucleophilic addition to the carbonyl group in a 5-*exo* mode, forming the rhodium(I) alkoxide intermediate **D**, which is readily hydrolyzed under protic conditions to regenerate **A** with liberation of product **3**. In the cyclization process, the enantiodifferentiating carborhodation[15] takes place preferentially from the *si* face of the ketone carbonyl through **C II** to avoid the steric congestion with bisphosphine ligand, thereby affording the *S* product.

In summary, we have developed a highly efficient rhodium-catalyzed asymmetric tandem arylation/cyclization of nitrogen- or oxygen-bridged 5-alkynones with arylboronic acids by using a structurally simple, commercially available chiral BINAP as ligand. The reaction showed remarkably broad substrate scope and excellent enantiocontrol (up to 99% ee). Importantly, this method offers a reliable and practical access to a variety of highly enantioenriched tertiary allylic alcohols containing a heterocyclic skeleton, such as tetrahydrofuran or tetrahydropyrrole, which are important units that have been found in numerous natural products and pharmaceutical compounds. Further applications of the methodology are currently underway in our laboratory.

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

Experimental methods and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

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