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Stereoselective Synthesis of Exocyclic Tetrasubstituted Vinyl Halides via Ru-Catalyzed Halotropic Cycloisomerization of 1,6-Haloenynes

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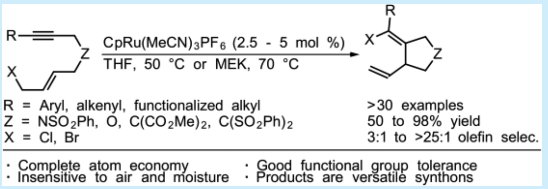
Supporting Information

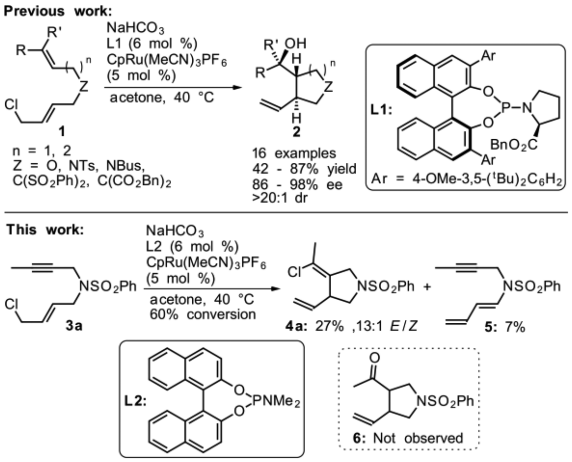
ABSTRACT: Herein, a ruthenium-catalyzed cycloisomerization that transforms 1,6-haloenynes into 5-membered carbo- and heterocycles that bear exocyclic, stereodefined, tetrasubstituted vinyl halides is reported. The reaction is insensitive to air and water, tolerates a variety of functional groups, and proceeds with good to excellent stereoselectivity and yield.



Cycloisomerizations are attractive reactions due to their ability to rapidly build molecular complexity from simpler starting materials while maintaining perfect atom economy. Transition-metal-catalyzed cycloisomerizations are particular useful, since judicious choice of the metal can impart differential reactivity and selectivity. Several reviews on transition-metal-catalyzed cycloisomerizations,[1] their application to total syntheses,[2] and asymmetric variants[3] have been published. After reporting the first transition-metal-catalyzed enyne cycloisomerization,[4] our group has maintained an interest in this field, particularly in cyclizations catalyzed by Pd[5] and Ru.[6]

Recently, our group reported an asymmetric interrupted metallo-ene reaction wherein a novel ruthenium-phosphoramidite catalyst system transformed 1,6- and 1,7-chlorodienes **1** into five- and six-membered rings **2** bearing exocyclic alcohols with excellent enantio- and diastereoselectivity (Scheme 1, top).[7] In light of these results, we sought to examine this methodology further in the context of 1,6-chloroenynes, envisioning that the additional unsaturation in the enyne would lead to the formation of the corresponding exocyclic ketones. When model substrate **3a** was subjected to reaction conditions similar to those employed for the interrupted metallo-ene reaction, none of the expected ketone product **6** formed (Scheme 1, bottom). Instead, partial conversion to vinyl chloride **4a** was observed, along with a small amount of dienamide **5**. In our prior studies with chlorodienes, adventitious water was a potent trapping agent, so it was surprising that no hydration was observed with enynes under similar conditions.

Scheme 1. Summary of Prior Work and Initial Results



This intriguing and unexpected result prompted us to examine this reaction further, particularly since **4a** was formed with good *E*/*Z* selectivity. Additionally, a survey of the literature revealed that while similar cycloisomerization reactions are precedented for alkynes conjugated with a carbonyl group, few examples have been reported for electron-neutral 1,6-chloroenynes. Rh(I)/Ag(I)[8] and Pd(II)[9] catalyze such cycloisomerizations, but both processes are limited to allylic chlorides and simple, unfunctionalized alkynes.

Given our previous success with phosphoramidite **L1**, we initiated our studies with this ligand. In addition to **L1**, we explored several other chiral ligands, but to no avail; vinyl chloride **4a** always formed with high *E*/*Z* selectivity, but the major *E* isomer was always racemic, leading us to believe that an external ligand was probably not involved in the enantiodetermining step. Further exploration of the isomerization with **3b** (Table 1) supported this hypothesis, as the reaction proceeded equally well with or without PPh_3. Both acetone and THF were suitable solvents, and a control experiment run in the absence of $CpRu(MeCN)_3PF_6$ resulted in no product formation. This reaction was quite robust, and all reactions were performed in ambient air using bulk solvents. Going forward, we evaluated the scope of this reaction in THF (Scheme 2).

The cycloisomerization does not depend on the starting olefin geometry; a 4:1 *E*/*Z* mixture of **3b** afforded identical results as the pure *E* isomer. Silyl ether **3c** was also a viable

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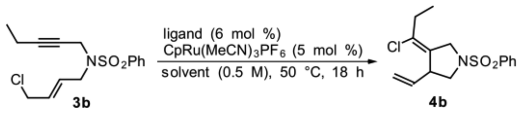
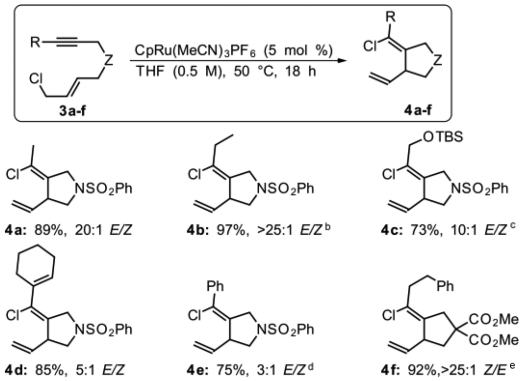
Table 1. Optimization for 1,6-Chloroenynes[a]



entry	ligand	solvent	result
1	PPh_3	acetone	84%, >25:1 *E*/*Z*
2	PPh_3	THF	90%, >25:1 *E*/*Z*
3	–	acetone	97%, >25:1 *E*/*Z*
4	–	**THF**	**Quant., >25:1 *E*/*Z***
5[b]	–	THF	NR

[a]All reactions on 0.05 mmol scale. Yields are isolated yields. Geometry confirmed by NOE and *E*/*Z* selectivity determined by ^{1}H NMR. [b]Control experiment without $CpRu(MeCN)_3PF_6$.

Scheme 2. Substrate Scope for 1,6-Chloroenynes[a]



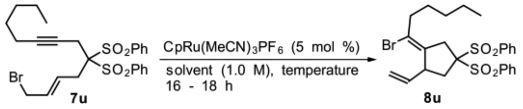
[a]All reactions on 0.10 mmol scale. Yields are isolated yields. Geometry confirmed by NOE, and *E*/*Z* selectivity determined by ^{1}H NMR after purification. [b]**4b** was a 4:1 *E*/*Z* mixture. [c]TBSCl/imidazole added. [d]Performed at 60 °C. [e]Major isomer assigned by analogy.

substrate, and although the TBS group was partially hydrolyzed during the reaction, it was easily reinstalled in the same pot by adding TBSCl and imidazole once the cycloisomerization was complete. Alkynes bearing conjugated π-unsaturation such as enyne **3d** and phenylacetylene **3e** gave reduced *E*/*Z* selectivity, and in the case of the latter, a higher temperature was required to achieve full conversion. The reaction was not limited to sulfonamide-linked enynes, as malonate **3f** also cyclized with excellent yield and *Z*/*E* selectivity.[10]

At this point, we were curious to see whether this methodology would also apply to 1,6-bromoenynes. Vinyl bromides are synthetically versatile intermediates, and furthermore, literature reports of a comparable cycloisomerization leading to vinyl bromides are scarce. Jang and co-workers reported a Sn(II)/Pt(II)-catalyzed cycloisomerization of 1,6-bromoenynes that was limited to aryl alkynes and gave either complete complementary geometrical selectivity to that which we observe or no selectivity at all, depending on the substrate.[11] Metallic indium[12] and In(III) salts[13] also promote the cyclization of 1,6-bromoenynes. An atom transfer pathway is invoked, and the identity of the vinyl halide is largely determined by the choice of halogenated solvent. As with the Pt(II)-catalyzed cycloisomerization, these indium-based methods provide a net *trans* addition of the allylic halide across the alkyne, whereas our method is selective for the net *cis* addition.

Since most bromoenynes underwent only partial conversion under our conditions for chloroenynes, we used bis(sulfone) **7u** to reoptimize the reaction conditions (Table 2). Changing from THF to acetone did not help, and adding PPh_3 slowed the

Table 2. Optimization for 1,6-Bromoenynes[a]



entry	solvent	*t* (°C)	result
1	THF	50	50% conversion
2[b]	THF	50	33% conversion
3	acetone	50	50% conversion
4	DMF	50 → 70	23% conversion[c]
5	**MEK**	**70**	**89%, 17:1 *Z*/*E***

[a]All reactions on 0.05 mmol scale. Conversion determined by ^{1}H NMR. [b]6 mol % PPh_3. [c]Full conversion after additional 10 h at 70 °C.

reaction further. Although the reaction was slow in DMF at 50 °C, full conversion was achieved when the temperature was increased to 70 °C, leading us to believe that a higher temperature was necessary. Indeed, when the reaction was performed at 70 °C in 2-butanone (MEK), full conversion was reliably obtained. This observation is consistent with work by Itoh, who showed that a π-allylruthenium(IV) bromide underwent reductive C−X bond formation slower than the corresponding chloride.[14]

Alkyl-substituted alkynes **7a** and **7b** were excellent substrates for this transformation, as were silyl ethers **7c** and **7f** (Scheme 3). Primary alcohols and alkyl bromides (**7g** and **7h**, respectively) were also well tolerated. Remarkably, **8d** was obtained cleanly, without any redox isomerization byproducts.[15] While a remote phenyl group (**7i**) had little impact on the *E*/*Z* selectivity, a conjugated phenyl group (**7e**) gave an *E*/*Z* ratio of 6:1.

Ethereal bromoenynes were also viable substrates, and while *E*/*Z* ratios were slightly lower than those observed for sulfonamides, it was possible to perform these reactions at decreased catalyst loading (2.5 mol %). Ethers bearing alkyl (**7j**), phenylsulfonyl (**7k**), silyl ether (**7m**−**n**), and aryl (**7o**) functionalities were all successfully employed. Unlike **8m**, **8n** did not require resilylation, demonstrating the robustness of the TBDPS group in this reaction. Nitrile **7l**, which could have acted as a Lewis basic catalyst poison, was also amenable to cycloisomerization when 5 mol % catalyst was used. A variety of carbon-linked bromoenynes were successfully employed in this reaction as well; malonates (**7p**−**t**) were excellent cycloisomerization substrates, as was bis(sulfone) **7u**.

Given the reduced *E*/*Z* selectivity observed with phenylacetylene-derived substrates, we were curious whether the electronic nature of the aryl substituent would affect the geometrical selectivity of the cycloisomerization (Table 3). Electron-neutral **7w** and electron-deficient **7x** afforded nearly identical results. With electron-rich **7y**, slightly lower *E*/*Z* selectivity was observed along with a small amount of ketone **9y**, which was isolated as a single diastereomer. Compound **7z** cyclized with essentially the same *E*/*Z* ratio as **7y**, and the yield of **9** was also identical. Interestingly, when $NaHCO_3$ was added to the cycloisomerization of **7z**, none of the ketone product (**9z**) formed (entry 4).

We propose the catalytic cycle shown in Scheme 4. The substrate (**A**) coordinates to ruthenium via both the alkene and the alkyne, giving rise to **B**. While **B** is likely ligated in its

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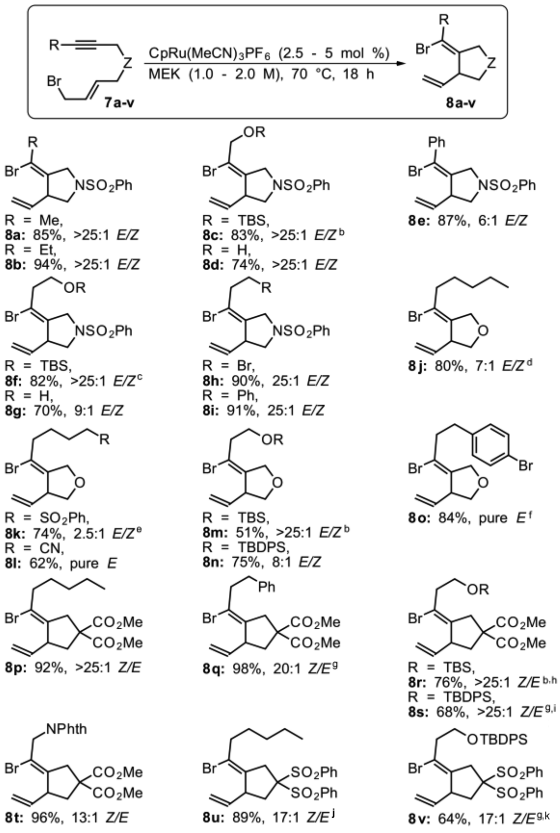
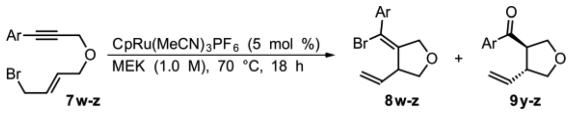
Scheme 3. Substrate Scope for 1,6-Bromoenynes[a]



[a]All reactions on 0.10 mmol scale. Yields are isolated yields. Geometry confirmed by NOE and *E*/*Z* selectivity determined by ^{1}H NMR after purification. **7j**−**k** and **m**−**o** 2.5% Ru at 2.0 M; all others 5% Ru at 1.0 M. [b]TBSCl/imid. added. [c]44% yield of **8f** + 38% yield of desilylated **8f**. [d]62% yield, 5:1 *E*/*Z* on 1.16 mmol. [e]*E*/*Z* by crude NMR. [f]12% yield of pure *Z* isomer. [g]Major isomer assigned by analogy. [h]78% yield, >25:1 *Z*/*E* on 0.69 mmol. [i]12% yield of desilylated **8s**. [j]0.05 mmol scale. [k]25% yield of desilylated **8v**.

Table 3. Examination of Phenylacetylene-Derived Substrates[a]

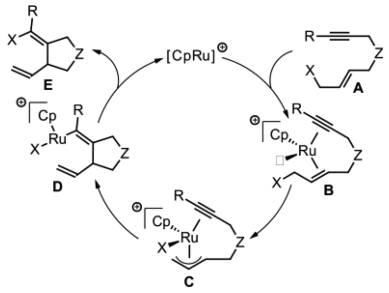


entry	Ar	result
1	Ph (**7w**)	72% of **8w**, 5:1 *E*/*Z*
2	4-AcC_6H_4 (**7x**)	78% of **8x**, 5:1 *E*/*Z*
3	4-OMeC_6H_4 (**7y**)	50% of **8y**, 3:1 *E*/*Z* + 11% of **9y**
4[b]	3,4,5-$(OMe)_3C_6H_2$ (**7z**)	82% of **8z**, 3:1 *E*/*Z*
5	3,4,5-$(OMe)_3C_6H_2$ (**7z**)	68% of **8z**, 3.4:1 *E*/*Z* + 10% of **9z**

[a]All reactions on 0.10 mmol scale. Yields are isolated yields. Geometry confirmed by NOE, and *E*/*Z* selectivity determined by crude ^{1}H NMR. [b]1.0 equiv of $NaHCO_3$ was added.

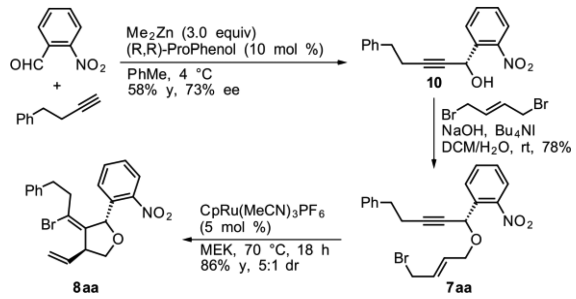
resting state, ligand dissociation to a 16-electron complex probably occurs prior to oxidative addition to form **C**, which is consistent with our observation that external ligands do not affect the outcome of the reaction. Migratory insertion to form vinylruthenium(IV) halide **D** followed by *syn*-reductive elimination affords the product (**E**). An R group capable of stabilizing positive charge, such as an alkene (**3d**) or arene (**3e**, **7e**, and **7w**−**z**), may increase the lifetime of **D** and allow for olefin isomerization prior to reductive elimination, which could account for the lower selectivities observed with these substrates. While vinyl iodides have been prepared via metal-catalyzed radical atom transfer processes, these reactions are typically unselective with regards to olefin geometry[16] or place the halogen on the less hindered face of the alkene.[17] Since our reaction installs the halogen on the *more* hindered alkene face, we do not believe a radical process is operative. Furthermore, the addition of 5 mol % of either TEMPO or BHT has no effect on the cycloisomerization of **7b** to **8b**, providing additional evidence against a radical mechanism.

Scheme 4. Proposed Catalytic Cycle



While we were unable to render our cycloisomerization asymmetric, we were curious to see if it might be diastereoselective, particularly since enantiomerically enriched propargyl stereocenters are readily accessible. To this end, chiral propargyl alcohol **10** was prepared via Zn-ProPhenol-catalyzed alkynylation[18] and alkylated under phase-transfer conditions to afford **7aa**, which was transformed into α-aryltetrahydrofuran **8aa** with 5:1 dr (Scheme 5).

Scheme 5. Diastereoselective Cycloisomerization[a]



[a]Cycloisomerization performed on 0.05 mmol scale. Stereochemistry confirmed by NOE; dr determined by crude ^{1}H NMR.

The products of this cycloisomerization reaction contain a unique juxtaposition of functionality, the versatility and utility of which is highlighted by some of the derivitizations we performed (Scheme 6). Suzuki coupling between **8k** and 2-vinylphenylboronic acid followed by Grubbs ring-closing metathesis afforded 6−7−5 tricycle **11**, which resembles the skeleton of rubriflordilactone A. A similar compound with a pyrrolidine in place of the tetrahydrofuran has been reported as an epithelial sodium channel blocker,[19] and 6−7−5 carbocycles have been studied as steroid mimics.[20] By changing the linker in **7**, our method could potentially be used to access all three sets of compounds. Buchwald's copper-free conditions[21] were uniquely effective for the Sonogashira coupling of **8r**, and the resulting dienyne underwent a Pauson−Khand reaction to

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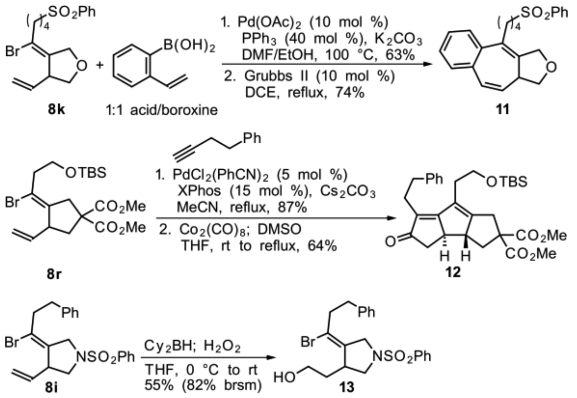
Scheme 6. Derivitizations of Vinyl Bromides



afford **12** as a single diastereomer. This sequence is noteworthy, as **12** maps nicely onto the carbon skeleton of several natural products, including hypnophilin and complicatic acid. Hydroboration−oxidation of **8i** was highly selective for the terminal alkene and afforded **13** with the vinyl bromide intact and primed for further functionalization.

In conclusion, we have developed a Ru-catalyzed halotropic cycloisomerization that transforms 1,6-haloenynes into five-membered rings that bear exocyclic tetrasubstituted vinyl chlorides and bromides. The reaction proceeds with good to excellent stereoselectivity and affords the products cleanly in high yields. Inert conditions are not required, and the reaction tolerates a variety of functionality, including protected and unprotected alcohols, alkyl bromides, nitriles, and aromatic rings. The vinyl bromides accessible using this cycloisomerization are versatile building blocks and can be rapidly transformed into complex carbon skeletons that may have utility in the synthesis of natural products and pharmaceuticals.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00879.

Experimental procedures and characterization data for all compounds and $^{1}H/^{13}C$ NMR spectra for **3**, **4**, **7**, **8**, and **11**−**13** (PDF)

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Notes

The authors declare no competing financial interest.

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