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Diastereoselective Rhodium Catalyzed [4 + 2] Cycloisomerization of Allenes

Jun Li and Scott R. Gilbertson*

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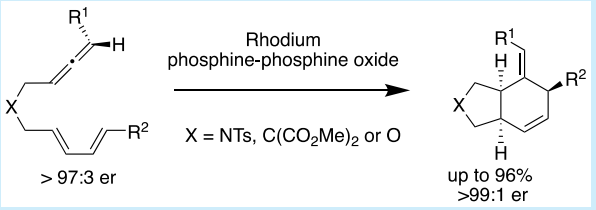
ABSTRACT: A diastereoselective [4 + 2] cycloisomerization of asymmetric allenyl dienes is reported. The asymmetric dienyl allenes are synthesized using the method reported by Ma. These substrates readily undergo diastereoselective intramolecular rhodium catalyzed [4 + 2] cycloisomerization analogous to thermal intramolecular Diels−Alder reactions. Overall, 29 examples are presented with tethers possessing nitrogen, oxygen, and carbon. Diastereoselectivities range from 99:1 to 90:10 in most examples.



We have had an ongoing program developing the use of transition metals, such as rhodium, in the catalysis of cycloisomerization reactions. In particular [4 + 2] and [4 + 2 + 2] products have been studied.[1−5] To date, there has been minimal work in the cyclization of allenes with dienes in an intramolecular fashion and even less with chiral substrates.[6−8] Wender reported nickel and rhodium versions[9] of this reaction with achiral starting material, while Trost reported two moderate rhodium examples.[10] Most recently Ma has reported select examples using chiral allenyl dienes.[11,12] Using gold as the catalyst, Toste has published select examples of intermolecular allene diene [4 + 2] cycloisomerizations on achiral allenes.[13] To our knowledge there are no large studies of the diastereoselective [4 + 2] cycloisomerizations of chiral allenes with dienes. Given that there are now efficient routes to chiral allenes, this should be a useful approach for the synthesis of chiral bicyclic structures.[14−17] A contrast from previous work with the gold system of Toste is that their system provides products with a *trans* ring juncture, while the rhodium systems provide *cis* fused products.

The synthesis of the necessary starting allene containing dienes is performed by the prolinol controlled copper catalyzed asymmetric synthesis of the allenes from an alkyne and an aldehyde.[17,18] This provides optically active allenes in excellent selectivity (Scheme 1 cpds **1** to **3**). The allenyl sulfonamides then undergo a Mitsunobu substitution with a dienyl alcohol (**6**) to provide the substrates with a sulfonamide tether (**7**). The substrates with a diester linker are accessed by reaction between a 1,3-diesterdiene (**8**) with a methanesulfonate ester allene. It is also possible to convert dienynes into the necessary allenes directly with this reaction (Scheme 1 cpds **10** to **12**).

A probe for the best rhodium system to catalyze this reaction was carried out using substrate **13** (Table 1). The reaction took place with rhodium cyclooctadiene dimer but in low yield and with no diastereoselectivity. Reaction with the chiral phosphine-phosphineoxide catalyst system (BozPHOS) resulted in products that were matched and mismatched in terms of the diastereoselectivity and the chiral induction provided by the catalyst (entries 3 and 4). (*S*,*S*)BozPHOS provided the product in a diastereomeric ratio of nearly 1 to 1, while (*R*,*R*)BozPHOS gives the [4 + 2] product in a ratio of 85:15. The system starting with rhodium cyclooctadiene dimer and adding the monoxide of BINAP [BINAP(O)] provided the

Scheme 1. Synthesis of Allenyl Diene Substrates

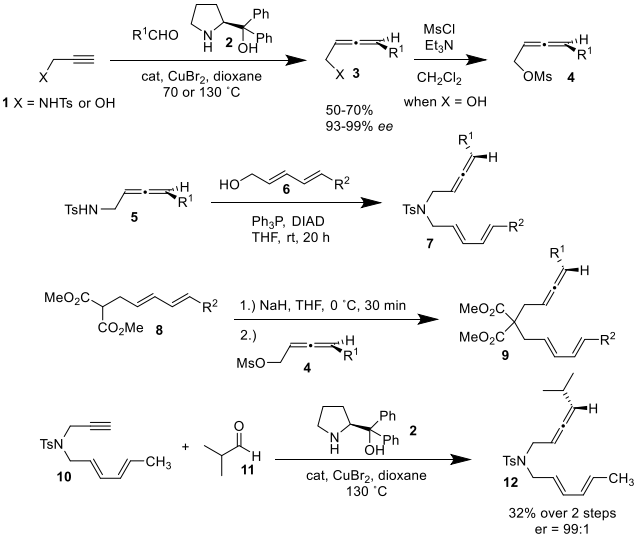


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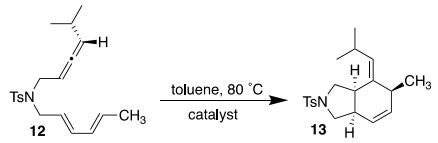
Table 1. Catalyst Screening



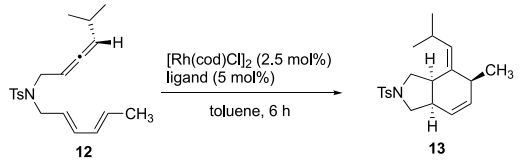
	complex	ligand	time (h)	yield[b] (%)	er[c]
1	$[Rh(cod)Cl]_2$ (2.5 mol %)		24	7	50:50
2	$[Rh(nbd)\{(S,S)$-Me-BozPHOS$\}^9]SbF_6$ (5 mol %)		12	37	54:46
3	$[Rh(nbd)\{(S,S)$-Me-BozPHOS$\}]SbF_6$ (5 mol %)		24	54	54:46
4	$[Rh(nbd)\{(R,R)$-Me-BozPHOS$\}]SbF_6$ (5 mol %)		24	57	85:15
5	$[Rh(cod)Cl]_2$ (2.5 mol %)	BINAP(O) (5%)	24	43	51:49
6	$[Rh(cod)Cl]_2$ (2.5 mol %)	BINAP (5%)	24	18	95:5
7	$[Rh(cod)Cl]_2$ (2.5 mol %)	dppe (5%)	24	57	92:8
8	$[Rh(cod)Cl]_2$ (2.5 mol %)	dppeO (5%)	24	83	97:3

[a]Reaction conditions: **12** (0.1 mmol), catalyst (2.5 mol %), ligand (5 mol %), toluene (1.0 mL). [b]Isolated yield. [c]As determined by chiral HPLC. The er value is the ratio of enantiomers obtained from a start material with an er of 97:3. Within the limits of detection only one diastereomer was observed.

product in moderate yield and nearly no selectivity. The same system using BINAP proceeded to give the product in fair yield and with better selectivity than BINAP(O). Testing dppe and dppeO illustrated that the best ligand system appears to be dppeO for substrate **12**. The reaction proceeded in shorter time, with the best selectivity and yield (6 h, 82% and 97:3 er).

Other phosphine-phosphine oxide systems with different tether lengths between the phosphorus atoms were tested, as were different reaction temperatures (Table 2). While dppeO

Table 2. Phosphine-Phosphineoxide Ligands Screen



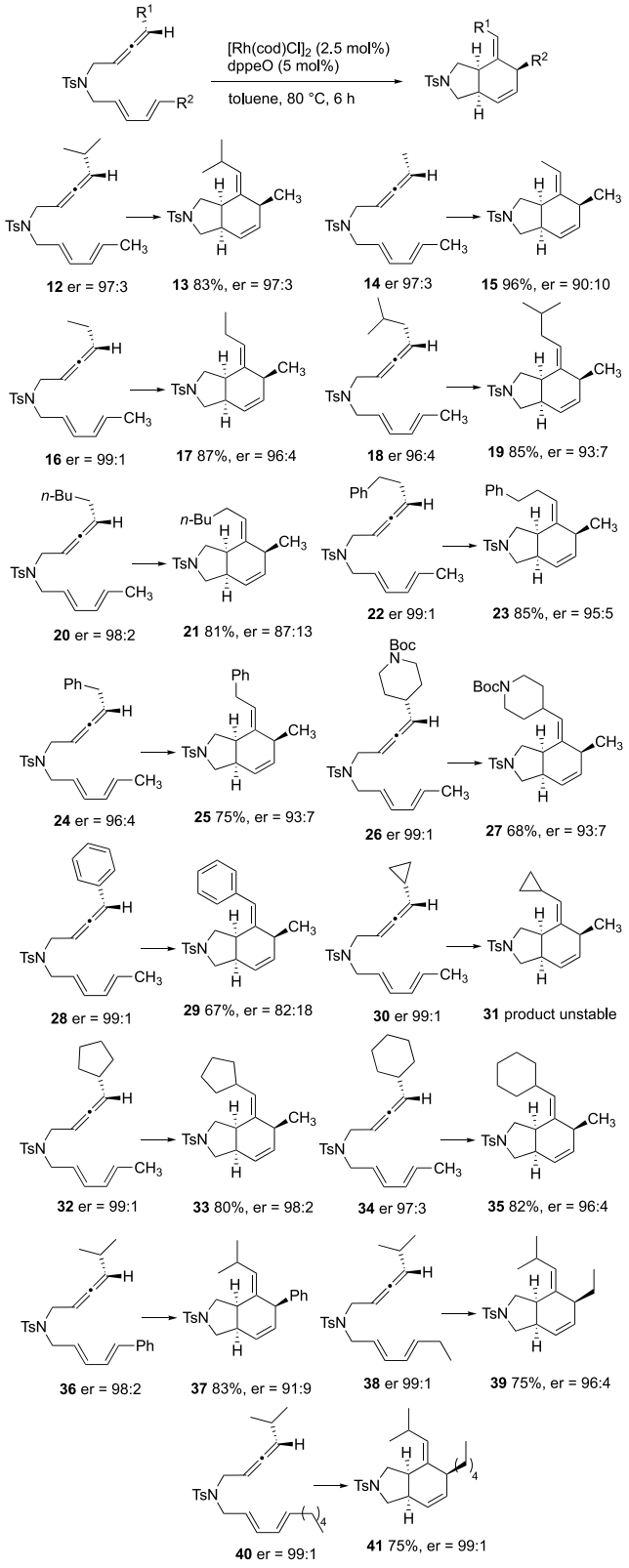
entry	t	ligand	temp (°C)	yield[b] (%)	er[c]
1	12	dppeO	80	82	97:3
2	6	dppeO	80	83	97:3
3	6	dppmO	80	88	97:3
4	6	dpppO	80	67	96:4
5	6	dppeO	55	30	97:3
6	6	dppeO	rt	trace	

[a]Reaction conditions: **12** (0.1 mmol), toluene (1.0 mL). [b]Isolated yield. [c]As determined by chiral HPLC.

is generally the best ligand, both dppeO and dppmO appear to be viable, with our best temperature for the reaction being 80 °C, with 55 °C providing lower yield even with extended reaction time. There was only a trace of product obtained at room temperature. The longer tethered ligand dpppO provides the product in lower yield but still good selectivity.

Using the dppeO conditions, a number of different allenyl diene structures were investigated (Scheme 2). In general alkyl

Scheme 2. Substrate Scope



groups on the chiral allene are well tolerated with isopropyl (**12**), ethyl (**16**), isobutyl (**18**), and phenethyl (**22**) providing nearly complete control. Primary carbons attached to the allene, such as methyl (**14**) and *n*-butyl (**20**), proceeded with slightly lower selectivity. Substrates with cyclic rings attached to the allene (**26**, **28**, **32**, **34**) proceeded with good to excellent

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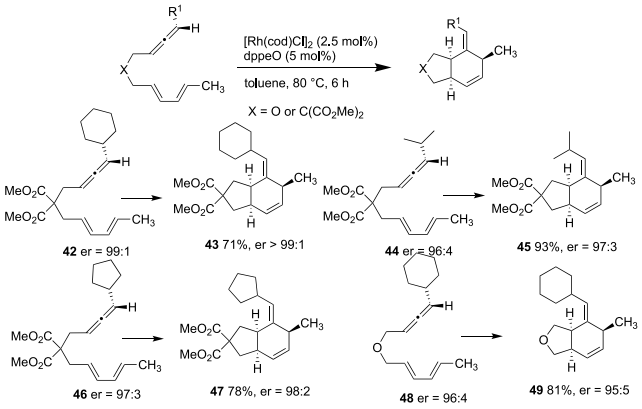
er and good yield, with the exception of the allene with cyclopropyl attached (**30**), where it was not possible to isolate the product. Versions with groups other than methyl on the diene (**36**, **38**, **40**) provided the products in good yield and with diastereoselectivity comparable to the simpler versions.

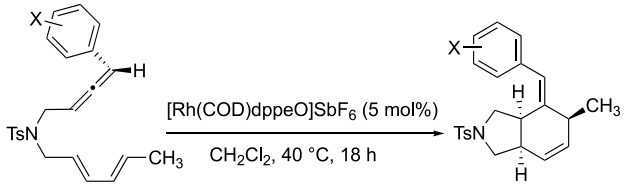
Select examples where a different tether, a diester or ether, was used to connect the allene and diene proceeded in good to excellent yield (Scheme 3). These versions with secondary

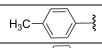
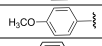
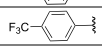
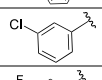
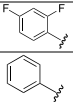
Scheme 3. Reaction with Other Tethers



carbons attached to the allene provide yields and selectivities comparable to the examples in Scheme 2. Typically examples with an aromatic group attached to the allene provided products with lower selectivity and yield (Table 3). It appears that over time substrates of this type isomerize as the reaction proceeds. Examination of the reaction in terms of enantio-

Table 3. Aromatic Allene Substrates



Entry	Cpd #	X =	allene er	product er	yield
1	51		99:1	90:10	61%
2	53		90:10	85:15	61%
3	55		98:2	85:15	53%
4	57		98:2	84:16	46%
5	59		98:2	87:13	67%
6	61		97:3	90:10	51%
7	63		99:1	92:8	53%
8	65		97:3	92:8	58%
9	67		98:2	95:5	53%
10	69		96:4	90:10	59%
11	29		99:1	99:1	51%

purity of the substrate over time illustrated that it isomerizes under the reaction conditions.

The formation and structure of the [Rh(COD)dppeO]SbF_6 complex was validated by X-ray structure determination (Figure 1). In the structure both the phosphine and the

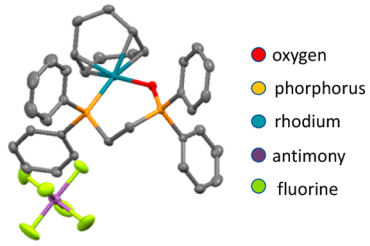


Figure 1. X-ray of [Rh[COD]dppeO]SbF_6.

oxygen of the phosphine oxide are coordinated to rhodium along with the cyclooctadiene. The reaction can be run under a number of different conditions. Either the discrete [Rh-(COD)dppeO]SbF_6 complex can be used in the reaction or 2.5 mol %[Rh(cod)Cl]$_2$ can be mixed with 5.0 mol % dppeO to form the catalyst in situ. Both approaches provide systems that give essentially the same result.

With this in mind, lower reaction temperatures were investigated. Optimal conditions were found to be 5 mol % [Rh(COD)dppeO]SbF_6 at 40 °C, CH_2Cl_2 solvent in a sealed tube. These conditions were later applied in the reaction of other aromatic substrates (Table 3).

The stereochemistry of products were verified by X-ray crystallography (Figure 2). Single crystal X-ray analysis of

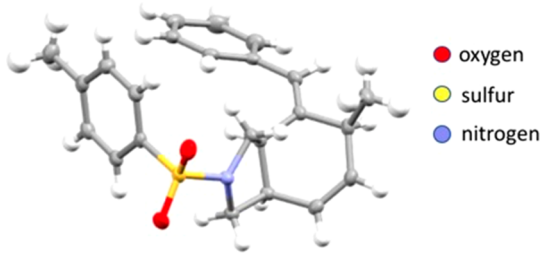


Figure 2. X-ray of product **29**.

product **29** illustrates that the stereochemistry at the ring juncture between the 5- and 6-membered rings is *cis*. This is in contrast to the *trans* ring fusions observed with gold catalyzed reactions reported by Toste.[13] Additionally the stereochemistry of the exocyclic double bond was found to be as drawn with the group on the allene positioned toward the five member ring. The NMR spectra for this product correlated with the other products reported here.

As of now the reaction does not proceed with 4 atom tethers that would form a [4.4.0] bicyclic system. Other tether systems are being examined, and chemistry to selectively carry the products forward to other products is being developed. In summary we have demonstrated that the chirality of the allene in this type of substrate can be used to control the selectivity of the of the subsequent cycloisomerizations. The unique structures obtained in this reaction have applications in small molecule library screening.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00554.

Complete experimental procedures including general considerations and characterization data and NMR spectra (PDF)

Accession Codes

CCDC 2062291 and 2062293 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

Scott R. Gilbertson − *Department of Chemistry, University of Houston, Houston, Texas 77204, United States;* orcid.org/0000-0003-3665-5693; Email: srgilbe2@central.uh.edu

Author

Jun Li − *Department of Chemistry, University of Houston, Houston, Texas 77204, United States*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.1c00554

Notes

The authors declare no competing financial interest.

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