

Diastereoselective Intramolecular Temporary Silicon-Tethered Rhodium-Catalyzed [4+2+2] Cycloisomerization Reactions: Regiospecific Incorporation of Substituted 1,3-Butadienes

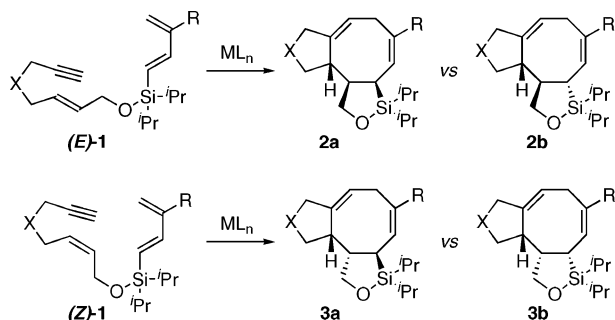
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We recently reported the *intermolecular* rhodium-catalyzed [4+2+2] carbocyclization for a series of heteroatom-tethered 1,6-enynes with 1,3-butadiene to afford eight-membered rings.^{1–4} Additional studies aimed at broadening the scope of this reaction demonstrated that substituted dienes either were unreactive or afforded mixtures of regioisomers.⁵ Hence, we envisioned that tethering the diene to the 1,6-enyne, thereby rendering the process *intramolecular*, would circumvent problems associated with low reactivity and poor regioselectivity. Herein, we now describe the development of a regiospecific and diastereoselective intramolecular temporary silicon-tethered (*TST*) rhodium-catalyzed [4+2+2] cycloisomerization reaction of 1,6-enynes (*E*)- and (*Z*)-**1** for the construction of tricyclic octanoids **2a** and **3a**, respectively (Scheme 1).

Scheme 1



Since the seminal work of Nishiyama⁶ and Stork⁷ on the use of “temporary silicon tethers” (*TST*) in free radical cyclization reactions, this strategy has been employed extensively in target directed synthesis.⁸ The most attractive features of the *TST* strategy are (i) the reactive components are generally easily tethered, (ii) the tethers provide intramolecularity, which render the processes regiospecific and stereoselective, and (iii) the tethers incorporate latent functionality that can be further manipulated. Despite the multitude of transformations that have successfully employed a temporary silicon tether, there remains a paucity of metal-catalyzed carbocyclization reactions employing this strategy.⁹ Nonetheless, we anticipated that application of the *TST* approach to the rhodium-catalyzed [4+2+2] carbocyclization reaction would provide rapid entry into various polycyclic octanoid derivatives having latent functionality necessary for further synthetic manipulation. Moreover, the inability to incorporate carbon tethers in the intermolecular reaction manifold prompted the reexamination of this tether in the context of the present reaction, *viz.* intramolecularity of the π -components. Hence, it was expected that the competing *ene*-cycloisomerization observed in the intermolecular reaction with carbon-tethered 1,6-enynes would be minimized.¹⁰

Preliminary studies tested the validity of this hypothesis, as outlined in Table 1. Attempted cycloisomerization of enyne (*Z*)-**1**

(where X = NTs, R = H)¹¹ using the reaction conditions successfully employed for the intermolecular reaction, led to the formation of a complex reaction mixture (entry 1),¹ as did the rhodium-*N*-heterocyclic carbene catalyst (entry 2).¹² It is well-established that the counterion of the silver salt additive is often highly significant in modifying the properties of the active catalytic species to thereby facilitate the requisite carbocyclization reaction. Interestingly, the hexafluoroantimonate counterion proved optimum in this regard, which is orthogonal to the trend observed for the intermolecular reaction (entry 3).¹ To further improve the efficiency and obviate the necessity for an *in situ* modification of the precatalyst, we elected to examine the Wender catalyst ([COD]Rh(Np)]SbF₆).¹³ Although this catalyst initially afforded only modest improvement (entry 4), the efficiency could be dramatically improved using the more coordinating solvent, acetonitrile (entry 5).

Table 1. Optimization of the Temporary Silicon-Tethered Rhodium-Catalyzed [4+2+2] Cycloisomerization Reaction (Scheme 1; (*Z*)-**1** Where X = NTs, R = H)^a

entry	catalyst ^b	additive ^c	solvent	<i>ds</i> ^d 3a/3b	yield ^e (%)
1	RhCl(PPh ₃) ₃	AgOTf	PhMe		0
2	RhCl(IMes)(COD)	“	“		0
3	“	AgSbF ₆	“	≥ 19:1	18
4	[(COD)Rh(Np)]SbF ₆	–	“	≥ 19:1	30
5	[(COD)Rh(Np)]SbF ₆	–	MeCN	≥ 19:1	60

^a All reactions were carried out on a 0.25 mmol reaction scale at 110 °C (0.08 M). ^b 20 mol %. ^c 2 equiv of AgX relative to the metal. ^d Diastereoselectivity (*ds*) was determined by 400 MHz NMR on the crude reaction mixtures. ^e Isolated yields.

Table 2 summarizes the scope of the intramolecular rhodium-catalyzed [4+2+2] cycloisomerization reaction. This study demonstrated that nitrogen and oxygen tethers could be utilized (entries 1–8); however, the sulfone tethers (where X = SO₂), which were utilized in the intermolecular reaction, proved unsuitable for this particular transformation. Interestingly, not only were the carbon-tethered enynes effective substrates, but they proved to be the most efficient tethers examined (entries 9–12). This reaction also proceeds efficiently with 1,3-disubstituted dienes, thereby circumventing the regiochemical problems associated with the intermolecular version (entries 2, 4, 6, *etc.*).⁵ The ability to vary the olefin geometry results in complementary diastereoselection, in which the (*E*)- and (*Z*)-olefins are stereospecifically incorporated, to afford the tricyclic octanoids **2a** and **3a** with excellent selectivity (entries 1–12). Furthermore, the (*E*)-isomers are superior substrates in terms of efficiency in the cycloisomerization, as compared to their (*Z*)-counterparts (entries 1/2 vs 3/4, *etc.*). Overall, this method represents one of the most versatile cycloisomerization reactions developed to date.

The stereospecificity with respect to the olefin geometry is in agreement with the model outlined in Figure 1. Initial complexation

Table 2. Scope of the Regio- and Diastereoselective TST Rhodium-Catalyzed [4+2+2] Cycloisomerization with Various Carbon- and Heteroatom-Tethered 1,6-Enynes^a

entry	1,6-enyne 1			<i>ds</i> ^{b,c}	yield (%) ^d	
	X	<i>E/Z</i>	R			
1	NTs	<i>E</i>	H	2a	≥ 19:1	75
2	"	"	Me	"	≥ 19:1	85
3	"	<i>Z</i>	H	3a	≥ 19:1	60
4	"	"	Me	"	≥ 19:1	71
5	O	<i>E</i>	H	2a	≥ 19:1	73
6	"	"	Me	"	≥ 19:1	85
7	"	<i>Z</i>	H	3a	≥ 19:1	39
8	"	"	Me	"	≥ 19:1	44
9	C(CO ₂ Et) ₂	<i>E</i>	H	2a	≥ 19:1	86
10	"	"	Me	"	≥ 19:1	88
11	"	<i>Z</i>	H	3a	≥ 19:1	71
12	"	"	Me	"	≥ 19:1	74

^a All reactions (0.25 mmol) were carried using 20 mol % [(COD)-Rh(Np)]SbF₆ in MeCN at 110 °C (0.08 M). ^b Diastereoselectivity (*ds*) was determined by 400 MHz NMR on the crude reaction mixtures. ^c The relative configuration of **2a** and **3a** (where X = NTs, R = Me) was proven by X-ray crystallography and related by analogy to the ¹H NMR of the other tethers. ^d Isolated yields.

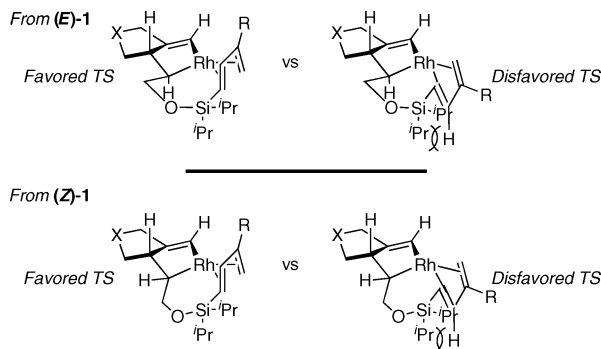


Figure 1. Proposed transition structures for the observed diastereoselectivity in the [4+2+2] with 1,6-enynes (*E*)- and (*Z*)-1.

and subsequent isomerization of the (*E*)- and (*Z*)-enynes **1** presumably result in the formation of the requisite metallacyclopentenes. The diastereoselectivity observed in the resulting intramolecular rhodium-catalyzed [4+2+2] cycloisomerization is consistent with the identical orientation of the diene in both cases. This preference can be attributed to a nonbonding interaction between one of the isopropyl groups on silicon and the C-2 proton on the 1,3-butadiene derivative.¹⁴

In conclusion, we have developed a regioselective and diastereoselective intramolecular temporary silicon-tethered rhodium-catalyzed [4+2+2] cycloisomerization reaction of a tethered enyne for the construction of tricyclic eight-membered heterocycles and carbocycles. This methodology also allows (*E*)- and (*Z*)-olefins to be utilized in a stereospecific manner. The ability to incorporate either alkene geometry is particularly significant, since related carbocyclization reactions are often limited in this respect. Finally, the ability to utilize carbon-tethered 1,6-enynes and to regioselectively incorporate substituted 1,3-butadiene derivatives provides exciting opportunities for future applications toward the total synthesis of cyclooctanoid-containing diterpenes.

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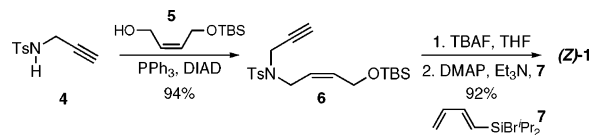
Supporting Information Available: Experimental procedures, X-ray crystallographic analysis of **2a** and **3a** (where X = NTs, R = Me), and spectral data for (*E*)- and (*Z*)-**1**, **2a**, and **3a**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

References

- (1) (a) Evans, P. A.; Robinson, J. E.; Baum, E. W.; Fazal, A. N. *J. Am. Chem. Soc.* **2002**, *124*, 8782. (b) Evans, P. A.; Robinson, J. E.; Baum, E. W.; Fazal, A. N. *J. Am. Chem. Soc.* **2003**, *125*, 14648.
- (2) For another example of a rhodium-catalyzed [4+2+2] carbocyclization reaction, see: Gilbertson, S. R.; DeBoef, B. *J. Am. Chem. Soc.* **2002**, *124*, 8784.
- (3) For related metal-catalyzed [4+2+2] carbocyclization reactions, see: (a) Greco, A.; Carbonaro, A.; Dall'Asta, G. *J. Org. Chem.* **1970**, *35*, 271. (b) Carbonaro, A.; Cambisi, F.; Dall'Asta, G. *J. Org. Chem.* **1971**, *36*, 1443. (c) Lyons, J. E.; Myers, H. K.; Schneider, A. *Ann. N.Y. Acad. Sci.* **1980**, *333*, 273. (d) Lautens, M.; Tam, W.; Lautens, J. C.; Edwards, L. G.; Crudden, C. M.; Smith, A. C. *J. Am. Chem. Soc.* **1995**, *117*, 6863. (e) Varela, J. A.; Castedo, L.; Saá, C. *Org. Lett.* **2003**, *5*, 2841.
- (4) For examples of other rhodium-catalyzed carbocyclization reactions leading to eight-membered rings, see: (a) [6+2]: Wender, P. A.; Correa, A. G.; Sato, Y.; Sun, R. *J. Am. Chem. Soc.* **2000**, *122*, 7815. (b) [5+2+1]: Wender, P. A.; Gamber, G. G.; Hubbard, R. D.; Zhang, L. *J. Am. Chem. Soc.* **2002**, *124*, 2876.
- (5) Treatment of the 1,6-enyne **i** with piperylene **ii** gave no reaction, whereas isoprene **ii** afforded the cycloadducts **iii/iv** in 60% yield, as a 1:1 mixture of regioisomers.

a R₁ = Me, R₂ = H
b R₁ = H, R₂ = Me

from **ii**: 0%
from **iii**: 60%; **iii/iv** = 1:1
- (6) Nishiyama, H.; Kitajima, T.; Matsumoto, M.; Itoh, K. *J. Org. Chem.* **1984**, *49*, 2298.
- (7) Stork, G.; Kahn, M. *J. Am. Chem. Soc.* **1985**, *107*, 500.
- (8) For recent reviews on TST strategies, see: (a) White, J. D.; Carter, R. G. In *Science of Synthesis: Houben-Weyl Methods of Molecular Transformations*; Fleming, I., Ed.; Georg Thieme Verlag: New York, 2001; Vol. 4, pp 371–412. (b) Skrydstrup, M. In *Science of Synthesis: Houben-Weyl Methods of Molecular Transformations*; Fleming, I., Ed.; Georg Thieme Verlag: New York, 2001; Vol. 4, pp 439–530 and pertinent references therein.
- (9) For examples of metal-mediated and metal-catalyzed TST carbocyclization reactions, see: (a) Kagoshima, H.; Hayashi, M.; Yukihiro, H.; Saigo, K. *Organometallics* **1996**, *15*, 5439. (b) Brummond, K. M.; Sill, P. C.; Rickards, B.; Geib, S. *J. Tetrahedron Lett.* **2002**, *43*, 3735 and references therein.
- (10) For an example of an *ene*-cycloisomerization and the consequence of olefin geometry, see: Cao, P.; Wang, B.; Zhang, X. *J. Am. Chem. Soc.* **2000**, *122*, 6490.
- (11) The 1,6-enyne (**Z**)-**1** (where X = NTs, R = H) was prepared using the three-step protocol outlined below. Mitsunobu coupling of the allylic alcohol **5** with the propargyl sulfonamide **4** furnished the allylic sulfonamide **6**. The *tert*-butyldimethylsilyl ether **6** was deprotected, and the primary alcohol coupled with the diene **7** to afford (**Z**)-**1** in 87% overall yield (3 steps).



- (12) This catalyst provided a general solution to the problem of diastereoselectivity in the intermolecular [4+2+2] carbocyclization of 3-substituted sulfonamide 1,6-enynes and 1,3-butadiene. Evans, P. A.; Fazal, A. N.; Baum, E. W. Manuscript in preparation.
- (13) Wender, P. A.; Williams, T. *J. Angew. Chem., Int. Ed.* **2002**, *41*, 4550.
- (14) (a) Sieburth, S. M.; Fensterbank, L. *J. Org. Chem.* **1992**, *57*, 5279. (b) Evans, P. A.; Cui, J.; Buffone, G. P. *Angew. Chem., Int. Ed.* **2003**, *42*, 1734.

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