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Intermolecular Transition Metal-Catalyzed [4 + 2 + 2] Cycloaddition Reactions: A New Approach to the Construction of Eight-Membered Rings

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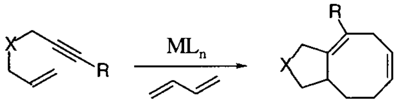
Transition metal-catalyzed cycloaddition reactions represent powerful methods for the construction of complex polycyclic systems.[1] The *inter*molecular [4 + 4] cycloisomerization is representative of this class of transformations, in which *acyclic* dienes undergo formal cycloaddition reactions to furnish the corresponding eight-membered rings.[2,3] A significant limitation with this process is the poor selectivity often obtained in *hetero*cycloadditions employing stereoelectronically different 1,3-butadiene derivatives. Although this limitation can be circumvented through *intra*molecularity[4] or related *inter*molecular variants, the direct carbocyclization of a tethered enyne with a 1,3-diene has not been described and would nonetheless provide a valuable addition to this family of cycloaddition reactions.[5] Herein, we now describe the *first* metal-catalyzed *inter*molecular [4 + 2 + 2] cycloaddition of the heteroatom-tethered enyne derivatives **1** with 1,3-butadiene for the construction of the bicyclic eight-membered heterocycles **2** (eq 1).



1 **2** (1)

The mechanistic hypothesis, outlined in Scheme 1 describes the basis of the *new* carbocyclization reaction. We anticipated that the tethered enyne **i** should coordinate the metal leading to the formation of the metallacycle **iii**, which upon addition of 1,3-butadiene should promote migratory insertion followed by a reductive elimination to afford the [4 + 2 + 2] cycloaddition adduct **v**. *The advantage of this approach is the ability to significantly increase the molecular complexity of the cycloadduct through the introduction of additional ring(s) and stereogenic centers.* Moreover, given the significant stereoelectronic difference between the enyne and diene components, it should be possible to suppress the formation of the *homo*cycloaddition and/or oligomerization.[6]

Preliminary studies tested the feasibility of this hypothesis, as outlined in Table 1. Treatment of the enyne **1a** with Wilkinson's catalyst (Rh(PPh$_3$)$_3$Cl) under an atmosphere of 1,3-butadiene in refluxing toluene, furnished a trace amount of **2a** (entry 1), owing to the propensity for the enyne **1a** to undergo *homo*cycloaddition to afford **3a** (*ds* $\geq$ 19:1). *Gratifyingly, the silver triflate modified rhodium catalyst, furnished the desired cycloaddition adduct **2a** in 85% yield (entry 2).* The ability to alter selectivity in this manner prompted additional studies to explore the effect of various silver salts on the cycloaddition (entries 2−5). Interestingly, a rather intriguing trend in selectivity emerged from this study. In the extreme case, the hexafluoroantimonate counterion completely reverses the selectivity for *hetero*cycloaddition in the presence of 1,3-butadiene, to afford the *homo*dimer **3a** in 89% yield. The origin of this selectivity was attributed to the propensity for these catalysts to promote oligomerization of 1,3-butadiene, thereby reducing its effective concentration. Analysis of the crude reaction mixture confirmed this hypothesis, in which the silver triflate *modified* catalyst furnished the least amount of oligomer, and thus explained the origin of the excellent selectivity for the *hetero*cycloaddition (entry 2).

Scheme 1

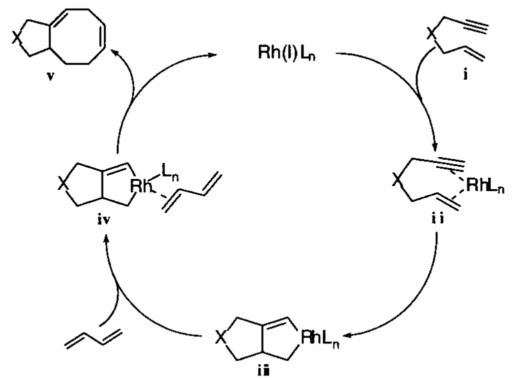
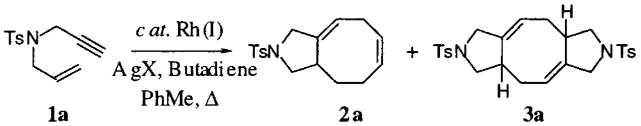


Table 1. Development of the Rhodium-Catalyzed [4 + 2 + 2] Cycloaddition Reaction



1a **2a** **3a**

entry	additive[a,b]	ratio of **2a**: **3a**[c]	yield of **2a** (%)[d,e]	yield of **3a** (%)[f]
1	none	1:8	7 (0)	57
2	***AgOTf***	***28:1***	***85 (4)***	***3***
3	AgBF$_4$	11:1	74 (0)	7
4	AgPF$_6$	2:1	49 (2)	27
5	***AgSbF$_6$***	***1:44***	***2 (6)***	***89***

[a] All reactions were carried out on a 0.5 mmol reaction scale using 10 mol % of Wilkinson's catalyst [Rh(PPh$_3$)$_3$Cl] in refluxing toluene under an atmosphere of 1,3-butadiene. [b] The rhodium catalyst was *modified* with 20 mol % of the silver salt as indicated. [c] Ratios of *hetero*- and *homo*-cycloaddition products were determined by capillary GLC and HPLC on aliquots of the crude reaction mixture. [d] GLC yields. [e] Yields in parentheses are for cyclooctadiene (by GLC). [f] HPLC yields.

Table 2 outlines the examination of the influence of various heteroatom tethers and alkyne substitution on the rhodium-catalyzed [4 + 2 + 2] cycloaddition.[7] This study demonstrated that nitrogen, sulfur, and oxygen containing tethered enynes furnish the corresponding cycloadducts in excellent yield and with analogous selectivity. The cycloaddition is tolerant of both substituted and unsubstituted alkynes, producing only trace amounts of the enyne

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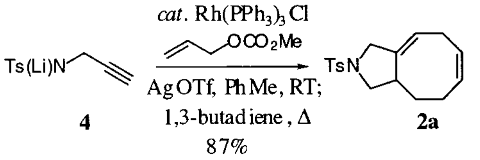
Table 2. Scope of the *Inter*molecular Rhodium-Catalyzed [4 + 2 + 2] Cycloaddition Reaction (eq 1)[a]

entry	X	R		ratio of **2**: **3**[b]	yield of **2** (%)[c]
1	TsN	H	**a**	≥19:1	91
2	“	Me	**b**	≥19:1	91
3	“	Ph	**c**	≥19:1	87
4	SO_2	H	**d**	≥19:1	79
5	“	Me	**e**	≥19:1	73
6	“	Ph	**f**	≥19:1	87
7	O	H	**g**	≥19:1	71
8	“	Me	**h**	≥19:1	81
9	“	Ph	**i**	≥19:1	92

[a] All reactions were carried out on a 0.5 mmol reaction scale using 10 mol % of Wilkinson's catalyst [$Rh(PPh_3)_3Cl$], modified with 20 mol % AgOTf, in refluxing toluene under an atmosphere of 1,3-butadiene. [b] Ratios of *hetero*- and *homo*cycloadducts were determined by 400 MHz ^{1}H NMR with the exception of **2a/3a** (26:1 by crude GLC/HPLC). [c] Isolated yields.

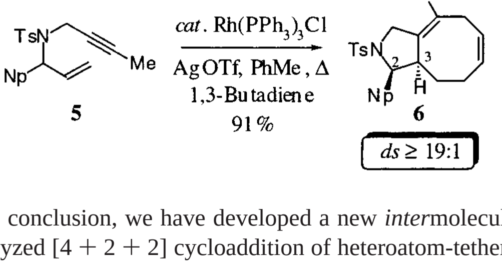
cycloisomerization and alkene isomerization products. Moreover, the sulfone tethers provide a new class of substrates for carbocyclization reactions that utilize tethered enynes.

We envisioned that the development of a *tandem* three-component allylic amination/cycloaddition would highlight the synthetic utility of this new carbocyclization reaction (eq 2).[8] Treatment of the lithium salt of *N*-tosylpropargylamine **4** with allyl carbonate in the presence of Wilkinson's catalyst, *modified* with silver triflate, at room temperature furnished the enyne **1a**. The reaction mixture was then heated at reflux for *ca*. 12 h under an atmosphere of 1,3-butadiene, to afford the cycloaddition adducts **2a/3a** in 87% yield, as a ≥19:1 mixture favoring the hetero-cycloaddition adduct **2a**.[9]



(2)

Encouraged by the results in Table 2, we decided to examine the diastereoselective *inter*molecular rhodium-catalyzed [4 + 2 + 2] cycloaddition using a C-2 substituted derivative to direct the carbocyclization. Preliminary attempts revealed that although the cycloaddition was feasible, the reaction required reduced concentration to suppress unwanted side reactions. Treatment of the enyne **5** under the optimized reaction conditions (0.0625M), furnished the azabicycles **6** in 91% yield, as a ≥19:1 mixture of diastereoisomers (eq 3). The stereochemistry was confirmed with the aid of an NOE experiment, which established the *syn* relationship of the protons at C-2/C-3.



(3)

In conclusion, we have developed a new *inter*molecular metal-catalyzed [4 + 2 + 2] cycloaddition of heteroatom-tethered enyne derivatives with 1,3-butadiene. This study demonstrates that excellent selectivity can be obtained for either the *homo*- or *hetero*-cycloaddition adducts through the judicious choice of metal counterion. The development of the *tandem* rhodium-catalyzed allylic substitution [4 + 2 + 2] cycloaddition provides a convenient three-component coupling that circumvents the prior formation of the enyne derivative. Finally, the introduction of a stereogenic center at C-2 leads to a diastereoselective cycloaddition, which provides a powerful new method for the construction of bicyclic octanoid ring systems applicable to target-directed synthesis.

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Supporting Information Available: Spectral data for **2a**−**i**, **3a**, and **6** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) The rhodium-catalyzed cycloisomerization of 1,3-butadiene is known to favor oligomerization rather than the formation of cyclooctadiene, see: Bosch, M.; Brookhart, M. S.; Ilg, K.; Werner, H. *Angew Chem., Int. Ed.* **2000**, *39*, 2304.

(7) Although the carbocyclization proceeds with heteroatom tethers, the carbon tethered derivatives lead to mixtures, in which enyne cycloisomerization was the major adduct. For a rhodium-catalyzed version, see: Cao, P.; Wang, B.; Zhang, X. *J. Am. Chem. Soc.* **2000**, *122*, 6490.

(8) For a related *tandem* rhodium-catalyzed allylic alkylation/Pauson−Khand annulation, see: Evans, P. A.; Robinson, J. E. *J. Am. Chem. Soc.* **2001**, *123*, 4609.

(9) *Representative Experimental Procedure*: Wilkinson's catalyst (46.1 mg, 10 mol %) was weighed into an oven-dried sealed tube and dissolved in anhydrous toluene (2.0 mL). Silver triflate (26.1 mg, 0.1 mmol) was then added in one portion, and the reaction vessel evacuated and reevacuated with argon (three times), then stirred at room temperature for *ca*. 20 min. Lithium hexamethyldisilyl azide (89.2 mg, 0.53 mmol) was added in a single portion from a tared vial to a stirred solution of *p*-toluenesulfonyl propargylic amine (114 mg, 0.55 mmol) in anhydrous toluene (2.0 mL) at room temperature, and stirred for *ca*. 10 min under an atmosphere of argon. The anion was then transferred *via* Teflon cannula to the preformed catalyst solution, rinsing with toluene (2 × 0.5 mL). Allyl carbonate (58.7 mg, 0.50 mmol) was then added in one portion *via* a tared 100-μL syringe. The sealed tube was then charged with 1,3-butadiene, and the reaction was allowed to stir at room temperature *ca*. 2 h, then placed in 110 °C oil bath, and heated at reflux for *ca*. 12 h. The reaction mixture was concentrated in vacuo and purified by flash chromatography (gradient elution 10−20% ethyl acetate/hexanes) to furnish the azabicycle **2a** (132 mg, 87%) as a white crystalline solid.

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