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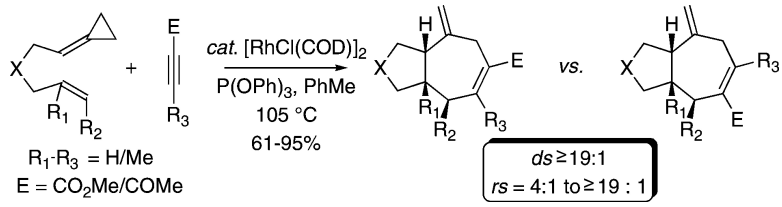

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Intermolecular Rhodium-Catalyzed [3+2+2] Carbocyclization of Alkenylidenecyclopropanes with Activated Alkynes: Regio- and Diastereoselective Construction of *cis*-Fused Bicycloheptadienes

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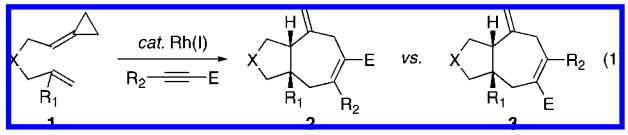
Polycyclic structures that contain seven-membered carbocycles constitute important structural motifs that are ubiquitous in several classes of bioactive natural products.[1] Although there are a variety of methods for the generation of this ring-system, metal-catalyzed carbocyclization reactions have proven among the most attractive for their construction, since they facilitate the rapid and stereoselective assembly of a specific carbocycle within a complex polycyclic scaffold.[2,3] In a program directed toward the development of higher-order carbocyclizations, we have recently described the merit of the rhodium-catalyzed [2+2+2] and [4+2+2] reactions of 1,6-enynes with alkynes and 1,3-butadienes.[4,5] Hence, it was envisioned that extension of this concept to the combination of alkenylidenecyclopropanes (ACPs) with alkynes would provide a new method for the construction of seven-membered carbocycles possessing an exocyclic methylene.[6] Although the intermolecular nickel-catalyzed [3+2+2] carbocyclization reaction of ethyl 2-cyclopropylideneacetate with alkynes and 1,7-diynes has been reported, the corresponding metal-catalyzed [3+2+2] carbocyclization of ACPs with unsymmetrical alkynes has not been forthcoming.[3c,7] Herein, we now describe the first regio- and diastereoselective intermolecular rhodium-catalyzed [3+2+2] carbocyclization reaction of ACP **1** with activated alkynes, for the construction of the bicycloheptadienes **2/3** (eq 1).



Preliminary studies examined several reaction conditions to determine the feasibility of this process (Table 1). Treatment of the ACP **1a** (X = NTs, R_1 = H) with $[Rh(COD)Cl]_2$ modified with trimethyl phosphite in the presence of methyl propiolate, furnished the bicyclic adducts **2/3** in 45% yield as a 1:1 mixture of regioisomers (entry 1). Although the yield and selectivity were initially modest, our studies demonstrated that improved efficiency could be garnered using triphenylphosphite (entries 1/2 *vs* 3) and increased ligand/metal stoichiometry (entry 3 *vs* 4).[8] Additional studies focused on the nature of the activating group present on the alkyne, which was anticipated to provide insight into improving regiocontrol.[9] In this regard, the *tert*-butyl ester afforded only modest improvement in regiocontrol, whereas the amide was less selective and efficient (entries 5 and 6). Gratifyingly, the methyl ketone provided the optimal selectivity (entry 7), which was tentatively attributed to the increased electrophilicity of the activating group (*cf.* entries 4−7). To garner additional insight into the factors that govern regiocontrol in this process, a disubstituted alkyne was examined. Interestingly, methyl but-2-ynoate furnished the bicycloheptadienes **2/3** in 80% yield, with 10:1 regioselectivity favoring **2** (entry 4 *vs* 8).

Table 1. Optimization of the Intermolecular Rhodium-Catalyzed [3+2+2] Carbocyclization Reaction (eq 1; **1a**, X = NTs, R_1 = H)[a]

entry	phosphite	equiv[b]	alkyne R_2	alkyne E	ratio of **2:3**[c]	yield (%)[d,e]
1	$P(OMe)_3$	2	H	CO_2Me	1:1	45
2	$P(O^iPr)_3$	"	"	"	2:1	47
3	$P(OPh)_3$	"	"	"	2:1	69
4	"	3	"	"	2:1	90
5	"	"	"	$CO_2{}^tBu$	3:1	94
6	"	"	"	$CON(CH_2)_4$	1:1	51
7	***$P(OPh)_3$***	***3***	***H***	***COMe***	***10:1***	***95***
8	***"***	***"***	***Me***	***CO_2Me***	***10:1***	***80***

[a] All reactions were carried out using $[Rh(COD)Cl]_2$ (4 mol%) on a 0.25 mmol reaction scale using 3 equiv of alkyne at 105 °C (0.05 M). [b] Relative to rhodium. [c] Regio- and diastereoselectivity were determined by 500 MHz NMR on the isolated product. [d] *ds* ≥19:1. [e] Isolated yields.

Table 2. Scope of the Intermolecular Rhodium-Catalyzed [3+2+2] Carbocyclization of ACPs with Unsymmetrical Alkynes[a]

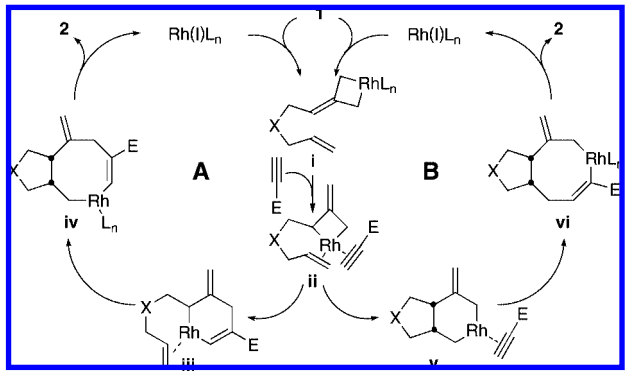
entry	ACP 1 X	ACP 1 R_1		alkyne E	alkyne R_2		ratio of **2:3**[b]	yield (%)[c,d]
1	NTs	H	**a**	CO_2Me	Me	**a**	10:1	80
2	"	Me	**b**	"	H	**b**	5:1	85
3	"	H	**a**	COMe	Me	**c**	≥19:1	82
4	"	Me	**b**	"	H	**d**	≥19:1	91
5	O	H	**c**	CO_2Me	Me	**e**	12:1	61
6	"	Me	**d**	"	H	**f**	≥19:1	68
7	"	H	**c**	COMe	Me	**g**	≥19:1	66
8	"	Me	**d**	"	H	**h**	≥19:1	83
9	$C(CO_2Me)_2$	H	**e**	CO_2Me	Me	**i**	9:1	88
10	"	Me	**f**	"	H	**j**	4:1	82
11	"	H	**e**	COMe	Me	**k**	≥19:1	81
12	"	Me	**f**	"	H	**l**	≥19:1	95

[a] All reactions (0.25 mmol) were carried out using $[Rh(COD)Cl]_2$ (4 mol%) modified with triphenylphosphite (24 mol%) in toluene at 105 °C (0.05 M). [b] Regio- and diastereoselectivity were determined by 500 MHz ^1H NMR on the isolated product. [c] *ds* ≥19:1. [d] Isolated yields.

Table 2 outlines the application of the optimized reaction conditions (Table 1, entry 7) to substituted carbon- and heteroatom-tethered ACPs with mono- and disubstituted alkynes. The carbocyclization is highly efficient and diastereoselective (*ds* ≥19:1 by ^1H NMR) in each case, albeit slightly less efficient for the ether tethers due to their inherent volatility. Although the level of regiocontrol with the ester-activated alkynes is influenced significantly by the ACP and the alkyne substitution (entries 1/2, 5/6, and 9/10), excellent regiocontrol is obtained for the ketone-activated alkynes regardless of the substitution (entries 3/4, 7/8, and 11/12). Another striking feature with this process is the ability to incorporate 1,1-disubstituted alkenes to facilitate the stereoselective introduction of quaternary carbon stereogenic centers. *Overall, this method*

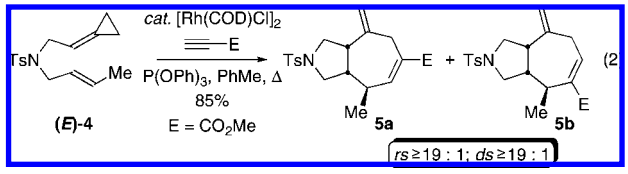
10.1021/ja803691p CCC: $40.75

Scheme 1. Proposed Catalytic Cycles for the Intermolecular Rhodium-Catalyzed [3+2+2] Carbocyclization



provides a regio- and diastereoselective route to cis-fused bicycloheptadienes that represent useful synthons for target directed synthesis.

Scheme 1 outlines two plausible catalytic cycles for this process.[6,10] Oxidative addition into the distal bond of the ACP **1** should afford the metallacyclobutene **i**, which can presumably rearrange to **ii** providing an opportunity for the bifurcation of this process through the carbometalation of either the alkyne or alkene. For example, *Cycle A* involves the carbometalation of the alkyne to afford **iii** (one regioisomer depicted for clarity), whereas *Cycle B* outlines the *intra*molecular carbometalation of the alkene to afford **v**. These metallacycles can then undergo further carbometalation to afford **iv** and **vi** (also depicted as one regioisomer), which will furnish the *cis*-fused bicycloheptadiene **2** upon reductive elimination. Although the regioselectivity will be affected by the nature of the alkyne in both pathways, alkene substitution is likely to have a greater impact on *Cycle B*. For example, the additional substituents from alkene substitution will influence the regioselectivity in the formation of **vi** from **v** (*Cycle B*), whereas the formation of **iii** can occur without the intervention of the alkene (*Cycle A*). Although this trend is evident with 1,1-disubstituted alkenes (Table 1, entry 4 *vs* Table 2, entry 2), we envisioned that the effect would be more dramatic for 1,2-disubstituted alkenes. Interestingly, treatment of ACP (***E***)**-4** (*cf.* Table 1, entry 4) with methyl propiolate under the optimal reaction conditions furnished the bicycloheptadiene **5a** in 85% yield, with excellent regioselectivity and the stereospecific incorporation of the *E*-alkene (eq 2; *rs* ≥19:1, *ds* ≥19:1, by ^{1}H NMR).[11,12] The regio- and stereochemistry of **5a** were confirmed by X-ray crystallographic analysis, which provides compelling support for the aforementioned hypothesis involving *Cycle B*.



In conclusion, we have developed the first regio- and diastereoselective *inter*molecular rhodium-catalyzed [3+2+2] carbocyclization of carbon- and heteroatom-tethered ACPs with mono- and disubstituted alkynes for the construction of *cis*-fused bicycloheptadienes. This study delineates some of the critical features for controlling regioselectivity in this process and demonstrates that *E*-alkenes can be incorporated in a stereospecific manner to afford products with up to three new stereogenic centers. The latter feature is particularly significant given that related carbocyclization reactions are often limited in this respect.[11] Finally, we anticipate that this transformation will provide exciting opportunities for future applications for the synthesis of cycloheptane-containing natural products.

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Supporting Information Available: Experimental procedures, X-ray crystallographic analysis for **2k**, **2l**, and **5a**, in addition to the spectral data for **1a**−**f**, **2a**−**l**, (***E***)**-4** and **5a**. This material is available free of charge *via* the Internet at http://pubs.acs.org.

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(8) The phosphite ligands proved superior in terms of efficiency to the monodentate and bidentate phosphine ligands. For example, the triphenylphosphine was completely ineffective, whereas 1,3-*bis*(diphenylphosphino)propane furnished **2a/3a** in 32% yield with 2:1 regiochemistry.

(9) The phenylacetylene and (trimethylsilyl)acetylene did not furnish any of the desired [3+2+2] carbocyclization products.

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