JOC Article

A General Synthetic Route to Differentially Functionalized Angularly and Linearly Fused [6−7−5] Ring Systems: A Rh(I)-Catalyzed Cyclocarbonylation Reaction

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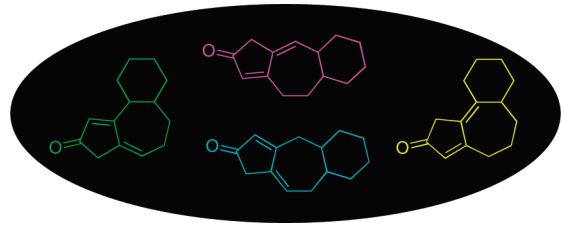

Investigations of a Rh(I)-catalyzed cyclocarbonylation reaction reveal its general synthetic utility for accessing highly functionalized tricyclic [6−7−5] linear and angular ring systems from allene−ynes. Three types of allene−ynes were prepared and subjected to Rh(I)-catalyzed cyclocarbonylation conditions. For three series of allene−ynes, the [6−7−5] ring systems were afforded in varying yields depending on the substrate structure. One series of allene−ynes afforded the [6−6−5] ring system possessing an α-alkylidene cyclopentenone as a result of a selective reaction with the proximal double bond of the allene.

Introduction

Since the Stork−Eschenmoser hypothesis of polyolefinic cyclizations,[1] rapid and selective assembly of polycyclic compounds from unsaturated precursors has intrigued the synthetic community.[2] Transition-metal catalysis has substantially increased the substrate scope of polyolefinic cyclizations; however, most are dependent upon selectivity factors imparted by both the substrate and the reagent. Selectivity achieved through only catalyst-based control elements has the highest potential for synthetic utility. Recently, our group has demonstrated that in nearly all intramolecular Rh(I)-catalyzed allenyl cyclocarbonylations and carbocyclizations examined to date the reactions occur selectively with the distal double bond of an allene.[3] Interestingly, this regioselective reaction affords bicyclo[4.3.0]nonadienones and bicyclo[5.3.0]decadienones. While obtaining the former skeleton via cyclocarbonylation chemistry has been accomplished, it has not been without difficulty.[4] Accessing the latter skeleton via this strategy has scarcely been accomplished, but not for lack of trying.[4c,d]

We[5] and others[6] have continued to explore the scope and limitations of the Rh(I)-catalyzed cyclocarbonylation reaction to form bicyclo[5.3.0]decadienones. Initially, we demonstrated the synthetic potential of this reaction by rapidly assembling the carbocyclic core of guanacastepene A.[7] By varying the position of the allene and alkyne on a cycloalkane scaffold (e.g., cyclohexane, **A**−**D**, Scheme 1), carbocycles are produced that possess a unique positioning of the resulting dienone functional-

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(6) Hirose, T.; Miyakoshi, N.; Mukai, C. *J. Org. Chem.* **2008**, *73*, 1061–1066.

(7) Brummond, K. M.; Gao, D. *Org. Lett.* **2003**, *5*, 3491–3494.

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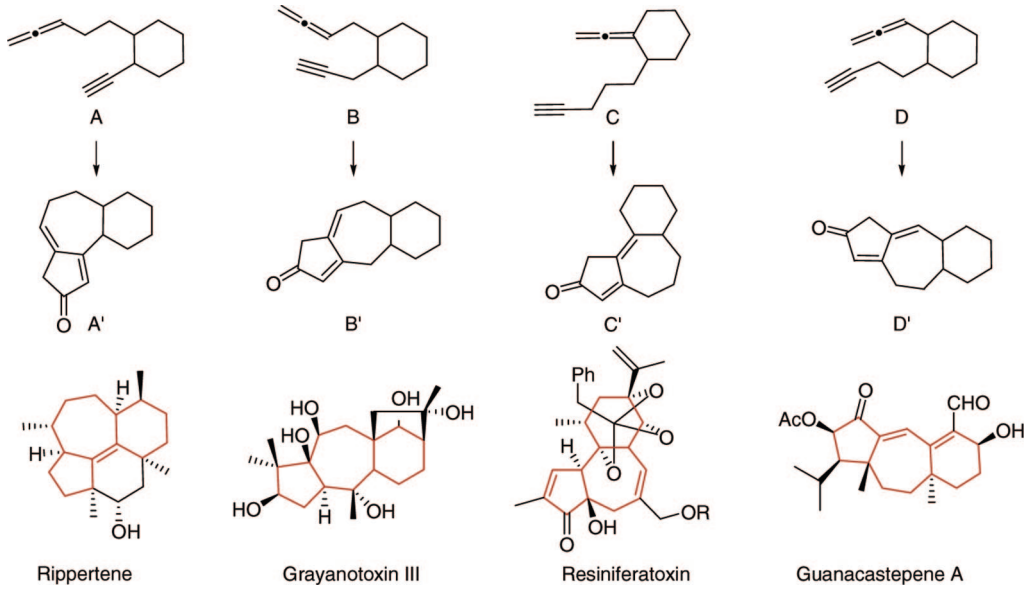
SCHEME 1. Angularly and Linearly Fused [6−7−5] Ring Systems



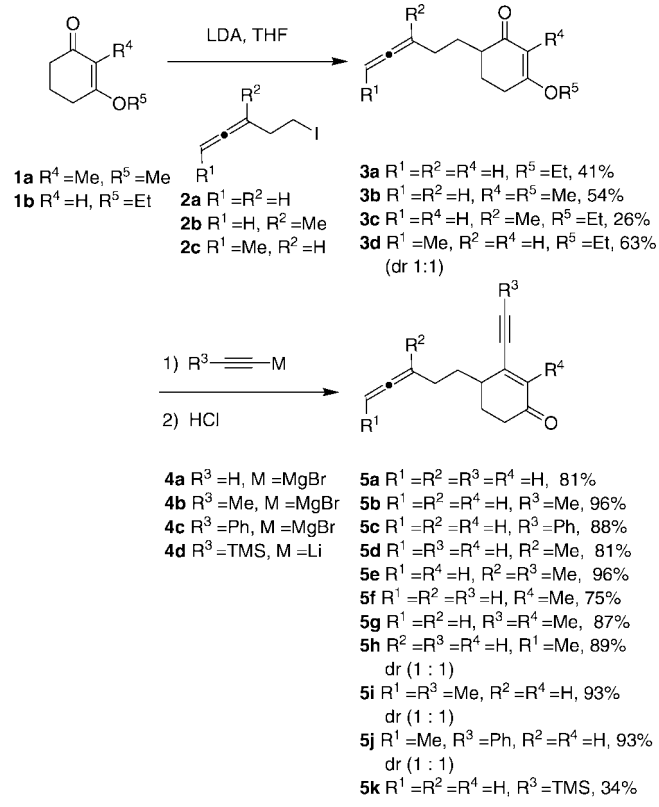
ity relative to the six-membered ring (**A′**−**D′**, Scheme 1). Rapid access to the bicyclo[5.3.0]decane ring system, in addition to the differential positioning of the dienone, provides entry into an abundance of biologically relevant compounds with functionally dense, angularly and linearly fused [6−7−5] ring systems (e.g., rippertene, grayanotoxin III, resiniferatoxin, and guanacastepene A, Scheme 1). The results of this scope and limitation study of a Rh(I)-catalyzed cyclocarbonylation reaction of allene−ynes of types **A**−**C** to form bicyclo[5.3.0]decadienones are reported within.

Results and Discussion

Preparation of Allene−Ynes Types A−C. Preparation of cyclocarbonylation precursors began with the synthesis of allene−yne type **A** (Schemes 1). Two methods were implemented for their formation. First, the Stork−Danheiser vinylogous ester methodology[8] was used; alkylation of the substituted 3-alkoxy-2-cyclohexenones **1a**,**b** with allenes **2a**−**c**[9] afforded the corresponding enones **3a**−**d** in 26−63% yield (Scheme 2.) These low to moderate yields are attributed to a competing E2 elimination reaction involving the homoallylic iodide of the allene. Because allenes **2a**−**c** are the most valuable component in these reactions, we were reluctant to increase the allene equivalents. Enone **3d** was formed as a 1:1 mixture of diastereomers which were not separated and carried on as a mixture. Addition of acetylides **4a**−**d** to enones **3a**−**d**, followed by acidic hydrolysis afforded allene−ynes **5a**−**k** in 34−96% yield.

An alternate route to allene−yne type **A** began by alkylating ethyl 2-oxocyclohexanecarboxylate (**6**) with 5-iodopenta-1,2-diene (**2a**) utilizing K_2CO_3 in refluxing acetone, affording **7** in 60% yield (Scheme 3). Subsequently, addition of ethynylmagnesium bromide (**4a**) or propynylmagnesium bromide (**4b**) to the ketone gave allene−yne **8a** and **8b** in 89% and 97% yield, respectively. Interestingly, **8a** was obtained as an inseparable

SCHEME 2. Synthesis of Allene−Ynes 5a−k



1a R^4 =Me, R^5 =Me
1b R^4 =H, R^5 =Et

2a R^1 =R^2 =H
2b R^1 =H, R^2 =Me
2c R^1 =Me, R^2 =H

3a R^1 =R^2 =R^4 =H, R^5 =Et, 41%
3b R^1 =R^2 =H, R^4 =R^5 =Me, 54%
3c R^1 =R^4 =H, R^2 =Me, R^5 =Et, 26%
3d R^1 =Me, R^2 =R^4 =H, R^5 =Et, 63% (dr 1:1)

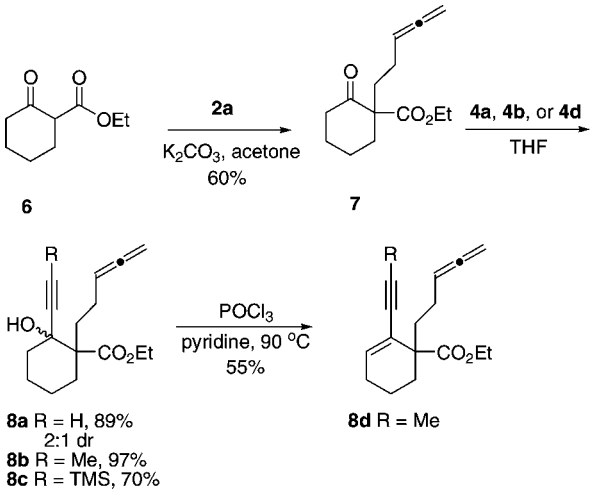
4a R^3 =H, M =MgBr
4b R^3 =Me, M =MgBr
4c R^3 =Ph, M =MgBr
4d R^3 =TMS, M =Li

5a R^1 =R^2 =R^3 =R^4 =H, 81%
5b R^1 =R^2 =R^4 =H, R^3 =Me, 96%
5c R^1 =R^2 =R^4 =H, R^3 =Ph, 88%
5d R^1 =R^3 =R^4 =H, R^2 =Me, 81%
5e R^1 =R^4 =H, R^2 =R^3 =Me, 96%
5f R^1 =R^2 =R^3 =H, R^4 =Me, 75%
5g R^1 =R^2 =H, R^3 =R^4 =Me, 87%
5h R^2 =R^3 =R^4 =H, R^1 =Me, 89% dr (1 : 1)
5i R^1 =R^3 =Me, R^2 =R^4 =H, 93% dr (1 : 1)
5j R^1 =Me, R^3 =Ph, R^2 =R^4 =H, 93% dr (1 : 1)
5k R^1 =R^2 =R^4 =H, R^3 =TMS, 34%

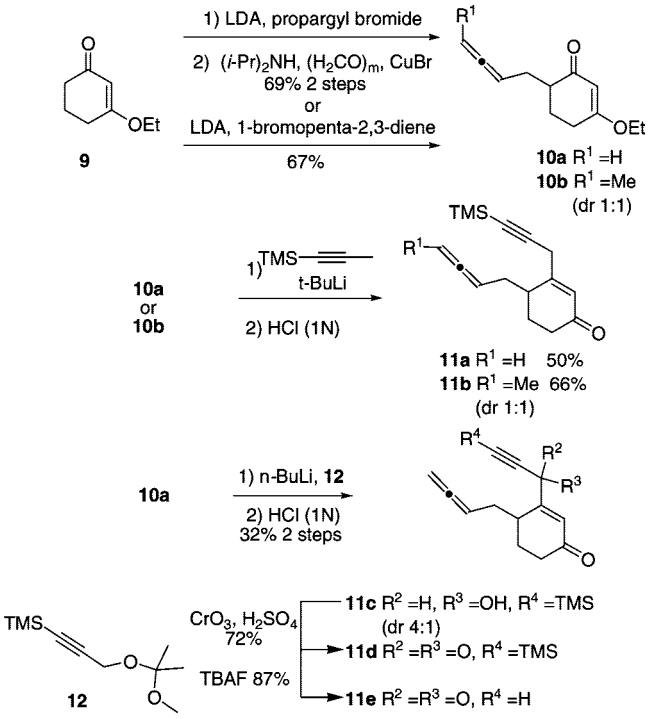
mixture of diastereomers (2:1 based upon ^{1}H NMR), and **8b** was obtained as a single diastereomer. Addition of the lithium trimethylsilylacetylide (**4d**) to ketone **7** gave allene−yne **8c** in 70% yield as a 2:1 mixture of diastereomers (based upon ^{1}H NMR). The diastereomers were separated by column chromatography and taken on independently. Dehydration of allene−yne **8b** with phosphorus oxychloride gave allene−yne **8d** in 55% yield.[10]

(8) Stork, G.; Danheiser, R. L. *J. Org. Chem.* **1973**, *38*, 1775–1776.
(9) Homoallenic iodides were prepared by a modified four-step reaction sequence on multigram scale and were freshly purified via flash chromatography prior to the alkylation reaction. Dauben, W. G.; Shapiro, G. *J. Org. Chem.* **1984**, *49*, 4252–4258.
(10) Trost, B. M.; Sorum, M. T.; Chan, C.; Harms, A. E.; Rühter, G. *J. Am. Chem. Soc.* **1997**, *119*, 698–708.

SCHEME 3. Formation of Allene−Ynes 8a−d

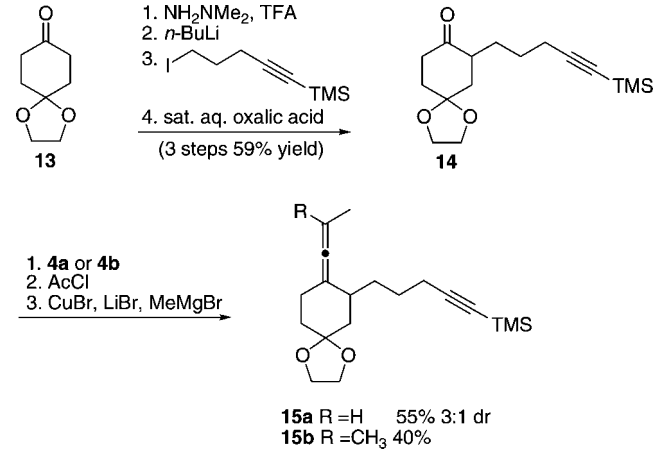


SCHEME 4. Formation of Allene−Ynes 11a−e

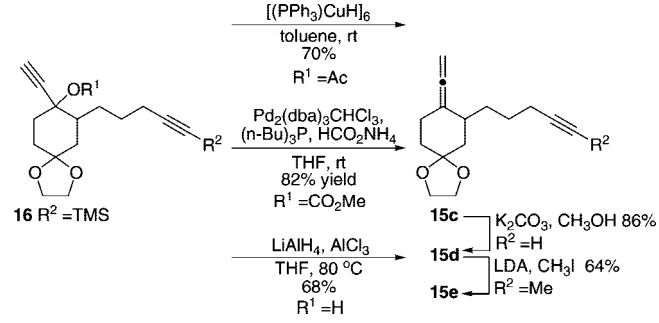


Preparation of allene−yne precursors type **B** began by alkylating the lithium enolate of 3-ethoxy-2-cyclohexenonone (**9**) with propargyl bromide, followed by a Crabbé homologation to convert the alkyne to terminal allene **10a** (Scheme 4.)[11] Alternatively, **10b** was prepared by direct alkylation of 3-ethoxycyclohexenon-2-one (**9**) with 1-bromopenta-2,3-diene. With **10a** and **10b** in hand, the alkyne moiety was installed by addition of the lithiate of 1-(trimethylsilyl)-1-propyne at −78 °C, giving **11a** and **11b** in 50% and 66% yield, respectively, after hydrolysis with 1 N HCl.[12] Addition of the lithium anion of propargyl ether **12** to **10a** followed by hydrolysis afforded **11c** in 32% yield. Oxidation of **11c** with Jones' reagent gave the alkynone **11d** in 72% yield. The trimethylsilyl group was removed from **11d** with tetra-*n*-butylammonium fluoride to provide the terminal alkynone **11e** in 87% yield.

SCHEME 5. Formation of Allene−Ynes 15a,b



SCHEME 6. Formation of Allene−Ynes 15c−e



Allene−ynes type **C** were prepared as follows. Alkylation of the *N*,*N*-dimethylhydrazone of 1,4-cyclohexanedione monoethylene ketal (**13**) with (5-iodopent-1-ynyl)trimethylsilane[13] gave **14** following a selective hydrolysis of the hydrazone in the presence of the ketal with oxalic acid (Scheme 5).[14] Hydrazone formation was necessary due to the low yields obtained of the monoalkylation product when direct alkylations of 1,4-cyclohexanedione monoethylene ketal were attempted using a variety of conditions (LDA, THF; KHMDS, THF or 1:1 toluene/DMF; KH, THF). Addition of ethynylmagnesium bromide (**4a**) or propynylmagnesium bromide (**4b**) followed by in situ acetylation using acetyl chloride furnished the corresponding propargyl acetates, which upon S_N2' addition of a dialkyl cuprate gave allene−ynes **15a** and **15b** in 55% and 40% yield, respectively, for three steps. Allene−yne **15a** was obtained as a 3:1 mixture of diastereomers.

Three protocols were examined for the formation of the 1,1-disubstituted allene **15c** (Scheme 6). Reaction of propargyl acetate **16** (R^1 = Ac) with Stryker's reagent ($[(PPh_3)CuH]_6$)[15] gave allene−yne **15c** in 70% yield. Treatment of propargyl carbonate **16** ($R^1 = CO_2Me$) to Tsuji's Pd(0)-catalyzed hydrogenolysis conditions[16] gave allene−yne **15c** in 82% yield. Reaction of the propargyl alcohol **16** (R^1 = H) to AlH_3 (generated in situ from $LiAlH_4$ and $AlCl_3$)[17] gave **15c** in 68% yield. While the Tsuji protocol was highest yielding, the direct

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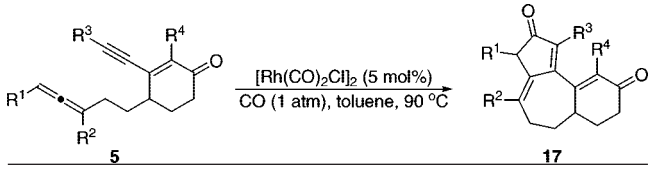
TABLE 1. Cyclocarbonylation Reactions of Allene−Ynes 5a−k Affording 17a−k



5 17

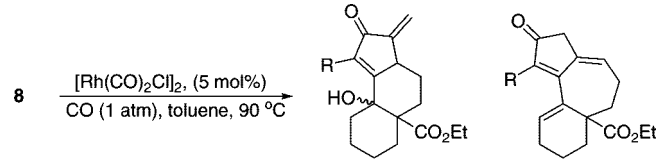
entry	reaction	time	dr	yield (%)
a	**5a**: $R^1 = R^2 = R^3 = R^4 = H$	100 min		85
b	**5b**: $R^1 = R^2 = R^4 = H$, $R^3 = Me$	130 min		67
c	**5c**: $R^1 = R^2 = R^4 = H$, $R^3 = Ph$	40 min		71
d	**5d**: $R^1 = R^3 = R^4 = H$, $R^2 = Me$	35 min		64
e	**5e**: $R^1 = R^4 = H$, $R^2 = R^3 = Me$	30 min		67
f	**5f**: $R^1 = R^2 = R^3 = H$, $R^4 = Me$	70 min		56
g	**5g**: $R^1 = R^2 = H$, $R^3 = R^4 = Me$	20 h		58
h	**5h**: $R^1 = Me$, $R^2 = R^4 = R^3 = H$	30 min	1.5:1	62
i	**5i**: $R^1 = R^3 = Me$, $R^2 = R^4 = H$	100 min	2:1	62
j	**5j**: $R^1 = Me$, $R^2 = R^4 = H$, $R^3 = Ph$	120 min	1:1	78
k	**5k**: $R^1 = R^2 = R^4 = H$, $R^3 = TMS$	9.5 h		57

conversion of the propargylic alcohol using AlH_3 was more convenient for accessing **15c**, due the ease of substrate preparation and the relative simplicity of the reaction and subsequent purification. Removal of the trimethylsilyl group from the alkyne of **15c** (R^2 = TMS) was accomplished using K_2CO_3 in methanol to give allene−yne **15d** (R^2 = H) in 86% yield. The alkyne terminus was methylated using LDA and MeI to give allene−yne **15e** (R^2 = Me) in 64% yield.

Cyclocarbonylation of Allene−Ynes Types A−C. The allene−ynes types **A**−**C** were next subjected to the Rh(I)-cyclocarbonylation reaction conditions. For each series of allene−ynes, the reaction conditions were not varied, in an effort to examine the effects of substrate functionality and substitution. Allene−ynes **5a**−**k** were reacted with 5 mol % of rhodium biscarbonyl chloride dimer $[Rh(CO)_2Cl]_2$ in toluene at 90 °C under a balloon of carbon monoxide. Cycloadducts **17a**−**j** were obtained in yields ranging from 56−85% (Table 1.) Especially interesting is the reaction of **5g**, where R^3 and R^4 are both methyl groups which afford the cyclocarbonylation product **17g** in 58% yield, albeit in 20 h. This long reaction time is likely due to the developing A (1,3) strain in the transition state between the methyl groups. Terminal alkynes were tolerated as exemplified by the formation of products **17a**, **17d**, **17f**, and **17h**. Allene−ynes **5h**−**j** were subjected to the cyclocarbonylation reaction conditions as 1:1 mixtures of diastereomers (entries h−j). The resulting cycloadducts **17h** and **17i** were obtained in enriched diastereomeric ratios (1.5:1 and 2:1, respectively). While the reason for this diastereoselectivity is not known, it is most likely due to the steric bulk of the methyl group at R^1 slightly biasing the cyclocarbonylation reaction of one diastereomer of **5h** and **5i** over the other.

The reaction of allene−ynes **8a**−**c** to the rhodium(I)-catalyzed cyclocarbonylation reaction conditions afforded **18a**−**c** and none of the expected [5−7−6] ring systems **19** (Table 2). We speculate that the hydroxyl group coordinates to the rhodium metal, directing the reaction to the proximal double bond of the allene, giving α-alkylidene cyclopentenones **18**. Indeed, this hypothesis is supported by the cyclocarbonylation reaction of **8d**, which affords **19** as a result of the selective reaction of the distal double bond in the absence of the hydroxyl group, albeit in low yield. These low-yielding cyclocarbonylation reactions were a concern, so the diastereomers of **8c** were separated and subjected independently to the reaction conditions. The major

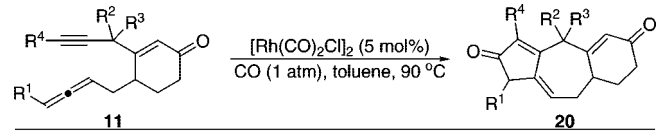
TABLE 2. Rh(I)-Catalyzed Cyclocarbonylation Reaction of 8a−d Affording 18a−c and 19



18 19

entry	reaction	time	yield (%)
a	**8a** → **18a**: R = H	190 min	32
b	**8b** → **18b**: R = Me	40 min	37
c	**8c** → **18c**: R = TMS	23 h	13
d	**8d** → **19**: R = Me	160 min	29

TABLE 3. Rh(I)-Catalyzed Cyclocarbonylation Reaction of Allene−Ynes 11a−eAffording 20a−d



11 20

entry	reaction	time (min)	yield (%)
a	**11a**: $R^1 = R^2 = R^3 = H$, $R^4 = TMS$	120	48
b	**11b**: $R^1 = Me$, $R^2 = R^3 = H$, $R^3 = TMS$	180	68
c	**11c**: $R^1 = R^2 = H$, $R^3 = OH$, $R^4 = TMS$	50	84
d	**11d**: R^1= H, $R^2 = R^3 = O$, $R^4 = TMS$	10	76
e	**11e**: $R^1 = H$, $R^2 = R^3 = O$, $R^4 = H$		[a]

[a] Decomposition was observed.

diastereomer of **8c** afforded the cycloadduct **18c** in 13% yield, and the minor diastereomer gave only trace quantities of **18c** (by ^1H NMR) along with significant decomposition. It is not clear at this time why the yield obtained for **18c** was notably lower than **18a** and **18b**; however, the significantly longer reaction time necessary for consumption of **8c** compared to **8a** and **8b** likely contributes to the low yields. In addition, the crude ^1H NMR spectra of **8b** and **8c** show substantial quantities of a substance(s) possessing broad peaks (δ 4.3−4.0 and 2.0−1.0). There have been no previously reported Rh(I)-catalyzed allenic cyclocarbonylation reactions showing exclusive reactivity for the proximal double bond of the allene.[18]

Allene−ynes **11a**−**e** were reacted with 5 mol % of $[Rh(CO)_2Cl]_2$ to give cyclocarbonylation adducts **20a**−**d** (Table 3). For substrates **11c** and **11d**, bearing an α-hydroxyl or carbonyl group adjacent to the alkyne (entries c and d), cyclocarbonylation resulted in high yields of the [5−7−6] cycloadducts. A trimethylsilyl group on the terminus of the alkynone was necessary for this series of allene−ynes, with **11e** possessing a terminal alkyne resulting in rapid decomposition. This result is not unexpected given the increased acidity of proton on the terminus of the alkyne and its higher propensity to react with the rhodium catalyst to form rhodium vinylidenes.[19] Attempts to prepare allene−ynes possessing either a methyl or phenyl group on the terminus of the alkyne were unsuccessful due to substantial quantities of byproduct formed during the addition of the corresponding propargyl anions to the vinylogous ester **10a**.

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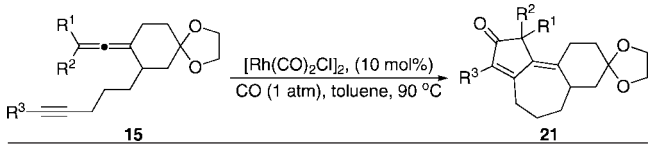
(18) Mukai and co-workers have found that electronically tuning the allene gives mixtures of cyclocarbonylation products with both the distal and proximal olefin reacting; the reaction with the distal olefin predominates in all cases. Inagaki, F.; Kawamura, T.; Mukai, C. *Tetrahedron* **2007**, *63*, 5154–5160.

(19) (a) Brummond, K. M.; Chen, D.; Painter, T. O.; Mao, S.; Seifried, D. D. *Synlett* **2008**, *5*, 759–764. (b) Trost, B. M.; Phan, L. T. *Tetrahedron Lett.* **1993**, *34*, 4735–4738.

TABLE 4. Rh(I)-Catalyzed Cyclocarbonylation Reaction of 15a−e Affording 21a,c−e

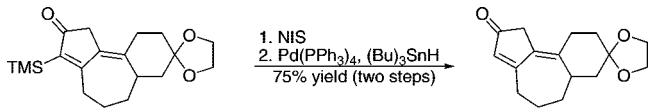


15 21

entry	reaction	time	yield (%)
a	**15a**: R^1 = Me, R^2 = H, R^3 = TMS	22 h	87
b	**15b**: R^1 = R^2 = Me, R^3 = TMS	72 h	[b]
c	**15c**: R^1 = R^2 = H, R^3 = TMS	2 h	91
d	**15d**: R^1 = R^2 = R^3 = H	40 min	27%[a]
e	**15e**: R^1 = R^2 = H, R^3 = Me	3 h	29

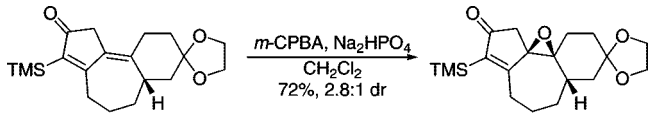
[a] Reaction run at 60 °C. [b] 40−60% starting material recovered.

SCHEME 7. Desilylation of 21c Affording 21d



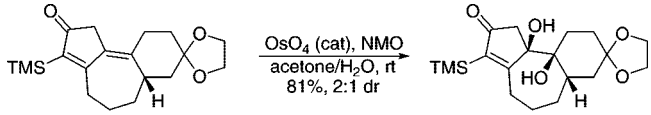
21c 21d

SCHEME 8. *m*-CPBA Epoxidation of 21c Affording Epoxide 22



21c 22

SCHEME 9. Upjohn Dihydroxylation of 21c Affording Diol 23



21c 23

Allene−ynes **15a** and **15c** readily cyclized under Rh(I)-cyclocarbonylation conditions to give **21a** and **21c** (Table 4). For this series of allene−yne substrates, the yield of the cyclocarbonylation reactions was dependent upon allene and alkyne substitution. For example, low yields of **21d** and **21e** were observed when the alkyne terminus possessed a methyl group or hydrogen atom. The reaction appears to tolerate some steric bulk at the terminus of the allene with **15a** and **15c** giving nearly identical yields of **21a** and **21c**, respectively. However, for **15b**, the only example investigated using a tetrasubstituted allene, no reaction was observed under the standard Rh(I) conditions (entry b), even when allowed to react several days. Ultimately, **21d** could be obtained by removal of the TMS group from **21c** in 75% yield over two steps (Scheme 7).[20]

While formation of a number of angular and linear [6−7−5] ring systems is useful, the ability to selectively introduce further functionality extends the synthetic value of this methodology. Having successfully obtained the [6−7−5] core ring systems, further functionalization was briefly examined. Substrate **21c** was subjected to Na_2HPO_4-buffered *m*-CPBA conditions to give epoxide **22** in 72% yield as a 2.8:1 mixture of diastereomers (Scheme 8.) The major diastereomer was tentatively assigned as **22** based upon a crystal structure of **23**.

In addition, dihydroxylation of **21c** using OsO_4/NMO conditions gave diol **23**, exclusively, in 81% yield as a 2:1 mixture of diastereomers (Scheme 9.) The diastereomers were readily separated by chromatography and the major diastereomer was assigned as **23** from the X-ray crystal structure.[21]

Conclusions

Four series of allene−ynes (types **A**−**C**) were prepared and subjected to a catalytic Rh(I)-catalyzed cyclocarbonylation reaction. Linearly and angularly fused tricyclic [6−7−5] ring systems were afforded for three of these series. Low yields of tricyclic [6−6−5] ring systems were obtained for one series of type A allene−ynes (**8a**−**c**) possessing a tertiary propargylic hydroxyl group, which is postulated to have a directing effect on the constitutional group selectivity of this reaction. Moreover, each series of allene−ynes behaved uniquely in the cyclocarbonylation reaction. For example, all allene−ynes **5a**−**j** (type **A**) underwent cycloaddition reactions with ease affording the cyclocarbonylation products **17a**−**k** in yields ranging from 56−85%. The substitution on the terminus of the alkyne or the allene did not substantially affect this reaction. Alternatively, allene−ynes **11** (type B) and **15** (type **C**) required that the alkyne terminus be substituted with a TMS group. Preliminary investigations into the possible functional group manipulations of the resulting dienones show that both epoxidation and dihydroxylation reactions occur with complete regioselectively affording epoxide **22** and diol **23**, respectively. Finally, the Rh(I)-catalyzed cyclocarbonylation reaction shows excellent functional group compatibility as evidenced by the tolerance of skipped enynes, ketals, enones, hydroxyl groups, and esters. Efforts are continuing in our laboratory to expand the scope of this reaction and to apply this methodology to the synthesis of more complex molecules.

Experimental Section

General Procedure for $[Rh(CO)_2Cl]_2$-Catalyzed Cyclocarbonylation Reaction. A flame-dried test tube equipped with a Teflon-coated stir bar was charged with allene−yne and toluene (10 mL/mmol). The tube was evacuated for 3−5 s (via a needle through the septa) and refilled with CO(g) (from a balloon) (3×). To the allene−yne solution was added $[Rh(CO)_2Cl]_2$ (0.05 equiv for **5**, **8**, and **11** and 0.10 equiv for **15**) in one portion and the test tube was evacuated and refilled with CO(g) (3×). The test tube was placed in a preheated 90 °C oil bath and stirred under CO(g). After the reaction was complete by TLC, the mixture was cooled to rt and filtered directly through a short pad of silica gel. Further purification was accomplished as necessary via flash chromatography.

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Supporting Information Available: Full experimental protocols and characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) Trost, B. M.; Yang, H.; Probst, G. D. *J. Am. Chem. Soc.* **2004**, *126*, 48–49.

(21) For crystallographic data, see the Supporting Information. This data (CCDC 629739) may also be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.