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Intramolecular Rhodium-Catalyzed [2+2+2] Cyclizations of Diynes with Enones

Amanda L. Jones and John K. Snyder*

Center for Chemical Methodology and Library Development, and the Department of Chemistry, Boston University, 590 Commonwealth Avenue, Boston, Massachusetts 02215

jsnyder@bu.edu

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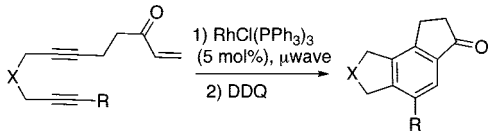
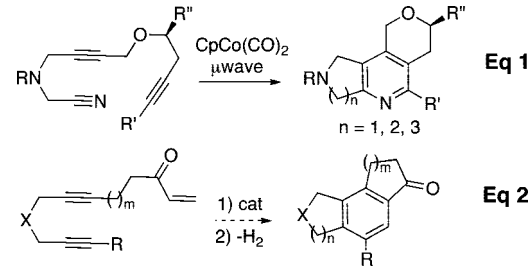


The Rh(I)-catalyzed inter- and intramolecular [2+2+2] cyclization of diynes with α,β-unsaturated enones proceeds with microwave promotion in good yields. This chemistry was applied to the synthesis of (−)-alcyopterosin I.

Transition metal-catalyzed [2+2+2] cyclizations of three nonconjugated π-systems exemplify synthetic organic processes that would have been considered extraordinary not all that long ago.[1] Along with other remarkable transformations mediated by transition metals, such as cross couplings and olefin metathesis, these ring-forming reactions have rapidly become valuable synthetic tools, able to accomplish chemistry in a single step that often would have required tedious and low-yielding multistep strategies. A great variety of such transition metal-catalyzed [2+2+2] cyclizations are now well-established using a variety of metals, and these have proven to be particularly effective at producing highly substituted aromatic and nonaromatic rings.[1,2]

We recently reported the application of a cobalt-catalyzed intramolecular [2+2+2] cyclization of diynes with tethered nitriles to produce tetrahydro-[1,6]-naphthyridines and related analogues (Scheme 1, eq 1),[3] which were later used as scaffolds for diversification, resulting in the discovery of several antituberculoid agents.[4] We have now begun to look at similar cyclizations using diynes tethered to enones as a strategy to prepare highly substituted tricyclic core structures with central benzene rings (Scheme 1, eq 2).

SCHEME 1



Examples of the participation of α,β-unsaturated carbonyl compounds in such chemistry, however, are quite limited, and there are no reports of intramolecular variants utilizing diyne−enone cyclizations to the best of our knowledge. Ikeda employed nickel catalysts to achieve cyclizations of cycloalkenones with alkynes in intermolecular reactions,[5] also achieving a modest level of enantioselectivity (up to 53% ee) with a dihydrooxazole ligand in some cyclizations (Scheme 2, eqs 1 and 2).[6] Montgomery had also observed α,β-enones participating in [2+2+2] cotrimerizations with alkynes using nickel catalysts, though two enone moieties had intriguingly cyclized with a single alkyne (Scheme 2, eq 3).[7] Shortly thereafter, Cheng reported the cyclization of methyl vinyl ketone with diynes using a similar nickel catalyst system with yields ranging from 29%

SCHEME 2

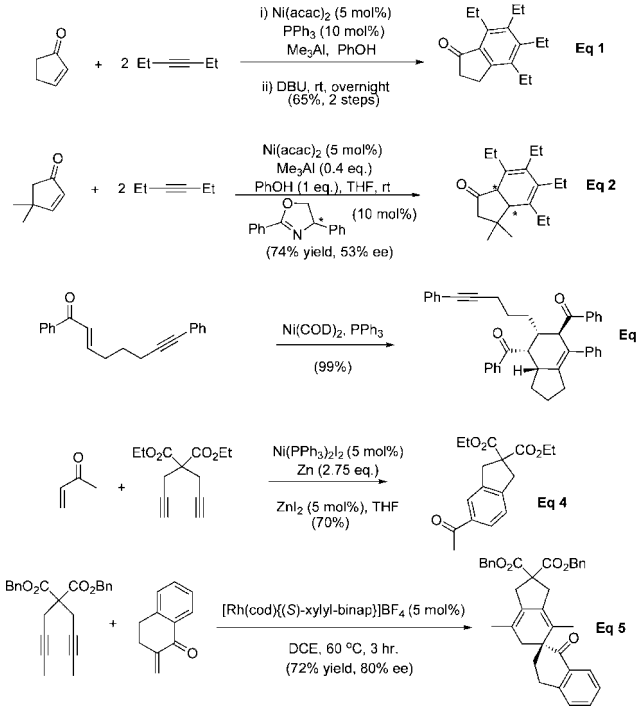


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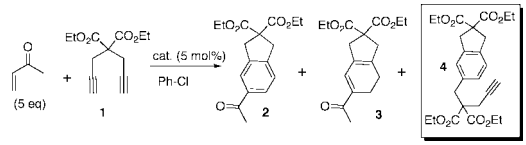
TABLE 1. Select Results of Catalyst Screening: Intermolecular [2+2+2] Cyclizations of Diyne 1 with MV.



item	catalyst	conditions[a]	2:3[b]
1	$RhCl(PPh_3)_3$	microwave, 150 °C, 15 min	3:53
2	$RhCl(PPh_3)_3$	120 °C, 5 h	0:18
3	$CpCo(CO)_2$[c]	microwave, 120 °C, 15 min	20:0
4	$Cp^*Ru(CH_3CN)_3PF_6$	microwave, 150 °C, 15 min	5:<5
5	$[Rh(CO)_2Cl]_2$	microwave, 150 °C, 15 min	19:5
6	$Rh(cod)_2BF_4$	microwave, 150 °C, 15 min	11:34
7	$[Rh(cod)_2Cl]_2$	microw, 150 °C, 15 min	6:0

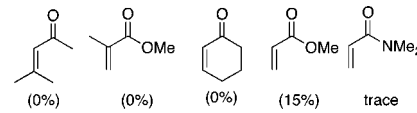
[a] All reactions were carried out in chlorobenzene, 0.04 M in diyne. [b] NMR yields for single trials. [c] 20 mol % catalyst used.

to 80%, though slow addition from a syringe pump was essential to minimize diyne dimerization (Scheme 2, eq 4).[8] More recently, Shibata has shown that asymmetric cyclizations of diynes with exocyclic enones can be achieved with a cationic Rh(I) catalyst using the (*S*)-xylylBINAP ligand (Scheme 2, eq 5).[9] Spirocenters were generated in up to 94% yield with ee values as high as 99%. Bisalkynyl diones have also been used by McDonald in intermolecular cyclizations with alkynes.[10]

We began catalyst screening with the Cheng reaction system:[8] diyne **1**, readily prepared from diethyl malonate,[11] with MVK (Table 1). We[3] and others[12,13] have already established the value of microwave irradiation in promoting transition metal-catalyzed [2+2+2] cyclizations using diynes, so this activation protocol was again applied.

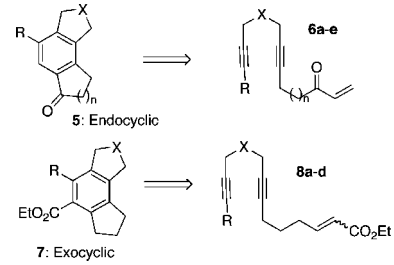
Of the catalysts screened, Co(I), Rh(I), and Ru(II) were all successful in producing [2+2+2] cyclization products. Both the aromatized product **2** and cyclohexadiene **3**, which presumably results from the double bond migration of the initially formed [2+2+2] adduct to conjugate the ketone with the diene system, were formed in varying amounts. Cyclohexadiene **3** slowly aromatized to **2** upon standing on the benchtop over several days. Diyne dimer **4** was also observed to a certain extent in all trials. Commercial Wilkinson's catalyst (item 1) and $Rh(cod)_2BF_4$ (item 6) gave the highest combined yields of the desired cyclization products **2** and **3** as determined by NMR analysis of the crude reaction mixtures. In addition, isolated yields of up to 63% of **2** were achieved in subsequent

CHART 1. Unreactive Reaction Partners with Diyne 1



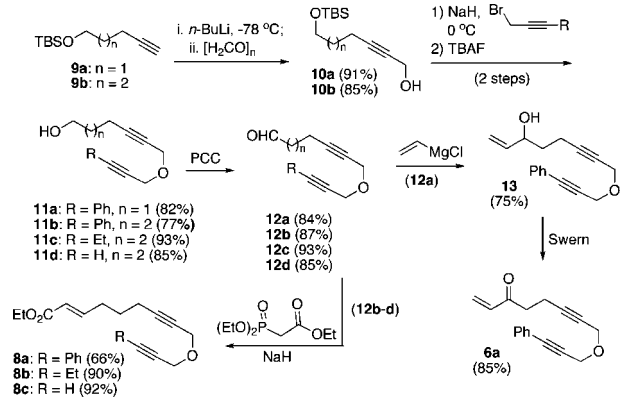
microwave-promoted experiments with use of Wilkinson's catalyst. Equally intriguing, the thermal reaction with Wilkinson's catalyst resulted in a lower combined yield of **2** and **3** (item 2). In this case, dimer **4** was observed as the major product. Thus, microwave irradiation seems better able to promote the [2+2+2] cyclization of diyne **1** and MVK rather than the unproductive dimerization pathway.[13] Other α,β-unsaturated carbonyl compounds, including amides, esters, and more substituted enones (Chart 1), were either poorly or completely unreactive under the screened conditions, yielding primarily diyne dimer **4**. The results from these preliminary studies confirmed the feasibility of using enones in [2+2+2] cyclizations, and led us to Wilkinson's catalyst for application in intramolecular variants where the entropic advantage might allow for cyclizations with α,β-unsaturated carbonyls in higher yields.

SCHEME 3



Intramolecular cyclizations were examined in two different subgroups. A cycloalkanone ring fused to the aromatic system is produced when the carbonyl is part of the tether linking the enone and diyne. When the carbonyl lies external to the tether, a carbonyl substituent on the aryl ring results (Scheme 3). The former system is referred to as the "endocyclic" cyclization while the latter is termed the "exocyclic" cyclization with reference to the location of the carbonyl group in the final product. Preliminary examination of the endocyclic process used vinyl ketones **6**, while the exocyclic precursors were α,β-unsaturated esters **8**, both varying the linker "X" between the two yne systems.

SCHEME 4



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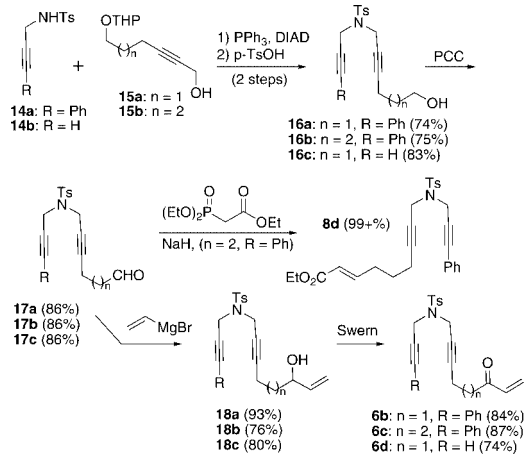
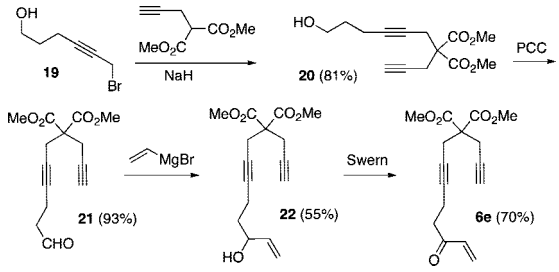
SCHEME 5



The preparations of the cyclization precursors were very straightforward. *O*-Linked substrates **6a** and **8a**−**c** were prepared by additions of the acetylides from the *O*-protected terminal alkynyl alcohols **9a**,**b** to formaldehyde, followed by propargylations and deprotections to give primary alcohols **11a**−**d** (Scheme 4). Oxidations (PCC) provided aldehydes **12a**−**d**. Vinyl Grignard addition to **12a**, then Swern oxidation of **13** gave *O*-linked endocyclic precursor **6a**. Horner−Wadsworth−Emmons olefinations of the aldehydes **12b**−**d** yielded exocyclic precursors **8a**−**c**.

N-Linked precursors **6b**−**d** and **8d** were prepared similarly beginning with the appropriate *N*-tosylpropargylamines **14a**,**b** (Scheme 5). Mitsunobu attachment of the terminal alkynyl alcohols **15a**,**b**, then deprotection, gave dipropargyl tosylamides **16a**−**c**. Conversion to the cyclization prescursors **6b**−**d** and **8d** then followed the same strategy as applied to the *O*-linked cyclization precursors. The malonate linked diyne **6e** was analogously prepared beginning with propargyl bromide **19** and commercially available dimethylpropargyl malonate (Scheme 6).

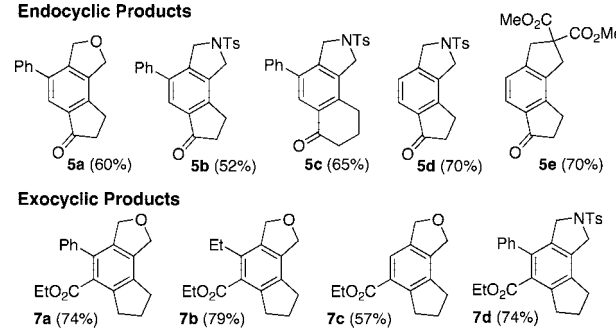
SCHEME 6



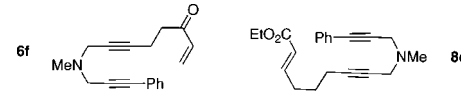
Intramolecular cyclizations employed the conditions optimized with the intermolecular chemistry ($RhCl(PPh_3)_3$, 5 mol %, microwave, 150 °C, 10 min in chlorobenzene, 0.02−0.04 M in cyclization precursor). Catalysts were not further screened for the intramolecular systems. Subsequent to the cyclizations, partial aromatization was observed during workup, so complete aromatization was accomplished with DDQ. The results for the cyclization/aromatization sequences are shown in Chart 2 with the reported isolated yields resulting after both the cyclization and aromatization steps.

From the results in Chart 2 it can be seen that both endocyclic and exocyclic cyclizations were successful. Both internal (**5a**−**c** and **7a**,**b**,**d**) and terminal (**5d**,**e** and **7c**) alkynes worked well in

CHART 2. Cyclization/Aromatization Products of Diyne−Enones (Yields over 2 steps, Scheme 3)

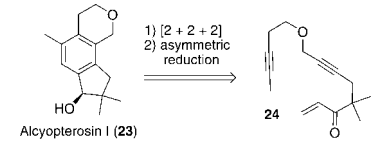


the cyclizations, and analogous 5- and 6-membered rings resulting from varying the tether length could be produced in comparable yields (**5b** and **5c**). Preparation of larger rings has not as yet been examined. Amino groups in the tether which did not have their Lewis basicity reduced with an electron withdrawing protecting group were not tolerated (**6f** and **8e**). Presumably coordination of the nucleophilic nitrogen to the rhodium catalyst prevented the cyclization. Amines protected as sulfonamides, however, worked well (**5b**−**d** and **7d**).



These studies demonstrated that enones do participate with diynes in [2+2+2] cyclizations with rhodium catalysts, and that the intramolecular cyclizations can be relatively easy to accomplish. To demonstrate the applicability of these studies, a short synthesis of the marine natural product alcyopterosin I (**23**), isolated from the Antarctic soft coral *Alcyonium paessleri*,[14] was undertaken. Members of this family of rare marine illudane sesquiterpenes are reported to have activity against human larynx and colon cancer cell lines, though no activity has been reported for **23**. While the synthesis of **23** has not been reported, other members of the alcyopterosin family and structurally similar analogues have been synthetically prepared.[15,16] Furthermore, several of these syntheses have employed a [2+2+2] cyclization as the key step.[16] Retrosynthetically, **23** was envisioned as arising from the cyclization of diyne−enone **24**, followed by reduction of the aryl ketone (Scheme 7).

SCHEME 7



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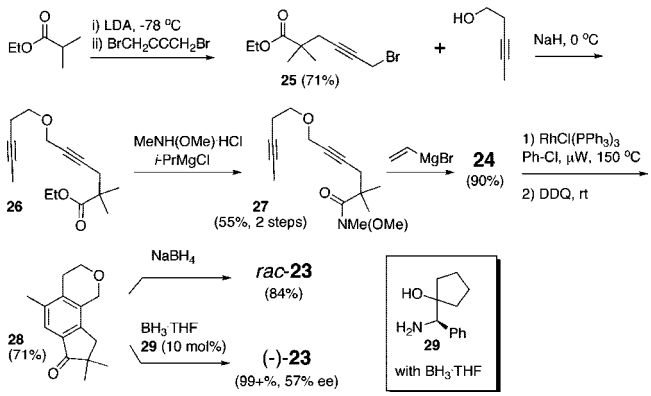
SCHEME 8



Cyclization precursor **24** was easily prepared by sequential bromide displacements on 1,4-dibromo-2-butyne,[17] first with the enolate of ethyl isobutyrate,[18] then with commercially available 3-pentyn-1-ol (Scheme 8). Subsequent formation of Weinreb amide **27**, then vinyl ketone formation by the addition of vinyl Grignard reagent gave **24** in only four steps and in 29% overall unoptimized yield. Cyclization with DDQ workup then produced aryl ketone **28**. Borohydride reduction of **28** gave racemic **23** in 84% yield, which had spectroscopic data identical with those of the naturally occurring compound.

Several procedures have been reported for the asymmetric reduction of aryl ketones, including Noyori's Ru(II)/diamine/KOH system,[19] the Rh(I)-PennPhos catalyst,[20] as well as Martens' aminoalcohol **29** with borane,[21] and Corey's oxazaborolidine/catechol borane.[22] We have had considerable success with the latter two in the past in aryl ketone reductions.[23] Our attempts with **29** as catalyst ligand in the reduction of **28** have produced *ent*-(−)-**23**, the enantiomer of naturally occurring alcyopterosin I, in quantitative yield, but in only 57% ee. Other asymmetric reduction attempts with a Ru(II) catalyst specifically developed by Noyori for similar *tert*-alkyl ketones[24] as well as a chiral, tartaric acid-derived boronic ester[25] resulted only in recovery of ketone **28**.

In conclusion, both inter- and intramolecular [2+2+2] cyclizations of diynes with α,β-unsaturated carbonyl compounds have been achieved under microwave irradiation with Wilkinson's catalyst. Diversity in the cyclized products was attained by variation of the diyne linking group, tether length, and the identity and location of the carbonyl function ("endo-" or "exocyclic"). This methodology was applied to a synthesis of *ent*-alcyopterosin I in 25% overall yield and 57% ee over 7 steps. Further work is focused on asymmetric cyclization catalytic systems to produce the cyclohexadienes, as well as trapping these products for use as library scaffolds.

Experimental Section

Representative Procedure for Microwave-Promoted [2+2+2] Cyclizations/DDQ Aromatization: Synthesis of 5,8,8-Trimethyl-3,4,8,9-tetrahydrocyclopenta[*h*]isochromen-7(1*H*)-one (28).[26] To a solution of diynyl enone **24** (15 mg, 0.06 mmol, 1.0 equiv) in chlorobenzene (1.5 mL, 0.04 M) was added commercial $RhCl(PPh)_3$ (3 mg, 3.2 μmol, 0.05 equiv). The tube was sealed and the reaction mixture was subjected to microwave irradiation (300 W, 150 °C maximum temperature as measured by a volume-independent microwave sensor located in the microwave cavity)[27] for 15 min. After irradiation, the crude reaction mixture was filtered through a silica gel plug to remove chlorobenzene and catalyst, washing with hexanes:EtOAc (1:1), and the solvent was removed in vacuo. To the crude residue was added CH_2Cl_2 (1.5 mL, 0.04 M), followed by DDQ (17.6 mg, 0.08 mmol, 1.2 equiv). The reaction mixture was stirred at rt for 1 h followed by quenching with H_2O (2 mL) and saturated aqueous $NaHCO_3$ (1 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 3 mL), and the combined organic layers were dried over Na_2SO_4 and filtered, and the solvent was removed in vacuo. The crude residue was purified via flash chromatography on silica gel to give **28** (hexanes: EtOAc, 90:10, R_f 0.26, 10.5 mg, 71% yield) as a white solid: mp 91−92 °C: IR (neat) 1707 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.20 (s, 6H), 2.27 (s, 3H), 2.71 (s, 2H), 2.76 (t, J = 5.6 Hz, 2H), 4.02 (t, J = 5.6 Hz, 2H), 4.73 (s, 2H), 7.45 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.0, 25.4 (2C), 27.0, 40.1, 45.5, 64.8, 65.7, 122.8, 132.1, 132.8, 136.4, 139.4, 145.8, 210.9; HRMS (ESI) m/z 231.1381 ([M + H],$^+$100%), calcd for $C_{15}H_{18}O_2$ 231.1385.

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Supporting Information Available: General experimental information, full experimental procedures and characterization data of all new compounds, and copies of ^1H and ^{13}C spectra of all new products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(26) See the Supporting Information for specific experimental details for all other cyclized products.
(27) All microwave reactions were run in sealed 10 mL thick-walled microwave pressure tubes.