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Rhodium-Catalyzed Intramolecular [4 + 2] Cycloadditions of Alkynyl Halides

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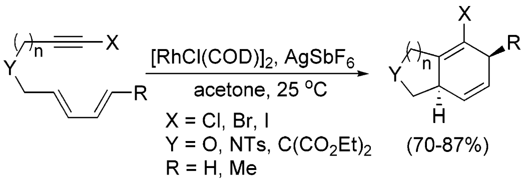
ABSTRACT

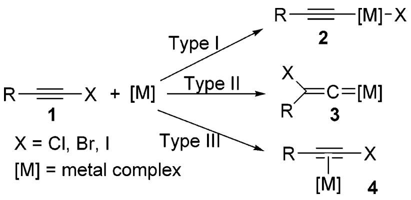


Cationic rhodium(I)-catalyzed intramolecular [4 + 2] cycloadditions of diene-tethered alkynyl halides were found to occur in good yields (70–87%). The halide moiety is compatible with the cycloaddition reactions, and no oxidative insertion to the alkynyl halide was observed. The halogen-containing cycloadducts could be transformed into a variety of products that are difficult or impossible to obtain via direct cycloaddition.

Alkynyl halides are useful building blocks in organic synthesis. Traditionally, alkynyl halides were accessible through the deprotonation of corresponding terminal alkynes with a strong base, followed by trapping with a halogenating agent.[1] However, several mild and convenient methods have been reported recently and thus have increased the attractiveness of this class of compounds in organic synthesis.[2] The alkynyl halide moiety can be conceived as a dual functionalized molecule in transition metal-catalyzed reactions (Scheme 1). In the presence of a low-valent transition metal, alkynyl halide **1** can undergo oxidative insertion into the metal to form the σ-acetylenic metal complex **2** (Type I). On the other hand, a halovinylidene−metal complex **3** can also be obtained from alkynyl halide **1** via a 1,2-migration of the halogen (Type II). Finally, the π-system of the acetylene can coordinate to the metal center in an η^2 fashion to form the acetylene π-complex **4** (Type III).

The most extensive studies and applications of alkynyl halides in transition metal-catalyzed reactions are metal-catalyzed cross-coupling reactions to form carbon−carbon bonds via the oxidative insertion of the metal to the carbon−halide bond (Type I). Useful building blocks such as enynes,[3] diynes,[4] triynes,[5] and ynamides[6] have been synthesized using this method. Formation of the halovinylidene−metal complex **3** (Type II) is not common but has been observed when an alkynyl iodide was treated with a tungsten complex, W(CO)$_5$(THF), to produce a iodovinylidene−tungsten complex that underwent a 6π-electrocyclization.[7] Formation of acetylene π-complex **4** (Type III) of alkynyl halides are also rare, probably due to the potential problems associated with the oxidative insertion of the metal into the carbon−halide bond (Type I). Therefore, very few successful

Scheme 1. Potential Reactivity Pathways of Alkynyl Halides in Transition Metal-Catalyzed Reactions



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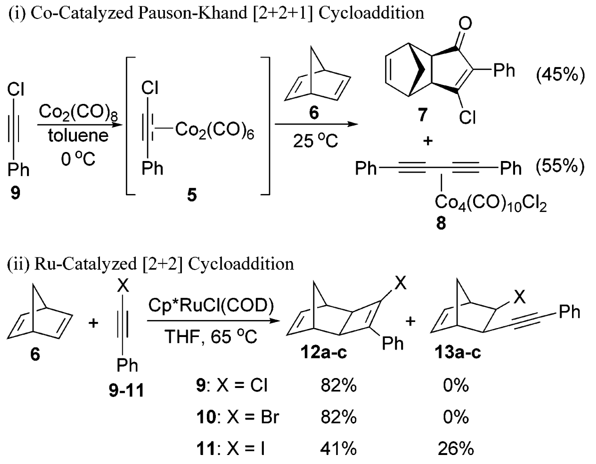
examples of any transition metal-catalyzed cycloadditions with alkynyl halides, which rely on the formation of the acetylene π-complex **4**, have been reported in the literature. In fact, to the best of our knowledge, there are only two examples in the literature of transition metal-catalyzed cycloadditions of alkynyl halides, a cobalt-catalyzed Pauson−Khand [2 + 2 + 1] cycloaddition and a ruthenium-catalyzed [2 + 2] cycloaddition (Scheme 2).[8,9] Balsells and co-workers found that the cobalt-catalyzed Pauson−Khand reaction between alkynyl chloride **9** and norbornadiene **6** gave the desired [2 + 2 + 1] cycloadduct **7** in only 45% yield. The major product obtained was complex **8**, which formed through a homocoupling of the alkynyl chloride **5**.[8]

Scheme 2. Transition Metal-Catalyzed Cycloaddition Reactions of Alkynyl Halides



We have recently reported the ruthenium-catalyzed [2 + 2] cycloadditions of alkynyl halides **9**−**11** with norbornadiene **6** and found that whereas the alkynyl chloride **9** and alkynyl bromide **10** provided the cyclobutene cycloadducts as the only products in good yields, alkynyl iodide **11** gave not only the cyclobutene cycloadduct **12c** (via an acetylene π-complex **4**, Scheme 1, Type III) but also an addition product **13c** (possibly via a σ-acetylenic metal complex **2**, Scheme 1, Type I).

Transition metal-catalyzed [4 + 2] cycloaddition is an efficient and important method for the construction of six-membered rings, especially between electronically similar dienes and dienophiles, which usually require extreme conditions for the thermal cycloaddition to occur.[10a] A number of excellent metal catalysts have been discovered and transition metal-catalyzed [4 + 2] cycloadditions are emerging as synthetically useful processes.[10−15] However, to the best of our knowledge, the use of alkynyl halides as the dienophile in both thermal and transition metal-catalyzed [4 + 2] cycloadditions is unexplored. In this paper, we report the first examples of thermal and rhodium-catalyzed intramolecular [4 + 2] cycloadditions of alkynyl halides. To initiate these studies, diene-tethered alkynyl bromide **14a** and **15** were prepared from the corresponding terminal alkynes using $AgNO_3$ and NBS in acetone,[16] and the results of the thermal Diels−Alder cycloadditions are shown in Table 1.

No reaction was observed when diene-tethered alkynyl bromide **14a** was stirred at 25 °C for 24 h. However, at 50 °C, Diels−Alder started to occur slowly (entries 2−4), and

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[3] For representative examples, see: (a) Jeffery, T. *Synthesis* **1987**, 70. (b) Bouyssi, D.; Gore, J.; Balme, G. *Tetrahedron Lett.* **1992**, *33*, 2811. (c) Beaudet, I.; Parrain, J.; Quintard, J. *Tetrahedron Lett.* **1995**, *33*, 3647. (d) Tanaka, H.; Yamada, H.; Matsuda, A.; Takahashi, T. *Synlett* **1997**, 381. (e) Kang, S.; Kim, W.; Jiao, X. *Synthesis* **1998**, 1252. (f) Liu, Y.; Shen, B.; Kotora, M.; Takahashi, T. *Angew. Chem., Int. Ed.* **1999**, *38*, 949. (g) Yoshida, H.; Shirakawa, E.; Kurahashi, T.; Nakao, Y.; Hiyama, T. *Organometallics* **2000**, *19*, 5671. (h) Timbart, L.; Cintrat, J. *Chem. Eur. J.* **2002**, *8*, 1637. (i) Liu, Y.; Zhong, Z.; Nakajima, K.; Takahashi, T. *J. Org. Chem.* **2002**, *67*, 7451.

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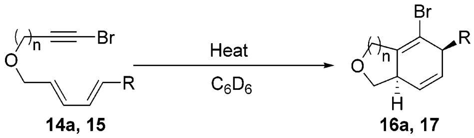
[16] See Supporting Information for the details of preparation of all of the diene-tethered alkynyl halides.

Table 1. Thermal Diels−Alder Reactions of Alkynyl Halides



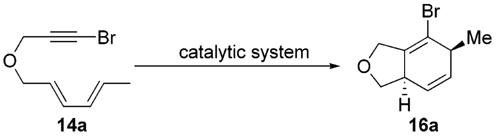
entry	alkynyl bromide	n	R	temp (°C)	time (h)	cycloadduct	conversion (%)[a]
1	**14a**	1	Me	25	24	**16a**	0
2	**14a**	1	Me	50	0.5	**16a**	0
3	**14a**	1	Me	50	5	**16a**	22
4	**14a**	1	Me	50	13	**16a**	36
5	**14a**	1	Me	75	17	**16a**	98[b]
6	**15**	2	H	80	24	**17**	0

[a] Followed by 400 MHz ^{1}H NMR. [b] 85% of cycloadduct **16a** was isolated after column chromatography.

when **14a** was stirred at 75 °C for 17 h, **14a** was almost totally consumed and cycloadduct **16a** was isolated in 85%. This is apparently the first example of a thermal Diels−Alder reaction of an alkynyl halide. Unfortunately, for the substrate with a longer tether (entry 6), no thermal [4 + 2] cycloaddition was observed even after prolonged heating. Attempts to catalyzed the Diels−Alder reactions using Lewis acids (e.g., $AlCl_3$, $FeCl_3$, $BF_3.OEt_2$, $ZrCl_4$, etc.) were unsuccessful and either no reaction was observed or the starting material decomposed under the reaction conditions.

In search of the most suitable set of conditions for the intramolecular [4 + 2] cycloaddition of diene-tethered alkynyl halides, several catalytic systems that are known to catalyze intramolecular Diels−Alder reactions were tested. Although the use of Ni,[11] Co,[13] and neutral Rh(I)[12] catalysts were all unsuccessful (Table 2, entries 1−3), in the presence of the cationic Rh(I) catalyst $[(naphthalene)Rh(COD)]BF_4$, developed by Chung and co-workers,[12g] the [4 + 2] cycloaddition of **14a** occurred smoothly at room temperature, giving the cycloadduct **16a** in 85% isolated yield (entry 4). Since this catalyst is not commercially available, we attempted to generate the active cationic Rh(I) species in situ using the commercially available catalyst $[RhCl(COD)]_2$ and a silver(I) salt. To our delight, this catalytic system was as effective as the Chung system (entry 5).[17]

Table 2. Searching for Catalytic Systems

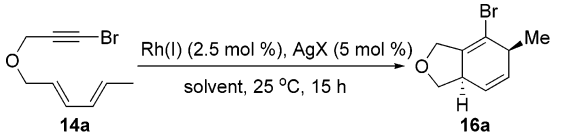


entry	catalytic system	yield (%)
1	$Ni(COD)_2$, $P(O\text{-}o\text{BiPh})_3$, THF, 45 °C	0[a]
2	$CoBr_2(dppe)$, Zn, ZnI_2, CH_2Cl_2, 25 °C	0[b]
3	$[RhCl(COD)]_2$, $P(O\text{-}o\text{BiPh})_3$, THF, 45 °C	0[a]
4	$[(naphthalene)Rh(COD)]BF_4$, CH_2Cl_2, 25 °C	85
5	$[RhCl(COD)]_2$, $AgBF_4$, CH_2Cl_2, 25 °C	85

[a] Only starting material was recovered. [b] Decomposition of starting material was observed.

Optimization of the reaction conditions were carried out using different Rh(I) catalysts (Table 3, entries 1−3), different solvents (entries 3−9), and different Ag(I) salts (entries 9−11). The most efficient reaction conditions for the intramolecular [4 + 2] cycloaddition of diene-tethered alkynyl bromide **14a** were found to be $[RhCl(COD)]_2$ (2.5 mol %) and $AgSbF_6$ (5 mol %)[18] in acetone (0.2 M) at 25 °C.

Table 3. Optimization of Cationic Rh(I)-Catalyzed [4 + 2] Cycloaddition



entry	Rh(I)	AgX	solvent	yield (%)
1	$RhCl(PPh)_3$	$AgBF_4$	CH_2Cl_2	0
2	$[RhCl(CO)_2]_2$	$AgBF_4$	CH_2Cl_2	20
3	$[RhCl(COD)]_2$	$AgBF_4$	CH_2Cl_2	85
4	$[RhCl(COD)]_2$	$AgBF_4$	dichloroethane	80
5	$[RhCl(COD)]_2$	$AgBF_4$	toluene	62
6	$[RhCl(COD)]_2$	$AgBF_4$	pentane	0
7	$[RhCl(COD)]_2$	$AgBF_4$	DMF	0
8	$[RhCl(COD)]_2$	$AgBF_4$	THF	83
9	$[RhCl(COD)]_2$	$AgBF_4$	acetone	87
10	$[RhCl(COD)]_2$	AgOTf	acetone	71
11	$[RhCl(COD)]_2$	$AgSbF_6$	acetone	87

To illustrate the general applicability of this catalytic system in the intramolecular [4 + 2] cycloaddition with diene-tethered alkynyl halides, a few different alkynyl halides were chosen[16] for further investigation, and the results are shown in Table 4. In general, all cationic Rh(I)-catalyzed [4 + 2] cycloadditions occurred smoothly at 25 °C in good yields (70−87%), and in all cases single stereoisomers were obtained (the R group and the H at the ring junction are *anti* to each other, as determined by GOESY NMR experiments).[19,20] Regardless of the halide (Cl, Br, or I), the cycloadditions occurred rapidly and without the formation

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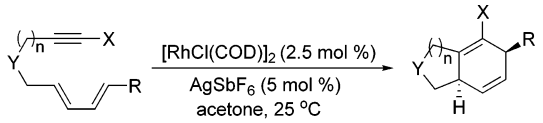
(17) We also found that this commercially available, simple catalytic system $[RhCl(COD)]_2/AgX$ (X = BF_4 or SbF_6) is as active as the Chung $[(naphthalene)Rh(COD)]BF_4$ system to catalyze intermolecular [4 + 2] cycloaddition between 2,3-dimethylbuta-1,3-diene with phenyl acetylene (70%) or ethyl propiolate (99%).

(18) Both $AgSbF_6$ and $AgBF_4$ gave the same results, but $AgSbF_6$ was chosen due to lower cost.

(19) GOESY is gradient enhanced nuclear Overhauser enhancement spectroscopy, see: (a) Stonehouse, J.; Adell, P.; Keeler, J.; Shaka, A. J. *J. Am. Chem. Soc.* **1994**, *116*, 6037. (b) Stott, K.; Stonehouse, J.; Keeler, J.; Hwang, T.-L.; Shaka, A. J. *J. Am. Chem. Soc.* **1995**, *117*, 4199. (c) Dixon, A. M.; Widmalm, G.; Bull, T. E. *J. Magn. Reson.* **2000**, *147*, 266.

(20) The stereochemistry of the cycloadducts are the same as those previously reported in the Rh-catalyzed [4 + 2] cycloadditions for nonhalogenated alkynes (e.g., X = TMS and Me instead of a halide).

Table 4. Cationic Rh(I)-Catalyzed [4 + 2] Cycloadditions of Various Diene-Tethered Alkynyl Halides



entry	alkynyl halide	X	Y	n	R	time (h)	cyclo-adduct	yield (%)[a]
1	**14b**	Cl	O	1	Me	0.5	**16b**	82
2	**14a**	Br	O	1	Me	0.5	**16a**	87
3	**14c**	I	O	1	Me	0.5	**16c**	75
4	**15**	Br	O	2	H	2.5	**17**	86
5	**18**	Br	NTs	1	Me	0.5	**22**	77
6	**19**	Br	NTs	2	Me	3	**23**	70
7	**20**	Br	C(COOEt)$_2$	1	H	0.5	**24**	78
8	**21**	Br	C(COOEt)$_2$	2	H	3	**25**	85

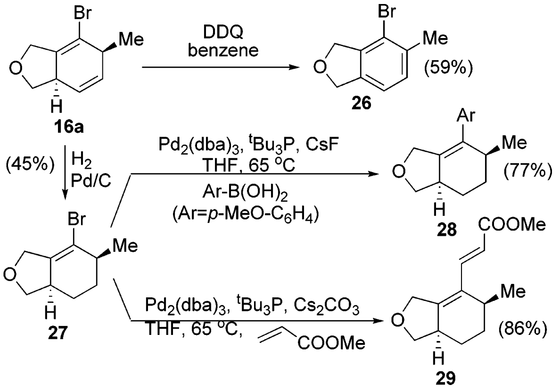
[a] Isolated yields after column chromatography.

of noticeable side products (by TLC and ^{1}H NMR of crude reaction mixtures), although the yield was slightly diminished with alkynyl iodide **14c** (Table 4, entries 1−3). For a longer oxygen-tethered substrate **15**, a longer reaction time was required (compare entries 2 and 4). Similar trends were observed with the nitrogen-tethered substrates (entries 5 and 6) and with the all-carbon tethered substrates (entries 7 and 8).

To illustrate the synthetic usefulness of the resulting halogenated cycloadducts, cycloadduct **16a** was converted to various products that are difficult or impossible to obtain via direct cycloaddition (Scheme 3). Aromatization of bromide **16a** was achieved using DDQ in benzene to provide the halogenated aromatic compound **26** in 59%. Partial hydrogenation of bromide **16a** with H$_2$/Pd/C afforded compound **27** in 45%. These halogenated derivatives could be further functionalzed by various metal-catalyzed coupling reactions. For example, palladium-catalyzed Suzuki coupling of vinyl bromide **27** gave compound **28** in 77%, and a palladium-catalyzed Heck reaction of vinyl bromide **27** provided compound **29** in 86%.

In summary, we have demonstrated the first examples of intramolecular thermal and cationic Rh(I)-catalyzed [4 + 2] cycloadditions of diene-tethered alkynyl halides. We found the alkynyl halides moieties to be compatible with the Rh(I)-catalyzed [4 + 2] cycloadditions and the cycloadditions occurred smoothly at room temperature, giving the halogenated cycloadducts as single stereoisomers in good yields. The halide-containing cycloadducts can be converted to products that are difficult to obtain via direct cycloaddition. Further investigations on the intermolecular version of the cycloaddition, and the use of the halogenated cycloadducts for the synthesis of more complex polycyclic natural products are currently in progress in our laboratory.

Scheme 3. Synthetic Applications of Halogenated Cycloadduct **16a**



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Supporting Information Available: Experimental procedures and compound characterization data of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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