

Ruthenium-Catalyzed [2 + 2] Cycloadditions between Bicyclic Alkenes and Alkynyl Halides

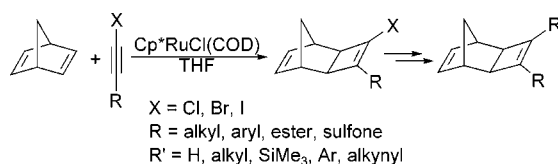
Karine Villeneuve, Nicole Riddell, Robert W. Jordan, Gavin C. Tsui, and William Tam*

Guelph–Waterloo Centre for Graduate Work in Chemistry and Biochemistry,
Department of Chemistry, University of Guelph, Guelph, Ontario, Canada N1G 2W1

wtam@uoguelph.ca

Received September 16, 2004

ABSTRACT



Ru-catalyzed [2 + 2] cycloadditions between norbornadiene and alkynyl halides were found to occur in moderate to good yields (32–89%). The presence of the halide moiety greatly enhances the reactivity of the alkyne component in the cycloaddition and can be transformed into a variety of products that are difficult or impossible to obtain via direct cycloaddition.

Transition metal-catalyzed cycloadditions have demonstrated their usefulness as efficient methods in the formation of rings and complex molecules.¹ The use of transition metal catalysts provides new opportunities for highly selective cycloaddition reactions since complexation of the metal to an unactivated alkene, alkyne, or diene significantly modifies the reactivity of this moiety, opening the way for enhanced reactivity and novel reactions. Recent developments in transition metal-catalyzed [2 + 2 + 1],² [4 + 2],³ [5 + 2],⁴ [4 + 4],⁵ and [6 + 2]⁶ cycloaddition reactions have provided efficient methods for the construction of five- to eight-membered rings. We and others have studied various aspects of transition metal-catalyzed [2 + 2] cycloadditions between an alkene and an alkyne for the synthesis of cyclobutene rings, in-

cluding development of novel catalysts, study of the intramolecular variant of the reaction, and investigation on the chemo- and regioselectivity of unsymmetrical substrates.^{7–10} More recently, we have demonstrated the first examples of

(1) For reviews on transition metal-catalyzed cycloadditions, see: (a) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49. (b) Hegedus, L. S. *Coord. Chem. Rev.* **1997**, *161*, 129. (c) Wender, P. A.; Love, J. A. In *Advances in Cycloaddition*; JAI Press: Greenwich, 1999; Vol. 5, pp 1–45.

(2) For recent reviews on transition metal-catalyzed [2 + 2 + 1] cycloadditions, see: (a) Pericas, M. A.; Balsells, J.; Castro, J.; Marchueta, I.; Moyano, A.; Riera, A.; Vazquez, J.; Verdager, X. *Pure Appl. Chem.* **2002**, *74*, 167. (b) Sugihara, T.; Yamaguchi, M.; Nishizawa, M. *Chem. Eur. J.* **2001**, *7*, 1589. (c) Brummond, K. M.; Kent, J. L. *Tetrahedron* **2000**, *56*, 3263. (d) Buchwald, S. L.; Hicks, F. A. In *Comprehensive Asymmetric Catalysis I–III*, Jabosen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999; Vol. 2, pp 491–510. (e) Keun Chung, Y. *Coor. Chem. Rev.* **1999**, *188*, 297.

(3) (a) Wender, P. A.; Jenkins, T. E. *J. Am. Chem. Soc.* **1989**, *111*, 6432. (b) Jolly, R. S.; Luedtke, G.; Sheehan, D.; Livinghouse, T. *J. Am. Chem. Soc.* **1990**, *112*, 4965. (c) Wender, P. A.; Jenkins, T. E.; Suzuki, S. *J. Am. Chem. Soc.* **1995**, *117*, 1843. (d) O'Mahoney, D. J. R.; Belanger, D. B.; Livinghouse, T. *Synlett* **1998**, 443. (e) Murakami, M.; Ubukata, M.; Itami, K.; Ito, Y. *Angew. Chem., Int. Ed.* **1998**, *37*, 2248. (f) Paik, S.-J.; Son, S. U.; Chung, Y. K. *Org. Lett.* **1999**, *1*, 2045. (g) Hilt, G.; Smolko, K. I. *Angew. Chem., Int. Ed.* **2003**, *42*, 2795. (h) Witulski, B.; Lumtscher, J.; Bergsträber, U. *Synlett* **2003**, 708. (i) Hilt, G.; Lüers, S.; Harms, K. *J. Org. Chem.* **2004**, *69*, 624.

(4) (a) Wender, P. A.; Takahashi, H.; Witulski, B. *J. Am. Chem. Soc.* **1995**, *117*, 4720. (b) Wender, P. A.; Rieck, H.; Fuji, M. *J. Am. Chem. Soc.* **1998**, *120*, 10976. (c) Trost, B. M.; Shen, H. *Angew. Chem., Int. Ed.* **2001**, *40*, 2313. (d) Wender, P. A.; Williams, T. *J. Angew. Chem., Int. Ed.* **2002**, *41*, 4550.

(5) (a) Wender, P. A.; Ihle, N. C. *J. Am. Chem. Soc.* **1986**, *108*, 4678. (b) Wender, P. A.; Nuss, J. M.; Smith, D. B.; Suarez-Sobrinio, A.; Vagberg, J.; Decosta, D.; Bordner, J. *J. Org. Chem.* **1997**, *62*, 4908.

(6) Wender, P. A.; Correa, A. G.; Sato, Y.; Sun, R. *J. Am. Chem. Soc.* **2000**, *122*, 7815.

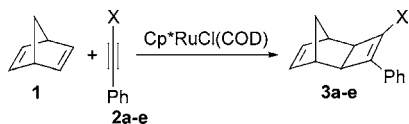
(7) Trost, B. M.; Yanai, M.; Hoogsteen, K. *J. Am. Chem. Soc.* **1993**, *115*, 5294.

(8) Mitsudo, T.; Naruse, H.; Kondo, T.; Ozaki, Y.; Watanabe, Y. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 580.

(9) (a) Huang, D.-J.; Rayabarapu, D. K.; Li, L.-P.; Sambaiah, T.; Cheng, C.-H. *Chem. Eur. J.* **2000**, *6*, 3706. (b) Chao, K. C.; Rayabarapu, D. K.; Wang, C.-C.; Cheng, C.-H. *J. Org. Chem.* **2001**, *66*, 8804.

asymmetric induction studies in ruthenium-catalyzed [2 + 2] cycloadditions between symmetrical bicyclic alkenes and alkynes bearing a chiral auxiliary, and excellent levels of asymmetric induction (up to 98.8% ee, after removal of the recoverable chiral auxiliary) in the cycloadditions were achieved.^{10c} Generally, excellent yields are obtained in the Ru-catalyzed [2 + 2] cycloadditions between bicyclic alkenes and electron-deficient alkynes (Table 1). However, limita-

Table 1. Ruthenium-Catalyzed [2 + 2] Cycloaddition between Norbornadiene and Alkynes Bearing Different Functional Groups



entry	alkyne	X	temp (°C)	time (h)	yield (%) ^a
1	2b	COOEt	60	48	90 ^b
2	2c	Me	95	90	22 ^c
3	2d	SiMe ₃	95	90	0 ^c
4	2e	Ph	100	120	23 ^d
5	2a	H	80	16	44 ^{d,e}

^a Yield of isolated cycloadducts **3**. ^b See ref 10b. ^c See Supporting Information. ^d See ref 8. ^e Homotrimerization of the terminal alkyne **2e** was also observed; see ref 8.

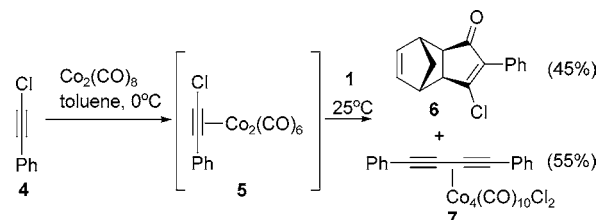
tions in the type of suitable alkynes are inevitable and low yields were obtained when non-electron-deficient or bulky alkynes were used (Table 1). This property of ruthenium-catalyzed [2 + 2] cycloadditions has, to a certain extent, limited the possible cycloadducts affordable through this methodology.

Alkynyl halides are an interesting class of alkynes to explore since their electron-withdrawing ability could potentially enhance the rate of the cycloaddition reaction. The halide moiety could also be used for further functionalization, thereby providing a complementary method for the preparation of those cycloadducts that are difficult or impossible to obtain via direct cycloaddition. To the best of our knowledge, all of the alkynes employed thus far in the ruthenium-catalyzed [2 + 2] cycloadditions only contain carbon substituents such as alkyl, aryl, ester, and ketone functionalities, and no studies on the use of alkynes attached directly to heteroatoms have been reported in the literature. In this paper, we report the first examples of ruthenium-catalyzed [2 + 2] cycloadditions of bicyclic alkenes with alkynyl halides. This investigation is important because it provides valuable information on the compatibility and reactivity of alkynyl halides in ruthenium-catalyzed [2 + 2] cycloadditions and also provides a method to obtain cycloadducts that are impossible to obtain via direct cycloaddition. Very few

(10) (a) Jordan, R. W.; Tam, W. *Org. Lett.* **2000**, *2*, 3031. (b) Jordan, R. W.; Tam, W. *Org. Lett.* **2001**, *3*, 2367. (c) Jordan, R. W.; Tam, W. *Tetrahedron Lett.* **2002**, *43*, 6051. (d) Villeneuve, K.; Jordan, R. W.; Tam, W. *Synlett* **2003**, 2123. (e) Villeneuve, K.; Tam, W. *Angew. Chem., Int. Ed.* **2004**, *43*, 610.

successful examples of any transition metal-catalyzed cycloadditions with alkynyl halides have been reported in the literature. This is probably due to the potential problems associated with a C–X oxidative addition at various stages of reaction.¹¹ For example, Balsells and co-workers investigated the cobalt-catalyzed Pauson–Khand reaction between 1-chloro-2-phenylethyne **4** and norbornadiene **1** (Scheme 1)

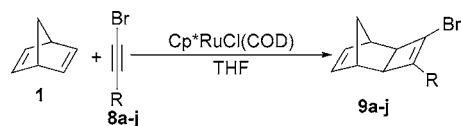
Scheme 1. Pauson–Khand Reaction of Norbornadiene **1** with 1-Chloro-2-phenylethyne **4**



and found that the desired [2 + 2 + 1] cycloadduct **6** was obtained in only 45% yield, and the major product obtained was complex **7**, which formed through a homocoupling of the alkynyl chloride **4**.¹² Much to our delight, alkynyl halides are compatible with the ruthenium-catalyzed [2 + 2] cycloaddition reaction with bicyclic alkenes and no homocoupling products have been observed, *vide infra*.

An initial investigation into various alkynyl bromides was first undertaken to determine the scope of their utility (Table 2). The alkynyl bromides were easily prepared in high yields through the treatment of their corresponding terminal alkynes

Table 2. Ruthenium-Catalyzed [2 + 2] Cycloaddition between Norbornadiene and Alkynyl Bromides



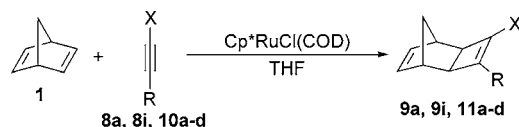
entry	alkyne	R	temp (°C)	time (h)	cycloadduct	yield ^a (%)
1	8a	C ₆ H ₅	60	41	9a	82
2			25	44		78
3	8b	<i>p</i> -MeO–C ₆ H ₄	65	72	9b	63 (17)
4	8c	<i>p</i> -Me–C ₆ H ₄	25	72	9c	75
5	8d	<i>o</i> -Me–C ₆ H ₄	65	72	9d	20 (16)
6			25	72		28 (38)
7	8e	<i>o</i> -CF ₃ –C ₆ H ₄	65	72	9e	42
8			40	168		21 (24)
9			25	72		8 (64)
10	8f	<i>m</i> -F–C ₆ H ₄	65	72	9f	75
11			25	72		40 (10)
12	8g	<i>n</i> -Bu	60	72	9g	38
13			25	168		32
14	8h	CH ₂ CH ₂ OTBS	65	69	9h	72
15			25	96		52 (15)
16	8i	CO ₂ Et	25	1	9i	85
17	8j	SO ₂ Tol	65	65	9j	48

^a Yield of isolated cycloadducts **9**. Yield of recovered alkyne in brackets.

with *N*-bromosuccinimide (NBS) in the presence of a catalytic amount of silver nitrate.¹³ In the presence of 5 mol % catalyst Cp*RuCl(COD) (Cp* = 1,2,3,4,5-pentamethylcyclopentadiene), [2 + 2] cycloadditions between alkynyl bromide **8a** (R = Ph) and norbornadiene **1** occurred smoothly at both 25 and 60 °C to provide the corresponding cycloadduct **9a** in 78 and 82% yields (Table 2, entries 1 and 2)). As the electron-donating capacity of the substituent increased, longer reaction times (R = *p*-Me-C₆H₄, Table 2, entry 3) and higher temperatures (R = *p*-MeO-C₆H₄, Table 2, entry 4) were required. It was also observed that steric hindrance associated with the alkyne affected the rate of reaction (compare **8c** vs **8d** and **8e** vs **8f**). It should be noted that less reactive alkynes did not allow a full recovery of the net molar balance (i.e., the combined yields of the cycloadduct and the recovered starting material did not add up to 100%). Alkynyl bromides are not very stable in the reaction conditions, and subsequently, when the reaction takes place over a long reaction time at higher temperatures, decomposition occurs prior to completion of the cycloaddition reaction. Control experiments showed that thermal decomposition of the alkynyl bromides was observed upon heating in THF; no decomposition was detected when the cycloadducts was subjected to the same conditions.

The effect of the halogen group on the cycloaddition reaction was also studied (Table 3).¹⁴ Two series of substrates

Table 3. Ruthenium-Catalyzed [2 + 2] Cycloaddition between Norbornadiene and Different Alkynyl Halides



entry	alkyne	R	X	temp (°C)	time (h)	cycloadduct	yield ^a (%)
1	10a	CO ₂ Et	Cl	25	1	11a	74
2	8i		Br	25	1	9i	85
3	10b		I	25	2	11b	89
4	10c	C ₆ H ₅	Cl	60	48	11c	82
5				25	49		80
6	8a		Br	60	48	9a	82
7				25	49		78
8	10d		I	65	43	11d	41 ^b
9				25	168		30 (30) ^b

^a Yield of isolated cycloadducts. Yield of recovered alkyne is in parentheses. ^b Side product (**12**) was also obtained (see text and Figure 1).

were investigated (R = Ph and CO₂Et). In the ester series (Table 3, entries 1–3), the cycloadditions of all the alkynyl

(11) For selected examples of transition metal-catalyzed reaction involving alkynyl halides, see: (a) Beaudet, I.; Parrain, J.-L.; Quintard J.-P. *Tetrahedron Lett.* **1992**, *33*, 3647. (b) Bouyssi, D.; Gore, J.; Balme, G. *Tetrahedron Lett.* **1992**, *33*, 2811. (c) Weigelt, M.; Becher, D.; Poetsch, E.; Bruhn, C.; Ströhl, D.; Steinborn D. *J. Prakt. Chem.* **1999**, *341*, 477. (d) Abele, E.; Rubina, K.; Fleisher, M.; Popelis, J.; Arsenyan, P.; Lukecics, E. *Appl. Organomet. Chem.* **2002**, *16*, 141.

(12) Balsells, J.; Moyano, A.; Riera, A.; Pericàs, M. *Org. Lett.* **1999**, *1*, 1981.

chloride, bromide, and iodide occurred smoothly even at 25 °C in 1–2 h giving the corresponding cycloadducts in good yields. For the phenyl series, although longer reaction times were required (~48 h), the cycloadditions of both alkynyl chloride and bromide occurred smoothly at 25 and 60 °C, respectively, providing the corresponding cycloadducts in good yields (Table 3, entries 4–7). An uncharacteristic difference in reactivity was observed for 1-iodo-2-phenylethyne **10d** (Table 3, entries 8 and 9). Other than the formation of the usual [2 + 2] cycloadduct **11d**, a new addition product (**12**, Figure 1) was also obtained in 26%

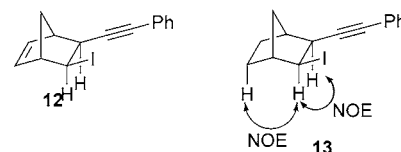


Figure 1. Side product obtained in the reaction between norbornadiene **1** and **10b** (**12**) and between norbornene and **10b** (**13**).

yield. The structure and stereochemistry of this byproduct **12** was determined using mass spectrometry and ¹H, ¹³C (JMOD), COSY, HSQC, and GOESY NMR experiments.^{15,16} We believe that the presence of this product can be explained by a combination of two factors. Since iodide is less electronegative than bromide and chloride and the rate of the reaction is increased by utilizing strong electron-withdrawing groups, the cycloaddition occurs at a much slower rate. In addition, because the C–I bond is weaker than both the C–Br and C–Cl bonds, it is easier to oxidatively insert the ruthenium metal into the C–I bond. To the best of our knowledge, this is the first example of a ruthenium-catalyzed haloalkynylation of alkynyl halide across a double bond.

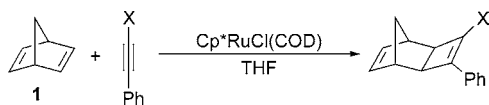
To estimate the reactivity of alkynyl halides in the ruthenium-catalyzed [2 + 2] cycloadditions, the relative rate of the ruthenium-catalyzed [2 + 2] cycloadditions of several alkynes with norbornadiene was measured by competition experiments between alkyne **2a** (R = Ph, X = COOEt) and other alkynes (Table 4). A typical competition experiment employed 4 equiv of equimolar amounts of alkyne **2a** (a stock solution of known concentration was prepared for **2a**) and alkyne **10c** (R = Ph, X = Cl) with 1 equiv of norbornadiene **1** in the presence of 5 mol % Cp*RuCl(COD)

(13) Kauffmann, T.; Abeln, R.; Wingbernhöle, D. *Angew. Chem., Int. Ed.* **1984**, *23*, 729.

(14) (a) For a general procedure for the preparation of alkynyl chlorides, see: Ariamala, G.; Balasubramanian, K. K. *Tetrahedron* **1989**, *45*, 309. (b) For the preparation of **10a**, see: Viehe, H. G. *Chem. Ber.* **1959**, *92*, 1950. (c) For a general procedure for the preparation of alkynyl iodides, see ref 13.

(15) When **12** was reduced with lithium aluminium hydride or treated with *tert*-butyllithium followed by a quench with methanol, the loss of iodide was observed.

(16) The *exo* stereochemistry of both groups was established by GOESY NMR experiments of product **13**, which was obtained through the same conditions using norbornene instead of norbornadiene. Compound **13** could also be prepared by hydrogenation of **12**.

Table 4. Relative Rate of Cycloaddition

entry	alkyne	X	cycloadduct	relative rate ^a
1	2b	Me	3b	0.01
2	2a	CO ₂ Et	3a	1
3	8a	Br	9a	2
4	10c	Cl	11c	9

^a Measured from competition experiments; see text. The number indicated is the average number from 3 to 5 runs.

in THF (large excesses of the alkynes were used in order to approach pseudo-first-order conditions).¹⁷ The reactivity of each alkyne was assessed by evaluation of the product ratio by capillary gas chromatography. The results of these reactivity studies are shown in Table 4. Alkyne **2a** is one of the most reactive alkyne studies so far in ruthenium-catalyzed [2 + 2] cycloadditions and reacts ~100 times faster than unactivated alkynes such as **2b** (R = Ph, X = Me). When comparing the reactivity of alkynyl halides **8a** (X = Br) and **10c** (X = Cl) with alkyne **2a** (X = CO₂Et), cycloadditions with these alkynyl halides appeared to occur even faster than alkyne **2a**. In fact, the rates of the cycloaddition of **8a** and **10c** with norbornadiene **1** were 2 and 9 times faster, respectively, than **2a**.

To illustrate the synthetic usefulness of the resulting halogenated cycloadducts, cycloadduct **9a** was treated under a variety of reaction conditions to achieve further functionalization. As shown in Scheme 2, lithium-halide exchange followed by trapping with various electrophiles led to products **3b,c,e** in moderate to good yields. Suzuki coupling between **9a** and phenylboronic acid provided **3d** in 75% yield, and Sonogashira coupling between **9a** and phenylacetylene gave **14** in 64% yield. As previously shown in

(17) Lautens, M.; Tam, W.; Edwards, L. E. *J. Chem. Soc., Perkin Trans. I* **1994**, 2143.

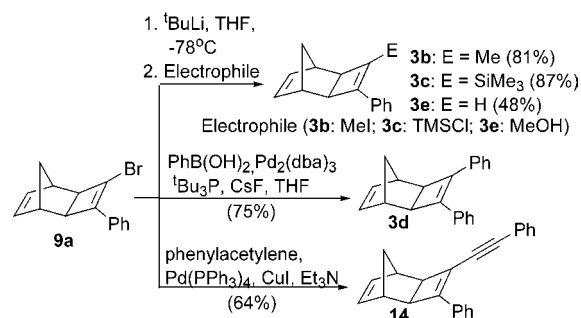
Scheme 2. Functionalization of **9a**

Table 1, these products are difficult or impossible to obtain via direct cycloaddition.

In summary, we have demonstrated the first examples of Ru-catalyzed [2 + 2] cycloadditions between alkynyl halides and norbornadiene (yields up to 89%). The presence of the halide moiety is compatible in the ruthenium-catalyzed [2 + 2] cycloadditions and greatly enhances the reactivity of the alkyne component in the cycloaddition. During this study, we have also discovered a novel haloalkynylation reaction between 1-iodo-2-phenylethyne and norbornadiene catalyzed by the catalyst Cp*RuCl(COD). Further investigation of the origin, reactivity, and application of this novel type of ruthenium-catalyzed haloalkynylation is ongoing in our laboratory.

Acknowledgment. This work was supported by NSERC (Canada) and Boehringer Ingelheim (Canada), Ltd. W.T. thanks Boehringer Ingelheim (Canada), Ltd., for a Young Investigator Award. NSERC and the Ontario Government are thanked for providing postgraduate scholarships to K.V., N.R., and R.W.J..

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>.

OL048111G