ORGANIC LETTERS

2008
Vol. 10, No. 21
4927−4929

Enyne Cross-Metathesis with Strained, Geminally-Substituted Alkenes: Direct Access to Highly Substituted 1,3-Dienes

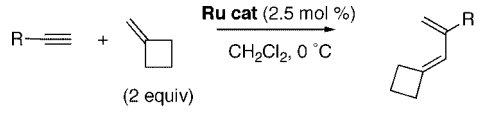
Daniel A. Clark, Brenda S. Basile, William S. Karnofel, and Steven T. Diver*

Department of Chemistry, University at Buffalo, The State University of New York, Amherst, New York 14260

diver@buffalo.edu

Received August 27, 2008

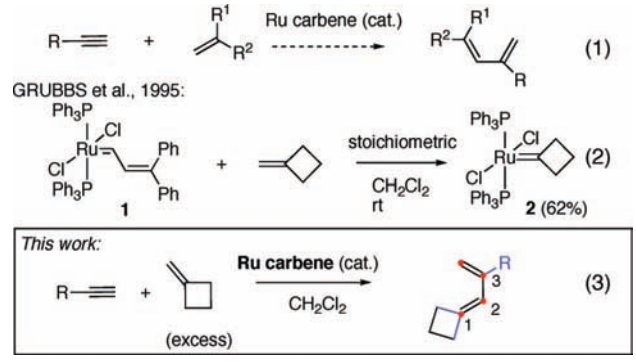
ABSTRACT



Angle strain in methylene cyclobutane was used to drive a cross-enyne metathesis with 1-alkynes, giving 1,1,3-trisubstituted 1,3-dienes in good isolated yields. An extensive survey of Grubbs' second-generation catalysts led to an optimized reaction conducted at 0 °C.

Enyne metathesis has become a useful method for carbon−carbon bond formation.[1] In its most commonly used form, the intermolecular (cross) enyne metathesis[2] between 1-alkene and an alkyne generates a 1,3-diene with the 1,3-disubstitution pattern ($R^1 = H$, eq 1, Scheme 1). Although enyne metathesis is often compared to alkene metathesis, there is one notable difference: in cross alkene metathesis, geminal alkenes can be crossed with 1-alkenes to give trisubstituted alkene products.[3] Knowing this, it seems like trisubstituted dienes of the 1,1,3-trisubstitution pattern should be accessible from geminally-substituted alkenes (eq 1, Scheme 1). However, 1,1-disubstituted alkenes display poor reactivity with the Grubbs catalyst. Because the enyne metathesis is believed to occur by an "alkylidene-first" mechanism,[4] the alkene is required to react with the catalyst to form the needed alkylidene. In this paper, we show that angle strain in methylene cyclobutane can effectively drive the cross enyne metathesis, giving rise to dienes of 1,1,3-trisubstitution pattern in a single catalytic metathesis step (eq 3, Scheme 1).

Scheme 1. Strained Alkenes Undergo Cross Metathesis



There is limited data on geminal alkene reactivity in metathesis. Strain in a geminal alkene can be used to drive the alkene initiation step. Examination of the literature provides two examples of geminal alkenes that were shown to *form* ruthenium

(1) Enyne reviews: (a) Poulsen, C. S.; Madsen, R. *Synthesis* **2003**, 1–18. (b) Mori, M. Ene-Yne Metathesis. In *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, 2003; Vol. 2, pp 176−204. (c) Diver, S. T.; Giessert, A. J. *Chem. Rev.* **2004**, *104*, 1317–1382.

(2) Stragies, R.; Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2518–2520.

(3) (a) Chatterjee, A. K.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 1751–1753. (b) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360–11370.

(4) (a) Hoye, T. R.; Donaldson, S. M.; Vos, T. J. *Org. Lett.* **1999**, *1*, 277–279. (b) Schramm, M. P.; Reddy, D. S.; Kozmin, S. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4274–4277. (c) Giessert, A. J.; Diver, S. T. *Org. Lett.* **2005**, *7*, 351–354. (d) Galan, B. R.; Giessert, A. J.; Keister, J. B.; Diver, S. T. *J. Am. Chem. Soc.* **2005**, *127*, 5762–5763.

10.1021/ol802007q CCC: $40.75
Published on Web 10/09/2008

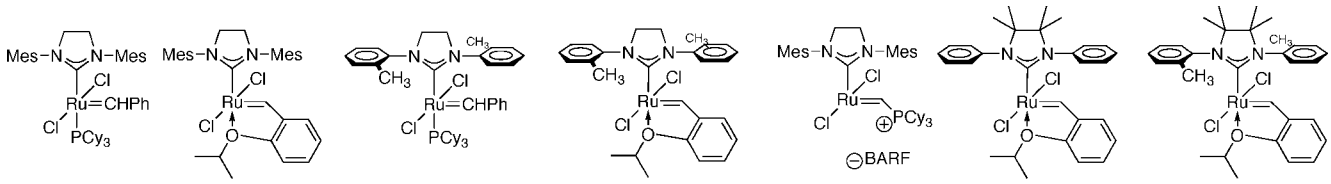


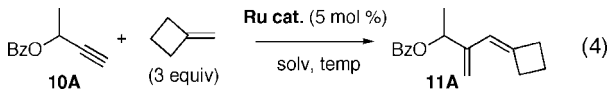
Figure 1. Grubbs' catalysts used in this study.

carbenes. In 1995, the Grubbs group showed that the neophylidene complex **1** reacted with both methylene cyclopropane and methylene cyclobutane (eq 2, Scheme 1).[5] The Caltech group structurally characterized the geminally-substituted metal carbene **2** derived from methylene cyclobutane. We took this as a positive indication that the strain release on going to the spirometallacycle could be used to effect initiation in the second generation Grubbs carbenes with the $(H_2IMes)(L)Cl_2Ru{=}CHPh$ ligand environment. Strain release might overcome the otherwise slow initiation step typical for geminally-substituted alkenes. Recently, Oishi and co-workers reported a single example of catalytic cross enyne metathesis using a large excess of the geminally-substituted alkene 2-methallyl alcohol.[6]

Reaction of methylene cyclobutane with alkyne **10A** was observed and optimized with respect to the carbene initiator. The highest reactivity in cross metathesis is typically achieved with the second generation Grubbs carbene complexes, so we focused on use of this family of Grubbs carbenes (Figure 1). The data is summarized in Table 1. In this screen, the number of alkene equivalents was kept constant at 3 equiv. With a volatile, low molecular weight alkene, we sought low temperature conditions. Temperatures lower than room temperature are not commonly used in the metathesis but are possible when using more active initiators. The parent Grubbs complex **3** did not initiate at 0 °C, but good reactivity could be obtained by conducting the reaction at rt or reflux (entries 2 and 3). The phosphine-free Hoveyda−Blechert[7] complex **4** proved to initiate at low temperature in CH_2Cl_2 and reacted well in DCE or benzene at rt. With the more active phosphine-containing bis(tolyl) complex **5**[8] good reactivity was found, with complete conversion observed at rt (entry 7, cf. entry 2). The phosphine-free variant **6** promoted the cross-enyne metathesis at 0 °C. The Piers catalyst **7**[9] reacted at rt (entry 9), and the newly reported Grubbs' complexes[10] **8** and **9** proved highly active, promoting the cross metathesis at 0 °C in less than 5 min (entries 10 and 11).

With a good survey of catalyst efficiency, we decided to fine-tune the conditions with respect to catalyst loading and number of equivalents alkene.[11] At this stage, we settled on a lower reaction temperature to maintain alkene concentration for potentially longer reaction times employing fewer equivalents alkene. The results are summarized in Table 2. First, the excess alkene was decreased to 2 equiv with acceptable yield using catalyst **4**, but further reduction of alkene concentration proved deleterious to reaction yield and efficiency (entries 1 and 2). The tolyl complex **6** performed better at both lower alkene concentration and at 2.5 mol % loading (entry 4). With 5 mol % of **6**, the alkene equivalents could be reduced further (entry 5). Complex **8** did not give complete conversion at very low loading (1 mol %, entry 6) but performed adequately at 5 mol

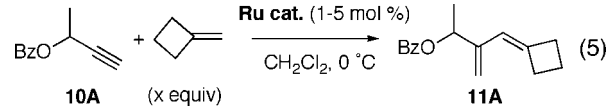
Table 1. Catalyst Screening[a]



entry	carbene complex	solvent	T (°C), time	% yield (NMR)[b]
1	**3**	CH_2Cl_2	0, 5 h	NR
2	**3**	CH_2Cl_2	rt, 1 h	93
3	**3**	CH_2Cl_2	reflux, 15 min	95
4	**4**	CH_2Cl_2	0, 15 min	97
5	**4**	DCE	rt, 15 min	86
6	**4**	PhH	rt, 15 min	99
7	**5**	CH_2Cl_2	rt, 20 min	99
8	**6**	CH_2Cl_2	0, 20 min	97
9	**7**	CH_2Cl_2	rt, 20 min	75
10	**8**	CH_2Cl_2	0, <5 min	99
11	**9**	CH_2Cl_2	0, <5 min	99

[a] Conditions: 0.1 M alkyne, 0.3 M methylene cyclobutane in solvent at temperature indicated. Reactions went to complete conversion of alkyne reactant unless otherwise noted. [b] NMR yield vs mesitylene internal standard.

Table 2. Refinement of Reaction Parameters[a]



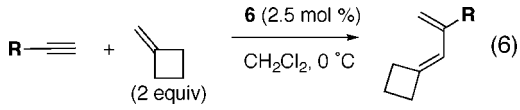
entry	carbene complex	loading (mol %)	equiv	T (°C), time	% yield
1	**4**	5	2	0, 2.5 h	92
2	**4**	5	1.25	0, 4 h	70
3	**6**	5	2	0, 30 h	99
4	**6**	2.5	2	0, 30 h	96
5	**6**	5	1.25	0, 30 h	91
6	**8**	1	3	0, 1.5 h	40
7	**8**	5	2	0, 3 h	89
8	**9**	1	3	0, 3 h	incomplete
9	**9**	5	2	0, 3 h	99

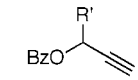
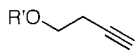
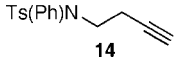
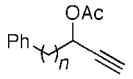
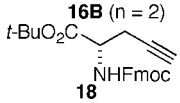
[a] Conditions: 0.1 M alkyne, variable methylene cyclobutane in solvent at temperature indicated. NMR yield vs mesitylene internal standard.

% over a 3 h reaction time (entry 7). The tolyl complex **9** showed similar performance at 1 mol %, and a higher conversion was found at 5 mol % loading (entry 9). These data suggest that the alkene concentration can be dropped to 2 equiv while maintaining catalyst loading at 2.5−5 mol %. The alkene concentration and catalyst loading cannot be simultaneously decreased without diminishing conversion and reaction yield. From Table 2 we adopted the conditions in entry 4 as our standard conditions.

The standard conditions were applied to a range of terminal alkynes as shown in Table 3. The propargylic benzoates gave

Table 3. Reaction Scope of the Enyne Metathesis with Methylenecyclobutane[a]



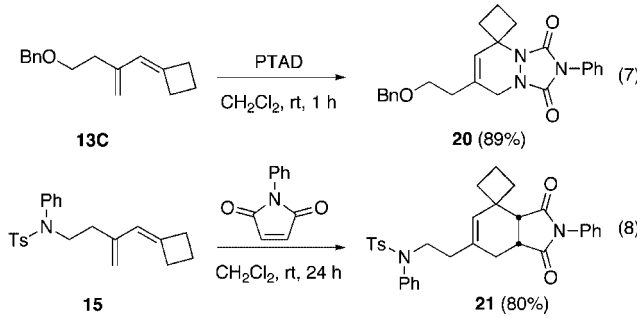
entry	alkyne	product	% yield[b]
			
1	**10A** (R' = Me)	**11A** (R' = Me)	96
2	**10B** (R' = H)	**11B** (R' = H)	93
			
3	**12A** (R' = Bz)	**13A** (R' = Bz)	99
4	**12B** (R' = TBS)	**13B** (R' = TBS)	97
5	**12C** (R' = Bn)	**13C** (R' = Bn)	92
			
6	**14**	**15**	95
			
7	**16A** (n = 1)	**17A** (n = 1)	96
8	**16B** (n = 2)	**17B** (n = 2)	95
			
9[c]	**18**	**19**	99

[a] Standard conditions: 0.2 M alkyne, 0.4 M alkene, 2.5 mol % of **6**, CH_2Cl_2, 0 °C, 1−3 h; 50 mol % KO_2CCH_2NC quench. (a) Isolated. (b) Performed at 0.1 M with 5 mol % **6**.

excellent results regardless of substitution (entries 1 and 2). Oxygen functionality at the homopropargylic position was also tolerated, as in typical[12] cross enyne metatheses with 1-alkenes (entries 3−5). Nitrogen functionality did not prove problematic (entry 6), and larger substituents in the propargylic position were acceptable and found to give rapid conversions under the standard reaction conditions (entries 7 and 8). Last, the homochiral amino acid derivative **18** underwent an effective cross metathesis to give the diene in quantitative chemical yield (entry 9). In summary, these reactions are very effective[13] and high yielding using a modest amount of methylene cyclobutane, low reaction temperatures, and low catalyst loading.

The resulting 1,3-dienes are reactive in room-temperature cycloadditions. The diene products in eq 6 (Table 3) possess angle strain due to the distortion of the cyclobutane ring from ideal sp^2 bond angles. As a result, dienes **13C** and **15**readily undergo Diels−Alder reaction to provide the corresponding cycloadducts in excellent yield (Scheme 2).

Scheme 2. Room-Temperature Cycloadditions



In conclusion, we have shown that a strained alkene gives a highly effective cross metathesis to furnish dienes with geminal substitution at the terminal position of the diene. A wide variety of highly active second generation Grubbs carbenes were screened in the optimization study. The use of angle strain in the geminal substituents of the alkene offers a means to overcome poor reactivity of geminal alkenes and elaborates the accessible substitution patterns by catalytic enyne cross metathesis. Studies using strain as a means of achieving catalytic efficiency and extending reaction scope further are ongoing and will be reported in due course.

Acknowledgment. This work was partially supported by the Petroleum Research Fund (PRF AC-44202) and the NSF (CHE-601206). We thank Materia (Pasadena, CA) for generously supplying Grubbs' catalyst.

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

OL802007Q

(5) Wu, Z.; Nguyen, S. T.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1995**, *117*, 5503–5511. For a discussion of the role of strain in promoting the initiation, see footnote 12 in the above paper by Grubbs et al.

(6) Watanabe, K.; Minato, H.; Murata, M.; Oishi, T. *Heterocycles* **2007**, *72*, 207–212. We thank a reviewer for bringing this to our attention.

(7) (a) Gessler, S.; Randl, S.; Blechert, S. *Tetrahedron Lett.* **2000**, *41*, 9973–9976. (b) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168–8179.

(8) (a) Stewart, I. C.; Ung, T.; Pletnev, A. A.; Berlin, J. M.; Grubbs, R. H.; Schrodi, Y. *Org. Lett.* **2007**, *9*, 1589–1592. (b) Stewart, I. C.; Douglas, C. J.; Grubbs, R. H. *Org. Lett.* **2008**, *10*, 441–444.

(9) Romero, P. E.; Piers, W. E.; McDonald, R. *Angew. Chem., Int. Ed.* **2004**, *43*, 6161–6165.

(10) Chung, C. K.; Grubbs, R. H. *Org. Lett.* **2008**, *10*, 2693–2696.

(11) Typically 3 equiv (or more) alkene are employed for a successful cross enyne metathesis.

(12) A notable difference in the present case is the lower reaction temperature, which is not typical of a cross enyne metathesis.

(13) Internal alkynes were found not to give the cross metathesis under the standard conditions reported here.