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Synthesis of 1,3-cyclohexadienes by tandem diene–alkyne metathesis: improved procedure

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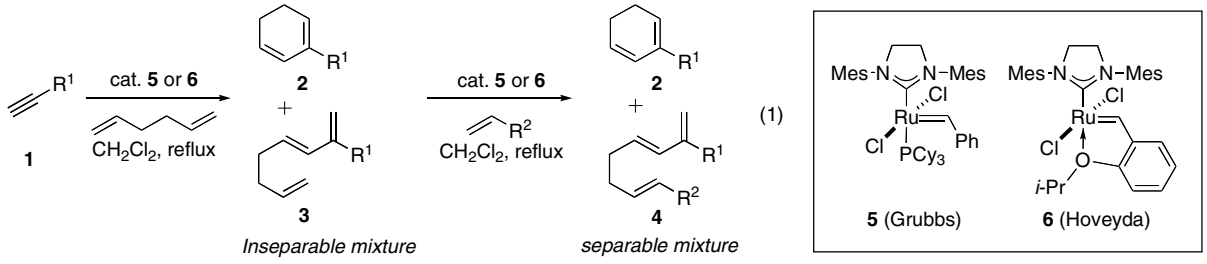
Abstract—A practical synthesis of 2-substituted 1,3-cyclohexadienes by the cross enyne metathesis between alkynes and 1,5-hexadiene is reported. The isolation of the 1,3-cyclohexadienes has been hampered by the formation of an inseparable triene by-product. The use of a second consecutive cross alkene metathesis to give water-soluble products allowed removal of this by-product. Using this one-pot procedure, a synthesis of cyclohexadienes from simple starting materials was developed. The procedure was used in a three-step synthesis of a functionalized tetrahydroquinoline using Pd(II)-catalyzed chloroacetoxylation (Bäckvall reaction) for cyclohexadiene functionalization.

In recent years, enyne metathesis has proved to be a particularly fertile area for the development of new approaches to complex molecule synthesis.[1] The use of tandem metathesis in particular, has proven to be a powerful method for ring construction. Although there are many elegant examples of tandem ring-closing enyne metathesis, there are few cases where the metathesis is initiated by an intermolecular enyne metathesis event. The use of the intermolecular reaction is complicated by lack of stereocontrol in the newly formed diene. In many cases, an *E*,*Z*-mixture of dienes is obtained.[2]

Recently, we demonstrated that a tandem enyne metathesis between alkynes and 1,5-hexadiene could be used for the rapid construction of 1,3-cyclohexadienes **2** (Scheme 1).[3] However, the utility of this methodology for the rapid construction of cyclohexadienes from simple acyclic precursors has been limited by the formation of the *E*-triene **3** that cannot be separated from the 1,3-cyclohexadiene **2** by regular flash column chromatography on silica gel. In order to address this problem, a one-pot procedure has been developed, in which the terminal end of the undesired triene **3** undergoes a second cross alkene metathesis to give **4**. Substituted triene **4** can then be readily separated from the desired cyclohexadiene **2** (Eq. 1).

The tandem metathesis of alkynes with 1,5-hexadiene provides a useful and functional group tolerant method for cyclohexadiene ring synthesis. We recently



Scheme 1. Cyclohexadiene synthesis.

Keywords: Enyne metathesis; Cross metathesis; 1,3-Cyclohexadienes; Tetrahydroquinoline; Grubbs catalyst; Hoveyda catalyst.
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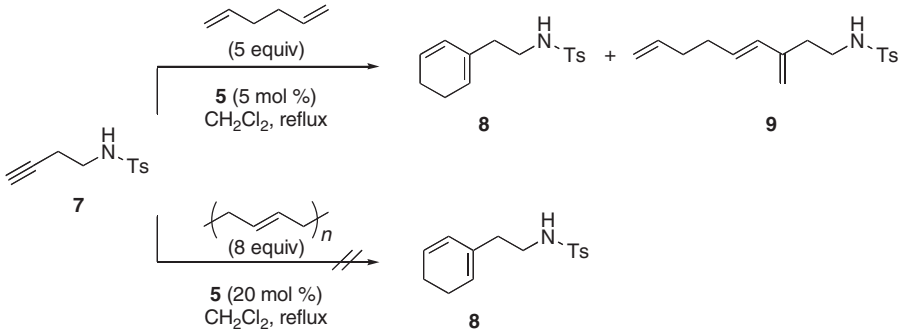


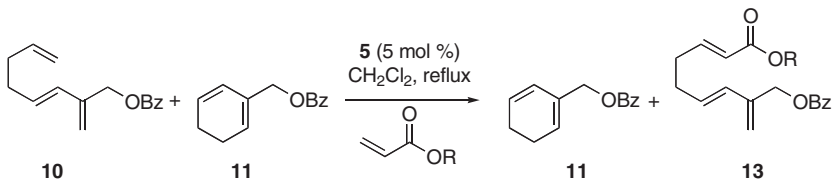
Scheme 2. Complementary methods for 1,3-cyclohexadiene synthesis.

developed conditions that are 'methylene-free' (lacking CH_2 sources), which slows down the rate of metathesis but improves the yields of 1,3-cyclohexadienes.[4] However, the slow rate of metathesis reduces the functional group tolerance relative to other enyne metathesis reactions because in methylene-free systems, the slower rate of catalyst turnover may result in greater catalyst decomposition due to coordination effects. As a result, functional groups on the alkyne are not well tolerated in methylene-free metathesis. For example, alkyne **7** reacts rapidly with 5 mol % of **5** (Grubbs' complex) to give complete conversion after 2.5 h to a 1.0:1.2 mixture of cyclohexadiene **8** and triene **9** (Scheme 2). When **7** was reacted with polybutadiene under standard methylene-free conditions, only trace amounts of **8** were obtained. Additional catalyst loading (20 mol %) did not improve conversion.

The Grubbs selectivity model for olefin cross metathesis led us to consider the possibility of modifying the more reactive 1-alkene of the triene by a second, chemoselective alkene cross metathesis.[5] We reasoned that the optimum cross coupling partner would be an alkene that is slow to self-metathesize ('homodimerization' process). This will help favor cross metathesis with the 1-alkene present in **3** (Scheme 1). The alkene partner was also selected to increase the polarity of the triene cross product by introduction of carbonyl functionality. The terminal alkene present in **3** should be more reactive to cross metathesis relative to the endocyclic diene of **2**.[6] If the alkene cross metathesis could be completed without degradation of the cyclohexadiene, then the separation of **2** and **4** by further chemical modification of the triene would be a viable synthetic proposition.

Separation of crude product mixtures was possible with successive cross metathesis. Initial work focused on the cross metathesis of isolated mixtures of triene **10** and diene **11** with acrylates (Eq. 2). The mixture **10/11** was isolated in 91% yield from 1-(benzyloxy)-2-propyne. For example, 0.5 mmol of a 1.3:1.0 ratio of triene **10** and diene **11** was reacted with 0.55 mmol of acrylic acid **12a**, or methyl acrylate **12b**, and catalyst **5**. After 6 h, the triene was no longer detected (GC), and the cyclohexadiene **11** was isolated in respective yields of 37% and 38% (the yields are 34% and 35% based on the alkyne reactant used in the previous tandem metathesis step).

Next, a one-pot procedure was developed. In this operation, the intermediates **10** and **11** were directly subjected to the second cross alkene metathesis. Table 1 illustrates the results using two different procedures. In the first procedure (A), excess 1,5-hexadiene was removed in vacuo after the first step. The crude mixture of diene and triene was redissolved in dichloromethane, followed by the addition of the second portion of catalyst and alkene (Eq. 3). The reaction proceeded well using catalyst **5** and either methyl acrylate or acrylic acid (entries 1 and 2). When acrylic acid **12a** was used, the excess acid and the cross product were removed from the reaction mixture via a simple extractive work-up, washing with aqueous sodium bicarbonate. Catalyst **6**



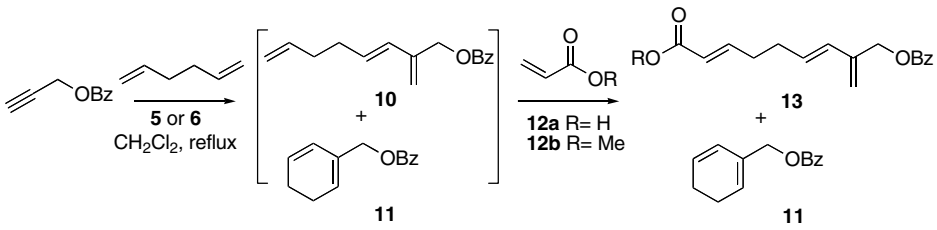
12a R=H 37%[a] (34%)[b]

12b R=Me 38%[a] (35%)[b]

(2)

(a) Isolated yield for this step. (b) Isolated yield based on alkyne used in the preceeding tandem metathesis.

Table 1. Optimization of the one-pot procedure

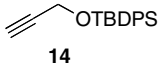
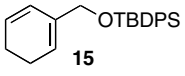
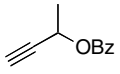
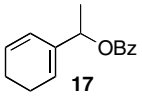
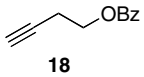
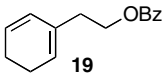
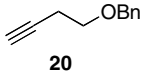
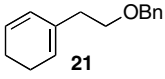
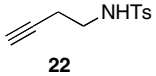
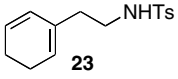
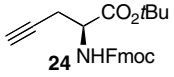
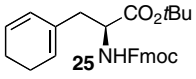
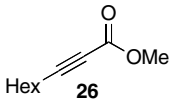
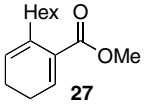
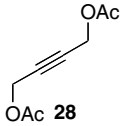
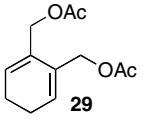


(3)

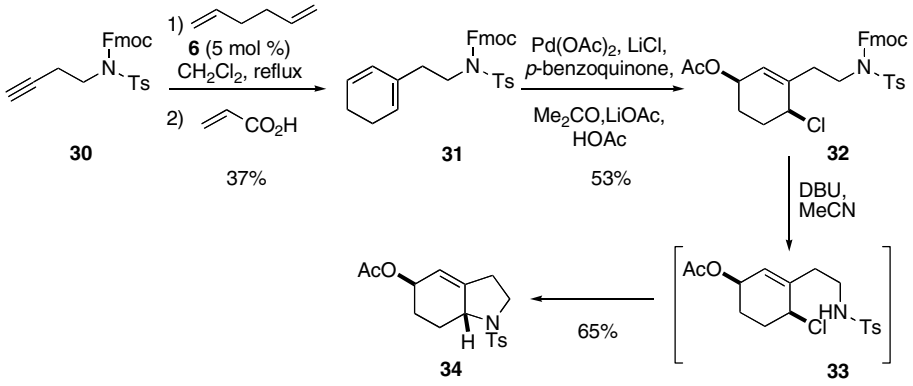
Entry	Diene/equiv	(Conc) alkyne	Catalyst (mol %)	Removal[a]	Alkene/equiv	Catalyst (mol %)	Yield[b,c] (%)
1	5	0.1	**5** (5 mol %)	A	**12a**, 9 equiv	**5** (5 mol %)	36
2	5	0.1	**5** (5 mol %)	A	**12b**, 9 equiv	**5** (5 mol %)	32
3	5	0.1	**6** (5 mol %)	A	**12b**, 9 equiv	**6** (5 mol %)	36
4	5	0.1	**6** (2.5 mol %)	A	First metathesis stalled		
5	5	0.1	**5** (5 mol %)	B	**12a**, 10 equiv	**5** (5 mol %)	39[d]
6	3	0.1	**5** (5 mol %)	B	First metathesis stalled		
7	3	0.25	**5** (5 mol %)	B	First metathesis stalled		
8	3	0.5	**5** (5 mol %)	B	**12a**, 10 equiv	**5** (5 mol %)	37
9	3	0.5	**5** (5 mol %)	B	**12a**, 10 equiv	No added catalyst	—[e]
10	3	0.5	**6** (5 mol %)	B	**12a**, 10 equiv	**6** (5 mol %)	38
11	3	0.5	**6** (5 mol %)	B	**12a**, 10 equiv	No added catalyst	36

Conditions: 0.5 mmol alkyne, *x* equiv 1,5-hexadiene in CH_2Cl_2, refluxed in a Schlenk tube with reflux condenser.
[a] Method A: Evaporation of volatiles after first step. Method B: No treatment.
[b] Isolated.
[c] Contains trace butadiene.
[d] 9.7:1 diene to triene.
[e] 2.2:1 diene to triene.

Table 2. Scope of the two-step, one-pot cross metathesis procedure

Entry	Substrate	Product	Isolated yield[a] (%)
1	 **14**	 **15**	41
2	 **16**	 **17**	34
3	 **18**	 **19**	31
4	 **20**	 **21**	34[b]
5	 **22**	 **23**	39[b]
6	 **24**	 **25**	36[b]
7	 **26**	 **27**	38
8	 **28**	 **29**	35

Conditions: 0.5 mmol alkyne, 1.5 mmol 1,5-hexadiene, 0.025 mmol **6** (5 mol %) in 1 mL CH_2Cl_2, refluxed in a Schlenk tube with reflux condenser; 10 equiv of acrylic acid added after the first reaction was complete.
[a] Yield over two steps, based on alkyne. Contains trace butadiene.
[b] Additional 2.5 mol % catalyst **6** added.



Scheme 3. Three-step synthesis of indoline **34**.

(Hoveyda complex) also proved effective in this procedure (entry 3). Lowering the loading of catalyst **6** to 2.5 mol % proved to be unsuccessful, leading to a failure of the initial tandem enyne/ring-closing metathesis (entry 4). The second procedure (B), does not require any manipulation of the mixture of **10**, **11**: the mixture is directly treated with excess acrylic acid and additional catalyst (entry 5). Dropping the equivalents of 1,5-hexadiene proved deleterious in the alkyne conversion step (entries 6 and 7), but this could be overcome by running the 1,5-hexadiene–alkyne cross reaction at higher concentration (entry 8). Without the addition of more catalyst, the triene **10** was still detected at the end of the reaction (entry 9). Catalyst **6** gave a good result (entry 10 vs entry 8) and significantly, did not require a second charge of catalyst for the cross alkene metathesis step (entry 11). This represents a highly efficient catalytic process where the catalyst **6** has promoted a cross enyne metathesis, a ring-closing alkene-alkene metathesis and a cross alkene-alkene metathesis.

The scope of the reaction was demonstrated for a range of functionalized alkynes (Table 2). The procedure enabled a variety of 2-substituted 1,3-cyclohexadienes to be synthesized and isolated in 'one-pot' from terminal alkynes.[7] The potentially coordinating propargyl silyl ether **14** worked well (entry 1). Propargylic substitution did not diminish the effectiveness of the procedure (entry 2). The presence of homopropargylic heteroatoms was tolerated, but an extra 2.5 mol % catalyst was required in order to push the second metathesis to completion (entries 4, 5, and 6). In general, nitrogen-containing functionality has posed difficulties in both the alkyne and alkene reactants, particularly if there is an NH bond.[1a] It is therefore noteworthy that homopropargylic amine derivatives were found to participate in the two-step metathesis without difficulty (entries 5 and 6). In addition to terminal alkynes, the one-pot procedure worked equally well for internal alkynes, giving access to 2,3-disubstituted 1,3-cyclohexadienes (entries 7 and 8). Internal alkynes have not been used in methylene-free metathesis.[4]

The procedure was applied to the synthesis of a functionalized tetrahydroquinoline ring system (Scheme 3). Alkyne **30** was converted to 1,3-cyclohexadiene **31** using the one-pot metathesis procedure in 37% yield. The diene **31** was then subjected to Bäckvall's conditions for palladium-catalyzed 1,4-chloroacetoxylation to give **32**.[8] When treated with DBU in acetonitrile, the Fmoc group was completely removed after 1 h to give amine **33**. Chloride displacement occurred in situ to afford indoline **34** in 65% isolated yield.[9]

In summary, a rapid synthesis of 1,5-hexadienes from simple alkyne precursors has been developed. The method is functional group-tolerant and is applicable to a wide range of alkynes. Furthermore, use of this procedure enabled the rapid synthesis of indoline **34** in only three linear steps from alkyne **30**. Current work is focused on improving the selectivity of the initial cross enyne metathesis step and in applying this methodology in target-directed synthesis.

Acknowledgements

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References and notes

1. For recent reviews see: (a) Diver, S. T.; Giessert, A. *J. Chem. Rev.* **2004**, *104*, 1317–1382; (b) Poulsen, C. S.; Madsen, R. *Synthesis* **2003**, 1–18.
2. (a) Lee, H.-Y.; Kim, B. G.; Snapper, M. L. *Org. Lett.* **2003**, *5*, 1855–1858; (b) Giessert, A. J.; Diver, S. T. *J. Org. Chem.* **2005**, *70*, 1046–1049.
3. Smulik, J. A.; Diver, S. T. *Tetrahedron Lett.* **2001**, *42*, 171–174.
4. Kulkarni, A. A.; Diver, S. T. *J. Am. Chem. Soc.* **2004**, *126*, 8110–8111.
5. Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360–11370.
6. Dienes are known to react in cross alkene metathesis but have not been categorized in Grubbs' model for selectivity in cross metathesis. See for example, (a) Royer, F.; Vilain, C.; Elkaiem, L.; Grimaud, L. *Org. Lett.* **2003**, *5*, 2007–2009; (b) Wang, X.; Porco, J. A. *J. Am. Chem. Soc.* **2003**, *125*, 6040–6041; (c) Funk, T. W.; Efskind, J.; Grubbs, R. H. *Org. Lett.* **2005**, *7*, 187–190.

7. *Representative experimental procedure:* The alkyne **28** (85 mg, 0.50 mmol), and 1,5-hexadiene (178 μL, 1.50 mmol) were dissolved in 1 ml of CH_2Cl_2 in an oven-dried 25 mL Schlenk tube equipped with cold finger condenser under an atmosphere of argon. The catalyst **6** (15.5 mg, 5 mol %) was then added and the solution was then brought immediately to reflux by immersion in a 50 °C oil bath. Heating was maintained for 3 h, the mixture was then cooled and acrylic acid (343 μL, 0.5 mmol) was added. The mixture was brought back to reflux and heated for a further 12 h. The mixture was then cooled, diluted with CH_2Cl_2 (10 mL) and washed with saturated aqueous $NaHCO_3$ (2×10 mL). The organic layer was then dried ($MgSO_4$), filtered and the solvent was then removed in vacuo. Further purification by eluting through a small plug of silica gel gave **29** (39 mg, 35%) as a colorless oil: R_f 0.42 (hexane-EtOAc, 4:1); ^1H NMR (500 MHz, $CDCl_3$) δ 5.97 (m, 2H), 4.63 (s, 4H), 2.20–2.15 (m, 4H), 2.07 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 130.7, 129.3, 65.4, 22.1, 21.1; IR (thin film) 2939, 2360, 1738, 1438, 1377, 1225, 1023, 963 cm^{-1}; HRMS (EI^+) Calcd for $C_{12}H_{16}O_4$ (M^+): 224.1049. Found: 247.0940 (M+Na), error 0.3 ppm.

8. (a) Bäckvall, J. E.; Nyström, J. E.; Nordberg, R. E. *J. Am. Chem. Soc.* **1985**, *107*, 3676–3686; (b) Bäckvall, J. E.; Granberg, K. L.; Hopkins, R. B. *Acta Chem. Scand.* **1990**, *44*, 492–499.

9. Procedure of the synthesis of **34**: The chloroacetate **33** (66 mg, 0.11 mmol) was dissolved in dry acetonitrile (5.5 mL), and DBU (37 μL) was added dropwise over 2 min. The mixture was stirred for 24 h and then the solvent was removed in vacuo. The residue was then purified by flash column chromatography on silica gel (hexanes-EtOAc, 3:1) to afford **34** (24 mg, 65%) as a clear oil: R_f 0.57 (hexanes-EtOAc, 1:1); ^1H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, $J = 8.0$ Hz, 2H), 7.33 (d, $J = 8.0$ Hz, 2H), 5.52 (s, 1H), 5.40–5.36 (m, 1H), 3.67–3.59 (m, 1H), 3.44–3.32 (m, 2H), 2.58–2.53 (m, 1H), 2.44 (s, 3H), 2.33–2.24 (m, 2H), 2.14–2.07 (m, 1H), 2.03 (s, 3H), 1.65–1.48 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 144.0, 143.8, 143.2, 129.9, 127.7, 120.4, 70.1, 58.7, 47.4, 30.4, 29.6, 27.2, 21.6, 21.3; IR (thin film) 2933, 1728, 1598, 1494, 1452, 1349, 1241, 1162, 1094, 1046, 1020, 974 cm^{-1}; HRMS (EI^+) Calcd for $C_{17}H_{21}NO_4S$ (M^+): 335.1191. Found: 358.1079 (M+Na), error 0.6 ppm.