Rhodium(I)-Catalyzed Cycloisomerization Reaction of Yne-Allenamides: An Approach to Cyclic Enamides

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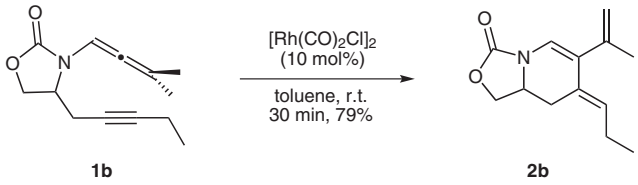
Abstract: In this paper, we demonstrate a successful conversion of alkynyl allenamides to triene-containing heterocycles via a rhodium(I)-catalyzed cycloisomerization reaction.

Key words: cycloisomerization, cyclocarbonylation, allenamide, enamide, Diels–Alder



Scheme 1

Transition-metal-catalyzed cycloisomerization reactions represent a powerful strategy for making carbon–carbon bonds.[1] Our group reported the first example of a rhodium(I)-catalyzed cycloisomerization reaction of an allenyne to afford a cross-conjugated triene.[2] The synthetic potential of this structurally interesting triene seems high, yet it has only seen limited use. In large, because of the limited methods available for their preparation, and controlling the reacting double bonds of the trienyl unit is challenging.[3] The rhodium(I)-catalyzed allenic Alder-ene reaction discovered in our lab, addresses both of these shortcomings. Firstly, the conditions required to generate the triene are mild and show a high degree of functional-group compatibility. Secondly, the newly formed triene is comprised of two structurally unique dienes capable of undergoing discreet reactions. Recently, we have extended the scope of the allenic Alder-ene reaction to include allenamides which cycloisomerize to provide enamide-containing trienes.[4] Enamides are important subunits frequently found in natural products and biologically active compounds.[5] They are also useful intermediates in organic transformations.[6] Herein, the results of this study are reported.

Initially, we conducted a reaction on allenamide **1b** using the standard conditions developed in our group {[$Rh(CO)_2Cl]_2$ (10 mol%), toluene, r.t., argon atmosphere} and in 30 minutes, enamide **2b** was obtained in 79% yield (Scheme 1). Encouraged by the successful cycloisomerization reaction of the allenamide **1b**, a variety of alkynyl allenamides were prepared to further explore the scope and limitations of this reaction.

A variety of alkyne-substituted carbamates were prepared using the protocols depicted in Scheme 2 and Scheme 3. The alkynes were installed by first alkylating the protected methyl ester of glycine **3**[7] with **4a**,**b** or **5b**,**c** to give **6a**,**b** and **7b**,**c**. Next the protecting group was removed from the amine using 1 N HCl, then the methyl ester was reduced to a hydroxyl group. Reaction of the resulting amino alcohol with triphosgene[8] afforded compounds **8a**,**b** and **9a**,**b** in 26–70% yield for the four steps. Finally, the terminus of the alkyne was further functionalized with trimethylsilyl, phenyl, and methoxyphenyl groups to give **8c**, **9c**, **8d** and **9d**, respectively.

Propargylic carbamates were prepared from Garner's aldehyde **10**.[9] Reacting **10** with dimethyl-1-diazo-2-oxopropylphosphonate (Seyferth reagent)[10] under basic conditions gave alkyne **11a** in 61% yield.[11] Compound **11a** was converted to **11b** in nearly quantitative yield by using *n*-BuLi and methyl iodide. Carbamates **12a** and **12b** were obtained by treatment of **11a** and **11b** with trifluoroacetic acid in MeOH followed by ring closure in the presence of triphosgene. The terminus of the alkyne was further functionalized with a trimethylsilyl and phenyl group to give **12c** and **12d** in 90% and 72% yield, respectively.

With carbamates **8a–d**, **9a–d**, and **12a–d** in hand, the coupling reaction with the allenyl halides was examined.[12] After some experimentation, it was determined that a slight modification to the Hsung protocol [copper thiophene-2-carboxylate (CuTC), *N*,*N*-dimethylethylenediamine (DMEDA), Cs_2O_3, BaO, and allenyl iodide at 50 °C] worked best for the preparation of allenamides.[13,14] The results of this study are reported in Tables 1 and 2. Reaction of the carbamate **12a** with allene **13b** using the modified Hsung coupling protocol (BaO was added as an acid scavenger), afforded none of the allenamide **14a**, instead only a trace amount of triene **15a** was isolated. The terminal alkyne was assumed to be a complicating factor in this reaction and as predicted, the reaction of carbamate **12b** (R = Me) under identical conditions gave allenamide **14b** in 52% yield (Table 1, entry 2). Interestingly, reaction of carbamate **12c** and **12d** with allene **13b** gave only trienes **15c** and **15d** in 52% and 53% yield, respectively (entries 3, 4). However, carbamate **12c**, possessing a TMS group on the terminus of the alkyne, underwent the cou-

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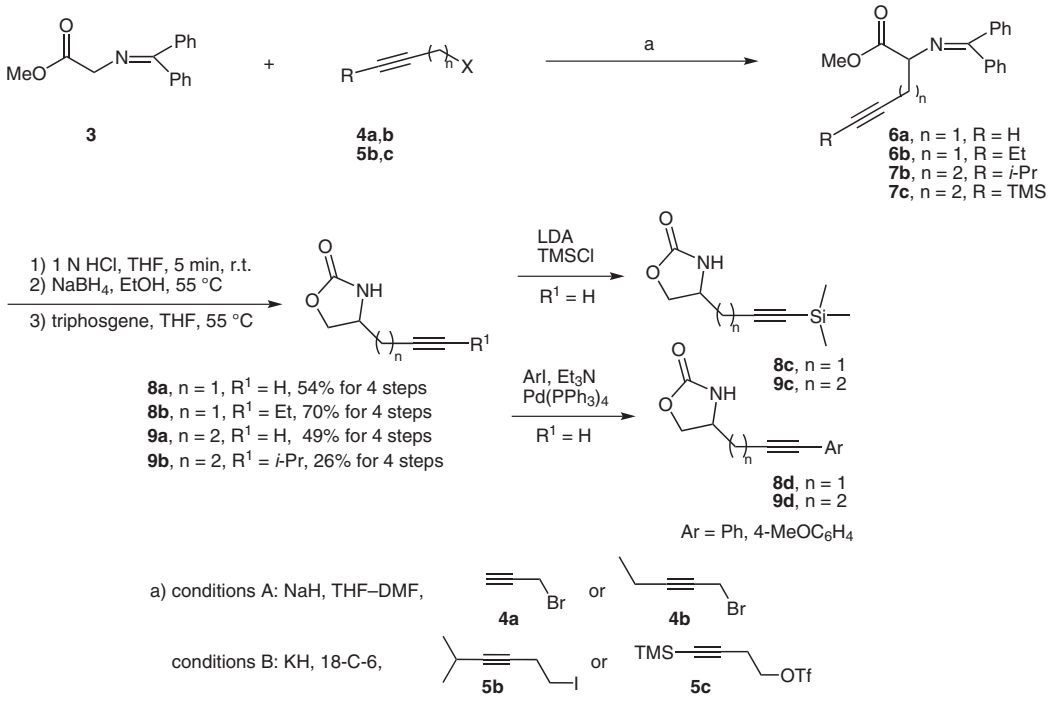
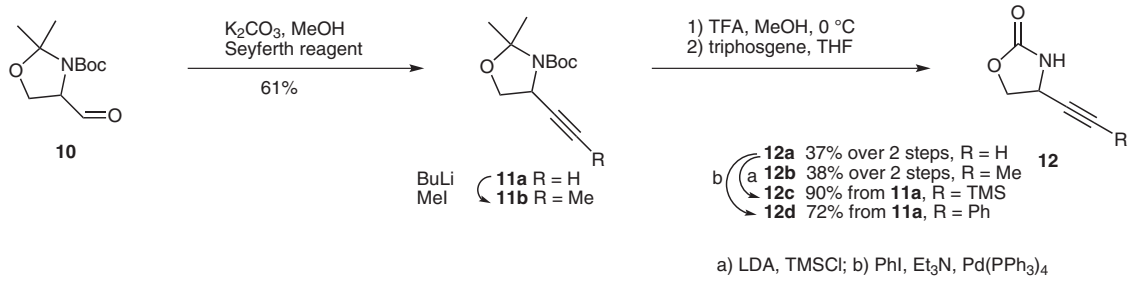


Scheme 2



Scheme 3

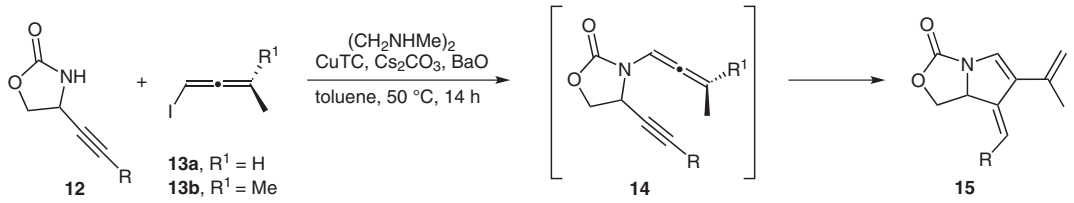
pling reaction with the less sterically encumbered allene **13a**, to give the allenamide **14e** in 56% yield (entry 5). These results suggest that complication can be partially attributed to the reactivity of the intermediate allenamide towards carbocyclization and the instability of the resulting trienes. Triene **15c** was not stable enough to obtain a ^{13}C NMR spectrum and **15d** decomposed upon storage overnight in the freezer. A control experiment was performed where **14d** was isolated and heated in toluene at 40 °C to give triene **15d**, suggesting that triene formation is a thermal process.

We turned to alkynes possessing one methylene unit between the alkyne and the carbamate moiety (Table 2). This series of substrates proved to be more tolerant of these coupling conditions, evidenced by terminal alkynes giving moderate yields of allenamides (entries 1 and 5). Carbamate **8c**, possessing an internal alkyne substituted with a trimethylsilyl group gave an 88% yield of allenamide **1c** (entry 3). Substitution of the alkyne with an ethyl group and an aryl group (4-$MeOC_6H_4$) gave allenamides **1b**[15] and **1d** in 79% and 35% yield, respectively (entries 2 and 4). Allenamide formation with the less sterically encumbered allene (**13a**) gave good yields of allenamide **1f–h** (entries 5–8). Also the carbamate **8b** underwent the coupling reaction with the electron-deficient allenyl iodide **13c**, to form the desired product, albeit in low yield (entry 9). This is the first example of coupling reaction between a carbamate and an electron-deficient allenyl iodide partner. The allenamides (**1e–i**) were isolated as a mixture of diastereomers (about 1:1).

The allenamide forming protocol was tested on a series of carbamates **9a–d** possessing two methylene units between the alkyne and the carbamate (Table 3). Surprisingly, the yield for the silyl-substituted alkynes (entries 2 and 5) were typically lower than that for terminal alkyne (entry 3) or alkynes substituted with alkyl (entries 1 and 4).

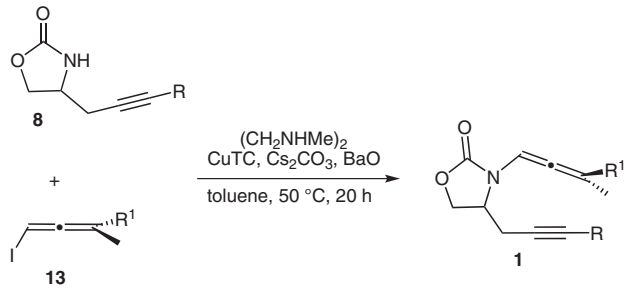
Each of the allenamides was subjected to the rhodium(I)-catalyzed Alder-ene reaction conditions developed in our lab {$[Rh(CO)_2Cl]_2$ (10 mol%) in toluene, under an argon atmosphere at r.t.}.[2] Exposure of allenamide **14b** to these conditions gave the triene **15b**[16] in 72% after 3.5 hours (Table 4, entry 1). Unfortunately, this triene is not stable

Table 1 Formation of Allenamides **14b**,**e** and Trienes



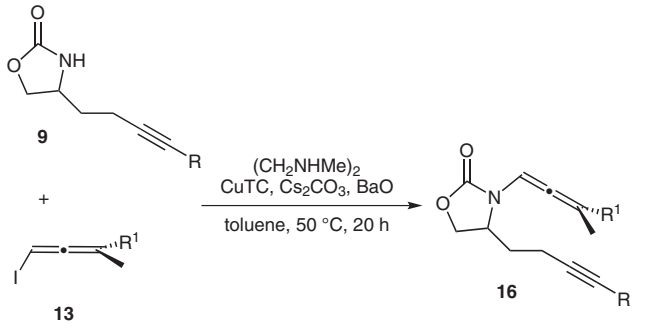
Entry	Carbamate	Allene	14	Yield (%)	15	Yield (%)
1	**12a** R = H	**13b** R^1 = Me	**14a**	–	**15a**	trace
2	**12b** R = Me	**13b** R^1 = Me	**14b**	52	–	–
3	**12c** R = TMS	**13b** R^1 = Me	**14c**	–	**15c**	52
4	**12d** R = Ph	**13b** R^1 = Me	**14d**	–	**15d**	53
5	**12c** R = TMS	**13a** R^1 = H	**14e**	56	–	–

Table 2 Copper-Catalyzed Coupling to Form Allenamides **1a–i**



Entry	Carbamate	Allene	1	Yield (%)
1	**8a** R = H	**13b** R^1 = Me	**1a**	40
2	**8b** R = Et	**13b** R^1 = Me	**1b**	79
3	**8c** R = TMS	**13b** R^1 = Me	**1c**	88
4	**8d** R = 4-$MeOC_6H_4$	**13b** R^1 = Me	**1d**	35
5	**8a** R = H	**13a** R^1 = H	**1e**	40
6	**8b** R = Et	**13a** R^1 = H	**1f**	59
7	**8c** R = TMS	**13a** R^1 = H	**1g**	86
8	**8d** R = 4-$MeOC_6H_4$	**13a** R^1 = H	**1h**	68
9	**8b** R = Et	**13c** R^1 = CO_2Me	**1i**	13

Table 3 Copper-Catalyzed Coupling to Form Allenamides **16a–f**



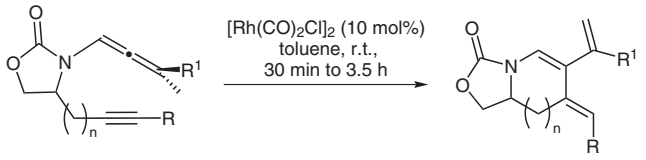
Entry	Carbamate	Allene	16	Yield (%)
1	**9b** R = *i*-Pr	**13b** R^1 = Me	**16a**	70
2	**9c** R = TMS	**13b** R^1 = Me	**16b**	40
3	**9a** R = H	**13a** R^1 = H	**16c**	59
4	**9b** R = *i*-Pr	**13a** R^1 = H	**16d**	66
5	**9c** R = TMS	**13a** R^1 = H	**16e**	32
6	**9d** R = Ph	**13a** R^1 = H	**16f**	30

and can only be stored at room temperature for 2–3 hours. Reaction of allenamide **14e** under these conditions gave a mixture of unidentifiable compounds (Table 4, entry 2).

Next, the cycloisomerization reaction of the allenamides **1a–i** was investigated. To our delight, each one of these substrates underwent an allenic Alder-ene reaction to afford the trienes in high yields (Table 4, entries 3–11). The mechanism for the formation of trienes **15** and **2** involves coordination of rhodium to the allenamides **14** and **1** to form the rhodium-metallocycle intermediate. β-Hydride elimination of the intermediate rhodium metallocycle followed by reductive elimination of a metallo-hydride species to give trienes **15** and **2**.[2a] Interestingly, the electron-deficient alkynoate **1i** underwent the Alder-ene reaction smoothly to give the desired triene **2i** in 85% yield (Table 4, entry 11). The presence of the ester can help to differentiate the reactivity of the double bonds of the triene. Furthermore, there is no different cycloisomerization rate observed between the diastereosiomers of allenamides **1e–i**.

Cycloisomerization of allenamides **16a–f** was examined (Table 5). Attempts to effect the cycloisomerization on trisubstitued allenamides **16a** and **16b** afforded trace quantities of a product resulting from an isomerization of the allene to a 1,3-diene along with small amount of cycloisomerization product **17** and cyclocarbonylation prod-

Table 4 Rhodium(I)-Catalyzed Alder-Ene Reaction of Allenamides to Form Five- and Six-Membered Trienes

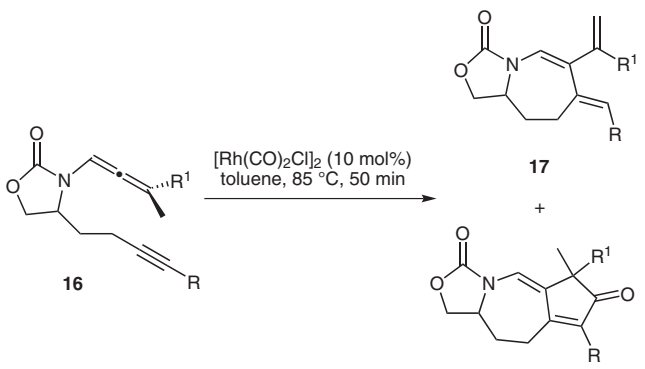


14b,**e**, n = 0
1a–**i**, n = 1

15b,**e**, n = 0
2a–**i**, n = 1

Entry	Allenamide	Triene	Yield (%)
1	**14b** R = Me, R^1 = Me, n = 0	**15b**	72
2	**14e** R = TMS, R^1 = Me, n = 0	**15e**	–
3	**1a** R = H, R^1 = Me, n = 1	**2a**	79
4	**1b** R = Et, R^1 = Me, n = 1	**2b**	79
5	**1c** R = TMS, R^1 = Me, n = 1	**2c**	95
6	**1d** R = 4-$MeOC_6H_4$, R^1 = Me, n = 1	**2d**	87
7	**1e** R = H, R^1 = H, n = 1	**2e**	68
8	**1f** R = Et, R^1 = H, n = 1	**2f**	71
9	**1g** R = TMS, R^1 = H, n = 1	**2g**	90
10	**1h** R = 4-$MeOC_6H_4$, R^1 = H, n = 1	**2h**	73
11	**1i** R = Et, R^1 = CO_2Me, n = 1	**2i**	85

Table 5 Rhodium(I)-Catalyzed Cyclizations of **16a**–**f** to Form Seven-Membered Rings



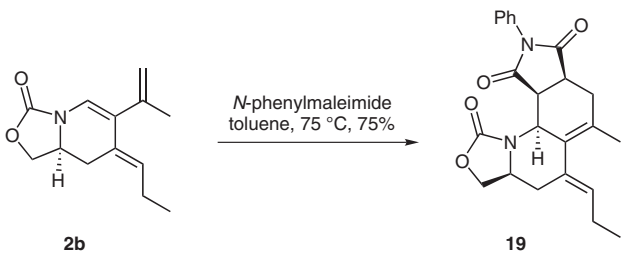
Entry	Allenamide	Atmosphere	Product	Yield (%)	dr
1	**16a** R = *i*-Pr, R^1 = Me	Ar	–[a]	–	–
2	**16b** R = TMS, R^1 = Me	Ar	–[a]	–	–
3	**16c** R = H, R^1 = H	Ar	**17a**	12	–
4	**16d** R = *i*-Pr, R^1 = H	Ar	**18a**	35	–
5	**16d** R = *i*-Pr, R^1 = H	CO	**18a**	75	3:1
6	**16e** R = TMS, R^1 = H	CO	**18b**	89	3:1
7	**16f** R = Ph, R^1 = H	CO	**18c**	75	3.6:1

[a] Isomerization of allene to 1,3-diene observed by crude ^{1}H NMR.

uct **18** (Table 5, entries 1 and 2). For the disubstituted allenamide **16c**, possessing a terminal alkyne, Alder-ene product **17a**[17] formed under cycloisomerization conditions, albeit in 12% yield (Table 5, entry 3). However, subjecting allenamide **16d** to the Alder-ene conditions afforded cyclocarbonylation product **18a** in 35% yield, but no Alder-ene product was observed (Table 5, entry 4). Changing the atmosphere from argon to carbon monoxide gave **18a** in 75% yield[18] (Table 5, entry 5). This Pauson–Khand-type reaction of allenamides to form bicyclo[4.3.0]nonadecadienones has also been reported by Hsung and co-workers.[19] Replacement of isopropyl group on the terminus of alkyne with trimethylsilyl or phenyl group gave **18b** and **18c** in 89% and 75% yield, respectively, as a mixture of diastereomers (Table 5, entries 6 and 7). The cyclocarbonylation products **18a**–**c** have diastereomeric ratios ranging from 3:1 to 3.6:1 and the starting allenamides **16d**–**f** have diastereomeric ratios ranging from 1:1 to 1.5:1. It is not known at this time whether the epimerization occurs during the cyclocarbonylation process or after the formation of products. It seems that the substitution pattern on the alkyne moiety of the disubstituted allenamide plays an important role. For the substituted alkyne, CO insertion is faster than β-H elimination affording the cyclocarbonylation products **18a**–**c**. However, for the terminal alkyne, β-H elimination is faster than CO insertion affording enamide triene **17a** as the only product.

Reactions involving the trienes were briefly examined. Triene **2b** underwent Diels–Alder reaction with *N*-phenylmaleimide to give the tetracyclic compound **19**[20] as a single diastereomer (Scheme 4). The stereochemistry was confirmed by X-ray crystallographic analysis.

In summary, a series of alkyne allenamides were prepared via a copper-catalyzed coupling reaction between carbamates and allenyl iodides. Allenic cycloisomerization reactions of the corresponding alkyne allenamides proceeded smoothly to give triene-containing enamides when embedded in a six-membered ring. Cycloisomerization reactions producing trienes as part of a five-membered ring were too reactive and decomposed upon short-term storage. For cycloisomerization reactions involving the formation of enamides embedded in a seven-membered ring, competing isomerization and cyclocarbonylation process-



Scheme 4

es were observed. The synthetic utility of these enamide-containing trienes has briefly been investigated and preliminary studies demonstrated chemo- and stereoselectivity in a Diels–Alder reaction.

References and Notes

(1) For a recent review, see: Brummond, K. M.; Loyer-Drew, J. A. *C–C Bond Formation (Part 1) by Addition Reactions: Alder-Ene Reaction,* In *Comprehensive Organometallic Chemistry III*, Vol. 10; Crabtree, R. H.; Mingos, M. P.; Ojima, I., Eds.; Elsevier: Oxford, **2007**, Chap. 10.12.

(2) (a) Brummond, K. M.; Chen, H.; Sill, P.; You, L. *J. Am. Chem. Soc.* **2002**, *124*, 15186. (b) Brummond, K. M.; Mitasev, B. *Org. Lett.* **2004**, *6*, 2245. (c) Subsequently a similar finding was reported: Shibata, T.; Takesue, Y.; Kadowaki, S.; Takagi, K. *Synlett* **2003**, 268.

(3) For example, see: (a) Brummond, K. M.; You, L. *Tetrahedron* **2005**, *61*, 6180. (b) Mitasev, B.; Yan, B.; Brummond, K. M. *Heterocycles* **2006**, *70*, 367; and references cited therein.

(4) For an enamide cycloisomerization, see: (a) Trost, B. M.; Pedregal, C. *J. Am. Chem. Soc.* **1992**, *114*, 7292. (b) Arisawa, M.; Terada, Y.; Theeraladanon, C.; Takahashi, K.; Nakagawa, M.; Nishida, A. *J. Organomet. Chem.* **2005**, *690*, 5398.

(5) For preparation of cyclic enamides and natural products containing cyclic enamides, see: (a) Kinderman, S. S.; Maarseveen, J. H. V.; Schoemaker, H. E.; Hiemstra, H.; Rutjes, F. P. J. T. *Org. Lett.* **2001**, *3*, 2045. (b) Klapars, A.; Campos, K. R.; Chen, C.-Y.; Volante, R. P. *Org. Lett.* **2005**, *7*, 1185. (c) Zhang, X.; Zhang, Y.; Huang, J.; Hsung, R. P.; Kurtz, K. C. M.; Oppenheimer, J.; Petersen, M. E.; Sagamanova, I. K.; Shen, L.; Tracey, M. R. *J. Org. Chem.* **2006**, *71*, 4170. (d) Toumi, M.; Couty, F.; Evano, G. *Angew. Chem Int. Ed.* **2007**, *46*, 572. (e) Yet, L. *Chem. Rev.* **2003**, *103*, 4283; and references cited therein.

(6) For an example, see: Zhang, W.; Zhang, X. *Angew. Chem. Int. Ed.* **2006**, *45*, 5515.

(7) O'Donnell, M. J.; Plot, R. L. *J. Org. Chem.* **1982**, *47*, 2663.

(8) Ni, Y.; Amarasinghe, K. K. D.; Ksebati, B.; Montgomery, J. *Org. Lett.* **2003**, *5*, 3771.

(9) (a) Garner, P.; Park, J. M. *J. Org. Chem.* **1987**, *52*, 2361. (b) Koskinen, A. M. P.; Otsomaa, L. A. *Tetrahedron* **1997**, *53*, 6473. (c) Roush, W. R.; Hunt, J. A. *J. Org. Chem.* **1995**, *60*, 798.

(10) (a) Seyferth, D.; Marbor, R. S.; Hilbert, P. *J. Org. Chem.* **1971**, *36*, 1379. (b) Ohira, S. *Synth. Commun.* **1989**, *19*, 561.

(11) (a) Crisp, G. T.; Jiang, Y.-L.; Pullman, P. J.; Savi, C. D. *Tetrahedron* **1997**, *53*, 17489. (b) Meffre, P.; Gauzy, L.; Branquet, E.; Durand, P.; Goffic, F. L. *Tetrahedron* **1996**, *52*, 11215. (c) Meffre, P.; Gauzy, L.; Perdigues, C.; Desanges-Levecque, F.; Branquet, E.; Durand, P.; Goffic, F. L. *Tetrahedron Lett.* **1995**, *36*, 877.

(12) Trost, B. M.; Stiles, D. T. *Org. Lett.* **2005**, *7*, 2117.

(13) Shen, L.; Hsung, R. P.; Zhang, Y.; Antoline, J. E.; Zhang, X. *Org. Lett.* **2005**, *7*, 3081.

(14) For a recent review, see: Wei, L.-L.; Xiong, H.; Hsung, R. P. *Acc. Chem. Res.* **2003**, *36*, 773; and references cited therein.

(15) **General Procedure for the Copper-Catalyzed Coupling Protocol to Prepare an Allenamide – Preparation of 3-(3-Methylbuta-1,2-dienyl)-4-(pent-2-ynyl)oxazolidin-2-one (1b)**
A flame-dried 25 mL round-bottom flask was charged with oxazolidinone **8b** (0.321 g, 2.10 mmol), copper(I) thiophene-2-carboxylate (CuTC, 0.040 g, 0.21 mmol), BaO (0.643 g, 4.20 mmol), and Cs_2CO_3 (1.367 g, 4.20 mmol). After flushing with nitrogen, toluene (15 mL) was added, followed by DMEDA (45 μL, 0.42 mmol), then 1-iodo-3-methylbuta-1,2-diene (500 μL, 4.20 mmol). The flask was covered with aluminum foil and heated at 50 °C for 20 h. The reaction was then cooled to r.t., filtered through a short pad of Celite, and concentrated in vacuo. The residue was purified by column chromatography [SiO_2, eluting with 95% to hexanes–EtOAc (1:1), 5% Et_3N] to afford the allenamide **1b** (0.363 g, 79%) as a pale yellow oil.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.57 (sept, *J* = 2.6 Hz, 1 H), 4.43 (app t, *J* = 8.7 Hz, 1 H), 4.32 (dd, *J* = 8.8, 4.3 Hz, 1 H), 3.97–3.90 (m, 1 H), 2.54–2.47 (m, 2 H), 2.20–2.11 (m, 2 H), 1.83 (d, *J* = 2.6 Hz, 3 H), 1.80 (d, *J* = 2.6 Hz, 3 H), 1.12 (t, *J* = 7.5 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 191.5, 155.5, 108.9, 93.0, 85.3, 72.8, 67.1, 53.8, 22.3, 22.0, 21.8, 14.2, 12.5. IR (neat): 1968, 1757 cm^{-1}. MS: *m/z* (%) = 220 (10), 219 (50), 204 (31), 190 (68), 152 (88), 108 (87), 81 (100), 67 (92). HRMS (EI): *m/z* calcd for $C_{13}H_{17}NO_2$ [M$^+$]: 219.1259; found: 219.1259.

(16) **General Procedure for the Alder-ene Reaction – Preparation of (7*Z*)-7-Ethylidene-7,7a-dihydro-6-(prop-1-en-2-yl)pyrrolo[1,2-*c*]oxazol-3(1*H*)-one (15b)**
To a flame-dried test tube equipped with a magnetic stirring bar was added allenamide **14b** (0.022 g, 0.12 mmol). The test tube was evacuated and charged with nitrogen (3×). Then, toluene (4.4 mL) was added followed by addition of $[Rh(CO)_2Cl]_2$ (0.002 g, 0.01 mmol). The reaction mixture was stirred at r.t. for 3.5 h and upon completion, the light yellow-brown solution was chromatographed [SiO_2, hexanes–EtOAc (4:1)] to give the desired cross-conjugated triene **15b** (0.016 g, 72% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.67 (s, 1 H), 5.76 (qd, *J* = 7.2, 3.1 Hz, 1 H), 5.21–5.11 (m, 3 H), 4.84 (app t, *J* = 8.5 Hz, 1 H), 4.24 (app t, *J* = 8.7 Hz, 1 H), 1.93 (s, 3 H), 1.68 (dd, *J* = 7.1, 1.8 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.4, 140.1, 135.8, 130.3 130.0, 116.5, 115.0, 70.7, 61.6, 23.3, 16.0. IR (neat): 1772 cm^{-1}. MS: *m/z* (%) = 191 (30), 146 (46), 132 (61), 117 (47), 91 (36), 86 (64), 84 (100). HRMS (EI): *m/z* calcd for $C_{11}H_{13}NO_2$ [M$^+$]: 191.0946; found: 191.0952.

(17) **(*Z*)-7,8,9,9a-Tetrahydro-7-methylene-6-vinyl-oxazolo[3,4-*a*]azepin-3-(1*H*)-one (17a)**
Following the general procedure for the Alder-ene reaction, **17a** was obtained in 12% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.62 (s, 1 H), 6.32 (dd, *J* = 17.1, 10.6 Hz, 1 H), 5.33 (dd, *J* = 17.1, 1.4 Hz, 1 H), 5.24 (br s, 1 H), 5.06 (dd, *J* = 10.6, 1.4 Hz, 1 H), 5.06 (s, 1 H), 5.05 (s, 1 H), 4.50 (app t, *J* = 8.4 Hz, 1 H), 4.20–4.10 (m, 1 H), 3.94 (app t, *J* = 8.4 Hz, 1 H), 2.71–2.65 (m, 1 H), 2.38–2.29 (m, 1 H), 2.16–2.08 (m, 1 H), 1.88–1.77 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.4, 142.0, 136.5, 126.3, 123.7, 117.9, 114.4, 68.4, 56.9, 35.1, 34.1. IR (neat): 1755, 1640 cm^{-1}. MS: *m/z* (%) = 191 (87), 176 (46), 158 (54), 157 (30), 129 (45), 105 (100), 104 (42). HRMS (EI): *m/z* calcd for $C_{11}H_{13}NO_2$ [M$^+$]: 191.0946; found: 191.0947.

(18) **General Procedure for the Pauson–Khand Reaction – Preparation of Enone 18a**
To a flame-dried test tube equipped with a magnetic stirring bar was added allenamide **16d** (0.009 g, 0.04 mmol). The test tube was evacuated and charged with carbon monoxide (3×), then toluene (5.2 mL) was added followed by $[Rh(CO)_2Cl]_2$ (0.002 g, 0.004 mmol). The reaction mixture was heated at 85 °C for 1 h. Upon completion of the reaction (TLC), the mixture was cooled to r.t. and chromatographed [SiO_2, hexanes–EtOAc (1:1)] to give **18a** as an oil (dr, 3:1, 0.008 g, 75% yield).
Major diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.68

(s, 1 H), 4.60 (app t, *J* = 8.3 Hz, 1 H), 4.19–4.09 (m, 1 H), 3.96 (dd, *J* = 10.0, 8.5 Hz, 1 H), 3.25 (dt, *J* = 18.4, 3.2 Hz, 1 H), 2.86–2.76 (m, 2 H), 2.61 (ddd, *J* = 17.1, 12.8, 3.5 Hz, 1 H), 2.09 (dt, *J* = 14.1, 4.0 Hz, 1 H), 2.00–1.86 (m, 1 H), 1.24 (d, *J* = 7.2 Hz, 6 H), 1.20 (d, *J* = 6.9 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 206.6, 159.8, 155.2, 146.5, 123.0, 117.8, 67.6, 58.6, 44.6, 29.2, 28.4, 25.7, 20.3, 20.1, 16.0. IR (neat): 1760, 1682, 1651 cm^{-1}. MS: *m/z* (%) = 261 (62), 246 (100), 232 (16), 218 (47), 174 (6). HRMS (EI): *m/z* calcd for $C_{15}H_{19}NO_3$ [M$^+$]: 261.1365; found: 261.1361.

(19) Xiong, H.; Hsung, R. P.; Wei, L.-L.; Berry, C. R.; Mulder, J. A.; Stockwell, B. *Org. Lett.* **2000**, *2*, 2869.

(20) **Diels–Alder Reaction – Preparation of Tetracyclic Compound 19**

To a solution of triene **2b** (0.006 g, 0.03 mmol) in toluene (0.5 mL) was added *N*-phenylmaleimide (0.005 g, 0.03 mmol). The reaction mixture was heated at 75 °C for 5 h then, after cooling to r.t. was chromatographed [SiO_2, hexanes–EtOAc, (1:1)] to give the product **19** as a white solid (0.008 g, 75% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.46–7.34 (m, 3 H), 7.11–7.08 (m, 2 H), 5.49 (t, *J* = 7.5 Hz, 1 H), 4.60 (dd, *J* = 9.0, 5.8 Hz, 1 H), 4.40 (t, *J* = 7.4 Hz, 1 H), 4.35–4.34 (m, 1 H), 4.11 (dd, *J* = 11.5, 7.8 Hz, 1 H), 3.95–3.84 (m, 1 H), 3.27 (ddd, *J* = 8.9, 7.1, 1.7 Hz, 1 H), 2.77 (dd, *J* = 14.5, 1.7 Hz, 1 H), 2.69 (dd, *J* = 12.7, 3.2 Hz, 1 H), 2.40–2.32 (m, 1 H), 2.17–2.07 (m, 2 H), 2.02 (s, 3 H), 1.87 (t, *J* = 12.3 Hz, 1 H), 1.00 (t, *J* = 7.5 Hz, 3 H). ^{13}C NMR (75 MHz, CD_2Cl_2): δ = 178.5, 176.7, 157.4, 134.8, 132.5, 130.4, 130.2, 129.3, 128.9, 128.6, 127.1, 69.6, 57.0, 52.8, 40.1, 39.3, 32.3, 28.9, 22.6, 21.7, 14.3. IR (neat): 1746, 1706 cm^{-1}. MS: *m/z* (%) = 393 (40), 392 (100), 377 (10), 333 (17), 219 (31), 190 (90), 91 (45). HRMS (EI): *m/z* calcd for $C_{23}H_{24}N_2O_4$ [M$^+$]: 392.1736; found: 392.1719.