ORGANIC LETTERS

2004
Vol. 6, No. 13
2245−2248

Allenes and Transition Metals: A Diverging Approach to Heterocycles

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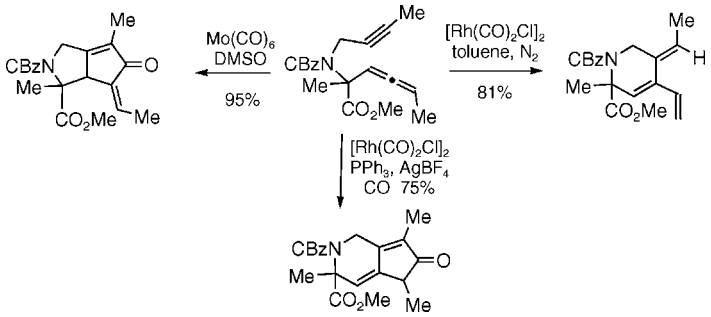
Received April 26, 2004

ABSTRACT

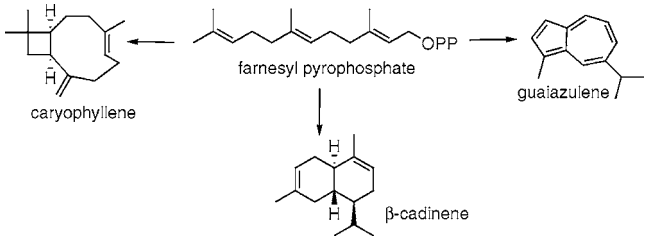


An alkynyl allene has been converted to heterocycles possessing an α-alkylidene cyclopentenone, a 4-alkylidene cyclopentenone, or a cross-conjugated triene. Thus, a common intermediate has been converted to three structurally unique compounds by changing only the reaction conditions and, therefore, controlling various reaction pathways.

Diversity-oriented synthesis (DOS) is a recognized tactic for synthesizing pools of new small molecules that will impact research, either as biological tools or pharmacological agents.[1] The DOS approach used most frequently involves sequential reactions where groups, structural and/or functional, are incorporated into the products, thereby generating diversity. An alternative and less common approach involves the construction of a pivotal compound that, when subjected to the appropriate reagents or catalysts, can give structurally distinct products. Nature has made extensive use of this latter diversification strategy, for example, enzyme-catalyzed construction of the various sesquiterpene carbon skeletons of secondary metabolites from one common precursor, farnesyl pyrophosphate (Scheme 1).

Recently, investigations aimed at increasing the scope of the allenic Pauson−Khand reaction have led to an interesting regiocontrol element that results in compounds not easily accessible using existing protocols. For example, treatment of an alkynyl allene with molybdenum hexacarbonyl results in a selective reaction with the internal double bond of the allene in most cases (pathway a, Scheme 2).[2] The same

Scheme 1. Nature's Construction of Secondary Metabolites



alkynyl allene, when subjected to rhodium biscarbonyl chloride dimer [$(Rh(CO)_2Cl)_2$] results in a selective reaction with the distal double bond of the allene (pathway b).[3] This unusual regiocontrol element has subsequently been applied

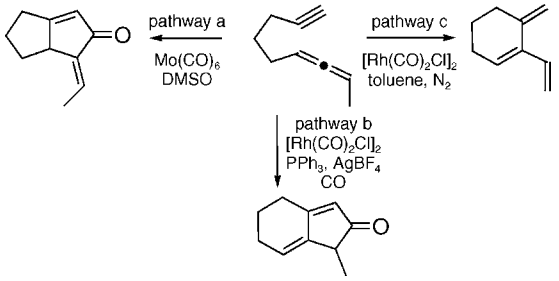
(1) Burke, M. D.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 46−58.

(2) In some cases, a steric bias can direct the reaction toward the other double bond. (a) Kent, J. L.; Wan, H.; Brummond, K. M. *Tetrahedron Lett.* **1995**, *36*, 2407. (b) Brummond, K. M.; Wan, H. *Tetrahedron Lett.* **1998**, *39*, 931. (c) Brummond, K. M.; Wan, H.; Kent, J. L. *J. Org. Chem.* **1998**, *63*, 6535. (d) Brummond, K. M. In *Advances in Cycloaddition*; Harmata, M., Ed.; JAI Press, Inc.; Stamford, CT, 1999; Vol. 6, p 211. (e) Brummond, K. M.; Lu, J. *J. Am. Chem. Soc.* **1999**, *121*, 5087. (f) Brummond, K. M.; Lu, J.; Petersen, J. L. *J. Am. Chem. Soc.* **2000**, *122*, 4915. Brummond, K. M.; Sill, P.; Rickards, B.; Geib, S. J. *Tetrahedron Lett.* **2002**, *43*, 3735.

10.1021/ol0492391 CCC: $27.50
Published on Web 06/04/2004

to other carbocyclization reactions. For example, if an argon or nitrogen atmosphere is used instead of carbon monoxide during the Rh(I)-catalyzed reaction of an alkynyl allene, high yields of cross-conjugated trienes are afforded via a postulated oxidative addition/β-hydride elimination/reductive elimination sequence (pathway c).[4] The facility of this latter reaction prompted us to consider an analogous reaction with an alkene group instead of an alkyne and a tether containing a nitrogen or an oxygen atom, which afforded azepines and oxepines, respectively, in good yields.[5]

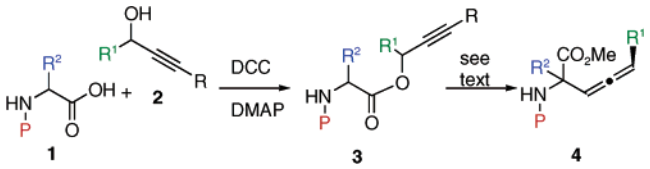
Scheme 2. Diverging Reaction Pathways



We believe that these discoveries are ideally suited for the preparation of small-molecule libraries, because in principle, one compound can be converted to *at least* three structurally unique scaffolds, an α-alkylidene cyclopentenone, a 4-alkylidene cyclopentenone, and a cross-conjugated triene. Moreover, transition metals are used extensively in the preparation of libraries of compounds; however, very few protocols utilize cycloisomerization processes. The high substrate specificity exhibited by these metals can be a serious limitation given that, in some cases, changing a single substituent can turn a high-yielding process into one that does not proceed at all. Thus, we report our results regarding the scope and limitations of this transition metal-catalyzed diverging strategy.

Since a long-term goal of this approach is to prepare compounds that are biologically relevant, the incorporation of a larger number of heteroatoms in the carbocyclization substrate was essential. Thus, inclusion of an amino acid subunit between the alkyne and the allene appeared to be ideal for two reasons: (1) Bolton has used a similar strategy for the construction of Pauson−Khand and Heck reaction precursors[6] and (2) there are known protocols for the preparation of allenic amino acids. First we began by exploring the allenic amino acid protocols reported by Castehano and Krantz (method I)[7] and Kazmaier (method II)[8] for the preparation of **4** (Scheme 3). Both methods start

Scheme 3. Synthesis of Allenic Amino Acids



from the propargylic ester **3**, which is prepared by the condensation of a protected amino acid **1** and substituted propargyl alcohol **2** in yields ranging from 78 to 95%.[9] In addition, each method produces an allenic amino acid **4** via a Claisen rearrangement of compound **3**. The two methods differ only in the protecting groups on the amine and the conditions used to effect the Claisen rearrangement. Method I uses a dehydrating protocol (PPh_3, CCl_4, NEt_3) that requires that the amine be protected as a benzamide in order to generate the oxazolone intermediate required for the Claisen rearrangement. A shortcoming of this method is that the rearrangement proceeds with low diastereoselectivity (dr ~3:2). Method II utilizes a chelate-controlled ester-enolate Claisen rearrangement (LDA, $ZnCl_2$) to provide allene **4**. The advantages to this protocol are the range of amine protecting groups that are compatible with the Claisen rearrangement conditions (Cbz, Boc and Ts), and the reaction proceeds with excellent stereocontrol, showing a single diastereomer by ^{1}H NMR. However, this method required substituting the terminus of alkyne **2** with a trimethylsilyl group (R = TMS) since the Claisen rearrangement step was not tolerant of a terminal alkyne.[10] The synthesis of the target alkynyl allene **6** was then completed by N-alkylation of the N-protected allenic amino acid. Standard N-alkylation conditions were employed using NaH as a base and propargylic halides. The yields for the latter reaction and the substrates prepared are included in Table 1.

Target substrates (15) have been synthesized in an effort to establish the effect of substrate specificity on the course of these transition metal-catalyzed reactions. Diversity was incorporated into the amino acid portion of the molecules by using amino acids comprising three different classes: alanine (nonpolar aliphatic R^2 group, entries a−e, l−n), phenylalanine (aromatic R^2 group, entries f−k), or TBS-protected serine (polar uncharged R^2 group, entry o). The

(3) Brummond, K. M.; Chen, H.; Fisher, K. D.; Kerekes, A. D.; Rickards, B.; Sill, P. C.; Geib, S. J. *Org. Lett.* **2002**, 11, 1931. Brummond, K. M.; Gao, D. *Org. Lett.* **2003**, *5*, 3491. Anomalies have been observed, especially if a coordinating group resides near the proximal double bond of the allene, which then directs the reaction to that double bond (unpublished results from our group).

(4) Brummond, K. M.; Chen, H.; Sill, P.; You, L. *J. Am. Chem. Soc.* **2002**, *124*, 15186. Shibata subsequently reported a similar finding: Shibata, T.; Takesue, Y.; Kadowaki, S.; Takagi, K. *Synlett* **2003**, 268.

(5) For preliminary investigations, see: Brummond, K. M.; Chen, H.; Mitasev, B.; Casarez, A. D. *Org. Lett.* **2004**, *6*, 0000. Initial disclosure of this type of cyclization: *Abstracts of Papers*, 226th National Meeting of the American Chemical Society, New York, NY, Sept 7, 2003; American Chemical Society: Washington, DC, 2003. For related observations, see: Makino, T.; Itoh, K. *Tetrahedron Lett.* **2003**, *44*, 6335. Makino, T.; Itoh, K. *J. Org. Chem.* **2004**, *69*, 395.

(6) Bolton, G. L. *Tetrahedron Lett.* **1996**, *37*, 3433. Bolton, G. L.; Hodges, J. C.; Rubin, J. R. *Tetrahedron* **1997**, *53*, 6611. Bolton, G. L.; Hodges, J. C. *J. Comb. Chem.* **1999**, *1*, 130.

(7) Castelhano, A. L.; Pliura, D. H.; Taylor, G. J.; Hsieh, K. C.; Krantz, A. *J. Am. Chem. Soc.* **1984**, *106*, 2734. Castelhano, A. L.; Horne, S.; Taylor, G. J.; *Tetrahedron* **1988**, *44*, 5451.

(8) Kazmaier, U.; Gorbitz, C. H. *Synthesis* **1996**, 1489.

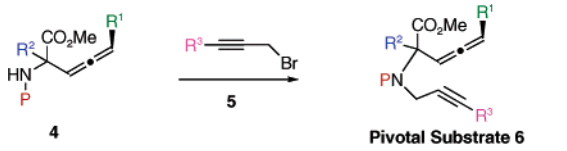
(9) See Supporting Information section for experimental/spectroscopic data for compounds that were not prepared by the authors in refs 7 and 8.

(10) Method II could be used to generate the allenic amino acids by increasing the equivalents of LDA (2.5 equiv instead of 1.2 equiv), but the product was formed as a 1:1 mixture of diastereomers. After the Claisen rearrangement, the silicon group was removed.

terminus of the alkyne (R^3) has been systematically varied to include H, alkyl, aryl, or silyl groups. For this initial study, the R^1 group on the allene terminus has only been varied slightly and is either an H or an alkyl group. The amine protecting group, while not considered to be a diversification element, is instead designed so that it is not limiting after carbocyclization (Cbz, Boc, and Bz).

The pivotal substrates **6a**−**o** were then systematically subjected to the transition metal-catalyzed reaction conditions enumerated in Scheme 2. Initially, the Alder-ene reaction was investigated. Treatment of a representative group of alkynyl allenes **6** with 5 mol % $[Rh(CO)_2Cl]_2$ in toluene at room temperature afforded the cross-conjugated trienes **7** in high yields (74−95%) in less than 10 min for each entry in Table 2 (entries a−j, o). This is a substantial rate increase

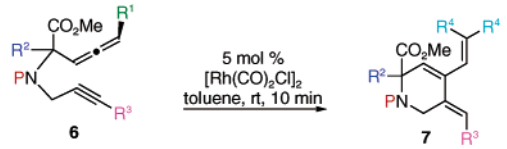
Table 1. Assembly of Alkynyl Allene **6**



entry	P	R^1	R^2	R^3	yield	entry	P	R^1	R^2	R^3	yield
a	CBz	Me	Me	H	77	i	Bz	Me	Bn	Ph	89
b	CBz	Me	Me	Me	84	j	Bz	H	Bn	Me	84
c	CBz	Me	Me	TMS	86	k	Bz	H	Bn	H	66
d	CBz	Me	Me	Ph	68	l	Bz	H	Me	Me	93
e	CBz	*i*-Pr	Me	Me	86	m	Bz	H	Me	H	94
f	Bz	Me	Bn	H	73	n	Boc	Me	Me	Me	64
g	Bz	Me	Bn	Me	83	o	Bz	Me	CH_2OR	Me	85
h	Bz	Me	Bn	TMS	75						

compared to those published previously (minutes vs hours). We attribute this in part to a Thorpe−Ingold effect arising from the carbomethoxy and alkyl/aryl functionality. Interestingly, these facile cyclizations did not require an inert atmosphere. All functional groups and substituents present in compound **6** were tolerant of the Alder-ene reaction conditions. Both *N*-benzoyl- (entries f−i, o) and carbamate-protected (entries a−e, n) substrates were tested with no apparent difference in the rate of the reaction. For the

Table 2. Formation of Cross-Conjugated Triene[a]



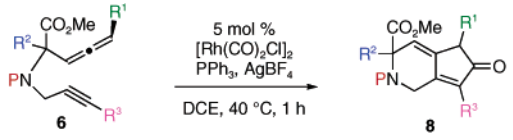
entry	P	R^1	R^2	R^3	R^4	Yield	entry	P	R^1	R^2	R^3	R^4	Yield
a	CBz	Me	Me	H	H	84%	f	Bz	Me	Bn	H	H	74%
b	CBz	Me	Me	Me	H	81%	g	Bz	Me	Bn	Me	H	80%
c	CBz	Me	Me	TMS	H	87%	h	Bz	Me	Bn	TMS	H	92%
d	CBz	Me	Me	Ph	H	95%	i	Bz	Me	Bn	Ph	H	81%
e	CBz	*i*-Pr	Me	Me	Me	95%	n	Boc	Me	Me	Me	H	79%
							o	Bz	Me	CH_2OR	Me	H	89%

[a] Entries j, k, l, and m cannot react to give triene **7**.

terminus of the alkyne (R^3), the reaction conditions were tolerant to a hydrogen (entries a, f), alkyl (entries b, e, g, n, o), TMS (entries c, h), or aryl groups (entries d, i). The only variations made so far on the terminus of the allene (R^1) are a methyl and an isopropyl group. A major reason for this is that the R^4 groups on the appending olefin are the same, and thus *E*/*Z* isomers are not an issue.[11]

Next, we examined these substrates in the Rh(I)-catalyzed Pauson−Khand reaction to form 4-alkylidene cyclopentenones. Previously, we had shown that by using rhodium biscarbonyl chloride dimer and simply changing the atmosphere to carbon monoxide, only CO insertion products were obtained without any of the cross-conjugated triene. However, due to the exceedingly fast rate of triene **7** formation for substrates **6**, trienes were the only products isolated even under a CO atmosphere, with CO only serving to slow the triene formation (1 h vs 10 min). Since it is postulated that the triene **7** and alkylidene **8** arise from the same rhodium metallocycle, it was hoped that by systematically changing the metal, ligands, metal counterion, and solvent, we could identify conditions for the desired CO insertion process. The best conditions were found to be 10 mol % rhodium biscarbonyl chloride dimer, 30 mol % triphenylphosphine, and 22 mol % silver tetrafluoroborate in dichloroethane at 40 °C. By using these newly developed conditions, alkynyl allene **6** was converted to 4-alkylidene cyclopentenone **8** selectively in good yields for all entries in Table 3 except

Table 3. Formation of 4-Alkylidene Cyclopentenones



entry[d]	P	R^1	R^2	R^3	yield	entry	P	R^1	R^2	R^3	yield
b	CBz	Me	Me	Me	75%	g	Bz	Me	Bn	Me	73%[b]
c	CBz	Me	Me	TMS	78%	h	Bz	Me	Bn	TMS	98%
d	CBz	Me	Me	Ph	75%	i	Bz	Me	Bn	Ph	74%[b]
e	CBz	*i*-Pr	Me	Me	74%	l	Bz	H	Me	Me	72%[a]
f	Bz	Me	Bn	H	0%	n	Boc	Me	Me	Me	73%[c]
						o	Bz	Me	CH_2OR	Me	81%

[a] Triene formation was not possible, so conditions used were 5 mol % $[Rh(CO)_2Cl]_2$, DCE, CO, rt, 2.5 h. [b] Diastereomeric ratio was 1.7:1. [c] Ratio of [6,5]:[5,5] CO insertion products was 5:1. [d] For entries 6a, f, k, and m, the reaction was not attempted since conditions are not compatable with a terminal alkyne; For entry 6j, the reaction was not attempted but should work based upon entry l.

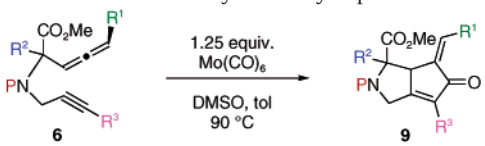
entry f, showing that these reaction conditions were not tolerant of a hydrogen atom on the terminus of the alkyne. All other changes to R^3 groups occurred without problems; i.e., R^3 = TMS (entries c, h), alkyl (entries b, e, g, l−o), and aryl (entries d, i). Both benzoyl and carbamate protecting groups and all three classes of amino acids were tolerated during this reaction.

Next, conversion of a subset of substrates **6** to α-alkylidene cyclopentenones **9** was accomplished by heating these

(11) *E*/*Z* selectivity of this double bond can be controlled using an Ir(I) catalyst (ref 4); however, a TMS group on the terminus of the alkyne is required, thus limiting the diversity of R^3.

allenynes with molybdenum hexacarbonyl and DMSO (Table 4). Unfortunately, a mixture of *E*/*Z* isomers of **9** were obtained for entries a, b, e, f−i, n, o. Changing the R^1 group on the terminus of the allene to a hydrogen solved this problem but led to the formation of both **8** and **9**, with **9** predominating (entries j−m). This increase in reaction with the distal double bond of the allene was attributed to the quaternary center next to the internal double bond by sterically directing the reaction to the more accessible olefin. This result is unique from our previously published examples, where none of the cases possessed a quaternary center vicinal to the allene. Finally, the low diastereoselectivities observed in the formation of the benzamide-protected allenic amino acids proved to be a serious problem. In some cases, the product mixtures obtained were so complex that they could not be separated (entries f, g, o). While these substrates give some of the highest yields observed to date for the molybdenum-mediated Pauson−Khand reaction, the low diastereoselectivities, the nonselective reaction with the double bonds of the allene, the mixture of *E*/*Z* isomers, and the use of stoichiometric molybdenum make this reaction pathway less than ideal for application to library synthesis in its present state of development.

Table 4. Formation of α-Alkylidene Cyclopentenones



entry[k]	P	R^1	R^2	R^3	Yield	entry	P	R^1	R^2	R^3	Yield
a	CBz	Me	Me	H	95%[c]	j	Bz	H	Bn	Me	79%[d]
b	CBz	Me	Me	Me	95%[a]	k	Bz	H	Bn	H	72%[e]
e	CBz	*i*-Pr	Me	Me	95%[b]	l	Bz	H	Me	Me	>95%[h]
f	Bz	Me	Bn	H	57%[f]	m	Bz	H	Me	H	>95%[g]
g	Bz	Me	Bn	Me	77%[f]	n	Boc	Me	Me	Me	90%[i]
i	Bz	Me	Bn	Ph	-- [j]	o	Bz	Me	CH_2OR	Me	95%[f]

[a] Mixture (20:1) of **9**:**8** gave a **9Z**:**9E** ratio of 7:1. [b] **9E**:**9Z** ratio was 6.4:1. [c] **9E**:**9Z** ratio was 7.6:1. [d] Mixture (5.7:1) of **9**:**8**; dr of **9** was 6.4:1. [e] Mixture (3:1) of **9**:**8**. [f] These entries afforded an inseparable mixture of diastereomers of **9Z**, **9E**, and **8**. [g] Mixture (14:1) of **9**:**8**; dr for **9** was 11:1. [h] Mixture (14:1) of **9**:**8**; dr for **9** was 10:1. [i] **9Z**:**9E** = 5:1. [j] For entries d and i, the reaction afforded a very complex mixture of products. For entries c and h, the reaction afforded a complex mixture of silylated and desilylated products.

In conclusion, by taking advantage of competing reaction pathways available via transition metal-catalyzed carbocyclization processes, we have shown the potential generality of converting a common intermediate to at least three structurally unique and heretofore unknown hetereocycles. Furthermore, as a result of this study, we have developed optimized conditions to control reaction pathway selectivity by changes to the transition metals. Finally, while the compounds generated thus far are new and will be tested for biological activity, it is the unique reactivity profile of each scaffold (α-alkylidene cyclopentenone, 4-alkylidene cyclopentenone, and cross-conjugated triene) and its potential to be differentially functionalized that are deemed to be the most useful feature of this approach.

Acknowledgment. We gratefully acknowledge the financial support provided by the National Institutes of Health (P50 GM067982), the University of Pittsburgh Center for Chemical Methodologies and Library Development, and Stefan Werner, from the Curran group, for providing compounds for entry n, Table 1, and entry j, Table 2.

Supporting Information Available: Characterization data and full experimental procedures for all compounds in Tables 1−4 except entry n, Table 1, and entry j, Table 2, which will be the topic of a future publication. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0492391