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On the Synthesis of Z-γ-Amino-α,β-unsaturated Esters via Ru-Catalyzed Coupling

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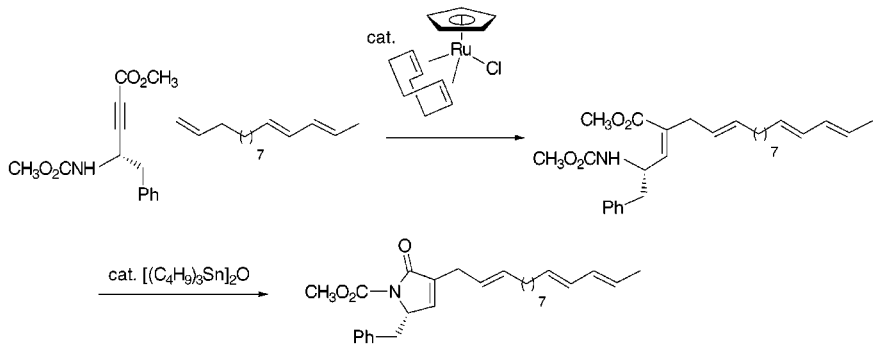
ABSTRACT



A synthesis of γ-amino acids and their cyclic derivatives, 3-pyrrolinones, from α-amino acids employs a ruthenium-catalyzed Alder ene reaction as a key step in the sequence. Cyclopentadienylruthenium (1,4-cyclooctadiene) chloride catalyzes the addition of γ-amido-α,β-alkynoate esters with monosubstituted alkenes. The major product arises from C−C bond formation at the α-carbon of the alkynoate. The reaction exhibits high chemoselectivity. The ruthenium-catalyzed addition occurs in preference to a Diels−Alder reaction. The two new double bonds are created with complete geometrical control. The initial γ-amido-α,β-unsaturated ester can be cyclized to the pyrrolinones with a tin catalyst.

The development of atom economical reactions provides an opportunity to maximize the use of raw materials and minimize waste.[1] The Alder ene reaction constitutes such a process. Except for a heteroatom version using carbonyl compounds as the enophile, the reaction has had little use synthetically, presumably because of poor scope and the rather extreme conditions needed.[2] Our discovery of a ruthenium-catalyzed reaction between an alkene and an alkyne begins to overcome these limitations.[3] Further, the ruthenium reaction also demonstrates unusual regioselectivity with alkynoates whereby C−C bond formation occurs preferentially at the α-carbon of the alkynoate, whereas the normal expectation for an Alder ene reaction would form this bond to the β-carbon.[4] In a program directed toward targets represented by the general structure A, e.g., an intermediate toward the cytochalasin family,[5] the question of the suitability of nitrogen-containing substrates such as B arises. The ease of poisoning the ruthenium catalyst by Lewis bases raises concerns about such reactants. In this paper, we record our preliminary observations that indicate their participation and a protocol for the synthesis of the 3-pyrrolin-2-ones. Since these products can derive from

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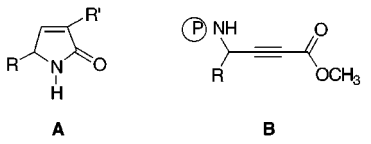
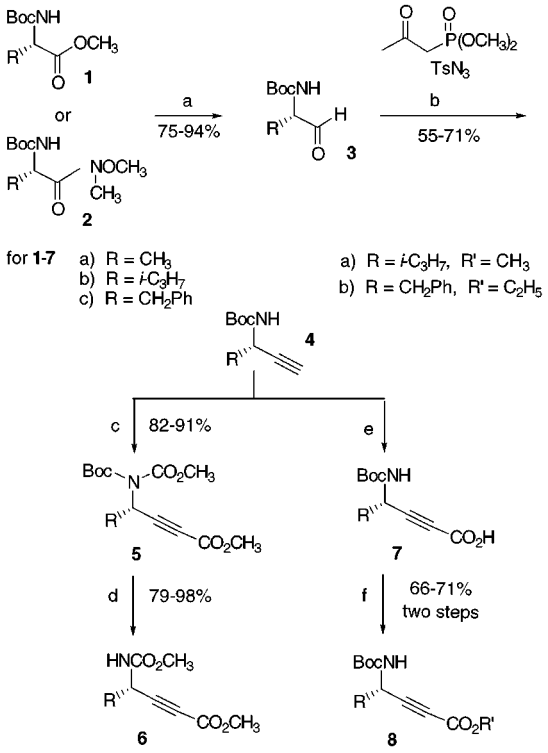
α-amino acids, this route can constitute an asymmetric synthesis of these targets.



A B

The substrates were available from the amino acids as outlined in Scheme 1. Reduction of either the methyl ester

Scheme 1. Synthesis of Substrates[a]



[a] (a) For **1**, DIBAL-H, $PhCH_3$, −78 °C; for **2**, LAH, ether or THF, rt. (b) K_2CO_3, 5:1 CH_3CN:CH_3OH, rt. (c) 2.2 equiv of *n*-C_4H_9Li, 3.5 equiv of $ClCO_2CH_3$, THF, −78 °C to rt. (d) CF_3CO_2H, CH_2Cl_2, rt. 2 equiv of *n*-C_4H_9Li, CO_2, THF, −78 °C to rt. (f) CH_3I or C_2H_5I, K_2CO_3, DMF, rt.

1 with DIBAL-H[6] or the Weinreb amide **2** with LAH[7] provided the aldehydes **3**[8] which were directly subjected to a diazophosphonate generated in situ[9] to give the alkynes **4**. This sequence did lead to some loss of enantiopurity as determined by optical rotations.[10,11] Because the goal was to study the ruthenium-catalyzed addition to alkynes, optimizing the protocol to minimize racemization was not pursued.

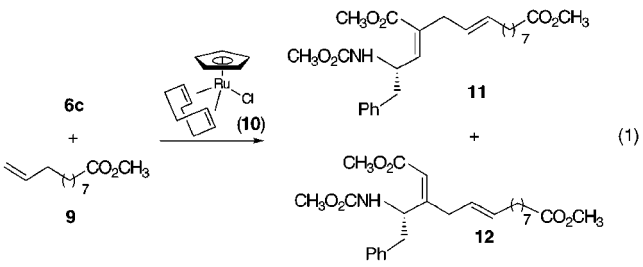
Carboxylation of the alkyne proved not to be simple since acylation of the amide nitrogen competed with C-acylation. Thus, two strategies were pursued. In the first, both N and C acylation to form **5** was carried out followed by selective removal of the Boc group with trifluoroacetic acid to give substrates **6**. Alternatively, using carbon dioxide as the acylating agent initially bis-carboxylates both N and C. Acidification during workup allows the *N*-carboxy substituent to undergo decarboxylation to form propynoic acids **7**. Alkylative esterification provides the Boc-protected substrates **8**.[11]

Table 1 summarizes the initial studies using urethane **6c** with methyl 10-undecenoate **9** according to eq 1. Although the reactions were normally allowed to proceed overnight, following the reaction by GC indicated they were complete within 5 h. Three solvents were explored—methanol, aqueous DMF, and acetone. Gratifyingly, the presence of the urethane function allowed the reaction to proceed in all solvents but the best yields were obtained in methanol or acetone. In the absence of catalyst, no reaction occurs (entry 1). Increasing acidity increases the α (**11**) vs *β* (**12**) C−C bond formation (entries 2−4 and 6−7) at the expense of some loss of yield.

Table 1. Effect of Reaction Conditions[a]

entry	solvent	additive	temp, °C	alkene[b] recovered, %	yield, %[c]	ratio[d] **11:12**
1[e]	CH_3OH	none	65	N.D.	N.R.	
2	CH_3OH	none	65	10	76 (94)	3.8:1
3	CH_3OH	100% NH_4PF_6	65	15	71 (83)	4.2:1
4	CH_3OH	40% CSA	65	15	70 (81)	5.0:1
5	CH_3OH	5% Ph_3P	65	N.D.	N.R.	
6	1:1 DMF−H_2O	none	100		55	3.0:1
7	1:1 DMF−H_2O	20% NH_4PF_6	100		45	5.6:1
8	1:1 DMF−H_2O	$In(OSO_2CF_3)_3$	100		57[f]	2.6:1
9	CH_3COCH_3		58	15	66 (78)	3.2:1
10	CH_3COCH_3	5% Ph_3P	58	N.D.	N.R.	

[a] All reactions were run with 5 mol % ruthenium complex **10** at 0.5 M. [b] Isolated alkene. [c] Isolated yields; yields in parentheses based upon amount of consumed starting material. [d] Determined by NMR spectroscopy. [e] This run was performed in the absence of the ruthenium complex. [f] Some cyclization to 3-pyrrolinone occurred.



(1)

(6) McNulty, J.; Still, I. W. J. *Synth. Commun.* **1992**, *22*, 979.
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(9) Müller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett* **1996**, 521. Roth, G. J.; Bestmann, H. J. Unpublished results.
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On the other hand, adding indium triflate[12] had a deleterious effect on the α:β ratio (entry 8). No racemization accompanies the reaction—the ee of the product **11** was the same as that of the starting material **6c** as determined by chiral HPLC. Because the highest yields were obtained under the conditions of entry 2, these conditions were adopted.

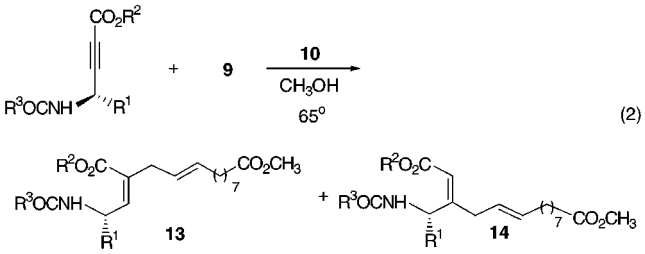
Equation 2 and Table 2 summarize a range of alkynoate substrates with alkene **9** as a standard. The ratio of the α- to β-alkylation product is influenced by the steric effect of the

Table 2. Effect of Alkyne Structure[a]

entry	R^1	R^2	R^3	% yield[b]	**13**:**14**
1	H	CH_3	CH_3	36 (59)	2.0:1
2	CH_2Ph	CH_3	CH_3	76 (94)	3.8:1
3	CH_3	CH_3	CH_3	72 (83)	4.2:1
4	*i*-C_3H_7	CH_3	CH_3	77 (90)	3.4:1
5	*t*-C_4H_9	C_2H_5	CH_3	81 (90)	10:1
6	CH_2Ph	C_2H_5	*t*-C_4H_9	61 (72)	3.5:1
7	*i*-C_3H_7	CH_3	*t*-C_4H_9	71 (Q)	4.3:1

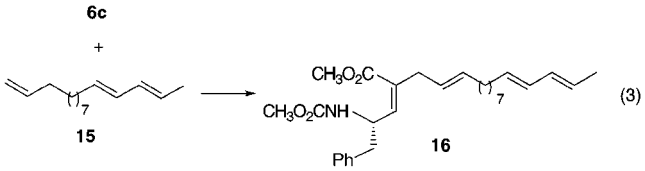
[a] All reactions were run with 5 mol % **10** in methanol at 65 °C. [b] Isolated yields; yields in parentheses based upon amount of consumed starting material.

alkyl group at the propargylic position. Replacing H by an alkyl group such as CH_3 increases the regioselectivity from 2:1 to 4.2:1. Furthermore, the *tert*-butyl-substituted substrate gave the highest amount of α-attack (entry 5). Changing the nature of the substituent on the nitrogen from methoxycarbonyl to *tert*-butoxycarbonyl had a small, if any, effect (entries 6 and 7).



(2)

The reaction requires a monosubstituted olefin as the alkene partner. This chemoselectivity can be utilized beneficially as in the example of eq 3.[13] Although conjugated dienes are normally more reactive than isolated alkenes,



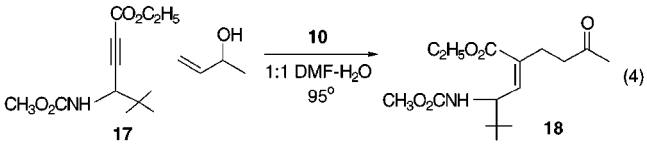
(3)

(12) Cf. Trost, B. M.; Portnoy, M.; Kurihara, H. *J. Am. Chem. Soc.* **1997**, *119*, 836.

(13) The triene **15** was prepared by the reaction of 10-undecenal with diethyl (*E*)-crotylphosphonate in the presence of KHMDS in THF.

reaction of triene **15** occurred in the "normal" fashion to give the ene type product **16** (4.2:1 ratio of α:β regioisomers) in 59% yield. It is also interesting to note that the Ru-catalyzed Alder ene reaction occurs rather than a Diels–Alder reaction, which is also feasible in this case.

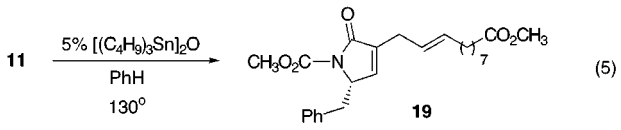
Allyl alcohols also serve as suitable alkene partners (eq 4).[14] Whereas low yields were obtained in methanol, a 58%



(4)

yield of a 4.1:1 ratio of the α– (**18**) to β-alkylated product was obtained in aqueous DMF. This example illustrates the ability to introduce a carbonyl functionalized side chain at the α-carbon.

Except when indium triflate was used as a cocatalyst in the initial exploratory work, no cyclization products accompanied the alkylation. Attempts to persuade the adducts to cyclize with bases such as sodium hydride or DMAP failed. Some cyclization of **11** (eq 5) occurred using di-*n*-butyltin oxide in benzene at 80 °C to form the pyrrolinone **19**. Chlorodi-*n*-butyltin oxide[15] gave complete cyclization

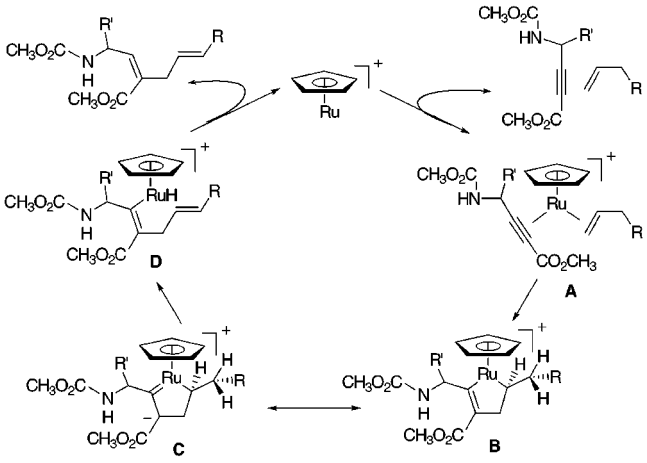


(5)

under the same conditions. A milder catalyst, tri-*n*-butyltin oxide, gave an 86% yield of the desired pyrrolinone.

The current reaction serves as a convenient entry to α-alkylated-γ-amino-*Z*-alkenoates and their cyclized derivatives. Only one olefin geometry is observed for both double bonds in the product. The regioselectivity and the double bond geometry are nicely rationalized by the ruthenacycle mechanism as outlined in Scheme 2.[3,4] Coordination of an

Scheme 2. Mechanistic Rationale



alkene and an alkyne sets the stage for a cycloisomerization to form the ruthenacycle B.

Considering that ruthenium accommodates oxidation states ranging from 0 to +8, the double bond may be polarized as shown in C which favors placement of an electron-withdrawing substituent like the ester at the β-carbon leading to α C−C bond formation. It is also possible that coordination of the urethane substituent to ruthenium, which can only occur in B, may contribute to this regioselectivity. Steric effects also contribute. In the conversion of A to B, steric interactions between the substituents closest to the alkyne and alkene carbons forming the new C−C bond appear to be more important than steric interactions with the Cp group on ruthenium. This has also been observed in cobalt-catalyzed reactions of alkynes.[16] β-Hydrogen elimination creates the nonconjugated double bond. The preferred conformation for this elimination that avoids the unfavorable eclipsing interaction between the R group and the ring methylene as depicted then generates an *E*-alkene. Reductive elimination from D generates the conjugated double bond which results from a cis addition of carbon and hydrogen. This reaction appears promising as a general strategy for α-alkylation of alkynoates to give γ-amino acids and their cyclized derivatives. The reaction exhibits exquisite chemoselectivity highlighted by the compatibility of a 1,3-diene. Since no racemization occurs during the ruthenium-catalyzed addition, this sequence serves as an asymmetric route to the extent the precursors are available in enantiomerically pure form.

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Supporting Information Available: Procedures for the Ru-catalyzed additions and the tin-catalyzed cyclization, characterization data for **13**, **14** of entries 3−7 (Table 2), **16**, **18**, and **19**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Cf. Trost, B. M.; Martinez, J. A.; Kulawiec, R. J.; Indolese, A. F. *J. Am. Chem. Soc.* **1993**, *115*, 10402.
(15) Otera, J.; Dan-oh, N.; Nozaki, H. *J. Org. Chem.* **1991**, *56*, 5307.
(16) Earl, R. A.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1983**, *105*, 6991.