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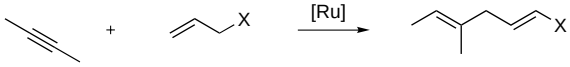
An Atom-Economic Three-Carbon Chain Extension to Give Enamides**

Barry M. Trost* and Jean-Philippe Surivet

Enamides represent a significant class of compounds because of their versatility as building blocks—a result of the enhanced nucleophilicity of the double bond—and as precursors to saturated amines.[1–3] Normally, such compounds are prepared by additions to aldehydes via imines or other equivalent intermediates.[2] As a continuation of our development of metal-catalyzed additions of alkenes and alkynes,[4] we have been interested in chain-extension reactions by means of additions catalyzed by ruthenium complexes [Eq. (1)]. Our recent discovery of the effectiveness of $[(\eta^5\text{-}C_5H_5)Ru(N{\equiv}CCH_3)_3]PF_6$ (**1**) [5, 6] suggested the prospect of



(1)

expanding the scope of such additions. If X was an amide function, this chain-extension method would directly create an enamide. A significant issue in such a reaction is the

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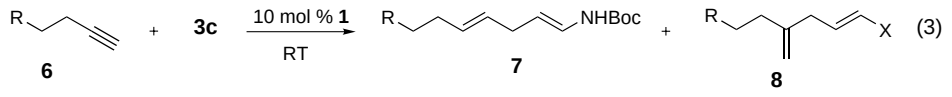
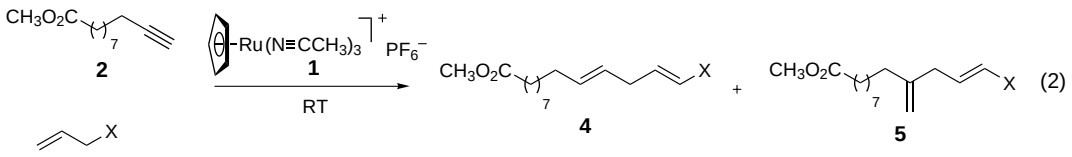
possibility of a low-valent ruthenium complex promoting ionization of the allylic leaving groups.[7] The ability of the Ru complex to function as a Lewis acid also raises the question of the compatibility of an amide substrate owing to its Lewis basicity, as well as the question of the stability of the enamide product under the reaction conditions.



a: R = 	66%	2.6	:	1
b: R = CH_3CO	66%	2.0	:	1
c: R = $NCCH_2$	75%	2.1	:	1
d: R = $TBDMSOCH_2CH_2$	69%	2.3	:	1

We chose a terminal alkyne with a series of allylic amides [Eq. (2)] to examine the feasibility simultaneously with the regioselectivity of this ruthenium-catalyzed chain-extension reaction. The initial experimental protocol involved the treatment of alkyne **2** and allyl amide **3** (1:1) with 10 mol% of complex **1** in acetone at room temperature [Eq. (2)].



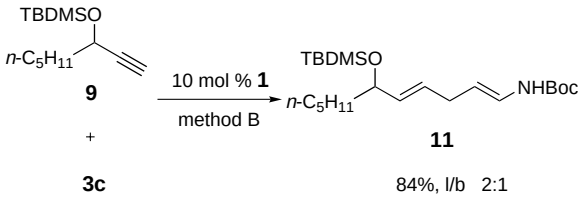
a:	2.6	:	1
b:	2.4	:	1
c:	2.6	:	1

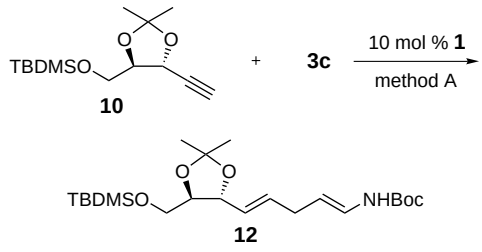
a: X = $NHCOCH_3$
b: X = NHCOPh
c: X = $NHCO_2C(CH_3)_3$
d: X = NPhth
e: X = NHTs

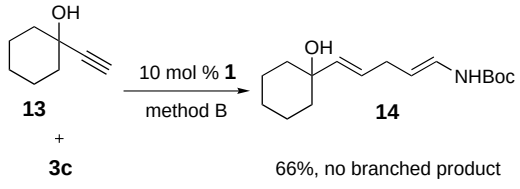
We used the phthalimide **3d** and sulfonamide **3e** to minimize the Lewis basicity of the allyl amide; however, the reactions gave low conversions even after prolonged reaction times. On the other hand, the acetamide **3a** gave a 62% yield of the adducts **4a** and **5a**[8] after only 1 h. When the amount of catalyst was decreased to 5 or even 3 mol%, yields of 66 and 55%, respectively, were obtained in the same time period. Surprisingly, the linear product **4a** dominated over the branched isomer **5a**, in contrast to alkenes (X = alkyl chain).[6, 9] However, our earlier studies with [CpRu(cod)Cl] (cod = 1,5-cyclooctadiene) as a catalyst in reactions with allyl alcohol did show a similar regioselectivity.[10] The benzamide **3b** showed virtually identical behavior, and gave the adducts **4b** and **5b**[8] within 1.5–2 h in combined yields of 72 or 76% when 5 or 3 mol%, respectively, of complex **1** was used. The *tert*-butoxycarbonyl (Boc) derivative **3c** gave a 63% yield of adducts **4c** and **5c**[8] within 2 h. In this last case, the choice of solvent had an effect on the yield. When a THF/acetone ratio of 5:1 was used, the yield increased to 81% with a 5 mol% catalyst load, but dropped to 67% with a 3 mol% load. Remarkably, the choice of amide had virtually no effect on the ratio of branched to linear products [Eq. (2)].

Using either acetone (method A) or THF/acetone 5:1 (method B) as the solvent, we explored a range of alkynes, [Eq. (3)]. Excellent chemoselectivity was observed in the addition of an acetal **6a**, a ketone **6b**, a cyano **6c**, and a silyl ether **6d** (TBDMS = *tert*-butyldimethylsilyl) to the carbamate ester **3c**. Evidently, all the enamide functional groups were stable under the reaction conditions, and gave the linear adducts **7**[8] as the major products. Generally, method B was preferred except for ketone **6b**.

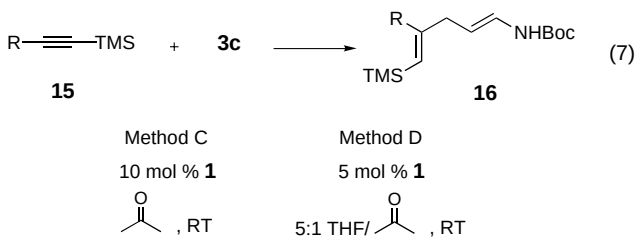
The introduction of a propargylic oxygen substituent was of interest to us because of the possibility of forming allenylidene complexes.[11] Nevertheless, as shown in Equations (4)–(6), no problems were encountered. A single branch at the propargylic position (e.g. **9** [Eq. (4)] and **10** [Eq. (5)]) had no effect on the regioselectivity, and resulted predominantly in the linear products **11**[8] and **12**,[8] respectively, but with significant amounts of branched products. When a substrate with a quaternary propargylic position (**13**) was used [Eq. (6)], only the linear regioisomer **14** was obtained.[8]





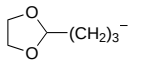


We used a trimethylsilyl group (e.g. **15**; TMS = trimethylsilyl) to examine the possibility of reversing the regioselectivity and thus favor the branched product [Eq. (7)].[12] These



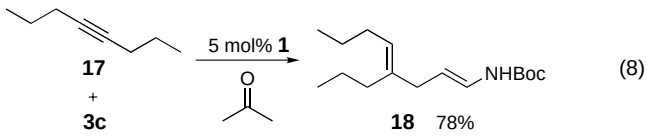
reactions proceeded very smoothly and in high yield, in contrast to our experience with the [CpRu(cod)Cl] catalyst. This reaction produced a single regioisomer **16**[8] in every case [Eq. (7), Table 1]. An advantage of the vinylsilanes is their use

Table 1. Three-carbon chain extension of silylalkynes [Eq. (7)].[a]

R	Method	Time [h]	Product	Yield [%]
$TBDMSO(CH_2)_5$-	D	1	**16a**	95
$Boc(Ts)NCH_2CH_2$-	C	3	**16b**	94
	D	0.67	**16c**	81
$HO(CH_2)_5$-	C	1	**16d**	97
$HO(CH_2)_3$-	D	9	**16e**	91
n-$C_{11}H_{23}CH(OH)$-	D	2	**16f**	90

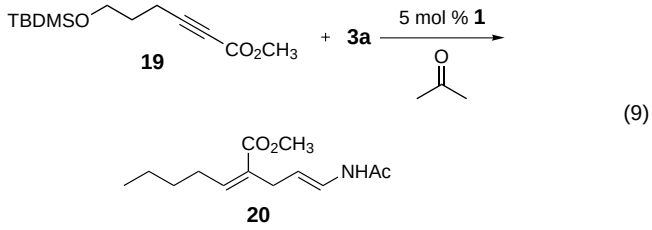
[a] All reactions were performed as in Equation (2). Ts = tosyl = *para*-toluenesulfonyl, NPHt = phthalamide.

in further elaborations—the silyl group can be replaced by electrophiles, including a proton, with control of the alkene geometry. The use of such processes allows trisubstituted alkenes of defined geometry and regioselectivity to be constructed. A simple internal alkyne **17** also served as an excellent partner; product **18**[8] was obtained in 78% yield, after a reaction time of 0.67 h at room temperature [Eq. (8)].

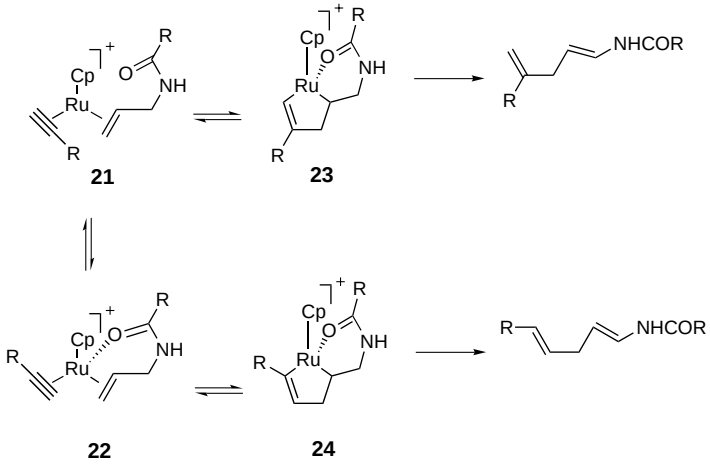


Alkynoates such as **19** also served as suitable substrates, although the reactions were slower; the adduct **20**[8] was isolated in 50% yield (82% based on recovered starting material) after 1.5 h [Eq. (9)]. As observed in other cases,[13] the major regioisomer (7:1) arose from the formation of the new C–C bond at the α-carbon atom of the α,β-alkynoate.

This atom-economic[14] three-carbon chain extension is a simple and mild approach for the simultaneous formation of enamides and di- or trisubstituted alkenes of defined geometry. This process demonstrates excellent chemoselectivity. The issue of regioselectivity is quite intriguing, and excellent regioselectivity was observed with a variety of disubstituted



alkynes. In the case of silylalkynes, a subsequent protodesilylation of the products provided a clear access to "branched"-type products like **8**. Interestingly, terminal alkynes led mainly to linear products, in contrast to the additions to alkenes bearing no heteroatoms at the allylic position. A reasonable rationale invokes metallacycle intermediates **23** and **24** (Scheme 1), which derive from the coordination complexes



Scheme 1. Rationale of regioselectivity.

21 and **22**, respectively. Because of the steric interactions between R and the bulky ligands around the ruthenium center in **22**, the formation of metallacycle **23** from complex **21** is kinetically favored. If β-hydrogen insertion and reductive elimination occurs more rapidly than metallacycle formation, the branched isomer dominates. On the other hand, the presence of electronegative substituents at the allylic position may slow down the rate of the β-hydrogen insertion.[15] In the latter scenario, the higher stability of **24** than **23** may be reflected in the product distribution, since there is no evident reason why the rate of this insertion should be noticeably different in these two metallacycles. Clearly, further work is required to probe these complex issues. Nevertheless, the current method constitutes a useful synthetic protocol.

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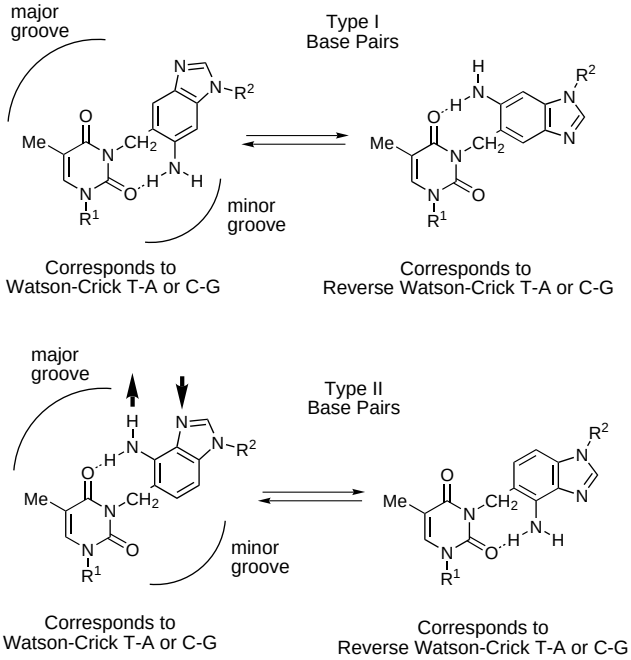
Synthesis of DNA Oligomers Possessing a Covalently Cross-Linked Watson–Crick Base Pair Model**

Hong-Yu Li, Yao-Ling Qiu, Elisabeth Moyroud, and Yoshito Kishi*

The concept of covalently cross-linked sections with molecular architecture similar to Watson–Crick hydrogen-bonded base pairs was introduced by Devadas and Leonard in the mid-1980's.[1] Since then, several types of covalently linked systems have been developed. However, these systems[2, 3] were generated from preformed double helices, as seen in the seminal work of Ferentz and Verdine. The Leonard system may offer unique opportunities to address questions regarding the chemistry of DNA and RNA, but this system has several drawbacks, including difficulty in attempted duplex formation and lack of conformational flexibility between the base pairs.[1]

We have recognized the possibility that CH_2-bridged base pair models may be uniquely suited to the chemical exploration of covalently cross-linked nucleosides/nucleotides. In addition to their increased chemical stability, these base pair models are expected to adopt only Watson–Crick or reverse Watson–Crick base pairings while maintaining conformational flexibility along the CH_2 bridge. We have focused on two specific types (types I and II) of base pair models (Scheme 1), with the anticipation that they might exhibit



Scheme 1. Covalently cross-linked Watson–Crick base pair models. A = 2′-deoxyadenosine, C = 2′-deoxycytidine, G = 2′-deoxyguanosine, T = 2′-deoxythymidine.

differing structural characteristics. Although both the type I and type II models adopt only Watson–Crick or reverse Watson–Crick base pairings in the sense of primary hydrogen-bonded base pairing, only the type II model provides a structural motif for formation of Hoogsteen triplets such as T–AT and C–GC: see the two bold arrows in Scheme 1 which indicate possible hydrogen-bonding sites in a major groove. We recently reported the synthesis and structural properties of type I and II base pairs.[4] In this paper, we present a method for incorporating these base pair models into DNA oligomers.

A priori, we considered that phosphoramidite-based solid-phase synthesis[3, 5] would best meet with our future needs, and we studied its applicability to three types of oligomers incorporating a covalently cross-linked base pair, the *n*, *h*, and *H* types. Our synthetic plan is schematically depicted in Scheme 2, with the order of chain elongation being indicated by a circled number. First, all of the proposed chain elongations take place in the 3′→5′ direction for *n*- and *h*-type oligomers, but the last chain elongation takes place in the 5′→3′ direction for *H*-type oligomers. Second, the order of the

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