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A new Ru catalyst for alkene–alkyne coupling

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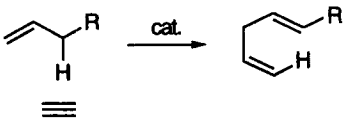
Abstract

$[CpRu(CH_3CN_3)]^+PF_6^-$ proves to be an effective catalyst for an intermolecular Alder ene type reaction that provides considerable broadening of scope of the process.

Keywords: ene type addition; ruthenium catalysis; atom economy; carbon–carbon bond formation; alkyne addition; alkene addition.

The need to utilize our raw materials more efficiently and minimize waste requires the expansion and improvement of atom economical reactions, notably simple additions.[1] A promising reaction is the cross-coupling of an alkene and an alkyne (Eq. 1) in an Alder ene type process.[2] The requirements of this reaction for the alkene to be monosubstituted provides extraordinary chemoselectivity with respect to other double bonds present but also a limitation.[3] The potential importance of this reaction, ideal from the point of view of atom economy since it is a simple addition, would increase significantly if a range of catalysts could be found that progressively expand the scope of the reaction. In this communication, we report our development of a new catalyst that achieves this objective.



(1)

The mechanism of this reaction led us to consider cationic ruthenium complexes as more reactive catalysts. The ease of availability of $[CpRu(CH_3CN)_3]^+PF_6^-$ (**1**) in three steps from ruthenium trichloride led us to consider it.[4] Our initial experiments utilizing acetonitrile as solvent were disappointing. Conjecturing that the excellent ligating properties of acetonitrile for ruthenium prevented coordination of the reactants moved us to utilize other somewhat polar solvents, notably acetone and DMF.[5] Initial experiments utilized a monosubstituted alkene to test the viability of the complex as a catalyst. Using the reactions of methyl 10-undecenoate (**2**) with alkyne **3a** as the standard (Eq. 2), a 1:1 mixture of these reactants in acetone in the presence of 10 mol% complex **1** and 30 mol% CSA (camphorsulfonic acid) at 50°C led to smooth reaction to form the adducts **4a/5a** in 78% isolated yield. The lack of regioselectivity

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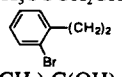
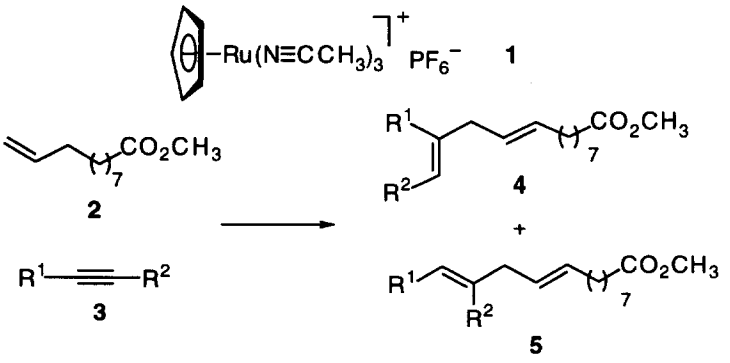
Table 1
Regioselective couplings of alkynes with methyl 10-undecenoate[a]

Entry	Alkyne R^1	Alkyne R^2	Yield[b]	Ratio **4**:**5**	Cmpd. # Suffix
1	$NC(CH_2)_3$	H	65	8:1	a
2	$PhCH(NHBoc)(CH_2)_2$	H	84	>20:1	b
3	$CH_3COCH_2CH_2$	H	86	5:1	c
4		H	75	10:1	d
5	$(CH_3)_2C(OH)$-	H	91	1:32	e
6	CO_2CH_3	$NC(CH_2)_3$	73	1:3.3	f
7	$CO_2C_2H_5$	$PhCH(NHCO_2CH_3)$-	62	5:1	g

a) All reactions, using a 1:1 ratio of alkene:alkyne (0.1 M), were performed at room temperature in DMF with 10 mol% **1**. b) Isolated yields.

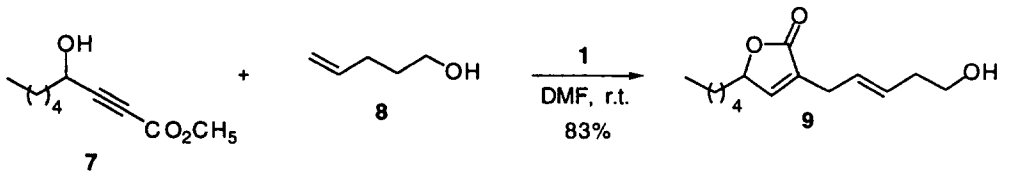
was disappointing since the adducts were formed in a 1:1.1 ratio. Changing the solvent to DMF and running the reaction at room temperature with no CSA afforded an 8:1 ratio of **4a**:**5a** (65% yield, see Table, entry 1). The significantly higher reactivity of **1** compared to CpRu(cod)Cl (**6**) is obvious from the much milder conditions needed for its reaction. Furthermore, a significantly improved regioselectivity which may, in part, derive from the milder conditions, was also observed.



(2)

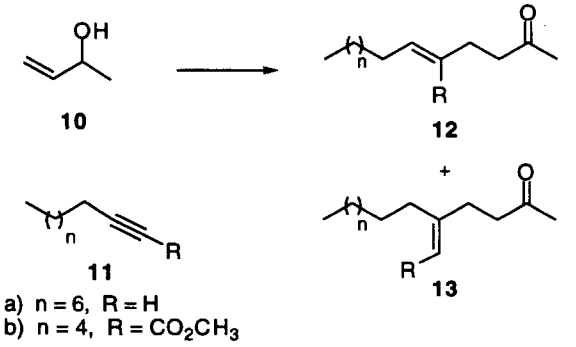
To determine the generality of these observations, a series of variously substituted alkynes with alkene **2** were explored and are summarized in Table 1. The compatibility of the numerous functional groups present in the substrates indicates the continued excellent chemoselectivity. The presence of polar groups as in entries 1–3 are not prerequisite for good regioselectivity for the branched adducts **4** as illustrated in entry 4. The presence of aromatic rings is tolerated despite the capability of the $CpRu^+$ fragment to bind arenes.[6] On the other hand, a sterically bulky alkyne substituent virtually completely reverses the regioselectivity (entry 5). Ester substituents on the alkyne normally lead to C–C bond formation at the carbon α to the ester. On the other hand, the cyanopropyl substituent normally directs C–C bond formation to the internal alkyne carbon proximal to this substituent. Apparently, the latter effect wins in the competition as illustrated in entry 6. The normal preference for α C–C bond formation returns in entry 7.

The new catalyst improved the regioselectivity in the synthesis of butenolides.[7] For example, the ynoate **7** added to alkenol **8** at room temperature in DMF in the presence of a catalytic amount of complex **1** to give butenolide **9** as the only detectable regioisomer in 83% yield (Eq. 3).



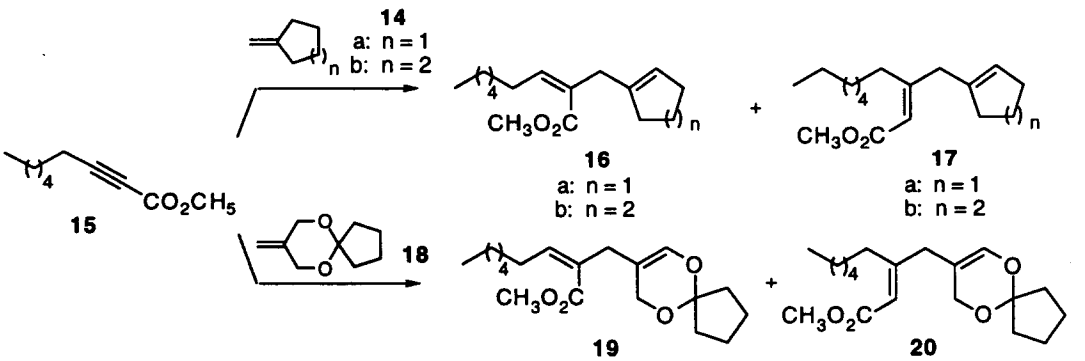
(3)

Complex **1** also more effectively catalyzes the addition of allyl alcohols, e.g. **10**, to alkynes, e.g. **11** (Eq. 4).[8] These reactions now proceed at room temperature in DMF. The regioselectivity bias for the 'linear' type product **12** characteristic of the allyl alcohols as substrate remains but is not improved (**12a**:**13a** 2.7:1, 78% yield; **12b**:**13b** 2.3:1, 82% yield).

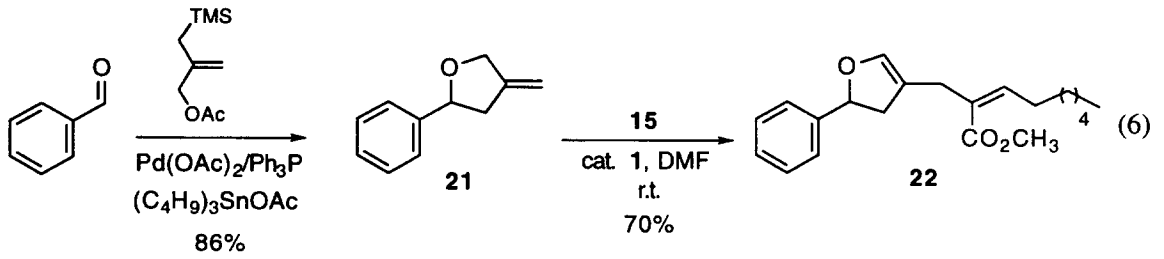


(4)

The effectiveness of complex **1** to catalyze the Alder type reaction of monosubstituted alkenes led to its examination with more substituted alkenes (Eq. 5). Gratifyingly, methylenecycloalkanes (**14**) added to ynoate **15** to give the normal adducts **16** and **17** (**16a**:**17a** 1.8:1, 73% yield; **16b**:**17b** 1.8:1.5, 78% yield) at room temperature in DMF, the same conditions used for monosubstituted alkenes. A more regioselective addition occurred to alkene **18** (**19**:**20** 4.4:1, 79% yield). Methylenecycloalkanes are readily available by the palladium catalyzed cycloadditions of trimethylenemethane.[9] To illustrate the utility of the tandem sequence, cycloaddition to an aldehyde led to the 4-methylenetetrahydrofuran **21** (Eq. 6). Addition of ynoate **15** occurred with excellent regioselectivity with respect to both the alkyne (9:1, major regioisomer **22**) and alkene (only a trace of the regioisomer is detectable in the ^1H NMR spectrum analysis of the crude mixture).

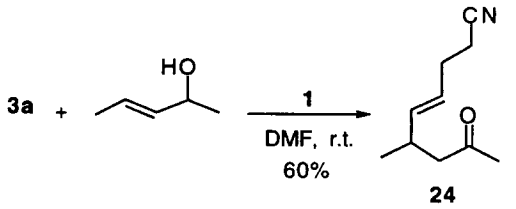


(5)

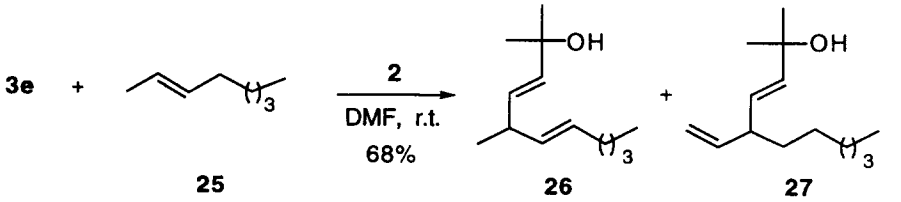


(6)

A 1,2-disubstituted alkene also participates. Thus, 2-penten-3-ol (**23**) reacts with alkyne **3a** at room temperature in DMF to give excellent regioselectivity with respect to the alkyne (7.9:1, major regioisomer **24**) and the alkene (only one detected), Eq. 7. An allylic alcohol is not necessary for the reaction with 1,2-disubstituted olefins to proceed. Reaction of alkyne **3e** with 2-octene (**25**) at room temperature in DMF affords the Alder-ene adducts with excellent alkyne regioselectivity (only one detected) and surprisingly good regioselectivity with respect to the alkene (2.6:1, **26**:**27**).



(7)



(8)

The effectiveness of this new catalyst raises questions regarding the mechanism of the process. Previously, we favored a pathway invoking a ruthenacyclopentene intermediate. While such a pathway may be operative here, an alternative possibility invoking ruthenium inserting into an allylic C–H bond must also be considered. Such a mechanism becomes very attractive to explain the equal facility of these substituted alkene cases to the unsubstituted one. Further studies will clearly be required to elucidate this point. This new catalyst **1** increases reactivity and, in many cases, selectivity compared to our earlier catalyst. Reactions now proceed normally at room temperature instead of 65–100°C. At the same time, chemoselectivity with respect to a broad array of functional groups (carbamates, ketones, aryl bromides, alcohols, esters, nitriles) is maintained. These facts coupled to the ease of preparation of the complex greatly increase the potential synthetic utility of the ruthenium catalyzed Alder-ene reaction.

Acknowledgements

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