ORGANIC
LETTERS

2001
Vol. 3, No. 13
2089−2091

Catalytic and Highly Efficient 1,4-Addition of Terminal Alkynes to Conjugated Enones by $[RuCl_2(p\text{-cymene})]_2$/Pyrrolidine

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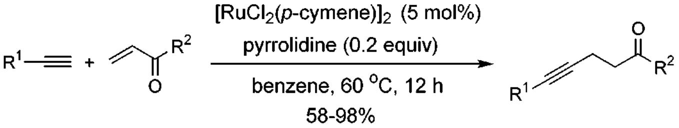
Received April 30, 2001

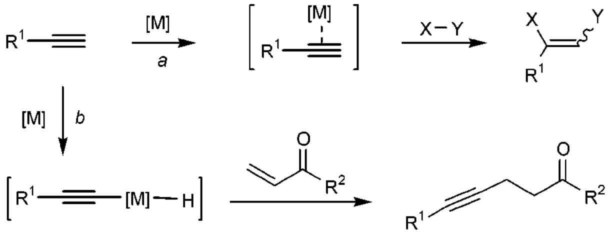
ABSTRACT



A wide range of terminal alkynes was added to conjugated enones in a 1,4-fashion by a ruthenium catalyst in the presence of catalytic amounts of an amine base, and the corresponding γ,δ-alkynyl ketones were obtained in good to excellent yields.

The excellent coordinating ability of alkynes for transition metal complexes makes transition metal catalyzed addition of various functional groups to activated alkynes a promising area for exploration (pathway *a* in Scheme 1).[1] The insertion of a transition metal into spC−H bonds and the subsequent addition of the metal alkynilide, or its equivalents, into organic acceptors such as enones (pathway *b* in Scheme 1) would also be highly valuable due to the wide utility of the produced difunctional adducts in organic synthesis.

Scheme 1



Whereas numerous demonstrations of the reaction pathway a have been disclosed,[2] metal-catalyzed transformations via pathway *b* are much more rare and only limited examples have been reported such as Zn-catalyzed addition of alkynes to C═N bonds[3] or Pd-catalyzed addition to conjugated C═C bonds.[4] Trost et al. recently developed an elegant multicomponent reaction protocol in which Ru catalyzes coupling reactions between alkynes and conjugated enones in the presence of heteroatom nucleophiles that initially add to alkynes to yield alkenyl ketones as the final products.[5] Although the first example of Ru-catalyzed Michael addition of terminal alkynes to butenone has recently been revealed,[6] its synthetic scope is rather limited and yields are low (20−

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[1] (a) Horn, K. A. *Chem. Rev.* **1995**, *95*, 1317. (b) Naota, T.; Takaya, H.; Murahashi, S.-I. *Chem. Rev.* **1998**, *98*, 2599. (c) Beletskaya, I.; Moberg, C. *Chem. Rev.* **1999**, *99*, 3435.

[2] (a) Doucet, H.; Martin-Vaca, B.; Bruneau, C.; Dixneuf, P. H. *J. Org. Chem.* **1995**, *60*, 7247. (b) Hua, R.; Shimada, S.; Tanaka, M. *J. Am. Chem. Soc.* **1998**, *120*, 12365. (c) Ohmura, T.; Yamamoto, Y.; Miyaura, N. *J. Am. Chem. Soc.* **2000**, *122*, 4990.

[3] Frantz, D. E.; Fässler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **1999**, *121*, 11245.

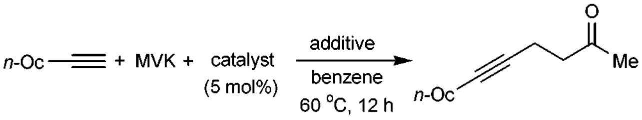
[4] (a) Trost, B. M.; Sorum, M. T.; Chan, C.; Harms, A. E.; Rühter, G. *J. Am. Chem. Soc.* **1997**, *119*, 698. (b) Trost, B. M.; Frontier, A. J. *J. Am. Chem. Soc.* **2000**, *122*, 11727.

10.1021/ol016047m CCC: $20.00

74%). We report here a highly efficient catalytic system for 1,4-addition of a wide range of terminal alkynes to conjugated enones to provide γ,δ-alkynyl ketones.[7] A possible pathway based on NMR studies and a deuterium-incorporation experiment will be also presented.

In a test reaction of 1-decyne and methyl vinyl ketone (MVK), we found that the transformation could be efficiently effected with the use of a dimeric ruthenium catalyst, $[RuCl_2(p\text{-cymene})]_2$ (**1**),[8] in the presence of catalytic amounts of certain bases (Table 1). A survey of various bases revealed that the highest reactivity was achieved with pyrrolidine (entry 5). An increase in the stoichiometry of the secondary amine base exhibited only marginal improvement in the reaction efficacy (entry 6).[9] Benzene was the solvent of choice among several reaction media screened. Although the benzene analogue of **1** resulted in only slightly decreased product formation (entry 7), other ruthenium complexes were much less effective compared to **1**.

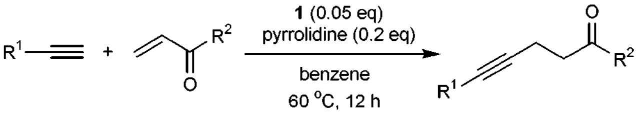
Table 1. Effect of Additives in the Ru-Catalyzed 1,4-Addition of 1-Decyne to Methyl Vinyl Ketone (MVK)[a]



entry	catalyst	additive (equiv)	GC yield,[b] %
1	$[RuCl_2(p\text{-cymene})]_2$	none	<5
2	$[RuCl_2(p\text{-cymene})]_2$	Cs_2CO_3 (0.1)	17
3	$[RuCl_2(p\text{-cymene})]_2$	$n\text{-}PrNH_2$ (0.1)	50
4	$[RuCl_2(p\text{-cymene})]_2$	piperidiine (0.1)	54
5	$[RuCl_2(p\text{-cymene})]_2$	pyrrolidine (0.1)	81
6	$[RuCl_2(p\text{-cymene})]_2$	pyrrolidine (1.0)	85
7	$[RuCl_2(benzene)]_2$	pyrrolidine (0.1)	61
8	$RuH_2(PPh_3)_4$	pyrrolidine (0.1)	<5
9	$RuCl_2(PPh_3)_3$	pyrrolidine (0.1)	<5
10	$[RuCl_2(p\text{-cymene})]_2$	1-Me-pyrrolidine (0.1)	60
11	$[RuCl_2(p\text{-cymene})]_2$	2,6-lutidine (0.1)	37

[a] All reactions were carried out with 3.0 equiv of MVK at 0.1 M concentrations. [b] GC yields were obtained on the basis of an internal standard (dodecane).

Table 2. Catalytic 1,4-Addition of Terminal Alkynes to Conjugated Enones by $[RuCl_2(p\text{-cymene})]_2$ (**1**)/Pyrrolidine[a]



entry	alkyne (R^1)	enone (R^2)	yield,[b] %
1	n-Oc	Me	91
2	Me_3Si	Me	77
3	$HOCH_2(CH_2)_2CH_2$	Me	58
4	t-Bu	Me	72
5	$NCCH_2CH_2CH_2$	Me	62
6	$ClCH_2CH_2CH_2$	Me	84
7	$CH_2{=}CH(CH_2)_2CO_2(CH_2)_3$	Me	68
8	$(p\text{-Me})C_6H_4$	Me	58
9[c]	$\text{-}(CH_2)_4\text{-}$	Me	60
10	1-cyclohexenyl	Me	63
11	$ClCH_2CH_2CH_2$	Et	82
12	n-Oc	Et	80
13[d]	$ClCH_2CH_2CH_2$	Ph	71
14[d]	n-Oc	Ph	98

[a] Unless otherwise noted, 3.0 equiv of enone was used. [b] Isolated yields after silica gel chromatography. [c] 5.0 equiv of MVK was used and the isolated product was a bis-addition adduct: 5,11-hexadecadiyne-2,15-dione. [d] 1.2 equiv of phenyl vinyl ketone was used.

As shown in Table 2, this catalytic new recipe of 1,4-addition of terminal alkynes to conjugated enones could be applied to a broad range of substrates, and it was found that a diverse range of functional groups were compatible with the reaction conditions.[10] For example, alkynes bearing silyl (entry 2), cyano (entry 5), halide (entry 6), or alkenyl groups (entry 7) smoothly reacted with methyl vinyl ketone in a 1,4-addition fashion to afford the corresponding γ,δ-alkynyl ketones in moderate to good yields. A good yield of the conjugated product was also obtained with a sterically demanding alkyne (entry 4). It should be noted that the most commonly employed protocol for the conjugate addition, in which generated stoichiometric metal acetylides are added to enones, could not be applied to such substrates as hydroxyl- (entry 3) or carbonyl-bearing alkynes (entry 7) due to the requirement of strong bases for the initial conversion of acetylenes into alkynylides. With diyne as a substrate, a bis-addition adduct was obtained as a major product albeit in moderate yield (entry 9). Conjugated enynes could also be employed as a substrate (entry 10). In addition to methyl vinyl ketone, several other enones examined were

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(5) (a) Trost, B. M.; Portnoy, M.; Kurihara, H. *J. Am. Chem. Soc.* **1997**, *119*, 836. (b) Trost, B. M.; Pinkerton, A. B. *J. Am. Chem. Soc.* **1999**, *121*, 1988. (c) Trost, B. M.; Brown, R. E.; Toste, F. D. *J. Am. Chem. Soc.* **2000**, *122*, 5877. (d) Trost, B. M.; Pinkerton, A. B. *Angew. Chem., Int. Ed.* **2000**, *39*, 360.

(6) Picquet, M.; Bruneau, C.; Dixneuf, P. H. *Tetrahedron* **1999**, *55*, 3937.

(7) Although this conversion has been previously accomplished in several ways based upon Al, B, and Sn chemistry, all of these methods require the use of stoichiometric amounts of some metal species, see: (a) Schwartz, J.; Carr, D. B.; Hansen, R. T.; Dayrit, F. M. *J. Org. Chem.* **1980**, *45*, 3053. (b) Kim, S.; Lee, J. M. *Tetrahedron Lett.* **1990**, *31*, 7627. (c) Kim, S.; Park, J. H. *Synlett* **1995**, 163. (d) Fujishima, H.; Tanaka, E.; Hara, S.; Suzuki, A. *Chem. Lett.* **1992**, 695. (e) Ikeda, S.-I. *Acc. Chem. Res.* **2000**, *33*, 511.

(8) For some recent reports of **1**-catalyzed organic transformations from this laboratory, see: (a) Na, Y.; Chang, S. *Org. Lett.* **2000**, *2*, 1887. (b) Lee, M.; Chang, S. *Tetrahedron Lett.* **2000**, *41*, 7507. (c) Lee, M.; Ko, S.; Chang, S. *J. Am. Chem. Soc.* **2000**, *122*, 12011.

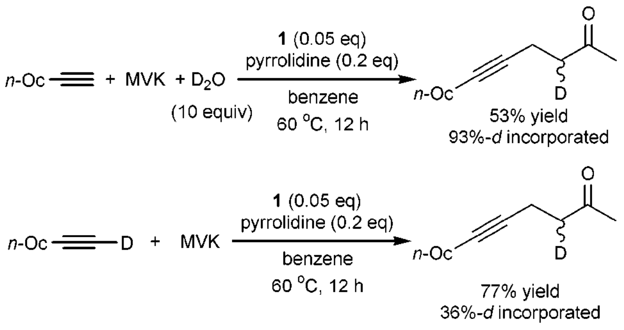
(9) Use of smaller amounts of the ruthenium catalyst resulted in longer reaction times to achieve the same conversion. For example, use of $[RuCl_2(p\text{-cymene})]_2$ (2 mol %)/pyrrolidine (0.1 equiv) under otherwise identical conditions afforded a 55% GC yield compared to entry 5 in Table 1.

(10) **Representative Experimental Procedure**: To a stirred solution of **1** (30.6 mg, 0.05 mmol) in benzene (4 mL) was added pyrrolidine (14.2 mg, 0.2 mmol), and the mixture was stirred for 10 min at room temperature followed by the addition of 1-decyne (138.4 mg, 1.0 mmol) and methyl vinyl ketone (210 mg, 3.0 mmol). After the reaction mixture was stirred for 12 h at 60 °C, 5-tetradecyne-2-one (189 mg, 91%) was isolated by column chromatography on silica gel (EtOAc/hexane = 1:3): ^1H NMR ($CDCl_3$, 250 MHz) δ 2.64 (2H, t, $J = 6.9$ Hz), 2.42 (2H, m), 2.17 (3H, s), 2.14−2.10 (2H, m), 1.46−1.43 (2H, m), 1.36−1.27 (10H, m), 0.88 (3H, t, $J = 1.8$ Hz); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 207.1, 81.1, 78.7, 43.3, 32.2, 30.1, 29.5, 29.4, 29.3, 29.1, 26.2, 22.9, 19.0, 14.4, 13.8; IR (neat) cm^{-1} 2928, 2330, 1721; HRMS (EI) calcd for $C_{14}H_{24}O$ $[M^+]$ 208.1828, found 208.1825.

also good Michael acceptors.[11] For example, reaction of alkynes with ethyl vinyl ketone or phenyl vinyl ketone proceeded with similar efficiency compared to methyl vinyl ketone under the same reaction conditions. It should be noted that the necessary amount of phenyl vinyl ketone (1.2 equiv to alkynes) for satisfactory yields was not as high as in the cases of MVK or ethyl vinyl ketone.[12]

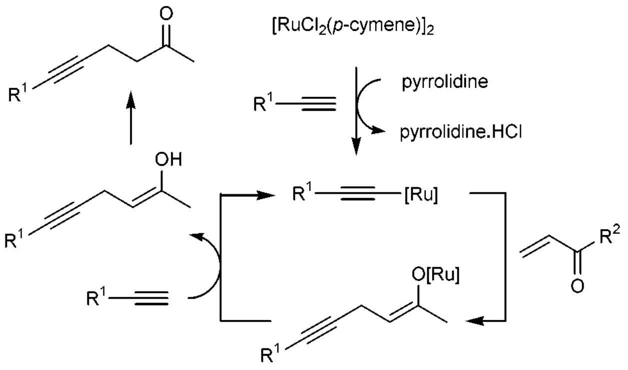
When the reaction was carried out in the presence of D_2O, an α-deuterated alkynyl ketone adduct was obtained in 52% yield with 93% *d*-incorporation (Scheme 2). No deuterium incorporation was observed at any positions when a γ,δ-alkynyl ketone was allowed to react with a large excess of D_2O (20 equiv) under the reaction conditions. Deuterium incorporation was also observed at the same position although to a lower extent when deuterated alkyne was allowed to react with enone under the same reaction conditions.

Scheme 2



A plausible pathway for the Ru-catalyzed 1,4-addition of alkynes to enones is presented in Scheme 3. Although we could not isolate the active intermediate species of the ruthenium catalyst, a monomeric ruthenium complex coordinated with the added amine base seems to be initially formed upon addition of amine bases.[13] NMR studies showed that the newly formed complex is in a 1:1 ratio between Ru and the added amine.[14] It is proposed that complexation of an alkyne with the active ruthenium species results in labilization of the terminal C−H bond such that even weakly basic amines can effect deprotonation of the bond with concomitant generation of the corresponding ruthenium-acetylide.[15] The ruthenium alkynylide is then added to enones in a 1,4- rather than a 1,2-fashion presumably due to steric reasons[16] leading to a ruthenium enolate species.[17] The Ru-enolate intermediate will be protonated upon abstraction of the terminal acetylene to form an alkynyl enol species and subsequent tautomerization of the enol adduct would afford γ-alkynyl ketone as the final product.

Scheme 3



In conclusion, we have demonstrated that a novel Ru-catalyzed strategy for the 1,4-addition of terminal alkynes to conjugated enones can be achieved under mild conditions. The process is simple to conduct and provides a diverse range of γ,δ-alkynyl ketones in good to excellent yields, and this catalytic protocol is an appealing alternative to the existing two-step Michael reaction route that requires stoichiometric generation of alkynylides.

Acknowledgment. We thank the Center for Molecular Design and Synthesis (CMDS) at KAIST for this work.

Supporting Information Available: Spectroscopic data for all new compounds obtained in this study. This material is available free of charge via Internet at http://pubs.acs.org.

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[11] Substituted enones were poorer Michael acceptors compared to ethenyl ketones. For example, reaction of 1-decyne and cyclohexenone afforded a 20−25% yield of the desired product under the same reaction conditions and the starting materials were recovered unchanged.

[12] When 1-decyne was reacted with 2.0 equiv of MVK under otherwise identical conditions, the desired product was isolated in 75% yield compared to entry 1 of Table 2. Due to the fact that reaction rates were very similar regardless of the types of the employed enons, high volatility of MVK or ethyl vinyl ketone is regarded as one of the main reasons for requiring large excess amounts of those enones (3.0 equiv) to alkynes for good yields.

[13] It has recently been reported that a monomeric species is formed by the reaction of $[RuCl_2(p\text{-cymene})]_2$ with 3-hydroxy-2-pyridone in the presence of a base, see: Piotrowski, H.; Polborn, K.; Hilt, G.; Severin, K. *J. Am. Chem. Soc.* **2001**, *123*, 2699.

[14] With addition of 2.0 equiv of pyrrolidine to the dimeric Ru-complex, a new set of ^1H NMR spectra are formed in which the integral ratio of *p*-cymene vs pyrrolidine is 1:1. The chemical shifts of *p*-cymene peaks in the amine-coordinated complex are changed as well as the coupling constants: see the Supporting Information.

[15] For some precedent examples involving Ru-acetylides, see: (a) Yi, C. S.; Liu, N. *Organometallics* **1998**, *17*, 3158. (b) Wakatsuki, Y.; Yamazaki, H.; Kumegawa, N.; Satoh, T.; Satoh, J. *J. Am. Chem. Soc.* **1991**, *113*, 9604.

[16] No reaction was observed when terminal alkynes were allowed to react with nonconjugated aldehydes or ketones under otherwise identical reaction conditions.

[17] Ruthenium enolates were proposed as intermediates in some transformations: (a) Hartwig, J. F.; Bergman, R. G.; Andersen, R. A. *Organometallics* **1991**, *10*, 3326. (b) Murahashi, S.-I.; Naota, T.; Taki, H.; Mizuno, M.; Takaya, H.; Komiya, S.; Mizuho, Y.; Oyasato, N.; Hiraoka, M.; Hirano, M.; Fukuoka, A. *J. Am. Chem. Soc.* **1995**, *117*, 12436. (c) Rasley, B. T.; Rapta, M.; Kulawiec, R. J. *Organometallics* **1996**, *15*, 2852. (d) Gómez-Bengoa, E.; Cuerva, J. M.; Mateo, C.; Echavarren, A. M. *J. Am. Chem. Soc.* **1996**, *118*, 8553. (e) Alvarez, S. G.; Hasegawa, S.; Hirano, M.; Komiya, S. *Tetrahedron Lett.* **1998**, *39*, 5209.