Ruthenium-Catalyzed Propargylic Alkylation of Propargylic Alcohols with Ketones: Straightforward Synthesis of γ-Keto Acetylenes

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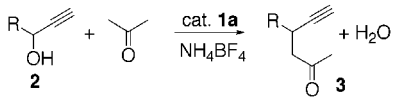
The allylic substitution reaction of allylic alcohol derivatives with nucleophiles catalyzed by transition-metal complexes is one of the most successful and reliable methods in organic synthesis.[1] The reaction proceeds via (η-allyl)metal species to afford a wide variety of allylated products with high chemo-, regio-, and stereoselectivities.[1] In sharp contrast, much less attention has been paid to the propargylic substitution reaction of propargylic alcohol derivatives with nucleophiles.[2] The Nicholas reaction is known to be an effective tool for such transformation but has some drawbacks: a stoichiometric amount of $Co_2(CO)_8$ is required, and several steps are necessary to obtain propargylic products from propargylic alcohols via cationic propargyl complexes $[(propargyl)Co_2(CO)_6]^+$.[3] We have recently disclosed the ruthenium-catalyzed propargylic substitution reactions of propargylic alcohols with various heteroatom-centered nucleophiles such as alcohol, amide, amine, thiol, and diphenylphosphine oxide to afford the corresponding propargylic products in high yields with complete regioselectivities.[4] Interestingly, the reactions are catalyzed by thiolate-bridged diruthenium complexes[5] such as $[Cp^*RuCl(\mu_2\text{-}SR)_2RuCp^*Cl]$ ($Cp^* = \eta^5\text{-}C_5Me_5$; R = Me (**1a**), Et, ^{n}Pr, ^{i}Pr (**1b**)) and $[Cp^*RuCl(\mu_2\text{-}S^iPr)_2RuCp^*(OH_2)]OTf$ (**1c**; OTf = OSO_2CF_3).[4] We have now extended this chemistry to a more valuable carbon−carbon bond formation reaction by using carbon-centered nucleophiles. Surprisingly, not only β-diketones such as acetylacetone but also *simple dialkyl ketones such as acetone* have been found to work effectively as nucleophiles, giving the corresponding propargylic alkylated products in high yields with complete regioselectivities. Preliminary results on this propargylic alkylation are described here.

Treatment of 1-phenyl-2-propyn-1-ol (**2a**) in acetone in the presence of **1a**[6] (5 mol %) and NH_4BF_4 (10 mol %) at reflux temperature for 4 h afforded 4-phenyl-5-hexyn-2-one (**3a**) in 78% isolated (85% GLC) yield (Table 1; run 1).[7,8] Neither allenic byproducts nor other regioisomers of **3a** were observed by GLC and ^{1}H NMR. The carbon−carbon bond formation exclusively occurred at the propargylic carbon of **2a**. The reaction proceeded even at room temperature, but 8 h was required to produce **3a** in 64% GLC yield (Table 1; run 2). Substantial isotope effect ($k_H/k_D = 2$) was observed when the reaction was carried out at 40 °C.[9] This result indicates that the C−H bond breaking at the α-position of acetone is involved in the rate-determining step. It is noteworthy that the propargylic alkylation of **2a** with acetone proceeds smoothly *under extremely mild and neutral reaction conditions*. This is in sharp contrast to the allylic alkylation catalyzed by a variety of transition-metal complexes where *a stoichiometric amount of base* is required to activate carbon-centered nucleophiles.[10]

Table 1. Propargylic Alkylation of Propargylic Alcohols (**2**) with Acetone Catalyzed by $[Cp^*RuCl(\mu_2\text{-}SMe)_2RuCp^*Cl]$ (**1a**)[a]



run		R	yield, %[b]	run		R	yield, %[b]
1	**2a**	Ph	**3a**, 78 (85)[c]	7	**2f**	*p*-$MeOC_6H_4$	**3f**, 56
2[d]	**2a**	Ph	**3a**, (64)[c]	8	**2g**	*p*-FC_6H_4	**3g**, 75
3	**2b**	*o*-$MeOC_6H_4$	**3b**, 72	9	**2h**	*p*-ClC_6H_4	**3h**, 67
4	**2c**	*o*-MeC_6H_4	**3c**, 74	10	**2i**	1-naphthyl	**3i**, 83
5	**2d**	*m*-MeC_6H_4	**3d**, 74	11	**2j**	2-naphthyl	**3j**, 88
6	**2e**	*p*-MeC_6H_4	**3e**, 82	12	**2k**	$Ph_2C{=}CH-$	**3k**, 55[e]

[a] All the reactions of **2** (0.60 mmol) were carried out in the presence of **1a** (0.03 mmol) and NH_4BF_4 (0.06 mmol) in acetone (36 mL) at reflux temperature for 4 h. [b] Isolated yield. [c] GLC yield. [d] Reaction was carried out at room temperature for 8 h. [e] 10 mol % of **1a** was used.

Reactions of various propargylic alcohols with acetone have been carried out in the presence of **1a** and NH_4BF_4. Propargylic substitution reactions of 1-aryl- and 1-alkenyl-substituted propargylic alcohols (**2b**−**k**) with acetone at reflux temperature for 4 h proceeded smoothly to afford the corresponding propargylic alkylated products (**3b**−**k**) in moderate to high yields (Table 1; runs 3−12). When (*R*)-1-phenyl-2-propyn-1-ol was treated with acetone at room temperature for 12 h, racemic **3a** was formed in 69% isolated yield. Reaction of 1,1-diaryl-substituted propargylic alcohols such as $Ph_2C(OH)C{\equiv}CH$ did not proceed even after a prolonged reaction time (72 h).

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(5) The thiolate-bridged diruthenium complexes (**1a**−**c**) have been found to provide unique bimetallic reaction sites for activation and transformation of various terminal alkynes, see: Nishibayashi, Y.; Yamanashi, M.; Wakiji, I.; Hidai, M. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 2909 and references therein.

(6) Preparation of **1a** is as follows. To a suspension of $[Cp^*RuCl_2]_2$ (8.3 g, 14 mmol) in THF (150 mL) was added $MeSSiMe_3$ (4.2 g, 35 mmol), and the mixture was stirred at room temperature for 24 h. A brown solid precipitated was filtered off, washed with *n*-hexane, and recrystallized from CH_2Cl_2−*n*-hexane to give brown crystals of **1a** (6.4 g, 10 mmol, 71%); ^{1}H NMR δ 1.62 (s, 30H, C_5Me_5), 2.51 (s, 6H, SMe_3).

(7) A typical experimental procedure for the reaction of **2a** with acetone catalyzed by **1a** is described below. In a 50 mL flask were placed **1a** (0.03 mmol) and NH_4BF_4 (0.06 mmol) under N_2. Anhydrous acetone (36 mL) was added, and then the mixture was magnetically stirred at room temperature. After addition of **2a** (0.60 mmol), the reaction flask was kept at reflux temperature for 4 h. The reaction mixture was treated with brine (150 mL) and extracted with diethyl ether (20 mL × 3). The ether layer was dried over anhydrous $MgSO_4$. For isolation, the extract was concentrated under reduced pressure by an aspirator, and then the residue was purified by TLC (SiO_2) with EtOAc−*n*-hexane (1/9) to give **3a** as a yellow solid (0.47 mmol, 78% yield).

(8) Other di- and monoruthenium complexes except for **1b** and **1c** were ineffective for the propargylic alkylation. See Supporting Information for experimental details.

(9) See Supporting Information for experimental details.

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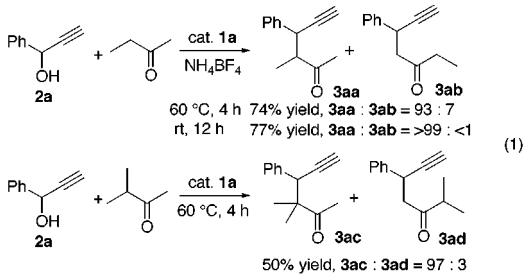
Striking regioselectivity was observed when unsymmetrical simple ketones were used as carbon-centered nucleophiles (eq 1). Thus, the propargylic alkylation occurred at the more

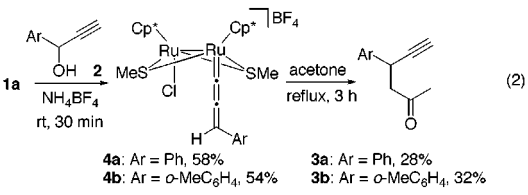


(1)

encumbered α-site of the ketones. The reaction at room temperature improved the regioselectivity of the products. This highly regioselective alkylation of the α-position of unsymmetrical ketones is of potential use in organic synthesis.[11,12]

Reactions with other symmetrical dialkyl ketones, β-diketones, and silyl enol ethers have been investigated. Typical results are shown in Table 2. When the reactions of **2a** with 3-pentanone, cyclopentanone, and cyclohexanone were carried out at 60 °C for 4 h, a mixture of two diastereomeric isomers was obtained in 71%, 52%, and 75% yields, respectively (Table 2; runs 1−3). Treatment of **2a** with 3 equiv of β-diketones and a silyl enol ether in $ClCH_2CH_2Cl$ at 60 °C for 4 h gave rise to the formation of the corresponding propargylic alkylated products in good yields, respectively (Table 2; runs 4−8).

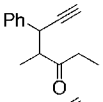
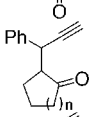
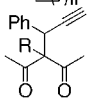
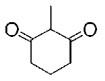
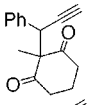
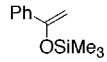
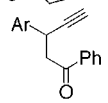
Reaction of **1a** with 1 equiv of propargylic alcohols (**2**) in the presence of NH_4BF_4 in tetrahydrofuran (THF) at room temperature for 30 min afforded the allenylidene complexes $[Cp^*RuCl(\mu_2\text{-}SMe)_2RuCp^*(C{=}C{=}CHAr)]BF_4$ (Ar = Ph (**4a**), Ar = *o*-$CH_3C_6H_4$ (**4b**)) in moderate yields (eq 2).[4] Heating of the allenylidene



(2)

complexes (**4a**, **4b**) in acetone at reflux temperature for 3 h led to the formation of **3a** and **3b** in 28% and 32% yields, respectively. Interestingly, when the reaction of **4b** with acetone was performed in the presence of 1 equiv of **2a**, the yield of **3b** was improved to 47% together with the formation of **3a** in 42% yield. Furthermore, reaction of **2b** with acetone in the presence of 5 mol % of **4b** at reflux temperature for 3 h afforded **3b** in 99% yield. These results indicate that the propargylic alkylation proceeds via the nucleophilic attack of an enolate carbon on the electrophilic C_γ atom in allenylidene intermediates[13] like **4**, but the detailed reaction mechanism involved in this reaction still remains unknown. Further investigations are currently in progress.

Table 2. Propargylic Alkylation of **2a** Catalyzed by **1a**

run	nucleophile	product	yield of **3** (%)[a]
1[b]		 **3ae**	71[c]
2[b]		 **3af** n = 1	52[d]
3[b]		**3ag** n = 2	75[e]
4[f]		 **3ah** R = H	52
5[f]		**3ai** R = Me	45
6[f]		 **3aj**	84
7[f]		 **3ak** Ar = Ph	50
8[f,g]		**3al** Ar = Fc	82

[a] Isolated yield. [b] Reaction of **2a** (0.60 mmol) with ketone (36 mL) was carried out in the presence of **1a** (0.03 mmol) and NH_4BF_4 (0.06 mmol) at 60 °C for 4 h. [c] Two diastereoisomers were formed with the isomer ratio of 63:37. [d] Two diastereoisomers were formed with the isomer ratio of 85:15. [e] Two diastereoisomers were formed with the isomer ratio of 70:30. [f] Reaction of **2a** (0.60 mmol) with 3 equiv of nucleophile was carried out in the presence of **1a** (0.03 mmol) and NH_4BF_4 (0.06 mmol) in $ClCH_2CH_2Cl$ at 60 °C for 4 h. [g] FcCH(OH)C≡CH (Fc = ferrocenyl) was used in place of **2a**.

In summary, we have found novel ruthenium-catalyzed propargylic alkylation of propargylic alcohols with various ketones *under mild and neutral reaction conditions* to afford the corresponding propargylic alkylated products in high yields with complete regioselectivities. This provides a versatile propargylic alkylation method directly from propargylic alcohols with ketones and ketone derivatives to afford the corresponding γ-keto acetylenes, which are very useful synthetic intermediates because of their regioselective convertibility to 1,4- and 1,5-diketones and, subsequently, to cyclopentenones and cyclohexenones.

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Supporting Information Available: Experimental procedures and spectral data for all of the new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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