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Transition Metal-Free Stereoselective α-Vinylation of Cyclic Ketones with Arylacetylenes in the Superbasic Catalytic Triad Potassium Hydroxide/*tert*-Butyl Alcohol/Dimethyl Sulfoxide

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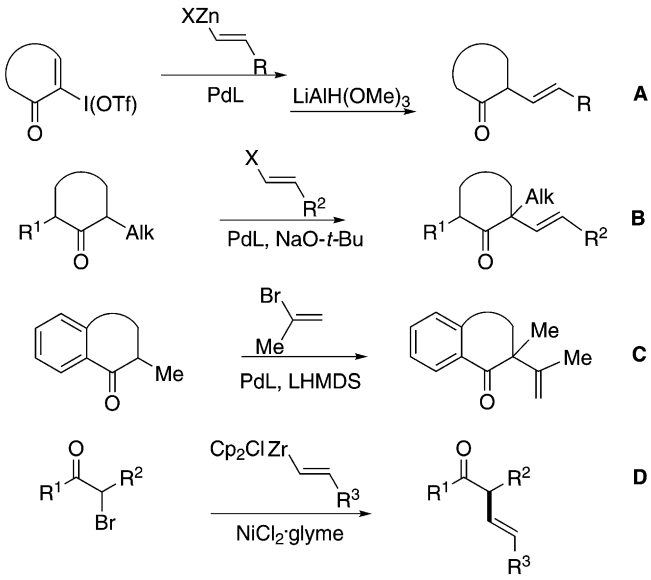
Abstract: A stereoselective α-vinylation of cycloaliphatic ketones with arylacetylenes under the transition metal-free conditions has been developed. The reaction is promoted by the superbasic catalytic triad potassium hydroxide/*tert*-butyl alcohol/dimethyl sulfoxide (80–110 °C, 1–2 h) to afford mainly (*E*)-β,γ-ethylenic ketones, their (*E*)-α,β-isomers being minor products, in up to 83% total yield.

Keywords: acetylenes; C–C bond formation; ketones; superbases; vinylation

The search for new sp^3-sp^2 C–C bond-forming reactions remains a standing challenge in the organic chemistry. In particular, such reactions might represent an important contribution to the synthesis of ethylenic cycloaliphatic ketones, which are versatile synthetic building blocks and key intermediates in drug design.[1] Therefore, straightforward catalytic methods for introducing an *E*- or *Z*-alkenyl group in an α-position of ketones with control of regiochemistry has been a subject of the research activity for a long time.[2] A special interest is directed to the β,γ-ethylenic carbonyl moiety as a highly reactive and chemically flexible structural unit.[3] The importance of the α-vinylation reactions of ketones stems not only from frequent appearance of the C=C double bond-carbonyl entities in natural products and biologically active compounds but also from the rich and well-studied chemistry of α,β- and β,γ-ethylenic ketones that enables expedient syntheses of complex structures. However, the approaches to such ketones often remain laborious and multi-step, requiring hardly accessible starting materials and transition metal catalysts with sophisticated ligands.[4] For instance, the α-alkenylation of cyclic ketones was performed *via* cyclic α-iodoenones and α-triflyloxyenones which were cross-coupled with alkenylzinc in the presence of palladium complexes [$Pd(PPh_3)_4$ or $Cl_2Pd(PPh_3)_2$ + 2*n*-BuLi] with further reduction of the resulting dienone with $LiAlH(OMe)_3$, the total yield over all the steps being fairly modest[5] (Scheme 1, **A**). Substituted cyclopentanones and cyclohexanones were vinylated with haloalkenes in the presence of $Pd_2(dba)_3$/aminophosphine ligand/NaO-*t*-Bu to produce the corresponding vinyl ketones in high yields and enantioselectivity[6] (Scheme 1, **B**). Later, a catalytic system [$PdP(t\text{-}Bu)_3Br]_2$/lithium hexamethyldisilazine was employed



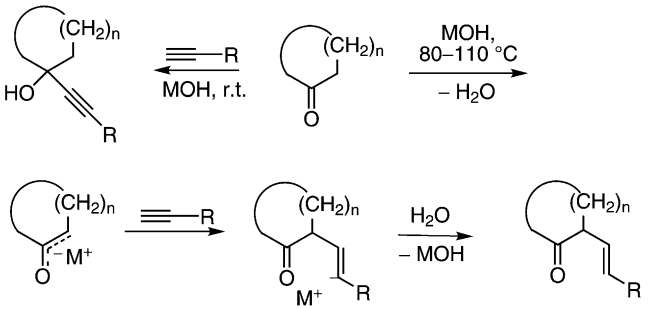
Scheme 1. Literature examples of the α-vinylation of cyclic ketones.

for the successful α-vinylation cyclic ketones such as 2-methyl-2,3-dihydroinden-1-one, 1-tetralone and 2-methyl-1-tetralone[7] (Scheme 1, **C**). Among the recent publications devoted to the synthesis of β,γ-ethylenic ketones (although acyclic ones), the enantioselective α-vinylation of ketones *via* nickel-catalyzed cross-coupling of α-bromo ketones with organozirconium reagents deserves attention[8] (Scheme 1, **D**).

The base-catalyzed nucleophilic addition of enolates to acetylenes might provide another direct entry to the chemistry of ethylenic ketones. But such an addition seemed to be precluded because, in the presence of basic catalysts, the formation of propargylic alcohols usually took place (Favorsky reaction).[9] However, recently, contrary to this common knowledge, alkyl aryl and alkyl hetaryl ketones were shown to be capable of regio- and stereoselective vinylation by acetylenes in the superbasic heterogeneous catalytic system MOH/DMSO (M = Na, K, Cs) to give the β,γ-ethylenic ketones.[10] Later, while describing the tandem assembling of methylene dispirocyclic ketals from cyclohexanones and arylacetylenes in the KOH/DMSO suspension, we also briefly mentioned about the formation of unsaturated ketones during this reaction.[11]

In the light of the above considerations, the possibility of the base-catalyzed vinylation of cyclic ketones with acetylenes until recently seemed fuzzy. First of all, the major obstacle for realization of this reaction would be due to the fact that the ketones readily added acetylide anions across the polar C=O bond to furnish propargylic alcohols.[9] Moreover, it was commonly accepted that enolate anions were unreactive as *C*-nucleophiles towards the unactivated multiple bonds on the basis of thermodynamic and kinetic grounds, for example, the formation of less thermodynamically favorable carbanions from more stable oxygen-centered (enolate) anions.[12] Among the experimental hurdles interfering in ketone vinylation with acetylene in the presence of bases were, apart from the aforementioned facile formation of acetylenic alcohols, the autocondensation of ketones and acetylide generation from terminal acetylenes. However, these rationalizations did not account for the expected electrophilic assistance from alkaline metal cations in stabilizing the emerging carbanions. Indeed, quantum chemical evaluation[13] showed that alkaline metal cations did facilitate nucleophilic attack at the C≡C triple bond. Experimentally, complexes of alkaline metal hydroxides with acetylenes (known as Tedeschi complexes)[14] were isolated and characterized. All this allows the superbase-induced reactions of acetylenes to be qualified as having essentially a metallocomplex character.

Having all this in mind, we systematically scrutinized the influence of experimental conditions for the reaction of cyclic ketones and arylacetylenes on the yield of ethylenic ketones to minimize the formation of the Favorsky product (Scheme 2). The Favorsky reaction itself as applied to cyclic ketones did not need improvement due to almost quantitative yields of the tertiary propargylic alcohols commonly achieved under optimal conditions.[13]



Scheme 2. Anticipated reaction of cyclic ketones with arylacetylenes in the presence of alkaline metal hydroxides.

However, our first experiments toward expansion of this synthesis over the cyclic ketones turned out to be disappointing. For instance, with the published catalytic systems, the yields of ethylenic ketones from cyclopentanone, cycloheptanone, cyclododecanone and phenylacetylene did not exceed 12%, generally being in the range 1–10%. Eventually, the screening of superbasic catalytic systems allowed us to arrive at a specific superbasic catalytic triad KOH/*t*-BuOH/DMSO securing fairly good preparative results, which are reported here.

We have found that in the presence of the above triad, cyclic ketones **1–6** added to arylacetylenes **7–12** (80–110 °C, 1-2 h, ketone:arylacetylene:KOH:*t*-BuOH molar ratio = 1:1:1:1) to furnish β,γ- (**13a–23a**, **16b**) and α,β- (**13b–15b**, **16c**, **17b–23b**) ethylenic ketones, both of *E* configuration, with the latter being minor products (on average 10% of the products mixture), in up to 83% total yield (Table 1).

The minor regioisomers of ethylenic ketones **13–23**, that is, α,β-ethylenic ketones **13b–15b**, **16c**, **17b–23b**, expectedly resulted from a partial 1,3-prototropic shift of the double bond toward the carbonyl moiety. The formation of a tertiary acetylenic alcohol (common product of the Favorsky reaction,[9] which might be anticipated here also) was not observed in this case.

The *E* configuration of β,γ-ethylenic ketones was confirmed by ^3J values (15.8–16.3 Hz) between protons at the double bond. The *E* configuration of minor α,β-ethylenic ketones was supported by the presence of characteristic cross-peaks in their NOESY spectra (Figure 1).

Table 1. Reaction of cyclic ketones **1–6** with arylacetylenes **7–12** in the superbasic catalytic triad KOH/*t*-BuOH/DMSO.

1–6 **7–12** **13a–23a** **13b–23b**

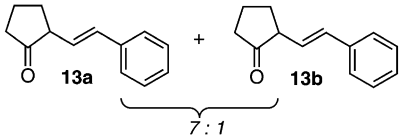
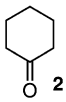
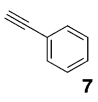
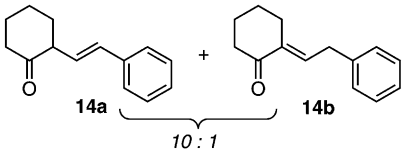
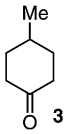
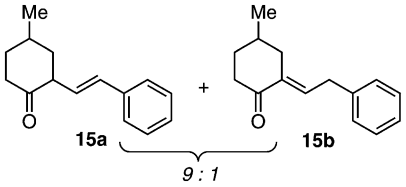
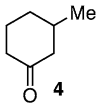
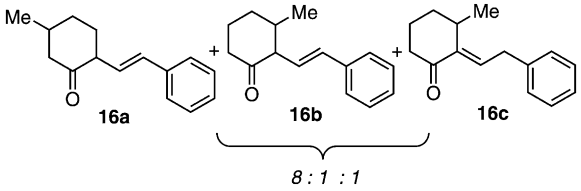
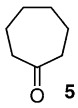
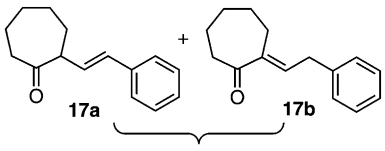
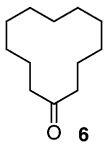
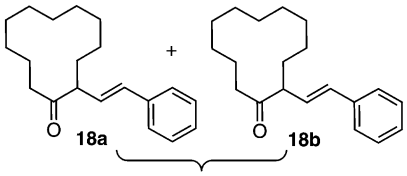
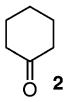
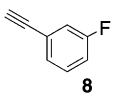
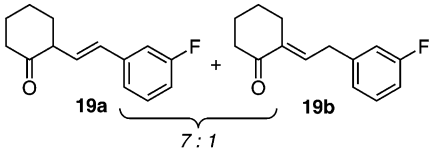
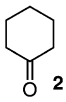
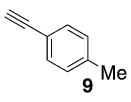
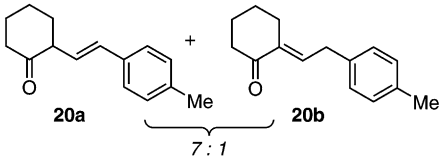
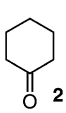
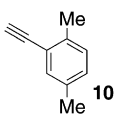
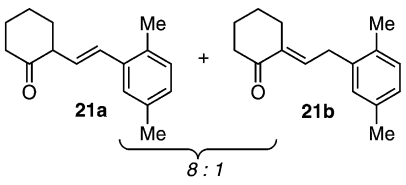
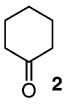
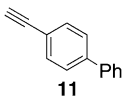
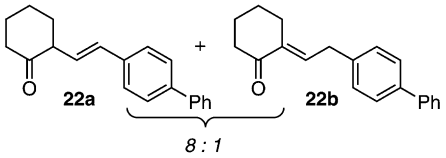
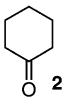
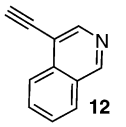
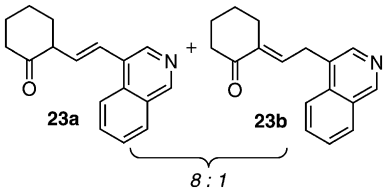
Ketone	Arylacetylene	Conditions	Product (isomer ratio)	Total yield [%][a]
 **1**	 **7**	80 °C, 2 h	 **13a** + **13b** *7 : 1*	25
 **2**	 **7**	100 °C, 1 h	 **14a** + **14b** *10 : 1*	83
 **3**	 **7**	100 °C, 1 h	 **15a** + **15b** *9 : 1*	51
 **4**	 **7**	100 °C, 1 h	 **16a** + **16b** + **16c** *8 : 1 : 1*	57
 **5**	 **7**	100 °C, 2 h	 **17a** + **17b** *8 : 1*	38
 **6**	 **7**	110 °C, 2 h	 **18a** + **18b** *8 : 1*	38
 **2**	 **8**	100 °C, 1 h	 **19a** + **19b** *7 : 1*	48
 **2**	 **9**	100 °C, 1 h	 **20a** + **20b** *7 : 1*	54
 **2**	 **10**	100 °C, 1 h	 **21a** + **21b** *8 : 1*	52

Table 1. (Continued)

Ketone	Arylacetylene	Conditions	Product (isomer ratio)	Total yield [%][a]
		100 °C, 1 h		45
		100 °C, 1 h		43

[a] Isolated yield after column chromatography.

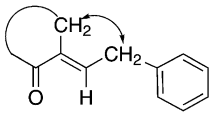
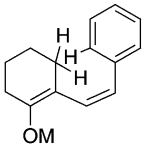


Figure 1. Characteristic NOESY correlations of α,β-ethylenic ketones.

The *E* configuration of the adducts **13**–**23** is unusual for a nucleophilic addition to monosubstituted acetylenes which is known to proceed as a concerted *trans*-addition leading to *Z* adducts.[15] Here, the uncommon stereochemistry can be explained by the fact that the kinetic products of the *Z* configuration undergo a rapid post-formation isomerization to the adducts of *E* configuration. A probable cause for the higher thermodynamic stability of the *E* isomers may lie in the enolization of β,γ-ethylenic ketones in the presence of a base. In a dienolate of the *E* configuration, the conjugation is assumed to be more effective, while in a *Z* dienolate, the steric repulsion of hydrogen atoms should destabilize this isomer.

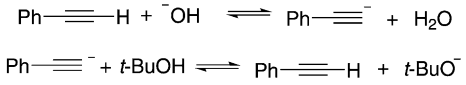


Notably, the major adducts of ketones to arylacetylenes have the structure of substituted styrenes (Table 1), that is, the double bond remains conjugated with the aromatic moiety despite the possibility of its migration toward the carbonyl group. This implies that conjugation in the styrene fragment is stronger than the competitive conjugation in the α,β-enone counterpart.

It is worthy to underline that, despite the modest to good isolated yields of α-vinylated cyclic ketones, the method here developed should not be underrated since it possesses clear beneficial preparative features such as high *E* stereoselectivity and a one-pot transition metal-free protocol using entirely accessible and inexpensive starting materials.

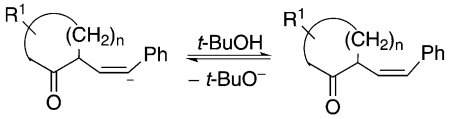
Thus, the key to the success of the vinylation of cyclic ketones is the introduction of a certain amount of *t*-BuOH as an active component of the catalytic system. The activating effect of *t*-BuOH makes it an important partner of the catalytic triad KOH/*t*-BuOH/DMSO that may be understood in terms of homogenizing the reaction mixture (*vs.* the KOH/DMSO heterogeneous suspension previously employed)[10] and hence increasing the concentration of the strongly basic catalyst in the solution.

Another role of *t*-BuOH as a co-catalyst is likely to be as a mild proton-transfer agent, which reduces the concentration of acetylenic carbanions, inactive toward the nucleophilic attack by the ketone carbanion [Eq. (1)].



(1)

Besides, *t*-BuOH as a controlled source of protons should facilitate the quenching of intermediate carbanions in a concerted manner [Eq. (2)].

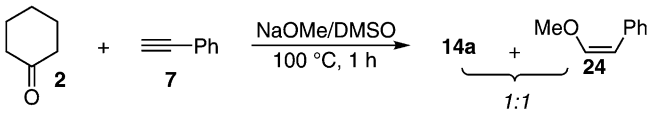


(2)

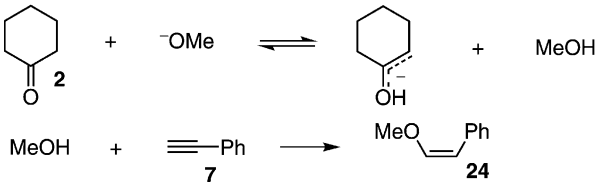
Fundamentally, the acidity of ketones is commonly known to be several orders higher as compared to that of acetylenes. For example, the pK_a values of ace-

tone, acetophenone and phenylacetylene measured in DMSO by Bordwell are 24.3[16], 22.5[16] and 26.5,[17] respectively. Consequently, the concentration of deprotonated ketones exceeds sizeably that of neutral molecules of acetylenes thus favoring the nucleophilic addition under study.

In the presence of the obviously more basic NaOMe/DMSO catalytic system, the reaction of cyclohexanone **2** with phenylacetylene **7** led to ~1:1 mixture of the expected α-vinylated ketone **14a** and a side product, (*Z*)-1-(2-methoxyvinyl)benzene **24**, the conversion of the starting ketone **2** being incomplete (~50%):



It follows that methanol, released upon deprotonation of the ketone, undergoes competitive vinylation with phenylacetylene:



Therefore, this competitive reaction is assumed to accompany (more or less) the α-vinylation of cyclic ketones in the presence of any alkaline metal alkoxide, thus complicating the isolation of the target products.

The yield of ethylenic ketones **13**–**23** was strongly dependent on the size of the cycle and the substituents therein. The best results were attained for cyclohexanones **2**–**4**, the most representative and synthetically meaningful family of cycloaliphatic ketones. 3-Methylcyclohexanone **4** was vinylated with phenylacetylene **7** under the same conditions (KOH/*t*-BuOH/DMSO, 100 °C, 1 h) to afford, along with α-ethylenic ketone **16a**, products of the α′-vinylation **16b** and **16c**. The ratio of ethylenic ketones **16a**:**16b**:**16c** was 8:1:1 (^{1}H NMR) and their total yield reached 57% (Table 1). As seen (Table 1), a methyl substituent in the cyclohexanone ring diminishes the total yield of vinylation products, assumingly due to the steric (in the case of ketone **4**), conformational and electron-donating effects of the methyl group, the latter decreasing the CH-acidity of the ketonic α-positions.

Cyclopentanone **1** gave with phenylacetylene **7** (80 °C, 2 h) the expected ethylenic ketones **13a** and **b** just in 25% yield, the conversion of ketone **1** being complete (seemingly, due to the base-catalyzed autocondensation). With a higher *t*-BuOH content (up to 3.0 equivalents relative to ketone **1**), the yield of ethylenic ketones **13a** and **b** was not improved. At a longer reaction time (80 °C, 3 h) and a higher temperature (100 °C, 1 h), a full tarring occurred, neither starting materials nor the anticipated products of C-vinylation of ketone **1** were detected in the reaction mixture (^{1}H NMR).

Generally, one of the major hurdles for the α-vinylation of cyclic ketones with arylacetylenes is the competitive based-catalyzed self-condensation of the former that remains a fundamental challenge that still needs to be overcome.

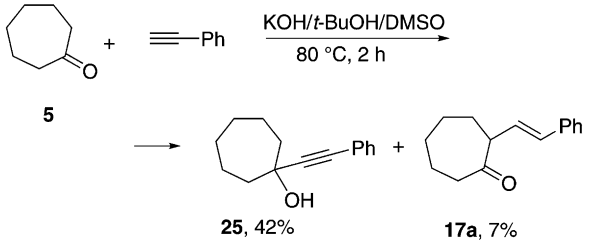
The larger ring-size ketones **5** and **6** afforded with phenylacetylene **7** the corresponding ethylenic ketones **17a** and **b** and **18a** and **b** in a better yield (38%, Table 1), although still lower than that in the case of cyclohexanones **2**–**4**.

At a lower temperature (80 °C, 2 h) the yield of adduct **17a** dropped to 7%, and the major reaction product became the corresponding tertiary propargylic alcohol **25** resulting from the Favorsky reaction (42% yield, Scheme 3).

The substitution in the benzene ring of arylacetylenes (3-F, 3-Me, 2,5-Me_2, 4-Ph) has no significant effect on the yield of the ethylenic ketones (Table 1).

It was shown (for the examples of ethylenic ketones **14a**, **15a**, **17a** and **22a**) that β,γ-ethylenic ketones can be isolated as pure isomers (without the corresponding α,β-ethylenic ketone admixtures) the column chromatography (SiO_2, eluent hexane-benzene with gradient from 1:0 to 0:1).

In summary, a straightforward transition metal-free, stereoselective α-vinylation of cycloaliphatic ketones with arylacetylenes in the presence of the superbasic homogeneous catalytic triad KOH/*t*-BuOH/DMSO to afford mainly β,γ-ethylenic ketones of the *E* configuration has been developed. The advantages of this new sp^3-sp^2 C–C bond-forming reaction are its high *E* stereoselectivity and use of the easily accessible superbasic catalytic system. The resulting styryl ketones (major products) are versatile and reactive, in-



Scheme 3. Reaction of cycloheptanone **5** with phenylacetylene **7** in the KOH/*t*-BuOH/DMSO system at 80 °C.

demand building blocks for organic synthesis and drug design.

Experimental Section

General Remarks

All chemicals and solvents are commercially available from Sigma Aldrich Chemie and were used without further purification. The elaborated procedure does not require degassing of DMSO and use of inert atmosphere and the benefit of DMSO as a solvent is that it is stable up to 150 °C for a long time (24 h, weight lost 0.1–1.0%).[18] ^{1}H and ^{13}C NMR spectra were recorded on a 400.13 and 100.61 MHz instrument, respectively, equipped with an inverse gradient 5 mm probe in $CDCl_3$ with hexamethyldisiloxane (HMDS) as an internal standard. All 2D NMR spectra were recorded by using the Bruker standard gradient pulse programs. The assignment of signals in the ^{1}H NMR spectrum was made using 2D COSY and NOESY experiments. Resonance signals of carbon atoms were assigned based on 2D ^{1}H-^{13}C HSQC and ^{1}H-^{13}C HMBC experiments.

Typical Procedure for the Reaction of Cycloaliphatic Ketones with Arylacetylenes (Reaction of Cyclohexanone 2 with Phenylacetylene 7 as Example)

A mixture of cyclohexanone **2** (2.00 g, 20.4 mmol), phenylacetylene **7** (2.08 g, 20.4 mmol), $KOH{\cdot}0.5\,H_2O$ (1.33 g, 20.4 mmol) and *t*-BuOH (0.15 g, 20.4 mmol) in DMSO (20 mL) was heated (100 °C) and stirred for 1 h. The reaction mixture, after cooling (20–25 °C), was diluted with H_2O (50 mL), neutralized with NH_4Cl and extracted with Et_2O (10 mL × 4). The organic extract was washed with H_2O (10 mL × 3) and dried (K_2CO_3). After removal of the solvent, a crude residue (3.89 g) was obtained. Column chromatography (SiO_2, eluent benzene) gave the pure vinyl ketones **14a** and **b** in a 10:1 ratio as a yellow oil; yield: 3.39 g (83%). Repeated column chromatography (SiO_2, eluent hexane-benzene with gradient from 1:0 to 0:1) gave the pure vinyl ketone **14a** and vinyl ketone **14b** with admixture of ketone **14a**.

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