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Base-Catalyzed Stereoselective Vinylation of Ketones with Arylacetylenes: A New C(sp^3)–C(sp^2) Bond-Forming Reaction

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Abstract: Alkylaryl- and alkylheteroarylketones, including those with condensed aromatic moieties, are readily vinylated with arylacetylenes (KOH/DMSO, 100 °C, 1 h) to give regio- and stereoselectively the (*E*)-β-γ-ethylenic ketones ((*E*)-3-buten-1-ones) in 61–84 % yields and with approximately 100 % stereoselectivity. This vinylation represents a new C(sp^3)–C(sp^2) bond-forming reaction of high synthetic potential.

Keywords: alkynes · C–C bond formation · ketones · superbases · vinylation

Introduction

C–C bond-forming reactions constitute the core of organic chemistry. Further progress in this area will profoundly contribute to the overall synthetic toolkit. Therefore, the efforts to discover new reactions of this type or improve known ones continue to gain pace. In recent years, particular attention has focused on the addition of the C–H moiety to C–C multiple bonds.

Most recently, the addition of cyclic ethers to arylacetylenes in the presence of a *tert*-butyl hydroperoxide/CuBr system has been reported.[1] This work was preceded by a communication about the ruthenium-catalyzed addition to alkenes of sp^3 C–H bonds adjacent to a nitrogen atom.[2] This pioneering publication was followed by more recent studies that showed that sp^3 C–H bonds adjacent to a heteroatom (nitrogen, oxygen, or sulfur) were more reactive than those next to a carbon atom and diverse catalytic systems were suggested for sp^3 C–H bond cleavage.[3] In this period, the catalytic oxidative cross-coupling of active methylene compounds with alkenes and alkynes to form C(sp^3)–C(sp^2) and C(sp^3)–C(sp) bonds was developed.[4] Also published was the iridium-catalyzed cyclization of alkene–amides in the cross-coupling reaction of an sp^3C–H bond with an alkene moiety.[5]

Over the last few years, another series of papers devoted to C(sp^3)–C(sp^2) bond-forming reactions, this time by the addition of 1,3-dicarbonyl compounds to acetylenes in the presence of $In(OTf)_3$, appeared.[6] The intramolecular cyclization of acetylenes, which have similar strong CH-acid moieties, for example H–C(CO_2Me), by employing NaH (*n*BuLi)[7] or $SnCl_4/Et_3N$ ($TiCl_4/Et_3N$)[8] was described.

In 1999, it was found that the superbase-catalyzed ($CsOH{\cdot}H_2O$/*N*-methylpyrrolidinone) addition of phenylacetonitrile carbanions to phenylacetylene led to a mixture of *E*/*Z* isomers of the adducts.[9] Previously, vinylation of similar CH-acids (2-phenylbutyronitrile[10] and *N*-(benzylidene)-glycinonitrile[11]) with acetylenes under basic phase-transfer conditions was performed. Earlier, stronger CH-acids, such as malonic nitriles and esters, were vinylated at the carbon atom with acetylene in the presence of cadmium and zinc stearates at high temperature (185–195 °C).[12] In the KOH/DMSO superbase system, 2-nitropropane and nitrocyclohexane added to acetylene to give the corresponding nitroalkenes.[13] In the sixties, base-catalyzed additions of polynitrofluoroalkanes to activated acetylenes, for example propynoates, were realized.[14]

Our scrutinized search of the literature gave not one hit concerning the direct base-catalyzed vinylation of ketones with acetylenes. The only report was a brief letter in the sixties on the radical-catalyzed addition of cyclohexanone to acetylene (di-*tert*-butyl peroxide, 150 °C, 10 atm) to afford 2-vinylcyclohexanone in a negligible yield (2.6 %) characterized by just the Raman spectrum.[15]

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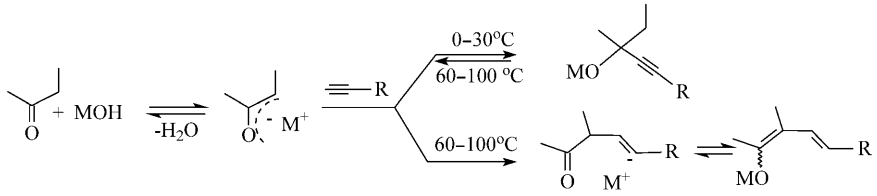
The reasons why the base-catalyzed vinylation of such a large and fundamental class of organic compounds as ketones remains so far unattained are of both theoretical and experimental nature. It is commonly accepted that an enolate anion is unreactive towards unactivated multiple bonds on thermodynamic and kinetic grounds, the major concern being the unfavorable thermodynamics due to the formation of less stable carbanions from more stable oxygen-centered (enolate) anions.[6c] Among the experimental arguments against ketone vinylation with acetylene in the presence of a base are the smooth base-catalyzed ethynylation of ketones to yield acetylenic alcohols (Favorsky reaction),[16] the easy autocondensation of ketones, and the deprotonation of terminal acetylenes, such as CH-acids, to generate carbanions. Meanwhile, these considerations disregard the role of alkali-metal cations, which may exert electrophilic assistance and stabilize emerging carbanions. Quantum chemical calculations[17] confirm that alkali-metal cations facilitate nucleophilic attack at the C≡C triple bond and the isolable complexes of alkali-metal hydroxides with acetylenes (Tedeschi complexes)[18] are known. Therefore, the reactions of acetylenes in the presence of alkali-metal hydroxides can be considered as having essentially metallocomplex character. After weighing up all the pros and cons, we have challenged the conventional wisdom (that based-catalyzed reactions of terminal acetylenes with ketones always give acetylenic alcohols) and have screened the conditions of the reaction of ketones with terminal arylacetylenes in the alkali-metal hydroxide/DMSO superbase system.[19] At low temperatures (0–30 °C),[17,20] this reaction is known to yield acetylenic alcohols,[16] which at higher temperature dissociate back to the starting materials (retro-Favorsky reaction)[21] and hence at elevated temperatures the addition reaction of ketone carbanions to acetylene might be competitive (Scheme 1).



Scheme 1. Anticipated reaction of ketones with acetylenes in the presence of alkali-metal hydroxides.

Results and Discussion

We found that in a KOH/DMSO suspension, alkylaryl- and alkylheteroarylketones **1–8**, including those with condensed aromatic moieties, added readily to arylacetylenes **9–12** (100 °C, 1 h) to deliver stereoselectively the products of C-vinylation of the ketones with the acetylenes, (*E*)-3-buten-1-ones **13–24** in 61–84 % yields and with about 100 % *E* stereoselectivity (Table 1). Upon heating to 100 °C, the KOH/DMSO suspension became homogeneous due to enolate formation.

As expected, as shown in the example of ketone **1** and acetylene **9**, at 0 °C (all other conditions as given in Table 1), the reaction gave the Favorsky acetylenic alcohol (2,4-diphenyl-3-butyn-2-ol) only, whereas at room temperature, a mixture of this alcohol and adduct **13** ($E/Z \approx 1:1$) in a ratio of 4:1 (as determined by ^{1}H NMR spectroscopy monitoring) had already formed, the conversion of ketone **1** not exceeding 60 %. In accordance with the above considerations (Scheme 1), at 60 °C only adduct **13** ($E/Z \approx 3:2$) was detected in the reaction mixture, the conversion of ketone **1** reaching 70 %.

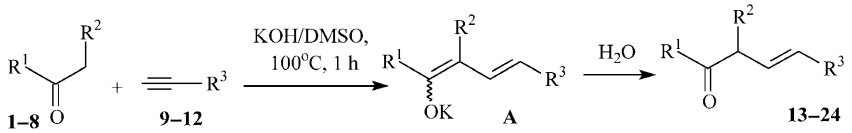
The KOH/reactant molar ratio has a key effect on the reaction results: with 10 mol % of KOH no products were detected (100 °C, 1 h), whereas with 50 mol % of KOH, the conversion of **1** was 25 % and solely adduct **13** was discernible (by ^{1}H NMR spectroscopy monitoring).

Apparently, the reaction proceeds through the intermediate dienolates **A**, which upon aqueous workup afford adducts **13–24**. With 4-nitrophenylacetylene (**12**), 2-(4-nitrophenyl)-5-phenylfuran (**25**) and 2-(4-nitrophenyl)-5-naphthylfuran (**26**) were isolated instead of the anticipated adducts. Obviously, in this case, the corresponding intermediates **A** cyclize to dihydrofurans **B** that are further oxidized (likely by **12**) to furans **25** and **26** (Scheme 2).

Special attention should be drawn to the high *E* stereoselectivity of the reaction. Normally, nucleophilic addition to monosubstituted acetylenes is a *trans*-concerted process leading to *Z* adducts.[22] As mentioned above, CsOH catalyzed addition of phenylacetonitriles to phenylacetylene was not stereoselective,[9] whereas a similar reaction with 1-propynyl benzene under the action of cesium alkoxides was found to be *E* stereoselective,[23] though no mechanistic explanation was given to this fact. Notably, our reaction, when conducted with CsOH, also lost its stereoselectivity (Table 2). Table 2 shows that the reaction is sensitive towards the nature of the alkali-metal cation.

Indeed, the effect of the alkali-metal cation in MOH on the ketone conversion and stereochemistry is crucial. The reaction is most stereoselective when conducted in the KOH/DMSO suspension, whereas with LiOH/DMSO no reaction occurs at all. Less effective and stereodirective is the system NaOH/DMSO. The CsOH/DMSO system, though it ensures full conversion of the ketone, appears to be the least stereodirective. LiOH is known to represent a tight ion pair and possesses a low basicity, whereas NaOH is intermediate (in the basicity and ion pair contact term) between that of lithium and potassium and hence is not as effective in the deprotonation of ketones as KOH. On the contrary, CsOH is commonly known to be a looser (solvent separated) ion pair and therefore, in this case, the hydroxide anion becomes a stronger base and consequently a more effective deprotonat-

Table 1. Stereoselective C-vinylation of ketones **1–8** with arylacetylenes **9–12** in the KOH/DMSO suspension.[a]



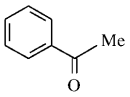
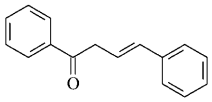
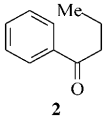
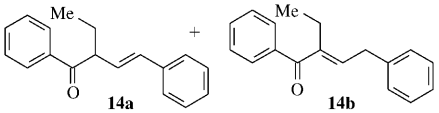
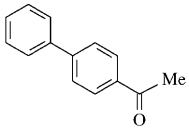
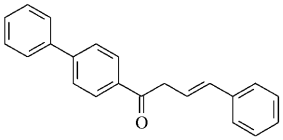
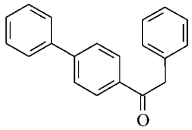
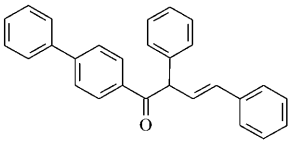
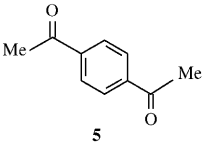
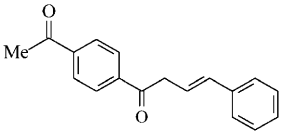
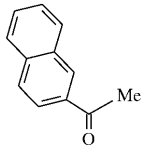
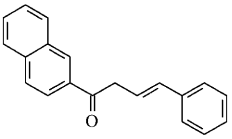
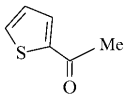
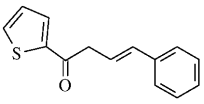
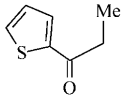
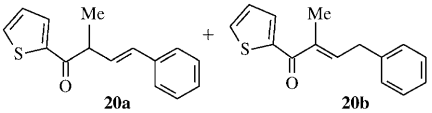
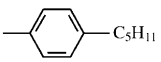
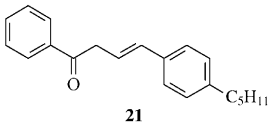
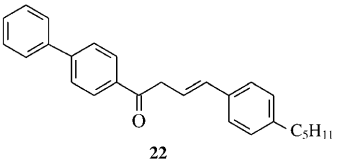
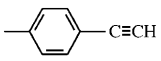
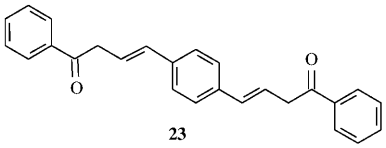
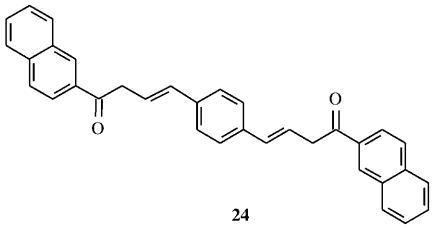
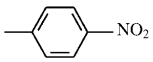
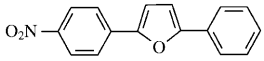
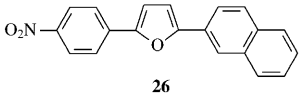
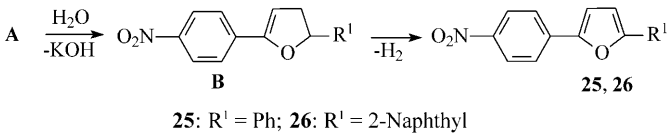
Ketone (R^1, R^2)	Acetylene (R^3)	Product	Yield [%][b]
 **1**	 **9**	 **13**	83
 **2**	**9**	 **14a** **14b**	79[c]
 **3**	**9**	 **15**	84
 **4**	**9**	 **16**	71
 **5**	**9**	 **17**	82
 **6**	**9**	 **18**	82
 **7**	**9**	 **19**	83
 **8**	**9**	 **20a** **20b**	81[c]
1	 **10**	 **21**	70
3	**10**	 **22**	83

Table 1. (Continued)

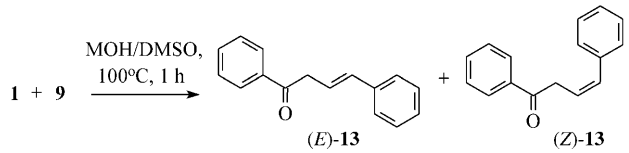
Ketone (R^1, R^2)	Acetylene (R^3)	Product	Yield [%][b]
1	 **11**	 **23**	61[d]
6	**11**	 **24**	63[d]
1	 **12**	 **25**	22[e]
6	**12**	 **26**	26[e]

[a] Reaction conditions: ketone **1–8** (10 mmol), arylacetylene **9–12** (10 mmol), KOH·0.5H_2O (10 mmol) in DMSO (30 mL), 100 °C, 1 h. [b] Yield of the isolated product. [c] Total yield, isomer ratio 4:1. [d] Ketone/acetylene molar ratio = 2:1. [e] The products resulted from further transformation of the adducts (Scheme 2).



Scheme 2. Formation of furans **25** and **26** by the cyclization of intermediates **A**, the initial adducts of ketones **1** and **6** with acetylene **12**.

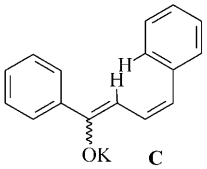
Table 2. Vinylation of ketone **1** with acetylene **9** in the MOH/DMSO system: the effect of the alkali-metal cation on the ketone conversion and the *E*/*Z* isomer ratio of adduct **13**.



MOH	conversion of **1** [%]	*E*/*Z*[a] ratio of **13**
LiOH	no reaction	
NaOH	70	10:1[b]
KOH·0.5H_2O	100	only *E* isomer
CsOH·H_2O	100	1:1[b]

[a] ^{1}H NMR spectroscopy monitoring. [b] For *E* isomer J_{trans} = 16.1 Hz, for *Z* isomer J_{cis} = 11.4 Hz.

ing species. Taking all this into account, the stereochemistry evolution as dependant of the metal cation nature can be tentatively rationalized as follows: the kinetic adduct is of *Z* configuration in agreement with a *trans*-concerted addition of nucleophiles to the triple bond[22] and the *E* configuration results from the post isomerization of the kinetic *Z* isomer, that is, the stereochemistry observed is a thermodynamically controlled process. This may be caused by more effective conjugation in the *E* isomer of the intermediate dienolate **A** and a steric repulsion of the hydrogen atoms in the corresponding *Z* isomer **C**.



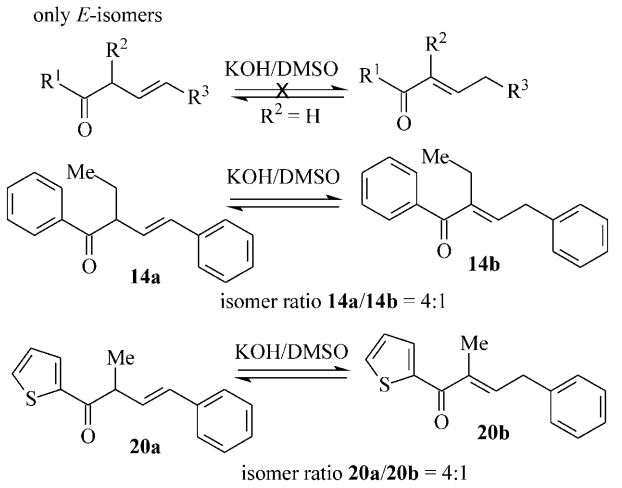
Kinetically, in the case of CsOH·H_2O, the concerted hydrogen transfer to quench the emerging carbanionic center should be most effective due to the looser ion pairing and a higher concentration of water (a proton transfer agent). Actually, when the reaction of ketone **1** with acetylene **9** in the CsOH/DMSO system was carried out with a longer reaction time (1.5 h instead of 1 h), the isolated product was adduct **13** of *E* configuration, whereas for a 1 h reaction time a mixture of *E*/*Z* = 1:1 isomers was formed (Table 2) indicating the conversion of the kinetic *Z* adduct to the thermodynamically controlled *E* isomer. The thermodynamic control of the *E* stereochemistry of the ketone vinylation at 100 °C also follows from the temperature dependence of the *E*/*Z* ratio of adduct **13**: as shown above, at room temperature the ratio *E*/*Z* = 1:1 is obtained, whereas at 60 °C this ratio changes in favor of the *E* isomer (3:2) and finally at 100 °C the *Z* isomer becomes indiscernible (by ^{1}H NMR spectroscopy) in the reaction mixture.

Apparently, the presence of DMSO as a coordinating solvent should be considered in the analysis: the geometry and coordination modes of MOH, acetylene, and the intermediate dienolates **A** and **C** in DMSO are certainly important.

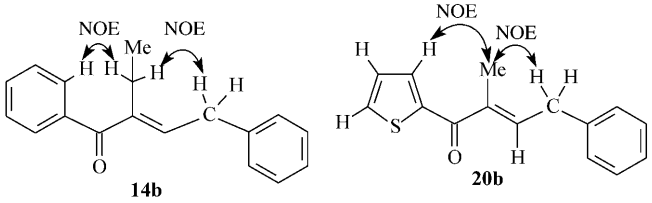
Within the ab initio approach (DFT) the formation of solvation shells of nondissociated alkali-metal hydroxides of the corresponding cations and the hydroxide ion in DMSO has recently been studied.[24] Complexes in which the alkali-metal cation (M^+) environment contains the coordinated acetylene molecule along with a DMSO molecule were shown to be formed. It was found that the accommodation of an acetylene molecule into the solvation sphere of nondissociated MOH is possible.

Notably, most of the adducts have the substituted styrene structure (Table 1), that is, with the ethenyl moiety conjugated with the benzene ring, in spite of the expected easy base-catalyzed migration (at least partially) of the double bond towards the carbonyl group. It follows that in these molecules the conjugation in the styrene unit is much stronger than the competitive conjugation in the α,β-enone counterpart. Apparently, the intermediate present before quenching is the dienolate and after aqueous treatment, the β,γ-ketone is kinetically formed. However, upon heating (1 h), also in the presence of KOH (10 % wt), no isomerization to α,β-ketones was discernible, thus implying that the β,γ-ketone is the thermodynamic product. Nonetheless, this partial double-bond migration still occurs in the case of adducts **14** and **20**, which exist as mixtures of the two structural isomers **14a**, **14b** and **20a**, **20b** both sets in a ratio of 4:1 (Scheme 3, Table 1). This is rationalized in terms of the double bond stabilization by alkyl substituents.

The geometry of the isomers **14b** and **20b** was determined from 2D NOESY spectra (Scheme 4).



Scheme 3. Stability of adducts to the KOH/DMSO-catalyzed isomerization.



Scheme 4. Characteristic NOE correlations of compounds **14b** and **20b**.

Conclusion

We have developed a new $C(sp^3)-C(sp^2)$ bond-forming reaction, that is, the MOH/DMSO-catalyzed (M = Na, K, Cs) stereoselective C-vinylation of alkylaryl- and heteroarylketones with arylacetylenes to afford 1,4-disubstituted 3-buten-1-ones of *E* configuration in high yields. Acylated condensed aromatic compounds and diphenyl derivatives as well as 1,4-diethynylbenzene tolerate the reaction conditions. The advantage of the reaction is the wide and practically inexhaustible range of starting materials (acylated aromatic, heteroaromatic, and condensed aromatic compounds together with diversely substituted arylacetylenes), that is, the coverage of all aromatics has been ensured. High regio- and stereoselectivity, easy product isolation procedures, and scalability are among the definite merits of the reaction found. Another advantage of the new synthesis is the simple, accessible, and transition-metal-free recoverable catalytic system (MOH/DMSO). The resulting 1,4-disubstituted (*E*)-3-buten-1-ones (allylic ketones) are synthetic intermediates for numerous chemical transformations, drug design, and in the creation of new optoelectronic materials.

Experimental Section

^1H and ^{13}C NMR spectra were recorded on a Bruker AVANCE 400 instrument (400.13 and 101.61 MHz 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 a standard gradient Bruker pulse programs. The procedure does not require degassing of DMSO or the use of an 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 %).[25] IR spectra were obtained on a Bruker Vertex 70 spectrometer. For full experimental data and spectroscopic data see the Supporting Information.

Synthesis of (*E*)-1,4-diphenyl-3-buten-1-one (13) (typical protocol): A mixture of acetophenone **1** (1.20 g, 10 mmol), phenylacetylene **9** (1.02 g, 10 mmol), and $KOH{\cdot}0.5H_2O$ (0.65 g, 10 mmol) in DMSO (30 mL) was heated (100 °C) stirred for 1 h. The reaction mixture, after cooling to RT, was diluted with water (70 mL), neutralized (NH_4Cl) and extracted with diethyl ether (10 mL × 4). The obtained organic extract was washed with water (10 mL × 3) and dried (K_2CO_3) overnight. After removal of the solvent, the crude residue (2.14 g) was obtained. Column chromatography (basic Al_2O_3, hexane) gave the pure product **13** (1.84 g, 83 %).

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[1] L. Huang, K. Cheng, B. Yao, J. Zhao, Y. Zhang, *Synthesis* **2009**, 3504–3610.
[2] N. Chatani, T. Asaumi, S. Yorimitsu, T. Ikeda, F. Kakiuchi, S. Murai, *J. Am. Chem. Soc.* **2001**, *123*, 10935–10941.
[3] a) V. G. Zaitsev, D. Shabashov, O. Daugulis, *J. Am. Chem. Soc.* **2005**, *127*, 13154–13155; b) M. Tobisu, N. Chatani, *Angew. Chem.* **2006**, *118*, 1713–1715; *Angew. Chem. Int. Ed.* **2006**, *45*, 1683–1684; c) S.-I. Murahashi, T. Nakae, H. Terai, N. Komiya, *J. Am. Chem. Soc.* **2008**, *130*, 11005–11012.

[4] a) Y. Zhang, H. Fu, Y. Jiang, Y. Zhao, *Org. Lett.* **2007**, *9*, 3813–3816; b) C.-J. Li, *Acc. Chem. Res.* **2009**, *42*, 335–344.
[5] B. DeBoef, S. J. Pastine, D. Sames, *J. Am. Chem. Soc.* **2004**, *126*, 6556–6557.
[6] a) M. Nakamura, K. Endo, E. Nakamura, *J. Am. Chem. Soc.* **2003**, *125*, 13002–13003; b) M. Nakamura, K. Endo, E. Nakamura, *Org. Lett.* **2005**, *7*, 3279–3281; c) K. Endo, T. Hatakeyama, M. Nakamura, E. Nakamura, *J. Am. Chem. Soc.* **2007**, *129*, 5264–5271; d) H. Tsuji, T. Fujimoto, K. Endo, M. Nakamura, E. Nakamura, *Org. Lett.* **2008**, *10*, 1219–1221.
[7] O. Kitagawa, T. Suzuki, H. Fujiwara, M. Fujita, T. Taguchi, *Tetrahedron Lett.* **1999**, *40*, 4585–4588.
[8] O. Kitagawa, H. Fujiwara, T. Suzuki, T. Taguchi, M. Shiro, *J. Org. Chem.* **2000**, *65*, 6819–6825.
[9] D. Tzalis, P. Knochel, *Angew. Chem.* **1999**, *111*, 1547–1549; *Angew. Chem. Int. Ed.* **1999**, *38*, 1463–1465.
[10] M. Makosza, J. Czyzewski, M. Jawdosiuk, *Org. Synth.* **1988**, *6*, 940–943.
[11] A. Jonezyk, Z. Pakulski, *Tetrahedron Lett.* **1996**, *37*, 8909–8912.
[12] M. Bukowska, J. Prejzner, *Pol. J. Chem.* **1983**, *57*, 867–873.
[13] B. F. Kukharev, V. K. Stankevich, G. R. Klimenko, *Mendeleev Commun.* **2002**, 63–64.
[14] V. Grakauskas, K. Braun, *J. Org. Chem.* **1969**, *34*, 3927–3930.
[15] N. I. Shuikin, B. L. Lebedev, V. G. Nikolskii, *Russ. Chem. Bull.* **1965**, *14*, 386.
[16] a) A. E. Favorsky, *Zh. Ross. Khim. Obshchestva* **1906**, *37*, 643; b) M. Smith, J. March, *March's Advanced Organic Chemistry*, 6th ed., Wiley, New York, **2007**, p. 1360.
[17] B. A. Trofimov, *Curr. Org. Chem.* **2002**, *6*, 1121–1162, and references therein.
[18] R. J. Tedeschi, *J. Org. Chem.* **1965**, *30*, 3045–3049.
[19] B. A. Trofimov in *Modern Problems of Organic Chemistry, Vol. 14* (Eds.: A. A. Potekhin, R. R. Kostikov, M. S. Baird), St.-Petersburg University Press, St.-Petersburg, **2004**, pp. 121–163.
[20] B. A. Trofimov, A. I. Mikhaleva, A. M. Vasil'tsov, R. N. Nesterenko, V. K. Stankevich, L. E. Belozerov, V. A. Khamataev, RF 2059597, **1996**; [*Chem. Abstr.* **1997**, *126*, 59646].
[21] G. T. Crisp, Y.-L. Jiang, *Synth. Commun.* **1998**, *28*, 2571–2576.
[22] J. I. Dickstein, S. I. Miller in *The Chemistry of the Carbon–Carbon Triple Bond, Part 2* (Ed.: S. Patai), Wiley, New York, **1978**, pp. 813–955.
[23] C. Koradin, A. Rodriguez, P. Knochel, *Synlett* **2000**, 1452–1454.
[24] E. Yu. Larionova, N. M. Vitkovksaya, V. B. Kobychev, I. L. Zaytseva, B. A. Trofimov, *J. Struct. Chem.* **2009**, *50*, 18–27.
[25] Dimethyl sulfoxide (DMSO), Technical Bulletin, Crown Zellerbach Chemical Products Division, Vancouver (Orchards), WA 98662, **1985**.

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