

Catalyzed Reactions of Enolates and Cations: A Novel Method for Enolate Alkylation

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Abstract: The first *tertiary* alkylations, alkoxyalkylations, and aldehyde enolate allylations are described proceeding with low catalyst loading (0.1 mol % to 5 mol %). The reactions proceed in short times, can be performed without solvent and under ambient conditions.

Keywords: alkylation; boron; catalysis; copper; enolate

The alkylation of ketone enolates constitutes one of the central reactions for the formation of carbon-carbon bonds in chemistry. To achieve this transformation enolates are usually generated under strongly basic conditions and are further reacted with an alkylating reagent.^[1] More recently these transformations have been achieved in the presence of catalysts.^[2] Despite intense efforts a drawback of these procedures is that high regio- and stereoselectivity of enolate generation is not always easy to achieve, especially in the case of ketones with sterically similar substituents. Also, the atom economy of the overall process is low.^[3] A different concept developed by Reetz allows for the reaction of S_N1 -active electrophiles with silyl enol ethers in the presence of stoichiometric amounts of Lewis acids.^[4] However, a general reaction catalytically generating an enolate and the alkylating reagent, ideally from one precursor, with high regio- and stereocontrol and atom economy has, until now, remained elusive.

We decided to address exactly these issues by employing enol ethers as enolate precursors based on the reports that many simple ethers can be cleaved in the presence of Lewis acids.^[5] A less general concept has been realized in Ferrier-type rearrangements.^[6] To the best of our knowledge, a catalytic or enantioselective variation of these systems has, as yet, not been described. A distinct advantage of our method is the stereoselective generation of enolates from the corresponding enol ethers with a double bond position and configuration established during enol ether synthesis. An example of the reaction is depicted in Figure 1.

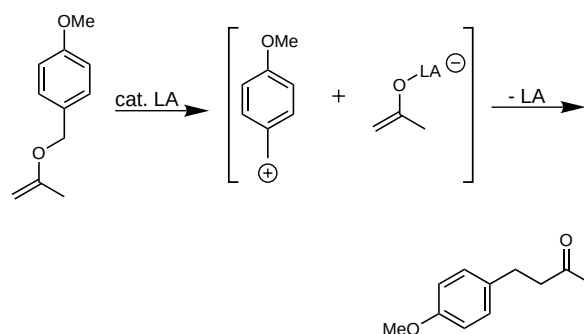


Figure 1. Concept for the Lewis acid-catalyzed alkylation of enolates.

Efficient and well established methods for the synthesis of enol ethers are olefinations of esters and isomerizations of allyl ethers either by transition metal complexes or base.^[7]

We reasoned that a good starting point would be the use of *p*-methoxybenzyl (PMB) enol ethers in the presence of $B(C_6F_5)_3$ or $Cu(OTf)_2$. Both Lewis acids have recently been successfully used in catalysis and are reasonably stable to water and air.^[8,9] Other Lewis acids, e.g., BPh_3 , ZnI_2 , $Zn(OTf)_2$, $Mg(OTf)_2$, and $La(OTf)_3$ induced no reaction, $TfOH$ catalyzes the reaction. Some of the results obtained are summarized in Table 1. The reaction proceeded swiftly (< 5 min) with low catalyst loading (1 mol %) of $B(C_6F_5)_3$ at 1 M concentration in CH_2Cl_2 . Polyalkylation was never observed. Entry 3 demonstrates the specific usefulness of our enol ether method. 3-Nonanone, the starting material for enolate alkylation under basic conditions, cannot be deprotonated regioselectively in the presence of bases.^[10]

Initially, the transformation was carried out under strictly anhydrous conditions and under Ar. However, these precautions were not necessary and performing the reaction under an atmosphere of air in undistilled solvents also led to a very satisfying result as shown in Entry 2. The turnover frequency of the catalyst is at least $800\ h^{-1}$ and thus very high for a Lewis acid catalyst in a carbon-carbon bond-forming reaction.

The method is not restricted to stabilized benzylic cations as exemplified by the efficient transformations

Table 1. Lewis-acid catalyzed reaction of enol ethers in CH₂Cl₂.

Entry	Substrate	Product	Catalyst	Yield [%]
1			B(C ₆ F ₅) ₃ 1 mol %	84 ^[a]
2			B(C ₆ F ₅) ₃ 1 mol %	80 ^[b]
3			B(C ₆ F ₅) ₃ 1 mol %	70 ^[c]
4			B(C ₆ F ₅) ₃ 1 mol %	78
5			B(C ₆ F ₅) ₃ 0.1 mol %	84 ^[d]
6			Cu(OTf) ₂ 0.25 mol %	81 ^[e]

^[a] (Z):(E) = 78:22; 1 M.^[b] As in [a] but reaction performed in undistilled solvents under an atmosphere of air.^[c] (Z):(E) = 88:12; 1 M.^[d] Ad = 1-adamantyl; (Z):(E) = 80:20; 3 M.^[e] (Z):(E) = 84:16; 2.5 M; 0.1 mol % catalyst, neat, 72% yield.

of the 1-adamantyl enol ether and the MOM-protected enol ether. For these cases we also investigated a further reduction of catalyst loading and found that high yields (>80%) could be obtained with as little as 0.25 or 0.1 mol % of the catalysts at 2.5–3 M concentration. As shown in Entry 6 it is even possible to conduct the reaction without solvent in the presence of 0.1 mol % catalyst, albeit at the expense of a slight reduction in yield (72%). Clearly, the above described attractive features compare well with the usual low temperature and inert conditions at low concentrations for enolate alkylation and meet the demands for efficient synthesis.

Another interesting and synthetically important class of stabilized cations are allyl cations. The necessary substrates, allyl vinyl ethers are, of course, also used in Claisen rearrangements and are therefore readily accessible.^[11] The ionic nature of the reaction described here does, however, lead to a fundamentally different course of events. After cleavage of the substrate into ions recombination to yield the products is governed by steric interactions between the enolate and the cation. This type of transformation has first been described by

Table 2. Lewis acid-catalyzed reaction of allyl vinyl ethers in CH₂Cl₂ (1 M).

Entry	Substrate	Product	Catalyst	Yield [%]
1			B(C ₆ F ₅) ₃ 1 mol %	72
2			Cu(OTf) ₂ 5 mol %	77 ^[a]
3			Cu(OTf) ₂ 5 mol %	75 ^[b]
4			Cu(OTf) ₂ 5 mol %	54 ^[c]
5			B(C ₆ F ₅) ₃ 1 mol % 0.25 mol %	90 84

^[a] (Z):(E) = 91:9, ds = 1:1.^[b] -65 °C.^[c] -40 °C.

Grieco in concentrated solutions of LiClO₄ in ether.^[12] The catalytic variation in LiClO₄ displays substantially lower reactivity.^[12c] However, the hazardous nature^[13] of this reagent can cause problems. Some of the results under our catalytic conditions are summarized in Table 2.

Diverse substitution of the enol ether poses no problems, even generating aldehyde enolates for facile alkylation can be readily utilized. Besides, trisubstituted allyl systems, methallyl, allyl, and diphenylallyl ethers can also be employed in the reaction. Entries 3 and 4 are especially remarkable since to the best of our knowledge these cations could not be formed in the highly polar and ionizing medium LiClO₄/Et₂O. In these cases the reaction temperatures are an indicator for the ease of ionic cleavage. Thus, for the least stable allyl cation a higher temperature has to be employed than for the methallyl cation. For Entries 3 and 5 the non-concerted ionic pathway was demonstrated by deuterium labeling studies as shown in Figure 2.

Entry 5 was chosen to demonstrate that the catalytic enolate alkylation is, in some instances, more efficient

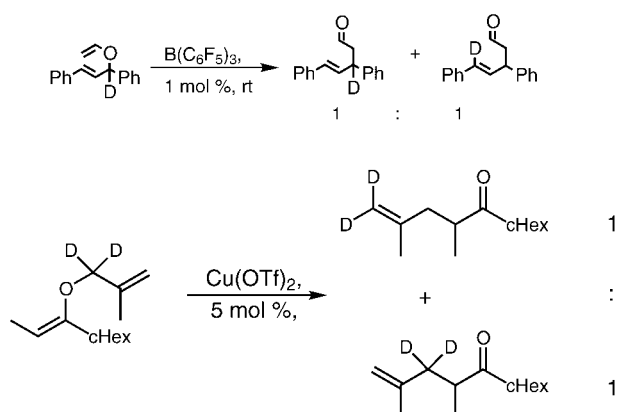


Figure 2. Deuterium labeling studies as evidence for a non-concerted mechanism.

than a concerted Claisen rearrangement.^[14] When the [3,3] rearrangement is catalyzed^[14b] by Yamamoto's excellent bulky aluminum reagents the best result (10 mol % catalyst, 45% yield after 13 h) is somewhat inferior to the result under our conditions (0.25 mol % catalyst, 84% yield after 5 h).

In summary, we have devised an efficient catalytic system for the alkylation of enolates based on the Lewis acid-catalyzed cleavage of enol ethers. We anticipate that the mild reaction conditions, insensitivity to ambient exposure, low catalyst loading, high to excellent turnover frequencies, and generality of our system meet the demands for efficient synthesis and will thus lead to considerable use in organic synthesis.

Experimental Section

Representative Procedures

1-(1-Phenylpropenyloxy)-adamantane (Table 1; entry 5): Under an argon atmosphere 40 mL of a 1.0 M solution of TiCl_4 in dichloromethane was added at 0 °C to 150 mL of dry THF. After the resulting yellow suspension was warmed up to room temperature TMEDA (12 mL, 80 mmol) was added and the brown solution was stirred for 10 min. Zinc (6.0 g, 90 mmol) was added and when the color of the suspension had changed from brown to dark greenish blue (ca. 30 min) 2.7 mL of 1,1-dibromoethane (2.7 mL, 22.0 mmol) and 1-adamantyl benzoate (2.56 g, 10.0 mmol) were added simultaneously and the mixture was stirred overnight. The reaction mixture was hydrolyzed by 6 mL of a saturated K_2CO_3 solution. Afterwards the complete reaction mixture was filtered through a short column of alumina (Merck, aluminum oxide 90 standardized) using diethyl ether as eluent. The solvent was removed under reduced pressure and the residue purified by column chromatography on alumina with light petroleum ether (bp 40/60 °C) to give 1-(1-phenylpropenyloxy)-adamantane as a mixture of diastereoisomers (*Z:E* = 80:20); yield: 2.5 g (9.3 mmol, 93%). R_f (PE): 0.6; ^1H NMR (400 MHz, C_6D_6): δ = 7.59–7.49** (m, 2.5H), 7.19–7.11** (m, 2H), 7.09–7.03** (m,

1H), 5.46* (q, J = 7.3 Hz, 1H), 5.37 (q, J = 6.8 Hz, 1H), 1.93–1.83** (m, 10H), 1.41* (m_c , 2H), 1.34 (m_c , 3H); ^{13}C NMR (100 MHz, C_6D_6): δ = 151.9, 150.2*, 142.8, 139.9*, 129.0, 128.1*, 127.3, 126.4*, 113.9, 113.3*, 78.4, 76.8*, 44.0, 43.7*, 36.5, 36.4*, 31.3, 31.2*, 13.3, 13.0*; HRMS (EI, 70 eV): calcd. for (M^+): 268.1827; found: 268.1822; IR (neat): ν = 3020, 2910, 2850, 1650, 1490, 1445, 1355, 1325, 1300, 1205, 1100, 1065, 1030, 965, 905, 810, 780, 760, 725, 700, 640 cm^{-1} . ** signals of minor and major isomer not separated, * signals of minor isomer.

2-Adamantan-1-yl-1-phenylpropan-1-one^[15] (Table 1; entry 5): $\text{B}(\text{C}_6\text{F}_5)_3$ (1.5 mg, 3 μmol) was dried by gentle heating (1 min) under vacuum and was dissolved in CH_2Cl_2 (1 mL). After addition of the enol ether (804 mg, 3.0 mmol) stirring was continued for 20 h at room temperature. After quenching by addition of 3 drops of triethylamine the solvent was removed and the residue purified by SiO_2 chromatography (cyclohexane/ethyl acetate = 99/1) to afford the desired product; yield: 680 mg (84%). $\text{C}_{19}\text{H}_{24}\text{O}$ (268.18 g/mol); R_f (PE: Et_2O = 98:2): 0.28; ^1H NMR (300 MHz, CDCl_3): δ = 7.97–7.80 (m, 2H), 7.51–7.43 (m, 1H), 7.41–7.31 (m, 2H), 3.24 (q, J = 7.0 Hz, 1H), 1.87 (bs, 3H), 1.74–1.37 (m, 12H), 1.02 (d, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3): δ = 205.2, 139.2, 132.6, 128.5, 128.2, 49.3, 40.2, 37.0, 35.9, 28.7, 11.5; HRMS (EI, 70 eV): calcd. for (M^+): 268.1827; found: 268.1823; IR (neat), ν = 2905, 2850, 1675, 15945, 1560, 1355, 1315, 1245, 1210, 1180, 1065, 960, 720, 695, 665 cm^{-1} .

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