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Catalytic ketone olefination with methyltrioxorhenium

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Abstract—Methyltrioxorhenium (MTO) catalyses the olefination of ketones with ethyl diazoacetate in the presence of triphenylphosphane. Unactivated ketones require the addition of 0.5 equiv of benzoic acid to achieve good yields, while trifluoromethyl ketones require no co-catalyst. The optimised system allows the olefination of aromatic, aliphatic, unsaturated, cyclic and trifluoromethyl ketones.

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1. Introduction

The olefination of aldehydes and ketones is an important transformation in organic synthesis. The Wittig reaction and its variations provide a highly effective and general method, but still have several drawbacks.¹ The catalytic approach to aldehyde olefination has received considerable attention in recent years,² while the research on ketone olefination is far less developed and only a few examples of transition metal complexmediated ketone olefination systems are known.³

Methyltrioxorhenium (MTO) is an easily accessible organometallic complex whose stability and high catalytic activity in several processes makes it an attractive target for new catalytic applications.⁴ Recently we published a detailed study on the catalytic aldehyde olefination reaction with several organometallic rhenium complexes and we observed that some MTO derived complexes are able to catalyse the olefination of ketones.⁵ Based on the good results obtained with MTO in the catalytic aldehyde olefination, where it was one of the first catalysts reported,^{2,6} we tested its suitability for the catalytic ketone olefination.

Herein, the results of our research on catalytic ketone olefination with MTO as catalyst are presented. The

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developed method proves to be general and straightforward to apply for a wide range of ketones.

2. Results and discussion

The olefination of cyclohexanone with triphenylphosphane (PPh₃) and ethyldiazoacetate (EDA) at 80 °C in toluene with 5 mol % MTO as catalyst (see Experimental part for details) proceeds comparatively slowly, affording less than 10% of olefin after 48 h of reaction time. The slow progress, being in contrast to the reaction rate of the correspondent aldehyde olefination system⁶ is expected since the ketone carbonyl group is generally much less electrophilic than the aldehyde carbonyl moiety. This difference is also known for the Wittig ketone olefination, which in the absence of other reactants usually requires harsh reaction conditions to obtain good results.⁷

To overcome this problem, ways to enhance the electrophilicity of the carbonyl group and render it a higher reactivity were surveyed. It is reasonable to assume that Lewis or Brönsted acids can form complexes with or protonate ketone's carbonyl group increasing its electrophilic character and possibly its reactivity. Therefore, the olefination of cyclohexanone using Lewis acids (SbCl₅ and Et₃OBF₄) as co-catalysts for the olefination of cyclohexanone under the same reaction conditions was attempted. Along with unreacted ketone, the main reaction products are the coupling products of EDA (ca. 35%), as well as the ring extension product 2-oxocycloheptane carboxylic acid ethyl ester (ca. 25%). The

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$$\frac{R^{1}}{R^{2}}C=O + PPh_{3} + N_{2}=CHCO_{2}Et \qquad \underbrace{\frac{5\% \text{ MTO, Toluene}}{80 \text{ °C, } 0.5 \text{ eq Benzoic Acid}} \xrightarrow{R^{1}} R^{2}C=C \underbrace{\mathcal{O}_{2}CO_{2}Et}^{\mathcal{H}} + N_{2} + Ph_{3}P=O$$

Scheme 1.

olefin yield remains below 10% showing that strong Lewis acids do not activate the ketones towards the olefination reaction.

The Wittig reaction between aldehydes⁸ or ketones^{8,9} and Ph_3P =CHCO₂Et can be strongly accelerated by sub-molar quantities of benzoic acid, and Zhang et al. have already successfully applied this Brönsted acid for catalytic ketone olefination^{3c,3d} applying Fe(TPP)Cl and Co(TPP) as the catalysts.

The olefination of cyclohexanone with PPh₃ and EDA at 80 °C in toluene, using 5 mol % MTO and 0.5 equiv of benzoic acid as co-catalyst (Scheme 1), affords 70% olefin after a reaction time of 48 h. This remarkable improvement in activity led us to further explore the potential of this reaction system.

The olefination of acetophenone under the same reaction conditions affords 65% of olefin with an *E:Z* ratio of 13:87 (Table 1, entry 3) after 48 h of reaction. If only 0.2 equiv of benzoic acid are used in the same reaction, the olefin yield remains below 15%. Therefore, 0.5 equiv of co-catalyst was applied throughout all further experiments.

A comparatively electron-deficient ketone such as 4-nitroacetophenone is more reactive than acetophenone and the olefination reaction is completed after 24 h with 70% olefin yield. Performing the reaction at room temperature causes a significant decrease of the reaction rate, though it is beneficial for the reaction's selectivity (entries 5 and 6).

Reducing the MTO loading to half (2.5 mol %) requires a longer time for the olefination of 4-nitroacetophenone to reach completeness, however, the yield and selectivity remain quite similar (entries 5 and 7). To test the effectiveness of MTO in the olefination of ketones, we extended the study to a series of other substrates (entries 8–12), using the optimised reaction conditions, namely, toluene at 80 °C with a catalyst loading of 5 mol % and 0.5 equiv of benzoic acid as co-catalyst.

This set of results allows drawing the following conclusions: activated ketones, that is, electron-deficient ketones, react well and reach good to excellent yields within short reaction times (entries 5 and 12). In fact α, α, α -trifluoro-acetophenone is active enough to be olefinated with quantitative yield in the absence of any co-catalyst with a high Z-isomer selectivity.^{3b}

The olefination of inactivated ketones (entry 8) is also possible although—as expected—with lower yields and longer reaction times. This outcome is due to the low electrophilicity of the unactivated carbonyl group.

The ability of MTO to catalyse a wide array of ketones is noteworthy: aromatic, cyclic, α , β -unsaturated, aliphatic and trifluoromethyl ketones can all be successfully olefinated by the MTO system, most importantly with the highest selectivities reported so far.

In conclusion, a useful process for the olefination of ketones under non-basic conditions could be developed, confirming once more that MTO is one of the most versatile catalysts available.

3. Experimental

3.1. General information

All reactions were carried under an inert gas atmosphere (Argon), using standard Schlenk techniques. Solvents

Table 1. Performance of MTO in ketone olefination with PPh3 and EDA using 0.5 equiv of benzoic acid as co-catalyst	
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Entry	Ketone	%MTO	T/°C	Yield ^a /%	$E:Z^{d}$	Reaction time
1	Cyclohexanone	5	80	<10 ^b	_	50
2	Cyclohexanone	5	80	71	_	50
3	Acetophenone	5	80	65	13:87	50
4	Acetophenone	5	80	15°	42:58	68
5	4-Nitro acetophenone	5	80	70	30:70	24
6	4-Nitro acetophenone	5	RT	40	20:80	48
7	4-Nitro acetophenone	2.5	80	70	31:69	44
8	4-Methoxy acetophenone	5	80	30	32:68	132
9	Cycloheptanone	5	80	40	_	72
10	2-Nonanone	5	80	54	48:52	120
11	(E)-4-Phenyl-3-buten-2-one	5	80	45	26:74	42
12	Trifluoro acetophenone	5	80	93	11:89	48

^a Isolated yields, product authenticity was checked by ¹H NMR and ¹³C NMR.

^b No co-catalyst used.

^c 0.2 equiv of benzoic acid used as co-catalyst.

 $^{d}E:Z$ ratios determined by GC.

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were dried following standard procedures and kept under Argon. MTO was synthesised following a literature procedure.¹⁰

3.2. General procedure for ketone olefination

Ketone (2 mmol), PPh₃ (0.577 g, 2.2 mmol), MTO (0.025 g, 0.1 mmol) and benzoic acid (0.122 g, 1 mmol) were dissolved in dry toluene (10 cm³) and heated to 80 °C. EDA (0.274 g, 2.4 mmol) dissolved in toluene (1 cm³) was added dropwise and allowed to react at 80 °C. After the reaction was completed, the solution was cooled to room temperature and the solvent was removed under vacuum. The residue was dissolved in *n*-hexane/ethyl acetate (5:1) and chromatographed over silica gel affording the olefin(s).

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