Michael addition catalyzed by difluorotris(pentafluoroethyl)phosphorane

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ABSTRACT

Difluorotris(pentafluoroethyl)phosphorane, $(C_2F_5)_3PF_2$, was found to be an active catalyst for the Michael addition reaction of 1,3-β-diketones or β-ketoesters (Michael donors) and linear or cyclic unsaturated ketones (Michael acceptors). The reaction proceeds under mild conditions with low catalyst loading and results in the formation of the Michael addition products in moderate to high yields. The developed protocol does not require the use of a base for the in situ generation of a carbanion (Michael donor).

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1. Introduction

The Michael addition reaction was originally described in 1887 and is one of the most useful methods for the formation of C–C bond [1,2]. The reaction proceeds via nucleophilic addition of a carbanion (Michael donor) to a carbon-carbon double bond, which is activated by the conjugation with an electron withdrawing group (Michael acceptor). In principle, the reaction mechanism involves three steps. The first step is the deprotonation of a diketone, diester or ketoester with a base. This leads to the formation of a carbanion, which is stabilized by electron withdrawing groups. In the second step this nucleophile (Michael donor) undergoes an addition to an electrophilic alkene. Finally, proton abstraction from the protonated base or the solvent results in the formation of the desired product. To avoid side reactions such as cyclization, self-condensation or the retro-Michael reaction, the use of a catalyst is beneficial [3–7]. The application of Lewis acid catalysts in Michael addition reactions allows the exclusion of a base to generate the carbanion. This significantly simplifies the product isolation procedure. Various transition metal salts were tested as catalysts in Michael addition reactions [8]. For instance, addition of β-diketones to α,β-unsaturated ketones can be catalyzed by Ru(HCOO)(CO$_2$)(PPh$_3$)$_2$ [9], Ni(acac)$_2$

[10], Cu(SbF$_6$)$_2$ or CuSO$_4$·5H$_2$O [11]. The catalysts FeCl$_3$·6H$_2$O, Yb(OTf)$_3$ and Ni(acac)$_2$ were tested as catalyst for Michael addition of acetylacetone to methylvinylketone in ionic liquid medium [bmim][BF$_4$] [12]. The authors reported an accelerating effect of the ionic liquid solvent in case of the Ni(acac)$_2$ catalyst. However, FeCl$_3$·6H$_2$O and Yb(OTf)$_3$ were less active in ionic liquid than under solvent-free conditions. Ytterbium triflate, Yb(OTf)$_3$, in combination with alanine was shown to be an active biphasic catalytic system in the reaction of various Michael acceptors providing high yields of the addition products [13]. Various transition metal triflates were tested as Lewis acid catalysts for the Michael addition reaction in water [14]. It was shown that Yb(OTf)$_3$ in combination with N,N,N',N'-tetramethylethylenediamine catalyzes the Michael addition more efficiently when compared to the ligand-free reaction. Other lanthanide salts, for example EuCl$_3$·6H$_2$O [15] or CeCl$_3$·7H$_2$O [16,17] can also be used as catalysts in the Michael addition reaction. Some other examples of the Michael addition catalyzed with various metals catalysts are published [18,19].

However, high catalyst loadings of 5 mol% [11] to 10 mol% [9,13,15,17,20] or in some cases up to 20 mol% [16] are required to efficiently catalyze the Michael reaction and to get products in a good yields. The drawback in the application of the above mentioned metal-based Lewis acid catalysts is a potential contamination of the product with metal salts. From this point of view, the use of organocatalysis has major advantages [21]. Recently, we have reported that difluorotris(pentafluoroethyl)-phosphorane, $(C_2F_5)_3PF_2$, is an active catalyst for the Diels–Alder

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reaction [22]. In the present study we have tested $(C_2F_5)_3PF_2$ as Lewis acid catalyst in the Michael addition reaction. Difluorotris(pentafluoroethyl)phosphorane is a clear and colorless liquid (b.p. 91–92 °C) which reacts with water and air-moisture at room temperature liberating HF (**Caution! HF is very toxic**). Difluorotris(pentafluoroethyl)-phosphorane, $(C_2F_5)_3PF_2$, is now-days produced in multi-ton quantities by the electrochemical fluorination (Simons process, ECF) of triethylphosphine [23,24].

2. Results and discussion

Difluorotris(pentafluoroethyl)phosphorane, $(C_2F_5)_3PF_2$, is a strong Lewis acid [25], stronger than PF_5 [26]. Here we report the use of difluorotris(pentafluoroethyl)-phosphorane, $(C_2F_5)_3PF_2$, as metal free Lewis acid catalyst for Michael addition reactions. Table 1 presents the results and conditions of the Michael reaction of 1,3-β-diketones or β-ketoesters (Michael donor) and linear or cyclic unsaturated ketones (Michael acceptor) catalyzed by the phosphorane, $(C_2F_5)_3PF_2$. The reaction proceeds in dichloromethane under mild conditions with low to moderate catalyst loadings (0.5–5 mol%) and results in the formation of product **3** in moderate to high yields (52–92%) (Scheme 1).

At the beginning of our study, we screened the addition of acetylacetone (**1a**) to various Michael acceptors (**2a–e**). For the reaction of acetylacetone (**1a**) with methylacrylate (**2c**), crotonic acid (**2d**) and acrylonitrile, $CH_2 = CH - CN$ (**2e**) no conversions have been observed within 24 h even with catalyst loadings up to 5 mol% calculated on the quantity of the Michael donor **1a**. However, only 0.5 mol% of $(C_2F_5)_3PF_2$ was required as catalyst to obtain 3-acetylhepta-2,6-dione (**3aa**) in 73% yield in the reaction of **1a** and **2a** (Table 1, entry 1).

On the other hand, in the case of the Michael reaction of **1a** and **2a** not only mono-adduct **3aa** but also di-adduct **3aa'** is formed (Scheme 2). Diaddition is dependent on the ratio of the reactants. If an excess of Michael acceptor **2a** was used (1.5: 1) than the mono-addition product **3aa** was obtained in 38% yield and the di-adduct **3aa'** in 24% yield. Furthermore, intramolecular aldol reaction occurred in this case resulting in the formation of cyclic product **4a** from **3aa'** (Scheme 2).

It is known that cyclic by-products are formed by *in situ* generated enolates which rapidly undergo intramolecular aldol condensation [27]. Similarly, the formation of a diadduct followed by the intramolecular aldol condensation was also observed in Michael reactions catalyzed by $[Ru(O_2CH)(CO(PPh_3)]_2$ [9]. The ratio

Table 1
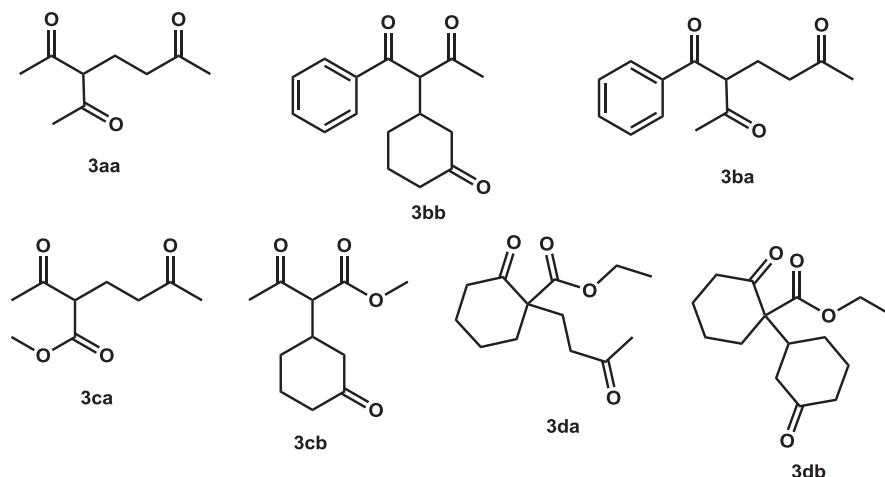Michael addition catalyzed by $(C_2F_5)_3PF_2$ in CH_2Cl_2 at RT.

Entry	R	R_1	R_2	R_3	R_4	Product	Catalyst loading [mol%]	Time[h]	Conversion[%]	Isolated yield[%]
1[a]	CH_3	H	CH_3	H	CH_3	3aa	0.5	0.5	86	73
2	C_6H_5	H	CH_3	$-(CH_2)_3-$		3bb	1.9	1	89	60
3	C_6H_5	H	CH_3	H	CH_3	3ba	1.1	100	92	
4	CH_3	H	OCH_3	H	CH_3	3ca	1	1	80	52
5	CH_3	H	OCH_3	$-(CH_2)_3-$		3cb	5	3^t	20	–
6	$-(CH_2)_4-$		OC_2H_5	H	CH_3	3da	1.4	0.2	96	77
7	$-(CH_2)_4-$		OC_2H_5	$-(CH_2)_3-$		3db	5	1^t	85	55

Michael donor: Michael acceptor ratio = 1:1.5, all yields refer to isolated pure compounds, whose structures were assigned on the basis of ^1H NMR data (400 MHz).
[a] Michael donor: Michael acceptor ratio = 1:1.^{t} Days, including 6 h at 40 ?C.
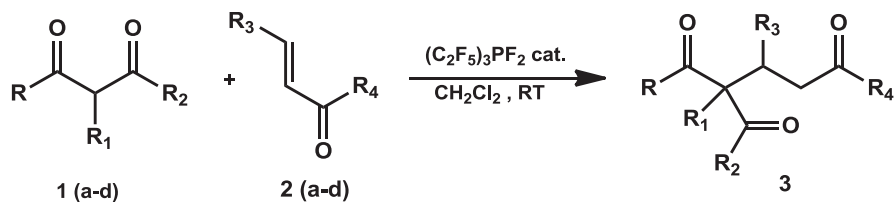
1a: R = CH_3, R_1 = H, R_2 = CH_3; **1b**: R = C_6H_5, R_1 = H, R_2 = CH_3; **1c**: R = CH_3, R_1 = H, R_2 = OCH_3; **1d**: R and R_1 = *cyclo*-$(CH_2)_4$, R_2 = OC_2H_5; **2a**: R_3 = H, R_4 = CH_3; **2b**: R_3 and R_4 = *cyclo*-$(CH_2)_3$; **2c**: R_3 = H, R_4 = OCH_3; **2d**: R_3 = CH_3, R_4 = OH.

Scheme 1. Products obtained in $(C_2F_5)_3PF_2$ catalyzed Michael addition reaction.