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Yb(OTf)$_3$–TMSOTf-catalyzed reactions of acylzirconocene chloride to imines

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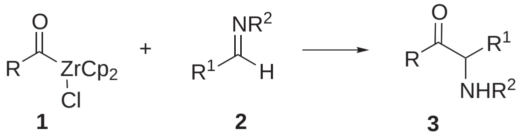
Abstract—Direct access of α-amino ketone derivatives through reactions of acylzirconocene chlorides with derivatives of *N*-benzylideneaniline, in which acylzirconocene chlorides react as an 'unmasked' acyl anion donor, was carried out for the first time under Yb(OTf)$_3$–TMSOTf-catalyzed conditions. © 2001 Elsevier Science Ltd. All rights reserved.

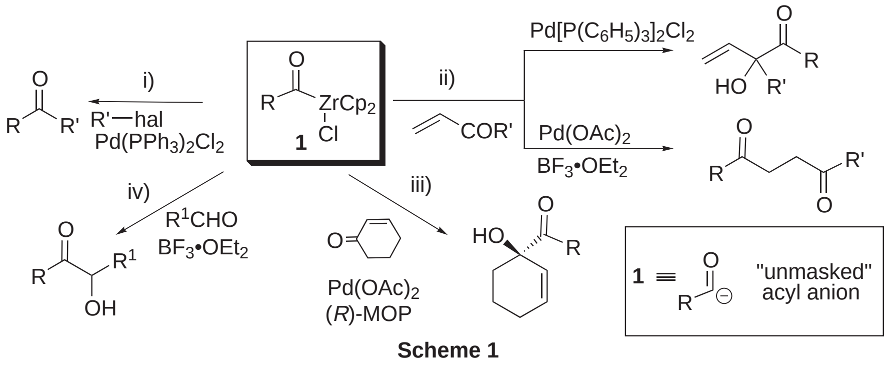
Our recent studies on the reactivity of easily accessible and stable acylzirconocene chloride derivatives **1**[1] have opened up the possibility of their use as a donor of 'unmasked' acyl anion in organic syntheses. In these studies, we indicated (i) Pd-catalyzed coupling reactions with organic halides,[2] (ii) Pd-catalyzed regiochemically adjustable nucleophilic acylation of α,β-enones,[3] (iii) Pd(OAc)$_2$–(*R*)-MOP-catalyzed enantioselective 1,2-additions to α,β-enone derivatives[4] and (iv) Lewis acid-mediated reactions with aldehydes[5] (Scheme 1).

An extension of the strategy to imine derivatives **2** would be expected to yield α-amino ketone compounds **3** (Eq. (1)), which constitute a variety of biologically important molecules.[6] To the best of our knowledge, however, there is no precedent of the direct access to the α-amino ketone compounds through an addition of the 'unmasked' acyl group to imine derivatives.



(1)

In this paper, we describe the formation of α-amino ketones **3** through Yb(OTf)$_3$–TMSOTf-catalyzed reactions of acylzirconocene chloride **1** to derivatives of imine **2**. Attempted reactions of *N*-benzylideneanilines (**2a**) with nonanoylzirconocene chloride (**1a**) in the presence of a stoichiometric amount of a Lewis acid, such as BF$_3$·OEt$_2$, TiCl$_4$, TMSOTf, AlCl$_3$, etc., failed to yield α-amino ketones. Recent disclosure[7] on the catalytic



Scheme 1.

Keywords: acylzirconocene chloride; Yb(OTf)$_3$–TMSOTf-catalyst; acyl anion; imine derivatives.

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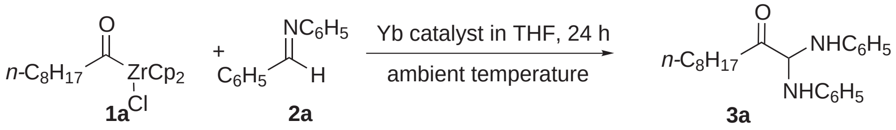


20 mol % catalyst	**3a** yield (%)
$Yb(OTf)_3$	23[a] (53)[b]
$Yb(OTf)_3$-TMSOTf (1 : 1)	64
$Yb(OTf)_3$-TMSOTf (1 : 5)	51
$Yb(OTf)_3$-TMSCl (1 : 1)	63

[a] ambient temperature, 72 h

[b] 50 °C, 8 h.

Scheme 2.

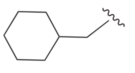
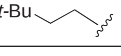
activity of transition metal complexes in the carbon–carbon bond forming reactions of imine derivatives suggested to us the use of ytterbium triflate [$Yb(OTf)_3$] as a Lewis acid in our attempted reactions. To our delight, in the presence of $Yb(OTf)_3$ (20 mol%), the reaction of **2a** with **1a** (1.3 equiv.) at ambient temperature in THF proceeded slowly (72 h, by TLC) to give **3a** in 23% yield. By heating the reaction mixture at 50°C for 8 h **3a** was obtained in 53% yield (Scheme 2). However, under the heating conditions, a longer reaction period (>8 h) tends to yield a contaminated reaction mixture (by TLC). Recently, the use of $Yb(OTf)_3$–TMSOTf in a 1:1 ratio has been reported to be an efficient catalyst for the ene-reactions of imine derivatives.[8] The application of the catalytic system (20 mol%, $Yb(OTf)_3$–TMSOTf, 1:1) in THF to our reaction indicated that the reaction of **1a** with **2a** proceeded at ambient temperature for 24 h to give **3a** in 64% yield. The use of a smaller amount of the catalyst (10 mol%) lowered the yield of **3a** (42%). Thus, the $Yb(OTf)_3$–TMSOTf (20 mol%, 1:1) system is preferable to the single-handed use of $Yb(OTf)_3$ as a catalytic system in the present reaction. A higher ratio of TMSOTf to $Yb(OTf)_3$ (5:1) turned out to be less efficient. The use of TMSCl as a substitute for TMSOTf gave **3a** in a comparable yield (63%).

The possibility of the intervention of TfOH as a catalyst, which might be generated by the hydrolysis of TMSOTf with a trace of water in the reaction media, was also examined.[8] Thus, an addition of TfOH (20 mol%) to a mixture of **1a** and **2a** at 0°C yielded a reaction mixture containing **3a** (10–20% by NMR).[9] The use of scandium triflate [$Sc(OTf)_3$] in place of $Yb(OTf)_3$ as a catalyst showed similar efficiency to that of $Yb(OTf)_3$. It turned out that, in the present $Yb(OTf)_3$–TMSOTf-catalyzed reactions, the employed solvent, THF, is crucial to bring about the reaction since the use of a solvent other than THF, such as CH_2Cl_2, CH_3CN, DMF or DME, retards the reaction (CH_2Cl_2, CH_3CN) or renders it complex (DMF or DME) (by TLC). Thus, we believe that the $Yb(OTf)_3$–TMSOTf (20 mol%, 1:1) in THF is the catalyst of choice in our present reactions.

Results of the $Yb(OTf)_3$–TMSOTf (20 mol%, 1:1)-catalyzed reactions of imine derivatives **2** with acylzirconocene chloride **1** in THF are listed in Table 1. The reactions proceed to give **3** in moderate yields (entries 1–9). The *para*-substituent on benzylidene portion did not show a notable effect on the reaction (entries 1–3). However, the reaction of *N*-2-methoxybenzylideneaniline (**2b**) gave a lower yield of **3** (37%) compared to *para*-isomer (entries 3 and 4).[10] The present reaction of **1** is restricted to derivatives of *N*-benzylideneaniline since imine derivatives derived from pivalaldehyde or cyclohexanecarbaldehyde with aniline reacted with **1a** to give products in less than 10% yields, respectively.[11]

In summary, we have indicated for the first time the nucleophilic additions of an 'unmasked' acyl anion to substituted *N*-benzylideneaniline derivatives. Although the reactivity of acylzirconocene chloride toward imine derivatives under $Yb(OTf)_3$–TMSOTf (20 mol%, 1:1)-catalyzed conditions was not necessarily high enough, the present results show a direct access to α-amino ketone derivatives and the further utility of the acylzirconocene chloride as an 'unmasked' acyl anion donor in organic synthesis.

Table 1. $Yb(OTf)_3$–TMSOTf-catalyzed addition reactions of acylzirconocene chlorides **1** to **2**

Entry	1	2		**3** Yield[a] (%)
	R	R^1	R^2	
1	n-C_8H_{17} **1a**	C_6H_5	C_6H_5 **2a**	64 **3a**
2		p-$CF_3C_6H_4$	C_6H_5	54
3		p-$CH_3OC_6H_4$	C_6H_5	65
4		o-$CH_3OC_6H_4$	C_6H_5 **2b**	37
5		1-Naphthyl	C_6H_5	41
6		C_6H_5	p-$CF_3C_6H_4$	51
7		C_6H_5	p-F-C_6H_4	55
8		**2a**		59
9				41

[a]Isolated yield.

Experimental procedure

Preparation of a THF solution of **1a**: A suspension of $Cp_2Zr(H)Cl$ (1.3 equiv.) and 1-octene (2.6 equiv.) in CH_2Cl_2 (4 mL) was stirred at ambient temperature for 0.5 h and the mixture was treated with carbon monoxide for 2 h (a CO balloon). After CH_2Cl_2 was evaporated in vacuo, THF (6 mL) was added to the residue.

Preparation of **3a**: To a solution of **1a** (1.3 equiv.) in THF (6 mL) was added a solution of **2a** (1 equiv.), $Yb(OTf)_3$ and TMSOTf (20 mol%, respectively) in THF (3 mL) at 0°C and the mixture was stirred at ambient temperature for 24 h. The reaction mixture was treated with satd aq. $NaHCO_3$ and extracted with ethyl acetate. After the usual workup, **3a** was purified by silica gel column chromatography (hexanes:ethyl acetate = 80:1) to give **3a** in 64% yield.

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9. The presence of **3a** was confirmed by the NMR analysis of the reaction mixture. This surprising result prompted us to examine the Brønsted acid as a promoter for the present reactions, and we found that Brønsted acids, such as 2,4-dinitrophenol, hydrochloric acid and $HClO_4$, are excellent promoters. The results will be published in due course.
10. *N*-Benzylidene-4-methoxyaniline gave a product in poor yield (27%). We have also examined the reaction of α,β-unsaturated acylzirconocene chloride with **2a**. However, the yield of the corresponding α-amino ketone was very low (12%).
11. Formations of the products, which correspond to **3**, were confirmed by NMR spectra of the isolated products. We are unable to obtain the product through the reaction of *N*-benzylidenetosylamide or *N*-benzylidenebenzylamine with **1a**.