Tetrahedron Letters 53 (2012) 2604–2607

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Al(OTf)$_3$ as a new efficient catalyst for the direct nucleophilic substitution of ferrocenyl alcohol substrates. Convenient preparation of ferrocenyl-PEG compounds

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ARTICLE INFO

Article history:
Received 24 January 2012
Revised 8 March 2012
Accepted 12 March 2012
Available online 21 March 2012

Keywords:
Nucleophilic substitution
Ferrocene
Aluminium triflate
PEG
Catalysis

ABSTRACT

The use of Al(OTf)$_3$ as a new efficient catalyst for the direct nucleophilic substitution of the hydroxy group of ferrocenyl alcohols is described. This catalyst, originally developed for the mono-substitution of ethylene glycol nucleophiles of different length has shown a high activity with other carbon-, nitrogen-, and sulfur-based nucleophiles. In all the studied cases, no more than 1 mol % of catalyst was needed to allow fast and clean reactions.

Ferrocene derivatives are widely used as components in biosensor applications.[1] They serve as electrochemical mediators between the enzyme cofactor (NAD = nicotinamide adenine dinucleotide or FAD = flavin adenine dinucleotide) and the electrode surface.[2] In order to increase the biocompatibility and the solubility in water of the ferrocenyl mediator, a polyethylene glycol (PEG) linker can be used and is attached at one end to the ferrocene moiety and at the other end to an electroactive platform.[3] In our project concerning the ferrocene immobilization on carbon nanotubes for bioelectrochemical application,[4] we were interested in attaching to the ferrocene short PEG linkers with defined length. The synthesis of such compounds **1** is poorly described in the literature and necessitates prior OH activation and mono-deprotonated ethylene glycols.[3b,5] In the present work, we describe a new catalyst to perform the linkage without OH activation and under neutral conditions (Fig. 1). No more than 1% of aluminium(III) triflate (Al(OTf)$_3$) is needed in this very fast transformation (less than 30 min). Moreover, we show that this catalyst is highly efficient with several other nucleophiles.

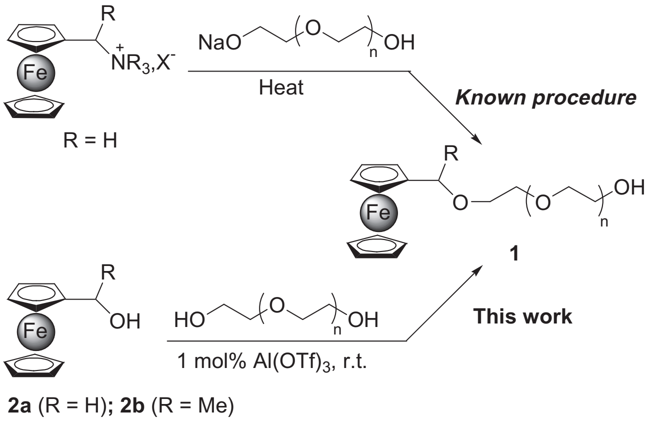

Figure 1. Synthesis of monoferrocenyl-PEG compounds.

Although, some studies reported on the direct hydroxy group displacement in ferrocenyl alcohols by carbon-, sulfur-, and nitrogen-based nucleophiles,[6] only two of them described the use of alcohol nucleophiles.[6c,g] In the first case, the ferrocenyl alcohol was reacted with 2 equiv of methanol in dichloromethane in the presence of 10 mol % of InBr$_3$ and in the second case, the reaction was conducted in alcohol as the solvent (methanol, ethanol, and propanol) with 5 mol % cerium ammonium nitrate (CAN). These two catalysts were therefore tested in the reaction of 1-ferrocenylethanol **2b** with 1 equiv of tetraethyleneglycol in dichloromethane (Table 1).

The desired ferrocenyl ether compound **1d** was obtained in low yields in both cases (entries 1 and 2). Among Lewis acids, metal triflates are known to promote a wide variety of organic reactions under very mild conditions.[7,8] Several metal triflate catalysts were

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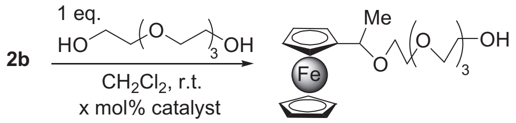
http://dx.doi.org/10.1016/j.tetlet.2012.03.042

Table 1
Effect of the catalyst on the reaction of **2b** with tetraethyleneglycol

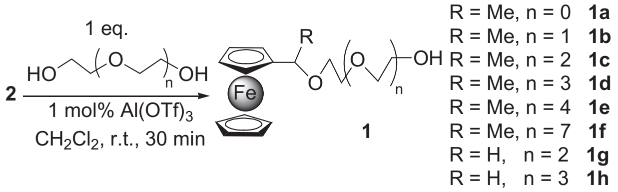


1d

Entry	Catalyst	Loading (x%)	Time (h)	Yield[a] (%)
1	$InBr_3$	10	2	31
2	CAN	5	2	26
3	$Zn(OTf)_2$	5	21	35
4	AgOTf	5	21	32
5	$Yb(OTf)_3$	5	21	35
6	$Bi(OTf)_3$	5	0.6	41
7	$Al(OTf)_3$	5	0.3	60
8	$Al(OTf)_3$	1	0.3	59
9	TfOH	5	0.6	0[b]

[a] Isolated yields.
[b] Compound **3** was formed quantitatively (see structure in Table 3).

Table 2
Reaction of **2a** and **2b** with different ethylene glycol



Entry	Substrate	n	Product	Yield[a] (%)
1[b]	**2b**	0	**1a**	63
2	**2b**	1	**1b**	61
3	**2b**	2	**1c**	69
4	**2b**	3	**1d**	59
5	**2b**	4	**1e**	54
6	**2b**	7	**1f**	30
7	**2a**	2	**1g**	66
8	**2a**	4	**1h**	47

[a] Isolated yields.
[b] Reaction in THF for 90 min.

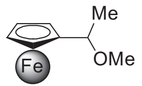
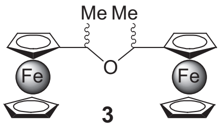
then tested in this reaction. The product was formed with $Zn(OTf)_2$ (entry 3), AgOTf (entry 4), and $Yb(OTf)_3$ (entry 5) in comparable yields around 30% but the reaction in each case was very slow. The reaction performed faster with $Bi(OTf)_3$ but the yield was not much improved (entry 6). Finally, the yield was increased by using $Al(OTf)_3$ (entry 7) and the catalyst loading could be diminished to 1 mol % with no loss in activity (entry 8). In order to show the importance of the metal in this reaction, trifluoromethanesulfonic acid (TfOH) was also tested (entry 9). The expected compound **1d** was not formed but instead the dimeric compound **3** was produced in an almost quantitative yield (see Table 3).

In contrast to rare earth metal and bismuth triflates,[7,8] the use of $Al(OTf)_3$ is quite limited in the literature. While this catalyst was first introduced in organic chemistry in the late 80's to early 90's as an efficient catalyst in the Friedel Crafts,[9] Michael[10] and Aldol reactions,[11] it is only recently that $Al(OTf)_3$ has found more applications. It can allow the ring opening of epoxides by alcohols[12] and amines,[13] the cycloisomerisation of unsaturated alcohols,[14] oximes[15], and carboxylic acids,[16] the acetylation of phenol,[17] the acetal formation from carbonyl compounds,[18] the reduction of azides,[19] the hydrosilylation of ketones,[20] the O-silylation of hydroxyl groups,[21] and the protection/deprotection of alcohols with a tetrahydropyranyl (THP) group.[22] Very recently, $Al(OTf)_3$ was used for the direct substitution of the hydroxyl group of propargylic alcohols.[23]

The optimized conditions of Table 1 were used with ethylene glycols of different length and the results are reported in Table 2.[24] Moderate to good yields were generally obtained except in the case of octaethyleneglycol ($n = 7$) for which the yield dropped to 30%. Whereas, the reaction rate was comparable for glycols from $n = 0$ to $n = 4$, it became much slower with octaethyleneglycol.

After having succeeded in the direct nucleophilic displacement of the hydroxy group in ferrocenyl alcohols by ethylene glycols, the scope of the reaction was expanded by using other nucleophiles (Table 3). The reaction performed very well between ferrocenyl ethanol **2b** and methanol nucleophile indifferent of the solvent used; methanol itself (entry 1) or other solvents such dichloromethane (entry 2), THF (entry 3) and acetonitrile (entry 4). The amount of methanol in dichloromethane could be reduced to 1 equiv without increasing the reaction time (entry 5). Interestingly, the reaction with methyl orthoformate as the methanol source gave the expected compound **4** although in a lower yield (entry 6). When the nucleophile was omitted, the dimeric compound **3** was formed by self-condensation (entry 7). When ethanol was used instead of methanol, the reaction worked as well to give

Table 3
Reaction of **2a** and **2b** with different nucleophiles

Entry	Substrate	Nucleophile (n equiv)	Reaction conditions	Product	Yield (%)
1	**2b**	–	MeOH, 1.5 h	 **4**	99
2	**2b**	MeOH (2)	CH_2Cl_2, 0.3 h	**4**	99
3	**2b**	MeOH (2)	CH_3CN, 0.3 h	**4**	99
4	**2b**	MeOH (2)	THF, 0.3 h	**4**	99
5	**2b**	MeOH (1)	CH_2Cl_2, 0.3 h	**4**	98
6	**2b**	$CH(OMe)_3$ (0.5)	CH_2Cl_2, 1 h	**4**	60
7	**2b**	–	CH_2Cl_2, 1.5 h	 **3**	77[a]

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