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Tetrahedron Letters 48 (2007) 1625–1627
Tetrahedron Letters
ELSEVIER

gem-Difluoropropargylation of aldehydes using cat. In/Zn in aqueous media

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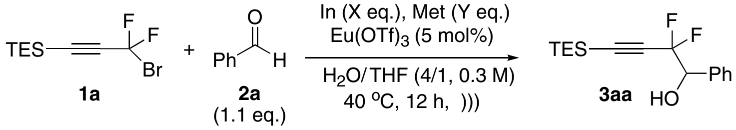
Received 25 October 2006; revised 22 December 2006; accepted 22 December 2006
Available online 23 January 2007

Abstract—Zn (0.9 equiv) in combination with catalytic amounts of In (0.1 equiv) and I_2 (0.1 equiv) was found to effect the reaction of several difluoropropargyl bromide derivatives with aldehydes to produce *gem*-difluorohomopropargyl alcohols in aqueous media under conditions suitable for large scale applications.

The formation of C–C bonds in aqueous media is an important goal of environmentally friendly synthetic methodologies.[1] Indium has shown potential for such reactions; notable examples include Reformatsky reaction,[2] Barbier type alkylation,[3] allylation,[4] and propargylation[5] of carbonyl compounds. An intrinsic

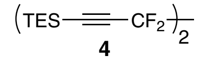
Table 1. Screening of the bimetallic system of Barbier type reaction



Entry	In (*X* equiv)	Metal (*Y* equiv)	Yields of product[a] (%) **1a**:**3aa**:**4**[b]
1	1.0	—	0:78:8
2	0.5	Zn (0.5)	0:73:9
3	0.1	Zn (0.9)	0:61:12
4	0.05	Zn (0.95)	0:55:15
5	0	Zn (1.0)	0:12:23
6	0.05	Mg (0.95)	46:4:Trace
7	0.05	Cu (0.95)	No reaction
8	0.05	Fe (0.95)	Decomposed
9	0.05	Al (0.95)	0:28:4
10	0.05	Mo (0.95)	No reaction
11	0.05	Sb (0.95)	54:3:Trace
12	0.05	Sn (0.95)	4:28:4

[a] Yield was determined by ^{19}F NMR.

[b] Dimer **4**.



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Keywords: Cat. indium; Zinc; Aqueous media; *gem*-Difluorohomopropargyl alcohols.

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0040-4039/$ - see front matter
doi:10.1016/j.tetlet.2006.12.134

drawback of indium is the need for almost stoichiometric amounts of this relatively expensive metal. In response to the cost factor, various combinations containing catalytic amounts of indium and a secondary cheaper metal (such as Al, Zn, Sn or Mn) have been developed,[6] but these protocols are still limited to few reactions, chiefly, the allylation of carbonyl compounds. Our interest in the synthesis of *gem*-difluorohomopropargyl alcohol **3** led us recently to its synthesis using indium and a catalytic amount of $Eu(OTf)_3$ (5 mol %) as a water tolerant Lewis acid.[7] In our continuous search for new cost-effective methods, we are now pleased to report an economical synthesis of **3** that relies on the utilization of zinc combined with the catalytic amounts of indium and iodine.

First, we studied the effects of varying the ratio of zinc and indium, using $Eu(OTf)_3$ as a catalyst. The results, shown in Table 1, indicated that the yield of product **3aa** decreases as lesser amounts of indium are employed (entries 1–5); zinc alone gave a very low yield of **3aa** accompanied by relatively large amounts of the dimeric byproduct **4** (entry 5). We then screened the effects of other readily available metals (entries 6–12), none of which matched zinc's performance.

Table 2. Effects of $Eu(OTf)_3$ versus I_2

Entry	In (*X* equiv)	Zn (*Y* equiv)	Additive	Yields of product[a] (%) **3aa**:**4**
1	0.05	0.95	$Eu(OTf)_3$ (5 mol %)	55:15
2	0.1	0.9	$Eu(OTf)_3$ (5 mol %)	61:12
3	0.05	0.95	I_2 (5 mol %)	52:8
4	0.1	0.9	I_2 (10 mol %)	66:6
5	0.1	1.1	I_2 (10 mol %)	55:9
6	0.1	0.9	—	43:12
7	—	0.9	I_2 (10 mol %)	24:16

[a] Yield was determined by ^{19}F NMR.

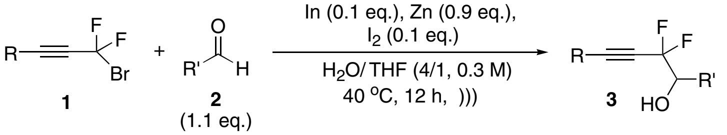
Although $Eu(OTf)_3$ is an effective catalyst in the reaction above, it is costly. Some metal halide complexes, on the other hand, are also well known water tolerant Lewis acid catalysts but available at a fraction of the cost.[8] Thus, a more economical solution would be the in situ generation of a metal halide complex by the addition of iodine to the reaction of **1** with **2**. As depicted in Table 2, iodine addition (entries 3–7) has a positive effect on the reaction outcome. When used in similar proportions, either iodine or $Eu(OTf)_3$ produced analogous results (compare entries 1 and 3, also 2 and 4). It is clear that the lack of either indium or iodine give low yields (entries 6 and 7).

The optimized reaction conditions (entry 4) were applied to the synthesis of **3** using various aldehyde substrates (Table 3).[10]

With the triethylsilyl (TES) group as a convenient synthetic handle, alcohols **3aa**–**ai** were obtained in good NMR yields, albeit moderate isolated yields (entries 1–5, 7–9). Only fluorinated propargyl alcohols were observed under the reaction conditions. In contrast, nonfluorinated propargyl bromides yield both allenyl and propargyl alcohols under similar conditions.[9] Interestingly, no reaction took place with 4-nitrobenzaldehyde, a normally reactive electrophile (entry 6). The type of substituent on the acetylenic moiety in **1** had a noticeable effect on the yield of product. Whereas the *n*-hexyl group (**1b**) did not have a deleterious effect on the yield of **3ba** (entry 10), a phenyl substituent (**1c**) furnished **3ca** in a very low yield, and always accompanied by unidentified nonfluorinated byproducts (entry 11).

In summary, the combination of zinc (0.9 equiv)/indium (0.1 equiv) and I_2 (0.1 equiv) is a cost-effective alternative to the use of $Eu(OTf)_3$. Although the resulting *gem*-difluorohomopropargyl alcohols are obtained in moderate yields, this reaction is highly regioselective as

Table 3. Barbier type reaction of **1** and several aldehydes **2**



Entry	R	R′	Isolate yield of **3**[a] (%)
1	TES (**1a**)	Ph (**2a**)	55 (66) [**3aa**]
2		4-Me–C_6H_4 (**2b**)	48 (55) [**3ab**]
3		3-MeO–C_6H_4 (**2c**)	48 (60) [**3ac**]
4		2,4-$(MeO)_2$–C_6H_3 (**2d**)	53 (67) [**3ad**]
5		4-Cl–C_6H_4 (**2e**)	42 (61) [**3ae**]
6		4-NO_2–C_6H_4 (**2f**)	No reaction
7		4-$CF_3C_6H_4$ (**2g**)	56 (81) [**3ag**]
8		2-F–C_6H_4 (**2h**)	47 (55) [**3ah**]
9		4-OH–C_6H_4 (**2i**)	53 (64) [**3ai**]
10	*n*-Hex (**1b**)	Ph (**2a**)	41 (42) [**3ba**]
11	Ph (**1c**)		0 (26) [**3ca**][b]

[a] The values in parentheses are ^{19}F NMR yields. These were determined using trifluorotoluene (entries 1–6 and 8–11) and hexafluorobenzene (entry 7) as the internal standard.

[b] Product could not be isolated from the complex mixture.

the corresponding fluoroallenyl alcohols were not detected.

Acknowledgment

The generous financial support of the National Science Foundation (CHE 0513483) is appreciated.

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10. *A typical reaction procedure is as follows*: To a flask were added indium (0.2 mmol, 0.1 equiv), zinc powder (1.8 mmol, 0.9 equiv), and I$_2$ (0.2 mmol, 10 mol %) then triethylsilyl difluoropropargylbromide (**1a**) (2.0 mmol) and 4-(trifluoromethyl)benzaldehyde (**2g**) (2.2 mmol, 1.1 equiv) with rinsing by THF/H$_2$O solution (1/4) (6.7 mL, 0.3 M). The reaction was sonicated at 40 °C for 12 h. The reaction was quenched with 10% HCl (10 mL), extracted by ethyl acetate (10 mL × 3) and the combined organic layers were washed with brine and dried over anhydrous MgSO$_4$. After evaporation of the solvent, the residue was purified by silica gel with hexane/EtOAc (40:1) to afford **3ag** (408 mg, 56%). ^{1}H NMR (CDCl$_3$): δ 0.62 (q, $J = 7.8$ Hz, 6H), 0.95 (t, $J = 7.8$ Hz, 9H), 2.97 (br s, 1H), 5.01 (t, $J = 8.3$ Hz, 1H), 7.65 (s, 4H); ^{19}F NMR (CDCl$_3$): δ −93.23 (d, $J = 277.3$ Hz, 1F), −95.04 (d, $J = 277.3$ Hz, 1F); ^{13}C NMR (CDCl$_3$): δ 3.7, 7.1, 75.7 (dt, $J = 29.3$, 12.1 Hz), 94.8 (t, $J = 37.4$ Hz), 112.8 (t, $J = 238.6$ Hz), 123.9 (q, $J = 271.8$ Hz), 125.0, 128.2, 131.2 (q, $J = 32.2$ Hz), 139.0; IR (neat) cm^{-1}: 3610, 3410, 2960, 2881, 2187, 1927, 1623, 1166; MS *m/z* (%): 364 (2, M$^+$), 346 (17), 326 (13), 290 (27), 224 (100), 183 (29), 155 (78), 68 (15); Anal. Calcd: C, 56.03; H, 5.81. Found: C, 56.25; H, 5.95.