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Propargylation of aromatic compounds using $Ce(OTf)_3$ as catalyst

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ABSTRACT

$Ce(OTf)_3$ was successfully employed as catalyst for the activation of the hydroxyl group in the Friedel–Crafts reaction of aromatic compounds with propargylic alcohols in nitromethane. The products were obtained in good to excellent yields.

Introduction

In view of their suitability for further transformations, propargylic derivatives of aromatic compounds are one of the most useful motifs found in synthetic intermediates. These compounds can undergo different modifications affording allenes, alkenes, alkynes, and enynes.[1] In addition, their cyclization is an important strategy toward various bicyclic systems, such as indenes,[2] benzofurans[3] and indoles.[4]

The Friedel–Crafts mediated propargylation of aromatic compounds with propargylic alcohols provides key intermediates for the synthesis of pharmaceuticals and natural products.[5] In recent years, this transformation has been studied using simple Brønsted[6] and Lewis acids,[7] as well as complexes involving metals such as rhenium,[8] ruthenium,[9] and gold.[10]

Lanthanide salts are often employed as catalysts in organic synthesis,[11] mainly due to their low toxicity, affordability, stability, and ease of handling.[12] In pursuit of our interest in developing new methods for reactions catalyzed by cerium(III) salts[13] and taking into account that lanthanide triflates have been reported as promoters of Friedel–Crafts reactions,[14] we decided to study the direct alkylation of aromatic compounds with propargylic alcohols under $Ce(OTf)_3$ assistance. This salt, which remains scarcely explored as catalyst,[15] is a highly stable and easy to handle solid, readily available from the reaction of $CeCl_3$ and triflic acid.

Table 1
Optimization of the propargylation reaction[a]

Entry	Solvent	$Ce(OTf)_3$ (equiv)	Temperature (°C)	Time (h)	Yield[b] (%)
1	CH_3CN	0.3	40	3.0	35
2	$MeNO_2$	0.3	40	1.75	75
3	Glycerol	0.3	40	3.0	–[d]
4	DMA	0.3	40	3.0	–[d]
5	2-PrOH	0.3	40	3.0	–[d]
6	$MeNO_2$	0.1	40	3.0	40
7	$MeNO_2$	0.2	40	3.0	60
8	$MeNO_2$	0.5	40	1.75	75
9	$MeNO_2$	0.3	80	1.75	75[c]
10	$MeNO_2$	0.3	rt	3.0	75

[a] The reactions were performed with phenol (**1a**, 1.0 mmol) and 2-methyl-4-phenylbut-3-yn-2-ol (**2b**, 1.1 mmol).
[b] Isolated yield.
[c] Isomeric ratio (*o*/*p*) = 1:4.
[d] No reaction.

Results and discussion

In preliminary experiments, the best reaction conditions were established by the use of phenol (**1a**, 1.0 mmol) and 2-methyl-4-phenylbut-3-yn-2-ol (**2b**, 1.1 mmol) as starting materials (Table 1). The effect of solvent, amount of catalyst, and reaction temperature were analyzed. The reaction was tested in CH_3CN, $MeNO_2$, glycerol, DMA, and 2-propanol (entries 1–5), employing 0.1–0.5 equiv of the catalyst (entries 2, 6–8). The results revealed that both variables affected the reaction, being the use 0.3 equiv of $Ce(OTf)_3$ in $MeNO_2$ the conditions furnishing the best performance (entry 2). A decrease in selectivity was observed when the transformation was carried out at 80 °C (entry 9, 1:4, *o*/*p* ratio),

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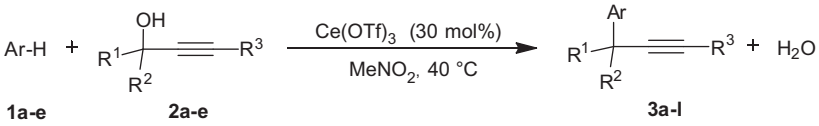


1a-e **2a-e** **3a-l**

R^1, R^2 = H, Me, Ph
R^3 = Ph, Bu
Ar = indole, phenol, anisole, *o*-cresol, furan.

Scheme 1. $Ce(OTf)_3$-catalyzed propargylation of aromatic compounds.

Table 2
Propargylation of aromatic compounds using $Ce(OTf)_3$ as catalyst at 40 °C

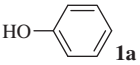
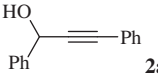
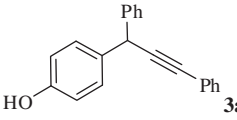
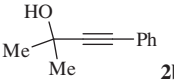
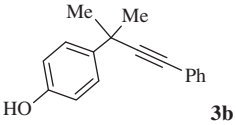
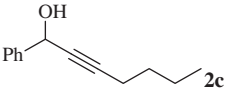
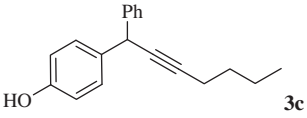
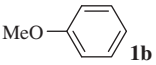
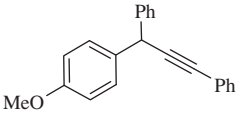
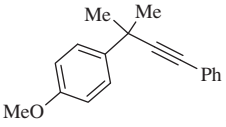
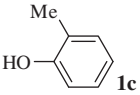
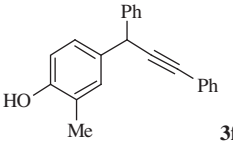
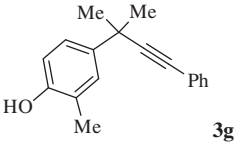
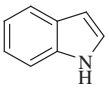
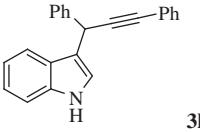
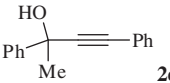
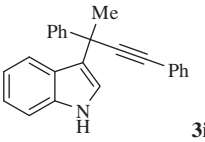
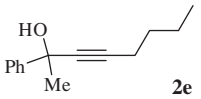
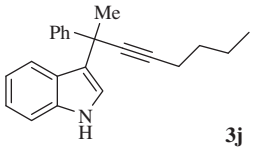
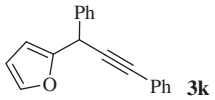
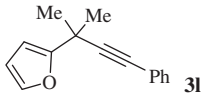
Entry	Aromatic compounds	Alcohol	Product	Time (min)	Yield[a] (%)
1	 **1a**	 **2a**	 **3a**	0.50	92[b]
2	**1a**	 **2b**	 **3b**	0.75	75
3	**1a**	 **2c**	 **3c**	2.50	65[b]
4	 **1b**	**2a**	 **3d**	0.50	95[b]
5	**1b**	**2b**	 **3e**	1.50	75
6	 **1c**	**2a**	 **3f**	0.25	93[b]
7	**1c**	**2b**	 **3g**	1.75	87
8	 **1d**	**2a**	 **3h**	1.50	83[c]
9	**1d**	 **2d**	 **3i**	1.50	53[c]

Table 2 (*continued*)

Entry	Aromatic compounds	Alcohol	Product	Time (min)	Yield[a] (%)
10	**1d**	 **2e**	 **3j**	2.75	45[c]
11	 **1e**	**2a**	 **3k**	1.50	77
12	**1e**	**2b**	 **3l**	1.75	60

[a] Isolated yields.
[b] The 2-substituted product was detected by GC–MS in the crude reaction mixture (**3a′**: 7%; **3c′**: 8%; **3d′**: 5%; **3f′**: 3%).
[c] The reaction performed at 80 °C.

while at room temperature slightly longer reaction times were required for completion (entry 10); therefore, 40 °C was selected as the most suitable reaction temperature.

In order to explore the scope and limitations of the method, the transformation of Scheme 1 was extended to other examples, under the optimized conditions.[16] The corresponding Friedel–Crafts products were obtained in good yields from aromatic compounds such as phenol, anisole, *o*-cresol, furan, and indole (Table 2).

The transformation was highly selective, as determined by ^{1}H NMR and GC–MS. Propargylation of furan took place selectively at position 2, while indole gave the 3-substituted derivative, and the phenolic substrates yielded mainly the corresponding 4-alkylated products, accompanied by small amounts of the related *ortho*-derivatives (entries 1, 3, 4, and 6). In the case of indole, the reaction was carried out at 80 °C in order to ensure complete consumption of starting materials in reasonable reaction times.

Comparatively lower yields were observed when hindered propargylic alcohols were employed. For example, the reaction of phenol (**1a**) with 1,3-diphenylprop-2-yn-1-ol (**2a**) gave 92% of **3a** in 0.5 h at 40 °C, while the same reaction with 2-methyl-4-phenylbut-3-yn-2-ol (**2b**) afforded 75% of **3b** after 1.75 h. Analogous variations can also be observed in other cases, suggesting that steric factors may have some influence on the transformation.

To probe the reaction mechanism, propargylation experiments of **1a** and **1b** were carried out with 2-methyl-4-phenylbut-3-yn-2-ol (**2b**), under different conditions. It was observed that addition of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) completely inhibited the reaction, and no product was observed even after 8 h at 40 °C. On the contrary, when triflic acid was employed instead of $Ce(OTf)_3$, a fast transformation took place at room temperature, furnishing mixtures of isomers, as detected by GC/MS. In the case of phenol, the reaction with 5 mol % TfOH gave 60% of a 38:62 (*o*/*p*) mixture, while use of 10 mol % of triflic acid provided a 72% yield of products, with the same isomeric ratio. The reaction of **1b** and **2b** in the presence of 10 mol % of triflic acid exhibited a similar behavior, affording a mixture of all 3 isomers [15:3:82 (*o*/*m*/*p*) by GC/MS] in an 80% yield. Olah and co-workers proposed that when Lewis acids are exposed to protic solvents or substrates, Brønsted acids may be the actual catalysts.[17] From the above experiments, it can be concluded that a mechanism involving a Brønsted acid is likely to be operating, the reaction being catalyzed by triflic acid, released to the medium from the cerium salt. Inhibition of the reaction by DTBMP, an organic base which is known not to interact with the metal catalyst,[18] shows that triflic acid is critical for the success of reaction. However, the cerium catalyst produces an additional effect evidenced by the high *para* regioselectivity obtained, even if the reaction is performed at high temperatures.

In summary, we have developed a simple and efficient $Ce(OTf)_3$-promoted propargylation of aromatic compounds. The promoter, which is stable, easy to prepare, and handle, affords good yields of products, with high regioselectivity and in short reaction times, being a useful alternative to triflic acid and other usual catalysts.

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16. *Typical procedure*. A mixture of the aromatic substrate (1.0 mmol) and $Ce(OTf)_3$ (0.176 g, 0.3 mmol) in $MeNO_2$ (2 mL) was treated with the appropriate propargylic alcohol (1.1 mmol). The reaction mixture was stirred at the temperature indicated in Table 2, and the reaction progress was monitored by GC–MS. After complete consumption of the aromatic substrate, the reaction mixture was cooled to rt, H_2O (15 mL) was added and the resulting mixture was extracted with EtOAc (3×10 mL). The combined organic phases were successively washed with water and brine, and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the residue was chromatographed (ethyl acetate–hexanes, 5:95). Spectral data of selected compounds. Compound **3a**:[19] ^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.40–7.46 (m, 4H), 7.19–7.31 (m, 8H), 6.74–6.76 (m, 2H), 5.13 (s, 1H), 4.12 (br s, 1H, OH). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 154.5, 142.0, 134.0, 131.6, 129.1, 128.6, 128.2, 127.9, 127.8, 126.8, 123.5, 115.4, 90.5, 84.7, 42.9. MS (EI): *m/z* (%) = 284 (100) [M$^+$], 207 (76), 191 (22), 73 (9). Compound **3b**:[20] ^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.48–7.37 (m, 4H), 7.28–7.25 (m, 3H), 6.81 (d, *J* = 8.5 Hz, 2H), 5.94 (s, 1H), 1.63 (s, 6H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 154.0, 139.3, 131.5, 128.1, 127.6, 126.8, 123.8, 114.9, 96.7, 81.8, 35.7, 31.8. MS (EI): *m/z* (%) = 236 (19) [M$^+$], 221 (100), 178 (6), 127 (18), 101 (5), 77 (7). Compound **3f**:[21] ^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.40–7.48 (m, 4H), 7.18–7.33 (m, 6H), 7.07–7.18 (m, 2H), 6.64–6.68 (d, *J* = 8.1 Hz, 1H), 5.10 (s, 1H), 4.57 (br s, 1H, OH), 2.17 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 152.7, 142.1, 133.8, 131.6, 130.4, 128.5, 128.2, 127.9, 127.7, 126.7, 126.4, 124.1, 123.5, 114.9, 90.6, 84.6, 42.9, 15.9. MS (EI): *m/z* (%) = 298 (100) [M$^+$], 283 (55), 207 (36), 191 (25), 126 (8), 73 (8). Compound **3i**:[6a] ^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.77 (s, 1H), 7.60–6.92 (m, 15H), 2.07 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 146.1, 137.0, 131.6, 128.1, 127.7, 126.5 (2C), 126.4, 125.9, 125.6, 123.7, 121.9, 121.5, 121.0, 119.2, 111.1, 95.0, 83.0, 39.8, 31.0. MS (EI): *m/z* (%) = 321 (69) [M$^+$], 306 (100), 244 (18), 152 (19). Compound **3k**:[22] ^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.49–7.45 (m, 4H), 7.39–7.27 (m, 7H), 6.32–6.26 (m, 2H), 5.25 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 153.7, 142.2, 138.8, 131.7, 128.6, 128.2, 128.1, 127.8, 127.3, 123.1, 110.3, 106.6, 87.4, 83.9, 37.8. MS (EI): *m/z* (%) = 258 (100) [M$^+$], 229 (97), 215 (38), 152 (33), 101 (12), 77 (11).
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