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$LiBF_4$: a mild and novel reagent for the O–H insertion reactions of α-diazoketones

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Abstract—Lithium tetrafluoroborate (10 mol%) is found to catalyze efficiently the O–H insertion reactions of α-diazoketones with various alcohols including benzylic, allylic, propargylic and cyclopropyl carbinols to produce the corresponding α-alkoxy ketones in excellent yields with high selectivity. A solution of 10 mol% of $LiBF_4$ in acetonitrile provides a convenient reaction medium to carry out the O–H insertion reactions under mild and neutral conditions.

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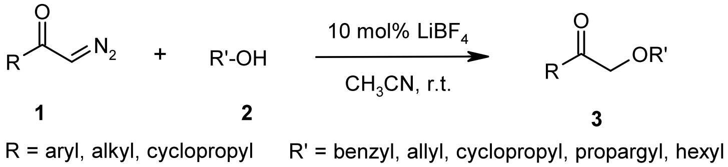
α-Diazocarbonyl compounds find widespread applications in organic synthesis especially in natural product synthesis.[1] The ready availability, relative stability and facile decomposition of α-diazocarbonyl compounds under thermal, photochemical, acid, base and transition metal catalysis conditions make them useful intermediates in organic synthesis.[2] Furthermore, α-diazoketones undergo a variety of transformations such as cyclopropanation, aziridine formation, ylide formation, C–H, X–H insertion reactions and cyclization reactions.[3] These reactions are chemoselective, which allow new carbon–carbon and carbon–hetero atom bond formation under mild conditions. Recently, asymmetric versions of diazocarbonyl reactions have also been reported to produce enantiomerically pure compounds.[4] Typically, transition metal catalysts such as Rh, Ru, Os, Pt and Cu salts are employed to promote the insertion reactions of α-diazocarbonyl compounds.[5] Although, diazocarbonyl reactions are typically catalyzed by transition metal salts, new catalytic systems are being continuously explored in search of improved efficiencies and cost effectiveness. Both protic acids as well as Lewis acids and metal triflates have been reported for O–H insertion reactions of α-diazocarbonyl compounds with alcohols.[6,7] However, the development of mild and neutral alternatives such as lithium tetrafluoroborate would extend the scope and generality of O–H insertion reactions of α-diazocarbonyl compounds.

The catalytic properties of lithium perchlorate in diethyl ether (LPDE) as a mild Lewis acid are well documented and involve specific solute–Li interactions with complexation to the diethyl ether and the less nucleophilic bulky counterion ClO_4^-. However, the inherently hazardous nature of perchlorate limits its use to specific cases only on a small scale. An alternative catalytic media was recently proposed. Acetonitrile solutions of $LiBF_4$ are safe and efficient catalytic media for various organic transformations. The catalytic applications of lithium tetrafluoroborate have recently been reviewed.[8]

Herein, we wish to report the use of lithium tetrafluoroborate as a novel Lewis acid catalyst for O–H



Scheme 1.

Keywords: α-diazoketones; insertion reactions; lithium salts; α-alkoxy ketones.

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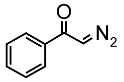
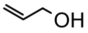
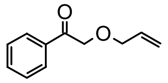
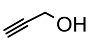
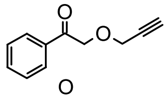
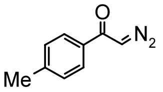
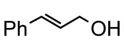
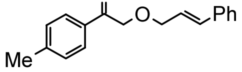
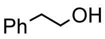
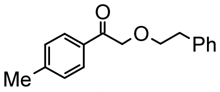
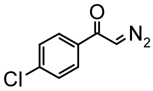
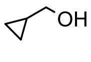
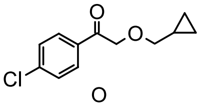
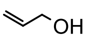
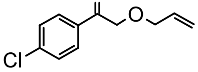
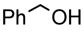
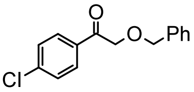
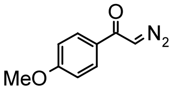
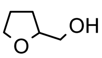
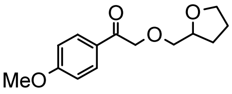
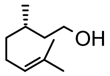
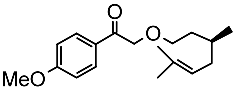
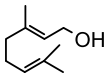
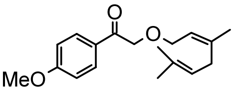
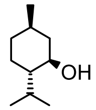
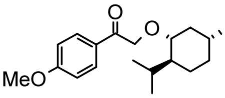
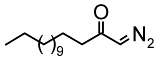
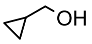
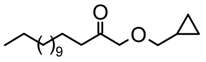
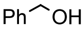
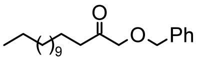
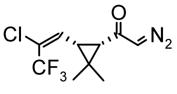
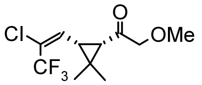
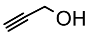
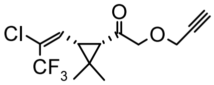
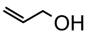
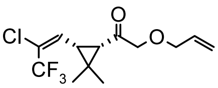
Table 1. $LiBF_4$-catalyzed O–H insertion reactions of α-diazoketones with alcohols

Entry	α–Diazoketone	Alcohol	Product[a]	Reaction time (h)	Yield[b] (%)
a				3.5	95
b	"			4.0	91
c				4.5	92
d	"			5.0	85
e				4.5	89
f	"			4.0	90
g	"			6.0	87
h				4.5	91
i	"			5.0	87
j	"			4.0	89
k	"			5.0	85
l				4.5	89
m	"			5.0	85
n		CH_3OH		4.0	87
o	"			4.5	89
p	"			4.0	92

[a] All products were characterized by ^1H NMR, IR and mass spectroscopy.
[b] Isolated and unoptimized yields.

insertion reactions of α-diazocarbonyl compounds with a range of alcohols to produce α-alkoxy ketones in excellent yields under very mild conditions (Scheme 1).

Accordingly, treatment of diazoacetophenone with allyl alcohol in the presence of 10 mol% lithium tetrafluoroborate in acetonitrile afforded 2-allyloxy-1-phenyl-1-ethanone in 95% yield (entry a). This remarkable catalytic activity of lithium tetrafluoroborate provided the incentive for further study of reactions with other α-diazocarbonyl compounds. Interestingly, various α-diazoketones reacted smoothly with a variety of alcohols in the presence of 10 mol% $LiBF_4$ at ambient temperature to give the corresponding α-alkoxy ketones as the products of OH insertion. Both aromatic and aliphatic diazoketones afforded the respective α-alkoxy ketones. The *cis*-cyhalothric acid derived diazoketone also gave similar results (entries n–p, Table 1). In all cases, the reactions proceeded efficiently at ambient temperature. The method is clean and the products are obtained in high yields with high selectivity.[9] No side product arising from a Wolff rearrangement was observed under these reaction conditions. Other side products such as α-halo ketones (the products of halide insertion) arising especially when Lewis acids such as indium or aluminium halides are used, were not detected under these conditions. To determine the efficiency of this procedure, we have also performed the reactions with various other lithium salts such as lithium perchlorate and lithium triflate. Among these catalysts, lithium tetrafluoroborate was found to be the most effective. In contrast to LPDE (where the Li^+ acts as a Lewis acid), the role of LTAN (lithium tetrafluoroborate in acetonitrile) as catalyst is ascribed to its low stability making it similar to BF_3. Acetonitrile can form a complex $CH_3CN^+–BF_3$ which acts as the catalytic species.[8] The limited solubility of $LiBF_4$ in common organic solvents restricted an extensive solvent study. Furthermore, the reactions were also carried out using 10 mol% $LiClO_4$ in acetonitrile to compare its efficiency with lithium tetrafluoroborate. In this reaction media, high temperature (refluxing acetonitrile) and longer reaction times (8–15 h) were typically required to achieve comparable yields to those obtained with $LiBF_4$. A comparison of the efficiency of both catalytic media showed that $LiClO_4$ can be adequately replaced by $LiBF_4$ which is much easier and safer to handle and even affords better yields in most cases. The scope of this method is illustrated with respect to various diazoketones and a range of alcohols and the results are presented in Table 1.

In summary, an acetonitrile solution of lithium tetrafluoroborate was shown to be a highly efficient and convenient catalytic medium for O–H insertion reactions of α-diazoketones with alcohols to produce α-alkoxy ketones. In addition to its simplicity and mild reaction conditions, this method provides high yields of products with high selectivity making it a useful and attractive strategy for the preparation of α-alkoxy ketones of synthetic importance.

Acknowledgements

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9. *General procedure*: A mixture of α-diazoketone (2 mmol), alcohol (2 mmol), $LiBF_4$ (0.2 mmol) in acetonitrile (10 mL) was stirred at room temperature for the appropriate time (Table 1). After completion of the reaction as indicated by TLC, the reaction mixture was quenched with water and extracted with ethyl acetate (2×15 mL). Evaporation of the solvent followed by purification on silica gel (Merck, 100–200 mesh, ethyl acetate–hexane, 0.5–9.5) afforded the pure α-alkoxy ketone.

   Spectroscopic data for selected products: **3e**: ^1H NMR (200 MHz, $CDCl_3$) δ: 0.15–0.25 (m, 2H), 0.48–0.57 (m, 2H), 1.0–1.15 (m, 1H), 3.35 (d, 2H, $J=6.5$ Hz), 4.60 (s, 2H), 7.45 (d, 2H, $J=8.0$ Hz), 7.90 (d, 2H, $J=8.0$ Hz). IR (KBr) ν: 3084, 2924, 1695, 1590, 1488, 1401, 1283, 1226, 1132, 1092, 980, 826 cm^{-1}. EIMS: m/z: 224 M^+, 154, 139, 125, 111, 75, 55, 39. HRMS calcd for $C_{12}H_{13}ClO_2$: 224.0604. Found: 224.0639.

3m: ^{1}H NMR (200 MHz, CDCl$_3$) δ: 0.90 (t, 3H, J=6.5 Hz), 1.20–1.39 (m, 20H), 1.50–1.70 (m, 2H), 2.45 (t, 2H, J=6.5 Hz), 4.0 (s, 2H), 4.60 (s, 2H), 7.15–7.20 (m, 5H). IR (KBr) ν: 3085, 2923, 2854, 1721, 1655, 1461, 1274, 1115, 721 cm^{-1}. EIMS: m/z: 332 M$^+$, 212, 128, 105, 91, 77, 57, 43. HRMS calcd for $C_{22}H_{36}O_2$: 332.2715. Found: 332.2751.

3p: ^{1}H NMR (200 MHz, CDCl$_3$) δ: 1.25 (s, 3H), 1.38 (s, 3H), 2.30 (dd, 1H, J=8.1, 8.5 Hz), 2.58 (d, 1H, J=8.1 Hz), 3.99–4.05 (m, 4H), 5.20–5.30 (m, 2H), 5.80–5.97 (m, 1H), 6.98 (d, 1H, J=8.5 Hz). IR (KBr) ν: 3080, 2929, 1711, 1651, 1412, 1291, 1139, 953, 732 cm^{-1}. EIMS: m/z: 296 M$^+$, 225, 197, 161, 141, 71, 41. HRMS calcd for $C_{13}H_{16}ClF_3O_2$: 296.0790. Found: 296.0827.