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# Niobium(V) pentachloride: an efficient catalyst for C-, N-, O-, and S-nucleophilic substitution reactions of benzylic alcohols

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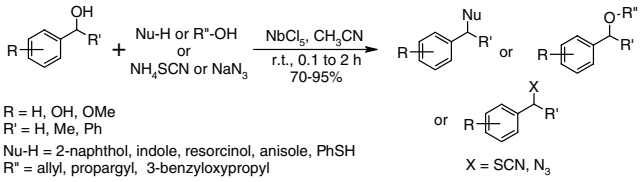
**Abstract**—Benzylic alcohols undergo easy C-, N-, O-, and S- centered nucleophilic substitution reactions with a catalytic amount of $NbCl_5$.

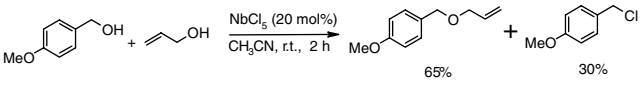

Carbocations are one of the most important intermediates in C–C bond formation and are easily generated from either alkyl halides,[1] alcohols,[2] or olefins.[3] The coupling of a carbocation with C-, O-, and N-atom centered nucleophiles is a direct approach for the construction of carbon–carbon, carbon–oxygen, and carbon–nitrogen bonds. Alcohols are an attractive source of electrophiles compared to alkyl halides from atom-economical and synthetic points of view as they are readily available and the only by product formed in the reaction is water. Since the alcohol is a poor leaving group, it has to be derivatized as an ester, mesylate, tosylate, or halide for easy displacement.[4] Thus, direct nucleophilic substitution reactions of alcohols have gained much attention and can generally be achieved in the presence of stoichiometric amounts of Lewis acid[5] or excess sulfuric acid or phosphoric acid.[6] This transformation can be achieved employing transition metals such as Fe,[7] Au,[8] Bi,[9] La, Sc, or Hf salts,[10] $InCl_3$,[11] *para*-toluenesulfonic acid monohydrate or polymer-supported *para*-toluenesulfonic acid.[12] However, many of these procedures require elevated temperatures, long reaction times, or stoichiometric amounts of the reagents. Thus, the introduction of a new and efficient method for this transformation under more convenient and general conditions would be welcome.

In continuation of our interest on the catalytic applications of $NbCl_5$ as a Lewis acid catalyst for various organic transformations,[13] we herein disclose $NbCl_5$ catalyzed arylation of aromatic compounds and the heteroatom centered nucleophilic substitution reactions of benzylic alcohols (Scheme 1).

Recently, group Vb halides have become a subject of interest due to their inherent Lewis acid properties. In this group, $TaCl_5$, a moisture sensitive solid has been used as an efficient catalyst for several organic transformations.[14] $NbCl_5$, a stable solid, which is easy to handle and soluble in many organic solvents, has also been well explored as a Lewis acid in promoting various organic transformations. Examples, where $NbCl_5$ has been utilized as an efficient Lewis acid catalyst, are an intramolecular oxidation reduction process,[15] Diels–Alder reaction,[16] Sakurai reaction,[17] Mannich type reaction,[18] dealkylation of alkyl aryl ethers,[19] homologation,[20] ring opening of epoxides,[21] Mukaiyama aldol reactions,[22] and allylation of aldehydes, imines[23] and nucleophilic additions to *N*-acyliminium ions[24] and in complex formation as Lewis acids.[25]




**Scheme 1.**




**Scheme 2.**

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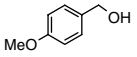
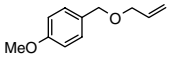
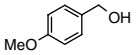
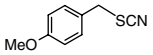
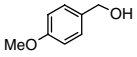
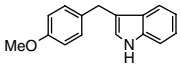
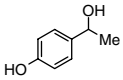
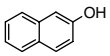
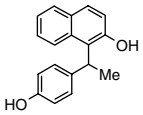
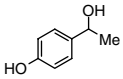
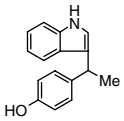
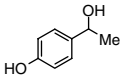
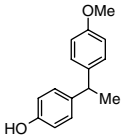
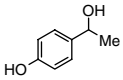
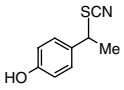
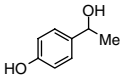
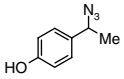
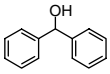
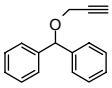
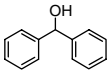
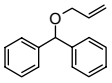
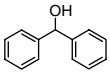
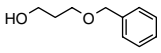
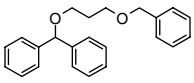
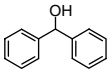
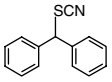
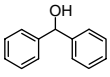
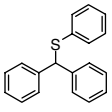
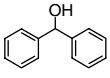
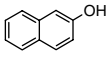
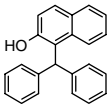
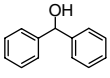
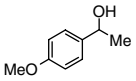
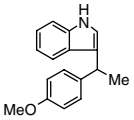
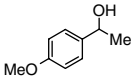
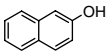
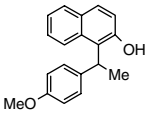
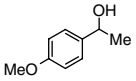
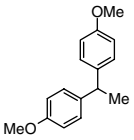
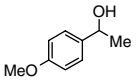
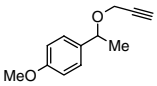
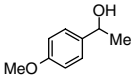
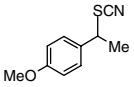
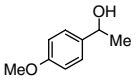
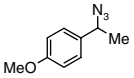
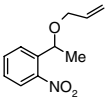
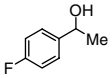
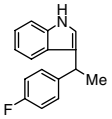
**Table 1.** C-, N-, O-, and S-atom centered nucleophilic substitution reactions of benzylic alcohols catalyzed by $NbCl_5$

| Entry | Aryl carbinol a | Nucleophile | Product[a] b | Time (min) | Yield[b](%) |
|---|---|---|---|---|---|
| 1 |  |  |  | 120 | 65 |
| 2 |  | $NH_4SCN$ |  | 120 | 70 |
| 3 |  |  |  | 120 | 75 |
| 4 |  |  |  | 20 | 92 |
| 5 |  |  |  | 20 | 92 |
| 6 |  |  |  | 30 | 86 |
| 7 |  | $NH_4SCN$ |  | 30 | 88 |
| 8 |  | $NaN_3$ |  | 40 | 86 |
| 9 |  |  |  | 15 | 93 |
| 10 |  |  |  | 10 | 95 |
| 11 |  |  |  | 15 | 90 |
| 12 |  | $NH_4SCN$ |  | 30 | 90 |
| 13 |  |  |  | 60 | 95 |
| 14 |  |  |  | 15 | 90 |
| 15 |  |  |  | 15 | 92 |
| 16 |  |  |  | 15 | 86 |

(*continued on next page*)

**Table 1** (*continued*)

| Entry | Aryl carbinol a | Nucleophile | Product[a] b | Time (min) | Yield[b](%) |
|---|---|---|---|---|---|
| 17 |  |  |  | 10 | 92 |
| 18 |  |  |  | 15 | 95 |
| 19 |  |  |  | 20 | 90 |
| 20 |  |  |  | 120 | 75 |
| 21 |  | $NH_4SCN$ |  | 30 | 92 |
| 22 |  | $NaN_3$ |  | 40 | 90 |
| 23 |  | $NaN_3$ |  | 50 | 84 |
| 24 |  |  |  | No reaction | |
| 25 |  |  |  | No reaction | |

[a] Products were characterized by IR, $^1H$ NMR, $^{13}C$ NMR, and mass spectroscopy.
[b] Isolated and unoptimized yields.

In continuation of our interest in the catalytic applications of $NbCl_5$, we envisioned its use to promote nucleophilic substitution reactions of benzylic alcohols. Thus, initially, we tested benzyl alcohol with allyl alcohol in presence of 20 mol % of $NbCl_5$ in anhydrous acetonitrile and observed no change. When *p*-methoxybenzyl alcohol was subjected to similar reaction conditions, we observed the complete consumption of the starting material resulting in two products, characterized as *p*-methoxybenzyl chloride and allyl *p*-methoxy benzyl ether (Scheme 2).

To increase the yield of the product, various concentrations of the catalyst were employed. We found that 5 mol % of the catalyst was best in terms of yields and duration for the nucleophilic substitution reaction. Acetonitrile and nitromethane provided excellent yields and proved to be the solvents of choice, whereas dichloromethane, THF, and 1,4-dioxane afforded lower yields.

Next, we investigated whether the diaryl carbinols could react in a similar way even though the benzylic cation would be more stabilized. We found that, the diaryl carbinols reacted more rapidly than the aryl alkyl carbinols. Also the aryl carbinols with electron-rich moieties yielded the products in good yields (see Table 1).[26] In all cases, no chlorinated product was observed. No eliminated side products were observed for α-substituted benzylic alcohols. After studying the O-nucleophilic substitutions with allylic alcohol and propargylic alcohol, aromatic compounds such as β-naphthol and resorcinal were examined. Gratifyingly, we observed only C-arylation of the aromatic compounds at the electron-rich site of the phenols. When anisole was used as the nucleophile, substitution occurred at the *para* position with respect to the methoxy moiety (entries 6 and 19).[27] Indole (entries 3, 5, 15, and 17) also underwent C-arylation. With the positive results obtained from C- and O-nucleophilic substitution reactions, we proceeded to N- and S-substitution reactions. The substitution

reactions worked well with $NH_4SCN$ and $NaN_3$ to give the corresponding thiocyanides (entries 2, 7, 12, and 21) and azides (entries 8, 22, and 23). The azido compounds could be easily converted into amines under standard conditions. Benzylic alcohols with electron withdrawing groups such as fluoro or nitro did not react under the present conditions (entries 24 and 25).

In conclusion, efficient nucleophilic substitution reactions of diaryl carbinols and aryl alkyl carbinols catalyzed by $NbCl_5$ have been developed. The method reported here is not only simple to operate but also yields the products in short durations and in high yields with water as the only by product. No heating[12] and also no prior derivatization[7] of the benzylic alcohols were required. Further investigations on the reaction mechanism are currently in progress.

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## References and notes

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26. *General experimental procedure*: To a solution of benzyl alcohol (1 mmol) in acetonitrile (3 mL) were added nucleophile (1.2 mmol) and $NbCl_5$ (5 mol %) and the mixture was stirred at room temperature until completion of the reaction. The reaction mixture was quenched with saturated aq $NaHCO_3$ solution (1 mL) and the product was extracted with ethyl acetate. Evaporation of the solvent gave the crude product, which was purified by column chromatography. Representative data of selected products: Compound **5b**: White solid. IR (KBr) $\nu_{max}$ 3444, 3024, 2964, 2855, 2372, 1876, 1599, 1509, 1444, 1331, 1254, 1090, 823, 743 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$+DMSO): $\delta$ 1.62 (d, $J = 7.0$ Hz, 3H), 4.20 (q, $J = 7.0$, 14.0 Hz, 1H), 6.62 (d, $J = 8.6$ Hz, 2H), 7.02 (d, $J = 8.6$ Hz, 2H), 6.83 (dt, $J = 1.1$, 8.9 Hz, 2H), 6.93–7.06 (m, 2H), 7.21–7.30 (m, 1H), 8.57 (br s, 1H, –NH), 10.13 (s, 1H, –OH). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 153.96, 136.45, 135.53, 126.79, 125.42, 119.75, 119.30, 117.95, 116.98, 113.87, 113.76, 110.08, 34.69, 21.41. EIMS: *m/z* 238 $(M+H)^+$. HRMS for $C_{16}H_{16}NO$: Calcd 238.1231; found, 238.1239. Compound **11b**: Yellow liquid. IR (neat): $\nu_{max}$ 3061, 3029, 2924, 2859, 1952, 1601, 1493, 1452, 1094,

1028, 739, 698 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 1.91 (p, $J = 6.1$ Hz, 2H), 3.53 (t, $J = 6.13$ Hz, 2H), 3.58 (t, $J = 6.2$ Hz, 2H), 4.44 (s, 2H), 5.26 (s, 1H), 7.13–7.30 (m, 15H). $^{13}C$ NMR (100 MHz, $CDCl_3$): 142.03, 138.09, 127.89, 127.17, 127.03, 126.89, 126.78, 126.51, 83.23, 72.50, 66.95, 65.54, 29.85. EIMS: $m/z$ 355 $(M+Na)^+$. HRMS for $C_{23}H_{24}O_2Na$: Calcd 355.1673; found, 355.1683. Compound **12b**: Yellow liquid. IR (neat) $\nu_{max}$ 3448, 3061, 3029, 2924, 2853, 2392, 2151, 2073, 1449, 697 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$) 5.79 (s, 1H,), 7.26–7.41 (m, 10H). $^{13}C$ NMR($CDCl_3$, 75 MHz): $\delta$ 64.82, 111.25, 126.37, 128.53, 129.29, 142.43. EIMS: $m/z$ 225 $(M^+)$. Compound **19b**: Yellow liquid: IR (neat) $\nu_{max}$ 2927, 2835, 2361, 1733, 1609, 1509, 1459, 1244, 1176, 828 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.56 (d, 3H, $J = 7.2$ Hz), 3.75 (s, 6H), 3.99 (q, 1H, $J = 7.2$ Hz), 6.74 (d, 4H, $J = 9.1$ Hz), 7.03 (t, 4H, $J = 9.1$ Hz). $^{13}C$ NMR ($CDCl_3$, 75 MHz): $\delta$ 22.41, 43.23, 55.39, 113.99, 129.88, 139.11, 158.05. EIMS: $m/z$ 243 $(M+H)^+$. HRMS for $C_{16}H_{18}O_2Na$: Calcd 265.1204; found, 265.1210.

27. *p*-Substitution occurred as confirmed by $^1H$ NMR spectroscopy.