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SYNTHESIS OF ARENES FROM PHENOLS BY COUPLING OF ARYL TRIFLATES WITH ORGANOCOPPER REAGENTS

by
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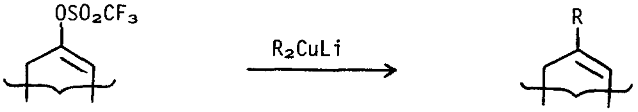
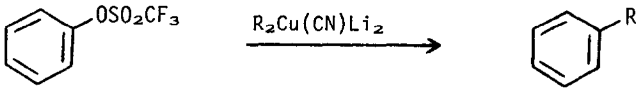
Abstract: Aryl triflates react with higher order mixed cuprates $R_2Cu(CN)Li_2$ to produce arenes in good yield. The aryl ring may have either an electron-donating or an electron-withdrawing substituent; the organocuprate may be either primary, secondary, tertiary, aryl, or vinyl.

We reported[1,2] recently a new method of regiospecific olefin synthesis by coupling of diorganocuprate reagents with enol triflates[3]. The reaction is general for both mono- and dienol triflates, and for alkyl, aryl, and vinylic cuprates.

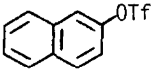
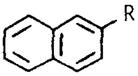
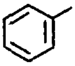
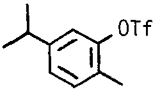
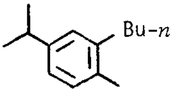
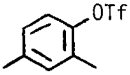
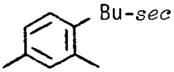
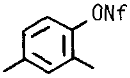
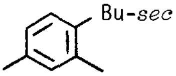
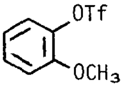
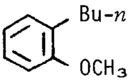
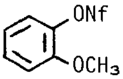
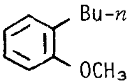
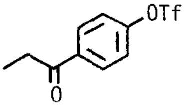
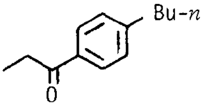


Considering the structural similarity of phenols to enols, it occurred to us that an analogous coupling reaction might effect the conversion of phenol triflates into arenes. Such a reaction could be of considerable use in synthesis since few methods exist for replacing a phenol hydroxyl by a carbon substituent[4,5]. Unfortunately, the reaction does not work. Treatment of a variety of aryl triflates with lithium dialkylcuprates R_2CuLi failed to yield appreciable amounts of the coupled arene products, giving instead the phenols arising from O-S cleavage. We have now found, however, that the desired coupling does indeed take place when the reaction is carried out using the higher order mixed cuprates of Lipshutz[6].



We have undertaken a brief study of the scope of the coupling reaction, and we wish to report the results shown in the Table.

Table. Reactions of Aryl Triflates With Higher Order Mixed Cuprates

Entry	Aryl Triflate	Cuprate $[R_2Cu(CN)Li_2]$	Product	Isolated Yield (%)
1		R = CH_3		85
2		R = *n*-Bu		72
3		R = *sec*-Bu		90
4		R = *tert*-Bu		96
5		R = $H_2C=CH-$		90
6		R = 		45
7		R = *n*-Bu		40
8		R = *sec*-Bu		50
9		R = *sec*-Bu		65
10		R = *n*-Bu		50
11		R = *n*-Bu		70
12		R = *n*-Bu		70

As indicated by the first six entries in the Table, 2-naphthyl triflate reacts in high yield with methyl, n-butyl, sec-butyl, tert-butyl, and vinyl cuprates, and in somewhat lesser yield with the phenyl cuprate reagent. Substituted phenyl triflates also undergo coupling but in uniformly lower yield than the corresponding naphthyl triflates. Thus, carvacrol triflate (entry 7) reacts with n-butyl cuprate in 40% yield whereas the corresponding naphthyl coupling takes place in 72% yield. Similarly, 2,4-dimethylphenyl triflate (entry 8) couples with sec-butyl cuprate in 50% yield whereas naphthyl triflate couples with the same reagent in 90% yield.

In an attempt to improve the coupling process, it occurred to us that the more reactive nonafluorobutanesulfonates (nonaflates) might be better substrates, and we therefore carried out the reaction shown in entry 9. The yield of coupling product from 2,4-dimethylphenyl nonaflate was indeed higher than from the corresponding triflate (65% versus 50%) though the difference was not dramatic. A similar improvement in yield was noted when o-methoxyphenyl triflate and nonaflate (entries 10 and 11) were coupled with n-butyl cuprate.

One final point we examined in this brief study was a determination of the effect of both electron-donating substituents (ortho methoxyl group, entry 10) and electron-withdrawing substituents (para propanoyl group, entry 12) on the course of the coupling reaction. As indicated in the Table, the coupling reaction appears to be little affected by substituents on the aromatic ring.

In a typical procedure (entry 10), the preparation[6] and coupling of the higher order mixed cuprate reagents were carried out in the following manner: a solution of n-BuLi (3.54 mmol) in tetrahydrofuran (THF) was added dropwise at -78 °C to a slurry of CuCN (167 mg, 1.86 mmol) in 4 mL THF. The resultant tan solution was allowed to warm to -20 °C and then recooled to -70 °C. o-Methoxyphenyl trifluoromethanesulfonate[7] (137 mg, 0.54 mmol) in 2 mL THF was added dropwise and the reaction mixture was allowed to warm slowly to -20 °C where it was kept for 40 h. The reaction was then quenched by addition of aqueous NH_4Cl and extracted with ether. The ether extracts were combined, washed with water and with brine, dried ($MgSO_4$), and concentrated at the rotary evaporator. Chromatography of the residue on silica gel gave 44 mg (50%) o-butylanisole; IR (neat), 1600, 1586, 1490, 1462 cm^{-1}; ^1H NMR ($CDCl_3$), δ 7.06 (m, 4 H), 3.86 (s, 3 H), 2.65 (t, J = 7 Hz, 2 H), 1.47 (m, 4 H), 0.93 (t, J = 7 Hz, 3 H); MS, M^+ = 164.

In summary, we have discovered what we believe to be a useful new synthetic procedure by which the hitherto difficult transformation of phenols into arenes can be accomplished. The reaction appears to be general, both with respect to the nature of the substituents on the aromatic ring and with respect to the nature of the organocuprate reagent.

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Notes and References

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