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Directed *ortho* Metalation Reaction of Aryl *O*-Carbamates on Solid Support

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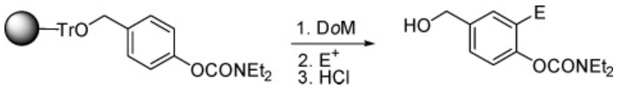
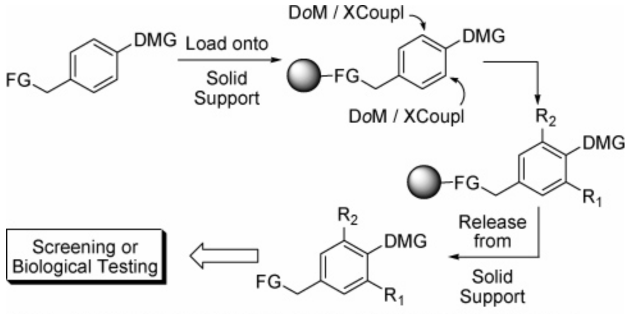
ABSTRACT



The first Directed *ortho* Metalation (D*o*M) reaction of aryl *O*-carbamates on polystyrene-divinylbenzene (PS-DVB) resin using a trityl linker is described. Using low temperatures and short metalation times, a range of electrophiles have been introduced to give, after cleavage from support, substituted benzyl alcohols in high purity.

Within the rapidly evolving field of synthetic reactions on solid support,[1] anionic chemistry has been limited to enolate and ylid chemistry using LDA,[2] metal halogen exchange reactions,[3] and singular reports of directed *ortho* metalation (D*o*M) reactions using OMOM (PS-DVB resin with a silicon linker[4]) and CONR$_2$ (PS-DVB[5] and Janda*Jel*,[6] both with aminomethyl linkers) directed metalation groups (DMGs). As part of efforts to parlay solution-phase D*o*M[7] and cross-coupling[8] strategies for solid-support adaptation (Scheme 1) and to establish connections with recent solid-support work on Suzuki−Miyaura,[9] Stille,[10] and related cross-coupling regimens,[11] we report on the first D*o*M reaction of aryl *O*-carbamates trityl-linked to PS-DVB resin.

Scheme 1. D*o*M/Cross-Coupling Connection on Solid Support



DoM = Directed ortho Metalation; **DMG** = Directed Metalation Group; **XCoupl** = Cross Coupling

In contrast to the previous requirement for higher temperatures (0 °C)[4−6] to effect metalation reactions, conditions that are incompatible for many DMGs (e.g., *O*-carbamates, tertiary amides) established for solution-phase chemistry, the developed low temperature (−78 °C) protocol for metalation-electrophile quench offers promising potential for generalization of D*o*M reactions on solid support.

Although in previous work[9,10] the solid-support Suzuki−Miyaura cross-coupling on Merrifield resin was linked to

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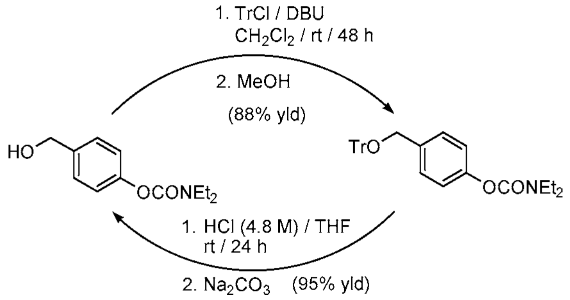
solid-phase D*o*M via use of *o*-DMG aryl boronic acids, extensive attempts to carry out D*o*M on this resin were unsuccessful. The demonstration that PS-DVB resin[4,6] and the trityl linker[12] are stable to *n*-BuLi encouraged the use of the versatile, commercially available trityl chloride resin, which may be used for the loading of alcohols, phenols, carboxylic acids and amines.[13]

To initiate the study, the reaction conditions for substrate loading onto polymer support, D*o*M, and substrate cleavage from the support were established using a trityl group to model the solid support (Scheme 2).[14] Typical conditions for loading trityl resins (pyr or DMAP/THF)[12,15] were not effective for our system. However, after some experimentation, DBU/CH_2Cl_2/rt/48 h was found to give the highest yields and reproducible trityl ether formation. Cleavage of the substrate from the trityl linker was also not uncomplicated. Application of organic acids (e.g., TFA) resulted in significant and instantaneous oxidation of the benzyl alcohol product to the benzaldehyde, which could be reduced but never fully suppressed by the addition of $(iPrO)_3SiH$ to the reaction mixture.[16] Application of mineral acids, on the other hand, eliminated undesired oxidation completely, and optimal conditions were established as 4.8 M HCl/THF/rt/24 h.

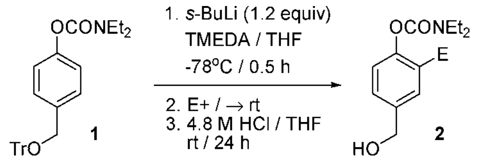
Scheme 2. Optimized Trityl Loading and Cleavage Conditions



Solution-phase D*o*M reactions of the model system were uneventful. The use of standard *s*-BuLi/TMEDA metalation conditions for carbamates,[17] followed by quench with various electrophiles and acid-catalyzed cleavage of the trityl group, led to the expected products in very good yields with no evidence of benzylic metalation[18] byproducts (Table 1).

Commercial trityl chloride resin (styrene-1% DVB) was subjected to the previously optimized etherification conditions (DBU/CH_2Cl_2/rt/48 h). Initial application of the D*o*M conditions determined for the solid-phase model (Table 1), using either I_2 or MeI quenches, resulted in product:starting material ratios indicating only 50% deprotonation (Table 2, entry 1).[19] Increasing the amount of *s*-BuLi improved the ratio, but beyond 5 equiv the additional *s*-BuLi was found to be detrimental and attack on the carbamate became a significant side reaction (entries 2−4). Since the detrimental influence of excess reagent is counterintuitive, we surmised that this effect was the result of poor swelling of the resin in the increasing amounts of hexanes of the *s*-BuLi solutions. This conjecture was borne out by dilution experiments that showed that increasing the amount of THF in the reaction (optimized at THF/hexane ratio of 10:1, entry 8) gave

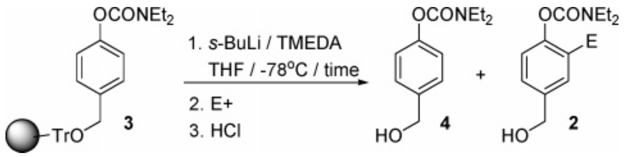
Table 1. Solution-Phase D*o*M on a Trityl Aryl *O*-Carbamate



E^+	E		yield (%)[a]
MeI	Me	**2a**	90
$ClCONEt_2$	$CONEt_2$	**2b**	80
C_2Cl_6	Cl	**2c**	83
$BrCH_2CH_2Br$	Br	**2d**	91
I_2	I	**2e**	86
TMSCl	TMS	**2f**	74

[a] Isolated yield of purified products.

Table 2. Optimization of Solid-Support D*o*M Conditions for the Trityl-Linked Aryl *O*-Carbamate



							purity (%)[a]	
entry	*s*-BuLi (equiv)	time (h)	mL THF/ g resin	TMEDA	E^+	E	**4**	**2**
1	1.2	0.5	10	yes	I_2	I	56	44
2	2.4	1	10	yes	I_2	I	53	47
3	5	1	10	yes	I_2	I	35	65
4	7	1	10	yes	I_2	I	55	45[b]
5	5	1	20	yes	I_2	I	32	68
6	5	1	20	no	I_2	I	19	81
7	5	1	20	no	MeI	Me	11	89
8	5	1	30	no	MeI	Me	1	99

[a] Purity determined via GC analysis using an external standard (undecane). [b] 4-(Hydroxymethyl)phenol observed.

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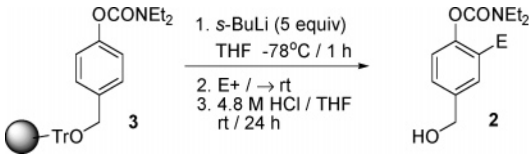
[19] Purity determined by GC analysis using a HP 6840 GC equipped with a fused silica stationary phase (0.5 μm fused) capillary column (0.53 mm i.d.).

complete and clean D*o*M reactions. TMEDA, a standard additive to solution-phase D*o*M of *O*-aryl carbamates, was found to be detrimental, and its exclusion from the solid-support reactions resulted in significantly improved results (compare entries 5 and 6).

Application of the optimized conditions[20] to other electrophiles demonstrated the generality of the solid-support D*o*M reaction, yielding products in moderate to high purity[19] and good yield (Table 3).[21] As evident, the bulkier electrophiles gave lower product yields and purities compared to those of smaller electrophiles. Product stability may also contribute to the low yield and purity observed, e.g., the TMS quench product (entry 6) may undergo protodesilylation under the conditions used for substrate cleavage from the resin.

Table 3. Generalization of the Solid-Support D*o*M Reaction for the Trityl-Linked Aryl *O*-Carbamate



entry	E+	E		purity (%)	yield (%)[a]
1	MeI	Me	**2a**	99	77
2	$ClCONEt_2$	$CONEt_2$	**2b**	79	75
3	C_2Cl_6	Cl	**2c**	79	45
4	$BrCH_2CH_2Br$	Br	**2d**	70	68
5	I_2	I	**2e**	69	46
6	TMSCl	TMS	**2f**	45	29

[a] Yields determined via GC analysis using an external standard (undecane).

In summary, we have devised a trityl-linked PS-DVB resin suitable for solid-support D*o*M chemistry of aryl *O*-carbamates at −78 °C. Since low-temperature conditions are obligatory for many DMGs,[17] the aryl *O*-carbamate, qualitatively the most powerful DMG,[17] may serve as a prototype for D*o*M reactions, overcoming previous solid-support systems[4−6] that appear to require higher temperature for metalation. Incorporation of halogen electrophiles (Table 3, entries 3−5) provides potential D*o*M-transition metal catalyzed coupling links[26] to Suzuki−Miyaura,[22] Stille[23] Heck,[24] and Sonogashira[25] reactions,[26] thereby augmenting the potential for parallel synthesis and library generation. Further efforts in these directions are in progress.

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Supporting Information Available: Experimental details and data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) **Procedure.** To the loaded resin, swelled with THF (30 mL/g of resin) and cooled to −78 °C was added *s*-BuLi (5 equiv) dropwise, and the mixture was stirred *gently* for 1 h. The electrophile was added dropwise (20 equiv), and the reaction mixture was stirred for 10 min at −78 °C and allowed to warm to room temperature over 6 h. The reaction mixture was subjected to filtration, and the polymer was successively washed with THF 10 mL × 5/g resin), H_2O (10 mL × 5/g resin), THF (10 mL × 5/g resin), H_2O (10 mL × 5/g resin), and acetonitrile (10 mL × 5/g resin). The polymer was then swelled with THF (10 mL/g of resin), 4.8 M HCl (10 equiv) was added, and the reaction mixture was stirred gently at room temperature for 24 h. The reaction mixture was subjected to filtration, and the polymer was washed with THF (3×). The filtrate was partitioned between Et_2O/H_2O and treated with aqueous Na_2CO_3 until neutral. The aqueous phase was extracted with Et_2O (2×), the organic layer was successively washed with aqueous $NaHCO_3$ (1×), H_2O (1×) and brine and dried (Na_2SO_4), and the solvent was removed in vacuo to give the product.

(21) Yields determined by GC analysis (HP 6840 GC with fused silica stationary phase (0.5 μm) capillary column (0.53 mm i.d.)) using an external standard (undecane).

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