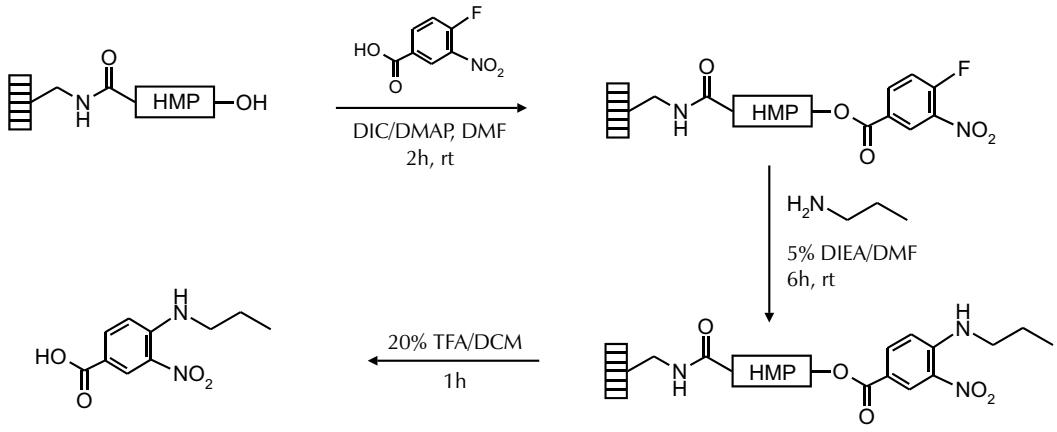
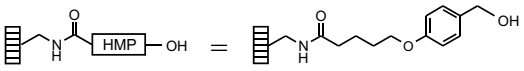
S_NAr Reaction of an Activated Aryl Fluoride with a Primary amine

A range of aniline derivatives may be prepared by treating a solid-bound aryl fluoride with primary amines, *via* S_NAr displacement. In the following example, an *o*-nitroaryl fluoride on SynPhase™ hydroxymethylphenoxy Lanterns is efficiently converted to an *N*-substituted *o*-nitroaniline. The performance of this type of reaction is enhanced when an electron withdrawing group is also present.



DMF:	dimethylformamide	DIC:	diisopropylcarbodiimide
DCM:	dichloromethane	rt:	room temperature
TFA:	trifluoroacetic acid		
DIEA:	diisopropylethylamine		
DMAP:	4-(dimethylamino)pyridine		



Attachment of 4-Fluoro-3-Nitrobenzoic Acid

Each D-Series HMP Lantern (initial specified loading: 35μmol) is treated with a 0.5mL solution of 4-fluoro-3-nitrobenzoic acid (0.56M, 280μmol, 8 mole equivalents), DIC (0.28M, 140μmol, 4 mole equivalents) and DMAP (0.02M, 10μmol, 0.3 mole equivalents) in DMF. The reaction mixture is stood at rt for 2h. The reagent solution is decanted and the Lanterns washed with DMF (3×3min), DCM (3×3min) and air dried.

S_NAr Reaction

Each of the D-Series Lanterns prepared above is treated with a 0.5mL solution of *n*-propylamine (0.35M, 175mol, 5 mole equivalents) in 5% DIEA/DMF. The reaction mixture is stood at rt for 6h.[1] The reagent solution is then decanted and the Lanterns washed with DMF (3×3min), DCM (3×3min) and air dried.

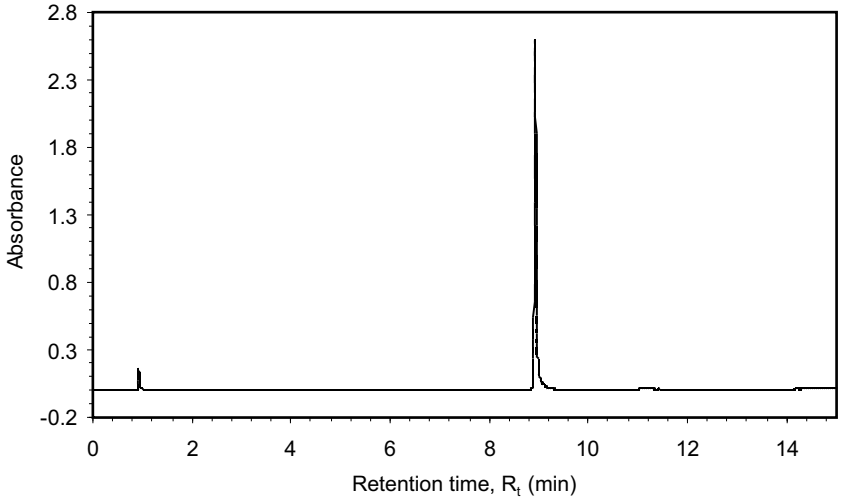
Cleavage

Individual Lanterns are placed in polypropylene tubes and treated with 20% TFA/DCM (0.6-0.8mL) for 1h. The Lanterns are removed and the cleaved products are concentrated using a centrifugal evaporator, then the residues are freeze-dried from 90% CH_3CN/H_2O. The yield of product was essentially quantitative. Samples are redissolved in the same solvent for HPLC and ES-MS analysis.

Analytical Data

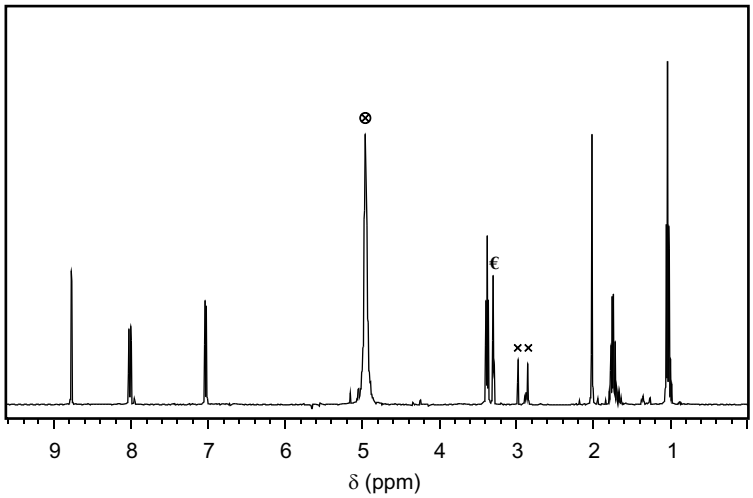
Reverse phase HPLC trace of the crude S_NAr product

Detection at 214nm



400MHz ^{1}H NMR spectrum of the crude S_NAr product (D_4-methanol)

(€) CH_3OH
(×) DMF
(⊗) H_2O



Note

1 For primary anilines, overnight heating at 60°C may be required for complete conversion.

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