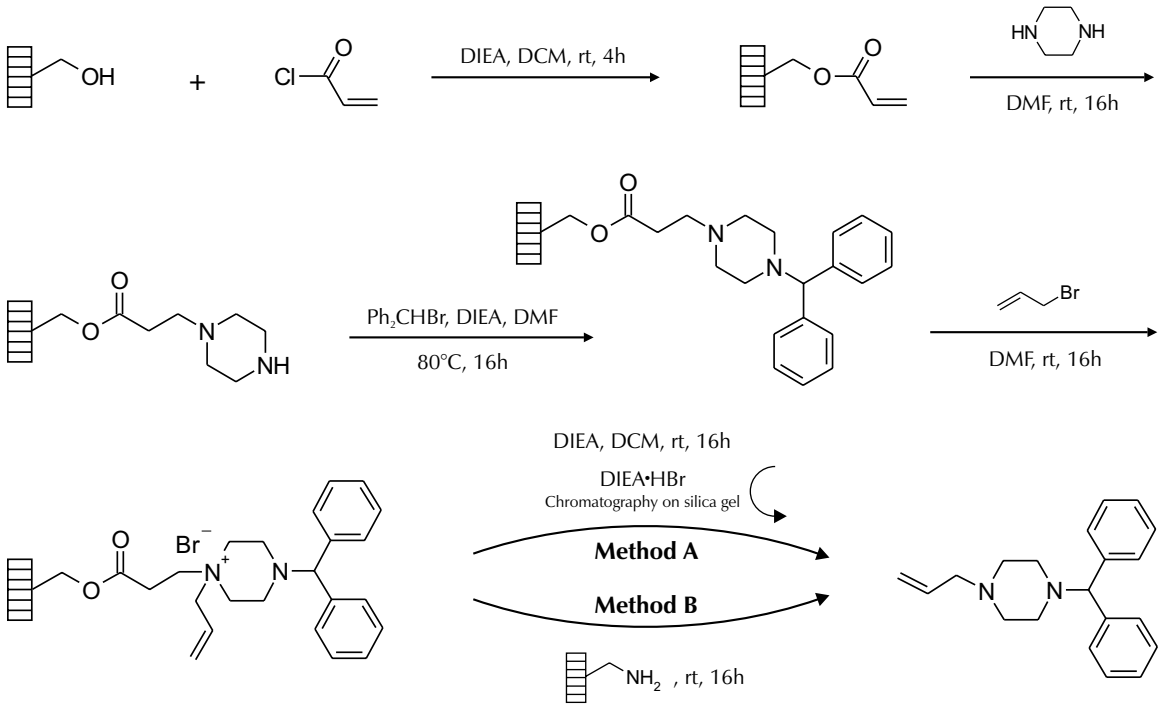
Preparation of Tertiary Amines *via* Acrylate-based REM Linker on SynPhase™ PS Hydroxymethyl Lanterns

Both sulfonylate-based[1] and acrylate-based[2] REM linkers have been used in the solid phase synthesis of tertiary amines from secondary amines. The synthesis involves (1) coupling the starting secondary amine to the REM linker (Michael addition), (2) modifying the attached amine (3) quaternization of the resultant tertiary amine (activation) and (4) cleavage of the product with a base such as diisopropylethylamine (Hofmann elimination). A shortcoming of this synthesis is that the final tertiary amine product is contaminated with the acid salt of the base. To remove the contaminant, chromatography on silica gel or ion-exchange resin is usually required.

In the following example, a tertiary amine is prepared *via* the acrylate REM linker on SynPhase™ PS hydroxymethyl Lanterns using the above mentioned chemistries.

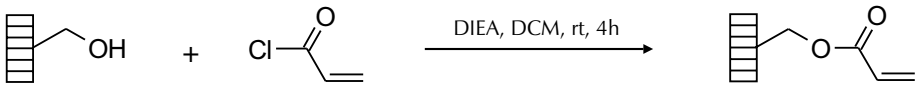
The Hofmann elimination cleavage, however, is accomplished using both conventional base[2] (Method A) and PS aminomethyl Lanterns as a solid phase reagent[3,4] (Method B). Using PS aminomethyl Lanterns as a base shows great advantage since no further purification is required to obtain the pure product.



DMF:	dimethylformamide	REM:	class of acrylate based linkers
DCM:	dichloromethane		
DIEA:	diisopropylethylamine	OH :	hydroxymethyl Lantern
rt:	room temperature		
TFA:	trifluoroacetic acid	NH_2 :	aminomethyl Lantern
NMP:	N-methyl pyrrolidone		

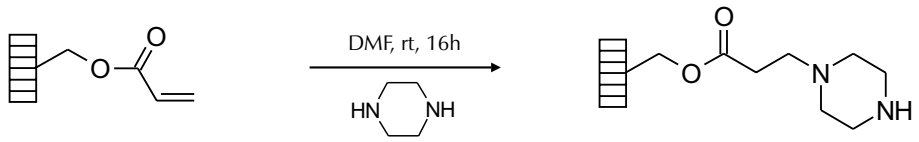
Preparation of REM Lanterns from hydroxymethyl Lanterns

Each PS hydroxymethyl D-Series Lantern (initial specified loading, 36μmol) is treated with 0.5mL of a solution of DIEA (50μL, 287μmol, 8 mole equivalents) in DCM. To the mixture is added acryloyl chloride (26μL, 287μmol, 8 mole equivalents). The reaction is allowed to stand at rt for 4 hours. The reagent solution is decanted and the Lanterns washed with DMF (3×3min) and DCM (3×3min).



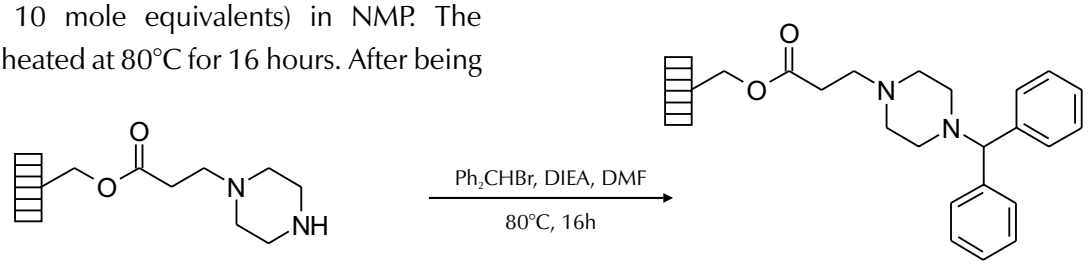
Michael Addition

Each D-Series acrylate REM Lantern is treated with 0.5 mL of a solution of piperizine (50μL, 287μmol, 8 mole equivalents) in DMF at rt for 16 hours. The reagent solution is decanted and the Lanterns washed with DMF (3×3min) and DCM (3×3min).



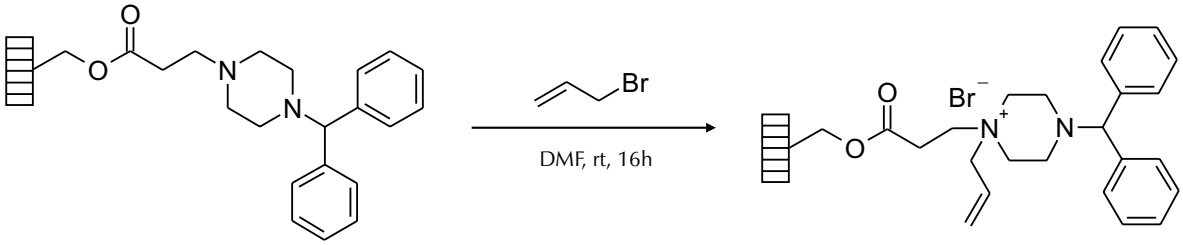
Alkylation

Each D-Series Lantern is treated with 0.5mL of a solution of DIEA (62μL, 360μmol, 10 mole equivalents), and bromodiphenylmethane (90mg, 360μmol, 10 mole equivalents) in NMP. The mixture is heated at 80°C for 16 hours. After being cooled to room temperature, the reagent solution is decanted and the Lanterns washed with DMF (3×3min) and DCM (3×3min).



Quaternization

Each D-series Lantern is treated with 0.5 mL of a solution of allyl bromide (19μL, 180μmol, 5 mole equivalents) in DMF at rt for 16 hours. The reagent solution is decanted and the Lanterns washed with DMF (3×3min) and DCM (3×3min).

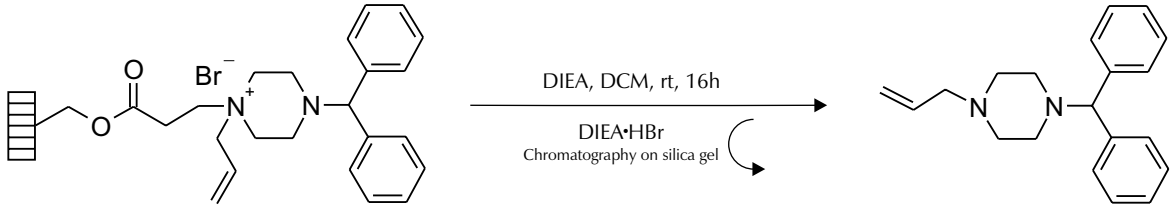


Cleavage (Hofmann elimination)

Method A: using DIEA as the base

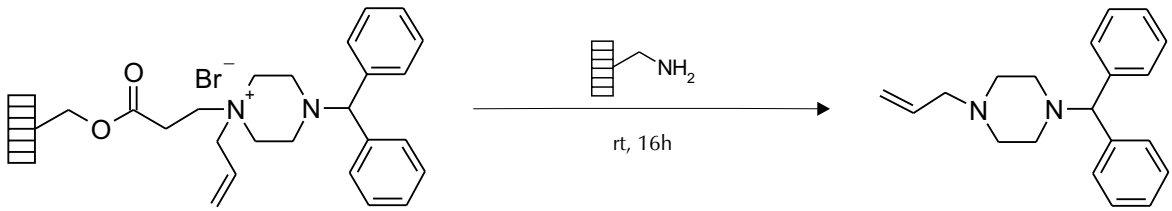
Each D-Series Lantern is treated with 0.5 mL of a solution of DIEA (15μL, 72μmol, 2 mole equivalents) in DCM at rt for 16 hours. The Lantern is removed (**caution!** retain the reaction solution) and washed with DCM (3×3min). The reaction solution is combined with the DCM washing solutions. The combined solution is concentrated.

The resultant residue is loaded on to a column of silica gel (50mg, Merck Silica gel 60, 230-400 mesh) and eluted with hexane (3mL), ethyl acetate (5mL) and 20% MeOH/ethyl acetate (5mL) to yield 3.2mg of product. The overall yield is 31%[5], based on the initial loading of hydroxymethyl Lanterns. Samples are dissolved in 90% CH_3CN/H_2O and in $CDCl_3$ for LC-MS and ^1H NMR analysis respectively.



Method B: using aminomethyl Lanterns as the base

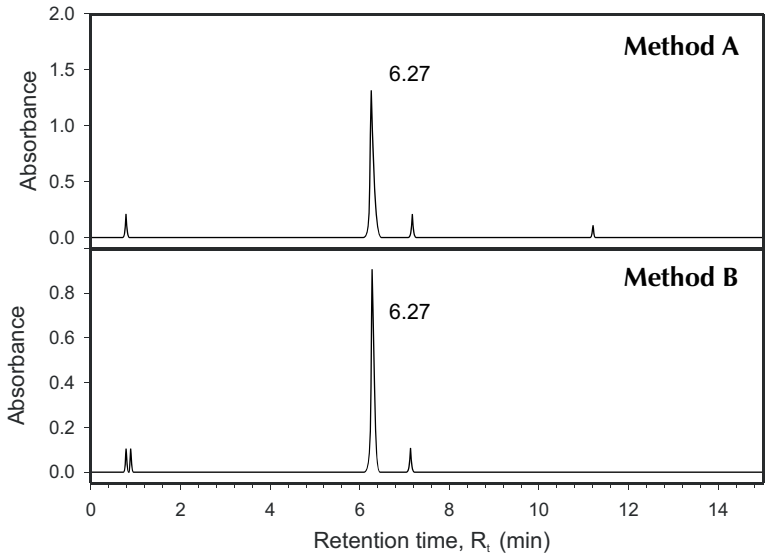
Each D-Series Lantern is treated with 2mL of DCM and 2 PS aminomethyl D-Series Lanterns[4] (72μmol, 2 mole equivalents) at rt for 16 hours with gentle agitation. The Lanterns are removed (**caution!** retain the reaction solution) and washed with DCM (3×3min). The reaction solution is combined with the DCM washing solutions. The combined solution is concentrated to yield 4.0mg of the final product. The overall yield is 38%[5], based on the initial loading of hydroxymethyl Lanterns. Samples are dissolved in 90% CH_3CN/H_2O and in $CDCl_3$ for LC-MS and ^1H NMR analysis respectively.

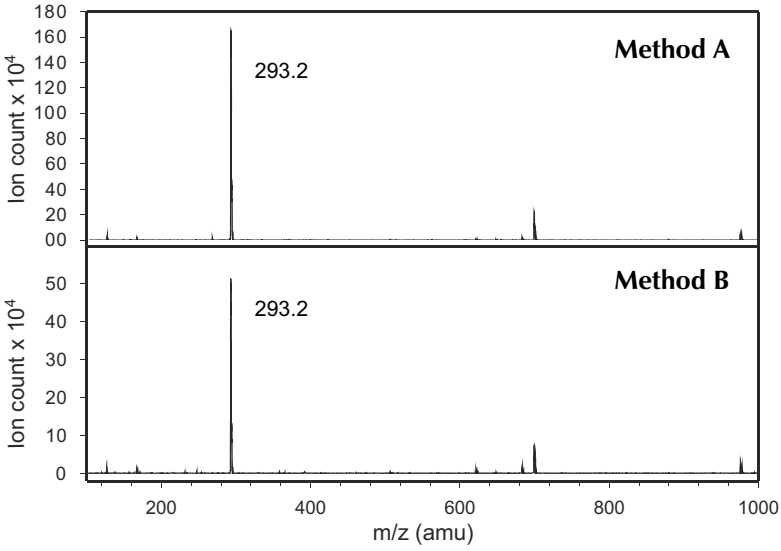


Analytical Data

Reverse phase HPLC trace of the tertiary amine product (Method A and B)

Detection at 214nm

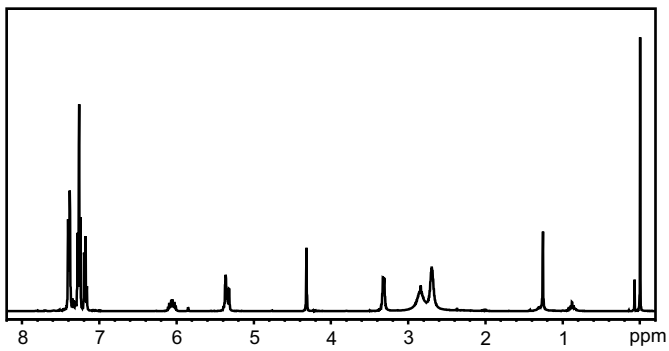




Electrospray MS trace of LC peak at R_t = 6.27min (Method A and B)

Molecular Formula: $C_{20}H_{24}N_2$
Monoisotopic Mol. Weight: 292.43
$[M+H]^+$ peak at 293.2amu

400MHz ^{1}H NMR spectrum of the tertiary amine product obtained *via* Method B ($CDCl_3$)



Notes and References

1 Heinonen, P. and Lonnberg, H., *Tetrahedron Lett*., 1997, **38**, 8569-8572.
2 Brown, A.R., Rees, D.C., Rankovic, Z. and Porphy, J.R., *J. Am. Chem. Soc*., 1997, **119**, 3288-3295.
3 Ouyang, X., Armstrong, R.W. and Murphy, M.M., *J. Org. Chem*., 1998, **63**, 1027-1032.

4 PS aminomethyl D-Series Lanterns supplied as TFA salt are neutralised with 5% DIEA in DMF/DCM (v/v, 1:1) (2×10min), then washed with DMF(3×3min) and DCM(3×3min), air dried.
5 Yields are comparable to those reported in references 1 and 2.

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