

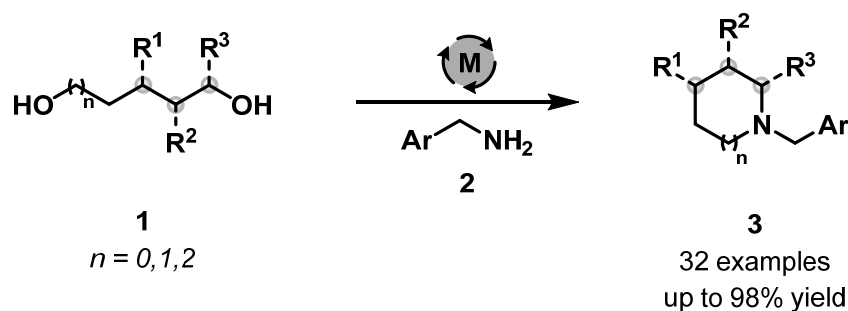
STEREOSELECTIVE SYNTHESIS OF SATURATED NITROGEN HETEROCYCLES VIA HYDROGEN BORROWING CATALYSIS

Anna E. R. Chamberlain^a, Kieran J. Paterson^a, Roly J. Armstrong^a, Heather Twin^b,
and Timothy J. Donohoe^a

^aDepartment of Chemistry, University of Oxford, Chemistry Research Laboratory, 12
Mansfield Road, Oxford, OX1 3TA, UK

^bVertex Pharmaceuticals, 86-88 Jubilee Avenue, Abingdon, OX14 4RW, UK

Small, saturated nitrogen heterocycles are highly privileged structures in pharmaceuticals and agrochemicals. Given the increasing complexity and 3D nature of drug candidates, we sought to develop methodology which allows for control of relative and absolute stereochemistry at the C2, C3 and C4 positions.



Scheme 1: Saturated nitrogen heterocycles, such as piperidines 3, are generated from diols 1 and amines 2 under hydrogen borrowing catalysis.

We have found that hydrogen borrowing catalysis can enable the direct synthesis of a wide range of piperidine scaffolds, generating water as the sole by-product. The process is mediated by a readily available transition metal catalyst which abstracts hydrogen from diol 1 to generate a reactive carbonyl intermediate, which can then condense with amine 2. The catalyst returns the 'borrowed' hydrogen and the cycle repeats, overall generating two new C-N bonds. A structurally diverse range of substrates 3 have been synthesized in high yields. Multiply substituted structures can be obtained with excellent diastereo- and enantioselectivity.