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Intramolecular Hydride Addition to Pyridinium Salts: New Routes to Enantiopure Dihydropyridones

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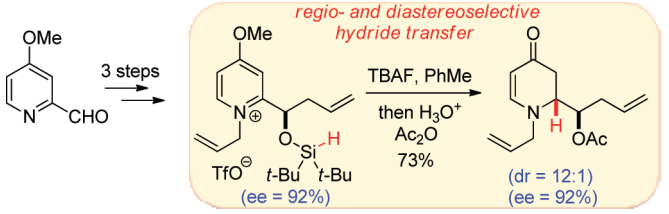
ABSTRACT



The transformation of a simple disubstituted pyridine into a pyridinium ion bearing an exocyclic hydroxyl group, protected as a silane, enabled an intramolecular hydride transfer reaction to take place when fluoride was used as a nucleophile. The addition was both regio- and stereoselective and enabled the formation of enantiopure dihydropyridones when enantiopure pyridine derivatives were used in this sequence. The heterocyclic products contain ample functionality for further elaboration reactions and subsequent derivatization.

The transformation of pyridines and pyridinium salts into saturated or partially saturated heterocycles has proven to be a worthwhile area of reseach, with the prospect of turning flat aromatic compounds into valuable, stereochemically defined, azacycles.[1,2]

Our research has focused on the reactions of 4-methoxy-2-acyl substituted pyridinium salts, serving as precursors to C-2 geminally disubstituted dihydropyridones. Transformations of these pyridine derivatives can be accomplished by single electron reduction (followed by electrophilic quench)[3] or by the direct addition of an organometallic nucleophile, guided by the adjacent acyl group (see **1**→**2**, Scheme 1).[4] Indeed, the heterocyclic templates generated by this approach have been used recently in the synthesis of cylindricines A and C.[5] However, the addition of an external nucleophile to a prochiral arene generates racemic products and methods were sought to expand the scope of the methodology so that single enantiomers could be produced and then used in synthetic endeavors (Scheme 1).

Two clear solutions to this problem would involve (i) the attachment of a chiral auxiliary to the arene, prior to nucleophilic attack,[6] or (ii) a chiral nucleophile in the addition process.[7] While both approaches are worthwhile and have witnessed several recent and exciting advances, we sought to expand the notion of an intramolecular hydride attack from a tethered silane onto the arene (**3**).

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(1) For a review of biological properties, see: (a) Michael, J. P. *Nat. Prod. Rep.* **2008**, *25*, 139. (b) Chemler, S. A. *Curr. Bioact. Compd.* **2009**, *5*, 2.

(2) For example, see: (a) Arnott, G.; Brice, H.; Clayden, J.; Blaney, E. *Org. Lett.* **2008**, *10*, 3089. (b) Arnott, G.; Clayden, J.; Hamilton, S. D. *Org. Lett.* **2006**, *8*, 5325. (c) Knapp, S.; Yang, C.; Pabbaraja, S.; Rempel, B.; Reid, S.; Withers, S. G. *J. Org. Chem.* **2005**, *70*, 7715. (d) Ege, M.; Wanner, K. T. *Org. Lett.* **2004**, *6*, 3553. (e) Mehmandoust, M; Marazano, C.; Das, B. C. *J. Chem. Soc., Chem. Commun.* **1989**, 1185. (f) Comins, D. L.; Brown, J. D. *Tetrahedron Lett.* **1986**, *27*, 4549.

(3) (a) Donohoe, T. J.; Johnson, D. J.; Mace, L. H.; Bamford, M. J.; Ichihara, O. *Org. Lett.* **2005**, *7*, 435. (b) Donohoe, T. J.; Johnson, D. J.; Mace, L. H.; Thomas, R. E.; Chiu, J. Y. K.; Rodrigues, J. S.; Compton, R. G.; Banks, C. E.; Tomcik, P.; Bamford, M. J.; Ichihara, O. *Org. Biomol. Chem.* **2006**, *4*, 1071.

(4) Donohoe, T. J.; Connolly, M. J.; Walton, L. *Org. Lett.* **2009**, *11*, 5562.

(5) Donohoe, T. J.; Brian, P. M.; Hargaden, G. C.; O'Riordan, T. J. C. *Tetrahedron* **2010**, *66*, 6411.

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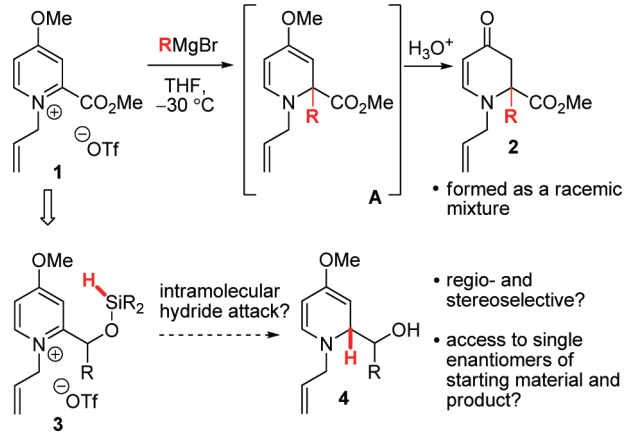
If we could render this reaction into a regio- and diastereoselective process, then the employment of enantiopure starting material in this sequence would furnish enantiopure products (see **3**→**4**, Scheme 1). In fact, the related intramolecular addition of a hydride nucleophile onto an oxonium ion (itself generated by a 1,2-hydride shift) has recently proven to be an efficient way of forming *trans* substituted tetrahydrofuran rings.[8]

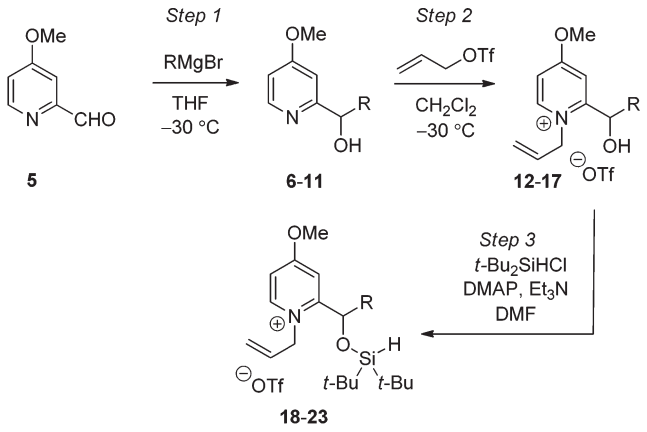
Scheme 1. General Concept



We set out to examine this reaction sequence by starting from readily available pyridine **5** (Scheme 2).[9] Addition of a nucleophile to the aldehyde was accomplished by the action of an organometallic reagent, and subsequent quaternerization of the nitrogen with allyl triflate[10] activated the pyridine toward nucleophilic attack. Finally, the nucleophilic hydride species was attached to the C-2 benzylic alcohol via a temporary silicon linker.

Taking methyl substituted compound **18** as an example, we then undertook experiments to encourage the silicon atom to release its hydride nucleophile by the addition of fluoride (TBAF, 1 equiv) to the heteroatom (Scheme 3). Using THF as a solvent, this reaction was partially successful giving **24** but was always in competition with simple desilylation of the starting material, producing **12**. Note that in each case the reaction was quenched with an acidic workup so that intermediate enol ethers would be hydrolyzed to the stable, and isolable, dihydropyridones (see **A**, Scheme 1). A breakthrough came about when we switched the solvent to toluene, hypothesizing that the loss of an alkoxide from a pentavalent silicon intermediate might be disfavored in such a nonpolar solvent. Indeed, dihydropyridone **24** was isolated in improved yield (52%) and with high diastereoselectivity when the reaction was conducted in toluene at 50 °C. While, in each case, the product was isolated as its silyl ether, we noticed that under the higher temperature conditions there was a significant amount of desilyation of the product. Therefore, the decision was made to add an excess (4 equiv) of TBAF to the reaction mixture to ensure complete removal of silicon from the product; in this case product isolation was made significantly easier by acetylation of the crude alcohol product. Using this regime, compound **25** was isolated in 85% yield and with 8:1 diastereoselectivity. The sense of stereoselectivity of the hydride transfer reaction was proven to be as shown by X-ray crystallography on a *para*-nitrobenzoate derivative (**26**) of the major diastereomer of compound **25**.

Scheme 2. Synthesis of Starting Materials



R	step 1 (product)	step 2 (product)	step 3 (product)
Me	92% (**6**)	91% (**12**)	92% (**18**)
Hexyl	80% (**7**)	88% (**13**)	75% (**19**)
Allyl	79% (**8**)	83% (**14**)	79% (**20**)
Vinyl	71% (**9**)	72% (**15**)	74% (**21**)
Benzyl	75% (**10**)	80% (**16**)	73% (**22**)
Phenyl	98% (**11**)	80% (**17**)	70% (**23**)

(6) (a) Wolfe, B. H.; Libby, A. H.; Al-awar, R. S.; Foti, C. J.; Comins, D. L. *J. Org. Chem.* **2010**, *75*, 8564. (b) Barbe, G.; Pelletier, G.; Charette, A. B. *Org. Lett.* **2009**, *11*, 3398. (c) Focken, T.; Charette, A. B. *Org. Lett.* **2006**, *8*, 2985. (d) Comins, D. L.; Sahn, J. J. *Org. Lett.* **2005**, *7*, 5227. (e) Legault, C.; Charette, A. B. *J. Am. Chem. Soc.* **2003**, *125*, 6360. (f) Yamada, S.; Morita, C. *J. Am. Chem. Soc.* **2002**, *124*, 8184. (g) Charette, A. B.; Grenon, M.; Lemire, A.; Pourashraf, M.; Martel, J. *J. Am. Chem. Soc.* **2001**, *123*, 11829. (h) Comins, D. L.; Joseph, S. P.; Goehring, R. R. *J. Am. Chem. Soc.* **1994**, *116*, 4719.

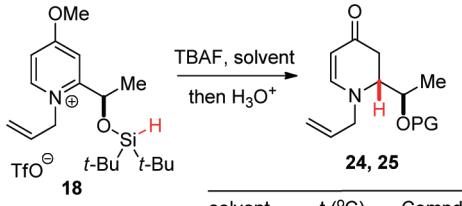
(7) (a) Fernández-Ibáñez, M. Á.; Maciá, B.; Pizzuti, M. G.; Minnaard, A. J.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2009**, *48*, 9339. (b) Black, D. A.; Beveridge, R. E.; Arndtsen, B. A. *J. Org. Chem.* **2008**, *73*, 1906. (c) Sun, Z.; Yu, S.; Ding, Z.; Ma, D. *J. Am. Chem. Soc.* **2007**, *129*, 9300. (d) Ichikawa, E.; Suzuki, M.; Yabu, K.; Albert, M.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 11808. (e) Nadeau, C.; Aly, S.; Belyk, K. *J. Am. Chem. Soc.* **2011**, *133*, 2878.

(8) (a) Donohoe, T. J.; Williams, O.; Churchill, G. H. *Angew. Chem., Int. Ed.* **2008**, *47*, 2869. (b) McCombie, S. W.; Ortiz, C.; Cox, B.; Ganguly, A. K. *Synlett* **1993**, 541. For a review see: (c) Larson, G. L.; Fry, J. L. *Org. React.* **2008**, *71*, 1.

(9) Compound **5** may be easily prepared by DIBAl-H reduction of the corresponding methyl ester (85% yield): Sundberg, R. J.; Jiang, S. *Org. Prep. Proced. Int.* **1997**, *29*, 117. Alternatively, **5** is commercially available, although expensive.

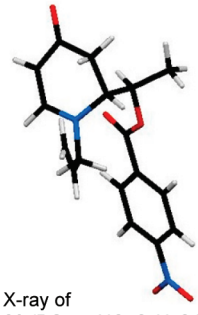
(10) Corey, E. J.; Helal, C. J. *Tetrahedron Lett.* **1996**, *37*, 5675. The allyl group is particularly convenient because it is stable to the reaction conditions and yet can be easily removed afterwards, if so desired; see ref 4.

Scheme 3. Diastereoselective Hydride Transfer



solvent	t (°C)	Compd	yield	dr
THF	rt	**24**	10%	
Toluene	rt	**24**	36%	
Toluene	50	**24**	52%	8:1
Toluene[a] then Ac_2O	50	**25**	85%	8:1

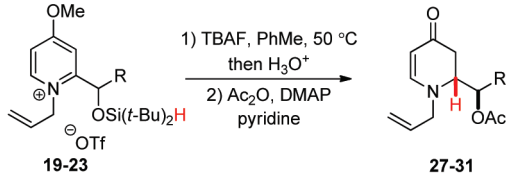
24, PG= Si(*t*-Bu)$_2$F
25, PG= Ac
[a] excess TBAF



X-ray of
26 (PG= *p*-$NO_2C_6H_4CO$)

Subjection of the analogous pyridinium salts **19**–**23** to the optimum conditions was also successful, in each case giving the corresponding dihydropyridone in good yield and (phenyl excepted) stereoselectivity (Scheme 4).

Scheme 4. Scope of the Methodology



R	product	yield	dr
Hexyl	**27**[a]	72%	12:1
Allyl	**28**	74%	12:1
Vinyl	**29**	75%	6:1
Benzyl	**30**	72%	8:1
Phenyl	**31**	70%	1.5:1

There is a clear correlation between the size of the R group and the diastereoselectivity that was observed during the hydride transfer reaction.[11] We presume that this relationship has its origins in the A$^{[1,3]}$ allylic strain encountered between the R group and the *N*-allyl group in the two reactive conformations **B** and **C** that lead to the major and minor products respectively (Figure 1).[12] The outcome from the attack onto phenyl substituted compound **23** is anomalous and may have its origins in an attractive interaction between the Ph-π system and the allyl group or even the ability of the Ph group to lie flat[13] in a transition structure such as **C**, thereby reducing its effective size.

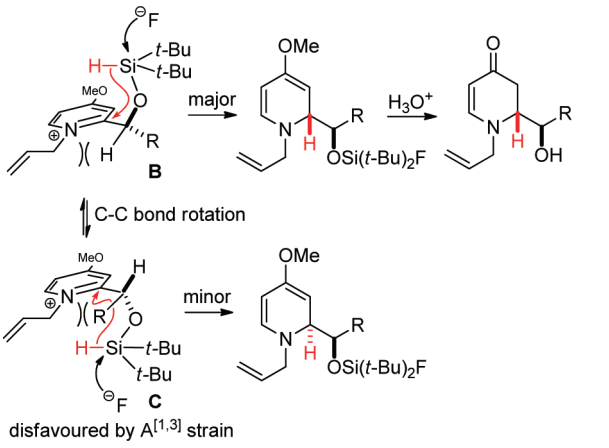
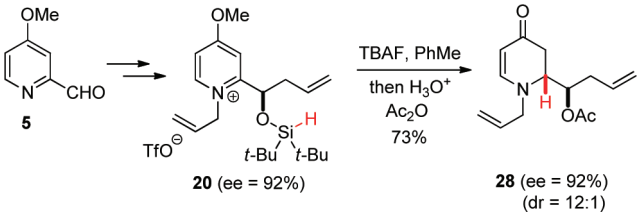


Figure 1. Rationalization of the outcome.

As expected, the addition of an enantiopure allyl nucleophile (+)-(Ipc)$_2$B-allyl to aldehyde **5** formed alcohol **8** with high enantiomeric excess (89% yield; 92% ee, proven by Mosher ester analysis and measured against a racemic standard).[14] Taking this material and performing an identical reaction sequence to that shown for the racemic material gave heterocycle **28**, with a 92% ee for the major diastereomer (Scheme 5). Clearly, this sequence opens up the possibility of making such azacycles in enantiomerically pure form and therefore provides an opportunity to progress them in total synthesis.

Scheme 5. Enantioenriched Heterocycles



(4) Donohoe, T. J.; Connolly, M. J.; Walton, L. *Org. Lett.* **2009**, *11*, 5562.

(11) We do not assume concomitant attack of the fluoride anion and loss of hydride from the silicon.

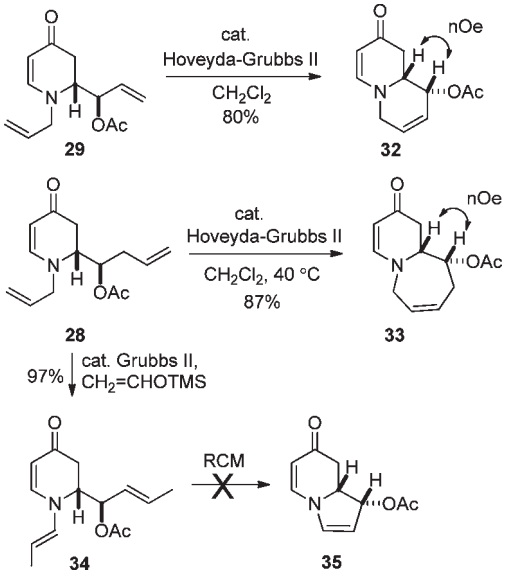
(12) The introduction of secondary and tertiary R groups would be expected to lead to even higher levels of diastereoselectivity. Unfortunately, realization of this sequence is currently not possible because of our failure to silylate the more hindered secondary alcohols that are present. Note also that while the intramolecular nature of the hydride transfer has not been proven unambiguously, initial crossover experiments do indicate that the hydride does not 'swap' between molecules of pyridinium salts.

(13) Wiberg, K. B.; Castejon, H.; Bailey, W. F.; Ochterski, J. *J. Org. Chem.* **2000**, *65*, 1181.

(14) The absolute configuration of **8** was proven to be (*R*) by NMR analysis of its Mosher's esters, see Supplementary and (a) Hoye, T. R.; Jeffrey, C. S.; Shao, F. *Nature Protocols* **2007**, *2*, 2451. Moreover, the (*R*)-configuration is that to be expected based on the model by which the (+)-(Ipc)$_2$B-allyl reagent imposes stereoselectivity during the allyl addition reaction; see: (b) Brown, H. C.; Jadhav, P. K. *J. Am. Chem. Soc.* **1983**, *105*, 2092. (c) Racherla, U. S.; Brown, H. C. *J. Org. Chem.* **1991**, *56*, 401.

Finally, the presence of allyl and vinyl groups in the heterocyclic products **28** and **29** prompted us to attempt ring closing metathesis as a means of accessing bicyclo derivatives (Scheme 6). Pleasingly, the 6,6-ring system **32**

Scheme 6. Ring Closing Metathesis on the Products



and the 6,7-ring system **33** were formed in excellent yields when dihydropyridones **29** and **28** were treated with catalytic amounts of Hoveyda–Grubbs II catalyst.[15] As a consequence of this, the *N*-allyl group, necessary to activate the pyridine core to nucleophilic attack, forms an integral part of the bicyclic products, increasing the overall atom economy of this methodology. NMR studies on the two products **32**, **33** revealed strong NOE enhancements as shown in Scheme 6, providing further evidence for the relative stereochemistry within; note that this assignment is also consistent with the model presented earlier (Figure 1). The bicyclo compounds produced herein provide ample functionality to ensure that many different types of derivatization may be possible. Our attempts to prepare the 6,5-ring system **35** were unsuccessful; after double alkene isomerization of the allyl groups within **28**,[16] we were unable to effect a ring closure from **34** using a variety of metathesis catalysts and conditions. Presumably, this sequence was frustrated by the ring strain inherent in preparing a 6,5-ring system containing up to six trigonal centers.

To conclude, we have shown that an intramolecular hydride attack onto substituted pyridinium salts can be both regio- and stereoselective, forming useful dihydropyridones in the process. Access to enantioenriched material is enabled by an asymmetric allylation reaction, allowing the preparation of enantiopure dihydropyridones. Finally, the alkene units present on C-1 and the nitrogen atom in the products can be joined by a ring closing metathesis protocol meaning that complex azabicyclo ring systems can be easily accessed.

Acknowledgment. We thank the EPSRC and Eli Lilly and Company Ltd. for funding this project.

Supporting Information Available. Full experimental details as well as ^{1}H and ^{13}C NMR spectra for all reported compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(15) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168.

(16) (a) Arisawa, M.; Terada, Y.; Nakagawa, M.; Nishida, A. *Angew. Chem., Int. Ed.* **2002**, *41*, 4732. (b) For a review, see: Donohoe, T. J.; O'Riordan, T. J. C.; Rosa, C. P. *Angew. Chem., Int. Ed.* **2009**, *48*, 1014.