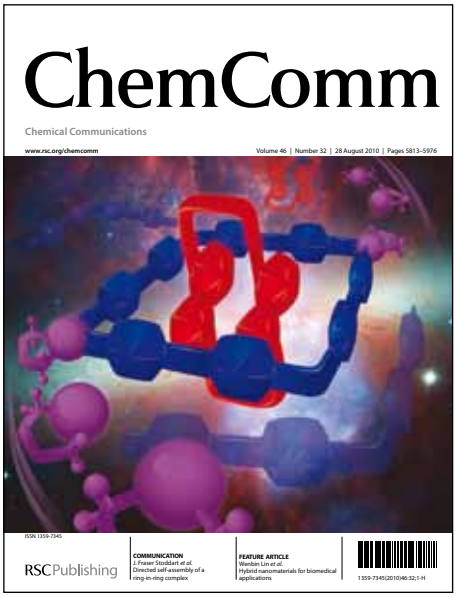
ChemComm

Accepted Manuscript



This is an *Accepted Manuscript*, which has been through the RSC Publishing peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, which is prior to technical editing, formatting and proof reading. This free service from RSC Publishing allows authors to make their results available to the community, in citable form, before publication of the edited article. This *Accepted Manuscript* will be replaced by the edited and formatted *Advance Article* as soon as this is available.

To cite this manuscript please use its permanent Digital Object Identifier (DOI®), which is identical for all formats of publication.

More information about *Accepted Manuscripts* can be found in the **Information for Authors**.

Please note that technical editing may introduce minor changes to the text and/or graphics contained in the manuscript submitted by the author(s) which may alter content, and that the standard **Terms & Conditions** and the **ethical guidelines** that apply to the journal are still applicable. In no event shall the RSC be held responsible for any errors or omissions in these *Accepted Manuscript* manuscripts or any consequences arising from the use of any information contained in them.

Journal Name ChemComm
Dynamic Article Links ►
View Online
Cite this: DOI: 10.1039/c0xx00000x
www.rsc.org/xxxxxx
ARTICLE TYPE

Carbenoid-mediated N-O Bond Insertion and its Application in the Synthesis of Pyridines

Xinxin Qi, Lu Dai and Cheol-Min Park*

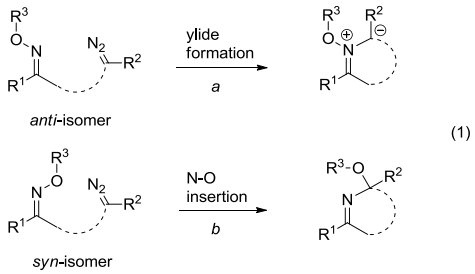
Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

Highly efficient synthesis of 3-hydroxypyridines has been developed based on carbenoid-mediated N-O bond insertion. Treatment of δ-diazo oxime ethers with dirhodium complex Rh_2(tfacam)$_4$ rapidly provides a variety of pyridines in 5-10 minutes in good to excellent yields.

Pyridines represent a highly valuable class of azacycles, which are frequently found in bioactive natural products, pharmaceuticals, and functional materials.[1] As a result, the development of more efficient synthesis of pyridines continues to draw a great deal of interest from the synthetic community.[2] Traditional synthesis of pyridines typically relies on condensation of amine and carbonyl compounds, which often results in poor regiochemical control and narrow substitution pattern.[3] Over the years, development of new methods based on cycloaddition reactions and multi-component couplings have been reported.[4] Also, transition metal-catalyzed reactions have received much attention.[5]

In our recent efforts, we have focused to investigate the reactivity of α-oximino carbenoids.[6] The versatile reactivity of these carbenoid species allowed us to develop the synthesis of various N-heterocycles; pyrroles via [3+2] cycloaddition,[6] 2*H*-azirines and 2-isoxazolines via 1,5-hydride shift,[7] 2-alkoxy/aryloxy-2*H*-azirines via N-O bond insertion,[8] and 2*H*-azirines and pyrroles via tandem Wolff rearrangement.[9] In particular, the observation of facile N-O bond insertion upon photolysis of α-diazo oxime ethers prompted us to further investigate the utility of this novel bond forming process.[8] We reasoned that construction of 6-membered azacycles may be realized if the analogous N-O bond insertion is successfully developed with δ-diazo oxime ethers.

N-O bond insertion has been rarely documented in the literature. It was only recently that Davies et. al reported a remarkable example of N-O bond insertion on isoxazoles and its application to pyridine synthesis.[10] In our approach for intramolecular carbenoid-mediated N-O bond insertion of oxime ethers, it is noteworthy that the reaction could potentially lead to two competitive pathways depending on the configuration of oxime ethers; a) azomethine ylide formation for *anti*-isomer. b) N-O bond insertion for *syn*-isomer (eqn (1)). Indeed, the former has been reported by Padwa and coworkers in which intramolecular reaction of carbenoid with *anti*-aldoxime ether leads to formation of azomethine ylide, which further participates in 1,3-dipolar cycloaddition.[11] We reasoned that this pathway may be suppressed and shunted to N-O bond insertion pathway by employing *syn*-isomers. Herein, we wish to report successful development of this strategy leading to efficient synthesis of 3-hydroxypyridines.



(1)

Our synthetic attempts began with screening various catalysts employing **1a** as a substrate (Table 1). The configuration of the oxime ether was unambiguously determined based on the X-ray structure of the 4-chlorophenyl analogue.[12] While copper complexes generally provided the desired product in poor yields, dirhodium catalysts gave more promising results. It was noted that the ability of dirhodium catalysts to promote the N-O bond insertion highly depends on the nature of their ligands. Whereas $Rh_2(OAc)_4$ in refluxing DCE gave 3-hydroxypyridine **2a** in 58% yield, dirhodium complexes with bulkier ligands resulted in diminished yields (Table 1, entries 5-7). Electron deficient catalysts such as $Rh_2(tfa)_4$ and $Rh_2(pfb)_4$ gave **2a** in comparable yields to $Rh_2(OAc)_4$. To our delight, the use of Rh_2(tfacam)$_4$ provided **2a** in quantitative yield. Further optimization of the reaction conditions revealed that the reaction proceeds with greater efficiency by employing higher temperature with shorter reaction time; 80℃, 5 min, 100% vs. 50 ℃, 1h, 74% (Table 1, entries 10 and 11, respectively). With respect to solvent effects,

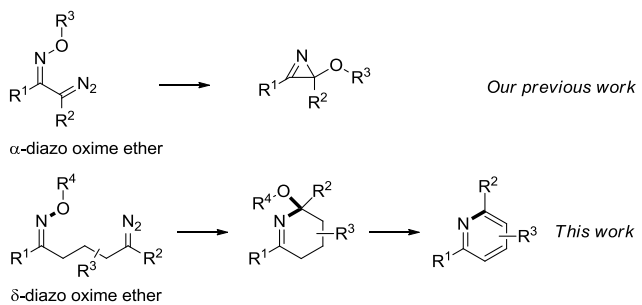
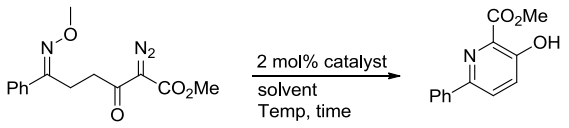


Table 1 Optimization of reaction conditions

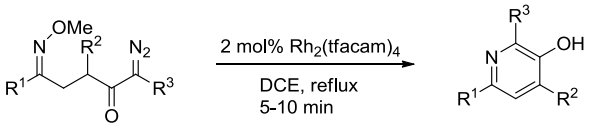


1a 2a

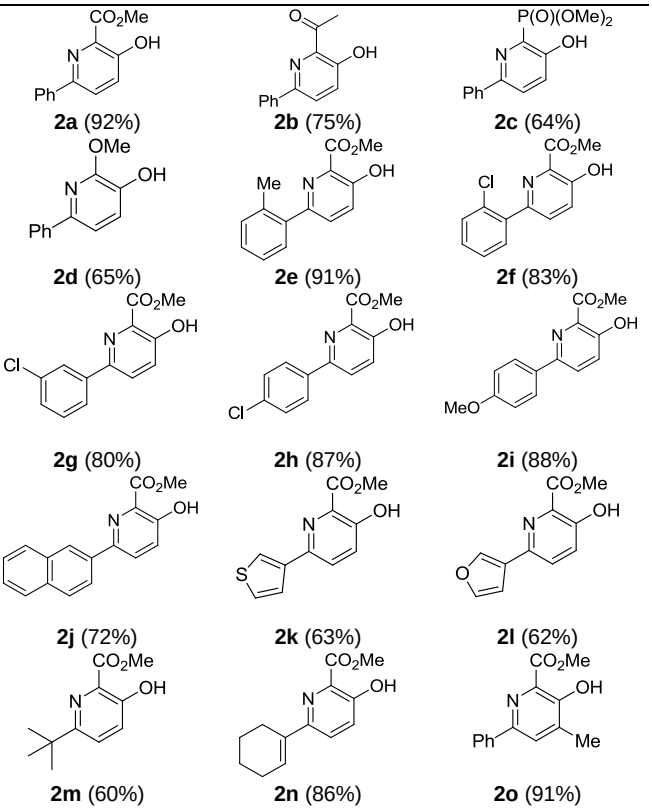
Entry	Catalyst[a]	Solvent[b]	Temp (℃)	time	Yield[c] (%)
1[d]	$Cu(hfacac)_2$	DCE	80	1h	25
2[d]	$Cu(OTf)_2$	DCE	80	1h	19
3[d]	CuOTf	DCE	80	1h	17
4	$Rh_2(OAc)_4$	DCE	80	10 min	58
5	$Rh_2(Piv)_4$	DCE	80	20 min	40
6	$Rh_2(Oct)_4$	DCE	80	20 min	35
7	$Rh_2(esp)_2$	DCE	80	30 min	51
8	$Rh_2(tfa)_4$	DCE	80	10 min	59
9	$Rh_2(pfb)_4$	DCE	80	10 min	59
10	**$Rh_2(tfacam)_4$**	**DCE**	**80**	**5 min**	**100**
11	$Rh_2(tfacam)_4$	DCE	50	1h	74
12	$Rh_2(tfacam)_4$	Benzene	80	5 min	84
13	$Rh_2(tfacam)_4$	Toluene	110	5 min	76

[a] hfacac = trifluoroacetylacetonate, tfa = trifluoroacetate, pfb = perfluorobutyrate, Piv = pivaloate, Oct = octanoate, esp = α,α,α′,α′-tetramethyl-1,3-benzenedipropionate, tfacam = trifluoroacetamide. [b] DCE = dichloroethane. [c] yields determined by NMR *vs.* standard. [d] 5 mol% catalyst.

Table 2 Substrate scope of 3-hydroxy pyridine synthesis[a]



1 2

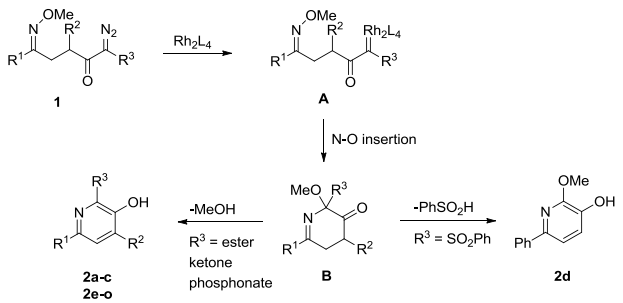


[a] Isolated yields.

DCE turned out to be an optimal solvent (Table 1, entries 10 vs. 12 and 13).

With the optimal conditions in hand, we turned our attention to examine the substrate scope of the reaction. As shown in Table 2, the intramolecular N-O bond insertion proceeded smoothly to give a variety of 3-hydroxypyridines in good to excellent yields. Substrates with common electron withdrawing groups (R^3) were tolerated well to afford pyridines substituted with the corresponding functional groups. It is noteworthy that **1d** bearing sulfonyl group provided 2-methoxy-3-hydroxypyridine **2d** resulting from elimination of the sulfonyl group in place of the methoxy group. Survey of aryl groups with various substituents indicated that the reaction is quite tolerant to steric and electronic influences (**2e-i**). In addition, substrates with 2-naphthyl (**2j**) and heteroaryl groups such as 2-thienyl (**2k**) and 2-furyl (**2l**) moieties smoothly participated in the reaction to give the corresponding pyridines in good yields. Encouraged by these results, we also examined those bearing alkyl and alkenyl groups for R^1. Substrates with both *tert*-Bu and 1-cyclohexenyl groups provided **2m** and **2n** in 86% and 60% yields, respectively. The cyclization reaction remained efficient even with substitution on the tether, providing **2o** in 91% yield.

Based on the observation, a plausible mechanism for the formation of 3-hydroxypyridine is proposed in Scheme 1. The reaction initiated by formation of dirhodium carbenoid **A** with expulsion of dinitrogen proceeds to undergo N-O bond insertion to give intermediate **B**. For substrates with R^3 = ester, ketone, and phosphonate, elimination of MeOH occurs to form pyridines retaining the R^3 moieties. In contrast, for the substrate with R^3 = sulfone, loss of sulfonyl group leads to formation of 2-methoxypyridine **2d**.



Scheme 1 Proposed reaction mechanism.

In summary, we have developed efficient synthesis of 3-hydroxypyridines based on N-O bond insertion of δ-diazo oxime ethers. Competitive formation of azomethine ylide could be

suppressed by controlling the configuration of oxime ethers and shunted to the N-O bond insertion pathway. This transformation features broad functional group tolerance, high efficiency and very rapid conversion under mild reaction conditions with low catalyst loading. In addition, the protocol allows for access to 2-alkoxy-3-hydroxypyridines by employing substrates bearing sulfonyl group (for example, **2d**).

We gratefully acknowledge Nanyang Technological University for funding of this research. We thank Dr. Yongxin Li for X-ray crystallographic analysis.

Notes and references

Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore 637371, Singapore.; Fax: +65-6513-2748; Tel: +65-6513-2748; E-mail: cmpark@ntu.edu.sg

† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

1. A. F. Pozharskii, A. Soldatenkov and A. R. Katritzky, Heterocycles in Life and Society: An Introduction to Heterocyclic Chemistry, Biochemistry and Applications, Wiley, 2011.
2. (a) K. Kral and M. Hapke, Angew. Chem. Int. Ed., 2011, **50**, 2434-2435; (b) M. D. Hill, Chem. – Eur. J., 2010, **16**, 12052-12062; (c) J. A. Joule and K. Mills, Heterocyclic Chemistry, John Wiley & Sons, 2010; (d) B. Heller and M. Hapke, Chem. Soc. Rev., 2007, **36**, 1085-1094; (e) H. Gavin D, Tetrahedron, 2004, **60**, 6043-6061; (f) R. Chinchilla, C. Nájera and M. Yus, Chem. Rev., 2004, **104**, 2667-2722; (g) C. Simon, T. Constantieux and J. Rodriguez, Eur. J. Org. Chem., 2004, **2004**, 4957-4980; (h) W. Q. Fan, A. R. Katritzky, C. W. Rees and E. F. V. Scriven, eds., Comprehensive Heterocyclic Chemistry II, Pergamon Press, Oxford, 1996.
3. (a) M. C. Bagley, C. Glover and E. A. Merritt, Synlett, 2007, **2007**, 2459-2482; (b) T. R. Kelly and R. L. Lebedev, J. Org. Chem., 2002, **67**, 2197-2205; (c) P. Baumgarten and A. Dornow, Chem. Ber., 1939, **72**, 563-566; (d) A. Hantzsch, Liebigs Ann., 1882, **215**, 1-82.
4. (a) J. Shao, W. Yu, Z. Shao and Y. Yu, Chem. Commun., 2012, **48**, 2785-2787; (b) F. Sha and X. Huang, Angew. Chem. Int. Ed., 2009, **48**, 3458-3461; (c) K. Guo, M. J. Thompson and B. Chen, J. Org. Chem., 2009, **74**, 6999-7006; (d) J.-Y. Lu, J. A. Keith, W.-Z. Shen, M. Schürmann, H. Preut, T. Jacob and H.-D. Arndt, J. Am. Chem. Soc., 2008, **130**, 13219-13221; (e) S. P. Stanforth, B. Tarbit and M. D. Watson, Tetrahedron, 2004, **60**, 8893-8897; (f) D. L. Boger, J. S. Panek and M. M. Meier, J. Org. Chem., 1982, **47**, 895-897.
5. (a) Y.-F. Wang and S. Chiba, J. Am. Chem. Soc., 2009, **131**, 12570-12572; (b) D. A. Colby, R. G. Bergman and J. A. Ellman, J. Am. Chem. Soc., 2008, **130**, 3645-3651; (c) S. Liu and L. S. Liebeskind, J. Am. Chem. Soc., 2008, **130**, 6918-6919; (d) J. Barluenga, M. Á. Fernández-Rodríguez, P. García-García and E. Aguilar, J. Am. Chem. Soc., 2008, **130**, 2764-2765; (e) K. Parthasarathy, M. Jeganmohan and C.-H. Cheng, Org. Lett., 2007, **10**, 325-328; (f) B. M. Trost and A. C. Gutierrez, Org. Lett., 2007, **9**, 1473-1476; (g) M. Movassaghi and M. D. Hill, J. Am. Chem. Soc., 2006, **128**, 4592-4593; (h) K. Tanaka, N. Suzuki and G. Nishida, Eur. J. Org. Chem., 2006, **2006**, 3917-3922; (i) M. M. McCormick, H. A. Duong, G. Zuo and J. Louie, J. Am. Chem. Soc., 2005, **127**, 5030-5031; (j) R. Tanaka, A. Yuza, Y. Watai, D. Suzuki, Y. Takayama, F. Sato and H. Urabe, J. Am. Chem. Soc., 2005, **127**, 7774-7780; (k) K. R. Roesch and R. C. Larock, J. Org. Chem., 2001, **67**, 86-94; (l) Y. Yamamoto, R. Ogawa and K. Itoh, J. Am. Chem. Soc., 2001, **123**, 6189-6190; (m) A. Naiman and K. P. C. Vollhardt, Angew. Chem. Int. Ed., 1977, **16**, 708-709.
6. E. Lourdusamy, L. Yao and C.-M. Park, Angew. Chem. Int. Ed., 2010, **49**, 7963-7967.
7. X. Qi, Y. Jiang and C.-M. Park, Chem. Commun., 2011, **47**, 7848-7850.
8. X. Qi, X. Xu and C.-M. Park, Chem. Commun., 2012, **48**, 3996-3998.
9. Y. Jiang, W. C. Chan and C.-M. Park, J. Am. Chem. Soc., 2012, **134**, 4104-4107.
10. (a) J. R. Manning and H. M. L. Davies, J. Am. Chem. Soc., 2008, **130**, 8602-8603; (b) J. R. Manning and H. M. L. Davies, Tetrahedron, 2008, **64**, 6901-6908.
11. A. Padwa, D. C. Dean, M. H. Osterhout, L. Precedo and M. A. Semones, J. Org. Chem., 1994, **59**, 5347-5357.
12. CCDC 895021 (**1h**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/cgi-bin/catreq.cgi.

Efficient synthesis of pyridines has been developed based on carbenoid-mediated N-O bond insertion of δ-diazo oxime ethers.