Rising Novel Organic Synthesis Methods Based on the Cleavage of N-N and N-O Bonds

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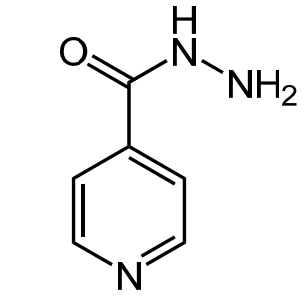
Kürti, L. *et al.*
Science **2014**, *343*, 61.

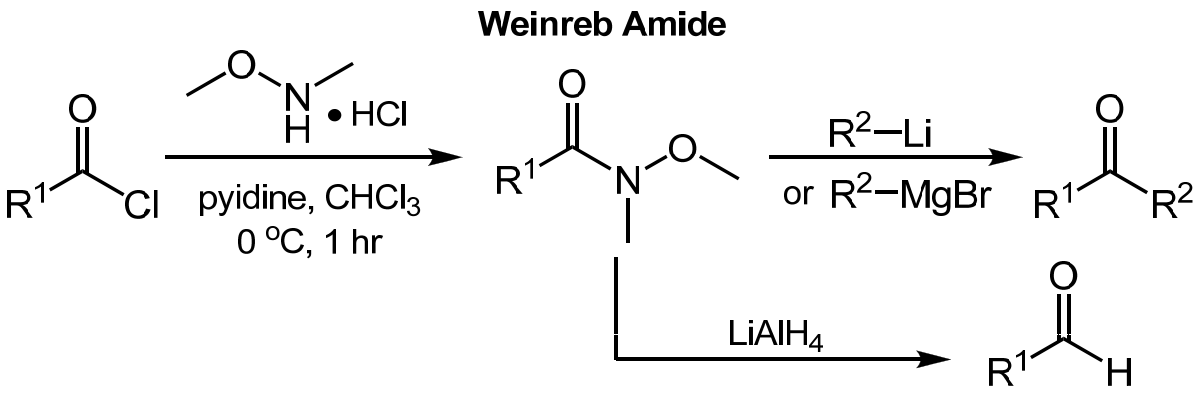
Contents

Background >> The Nature of Hydrazines and Hydroxylamines

Hydrazines are part of many organic synthesis, often those of practical significance in pharmaceuticals, such as the antituberculosis medication *isoniazid* and the antifungal *fluconazole*, as well as in textile dyes and in photography.



Isonicotinohydrazide

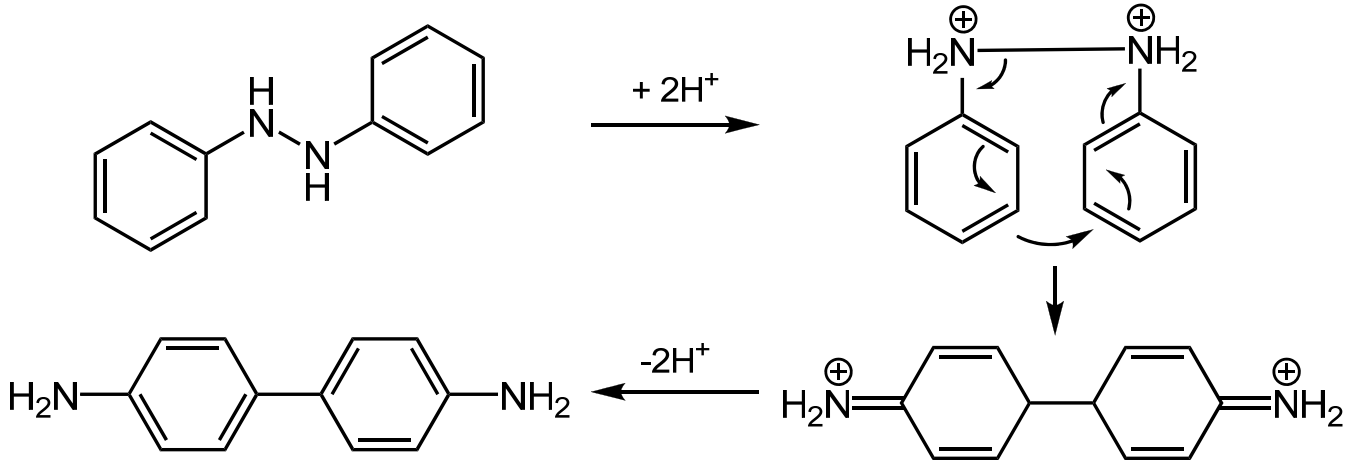


Hydroxylamines are commonly used as reducing agents in myriad organic and inorganic reactions. An example of compound containing a hydroxylamine functional group is *N,O-dimethylhydroxylamine* (a coupling agent, used to synthesis *Weinreb amides*).

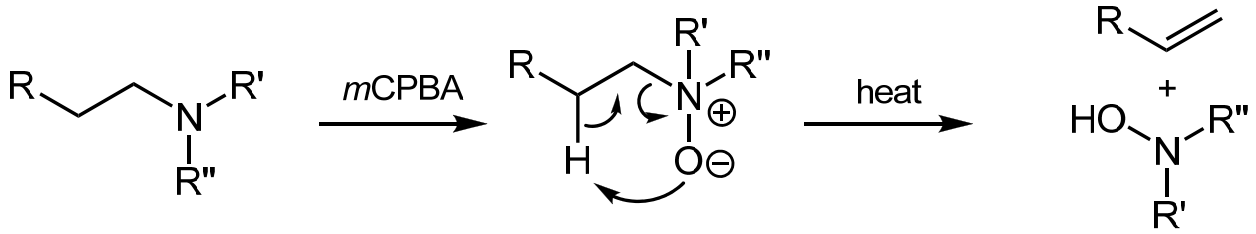
From Wikipedia

Cleavage of N-N and N-O Bonds Through Rearrangement and Elimination

Benzidine Rearrangement: treatment of this hydrazine with mineral acids induces a rearrangement reaction to 4,4'-benzidine.



Cope Elimination: an elimination reaction of the *N*-oxide of a tertiary amine to form an alkene and a hydroxylamine.

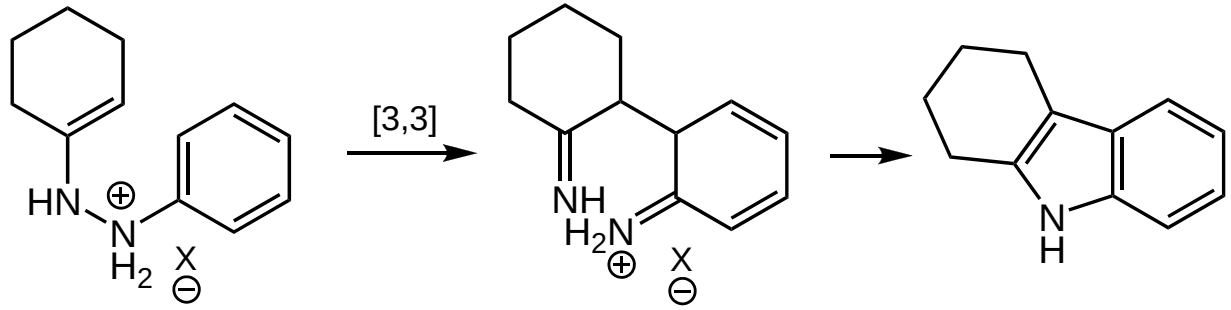


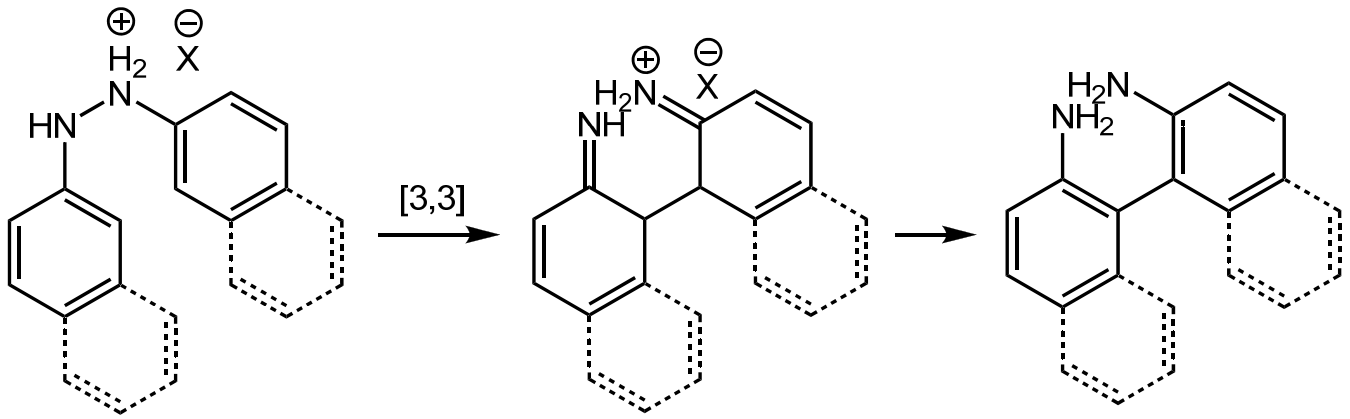
From Wikipedia

Cleavage of N-N and N-O Bonds Through Rearrangement and Elimination

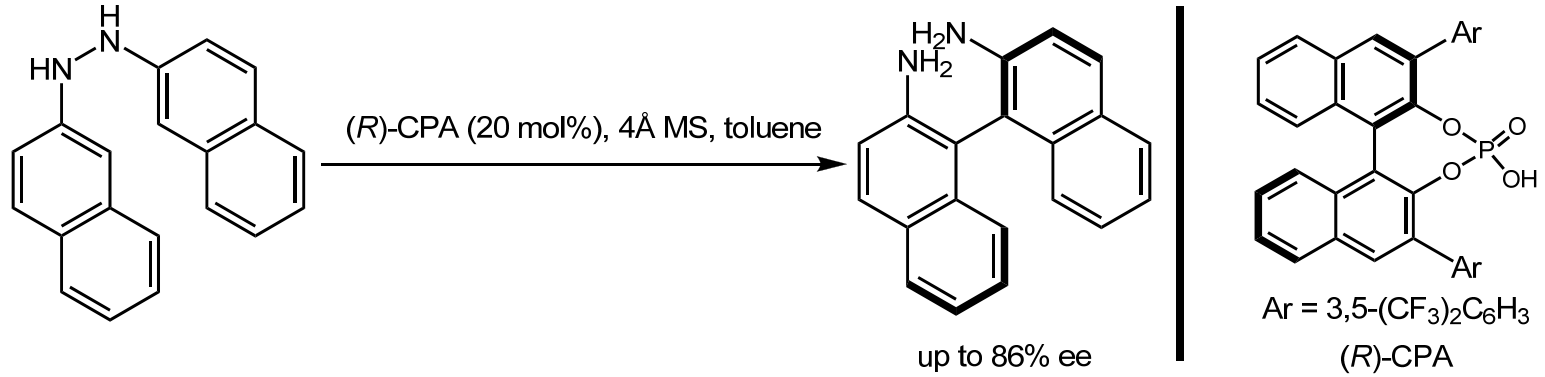
[3,3]-*diaza* Cope rearrangement

Fischer indolization

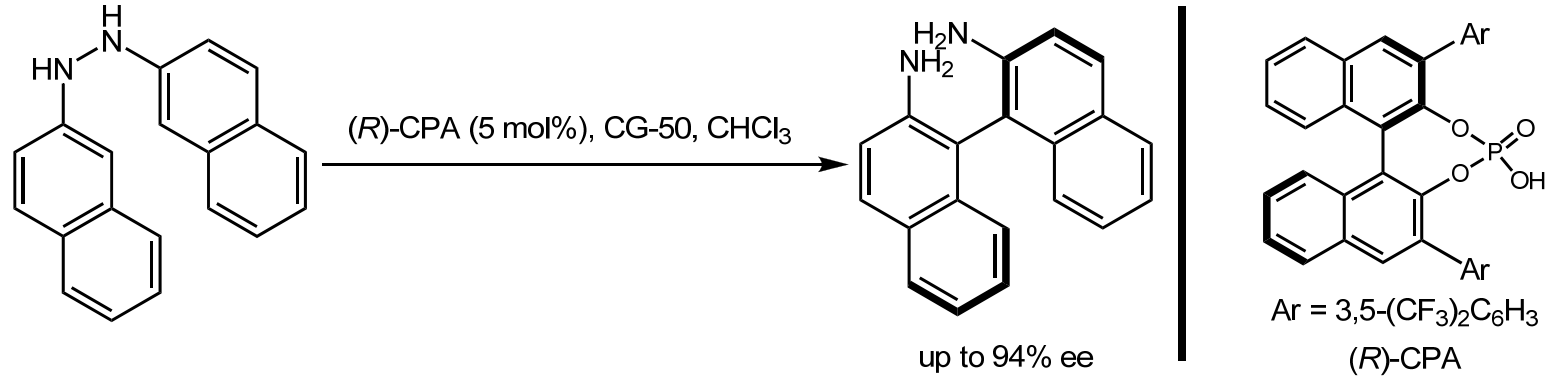




Cleavage of N-N and N-O Bonds Through Rearrangement and Elimination

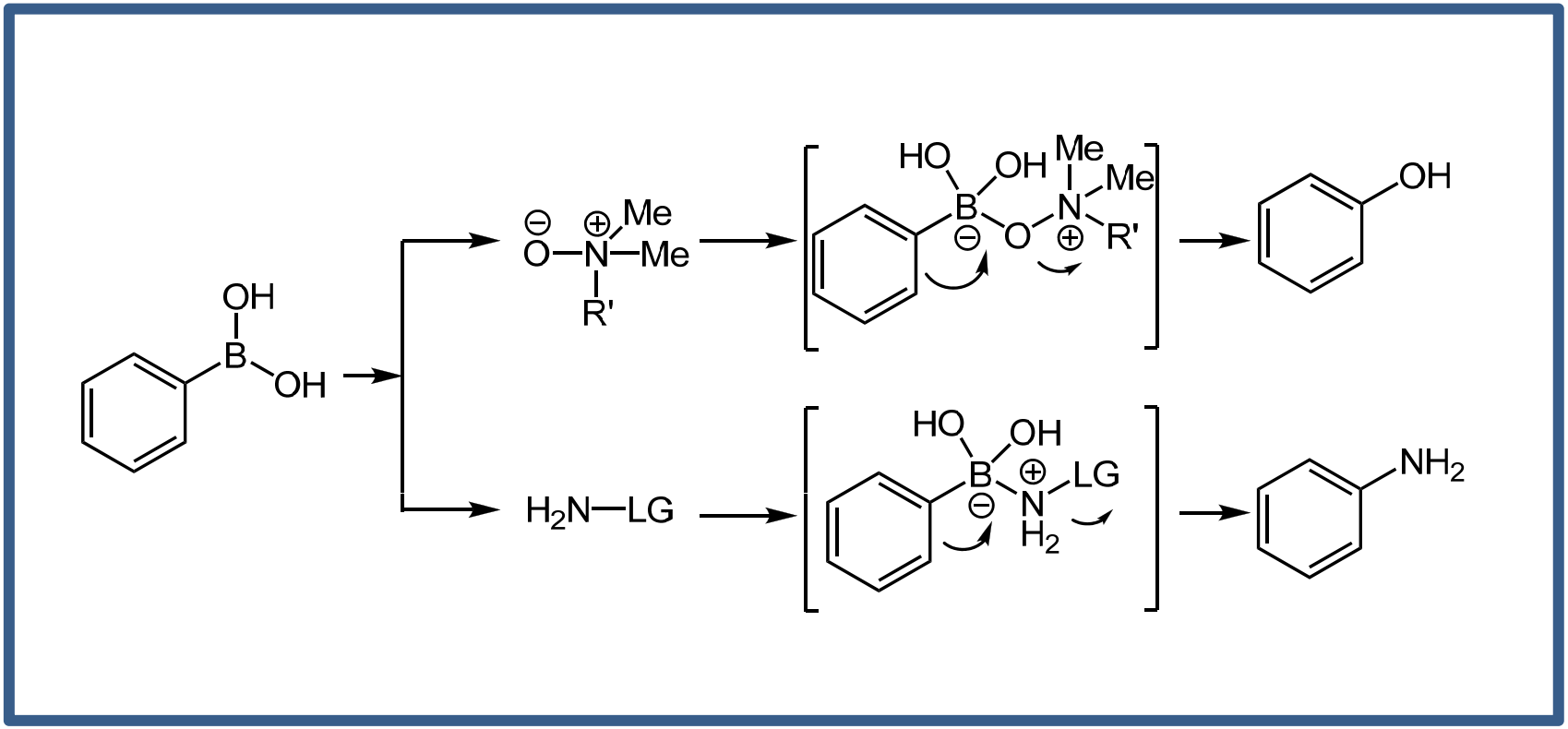


Kürti. L. *et al. J. Am. Chem. Soc*. **2013**, *135*, 7414.



List, B. *et al. Angew. Chem. Int. Ed.* **2013**, *52*, 9293.

Cleavage of N-N and N-O Bonds Through Substitution Reaction



Kürti. L. *et al. J. Am. Chem. Soc*. **2012**, *134*, 18253.

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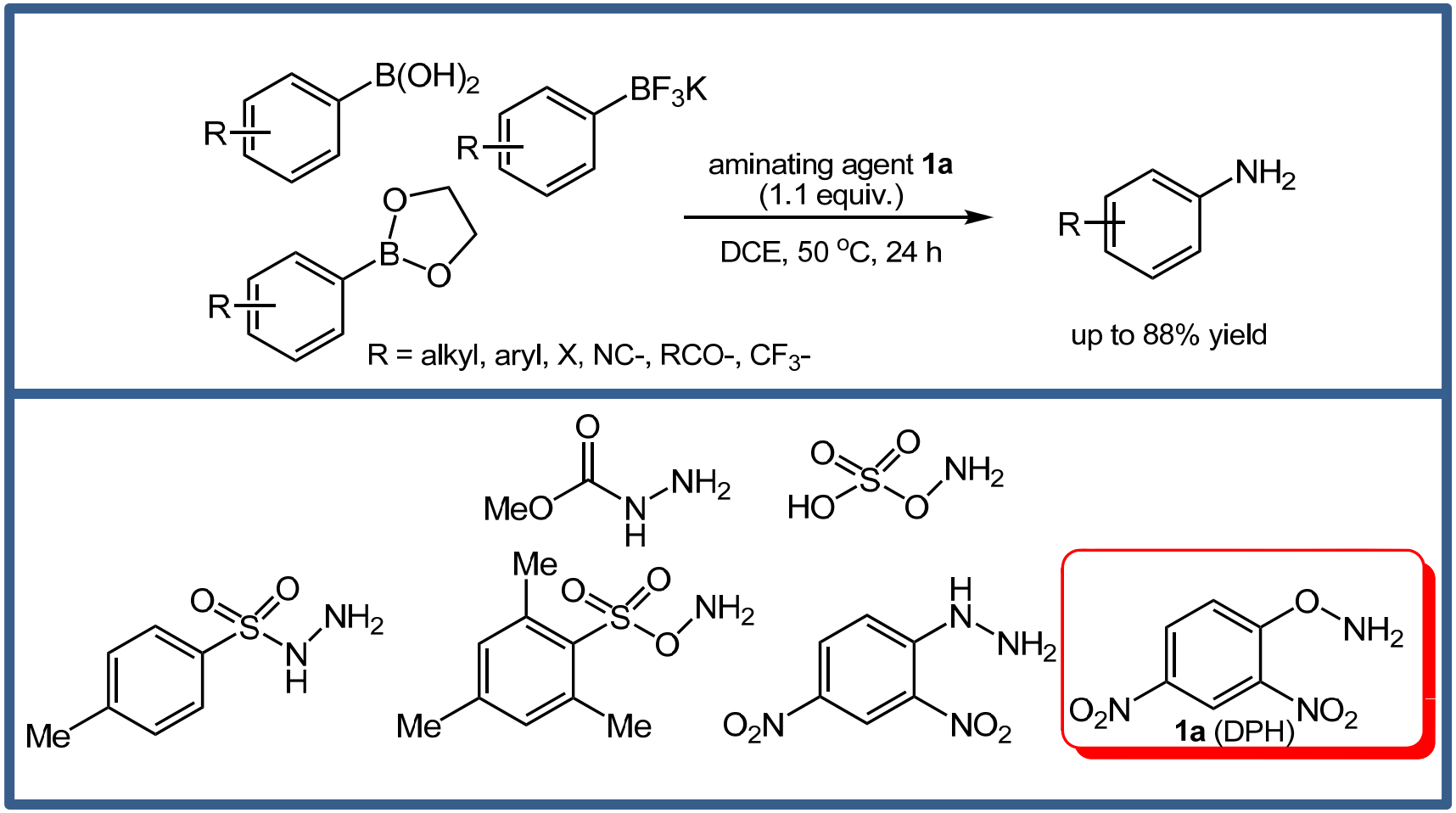

Kürti. L. *et al. J. Am. Chem. Soc*. **2012**, *134*, 18253.

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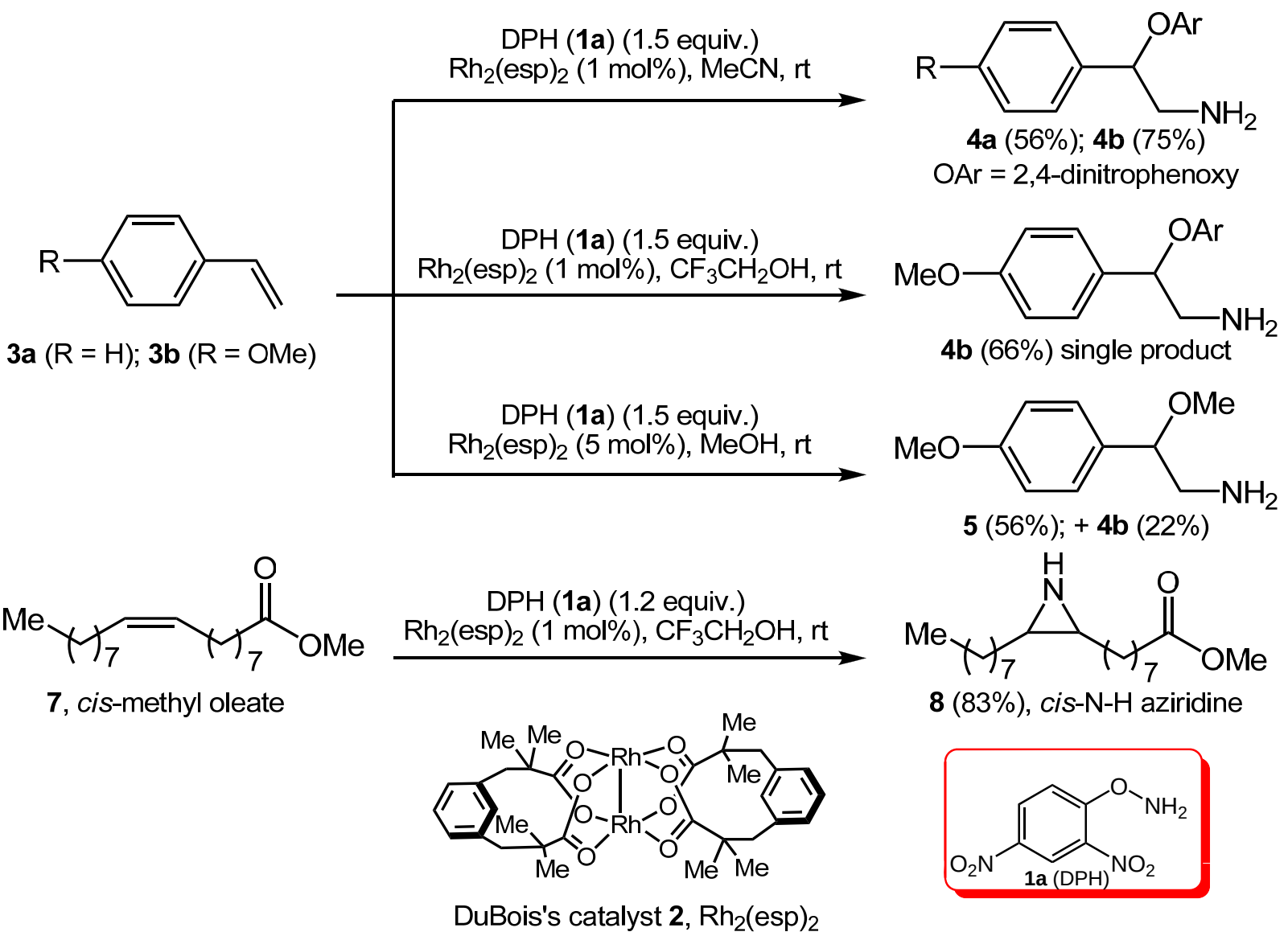
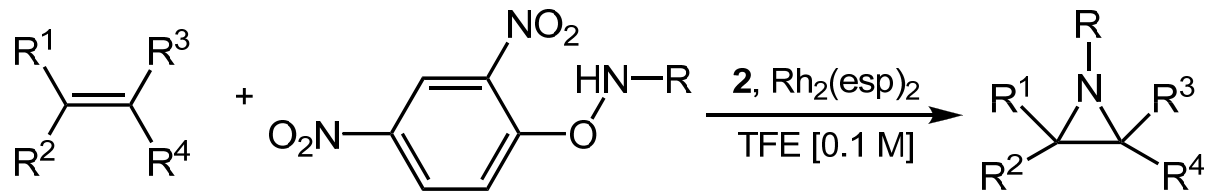
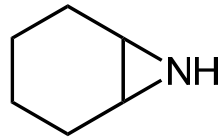


Kürti, L. *et al. Science* **2014**, *343*, 61.

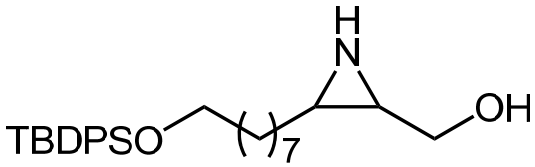
Cleavage of N-N and N-O Bonds Through Substitution Reaction



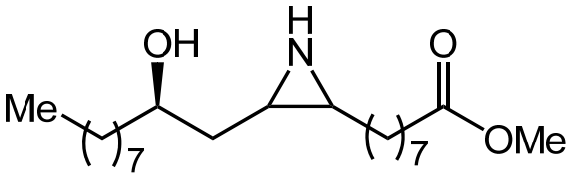
1a (R = H), **1b** (R = Me)



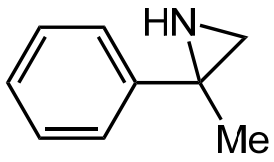
1a (1.2 equiv.), **2** (1 mol%)
25 °C, 71%



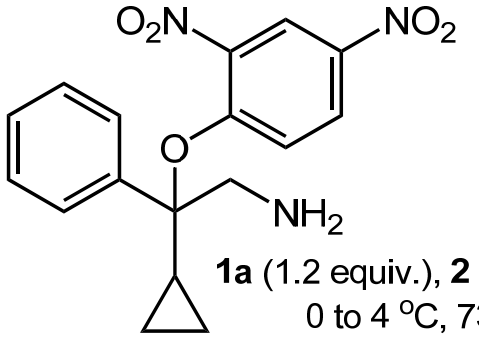
1a (1.2 equiv.), **2** (2 mol%)
25 °C, 64%



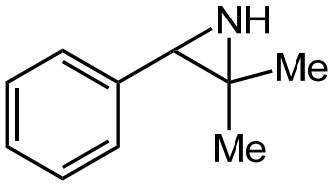
1a (1.2 equiv.), **2** (3 mol%)
25 °C, 82% [1:1 dr]



1a (1.2 equiv.), **2** (1 mol%)
0 °C, 64%



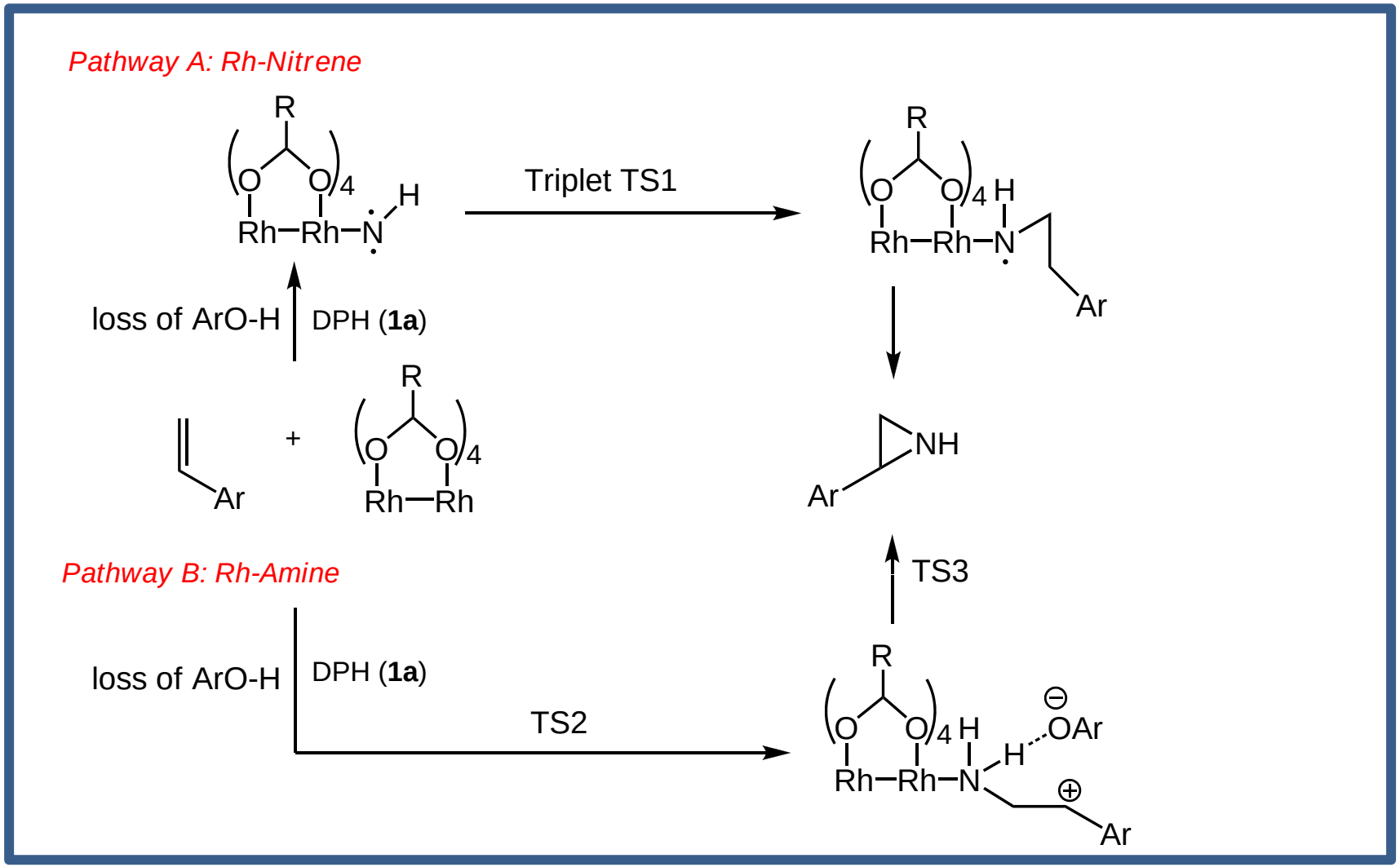
1a (1.2 equiv.), **2** (1 mol%)
0 to 4 °C, 73%



1a (1.1 equiv.), **2** (1 mol%)
25 °C, 92%; up to 81% on gram scale

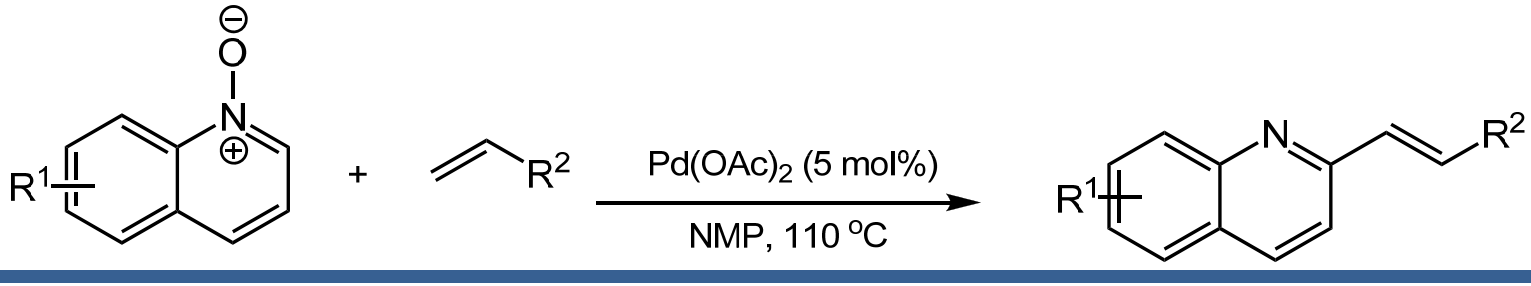
Kürti, L. *et al. Science* **2014**, *343*, 61.

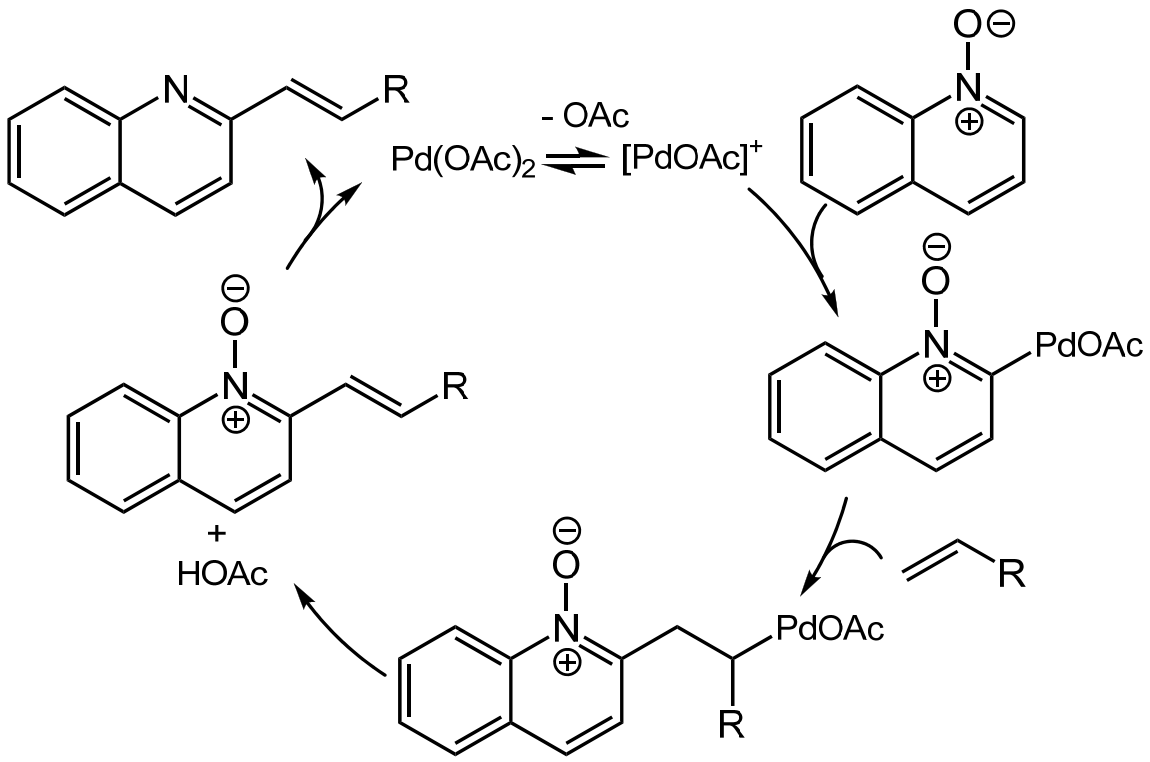
Cleavage of N-N and N-O Bonds Through Substitution Reaction



Kürti, L. *et al. Science* **2014**, *343*, 61.

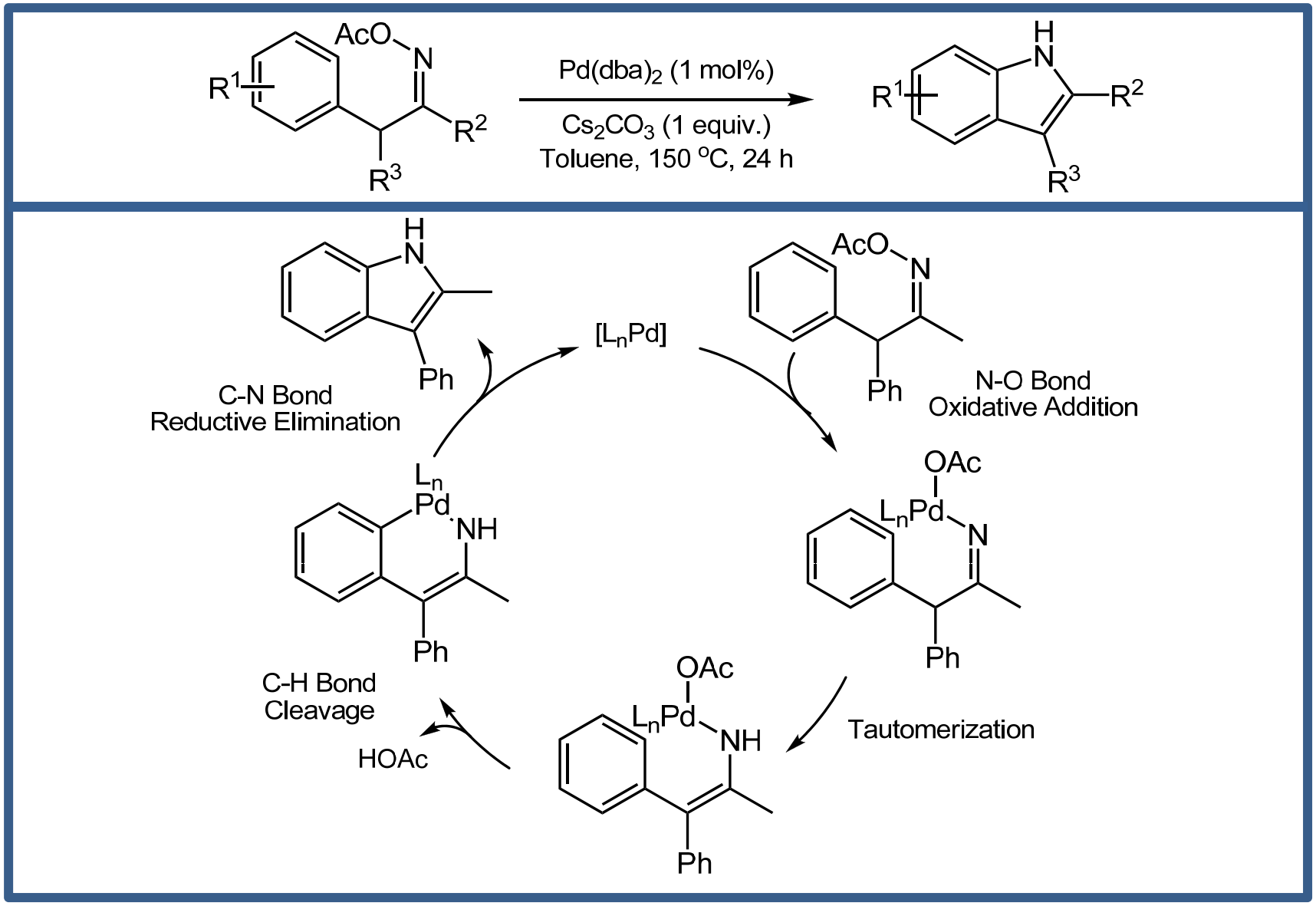
Cleavage of N-N and N-O Bonds with C-H Activation





Wu, Y. *et al. J. Am. Chem. Soc*. **2009**, *131*, 13888.

Cleavage of N-N and N-O Bonds with C-H Activation



Hartwig, J. F. *et al. J. Am. Chem. Soc*. **2010**, *132*, 3676.

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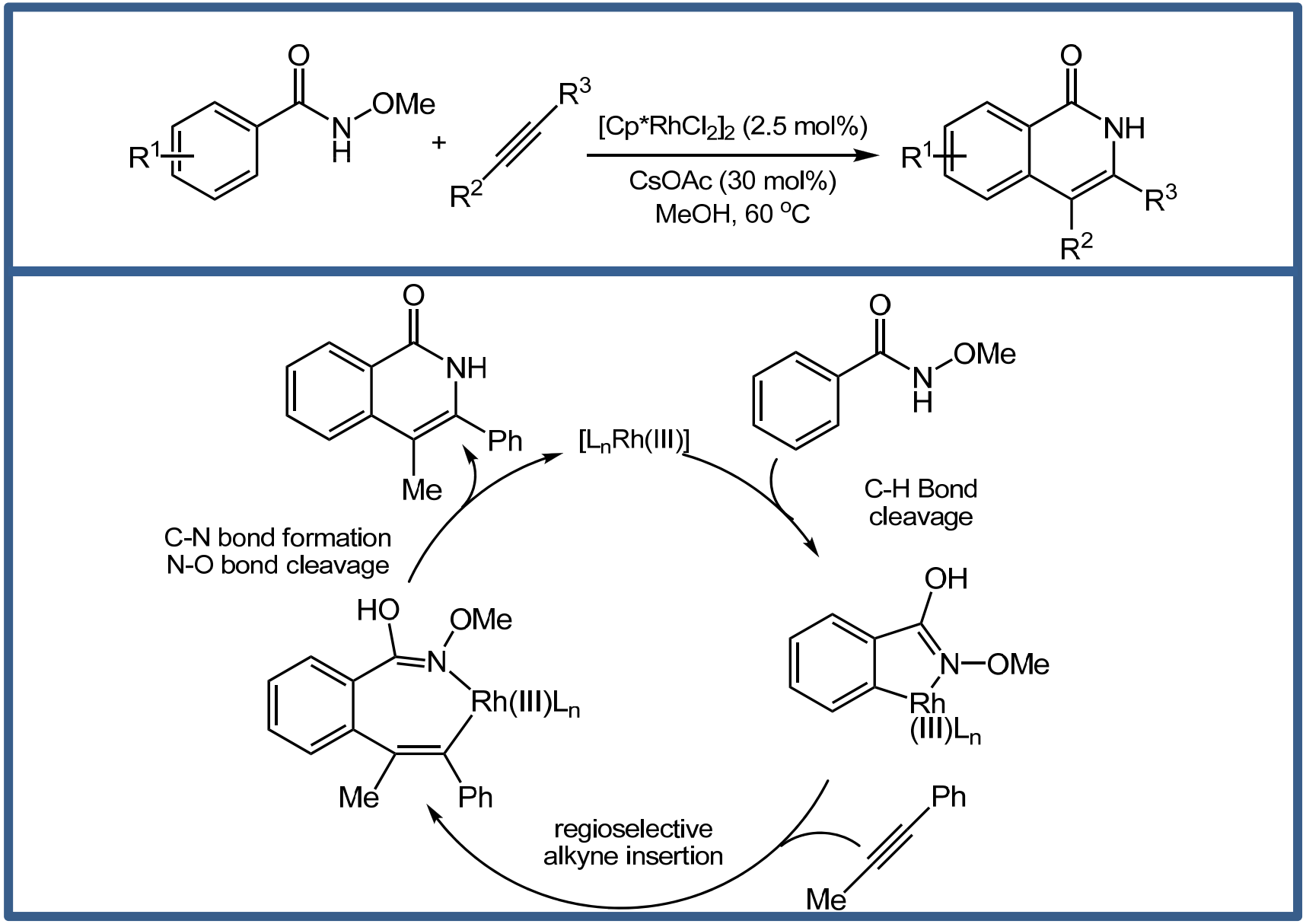

Guimond, N. *et al. J. Am. Chem. Soc*. **2010**, *132*, 6908.

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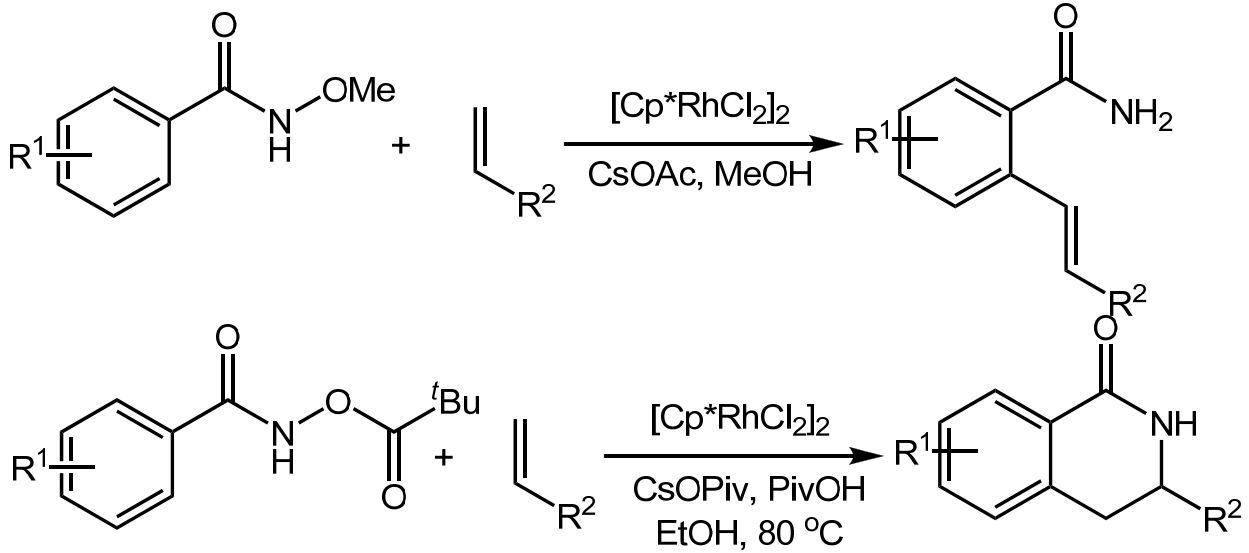
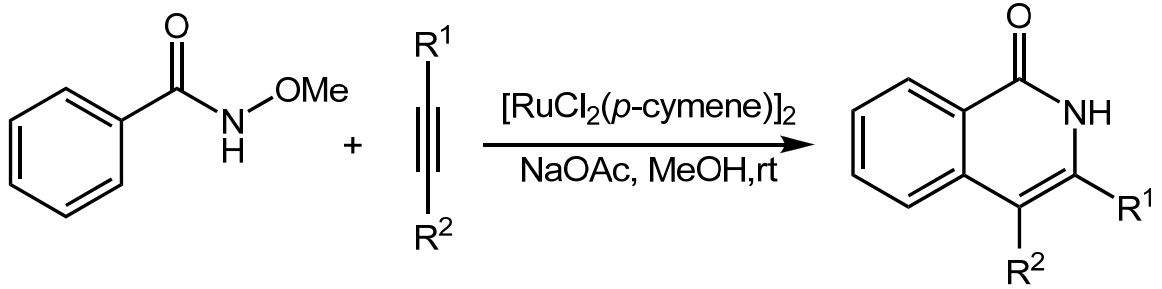
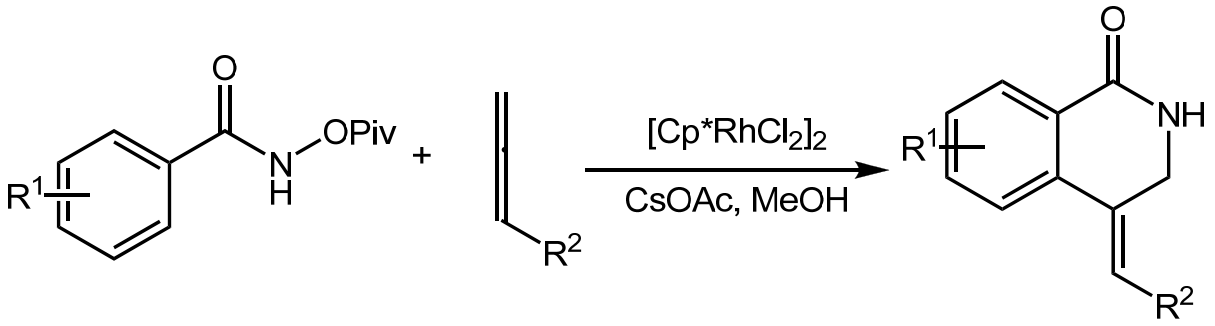


Glorius, F. *et al. J. Am. Chem. Soc*. **2011**, *133*, 2350.

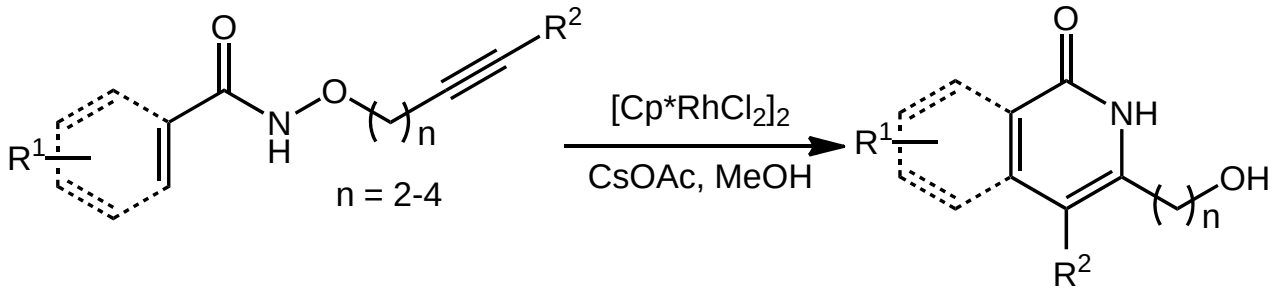


Wang, B. *et al*. *Chem. Eur. J.* **2011**, *17*, 12573.

Cleavage of N-N and N-O Bonds with C-H Activation

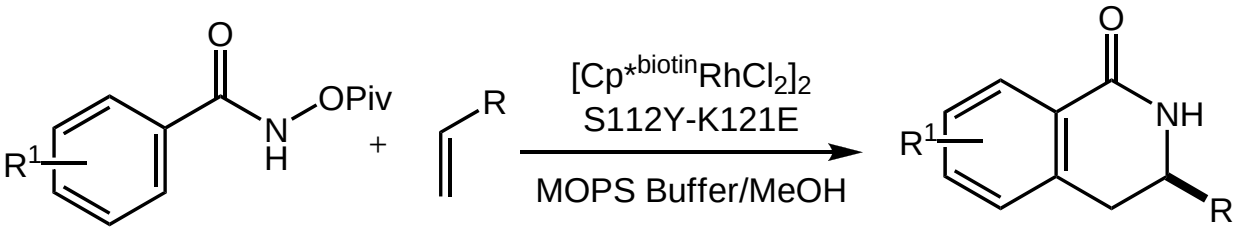


Glorius, F. *et al*. *Angew. Chem. Int. Ed.* **2012**, *51*, 7318.

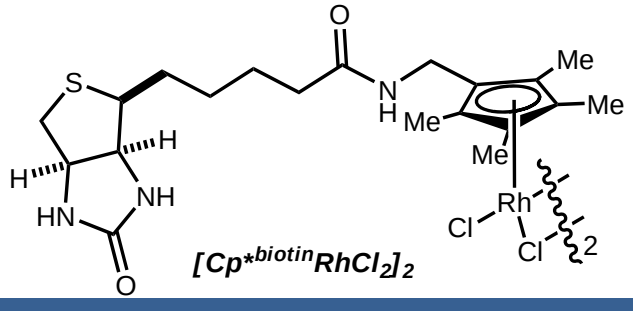


Park, C.-M. *et al*. *Angew. Chem. Int. Ed.* **2012**, *51*, 9372.

Cleavage of N-N and N-O Bonds with C-H Activation

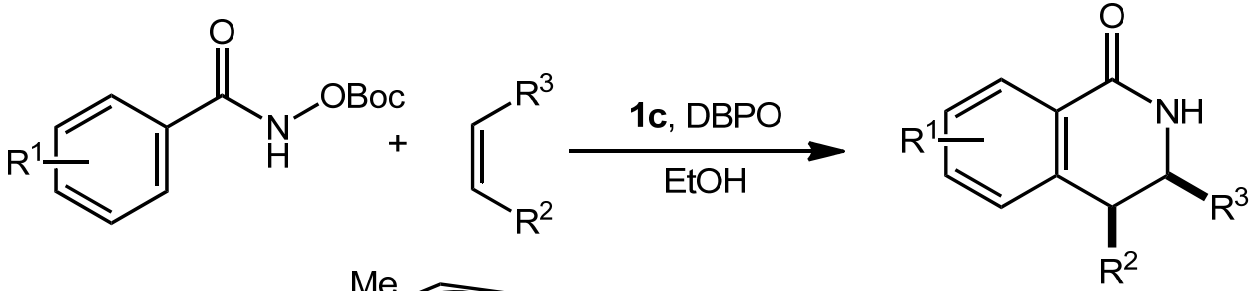


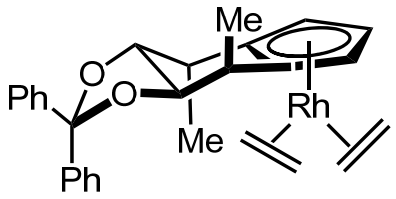
up tp 86% ee



*[Cp*biotinRhCl2]2*

Rovis, T. *et al. Science* **2012**, 338, 500.



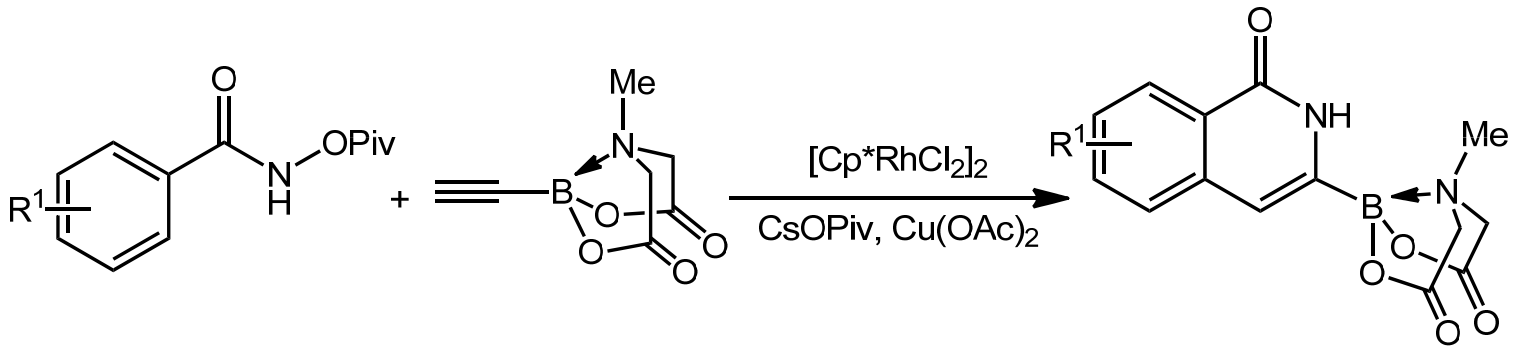


1c

up tp 95% ee

Cramer, N. *et al. Science* **2012**, 338, 504.

Cleavage of N-N and N-O Bonds with C-H Activation



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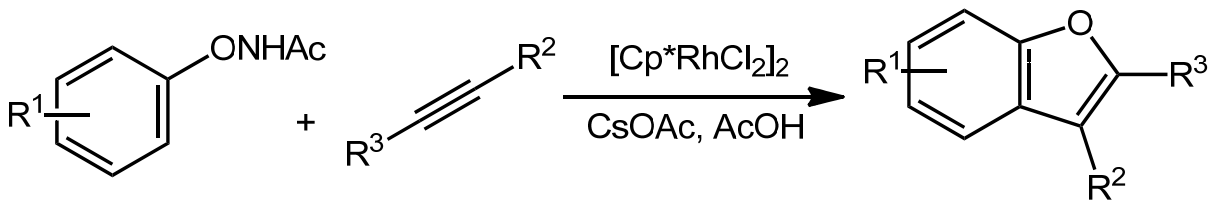
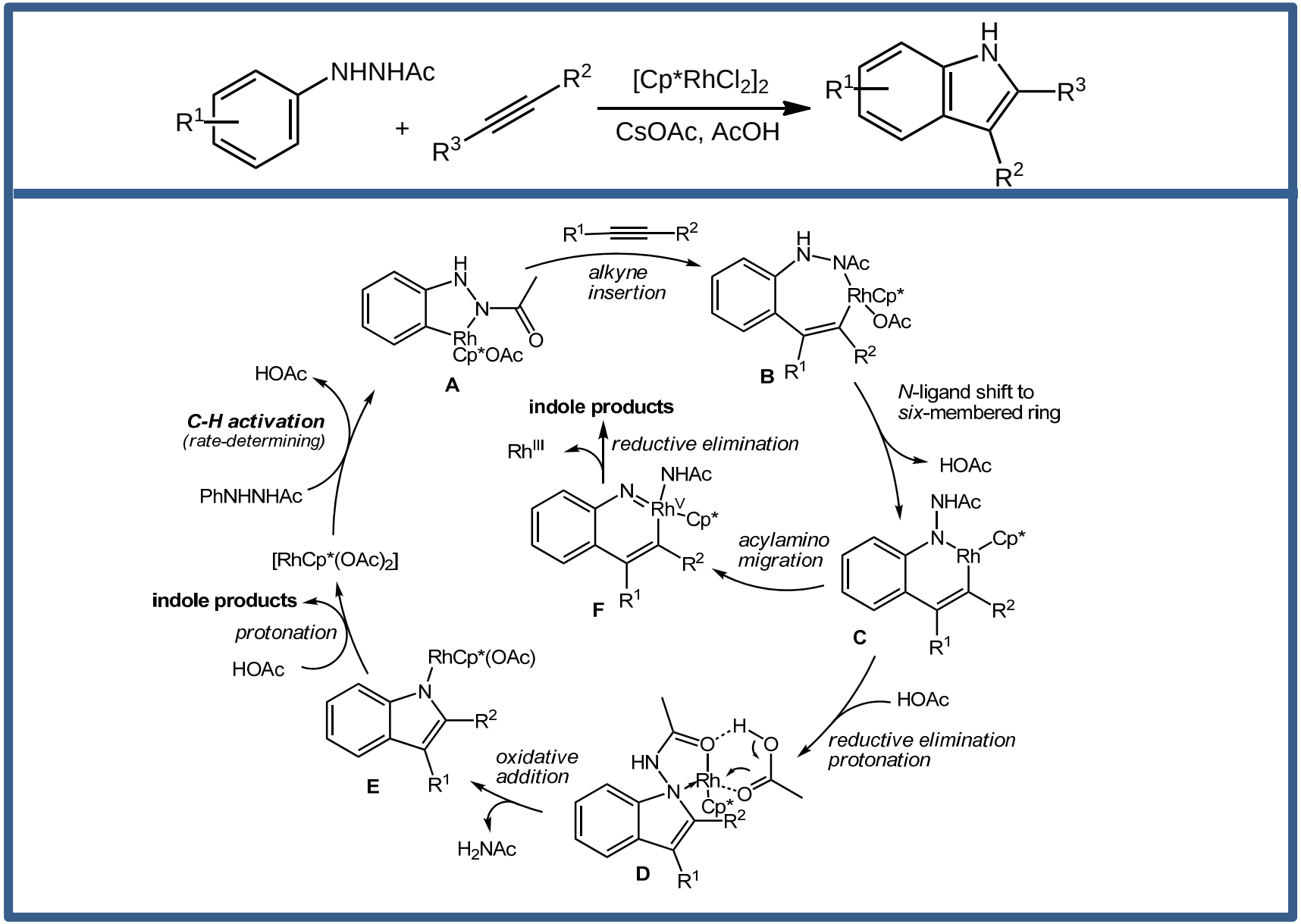


Lu, X. *et al. Angew. Chem. Int. Ed.* **2013**, *52*, 6033.

Cleavage of N-N and N-O Bonds with C-H Activation



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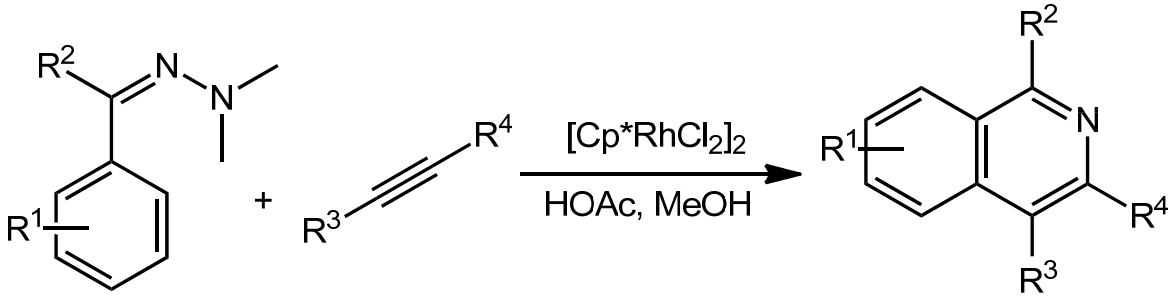
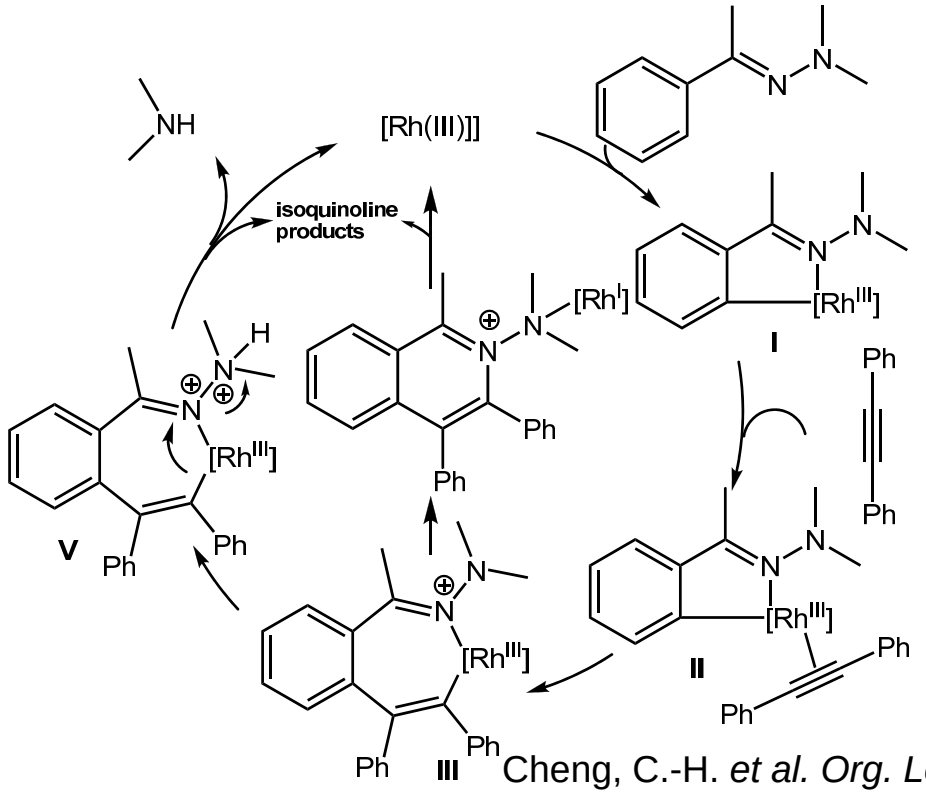
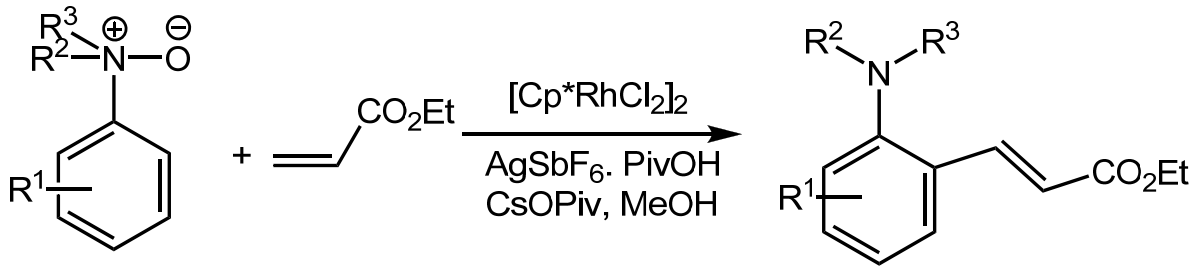
Cleavage of N-N and N-O Bonds with C-H Activation





Cheng, C.-H. *et al. Org. Lett.* **2013**, 15, 5750.

Cleavage of N-N and N-O Bonds with C-H Activation



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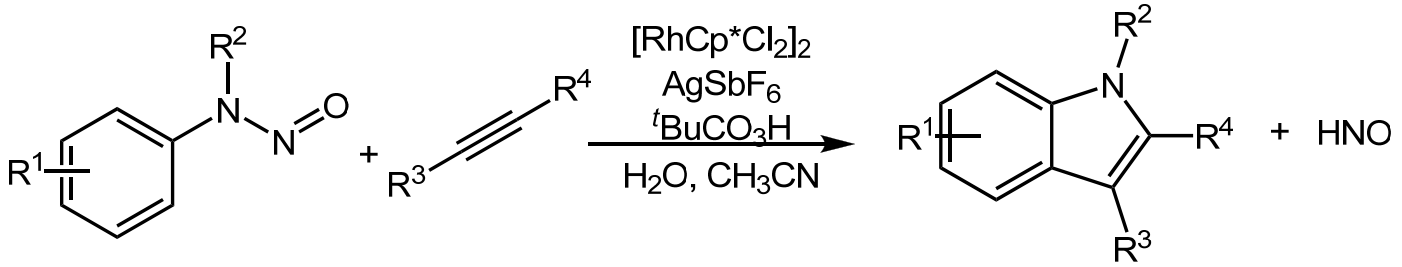
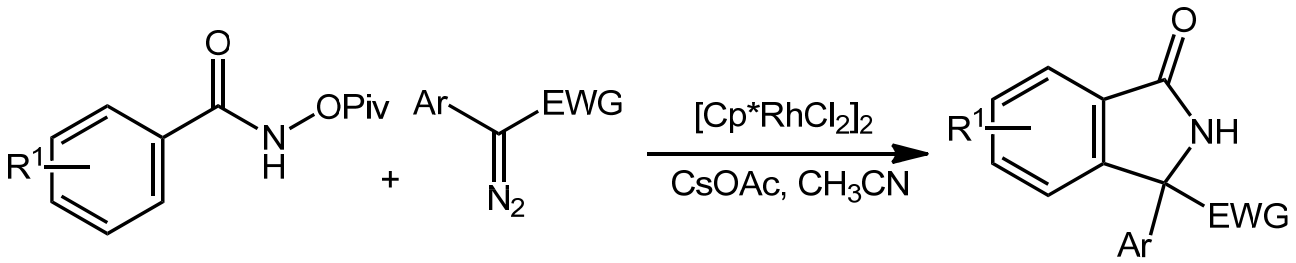


Zhu, J. *et al. J. Am. Chem. Soc*. **2013**, *135*, 16625.

Cleavage of N-N and N-O Bonds with C-H Activation



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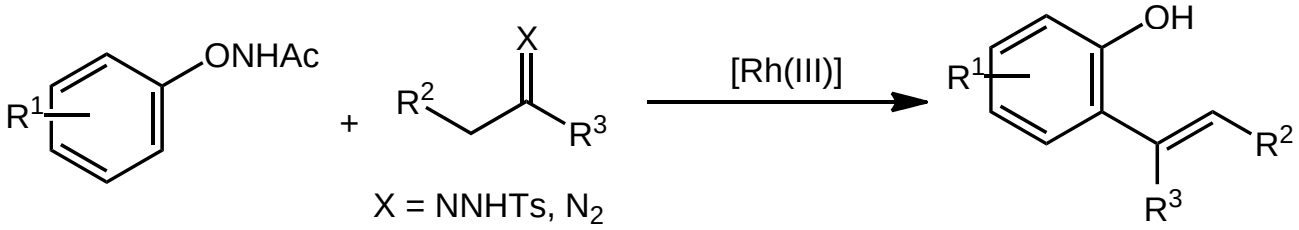
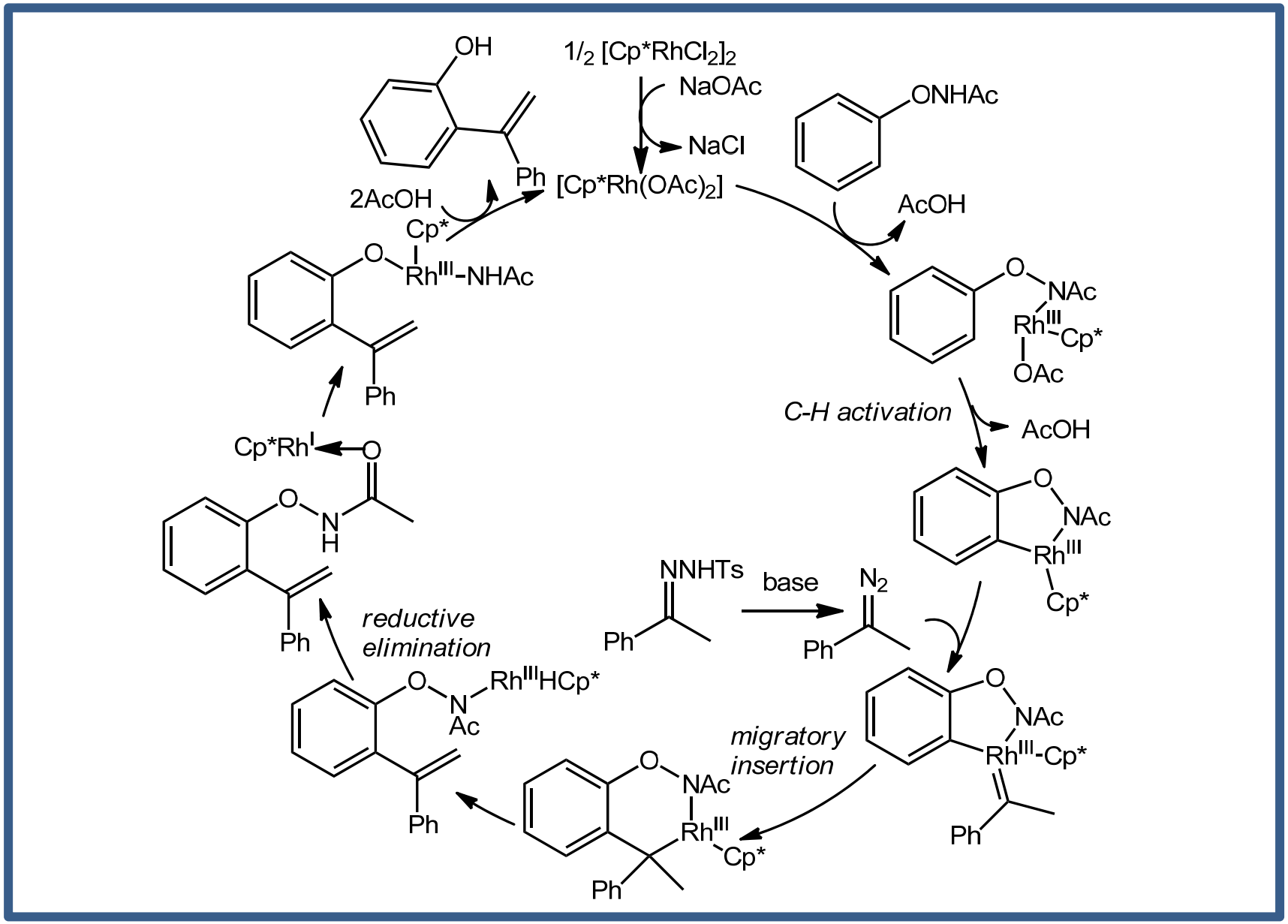


Wang, J. *et al*. *Angew. Chem. Int. Ed*. **2014**, *53*, 1364.

Cleavage of N-N and N-O Bonds with C-H Activation



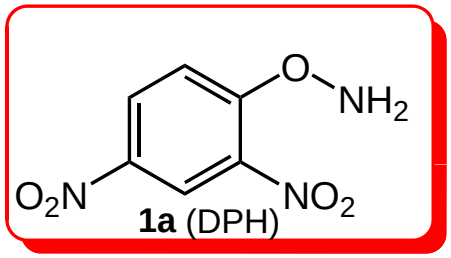
Wang, J. *et al*. *Angew. Chem. Int. Ed*. **2014**, *53*, 1364.

Sumary

Rearrangement and Elimination

Benzidine Rearrangement
Cope Elimination
[3,3]-*diaza* Cope rearrangement

Substitution Reaction

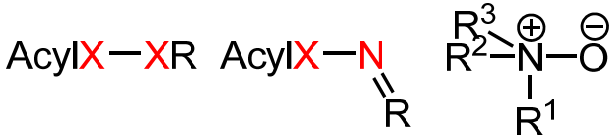


1a (DPH)

C-H Activation (*Redox Neutral Reaction*)

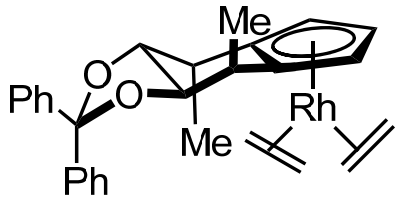
Metal Precursor: Pd, Rh, Ru

Substrate



Enantioselective

$[Cp^{*biotin}RhCl_2]_2$



Aziridines, the triangular, comparably highly strained nitrogen analogs of epoxides, are important synthetic intermediates (i.e., building blocks) en route to structurally complex molecules because of their versatility in myriad regio- and stereoselective transformations (ring openings and expansions, as well as rearrangements). The aziridine structural motif, predominantly N-H and to a lesser extent N-alkyl, also appears in biologically active natural products (e.g., azinomycins and mitomycins) . As a result, the synthesis and chemistry of aziridines have been the subject of intense research during the past 25 years, resulting in multiple aziridination methods. Most of these methods rely either on the transfer of substituted nitrenes, which are generated by using strong external oxidants, to the C=C bond of olefins or the transfer of substituted carbenes to the C=N bond of imines. Normally, the result is an aziridine bearing a strongly electron-withdrawing N-protecting group (e.g., Ts: para-toluenesulfonyl; Ns: para-nitrophenylsulfonyl); removal of these N-sulfonyl protecting groups is problematic as it often results in the undesired opening of the aziridine ring.

In addition, the high reactivity of N-protected nitrenes might give rise to nonproductive allylic C-H amination products, as well as the loss of stereospecificity. Clearly, the direct synthesis of N-H (i.e., N-unprotected) and N-alkyl aziridines would alleviate the above problems. However, a practical, functional group-tolerant and environmentally benign direct preparation of N-H aziridines from structurally diverse olefins has so far eluded synthetic chemists. Here, we report an operationally simple, inherently safe, chemoselective and stereospecific conversion of a wide range of olefins to the corresponding N-H or N-Me aziridines via a rhodium-catalyzed pathway free of external oxidants.

As alternatives to nitrene pathways, we also explored polar mechanisms involving Rh-amine and Rh-alkene coordination modes (see supplementary materials). One of several possible polar mechanisms is outlined as pathway B in Fig. 4. This pathway is akin to the mechanism proposed for amination of aryl boronic acids with **1a** . Although this mechanism may account for aminooxyarylated products (e.g., 4a and 4b) observed under some experimental conditions, the calculated barrier for this mechanism, as well as alternative polar mechanisms, is higher in energy than the nitrene mechanism presented in pathway A.