Oxygen-Fueled Iterative Hydride Transfer Driven by a Rigid Planar Architecture

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An iterative hydride reduction/oxidation process was promoted under ambient conditions by a quasi-planar iminium cation rigidified by two concatenated quinoline units. The iminium proton was fixed by hydrogen bonding from neighboring quinoline nitrogen atoms, rendering the imine highly susceptible to hydride reduction with weak reductants, e.g., 1,4-dihydropyridines. The thus-formed amine was readily oxidized by molecular oxygen to regenerate the quasi-planar iminium cation under ambient conditions. This process was exploited for catalytic oxidation of 1,4-dihydropyridines as well as 9,10-dihydroacridine to highlight an intriguing rigidity-driven catalysis.

Key words catalytic oxidation; imine; planar macrocycle; amine; quinoline; hydride transfer

Introduction

Imines featuring a carbon-nitrogen double bond are generally regarded as reactive electrophilic functional groups similar to carbonyls featuring a carbon-oxygen double bond. Owing to the trivalency of the nitrogen atom, the electrophlicity of imines can be manipulated by appended groups on the imine nitrogen, thereby providing broad opportunities to couple with nucleophiles of interest. This process is widely exploited to produce a myriad of amine products in both a racemic and stereoselective fashion. In contrast, the reverse reaction, amines to imines transformation, has received significantly less attention in organic synthesis and currently available options are limited. More than stoichiometric amounts of oxidants are typically required to fulfill high conversion, suffering from relatively poor functional group tolerance1–9) (Fig. 1A).

Fig. 1. Prior Arts of Dehydrogenation of Amines to Imines

Fig. 2. Final Stage of the Synthesis of TriQuinoline (TQ) (TFA Is Omitted for Clarity)

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Recent advances provide a catalytic option for this process utilizing both heterogeneous and homogeneous transition metal complexes, albeit with the use of generally stoichiometric amounts of additives.\(^{10–15}\) (Fig. 1B). Given the sustained interest in photocatalysis over the last decade,\(^{16–19}\) a growing number of examples for greener metal-free photocatalytic transformation of amines to imines were revealed to promote this transformation as a synthetically robust reaction manifold.\(^{20–25}\) In this context, we came across an amine that was spontaneously converted to the corresponding imine under ambient conditions with dioxygen (Fig. 1C). The facilitated dehydrogenation of the amine to the imine proceeded in a synthetically useful timescale, which was productively coupled with hydride reduction of the imine in the same pot to render the catalytic oxidation of hydride donors. This unusual oxidative susceptibility of the amine likely originated from its unique quasi-planar rigid structure to favor the imine state over the amine state.

### Results and Discussion

We previously reported the synthesis of TriQuinoline (TQ) as a miniaturized model of a nitrogen-doped graphitic material featuring an atomic size defect surrounded by three pyridinic nitrogen atoms\(^{26}\) (Fig. 2). The key precursor for TQ, diquinoline imine (DQ-Im), was sufficiently reactive in the following formal cycloaddition with \(n\)-butyl vinyl ether 1. The assumed intermediate, dihydroquinoline 3, however, was not observed at all, suggesting that DQ-Im played a pivotal role in accepting a hydride to produce TQ with concomitant formation of diquinoline amine (DQ-Am). Unexpectedly, DQ-Am underwent spontaneous dehydrogenation under ambient conditions to regenerate DQ-Im, and the reaction of DQ-Im and 1 converged to TQ as a final product. We reasoned that the unusual oxidative susceptibility of DQ-Am could be exploited to achieve catalytic oxidation of partially reduced heterocycles,
The authors declare no conflict of interest.

Supplementary Materials This article contains supplementary materials.
References and Notes

1) Buckle D. R., “Encyclopedia of Reagents for Organic Synthesis,” John Wiley & Sons, Inc., New York, 2010.
2) Fu P. P., Harvey R. G., Chem. Rev., 78, 317–361 (1978).
3) Barton D. H. R., Billion A., Boivin J., Tetrahedron Lett., 26, 1229–1232 (1985).
4) Murahashi S.-I., Naota T., Taki H., J. Chem. Soc. Chem. Commun., 613–614 (1985).
5) Maruyama K., Kusukawa T., Higuchi Y., Nishinaga A., Chem. Lett., 20, 1093–1096 (1991).
6) Matsuji K., Kawana A., Fukuda Y., Mukiyama T., Chem. Lett., 30, 712–713 (2001).
7) Mukaiyama T., Kawana A., Fukuda Y., Matsuji K., Chem. Lett., 30, 390–391 (2001).
8) Nicolau K. C., Mathison C. J., Montagnon T., Angew. Chem. Int. Ed., 42, 4077–4082 (2003).
9) Nicolau K. C., Mathison C. J., Montagnon T., J. Am. Chem. Soc., 126, 5192–5201 (2004).
10) Yamaguchi K., Mizuno N., Angew. Chem. Int. Ed., 42, 1479–1483 (2003).
11) Samec J. S., Ell A. H., Backvall J. E., Chem. Eur. J., 11, 2327–2334 (2005).
12) Wang J.-R., Fu Y., Zhang B.-B., Cui X., Liu L., Guo Q.-X., Tetrahedron Lett., 47, 8293–8297 (2006).
13) Choi H., Doyle M. P., Chem. Commun., 2007, 745–747 (2007).
14) So M. H., Liu Y., Ho C. M., Che C. M., Chem. Asian J., 4, 1551–1561 (2009).
15) Iosub A. V., Stahl S. S., Org. Lett., 17, 4404–4407 (2015).
16) Twilton J., Le C., Zhang P., Shaw M. H., Evans R. W., MacMillan D. W. C., Nat. Rev. Chem., 1, 0052 (2017).
17) Melchionna M., Fornasiero P., ACS Catal., 10, 5493–5501 (2020).
18) Das S., Cauwenbergh R., Synlett, 33, 129–149 (2021).
19) Candish L., Collins K. D., Cook G. C., Douglas J. J., Gomez-Suarez A., Jolt A., Kees S., Chem. Rev., 122, 2907–2980 (2022).
20) Riemer D., Schilling W., Goetz A., Zhang Y., Gehrke S., Tkach I., Hollóczki O., cit. S., ACS Catal., 8, 11679–11687 (2018).

21) Davis H. J., Haussinger D., Ward T. R., Okamoto Y., ChemCatChem, 12, 4512–4516 (2020).
22) Markushyna Y., Lamagni P., Catalano J., Lock N., Zhang G., Antonietti M., Savateev A., ACS Catal., 10, 7336–7342 (2020).
23) Stanek F., Pawlowski R., Morawska P., Bujok R., Studulski M., Org. Biomol. Chem., 18, 2103–2112 (2020).
24) Yang R., Yue S., Tan W., Xie Y., Cai H., J. Org. Chem., 85, 7501–7509 (2020).
25) Chen Y., Jiang J., Sustain. Energy Fuels, 5, 6478–6487 (2021).
26) Adachi S., Shibasaki M., Kumagai N., Nat. Commun., 10, 3820 (2019).
27) After preparation of a DQ-Im CD3OD solution, O2 gas was flushed without bubbling.
28) See Supplementary Material for the results of H2O2 test strips by occasional sampling of reaction mixture.
29) Synthesis of amine 5 is described in Supplementary Material.
30) Romero N. A., Margrey K. A., Tay N. E., Nicewicz D. A., Science, 349, 1326–1330 (2015).