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Hydrogen-Free Alkene Reduction in Continuous Flow

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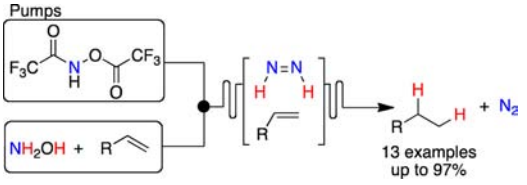
ABSTRACT

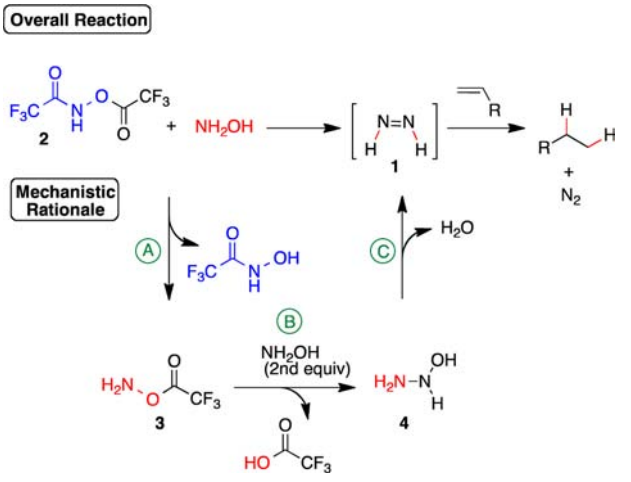


The first continuous hydrogenation that requires neither H_2 nor metal catalysis generates diimide by a novel reagent combination. The simple flow reactor employed minimizes residence time by enabling safe operation at elevated temperature.

Herein we report the first continuous method for H_2-free hydrogenation[1] via diimide (diazene, HN=NH **1**)[2] generated from the new reagent combination of *N*,*O*-bistrifluoroacetylhydroxylamine **2** and hydroxylamine (Scheme 1). This transformation proceeds with significantly reduced reaction times relative to batch reductions, enjoys a wide substrate scope with excellent functional group compatibility, and features a user-friendly flow reactor easily constructed from commercial components.

While diimide reductions in batch mode provide a degree of complementarity to transition metal mediated hydrogenation, they are not without their own set of limitations.[3] Among these are prolonged reaction times, inconsistencies in reproducibility, and large excesses of reagents. We hypothesized that continuous flow, in contrast, would provide a platform for improvement of diimide reductions due to enhanced mixing and the ability to heat reaction mixtures effectively. Additionally, continuous flow conditions are particularly attractive for the development of reactions that involve highly reactive intermediates or harsh conditions, as exposure to the elevated temperatures is limited to small quantities of material at any given

Scheme 1. Novel Method of Diimide Generation



(1) Pioneering flow hydrogenation protocols and instrumentation have been developed. Homogeneous: (a) Newton, S.; Ley, S. V.; Arcé, E. C.; Grainger, D. M. *Adv. Synth. Catal.* **2012**, *354*, 1805. (b) Mercadante, M. A.; Kelly, C. B.; Lee, C. X.; Leadbeater, N. E. *Org. Process Res. Dev.* **2012**, *16*, 1064. Heterogeneous: (c) Kirschning, A.; Solodenko, W.; Mennecke, K. *Chem.—Eur. J.* **2006**, *12*, 5972. (d) Irfan, M.; Glasnov, T. N.; Kappe, C. O. *ChemSusChem* **2011**, *4*, 300.

(2) (a) Pasto, D. J.; Taylor, R. T. *Org. React.* **1991**, *40*, 91. (b) Miller, C. E. *J. Chem. Educ.* **1965**, *42*, 254. (c) Corey, E. J.; Mock, W. L.; Pasto, D. J. *Tetrahedron Lett.* **1961**, *11*, 347.

(3) For an excellent discussion, see: Smit, C.; Fraaije, M. W.; Minnaard, A. J. *J. Org. Chem.* **2008**, *73*, 9482.

(4) For example, handling azides: (a) Palde, P. B.; Jamison, T. F. *Angew. Chem., Int. Ed.* **2011**, *50*, 3525. (b) Gutmann, B.; Roduit, J.-P.; Roberge, D.; Kappe, C. O. *Angew. Chem.* **2010**, *122*, 7255. *Angew. Chem., Int. Ed.* **2010**, *49*, 7101. Diazos: (c) Martin, L. J.; Marzinzik, A. L.; Ley, S. V.; Baxendale, I. R. *Org. Lett.* **2011**, *13*, 320. Diazo-methane: (d) Struempel, M.; Ondruschka, B.; Daute, R.; Stark, A. *Green Chem.* **2008**, *10*, 41. Aromatic nitration: (e) Kulkami, A. A.; Kalyani, V. S.; Joshi, R. A.; Joshi, R. R. *Org. Process Res. Dev.* **2009**, *13*, 999.

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time.[4] Thus, safety concerns regarding pressure build-up from nitrogen gas generation at elevated temperatures would be mitigated by this approach.

Of the reported conditions for diimide generation, we considered several, including acid-promoted decarboxylation of potassium diazodicarboxylate[5] and treatment of sulfonylhydrazines with base.[6] Ultimately, inconsistent results, largely due to low solubility and heterogeneity, prompted us to design a new reagent combination. Inspired by diimide formation via elimination of water from hydrazine oxide **4** (Scheme 1, step C),[7] we reasoned that electrophilic amination of hydroxylamine would provide a safe, metal-free, alternative to classical hydrazine oxidation.[8] Namely, with an appropriate reagent, selective *O*-functionalization (e.g., trifluoroacetylation, Scheme 1, step A) of hydroxylamine would generate an electrophilic nitrogen source in the form of an *O*-trifluoroacetylhydroxylamine (**3**).[9] Amination of a second equivalent of hydroxylamine by **3** (step B) would then form **4**.

Paramount to the success of this approach was discovery of a reagent selective for *O*-functionalization of hydroxylamine. Jencks assayed the *N*- versus *O*-selectivity of various acyl electrophiles, finding nearly exclusive *O*-acylation with *N*,*O*-diacetylhydroxylamine.[10] We thus evaluated a collection of related derivatives for alkene reduction and identified *N*,*O*-bistrifluoroacetylhydroxylamine (**2**) as the most efficient.[11] Originally developed for conversion of aldehydes to nitriles,[12] **2** is a stable, commercially available reagent.[13] Preliminary studies revealed 1.5 equiv of **2** in 1,4-dioxane with 5 equiv of hydroxylamine to be sufficient for further reaction development. Of particular note is the importance of solvent in this reaction; high solubility of hydroxylamine is necessary, and therefore, hydrogen bond acceptors were found to be the most effective solvents.

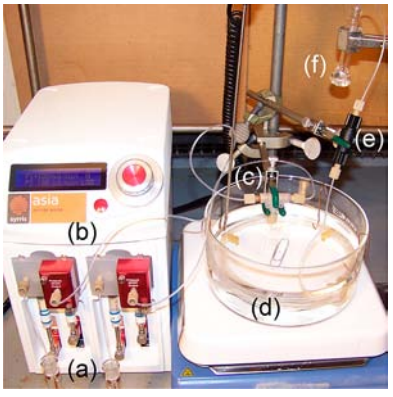


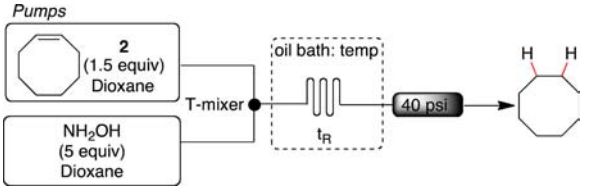
Figure 1. Reaction setup: (a) reagent solutions; (b) syringe pumps; (c) T-shaped mixer (i.d. = 500 μm); (d) PFA tubing reactor (i.d. = 760 or 1,000 μm); (e) bpr (40 or 100 psi); (f) sample collection flask.

With an initial set of reaction parameters in hand, we commenced our studies in a continuous flow reactor (Figure 1). The small-footprint setup (60 cm × 60 cm) conveniently fits inside a standard fume hood and consists of (a) the reagent solutions, (b) two syringe pumps, (c) a T-shaped mixer (i.d. = 500 μm), (d) a perfluoroalkoxy (PFA) tubing reactor (i.d. = 750 or 1,000 μm), (e) a back pressure regulator (bpr, 40 or 100 psi), and (f) the sample collection flask.[11] Elevated temperatures are conveniently (and safely) achieved with a standard oil bath, and hydroxylamine solutions are prepared directly from commercially available 50% aqueous solutions. For ease of setup we typically execute this reaction employing a two-pump setup with a T-mixer,[14] necessitating that the substrate be premixed with either hydroxylamine or **2**. (Both are equally effective; *vide infra*.)

During the course of the reaction, nitrogen gas is generated and a gas−liquid segmented flow is observed. This byproduct formation necessitates employing the back-pressure regulator to not only mitigate unsafe pressure buildup but also maintain a uniform flow rate throughout the system. Ultimately, the gas generation may in fact be advantageous to the overall efficinecy of the reaction through increased mixing efficiency as a result of the segmented flow.[15]

Hydrogenation of cyclooctene was used for comparison of conditions (Table 1). The reaction was found to be sensitive to both residence time (t_R) and temperature (entries 1−4). The optimal conditions were determined to be heating at 100 °C with a t_R of 20 min (entry 5).

Table 1. Continuous Flow Temperature and t_R Optimization

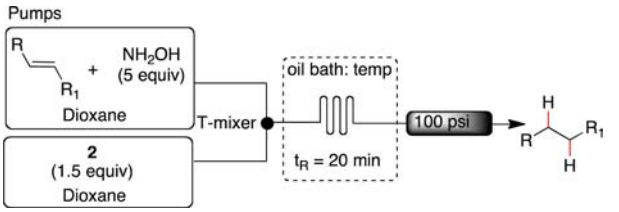


entry	temp (°C)	t_R (min)	yield (%)[a]
1	80	20	72
2	80	30	86
3	90	20	92
4	90	10	69
5	100	20	98

[a] GC yield.

(5) Hamersma, J. W.; Snyder, E. I. *J. Org. Chem.* **1965**, *30*, 3985.
(6) (a) Haukaas, M. H.; O'Doherty, G. A. *Org. Lett.* **2002**, *4*, 1771. (b) Marsh, B. J.; Carbery, D. R. *J. Org. Chem.* **2009**, *74*, 3186.
(7) Dürckheimer, W. *Liebigs Ann. Chem.* **1969**, *721*, 240.
(8) For classical hydrazine oxidation methods, see: (a) Aylward, F.; Sawistowska, M. *Chem. Ind.* **1962**, 484. (b) Lamani, M.; Ravikumara, G. S.; Prabhu, K. R. *Adv. Synth. Catal.* **2012**, *354*, 1437. For recent use of flavins for hydrazine oxidation, see: (c) Imada, Y.; Iida, H.; Naota, T. *J. Am. Chem. Soc.* **2005**, *127*, 14544. (d) Smit, C.; Fraaije, M. W.; Minnaard, A. J. *J. Org. Chem.* **2008**, *73*, 9482. (e) Imada, Y.; Kitagawa, T.; Ohno, T.; Iida, H.; Naota, T. *Org. Lett.* **2010**, *12*, 32. (f) Imada, Y.; Iida, H.; Kitagawa, T.; Naota, T. *Chem.—Eur. J.* **2011**, *17*, 5908. (g) Marsh, B. J.; Heath, E. L.; Carbery, D. R. *Chem. Commun.* **2011**, *47*, 280. (h) Teichert, J. F.; den Hartog, T.; Hanstein, M.; Smit, C.; ter Horst, B.; Hernandez-Olmos, V.; Feringa, B. L.; Minnaard, A. J. *ACS Catal.* **2011**, *1*, 309.
(9) Wade, P. A.; Amin, N. V. *Synth. Commun.* **1982**, *12*, 287.

Table 2. Substrate Scope



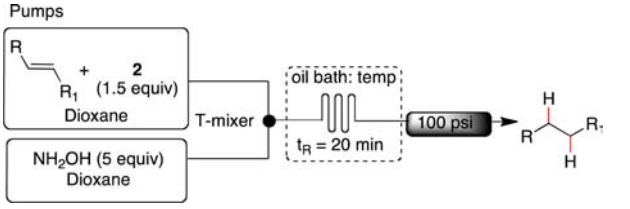
entry	substrate	product	temp (°C)	yield (%)[a]
	NHR_2	H, NHR_2		
1	R_2 = Boc **5**	**6**	100	96%
2	R_2 = Bz **7**	**8**	100	84%
3	OBn **9**	H, OBn **10**	100	69%
4	*t*Bu **11**	H, H, *t*Bu **12**	100	87%
5	Me, OH **13**	H, Me, OH, H **14**	140	89%[b]
6	Ph, OH **15**	H, Ph, OH, H **16**	140	84%
7	Me, OTBDPS **17**	H, Me, OTBDPS **18**	140	80%
8	MeO, Me **19**	H, MeO, Me, H **20**	140	92%
9[c]	OBn **21**	H, H, OBn, H **22**	100	93%

[a] Isolated yield. [b] GC yield. [c] NH_2OH, 10 equiv; **2**, 3.0 equiv.

We found these conditions to be suitable for the hydrogenation of a variety of alkenes in the presence of a range of functional groups. The saturated products were generally afforded in good to excellent yield (Table 2). Although an equivalent of TFA is formed in the reaction (see Scheme 1), acid-sensitive functional groups, including the Boc protecting group (entry 1) and polymerizable styrenes (entry 4), are tolerated. The benzoyl (entry 2), benzyl (entries 3 and 9), and silicon-containing TBDPS (entry 7) protecting groups are stable under the reaction conditions. This method is suitable for the hydrogenation of 1,1-disubstituted alkenes (entry 7) and 1,2-disubstituted alkenes (entries 5, 6, and 8), although these substrates do require heating at 140 °C to achieve complete conversion. Doubling the stoichiometry of **2** and hydroxylamine employed enabled the reduction of terminal alkynes (entry 9). Internal alkynes suffered from incomplete conversion and product mixtures. Further substrate limitations include aldehydes, as condensation with hydroxylamine and/or **2** is a competing process.

For substrates that may react with hydroxylamine in the stock solution, the substrate was premixed with **2** (Table 3). This setup enabled the selective reduction of the alkene of *m*-nitrostryene (entry 1). Additionally, alkenes of α,β-unsaturated esters and amides (entries 2 and 3, respectively) were efficiently reduced with no observed formation of the corresponding hydroxamic acids. It should be noted that in nearly all cases the products were of high purity (> 95%) upon simple aqueous workup and generally did not require additional purification.

Table 3. Functional Group Compatibility



entry	substrate	product	temp (°C)	yield (%)[a]
1	NO_2 **23**	H, H, NO_2 **24**	100	97%
2	Me, Et, N, O, Me **25**	Me, Et, H, N, O, H, Me **26**	140	68%
3	Ph, OMe, O **27**	H, Ph, OMe, H, O **28**	140	89%

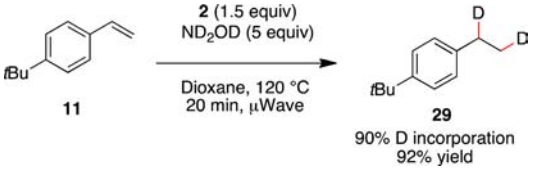
[a] Isolated yield.

Another feature of this reaction is that it is readily modified for site-specific deuterium incorporation. Employing hydroxylamine-d_3 (90% deuterium) and **2** in the

(10) Jencks, W. P. *J. Am. Chem. Soc.* **1958**, *80*, 4581. (b) Jencks, W. P. *J. Am. Chem. Soc.* **1958**, *80*, 4585.
(11) Please see Supporting Information for details.
(12) Pomeroy, J. H.; Craig, C. A. *J. Am. Chem. Soc.* **1959**, *81*, 6340.
(13) **2** is readily, and cheaply, prepared on multigram scale as outlined in ref 12.
(14) A three-pump setup employing a cross mixer could also be employed; for simplicity we preferred the two-pump setup described.
(15) (a) Günther, A.; Jhunjhunwala, M.; Thalmann, M.; Schmidt, M. A.; Jensen, K. F. *Langmuir* **2005**, *21*, 1547. (b) Yen, B. K.; Günther, A.; Schmidt, M. A.; Jensen, K. A.; Bawendi, M. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 5447.
(16) (a) Corey, E. J.; Pasto, D. J.; Mock, W. L. *J. Am. Chem. Soc.* **1961**, *83*, 2957. (b) Berson, J. A.; Poonian, M. S. *J. Am. Chem. Soc.* **1966**, *88*, 170.

reduction of *tert*-butylstyrene **11** (Scheme 2) afforded **29** in 92% yield with 90% deuterium incorporation (as determined by ^{1}H NMR). This method is complementary to previous reports of diimide mediate deuterium incorporation.[16]

Scheme 2. D_2-Incorporation



In conclusion, we have developed the first H_2-free continuous flow hydrogenation protocol. This reaction proceeds via diimide generated from the reaction of hydroxylamine with *N,O*-bistrifluoroacetylhydroxylamine **2** and without added transition metal. The flow setup requires no specialized equipment and is safely operated at elevated temperatures. A range of substrates are reduced using a 20-min residence time, and products are generally isolated with high purity upon simple aqueous workup. Finally, employing hydroxylamine-d_3 enables deuterium incorporation and, by extension, incorporation of the radioactive isotope tritium.

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Supporting Information Available. Experimental procedures, experimental setups, analytical characterization data, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.