Published in final edited form as:

Angew Chem Int Ed Engl. 2014 December 15; 53(51): 14051–14054. doi:10.1002/anie.201407723.

A Nanopalladium-Nanomicelle Combination for Stereoselective Semi-Hydrogenation of Alkynes in Water at Room Temperature**

Eric D. Slack^[+],

Department of Chemistry and Biochemistry, University of California, Santa Barbara, CA 93106, USA

Christopher M. Gabriel^[+], and

Department of Chemistry and Biochemistry, University of California, Santa Barbara, CA 93106, USA

Bruce H. Lipshutz

Department of Chemistry and Biochemistry, University of California, Santa Barbara, CA 93106, USA

Bruce H. Lipshutz: lipshutz@chem.ucsb.edu

Abstract

Interactions between palladium nanoparticles and nanomicelles containing in situ-generated hydrogen and an alkyne lead to high yields of product Z-alkenes. These reactions are general, take place in water at ambient temperatures, and offer recycling of the aqueous reaction mixture along with low overall E Factors.

Keywords

semi-hydrogenations; Lindlar reductions; Pd nanoparticles; micellar catalysis; green chemistry

The Lindlar reduction of an alkyne has stood the test of time, routinely appearing in textbooks as a fundamental approach to Z-alkenes. Dating back to the original report in 1952¹, this semi-hydrogenation process traditionally relies on a heterogeneous catalytic source of palladium (e.g., Pd/CaCO₃) deactivated with lead, the stereoselectivity of which is further enhanced by the presence of a “poison” such as quinolone (Scheme 1). And while the expected outcome is oftentimes achieved, especially in simpler cases of dialkyl-substituted acetylenes, more highly functionalized substrates have proven to be challenging. Moreover, losses due to generation of the undesired E-isomer, as well as complications oftentimes associated with high surface area-containing solid supports are not uncommon. These limitations have led to a plethora of alternative literature procedures just within the

**Financial support of our program in green chemistry provided by the NIH (GM 86485) is warmly acknowledged. Early work on this project by Mr. Anish Bhattacharjya is appreciated. Cryo-TEM images from Dr. Stephan Kraemer are also appreciated.

Correspondence to: Bruce H. Lipshutz, lipshutz@chem.ucsb.edu.

[+]These authors contributed equally to this work.

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past decade alone. While palladium catalysis remains a popular approach,² net semi-hydrogenation can be effected with several other metal catalysts, including those containing Cu,³ Au,⁴ Ru,⁵ Rh,⁶ Pt,⁷ Ni,⁸ Cr,⁹ V,¹⁰ and Fe.¹¹ While each of these updated processes has its virtues, the sheer number of reports suggests that no single methodology appears to be sufficiently general. Moreover, the unaddressed question remains as to what extent a Lindlar reduction, or these updated alternatives, is environmentally benign. In other words, how “green” are they? In fact, virtually all fail to adhere to most of the 12 Principles of Green Chemistry;¹² each relies on one or more organic solvents in which the reduction is conducted, many need an investment in energy in the form of heat, and recycling of the reaction medium is rare^{13, 2d}(Scheme 1).

In this report we disclose a very simple, safe, general, and environmentally responsible protocol for alkyne semi-hydrogenation that applies to most alkyne substitution patterns of interest. The newly developed methodology takes advantage of (1) the far greater dissolution properties of gases, including hydrogen, in hydrocarbon as opposed to water;¹⁴ thus, under micellar conditions, higher concentrations of hydrogen should be present inside a micelle as opposed to the surrounding aqueous medium, and (2) the attractive interactions between metal nanoparticles and polyethylene glycol (PEG).¹⁵ To avoid excessive hydrogen gas and the need for reactions to be run under pressure in sealed vessels, generation of H₂ was accomplished by adding sub-stoichiometric amounts of NaBH₄ to the reaction mixture (Scheme 2). Release of hydrogen gas is effected, therefore, upon addition of a catalytic amount of inexpensive Pd(OAc)₂ (1 mol %) admixed with NaBH₄ (initially 0.05 equiv, then 0.35 equiv; *vide infra*) to water in which is dissolved the designer surfactant TPGS-750-M (2 wt. %) which contains MPEG-750.¹⁶

With stirring at room temperature, the mixture turns to a black, seemingly homogeneous aqueous solution in which spherical micelles aggregate around palladium nanoparticles (Figure 1). The hydrogen formed seeks preferential dissolution within the inner lipophilic micellar cores, although adsorption onto the surface of the metal is also likely. Introduction of an alkyne leads to its dissolution within surfactant nanoreactors that interact with palladium. Reduction to Z-olefinic products then occurs at room temperature in *ca.* an hour in excellent yields. Stock solutions of this reagent can be stored and used over time.¹⁷

Curiously, while several other group 10 metal salts or complexes (e.g., NiCl₂, Ni(OAc)₂, Pd₂(dba)₃) were either inactive or led to mixtures of *E*- and *Z*-alkenes, and alkane,¹⁸ PdCl₂ gave complete, quantitative reduction to the corresponding alkane (Scheme 3). Alternatively, the same outcome can be realized using a balloon of hydrogen gas in place of prior reduction of Pd(OAc)₂ with NaBH₄.

When functionalized alkynes, e.g., propargylic alcohols, were exposed to these conditions, far lower *Z*-selectivities were observed. Fortunately, it was discovered that under otherwise identical conditions but in the presence of LiCl (2 equiv), both the yields and extent of *Z*-alkene formation are very high. Neither other salts of lithium (LiBr, Li₂CO₃, LiOH), nor sodium (NaCl), was nearly as effective as this additive.¹⁹

The choice of TPGS-750-M as surfactant was also shown to be critical in its key role as reaction solvent (Table 1). Thus, while the corresponding hydrogenation “on water”²⁰ (i.e., in the absence of the surfactant) afforded mostly the over-reduced, saturated product (entry 1), none of the several alternative, commercially available surfactants led to the desired Z-alkene in synthetically useful amounts (entries 2–6). Likewise, to assess overall scope, an expanded study was undertaken examining several types of alkynes, including unsymmetrically disubstituted, terminal, and conjugated cases (Table 2). Additional examples of propargylic and homopropargylic alcohols and their ester derivatives were very amenable to semi-reduction (entries 1–5), as was the corresponding acetal (entry 6). A conjugated aryl alkyl alkyne (entry 7) afforded the corresponding styrenyl array in a 95:5 Z to E ratio. Characteristic of this chemistry in water, free hydroxyl and amino groups (entries 1, 4, 5, 7, and 15) presented no obvious limitations. Other conjugated acetylenes bearing ester moieties led to 95% of the desired Z- α,β -unsaturated esters, including those containing ketone (entry 10) and epoxide (entry 11) residues. Terminal cases (entries 12–15) reacted to afford the targeted mono-substituted alkenes. While stereodefined centers present in α -amino acids such as proline and alanine derivatives (entries 13, 14) remained fully intact, as did their N-Cbz groups, some reduction of the olefin in an acrylate was observed leading to the drop in yield (entry 12). Interestingly, a representative silylalkyne was fully inert to these semi-hydrogenation conditions (entry 16), which could be used to synthetic advantage.

Another major feature characteristic of this process is the opportunity to recycle the contents of the entire reaction mixture. Once the reduction is complete, in-flask extraction with a minimum of a single organic solvent allows for the isolation and eventual purification of the desired product. Both a typical reaction mixture and the in-flask extraction with an ethereal solvent (Et₂O or MTBE) or hydrocarbon (e.g., hexanes) are shown in Figure 2. Remaining in the water are the surfactant, LiCl, and the palladium catalyst. Addition of fresh NaBH₄ (0.35 equiv) led to an active catalyst ready for re-introduction of the educt. As illustrated in Scheme 3, this process could be repeated five times without change in yield or stereochemical outcome. The use of very limited amounts of organic solvent for these extractions results in an especially low E Factor of 3.4, based solely on organic solvent usage, which is on the low end of those characteristic of the fine chemicals area, and over five times lower than typical values of 25–100 associated with pharmaceutical companies.^{21, 22} The flexibility of this sequence is further manifested upon alteration of the nature of the alkyne participating in each recycle (Scheme 4).

In an effort to determine the source of both hydrogens in the product alkenes, semi-reduction of a conjugated alkyne was carried out under our standard conditions replacing water with D₂O. Interestingly, two enoates were isolated in an essentially 1:1 ratio, with each containing one hydrogen and one deuterium (Scheme 5). This suggests, contrary to the traditional *cis*-mode of addition, that Pd-H is adding in a random fashion to the alkyne, followed by protio/deuterio-quenching of the C-Pd bond by H₂O or D₂O, respectively. Since water is not present within the hydrophobic interior, such quenching must occur outside of the inner micellar core.

Remarkably, semi-hydrogenation of a *non-conjugated* alkyne in D₂O afforded the non-deuterated Z-alkene (Scheme 6 A), indicative of both hydrogen atoms arising from NaBH₄. Likewise, use of NaBD₄ in H₂O gave the Z-di-deuterated olefin (Scheme 6 B). Thus, unlike conjugated alkynes (*vide supra*), the aqueous medium plays no role in providing hydrogen, suggesting that the transfer of both hydrogen atoms takes place at the interface between the metal and the hydrogen-containing micelles.

In summary, interactions between metal and micellar nanoparticles in water has been used to synthetic advantage, enabling development of new technology that provides a broadly applicable solution to the problem of alkyne semi-reductions, including disubstituted, terminal, and conjugated systems. The procedure that has been crafted, with particular attention to its environmental impact, is especially straightforward, leads to high levels of Z-selectivity, and generates product olefins in excellent isolated yields. Several green aspects to this chemistry include use of very limited amounts of a commercially available designer surfactant,²³ organic solvent for extraction purposes only, minimal use of water as the reaction medium, and recycling of all elements present in the aqueous mixture. Additional processes (*e.g.*, oxidations) enabled by tailor-made amphiphiles that form nanoparticles and contain highly localized concentrations of gases are under study and will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Cryo-TEM showing palladium nanoparticles (dark; arrows) aggregated around spherical nanomicelles in water

Figure 2.
Appearance of a reaction mixture during the semi-hydrogenation process, and upon extraction with ether

*traditional Lindlar semi-hydrogenation:
functional group compatibility? how "green"?*

Scheme 1.

Textbook Lindlar reduction conditions.

Scheme 2.

Approach to alkyne semi-hydrogenation in aqueous nanomicelles

Scheme 3. Full reduction of alkyne using PdCl_2

Scheme 3.

Recycling and E Factor for alkyne semi-hydrogenation

Scheme 4.

Recycling of the aqueous reaction mixture using different educts (MTBE extraction)

Scheme 5.
Semi-hydrogenation of a conjugated alkyne in D_2O

Scheme 6.**A:** Semi-hydrogenation with NaBH_4 in D_2O ; **B:** NaBD_4 in H_2O

entry	solvent	Pd ^a	conversion ^b	Z	E	alkane
1	water	Pd(OAc) ₂	100	25	25	50
2	cremophor ^c	Pd(OAc) ₂	100	25	25	50
3	Brij 30 ^c	Pd(OAc) ₂	100	0	0	100
4	Triton X-100 ^c	Pd(OAc) ₂	100	50	25	25
5	SDS ^c	Pd(OAc) ₂	100	14	14	72
6	SPGS ^c	Pd(OAc) ₂	100	14	28	58
7	TPGS ^c	Pd(OAc) ₂	100	95	5	<1
8	TPGS ^c	PdI ₂	100	95	5	<1
9	TPGS ^d	Pd(OAc) ₂	100	90	5	5
10	DME	Pd(OAc) ₂	58	50	7	1
11	MeCN	Pd(OAc) ₂	8	96	4	<1
12	THF	Pd(OAc) ₂	9	89	8	3

All reactions were run at 0.5 M in substrate; ratios were determined by GCMS and confirmed by ^1H NMR;

a 1 mol % Pd;

^b Determined by GCMS; c 2 wt % solution. $d_{5 \text{ wt } \% \text{ solution.}}$

Table 2

Scope of the semi-hydrogenation in water at room temperature

entry	alkyne	conv.	Z	E	alkane	yield (%)
1		100	96	4	-	90
2		100	99	<1	-	99
3		100	99	<1	-	96
4		100	99	<1	-	98
5		96	99	<1	-	91
6		100	99	<1	<1	98
7		93	95	5	-	90
8		95	99	trace	-	85
9		100	95	<1	5	90

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