

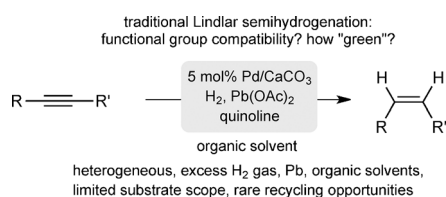
Semihydrogenation

A Palladium Nanoparticle–Nanomicelle Combination for the Stereoselective Semihydrogenation of Alkynes in Water at Room Temperature**

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Abstract: The addition of NaBH_4 to $\text{Pd}(\text{OAc})_2$ in water containing nanomicelles leads to the generation of H_2 and Pd nanoparticles. Subsequent reduction of disubstituted alkynes affords *Z*-alkenes in high yields. 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.

The Lindlar reduction of alkynes has stood the test of time, routinely appearing in textbooks as a fundamental approach to *Z* alkenes. Dating back to the original report in 1952,^[1] this semihydrogenation process traditionally relies on a heterogeneous catalytic source of palladium (e.g., Pd/CaCO_3) deactivated with lead, and the stereoselectivity of the reaction is further enhanced by the presence of a “poison” such as quinoline (Scheme 1). While the expected outcome is often

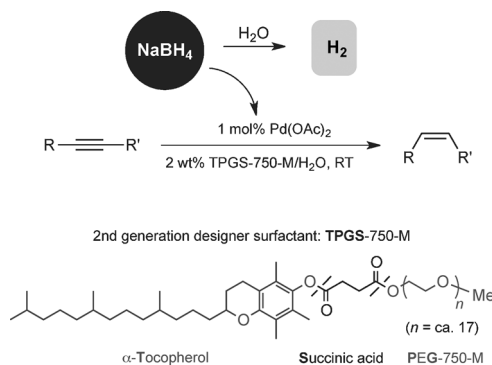


Scheme 1. Textbook Lindlar reduction conditions.

achieved, especially in simpler cases of dialkyl-substituted acetylenes, more highly functionalized substrates have proven to be challenging. Moreover, losses as a result of the generation of the undesired *E* isomer, as well as complications associated with solid supports containing a high surface area are not uncommon. These limitations have led to a plethora of alternative procedures reported within the past decade alone. While palladium catalysis remains a pop-

ular approach,^[2] net semihydrogenation 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 processes has its virtues, the sheer number of reports suggests that no single methodology appears to be sufficiently general. Moreover, the question remains as to what extent a Lindlar reduction, or these alternatives, is environmentally benign. In other words, how “green” are they? In fact, virtually all of them 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 energy in the form of heat, and recycling of the reaction medium is rare^[2d,13] (Scheme 1).

Here we disclose a very simple, safe, general, and environmentally responsible protocol for alkyne semihydrogenation 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 H_2 , in hydrocarbons as opposed to water;^[14] thus, under micellar conditions, higher concentrations of H_2 should be present inside a micelle compared to the surrounding aqueous medium, and 2) the attractive interactions between metal nanoparticles and poly(ethylene glycol) (PEG).^[15] To avoid excessive amounts of hydrogen gas and the need for reactions to be run under pressure in sealed vessels, generation of H_2 was accomplished by adding substoichiometric amounts of NaBH_4 to the reaction mixture (Scheme 2). The release of hydrogen gas is effected upon addition of a catalytic amount of inexpensive $\text{Pd}(\text{OAc})_2$ (1 mol%) admixed with NaBH_4 (initially 0.05 equiv, then 0.35 equiv; see below) to water, in which is dissolved the designer surfactant TPGS-750-M (2 wt %), which contains MPEG-750.^[16]



Scheme 2. Approach to alkyne semihydrogenation in aqueous nanomicelles.

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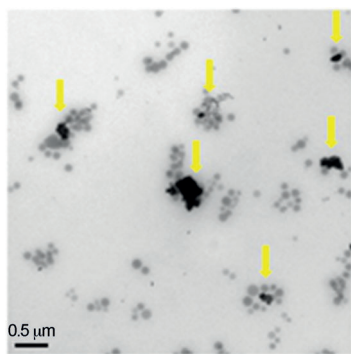
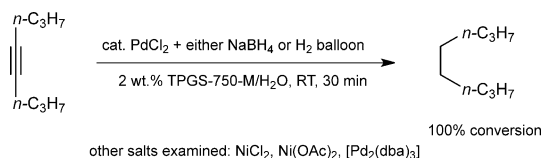


Figure 1. Cryo-TEM image showing palladium nanoparticles (dark; arrows) aggregated around spherical nanomicelles in water.

With stirring at room temperature, the mixture turns to a black, seemingly homogeneous aqueous solution in which spherical micelles aggregate around palladium nanoparticles generated by the NaBH_4 (Figure 1). The newly formed H_2 seeks preferential dissolution within the 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 about one hour in excellent yields. Stock solutions of this reagent can be stored and used over time.^[17]

Curiously, while several other salts or complexes of Group 10 metals (e.g., NiCl_2 , $\text{Ni}(\text{OAc})_2$, $[\text{Pd}_2(\text{dba})_3]$) were either inactive or led to mixtures of *E* and *Z* alkenes and alkanes,^[18] PdCl_2 resulted in the quantitative reduction to the corresponding alkane (Scheme 3). Alternatively, the same over-reduction is observed using a balloon of hydrogen gas in place of prior reduction of $\text{Pd}(\text{OAc})_2$ with NaBH_4 .



Scheme 3. Full reduction of alkyne using PdCl_2 .

When functionalized alkynes, for example, propargylic alcohols, were exposed to our standard conditions, far lower *Z* selectivities were observed. Fortunately, we 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 , Li_2CO_3 , LiOH), nor sodium (NaCl), were 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 (Table 1, entry 1), none of the alternative commercially available surfactants led to the desired *Z* alkene in synthetically useful amounts (entries 2–

Table 1: Surfactant screening.

$$n\text{-C}_5\text{H}_{11}\text{C}\equiv\text{CCH}_2\text{CH}_2\text{OH} \xrightarrow[\text{RT, 1 h}]{\begin{smallmatrix} 1 \text{ mol \% "Pd" } \\ \text{NaBH}_4 \text{ (0.5 equiv)} \\ \text{LiCl (2.0 equiv)} \end{smallmatrix}} n\text{-C}_5\text{H}_{11}\text{CH=CHCH}_2\text{CH}_2\text{OH}$$

Entry	Solvent	Pd source ^[a]	Conv. ^[b] [%]	Z	E	Alkane
1	water	$\text{Pd}(\text{OAc})_2$	100	25	25	50
2	cremophore ^[c]	$\text{Pd}(\text{OAc})_2$	100	25	25	50
3	Brij 30 ^[c]	$\text{Pd}(\text{OAc})_2$	100	0	0	100
4	Triton X-100 ^[c]	$\text{Pd}(\text{OAc})_2$	100	50	25	25
5	SDS ^[c]	$\text{Pd}(\text{OAc})_2$	100	14	14	72
6	SPGS ^[c]	$\text{Pd}(\text{OAc})_2$	100	14	28	58
7	TPGS ^[c]	$\text{Pd}(\text{OAc})_2$	100	95	5	< 1
8	TPGS ^[c]	PdI_2	100	95	5	< 1
9	TPGS ^[d]	$\text{Pd}(\text{OAc})_2$	100	90	5	5
10	DME	$\text{Pd}(\text{OAc})_2$	58	50	7	1
11	MeCN	$\text{Pd}(\text{OAc})_2$	8	96	4	< 1
12	THF	$\text{Pd}(\text{OAc})_2$	9	89	8	3

All reactions were run at a substrate concentration of 0.5 M; ratios were determined by GC-MS and confirmed by ^1H NMR spectroscopy.

[a] 1 mol % Pd. [b] Determined by GC-MS. [c] 2 wt % solution. [d] 5 wt % solution.

6). 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 semireduction (Table 2, entries 1–5), as was the corresponding acetal (entry 6). A conjugated aryl alkyl alkyne (Table 2, entry 7) afforded the corresponding styrenyl array in a *Z* to *E* ratio of 95:5. Characteristic of this chemistry in water, free hydroxy and amino groups (Table 2, entries 1, 4, 5, 7, and 15) presented no obvious limitations. Other conjugated acetylenes bearing ester moieties led to more than 95% of the desired *Z*-configured α,β -unsaturated esters, including those containing ketone (Table 2, entry 10) and epoxide (entry 11) residues. Terminal alkynes (entries 12–15) reacted to afford the targeted monosubstituted alkenes. While stereodefined centers present in α -amino acids such as proline and alanine derivatives (Table 2, entries 13 and 14) remained fully intact, as did their *N*-Cbz groups, some reduction of the olefin in an acrylate was observed, leading to a drop in the yield (entry 12). Interestingly, a representative silylalkyne was fully inert to these semihydrogenation conditions (Table 2, entry 16), which could be used to synthetic advantage.

Another major 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 single organic solvent allows the isolation and eventual purification of the desired product. Both a typical reaction mixture and the in-flask extraction with an ethereal solvent (Et_2O 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 NaBH_4 (0.35 equiv) leads to an active catalyst ready for re-introduction of the starting material. As illustrated in Scheme 4, this process could be repeated five times without a change in yield or

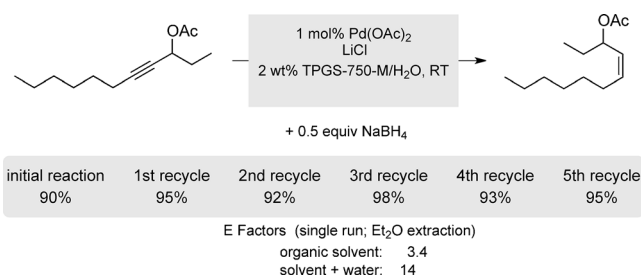
Table 2: Scope of the semihydrogenation in water at room temperature.

Entry	Alkyne	Conv. [%]	Z	E	Ratio of 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	< 1	—	85
9[d]		100	95	< 1	5	90
10[c]		100	99	< 1	—	95
11		100	99	< 1	—	90
12		100	—	—	< 1	82
13		100	—	—	< 1	98
14		100	—	—	< 1	97
15		93	—	—	< 1	90
16		0	0	—	—	0

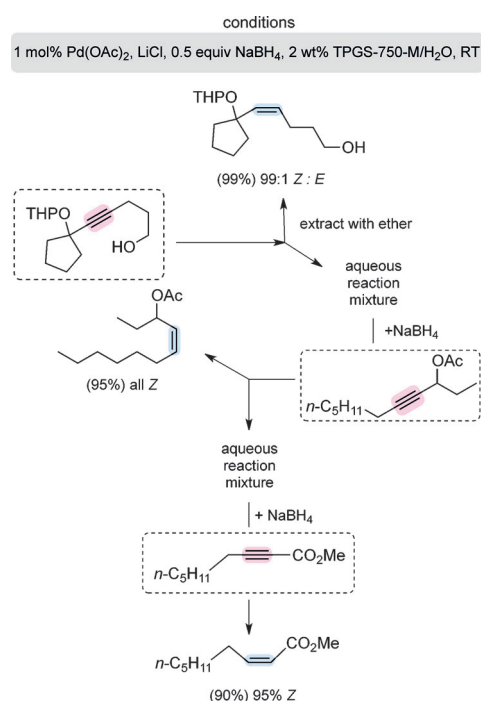
All reactions were run at a substrate concentration of 0.5 M, with 2 equiv LiCl, 0.5 equiv NaBH₄, and 1 mol% Pd(OAc)₂ with standard generation of the catalyst unless stated otherwise. [a] Run with 1 equiv LiCl. [b] No deprotection of protected alcohols or amines was detected. [c] Reduction of ketone was observed if no palladium was present. [d] No LiCl.


Figure 2. Appearance of a reaction mixture during the semihydrogenation process (left) and upon extraction with ether (right).

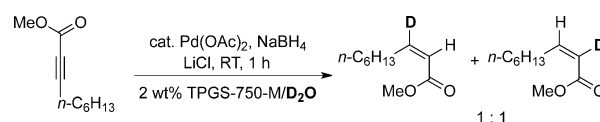
stereochemical outcome. The use of very limited amounts of organic solvent for these extractions resulted in an especially low E Factor of 3.4, based solely on organic solvent usage, which is on the low end of those characteristic of the fine


Scheme 4. Recycling and E Factor for alkyne semihydrogenation.

chemicals area, and over five times lower than typical values of 25–100 typical of 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 5).

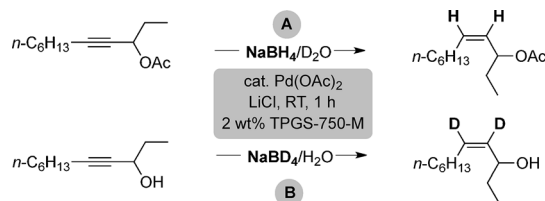

Scheme 5. Recycling of the aqueous reaction mixture using different starting materials (MTBE extraction).

In an effort to determine the source of both hydrogen atoms in the product alkenes, semireduction of a conjugated alkyne was carried out under our standard conditions replacing water with D₂O. Interestingly, two enoates were isolated in a 1:1 ratio, with each containing one H and one D atom (Scheme 6). This suggests, contrary to the traditional *cis* mode of addition, that Pd–H is adding in a random fashion to the


Scheme 6. Semihydrogenation of a conjugated alkyne in D₂O.

alkyne, followed by protio/deuterio quenching of the C–Pd bond by H₂O or D₂O, respectively. As water is not present within the hydrophobic interior, such quenching must occur outside of the inner micellar core.

Remarkably, semihydrogenation of a nonconjugated alkyne in D₂O afforded the nondeuterated *Z* alkene (Scheme 7A), indicative of both hydrogen atoms arising from



Scheme 7. Semihydrogenation with A) NaBH_4 in D_2O ; B) NaBD_4 in H_2O .

NaBH_4 . Likewise, use of NaBD_4 in H_2O gave the *Z*-bisdeuterated olefin (Scheme 7B). Thus, unlike conjugated alkynes (see above), the aqueous medium plays no role in providing H₂, 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 have led to the development of new technology that provides a broadly applicable solution to the problem of alkyne semireductions, including those of 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 olefins in excellent yields. Several green aspects to this chemistry include the 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.

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