Transfer Hydrogenation

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Transfer Semihydrogenation of Alkynes Catalyzed by a Zero-Valent Palladium N-Heterocyclic Carbene Complex**

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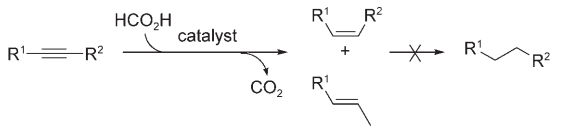
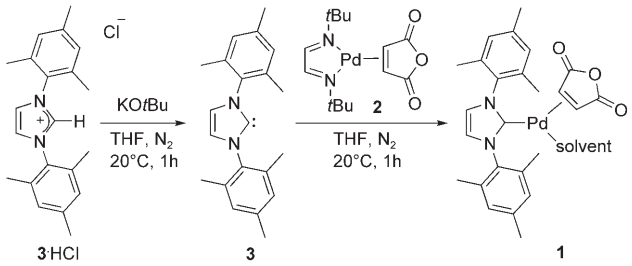
Catalytic transfer hydrogenation is a mild and effective way of reducing carbonyl functionalities that involves alcohols or ammonium formate as hydrogen donors and Ru^{II}, Ir^{I}, or Rh^{I} complexes as catalysts.[1,2] Transfer hydrogenation of ketones and imines is well known since these polar double bonds are easily reduced to the corresponding alcohols and amines,[3–5] whereas transfer hydrogenation of non-polarized carbon–carbon multiple bonds is more difficult.[2a,5–7] Thus, although several homogeneous catalytic systems are known for the transfer hydrogenation of alkenes, only one has been reported for the transfer semihydrogenation of alkynes to alkenes (Scheme 1). This procedure is not chemoselective for aromatic alkynes, and the product alkene can be further hydrogenated to the corresponding alkane. Furthermore, the catalyst contains large amounts of oxophilic phosphine ligand.[7] Aromatic alkynes have also proven to be difficult substrates in other reactions, particularly transfer hydrogenation and hydrogenation using dihydrogen.[8]



Scheme 1. Transfer semihydrogenation of alkynes with formic acid as hydrogen donor.

The semihydrogenation of alkynes is traditionally performed with Lindlar's catalyst and dihydrogen. This system reduces alkynes to *Z* alkenes but requires an elaborate experimental setup and strict monitoring of the hydrogen uptake to prevent over-reduction to the alkane. Apart from these practical inconveniences, partial isomerization of the *Z* alkene to the *E* alkene, a double-bond shift, and problems with reproducibility are typical for this reaction.[9] Thus, the development of a general and simple method for this important transformation remains a challenge, especially for aromatic alkynes.

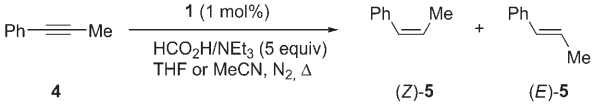
We have reported that the mechanism of alkyne hydrogenation catalyzed by palladium(0) diimine complexes involves heterolytic dihydrogen activation.[8d] This led us to consider the possibility that the palladium-catalyzed hydrogenation of alkynes may also proceed in the presence of an ionic hydrogen donor, such as formic acid/triethylamine. We report herein the first stereo- and chemoselective semihydrogenation of aromatic as well as aliphatic internal alkynes under hydrogen-transfer conditions. The catalyst for this reaction is the zero-valent Pd complex **1**, which is generated in situ from the Pd precursor complex **2**[10] and 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene (IMes, **3**; Scheme 2).[8d,11]



Scheme 2. Synthesis of catalyst **1**.

It has been shown for the Pd(NHC)-catalyzed reduction of alkynes with dihydrogen that complexes of type **1**, and similar species, formed in situ are more active than well-defined [Pd(IMes)(MA)$_2$] (MA = maleic anhydride) complexes.[8d] Hence, similar conditions were selected for transfer hydrogenation of the model substrate 1-phenyl-1-propyne (**4**) by employing a fivefold excess of HCO_2H/NEt_3 as the hydrogen donor and 1% of in situ generated **1** in refluxing THF or MeCN (Scheme 3).

Table 1 shows the reactivity and product distribution of the Pd^0(IMes)-catalyzed transfer hydrogenation of a number



Scheme 3. Transfer hydrogenation of 1-phenyl-1-propyne (**4**) to β-methylstyrene ((*Z*/*E*)-**5**) with HCO_2H/NEt_3 as the hydrogen source. Catalyst **1** was prepared in situ according to Scheme 2.

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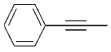
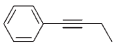
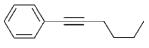
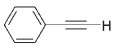
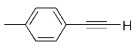
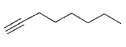
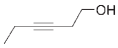
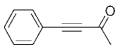
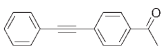
Table 1: Transfer hydrogenation of alkynes with catalyst **1**.[a]

Entry	Substrate	Solvent	Conv. [%]	t [h][b]	Z alkene/ E alkene/ alkane[c]
1		THF	>99	4	91/7/2
2		MeCN	>99	12	96/4/1
3		THF	>99	4	98/2/–
4		MeCN	>99	8	95/–/5
5		MeCN	35	24	98/1/1[d]
6		THF	>99	7	98/–/2[d]
7		MeCN	>99	<24[e]	>99/–/–[d]
8		THF	80	24[f]	–/99/–
9		MeCN	>99	<24[e]	93/3/4
10		THF	>99	<2	50/50[f]
11		MeCN	85	24	>99/–[f]
12		MeCN	>99	<24	>99/–[d,f]
13		THF	96[g]	2[e]	88/12[f,h]
14		MeCN	>99[g]	7	95/5[f,h]
15		MeCN	>99	<24[e]	>99/–/–[d]
16		MeCN	>99	<24[e]	91/9/–[d]
17		THF	>99	6	7/93/–[d,i]
18		MeCN	52	24	75/25/–[d,i]
19		MeCN	90	24	69/–/31[d,i]
20		THF	29[f]	1	46/54/–[d,i]
21		MeCN	88	24	59/22/7[d,i]
22		THF	>99	<3	several
23		MeCN	>99	<24	products
24		THF	un-	24	Z and E
25		MeCN	known		(di)enes[d]

[a] Reaction conditions: 160 mM of substrate, 1.6 mM of catalyst, and 800 mM of HCO_2H/NEt_3 in the specified solvent at reflux. [b] Time at full conversion determined by extrapolation. [c] Product distribution as determined by GC and ^{1}H NMR spectroscopy. [d] Product distribution as determined by ^{1}H NMR spectroscopy. [e] The exact time for full conversion is not known but no more starting material was present after 24 h. [f] Product distribution is depicted as alkene/alkane ratio. [g] Conversion ceases after the specified time then the alkenes slowly isomerize. [h] A double-bond shift occurs after 7 h. 2-, 3-, and 4-Octenes were identified by ^{1}H NMR spectroscopy but could not be separated from the over-reduction product by GC. [i] No reduction of carbonyl functionalities was observed.

of substrates. Both aromatic (Table 1, entries 1–7) and simple aliphatic (Table 1, entry 9) internal alkynes are readily hydrogenated to the desired Z alkene with good to excellent stereoselectivity and, importantly, hardly any over-reduction to alkane. We note that performing the reaction in the more strongly coordinating solvent MeCN results in a longer reaction time but generally gives a higher selectivity for the desired product. Simple terminal alkynes (Table 1, entries 10–14) react equally well but tend to give minor amounts of by-products (<5%). The initial chemoselectivity towards alkynes over alkenes is equally good but in THF over-reduction of the alkene starts after about 90% conversion. The results are essentially the same for terminal aliphatic alkenes in MeCN, although no over-reduction is observed for styrene or *p*-tolylstyrene.

To further explore the chemoselectivity we performed the reaction with mixtures of 1-phenyl-1-propyne and phenylacetylene to determine the catalyst's selectivity towards internal and terminal alkynes. The reaction profiles of the transfer hydrogenation of these mixtures look very similar to the respective individual reactions. The main difference is seen in the first hour: whereas phenylacetylene reaches 50% conversion in the first half hour, 1-phenyl-1-propyne seems to lag somewhat, with less than 5% conversion after the first half hour (it would normally be approximately 20%). Once about 90% of the terminal alkyne has been converted (after 1 h), the catalyst also begins to hydrogenate the internal alkyne, after which the same product distributions are obtained. We can therefore conclude that the catalyst has a preference for terminal alkynes over internal alkynes.

Hydrogenation of alkynes containing several other functionalities was also carried out. These experiments revealed that neither alcohols nor ketones inhibit catalytic activity and lead, with good to excellent chemoselectivity, to semihydrogenation of the alkyne functionality only (Table 1, entries 15–19). Since the reactions are performed in MeCN, it seems safe to assume that the catalyst is also compatible with nitrile functionalities. The α,β-unsaturated ketone 4-phenyl-3-butyne-2-one initially gives the Z alkene, but during the time required to reach full conversion it isomerizes to give the thermodynamically more stable E alkene as the main product, probably via the enolate (Table 1, entry 17). No hydrogenation of ketones to alcohols was observed, which is remarkable because most transfer-hydrogenation reactions (based on Ru^{II} catalysts) specifically lead to reduction of carbonyl functionalities. To our knowledge, this is therefore the first example of a homogeneous transfer-hydrogenation catalyst that specifically reduces alkynes in the presence of ketones.

Hydrogenation of the electron-poor alkyne dimethyl butynedioate (Table 1, entries 20 and 21) was less successful, thereby setting some boundaries to the selectivity of our catalyst. This could have been expected as the products of this reaction are known to form relatively stable alkene complexes with low-valent palladium, which could deactivate the active species; the formation of palladacyclic compounds may also play a role. In fact, dimethyl fumarate has previously been used to isolate reactive species, such as Pd^0(NHC) complexes.[8b] Note that this deactivation is much more pronounced in the less strongly coordinating solvent THF than in MeCN.

The limits of the chemoselectivity of the catalyst are reached when an enyne such as 1-ethynylcyclohexene or a diyne such as diphenylbutadiyne (Table 1, entries 22–25) are employed. The enyne initially behaves the same as 1-octyne—the alkyne moiety is semihydrogenated—and the alkene produced is slowly hydrogenated only when most of the alkyne has been hydrogenated. Isomerization to the more stable 3-ethylidenecyclohexene, which in turn is partly hydrogenated, is observed and this leads to a rather complex mixture of several $C_8H_{12/14}$ isomers. Transfer hydrogenation of the diyne also gives a mixture of compounds. Both Z and E alkenes (enynes, dienes) are detected by NMR spectroscopy whereas the fully reduced product is clearly not detected. The Pd^0(NHC) complex employed is therefore a very good to excellent chemo- and stereoselective catalyst for the semi-

hydrogenation of a large range and variety of alkyne-containing substrates.

Despite the high chemoselectivity, some over-reduced products were observed in several cases, albeit generally only in trace amounts. Experiments using a lower catalyst loading showed that alkane formation decreases with decreasing catalyst loading. Thus, no alkane was observed at all for 1-phenyl-1-propyne at a catalyst loading of 0.2% in THF, although the reaction becomes rather sluggish. Hence, the over-reduction of these substrates only appears to take place at the start of the reaction, after which the level remains nearly constant. We therefore propose that species **1** (Scheme 2) is the source of the active catalyst, with the coordinated solvent being replaced by the alkyne, which is subsequently hydrogenated. A new molecule of alkyne or a coordinating solvent then displaces the product alkene, thereby completing the catalytic cycle. This proposal would imply that the initially formed catalyst **1** is not the active species but merely a precatalyst that generates a certain amount of over-reduced product prior to or during its conversion into the actual catalyst. It is worth mentioning that the reported chemoselectivity is only attained when a slight excess of carbene **3** is used during preparation of the precatalyst **1**. When the Pd^0 precursor **2** is used in excess, some of the alkenes formed are slowly reduced to the corresponding alkane (2–10% in 18 h). This is the only instance in which visible formation of palladium black accompanies an increase in alkane formation.

Performing the reactions in MeCN gives better results than in THF. To discriminate between polarity effects and coordinative properties, we compared THF and MeCN with the polar but noncoordinating solvent CH_2Cl_2 (Table 2). The reaction in CH_2Cl_2 was faster than in THF at the same temperature but extensive formation of Pd black was soon evident and the conversion ceased after 3 h (Table 2, entries 1 and 2). The selectivity is good under these conditions but in the absence of additional stabilizing ligands or solvent the catalyst decomposes before the transfer semihydrogenation reaches full conversion.

Performing the reaction in MeCN at 65 °C led to a slower conversion than in THF at the same temperature but a much better chemo- and stereoselectivity (Table 2, entries 3 and 4.) As MeCN has a higher boiling point, the reaction was also performed at its reflux temperature, where full conversion was reached in 8 h with equally good selectivity (Table 2, entry 5). After heating under reflux for an additional 14 h in MeCN there was still no sign of Pd black formation and no substantial isomerization or over-reduction had occurred. An additional equivalent of 1-phenyl-1-propyne was added at this point to check whether the catalyst was still active. After 24 h, 28% of the alkyne had been converted and the conversion amounted to 40% after 48 h with the same high selectivity. The catalyst eventually deactivates even in the strongly coordinating MeCN, but only after 70 h at 80 °C. These results reveal that the active species is indeed homogeneous and that using a strongly coordinating solvent safeguards the high chemo- and stereoselectivity of the catalyst.

Table 2: Pd^0(IMes)-catalyzed transfer hydrogenation of 1-phenyl-1-propyne in various solvents.[a]

Entry	Solvent	T [°C]	t [h][b]	Conv. (1 h) [%][c,d]	Z alkene/E alkene/ alkane[c]
1	CH_2Cl_2	40	6(21%)	7	95/5/<1
2	THF	40	24	4	79/13/8
3	THF	65	8	30	86/7/4
4	MeCN	65	28	21	97/2/<1
5	MeCN	82	8	44	97/2/<1

[a] Reaction conditions: 160 mM of 1-phenyl-1-propyne, 1.6 mM of catalyst **1**, and 800 mM of HCO_2H/NEt_3 in the given solvent at the given temperature. [b] Total reaction time. Reactions were allowed to reach full conversion, after which the product distribution was constant. The yield of reactions that did not go to completion is given in parentheses. [c] Conversion and product distribution as determined by GC and ^{1}H NMR spectroscopy. [d] Conv. (1 h): Conversion after first hour.

Next, we argued that the observed absence of over-reduction may also be due to gradual deactivation and/or decomposition of the catalyst. If that were the case the catalyst would merely be more active towards alkynes than alkenes, and deactivation of the catalyst would have occurred before alkenes were reduced to a considerable extent. To disprove this possibility, additional portions of alkyne were added at 90% conversion, at one hour after full conversion, and at 24 h after full conversion (in THF). It can be seen from Figure 1a that the catalyst activity does not diminish after full conversion: the reaction rate and selectivity for the three subsequent batches of substrate are identical, with no significant increase in alkane concentration. After 24 h in the absence of substrate, additional substrate was no longer converted (not shown). These findings were confirmed in a separate experiment in which an additional 100 equivalents of

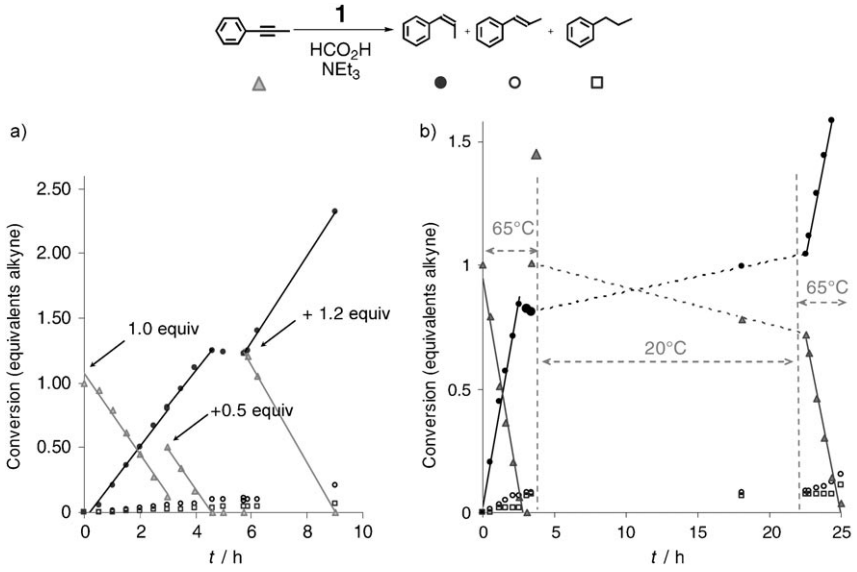


Figure 1. a) Transfer hydrogenation of 1-phenyl-1-propyne in THF, catalyzed by **1**, after adding subsequent equivalents: product distribution vs. time. b) Transfer hydrogenation of 1-phenyl-1-propyne in THF after adding one additional equivalent prior to stirring overnight at 20 °C: product distribution versus time.

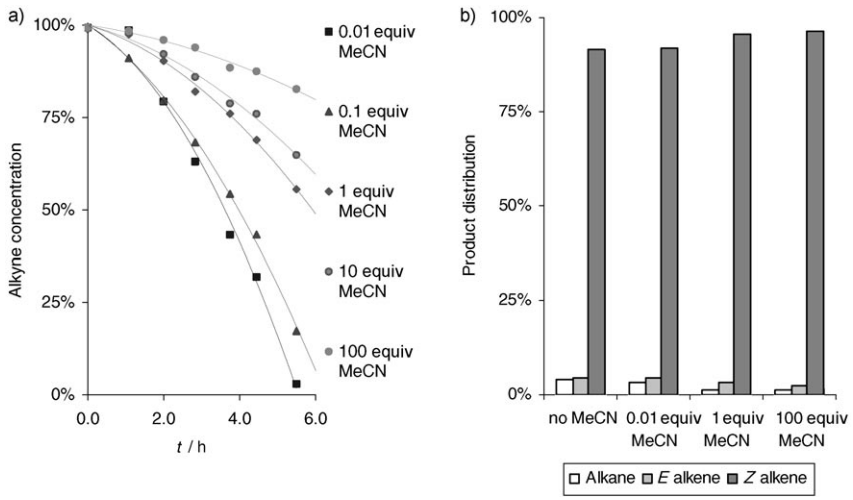


Figure 2. Transfer hydrogenation of 1-phenyl-1-propyne in THF, catalyzed by **1**, with increasing amounts of MeCN: a) alkyne concentration versus time; b) product distributions after 5.5 h.

alkyne (relative to Pd) was added after full conversion at 65 °C. The reaction mixture was stirred at 20 °C overnight so as not to fully consume the substrate. The reaction again proceeded at a comparable rate and selectivity upon increasing the temperature to 65 °C again. This result shows that deactivation of the catalyst is probably due to a lack of stabilizing ligand—alkynes are good but the product alkenes and THF are not sufficiently coordinating to provide effective stabilization.

Since the catalyst is prepared in situ as an activated species it is difficult to ascertain the nature of the "true" catalytically active species. As reactions in MeCN give higher selectivity but are slower than in THF, we decided to take a closer look at the competition between alkyne, alkene, and these solvents. It seemed reasonable to assume that the alkyne can still coordinate in MeCN, where the less strongly coordinating alkene cannot compete with the abundant solvent molecules. To verify this hypothesis, a competition experiment was devised in which the reaction was performed in THF with amounts of MeCN ranging from 0.01 to 100 equivalents relative to Pd. The results are shown in Figure 2, which clearly shows that the catalyst activity gradually decreases upon addition of MeCN while the product selectivity increases. We conclude from this finding, and the information already presented, that the catalytic cycle has a resting state in which a solvent molecule is coordinated to palladium.

We also performed the transfer semihydrogenation of **4** using DCO_2D as the putative hydrogen donor. This experiment proved that formic acid is indeed the hydrogen donor since the dideuterated *Z* alkene with deuterium atoms at the alkenic positions is formed exclusively, as judged from the ^1H and ^2H NMR spectra of the crude product.

In summary, we have shown that a palladium(0) carbene complex is an excellent catalyst for the semihydrogenation of alkynes under hydrogen-transfer conditions. The combination of a very high stereoselectivity with a previously unseen chemoselectivity, obtained under mild reaction conditions in a simple procedure, provides a very useful synthetic tool. We are currently trying to expand the scope of this powerful reaction and are investigating its mechanism in greater detail.

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Keywords: alkynes · carbene ligands · hydrogen transfer · hydrogenation · palladium

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