Article

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Direct *Trans*-Selective Ruthenium-Catalyzed Reduction of Alkynes in Two-Chamber Reactors and Continuous Flow

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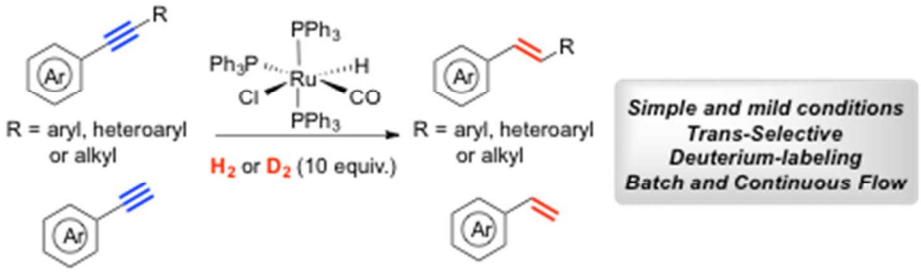
Abstract

An efficient *trans*-selective hydrogenation of alkynes under low hydrogen pressure and low reaction temperatures is reported applying a commercially available ruthenium-hydride complex. The developed reaction conditions, which tolerate a variety of functional groups, are carried out in a two-chamber set-up with *ex-situ* generated hydrogen. The reaction set-up is highly suitable for deuterium labeling. The *trans*-selective hydrogenation was extrapolated to a transfer hydrogenation protocol, employing a packed bed immobilized ruthenium hydride catalyst in continuous flow with a retention time of only 10 minutes.



Keywords: hydrogenation, alkynes, ruthenium-catalysis, deuterium-labeling, *trans*-alkenes, continuous flow

Introduction

Olefins are biologically important structures, present in a plethora of pharmaceuticals, natural products and fragrances.[1] The stereochemistry of the carbon–carbon double bond is decisive for the biological activity, and hence the ability to construct these olefins in a stereoselective manner is highly desirable. One approach relies on the partial metal-mediated hydrogenations of internal alkynes. The formation of *cis*-olefins generally relies on the use of Lindlar's catalyst, due to its high functional group tolerance and selectivity against over-reduction.[2] However, the selective conversion of internal alkynes to *trans*-alkenes still remains a challenge. Dissolving metal reductions is one approach, but is limited due to poor functional group tolerance.[3] More recent processes rely on transition metal-catalyzed semi-hydrogenations, but many of these apply organic or inorganic acids as hydrogen sources, which can restrict the functional group tolerance, and in general require reaction temperatures ranging from 80–145 °C.[4] Other protocols rely on H_2O as the hydrogen source in the presence of a reductant in combination with elevated reaction temperatures.[5] Two-step protocols to *trans*-alkenes have also been published, such as the Ru-catalyzed selective *trans*-hydrosilylation followed by protodesilylation.[6]

In 2013, two reports on transition metal catalyzed *trans*-selective hydrogenations of alkynes applying hydrogen gas (H_2-gas) were published by the groups of Fürstner with [Cp*Ru(cod)Cl],[7] and Milstein employing an iron pincer complex.[8] Remarkably, in the former case internal aliphatic alkynes show high *trans*-selectivity and a mechanism involving a metal-carbene intermediate has recently been suggested.[7] Both methods are run at hydrogen pressures up to 10 bars.

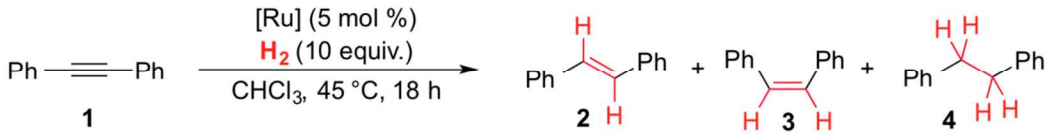
In this paper, we wish to report an operationally simple, mild and highly *trans*-selective hydrogenation of di(hetero)aryl- and alkyl–arylacetylenes, applying a simple and commercially available ruthenium–hydride catalyst. A particularly attractive feature of this protocol is the possibility to run the semi-hydrogenations at reaction temperatures as low as 45 ^{o}C, and applying a maximum of only 10 equivalents of H_2-gas. The reactions were conducted in a two-chamber system COware,[9] with hydrogen being generated *ex situ*. Given the simple setup the method can easily be adapted to deuterium labelling using *ex situ* generated D_2-gas.[10] Next, successful immobilization of the ruthenium catalyst onto triphenylphosphine-modified styrene beads allowed the construction of a continuous flow packed bed reactor. Using formic acid at the hydrogen donor this afforded a continuous flow protocol with a retention time of only 10 minutes.

Results and Discussion

The optimization of the *trans*-hydrogenation took its starting point in a catalyst screening using diphenylacetylene (**1**) as the test substrate (Table 1). First, the catalyst employed by Fürstner and co-workers was reexamined using our two-chamber system and 10 equiv. of hydrogen gas providing a partial pressure of only 3 bars. This provided a 75% yield of the desired *trans*-stilbene (**2**) along with 25% of the undesired fully reduced alkane (**4**, Table 1, entry 1) paralleling Fürstner's earlier published

results.[7] A number of other Ru-catalysts were then tested in order to achieve full selectivity. Several of the tested complexes did not display any reactivity with only recovered starting material **1** (Table 1, entries 3, 5, 6 and 10). For other complexes conversion was obtained, however, the selectivity was poor (Table 1, entries 2 and 8). When either $Ru(PPh_3)_3Cl_2$ or $Ru(PPh_3)_4H_2$ was applied, full conversion was attained but with selectivity towards the *cis*-stilbene (**3**, Table 1, entries 4 and 9). To our delight, $Ru(PPh_3)_3CO(Cl)H$ proved not only to be active for the semi-hydrogenation, but importantly, only generated the desired *trans*-stilbene **2** (Table 1, entry 7). It was furthermore possible to reach the same result with a catalyst loading of only 2.5 mol% (Table 1, entry 11). Nevertheless, lowering the catalytic loading to 1 mol%, resulted in a drop in conversion, while still retaining the high *trans*-selectivity (Table 1, entry 12).[11]

Table 1. Catalyst screening for the Ru-catalyzed semi-hydrogenation[a,b]



Entry	[Ru]	1 [%]	2 [%]	3 [%]	4 [%]
1	Cp*Ru(cod)Cl	0	75	0	25
2	$Ru(Me\text{-}allyl)_2cod$	55	12	33	0
3	$[(p\text{-cymene})RuCl_2]_2$	100	0	0	0
4	$Ru(PPh_3)_3Cl_2$	0	5	95	0
5	$Ru(acac)_3$	100	0	0	0
6	$[RuCp(CO)_2]_2$	100	0	0	0
7	$Ru(PPh_3)_3CO(Cl)H$	0	100	0	0
8	$Ru_3(CO)_{12}$	75	4	21	0
9	$Ru(PPh_3)_4H_2$	0	4	96	0
10	$RuCl_3$	100	0	0	0

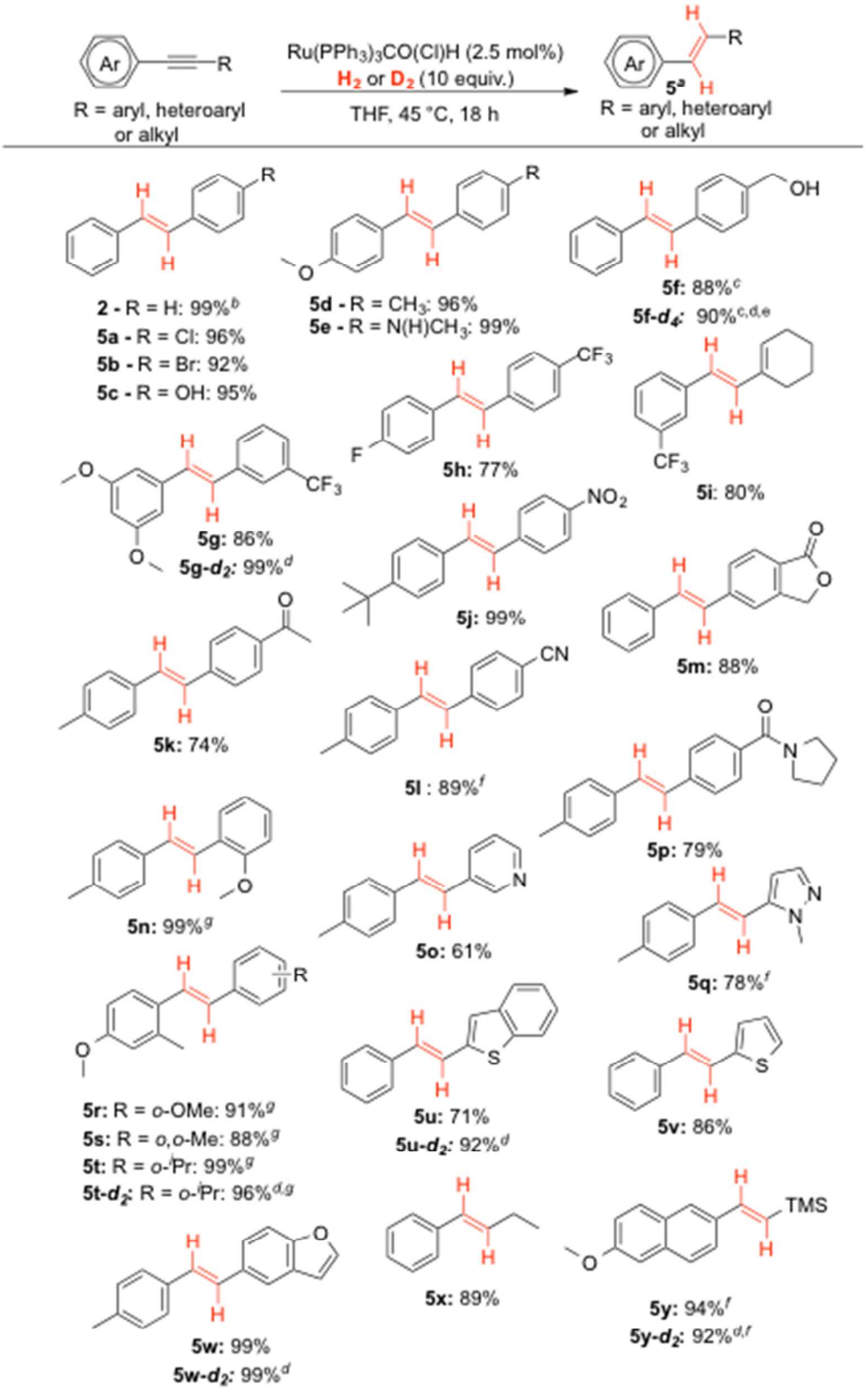
11[c]	$Ru(PPh_3)_3CO(Cl)H$	0	100	0	0
12[d]	$Ru(PPh_3)_3CO(Cl)H$	11	86	3	0

[a]H_2 was generated *ex situ* from Zn and HCl (6 M). See experimental section. [b]Product distribution is determined by GC analysis. [c]2.5 mol% of $Ru(PPh_3)_3CO(Cl)H$ was employed. [d]1 mol% of $Ru(PPh_3)_3CO(Cl)H$ was used.

The reaction was also examined using a H_2-balloon (1 atm partial pressure of H_2) resulting in only 50% conversion, but still with *trans*-selectivity (results not shown). Finally, a small solvent screening was performed, showing that the reaction worked equally well in THF and toluene. However, running the reaction in MeCN and MeOH impeded the catalytic activity as only low conversion was observed.[12] Simple mechanistic experiments on diphenylacetylene indicate that the *trans*-hydrogenation occurs in a two-step process with the initial reduction to *cis*-stilbene. *cis*-Stilbene is then isomerized into the desired *trans*-stilbene under the same catalytic conditions (see Supporting Information Figures S1 and S2). It is interesting to note that hydrogen/deuterium exchange occurs quite effectively on *trans*-stilbene under the developed conditions without formation of the fully reduced 1,2-diphenylethane (Figure S2).

With an efficient catalytic system for the *trans*-selective semi-hydrogenation of diphenylacetylene in hand, we set out to examine the functional group tolerance and hence the generality of the developed reaction conditions (Scheme 1). Aromatic alkynes bearing either electron withdrawing- (**5a**, **5b**, **5g**, **5h**) or donating groups (**5d**, **5e**, **5g**) were successfully hydrogenated in excellent yields and selectivity. Furthermore, a wide range of reducible functional groups, such as nitro- (**5j**), cyano- (**5l**) or various carbonyl-functionalities (**5m**, **5k**, **5p**) were tolerated under the developed reaction conditions and delivered the desired *trans*-olefins in good to excellent yields. When the reaction was performed in the presence of an aldehyde, the carbonyl group was reduced along with the alkyne in an 88% yield (compound **5f**). As depicted in Scheme 1, various heteroaromatic alkynes, bearing pyridine (**5o**),

pyrazole (**5q**), (benzo)thiophene- (**5u**, **5v**) or benzofurane (**5w**) moieties were readily reduced in yields ranging from 61% to 89% using hydrogen gas. When alkynes bearing arenes with *ortho*-substituents were examined, the reactivity turned out to be poor at 45 ^{o}C. However, these compounds could be selectively hydrogenated by increasing the reaction temperature to 90 °C in toluene. Thus, methoxy (**5n**, **5r**), methyl (**5r**–**5s**) and isopropyl (**5t**) substituents were tolerated in the *ortho*-position, affording the desired products in yields ranging from 91–99%. Remarkably, even the diaryl-alkyne bearing three methyl groups in the *ortho*-positions was hydrogenated *trans*-selectively in an 88% yield (compound **5s**). It was also possible to hydrogenate alkynes bearing a trimethylsilyl group (**5y**, 94%) or an aliphatic group such as ethyl (**5x**, 89%). Finally, when di-aliphatic alkynes were examined, only complicated mixtures of products with double bond migration was observed. Scaling the semihydrogenation of diphenylacetylene up to a 10 mmol scale proved to be successful as well. This led to the isolation of the *trans*-stilbene in a 99% yield only requiring 0.001 mol% of the ruthenium catalyst and 1.2 equivalents of hydrogen if the reaction was run at 90 ^{o}C.

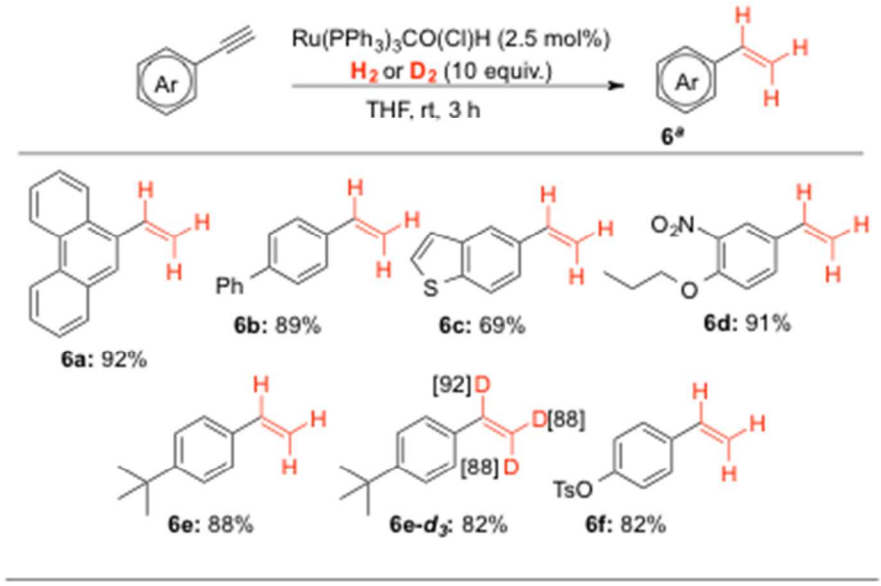

Ar
R
R = aryl, heteroaryl or alkyl
Ru(PPh3)3CO(Cl)H (2.5 mol%)
H2 or D2 (10 equiv.)
THF, 45 °C, 18 h
5a
R = aryl, heteroaryl or alkyl
2 - R = H: 99%b
5a - R = Cl: 96%
5b - R = Br: 92%
5c - R = OH: 95%
5d - R = CH3: 96%
5e - R = N(H)CH3: 99%
5f: 88%c
5f-d4: 90%c,d,e
5g: 86%
5g-d2: 99%d
5h: 77%
5i: 80%
5j: 99%
5k: 74%
5l : 89%f
5m: 88%
5n: 99%g
5o: 61%
5p: 79%
5q: 78%f
5r: R = o-OMe: 91%g
5s: R = o,o-Me: 88%g
5t: R = o-iPr: 99%g
5t-d2: R = o-iPr: 96%d,g
5u: 71%
5u-d2: 92%d
5v: 86%
5w: 99%
5w-d2: 99%d
5x: 89%
5y: 94%f
5y-d2: 92%d,f

[a]Alkyne (0.2 mmol, 0.2 M). H_2 was generated *ex situ* from Zn (3.4 mmol) and HCl (1 mL, 6 M). All yields refer to pure isolated material. [b]Reaction performed on a 10 mmol scale using 0.001 mol% $Ru(PPh_3)_3CO(Cl)H$ and 1.2 equiv. of H_2 at 90 °C. [c]Starting from 4-(phenylethynyl)benzaldehyde. [d]D_2 was used and generated *ex situ* from Zn (3.4 mmol) and DCl (1 mL, 6 M). [e]Full deuteration of the alkene and 70% deuteration of the methylene group. [f]Reaction was conducted at 60 °C in toluene. [g]Reaction was conducted at 90 °C in toluene.

Scheme 1. Trans-selective semi-hydrogenation of internal alkynes[a]

Next, we examined the propensity of terminal alkynes to be selectively reduced to the corresponding styrenes. This would provide the opportunity to prepare deuterated styrenes applying D_2 instead of H_2. Only a few examples exist on the synthesis of deuterated styrenes, either starting from the deuterated alkyne, or by hydrogen-deuterium exchange with the styrene.[13] The reaction with terminal alkynes had to be slightly optimized, as over-reduction was observed to a large degree when employing the standard reaction conditions. Gratifyingly, it was found that the reduction could be carried out at 20 °C for 18 h giving the desired styrene in an 86% yield along with a 14 % yield of the fully reduced compound. From time experiments, we observed that full conversion to the styrene could be achieved after 3 h (selectivity >95%:5% styrene:fully reduced, as observed by ^{1}H NMR analysis of the crude reaction mixture). Other successful semireductions of terminal alkynes are depicted in Scheme 2. Good to excellent yields were obtained in all cases (**6a**-**6f**), and switching to deuterium gas led to high deuterium incorporation as seen for **6e-*d*$_3$**. Interestingly, tri-deuteriation was observed for the olefinic part of **6e-*d*$_3$** presumably originating from non-selective readdition of the active Ru-D catalyst after the primary reduction event. Rotation of the carbon-carbon bond followed by β-hydride elimination would

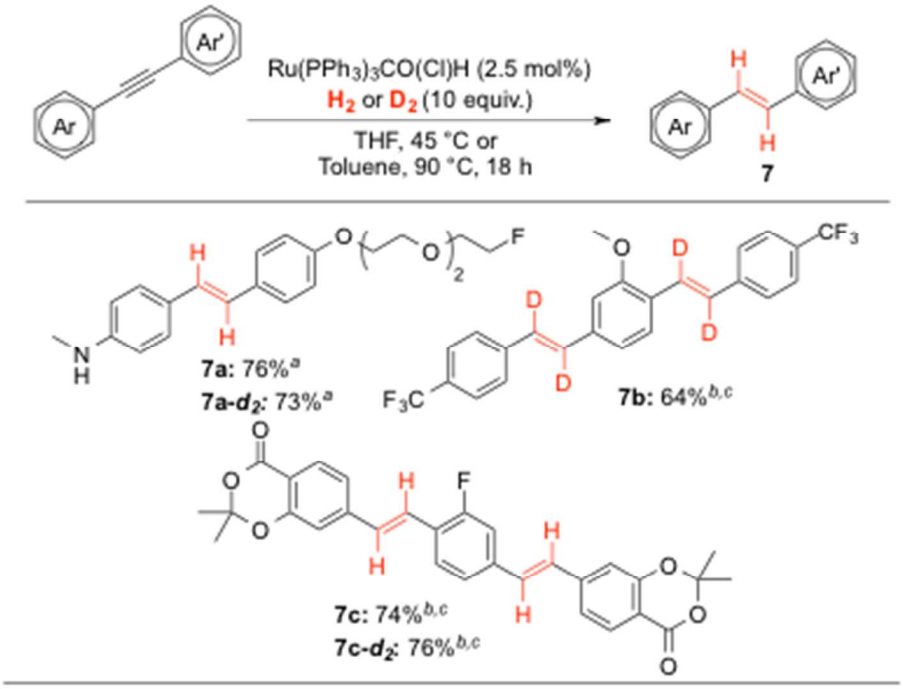
result in deuterium exchange of all olefinic hydrogens. This similar deuterium exchange was also observed for both *cis*- and *trans*-stilbene (see Figure S2 in the Supporting Information).



[a]Alkyne (0.2 mmol, 0.2 M). H_2 and D_2 were generated *ex situ* from Zn (3.4 mmol) and HCl or DCl (6 M, 1 mL). All yields refer to isolated material; the numbers in square brackets indicate the amount of deuterium incorporation in percentage.

Scheme 2. Reduction and deuterium labeling of terminal alkynes[a]

In order to show the importance of the developed reaction conditions, we applied the *trans*-selective reduction conditions to the synthesis of three biologically relevant compounds (Scheme 3). The ^{19}F-isotope analogue **7a** of the β-amyloid fibril tracer, fluorobetaben,[14] and its D_2-isotope derivative **7a-*d*$_2$** were prepared in a 76% and 73% isolated yield, resp. from the *trans*-hydrogenation of the corresponding alkyne. Double *trans*-selective reductions were examined with substrates possessing two internal alkynes. Hence, for another class of Aβ-plaque ligands, based on the FSB structure,[15] compounds **7b-*d*$_2$**, **7c** and **7c-*d*$_2$** could be prepared in good yields again with full deuterium incorporation on both olefin moieties.

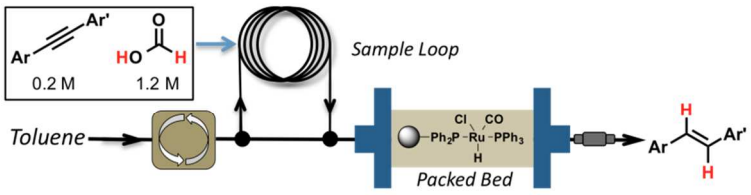


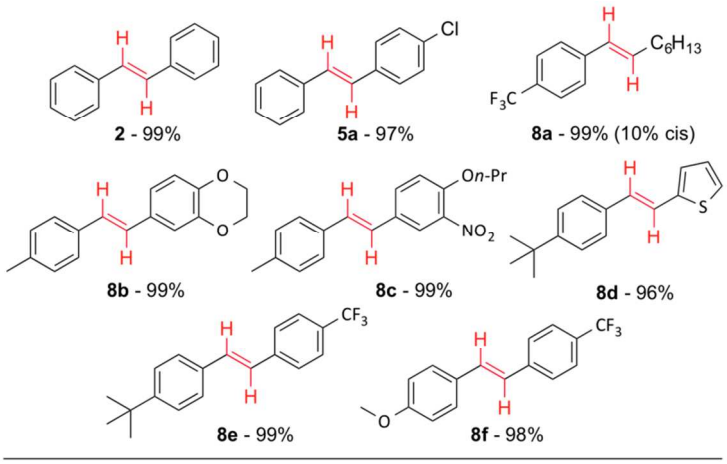
[a]Alkyne (0.2 mmol), $Ru(PPh_3)_3CO(Cl)H$ (2.5 mol%), THF (1 mL). H_2 and D_2 were generated *ex situ* from Zn (2.1 mmol) and HCl or DCl (6 M, 1 mL). Stirred at 45 °C for 18 h. [b]Deuterium incorporation >95% according to

the ^{1}H NMR spectrum. [c]Alkyne (0.2 mmol), $Ru(PPh_3)_3CO(Cl)H$ (2.5 mol%), toluene (1 mL). D_2 and H_2 were generated *ex situ* from Zn (2.1 mmol) and DCl or HCl (6 M, 1 mL). Stirred at 90 °C for 18 h.

Scheme 3. Synthesis of Aβ tracers Fluorbetaben 7a, FSB-analogs 7b and 7c[a]

Next, it was decided to test the trans-selective Ru-hydride catalyst under hydrogen transfer conditions using formic acid as the hydrogen donor. A continuous flow setup was constructed towards this purpose with the Ru-catalyst being immobilized on styrene supported triphenylphosphine beads loaded in a packed bed reactor.[16] Due to low solubility of the $Ru(PPh_3)_3CO(Cl)H$ complex, its diphenylacetylene added derivative, previously prepared by the group of Santos, was prepared and loaded onto the modified styrene beads.[17] The styrene beads carrying the catalyst precursor were next placed in a packed bed reactor. Flushing the catalyst bound packed bed with a 2% formic acid solution in toluene at 90 °C successfully expelled *trans*-stilbene rendering the active phosphine coordinated Ru-hydride catalyst.[11] For the reaction setup, toluene was pumped continuously through the flow reactor while a mixture of diaryl-alkyne (0.2 M) and formic acid (1.2 M) in toluene (9 mL in total) was loaded onto a 10 mL sample loop prior to being passed through the heated packed bed reactor (Scheme 4).





Scheme 4. Selective *trans*-hydrogenations in continuous flow.

Immediately, this system turned out to selectively reduce diphenylacetylene to *trans*-stilbene and only a short optimization was required to obtain the desired product **2** in a quantitative yield.[11] The retention time of the transformation was successfully lowered to *10 minutes* when performing the transfer hydrogenation at 110 °C or 115 °C. Besides diphenylacetylene, 7 other diarylacetylene derivatives were tested the results of which are shown in Scheme 4. Given that the ruthenium catalyst remains immobilized there was no need for purification of the obtained products resulting in near-quantitative isolated yields for all entries (**2b**, **7a-f**).[18] Compound **7a** was isolated along with 10% of the *cis*-isomer indicating that somewhat longer retention time is required for this particular entry. Also one example of a heteroaromatic thiophene derived acetylene proved reactive under the conditions with an excellent 96% isolated yield (Compound **7d**).

In conclusion, a mild and efficient Ru-catalyzed *trans*-selective hydrogenation of alkynes has been developed applying a commercially available Ru–hydride complex in an operationally simple two-chamber reactor with *ex-situ* generated hydrogen or deuterium. A variety of functional groups could be

tolerated under the catalytic conditions, even reducible groups, such as nitro, cyano, halides and amides. The developed conditions could be applied for the reduction and deuterium labeling of terminal alkynes, providing simple access to styrenes. The method was applied in the synthesis of compounds relevant for β-amyloid fibril detection, which have relevance for diagnostic tests for Alzheimer's disease. Finally, the method was extrapolated to a hydrogen transfer protocol in a continuous flow setup with the active ruthenium hydride being immobilized on triphenylphosphine modified styrene beads. A retention time of only 10 minutes was required under continuous flow conditions affording the desired compounds in near quantitative yields and with the same high selectivity for the *trans* isomer.

Associated Content

The supporting information is available free of charge. Optimization tables, procedures and ^{1}H, ^{13}C, ^{19}F NMR spectra for all produced compounds.

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Notes

The authors declare the following competing financial interest: Anders T. Lindhardt and Troels Skrydstrup are co-owners of SyTracks Aps, which commercializes the two-chamber technology.

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a mild method for alkyne reductions, the in situ hydrogen generation results in a decreased functional group tolerance as seen from competing reduction of functionalities such as the nitro group.

[12] See Electronic Supporting Information for further details.

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