E-Alkenes

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Catalytic Stereoselective Semihydrogenation of Alkynes to *E*-Alkenes**

*Iacovos N. Michaelides and Darren J. Dixon**

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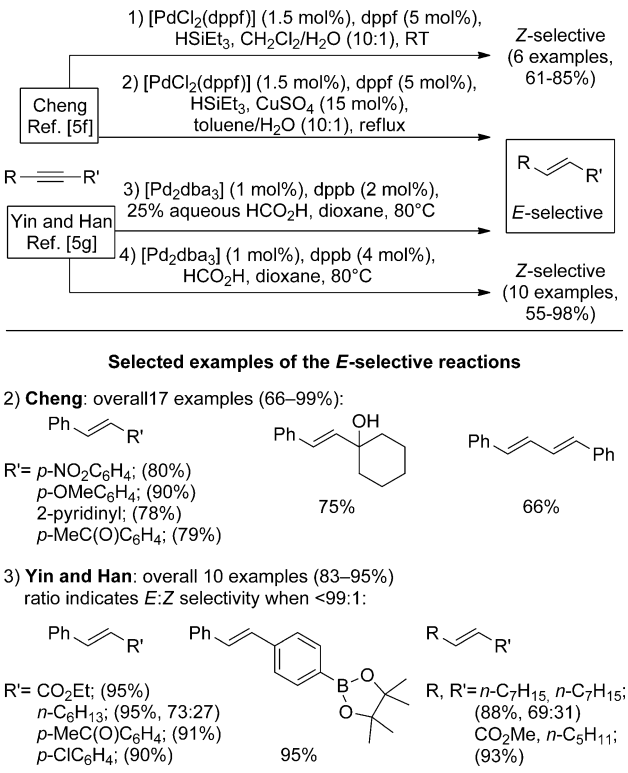
Installing the alkyne functionality as a synthetic precursor to *Z*-configured carbon–carbon double bonds through *syn*-selective semihydrogenation is a common approach in organic synthesis.[1] Many mild, functional-group-tolerant, and high-yielding catalytic (homogeneous and heterogeneous) and noncatalytic methods exist,[2] with the Lindlar protocol[2c] being the most popular choice. However, the analogous direct reduction of the alkyne functionality to the *E*-configured alkene is a transformation that remains a major challenge, particularly in late-stage synthesis. The textbook example of Birch-type reduction using NH_3 or amines and noncatalytic dissolving metals[3] does indeed provide good *E*-selectivities, however, functional-group intolerance is a major limitation owing to the aggressive nature of the reaction conditions. Although some improvement in the scope of the *E*-selective hydrogenation reaction has been achieved through the use of overstoichiometric amounts of chromium reagents,[4] the use of noncatalytic, toxic reagents is not ideal. Herein, we focus on the significant advancements made in recent years toward the development of an *E*-selective, catalytic, functional-group-tolerant semihydrogenation of alkynes through transition-metal catalysis.

Particular focus has been put on the selective catalytic transfer hydrogenation of alkynes,[5] using water[5e,f,i] or organic hydrogen donors, such as alcohols,[5d] carboxylic acids,[5a,b,g,i] and amines.[5h] These methods are relatively mild, safe (avoiding the use of a potentially hazardous pressurized H_2 atmosphere), and in some cases environmentally friendly. Recent advancements have even provided stereocomplementary methods, giving both *Z*- and *E*-selectivity by means of only slight modifications to the reaction procedures (Scheme 1). In one of the most developed methodologies, Cheng and co-workers[5f] demonstrated an effective Pd-catalyzed reduction of mono- and diarylalkynes, employing $HSiEt_3$ and H_2O as the hydrogen donors. In their *E*-selective reaction, addition of catalytic $CuSO_4$ isomerized the nascent



Scheme 1. Efficient catalytic stereocomplementary transfer hydrogenations of alkynes. dba = *trans*,*trans*-dibenzylideneacetone, dppb = 1,1′-bis(diphenylphosphanyl)butane, dppf = 1,4-bis(diphenylphosphanyl)ferrocene.

Z-alkene to the more stable *E*-alkene. Furthermore, in a collaborative effort, Yin and Han[5g] have shown that by changing the hydrogen donor from formic acid to 25% aqueous formic acid in their Pd-catalyzed reaction, they also get a switch from *Z*- to *E*-selectivity, again through an in situ $Z \rightarrow E$ isomerization. Although such transfer hydrogenation methods mostly provide excellent *E*-selectivities and yields, their dependence on a $Z \rightarrow E$ isomerism largely restricts the substrate scope to internal, conjugated alkynes. More challenging nonconjugated internal alkynes gave poor stereoselectivity. For example, hexadec-8-yne afforded a 69:31 (*E*:*Z*) selectivity, albeit in 88% yield.

In a different approach, Bargon and co-workers conducted a pioneering NMR study on the direct *E*-selective semi-

[*] I. N. Michaelides, Prof. Dr. D. J. Dixon
Chemistry Research Laboratory
Department of Chemistry, University of Oxford
12 Mansfield Road, Oxford, OX1 3TA (UK)
E-mail: darren.dixon@chem.ox.ac.uk

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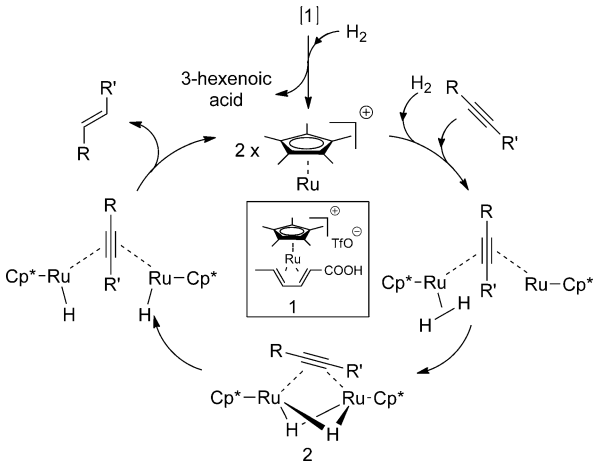
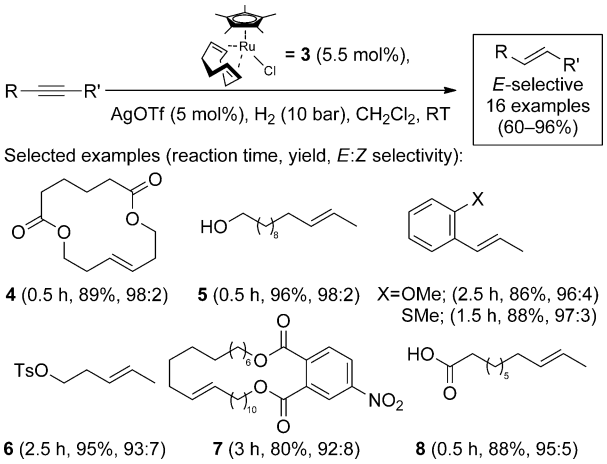
hydrogenation of alkynes using H_2 (1 bar) and mononuclear ruthenium catalyst **1** in MeOD at 25 °C.[6] They accomplished the desired transformation, even reducing a range of non-conjugated alkynes that bear hydroxy, carbonyl, acetal, and terminal-alkyne functionalities (only internal alkynes were reduced). More importantly, using in situ *para*-hydrogen-induced polarization experiments, they excluded the possibility of $Z \rightarrow E$ isomerism in their reaction and proved the unprecedented direct *E*-hydrogenation potential of the investigated mononuclear catalyst. Further to proving that the two delivered hydrogen atoms belonged to the same H_2 molecule, they rationalized the direct transformation by suggesting a bridged alkyne–dihydrogen dinuclear ruthenium complex **2** as an intermediate in their catalytic cycle (Scheme 2).[7,8]



Scheme 2. Bargon's proposed dinuclear mechanism for the Cp*Ru-catalyzed *E*-selective reduction. Cp* = pentamethylcyclopentadienyl.

In search of a general and direct method for the desired *E*-selective transformation, Fürstner and co-workers recently disclosed a catalytic method that finally combines the best of both worlds.[9] While maintaining the *E*-selectivities observed in Birch-type reductions, they provide a substrate scope that significantly supersedes past methods. Inspired by the seminal work of Trost and co-workers in the Ru-catalyzed *trans*-silylation of triple bonds,[10] and acknowledging the isolobal relationship between H and R_3Si, they investigated ruthenium catalysis for the analogous *trans* hydrogenation of alkynes. In fact, their goal was realized when, through a series of optimization experiments on a model substrate, they discovered that the commercial catalyst [Cp*Ru(cod)Cl] (**3**) in CH_2Cl_2, with H_2 (10 bar) at ambient temperature, gave rise to the corresponding alkene **4** in 89% yield with excellent *E*/*Z* selectivity (98:2) (Scheme 3). Furthermore, addition of AgOTf to the reaction led to an increase in the reaction rate, while maintaining the impressive *E*-selectivity. Consistent with Bargon's observations, they demonstrated that the *E*-selectivity is controlled by the catalyst in the hydrogenation step and not a result of subsequent $Z \rightarrow E$ isomerization.

With a promising, highly efficient catalytic system in hand, they set out to investigate the "Achilles' heel" of *E*-selective



Scheme 3. Fürstner's functional-group-tolerant *trans* hydrogenation (yield is a combination of *E*/*Z* stereoisomers and the alkane (5–15%, as determined by GC analysis)). Tf = trifluoromethanesulfonyl.

semihydrogenation, its functional-group tolerance. With most reactions complete in less than 4 h, and with excellent yields and selectivities, they showed that a range of functional groups are tolerated in this novel direct transformation (Scheme 3). Not only were a number of challenging non-conjugated alkynes reduced (**4**–**8**), but also sensitive substrates, including those with elimination-prone (**6**) and reducible nitro functionalities (**7**), were all successfully transformed with impressive *E*-selectivities. On the other hand, although terminal alkenes were tolerated, neither terminal alkynes nor conjugated 1,3-diene- and 1,3-enyne-bearing alkynes were reactive substrates; probably because of efficient complexation to an active ruthenium species which disrupts the catalytic cycle.

With the exception of the high-pressure requirement (used for rate enhancement) and the sometimes significant (>15%) alkane and/or isomeric alkene by-product formation observed in isolated cases, this method represents the first direct, efficient, selective, and broadly functional-group-tolerant semihydrogenation of alkynes to *E*-alkenes. It supports Bargon's findings and further demonstrates the potential of mononuclear catalysts for this transformation. Broad in scope, it demonstrates that, at least for the time being, this type of catalysis is superior to the use of multinuclear metal catalysts, a once assumed requirement for the delivery of two hydrogen atoms to opposite sides of a triple bond.[7]

Now that a significant milestone in the *E*-selective semihydrogenation of alkynes has been reached, further mechanistic insight will inevitably lead to developments and improvements. Future applications in late-stage modification of complex polyfunctional molecules, as well as in total synthesis, will likely follow and confirm the synthetic value of this new methodology.

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