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Ligand-controlled iridium-catalyzed semihydrogenation of alkynes with ethanol: highly stereoselective synthesis of *E*- and *Z*-alkenes†

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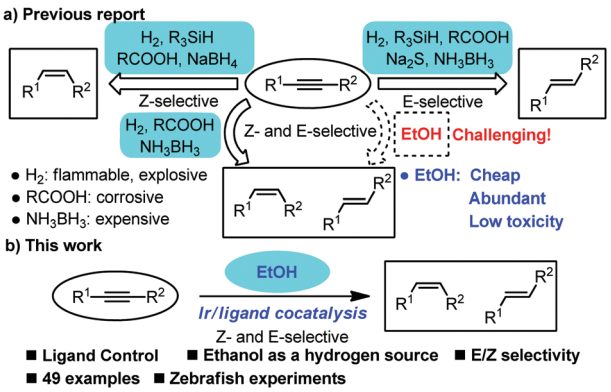
A ligand-controlled iridium-catalyzed semihydrogenation of alkynes to *E*- and *Z*-alkenes with ethanol was developed. Effective selectivity control was achieved by ligand regulation. The use of 1,2-bis(diphenylphosphino)ethane (DPPE) and 1,5-cyclooctadiene (COD) was critical for the stereoselective semihydrogenation of alkynes. The general applicability of this procedure was highlighted by the synthesis of more than 40 alkenes, with good stereoselectivities. The value of our approach in practical applications was investigated by studying the effects of pinosylvin and 4,4′-dihydroxystilbene (DHS) on zebrafish as a vertebrate model.

The selective semihydrogenation of unsaturated compounds is one of the most important reactions in organic synthesis,[1] and has been widely used for the synthesis of synthetic intermediates, natural products, fragrances, pharmaceuticals, and agrochemical products.[2] Several catalytic systems for alkyne semihydrogenation,[3] *e.g.*, Lindlar reduction,[4] have been reported. The homogeneous or heterogeneous catalytic hydrogenation of inner alkynes shows intrinsic stereoselectivity for *Z*-alkenes because the reaction proceeds *via syn* addition. Many methods for semihydrogenation of alkynes to *Z*-alkenes have been reported,[1,3,5] and these can provide good *Z*-selectivity. However, these methods require the use of flammable, explosive, corrosive, or expensive hydrogenating agents to achieve the semihydrogenation reaction and to obtain good product yields. The stereocomplementary formation of *E*-alkenes by hydrogenation is much more difficult than *Z*-alkene formation.[6] This is, in part, because addition of the hydrogenation agent favors one side of the substrate and therefore leads to *cis* addition. *E*-Selective alkyne reductions are therefore being actively researched, and some promising catalytic systems have been developed recently. These involve use of transition-metal complexes in combination with hydrogen gas or various transfer hydrogenation agents (Scheme 1a).[7] However, few catalytic systems allow switchable selectivity for either the *E*- or *Z*-alkene isomer in a single transformation.[8] Recently, Du,[9] Moran,[10] and Liu[7k] have reported methods that give switchable selectivity for either the *E*- or *Z*-alkene isomer. However, to obtain good product yields, these methods require flammable, explosive, corrosive, or expensive hydrogenation agents such as hydrogen, formic acid, and ammonia borane, and this has limited their use. The development of safer, convenient, and economical stereoselective semihydrogenation methods is therefore still necessary. Ethanol is the best choice of transfer hydrogenation agent and the development of methods for synthesizing *E*- and *Z*-alkenes with ethanol as the hydrogen source is desirable. Very recently, Grützmacher,[11] Swamy,[12] and Huang[13] reported transfer hydrogenation with ethanol. Unfortunately, the semi-hydrogenation of simple disubstituted acetylene cannot be achieved by all three systems. Here, we report an example of ligand-controlled iridium-catalyzed semihydrogenation of alkynes to *E*- and *Z*-alkenes with ethanol as the transfer hydrogenation agent (Scheme 1b).



Scheme 1 Various strategies for semihydrogenation of alkynes.

Z-Alkene synthesis by transition metal catalytic hydrogenation intrinsically involves *cis* hydrometalation of alkynes. The *E*-alkene is usually obtained by isomerization of the *Z*-alkene (Scheme 2). Isomerization is usually achieved by *Z*-alkene coordination with a metal center, followed by migration insertion, and then

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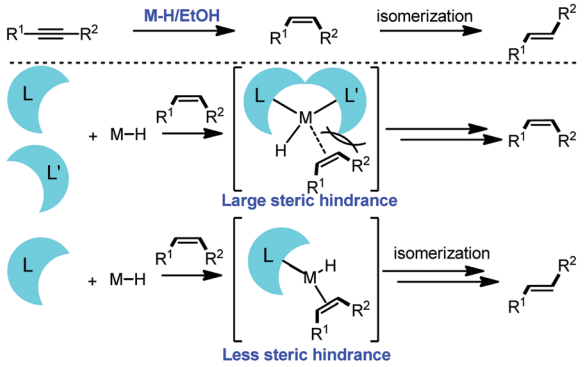


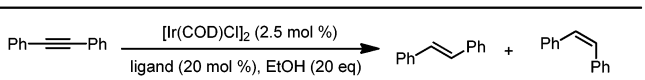
Scheme 2 Strategy for ligand control of stereo effects.

β-hydrogen elimination. In theory, coordination and insertion of the *Z*-alkene intermediate require a less sterically hindered metal center with an open coordination site, and this facilitates the following β-hydride elimination step. We therefore envisaged that isomerization to obtain *E*-alkenes requires a ligand that causes less steric hindrance. Conversely, isomerization could be suppressed by using an appropriate bulky ligand because coordination and insertion of the *Z*-alkene would be sterically unfavorable. This would result in selective generation of *Z*-alkene products. Ligand-controlled stereodivergent transfer hydrogenation of alkynes is therefore a promising approach.

We began by treating 1,2-diphenylethyne and ethanol with 2.5 mol% $[Ir(COD)Cl]_2$ as a catalyst, with DPPE as a ligand. Initially, we screened various potential reaction solvents to identify a suitable reaction solvent. THF was found to be the best solvent for the semihydrogenation of alkynes to *E*-alkenes with ethanol (Table 1, entries 1–8). To improve the reaction efficiency, we examined a wide range of reaction temperatures (Table 1, entries 9–12). The results show that 120 °C was the optimum temperature, and the corresponding (*E*)-1,2-diphenylethene was obtained in 92% yield with >99 : 1 *E*/*Z* selectivity. It is worth noting that there is a small amount of excessive hydrogenation product formation when the temperature is raised to 130 °C. To increase conversion to the *Z*-alkene, we replaced DPPE with large sterically hindering ligands (Table 1, entries 13–16). GC analysis showed that a 3% yield of (*Z*)-**3a** was obtained with DIPAMP, and a 13% yield was obtained when BINAP was used. To further increase the conversion rate to the *Z*-alkene, we added both COD and DPPE ligands to increase the steric hindrance at the metal center. An 84% yield of **3a** was obtained, with 12 : 1 *Z*/*E* selectivity (Table 1, entry 16). This shows that these two ligands have crucial roles. The stereostructure of the metal center is a key factor in the formation of *cis*-alkenes. These results therefore support our initial hypothesis that the *E*/*Z* selectivity can be well controlled by the level of steric hindrance at the metal center. No over-reduced alkane byproducts were detected in this catalytic system.

With the optimum reaction conditions in hand, a series of 1,2-disubstituted acetylene were investigated for extending the substrate scope (Scheme 3). This ligand-controlled iridium-catalyzed semihydrogenation of alkynes with ethanol shows good functional group tolerance. Diarylethynes with electron-neutral or electrondonating groups such as alkyl, phenyl, and methoxy

Table 1 Effects of solvent, temperature, and ligand. 1,2-Diphenylethyne (0.2 mmol), ethanol (4 mmol), $[Ir(COD)Cl]_2$ (10 μmol), ligand (0.04 mmol), THF (1.5 mL), at 120 °C under N_2 for 22 h

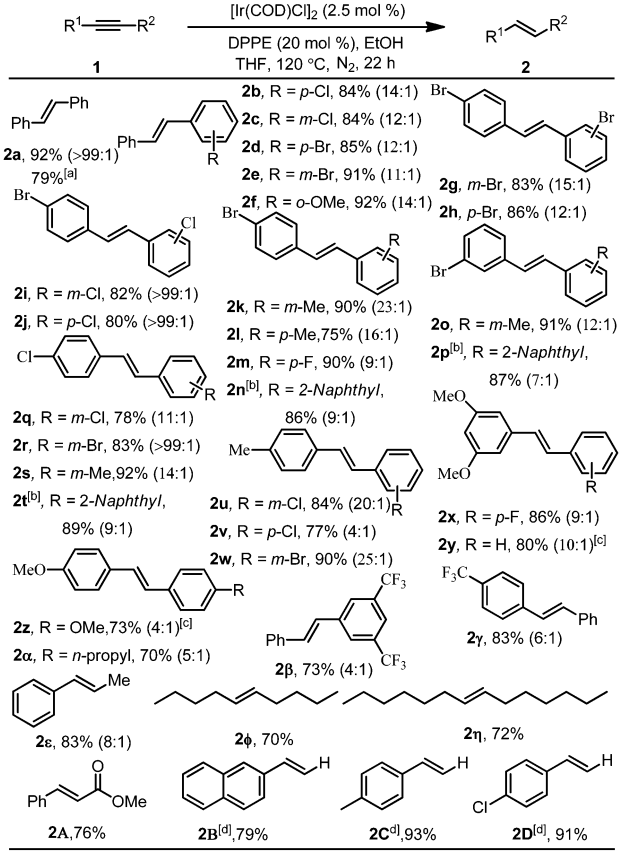


Entry	Ligand	Solvent	*T* (°C)	Conv. **1a** (%)	Yield **2a**[a] (%)	Yield **3a**[a] (%)
1	DPPE	*p*-Xylene	130	17	17	0
2	DPPE	Mesitylene	130	27	27	0
3	DPPE	*n*-Hexane	130	0	0	0
4	DPPE	Dioxane	130	0	0	0
5	DPPE	DMF	130	5	2	3
6	DPPE	Toluene	130	5	2	3
7	DPPE	DMSO	130	0	0	0
8	DPPE	THF	130	79	75	3
9	**DPPE**	**THF**	**120**	**92**	**92**	**0**
10	DPPE	THF	110	81	78	3
11	DPPE	THF	100	34	6	28
12	DPPE	THF	90	19	5	14
13[b]	DPPBde	THF	120	1	1	0
14[c]	DIPAMP	THF	120	83	80	3
15[d]	BINAP	THF	120	20	7	13
16[e]	**DPPE + COD**	**THF**	**120**	**91**	**7**	**84**
17	None	THF	120	46	38	8
18[f]	DPPE	THF	120	0	0	0
19[g]	DPPE	THF	120	0	0	0

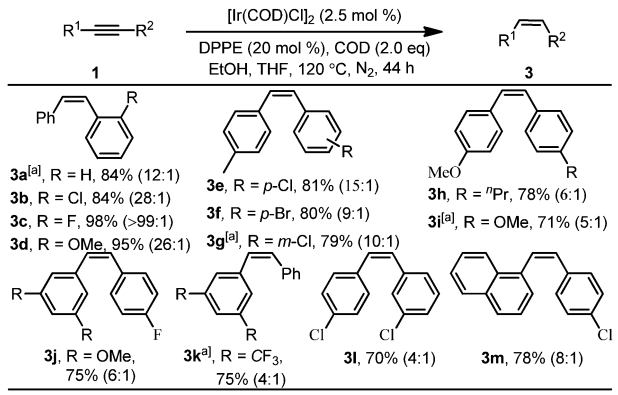
[a] Yields were determined by GC analysis. [b] DPPBde = 2-diphenylphosphinobenzaldehyde. [c] DIPAMP = ethylenebis(2-methoxyphenylphenylphosphine). [d] BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthalene. [e] COD (0.4 mmol), 40 h. [f] Without $[Ir(COD)Cl]_2$. [g] Without ethanol.

on the aryl rings all gave the corresponding (*E*)-1,2-diarylethenes with high selectivities and in good yields. Aryls containing an electron-withdrawing group such as fluoro, chloro, bromo, and trifluoromethyl were also tolerated and afforded the corresponding (*E*)-1,2-diarylethenes **2b–2v** in moderate to good yields with highly *Z*/*E* selectivities. Moreover, the reaction of 1,2-diarylethynes containing two methoxy substituents or two trifluoromethyl substituents at the *meta* positions of the aromatic rings also gave the corresponding (*E*)-1,2-diarylethene products **2w**, **2x**, and **2α** in good yields. To our delight, dialkylalkynes and methyl 3-phenylpropiolate are also suitable for this system, the corresponding products **2ε**, **2ϕ** and **2η** were obtained in good yields. In addition, terminal alkynes all give corresponding products **2A**, **2B** and **2C** in good to excellent yields. These results indicate that various groups, *e.g.*, alkyl, phenyl, fluoro, chloro, bromo, methoxy, trifluoromethyl and ester, were tolerated under the optimum reaction conditions. More importantly, pinosylvin or DHS can be easily obtained by demethylating **2x** or **2y**.

As mentioned above, regulation of *Z*-selective semireduction of alkynes can be achieved by increasing the steric hindrance at the metal center. The substrate scope was surveyed to investigate the versatility of this iridium-catalyzed transfer hydrogenation of alkynes for the synthesis of *Z*-alkenes, with use of a combination of DPPE/COD as ligands. The *Z*-alkene products were obtained in good yields with high *Z*/*E* selectivities for most tested substrates. A wide range of functional groups were also well tolerated. The results, which are summarized in Scheme 4, show that aryls containing electron-neutral, electron-donating,



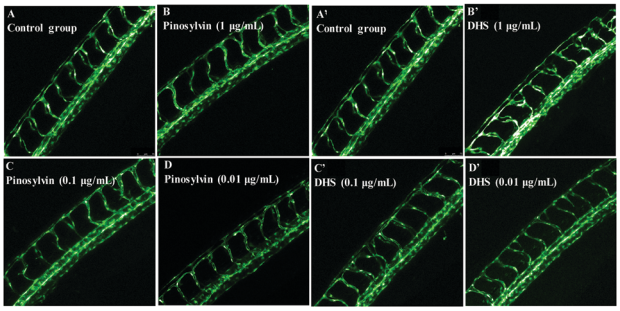
Scheme 3 Isolated product yields and reaction conditions: substrate **1** (0.2 mmol), ethanol (4 mmol), $[Ir(COD)Cl]_2$ (10 μmol), DPPE (0.04 mmol), THF (1.5 mL), at 120 °C under N_2 for 22 h. [a] Gram-scale synthesis. [b] 30 h. [c] There is a partial over-reduction product generation. [d] 70 °C.



Scheme 4 Isolated product yields and reaction conditions: substrate **1** (0.2 mmol), ethanol (4 mmol), $[Ir(COD)Cl]_2$ (10 μmol), DPPE (0.04 mmol), COD (0.4 mmol), THF (1.5 mL), at 120 °C under N_2 for 44 h. [a] 40 h.

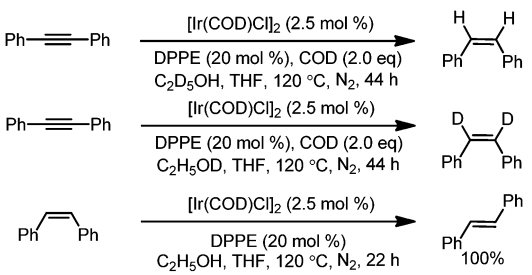
and electron-withdrawing groups all gave the corresponding (*Z*)-alkenes with high selectivities and in good yields.

The synthetic utility of the current method was tested by performing a gram-scale ligand-controlled iridium-catalyzed semihydrogenation of an alkyne with ethanol under the optimum conditions. The target (*Z*)-**2a** was obtained in 79% yield. The zebrafish has become an important vertebrate model for evaluating drug effects.[14] To demonstrate the value of our approach in practical applications, we study the effects of pinosylvin and DHS, with zebrafish as a vertebrate model. On the basis of Ragunathan's work,[15] we envisaged that the effects of pinosylvin and DHS on the vascular system would differ from those of resveratrol. We therefore examined the activities of pinosylvin and DHS in zebrafish. The test results show that treatment of zebrafish embryos with 1 μg mL^{-1} pinosylvin or DHS resulted in morphological malformations, and treatment with 0.01–0.1 μg mL^{-1} pinosylvin or DHS led to post-antiangiogenic defects (Scheme 5). The results of this study will be of great significance in research on drugs for treating cardiovascular and cerebrovascular diseases.



Scheme 5 Effects of treatment with pinosylvin and DHS on vascular system in trunk of Tg(kdrl:EGFP) zebrafish embryos at 48 hpf. (A–D) Control group, pinosylvin and DHS group treated with 1, 0.1, and 0.01 μg mL^{-1}. Scale bar, 75 μm.

Additional experiments were performed to gain a better understanding of the roles of the ligand, reductant, and iridium in the stereoselective semihydrogenation of alkynes. Control experiments showed that the absence of ethanol or $[Ir(COD)Cl]_2$ shut down the reaction, and the absence of the ligand significantly decreased the reaction selectivity and yield (Table 1, entries 17–19). These results imply that each of the components is essential to this reaction. We confirmed that one hydrogen atoms in the reaction product were provided by ethanol by conducting deuterium-labeling experiments (Scheme 6). When C_2D_5OH was used, the reduction product was not deuterated in the presence of $[Ir(COD)Cl]_2$/DPPE/COD. Conversely, the di-deuterated *cis* product was isolated when C_2H_5OD was used. Notably, the di-deuterated *cis* product is difficult to be separated because of the similar polarity to 1,2-diphenylethyne. These results show that the hydroxyl group in ethanol acts as a hydrogen source in the semihydrogenation reaction.



Scheme 6 Mechanism experiments.

Moreover, (*Z*)-1,2-diphenylethene can be completely converted to (*E*)-1,2-diphenylethene in the presence of $[Ir(COD)Cl]_2$/DPPE. Based on these results, we propose the catalytic cycle (see the Fig. S1 for details, ESI†).

In summary, we have developed a highly efficient ligand-controlled iridium-catalyzed semihydrogenation of alkynes to *E*- and *Z*-alkenes with ethanol as a transfer hydrogenation agent. This method is safer, more convenient, and more economical than traditional strategies. It is compatible with a range of functional groups and is suitable for gram-scale reactions. The value of our approach in practical applications was shown by studying the effects of treatment with pinosylvin and DHS, with zebrafish as a vertebrate model. The test results show that pinosylvin and DHS significantly affect angiogenesis. The results of this study will be of great significance in research on drugs for treating cardiovascular and cerebrovascular diseases. Further investigations of the use of cheaper metals, animal experiments, and other reaction types are underway in our laboratory.

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Conflicts of interest

There are no conflicts to declare.

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