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PALLADIUM (II)-CATALYZED SELECTIVE REDUCTION OF 4'-(PHENYLETHYNL)ACETOPHENONE IN THE PRESENCE OF A FORMIC ACID-TRIETHYLAMINE MIXTURE

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1. INTRODUCTION

The selective reduction of internal alkynes to alkenes is a challenging and essential transformation required for several industrial and pharmaceutical applications (Huang et al., 2019). This reduction can be realized through two main catalytic processes (Iwasaki et al., 2018): 1) direct hydrogenation using molecular hydrogen in the presence of Pd/C catalysts and their analogs; 2) transfer hydrogen reaction using hydrogen donor sources such as alcohols and acids. Transfer hydrogenation has shown various advantages, such as avoiding high hydrogen pressure and hazardous reductants and better chemo- and stereoselectivity of the resulting alkenes (Li et al., 2010; Baráth, 2018).

Several studies involving the use of the stable and inexpensive formic acid as a reductant and a substitute for flammable H_2 were reported for transfer hydrogenation (Oger et al., 2013). Nevertheless, the use of formic acid in conjunction with an additive, such as amines, was effective in the presence of homogeneous and heterogeneous Pd (Iwasaki et al., 2018; Hauwert et al., 2008), Ni (Richmond & Moran, 2015), Ru (Kusy & Grela, 2016), and Au (Li et al., 2016) catalysts. The base has shown an increased catalytic activity by deprotonating the substrate and promoting its complexation with the metal ion.

In literature, most of the studies report the selective semi-reduction of diphenylacetylene (Huang et al., 2019; Reyes-Sánchez et al., 2011; Li et al., 2012; Li et al., 2011). Among these studies, homogeneous ruthenium and nickel-based catalysts were implemented. Recently, copper(0) nanoparticles successfully reduced the diphenylacetylene to its corresponding *cis*-alkene in high yields (Moran et al., 2021). Nonetheless, many palladium-based systems reported for transfer semi-hydrogenation yielded *trans*-alkenes at relatively low conversion with *trans*/*cis* isomerization after long reaction times (Decker et al., 2020). Recently, we reported the transfer hydrogenation of internal alkynes by using palladium complexes as catalysts and $HCOOH/Et_3N$ as the hydrogen source (Chayya et al., 2021). Excellent selectivity and high yields were obtained upon reducing the diphenylacetylene catalyzed by $PdCl_2(PPh_3)_2$ in the presence of HCOOH and Et_3N.

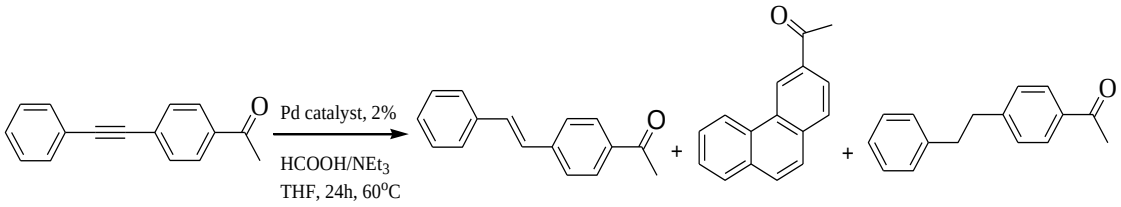
This paper reports an efficient and selective transfer semihydrogenation of diarylacetylene bearing a ketone group, specifically 4'-(phenylthynyl)acetophenone, using palladium (II) complex catalyst in the presence of a H-donor. Several reaction conditions were investigated and optimized to reduce the studied substrate, and GC-MS and NMR were used to monitor selectivity.

2. RESULTS AND DISCUSSION

Different reaction parameters were examined to successfully reduce the internal alkyne 4'-(phenylethynyl)acetophenone cost-effectively and under mild conditions. The reaction conversion was determined by GC-MS, and the yield was calculated by integration of the GC-MS peaks. The optimal selective reduction conditions were reached by varying one factor at a time.

We investigated the reduction efficiency and selectivity of 4'-(phenylethynyl)acetophenone (**A**) using various palladium catalysts, and results are shown in Table 1. Using the $HCOOH/Et_3N$ as a hydrogen source, a complete conversion of the starting material was observed in all reactions. No-matter-what palladium catalyst was used in this study, the reduction led to the formation of (*E*)-1-(4-styrylphenyl)ethanone (**B**) and an acetylphenanthrene dervivative, namely 1-(phenanthrene-3-yl)ethenone (**C**) (Gore & Kamonah, 1979). The latter may be formed by electrocyclic ring closure under thermal conditions (60 ^{o}C) of (*Z*)-1-(4-styrylphenyl)ethanone that was not isolated (Scheme 1). Furthermore, over reduction did not occur, and the alkane (**D**) was not formed. Based on the results presented in Table 1, we decided to focus on the better selectivity of the cyclic-one product (**C**) and continue our study by using $Pd(acac)_2$ catalyst (Entry 3).

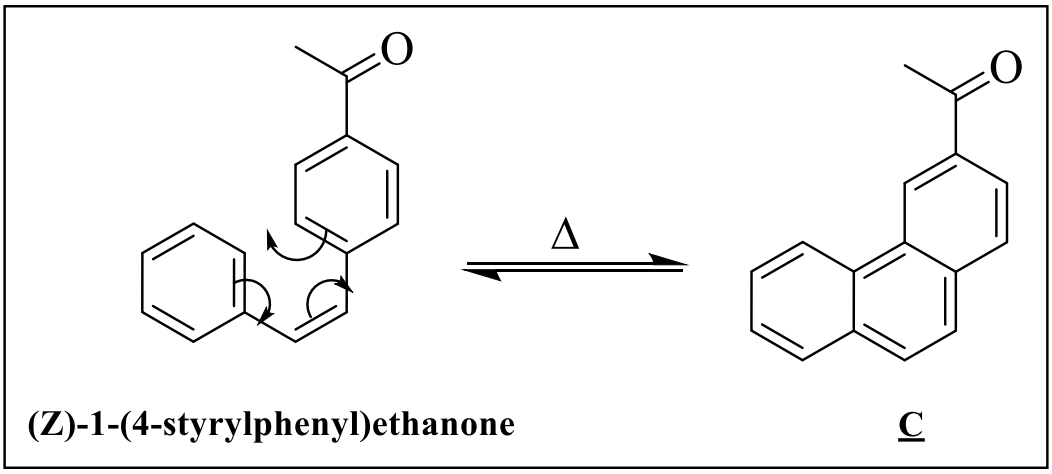
Table 1: Reduction of 4'-(phenylethynyl)acetophenone: effect of different palladium catalysts



A **B** **C** **D**

Entry	Catalyst	Conversion [%]*	Ratio [%]*			
			A	**B**	**C**	**D**
1	$Pd(OAc)_2$	100	-	50	50	-
2	$PdCl_2$	100	-	59	41	-
3	$Pd(acac)_2$	100	-	31	69	-

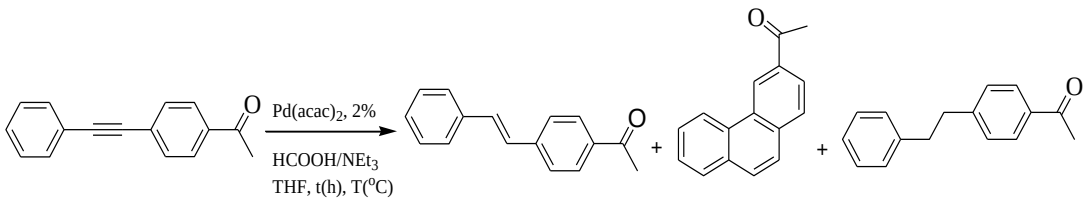
Reaction conditions: THF, 24 h, 60 °C, [**A**] = 1.5 ×10^{-3} M, HCOOH (5 eq. compared to **A**), NEt_3 (5 eq. compared to **A**). *Determined by GC-MS



Scheme 1: Electrocyclic ring closure of the (*Z*)-1-(4-styrylphenyl)ethanone to form (**C**)

Next, the reduction reaction was performed at two different temperatures (60 and 80 °C) for different reaction times. Complete conversion of the starting material was attained in all the tested conditions. The results are summarized in Table 2. The semi-reduction of 4'-(phenylethynyl)acetophenone at 60 °C for 7 h (Entry 1) led to the almost equal formation of the (*E*)-alkene (**B**) and the cyclic compound (**C**). However, after 24 h at the same temperature (Entry 2), the selectivity of (**C**) increased compared to (**B**). In another attempt, the selectivity of the 1-(phenanthrene-3-yl)ethenone improved from 96% to 100% by heating at 80 °C for 7 h (Entry 3) and 24 h (Entry 4), respectively. In addition, over reduction was not observed in all the presented entries (Table 2).

Table 2: Reduction of 4'-(phenylethynyl)acetophenone: effect of temperature and time.

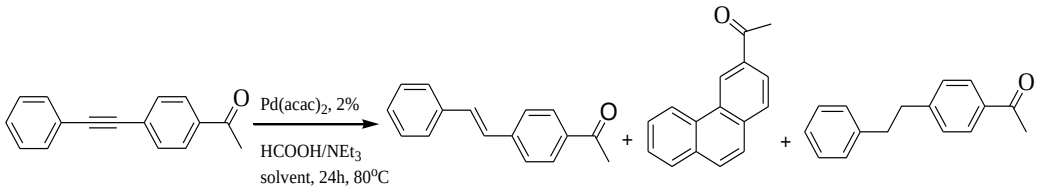


A **B** **C** **D**

Entry	T (°C)	Time (h)	Conversion [%]*	Ratio [%]*			
				A	**B**	**C**	**D**
1	60	7	100	-	48	52	-
2	60	24	100	-	31	69	-
3	80	7	100	-	4	96	-
4	80	24	100	-	-	100	-

Reaction conditions: THF, t (h), T (°C), [**A**] = 1.5 ×10^{-3} M, HCOOH (5 eq. compared to **A**), NEt_3 (5 eq. compared to **A**). *Determined by GC-MS

Table 3: Reduction of 4'-(phenylethynyl)acetophenone: effect of solvent



A **B** **C** **D**

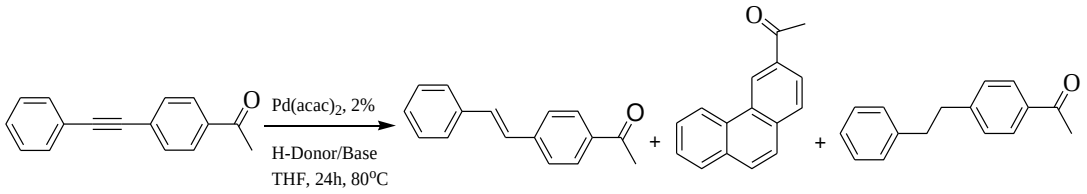
Entry	Solvent	Conversion [%]*	Ratio [%]*			
			A	**B**	**C**	**D**
1	Dioxane	100	-	100	-	-
2	Toluene	100	-	40	60	-
3	DCM	100	-	-	-	100
4	DMSO	100	-	66	34	-
5	THF	100	-	-	100	-

Reaction conditions: 24 h, 80 °C, [**A**] = 1.5 ×10^{-3} M, HCOOH (5 eq. compared to **A**), NEt_3 (5 eq. compared to **A**). *Determined by GC-MS.

As the choice of the solvent used in the transfer hydrogenation reaction has a significant effect, several experiments were conducted by deploying various solvents to investigate their impact on the reaction efficiency and selectivity. The corresponding results are shown in Table 3. The collected data shows that the selectivity of the reaction changed upon changing the solvent. Deploying dioxane as a solvent favored the total conversion of the yne-one starting material (**A**) to (*E*)-ene-one product **B** (Entry 1). However, 100% cyclic-one product **C** was obtained in THF after the complete conversion of the starting material (Entry 5). Nevertheless, a mixture of (*E*)-ene-one product **B** and cyclic-one product **C** was obtained using toluene or DMSO (Entry 2 & 4). On the other hand, the ane-one product **D** was solely formed using DCM (Entry 3), indicating the over-reduction of the yne-one starting material.

Based on these results, we subsequently turned our attention toward the hydrogen source in this transfer hydrogenation reaction. Various H-donors/base combinations were examined, and the results are shown in Table 4. In the presence of Et_3N base combined with formic acid, isopropanol, or dimethylformamide as H-donors, total conversion and excellent selectivity of the cyclic-one product **C** were obtained (Entry 1, 3, & 5). However, when formic acid was used as a H-donor in conjunction with K_2CO_3 base (Entry 2), the internal alkyne (**A**) was fully converted to **B**. On the other hand, selectivity was reduced and a mixture of two products was obtained in the presence of the DMF/KOH combination (Entry 4). In all cases, over-reduction was not detected.

Table 4: Reduction of 4'-(phenylethynyl)acetophenone: effect of H-donor/base

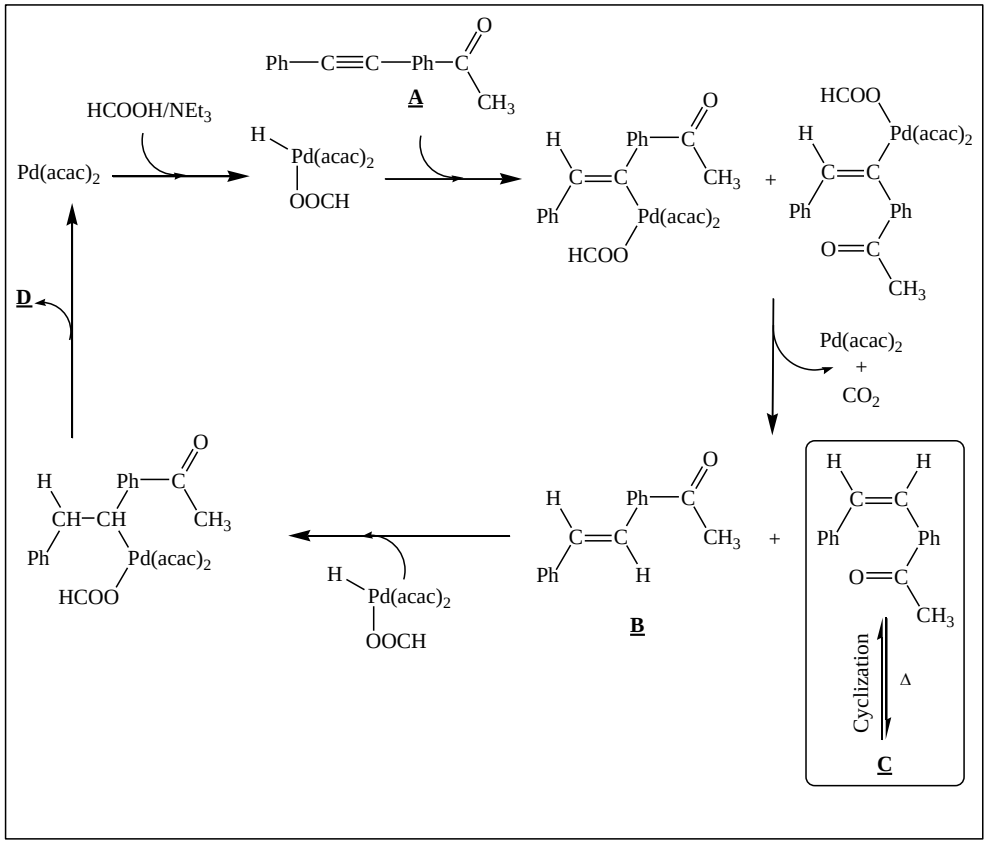


A **B** **C** **D**

Entry	H-Donor/Base	Conversion [%]*	Ratio [%]*			
			A	**B**	**C**	**D**
1	$HCOOH/Et_3N$	100	-	-	100	-
2	$HCOOH/K_2CO_3$	100	-	100	-	-
3	$iPrOH/Et_3N$	100	-	-	100	-
4	DMF/KOH	100	-	64	36	-
5	DMF/Et_3N	100	-	-	100	-

Reaction conditions: THF, 24 h, 80 °C, [**A**] = 1.5×10^{-3} M, H-donor (5 eq. compared to **A**), base (5 eq. compared to **A**). *Determined by GC-MS.

The present selective transfer hydrogenation mechanism is well developed and described in literature [3,15] and can be represented as shown in Scheme 2. In the presence of Et_3N, the formate ion is first coordinated to the palladium (II) complex. A palladium-alkene complex is selectively formed after introducing the internal alkyne (**A**). This intermediate is then decarboxylated, yielding the (*E*)-ene-one product (**B**) and/or the (*Z*)-ene-one product, which undergoes an electrocyclization at the studied temperature forming the cyclic-one product (**C**). Further hydrogen transfer leads to the ane-one product (**D**) formation, which was rarely observed in this study. Furthermore, and under all the studied conditions, the carbonyl group remained intact, and the reduction took place at the alkyne functionality only.



Scheme 2: Proposed mechanism of the catalyzed reduction of 4'-(phenylethynyl)acetophenone in the presence of HCOOH/Et_3N.

3. CONCLUSIONS

In this paper, we have demonstrated a convenient and easy-to-use catalytic-synthetic protocol for the selective transfer hydrogenation of 4'-(phenylethynyl)acetophenone using the stable and commercially available palladium acetylacetonate complex in the presence of formic acid and trimethylamine. This combination has shown a high stereo- and chemoselectivity, transforming the internal aromatic alkyne to either (*E*)-alkene or the acetylphenanthrene under the optimum conditions and with very high conversions. Besides forming the cyclic product in a single step, this catalytic system has unveiled many advantages, including the selective reduction of the internal alkyne over the ketone functional group that remained intact, as well as the rare over-reduction.

4. EXPERIMENTAL

4'-(phenylethynyl)acetophenone, palladium (II) acetate ($Pd(OAc)_2$), palladium (II) acetylacetonate ($Pd(acac)_2$), and palladium (II) chloride ($PdCl_2$) were supplied by Sigma-Aldrich. Formic acid (HCOOH) and triethylamine (Et_3N) were purchased from BDH. Dimethylformamide (DMF), isopropanol (i-PrOH), and potassium carbonate (K_2CO_3) were bought from VWR chemicals. The various solvents used in this study were supplied as follows: 1,4-dioxane (JT Baker), dichloromethane (DCM, Scharlau), tetrahydrofuran (THF, VWR chemicals), toluene (Merck), and dimethyl sulfoxide (DMSO, Merck). The silica gel used in purification and the ethyl acetate used as eluent were supplied from Sigma-Aldrich. The Gas Chromatography-Mass Spectrometry (GC-MS) analysis was conducted on GCQP2010-SHIMADZU. The Nuclear Magnetic Resonance (NMR) spectra were recorded on a Bruker AC 500 Spectrometer using d-chloroform ($CDCl_3$) as a solvent and methyl silane ($SiMe_4$) as reference. The chemical

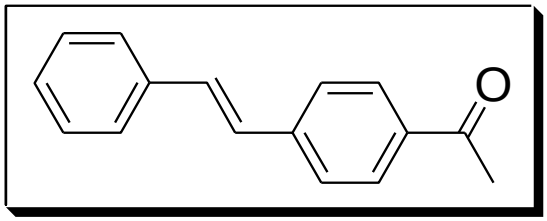
shifts and coupling constants are given in parts per million (ppm) and Hertz (Hz), respectively.

4.1 Typical reaction procedure

Palladium (II) catalyst was dissolved in the appropriate solvent and placed into a Schlenk tube under a nitrogen atmosphere. Then, the base and 4'-(phenylethynyl)acetophenone were introduced, and a solution of H-donor dissolved in a solvent was added dropwise. The reaction mixture was then heated at 60 or 80 ^{o}C and stirred for 7 or 24 h under nitrogen gas. After cooling to room temperature, the product formed was purified by column chromatography several times. The solvent was then evaporated, and a sample was analyzed by GC-MS to determine the nature of the product, conversion rate, and the ratio of the products. Each time, this typical procedure was repeated by varying one of the following experimental parameters: the catalyst, the solvent, the hydrogen donor, and the base. In addition, the products were characterized by ^{1}H NMR.

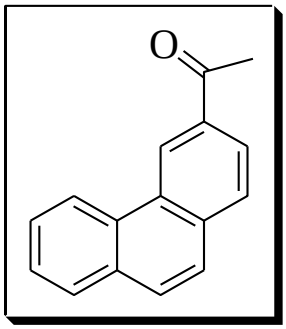
4.2. Characterization data of the products

(E)-1-(4-styrylphenyl)ethanone



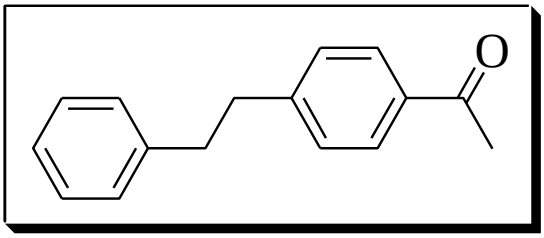
^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 8.43 (d, J = 8.2 Hz, 1H), 7.92 (d, J = 8.5 Hz, 1H), 7.61 (d, J = 8.0 Hz, 1H), 7.55 (m, 3H), 7.36 (m, 3H), 2.60 (s, 3H). **GC-MS *m/z*** (% relative intensity) 207 (100), 178 (85), 152 (25), 89 (20), 32 (20).

1-(phenanthrene-3-yl)ethenone



^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.81 (d, J = 8.2 Hz, 2H), 7.32 (d, J = 8.2 Hz, 2H), 7.23-7.26 (m, 5H), 6.72 (d, J = 12.3 Hz, 1H), 6.60 (d, J = 12.3 Hz, 1H), 2.60 (s, 3H). **GC-MS *m/z*** (% relative intensity) 205 (100), 176 (80), 151 (40), 88 (40), 75 (20), 44 (20), 32 (70).

1-{4-[2-phenylethyl] phenyl}ethanone



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^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.81 (d, J = 8.2 Hz, 2H), 7.32 (d, J = 8.2 Hz, 2H), 7.23-7.26 (m, 5H), 3.10 (m, 4H), 2.60 (s, 3H). **GC-MS *m/z*** (% relative intensity) 181 (10), 91 (100), 32 (20).

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REFERENCES

- Baráth, E. (2018). Hydrogen Transfer Reactions of Carbonyls, Alkynes, and Alkenes with Noble Metals in the Presence of Alcohols/Ethers and Amines as Hydrogen Donors, *Catalysts*, 8, 671.
- Chayya, S., El-Dakdouki, M.H., Hijazi, A., Younes, G., Ibrahim, G., Hachem, A., Alaaeddine, A. (2021). Selective Reduction of Aromatic Alkynes Catalyzed by Palladium with Formic Acid as the Hydride Source, *Current Organocatalysis*, 8, 353–361.
- Decker, D., Drexler, H.-J., Heller, D., Beweries, T. (2020). Homogeneous Catalytic Transfer Semihydrogenation of Alkynes – An Overview of Hydrogen Sources, Catalysts and Reaction Mechanisms, *Catalysis Science and Technology*, 10, 6449–6463.
- Gore, P.H., Kamonah, F.S. (1979). A New Synthesis of 4-Acetylphenanthrene, *Synthetic Communications*, 9, 377–382.
- Hauwert, P., Maestri, G., Sprengers, J.W., Catellani, M., Elsevier, C.J. (2008). Transfer Semihydrogenation of Alkynes Catalyzed by a Zero-Valent Palladium N-Heterocyclic Carbene Complex, *Angewandte Chemie International Edition*, 47, 3223–3226.
- Huang, W., Li, J., Chen Q., Cai, M. (2019). Highly Stereoselective Heterogeneous Palladium-Catalyzed Transfer Semihydrogenation of Internal Alkynes to Access *cis*-Alkenes, *Journal of Chemical Research*, 43, 189–195.
- Iwasaki, R., Tanaka, E., Ichihashi, T., Idemoto, Y., Endo, K. (2018). Semireduction of Alkynes Using Formic Acid with Reusable Pd-Catalysts, *Journal of Organic Chemistry*, **83**, 13574–13579.
- Kusy, R., Grela, K. (2016). E- and Z-Selective Transfer Semihydrogenation of Alkynes Catalyzed by Standard Ruthenium Olefin Metathesis Catalysts, *Organic Letters*, 18, 6196–6199.
- Li, J., Hua, R. (2011). Stereodivergent Ruthenium-Catalyzed Transfer Semihydrogenation of Diaryl Alkynes, *Chemistry – A European Journal*, 17, 8462–8465.
- Li, J., Hua, R., Liu, T. (2010). Highly Chemo- and Stereoselective Palladium-Catalyzed Transfer Semihydrogenation of Internal Alkynes Affording cis-Alkenes, *Journal of Organic Chemistry*, 75, 2966–2970.
- Li, J., Zeng, R., Hua, R. (2012). $HCOOH/RuCl_3{\cdot}3H_2O$: An Efficient Hydrogen Transfer System for Highly Chemo- and Stereoselective Semihydrogenation of Diaryl Acetylenes Affording *trans*-Stilbenes, *Current Catalysis*, 1, 125–128.
- Li, S.-S., Tao, L., Wang, F.-Z.-R., Liu, Y.-M., Cao, Y. (2016). Heterogeneous Gold-Catalyzed Selective Semireduction of Alkynes using Formic Acid as Hydrogen Source, *Advanced Synthesis & Catalysis*, 358, 1410–1416.
- Moran, M.J., Martina, K., Bieliunas, V., Baricco, F., Tagliapietra, S., Berlier, G., De Borggraeve, W.M., Cravotto, G. (2021). Copper(0) nanoparticle catalyzed Z-Selective Transfer Semihydrogenation of Internal Alkynes, *Advanced Synthesis & Catalysis*, 363, 2850–2860.
- Oger, C., Balas, L., Durand, T., Galano, J.-M. (2013). Are Alkyne Reductions Chemo-, Regio-, and Stereoselective Enough To Provide Pure (Z)-Olefins in Polyfunctionalized Bioactive Molecules?, *Chemical Reviews*, 113, 1313–1350.
- Reyes-Sánchez, A., Cañavera-Buelvas, F., Barrios-Francisco, R., Cifuentes-Vaca, O.L., Flores-Alamo, M., García, J.J. (2011). Nickel-Catalyzed Transfer Semihydrogenation and Hydroamination of Aromatic Alkynes Using Amines As Hydrogen Donors, *Organometallics*, 30, 3340–3345.
- Richmond, E., Moran, J. (2015). Ligand Control of E/Z Selectivity in Nickel-Catalyzed Transfer Hydrogenative Alkyne Semireduction, *Journal of Organic Chemistry*, 80, 6922–6929.

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