*Reductive C–C Coupling Reaction*

# A New Catalytic C–C Bond-Forming Hydrogenation: Reductive Coupling of Dienes and Glyoxals under Catalytic Hydrogenation Conditions**

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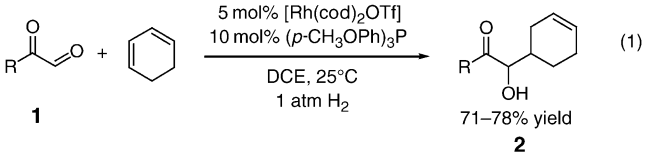
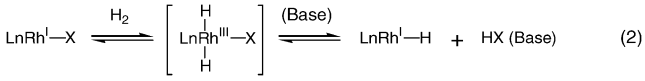
Catalytic reductive C–C bond formation is emerging as an important class of chemical transformation.[1–5] Recently, progress has been made with regard to the nucleophilic activation of diverse precursors containing π bonds (alkenes,[1] alkynes,[2] enones,[3,8] and dienes[4,5]) in regard to catalytic reductive couplings to carbonyl partners. Hydrometallative transformations of this type employ silanes, alanes, and boranes as the terminal reductant, which results in the generation of stoichiometric by-products. While use of elemental hydrogen as the terminal reductant would enable completely atom-economical variants of these catalytic transformations, C–C bond formation has only been observed under hydrogenation conditions in the case of alkenes hydroformylation and Fischer–Tropsch-type processes, that is, catalytic processes involving migratory insertion of carbon monoxide.[6,7]

Recently, we described a catalytic method for the intra- and intermolecular reductive coupling of enone pronucleophiles with aldehyde and ketone partners under hydrogenation conditions.[8] These results demonstrate that the organometallic intermediates obtained in the course of catalytic hydrogenation are subject to electrophilic trapping, thus establishing nucleophilic activation under hydrogenation conditions as a novel pattern of reactivity and encouraging us to explore related catalytic C–C bond-forming hydrogenations. Here, we describe a new example of this uncommon reaction type: the reductive coupling of dienes to aryl and alkyl glyoxal partners under hydrogenation conditions [Eq. (1)]. In addition we report on mechanistic studies that support an unusual catalytic mechanism.




**1** **2** (1)

In the course of developing the rhodium-catalyzed reductive coupling of enones to aldehydes and ketones under hydrogenation conditions, it was recognized that simple conjugate reduction manifolds are attenuated upon adoption of monohydride-based catalytic cycles induced through formal heterolytic activation of elemental hydrogen [Eq. (2)].[8] Cationic rhodium complexes are especially effective at promoting heterolytic activation of elemental hydrogen,[9,10] owing to the acidity of the dihydride intermediates that result upon oxidative addition.[11]




(2)

Given the elegant studies of Osborn and Schrock, who reported the selective hydrogenation of conjugated dienes to monoolefins using cationic rhodium catalysts,[10a] we were interested in determining whether the organometallic intermediates derived upon hydrogenation of dienes are subject to electrophilic trapping by exogenous carbonyl partners. Consequently, the reductive condensation of 1,3-cyclohexadiene and phenyl-substituted glyoxal **1a** (R = Ph) was examined under hydrogenation conditions. Initial studies employing

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Wilkinson's catalyst reveal simple reduction of both 1,3-cyclohexadiene and glyoxal **1a** (Table 1, entry 1). In accordance with the aforementioned analysis, rhodium complexes with cationic character should promote monohydride-based catalytic cycles, thus attenuating simple reduction manifolds.

***Table 1:*** Reductive condensation of 1,3-cyclohexadiene and **1a** (R = Ph) [Eq. (1)].[a]

| Entry | Catalyst (mol%) | Ligand (mol%) | Yield [%][b] |
|---|---|---|---|
| 1 | $[Rh(PPh_3)_3Cl]$ (10) | – | –[c] |
| 2 | $[Rh(cod)_3OTf]$ (10) | $Ph_3P$ (20) | 61 |
| 3 | $[Rh(cod)_3OTf]$ (10) | $(p\text{-}CF_3Ph)_3P$ (20) | 24 |
| 4 | $[Rh(cod)_3OTf]$ (10) | $(p\text{-}CH_3OPh)_3P$ (20) | 77 |
| 5 | $[Rh(cod)_3BF_4]$ (10) | $(p\text{-}CH_3OPh)_3P$ (20) | 79 |
| 6 | $[Rh(cod)_3OTf]$ (5) | $(p\text{-}CH_3OPh)_3P$ (20) | 76 |

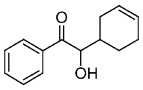
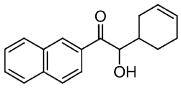
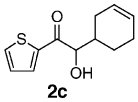
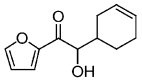
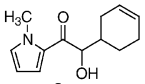
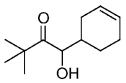
[a] In all cases, 1 equiv phenyl glyoxal **1a** and 5 equiv 1,3-cyclohexadiene were employed. [b] Yield of product after purification by silica gel chromatography. [c] Simple reduction of **1a** was observed.

Indeed, the reductive coupling product **2a** (R = Ph) is obtained in 61% yield when $[Rh(cod)_2OTf]$ (cod = cyclooctadiene, Tf = trifluoromethanesulfonyl) is used in conjunction with $PPh_3$ (Table 1, entry 2). Profound ligand electronic effects are observed in reactions with several *para*-substituted triphenylphosphane derivatives. Whereas reactions with $(p\text{-}CF_3Ph)_3P$ as the ligand provide **2a** in 24% yield, use of $(p\text{-}CH_3OPh)_3P$ provides **2a** in 77% yield (Table 1, entries 3 and 4). Precatalysts derived from other cationic rhodium sources, such as $[Rh(cod)_2BF_4]$, exhibit similar efficiencies when used in conjunction with $(p\text{-}CH_3OPh)_3P$ (Table 1, entry 5). Comparable yields are obtained with 5-mol% loadings of the commercially available precatalyst $[Rh(cod)_2OTf]$ with $(p\text{-}CH_3OPh)_3P$ (Table 1, entry 6). In all cases **2a** was obtained as a roughly equimolar mixture of diastereomers. The structure of **2a** was corroborated by single-crystal X-ray diffraction analysis. Bidentate phosphane ligands were found to retard the rate of reaction, resulting in diminished yields of **2a**.

Under these optimized conditions (5 mol% $[Rh(cod)_2OTf]$, 10 mol% $(p\text{-}CH_3OPh)_3P$, ambient temperature and pressure, 1,2-dichloroethane (DCE)), the catalytic reductive coupling of 1,3-cyclohexadiene with diverse glyoxal partners was examined. Both aryl and heteroaryl glyoxals provide reductive coupling products **2a**–**2e** (Table 2) in good yield. Aliphatic glyoxal partners also participate in the reaction, as evidenced by the formation of *tert*-butyl-substituted α-hydroxy ketone **2f**. Reductive condensation of 1,3-cyclohexadiene with ethyl glyoxalate does not occur under these conditions. Additionally, the use of acyclic dienes gave reductive coupling products in diminished yield; for example, the coupling of 2,4-hexadiene with phenyl glyoxal proceeds in 52% yield. In all cases reductive condensation products **2a**–**2f** were obtained as roughly equimolar mixtures of diastereomers (Table 2).

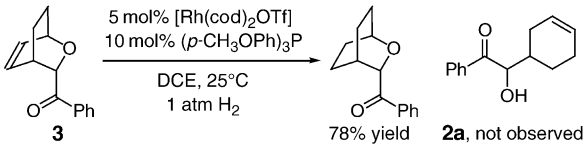
To address the design of second-generation catalyst systems, an understanding of the catalytic mechanism is required. As Rh-catalyzed reductive ring-opening of oxabicyclic alkenes is well known,[12] it was important to determine whether the reductive coupling proceeds through initial

***Table 2:*** Reductive condensation of 1,3-cyclohexadiene and assorted glyoxals.[a]

| Product | Yield | Ratio of isomers |
|---|---|---|
|  **2a** | 76% | 1:1.6 |
|  **2b** | 77% | 1:1.5 |
|  **2c** | 74% | 1:1.4 |
|  **2d** | 78% | 1:1.3 |
|  **2e** | 73% | 1:1.4 |
|  **2f** | 71% | 1:1.6 |

[a] Procedure: To a solution of glyoxal (100 mol%) and 1,3-cyclohexadiene (500 mol%) in DCE at ambient temperature was added $[Rh(cod)_2OTf]$ (5 mol%) and $(p\text{-}CH_3OPh)_3P$ (10 mol%). The system was purged with hydrogen gas, and the reaction was allowed to stir at 25 °C under 1 atm $H_2$ until the substrate was completely consumed. The reaction mixture was evaporated onto silica gel and the product was purified by silica gel chromatography.

hetero-Diels–Alder cycloaddition. Exposure of 1,3-cyclohexadiene to phenyl glyoxal in dichloroethane at ambient temperature does not produce the Diels–Alder adduct. Nor is the Diels–Alder adduct obtained upon exposure of 1,3-cyclohexadiene to phenyl glyoxal under standard coupling conditions but without hydrogen. Unreacted starting materials were observed in these experiments. An independent synthesis of the Diels–Alder adduct of phenyl glyoxal and 1,3-cyclohexadiene was carried out.[13] Subjection of the Diels–Alder adduct **3** to the reductive coupling conditions does not provide **2a**. Instead, the simple alkene hydrogenation product is obtained in 78% yield [Eq. (3)]. These results



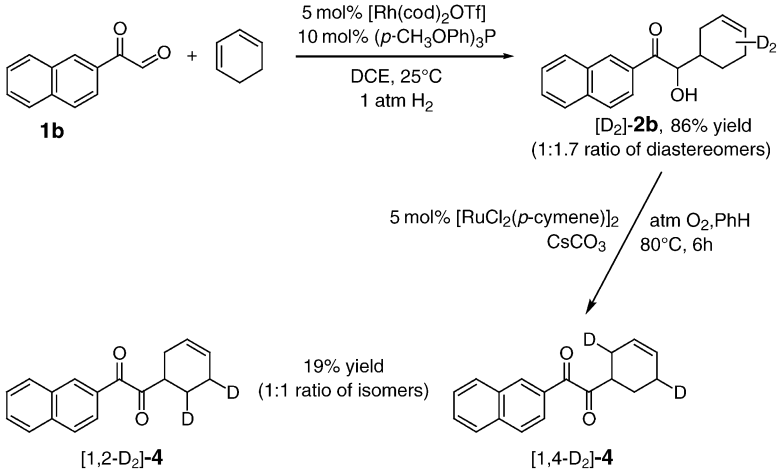

(3)

suggest that catalytic reductive coupling under hydrogenation conditions does not proceed through the intermediacy of a Diels–Alder adduct.

Surprisingly, the reductive condensation of 1,3-cyclohexadiene with naphthyl glyoxal **1b** under one atmosphere of $D_2$

results in the incorporation of precisely two deuterium atoms, as revealed by high-resolution mass spectrometric analysis of the product of reductive condensation, [$D_2$]-**2b** (Scheme 1). The regio- and stereochemistry of the deuterium incorporation could not be determined by two-dimensional $^1$H NMR analysis. Thus, for the purpose of structural assignment, [$D_2$]-**2b** was converted into the corresponding α-diketone,[14] which was shown to be an equimolar mixture of the 1,2- and 1,4-dideuterated isomers [1,2-$D_2$]-**4** and [1,4-$D_2$]-**4** (Scheme 1). The relative stereochemistry of these compounds could not be assigned.




***Scheme 1.*** Catalytic reductive condensation of **1b** with 1,3-cyclohexadiene under an atmosphere of $D_2$.

Based on the collective results, the catalytic cycle proposed in Scheme 2 serves as a working mechanistic hypothesis. The starting $Rh^I$ deuteride complex is derived as illustrated in Equation (2). Deuteriometalation of the diene affords the homoallyl rhodium intermediate **A**, which adds to the glyoxal to afford the rhodium alkoxide **B**. The indicated regiochemistry of the C–C bond formation is consistent with that observed by Loh et al. in the nickel-catalyzed reductive coupling of 1,3-cyclohexadiene with aldehydes.[5e] Allylic C–H insertion gives the π-allyl intermediate **C**, which upon O–H reductive elimination gives intermediate **D**. Finally, the catalytic cycle is completed by oxidative addition of elemental deuterium to give dideuteride **E** followed by C–D reductive elimination. The intermediacy of π-allyls **C**–**E** is required to account for the incorporation of precisely two deuterium atoms in the equimolar mixture of 1,2- and 1,4-dideuterated isomers. As [1,2-$D_2$]-**4** and [1,4-$D_2$]-**4** may be regarded as alkene isomers, it is noteworthy that the isomerization of alkenes through the intermediacy of π-allyls has been documented.[15]

Subjecting **2b** to standard conditions for catalytic reductive coupling under an atmosphere of $D_2$ does not provide [$D_2$]-**2b**. Nor does exposure of [Rh(**2b**)(cod)]$_2$ in dichloroethane solvent to an atmosphere of $D_2$ provide [$D_2$]-**2b**. Rather, in each case, the product of alkene hydrogenation is obtained. These results are consistent with the notion that 1,3-cyclohexadiene serves as a ligand for the catalytically active metal complex in the reductive coupling of 1,3-cyclohexadiene with glyoxals. The fact that reductive coupling product **2b** is not overreduced under the conditions in which it is formed, yet is readily hydrogenated when resubmitted to the reductive coupling conditions in the absence of 1,3-cyclohexadiene is also consistent with this hypothesis. Indeed, Mori et al. have observed that the addition of exogenous 1,3-cyclohexadiene induces 1,4-regiochemistry in related nickel-promoted diene/aldehyde cyclizations.[4b]

In summary, while catalytic homogeneous hydrogenation has been practiced routinely since Calvin's initial discovery in 1938,[16] to our knowledge, the present studies are the first examples of the catalytic nucleophilic activation of simple π-unsaturated precursors under the conditions of catalytic hydrogenation in the absence of carbon monoxide. The scope of this transformation with the present catalyst system appears limited to the reductive coupling of cyclohexadiene to aryl, heteroaryl, and alkyl glyoxals. Future studies will be devoted to expanding the scope of this new reaction type, including the development of related reductive couplings to alkyne and alkene partners.

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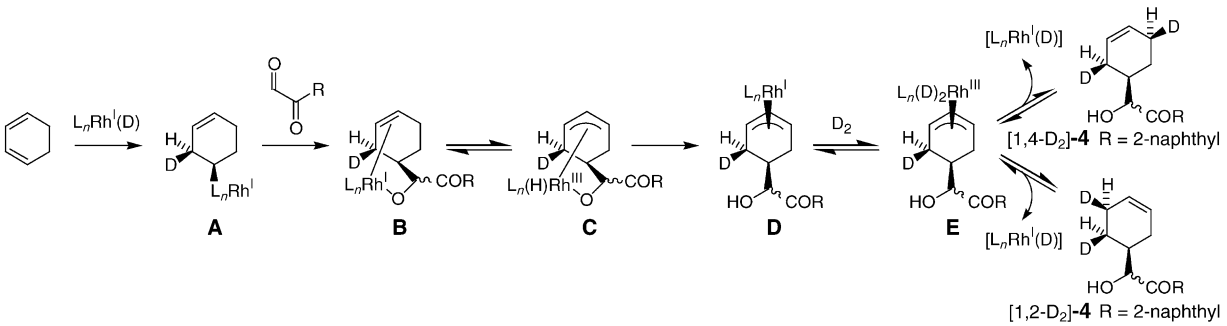
**Keywords:** C–C coupling · hydrogenation · reduction · rhodium




***Scheme 2.*** A plausible catalytic cycle accounting for the formation of [1,2-$D_2$]-**4** and [1,4-$D_2$]-**4**.

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