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Formic Acid Mediated Direct *Z*-Selective Reductive Coupling of Dienes and Aldehydes

Christopher Cooze, Raphael Dada, and Rylan J. Lundgren*[a]

Abstract: Methods for the addition of unsaturated nucleophiles to carbonyls to generate *Z*-olefin products remain rare and often require alkyl borane or zinc reductants, limiting their utility. We demonstrate that formic acid mediates the Rh-catalyzed, *Z*-selective coupling of dienes and aldehydes. The process is distinguished by broad tolerance towards reducible or electrophilic groups. Kinetic analysis suggests that generation of the catalytically active Rh-intermediate by ligand dissociation is the rate determining step. The rapid generation and trapping of Rh-allyl intermediates is key to preventing chain-walking isomerization events that plague related protocols. Insights gained through this study may have wider implications in selective metal-catalyzed hydrofunctionalization reactions.

Introduction

The addition of carbon-based nucleophiles to carbonyl units is one of the most fundamental reactions in synthetic organic chemistry. Since organometallic reagents often require an additional preparative step to obtain and exhibit limited functional group compatibility,[1] reductive coupling strategies that use olefins as pro-nucleophiles can streamline synthetic routes that involve carbonyl alkylation.[2] Early olefin-aldehyde reductive coupling protocols employed aggressive reducing agents like alkyl borane or alkyl zinc reagents to generate the metal hydride intermediate required for nucleophile formation. More recently, the use of milder reductants, such as molecular hydrogen or isopropanol, in combination with suitable transition metal catalysts, has been pioneered by Krische to dramatically broadened the scope and utility of olefin-based carbonyl additions.[3] Despite advances in catalytic carbonyl reductive coupling processes,[4] addition reactions involving diene or alkyne pro-nucleophiles that generate less thermodynamically stable *Z*-olefin products remain rare.[5] The *Z*-selective coupling of aldehydes and dienes can be promoted by Rh-based catalysts, however the requirement for stoichiometric Et_3B to generate a Rh-hydride intermediate limits chemoselectivity.[6] Under these conditions, products derived from chain-walking isomerization are observed,[6b] restricting access to a narrow range of product classes.[7] The lack of generality in *Z*-selective diene additions highlights the difficulty in controlling both site- and stereoselectivity in catalytic diene functionalization,[8] particularly in those reactions that generate thermodynamically less favorable product isomers.[9]

From a mechanistic perspective, improving reductive chemoselectivity while inhibiting chain-walking events in diene-aldehyde coupling can potentially be realized by tailoring the reactivity of the Rh-intermediates involved in the reaction pathway. Specifically, if both diene insertion into the Rh–hydride catalyst *and* electrophilic capture of the resultant Rh-allyl outpace undesirable isomerization, β-hydride elimination, or other reductive processes, a direct and selective coupling process should be possible. We recently reported that formic acid acts as reducing agent for the *Z*-selective 1,6-reduction of dienyl esters[10] and questioned whether this pathway could be diverted to enable reductive coupling. Formic acid has been used as a reductant for metal-catalyzed C-C bond forming carbonyl allylation and vinylation processes.[11] In this report, we demonstrate that mixtures of Rh-precatalysts, 1,5-cyclooctadiene (COD), and PPh_3 mediate the isomerization-free, stereoselective addition of diene-derived nucleophiles to aldehydes (Figure 1). The process delivers substituted *Z*-homoallylic alcohols with typically >95:5 *syn*- and *Z*-selectivity without interference from other reducible functionality. The role of each of the catalyst components is delineated through kinetic studies; generation of the catalytically active Rh-species is the overall rate determining step which helps to impart high selectivity at reduced catalysts loadings.

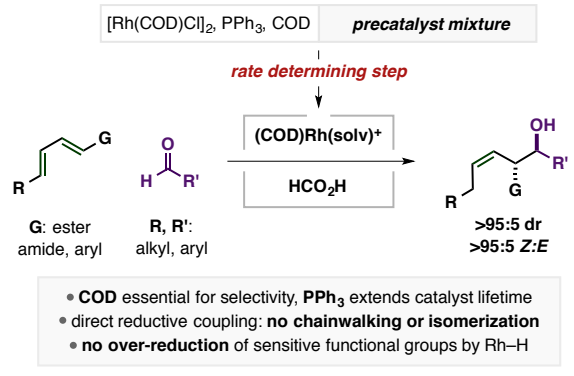

Figure 1. Formic acid enables the Rh-catalyzed *Z*-selective reductive coupling of dienes and aldehydes without isomerization or competitive reduction of other functional groups.

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Results and Discussion

We surveyed a range of experimental conditions to ultimately find that dienoate **1a** can be reductively coupled to benzaldehyde using formic acid/diisopropylethylamine (DIPEA) in the presence of $[Rh(COD)Cl]_2$ and PPh_3 to generate *Z*-homoallylic alcohol **2a** as a single isomer in good yield (>98:2 *syn*/*anti* and *Z*/*E*, 77% yield). Figure 2a provides an overview of important reaction parameters. The use of other Rh-based catalysts, including Wilkinson's catalyst or $[Rh(COE)Cl]_2$, as well as $[Ir(COD)Cl]_2$ consumed diene without significant product formation, while other transition metal complexes (Ru-, Pd-, and Cu-based) were completely inactive. Catalyst loadings as low as 0.25 mol% $[Rh(COD)Cl]_2$ gave good yields when additional COD was added. DIPEA was essential to observe good yields of reductive coupling product over diene transfer hydrogenation. The stereochemistry of the diene starting material (*E,E*-, *Z,E*- or *E,Z*-) had minimal impact on reaction outcomes and rates, allowing for the use of crude mixtures of substrates obtained from standard diene syntheses.[12]

The reductive chemoselectivity of the reaction was assessed by a comprehensive functional group compatibility screen (Figure 2b), which demonstrated that related carbonyl groups (ketones, esters, amides), activated and unactivated olefins, other dienes, alkyl halides, epoxides, and protic NH- and OH-groups are well tolerated (>60% product yield with one equivalent of additive and >85% recovery of additive, see the SI for complete details). Of the functional groups screened, only alkynes and alkyl bromides were impacted under the standard reaction conditions.

The formic acid mediated coupling process yields products of direct aldehyde *Z*-allylrhodation without isomerization (Figure 2c). For example, diester **1b** underwent reaction to give a single coupling product in 73% yield, chain-walking and addition adjacent to the remote ester was not observed. Even where there is a clear thermodynamic driving force for isomerization, like in the cases of ester-tethered aryl diene **1c**, only direct coupling product **2c** is obtained, contrasting approaches with alternative reducing agents.[6b]

The role of the catalyst components was elucidated by mechanistic studies (Figure 3). Overall, the process exhibits pseudo zero-order kinetics and is not positive order in any of the substrate components (Figure 3a, essentially zero order in aldehyde and formic acid/DIPEA, partial negative order in diene, see the SI for plots).[13] The reaction is positive order in Rh and COD, while is negative order in PPh_3. We rationalize these observations by proposing that diene substrate, COD, and PPh_3 ligate Rh in various species that undergo ligand exchange processes. Most of the Rh-species exist as off-cycle intermediates and the active species that enters the catalytic cycle is likely a solvated $Rh(COD)^+$. The generation of this species by ligand dissociation is rate determining and subsequent reaction

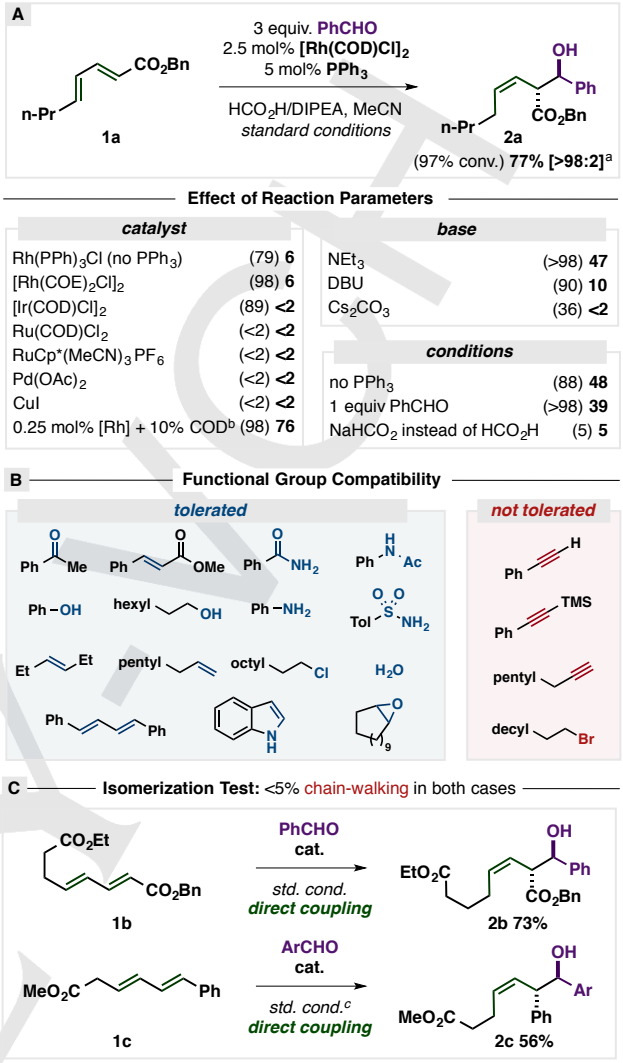

Figure 2. A Effect of reaction parameters on the Rh-catalyzed formic acid-mediated reductive coupling. **B** Functional group compatibility, one equivalent of additive, tolerated indicates >60% product yield and >85% additive recovery. **C** Direct reductive coupling of dienes that can undergo isomerization prior to addition to the aldehyde. Conversions (indicated in parentheses) and yields (indicated in bold) determined by calibrated ^1H NMR spectroscopy, 0.2-0.5 mmol scale, 0.25 M at 35 °C, 1.2 equiv. of HCO_2H unless otherwise noted. Ar = 4-$CF_3C_6H_4$. [a] Isolated yield. [b] At 45 °C. [c] 1.7 equiv. of HCO_2H.

with formate generates a Rh–H to initiate the reductive coupling of substrates. COD is essential for reactivity, $[Rh(COE)_2Cl]_2$ or $[Rh(ethylene)_2Cl]_2$ are inactive until COD is added. The validity of ancillary diene ligated Rh intermediates being involved in the catalytic cycle was confirmed by the observation of modest enantio-induction by use of structurally related chiral diene ligands in place of COD.[13c] The role of phosphine ligand is to prevent the irreversible decomposition of off-cycle Rh-species under the reductive conditions (Figure 3b). While PPh_3 slows the rate of reaction, its presence prevents precipitation of Rh from solution, an event that leads to an erosion in selectivity. The impact of PPh_3 and COD are more dramatic at reduced catalyst

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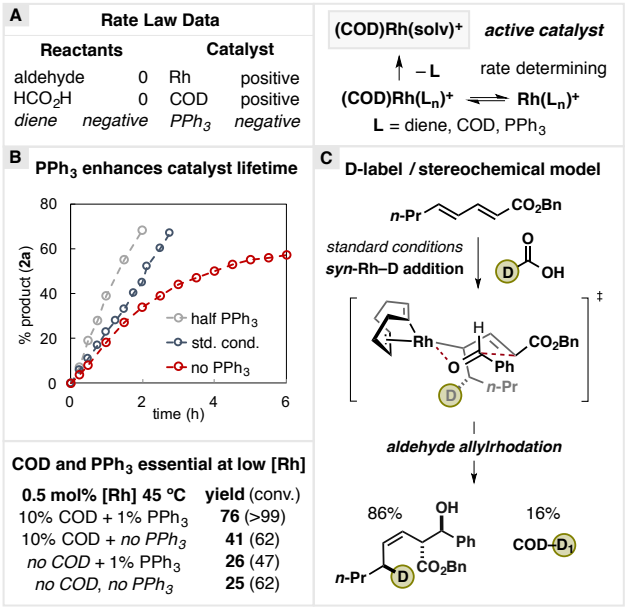

Figure 3. A Reaction rate law data and mechanistic proposal that generation of the catalytically active (COD)Rh(solv)+ is the overall rate determining step. **B** Effect of PPh_3 concentration on reaction rate and overall efficiency. **C** D-labelling studies give products from *syn*-Rh–D addition and allylrhodation, some of the D-label is incorporated into COD. Unless noted, reactions conducted under standard conditions noted in Figure 2 except at 50 °C.

loadings, where both reaction rates and selectivities are reduced without the co-additives (Figure 3b, see the SI for a more detailed plot and analysis). Experiments using formyl labelled d_1-formic acid gave results consistent with a *syn*-hydrorhodation of diene substrate followed by aldehyde allylrhodation that occurs via a chair-like transition state (Figure 3c).[6] No D-label was found at any other position; however, D-label was found incorporated into

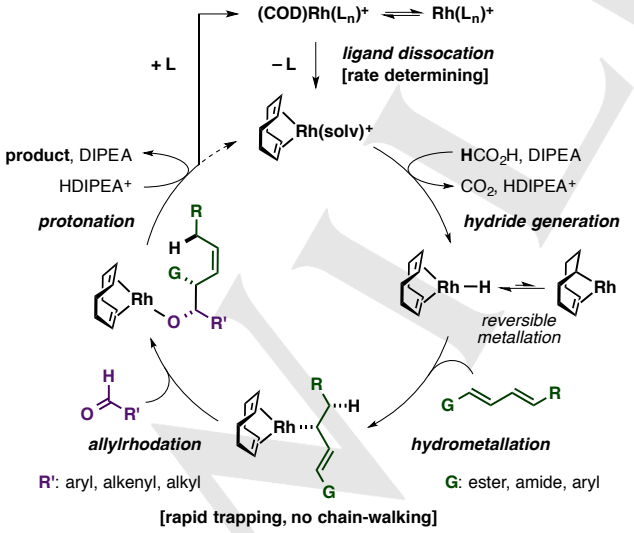

Figure 4. Complete catalytic cycle for the formic acid mediate reductive coupling of dienes and aldehydes. L = PPh_3, diene substrate or COD, solv = MeCN. Steps are shown as irreversible for clarity. See the SI for additional details.

COD, suggesting that while the diene substrate does not undergo reversible Rh–hydride insertion/β-hydride elimination, the ancillary diene ligand can, further demonstrating the importance of the COD ligand framework on catalysis. Figure 4 provides a complete potential catalytic cycle. These individual steps likely mirror those in reductive coupling reactions employing Et_3B, with the notable exception that catalyst generation is the rate determining step and the Rh-allyl species is trapped faster than undesirable isomerization events. Upon product release from the catalyst, Rh is likely re-trapped by PPh_3 (at higher loadings, PPh_3 significantly slow the reaction rate, see the SI for details).

The mechanistic features of the reductive coupling allow for the use of a broad range of diene and aldehyde partners with functional groups that would be incompatible with more aggressively reducing conditions (Figure 5). Alkyl substituted dienoates, including those with bulky groups (**2f**, **2g**), isolated alkene units (**2h**, **2m**), halogen (**2i**), nitrile (**2j**), carbamates and imides (**2k**, **2n**), ester, and (hetero)aryl substitution undergo reaction to give products with good to moderate yields and uniformly high *syn*- and *Z*-selectivity. The aryl aldehyde partner can take on a range of electronic properties (**2r**, **2s**; more electron-poor aryl aldehydes react selectively in competition studies, see the SI for details) or contain boronic ester (**2t**), aryl halide (**2u**, **2v**, **2w**, **2z**), or reducible functional groups (nitrile **2y**, ketone **2aa**, or nitro **2ae**), as well as heterocyclic groups (**2ab**, **2ac**). The reaction accommodates a range of ester groups, including *i*-Pr (**2af**), *t*-Bu (**2ag**), and more complex alkene (**2ah**, **2ai**), carbamates (**2aj**, **2ak**), alkyl chloride (**2al**) or polyfunctionalized groups (**2am**). Aryl dienes are reductively coupled to aldehydes with similar efficiency and selectivity, including those with alcohol (**2ao**), ester (**2c**), nitrile (**2aq**), and ketone groups (**2ar**). Weinreb (**2as**) and morpholine (**2at**) dienyl amides are viable substrates, as are alkyl (**2au**, **2av**) or α,β-unsaturated aldehydes (**2aw**).[13d]

The value of the reaction to generate complex bio-active molecules was demonstrated by the diastereoselective preparation of diarylmethane **6**, a key intermediate in the synthesis of a glucagon receptor antagonist (Figure 5). The carbon–carbon bond framework was readily obtained by reductive coupling of diene **3** with 4-chlorobenzaldehyde using 1 mol% $[Rh(COD)Cl]_2$ followed by alkene hydrogenation and ester hydrolysis to give **4** in 69% overall yield over three steps. Friedel–Crafts alkylation of the alcohol with substituted indole **5** delivers the target molecule **6** in 76% yield, which can be converted to the drug-candidate via an established protocol.[14]

The stereochemically defined *Z*-allylic alcohols generated by formic acid mediated reductive coupling are useful building blocks for more complex fragments (Figure 6). Straight-forward access to 2,5-dihydrofurans (**7**),[15] epoxide[16] and aziridine[17] stereotetrads (**8**, **9**), tertiary alcohols (**10**),[18] and tetrasubstituted tetrahydrofurans (**11**)[12] is possible by the high-yielding stereoselective functionalization of product **2a** by standard synthetic protocols.

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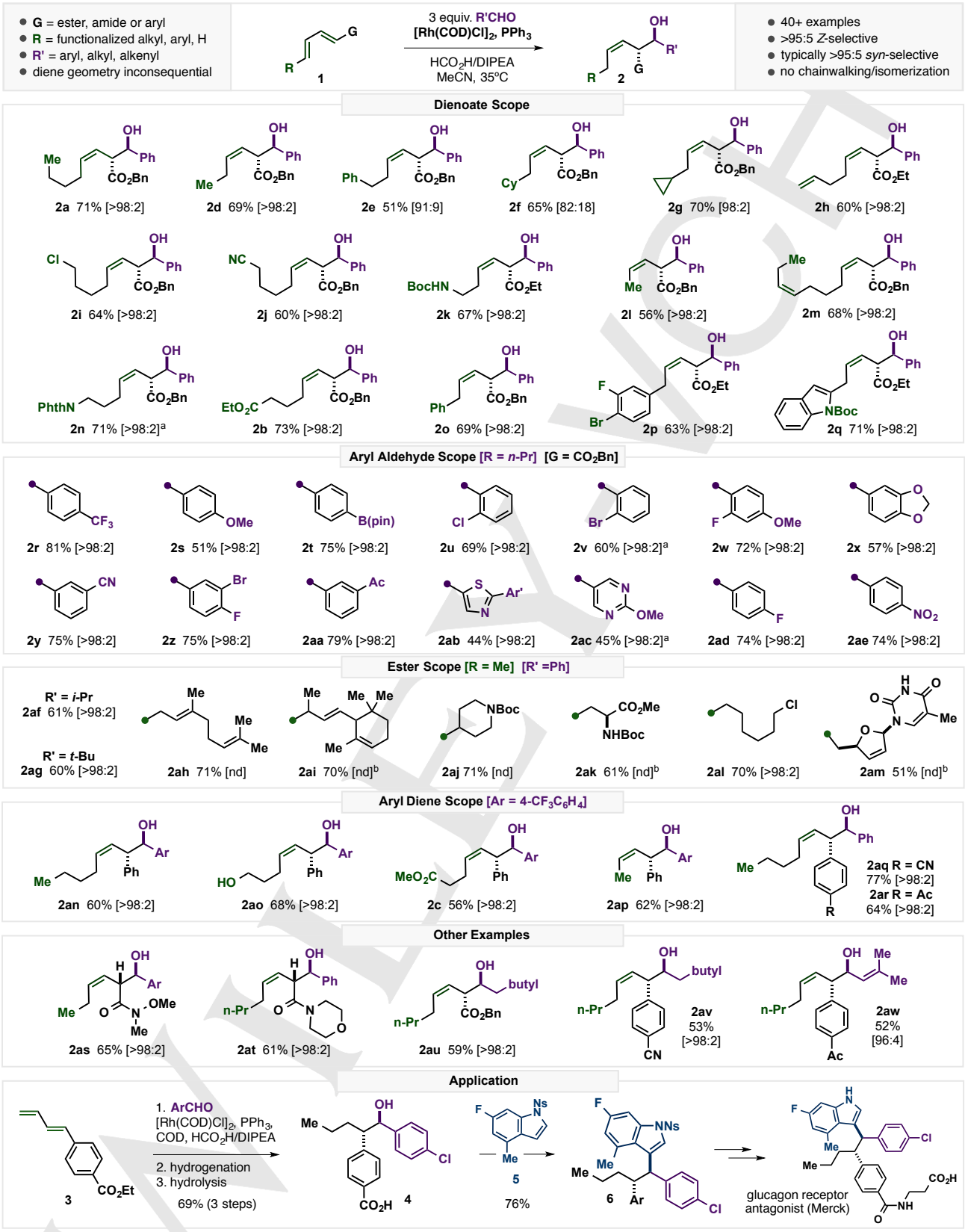

Figure 5. Scope for the formic acid mediated reductive coupling of dienes and aldehydes. Yields are of isolated material under standard conditions (Fig. 2). See the SI for examples at lower [Rh] loading and minor modifications conditions dependent on substrate. Ar' = 4-$CF_3C_6H_4$, *dr* with chiral esters is ~1:1. [n.d] = crude reaction mixture *dr* could not be measured, *syn dr* of isolated material is >95:5.

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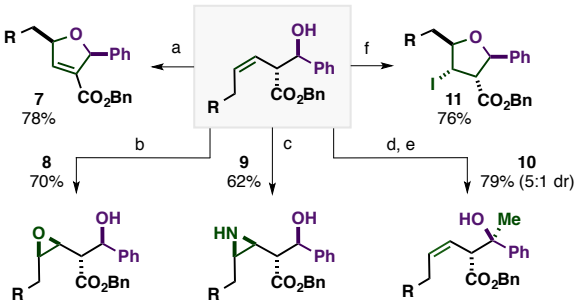

Figure 6. Derivatization of *Z*-β-ester homoallylic alcohols. a) 10% Ph_2Se_2, $(NH_4)_2S_2O_8$, b) 2% $VO(acac)_2$, t-BuO_2H, c) 2% $Rh_2(esp)_2$, hydroxylamine O-sulfonic acid, d) Dess-Martin periodinane e) $AlMe_3$, f) I_2, $NaHCO_3$. R = *n*-Pr, see SI for complete details.

Conclusion

The Rh-catalyzed, formic acid mediated reductive coupling of dienes and aldehydes provides a direct route to stereochemically defined *Z*-homoallylic alcohols. The mildly reducing conditions allow for tolerance towards functional groups that would interfere with organometallic reagents or highly polarized hydride donors. A complete absence of chain-walking isomerization is facilitated by comparatively slow liberation of the active catalyst species followed by rapid Rh–H insertion and trapping. This general concept should be amendable to related chemoselective olefin hydrofunctionalization processes.

Experimental Section

General Procedure: In an atmosphere controlled glovebox, $[Rh(COD)Cl]_2$ (6.2 mg, 0.0125 mmol, 0.025 equiv.) and PPh_3 (6.6 mg, 0.025 mmol, 0.05 equiv.) were weighed into separate one dram vials. To the vial containing $[Rh(COD)Cl]_2$ was added MeCN (1 mL) and the solution was transferred into the vial containing PPh_3. MeCN (0.4 mL) was used to wash the remaining Rh solution into the vial containing the PPh_3 catalyst mixture. To a separate one dram vial was weighed diene (0.5 mmol, 1 equiv.) followed by aldehyde (1.5 mmol, 3 equiv.). To this mixture was transferred the catalyst solution using MeCN (0.3 mL) to rinse the remaining solution into the reaction mixture. DIPEA (174 μL, 1 mmol, 2 equiv.) was added followed by a freshly prepared 2 M HCO_2H solution (0.3 mL, 0.6 mmol, 1.2 equiv). A stir bar was added to the vial which was capped with a PTFE-lined cap, taken out of the glovebox and placed in an aluminum block heated to 35 °C. The reaction progress was monitored periodically via ^{1}H NMR. At >95% conversion, the solution was diluted with toluene, concentrated and purified by silica gel chromatography. Reactions set up without the use of a glovebox and conducted under air provide similar results. See the SI for complete details.

Acknowledgements

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Keywords: homogeneous catalysis • reductive coupling • chemoselectivity • *Z*-alkenes • rhodium

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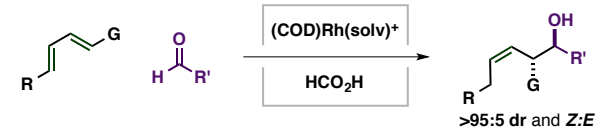

- tolerates reducible groups
- *Z*-selective
- no chain-walking isomerization

Formic acid mediates the Rh-catalyzed, *Z*-selective coupling of dienes and aldehydes. The process is distinguished by broad tolerance towards reducible or electrophilic groups without chain-walking isomerization.

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Formic Acid Mediated Direct *Z*-Selective Reductive Coupling of Dienes and Aldehydes