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Chemoselective *Z*-Olefin Synthesis via Rh-Catalyzed, Formate Mediated 1,6-Reduction

Raphael Dada,[†] Zhongyu Wei,[†] Ruohua Gui, Rylan J. Lundgren*[a]

Abstract: *Z-olefins are important functional units in synthetic chemistry; thus their preparation has received considerable attention. Many prevailing methods for cis-olefination are complicated by the presence of multiple unsaturated units or electrophilic functional groups. In this study, Z-olefin products are delivered via selective reduction of activated dienes using formic acid. The reaction proceeds with high regio- and stereoselectivity (typically >90:10 and >95:5 respectively) and preserves other alkenyl, alkynyl, protic and electrophilic groups.*

A large number of bioactive molecules contain *cis*-alkene units, and stereospecific transformations of *Z*-olefins are commonly used to develop molecular complexity. Thus, the synthesis of less thermodynamically stable alkenes is an important goal. An array of methods generate *Z*-olefins with high stereoselectivity;[1] however control over chemo- and regioselectivity when employing unprotected, polyfunctionalized substrates remains a challenge. *Cis*-selective carbonyl olefination reactions using phosphorus-, silicon- or sulfur-containing precursors have enabled the preparation of *Z*-olefins in a myriad of settings.[2] The requirement for stoichiometric generation of main-group element ylide intermediates limits efficiency. Furthermore, the strongly basic reaction conditions are often incompatible with protic or electrophilic functionality.[3] Alternative methods for *Z*-olefin synthesis include *Z*-selective alkyne reductions[4] and alkene metathesis reactions.[5,6] Despite their remarkable and growing utility, alkyne semi-reduction and *Z*-selective metathesis reactions can exhibit poor chemoselectivity on targets bearing multiple alkyne or olefin units. There remains a need for complementary catalytic approaches to *Z*-olefin synthesis in the presence of other carbon-carbon π-bonds and protic or electrophilic groups.

Catalyst-controlled addition of nucleophiles to carbonyl-activated dienes is a pivotal method to generate functionalized olefins.[7] In select cases, these transformations enable highly regioselective 1,6-addition to deliver γ-substituted *E*-alkenes.[8] By contrast, *Z*-selective 1,6-additions to electron-poor dienes remain rare.[9] The addition of hydrogen or hydride equivalents to extended Michael acceptors generating *cis*-olefin products are limited to Cr-promoted reactions requiring forcing conditions (typically ≥150 °C).[10] The 1,6-*cis* reduction of sorbic acid has been documented with Ru-based catalysts, however careful monitoring of the reaction is required to prevent substrate over-reduction and isomerization.[11] Herein, we report a formate-mediated reduction of activated dienes to generate *Z*-olefins.[12] Substrate coordination and hydride delivery from a Rh-catalyst dictate a chemo- and regioselective process. Other unsaturated groups such as non-activated olefins or dienes, α,β-unsaturated esters, internal alkynes and a host of electrophilic groups are tolerated (Figure 1). The process offers a new opportunity to prepare polyfunctionalized *Z*-olefins in complex substrate environments without protecting groups.

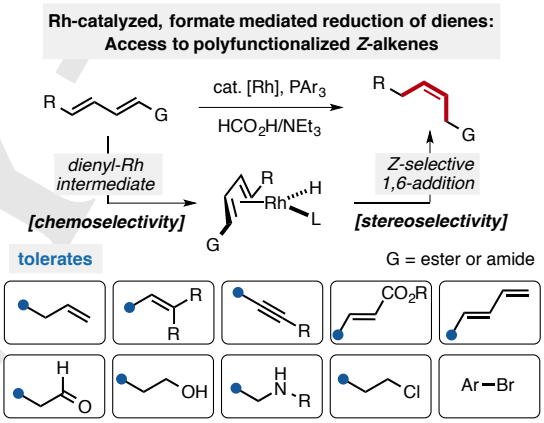

Figure 1. Rh-catalyzed hydride addition to generate *Z*-olefins: overview of the developed method.

We found 2.5 mol% $[Rh(COD)Cl]_2$ and 15 mol% PPh_3 in the presence of formic acid/NEt_3 in acetonitrile provided the desired mono-reduced olefin **2a** in 80% yield with 96:4 *Z/E* selectivity (Figure 2a, entry 1). $RhCl(PPh_3)_3$, alternative Rh/PPh_3 stoichiometries, or the use of other ligands resulted in reduction with moderate to low *E*-selectivity (Figure 2a, entries 2-7). Other metals, including Ir, Cu, and Pd did not generate the *Z*-olefin product (entries 8-11). Reactions conducted with lower catalysts loadings (0.5 mol% $[Rh(COD)Cl]_2$) at 50 °C resulted in similar product yields and selectivities (entry 12).[13]

A preliminary mechanistic hypothesis involved a chelation-controlled 1,6-reduction of the diene substrate. Concomitant over-reduction or isomerization was not observed under the standard reaction conditions, suggesting the potential to conduct chemoselective hydride additions. We reasoned electron-rich olefins, polar unsaturates, and suitably substituted alkynes should not be reduced at rates competitive with bidentate extended Michael acceptors. To rapidly test this hypothesis, a functional group tolerance screen with an array of unsaturated substrates was conducted (Figure 2b).[14] Under standard reaction conditions,

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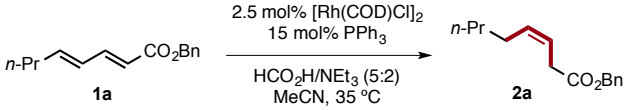
aryl/silyl and dialkyl alkynes, internal and terminal olefins, α,β-unsaturated esters, electron-rich dienes and aldehydes were tolerated (>70% product formation, <20% additive consumption). Terminal and diaryl alkynes were found to be incompatible.



a effect of catalyst and reductant

entry	deviation from above	conv. (%)	yield (%) [*Z*/*E*]
1	**none**	**91**	**80 [96:4]**
2	$Rh(PPh)_3Cl$ (no PPh_3)	94	41 [31:69]
3	1:1 Rh:PPh_3 instead of 1:3	93	40 [28:72]
4	no PPh_3	93	52 [25:75]
5	$P(OPh)_3$ instead of PPh_3	59	47 [50:50]
6	dppp instead of PPh_3	76	53 [90:10]
7	BINAP instead of PPh_3	41	11 [36:64]
8	$[Ir(COD)Cl]_2$	24	<2
9	CuI	<2	<2
11	$Pd(OAc)_2$	20	<2
12[a]	0.5 mol% $[Rh(COD)Cl]_2$ 3 mol% PPh_3	89	79 [96:4]

0.2 mmol scale, 1.0 equiv. HCO_2H, 0.2 M, 20-30 h; yields, selectivities, and conversions determined by calibrated ^1H NMR. [a]at 50 °C, 48h;

b unsaturated functional group tolerance survey

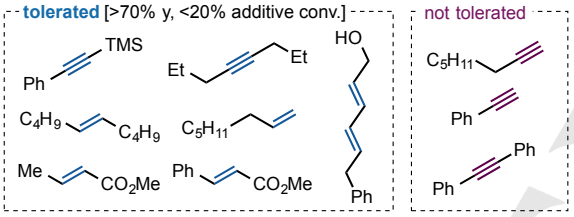
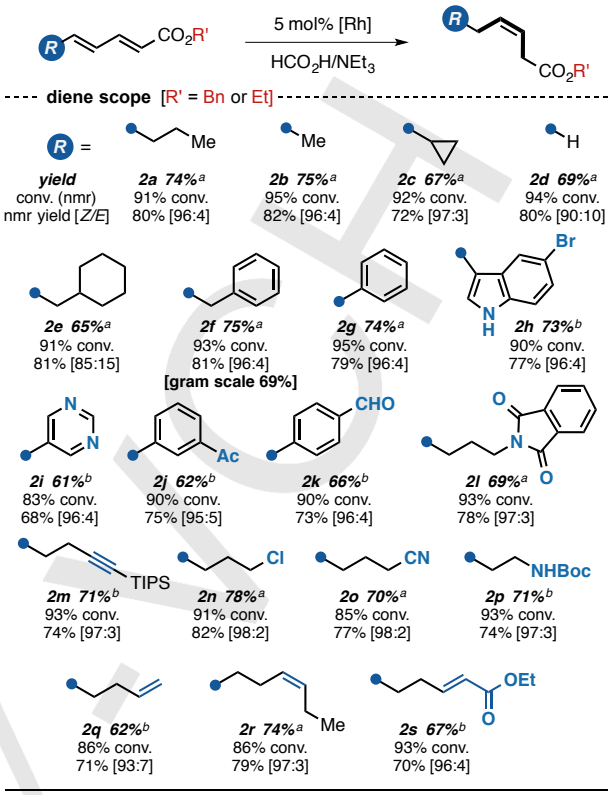


Figure 2. (a) Effect of selected reaction parameters on the Rh-catalyzed *Z*-selective 1,6-reduction of dienyl esters. (b) Unsaturated functional group tolerance screen.



see Fig 2 for conditions and SI for full details, [a]R' = Bn; [b]R' = Et;

Figure 3. Diene scope of the Rh-catalyzed formate-mediated *Z*-selective 1,6-reduction.

The scope of the Rh-catalyzed *Z*-selective 1,6-reduction was evaluated (Figure 3 and 4). Aliphatic and aryl groups at the terminal position of the dienoate led to product formation in similarly high selectivities (**2a**-**2g**), including unsubstituted (**2d**) and cyclopropyl (**2c**) substituted species. Substrates bearing electron-rich- (**2h**) or electron-poor heterocycles (**2i**), electrophilic ketone (**2j**) and aldehyde (**2k**) functionality, as well as amines (**2l**, **2m**), alkyl chlorides (**2n**), and alkyl nitriles (**2o**) gave *Z*-olefin products in good yield and typically >95:5 *Z*:*E* selectivity. The formate-mediated reduction method allowed for the preparation of *Z*-olefin containing molecules that contain pendent C–C unsaturation, including terminal olefins (**2q**), internal olefins (**2r**), α,β-unsaturated esters (**2s**), and alkynes (**2m**). These types of stereochemically defined polyunsaturated products would be difficult to obtain directly via established catalytic semi-reduction or metathesis reactions. The process can be scaled to deliver gram-quantities of product (1.2 g **2f**, 69% yield).

The ester group of the dienoate can be varied from benzyl or ethyl to a bulky *tert*-butyl group (**3a**); amine-containing moieties, including a protected amino acid derivative (**3b**, **3c**); and esters containing multiple olefin units (**3d**, **3e**) (Figure 4). The functional group tolerance of the reaction was also examined with derivatives of bioactive molecules. Dienyl esters of the hydroxylated sterol methyl cholate (**3f**), nucleoside analog stavudine (**3g**), polyketide ivermectin (**3h**) and quinoline alkaloid camptothecin (**3i**) could be reduced with acceptable yields and minimal complication from the array of chemical functionality present. Complex substrates like **3f**-**3i** would pose considerable difficulty in established *Z*-olefin forming processes. Under slightly modified conditions, a series of amidyl dienes, including the Weinreb amide (**3m**) were reduced with good selectivity (**3j**-**3m**).[13b]

The β-carbonyl containing *Z*-olefins are useful precursors to a range of other product classes (Figure 5). *Z*-homoallylic alcohols (**4a**), skipped *Z*,*E*-dienes (**4b**), propargylic *Z*-1,5- enynes (**4c**), and α-amino esters (**4d**) can be readily obtained in good yields using standard synthetic protocols.

Mechanistic experiments help to rationalize the high selectivity for *Z*-1,6 addition. Reduction of dienoate **1a** with D-labelled formic acid at the formyl position under otherwise standard conditions leads to exclusive hydride addition to the remote 6-position. Formic acid labelled at the carboxylic site results in labelling at the α-carbonyl position (Figure 6a).[13c] This suggested a mechanism in which Rh–H conjugate addition is

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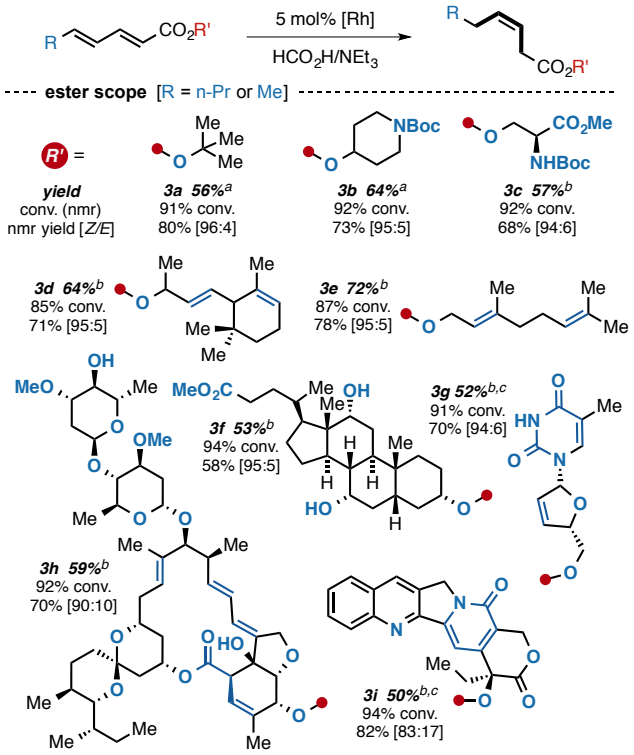

see Fig 2 for conditions and SI for full details, [a] R = *n*-Pr; [b] R = Me; [c] 5 mol% $[Rh(COD)Cl]_2$, 30 mol% PPh_3, 4:1 MeCN:DMSO, 2-3 equiv HCO_2H; [d] $(4\text{-}C_6H_4F)_3P$ instead of PPh_3 at 60 °C.

Figure 4. Ester and amide scope of the Rh-catalyzed formate-mediated *Z*-selective 1,6-reduction.

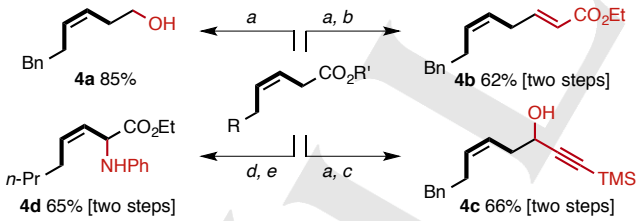

Figure 5. (a) $LiAlH_4$; (b) DMP then triethyl phosphonoacetate (c) DMP then Li-TMS acetylene; (d) *p*-ABSA, DBU; (e) $Rh_2(OAc)_4$, $PhNH_2$. See the SI for full details.

followed by protonolysis of a Rh-enolate. Reaction progress kinetic analysis of the reduction revealed the process to be positive order in catalyst mixture and formic acid, and partial negative order in substrate (see the SI).[13d] High selectivity for *Z*-1,6-reduction is maintained throughout the reaction under standard conditions. When excess formate is added both olefin isomerization and reduction to the saturated ester is observed after diene substrate **1a** is consumed (Figure 6b). Reintroduction of **1a** inhibits these side reactions and olefin **2a** is smoothly generated again (see the SI for a plot).

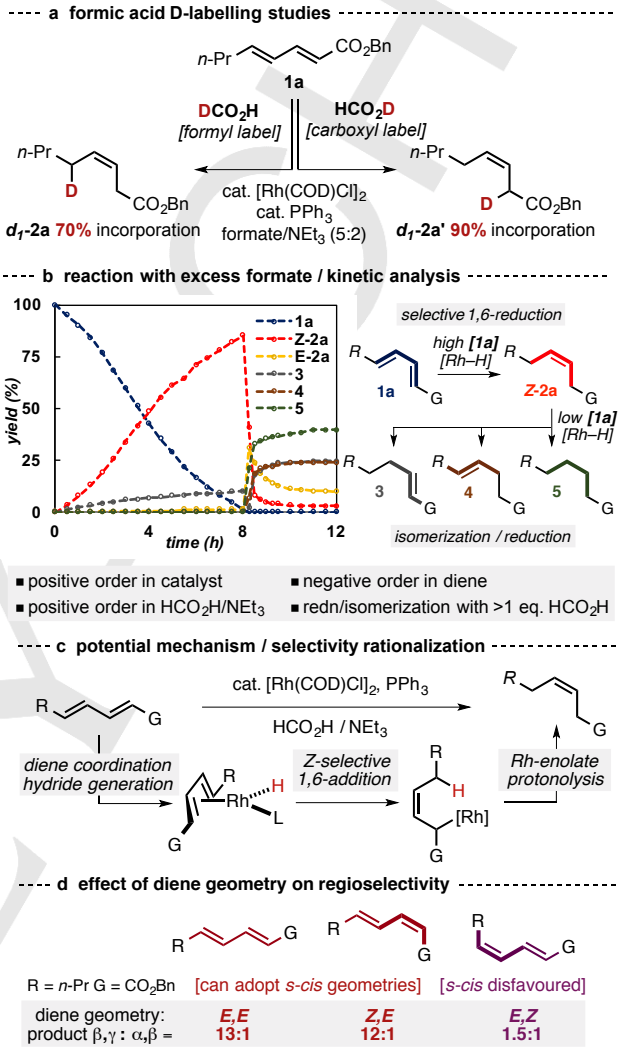

Figure 6. (a) D-labelling studies using DCO_2H and HCO_2D; (b) Kinetic profile of reaction conducted with excess formic acid and reaction order. (c) Potential selectivity driving steps in the reduction process; (d) Impact of diene geometry on reduction selectivity.

A mechanism to explain the observed selectivity involves coordination of the electron-poor diene moiety to a Rh(I) species which then undergoes selective hydride addition. The chelation-driven, *Z*-selective process generates a Rh-enolate species readily protonated to deliver the non-conjugated *cis*-olefin. (Figure 6c). The ability to selectively generate a diene coordinated Rh-hydride under the optimized conditions appears to be key to an efficient transformation.[15,16] In line with this argument, both *E,E* and *Z,E*-dienoates that can readily adopt *s-cis* conformations undergo 1,6-reduction with high regioselectivity (>10:1 for the β,γ product). A *E,Z*-dienoate that would experience significant steric repulsion in an *s-cis* configuration from the *Z*-positioned

alkyl group is reduced with low selectivity (Figure 6d, β,γ:α,β = 1.5:1).

In summary, a simple Rh(I)/phosphine catalyst system enables the formate-mediated *Z*-selective reduction of activated dienes via a 1,6-addition process. Mechanistic studies suggest the 1,6-addition process is key to enabling chemoselective diene reductions in the presence of alternative olefin and alkyne units, overcoming difficulties associated with existing catalytic methods. We envision this general concept to extend to related *Z*-selective diene hydrofunctionalization reactions.

Acknowledgements

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Keywords: *Z*-alkenes • homogeneous catalysis • chemoselectivity • rhodium • 1,6-addition

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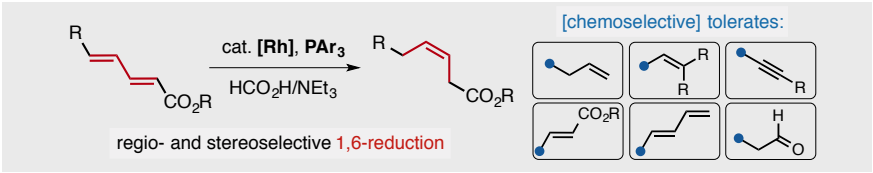

The stereoselective formation of *Z*-alkenes in the presence of related unsaturated or electrophilic groups remains a challenge. Herein, we report the Rh-catalyzed *Z*-selective 1,6-reduction of activated dienes. The reaction proceeds with high regio- and stereoselectivity while preserving other alkenyl, alkynyl, protic and electrophilic groups.

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Page No. – Page No.

Chemoselective *Z*-Olefin Synthesis via Rh-Catalyzed, Formate Mediated 1,6-Reduction