JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Cite This: J. Am. Chem. Soc. XXXX, XXX, XXX−XXX
Communication
pubs.acs.org/JACS

Conversion of Aldehydes to Branched or Linear Ketones via Regiodivergent Rhodium-Catalyzed Vinyl Bromide Reductive Coupling−Redox Isomerization Mediated by Formate

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Supporting Information

ABSTRACT: A regiodivergent catalytic method for direct conversion of aldehydes to branched or linear alkyl ketones is described. Rhodium complexes modified by P^{t}Bu$_2$Me catalyze formate-mediated aldehyde−vinyl bromide reductive coupling−redox isomerization to form branched ketones. Use of the less strongly coordinating ligand, PPh$_3$, promotes vinyl- to allylrhodium isomerization *en route* to linear ketones. This method bypasses the 3-step sequence often used to convert aldehydes to ketones involving the addition of pre-metalated reagents to Weinreb or morpholine amides.

Ketones are of commercial significance across the pharmaceutical, agrochemical, and flavor−fragrance industries. Convergent manufacturing routes to ketones from aldehydes often rely on 3-step sequences involving the addition of stoichiometric organometallic reagents to alkoxy-amides,[1] such as the Weinreb amide[2,3] or morpholine amides (Figure 1).[4] Alternatively, 2-step ketone syntheses can be achieved through the addition of vinylmetal reagents to aldehydes followed by internal redox isomerization of the resulting allylic alcohols.[5,6] In connection with long-standing efforts to develop reductive C−C couplings via transfer hydrogenation,[7,8] we envisioned a direct protocol for the conversion of aldehydes to ketones wherein vinyl halide−carbonyl reductive coupling is followed by internal redox isomerization. This transformation finds precedent in our recently reported rhodium-catalyzed aryl halide−aldehyde reductive coupling mediated by sodium formate,[9,10] as well as related redox-neutral aryl halide−aldehyde C−C couplings to form aryl ketones.[11] As described herein, our pursuit of this goal has resulted in the development of a direct, regiodivergent[12] vinyl bromide−aldehyde reductive coupling to form either linear or branched ketone products.[13−16]

In an initial experiment, piperonal **1a** (100 mol%) and 2-bromopropene **2a** (200 mol%) were exposed to NaO$_2$CH (300 mol%) and Cs$_2$CO$_3$ (100 mol%) in the presence of the catalyst assembled from Rh(acac)(CO)$_2$ (5 mol%) and P^{t}Bu$_2$Me (11 mol%) in DME (0.2 M) at 130 °C.[9] The anticipated branched ketone product **3a** was formed in 45% yield after isolation by flash column chromatography (Table 1, entry 1). A survey of phosphine ligands was undertaken (Table 1, entries 1−10). Remarkably, use of PPh$_3$ under otherwise identical conditions led to a 48% yield of the *linear* ketone product **4a**.[13] The isolated

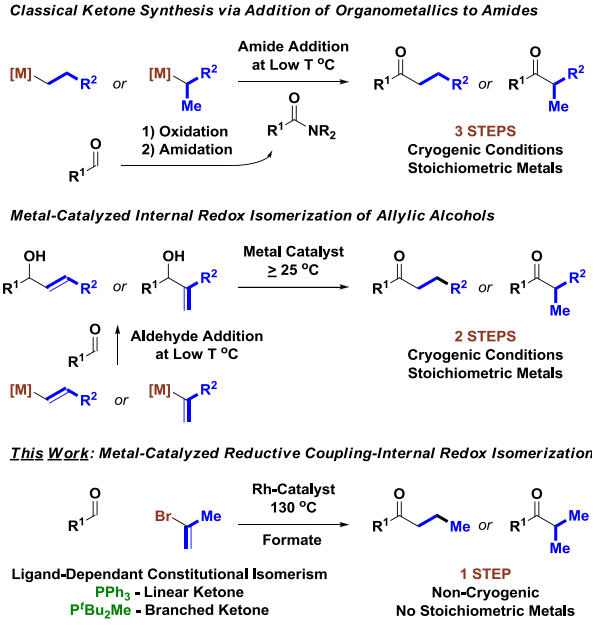


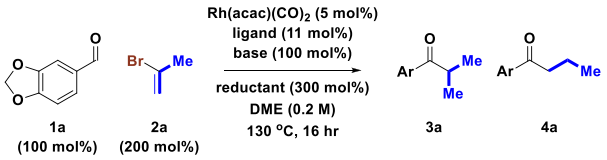
Figure 1. Classical and contemporary strategies for the convergent construction of linear or branched alkyl ketones.

yield of linear ketone **4a** was elevated to 77% yield upon use of KO$_2$CH (300 mol%) and K$_2$CO$_3$ (100 mol%) (Table 1, entry 12). Finally, by lowering the loading of K$_2$CO$_3$ (70 mol%), the formation of a competing elimination side product, 5-(1-butenyl)-1,3-benzodioxole, could be attenuated, enabling formation of linear ketone **4a** in 92% yield (Table 1, entry 13). Dry KO$_2$CH (*vide infra*) and dry DME were required for optimal isolated yields. Using P^{t}Bu$_2$Me as ligand under these conditions delivered the branched ketone **3a** in 54% yield (Table 1, entry 14), and at higher concentration (0.4 M) the isolated yield of **3a** was increased to 80% (Table 1, entry 15). Notably, while optimal conditions for formation of the linear and branched ketones **3a** and **4a** differ primarily on the basis of ligand (Table 1, entries 13 vs 15), virtually complete partitioning of these constitutionally isomeric products was observed (>40:1 isomeric ratios were observed by ^{1}H NMR analysis of crude reaction mixtures).

Received: March 21, 2019

DOI: 10.1021/jacs.9b03113
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

Table 1. Selected Optimization Experiments in the Rhodium-Catalyzed Reductive Coupling of 2-Bromopropene 2a with Piperonal 1a To Form the Isomeric Ketones 3a and 4a[a]



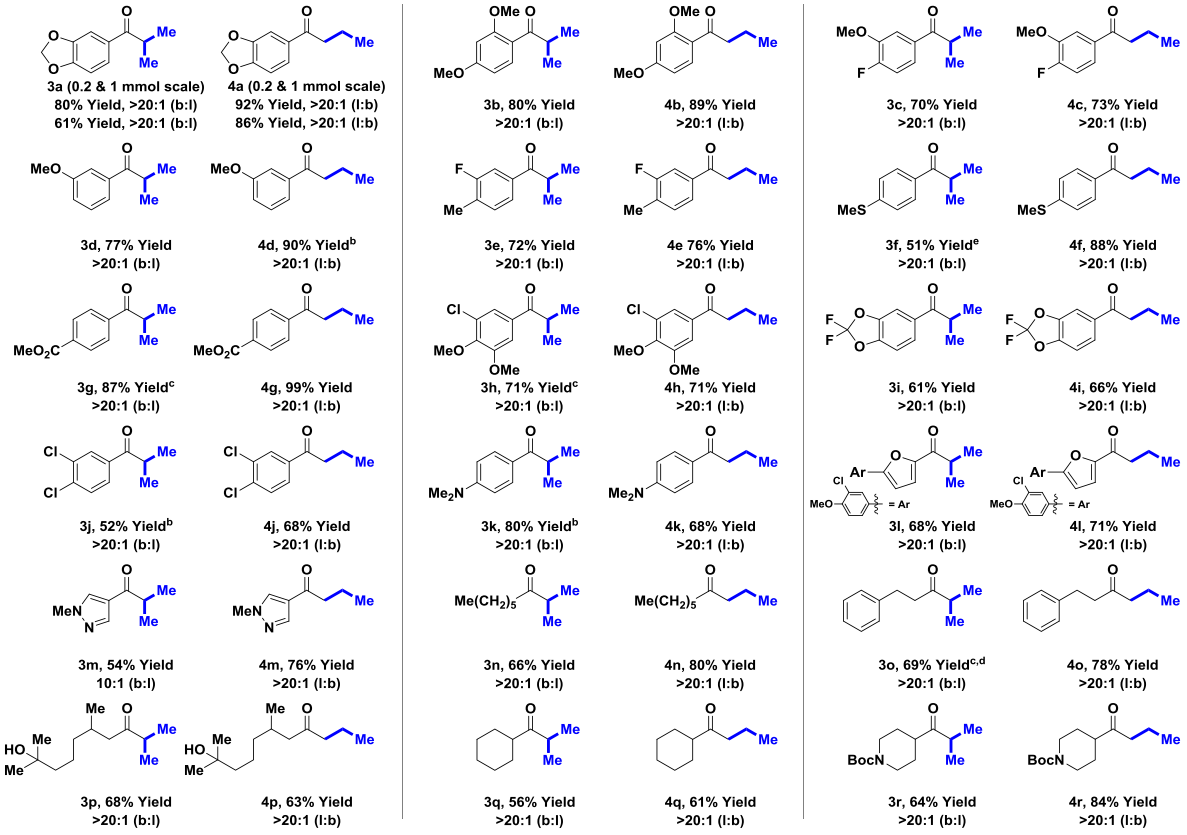
entry	ligand	base	reductant	3a (yield)	4a (yield)
1	P^tBu_2Me	Cs_2CO_3	NaO_2CH	45%	---
2	P^tBu_3	Cs_2CO_3	NaO_2CH	43%	4%
3	PCy_3	Cs_2CO_3	NaO_2CH	28%	---
4	P^tBu_2Ph	Cs_2CO_3	NaO_2CH	21%	2%
5	P^tBuPh_2	Cs_2CO_3	NaO_2CH	29%	2%
6	PPh_3	Cs_2CO_3	NaO_2CH	---	48%
7	dippf	Cs_2CO_3	NaO_2CH	---	< 5%
8	dppe	Cs_2CO_3	NaO_2CH	---	< 5%
9	dppp	Cs_2CO_3	NaO_2CH	---	< 5%
10	dppb	Cs_2CO_3	NaO_2CH	---	47%
11	PPh_3	K_2CO_3	NaO_2CH	---	50%
12	PPh_3	K_2CO_3	KO_2CH	---	77%
13[b]	PPh_3	K_2CO_3	KO_2CH	---	92%
14[b]	P^tBu_2Me	K_2CO_3	KO_2CH	54%	---
15[b,c]	P^tBu_2Me	K_2CO_3	KO_2CH	80%	---

[a]Yields are of chromatographically isolated isomerically pure (>20:1) material. $P^tBu_2Me{\cdot}HBF_4$, $P^tBu_3{\cdot}HBF_4$, and P^tBu_2Ph (PhMe, 50 wt%) were used. Bidentate ligands (5.5 mol%). See Supporting Information for experimental details. [b]K_2CO_3 (70 mol%). [c]DME (0.4 M).

To evaluate reaction scope, optimal conditions identified for the conversion of piperonal **1a** to the constitutionally isomeric branched and linear ketone products **3a** and **4a** were applied to diverse aldehydes **1a**–**1r** (Table 2). Aromatic aldehydes **1a**–**1k**, heteroaromatic aldehydes **1l**–**1m**, and aliphatic aldehydes **1n**–**1r** were converted to the respective branched ketones **3a**–**3r** or linear ketones **4a**–**4r** in generally good yields. With the exception of branched ketone **3m**, the chromatographically isolated products appeared to be isomerically pure by ^{1}H NMR analysis. For **3m**, delocalization of the pyrazole nitrogen might deactivate the aldehyde toward insertion, providing a kinetic window for competing branched-to-linear isomerization. For optimal results, it was necessary to use freshly distilled DME and KO_2CH recrystallized from ethanol. The recrystallized KO_2CH was collected by filtration and washed with diethyl ether under an inert atmosphere. If wet KO_2CH is used, significant quantities of aldehyde reduction and oxidative esterification are observed. For reactions run on a 1 mmol scale, it was important to utilize a narrow reaction vessel at low volume (10–20%).

The feasibility of utilizing alternate vinyl bromides **2b** and **2c** in regiodivergent reductive coupling–internal redox isomerization was briefly investigated in reactions of piperonal **1a**. Under optimal conditions using P^tBu_2Me as ligand, the anticipated branched ketones **3s** and **3t** were formed in good yields (eq 1). However, when optimal conditions for formation

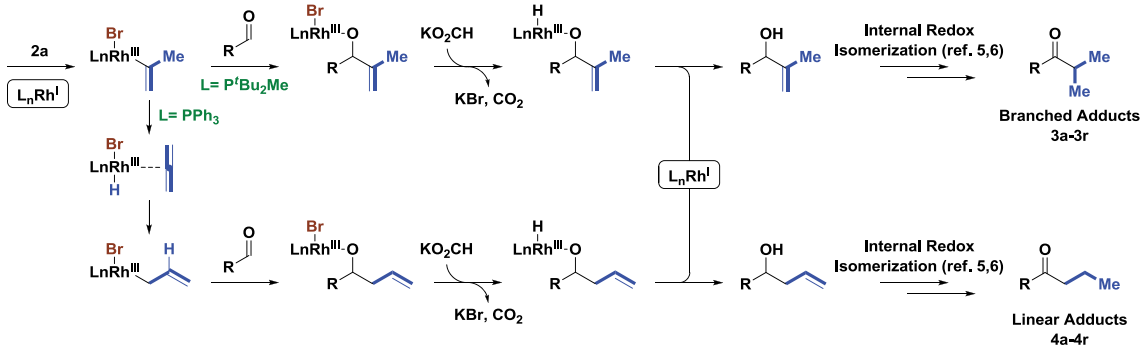
Table 2. Rhodium-Catalyzed Reductive Coupling–Internal Redox Isomerization of 2-Bromopropene 2a with Aldehydes 1a–1r To Form the Branched Ketones 3a–3r or Linear Ketones 4a–4r[a]

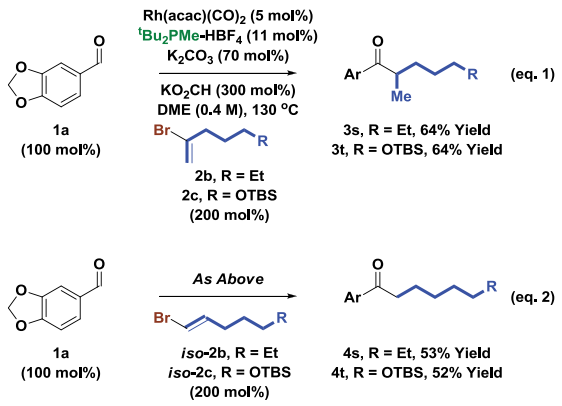


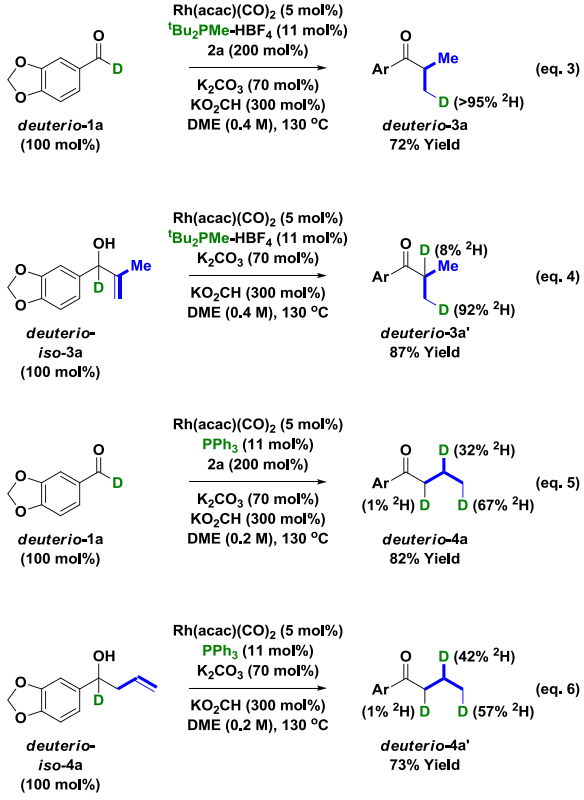
[a]Standard conditions: Branched: aldehyde **1a**–**1r** (100 mol%), 2-bromopropene (200 mol%), $Rh(acac)(CO)_2$ (5 mol%), $P^tBu_2Me{\cdot}HBF_4$ (11 mol%), K_2CO_3 (70 mol%), KO_2CH (300 mol%), DME (0.4 M), 130 °C. Linear: aldehyde **1a**–**1r** (100 mol%), 2-bromopropene (200 mol%), $Rh(acac)(CO)_2$ (5 mol%), PPh_3 (11 mol%), K_2CO_3 (70 mol%), KO_2CH (300 mol%), DME (0.2 M), 130 °C. [b]K_2CO_3 (30 mol%). [c]K_2CO_3 omitted. [d]DME (0.2 M), 130 °C. [e]120 °C. Yields are of chromatographically isolated material. As the isomeric ketone products are inseparable via conventional flash chromatography, isomeric ratios were determined from ^{1}H NMR analysis of isolated products.

DOI: 10.1021/jacs.9b03113
J. Am. Chem. Soc. XXXX, XXX, XXX–XXX

Scheme 1. General Catalytic Mechanism Accounting for Regiodivergence in the Rhodium-Catalyzed Aldehyde Reductive Coupling of 2-Bromopropene 2a To Form Isomeric Ketones 3a–3r and 4a–4r







of the linear products using PPh_3 as ligand were applied, the linear ketones were not obtained in isomerically pure form. This limitation was easily overcome through use of the isomeric terminal vinyl bromides *iso*-**2b** and *iso*-**2c**, which deliver the constitutionally isomeric linear ketones **4s** and **4t**, albeit in modest yield (eq 2).

To gain insight into the catalytic cycle, a series of deuterium labeling experiments were performed (eqs 3–6). Exposure of aldehyde *deuterio*-**1a** to 2-bromopropene **2a** under standard conditions favoring formation of the branched regioisomer delivers *deuterio*-**3a**, which incorporates a single deuterium atom (>95% ^{2}H) at the methyl group of the isopropyl ketone (eq 3). As *deuterio*-**3a** is postulated to arise via isomerization of the corresponding allylic alcohol *deuterio-iso*-**3a**, the latter compound was subjected to standard conditions favoring formation of the branched regioisomer (eq 4). In this case, deuterium was incorporated at both the methyl group (92% ^{2}H) and the methine moieties (8% ^{2}H) of the isopropyl ketone. Similarly, *deuterio*-**1a** and the homoallylic alcohol *deuterio-iso*-**4a** were exposed to standard conditions favoring formation of the linear regioisomer (eqs 5 and 6). The resulting *n*-propyl ketones *deuterio*-**4a** and *deuterio*-**4a′** display similar but non-identical patterns of deuterium incorporation. These data corroborate allylic and homoallylic alcohols as reactive intermediates *en route* to the branched and linear ketone products, respectively. The non-identical patterns of deuterium incorporation between *deuterio*-**3a** vs *deuterio*-**3a′** and *deuterio*-**4a** vs *deuterio*-**4a′** suggest that redox isomerization may occur in part from the kinetic rhodium alkoxide.

Based on the collective data, the catalytic cycle shown in Scheme 1 is proposed. Vinyl bromide oxidative addition forms the indicated vinylrhodium(III) species.[17] For the strong σ-donor ligand P^{t}Bu$_2$Me, aldehyde insertion occurs to form a rhodium alkoxide.[18] The bromide moiety of the kinetic rhodium alkoxide can react with KO_2CH to form a hydride, which upon O–H reductive elimination[19] delivers the allylic alcohol and, therefrom, the branched ketone. Alternatively, the kinetic rhodium alkoxide can undergo β-hydride elimination to form an enone, which undergoes conjugate reduction to form the branched ketone (not shown). For the weak σ-donor ligand PPh_3, phosphine dissociation at the stage of the vinylrhodium(III) intermediate triggers β-hydride elimination to form a transient allene, which upon hydrometalation delivers an allylrhodium(III) species.[13] Aldehyde insertion delivers a homoallylic rhodium alkoxide,[18] which is ultimately converted to the linear ketone. Coupling products were not formed in reactions using other weakly coordinating monodentate ligands, for example, $P(OPh)_3$, $P(C_6F_5)_3$, or $P(2\text{-Fur})_3$.

In summary, we report a catalytic method enabling direct conversion of aldehydes to alkyl ketones[20–22] and establish conditions for regiodivergent access to either the branched or

DOI: 10.1021/jacs.9b03113
J. Am. Chem. Soc. XXXX, XXX, XXX–XXX

linear ketone isomers. Specifically, using the rhodium catalyst modified by P^tBu_2Me, vinyl halide−aldehyde reductive coupling mediated by formate is followed by redox isomerization of the resulting allylic alcohol to form branched ketone products. In contrast, use of a less strongly coordinating ligand, Ph_3P, promotes vinyl- to allylrhodium isomerization *en route* to linear ketones. This method bypasses the 3-step sequence often used to convert aldehydes to ketones involving the addition of stoichiometric organometallic reagents to Weinreb or morpholine amides.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.9b03113.

Experimental procedures and spectral data (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors thank the Robert A. Welch Foundation (F-0038) and the NIH-NIGMS (RO1-GM069445) for support. Eli Lilly and Company is acknowledged for LIFA postdoctoral fellowship funding (R.A.S.).

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DOI: 10.1021/jacs.9b03113
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX