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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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Abstract

A regiodivergent catalytic method for direct conversion of aldehydes to branched or linear alkyl ketones is described. Rhodium complexes modified by P^tBu_2Me , 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 premetalated reagents to Weinreb or morpholine amides.

Graphical Abstract

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

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^bK₂CO₃ (30 mol%).

^cK₂CO₃ omitted.

^dDME (0.2 M), 130 °C.

^e120 °C. Yields are of chromatographically isolated material. As the isomeric ketone products are inseparable via conventional flash chromatography, isomeric ratios were determined from ¹H NMR analysis of isolated products.

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 longstanding 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, regiodivergent¹² 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 NaO₂CH (300 mol%) and Cs₂CO₃ (100 mol%) in the presence of the catalyst assembled from Rh(acac)(CO)₂ (5 mol%) and P^tBu₂Me (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 PPh₃ under otherwise identical conditions led to a 48% yield of the *linear* ketone product **4a**.¹³ The isolated yield of linear ketone **4a** was elevated to 77% yield upon use of KO₂CH (300 mol%) and K₂CO₃ (100 mol%) (Table 1, entry 12). Finally, by lowering the loading of K₂CO₃ (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 KO₂CH (*vide infra*) and dry DME were required for optimal isolated yields. Using P^tBu₂Me 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 ¹H NMR analysis of crude reaction mixtures).

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 ¹H 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 KO₂CH recrystallized from ethanol. The recrystallized KO₂CH was collected by filtration and washed with diethyl ether under an inert atmosphere. If wet KO₂CH is used, significant quantities of aldehyde reduction and oxidative esterification is 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 redoxisomerization was briefly investigated in reactions of piperonal **1a**. Under optimal conditions using $P^t\text{Bu}_2\text{Me}$ as ligand, the anticipated branched ketones **3s** and **3t** were formed in good yields (eq. 1). However, when optimal conditions for formation 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).

(eq. 1)

(eq. 2)

To gain insight into the catalytic cycle, a series of deuterium labelling experiments were performed (eq. 3–6). Exposure of aldehyde *deuterio-1a* to 2-bromopropene **2a** to standard conditions favoring formation of the branched regioisomer delivers *deuterio-3a*, which incorporates a single deuterium atom (>95% ^2H) 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% ^2H) and the methine moieties (8% ^2H) 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 (eq. 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'* suggests redox isomerization may occur in part from the kinetic rhodium alkoxide.

(eq. 3)

(eq. 4)

(eq. 5)

(eq. 6)

Based on the collective data the following catalytic cycle is proposed (Scheme 1). Vinyl bromide oxidative addition forms the indicated vinylrhodium(III) species.¹⁷ For the strong σ -donor ligand $\text{P}^t\text{Bu}_2\text{Me}$, 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 elimination¹⁹ 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 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 , $\text{P(C}_6\text{F}_5)_3$ or P(2-Fur)_3 .

In summary, we report a catalytic method enabling direct conversion of aldehydes to alkyl ketones^{20,21} and establish conditions for regiodivergent access to either the branched or linear ketone isomers. Specifically, using the rhodium catalyst modified by $\text{P}^t\text{Bu}_2\text{Me}$, 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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

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**. Competing pathways involving β -hydride elimination from the kinetic rhodium alkoxide are not depicted.

Table 1.

Selected optimization experiments in the rhodiumcatalyzed reductive coupling of 2-bromopropene **2a** with piperonal **1a** to form the isomeric ketones **3a** or **4a**.^a

entry	ligand	base	reductant	3a (yield)	4a (yield)
1	P ^t Bu ₂ Me	CS ₂ CO ₃	NaO ₂ CH	45%	---
2	P ^t Bu ₃	CS ₂ CO ₃	NaO ₂ CH	43%	4%
3	PCy ₃	CS ₂ CO ₃	NaO ₂ CH	28%	---
4	P ^t Bu ₂ Ph	CS ₂ CO ₃	NaO ₂ CH	21%	2%
5	P ^t BuPhj	GS ₂ CO ₃	NaO ₂ CH	29%	2%
6	PPh ₃	GS ₂ CO ₃	NaO ₂ CH	---	48%
7	dippf	CS ₂ CO ₃	NaO ₂ CH	---	<5%
8	dppe	CS ₂ CO ₃	NaO ₂ CH	---	<5%
9	dppp	CS ₂ CO ₃	NaO ₂ CH	---	<5%
10	dppb	CS ₂ CO ₃	NaO ₂ CH	---	47%
11	PPh ₃	K ₂ CO ₃	NaO ₂ CH	---	50%
12	PPh ₃	K ₂ CO ₃	KO ₂ CH	---	77%
13 ^b	PPh ₃	K ₂ CO ₃	ko ₂ ch	---	92%
14 ^b	P ^t Bu ₂ Me	k ₂ co ₃	ko ₂ ch	54%	---
15 ^{b,c}	P ^t Bu ₂ Me	k ₂ co ₃	ko ₂ ch	80%	---

^aYields are of chromatographically isolated isomerically pure (>20:1) material. P^tBu₂Me•HBF₄, P^tBu₃•HBF₄ and P^tBu₂Ph (PhMe, 50 wt%) were used. Bidentate ligands (5.5 mol%). See Supporting Information for experimental details.

^bK₂CO₃ (70 mol%).

^cDME (0.4 M).

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

^aStandard Conditions: [branched] Aldehyde **1a-1r** (100 mol%), 2-bromopropene (200 mol%), Rh(acac)(CO)₂ (5 mol%), P^tBu₂Me•HBF₄ (11 mol%), K₂CO₃ (70 mol%), KO₂CH (300 mol%), DME (0.4 M), 130 °C. [linear] Aldehyde **1a-1r** (100 mol%), 2-bromopropene (200 mol%), Rh(acac)(CO)₂ (5 mol%), PPh₃ (11 mol%), K₂CO₃ (70 mol%), KO₂CH (300 mol%) DME (0.2 M), 130 °C.