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Vinyl Triflate-Aldehyde Reductive Coupling-Redox Isomerization Mediated by Formate: Rhodium-Catalyzed Ketone Synthesis in the Absence of Stoichiometric Metals

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<Graphical Abstract>

Beyond Stoichiometric Metals. Direct conversion of aldehydes to ketones is achieved *via* rhodium-catalyzed vinyl triflate-aldehyde reductive coupling-redox isomerization mediated by potassium formate. This method circumvents premetalated *C*-nucleophiles and discrete redox manipulations typically required to form ketones from aldehydes.

Keywords: Rhodium, Redox-Isomerization, Transfer Hydrogenation, Formate, C-C Bond Formation.



Vinyl Triflate-Aldehyde Reductive Coupling-Redox Isomerization Mediated by Formate: Rhodium-Catalyzed Ketone Synthesis in the Absence of Stoichiometric Metals**

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Metal-catalyzed carbonyl reductive coupling offers an alternative to the use of stoichiometric organometallic reagents in an ever-increasing range of C-C bond forming processes.^[1] Despite significant advances in this field, many catalytic reactions of this type exploit reductants that are metallic (Mn, Zn), pyrophoric (Et₃B, Et₂Zn) or expensive/massintensive (R₃SiH, TDAE), which pose issues of safety and waste generation, impacting the ultimate metric of cost.^[2] Inspired by the enormous impact of hydroformylation, our laboratory has advanced methods for catalytic carbonyl reductive coupling via hydrogenation, transfer hydrogenation and hydrogen auto-transfer.^[3] In the course of these studies, ketone syntheses were developed based on hydrogen-mediated styrene-anhydride reductive coupling,^[4] hydrogenmediated aryl halide-ketone reductive cyclizations,^[5] and the transfer hydrogenative coupling of alcohols (or aldehydes) with dienes or alkynes.^[6] In a recent step forward, a regiodivergent rhodium-catalyzed ketone synthesis was developed wherein aldehydes are directly converted to branched or linear alkyl ketones through formate-mediated vinyl bromide-aldehyde reductive coupling-redox isomerization.^[7,8,9,10] The ability to transfer aliphatic fragments complements the scope of related redox-neutral ketone formations involving aryl halide-aldehyde C-C coupling.^[11,12,13] Further, unlike ketone formation through metal-catalyzed reductive couplings to carboxylic acid derivatives^[14,15] (including redox-active esters^[16]), stoichiometric metallic reductants are not required.

Given the well-established ability of rhodium(I) complexes to engage vinyl and aryl sulfonates in oxidative addition,^[17] along with their ability to catalyze redox isomerization^[9,10] and reductive C-C coupling,^[1,3] it was posited that vinyl triflates might be competent partners for rhodium-catalyzed aldehyde reductive coupling-redox isomerization mediated by formate. The availability of vinyl triflates from structurally diverse ketones provided further impetus to explore their use in this capacity.^[18] Here, we report that vinyl triflates derived from ketones

engage in efficient reductive coupling-redox isomerization to form cycloalkyl ketones. Like the parent vinyl bromide-aldehyde reductive coupling-redox isomerizations, this protocol may be viewed as an alternative to the addition of stoichiometric organometallic reagents to Weinreb or morpholine amides,^[19,20] however, complementing the scope of the corresponding vinyl bromide couplings, cycloalkyl fragments are amenable to transfer.

In an initial series of experiments, conditions optimized for the rhodium-catalyzed reductive coupling-redox isomerization of vinyl bromides mediated by formate were applied to the coupling of piperonal **1a** with vinyl triflate **2a** (Table 1).^[7] Remarkably, although cyclic vinyl bromides were not competent pronucleophiles for rhodium-catalyzed reductive coupling-redox isomerization (<40% yield despite extensive optimization), the desired product **3a** could be formed from equimolar quantities of **1a** and **2a** in 79% yield after chromatographic isolation. Notwithstanding the aforesaid change in stoichiometry, deviation from these conditions did not avail further improvement. As corroborated by GC-MS, application of these conditions to acyclic vinyl triflates (e.g. hex-1-en-2-yl trifluoromethanesulfonate) provides <10% yield of the desired coupling products due to competing elimination to form alkyne byproducts.^[21]

Table 1. Selected optimization experiments in the rhodium-catalyzed reductive coupling-redox isomerization of piperonal 1a with vinyl triflate 2a.^a



^aYields are of material isolated by silica gel chromatography. See Supporting Information for further experimental details.

To assess the scope of this process, optimal conditions for the rhodium-catalyzed reductive coupling-redox isomerization of piperonal **1a** with vinyl triflate **2a** were applied to structurally diverse aldehydes **1a-1n**. Aromatic aldehydes **1a-1h**, heteroaromatic aldehydes **1i**-**1k**, and aliphatic aldehydes **11-1n** were converted to the corresponding cyclohexyl ketones **3a-3n** in moderate to good yield. As illustrated by the formation of products **3d-3f** and **3j**, aryl fluoride and aryl chloride functional groups are tolerated. Additionally, the formation of product **3m**





^aYields are of material isolated by silica gel chromatography. See Supporting Information for further experimental details.

demonstrates compatibility with olefinic functional groups under the reducing conditions of the reaction. The formation of adducts **3l-3n**, which are derived from aliphatic aldehydes, was accompanied by trace (<5% yield) quantities of aldol dimerization product (Table 2).

The feasibility of utilizing alternate vinyl triflates 2b-g was examined in reductive couplings with piperonal 1a (Table 3). The carbocyclic vinyl triflates 2b-2d, which include the ketal-containing vinyl triflate 2b, the sterically hindered vinyl triflate 2c derived from (+)-nopinone, and the vinyl triflate 2d derived from cyclooctanone, were competent partners for reductive coupling-redox isomerization. Additionally, the heterocyclic vinyl triflates derived from tetrahydro-4-pyranone (2e) and 4-piperidinone (2f) were converted to the corresponding ketones 3r and 3s in good yields. Notably, these processes complement the scope of corresponding vinyl bromide couplings, which are restricted to acyclic proelectrophiles.^[7] Conversely, with the exception of vinyl triflates are inefficient (<10% yield) due to competing elimination to form alkynes (*vide supra*).^[21]

Table 3. Rhodium-catalyzed reductive coupling-redox isomerization of piperonal **1a** with vinyl triflates **2b-2g** to form ketones **3o-3t**.^a



^aYields are of material isolated by silica gel chromatography. ^bVinyl triflate (200 mol%). See Supporting Information for further experimental details.

The catalytic mechanism was corroborated through a series of deuterium labeling experiments (Scheme 1). Exposure of aldehyde *deuterio*-1a and vinyl triflate 2a to standard reaction conditions provides *deuterio*-3a, which incorporates deuterium (>95% ²H) at the β -carbon. Exposure of *deuterio*-iso-3a to

standard reaction conditions provides *deuterio*-3a, with an identical pattern of deuterium incorporation (>95% 2 H). These results are consistent with vinyl triflate-aldehyde reductive coupling to form a transient allylic alcohol that is subject internal redoxto isomerization.^[7,9,10] Finally, aldehyde **1a** was exposed to NaO₂D under standard conditions. Deuterium was not incorporated, which is again consistent with internal redox-isomerization of a transient allylic alcohol.

In summary, we report a method for the direct conversion of aldehydes to ketones via rhodium-catalyzed vinyl triflate-aldehyde reductive coupling-

Scheme 1. Proposed catalytic mechanism as corroborated by isotopic labelling studies.^a



^aThe pattern and extent of deuterium incorporation was assessed through ¹H, ²H NMR and HRMS analyses. See Supporting Information for further experimental details.

redox isomerization mediated by potassium formate. Unlike classical protocols for the preparation of ketones from aldehydes, the present method circumvents the use of stoichiometric metals, premetalated *C*-nucleophiles and discrete redox manipulations. More broadly, this work adds to a growing body of metal-catalyzed reductive couplings that signify a departure from the use of stoichiometric organometallic reagents in C-C bond formation.^[3]

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