Low-Valent Tungsten Redox Catalysis Enables Controlled Isomerization and Carbonylative Functionalization of Alkenes

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Abstract: Tungsten catalysis has played an instrumental role in the history of organometallic chemistry, with electrophilic, fully oxidized W(VI) catalysts featuring prominently in olefin polymerization and metathesis reactions. Here, we report that the simple W(0) precatalyst, W(CO)\textsubscript{6}, catalyzes the isomerization and hydrocarbonylation of alkenes via a W(0)/W(II) redox couple. The 6- to 7-coordinate geometry changes associated with this redox process are key in allowing isomerization to take place over multiple positions and stop at a defined unactivated internal site that is primed for \textit{in situ} functionalization. DFT studies and crystallographic characterization of multiple directing-group-bound W(II) model complexes illuminate potential intermediates of this redox cycle and showcase the capabilities of the 7-coordinate W(II) geometry to facilitate challenging alkene functionalizations.

Main Text: Tungsten is widely employed in commercial applications of central importance to modern society, including hard materials (e.g., tungsten carbide and metal alloys) and petroleum upgrading processes (1) (e.g., the Shell Higher Olefin Process and the Neohexene Process). Tungsten has also played an historically important role in the development of the field of homogeneous catalysis (2). Most notable in this context are catalytic processes that employ high-valent tungsten (e.g., +6) in a fixed oxidation state for alkene and alkyne metathesis (3) and polymerization reactions (4). Low-valent tungsten (e.g., +0), on the other hand, has a strikingly different reactivity profile, in that it possesses the potential for redox reactions, such as oxidative addition and reductive elimination. Moreover, the archetypal W(0) complex, W(CO)\textsubscript{6}, is a bench-stable solid with high functional group tolerance, whereas fully oxidized W(VI) species are generally highly Lewis acidic and oxophilic, manifesting in sensitivity to air, moisture, and many common Lewis basic functional groups. Despite these promising features and the intriguing reactivity that has been demonstrated with stoichiometric low-valent tungsten, such as dearomatization (5-6) and alkene hydrofunctionalization (7-9), low-valent tungsten redox catalysis has been limited to a few specific types of transformations, including alkene isomerization, hydrogenation, and allylic substitution (10-12) (Fig. 1a).
High oxidation state (d⁵–d⁶)
- Extremely reactive towards air and moisture
- Fixed oxidation state, difficult to reduce
- Widely used in catalysis

Low oxidation state (d⁶–d⁷)
- Bench-stable
- Capable of changes in oxidation state
- Rarely used in catalysis

Catalytic alkene isomerization
[Gray, 1973] (Ref. 11)

Cat. W(CO)₆ [limited to hydrocarbons]
[Gray, 1973] (Ref. 11)

Stoichiometric alkene hydroformylation
[Symons et al., 2006] (Ref. 7)

Cat. W(CO)₆ [limited to norbornenes]
[Gray, 1973] (Ref. 11)

Fig. 1. (a) Background of tungsten catalyzed reactions. (b) Coordination chemistry of W(0)/W(II) redox cycle. (c) Known regioselective methods for hydrocarbonylation reactions. (d) This work.

We were drawn to the W(0)/W(II) redox cycle because of the ability of the metal to naturally fluctuate between 6-coordinate octahedral and noncanonical 7-coordinate geometries (Fig. 1b). In theoretical (13-14) and experimental (15-17) studies it has been shown that the facile nature of migratory insertion and reductive elimination at 7-coordinate W(II) or Mo(II) is due to the spatial proximity of the ligands and attractive non-bonding interactions. Additionally, 6-coordinate alkyltungsten(II) species are known to undergo rapid β-H elimination to form 18-electron 7-coordinate W(II)–H species (18-19).

With these findings in mind, we hypothesized that the interplay between 6- and 7-coordinate species could be exploited to address a synthetically important problem, namely tandem isomerization and hydrocarbonylation of alkenes at a classically disfavored position. Alkene isomerization/hydroformylation is one of the highest volume homogenous catalytic reactions in the chemical industry (20), making it a useful reaction for benchmarking reactivity and selectivity patterns. Typically, in this family of reactions, the regioselectivity is dictated by thermodynamics, with functionalization occurring at the most stable alkylmetal intermediate (21-22). In particular, migration of the metal to the terminal position or to a carbon next to a π-system can reliably give linear or α-functionalized products, respectively, in high regioselectivity. Nevertheless, for a given molecule of interest, alternative positions cannot generally be functionalized with current methodology (Fig. 1c). More broadly speaking, controlled alkene isomerization to classically inaccessible internal positions has been limited to a few examples where the isomerization is coupled to an intramolecular cyclization or rearrangement, including 5-endo cyclizations by Kochi (23-26) and [3,3]-sigmatropic rearrangements by Marek (27). Capturing these intermediates via intermolecular functionalization, namely coupling with CO, would offer new possibilities in regiocontrolled alkene functionalization.
We reasoned that the isomerization and tandem carbonylation process could be guided to a traditionally unfavorable position via metallacycle ring contraction (28) or “metallacycle zipping,” with site-selectivity governed by the nature of the directing group employed (29). We envisioned the geometric flexibility of 7-coordinate W(II) would facilitate otherwise challenging endocyclic β-H eliminations required for the directed alkene isomerization. Stabilizing an alkylmetal species of a defined ring size through coordination of the directing group would then allow carbonylative functionalization (30) to take place (Fig. 1c) with high regioselectivity (31). The development of a W(0)-catalyzed directed migratory carbonylation would complement other substrate-directed tandem alkene isomerization/functionaziliation reactions, such as oxidative arylation and hydroalkylation catalyzed by nickel (32-33).

To initiate the study, we tested a library of known directing groups (DGs) for their ability to facilitate isomerization and carbonylation of an alkenyl carboxylic acid derivative with stoichiometric W(CO)₆ at 150 °C (Fig. 2a). Chatani’s NHPic (Pic = 2-picolinyl) directing group (DG4), which was originally developed for ruthenium-catalyzed C(sp²)–H carbonylation (34), gave quantitative yield of the desired product as a single regioisomer. All other directing groups examined failed to give any carbonylated products. Given that W(CO)₆ readily dissociates CO upon UV irradiation (7-8, 11, 18-19, 35-36) we questioned whether the reaction would take place at lower temperature (25 °C) under photocatalytic conditions. Indeed, the desired product was formed in good yield when using stoichiometric W(CO)₆ under an argon atmosphere with irradiation from a 450 Watt UV lamp (Fig. 2, entry 1). With 20 mol% W(CO)₆, there was evidence of turnover (entry 2), but all reactivity shut down with catalytic tungsten under an atmosphere of CO (Fig. 2, entries 3–6). One explanation is that the relatively high concentration of CO in solution at room temperature leads to poisoning of the catalyst. Under thermal conditions (150 °C), 93% of product 2a was obtained using 20 mol% W(CO)₆ under 1 atm CO (entry 8). Other homoleptic metal carbonyls were less effective (Mo, entry 10) or ineffective all together (Cr and Fe, entries 11–12). Although molybdenum is known to exhibit similar reactivity and coordination chemistry to tungsten (9-11, 17) we attribute the higher yield of tungsten in this case to its greater kinetic stability (35). Additionally, a representative panel of Rh, Ru, Co, and Ir precatalysts failed to promote the reaction or did so with low efficiency (See SI for additional screening data).

![Fig. 2](image)

**Fig. 2.** (a) Directing group optimization (see Supporting Information for details). (b) Reaction condition optimization. *a* 1 atm of argon with no added CO. *b* Yield determined by ¹H NMR.
Having optimized the reaction conditions, we next investigated the reaction scope (Fig. 3a). Notably, γ,δ-unsaturated amides bearing various substitution patterns are readily accessible via numerous robust organic reactions (37) including the Diels–Alder cycloaddition, Ireland– or Johnson–Claissen rearrangement, and Wittig olefination. γ,δ-Unsaturated amides containing a terminal alkene and α-monosubstitution afforded the products with high yields and moderate d.r. (2b–2c), while an α,α-disubstituted alkenyl amide (2d) gave lower yield. A derivative of (S)-allylglycine underwent the transformation (2e) and retained high ee (98%) at the α-stereocenter in the case of the major diastereomer. The minor diastereomer showed erosion to 52% ee, suggesting epimerization of the kinetically favored cis product to the thermodynamically preferred trans product. The reaction was effective with 1,1- and 1,2-disubstituted alkenes (2f–2h). The presence of a primary alkyl chloride (2i) or a second, more distal alkene (2j) was well tolerated.

Next, we investigated substrates that require thermodynamically uphill alkene isomerization, which we reasoned could be compensated for in the highly exergonic carbonylation step (vide infra). Indeed, trisubstituted alkenes were isomerized to disubstituted alkenes, which then afforded the desired carbonylated products (2k–2n, 2w) in moderate to high yields. Endocyclic alkenes represent another class of challenging substrates for selective alkene isomerization/functionalization reactions. Pleasingly, Diels–Alder-derived substrates bearing di- (2u–2v) or trisubstituted (2w) alkenes gave moderate yield with exclusively cis stereochemistry at the ring juncture. A cyclopentenyl substrate (2t) also reacted in high yield. Remarkably, exocyclic methyldiene cyclobutane was efficiently isomerized and carbonylated via the intermediacy of a highly strained endocyclic cyclobutene, providing 2o in modest yield and >20:1 dr. Various conjugated alkenes were next evaluated. An α,β-unsaturated ester (2q) provided the product in high yield and with high chemoselectivity. Styrenes with versatile (and potentially sensitive) functional handles, including aryl iodides, bromides, and nitriles (2q–2s) proceeded in high yields.

Lastly, we probed the distance dependence of this isomerization/carbonylation process (Fig. 3b). A substrate requiring no initial isomerization (2x) or isomerization over one position (2a) gave the corresponding products in greater than 90% yield. Moving the alkene farther away led to a gradual decrease in yield from 71% (2g) to 6% (2h). In cases with incomplete conversion to carbonylated product, we observed formation of a mixture of internal alkene isomers accompanied by gradual catalyst death, as evidenced by precipitation of tungsten black. We attribute the decrease in product yield over distance to increased activation entropy in the directed isomerization pathway and the sluggish nature of the alternative non-directed pathway (11). Synthesis of 2a on 5 mmol scale provided the product in 89% yield (951 mg), which could then be hydrolyzed to provide the corresponding 1,4-dicarboxylic acid in 92% yield (See SI).

We were then curious if chiral branched variants of DG4 could control relative stereochemistry in the CO insertion step to provide diastereoselective carbonylated products (Fig. 3c). Introduction of a methyl group at the benzylic carbon (DG7) led to 5:1 d.r. and 82% yield, while progressively more bulky alkyl groups (DG8–DG10) did not lead to further improvement in diastereoselectivity and eventually led to a drastic drop in yield. Use of commercially available, enantiopure (S)-DG7 under catalytic conditions provided the product 2aa in 75% yield and 5:1 d.r. (>99% ee for both diastereomers). Overall, this result establishes a platform for further development of chiral directing auxiliaries for stereocontrolled isomerization/hydrofunctionalization reactions.
The unique features of this catalytic isomerization/carbonylation process motivated us to interrogate the reaction mechanism and the underlying coordination chemistry of the intermediates involved. To examine the potential involvement of W(0)/W(II) redox processes, we first attempted direct synthesis of organometallic intermediates from an alkenyl amide starting material (1xa) by treatment with W(MeCN)$_3$(CO)$_3$ (1 equiv) in CDCl$_3$ at temperatures ranging from 3–60 °C, but...
these experiments only showed formation of the organic product \(2x\) and unreacted starting material \(1xa\) by \(^1\)H NMR (see SI). Thus, we next turned our attention to independent synthesis of isolable model complexes \(W-1\)–\(W-3\) in an effort to establish the feasibility of these W(II) intermediates to undergo CO migratory insertion and reductive elimination (Fig. 4a). Oxidative addition of alkyl iodide \(SM-1\) to \(W(\text{MeCN})_3(\text{CO})_3\) furnished model complex \(W-1\) which is stable in solution for several days. After full conversion of \(SM-1\), AgOTf and KO\(^t\)-Bu/18-crown-6 were added to \(W-1\) at room temperature, triggering migratory insertion and reductive elimination to afford the desired product \((P-1)\) in high yield. Due to our inability to isolate this alkyl tungsten(II) intermediate in crystalline form, further studies focused on more thermally stable aryltungsten(II) species \((37)\) to facilitate analysis by X-ray crystallography.

Using an analogous synthetic sequence, the complexes \(W-2\) and \(W-3\) were prepared by oxidative addition of the corresponding aryl iodides \(SM-2\) and \(SM-3\) to \(W(0)\) \((39)\). \(W-3\) was then treated with AgOTf to abstract the iodide, and further treatment with KO\(^t\)-Bu/18-crown-6 deprotonated the amide. PMe\(_3\) (2.5 equiv) was added to prevent migratory insertion and reductive elimination, as was observed with \(W-1\). Without addition of PMe\(_3\), we were unable to isolate any organotungsten species at this stage, and other ligands (PPh\(_3\), PhCN, tert-butyl isocyanide, or pyridine) failed to form isolable complexes. While \(W-2'\) was found to be unisolable, \(W-3'\) is air- and moisture-stable and can be purified by column chromatography on neutral alumina. The X-ray structure of \(W-3'\) revealed the directing group to be bound in the amidate-form, demonstrating the feasibility of this coordination mode.

![Fig. 4. (a) Synthesis and reactivity studies of organotungsten model complexes. (b) X-ray structures of complexes W-3 (CCDC 2020047) and W-3' (CCDC 204639) with solvent omitted for clarity.](image-url)
Having established plausible oxidation states and coordination structures for many of the key proposed intermediates, we next investigated the mechanism of alkene isomerization. Earlier observations that the amino acid substrate (2e) maintained its stereochemistry at the α-position and that the α,α-disubstituted substrate (2d) gave product indicated that the carbonylation reaction likely proceeds through the β,γ-unsaturated isomer (as drawn in Fig. 3a). To further exclude the alternative hypothesis that the carbonylation proceeds through the conjugated α,β-unsaturated amide, we subjected crotonyl amide 1xb to the standard reaction conditions, and <10% product 23 was observed by 1H NMR of the crude reaction mixture, with the remainder being unreacted starting material (Fig. 5).

Having established the positional aspects of isomerization, we then considered possible mechanisms, namely 1,2- and 1,3-hydride shift pathways (40–41), through a series of deuterium labeling experiments and DFT calculations. To test the feasibility of tungsten to undergo N–H oxidative addition and W(II)–H insertion into alkenes, we conducted a series of experiments in which the amide N–H was exchanged to N–D in situ via treatment with excess CH3OD under the reaction conditions (see SI). Evaluation of different deuterated substrates with terminal alkenes (Fig. 5) of varying distances from the amide gave evidence for this mechanism with 52–96% deuterium incorporation into the terminal position.

Density functional theory (DFT) calculations were performed to identify the catalytically active W species and its reactivity in promoting N–H oxidative addition and alkene isomerization (Fig. 4b) (42). The six-coordinate W(0) complex 1-1 was found to be the most likely species in N–H oxidative addition (see SI for details), leading to a seven-coordinate W(II)–H 1-2. Subsequent metal–hydride insertion (TS2), endocyclic β-hydride elimination (TS3), and metal–hydride reinsertion (TS4) are all facile, leading to a more stable five-membered metallacycle (1-5). An agostic interaction with the endocyclic β-C–H bond in 1-3 promotes the otherwise challenging endocyclic β-hydride elimination (TS3). The seven-coordinate geometry of TS3 and the flexibility of the DG are both critical to alleviate strain in the transition state with a bidentate DG. After CO insertion (TS5) and binding with another CO molecule, the C–N reductive elimination from the seven-coordinate W(II) 1-7 requires a very low barrier (TS6) and is highly exergonic. These DFT results in combination with the mechanistic experiments above show that this 1,2-hydride shift
pathway is the prevailing mode of isomerization, while 1,3-hydride shift is kinetically less favorable (see SI for details).

During the course of the isomerization process, buildup of intermediate internal alkenes is detected for reactions halted prior to completion (see SI), suggesting substrate dissociation and re-association are likely occurring, which is further supported by incorporation of multiple deuterium equivalents at different chain positions. DFT also predicts that ligand exchange of the coordinated alkene with free CO is energetically feasible (see SI for details), which can explain why intermediate internal alkenes can be observed when stopping the reaction early. In chain-walking reactions, premature dissociation of the alkene from the substrate is typically deleterious and leads to side products or intermediates that cannot feed back into the catalytic cycle (43); however, in this reaction it appears to have little effect on the overall yield and regioselectivity.

The results with deuterium-labeled substrate 1g-d revealed an unusual phenomenon (43) that isomerization proceeds in a uni-directional fashion exclusively towards the directing group. Running the complementary experiment with internal alkene 1gb further corroborated the uni-directional nature of isomerization, as no deuterium was detected in the terminal position (Fig. 5). The uni-directional alkene isomerization is consistent with the greater stability of the π-complex with internal alkene (1-4) than the terminal alkene complex (1-2).

When compared to relevant industrial carbonylation processes, this method still has drawbacks that will be addressed in future work, namely the requirement for a stoichiometric auxiliary and relatively high catalyst loadings. Along these lines, directed alkene isomerization/functionalization employing native functional groups holds great promise owing the ability of W(0) to form table adducts with weakly Lewis basic groups (44). Nevertheless, these findings provide an experimental and computational framework for exploring W(0)/W(II) catalytic processes and illustrate how this catalytic cycle can enable exceptional regioselectivity with a diverse range of alkenes in a challenging tandem isomerization/functionalization transformation.
References and Notes:


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Supplementary Materials:
Materials and Methods
Figures S1–S22
Tables S1–S28
Schemes S1–S7
References (42–57)