

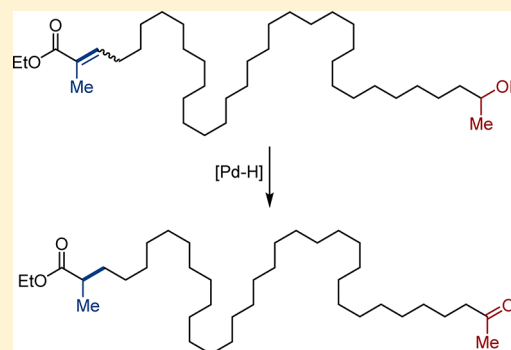
Palladium-Catalyzed Long-Range Deconjugative Isomerization of Highly Substituted α,β -Unsaturated Carbonyl Compounds

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S Supporting Information

ABSTRACT: The long-range deconjugative isomerization of a broad range of α,β -unsaturated amides, esters, and ketones by an in situ generated palladium hydride catalyst is described. This redox-economical process is triggered by a hydrometalation event and is thermodynamically driven by the refunctionalization of a primary or a secondary alcohol into an aldehyde or a ketone. Di-, tri-, and tetrasubstituted carbon–carbon double bonds react with similar efficiency; the system is tolerant toward a variety of functional groups, and olefin migration can be sustained over 30 carbon atoms. The refunctionalized products are usually isolated in good to excellent yield. Mechanistic investigations are in support of a chain-walking process consisting of repeated migratory insertions and β -H eliminations. The bidirectionality of the isomerization reaction was established by isotopic labeling experiments using a substrate with a double bond isolated from both terminal functions. The palladium hydride was also found to be directly involved in the product-forming tautomerization step. The ambiphilic character of the in situ generated [Pd–H] was demonstrated using isomeric trisubstituted α,β -unsaturated esters. Finally, the high levels of enantioselectivity obtained in the isomerization of a small set of α -substituted α,β -unsaturated ketones augur well for the successful development of an enantioselective version of this unconventional isomerization.



INTRODUCTION

The remote functionalization of an organic molecule by alkene isomerization along a carbon skeleton has witnessed increased interest and has inspired the development of particularly intriguing and innovative synthetic methodologies in recent years.¹ The two most critical aspects for the successful realization of such transformations are (i) the triggering event and (ii) the nature of the terminal functional group undergoing refunctionalization (which typically serves as the thermodynamic driving force). Because these reactions often commence with a site-selective insertion of a metal–hydride or a metal–carbon intermediate across the remote C=C bond, the geometry, the substitution pattern, and the polarity of the olefinic moiety constitute additional sources of difficulty. The reactivity of the alkene is typically reduced with increased substitution, and not surprisingly, the majority of reported examples utilize only substrates with a terminal or a disubstituted olefin. This limitation has certainly precluded the development of enantioselective reactions initiated by a hydrometalation event. Finally, sustained-olefin migration becomes more challenging as the span between both ends of the substrate increases. A longer distance may also influence site selectivity of the triggering event with a gradual decay of the directing electronic and steric effects.^{1c} In Figure 1A are displayed some of the most notable and successful examples of recently developed long-range alkene isomerization with substrates possessing a refunctionalizable terminus.^{2,3} In 2000, Mori and co-workers disclosed the thermodynamically counter-

intuitive long-range deconjugative isomerization of α,β -unsaturated amides and esters using a well-defined [Ru–H] precatalyst (Figure 1, A.1).⁴ Although several terminal functions were demonstrated to be compatible (–OBn, –C≡CSiR₃, –HC=CH–Ph, –OSiR₃, –CH(SnR₃)₂), only disubstituted olefins were employed and the products were obtained as statistical *E/Z* mixtures. Grotjahn and co-workers have reported a bifunctional ruthenium catalyst for the isomerization of alkenyl alcohols and alkenyl silyl ethers (Figure 1, A.2).⁵ Notably, long-range olefin migration was only accomplished for substrates with a terminal double bond. When more substituted alkenes were employed, olefin migration occurred only by one carbon atom with essentially unpredictable directionality. Using a typical Pd catalyst employed for olefin polymerization, Kochi and co-workers developed an elegant cycloisomerization of 1,*n*-dienes triggered by [Pd–H] insertion across a terminal C=C bond, followed by chain walking along a linear alkyl chain and a final C–C bond forming event to produce five-membered ring derivatives (Figure 1, A.3).^{6,7} Starting from alkylidene cyclopropanes, a remote and double functionalization was achieved by the Marek group through a zirconocene-mediated allylic C–H bond activation followed by a highly selective C–C bond cleavage (Figure 1, A.4).^{8,9} Although noncatalytic, this approach illustrates how judicious design of the long-range process and

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A. Notable examples of mediated and catalytic transformations involving long-range isomerizations

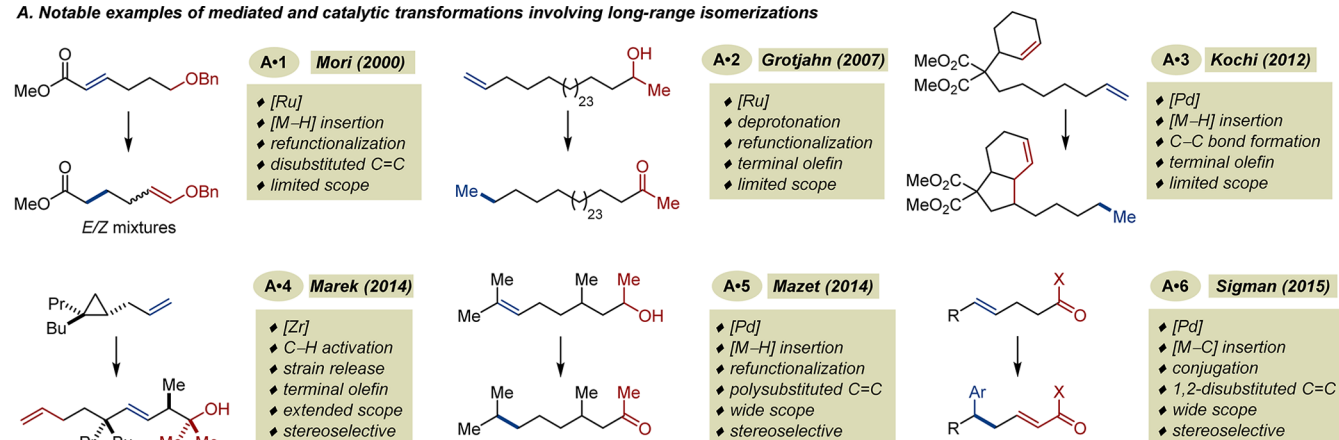
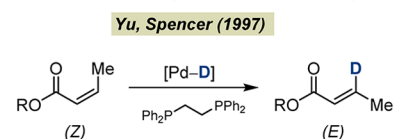
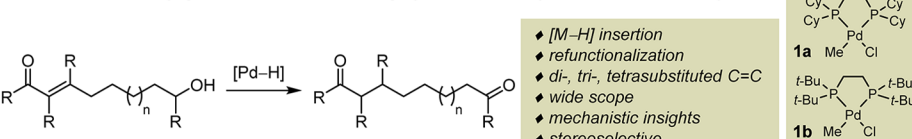
B. Isomerization of α,β -unsaturated carbonylsC. This work: deconjugative isomerization of highly substituted α,β -unsaturated carbonyls

Figure 1. (A) Overview of long-range isomerizations reactions of substrates with a refunctionalizable terminus. Emphasis is placed on the transition metal employed, the triggering event, the thermodynamic driving force, the nature of the C=C bond, and the scope of the process. (B) Site selectivity in the Pd-catalyzed isomerization of crotonyl derivatives. (C) Development of a general Pd-catalyzed deconjugative long-range isomerization of α,β -unsaturated carbonyls.

proper selection of the triggering event may allow a rapid increase in molecular complexity, as high levels of diastereocontrol were achieved. Our group recently disclosed the long-range isomerization of *highly substituted* alkenyl primary and secondary alcohols using either well-defined or in situ generated cationic [Pd-H] catalysts (Figure 1, A-5).¹⁰ Aside from a wide functional group tolerance, the system is essentially insensitive to the number, position, and nature of the substituents of the olefinic moiety. A chain-walking process that operates by iterative sequences of migratory insertion/ β -H elimination was supported by experimental and theoretical investigations. Building on seminal observations made by Molpolder and Heck,¹¹ over the past few years Sigman and co-workers have developed a series of highly enantioselective long-range redox-relay reactions initiated by the arylation of a remote alkene.^{12,13} In their most recent study, the formation of conjugated α,β -unsaturated carbonyls constituted the thermodynamic driving force of the reaction. Site selectivity of [Pd-C] insertion was found to be highly dependent on the length of the alkyl chain, and optimal results were obtained for arylation at the δ -position (Figure 1, A.6). Although differing under many experimental aspects, the dichotomous outcome of the reactions developed by Mori and Sigman is intriguing and delineates a wide spectrum of potentialities offered by long-range isomerization strategies.

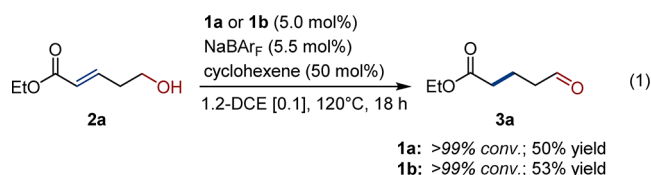
As part of our ongoing program on the development of [M-H]-catalyzed selective isomerization reactions,¹⁴ we set out to develop a general deconjugative long-range isomerization of α,β -unsaturated carbonyls triggered by a hydrometalation event and where refunctionalization of terminal primary or secondary alcohols into aldehydes or ketones would serve as a thermodynamic driving force. Ideally, to become synthetically useful, the reaction should be insensitive to the *nature*, *position*, and *number* of substituents of the C=C bond and migration sustained over alkyl chains of any length. The ultimate prospect

of this approach would be the development of a redox-neutral enantioselective version of this unorthodox reaction which would allow installation of a stereolabile tertiary center α to the initial carbonyl functionality.¹⁵ We hypothesized that the [(dialkylphosphinoethane)Pd] catalysts developed in our group for the long-range isomerization of alkenyl alcohols may offer a potential entry into this area. Nonetheless, according to the seminal study by Yu and Spencer (who used diphenylphosphinoethane (dppe), an analogous bisphosphine ligand), this would require overriding the natural site selectivity of [Pd-H] insertion into α,β -unsaturated carbonyls to observe productive catalysis (Figure 1B).¹⁶

In this article we report the successful realization of our objectives using (bisphosphine)-palladium complexes. We also provide mechanistic information on the site selectivity of the inductive hydrometalation event and on the directionality and termination of the process (Figure 1C).

RESULTS AND DISCUSSION

Reaction Development. Exploratory experiments were conducted with the two palladium precatalysts (**1a–b**) which were recently employed in our laboratories for the long-range isomerization of highly substituted alkenyl alcohols.¹⁰ These complexes, supported by electron-rich and sterically demanding C2-symmetric bisphosphine ligands (dcpe or dtbpe), are air-stable and readily accessible from commercially available precursors. Using the protocol for in situ generation of the active [Pd-H] species, emphasis was first placed on identifying which carbonyl derivatives would be potentially engaged in a deconjugative remote functionalization using substrates with a minimally substituted olefinic moiety. Gratifyingly, productive and quantitative deconjugative isomerization of (*E*)-ethyl-5-hydroxypent-2-enoate **2a** was observed with both catalysts and aldehyde **3a** was isolated in similar yields after column chromatography (50% and 53% respectively; eq 1). The



somewhat moderate yields are attributed to the volatility and relative instability of the aldehyde product. Further optimization of the experimental protocol did not lead to any significant improvement (see Supporting Information (SI)).¹⁷ Subsequently, analogous α,β -unsaturated carbonyls were subjected to identical reaction conditions using **1b** as a precatalyst. For the sake of simplicity and practicality a single protocol was used in all cases (Figure 2A).

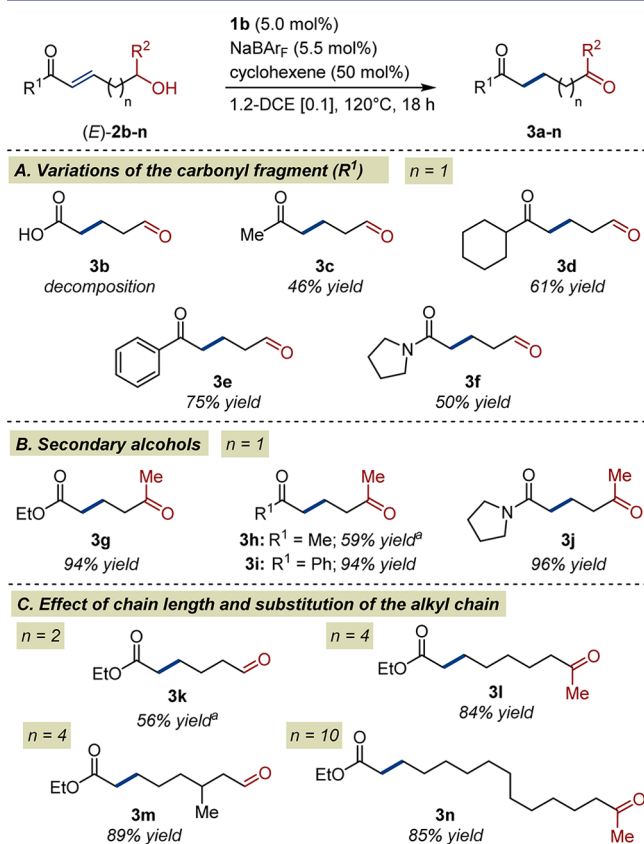


Figure 2. Reactions performed on a 0.25–0.50 mmol scale. Isomerization of disubstituted α,β -unsaturated carbonyls. ^a Using catalyst **1a**.

Whereas a carboxylic acid (**2b**) only led to decomposition products, all other carbonyl groups investigated proved to be competent substrates for the long-range isomerization reaction and were systematically completely consumed (**3c–f**). Isolated yields varied between 46% for the most volatile methyl ketone derivative (**3c**) to 75% for **3e**, obtained from an α,β -unsaturated phenyl ketone. Overall, α,β -unsaturated esters, aryl or alkyl ketones, and amides proved to be viable substrates for the palladium-catalyzed deconjugative isomerization reaction using **1b**.

In line with observations made during the development of the remote isomerization of alkenyl alcohols, α,β -unsaturated carbonyls with a secondary alcohol terminus were usually isomerized into the corresponding ketones in higher yields than

the corresponding primary alcohols (Figure 2B). Representatively, 1,5-keto ester **3g** was isolated in 94% yield vs 53% for **3a** (compare with second run on eq 1). We believe that this difference in productivity is mostly due to the higher stability of ketones over aldehydes and their reduced tendency to form oligomeric materials.¹⁸ Increasing the alkyl chain length has virtually no impact on the efficiency of the process and **2n**—a substrate with 10 C-atoms between the β -position and the carbinol carbon—was isomerized in **3n** in 85% yield (Figure 2C). Of significant note, the presence of an alkyl substituent along the chain does not interrupt catalysis (**3m**, 89% yield).

Scope of α,β -Unsaturated Carbonyls with a Highly Substituted C=C Bond. We next set out to explore the effect of increased substitution of the C=C bond on the feasibility of the process. We were pleased to observe that the presence of a substituent in the α - or β -positions of the unsaturation of the carbonyl derivative did not compromise the efficiency of the reaction, as apparent from the overall results displayed on Figure 3. Long-range isomerization of α,β -unsaturated aryl or alkyl ketones with an α -alkyl substituent led to the corresponding dicarbonyl products (i.e., 1,5 keto-aldehydes) in moderate to good yields (41%–72% yield). Substrates with an α -aryl substituent proved more difficult to isomerize, and the refunctionalized products were isolated in moderate to low yields (22%–42% yield; Figure 3A). Isomerization of trisubstituted α,β -unsaturated esters usually gave higher yields because secondary alcohols were employed in most cases (Figure 3B). Interestingly, the presence of an α -methyl or a β -methyl substituent did not affect the site selectivity of [Pd–H] insertion across the C=C bond and the corresponding dicarbonyl compounds were isolated in similar yields (**3k**: 53%; **3m**: 56%). A similar observation was made for α -aryl- and β -aryl-substituted precursors (**3n**: 40%; **3o**: 49%). Electron-rich, electron-poor, and sterically demanding α -aryl substituents were particularly well-tolerated (**3p–3t**: 63–97% yield) as was the case for α -O- and α -N-containing heterocyclic rings (**3u**: 72%; **3v**: 61%). A substrate with a tetrasubstituted C=C bond was effectively isomerized affording **3x** in 41% yield as a 1:1 mixture of *syn/anti* isomers. Despite the moderate yield, this result is particularly remarkable because examples of remote alkene isomerization of substrates with a highly substituted olefinic moiety are very rare. Finally, to further explore the limits of precatalyst **1b** in effecting remote deconjugative isomerization, a trisubstituted α,β -unsaturated ester with 30 C-atoms between the β -position and the carbinol carbon of the secondary alcohol located at the other end of the alkyl chain (**4y**) was subjected to the optimized reaction conditions (Figure 3C). Much to our satisfaction, complete consumption of the starting material was observed and **5y** was isolated in 72% yield after purification by column chromatography.

Mechanistic Investigations. In a preliminary effort to gather information on the mechanism of this long-range deconjugative isomerization of α,β -unsaturated carbonyls, a series of complementary experiments were conducted. Isomerization of the optically active 1,2-disubstituted α,β -unsaturated ester **2m** (97% *ee*) afforded aldehyde **3m** in 72% yield in racemic form (Figure 4A). By analogy with the isomerization of alkenyl alcohols using an identical catalyst and similar reaction conditions, this result suggests that (i) a chain-walking mechanism consisting of iterative migratory insertions/ β -H eliminations is also operating for the deconjugative isomerization reaction and (ii) that the catalyst dissociates from the substrate during the C=C bond migration process. To

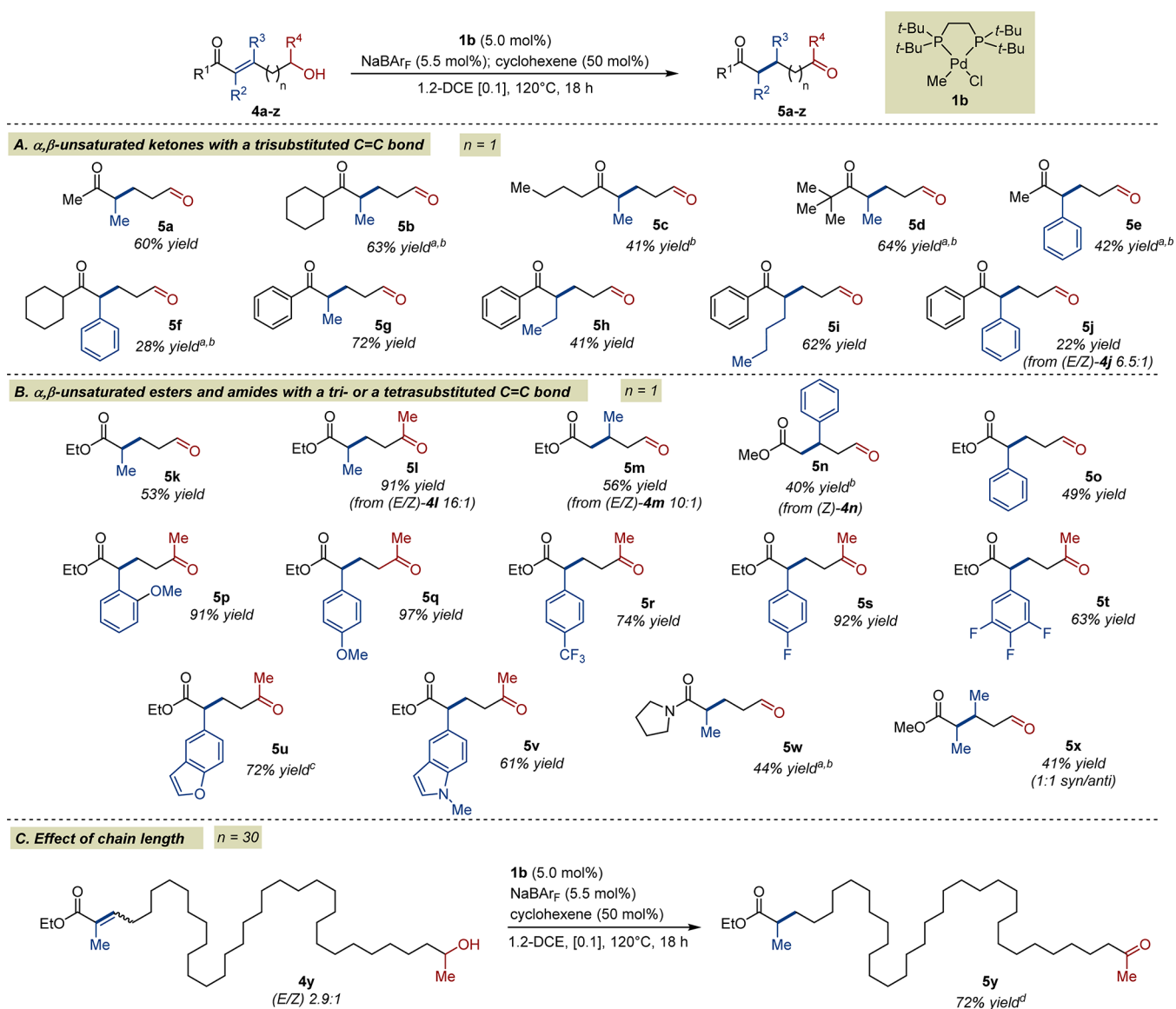


Figure 3. Reactions conducted on a 0.25–0.50 mmol scale. (A) Remote isomerization of α,β -unsaturated ketones with a trisubstituted C=C bond. (B) Remote isomerization of α,β -unsaturated esters and amides with a tri- or tetrasubstituted C=C bond. (C) Effect of chain length. All substrates were prepared as geometrically pure (*E*) isomers unless otherwise noted. ^a Using microwave irradiations (2 h, 140 °C). ^b With **1a**. ^c 10 mol % of **1b**, 11 mol % NaBAR_F, and 100 mol % cyclohexene. ^d Reaction performed on 0.1 mmol scale.

qualitatively investigate the directionality of the reaction, isotopic labeling experiments were carried out next using **2o**, a substrate with a C=C bond isolated from both the carbonyl and the secondary alcohol functionalities. The palladium deuteride was generated in situ using various amounts of precatalyst **1b**, NaBAR_F, and cyclohexene-*d*₁₀, and the reactions were analyzed by ¹H and ²H NMR of the crude mixtures (Figure 4B). Similar degrees of D-incorporation were measured in all positions, independently of the initial catalyst loading. Deuterium was detected at all methylenic positions to relatively similar extents indicating very poor site selectivity for [Pd–D] insertion. Importantly, incorporation at positions C1, C2, C5, and C7 further supports the chain-walking nature of the isomerization reaction and, more importantly, clearly indicates that the process is bidirectional. Observation of deuterium at the enolizable position C7 is consistent with a Pd-assisted tautomerization.¹⁹ Of note, no D-incorporation was observed when a nondeuterated keto-product was subjected to catalysis,

supporting the notion that the product forming step is certainly irreversible. To question further the site selectivity of [Pd–H] insertion across the C=C bond of the α,β -unsaturated carbonyl, substrate **2p** was submitted to the typical conditions for long-range isomerization (Figure 4C). After 18 h, the α,β -unsaturated ester **2q** and the 1,6-keto ester **3p** resulting from productive catalysis were formed in 30% and 39% yield respectively. After isolation, **2q** was successfully resubmitted to catalysis and quantitatively converted to **3p**, indicating it constitutes a viable intermediate in the conversion of **2p** into **3p**. Collectively, these results demonstrate the ambiphilic nature of the in situ generated [Pd–H] intermediates, as they can insert both in the α - and β -positions of a trisubstituted α,β -unsaturated ester to yield the refunctionalized product. This result is in contrast with the perfect site selectivity of [Pd–H] insertion reported by Yu and Spencer in the isomerization of crotonyl esters.¹⁶ Because subtle variations in ligand design can have a strong impact on the hydridic/acidic character of [M–

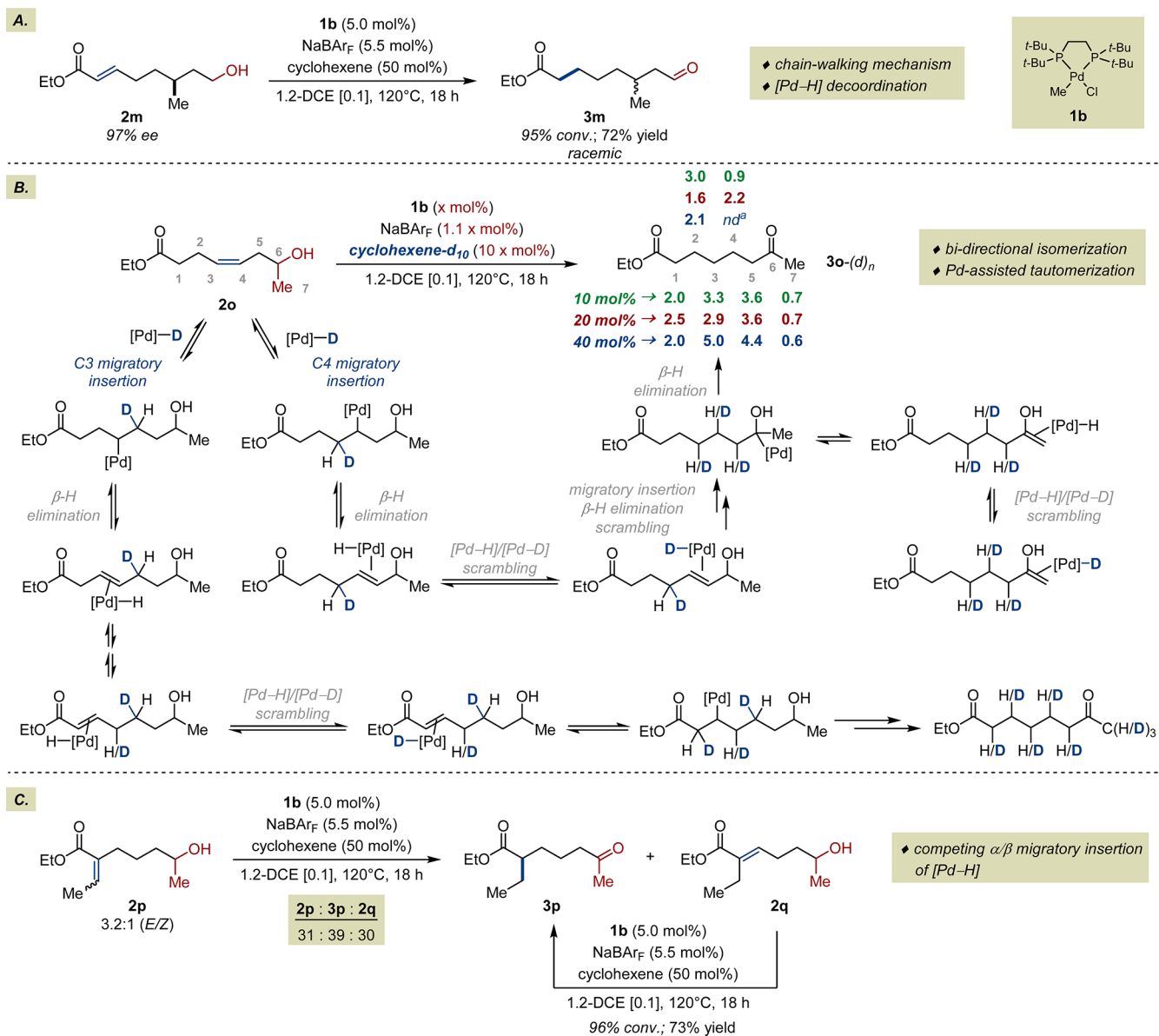


Figure 4. Reactions conducted on a 0.10–0.25 mmol scale. (A) Determination of the chain-walking nature of the isomerization process using optically active α,β -unsaturated ester **2m**. (B) Assessment of the directionality of the isomerization reaction by isotopic labeling experiments. Extent of D-incorporation (in %). (C) Interrogating site selectivity of $[\text{Pd-H}]$ insertion across the $\text{C}=\text{C}$ bond using trisubstituted α,β -unsaturated esters **2p** and **2q**. ^a Not determined due to signal overlap with the deactivated catalyst.

H] bonds, it is likely that the electronic and steric difference between dppe and dtbpe (or dcpe) may explain this divergent behavior.^{10,20,21}

Enantioselective Catalysis. Exploratory investigations were performed using substrates **4a–b,g,k** to identify a chiral catalyst suitable for the development of a highly enantioselective variant of the long-range deconjugative isomerization of α,β -unsaturated carbonyls (Figure 5). To accelerate the pace of ligand evaluation, we found that isomerization reactions could be conducted with similar productivity within only 2 h at 140 °C under microwave irradiations (see SI for details). From a preliminary screening of commercially available chiral bisphosphines, (*S*)-binapine was identified as the most promising candidate.²² The long-range isomerization of α,β -unsaturated ester **4k** delivered the corresponding dicarbonyl product **5k** in low yield and modest enantioselectivity (10% yield, 53% *ee*). Nonetheless, the very promising results obtained in the

isomerization of α,β -unsaturated ketones **4a–b,g** clearly establish a solid proof-of-concept for the enantioselective long-range deconjugative isomerization. Representatively, isomerization of **4g** afforded **5g** quantitatively in 88% *ee*. Achieving such a high level of enantio-induction is simply remarkable when considering the issue associated with site-selective $[\text{Pd-H}]$ insertion across the $\text{C}=\text{C}$ bond and the bidirectional nature of the migration process.²³ Synthetically, this transformation is of interest because (i) upon isomerization two carbonyl groups with distinct oxidation states are generated at both ends of the molecule, a situation favorable for subsequent orthogonal derivatizations, and (ii) a potentially stereolabile α -alkyl tertiary center is generated with a high level of stereocontrol under redox-neutral reaction conditions.¹⁵

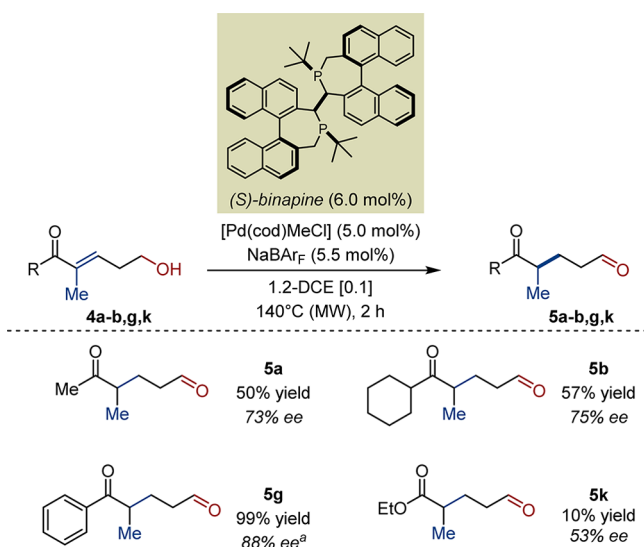


Figure 5. Enantioselective deconjugative isomerization of α,β -unsaturated ketones **4a–b,g** and ester **4k**. Reactions performed on a 0.25 mmol scale. ^a With 50 mol % cyclohexene.

CONCLUSION

In conclusion, we have developed a catalytic system for the long-range deconjugative isomerization of α,β -unsaturated amides, esters, and ketones. The reaction is initiated by a hydrometalation step with an in situ generated $[\text{Pd}-\text{H}]$, and the refunctionalization of a primary or a secondary alcohol positioned at the end of an alkyl chain into an aldehyde or a ketone serves as a strong thermodynamic driving force. Not only substrates with a disubstituted olefinic moiety are efficiently isomerized but also more challenging α,β -unsaturated carbonyls with a tri- or tetrasubstituted $\text{C}=\text{C}$ bond are also competent for this reaction. This is unusual because a recurrent limitation to the development of efficient isomerization reactions is the difficulty of most catalysts to coordinate and react with highly substituted olefins. The refunctionalized products are usually isolated in good to excellent yield. A variety of functional groups and substitution patterns are tolerated, and olefin migration was achieved over 30 carbon atoms. Preliminary mechanistic studies point to a chain-walking isomerization process consisting of iterative migratory insertion/ β -H elimination sequences. In addition, we clearly demonstrated that the catalyst can decoordinate from the substrate but catalysis is not interrupted. Isotopic labeling experiments were used to demonstrate the bidirectionality of the isomerization reaction, and the transient palladium hydrides were shown to participate in the product-forming tautomerization. Further studies clearly established that the in situ generated $[\text{Pd}-\text{H}]$ species are ambiphilic in nature. Finally, high levels of enantio-induction have been obtained in the enantioselective deconjugative isomerization of a handful of α,β -unsaturated ketones. Efforts in our laboratories are currently directed at identifying a general chiral catalyst for this unusual transformation.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b06390.

Experimental procedures, characterization of all new compounds, and spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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