RESEARCH ARTICLE

Stereodivergent, Kinetically Controlled Isomerization of Terminal Alkenes via Nickel Catalysis

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Abstract: Because internal alkenes are more challenging synthetic targets than terminal alkenes, metal-catalyzed olefin mono-transposition (i.e., positional isomerization) approaches have emerged to afford valuable *E*- or *Z*- internal alkenes from their complementary terminal alkene feedstocks. However, the applicability of these methods has been hampered by lack of generality, commercial availability of precatalysts, and scalability. Here, we report a nickel-catalyzed platform for the stereodivergent *E*/*Z*-selective synthesis of internal alkenes at room temperature. Commercial reagents enable this one-carbon transposition of terminal alkenes to valuable *E*- or *Z*-internal alkenes via a Ni–H-mediated insertion/elimination mechanism. Though the mechanistic regime is the same in both systems, the underlying pathways that lead each of the active catalysts are distinct, with the *Z*-selective catalyst forming from comproportionation of an oxidative addition complex followed by oxidative addition with substrate and the *E*-selective catalyst forming from protonation of the metal by the trialkylphosphonium salt additive. In each case, ligand sterics and denticity control stereochemistry and prevent over-isomerization.

Introduction

Alkenes are simple yet reactive functional groups that can engage in a myriad of functionalization reactions.[1] Their unique reactivity profile makes them important intermediates in multi-step chemical syntheses.[2, 3] Beyond their role as synthetic intermediates, alkenes are abundant in industrial and fine chemicals, and entire fields have been dedicated to their synthesis, such as the areas of olefin metathesis and carbonyl olefination (Figure 1A).[4-6] While terminal alkenes are often commercial or relatively simple to access, internal ones represent a greater synthetic challenge and require specialized reagents and/or catalysts. Commodity chemical syntheses such as the Shell Higher Olefin Process (SHOP) exploit the chemical efficiency of base-catalyzed isomerization to form mixtures of internal alkenes that are diverted towards different product streams. In contrast, fine chemical synthesis tends to involve more controlled, less atom-economical ways to introduce internal C=C bonds (Figure 1B).[7, 8a-d]

Controlling alkene isomerization is a challenge because of the similar thermodynamic stabilities of the multiple unsubstituted internal alkenes that can arise.[7b, 8e-i] In addition to the existence of positional isomers, internal alkenes exist as the *E*- or *Z*-isomer. Due to the prochiral nature of *E*- or *Z*-alkenes, and the reactivity differences between the two, it is desirable to form internal alkenes in an entirely *E*- or *Z*-selective fashion.[8g, 9] Yet, the entropy term in Gibbs free energy denotes that thermodynamic isomerization reactions will lead to both stereoisomers, and therefore, moving beyond thermodynamic control to achieve *E*/*Z* selectivity remains challenging.[8e]

Many research groups have attempted to address positional and stereochemical isomerism within alkene isomerization (Figure 1C). Approaches using thermodynamic control allow selective formation of conjugated, tri-, or tetra-substituted alkenes via alkylmetal chain walking, but these positional isomers are not always desired.[10] Our laboratory and others have reported strategies that rely on catalysts that chelate to the substrate, thereby directing isomerization to a single position.[11] However, this approach limits the substrate classes to those that contain specific directing groups. The only way to control positional isomerization without substrate modification is to achieve kinetic selectivity using a catalyst or mediator. In this regime, a single transposition of a terminal olefin is more favorably followed by dissociation of product and chelation of starting material than further C=C transposition. Within base-metal catalysis, kinetic alkene transposition to *Z*- and *E*-isomers has been reported (Figure 1D).[8e, 12-15] A comparison of methods for the isomerization of homoallyl arenes, which are informative model

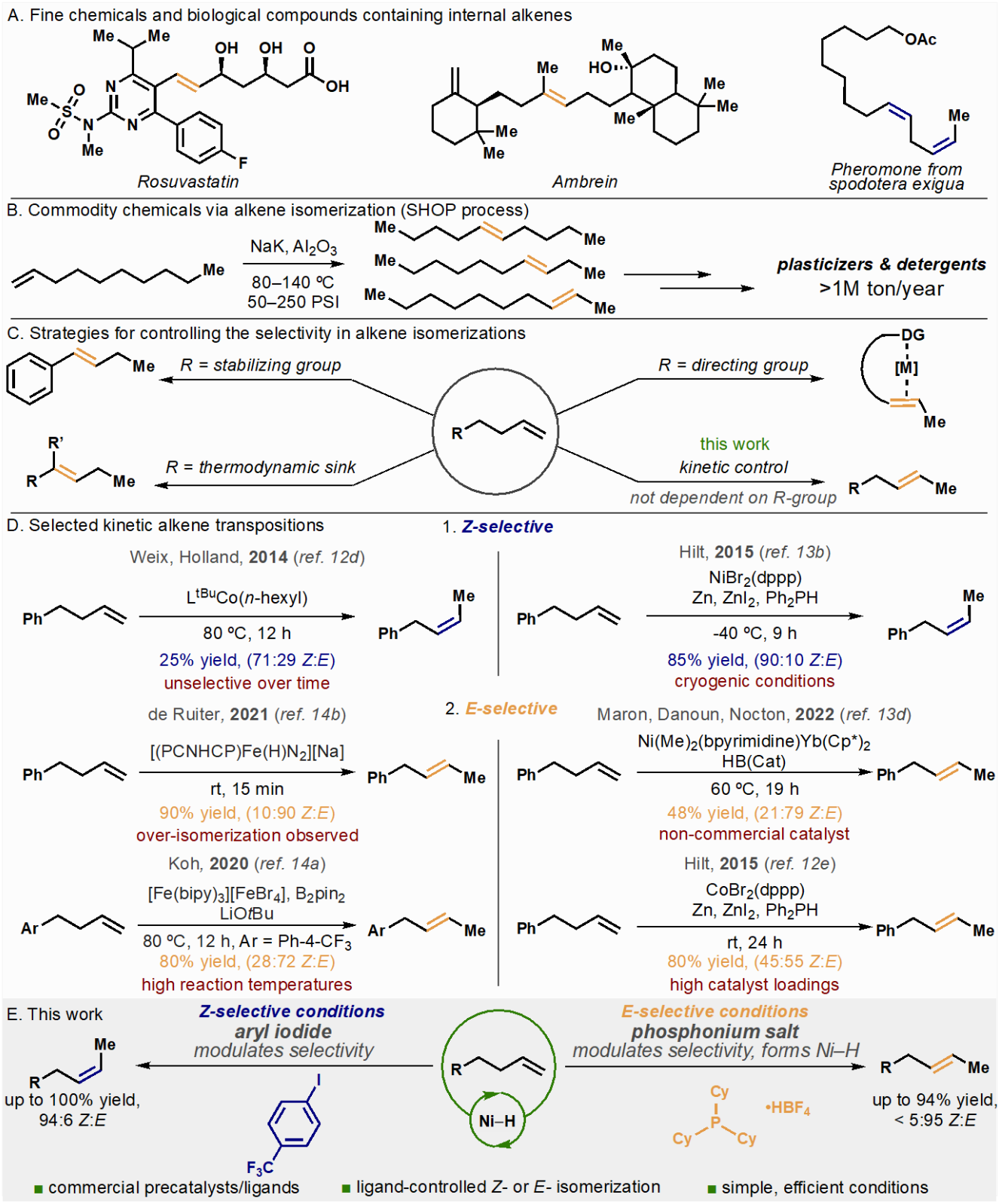


Figure 1. Relevance, precedents, and synopsis of work.

substrates due to the possibility of competing chain-walking isomerization, reveals persistent limitations including the use of low temperatures or long reaction times.[16] Exogenous hydride additives and uncaged radical mechanisms diminish the functional group tolerance and scope of some of the reported transformations, while others must be monitored and stopped before selectivity erodes.

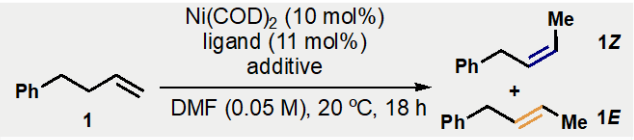
Herein, we report a stereodivergent platform for the *E*- or *Z*-selective isomerization of alkenes under kinetic control (Figure 1E). Commercial reagents enable this one-carbon transposition

of terminal alkenes to valuable *E*- or *Z*-internal alkenes via a Ni–H-mediated insertion/elimination mechanism. Though the overall mechanistic regime is the same in both systems, the underlying pathways that lead each of the active Ni–H catalysts are distinct. The *Z*-selective Ni–H forms from oxidative addition of substrate, and the *E*-selective catalyst forms from protonation of the metal by the additive. Further, ligand sterics and denticity control stereochemistry. A hindered, bidentate bisphosphine and inner-sphere halogen derived from comproportionation of an aryl iodide are important for high *Z*-selectivity. In contrast, a moderately-sized, monophosphine promotes formation of the *E*-isomer without leading to over-isomerization. Important features of this work include mild conditions (i.e., room temperature without reductants), operational simplicity, and tolerance for many classes of functional groups.

Results and Discussion

Optimization and Substrate Scope

The *Z*-selective alkene mono-transposition reaction was discovered during an otherwise unrelated study. *Z*-Enriched internal alkene **1*Z*** formed from 4-phenyl-1-butene (**1**), and it was quickly concluded that the electron-poor aryl iodides played a key role in mediating stereoselectivity.



Entry	Ligand	Additive	Yield	*Z*:*E* ratio
1	dppf	-	78%	58:42
2	PCy_3	-	trace	-
3	dppf	*p*-$CF_3C_6H_4I$ (0.5 equiv)	90%	84:16
4	dppb	*p*-$CF_3C_6H_4I$ (0.5 equiv)	53%	87:13
5	Xantphos	*p*-$CF_3C_6H_4I$ (0.5 equiv)	28%	76:24
6	PCy_3	*p*-$CF_3C_6H_4I$ (0.5 equiv)	n.d.	-
7[a]	dppf	*p*-$CF_3C_6H_4I$ (0.5 equiv)	91%	93:7
8	dppf	collidine•HBF_4 (0.1 equiv)	72%	56:44
9	xantphos	collidine•HBF_4 (0.1 equiv)	trace	-
10	PPh_3	collidine•HBF_4 (0.1 equiv)	72%	26:74
11	PCy_3	collidine•HBF_4 (0.1 equiv)	67%	16:84
12[b]	PCy_3•HBF_4	-	83%	17:83
13	PCy_3•HBF_4	H_2O (0.5 equiv)	95%	18:82

Table 1. Optimization of reaction conditions. Reactions were performed on 0.10 mmol scale unless otherwise noted. Yields and selectivities were determined by ^{1}H NMR using CH_2Br_2 as internal standard. [a] Reaction performed in DMA (0.1 M) with 7.5 mol% dppf on 0.15 mmol scale. [b] Reaction performed on 0.15 mmol scale.

During ligand evaluation, replacement of dppf (1,1′-bis(diphenylphosphino)ferrocene) with Cy_3P•HBF_4 (tricyclohexylphosphonium tetrafluoroborate), a source of phosphine ligand and acid to generate a cationic Ni–H (vide infra), was found to switch product selectivity from ***1Z*** to **1*E*** in 18:82 *Z*:*E* ratio. The regiodivergent reaction conditions were then tested with a variety of phosphines, either using electron-deficient 4-$CF_3C_6H_4I$ or collidine•HBF_4 as additive (Table 1). Bidentate ligands, in combination with aryl iodide, led to the highest *Z*-selectivity. Additionally, the loading of $Ni(COD)_2$ [bis(cyclooctadiene)nickel(0)] could be lowered to 2.5 mol%, with alkene **1*Z*** forming in 85% yield and 92:8 *Z*/*E* selectivity. A small panel of substrates was tested at this catalyst loading (SI Figure S1). Monophosphines led to the most *E*-selective catalyst when combined with an acid source but were inactive without it. Half an equivalent of water was found to increase the yield of the *E*-selective reaction by preventing over-isomerization.[17]

Following evaluation of the reaction parameters, the performance of the two protocols was demonstrated across three substrate classes: those in which mono-transposition furnishes an unactivated olefin, a conjugated olefin, or an olefin α to a heteroatom.[18] Isolated yields, *Z*:*E* selectivities of crude reaction mixtures, and relative conversions to mono-transposition versus over-isomerized products are reported. Selectivity for kinetic isomerization product is high, and cases with moderate to low isolated yields are due to substrate volatility or remaining starting material. Olefin transposition into unactivated positions led to internal alkenyl alcohols, boronic esters, thioethers, alkyl chlorides, amides, epoxides, and alkyl fluorides, affording *Z*- or *E*-alkenes in high yields and selectivities (Table 2A, **2**–**4** and **6**–**9**). While substrate **5** demonstrates the compatibility of carboxylic acids under the reaction conditions, both protocols selectively led to the *E*-isomerized product in moderate yields, likely due to a directivity effect of the carbonyl moiety that overrides ligand control.[19, 20] Styrenyl diene **11** was not tolerated using **protocol *E*** but led to **11*Z*** using **protocol *Z***. While pyridines were well-tolerated under **protocol *E*** and ***Z***, the latter led to the conjugated alkene with perfect *E*-selectivity (**10*E'***). **Protocol *E*** led to trisubstituted alkene **12P** from vinyl cyclohexane, while **protocol *Z*** did not yield any product from this substrate. Both protocols were scaled up with **1** as model substrate (1-g scale), and products **1*Z*** and **1*E*** were isolated in high yields and selectivities. Reported methods for kinetic alkene transposition can be low yielding for products that contain conjugated olefins.[12j] Under **protocols *E*** and ***Z***, the isomerization was not hampered by such substrates, and aryl chlorides, aryl fluorides, cyclic alkenes, and phenols were well-tolerated (Table 2B, **13**, **15**, **17**-**18**). For nonpolar substrates **13**-**15** and **18**, use of the more polar aryl iodide *p*-CNC_6H_4I enabled isolation of pure product by column chromatography. An aryl bromide was also tolerated, albeit giving lower conversion (**14**). Although *E*-selective in both protocols, a substrate bearing an aniline moiety (**16**) was tolerated under the reaction conditions. A styrenyl alkyne was not tolerated under **protocol *E***, but **19*Z*** formed smoothly.

Under modified conditions in which dppf is exchanged with dppb (1,4-bis(diphenylphosphino)butane), **protocol *Z*** can mediate olefin isomerization to positions α to heteroatoms in high yield and

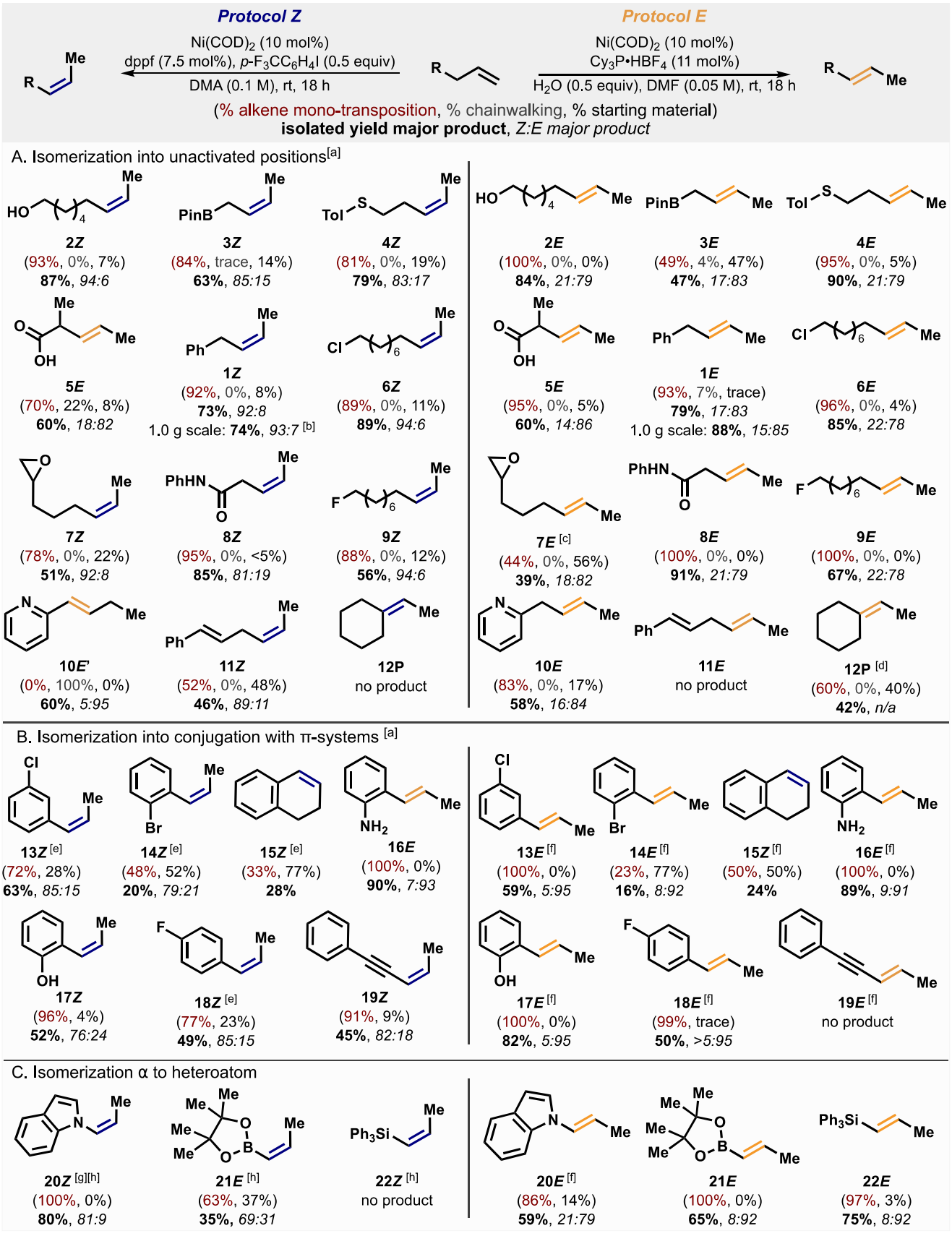
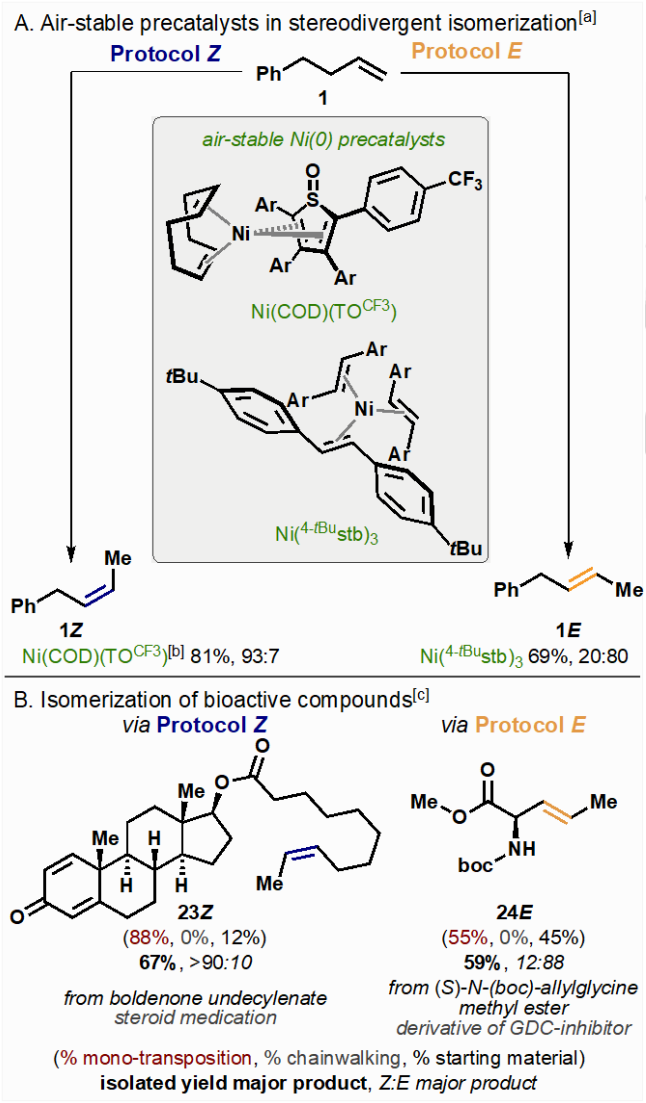


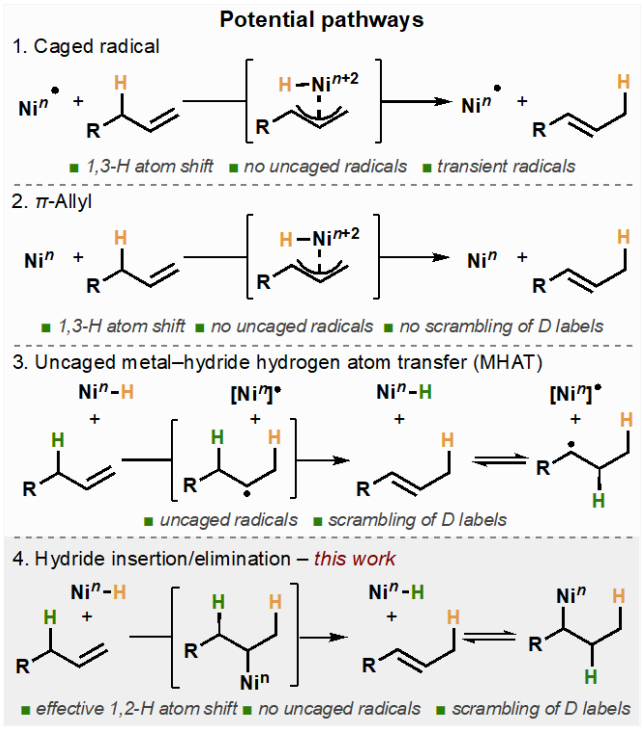
Table 2. Substrate scope. Reactions were run on 0.25 mmol scale unless otherwise stated. [a] Isolated yields are calculated adjusted for remaining starting material when appropriate (see SI for more details). Selectivities were determined by ^{1}H NMR of the crude reaction. [b] 2.5 mol% $Ni(COD)_2$ and 0.4 M DMF [c] No water added. [d] Product was not isolated due to volatility. Yield represents ^{1}H NMR yield relative to 1,1,2,2-tetrachloroethane internal standard. [e] *p*-CNC_6H_4I used instead of *p*-$CF_3C_6H_4I$. [f] TBABr (0.5 equiv) added. [g] 55 °C. [h] dppb instead of dppf.

selectivity of indole **20*Z*** and moderate yield and selectivity of boronic ester **21*E***. These two substrates and allyl silane **22** lead to high yields and selectivities of **20*E*–22*E*** under **protocol *E***.[21] To further improve the synthetic utility of the two protocols, compatible air-stable Ni(0) precatalysts were identified. Using 20 mol% of Ni(COD)(TO^{CF3}) (TO = thiophene oxide) from the Ni(COD)(EDD) (EDD = electron deficient diene) precatalyst family provided high yield and selectivity of product **1*Z***, and 10 mol% of Ni(^{tBu}stb)$_3$ from the Ni(stb)$_3$ (stb = stilbene) precatalyst family gave good yield and selectivity of **1*E*** (Scheme 1).[22] Both protocols lead to slightly lower yield but comparable selectivity to Ni(COD)$_2$. A handful of bioactive compounds and their derivatives were evaluated using the two protocols.[21] Boldenone undecylenate, a veterinary steroid medication, could be isomerized to **23*Z*** in high conversion and *Z*-selectivity. Chiral amino acid **24**, which is a derivative of a GDC (glutamate decarboxylase) inhibitor, could be isomerized in moderate conversion and *E*-selectivity under **protocol *E***. These experiments demonstrate that good selectivities and yields can be achieved with complex bioactive compounds.



Scheme 1. Air-stable precatalysts for *E*- and *Z*-selective isomerization reactions. [a] Reactions were performed on 0.15 mmol scale. Yields and selectivities were determined by ^{1}H NMR with CH_2Br_2 internal standard. Ratios are formatted as *Z*:*E*. [b] 20 mol% [Ni] and 15 mol% dppf. [c] Reactions were performed on 0.25 mmol scale. Isolated yields are calculated adjusted for remaining starting material when appropriate (see SI for more details). Selectivities were determined by ^{1}H NMR of the crude reaction.

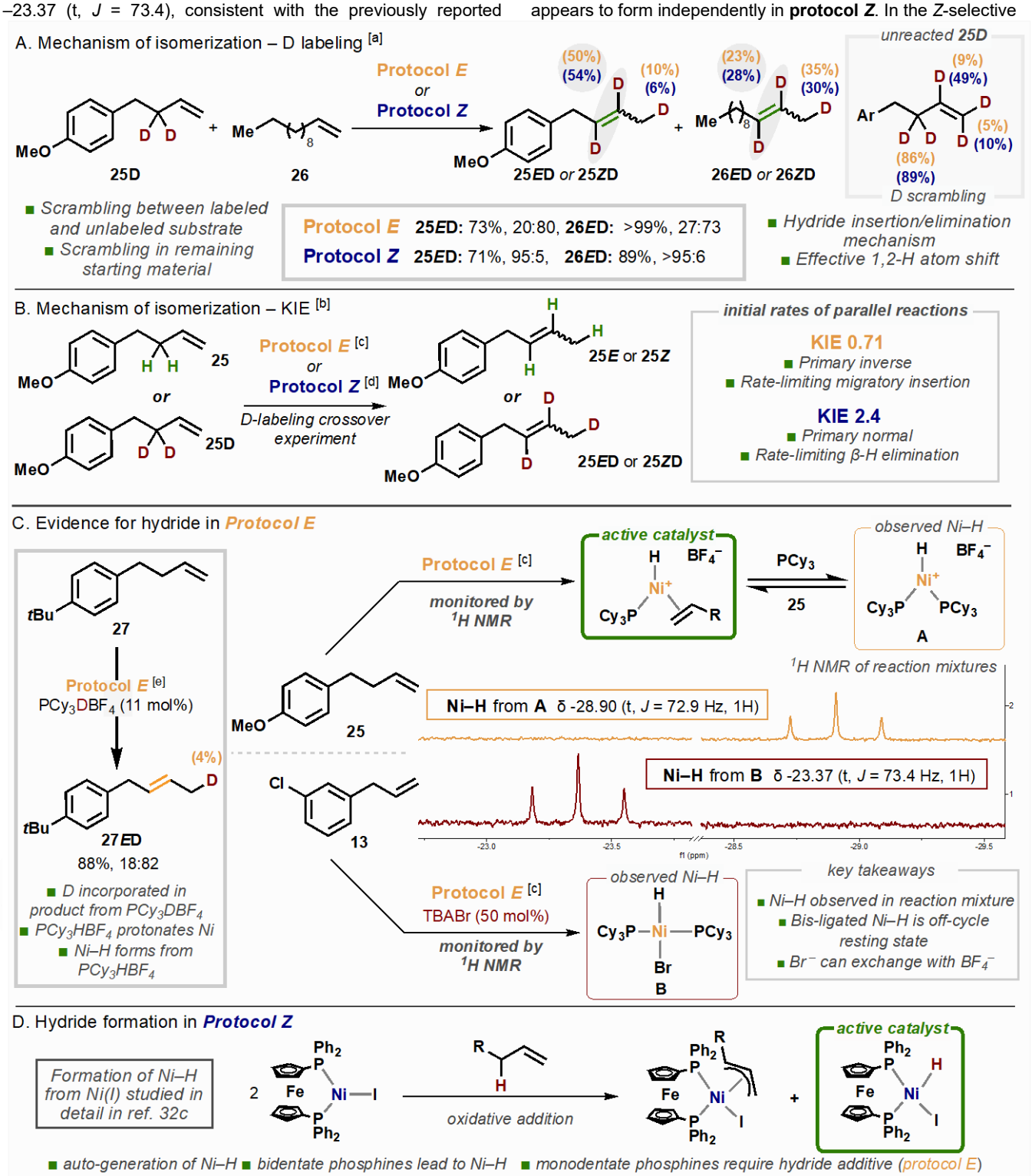
Mechanistic Studies



Scheme 2. Potential pathways of olefin isomerization.

Mechanistic studies were undertaken to understand how the additives in each reaction lead to the active catalysts that offer divergent selectivity. Four general mechanisms for catalytic olefin isomerization were considered: caged radical,[10e] π-allyl,[3, 7b, 8d, 8f, 8g, 9, 11d, 13f, 23a, 23c] uncaged metal–hydride,[8f, 24b] and hydride insertion/elimination (i.e., 1,2-hydrogen atom shift).[3, 7b, 8d, 8f, 8g, 9, 13g, 23a, 23c, 24] (Scheme 2).[22d] Experiments with radical traps and radical clocks indicated that radical-based mechanisms are not operative.[25] To distinguish between the two closed-shell mechanisms, deuterium-labeling experiments were performed. Allylic D$_2$-labeled alkene led to scrambling of the D-label, and crossover was observed between labeled and unlabeled substrates as well as within the remaining starting material (Scheme 3A). Thus, despite the differences in additives between the two reactions, a Ni–H-mediated insertion/elimination mechanism is operative in both reaction systems. Kinetic isotope experiments (KIE) using parallel reactions with labeled and unlabeled substrate were performed next (Scheme 3B). A primary, inverse KIE of 0.71 was measured for **protocol *E***. This inverse KIE is consistent with turnover-limiting migratory insertion of the Ni–H into the alkene.[26] However, an alternative scenario of pre-equilibrium protonation of the nickel center prior to migratory insertion, with H/D identity influencing the observed KIE value, cannot be ruled out at this time.[27] A primary normal KIE of 2.4 was measured for **protocol *Z***, indicating that β–H elimination is

turnover-limiting.[12i-12j, 28] Use of PCy_3•DBF_4 resulted in deuterium incorporation in the methyl position of product **1*ED***, which indicates that the trialkylphosphonium salt generates the Ni–H. In situ ^{1}H NMR reaction monitoring of **protocol *E*** revealed a peak at –28.90 (t, *J* = 72.9), which we assign to the cationic bisphosphine species $(PCy_3)_2NiH(BF_4)$, which is a plausible catalyst resting state (Scheme 3C).[29] Addition of TBABr (tetrabutylammonium bromide) resulted in a new resonance at –23.37 (t, *J* = 73.4), consistent with the previously reported bromide complex, $(PCy_3)_2NiHBr$, supporting our assignment.[30] Protonated phosphine salts were originally designed as air-stable phosphine precursors that can be revealed in the presence of base, [31] but incorporation of deuterium from PCy_3•DBF_4 in the product indicates that Ni^0 is sufficiently basic to deprotonate the phosphonium to form the cationic Ni–H, which can then ligate the PCy_3 (Scheme 3C, left). Though acid must be added in the form of an HBF_4 salt for isomerization to occur in **protocol *E***, hydride appears to form independently in **protocol *Z***. In the *Z*-selective

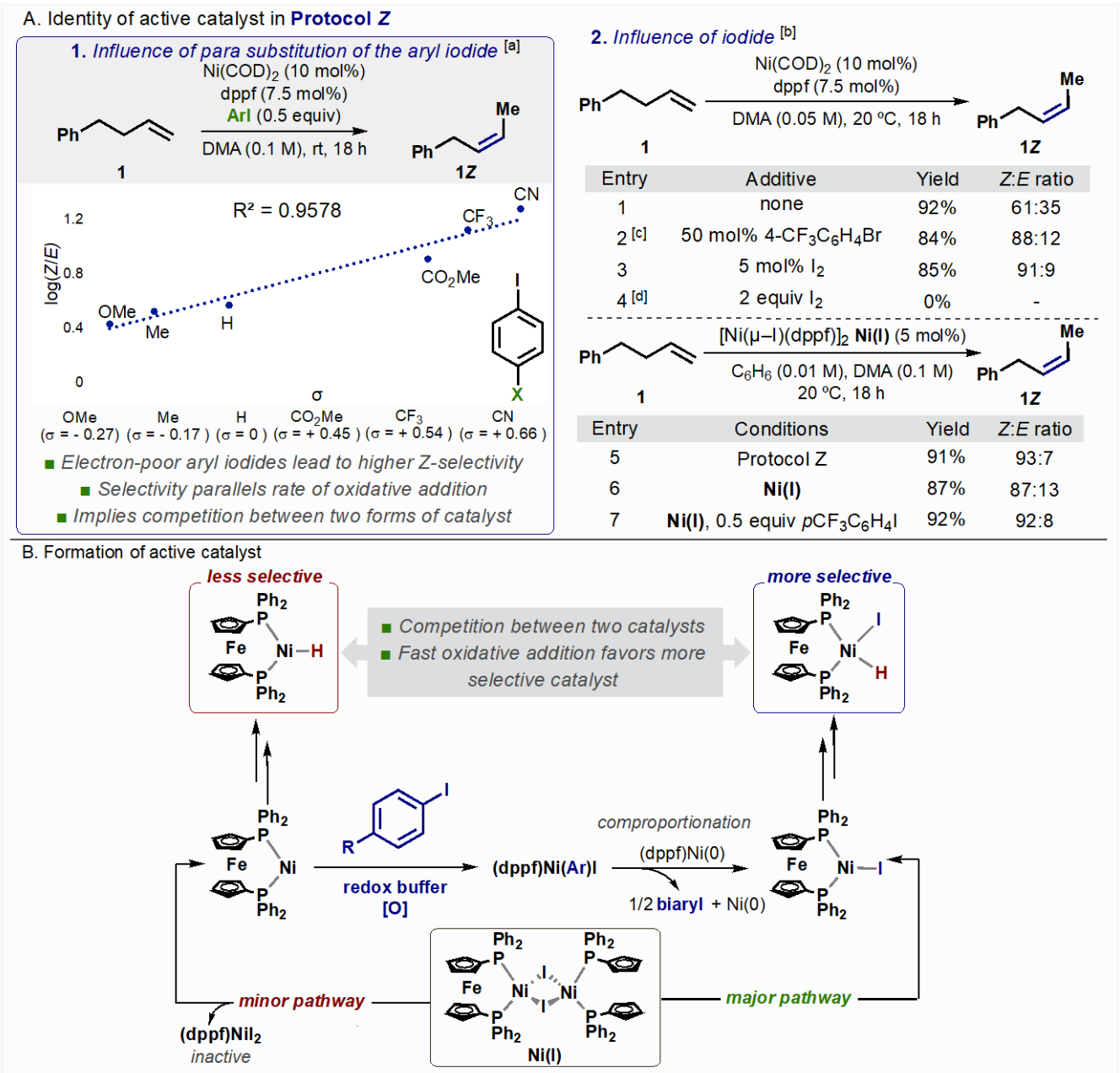


Scheme 3. Investigation of the mechanism of *Z*-selective olefin isomerization. Reactions were performed on 0.15-mmol scale unless otherwise stated.

Yields and selectivities were determined by ^{1}H NMR relative to CH_2Br_2 internal standard. Ratios are formatted as *Z*:*E*. [a] Percentage D represent percent incorporation at each position(s) and was determined by quantitative ^{1}H NMR. Reactions were performed on 0.10-mmol scale. [b] KIE values represent average values of three experiments. Initial rates were determined by in situ ^{1}H NMR monitoring of the reaction mixture with 1,3,5-tri-tert-butylbenzene as internal standard. [c] Reactions were performed on 0.050 mmol scale in DMF-d_7. [d] Reactions were performed on 0.075 mmol scale in acetone-d_6. [e] Reaction was performed on 0.25 mmol scale. Deuterium incorporation was determined by ^{2}H NMR relative to $CDCl_3$ internal standard. Incorporation of deuterium is 4% in **1*ED***, which correlates to 36% from PCy_3DBF_4.

reaction, the Ni–H was not observed in situ, but literature precedent indicates that active Ni–H may arise via an oxidative process of the allylic C–H bond by two equivalents of Ni^I halide (Scheme 3D).[32c] The formation of the latter Ni^I complex is discussed in detail (vide infra).

Though the mechanisms of the reactions share many similarities, the origin of divergent selectivity between the two protocols was unclear from the above results. Optimization indicated that the aryl iodide was essential for *Z*-selectivity, but more information was required to determine if both the aryl and the iodide component are present on the active catalyst. Aryl iodides undergo oxidative addition upon combination with Ni^0 species to form oxidative addition complexes. After generation of the oxidative addition complex, comproportionation to give biaryl and a nickel^I halide often proceeds (Scheme 4B).[33b] In fact, Ni^I halides have been shown to catalyze alkene isomerization.[32] To ascertain whether comproportionation occurs or the aryl remains bound to the active catalyst, the electronics of the aryl iodide were modified systematically, and the corresponding selectivity was measured (Scheme 4A.1). The resulting natural log of *Z*/*E* ratio



Scheme 4. Investigation of the mechanism of the *Z*-selective olefin isomerization. [a] Reactions were performed on 0.15 mmol scale. Selectivites were

determined by ^{1}H NMR. [b] Reactions were performed on 0.15 mmol scale unless otherwise noted. Yields and selectivities were determined by ^{1}H NMR compared to CH_2Br_2 internal standard. [c] Performed on 0.10 mmol scale. [d] 20 mol% Ni and dppf at 0.1 M.

was plotted against the Hammett ρ-value for the substituent on the aryl iodide, revealing a positive, linear relationship, with electron-poor aryl iodides giving the best selectivity (Scheme 4A.1). Close analysis of the Hammett plot reveals that the positive relationship between aryl iodide electronics and selectivity parallels the trend in rates of oxidation addition of aryl iodides to Ni^0, namely that oxidative addition occurs faster for more electron-poor aryl iodides.[33b, 34] These results indicate that oxidative addition of the aryl iodide might lead to a catalyst that outcompetes a less-selective catalyst. Nickel, ligand, and olefin substrate were combined in the absence of aryl iodide, and the reaction proceeded in high yield but low *Z*/*E* ratio, confirming the hypothesis that the rate of oxidative addition is important to outcompete the less-selective non-oxidized catalyst (Scheme 4A.2, entry 1). Moreover, 5 mol% addition of I_2 recapitulated the yield and selectivity of the optimized conditions, indicating that the aryl component is not necessary for high selectivity (entry 3). Higher loading of I_2 suppressed the reaction, potentially due to catalyst deactivation via over-oxidation (entry 4). If the role of aryl iodide in these experiments is to oxidize the metal center to a Ni^I–I species, it would stand to reason that the isolable Ni^I–I dimer, $[(dppf)Ni(\mu\text{-}I)]_2$, should also give high yield and selectivity, but both performance metrics were lower with this Ni^I precatalyst (entry 6). Addition of $pCF_3C_6H_4I$ to the conditions, however, restored the high yield and selectivity of product **1*Z*** (entry 7). This suggests that the primary dissociation product of the dimer is two equivalents of Ni^I–I monomer but that small amounts of inactive NiI_2 and the less selective Ni^0 also form. The latter decreases reaction selectivity unless aryl iodide is present to regenerate Ni^I. A summary of this process is depicted in Scheme 4B. The less-selective Ni^I–H is proposed to form via C(allylic)–H oxidative addition followed by comproportionation with remaining Ni(0).

Viewed in totality, these experiments and previous literature reports, indicate that a large, inner-sphere anion and a bulky bidentate phosphine support *Z*-selectivity in **protocol *Z***. In contrast, the selectivity in **protocol *E*** relies on coordination of a single, monodentate phosphine that is sufficiently small to favor the *E* isomer but large enough to disfavor over-isomerization through chain walking. Notably, the regio- and stereochemistry of the product are defined simultaneously and irreversibly for both protocols as stereochemically enriched **1** could not be converted to the opposite isomer under either protocol.[35, 36]

Conclusion

Overall, a nickel-based catalytic platform for the stereodivergent *E*/*Z*-selective synthesis of internal alkenes is established. The two protocols are robust and simple to perform with commercial reagents, enabling the selective alkene single-carbon transposition of a variety of feedstock terminal alkenes. Substrates that contain a diverse array of functional groups, including alkyl and aryl halides, boronic esters, free acids, and heterocycles, can undergo the transformation. Despite their stereodivergence, both protocols were found to operate through a common Ni–H mediated insertion/elimination mechanism. For the *Z*-selective reaction, an electron-poor aryl iodide ensures oxidation of the nickel to a hindered, *Z*-selective Ni^{II} catalyst. In the *E*-selective protocol, the addition of a Brønsted acid facilitates the formation of a cationic (trialkylphosphino)Ni–H, with the monophosphine ligand being small enough to favor the *E*-isomer while preventing over-isomerization.

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Conflicts of interest

The authors declare no competing interests.

Data availability

The data to support the findings of this study are provided in the Supplementary Information.

Keywords: alkene• isomerization • nickel • regioselectivity • stereoselectivity

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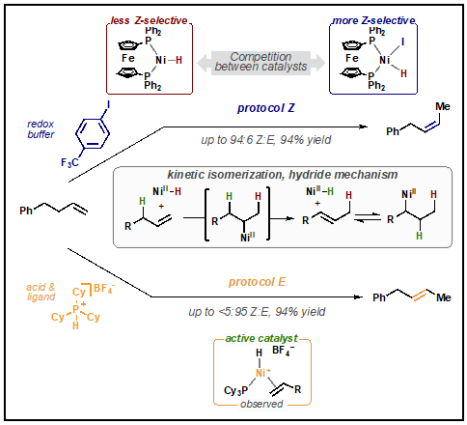

The nickel-catalyzed kinetic alkene mono-transposition generates *E*- or *Z*-olefins depending on the steric properties and denticity of the ligand employed. Mechanistic studies reveal that the aryl iodide additive acts as a redox buffer for nickel in the *Z*-selective reaction, generating the most-selective Ni^{I} that outcompetes less *Z*-selective low-valent nickel species. For the *E*-selective reaction, the phosphonium salt plays a dual role as an acid and ligand, forming a phosphine-bound cationic Ni–H catalyst in situ.

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