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Iron-Catalyzed Tunable and Site-Selective Olefin Transposition

Xiaolong Yu,[†] Haonan Zhao,[†] Ping Li[†] and Ming Joo Koh*,[†]

[†]Department of Chemistry, National University of Singapore, 12 Science Drive 2, Republic of Singapore, 117549

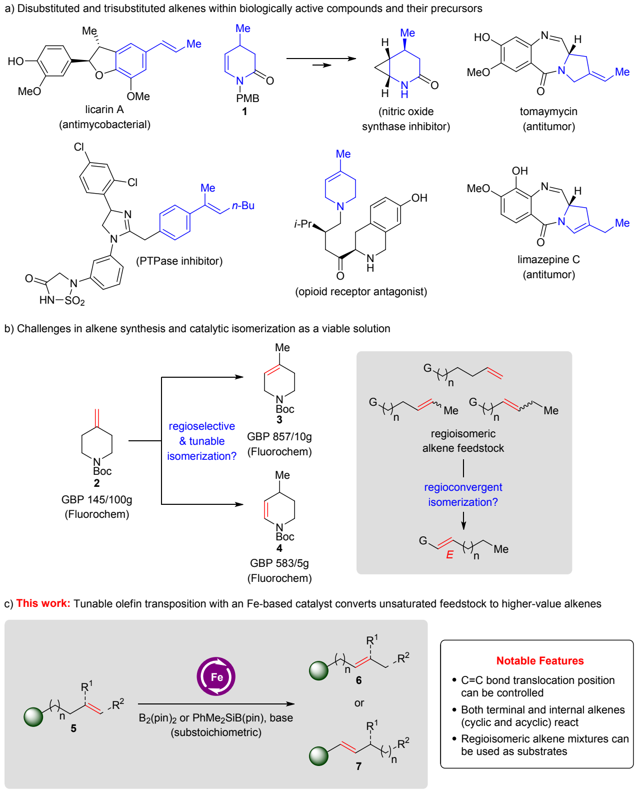
ABSTRACT: The catalytic isomerization of C–C double bonds is an indispensable chemical transformation used to deliver higher-value analogues and has important utility in the chemical industry. Notwithstanding the advances reported in this field, there is compelling demand for a general catalytic solution that enables precise control of the C=C bond migration position, in both cyclic and acyclic systems, to furnish disubstituted and trisubstituted alkenes. Here, we show that catalytic amounts of an appropriate earth-abundant iron-based complex, a base and a boryl compound promote efficient and controllable alkene transposition. Mechanistic investigations reveal that these processes likely involve in situ formation of an iron-hydride species which promotes olefin isomerization through sequential olefin insertion/β-hydride elimination. Through this strategy, regiodivergent access to different products from one substrate can be facilitated, isomeric olefin mixtures commonly found in petroleum-derived feedstock can be transformed to a single alkene product, and unsaturated moieties embedded within linear and heterocyclic biologically active entities can be obtained.

INTRODUCTION

Alkenes are one of the most important and versatile functionalities in chemistry.[1] Among the plethora of synthetic methods devised to install olefins, the transposition of an existing C–C double bond giving rise to a new positional isomer represents an attractive atom-economical approach to access higher-value compounds with minimal skeletal modification and by-product formation. To this end, metal-catalyzed alkene isomerization has emerged as a powerful strategy with far-reaching applications in the production of high-value chemicals (e.g. gasoline, polymers, fragrances, pharmaceuticals) across industry and academia.[1a,2] A vast number of C=C bond migration protocols have been developed using catalysts derived from noble metals (e.g. Ir, Rh, Pd, Ru)[3] as well as base metals (e.g. Co, Ni, Fe, Mo).[4] A recent disclosure involving visible light/Co dual catalysis offers controllable isomerization of terminal alkenes to different regioisomers in the presence of suitable ligands.[5] Despite the remarkable developments and merits associated with each of these transformations, enduring shortcomings remain to be addressed: (i) Except for specific examples, most protocols either involve mono-isomerizations (i.e. terminal alkenes to 2-alkenes) or isomerizations to the thermodynamically most stable internal alkene. Methods that offer both possibilities are scarce, and reported cases are limited to terminal alkenes.[5] (ii) Tunable C=C bond transposition over multiple positions, which will provide regiodivergent access to different olefin positional isomers from one substrate, continues to be a formidable challenge. (iii) Conversion of regioisomeric alkene mixtures to a single olefin product, which is particularly useful for streamlining chemical synthesis,[6] is yet to be implemented.

Iron is the most abundant non-toxic transition metal in the earth's crust (~6%) and is cheaper than other base metals.[7] Added to these appealing traits is the commercial availability and ease of synthesis associated with iron-based complexes.[8] Although iron catalysis had been previously examined for C=C bond transposition to access olefin products, the scope was largely limited to shifts over one position employing terminal alkene substrates.[4h,4i] In light of our interest in organoiron chemistry and the rising global demand for sustainable synthesis to reduce reliance on precious metals,[8,9] we sought to devise an operationally simple Fe-catalyzed protocol to facilitate tunable C=C bond migrations for the concise preparation of unsaturated motifs embedded within synthetically valuable bioactive entities (Scheme 1a). The new C=C bond isomerization manifold will be complementary to existing methods and may be leveraged to overcome longstanding challenges in alkene synthesis as highlighted in Scheme 1b. In this work, we disclose the development of a versatile catalytic regime that successfully accomplishes the regiodivergent conversion of inexpensive terminal and internal alkenes **5** (both cyclic and acyclic) to either **6** (over one position) or **7** (over multiple positions), as well as the regioconvergent transformation of isomeric olefin mixtures commonly found in unrefined raw materials from petroleum processing to value-added isomerically pure products (Scheme 1c).

Scheme 1. The significance of developing site-selective alkene isomerization reactions with iron catalysis

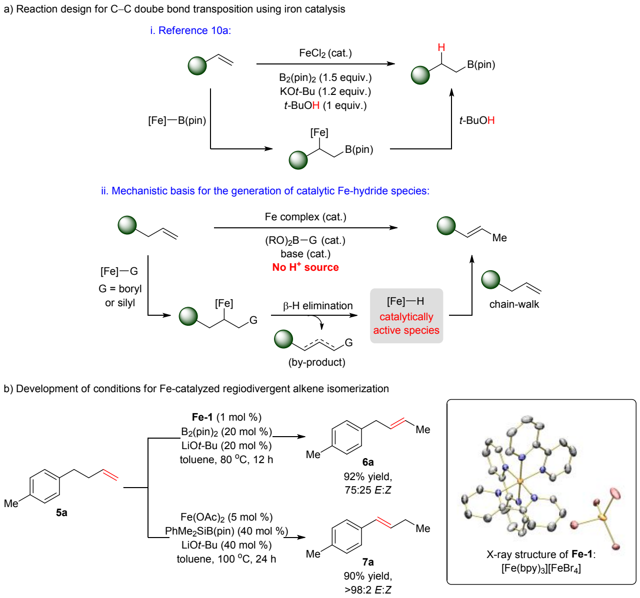


RESULTS AND DISUSSION

Reaction design and mechanistic studies

A survey of the Fe-catalyzed isomerization strategies reported to date showed that the C=C bond migration process could be triggered either by an intramolecular 1,3-hydride shift via a π-allyl intermediate,[4i] or through an olefin migratory insertion/β-H elimination pathway involving an iron-hydride species generated from base/water additives.[4h] Our inspiration for reaction design arose from a reported borylalkane synthesis method that takes advantage of an Fe-based catalyst and stoichiometric amounts of a commercially available diboryl reagent/base to promote iron-boryl insertion followed by protonolysis of the resulting iron-alkyl complex (Scheme 2a, i).[10] In our pursuit for a general catalytic solution, we speculated that in the *absence* of a protic source (thereby obviating protodemetallation), a diboryl (or silylboryl) reagent and base could be employed in catalytic or substoichiometric amounts to initiate formation of the putative iron-hydride species (from adventitious olefin iron-boryl addition/β-H elimination) necessary for promoting C–C double bond transposition (Scheme 2a, ii). The daunting challenge remains whether appropriate Fe-based catalysts can be identified to promote site-selective isomerization (for both terminal and internal alkenes) to the desired location under conditions that completely suppress undesired boryl (or silyl) addition to the C=C bond.[10]

Scheme 2. Design principles for achieving tunable and regioselective olefin transposition



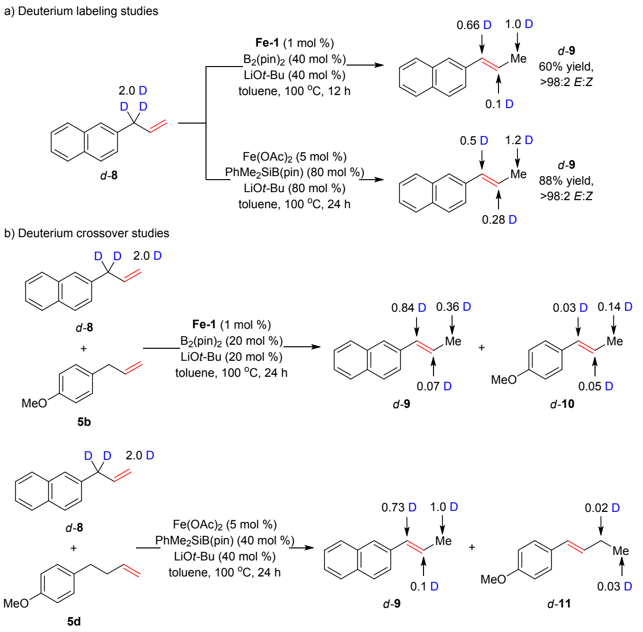
After an extensive survey of various Fe(II)- and Fe(III)-based complexes, boryl reagents, bases, solvents and temperature (see Supporting Information for details), we found that the mono-isomerization of alkene **5a** to **6a** (obtained in 75:25 *E*:*Z* ratio) could be best achieved with 1 mol % of **Fe-1**, 20 mol % of bis(pinacolato)diboron and lithium *tert*-butoxide in toluene at 80 °C, furnishing the product in 92% isolated yield within 12 hours (Scheme 2b, top). **Fe-1** consists of a discrete $[Fe(bpy)_3]^{2+}$ cation and $[FeBr_4]^{2-}$ anion as ascertained by X-ray crystal structure analysis (recrystallization from DME/DMA). No reaction was observed (>98% recovery of **5a**) when **Fe-1** was replaced with a separately synthesized $[Fe(bpy)_3][PF_6]_2$, while switching **Fe-1** to $[Et_4N]_2[FeBr_4]$ under analogous conditions gave a mixture of unreacted **5a**, **6a** and over-isomerized **7a** in 50:18:32 ratio (see Supporting Information for details). Although the role of each iron component in **Fe-1** remains to be determined, these results imply that both components are required in promoting efficient and selective isomerizations over one position.

On the other hand, **5a** could be converted to the thermodynamically most favored alkene **7a** in 90% isolated yield as a single *E* isomer using 5 mol % of $Fe(OAc)_2$, 40 mol % of (dimethylphenylsilyl)boronic acid pinacol ester and lithium *tert*-butoxide in toluene at 100 °C for 24 hours (Scheme 2b, bottom). In general, alkene isomerization was less efficient when Fe(III)-based salts or other solvents were used (see Supporting Information for details). Furthermore, in both conditions (Scheme 2b), trace amounts of the alkenyl boronate (or silane) initiation by-product could be detected by GC analysis (cf. Scheme 2a, ii). It merits mention that our attempts to access the iron-hydride catalytic species by using hydrosilanes following previously disclosed procedures[11] led to a mixture of recovered **5a** and its fully hydrogenated derivative (see Supporting Information for details).

Further studies were conducted to gain insights into the operating mechanism of the Fe-catalyzed transformations (Scheme 3a). Olefin isomerization with *d*-**8** resulted in deuterium scrambling across the entire hydrocarbon skeleton in *d*-**9**, suggesting formation of a free iron-hydride(deuteride) rather than a π-allyl species[4i] during the course of the reaction. This was substantiated by deuterium crossover experiments in which intermolecular crossover between *d*-**8** and a non-deuterated alkene was detected in both catalytic systems

(Scheme 3b), meaning that dissociation of the catalyst from the alkene occurs to a certain extent. The slight erosion of deuterium content was likely caused by adventitious reaction of a free Fe-deuteride species with moisture in the mixture.

Scheme 3. Mechanistic studies to probe the nature of alkene isomerization

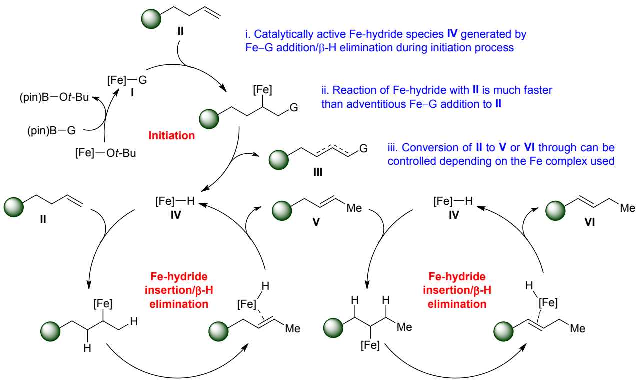


Given the surmised intermediacy of an iron-hydride complex, the question arises whether the latter could induce C=C bond transposition through one of these pathways: (a) iron-hydride addition/β-H elimination,[4h] or (b) metal-hydride hydrogen atom transfer (MHAT).[12] Although isomerization studies with a vinylcyclopropane substrate led to 1,3-diene products (see Supporting Information for details), these results were inconclusive as ring-opening could also be attributed to non-radical processes.[13] Analysis of the reaction mixture in both Fe-catalyzed systems by time- and temperature-dependent electron paramagnetic resonance (EPR) studies showed no signals that would be expected to arise from radical species generated in a MHAT process (see Supporting Information for details). Control experiments with (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) or 5,5-dimethyl-1-pyrroline *N*-oxide (DMPO)[14] also did not support the possibility of related radical intermediates (see Supporting Information for details).

Based on the aforementioned results, a plausible non-radical mechanism for the present transformation is proposed in Scheme 4. We believe that an initiation process involving adventitious formation of catalytic amounts of iron-hydride **IV** (obtained from sequential addition of iron-boryl(silyl) **I** to alkene **II** followed by β-H elimination with concomitant release of by-product **III**) is crucial to kick-start olefin isomerization. Iron-hydride **IV** coordinates and reacts with another molecule of **II** by a series of migratory insertion/β-H elimination steps, engendering migration of the C=C bond along the chain. Successful implementation of the current protocol relies on faster reaction between **IV** and **II** (vs. reaction between **I** and **II**), consequently suppressing undesired formation of boryl/silyl adducts.

Scheme 5. Isomerization over one position with terminal olefins[a]

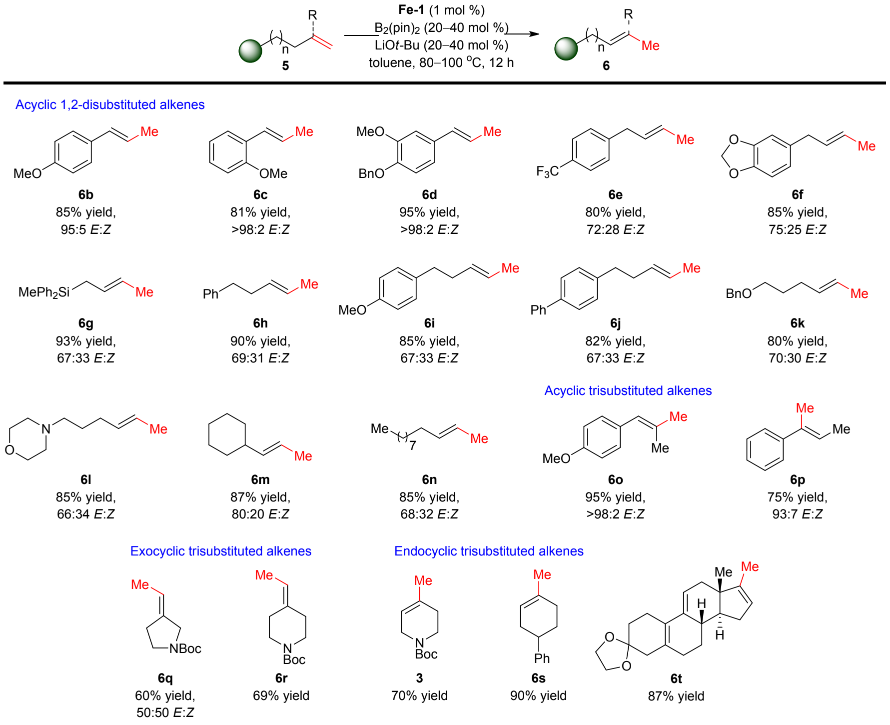
Scheme 4. Proposed mechanism for Fe-catalyzed C=C bond migration



The difference in reactivity profiles between the catalytic manifolds mediated by **Fe-1** and Fe(OAc)$_2$ was evident from time course studies (see Supporting Information for details). In the presence of the organoiron species derived from the sterically encumbered and presumably less active **Fe-1**, Fe-olefin coordination could be weakened causing internal alkene **V** to completely dissociate after a single migration. Conversely, under the conditions with ligand-less Fe(OAc)$_2$, chain-walking could continue to ultimately deliver the most stable olefin regioisomer **VI**. Whereas alkene isomerization using Fe(OAc)$_2$ may be thermodynamically-driven, the mechanistic underpinnings for **Fe-1**'s ability to engage in one double-bond shifts remain to be elucidated in ongoing studies. The *E*:*Z* ratios obtained for the products (cf. **5a** and **6a** in Scheme 2b) are probably influenced by steric effects arising from substituents of the incipient double bond during the course of the reaction (i.e. greater steric repulsion results in higher *E*:*Z* ratios). More detailed investigations to determine the active organoiron species (e.g. oxidation, spin states) involved in the system will also be carried out in due course.

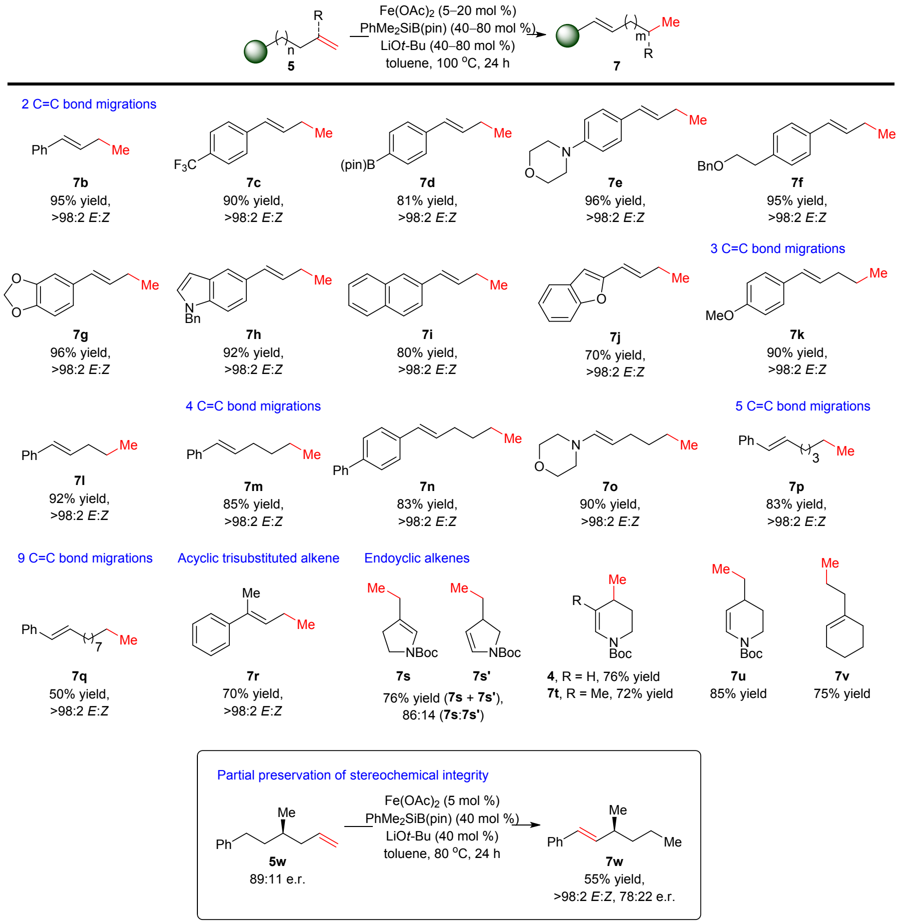
Scope and applications of the method

Conceiving a general catalytic isomerization protocol that is applicable to alkenes of different substitution patterns is a sought-after goal in chemistry. We first examined a range of functionalized terminal (monosubstituted and 1,1-disubstituted) olefins under mono-isomerization conditions (Scheme 5). In general, single double-bond shifts could be accomplished with a variety of monosubstituted substrates bearing different carbon chain length and functional groups (e.g. arenes, ethers, amines, silanes), furnishing 1,2-disubstituted olefins **6b–n** in 78–95% yield. Styrenyl products **6b–d** were obtained in ≥95% *E* selectivities, although non-aryl-substituted alkenes **6e–n** could only be generated in moderate *E*:*Z* ratios. The method is also amenable to the synthesis of trisubstituted double bonds including linear olefins (**6o–p**) as well as exocyclic (**6q–r**) and endocyclic (**3**, **6s–t**) products. Complete isomerization to an internal olefinic site was next assessed in Scheme 6. Transpositions over two positions could be effected with homoallylic arenes and heteroarenes bearing either electron-donating or electron-withdrawing substituents, furnishing β-ethylstyrenes **7b–j** in 70–96% yield and >98:2 *E*:*Z* ratios.



[a]Yields are for isolated and purified products (*E*:*Z* mixtures). For **6b–d** and **6o–p**, the reactions were conducted with Fe(OAc)$_2$ (5 mol%), PhMe$_2$SiB(pin) (40 mol %) and LiO*t*-Bu (40 mol %) in toluene at 100 °C for 24 h. For **6m**, yield was determined by GC analysis against internal standard. For **6q** and **6r**, the reactions were conducted with [(bpy)FeCl$_2$]$_2$ (**Fe-2**; 3-5 mol %), B$_2$(pin)$_2$ (40 mol %) and LiO*t*-Bu (40 mol %) in toluene at 100 °C for 24 h. For **3** and **6s**, the reactions were conducted with (6,6'-dimethyl-2,2'-bipyridine)FeCl$_2$ (**Fe-3**; 5 mol %), B$_2$(pin)$_2$ (40 mol %) and LiO*t*-Bu (40 mol %) in toluene at 100 °C for 24-36 h. For **6t**, the reaction was conducted with Fe(OAc)$_2$ (5 mol%), B$_2$(pin)$_2$ (80 mol %) and LiO*t*-Bu (80 mol %) in toluene at 100 °C for 24 h. See Supporting Information for details.

Scheme 6. Isomerization over multiple C=C bonds with terminal olefins[a]



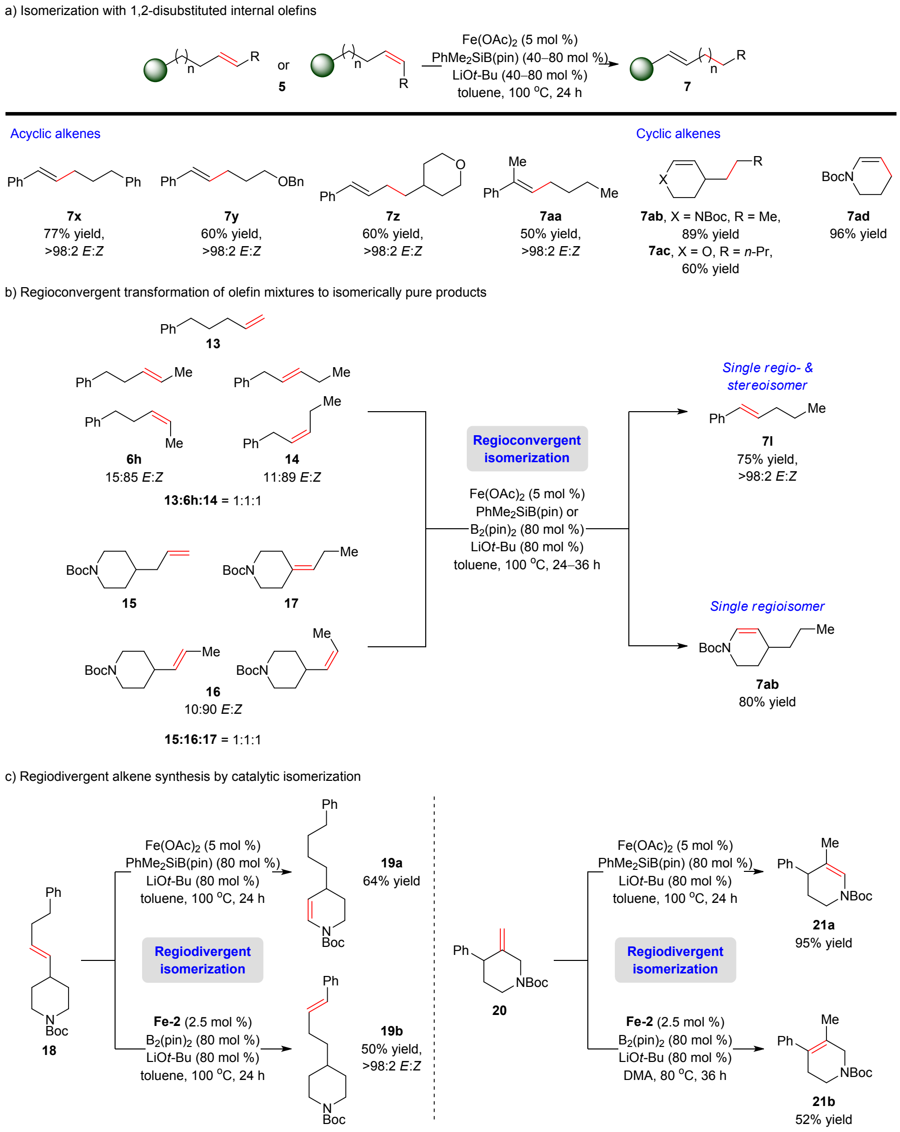
[a]Yields are for isolated and purified products. For **7j**, the reaction was conducted with Fe(OAc)$_2$ (5 mol%), (*R*)-DTBM-SEGPHOS (6 mol %), PhMe$_2$SiB(pin) (80 mol %) and LiO*t*-Bu (80 mol %) in toluene at 100 °C for 24 h. For **7s** and **7u**, B$_2$(pin)$_2$ was used instead of PhMe$_2$SiB(pin). For **7o** and **7v**, yields were determined by GC analysis against internal

standard. For **7q**, yield was determined by ^{1}H NMR analysis against internal standard. For **7r**, ~5% of inseparable alternative isomers were detected. Ratio of **7s** and **7s'** was determined by ^{1}H NMR analysis against internal standard. See Supporting Information for details.

Migrations over extended carbon skeletons were similarly efficient, affording the corresponding 1,2-disubstituted *E* alkenes **7k–q** in up to 92% yield. Isomerization could be terminated by an amino group to deliver acid-labile *E*-enamine **7o** in 90% yield. It is worth nothing that the transformation leading to **7q** (50% yield) features a transposition over nine C=C double bonds and compares favorably with a previous report (37% yield).[4b] Trisubstituted alkenes (**7r**) could also be accessed through a double olefin migration. Synthesis of endocyclic olefin **7v** as well as pharmaceutically relevant five- and six-membered heterocyclic building blocks containing enecarbamate moieties[15] (**4**, **7s**/**7s'** and **7t–u**) by the Fe-catalyzed protocol is further testament to the robust versatility of the isomerization regime. The reaction with **5w** containing a pre-existing stereogenic center lent additional credence to the mechanistic proposal in Scheme 3. Under standard conditions, isomerization to **7w** could proceed, albeit with considerable erosion in enantioselectivity at 100 °C (89:11 e.r. → 69:31 e.r.). By lowering the temperature to 80 °C, dissociation of the iron catalytic species from the alkene substrate is reduced, allowing stereochemical integrity to be partially retained (78:22 e.r.) during the chain-walking process.[6,16]

Besides terminal olefins, sterically more encumbered internal alkenes also served as effective substrates under our developed Fe-catalyzed conditions (Scheme 7a). Complete site-selective isomerization to presumably the most stable regioisomer proceeded to give disubstituted or trisubstituted styrenes, enecarbamates and vinyl ethers **7x–ad** in up to 96% yield. The example with **7ad** demonstrates that endocyclic C=C bonds can also undergo transposition. However, selective single C=C bond migrations that afford 1,2-dialkyl-substituted alkenes (vs. using terminal olefins as substrates in Scheme 5) are difficult to control and pose complicating issues of over-isomerization.

Scheme 7. Isomerization with internal olefins and regioselective convergent and divergent reactions^a



^{a}Yields are for isolated and purified products. See Supporting Information for details.

The ability to react with both terminal and internal C–C double bonds offers an opportunity to integrate our catalytic platform for the transformation of abundant raw materials derived from petroleum processing, such as unrefined isomeric olefin mixtures, to a single alkene product. Treatment of a 1:1:1

mixture of **6h** (*E*:*Z* mixture), **12** and **13** (*E*:*Z* mixture) to standard isomerization conditions successfully furnished *E*-**7l** as the sole product in 75% yield (Scheme 7b). For comparison, repeating the reaction using conditions devised from a recent Ni-catalyzed disclosure[4b] only led to an inseparable mixture of isomeric compounds (see Supporting Information for details). The corresponding Fe-catalyzed reaction of a complex mixture of isomeric **14**, **15** and **16** cleanly delivered **7ab** in 80% yield. These regioconvergent transformations represent a viable strategy for the streamlined value-enhancing conversion of inexpensive olefin feedstock to prized isomerically pure alkenes.

To further challenge the limits of our catalytic method, we examined alkenes **18** and **20**, each of which bears at least two possible sites that may serve to direct C=C bond migration (Scheme 7c). In the event, subjecting **18** to conditions promoted by ligand-free $Fe(OAc)_2$ predominantly afforded pure enecarbamate **19a** in 64% yield (~12% **19b** detected). Remarkably, by switching the Fe-based complex to the sterically more demanding $[(bpy)FeCl_2]_2$ (**Fe-2**), the direction of olefin transposition could be reversed and regioisomer **19b** was obtained as the major product (~80% conversion, 50% yield) in >98% *E* selectivity. Control experiments showed that **Fe-1** was inefficient in promoting olefin transposition in **18**. In a similar fashion, regiodivergent transformation of **20** to either **21a** or **21b** could be achieved with the established catalytic systems. **21a** was isolated exclusively under standard conditions with $Fe(OAc)_2$ or **Fe-1**, whereas pure **21b** was secured in 52% yield using **Fe-2** as the catalyst (4:1 ratio of **21b**:**21a** detected; see Supporting Information for details). Attempts to isomerize **20** to **21b** by performing the reaction in the presence of alternative solvents or other Fe-based complexes under analogous conditions in DMA only led to unsatisfactory ratios of **21a** and **21b** (see Supporting Information for details).

Density functional theory (DFT) calculations further revealed that the products (**19a–b** and **21a–b**) are energetically more stable than the substrates (**18** and **20**, respectively), and the relative free energy difference between the products (i.e. **19a** vs. **19b** and **21a** vs. **21b** is ~3 kcal/mol (see Supporting Information for details). Our studies highlight the versatility of the present iron-based catalytic manifold in facilitating controllable and site-selective access to different alkene isomers from one substrate, thereby providing an important avenue to generate functional and structural diversity.[17] More extensive investigations are ongoing to elucidate the origin of the observed regiochemical outcomes in Scheme 7c.

CONCLUSIONS

In conclusion, we showed that the combination of a suitable iron-based catalyst with substoichiometric amounts of a commercially available boryl reagent and base enables tunable C=C bond transposition over one or multiple positions along the skeleton of an unsaturated hydrocarbon molecule. Transformations are robust and tolerant of a broad substrate class consisting of both terminal and internal olefins with various substitution patterns. Mechanistic investigations unveil an Fe-catalyzed olefin insertion/β-H elimination process that is capable of facilitating site-selective migrations, including transformations of isomeric olefin mixtures to value-added isomerically pure products, as well as tunable transpositions to different regioisomers. By virtue of such catalytic capacity coupled with the operational ease and availability of inexpensive organoiron complexes and reagents, we believe that the present catalytic approach is a significant addition to an existing toolbox of metal-catalyzed olefin isomerization reactions for the preparation of high-value industrially relevant chemicals.

ASSOCIATED CONTENT

Supporting Information

This material is available free of charge via the Internet at http://pubs.acs.org.

Experimental procedures and analytical data for all compounds

AUTHOR INFORMATION

Corresponding Author

Ming Joo Koh – *Department of Chemistry, National University of Singapore, 12 Science Drive 2, Republic of Singapore, 117549*; ORCID: 0000-0002-2534-4921; Email: chmkmj@nus.edu.sg.

Authors

Xiaolong Yu – *Department of Chemistry, National University of Singapore, 12 Science Drive 2, Republic of Singapore, 117549.*

Haonan Zhao – *Department of Chemistry, National University of Singapore, 12 Science Drive 2, Republic of Singapore, 117549.*

Ping Li – *Department of Chemistry, National University of Singapore, 12 Science Drive 2, Republic of Singapore, 117549.*

Notes

The authors declare no competing financial interests.

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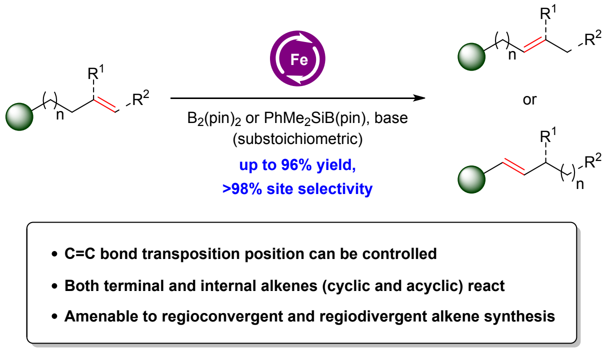

- C=C bond transposition position can be controlled
- Both terminal and internal alkenes (cyclic and acyclic) react
- Amenable to regioconvergent and regiodivergent alkene synthesis