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Iron Catalyzed Isomerization of α-Alkyl Styrenes to Access Trisubstituted Alkenes

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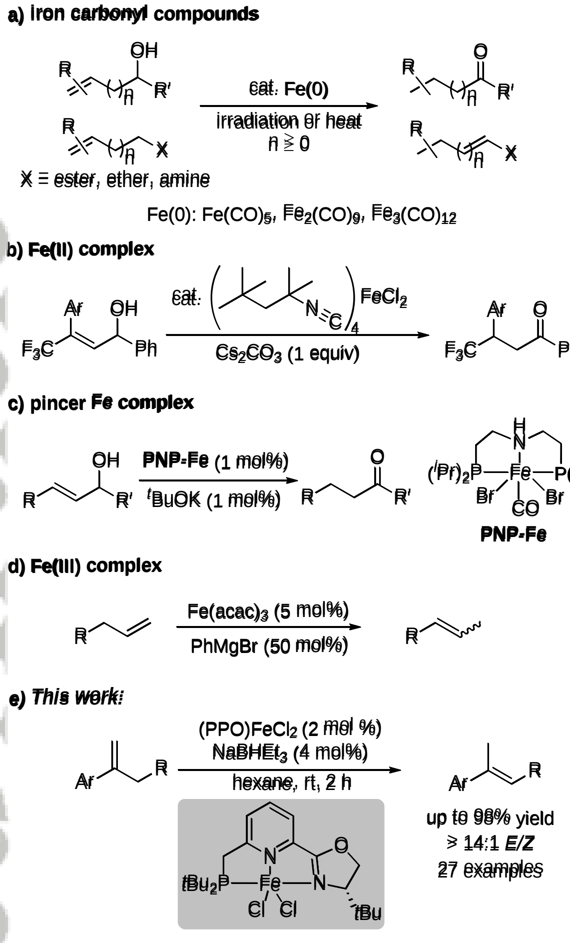
Stereoselective isomerization of α-alkyl styrenes is accomplished using a new iron catalyst supported by phosphine-pyridine-oxazoline (PPO) ligand. The protocol provides an atom-efficient and operationally simple approach to trisubstituted alkenes in high yields with excellent regio- and stereoselectivities under mild conditions. The results of deuterium-labelling and radical trap experiments are consistent with an iron-hydride pathway involving reversible alkene insertion and β-H elimination.

Background and Originality Content

Trisubstituted alkenes are important skeletons in both natural and synthetic molecules, and act as versatile intermediates in various transformations.[1] Since efficient procedures are now available for the synthesis of terminal alkenes with high regioselectitiy,[2] waste-free isomerization of readily accessible terminal alkenes[3] provides an attractive route to valuable trisubstituted alkenes. Such a transformation is conceptually simple, but controlling regio- and stereoselectivity poses a large challenge. Catalysts based on precious transition metals, such as Rh,[4] Pd,[5] and Ru,[6] have been developed to effect the isomerization of α-alkyl styrenes to trisusbtituted alkenes, which usually suffers from poor stereoselectivity and limited substrate scope. In this context, it is highly desirable to develop efficient catalysts, especially those with low-cost and high sustainability, for this transformation. During the preparation of this manuscript, three Co catalysts were independently disclosed by the groups of Lu, Findlater and Xia, for chemo and stereoselective alkene isomerization to afford trisubstituted alkenes.[7] In contrast, catalyst systems using the most earth-abundant metal, iron, which has a minimal environmental and toxicological impact, have received little attention in this area.[8]

Early studies showed that iron carbonyl complexes $Fe(CO)_5$, $Fe_2(CO)_9$, and $Fe_3(CO)_{12}$, are versatile catalysts for isomerization of unsaturated alcohols, esters, ethers and amines into corresponding carbonyl compounds, conjugated esters, ethers and amines, respectively (Scheme 1a).[9] However, these carbonyl iron complexes need thermal or photo-activation to release CO ligand and generate catalytically active metal species, limiting their practicability. In 2013, Gahard and Renaud *et. al.* demonstrated that a tetra(isonitrile) iron(II) complex could replace toxic iron carbonyls for the isomerization of trifluoromethylated allylic alcohols into the corresponding ketones (Scheme 1b).[10] Later, de Vries *et. al.* found a well-defined pincer iron complex was highly effective for the isomerization of allylic alcohols to ketones using *t*BuOK as the activator with broad substrate scope (Scheme 1c).[11] In addition to the isomerization driven by the stabilizing effects exerted by the heteroatoms, unfunctionalized alkenes could also be isomerized under iron catalysis. In 2011,

Scheme 1 Iron Catalysed Alkene isomerization

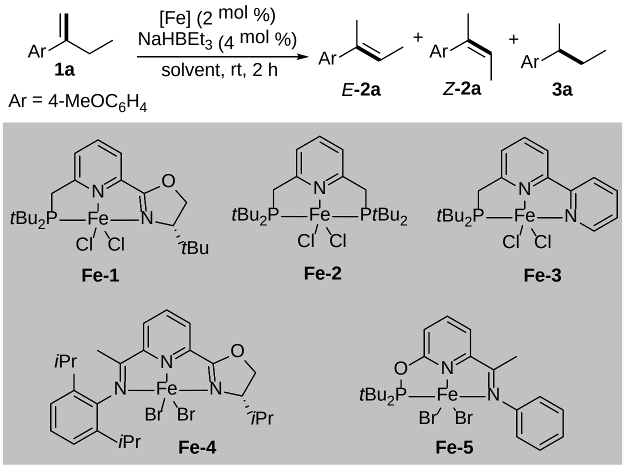


von Wangelin and coworkers developed a catalytic system of $Fe(acac)_3$/ArMgBr combination for the isomerization of 1-alkenes to 2-alkenes (Scheme 1d).[12] Despite these achievements, iron catalyzed stereoselective alkene isomerization to access trisubstituted alkenes without the aid of heteroatoms[9c] remains underdeveloped.

Driven by our interest in the development of base metal catalysis,[13] we report herein a catalytic isomerization of α-substituted styrenes to trisubstituted olefins with an iron complex of phosphine-pyridine-oxazoline (PPO) ligand (Scheme 1e). Preliminary mechanistic experiments revealed that the isomerization event likely occurs through an alkene insertion and β-H elimination pathway.

Results and Discussion

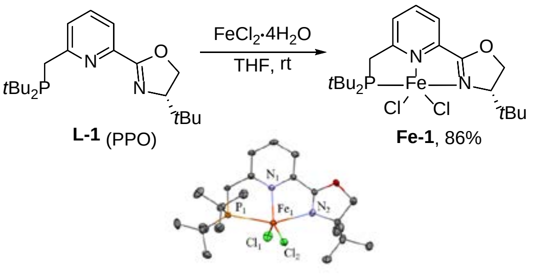
Table 1 Evaluation of Iron Catalyst for Isomerization of α-Ethylstyrene [a]



entry[a]	Cat.	solvent	Conv. (%)[b]	Yield (%)[b]		
				E-**2a**	*Z*-**2a**	**3a**
1	**Fe-1**	pentane	97	96	ND	1
2	**Fe-2**	pentane	79	76	ND	3
3	**Fe-3**	pentane	76	75	ND	1
4	**Fe-4**	pentane	77	76	ND	1
5	**Fe-5**	pentane	<5	ND	ND	ND
6	**Fe-1**	THF	96	95	ND	1
7	**Fe-1**	toluene	96	95	ND	1
8	**Fe-1**	Et_2O	0	ND	ND	ND

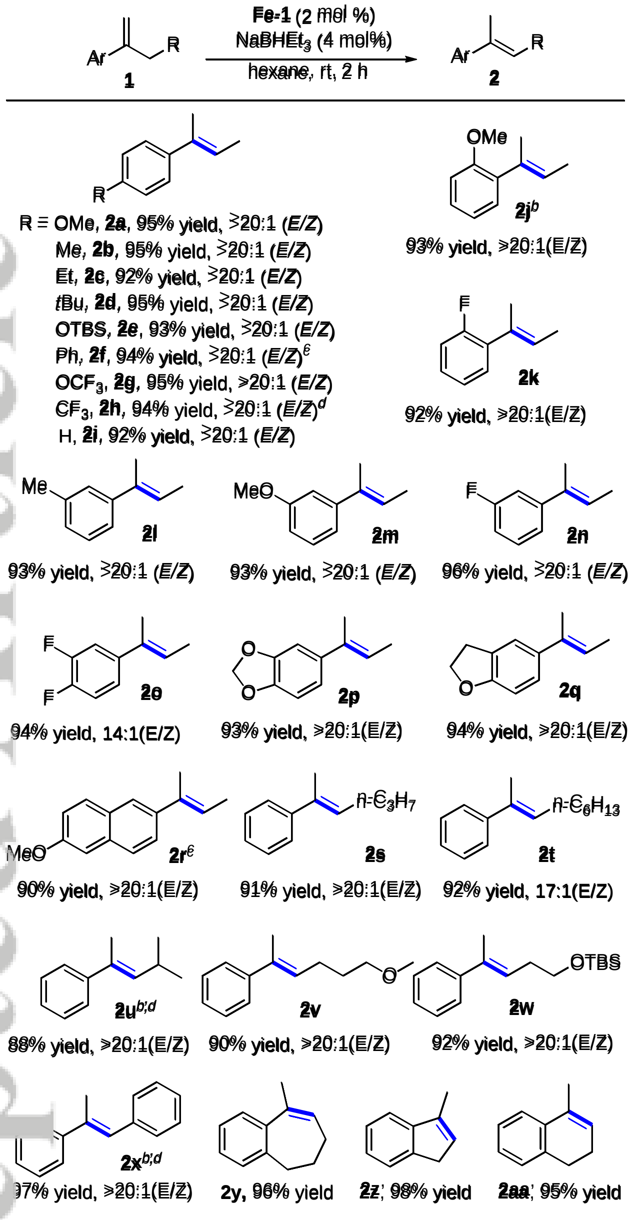
[a]Reaction condition: **1a** (0.5 mmol), [Fe] (0.01 mmol, 2 mol %) and $NaHBEt_3$ (0.02 mmol, 4 mol %) in solvent (2 mL) at room temperature for 2h. [b]Determined by GC analysis using mesitylene as the internal standard. ND = not detected.

Scheme 2. Synthesis and Molecular Structure of **Fe-1**



We initiated our study by evaluating the catalytic efficiency of several iron complexes bearing different pincer ligands for alkene

Scheme 3. Scope of Iron-Catalyzed Alkene Isomerization.

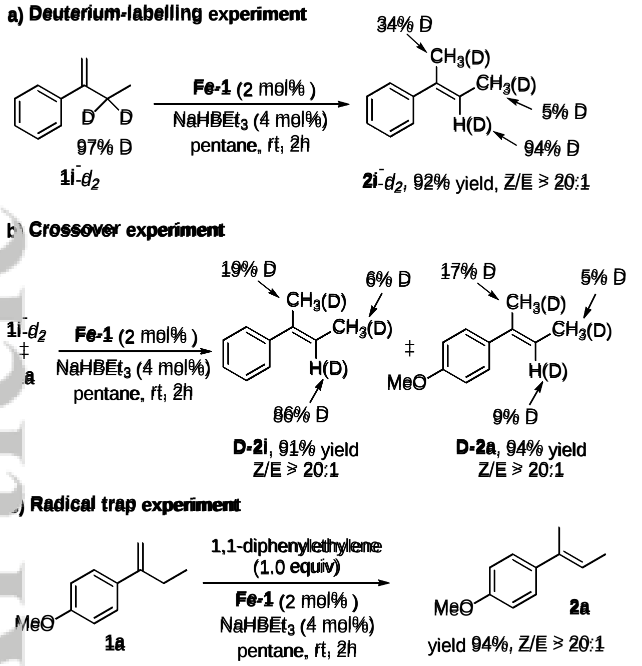


^{a}Reaction condition: **1** (0.5 mmol), **Fe-1** (0.01 mmol) and NaHBEt$_3$ (0.02 mmol) in pentane (2 mL) at room temperature for 2h. Isolated yields. ^{b}**1h** (0.2 mmol). ^{c}Toluene was used as solvent. ^{d}8 h.

isomerization using methoxy substituted α-ethylstyrene **1a** as the model substrate and NaHBEt$_3$ as the activator (table 1). Note that the pincer ligands investigated here can be readily prepared in two-to-three steps from commercially available starting materials. A new iron complex **Fe-1** was synthesized by treatment of a phosphine-pyridine-oxazoline (PPO) ligand[13d] with iron dichloride in THF, and its solid structure was established by X-ray diffraction analysis. To our delight, isomerization of **1a** proceeded smoothly at room temperature in pentane to give **2a** in high yield (96%) with striking *E*-selectivity when (PPO)Fe complex **Fe-1** was used as the precatalyst (entry 1). In this case, the *Z*-isomer and the hydrogenation product **3a** were barely observed. Replacing the oxazoline arm with phosphino or pyridine arm, **Fe-2**[14] and **Fe-3**[13a] exhibited excellent selectivity but the yields decreased significantly, with substantial amount of starting material recovered (entries 2 and 3). Similarly, the use of imino-pyridine-oxazoline (IPO) iron complex (**Fe-4**)[13c] afforded isomerization product *E*-**2a** in 76% yield with trace amount of *Z*-**2a** and **3a** (entry 4). An iron complex **Fe-5**[13b] bearing phosphinite-iminopyridine ligand was proved to be inactive for the isomerization (entry 5). The influence of the solvent on the isomerization reaction was investigated with **Fe-1** as the precatalyst. While the use of pentane, toluene, THF gave comparable reaction outcomes, no reaction happened in ether (entries 6-8). The coordination ability of ether to the metal center may poison the catalytically active species and deactivate the catalyst.

The substrate scope of the (PPO)Fe catalyzed alkene isomerization was explored (Scheme 3). A wide range of geminal disubstituted arylalkenes were successfully isomerized to furnish the desired trisubstituted (*E*)-alkene in high yields with remarkable regio- and stereo-control. The catalytic system was effective for α-ethyl styrenes with both electron–donating (**2a**, **2e**, **2j**, **2m**, **2p**-**2r**) and -withdrawing groups (**2h**, **2k**, **2n**, **2o**) on the aryl ring. Various functionalities such as methoxy, silyl ether, CF$_3$, OCF$_3$ and fluoro groups were well tolerated. The substituents at *para-*, *ortho*, and *meta*-position of the phenyl ring had little impact on the isomerization (**2a**-**2q**). Naphthyl alkene could be readily isomerized to afford the corresponding trisubstituted alkene **2r** in 90% yield with excellent *E*-selectivity. The α-alkyl styrenes in which the R group is larger than a methyl group underwent isomerization smoothly to gain satisfied outputs. The isomerization of alkene **1u** with a bulky propyl group in the homoallylic position gave the trisubstituted alkene **3u** in 88% yield with 10% of **1u** recovered.[15] To be note, this iron based catalytic system was compatible with α-benzyl styrene, affording diaryl substituted alkene **2x** in 96% yield with *E/Z* ratio more than 20:1. Moreover, exocydic alkenes were suitable substrates, producing the endocyclic alkenes (**2y**-**2aa**) in excellent yields with exclusive regioselectivity.

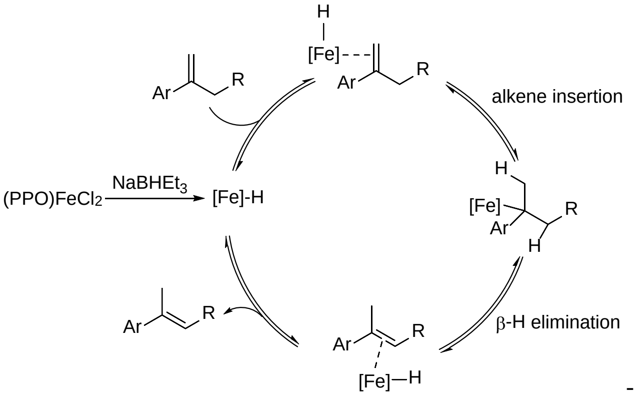
Scheme 4. Mechanistic studies



Deuterium-labelling and radical trap experiments were carried out to provide insights into the mechanism. The deuterated substrate **1i**-*d*$_2$ containing an allylic CD$_2$ unit was submitted to the standard catalytic conditions, affording trisubstituted alkene **2i**-*d*$_2$ in 92% yield with 34% D-content in the newly formed methyl group, 94% D in the vinyl group and 5% D in the methyl group *trans* to the phenyl group (Scheme 4a). The intramolecular H/D scrambling indicates that the formation and cleavage of C-H bond during isomerization is reversible. To probe the possibility of intermolecular H/D scrambling, a 1:1 mixture of **1i**-*d*$_2$ and **1a** was subjected to the reaction (Scheme 4b). The NMR analysis of the two isolated isomerization products revealed a decreased deuterium incorporation in **D-2i** along with a crossover deuterium incorporation into **D-2a**. The intermolecular H/D scrambling ruled out the concerted H-transfer pathways such as 1,3-H shift mechanism via allylic metal species and oxidative cyclization mechanism. Furthermore, the reaction of **1a** in the presence of a radical scavenger 1,1-diphenylethylene proceeded smoothly without obvious influence on the reaction outputs (Scheme 4c), indicating a radical pathway may not be an operative pathway.

Based on all these experimental observations and previous literature,[8a] the (PPO)Fe catalyzed alkene isomerization most likely occurred via a stepwise H-transfer pathway involving a Fe-hydride intermediate, which undergoes reversible alkene insertion and β-H elimination to produce the isomerized alkene and regenerate the catalytically active Fe-H species (Scheme 5). The additive NaBHEt$_3$ reduces the precatalyst to form Fe-H species to initiate the catalytic cycle. However, the exact structure of Fe-H intermediate is unclear at present.

Scheme 5. Plausible Mechanism



Conclusions

In summary, we successfully developed an iron catalyzed stereoselective isomerization of α-alkyl styrenes to trisubstituted alkenes with phosphine-pyridine-oxazoline(PPO) as the ligand. A broad scope of substrates compatible with many common functional groups were readily isomerized under mild conditions. Deuterium labelling and radical trapping experiments support a stepwise H-transfer pathway with an intermediacy of Fe-H species, involving an alkene insertion and β-H elimination sequence.

Experimental

General Description. All manipulations were carried out in a nitrogen-filled glovebox or under an atmosphere of dry argon using standard Schlenk techniques, unless stated otherwise. Pentane, tetrahydrofuran (THF) and ether were purchased from Sinopharm Group Chemical Co., Ltd. and dried over LiAlH$_4$ overnight under an atmosphere of dry argon, then distilled prior to use and stored in an argon atmosphere glovebox. Toluene was distilled from sodium benzophenone ketyl prior to use. Iron complexes were prepared according to previously reported procedures.[13-14] All other reagents and solvents used in this study were purchased from commercial sources and used as received. NMR spectra were recorded on Agilent 400 MHz, Varian 400 MHz and Bruker 400 MHz at ambient temperature. The residual peak of deuterated solvent was used as a reference for ^{1}H and ^{13}C chemical shifts. GC analysis was acquired on Agilent 7890A gas chromatograph equipped with a flame-ionization detector.

General procedure for isomerization of α-Alkyl styrenes. In an nitrogen-filled glove-box, an oven-dried 10 mL thin-wall glass tube was charged with **Fe-1** (10 μmol, 4.8 mg), pentane (2 mL), α-alkyl styrenes (0.5 mmol). The resulting solution was added NaHBEt$_3$ (20 μmol, 1 M in THF). The tube was sealed with a Teflon plug, and the reaction mixture was stirred at room temperature for 2h. The reaction was quenched by exposing the reaction mixture to air. The solvent was removed under vacuum and the residue was purified by flash silica gel column chromatography to give the product, which was analyzed by ^{1}H NMR to determine the stereoselectivity.

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2018xxxxx.

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[15] Prolonging the reaction time or increasing the catalyst loading failed to improve the conversion. Treatment of **2u** under the standard reaction conditions resulted in the formation of **1u** in 10% yield. These observations imply that there is an equilibrium between the terminal alkenes and the internal alkenes under isomerization conditions.

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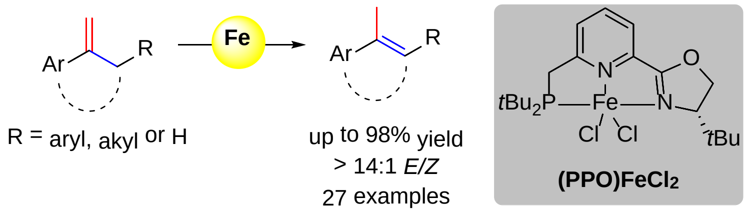

A well defined iron complex of phosphine-pyridine-oxazoline catalyzes stereoselective isomerization of α-alkyl styrenes, providing an atom-efficient and operational simple approach to trisubstituted alkenes in high yields with excellent regio- and stereoselectivities.

Songgen Xu, Guixia Liu,* and Zheng Huang*

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