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Cobalt (II)-Catalyzed Stereoselective Olefin Isomerization: Facile Access to Acyclic Trisubstituted Alkenes

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Cobalt (II)-Catalyzed Stereoselective Olefin Isomerization: Facile Access to Acyclic Trisubstituted Alkenes

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ABSTRACT: Stereoselective synthesis of trisubstituted alkenes is a long-standing challenge in organic chemistry, due to the small energy differences between *E* and *Z* isomers of trisubstituted alkenes (compared with 1,2-disubstituted alkenes). Transition metal-catalyzed isomerization of 1,1-disubstituted alkene can serve as an alternative approach to trisubstituted alkenes, but it remains underdeveloped owing to issues relating to reaction efficiency and stereoselectivity. Here we show a novel cobalt catalyst can overcome these challenges to provide an efficient and stereoselective access to a broad range of trisubstituted alkenes. This protocol is compatible with both mono- and dienes and exhibits a good functional group tolerance and scalability. Moreover, it has proven to be a useful tool to construct organic luminophores and a deuterated trisubstituted-alkene. A preliminary study of the mechanism suggests a cobalt-hydride pathway is involved in the reaction. The high stereoselectivity of the reaction is attributed to both a π-π stacking effect and the steric hindrance between substrate and catalyst.
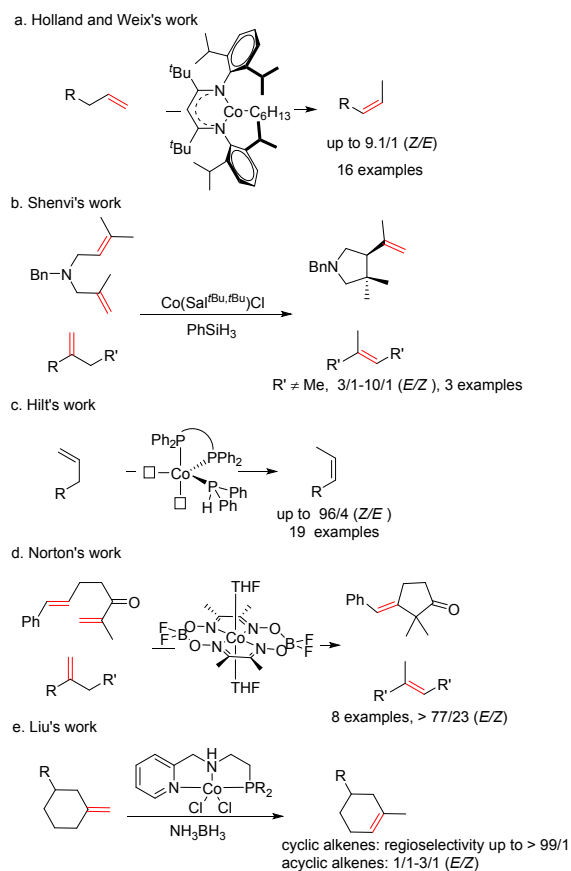
INTRODUCTION

Trisubstituted alkenes are widely distributed in molecules of great interest: natural products, pharmaceuticals and organic materials.[1] Moreover, they are versatile building blocks in synthetic organic chemistry.[2] Consequently, the stereoselective synthesis of trisubstituted alkenes has received a great deal of attention.[3] The Wittig reaction is regarded as a classical and direct approach towards olefin synthesis, however typically only limited stereoselectivity can be achieved in the case of trisubstituted alkenes.[4] In this context, a more general method to access (stereoselectively) trisubstituted olefins is still highly desirable.

Transition metal-catalyzed alkene isomerization has emerged as a fundamental and atom-economic transformation, which can readily convert terminal alkenes to internal alkenes.[5] Prior reports of alkene isomerization usually rely on noble metals, such as, ruthenium, rhodium, palladium, iridium and platinum.[6] Owing to the low abundance and high toxicity of these precious metals, attention has recently been shifting towards base-metal alternatives.[5i] The past few decades have witnessed tremendous progress in this field, particularly in cobalt-catalyzed olefin isomerization. For example, impressive work in *Z*-selective alkene isomerization was disclosed by Holland and Weix (Scheme 1a).[7] In the same year, a radical triggered isomerization and cycloisomerization was reported by Shenvi employing a Co-salen catalyst (Scheme 1b).[8] Subsequently, Hilt and coworkers unveiled a Co-dppp catalyzed monoisomerization of 1-alkenes to (*Z*)-2-alkenes (Scheme 1c).[9] In another example of radical isomerization, a novel catalyst Co(dmgBF$_2$)$_2$(THF)$_2$ was reported by Norton and co-workers (Scheme 1d).[10] More recently, a

kinetically controlled isomerization was achieved by the Liu group, affording the target alkenes in good to excellent regioselectivity for cyclic alkenes (Scheme 1e).[11] Despite these impressive developments, the stereoselective alkene isomerization geared towards the synthesis of acyclic trisubstituted alkenes remains a challenging transformation.

Scheme 1. Cobalt-catalyzed alkene isomerization

a. Holland and Weix's work

b. Shenvi's work

Co(Sal^{tBu,tBu})Cl
PhSiH$_3$

R' ≠ Me, 3/1-10/1 (*E/Z*), 3 examples

c. Hilt's work

up to 96/4 (*Z/E*)
19 examples

d. Norton's work

8 examples, > 77/23 (*E/Z*)

e. Liu's work

NH$_3$BH$_3$

cyclic alkenes: regioselectivity up to > 99/1
acyclic alkenes: 1/1-3/1 (*E/Z*)

a. H$^•$ radical initiated isomerization

[M-H] ⟶ H$^•$ + M$^•$

HAT   **Stereoselectivity issue**

b. Metal-hydride involved isomerization

[M-H]
alkene insertion
Reactivity issue

c. Our work

^{t}BuONa
BH$_3$•NH$_3$

44 examples
up to **98%** yield
up to **130/1** (*E/Z*)

precatalyst

Low reaction efficiency and poor stereoselectivity are significant problems in alkene isomerization. These issues can be rationalized using the two major proposed reaction pathways:[5i,12] a) H radical initiated isomerization (Scheme 2a); b) metal-hydride involved isomerization (Scheme 2b). In the radical pathway, hydrogen atom transfer (HAT) should be a facile step due to formation of a stable radical, however, hydrogen abstraction can occur with less stereo-control under a radical pathway as shown in the work of Shenvi and Norton (Scheme 2a).[8,10] In contrast, the alkene insertion step, in the metal-hydride triggered isomerization, can be sluggish owing to the high-energy barrier associated with formation of a quaternary metal-carbon intermediate (Scheme 2b).[13] Moreover, thermodynamically, the energy differences between *E* and *Z* isomers of trisubstituted alkene are much smaller compared with 1,2-disubstituted alkenes.[14] In this context, developing a stereoselective metalloradical catalyst or a robust metal-hydride catalyst would prove key in mitigating these problems.

**Scheme 2. Typical mechanisms for olefin isomerization and our strategy in present work**
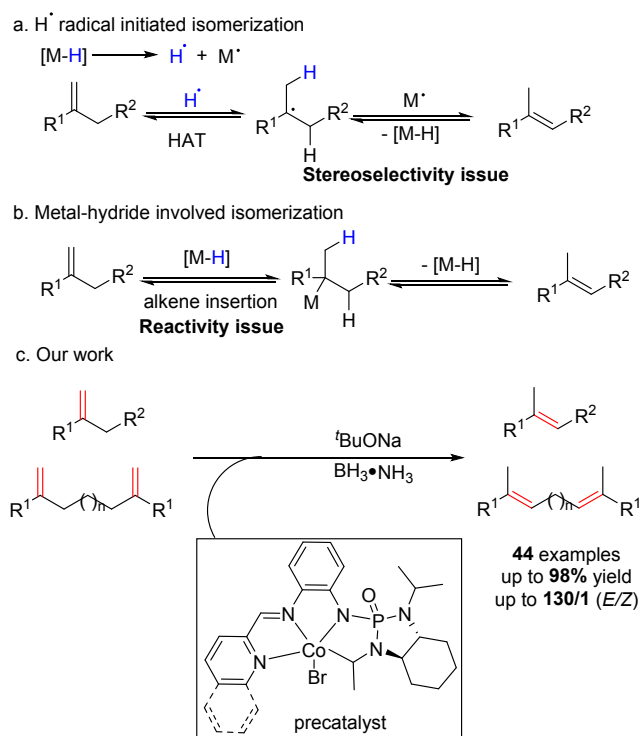
As part of our ongoing work on base-metal catalysis,[15] herein we report the development of a novel Co-hydride catalyst by incorporating phosphamide group[16] into the ligand (Scheme 2c). The *in-situ* generated metal-hydride catalyst could readily facilitate challenging isomerizations to afford a wide range of trisubstituted alkenes and dienes (44 examples) with up to 98% yield and 130/1 (*E/Z*) stereoselectivity. Interestingly, some of the trisubstituted alkenes were observed to display aggregation-induced emission enhancement. Thus, the present approach can provide material scientists a potent tool to construct functional trisubstituted-alkenes. Additionally, a deuterium labelled trisubstituted-alkene can be readily obtained with this protocol, which might be useful in pharmaceuticals.[17]

RESULTS AND DISCUSSION

Catalyst Screening. At the outset, α-ethylstyrene (**1a**) was selected as a model substrate with which to optimize the isomerization conditions (Table 1). It was found that the best results were obtained when **L1** was employed as a ligand with CoBr$_2$ as metal salt, ^{t}BuONa as activator and BH$_3$·NH$_3$ as a hydride source (Entry 1). Any deviation from the optimal conditions shut down the reaction (Entries 2-5). These results indicate that all these components are crucial for the reaction. In a control experiment, it was demonstrated that ^{t}BuONa does not promote the reaction (Entry 6), which precludes the possibility of a base-mediated isomerization. Replacing **L1** with **L2** or **L3** led to lower stereoselectivity (Entries 7-8). Inferior results were obtained by varying hydride source and solvents (Entries 9-10). The important role of BH$_3$·NH$_3$ and toluene might be attributed to the poor solubility of BH$_3$·NH$_3$ in toluene, which enables a slow release of hydride. Use of ^{t}BuOK in place of ^{t}BuONa afforded moderate yield and *E/Z* selectivity.

**Table 1. Optimization of cobalt-catalyzed isomerization of α-ethylstyrene**[a]
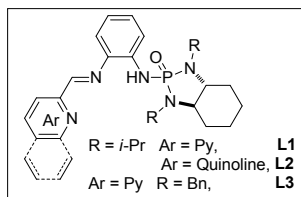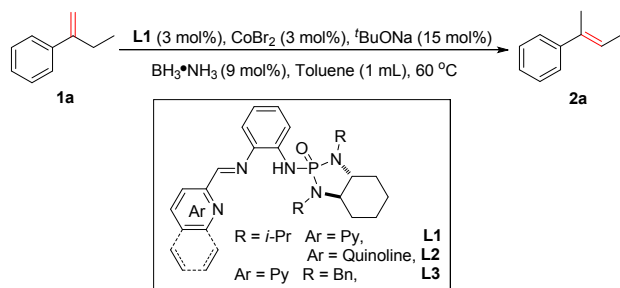
Entry	Changes from standard conditions	Yield (%)[b]	E/Z[c]
1	None	95	104/1
2	Removal of CoBr$_2$	trace	n.d.
3	Removal of ^{t}BuONa	trace	n.d.
4	Removal of BH$_3$·NH$_3$	trace	n.d.
5	Removal of **L1**	12	5/1
6	Only using ^{t}BuONa as catalyst	trace	n.d.
7	**L2** was used as ligand	96	11/1
8	**L3** was used as ligand	96	38/1
9	PhSiH$_3$ was used as 'H' source	62	8/1
10	THF was used as solvent	87	11/1
11	^{t}BuOK was used as activator	68	7/1

^{a} The reaction of **1a** (0.5 mmol) was performed in the presence of CoBr$_2$ (0.015 mmol, 3mol%), **L** (0.015 mmol, 3 mol%), ^{t}BuONa (0.075 mmol, 15 mol%) and BH$_3$·NH$_3$ (0.045 mmol, 9 mol%) in solvent (1 mL) at 60 ºC for 12 h under argon. ^{b} Isolated yield. ^{c} The ratio of E/Z was determined by the ^{1}H NMR of crude product.

To place the performance of our cobalt complex in the proper context, we carried out a comparison with other cobalt catalysts known to effect olefin isomerization. All cobalt-based catalysts were examined using a common substrate, **1a** (Table 2). As shown in Table 2, low catalytic efficiency was observed in the cases of **Cat. 1, Cat. 2** and **Cat. 3** (Entries 1-3), although an excellent E/Z selectivity (> 100/1) was detected in the case of **Cat. 1**. In contrast, **Cat. 4** and **Cat. 5** served as efficient catalysts and afforded the isomerized product **2a** with good yields (94% and 92%, respectively, Entries 4-5). However, both catalysts suffered from reduced stereoselectivity, especially in the case of **Cat. 4** (10/1). Thus, it seemed like **Cat. 4** and **Cat. 5** were promising alternatives. However, in moving from the model substrate to α-benzylstyrene (data in parentheses of entries **4-6**), it was found that the isomerization proceeded with a lower stereoselectivity (6/1) and lower yield (54%) in the presence of **Cat. 4** and **Cat. 5**, respectively. It should be mentioned that a cobalt-catalyzed isomerization was reported by Lu with thiazoline iminopyridine ligand while the revision of our manuscript. In the report, α-benzylstyrene has never been explored.[18] Consequently, these results highlight the unique advantage of our novel cobalt catalyst (Entry 6).

**Table 2. Performance of known cobalt catalysts in olefin isomerization**
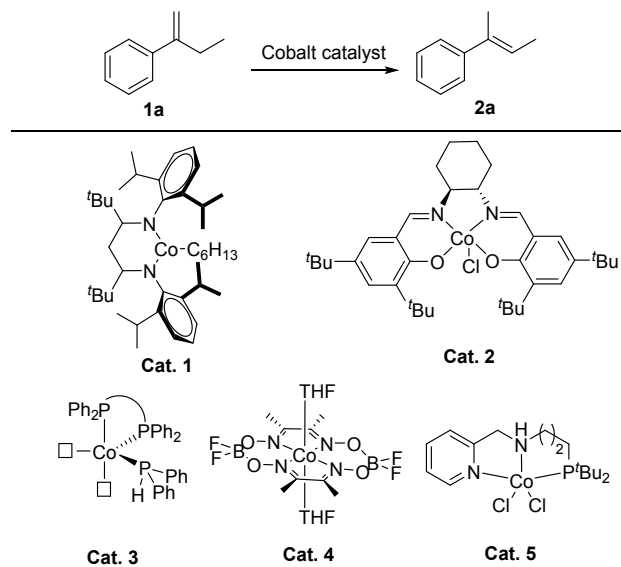
Entry	Standard conditions	Yield (%)[a]	E/Z[b]	Ref.
1	**Cat. 1** (5 mol%), 0.5 mL benzene, 80 ºC, 48h	23	>100/1	7
2	**Cat. 2** (5 mol%), PhSiH3 (10 mol%), 5 mL benzene, rt, 24h	19	6/1	8
3	**Cat.3**: dppp (10 mol%), CoBr$_2$ (10 mol%), Zn (20 mol%), ZnI$_2$ (20 mol%), Ph$_2$PH (5 mol%), 0.5 mL DCM, 48h	trace	n.d.	9
4	**Cat. 4** (7 mol%), 6 atm hydrogen, 1 mL benzene, 50 ºC, 48h	94% (97%)[c]	10/1 (6/1)[c]	10
5	**Cat. 5** (1 mol%), BH$_3$·NH$_3$ (10 mol%), 1 mL MeOH, rt, 3h	92% (54%)[c]	49/1 (30/1)[c]	11
6	our optimal conditions	95% (93%)[c]	104/1 (33/1)[c]	

^{a} Isolated yield. ^{b} The ratio of E/Z was determined by the ^{1}H NMR of crude product. ^{c} The data in parentheses was obtained using α-benzylstyrene as a substrate.

Substrate Scope. With these optimized conditions in hand, various geminal disubstituted alkenes were synthesized and screened in isomerization chemistry (Scheme 3). Initially, a series of alkyl groups (R^2) were investigated (**1a-1g**) and the corresponding products were obtained with slightly lower yields and ≥15/1 E/Z selectivities. Remarkably, 2-norbornaneacetic acid and 5β-cholanic acid derived alkenes underwent the reaction smoothly to afford the products (**2f-2g**) with high stereocontrol. Subsequently, various α-ethylstyrenes were explored under optimized conditions, and uniformly good results were observed regardless of the electronic properties or substitution patterns (**2h-2n**). *It was particularly noteworthy that a bromine substituent was well*

tolerated under this protocol without giving rise to any dehalogenation products (**2n**). To further evaluate the substrate scope, we tested a large number of diaryl-substituted alkenes (**2o-2ah**), which could provide more conjugated trisubstituted alkenes. Gratifyingly, increased reaction performance was observed among these substrates in terms of both yields (up to 98%) and stereoselectivity (up to 112/1) (**2o-2ah**). Moreover, some reactive functional groups (**2af-2ag**), such as, heteroarenes, amines and ester groups proved to be suitable in the reaction, albeit with a lower yield and selectivity. However, the ester group did lead to a reduced reaction performance (**2ah**). This might be attributed to the relative ease of reduction of the ester under reaction conditions which generate a highly reactive metal-hydride species. Finally, cyclic alkenes were also found to be amenable substrates (**2ai-2ak**). Specifically, high regioselectivity (29/1) was observed in the case of substrate **1ak** and the thermodynamically stable product was obtained as the major product.
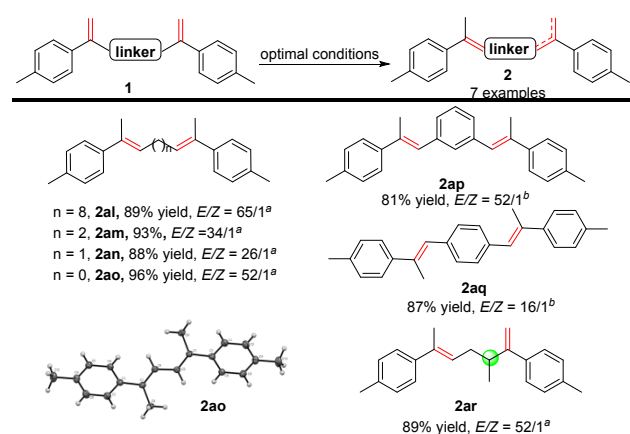
Scheme 3. Scope of monoenes in isomerization chemistry
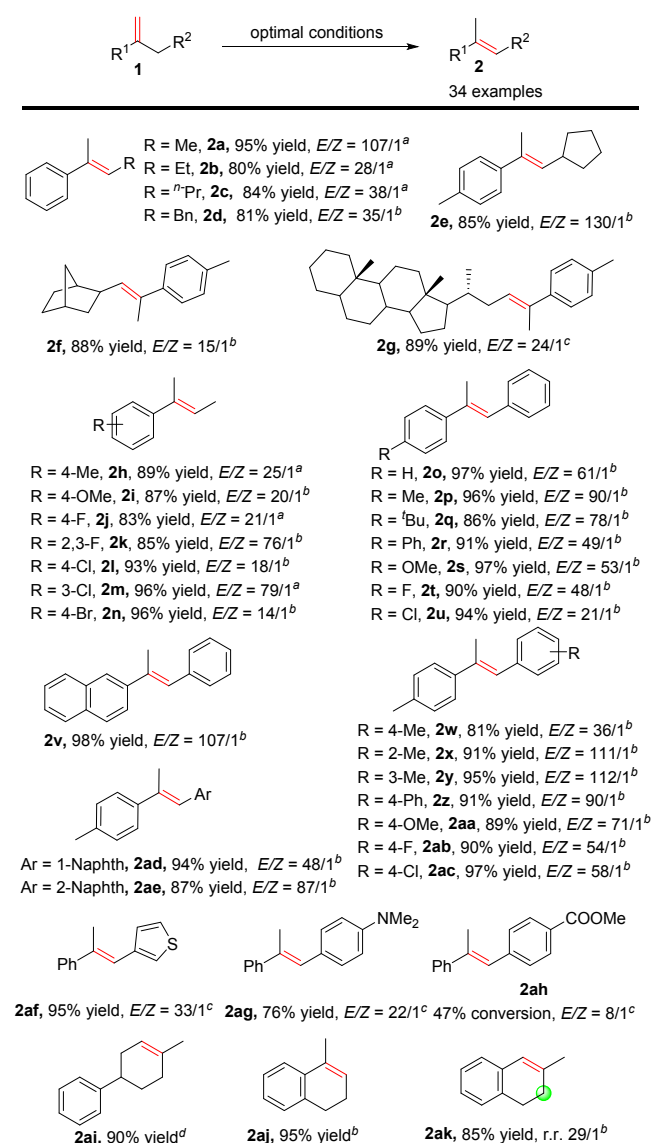
[a] The reaction of **1** (1 mmol) was performed in the presence of $CoBr_2$ (0.03 mmol, 3mol%), **L1** (0.03 mmol, 3 mol%), ^tBuONa (0.15 mmol, 15 mol%) and $BH_3 \cdot NH_3$ (0.09 mmol, 9 mol%) in toluene (1 mL) at 60 °C for 12 h under argon. [b] Condition II: **L2** was used instead of **L1**. [c] Condition III: **L2** was used as ligand and 5 mol% catalyst loading was employed. [d] Condition IV: 5 mol% catalyst loading was employed.

Compared to the isomerization of monoenes, dienes were considered as more challenging substrates in prior reports, due to undesired radical-initiated cyclization.[8,10] Under modified conditions, excellent yields and stereoselectivities were observed in both conjugated and non-conjugated diene products (**2al-2ao**, Scheme 4). The configuration of product **2ao** was assigned using X-ray diffraction. Additionally, *m*- and *p*-phenylenediacetic acid derived dienes were also explored (**2ap-2aq**). Using 5 mol% catalyst loading, isomerization reactions proceeded smoothly to afford the products which containing more freely-rotating groups. Notably, a chemoselective isomerization was observed in the case of substrate **1ar** and the sterically hindered terminal double bond was untouched in the reaction (**2ar**).

Scheme 4. Scope of dienes

[a] The reaction of **1** (1 mmol) was performed in the presence of $CoBr_2$ (0.03 mmol, 3mol%), **L2** (0.03 mmol, 3 mol%), ^tBuONa (0.15 mmol, 15 mol%) and $BH_3 \cdot NH_3$ (0.09 mmol, 9 mol%) in toluene (1 mL) at 60 °C for 12 h under argon. [b] 5 mol% catalyst loading was employed.

Intriguingly, some of these trisubstituted alkenes displayed promising aggregation-induced emission (AIE)[19] properties. The fluorescence images of selected examples are shown below (Figure 1). Remarkably, the photoluminescence (PL) quantum yields of selected solid examples range from 90.9% to 95.6%, and the emission peaks fall on the range of blue light (from 417 nm to 433 nm). To the best of our knowledge, excellent blue luminogens are still challenging to material chemists due to their large band gap.[20] These promising photophysical properties might provide an alternative tool to construct blue luminogens. As shown in Figure 1d, increasing the fraction of water led to a stronger luminescence of **2aq** solution, which clearly suggested the AIE property of the product.
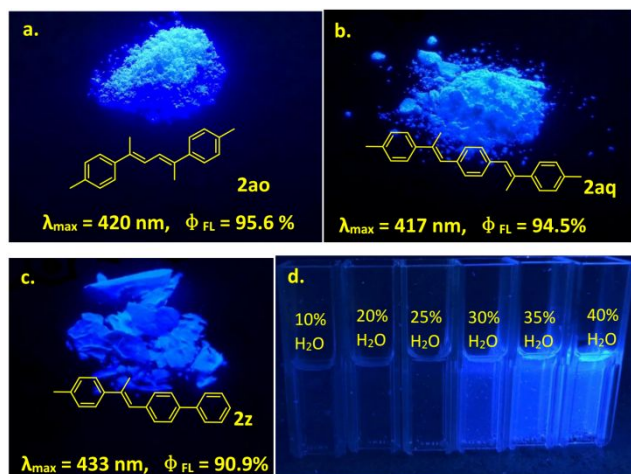
Figure 1. a. Fluorescence image **2ao** under ultraviolet (UV) light (365 nm); b. Fluorescence image **2aq** under ultraviolet (UV) light (365 nm); c. Fluorescence image **2z** under ultraviolet (UV) light (365 nm); d. Fluorescence image of **2aq** in mixed solvent of DMF/water ($5*10^{-5}$ M) under ultraviolet (UV) light (365 nm).

To further demonstrate the synthetic utility of our approach, a deuterated substrate **1a-D$_2$**, which was readily prepared through H/D exchange and Wittig reaction, was employed in the reaction to construct deuterated trisubstituted-alkene (Scheme 5a). As expected, an intramolecular deuterium transfer proceeded smoothly affording product **2a-D$_2$** with an exclusive site-selectivity (Scheme 5a). Regioselective deuteration of sp^3 C-H and sp^2 C-H is commonly regarded as a long-standing challenge.[21] Our approach would serve as an alternative means to access this synthetically challenging product. Moreover, the gram-scale isomerization of **1a** was performed with a lower catalyst loading (1 mol%). An isolated yield of 1.24 g (**2a**) was obtained with a slightly lower *E/Z* selectivity (64/1, Scheme 5b). Furthermore, a catalyst recycling experiment was also explored, and is enabled by virtue of the poor solubility of the catalyst in hexanes.[16] The catalyst could be precipitated from the reaction mixture by treatment with hexanes. A moderately diminished yield and stereoselectivity was observed upon use of the recycled catalyst (Scheme 5c). However, the third run (second recycling) of the reaction suffered a dramatic decrease in the catalytic activity. The recycling experiment was performed in three times, and (currently) the recyclability of the catalyst cannot be further improved. We are currently examining the cause of the loss of activity.
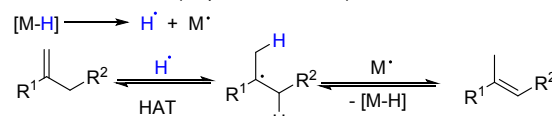
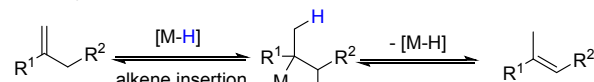**Scheme 5. Synthetic utility of the reaction and catalyst-recycling experiment**
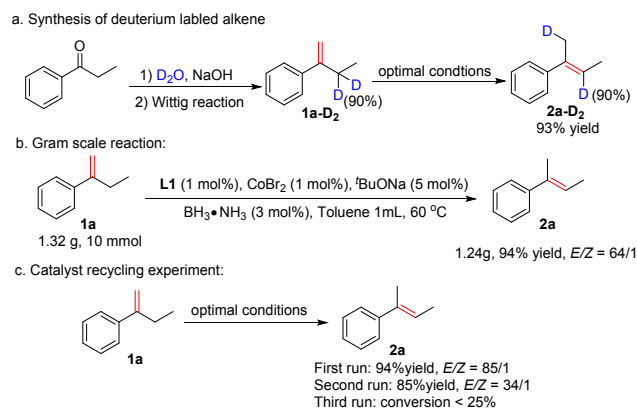
Mechanistic studies. There are four main pathways[5i] invoked in transition-metal catalyzed olefin isomerization: a) radical mechanism (Scheme 6a); b) metal hydride mechanism (Scheme 6b); c) 1,3-hydrogen shift mechanism (Scheme 6c); d) oxidative cyclization mechanism (Scheme 6d). These mechanism can be classified into two types of pathway according to the means of H-transfer: stepwise (pathways a and b) and concerted (pathways c and d).
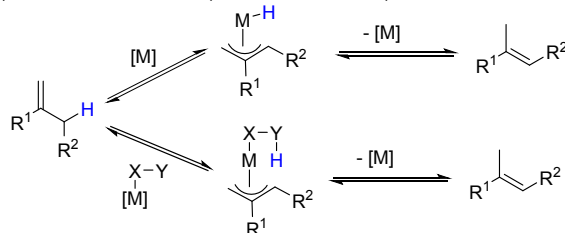
Scheme 6. Four main pathways of the transition-metal catalyzed olefin isomerization
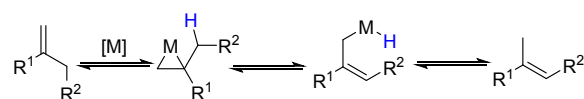
To distinguish the reaction pathway, a series of experiments were carried out with the goal of ruling out certain mechanisms (Scheme 7). A crossover experiment using mixed **1a-D$_2$** and **1s** was investigated and the crossover deuterated product **2s** was observed (Scheme 7a). This result ruled out the concerted H-transfer pathways (pathway c and d).[5i] Subsequently, a common radical scavenger 1,1-diphenylethylene was included in the reaction of **1a**, which caused negligible effects on the reaction yield and stereocontrol (Scheme 7b). This observation excluded a possible H radical reaction pathway.

Taken together, the metal-hydride pathway emerges as the most plausible reaction mechanism.

Scheme 7. Control experiments to distinguish reaction pathway

a. Crossover experiment

b. Radical trapping experiment
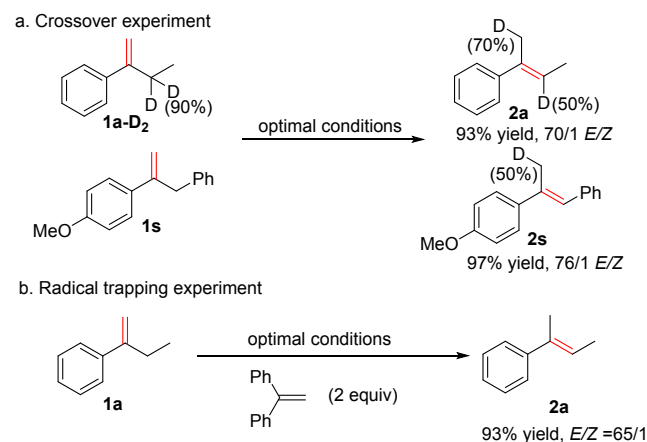
Kinetic isotope effect studies of the isomerization were further studied by using mixed **1a** and **1a-D₂** (Scheme 8a). The proportion of deuterium in the product suggested 1/1 ratio of k_H/k_D, indicating the cleavage of C-H is not the rate-determining step in the reaction. Additionally, mixed isomers of product (Z/E= 4.4/1) were tested under our optimized conditions to explore the origin of stereoselectivity in the reaction (Scheme 8b). Although an increase in the ratio of E isomer was detected in the product, the stereoselectivity of the reaction should mainly stem from the isomerization of terminal to internal alkenes, not from the isomerization of E/Z isomers of trisubstituted alkene product. The reaction of **1as** produced product **2a** with far less E/Z selectivity (20/1) compared with the reaction of **1a**. This result further supports our conclusions on the origins of stereoselectivity. Additionally, π-π stacking effects between the substrate and catalyst were explored by using the aliphatic alkene but-1-en-2-ylcyclohexane (**1at**) (Scheme 8c). A significantly reduced conversion (45%) and stereoselectivity (3/1) was observed. This observation suggests that the presence of π-π stacking interactions are possibly crucial for both reaction efficiency and selectivity.

Scheme 8. KIE study and stereoselectivity origin study

a. KIE study:

b. Steroselectivity origin study

c. π-π Stacking effect investigation
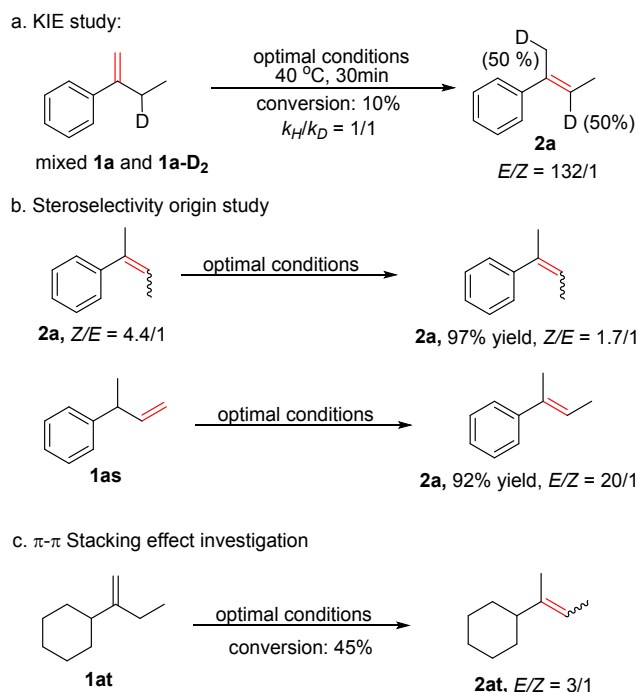
Based on our experimental observations and the single crystal structure of the precatalyst, we propose a Co-hydride catalytic pathway as shown in Figure 2. The active cobalt-hydride catalyst (**Co-H**) initiates the reaction through a double bond insertion giving an alkyl cobalt intermediate **I-1**. On the basis of the KIE study, this process should be the rate-determining step. Then the alkyl cobalt species (**I-1**) experiences a stereoselective β-H elimination through a transition state **TS-1**. In the transition state, π-π stacking effects between the pyridine (or quinoline) ring and an aromatic ring in the substrate, as well as the steric influence of the phosphamide moiety in the catalyst plays an important role in the high E/Z selectivity of the reaction. This step should be a fast, but a stereoselective process.
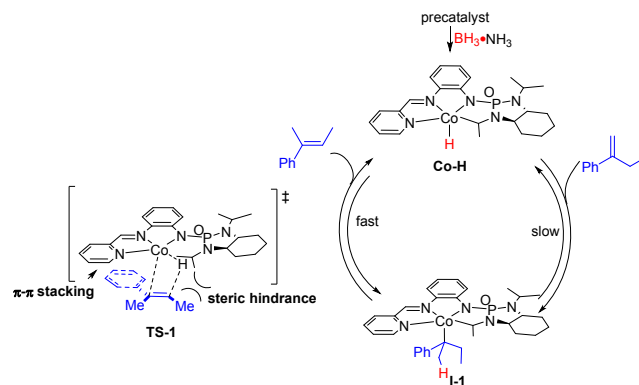

Figure 2. Proposed catalytic cycle

CONCLUSIONS

In conclusion, we have reported a stereoselective olefin isomerization catalyzed by a (postulated) novel cobalt-hydride catalyst. The mild reaction conditions and high efficiency allows a scalable access to acyclic trisubstituted alkenes with high stereoselectivity. Moreover, a preliminary catalyst-recycling experiment shows that the

catalyst is (moderately) recyclable. The interesting AIE property of products arising from diene substrates makes this protocol useful in novel material preparation. The synthetic utility of this reaction is also demonstrated by the synthesis of a deuterated trisubstituted alkene. Additionally, a plausible catalytic cycle is proposed to rationalize the mechanistic observations.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental details and spectra (PDF)

Crystallographic data (CCDC 1945169) (CIF)

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Notes

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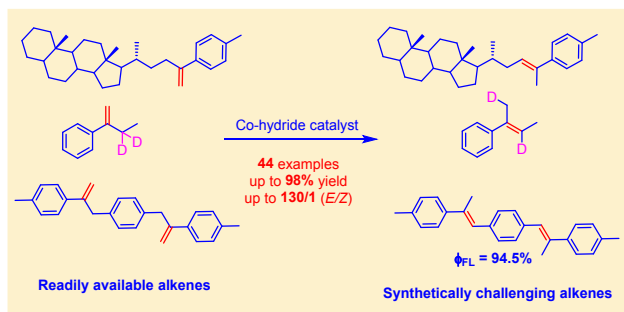
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Co-hydride catalyst

44 examples
up to **98%** yield
up to **130/1** (*E/Z*)

ϕ_{FL} = **94.5%**

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