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Highly Stereoselective Positional Isomerization of Styrenes via Acid-Catalyzed Carbocation Mechanism

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Keywords

Alkene positional isomerization | Stereoselective | Carbocation mechanism | Hidden Brønsted acid catalysis

Main observation and conclusion

The first transition metal-free highly stereoselective positional isomerization of various α -alkyl styrenes through a carbocation mechanism triggered strategy is developed by using Al(OTf)₃ as a hidden Brønsted acid catalyst, which provides facile access to value-added acyclic tri- and tetra-substituted alkenes in good yields with high stereoselectivity under mild conditions. The practicality of this protocol is further highlighted by the gram-scale synthesis, high stereoselectivity, good functional group tolerance, and simple operation. Mechanistic studies support that Al(OTf)₃ act as a hidden Brønsted acid catalyst, and the formation of a carbocation intermediate.

Comprehensive Graphic Content

The first highly stereoselective alkene positional isomerization via a carbocation mechanism



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Background and Originality Content

Alkene isomerization is a very useful and atom-economic transformation, which constitutes a powerful strategy for the synthesis of internal alkenes in a stereoselective manner.^[1] The past few decades have witnessed tremendous progress in this area, and a variety of efficient catalytic systems based on either noble-metal (eg. Ru,^[2] Rh,^[3] Pd,^[4] Ir,^[5] and Pt^[6]) or base-metal (eg. Co,^[7] Ni,^[8] Fe,^[9] and Mo^[10]) complexes have been developed for the positional isomerization of aliphatic mono-substituted or 1,2-dialkyl alkenes. Spite these achievements, the stereoselective positional isomerzation of α -alkyl- α -aryl alkenes remains underexplored and is still a hallenge. Therefore, the development of efficient catalytic strategies for realizing such isomerization is highly sought after, which v ould provide a facile route for accessing value-added acyclic tri- or trasubstituted alkenes that are a kind of structural units widely distributed in natural products, pharmaceuticals and materials,^[11] nd serve as a versatile precursor in modern organic synthesis.^[12]

In this context, much effort has been paid to developing this ansformation in the past few years. Consequently, a variety of catalytic systems based on three main mechanisms: (a) metal-hydride mechanism;^[13] (b) hydrogen (H) radical mechanism;^[14] (c) π -almetal intermediate based 1,3-hydrogen shift mechanism,^[15] have been established by transition-metal catalysis (Scheme 1a). For exnple, in 2009, RajanBabu reported a Pd(II)-catalyzed isomerization of α -alkyl styrenes via a Pd-H insertion and β -H elimination pathway.^[13a] Recently, the groups of Lu,^[13b] Findlater,^[13c] and Xia^[13d] independently reported the cobalt(II)-catalyzed highly stereoselective positional isomerization of α -alkyl styrenes through Co-H mechanism, which delivered the desired acyclic trisubstituted alnes with excellent stereoselectivity by employing their developed thiazoline iminopyridine, phosphamide iminopyridine, or phosnine-amidooxazoline ligand. Most recently, Huang and Liu reported an iron-catalyzed isomerization of α -alkyl styrenes to trisubs' ituted alkenes with chiral phosphine-pyridine-oxazoline ligand via e-H mechanism.^[13f] Through H radical initiated mechanism, Norton et al. developed an isomerization of α-functionalized alkyl stynes by cobalt catalysis under H₂ pressure.^[14]

(a) State of the art: Known three main mechanism for poitional isomerization of α -alkyl styrenes



Besides, noble-metal ruthenium (Ru) or rhodium (Rh) based complexes were found to be capable of catalyzing the similar isomerization through a concerted 1,3-H shift mechanism. Grotjahn developed a stereoselective alkene isomerization catalyzed by their bifunctional Ru complex.^[15a] Zhao, Liu and coworkers accomplished a Rh catalyzed positional isomerization of functionalized α -alkyl styrenes via π -allylmetal intermediate.^[15b] Although these protocols were proven to be suited for the synthesis of certain classes of acyclic trisubstituted alkenes, further progress is required to expand the substrate scope, to improve the stereoselectivity, and to avoid the use of transition-metal catalysts, a complex ligand that is usually not easy to obtain, and/or additives (Scheme 1a). In addition, Brønsted acid mediated alkene isomerization via a carbocation mechanism^[16] has also emerged as an alternative strategy.^[17] However, although the positional isomerization of several cyclic alkenes has been reported,^[17] the acyclic alkene isomerization remains underdeveloped,^[17c,e] possibly due to the challenging *E/Z* selectivity control and reaction efficiency issues.

Recently, we have developed an unprecedently Markovnikov regioselective hydrodifluoroalkylation of alkenes with difluoroenoxysilanes via carbocation intermediate.^[18] During the mechanistic studies, we found that the generated in situ carbocation intermediate from tertiary alcohol would eliminate a β -proton to deliver an *E*-alkene with high stereoselectivity under the catalysis of hidden Brønsted acid Mg(ClO₄)₂ \Box 6H₂O, and the observation of alkene isomerization phenomenon in the deuterated experiment.^[18] Motivated by these interesting findings, we wondered whether it was possible to develop a transition-metal-free highly stereoselective positional isomerization of acyclic alkenes via a carbocation mechanism using hidden Brønsted acid catalysis^[19] (Scheme 1b). Herein, we report our successful implementation of this transformation under mild and operationally simple conditions, which constitutes a facile tactic for alkene positional isomerization

Results and Discussion

At the outset, α -ethylstyrene **1a** was chosen as a model substrate for the optimization of reaction conditions, as shown in Table 1. Mg(ClO₄)₂ \square 6H₂O, which was previously an effective catalyst for the alkene hydrodifluoroalkylation,^[18] was first examined for the isomerization of **1a** in ClCH₂CH₂Cl at room temperature, unfortunately, no any desired product **2a** was detected after 12 h (entry 1).

 Table 1 Optimization of conditions^a

		Cat. (5 mol%)			
1a _{(0.2} mmol)		solvent, rt,12 h	2a		
Entry	Cat.	Solvent	Yield(%) ^b	E/Z ^c	
1	Mg(ClO ₄) ₂ .6H ₂ O	CICH ₂ CH ₂ CI	0	-	
2	Al(ClO ₄) ₃ ·9H ₂ O	CICH ₂ CH ₂ CI	14	18/1	
3	In(ClO₄)₃·8H₂O	CICH ₂ CH ₂ CI	44	21/1	
4	Cd(ClO ₄) ₂ ·6H ₂ O	CICH ₂ CH ₂ CI	58	6.4/1	
5	Ga(OTf)₃	CICH ₂ CH ₂ CI	60	6.8/1	
6	In(OTf)₃	CICH ₂ CH ₂ CI	72	6.9/1	
7	Fe(OTf)₃	CICH ₂ CH ₂ CI	90	8.5/1	
8	Bi(OTf)₃	CICH ₂ CH ₂ CI	50	5.3/1	
9	Sc(OTf)₃	CICH ₂ CH ₂ CI	16	27/1	
10	AI(OTf)₃	CICH ₂ CH ₂ CI	87 (82) ^d	24/1	
11	Cu(OTf) ₂	CICH ₂ CH ₂ CI	0	-	
12	Mg(OTf) ₂	CICH ₂ CH ₂ CI	0	-	
13	Al(OTf)₃	CH_2Cl_2	81	25/1	
14	Al(OTf)₃	EtOAc	0	-	
15	Al(OTf)₃	Toluene	0	-	

^{*a*} The reaction was conducted using alkene **1a** (0.2 mmol) and **Cat.** (5 mol%) in solvent (2 mL) at room temperature for 12 h in air. ^{*b*} Determined by ¹H NMR analysis of the crude product using 1,3,5-trimethoxybenzene as internal standard. ^{*c*} The *E/Z* ratio was determined by the ¹H NMR of crude product. ^{*d*} The value in parentheses indicates an isolated yield of **2a**.

Scheme 1 Strategies for isomerization of α-alkyl styrenes

Further investigation of other metal perchlorate hydrates such as Al(ClO₄)₃ 9H₂O, In(ClO₄)₃ 8H₂O, and Cd(ClO₄)₂ 6H₂O revealed that the isomerization indeed proceeded smoothly, and the desired trisubstituted alkene 2a could be generated in moderate to high E/Z stereoselectivity, albeit with low to moderate yields (entries 2-4). Meanwhile, a series of metal triflates, including Ga(OTf)₃, In(OTf)₃, Fe(OTf)₃, Bi(OTf)₃, Sc(OTf)₃, Al(OTf)₃, Cu(OTf)₂, and Mg(OTf)₂ were also investigated (entries 5-12). Although no product 2a was observed in the presence of Cu(OTf)₂ and Mg(OTf)₂ (entries 11-12), all other tested catalysts furnished product 2a, and the use of 5 mol% • Al(OTf)₃ turned to be the best choice in terms of reactivity and selectivity,^[20] affording 82% yield of **2a** with 24:1 *E/Z* selectivity (entry 10). Next, the solvent effects were examined using $AI(OTf)_3$ as me catalyst. It was found that CH₂Cl₂ was also a suitable solvent, and gave rise to 2a with 25:1 E/Z selectivity but slightly lower yield (1% NMR yield) (entries 13 vs 10). And the use of ethyl acetate (EtOAc) and toluene could not afford the product at all (entries 14-15). For more details of optimization of conditions, see section 2 of the supporting information (SI).

With the optimized condition in hand, the scope of alkenes was then explored (Table 2). A wide range of α -ethyl styrenes bearing

different substituents on the phenyl ring were all tolerated, and afforded the corresponding trisubstituted alkenes 2a-2i in good to high yields and E/Z ratio, regardless of the position and nature of the substituents. 2-(But-1-en-2-yl)naphthalene could also deliver the desired product **2j** in 53% yield with 17:1 E/Z ratio. α -Benzyl styrenes with electron-withdrawing or electron-donating group proceeded smoothly as well to produce the conjugated trisubstituted alkenes 2k-2o with good results (up to 93% yield, 14:1 E/Z selectivity). α -Propyl, α -isobutyl, and α -phenylethyl substituted styrenes were viable substrates, providing the desired alkenes 2p-2r in good to excellent yields and E/Z selectivity. However, α -ethylstyrenes bearing a strong electron-withdrawing CF3 or CN group led to almost no reaction, possibly because the corresponding carbocation intermediates are not easy to form. And no target was observed in the case of alkenes bearing a 2-thienyl or 2-benzofuryl functionality; only olefin dimerization and/or trimerization byproducts detected by GC-MS analysis. Five-, six-, and seven-membered exocyclic 1,1-disubstituted olefins were found to be amenable substrates, delivering the corresponding endocyclic trisubstituted alkenes 2s-2v with 63-88% yields.



^{*a*} The reaction was conducted using alkenes (0.5 mmol), Al(OTf)₃ (5 mol%) and ClCH₂CH₂Cl (5 mL), in air at room temperature for 12 h. The *E/Z* ratio was determined by the ¹H NMR analysis of crude product. ^{*b*} Using 10 mol% Al(OTf)₃. ^{*c*} Using 15 mol% Al(OTf)₃. ^{*d*} Using 15 mol% Al(OTf)₃, at 50 °C. ^{*e*} Using 3 mol% Al(OTf)₃. ^{*f*} At 50 °C.

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Moreover, functionalized trisubstituted alkenes **3a-3e** featuring halogen atom, ester, ether, or cyano group at the alkyl chain were effectively achieved in good to high yields with moderate to excellent *E/Z* ratio. A salient feature is that halogen atoms on both aromatic ring and aliphatic chain were tolerable under the current catalytic system, allowing further transformation. Remarkably, tetrasubstituted alkenes **3f-3i** could be formed in up to 89% yields, by employing bulky 1,1-disubstituted alkenes that were a kind of problematic substrates in previous conditions.^[13] 2-Fluoro-1-methylene-2,3-dihydro-1*H*-indene could be isomerized into tetrasubstiti ted monofluoroalkene **3j**, which is not easy to synthesize by other methods,^[21] with a yield of 63%.

To demonstrate the synthetic utility of this methodology further, a gram-scale isomerization of **1a** (15 mmol) was conducted. Under the catalysis of 5 mol% Al(OTf)₃ at room temperature, 1.64 g of **2a** as obtained in 83% yield with a slightly lower E/Z ratio (Scheme 2a). Besides, the alkenyl functionality in the products was capable undergoing a variety of diversifying reactions.^[13b]

To gain insights into the isomerization mechanism, several control experiments were performed. First, the possibility of Al(OTf)₃ runction as a hidden Brønsted acid in the reaction was investigated,^[22] and found that the addition of 10 or 15 mol% noncoordinting bulky base 2,6-di-*tert*-butylpyridine (DTBP) terminated the reaction completely (Scheme 2b). Meanwhile, the use of 0.5 mol% H'DTf was also able to catalyze the isomerization, although no desired product was detected in the presence of 5 mol% HOTf (because severe olefin dimerization occurred by GC-MS analysis in this case).^[23] These results supported the idea that Al(OTf)₃ functioned as a hidden Brønsted acid catalyst, and the *in situ* generated trace amount of HOTf was the real catalytic species. The gradually releasir g HOTf from Al(OTf)₃ and trace amount of moisture in the reaction system inhibited the dimerization or other undesired pathway,

scheme 2 Gram-scale synthesis and mechanistic studies



In summary, we have disclosed the first transition-metal-free highly stereoselective positional isomerization of α -alkyl styrenes through a carbocation mechanism, allowing facile synthesis of various acyclic tri- and tetra-substituted alkenes with high stereoselectivity by using Al(OTf)₃ as a hidden Brønsted acid catalyst. The salient features, including mild conditions, inexpensive & commercially available acid catalyst, good functional group tolerance, simple op-

thereby ensuring a higher yield and selectivity.

Second, a deuterium labeling experiment using a deuterated alkene 1a-D (95% D) was carried out under standard conditions in a glove box, giving the deuterated 2a-D with 17% D on the methyl group and 95% D on the vinyl group (Scheme 2c). The low deuterium abundance at the methyl group illustrated that the step for the protonation of terminal alkenes 1 was likely reversible. Meanwhile, the addition of D_2O led to the incorporation of 8% D on the vinyl group of **2a-D** suggested that the last step for the removal of β -proton might be also reversible, and Al(OTf)₃, as a hidden Brønsted acid, would be partially hydrolyzed to HOTf as the real catalytic species. Third, an intramolecular trapping experiment using an alkenol 4 was carried out under the standard conditions, and found that 52% yield of tetrahydrofuran 5 was formed as the product via acid catalyzed alkene hydroalkoxylation pathway, which further supported that the reaction proceeds via a carbocation intermediate (Scheme 2d).^[24] Additionally, a mixed isomer of product **2a** (Z/E = 3.6:1) was subjected to the standard conditions to explore the origin of stereoselectivity, and the E/Z ratio of 2a just increased slightly to 1:2.2 after 12 h (Scheme 2e), which was far less than 24:1 E/Z selectivity produced from the isomerization of 1a. These reaction outcomes suggested the stereoselectivity might mainly originate from the positional isomerization of terminal alkenes 1 to internal alkenes 2,^[25] not from the geometrical isomerization of trisubstituted alkenes 2.^[13c] Based on the above mechanistic studies, together with our previous work,^[18] a plausible reaction pathway involved a carbocation intermediate was proposed in Scheme 2f. The active catalytic species HOTf was gradually generated in the reaction system, which would react with the alkenes 1 to form a key carbocation intermediate I. After undergoing a deprotonation, the desired tri- or tetrasubstituted alkenes would be produced, accompanied by the regeneration of HOTf.



eration, and easy to the scale-up application, make our method potentially very useful. Mechanistic studies reveal that a carbocation intermediate initiated reaction pathway should be involved in this reaction.

Carbocation intermediate

Experimental

General procedure for the alkene isomerization is as follows: To a 25.0 mL tube were added Al(OTf)₃ (11.9 mg, 0.025 mmol, 5.0 mol%, unless otherwise noted) and anhydrous ClCH₂CH₂Cl (5.0 mL),

2 or 3

followed by the sequential addition of alkenes (0.5 mmol). After being stirred at room temperature under air for 12 h, the reaction mixture was filtrated through a short pad of silica gel, and washed with dichloromethane. The combined organic phases were concentrated under vacuo to give the crude products. To determine the E/Z selectivity of products, the crude residue was first dissolved in CDCl₃, and took some samples for ¹H NMR analysis. Then the sample for analysis and the rest of crude residue were recombined and purified by silica gel column chromatography using the indicated eluent to afford the corresponding products **2** or **3**.

Supporting Information

The supporting information for this article is available on the V 'WW under https://doi.org/10.1002/cjoc.2021xxxxx.

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uniqueness and superiority of Al(OTf)₃ as a hidden Brønsted acid catalyst in this reaction. This is possibly due to the gradually release of Brønsted acid catalyst HOTf via hydrolysis of Al(OTf)₃ played a crucial role, thus maintaining a low concentration of HOTf to suppress side reactions, while the direct use of Brønsted acids would give a false impression of catalytic inefficiency of the Brønsted acid owing to competitive side reactions, such as dimerization or polymerization of the substrate or product at high concentrations of acid.

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the reaction time in the model reaction, and found that the E/Z ratio of **2a** was same (24:1 E/Z) after 2 h, 4 h, 6 h, and 10 h, which suggested that the selectivity was likely not based on thermodynamic control.

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Highly Stereoselective Positional Isomerization of Styrenes via Acid-Catalyzed Carbocation Mechanism Xiao-Si Hu,^a Jun-Xiong He,^a Ying Zhang,^a Jian Zhou,^{*,ab} and Jin-Sheng Yu^{*,a} Chin. J. Chem. 2021, 39, XXX-XXX. DOI: 10.1002/cjoc.202100XXX



The first transition-metal-free highly stereoselective positional isomerization of various α -alkyl styrenes through a carbocation mechanism is developed by using Al(OTf)₃ as a hidden Brønsted acid catalyst.

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