Morita-Baylis-Hillman Reaction Inspired [3,3]-Rearrangement of Aryl Iodanes with α,β -Unsaturated Oxazolines

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Article

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Abstract

The [3,3]-rearrangement of aryl iodanes with α,β -unsaturated oxazolines has been developed by merging Morita-Baylis-Hillman (MBH) process into the rearrangement reaction. The method allows for the exclusively E-selective synthesis of a wide variety of valuable α -aryl α,β -unsaturated oxazolines which can be difficult to synthesize with other known methods. Experimental and computational mechanistic studies unraveled that the reaction proceeds via the assembly of both coupling partners followed by MBH-type addition to form rearrangement precursor, [3,3]-rearrangement, and stepwise E1cb-elimination. The E-selectivity of the reaction is favored both kinetically and thermodynamically.

Introduction

The aromatic Claisen rearrangement is one of the most powerful synthetic tools for functionalization of arenes.¹⁻⁴ This classic [3,3]-rearrangement reaction generally requires the pre-synthesis of relatively stable rearrangement precursors (e.g. allyl phenyl ethers). Unlike classic Claisen rearrangement, the iodonio-Claisen rearrangement can be conducted by directly mixing activated aryl iodanes with certain nucleophiles, which allows in situ and transient assembly of a highly reactive rearrangement precursor (Fig. 1A).⁵⁻⁶ The subsequent [3,3]-rearrangement occurs spontaneously leading to synthetically appealing *ortho*-functionalized aryl iodides. In the past three decades, an array of nucleophiles such as allyl/propargyl silanes,⁷⁻¹⁴ carbonyl compounds,^{15,16} phenols,¹⁷ α -stannyl nitriles,¹⁸⁻²¹ and enol silyl ethers²² have been found to be suitable for the rearrangement process. Despite the progresses made, the reaction scope of carbonyl nucleophiles is limited to structurally defined carbonyl compounds (Fig. 1A).^{15,16} Recently, we employed an indirect protocol called “assembly/deprotonation”, in lieu of the well-established direct “assembly”, for the construction of rearrangement precursors (Fig. 1B).²³ Owing to the more precisely control of the process, the indirect strategy not only significantly broadened the scope of nucleophiles but also enabled the reaction to proceed in a 3D-controlled manner. Inspired by this progress, we herein report our endeavour to advance the indirect protocol to achieve [3,3]-rearrangement of aryl iodanes with α,β -unsaturated carbonyls. Unlike the assembly/deprotonation approach to generate the rearrangement precursor, the present reaction passes through a precursor formed via a strategy which can be characted as “assembly/addition”.

The Morita-Baylis-Hillman (MBH) reaction is a well-known method for α -functionalization of α,β -unsaturated carbonyls.²⁴⁻²⁶ As depicted in Figure 1C, the reaction involves the Lewis base (LB) addition to α,β -unsaturated carbonyls, enolate addition to electrophiles (e.g. aldehydes and imines), proton transfer and β -elimination.^{27,28} The MBH addition to form a transient enolate intermediate from readily available α,β -unsaturated carbonyls attracted our attention. We envisioned that the MBH-addition model could be applied to achieve novel iodonio-Claisen rearrangement. Specifically, as illustrated in Figure 1D, the assembly of aryl iodane with α,β -unsaturated carbonyl first forms an iodine (III)- α,β -unsaturated carbonyl adduct. The LB addition then affords an iodine(III)-enolate species that could be an ideal rearrangement precursor. Subsequent [3,3]-rearrangement and β -elimination take place, finally producing

valuable α -aryl α,β -unsaturated carbonyls that have significant utility in chemical synthesis²⁹⁻³³ but may be difficult to make with *E/Z* selectivity through other known methods³⁴⁻³⁶. It should be noted that, while our study was underway, Wengryniuk reported an elegant iodonio-Claisen rearrangement of β -pyridinium silyl enol ethers that allows for α -arylation of α,β -unsaturated ketones.³⁷ However, the generation of β -pyridinium silyl enol ethers has long been suffering from limited substrate scope³⁸⁻⁴⁰ that restricts the scope of Wengryniuk's protocol to structurally defined cyclic enones. As such, new reaction patterns are required for implementing iodonium-[3,3]-rearrangement of simple α,β -unsaturated carbonyls and overcoming the potential *E/Z* selectivity issue (Fig. 1D).

Results

Initial discovery and optimization. To verify our hypothesis, we studied the reaction of $\text{PhI}(\text{OAc})_2$ **1a** with α,β -unsaturated carbonyl derivatives including α,β -unsaturated aldehyde **2a**, ketone **2b**, ester **2c**, amide **2d**, and 2-oxazoline **3a**, as shown by entries 1-5 in Table 1. DABCO, which is often used as Lewis base for the MBH reaction, was employed for our initial exploration. Although no desired products **4a-4d** could be determined from the reactions of **2a-2d**, α,β -unsaturated oxazoline **3a** was found to be promising for the transformation albeit giving desired product **5aa** in low yield (19%). The feasibility of oxazoline **3a** could be attributed to its higher nucleophilicity than other unsaturated carbonyls, which enhanced its interaction with aryl iodanes. Due to part of the same effect, the use of 2-oxazolines also significantly broadened the reaction scope of our previously studied [3,3]-rearrangement of aryl iodanes as depicted in Figure 1B.²³ Further studies revealed that the choice of bases was critical to the reaction. Pyridine derivatives were more effective than aliphatic tertiary amines (entries 6-9). This was probably due to the lack of β -hydrogens of pyridines, thus avoiding undesired oxidation by hypervalent iodine species. Further optimization of the reaction temperatures and reaction times identified the best conditions giving **5aa** in 71% yield (entry 12).⁴¹

Reaction scope. With the optimized conditions in hand, we investigated the reaction scope with respect to α,β -unsaturated oxazolines **3** and aryl iodanes (Table 2). To our delight, a wide variety of α,β -unsaturated oxazolines **3** were suitable for the process. Regardless of the length of the terminal alkyl chains, oxazolines **3b-3d** smoothly afforded **5ab-5ad** in similar yields (69-72%). The method was also applicable to bulky oxazolines **3g-3k** bearing β -cyclopropyl, cyclopentyl, cyclohexyl, cyclohexenyl, and piperidine groups that afforded stereohindered alkenes **5ag-5ak** in synthetically useful yields (47-57%). Remarkably, β,β' -dimethyl substituted oxazoline **3l** could even furnish tetrasubstituted alkene **5al**, albeit in a low yield (25%). In addition to β -alkyl oxazolines, β -aryl oxazoline **3m** also proved suitable for the process giving **5am** in a modest yield (49%). Further studies demonstrated that the reaction possessed excellent functional group (FG) compatibility. An array of FGs including alkene groups (**5aj**, **5ax** and **5az**), protected amines (**5ak** and **5aa'**), alkyl/aryl halides (**5an**, **5at**, **5au** and **5ay**), ethers (**5ao-5aq**, **5av** and **5aw**), esters (**5ar-5au** and **5ax-5az**), propargyl groups (**5av**), and nitrile groups (**5aw**) were all well tolerated in the reaction. Notably, alkene, alkynyl and heteroaryl groups that could be readily oxidized by hypervalent iodines were also tolerated here. This unconventional FG compatibility could be attributed to the relatively

high affinity of oxazolines with iodine (III) species, which inhibited the undesired oxidation of electron-rich FGs. In addition, the highly electrophilic α,β -unsaturated esters (**5ax** and **5az**) that can be challenging substrates for conventional cross-coupling reactions were also compatible with the current reaction conditions. The broad scope of FGs adopted in the reaction provided a versatile platform for further elaboration of the products and demonstrated the practicability of the protocol.

Next, the scope of aryl iodanes **1** was explored under the optimum conditions (Table 2). *para*-Alkylated aryl iodanes (**5bb** and **5cb**) were slightly more productive than those bearing *para*-halide substituents (**5db-5gb**). Impressively, aryl iodanes **1** bearing functional groups including alkyl/aryl halides (**5db-5gb**, **5rb** and **5vb**), *N*-protected amines (**5ib** and **5sb-5ub**), esters (**5ib** and **5pb-5rb**), ethers (**5lb-5ob**), and nitriles (**5ob**) were all suitable for the reaction. Even highly reactive benzylic chlorides (**5hb**) and α,β -unsaturated esters (**5qb**) that can be problematic FGs for conventional arylation reactions could be tolerated in the reaction. Aryl iodane **1j** with electron withdrawing groups (benzoyl group) failed to furnish any desired products **5jb** under optimum conditions. This was probably due to the relatively low nucleophilicity of this electron-poor substrate, which made the electrophilic activation of **1j** with TMSOTf more difficult. However, raising the activation temperature from -78 °C to rt, **1j** still afforded **5jb** albeit in a low yields (33%). Remarkably, *meta*-substituted aryl iodanes exclusively produced less hindered products (**5kb-5wb**) demonstrating an excellent regioselectivity. It is also impressive that sterically hindered substrates furnished intriguing polysubstituted arenes (**5xb-5zb**) without loss of efficiency. In addition to phenyl iodanes, the method could also be applicable to naphthalene and thiophene iodanes (**5a'b** and **5b'b**) albeit giving relatively low yields.

Experimental and computational studies. To verify whether the reaction actually proceeded in a way we envisioned in Figure 1D and understand the *E*-selectivity of the reaction, we combined DFT calculations (Fig. 2, see SI6 for computational details) and control experiments to study the reactions of **1a** with *E*-**3c** and *Z*-**3c** (Fig. 3).

Figure 2A shows the reaction pathways leading *E*-**3c** to the product *E*-**5ac**. The reaction takes place via sequential three stages. After TMSOTf activates $\text{PhI}(\text{OAc})_2$ to give $\text{PhI}(\text{OTf})_2$,⁴²⁻⁴⁵ stage I generates an intermediate **IM2** for the subsequent rearrangement process. The stage takes place by assembling $\text{PhI}(\text{OTf})_2$ with *E*-**3c** to give **EIM1**,⁴⁶⁻⁴⁹ followed by a MBH-like nucleophilic addition of 4-methylpyridine (denoted as **Py**) to an alkene carbon of **EIM1**. As depicted in Figure 2, **Py** can attack **EIM1** from either side of the alkene plane via (*R*)**ETS1** or (*S*)**ETS1**, leading to (*R*)**IM2** or (*S*)**IM2**. Stage II from **IM2** to **IM4** forms a C-C bond via dearomative [3,3]-sigmatropic rearrangement through **TS2**, followed by rearomatization via **TS3**. Finally, a stepwise E1cb elimination (stage III) converts **IM4** to **IM5** by deprotonation via **TS4** first and then **Py** elimination via **TS5**, giving the final product *E*-**5ac**. It is worth noting that the N-protonation of oxazoline with HOTf (generated in stage II) of **IM4** is crucial for the E1cb elimination. For example, in the absence of the N-protonation, the deprotonation of (*S*)**IM4** has a barrier of 27.0 kcal/mol, which is much higher than the 13.9 kcal/mol from (*S*)**IM4** to (*S*)**TS4**.

Energetically, as the reaction proceeds, the system becomes more and more stable with an overall exergonicity of 96.6 kcal/mol. Among all the elementary steps, the rate determining step lies at the deprotonation of **IM4**, with a barrier of 12.6 and 13.9 kcal/mol for (*R*)- and (*S*)-pathway, respectively. The favorable energetics rationalizes why the reaction could proceed smoothly, thus corroborating our strategy using MBH-like addition to generate a reactive rearrangement precursor (i.e. **IM2**). It's worth noting that the molecular weight of the cation of **IM4** (435) could be detected by mass spectrometry. Unfortunately, we were unable to further confirm the structure of **IM4** by NMR spectrum even after great efforts.⁵⁰

Using the (*R*)-pathway in Figure 2A as a representative, we next understand the *E*-selectivity of the reaction. Along the (*R*)-pathway, all structures from (*R*)**IM2** to (*R*)**IM5** were optimized with restriction to the conformations with *n*-Pr and oxazoline groups in a trans arrangement, thus giving *E*-**5ac**. To gain insight to the *E*-selectivity, we derived how *Z*-**5ac** can be produced by considering other possible conformations of **IM5**, in addition to the trans (*R*)**IM5** we already considered in Figure 2A. As illustrated in Figure 2C, we were able to locate another *cis* conformation (i.e. (*R*²)**IM5**) of **IM5**, which can lead to *Z*-**5ac** by crossing (*R*²)**TS5**. However, because the two conformations can convert each other easily with a barrier (*R*)**TS6** lower than (*R*)**TS5** and *E*-**5ac** is also lower than *Z*-**5ac**, the formation of *E*-**5ac** is favored in terms of both kinetics and thermodynamics, explaining the exclusive *E*-selectivity of the reaction. It should be noted that all structures prior to **IM5** should also have other conformations, but because the two conformations of **IM5** can convert each other easily, the conformations of these structures prior to **IM5** cannot affect the selectivity of the reaction. Similar discussion can be applied to the (*S*)-pathway (see Fig. 2D), which show that *E*-**5ac** is also both kinetically and thermodynamically favored product. Thus, the reaction exclusively gives *E* product.

After understanding the reaction of *E*-**3c**, we considered the selectivity of the reaction if *Z*-**3c** is used. Figure 2B shows the stage I of *Z*-**3c**. It can be observed that the stage I of *Z*-**3c** merges to that of *E*-**3c** at (*R*)**IM2** and (*S*)**IM2**, respectively. This is understandable, because the MBH-like addition of **Py** converts the sp² hybridized carbon to the sp³ hybridized carbon. Therefore, the configuration of **3c** cannot affect the selectivity of the reaction. To verify the prediction, we used *E*-**3c** and *Z*-**3c** to carry out the reaction, separately (eq 1 and eq 2 in Fig. 3). Indeed, under the standard experimental conditions, no matter which configuration **3c** adopts, the reactions converged to *E*-**5ac** with comparable yields. Expectedly, this should hold true for other substrates in Table 2.

Applications and attempts of [5,5]-rearrangement. To our delight, the method followed by hydrolysis of oxazolines could be used for gram-scale synthesis of α-aryl α,β-unsaturated carboxylic acids **6a** and **6b** with synthetically useful yields (Fig. 4A). The remaining iodide atom allowed for elaborating alkenes with a boryl group (**7**) or vinyl ester moieties (**8a** and **8b**), and incorporating an alkynyl group into phenyl ring (**9a** and **9b**) (Fig. 4B). The product **6** could also be readily converted to intriguing arylcyclopropanes (**10a** and **10b**) and α-aryl-β-amine ester (**11**) via conventional cyclopropanation and Michael addition, respectively. In addition, the reduction of **6b** afforded valuable 2-aryl allylic alcohol **12**. Encouraged by the success of the MBH-type [3,3]-rearrangement, we attempted to examine the possibility of corresponding

[5,5]-rearrangement by employing 1,3-diene-1-oxazoline **3b'** (Fig. 4C). Excitingly, the reaction indeed afforded *para*-C-H functionalized product **13** (31% yield) with *ortho*-functionalized product **5ab'** (36% yield).⁵¹⁻⁵³ Although suffering from a poor selectivity, this preliminary result demonstrated the feasibility of applying the current protocol for developing MBH-type [5,5]-rearrangement reactions.

Discussion

In summary, inspired by the Morita-Baylis-Hillman (MBH) reaction, we have developed the [3,3]-rearrangement of aryl iodanes with α,β -unsaturated oxazolines. The method allows for the mild synthesis of a wide variety of valuable α -aryl α,β -unsaturated oxazolines in a redox-neutral manner. In addition to the excellent chemo- and regioselectivity, the reaction showed a remarkable *E*-selectivity. Experimental and computational mechanistic studies revealed that the transformation involves the assembly of both coupling partners, MBH-like addition triggered [3,3]-rearrangement, and E1cb elimination to give the final products. The formation of *E*-product is both kinetically and thermodynamically favorable. Further exploration of MBH-type rearrangement reactions is currently under way in our laboratory.

Methods

General procedure for [3,3]-rearrangement of aryl iodanes with α,β -unsaturated oxazolines. To a solution of aryl iodane **1** (0.5 mmol) in DCM (5 mL) was added TMSOTf (181 μ L, 1.0 mmol) at -78 °C. After stirring for 15 min, α,β -unsaturated oxazolines **3** (1.0 mmol) was added to the mixture. The mixture was then stirred for another 15 min, and then 4-methylpyridine (93 mg, 1.0 mmol) was added. The reaction mixture was gradually warmed to -10 °C. After stirring for 24 h, the mixture was treated with saturated aqueous NaHCO₃ solution and extracted with DCM. The organic layer was dried over Na₂SO₄ and concentrated. The obtained residue was purified by silica gel column chromatography to afford the title compound **5**. Note that TMSOTf was added at room temperature for the reaction of aryl iodane **1j**.

Data availability

Full experimental details, characterization data, and NMR spectra for all new compounds are available within this paper and its Supplementary Information.

Declarations

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Author Contributions

B. P. conceived and supervised the project. L. Z. and W. B. developed the reaction and performed experiments with W. P., D. L. and L. K. DFT calculations were conducted by Y. L. and Z-X. W. The manuscript was prepared by B. P. and Z-X. W.

Competing interests

The authors declare no competing financial interests.

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Tables

Table 1. Development of the reaction^a

Reaction scheme: $\text{Ar-I} + \text{CH}_2=\text{CH}-\text{C}(=\text{O})-\text{Nu} \xrightarrow[\text{DCM, -78 } ^\circ\text{C, 30 min}]{\text{TMSOTf}} \xrightarrow[\text{t h, -78 to T } ^\circ\text{C}]{\text{base}} \text{Ar}-\text{CH}(\text{Nu})-\text{CH}=\text{CH}-\text{C}(=\text{O})-\text{Nu}$

entry	Nu	base	T, t	yield ^b
1	2a	DABCO	0 °C, 12 h	4a , 0% ^c
2	2b	DABCO	0 °C, 12 h	4b , 0% ^d
3	2c	DABCO	0 °C, 12 h	4c , 0% ^c
4	2d	DABCO	0 °C, 12 h	4d , 0% ^d
5	3a	DABCO	0 °C, 12 h	5aa , 19%
6	3a	DBU	0 °C, 12 h	5aa , 16%
7	3a	<i>i</i> -Pr ₂ EtN	0 °C, 12 h	5aa , 32%
8	3a	pyridine	0 °C, 12 h	5aa , 39%
9	3a	4-methylpyridine	0 °C, 12 h	5aa , 42%
10	3a	4-methylpyridine	-10 °C, 12 h	5aa , 58%
11	3a	4-methylpyridine	-20 °C, 12 h	5aa , 53%
12	3a	4-methylpyridine	-10 °C, 24 h	5aa , 71%
13	3a	4-methylpyridine	-10 °C, 36 h	5aa , 69%

2a

2b

2c

2d

3a

^aReactions were performed on 0.5 mmol scale. α,β -unsaturated carbonyl **2a–2d** (2.0 equiv), **3a** (2.0 equiv), TMSOTf (2.0 equiv) and bases (2.0 equiv) were used. ^bIsolated yield. ^c**2a** and **2c** deteriorated after the reaction. ^d**2b** (83%) and **2d** (47%) were recovered after the reaction.

Table 2. Reaction Scope^a

^aThe reaction was performed on 0.5 mmol scale. (E)- α,β -unsaturated oxazolines **3** (2.0 equiv), TMSOTf (2.0 equiv) and 4-methylpyridine (2.0 equiv) were used.
^bTMSOTf was added at rt.

Figures

Figure 1

Background and initial results. (A) Well-studied iodonio-Claisen rearrangement via a direct "assembly" protocol. (B) Asymmetric [3,3]-rearrangement via an "assembly/deprotonation" sequence (our previous work). (C) Simplified model for the Morita-Baylis-Hillman (MBH) reaction. (D) This design: combination of MBH reaction with iodonio-Claisen rearrangement

Figure 2

DFT computation results. (A) Free energy profiles for the reaction of with E-3c. (B) Stage I of Z-3c. (C) (R)-Pathway to form E-5ac. (D) (S)-Pathway to form E-5ac.

Figure 3

Control experiments

Figure 4

Applications and attempts of [5,5]-rearrangement. A) Gram-scale reactions.(B) Synthetic utility. (1) K₂CO₃, MeI, DMF; then Pd(OAc)₂ (5 mol%)/ligand (7.5 mol%), B₂(Pin)₂, CsOAc, THF. (2) K₂CO₃, MeI, DMF; then Pd(OAc)₂ (5 mol%)/ligand (10 mol%), ethyl acrylate, CsOAc, THF. (3) Pd(PPh₃)₄ (5 mol%), CuI (10 mol%), phenylacetylene, toluene/Et₃N. (4) (CH₃)₃SOI, NaH, DMSO. (5) N,N-dibenzylamine, DBU, THF. (6) K₂CO₃, MeI, DMF; then DIBAL-H, THF. (C) Attempts of MBH-type [5,5]-rearrangement.

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