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Synthesis of seven-membered lactones by regioselective and stereoselective iodolactonization of electron-deficient olefins

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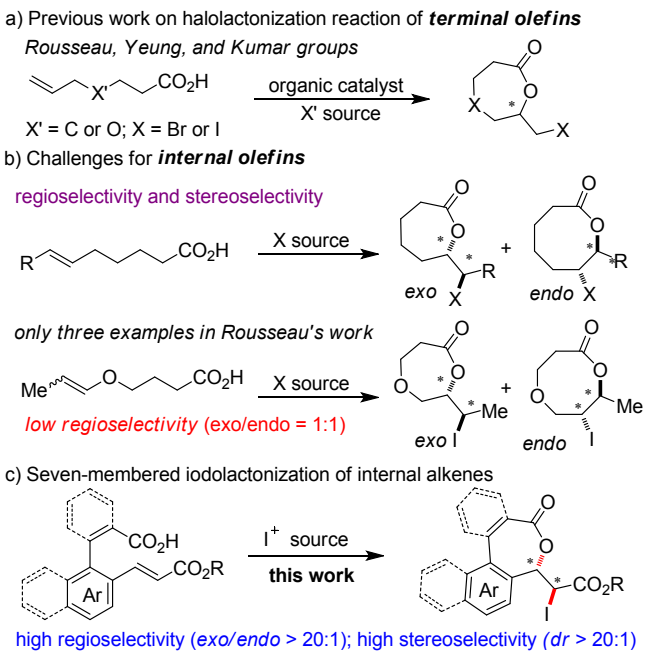
A regio- and stereoselective iodolactonization of internal eletron-deficient olefinic acid has been reported, which provides a straightforward access to a series of multi-functionalized seven-membered lactones containing consecutive two chiral centers. The ester substituents on olefins played key role in achieving high regional selectivity. This result was proved through the experiments and DFT calculation.

Lactones are ubiquitous frameworks in a variety of natural products and drug molecules.[1] Among them, seven-membered lactone has a special medium-ring structure and exhibits numerous biological activities such as antitumor activity, tyrosine kinase inhibitor and cytotoxic activity.[2] In the light of this fact, there is a fundamental need for the development of efficient methods to construct seven-membered lactone motif. Traditional method for the synthesis of seven-member lactone via hydration reaction,[3] Tishchenko reaction[4] and oxidative lactonization of diols[5] has been well-developed. High-dilution and slow addition techniques are usually employed to avoid intermolecular side reactions. However, various condensation reagents and metal compounds are essential for high efficiency. Moreover, most of these approaches are limited to symmetrical substrates to avoid the chemical selectivity, which lack of diversity in product structure. Recently, Shi *et al.* reported a novel method for the preparation of seven-membered lactones from benzoic acids and benzyl thioethers via rhodium-catalyzed double C-H activation, which allows to access to a series of seven-membered lactones with different functional groups.[6] Unfortunately, harsh reaction conditions, expensive rhodium catalyst and silver oxidant are required for high efficiency. Thus, highly efficient and economical method to prepare seven-membered lactones is in high demand.



Scheme 1 Approaches to access seven-membered lactones.

Halolactonization of olefin represents an important class of reactions for the construction of lactones with halogen functional group.[7] Although great achievements have been made on the synthesis of small halolactones, i.e. five-[8] and six-membered[9] lactones, few methods have been developed for the synthesis of seven-membered lactone.[10] Early in 1995, Rousseau *et al.* disclosed a pioneering work on the synthesis of seven-membered lactone, in which oxygen-containing unsaturated acids were utilized as substrates (**Scheme 1a**).[10a] In 2012, Yeung group reported a general and efficient organicsulfur-catalyzed halolactonization reaction to prepare the seven-membered lactones from long-chain olefinic acids (**Scheme 1a**).[10e] Then, Kumar et al. developed an organoselenium and DMAP co-catalyzed synthesis of seven-

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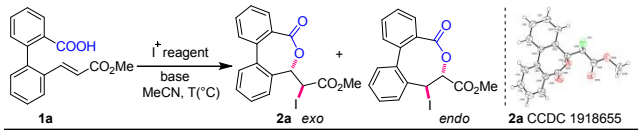
membered lactones from unactivated alkenes.[10g] Despite these advances, these reactions are limited to the terminal and electron-rich olefins. Moreover, these methods are not suitable for the synthesis of complex seven-membered lactones with consecutive two chiral carbon centers. Only three substrates have been reported in Rousseau's work, but poor regioselectivity were obtained (*exo*:*endo* = 1:1), giving a mixture of seven-membered and eight-membered products (**Scheme 1b**).[10a] Thus, developing novel methods for the synthesis of complex seven-membered lactones from internal alkenes via halolactonization reaction is urgent but challenging (**Scheme 1b**). We envision that the incorporation of electron-withdrawing group to olefin may promote the regioselectivity of the halolactonization reaction due to the different electron density of the double bond. Herein, we present a general and efficient protocol for the construction of seven-membered lactones with two chiral carbon centers from ester-substituted internal olefins via regioselective and stereoselective iodolactonization reaction (**Scheme 1c**).

Table 1 Optimization of the reaction conditions[a]



Entry	Base	I+ reagent	T/°C	Yield of 2a	*dr* of 2a	*exo*/*endo*
1	K_2CO_3	I_2	100	40%	1.3:1	20:1
2	Cs_2CO_3	I_2	100	57%	1.7:1	> 20:1
3	Li_2CO_3	I_2	100	65%	2:1	> 20:1
4	$KHCO_3$	I_2	100	13%	3:1	13:1
5	$KHSO_4$	I_2	100	51%	4:1	17:1
6	K_2HPO_4	I_2	100	56%	2:1	18:1
7	KOH	I_2	100	42%	1:1	> 20:1
8	NaO^{t}Bu	I_2	100	58%	4:1	19:1
9	none	I_2	100	11%	1:1	6:1
10	NaO^{t}Bu	I_2	80	63%	10:1	13:1
11	NaO^{t}Bu	I_2	60	65%	15:1	14:1
12	NaO^{t}Bu	I_2	rt	70%	18:1	14:1
13[b]	NaO^{t}Bu	NIS	rt	90%	> 20:1	> 20:1
14[c]	NaO^{t}Bu	NIS	rt	88%	> 20:1	> 20:1
15	$KHCO_3$	NIS	rt	76%	> 20:1	> 20:1
16[d]	NaO^{t}Bu	NIS	rt	81%	> 20:1	> 20:1
17	NaO^{t}Bu	---	rt	0%	---	---

[a]Reaction conditions: **1a** (0.1 mmol), base (1.0 eq.) iodine reagent (3.0 eq.), in 0.5 mL of MeCN at room temperature under air, 12 h. Yield, dr and exo/endo were determined by ^{1}H NMR analysis. [b]Isolated yield. [c]In Ar condition. [d]1.5 eq. of NIS. Dr = diastereoselectivity.

Initially, we selected (E)-2'-(3-methoxy-3-oxoprop-1-en-1-yl)-[1,1'-biphenyl]-2-carboxylic acid **1a** as the model substrate as the seven-membered lactone product belongs to an important motif in natural products and bioactive molecules.[2] When the substrate **1a** was treated with 3 equiv of I_2 and 1 equiv of K_2CO_3 at 100°C under air condition in MeCN for 12 h, the desired seven-membered lactone **2a** via exo-cyclization reaction was obtained in 40% yield with high regioselectivity (*exo*/*endo* = 20:1) and low stereoselectivity (*dr* = 1.3:1) (Table 1, entry 1). The structure of **2a** was determined by single-crystal X-ray diffraction.[11] Based on this encouraging finding, a series of bases were screened (entries 2-8). Although most of bases had a promoting effect on the reaction, NaO^{t}Bu showed the highest activity, giving the product **2a** in 58% yield and an improved stereoselectivity (*dr* = 4:1) (entry 8). To further enhance the stereoselectivity, we next investigated the reaction temperature (entries 10-12). When the reaction was conducted at room temperature, the diastereoselectivity of reaction could be raised up to 18:1. However, the yield of seven-membered lactone **2a** was moderate. Finally, when *N*-Iodosuccinimide (NIS) was used as iodinating reagent instead of I_2, the yield of **2a** could be imporved to 90% with high stereoselectivity (*dr* > 20:1) and regioselectivity (*exo/endo* > 20:1) (entry 13). The iodolactonization reaction could proceed smoothly under argon atmosphere (entry 14). Weak base such as $KHCO_3$ could promote the reaction, giving a low yield (entry 15). The reaction afforded a low yield with 1.5 eq. of NIS and no product was observed in the absence of NIS (entries 16-17).

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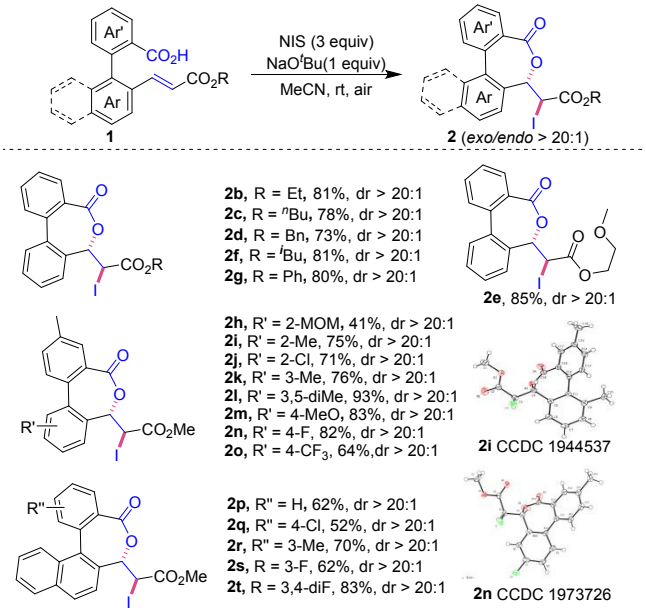
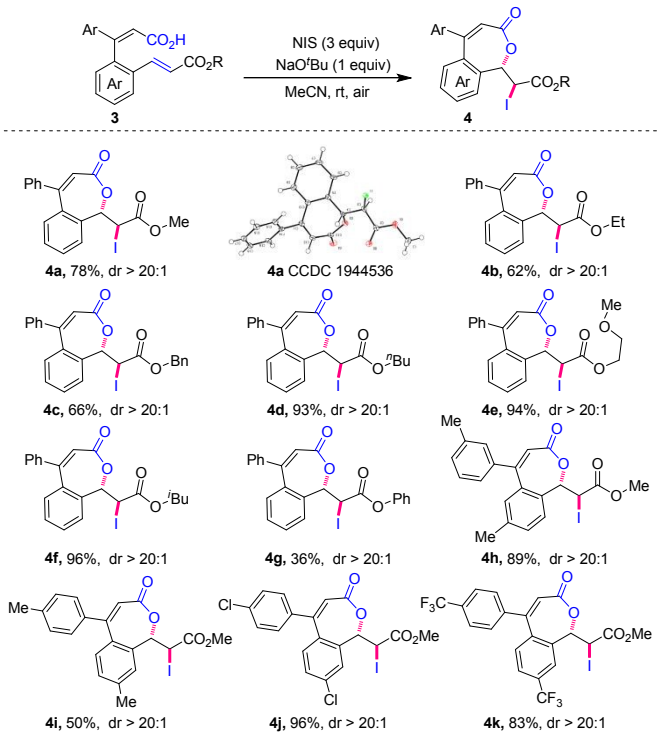


Scheme 2 Synthesis of dibenzooxepinones. **1** (0.15 mmol), NaO^{t}Bu (0.15 mmol), NIS (0.45 mmol), in 0.5 mL of MeCN at room temperature under air, 12 h, isolated yield.

With the optimal conditions in hand, we next investigated the generality of this protocol for the synthesis of dibenzooxepinones and a range of multi-functionalized and iododibenzooxepinones were synthesized with high regioselectivity (*exo/endo* > 20:1) and stereoselectivity (*dr* > 20:1) for the first time (**Scheme 2**). Olefins with various ester groups such as, alkyl ester (**2b-f**) and aryl ester (**2g**) could give the desired products in high yields (73-81%). Notably, ether group is compatible in the reaction and gave the desired product **2e** in high yield. Substrates with electron-donating and electron-withdrawing group on the biaryl motif could proceed smoothly, generating the corresponding dibenzooxepinone

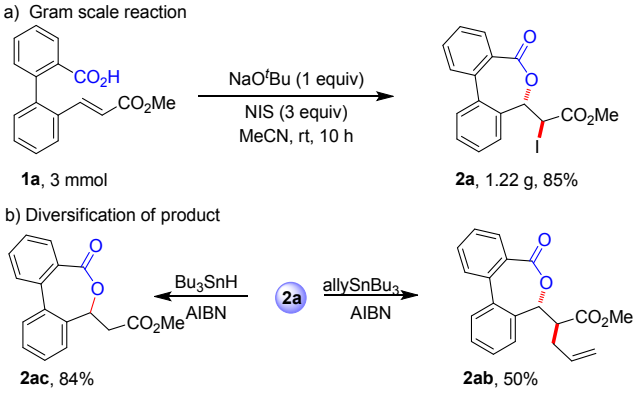
products in moderate to excellent yields (**2h**-**2o**, 41-93%). The substituents at ortho, meta, and para-position of the bottom phenyl ring were all tolerated, even the ortho MOM-substituted substrate **2h** afforded the desired product in an acceptable yield. Moreover, substrates with naphthyl group were also suitable the reaction, providing the desired products in moderate to good yields (**2p**-**2t**). The structures of **2e, 2i, 2n** and **2o** were characterized by X-ray crystallographic analyses.[11] This protocol provides a powerful tool for the synthesis multi-substituent benzooxepinones.



Scheme 3 Synthesis of α, β-unsaturated seven-membered lactones. Reaction conditions: **3** (0.15 mmol), NIS (0.45 mmol), NaO^{t}Bu (0.15 mmol) in 0.5 mL of MeCN at room temperature under air, 12 h, isolated yields.

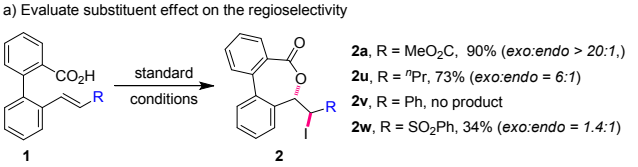
Next, this protocol was applied to synthesis of α, β-unsaturated seven-membered lactones from dienes via iodolactonization reaction with high regioselectivity and stereoselectivity (**Scheme 3**). The diene substrates with different ester groups proceeded smoothly and generated the desired α, β-unsaturated seven-membered iodolactones (**4a**-**4g**) in moderate to excellent yields (36-96%). The structure of **4a** was determined by single-crystal X-ray diffraction.[11] Among them, the reactivity of substrates with alkyl ester (**4a**-**4f**) is higher than that with aryl ester (**4g**), probably due to weaken electron-withdrawing effect of aryl ester group. The unsaturated dienes with different substituents on aromatic ring, such as Me (**4h**, **4i**), Cl (**4j**) and CF_3 (**4k**) were efficiently converted into α, β-unsaturated products in moderate to excellent yields (*dr* > 20:1).

To prove the applicability of this protocol, the substrate **1a** was performed on a gram scale reaction, affording the seven-membered lactone product **2a** in 85% yield (1.22 g) (**Scheme 4a**). Furthermore, the iodolactone product **2a** could be further converted into other seven-membered lactone derivatives through deiodination reaction and allylation reaction (**Scheme 4b**). Notably, the allylation reaction of **2a** via radical process had high stereoselectivity, giving the allylation product **2ab** with configuration retention, which may provide a significant method for the synthesis of optically pure seven-membered lactones.



Scheme 4 Synthetic application

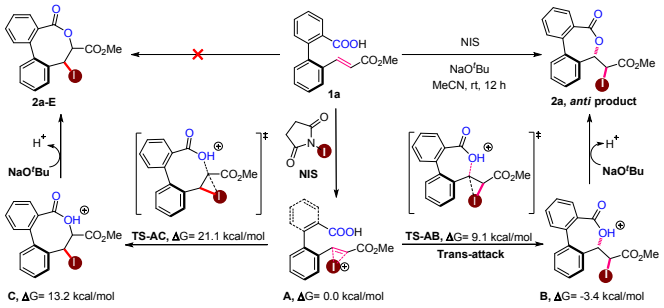
To evaluate the substituent effect of olefin on the regioselectivity of iodolactonization reaction, olefins with different functional groups, such as alkyl and aryl substituent were subjected to the standard reaction conditions (**Scheme 5a**). As expected, the alkyl-substituted substrate **1u** gave a low yield (73%) and regioselectivity (*exo*/*endo* = 6:1), while the aryl-substituted olefin **1v** could not generate the seven-membered iodolactone product. Although substrate with sulfonyl substituent **1w** could react under reaction conditions, it gave a low yield and regioselectivity. These experimental results proved that the ester group played a significant role in controlling the regioselectivity of iodolactonization reaction.



Scheme 5 Mechanistic studies.

Aiming to further elucidate the reaction mechanism, density functional theory (DFT) calculations (for computational details see Supporting information) were carried out by taking **1a** as representative substrate **(Scheme S1)**. The reaction is initiated by the electrophilic addition of NIS to the carbon-carbon double bond of **1a**, leading to the formation of C-C-I three-membered ring intermediate **A**. After the formation of **A**, it could transfer by intramolecular carboxylation and deprotonation. However, the deprotonation leads to the formation of stable lactone intermediate, which inhibit the intramolecular carboxylation (see SI for details). On the other hand, the reaction takes place through carboxylation following by deprotonation is accessible. The carboxylate could achieve

by attacking the C-C-I moiety through both α-C and β-C. Attributing to the iodolactonization of the C=C double bond, the NPA charge of α-C changes from -0.169 to 0.055, while that of β-C becomes more negative (see Figure S1). As a result, the carboxylate of intermediate **A** prefers to take place on the α-C rather than the β-C. This can be proved by the free energy barriers of these two processes. As shown in **Scheme S1**, the free energy barrier of the former (**TS-$_{AB}$**) is 12.0 kcal/mol lower than that of the latter (**TS-$_{AC}$**). The attacking of α-C leads to the formation of seven-membered ring intermediate **B**, which is exothermic by 3.4 kcal/mol. On the other hand, the attacking of β-C produces eight-membered ring intermediate **C**, which is endothermic by 13.2 kcal/mol. It is obvious that the former is favourable thermodynamically as well. The intermediate **B** will be deprotonated with the formation of final iodolactonization product **2a**. It is in good accordance with the experimental observed seven-membered lactones products.



Scheme 6 Mechanism diagram.

In summary, we have disclosed a highly regioselective and stereoselective iodolactonization reaction of electron-deficient olefins via an electronic addition process, which rapidly constructs divers seven-membered lactones with consecutive two chiral carbon centers. By installing an ester group, we changed the electronic density of double bond, and thus controlled the regioselectivity of electronic addition step, which was proved by experimental results and DFT calculation. This methodology may serve as a powerful tool for the synthesis of natural products and potentially active drug molecules containing seven-membered lactone motif. Moreover, the methodology may provide a general introduction for regioselective and stereoselective construction of medium and large sized lactones.

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Conflicts of interest

There are no conflicts to declare.

Notes and references

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11 For crystallographic data: **2a** (CCDC 1918655), **2e** (CCDC 1944538), **2o** (CCDC 1973725), **2i** (CCDC 1944537), **2n** (1974644) and **4a** (CCDC 1944536) (CIF).

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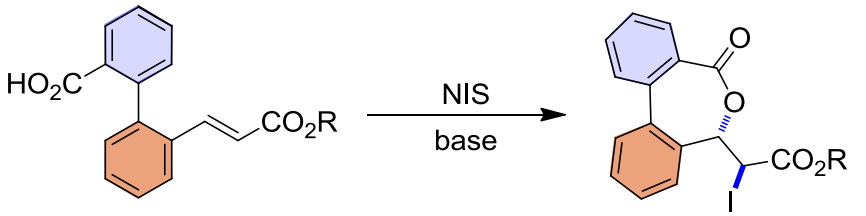

regioselectivity > 20:1; diastereoselectivity > 20:1; up to 29 examples