

Remarkable rate acceleration of intramolecular Diels–Alder reaction in ionic liquids†

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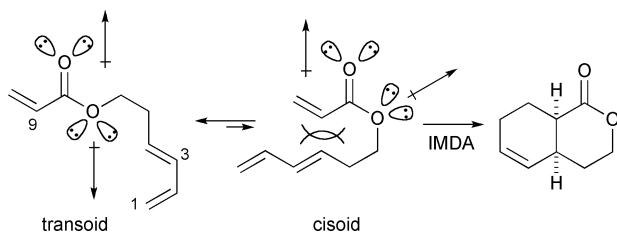
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The intramolecular Diels–Alder reaction of an ester-tethered 1,3,9-decatriene system was significantly accelerated in ionic liquids such as [emim]BF₄, [bmim]BF₄ and [bdmim]BF₄. Under the present conditions, the IMDA reaction proceeded smoothly without the use of Lewis acid catalysts to give *cis*-fused bicyclic lactones in good yield with high diastereoselectivity.

The intramolecular Diels–Alder (IMDA) reaction is one of the most powerful strategies for the stereoselective construction of highly functionalized polycyclic systems.¹ In the IMDA reactions, the reactivity of triene substrates and the stereochemical outcome are highly dependent upon the structure of the tether moiety between the diene and dienophile parts. For example, although the IMDA reaction of an ester-tethered 1,3,9-decatriene system requires a particularly high reaction temperature and long reaction time to obtain the desired cycloadduct in a reasonable yield,² a *cis*-fused oxabicyclo[4.4.0]decenone framework can be constructed with excellent diastereoselectivity due to the stereoelectronic effect of ester functionality in the transition state (Scheme 1).³ It is known that the IMDA reactivity of triene substrates tethered by ester functionality is considerably lower than those of amide- and ketone-tethered trienes.⁴ The low reactivity of ester-tethered trienes is attributed to the conformational behavior of the ester functionality. That is, a repulsive dipole interaction between the two oxygen atoms in the ester functionality and the steric repulsion between the two alkyl substituents existing in the carboxylic acid part and in the alcohol part make the *transoid* form preferable relative to the *cisoid* form of triene substrates.^{5,6}



Scheme 1

For the intramolecular cycloaddition of ester-tethered substrates under mild conditions, we have already succeeded in

developing several aluminium binuclear complexes as powerful and effective Lewis acid catalysts.^{7,8} We also reported that, in a mixed solvent of H₂O and propan-2-ol as a green and polar reaction media, the IMDA reaction of an ester-tethered 1,3,9-decatriene system was nicely catalyzed by a water-compatible Lewis acid such as In(OTf)₃.⁹ Although these studies realized the intramolecular cycloaddition chemistry of ester-tethered substrates under mild conditions, the use of Lewis acidic metal complexes is essential for a smooth reaction. To avoid the use of metal complexes, we were interested in the IMDA reaction in room temperature ionic liquids (RTILs). That is, the polarity of ILs (exemplified by dipolarity/polarizability index π^*) should cause the relaxation of the repulsive dipole interaction between two oxygen atoms in the ester functionality. Furthermore, the high microscopic viscosity of ILs is also an important factor for the conformation of the substrate leading the diene and dienophile parts closer to the transition state geometry.¹⁰ In addition, despite the several favorable properties of ILs as green reaction media, *e.g.* high thermal stability, negligible vapor pressure, and recyclability¹¹, their applications to intramolecular reactions are limited.^{10,12} In intramolecular reactions in ILs, poor solubility of relatively nonpolar organic substrates, slow rate of diffusion and rate acceleration of the *intermolecular* reaction would result in competitive intermolecular reactions as a serious problem compared to reactions in organic solvent.¹³ However, since the macroscopic viscosity of ILs is rapidly reduced by rising temperature, intramolecular cycloadditions by thermal reaction could be a promising approach. Herein, we disclose a significant rate acceleration in the IMDA reaction of ester-tethered triene substrates in ILs. This study clearly demonstrates that the IMDA reaction of the less reactive ester-tethered triene proceeds under mild conditions without the use of any Lewis acidic metal complexes to give *cis*-fused bicyclic lactones in good yield with excellent diastereoselectivity.

To find suitable ILs for the IMDA reaction of ester-tethered 1,3,9-trienes, we examined the reaction of the model substrate **1a** in various imidazolium-based ILs. The results are summarized in Table 1. On heating **1a** at 80 °C for 21 h in 1-ethyl-3-methylimidazolium tetrafluoroborate ([emim]BF₄), the desired cycloadduct **2a** was obtained in 49% yield accompanied by the formation of the intermolecular cycloadduct **3a** in 16% yield (entry 1). To avoid the dimerization of **1a**, dilution was found to be effective. Thus, when the reaction was conducted at 0.07 M of **1a** in [emim]BF₄ under similar conditions, cycloadduct **2a** was obtained in 78% yield along with a trace amount of **3a** (entry 2). Increasing the reaction temperature to 100 °C, the reaction was completed within only 6 h to give **2a** as a sole diastereomer in 80% yield (entry 3). Under similar conditions, the reactions in

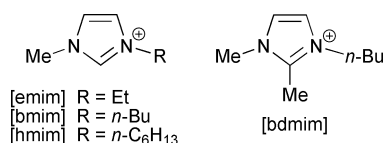
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Table 1 Optimization of conditions for IMDA reaction of **1a**

Entry	IL (conc. of 1a , M)	Temp./°C	Time/h	Yield ^a (%)	
				2a	3a
1	[emim]BF ₄ (0.17)	80	21	49	16
2	[emim]BF ₄ (0.07)	80	21	78	trace
3	[emim]BF ₄ (0.07)	100	6	80	trace
4	[bmim]BF ₄ (0.07)	100	6	78	trace
5	[bdmim]BF ₄ (0.07)	100	6	74	trace
6	[hmim]BF ₄ (0.07)	100	6	62	trace
7	[emim]OTf (0.07)	80	21	complex	complex
8	[emim]NTf ₂ (0.17)	80	21	complex	complex
9	CH ₃ CN (0.07)	80	21	25	0
10 ^b	chlorobenzene	132	47	70 ^c	—

^a Isolated yield. ^b Reference **2c**. ^c *Endo/exo* = 12:1.



[bmim]BF₄ or in [bdmim]BF₄ gave cycloadduct **2a** in good yield (entries 4; 78% yield, entry 5; 74% yield). Recently, Chiappe and Welton have pointed out that the hydrogen bonding between dienophiles and imidazolium-based ILs, which have an acidic proton at the imidazolium C-2 position, plays a crucial role in the rate acceleration of the *intermolecular* DA reaction of acrolein with cyclopentadiene. However, such a rate acceleration was not observed in the case of methyl acrylate.¹⁴ Likewise, in the IMDA reaction of dienyl acrylate, a notable rate difference between the reaction of **1a** in [bmim]BF₄ and that in [bdmim]BF₄, which has a methyl group at the C-2 position in place of an acidic proton at this position in imidazolium cation, was not observed (entries 4, 5).

Table 2 IMDA reaction of ester-tethered triene **1**

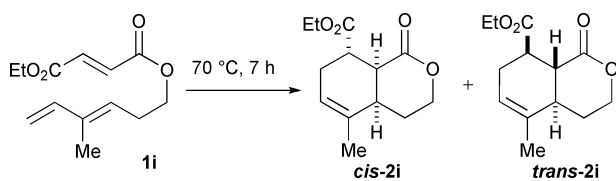
Entry	1	R ¹	R ²	R ³	R ⁴	Temp./°C	Time/h	Yield ^a (%)	Dr ^b
1	1b	H	CH ₂ CH ₂ Ph	H	H	100	5	81	single
2	1c	H	Ph	H	H	100	6	73	single
3	1d	H	4-BrC ₆ H ₄	H	H	100	6	72	single
4	1e	H	4-(CO ₂ Me)C ₆ H ₄	H	H	100	7	83	single
5	1f	H	H	Me	H	100	5	83	single
6	1g	H	H	H	<i>n</i> -Pr	120	24	48	single
7	1h	CO ₂ Et	H	H	H	70	7	86	6.0 : 1 ^c
8	1i	CO ₂ Et	H	Me	H	80	5	84	3.6 : 1 ^c
9	1j	CO ₂ <i>t</i> -Bu	H	H	H	80	8	70	7.6 : 1 ^c

^a Isolated yield. ^b Based on ¹H NMR of a crude mixture. ^c *Cis/trans* ratio.

On the other hand, the use of more lipophilic [hmim]BF₄ brought about a relatively slow reaction to give **2a** in 62% yield after the reaction at 100 °C for 6 h (entry 6). We also found that the counter anion of ILs is one of the important factors for the success of this IMDA reaction. That is, the reactions in ILs, having a nucleophilic counter anion such as triflate or bis-triflic imidate, provided a complex mixture (entries 7, 8). As shown in entry 10, it was reported that the IMDA reaction of **1a** in chlorobenzene required both a higher reaction temperature and prolonged reaction time (at 132 °C for 47 h) to obtain **2a** in a reasonable yield.^{2d} In addition, the reaction in acetonitrile, which was used as an aprotic polar organic solvent, gave poor conversion of **1a** (entry 9). These findings clearly demonstrate that the use of imidazolium-based ILs such as [emim]BF₄, [bmim]BF₄, or [bdmim]BF₄ results in a notable rate acceleration in the IMDA reaction of ester-tethered 1,3,9-triene substrates.

Next, we examined the IMDA reaction of various ester-tethered 1,3,9-trienes in [emim]BF₄. The results are summarized in Table 2. The reaction of several 6-substituted trienes **1b–1e** in [emim]BF₄ smoothly proceeded at 100 °C within a short reaction time to give the corresponding *cis*-fused bicyclic lactones **2b–2e** in excellent yield with perfect diastereoselectivity (entries 1–4). This finding strongly supported that the IMDA reaction of ester-tethered 1,3,9-decatrienes in [emim]BF₄ proceeds *via* an *endo*-boat transition state.³ Likewise, the reaction of 3-methyl triene **1f** gave the DA adduct **2f** in 83% yield as a sole diastereomer (entry 5). Although 1-propyl derivative **1g** was a less reactive substrate, the DA adduct **2g** was obtained in a moderate yield by the reaction at 120 °C for 24 h (entry 6). A significant rate acceleration in [emim]BF₄ was also observed in the reaction of substrates equipped with fumarate structure as the dienophile part. For example, the IMDA reaction of ethyl hexadienyl fumarate **1h** was completed at 70 °C for 7 h to give the DA adduct **2h** in 86% yield as a mixture of two diastereomers in a ratio of 6.0:1 (entry 7). The reactions of **1i** and **1j** at 80 °C resulted in the clean formation of **2i** and **2j** with moderate diastereoselectivity, respectively (entries 8, 9).

To reveal the synthetic advantages of the present conditions, we carried out the IMDA reaction of fumarate **1i** in several reaction media (Scheme 2). In toluene, the heating of **1i** at 70 °C for 7 h



in [emim]BF ₄	84% (<i>cis/trans</i> = 3.6 : 1)
in toluene	14% (<i>cis/trans</i> = 4.6 : 1)
on H ₂ O	43% (<i>cis/trans</i> = 4.1 : 1)

Scheme 2

resulted in poor conversion of **1i** and the desired cycloadduct **2i** was obtained in only 14% yield.¹⁵ Under similar conditions, the reaction of **1i** in water gave **2i** in a moderate yield with a competitive intermolecular DA reaction due to the low solubility of **1i** in pure water.¹⁶

Regarding the present rate acceleration of the IMDA reaction of ester-tethered 1,3,9-decatrienes, we propose that the solvent effects by imidazolium-based ILs attributed to both the conformational behavior of ester functionality and the kinetic acceleration in the C–C bond forming process. In the *intermolecular* DA reaction of methyl acrylate with cyclopentadiene, rate constant *k* is proportional to solvent parameters such as dipolarity/polarizability π^* and hydrogen bond donor acidity α .¹⁷ Likewise, these solvent effects possibly influence the rate of the IMDA reaction of diene acrylates. However, since *k* of *intermolecular* DA reaction in [bmim]BF₄ is only two fold larger than that in acetonitrile¹⁴, the observed rate acceleration in the IMDA reaction is not considered just a simple kinetic acceleration in the C–C bond forming step by ILs. For the rational explanation for the significant acceleration in the present IMDA reaction, we propose some alternative factors such as the conformational control of ester functionality by ILs. That is, since the π^* values of ILs are notably higher than those of organic solvents such as acetonitrile and toluene, the repulsive dipole interaction between the two oxygen atoms in ester functionality should relax to form the *cisoid* form. In addition, the microviscosity of ILs should control the conformation of the ester and diene parts to stabilize the transition state.¹⁰

In summary, we found that the IMDA reaction of ester tethered 1,3,9-decatrienes can be significantly accelerated in imidazolium-based ILs such as [emim]BF₄, [bmim]BF₄ and [bdmim]BF₄. It is well known that the IMDA reaction of ester tethered substrates in several organic solvents requires both a high reaction temperature and a long reaction time to obtain the cycloadducts in a reasonable yield. The present reaction in ILs realized the highly diastereoselective construction of a *cis*-fused bicyclic lactone structure under mild conditions. In addition, since the reaction in ILs did not require the use of any Lewis acidic metal complexes and the ILs used can be recycled after the removal of volatile residue simply under reduced pressure, the present conditions are greener than the previous conditions reported by our research group.

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