

# Effect of Counterion Structure on Rates and Diastereoselectivities in $\alpha,\beta$ -Unsaturated Iminium-Ion Diels–Alder Reactions

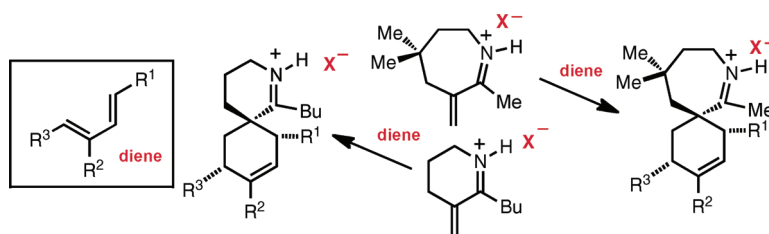
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## ABSTRACT



The use of cyclic  $\alpha,\beta$ -unsaturated iminium-ion dienophiles is documented in two highly diastereoselective Diels–Alder (DA) reactions. The dienophilic counterion was found to have a significant effect on reactivity.

Iminium-ion LUMO-lowering activation<sup>1</sup> has been extensively studied in the context of Diels–Alder (DA) reactions and related organocatalyzed transformations.<sup>2</sup> In some cases, the nature of the achiral counterion has been demonstrated to have an important effect on the selectivity of a given reaction, although its effect on reactivity has not been explicitly studied.<sup>3</sup>

The purpose of this communication is to document the counterion-dependent rate acceleration of endoselective iminium ion DA reactions *vide supra*.

As illustrated in Figure 1, spiroimine-containing alkaloids such as **1** and **2** each contain the prominent DA retron of interest (blue, dienophile; red, diene).

(1) For seminal publications, see: (a) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243–4244. (b) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 2458–2460.

(2) For selected reviews, see: (a) Erkkilä, A.; Majander, I.; Pihka, P. M. *Chem. Rev.* **2007**, *107*, 5416–5470. (b) MacMillan, D. W. C.; Lelais, G. In *New Frontiers in Asymmetric Catalysis*; Mikami, K., Lautens, M., Eds.; John Wiley & Sons: Hoboken, NJ, 2007. (c) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570–1581. (d) Lelais, G.; MacMillan, D. W. C. *Aldrichimica Acta* **2006**, *39*, 79–87. (e) MacMillan, D. W. C. *Nature* **2008**, *455*, 304–308.

(3) Ogilvie has observed an effect of counterion on yields. For additional information, see: (a) Lemay, M.; Ogilvie, W. W. *Org. Lett.* **2005**, *7*, 4141–4144. (b) Lemay, M.; Ogilvie, W. W. *J. Org. Chem.* **2006**, *71*, 4663–4666. (c) Lakhdar, S.; Mayr, H. *Chem. Commun.* **2011**, *47*, 1866–1868.

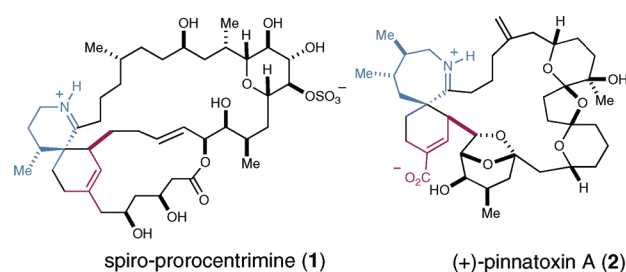


Figure 1. Examples of spiro-imine containing natural products.

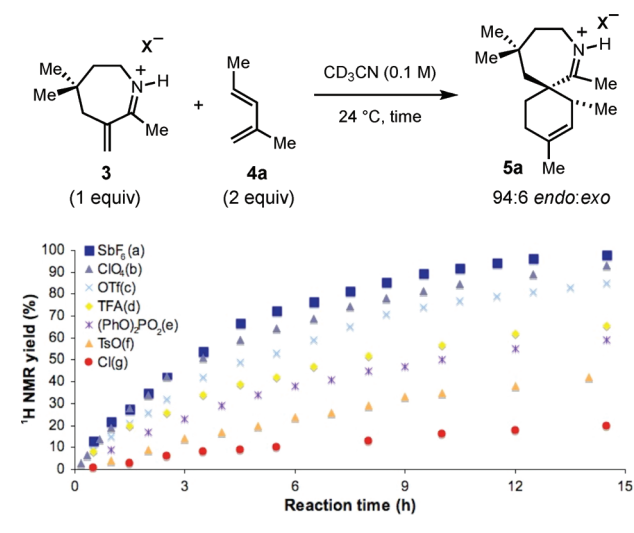
These marine natural products have attracted attention as a consequence of their architecture and biological properties.<sup>4</sup> These structures contain congested [6,6]- or [7,6]-aza-spirocycles. As none of the published approaches to these illustrated structures has employed an

(4) (a) Lu, C.-K.; Lee, G.-H.; Huang, R.; Chou, H.-N. *Tetrahedron Lett.* **2001**, *42*, 1713–1716. (b) Stewart, M.; Blunt, J. W.; Munro, M. H. G.; Robinson, W. T.; Hannah, D. J. *Tetrahedron Lett.* **1997**, 384889–4890. (c) Uemura, D.; Chou, T.; Haino, T.; Nagatsu, A.; Fukuzawa, S.; Zheng, S.; Chen, H. *J. Am. Chem. Soc.* **1995**, *117*, 1155–1156. (d) Hu, T.; Burton, I. W.; Cembella, A. D.; Curtis, J. M.; Quilliam, M. A.; Walter, J. A.; Wright, J. L. C. *Nat. Prod.* **2001**, *64*, 308–312. (e) Guéret, S. M.; Brimble, M. A. *Nat. Prod. Rep.* **2010**, *27*, 1350–1366.

iminium ion retron,<sup>5</sup> we have focused our attention on the development of these DA variants.

The proposed approach to a generic [7,6]-aza-spiro-cycle involves the cycloaddition between iminium-ion **3** and diene **4a** (Scheme 1). This initial study involved achiral dienophiles so that endo/exo diastereoselection might be readily monitored without the intervention of additional diastereomers. Previous literature examples have revealed a significant range of endo/exo stereo-selectivities for these reactions.<sup>6–8</sup>

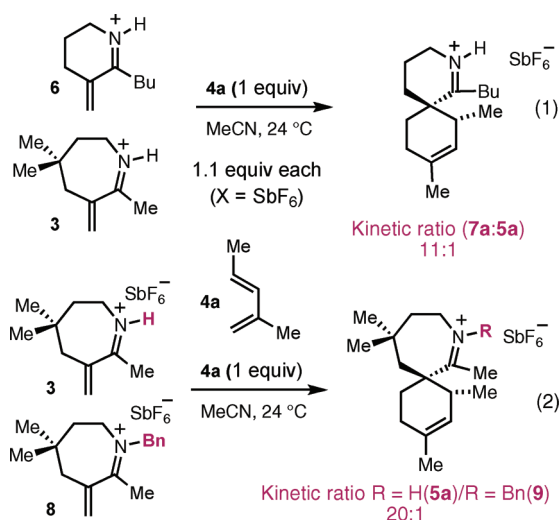
**Scheme 1.** Counterion-Dependent DA Rate Acceleration



**Counterion Effects.** The results of the reaction of **3**<sup>i,9</sup> ( $X = \text{OTf}$ ) with diene **4a** are summarized in Scheme 1. When it was found that this lead reaction required four days to reach completion at rt, the subsequent counterion study was undertaken. With the  $\text{SbF}_6^-$  and  $\text{ClO}_4^-$  counterions, the reaction is complete in 15 and 17 h respectively.<sup>10</sup> Consistently good endo diastereoselection (> 90:10) was observed for all cases. Polar solvents failed to reveal any dramatic effects as similar rates and diastereoselectivities

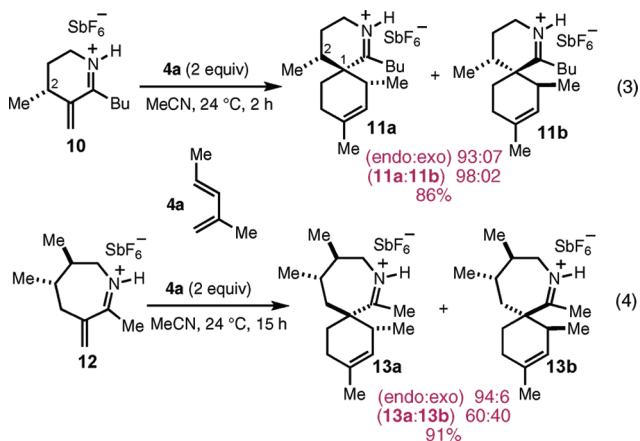
were observed in MeCN, MeOH, and *i*-PrOH. The use of chlorinated solvents ( $\text{CH}_2\text{Cl}_2$ ,  $\text{CHCl}_3$ ) led to diene polymerization while dienophile insolubility was noted in other instances (PhH and PhMe).

We then submitted other dienes (**4b–d**) to the DA reaction with dienophile **3** and its six-membered counterpart **6**. We were pleased to observe good diastereoselectivities and yields in all cases (Table 1). We also found that the six-membered iminium-ion **6** was qualitatively more reactive. In some cases, a decrease in temperature was shown to be beneficial to reaction selectivity with **6** (entry 6). The greater reactivity of the six-membered dienophile **6** compared to its seven-membered counterpart **3** is highlighted in the illustrated competition experiment (eq 1).



We have also evaluated the impact of the dienophilic nitrogen substituent on reaction rate in a related competition experiment where an *N*-benzyl was employed as a proton surrogate (eq 2). Dienophile **3** ( $X = \text{SbF}_6^-$ ) proved to react 20–times faster than its *N*-benzylated counterpart **8** ( $X = \text{SbF}_6^-$ ) in the cycloaddition reaction with diene **4a**.

From this data set, it is believed that the benzylic C–H bonds stabilize, rather than destabilize, iminium-ion **8**, possibly through hyperconjugation. This reactivity trend was not anticipated. This observation negates our initial premise that the relative electronegativities of the N-substituents (H vs C) would influence electrophilic reactivity.



(5) (a) Stivala, C. E.; Zakarian, A. *J. Am. Chem. Soc.* **2008**, *130*, 3774–3776. (b) Nakamura, S.; Kikuchi, F.; Hashimoto, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 7091–7094. (c) McCauley, J. A.; Nagasawa, K.; Lander, P. A.; Mischke, S. G.; Semones, M. A.; Kishi, Y. *J. Am. Chem. Soc.* **1998**, *120*, 7647–7648. (d) Sakamoto, S.; Sakazaki, H.; Hagiwara, K.; Kamada, K.; Ishii, K.; Noda, T.; Inoue, M.; Hirama, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 6505–6510. (e) Beaumont, S.; Ilardi, E. A.; Tappin, N. D. C.; Zakarian, A. *Eur. J. Org. Chem.* **2010**, 5743–5765.

(6) For a recent review, see: Merino, P.; Marqués-López, E.; Tejero, T.; Herrera, R. P. *Synthesis* **2010**, 1–26.

(7) Johannes, J. W.; Wenglowsky, S.; Kishi, Y. *Org. Lett.* **2005**, *7*, 3997–4000.

(8) For other iminium-ion dienophiles in Diels–Alder reactions, see: (a) Kim, J.; Thomson, R. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 3104–3106. (b) Zou, Y.; Che, Q.; Snider, B. B. *Org. Lett.* **2006**, *8*, 5605–5608. (c) O'Connor, P. D.; Körber, K.; Brimble, M. A. *Synlett* **2008**, 1036–1038. (d) Boeckman, R. K., Jr.; Miller, Y.; Ryder, T. R. *Org. Lett.* **2010**, *12*, 4524–4527.

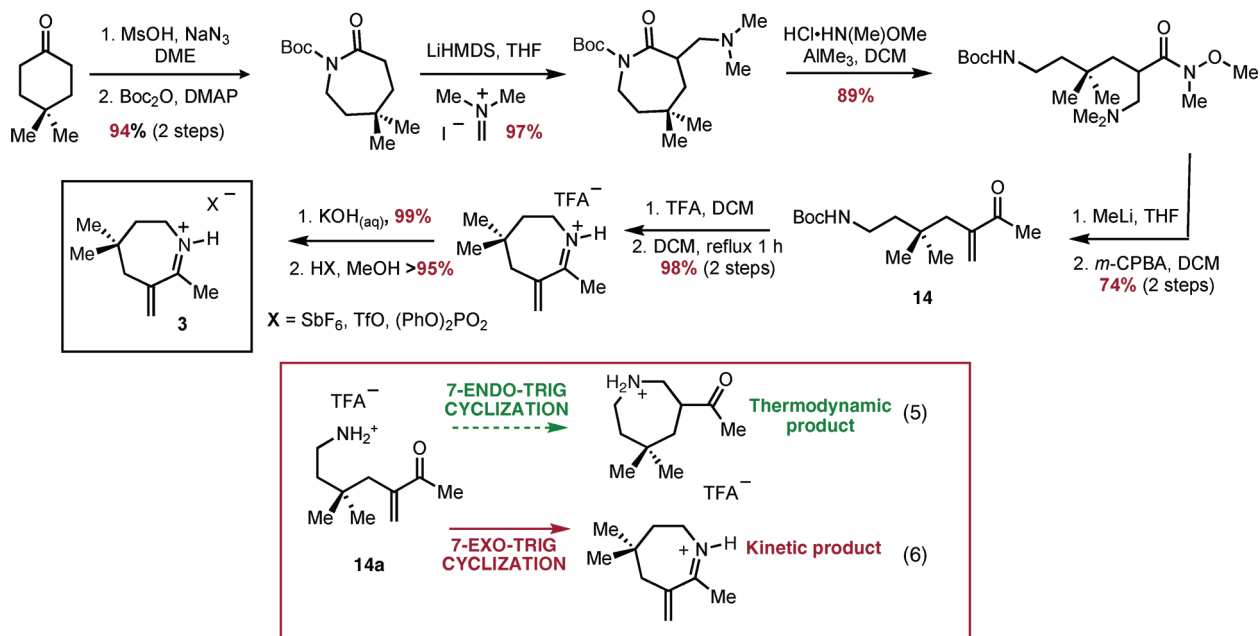
(9) See Supporting Information for experimental details.

(10)  $\text{BAR}_F$  (tetrakis(3,5-bis(trifluoromethyl)phenyl)borate) and  $\text{BF}_4^-$  have also been investigated.  $\text{BAR}_F$  gives results similar to  $\text{ClO}_4^-$  while  $\text{BF}_4^-$  is related to  $\text{OTf}$ . They have been omitted for clarity. See Supporting Information for more details.

**Table 1.** Scope of Iminium-Ions **3** and **6** in Diels–Alder Cycloadditions

entry	diene	product	temp (°C) <sup>a</sup>	endo:exo <sup>b</sup>	yield (%) <sup>c</sup>	entry	diene	product	temp (°C) <sup>a</sup>	endo:exo <sup>b</sup>	yield (%) <sup>c</sup>
1		<b>5a</b> R <sup>1</sup> , Me R <sup>2</sup> , Me R <sup>3</sup> , H	24 (15)	94:6	94 (93)	5	<b>4a</b>	<b>7a</b> R <sup>1</sup> , Me R <sup>2</sup> , Me R <sup>3</sup> , H	24 (2) 0 (10)	90:10 92:8	94 (90) 91
2		<b>5b</b> R <sup>1</sup> , Ph R <sup>2</sup> , H R <sup>3</sup> , H	24 (24)	92:8	98	7	<b>4b</b>	<b>7b</b> R <sup>1</sup> , Ph R <sup>2</sup> , H R <sup>3</sup> , H	24 (13)	77:23	94
3		<b>5c</b> R <sup>1</sup> , Me R <sup>2</sup> , H R <sup>3</sup> , Me	60 (24)	93:7	91	8	<b>4c</b>	<b>7c</b> R <sup>1</sup> , Me R <sup>2</sup> , H R <sup>3</sup> , Me	40 (24)	81:19	98
4		<b>5d</b> R <sup>1</sup> , CH <sub>2</sub> OBn R <sup>2</sup> , H R <sup>3</sup> , Me	40 (15)	95:5	96	9	<b>4d</b>	<b>7d</b> R <sup>1</sup> , CH <sub>2</sub> OBn R <sup>2</sup> , H R <sup>3</sup> , Me	24 (13)	87:13	98

<sup>a</sup> Reaction times in h are provided in parentheses. <sup>b</sup> Determined by <sup>1</sup>H NMR analysis of the unpurified reaction mixture. <sup>c</sup> Combined isolated yield. Yields in parentheses refer to the isolated free imine.

**Scheme 2.** Synthesis of Seven-membered Iminium Ion **3**

**Chiral Azadienes.** Equations 3 and 4 illustrate two chiral cyclic iminium ions of interest to several spiroimine natural products (*cf.* Figure 1). In the case of the more reactive 6-membered iminium-ion **10**, we anticipated that the resident methyl substituent would be sufficient to control the facial selectivity of the reaction. Indeed, high facial selectivity was observed when **10** reacted with

alkene **4a** under the optimal reaction conditions (eq 3), as only two of the four possible DA adducts were observed. In contrast, the facial selectivity of the 7-membered iminium ion **12** represents a more ambiguous case. In this instance, with the illustrated diene, face selectivity is poor. In both instances, endo selectivities were impressive.

**Dienophile Syntheses.** The synthesis of iminium ion dienophile **3** is summarized in Scheme 2.<sup>11</sup> The point of interest in the synthesis of **3** is the transformation of the protected ketoamine **14** to its derived cyclization product. As illustrated, cyclization precursor **14a** is presented with the options of kinetic or thermodynamic control. The competing 7-endo- or 7-exo-cyclization modes are presented (eq 5, eq 6). In accord with Baldwin's Rules,<sup>12</sup> it is tempting to speculate that thermodynamic control might dominate this process (eq 5); nevertheless, kinetic selection for the 7-exo-cyclization mode is clearly revealed under kinetic cyclization conditions (CHCl<sub>3</sub> reflux for one h) (eq 6). After prolonged heating under these conditions (~18 h), the thermodynamic product was observed. It is noteworthy that the gem-dimethyl moiety is required for kinetic control (Thorpe-Ingold) in this instance in spite of the fact that this control element is present in both cyclization modes (Scheme 2) It is also interesting that the vicinal dimethyl substitution pattern

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(11) The synthesis of the six-membered dienophile **6** proceeds along the same lines.

(12) Baldwin, J. E. *J. Chem. Soc. Chem. Commun.* **1976**, 734–735 and subsequent literature citations.

in iminium ion **12** also promotes the desired kinetic cyclization pathway.

The iminium ion DA cycloadditions included in this study afford uniformly good endo diastereoselection. Counterion effects may be relied upon to provide synthetically useful rate accelerations for large non-coordinating counterions (X = SbF<sub>6</sub>) versus their chloride ion counterparts. These observations should be relevant to the further development of a variety of organocatalytic and diastereoselective reactions involving iminium ion reactants.

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**Supporting Information Available.** Complete experimental details, proton and carbon NMR spectra for all new compounds, and stereochemical determination. This material is available free of charge via the Internet at <http://pubs.acs.org>.