Published in final edited form as:

Org Lett. 2011 July 15; 13(14): 3758–3761. doi:10.1021/ol201448h.

Effect of Counterion Structure on Rates and Diastereoselectivities in α,β -Unsaturated Iminium-Ion Diels-Alder Reactions

David Marcoux, Pascal Bindschädler, Alexander W. H. Speed, Anna Chiu, Joseph E. Pero, George A. Borg, and David A. Evans*

Department of Chemistry and Chemical Biology, Harvard University, Cambridge, Massachusetts 02138, USA

Abstract

The use of cyclic α,β -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 activation¹ has been extensively studied in the context of Diels-Alder (DA) reactions and related organocatalyzed transformations.² 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.³

The purpose of this communication is to document the counterion-dependent rate acceleration of endo-selective 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).

These marine natural products have attracted attention as a consequence of their architecture and biological properties.⁴ These structures contain congested [6,6]- or [7,6]-aza-spirocycles. As none of the published approaches to these illustrated structures has employed an iminium ion retron,⁵ we have focused our attention on the development of these DA variants.

The proposed approach to a generic [7,6]-aza-spirocycle 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

evans@chemistry.harvard.edu.

Supporting Information Available. Complete experimental details, proton and carbon NMR spectra for all new compounds, and stereochemical determination are available in the Supporting Information document (PDF files, 96 pages). This material is available free of charge via the Internet at <http://pubs.acs.org>.

additional diastereomers. Previous literature examples have revealed a significant range of endo/exo stereo-selectivities for these reactions.^{6,7,8}

Counterion effect

The results of the reaction of **3f**^{i,9} (X = OTs) 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 SbF₆ and ClO₄ counterions, the reaction is complete in 15 and 17 h respectively.¹⁰ 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 (CH₂Cl₂, CHCl₃) 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).

(1)

(2)

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 = SbF₆) proved to react 20–times faster than its *N*-benzylated counterpart **8** (X = SbF₆) 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.

(3)

(4)

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 2.¹¹ 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,¹² 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 (CHCl₃ 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 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 = SbF₆) 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Financial support has been provided by the National Institutes of Health (GM-33328–24). Fellowships were provided to D.M. and A.W.H.S. by NSERC (Canada) and to P.B. by the SNSF (Switzerland) and Novartis Foundation.

References

1. For seminal publications, see; Ahrendt KA, Borths CJ, MacMillan DWC. *J Am Chem Soc.* 2000; 122:4243–4244. Northrup AB, MacMillan DWC. *J Am Chem Soc.* 2002; 124:2458–2460. [PubMed: 11890793]
2. For selected reviews, see; Erkkilä A, Majander I, Pihka PM. *Chem Rev.* 2007; 107:5416–5470. [PubMed: 18072802] MacMillan DWC, Lelais G, Mikami K, Lautens M. In *New Frontiers in Asymmetric Catalysis*. John Wiley & Sons Hoboken, NJ 2007. Enders D, Grondal C, Hüttel MRM. *Angew Chem, Int Ed.* 2007; 46:1570–1581. Lelais G, MacMillan DWC. *Aldrichim Acta.* 2006; 39:79–87. MacMillan DWC. *Nature.* 2008; 455:304–308. [PubMed: 18800128]
3. Ogilvie has observed an effect of counterion on yields. For additional information, see; Lemay M, Ogilvie WW. *Org Lett.* 2005; 7:4141–4144. [PubMed: 16146372] Lemay M, Ogilvie WW. *J Org Chem.* 2006; 71:4663–4666. [PubMed: 16749802] Lakhdar S, Mayr H. *Chem Commun.* 2011; 47:1866–1868.
4. (a) Lu CK, Lee GH, Huang R, Chou HN. *Tetrahedron Lett.* 2001; 42:1713–1716. (b) Stewart M, Blunt JW, Munro MHG, Robinson WT, Hannah DJ. *Tetrahedron Lett.* 1997; 38:4889–4890. (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 IW, Cembella AD, Curtis JM, Quilliam MA, Walter JA, Wright JLC. *Nat Prod.* 2001; 64:308–312. (e) Guéret SM, Brimble MA. *Nat Prod Rep.* 2010; 27:1350–1366. [PubMed: 20585694]
5. (a) Stivala CE, Zakarian A. *J Am Chem Soc.* 2008; 130:3774–3776. [PubMed: 18311987] (b) Nakamura S, Kikuchi F, Hashimoto S. *Angew Chem, Int Ed.* 2008; 47:7091–7094. (c) McCauley JA, Nagasawa K, Lander PA, Mischke SG, Semones MA, 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, Hiramama M. *Angew Chem, Int Ed.* 2004; 43:6505–6510. (e) Beaumont S, Ilardi EA, Tappin NDC, Zakarian A. *Eur J Org Chem.* 2010:5743–5765.
6. For a recent review, see; Merino P, Marqués-López E, Tejero T, Herrera RP. *Synthesis.* 2010:1–26.
7. Johannes JW, Wenglowsky S, Kishi Y. *Org Lett.* 2005; 7:3997–4000. [PubMed: 16119951]
8. For other iminium-ion dienophiles in Diels-Alder reactions, see; Kim J, Thomson RJ. *Angew Chem, Int Ed.* 2007; 46:3104–3106. Zou Y, Che Q, Snider BB. *Org Lett.* 2006; 8:5605–5608. [PubMed: 17107083] O'Connor PD, Körber K, Brimble MA. *Synlett.* 2008:1036–1038. Boeckman RK Jr, Miller Y, Ryder TR. *Org Lett.* 2010; 12:4524–4527. [PubMed: 20843021]
9. See Supporting Information for experimental details.
10. BAR_{F} (tetrakis(3,5-bis(trifluoromethyl)phenyl)borate) and BF_4 have also been investigated. BAR_{F} gives results similar to ClO_4 while BF_4 is related to OTf. They have been omitted for clarity. See Supporting Information for more details.
11. The synthesis of the six-membered dienophile **6** proceeds along the same lines.
12. Baldwin JE. *J Chem Soc Chem Commun.* 1976:734–735. and subsequent literature citations.

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

Scheme 1.
Counterion-Dependent DA Rate Acceleration

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

Table 1

Scope of Iminium-Ions **3** and **6** in Diels-Alder Cycloadditions

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

^aReaction times in h are provided in parenthesis.

^bDetermined by ¹H NMR analysis of the unpurified reaction mixture.

^cCombined isolated yield. Yields in parenthesis refer to the isolated free imine.