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Asymmetric Diels–Alder reactions in ionic liquids

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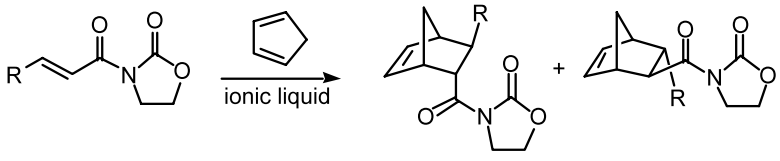
Abstract—Recent interest in ionic liquids has developed various uses for them, including some applications by synthetic chemists. Ionic liquids have joined the potential list of non-traditional solvents for Diels–Alder reactions. We report here our own efforts to examine the rates and selectivities of carbon Diels–Alder reactions. Our investigations show that excellent diastereoselective and enantioselective carbon Diels–Alder reactions can be achieved in imidazolium ionic solvents at room temperature.

The variety of applications for which ionic liquids can be used has sparked an increasing interest in these compounds.[1,2] Ionic liquids have potential as environmentally friendly solvents for synthesis.[3] The solvent effect of ionic liquids is being investigated using transition metal mediated reactions, such as palladium,[4] ruthenium,[5] and nickel,[6] as well as enzymatic[7] and other reactions.[8] Ionic liquids also appear to have potential as extraction solvents.[9] Previously, solvents such as water and 5 M lithium perchlorate in ether have been explored as non-traditional solvents for Diels–Alder reactions;[10] ionic liquids have now joined this list of potential non-traditional solvents as they have been tested in simple Diels–Alder reactions.[11] To our knowledge, the present communication reports for the first time, the high stereoselectivities for substrate and reagent controlled asymmetric Diels–Alder reactions in ionic liquids. These investigations indicate excellent diastereoselective and enantioselective Diels–Alder reactions. The selectivities in room temperature ionic liquid rival the reaction in conventional solvents at −78°C.

The ionic solvents chosen for initial investigation were hydrogen butylimidazolium tetrafluoroborate (HBuIm) and 1,3-dibutylimidazolium tetrafluoroborate (DiBuIm) (Fig. 1).[12] These ionic solvents were chosen because they were known to catalyze Diels–Alder reactions.[11a] The protonated HBuIm were also looked at for the potential increase in reactivity of the system. The Diels–Alder substrates were substituted oxazolidinones and cyclopentadiene (Eq. (1)). The reactions proceeded well in HBuIm with excellent *endo-exo* ratios for the acryloyl oxazolidinone (entry a, Table 1). However, for the crotonyl oxazolidinone, use of HBuIm or DiBuIm gave low yields but high *endo-exo* selectivities (entries b and c). Addition of $ZnCl_2$ to the ionic liquids gave mixed results. The presence of 1% $ZnCl_2$ in DiBuIm increased the rate of reaction to give a 68% yield of the cycloadduct in 92:8 *endo-exo* ratio (entry d). However, $ZnCl_2$ in HBuIm gave no product (entry e). These Diels–Alder reactions were

1 **2**

Figure 1. Hydrogenbutylimidazolium tetrafluoroborate (HBuIm) and 1,3-dibutylimidazolium tetrafluoroborate (DiBuIm).



3, R=H
6, R=CH_3

4, R=H
7, R=CH_3

5, R=H
8, R=CH_3

(1)

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Table 1. Reactions of oxazolidinones **3** or **6** with cyclopentadiene (Eq. (1)).

Entry	R	Rxn conditions	Diene (equiv.)	M[a]	Time	Yield[b] (%)	*endo*:*exo*[c]
a	H	HBuIm	3.0	0.5	3 h	65	100:0[e]
b	CH_3	DiBuIm	7.0	1.0	48 h	11	87:13
c	CH_3	HBuIm	6.4	1.0	48 h	7	100:0[e]
d	CH_3	1% $ZnCl_2$/DiBuIm	3.0	2.0	40 min	68	92:8
e	CH_3	1% $ZnCl_2$/HBuIm	3.0	1.7	45 min	0	0
f	CH_3	1% $Zn(OAc)_2/CH_2Cl_2$	2.4[d]	1.3	12 h	2	87:13
g	CH_3	1% $ZnCl_2$/ether	2.5[d]	1.0	12 h	13	95:5

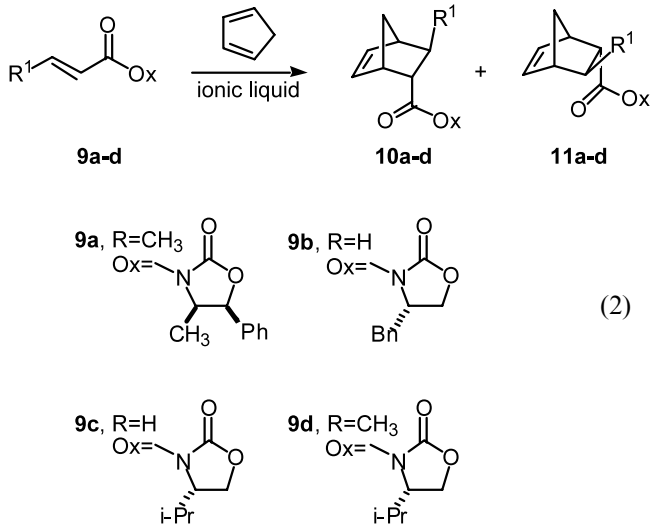
[a] Molarity of **3** or **6**.
[b] Isolated yield except entries f and g, which are percent conversion as determined by NMR.
[c] Determined by ^1H NMR spectra of the crude material.
[d] Diene added in two equal portions 2 h apart.
[e] Within the detection limits of a 200 MHz ^1H NMR spectrometer.

Table 2. Reactions of chiral oxazolidinones with cyclopentadiene (Eq. (2))

Entry	Substrate	Rxn conditions	T (h)	**10**:**11**[b]	*endo*:*exo*[b,d]	Yield (%)
a	**9a**	1% $ZnCl_2$/DiBuIm	13	79:21	100:0[c]	67
b	**9a**	1% $Zn(OAc)_2/CH_2Cl_2$	12	–	100:0[c]	Traces
c	**9a**	1% $ZnCl_2$/ether	12	–	–	0
d	**9b**	1% $ZnCl_2$/DiBuIm	3.25	0:100[b]	100:0[c]	55
e	**9c**	1% $ZnCl_2$/DiBuIm	12	10:90	90:10	97
f	**9d**	1% $ZnCl_2$/DiBuIm	12	5:95	100:0[c]	55
g	**9d**	Et_2AlCl/CH_2Cl_2[a]	12	48:52	80:20	62
h	**9d**	1% $ZnCl_2$/ether	12	–	-	Traces

[a] 1.4 equiv. Et_2AlCl relative to **9c**.
[b] Determined by ^1H NMR.
[c] Within the detection limits of a 200 MHz ^1H NMR spectrometer.
[d] *endo*-*exo* Ratios of the major isomer **10** or **11**.

also carried out in more typical solvents: $Zn(OAc)_2$ or $ZnCl_2$ in CH_2Cl_2 or Et_2O gave low reaction yields even with additional diene (entries f and g). GC analysis of the reactions showed a marked increase in the dimerization of cyclopentadiene in the ionic liquids. In the case of 1% $ZnCl_2$ in HBuIm, the dimerization was very rapid. The ionic solvent increases the rates of both the Diels–Alder reaction and the dimerization of cyclopentadiene.



(2)

Next, the stereoselectivity of the cycloaddition using chiral oxazolidinones **9a**–**d** (Eq. (2)) was examined.[13] Use of 1% $ZnCl_2$ in DiBuIm at room temperature resulted in 55–97% yields and high *endo*-*exo* selectivities for the cycloadducts of the chiral dienophiles (Table 2). As previously noted, the use of Lewis acids in CH_2Cl_2 or Et_2O still gave trace amounts or no product, however, use of 1.4 equiv. of Et_2AlCl in CH_2Cl_2 gave 62% cycloadduct (entries b, c, g, and h). The reactions that used 1% $ZnCl_2$ in DiBuIm at room temperature gave very high diastereoselectivities that arose from the chiral center on the oxazolidinones. The lowest diastereoselectivity of 79:21 was obtained for **9a** (entry a). For **9b**, only one isomer was detected (entry d). For **9c** and **9d**, 10:90 and 5:95 ratios were detected (entries e and f). For comparison purposes, the reaction of **9d** was repeated in Et_2AlCl/CH_2Cl_2 at room temperature, from which a ratio of 48:52 was obtained.

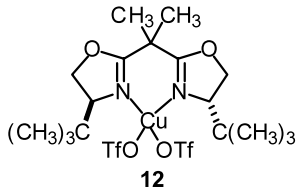
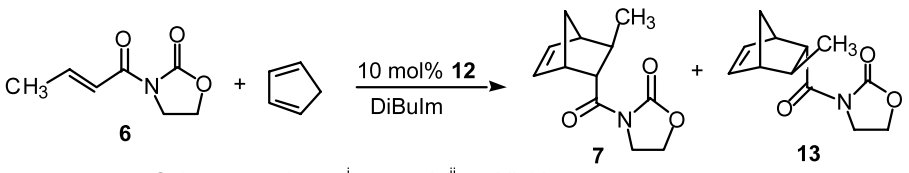


Figure 2. Copper bisoxazoline based chiral Lewis acid.

Enantioselective reactions of dienophile **6** with chiral catalyst **12** were also attempted (Fig. 2, and Eq. (3)).[14] The catalytic activity of the reaction in DiBuIm was compared to its activity in CH_2Cl_2 at room temperature, and a much faster reaction was observed in the ionic liquid. The reaction in DiBuIm gave a 65% yield compared to a 4% yield for the reaction in CH_2Cl_2. The *endo-exo* ratios were also higher: 93:7 for the ionic liquid versus 79:21 for CH_2Cl_2. The enantioselectivity in DiBuIm gave 96:4, whereas the reaction in CH_2Cl_2 gave an enantioselectivity of 76:24.



(3)

Solvent	endo:exo[i]	7:13[ii]	Yield
CH_2Cl_2	79:21	76:24	4%
DiBuIm	93:7	96:4	65%

[i] Endo-exo of the major isomer as determined by ^1H NMR. [ii] Determined by HPLC using a chiral column.

In summary, ionic solvents gave unusually high stereoselectivities for the present substrates in the Diels–Alder reactions at room temperature, as opposed to the necessarily low temperatures required of these reactions to effect good stereoselectivities in the traditional solvents. Although, the results show that ionic solvents increases the rate of reaction, the mechanism which gives the Diels–Alder reactions such high diastereoselectivities or enantioselectivities at room temperature is unclear at this time. We have initiated mechanistic investigations to elucidate the interaction between the ionic liquid and the substrates that can account for the high selectivities.

Experimental procedure for the substrate **9c** is as follows (Eq. (2)). To a solution of 1% $ZnCl_2$ in DiBuIm (0.58 mL) was added (4*S*)-3-(2-propenoyl)-4-(1-methylethyl)-2-oxazolidinone **9c** (0.106 g) and cyclopentadiene (0.08 mL). The solution was stirred for 2 h, after which a second portion of cyclopentadiene (0.08 mL) was added, and this was repeated after another 2 h. The solution was stirred for an additional 9 h, after which it was extracted using warm ether (7×3 mL). The ether layers were combined and concentrated under vacuum, and the product was purified by flash column chromatography using 32:1 hexanes:EtOAc to afford 0.140 g (97%) of Diels–Alder adduct as a white solid.[15]

The experimental procedure for asymmetric Diels–Alder reaction with a chiral catalyst is as follows (Eq. (3)). Under an inert atmosphere of N_2, a mixture of 2,2′-isopropylidene-bis[(4*S*)]4-*tert*-butyl-2-oxazoline] (0.037 g), Cu(II)OTf (0.038 g), and DiBuIm (2 mL) was stirred for 5 h. To this mixture was added 3-(2-butenoyl)-2-oxazolidinone (0.142 g), cyclopentadiene (0.250 mL) and was stirred for an additional 19 h. The reaction was extracted with warm ether (7×3 mL). The combined organic layers were dried over Mg_2SO_4, concentrated, and flash column chromatographed (2:1 hexanes:EtOAc) to yield 0.1310 g (65%) of **7** and **13**.[15] The *endo*:*exo* ratios were analyzed by measuring the integrals of the vinyl peaks on the ^1H NMR spectrum. The enantiomeric excess of the *endo*-isomers were determined using an HPLC column (Chiralcel OD-H) and a mobile phase of 95% hexanes, 2% 2-propanol, and 3% EtOAc at a flow rate of 0.95 mL/min (681 psi), and the retention time of each enantiomer was: t_R (**7**) = 17.74 min, t_R (**13**) = 19.43 min.

Acknowledgements

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