Novel Use of *N*-Carboalkoxy α,β-Unsaturated Iminium Ions as Dienophiles in Diels–Alder Reactions

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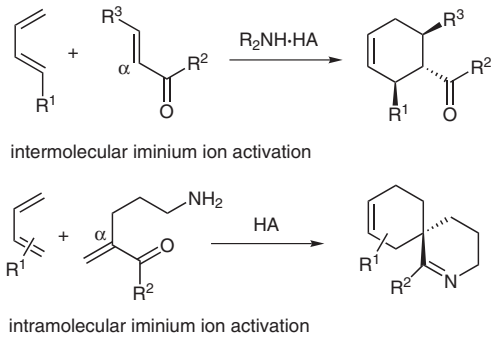
Abstract: Tricyclic spiro-*N*,*O*-acetals have been assembled in a single step by cycloaddition of hydroxymethyl-substituted dienes to iminium ion activated dienophiles that were generated by acidolysis of α,β-unsaturated-*N*-carboalkoxy-*N*,*O*-acetals or β-methoxymethyl-*N*-carboalkoxy-enamines. The cycloaddition was conducted using $Sc(OTf)_3$ as a mild Lewis acid affording the *endo* adducts in moderate yields.

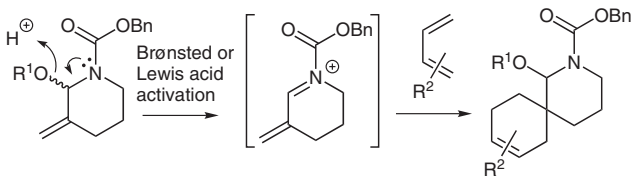
Key words: iminium ion, Diels–Alder, cycloaddition

The last decade has witnessed a significant increase in the number of examples of iminium ion catalyzed Diels–Alder cycloadditions. Largely thanks to the work of the MacMillan group, a range of imidazolidinone salts now commercially available that can be used to achieve intermolecular asymmetric organocatalysis of Diels–Alder cycloadditions by iminium ion activation of both enal and more impressively, enone dienophiles.[1] Despite exhibiting broad scope, this method of intermolecular iminium ion activation has not yet been reported to tolerate α-functionalization of the dienophile with only limited examples of intramolecular iminium ion activation of dienophiles involving α-functionalized cyclic imines being disclosed (Scheme 1).[2]



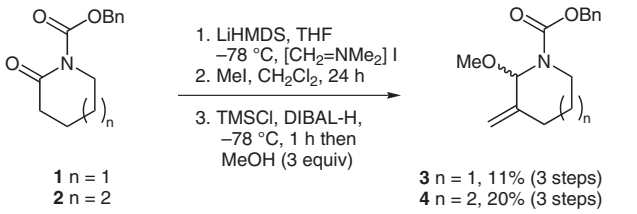
Scheme 1 Iminium ion activation of Diels–Alder cycloadditions

As a novel extension to recently developed Diels–Alder organocatalytic methodology we decided to explore the possibility of forming cyclic iminium ion dienophiles via acidolysis of cyclic *N*-carboalkoxy *N*,*O*-acetals, that are well known for their ability to generate electrophilic *N*-carboalkoxy iminium species upon treatment with acid (Scheme 2).[3]



Scheme 2 Putative *N*-carboalkoxy iminium ion activated Diels–Alder cycloaddition

Ionic Diels–Alder cycloadditions have previously been reported by Gassman et al.[4] in which highly reactive oxonium ion dienophiles, generated by the acidolysis of acrolein derived *O*,*O*-acetals, participated in Diels–Alder additions with a number of dienes. With these ideas in mind, we focused our attention on the synthesis of cyclic α,β-unsaturated *N*-carboalkoxy *N*,*O*-acetals as precursors to putative iminium ion dienophiles. Towards that end, the readily available *N*-Cbz-protected lactams **1** and **2**[5] were α-methylenated by alkylation of the amide enolates with Eschenmoser's salt followed by Hofmann elimination to afford the α,β-unsaturated amides (Scheme 3). The amide carbonyl was then reduced using DIBAL-H in the presence of TMSCl. By quenching the reaction at low temperature the desired *N*,*O*-acetals **3** and **4** were obtained albeit in low yields.



Scheme 3 Synthesis of α,β-unsaturated *N*-carboalkoxy *N*,*O*-acetals

An alternative route to the required iminium dienophile involving methylenation of hemiaminal **6** was next investigated (Scheme 4). The *N*-Cbz piperidine intermediate **5**[6] was subjected to electrochemical oxidation to furnish the hydrogen bonded hemiaminal **6**.[7] This less conventional electrochemical method provided **6** in superior yield to the alternative literature procedure based on Swern oxidation of the open-chain Cbz-protected amino alcohol.[8] Methylenation of **6** using Pihko's organocatalytic method[8] afforded α,β-unsaturated aldehyde **7** that notably existed as

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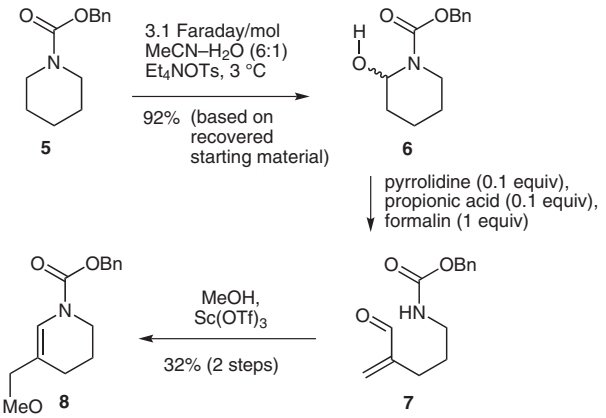
the open-chain tautomer. This reaction was hampered by the competing formation of the enecarbamate,[9] and moreover as noted by Pihko, aldehydes that exist predominantly as hemiacetals are poor methylenation substrates. The crude enal **7** was next treated with a catalytic quantity of scandium triflate in methanol to unexpectedly afford enamine **8** in multigram quantities. To the best of our knowledge the resultant β-alkoxy-*N*-carboalkoxy enamines, despite their synthetic utility,[10] have not been prepared by the simple alcoholysis of acyclic starting materials. Notably, enamine **8** is formed under thermodynamic conditions in contrast to its constitutional isomer **3**, which is formed under kinetic conditions using a low-temperature DIBAL-H reduction.

We reasoned, however, that both compounds **3** and **8** under acidic conditions would form the same α,β-unsaturated iminium ion that could then be trapped as a Diels–Alder adduct. Iminium ion precursors **3**, **4**, and **8** did not react with simple butadienes such as isoprene despite screening a range of Lewis acids for their ability to mediate this reaction. Gratifyingly, reaction of **3**, **4**, and **8** with PMB-protected hydroxymethyl diene **9**[11] in the presence of 20 mol% $BF_3{\cdot}OEt_2$ furnished the tricyclic adducts **10** and **11** (Table 1) in which in situ deprotection of the PMB ether appeared to precede intramolecular *N*,*O*-acetal formation.

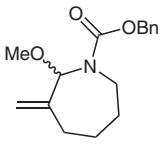
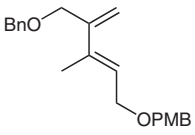
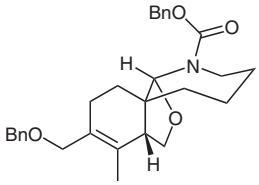
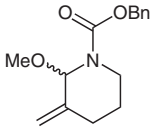
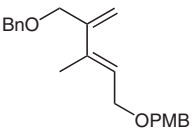
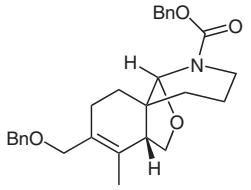
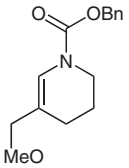
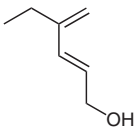
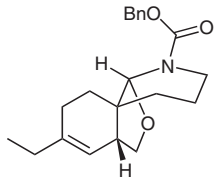
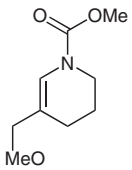
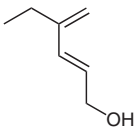
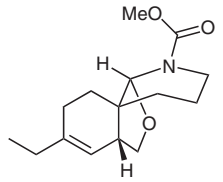


Scheme 4 Synthesis of α,β-unsaturated *N*-carboalkoxy *N*,*O*-acetals

In order to further probe this novel reaction we next prepared adducts **12** and **13** by reaction of enamine **8** with the unprotected hydroxy diene **14**.[12] The isomeric iminium ion precursor **8** was equally amenable to the use of $Sc(OTf)_3$ or $BF_3{\cdot}OEt_2$ to catalyze the cycloaddition.

Cycloadducts **10**–**13** were assigned as the thermodynamically favored[13] *anti*-methine *endo* adducts on the basis of NOE evidence. Typically, cyclic *exo*-methylene dienophiles give *exo* cycloadducts due to a combination of steric and electronic factors[14] associated with *s-cis* dienophile

Table 1 Novel Iminium Ion Activated Diels–Alder Cycloaddition

Dienophile	Diene	Reagents	Product	Yield (%)
 **4**	 **9**	$BF_3{\cdot}OEt_2$ (20 mol%), –78 °C to r.t., 2 h	 **10**	78
 **3**	 **9**	$BF_3{\cdot}OEt_2$ (10 mol%), –78 °C to r.t., 2 h	 **11**	53
 **8**	 **14**	$Sc(OTf)_3$ (3.5 mol%), CH_2Cl_2, 0 °C, 2 h	 **12**	60
 **15**	 **14**	$Sc(OTf)_3$ (5 mol%), CH_2Cl_2, 0 °C, 2 h $BF_3{\cdot}OEt_2$ (10 mol%), –78 °C to r.t., 2 h	 **13**	41 68

configuration. However in the present case, the formation of the *endo* adduct is consistent with secondary orbital overlap between the diene and the *s-trans* configured iminium dienophiles.

Given that the presence of a hydroxy group on the diene is essential for reactivity, it is reasoned that the cycloaddition proceeds through a metal-templated intermediate. Following cycloaddition, the incipient iminium ion is trapped by the alkoxide ion to form the tricyclic adduct. Confirmation of this mechanistic proposal awaits a theoretical investigation.

In summary, we have developed a novel application of Pihko's organocatalytic methylenation that has led to a concise synthesis of synthetically useful β-methoxymethyl-*N*-carboalkoxy-enamines. Both the aforementioned enamines and their isomeric *N*,*O*-acetals were shown to undergo novel diastereoselective iminium ion activated cycloadditions to furnish 6,6,5- and 7,6,5-spirotricyclic *N*,*O*-acetals.

Procedure for the organocatalytic formation of 7

A 25 mL round-bottom flask equipped with stirrer bar was charged with hemiaminal 6 (1.39 g, 5.91 mmol), pyrrolidine (42 mg, 590 μmol), propionic acid (44 mg, 590 μmol), formalin (0.50 mL, 6 mmol), and *i*-PrOH (0.5 mL) and the mixture was heated to 45 °C for a period of 24 h. The reaction was quenched with sat. $NaHCO_3$, extracted with CH_2Cl_2 (3 × 20 mL), and dried over $MgSO_4$. Evaporation of the solvent afforded an oil that was further purified by silica gel chromatography eluting with hexane–EtOAc (3:1) to give **7** as a colorless oil (580 mg, 40%). IR (film): 2943, 1694, 1531, 1256 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 9.56 (s, 1 H), 7.41–7.30 (m, 5 H), 7.19–6.90 (br m, 1 H), 6.39–6.37 (m, 1 H), 6.17–6.16 (m, 1 H), 5.05 (s, 2 H), 3.07–3.00 (m, 2 H), 2.24–2.17 (m, 2 H), 1.64–1.53 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 195.5 (C), 149.6 (C), 138.0 (C), 135.4 (CH), 128.9 (CH), 128.2 (CH), 128.1 (CH), 65.8 (CH_2), 28.3 (CH_2), 25.2 (CH_2) ppm. HRMS (EI): *m/z* calcd for $C_{14}H_{17}NO_3$ [M^+]: 247.1208; found: 247.1203.

Procedure for the Conversion of 7 into 8

To a stirred solution of unsaturated aldehyde **7** (914 mg, 3.70 mmol) in CH_2Cl_2 (30 mL) and MeOH (5 mL) at 0 °C was added $Sc(OTf)_3$ (21 mg, 427 μmol). After stirring at 0 °C for 3 h the reaction was quenched with sat. $NaHCO_3$, extracted with CH_2Cl_2 (3 × 20 mL), dried over $MgSO_4$, and the solvent evaporated. Purification by silica gel chromatography eluting with hexane–EtOAc (4:1) afforded the title compound as a colorless oil (648 mg, 67%). IR (film): 2930, 1705, 1673, 1411 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6, 70 °C): δ = 7.44–7.35 (m, 5 H), 6.87 (m, 1 H), 5.21 (s, 2 H), 3.83 (s, 2 H), 3.60–3.55 (m, 2 H), 3.22 (s, 3 H), 2.07–2.01 (m, 2 H), 1.87–1.77 ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.2, 137.2, 129.0, 128.5, 128.3, 123.2, 116.4, 74.8, 67.4, 57.2, 42.5, 23.1, 21.6 ppm. HRMS (EI): *m/z* calcd for $C_{15}H_{19}NO_3$ [M^+]: 261.1365; found: 261.1365.

Procedure for Iminium Diels–Alder Cycloaddition

To a solution of enamine **8** (126 mg, 482 μmol) and diene **14** (206 mg, 1.84 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added $Sc(OTf)_3$ (10.5 mg, 21.3 μmol). After stirring for 2 h the mixture was quenched with sat. $NaHCO_3$ (10 mL), extracted with CH_2Cl_2 (3 × 20 mL), dried over $MgSO_4$, and evaporated. Purification by silica gel chromatography eluting with hexane–EtOAc (6:1) afforded **12** as a colorless oil (99 mg, 60%). IR (film): 2931, 1708, 1430, 1281 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6, 70 ºC): δ = 7.38–7.30 (m, 5 H, H_{Ph}), 5.49 (s, 1 H, H_{4a}), 5.27–5.23 (m, 1 H, H_7), 5.16 (d, *J* = 12.6 Hz, 1 H, $H_{2'}$), 5.06 (d, *J* = 12.6 Hz, 1 H, $H_{2'}$), 4.17 (dd, *J* = 8.2, 7.4 Hz, 1 H, $H_{6\alpha}$), 3.86–3.78 (m, 1 H, H_3), 3.37 (dd, *J* = 8.3, 3.0 Hz, 1 H, $H_{6\beta}$), 2.99–2.89 (m, 1 H, H_3), 2.43–2.36 (m, 1 H, H_{6a}), 1.96 (q, *J* = 7.5 Hz, 2 H, $H_{1'}$), 1.91–1.79 (m, 3 H), 1.65–1.51 (m, 3 H), 1.43–1.31 (m, 2 H), 0.95 (t, *J* = 7.5 Hz, 1 H, $H_{2'}$). ^{13}C NMR (75 MHz, DMSO-d_6, 70 °C): δ = 154.8 ($C_{1''}$), 137.7 (C_8), 136.2 (C_{Ph}), 127.8 (2 C_{Ph}), 127.3 (C_{Ph}), 126.9 (2 C_{Ph}), 120.8 (C_7), 83.7 (C_{4a}), 69.4 (C_6), 66.0 ($C_{2''}$), 38.3 (C_3), 37.6 ($C_{10'}$), 31.0 (C_1), 29.1 ($C_{1'}$), 25.5 (C_2), 23.6 (C_9), 19.3 (C_{10}), 11.6 ($C_{2'}$). HRMS (EI): *m/z* calcd for $C_{21}H_{27}NO_3$ [M^+]: 341.1991; found: 341.1993.

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