

## Hetero Diels–Alder Reactions of Imines Derived from Cyclohexanones

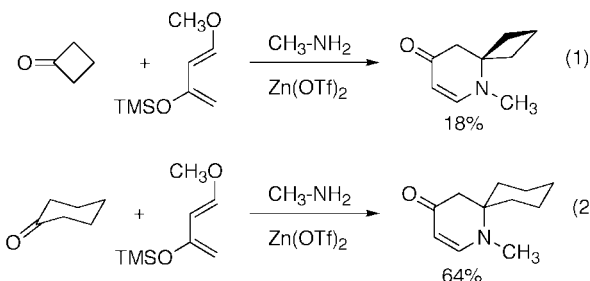
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Construction of nitrogen heterocycles through the use of imino dienophiles in Diels–Alder reactions has received much attention recently.<sup>1–6</sup> The use of Lewis acids and activated dienes to counteract the low reactivity has further increased the potential of the imino Diels–Alder reaction in synthesis.<sup>2</sup> The Lewis acid-catalyzed reactions to date have focused on the imines derived from aldehydes. Hetero Diels–Alder reactions with imines derived from ketones have obtained little attention probably due to their low reactivity. Further development of aza Diels–Alder reaction with imines derived from cyclic ketones would give an excellent entry into the aza-spirane ring system. Herein, we describe our investigation of hetero Diels–Alder reaction of imines derived from cyclohexanones.

Previous work with imines derived from aldehydes has led to the discovery that Zn(OTf)<sub>2</sub> is an excellent promoter for imino Diels–Alder reactions.<sup>7</sup> Our survey of Diels–Alder reactions of imines derived from 4- to 9-membered cyclic ketones with Danishefsky's diene<sup>8</sup> resulted in cycloadducts for the 4- and 6-membered ketones (eqs 1 and 2).



The yields for the cyclohexanone adduct were in the 60% range. This led us to survey several cyclohexanone derivatives.

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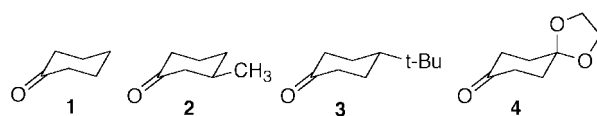


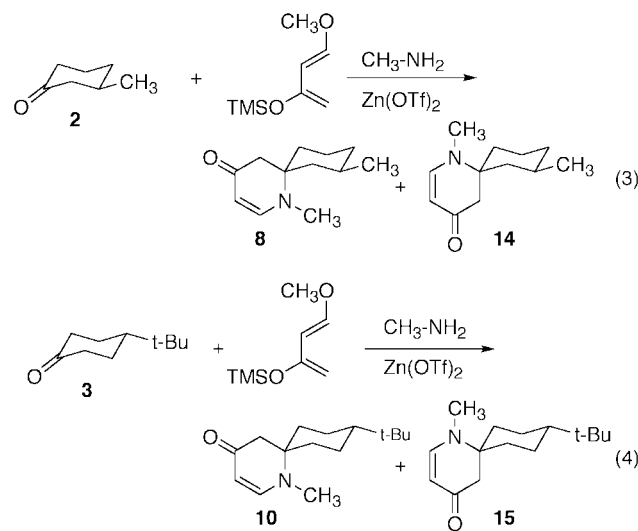
Figure 1. Ketone substrates.

Table 1. Diels–Alder Reactions of Cyclohexylimines

entry	substrate	amine	product	yield (%)
1	<b>1</b>	CH <sub>3</sub> NH <sub>2</sub>	<b>5</b>	51–64
2	<b>1</b>	<i>n</i> -BuNH <sub>2</sub>	<b>6</b>	36
3	<b>1</b>	<i>s</i> -BuNH <sub>2</sub>	<b>7</b>	7
4	<b>1</b>	<i>t</i> -BuNH <sub>2</sub>	<b>8</b>	0
5	<b>2</b>	CH <sub>3</sub> NH <sub>2</sub>	<b>8</b>	76
6	<b>2</b>	<i>n</i> -BuNH <sub>2</sub>	<b>9</b>	70
7	<b>2</b>	PhCH <sub>2</sub> NH <sub>2</sub>	<b>10</b>	0
8	<b>3</b>	CH <sub>3</sub> NH <sub>2</sub>	<b>10</b>	49
9	<b>3</b>	PhCH <sub>2</sub> NH <sub>2</sub>	<b>11</b>	29
10	<b>4</b>	CH <sub>3</sub> NH <sub>2</sub>	<b>12</b>	84
11	<b>4</b>	PhCH <sub>2</sub> NH <sub>2</sub>	<b>13</b>	40
12	<b>4</b>	Ph(CH <sub>3</sub> )CHNH <sub>2</sub>	<b>13</b>	0

Survey of compounds **1–4** with a variety of amines led to interesting trends (Figure 1, Table 1). Substitution groups at the 3- and 4-positions were tolerated in the cycloaddition. Attempted reactions with groups in the 2-position failed to give cycloaddition adducts. Experimentation with equivalents of Lewis acids and amines show that the cleanest reaction resulted with less than 1 equiv of Zn(OTf)<sub>2</sub> and excess amines. Excess Lewis acids (1–3 equiv) led to higher rates of reaction; however, it also led to significant amounts of polymers and diene decomposition. It made little difference whether the imines were generated in situ or preformed to the outcome of the reaction.

There are two potential products in the cycloaddition of imines derived for ketones **2** and **3** with Danishefsky's diene (eqs 3 and 4). The <sup>1</sup>H NMR of the crude product



show only one detectable isomer. Purification by flash chromatography gave product **8** in 76% and **10** in 49%

(8) For a review on this siloxy diene, see: Danishefsky, S. *Acc. Chem. Res.* **1981**, *14*, 400.

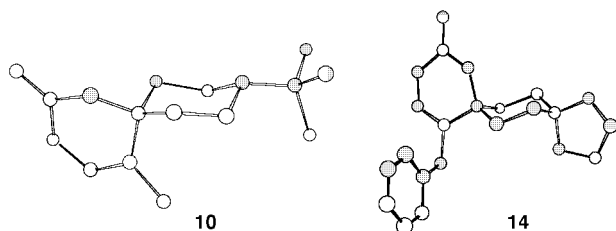


Figure 2. Crystal structures of **10** and **13**.

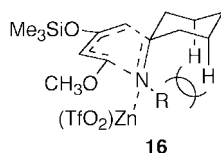


Figure 3. Transition state.

yield. The gross structures were determined by  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR, and IR, but the relative stereochemistry could not be determined by these spectral methods. The stereochemical relationship was found by a single-crystal X-ray of compounds **10** and **13** (Figure 2).<sup>9</sup> The stereochemical outcome indicates the diene approaches the imine from the equatorial direction. This correlates with the known fact that the sterically demanding reactants prefer the equatorial approach in this type of system.<sup>10</sup> The selectivity in this case is excellent due to the large steric demand of the diene. The crystal structures show an  $\text{sp}^2$  nitrogen, confirming the conjugation of the carbonyl and nitrogen, showing the vinylogy as expected in a vinylogous amide. The crystal structure of **13** also confirms the equatorial preference of the nitrogen. Table 1 also shows that, for each substrate, as the steric demand of the nitrogen increases, the yield decreases until no product is obtained for the more hindered amines. This can be rationalized by transition state **16** (Figure 3). In the formation of the product, the N–R group initially develops axially and the 1,3-diaxial interaction becomes a factor. With the more hindered amines, this interaction becomes large enough to prevent cycloaddition.

The above results show that  $\text{Zn}(\text{OTf})_2$  is an excellent promoter of imino Diels–Alder reactions with cyclohexanone-derived imines. Excellent selectivity was observed with 3- and 4-substituted cyclohexanones. The cycloadducts also have functional group handles for further manipulations. This method allows for ready construction of the aza-spirane ring systems.

## Experimental Section

**General Methods.** All reactions were carried out under an atmosphere of argon or nitrogen. Dichloromethane was distilled from  $\text{CaH}_2$  prior to use. TLC was performed on silica gel precoated plates. Bruker AC 200 nuclear magnetic resonance spectrometer was used to obtain  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra in  $\text{CDCl}_3$ .

A representative procedure is shown with compound **5**.

**1-Methyl-1-aza-6-spiro[5.5]undec-2,3-en-4-one (5).** To a stirred solution of cyclohexanone (196 mg, 2.0 mmol) in  $\text{CH}_2\text{Cl}_2$

(5 mL) were added  $\text{Zn}(\text{OTf})_2$  (363 mg, 1.0 mmol),  $\text{CH}_3\text{NH}_2$  (2.0 M THF solution, 4.0 mL, 8.0 mmol), and *trans*-1-methoxy-3-[(trimethylsilyloxy)-1,3-butadiene (0.78 mL, 4.0 mmol). The reaction mixture was stirred at room temperature for 12 h followed by the addition of a saturated solution of  $\text{NH}_4\text{Cl}$  (20 mL) and  $\text{CH}_2\text{Cl}_2$  (20 mL). This mixture was stirred for 2 h and the organic layer separated. The aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  (10 mL  $\times$  2). The combined organic extracts were dried over  $\text{Na}_2\text{SO}_4$  and evaporated. Flash column chromatography (1:1 hexanes–ethyl acetate to ethyl acetate gradient) afforded 226 mg (64%) of **5**:  $R_f = 0.20$  ( $\text{SiO}_2$ , ethyl acetate); IR 1629, 1582  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR  $\delta$  6.84 (1H, d,  $J = 7.4$  Hz), 4.84 (1H, d,  $J = 7.4$  Hz), 2.92 (3H, s), 2.54 (2H, s), 1.85–1.40 (9H, m), 1.12 (1H, m).  $^{13}\text{C}$  NMR  $\delta$  191.3, 154.3, 96.6, 60.5, 43.4, 37.2, 30.6, 25.5, 21.7; GCMS (70 eV)  $m/z$  179 ( $\text{M}^+$ , 39), 150 (6), 136 (45), 123 (100), 94 (38), 84 (42), 68 (15), 55 (20); MS calcd for  $\text{C}_{11}\text{H}_{17}\text{NO}$  179.26, found 179.15.

**1-[(2-Butyl)methyl]-1-aza-6-spiro[5.5]undec-2,3-en-4-one (6):**  $R_f = 0.28$  ( $\text{SiO}_2$ , 1:1 hexanes/EtOAc); IR 1631, 1576  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR  $\delta$  6.93 (1H, d,  $J = 7.4$  Hz), 4.92 (1H, d,  $J = 7.4$  Hz), 3.8 (2H, t,  $J = 7.4$  Hz), 2.60 (2H, s), 1.95 (2H, m), 1.8–1.1 (12H, m), 0.96 (3H, t,  $J = 7.2$  Hz);  $^{13}\text{C}$  NMR  $\delta$  191, 155, 97, 62, 49, 44, 34, 32, 26, 22, 20, 14; GCMS (70 eV)  $m/z$  221 ( $\text{M}^+$ , 56), 192 (7), 178 (72), 165 (37), 150 (72), 135 (35), 122 (65), 109 (31), 82 (100), 68 (28), 55 (39); MS calcd for  $\text{C}_{14}\text{H}_{23}\text{NO}$  221.34, found 221.15.

**(6*R*\*,8*R*\*)-1,8-Dimethyl-1-aza-6-spiro[5.5]undec-2,3-en-4-one (8):**  $R_f = 0.16$  ( $\text{SiO}_2$ , EtOAc); IR 1633, 1584  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR  $\delta$  6.89 (1H, d,  $J = 7.3$  Hz), 4.91 (1H, d,  $J = 7.3$  Hz), 3.23 (3H, s), 2.4–2.16 (4H, m), 1.88–1.58 (4H, m), 1.4–1.2 (2H, m), 1.0 (1H, m), 0.92 (3H, d,  $J = 6.4$  Hz);  $^{13}\text{C}$  NMR  $\delta$  192.0, 154.6, 96.8, 59.1, 51.5, 42.1, 41.0, 33.7, 32.7, 28.6, 22.9, 22.3; GCMS (70 eV)  $m/z$  193 ( $\text{M}^+$ , 3), 123 (7), 89 (26), 70 (12), 61 (16), 43 (100), 32 (25), 28 (56), 18 (12); MS calcd for  $\text{C}_{12}\text{H}_{19}\text{NO}$  193.29, found 193.25.

**(6*R*\*,8*R*\*)-1-*n*-Butyl-8-methyl-1-aza-6-spiro[5.5]undec-2,3-en-4-one (9):**  $R_f = 0.40$  ( $\text{SiO}_2$ , EtOAc); IR 1634, 1574  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR  $\delta$  6.91 (1H, d,  $J = 7.3$  Hz), 4.97 (1H, d,  $J = 7.3$  Hz), 3.40 (2H, dt,  $J = 3.8$  Hz, 7.6 Hz), 2.37 (2H, d,  $J = 3.0$  Hz), 2.3–2.1 (2H, m), 1.82–1.47 (6H, m), 1.4–1.2 (5H, m), 0.97 (3H, t,  $J = 7.2$  Hz), 0.93 (3H, d,  $J = 6.4$  Hz);  $^{13}\text{C}$  NMR  $\delta$  192.6, 153.7, 97.7, 60.2, 52.4, 52.0, 40.9, 34.8, 33.4, 32.9, 28.6, 22.8, 22.0, 20.1, 13.9; GCMS (70 eV)  $m/z$  235 ( $\text{M}^+$ , 92), 192 (100), 150 (78), 137 (48), 126 (77), 122 (54), 82 (83), 41 (64), 29 (41); MS calcd for  $\text{C}_{15}\text{H}_{25}\text{NO}$  235.37, found 235.20.

**(6,9-*cis*)-9-*tert*-Butyl-1-methyl-1-aza-6-spiro[5.5]undec-2,3-en-4-one (10).** The compound was crystallized with ether–hexanes solvent mixture for X-ray analysis:  $R_f = 0.21$  ( $\text{SiO}_2$ , EtOAc); mp 139–145  $^\circ\text{C}$ ; IR 1631, 1582  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR  $\delta$  6.85 (1H, d,  $J = 7.3$  Hz), 4.84 (1H, d,  $J = 7.3$  Hz), 3.20 (3H, s), 2.38–2.18 (3H, m), 2.24 (2H, s), 1.67–1.64 (2H, m), 1.30–1.21 (4H, m), 0.82 (9H, s);  $^{13}\text{C}$  NMR  $\delta$  192.6, 154.5, 96.9, 57.9, 51.1, 46.6, 42.2, 33.2, 32.5, 27.4, 23; GCMS (70 eV)  $m/z$  235 ( $\text{M}^+$ , 26), 178 (19), 136 (100), 123 (84), 94 (34), 84 (97), 57 (48), 55 (31), 42 (54), 41 (51), 29 (23); MS calcd for  $\text{C}_{15}\text{H}_{25}\text{NO}$  235.37, found 235.25.

**(6,9-*cis*)-1-Benzyl-9-*tert*-butyl-1-aza-6-spiro[5.5]undec-2,3-en-4-one (11):**  $R_f = 0.33$  ( $\text{SiO}_2$ , 1:1 hexane/EtOAc); IR 1634, 1574, 1558  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR  $\delta$  7.40–7.26 (5H, m), 6.96 (1H, d,  $J = 7.4$  Hz), 5.05 (1H, d,  $J = 6.4$  Hz), 4.69 (2H, s), 2.38 (2H, s), 2.38–2.07 (4H, m), 1.70–1.56 (1H, m), 1.29–1.24 (4H, m), 0.88 (9H, s);  $^{13}\text{C}$  NMR  $\delta$  192.7, 154.6, 139.9, 129.3, 128.0, 126.5, 98.5, 58.5, 57.0, 52.1, 46.5, 33.3, 33.0, 27.6, 23.5.

**1-Methyl-9,1'-(2',5'-dioxolane)-1-aza-6-spiro[5.5]undec-2,3-en-4-one (12):**  $R_f = 0.07$  ( $\text{SiO}_2$ , EtOAc); mp 155–160  $^\circ\text{C}$ ; IR 1636, 1584  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR  $\delta$  6.91 (1H, d,  $J = 7.5$  Hz), 4.91 (1H, d,  $J = 7.5$  Hz), 3.93 (4H, s), 2.97 (3H, s), 2.60 (2H, s), 2.04–1.66 (4H, m);  $^{13}\text{C}$  NMR  $\delta$  190.5, 154.7, 106.8, 96.6, 64.1, 64.1, 59.5, 42.9, 37.3, 30.5, 27.6; GCMS (70 eV)  $m/z$  237 ( $\text{M}^+$ , 24), 194 (20), 180 (5), 164 (9), 138 (18), 123 (57), 101 (100), 84 (44), 55 (18), 42 (23); MS calcd for  $\text{C}_{13}\text{H}_{19}\text{NO}_3$  237.30, found 237.20.

**1-Benzyl-9,1'-(2',5'-dioxolane)-1-aza-6-spiro[5.5]undec-2,3-en-4-one (13):**  $R_f = 0.20$  ( $\text{SiO}_2$ , 9:1 EtOAc); mp 132–142  $^\circ\text{C}$ ; IR 1634, 1574  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR  $\delta$  7.37–7.27 (m, 5H), 7.01 (1H, d,  $J = 7.6$  Hz), 5.02 (1H, d,  $J = 7.6$  Hz), 4.43 (2H, s), 3.91 (4H, s), 2.68 (2H, s), 1.84–1.81 (4H, m), 1.64–1.60 (4H, m);  $^{13}\text{C}$  NMR  $\delta$  191.0, 154.7, 138.3, 128.8, 127.6, 126.6, 107.2, 97.4, 64.4, 64.1

(9) Duque, R.; Hardcastle, K.; Huang, P.; Isayan, K.; Visi, M.; Oh, T. Manuscript in preparation.

(10) For a review on stereoelectronics in this type of system, see: Delongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: Oxford, 1983; Chapter 6, pp 210–211.

60.8, 53.2, 43.4, 30.5, 28.7; GCMS (70 eV)  $m/z$  313 ( $M^+$ , 18), 270 (11), 160 (16), 101 (63), 91 (100), 65 (15), 28 (16); MS calcd for  $C_{19}H_{23}NO_3$  313.40, found 313.25.

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**Supporting Information Available:**  $^1H$  and  $^{13}C$  NMR spectra of compounds **5**, **6**, and **8–13** (16 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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