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Chiral cycloalkylidene α,β-unsaturated iminium approach to stereoselective formal [3+3] cycloaddition reaction in spiroheterocycle synthesis

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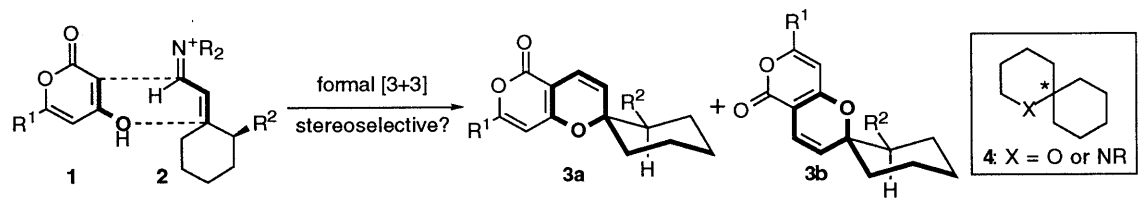
Abstract—An approach to stereoselective formal [3+3] cycloaddition reaction using chiral cycloalkylidene α,β-unsaturated iminiums is described here leading to preparations of spiroheterocycles in modest stereoselectivity. The reversibility of 6π-electron electrocyclic ring closure did not always lead to the thermodynamically more favored product. These observations led to other useful mechanistic understanding of electrocyclic ring closure of 1-oxatrienes. © 2001 Elsevier Science Ltd. All rights reserved.

Reactions of α,β-unsaturated carbonyl systems with 1,3-diketo equivalents involve a tandem process consisting of a Knoevenagel condensation followed by a 6π-electron electrocyclic ring closure.[1–3] The net result of this step-wise or formal [3+3] cycloaddition reaction[4,5] is the formation of two σ-bonds in addition to a new stereocenter adjacent to the heteroatom. Our work in this area specifically using α,β-unsaturated iminiums[6] has provided a general solution to the regiochemical problems that occurred in previous studies,[1,2] and led to the development of an attractive approach for constructing complex heterocycles from simple intermediates.[7,8] Having established its synthetic feasibility, we have been exploring asymmetric variants of this formal cycloaddition. Recently, we successfully utilized chiral vinylogous amides as diketo equivalents to achieve high diastereomeric control at the stereocenter adjacent to the nitrogen atom.[9] These studies led us to explore another approach to stereoselective formal [3+3] cycloaddition using chiral cycloalkylidene α,β-unsaturated iminiums **2** (Scheme 1). This could lead to a novel concept in achieving stereocontrol at the spirocenter of heterocycles such as **4**.[10] We report here our studies of formal [3+3] cycloaddition reactions of chiral cycloalkylidene α,β-unsaturated iminiums with 4-hydroxy-pyrones.

Chiral cycloalkylidene α,β-unsaturated iminiums were generated in EtOAc at 85°C from corresponding aldehydes **5**–**9**[11,12] using 1.0 equiv. of piperidine and 1.0 equiv. of Ac_2O (Table 1).[6] Mixtures of *E* and *Z* were used throughout these reactions, but isomerization of the *Z* isomer to *E* was very fast under the reactions conditions. Subsequent reactions of these iminiums with 6-methyl-4-hydroxy-2-pyrone led to isomeric spiroheterocycles **10**–**14** in good yields (entries 1–5). However, the diastereomeric ratio was at best 70:30 (determined by ^{1}H NMR) for the compound **10** in favor of the isomer **a** as assigned by nOe experiments.[13] There is a noticeable inverse relationship between the ratio and size of the R groups. When R is changed from a Me to a *t*-Bu group, the ratio switched to 44:55



Scheme 1.

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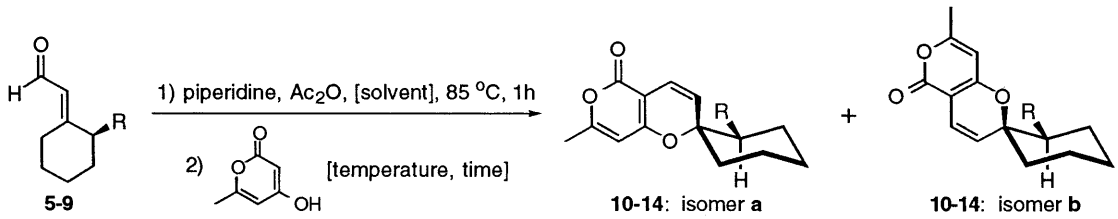
Table 1.



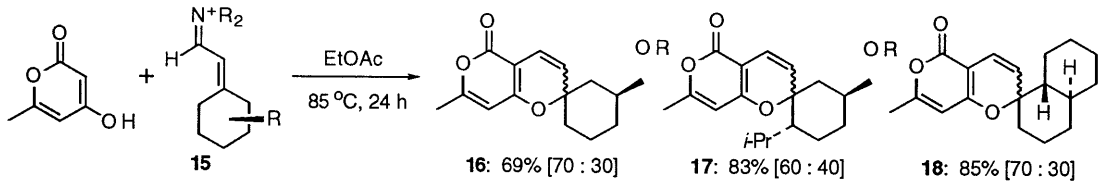
entry	enal	solvent	temperature	time	product	isolated yield	ratio of **a** : **b**
1	**5**: R = Me	EtOAc	85 °C	18 h	**10**: R = Me:	72 %	70 : 30
2	**6**: R = *n*-Bu	EtOAc	85	24	**11**: R = *n*-Bu:	78	60 : 40
3	**7**: R = Bn	EtOAc	85	24	**12**: R = Bn:	69	60 : 40
4	**8**: R = *t*-Bu	EtOAc	85	96	**13**: R = *t*-Bu:	55	45 : 55
5	**9**: R = OMe	EtOAc	85	18	**14**: R = OMe:	71	55 : 45
6	**5**	toluene	85 °C	18 h	**10**	62 %	66 : 34
7	**5**	$(CHCl)_2$	85	18	**10**	49	66 : 34
8	**5**	CH_3CN	85	18	**10**	47	60 : 40
9	**5**	HOAc	85	18	**10**	59	60 : 40
10	**5**	DMF	85	18	**10**	20	60 : 40
11	**5**	EtOAc	0 °C	18 h	**10**	30 %	20 : 80
12	**5**	EtOAc	25	18	**10**	30	25 : 75
13	**5**	EtOAc	40	18	**10**	48	34 : 66
14	**5**	EtOAc	85	18	**10**	72	70 : 30
15	**5**	EtOAc	120	18	**10**	70	60 : 40

in favor of the isomer **13b** (entry 4). In addition, there appears to be no heteroatom effect on the stereochemistry since the compound **14a** with R being a MeO group was obtained with a ratio of 55:45 in favor of the isomer **a** (entry 5), but only **14a** and **14b** can be separated via column chromatography.

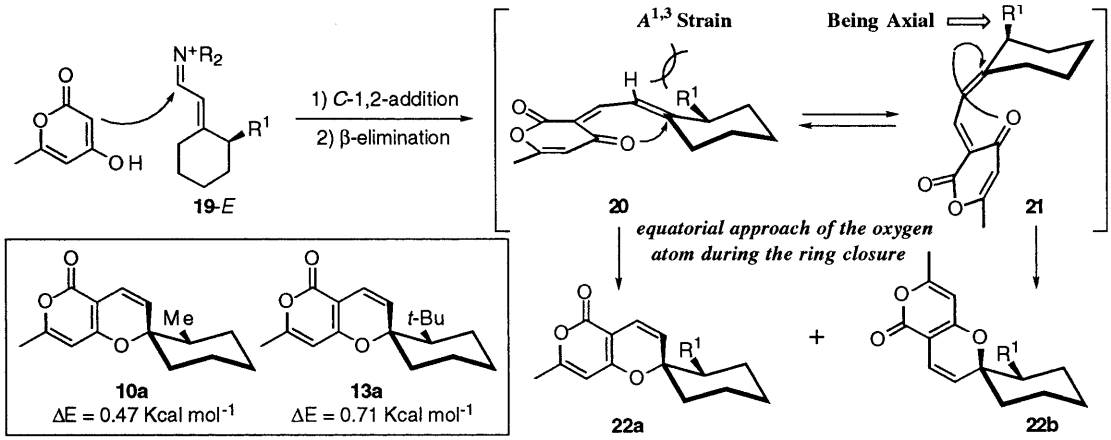
Our previous study using chiral vinylogous amides suggests that the observed stereoinduction is in part a result of thermodynamic control due to the reversibility of the 6π-electron electrocyclic ring closure.[9] To examine if these isomeric ratios also represent thermodynamic ratios, a mixture of **10a**/**b** (R = Me; 70:30) was heated at 220–240°C in toluene. The ratio only changed to 65:35 after heating for 72 h without noticeable material depreciation. When trying to obtain a single crystal of the pure **14a**, it was found that after storing at −10 to −20°C in ether/pentane for over 21 days, **14a** had actually epimerized presumably via iterative ring opening and closure at a very low temperature, leading to a mixture of **14a** and **14b** with a ratio of 1:1. These control experiments suggest that ratios in entries 1–3 and 5 closely represent thermodynamic ratios. However, when compound **13a**/**b** (R = *t*-Bu) was heated at 240°C for 72 h, the ratio remained the same at 45:55 in favor of **13b** which is the relatively much less stable isomer (see discussions later in Scheme 3).

Solvent polarities appear to have a minimum effect on the stereoselectivity of this reaction (entries 6–10). However, there is a noticeable temperature effect on the stereoselectivity. The reaction of 6-methyl-4-hydroxy-2-pyrone with the iminium generated from aldehyde **5** could proceed at lower temperatures such as 0 and 25°C (entries 11 and 12), although the conversion rate is slower as indicated by the lower isolated yields (starting materials were recovered). However, diastereomeric ratios were found to be eroded from 70:30 observed at 85°C (entry 1) to 20:80 and 25:75 at 0 and 25°C, respectively (entries 11 and 12). These observations suggest that the less stable isomer **10b** can be accessed via a kinetic ring closure at lower temperatures. Such a dependence on temperature during a 6π-electron electrocyclic ring closure has not been well noted for heteroatom substituted trienes.[14–16]

Finally, as shown in Scheme 2, utilizing chiral cycloalkylidene α,β-unsaturated iminiums (**15**) possessing



Scheme 2.



Scheme 3.

either a remote stereocenter, two stereocenters, or a more conformationally rigid decalin template did not lead to improved diastereoselectivities, although yields were quite high and compounds **16**–**18** are structurally interesting and potentially useful spiroheterocycles.

Although the stereoselectivities observed here are modest, it is still remarkable and deserves further comments. As shown in Scheme 3, the stereochemistry is likely determined after the Knoevenagel condensation involving the iminium **19**-*E* and during the 6π-electron electrocyclic ring closure.[14,15] Two possible 1-oxatriene intermediates, **20** and **21**, may be present in an equilibrium that could either favor the intermediate **20** when $A^{1,3}$ strain is minimum with small R^1 groups, or may lean toward **21** when $A^{1,3}$ strain is more severe, although the R^1 group is now also axial leading to less desired 1,3-diaxial interactions.

If a simple rotation (or a *torque* action) of the vinyl strand (exocyclic to the cyclohexane ring) in either direction during the ring closure can account for the formation of either the isomer **22a** or **22b**, then the observed stereoinduction is quite surprising since there is no apparent reason for any *torquoselectivity* or for the rotation in one direction to be favored over the other.[9,16,17] In addition, based on the reversibility of the 6π-electron electrocyclic ring closure,[9] the observed stereoselectivity here should simply be a result of thermodynamic distributions of final cycloadducts as indicated in the control studies. However, it does not agree well with the observation that when $R^1 = t$-Bu, the relatively much less stable isomer **13b** (by about 0.71 kcal mol^{-1} using Spartan™ AM1 calculations) became favored.

These observations suggest that there must be other factors in addition to simple thermodynamic equilibration in the stereochemical control during the ring closure of heteroatom substituted trienes.[14,15] Given the understanding that the direction in the ring closure of 1-oxatrienes or 1-azatrienes starts with the lone pair of the heteroatom,[14,15] and by applying Stork's postulation that heteroatoms prefer to approach toward the equatorial face of a cyclohexane template during pericyclic reactions,[18] a working model is proposed here to account for the observed stereoselectivity difference in **10** and **13**. This model is also based on the assumption that the more dominant intermediate in the equilibrium leads to the major isomer.

When $R^1 = Me$, the equilibrium should more distinctly favor the intermediate **20** with minimum $A^{1,3}$ strain. Thus, an equatorial approach of the oxygen atom during the ring closure via **20** would lead to the major isomer **22a** as observed for **10a**. On the other hand, when $R^1 = t$-Bu, both **20** and **21** suffer from severe $A^{1,3}$ strain and 1,3-diaxial interactions, respectively. Thus, the position of the equilibrium could shift toward the intermediate **21** by alleviating the $A^{1,3}$ strain,[18b] thereby leading to **20** and **21** in relatively equal amount. Subsequent equatorial approach of the oxygen atom during the ring closure could then afford both isomers **22a** and **22b** either in equal amount or slightly in favor of **22b** as observed for **13b**.

We have demonstrated that chiral cycloalkylidene α,β-unsaturated iminiums can be used in stereoselective formal [3+3] cycloaddition reactions leading to modest stereoinduction at the spirocenter. Despite the reversibility of 6π-electron electrocyclic ring closure, the thermodynamic product was not always favored. These observations led to understandings of other factors in the electrocyclic ring closure involving heteroatom substituted triene systems.

Acknowledgements

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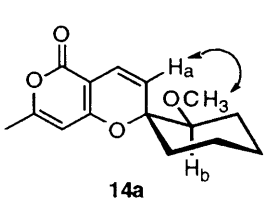
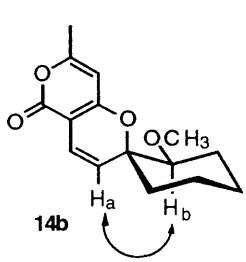
11. The cycloalkylidene α,β-unsaturated aldehydes **5**–**7** and **9** were prepared from their corresponding cyclohexanones in three steps: (1) Wittig olefination using $(EtO)_2PCH_2$-COOEt, (2) Dibal-H reduction, and (3) Ley's TPAP or Dess–Martin oxidation. The aldehyde **8** was prepared from 2-*t*-Bu-cyclohexanone in two steps: (1) vinylmagnesiumbromide, and (2) PCC oxidation.
12. All new compounds are characterized by ^{1}H NMR, ^{13}C NMR, FTIR, and mass spectroscopy. See Ref. 19 for spectroscopic and physical characterization of selected new compounds.
13. nOe experiments were carried out on pure isomers **14a** and **14b**. The following observations were made. Compounds



14a



14b

were assigned by direct correlations with **14** using ^{1}H NMR.

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19. Characterizations of selected new compounds: **10**: mp = 91–92°C, R_f = 0.40 (silica gel, 25% ethyl acetate/hexane); ^{1}H NMR (300 MHz, $CDCl_3$): isomer **a** δ 6.41 (d, 1H, J = 10.2 Hz), 5.85 (s, 1H), 5.20 (d, 1H, J = 10.2 Hz), 2.21 (s, 3H), 2.17 (m, 1H), 1.43–1.79 (m, 6H), 1.21–1.39 (m, 2H), 0.93 (d, 3H, J = 3.3 Hz); isomer **b** δ 6.49 (d, 1H, J = 10.2 Hz), 5.62 (s, 1H), 5.58 (d, 1H, J = 10.2 Hz), 2.21 (s, 3H), 2.19 (m, 1H), 1.43–1.79 (m, 6H), 1.21–1.39 (m, 2H), 0.91 (d, 3H, J = 3.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): isomer **a** δ 164.6, 162.3, 124.7, 116.9, 100.3, 86.0, 83.6, 41.1, 40.5, 37.0, 30.6, 28.9, 25.4, 20.2, 16.6; isomer **b** δ 165.1, 162.5, 119.3, 118.0, 110.3, 100.2, 97.9, 40.1, 38.7, 28.4, 25.0, 22.0, 20.1, 18.3, 16.2; IR (thin film) cm^{-1} 2932(s), 2855(s), 1716(s), 1646(s), 1560(s), 1447(m), 1387(m); mass spectrum (EI): m/e (% relative intensity) 246 (50) M^+, 203 (25), 190 (16), 189 (100), 176 (14); HRMS (EI): m/e calculated for $C_{15}H_{18}O_3$: 246.3042, measured 246.1257; anal. calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37; found: C, 72.99; H, 7.24. **13**: R_f = 0.54 (silica gel, 50% ethyl acetate/hexane); ^{1}H NMR (300 MHz, $CDCl_3$): isomer **a** δ 6.38 (d, 1H, J = 10.2 Hz), 5.80 (s, 1H), 5.78 (d, 1H, J = 10.2 Hz), 2.20 (s, 3H), 2.04 (m, 1H), 1.58–1.77 (m, 2H), 1.53–1.58 (m, 2H), 1.40–1.43 (m, 2H), 1.24–1.30 (m, 2H), 0.94 (s, 9H); isomer **b** 6.22 (d, 1H, J = 10.2 Hz), 5.70 (s, 1H), 5.46 (d, 1H, J = 10.2 Hz), 2.21 (s, 3H), 2.04 (m, 1H), 1.58–1.77 (m, 2H), 1.53–1.58 (m, 2H), 1.40–1.43 (m, 2H), 1.24–1.30 (m, 2H), 0.98 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): isomer **a** δ 171.1, 163.8, 162.5, 162.5, 121.1, 115.8, 100.4, 86.8, 55.0, 54.4, 42.9, 29.7, 29.4, 27.6, 26.8, 26.3, 22.1, 20.3; isomer **b** δ 168.5, 163.1, 162.6, 162.1, 129.1, 112.7, 100.4, 84.4, 55.0, 53.9, 39.8, 30.4, 27.8, 26.1, 25.6, 23.5, 20.2; IR (neat) cm^{-1} 2938(s), 2866(s), 2360(w), 1716(s), 1645(s), 1563(s), 1447(m), 1321(m); mass spectrum (EI): m/e (% relative intensity) 288 (22) M^+, 273 (5), 231 (12), 190 (15), 189 (100); anal. calcd for $C_{18}H_{24}O_3$: C, 74.97; H, 8.39; found: C, 74.74; H, 8.50. **14**: isomer **a**: mp = 65–67°C, R_f = 0.71 (silica gel, 50% ethyl acetate/hexane); isomer **b**: mp = 85°C, R_f = 0.60 (silica gel, 50% ethyl acetate/hexane); ^{1}H NMR (300

MHz, $CDCl_3$): isomer **a** δ 6.52 (d, 1H, $J=10.2$ Hz), 5.82 (s, 1H), 5.65 (d, 1H, $J=10.2$ Hz), 3.38 (s, 3H), 3.34 (dd, 1H, $J=4.2$, 10.5 Hz), 2.23 (s, 3H), 1.90–1.99 (m, 2H), 1.47–1.71 (m, 4H), 1.29–1.44 (m, 2H); isomer **b** δ 6.51 (d, 1H, $J=10.2$ Hz), 5.88 (s, 1H), 5.35 (d, 1H, $J=10.2$ Hz), 3.41 (s, 3H), 3.11 (dd, 1H, $J=4.2$, 10.5 Hz), 2.10 (s, 3H), 1.90–1.99 (m, 2H), 1.47–1.71 (m, 4H), 1.29–1.44 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): isomer **a** δ 171.1, 164.0, 162.4, 122.6, 120.5, 118.0, 117.7, 100.1, 82.3, 57.7, 35.3, 25.8, 21.7, 20.6, 20.1; isomer **b** δ 168.5, 163.0, 162.3, 131.3, 131.0, 117.7, 117.4, 100.4, 83.6, 58.0, 35.6, 25.2, 23.3, 21.7, 19.7; IR (thin film) cm^{-1} 2936(s), 2864(m), 1718(s), 1646(s), 1561(s), 1447(s), 1423(m), 1324(s), 1230(m); mass spectrum (EI): m/e (% relative intensity) 262 (47) M^+, 247 (37), 189 (100), 176 (20), 163 (17); anal. calcd for $C_{15}H_{18}O_4$: C, 68.69; H, 6.92; found: C, 68.88; H, 6.88. **17**: $R_f=0.65$ (silica gel, 50% ethyl acetate/hexane), $[\alpha]_D=-22.0°$ ($c=0.1$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): isomer **a** δ 6.40 (d, 1H, $J=10.5$ Hz), 5.75 (s, 1H), 5.18 (d, 1H, $J=10.5$ Hz), 2.17 (s, 3H), 1.79 (m, 4H), 1.41–1.58 (m, 3H), 1.06–1.20 (m, 2H), 0.88 (d, 3H, $J=7.8$ Hz), 0.82 (d, 3H, $J=6.3$ Hz), 0.76 (d, 3H, $J=6.9$ Hz); isomer **b** δ 6.40 (d, 1H, $J=10.5$ Hz), 5.75 (s, 1H), 5.66 (d, 1H, $J=10.5$ Hz), 2.17 (s, 3H), 1.79 (m, 4H), 1.41–1.58 (m, 3H), 1.06–1.20 (m, 2H), 0.88 (d, 3H, $J=7.8$ Hz), 0.82 (d, 3H, $J=6.3$ Hz), 0.76 (d, 3H, $J=6.9$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): isomer **a** δ 166.0, 163.8, 162.3, 125.1, 113.0, 100.4, 85.3, 51.5, 50.4, 49.2, 34.5, 28.0, 26.4, 23.4, 21.9, 20.2, 20.1, 17.9; isomer **b** δ 168.0, 164.7, 162.4, 121.1, 116.6, 97.6, 86.3, 52.9, 51.5, 50.7, 46.6, 33.6, 28.3, 27.4, 23.5, 22.1, 19.6, 28.6; IR (neat) cm^{-1} 2953(s), 2869(m), 1717(s), 1646(s), 1560(s), 1447(m), 1424(m), 1326(m); mass spectrum (EI): m/e (% relative intensity) 288 (15) M^+, 273 (9), 203 (100); anal. calcd for $C_{18}H_{24}O_3$: C, 74.70; H, 8.39; found: C, 74.44; H, 8.19. **18**: $R_f=0.62$ (silica gel, 50% ethyl acetate/hexane); ^{1}H NMR (300 MHz, $CDCl_3$): isomer **a** δ 6.37 (d, 1H, $J=10.2$ Hz), 5.80 (s, 1H), 5.12 (d, 1H, $J=10.2$ Hz), 2.18 (s, 3H), 1.48–1.74 (m, 6H), 1.40–1.44 (m, 2H), 1.03–1.29 (m, 4H), 0.86–1.06 (m, 4H); isomer **b** δ 6.43 (d, 1H, $J=10.2$ Hz), 5.74 (s, 1H), 5.57 (d, 1H, $J=10.2$ Hz), 2.18 (s, 3H), 1.48–1.74 (m, 6H), 1.40–1.44 (m, 2H), 1.03–1.29 (m, 4H), 0.86–1.06 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): isomer **a** δ 168.9, 165.2, 162.6, 124.5, 124.4, 100.4, 85.8, 51.9, 50.9, 49.6, 39.7, 39.6, 36.1, 33.3, 26.7, 26.6, 21.1, 20.1; isomer **b** δ 171.7, 164.5, 162.4, 120.1, 117.1, 100.2, 83.5, 51.8, 51.0, 45.5, 38.0, 37.9, 37.4, 33.3, 27.1, 26.2, 20.2, 19.9; IR (neat) cm^{-1} 2926(s), 2852(s), 1718(s), 1646(s), 1560(s), 1448(s), 1424(m), 1324(m); mass spectrum (EI): m/e (% relative intensity) 286 (65) M^+, 243 (53), 176 (25), 163 (240, 147 (18); anal. calcd for $C_{18}H_{22}O_3$: C, 75.50; H, 7.74; found: C, 75.48; H, 7.71.