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Electron Transfer-Initiated Diels−Alder Cycloadditions of 2′-Hydroxychalcones

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A number of biologically active prenylflavonoid natural products have been isolated from the mulberry tree and related plants.[1] For example, kuwanon G (**1**)[2] and multicaulisin (**2**)[3] are Diels−Alder cycloadducts between prenylflavonoid dienes and 2′-hydroxychalcones (Figure 1). Related Diels−Alder cycloadducts[4] include (−)-panduratin A (**3**)[5] and nicolaioidesin C (**4**).[6] To access these natural products, we wished to develop methodology to construct the cyclohexenyl chalcone nucleus employing electron-rich 2′-hydroxychalcone dienophiles.[7] In this Communication, we report examples of such [4 + 2] cycloadditions in a process likely involving electron transfer.[8]

Our studies began with model reactions of *trans*-2′-hydroxy chalcone **5** and 2,3-dimethylbutadiene **6** (Table 1). Owing to our inability to effect cycloaddition using Lewis acid-promoted ("LUMO" lowering) conditions,[9] we considered alternative modes of catalysis. On the basis of a recent report involving Diels−Alder dimerization of piperine,[10] we evaluated Co(I) catalysis[11] for cycloaddition. Initial studies revealed that cycloadduct **7** was observed as a single *trans* diastereomer using $\mathrm{CoI_2}$/1,10-phenanthroline (**8**)/$\mathrm{ZnI_2}$/$\mathrm{Bu_4NBH_4}$ (10/10/30/10 mol %) (entry 1),[12] which is in contrast to the 1,4-hydrovinylation of dienes and terminal alkenes employing a similar Co(I) catalyst system reported by Hilt and co-workers.[11c] Further investigation revealed that the amount of $\mathrm{ZnI_2}$ had a significant effect on the catalytic process (entries 1−3). Near quantitative conversion and isolated yield of **7** were obtained with $\mathrm{CoI_2}$/**8**/$\mathrm{ZnI_2}$/$\mathrm{Bu_4NBH_4}$ (10/10/60/10 mol %) as catalyst (entry 3). Lower conversion was obtained in the absence of ligand **8** (entry 4). Remarkably, cycloaddition in the absence of cobalt proceeded in slightly lower yield employing $\mathrm{ZnI_2}$ and a catalytic amount of $\mathrm{Bu_4NBH_4}$ (entry 5), either of which did not mediate the reaction alone (entries 6, 7). Moreover, no desired cycloadduct was observed with $\mathrm{Zn(BH_4)_2}$ as catalyst.

Further studies were undertaken to probe modifications of the chalcone dienophile (Table 2). Removal or methylation of the 2′-hydroxyl group (entries 1, 2) led to production of cycloadducts in lower overall yield in comparison to **7**. Reactions conducted without cobalt generally afforded lower isolated yields. Surprisingly, 4′-hydroxychalcone **13** did not undergo cycloaddition (entry 3), implying that chelation of **5** to $\mathrm{ZnI_2}$[13] may be necessary for cycloaddition. Additionally, a counterion effect for the Zn(II) source was observed (I > Br > Cl) with $\mathrm{ZnF_2}$, $\mathrm{Zn(OAc)_2}$, and $\mathrm{Zn(OTf)_2}$ proving to be unreactive.[12]

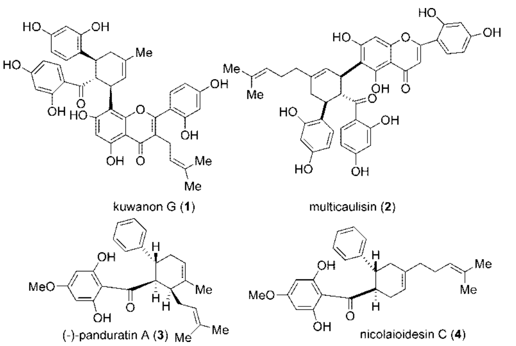
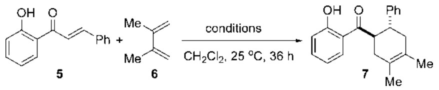


Figure 1. Select Diels−Alder natural products derived from 2′-hydroxychalcones.

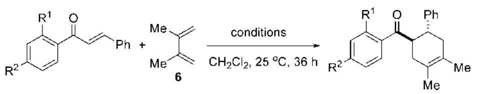
Table 1. Optimization of the Diels-Alder Cycloaddition of **5** and **6**[a]



entry	$\mathrm{CoI_2}$:**8**:$\mathrm{ZnI_2}$:$\mathrm{Bu_4NBH_4}$	conversion (%)[b]
1	10:10:30:10 mol %	23
2	10:10: 0:10 mol %	<2[d]
3	10:10:60:10 mol %	96(95[c])
4	10: 0:60:10 mol %	74
5	0: 0:60:10 mol %	85(82[c])
6	0: 0:60: 0 mol %	<2[d]
7	0: 0: 0:10 mol %	<2[d]

[a] See Supporting Information for experimental details. [b] Based on ^{1}H NMR integration (average of two experiments). [c] Isolated yield. [d] Not observed.

Table 2. Chalcone Modifications



entry	2′-hydroxychalcone	product	condition[a]	yield (%)[b]
1	**9**: R^1, R^2 = H	**10**	A	38
			B	28
2	**11**: R^1 = OMe, R^2 = H	**12**	A	55
			B	50
3	**13**: R^1 = H, R^2 = OH	**14**	A	<2[c]
			B	<2[c]

[a] Condition A: 10/10/60/10 mol % $\mathrm{CoI_2}$/**8**/$\mathrm{ZnI_2}$/$\mathrm{Bu_4NBH_4}$; condition B: 60/10 mol % $\mathrm{ZnI_2}$/$\mathrm{Bu_4NBH_4}$, see Supporting Information. [b] Isolated yield. [c] Not observed.

Encouraged by the success of the model reaction, we next evaluated a range of dienes and 2′-hydroxychalcones. [4 + 2] cycloadditions of select dienes and **5** were conducted in satisfactory isolated yield using $\mathrm{CoI_2}$/**8**/$\mathrm{ZnI_2}$/$\mathrm{Bu_4NBH_4}$ (10/10/60/10 mol %) at 40 °C (Table 3). Reactions without cobalt showed decreased reactivity (entries 1, 2). Notably, single regioisomers were observed for unsymmetrical dienes (entries 1, 4−6). Trisubstituted diene **25**, poorly reactive in conventional [4 + 2] cycloadditions,[14] afforded cycloadduct **26** in moderate yield (entry 6). A number of highly electron-rich 2′-hydroxychalcones were also investigated (Table 4). For these dienophiles, a 20/40/120/20 mol % $\mathrm{CoI_2}$/**8**/$\mathrm{ZnI_2}$/$\mathrm{Bu_4NBH_4}$ catalyst loading was found to be optimal. Lower yields were obtained with additional alkoxy substitution of the chalcone (entries 1, 3, and 5). The corresponding acetylated 2′-hydroxychalcones maintained high reactivity likely due to their less electron-rich character (entries 2, 4, and 6).

The utility of acetylated 2′-hydroxychalcones in [4 + 2] cycloadditions was further established by the total synthesis of nicolaioidesin C (**4**)[6] (Scheme 1). Acetylated chalcone **39** was prepared in four steps[12] (74% overall yield) from commercially available 2′,6′-dihydroxy-4′-methoxyacetophenone. Diels−Alder cycloaddition of **39** and myrcene

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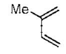
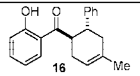
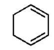
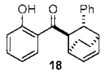
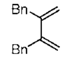
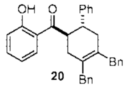
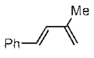
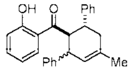
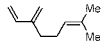
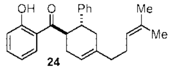
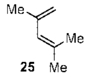
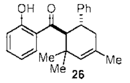
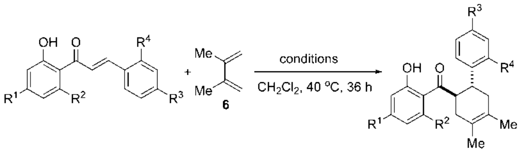
Table 3. Diels-Alder Reactions of **5** and Dienes

entry	diene	product	condition^{a}	yield(%)^{b}
1	 **15**	 **16**	A B	97^{c} 67^{c}
2	 **17**	 **18**	A B	97^{d} 65^{d}
3	 **19**	 **20**	A	99
4	 **21**	 **22**	A	97^{c,e}
5	 **23**	 **24**	A	96^{c}
6	 **25**	 **26**	A	55^{c}

^{a} Condition A: 10/10/60/10 mol% CoI_2/**8**/ZnI_2/Bu_4NBH_4, 40 °C; condition B: 60/10 mol% ZnI_2/Bu_4NBH_4, 40 °C, see Supporting Information. ^{b} Isolated yields. ^{c} Single regioisomer. ^{d} Single *endo* isomer. ^{e} 1.5:1 *exo*/*endo* ratio.

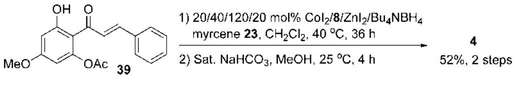
Table 4. Diels-Alder Reactions of Electron-Rich 2′-Hydroxychalcones



entry	2′-hydroxychalcone	product	condition^{a}	yield (%)^{b}
1	**27**: R^1=OMe, R^2,R^3,R^4=H	**28**	A B	68 36
2	**29**: R^1=OAc, R^2,R^3,R^4=H	**30**	A B	84 55
3	**31**: R^1,R^2=OMe, R^3,R^4=H	**32**	A	33
4	**33**: R^1,R^2=OAc, R^3,R^4=H	**34**	A	72
5	**35**: R^1,R^3,R^4=OMe, R^2=H	**36**	A	18
6	**37**: R^1,R^3,R^4=OAc, R^2=H	**38**	A	61

^{a} Condition A: 20/40/120/20 mol % CoI_2/**8**/ZnI_2/Bu_4NBH_4; condition B: 120/20 mol % ZnI_2/Bu_4NBH_4, see Supporting Information. ^{b} Isolated yields.

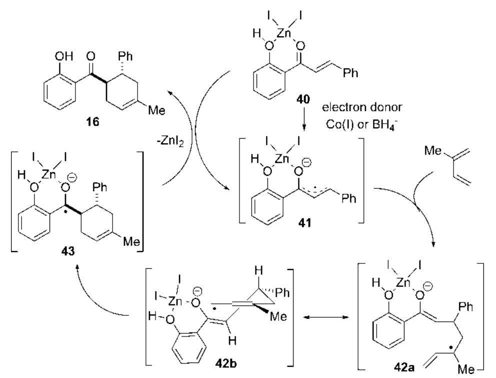
Scheme 1. Synthesis of Nicolaioidesin C



23, followed by saponification, afforded **4** as a single regioisomer in 52% yield. A 15% yield of **4** was observed in the corresponding reaction conducted without cobalt.[12]

Our finding that cycloadditions are observed with Bu_4NBH_4/ZnI_2[15] in conjunction with literature reports documenting electron transfer from Bu_4NBH_4 to acceptor substrates[16] suggests that radical anions[17] may be involved in the catalysis. As shown in Scheme 2, coordination of ZnI_2 to 2′-hydroxychalcone **5** may afford complex **40**. Preliminary cyclic voltammetry studies[12] indicate that **5** in the presence of ZnI_2 in CH_2Cl_2 shows two new irreversible reduction peaks ($E_{p,c}$ −0.59, 0.36 V vs SCE, respectively) compared to **5** alone ($E_{p,c}$ −1.25 V vs SCE). The apparent shift in the half-wave reduction potentials to less negative values is expected to parallel the promotion of electron transfer, and may be attributed to carbonyl activation by ZnI_2. In the presence of electron donors such as Co(I)[11a] or borohydride, **40** may undergo metal ion-promoted single electron transfer[18] to generate a chalcone radical anion **41**.[19] Regioselective addition of **41** to isoprene[20] should afford a stabilized, allylic radical **42a** which may undergo ring-closing cyclization to produce ketyl intermediate **43**. Loss of ZnI_2 from **43** and subsequent single electron transfer to another complex **40** may afford cycloadduct **16** and radical anion **41**, thereby restarting the catalytic cycle.

Scheme 2. Generalized Mechanism for [4 + 2] Cycloadditions



In summary, we have developed [4 + 2] cycloadditions of highly electron-rich 2′-hydroxychalcones and dienes using catalyst systems composed of electron donor (Co(I) or BH_4^-) and a Lewis acid (ZnI_2). Mechanistic studies and further applications toward the syntheses of other natural product targets are currently in progress and will be reported in due course.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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