Published in final edited form as:
J Am Chem Soc. 2008 July 23; 130(29): 9214–9215. doi:10.1021/ja803094u.

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] In order 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). Due to our inability to effect cycloaddition using Lewis acid-promoted (“LUMO” lowering) conditions,[9] we considered alternative modes of catalysis. Based on 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 CoI_2/1,10-phenanthroline (**8**)/ZnI_2/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 coworkers.[11c] Further investigation revealed that the amount of ZnI_2 had a significant effect on the catalytic process (entries 1-3). Near quantitative conversion and isolated yield of **7** were obtained with CoI_2/**8**/ZnI_2/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 ZnI_2 and a catalytic amount of Bu_4NBH_4 (entry 5), either of which did not mediate the reaction alone (entries 6, 7). Moreover, no desired cycloadduct was observed with $Zn(BH_4)_2$ 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 ZnI_2[13] may be necessary for cycloaddition. Additionally, a counterion effect for the Zn(II) source was observed (I > Br > Cl) with ZnF_2, $Zn(OAc)_2$, and $Zn(OTf)_2$ proving to be unreactive.[12]

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 CoI_2/**8**/ZnI_2/Bu_4NBH_4 (10/10/60/10 mol%) at 40 °C (Table 3). Reactions

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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.

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% CoI_2/**8**/ZnI_2/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 **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 (CH_2Cl_2) shows two new irreversible reduction peaks ($E_{p,c}$ −0.59 V, 0.36 V *vs.* SCE, respectively) compared to **5** alone ($E_{p,c}$ −1.25 V *vs.* SCE). The apparent shift in the halfwave 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**. Subsequent single electron transfer between **43** and another complex **40** may afford cycloadduct **16** and radical anion **41**, thereby restarting the catalytic cycle.

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 towards the syntheses of other natural product targets are currently in progress and will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment

Financial support from the NIH (GM-073855), Merck, and Wyeth is gratefully acknowledged. We thank Dr. Aaron Beeler and Ms. Susan Cunningham (CMLD-BU) for HPLC assistance, and Dr. Branko Mitasev (Boston University) and Dr. Bruce Branchaud (Invitrogen) for helpful discussions.

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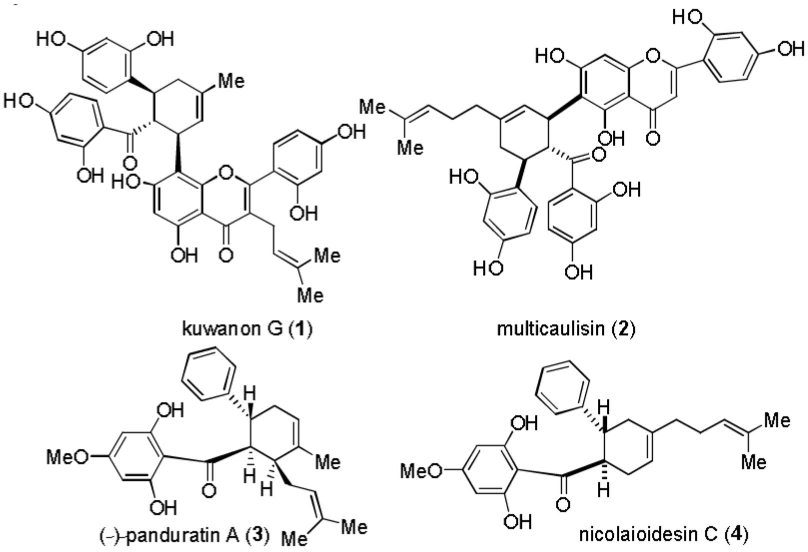


kuwanon G (**1**)

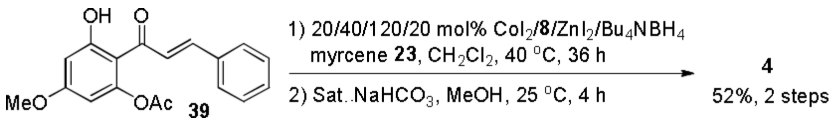
multicaulisin (**2**)

(-)-panduratin A (**3**)

nicolaioidesin C (**4**)

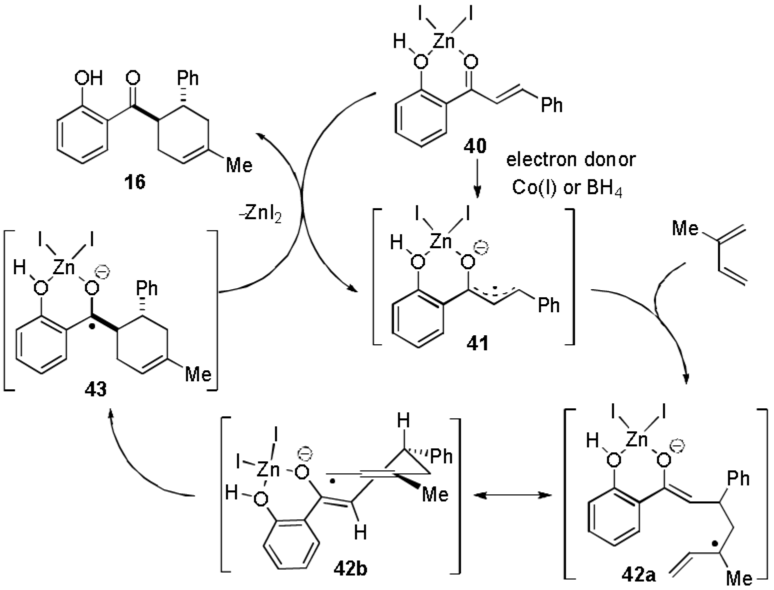
Figure 1.

Select Diels-Alder Natural Products Derived from 2′-Hydroxychalcones



Scheme 1.

Synthesis of nicolaioidesin C

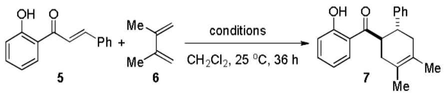


Scheme 2.

Generalized Mechanism for [4+2] Cycloadditions

Table 1

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



entry	CoI_2:8:ZnI_2:Bu_4NBH_4	conv. (%)[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.

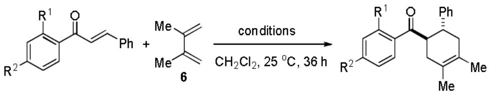
[b] Based on ^{1}H NMR integration (average of two experiments).

[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 B	38 28
2	**11**: R^1 = OMe, R^2 = H	**12**	A B	55 50
3	**13**: R^1 = H, R^2 = OH	**14**	A B	<2[c] <2[c]

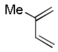
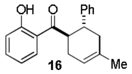
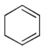
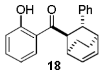
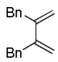
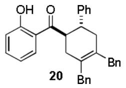
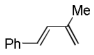
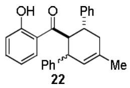
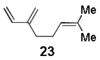
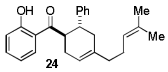
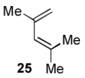
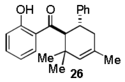
[a] Condition A: 10/10/60/10 mol% CoI_2/**8**/ZnI_2/Bu_4NBH_4; condition B: 60/10 mol% ZnI_2/Bu_4NBH_4, see Supporting Information.

[b] Isolated yield.

[c] Not observed.

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.

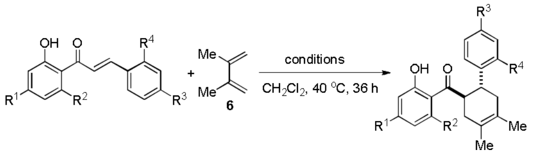
[c] Single regioisomer.

[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.