Asymmetric Catalysis

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Highly Enantio- and Regioselective Quinone Diels–Alder Reactions Catalyzed by a Tridentate [(Schiff Base)Cr^{III}] Complex**

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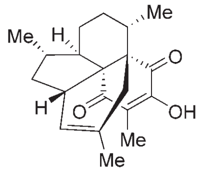
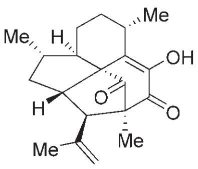
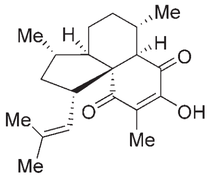
The octocoral *Pseudopterogorgia elisabethae* produces a variety of terpenoids, such as colombiasin A, elisapterosin B, and elisabethin A, that display diverse structural frameworks and bioactivities.[1] These secondary metabolites are possibly derived from a relatively simple common biosynthetic precursor; indeed, compounds such as **1**, which could undergo transformation to the more complex polycyclic natural products by divergent cyclization pathways, have been isolated from the same organism.[2] We became interested in developing efficient quinone Diels–Alder (qDA) catalysts for the preparation of intermediates related to **1** [e.g. **2**, Eq. (1)] as part of a unified biomimetic strategy for the syntheses of this family of natural products. Herein, we report a new method for highly enantioselective qDA reactions of quinones with a variety of dienes catalyzed by a new, monomeric [(Schiff base)Cr^{III}] complex.[3] In the following paper in this issue, we describe concise asymmetric catalytic syntheses of (−)-colombiasin A and (−)-elisapterosin B employing this methodology in the pivotal step.[4]



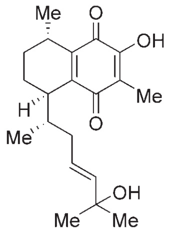
Colombiasin A



Elisapterosin B



Elisabethin A



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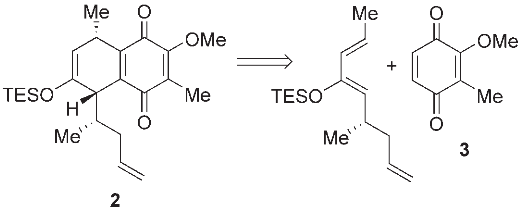
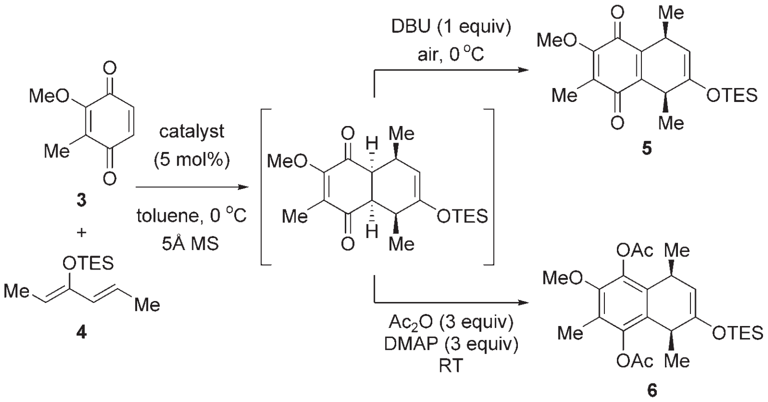


(1)

The reaction of quinones with dienes was the first class of cycloaddition pathways to be recognized by Diels and Alder,[5] and it has enjoyed widespread use in organic synthesis ever since.[6] However, until recently, effective catalysts for enantioselective qDA reactions have remained elusive. In seminal studies by Mikami and co-workers, Ti–binolate complexes were found to be effective for a limited range of substrates.[7,8] Subsequently, Evans and co-workers reported bis(oxazoline)–lanthanide complexes as asymmetric catalysts for reactions of methyl-substituted dienes with ester-substituted quinones capable of two-point binding.[9] Corey and co-workers described the use of cationic oxazaborilidines as enantioselective qDA catalysts that promote cycloaddition through single-point binding, with unsymmetrical quinones undergoing reaction by activation of the most Lewis basic carbonyl group.[10] Despite these important advances, identification of new and highly active qDA catalysts with broad substrate scope remains an important goal, particularly for accessing the diversity of cycloadducts of interest in the synthesis of biologically active compounds.



Scheme 1. Quinone Diels–Alder (qDA) reaction followed by in situ derivatization of the cycloadduct. TES = triethylsilyl; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; DMAP = 4-dimethylaminopyridine.

Our own catalyst development studies focused initially on the reaction of quinone **3** and diene **4**, a model relevant to the colombiasin A effort and designed to gauge both catalyst enantioselectivity and regioselectivity (Scheme 1). As the qDA cycloadduct obtained is not stable to air or silica gel at room temperature, further functionalization of the cycloadduct was performed to facilitate isolation and analysis. In situ air oxidation to the quinone **5**, or tautomerization and

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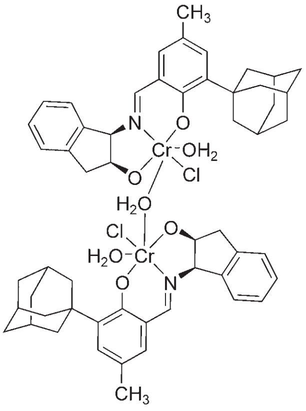
trapping with acetic anhydride to **6**, provided stable materials that could be handled easily using standard laboratory techniques.[11,12]

Recognizing the demonstrated ability of chiral [(Schiff base)Cr^{III}] catalysts to activate simple carbonyl compounds to cycloaddition through one-point binding mechanisms,[3,13] we explored their possible application to the qDA reaction. Preliminary studies with the broadly useful dimeric catalyst **8**[14] led to an intriguing and unexpected observation: catalysts prepared by different extractive workup procedures led to dramatically different results in the model reaction (Table 1).



8

Table 1: Effect of catalyst preparation conditions on the asymmetric qDA reaction of quinone **3** with diene **4**.[a]

Entry	Catalyst preparation		Quinone Diels–Alder			
	Extractive workup	Predominant species	Reaction time	Yield [%][b]	*ee* [%]	Regioselectivity[c]
1	H_2O	**8**	26 h	82	39	3.3:1
2	1 N HCl	**8** (+**9**)	35 min	70	96	12:1
3	3 N HCl	**9**	10 min	86	96	12:1

[a] Reactions were carried out with 5 mol% catalyst and 1.5 equiv diene **4** in the presence of crushed 5 Å molecular sieves in toluene (0.2 M). [b] Yield of isolated product after oxidation to quinone **5** and purification by silica gel chromatography. [c] Determined by HPLC analysis with commercial chiral stationary phases. See Supporting Information for full details.

We had found previously that synthesis of **8** accompanied by aqueous workup under either neutral or acidic (1 N HCl) conditions afforded catalysts that performed similarly in hetero-Diels–Alder (HDA) reactions, with the preferred method of catalyst preparation involving extraction with neutral H_2O.[15] Catalyst prepared in this manner is dimeric in the solid state[3b] and in solution.[16] However, the qDA reaction catalyzed by dimer **8** was sluggish and afforded products with low enantio- and regioselectivity, whereas catalyst prepared by acidic workup procedures afforded markedly improved results (Table 1, entry 2, 96% *ee*, 12:1 regioselectivity). This suggested that another chromium–ligand complex was being generated as a minor component under the acidic workup conditions, and that this impurity could be the active species in the quinone DA reaction. The conditions for catalyst preparation were therefore varied systematically to optimize the rate and enantioselectivity in the qDA reaction. Catalyst prepared by using 3 N HCl for the extractive workup proved most effective, affording product **5** with 96% *ee* and 12:1 regioselectivity after a reaction time of only 10 min. The major regioisomer was found to be that which would arise from Lewis acid coordination to the less Lewis basic carbonyl group, as would be required for our syntheses of colombiasin A and related natural products.[17]

Catalyst prepared by using the 3 N HCl workup protocol was recrystallized to afford single crystals suitable for X-ray analysis. In the solid state, complex **9** has a monomeric, pseudooctahedral structure with two water molecules and a chloride ligand in the coordination sphere of the metal (Figure 1).[18] This crystalline material was introduced in the qDA reaction between **3** and **4**, and it exhibited nearly identical selectivity to the bulk catalyst (95% *ee* versus 96% *ee*, 12:1 regioselectivity). Thus, Cr^{III} complexes derived from the same tridentate Schiff base ligand **7** are generated in different aggregation states depending only on the workup conditions (Figure 1), with the dimeric complex **8** being optimal for HDA reactions, and the monomeric complex **9** optimal for qDA reactions.[19] While the aggregation state of the active catalyst derived from **9** has not yet been elucidated, it is clear that it is distinct from the dimeric catalyst derived from **8**.[20]

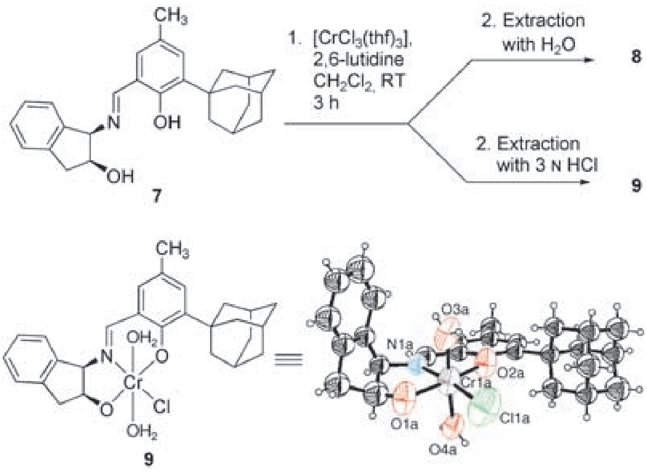
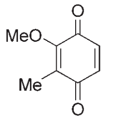
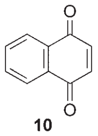
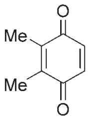
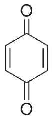


Figure 1. Preparation of catalysts **8** and **9**, and the X-ray crystal structure of **9**. Ellipsoids are drawn at the 30% probability level.

The scope of catalyst **9** in qDA reactions is illustrated by the examples in Tables 2 and 3. A variety of cycloadducts were prepared with greater than 90% *ee* in reactions carried out at 0 °C.[21] Despite the fact that quinone **3** undergoes reaction by apparent activation of the less basic carbonyl group adjacent to the methoxy group, bidentate chelation to the catalyst by the quinone is not required. Thus, naphthoquinone (**10**) and 2,3-dimethylquinone both underwent reaction with diene **4** to yield products in 94% *ee* (Table 2, entries 2 and 3). The same sense of stereoinduction was observed in reactions with **3** as in reactions with quinones incapable of two-point binding.[22]

Table 2: Enantio- and regioselective qDA reactions of a variety of quinones with diene **4**.[a]

Entry	Quinone	Temperature [°C]	Reaction time	Yield [%][b]	*ee* [%], regioselectivity[c]
1	 **3**	0	10 min	83 (q)	96, 12:1
2	 **10**	0	10 min	85 (q)	94
3[d]		0	30 min	75 (q)	94
4		−40	3 h	80 (hd)	86

[a] Unless noted otherwise, reactions were carried out using 5 mol% catalyst **9** with 1.1 equiv diene **4** in the presence of crushed 5 Å molecular sieves in toluene (0.2 M). [b] Yields of isolated quinone (q) or hydroquinone diacetate (hd, see Scheme 1), after purification by silica gel chromatography. [c] Determined by HPLC. [d] Reaction carried out at higher concentration (0.8 M in quinone). See Supporting Information for full details.

The reactions of a variety of dienes with napthoquinone (**10**) and methoxy-substituted quinone **3** were also examined (Table 3). Electronic activation of the diene by silyloxy or alkoxy substituents is not required, as dienes such as 1,3-pentadiene and 2-methyl-1,3-pentadiene were found to undergo reaction with acceptable rates to afford highly enantioenriched qDA products (Table 3, entries 1–3). Sterically demanding substituents at both the 1- and 3-positions of the diene are well tolerated: *i*Pr-substituted dienes **11** and **12** (Table 3, entries 6 and 8) required prolonged reaction times, but afforded products with high levels of enantioselectivity (90 and 96% *ee*, respectively). Reaction of diene **11** with quinone **3**, a model system for our synthetic efforts [see Eq. (1)], provided the required isomer with high regioselectivity (9:1).

In conclusion, a seemingly minor change in the conditions used for workup in the catalyst synthesis resulted in the identification of a new, monomeric [(Schiff base)Cr^{III}] complex with broad scope in the asymmetric qDA reaction. The utility of this catalyst in natural product synthesis is illustrated in the following communication, where we report the total syntheses of (−)-colombiasin A and (−)-elisapterosin B.[4] Further studies related to the scope and mechanism of catalyst **9** are underway.

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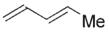
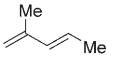
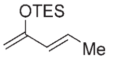
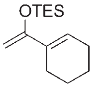
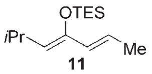
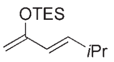
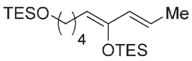
Table 3: Enantio- and regioselective qDA reactions of a variety of dienes with quinones **3** and **10**.[a]

Entry	Quinone	Diene	Temperature [°C]	Reaction time	Yield [%][b]	*ee* [%], regioselectivity[c]
1[d]	**10**		0	14 h	90 (hd)	90
2	**3**		−40	15 h	86 (hd)	93, >30:1
3	**10**		0	1.5 h	75 (hd)	91
4	**3**		−40	1 h	62 (hd)	97, 25:1
5[e]	**10**		0	25 min	91 (hd)	90
6[f,g]	**3**	 **11**	0	20 h	75 (q)	90, 9:1
7[f,g]	**10**		−20	43 h	88 (q)	97
8[d]	**10**	 **12**	−40	19 h	83 (hd)	96
9[d]	**10**		0	1 h	62 (hd)	91

[a] Unless noted otherwise, reactions were carried out with 5 mol% catalyst **9** and 1.5 equiv diene in the presence of crushed 5 Å molecular sieves in toluene (0.8 M). [b] Yields of isolated quinone (q) or hydroquinone diacetate (hd), after purification by silica gel chromatography. [c] Determined by HPLC. [d] 3 equiv diene. [e] 0.2 M [quinone]. [f] 10 mol% catalyst **9**. [g] 1.2 equiv diene. See Supporting Information for full details.

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[1] a) A. D. Rodriguez, C. Ramirez, *Org. Lett.* **2000**, *2*, 507–510; b) A. D. Rodriguez, C. Ramirez, I. I. Rodriguez, C. L. Barnes, *J. Org. Chem.* **2000**, *65*, 1390–1398; c) A. D. Rodriguez, E. Gonzalez, S. D. Huang, *J. Org. Chem.* **1998**, *63*, 7083–7091.
[2] a) A. D. Rodriguez, Y.-P. Shi, *Tetrahedron* **2000**, *56*, 9015–9023; b) for a discussion, see reference [1b].
[3] a) A. G. Dossetter, T. F. Jamison, E. N. Jacobsen, *Angew. Chem.* **1999**, *111*, 2549–2552; *Angew. Chem. Int. Ed.* **1999**, *38*, 2398–2400; b) K. Gademann, D. E. Chavez, E. N. Jacobsen, *Angew. Chem.* **2002**, *114*, 3185–3187; *Angew. Chem. Int. Ed.* **2002**, *41*, 3059–3061; c) R. T. Ruck, E. N. Jacobsen, *J. Am. Chem. Soc.* **2002**, *124*, 2882–2883; d) R. T. Ruck, E. N. Jacobsen, *Angew. Chem.* **2003**, *115*, 4919–4922; *Angew. Chem. Int. Ed.* **2003**, *42*, 4771–4774.
[4] See following paper in this issue: A. A. Boezio, E. R. Jarvo, B. M. Lawrence, E. N. Jacobsen, *Angew. Chem.* **2005**, *117*, in press; *Angew. Chem. Int. Ed.* **2005**, *44*, in press; DOI: 10.1002/anie.200502178.
[5] O. Diels, K. Alder, *Justus Liebigs Ann. Chem.* **1928**, *460*, 98–122.
[6] a) K. C. Nicolaou, S. A. Snyder, T. Montagnon, G. Vassilikogiannakis, *Angew. Chem.* **2002**, *114*, 1742–1773; *Angew. Chem. Int. Ed.* **2002**, *41*, 1669–1698; ; b) Q.-Y. Hu, G. Zhou, E. J. Corey, *J. Am. Chem. Soc.* **2004**, *126*, 13708–13713.
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[8] The Mikami catalytic qDA was applied successfully in the Nicolaou synthesis of colombiasin A: K. C. Nicolaou, G. Vassilikogiannakis, W. Magerlein, R. Kranich, *Chem. Eur. J.* **2001**, *7*, 5359–5371.

[9] D. A. Evans, J. Wu, *J. Am. Chem. Soc.* **2003**, *125*, 10162–10163.

[10] D. H. Ryu, G. Zhou, E. J. Corey, *J. Am. Chem. Soc.* **2004**, *126*, 4800–4802, and references therein.

[11] Y. Naruta, K. Maruyama in *The Chemistry of the Quinoid Compounds, Vol. II* (Eds.: S. Patai, Z. Rappoport), Wiley, Chicester, **1988**, pp. 242–336.

[12] All yields therefore reflect a one-pot, two-step procedure. ^{1}H NMR analyses of the unpurified qDA reaction mixtures suggest that the cycloadditions are clean and that product loss occurs during workup.

[13] Cr^{III}–salen complexes have also been shown to catalyze enantioselective Diels–Alder reactions of 1-amino-1,3-butadienes. See: Y. Huang, T. Iwama, V. H. Rawal, *Org. Lett.* **2002**, *4*, 1163–1166, and references therein.

[14] For selected examples of the application of **8** in target-oriented synthesis, see: a) FR901464: C. F. Thompson, T. F. Jamison, E. N. Jacobsen, *J. Am. Chem. Soc.* **2000**, *122*, 10482–10483; C. F. Thompson, T. F. Jamison, E. N. Jacobsen, *J. Am. Chem. Soc.* **2001**, *123*, 9974–9983; b) fostriecin: D. E. Chavez, E. N. Jacobsen, *Angew. Chem.* **2001**, *113*, 3779–3782; *Angew. Chem. Int. Ed.* **2001**, *40*, 3667; ; c) ambruticin: P. Liu, E. N. Jacobsen, *J. Am. Chem. Soc.* **2001**,*123*, 10772; d) apicularen A: A. Bhattacharjee, J. K. De Brabander, *Tetrahedron Lett.* **2000**, *41*, 8069–8073; e) laulilamide: I. Paterson, C. De Savi, M. Tudge, *Org. Lett.* **2001**, *3*, 3149–3152; f) iridoid natural products: D. E. Chavez, E. N. Jacobsen, *Org. Lett.* **2003**, *5*, 2563–2565; g) thiomarinol antibiotic: X. Gao, D. G. Hall, *J. Am. Chem. Soc.* **2005**, *127*, 1628–1629.

[15] D. E. Chavez, E. N. Jacobsen, *Org. Synth.*, in press.

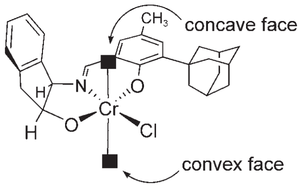
[16] Kinetic and mechanistic studies of HDA reactions promoted by **8** indicate a dimeric catalyst structure both in the ground state and in the rate-determining transition state. R. T. Ruck, E. N. Jacobsen, unpublished results.

[17] See Supporting Information for details. Cationic oxazaborolidine catalysts afford products with opposite regioselectivity (see ref. [10]).

[18] Details of the crystal structure analysis are provided as Supporting Information. CCDC-262884 (**9**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[19] For example, the inverse electron demand hetero-Diels–Alder reaction employed in the first step of the colombiasin synthesis (see preparation of **6** in Scheme 3 in reference [4]) proceeded with 78 % *ee* with monomeric catalyst **9** and 93 % *ee* with dimeric catalyst **8**.

[20] If a monomeric catalyst structure analogous to that of **9** is assumed in the *ee*-determining step with one of the water molecules replaced by the quinone substrate, then the intriguing question arises about which of the two stereochemically inequivalent binding sites is engaged. Qualitatively, it would appear that binding to the inner, concave face of the catalyst would be most consistent with the high enantioselectivities observed in the qDA.



[21] Reactions carried out at −40 °C generally afforded higher enantioselectivity, albeit with slower rates; these conditions were employed for those substrates that were generated in $<$ 90 % *ee* at 0 °C. For example, the reaction of benzoquinone with diene **4** afforded cycloadduct in 79 % *ee* at 0 °C, and 86 % *ee* at −40 °C (Table 2, entry 4).

[22] See Supporting Information for details.