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ASYMMETRIC QUINONE-BASED DIELS-ALDER REACTIONS

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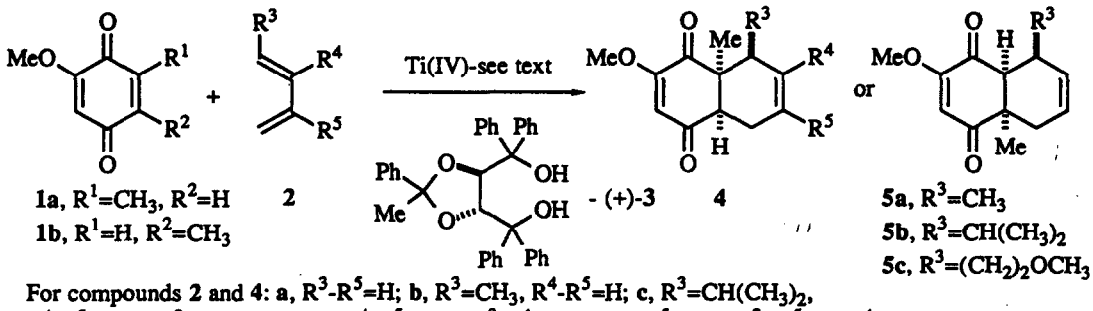
ABSTRACT. Asymmetric Diels-Alder reactions of 2-methoxy-1,4-benzoquinones utilizing a chiral Ti(IV) complex as a Lewis acid promoter are reported.

The Diels-Alder reaction is generally acknowledged as one of the most powerful synthetic tools. 1,4-Benzoquinones have particular notoriety in these reactions due to their superb reactivity, their high and predictable stereoselectivity and the broad utility of the products in stereoselective synthesis of a wide variety of targets through routine modification.[1] In view of this, it is surprising that asymmetric quinone-based Diels-Alder reactions, particularly those involving chiral catalysts, have received relatively little attention.[2] Reports from Narasaka and co-workers[3a-d] on asymmetric Diels-Alder reactions of oxazolidinone dienophiles catalyzed by chiral complexes of the type $(RO)_2TiCl_2$ and our own recent studies on the application of these complexes to asymmetric reactions of quinones with styrenes[4] led us to examine quinone Diels-Alder reactions. The recent reports of Corey[3e], Oh[3f] and Quinkert[3g] on Diels-Alder reactions utilizing similar chiral Lewis acid catalysts prompts us to report our results at this time.

Addition of 2-methoxy-1,4-benzoquinones **1a/b** to a complex formed from $TiCl_4$, $Ti(OiPr)_4$ and the (+)-diol **3** (*vide infra*) followed by dienes **2** gave the Diels-Adler products **4** or **5** in excellent yield and moderate to excellent stereoselectivity and enantioselectivity (Table). The high crystallinity of the products is a notable advantage. In several cases (entries 1-5), the experiments have been scaled up to provide gram quantities of a single enantiomer by simple recrystallization of the reaction products (EtOAc: hexanes or THF: hexanes). The enantiometric purity of the products was determined by 500-MHz ^1H NMR analysis with (*R*)-(-)-2,2,2-trifluoro-1-(9-anthryl)ethanol as a chiral solvating agent. The assignment



1a, R^1=CH_3, R^2=H
1b, R^1=H, R^2=CH_3

2

- (+)-**3**

4

5a, R^3=CH_3
5b, R^3=$CH(CH_3)_2$
5c, R^3=$(CH_2)_2OCH_3$

For compounds **2** and **4**: **a**, R^3-R^5=H; **b**, R^3=CH_3, R^4-R^5=H; **c**, R^3=$CH(CH_3)_2$, R^4-R^5=H; **d**, R^3=$(CH_2)_2OCH_3$, R^4-R^5=H; **e**, R^3-R^4=-$(CH_2)_4$-, R^5=H; **f**, R^3=R^5=H, R^4=CH_3; **g**, R^3=R^5=H, R^4=$CH(CH_3)_2$.

of relative stereochemistry of the major isomers was established by NOE and HMBC NMR experiments (Figure).[5] To assign the absolute configuration of the products, compound **4b** was converted to **6**, the structure of which was determined by single crystal X-ray analysis.[6] Since the sign of the specific rotations, the shape of the ORD curves and the ^1H NMR spectra in the presence of the chiral solvating agent are similar for all of the Diels-Alder products **4a-g**, their configurations are likely the same as well.

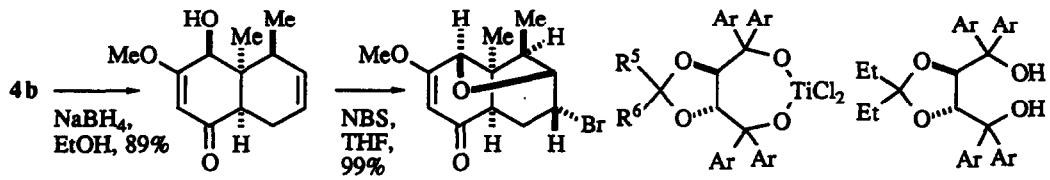
The method for preparation of the Ti(IV)-diol complex used in these reactions is critical. Best results to date[7] involve the formation of a "Ti(IV)-solid" by precipitation of a light yellow powder from a 5:1 mixture of $TiCl_4$ and $Ti(OiPr)_4$ in CH_2Cl_2 at room temperature. The structure of this material is not known. For the Diels-Alder reactions, the diol is added to the "Ti(IV)-solid" in a 1.5:1 ratio by weight in $PhCH_3$ at -78°C followed by warming to room temperture and then re-cooling to -78°C. A solution of the quinone in CH_2Cl_2 and then the diene are added at -78°C; the diol:quinone:diene ratio is 2:1:2. The excess diol is readily reclaimed on chromatography of the crude reaction mixture.

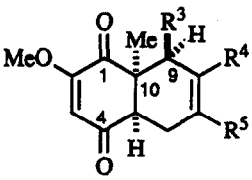
Narasaka and Corey have reported asymmetric catalysis of *N*-α,β-alkenoyl-oxazolidinone Diels-Alder reactions[3a-e] utilizing complexes identified as **7** and **8** (prepared from **3** and **9**, respectively) and Oh[3f] has reported asymmetric Diels-Alder reactions of methyl acrylate and dimethyl fumarate with stoichiometric quantities (or larger) of a Ti(IV)-(*R,R*)-hydrobenzoin complex. There are apparent differences, however, between the diol complex formed from the "Ti(IV)-solid" as described above and the Narasaka/Corey complexes.[8] We have prepared the catalyst **7** by the Narasaka method and successfully reproduced the asymmetric 3-(2-butenoyl)-2-oxazolidinone/cyclopentadiene reaction. In our hands, stoichiometric amounts of complex **7** failed to promote the quinone Diels-Alder reactions at -78°C although upon warming a reaction of **1a** with **2a** to room temperature, a 55% yield of **4a** was found with less than 20% ee. Catalytic quantities of the asymmetric Ti(IV) complex **8** as prepared by the Corey method did promote the quinone Diels-Alder reactions, however, the reactions were slower, required higher temperatures (room temperature) and the yields and ee's were lower (~45% ee) than those reported in the Table. Interestingly, use of stoichiometric amounts of catalyst **8** in reactions of quinone **1a** with diene **2a** gave **4a** in only 5% ee. More importantly from the standpoint of synthetic design is that the complexes formed from either diol **3** or **9** by the Corey method gave the (-)-antipode of the quinone Diels-Alder product **2a** whereas the complex formed from either diol **3/9** and the "Ti(IV)-solid" gave the (+)-antipode.[9] Finally, as noted above, the Narasaka and Corey complexes are true catalysts in promoting reactions of the oxazolidinone dienophiles; ≤20 mol% of the complexes (with respect to the dienophile) are required. Attempts to employ catalytic quantities of the "Ti(IV)-solid"-diol **3** complex in the quinone Diels-Alder reactions either with or without added 4 Å molecular sieves[3a] failed (~5% ee). Similarly, in Oh's work[3f], the acrylate and fumarate Diels-Alder reactions required at least stoichiometric amounts of the chiral Ti(IV)-dihydrobenzoin complex for good asymmetric induction.

Table. Asymmetric Diels-Alder Reactions of 2-Methoxy-1,4-benzoquinones with Dienes.[a]

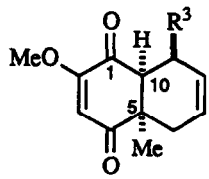
Entry	Quinone	Diene	Product	% Yield	Diastereomeric or Regioisomeric Ratio[b]	% ee[c]
1	1a	2a	4a	88	na	63
2	1a	2b	4b	94	>20:1[d]	80
3	1a	2c[e]	4c	90	>20:1	92
4	1a	2d	4d	91	18:1	81
5	1a	2e	4e	100	>20:1	68
6	1a	2f	4f	94	8.2:1	67
7	1a	2g	4g	97	8.9:1	82
8	1b	2b	5a	89	>20:1	66
9	1b	2c[e]	5b	76	>20:1	54
10	1b	2d	5c	89	31:1	48

[a] All reactions were conducted at -78°C in $PhCH_3$:CH_2Cl_2 (~5:2; the CH_2Cl_2 is required for quinone solubility). [b] Determined by 500 MHz ^{1}H NMR. The structure of the minor isomer was not determined. [c] Determined by 500 MHz ^{1}H NMR in the presence of (*R*)-(-)-2,2,2-trifluoro-1-(9-anthryl)ethanol as a chiral solvating agent. [d] Only one isomer was detected by 500 MHz ^{1}H NMR. [e] The diene was used as a 2.5:1 ratio of trans:cis isomers.





4a: H-5, 5.8%; 4b: H-5, 5.5%; H-9, 5.4%; R^3, 0%; 4c: H-5, 8%; H-9, 8.1%; 4d: H-5, 6.3%; H-9, 7.8%; 4e: H-5, 7.3%; H-9, 8.0%; 4f: H-5, 5.7%.



5a: H-10, 7.1%. 5b: H-9, 4.1%; H-10, 4%. 5c: H-9, 10%; H-10, 6.3%.

Figure. Summary of representative NOE enhancements upon irradiation of the Me group at C-10 in adducts **4** and of the C-5 Me group in **5**. The chemical shifts of the hydrogen signals were determined by HMBC experiments, when necessary.

In summary, products from 2-methoxy-1,4-benzoquinone Diels-Alder reactions are available in large quantity and moderate to excellent ee utilizing the method reported herein. Although the chiral Ti(IV)-diol complex used would seem to be similar to other Ti(IV)-diol complexes reported previously, there appear to be significant differences. Efforts are underway to identify the structure of the "Ti(IV)-solid" and the Ti(IV)-diol complex and to modify the system so that catalytic quantities of the complexes are effective in promoting the asymmetric quinone Diels-Alder reactions.

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6. The configuration was confirmed by the anomalous dispersion effect.
7. Initial investigations utilized CH_2Cl_2 or toluene solutions of $TiCl_4$ and $Ti(OiPr)_4$ mixed just prior to addition of the diol. The $TiCl_4$:$Ti(OiPr)_4$: diol ratio was 1:1:1. Although this system did give enantionmerically enriched products in reactions of the dienes with the quinones, the results were not as consistently reproducible as those with the "Ti(IV)-solid".
8. The main difference is apparently due to the nature of the Ti(IV) before addition of the diol. The ^1H and ^{13}C -NMR spectra of the "Ti(IV)-solid" [^1H-(300 MHz, $CDCl_3$) δ 1.60 (d, J=6Hz, 7H), 5.15 (septet, J=6Hz, 1H); ^{13}C-(125 MHz, $CDCl_3$) δ 24.76, 95.55] is quite different than that of $TiCl_2(OiPr)_2$ [^1H-(300 MHz, $CDCl_3$) δ 1.42 (d, J=6Hz, 7H), 4.85 (septet, J=6Hz, 1H); $^{13}C^{10}$-(δ 25.5, 88] which is used by Narasaka and is formed as a white solid from a 1:1 mixture of $TiCl_4$ and $Ti(OiPr)_4$ in hexane.
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