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# Asymmetric Reaction of *p*-Quinone Diimide: Organocatalyzed Michael Addition of α-Cyanoacetates

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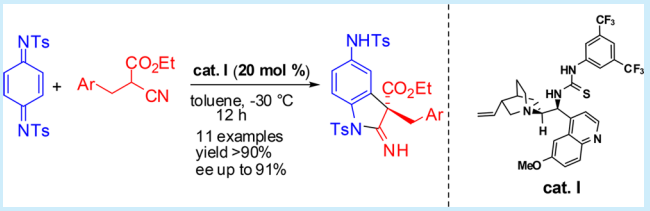
Supporting Information

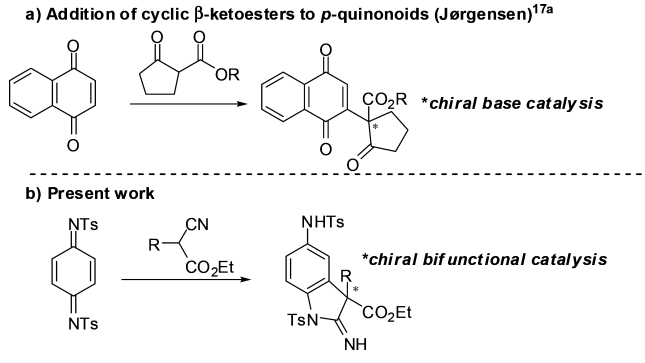
**ABSTRACT:** Hitherto unknown catalytic enantioselective transformation of *p*-quinone diimides is achieved using chiral bifunctional organic molecules. Bifunctional thiourea compounds catalyze the Michael addition of cyanoacetates with excellent yields and enantioselectivities. The initially formed Michael adducts undergo cyclization to yield functionally rich, fused cyclic imidines bearing a quaternary benzylic chiral center. Density functional theory calculations of the competing transition states (TSs) were carried out to explain the observed stereochemical outcome.




Quinones are interesting structural motifs and have attracted immense attention due to their biological relevance, chemical versatility, and industrial importance.[1] Their unique electronic properties, which play a crucial role in the biological world, often render quinones nonamenable to a variety of chemical reactions that proceed well with other electron-deficient alkenes. Cycloaddition and nucleophilic addition are the most widely used functional transformations of quinones. The chemistry of *p*-quinone diimines/diimides, in stark contrast to quinones, has garnered only limited attention, although their existence dates back to the early 20th century.[2] The bulk of the quinone imide chemistry, akin to their oxa analogues, has centered around cycloaddition and nucleophilic addition. Nucleophilic additions of phenol and thiophenol, [3 + 2] cycloaddition of diazomethane, Freidel−Crafts reaction with benzene, etc. were reported by Adam's group.[3] Silyl enol ethers,[4] enamines,[5] sodium arenesulfinate,[6] azide,[7] ketene *S,N*-acetals,[8] and piperidine[9] have been reported to add to quinone diimides, often promoted by Lewis/mineral acids. Recent reports indicate that allyltin[10] and allylsilane[11] undergo conjugate addition to *p*-quinone diimides. The addition of active methylene compounds, under alkaline conditions, to *p*-quinone imides was also studied by Adams et al., although the exact nature of the adducts was not fully established.[12] Catalytic enantioselective transformation of *p*-quinone diimides is one area that still remains in total oblivion, despite some data indicating that more than 80% of FDA-approved small molecule drugs bear at least one nitrogen atom.[13] Moreover, the direct functionalization of diiminoquinonoid has been employed to improve the poor processability of polyaniline (PAN), which is an important conducting polymer.[14]

Organocatalysis, in general, and the enantioselective variant, in particular, has recently garnered a lot of interest.[15] One class of reactions that has benefited immensely with the advent of organocatalysis is the conjugate addition of nucleophiles to electron-deficient alkenes,[16] and a large number of carbon and heteroatom nucleophiles have been utilized in these reactions. However, literature reports on the organocatalyzed asymmetric transformations of benzoquinonoid compounds are few and far between, probably due to their propensity to form electron/charge transfer complexes with many of the catalyst classes. Among the quinonoids, quinones have attracted the most attention,[17] while quinone monoimides[18] have also garnered some interest (Scheme 1). It is worth noting that in the majority of the reports available in the literature, *p*-naphthoquinone is the quinonoid compound of choice. More recently, enantioselective transformations of *o*-quinones, *o*-quinone monoimides, and *o*-quinone diimides have been achieved by Lectka's group.[19]

**Scheme 1. Organocatalyzed Carbon Acid Addition to *p*-Quinonoids**

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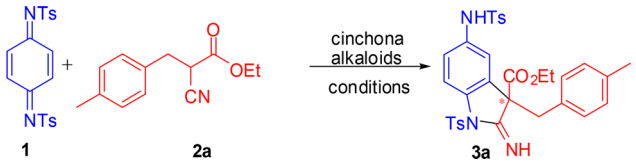
Jørgensen's group has studied the enantioselective addition of enamines to in situ generated *p*-quinonoids. *p*-Quinone and *p*-quinone monoimide furnished the corresponding Michael adducts, while *p*-benzoquinone diimides did not participate in the reaction.[17d] Intrigued by the conspicuous absence of literature on *p*-quinone diimides as substrates in catalytic asymmetric transformations, we initiated a study on the enantioselective reactions of this class of compounds catalyzed by chiral organic molecules, and our initial findings are reported herein.

Jørgensen's seminal paper on the addition cyclic ketoesters to *p*-quinones provided us with the starting point, and thus, we initially employed the cinchona alkaloids as catalysts. Under various reaction conditions, *p*-benzoquinone ditoluenesulfonimide (**1**) and *α*-substituted cyanoacetate (**2a**) were reacted in the presence of a catalytic amount of cinchonine, cinchonidine, quinine, and quinidine. At −30 °C in toluene, the reaction afforded the adduct **3a** in excellent yield but with poor selectivity (Table 1).

**Table 1. Cinchona Alkaloid Catalyzed Cyano Ester Addition to *p*-Quinone Diimide**[a]



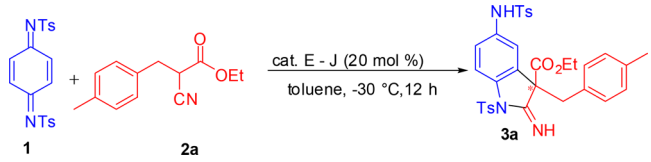

**1** **2a** **3a**

| entry | cat. | solvent | temp (°C) | yield[b] (%) | ee[c] |
|---|---|---|---|---|---|
| 1 | A | toluene | 0 | >90 | |
| 2 | A | toluene | −20 | >90 | −14 |
| 3 | A | toluene | −30 | >90 | −20 |
| 4 | B | toluene | −30 | >90 | 25 |
| 5 | C | toluene | −30 | >90 | 20 |
| 6 | D | toluene | −30 | >90 | −25 |
| 7 | B | *o*-xylene | −30 | >90 | 20 |
| 8 | B | $CH_2Cl_2$ | −30 | 80 | |
| 9 | B | $CHCl_3$ | −30 | >90 | |
| 10 | B | THF | −30 | | |

[a]Reaction conditions: **1** (0.12 mmol), **2a** (0.12 mmol), catalyst (20 mol %) in 2 mL of solvent. [b]Isolated yield after column chromatography. [c]Determined by HPLC using a chiral column (Chiralpak-IC3).

The structural analysis of the adduct **3a** revealed that the reaction sequence involved a cyclization step (aza-Pinner type) subsequent to the initial Michael addition, forming a cyclic amidine, the bis-nitrogen analogue of *γ*-lactone. Interestingly, the functionally rich product bears a quaternary chiral center directly attached to a phenyl ring.[20] The choice of *α*-substituted cyanoacetate (**2a**) as the active methylene compound was deliberate, as it offers a variety of advantages such as high reactivity, functional group abundance, and configurational stability of the newly formed quaternary center.[21] It is worth mentioning that the reaction of *α*-unsubstituted cyanoacetates with *p*-quinone diimide **1** under identical reaction conditions resulted in an intractable mixture. In spite of the mediocre selectivity observed, the initial results encouraged us to pursue the reaction further, since the prior attempts to carry out even the achiral version of this reaction under various conditions did not lead to any meaningful products.[12] We then turned our attention to chiral bifunctional organic molecules.[22] Endowed with complementary hydrogen-bonding functionalities, these chiral bifunctional molecules can, in principle, activate both the electrophilic and nucleophilic counter parts—the *p*-quinone diimide and the active methylene compound—while possibly transferring the inherent stereochemical information. To identify the best conditions, we carried out a catalyst screen, and our results are compiled in Table 2.

**Table 2. Reaction of Cyanoacetate with *p*-Quinone Diimide: Catalyst Screen**[a]




**1** **2a** **3a**

| entry | cat. | yield[b] (%) | ee[c] |
|---|---|---|---|
| 1 | E | >90 | −38 |
| 2 | F | >90 | −41 |
| 3 | G | >90 | 65 |
| 4 | H | >90 | 85 |
| 5 | I | >90 | 91 |
| 6 | J | >90 | −60 |

[a]Reaction conditions: **1** (0.12 mmol), **2a** (0.12 mmol), catalyst (20 mol %) in 2 mL of toluene. [b]Isolated yield after column chromatography. [c]Determined by HPLC using a chiral column (Chiralpak-IC3).

We have employed squaramide and thiourea-derived bifunctional catalysts **E**–**J** (Figure 1). Although the squaramide

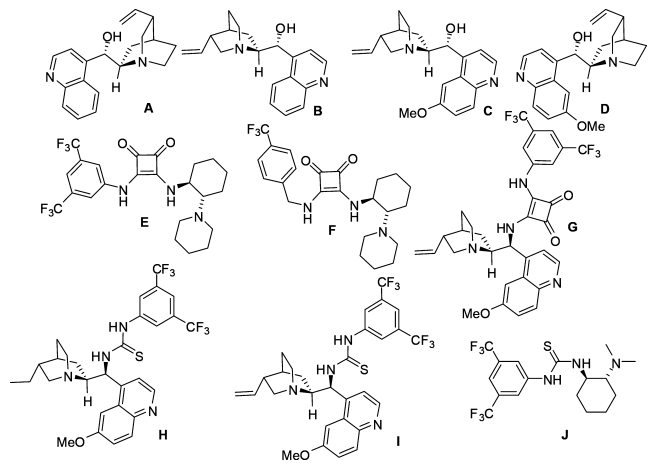



**Figure 1.** Bifunctional catalysts employed in the study.

catalysts were better when compared to the cinchona alkaloids (**A**–**D**), the selectivity was only moderate (entries 1–3; Table 2). Gratifyingly, the thiourea catalysts were proven ideal with cinchona alkaloid derived molecules **H** and **I** affording the product in excellent yield and selectivity. The selectivity was moderate with Takemoto catalyst **J**. Our efforts to isolate the initial Michael adduct were unsuccessful, and in all cases, the Michael–aza Pinner product resulted. We believe that the conjugate acid of the hydrogen-bond acceptor of the bifunctional catalyst (a quaternary ammonium species) would further act as a proton source and catalyze the cyclization step.

Having identified Soós' catalyst (**I**) as the best of the group, we proceeded to explore the generality of the reaction by employing



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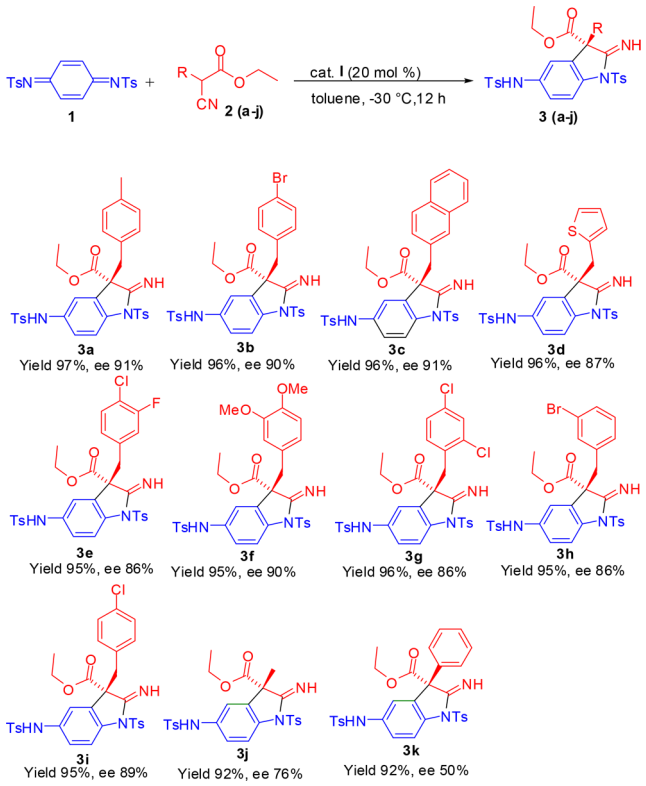
different cyano esters, as illustrated in Scheme 2. It is evident that catalyst **I** is extremely efficient in promoting the reaction. In all

**Scheme 2. Reaction of Cyanoacetate with *p*-Quinone Diimide: Substrate Screen**[a]




[a]The yields reported are isolated yields; ee values were determined by chiral HPLC; the absolute configuration of **3b** was determined by single-crystal X-ray analysis.

cases, cyclic imidine, the addition−cyclization product, is formed in high yields. Enantioselectivity is also excellent, ranging from 76 to 91%, except for **3k**, in which case the reaction proceeds with moderate selectivity (50% ee). The absolute configuration of **3b** was determined as (*S*) by single-crystal X-ray structure analysis (see the Supporting Information, SI). This particular reaction was carried out on a 1.2 mmol scale, and the yield and the selectivity obtained were comparable to small-scale reaction (see the SI).

To gain insight into the mechanism of the reaction, density functional theory (DFT) calculations were carried out employing the M06-2X functional. The initial step in the reaction sequence is the deprotonation of the active methylene compound, which precedes the rate-determining C−C bond-forming step. There are at least two distinct activation modes possible, depending on the substrate−catalyst alignment at the active space stabilized by multiple hydrogen-bonding interactions. In one of the modes, the quinone diimide (electrophile) is activated by the thiourea moiety of the catalyst, while the active methylene compound (nucleophile) binds to the protonated amine (quinuclidine ring) moiety of the catalyst (mode A, **I** Figure 2). In mode B, the quinone diimide is bound to the protonated quinuclidine ring of the catalyst, and the active methylene compound interacts with the thiourea part of the catalyst (**II**). Since these prereaction complexes **I** and **II** equilibrate rapidly, their relative stabilities are unlikely to play

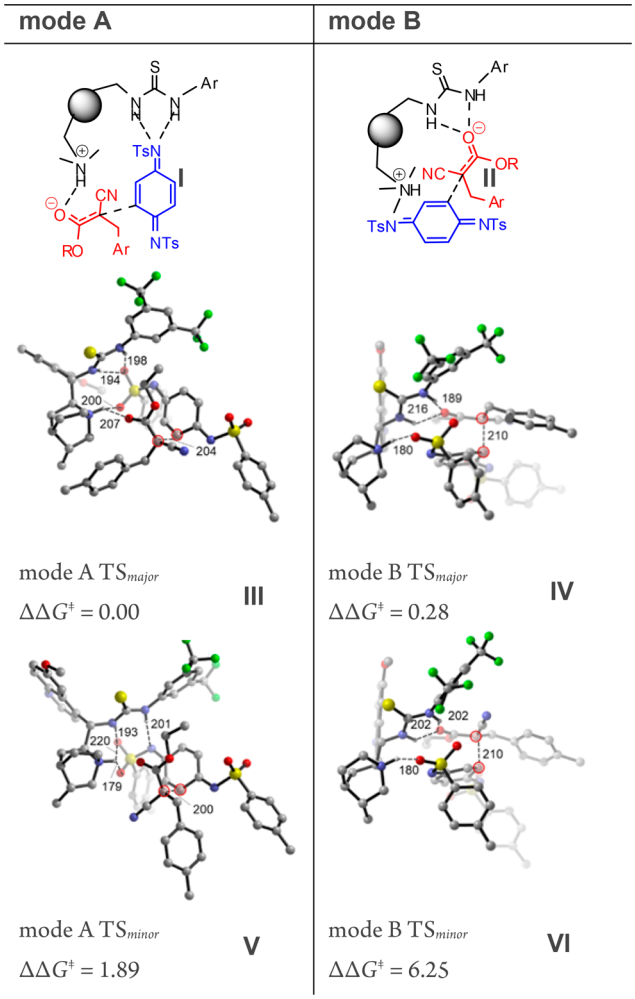



**Figure 2.** (I) Activation mode A; (II) activation mode B; (III−VI) C−C bond-forming TSs calculated at the M06-2X/def2-TZVPP level of theory for major and minor products through activation modes A and B. (Noncritical hydrogen atoms are omitted for clarity. All distances are in pm. $\Delta\Delta G^{\ddagger}$, in kcal mol$^{-1}$, is the free energy difference with reference to the mode A TS$_{major}$. Carbon atoms participating in the C−C coupling are enclosed in red circles.)

any role in the outcome of the reaction. Hence, the C−C bond-forming transition state (TS) energies in both modes are crucial. The summary of the DFT calculation studies is given in Figure 2 (see the SI for details). The lowest energy TS corresponds to mode A TS$_{major}$, which leads to the major product formed experimentally as well. The mode B TS corresponding to major product, mode B TS$_{major}$, is nearly of the same energy ($\Delta\Delta G^{\ddagger}$ = 0.28 kcal mol$^{-1}$). Unlike the systems with nitroalkane,[23] here, both modes are equally probable. Notably, the TSs in both modes corresponding to the minor product, TS$_{minor}$, were appreciably high in energy with respect to the mode A TS$_{major}$. The hydrogen-bonding and $\pi-\pi$ stacking interactions are key components contributing to the relative stability of the TSs.

In summary, we have achieved the first catalytic asymmetric reaction of *p*-quinone diimides, the organocatalytic Michael addition of cyanoacetates. Interestingly, even the achiral version of this reaction does not have any literature precedence. Chiral bifunctional molecules efficiently promote the reaction in excellent yield and selectivity, affording the functionally rich cyclic imidines with an all-carbon quaternary chiral center directly attached to a phenyl ring.[24] Further, relative energies



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calculated using DFT for the various transition states possible indicated that the lowest energy TS corresponds to the major product formed experimentally. Meanwhile, efforts to further broaden the scope of the reaction by including various nucleophiles and different quinonoid species are currently in progress and will be reported in due course.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00771.

Experimental procedures, characterization details, $^{1}H$, $^{13}C$ NMR spectra and HPLC data of all new compounds, and computational details and coordinates (PDF)

### Accession Codes

CCDC 1457062 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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### Notes

The authors declare no competing financial interest.

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