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para-Quinone Methide: a New Player in Asymmetric Catalysis

Alejandro Parra,[a] and Mariola Tortosa*[a]

para-Quinone methides (*p*-QMs)[1] have been known as reaction intermediates for more than a century.[2] They consist of a cyclohexadiene moiety in *para*-conjugation with a carbonyl group and an *exo*-methylene component (**C**, Figure 1). *p*-QMs are neutral molecules with an aromatic zwitterionic resonance structure which makes them more reactive than structurally related *para*-quinone **A** and *para*-quinone dimethide **B** (Figure 1). This enhanced electrophilicity[3] has been used in a variety of medicinal and biological processes such as DNA alkylation, cross-linking and enzyme inhibition.[4] The *para*-quinone methide moiety is also present in a variety of biologically active compounds and has been proposed as an intermediate in the biosynthesis of a number of natural products.[5]

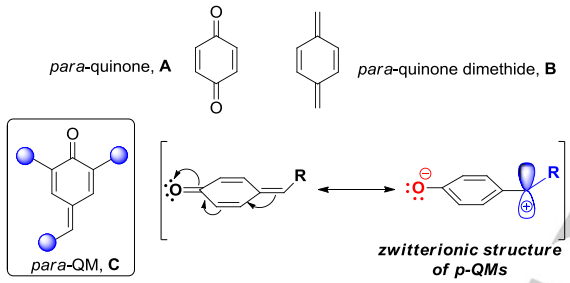
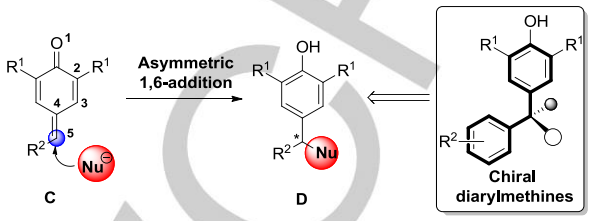


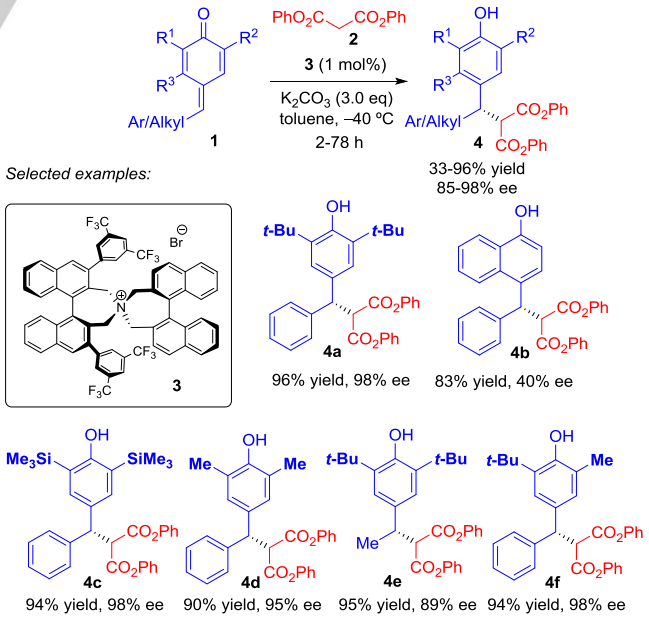
Figure 1 *p*-Quinone, *p*-quinone dimethide and *p*-quinone methide derivatives.

Surprisingly, while *ortho*-quinone methides have been broadly used in asymmetric synthesis,[7],[8] *p*-QMs have received relatively little attention, particularly among catalyzed methods. Until recently, the only enantioselective reactions reported were in the context of asymmetric polymerizations, and low stereoselectivities were observed.[8] While unsubstituted *p*-QMs are too reactive to be studied in asymmetric catalysis, the use of more stable 2,6-disubstituted *p*-QMs **C** offers the possibility of addressing this challenge. Intermediates **C** represent attractive targets, because asymmetric 1,6-additions[9] could rapidly afford important chiral diarylmethines (Scheme 1).[10] This idea has been nicely developed by the groups of Fan and Jørgensen, opening a new entry to enantiomerically enriched benzyl derivatives.



Scheme 1. *p*-Quinone methides as synthons for chiral diarylmethines.

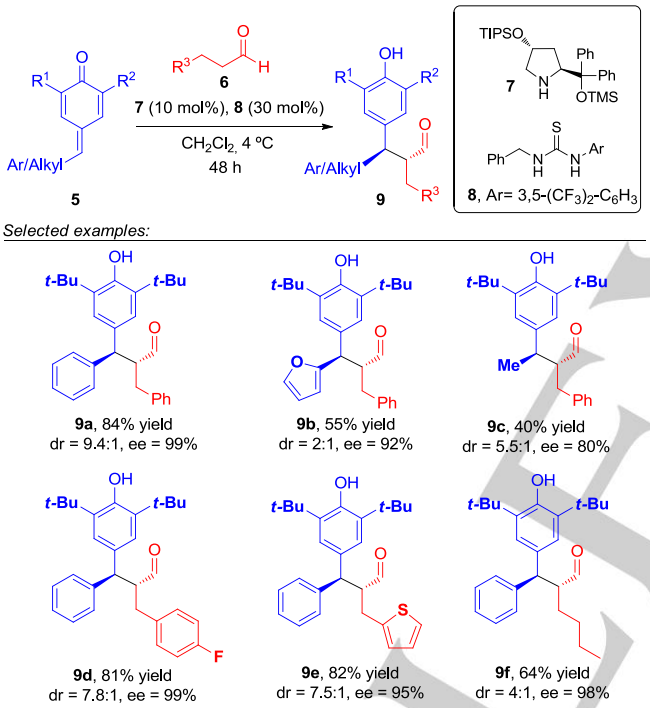
Fan *et al.*[11] recently reported the use of 2,6-disubstituted *p*-QMs **1** as stable prochiral starting materials in a catalytic asymmetric transformation. They reported the 1,6-addition of diphenyl malonate **2** to *p*-QMs **1** using chiral ammonium phase transfer catalysis.[12] The use of center-chiral catalysts such as *N*-bridged cinchona or tartrate-derived ammonium salts was not effective. However, the binaphthyl-modified ammonium bromide **3**, with axial chirality, gave excellent results. Several enantiomerically enriched malonates were prepared in good yields and high enantiomeric excesses (Scheme 2). The catalytic system worked well with *p*-QMs bearing both aromatic and aliphatic substituents. Interestingly, a *p*-QM derived from the 1,4-naphthoquinone (**4b** precursor) was described for the first time although only a moderate enantiomeric excess was obtained (**4b**, 40% ee). A plausible transition-state model was also proposed to explain the observed enantioselectivity.



Scheme 2. Asymmetric 1,6-addition of malonates to *p*-QMs

[a] Dr. Alejandro Parra and Dr. Mariola Tortosa
Departamento de Química Orgánica (Módulo 1), Facultad de Ciencias, Universidad Autónoma de Madrid. Cantoblanco, 28049-Madrid
Fax: (34) 914973966
E-mail: mariola.tortosa@uam.es

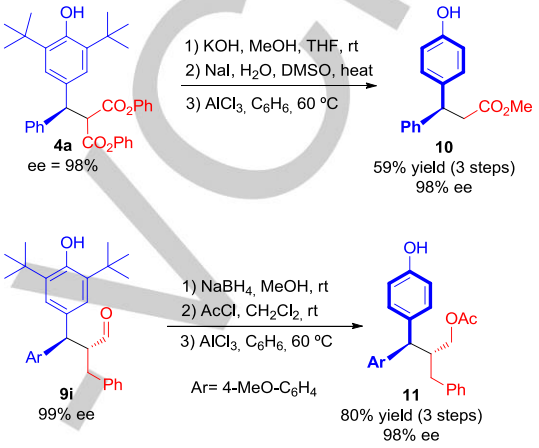
Very recently, Jørgensen *et al.*[13] published a novel approach for the α-alkylation of aldehydes using *p*-QMs as alkylating agents under organocatalytic enamine catalysis[14] (Scheme 3). Although the Jørgensen–Hayashi catalyst afforded the products with good yields and high enantioselectivities, the diastereomeric ratios were poor. A new secondary amine **7** was then designed to solve this problem (Scheme 3). The bulky tiisopropylsilyloxy group at C_4, *anti* to the C_1 substituent, was key to determine the approach of the *p*-QM to the enamine and therefore to control the diastereoselectivity Additionally, the use of 30 mol% of thiourea **8** significantly improved yields, probably by activation of the carbonyl group on **5** though hydrogen bonding. A wide range of α-alkylated aldehydes **9** were prepared in good yields (40-90%), moderate to good diastereoselectivities (dr = 2:1-11:1) and excellent enantiocontrol (ee = 80-99%). Despite the high reactivity of *p*-QMs **5**, the process was highly chemoselective and *N*-alkylation of catalyst **7** was not observed.



Scheme 3. Asymmetric enamine addition to *p*-QMs. TIPS= triisopropylsilyl. TMS= trimethylsilyl.

In most cases, both Fan and Jørgensen used 2,6-di-*tert*-butyl *para*-quinone methides[4] due to their inherent stability and facile preparation. Notably, the role of the *tert*-butyl group is doubly important because it stabilizes the starting *p*-QMs, making their isolation far more practical, and can be easily removed afterwards with $AlCl_3$ (Scheme 4).

In summary, *p*-QMs have been successfully used for the first time in asymmetric catalysis in two different processes: the 1,6-addition of phenyl malonate under phase transfer catalysis, and the α-alkylation of aldehydes using enamine catalysis. In both cases, the products were obtained in good yields and high enantioselectivities. These two publications represent a powerful entry towards the synthesis of enantiomerically enriched diarylmethines and will undoubtedly inspire the development of other catalytic asymmetric transformations in the future. Applications of *p*-quinone methides with other modes of activation in organocatalysis as well as metal-catalyzed reactions are still waiting to be explored.



Scheme 4. Elimination of the *t*-Butyl group on the phenolic ring.

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Keywords: quinone methide • asymmetric catalysis• reaction intermediate • organocatalysis • 1,6-addition

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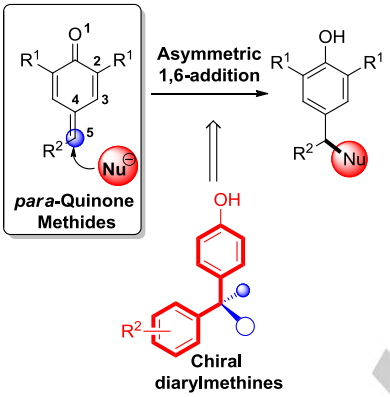
HIGHLIGHT

p-QMs have been successfully used in asymmetric organocatalysis. Particularly, the asymmetric 1,6-addition of phenyl malonate and different aldehydes to 2,6-disubstituted *p*-QMs has provided a rapid access to important chiral diarylmethines, highlighting the importance of these synthetic intermediates. These new structures will open up the development of important asymmetric transformations in the future.



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