

*Communication*

## Aqueous Ti(IV)-Catalyzed Diels-Alder Reaction

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**Abstract:** The aqueous Diels-Alder reaction of 1,3-cyclohexadiene with 1,4-benzoquinone was compared and contrasted to the same reaction catalyzed with Flextyl P™, a novel Ti(IV) performance catalyst. The catalyst improved conversion by 22% versus the uncatalyzed reaction and represents a rare example of a Ti(IV) catalyzed Diels-Alder reaction in water.

**Keywords:** Diels-Alder reaction, aqueous, cyclohexadiene, benzoquinone, Lewis acid catalysis, green chemistry, water-soluble Lewis acid catalyst.

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### Introduction

Traditional synthetic chemistry has acquired a wealth of information on the synthesis and structure of thousands of simple and complex molecules [1]. Yet increasingly, chemists are becoming conscious of the need to develop safe, environmentally benign reactions and processes [2]. Four predominant strategies in the “green” approach to chemistry include: i) using water instead of organic solvents, ii) using solventless processes, iii) employing catalysts to enhance yield, reaction rate, as well as selectivity, and iv) promoting biosynthetic processes where appropriate [3]. The modern synthetic paradigm now considers the process as important as the product itself.

When considering the process, solvent selection is a major consideration. Water is ubiquitous and abundant. Despite these obvious advantages, water has been historically undervalued as a reaction medium in organic synthesis. Not surprisingly, the shift towards “green” chemistry has resurrected interest in water owing to many unexpected recent discoveries. For example, the rates and stereoselectivities of Diels-Alder (DA) reactions are strongly affected by water [4]. Considering the

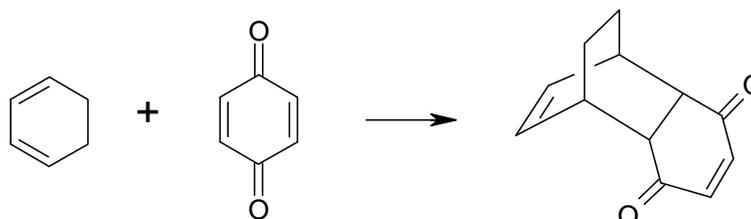
DA reaction can be greatly enhanced by Lewis acids, the combination of effects are conceptually quite promising [5].

Ti(IV) is an electropositive metal and as such is a strong Lewis acid even in the presence of electron-donating ligands such as alkoxides or cyclopentadienides (Cp) [6]. To date, the only Ti(IV) complex with demonstrated DA catalytic activity in the presence of water is Bosnich's complex,  $[\text{Cp}'_2\text{Ti}(\text{H}_2\text{O})]^{2+}$ , which does undergo some hydrolysis in solution and a retardation of turnover frequency [7]. In the present study, we compared the uncatalyzed DA reaction of 1,3-cyclohexadiene and 1,4-benzoquinone (Scheme 1) to the same reaction catalyzed with a novel, water soluble Ti(IV) material. The results of this study were compared and contrasted to those reported by Kuroda *et al.* [8].

## Results and Discussion

The aqueous DA reaction of 1,3-cyclohexadiene and *p*-benzoquinone were investigated according to the general methods of Kuroda *et al.* (Scheme 1). Upon addition of the catalyst, the aqueous solution of benzoquinone turns from golden yellow to olive green in color, indicating coordination of the dienophile with the Ti(IV) Lewis acid. After adding the diene, the reaction proceeds with formation of a dense light yellow precipitate from the opaque olivine solution. Without the catalyst, the consistency of the precipitate is markedly less dense and the solution remains golden yellow throughout the reaction with fading color intensity. After 20 hours, the reaction mixtures were filtered and dried *in vacuo* overnight at ambient temperature to afford exclusively the product, *endo*-tricyclo[6.2.2.0<sup>2,7</sup>]dodeca-4,9-3,6-dione, as confirmed by <sup>1</sup>H-NMR [9].

**Scheme 1.**



The yield of the catalyzed reaction was improved 22% in comparison to the uncatalyzed aqueous DA reaction (Table 1). After 20 hours, the yield in the absence of catalyst compared favorably to the 67% yield noted by Kuroda over 48 hours. Kuroda was able to increase the conversion to 83% albeit in 15 molal guanidinium chloride (GnCl).

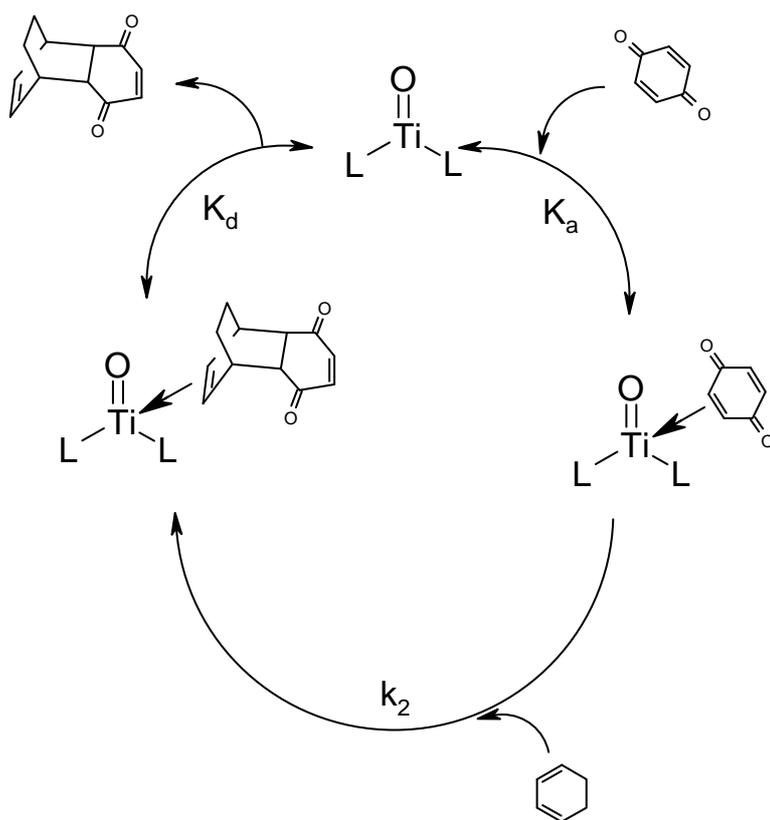
**Table 1.** Aqueous Diels-Alder Reactions.

[Catalyst]	% Yield* (std deviation)
0 mole %	61% ( $\pm 1.5\%$ )
5 mole %	83% ( $\pm 1.5\%$ )

\* triplicate

In order to clarify the role of  $\text{GnCl}$ , Kuroda investigated related additives and postulated that hydrogen bonding between  $\text{GnCl}$  and 1,4-benzoquinone accounted for the increased conversion. This explanation was consistent with that of Engberts *et al.* Engberts postulated that hydrogen bonding withdraws electron density from the double bond of the dienophile, thereby lowering the LUMO energy and facilitating interaction with the diene HOMO [5d]. The mechanism for Lewis acid catalyzed DA reactions is analogous to the effect of hydrogen bonding. Given the immediate and rapid association of benzoquinone with the added catalyst, the insolubility of the resulting DA product, and the increased conversion in the catalyzed reaction, the mechanism of reaction likely follows that first postulated by Engberts for the aqueous catalytic DA reaction (Scheme 2) [5d]. The mechanism likely involves: i) dative coordination of the dienophile to  $\text{Ti(IV)}$  that withdraws electron density from the double bond of BQ which ii) activates BQ towards interaction with 1,3-cyclohexadiene, iii) after the irreversible DA reaction, iv) the product dissociates from the complex, regenerating the active metal species. Exactly how the dienophile coordinates remains to be determined as either dative coordination via the quinoidal oxygen or the alkenyl moiety are both possible and both are likely to reduce electron density at the double bond.

**Scheme 2.** The Lewis Acid Catalyzed Diels-Alder Reaction.



## Conclusions

The aqueous  $\text{Ti(IV)}$ -catalyzed Diels-Alder reaction of 1,3-cyclohexadiene with 1,4-benzoquinone significantly improved the conversion with respect to the uncatalyzed reaction. It was postulated that the mechanism of action follows Engberts' mechanism. The reaction represents a rare example of  $\text{Ti(IV)}$ -catalyzed Diels-Alder reaction in water.

## Experimental

### General

NMR spectra were recorded in CDCl<sub>3</sub> at 300 MHz (<sup>1</sup>H) and 75.5 MHz (<sup>13</sup>C) on a Bruker AM 300 spectrometer. Chemical shifts are in ppm relative to residual solvent. 1,3-Cyclohexadiene and 1,4-benzoquinone were purchased from Aldrich and used as received. Flextyl™ was obtained as a 10%(w/w) [0.4 M] aqueous solution from Applied Nanoworks and used as received. The uncatalyzed, aqueous Diels-Alder reaction was performed in triplicate according to the general method of Kuroda over the course of 20 hours, (0.57 g, 61% conversion) [8].

### Typical Ti(IV)-catalyzed reaction

In a 100 mL round-bottomed flask, an aqueous solution (54 mL) of *p*-benzoquinone (0.54 g, 5.0 mmol) was charged with Flextyl P™ (0.615g, 0.25 mmoles). To this mixture was added 1,3-cyclohexadiene (0.399 mg, 0.50 mmol) with vigorous mixing. The homogeneous reaction mixture was stirred for 20 hours producing an insoluble product which was collected by filtration, dried *in vacuo*, and weighed (0.778 g, 83% conversion). Comparison of the <sup>1</sup>H-NMR to the published spectra confirmed identification of the product [9]. The procedure was performed in triplicate.

## References and Notes

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*Sample Availability:* Samples of the compounds are available from author.

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