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A Diels-Alder Reaction Conducted Within the Parameters of Aqueous Organocatalysis: Still Just Smoke and Mirrors

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Abstract

Conducting reactions using water as solvent is a highly prized goal for the organic chemist. Based upon recent literature and our continuing interest in the field of aqueous organocatalysis, we tested the scope of an enamine based Diels-Alder reaction using (±)-nornicotine, proline and a proline derivative as aqueous organocatalysts. Unfortunately, none of the examined catalysts under aqueous conditions proved useful, leaving the aqueous Diels-Alder reaction as an elusive goal.

Keywords

Nornicotine; Organocatalysis; Diels-Alder; Aqueous

The ever-expanding field of organocatalysis offers the capacity of conducting a wide variety of synthetically useful transformations such as Michael,^{1–5} Diels-Alder,^{6–10} Mannich^{11–14} and Henry^{15–17} reactions, to name a few. In addition to the capacity for use of non-stoichiometric quantities of catalyst, the inherent chirality present in many organocatalysts offers the capability to conduct asymmetric reactions with extremely high selectivity. Some advantages of organocatalysis are: 1) operational simplicity; it can often be conducted without the need for an inert atmosphere under ambient temperature and pressure, 2) lack of expensive transition metals necessary for organometallic transformations, and 3) the possibility for the use of water as reaction solvent. Of these listed organocatalysis advantages, we consider the use of aqueous solvent of special importance due to its inherent character as a low impact, environmentally sustainable solvent without the carbon footprint embodied by traditional organic solvents.

Given our previous success in the field of aqueous organocatalysis^{18–21} and our continuing interest in the synthesis of analogs of commonly abused drugs^{22,23} we became intrigued by the recently published work of Xu et al., who used proline derivatives at room temperature to conduct enamine catalyzed Diels-Alder reactions of cyclohex-2-enone and β-nitrostyrene employing brine or seawater as the solvent of choice (Scheme 1).²⁴ In addition to the use of seawater/brine as solvent, this work employed a variety of organic acid additives, such as benzoic acid and derivatives thereof, to optimize reaction conversion and selectivity (Scheme 2).

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However, we reasoned these organic acid additives could be entirely unnecessary, and that the reaction could be optimized equally as well using an organocatalyst and buffer of correct pH value. As such, we set out to study the same Diels-Alder reaction as performed by Xu et al. using ($\pm$) nornicotine as organocatalyst (Scheme 3A). We felt ($\pm$) nornicotine presented an excellent opportunity to test our theory for optimization of aqueous organocatalysis without the need for acid additives given its structural similarities to the catalysts **2–4** used by Xu et al. We did not employ nicotine **11** in this study since the required enamine reaction intermediate would not be generated by the tertiary amine of this compound, as determined by our previous research.²⁰

We were aware at the onset of this study that using racemic nornicotine would not confer any enantio- or diastereomeric excess to the reaction product. However, we decided that initial optimization of Diels-Alder reaction conversion in buffer was critical before attempting to confer chiral selectivity in the reaction process.

Our initial test of the enamine-based Diels-Alder reaction utilized 30% proline in DMSO solvent following Cordova's procedure.²⁵ We were pleased to observe that proline did indeed behave as a reasonable organocatalyst, providing the product in 80% yield as a >25:1 diastereomeric ratio (*dr*) in similar fashion to the high diastereoselectivity reported by Cordova (>25:1 *dr*). However, the enantiomeric excess (8%) of the major diastereomer was less than Cordova's results (*ee* = 25%, Table 1).

After this proof of concept experiment, we pressed forward and conducted the aqueous Diels-Alder reaction using ($\pm$)-nornicotine as organocatalyst and either brine (benzoic acid additive) or sodium phosphate (NaPi) buffer solvent. Disappointingly, catalytic amounts (20%) of ($\pm$)-nornicotine in brine as well as three different buffer pH values (pH = 6.0, 7.0, 8.0) did not mediate any reaction. In fact, we discovered that only when a stoichiometric quantity of ($\pm$)-nornicotine was used did we detect any product for both solvent systems. We were able to isolate Diels-Alder product **7** from these experimental variations using NaPi buffer or brine as reaction solvent, but poor yields were obtained for each trial (Table 1).

Given these suboptimal results using ($\pm$)-nornicotine **10** as an aqueous organocatalyst, we synthesized proline derivative **4** of Xu et al. in an attempt to repeat their Diels-Alder reaction protocol using brine as solvent and benzoic acid as the organic acid additive. Using this procedure, Xu reported a conversion of >99% at a 20% loading of catalyst and benzoic acid. Unfortunately, we did not observe any reaction to occur employing these conditions. Instead, we found that only after we increased the loading of catalyst and benzoic acid to 40% did we observe any reaction product at a disappointing 10% isolated product yield (Table 1). However, the use of Xu's catalyst and benzoic acid additive at 40% loading did yield bicyclic reaction product **7** with diastereomeric ratio of >25:1 and enantiomeric excess of 83%, in agreement with the reported values (Table 1).

Thus, we conclude our hypothesis of ($\pm$)-nornicotine catalyzing the aqueous enamine-based Diels-Alder reaction to be untenable, despite our previous success with aldol reactions in aqueous solvent employing what we believe to be a similar mechanism. We are currently unsure of the underlying reason for the disappointing results obtained, but it could stem from aqueous instability of the transient imine or enamine necessary for reaction completion. Additional research will be required to examine these suppositions. We also stress that while the selectivity of Xu's catalyst was similar to reported values (>25:1 *dr*, 85% *ee*), we were not able to obtain their outstanding yields with catalyst loads of 20 and 40 percent.

In summary, we conclude that high-yielding aqueous organocatalysis of the enamine-based Diels-Alder reaction still remains an elusive goal, and the bar is reset for future investigations in this realm of research.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Brown SP, Goodwin NC, MacMillan DWC. *J Am Chem Soc.* 2003; 125:1192. [PubMed: 12553821]
2. Mase N, Watanabe K, Yoda H, Takabe K, Tanaka F, Barbas CF. *J Am Chem Soc.* 2006; 128:4966. [PubMed: 16608326]
3. Wu C, Li W, Yang J, Liang X, Ye J. *Org Biomol Chem.* 2010; 8:3244. [PubMed: 20495718]
4. Zhu S, Yu S, Wang Y, Ma D. *Angew Chem Int Ed.* 2010; 49:4656.
5. Betancort JM, Barbas CF. *Org Lett.* 2001; 3:3737. [PubMed: 11700126]
6. Wilson RM, Jen WS, MacMillan DWC. *J Am Chem Soc.* 2005; 127:11616. [PubMed: 16104734]
7. Kano T, Tanaka Y, Maruoka K. *Org Lett.* 2006; 8:2687. [PubMed: 16774232]
8. Juhl K, Jørgensen KA. *Angew Chem.* 2003; 115:1536.
9. Li JL, Han B, Kun J, Wei D, Chen YC. *Bioorg Med Chem Lett.* 2009; 19:3952. [PubMed: 19318249]
10. Thayumanavan R, Dhevalapally B, Sakthivel K, Tanaka F, Barbas CF. *Tetrahedron Lett.* 2002; 43:3817.
11. Wang X, Yongbo Z, Haibo T, Yanchao W, Peng H, Wang DZ. *J Org Chem.* 2010; 75:2403. [PubMed: 20196532]
12. Enders D, Grondal C, Vrettou M, Raabe G. *Angew Chem Int Ed.* 2005; 44:4079.
13. Notz W, Tanaka F, Watanabe SI, Chowdari NS, Turner JM, Thayumanavan R, Barbas CF. *J Org Chem.* 2003; 68:9624. [PubMed: 14656087]
14. Lou S, Taoka B, Ting A, Schaus SE. *J Am Chem Soc.* 2005; 127:11256. [PubMed: 16089450]
15. Bernardi L, Fini F, Herrera RP, Ricci A, Sgarzani V. *Tetrahedron.* 2006; 62:375.
16. Palomo C, Oiarbide M, Mielgo A. *Angew Chem Int Ed.* 2004; 43:5442.
17. Robak MT, Trincado M, Ellman JA. *J Amer Chem Soc.* 2007; 129:15110. [PubMed: 18004853]
18. Rogers CJ, Dickerson TJ, Janda KD. *Tetrahedron.* 2006; 62:352.
19. Dickerson TJ, Janda KD. *J Am Chem Soc.* 2002; 124:3220. [PubMed: 11916401]
20. Rogers CJ, Dickerson TJ, Brogan AP, Janda KD. *J Org Chem.* 2005; 70:3705. [PubMed: 15845010]
21. Brogan AP, Dickerson TJ, Janda KD. *Angew Chem.* 2006; 118:8278.
22. De Figueiredo RM, Christmann M. *Eur J Org Chem.* 2007:2575.
23. Meijler MM, Matsushita M, Wirsching P, Janda KD. *Curr Drug Disc Tech.* 2004; 1:77.
24. Xu D, Xia A, Luo S, Tang J, Zhang S, Jiang RJ, Xu Z. *Angew Chem Int Ed.* 2009; 48:3821.
25. Sundén H, Rios R, Xu Y, Eriksson L, Cordova A. *Adv Synth Catal.* 2007; 349:2549.

Scheme 1.

Previous approach and mechanistic interpretation of organocatalyzed Diels-Alder reactions via an enamine intermediate.

Scheme 2.
Aqueous Diels-Alder and acid additives of Xu et al.

Scheme 3.

A) Catalysis by (±)-nornicotine in buffer solvent. B) Structures of Xu's catalyst **4**, (±)-nornicotine **10** and nicotine **11**.

TABLE 1

Diels Alder Reaction Using Proline, Proline Derivative 4 and (±)-Normicotine 10.

Amine	Catalyst Load	Solvent	pH	Acid	Yield (%) ^d	<i>dr</i> ^e	<i>ee</i> ^f (%)
Proline	30%	DMSO	--	--	80%	>25:1	8
10	50%	DMSO	--	--	N.R.	--	--
10	20%	NaPi ^b	6.0	--	N.R.	--	--
10	20%	NaPi	7.0	--	N.R.	--	--
10	20%	NaPi	8.0	--	N.R.	--	--
10	100%	NaPi	6.0	--	>10%	--	--
10	100%	NaPi	7.0	--	>10%	--	--
10	100%	NaPi	8.0	--	>10%	--	--
10	100%	Brine ^c	--	8 ^a	>10%	--	--
4	20%	Brine	--	8 ^a	N.R.	--	--
4	40%	Brine	--	8 ^a	10%	>25:1	85

^a Benzoic acid used as acid additive.

^b 200 mM sodium phosphate buffer.

^c 7.5% aqueous brine.

^d Refers to isolated yield of Diels-Alder product. No reaction is abbreviated N.R.

^e Achiral HPLC used for determination of *dr*.

^f Chiral HPLC used for determination of *ee*.