


Advanced 

Synthesis & Catalysis

Accepted Article

Title: Enantioselective organocatalytic enamine C-H oxidation/Diels Alder reaction

Authors: Zdravko Dzambaski, Dimitrios Ioannis Tzaras, Sunggi Lee, Christoforos Kokotos, and Bojan Bondzic

This manuscript has been accepted after peer review and appears as an Accepted Article online prior to editing, proofing, and formal publication of the final Version of Record (VoR). This work is currently citable by using the Digital Object Identifier (DOI) given below. The VoR will be published online in Early View as soon as possible and may be different to this Accepted Article as a result of editing. Readers should obtain the VoR from the journal website shown below when it is published to ensure accuracy of information. The authors are responsible for the content of this Accepted Article.

To be cited as: *Adv. Synth. Catal.* 10.1002/adsc.201900061

Link to VoR: <http://dx.doi.org/10.1002/adsc.201900061>

DOI: 10.1002/adsc.201((will be filled in by the editorial staff))

Enantioselective organocatalytic enamine C-H oxidation/Diels-Alder reaction


Zdravko Džambaski,^a Dimitrios-Ioannis Tzaras,^b Sunggi Lee,^c Christoforos G. Kokotos,^b and Bojan P. Bondzic^{a,*}

^a Center for Chemistry, ICTM institute, University of Belgrade, Njegoseva 12, 11 000 Belgrade, Serbia
e-mail: bbondzic@chem.bg.ac.rs

^b Laboratory of Organic Chemistry, Department of Chemistry, National and Kapodistrian University of Athens, Panepistimiopolis 15771, Athens, Greece

^c Max-Planck-Institut für Kohlenforschung Kaiser-Wilhelm-Platz 1, 45470 Mülheim an der Ruhr, Germany

Received: ((will be filled in by the editorial staff))

 Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/adsc.201#####>. ((Please delete if not appropriate))

Abstract. α,β -unsaturated aldehydes have been traditionally used in LUMO lowering asymmetric aminocatalysis (iminium catalysis), while the use of saturated aldehydes as substrates in this type of catalysis has been elusive, until recently. Herein, we demonstrate that organic, single-electron oxidants in the presence of diarylprolinol silylether type catalysts serve as effective tools for the transformation of electron rich enamines to iminium ions which partake in a subsequent Diels-Alder reaction. This enantioselective one-pot transformation represents the first example of saturated aldehydes being used in domino Diels-Alder reaction processes and demonstrates the power of this protocol for construction of stereo-defined chiral compounds and building blocks.

Keywords: Asymmetric catalysis; Cycloaddition; C-H oxidation; Diarylprolinols; Organocatalysis

The Diels-Alder reaction is one of the most important synthetic methods for assembling a highly functionalized regio- and stereo-chemically defined cyclohexane frameworks which are important building blocks in the synthesis of natural products and biologically interesting compounds.¹ In their seminal work MacMillan and co-workers developed the first Diels-Alder reaction involving an organocatalyst, and proceeding by a nowadays well established LUMO-lowering activation mechanism.² Since then several asymmetric Diels-Alder reactions involving organocatalysts have been reported.³ Some of the most notable organocatalytic iminium Diels-Alder reactions involving LUMO lowering mechanism include work by Hayashi et al., who employed secondary amine catalyst in highly enantio-

and exo-selective Diels-Alder reactions of α,β -unsaturated aldehydes with dienes. Chiral primary and secondary amine catalyzed Diels-Alder reactions of hindered α -substituted acroleins, which are useful for the construction of a chiral quaternary carbon centers have been reported recently.⁵⁻⁷ LUMO lowering mechanism is operational not only in iminium activation catalysis but also in non-covalent activation modes such as hydrogen bond donor catalysis.⁸⁻¹² On the other hand, base-catalyzed Diels-Alder reactions operate under HOMO raising catalysis mechanism.^{13, 14} However, despite all the progress that has been made in this field one of the great synthetic challenges still remaining in the organocatalyzed Diels-Alder reaction is application of enolizable saturated aldehydes as dienophiles, in diastereo- and enantio-selective manner.

Until recently, iminium catalysis relied exclusively on the use of α,β -unsaturated aldehydes (Fig 1, eq. b). Reversal of reactivity of enamines and their transformation from electron-rich alkenes that act as an electrophilic species (HOMO raising catalysis) into electron-deficient iminium ions acting as a nucleophilic species (LUMO lowering catalysis) has been just recently accomplished using organic single electron oxidizing agents.¹⁵⁻¹⁷ Our design plan to use saturated aldehydes in DA reaction would involve an enamine oxidation to the corresponding iminium ion, and subsequent reaction of the chiral dienophile with diene present in reaction mixture (Fig 1. path A→C→D). To the best of our knowledge, there is neither cascade nor one pot process that allowed this transformation to date.

Accepted Manuscript

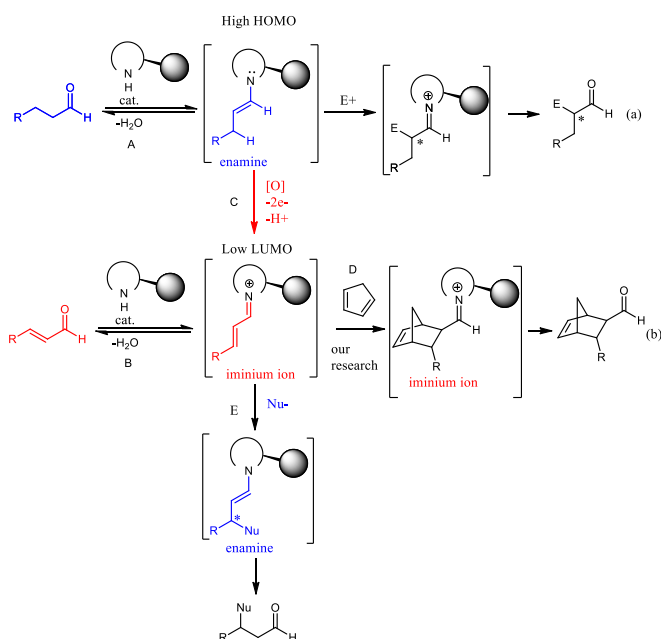


Figure 1. Iminium and enamine catalysis, oxidation of enamine to iminium ion and reversal of reactivity, (a) Enamine catalysis, (b) Iminium catalysis

Our investigation started by testing the ability of different oxidizing agents to convert the chiral enamine to the corresponding α,β -unsaturated aldehyde in the absence or in the presence of diene. Due to the subtle dependence of reaction yields and levels of enantio- and/or diastereo-selectivity to reaction conditions, the oxidant and resulting byproducts should not interfere with the subsequent asymmetric Diels-Alder reaction. Accordingly, the reaction medium should be compatible with both the oxidation and the cycloaddition reaction to enable the achievement of high reaction efficiencies and selectivities. We choose diphenyl- and diaryl-prolinol silyl ethers **1-3** as catalysts for our investigation (Table 1). Catalyst **1** was the catalyst of choice in the oxidative enamine catalysis conjugate addition reactions^{15, 16} however; it is known that in the presence of catalyst **1**, Michael-type addition reaction between α,β -unsaturated aldehyde and cyclopentadiene might also take place.¹⁸ On the other hand, electron-deficient diaryl-prolinol silyl ethers **2** or **3** are the catalysts of choice for organocatalyzed Diels-Alder reaction of α,β -unsaturated enals (vide supra) but haven't been utilized in cascade reactions involving oxidative enamine catalysis so far. Initial test was carried out in the presence of catalyst **1** with DDQ as the oxidant and TFA as the additive in toluene. After 2h, full conversion of the starting material **4** to α,β -unsaturated aldehyde **5** was observed. Upon addition of cyclopentadiene Diels-Alder reaction proceeded but was very slow and sluggish and thus after 72h gave only 28% of desired products in 82/18 exo/endo ratio with 89% ee for

Table 1. Optimization of reaction conditions for asymmetric enamine Oxidation/Diels-Alder reaction

Entry	Cat	Oxidant	conv. ^a 5 %	Yield ^b 6, 7 %	Exo/ endo ^a	ee ^c exo/endo
1	1	DDQ	quant	28	82/18	89/81
2	2	DDQ	quant	71(87) ^d	85/15	91/82
3 ^e	2	DDQ	70	35	86/14	93/84
4 ^f	2	DDQ	quant	/	/	/
5	3	DDQ	quant	88 ^d	84/16	92/80
6 ^g	1	IBX	60	<10	85/15	/
7	1	IBX	/	/	/	/
8 ^g	3	IBX	/	/	/	/
9 ^h	1	IBX	quant	<10	86/14	/
10	3	Chloranil	85	38	84/16	95/87

Reaction conditions unless otherwise indicated: 3-phenylpropanal (0.5 mmol), catalyst (0.05 mmol), additive (0.1 mmol), Oxidant (0.5 mmol), and toluene (1 mL) stirred at room temperature for 2h. Subsequently cyclopentadiene (1.5 mmol) was added, after 24 h additional cyclopentadiene (1 mmol) was added and reaction mixture stirred for 24 h. [a] Determined by ¹H NMR spectroscopy; [b] Isolated yield after column chromatography; [c] ee was determined by chiral phase HPLC analysis after NaBH₄ reduction of aldehyde to alcohol; [d] 15 mol% of catalyst and 30 mol% of TFA was used; [e] Cyclopentadiene (1.5 mmol) was added to reaction mixture initially; [f] Reaction run in THF; [g] Reaction run without TFA; [h] Reaction run in MeOH; IBX (Iodoxybenzoic acid); TFA (Trifluoroacetic acid).

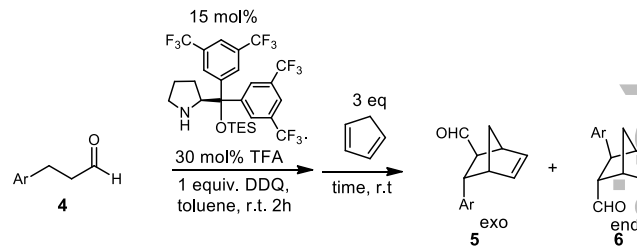
the major diastereoisomer (Table 1, Entry 1). Under the same reaction conditions, the electron-deficient catalyst **2** after 2h lead to full conversion of **4** to **5**. Upon addition of cyclopentadiene and 72h of reaction time 77% of desired Diels-Alder product (87% yield when 15mol% of catalyst was used) was obtained. The product was obtained in 85/15 diastereomeric ratio, favoring exo isomer; and in 91% ee and 82% ee for exo and endo isomers respectively (Table 1, Entry 2). If cyclopentadiene was added at the outset of the reaction with catalyst **2**, significant amount of side product was obtained stemming from cycloaddition reaction of DDQ with cyclopentadiene. Desired Diels-Alder product was obtained as well but in significantly lowered yield of 35%, while diastereoselectivity and enantioselectivity remained high (Table 1, Entry 3). This result showed that presence of unreacted DDQ leads to undesired side reaction and that complete oxidation of starting material, preceding addition of diene, is prerequisite for a successful realization of our reaction scenario.

When the reaction was run in THF oxidation step proceeded smoothly but no Diels-Alder product was observed even after prolonged reaction time (Table 1, Entry 4). Finally use of electron deficient but sterically bulkier TES ether **3** afforded 87% yield of desired product, in 84/16 exo/endo ratio and in excellent enantioselectivity, 98% and 89% respectively (Table 1, Entry 5). The use of other potential oxidants such as IBX (2-Iodoxybenzoic acid) was tested in the presence of catalyst **1**, without additives, and afforded 60% conversion of starting material **4** after 2 h and less than 10% of desired Diels-Alder product upon addition of cyclopentadiene (Table 1, Entry 6). Addition of TFA as an additive in the presence of catalyst **1** and IBX completely inhibited the oxidation reaction and starting material was recovered intact (Table 1, Entry 7). Use of catalyst **3** in the presence of IBX, without any additive, didn't convert the starting material (Table 1, Entry 8). IBX most probably interferes with the catalyst **3** thus preventing the oxidation and subsequent Diels-Alder reaction, contrary to catalyst **1** which catalyzes conversion of starting material in toluene in the presence of IBX (Table 1, Entry 6 vs 8). Use of catalyst **1** and IBX in MeOH promoted complete conversion of starting material **4** to α,β -unsaturated aldehyde **5**, however, Diels-Alder reaction was sluggish and only less than 10% of desired products were obtained after 72 h (Table 1, Entry 9). Chloranil as an oxidant in the presence of catalyst **3** gave 85% conversion of **4** after 2 h. Upon addition of cyclopentadiene, 38% of desired Diels-Alder products in 81/19 exo/endo selectivity and in 95% ee and 87% ee respectively were obtained (Table 1, Entry 10).

To summarize combination of catalyst **3** and DDQ as an oxidant in toluene provided the best results for our reaction. Reactions in the presence of IBX did not proceed to full conversion for the oxidation step, except when MeOH was used as a solvent but in that case Diels-Alder reaction was very sluggish. Chloranil was less efficient oxidant than DDQ and unreacted chloranil (due to incomplete oxidation step) reacts with cyclopentadiene affording cycloaddition side product. Since the combination of catalyst **3**, DDQ as an oxidant and TFA as an additive gave best yields, diastereo- and enantio-selectivities, this combination was chosen to test the substrate scope (Scheme 2, table with full details is in SI). Range of 3-aryl propanals was tested. 3-phenylpropanal gave 88% yield of exo and endo products in 84/16 ratio and 98% and 89% ee respectively (Scheme 1, Entry 1). Substrates possessing electron-withdrawing halogen atoms Cl, Br or F in *para* position reacted in a similar manner to 3-phenylpropanal. Diastereomeric ratios of approximately 85/15 exo/endo and ee's of 94%, 92%

and 95% for major exo stereoisomer were obtained respectively (Scheme 1, Entries 2-4). Substrates with electron donating Me- and MeO- substituents in *para* position afforded lower yields of 65% and 68% respectively but with excellent ee's for major exo isomer of 95% ee for Me- and 94% ee for MeO-substituted substrate

Table 2. Scope of organocatalyzed asymmetric enamine oxidation/Diels-Alder reaction of 3-aryl propanals



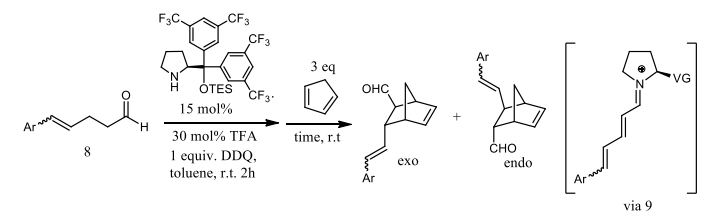
Entry	Ar	Yield %	Exo/endo ^b	ee % ^c exo	ee % ^c endo
1	Ph (5a)	88	84:16	98 (2S)	89 (2S)
2	<i>p</i> -ClC ₆ H ₄ (5b)	75	83:17	94	72
3	<i>p</i> -BrC ₆ H ₄ (5c)	81	84:16	92	74
4	<i>p</i> -FC ₆ H ₄ (5d)	72	84:16	95	72
5	<i>p</i> -MeC ₆ H ₄ (5e)	65	87:13	95	84
6	<i>p</i> -MeOC ₆ H ₄ (5f)	68	87:13	94	77
7	<i>o</i> -MeC ₆ H ₄ (5g)	58	76:24	96	9
8	<i>m</i> -ClC ₆ H ₄ (5h)	67	86:14	90	87
9	3,4-diCl C ₆ H ₃ (5i)	86	85:15	89	51
10	2-F-5-Br C ₆ H ₃ (5j)	87	88:12	94	80
11	3,5-diFC ₆ H ₃ (5k)	68	75:25	97	94
12	<i>p</i> -CF ₃ C ₆ H ₄ (5l)	79	86:14	84	58
13	2-Naph (5m)	76	87:13	92	67
14	2-thienyl (5n)	61	84:16	92	61

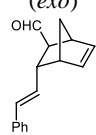
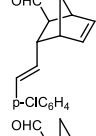
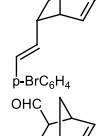

See the Supporting Information for details. ^[a] Isolated yield after column chromatography; ^[b] Determined by ¹H NMR spectroscopy; ^[c] ee was determined by chiral phase HPLC analysis after NaBH₄ reduction of aldehyde to alcohol.

(Scheme 1, Entries 5 and 6). Aldehyde possessing electron-donating *o*-Me group gave lower yield (58%) presumably due to the increased steric congestion close to reaction centre. Diastereoselectivity dropped to approximately 3/1 for exo/endo isomers, but excellent enantioselectivity of 96% ee was observed (Scheme 1, Entry 7). Substrate possessing electron withdrawing *m*-Cl substituent gave 68% of desired products with 90% ee for major isomer (Scheme 1, Entry 8). Substrates with two electron withdrawing substituent reacted very efficiently as well giving desired products in good yields and excellent enantioselectivities (Scheme 1, Entries 9-11). Substrate with strong electron withdrawing CF₃ substituent gave product in 79%

yield and 84% ee (Scheme 1, Entry 12). Substrate possessing the voluminous 2-naphthyl group led to 76% of desired products in 87/13 *exo/endo* ratio and in 92% ee for major isomer (Scheme 1, Entry 13). In addition to aromatic substituents, heteroaromatic group such as 2-thienyl was successfully employed to give 61% of desired products in 87/13 *exo/endo* ratio and in 92% ee for major *exo* isomer (Scheme 1, Entry 14). Unfortunately, linear unsubstituted aliphatic aldehydes such as hexanal and nonanal did not undergo the oxidation reaction, and starting material was recovered in these cases. Aldehydes such as 7-phenylhept-4-enal and 3-benzyloxypropanal are not suitable substrates for the DDQ oxidation step in the presence of secondary amine catalysts.^{15b} Presence of extended π system or other stabilizing group is a prerequisite for reaction to progress. Pent-4-enal derivatives **8** undergo oxidation reaction since they possess extended π system that can stabilize charge and/or radical intermediate.¹⁵ These substrates upon enamine formation and oxidation would form $\alpha,\beta,\gamma,\delta$ -unsaturated iminium ion **9**. This type of the $\alpha,\beta,\gamma,\delta$ -unsaturated iminium ion system may undergo 1,4- or 1,6-conjugate addition reactions in the presence of diphenylprolinol silyl ether type catalyst, however, 1,4-addition is prevalent mode of reactivity.¹⁹ In a similar manner diene may react at α,β - or at γ,δ -double bonds of iminium ion **9**. Using standard reaction conditions we tested 5-substituted pent-4-enals **8** in our reaction setup using diaryl prolinol catalyst **3** (Table 2). An aromatic groups with *E*-configuration at the double bond were employed, affording the products in good yield. Ph substituted *E*-olefinic substrate gave good yield of 67% of *exo* isomer in 92% ee (Table 3, Entry 1). Substrates possessing electron-withdrawing *p*-Cl and *p*-Br substituents at the phenyl ring also efficiently reacted affording 70% and 72% yield, and 92% and 91% ee respectively (Table 3, Entries 2 and 3). However, when *Z*-substituted olefin was used as a substrate, *E*-olefinic *exo* isomer was isolated in 82/18 ratio of *exo/endo* isomers, with pure *exo* isomer being isolated in 63% yield and in 94% ee. In case of *Z*-olefin isomerisation under reaction conditions occurred which might be indicative of radical cation intermediate and single electron transfer oxidation mechanism. *Cis-Trans* Isomerisation of allylic radicals is a well known process.²⁰ In all cases *exo* isomers were isolated and their ee values were determined. The minor *endo* isomers were isolated as mixtures with small amount of Diels-Alder reaction product at γ,δ double bond as inseparable mixture of products.

Table 3. Scope of organocatalyzed asymmetric enamine oxidation/Diels-Alder reaction of 5-substituted pent-4-enals



Entry	Ar	Isolated Product (<i>exo</i>)	Time [h]	Yield ^a <i>exo</i> %	<i>Exo/endo</i> ^b	ee <i>exo</i> % ^c
1	<i>E</i> -Ph		72	67	86:14	92
2	<i>p</i> -ClC ₆ H ₄		72	70	85:15	92
3	<i>p</i> -Br C ₆ H ₄		72	72	84:16	91
4	<i>Z</i> -Ph		96	63	82:18	94

Reaction conditions unless otherwise indicated: Pent-4-enal derivative (0.5 mmol), catalyst (0.075 mmol), additive (0.15 mmol), Oxidant (0.5 mmol), and toluene (1 mL) stirred at room temperature for 2h. Subsequently cyclopentadiene (1.5 mmol) was added and reaction mixture stirred for designated period of time. See the Supporting Information for details. ^[a] Isolated yield after column chromatography; ^[b] Determined by ¹H NMR spectroscopy; ^[c] ee was determined by chiral phase HPLC analysis after NaBH₄ reduction of aldehyde to alcohol.

We have tested less reactive dienes, 2-methyl-1,3-butadiene and 2,3-dimethyl-1,3-butadiene using our optimized reaction conditions but they were unreactive with our standard substrates. The first step of the reaction i.e. DDQ oxidation of the enamine is thought to proceed via single-electron transfer from enamine to DDQ.²¹ A resonance-stabilized allylic radical cation is formed, from which hydrogen transfer would proceed to provide iminium ion (Figure 2). C-H bond dissociation energy of the radical cation has significantly lower energy than in starting material, allowing it to be abstracted by DDQ.

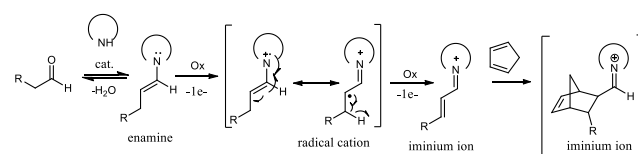
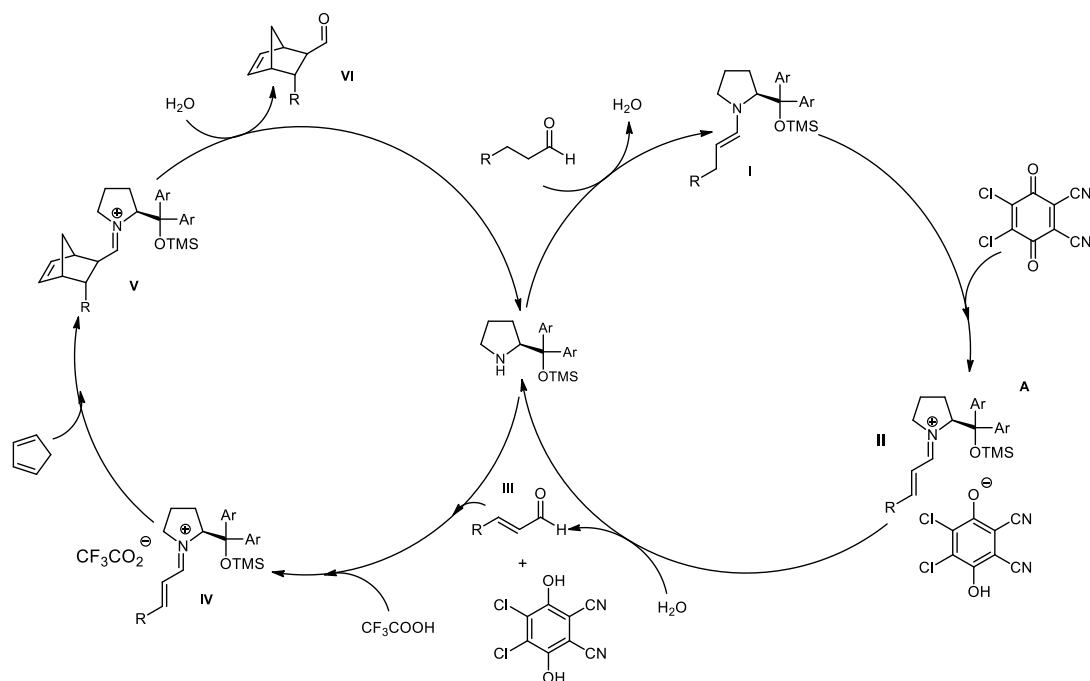


Figure 2. Proposed mechanisms for DDQ oxidation of enamines to iminium ions.



Scheme 1. Proposed catalytic cycle of DDQ oxidation/Diels-Alder reaction

In case of pent-4-enal substrates **8**, allylic radical intermediate is formed which in case of *Z*-substitution undergoes rapid *cis/trans* isomerisation providing *E* isomer of final product. When a solution of starting aldehyde **8** was combined with DDQ, we observed the immediate formation of a deep green to brown color that might be indicative of charge-transfer complex A (Scheme 1). Reaction is thought to proceed via the following catalytic cycle. Upon condensation of the catalyst with the saturated aldehyde enamine species **I** is formed. DDQ oxidizes enamine **I** to iminium ion **II**, that hydrolyzes to α,β -unsaturated aldehyde **III**. Upon addition of TFA, counter-ion change occurs, forming **IV**, which reacts with cyclopentadiene to form the Diels-Alder reaction product **V**. Upon hydrolysis, the transient iminium species **V** is converted to product **VI** and the catalyst is released and enters the new cycle.

In summary we have demonstrated the first example of an one-pot Diels-Alder reaction that commences from saturated aldehyde, to give Diels-Alder adducts in high yields and excellent enantioselectivities. Use of DDQ as an oxidant, in the presence of a secondary amine catalyst served as an effective system for promotion of swift conversion of enamines to iminium ions which subsequently react with a diene present in the reaction mixture to give the Diels-Alder products. This reversal of reactivity from electron-rich enamine to electron-deficient iminium ion served as a mechanistic foundation for our

reaction. Due to its operational simplicity and insensitivity to traces of water or air in the reaction mixture this very easily performed reaction setup can be of great use to the organic synthesis practitioners.

Experimental Section

Catalyst **3** (0.075 mmol) was added to a stirred solution of aldehyde (0.5 mmol) in toluene (1.2 ml) and allowed to stir for 15 minutes. Then DDQ (0.5 mmol) was added and solution was stirred at room temperature until TLC showed full conversion of starting aldehyde (typically 1-2h). Subsequently TFA (0.15 mmol) was added, solution stirred for 15 min and then cyclopentadiene (1.5 mmol) was added; after 24h additional cyclopentadiene (1 mmol) was added and reaction mixture stirred for additional 24-48h. Upon completion of reaction, excess of cyclopentadiene and toluene was evaporated under reduced pressure on the vacuum evaporator. Residue was redissolved in CH_2Cl_2 and solids were removed by filtration through cellite, solvent evaporated and remaining organic material submitted for ^1H NMR analysis. Purification was performed using SiO_2 column chromatography with Petrol ether/Ethyl acetate as an eluents. Enantiomeric excess was determined by chiral phase HPLC analysis after NaBH_4 reduction of isolated aldehyde to alcohol.

Acknowledgements

This work was supported by the Ministry of Education, Science and Technology of the Republic of Serbia (Grant No. 172020). We gratefully acknowledge COST action CA15106: C-H activation in organic synthesis (CHAOS) for support.

We thank Prof. Dr. Benjamin List for use of his HPLC equipment. D.-I. T and C.G.K gratefully acknowledge the Special Account for Research Grants of the National and Kapodistrian University of Athens for financial support

References

- [1] For reviews of enantioselective Diels-Alder reactions, see: a) D. A. Evans, J. S. Johnson in *Comprehensive Asymmetric Catalysis*, Vol.3 (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, New York, 1999, p. 1177; b) E. J. Corey, *Angew.Chem.Int. Ed.* **2002**, *41*, 1650; *Angew. Chem.* **2002**, *114*, 1724c) K. C. Nicolaou, S. A. Snyder, T. Montagnon, G. Vassilikogiannakis, *Angew.Chem.Int. Ed.* **2002**, *41*, 1668; *Angew.Chem.* **2002**, *114*, 1742; d) Y. Hayashi in *Cycloaddition Reaction in Organic Synthesis* (Eds.: S. Kobayashi, K. A. Jørgensen), Wiley-VCH, Weinheim, **2002**, chap. 1.
- [2] a) K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 4243; b) A. B. Northrup, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 2458; c) R. M. Wilson, W. S. Jen, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2005**, *127*, 11616.
- [3] a) K. H. Kim, S. Lee, D.-W. Lee, D.-H. Ko, D.-C. Ha, *Tetrahedron Lett.* **2005**, *46*, 5991; b) M. Lemay, W. W. Ogilvie, *Org. Lett.* **2005**, *7*, 4141; c) T. Kano, Y. Tanaka, K. Maruoka, *Org. Lett.* **2006**, *8*, 2687; d) M. Lemay, W. W. Ogilvie, *J. Org. Chem.* **2006**, *71*, 4663.
- For reviews on organocatalysis and organocatalytic cycloadditions, see: a) *Asymmetric Organocatalysis*; A. Berkessel, H. Groger, Eds.; Wiley-VCH: Weinheim, **2005**; b) P. I. Dalko, L. Moisan, *Angew.Chem.Int. Ed.* **2004**, *43*, 5138; *Angew.Chem.* **2004**, *116*, 5248; c) M. Marigo, K. A. Jørgensen, *Chem.Comm.* **2006**, 2001; d) M. J. Gaunt, C. C. C. Johnsson, A. McNally, N. T. Vo, *Drug Discovery Today* **2007**, *12*, 8; e) *Enantioselective Organocatalysis* (Ed.: P. I. Dalko), Wiley-VCH, Weinheim, **2007**. f) H. Pelisier, *Tetrahedron* **2012**, *68*, 2197; g) S. Meninno, A. Lattanzi, *Chem. Comm.* **2013**, *49*, 3821; h) V. Marcos, J. Aleman, *Chem. Soc. Rev.* **2016**, *45*, 6812; i) L. Klier, F. Tur, P. H. Poulsen, K. A. Jørgensen, *Chem. Soc. Rev.* **2017**, *46*, 1080; j) V. Marcos, J. Aleman, *Chem. Soc. Rev.* **2016**, *45*, 6812.
- [4] a) H. Gotoh, Y. Hayashi, *Org. Lett.* **2007**, *9*, 2859; b) Y. Hayashi, S. Samanta, H. Gotoh, H. Ishikawa, *Angew. Chem. Int. Ed.* **2008**, *47*, 6634; *Angew. Chem.* **2008**, *120*, 6736.
- [5] a) K. Ishihara, K. Nakano, *J. Am. Chem. Soc.* **2005**, *127*, 10504; b) A. Sakakura, K. Suzuki, K. Nakano, K. Ishihara, *Org. Lett.*, **2006**, *8*, 2229; c) A. Sakakura, K. Suzuki, K. Ishihara, *Adv. Synth. Catal.* **2006**, *348*, 2457; d) K. Ishihara, K. Nakano, M. Akakura, *Org. Lett.* **2008**, *10*, 2893.
- [6] T. Kano, Y. Tanaka, K. Osawa, T. Yurino, K. Maruoka, *Chem. Commun.* **2009**, 1956.
- [7] a) Y. Hayashi, B. P. Bondžić, T. Yamazaki, G. Yogesh, S. Ogasawara, T. Taniguchi, K. Monde, *Chem. Eur. J.* **2016**, *22*, 15874; b) N. O. Häggman, B. Zank, H. J. Jun, D. Kaldre, J. L. Gleason, *Eur. J. Org. Chem.* **2018**, 5412.
- [8] a) Y. Huang, A. K. Unni, A. N. Thadani, A. H. Rawal, *Nature*, **2003**, *424*, 146; b) A. N. Thadani, A. R. Stankovic, A. H. Rawal, *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101*, 5846; c) A. K. Unni, N. Takenaka, H. Yamamoto, V. H. Rawal, *J. Am. Chem. Soc.* **2005**, *127*, 1336.
- [9] a) P. R. Schreiner, A. Wittkopp, *Org. Lett.*, **2002**, *4*, 217; b) A. Wittkopp, P. R. Schreiner, *Chem.-Eur. J.* **2003**, *9*, 407.
- [10] D. Nakashima, H. Yamamoto, *J. Am. Chem. Soc.* **2006**, *128*, 9626.
- [11] N. Momiyama, K. Funayama, H. Noda, M. Yamanaka, N. Akasaka, S. Ishida, T. Iwamoto, M. Terada, *ACS Catal.* **2016**, *6*, 949.
- [12] M. Hatano, Y. Goto, A. Izumiseki, M. Akakura, K. Ishihara, *J. Am. Chem. Soc.* **2015**, *137*, 13472.
- [13] a) M. Koerner, B. Rickborn, *J. Org. Chem.* **1989**, *54*, 6; b) M. Koerner, B. Rickborn, *J. Org. Chem.* **1990**, *55*, 2662 c) H. Okamura, T. Iwagawa, M. Nakatani, *Tetrahedron Lett.* **1995**, *36*, 5939; d) H. Okamura, Y. Nakamura, T. Iwagawa, M. Nakatani, *Chem. Lett.* **1996**, 193; e) H. Okamura, H. Nagaike, T. Iwagawa, M. Nakatani, *Tetrahedron Lett.* **2000**, *41*, 4147.
- [14] Y. Wang, H. Li, Y.-Q. Wang, Y. Liu, B. M. Foxman, L. Deng, *J. Am. Chem. Soc.* **2007**, *129*, 6364.
- [15] a) Y. Hayashi, T. Itoh, H. Ishikawa, *Angew. Chem. Int. Ed.* **2011**, *50*, 3920; *Angew. Chem.* **2011**, *123*, 4006; b) Y. Hayashi, T. Itoh, H. Ishikawa, *Adv. Synth. Catal.* **2013**, *355*, 3661.
- [16] S.-L. Zhang, H.-X. Xie, J. Zhu, H. Li, X.-S. Zhang, J. Li, W. Wang *Nature communications* **2011**, Article No 211.
- [17] a) Z. Huang, G. Dong, *Tet. Lett.* **2014**, *55*, 5869-5889. b) Y.-L. Zhao, Y. Wang, X.-Q. Hu, P.-F. Xu, *Chem. Commun.*, **2013**, *49*, 7555. c) Y. K. Kang, D. Y. Kim, *Chem. Commun.* **2014**, *50*, 222. d) C. W. Suh, S. B. Woo, D. Y. Kim, *Asian J. Org. Chem.* **2014**, *3*, 399 - 402. e) L. Wang, J. Xiao, T.-P. Loh, *ChemCatChem*, **2014**, *6*, 1183 - 1185.
- [18] a) H. Gotoh, R. Masui, H. Ogino, M. Shoji, Y. Hayashi, *Angew. Chem. Int. Ed.* **2006**, *45*, 6853; *Angew. Chem.* **2006**, *118*, 7007; b) H. Gotoh, T. Uchimarui, Y. Hayashi, *Chem. Eur. J.* **2015**, *21*, 12337.
- [19] Y. Hayashi, D. Okamura, S. Umemiya, T. Uchimarui, *ChemCatChem* **2012**, *4*, 959; b) A. Ma, S. Zhu, D. Ma, *Tetrahedron Lett.* **2008**, *49*, 3075.
- [20] a) D. Cheng, W. Bao, *Adv. Synth. Catal.* **2008**, *350*, 1263; b) P. C. Montevicchi, M. L. Navacchia, *J. Org. Chem.* **1998**, *63*, 8035; c) Y. Zhang, C.-J. Li, *J. Am. Chem. Soc.* **2006**, *128*, 4242; d) B.-P. Ying, B. G. Trogden, D. T. Kohlman, S. X. Liang, Y.-C. Xu, *Org. Lett.* **2004**, *6*, 1523.
- [21] R. M. Hoyte, D. B. Denney, *J. Org. Chem.* **1974**, *39*, 2607.

COMMUNICATION

Enantioselective organocatalytic enamine C-H oxidation/Diels-Alder reaction

Adv. Synth. Catal. **Year**, *Volume*, Page - Page

Zdravko Džambaski,^a Dimitrios-Ioannis
Tzaras,^b Sunggi Lee,^c Christoforos G.
Kokotos,^b and Bojan P. Bondzic^{a, *}

