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Authors: Subhas Chandra Pan and Rajendra Maity

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Dienamine- Mediated Asymmetric Inverse-Electron-Demand Hetero-Diels-Alder Reaction of Linear Deconjugated Enones: Diversity Oriented Synthesis of 3,4-Dihydropyrans

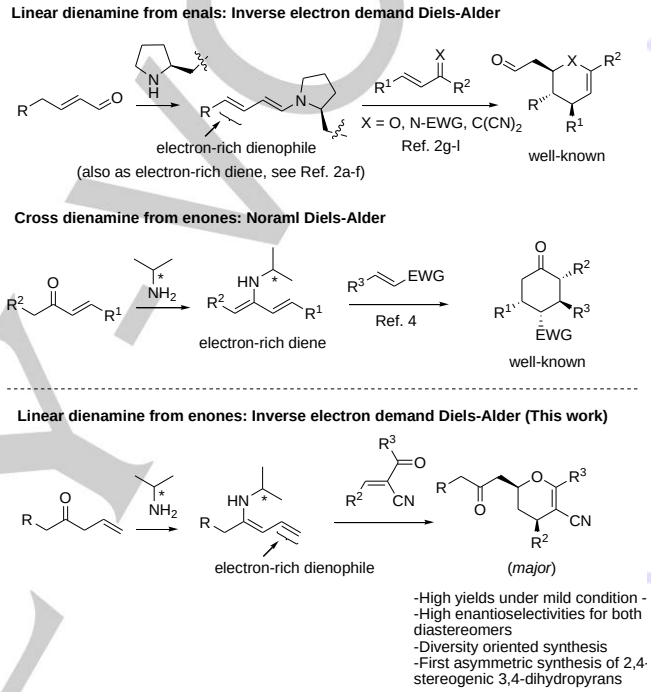
Rajendra Maity and Subhas Chandra Pan*[a]

Dedication ((optional))

Abstract: The first organocatalytic asymmetric inverse electron demand Diels-Alder reaction of deconjugated enones *via* linear dienamine is disclosed. Electron poor oxadienes having cyano group was found to be suitable in this reaction. With 20 mol% of quinine derived primary amine catalyst, high yields as well as excellent enantioselectivities are attained for a variety of 2,4-stereogenic 3,4-dihydropyran products under mild reaction conditions.

Over the last decade, asymmetric dienamine catalysis[1] has been broadly explored for the synthesis of structurally diverse chiral molecules. Both enals and enones were employed in this mode of catalysis. After the initial work by Jørgensen group[2a] on dienamine catalysis of enals having *γ*-CH, it has been extensively used both as electron-rich diene in normal Diels-Alder reaction[2a-f] and as electron-rich dienophile in inverse electron-demand Diels-Alder reactions[2g-m,3] (Scheme 1). Similarly, conjugated enones having *ά*-CH in general make the preferential formation of cross-conjugated dienamines and this lead to a variety of cyclization reactions (Scheme 1).[4] Melchiorre group[5] first demonstrated primary amine catalyzed asymmetric vinylogous addition[6] reactions with *β*-substituted 2-cyclohexenones via extended dienamines. Chen and co-workers later disclosed an alternate generation of extended dienamines from deconjugated linear ketones having *ά*-CH groups and applied in asymmetric vinylogous Michael addition to maleimides.[7] In a parallel way, deconjugated linear ketones having non-enolizable aryl or *tert*-butyl groups were employed in vinylogous additions using a variety of organocatalysts[8] and magnesium complex.[9] However, to the best of our knowledge, deconjugated linear enones have not been explored in Diels-Alder cyclization reactions via dienamine or other mode of catalysis.

Stereogenic dihydropyrans are important structural motif present in a wide range of natural products and bioactive compounds.[10] In addition, because of the presence of double bond, dihydropyrans undergo a variety of chemical transformations and can be converted to biologically important tetrahydropyrans.[11] Accordingly a number of approaches have been reported in the chiral synthesis of a range of of dihydropyrans.[12, 13] Asymmetric inverse-electron-demand Diels-Alder reaction[3] appears to be a powerful method for the synthesis of dihydropyrans. Jorgensen and co-workers have elegantly applied this strategy in dienamine mediated cyclization reaction of enals with electron deficient *α*-keto esters.[2i] Lu and co-workers reported phosphine catalyzed [4+2] annulation reaction between allenones and *β*,*γ*-unsaturated *α*-ketoesters.[12g] Also different amine catalyzed cascade/cyclization reactions have been developed for the synthesis of chiral dihydropyrans.[13] Despite these methods direct synthesis of chiral dihydropyrans with skeletal and stereogenic divergence is still a difficult task. Here in we like to present dienamine mediated asymmetric inverse-electron- demand Diels-Alder reaction of deconjugated enones bearing *ά*-CH groups with oxadienes for the synthesis of 2,4-stereogenic 3,4-dihydropyrans (Scheme 1).



Scheme 1. Asymmetric dienamine catalysis in Diels-Alder reactions.

Our investigation was started by performing a model reaction between deconjugated 3-enone **1a** and readily accessible oxadiene **2a** with commercially available (*R*,*R*)-1,2-diphenylethanediamine (**I**) in combination with benzoic acid (Table 1). Pleasingly the desired inverse electron demand Diels-

[a] R. Maity and Prof. Dr. S. C. Pan
Department of Chemistry
Indian Institute of Technology Guwahati
Assam, 781039, India
E-mail: span@iitg.ernet.in
Webpage: www.iitg.ac.in/span

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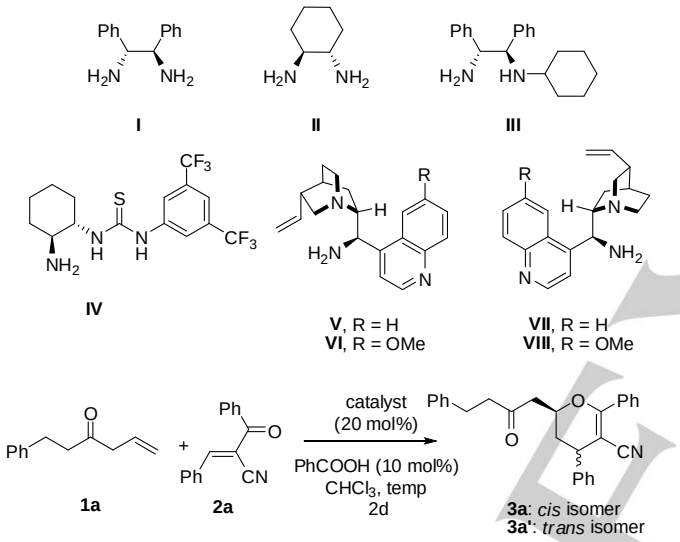
Alder products **3a/3a'** were formed in 80% yield with 1.3:1 diastereomeric ratio albeit moderate enantiomeric excesses were obtained (major-59% ee, minor 68% ee). The structure of the major *endo cis* diastereomer **3a** was confirmed by X-ray crystallography.[14] The enantioselectivity was not improved using (*S*,*S*)-1,2-cyclohexyldiamine **II** (entry 2). Interestingly, catalyst **III** having secondary amine moiety delivered the products in higher enantioselectivities though similar diastereoselectivities were obtained (entry 3). Bifunctional thiourea catalyst **IV** provided the products in similar enantioselectivities (entry 4). Then we turned our attention on the use of cinchona alkaloid derived primary amines **V-VIII** (entries 5-8). Gratifyingly, these catalysts were found to be efficient and in particular, 9-amino-9-deoxyepiquinine **VIII** was the best providing excellent enantioselectivities (95% and 93% ee) for both diastereomers (entry 8). Delightfully, the diastereoselectivity was further enhanced to 2.6:1 by lowering the reaction temperature to 0 °C (entry 9). Screening of other reaction parameters such as solvent and acid additives were also performed but resulted in inferior results (see supporting information for details).

With the optimized conditions in hand we ventured in the scope of the reaction. Initially a variety of oxadienes **2** having substitutions on the aryl group of the olefin was examined (Table 2). It turned out that a variety of electron-withdrawing and electron-donating groups can be incorporated in the *ortho*-, *meta*- and *para*-position of the aryl group and excellent enantioselectivities were maintained. For example, enone **2b**

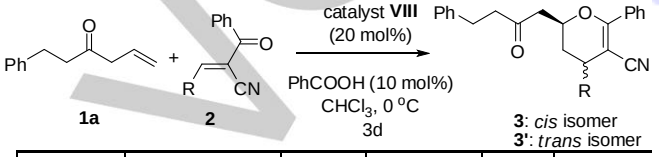
Table 1: Catalyst Screening and Optimization of Reaction Conditions



Entry[a]	Catalyst	Temp	Yield [%][b]	d.r.[c]	ee [%][d]
1	**I**	RT	80	1.3:1	-59/-68
2	**II**	RT	80	1.5:1	55/50
3	**III**	RT	90	1.5:1	-82/-91
4	**IV**	RT	60	1.2:1	80/82
5	**V**	RT	92	1.8:1	-79/-84
6	**VI**	RT	90	2:1	-81/-82
7	**VII**	RT	92	1.2:1	90/88
8	**VIII**	RT	98	1.5:1	95/93
9[e]	**VIII**	0 °C	91	2.6:1	96/93

[a] Unless otherwise mentioned, reactions were carried out with 0.1 mmol of **1a** with 0.1 mmol of **2a** in 1 ml solvent. [b] Isolated yield after silica gel column chromatography. [c] Determined by 1H NMR, major **3a**. [d] Ee of both diastereomers were determined by chiral HPLC. [e] Reaction time 3d.

Table 2: Scope of Oxadiene with Varied Double Bond Substituents



Entry[a]	R	3	Yield [%][b]	d.r.[c]	ee [%][d]
1	Ph	**3a/3a'**	98	2.6:1	98/93
2	4-MeC_6H_4	**3b/3b'**	99	1.6:1	97/91
3	4-OMeC_6H_4	**3c/3c'**	62	2.1:1	98/95
4	4-*i*PrC_6H_4	**3d/3d'**	80	2.6:1	98/94
5	4-N$Me_2C_6H_4$	**3e/3e'**	89	1.9:1	98/95
6	4-PhC_6H_4	**3f/3f'**	95	1.2:1	97/92
7	4-ClC_6H_4	**3g/3g'**	98	1.1:1	93/92
8	4-BrC_6H_4	**3h/3h'**	70	1.9:1	96/98
9	4-$NO_2C_6H_4$	**3i/3i'**	80	1:1	99/94
10	3-MeC_6H_4	**3j/3j'**	98	4.5:1	98/97
11	3-BrC_6H_4	**3k/3k'**	80	1.8:1	94/93
12	3-$NO_2C_6H_4$	**3l/3l'**	67	1.4:1	93/96
13	2-MeC_6H_4	**3m/3 m'**	98	1.2:1	95/95
14	2-naphthyl	**3n/3n'**	88	1.6:1	95/97
15	2-furyl	**3o/3o'**	98	1.6:1	97/99
16	3,4-$(OMe)_2C_6H_3$	**3p/3p'**	86	2.3:1	97/96
17	*c*Hexyl	**3q/3q'**	85	7:1	94

[a] All reactions were carried out with 0.1 mmol of **1a** with 0.1 mmol of **2** in 1 ml solvent. [b] Isolated yield after silica gel column chromatography. [c] Determined by 1H NMR. [d] Ee of both diastereomers were determined by chiral HPLC.

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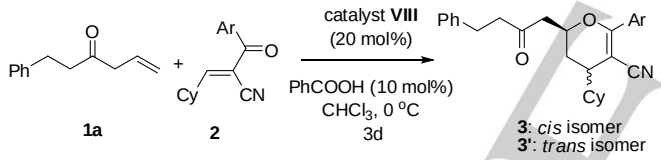
having *p*-tolyl moiety provided products **3b/3b'** in 99% yield with 1.6:1 dr and 97%/91% ees were achieved (Table 2, entry 2). Other 4-substituted aryl groups were also screened and the products were attained in excellent enantioselectivities (entries 3-9). Next different *meta*-substitutions were investigated and the products were similarly obtained in high enantioselectivities (entries 10-12). In particular, fair 4.5: 1 dr was achieved from *m*-tolylsubstituted oxadiene **2j** (entry 10). *ortho*-Substituted aryl enone **2m** also reacted smoothly to provide 98% yield of the products (entry 13). Moreover, 2-naphthyl and 2-furyl as well as 3,4-*di*-substituted aryl containing oxadiene substrates could also be employed in our reaction condition preserving high enantioselectivities (entries 14-16). Gratifyingly, our methodology is also appropriate for aliphatic enone such as cyclohexylsubstituted enone **2q**, and the desired products **3q**/**3q'** were obtained in a decent 7:1 dr with 94% ee for the major diastereomer.

The generality of the reaction was further demonstrated by applying oxadienes **2** with varied ketone functionalties (Table 3). Accordingly, a variety of cyclohexyl substituted oxadienes **2r-v** were prepared and subjected in the reaction. To our delight, the reaction was in general irrespective of the electronic nature of the aryl group and up to 99% enantiomeric excess was obtained with fair diastereomeric ratios (entries 1-5). The diastereomeric ratio was lower for oxadiene **2w** having phenyl group but again excellent enatioselectivities were achieved (entry 6).

Table 3: Scope of Oxadiene with Varied Ketone Substituents

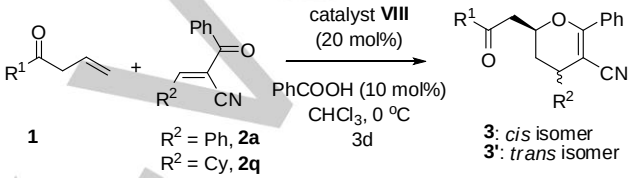


Entry[a]	Ar	3	Yield [%][b]	d.r.[c]	ee [%][d]
1	4-MeC_6H_4	**3r/3r'**	82	3.6:1	92/86
2	4-$OMeC_6H_4$	**3s/3s'**	60	4.9:1	94/99
3	4-ClC_6H_4	**3t/3t'**	60	3:1	96/96
4	4-BrC_6H_4	**3u/3u'**	91	2.5:1	95/95
5	3-ClC_6H_4	**3v/3v'**	68	2.9:1	93/92
6[e]	4-ClC_6H_4	**3w/3w'**	80	1:1	94/97

[a] All reactions were carried out with 0.1 mmol of **1a** with 0.1 mmol of **2** in 1 ml solvent. [b] Isolated yield after silica gel column chromatography. [c] Determined by 1H NMR. [d] Ee of both diastereomers were determined by chiral HPLC. [e] Phenyl (Ph) group instead of cyclohexyl (Cy) in **2**.

The next phase of experiments involved screening of different deconjugated enones **1** in this method (Table 4). It turns out that a wide range of alkyl groups could be employed in the reaction and excellent enantioselectivities were attained with modest to good diastereomeric ratios. Initially, different substitutions on the phenyl moiety of hydrocinnamyl group were studied and delightfully excellent results were obtained (entries 1-4). For example, after reaction with oxadiene **2q**, enone **1b** provided the corresponding products **3x**/**3x'** in excellent yields and with high enantiomeric excesses (entry 1). Interestingly enone **1d** delivered products with **2a** and **2q** in similar enatioselectivities and to our delight higher diastereomeric excess was obtained for products **3z**/**3z'** (entry 3). Then enone **1e** having benzyl group was employed and the corresponding products **3ab**/**3ab'** were attained in high enantioselectivities (entry 5). Then we focused on the investigation of different branched and unbranched alkyl group substituted enones (entries 6-11) and gratifyingly, irrespective of the chain length, they exhibited similar reactivities and outcomes.

Table 4: Scope of Deconjugated Enones



Entry[a]	R^1	2	3	Yield [%][b]	d.r.[c]	ee [%][d]
1	4-$OMeC_6H_4(CH_2)_2$	**2q**	**3x/3x'**	90	5.9:1	99/85
2	4-$ClC_6H_4(CH_2)_2$	**2q**	**3y/3y'**	40	2.2:1	96/96
3	2-$OMeC_6H_4(CH_2)_2$	**2q**	**3z/3z'**	65	4.4:1	99/72
4	2-$OMeC_6H_4(CH_2)_2$	**2a**	**3aa/ 3aa'**	55	2:1	97/86
5	Benzyl	**2a**	**3ab/ 3ab'**	93	1.1:1	94/90
6	Ethyl	**2a**	**3ac/ 3ac'**	45	1.9:1	97/84
7	*n*Propyl	**2a**	**3ad/ 3ad'**	86	1.9:1	95/87
8	*n*Butyl	**2a**	**3ae/ 3ae'**	72	1.5:1	95/92
9	*n*Pentyl	**2a**	**3af/ 3af'**	94	1.3:1	94/91
10	*n*Hexyl	**2a**	**3ag/ 3ag'**	90	2.5:1	97/94
11	*i*Butyl	**2a**	**3ah/ 3ah'**	53	1:1	92/95

[a] All reactions were carried out with 0.1 mmol of **1** with 0.1 mmol of **2a/2q** in 1 ml solvent. [b] Isolated yield after silica gel column chromatography. [c] Determined by 1H NMR. [d] Ee of both diastereomers were determined by chiral HPLC.

The absolute configuration of product **3a** was unambiguously confirmed by X-ray crystallography and was found to be (2*R*, 4*S*) (Figure 1).[14] The absolute structure of the other dihydropyran products was thought to be (2*R*, 4*S*) by analogy.

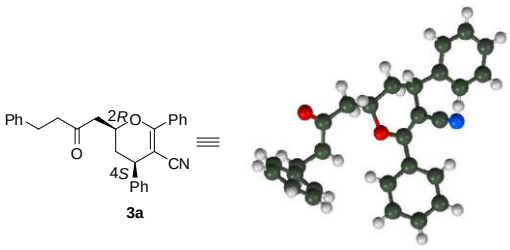


Figure 1. X-ray structure of **3a**.

In summary, we have developed a fascinating inverse electron demand Diels-Alder reaction of linear deconjugated enones catalyzed by easily available quinine derived primary amine and benzoic acid.[15] The dihydropyran products having two stereogenic centres are important frameworks and could be applied in the synthesis of pharmaceuticals and bioactive natural products. Investigation of the preparation of other heterocyclic and carbocyclic rings using this strategy is currently in progress in our laboratory.

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Keywords: dihydropyran • organocatalysis • dienamine• inverse electron-demand Diels-Alder• enantioselectivity

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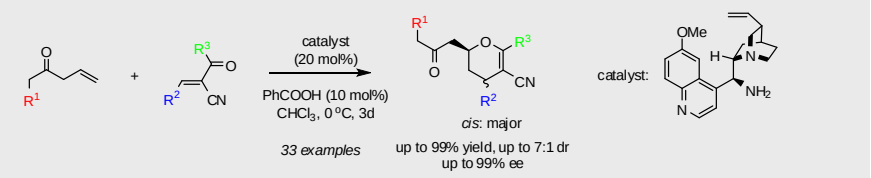

*Rajendra Maity, Subhas Chandra Pan**

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Dienamine- Mediated Asymmetric Inverse-Electron-Demand Hetero-Diels-Alder Reaction of Deconjugated Enones: Diversity Oriented Synthesis of 3,4-Dihydropyrans

A highly efficient and enantioselective synthesis of 2,4-stereogenic 3,4-dihydropyrans has been developed using dienamine mediated inverse-electron-demand hetero-Diels-Alder reaction. Deconjugated enones having ά-CH groups and electron deficient oxadienes with cyano group have been engaged in this transformation. With 20 mol% of primary amine and benzoic acid, high yields and excellent enantioselectivities were obtained for a range of 3,4-dihydropyrans.

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