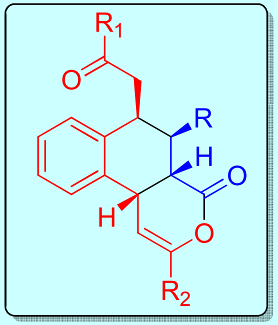
Angewandte Chemie International Edition

Faisal NAWAZ
RCC-2, 10-02-2011
ISM2, Marseille

A Highly Regio- and Stereoselective Cascade Annulation of Enals and Benzodi(enone)s Catalyzed by N-Heterocyclic Carbenes**



X. Fang, K. Jiang, C. Xing, L. Hao, and Y. R. Chi*

***Angew. Chem. Int. Ed.* 2011**

Early view DOI: 10.1002/anie.201007144

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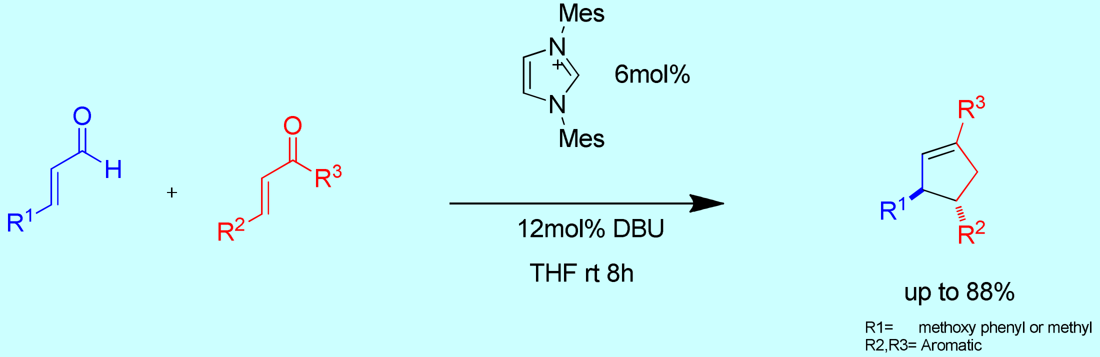
Division of Chemistry & Biological Chemistry School of Physical & Mathematical Sciences

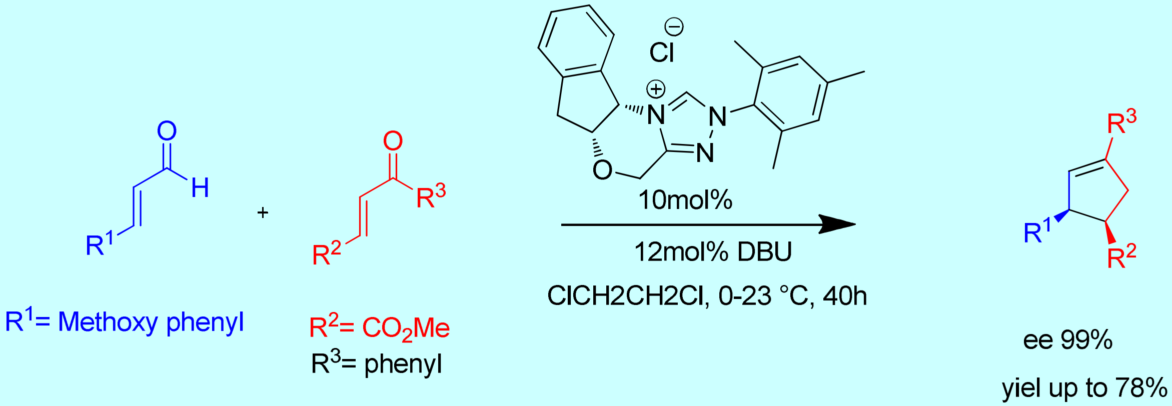
Background……



up to 88%

R1= methoxy phenyl or methyl
R2,R3= Aromatic

V. Nair et al, JACS 2006 8736



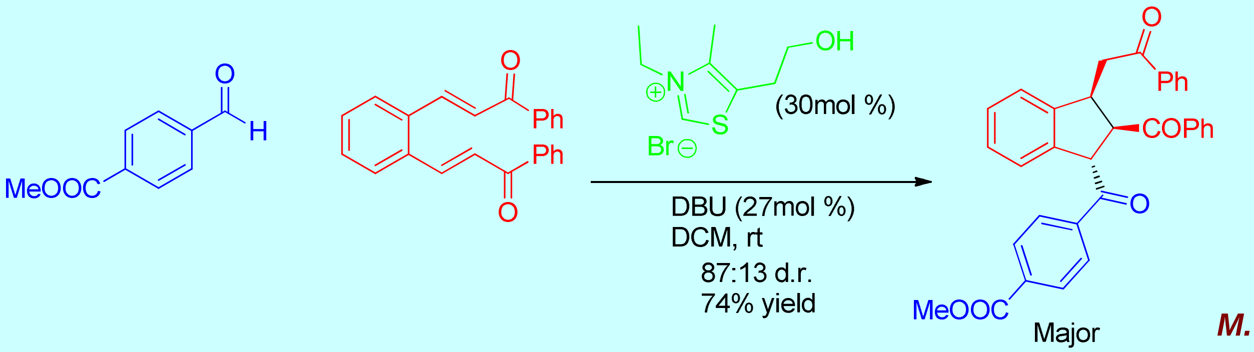
R^1= Methoxy phenyl

R^2= CO_2Me
R^3= phenyl

ee 99%

yiel up to 78%

W.Bode et al JACS 2007, 3520



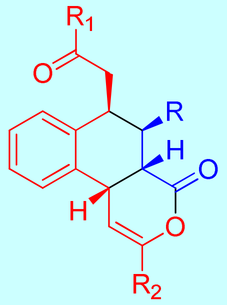
87:13 d.r.
74% yield

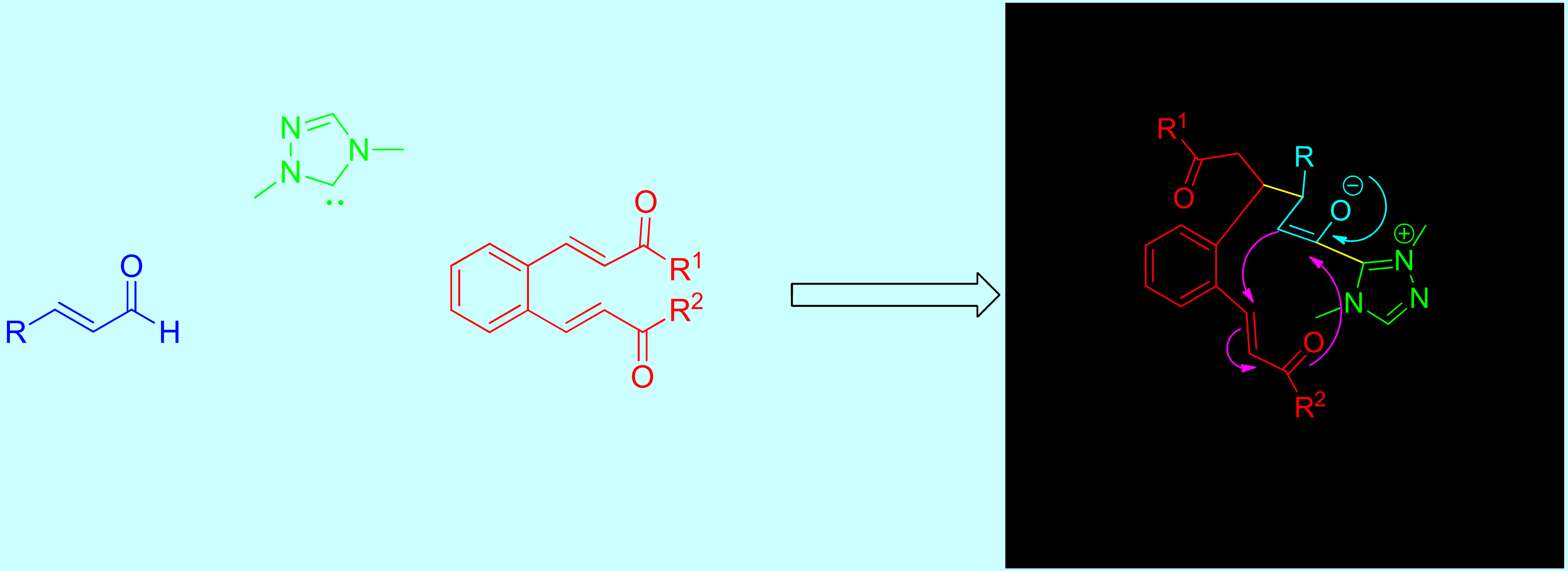
Major

M. Gravel et al JOC 2009, 7536

Present reaction…..

new annulation of enals and di(enone)s that generates benzotricyclic products





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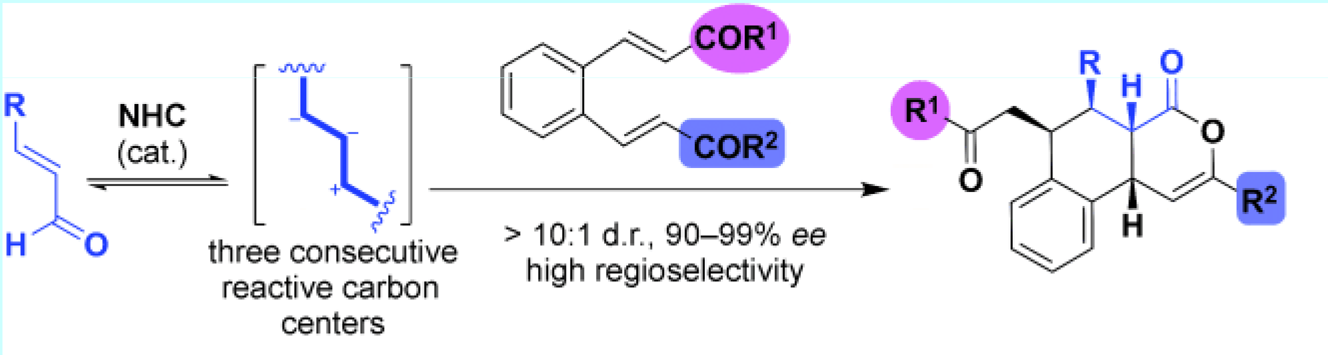
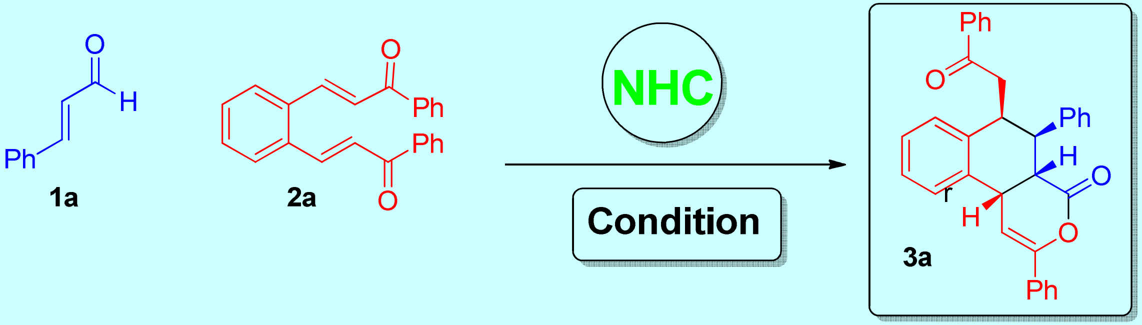
Three stereogenic centers in a row:

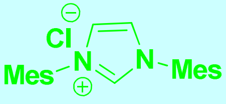
The unconventional activation of enal compounds mediated by an N-heterocyclic carbene (NHC) has generated three consecutive reactive carbon centers that undergo highly regio- and stereoselective annulations with di(enone)s to generate benzotricyclic products containing multiple stereogenic centers

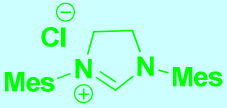


X. Fang, K. Jiang, C. Xing, L. Hao, and Y. R. Chi Angew. Chem. Int. Ed.* 2011,

Catalyst and conditions screened in the intitial study:




A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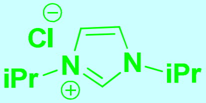
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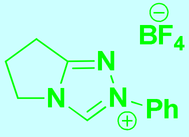
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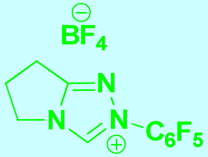
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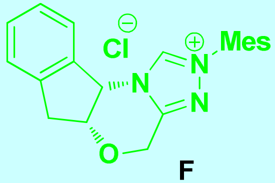
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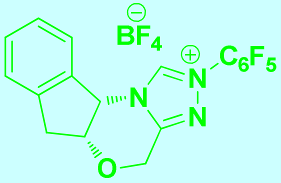
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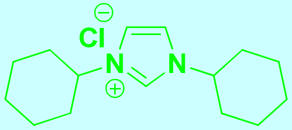
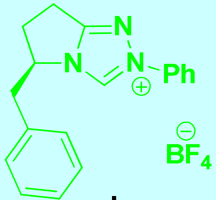

H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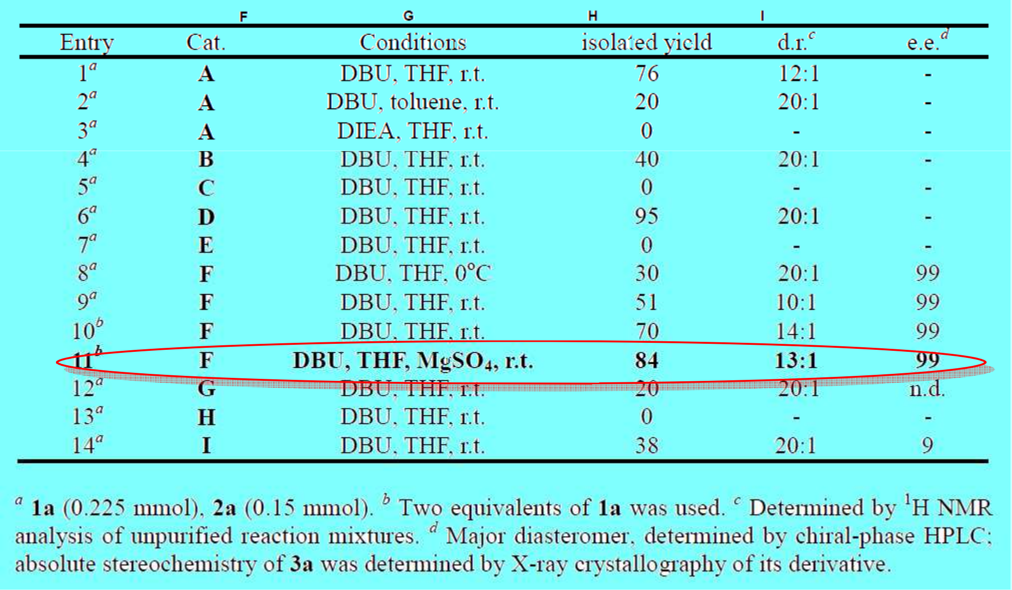

Entry	Cat.	Conditions	isolated yield	d.r.[c]	e.e.[d]
1[a]	**A**	DBU, THF, r.t.	76	12:1	-
2[a]	**A**	DBU, toluene, r.t.	20	20:1	-
3[a]	**A**	DIEA, THF, r.t.	0	-	-
4[a]	**B**	DBU, THF, r.t.	40	20:1	-
5[a]	**C**	DBU, THF, r.t.	0	-	-
6[a]	**D**	DBU, THF, r.t.	95	20:1	-
7[a]	**E**	DBU, THF, r.t.	0	-	-
8[a]	**F**	DBU, THF, 0°C	30	20:1	99
9[a]	**F**	DBU, THF, r.t.	51	10:1	99
10[b]	**F**	DBU, THF, r.t.	70	14:1	99
11[b]	**F**	**DBU, THF, $MgSO_4$, r.t.**	**84**	**13:1**	**99**
12[a]	**G**	DBU, THF, r.t.	20	20:1	n.d.
13[a]	**H**	DBU, THF, r.t.	0	-	-
14[a]	**I**	DBU, THF, r.t.	38	20:1	9

[a] **1a** (0.225 mmol), **2a** (0.15 mmol). [b] Two equivalents of **1a** was used. [c] Determined by ^1H NMR analysis of unpurified reaction mixtures. [d] Major diasteromer, determined by chiral-phase HPLC; absolute stereochemistry of **3a** was determined by X-ray crystallography of its derivative.

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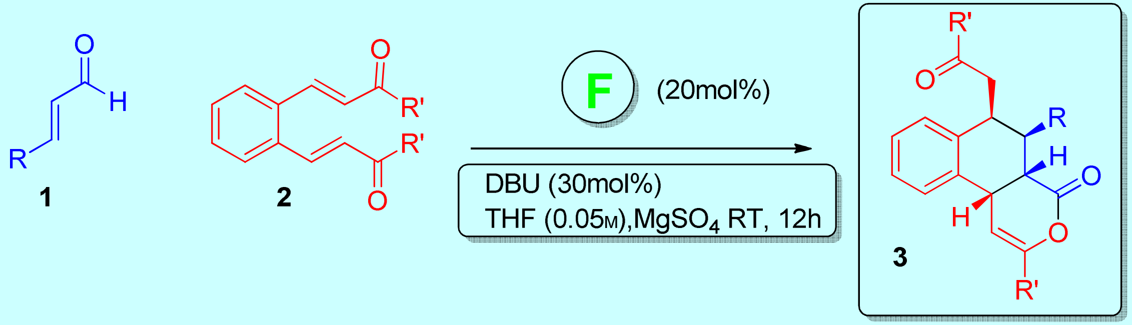

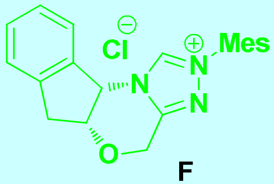

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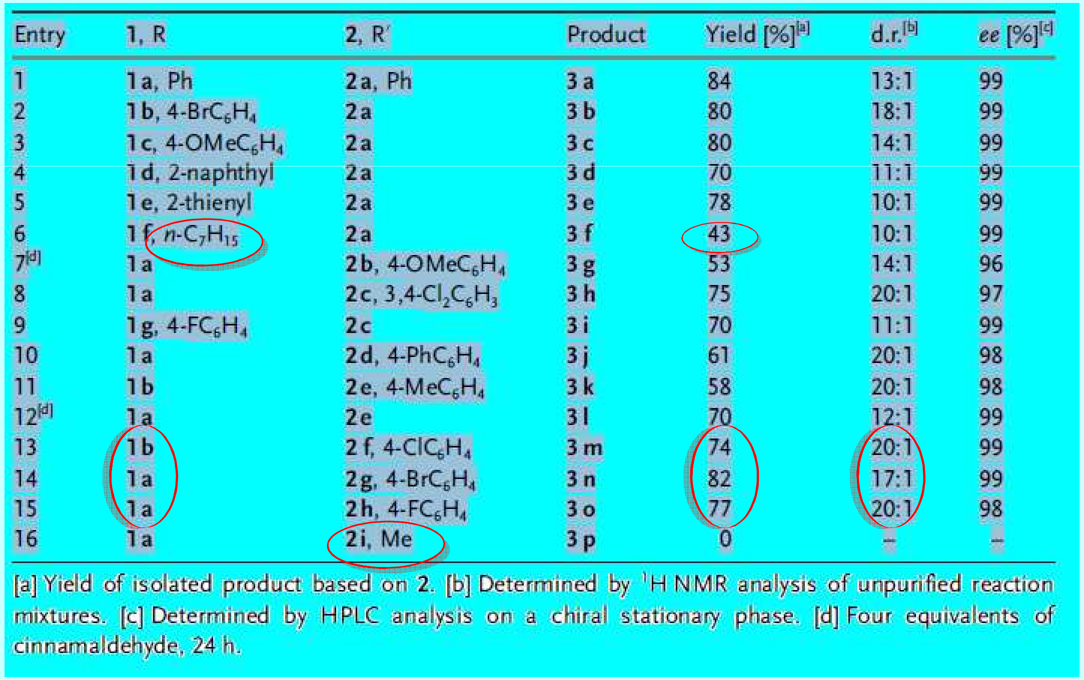

Entry	1, R	2, R′	Product	Yield [%][a]	d.r.[b]	*ee* [%][c]
1	**1a**, Ph	**2a**, Ph	**3a**	84	13:1	99
2	**1b**, 4-BrC_6H_4	**2a**	**3b**	80	18:1	99
3	**1c**, 4-OMeC_6H_4	**2a**	**3c**	80	14:1	99
4	**1d**, 2-naphthyl	**2a**	**3d**	70	11:1	99
5	**1e**, 2-thienyl	**2a**	**3e**	78	10:1	99
6	**1f**, *n*-C_7H_{15}	**2a**	**3f**	43	10:1	99
7[d]	**1a**	**2b**, 4-OMeC_6H_4	**3g**	53	14:1	96
8	**1a**	**2c**, 3,4-$Cl_2C_6H_3$	**3h**	75	20:1	97
9	**1g**, 4-FC_6H_4	**2c**	**3i**	70	11:1	99
10	**1a**	**2d**, 4-PhC_6H_4	**3j**	61	20:1	98
11	**1b**	**2e**, 4-MeC_6H_4	**3k**	58	20:1	98
12[d]	**1a**	**2e**	**3l**	70	12:1	99
13	**1b**	**2f**, 4-ClC_6H_4	**3m**	74	20:1	99
14	**1a**	**2g**, 4-BrC_6H_4	**3n**	82	17:1	99
15	**1a**	**2h**, 4-FC_6H_4	**3o**	77	20:1	98
16	**1a**	**2i**, Me	**3p**	0	–	–

[a] Yield of isolated product based on **2**. [b] Determined by ^{1}H NMR analysis of unpurified reaction mixtures. [c] Determined by HPLC analysis on a chiral stationary phase. [d] Four equivalents of cinnamaldehyde, 24 h.

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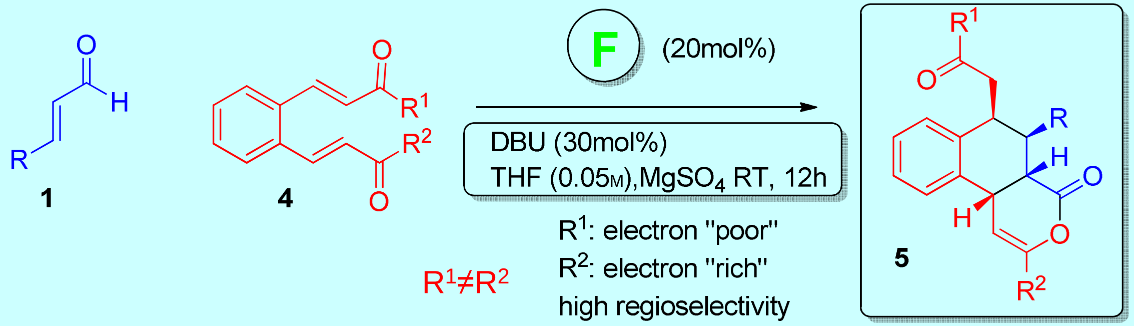
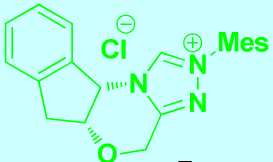


(20mol%)

DBU (30mol%)
THF (0.05M),$MgSO_4$ RT, 12h

R^1: electron "poor"
R^2: electron "rich"
high regioselectivity

$R^1 \neq R^2$



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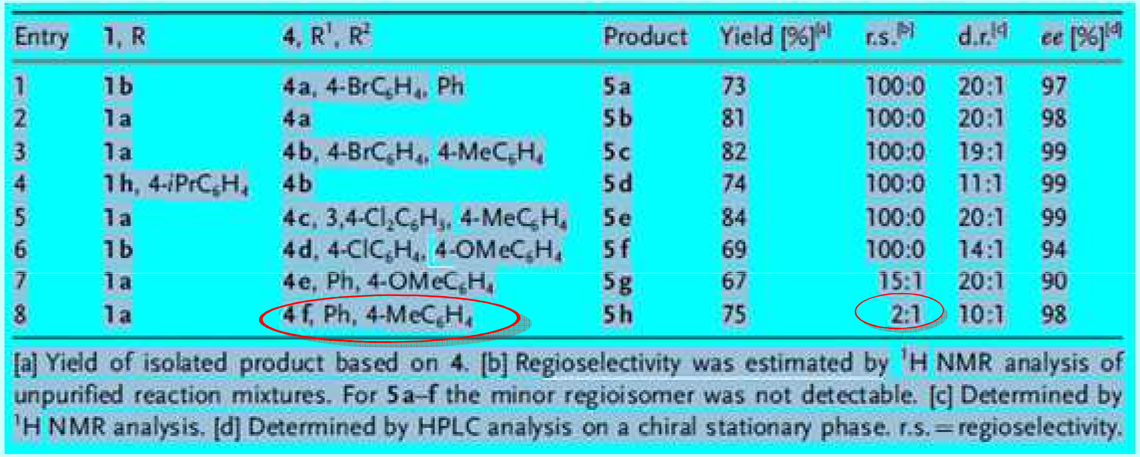
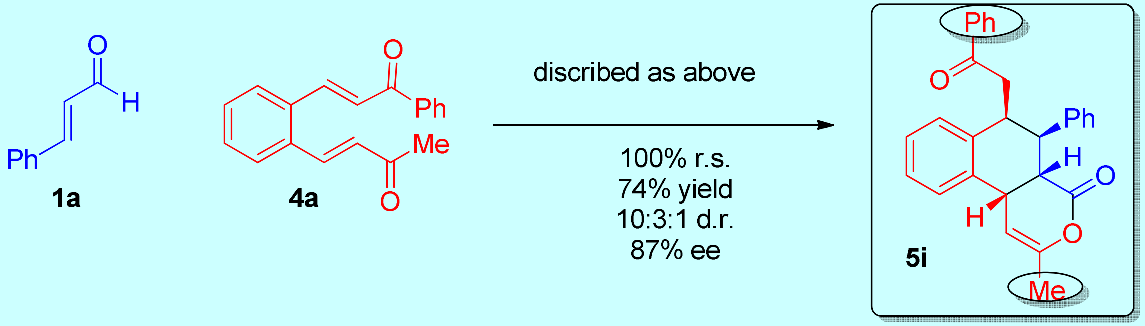


Entry	1, R	4, R^1, R^2	Product	Yield [%][a]	r.s.[b]	d.r.[c]	*ee* [%][d]
1	**1b**	**4a**, 4-BrC_6H_4, Ph	**5a**	73	100:0	20:1	97
2	**1a**	**4a**	**5b**	81	100:0	20:1	98
3	**1a**	**4b**, 4-BrC_6H_4, 4-MeC_6H_4	**5c**	82	100:0	19:1	99
4	**1h**, 4-*i*PrC_6H_4	**4b**	**5d**	74	100:0	11:1	99
5	**1a**	**4c**, 3,4-$Cl_2C_6H_3$, 4-MeC_6H_4	**5e**	84	100:0	20:1	99
6	**1b**	**4d**, 4-ClC_6H_4, 4-$OMeC_6H_4$	**5f**	69	100:0	14:1	94
7	**1a**	**4e**, Ph, 4-$OMeC_6H_4$	**5g**	67	15:1	20:1	90
8	**1a**	**4f**, Ph, 4-MeC_6H_4	**5h**	75	2:1	10:1	98

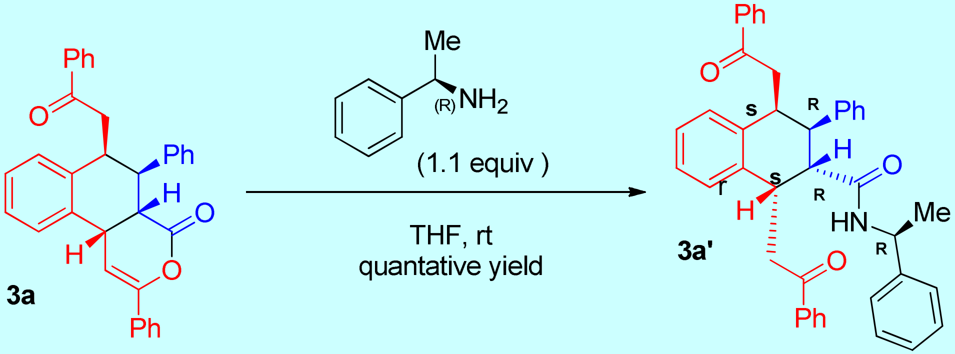
[a] Yield of isolated product based on **4**. [b] Regioselectivity was estimated by ^1H NMR analysis of unpurified reaction mixtures. For **5a–f** the minor regioisomer was not detectable. [c] Determined by ^1H NMR analysis. [d] Determined by HPLC analysis on a chiral stationary phase. r.s. = regioselectivity.

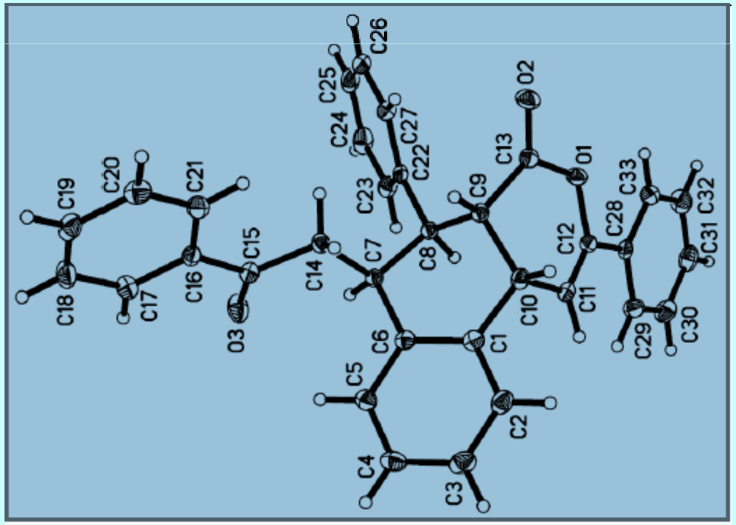


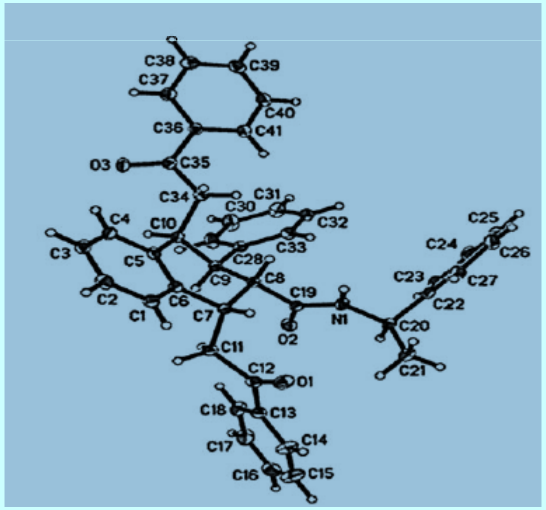
discribed as above

100% r.s.
74% yield
10:3:1 d.r.
87% ee

Stereochemistry determination via X-Ray Crystallographic analysis.







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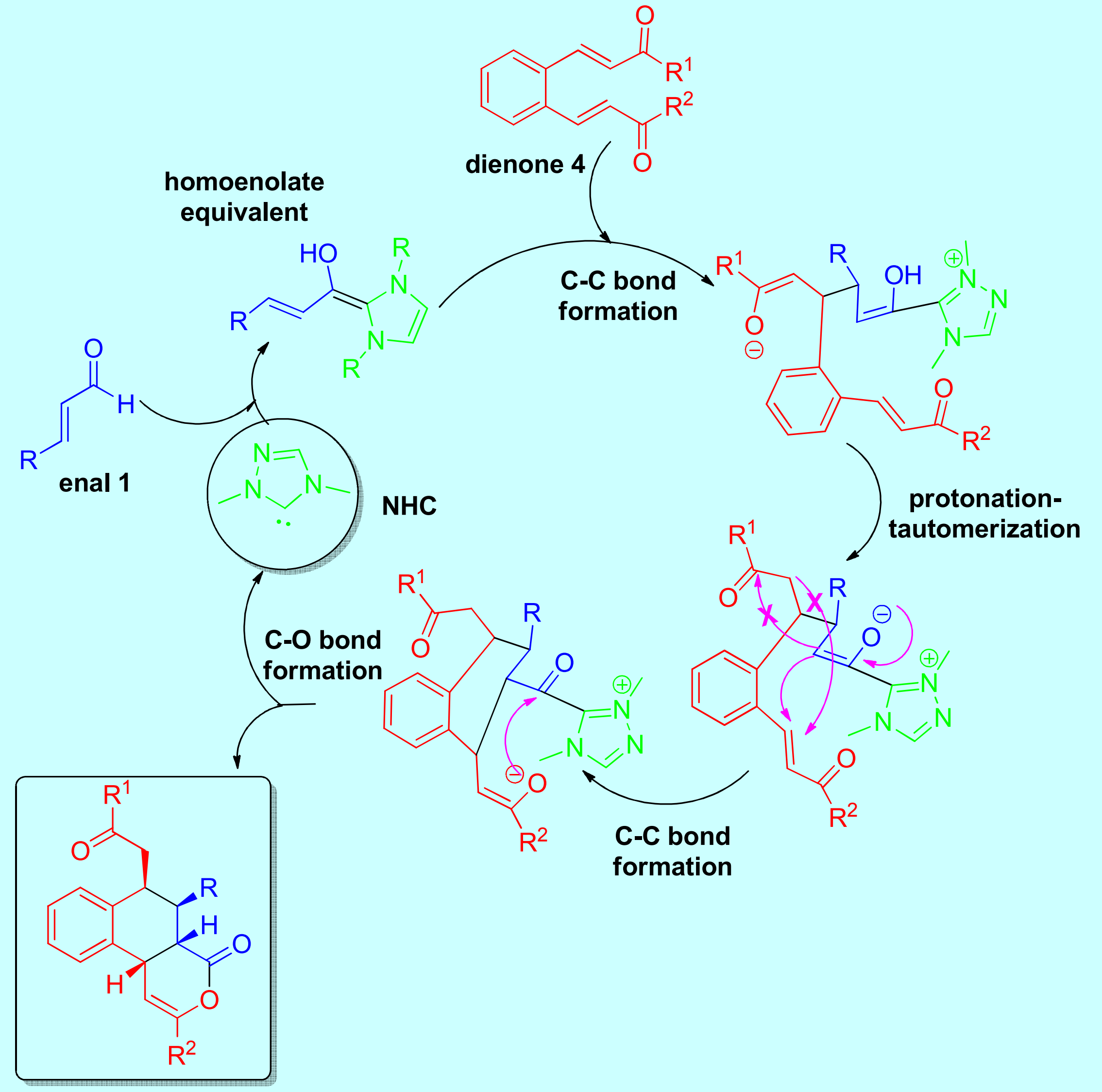
Mechanism…….



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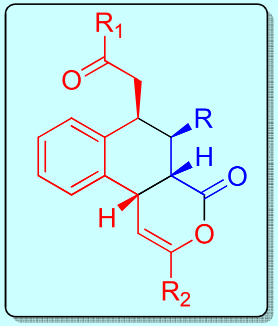
conclusion

- Developed a new annulation of di(enone) and enal substrates mediated by NHCs to generate substituted multicyclic compounds with high regio- and stereoselectivities.

- The observed regioselectivity is consistent with a Michael-type addition of the enal β-carbon atom to the enone to form the first new C-C bond of the cascade product.

- The method provides a rapid entry to relatively complex structures from simple starting materials in a highly selective manner.



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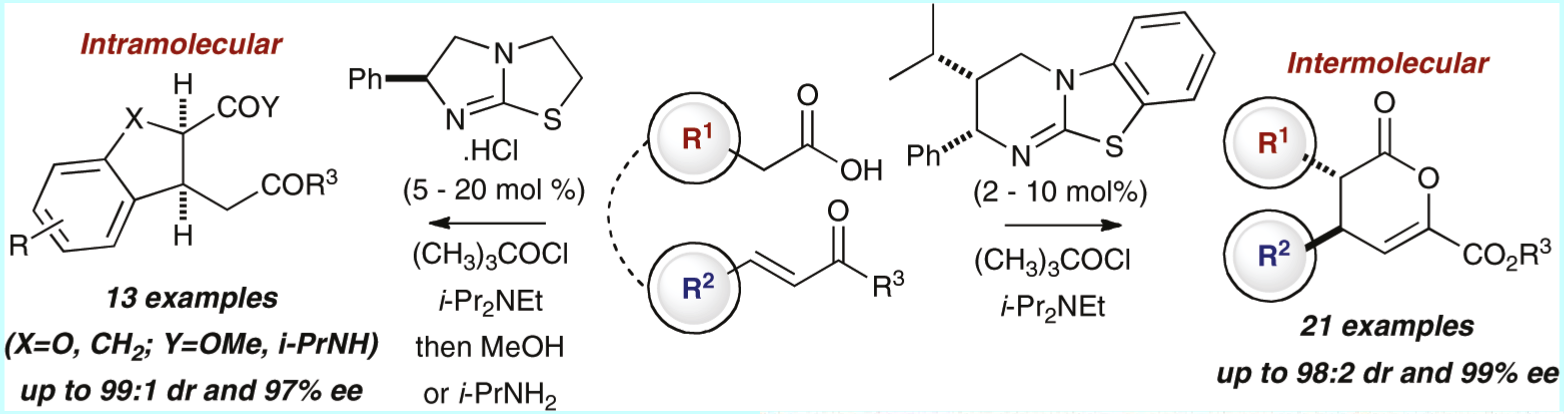
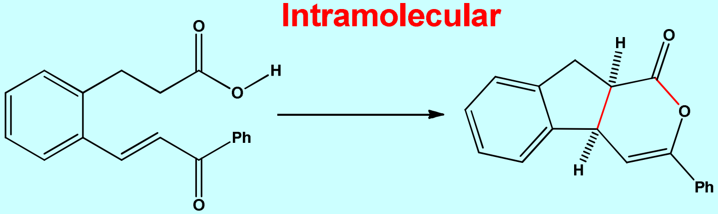
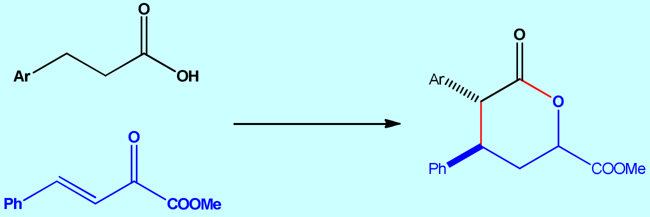
Organocatalytic Functionalization of Carboxylic Acids: *Isothiourea-Catalyzed Asymmetric Intra- and Intermolecular Michael Addition-Lactonizations*

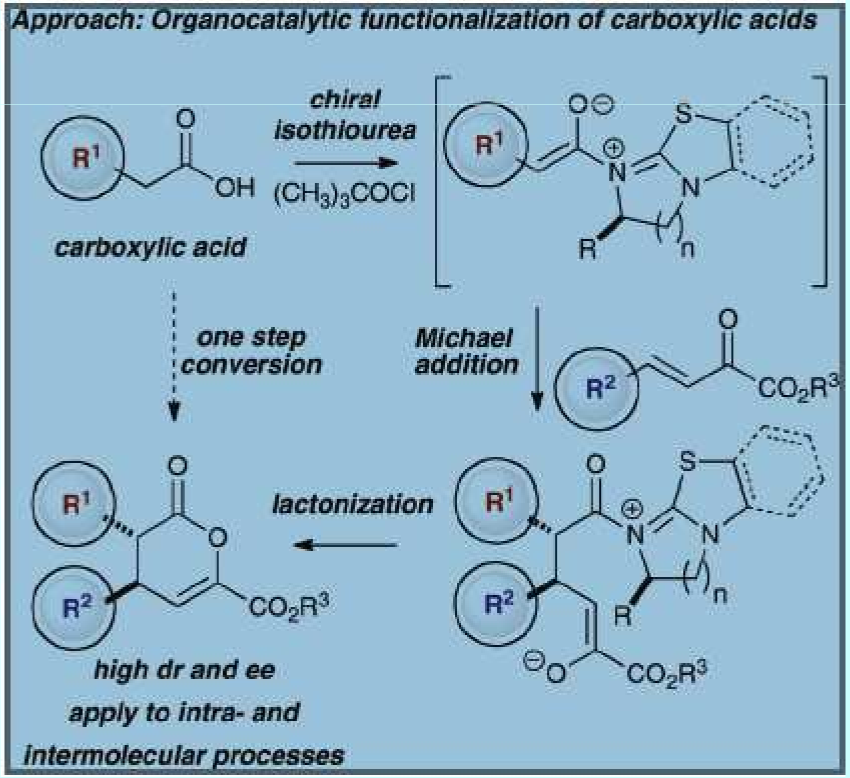


Intramolecular



Intermolecular




Approach: Organocatalytic functionalization of carboxylic acids

Andrew D. Smith et al JACS. 2011 ASAP

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UMR 6263

Thank you for your kind attention!

Sawat vally Pakistan

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