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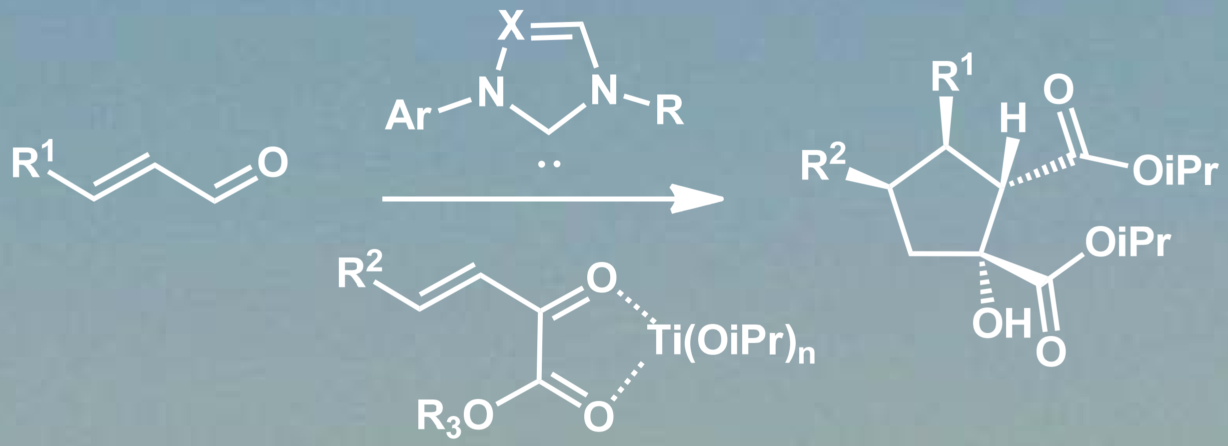
Synthèse Totale et Réactivité Organique

Lewis Acid Activated Synthesis of Highly Substituted Cyclopentanes by the N-Heterocyclic-Carbene-Catalyzed Addition of Homoenolate Equivalents to unsaturated Ketoesters

Daniel T. Cohen, Dr. Benoit Cardinal-David, Prof. Karl A. Scheidt



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RCC du 03-02-2011
Loïc Tomas

Introduction

- **Objectives :**
  - **New tools for the construction of highly functionalized carbocycles (small and medium sized)**
  - **Utilisation of simple substrates as starting materials**

- **Strategy :**
  - **Design of organic molecules for efficient catalysis of selective cascade reactions**

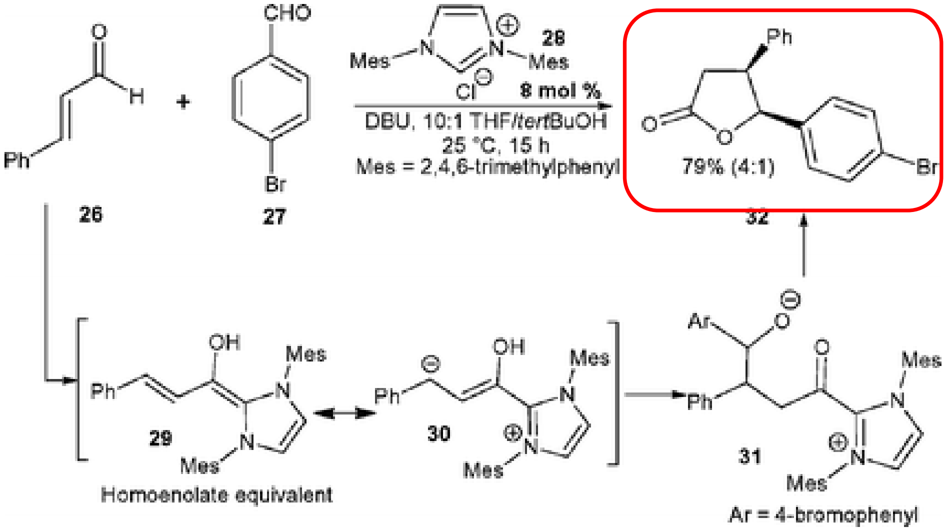
=> Asymmetric organocatalytic domino reactions

- **Amine (iminium/enamine…)**[1]
- **Bronsteid acid**[1]
- **N-Heterocyclic Carbene (NHC)**[2]

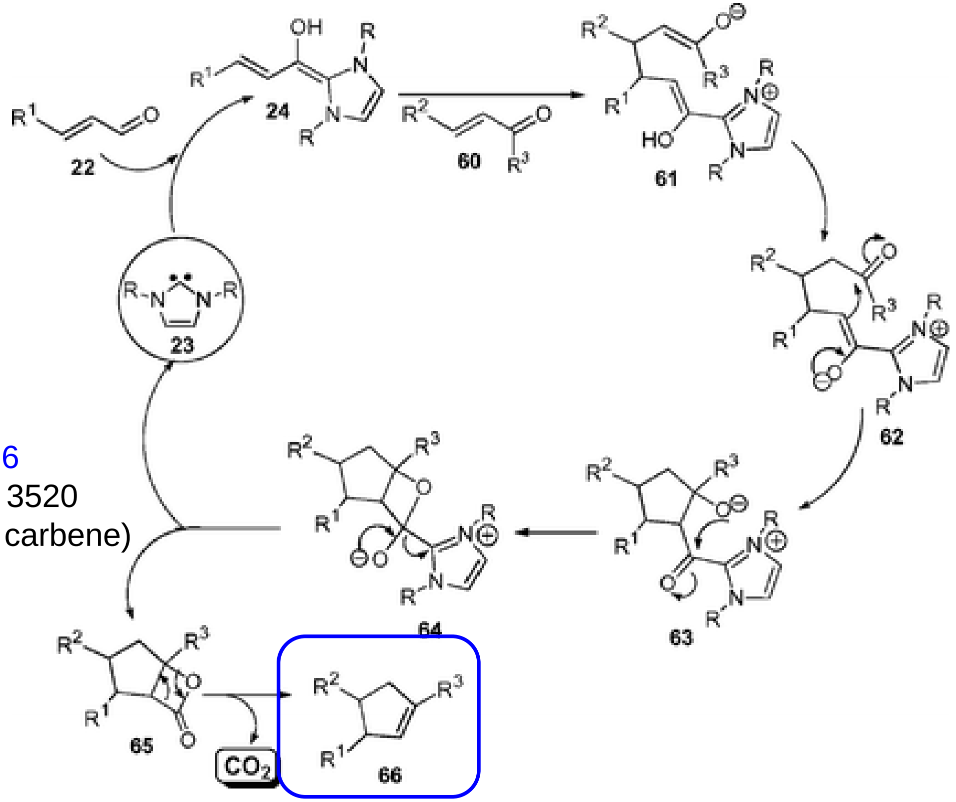
(**1**) Enders *et al. Angew. Chem. Int. Ed.* **2007**, *46*, 1570 (**2**) Enders *et al. Acc. Chem. Res* **2004**, *37*, 534

NHC catalysis : cascade reactions

- **Generation of homoenolate equivalents from enals by NHCs lead to a powerful tool for the synthesis of hetero and carbocycles :**



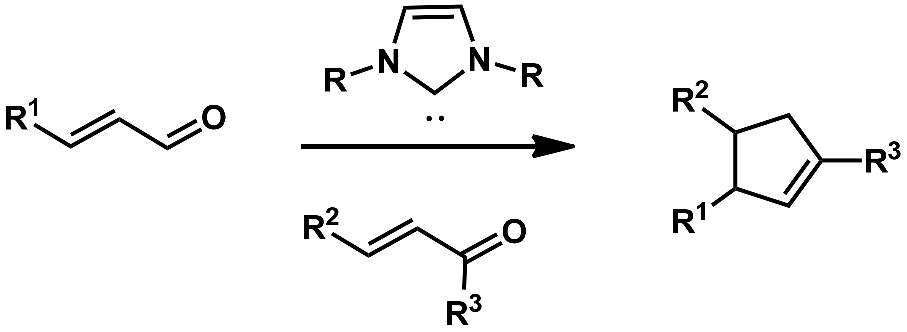
J. W. Bode, *J. Am. Chem. Soc.*, 2004, **126**, 14370
F. Glorius, *Angew. Chem., Int. Ed.*, 2004, **43**, 6205



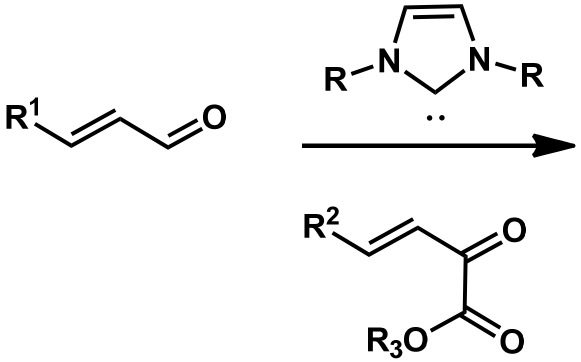
V. Nair, *J. Am. Chem. Soc.*, 2006, **128**, 8736
J. W. Bode, *J. Am. Chem. Soc.*, 2007, **129**, 3520
(asymmetric version with *N*-mesityl triazole carbene)

NHC catalysis : carbocycle synthesis

- **Limitations for carben driven carbocycle synthesis :**
  - **Only chalcones and oxobutenoates as coupling partners of the enal**
  - **Cyclic structures often present an olefine**



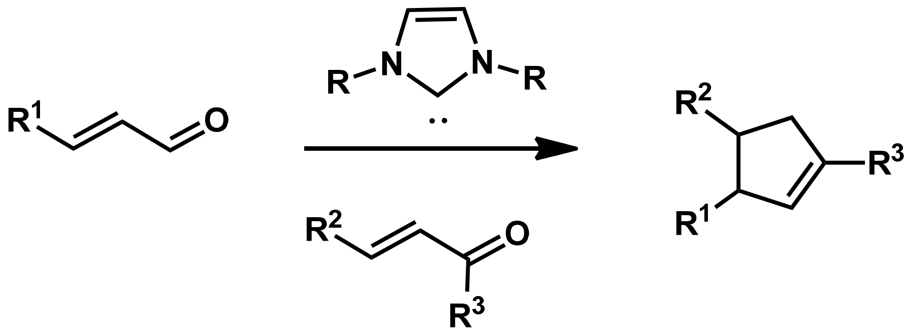
- **Strategy proposed by the authors :**



Synthesis of carbocycle
with potentially more functional groups

NHC catalysis : carbocycle synthesis

- **Limitations for carben driven carbocycle synthesis :**
  - **Only chalcones and oxobutenoates as coupling partner of the enal**
  - **Cyclic structures always containing an olefine**



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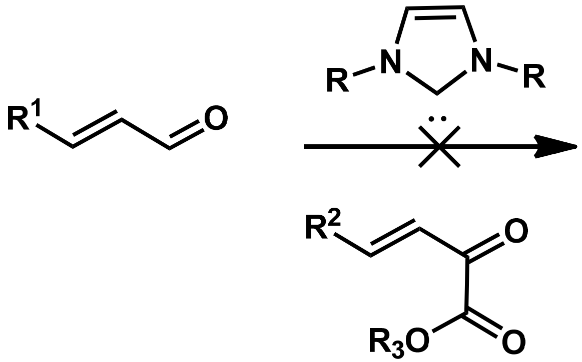
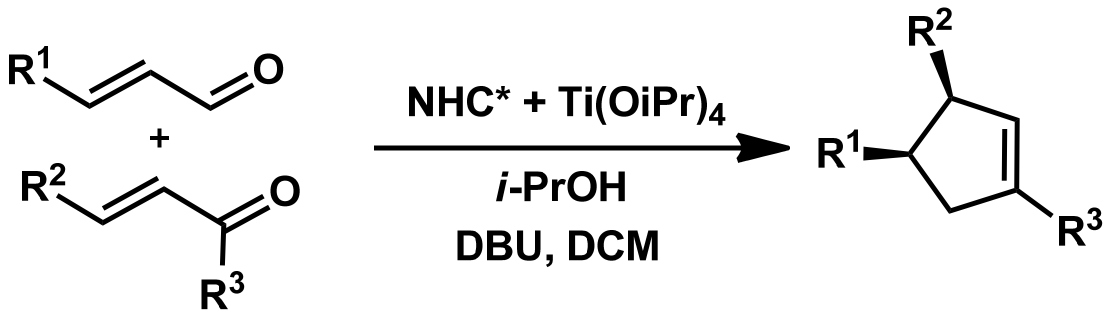


➢ ***Unsuccessful conditions !!!***

➢ ***Orientation toward a cooperative Carbene – Lewis acid catalysis***

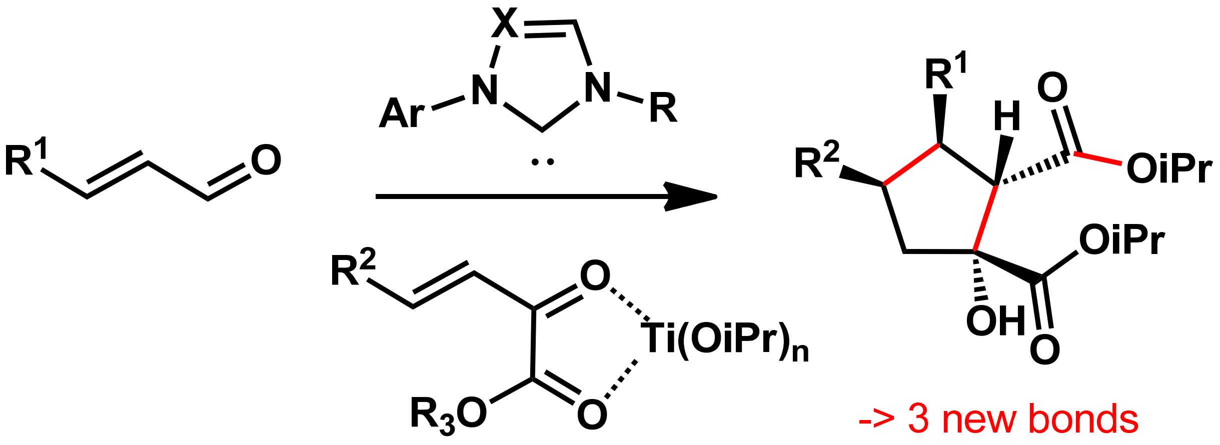
NHC – Lewis acid catalysis : carbocycle synthesis

- **Previous work from the authors :**



J. AM. CHEM. SOC. 2010, *132*, 5345

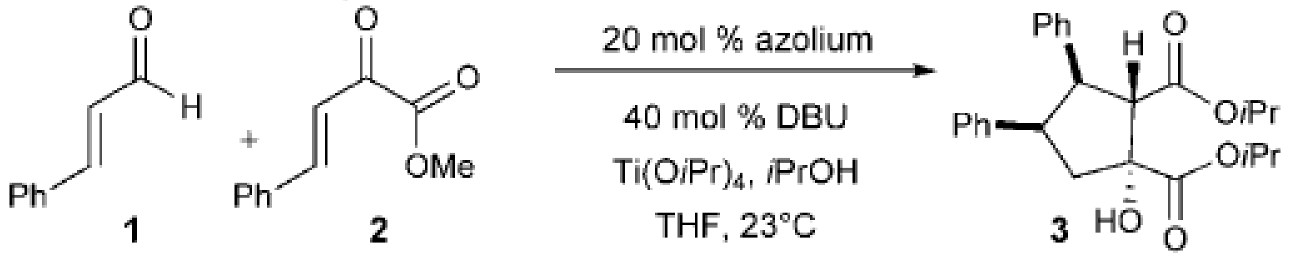
➢ ***Application to the coupling of enal and β–γ*** **unsaturated *α*–ketoesters**



-> 3 new bonds

-> 4 stereocenters

NHC – Lewis acid catalysis : optimisation



20 mol % azolium

40 mol % DBU

$Ti(OiPr)_4$, iPrOH

THF, 23°C

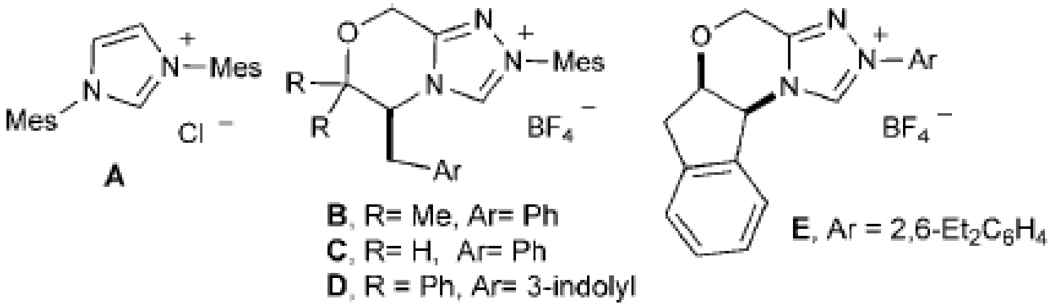
Entry	Azolium	$Ti(OiPr)_4$ [equiv]	iPrOH [equiv]	Yield [%][a]	d.r.[b]	ee [%][c]
1	A	–	6	0[d]	–	–
2	A	2	–	69	>20:1	–
3	B	2	–	76	12:1	70
4	C	2	–	44	10:1	86
5	D	2	–	69	20:1	20
6	E	2	–	68	7:1	90
7	E	2	6	63	18:1	96
8	E	5	6	84	20:1	95
9	E	–	6	0[d]	–	–
10	E	–	–	0[d]	–	–

High diastereoselectivity

Development of the enantioselective version

Better Yield

No catalyst = No reaction



A

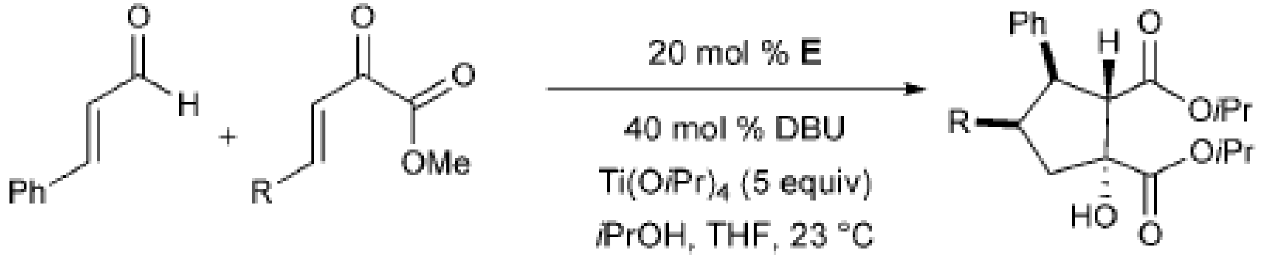
B, R= Me, Ar= Ph

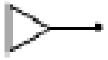
C, R= H, Ar= Ph

D, R = Ph, Ar= 3-indolyl

E, Ar = 2,6-$Et_2C_6H_4$

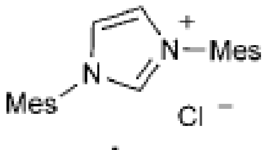
NHC – Lewis acid catalysis : scope of the reaction



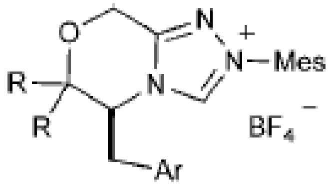
Entry	R	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	Ph	84 (3)	20:1	95
2	4-Cl-C_6H_4	69 (4)	20:1	97
3	2-Cl-C_6H_4	72 (5)	13:1	95
4	4-OMe-C_6H_4	82 (6)	20:1	96
5	4-Me-C_6H_4	82 (7)	20:1	97
6	3-Me-C_6H_4	68 (8)	20:1	97
7	4-pyridyl	52 (9)	12:1	97
8	2-furyl	77 (10)	20:1	97
9	2-thienyl	85 (11)	20:1	97
10		61 (12)	20:1	99
11		62 (13)	20:1	94

Electron withdrawing and electron donating => Good reactivity

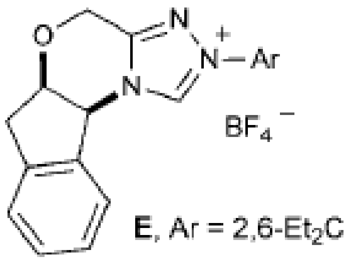
Heterocyclic compounds good compatibility with Ti(OiPr)$_4$



A

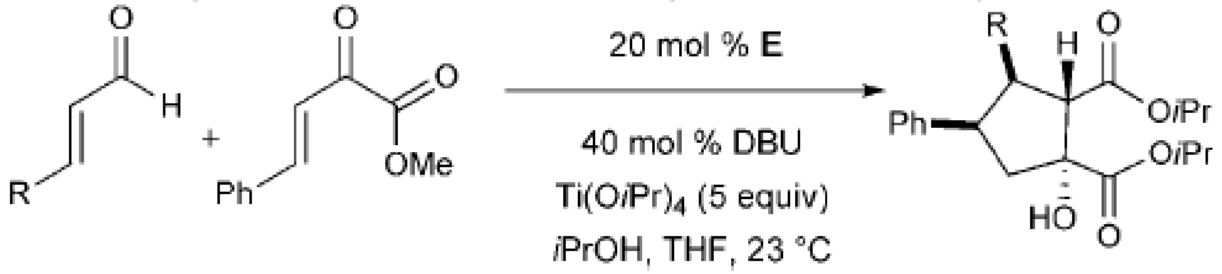


B, R= Me, Ar= Ph
C, R= H, Ar= Ph
D, R = Ph, Ar= 3-indolyl



E, Ar = 2,6-$Et_2C_6H_4$

NHC – Lewis acid catalysis : scope of the reaction

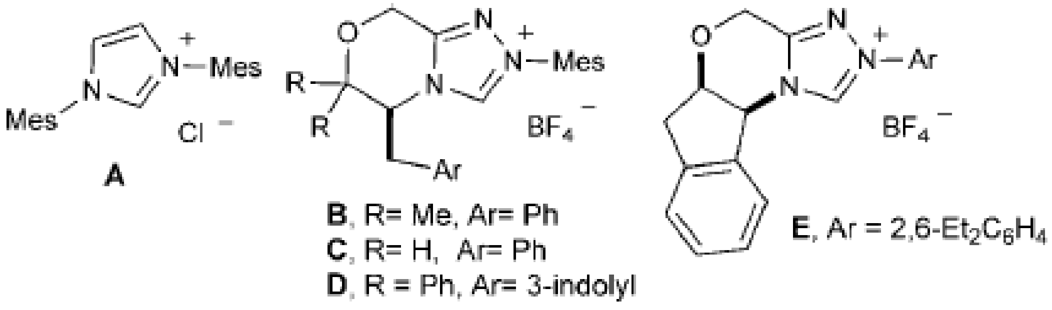


Entry	R	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	4-Cl-C_6H_4	74 (14)	20:1	97
2	3-Cl-C_6H_4	73 (15)	20:1	97
3	2-Cl-C_6H_4	68 (16)	10:1	98
4	4-Br-C_6H_4	75 (17)	20:1	96
5[e,f]	4-CO_2Me-C_6H_4	82 (18)	18:1	91
6	4-Me-C_6H_4	68 (19)	20:1	97
7	4-MeO-C_6H_4	56 (20)	17:1	96
8	2-MeO-C_6H_4	62 (21)	5:1	97
9	1-napthyl	78 (22)	12:1	97
10	2-napthyl	77 (23)	16:1	96

Electron withdrawing
=> Good tolerance

Electron donating
=> Decrease of the Yield

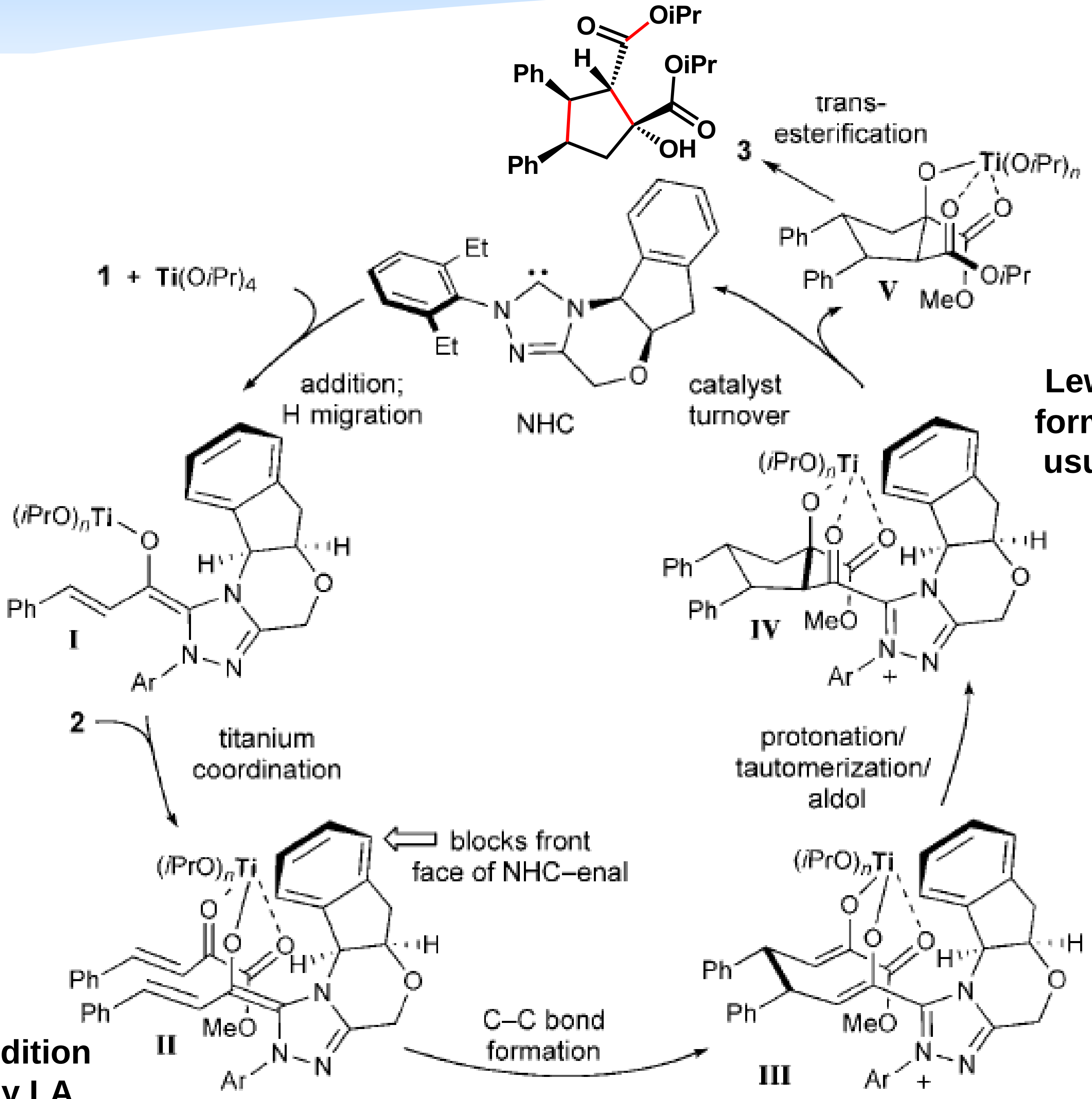
Lower
diastereoselectivity



B, R= Me, Ar= Ph
C, R= H, Ar= Ph
D, R = Ph, Ar= 3-indolyl

E, Ar = 2,6-$Et_2C_6H_4$

NHC – Lewis acid catalysis : proposed pathway



Breslow Intermediate type

Lewis Acid avoid the formation of β-lactone usually conducing to cyclopentene structures

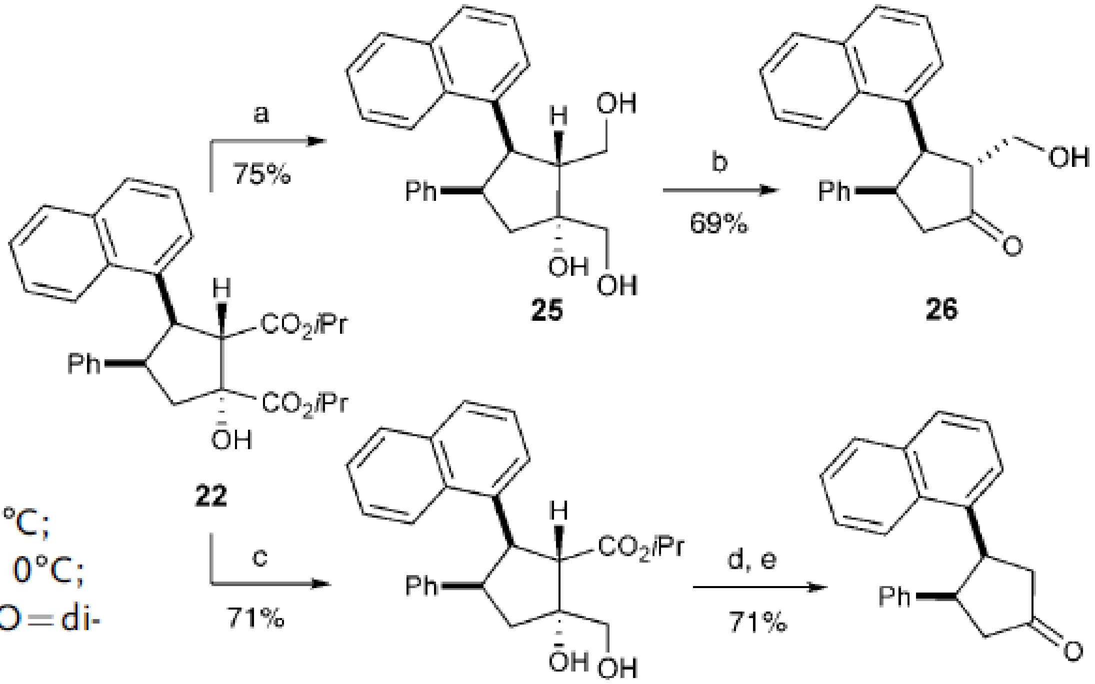
Conjugate addition promotted by LA

Conclusion

- **First NHC-catalyzed addition of homoenolates to β–γ unsaturated α–ketoesters**

- **Utilisation of a mild LA compatible with NHC catalysis and essential for activation of the electrophile and conjugate addition**

- **Rapid assembly of highly substituted and functionalizable cyclopentanols from simple substrates**
    - **High level of diastereo and enantioselectivity**
    - **Acces to enantiomerically enriched cyclopentanones**



Scheme 3. Synthetic transformations: a) $LiAlH_4$, THF, 0–25 °C; b) $NaIO_4 \cdot SiO_2$, CH_2Cl_2, 25 °C; c) $NaBH_4$, THF/MeOH (2:1), 0°C; d) $NaIO_4 \cdot SiO_2$, CH_2Cl_2, 25 °C; e) DMSO/H_2O, 130°C. DMSO = dimethyl sulfoxide.

MERCI POUR VOTRE ATTENTION

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