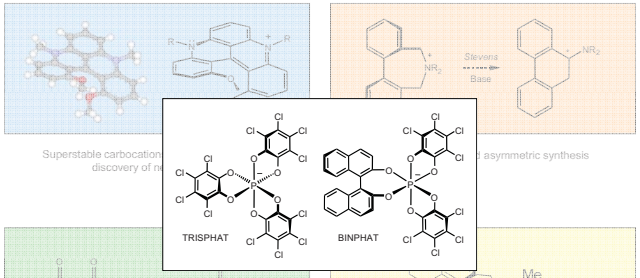
Playing with Charges in Asymmetric Synthesis and Catalysis

Prof. Jérôme Lacour,
Organic Chemistry Department

ISCHIA, September 2010

UNIVERSITÉ DE GENÈVE

Plus / Minus

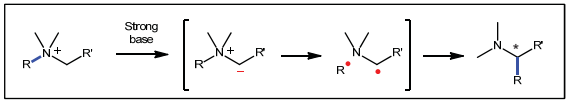


Allylic substitution and *enantioselective* catalysis

atropos and *tropos* molecules and asymmetric catalysis

[1,2]-Stevens Rearrangement

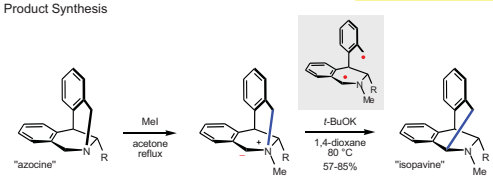
■ Principle



West *et al. Tetrahedron* **2006**, *62*, 1043
Markó in *Comprehensive Organic Synthesis*, (Eds. Trost, Fleming, Pattenden), Pergamon, Oxford, **1991**, 913
Ollis *J. Chem. Soc. Perkin Trans. 1* **1983**, 1009 and *J. Chem. Soc.* **1983**, 1049

Strict enantioselective [1,2]-Stevens unknown

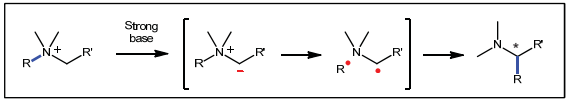
■ Natural Product Synthesis



Hanessian, Mauduit, *ACIE* **2001**, *40*, 3810

[1,2]-Stevens Rearrangement

■ Principle



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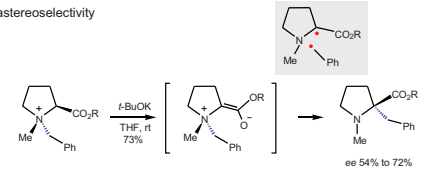
■ Diastereoselectivity



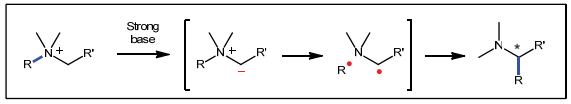
ee 54% to 72%

partial transfert of chirality

West *Org. Lett.* **1999**, *1*, 31; Tayama *Chem. Lett.* **2006**, *35*, 478

[1,2]-Stevens Rearrangement

■ Principle



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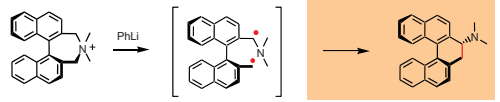
■ Diastereoselectivity



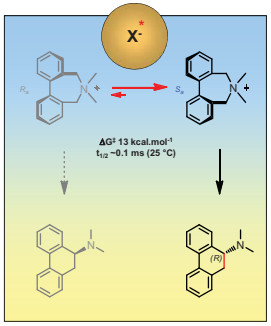
Diastereoselectivity
d.e. > 96%

Zavada et al *J. Am. Chem. Soc.* **1994**, *116*, 5084
See also Mislow et al *J. Am. Chem. Soc.* **1968**, *90*, 4884

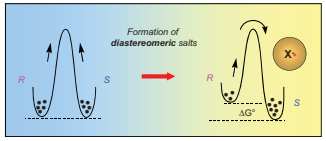
Can this transformation be the basis for an enantioselective reaction ?

[1,2]-Stevens Rearrangement

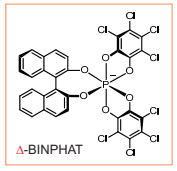
■ Configurational Lability



■ Asymmetric Ion Pairing Strategy



■



Org. Lett. **2002**, *4*, 3939; *Angew. Chem. Int. Ed.* **2003**, *42*, 3162;
J. Org. Chem. **2006**, *71*, 7412; *J. Am. Chem. Soc.* **2008**, 1845.

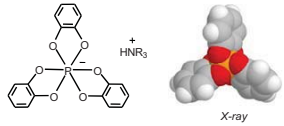
The PHAT anion family

■ Chiral Hexacoordinated Phosphate Anions

- Simple Synthesis & Resolution
- Low Nucleophilicity
- High Solubility / Stability
- Effective Resolving Agents
- Superb NMR Chiral Solvants
- Efficient Asymmetric Inducers

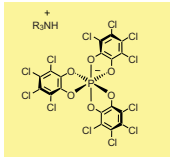
Chem. Soc. Rev. 2003, *32*, 373; *Org. Biomol. Chem.* 2005, *3*, 15
Science 2007, *317*, 462; *Chem. Rec.* 2007, *7*, 275;

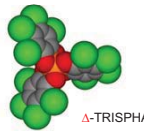
■ Early example

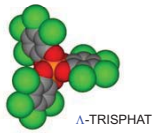


Hellwinkel *Chem. Ber.* 1970, *103*, 1056.
Koenig and Klaebe *Tetrahedron Lett.* 1979, 795
Koenig, Klaebe, Munoz and Wolf *J. Chem. Soc., Perkin Trans. 2* 1979, 40

■ EWG effect : Configurationally Stable Anions







Angew. Chem. Int. Ed. 1997, *36*, 608;
J. Org. Chem. 2004, *69*, 8521

Commercially available

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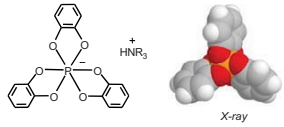
Science 2007, *317*, 462; *Chem. Rec.* 2007, *7*, 275

■ Early example



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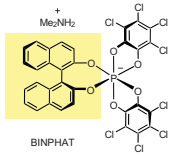

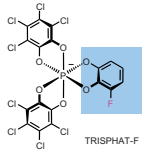

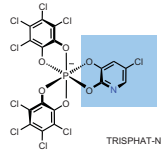

Org. Lett. 2002, *4*, 3939; *ACIE.* 2003, *42*, 3162;
JOC 2006, *71*, 7412; *JACS* 2008, *130*, 1845

ACIE 2005, *44*, 5060

Organometallics 2007, *26*, 2141
ACIE 2007, *46*, 8979

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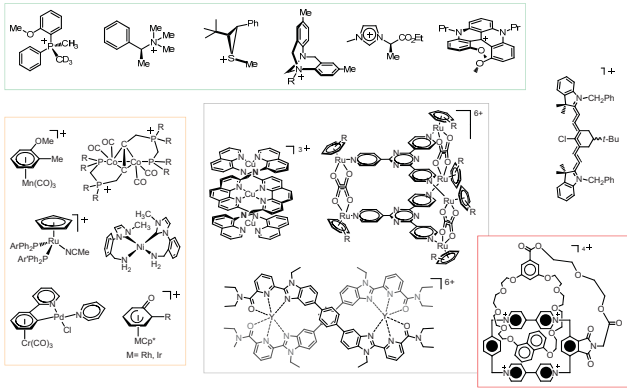
Very effective NMR Chiral Solvating Agents



Many independent reports from Amouri, Fontecave, Gruselle, Hamelin, LeBozec, Maury, Mikami, Nitschke, Rose-Munch, Shionoya, Stoddart, Therrien

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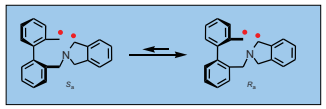
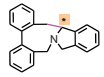
Spiro Azepinium Cations : Stevens Rearrangement

■ Asymmetric Induction



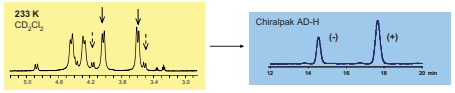
P_4-*t*-Bu

CH_2Cl_2, -80 °C



Anion	*de*	Yield	*ee*	Transfer of Chirality
rac-TRISPHAT	-	30%	0%	-
Δ-BINPHAT	76% (*R*)	28%	35% (+)	45%
Λ-BINPHAT	76% (*S*)	28%	35% (-)	45%

How to improve ?



Unpublished results

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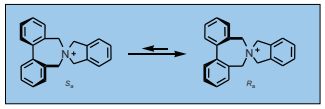
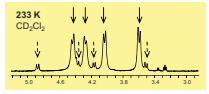
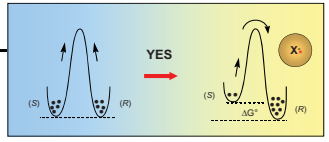
Spiro Azepinium Cations : Stevens Rearrangement

■ Asymmetric Induction



Anion	*de*
rac-TRISPHAT	-
Δ-BINPHAT	76% (*R*)
Λ-BINPHAT	76% (*S*)





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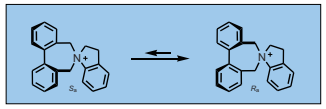
Spiro Azepinium Cations : Stevens Rearrangement

■ Asymmetric Induction

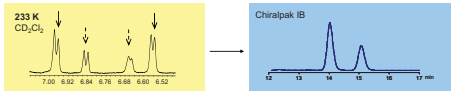


P_4-*t*-Bu

CH_2Cl_2, -80 °C

Anion	Yield	*de*	*ee*	Transfer of Chirality
Br^-	92%	-	0%	-
Δ-BINPHAT	90%	33%	33% (+)	100%
Λ-BINPHAT	88%	33%	33% (-)	100%

How to improve ?



Chem. Commun. **2008**, 829

Spiro Azepinium Cations : Stevens Rearrangement

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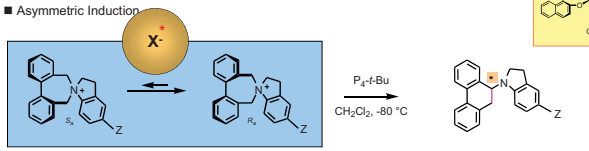
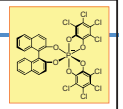


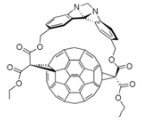


Z	Yield	*de*	*ee*	Transfer of Chirality
H	90%	33%	33% (+)	100%
OMe	52%	30%	27% (+)	90%
OBn	50%	20%	20% (+)	100%
F	**50%**	**50%**	**49% (+)**	**98%**
Cl	**48%**	**60%**	**55% (+)**	**92%**

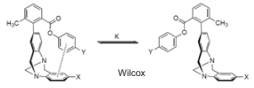
... the 1st enantioselective [1,2]-Stevens without any stereogenic N-atom

Chem. Commun. **2008**, 829

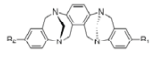
[1,2]-Stevens rearrangement of privileged structures



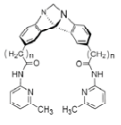
Diederich



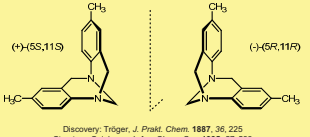
Wilcox



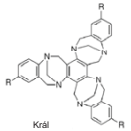
Elguero



Goswani



Discovery: Tröger, *J. Prakt. Chem.* **1887**, *36*, 225
Structure: Spielman, *J. Am. Chem. Soc.* **1935**, *57*, 583
Mechanism: Wagner, *J. Am. Chem. Soc.* **1941**, *63*, 832
Resolution: Prelog, Wieland, *Helv. Chim. Acta* **1944**, *27*, 1127
Configuration: Wilen*J. Org. Chem.* **1991**, *56*, 485



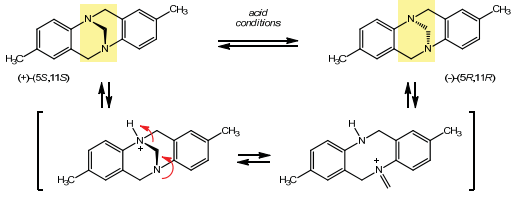
Král

1286 references in SFS containing either the concept "**troger**" or the concept "**troeger**" in July 2010
Only 10-15 references on their use as **ligands** for organometallic chemistry or as **organocatalysts**

Reviews: Demeunynck *Prog. Heterocyclic Chem.* **1999,** 1-20; Král *Adv. Heterocyclic. Chem.* **2007;** Sergeyev, *Helv Chim Acta* **2009**, *92*, 415

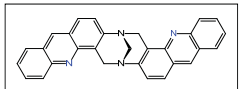
Configurational Lability

■ Facile racemization

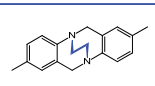


■ Solutions

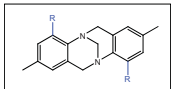
Vögtle, Schurig *Chem. Eur. J.* **2002**, *8*, 3629
$\Delta G^{\ddagger}$ (298 K) = 23.9 kcal.mol^{-1}
10.5 h half-life



Demeunynck
Chem.Commun. **1999**, 161



Hamada, Mukai
Tetrahedron:Asymmetry **1996**, *7*, 2671



Kostyanovsky, Lenev
Chem. Eur. J. **2006**, *12*, 6412

Configurational Lability

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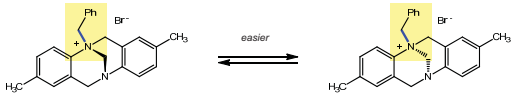

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11 min half-life

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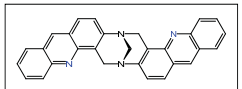
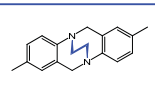


Demeunynck
Chem.Commun. **1999**, 161



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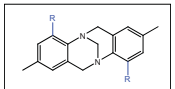
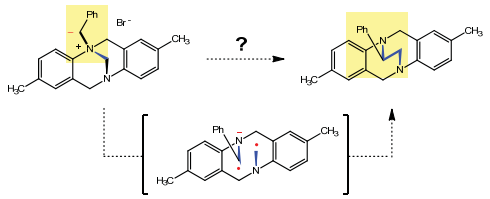


Kostyanovsky, Lenev
Chem. Eur. J. **2006**, *12*, 6412

[1,2]-Stevens rearrangement ?

- A novel transformation



- Solutions

Demeunynck
Chem.Commun. **1999**, 161

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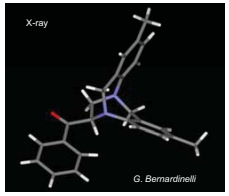
Tetrahedron:Asymmetry **1996**, *7*, 2671

Kostyanovsky, Lenev
Chem. Eur. J. **2006**, *12*, 6412

[1,2]-Stevens rearrangement of privileged structures

- Basic Al_2O_3, $CHCl_3$, 85% yield

- X-ray



single diastereoisomer
d.r. > 99:1

Chem. Commun. **2010**, *46*, 2206

Chem. Commun. **2010**, *46*, 2206

[1,2]-Stevens rearrangement of privileged structures

- Basic Al_2O_3, $CHCl_3$

- 51%, 85%, 35%, 65%, 35%

single diastereoisomer
d.r. > 99:1

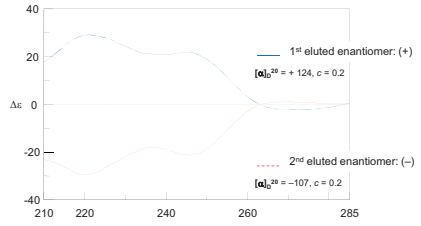
Chem. Commun. **2010**, *46*, 2206

[1,2]-Stevens rearrangement of privileged structures

- *Configurationally Stable at 100 °C in toluene pTsOH (1.0 equiv)*

- *CSP-HPLC Resolution*
  Chiralcel OJ
  n-heptane:ethanol 90:10

Collaboration with
E. Francotte (Novartis)



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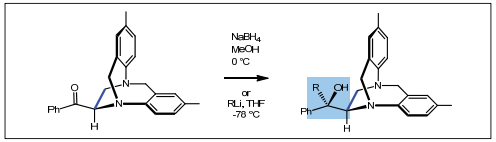
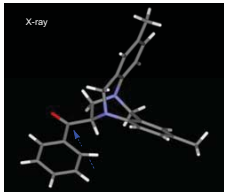
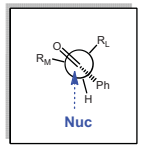
[1,2]-Stevens rearrangement of privileged structures

- 

- 



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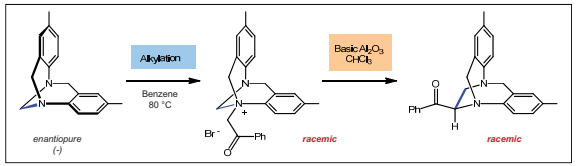
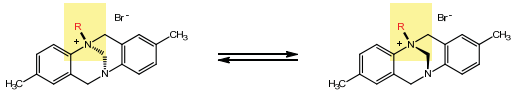
[1,2]-Stevens rearrangement of privileged structures

- Enantiospecificity ?



- Lability of the intermediate !



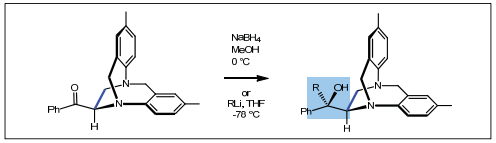
R = **Bn**, $\Delta G^{\ddagger}$ (298 K) = 21.5 kcal.mol^{-1}
11 min half-life

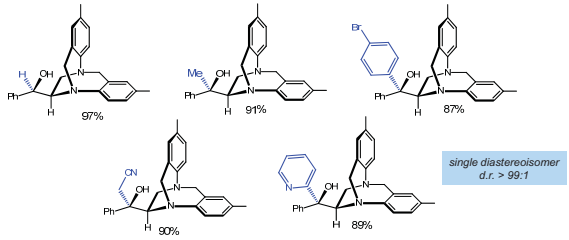
Vögtle, Schurig *Chem. Eur. J.* **2002**, *8*, 3629

Unpublished results

UNIVERSITÉ DE GENÈVE

[1,2]-Stevens rearrangement of privileged structures

- 

- 

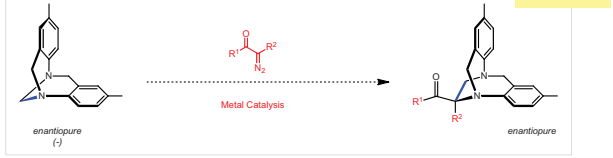
single diastereoisomer
d.r. > 99:1

Chem. Commun. **2010**, *46*, 2206

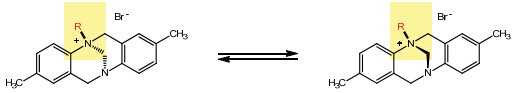
UNIVERSITÉ DE GENÈVE

[1,2]-Stevens rearrangement of privileged structures

- Enantiospecificity ?



- Lability of the intermediate !



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11 min half-life

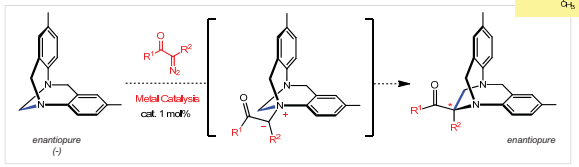
Vögtle, Schurig *Chem. Eur. J.* **2002**, *8*, 3629

Unpublished results

UNIVERSITÉ DE GENÈVE

[1,2]-Stevens rearrangement of privileged structures

- Direct Ylide Chemistry



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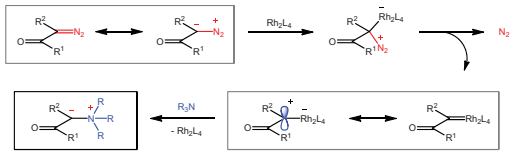
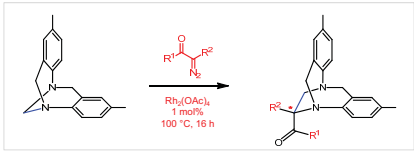


Unpublished results

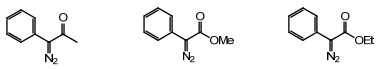
UNIVERSITÉ DE GENÈVE

[1,2]-Stevens rearrangement of privileged structures

- Direct Ylide Synthesis



- High diastereoselectivity



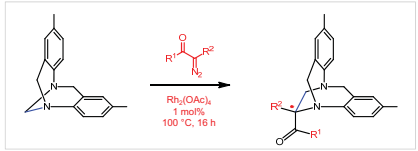
56%, *dr* 5.0 : 1 | **74%, *dr* 10 : 1** | **50%, *dr* > 49: 1**

Unpublished results

UNIVERSITÉ DE GENÈVE

[1,2]-Stevens rearrangement of privileged structures

- Direct Ylide Synthesis



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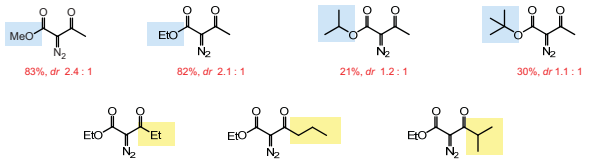


83%, *dr* 2.4 : 1 | 82%, *dr* 2.1 : 1 | 21%, *dr* 1.2 : 1 | 30%, *dr* 1.1 : 1

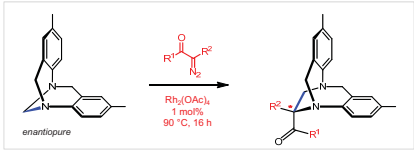
17%, *dr* 2.4 : 1 | 25%, *dr* 2.7 : 1 | -

Unpublished results

UNIVERSITÉ DE GENÈVE

[1,2]-Stevens rearrangement of privileged structures

- Enantiospecificity



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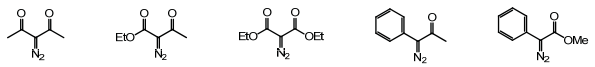

- | 80%, *ee* 5% *dr* 2:1 | 85%, *ee* 30% | 65%, *ee* 15% *dr* 5:1 | **71% *, *ee* 99% *dr* 10:1**

Unpublished results

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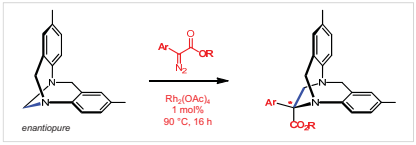
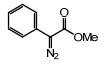
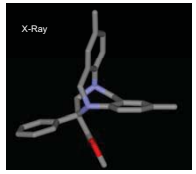
[1,2]-Stevens rearrangement of privileged structures

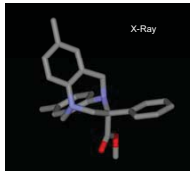
- Enantiospecificity





71%, *ee* 99%





Isolated yield for the major diastereomer

Unpublished results

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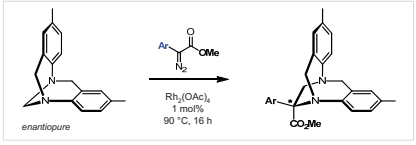
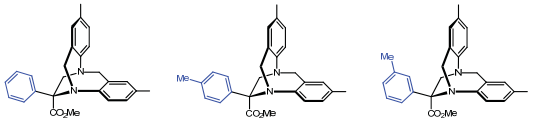
[1,2]-Stevens rearrangement of privileged structures





71%, *ee* 99% 72%, *ee* 98% 70%, *ee* 98%

80%, *ee* 98% 83%, *ee* 98%

Isolated yield for the major diastereomer

Unpublished results

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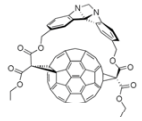
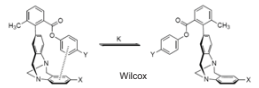
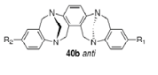
[1,2]-Stevens rearrangement of privileged structures

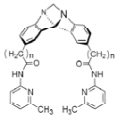


Diederich

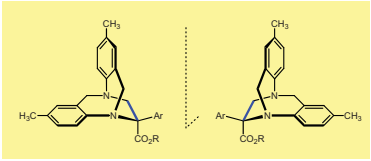


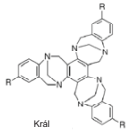


Elguero



Goswani





Král

One-step synthesis from *methano*-Troeger derivatives
Quaternary carbon atom introduction
Highly diastereoselective
Highly enantiospecific

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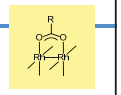
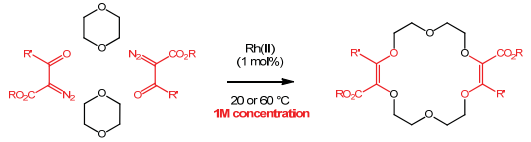
New Metal Carbene Chemistry

- New C-O opening reactivity





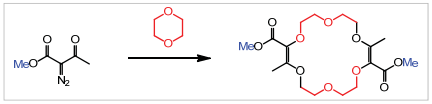
A unique
one-pot 4-component macrocyclization

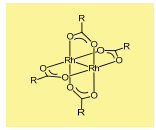
high concentration (≥ 1 M),
non-templated conditions
two classes of readily-available building blocks
primarily intermolecular connections.

McKervey, *Chem. Rev.* **1994**, *94*, 1091-1160
Wang, *Chem. Commun.* **2009**, 5350-5361;
Doyle *Chem. Rev.* **2010**, *110*, 704-724

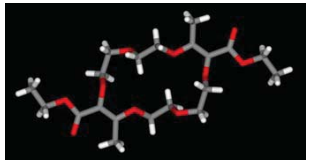
ACIE, in press, DOI: 10.1002/anie.201003559

■ New C-O opening reactivity



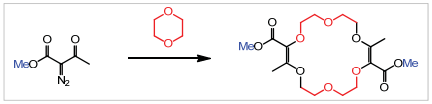


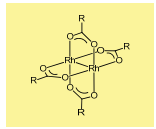
Single product



ACIE, in press, DOI: 10.1002/anie.201003559

■ New C-O opening reactivity





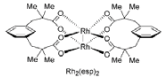
■ Conditions Screening

Catalyst 0.5 mol%

0.5 M concentration

60 °C

Catalyst	Yield
-	-
Rh_2OAc_4	45%
Rh_2esp_2	49%
Rh_2Oct_4	51%
Rh_2TFA_4	23%

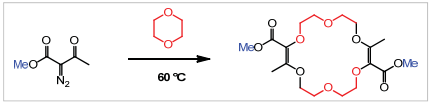


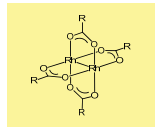
$Rh_2(esp)_2$

Dubois JACS **2004**, 15378

ACIE, in press, DOI: 10.1002/anie.201003559

■ New C-O opening reactivity



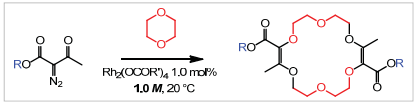


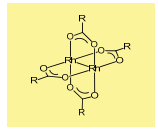
■ Conditions Screening

Catalyst	Mol %	Conc.	Yield
Rh_2Oct_4	1.0 %	0.05 M	18%
Rh_2Oct_4	1.0 %	0.5 M	37%
Rh_2Oct_4	**1.0 %**	**1.0 M**	**54%**
Rh_2Oct_4	1.0 %	2.0 M	54%

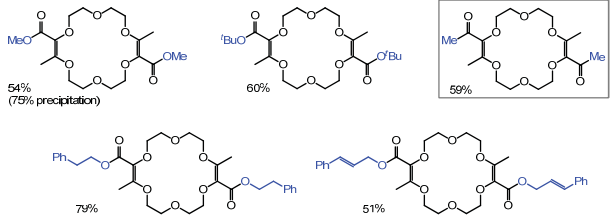
ACIE, in press, DOI: 10.1002/anie.201003559

■ New C-O opening reactivity





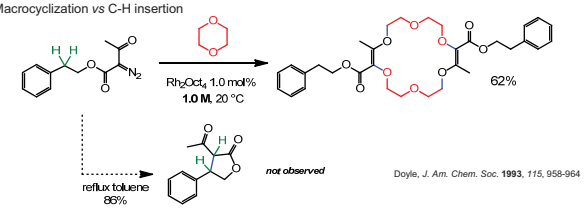
■ Exemples



ACIE, in press, DOI: 10.1002/anie.201003559
and unpublished results

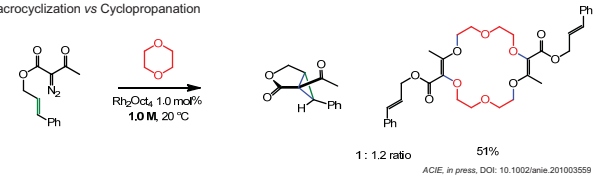
Synthesis of Functionalized Polyether Macrocycles

■ Macrocyclization *vs* C-H insertion



Doyle, *J. Am. Chem. Soc.* **1993**, *115*, 958-964

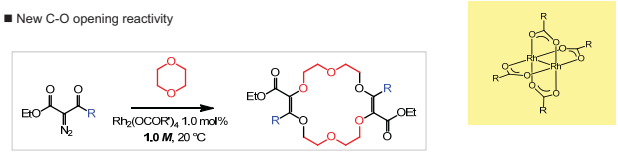
■ Macrocyclization *vs* Cyclopropanation



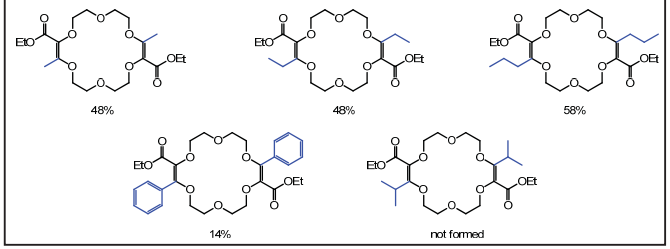
ACIE, in press, DOI: 10.1002/anie.201003559

Metal Carbene Chemistry

■ New C-O opening reactivity

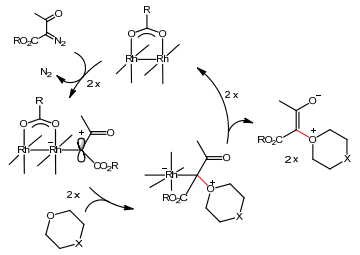


■ Exemples



Metal Carbene Chemistry

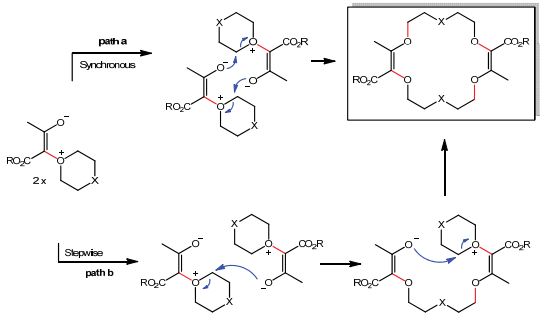
■ Why and How ?



ACIE, **2010** *in press*

Metal Carbene Chemistry

■ Why and How ?



ACIE, **2010** *in press*