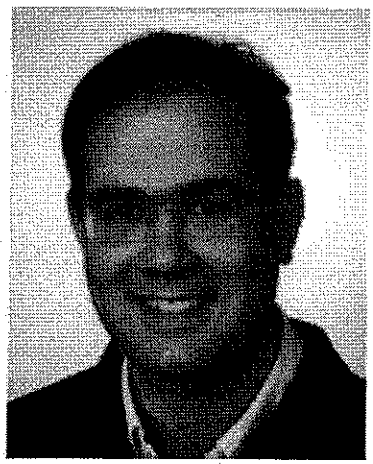
# *Efficient Synthetic Strategy For Vicinal Diamine Product*

## Contents



## 1. Introduction

Vicinal diamines represent an important class of organic compounds which are of upmost importance in various areas of today's chemistry including medicinal and biological chemistry, asymmetric synthesis.
The synthesis of diastereomerically and enatiomerically pure derivatives of 1,2-diaminogroup is therefore of high importance.



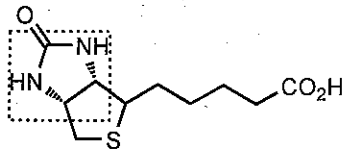
### Kilian Muniz

Kilian Muniz was born in Hildesheim, Germany in 1970.
From 1990 to 1996 he studied Chemistry at Hannover University, Germany, at the Imperial College London, UK and at University of Oviedo, Spain working in the groups of Professors H. M. R. Hoffmann, Susan E. Gibson and Jose Barluenga.
In 1996 he joined the group of Professor Carsten Bolm at the RWTH Aachen, Germany to obtain his doctorate in 1998.
From 1999 to 2000 he carried out postdoctoral work with Professor Ryoji Noyori at Nagoya University, Japan working on ruthenium hydride catalyst precursors and on the mechanism of the BINAP/1,2-diamine-ruthenium (II)-catalysed ketone hydrogenation.
Since December 2000 he has been a Habilitand associated with Professor Karl Heinz Dotz at the Kekule Department in Bonn, Germany.
His research centres on enantioselective oxidative nitrogen transfer reactions and mechanistic elucidation of asymmetric transition metal oxidations.

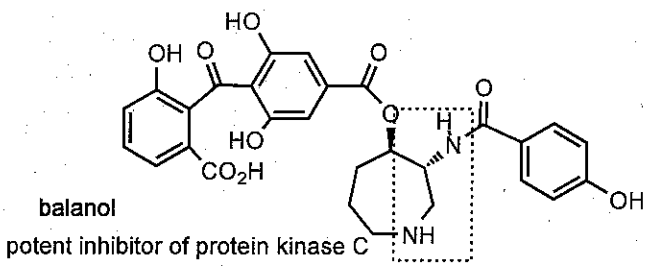
## 2. Utilities of vicinal diamines

### Natural products and pharmaceuticals

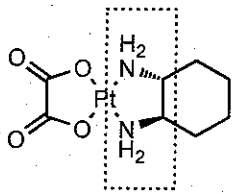
The 1,2-diamine functionality can be found in various compounds displaying a broad spectrum of biological activity.



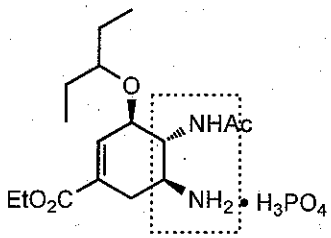
biotin (Vitamin H)
coenzyme of carboxylase



balanol
potent inhibitor of protein kinase C

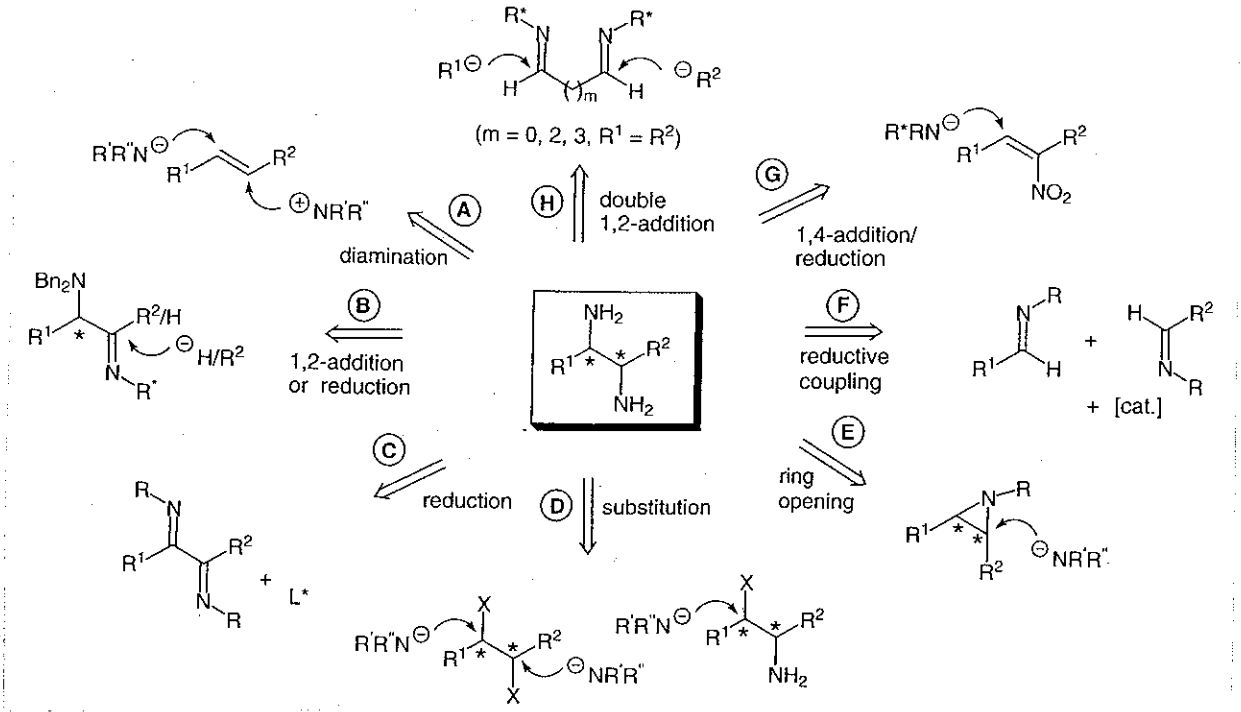


oxaliplatin
higher antitumoral activity than cisplatin



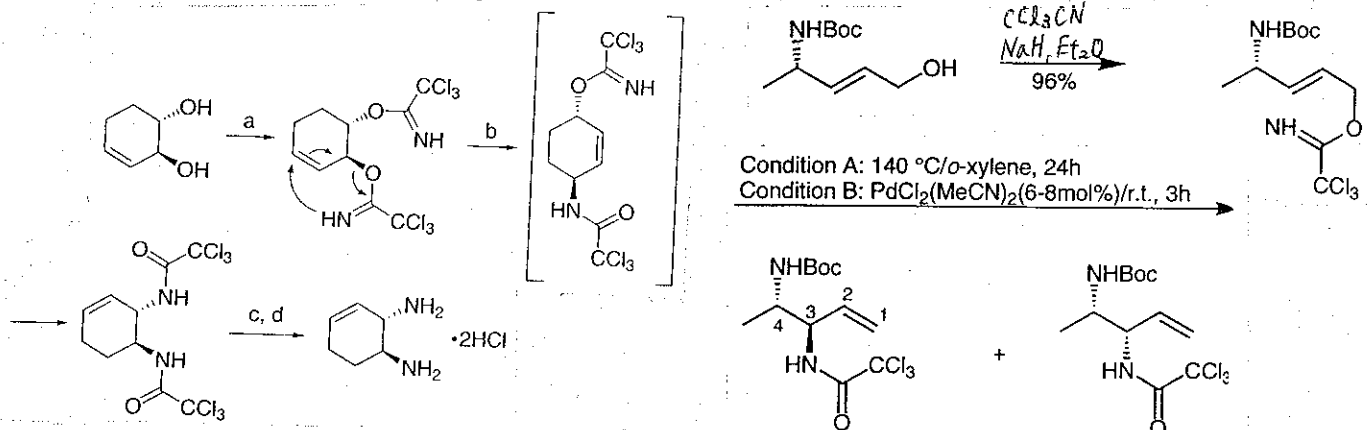
Tamiflu
neuramidase inhibitor
anti-influenza drug

# 3. Methods of preparation of vicinal diamines




## Other synthetic strategy to vicinal diamine

### 1. Double overman rearrangement




**Scheme 4** Reagents and conditions: (a) CCl3CN (2 equiv), l (0.2 equiv), THF, 0 °C; (b) xylene, reflux, 6 h; (c) 6 M NaOH, 8: 6 h; (d) 37 % HCl, EtOH

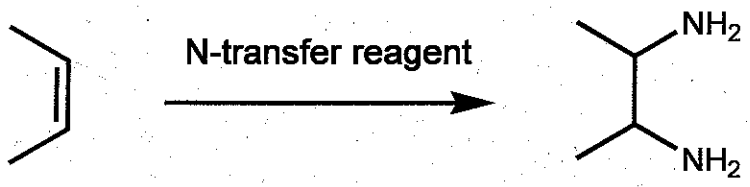
P. Knochel et al, Synthesis, 2001, 863.

Condition A: 85% 62:38
Condition B: 48% > 99:1

D. Bellus et al Synthesis, 1993, 729

**Though a variety of approaches have been devised, those methods need many steps ....**

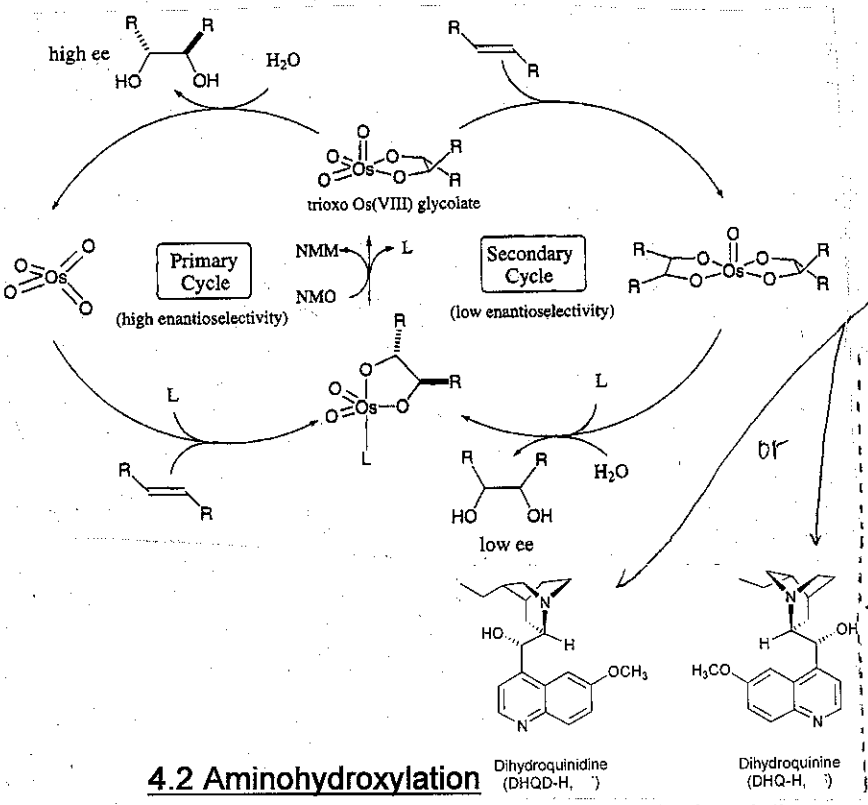
**If a simple double bond can be oxidize to diamine product directly, it must become most powerful and useful way to vicinal diamine!**



# 4. Dihydroxylation and aminohydroxylation

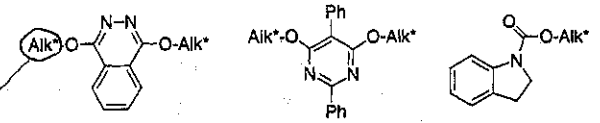
## 4.1 Dihydroxylation

The two catalytic cycles for asymmetric dihydroxylation using NMO as cooxidant

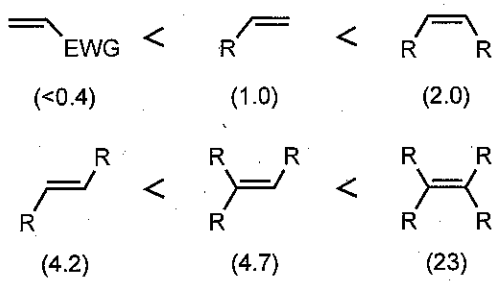



Recommended ligands for each olefine class

| *Olefin class* | | | | | | |
|---|---|---|---|---|---|---|
| *Preferred ligand* | PYR PHAL | PHAL | IND | PHAL | PHAL | PYR PHAL |
| *ee range* | 30-97 % | 70-97 % | 20-80 % | 90-99.8 % | 90-99 % | 20-97 % |



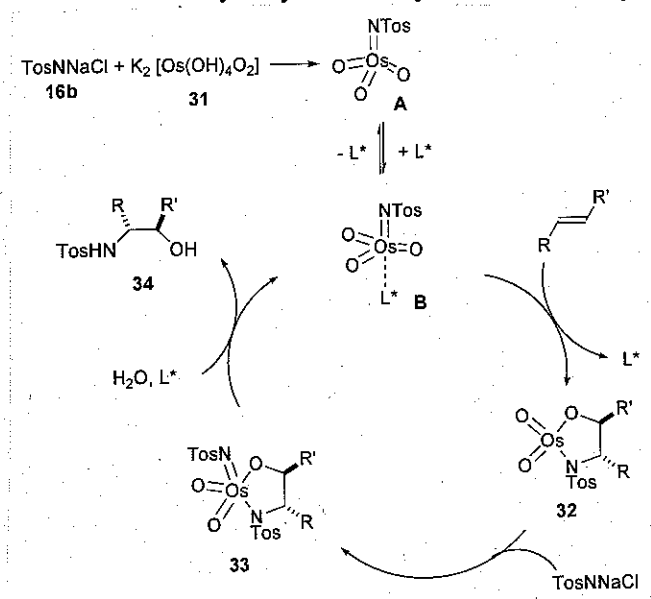

Reactivity of $OsO_4$ for each olefine class



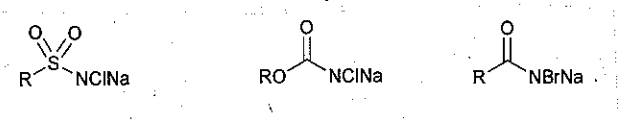

(Relative rate terminal olefine= 1.0)

## 4.2 Aminohydroxylation

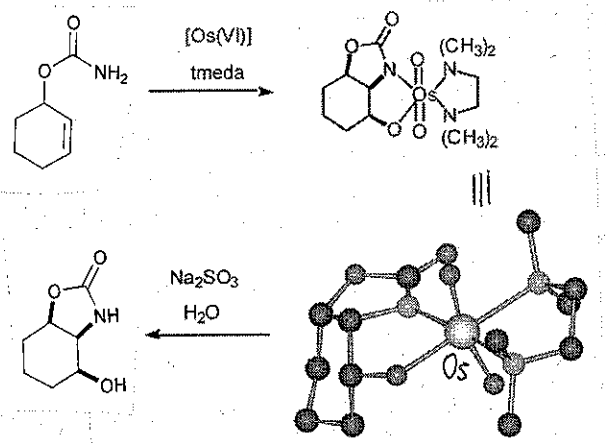
The catalytic cycles for asymmetric aminohydroxylation



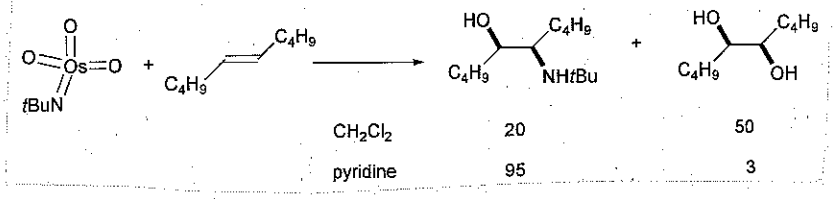

Various nitrene precusors



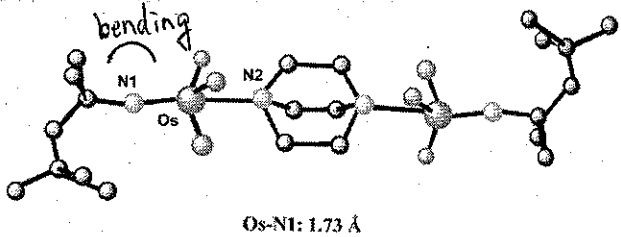

The evidence of this catalytic mechanism




Solvent effect for chemoselectivity

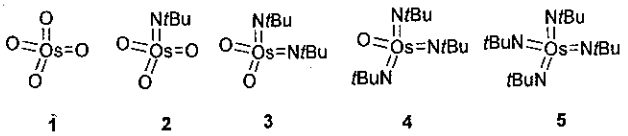



Explanation of chemoselectivity



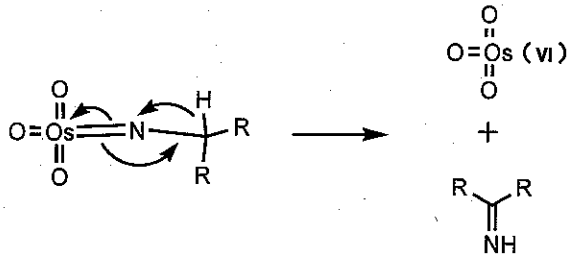
# 5. Propeties of Os complex

## Various kinds of Os complex



1 2 3 4 5

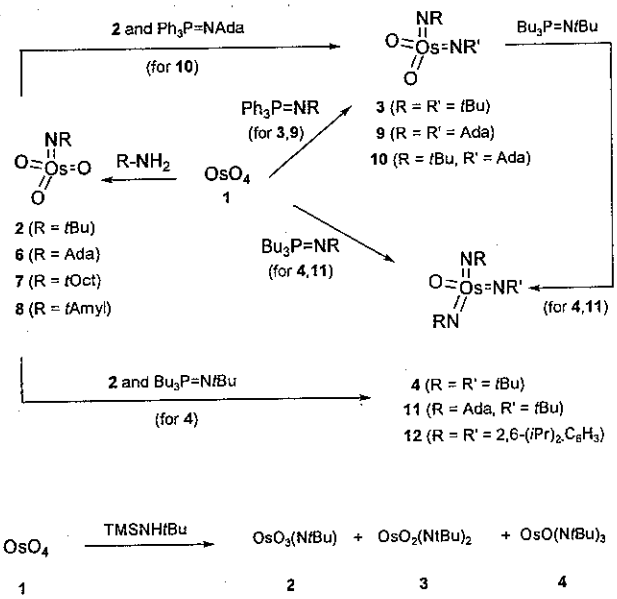
Fig. 1 *tert*-Butyl imido compounds as derivatives of $OsO_4$.



Tetrakis(tbutylimido)osumium is unstable.

Only tert-alkylimido derivatives can stabilize the imido complex.

## Synthesis of various imidoosmium compounds

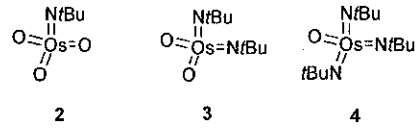






Scheme 1 Synthesis of various imidoosmium(VIII) compounds.

## NMR data




| | 2 | 3 | 4 |
|---|---|---|---|
| $^1$H nmr, δ ($C_6D_6$)/ppm | 0.87 | 1.12 | 1.27 |
| $^{13}$C nmr, δ ($C_6D_6$)/ppm | 26.1, 81.6 | 28.3, 73.9 | 28.7, 70.2 |
| $\Delta\delta_C$ | 55.5 | 45.6 | 41.5 |

Shift to higher field

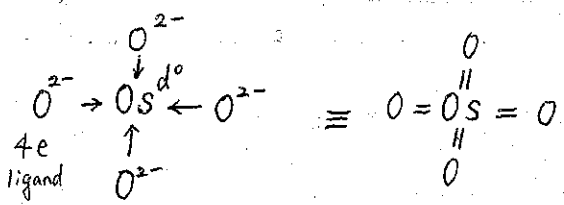
## IR data

| Complex | ν(Os=N), $cm^{-1}$ | ν(Os=O), $cm^{-1}$ | Ref |
|---|---|---|---|
| $OsO_4$ | | 955 | 6 |
| $OsO_3$(N-*t*-Bu) | 1184 | 925, 912 | 5 |
| $OsO_2$(N-*t*-Bu)$_2$ | 1200 | 888, 878 | |
| $OsO_2$(N-Ad)$_2$ | 1175, (1100) | 880, 865 | |
| $OsO_2$(N-Ad)(N-*t*-Am) | 1180, (1100) | 885, 875 | |
| OsO(N-*t*-Bu)$_3$ | 1190, (1100) | 838 | |
| OsO(N-Ad)$_2$(N-*t*-Bu) | 1160, (1100) | 838 | |

cf.

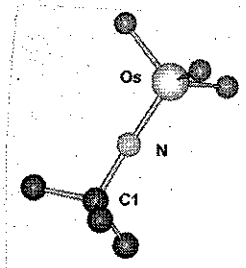
Os … 原子番号76.
第6周期、Fe, Ru と同じ
8族に属する.
[Xe] $4f^{14} 5d^6 6s^2$

⇒

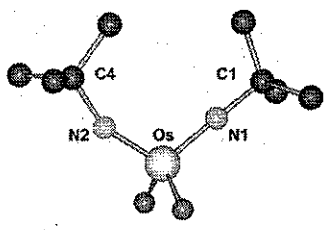



16 e

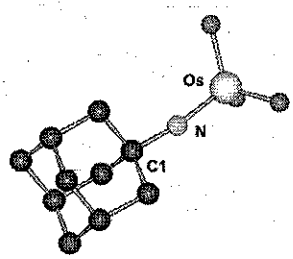
## X-ray structure of imido complex




Os-N: 1.69 Å
Os-N-C1: 175°




Os-O: 1.74 Å
Os-N1: 1.71 Å
Os-N2: 1.72 Å
Os-N1-C1: 179°
Os-N2-C4: 155°




Os-N: 1.70 Å
Os-N-C1: 171°

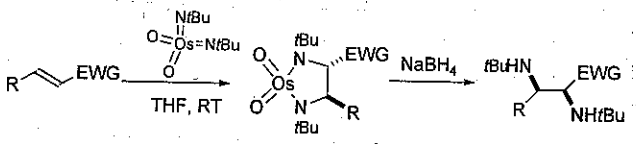
tert-butylimidoosmium | Bis(tert-butylimido)osmium | Adamantylimidoosmium

**Considering these results, electronic density of as more imido moiety is introduced.**

# 6. Diamination of olefines

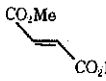
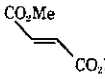
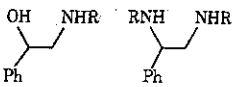
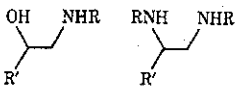
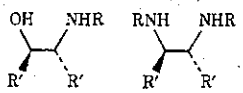
## 1. Stoichiometric reaction

### General scheme of diamination

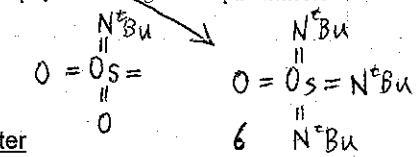



### Scope and limitations

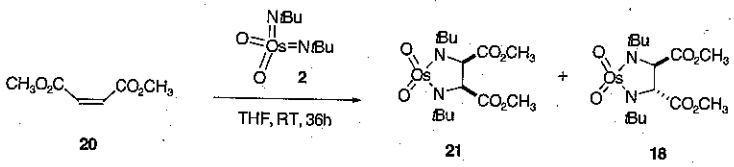
Eledtro-demanding and neutral olefines

| Olefin | Imido complex | Temp, °C | Products[b] (% yield) |
|---|---|---|---|
|  | 5 | 25 | 11a [60][c] |
|  | 6 | 25 | 12 [72] |
| Styrene | 5 | 25 |  (10)[d] (73) |
| Styrene | 6 | 25 | ( 3) (89) |
| 1-Decene | 5 | 25 |  (25) (41) |
| 1-Decene | 6 | 40 | (11) (63) |
| (*E*)-5-Decene | 5 | 40 |  (20) (76) |
| (*E*)-5-Decene | 6 | 40 | ( 3) (69) |

[a] Reactions were performed in carbon tetrachloride at 25 or 40 °C. [b] All new compounds were characterized by spectral and analytical data. [c] Yields given in brackets are isolated yields after preparative thin layer chromatography. [d] Yields given in parentheses were determined by GLC.




Diamination of maleic ester



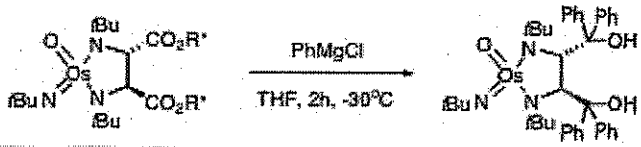

21/18 1.3:1 (crude product)

21/18 1:1.7 (isolated material, 84% yield)

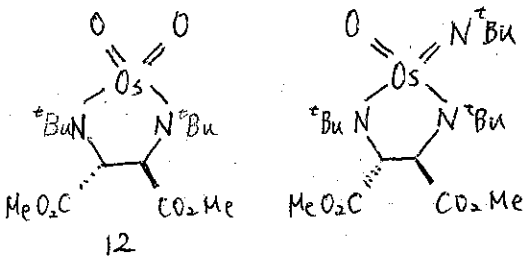
Diamination of maleic ester **20**.

Cis-product is unstable, so isomerization occures easily in purification.

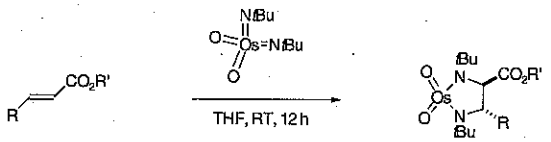
### Further conversion of osmaimidazolidine compound




Osmaimidazolidine skeletone is very stable, so it can be subjected under various conditions.




### Various acrylic esters

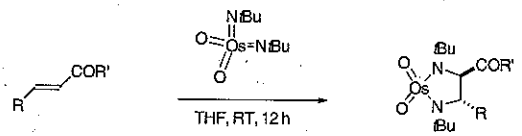



Scheme 3. Diamination of acrylic esters with bisimido complex **2**.

Table 1. Diamination of acrylic esters.

| | Substrate | R | R′ | Yield [%][a] | Product |
|---|---|---|---|---|---|
| 1 | **4** | $C_6H_5$ | $CH_3$ | 94 | **12** |
| 2 | **5** | $C_6H_5$ | $C(CH_3)_3$ | 96 | **13** |
| 3 | **6** | $C_6H_5$ | $CH_2C_6H_5$ | 89 | **14** |
| 4 | **7** | $CH_3$ | $CH_3$ | 91 | **15** |
| 5 | **8** | $CH_3$ | $C_2H_5$ | 92 | **16** |
| 6 | **9** | H | $CH_3$ | 98 | **17** |
| 7 | **10** | $CO_2CH_3$ | $CH_3$ | 90 | **18** |
| 8 | **11** | 3-pyridinyl | $CH_3$ | 78 | **19** |

### Other electro-deficient olefines




Scheme 5. Diamination of electron-deficient olefins.

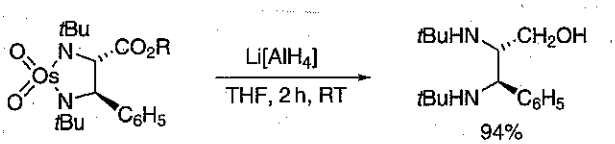
Table 2. Diamination of electron-deficient olefins.

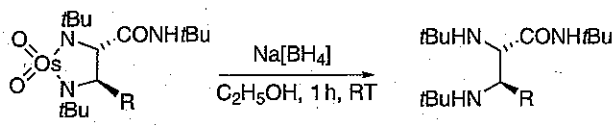
| | Substrate | R | R′ | Yield [%][a] | Product |
|---|---|---|---|---|---|
| 1 | **22** | $C_6H_5$ | $NHC(CH_3)_3$ | 89 | **28** |
| 2 | **23** | $CH_3$ | $NHC(CH_3)_3$ | 86 | **29** |
| 3 | **24** | H | $NHC(CH_3)_3$ | 89 | **30** |
| 4 | **25** | $C_6H_5$ | $NCH_3(OCH_3)$ | 84 | **31** |
| 5 | **26** | $C_6H_5$ | $C_6H_5$ | 91 | **32** |
| 6 | **27** | $C_6H_5$ | H | 92 | **33** |

[a] Isolated yield after column chromatography.

Functional tolerence against aldehyde, ketone, amide is observed.

### Liberation of vicinal diamine product

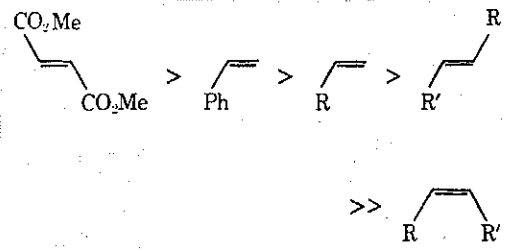


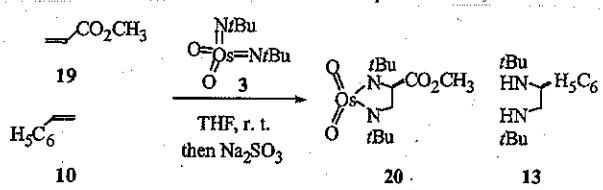

R = $C_6H_5$ (95%)
R = $CH_3$ (89%)

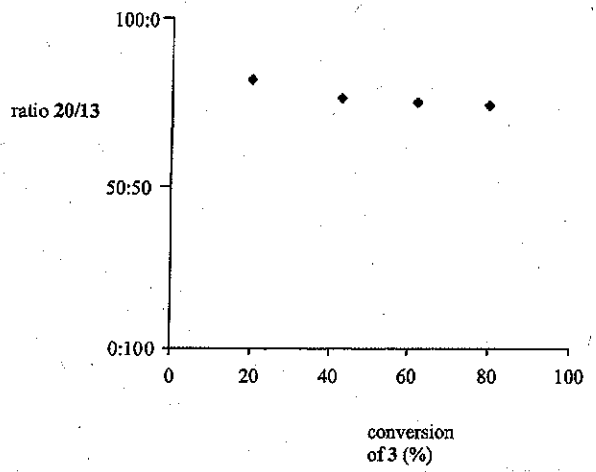
× $Na_2SO_3$ (reductive reagent)
Chloramine-T, NMO, TBHP (oxydants)

## Reactivity for each olefine class

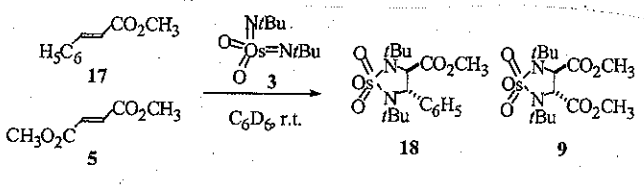


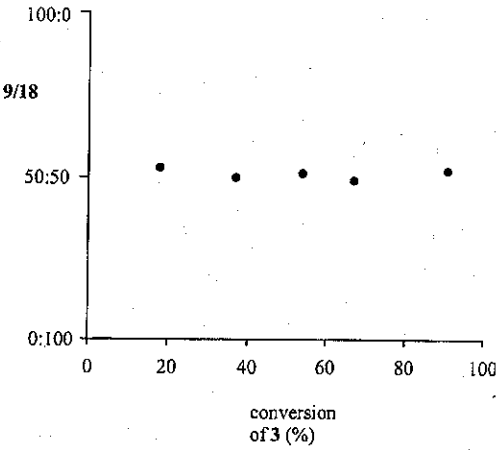

## Observation of each Os complex reactivities



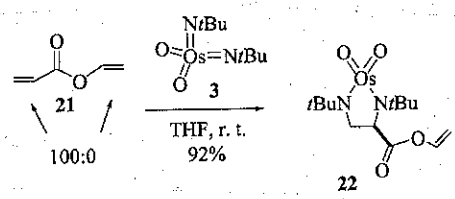




Competition experiment for diamination with 3
electro-demanding vs neutral olefine




Competition experiment for diamination with 3




Competition experiment of vinyl acrylate

These result shows that electro-withdrawing group enhance the rate,
and one electron-withdrawing group is apparently sufficient for the reaction to reach maximum rate.

## Electronic property of each Os complex

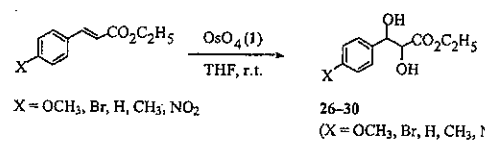
Hammet equation

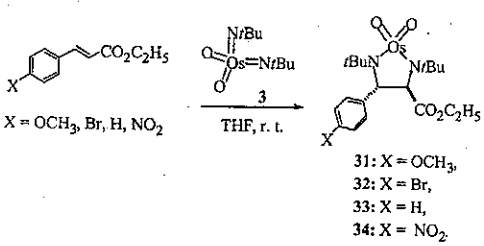
$$\ln (k_H / k_X) = \rho \cdot \sigma_X$$

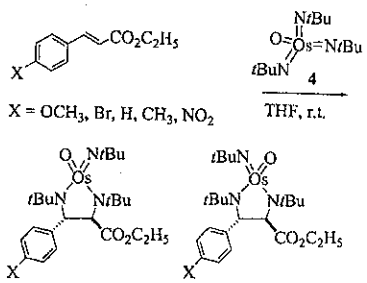
ρ = reaction constant
(if this value is positive, the reaction is enhanced by the electron withdrowing group)

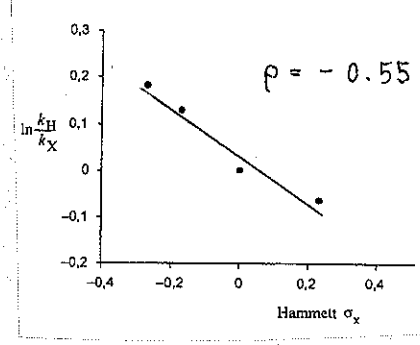
$\sigma_X$ = substituent constant
(positive value means electron-withdrawing group)

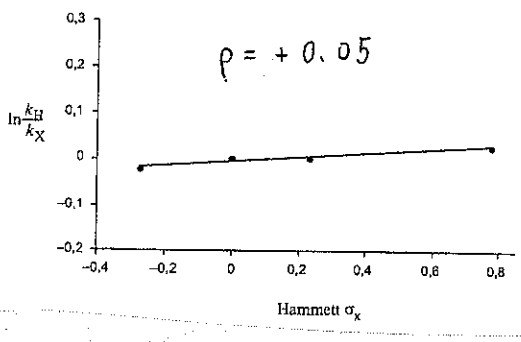
| substituent | $\sigma_X$ |
|---|---|
| OMe | - 0.28 |
| $CH_3$ | - 0.14 |
| H | 0 |
| Br | +0.22 |
| $NO_2$ | +0.81 |

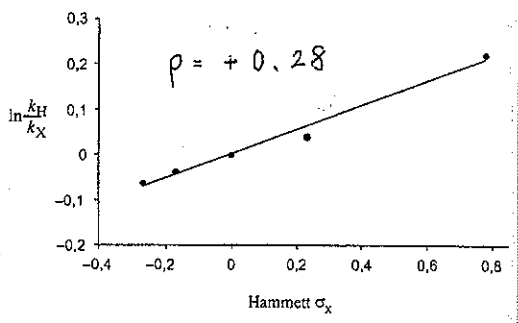


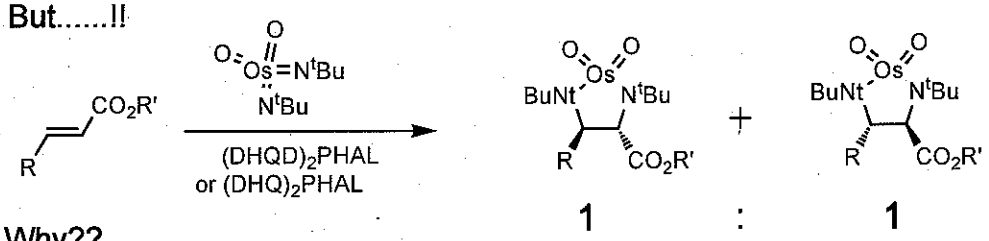



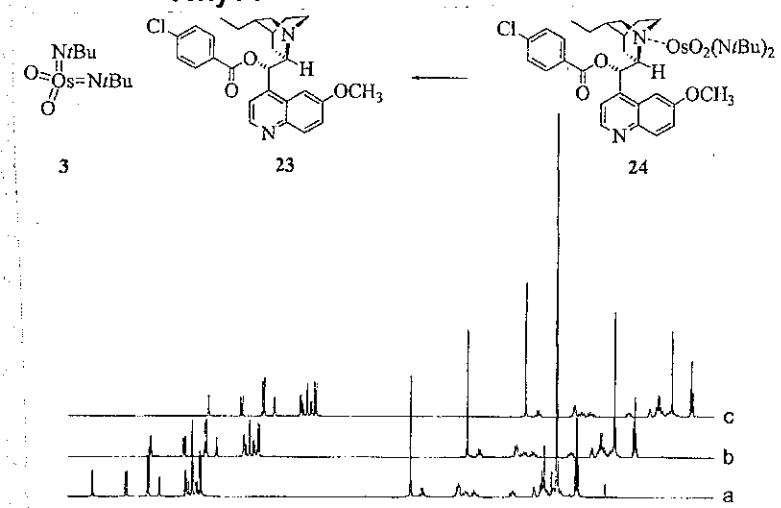
## 2. Development of asymmetric diamination

At first the *cinchona alkaloid* such as DHQ or DHQD was examined as chiral ligand.

**But.....!!**




**Why??**




$^1$H NMR spectra for titration of 3 with Cincona alkaloid 23 for ratio of 23/3, 1:1 (a), 5:1 (b), and 20:1 (c)

**No cordination between 3 and 23 was detected.**

**So it seems to be very difficult to induce enantioselectivity using the chiral ligand .**

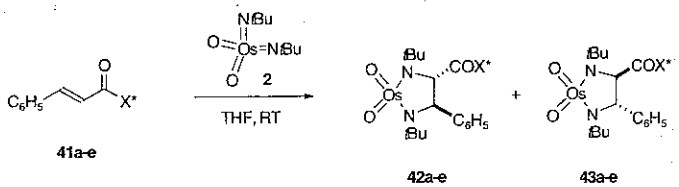
⇓

**Different approach is needed !!**

## Diastereoselective reaction

K. Muniz et al, *Synlett*, 2003, 211.

### Chiral auxiliary screening




Scheme 8. Auxiliary screening for asymmetric osmaimidazolidine formation.

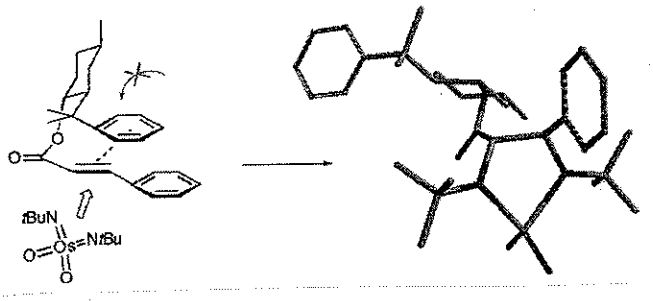
Table 3. Diastereomeric ratios for diamination with selected chiral auxiliaries. The absolute configuration in products **42a–c,e** and **43a–c,e** are undetermined.

| | Substrate | X*H | Ratio **42**:**43**[a] |
|---|---|---|---|
| 1 | **41a** | 1-phenyl ethanol | 1:1 |
| 2 | **41b** | campher sultame | 2.6:1 |
| 3 | **41c** | (–)-menthol | 1.5:1 |
| 4 | **41d** | (–)-8-phenyl menthol | 3.2:1 |
| 5 | **41e** | fenchol | 1.4:1 |

[a] Determined from $^1$H NMR spectra of the crude reaction mixture.

(-)-8-phenyl menthol is most effective.

### Transition state for explanation of stereodiscrimination

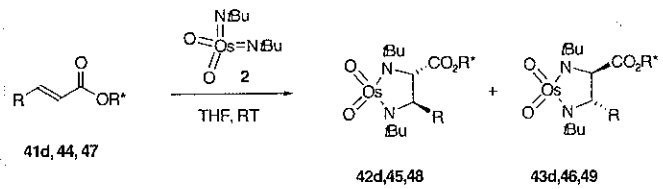



### Substrate generality

Table 4. Diastereomeric ratios for diamination with (–)-8-phenyl menthol as chiral auxiliary.

| | Substrate | R | Yield [%][a] | Product ratio[b] |
|---|---|---|---|---|
| 1 | **41a** | $C_6H_5$ | 68 | 78:22 (**42d/43d**) |
| 2[c] | **41a** | $C_6H_5$ | 56 | 94:6 (**42d/43d**) |
| 3 | **44** | $CH_3$ | 81 | 72:28 (**45/46**) |
| 4 | **47** | H | 96 | 88:12 (**48/49**) |
| 5[c] | **47** | H | 88 | 95:5 (**48/49**) |

[a] Diastereomeric mixture after column chromatography. [b] Determined by analytical HPLC. [c] The reaction was run at –15 °C.




Scheme 9. Asymmetric diamination with (–)-8-phenyl menthol as chiral auxiliary [R*OH = (–)-8-phenyl menthol].

**Si face is effectively blocked by phenyl moiety and the reagent approaches from Re face**

⇓

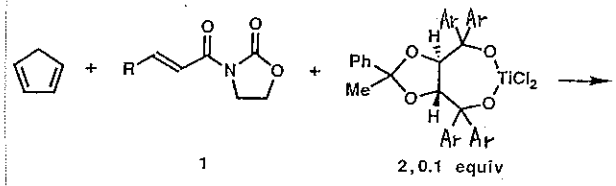
**π-stacking model**

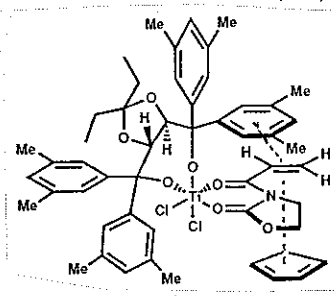
## What is π-stacking model??

Phenyl moiety is interacted to olefine.
It is caused from the electron donation from π orbital of phenyl group to π* orbital of electron deficient olefine.
and the interacted phenyl moiety blocks one olefine face.

For example...

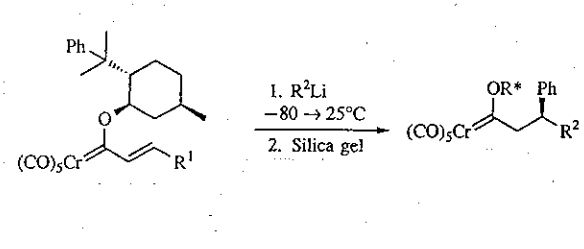
**Enantioselective Diels-Alder reaction** E.J.Corey et al, *Tetrahedron Letters*, 1991, *32*, 6289.



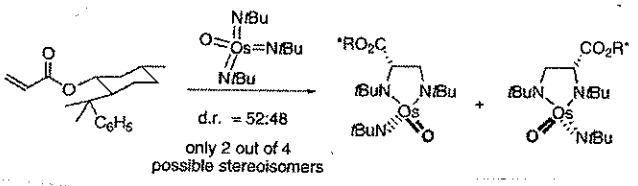
| Catalyst, Ar | % ee (*endo*) |
|---|---|
| Ph | 73 |
| β-Naphth | 68 |
| 6-MeO-β-Naphth | 82 |
| 3,5-diMe-Ph | 94 |
| 3,5-di$CF_3$-Ph | 68 |
| 3,5-diCl-Ph | 44 |

**Asymmetric Michael addition reaction** J. Barluenga, Angew. Chem. Int. Ed, 1994, *33*, 1392.

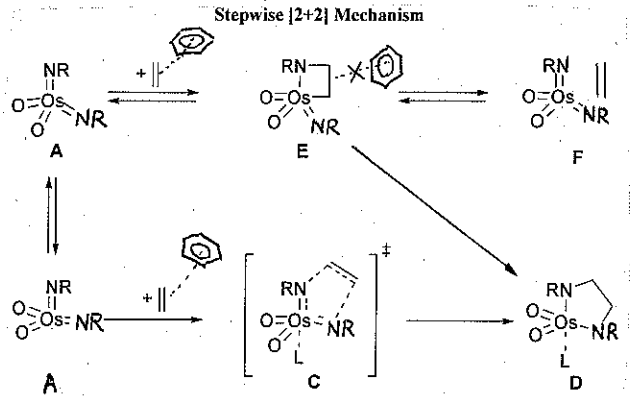



d.e. = 90%.

Interestingly, this chiral auxiliary didn't work well using Tris(tert-butylimido)osmium complex.



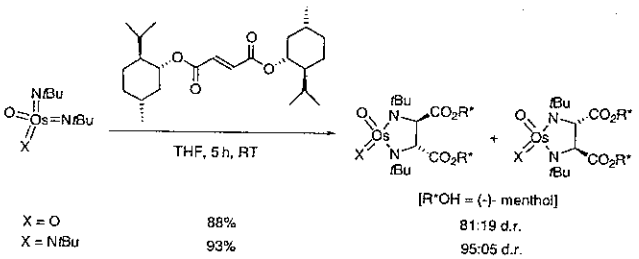

**Stepwise [2+2] Mechanism**




It might be caused from the difference of mechanism shown in right side.
Stepwise [2+2] pathway is in equilibrium.
After making the osmaazetane,
π-stacking is disappeared, so selectivity is not observed.

**Concerted [3+2] Mechanism**

(-)-8-phenyl menthol is expensive.... ⟹ Is there any chiral auxiliaries which is not expensive??

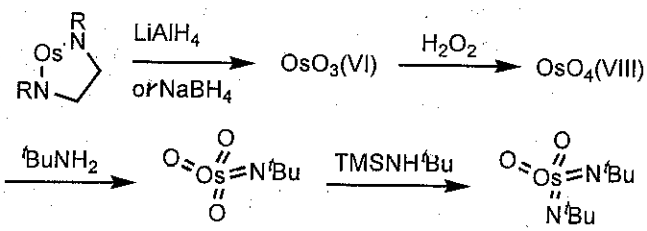


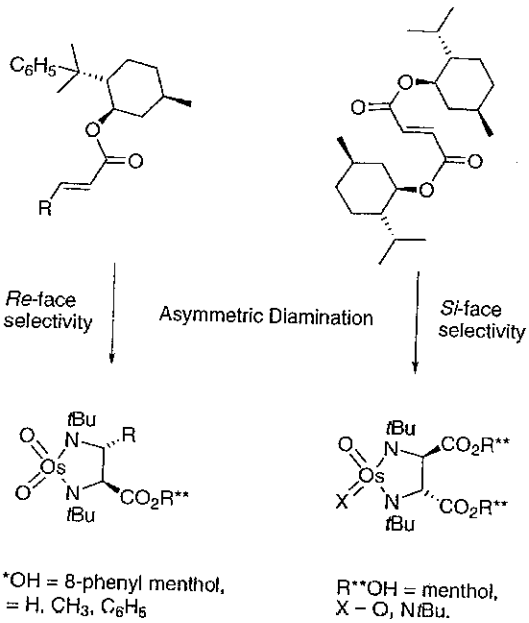

| | | |
|---|---|---|
| X = O | 88% | 81:19 d.r. |
| X = N*t*Bu | 93% | 95:05 d.r. |

**Scheme 11** First asymmetric diaminations of alkenes.

Using dimenthyl fumarate, the selectivity is greatly improved, especially with trisimidoosmium complex.

### The way of recycling Osmium




R*OH = 8-phenyl menthol,
R = H, $CH_3$, $C_6H_5$

R**OH = menthol,
X = O, N*t*Bu.

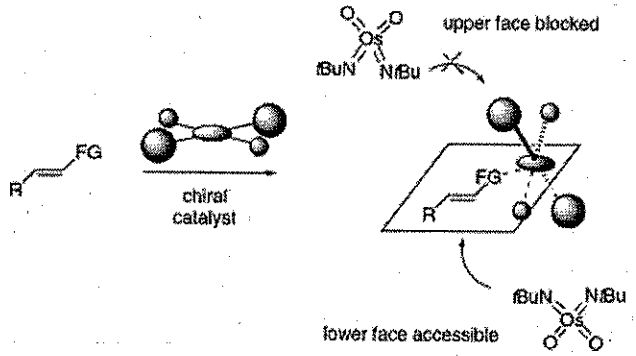
**Scheme 12** Comparison of face selectivity in auxiliary-controlled asymmetric diamination of alkenes.

## Enantioselective reaction

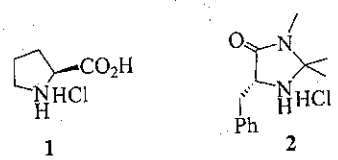
K. Muniz et al, *Chem. Comun,* 2005. 2729.

The enantioselctivity can be introduced using chiral auxiliary.
But the stoichiometric amount of chiral information is still needed.

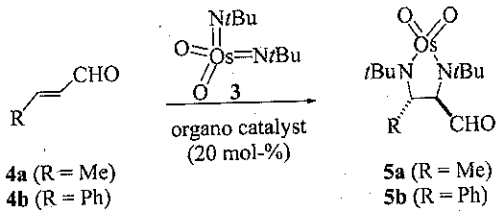
### Strategy of enantioselective reaction using chiral catalyst




### Organo catalyst



1 2




**4a** (R = Me)
**4b** (R = Ph)

**5a** (R = Me)
**5b** (R = Ph)

### Result using organo catalyst

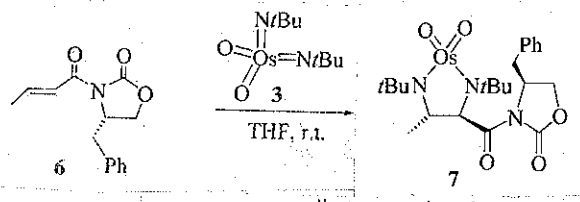
Table 1. Diamination of **4a** and **4b** with the bisimido reagent **3** in the presence of organocatalysts **1** (20 mol-%) and **2**.

| Entry | Substrate | Catalyst | Solvent | Product | Yield [%][a] | Enantiomeric excess [%][b] |
|---|---|---|---|---|---|---|
| 1 | **4a** | **1** | MeOH/THF | **5a** | 75 | 0 |
| 2 | **4b** | **1** | MeOH/THF | **5b** | 62 | 3 |
| 3 | **4a** | **2** | acetone | **5a** | 81 | 2 |
| 4 | **4a** | **2** | MeOH/THF | **5a** | 95 | 2 |
| 5 | **4a** | **2** | $CH_2Cl_2$ | **5a** | 79 | 8 |
| 6[c] | **4a** | **2** | $CH_2Cl_2$ | **5a** | 82 | 38 |
| 7[c] | **4a** | **2** | MeOH/THF | **5a** | 76 | 43 |
| 8[c] | **4b** | **2** | MeOH/THF | **5b** | 79 | 27 |

[a] Isolated yield after column chromatography. [b] Determined by chiral HPLC analysis. [c] Stoichiometric reactions.

These results mean it is difficult to apply organo catalyst to asymmetric diamination.

### Evans condition

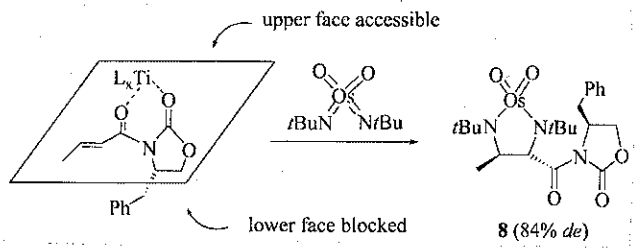



6 7 8

diastereomeric ratio

| | |
|---|---|
| no additive: | 44:56 |
| $Ti(OiPr)_4$: | 21:79 |
| $Cl_2Ti(OiPr)_2$: | 08:92 |

### Transition state



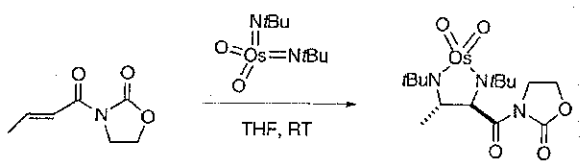

**8** (84% *de*)

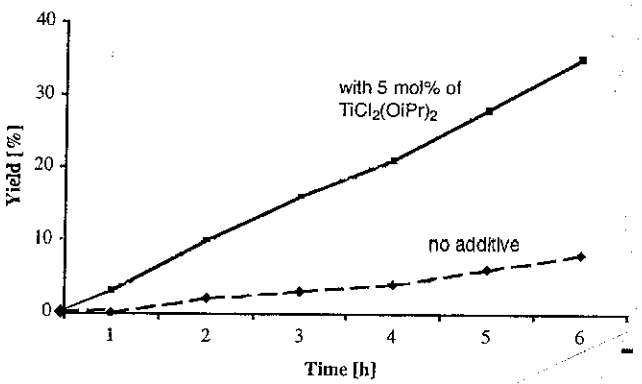
The yield is decreased using $TiCl_4$ because of its acidity.

## Why is this possible??

The reaction should proceed in the absence of Titanium catalyst!!

### Catalyst acceleration



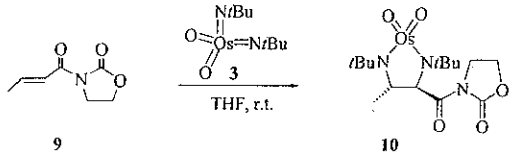




Because the reaction rate with $TiCl_2(O^iPr)_2$ is 6 times as fast as that without the additive.

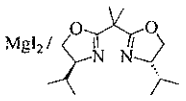
⇓

Consideration this result,
there is possibility to develop
the enantioselective diamination
combinating lewis acid and chiral ligand !

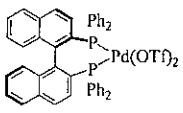
## Screening of lewis acid and chiral ligand



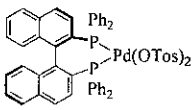

9 10



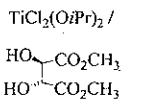

76% yield, 7% *ee*



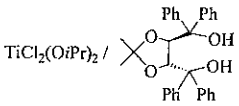

83% yield, 1% *ee*



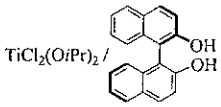

71% yield, 9% *ee*




78% yield, 12% *ee*

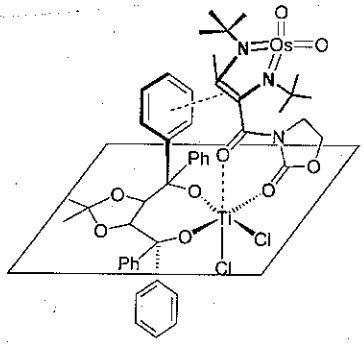



91% yield, 22% *ee*
92% yield, 88% *ee* (preformed)




87% yield, 18% *ee*
88% yield, 54% *ee* (preformed)

## Proposed transition state model




**transition state model**

## Substrate generality

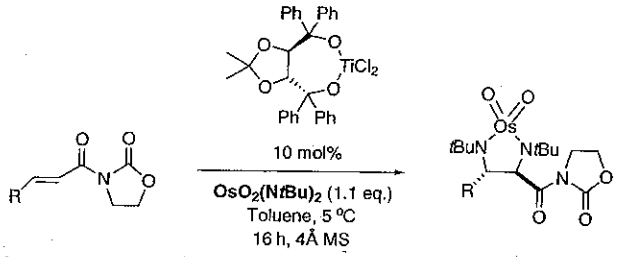



Table 2. Enantioselective diamination of olefins with (*R*,*R*)-Ti-TADDOLate catalysis.

| Entry | Substrate (R) | Product | Yield [%][a] | *ee* [%][b] |
|---|---|---|---|---|
| 1[c] | **9** ($CH_3$) | (+)-**10** | 91 | 22 |
| 2 | **9** ($CH_3$) | (+)-**10** | 92 | 88 |
| 3[d] | **9** ($CH_3$) | (–)-**10** | 90 | 86 |
| 4[e] | **9** ($CH_3$) | (–)-**10** | 81 | 90 |
| 5 | **11** (H) | (+)-**12** | 97 | 82 |
| 6 | **13** (*n*-Pr) | (+)-**14** | 91 | 86 |
| 7 | **15** ($C_6H_5$) | (+)-**16** | 95 | 78 |
| 8 | **17** ($CO_2CH_3$) | (–)-**18** | 83 | 90 |

[a] Isolated yield after workup and column chromatography. [b] Determined on a Chiralpak AD column (see Experimental Section for details). [c] With catalyst generated in situ. [d] With the enantiomeric (*S*,*S*)-TADDOL ligand. [e] With an equimolar amount of (*S*,*S*)-TADDOL-Ti complex.

## 3. The quest for a catalytic diamination of alkenes

K.Muniz et al, *Chem. Eur.J.* 2004, *10*, 2475

Os reagent is very precious and highly toxic...
Development of catalytic diamination is strongly demanded.

In this section the possibility of catalytic diamination is examined using DFT study.

### DFT (Density functional theory)

密度汎関数理論と呼ばれるもので、電子系のエネルギーなどの物性を電子密度から計算することが可能とする理論。
分子の動きをシミュレーションし、その間でのエネルギー遷移を計算によって求めることができる。

### Mechanistic study of diamination

[3+2] vs [2+2]

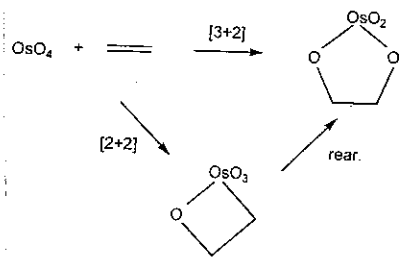



Table 1. Peri- and chemoselectivity in the addition of $OsO_2(NH)_2$ to ethylene. Activation energies ($\Delta E_a$) and reaction energies ($\Delta E_r$) calculated at the B3LYP/III+//B3LYP/II level and free enthalpies ($\Delta G_a$, $\Delta G_r$) at 298.15 K. All values in kcal mol$^{-1}$.

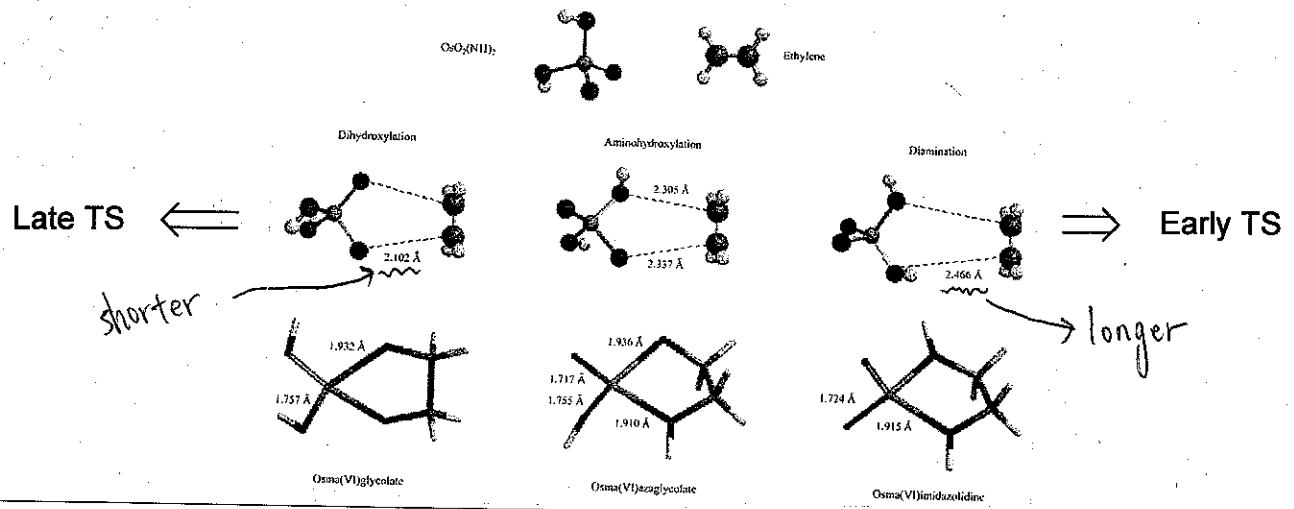
| Reaction | | $\Delta E_a$ | $\Delta G_a$ | $\Delta E_r$ | $\Delta G_r$ |
|---|---|---|---|---|---|
| [2+2] | Os=O[a] | 46.5 | 59.8 | 7.1 | 22.3 |
| [2+2] | Os=NH[a] | 42.5 | 56.3 | −8.4 | 8.5 |
| [3+2] | O=Os=O | 8.3 | 22.8 | −23.9 | −6.0 |
| [3+2] | O=Os=NH | 6.1 | 19.9 | −46.4 | −27.3 |
| [3+2] | NH=Os=NH | 0.4 | 12.1 | −67.2 | −46.2 |

[a] Only the stereoisomer lowest in energy is listed.

$\Delta G_a$ for [2+2] addition (> 55kcal/mol) is much higher than that for [3+2] addition (< 25 kcal/mol).

These values mean diamination proceeds through [3+2] addition.

### Rationalization of chemoselectivity




| Contribution | $\Gamma_i$ | O=Os=O | NH=Os=NH[a] | change in %[b] |
|---|---|---|---|---|
| $\Delta E_{str}$ ethylene | | 12.0 | 12.0 | |
| $\Delta E_{str}$ $OsO_2(NH)_2$ | | 15.2 | 10.0 | −34 |
| $\Delta E_{str}$ total | | 27.2 | 22.0 | |
| $\Delta E_{Pauli}$ | | 138.6 | 172.0 | 25 |
| $\Delta E_{elst}$ | | −65.8 | −81.8 | 24 |
| $\Delta E_{orb}$ | | −92.1 | −116.6 | 27 |
| **$\Delta E_{orb}$ ($\Gamma_i$)** | **$a_1$** | **−61.4** | **−70.6** | **15** |
| | **$a_2$** | **−1.3** | **−2.9** | |
| | **$b_1$** | **−1.2** | **−1.8** | |
| | **$b_2$** | **−28.2** | **−41.3** | **46** |
| $\Delta E_{int} = \Delta E_{Pauli} + \Delta E_{elst} + \Delta E_{orb}$ | | −19.4 | −26.4 | 36 |
| $\Delta E = \Delta E_{str} + \Delta E_{int}$ | | 7.8 | −4.4 | |
| $\Delta E_{orb}/\Delta E_{elst}$ | | 1.40 | 1.42 | |
| $\Delta E_{orb}(a_1)/\Delta E_{orb}(b_2)$ | | 2.17 | 1.71 | |

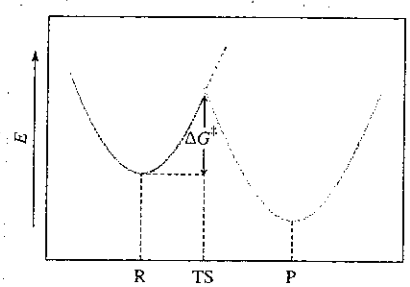
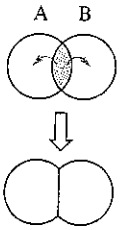



図 5・2 Bell-Evans-Polanyi のモデル

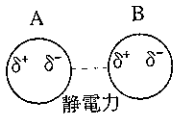
$\Delta E_{str}$ is strain energy for TS.

$\Delta E_{orb}$ (軌道相互作用)

$\Delta E_{Pauli}$
(被占軌道間の交換相互作用)

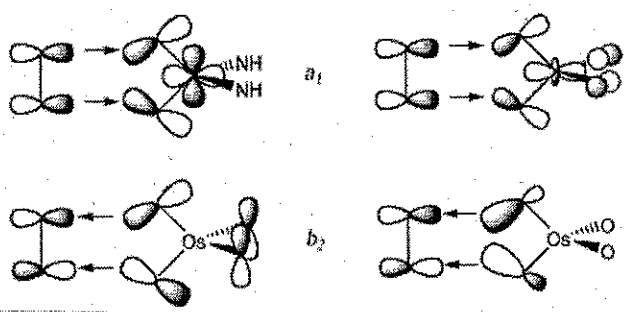



$\Delta E_{elst}$
(静電相互作用)




O=Os=O addition

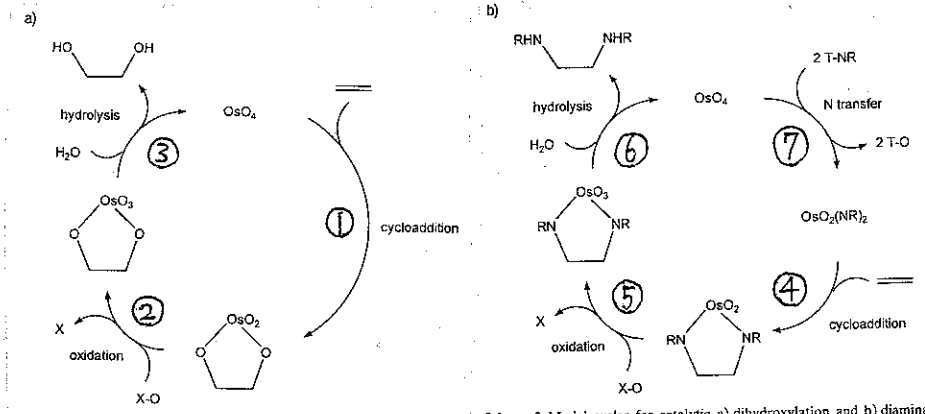
NH=Os=NH addition



## Diamination vs dihydroxylation

### Catalytic cycle of dihydroxylation

### Model catalytic cycle of diamination




Scheme 3. Model cycles for catalytic a) dihydroxylation and b) diamination. X-O = oxidant, T-NR = imido-transfer agent.

Table 3. Calculated thermodynamic reaction profile ($\Delta G_r$) for model catalytic cycles of dihydroxylation and diamination, according to Scheme 3a and 3b. Free enthalpies relative to the corresponding reaction in the dihydroxylation cycle are also given. All values in kcal mol$^{-1}$.

| Reaction | absolute | relative to dihydrox. |
|---|---|---|
| Dihydroxylation (Scheme 3a) | | |
| ① $OsO_4 + C_2H_4 \rightarrow$ dioxoosma-2,5-dioxolane | −4.1 | 0.0 |
| ② dioxoosma-2,5-dioxolane + $H_2O_2 \rightarrow$ trioxoosma-2,5-dioxolane + $H_2O$ | −35.7 | 0.0 |
| ③ trioxoosma-2,5-dioxolane + $H_2O \rightarrow OsO_4$ + $(HO)CH_2CH_2(OH)$ | −18.0 | 0.0 |
| Diamination (Scheme 3b) | | |
| ④ $OsO_2(NH)_2 + C_2H_4 \rightarrow$ dioxoosma-2,5-diazolidine | −46.2 | −42.1 |
| ⑤ dioxoosma-2,5-diazolidine + $H_2O_2 \rightarrow$ trioxoosma-2,5-diazolidine + $H_2O$ | −24.5 | 11.2 |
| ⑥ trioxoosma-2,5-diazolidine + $H_2O \rightarrow OsO_4$ + $(H_2N)CH_2CH_2(NH_2)$ | −13.9 | 4.1 |
| ⑦ $OsO_4 + 2NH_3 \rightarrow OsO_2(NH)_2 + 2H_2O$ | 24.4 | 24.4 |

- Step ④ is very exergonic by -46 kcal/ mol
- Step ⑤ is less favorable than step ② by only 11 kcal/ mol.
- Step ⑥ is less favorable than step ③ by only 4 kcal/ mol.
- Step ⑦ is only endergonic.
- Large driving force of forming dioxoosma -2,5-diazolidine arises from the weak metal=N bond in complex.

There is an apparent discrepancy(矛盾) between the weaker Lewis acidity of the imidocomplex and the relative instability of Os=N bond.

Thermodynamic hill

This step is not required in dihydroxylation.

## Rationalization of the discrepancy

Table 6. Electrostatic versus covalent nature of oxo and imido-osmium(VIII) bonds. Energy decomposition of the Os=O and Os=NH bonds in $C_{3v}$-symmetric $OsO_4$ and $OsO_3(NH)$, respectively, at the BLYP/IV' level. Bold: contributions of the $\Gamma_i$ symmetry orbitals to the stabilizing orbital-interaction energy $\Delta E_{orb}$. All energies in kcal mol$^{-1}$.

| Contribution | $\Gamma_i$ | $OsO_4$ | $OsO_3(NH)$[a] |
|---|---|---|---|
| $\Delta E_{str}$ $O^{2-}$ or $NH^{2-}$ | | 0.0 | 1.8 |
| $\Delta E_{str}$ $OsO_3^{2+}$ | | 5.2 | 5.7 |
| $\Delta E_{str}$ total | | 5.2 | 7.5 |
| $\Delta E_{Pauli}$ | | 539.0 | 492.4 |
| $\Delta E_{elst}$ | | −1101.7 | −1011.3 |
| $\Delta E_{orb}$ | | −425.7 | −452.6 |
| **$\Delta E_{orb}(\Gamma_i)$** | $a_1$ | **−196.0** | **−173.6** |
| | $a_2$ | **−1.2** | **−1.2** |
| | $e$ | **−228.6** | **−277.8** |
| $\Delta E_{int} = \Delta E_{Pauli} + \Delta E_{elst} + \Delta E_{orb}$ | | −988.4 | −971.5 |
| $\Delta E = \Delta E_{str} + \Delta E_{int}$ | | −983.2 | −964.0 |
| $\Delta E_{orb}/\Delta E_{elst}$ | | 0.39 | 0.45 |
| $\Delta E_{orb}(a_1)/\Delta E_{orb}(e)$ | | 0.86 | 0.62 |

[a] A $C_s$-symmetric structure of $OsO_3(NH)$ with a bent imido ligand (Os-N-H angle 135.4) is more stable by 0.2 kcal mol$^{-1}$.

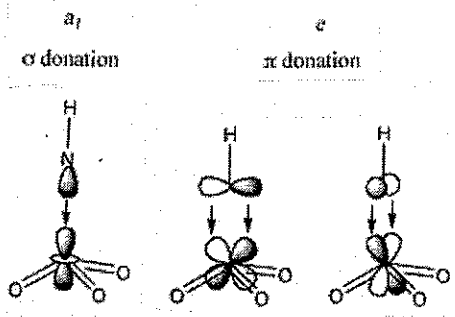



Figure 3. $a_1$ and $e$ symmetry orbitals in $C_{3v}$-symmetric $OsO_4$ and $OsO_3(NH)$.

Amine source is $NH_3$.

Point of this analysis

It is clear that the strong Os=O bond is relied on the much stronger electrostatic component $\Delta E_{elst}$ than that of Os=N bond.

### Substituted amine is employed.

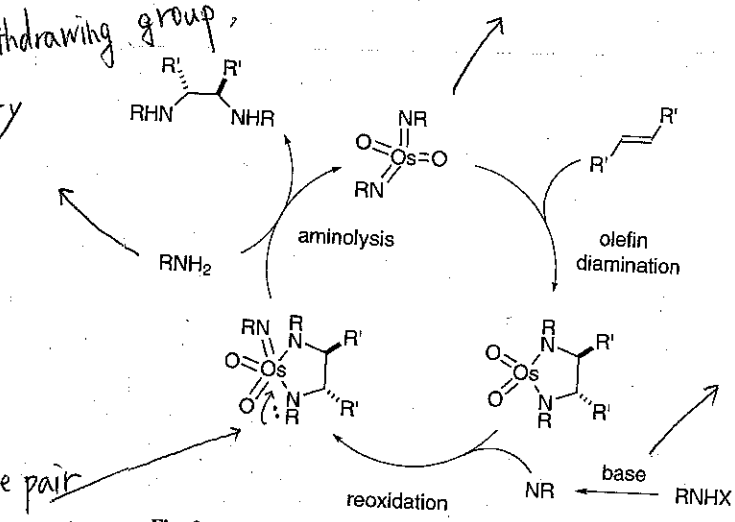
| Reaction | Absolute | Relative to dihydrox. | Relative to R = H |
|---|---|---|---|
| R = Me | | | |
| $OsO_2(NR)_2 + C_2H_4 \rightarrow$ dioxoosma-2,5-diazolidine | −35.1 | −31.0 | 11.1 |
| dioxoosma-2,5-diazolidine + $H_2O_2 \rightarrow$ trioxoosma-2,5-diazolidine + $H_2O$ | −18.8 | 16.9 | 5.7 |
| trioxoosma-2,5-diazolidine + $H_2O \rightarrow OsO_4$ + $(NHR)CH_2CH_2(NHR)$ | −13.3 | 4.7 | 0.6 |
| $OsO_4 + 2RNH_2 \rightarrow OsO_2(NR)_2 + 2H_2O$ | 2.4 | 2.4 | −22.0 |
| R = tBu | | | |
| $OsO_2(NR)_2 + C_2H_4 \rightarrow$ dioxoosma-2,5-diazolidine | −22.5 | −18.4 | 23.7 |
| dioxoosma-2,5-diazolidine + $H_2O_2 \rightarrow$ trioxoosma-2,5-diazolidine + $H_2O$ | −4.1 | 31.6 | 20.4 |
| trioxoosma-2,5-diazolidine + $H_2O \rightarrow OsO_4$ + $(NHR)CH_2CH_2(NHR)$ | −31.0 | −13.0 | −17.1 |
| $OsO_4 + 2RNH_2 \rightarrow OsO_2(NR)_2 + 2H_2O$ | 0.6 | 0.6 | −23.8 |
| R = $CF_3$ | | | |
| $OsO_2(NR)_2 + C_2H_4 \rightarrow$ dioxoosma-2,5-diazolidine | −49.4 | −45.3 | −3.2 |
| dioxoosma-2,5-diazolidine + $H_2O_2 \rightarrow$ trioxoosma-2,5-diazolidine + $H_2O$ | −11.1 | 24.6 | 13.4 |
| trioxoosma-2,5-diazolidine + $H_2O \rightarrow OsO_4$ + $(NHR)CH_2CH_2(NHR)$ | −38.2 | −20.2 | −24.3 |
| $OsO_4 + 2RNH_2 \rightarrow OsO_2(NR)_2 + 2H_2O$ | 35.7 | 35.7 | 11.3 |

| | Steric effects (Me, tBu) | Electron-withdrawing ($CF_3$) |
|---|---|---|
| cycloaddition | disfavor | favor |
| oxidation | strongly disfavor | favor |
| hydrolysis | favor | no effect |
| oxo-imido exchange | no effect | strongly disfavor |

If R is electron-withdrawing group, bisimido osmium complex is unstable.

Aminolysis strategy

If R is electron-withdrawing group, this amine's nucleophilicity might be decreased.




same as one in aminolysis

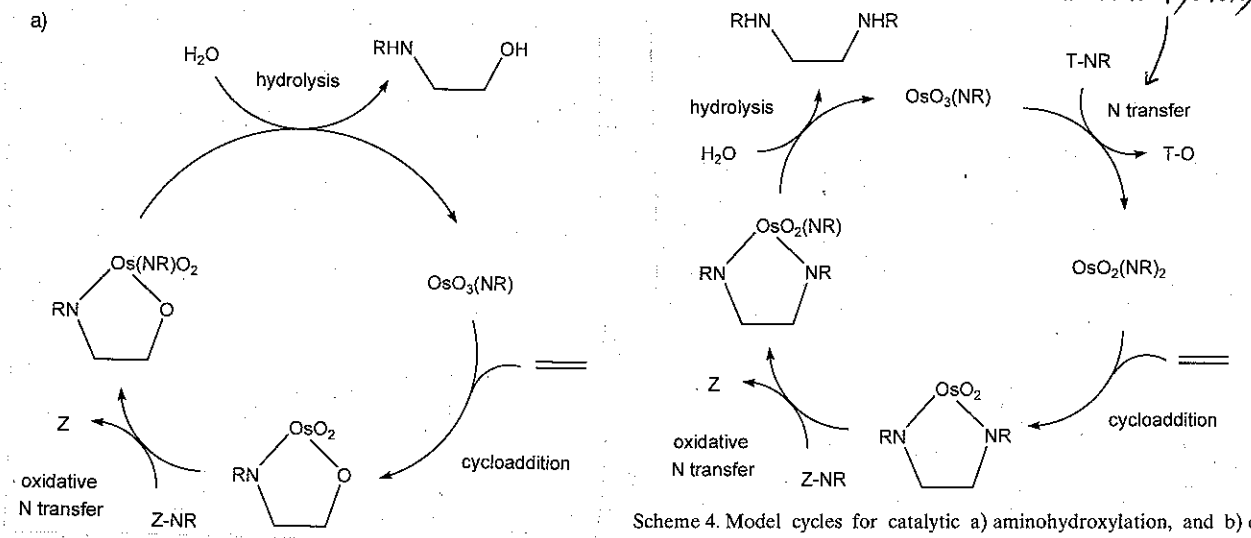
The donation of lone pair stabilize the osmaimidazolidine.

⇓

If R is electron-withdrawing group, the osmaimidazolidine become unstable.

**Fig. 8** Proposed catalytic cycle for diamination of alkenes.

Diamination vs Aminohydroxylation




This step isn't necessary in aminohydroxylation.

Scheme 4. Model cycles for catalytic a) aminohydroxylation, and b) diamination. Z-NR = oxidative imido-transfer agent, T-NR = non-oxidative imido-transfer agent.

It is difficult to identify oxidative and non-oxidative nitrogen transfer.
**Electron-releasing group** at the imido ligand **favors** the **non-oxidative N-transfer** event, whereas the presence of **sterically demanding substituent disfavors oxidative N-transfer** event.

## Conclusion

### In any model catalytic cycles

- Electron-withdrawing group disfavors the formation of imido complex.
- Electron-releasing group disfavors the oxidation and hydrolysis step.

**Namely, dihydroxylation and aminohydroxylation is preferred to diamination.**

⇓

**It is impossible to develop the catalytic diamination with <u>osmium bisimido complex</u>.**

# 7. Current and future works

## Catalytic diamination

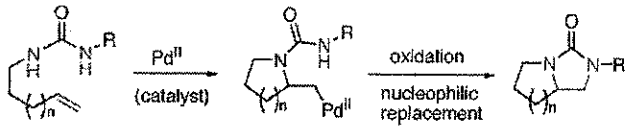
K. Muniz et al. *J. Am. Chem. Soc.* 2005, *127*, 14587.

Catalytic diamination of alkenes was elusive reaction so far.

Because the diamine products cordinate to almost all transition metals and deactivate it.

**But this time one elegant examination is reported !!**

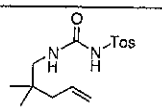
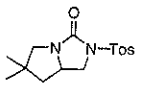
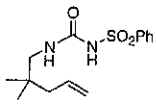
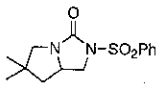
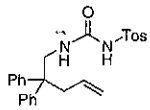
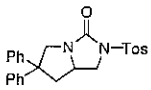
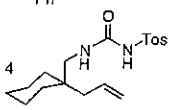
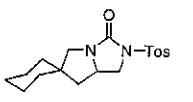
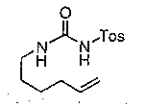
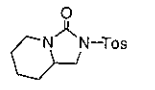
### General scheme

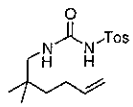
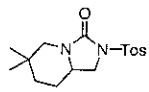
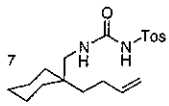
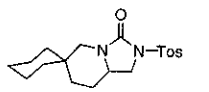
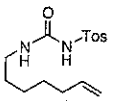
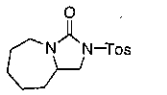
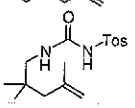
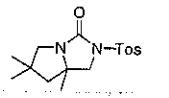



This strategy is applied to only intramolecular reaction.

### Substrate generality

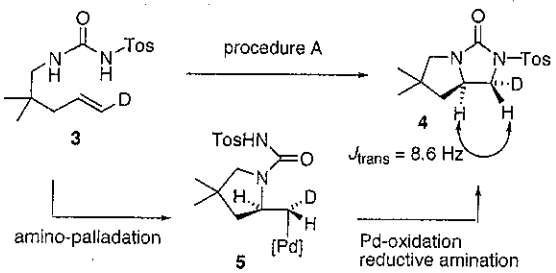
*Table 1.* Palladium-Catalyzed Intramolecular Diamination of Alkenes

| Entry | Substrate | Procedure[a] | Product | Conversion [%][b] | Yield [%][c] |
|---|---|---|---|---|---|
| 1 |  | A |  | 100 | 92 |
| 2 |  | A |  | 100 | 93 |
| 3 |  | A |  | 100 | 95 |
| 4 |  | A |  | 100 | 91 |
| 5 |  | B |  | 98 | 86 |

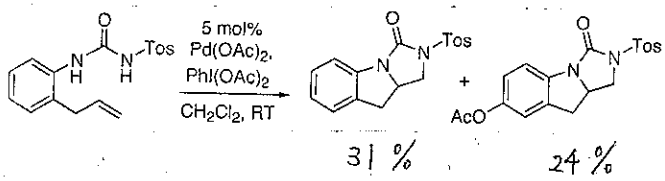
| Entry | Substrate | Procedure[a] | Product | Conversion [%][b] | Yield [%][c] |
|---|---|---|---|---|---|
| 6 |  | B |  | 100 | 87 |
| 7 |  | B |  | 100 | 78 |
| 8 |  | C |  | 94 | 89 |
| 9 |  | A |  | 100 | 94 |

[a] Procedure A: 5 mol % of $Pd(OAc)_2$, $PhI(OAc)_2$ (2.2 equiv), $NMe_4Cl$/NaOAc (1 equiv), $CH_2Cl_2$, RT, 12 h. Procedure B: 25 mol % of $Pd(OAc)_2$, $PhI(OAc)_2$ (2.2 equiv), $CH_2Cl_2$, RT, 48 h. Procedure C: 10 mol % of $Pd(OAc)_2$, $PhI(OAc)_2$ (2.2 equiv), $CH_2Cl_2$, RT, 12 h. [b] Determined from crude $^1H$ NMR spectra and TLC control. [c] Given yields refer to isolated analytically pure material after column chromatography.

### Mechanistic proposal




### Synthesis of tricyclic heterocycles




It is possible to liberate the diamine from the cyclic urea under reductive conditions.

**Advantage**

- It is easy to liberate the free diamine.
- Catalytic amount of metal is needed.
- No side product is detected.

**Disadvantage**

- Only intramolecular reaction.
- It's not asymmetric reaction.

**In the future intermolcular diamination reaction will be developed...**
**And if the catalytic asymmetric diamination is accomplished,**
**this strategy will become most powerful in all synthetic strategies of diamine.**