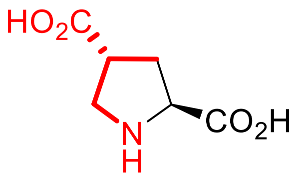
# Palladium catalyzed intermolecular aminocarbonylation of alkenes

J. Cheng, X. Qi, M. Li, P. Chen, G. Liu, *JACS*, **2015**, *137*, 2480.

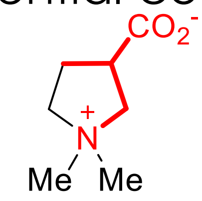
RCC Mylène ROUDIER
19,03,2015

# β-amino acids

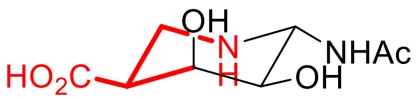
- β-aminoacids identified as essential component in natural products




pyrrolidine-2.4-dicarboxylic acid




β-prolinebetaine
= found in citrus foods




siastatine B
(natural iminoglycoside)

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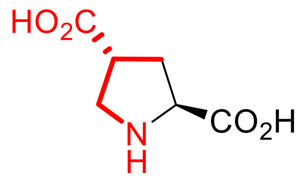


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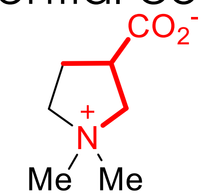


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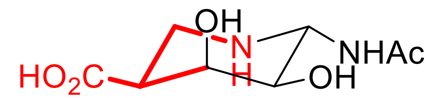


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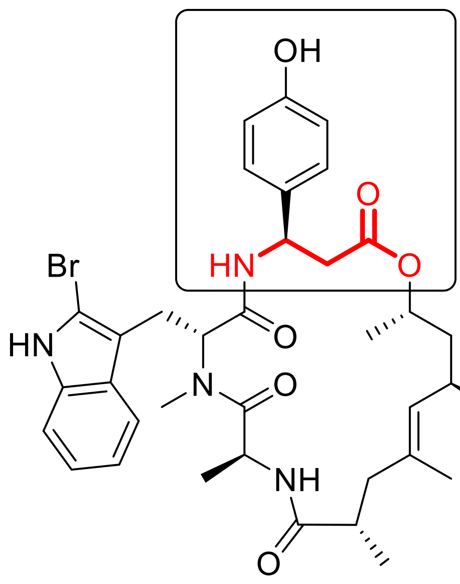
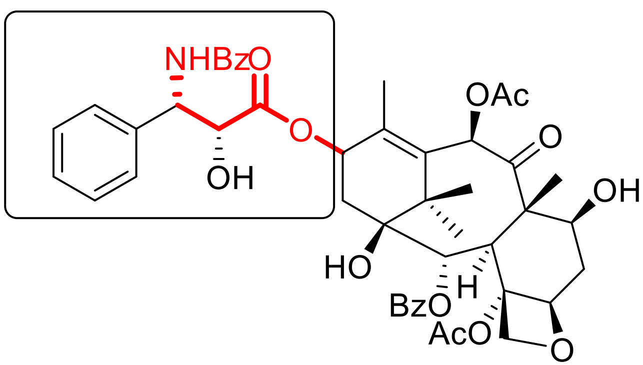



= β-Tyrosine

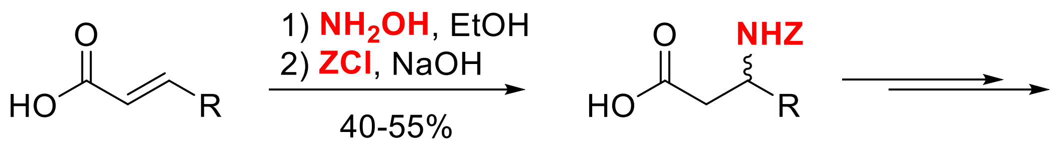
Jasplakinolide
= from marine organism
insectividal, antifungal properties

= phenylisoserine




Taxol
= antitumour agent

- Amination of α,β-insaturated carboxylic acids

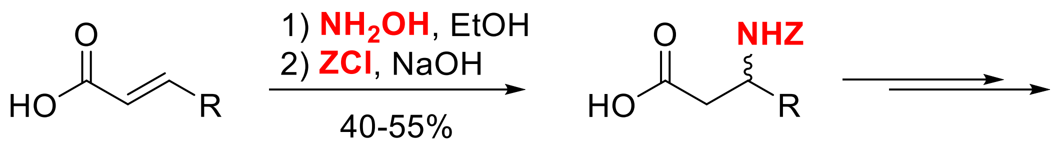



I. Braschi, G. Cardillo, C. Tomasini, R. Venezia, *J. Org. Chem.*, **1994**, *59*, 7292

*Chem. Soc. Rev.*, **1996**, 117-128
For a recent review of asymmetric synthesis of α- and β-amino acids : *ACIE*, **2003**, *42*, 4290-4299.

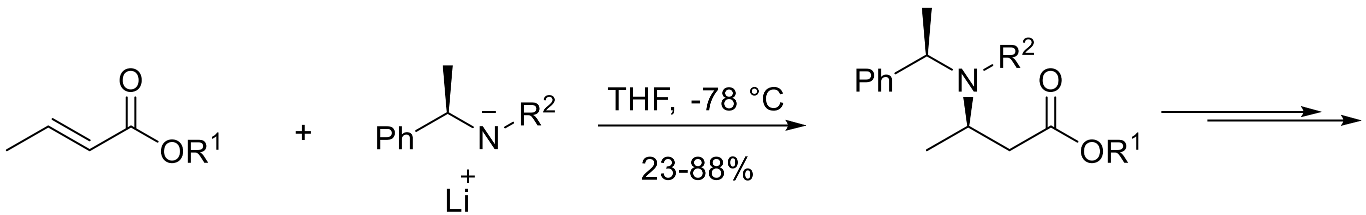
# β-amino acids synthesis

- Amination of α,β-insaturated carboxylic acids




I. Braschi, G. Cardillo, C. Tomasini, R. Venezia, *J. Org. Chem.*, **1994**, *59*, 7292

- Amination of α,β-insaturated esters



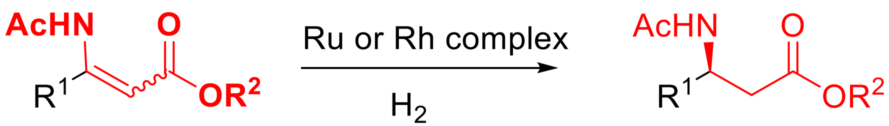

S. G. Davies, O. Ichihara, *Tetrahedron asymmetry*, **1991**, *2*, 183

*Chem. Soc. Rev.*, **1996**, 117-128

For a recent review of asymmetric synthesis of α- and β-amino acids : *ACIE*, **2003**, *42*, 4290-4299.

# β-amino acids synthesis

❖ Hydrogenation of β- aminoacrylic acids




Y.-G. Zhou, W. Tang, W.-B. Wang, W. Li, X. Zhang, *JACS*, **2002**, *124*, 4952.

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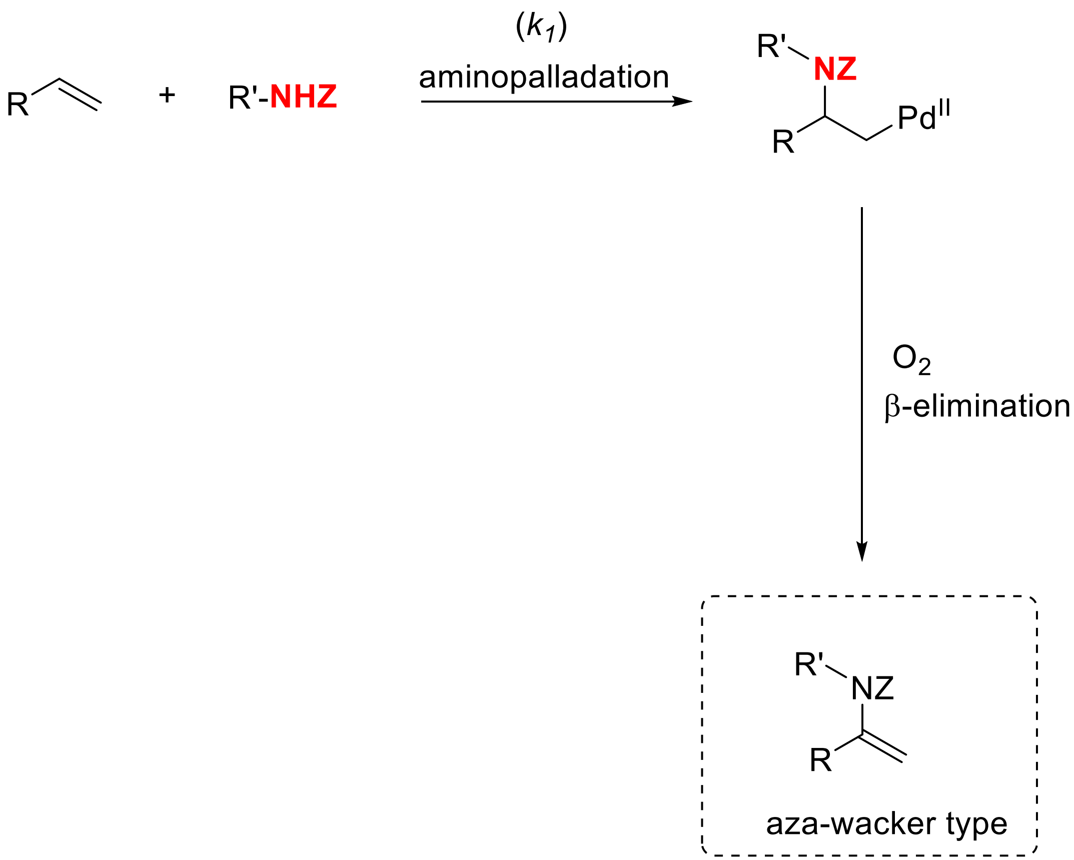
For a recent review of asymmetric synthesis of α- and β-amino acids : *ACIE*, **2003**, *42*, 4290-4299.

# This work

❖ Direct amination of olefins




Sthal, *JACS*, **2003**, *125,* 12996

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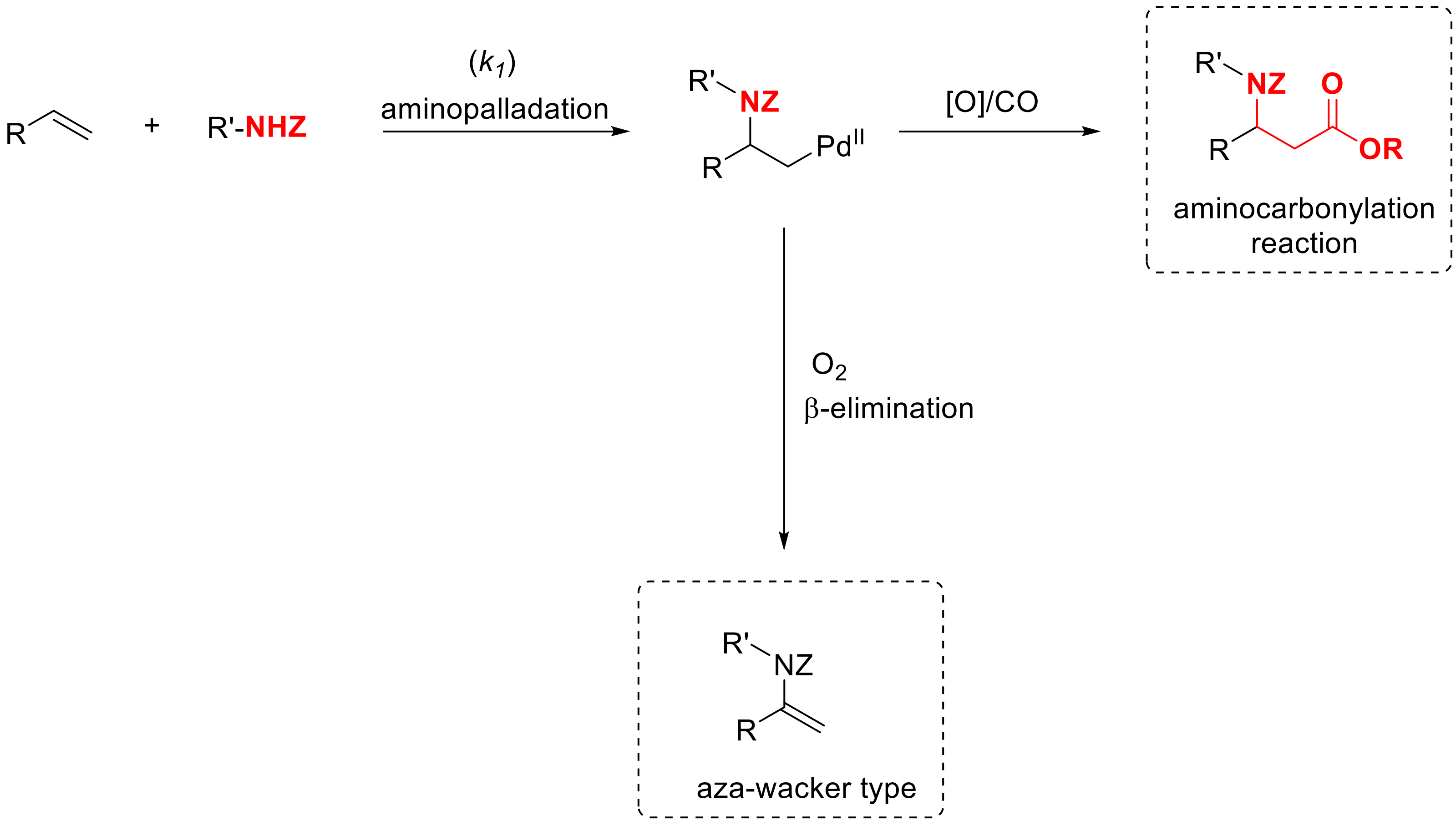


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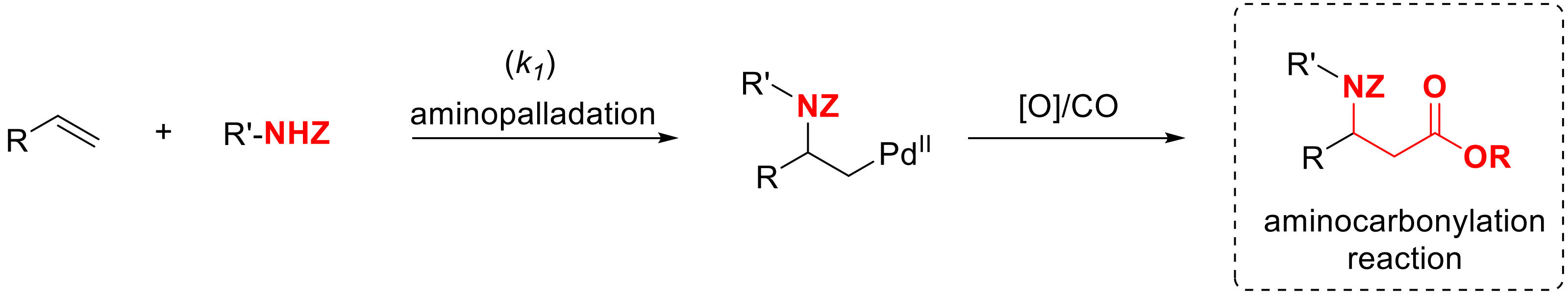


-> Pd-benzoquinone or Pd-Cu(II) salt systems as oxidants for aminocarbonylation

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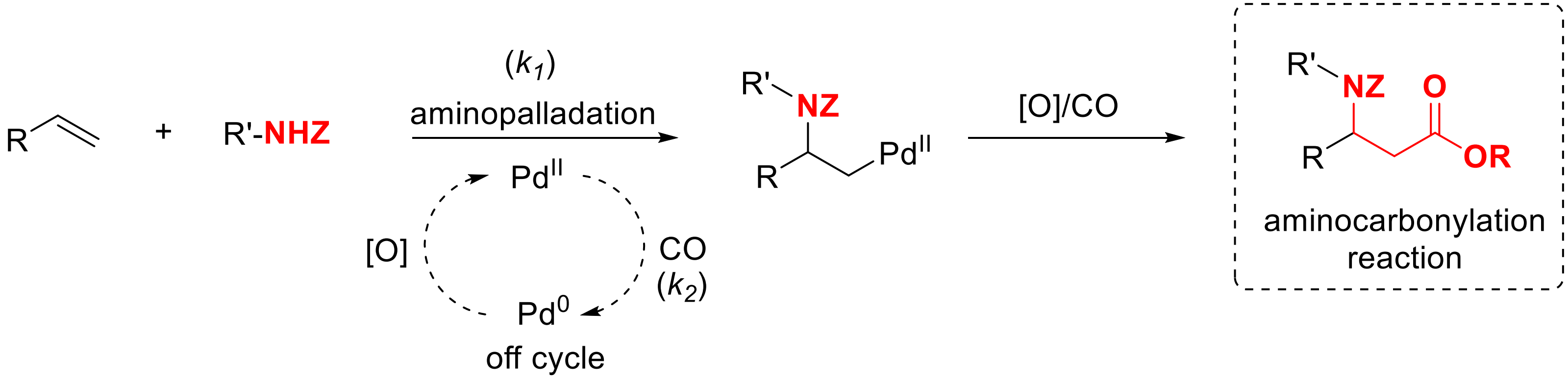


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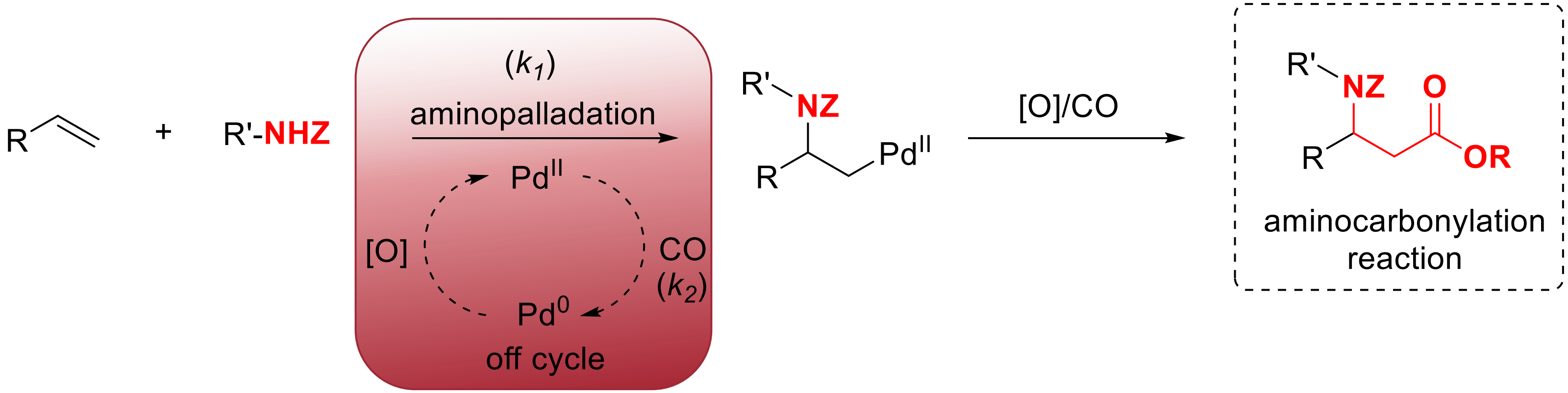


X $k_2 > k_1$

How to favor the aminopalladation ?

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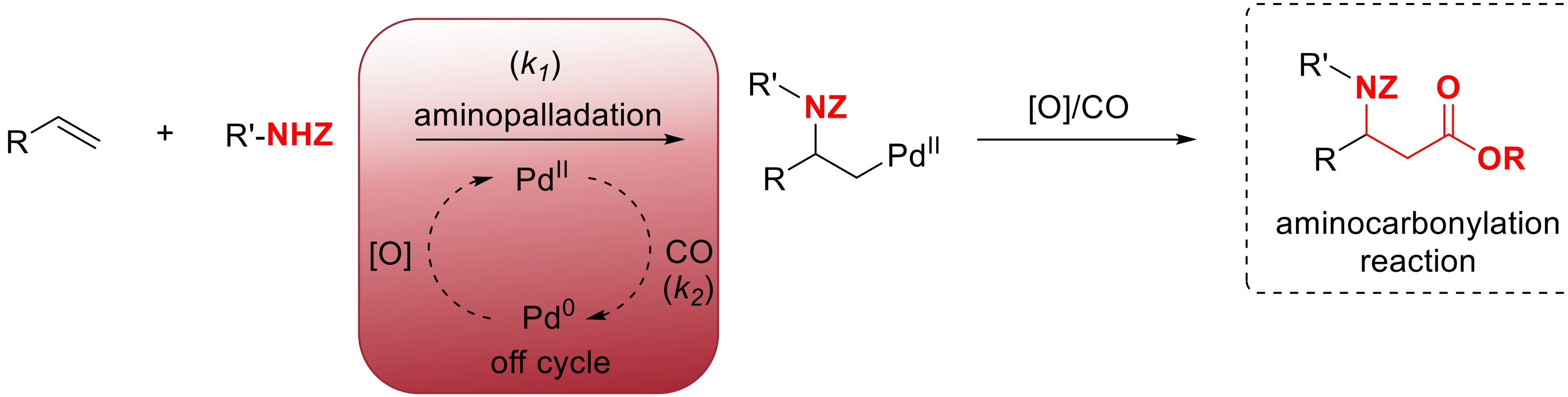


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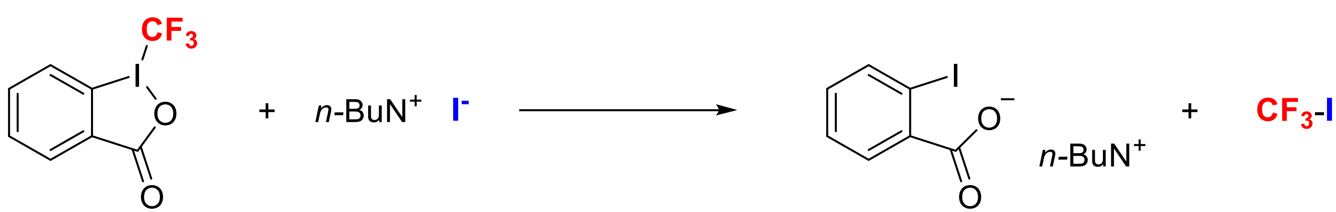
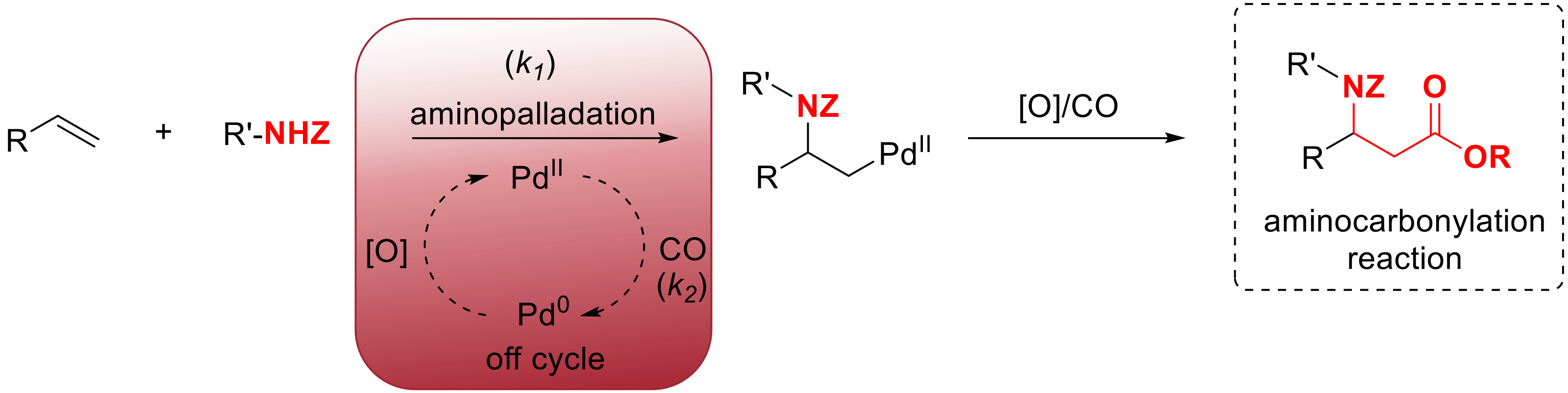



Togni's reagent could react with Iodide
Nevado and al., *ACIE*, **2013**, *52*, 13086

# This work

- Direct amination of olefins

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How to favor the aminopalladation ?

$Pd(O_2CCF_3)_2$ + $PhI(O_2CAd)_2$ ⟶ $Pd(O_2CCF_3)^+$ + $PhI(O_2CAd)(O_2CCF_3)$ + $O_2CAd^-$

more activated Pd specie

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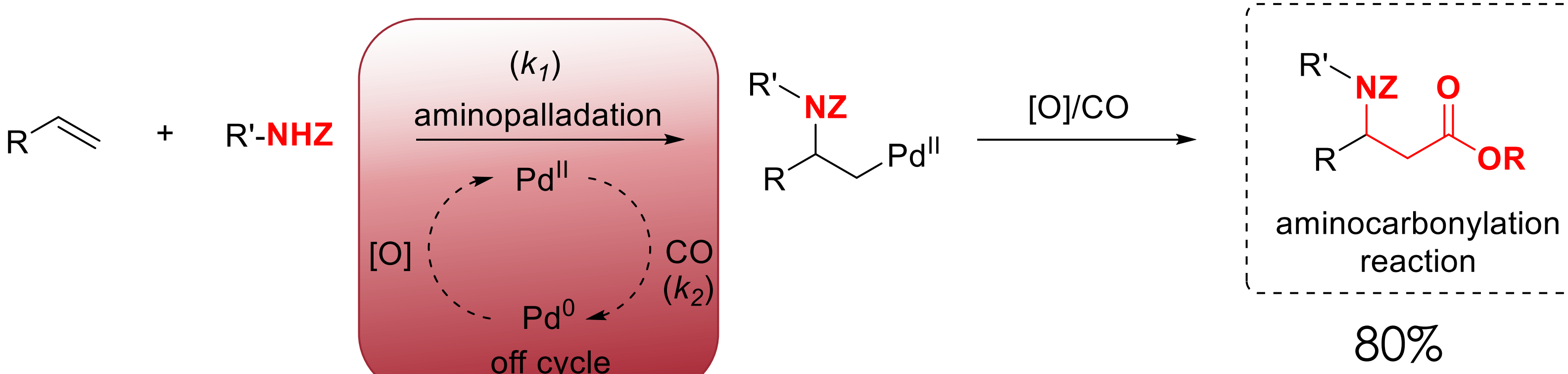



X $k_2 > k_1$

✓ $k_2 << k_1$

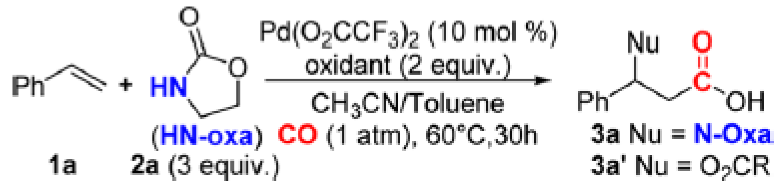
How to favor the aminopalladation ?

$$Pd(O_2CCF_3)_2 + PhI(O_2CAd)_2 \longrightarrow Pd(O_2CCF_3)^+ + PhI(O_2CAd)(O_2CCF_3) + O_2CAd^-$$

more activated Pd specie

# Optimization

## Table 1. Optimization of Reaction Conditions[a]




Due to oxycarbonylation reaction

| entry | Pd catalyst | oxidant | yield (%)[b] 3a | yield (%)[b] 3a′ (R) |
|---|---|---|---|---|
| 1 | $Pd(OAc)_2$ | $PhI(OAc)_2$ | 45 | 4 (Me) |
| 2 | $Pd(CH_3CN)_2Cl_2$ | $PhI(OAc)_2$ | 65 | 5 (Me) |
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| 5 | $Pd(OTFA)_2$ | $PhI(OPiv)_2$ | 55 | 5 ($^t$Bu) |
| 6 | $Pd(OTFA)_2$ | $PhI(O_2CAd)_2$ | 90 (83)[f] | 5 (Ad) |
| 7[c] | $Pd(OTFA)_2$ | $PhI(O_2CAd)_2$ | 80 | 13 (Ad) |
| 8[d] | $Pd(OTFA)_2$ | $PhI(O_2CAd)_2$ | 85 | 10 (Ad) |
| 9 | $Pd(OTFA)_2$ | $(NH_4)_2S_2O_8$ | 31 | 0 |
| 10 | $Pd(OTFA)_2$ | oxone | 27 | 0 |
| 11[e] | $Pd(OTFA)_2$ | 35% aq $H_2O_2$ | 21 | 0 |
| 12 | none | $PhI(O_2CAd)_2$ | 0 | 0 |

[a] All reactions were run at 0.2 mmol scale. [b] Yield obtained by $^1$H NMR with $CF_3$-DMA as internal standard. [c] 2a (1.2 equiv). [d] 2a (2.0 equiv). [e] Oxidant (5.0 equiv). [f] Isolated yield of ester 4a.

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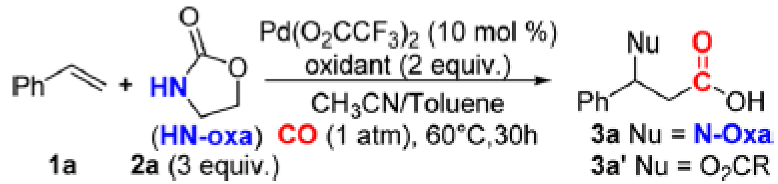


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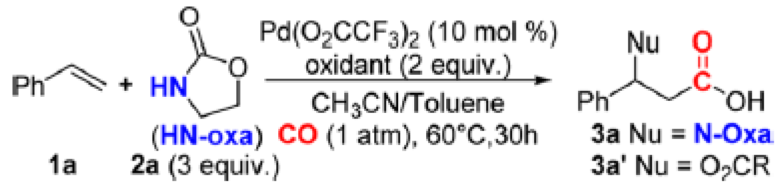


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Best conditions (entry 6)

Strong oxidants (entries 9–11)

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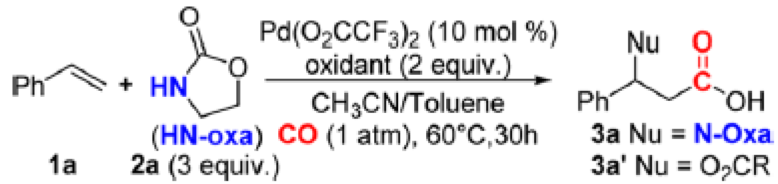


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Best conditions (entry 6)

Without palladium (entry 12)

[a] All reactions were run at 0.2 mmol scale. [b] Yield obtained by $^1$H NMR with $CF_3$-DMA as internal standard. [c] 2a (1.2 equiv). [d] 2a (2.0 equiv). [e] Oxidant (5.0 equiv). [f] Isolated yield of ester 4a.

# Role of $PhI(O_2CAd)_2$

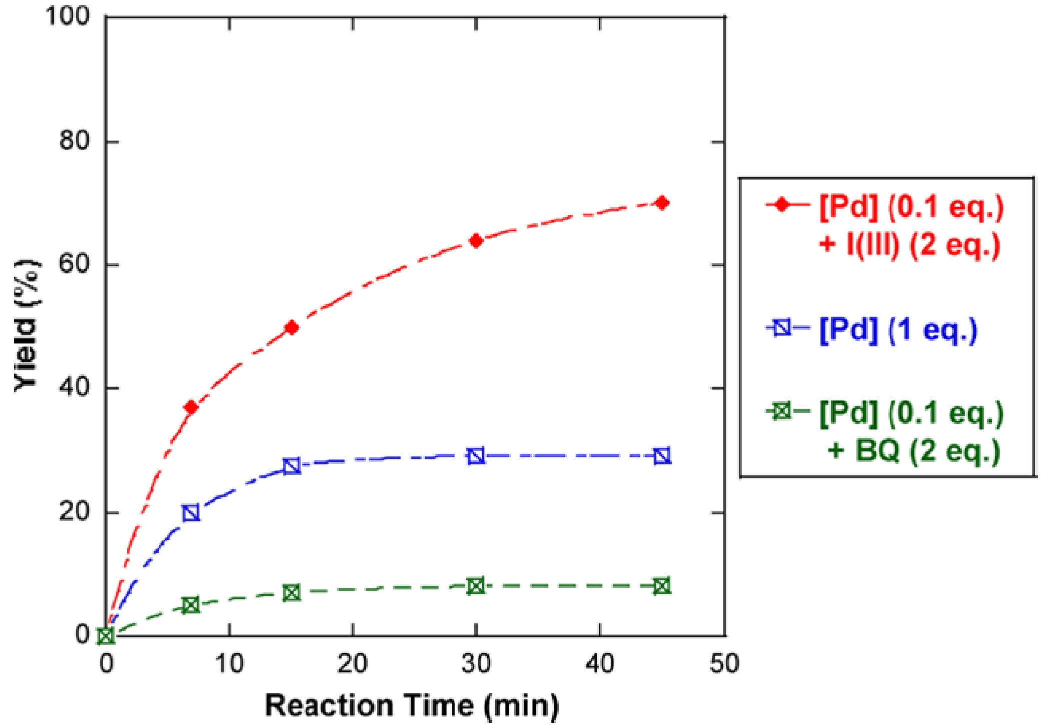
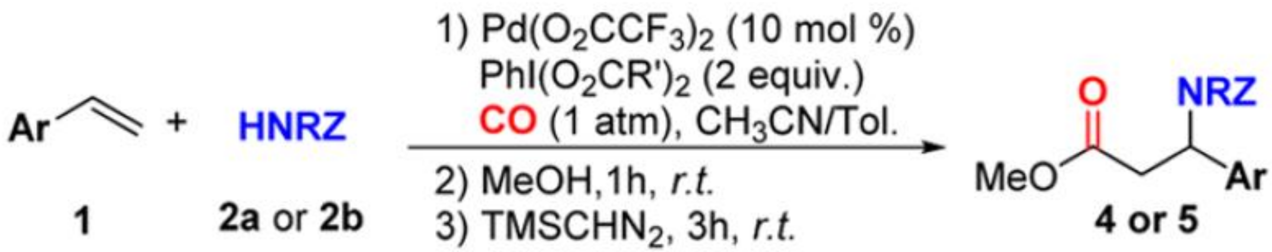


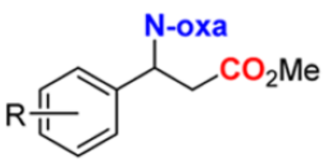

**Figure 1.** Time course of controlling experiments. [Pd] = $Pd(O_2CCF_3)_2$, I(III) = $PhI(O_2CAd)_2$, BQ = benzoquinone.

# Reaction scope

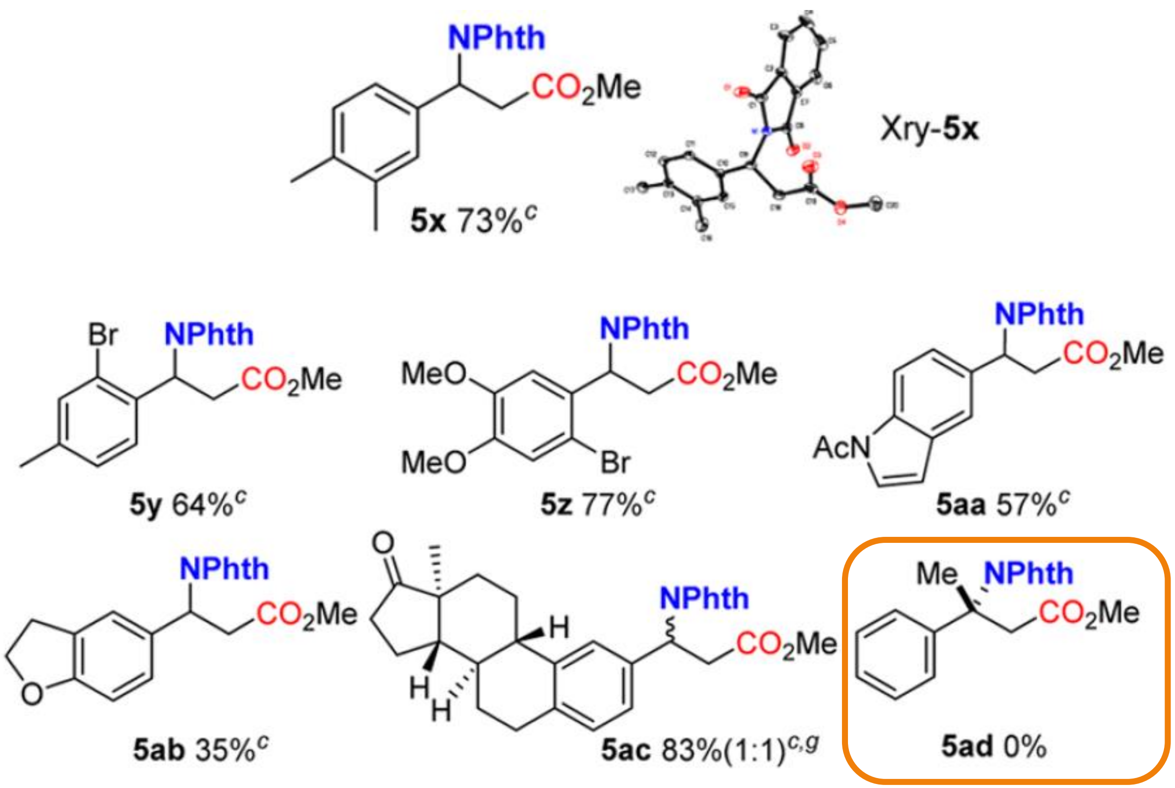
Some examples..




2a = HN-oxa

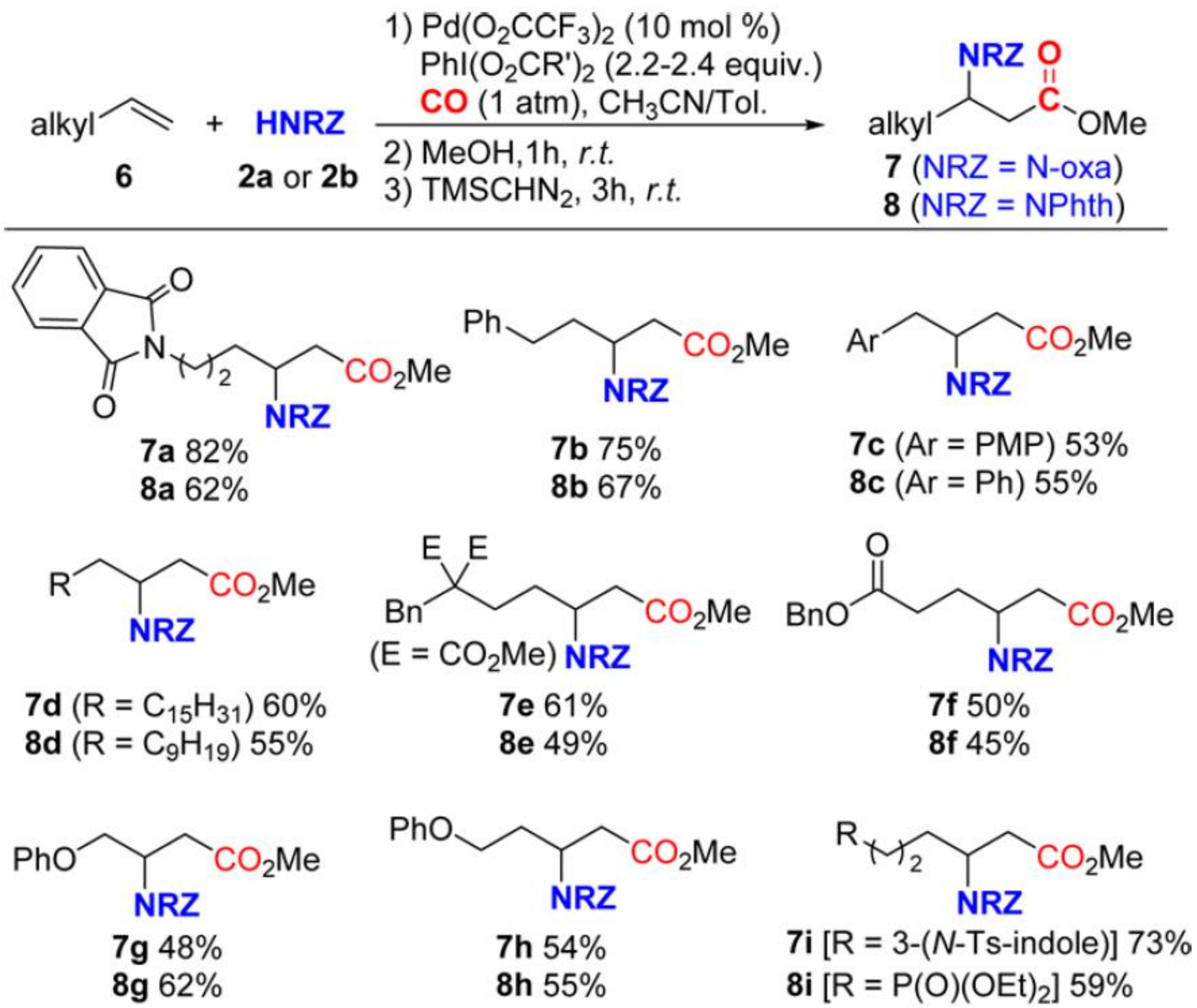



| R | | |
|---|---|---|
| R = *p*-H | **4a** | 83% |
| Me | **4b** | 59% |
| $CH_2CN$ | **4c** | 68% |
| Ph | **4d** | 69% |
| $^t$Bu | **4e** | 82% |
| $^i$Pr | **4f** | 68% |
| OMe | **4g** | 68% |
| OBn | **4h** | 72% |
| OAc | **4i** | 81% |
| F | **4j** | 92% |
| Cl | **4k** | 75% |
| Br | **4l** | 64% |
| I | **4m** | 63% |
| $CF_3$ | **4n** | 35% |
| $NO_2$ | **4o** | 0% |

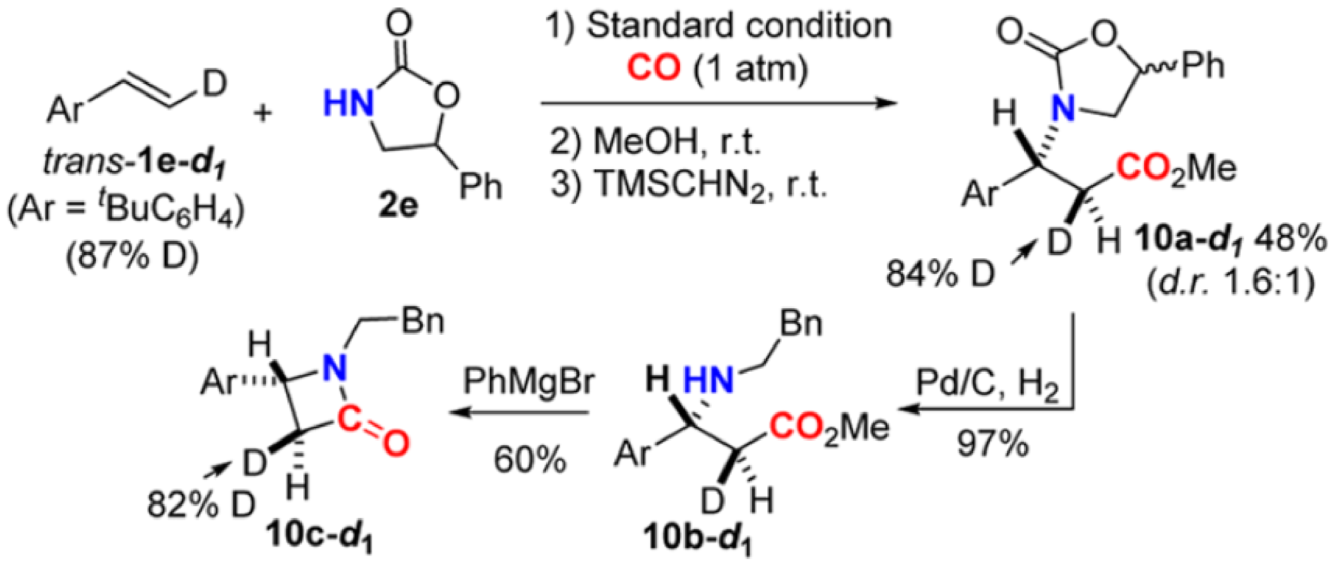


# Reaction scope

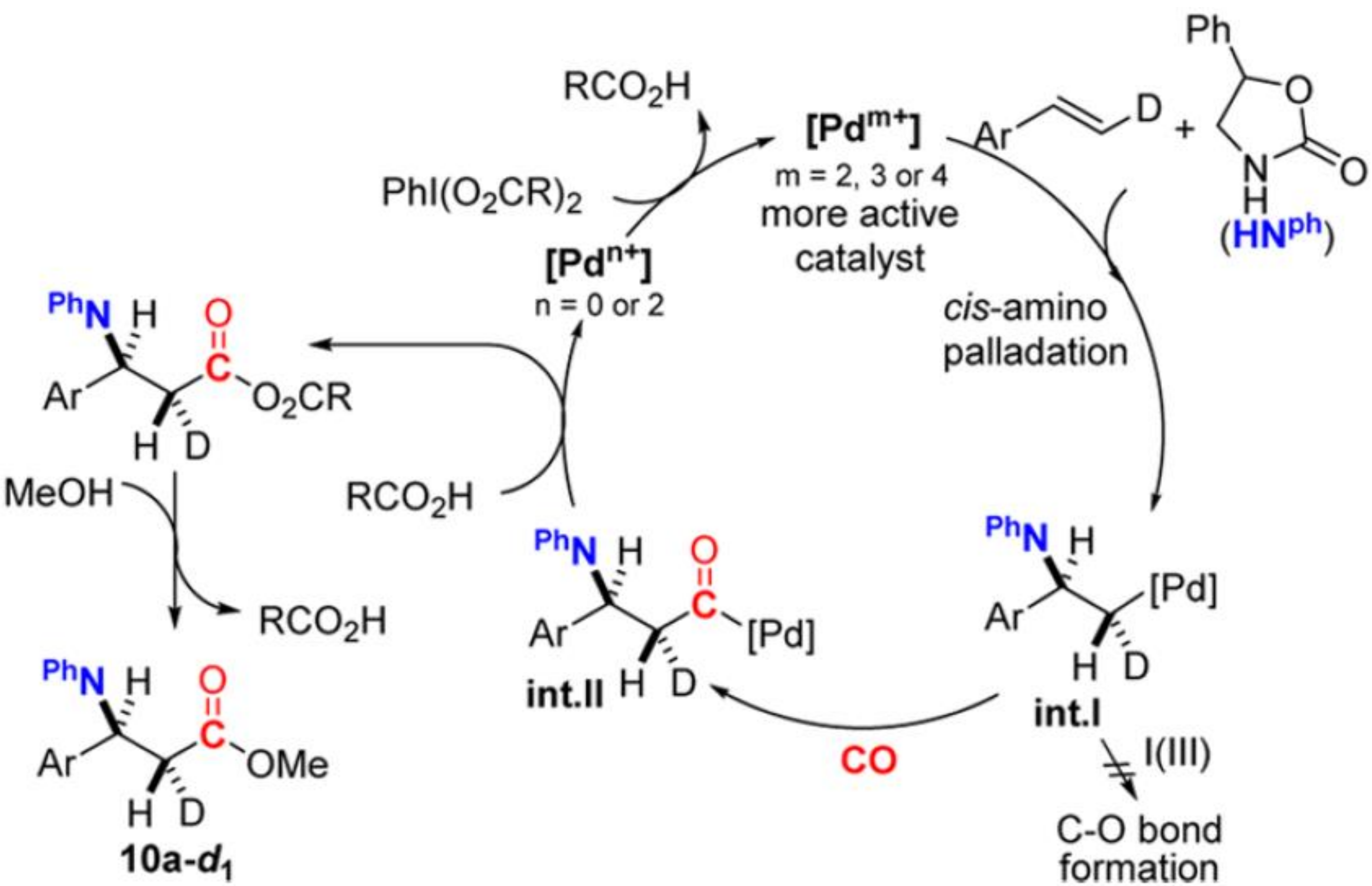
Unreactive alkenes..



Deuterium labeling..



# Mechanism



RCO$_2$H
[Pd$^{m+}$]
m = 2, 3 or 4
more active
catalyst
Ar
D
+
Ph
O
N
H
O
(HN$^{ph}$)
PhI(O$_2$CR)$_2$
[Pd$^{n+}$]
n = 0 or 2
cis-amino
palladation
PhN H
O
C
O$_2$CR
Ar
H D
MeOH
RCO$_2$H
RCO$_2$H
PhN H
O
C
[Pd]
Ar
int.II
H D
PhN H
[Pd]
Ar
H D
int.I
I(III)
C-O bond
formation
CO
PhN H
O
C
OMe
Ar
H D
10a-$d_1$

# Conclusion

- First intermolecular aminocarbonylation pallado-catalyzed.
- Functionnalized β-aminoacids from simple and available alkenes.
- $PhI(O_2CAd)_2$ not only used as oxidant but can improve the reactivity of Pd catalyst.
- The mechanism need to be more studied to understand exactly the role of the hypervalent iodine.

# Conclusion

❖ Thank you for your attention