Chiral Transient Imine Directing Group in Transition Metal-Catalyzed Asymmetric C(sp^2)-H functionalization

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Supervisor: Prof. Shengming Ma
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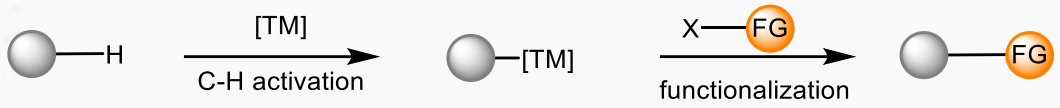
CONTENT

1 Background

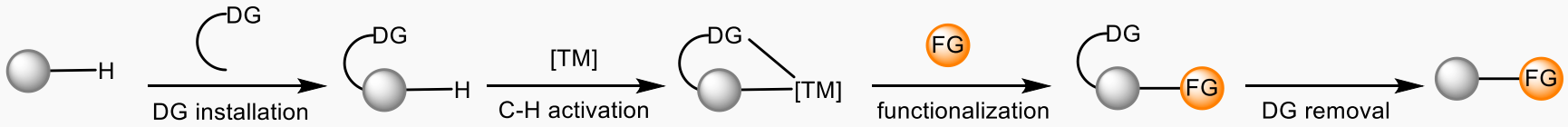
1 Background

➢ General approach of C-H activation



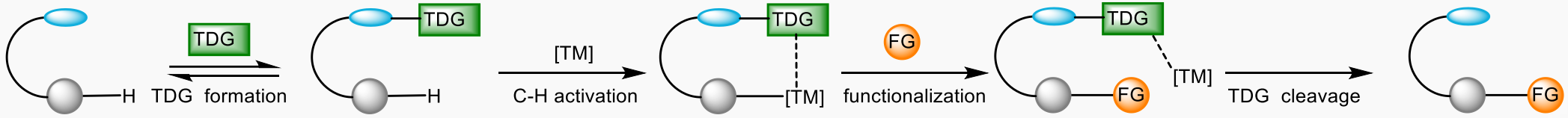
➢ Directing Group (DG) Strategy

- Always strong coordinating groups
- Extra steps to install and remove DG



➢ Transient Directing Group (TDG) Strategy

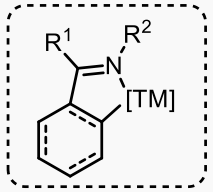
- Efficiently and reversibly form new DG
- Atom- and step economy



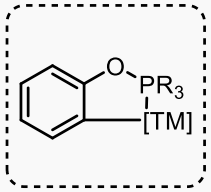
Nat. Rev. Chem. **2021**, *5*, 646–659.

1 Background

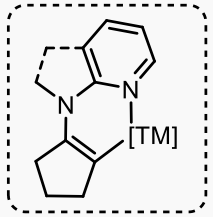
The types of TDG mode in TM-catalyzed asymmetric C-H functionalization



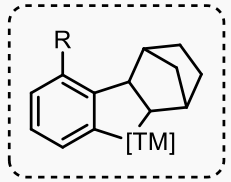
Imine



Phosphite

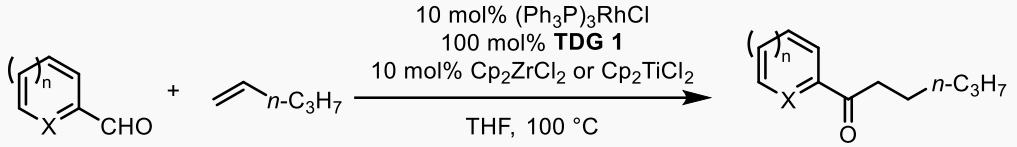


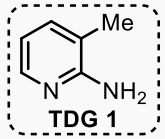
Enamine

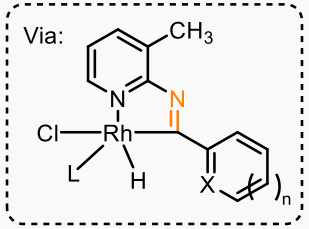


Norbornene

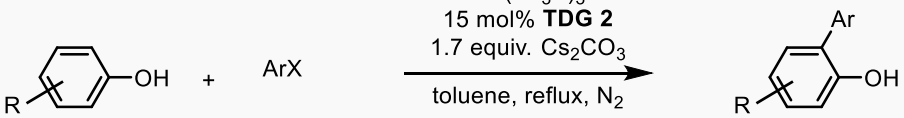
Chul-Ho Jun, 1997

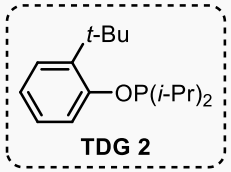


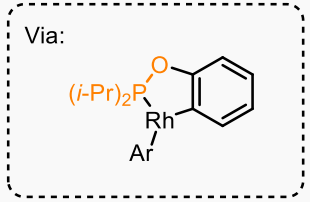




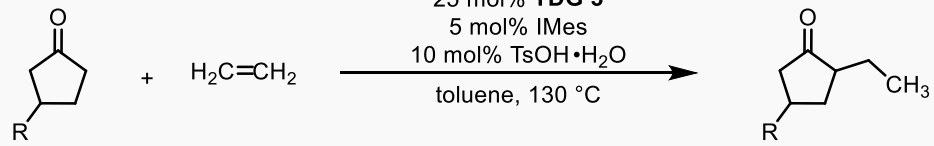
Robin B. Bedford, 2003

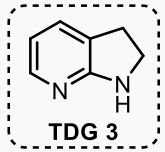


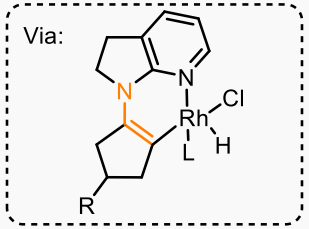




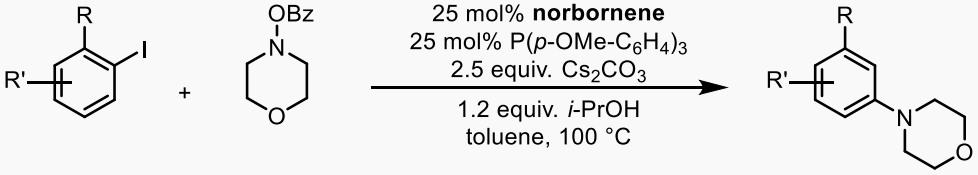
Guangbin Dong, 2014

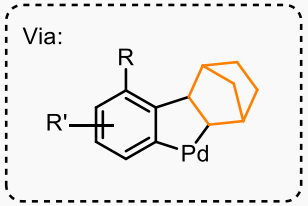






Guangbin Dong, 2013





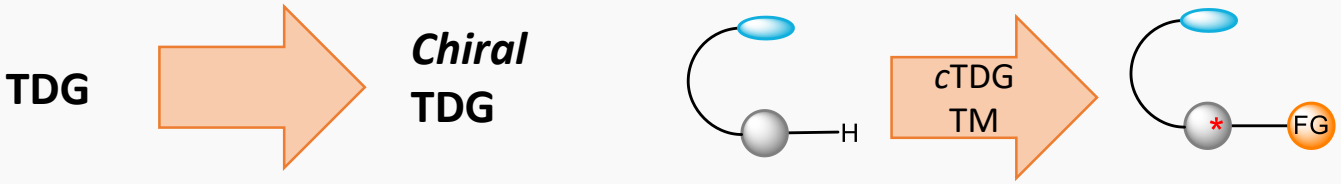
Jun, C.-H.* et al. *Tetrahedron Lett.* **1997**, *38*, 6673–6676.

Bedford, R. B.* et al. *Angew. Chem., Int. Ed.* **2003**, *42*, 112−114.

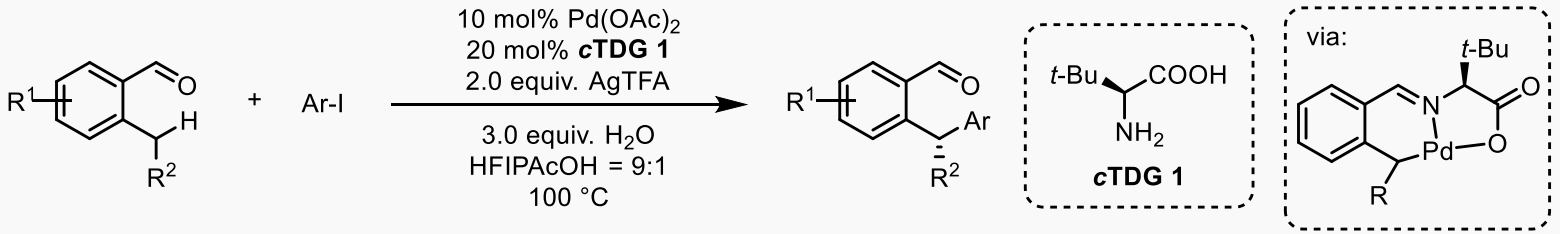
Dong, G.* et al. *Science* **2014**, *345*, 68–72.

Dong, G.* et al. *J. Am. Chem. Soc.* **2013**, *135*, 18350−18353

1 Background



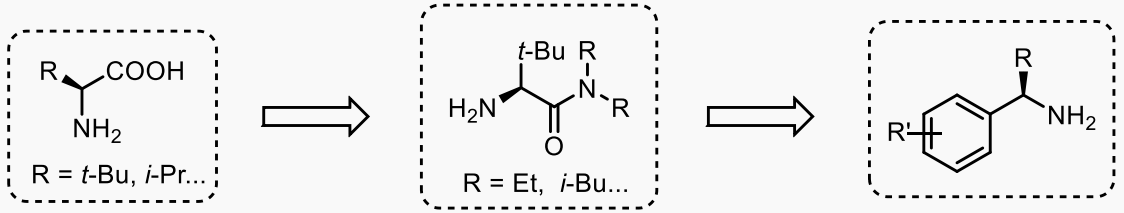
Jin-Quan Yu, 2016



Yu, J.-Q.* et al. *Science* **2016**, *351*, 252–256.

1 Background

The development of chiral organocatalyst in TM-catalyzed asymmetric C-H functionalization

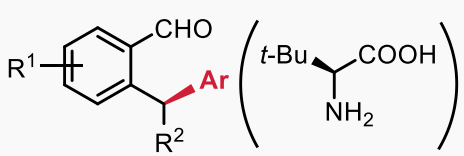


Amino acids
first developed by Yu, 2016

Amino amides
first developed by Yu, 2018

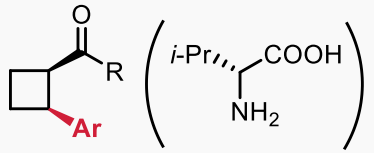
Benzylamines
first developed by Wang, 2019

Asymmetric C(sp^3)-H functionalization



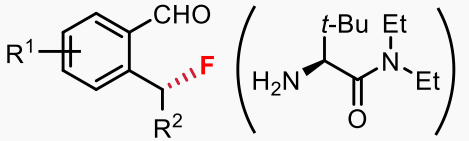
54-88% yield
90-96% ee

Yu, J.-Q.* et al. *Science* **2016**, *351*, 252−256.



35-82% yield
76-98% ee

Yu, J.-Q.* et al. *Angew. Chem., Int. Ed.* **2020**, *59*, 9594−9600.



36-61% yield
86-99% ee

Yu, J.-Q.* et al. *Nat. Chem.* **2018**, *10*, 755−762.

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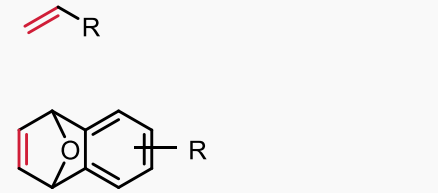
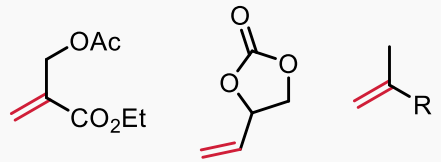
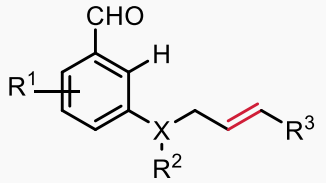
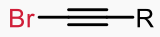
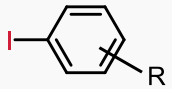
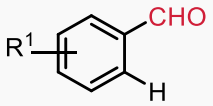
Chiral transient imine DG in Transition matal catalyzed asymmetric C(sp^2)-H functionalization

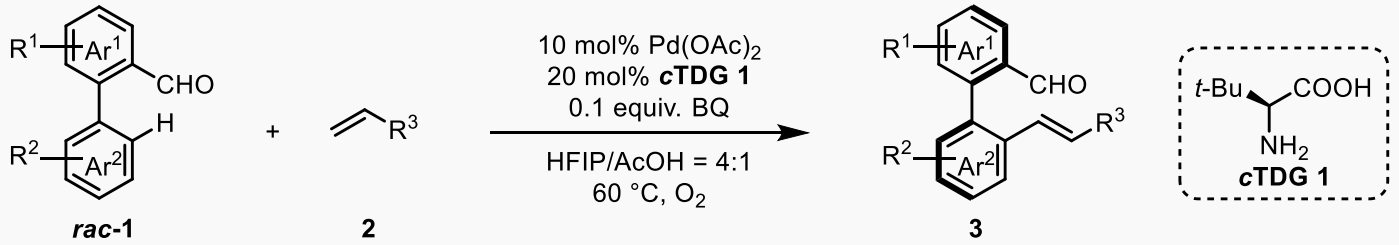
- Alkenes
  -  Alkenylation
  - Naphthylatiorn
  -  Allylation
  -  Intramolecular Hydroarylation

  X = N or O
- R-X
  -  Alkynylation
  -  Arylation
- Benzaldehydes —  Coupling reactions

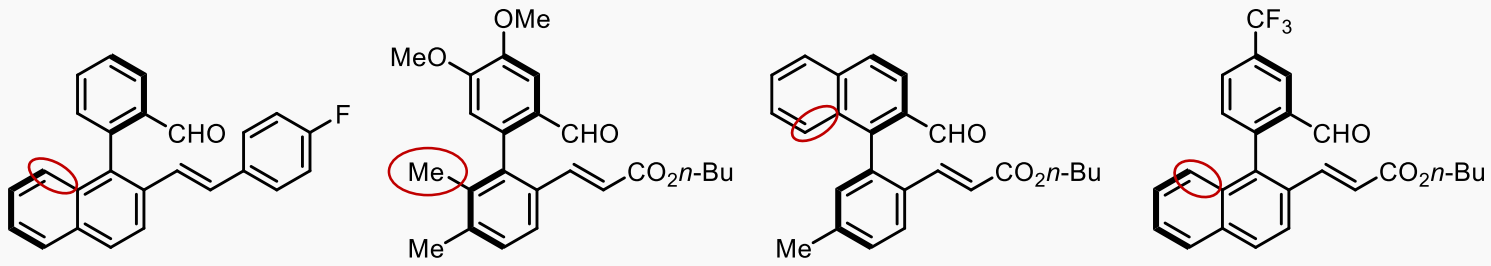
2.1 Alkenes as electrophiles

2.1.1 Alkenylation of biaryl aldehydes with acrylates and styrenes

Bing-Feng Shi, 2017 First atroposelective C-H functionalization using cTDG strategy



selected examples



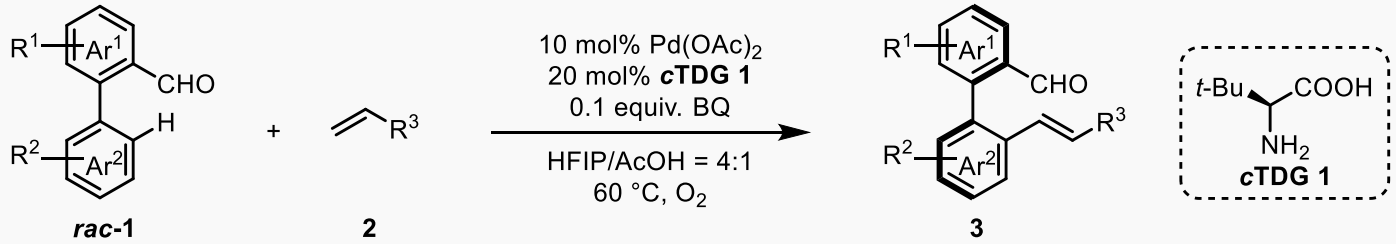
Dynamic Kinetic Resolution

Low rotation barriers

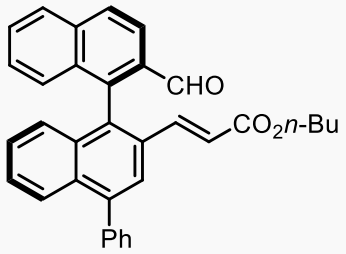
Shi, B.-F.* et al. *Angew. Chem., Int. Ed.* **2017**, *56*, 6617−6621.

2.1.1 Alkenylation of biaryl aldehydes with acrylates and styrenes

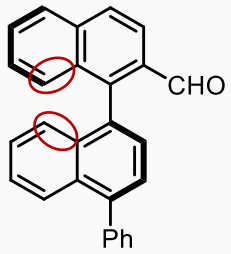
Bing-Feng Shi, 2017



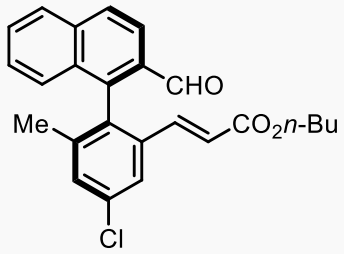
selected examples



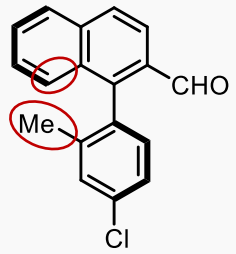
3eb,46%, >99% ee



1e,54%, 89% ee, s = 600



3fb, 40%, 99% ee



1f, 60%, 70% ee, s = 419

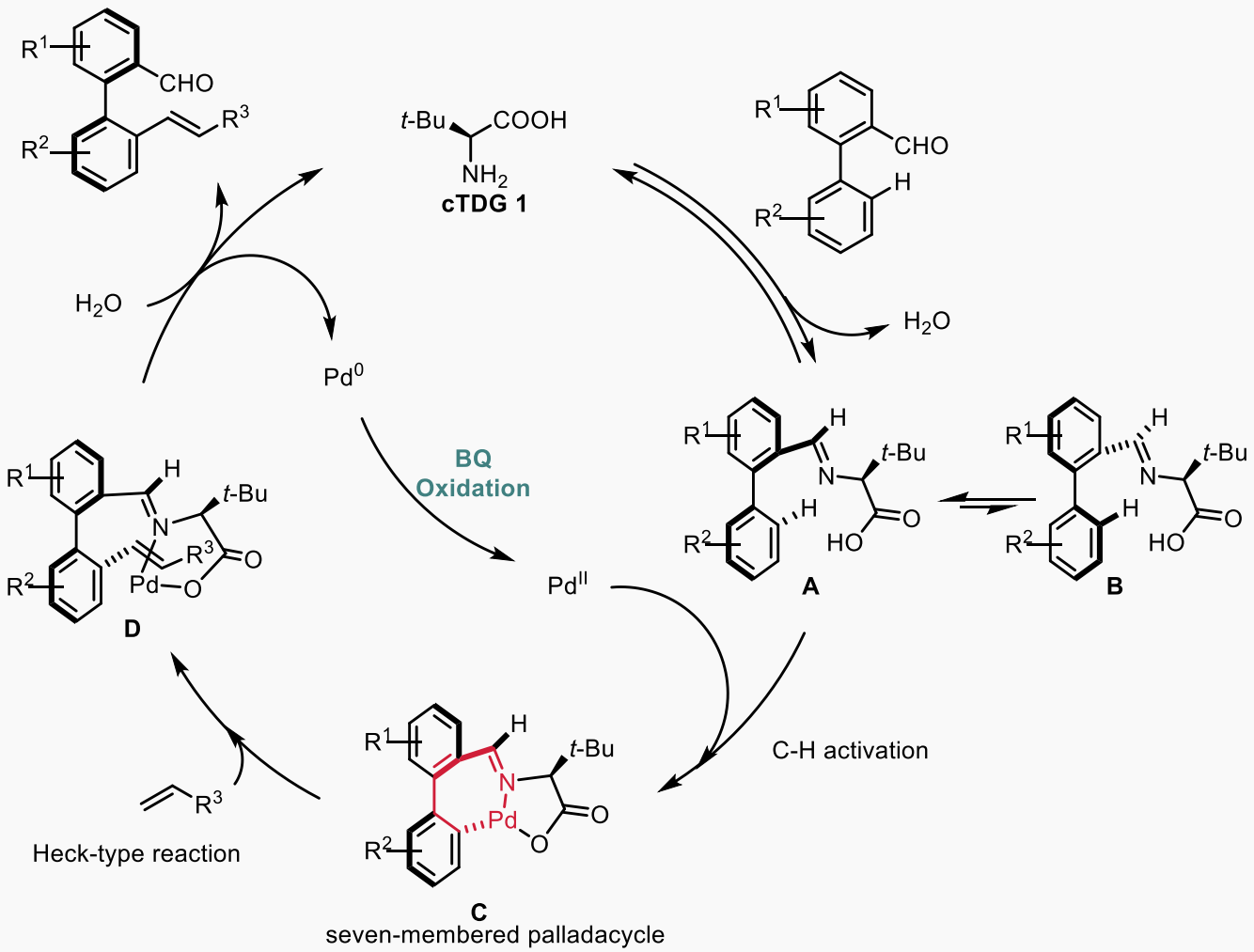
Kinetic Resolution

$s = \ln[(1-C)(1-ee_s)]/\ln[(1-C)(1+ees)]$, $C=ee_s/(ee_s+ee_p)$ High rotation barriers

Shi, B.-F.* et al. *Angew. Chem., Int. Ed.* **2017**, *56*, 6617−6621.

2.1.1 C(sp^2)-H Alkenylation

Mechanism

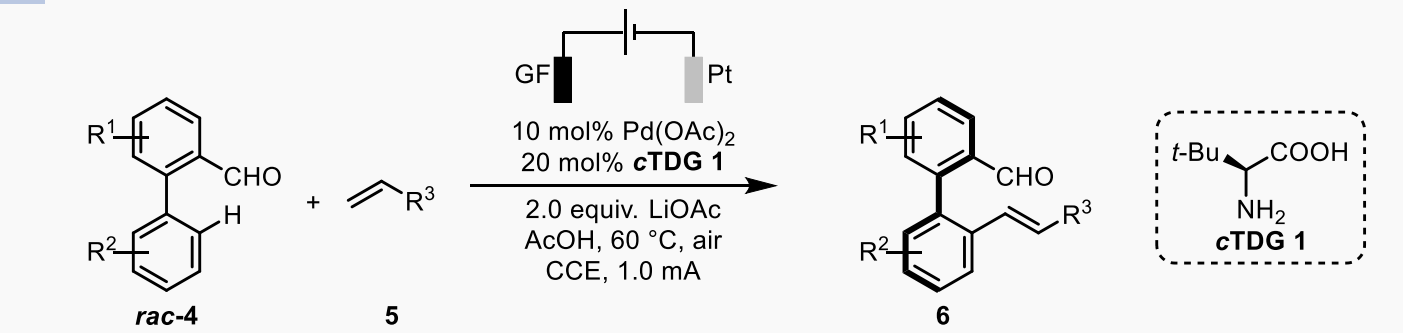


Shi, B.-F.* et al. *Angew. Chem., Int. Ed.* **2017**, *56*, 6617−6621.

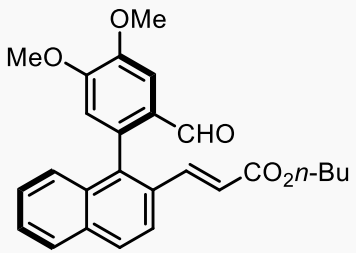
2.1.1 Alkenylation of biaryl aldehydes with alkenes

Lutz Ackermann, 2020

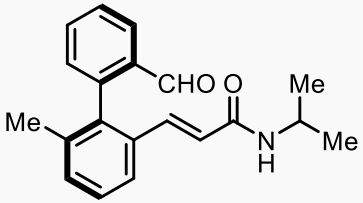
Electrochemical version



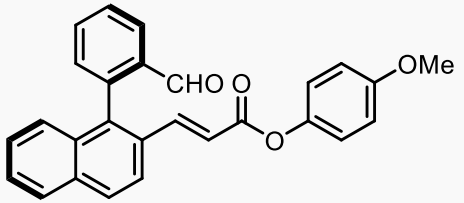
selected examples



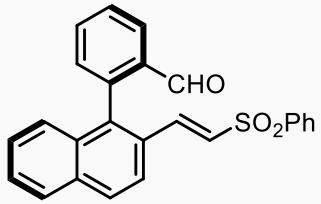
6aa, 60%, 98% ee



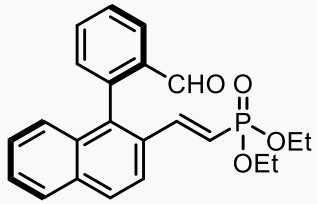
6bb, 55%, 96% ee



6cc, 68%, 98% ee



6cd, 52%, 98% ee

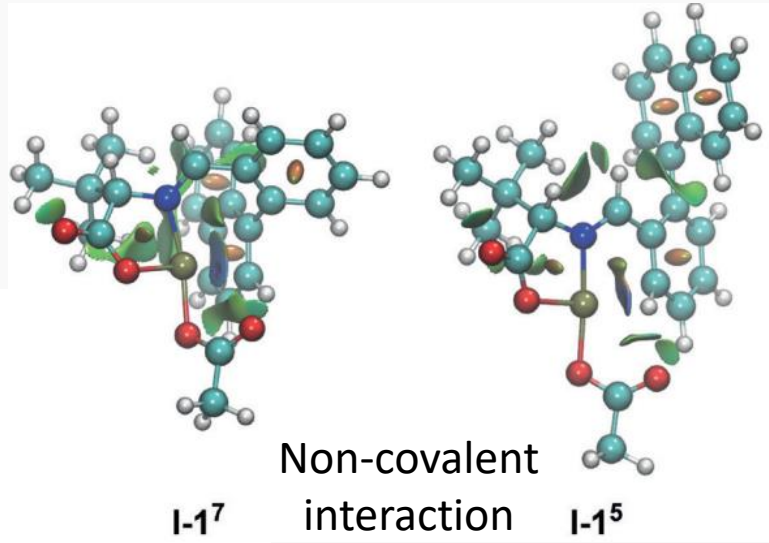


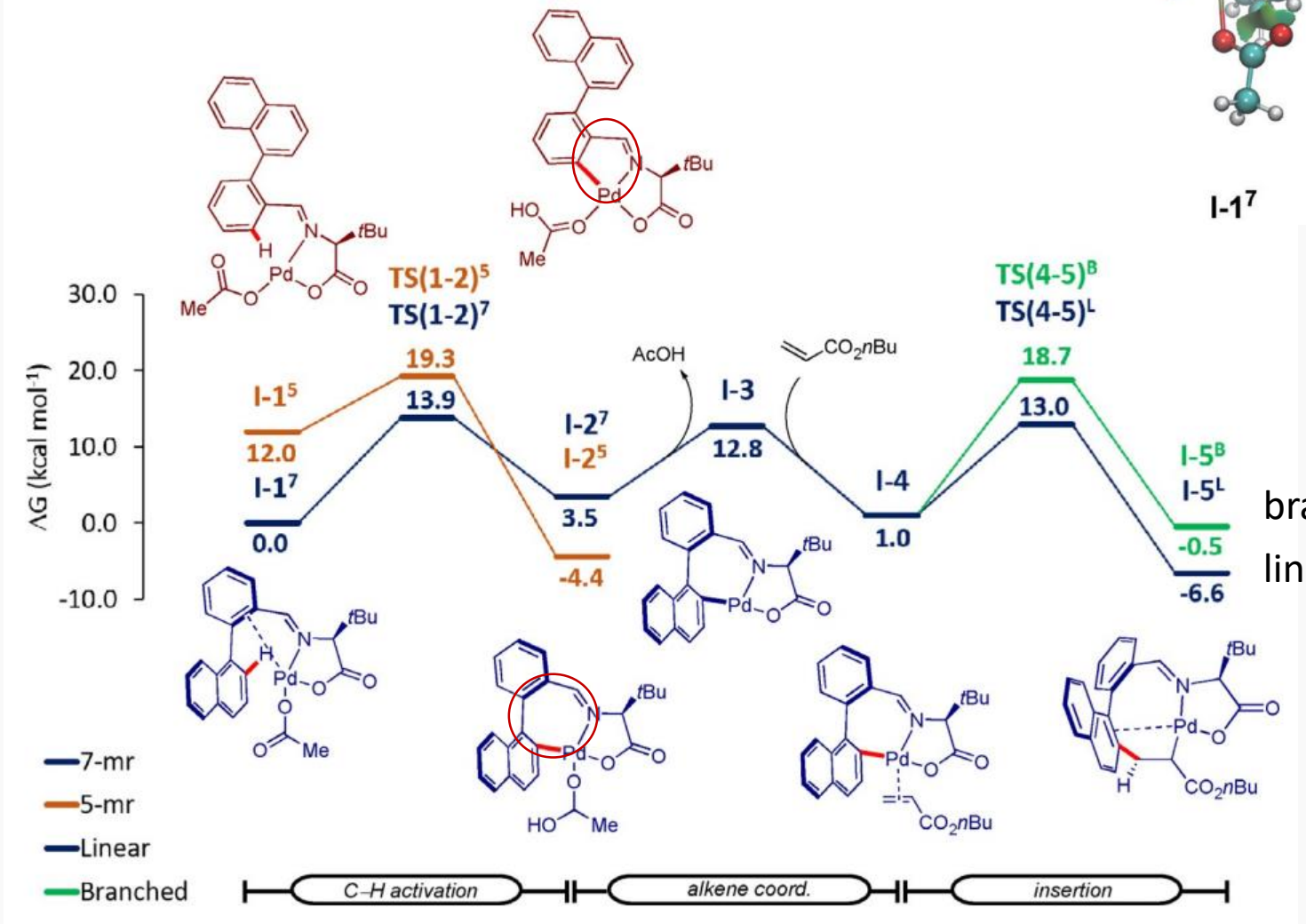
6ce, 68%, 99% ee

Ackermann, L.* et al. *Angew. Chem., Int. Ed*. **2020**, *59*, 13451−13457.

2.1.1 Alkenylation of biaryl aldehydes with alkenes

DFT calculation



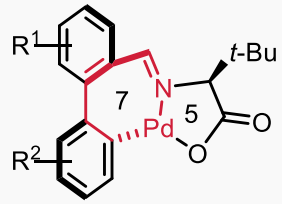


branched

linear

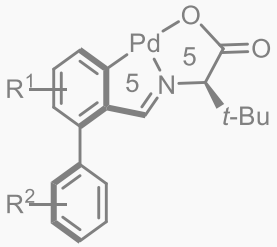
Ackermann, L.* et al. *Angew. Chem., Int. Ed.* **2020**, *59*, 13451−13457.

☆ Site selectivity control in biaryl system

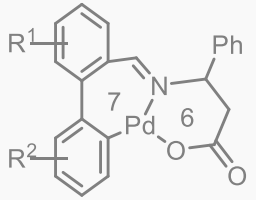


seven,five-membered coordination

VS

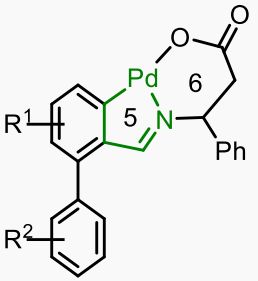


five,five-membered coordination

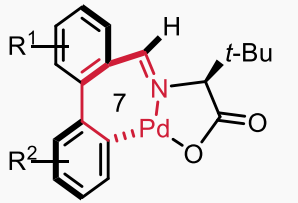


seven,six-membered coordination

VS

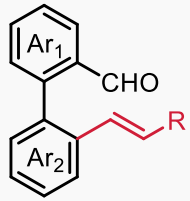


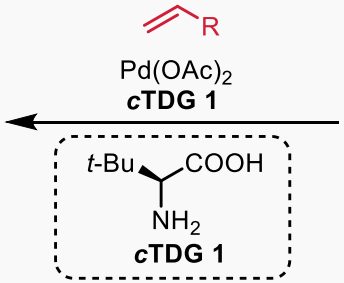
five,six-membered coordination



seven-membered palladacycle

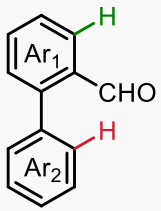
Coplanarity
Non-covalent interaction

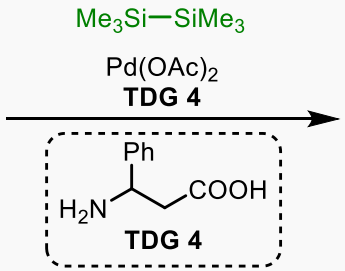




α-amino acid

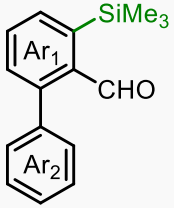
Interannular
C-H functionalization

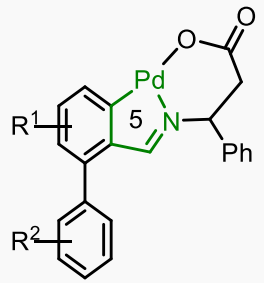




β-amino acid

Intraannular
C-H functionalization





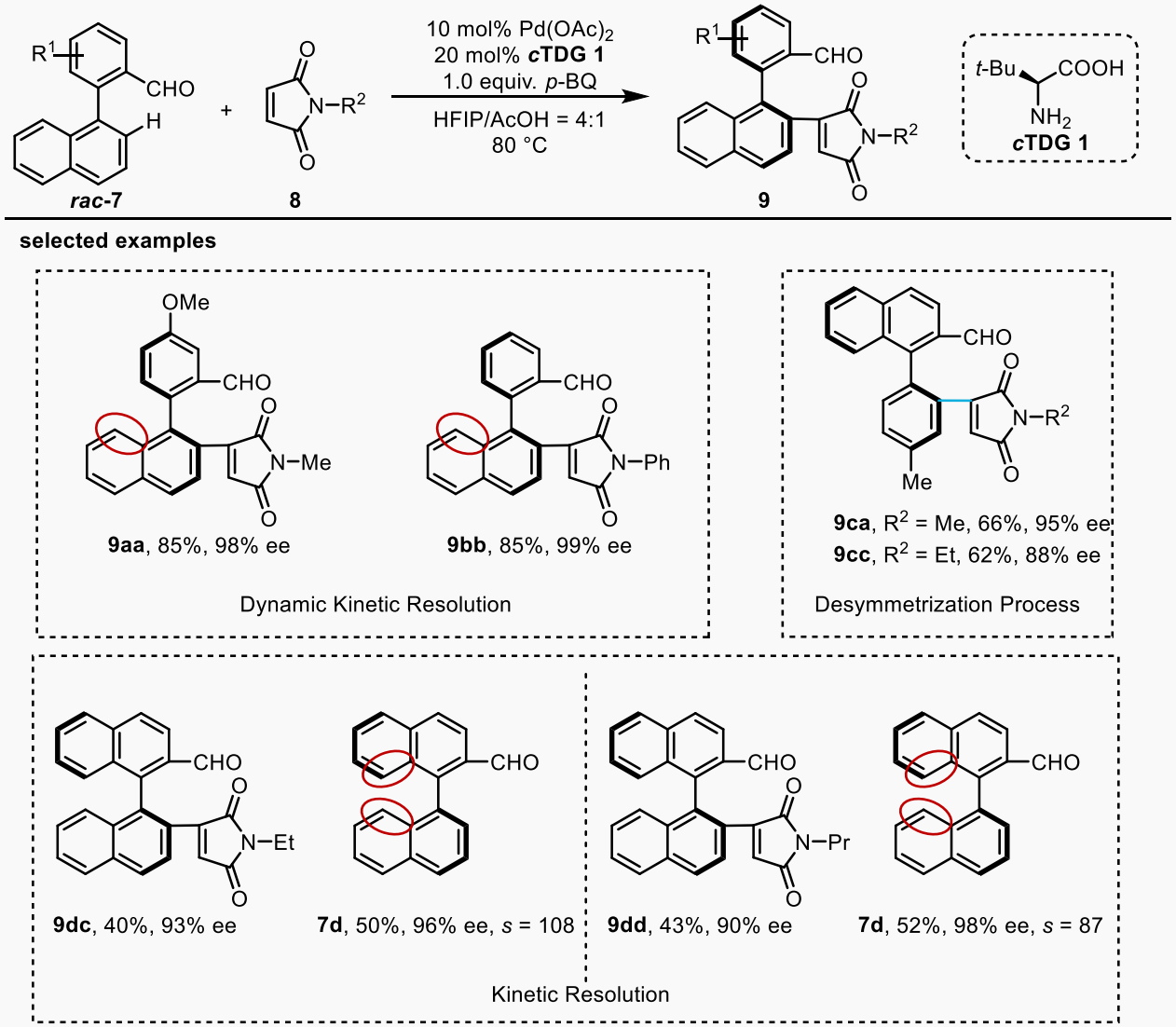
five-membered palladacycle

- Site selectivity of C−H cleavage is controlled by the **bite angle** of the TDG.
- Using different TDG leads to different energy of inter- or intra-annular intermediate, so that site selectivity would determined by a **transition state with lower energy**.

Shi, B.-F.* et al. *Angew. Chem., Int. Ed.* **2017**, *56*, 6617−6621.
Shi, B.-F.* et al. *Sci. China Chem.* **2020**, *63*, 875−880.
Yu, J.-Q.* et al. *J. Am. Chem. Soc*. **2022**, *144*, 4727–4733.
Ackermann, L.* et al. *Angew. Chem., Int. Ed*. **2020**, *59*, 13451−13457.

2.1.1 Alkenylation of biaryl aldehydes with maleimides

Upendra Sharma, 2022

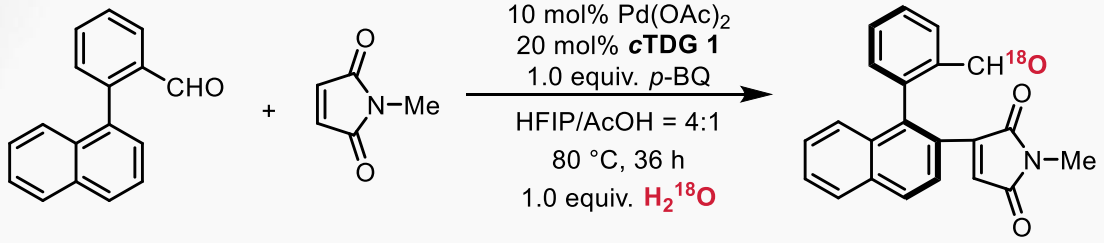


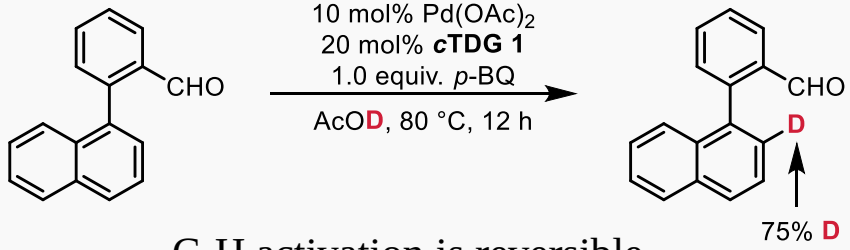
$s = \ln[(1-C)(1-ee_s)]/\ln[(1-C)(1+ee_s)]$, $C=ee_s/(ee_s+ee_p)$

Sharma, U.* et al. *Adv. Synth. Catal*. **2022**, *364*, 897– 908.

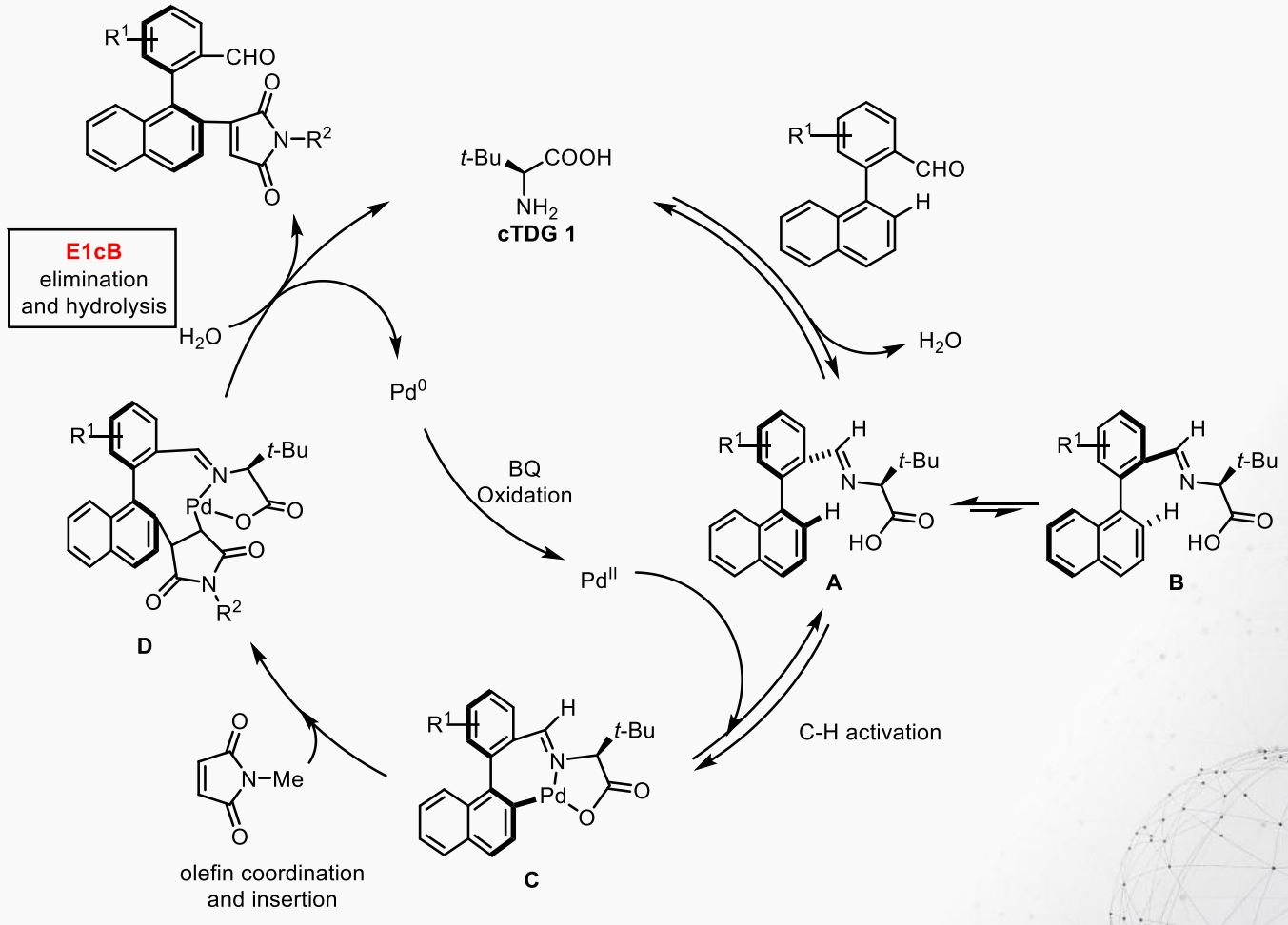
2.1.1 Alkenylation of biaryl aldehydes with maleimides

Mechanism





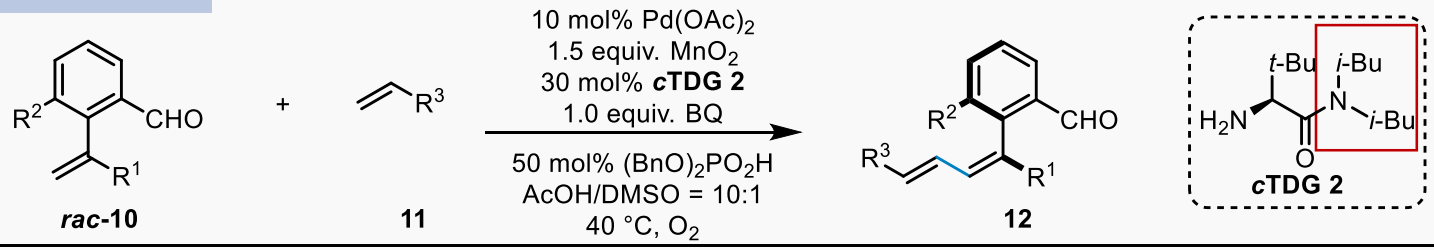
C-H activation is reversible



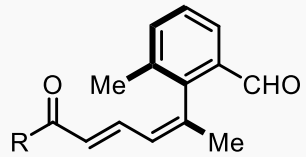
Sharma, U.* et al. *Adv. Synth. Catal*. **2022**, *364*, 897 – 908.

2.2.2 Alkenylation of styrenes with alkenes

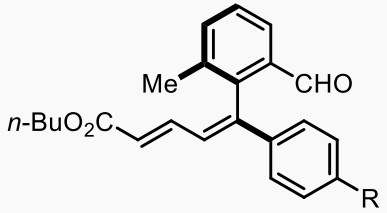
Jian Zhang & Guofu Zhong, 2022



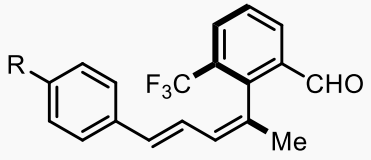
selected examples



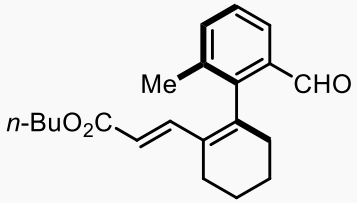
12aa, R = O*n*-Bu, 82%, 98% ee
12ab, R = OEt, 67%, 98% ee
12ac, R = OPh, 70%, 99% ee



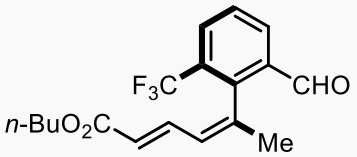
12ba, R = H, 89%, 99% ee
12ca, R = OMe, 78%, 99% ee
12da, R = F, 84%, > 99% ee



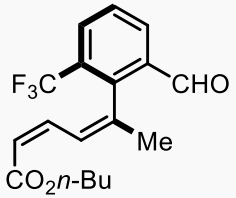
12dd, R = H, 82%, 95% ee
12de, R = OMe, 79%, > 99% ee
12df, R = CF_3, 76%, > 99% ee



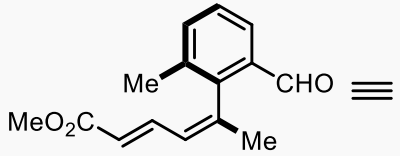
12ea, 89%, > 99% ee



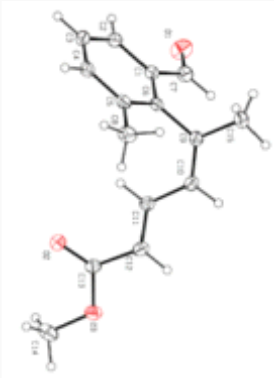
12fa, 70%, > 99% ee



12f'a,23%, > 99% ee



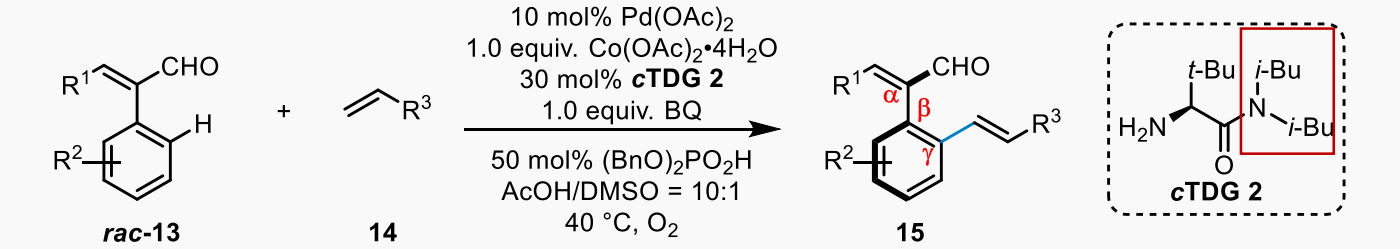
12ag, 76%, 98% ee
$\Delta G^{\neq}$ = 32.5 kcal/mol
$t_{1/2}$ = 2419 years (25 °C)
$t_{1/2}$ = 166 years (40 °C)



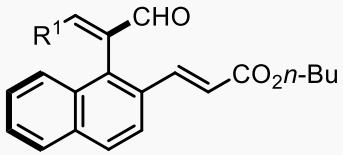
Zhang, J.*; Zhong, G.* et al. *Org. Chem. Front.* **2022**, *9*, 2109–2115.

2.1.1 Alkenylation of styrenes with alkenes

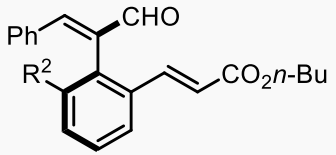
Bing-Feng Shi, 2020



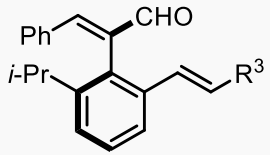
selected examples



15aa, R^1 = *o*-OMePh, 65%, 83% ee
15ba, R^1 = *p*-NMe_2Ph, 63%, 92% ee
15ca, R^1 = *t*-Bu, 33%, 99% ee



15da, R^2 = *i*-Pr, 85%, 96% ee
15ea, R^2 = Me, 79%, 73% ee
15fa, R^2 = Et, 60%, 94% ee

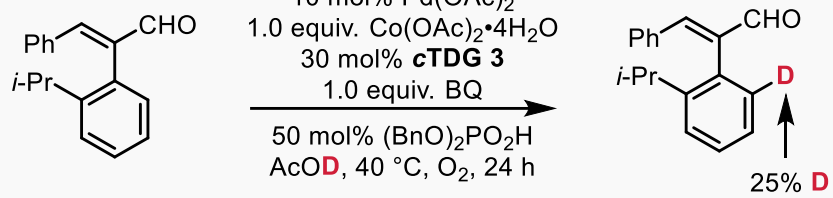


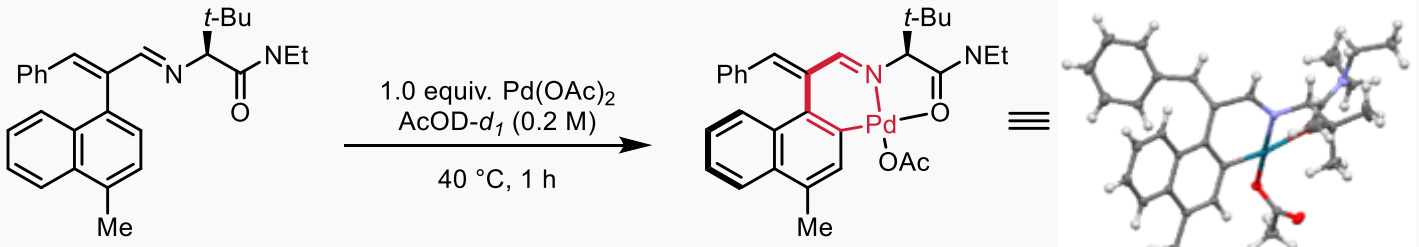
15db, R^3 = CO_2Et, 75%, 97% ee
15dc, R^3 = C_6H_5, 81%, 94% ee
15de, R^3 = $PO(OEt)_2$, 42%, 98% ee

Shi, B.-F.* et al. *Angew. Chem., Int. Ed.* **2020**, *59*, 6576−6580.

2.2.1 Alkenylation of styrenes with alkenes

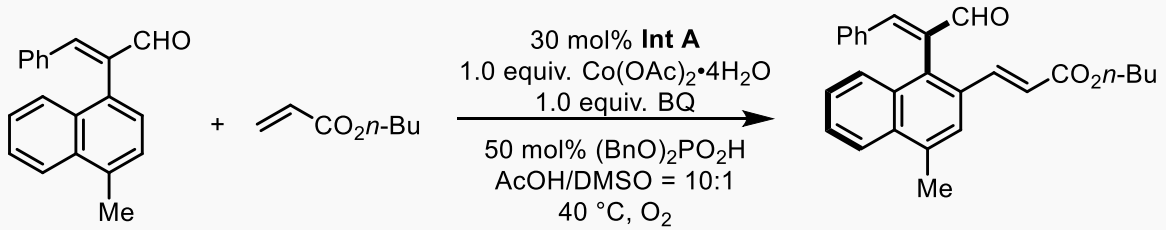
Mechanistic study



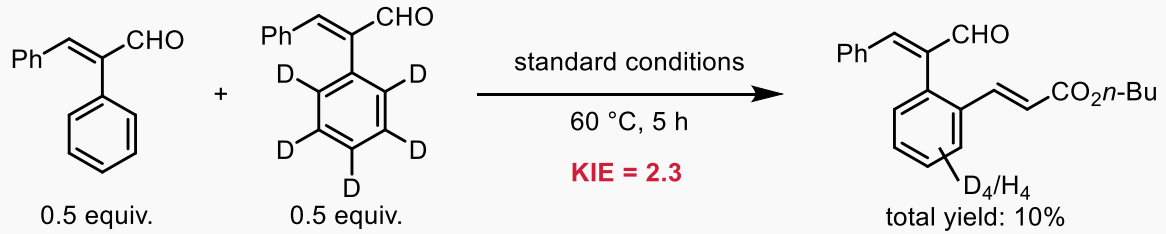


Int A, yield: 35%

six-membered palladacycle



88%, 80% ee



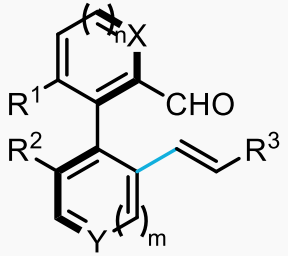
0.5 equiv. 0.5 equiv.

KIE = 2.3

total yield: 10%

Shi, B.-F.* et al. *Angew. Chem., Int. Ed.* **2020**, *59*, 6576–6580.

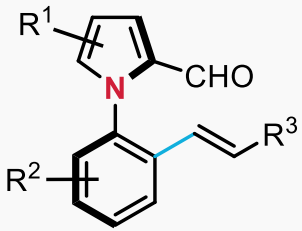
2.1.1 Alkenylation of heterobiaryl aldehydes with alkenes



16

X, Y = **S** or **O**
m, n = 0 or 1

Shi, B.-F.* et al.
Organometallics **2019**, *38*, 4022−4028..



17

N-C axial chirality

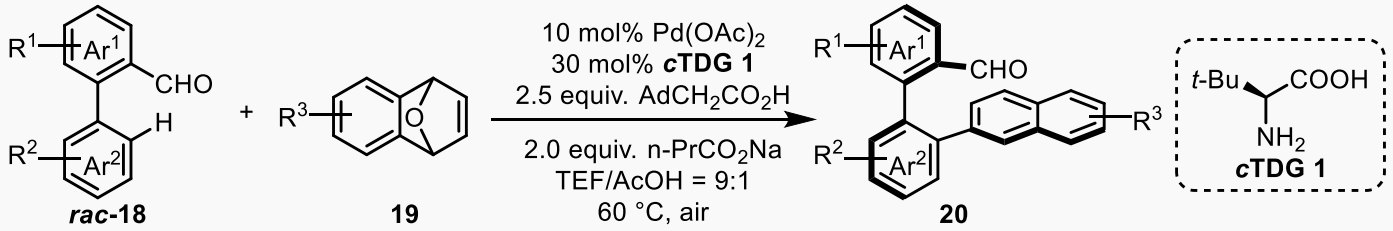
Zhang, J.*; Xie, M.* et al. *Org. Lett.* **2019**, *21*, 6361−6365.

Ackermann, L.* et al. *Angew. Chem., Int. Ed.* **2020**, *59*, 13451−13457.

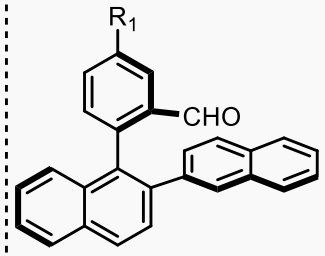
Ackermann, L.* et al. *Chem. Sci*. **2021**, *12*, 14182–14188.

2.1.2 Naphthylation of biaryl aldehydes with 7-oxabenzonorboranadienes

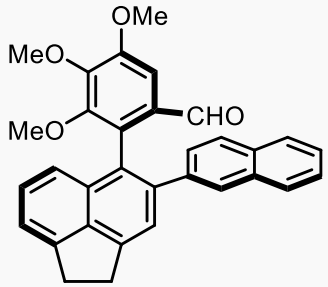
Bing-Feng Shi, 2019



selected examples

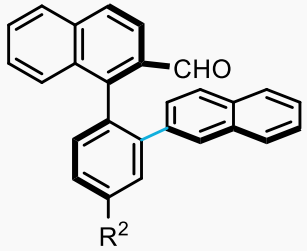


20aa, R^1 = OMe, 59%, 99% ee
20ba, R^1 = CF_3, 52%, 99% ee



20ca, 62%, 98% ee

Dynamic Kinetic Resolution Process



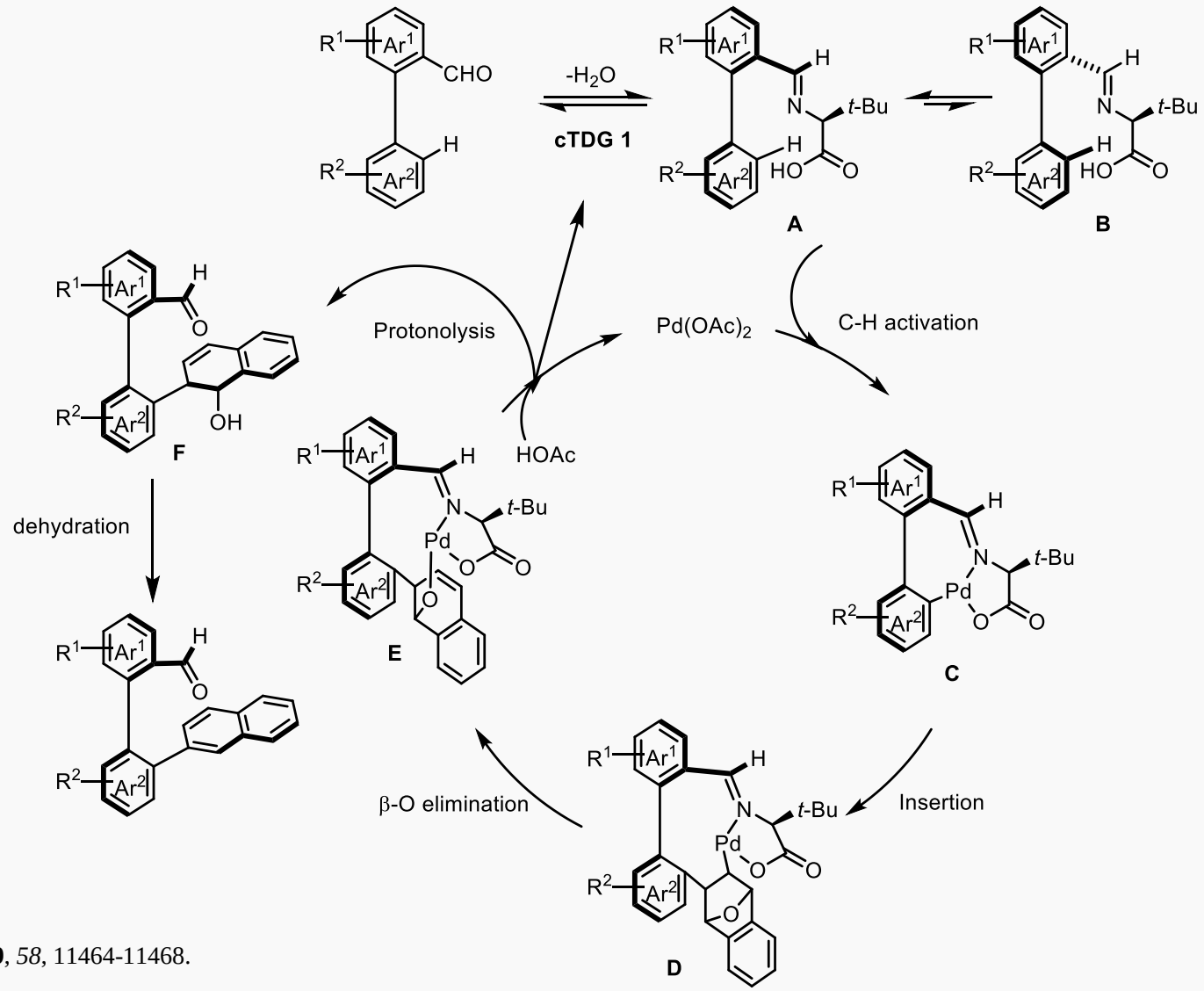
20da, R^2 = OMe, 82%, > 99% ee
20ea, R^2 = Me, 59%, > 99% ee

Desymmetrization Process

Shi, B.-F.* et al. *Angew. Chem., Int. Ed.* **2019**, *58*, 11464-11468.

2.1.2 Naphthylation of biaryl aldehydes with 7-oxabenzonorboranadienes

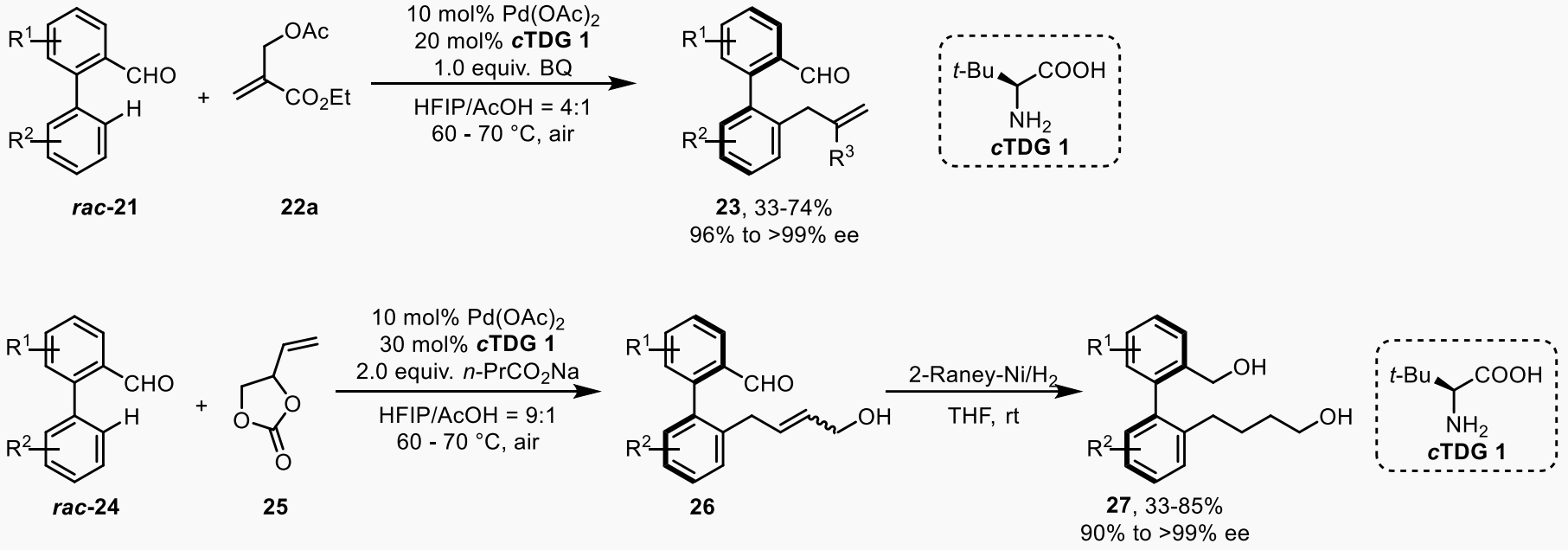
Mechanism



Shi, B.-F.* et al. *Angew. Chem., Int. Ed.* **2019**, *58*, 11464-11468.

2.1.3 Allylation of biaryl aldehydes with allylic acetate

Bing-Feng Shi, 2018

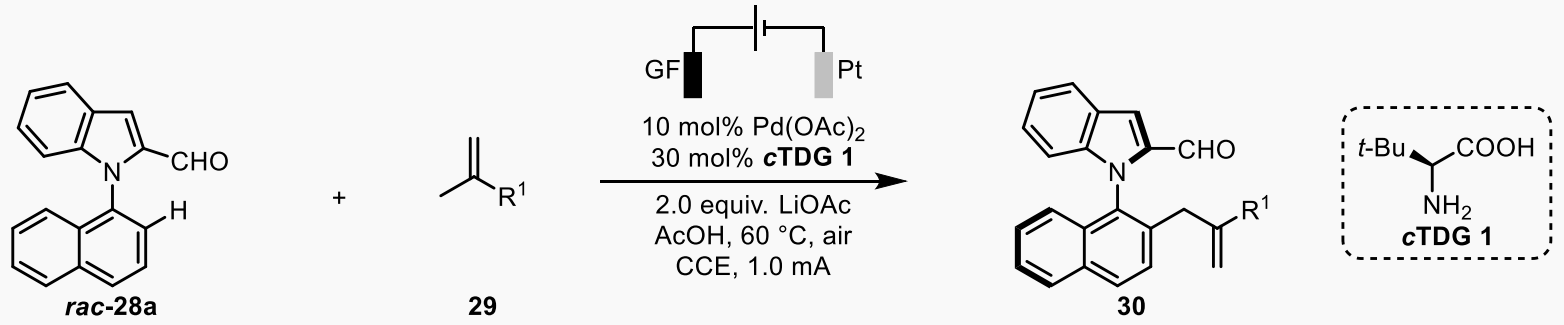


Shi, B.-F.* et al. *Angew. Chem. Int. Ed.* **2018**, *57*, 17151-17155.

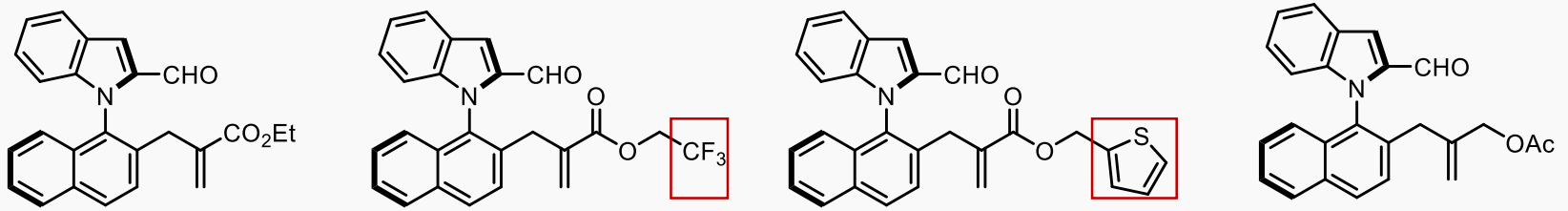
2.1.3 Allylation of heterobiaryl aldehydes with 1,1-disubstituted alkenes

Lutz Ackermann, 2021

N-C axial chirality



selected examples



30aa: 35%, 92% ee
28a: 42%, 74% ee, *s* = 53

30ab: 38%, 86% ee
28a: 53%, 65% ee, *s* = 26

30ac: 30%, 95% ee
28a: 41%, 54% ee, *s* = 67

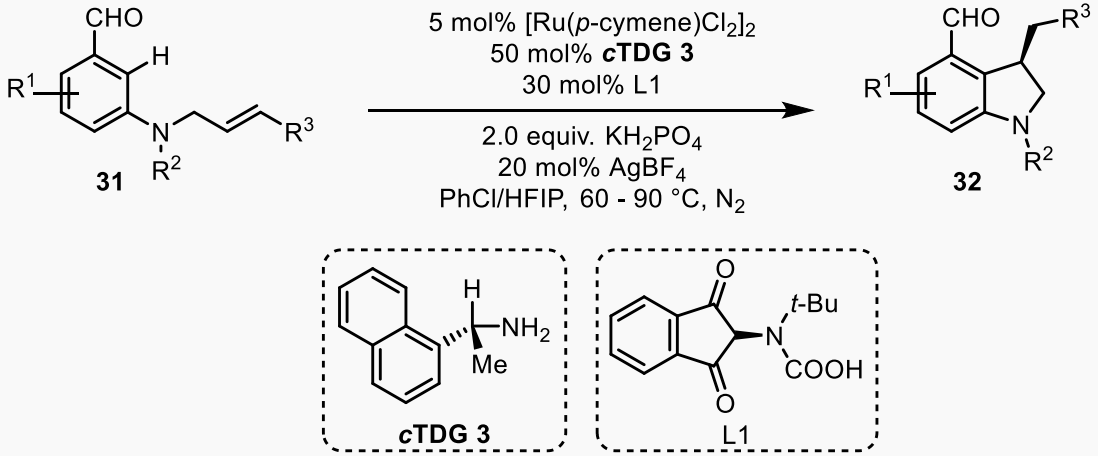
30ad: 35%, 98% ee
28a: 38%, 53% ee, *s* = 169

Kinetic Resolution

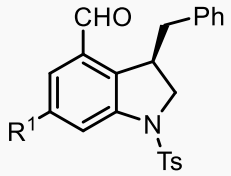
Ackermann, L.* et al. *Chem. Sci.* **2021**, *12*, 14182–14188.

2.1.4 Synthesis of indolines

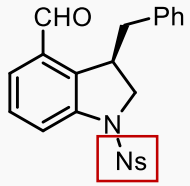
Xin Cui, 2019



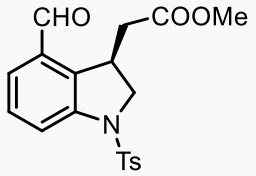
selected example



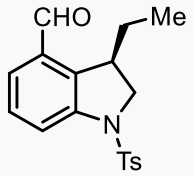
32a, R^1 = OMe, 86%, 94% ee
32b, R^1 = F, 69%, 94% ee



32c, 74%, 92% ee



32d, 55%, 81% ee

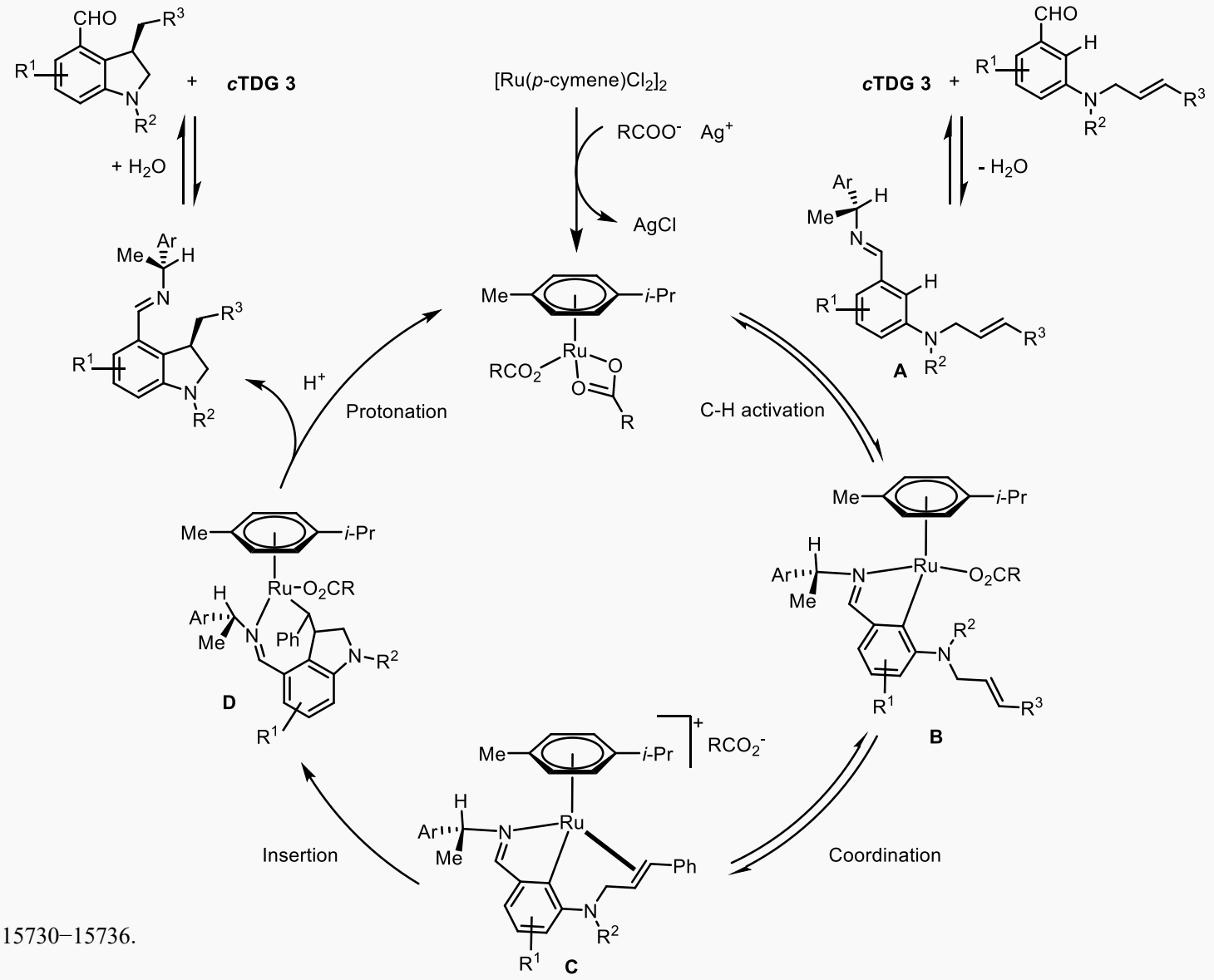


32e, 92%, 96% ee

Cui, X.* et al. *J. Am. Chem. Soc*. **2019**, *141*, 15730−15736.

2.1.4 Synthesis of indolines

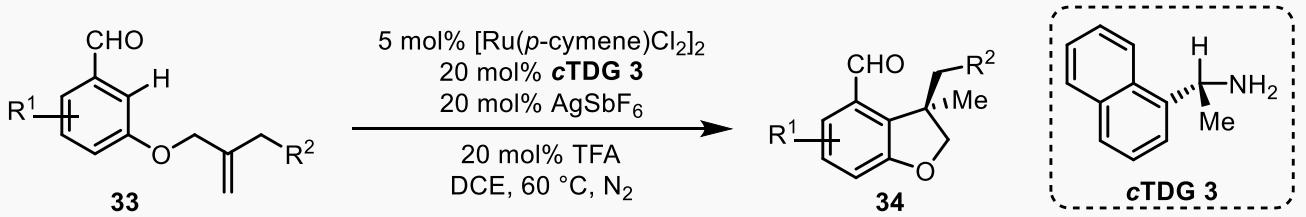
Mechanism



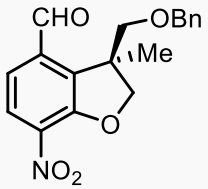
Cui, X.* et al. *J. Am. Chem. Soc.* **2019**, *141*, 15730−15736.

2.1.4 Synthesis of 2,3-dihydrobenzofuran

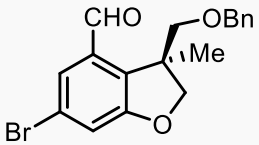
Jun Wang, 2020



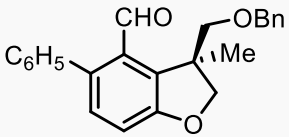
selected example



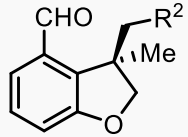
34a, 90%, 96% ee



34b, 93%, 98% ee



34c, 86%, 95% ee



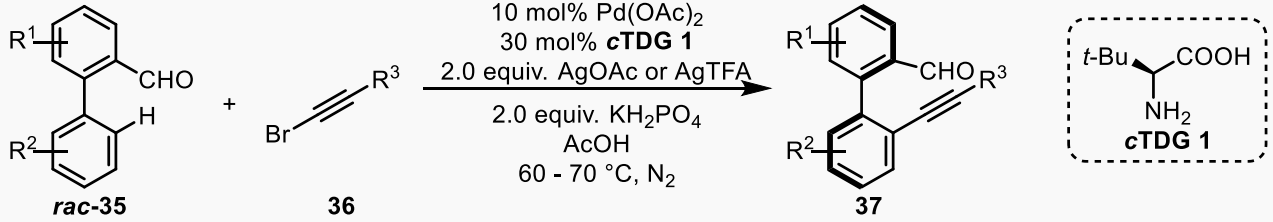
34d, R^2 = OAc, 90%, 95% ee
34e, R^2 = OTBS, 86%, > 99% ee
34f, R^2 = Bn, 86%, 94% ee
34g, R^2 = C_6H_5, 94%, > 92% ee

. Wang, J.* et al. *Angew. Chem., Int. Ed.* **2020**, *59*, 3475−3479.

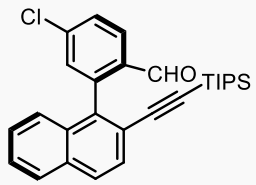
2.2 R-X as electrophiles

2.2.1 Alkynylation of biaryl aldehydes with silyl protected alkynyl bromides

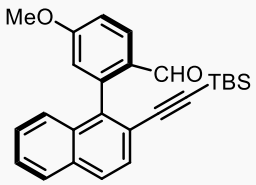
Bing-Feng Shi, 2018



selected examples

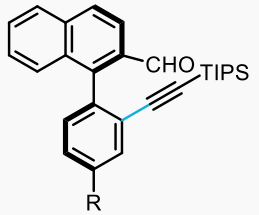


37aa, 77%, 94% ee



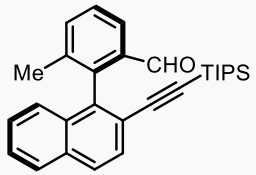
37bb, 74%%, 99% ee

Dynamic Kinetic Resolution

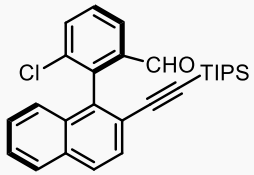


37ca, R = Cl, 61%, 90% ee
37da, R = Cl, 54%, 92% ee
37ea, R = Me, 61%, 94% ee

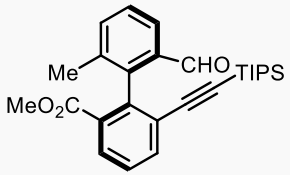
Desymmetrization Process



37fa: 42%, 96% ee
35f: 49%, 90% ee, *s* = 152



37ga: 46%, 99% ee
35g: 46%, 89% ee, *s* = 600



37hb: 31%, 98% ee
35h: 61%, 63% ee, *s* = 190

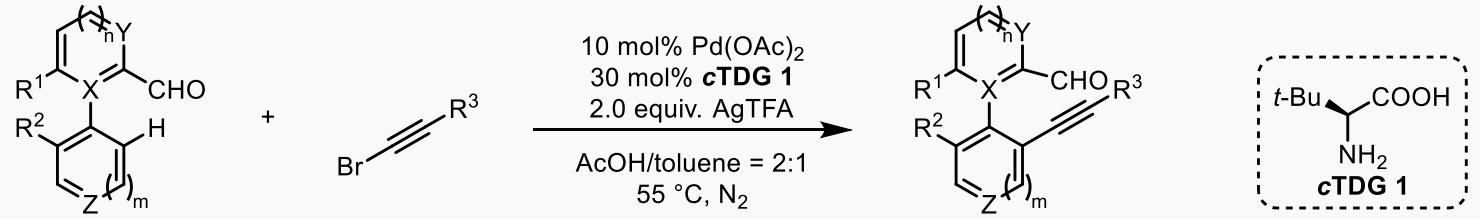
Kinetic Resolution

$s = \ln[(1-C)(1-ee_s)]/\ln[(1-C)(1+ees)]$, $C=ee_s/(ee_s+ee_p)$

Shi, B.-F.* et al. *Angew. Chem., Int. Ed.* **2018**, *57*, 3661−3665.

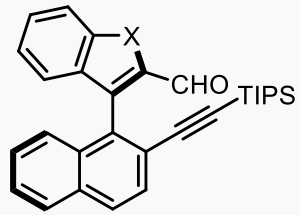
2.2.1 Alkynylation of heterobiaryl aldehydes with alkyne bromides

Bing-Feng Shi, 2019

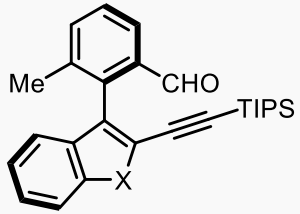


rac-38 + 39 → 40 X= C or N; Y,Z = C, S or O; m, n = 0 or 1

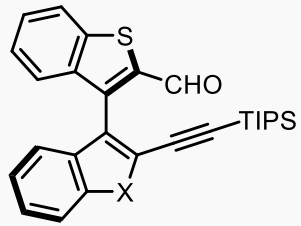
selected examples



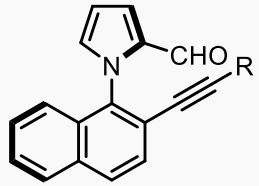
40aa, X = S, 47%, 99% ee
40ba, X = *O*, 77%, 90% ee



40ca, X = S, 84%, 92% ee
40da, X = *O*, 82%, 71% ee



40ea, X = S, 98%, 93% ee
40fa, X = *O*, 98%, 5% ee

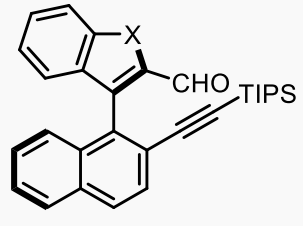


40gb, R = TBS, 50%, 97% ee
40hc, R = *t*-Bu, 66%, 84% ee

Shi, B.-F.* et al. *ACS Catal.* **2019**, *9*, 1956−1961.

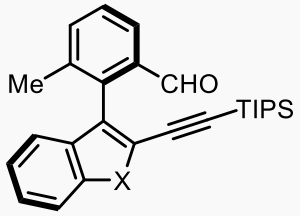
2.2.1 Alkynylation of heterobiaryl aldehydes with alkyne bromides

DFT calculation



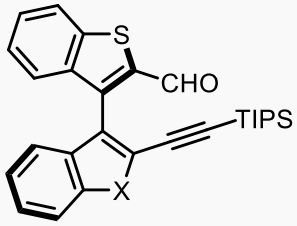
40aa, X = S, 47%, 99% ee
$\Delta G^{\neq}$ = 35.9 kcal/mol
$t_{1/2}$ = 1270 years

40ba, X = *O*, 77%, 90% ee
$\Delta G^{\neq}$ = 30.8 kcal/mol
$t_{1/2}$ = 187 days



40ca, X = S, 84%, 92% ee
$\Delta G^{\neq}$ = 36.8 kcal/mol
$t_{1/2}$ = 5046 years

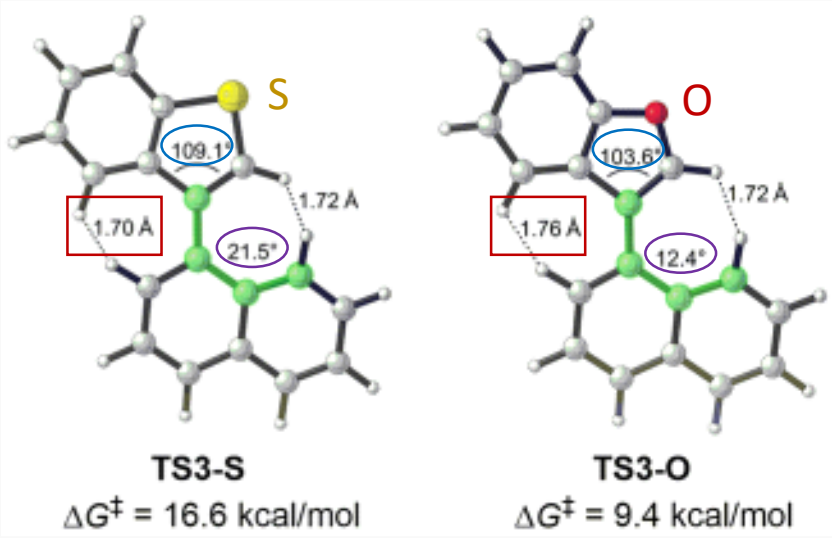
40da, X = *O*, 82%, 71% ee
$\Delta G^{\neq}$ = 29.6 kcal/mol
$t_{1/2}$ = 30 days



40ea, X = S, 98%, 93% ee
$\Delta G^{\neq}$ = 31.6 kcal/mol
$t_{1/2}$ = 2 years

40fa, X = *O*, 98%, 5% ee
$\Delta G^{\neq}$ = 24.6 kcal/mol
$t_{1/2}$ = 1204 seconds

Calculated rotational barriers and corresponding half-life

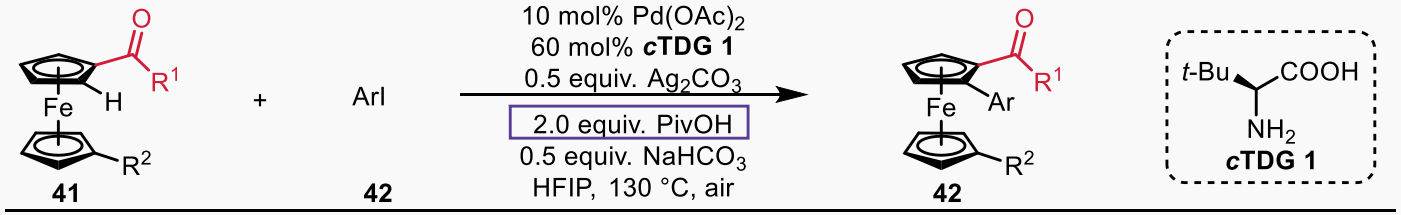


DFT-optimized transition states and free energy barriers

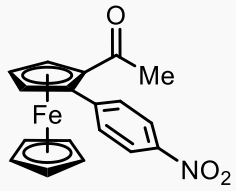
Shi, B.-F.* et al. *ACS Catal.* **2019**, *9*, 1956−1961.

2.2.2 Arylation of ferrocenes with aryl iodides

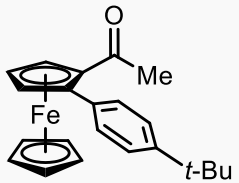
Xiaohua Xu & Zhong Jin, 2018



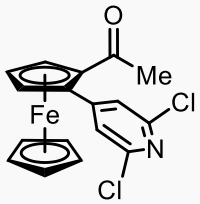
selected example



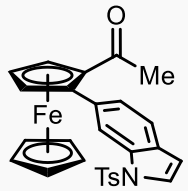
43aa, 72%, 95% ee
mono:di = 98:2



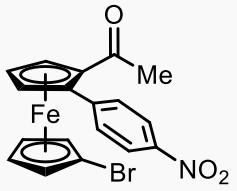
43ab, 42%, 94% ee
mono:di = 99:1



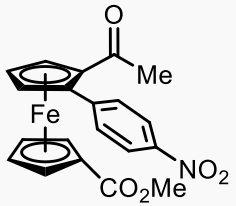
43ac, 60%, 97% ee
mono:di = 99:1



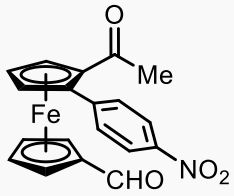
43ae, 55%, 95% ee
mono:di = 99:1



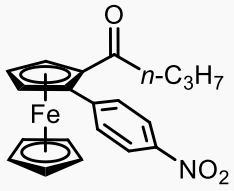
43ba, 61%, 92% ee



43ca, 54%, 92% ee



43da, 49%, 97% ee

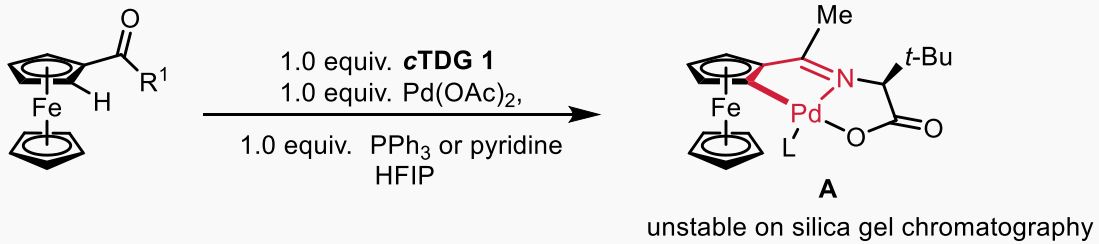


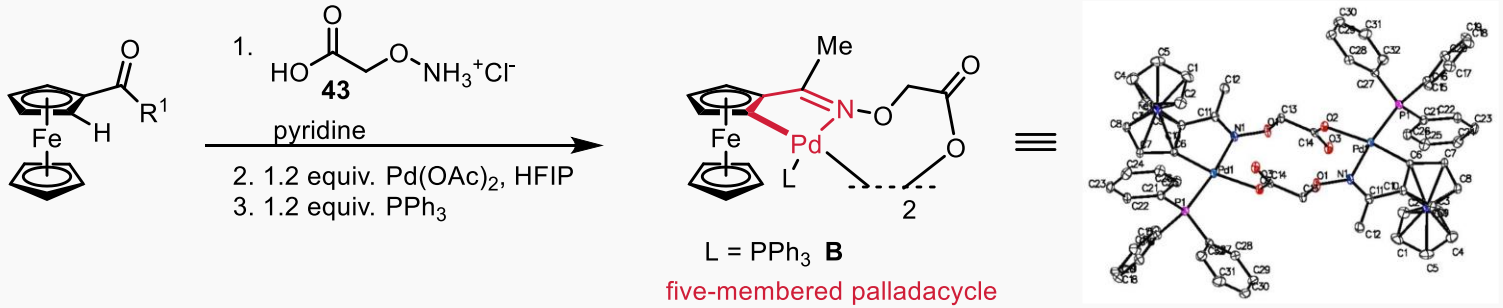
43ea, 40%, 92% ee

Xu, X.*; Jin, Z.* et al. *Chem. Commun.* **2018**, *54*, 689−692.

2.2.2 Arylation of ferrocenes with aryl iodides

Mechanistic study





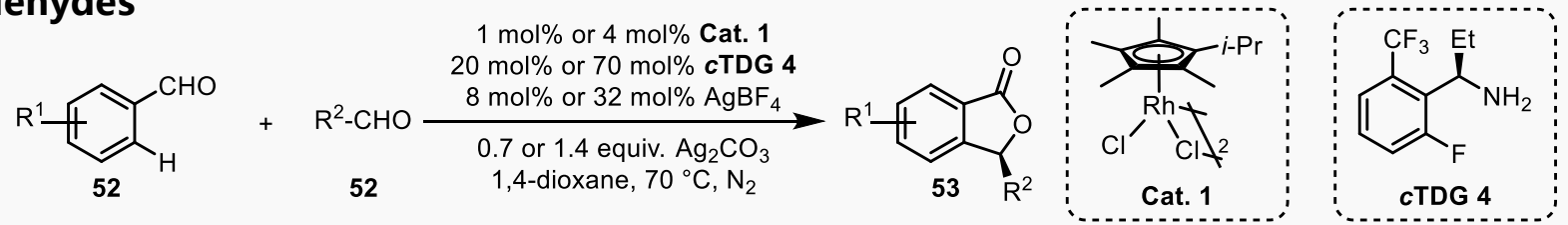
Xu, X.*; Jin, Z.* et al. *Chem. Commun.* **2018**, *54*, 689−692.

2.3 Benzaldehydes as electrophiles

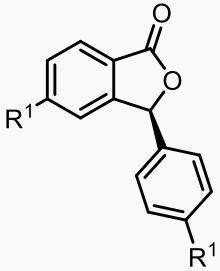
2.3 Benzaldehydes as electrophiles

2.3 Coupling of benzaldehydes

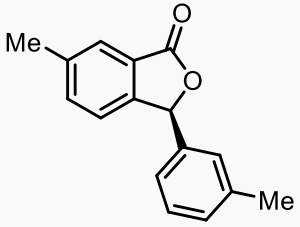
Jun Wang, 2019



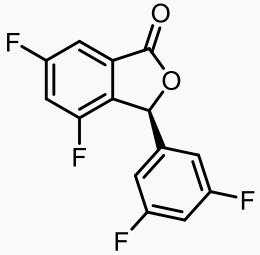
selected examples



53a, $R^1 = C_6H_5$, 42%, 91% ee
53b, $R^1 = CF_3$, 34%, 92% ee
53c, R^1 = Me, 50%, 93% ee
53d, R^1 = Br, 43%, 93% ee

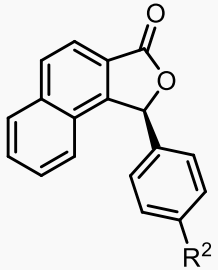


53e, 57%, 95% ee

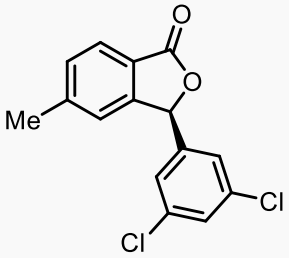


53f, 61%, 87% ee

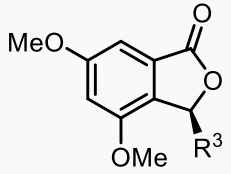
Homo-coupling



53g, $R^2 = SO_2Me$, 71%, 91% ee
53h, $R^2 = CF_3$, 73%, 96% ee
53i, $R^2 = CO_2Me$, 54%, 85% ee



53k, 63%, 98% ee



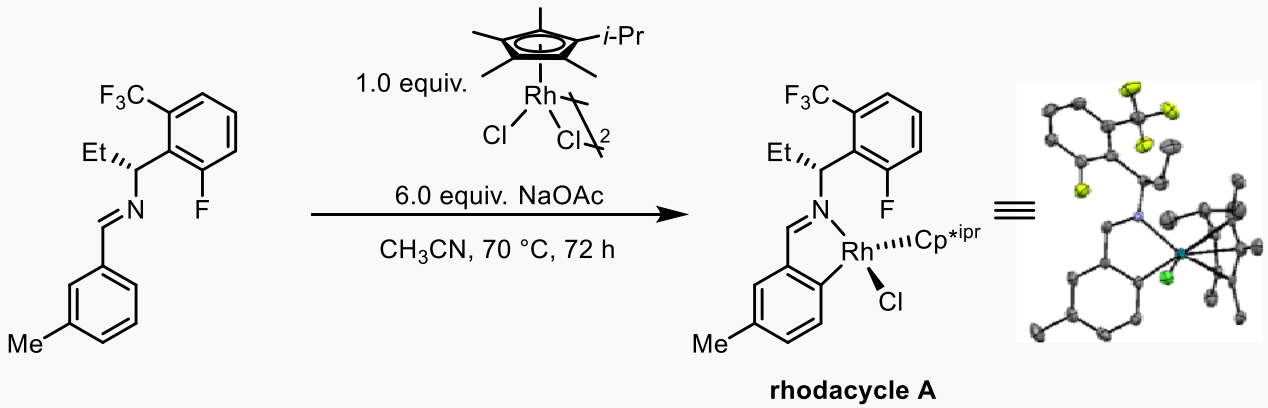
53l, $R^3 = CO_2Et$, 64%, 76% ee
53m, R^3 = *n*-Bu, 13%, 93% ee
53n, R^3 = cyclohexyl, 22%, 93% ee

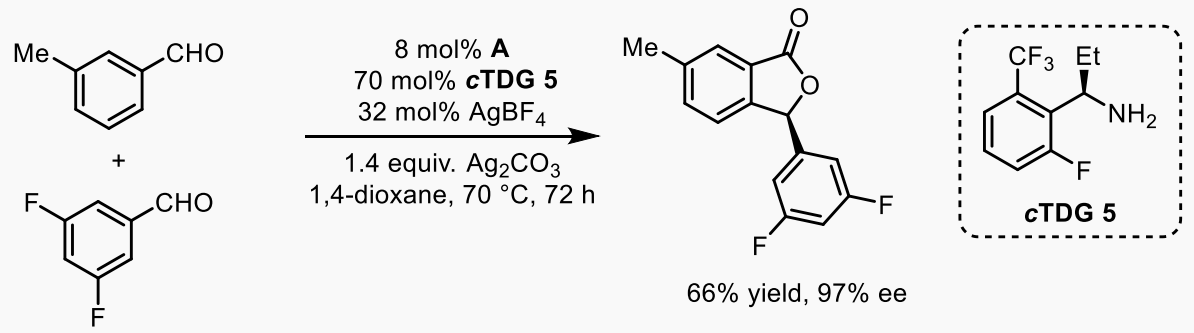
Cross-coupling

Wang, J.* et al. *Chem. - Eur. J.* **2019**, *25*, 4688–4694.

2.3 Benzaldehydes as electrophiles

Mechanistic study

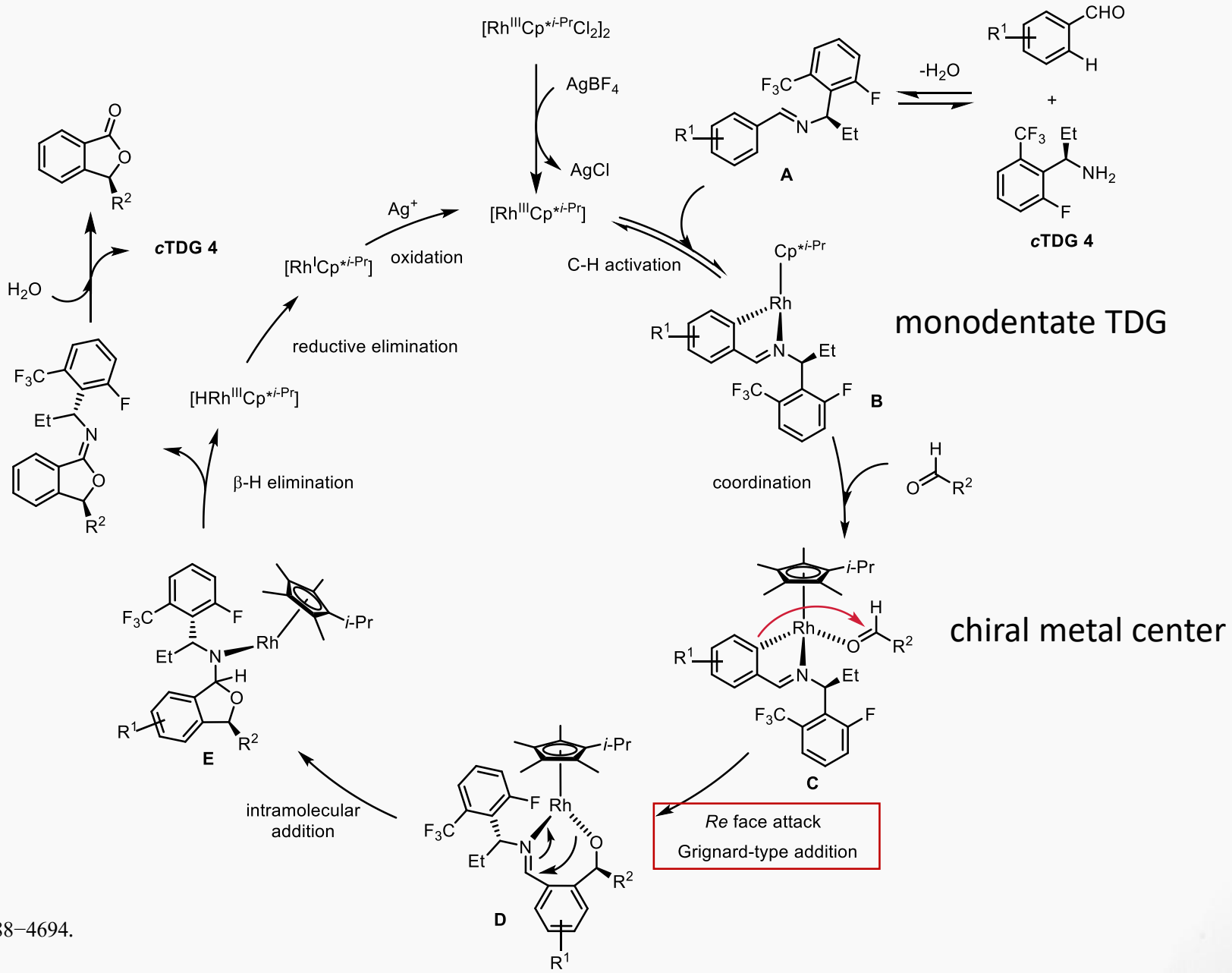




Wang, J.* et al. *Chem. - Eur. J.* **2019**, *25*, 4688–4694.

2.3 Benzaldehydes as electrophiles

Mechanism

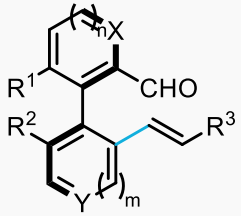
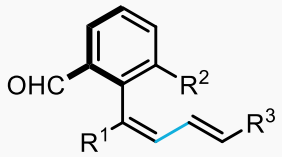
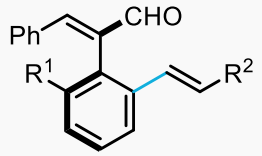
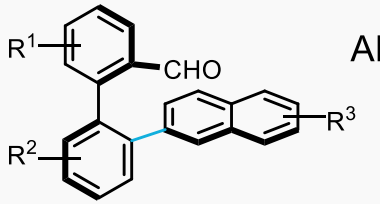
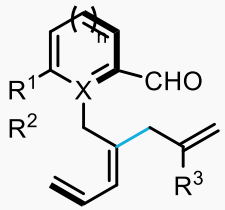
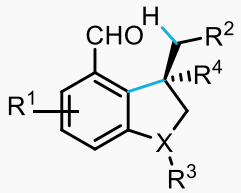
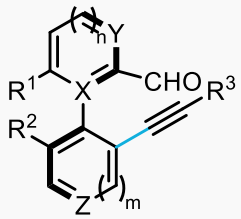


Wang, J.* et al. *Chem. - Eur. J.* **2019**, *25*, 4688–4694.

3 Summary and Outlook

3 Summary

Chiral transient imine DG in Transition matal catalyzed asymmetric C(sp^2)-H functionalization

- Alkenes
  - Alkenylation
    - 
    - 
    - 
    - [Pd]
  - Naphthylatiorn
    - 
    - [Pd]
  - Allylation
    - 
    - [Pd]
  - Intramolecular Hydroarylation
    - 
    - X = N or O
    - [Ru]
- R-X
  - Alkynylation
    - 
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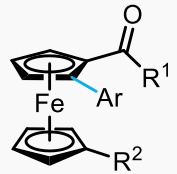
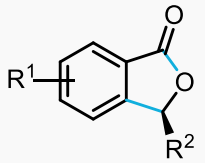
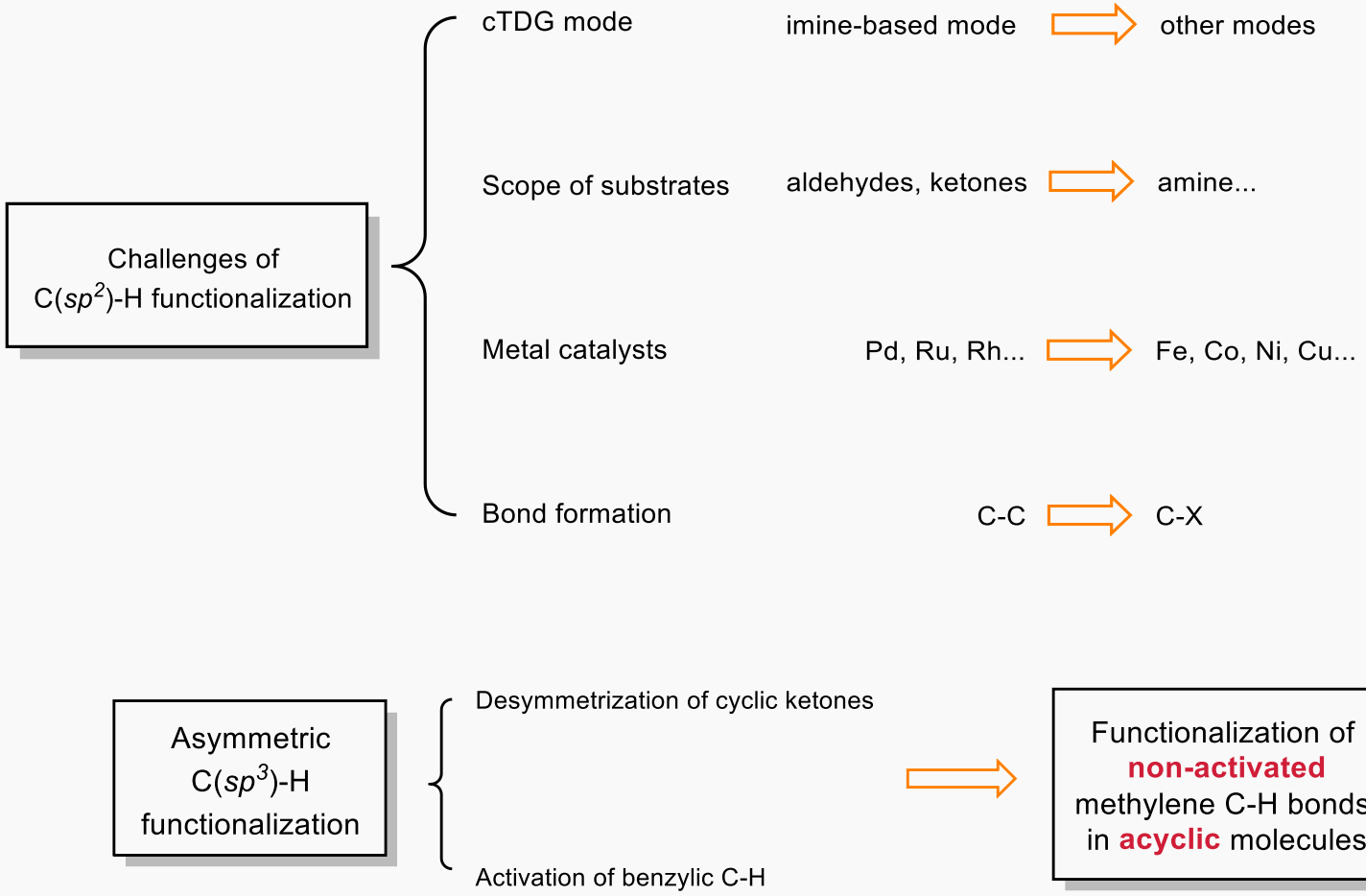
  - Arylation
    - 
    - [Pd]
- Benzaldehydes
  - Coupling reactions
    - 
    - [Rh]

3 Outlook



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Nat. Chem. **2018**, *10*, 755-762.
Science **2016**, *351*, 252-256.

THANK YOU

Chiral Transient Imine Directing Group in Transition Metal Catalyzed C(sp^2)-H functionalization

Qian Zhang