Electronic Supplementary Material (ESI) for Chemical Society Reviews.

Transition-metal catalysed C–N bond activation

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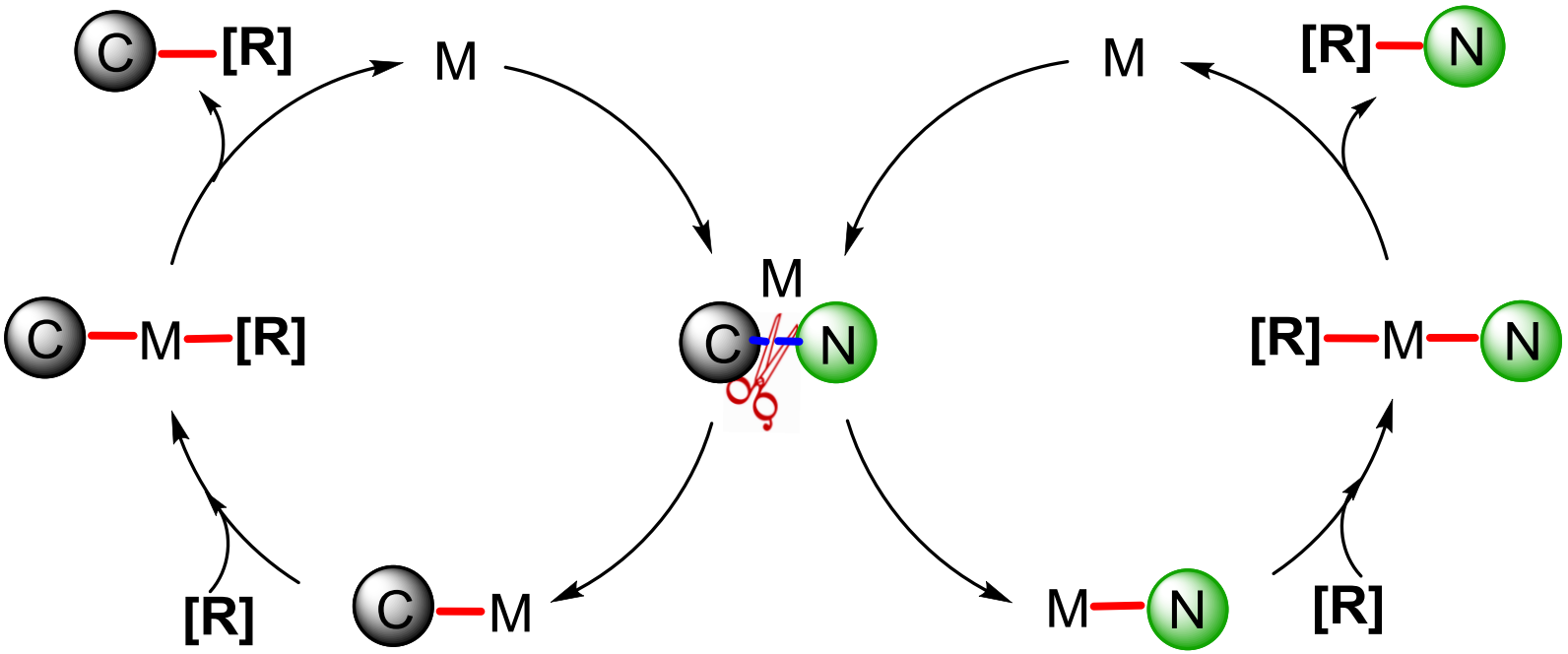
Key learning points

- 1）The advantages of the synthetic strategy *via* transition-metal catalysed C–N bond activation
- 2）The typical methods of the C–N bond activation
- 3）The general mechanisms
- 4）The applications of C–N bond activation in organic synthesis
- 5）The challenge and future perspective

The contents of the tutorial review

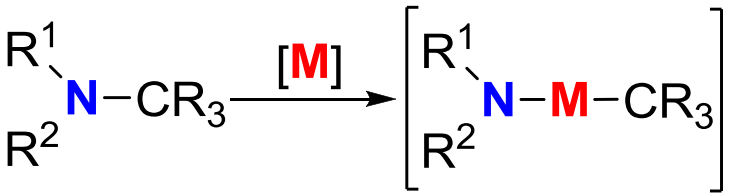
1. Introduction



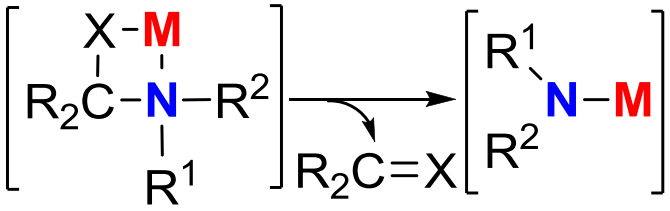
New transformations *via* C–N bond activation

1. Introduction

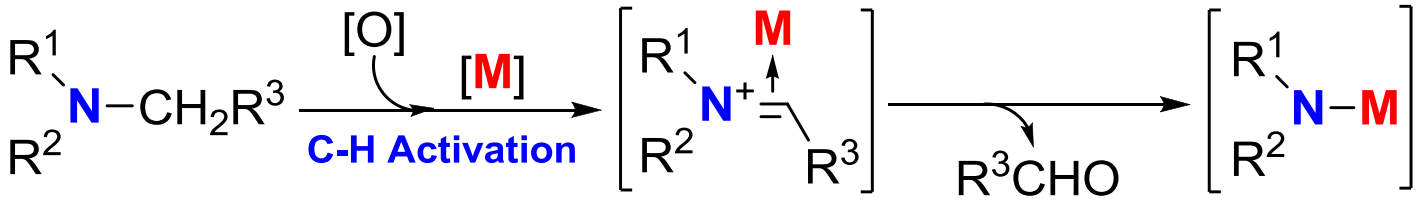
i) Oxidative addition



ii) β-N elimination

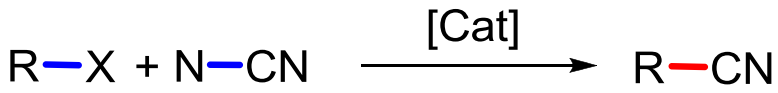


iii) C-H bond cleavage triggered C-N bond activation



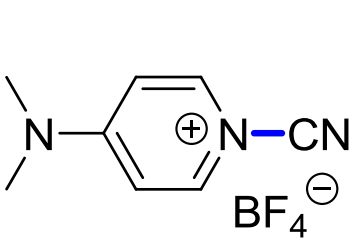
Three general mechanisms for transition−metal‑mediated C−N bond metalation

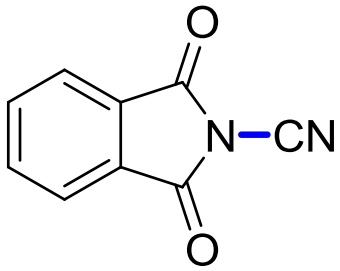
2. Activation of C(sp)−N bond

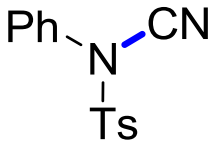


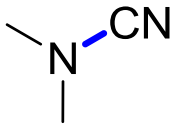
[Cat] = [Rh], [Co], [Pd] or [Fe]

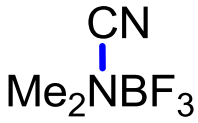
Selected less toxic organic CN source:









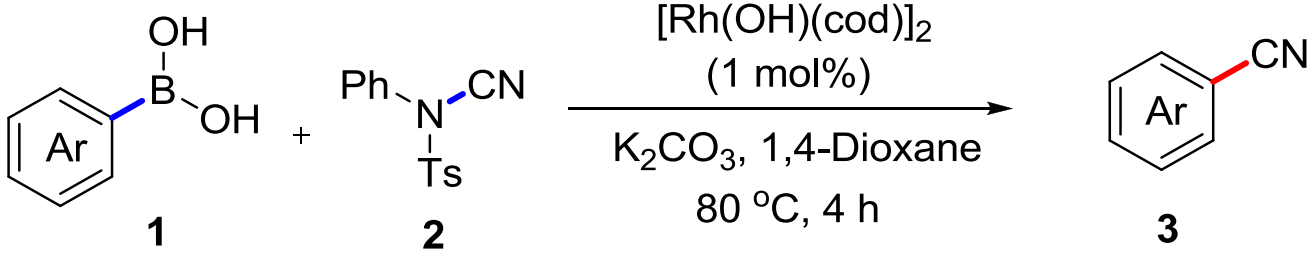


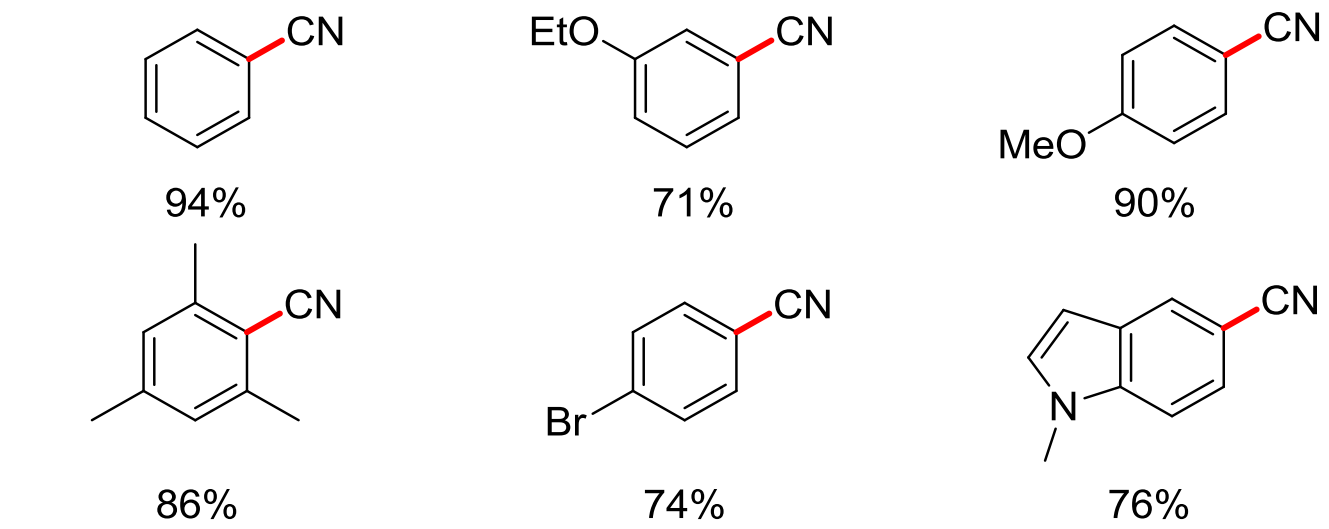
Traditional toxic CN source: NaCN, KCN, CuCN and so on

Cyanations reaction with organic N−CN cyanation reagents

K. Fukumoto, T. Oya, M. Itazaki and H. Nakazawa, *J. Am. Chem. Soc.*, 2009, **131**, 38.
P. Anbarasan, H. Neumann and M. Beller, *Angew. Chem., Int. Ed.*, 2011, **50**, 519

2. Activation of C(sp)−N bond

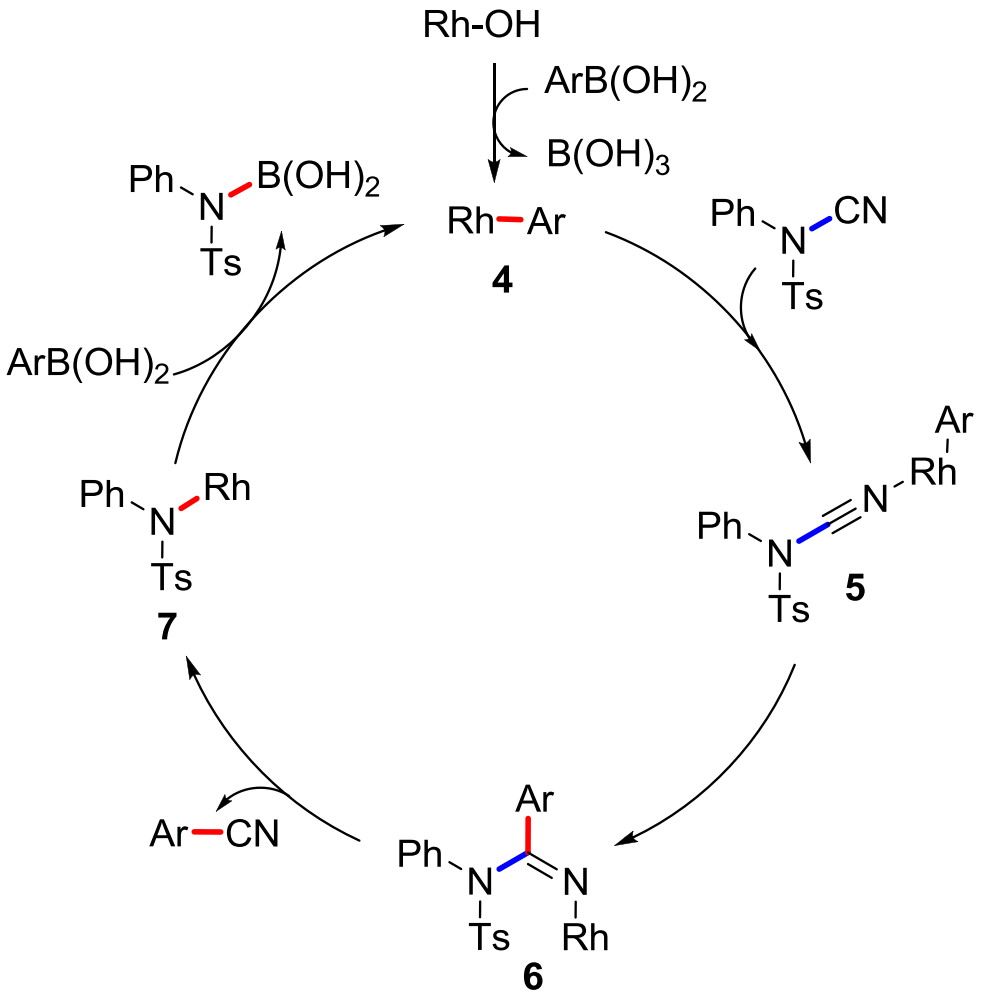




Rhodium−catalysed cyanation of aryl boronic acids

P. Anbarasan, H. Neumann and M. Beller, *Angew. Chem., Int. Ed.*, 2011, **50**, 519

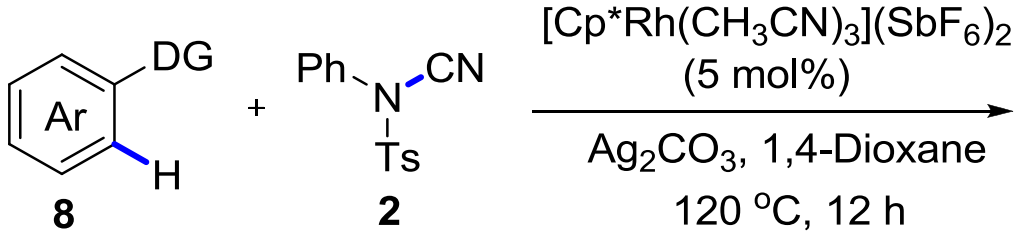
2. Activation of C(sp)−N bond

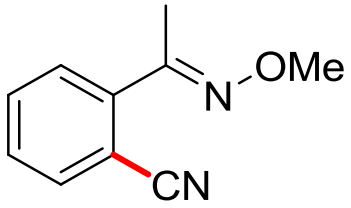


Proposed mechanism for cyanation of aryl boronic acids

P. Anbarasan, H. Neumann and M. Beller, *Angew. Chem., Int. Ed.*, 2011, **50**, 519

2. Activation of C(sp)–N bond





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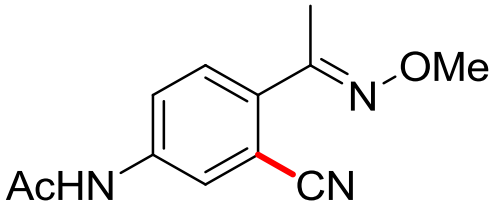

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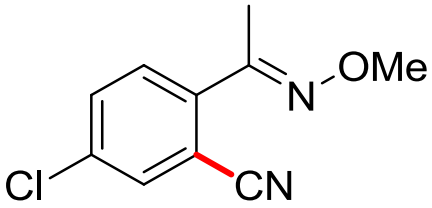

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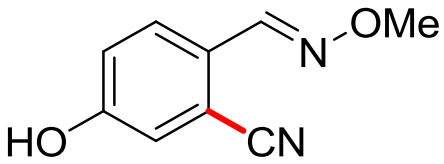

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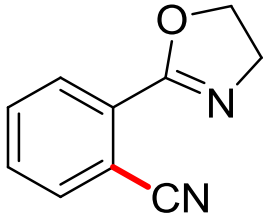
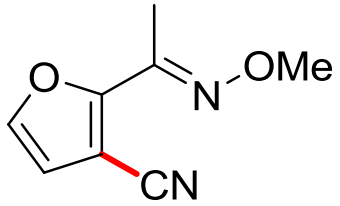


76%

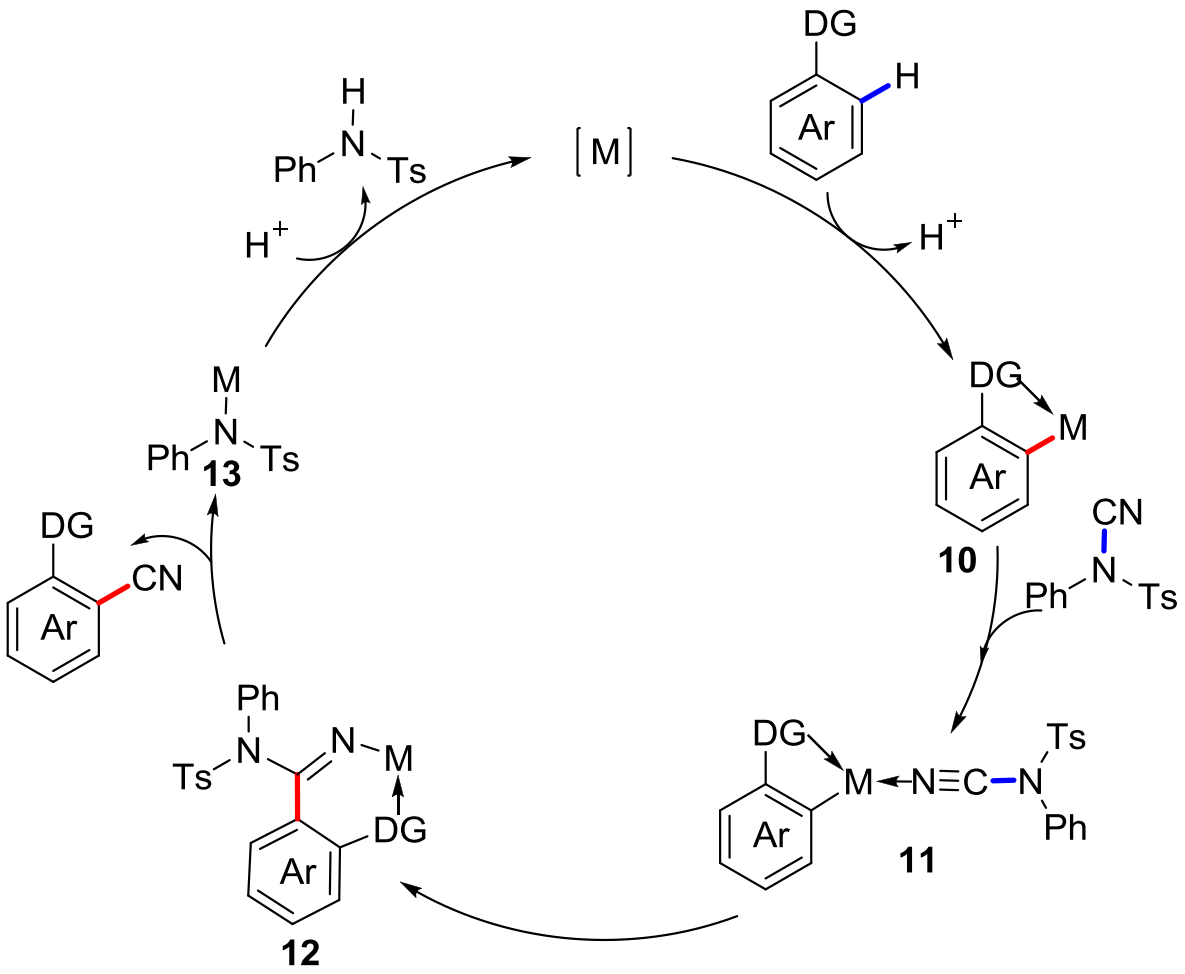


67%

Rhodium–catalysed cyanation of arenes

T.-J. Gong, L. Liu and Y. Fu et. al., *J. Am. Chem. Soc*., 2013, **135**, 10630

2. Activation of C(sp)−N bond

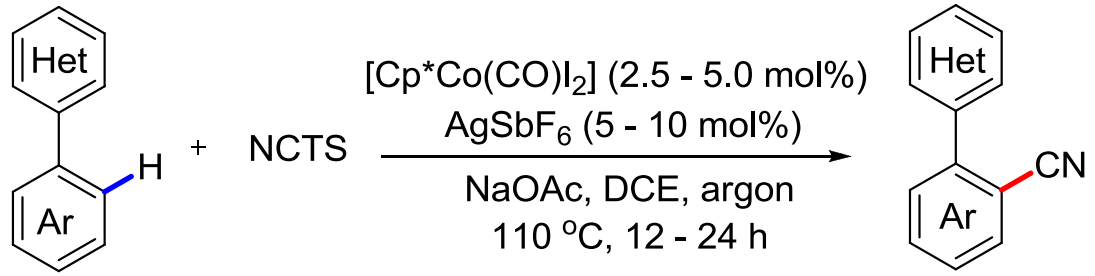


Proposed mechanism for transition−metal catalysed cyanation

T.-J. Gong, L. Liu and Y. Fu et. al., *J. Am. Chem. Soc.*, 2013, **135**, 10630

2. Activation of C(sp)−N bond

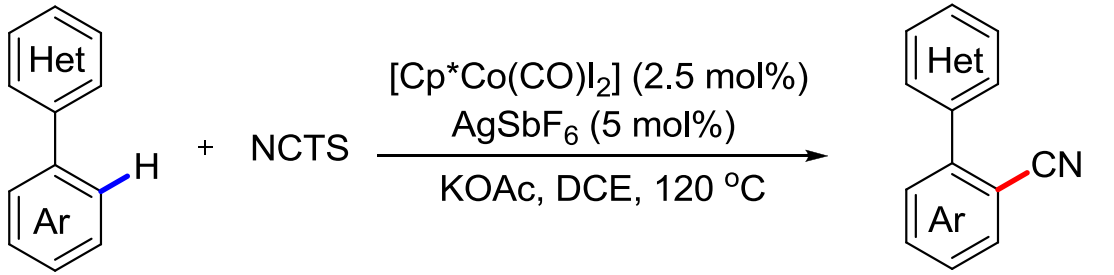
Glorius' work



Het = pyridine, pyrimidine, pyrazole
Ar = indole, benzene, pyrrole

14 examples
70 - 96% yield

Ackermann' work



Het = pyridine, pyrimidine, pyrazole
Ar = indole, benzene, thiophene, pyrrole

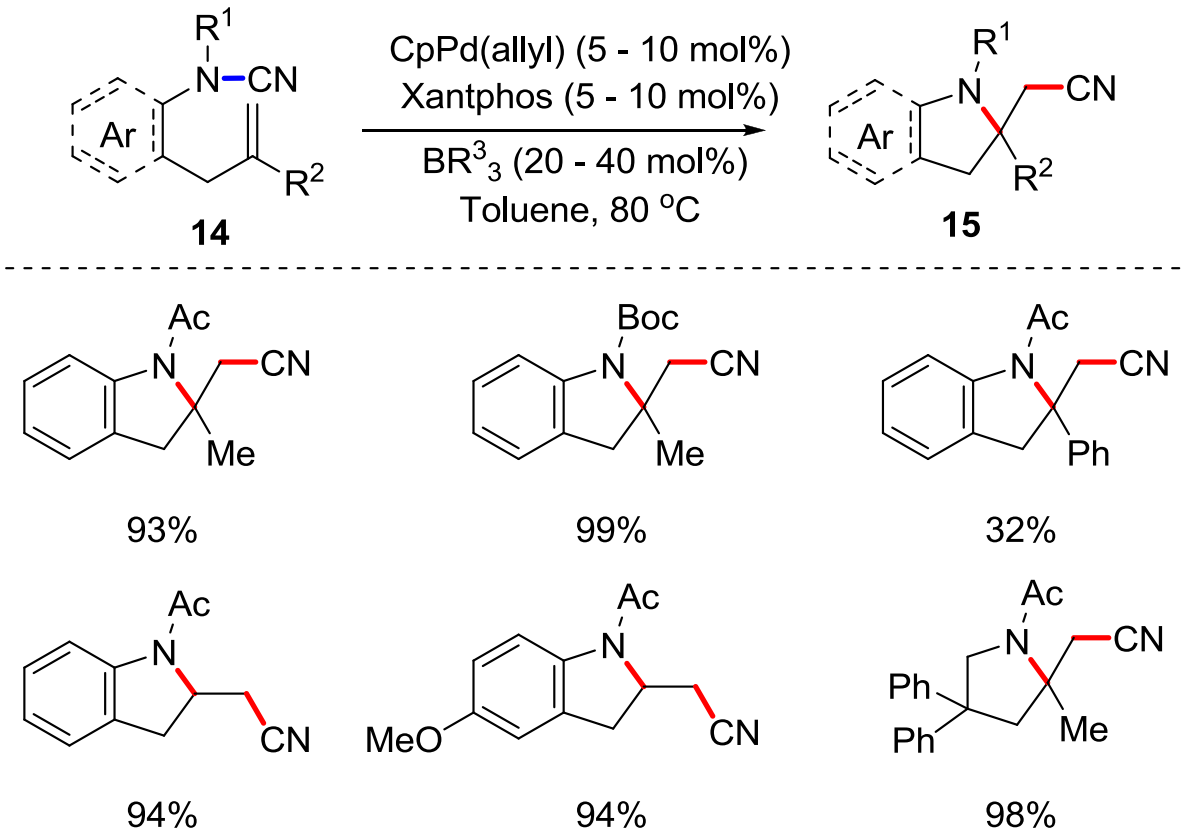
24 examples
60 - 99% yield

Transition−metal catalysed cyanation

D.-G. Yu, T. Gensch, F. de Azambuja, S. V. Céspedes and F. Glorius, *J. Am. Chem. Soc.*, 2014, **136**, 17722

J. Li and L. Ackermann, *Angew. Chem., Int. Ed.*, 2015, **54**, 3635

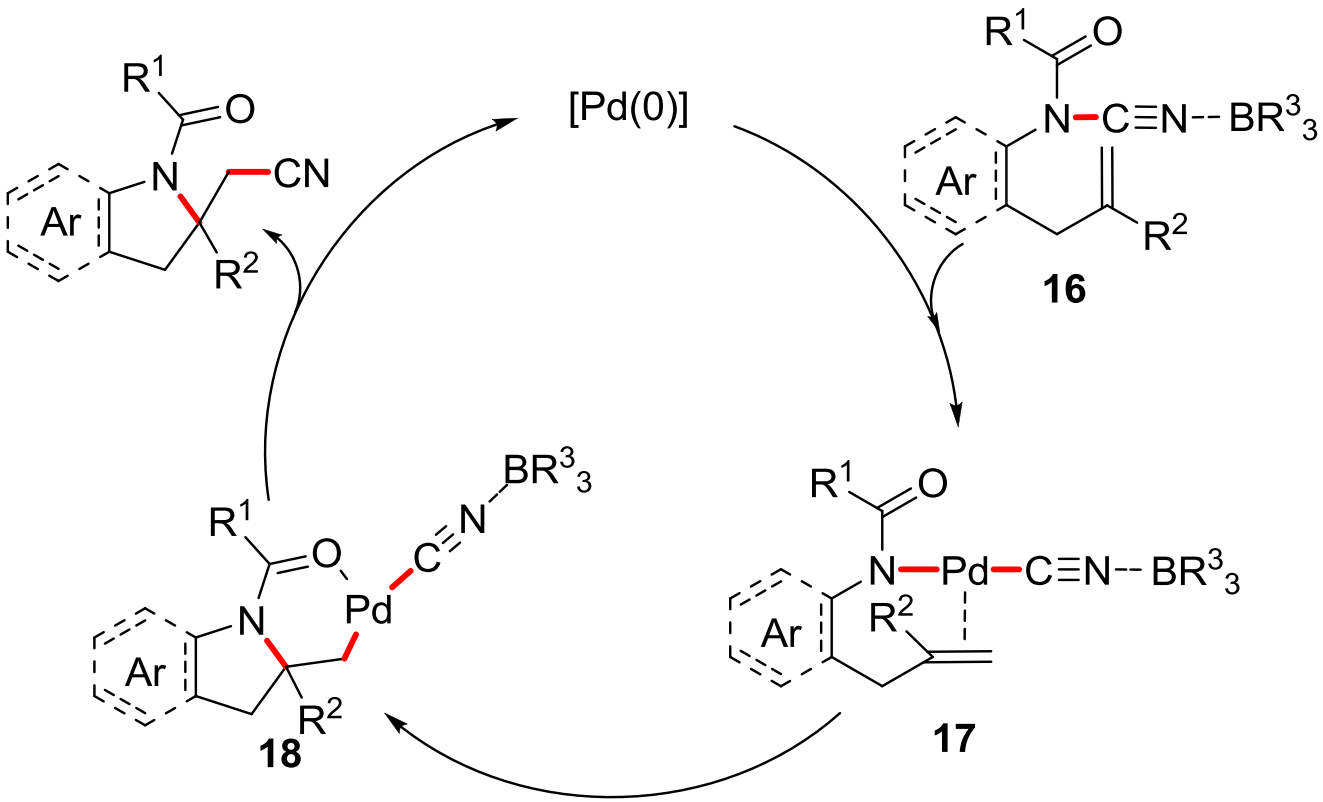
2. Activation of C(sp)−N bond



Palladium−catalysed intramolecular aminocyanation of alkenes

Y. Miyazaki, N. Ohta, K. Semba and Y. Nakao, *J. Am. Chem. Soc.*, 2014, **136**,3732

2. Activation of C(sp)−N bond



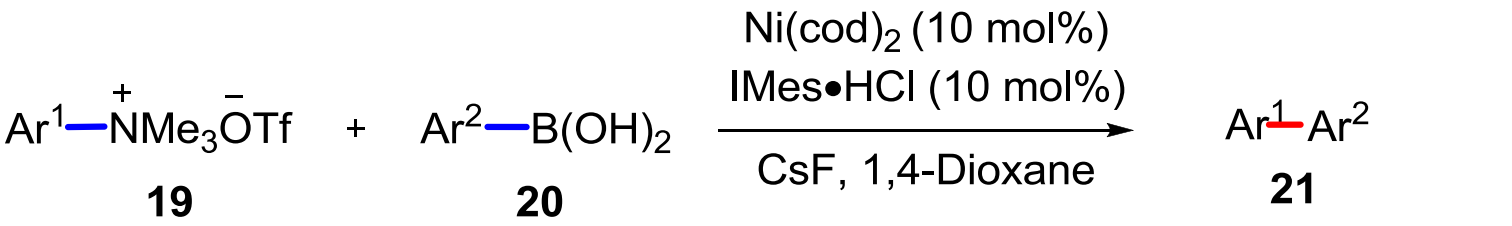
Proposed mechanism for intramolecular aminacyanation of alkenes

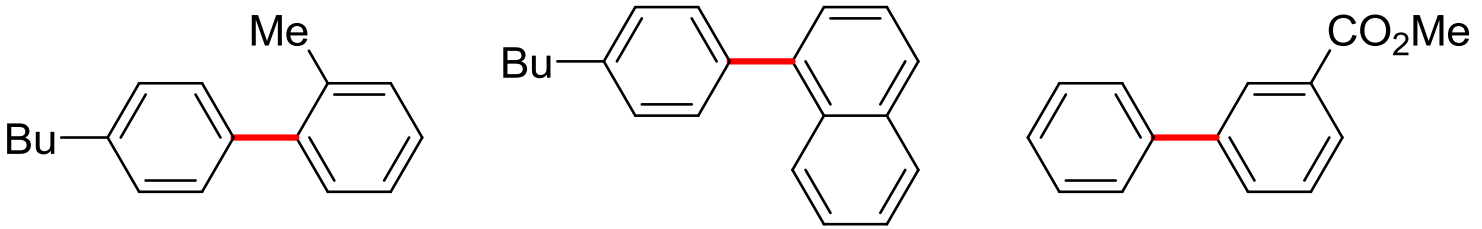
Y. Miyazaki, N. Ohta, K. Semba and Y. Nakao, *J. Am. Chem. Soc.*, 2014, **136**,3732

3. Activation of C(sp2)–N bond

3. Activation of C(sp2)–N bond

3.1 Activation of aryl C(sp^2)–N bond



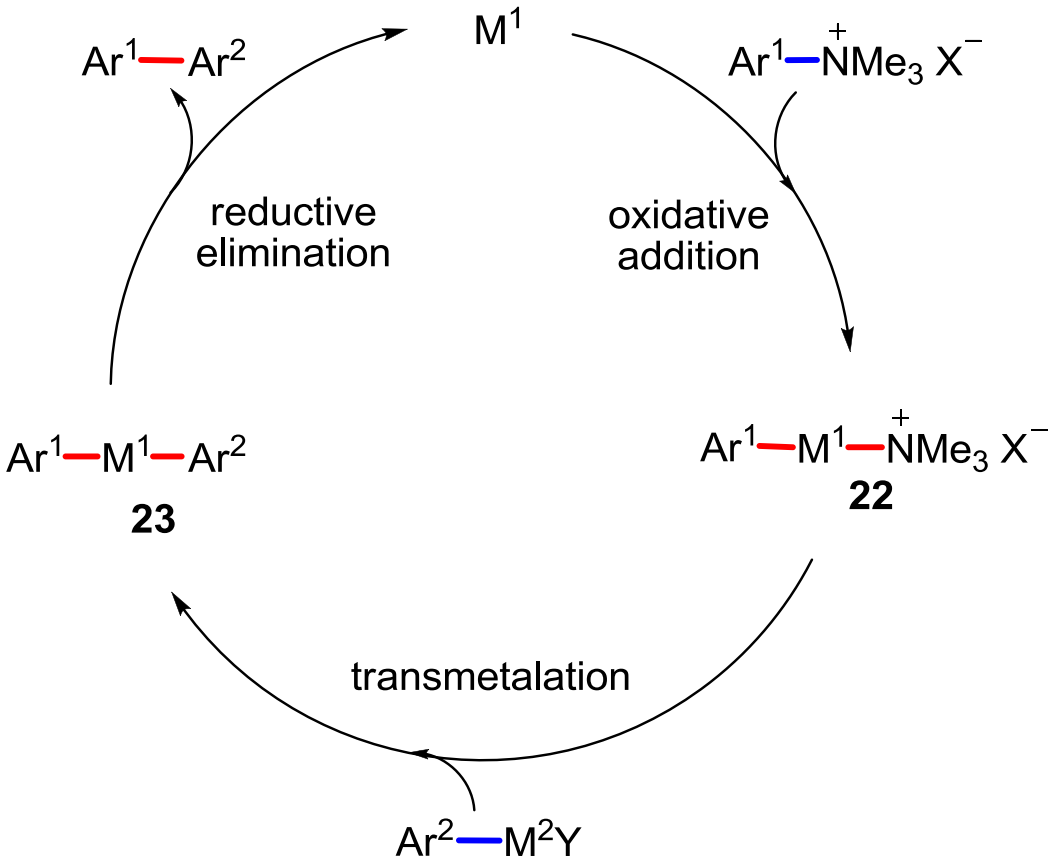


Nickel–catalysed cross–coupling reaction

S. B. Blakey and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2003, **125**, 6046

3. Activation of C(sp2)−N bond

3.1 Activation of aryl C(sp^2)−N bond

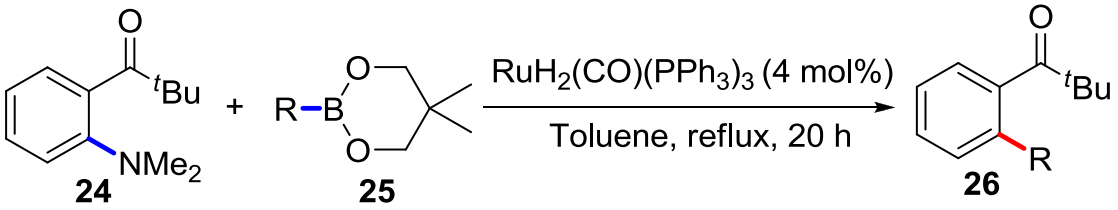


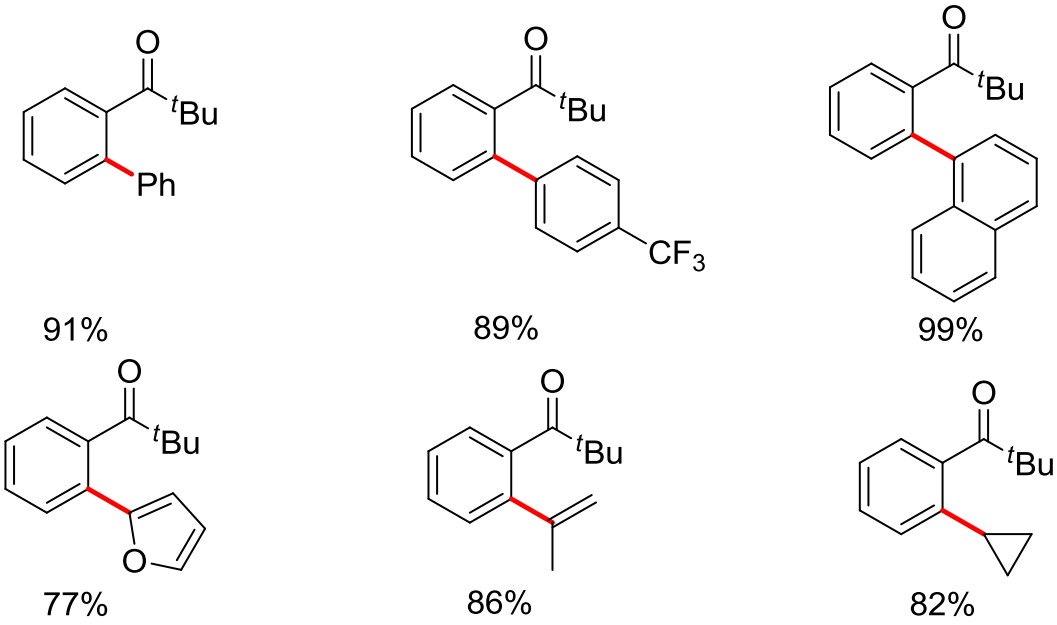
Proposed mechanism for cross−coupling

S. B. Blakey and D. W. C. MacMillan, *J. Am. Chem. Soc*., 2003, **125**, 6046
L.-G. Xie and Z.-X. Wang, *Angew. Chem., Int. Ed*., 2011, **50**, 4901
J. T. Reeves et. al., *Org. Lett.*, 2010, **12**, 4388

3. Activation of C(sp2)−N bond

3.1 Activation of aryl C(sp^2)−N bond



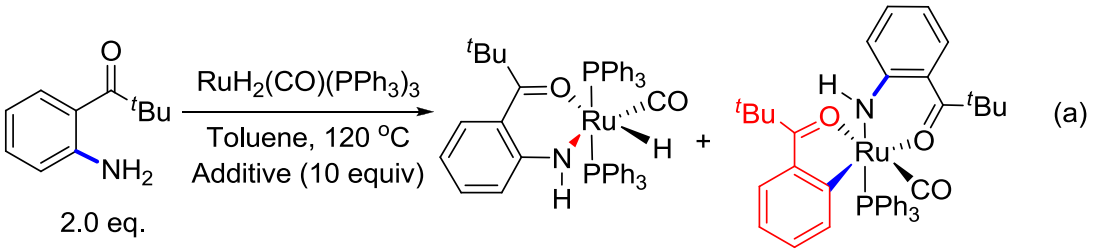


The ruthenium−catalysed cross−coupling reaction

S. Ueno, N. Chatani and F. Kakiuchi, *J. Am. Chem. Soc.*, 2007, **129**, 6098

3. Activation of C(sp2)−N bond

3.1 Activation of aryl C(sp^2)−N bond



entry	additive	time	isolated yield	isolated yield
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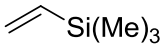
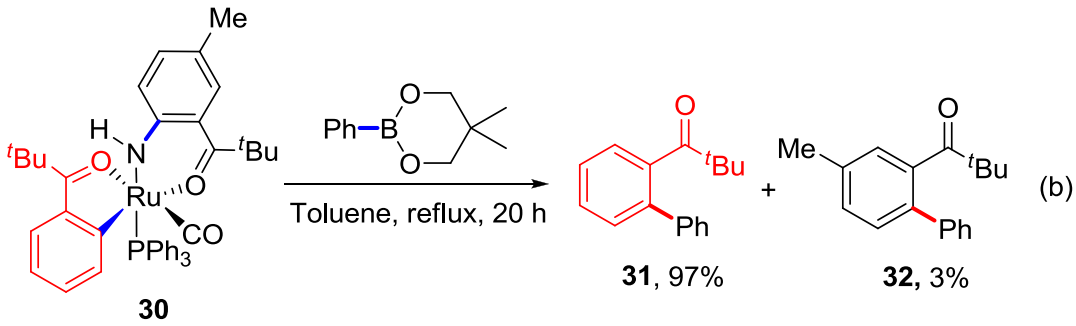
2	none	3 days	42%	6%
3		3 days	-	56%

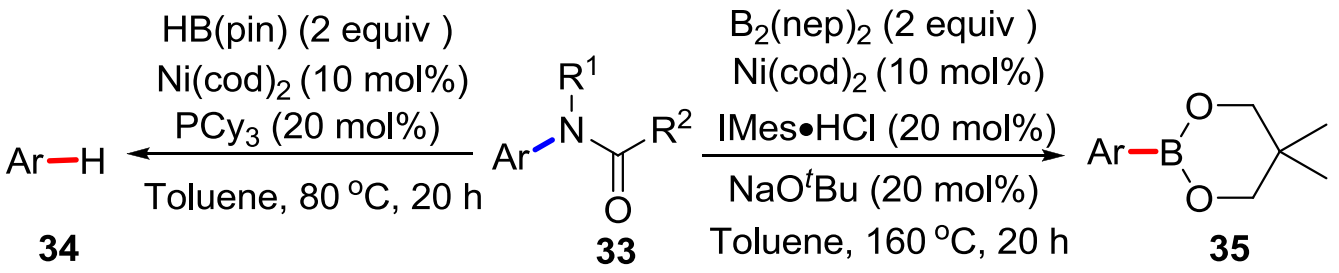


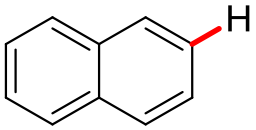
The ruthenium−catalysed cross−coupling reaction

T. Koreeda, T. Kochi, and F. Kakiuchi, *J. Am. Chem. Soc.*, *2009,* **131**, 7238

3. Activation of C(sp2)–N bond

3.1 Activation of aryl C(sp^2)–N bond





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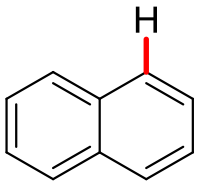
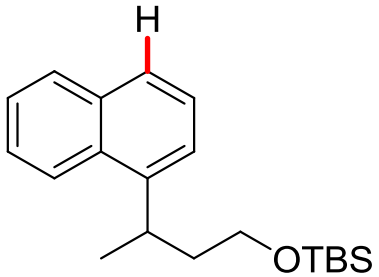
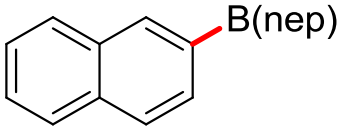


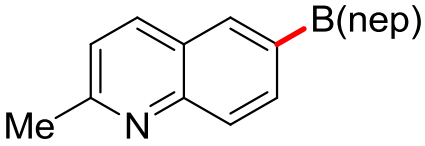
60%



71%, 60% ee



55%



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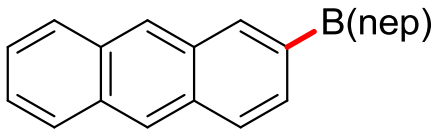


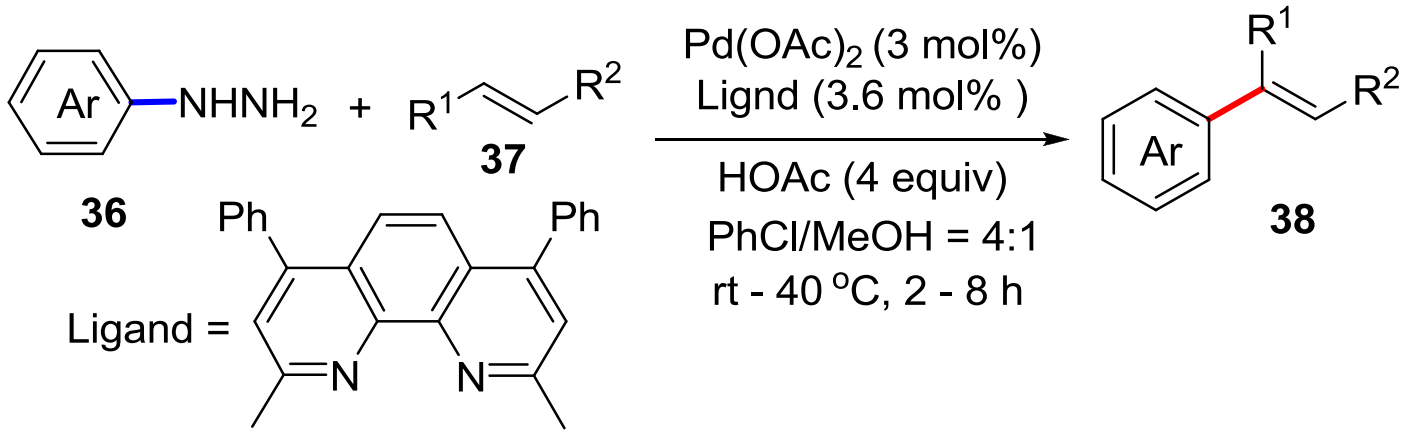
72%

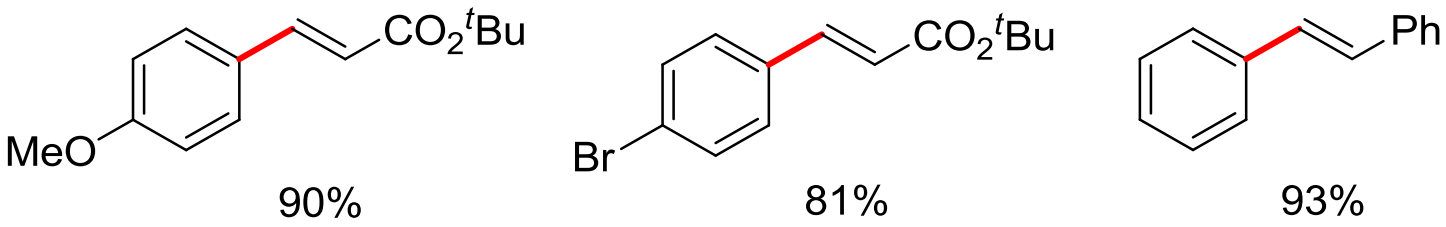
Nickel–catalysed cleavage of C–N bond of aromatic amides

M. Tobisu, K. Nakamura and N. Chatani, *J. Am. Chem. Soc.*, 2014, **136**, 5587

3. Activation of C(sp2)–N bond

3.1 Activation of aryl C(sp^2)–N bond



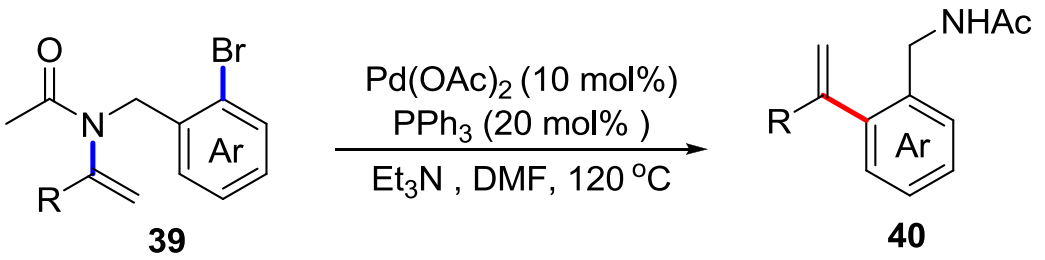


Palladium–catalysed cross–coupling arylhydrazines with olefins

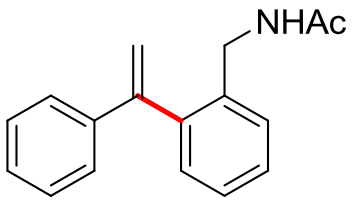
M.-K. Zhu, J.-F. Zhao and T.-P. Loh, *Org. Lett.*, 2011, **13**, 6308

3. Activation of C(sp2)–N bond

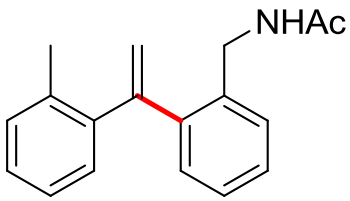
3.2 Activation of olefinic C(sp^2)–N bond



39 **40**



80%



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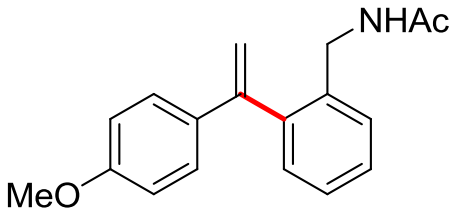

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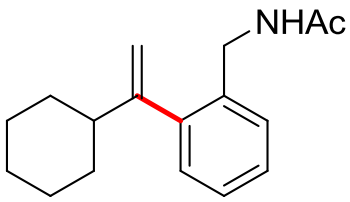

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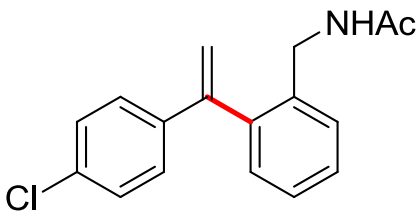

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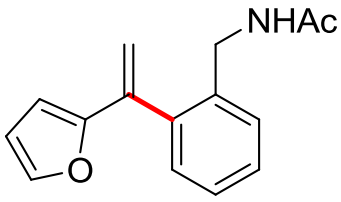


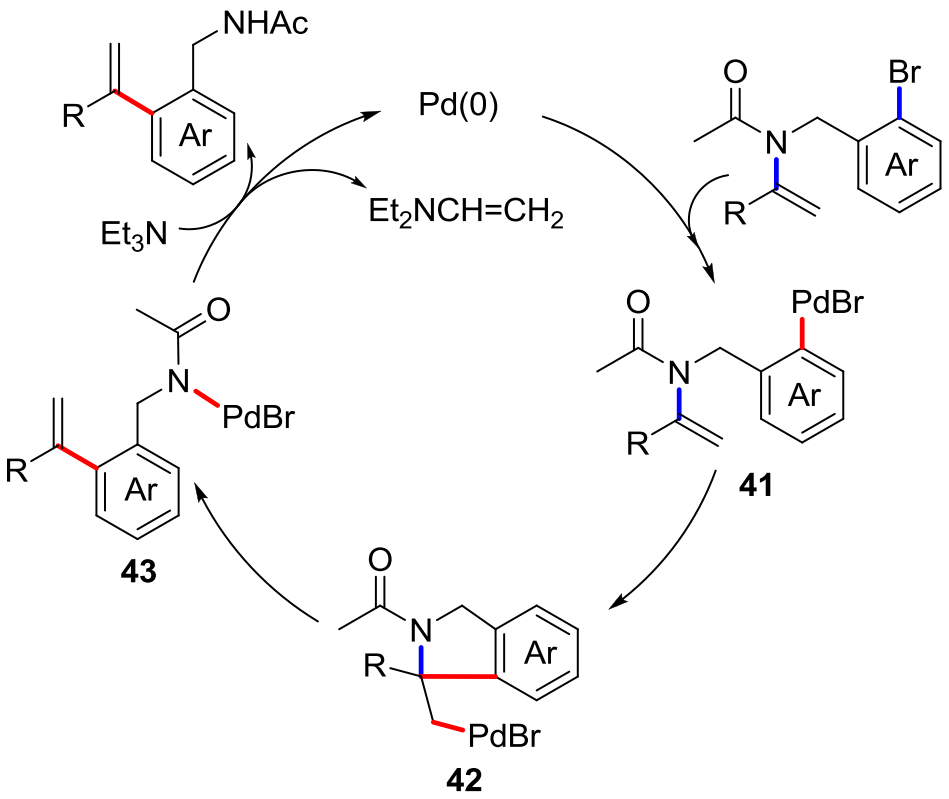
61%

Heck reaction of *N*–vinylacetamide derivatives

M. Wang, X. Zhang, Y.-X. Zhuang, Y.-H. Xu and T.-P. Loh, *J. Am. Chem. Soc.*, 2015, **137**, 1341

3. Activation of C(sp2)–N bond

3.2 Activation of olefinic C(sp^2)–N bond

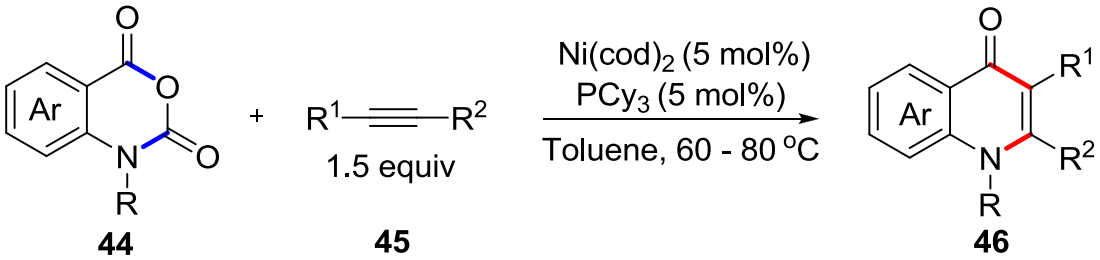


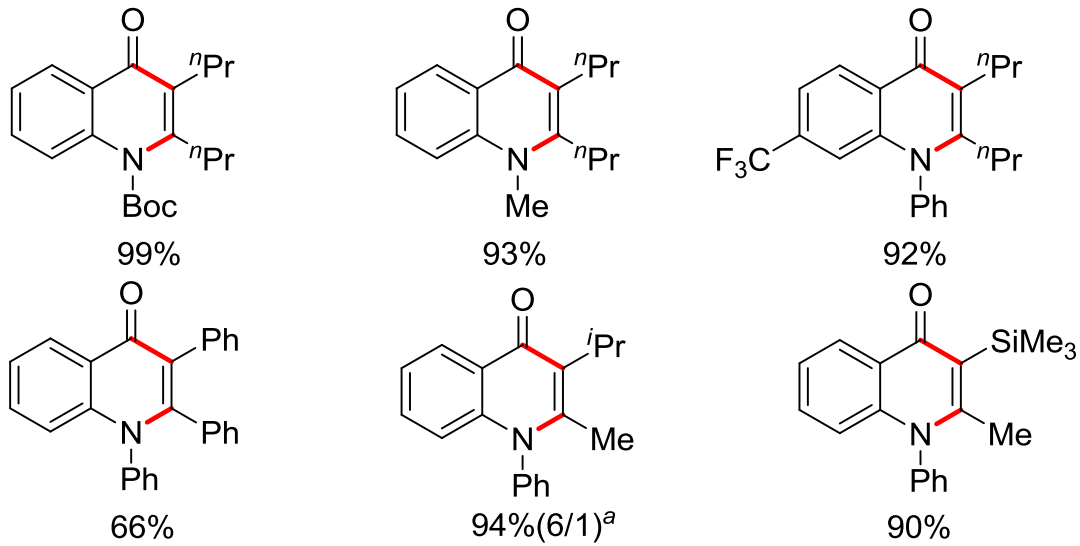
Proposed mechanism for Heck reaction of *N*–vinylacetamide derivatives

M. Wang, X. Zhang, Y.-X. Zhuang, Y.-H. Xu and T.-P. Loh, *J. Am. Chem. Soc.*, 2015, **137**, 1341

3. Activation of C(sp2)–N bond

3.3 Activation of amidic C(sp^2)–N bond





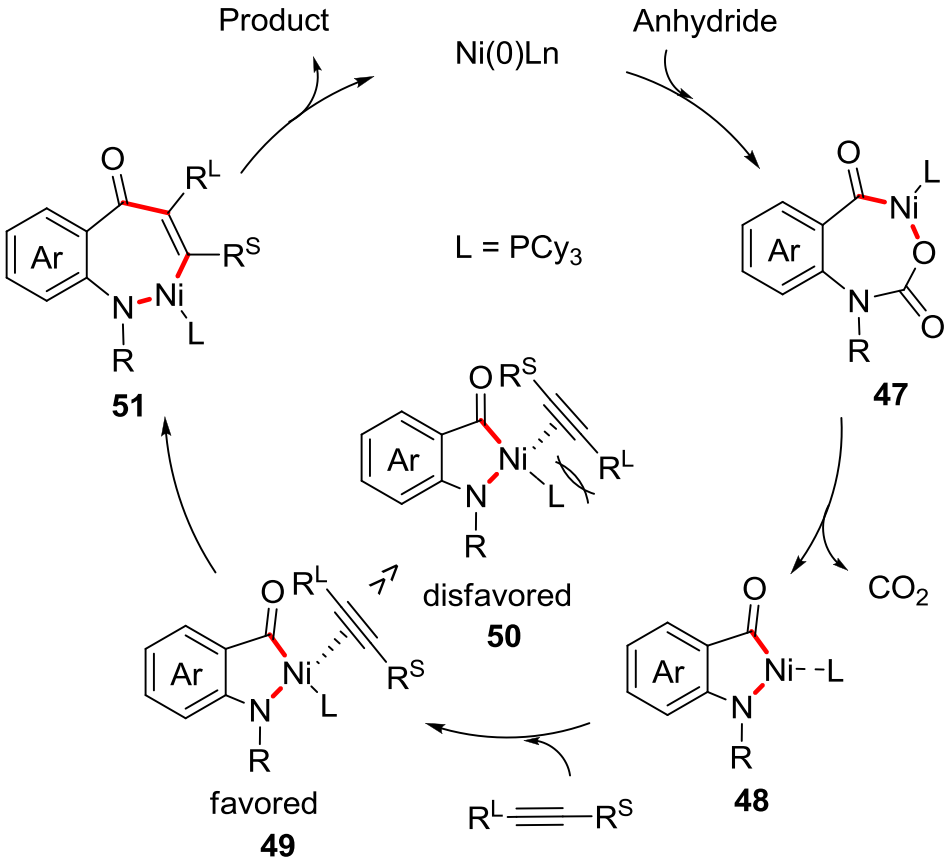
[a] Ratio of regioisomers

Nickel(0)–catalysed decarboxylative carboamination

Y. Yoshino, T. Kurahashi and S. Matsubara, *J. Am. Chem. Soc.*, 2009, **131**, 7494

3. Activation of C(sp2)–N bond

3.3 Activation of amidic C(sp^2)–N bond

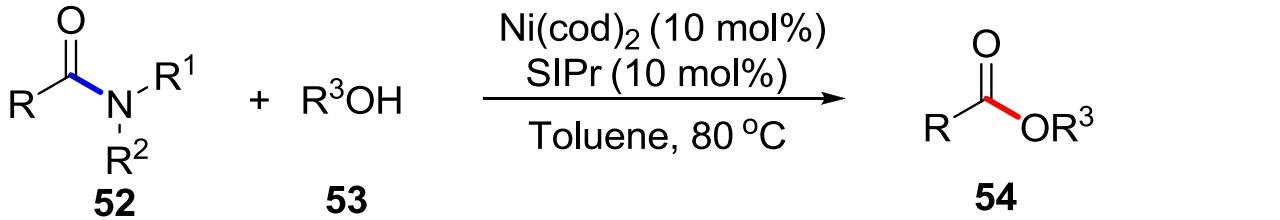


Proposed mechanism for decarboxylative carboamination

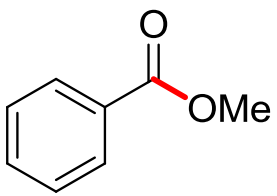
Y. Yoshino, T. Kurahashi and S. Matsubara, *J. Am. Chem. Soc.*, 2009, **131**, 7494

3. Activation of C(sp2)–N bond

3.3 Activation of amidic C(sp^2)–N bond



52 **53** **54**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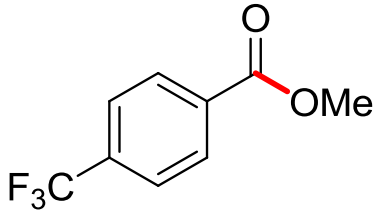
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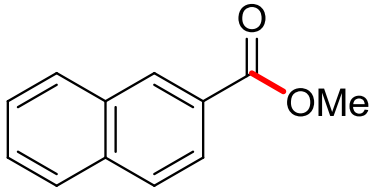
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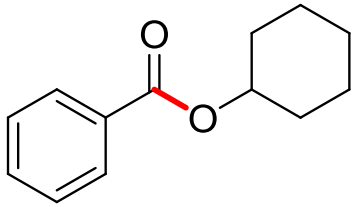
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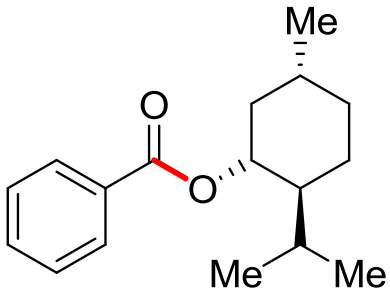
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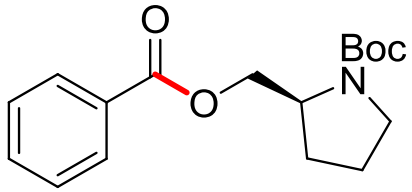
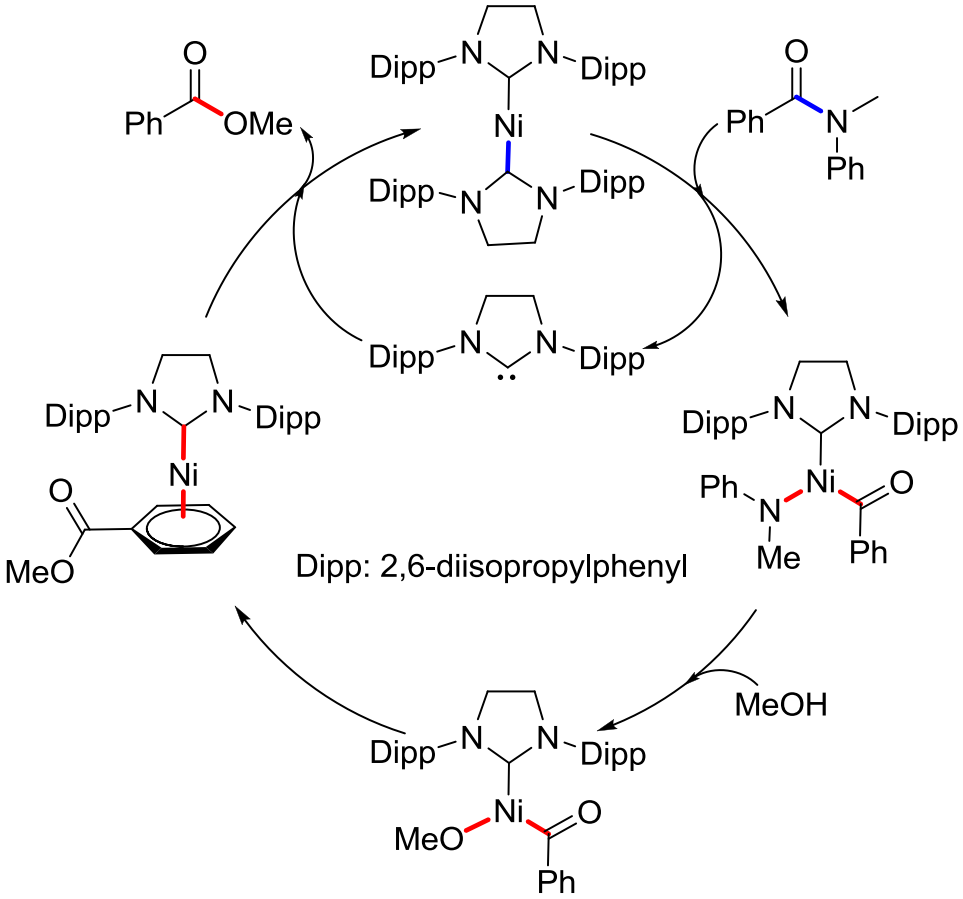

67%

Nickel–catalysed esterification of amides

L. Hie, K. N. Houk and N. K. Garg et al., *Nature*, 2015, **524**, 79

3. Activation of C(sp2)–N bond

3.3 Activation of amidic C(sp^2)–N bond

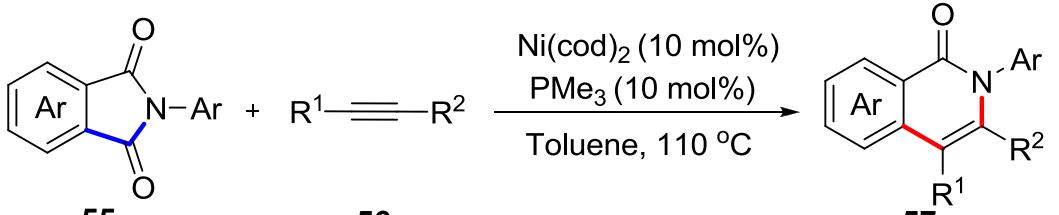


The proposed mechanism esterification of amides

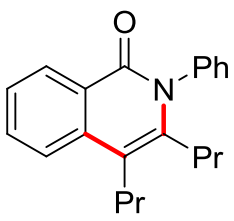
L. Hie, K. N. Houk and N. K. Garg et al., *Nature*, 2015, **524**, 79

3. Activation of C(sp2)–N bond

3.3 Activation of amidic C(sp^2)–N bond



55 **56** **57**



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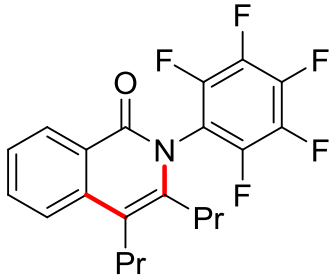

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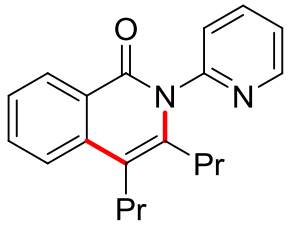

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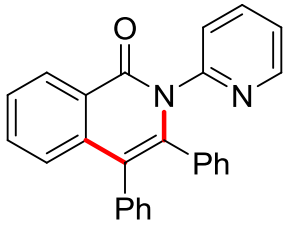

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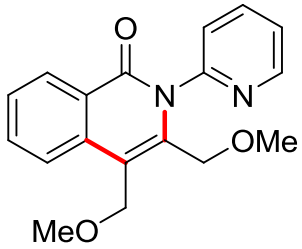
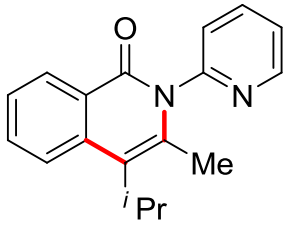


90%



93% (2/1)[a]

[a] Ration of regiosomers

Nickel–catalysed carboamination of alkyne

Y. Kajita, S. Matsubara and T. Kurahashi, *J. Am. Chem. Soc.*, 2008, **130**, 6058

4. Activation of C(sp3)–N bond

4.1 Activation of C(sp^3)–N bond in amine.

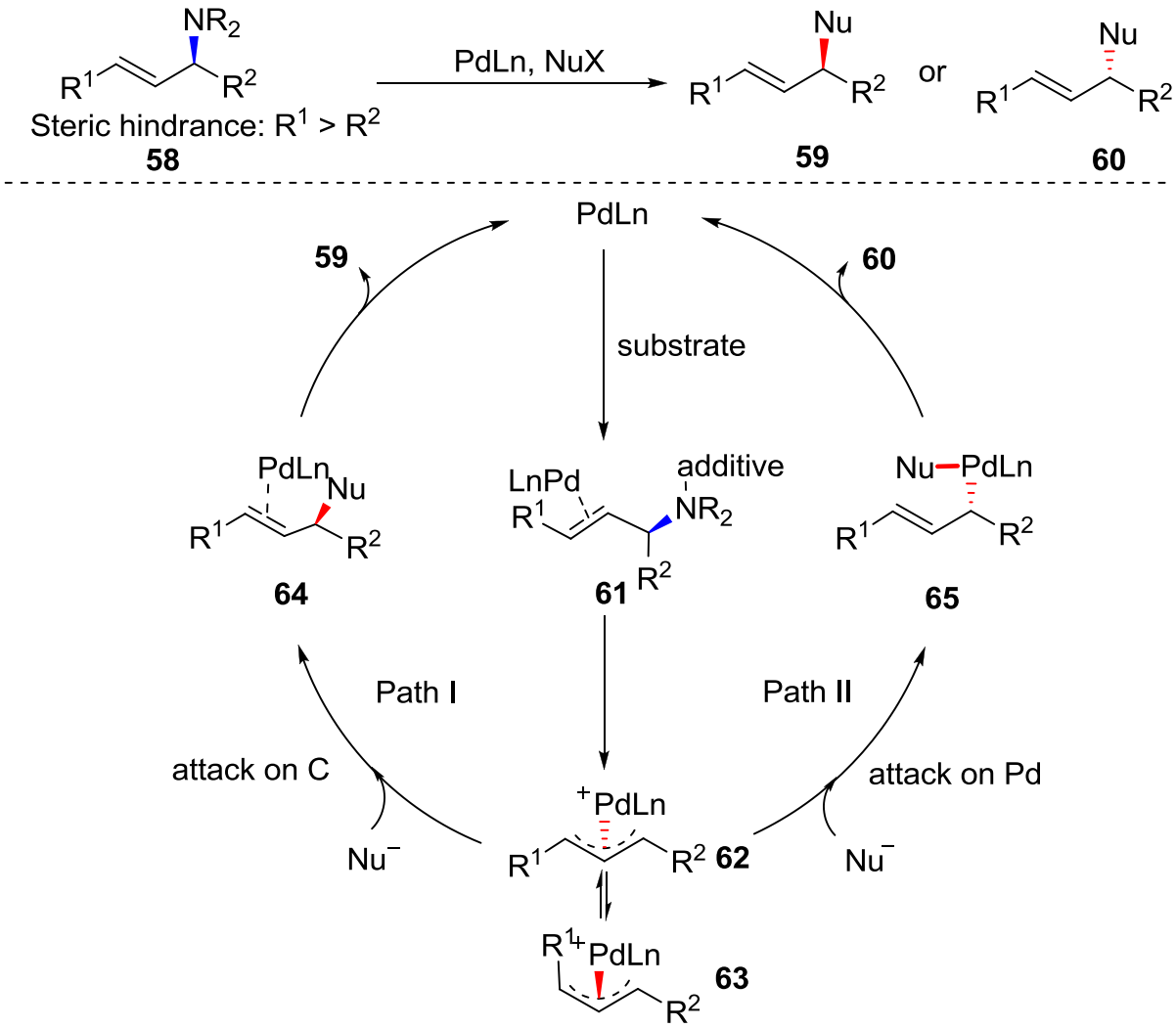
- 4.1.1 Activation of C(sp^3)–N bond in allylic amine
- 4.1.2 Activation of C(sp^3)–N bond in aliphatic amine
- 4.1.3 Activation of C(sp^3)–N bond in aminal

4.2 Activation of C(sp^3)–N bond in aziridine

4.3 Activation of C(sp^3)–N bond in azetidine

4. Activation of C(sp3)−N bond

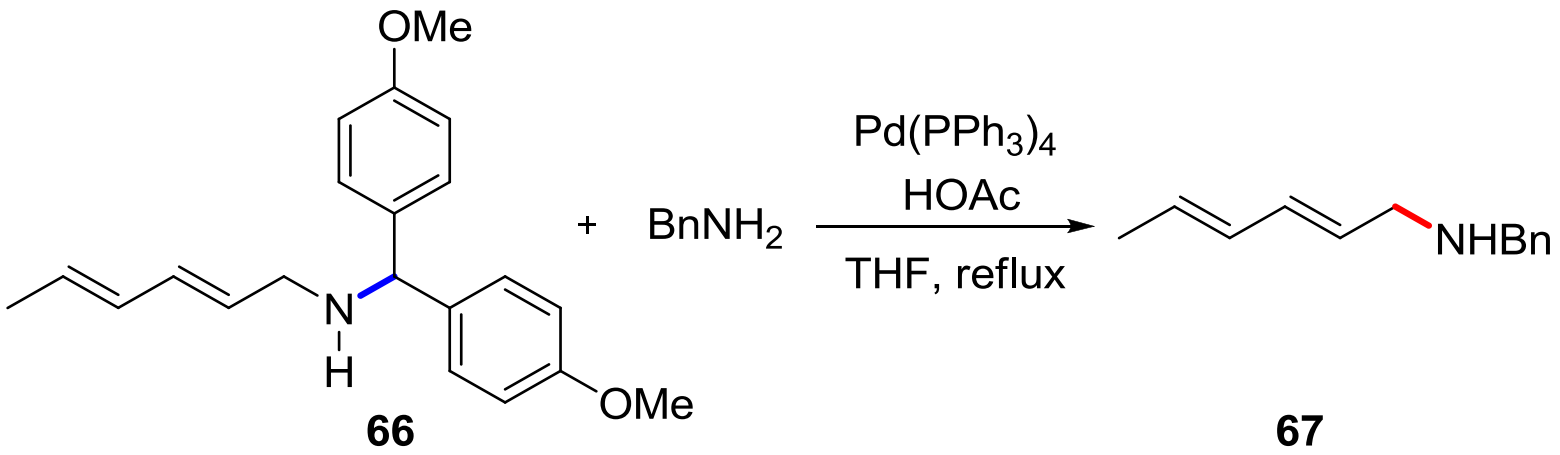
4.1 Activation of C(sp^3)−N bond in amine



Proposed mechanism for C−N bond activation of allylic amines

4. Activation of C(sp3)−N bond

4.1 Activation of C(sp^3)−N bond in amine

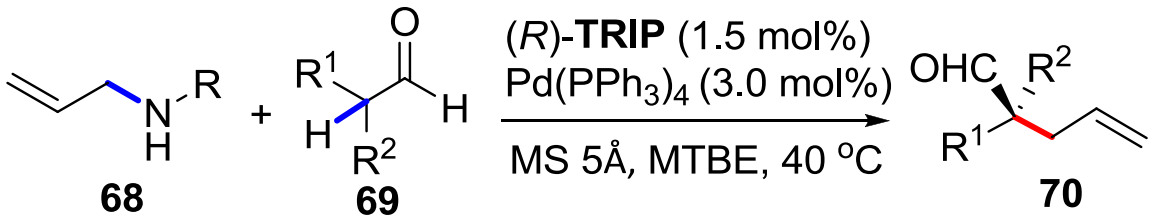


Palladium−catalysed amine exchange reaction of allylic amine

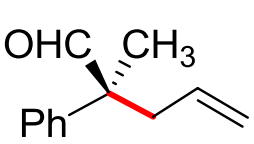
B. M. Trost and E. Keinan, *J. Org. Chem.*, 1980, **45**, 2741

4. Activation of C(sp3)−N bond

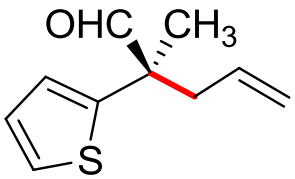
4.1 Activation of C(sp^3)−N bond in amine



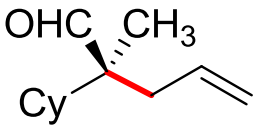
68 **69** **70**



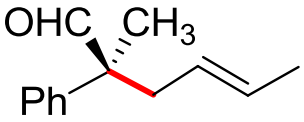
85% , 97% ee



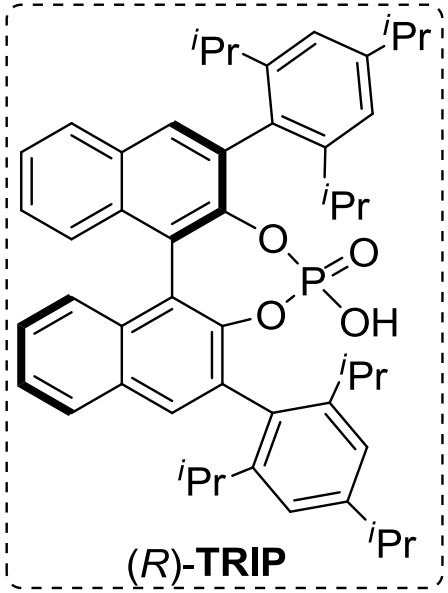
80% , 86% ee



65% , 70% ee



40% , 92% ee

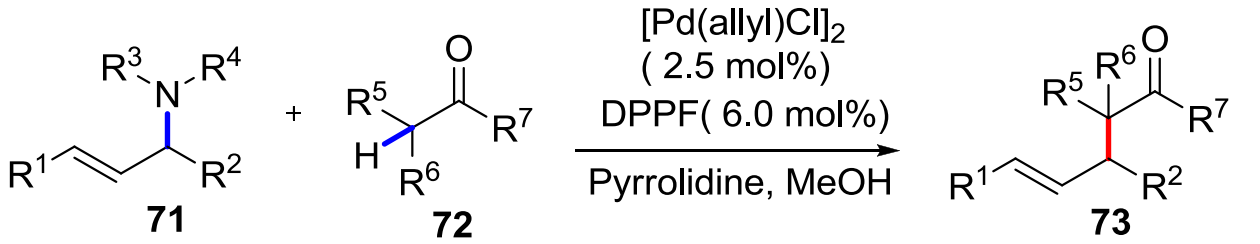


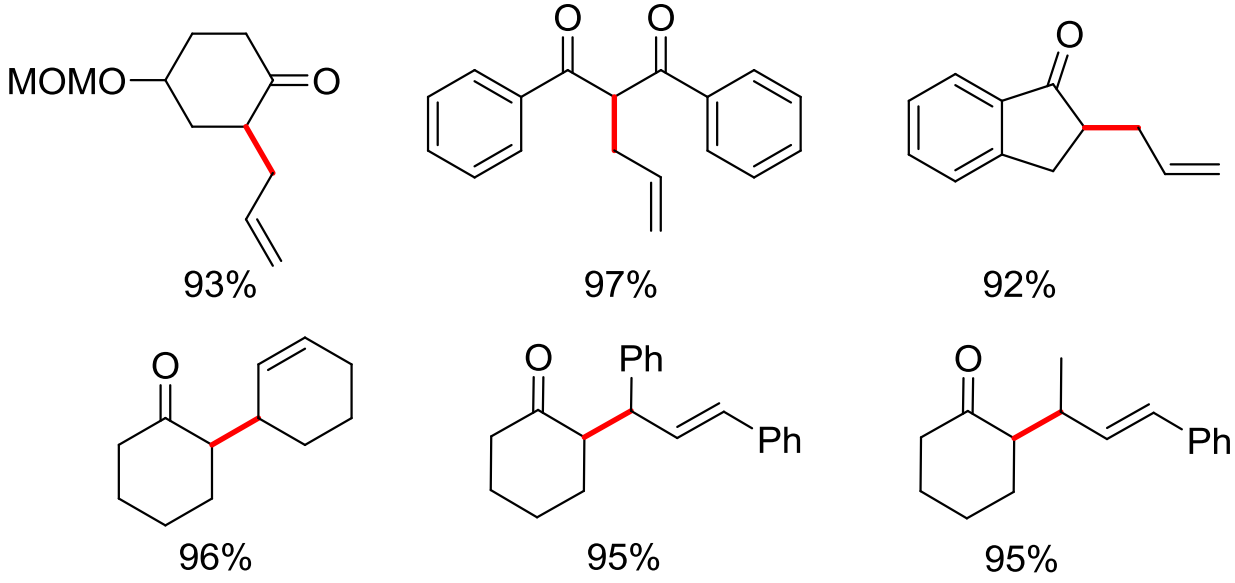
Palladium/Brønsted acid−catalysed allylation reaction of aldehyde

S. Mukherjee and B. List, *J. Am. Chem. Soc.*, 2007, **129**, 11336

4. Activation of C(sp3)−N bond

4.1 Activation of C(sp^3)−N bond in amine



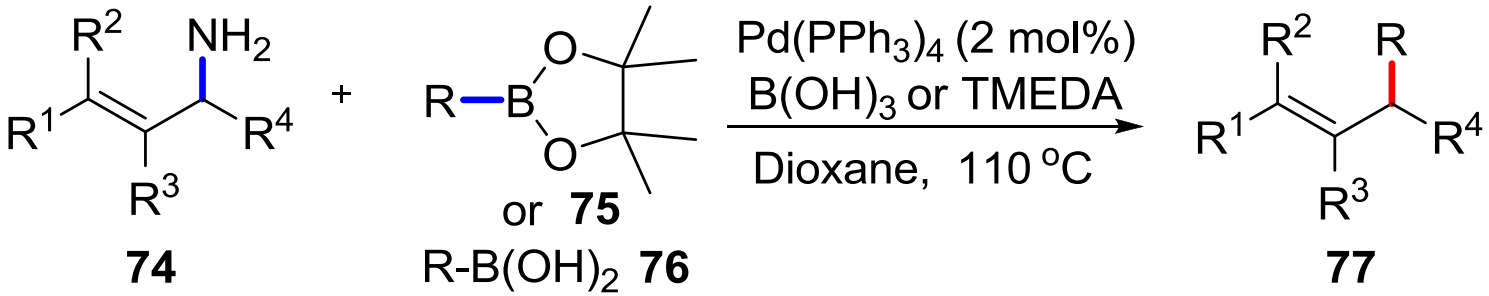


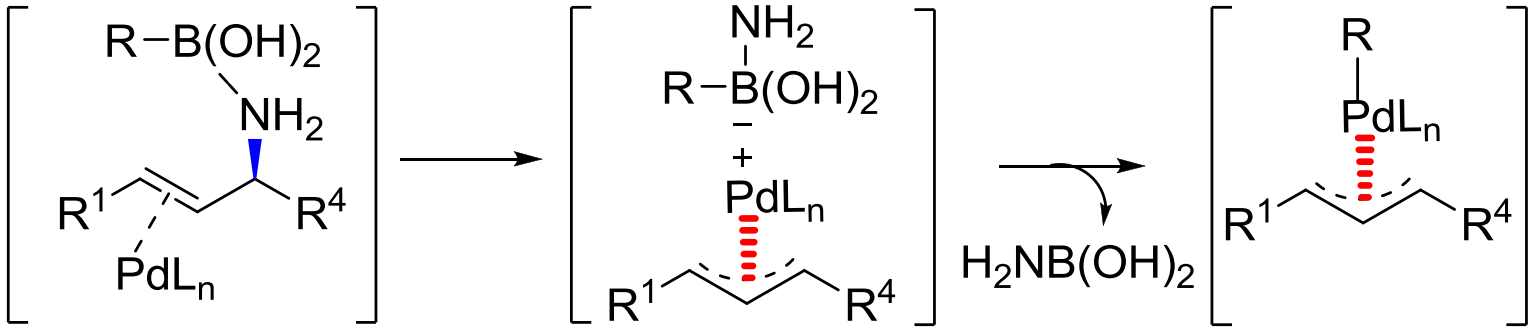
Palladium−catalysed allylic alkylation of carbonyl compounds

X. Zhao, D. Liu, H. Guo, Y. Liu and W. Zhang, *J. Am. Chem. Soc.*, 2011, **133**, 19354

4. Activation of C(sp3)–N bond

4.1 Activation of C(sp³)–N bond in amine



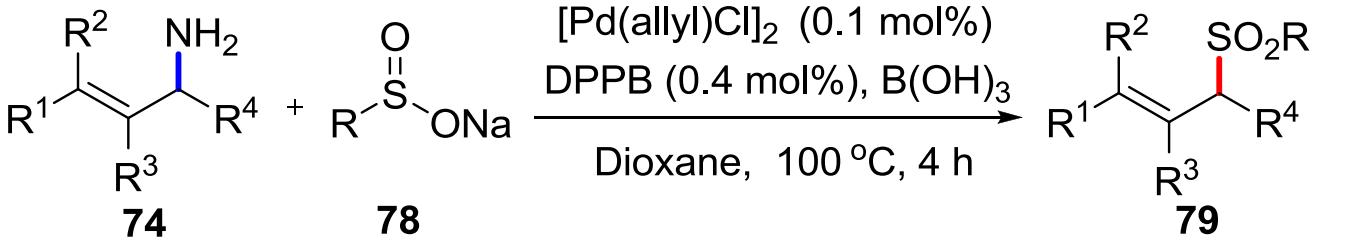


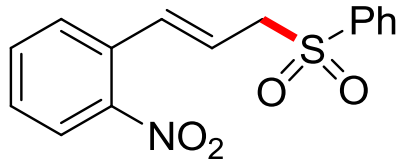
Palladium–catalysed cross–coupling of organoboronic acids

M.-B. Li, Y. Wang and S.-K. Tian, *Angew. Chem., Int. Ed.*, 2012, **51**, 2968

4. Activation of C(sp3)−N bond

4.1 Activation of C(sp³)−N bond in amine





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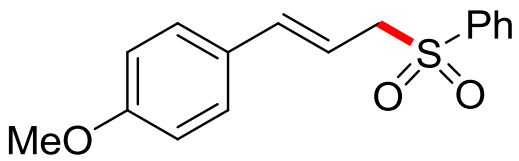

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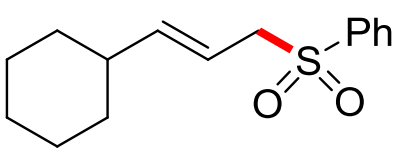
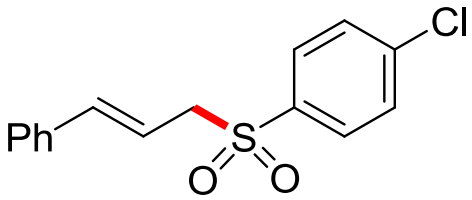


76%



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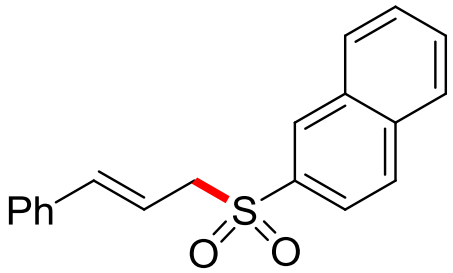


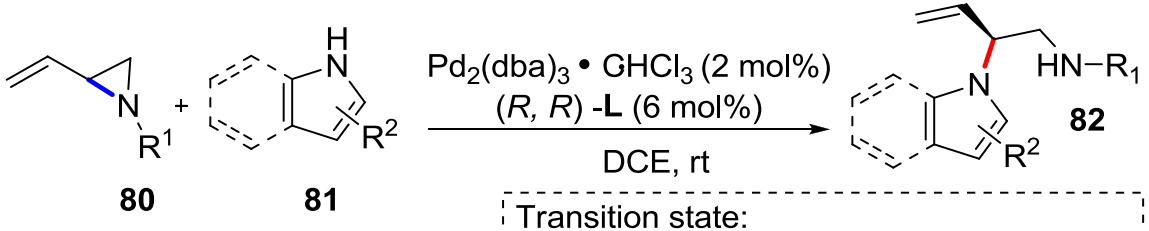
80%

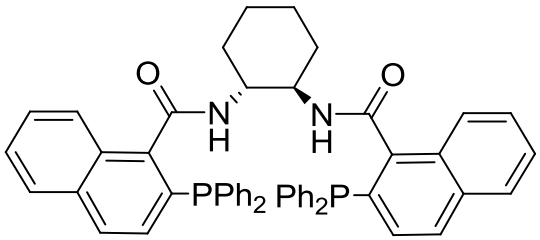
Palladium−catalysed C−N bond activation of allylic amines

X.-S. Wu, Y. Chen, M.-B. Li, M.-G. Zhou and S.-K. Tian, *J. Am. Chem. Soc.*, 2012, **134**, 14694

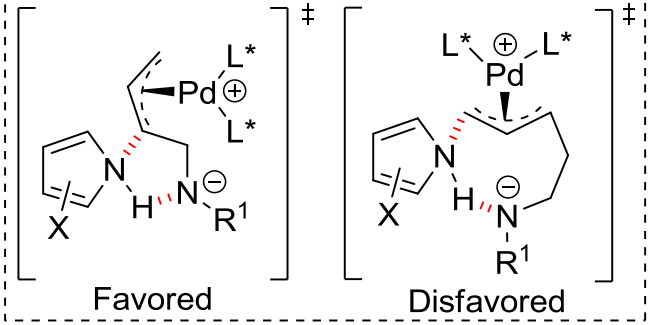
4. Activation of C(sp3)−N bond

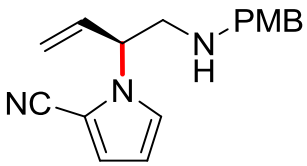
4.1 Activation of C(sp^3)−N bond in amine



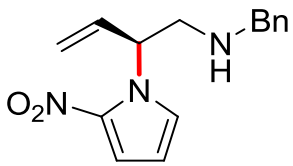


(*R, R*)-**L**

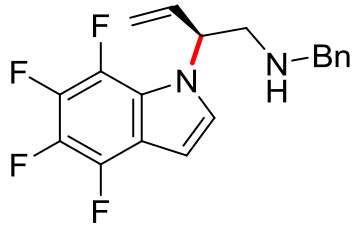




99%, 89% *ee*



77%, 89% *ee*



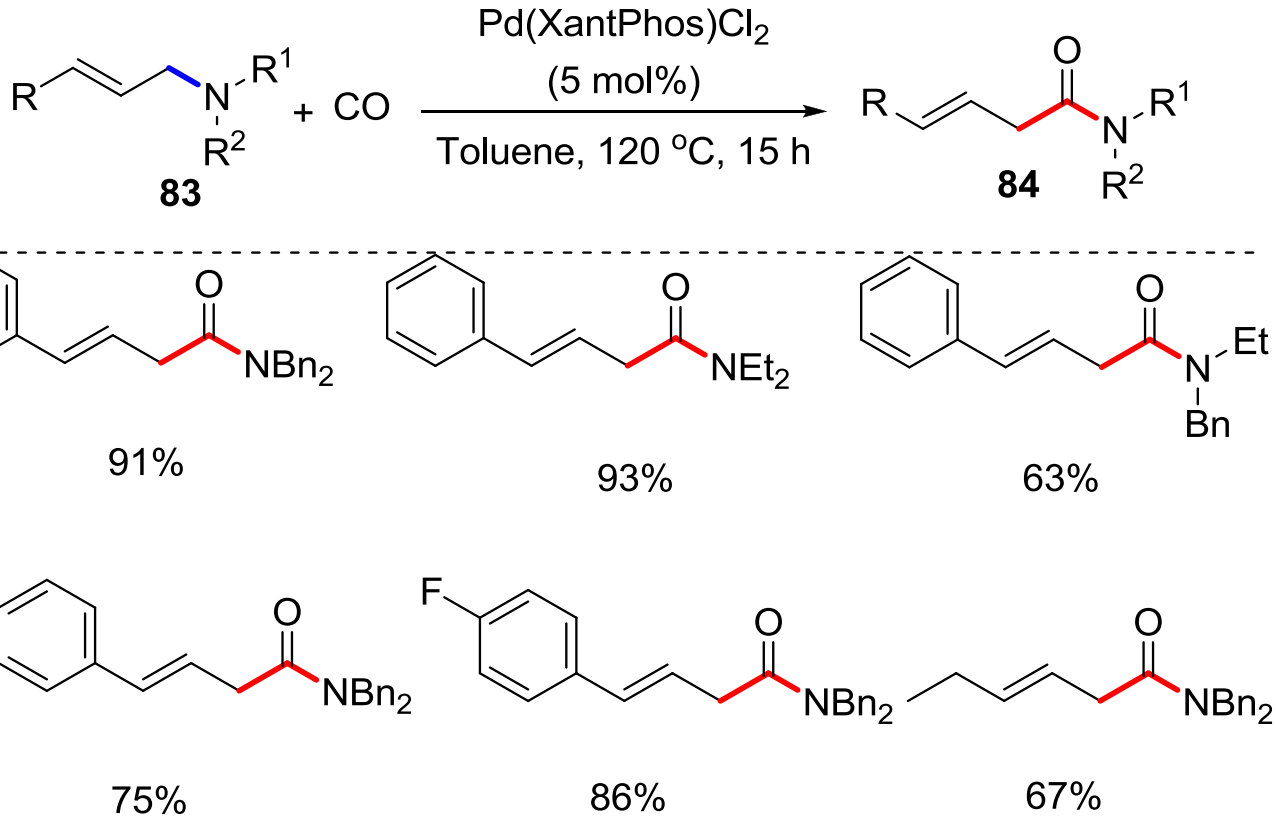
96%, 92% *ee*

Dynamic kinetic asymmetric transformation of vinyl aziridine

B. M. Trost, M. Osipov and G. Dong, *J. Am. Chem. Soc.*, 2010, **132**, 15800

4. Activation of C(sp3)−N bond

4.1 Activation of C(sp^3)−N bond in amine

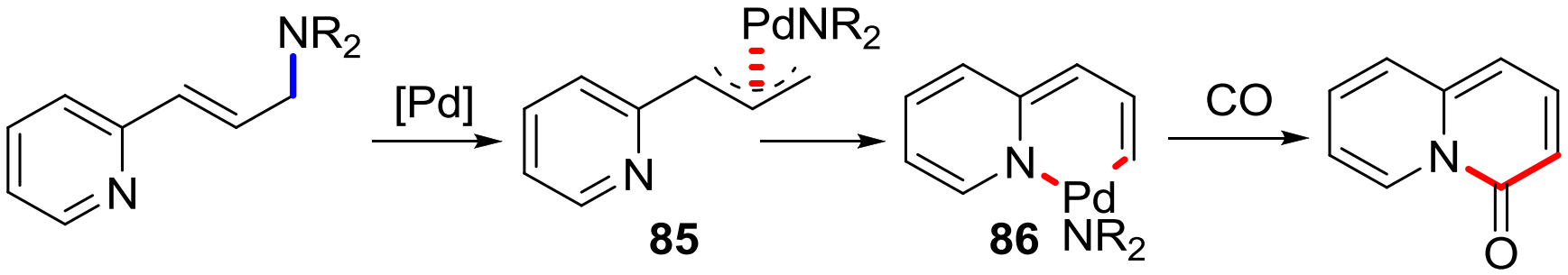


Palladium−catalysed carbonylation of allylamines

H. Yu, G. Zhang, Z.-J. Liu and H. Huang, *RSC Adv.*, 2014, **4**, 64235

4. Activation of C(sp3)–N bond

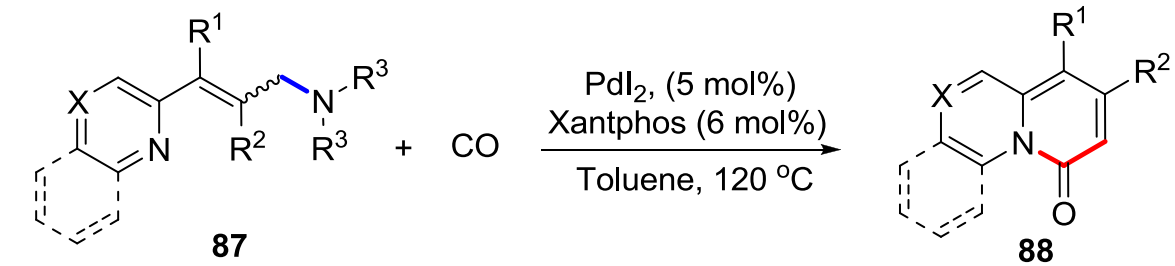
4.1 Activation of C(sp^3)–N bond in amine



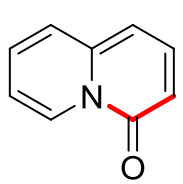
Strategy for palladium–catalysed dearomative cyclocarbonylation

4. Activation of C(sp3)−N bond

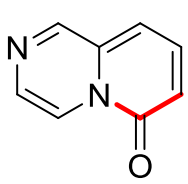
4.1 Activation of C(sp^3)−N bond in amine



87 88



87%



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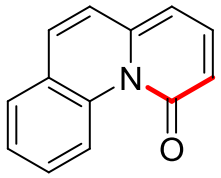

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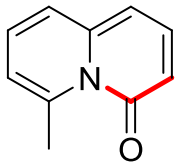

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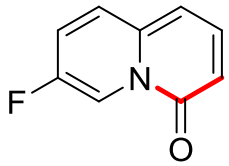

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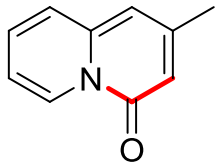

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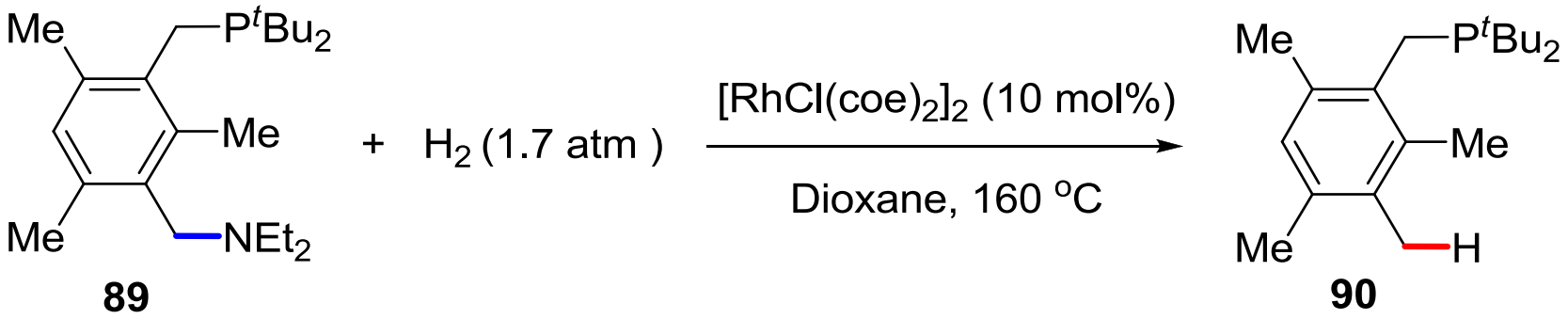
Palladium−catalysed dearomative cyclocarbonylation

H. Yu, G. Zhang and H. Huang, *Angew. Chem., Int. Ed.,* 2015, **54**, 10912

4. Activation of C(sp3)−N bond

4.1 Activation of C(sp^3)−N bond in amine

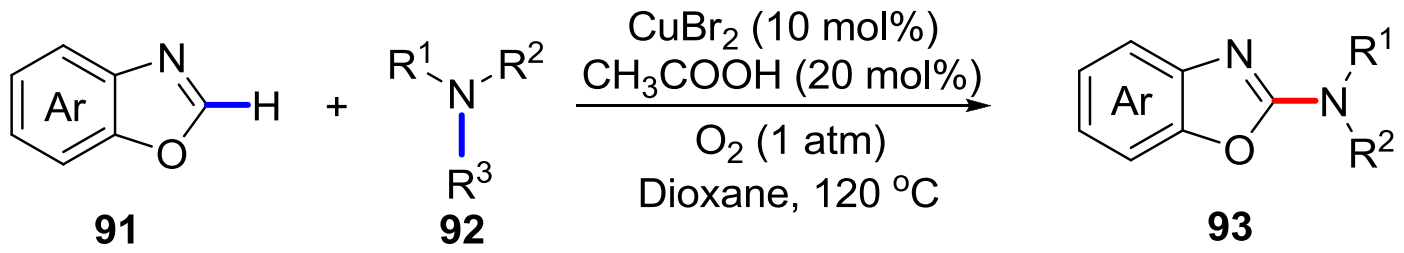


Rhodium−catalysed hydro−denitrogenation

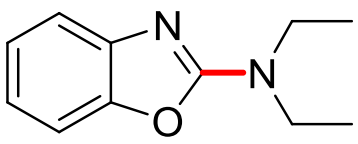
M. Gandelman and D. Milstein, *Chem. Commun.,* 2000, 1603

4. Activation of C(sp3)−N bond

4.1 Activation of C(sp^3)−N bond in amine



91 **92** **93**



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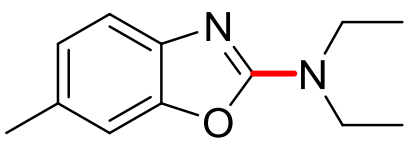

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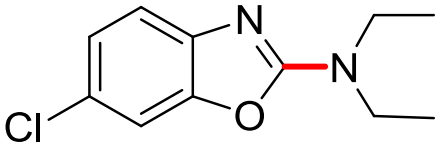

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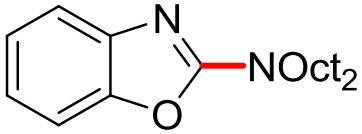

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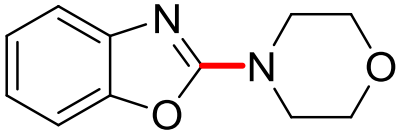

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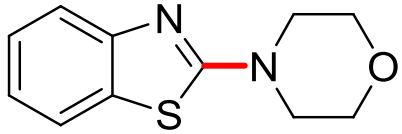

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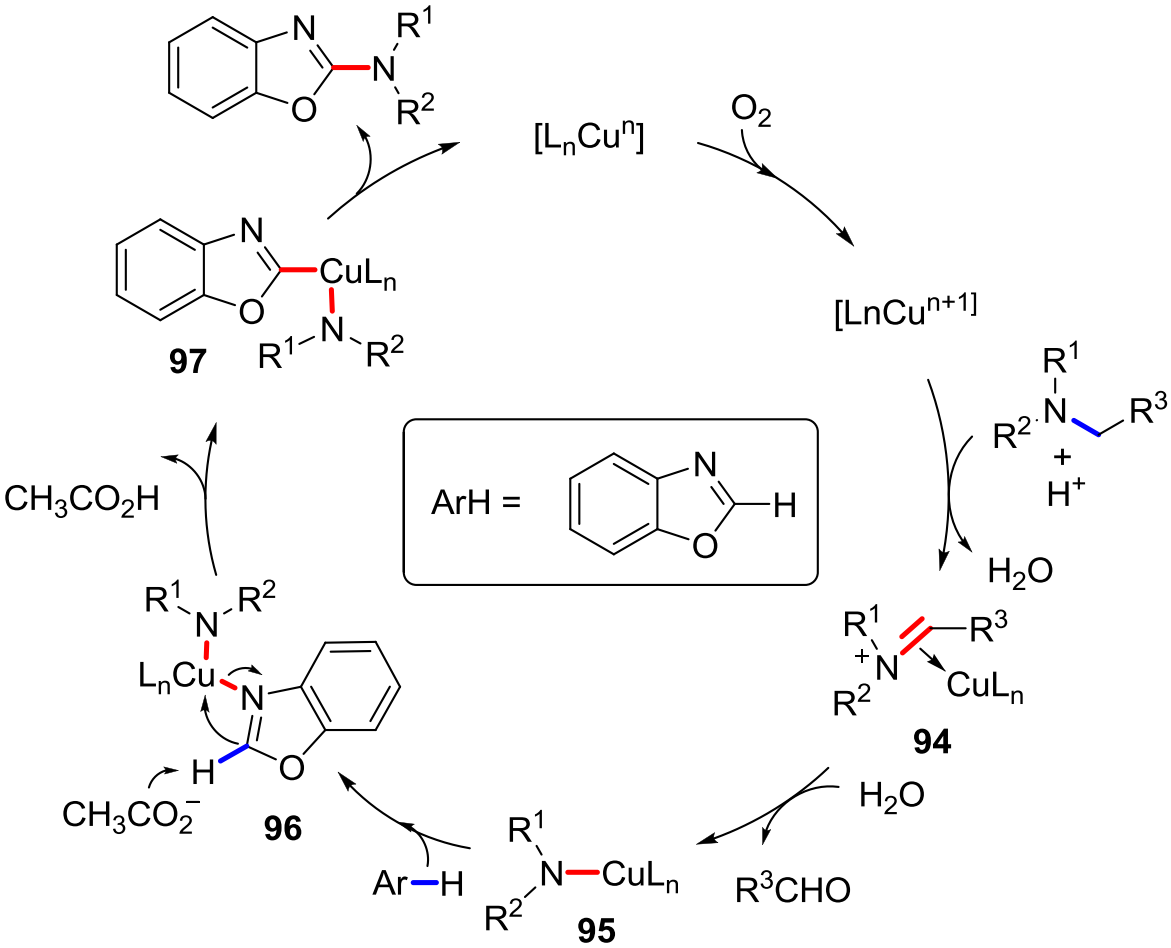
Copper−catalysed oxidative amination of azoles with tertiary amines

S. Guo, B. Qian, Y. Xie, C. Xia and H. Huang, *Org. Lett.,* 2011, **13**, 522

4. Activation of C(sp3)−N bond

4.1 Activation of C(sp³)−N bond in amine

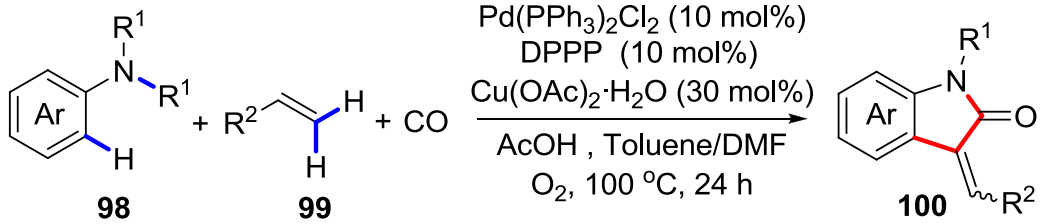


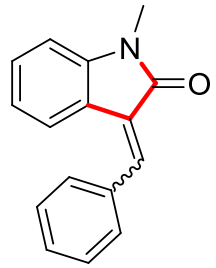
Proposed mechanism for copper−catalysed oxidative amination

S. Guo, B. Qian, Y. Xie, C. Xia and H. Huang, *Org. Lett.*, 2011, **13**, 522

4. Activation of C(sp3)−N bond

4.1 Activation of C(sp^3)−N bond in amine





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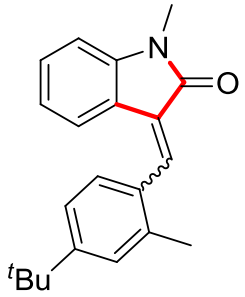

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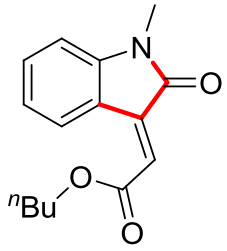

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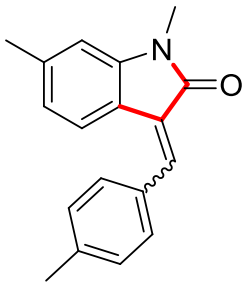

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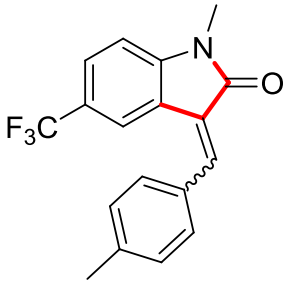

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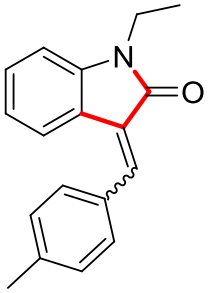


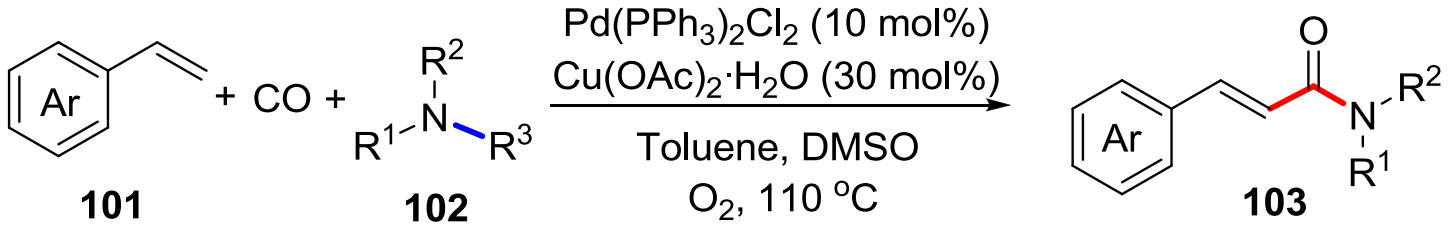
63% (2.7/1)

Oxidative C−H alkenylation/*N*−dealkylative carbonylation

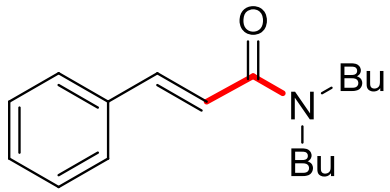
R. Shi, L. Lu, H. Zhang, B. Chen, Y. Sha, C. Liu and A. Lei, *Angew. Chem., Int. Ed.*, 2013, **52**, 10582

4. Activation of C(sp3)−N bond

4.1 Activation of C(sp³)−N bond in amine



101 **102** **103**



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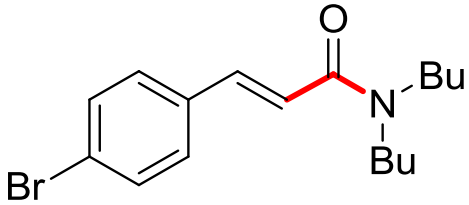

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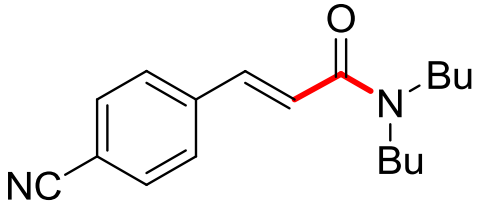

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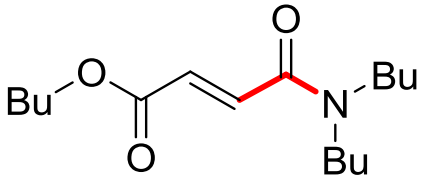

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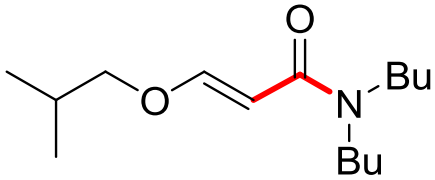

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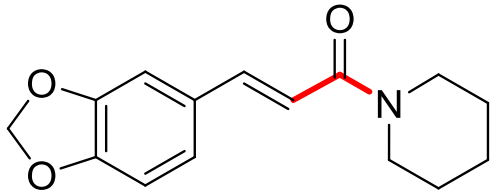

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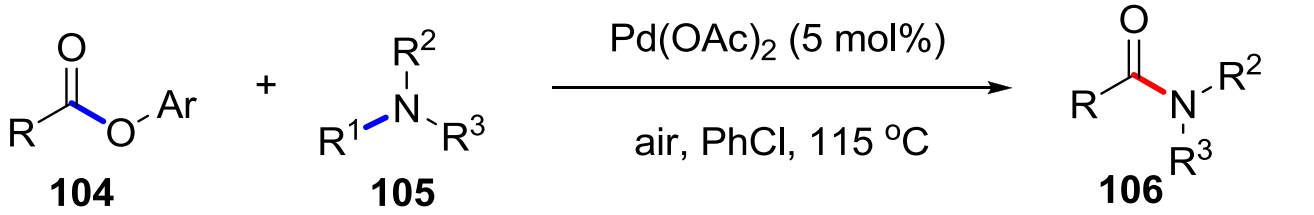
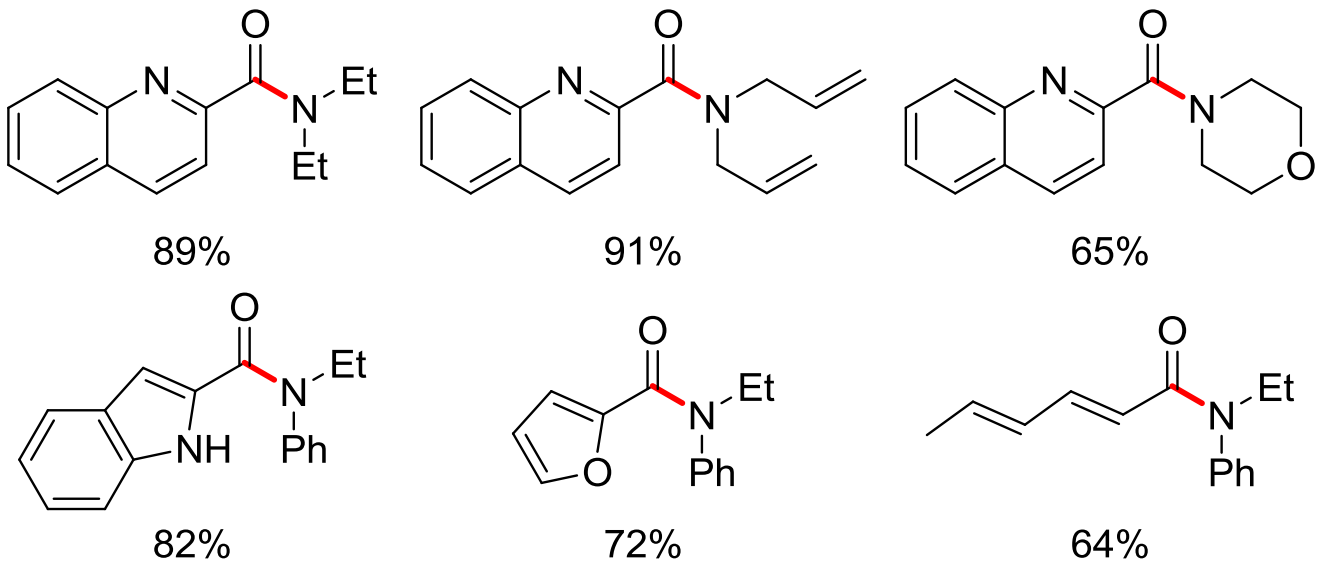
Intermolecular oxidative *N*–alkylative carbonylation

R. Shi, M. Beller and A. Lei et al., *Chem. Commu.,* 2015, **51**, 3247

4. Activation of C(sp3)–N bond

4.1 Activation of C(sp^3)–N bond in amine



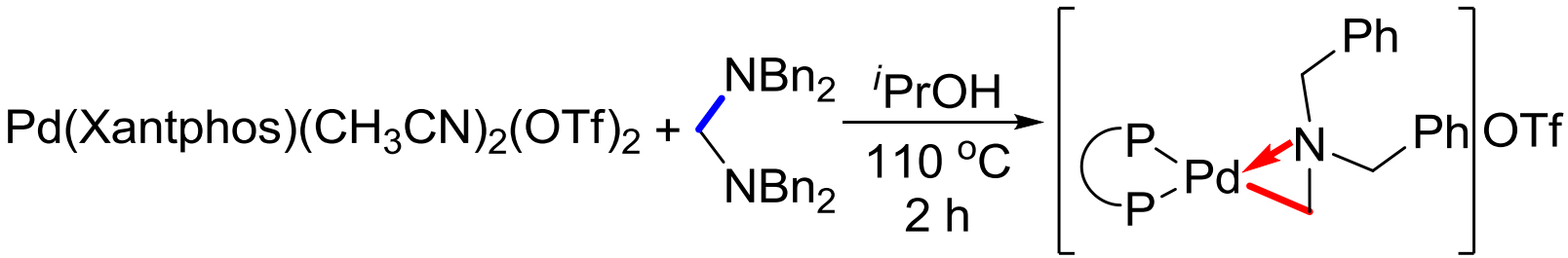


Palladium–catalysed oxidative coupling

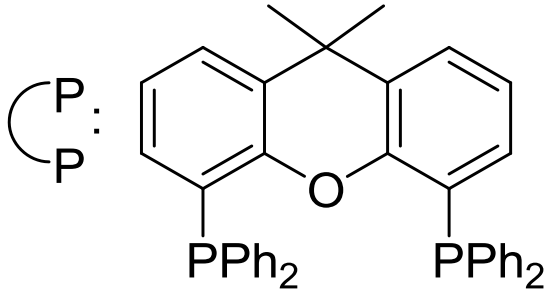
Y.-S. Bao, B. Zhaorigetu, B. Agula, M. Baiyin and M. Jia, *J. Org. Chem.,* 2014, **79**, 803

4. Activation of C(sp3)−N bond

4.1 Activation of C(sp^3)−N bond in amine



107 **108** **109**



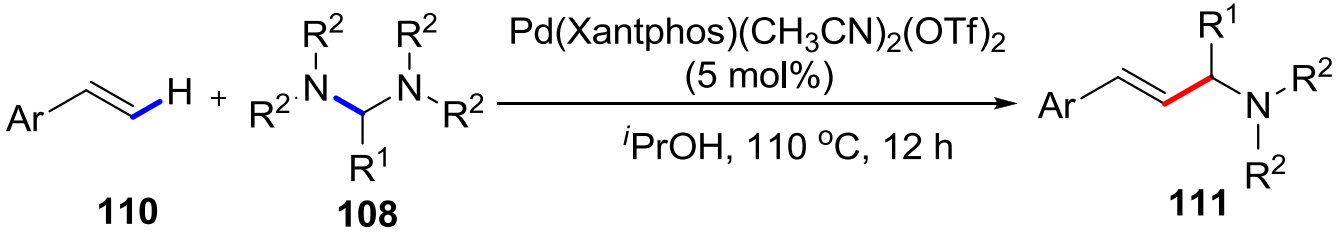
Xantphos

Synthesis of three−membered cyclopalladated complex

Y. Xie, J. Hu, Y. Wang, C. Xia and H. Huang, *J. Am. Chem. Soc.*, 2012, **134**, 20613

4. Activation of C(sp3)−N bond

4.1 Activation of C(sp^3)−N bond in amine



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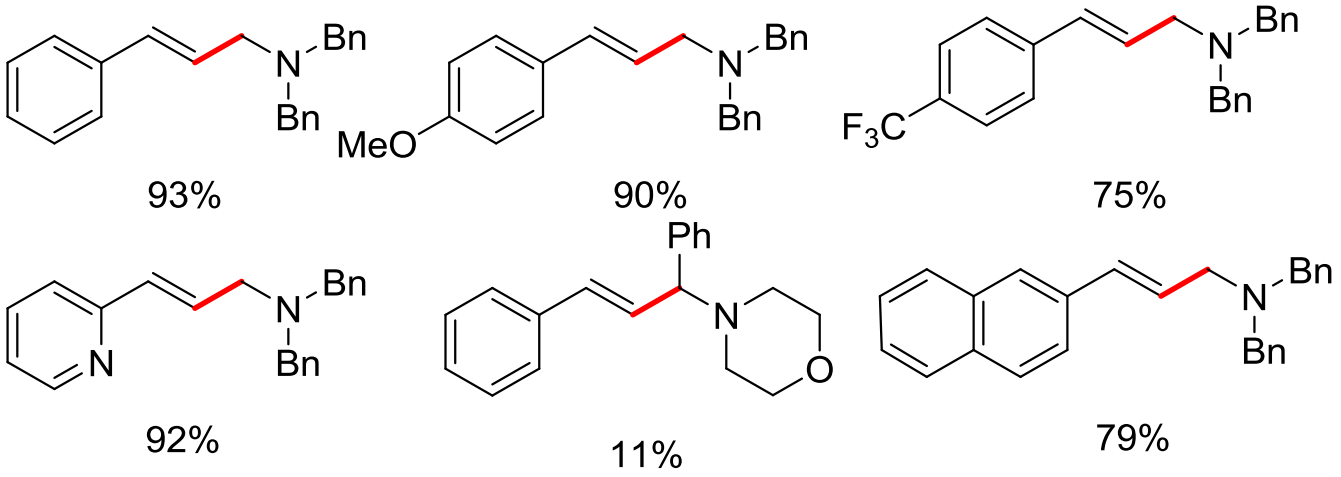
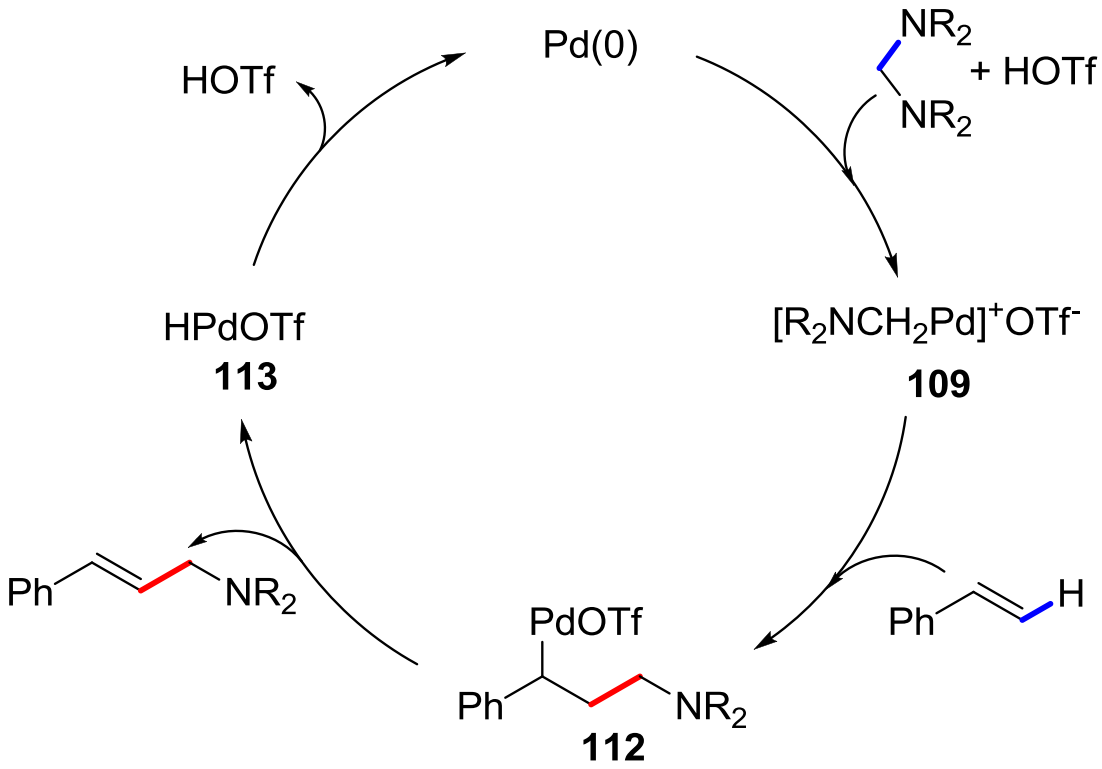


Palladium−catalysed vinylation of aminals

Y. Xie, J. Hu, Y. Wang, C. Xia and H. Huang, *J. Am. Chem. Soc.*, 2012, **134**, 20613

4. Activation of C(sp3)−N bond

4.1 Activation of C(sp^3)−N bond in amine



Proposed mechanism for Pd−catalysed vinylation of aminals

Y. Xie, J. Hu, Y. Wang, C. Xia and H. Huang, *J. Am. Chem. Soc.*, 2012, **134**, 20613

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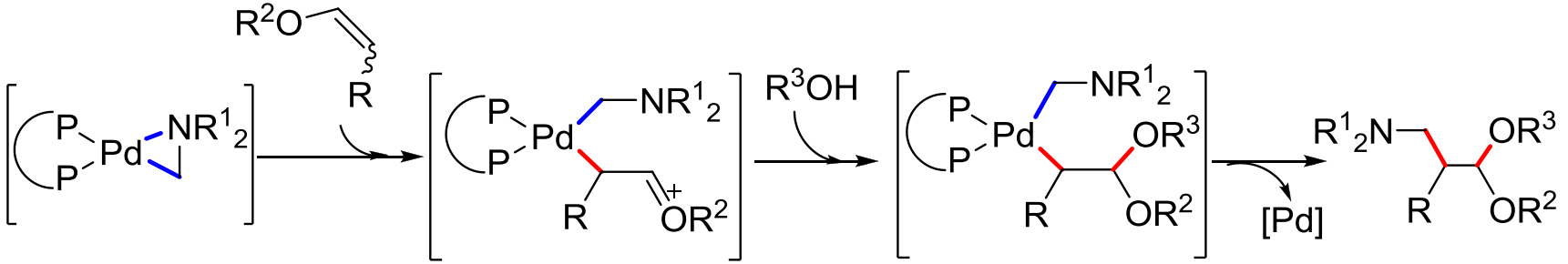


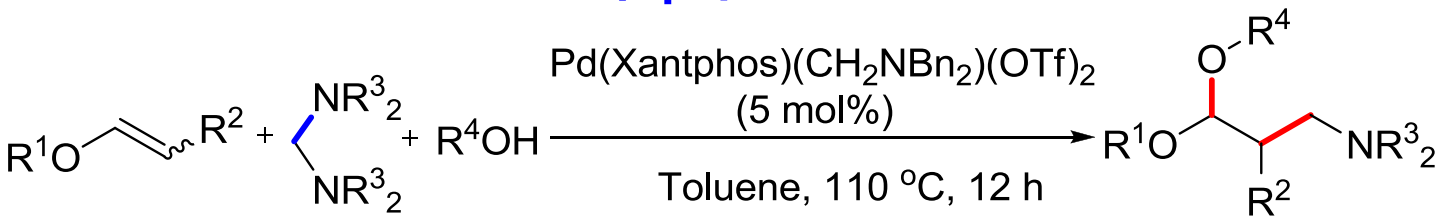
114 115

New strategy for difunctionalization of enol ethers

Y. Xie, J. Hu, P. Xie, B. Qian and H. Huang, *J. Am. Chem. Soc.,* 2013, **135,** 18327

4. Activation of C(sp3)−N bond

4.1 Activation of C(sp³)−N bond in amine



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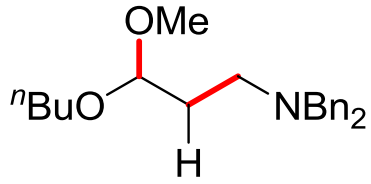

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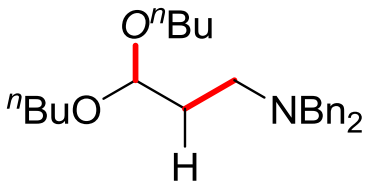

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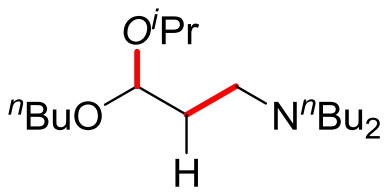

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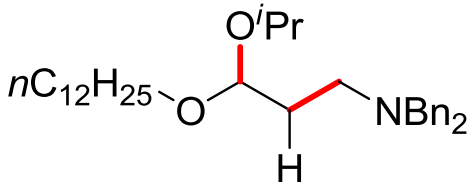

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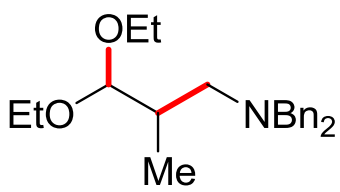

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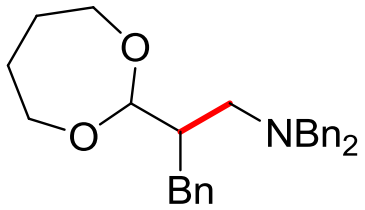

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Palladium−catalysed difunctionlization of enol ethers

Y. Xie, J. Hu, P. Xie, B. Qian and H. Huang, *J. Am. Chem. Soc.,* 2013, **135,** 18327

4. Activation of C(sp3)−N bond

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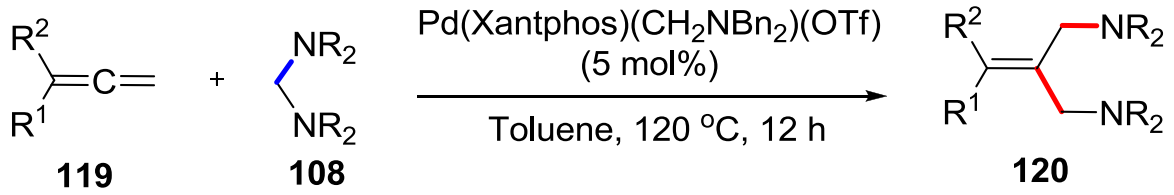

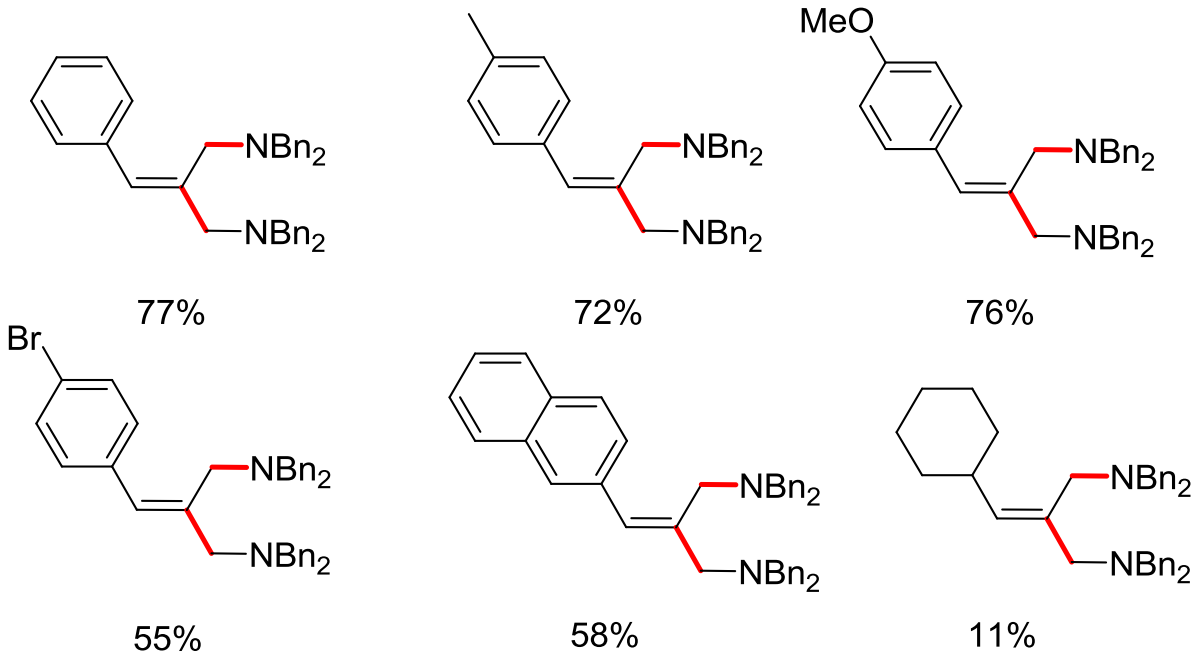

Palladium−catalysed difunctionalization of allenes with aminals

J. Hu, Y. Xie and H. Huang, *Angew. Chem., Int. Ed.*, 2014, **53**, 7272

4. Activation of C(sp3)−N bond

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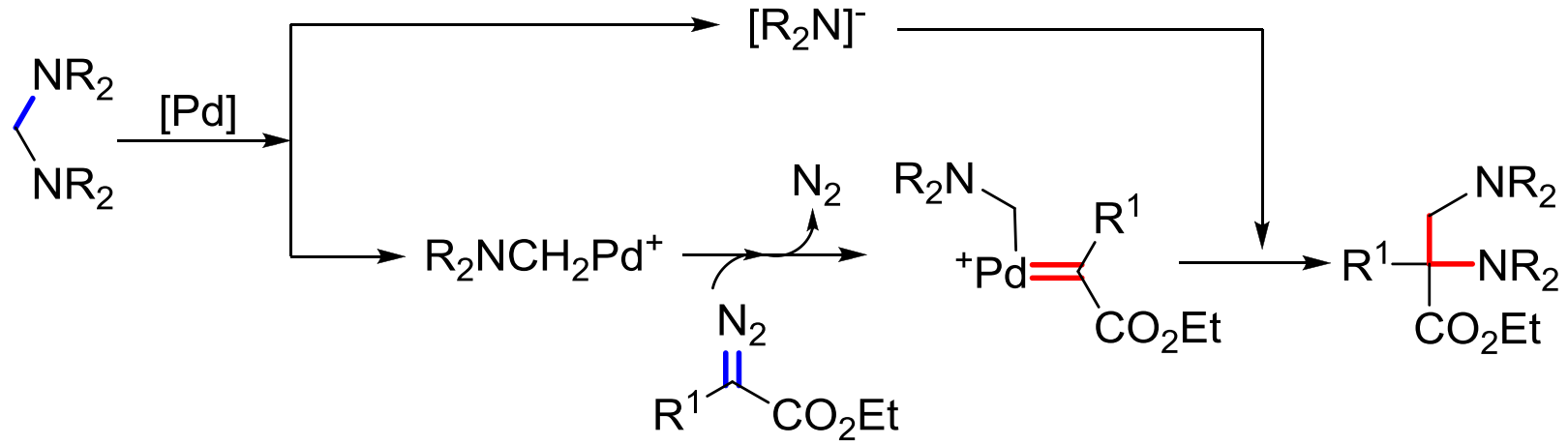
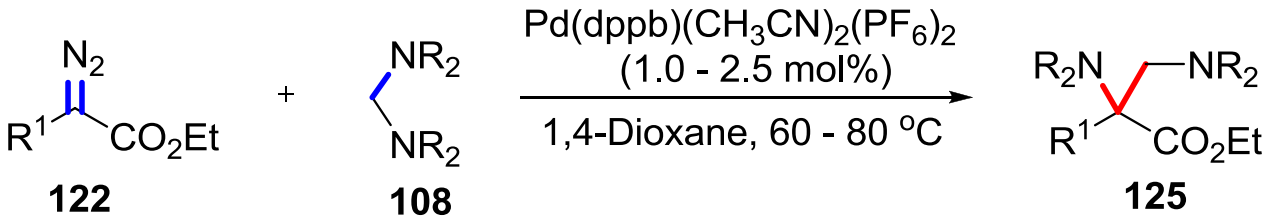


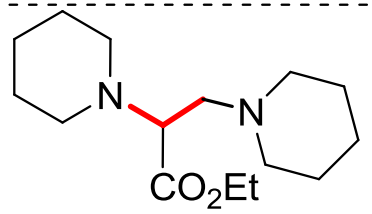
New strategy for insertion of C−N bond of aminal to carbenoid

G. Qin, L. Li, J. Li and H. Huang, *J. Am. Chem. Soc.*, 2015, ***137***, 12490

4. Activation of C(sp3)−N bond

4.1 Activation of C(sp^3)−N bond in amine





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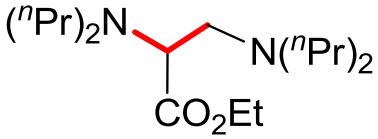

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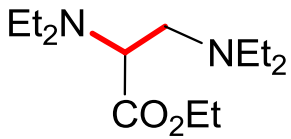

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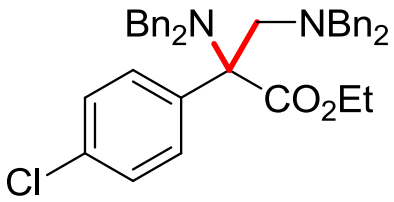

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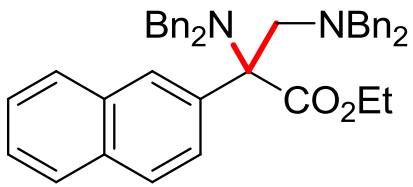

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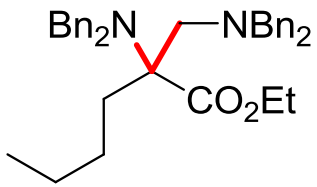

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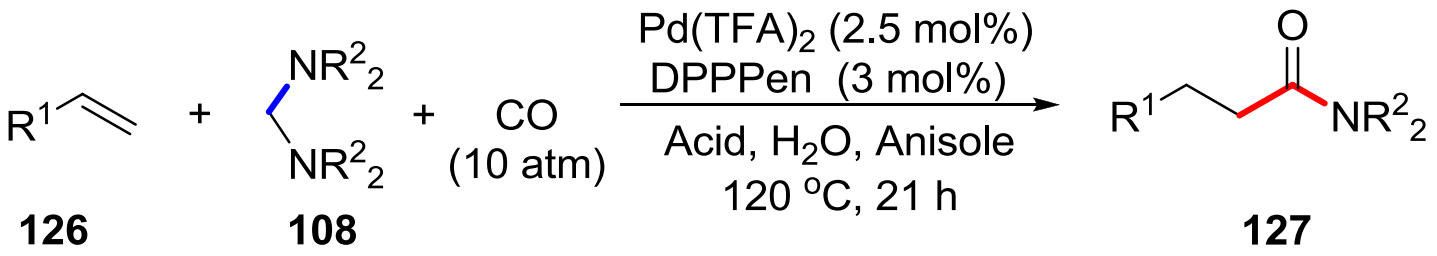
Palladium−catalysed formal insertion of carbenoids into Aminals

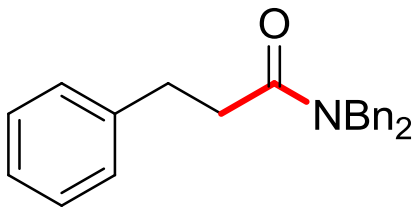
G. Qin, L. Li, J. Li and H. Huang, *J. Am. Chem. Soc.*, 2015, ***137***, 12490

4. Activation of C(sp3)−N bond

4.1 Activation of C(sp^3)−N bond in amine



126 **108** **127**



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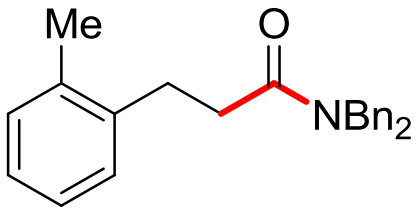

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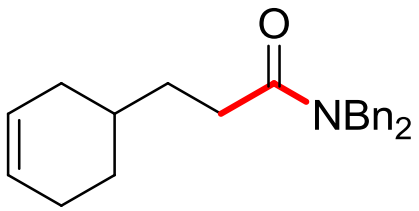

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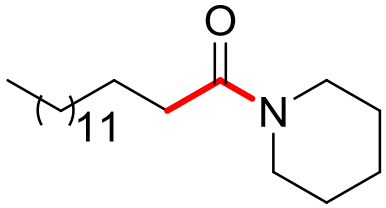

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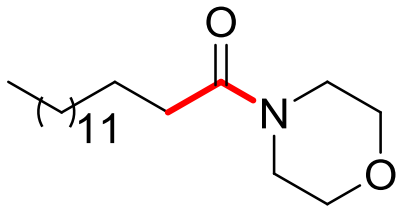

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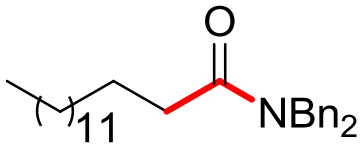


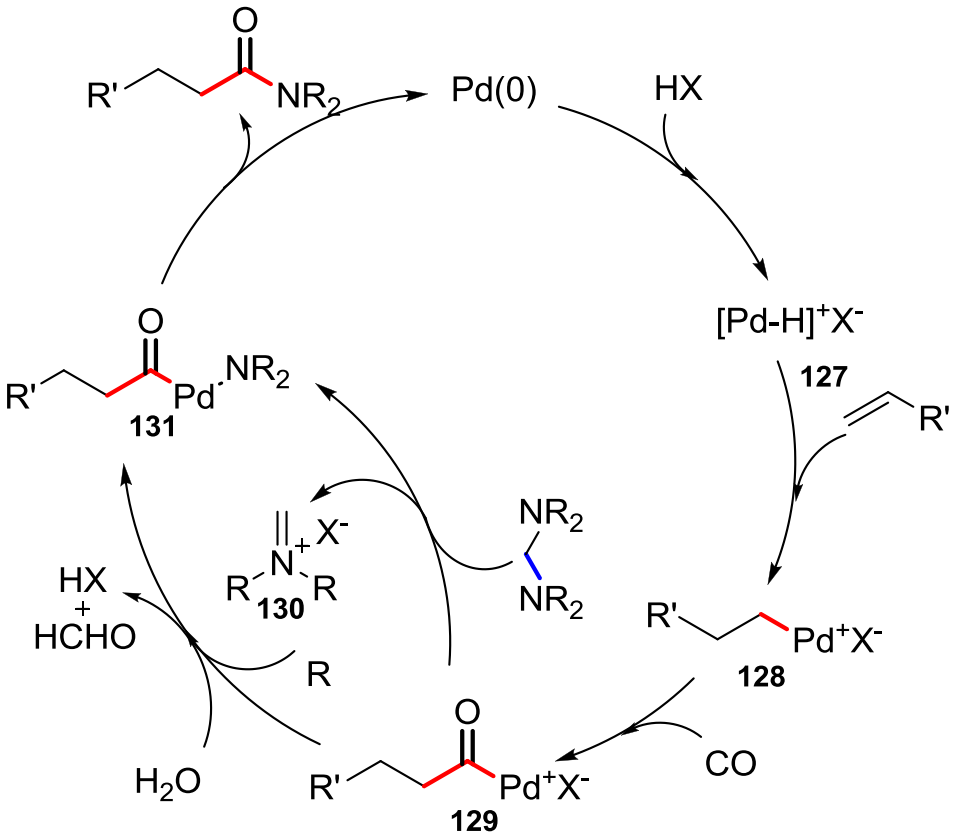
84%

Palladium−catalysed hydroaminocarbonylation of simple alkenes

G. Zhang, B. Gao and H. Huang, *Angew. Chem., Int. Ed.*, 2015, **54**, 7657

4. Activation of C(sp3)−N bond

4.1 Activation of C(sp^3)−N bond in amine



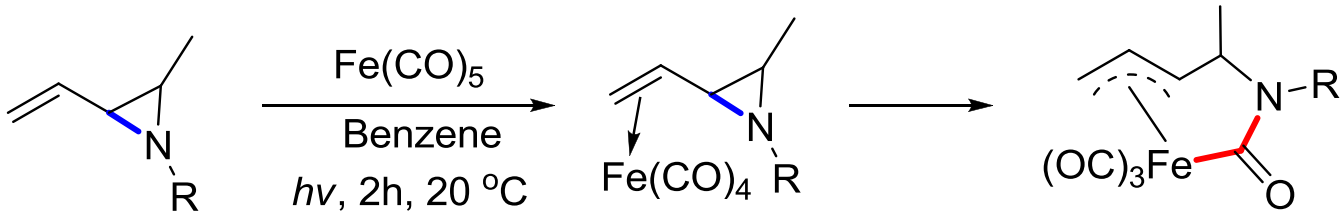
Proposed mechanism for hydroaminocarbonylation

G. Zhang, B. Gao and H. Huang, *Angew. Chem., Int. Ed.*, 2015, **54**, 7657

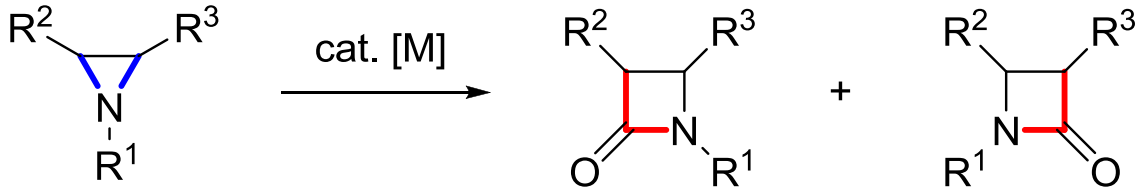
4. Activation of C(sp3)−N bond

4.2 Activation of C(sp^3)−N bond in aziridines

Aumann's stoichiometric reaction



Alper's transition-metal catalyzed carbonylative ring expansion of aziridine



[M] = [Rh], [Pd] and [Co]

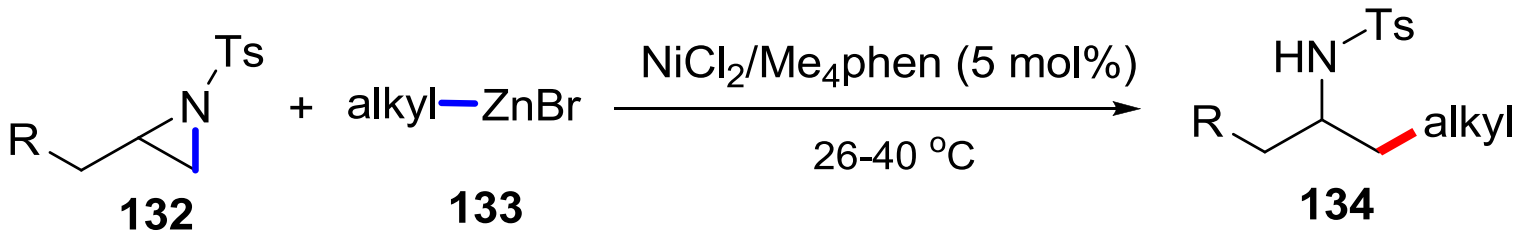
Transition−metal catalysed carbonylative ring expansion of aziridine

R. Aumann, K. Fröhlich and H. Ring, *Angew. Chem., Int. Ed*., 1974, **13**, 275

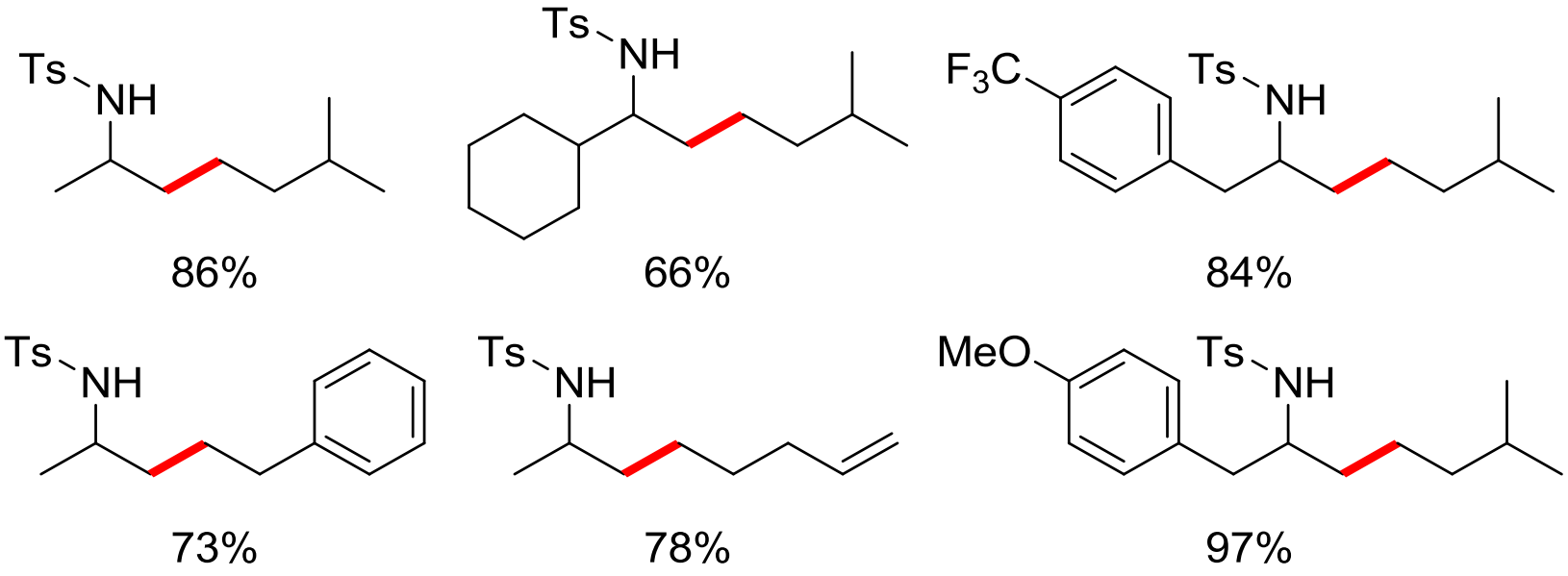
C.-Y. Huang and A. G. Doyle, *Chem. Rev*., 2014, **114**, 8153

4. Activation of C(sp3)–N bond

4.2 Activation of C(sp^3)–N bond in aziridines



132 **133** **134**

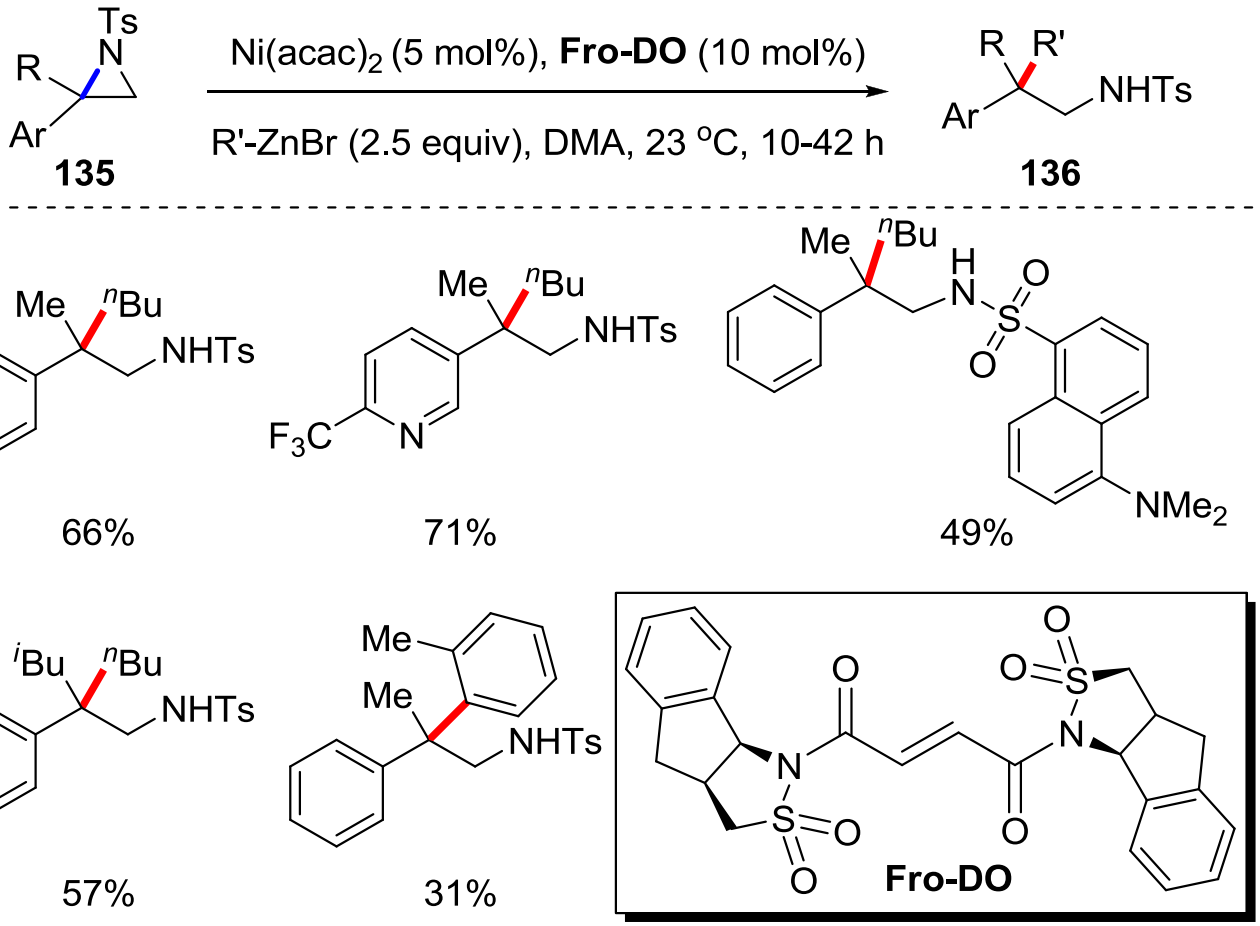


Nickel–catalysed Negishi–type coupling reaction of aziridines

K. L. Jensen, E. A. Standley and T. F. Jamison, *J. Am. Chem. Soc.,* 2014, **136**, 11145

4. Activation of C(sp3)–N bond

4.2 Activation of C(sp^3)–N bond in aziridines

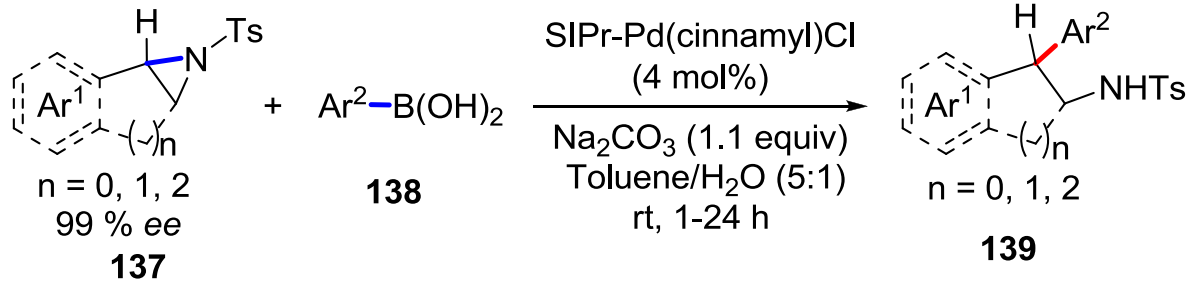


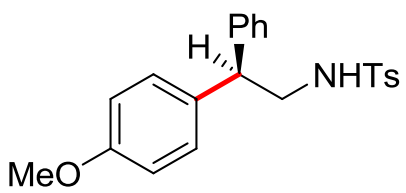
Nickel–catalysed Negishi–type coupling reaction of aziridines

C.-Y. Huang and A. G. Doyle, *J. Am. Chem. Soc.*, 2015, **137**, 5638

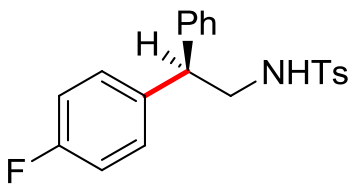
4. Activation of C(sp3)–N bond

4.2 Activation of C(sp^3)–N bond in aziridines

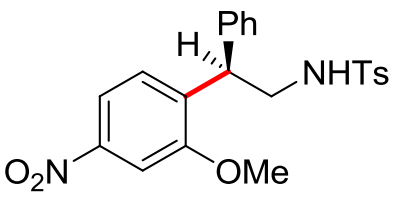




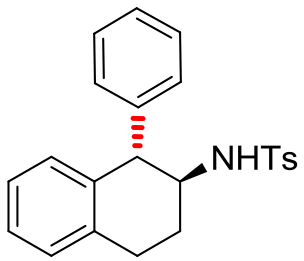
98%, 99% ee



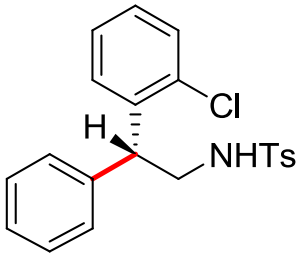
84%, 99% ee



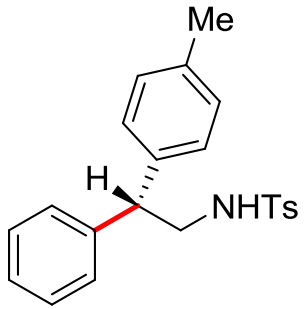
82%, 99% ee



62%, 99% ee



85%, 99% ee



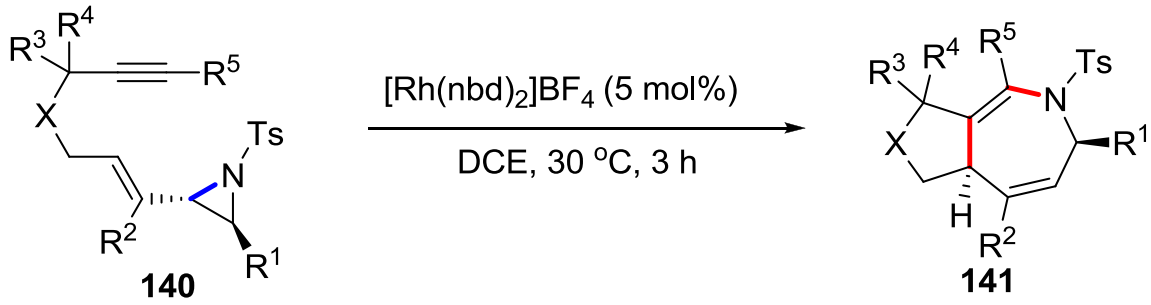
87%, 99% ee

Palladium–catalysed Suzuki–type coupling reaction

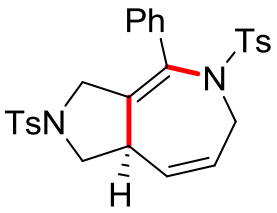
Y. Takeda, Y. Ikeda, A. Kuroda, S. Tanaka and S. Minakata, *J. Am. Chem. Soc.*, 2014, **136,** 8544

4. Activation of C(sp3)–N bond

4.2 Activation of C(sp^3)–N bond in aziridines



140 141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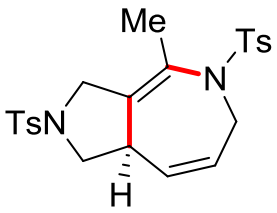
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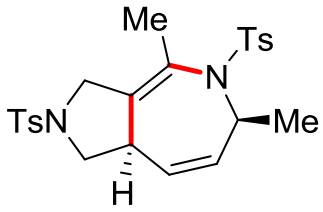
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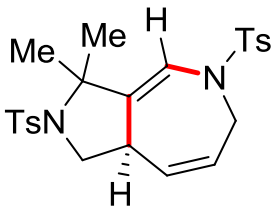
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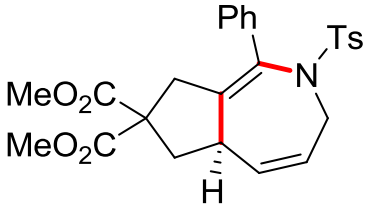
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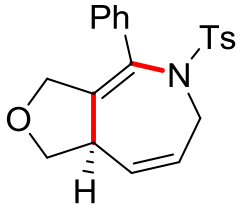
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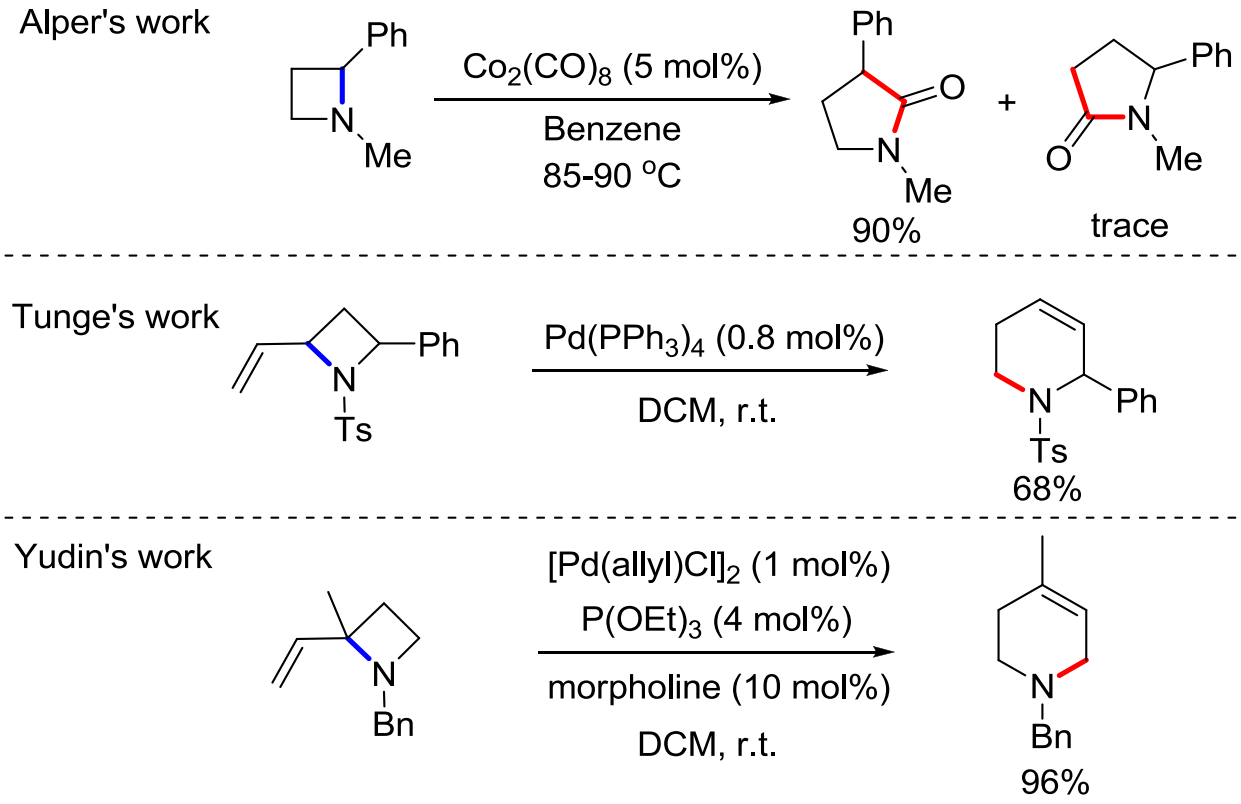
Rhodium–catalysed hetero–[5+2] cycloaddition

J.-J. Feng, T.-Y. Lin, H.-H. Wu and J. Zhang, *J. Am. Chem. Soc.*, 2015, ***137***, 3787

4. Activation of C(sp3)−N bond

4.3 Activation of C(sp^3)−N bond in azetidines



Transition−metal catalysed C−N bond in azetidine

D. Roberto and H. Alper, *J. Am. Chem. Soc.*, 1989, **111**, 1539;
C. Wang and J. A. Tunge, *Org. Lett.*, 2006, **8**, 3211;
I. Dubovyk, D. Pichugin and A. K. Yudin, *Angew. Chem., Int. Ed.*, 2011, **50**, 5924.

5. Conclusions and Perspectives

In this tutorial review, efficient strategies for catalytic cleavage of C(sp)-N, C(sp^2)-N and C(sp^3)-N bond and their applications in new C-C and C-N bond formation reactions are summarized. The appealing advantage of transition-metal catalysed C-N bond activation has prompted many methods for their applications. However, there are still enormous challenges for the development of novel and practical coupling reactions *via* C–N bond activation.

In the future, C-N bond activation focused on the aspects as followed would attract much attention: full atom economy C-N bond activation reaction; the application for the synthesis of natural products and medical compounds; highly efficient and enantioselective reactions via C–N bond activation .

6. Acknowledgements

We thank the Chinese Academy of Sciences and National Natural Science Foundation of China (Grant Nos. 21133011, 21222203, 21172226, and 21372231) for generous and continuous financial support.

7. Notes and references