

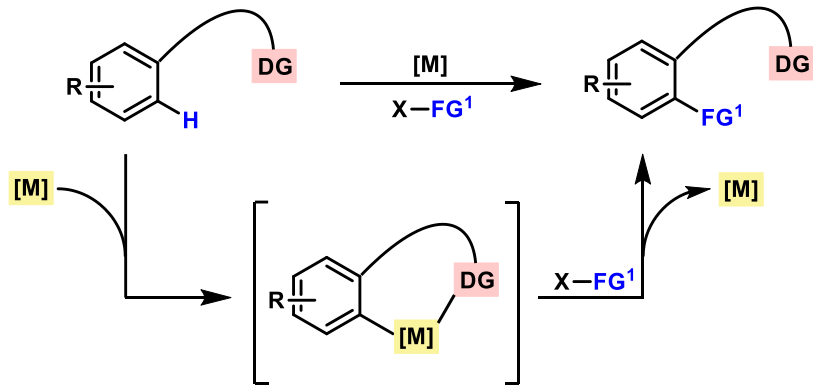
The Catellani reaction – development and application

Lena Emmes

Konstanz, 10.08.2022

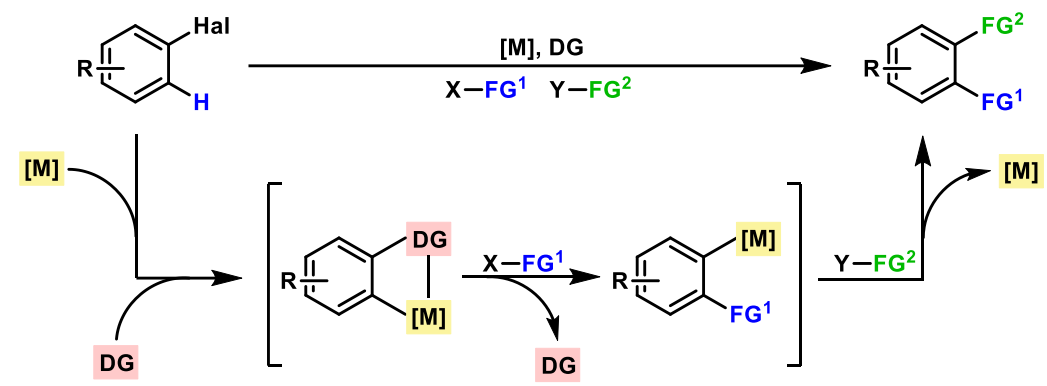
C-H functionalization and the need for the Catellani reaction

Directing group mediated C-H activation



- *ortho*- and *meta*-C-H functionalization of arenes reported
 - preinstallation and removal of directing groups necessary
 - site for installation of DG might be missing
- *in situ* generation of DG with subsequent departure desirable

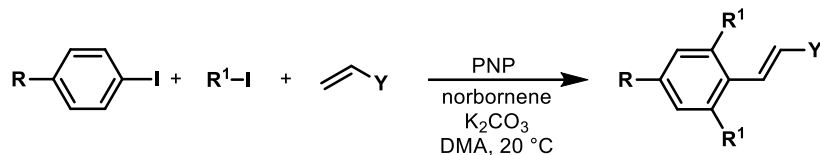
The Catellani reaction



- functionalization of *ortho*- and *ipso*-position in one transformation
- trapping with a wide variety of terminating agents possible

The Catellani reaction: initial studies

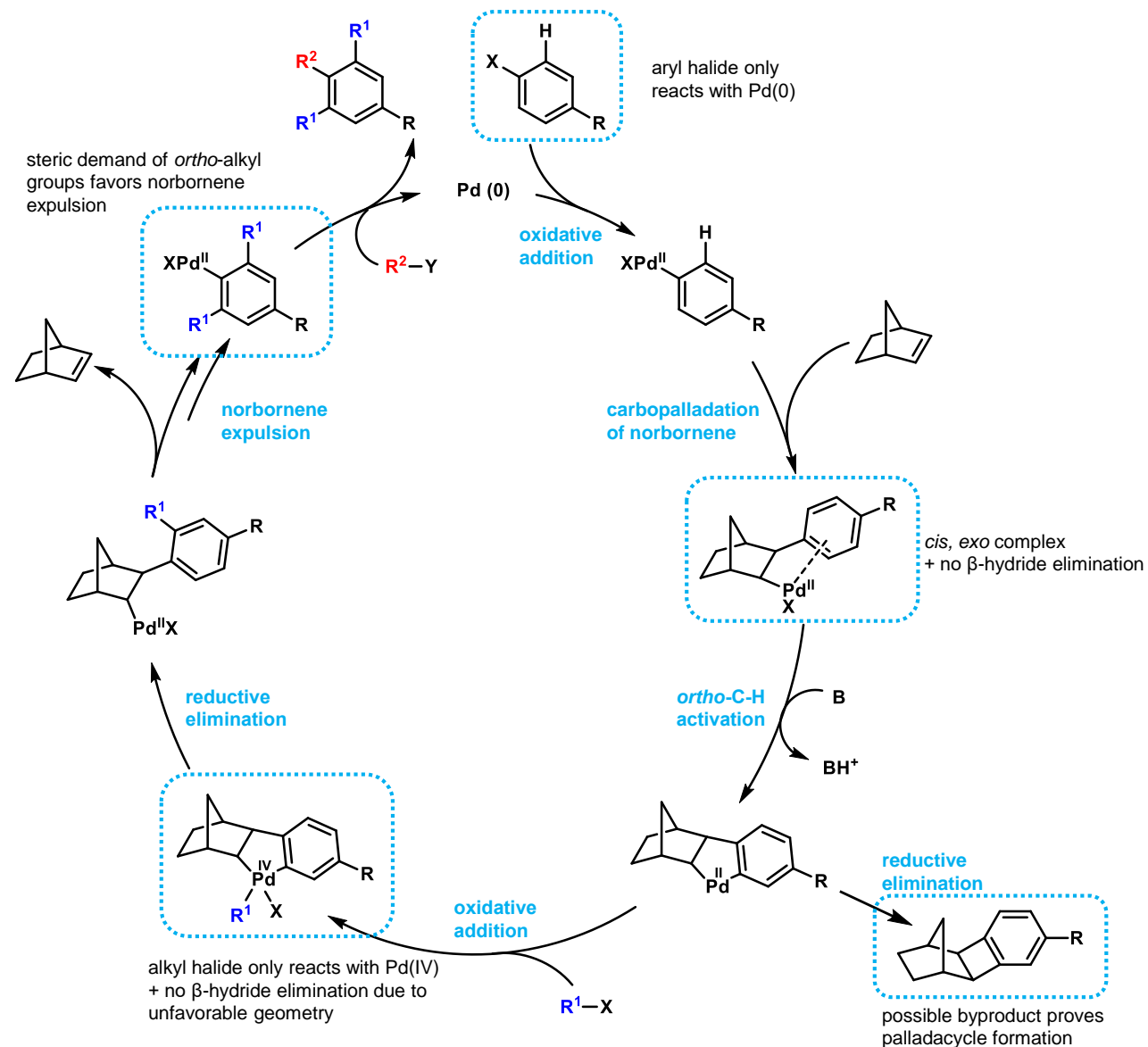
Initial scope



entry	R	R ¹	Y	conversion	selectivity
1	H	<i>n</i> -But	CO ₂ Me	100	93
2	H	<i>n</i> -But	CO ₂ Me	86	95
3	H	CH ₂ CH ₂ Ph	CO ₂ Me	33	95
4	Me	<i>n</i> -But	CO ₂ Me	44	93
5	CO ₂ Me	<i>n</i> -But	CO ₂ Me	82	89
6	H	<i>n</i> -But	CO ₂ Me	42	90
7	H	<i>n</i> -But	Ph	31	91
8	H	<i>n</i> -But	<i>n</i> -Hex	43	90

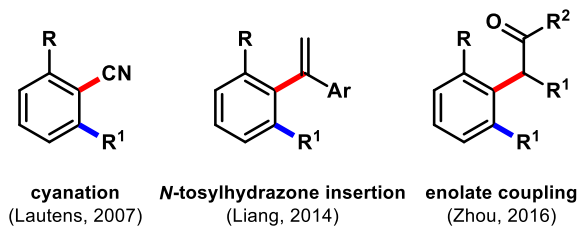
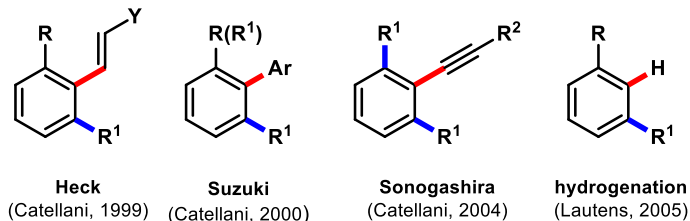
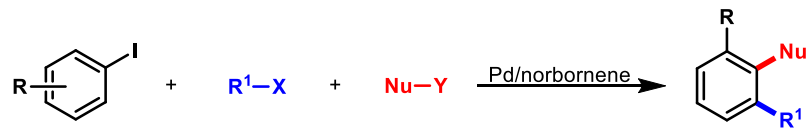
Selectivity in the catalytic cycle

- competing reactivity of alkyl halide and aryl halide
- selectivity relies on different reactivities of Pd(0), Pd(II) and Pd(IV)

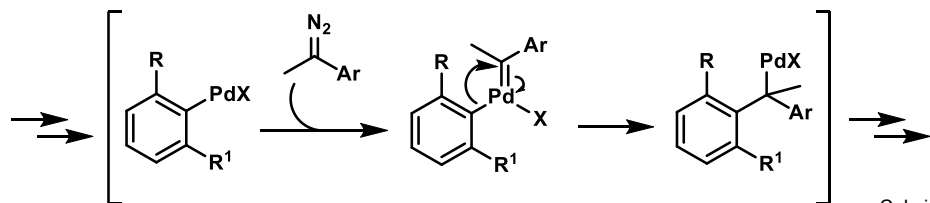


Aromatic *ortho*-alkylation

General overview



Mechanistic reminder



M. Catellani, F. Cugini, *Tetrahedron* **1999**, 55, 6595-6602.

M. Catellani, E. Motti, M. Minari, *Chem. Commun.* **2000**, 157-158.

E. Motti, M. Rossetti, G. Bocelli, M. Catellani, *J. Organomet. Chem.* **2004**, 689, 3741-3749.

C. Lei, J. Cao, J. Zhou, *Org. Lett.* **2016**, 18, 6120-6123.

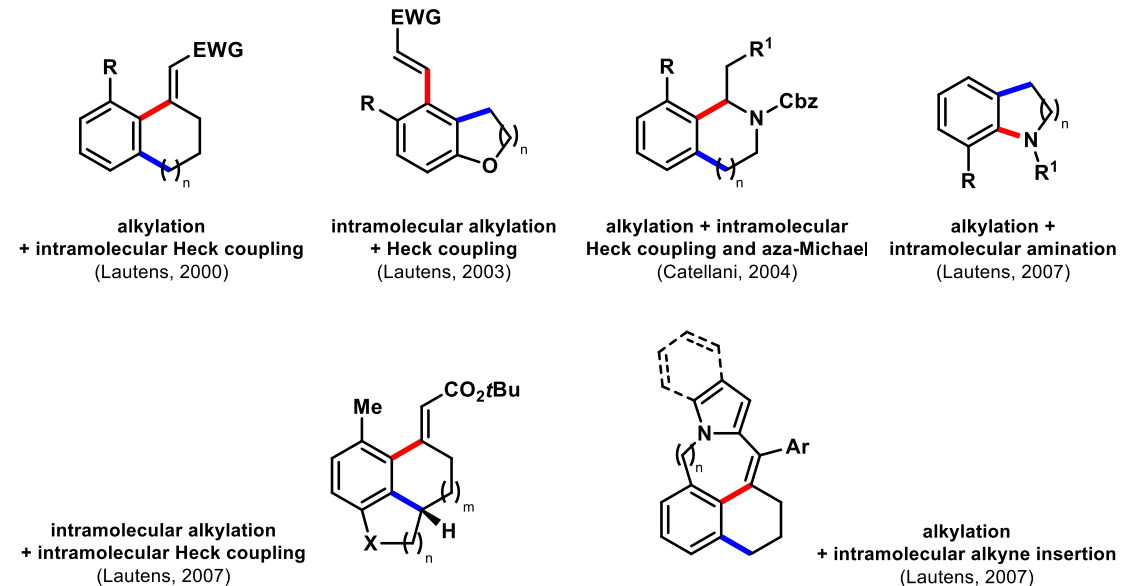
P.-X. Zhou *et al*, *Chem.-Eur. J.* **2014**, 20, 6745-6751.

M. Lautens, S. Piguél, *Angew. Chem. Int. Edit.* **2000**, 39, 1045-1046.

S. Pache, M. Lautens, *Org. Lett.* **2003**, 5, 4827-4830.

R. Ferraccioli, D. Carenzi, M. Catellani, *Tetrahedron Lett.* **2004**, 45, 6903-6907.

Some more complex examples



B. Mariampillai, J. Alliot, M. Li, M. Lautens, *J. Am. Chem. Soc.* **2007**, 129, 15372-15379.

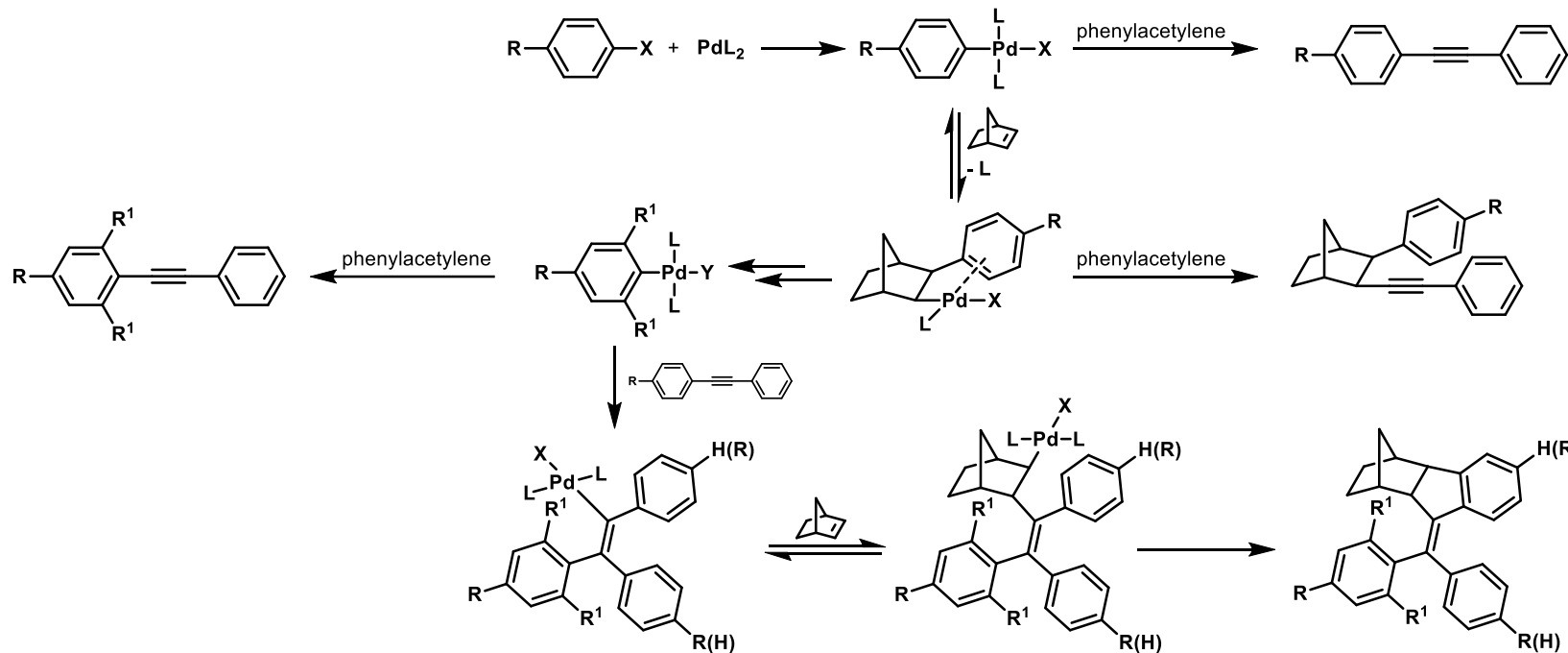
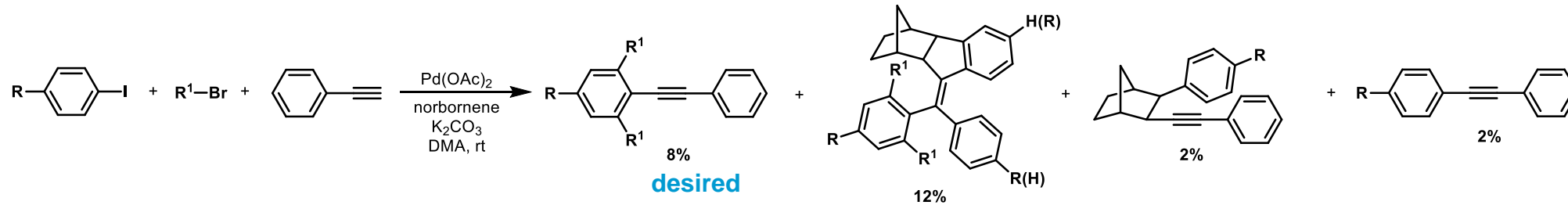
T. Wilhelm, M. Lautens, *Org. Lett.* **2005**, 7, 4053-4056 P. Thansandote, M. Raemy, A.

Rudolph, M. Lautens, *Org. Lett.* **2007**, 9, 5255-5258.

A. Rudolph, N. Rackelmann, M. Lautens, *Angew. Chem. Int. Edit.* **2007**, 46, 1485-1488.

V. Aureggi, M. Davoust, K. M. Gericke, M. Lautens, *Synlett* **2009**, 2009, 1004-1008.

Selectivity problems in the Sonogashira termination approach

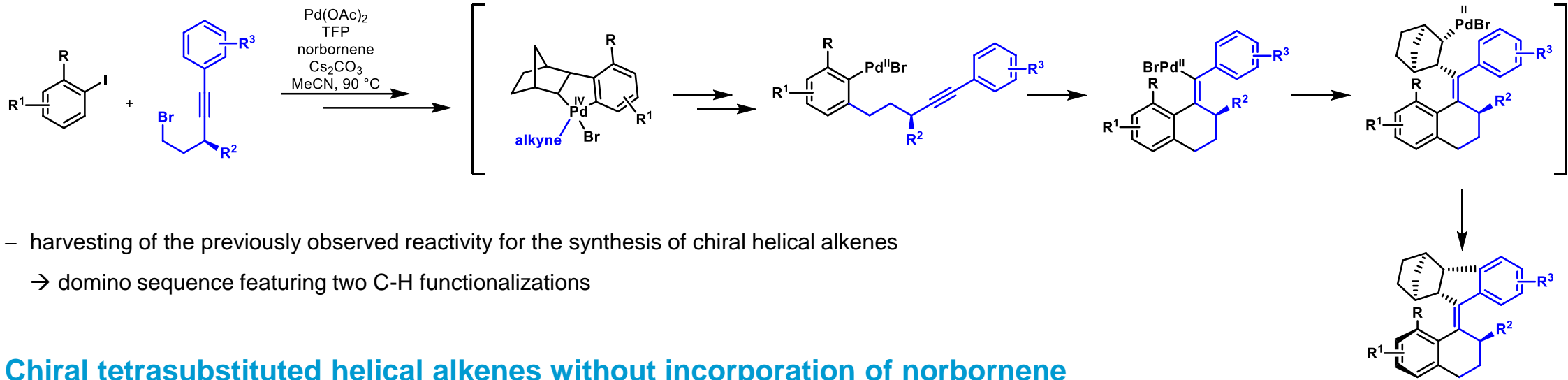


prevention of byproduct formation by:

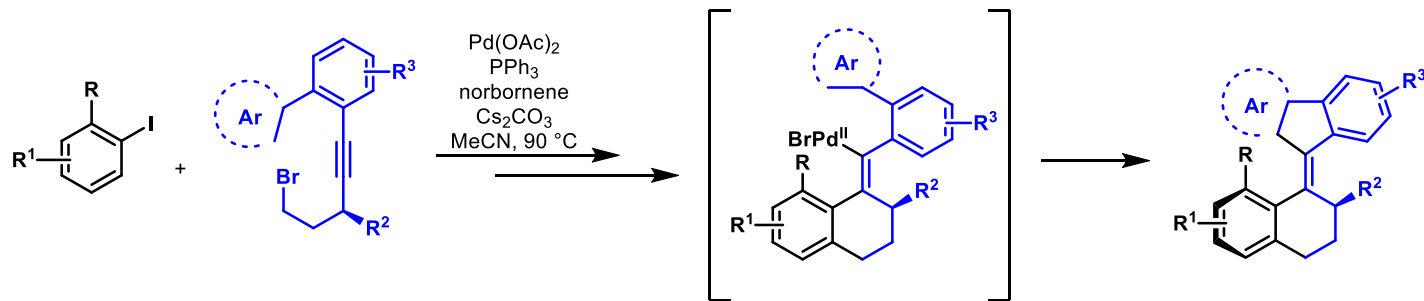
- 1) employing KOAc instead of K_2CO_3
- 2) large excess of alkyl bromide + gradual addition
- 3) run reaction at rt
- 4) gradual addition of phenylacetylene

Chiral helical alkenes

Chiral tetrasubstituted helical alkenes

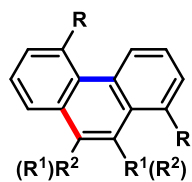
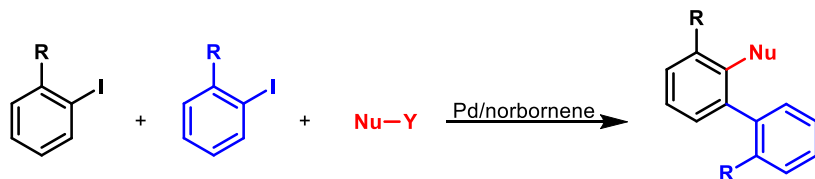


Chiral tetrasubstituted helical alkenes without incorporation of norbornene

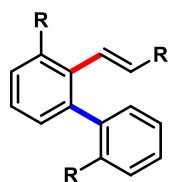


Aromatic *ortho*-arylation and the *ortho*-effect

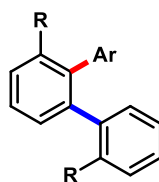
Aromatic *ortho*-arylation



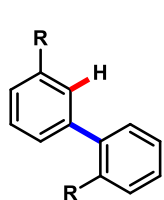
triple bond insertion
(Catellani, 2001)



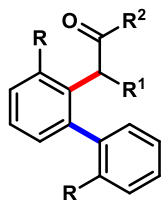
Heck
(Catellani, 2003)



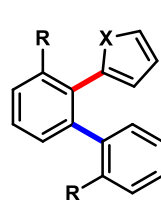
Suzuki
(Catellani, 2003)



hydrogenation
(Catellani, 2005)



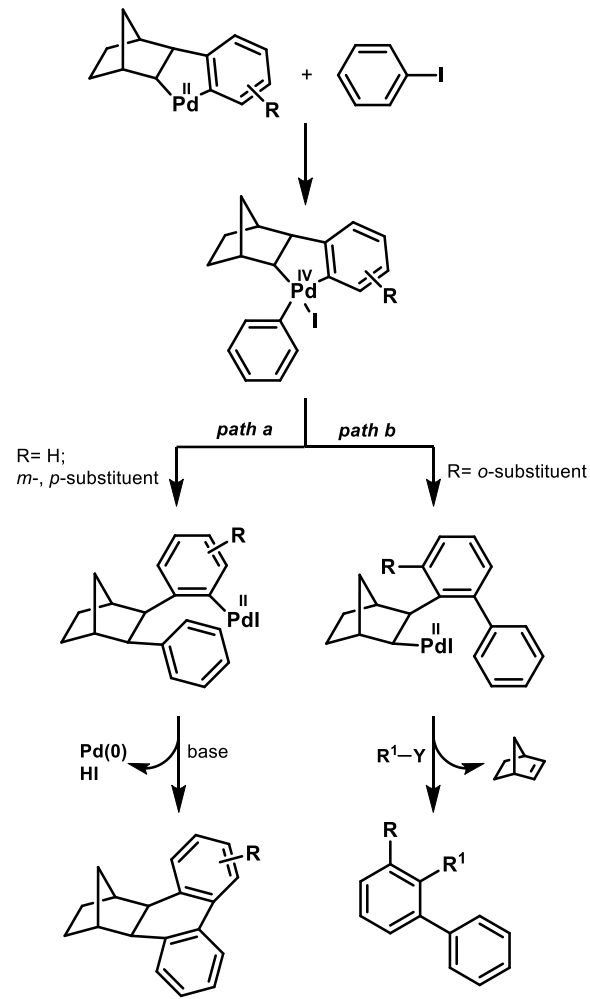
enolate coupling
(Catellani, 2009)



heteroaryl coupling
(Catellani, 2009)

X = O, S, NR

ortho-Effect



path a

- strong tendency of sp^2 - sp^3 C-C bond formation
- migration of aryl occurs onto norbornyl site of palladacycle

path b

- sp^2 - sp^2 C-C bond formation upon introduction of *ortho*-substituent

M. Catellani, E. Motti, *New J. Chem.* **1998**, 22, 759-761.

M. Catellani, E. Motti, S. Baratta, *Org. Lett.* **2001**, 3, 3611-3614.

E. Motti, G. Ippomei, S. Deledda, M. Catellani, *Synthesis* **2003**, 2003, 2671-2678.

E. Motti, A. Mignozzi, M. Catellani, *J. Mol. Catal. A Chem.* **2003**, 204-205, 115-124.

S. Deledda, E. Motti, M. Catellani, *Can. J. Chem.* **2005**, 83, 741-747.

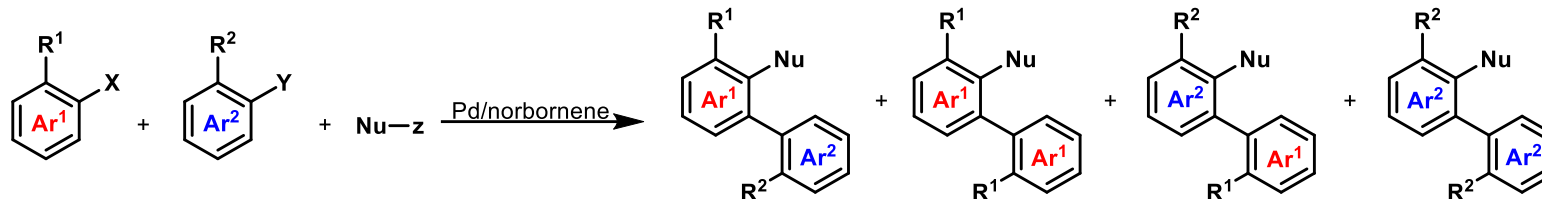
G. Maestri, N. Della Ca', M. Catellani, *Chem. Commun.* **2009**, 4892-4894.

N. Della Ca', G. Maestri, M. Catellani, *Chem.-Eur. J.* **2009**, 15, 7850-7853.

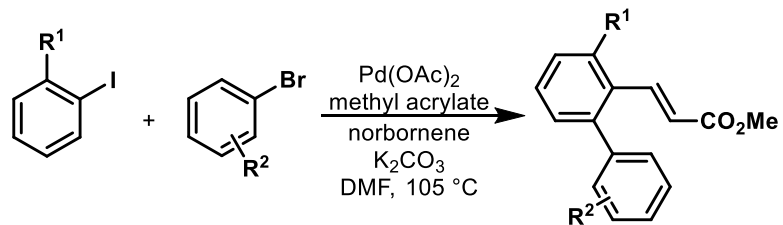
Aromatic *ortho*-arylation: cross-coupling of aryl halides

Chemoselectivity issue

- 1) tuning of electronic properties of aryl halides to distinguish between Pd(0) and Pd(II)
 2) *ortho*-coordination-induced chemoselective addition to Pd(II)

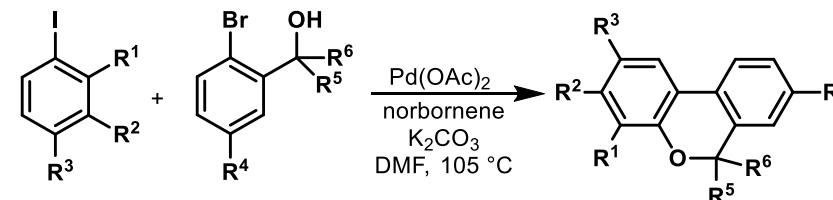


1) Adjustment of electronic properties (Catellani, 2004)



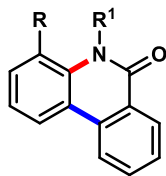
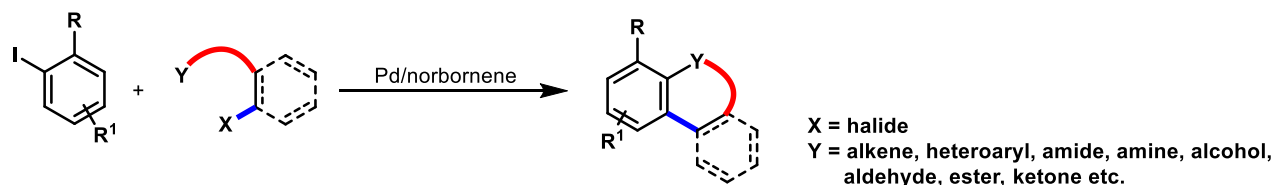
entry	R ¹	R ²	yield	entry	R ¹	R ²	yield
1	Me	<i>o</i> -CO ₂ Me	80	8	Me	<i>p</i> -CO ₂ Me	71
2	<i>t</i> Bu	<i>o</i> -CO ₂ Me	37	9	Me	<i>o</i> -CN	13
3	OMe	<i>o</i> -CO ₂ Me	83	10	Me	<i>m</i> -CN	62
4	NMe ₂	<i>o</i> -CO ₂ Me	82	11	Me	<i>p</i> -CN	79
5	Ph	<i>o</i> -CO ₂ Me	73	12	Me	<i>m</i> -CF ₃	71
6	Me	<i>m</i> -CO ₂ Me	37	13	Me	<i>p</i> -CF ₃	80

2) *ortho*-Coordination induced selectivity (Catellani, 2012)

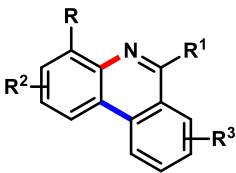


entry	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	yield
1	Me	H	H	H	Me	Me	79
2	<i>i</i> Pr	H	H	H	Me	Me	75
3	(CH=CH) ₂		H	H	Me	Me	66
4	<i>n</i> Pr	H	H	H	Et	Et	98
5	OMe	H	H	H	Et	Et	90
6	(CH=CH) ₂		H	OMe	Et	Et	98

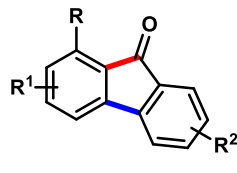
Polycyclic compounds from bifunctional reagents



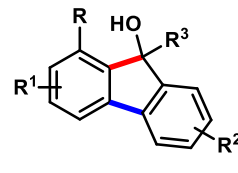
ortho-arylation +
N-aryl coupling
(Catellani, 2004)



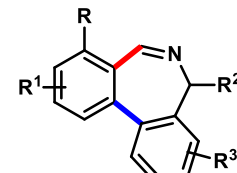
ortho-arylation +
N-aryl coupling
(Lautens, 2009)
(Malacria, 2010)



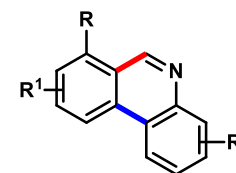
ortho-arylation +
aldehyde addition
(Lautens, 2009)



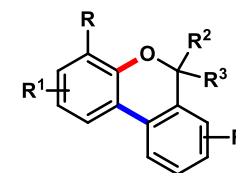
ortho-arylation +
ketone addition
(Lautens, 2009)



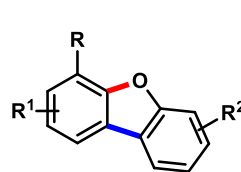
ortho-arylation +
Heck + aza-Michael
(Malacria, 2014)



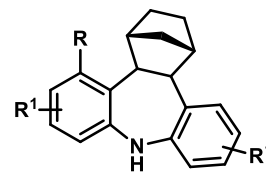
ortho-arylation +
Heck + aza-Michael +
"retro-Mannich"
(Catellani, 2010)



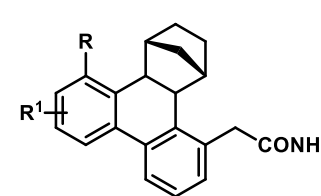
ortho-arylation +
O-aryl coupling
(Catellani, 2012)



ortho-arylation +
O-aryl coupling
(Catellani, 2013)



ortho-arylation +
norbornene insertion
+ C-N coupling
(Catellani, 2011)



ortho-arylation +
norbornene insertion
(Malacria, 2011)

R. Ferraccioli, D. Carenzi, O. Rombolà, M. Catellani, *Org. Lett.* **2004**, *6*, 4759-4762.

G. Maestri, M.-H. Larraufie, É. Derat, C. Ollivier, L. Fensterbank, E. Lacôte, M. Malacria, *Org. Lett.* **2010**, *12*, 5692-5695.

D. A. Candito, M. Lautens, *Angew. Chem. Int. Edit.* **2009**, *48*, 6713-6716.

Y.-B. Zhao, B. Mariampillai, D. A. Candito, B. Laleu, M. Li, M. Lautens, *Angew. Chem. Int. Edit.* **2009**, *48*, 1849-1852.

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E. Motti, N. Della Ca', D. Xu, A. Piersimoni, E. Bedogni, Z.-M. Zhou, M. Catellani, *Org. Lett.* **2012**, *14*, 5792-5795.

N. Della Ca', G. Maestri, M. Malacria, E. Derat, M. Catellani, *Angew. Chem. Int. Edit.* **2011**, *50*, 12257-12261.

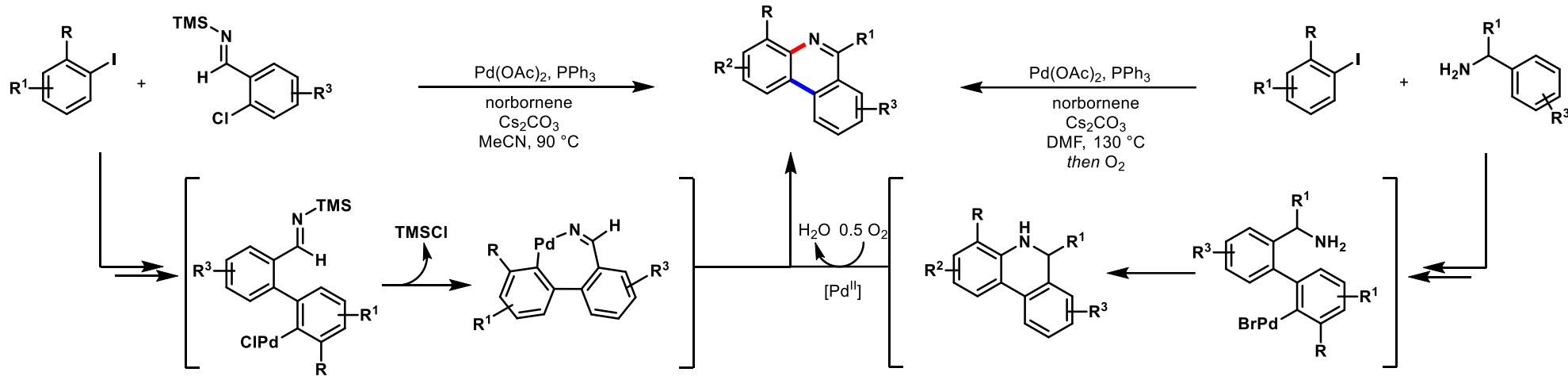
E. Motti, N. Della Ca, D. Xu, S. Armani, B. M. Aresta, M. Catellani, *Tetrahedron* **2013**, *69*, 4421-4428.

N. D. Ca', E. Motti, A. Mega, M. Catellani, *Advanced Synthesis & Catalysis* **2010**, *352*, 1451-1454.

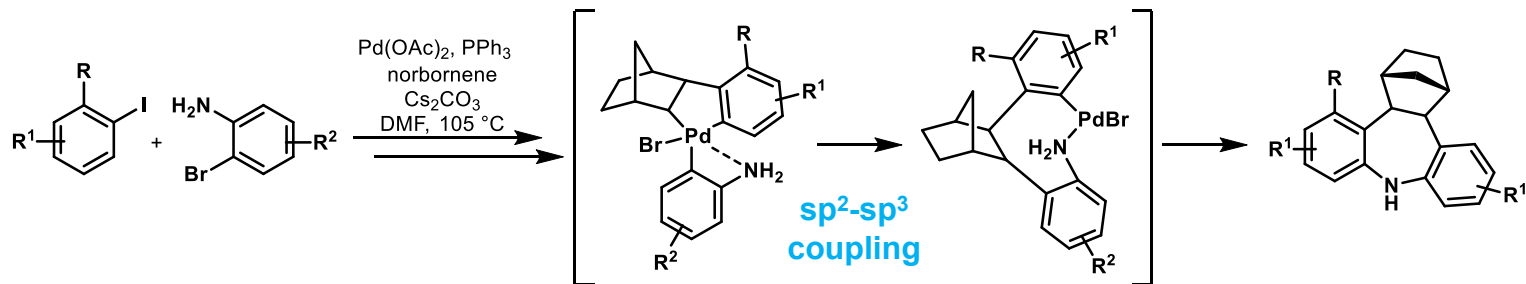
M.-H. Larraufie, G. Maestri, A. Beaume, É. Derat, C. Ollivier, L. Fensterbank, C. Courillon, E. Lacôte, M. Catellani, M. Malacria, *Angew. Chem. Int. Edit.* **2011**, *50*, 12253-12256.

Polycyclic compounds – a closer look

Phenanthridines (Lautens, 2009/Malacria, 2010)



Dibenzoazepines (Catellani, 2011)



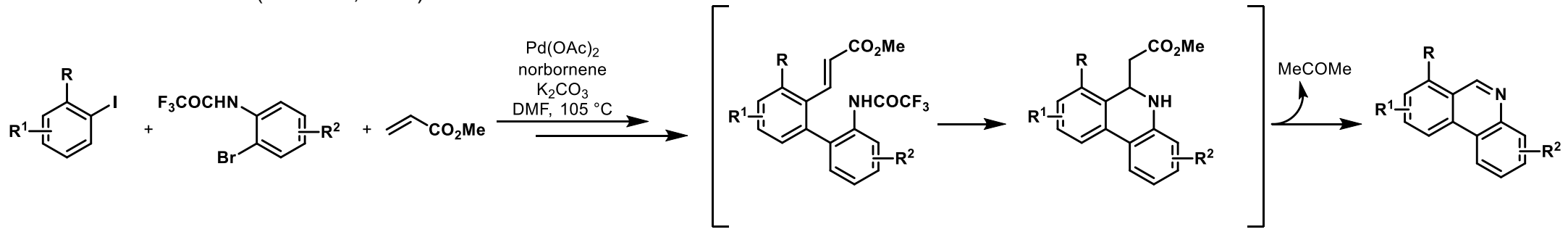
G. Maestri, M.-H. Larraufie, É. Derat, C. Ollivier, L. Fensterbank, E. Lacôte, M. Malacria, *Org. Lett.* **2010**, *12*, 5692-5695.

D. A. Candito, M. Lautens, *Angew. Chem. Int. Edit.* **2009**, *48*, 6713-6716.

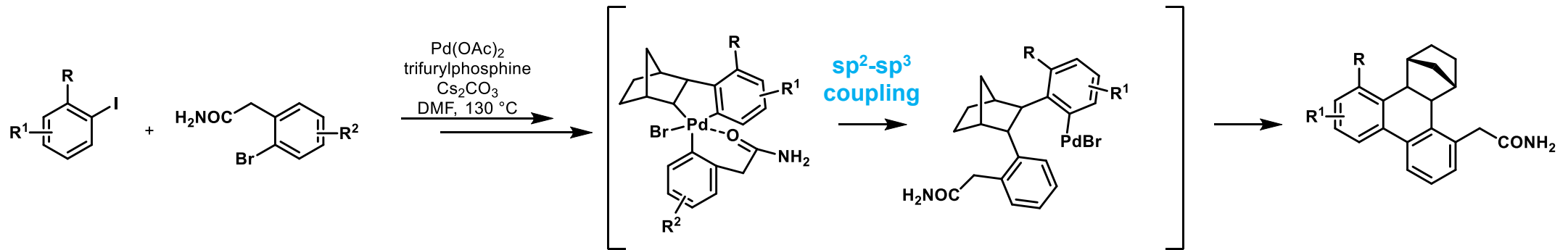
N. Della Ca', G. Maestri, M. Malacria, E. Derat, M. Catellani, *Angew. Chem. Int. Edit.* **2011**, *50*, 12257-12261.

Polycyclic compounds – a closer look

Phenanthridines (Catellani, 2010)



Dihydrophenanthrene (Malacria, 2011)

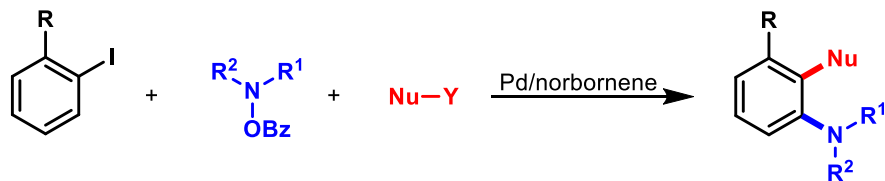


N. D. Ca', E. Motti, A. Mega, M. Catellani, *Advanced Synthesis & Catalysis* **2010**, 352, 1451-1454.

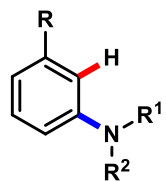
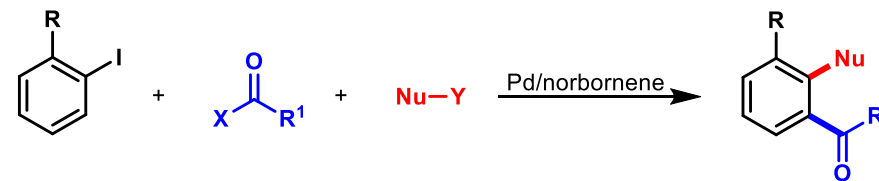
M.-H. Larraufie, G. Maestri, A. Beaume, É. Derat, C. Ollivier, L. Fensterbank, C. Courillon, E. Lacôte, M. Catellani, M. Malacria, *Angew. Chem. Int. Edit.* **2011**, 50, 12253-12256.

Aromatic *ortho*-amination/-acylation

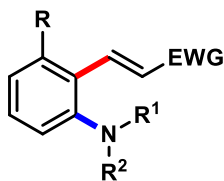
ortho-Amination



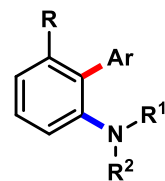
ortho-acylation



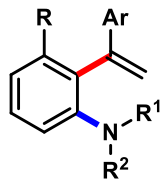
hydrogenation
(Dong, 2013)



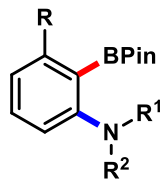
Heck
(Chen, 2014)



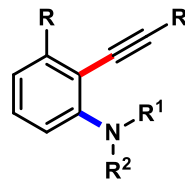
Suzuki
(Chen, 2014)



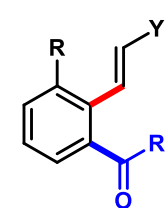
N-tosylhydrazone insertion
(Liang, 2014)



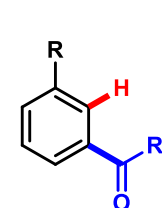
borylation
(Ritter, 2015)



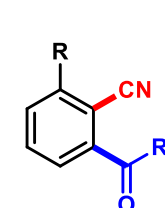
alkynylation
(Gu, 2015)



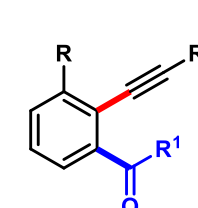
Heck
(Liang, 2015)
(Gu, 2015)



hydrogenation
(Dong, 2015)



cyanation
(Chen, 2016)



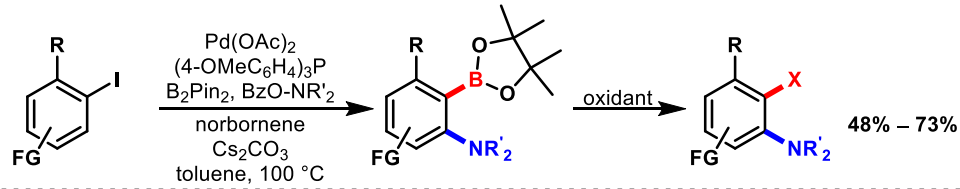
alkynylation
(Shi, 2018)

E. J. Yoo, S. Ma, T.-S. Mei, K. S. L. Chan, J.-Q. Yu, *J. Am. Chem. Soc.* **2011**, *133*, 7652-7655.
Z.-Y. Chen, C.-Q. Ye, H. Zhu, X.-P. Zeng, J.-J. Yuan, *Chem.-Eur. J.* **2014**, *20*, 4237-4241.
C. Ye, H. Zhu, Z. Chen, *J. Org. Chem.* **2014**, *79*, 8900-8905.
F. Sun, Z. Gu, *Org. Lett.* **2015**, *17*, 2222-2225.
H. Shi, D. J. Babinski, T. Ritter, *J. Am. Chem. Soc.* **2015**, *137*, 3775-3778.

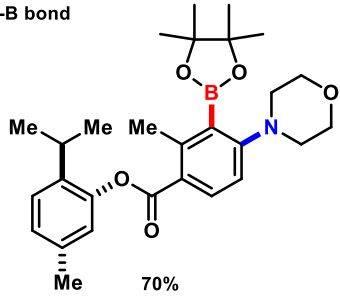
Zhou, P.-X.; Ye, Y.-Y.; Liu, C.; Zhao, L.-B.; Hou, J.-Y.; Chen, D.-Q.; Tang, Q.; Wang, A.-Q.; Zhang, J.-Y.; Huang, Q.-X.; Xu, P.-F.; Liang, Y.-M., *ACS Catal.* **2015**, *5*, 4927-4931.
Dong, Z.; Wang, J.; Ren, Z.; Dong, G., *Angew. Chem., Int. Ed.* **2015**, *54*, 12664-12668.
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Yu, S.-P.; Zhong, Y.; Gu, T.; Wu, W.-Y.; Fan, T.-Y.; Li, N.-G.; Shi, Z.-H.; Tang, Y.-P.; Duan, J.-A., *Tetrahedron* **2018**, *74*, 5942-5949.

Aromatic *ortho*-amination + hetero-bond formation

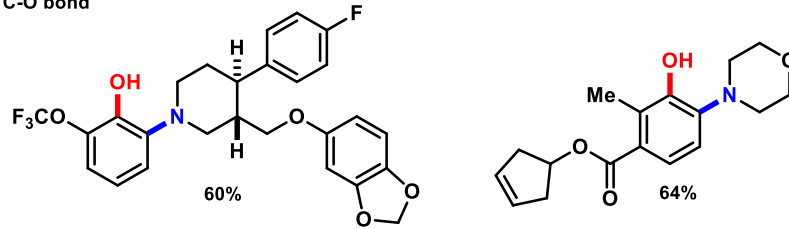
General scope



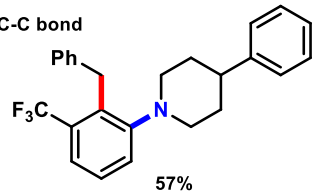
C-B bond



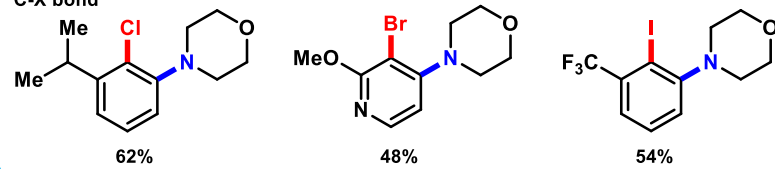
C-O bond



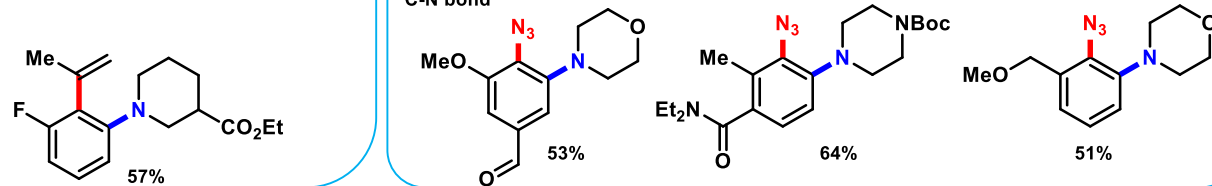
C-C bond



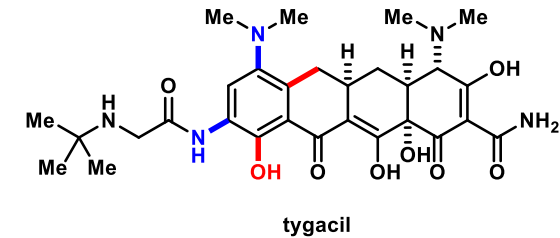
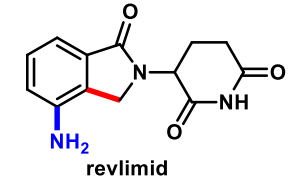
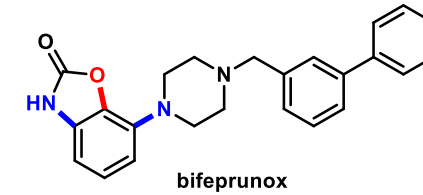
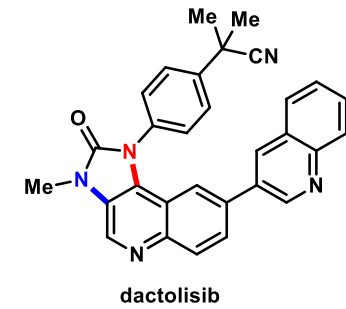
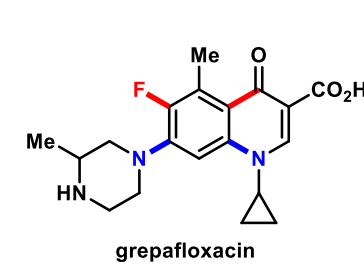
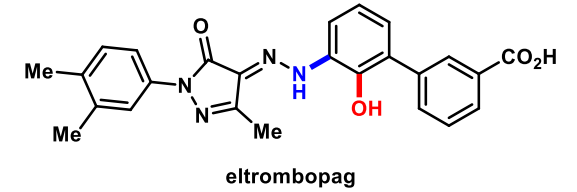
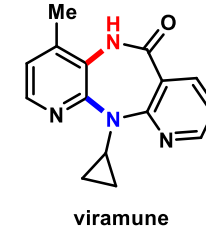
C-X bond



C-N bond

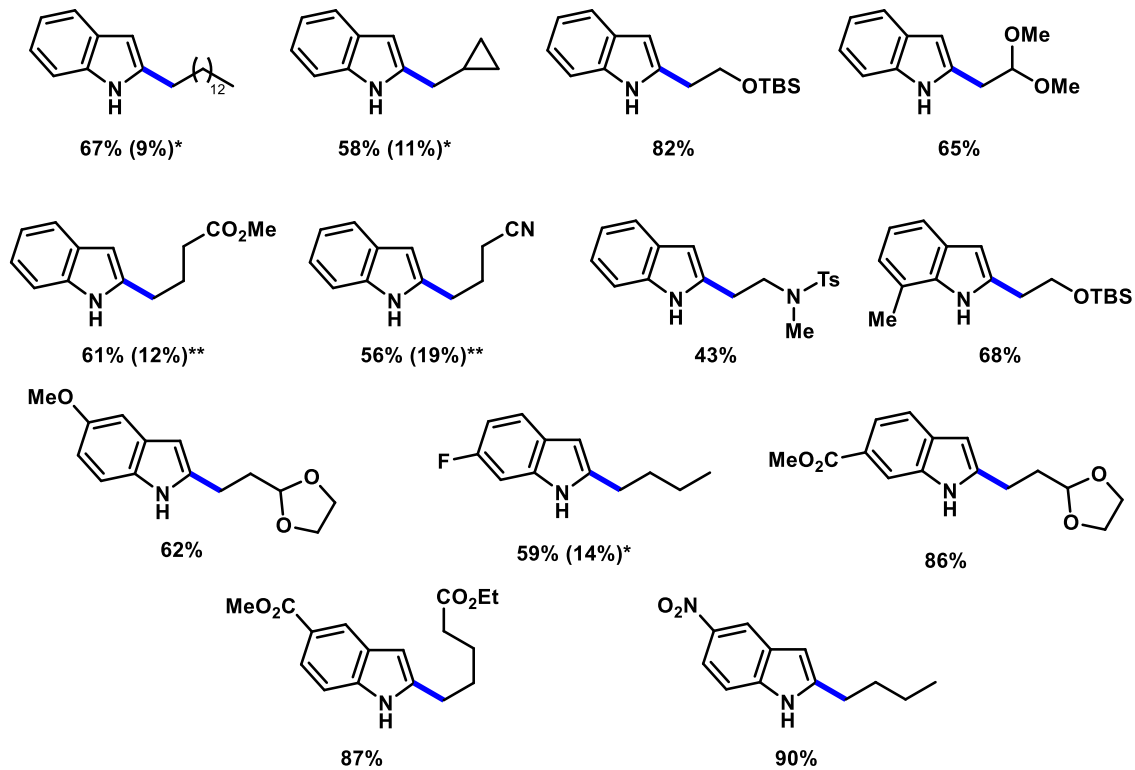
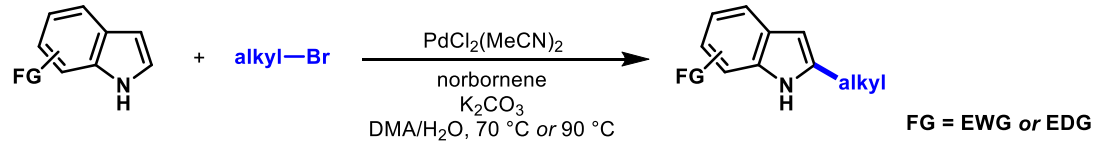


Reoccurring motif in pharmaceuticals



C2-Alkylation of indole and pyrrole derivatives

Alkylation of indoles

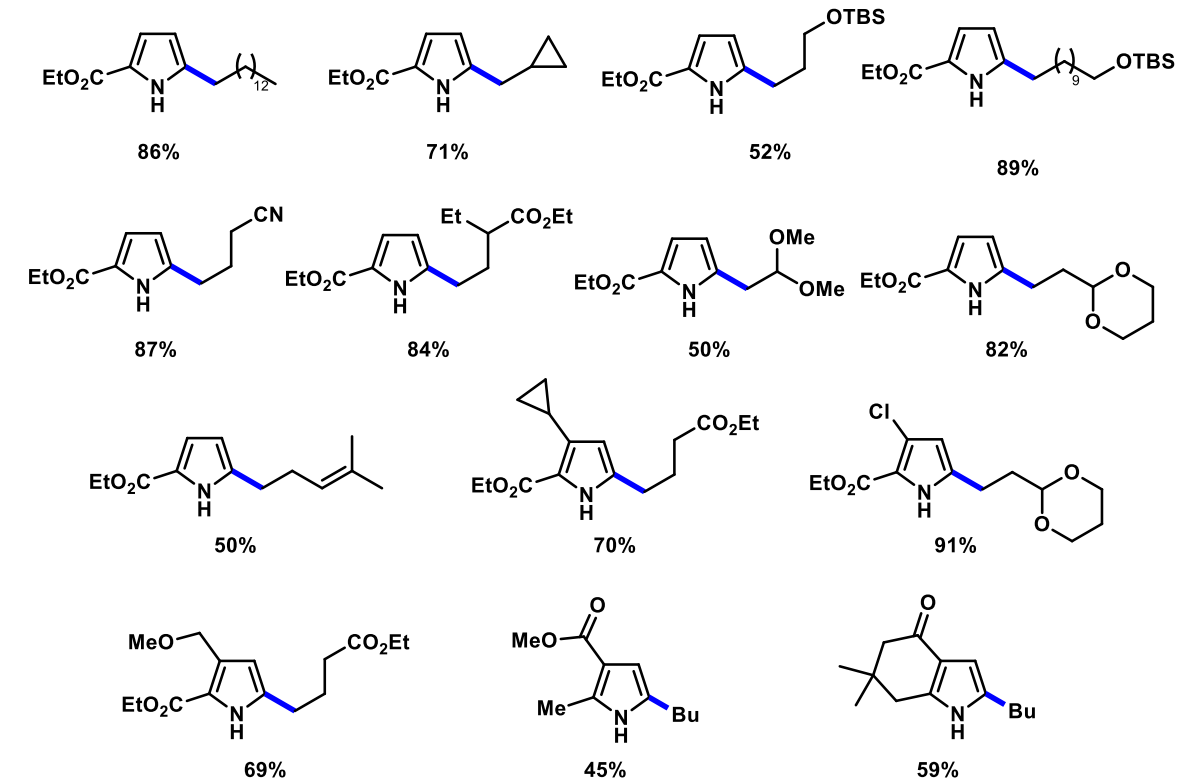
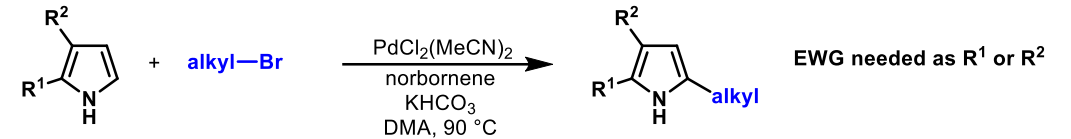


* Yield for the corresponding 2,3-dialkylated product.

** Dialkylation could be suppressed by employing 2 equiv. indole and 1 equiv. bromide.

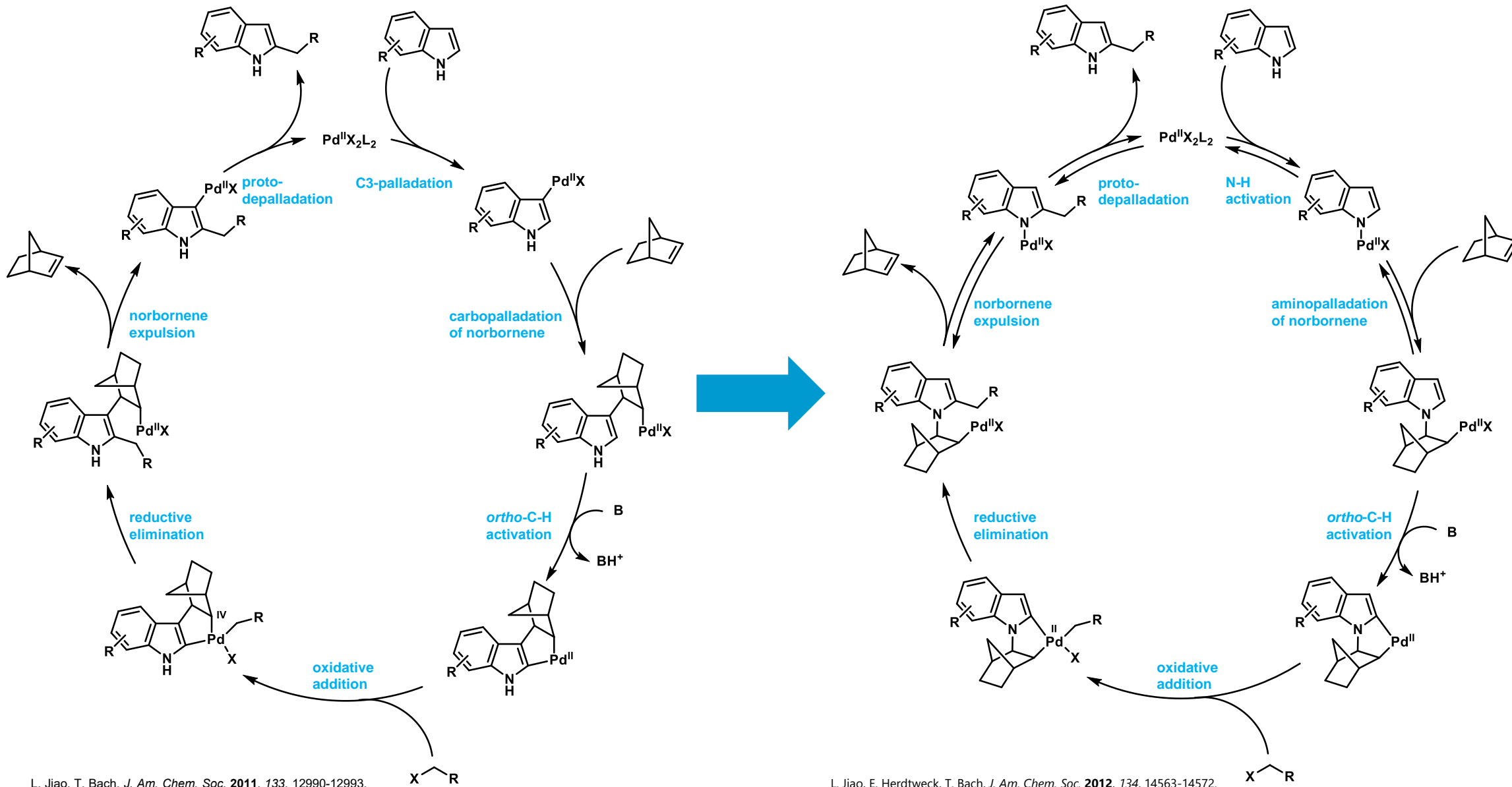
L. Jiao, T. Bach, *J. Am. Chem. Soc.* **2011**, *133*, 12990-12993.

Alkylation of pyrroles



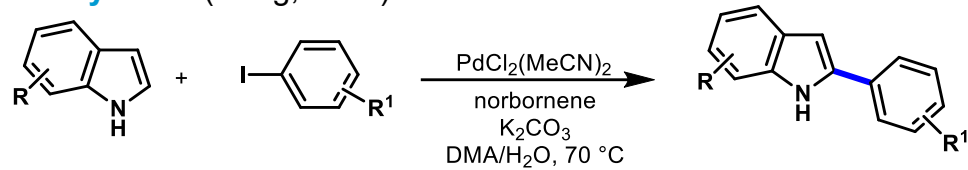
L. Jiao, T. Bach, *Angew. Chem. Int. Edit.* **2013**, *52*, 6080-6083.

2-Alkylation of indoles: revision of the catalytic cycle



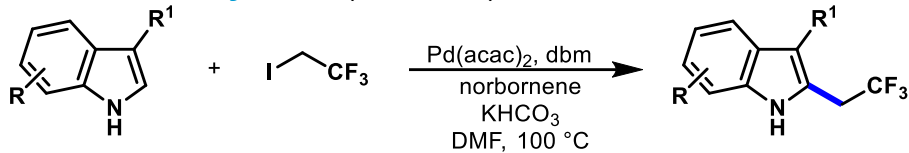
Advancement in methodology and synthetic applications

C2-arylation (Jiang, 2017)



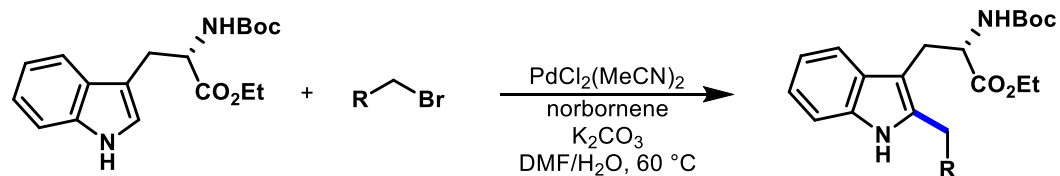
- R = EWG or EDG tolerated, but e-rich indole + e-deficient aryl iodide work best

C2-trifluoroethylation (Liu, 2018)



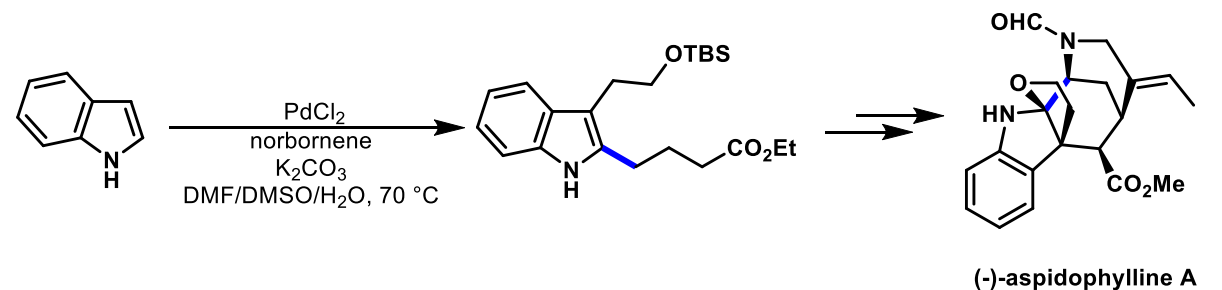
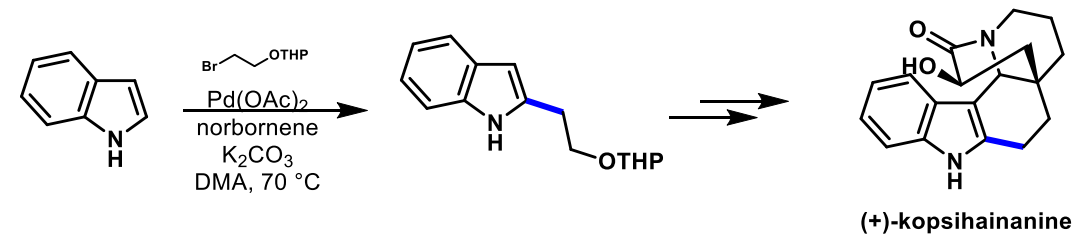
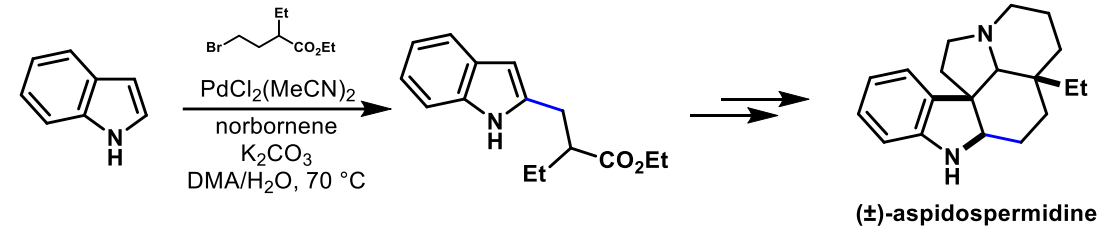
- anionic ligands needed to enhance nucleophilicity of palladacycle

C-H alkylation of tryptophan (Bach, 2013)



- Boc-protection prevents interference of the NH-position with palladation of indolic nitrogen

Natural products



Y. Gao, W. Zhu, L. Yin, B. Dong, J. Fu, Z. Ye, F. Xue, C. Jiang, *Tetrahedron Lett.* **2017**, *58*, 2213-2216.
H. Zhang, H.-Y. Wang, Y. Luo, C. Chen, Y. Cao, P. Chen, Y.-L. Guo, Y. Lan, G. Liu, *ACS Catal.* **2018**, *8*, 2173-2180.
H. K. Potukuchi, T. Bach, *J. Org. Chem.* **2013**, *78*, 12263-12267.

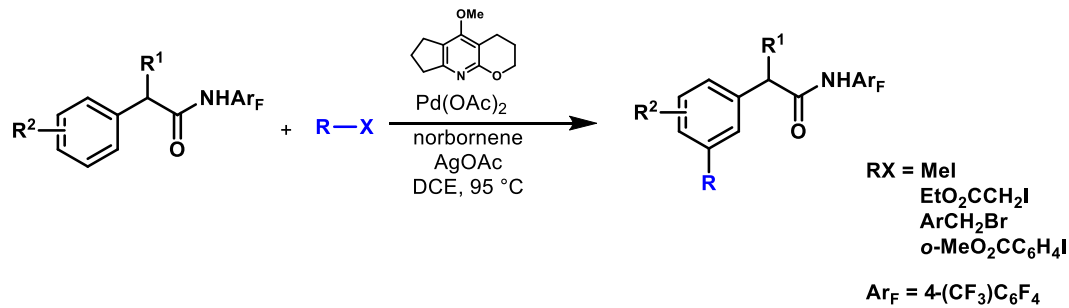
L. Jiao, E. Herdtweck, T. Bach, *J. Am. Chem. Soc.* **2012**, *134*, 14563-14572.
M. Mizutani, S. Yasuda, C. Mukai, *Chem. Commun.* **2014**, *50*, 5782-5785.
S.-Z. Jiang, X.-Y. Zeng, X. Liang, T. Lei, K. Wei, Y.-R. Yang, *Angew. Chem. Int. Edit.* **2016**, *55*, 4044-4048.

meta-Selective C-H bond activation

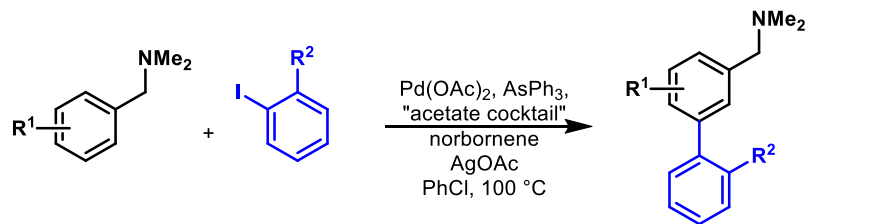
General idea

- combination of chelation-assisted Pd(II) ortho-C-H activation and Pd(II)/Pd(IV) norbornene chemistry

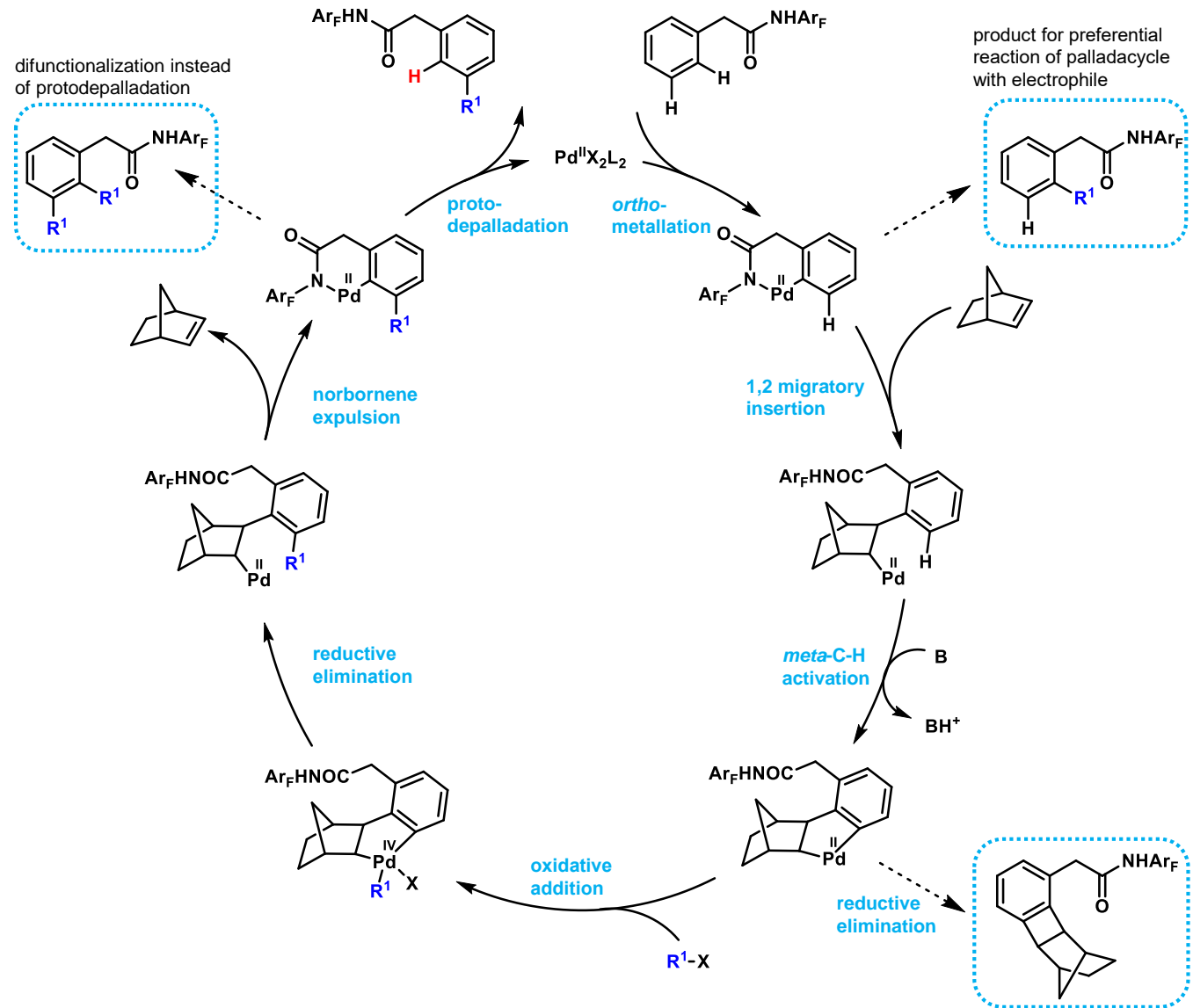
meta-Alkylation (Yu, 2015)



meta-Arylation (Dong, 2015)

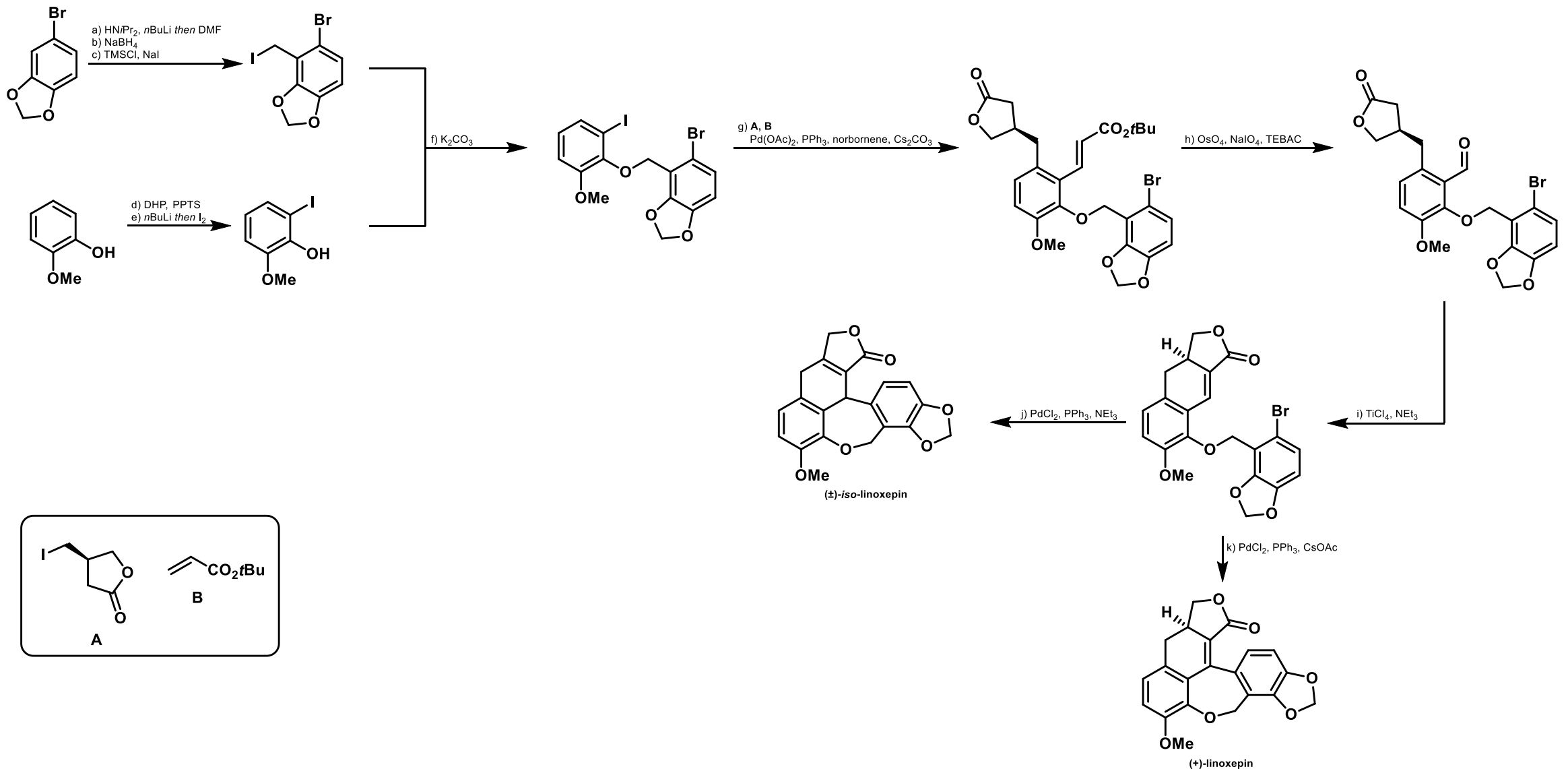


- acetate cocktail...? → LiOAc•2H₂O, CsOAc, Cu(OAc)₂•H₂O



X.-C. Wang, W. Gong, L.-Z. Fang, R.-Y. Zhu, S. Li, K. M. Engle, J.-Q. Yu, *Nature* **2015**, 519, 334-338.
Z. Dong, J. Wang, G. Dong, *J. Am. Chem. Soc.* **2015**, 137, 5887-5890.

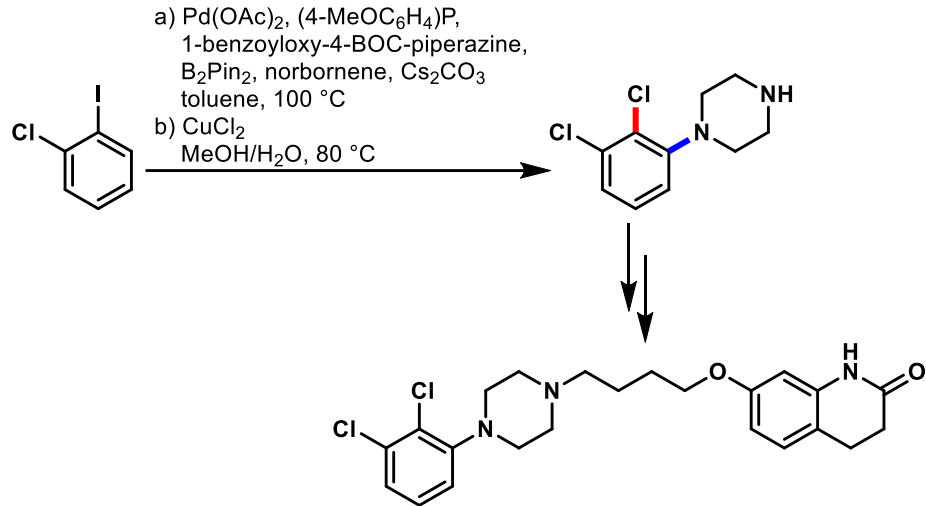
Applications: Total synthesis of (+)-linoxepin



H. Weinstabl, M. Suhartono, Z. Qureshi, M. Lautens, *Angew. Chem. Int. Edit.* **2013**, 52, 5305-5308.

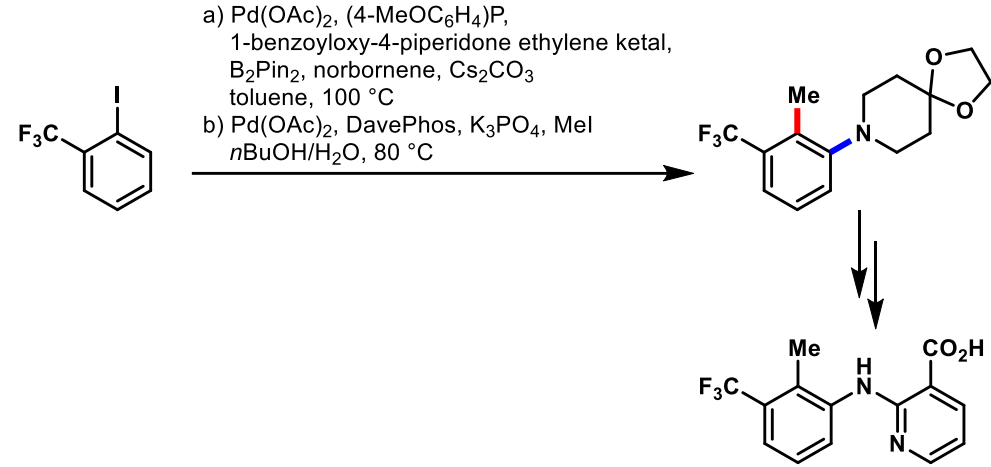
Applications: The Catellani reaction as key step in total synthesis

Abilify



H. Shi, D. J. Babinski, T. Ritter, *J. Am. Chem. Soc.* **2015**, *137*, 3775-3778.

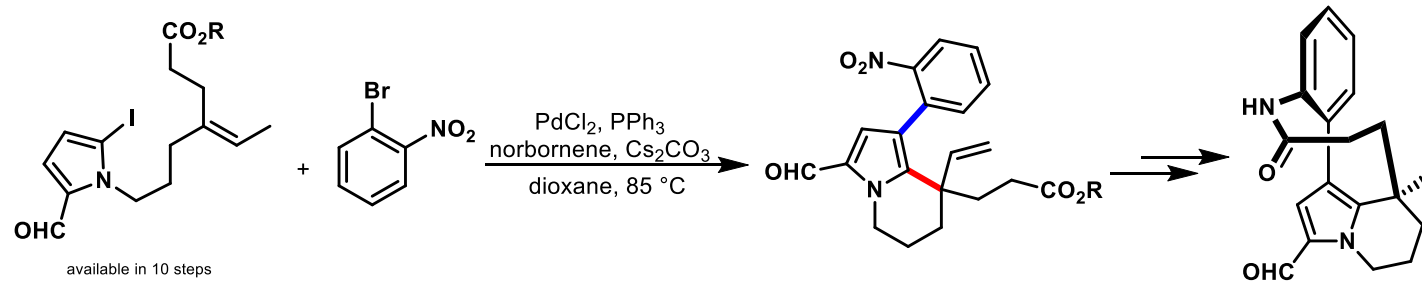
Flunixin



R. Jaouhari, P. Quinn, *Heterocycles* **1994**, *38*, 2243.

H. Shi, D. J. Babinski, T. Ritter, *J. Am. Chem. Soc.* **2015**, *137*, 3775-3778.

Rhazinal

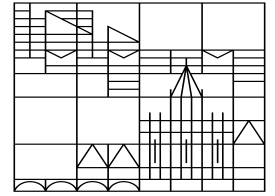


X. Sui, R. Zhu, G. Li, X. Ma, Z. Gu, *J. Am. Chem. Soc.* **2013**, *135*, 9318-9321.

Additional reviews and literature

- Catalytic Multistep Reactions *via* Palladacycles (M. Catellani, *Synlett* **2003**, 3, 298-313.)
- Palladium-Catalyzed Chemoselective Catellani *ortho*-Arylation Reactions and Their Applications in Natural Products Synthesis (X. Sui, R. Zhu, Z. Gu, *Synlett* **2013**, 24, 2023-2031.)
- Palladium-catalysed norbornene-mediated C–H functionalization of arenes (J. Ye, M. Lautens, *Nature Chemistry* **2015**, 7, 863-870.)
- Pd/Norbornene: A Winning Combination for Selective Aromatic Functionalization via C–H Bond Activation (N. Della Ca', M. Fontana, E. Motti, M. Catellani, *Accounts of Chemical Research* **2016**, 49, 1389-1400.)
- Catellani Reaction: An Enabling Technology for Vicinal Functionalization of Aryl Halides by Palladium(0)/Norbornene Cooperative Catalysis (S. Dong, X. Luan, *Chinese Journal of Chemistry* **2021**, 39, 1690-1705.)
- Martins, A., Mariampillai, B., Lautens, M. (2009). Synthesis in the Key of Catellani: Norbornene-Mediated *ortho* C–H Functionalization. In: Yu, JQ., Shi, Z. (eds) C-H Activation. Topics in Current Chemistry, vol 292. Springer, Berlin, Heidelberg.

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**Thanks for your kind
attention!**

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