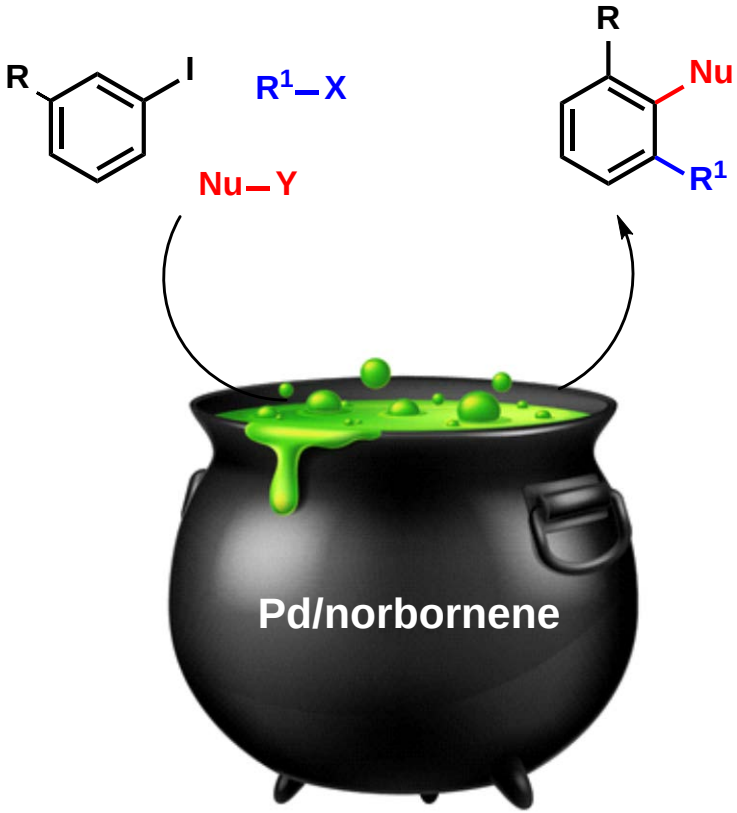
Universität Konstanz



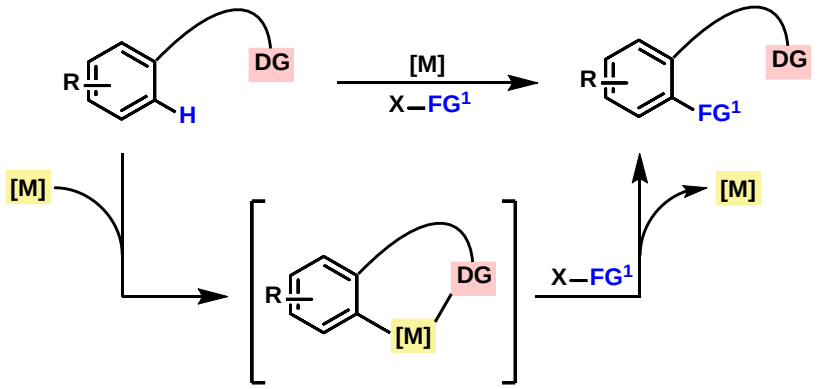
The Catellani reaction – development and application

Lena Emmes

Konstanz, 10.08.2022

C-H functionalization and the need for the Catellani reaction

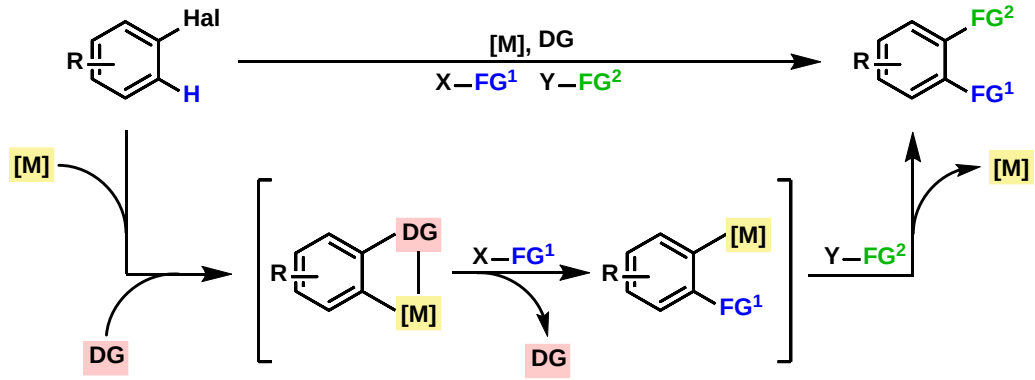
Directing group mediated C-H activation



- *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

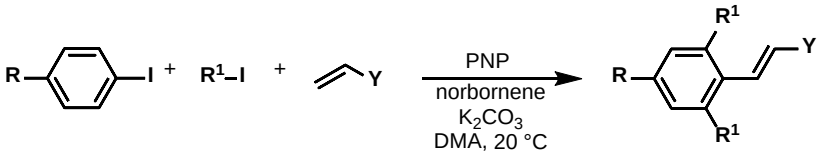


- functionalization of *ortho*- and *ipso*-position in one transformation
- trapping with a wide variety of terminating agents possible

J. Ye, M. Lautens, *Nature Chemistry* **2015**, *7*, 863-870.

The Catellani reaction: initial studies

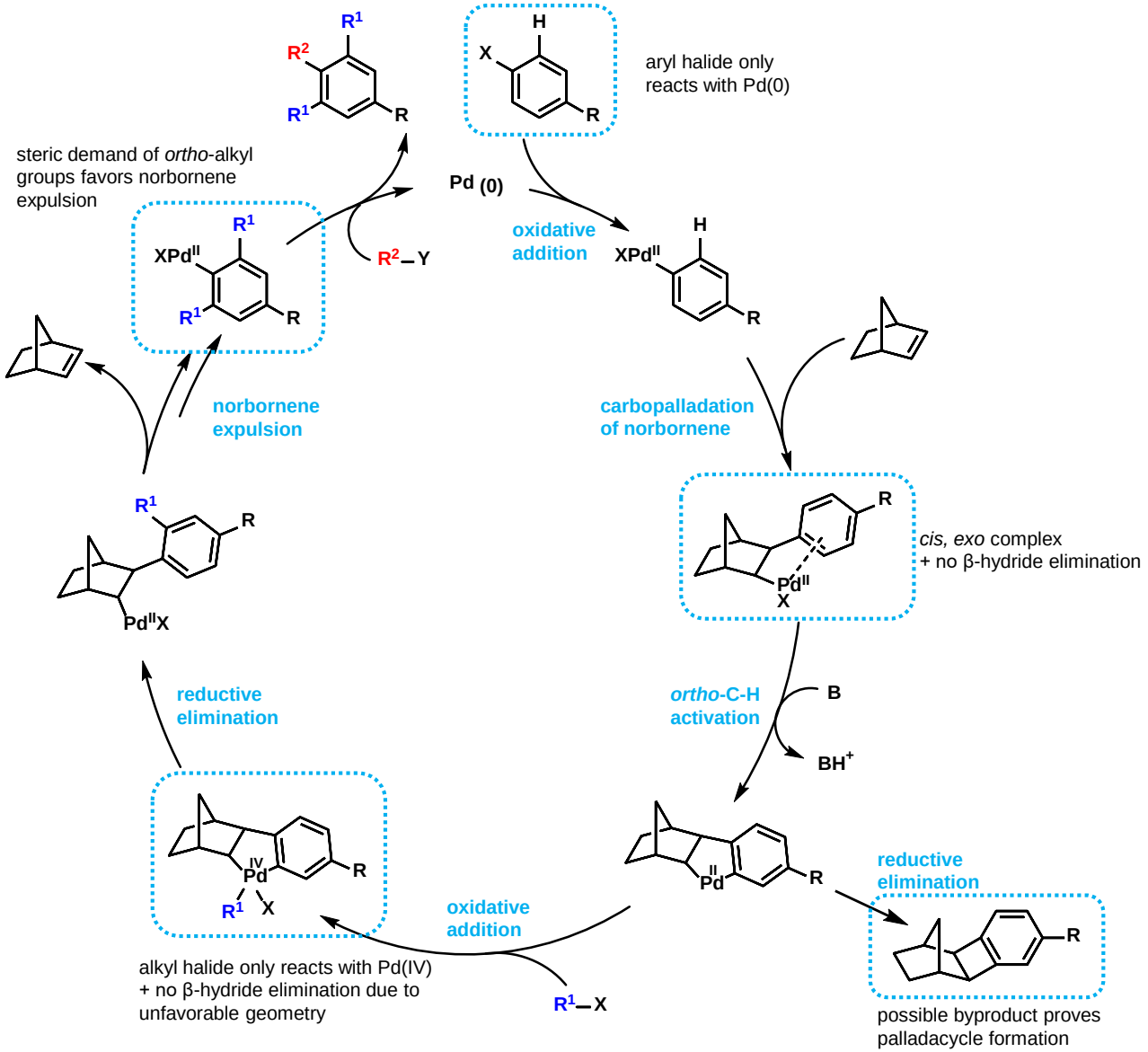
Initial scope



entry	R	R¹	Y	conversion	selectivity
1	H	*n*-But	CO_2Me	100	93
2	H	*n*-But	CO_2Me	86	95
3	H	CH_2CH_2Ph	CO_2Me	33	95
4	Me	*n*-But	CO_2Me	44	93
5	CO_2Me	*n*-But	CO_2Me	82	89
6	H	*n*-But	CO_2Me	42	90
7	H	*n*-But	Ph	31	91
8	H	*n*-But	*n*-Hex	43	90

Selectivity in the catalytic cycle

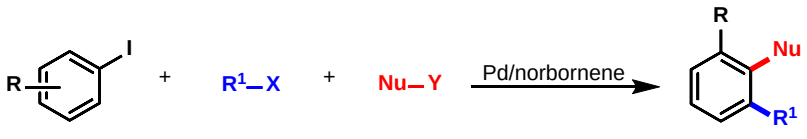
- competing reactivity of alkyl halide and aryl halide
- selectivity relies on different reactivities of Pd(0), Pd (II) and Pd(IV)

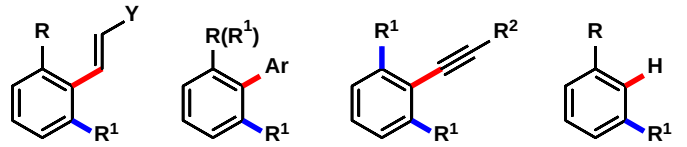


M. Catellani, F. Frignani, A. Rangoni, *Angew. Chem. Int. Edit.* **1997**, 36, 119-122.

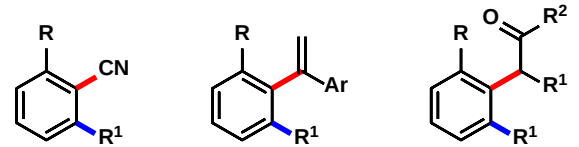
Aromatic *ortho*-alkylation

General overview



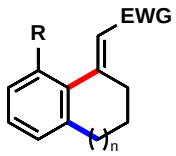


Heck (Catellani, 1999) **Suzuki** (Catellani, 2000) **Sonogashira** (Catellani, 2004) **hydrogenation** (Lautens, 2005)

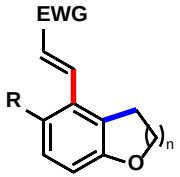


cyanation (Lautens, 2007) ***N*-tosylhydrazone insertion** (Liang, 2014) **enolate coupling** (Zhou, 2016)

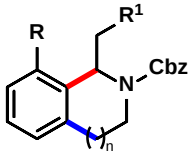
Some more complex examples



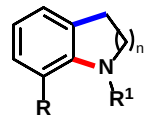
alkylation + intramolecular Heck coupling (Lautens, 2000)



intramolecular alkylation + Heck coupling (Lautens, 2003)

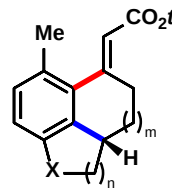


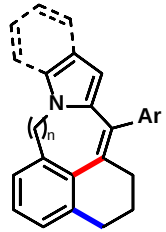
alkylation + intramolecular Heck coupling and aza-Michael (Catellani, 2004)



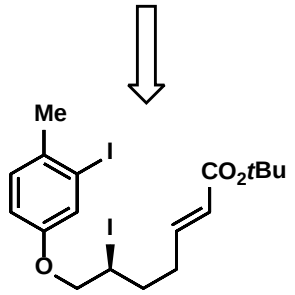
alkylation + intramolecular amination (Lautens, 2007)

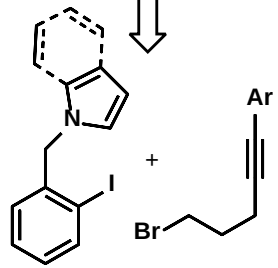
intramolecular alkylation + intramolecular Heck coupling (Lautens, 2007)



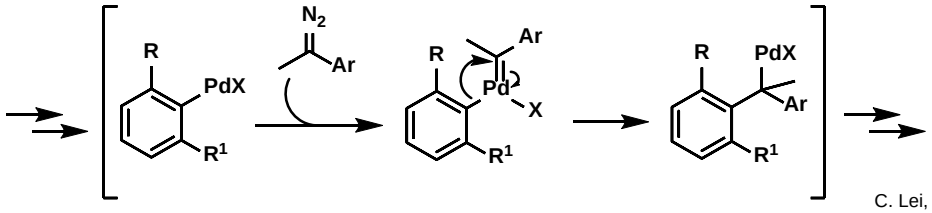


alkylation + intramolecular alkyne insertion (Lautens, 2007)



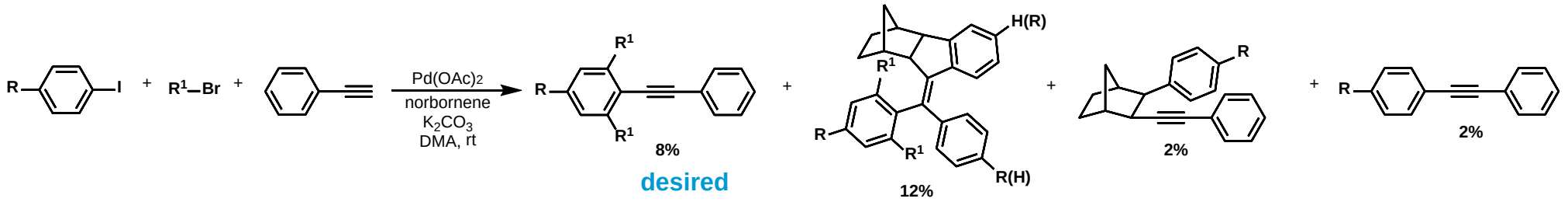


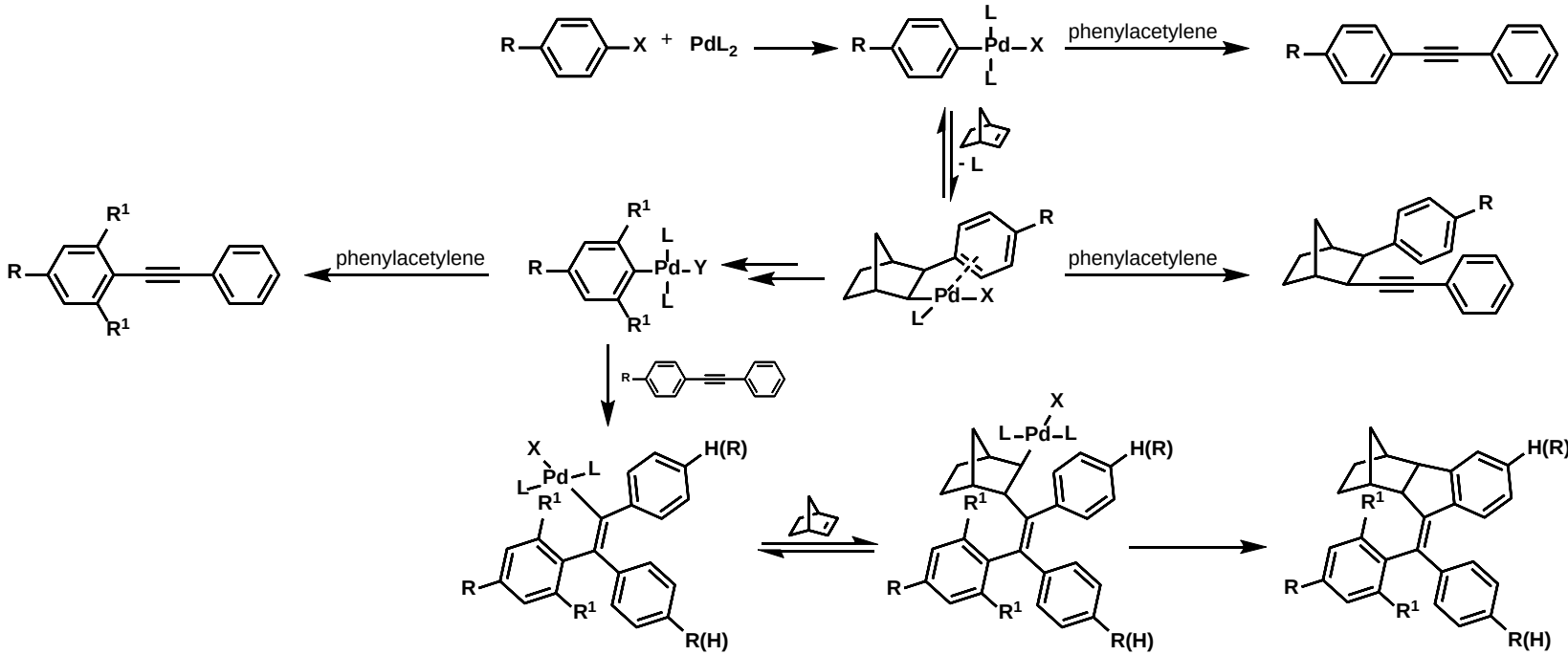
Mechanistic reminder



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. Piguel, *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.
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





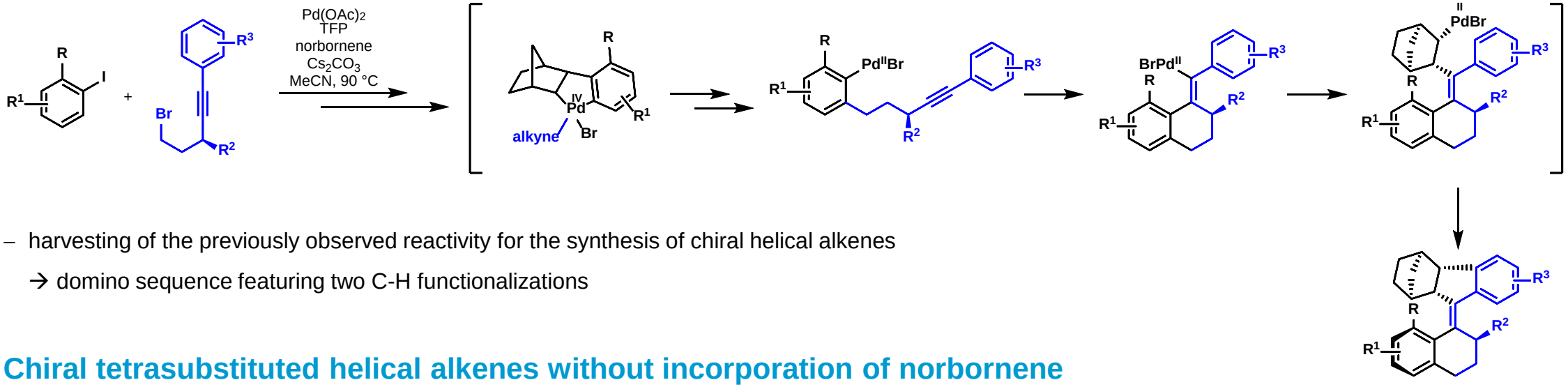
prevention of byproduct formation by:

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

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

Chiral helical alkenes

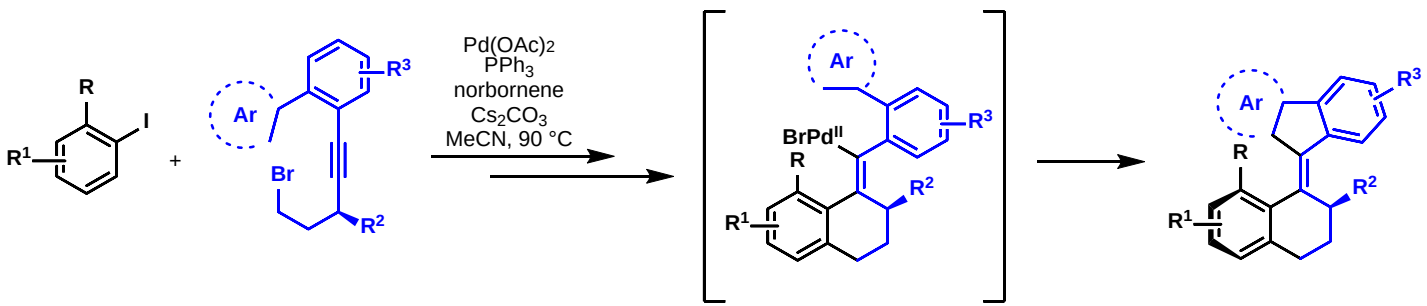
Chiral tetrasubstituted helical alkenes



– harvesting of the previously observed reactivity for the synthesis of chiral helical alkenes

→ domino sequence featuring two C-H functionalizations

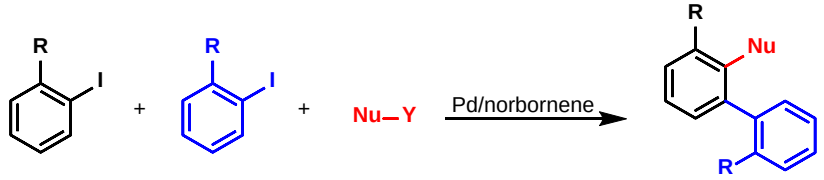
Chiral tetrasubstituted helical alkenes without incorporation of norbornene

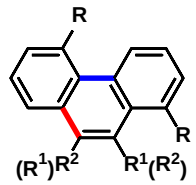


K. M. Gericke, D. I. Chai, N. Bieler, M. Lautens, *Angew. Chem. Int. Edit.* **2009**, *48*, 1447-1451.
H. Liu, M. El-Salfiti, D. I. Chai, J. Auffret, M. Lautens, *Org. Lett.* **2012**, *14*, 3648-3651.

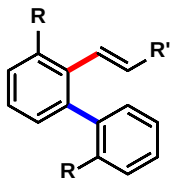
Aromatic *ortho*-arylation and the *ortho*-effect

Aromatic ortho-arylation

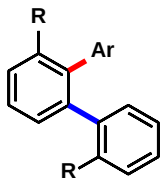




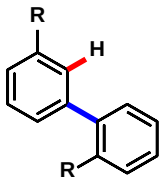
triple bond insertion
(Catellani, 2001)



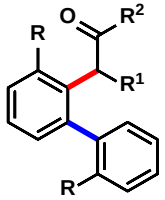
Heck
(Catellani, 2003)



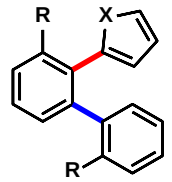
Suzuki
(Catellani, 2003)



hydrogenation
(Catellani, 2005)



enolate coupling
(Catellani, 2009)

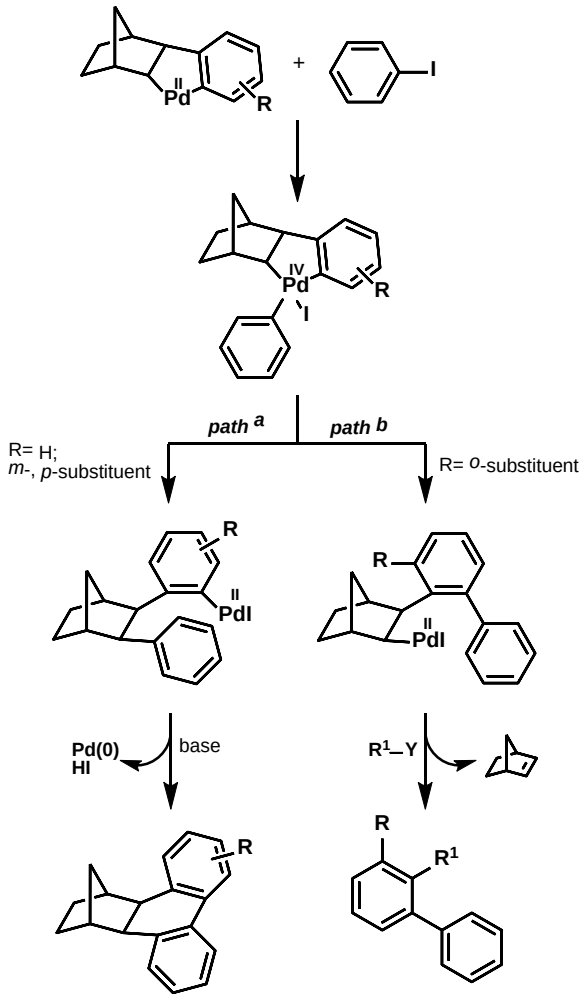


heteroaryl coupling
(Catellani, 2009)

X = O, S, NR

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. Cata.l A Chem.* **2003**, *204-205*, 115-124.

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

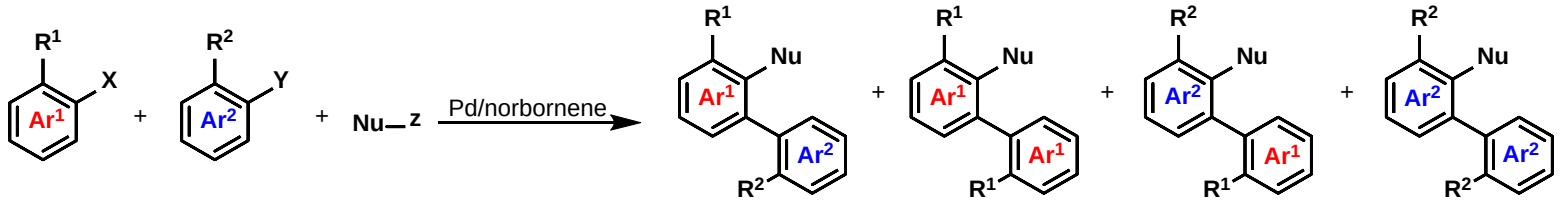
S. Deledda, E. Motti, M. Catellani, *Can. J. Chem.* **2005**, *83*, 741-747.
G. Maestri, N. Della Ca', M. Catellani, *Chem. Commun.* **2009**, 4892-4894.
N. Della Ca', G. Maestri, M. Catellani, *Chem.-Eur. J.* **2009**, *15*, 7850-7853.

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

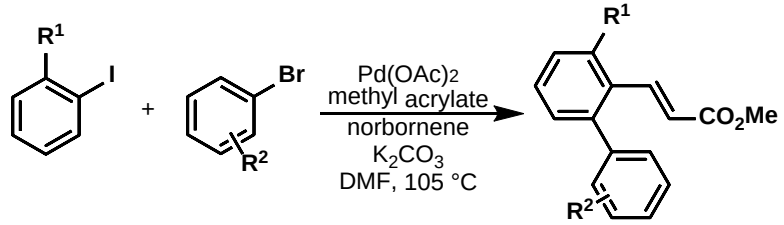
Chemoselectivity issue

→ 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)



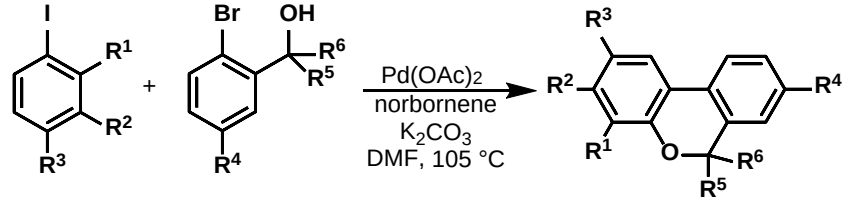
1) Adjustment of electronic properties (Catellani, 2004)



entry	R^1	R^2	yield	entry	R^1	R^2	yield
1	Me	*o*-CO_2Me	80	**8**	Me	*p*-CO_2Me	71
2	*t*Bu	*o*-CO_2Me	37	**9**	Me	*o*-CN	13
3	OMe	*o*-CO_2Me	83	**10**	Me	*m*-CN	62
4	NMe_2	*o*-CO_2Me	82	**11**	Me	*p*-CN	79
5	Ph	*o*-CO_2Me	73	**12**	Me	*m*-CF_3	71
6	Me	*m*-CO_2Me	37	**13**	Me	*p*-CF_3	80

F. Faccini, E. Motti, M. Catellani, *J. Am. Chem. Soc.* **2004**, *126*, 78-79.

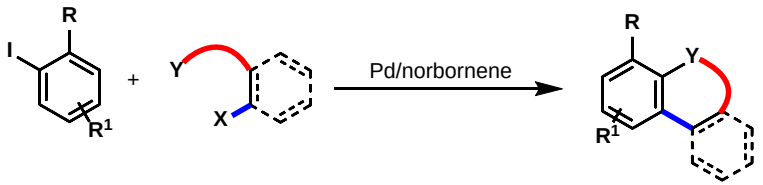
2) *ortho*-Coordination induced selectivity (Catellani, 2012)



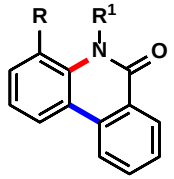
entry	R^1	R^2	R^3	R^4	R^5	R^6	yield
1	Me	H	H	H	Me	Me	79
2	*i*Pr	H	H	H	Me	Me	75
3	$(CH=CH)_2$		H	H	Me	Me	66
4	*n*Pr	H	H	H	Et	Et	98
5	OMe	H	H	H	Et	Et	90
6	$(CH=CH)_2$		H	OMe	Et	Et	98

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

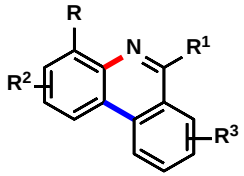
Polycyclic compounds from bifunctional reagents



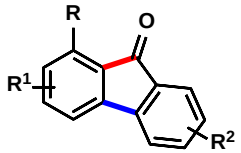
X = halide
Y = alkene, heteroaryl, amide, amine, alcohol, aldehyde, ester, ketone etc.



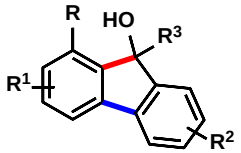
***ortho*-arylation + N-aryl coupling**
(Catellani, 2004)



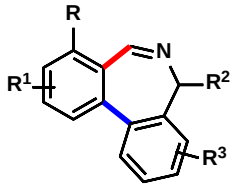
***ortho*-arylation + N-aryl coupling**
(Lautens, 2009)
(Malacria, 2010)



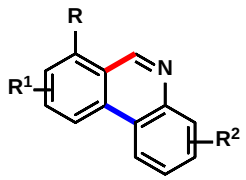
***ortho*-arylation + aldehyde addition**
(Lautens, 2009)



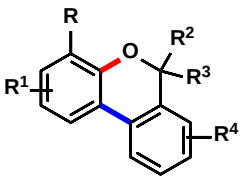
***ortho*-arylation + ketone addition**
(Lautens, 2009)



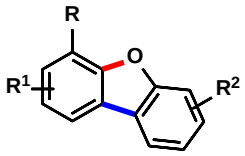
***ortho*-arylation + Heck + aza-Michael**
(Malacria, 2014)



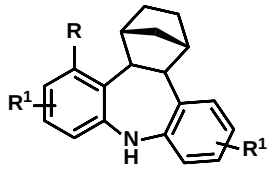
***ortho*-arylation + Heck + aza-Michael + "retro-Mannich"**
(Catellani, 2010)



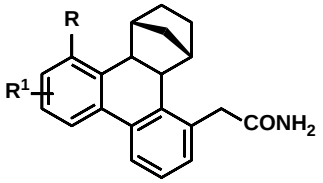
***ortho*-arylation + O-aryl coupling**
(Catellani, 2012)



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



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



***ortho*-arylation + norbornene insertion**
(Malacria, 2011)

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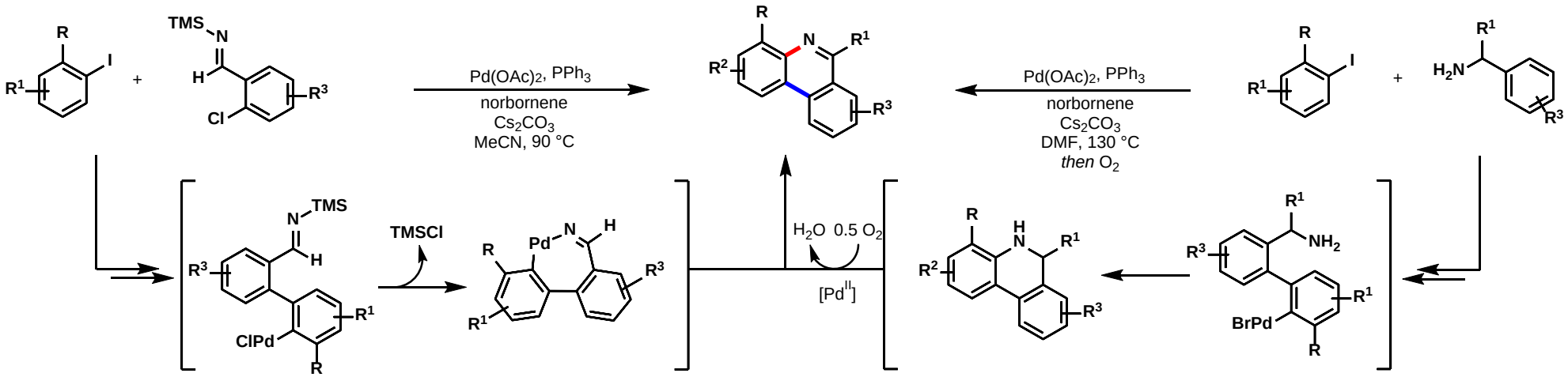
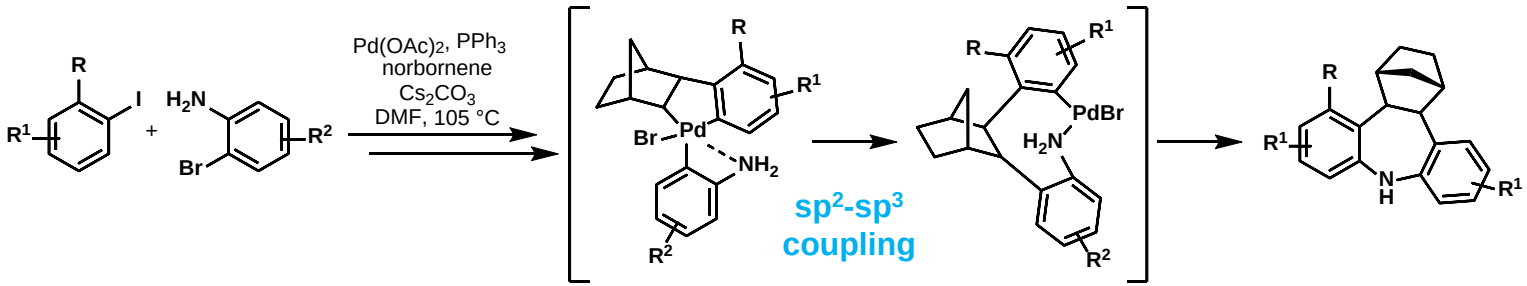
Polycyclic compounds – a closer look

Phenanthridines (Lautens, 2009/Malacria, 2010)



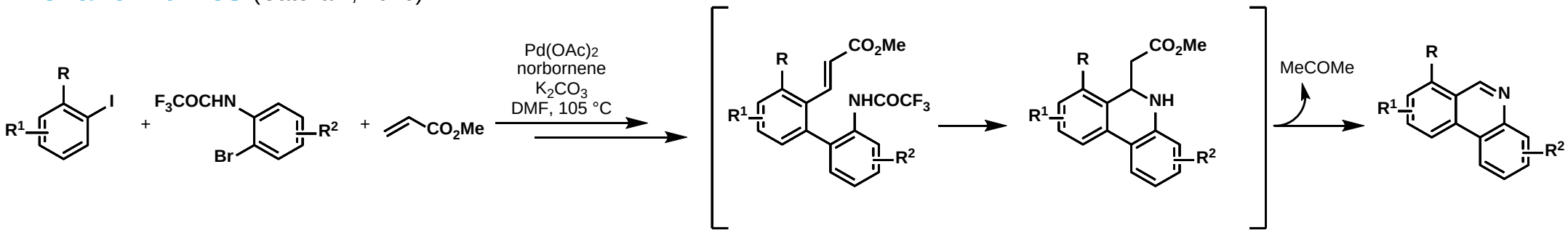
Dibenzoazepines (Catellani, 2011)



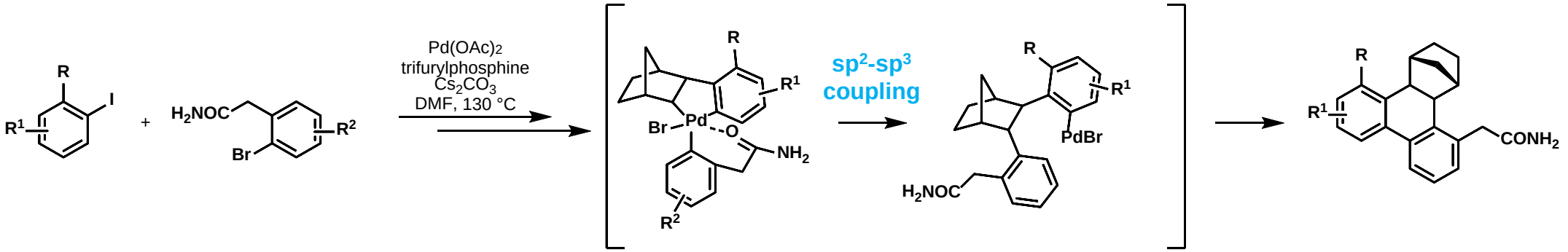
G. Maestri, M.-H. Larraufie, É. Derat, C. Ollivier, L. Fensterbank, E. Lacôte, M. Malacria, *Org. Lett.* **2010**, *12*, 5692-5695.
D. A. Candito, M. Lautens, *Angew. Chem. Int. Edit.* **2009**, *48*, 6713-6716.
N. Della Ca', G. Maestri, M. Malacria, E. Derat, M. Catellani, *Angew. Chem. Int. Edit.* **2011**, *50*, 12257-12261.

Polycyclic compounds – a closer look

Phenanthridines (Catellani, 2010)



Dihydrophenanthrene (Malacria, 2011)



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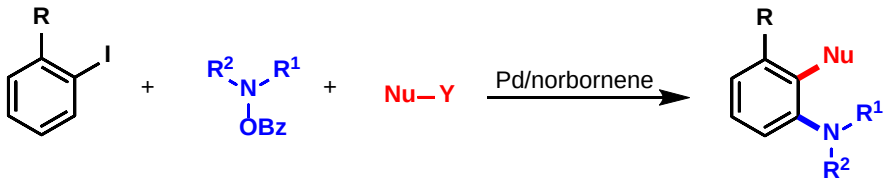
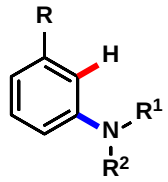
M.-H. Larraufie, G. Maestri, A. Beaume, É. Derat, C. Ollivier, L. Fensterbank, C. Courillon, E. Lacôte, M. Catellani, M. Malacria, *Angew. Chem. Int. Edit.* **2011**, *50*, 12253-12256.

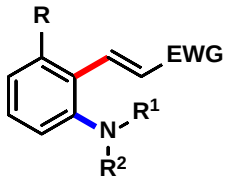
Aromatic *ortho*-amination/-acylation

ortho-Amination

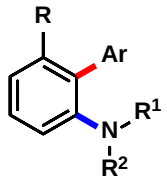




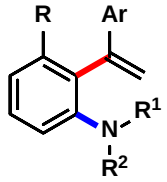
hydrogenation
(Dong, 2013)



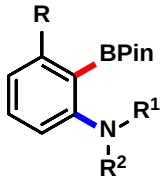
Heck
(Chen, 2014)



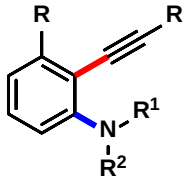
Suzuki
(Chen, 2014)



***N*-tosylhydrazone insertion**
(Liang, 2014)

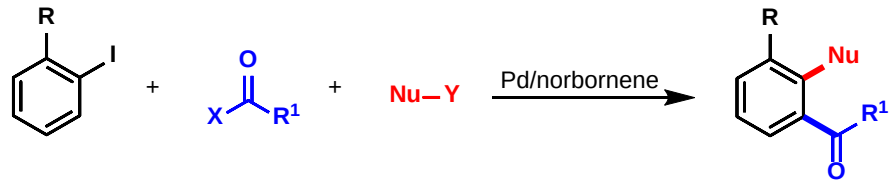


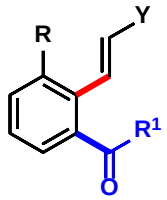
borylation
(Ritter, 2015)



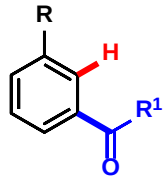
alkynylation
(Gu, 2015)

ortho-acylation

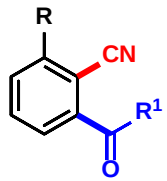




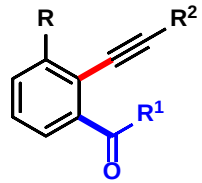
Heck
(Liang, 2015)
(Gu, 2015)



hydrogenation
(Dong, 2015)



cyanation
(Chen, 2016)



alkynylation
(Shi, 2018)

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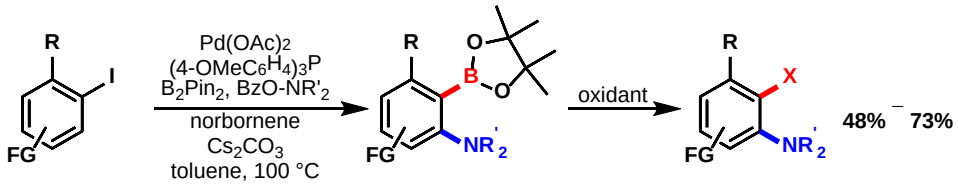
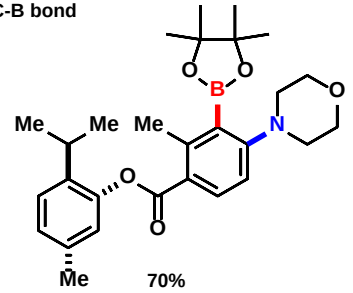
Aromatic *ortho*-amination + hetero-bond formation

General scope

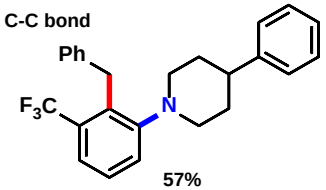


C-B bond



70%

C-C bond



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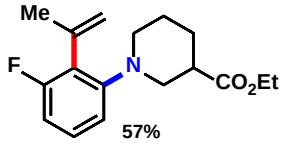

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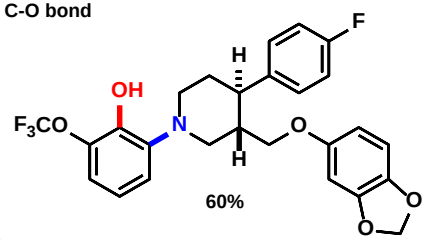
C-O bond



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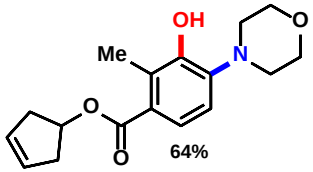
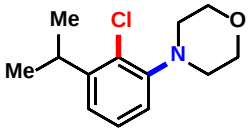


64%

C-X bond



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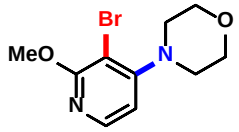

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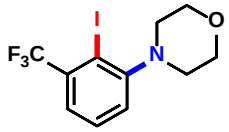
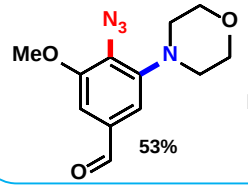


54%

C-N bond



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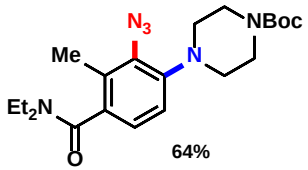

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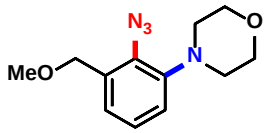
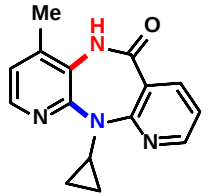
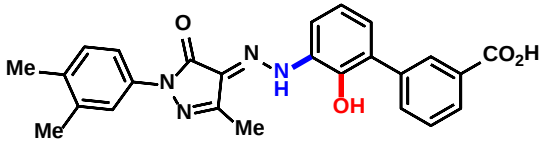


51%

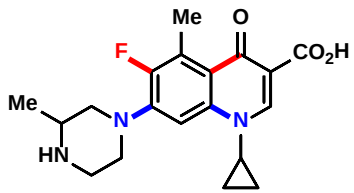
Reoccurring motif in pharmaceuticals



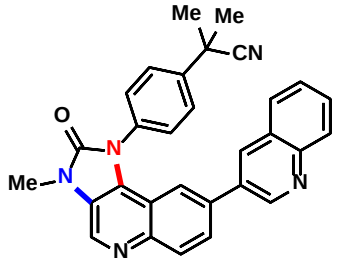
viramune



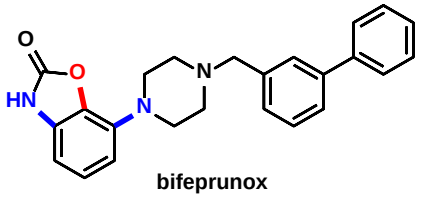
eltrombopag



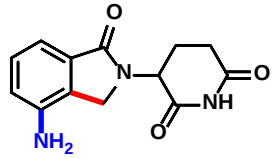
grepafloxacin



dactolisib



bifeprunox



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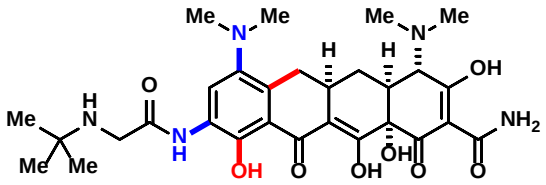
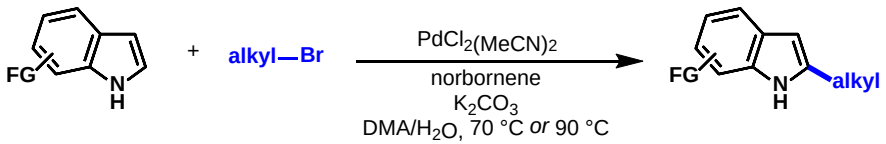


tygacil

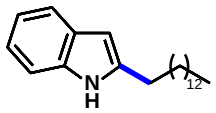
H. Shi, D. J. Babinski, T. Ritter, *J. Am. Chem. Soc.* **2015**, *137*, 3775-3778.

C2-Alkylation of indole and pyrrole derivatives

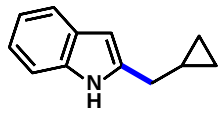
Alkylation of indoles



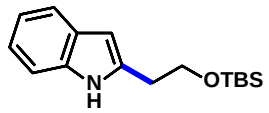
FG = EWG *or* EDG



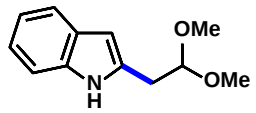
67% (9%)*



58% (11%)*



82%



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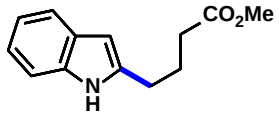
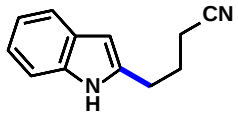
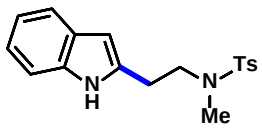


61% (12%)**



56% (19%)**



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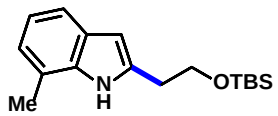

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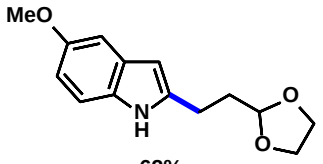

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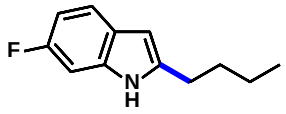
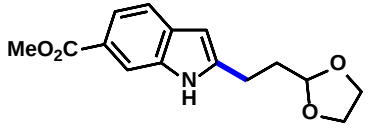
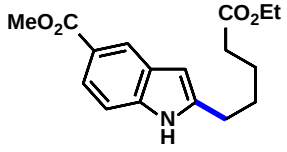


59% (14%)*



86%



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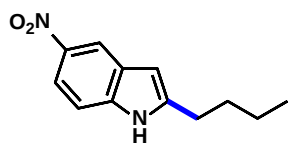
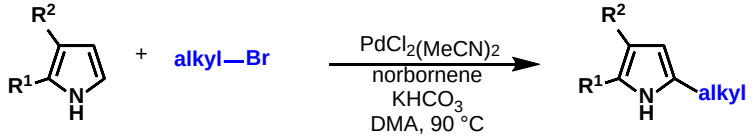


90%

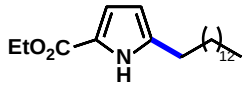
* Yield for the corresponding 2,3-dialkylated product.
** Dialkylation could be suppressed by employing 2 equiv. indole and 1 equiv. bromide.

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

Alkylation of pyrroles



EWG needed as R^1 or R^2



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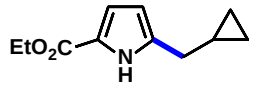

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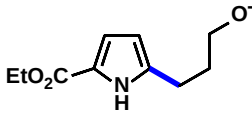

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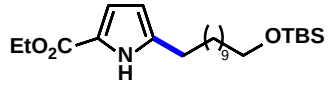

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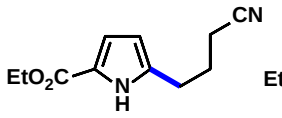

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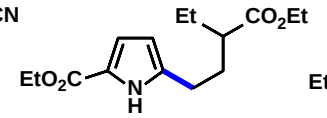

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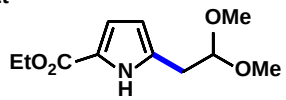

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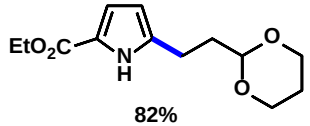

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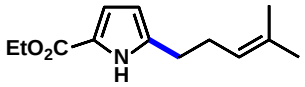

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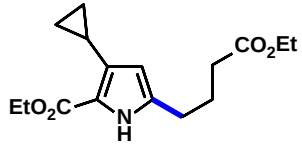

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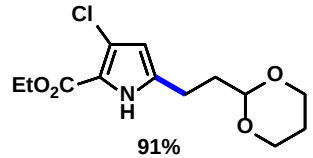

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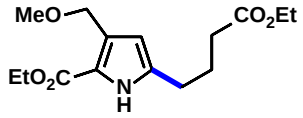

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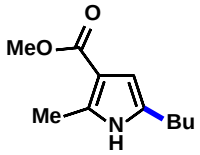

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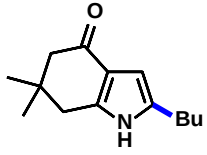

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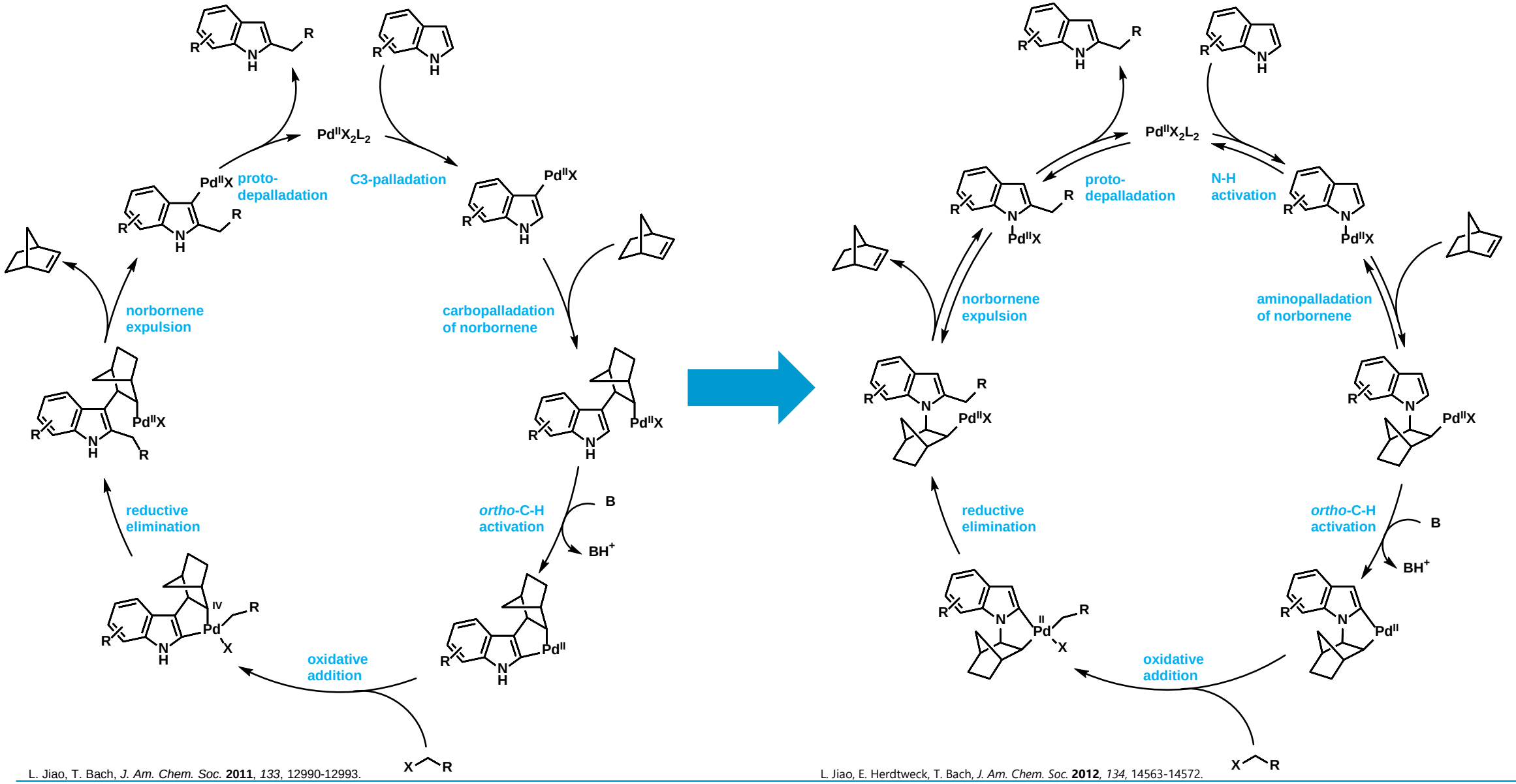
L. Jiao, T. Bach, *Angew. Chem. Int. Edit.* **2013**, *52*, 6080-6083.

2-Alkylation of indoles: revision of the catalytic cycle

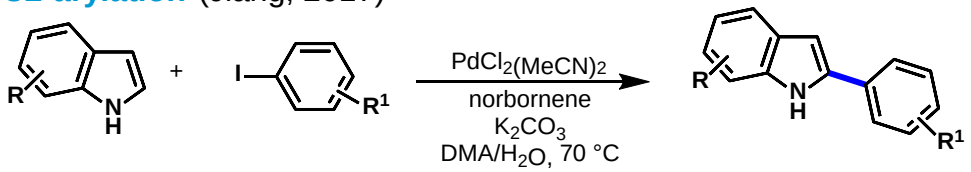


L. Jiao, T. Bach, *J. Am. Chem. Soc.* **2011**, *133*, 12990-12993.

L. Jiao, E. Herdtweck, T. Bach, *J. Am. Chem. Soc.* **2012**, *134*, 14563-14572.

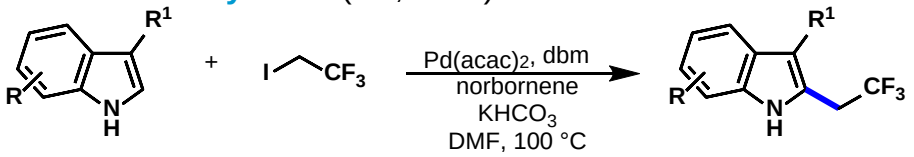
Advancement in methodology and synthetic applications

C2-arylation (Jiang, 2017)



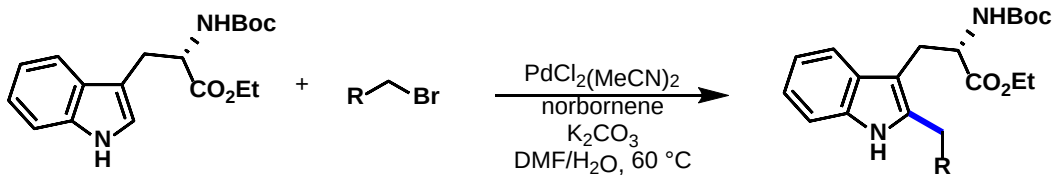
– R = EWG or EDG tolerated, but e⁻-rich indole + e⁻-deficient aryl iodide work best

C2-trifluoroethylation (Liu, 2018)



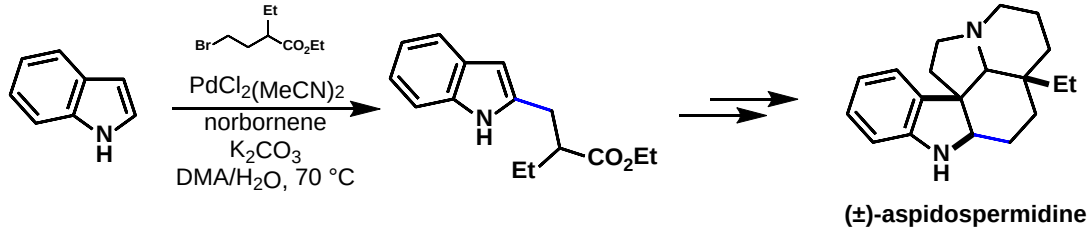
– anionic ligands needed to enhance nucleophilicity of palladacycle

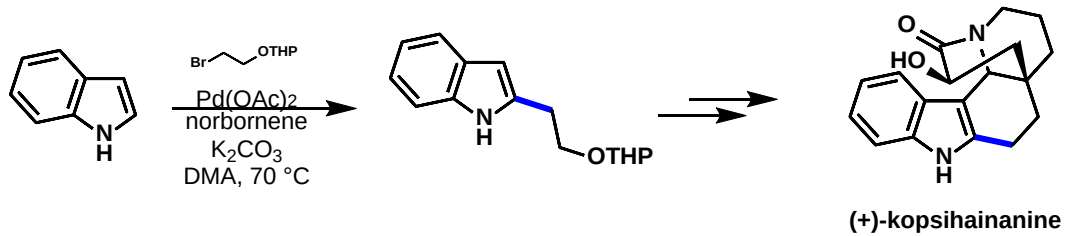
C-H alkylation of tryptophan (Bach, 2013)

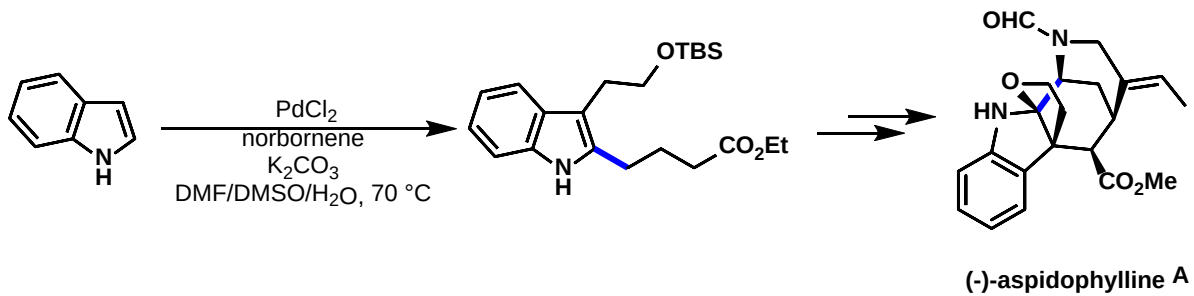


– Boc-protection prevents interference of the NH-position with palladation of indolic nitrogen

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.
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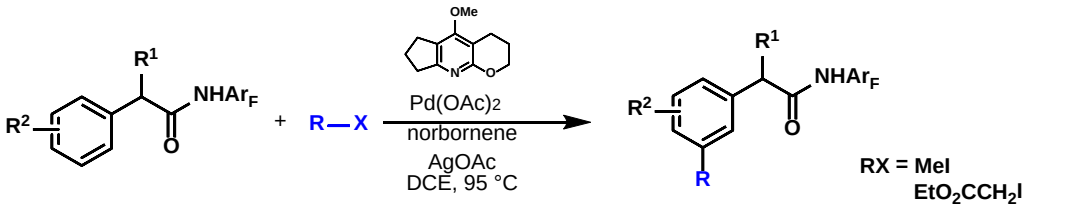
meta-Selective C-H bond activation

General idea

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

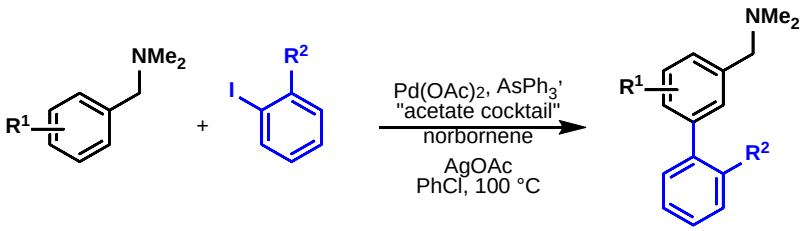
meta-Alkylation (Yu, 2015)



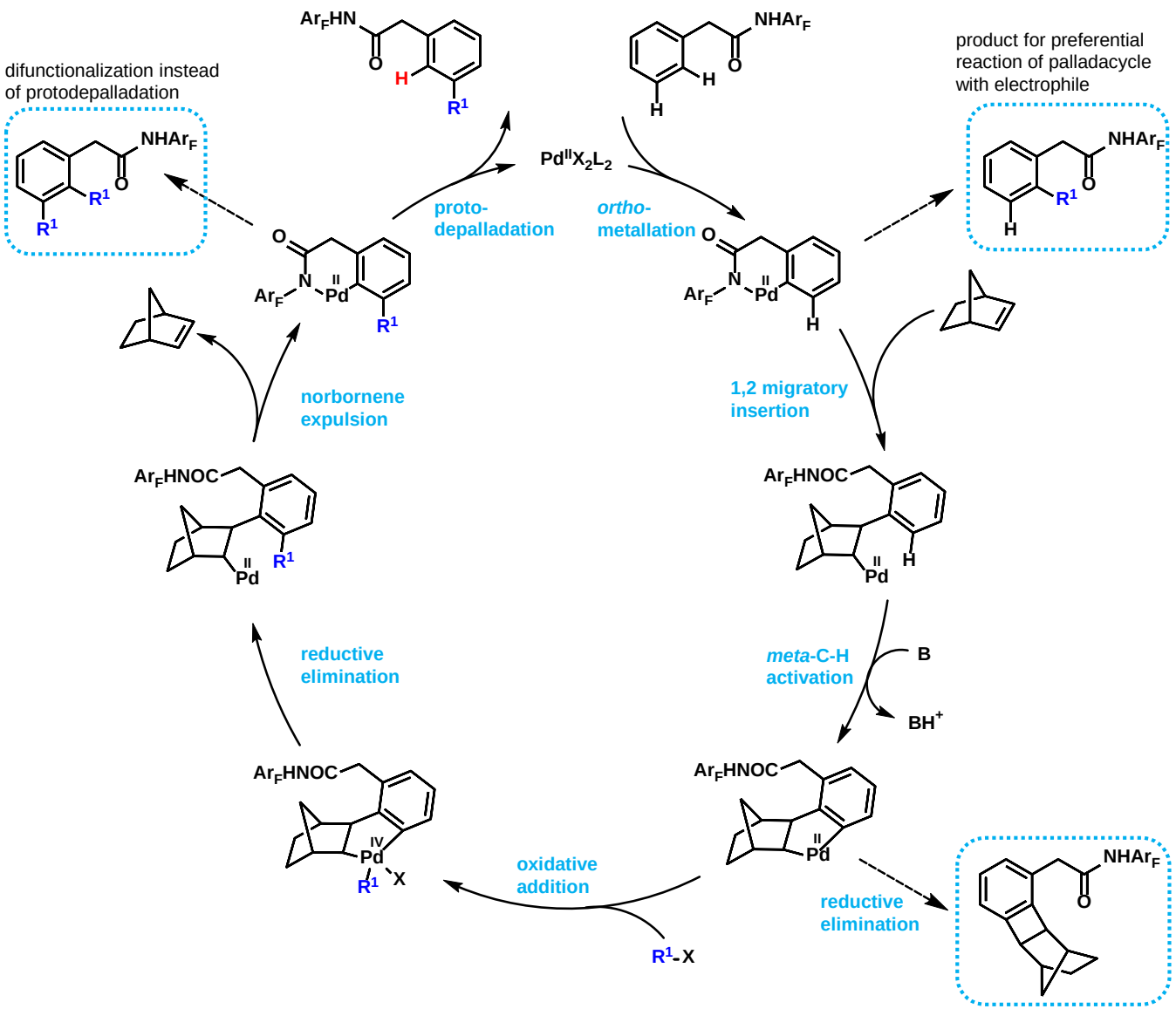
RX = MeI
EtO_2CCH_2I
$ArCH_2Br$
o-$MeO_2CC_6H_4I$

Ar_F = 4-$(CF_3)C_6F_4$

meta-Arylation (Dong, 2015)

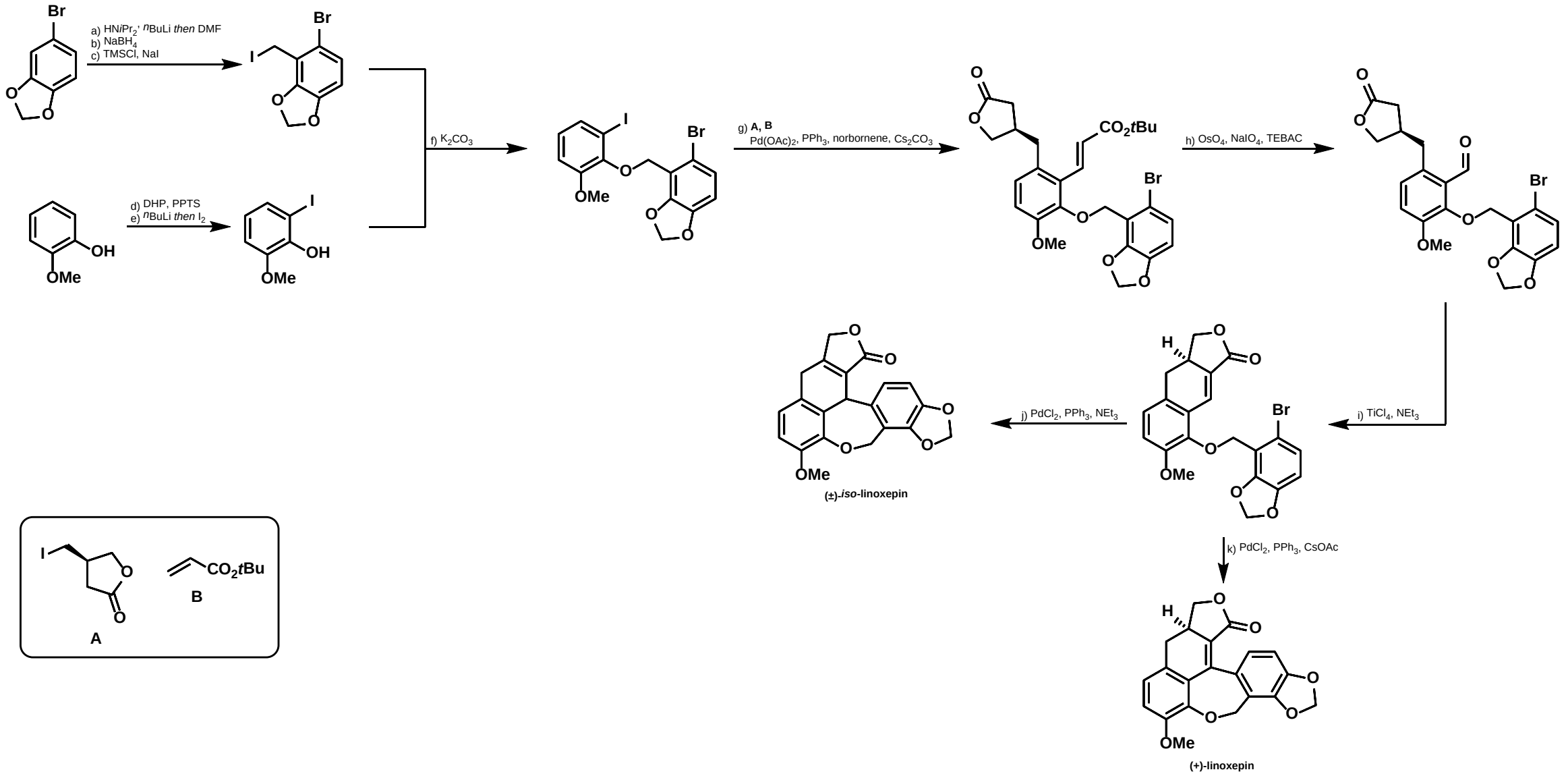


– acetate cocktail…? → $LiOAc•2H_2O$, $CsOAc$, $Cu(OAc)_2•H_2O$



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.

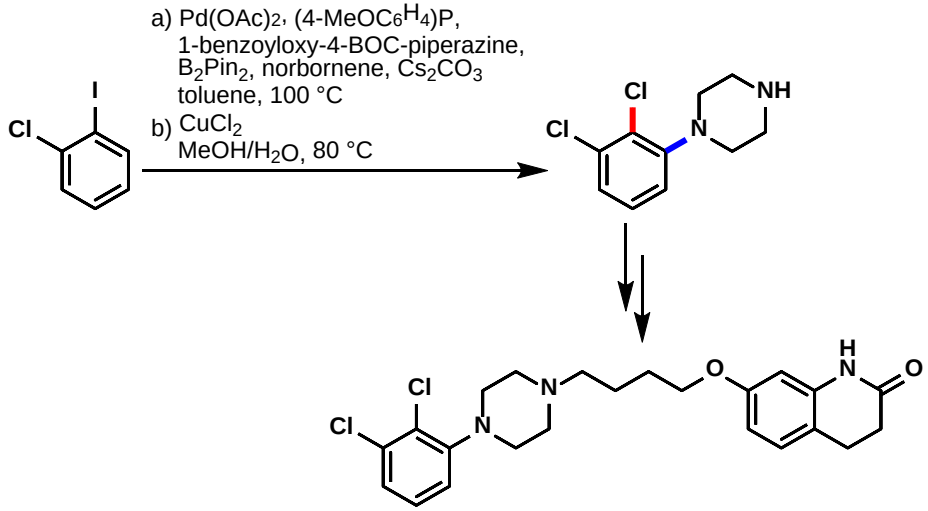
Applications: Total synthesis of (+)-linoxepin



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

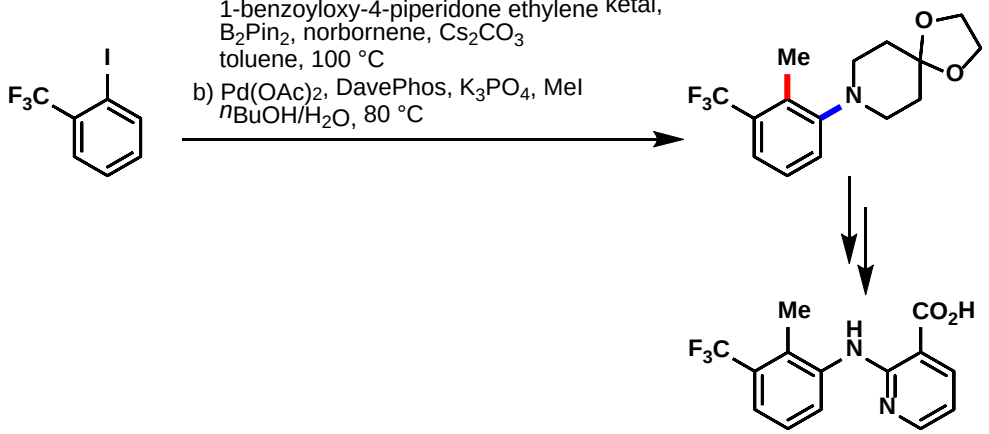
Applications: The Catellani reaction as key step in total synthesis

Abilifly



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

Flunixin



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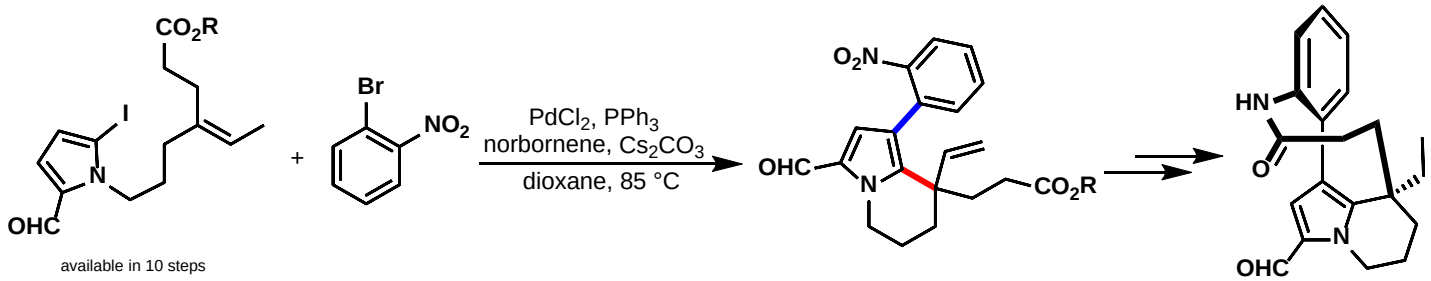
Rhazinal



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.

Universität Konstanz

Thanks for your kind attention!

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