

Reviews:

Abel-Magid, A. F.; Mehrman, S. J. *Org. Proc. Res. Devel.* **2006**, *10*, 971–1031.

Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849–3862.

Bhattacharyya, S. *Tetrahedron Lett.* **1994**, *35*, 2401–2404.

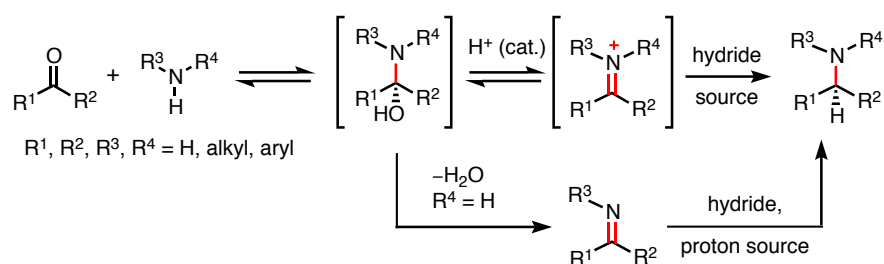
Hutchins, R. O.; Hutchins, M. K., Reduction of CdN to CHNH by Metal Hydrides. In *Comprehensive Organic Synthesis*; Trost, B. N., Fleming, I., Eds.; Pergamon Press: New York, **1991**; Vol. 8.

Overview:

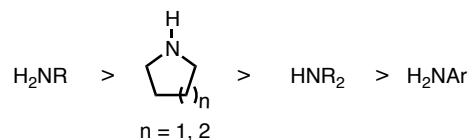
- The reductive amination of aldehydes and ketones is an important method for the synthesis of primary, secondary, and tertiary amines.
- Reductive amination is a powerful and reliable strategy for the formation of C–N bonds, and can avoid the problem of overalkylation that often accompanies direct alkylation of amines with alkyl halides.

Mechanism:

- Reductive amination involves a one- or two-step procedure in which an amine and a carbonyl compound condense to afford an imine or iminium ion that is reduced *in situ* or subsequently to form an amine product.



- relative rates of reductive amination:

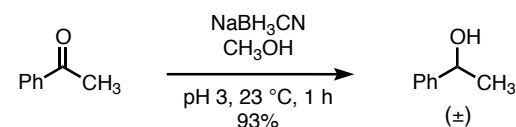


Reducing Agents

- Common reducing agents: NaCNBH_3 , $\text{Na(OAc)}_3\text{BH}$, $\text{H}_2/\text{catalyst}$
- Iminium ions are reduced selectively in the presence of their carbonyl precursors. Reagents such as sodium cyanoborohydride and sodium triacetoxyborohydride react selectively with iminium ions and are frequently used for reductive aminations.

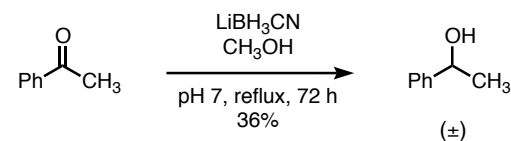
Reduction with Sodium Cyanoborohydride:

- Borch and co-workers showed that sodium cyanoborohydride and lithium cyanoborohydride are acid-stable reagents capable of rapidly reducing carbonyl compounds to alcohols at pH 3–4, presumably via a protonated carbonyl cation.



Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897–2904.

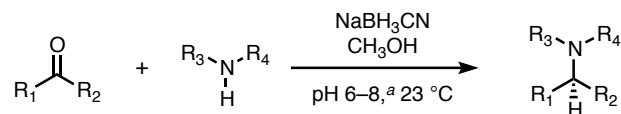
- At pH 7, reduction of carbonyl compounds with lithium cyanoborohydride is very slow, even at reflux in methanol.

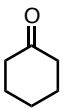
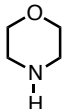
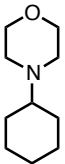
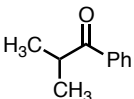
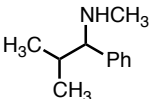

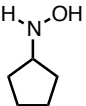
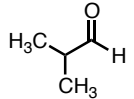
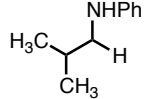
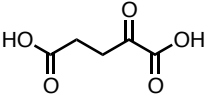
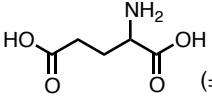


Borch, R. F.; Durst, H. D. *J. Am. Chem. Soc.* **1969**, *91*, 3996–3997.

Jonathan William Medley, Fan Liu

- With care to maintain a pH of 6–7, a mixture of a ketone or aldehyde reactant, an amine, and sodium cyanohydrin provides products of reductive amination selectively, without competitive reduction of the carbonyl substrate.
- Though the conditions of the Borch reduction are mild, sodium cyanoborohydride is highly toxic, as are its byproducts.



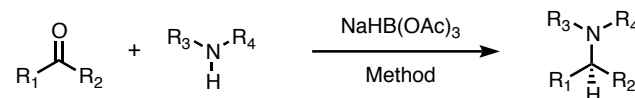
| carbonyl compound | amine | product | isolated yield (%) |
|---|---|---|--------------------|
|  |  |  | 79 |
|  | CH_3NH_2 |  | 90 |
|  | H_2NOH |  | 66 |
|  | PhNH_2 |  | 78 |
|  | NH_3 |  (±) | 51 |


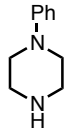
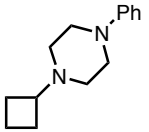
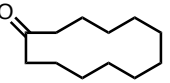
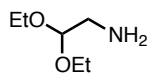
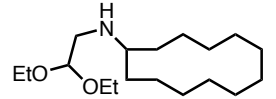
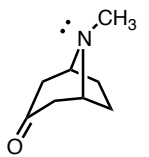
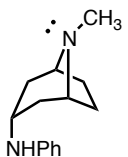
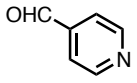
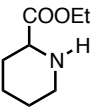
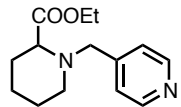
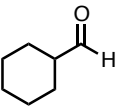
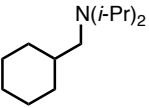
^aThe pH was maintained by addition of HCl and/or KOH as needed using bromocresol green as an indicator.

Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897–2904.

Reduction with Sodium Triacetoxyborohydride:

- Sodium triacetoxyborohydride has been found to be a highly selective reducing agent for reductive amination; acetic acid is frequently employed as a proton donor.
- This protocol is generally high yielding, highly functional group tolerant, and proceeds without release of cyanide salts. The substrate scope includes aromatic and aliphatic aldehydes, ketones, and primary and secondary amines. Ammonia can be employed successfully if used in large excess as its acetate salt.

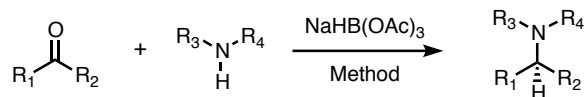



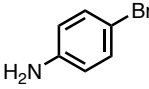
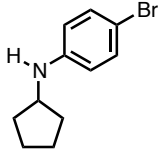

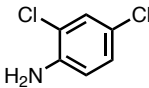
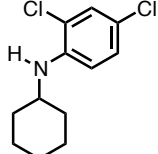
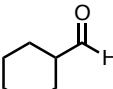
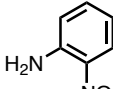
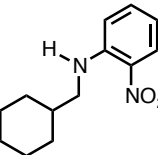

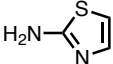
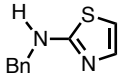


| carbonyl compound | amine | method ^a | product | yield (%) |
|---|---|---------------------|---|-----------------|
|  |  | II |  | 96 |
|  |  | II |  | 88 |
| cycloheptanone | NH_4OAc (10 equiv) | II ^b | cycloheptylamine | 80 ^c |
|  | PhNH_2 | I |  | 96 |
|  |  | II |  | 95 |
|  | $(i\text{-Pr})_2\text{NH}$ | II |  | 88 |

^aMethod I: $\text{ClCH}_2\text{CH}_2\text{Cl}$, AcOH (1–2 equiv), $\text{NaBH}(\text{OAc})_3$ (1.3–1.6 equiv). Method II: $\text{ClCH}_2\text{CH}_2\text{Cl}$, $\text{NaBH}(\text{OAc})_3$ (1.3–1.6 equiv). ^b Et_3N (1.5–2.0 equiv) added. ^cyield of HCl salt.

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Reaction with Weakly Nucleophilic Amines:



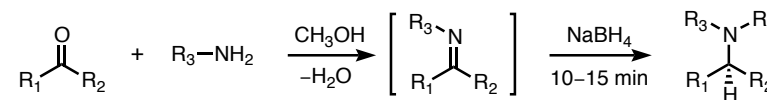
| carbonyl compound | amine | method ^a | product | yield (%) |
|---|---|---------------------|---|-----------------|
|  |  | III |  | 89 ^b |
|  |  | IV |  | 95 |
|  |  | IV |  | 95 |
|  |  | IV |  | 60 |
|  | H ₂ N-Ts | IV ^c |  | 80 |

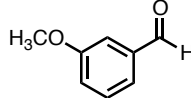
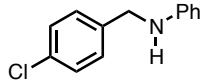
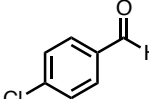

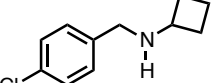
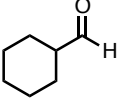
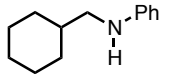
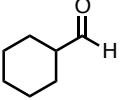
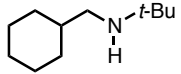
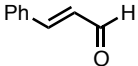
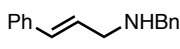
^aMethod III: ClCH₂CH₂Cl, AcOH (1 equiv), NaBH(OAc)₃ (1.4 equiv). Method IV: ClCH₂CH₂Cl, AcOH (2–5 equiv), carbonyl compound (1.5–2 equiv), NaBH(OAc)₃ (2.0–2.8 equiv). ^byield of HCl salt. ^cEt₃N (2.0 equiv) added.

Reduction with Sodium Borohydride:

• Reductive amination of carbonyl compounds with primary amines can be complicated by overalkylation. In these cases, formation and isolation of the imine followed by reduction can prove to be a superior alternative.

• It was found that the use of methanol as solvent allows for rapid (< 3h) and nearly quantitative imine formation from aldehydes without the need for dehydrating reagents.



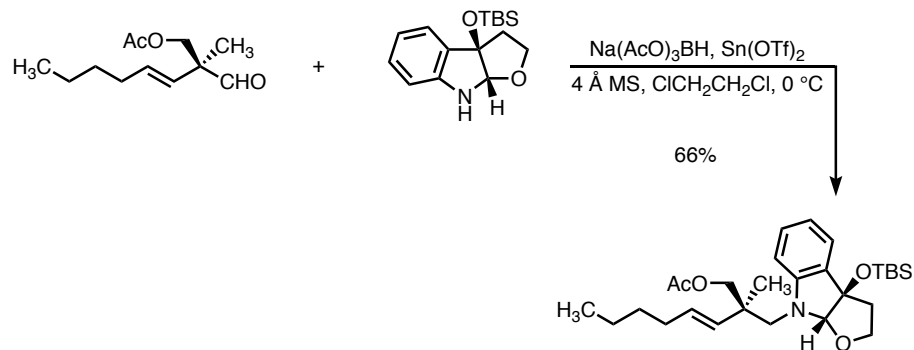
| aldehyde | amine | product | yield (%) ^a |
|---|---|---|------------------------|
|  | PhNH ₂ |  | 84 |
|  |  |  | 89 |
|  | PhNH ₂ |  | 90 |
|  | <i>t</i> -BuNH ₂ |  | 83 |
|  | BnNH ₂ |  | 85 |

^aproducts isolated as HCl salts.

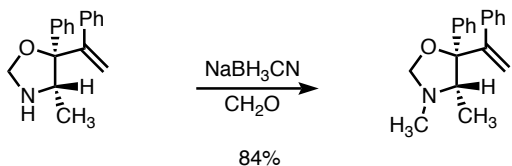
Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849–3862.

Jonathan William Medley

Examples in Synthesis

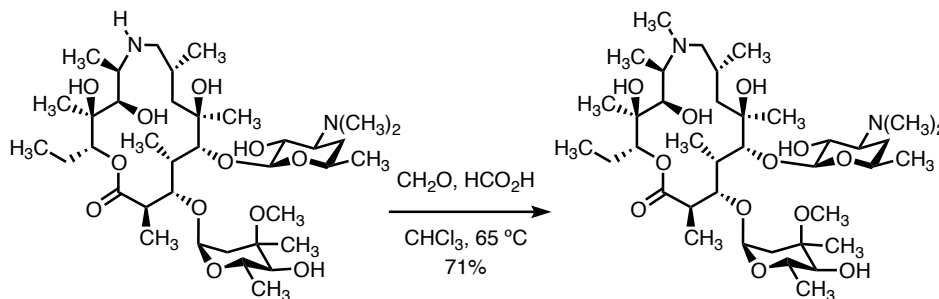


Hosokawa, S.; Sekiguchi, K.; Hayase, K.; Hirukawa, Y.; Kobayashi, S. *Tetrahedron Lett.* **2000**, *41*, 6435-6439.

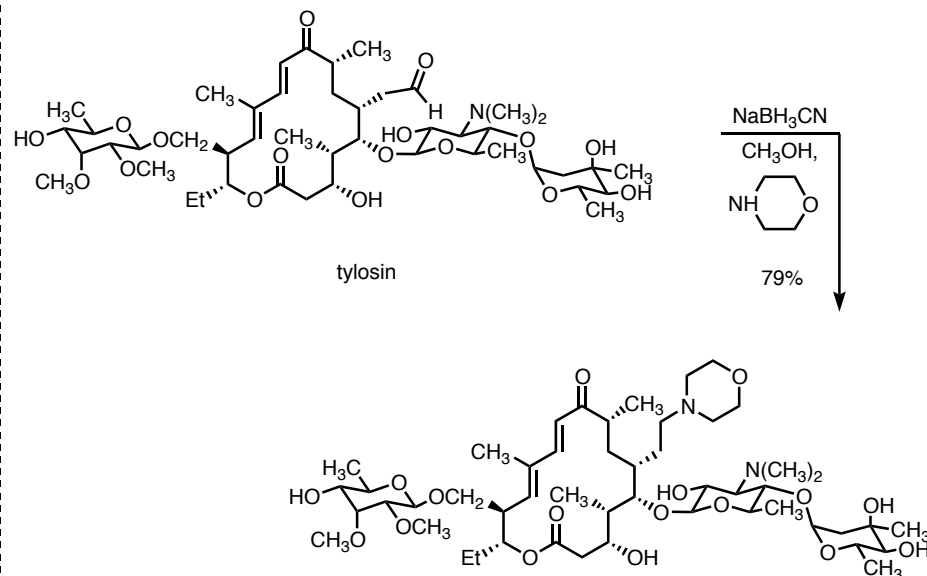


Jacobsen, E. J.; Levin, J.; Overman, L. E. *J. Am. Chem. Soc.* **1988**, *110*, 4329-4336.

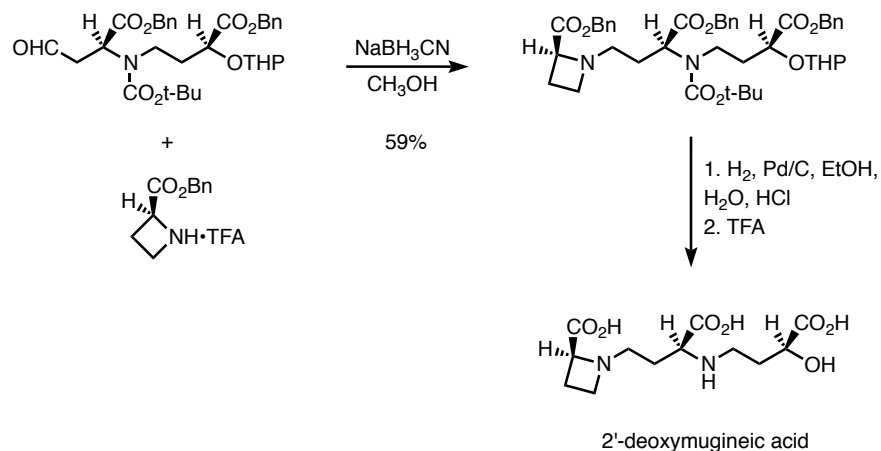
- Formic acid can also be used as a hydride donor:



Dokic, S.; Kobrehel, G.; Lopotar, N.; Kamenar, B.; Nagl, A.; Mrvos, D. *J. Chem. Res (S)*. **1988**, 152.



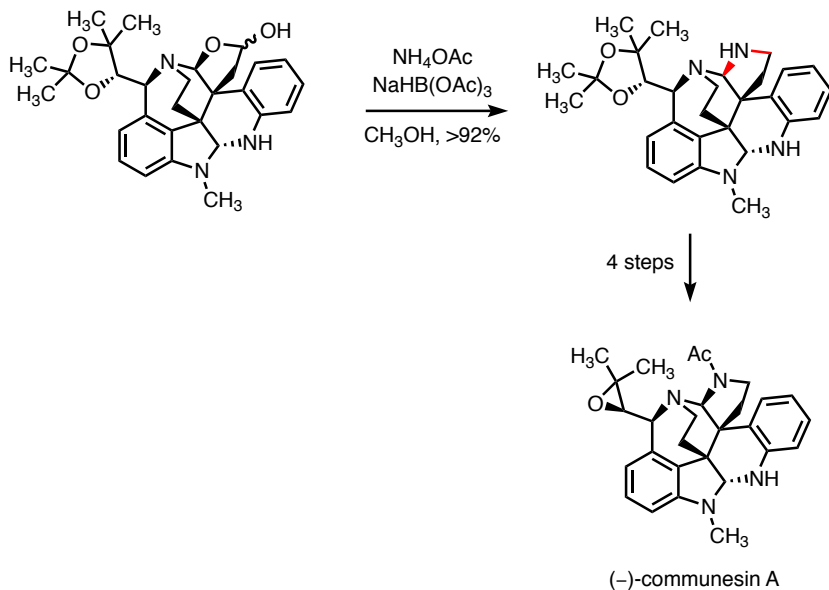
Matsubara, H.; Inokoshi, J.; Nakagawa, A.; Tanaka, H.; Omura, S. *J. Antibiot.* **1983**, *36*, 1713-1721.



Ohfuné, Y.; Tomita, M.; Nomoto, K. *J. Am. Chem. Soc.* **1981**, *103*, 2409-2410.

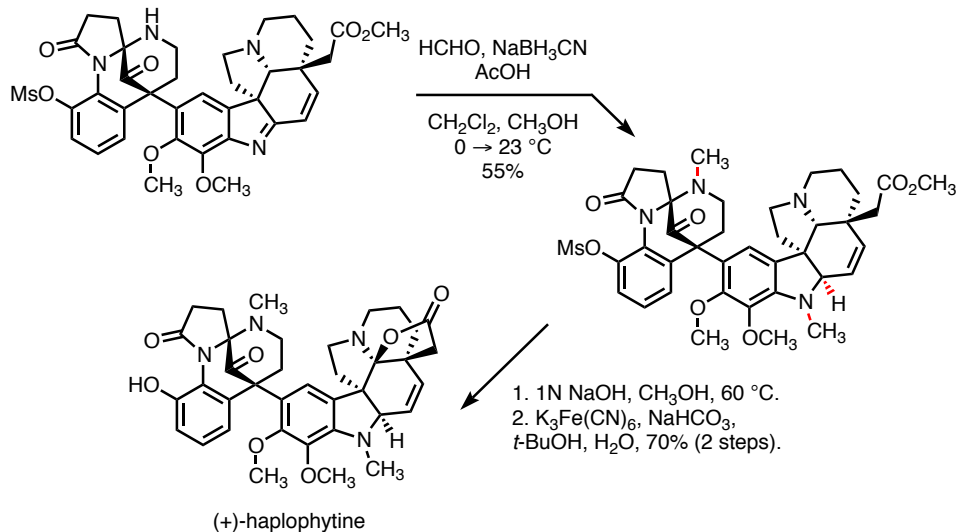
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- A regioselective reductive amination using sodium triacetoxyborohydride was employed in the construction of the pyrrolidine ring of (–)-communesin A:



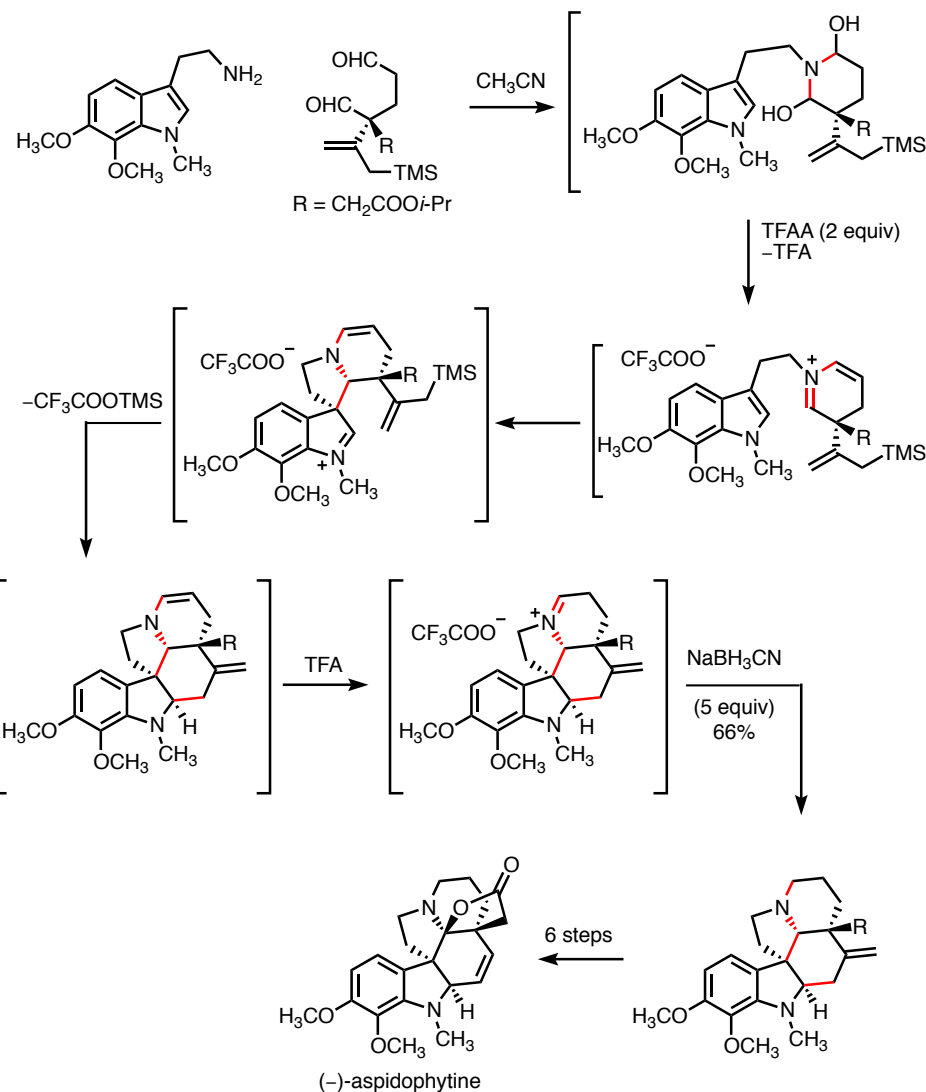
Zuo, Z.; Ma, D. *Angew. Chem., Int. Ed.* **2011**, *50*, 12008–12011.

- Regio- and stereoselective indolenine reduction and reductive methylation of two secondary amines was achieved using Borch conditions en route to (+)-haplophytine.



Ueda, H.; Satoh, H.; Matsumoto, K.; Sugimoto, K.; Fukuyama, T.; Tokuyama, H. *Angew. Chem., Int. Ed.* **2009**, *48*, 7600–7603.

- In a complex transformation, a tryptamine derivative and an enantioenriched dialdehyde were combined to give a cyclic bis-hemiaminal intermediate; electrophilic activation with trifluoroacetic anhydride initiated a Mannich/Sakurai cascade. Subsequent iminium reduction with sodium cyanoborohydride afforded a pentacyclic diamine en route to (–)-aspidoptytine.



He, F.; Bo, Y.; Altom, J.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 6771–6772.

Jonathan William Medley

Reviews:

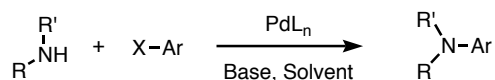
Surry, D. S.; Buchwald, S. L. *Chem. Sci.* **2011**, *2*, 27–50.

Klinkenberg, J. L.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2011**, *50*, 86–95.

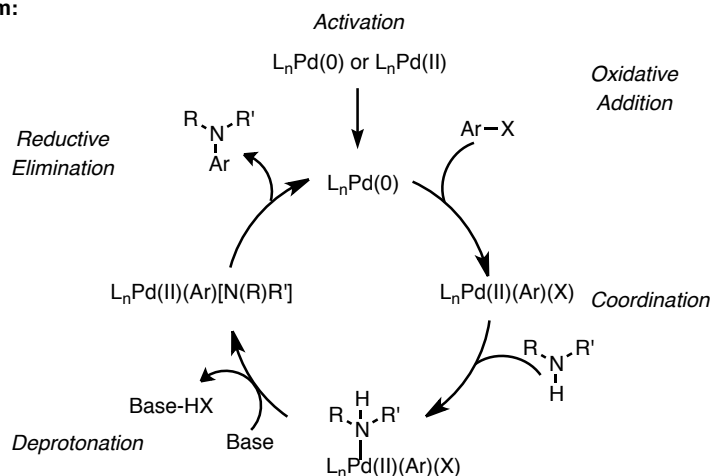
Industrial Review of C-N and C-O Coupling:

Schlummer, B.; Scholz, U. *Adv. Synth. Catal.* **2004**, *346*, 1599–1626.

- The Buchwald-Hartwig reaction is the coupling of an amine with an aryl halide mediated by a palladium catalyst.



Mechanism:



The Base (bolded bases are the most commonly used):

- For fast reactions: strong bases such as **NaOt-Bu**, KOH (uncrushed pellets)
- For substrates bearing sensitive functional groups: weaker bases such as K_3PO_4 , Cs_2CO_3 , **K_2CO_3 with *t*-BuOH or *t*-amyl alcohol**
- For substrates bearing acidic functional groups, use of LiHMDS as base affords lithiates that can prevent catalyst inhibition.

Harris, M. C.; Huang, X.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 2885–2888.

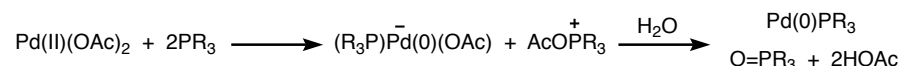
Solvent Choices:

- Most general: toluene, THF, DME, dioxane, and tertiary alcohols
- Water is compatible but rates of reaction are often slower.
- DMF, NMP, MeCN, acetone, etc., should be avoided as single solvents, but they can be great co-solvents, especially for substrates containing potentially chelating functional groups that otherwise might inhibit catalysis.

Activation

- In order for the catalytic cycle to begin, palladium must be in the Pd(0) oxidation state. One of the most common Pd(0) sources is Pd_2dba_3 .

- Pd(II) sources can be used and are more stable, but they require reduction to Pd(0). One of the most common activation methods is via reduction of $\text{Pd}(\text{OAc})_2$ with PR_3 , water, and heat.

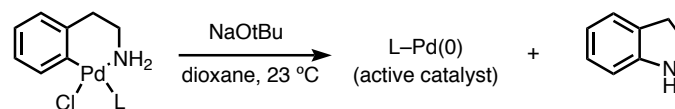


Ozawa, F.; Kubo, A.; Hayashi, T. *Chem. Lett.* **1992**, *11*, 2177–2180

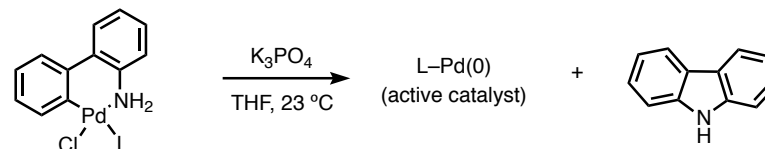
Amatore, C.; Carre, E.; Jutand, A.; M'Barki, M. *Organometallics* **1995**, *14*, 1818–1826

Fors, B. P.; Krattiger, P.; Strieter, E.; Buchwald, S. L. *Org. Lett.* **2008**, *10*, 3505–3508.

- Precatalyst systems allow for lower reaction temperatures.



Biscoe, M. R.; Fors, B. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, *130*, 6686–6687.

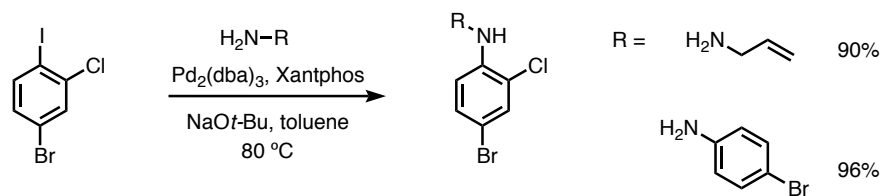


Kinzel, T.; Zhang, Y.; Buchwald, S. L. *J. Am. Chem. Soc.* **2010**, *132*, 14073–14075.

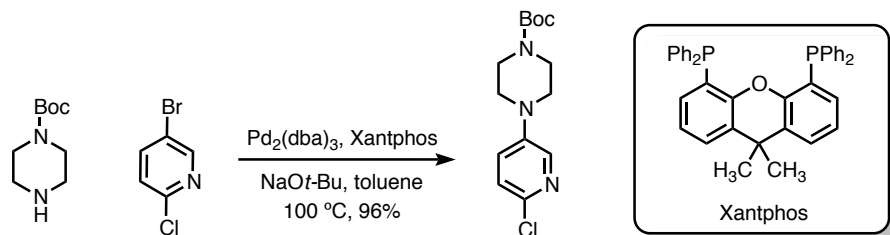
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Oxidative Addition

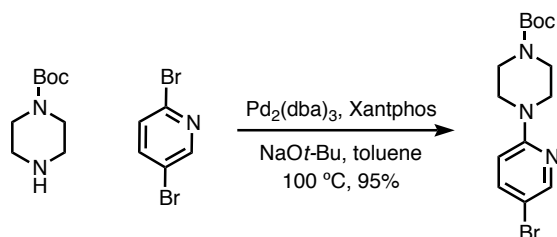
- Electron-rich and sterically hindered aryl halides undergo **slower** oxidative addition. Reactivity order: I > Br > OTf > Cl > OTs.



Larsen, S. B.; Bang-Andersen, B.; Johansen, T. N.; Jorgensen, M. *Tetrahedron*, **2008**, *64*, 2938–2950.



- OTf and OTs may undergo competing hydrolysis.
- Iodides are less frequently used because they tend to be more expensive, dehalogenate more readily, and tend to form bridged palladium dimers.
- Halides in the 2- and 4-positions of 6-membered heterocycles are predisposed towards oxidative addition.



Ji, J.; Li, T.; Bunnelle, W. H. *Org. Lett.* **2003**, *5*, 4611–4614.

Maes, B. U. W.; Loones, K. T. J.; Jonckers, T. H. M.; Lemiere, G. L. F.; Dommissie, R. A.; Haemers, A. *Synlett*, **2002**, 1995–1998.

Coordination

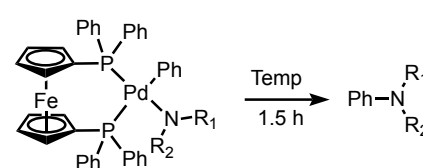
- Electron-rich amines are superior substrates due to their enhanced nucleophilicities.

Deprotonation

- Binding to Pd increases the acidity of the amine, which facilitates deprotonation.

Reductive Elimination

- Electron deficient amines** undergo **slower** reductive elimination.
- Bulky ligands** help to accelerate reductive elimination through steric repulsion.

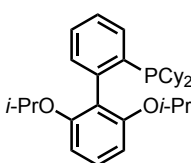


| Amine | pKa (HNR ₂) | Temp (°C) | Yield (%) |
|------------------------|-------------------------|-----------|-----------|
| —N(tolyl) ₂ | 25 | 85 | 90 |
| —NHPh | 30 | 25 | 80 |
| —NH <i>t</i> -Bu | 41 | 0 | 64 |

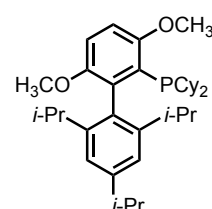
Hartwig, J. F. *Inorg. Chem.* **2007**, *46*, 1936–1947.

Examples of Ligands

Buchwald

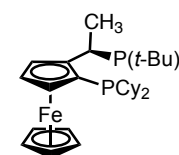


RuPhos
(for 2° amines)

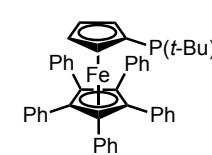


BrettPhos
(for 1° amines)

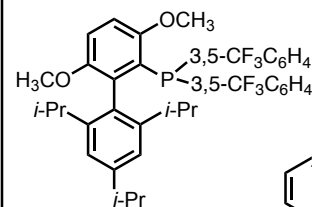
Hartwig



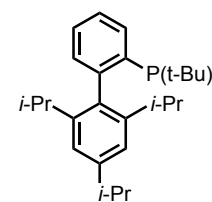
Josiphos
CyPF*t*Bu



Q-phos



JackiePhos

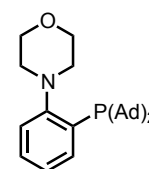


*t*BuXPhos

Pre-Ru: L = RuPhos

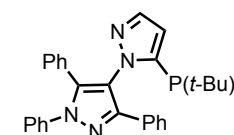
Pre-Brett: L = BrettPhos

Stradiotto



Mor-DalPhos

Singer



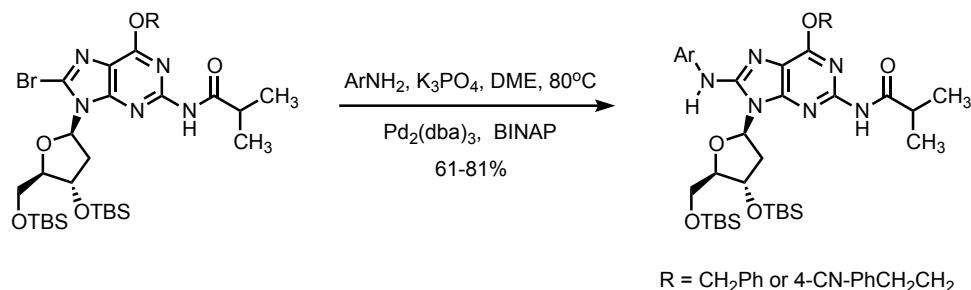
Bippyphos

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Nitrogen nucleophiles

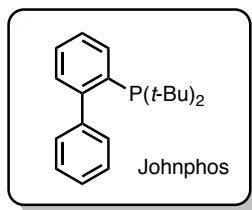
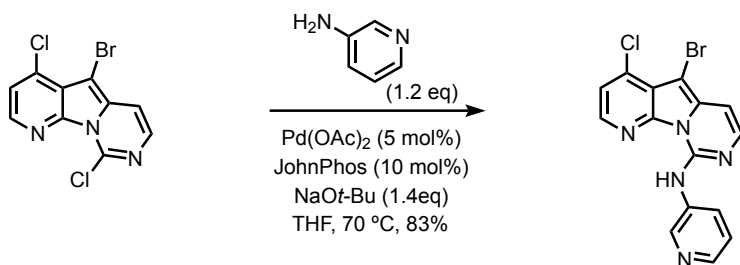
- Listed, in decreasing order, by approximate ease of coupling: anilines, secondary amines, primary amines, amides, sulfamides, five-membered heterocycles (i.e. pyrazole, imidazole, etc.), and ammonia.

Anilines



Meier, C.; Sonja, G. *Synlett* **2002**, 802–804.

- A selective C–N coupling reaction was used in the synthesis of the core of variolins, a group of marine natural products with potent cytotoxic activities against murine leukemia cells:

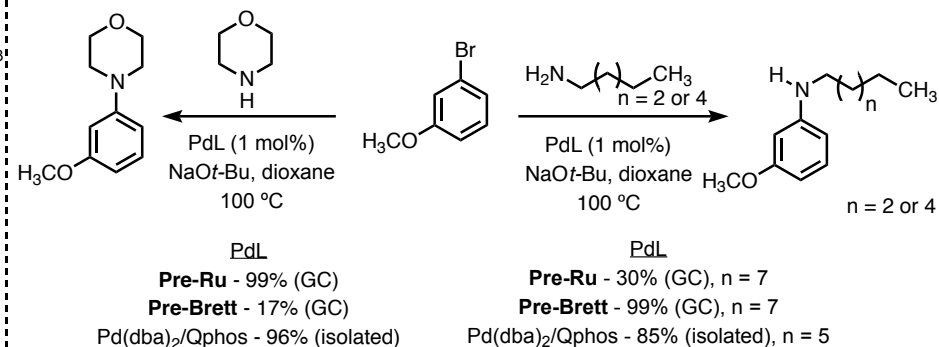


- The selectivity in this case is attributed to the directing effects of the neighboring nitrogen atoms.

A. Baeza, C. Burgos, J. Alvarez-Builla, J. J. Vaquero, *Tetrahedron Lett.* **2007**, 48, 2597

Secondary Amines vs. Primary Amines

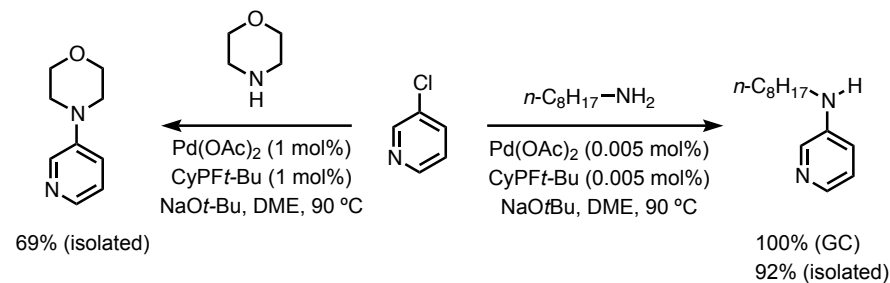
- Ligand choice is important. A catalyst that is too hindered inhibits reactions with secondary amines, while primary amines require a hindered ligand, to avoid double arylation.



Fors, B.; Buchwald, S. L. *J. Am. Chem. Soc.*, **2010**, 132, 15914–15917.

Kataoka, N.; Shelby, Q.; Stambuli, J. P.; Hartwig, J. F. *J. Org. Chem.* **2002**, 67, 5553–5566.

- The combination of $\text{Pd}(\text{OAc})_2$ and CyPFt-Bu is highly effective for monoarylation of primary amines. While it can be used to effect arylation of secondary amines, the rate is slower and higher catalyst loading is required:

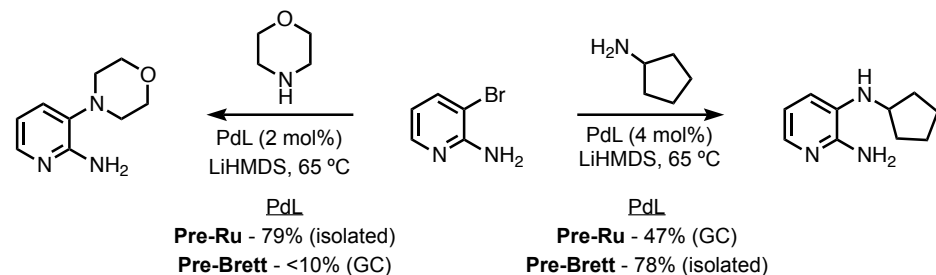


Shen, Q.; Ogata, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, 130, 6586–6596.

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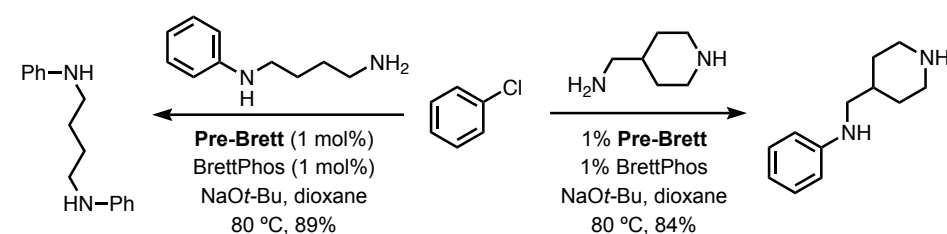
Challenging Substrate for Coupling

- Aminopyridines frequently function as chelating ligands with palladium. This effect can be mitigated by the use of LiHMDS and hindered, reactive ligands.



Perez, F.; Minatti, A. *Org. Lett.* **2011**, *13*, 1984–1987.

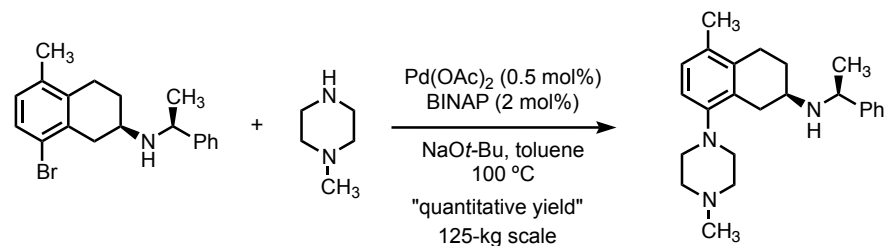
Selective Coupling of Primary over Secondary Amines



Fors, B. P.; Watson, D. A.; Biscoe, M. R.; Buchwald, S. L. *J. Am. Chem. Soc.*, **2008**, *130*, 13552–13554.

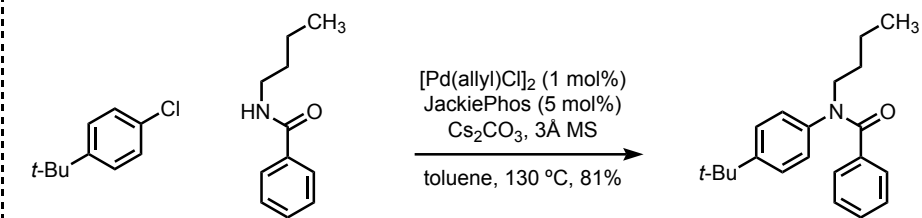
Large-Scale Amination

- Application to the synthesis of a CNS-Active aminotetralin:



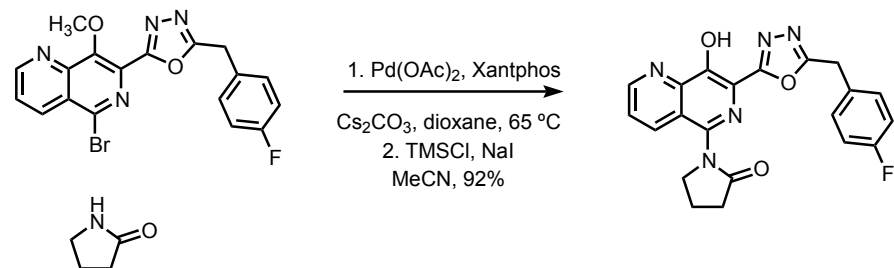
Federsel, H.-J.; Hedberg, M.; Qvarnström, F. R.; Tian, W. *Org. Process Res. Dev.* **2008**, *12*, 512–521.
 Federsel, H.-J.; Hedberg, M.; Qvarnström, F. R.; Sjögren, M. P. T.; Tian, W. *Acc. Chem. Res.* **2007**, *40*, 1377–1384.

Amides as Substrates



Hicks, J. D.; Hyde, A. M.; Cuezva, A. M.; Buchwald, S. L. *J. Am. Chem. Soc.*, **2009**, *131*, 16720–16734.

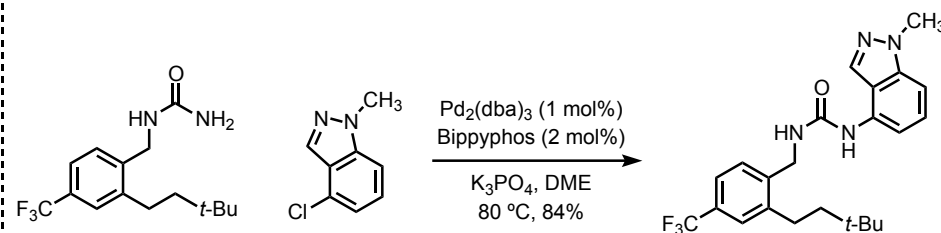
- Application to the synthesis of an HIV-1 integrase inhibitor:



Johns, B. A.; Weatherhead, J. G.; Allen, S. H.; Thompson, J. B.; Garvey, E. P.; Foster, S. A.; Jeffrey, J. L.; Miller, W. H. *Bioorg. Med. Chem. Lett.*, **2009**, *19*, 1807–1810.

Ureas as Substrates

- Application to the synthesis of a TRPV1 receptor antagonist:

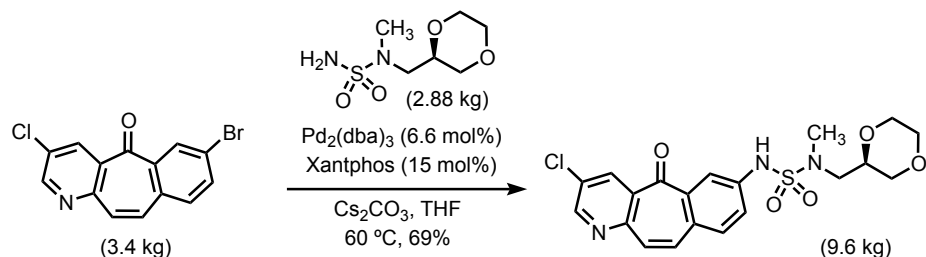


Yu, S.; Haight, A.; Kotecki, B.; Wang, L.; Lukin, K.; Hill, D. R. *J. Org. Chem.*, **2009**, *74*, 9539–9542.

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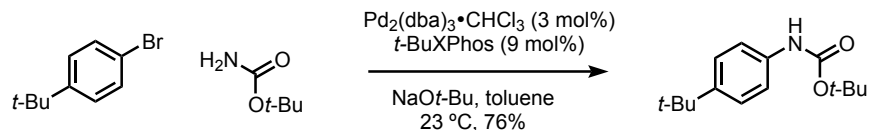
Sulfamides as Substrates

- Application to the synthesis of a c-Met Kinase Inhibitor:

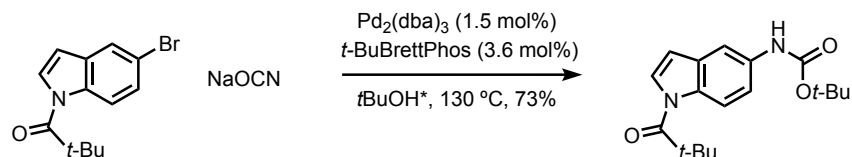


Stewart, G. W.; Brands, K. M. J.; Brewer, S. E.; Cowden, C. J.; Davies, A. J.; Edwards, J. S.; Gibson, A. W.; Hamilton, S. E.; Katz, J. D.; Keen, S. P.; Mullens, P. R.; Scott, J. P.; Wallace, D. J.; Wise, C. S. *Org. Process Res. Dev.* **2010**, *14*, 849–858

Carbamates as Substrates



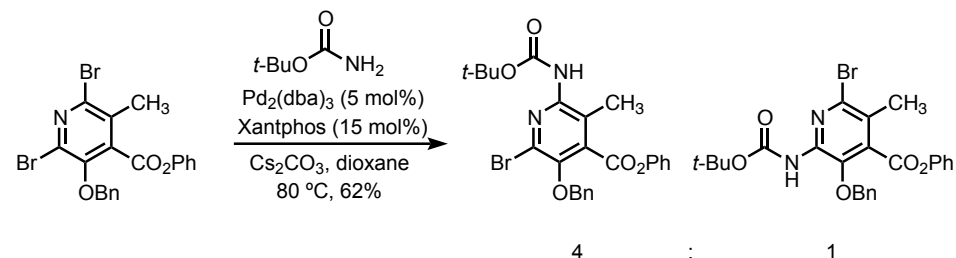
Bhagwanth, S.; Waterson, A. G.; Adjabeng, G. M.; Hornberger, K. R. *J. Org. Chem.*, **2009**, *74*, 4634–4637.



*Other alcohols can be used to make other carbamates

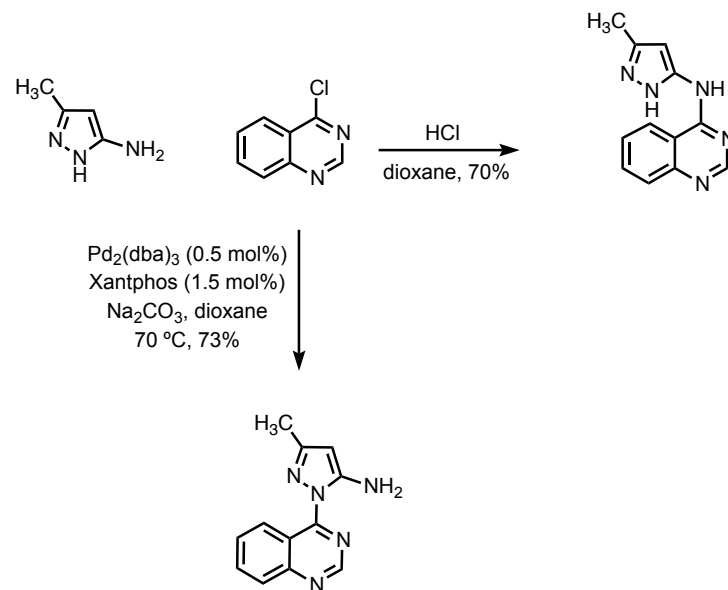
Perez, F.; Minatti, A. *Org. Lett.* **2013**, *15*, 1394–1397.

- Application to the synthesis of an intermediate en route to a tetracycline antibiotic:



Clark, R. B.; He, M.; Fyfe, C.; Lofland, D.; O'Brien, W. J.; Plamondon, L.; Sutcliffe, J. A.; Xiao, X.-Y. *J. Med. Chem.*, **2011**, *54*, 15-11-1528

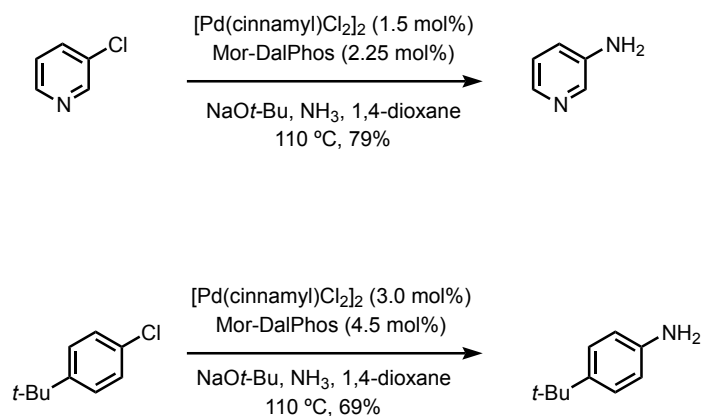
N-Heterocycles as Substrates



Shen, Z.; Hong, Y.; He, X.; Mo, W.; Hu, B.; Sun, N.; Hu, X. *Org. Lett.* **2010**, *12*, 552–555.

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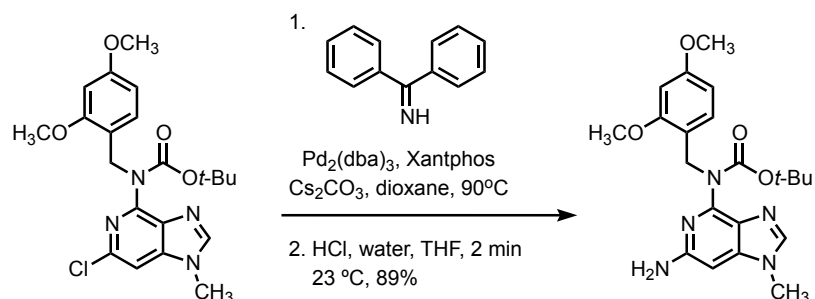
Ammonia as a substrate



Lundgren, R. J.; Peters, B. D.; Alsabeh, P. G.; Stradiotto, M. *Angew. Chem. Int. Ed.*, **2010**, *49*, 4071–4074.

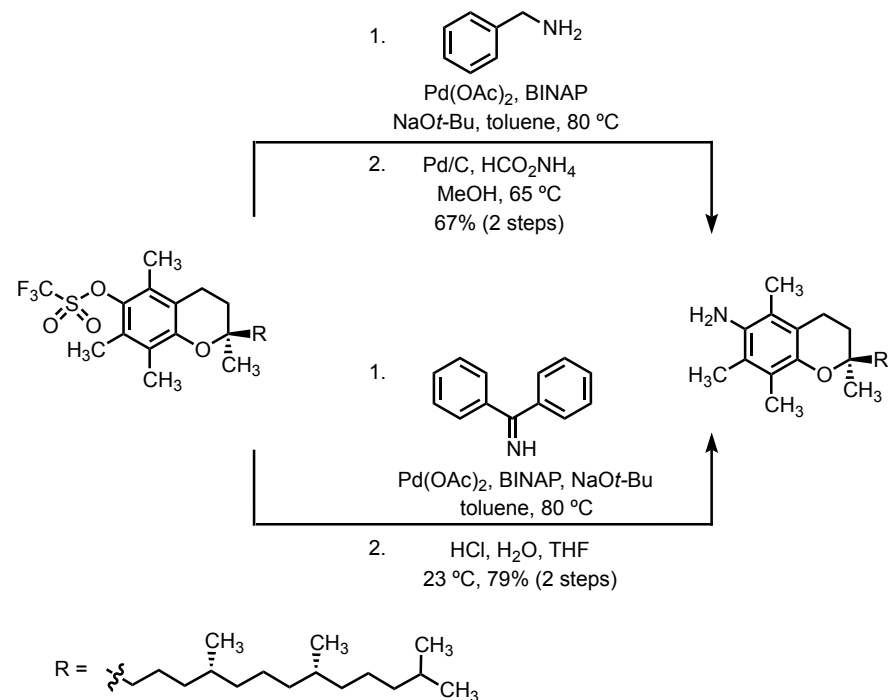
Ammonia Surrogates

- Application to the synthesis of a JAK2 Inhibitor:

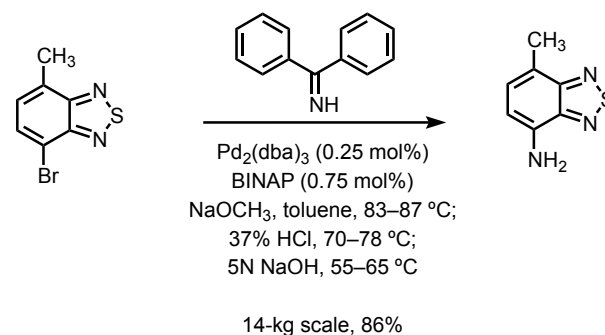


PCT Int. Appl., 2011028864, 10 Mar 2011.

- Application to the synthesis of Vitamin E Amines:



Mazzini, F.; Netscher, T.; Salvadori, P. *Eur. J. Org. Chem.* **2009**, 2063–2068.



Liu, Y.; Prashad, M.; Repic, O.; Blacklock, T. J. *J. Heterocyclic Chem.* **2003**, *40*, 713–716.

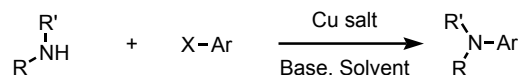
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Reviews:

- Surry, D. S.; Buchwald, S. L. *Chem. Sci.* **2010**, *1*, 13–31.
 Monnier, F.; Taillefer, M. *Angew. Chem. Int. Ed.* **2009**, *48*, 6954–6971.
 Ma, D.; Cai, Q. *Acc. Chem. Res.* **2008**, *41*, 1450–1460.
 Ley, S. V.; Thomas, A. W. *Angew. Chem. Int. Ed.* **2003**, *42*, 5400–5449.

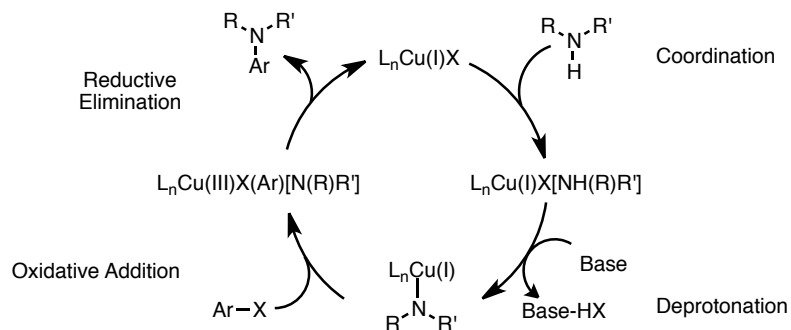
A comparison between Pd- and Cu-catalyzed C–N Bond-Forming Processes:
 Beletskaya, I. P.; Cheprakov, A. V. *Organometallics* **2012**, *31*, 7753–7808.

Overview



- The Ullman-type reaction involves coupling amines and other nitrogen nucleophiles with an aryl halide, catalyzed by copper salts.
- Copper is highly effective for coupling aryl halides with amides, carbamates, azoles and ureas. These substrates tend to be problematic in Pd-catalyzed couplings.
- The mechanism may follow the same cycle as with Pd, but is more likely to involve coordination of the amine prior to oxidative addition (Strieter, E. R.; Blackmond, D. G.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4120–4121).

Mechanism:

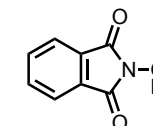
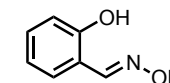
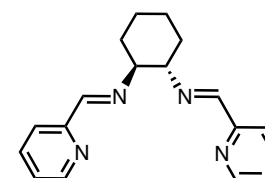
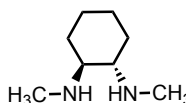
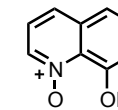
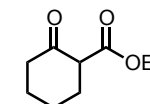
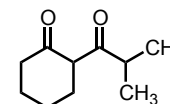
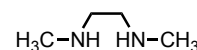
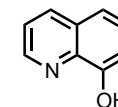
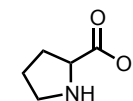
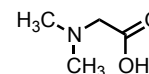
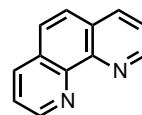


- an alternative mechanism involves oxidative addition prior to coordination.

Typical Ligands:

1,2-diamines (most common), amino acids, 1,3-dicarbonyls, 1,2-amino alcohols, 1,2-diols

• Examples



- 1,2-Diamines are among the most general supporting ligands in Cu-Catalyzed C–N Couplings: The amine nucleophiles often coordinate to copper to form a stable bis-amine complex which impedes catalysis. Diamine chelation suppresses this undesired pathway.

Critical Features of Ligand Design:

Ethylene or cyclohexane backbone is most effective.

R = CH₃ gives highest reaction rate; larger groups impede rate.

Further substitution to give tertiary amine, such as TMEDA, leads to ineffective ligands.

R = H leads to ligand arylation.

Typical Cu salts:

CuI (most common), CuBr, CuOAc, Cu₂O.

Typical Solvents:

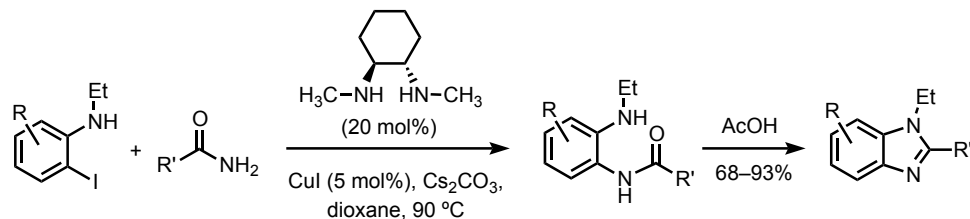
NMP, DMAC, DMSO, DMF, toluene, THF, DME, dioxane.

Typical Bases:

Most general: Cs₂CO₃. Commonly used: K₂CO₃, K₃PO₄.

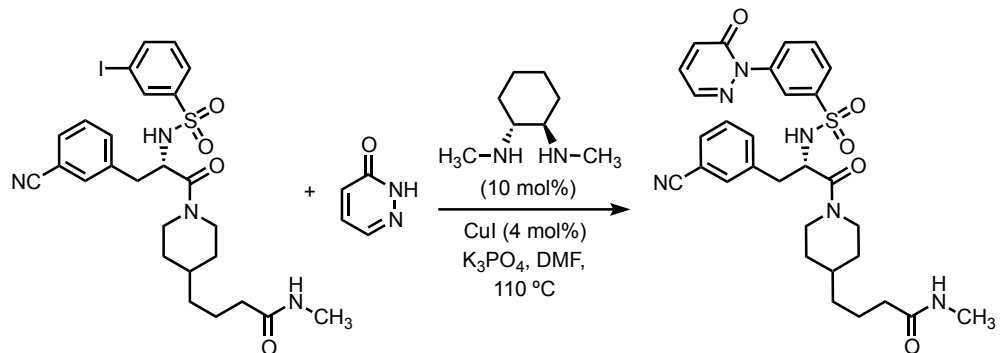
May be used: KOH, CsF, CsOAc.

Preparation of benzimidazoles:



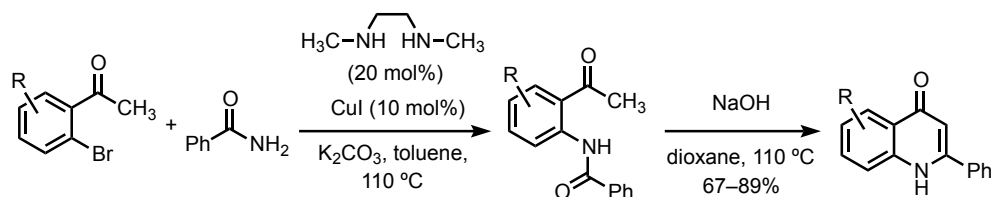
Zheng, N.; Buchwald, S. L. *Org. Lett.* **2007**, *9*, 4749–4751.

Selective coupling of pyridazinone in the presence of a sulfonamide and a secondary amide:



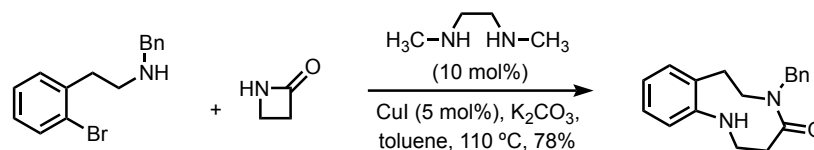
Schweinitz, A.; Dönnecke, D.; Ludwig, A.; Steinmetzer, P.; Schulze, A.; Kotthaus, J.; Wein, S.; Clement, B.; Steinmetzer, T. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1960–1965.

Preparation of quinolones:



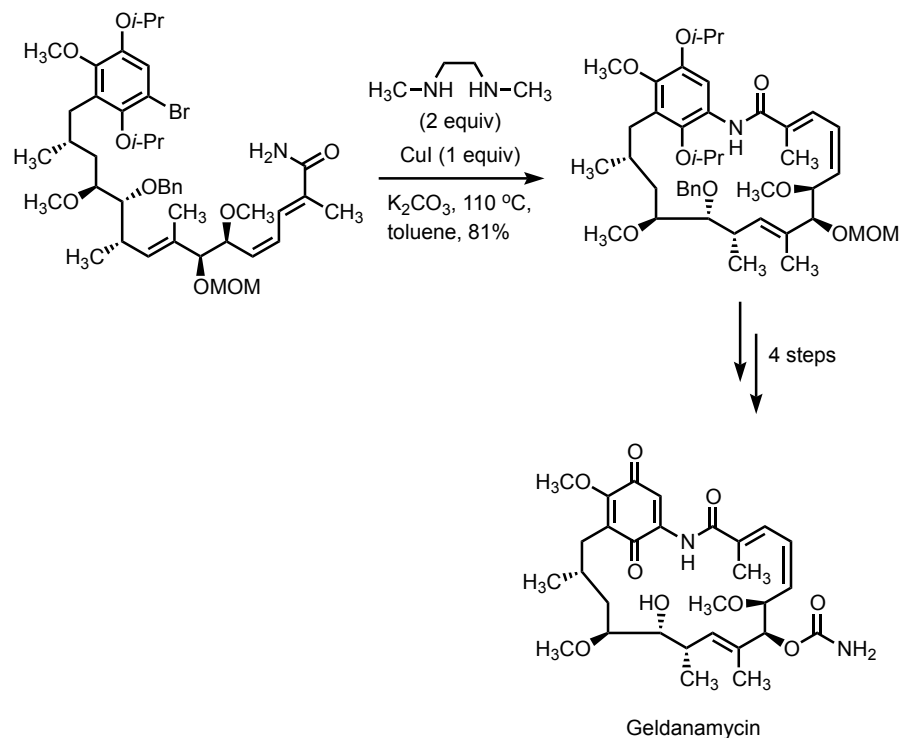
Jones, C. P.; Anderson, K. W.; Buchwald, S. L. *J. Org. Chem.* **2007**, *72*, 7968–7973.

Lactams couple selectively over secondary amines:



Klapars, A.; Parris, S.; Anderson, K. W.; Buchwald, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 3529–3533.

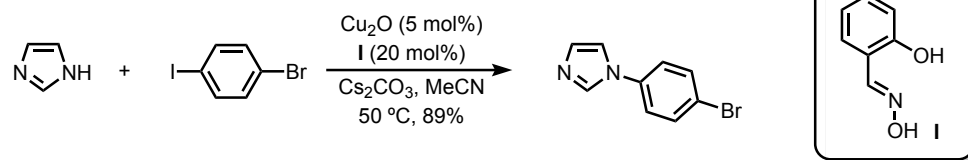
Application to the Synthesis of the Natural Product Geldanamycin



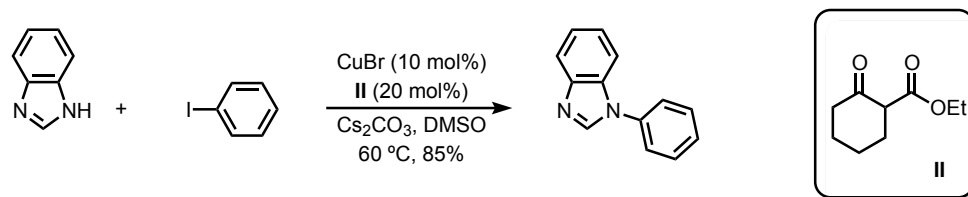
Qin, H.-Li.; Panek, J. S. *Org. Lett.* **2008**, *10*, 2477–2479.

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Couplings of Azoles

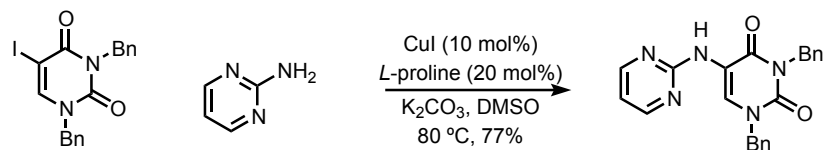


Cristau, H.-J.; Cellier, P. P.; Spindler, J.-F.; Taillefer, M. *Chem. Eur. J.* **2004**, *10*, 5607–5622.



Lv, X.; Bao, W. *J. Org. Chem.* **2007**, *72*, 3863–3867.

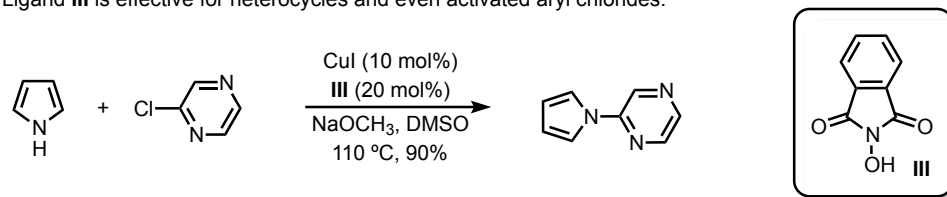
Inexpensive amino acids can be used as ligands and demonstrate a broad substrate scope:



Cai, Q.; Zhu, W.; Zhang, H.; Zhang, Y.; Ma, D. *Synthesis* **2005**, 496–499.

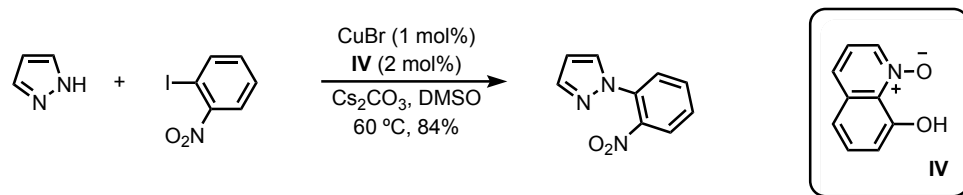
Zhang, H.; Cai, Q.; Ma, D. *J. Org. Chem.* **2005**, *70*, 5164–5173.

Ligand III is effective for heterocycles and even activated aryl chlorides:



Ma, H.-C.; Jiang, X.-Z. *J. Org. Chem.* **2007**, *72*, 8943–8946.

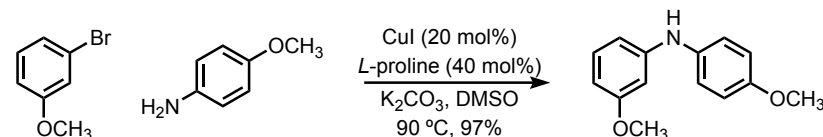
Couplings catalyzed by Ligand IV proceed under mild conditions and with a low loading of the copper catalyst:



Yang, K.; Qiu, Y. Q.; Li, Z.; Wang, Z.; Jiang, S. *J. Org. Chem.* **2011**, *76*, 3151–3159.

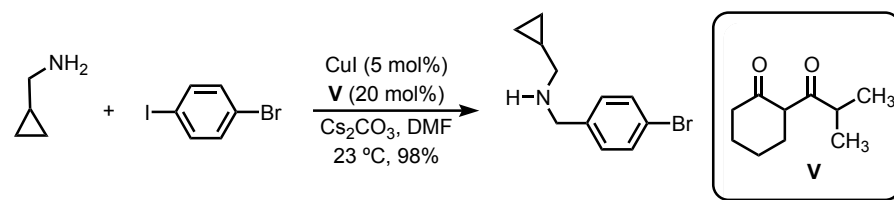
Couplings of Primary Amines:

Proline is one of few ligands that can facilitate Cu-catalyzed C–N coupling with anilines:



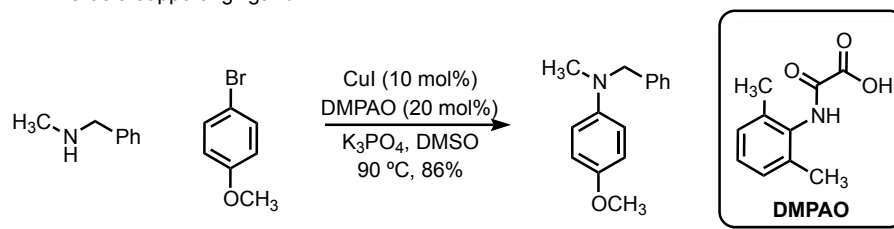
Zhang, H.; Cai, Q.; Ma, D. *J. Org. Chem.* **2005**, *70*, 5164–5173.

Room-temperature C–N coupling can be achieved using ligand V:



Shafir, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2006**, *128*, 8742–8743.

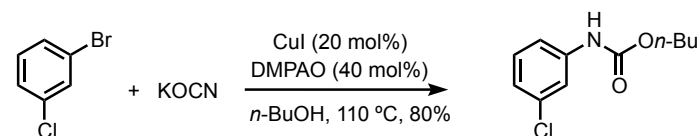
Couplings of acyclic secondary amines was virtually unprecedented until the discovery of DMPAO as a supporting ligand:



This methodology can also be applied to primary amines and cyclic secondary amines, but not to anilines.

Zhang, Y.; Yang, X.; Tao, Q.; Ma, D. *Org. Lett.* **2012**, *14*, 3056–3059.

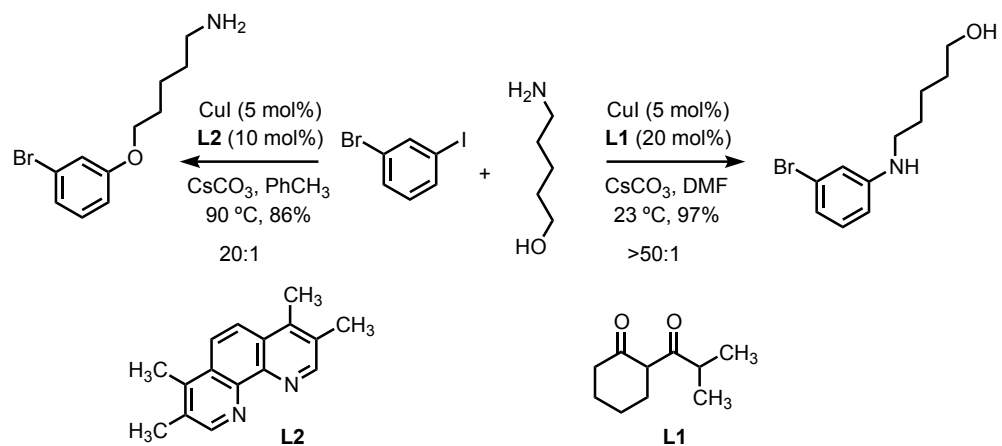
DMPAO can also be applied to the synthesis of aryl carbamates:



Yang, X.; Zhang, Y.; Ma, D. *Adv. Synth. Catal.* **2012**, *354*, 2443–2446.

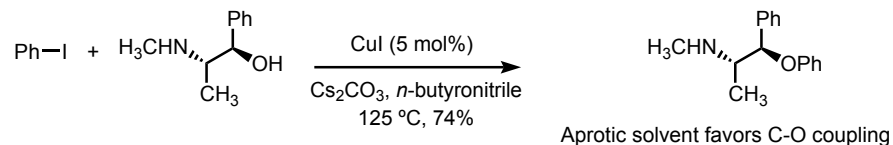
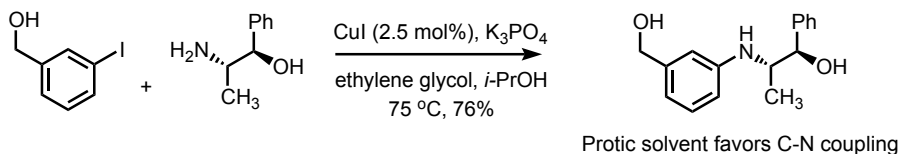
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Ligand-controlled N-Arylation versus O-arylation of amino alcohols



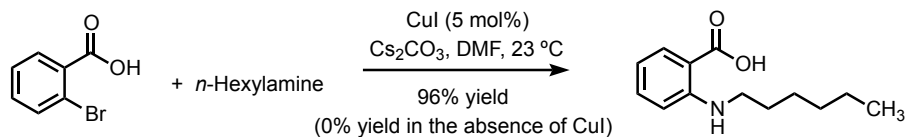
Shafir, A.; Lichtor, P. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 3490–3491.

- Chemoselective N-Arylation of 1,2-amino alcohols: the substrate functions as the ligand. The choice of solvent dictates C–N versus C–O bond formation.



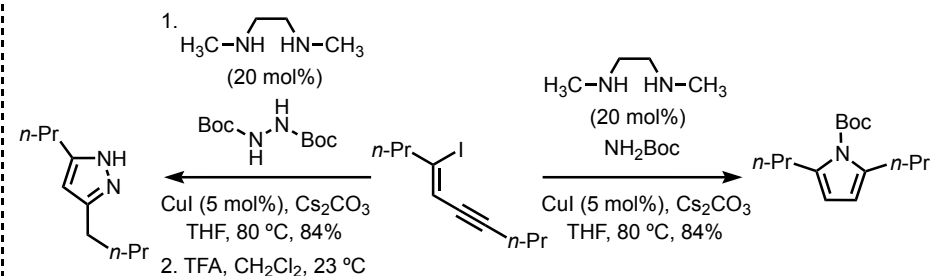
Job, G. E.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 3703–3706.

- C–N coupling can be facilitated by ortho-chelating groups:



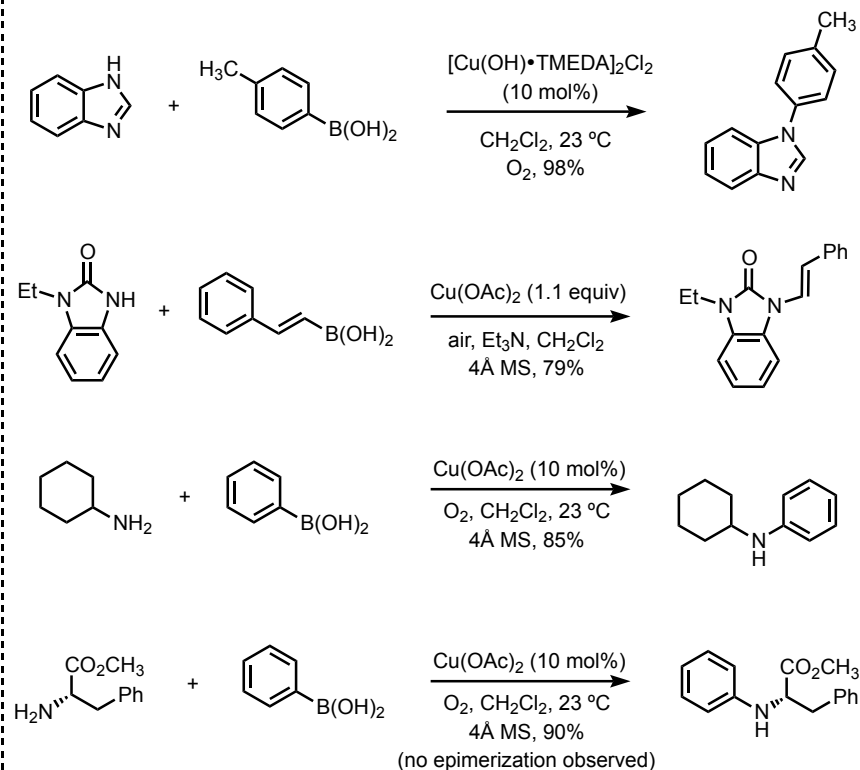
Diao, X.; Xu, L.; Zhu, W.; Jiang, Y.; Wang, H.; Guo, Y.; Ma, D. *Org. Lett.* **2011**, *13*, 6422–6425.

Heterocycle formation via tandem coupling and hydroamidation



Martin, R.; Rivero, M. R.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2006**, *45*, 7079–7082.

Cu-catalyzed C–N couplings with boronic acids



Lam, P. Y. S.; Vincent, G.; Clark, C. G.; Deudon, S.; Jadhav, P. K. *Tetrahedron Lett.* **2001**, *42*, 3415–3418.

Collman, J. P.; Zhong, M. *Org. Lett.* **2000**, *2*, 1233–1236.

Quach, T. D.; Batey, R. A. *Org. Lett.* **2003**, *5*, 4397–4400.

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