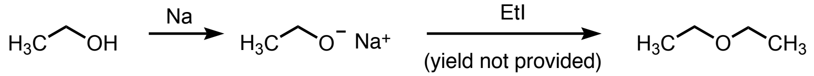
Williamson Ether Synthesis

Background

- The synthesis of ethyl ether from sodium ethoxide and ethyl iodide was first reported by Alexander W. Williamson in 1851:



Williamson, W. *Liebigs Ann. Chem*. **1851**, *77*, 37–49.
Williamson, W. *J. Chem. Soc*. **1852**, *106*, 229–239.

- Since its original discovery, the Williamson ether synthesis method has become widely used in both academic and industrial settings.

Overview

$$R{-}OH \xrightarrow{\text{base}} R{-}O^{-} \xrightarrow{R'{-}X} R{-}OR'$$

- R = 1º, 2º, and 3º alkyl
  allyl, benzyl, aryl, heteroaryl
- R' = 1º, and 2º alkyl, allyl, benzyl
- X = I, Br, Cl, OSO_2R
- Base = alkali metals/NH_3(*l*), metal hydrides
  LHMDS, LDA, NaOH, KOH, K_2CO_3, Cs_2CO_3.
- Solvents: alcohol (alkoxide), DMF, DMSO and HMPA.

Mechanism

- The reaction proceeds through an S_N2 pathway.

Limitations

- For hindered substrates, base-catalyzed elimination of the alkylating agent can be problematic.
- For phenoxides, C–alkylation can compete with O–alkylation.

Relative Reactivities:

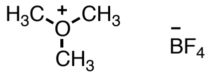
- Relative reactivities of electrophiles, with respect to the alkyl substituent:

Me, allylic, benzylic > 1º alkyl > 2º alkyl > branched 2º alkyl >> neopentyl, 3º alkyl

- Relative reactivities of electrophiles, with respect to the leaving group:

I > Br > Cl OTf > OTs > OMs

- Trimethyloxonium tetrafluoroborate (Meerwein's salt) is a powerful alkylating agent:



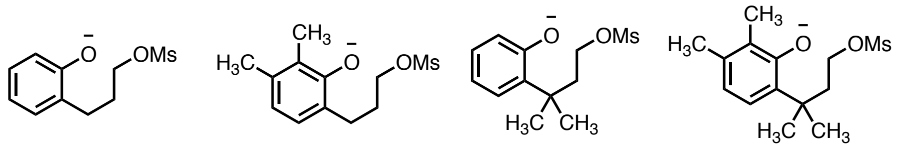
Intramolecular Williamson Ether Synthesis:

- Relative rates of ring formation:

Ring size: 3 ~ 5 > 6 > 4 > 7 > 8

Fast ⟶ Slow

- Proximity effect: in the following intramolecular etherification reaction, successive addition of methyl groups on the substrate places the electrophile and nucleophile in closer proximity.

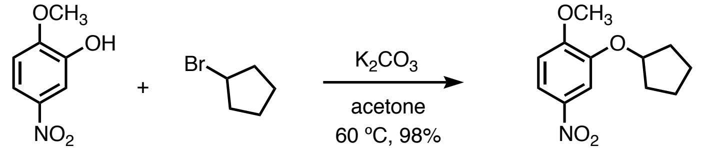


relative rate of ether formation	1	3.5	3×10^3	8.6×10^5

Kirby, A. J. *Adv. Phys. Org. Chem.* **1980**, *17*, 183–179.
Anslyn, E. V.; Dougherty, D. A. *Modern Physical Organic Chemistry*; University Science Books: Sausalito, CA, **2006**; pg 497.

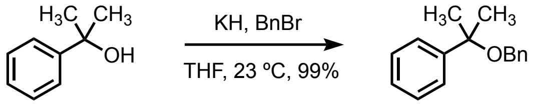
Angela Puchlopek-Dermenci, Alpay Dermenci, Fan Liu

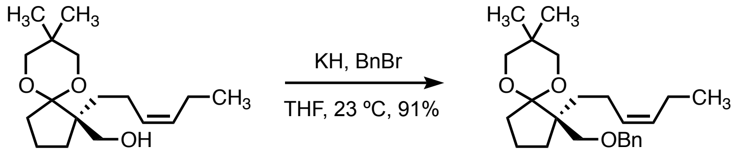
Examples



Garcia, A. L. L.; Carpes, M. J. S.; de Oca, A. C. B. M.; dos Santos, M. A. G.; Santana, C. C.; Correia, C. R. D. *J. Org. Chem.* **2005**, *70*, 1050–1053.

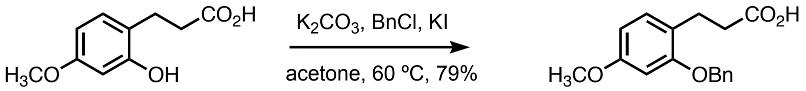
- For hindered substrates, KH often performs better than NaH.
- KH is highly flammable and is supplied commercially as a 30% w/w slurry in mineral oil. In the examples below, the authors used a 50% by weight homogenate of KH in paraffin, which is observed to be air stable and operationally more convenient:



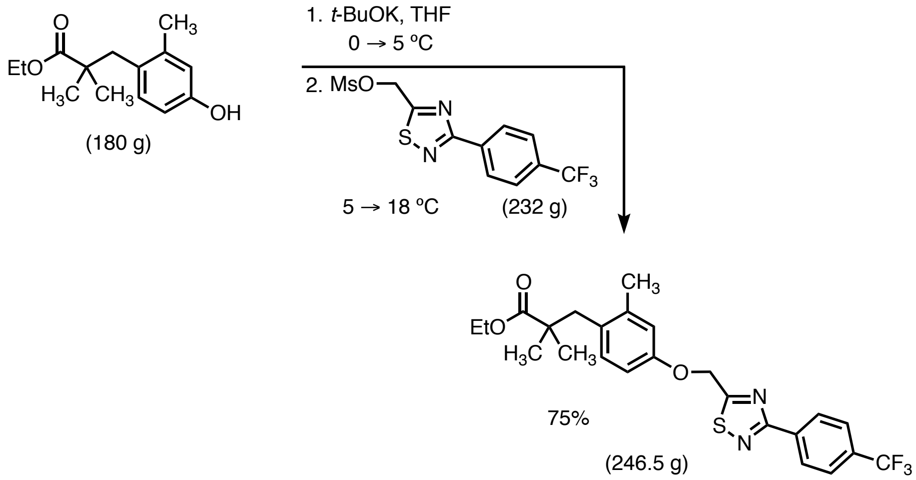


Huang, H.; Nelson, C. G.; Taber, D. F. *Tetrahedron Lett.* **2010**, *51*, 3545–3546.

- Alkyl chlorides can be converted *in situ* to the more reactive alkyl iodide:

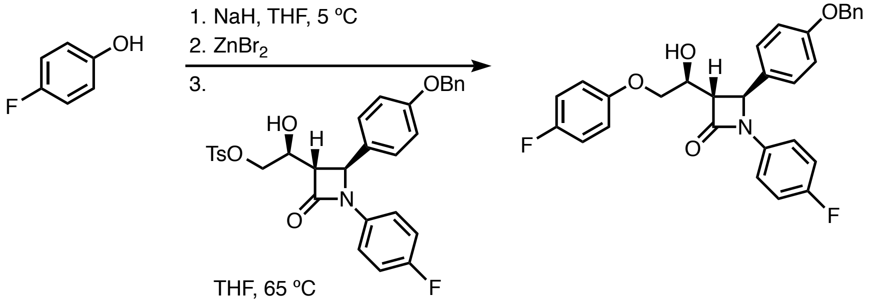


Bourke, D. G.; Collins, D. J. *Tetrahedron* **1997**, *53*, 3863–3878.

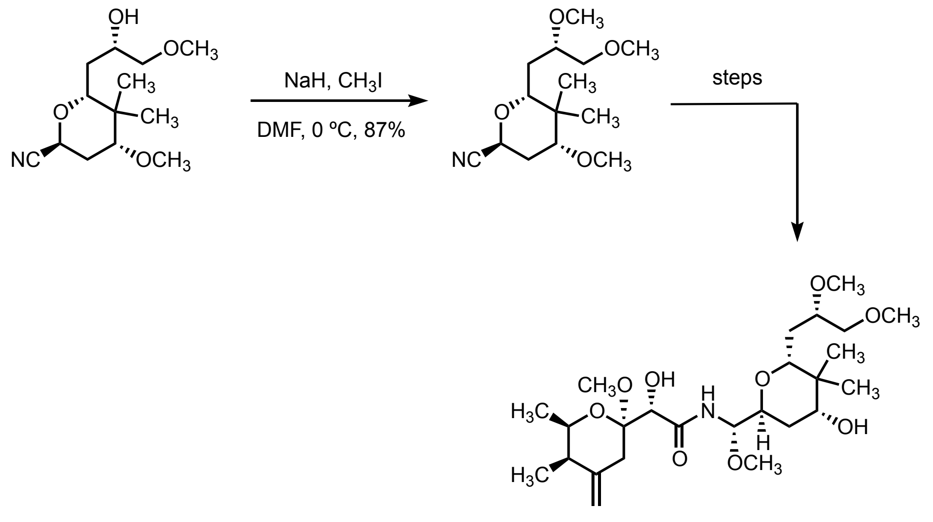


Reuman, M.; Hu, Z.; Kuo, G.-H.; Li, X.; Russell, R. K.; Shen, L.; Youells, S.; Zhang, Y. *Org. Process Res. Dev.* **2007**, *11*, 1010–1014.

- In the following example, etherification proceeds via an epoxide intermediate. Addition of $ZnBr_2$ was found to promote epoxide opening:



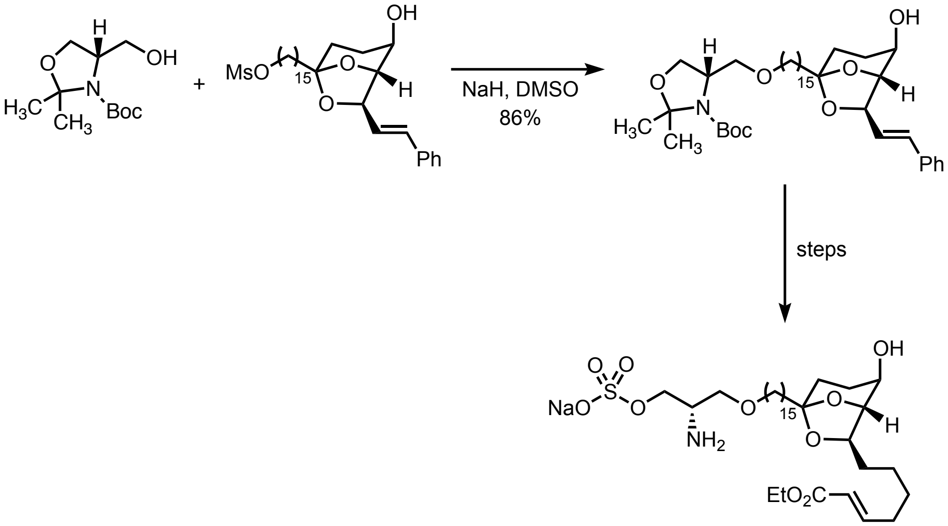
Wu, G. G. *Org. Process Res. Dev.* **2000**, *4*, 298–300.



Pederin

Wan, S.; Wu, F.; Rech, J. C.; Green, M. E.; Balachandran, R.; Horne, W. S.; Day, B. W.; Floreancig, P. E. *J. Am. Chem. Soc.* **2011**, *133*, 16668–16679.

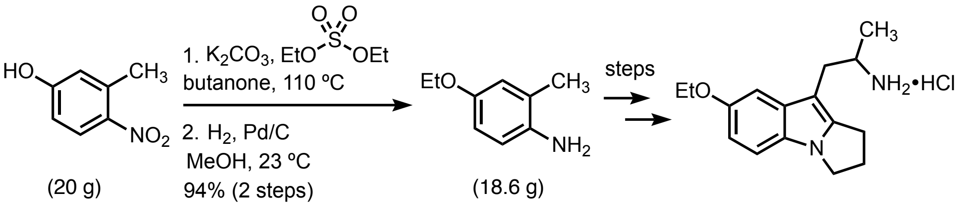
- Synthesis of didemniserinolipid B:



didemniserinolipid B

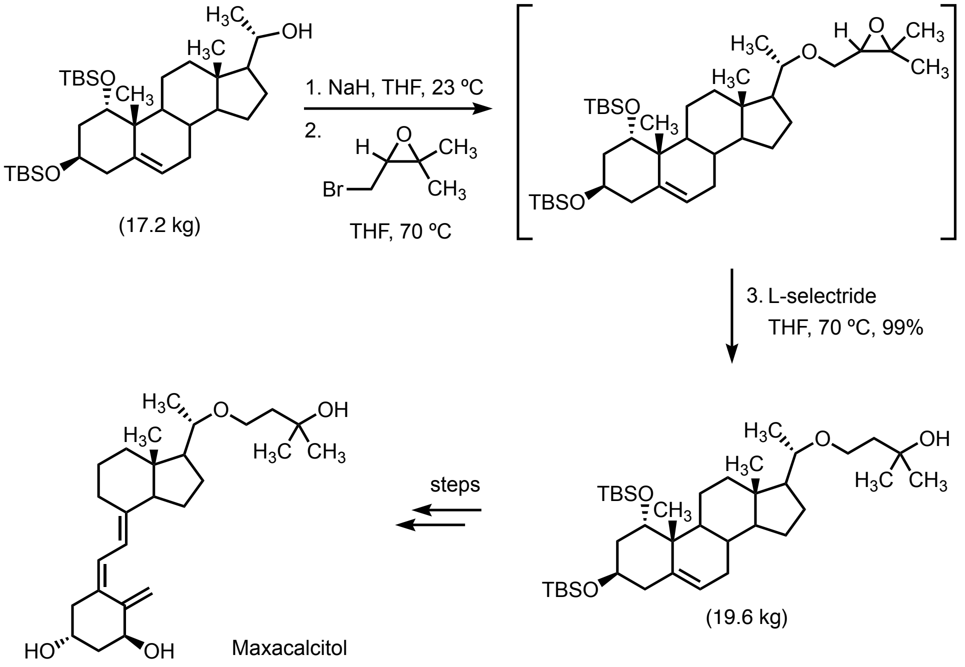
Marvin, C. C.; Voight, E. A.; Burke, S. D. *Org. Lett.* **2007**, *9*, 5357–5359.

- Synthesis of a 5-HT_{2C} receptor agonist :



Peters, R.; Waldmeier, P.; Joncour, A. *Org. Proc. Res. Dev.* **2005**, *9*, 508–512

- Synthesis of maxacalcitol (Oxarol®), an antihyperparathyroidism and antipsoriatic vitamin D_3 analogue:



Shimizu, H.; Shimizu, K.; Kubodera, N.; Mikami, T.; Tsuzaki, K.; Suwa, H.; Harada, K.; Hiraide, A.; Shimizu, M.; Koyama, K.; Ichikawa, Y.; Hirasawa, D.; Kito, Y.; Kobayashi, M.; Kigawa, M.; Kato, M.; Kozono, T.; Tanaka, H.; Tanabe, M.; Iguchi, M.; Yoshida, M. *Org. Proc. Res. Dev.* **2005**, *9*, 278–287.

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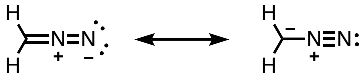
Introduction

- Diazo compounds are uniquely reactive 1,3-dipoles



- Diazo compounds are toxic and potentially explosive. They covalently modify nucleobases and thus are mutagens. Consequently, care must be taken when handling these compounds.

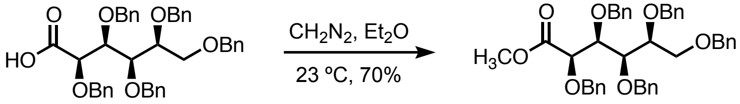
Fulton, J. R.; Aggarwal, V. K.; de Vicente, J. *Eur. J. Org. Chem.* **2005**, 1479–1492.

Esterification and Etherification Using Diazomethane

Sammakia, T. Diazomethane in *Encyclopedia of Reagents for Organic Synthesis.*

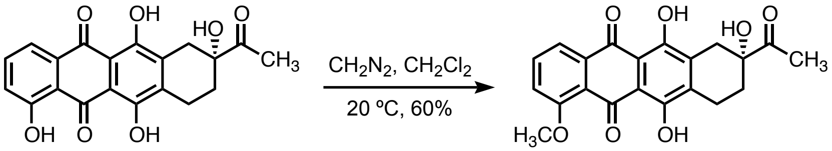
- Diazomethane is one of the most effective reagents for the preparation of methyl esters from carboxylic acids. The carboxylic acid protonates the diazomethane reagent to generate a diazonium-carboxylate ion pair, which collapses to form the methyl ester.

- Products can typically be isolated by simple evaporation of the volatile ethereal solvent (ethereal solutions of diazomethane are obtained by distillation using special fire-polished glassware, to prevent explosion). Diazomethane itself is highly volatile (bp = –23 ºC).



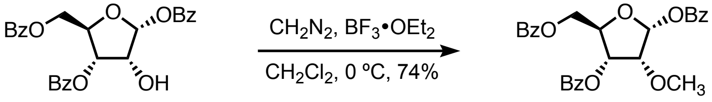
Schmidt, R. R.; Frick, W. *Tetrahedron* **1988**, *44*, 7163–7169.

- Other acidic functional groups, such as phenols, can also be methylated.



Blade, R. J.; Hodge, P. *J. Chem. Soc. Chem. Commun.* **1979**, 85–86.

- Alcohols are not sufficiently acidic to protonate diazomethane and require a catalyst to react. Common catalysts include BF_3•OEt_2, HBF_4, $SnCl_2$ and silica gel:

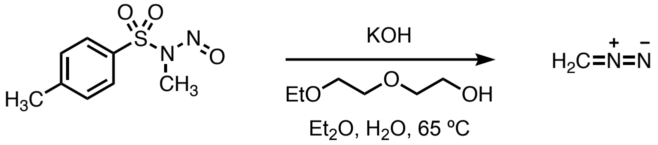


Chavis, C.; Dumont, F.; Wightman, R. H.; Ziegler, J. C.; Imbach, J. L. *J. Org. Chem.* **1982**, *47*, 202–206.

Preparation of Diazomethane

- Diazomethane is prepared by the decomposition of a variety of *N*-methyl-*N*-nitrosoamines and is obtained most often as a solution in ethyl ether.

- The example below utilizes *N*–methyl-*N*-nitroso-*p*-toluenesulfonamide (Diazald®).



Hudlicky, M. *J. Org. Chem.* **1980**, *45*, 5377–5378.
de Boer, T. J.; Backer, H. J.; *Org. Synth.* **1963**, *4*, 250–253.

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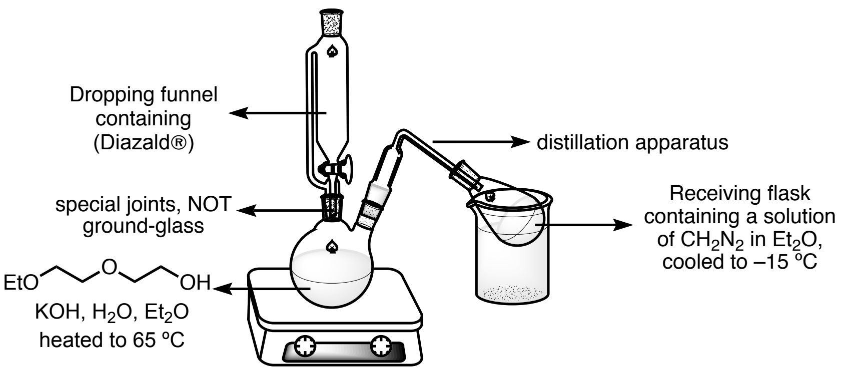
- Reaction set-up:



- Kits can be purchased which include non-ground glassware to decrease the likelihood of diazomethane explosion.

- Leftover diazomethane should be quenched with dilute acetic or oxalic acid.

- If a pipette is to be used to transfer diazomethane, it must be fire polished first.

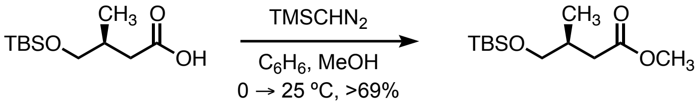
- Diazomethane is one of the most dangerous diazo compounds because of its volatility and propensity to detonate. All operations should be conducted behind a blast shield and care must be taken when handling this compound.

Hudlicky, M. *J. Org. Chem.* **1980**, *45*, 5377–5378.
de Boer, T. J.; Backer, H. J.; *Org. Synth.* **1963**, *4*, 250–253.

Trimethylsilyldiazomethane

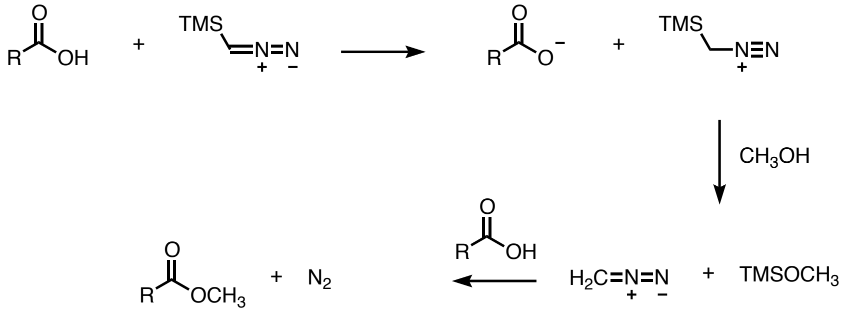
Shioiri, T.; Aoyama, T. Trimethylsilyldiazomethane in *Encyclopedia of Reagents for Organic Synthesis.*

- Because of the high volatility and toxicity of diazomethane, the safer, less volatile reagent, trimethylsilyldiazomethane is often used, solutions of which are commercially available.



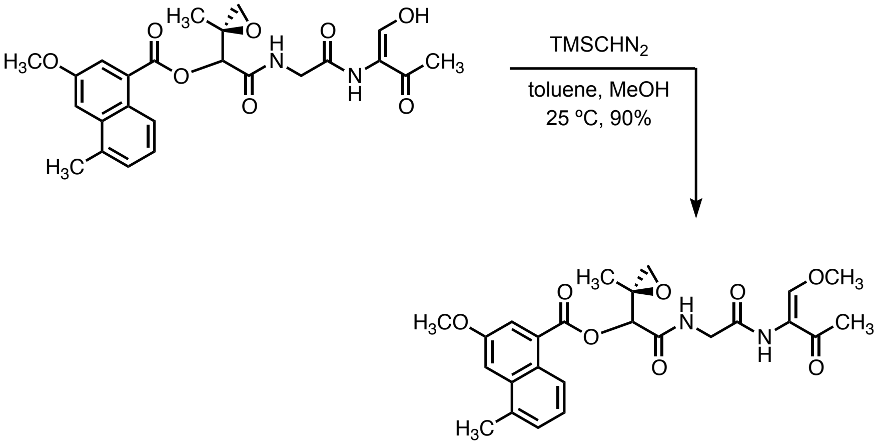
Evans, M. A.; Morken, J. P. *Org. Lett.* **2005**, *7*, 3371–3373.

- The reaction proceeds through *in situ* generation of the active methylating agent, diazomethane.



Kühnel, E.; Laffan, D. D. P.; Lloyd-Jones, G. C.; Martinez del Campo, T.; Shepperson, I. R.; Slaughter, J. L. *Angew. Chem. Int. Ed.* **2007**, *46*, 7075–7078.

- Enols can also be methylated:



Coleman, R. S.; Tierney, M. T.; Cortright, S. B.; Carper, D. J. *J. Org. Chem.* **2007**, *72*, 7726–7735.

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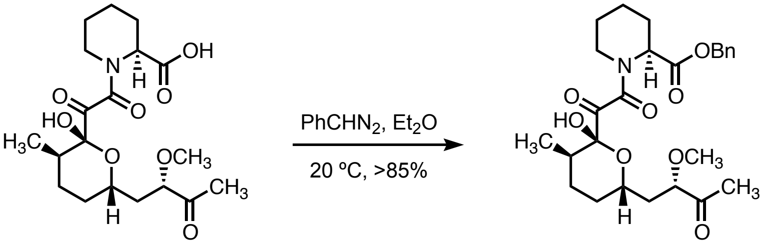
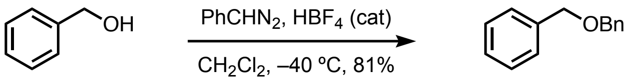
Esterification and Etherification Using Phenyldiazomethane

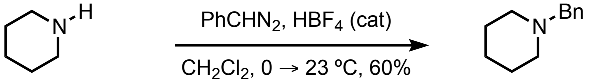
Sammakia, T. Phenyldiazomethane in *Encyclopedia of Reagents for Organic Synthesis.*

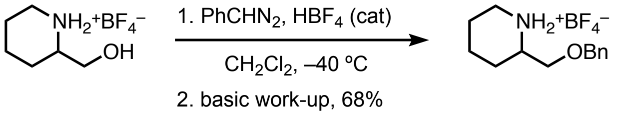


Goulet, M. T.; Boger, J. *Tetrahedron Lett.* **1990**, *31*, 4845–4848.

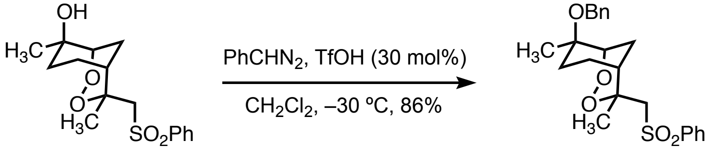
- HBF_4 can be used as an acid catalyst for the benzylation of alcohols and amines using phenyldiazomethane. Amines react more slowly under these conditions:







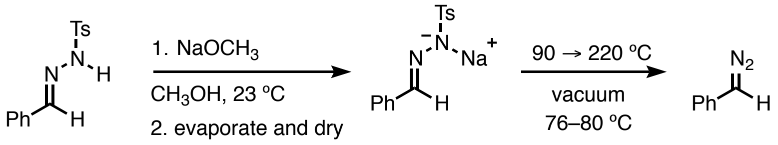
Liotta, L. J.; Ganem, B. *Tetrahedron Lett.* **1989**, *30*, 4759–4762.



Bachi, M. D.; Korshin, E. E.; Hoos, R.; Szpilman, A. M.; Ploypradith, P.; Xie, S.; Shapiro, T. A.; Posner, G. H. *J. Med. Chem.* **2003**, *46*, 2516–2533.

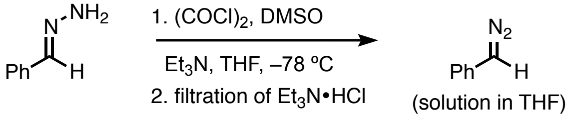
Preparation of Phenyldiazomethane

- Neat phenyldiazomethane is commonly prepared by vacuum pyrolysis of the sodium salt of benzaldehyde tosylhydrazone:



Creary, X. *Org. Synth.* **1990**, *7*, 438–443.

- Alternatively, phenyldiazomethane can be prepared by dehydrogenation of benzaldehyde hydrazone using Swern-like conditions:



Javed, M. I.; Brewer, M. *Org. Lett.* **2007**, *9*, 1789–1792.
Wommack, A. J.; Moebius, D.; Travis, A.; Kingsbury, J. S. *Org. Lett.* **2009**, *11*, 3202–3205.

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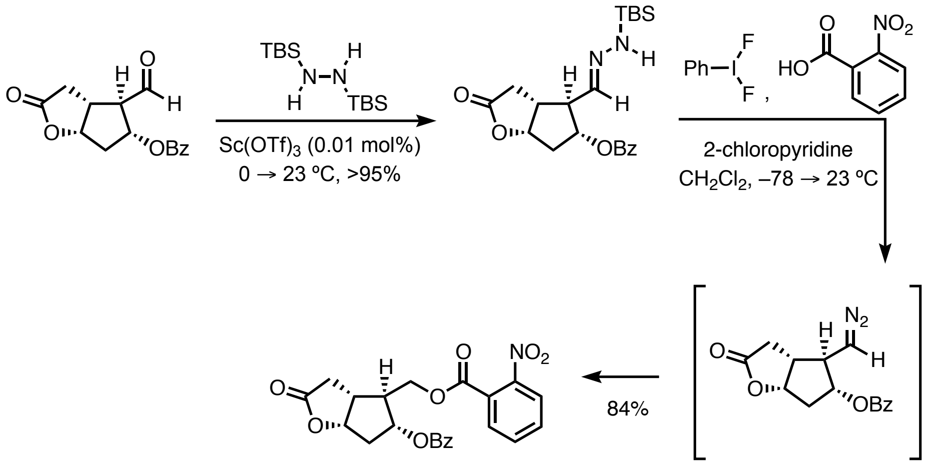
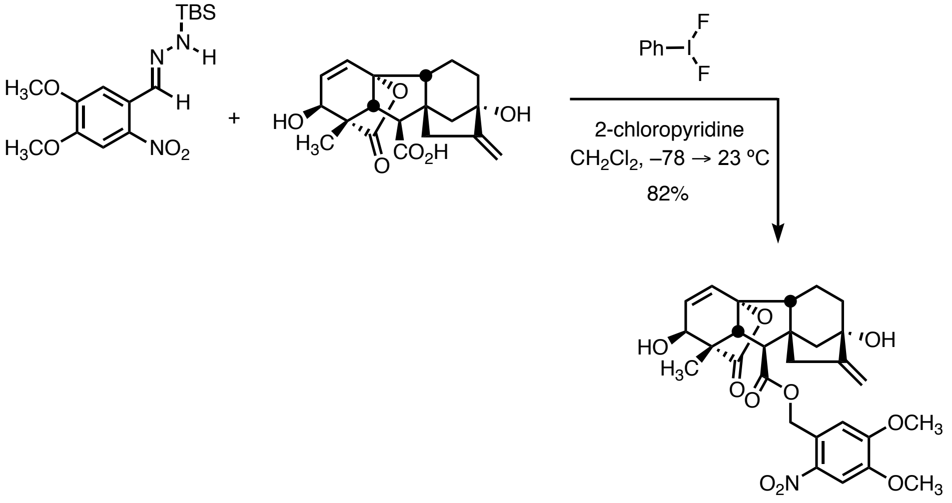
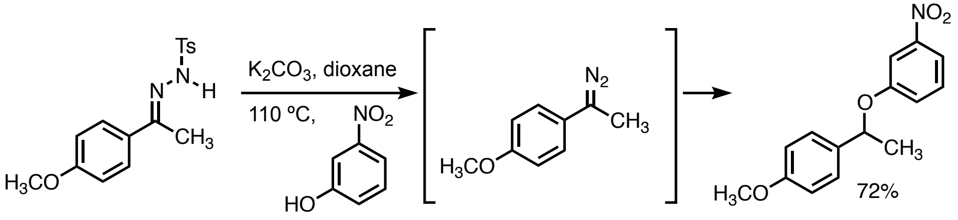
- More complex esterification reagents can be generated by *in situ* oxidation of their corresponding *N-tert*-butyldimethylsilylhydrazones with (difluoroiodo)benzene:

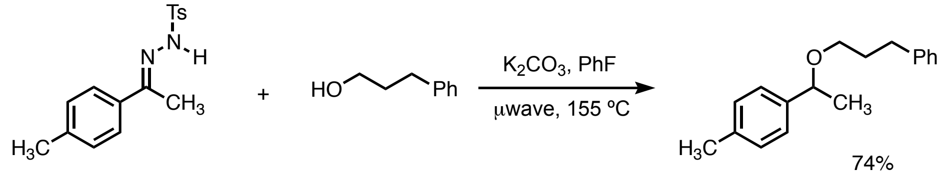




Furrow, M. E.; Myers, A. G. *J. Am. Chem. Soc.* **2004**, *126*, 12222–12223.
Furrow, M. E.; Myers, A. G. *J. Am. Chem. Soc.* **2004**, *126*, 5436–5445.

- Diazoalkanes can also be generated *in situ* from the corresponding tosyl hydrazone at high temperature:





Barluenga, J.; Tomas-Gamasa, M.; Aznar, F.; Valdes, C. *Angew. Chem. Int. Ed.* **2010**, *122*, 5113–5116.

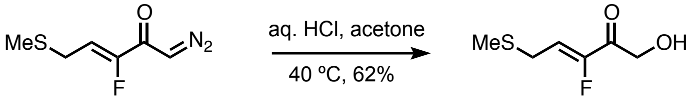
Rhodium-Mediated Etherification Reactions

Reviews:

Valdes, C.; Barluenga, J. *Angew. Chem. Int. Ed.* **2011**, *50*, 7486–7500
Fulton, J. R.; Aggarwal, V. K.; de Vicente, J. *Eur. J. Org. Chem.* **2005**, 1479–1492.

- Diazo compounds bearing an electron-withdrawing group are considered much safer than diazomethane because of resonance stabilization by the electron-withdrawing group. In addition, stabilized diazo compounds tend to much less volatile.

- Treatment of simple α-diazoketones in aqueous acids provides the corresponding alcohols.



Pirrung, M. C.; Rowley, E. G.; Holmes, C. P. *J. Org. Chem.* **1993**, *58*, 5683–5689.

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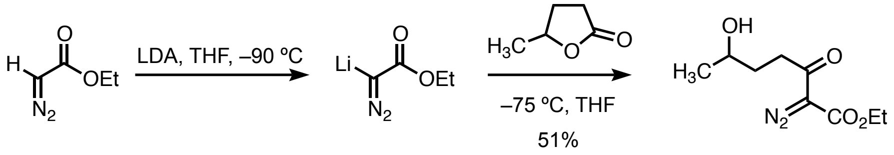
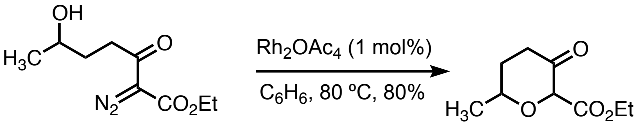
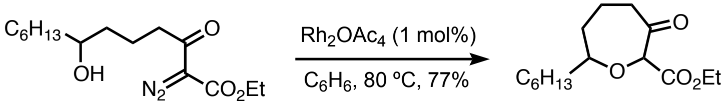
- Ethyl diazoacetate can be deprotonated with LDA at low temperature. The resulting anion can be trapped with electrophiles.

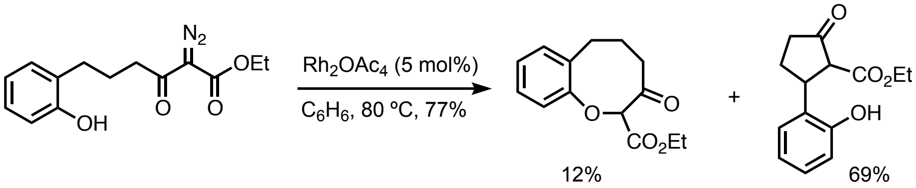


- Rhodium catalysts readily transform α-diazoesters into stabilized carbenoids, which readily etherify alcohols:



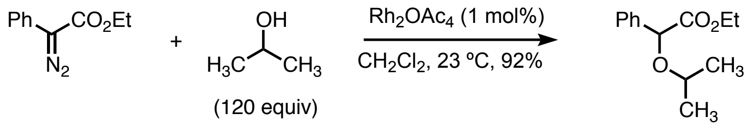


- Formation of medium-sized rings is entropically unfavorable and competitive C–H insertion by the rhodium carbenoid is observed:



Moody, C. J.; Taylor, R. J. *J. Chem. Soc. Perkin Trans. 1* **1989**, 721–731.

- Intermolecular trapping is also possible:



Cox, G. G.; Miller, D. J.; Moody, C. J.; Sie, E.-R. H. B.; Kulagowski, J. J. *Tetrahedron* **1994**, *50*, 3195–3212.

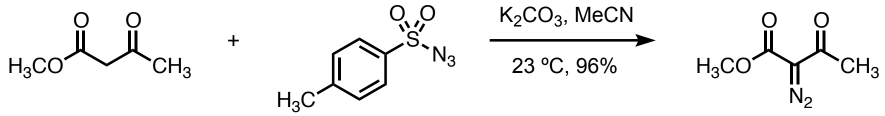
Synthesis of Diazo Compounds

Reviews:

Heydt, H. *Sci. Synth.* **2004**, *27*, 843–937.

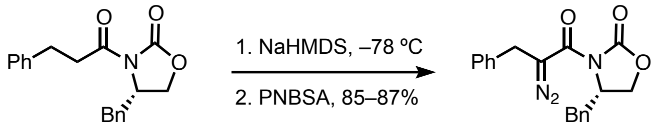
- In addition to the methods described above for the generation of reactive diazo reagents, diazo compounds can be prepared by the following methods:

- Regitz Diazo Transfer Reaction
- Reaction of an enolate with sulfonyl azide affords diazo compounds:

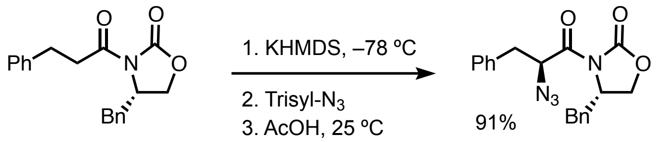


Koskinen, A. M. P.; Munoz, L. *J. Chem. Soc. Chem. Commun.* **1990**, 652–653.

- *p*-nitrobenzenesulfonyl azide (PNBSA) was found to be an effective diazo transfer agent for carboximide enolates:



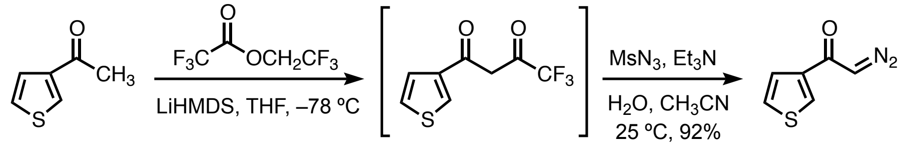
- The above reaction is highly sensitive to the enolate counterion, the quenching reagent, and the sulfonyl azide structure: using triisopropylsulfonyl azide (trisyl azide) instead led to selective azide transfer.

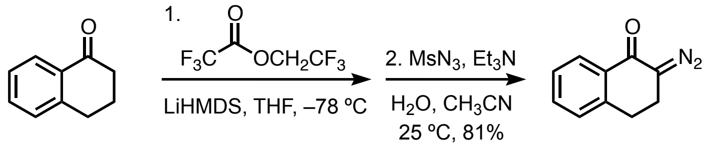


Evans, D. A.; Britton, T. C.; Ellman, J. A.; Dorow, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 4011–4030.

Fan Liu

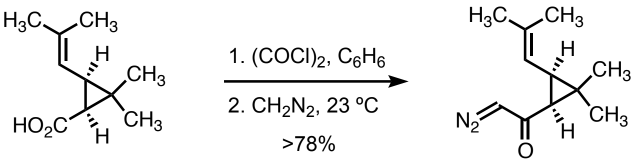
- When only one electron-withdrawing group is present on the substrate, a second electron-withdrawing group is usually introduced to activate the parent compound towards diazo transfer. The second electron-withdrawing group is removed at the end of the reaction:





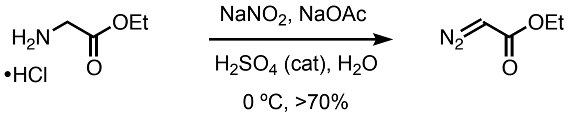
Danheiser, R. L.; Miller, R. F.; Brisbois, R. G.; Park, S. Z. *J. Org. Chem.* **1990**, *55*, 1959–1964.

- Reaction of acyl chlorides or anhydrides with diazomethane yields diazo compounds:



Smith, A. B.; Dorsey, B. D.; Visnick, M.; Maeda, T.; Malamas, M. S. *J. Am. Chem. Soc.* **1980**, *108*, 3110–3112.

- Diazotization of primary amines also affords diazo compounds:



Wuzr, R. P.; Charett, A. B. *Org. Lett.* **2002**, *4*, 4531–4533.

Fan Liu

Metal-Catalyzed C–O Bond-Forming Reactions: Buchwald–Hartwig Coupling

Reviews:

Hartwig, J. F. *Organotransition Metal Chemistry*, 1st Edition; University Science Books: USA, **2009**.

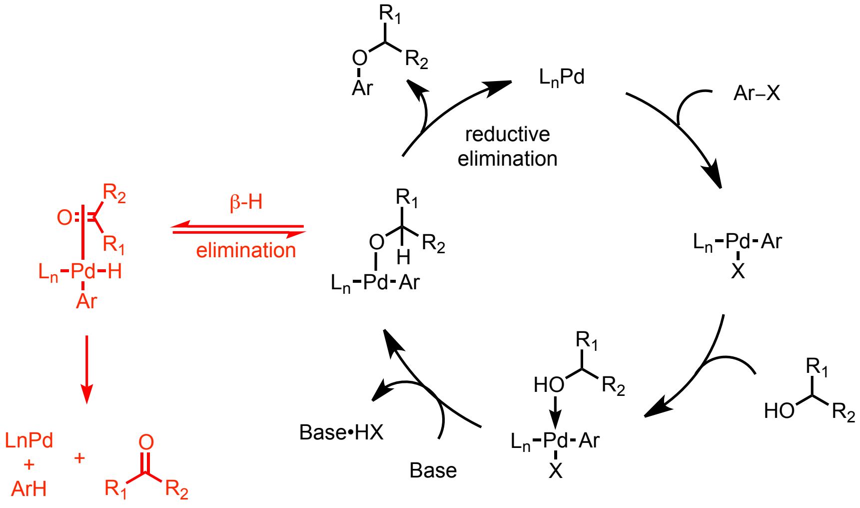
Frlan, R.; Kikelj, D. *Synthesis*, **2006**, *14*, 2271–2285.

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

Reaction Highlights

- The main challenge in the Pd-catalyzed C-O bond forming reactions is to prevent β-H elimination of the alcohol substrate. Many factors, including Pd source, ligand, base, solvent, and temperature can influence the efficiency of the reaction.
- Much of the improvement in this field has come from the development of ligands, which permits couplings of substrates with varying steric and electronic parameters.
- The development of ligands has also improved the reactivity of unactivated aryl halides.

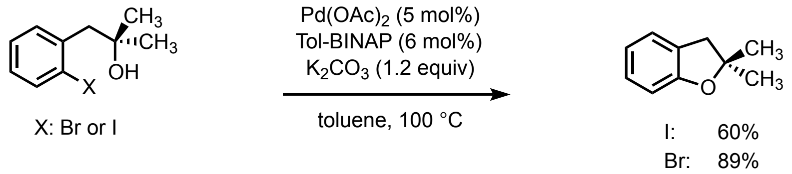
General Mechanism



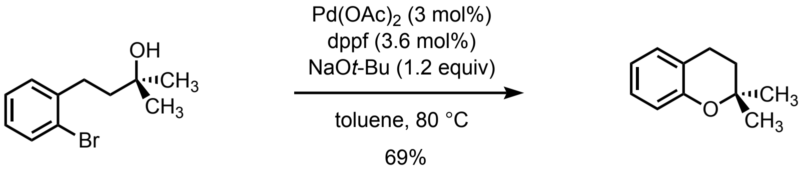
Initial Reports:

- Buchwald and co-workers reported an intramolecular C-O coupling procedure following a mechanism similar to that of Pd-catalyzed amination. Bidentate phosphine ligands afford high conversions to product.

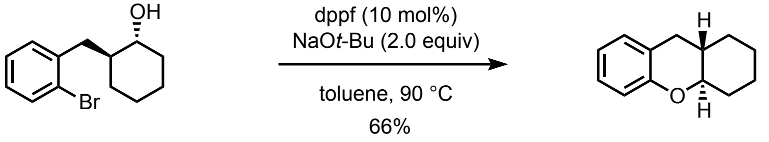
Condition A:



Condition B:



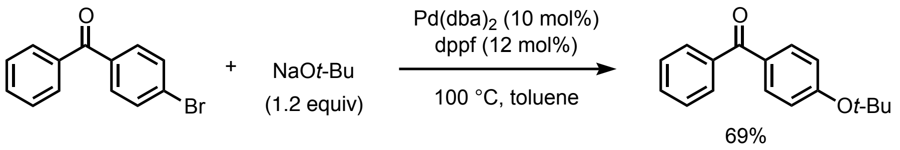
Condition C:



Condition **A** (24–36 h) gives product cleanly while Condition **B** gives product with a faster reaction rate (1–6 h). Condition **C** works well for secondary alcohols.

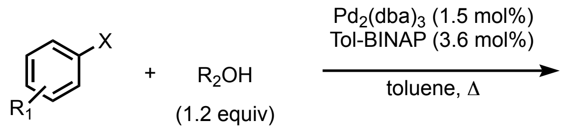
Palucki, M.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 10333–10334.

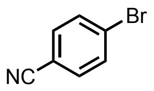
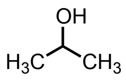
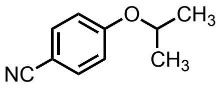
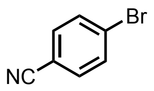
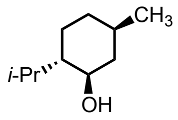
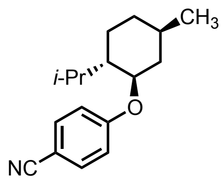
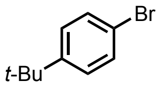
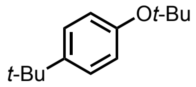
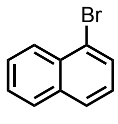
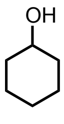
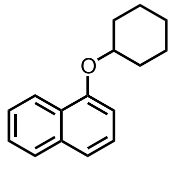
- Electron-deficient aryl bromides were found to be more reactive than electron-neutral and electron-rich aryl bromides.



Mann, G.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 13109–13110.

- The methodology was extended to intermolecular cross-coupling with primary and secondary alcohols.

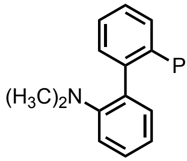


Aryl halide	**Alcohol**	**Product**	**Temp (°C)**	**Yield (%)[a]**
			50	80 (76)
			70	77 (73)
	NaO*t*-Bu		100	53 (<10)
			70	65 (<5)

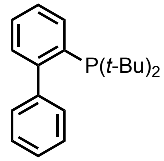
[a]Values in parentheses are yields with no catalyst (DMF as solvent).

Palucki, M.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 3395–3396.

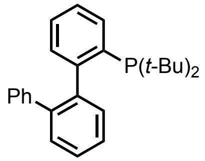
- **Ligands and Their Applications**
- A series of ligands developed by Buchwald and co-workers improved reactivities of a combination of substrates, including unactivated aryl halides and triflates.



Ligand **A**

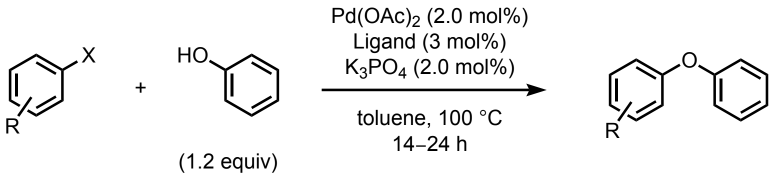


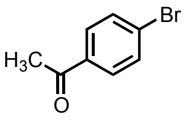
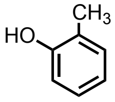
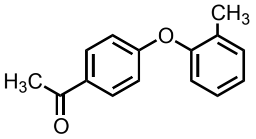
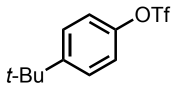
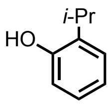
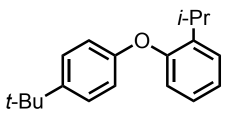
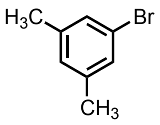
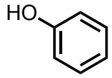
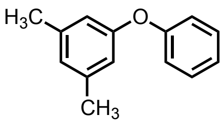
Ligand **B**



Ligand **C**

Biaryl Ether Synthesis



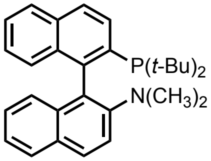
Aryl halide	**Phenol**	**Ligand**	**Product**	**Yield (%)**
		**A**		96 (95)[a]
		**B**		84
		**C**		83

[a]Reaction run with 0.1 mol% Pd(OAc)$_2$, 0.15 mol% ligand.

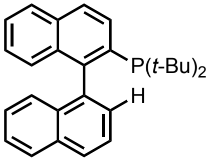
Aranyos, A.; Old, D. W.; Kiyomori, A.; Wolfe, J. P.; Sadighi, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 4369–4378.
Kuwabe, S.-i.; Torraca, K. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001,** *123,* 12202–12206.

Alpay Dermenci

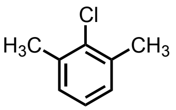
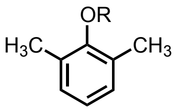
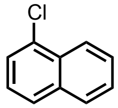
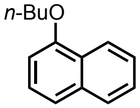
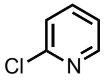
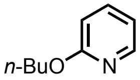
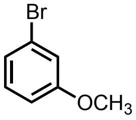
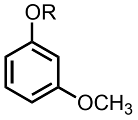
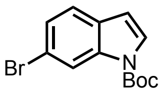
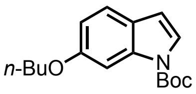
- It was discovered that binaphthyl ligands such as **D** and **E** can improve reactivity and yield and allow for the intermolecular coupling of primary alcohols and aryl halides with minimal arene reduction.



Ligand **D**

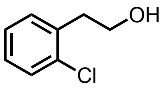
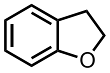
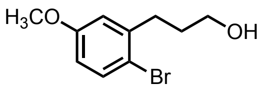
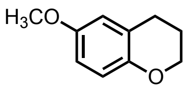
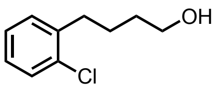
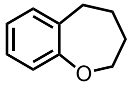


Ligand **E**

Aryl halide	**Alcohol** (2 equiv)	**Product**	**Ligand**	**Yield (%)**
	*n*-BuOH		**E**	90
	$PhCH_2OH$		**E**	95
	i-BuOH		**E**	88
	EtOH		**E**	93
	*n*-BuOH		**E**	88
	*n*-BuOH		**E**	79
	*n*-BuOH		**D**	80
	$PhCH_2OH$		**D**	80
	*n*-BuOH		**D**	72

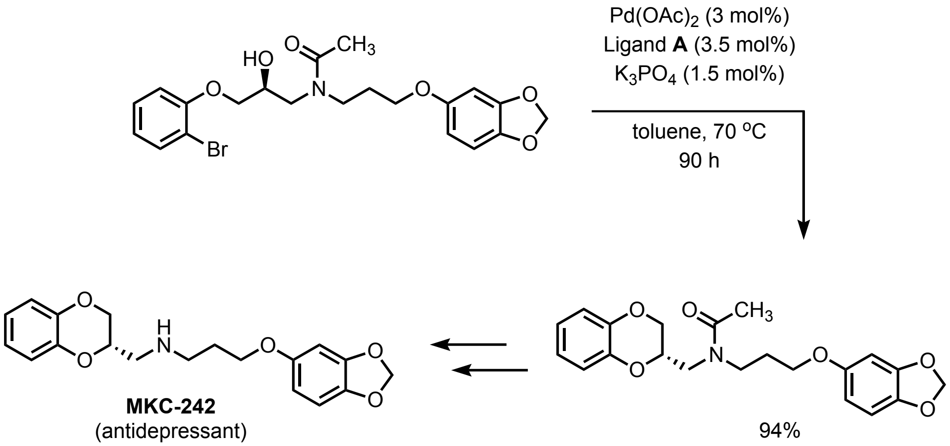
Torraca, K. E.; Huang, X.; Parrish, C. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 10770–10771.

Intramolecular Synthesis of Cyclic Aryl Ethers

Substrate	**Temp. (°C)**	**Product**	**Yield (%)**
	50		71
	50		71
	70		74

Conditions: $Pd(OAc)_2$ (2–3 mol%), ligand **E** (2.5–3.5 mol%), Cs_2CO_3, toluene.

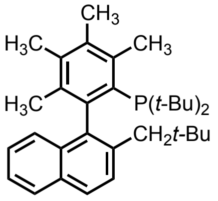
Application to the Synthesis of MKC-242



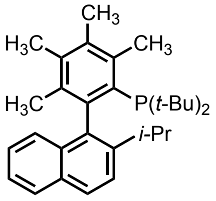
Torraca, K. E.; Kuwabe, S.-I.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 12907–12908.
Kuwabe, S.-i.; Torraca, K. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 12202–12206.

Alpay Dermenci

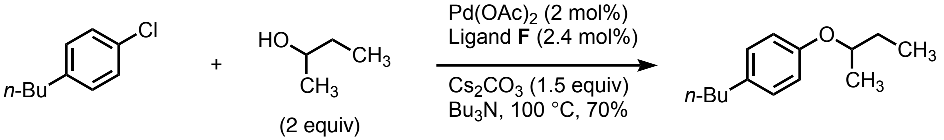
- The substrate scope was expanded to include secondary, allylic and propargylic alcohols with ligands **F** and **G**.

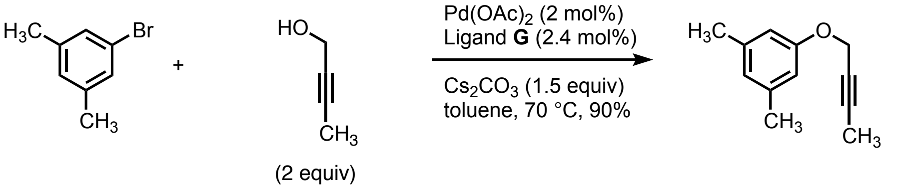


Ligand **F**

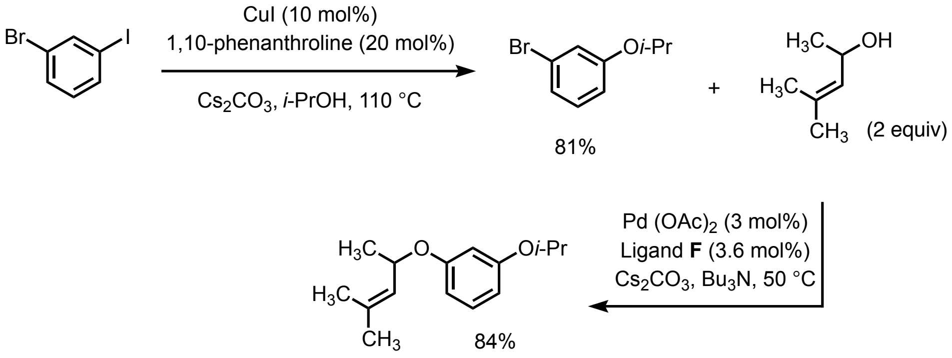


Ligand **G**



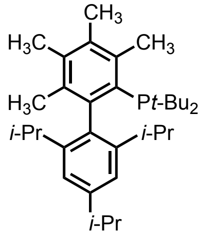


- This methodology can be used in conjunction with Cu-mediated Ullman-type couplings (discussed in that chapter).

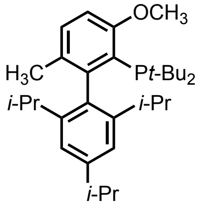


Vorogushin, A. V.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 8146–8149.

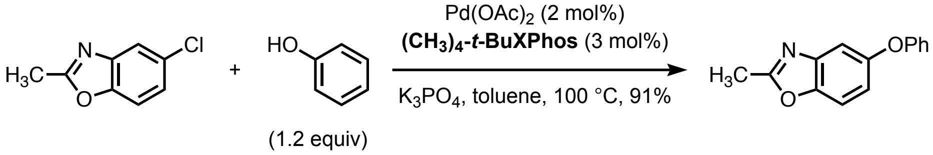
- $(CH_3)_4$-*t*-BuXPhos and RockPhos allow for improved coupling of aryl halides with phenols and secondary/primary alcohols, respectively.

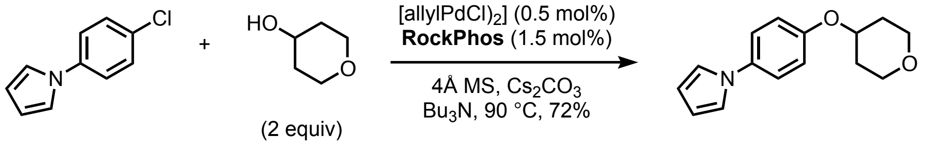


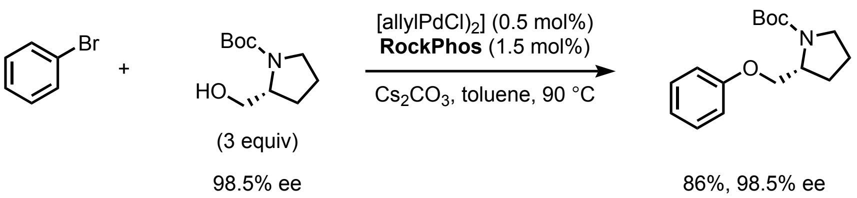
$(CH_3)_4$-*t*-BuXPhos



RockPhos







Burgos, C. H.; Barder, T. E.; Huang, X.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2006**, *45*, 4321–4326.

Wu, X.; Fors, B. R.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2011**, *50*, 9943–9947.

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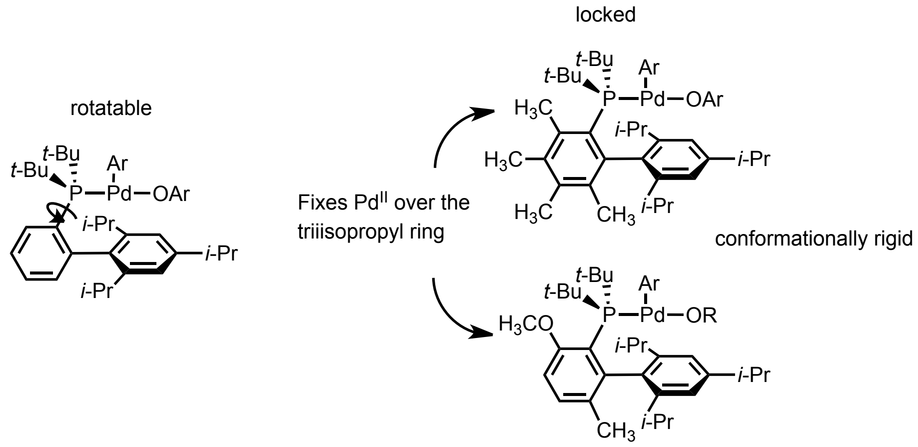
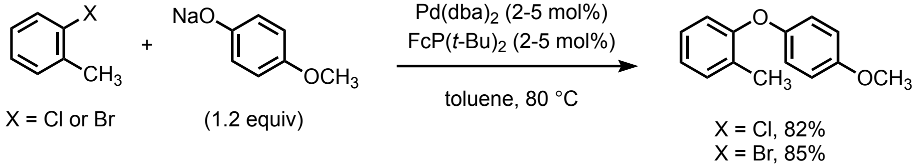
- The superiority of these ligands stems from their effectiveness in promoting reductive elimination.

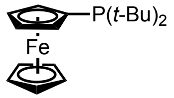


- **Hartwig Ligands**

- Hartwig and co-workers discovered that the sterically hindered FcP(t-Bu)$_2$ promotes reductive elimination and formation of diaryl ethers from unactivated aryl halides.

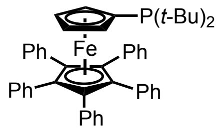


FcP(t-Bu)$_2$ = ferrocenyldi-*tert*-butylphosphine

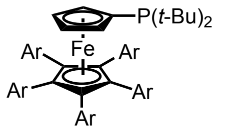


Mann, G.; Incarvito, C.; Rheingold, A. L.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 3224–3225.

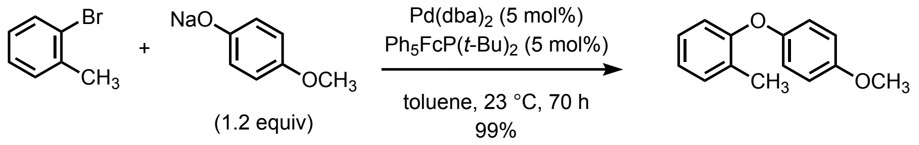
- Ph$_5$FcP(t-Bu)$_2$ was later found to be a superior ligand, while substituting the ferrocene ring with electron-donating substituents was found to increase both the reaction rate and yields.

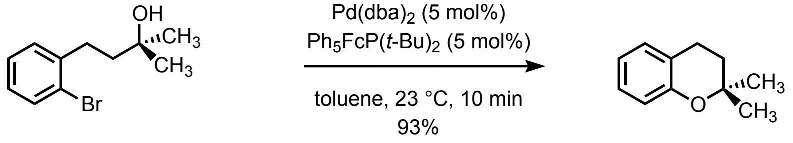


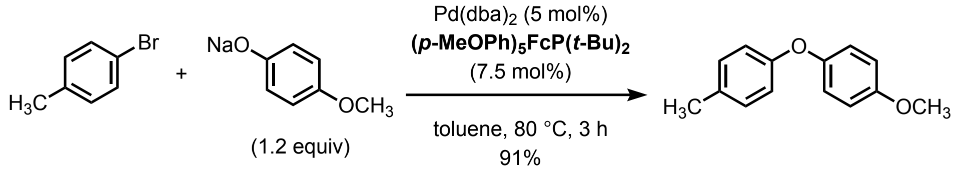
Ph$_5$FcP(t-Bu)$_2$

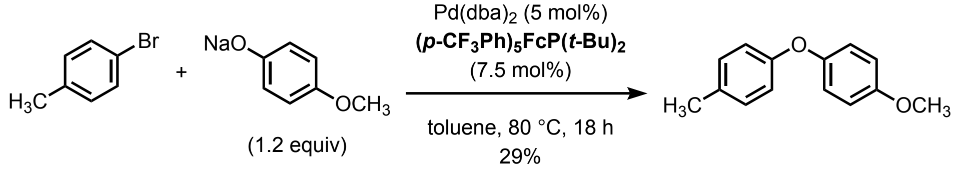


Ar = p-MeOC$_6$H$_4$: (p-MeOPh)$_5$FcP(t-Bu)$_2$
Ar = p-CF$_3$C$_6$H$_4$: (p-CF$_3$Ph)$_5$FcP(t-Bu)$_2$









Shelby, Q.; Kataoaka, N.; Mann, G.; Hartwig, J. *J. Am. Chem. Soc.* **2000**, *122*, 10718–10719.
Kataoka, N.; Shelby, Q.; Stambuli, J. P.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 5553–5566.

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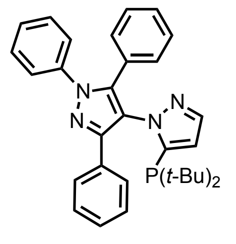
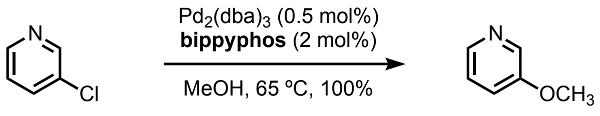
- **Other Ligands**
- In addition to ligands developed by Buchwald and Hartwig, Singer and co-workers have developed a structurally different ligand, bippyphos (prepared on multi-kilogram scale), which allows coupling of aryl halides and alcohols.

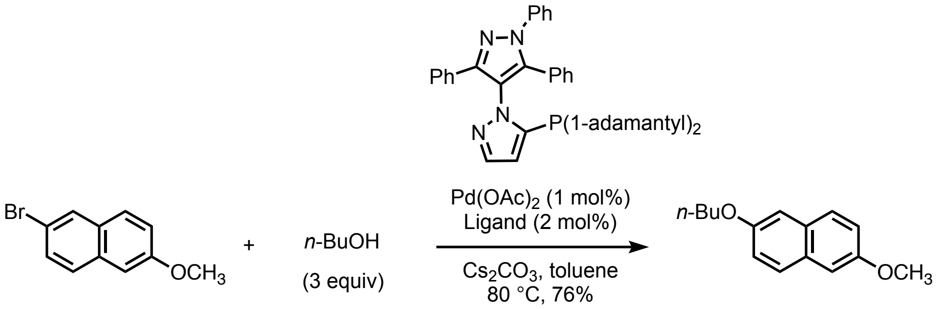


bippyphos

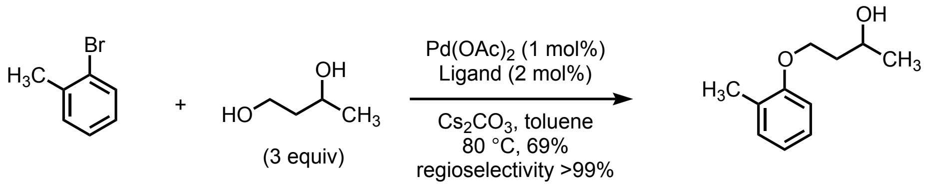


Singer, R. A.; Caron, S.; McDermott, R. E.; Arpin, P.; Do, N. M. *Synthesis*, **2003**, 1727–1731.
Withbroe, G. J.; Singer, R. A.; Sieser, J. E. *Org. Proc. Res. Dev.* **2008**, *12*, 480–489.

- Beller and co-workers have developed a modified bippyphos ligand that is effective for the coupling of aryl halides with primary and secondary alcohols.

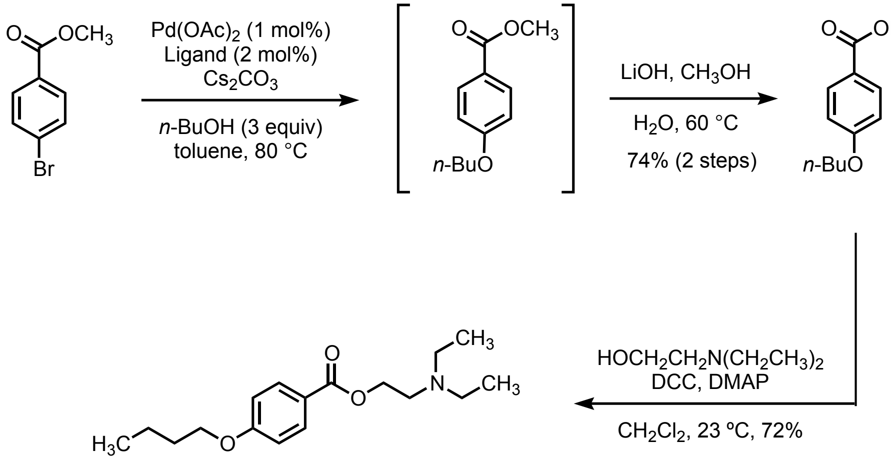


- Primary alcohols are selectively coupled in the presence of secondary alcohols:



Gowrisankar, S.; Sergeev, A. G.; Anbarasan, P.; Spannenberg, A.; Neumann, H.; Beller, M. *J. Am. Chem. Soc.* **2010**, *132*, 11592–11598.

- Application to synthesis of butoxycaine, a local anesthetic:



Butoxycaine

Harkal, S.; Kumar, K.; Michalik, D.; Zapf, A.; Jackstell, R.; Rataboul, F.; Riermeier, T.; Monsees, A.; Beller, M. *Tetrahedron Lett.* **2005**, *46*, 3237–3240.

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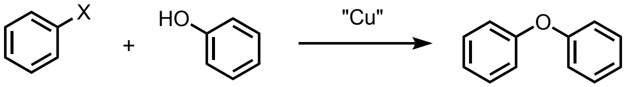
Reviews

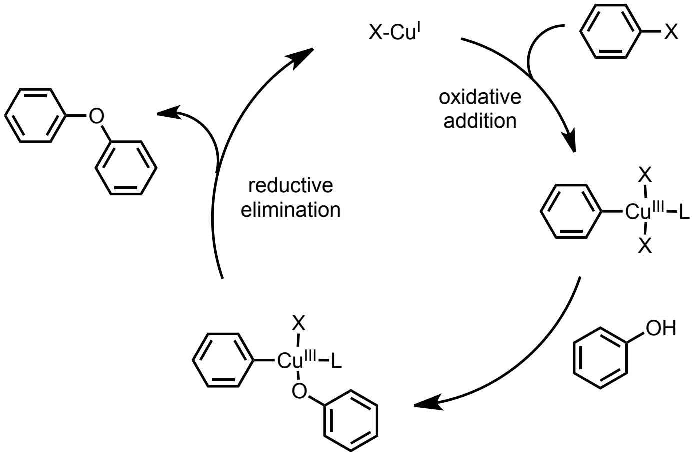
Rao, K. S.; Wu, T. S. *Tetrahedron* **2012**, *68*, 7735–7754.
Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008**, *108*, 3054–3131.
Ley, S. V.; Thomas, A. W. *Angew. Chem. Int. Ed.* **2003**, *42*, 5400–5449.
Kunz, K.; Scholz, U.; Ganzer, D. *Synlett*, **2003**, *15*, 2428–2439.
Sawyer, J. S. *Tetrahedron* **2000**, *56*, 5045–5065.

Original Report (Ullman, 1904):



Ullman, F. *Ber.* **1904**, *37*, 853–854.
Ullman, F.; Sponagel, P. *Ber.* **1905**, *38*, 2211–2212.

Mechanism: The mechanism for the Ullman arylation of alcohols is not well understood. It is likely that the reaction involves a Cu^{I} species.



Litvak, V. V.; Shein, S. M. *Zh. Org. Khim.* **1975** *11*, 92–96.
Ley, S. V.; Thomas, A. W. *Angew. Chem. Int. Ed.* **2004**, *43*, 5400–5449.

Generalized Cross-Coupling:

$$RX + HOR' \xrightarrow{Cu^{I}} R{-}OR'$$

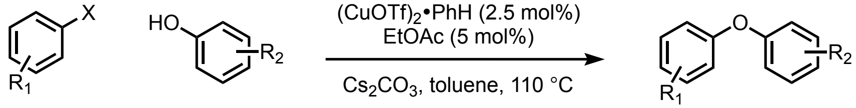
X = I, Br, $B(OH)_2$, $BF_3^{-}K^{+}$

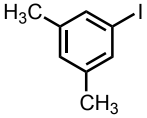
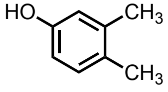
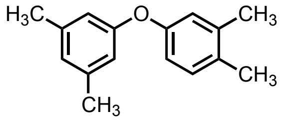
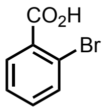
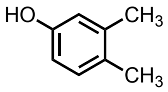
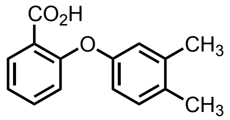
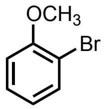
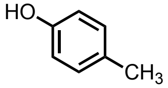
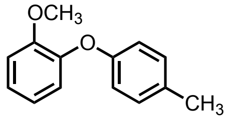
General Reaction Features:

- Good functional group compatibility.
- Mild reaction conditions.
- A base is often required.
- Typically an excess of one of the coupling partners is necessary.

Ullman Coupling with Aryl Halides

- A general procedure was reported for the coupling of aryl bromides and iodides with phenols:



Aryl halide	Phenol	Product	Yield (%)
	 1.4 equiv		90%
	 2.0 equiv		84%
	 2.0 equiv		79%[a]

[a] 1-naphthoic acid and 5Å molecular sieves were added.

Marcoux, J.-F.; Doye, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 10539–10540.

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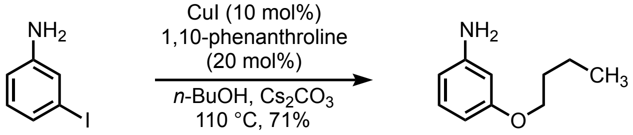
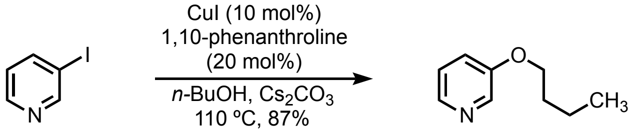
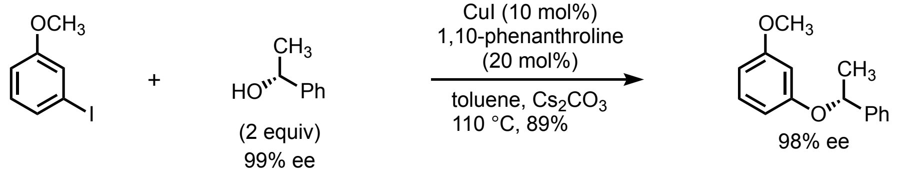
Metal-Catalyzed C–O Bond-Forming Reactions: Ullman Coupling

Synthesis of Alkoxy Aryl Ethers

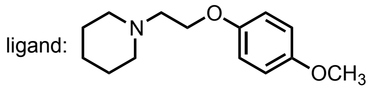


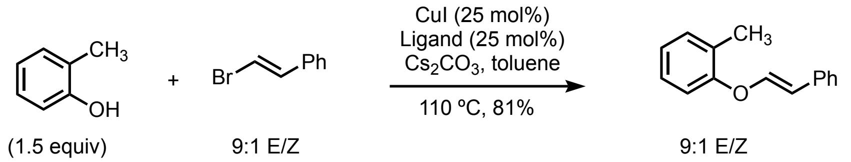


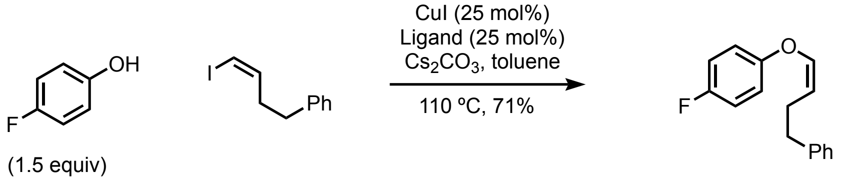


Wolter, M.; Nordmann, G.; Job, G. E.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 973–976.

Synthesis of Aryl Vinyl Ethers



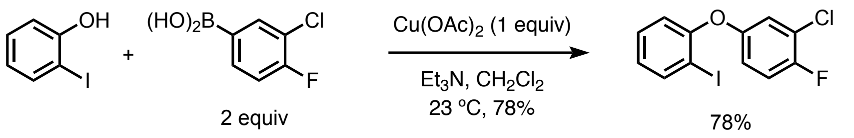




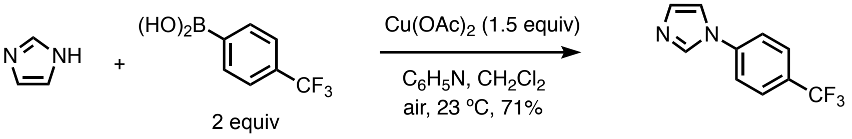
Wan, Z.; Jones, C. D.; Koenig, T. M.; Pu, Y. J.; Mitchell, D. *Tetrahedron Lett.* **2003**, *44*, 8257–8259.

Ullman Coupling with Boronic Acids:

- Chan, Lam, and Evans have reported milder conditions for the synthesis of diaryl ethers using boronic acids and stoichiometric amounts of copper acetate at room temperature.

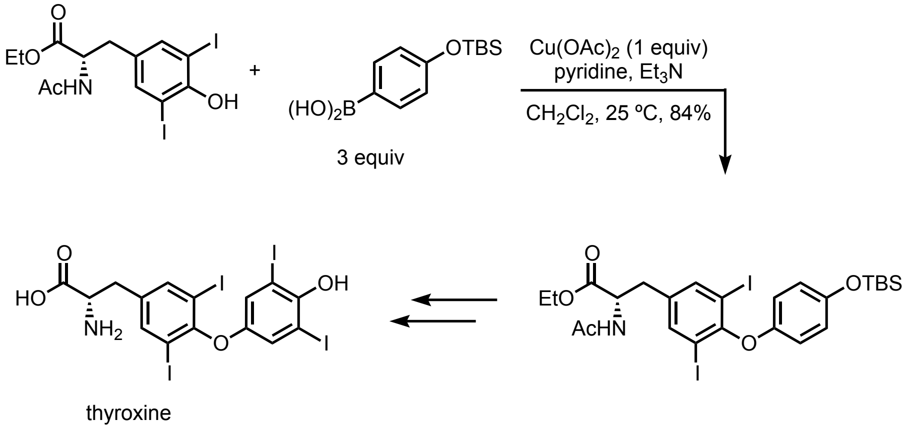


Chan, D. M. T.; Monaco, K. L.; Wang, R.-P.; Winters, M. P. *Tetrahedron Lett.* **1998**, *39*, 2933–2936.



Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Winters, M. P.; Chan, D. M. T.; Combs, A. *Tetrahedron Lett.* **1988**, *39*, 2941–2944.

- Evans and co-workers employed a method involving coupling of boronic acids en route to thyroxine.



Evans, D. A.; Katz, J. L.; West, T. R. *Tetrahedron Lett.* **1998,** *39,* 2937–2940.

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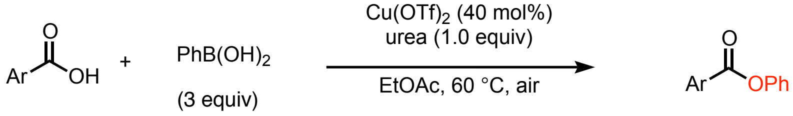
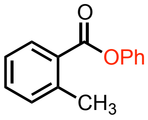
Carboxylic Acids

- Coupling of phenyl boronic acid with a wide range of carboxylic acids occurs in the presence of urea as an additive:





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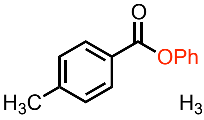

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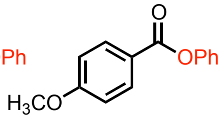

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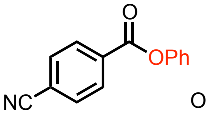

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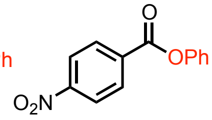

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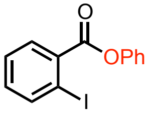

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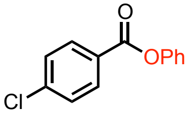

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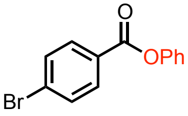

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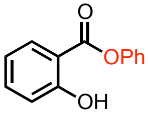

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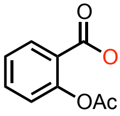

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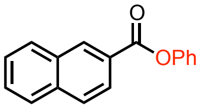

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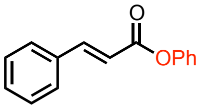

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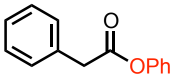

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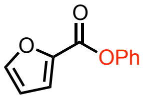


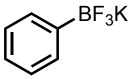
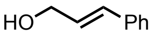
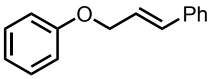
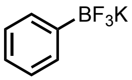
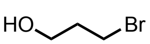
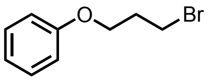
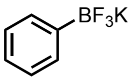
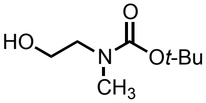
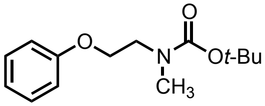
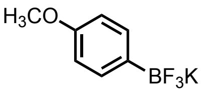
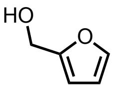
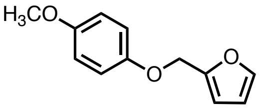
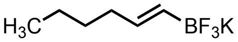
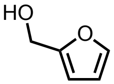
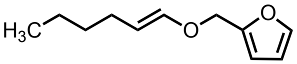
95%

Zhang, L.; Zhang, G.; Zhang, M.; Cheng, J. *J. Org. Chem.* **2010**, *75*, 7472–7474.

Ullman Coupling with potassium organotrifluoroborate salts —— Batey Modification

- Aryltrifluoroborates are more robust, more easily purified, and less prone to protodeboronation than aryl boronic acids.
- This procedure is effective for coupling both aliphatic alcohols and phenols at room temperature under pH-neutral conditions.

$$\underset{\text{(2 equiv)}}{\mathrm{ArBF_3^{-}K^{+}}} + \mathrm{HOR} \xrightarrow[\mathrm{CH_2Cl_2,\ 4Å\ MS;\ O_2,\ 23\ °C}]{\mathrm{Cu(OAc)_2{\bullet}H_2O\ (10\ mol\%)},\ \mathrm{DMAP\ (20\ mol\%)}} \mathrm{Ar{-}OR}$$

Borate salt	Phenol/Alcohol	Product	Yield
			89
			93
			93
			99
			55

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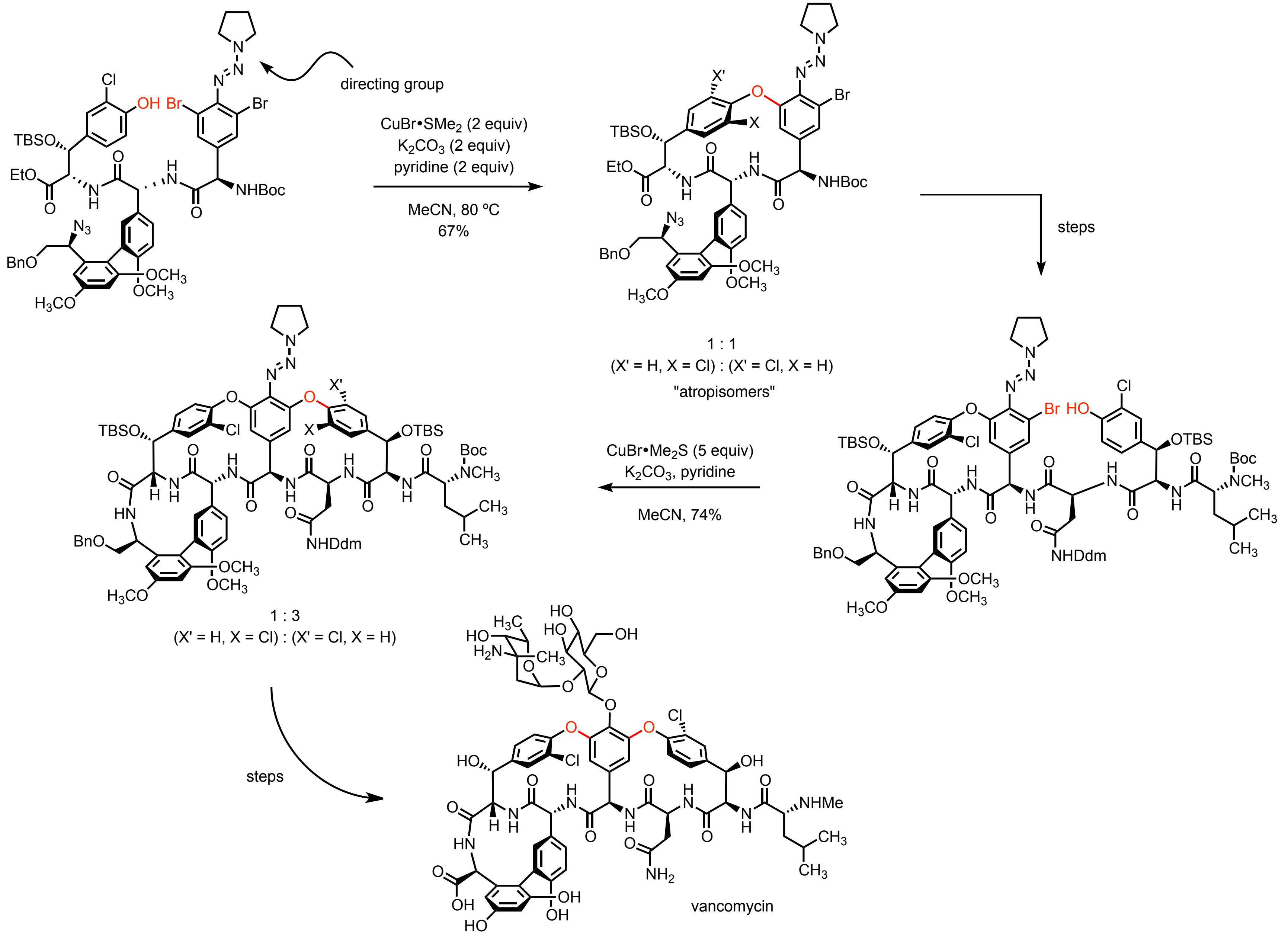
Examples in Natural Product Synthesis



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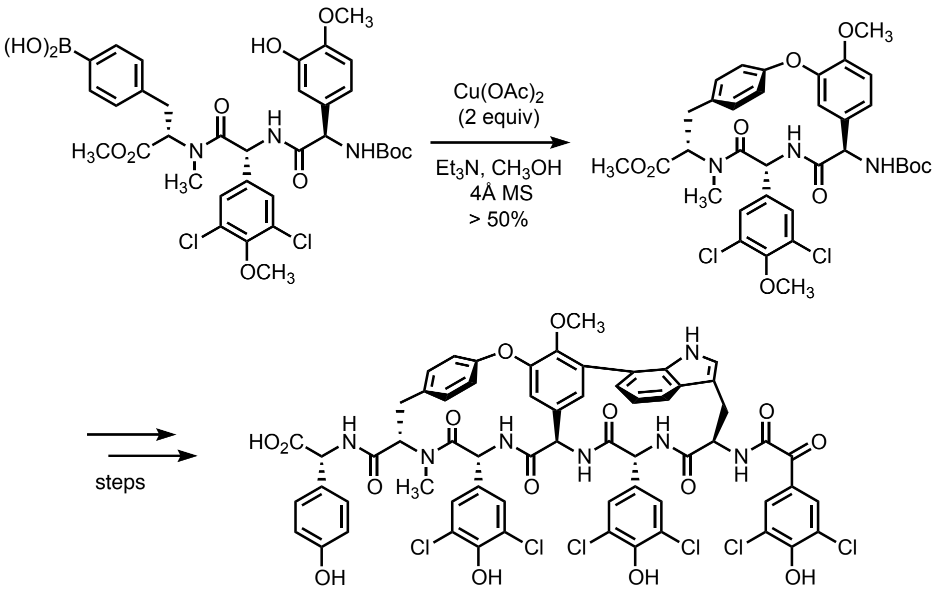
Metal-Catalyzed C–O Bond-Forming Reactions: Ullman Coupling



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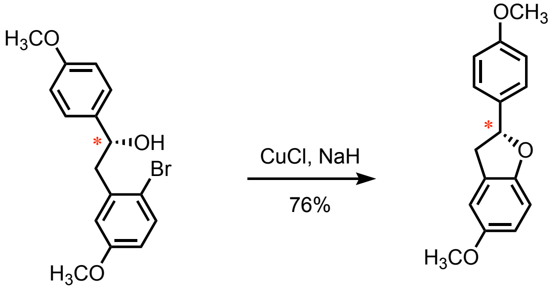

Corsifuran A

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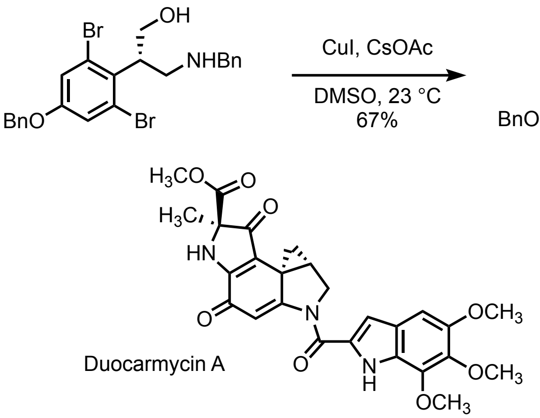
Selective C–N over C–O Intramolecular Ullman Coupling



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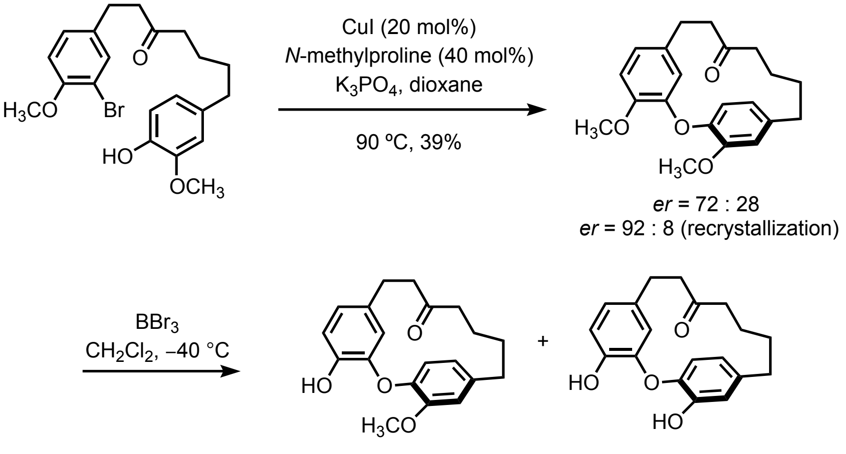
Enantioselective Ullman Coupling



er = 72 : 28
er = 92 : 8 (recrystallization)

(+)-galeon
43% (92:8 er)

(+)-pterocarine
45% (92:8 er)

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