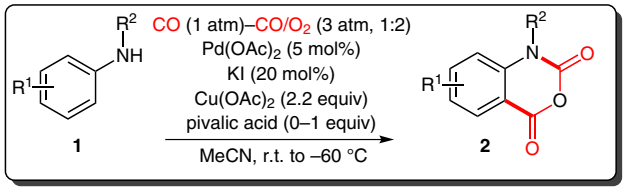
Z.-H. GUAN,* M. CHEN, Z.-H. REN (NORTHWEST UNIVERSITY, XI'AN, P. R. OF CHINA)

Palladium-Catalyzed Regioselective Carbonylation of C–H Bonds of N-Alkyl Anilines for Synthesis of Isatoic Anhydrides

*J. Am. Chem. Soc.* **2012**, *134*, 17490–17493.

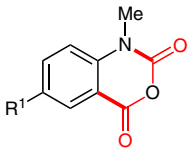
# Isatoic Anhydrides via C–H Activation




***Starred examples were run with pivalic acid (1 equiv):**

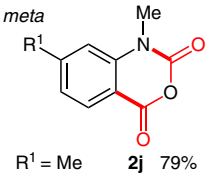
**Substrate scope – aryl**

*para*



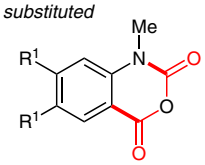
$R^1$ = H **2a** 85%
= OMe **2b** 70%
= Me **2c** 76%
= F **2d** 66%*
= Cl **2e** 78%*
= Br **2f** 86%*
= OCOEt **2g** 85%*
= COMe **2h** 80%*
= CHO **2i** 77%*

*meta*

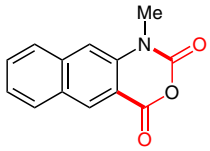


$R^1$ = Me **2j** 79%
= Cl **2k** 76%*
= $NO_2$ **2l** 63%*

*bis substituted*

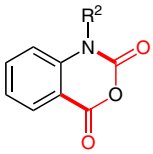


$R^1$ = Me **2m** 65%
= OMe **2n** 62%

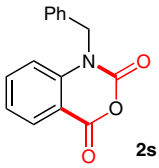


**2o** 68%

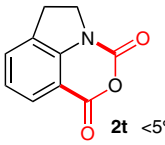
**Substrate scope – alkyl**



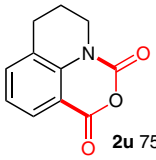
$R^2$ = Et **2p** 84%
= Pr **2q** 63%
= Cy **2r** 51%



**2s** 72%

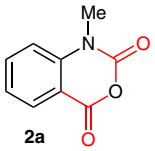


**2t** <5%



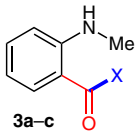
**2u** 75%*

**Derivatization**



**2a**

solvolysis/
aminolysis



**3a–c**

X = OH **3a** conditions: HCl (15 mol%), 100 °C, 99%
X = OEt **3b** conditions: $K_2CO_3$, EtOH, 100 °C, 89%
X = $NH_2$ **3c** conditions: $NH_3 \cdot H_2O$, MeCN, r.t., 97%

**Significance:** Reported is the synthesis of isatoic anhydrides **2** via the carbonylation of substituted anilines **1** utilizing a C–H activation procedure. Optimization studies demonstrated the beneficial effects of potassium iodide and the importance of oxidant and solvent choice. A substrate-scope screen showed that electron-rich anilines were the most reactive (**2a–c**). However, electron-deficient anilines proved useful substrates with the addition of pivalic acid and increased pressure (**2d–i**). In the case of **2a**, a catalytic procedure [with respect to $Cu(OAc)_2$] using oxygen as the terminal oxidant was demonstrated, affording the desired isatoic anhydride in marginally reduced yield. Derivatization of **2a** to the *ortho*-amino acid **3a**, ester **3b**, and primary amide **3c** was reported.

**Comment:** Isatoic anhydrides are useful reagents for the preparation of anthranilic acid derivatives and various heterocycles alike (see Review below). Traditionally these heterocycles have been prepared via various multi-step sequences, for example from the anthranilic acids themselves (E. C. Wagner, M. F. Fegley *Org. Synth.* **1947**, *27*, 45) or via oxidation of phthalimides. The current report is attractive for several reasons, including circumventing the need for regioselective pre-functionalization and employing readily available anilines **2** as starting material.

**Review:** G. M. Coppola *Synthesis* **1980**, 505–536.

**SYNFACTS Contributors:** Victor Snieckus, Matthew O. Kitching
Synfacts 2013, 9(1), 0019 Published online: 17.12.2012
**DOI:** 10.1055/s-0032-1317877; **Reg-No.:** V16112SF



**Category**

**Synthesis of Heterocycles**

**Key words**

**carbonylation**
**palladium**
**aniline**
**C–H activation**

**Category**

**Synthesis of Heterocycles**

**Key words**

**azlactones**

**asymmetric catalysis**

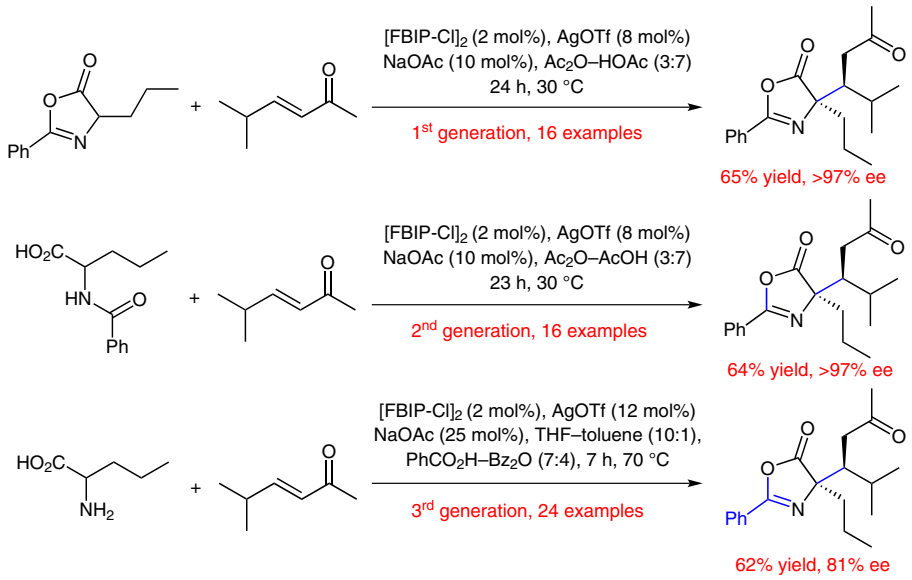
**peptides**

**quaternary amino acids**

M. WEBER, S. JAUTZE, W. FREY, R. PETERS* (UNIVERSITÄT STUTTGART, GERMANY)

Bispalladacycle-Catalyzed Michael Addition of In Situ Formed Azlactones to Enones
*Chem. Eur. J.* **2012**, *18*, 14792–14804.

# Access to Quaternary Amino Acids via Dynamic Kinetic Resolution of Azlactones




**Significance:** Due to their ability to both provide greater stability against degradation and to restrict conformational flexibility of peptides, quaternary α-amino acids are an important compound class. Azlactones have been extensively used for the asymmetric assembly of these quaternary centers taking advantage of the tendency for enolization at the C4-position owing to the aromatic character of the enol tautomer. The current study provides the first report on the 1,4-addition of azlactones to enones mediated by a readily accessible (four steps from ferrocene) planar-chiral ferrocene bis-imidazoline bispalladacycle (FBIP). Three protocols are developed including enabling the intermediate azlactone to be assembled in situ from a racemic amino acid. High levels of enantiocontrol are obtained for the reactions and the range of synthetic utility of the products is demonstrated in the synthesis of amino acids, proline derivatives, cyclic dipeptides and (pyro)glutamic acids.

**Comment:** In all cases of the Michael addition of azlactones to enones examined, the products were formed in diastereomerically pure form. The optimal C2-substituent was phenyl and the enantioselectivity of the reaction increased with the steric bulk of the C4-substituent. Key to the reaction is addition of both a silver salt (AgOTf), and sodium acetate using a solvent system of acetic acid–acetic anhydride. The ability to recycle the catalyst system with minimal loss of performance over seven cycles was demonstrated. A system to utilize unprotected amino acids was also described. In this case, significant optimization was required to minimize competing formation of the regioisomeric C2-addition product (generated as a racemic mixture). Detailed mechanistic studies suggest the operation of a bimetallic activation pathway.

**SYNFACTS Contributors:** Victor Snieckus, Paul Richardson (Pfizer)
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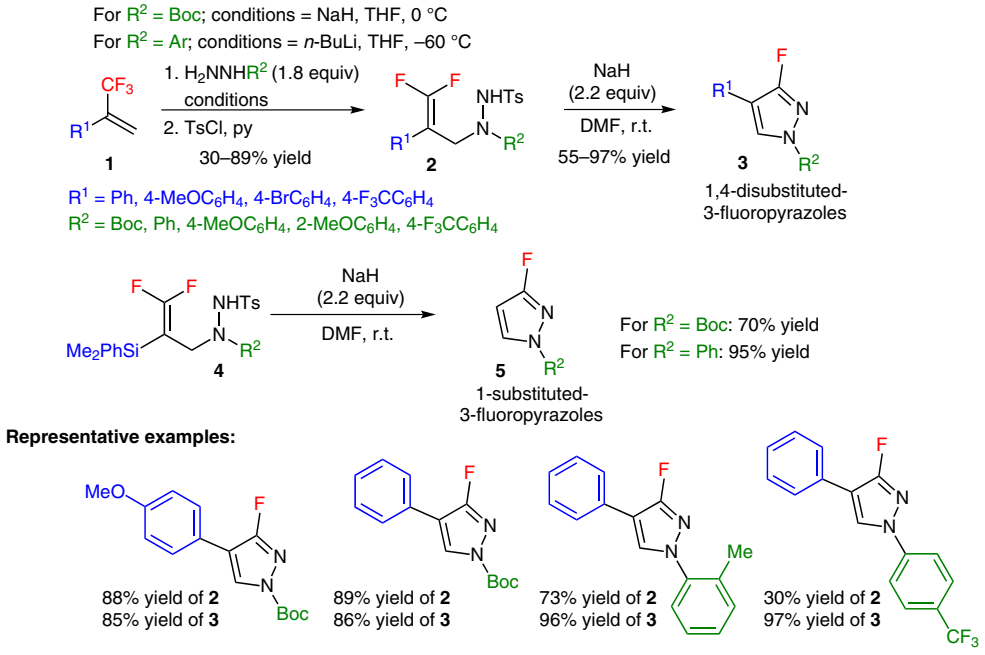
**DOI:** 10.1055/s-0032-1317876; **Reg-No.:** V16012SF

K. FUCHIBE, M. TAKAHASHI, J. ICHIKAWA* (UNIVERSITY OF TSUKUBA, JAPAN)
Substitution of Two Fluorine Atoms in a Trifluoromethyl Group: Regioselective Synthesis of 3-Fluoropyrazoles
*Angew. Chem. Int. Ed.* **2012**, *51*, 12059–12062.

# Synthesis of 3-Fluoropyrazoles from 2-Trifluoromethyl-1-alkenes




**Significance:** Reported is a three-step protocol for the de novo synthesis of substituted 3-fluoropyrazoles through annulation of 2-trifluoromethyl-1-alkenes with monosubstituted hydrazines. The first step in this unconventional approach is an $S_N2'$ addition of an N-deprotonated hydrazine to the trifluoromethyl-substituted alkene to give a 3,3-difluoro allylic hydrazide, which is subsequently tosylated (**1**→**2**). While N-alkylation proceeds in a highly regioselective manner when aryl- and Boc-substituted hydrazines are employed, methylhydrazine affords a 55:45 mixture of N-regioisomers (66% combined yield, not shown above). Treatment of **2** with NaH in DMF affords the substituted 3-fluoropyrazole **3**; control experiments established the need to employ tosylhydrazides in this reaction. 4-Unsubstituted 3-fluoropyrazoles **5** were accessible from the corresponding 2-silyl allylic hydrazide **4**.

**Comment:** Pyrazoles are among the most metabolically stable unsaturated five-membered heterocycles (see Review below) and are frequently incorporated into drug candidates. A successful example is the COX-2 inhibitor celebrex®. The present method provides efficient access to synthetically challenging substituted 3-fluoropyrazoles through a non-obvious and generally high-yielding annulation sequence that utilizes readily accessible starting materials. On the down side, no mention was made of attempts to achieve the synthesis of C5-substituted pyrazoles; alkyl substitution at C4 was also not explored. Control experiments suggest that base-mediated ring closure (**2**→**3**) proceeds through neither direct nucleophilic vinylic substitution ($S_NV$) nor an intermediate nitrene. Instead, an unusual pathway is suggested that features an azomethine imine intermediate.

**Review:** D. K. Dalvie et al. *Chem. Res. Toxicol.* **2002**, *15*, 269–299.

**SYNFACTS Contributors:** Victor Snieckus, Matthew S. Dowling (Pfizer)
Synfacts 2013, 9(1), 0021 Published online: 17.12.2012
**DOI:** 10.1055/s-0032-1317874; **Reg-No.:** V15812SF



**Category**

**Synthesis of Heterocycles**

**Key words**

**3-fluoropyrazoles**

**hydrazines**

**trifluoromethyl-styrenes**

**Category**

**Synthesis of Heterocycles**

**Key words**

**1,4-benzoxazines**

**aziridines**

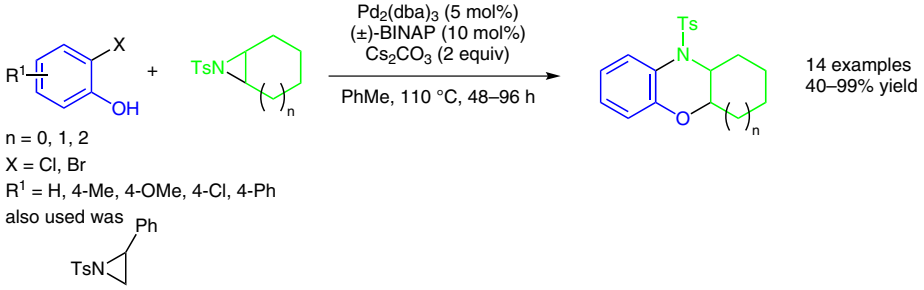
**2-halophenols**

**Buchwald–Hartwig cross-coupling**

R. K. RAO, I. KARTHIKEYAN, G. SEKAR* (INDIAN INSTITUTE OF TECHNOLOGY MADRAS, CHENNAI, INDIA)

Domino Aziridine Ring Opening and Buchwald–Hartwig Type Coupling–Cyclization by Palladium Catalyst
*Tetrahedron* **2012**, *68*, 9090–9094.

# A C–O/C–N Coupling Route to 1,4-Benzoxazines




n = 0, 1, 2
X = Cl, Br
$R^1$ = H, 4-Me, 4-OMe, 4-Cl, 4-Ph
also used was



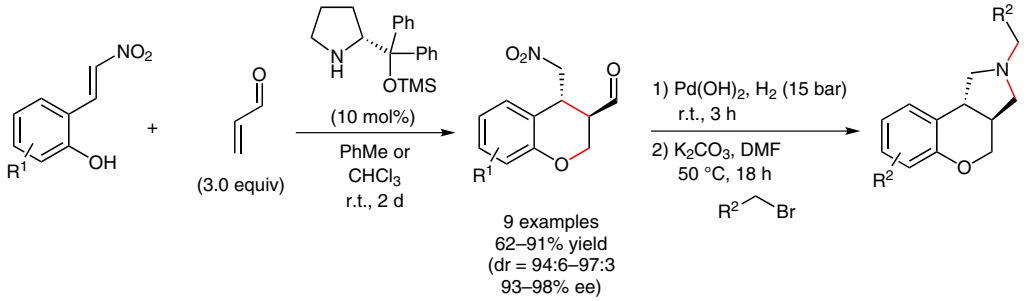

**Significance:** Reported is the synthesis of substituted 1,4-benzoxazines through a (proposed) domino sequence, initiated by phenol-based aziridine ring opening to expose a tosyl-protected amine which then undergoes Buchwald–Hartwig C–N cross-coupling to provide the observed products. No evidence for this sequence was provided, although it seems reasonable when considered together with previous literature. Of the fused aziridines tested, six-membered rings gave the best results as there was a reduction in yield when moving to five- or seven-membered rings. Slight reductions in yield were observed when moving from electron-neutral 2-bromophenol to those with electron-donating or electron-withdrawing groups. Unsurprisingly, 2-bromophenols performed better than 2-chlorophenols. The use of optically active (*S*)-BINAP as a ligand gave only partially resolved product.

**Comment:** 1,4-Benzoxazines are known to have a variety of biologically significant effects and several of these biologically important molecules are shown in the introduction to the current work together with their area of activity. This class of heterocycles has traditionally been synthesized using 2-aminophenols or 2-nitrophenols, both of which can be unavailable and difficult to synthesize if substituted. More modern methods using epoxides as starting materials are also outlined well in the introduction. The method presented above should prove to be a useful and complementary addition to the established methods for 1,4-benzoxazine synthesis in view of the use of readily purchased or easily synthesized starting materials. In addition, the method is operationally simple, uses an inexpensive solvent, and a relatively inexpensive palladium source and ligand. The reaction was optimized with respect to palladium source, ligand, solvent, and base and the substrate scope was modestly examined.

**SYNFACTS Contributors:** Victor Snieckus, Johnathan Board
Synfacts 2013, 9(1), 0022 Published online: 17.12.2012
**DOI:** 10.1055/s-0032-1317871; **Reg-No.:** V15512SF

C. WANG, X. YANG, G. RAABE, D. ENDERS* (RWTH AACHEN UNIVERSITY, GERMANY)
A Short Asymmetric Synthesis of the Benzopyrano[3,4-*c*]pyrrolidine Core *via* an Organocatalytic Domino Oxa-Michael/Michael Reaction
*Adv. Synth. Catal.* **2012**, *354*, 2629–2634.

# Organocatalytic Synthesis of Chromans and Benzopyrano[3,4-*c*]pyrrolidine




**Significance:** Reported is the enantioselective synthesis of *trans*-disubstituted chromans through the use of a sequential oxa-Michael–Michael reaction sequence and the subsequent synthesis of benzopyrano[3,4-*c*]pyrrolidine via reductive amination and N-alkylation. *trans*-Disubstituted chromans were obtained in 62–91% isolated yield with diastereomeric ratios ranging from 94:6 to 97:3 and 93–98% ee. The reaction conditions are quite mild and the success of the reaction in either toluene or chloroform allows for a wider solubility range of the phenol starting material. Although the use of many pyrrolidine-containing organocatalysts resulted in product formation, (2*R*)-2-{diphenyl[(trimethylsilyl)oxy]methyl}-pyrrolidine gave the highest product yield. A limitation was the failure of an electron-rich methoxy-substituted phenol to provide the corresponding chroman.

**Comment:** Benzopyrano[3,4-*c*]pyrrolidines have been investigated in a wide variety of therapeutic areas, including anti-psychotics or anti-depressants (Lavielle et al. EP691243 A1, **1996**), Alzheimer's disease (Asberom et al. WO2007084595 A2, **2007**), obesity, insulin resistance, hypertension (Yao et al. WO2006002349 A1, **2006**), and benign prostatic hyperplasia (A. R. Haight et al. *Org. Process Res. Dev.* **2004**, *8*, 897). Given this variety of therapeutic applications, this new method should garner a fair amount of interest from the drug discovery community. This method appears to be quite suitable for process-scale chemistry, due to its mild conditions and synthetic step reduction when compared to more common techniques, such as the one described by Dubuffet and coworkers (*Bioorg. Med. Chem. Lett.*, **1999**, *9*, 2059). This method also circumvents the use of chiral column chromatography, accelerating the drug discovery process even further.

**SYNFACTS Contributors:** Victor Snieckus, Daniel P. Uccello (Pfizer)
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**DOI:** 10.1055/s-0032-1317872; **Reg-No.:** V15612SF



**Category**

**Synthesis of Heterocycles**

**Key words**

**benzopyrano-[3,4-c]pyrrolidine**

**oxa-Michael reaction**

**domino reaction**

**organocatalysis**

**chroman**

Key words

pyridones

enaminones

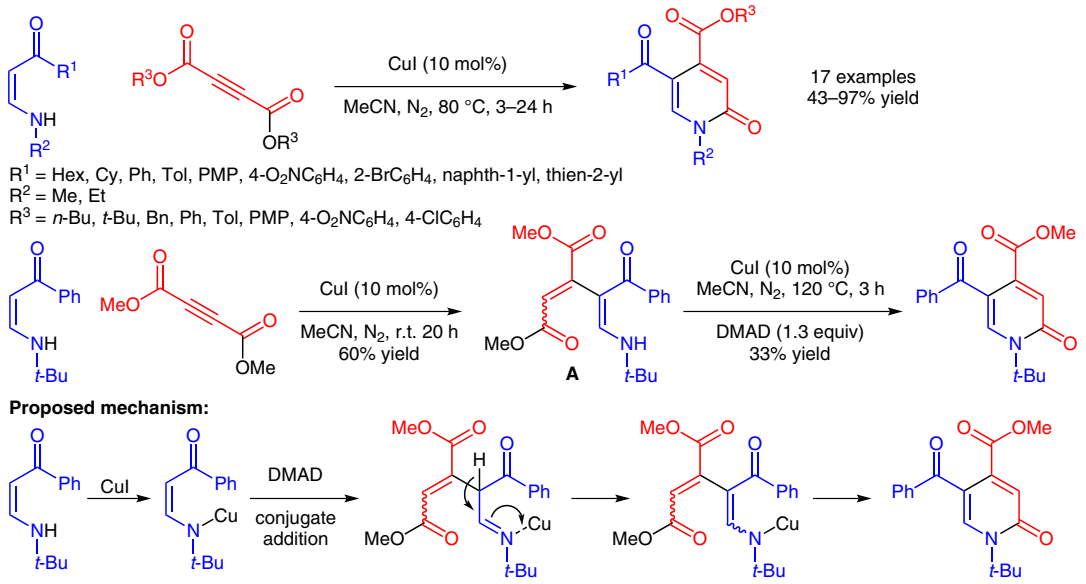
alkynes

copper catalysis

Y. SHAO, W. YAO, J. LIU, K. ZHU, Y. LI* (EAST CHINA NORMAL UNIVERSITY, SHANGHAI, P. R. CHINA)

Copper-Catalyzed Selective Synthesis of Highly Substituted Pyridones by the Reaction of Enaminones with Alkynes
*Synthesis* **2012**, *44*, 3301–3306.

# De Novo Synthesis of Pyridones From Enaminones and Alkynes




**Significance:** Reported is the copper-catalyzed synthesis of substituted pyridones from the reaction of dialkyl acetylenedicarboxylates with enaminones. Although simple dialkyl acetylenedicarboxylates (e.g. dimethyl acetylenedicarboxylate, DMAD) are commercially available, the enaminones must be synthesized. A method for their synthesis was not explicitly disclosed, but a quick search of the literature provides several different methods (e.g. a one-pot Sonogashira coupling of an acid chloride with ethynyltrimethylsilane followed by the addition of an amine and methanol; A. S. Karpov, T. J. J. Müller *Org. Lett.* **2003**, *5*, 3451). A mechanism for the reaction was proposed and studied through the isolation of intermediate **A**. This was re-subjected to the reaction conditions but did not generate product until more DMAD was added and the temperature was raised. This suggests that DMAD may be involved with the copper in generating a catalytically active species for the subsequent cyclization.

**Comment:** Pyridones are important building blocks for the synthesis of substituted pyridines and other heterocycles and also represent pharmacologically relevant structures in their own right (e.g. M. A. Ciufolini, B. K. Chan *Heterocycles* **2007**, *74*, 101). Thus, the current method should be a useful addition to the plethora of established synthetic routes as it operates under mild conditions and uses inexpensive and easily synthesized starting materials. The reaction was optimized with respect to catalyst, catalyst stoichiometry and solvent. In addition, it was found that the reaction must be conducted under inert atmosphere to avoid the formation of pyrrole byproducts. The substrate scope was modestly examined and showed that the yields are generally good for enaminones with electron-donating groups and good to moderate for enaminones with electron-withdrawing groups. The reaction was relatively insensitive to the electronics of the enaminone carbonyl unit.

**SYNFACTS Contributors:** Victor Snieckus, Johnathan Board
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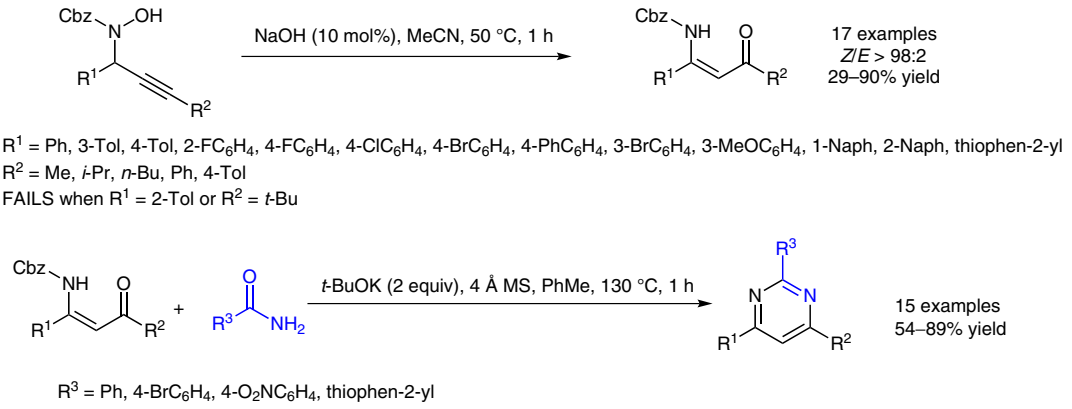
**DOI:** 10.1055/s-0032-1317870; **Reg-No.:** V15412SF

E. GAYON, M. SZYMCZYK, H. GÉRARD,* E. VRANCKEN,* J.-M. CAMPAGNE* (INSTITUT CHARLES GERHARDT, MONTPELLIER AND UPMC–UNIVERSITÉ PARIS 06, FRANCE)
Stereoselective and Catalytic Access to β-Enaminones: An Entry to Pyrimidines
*J. Org. Chem.* **2012**, *77*, 9205–9220.

# Synthesis of Pyrimidines from Propargylic Hydroxylamines




**Significance:** Reported is a highly stereoselective access to β-enaminones based on base-catalyzed isomerization of propargylic hydroxylamines, obtained by $FeCl_3$-catalyzed substitution of propargylic alcohols with Cbz-protected hydroxylamines. NaOH (10 mol%) was the optimal base to achieve the isomerization, although other inorganic bases were successful as well. An organic base ($Et_3N$) did not afford any product and a larger amount of NaOH was detrimental to the reaction. DFT calculations and additional experiments were undertaken to understand the mechanism, which apparently is initiated by the β-elimination of the hydroxyl group. The synthesized enaminones are utilized in a reaction with aryl amides to afford pyrimidines in moderate to good yield. Use of aryl nitriles instead of aryl amides resulted in low yields of the pyrimidine products.

**Comment:** β-Enaminones are versatile compounds exhibiting pharmacological properties and constituting building blocks for the synthesis of natural products and heterocycles (J. J. Neumann, M. Suri, F. Glorius *Angew. Chem. Int. Ed.* **2010**, *49*, 7790), such as pyrimidines. The current report demonstrates the synthesis of enaminones in a stereospecific fashion from inexpensive starting materials under simple and mild reaction conditions in high yield. The utility of enaminones in the synthesis of pyrimidines is well appreciated and in the present report one synthesis of a pyrimidine is also performed on a gram scale.

**SYNFACTS Contributors:** Victor Snieckus, Toni Rantanen
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**DOI:** 10.1055/s-0032-1317863; **Reg-No.:** V14912SF

**Category**

**Synthesis of Heterocycles**

**Key words**

**indoles**

**azaindoles**

**Heck coupling**

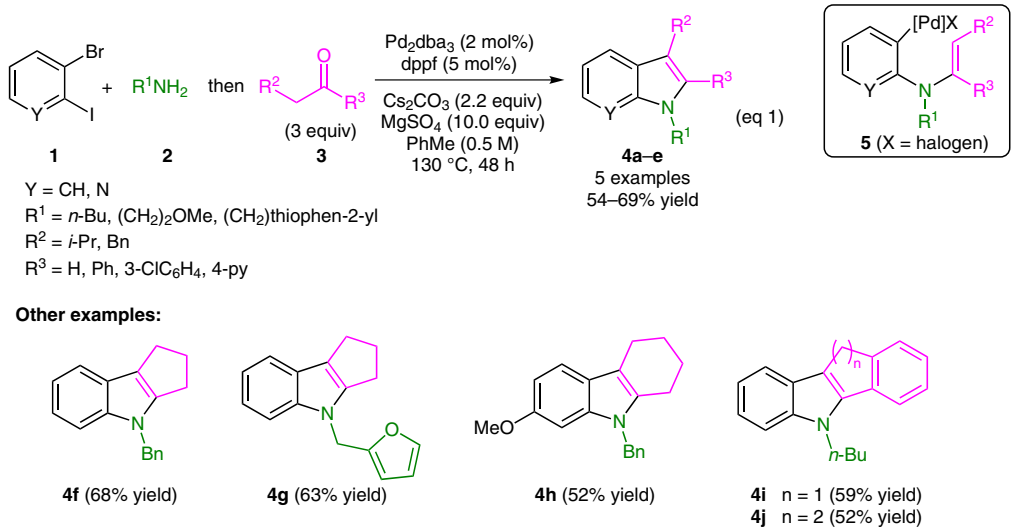
**Buchwald–Hartwig cross-coupling**

**palladium catalysis**

J. M. KNAPP, J. S. ZHU, D. J. TANTILLO, M. J. KURTH* (UNIVERSITY OF CALIFORNIA DAVIS, USA)

Multicomponent Assembly of Highly Substituted Indoles by Dual Palladium-Catalyzed Coupling Reactions
*Angew. Chem. Int. Ed.* **2012**, *51*, 10588–10591.

# Palladium-Catalyzed C–N/C–C Coupling Route to Substituted Indoles




**Significance:** Reported is the one-pot synthesis of highly substituted indoles **4** via a sequential palladium-catalyzed C–N and C–C coupling reaction of *o*-bromoiodo arenes **1**, carbonyl derivatives **3**, and amines **2**. The reaction is proposed to proceed by C–N coupling to generate aryleneamine intermediate **5** which undergoes an intramolecular arene–alkene coupling reaction (eq 1). This sequence of events is supported by an adequate number of experiments. The authors also suggest that the mechanism of the final step differs from a traditional Heck reaction. Among several ligands, bases and solvents tested, 1,1′-bis(diphenylphosphanyl)ferrocene (dppf) in combination with a weak base ($Cs_2CO_3$) in toluene was suited best. The addition of $MgSO_4$ proved beneficial, presumably by favoring eneamine formation. The reaction failed when $Pd(OAc)_2$ was used in place of $Pd_2dba_3$. Both aldehydes and cyclic/acyclic ketones gave moderate yields of indoles. Two examples of azaindoles (Y = N) were also reported. A pyridine derivative ($R^3$ = 4-py) was also tolerated.

**Comment:** The synthesis and functionalization of indoles has been a major area of focus for organic chemists due to its importance in the pharmaceutical field (see Book below). Numerous synthetic methods for indoles including Fischer indole synthesis and its modifications have been reported (see Review below). The current one-pot three-step method provides highly functionalized indoles in moderate yield using readily available starting materials. Although it was indicated that the reaction failed with a carbomethoxy derivative of **3**, the reaction scope and limitations were not well investigated.

**Book:** *Heterocyclic Scaffolds II: Reactions and Applications of Indoles*, Vol. 26.; G. W. Gribble, Volume Ed.; In *Topics in Heterocyclic Chemistry*; B. U. W. Maes, Series Ed.; Springer: New York, **2010**.

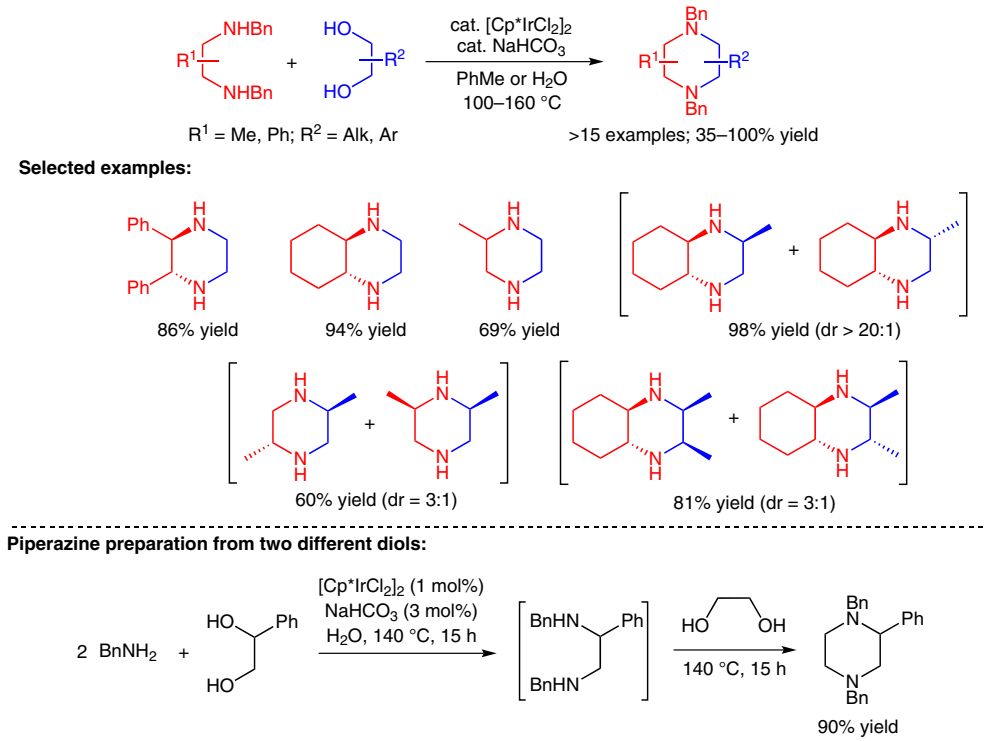
**Review:** G. R. Humphrey, J. T. Kuethe *Chem. Rev.* **2006**, *106*, 2875–2911.

**SYNFACTS Contributors:** Victor Snieckus, Suneel P. Singh
Synfacts 2013, 9(1), 0026 Published online: 17.12.2012
**DOI:** 10.1055/s-0032-1317869; **Reg-No.:** V15312SF

L. L. R. LORENTZ-PETERSEN, L. U. NØRDSTROM, R. MADSEN* (TECHNICAL UNIVERSITY OF DENMARK, LYNGBY, DENMARK)

Iridium-Catalyzed Condensation of Amines and Vicinal Diols to Substituted Piperazines
*Eur. J. Org. Chem.* **2012**, 6752–6759.

# Iridium-Catalyzed Synthesis of Substituted Piperazines




**Significance:** Reported is the preparation of substituted piperazines by an iridium-catalyzed alkylation of amines with vicinal diols. Using a catalyst system composed of $[Cp^*IrCl_2]_2$, either $NaHCO_3$ or TFA as additives, and toluene or water as the solvent, a variety of piperazines with different substitution patterns are prepared by condensation of readily available primary alkylamines or 1,2-diamines with 1,2-diols. In order to achieve efficient cyclization, at least one substituent on either the diamine or diol is required. In most cases, mixtures of regioisomeric products are reported for those substrates possessing unsymmetrical substitution and, when a stereocenter is generated, the formation of the most stable isomer with equatorial substituent orientation is observed.

**Comment:** The development of efficient and modular methods for the preparation of substituted piperazine scaffolds has a significant impact in medicinal chemistry, as this motif is a commonly employed pharmacophore. This article describes a route for the preparation of these important frameworks, which proceeds through readily available 1,2-diamine and 1,2-diol starting materials. In general, piperazines were obtained in high yield (>70%); however, the poor regioselectivity reported for unsymmetrical diol–diamine combinations suggests that more complicated piperazines will be difficult to access selectively by the current system. In addition, no comment was offered as to whether commonly encountered functional groups or other heterocycles were compatible with this catalyst system.

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**Category**

**Synthesis of Heterocycles**

**Key words**

**amination**
**cyclization**
**iridium catalysis**
**piperazines**

**Category**

**Synthesis of Heterocycles**

**Key words**

**pyrazoles**

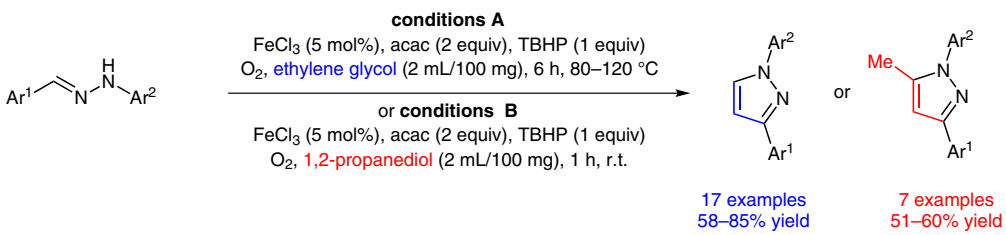
**iron catalysis**

**hydrazones**

N. PANDA,* A. K. JENA (NATIONAL INSTITUTE OF TECHNOLOGY, ROURKELA, INDIA)

Fe-Catalyzed One-Pot Synthesis of 1,3-Di- and 1,3,5-Trisubstituted Pyrazoles from Hydrazones and Vicinal Diols
*J. Org. Chem.* **2012**, *77*, 9401–9406.

# Iron-Catalyzed Synthesis of Pyrazoles from Hydrazones




$Ar^1$ = Ph, 2-$ClC_6H_4$, 4-$ClC_6H_4$, 3-$O_2NC_6H_4$, 4-$O_2NC_6H_4$, PMP, 2-$HOC_6H_4$, 4-$HOC_6H_4$, 2-hydroxy-1-naphthyl, thiophen-2-yl, *N*-Ph-3-Me-5-Cl-pyrazol-4-yl
$Ar^2$ = Ph, Tol, 4-$ClC_6H_4$, 4-$O_2NC_6H_4$

**Significance:** The synthesis of pyrazoles from a condensation of α-hydroxycarbonyl compounds with aryl hydrazones is reported. The requisite intermediate α-hydroxy carbonyl compounds are formed by an iron-based in situ oxidation of vicinal diols by *tert*-butyl hydroperoxide (TBHP). Whilst studying optimization, it was found that by adding a ligand, the desired pyrazoles are obtained directly. Acetylacetone (acac) is the optimal ligand with anhydrous $FeCl_3$ being the optimal iron source. The reaction is lower yielding under nitrogen or air, as opposed to an oxygen balloon. The substrate scope was reasonably well studied, although incorporation of vicinal diols beyond the presented two would have been welcome. A limitation seems to be the electron-withdrawing substituents on nitrogen, as the reaction with $Ar^2$ = 4-$O_2NC_6H_4$ fails.

**Comment:** The presence of a pyrazole motif in several drugs and pesticides has undoubtedly stimulated the development of new and complementary methods for their synthesis. In particular, transition-metal catalysis has been successfully used for the synthesis of polysubstituted pyrazoles. The reported method draws upon the pioneering work of Bolm, Beller and Repo in the field of iron-catalyzed oxidation (e.g., C. Bolm, M. Nakanishi *Adv. Synth. Catal.* **2007**, *349*, 861). The protocol utilizes inexpensive materials, and the conditions are mild especially for the synthesis of 1,3,5-trisubstituted pyrazoles (room temperature) which should have warranted further studies on substituted diols. The drawback is the necessity for super-stoichiometric amounts (2 equiv) of a ligand, which is quite wasteful.

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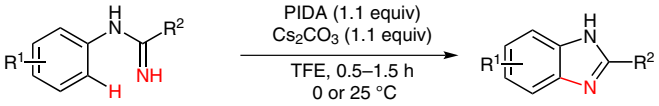
Synthesis of Benzimidazoles by PIDA-Promoted Direct C($sp^2$)–H Imidation of *N*-Arylamidines
*Chem. Eur. J.* **2012**, *18*, 13964–13967.

# Phenyliodine(III) Diacetate-Promoted Synthesis of Benzimidazoles




$R^1$ = H, 2-Br, 2-F, 4-I, 4-Br, 4-Cl, 4-F, 2-Me, 2-*t*-Bu, 3-Me, 3,5-$Me_2$, 4-Me, 4-OMe, 4-$NO_2$
$R^2$ = H, 2-Cl, 3-Me, 4-Br, 4-Cl, Me, 3,4-$Me_2$, *c*-Pr, Cy, Bn, *t*-Bu, *i*-Bu

**Significance:** Reported is the synthesis of 2-substituted benzimidazoles by the reaction of *N*-arylamidines with phenyliodine(III) diacetate under mild conditions via an intramolecular oxidative imidation process. The C–H activation reaction is proposed to proceed by the formation of free radical intermediates which was partially supported by a free radical inhibition experiment.

**Comment:** Compounds containing the benzimidazole moiety are reported to possess a number of interesting biological activities (K. Vijaykumar, A. J. Ahemed *J. Chem. Pharm. Res.* **2010**, 2, 215). Several syntheses of similar 2-substituted benzimidazoles have been reported involving an intramolecular Cu-catalyzed N-arylation (C. Chen et al. *J. Org. Chem.* **2011**, *76*, 716). In comparison, the present synthesis occurs under metal-free, mild conditions. However, the reaction suffers from poor regioselectivity for *meta*-substituted substrates, leading to mixture of isomers.

**SYNFACTS Contributors:** Victor Snieckus, Ashish Maheta
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**Category**
**Synthesis of Heterocycles**

**Key words**
**arylbenzamidines**
**phenyliodine(III) diacetate**
**benzimidazoles**
**C–H imidation**

**Category**

**Synthesis of Heterocycles**

**Key words**

**benzo[b][1,4]-oxazepines**

**domino reaction**

**palladium**

**bromoalkynes**

**isocyanides**

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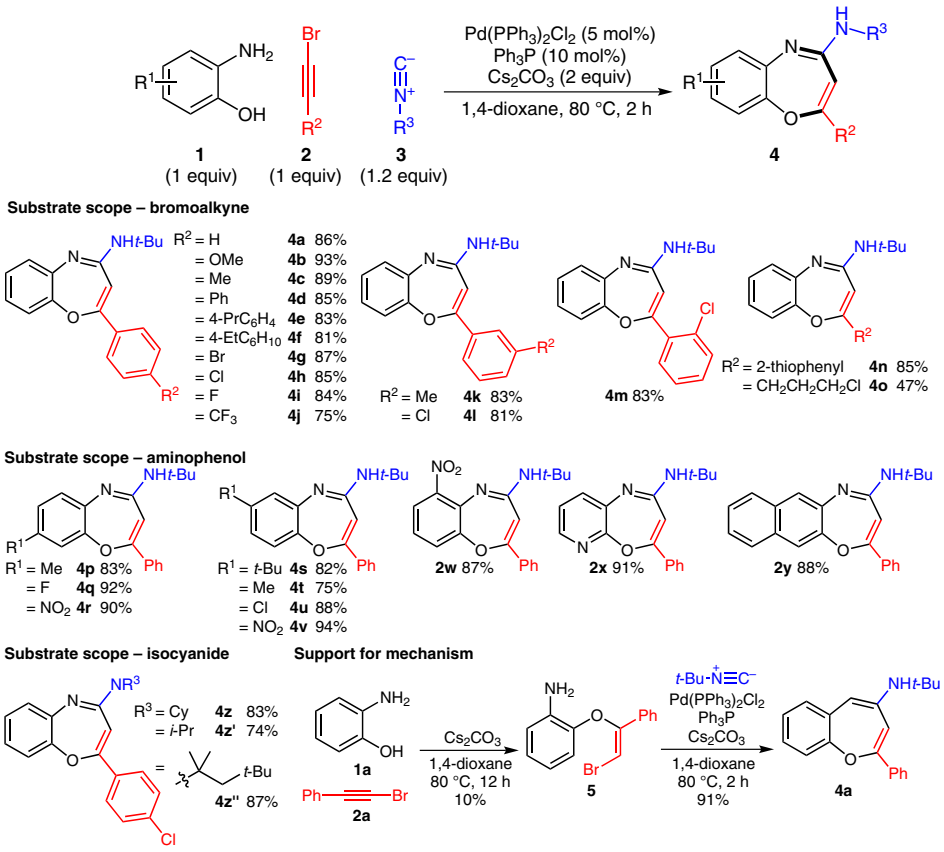
Palladium-Catalyzed Tandem Reaction of *o*-Aminophenols, Bromoalkynes and Isocyanides to Give 4-Amine-benzo[*b*][1,4]oxazepines

*Chem. Commun.* **2012**, *48*, 11446–11448.

# Palladium-Catalyzed Synthesis of Benzo[b][1,4]oxazepines




**Significance:** Reported is the palladium-catalyzed synthesis of benzo[b][1,4]oxazepines **4** via the annulation of *o*-aminophenols **1** with bromoalkynes **2** and isocyanides **3**. Substrate-scope investigation revealed broad tolerance to variation of all components **1**–**3**, particularly across sterically and electronically differentiated aryl bromoalkynes **2**, with a reduction in yield noted for alkyl bromoalkynes (**4o**). Experiments demonstrating the competency of **5** under the standard reaction conditions are offered in support of the proposed mechanism.

**Comment:** Building on their previous investigations into combining the nucleophilic addition of isocyanides **3** to bromoalkynes **2** with palladium catalysis (*Chem. Commun.* **2012**, 48, 3545), the current report extends this methodology allowing the synthesis of benzoazepines traditionally synthesized by multiple-step procedures. Taking advantage of the established addition of phenols to bromoalkynes (For furan synthesis, see: S. Wang et al. *Org. Lett.* **2011**, 13, 5968) the current report, intercepting intermediate **5**, appears to have exceptional scope.

**SYNFACTS Contributors:** Victor Snieckus, Matthew O. Kitching
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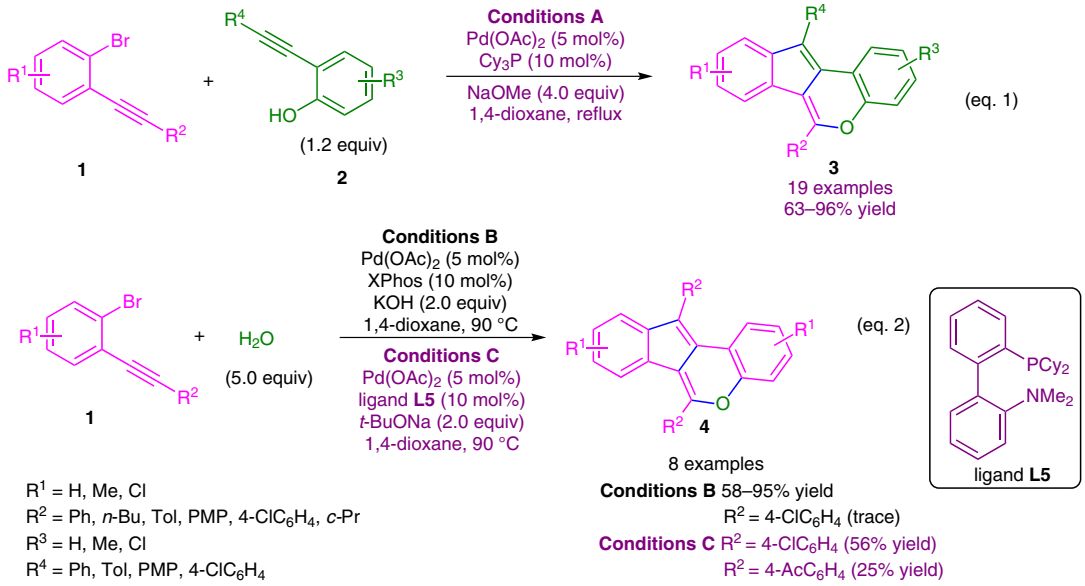
**DOI:** 10.1055/s-0032-1317878; **Reg-No.:** V16212SF

X. PAN, H. NIE, Y. LUO, Y. GAO,* J. WU* (FUDAN UNIVERSITY, SHANGHAI, SHANGHAI UNIVERSITY OF T.C.M. AND SHANGHAI INSTITUTE OF ORGANIC CHEMISTRY, P. R. OF CHINA)

Facile Assembly of Indeno[1,2-*c*]chromenes via a Palladium-Catalyzed Reaction of 2-Alkynylhalobenzene
*Org. Biomol. Chem.* **2012**, *10*, 8244–8250.

# Pd-Catalyzed Synthesis of Indeno[1,2-*c*]-chromenes from 2-Alkynylhalobenzenes




**Significance:** Reported is the synthesis of indeno[1,2-*c*]chromenes **3** and **4** via a palladium-catalyzed reaction of 2-alkynylbromobenzenes **1** with either 2-(2-arylethynyl)phenols **2** or with water. A range of ligands was used during the optimization study to reveal that the reaction proceeds only with $Cy_3P$ as ligand (eq. 1). Sodium methoxide in toluene or 1,4-dioxane was better than other combinations. The substrate scope of this transformation was modestly demonstrated. The reaction also proceeded to give **3** in 78% yield by treatment of 1-chloro-2-(2-phenylethynyl)benzene with **2** ($R^3$ = H, $R^4$ = Ph). Surprisingly, re-optimization was required in the reaction of **1** with water (eq. 2). Both alkyl- and aryl-substituted alkynes were tolerated under the optimized conditions. However, the reaction parameters had to be re-screened to give a satisfactory yield of compounds with electron-withdrawing groups ($R^2$ = 4-$ClC_6H_4$, 4-$AcC_6H_4$).

**Comment:** The [6.5.6.6]-tetracyclic core of indenochromenes **3** and **4** is present in several bioactive compounds (B. S. Min et al. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 7436). Very few synthetic methods such as iron-mediated [3+2]-annulation reactions are available to provide access to this tetracyclic system (Z.-Q. Wang et al. *Org. Lett*. **2011**, *13*, 14). The present method provides a rapid construction of various substituted indenochromenes from easily accessible starting materials. One drawback of this method is the lower yield for electron-poor substrates. Although, this work provides a facile synthesis of indeno[1,2-*c*]-chromenes, it is strikingly similar to the authors' previous work (Y. Luo, L. Hong, J. Wu *Chem. Commun*. **2011**, *47*, 5298) .

**SYNFACTS Contributors:** Victor Snieckus, Suneel P. Singh
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**Category**
Synthesis of Heterocycles

**Key words**
indeno[1,2-*c*]-chromenes
2-alkynyl-bromobenzenes
2-(2-phenylethynyl)-phenols
palladium catalysis

**Category**

**Synthesis of Heterocycles**

**Key words**

**oxazolines**

**oxazines**

**carbon monoxide**

**multicomponent reaction**

**palladium catalysis**

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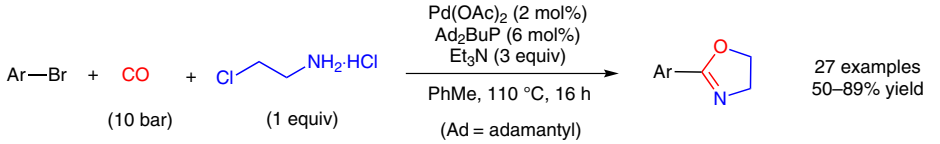
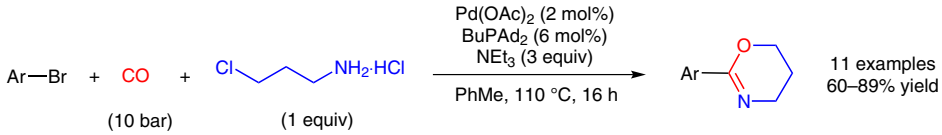
A General and Efficient Palladium-Catalyzed Carbonylative Synthesis of 2-Aryloxazolines and 2-Aryloxazines from Aryl Bromides

*Chem. Eur. J.* **2012**, *18*, 13619–13623.

# Palladium-Catalyzed Three-Component Synthesis of Oxazolines and Oxazines




Ar = Ph, Tol, 2-*i*-PrC$_6$H$_4$, 4-PhC$_6$H$_4$, 4-F$_3$CC$_6$H$_4$, 4-NCC$_6$H$_4$, 4-OHCC$_6$H$_4$, 4-Me(O)CC$_6$H$_4$, 4-*t*-BuO$_2$CC$_6$H$_4$, 4-*i*-Pr$_2$N(O)CC$_6$H$_4$, 4-FC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-Me$_2$NC$_6$H$_4$, PMP, 3,4-(MeO)$_2$C$_6$H$_3$, 4-MeSC$_6$H$_4$, 1-Naph, 2-Naph, 6-MeONaph-2-yl, 2-thiophenyl, 3-thiophenyl, 3-benzo[*b*]thiophenyl, 3-py, 1-methyl-1*H*-indole-5-yl, 3-quinolinyl, 6-quinolinyl, 7-quinoxalinyl




Ar = Ph, 4-NCC$_6$H$_4$, 4-Me(O)CC$_6$H$_4$, 4-Me$_2$NC$_6$H$_4$, PMP, 4-MeSC$_6$H$_4$, 1-Naph, 3-thiophenyl, 3-benzo[*b*]thiophenyl, 3-Py, 1-methyl-1*H*-indole-5-yl

**Significance:** Described is the synthesis of oxazolines via a three-component process, in which readily available aryl bromides, carbon monoxide and 2-chloroethylamine undergo a palladium-catalyzed carbonylation and a subsequent cyclization to afford 2-aryloxazolines in good yield. Replacing 2-chloroethylamine with 3-chloropropylamine also works well and in this case the corresponding 2-aryloxazine derivatives are formed. Notably, both electron-donating and electron-withdrawing groups are tolerated in this process. However, the scope of the three-component process was not well investigated, especially for *ortho*- and *meta*-substituted aryl bromides.

**Comment:** Oxazolines and oxazoles are important heterocycles for organic synthesis and materials chemistry (see Book below). A number of methodologies for the construction of the oxazoline ring from aryl aldehydes, nitriles, carboxylic acids and related derivatives have been developed (e.g., S. Takahashi, H. Togo *Synthesis* **2009**, 2329). In comparison with those, the present carbonylation–cyclization strategy offers a straightforward way for the synthesis of oxazolines and their analogues from easily available starting materials. A drawback of this method is the high pressure required (10 bar).

**Book:** *Oxazoles: synthesis, reactions, and spectroscopy, Part 2*; D. C. Palmer, Ed.; Wiley: Hoboken, **2004**.

**SYNFACTS Contributors:** Victor Snieckus, Yigang Zhao
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**DOI:** 10.1055/s-0032-1317865; **Reg-No.:** V15112SF

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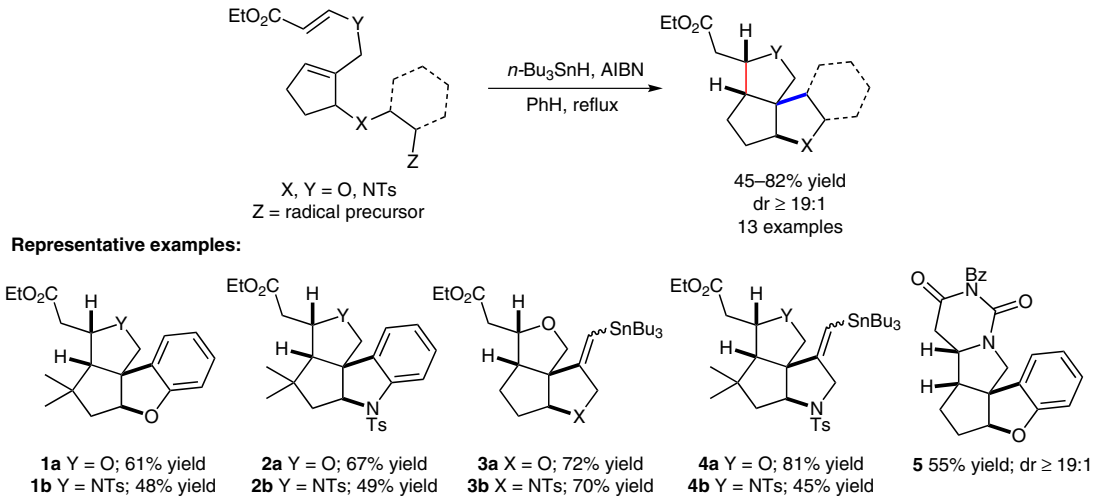
Stereoselective Synthesis of Oxa- and Aza-Angular Triquinanes Using Tandem Radical Cyclization to Vinylogous Carbonates and Carbamates
*Org. Lett.* **2012**, *14*, 5476–5479.

# Synthesis of Heterocyclic Triquinanes via Sequential Radical Cyclizations




**Significance:** Tandem radical cyclizations are a powerful synthetic strategy to form polycyclic motifs from acyclic precursors (D. P. Curran *Synlett* **1991**, 63). Numerous synthetic strategies have been applied to the synthesis of all-carbon triquinane frameworks as they are related to various terpene natural product skeletons (G. Mehta, A. Srikrishna *Chem. Rev.* **1997**, *3*, 671; V. Singh, B. Thomas *Tetrahedron* **1998**, *54*, 3647). Highlighted in this report is the synthesis of angular *O*- and *N*-triquinanes. The proposed mechanism describes radical initiation using standard conditions from either an aryl iodide or terminal alkyne, followed by successive *5-exo*-trig cyclizations. The high level of diastereoselectivity observed in the cyclization is attributed to developing steric interactions observed in the transition state of the second cyclization event. The method affords complex products with a predictable outcome and a high level of stereochemical fidelity in an efficient manner.

**Comment:** The cyclization precursors are generated using a three-to-four step sequence using standard synthetic transformations in moderate to high yield. The method described is not limited to aryl substitution (**1**, **2**) as exposure of terminal alkyne precursors to the reaction conditions affords vinyl stannane products (**3**, **4**). Proto-destannylation of the aforementioned intermediates using either $SiO_2$ or TsOH provides the terminal olefin products. The vinyl stannanes are valuable precursors for further functionalization using transition-metal-mediated processes, which was not described. The major drawback to the methodology, due to inherent toxicity issues, is the use of stoichiometric quantities of tin.

**SYNFACTS Contributors:** Victor Snieckus, Nathan E. Genung (Pfizer)
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**Category**

**Synthesis of Heterocycles**

**Key words**

**tandem radical cyclization**

**triquinanes**

**aza-triquinanes**

**carbonates**

**carbamates**