Isatoic Anhydrides via C–H Activation

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.

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 bisimidazoline 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.
Synthesis of 3-Fluoropyrazoles from 2-Trifluoromethyl-1-alkenes

K. Fuchibe, M. Takahashi, J. Ichikawa* (University of Tsukuba, Japan)

Substitution of Two Fluorine Atoms in a Trifluoromethyl Group: Regioselective Synthesis of 3-Fluoropyrazoles


Significance: Reported is a three-step protocol for the de novo synthesis of substituted 3-fluoro-
pyrazoles through annulation of 2-trifluoromethyl-1-alkenes with monosubstituted hydrazines. The
first step in this unconventional approach is an SN2′ 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, methyl-hydrazine affords a 55:45 mixture of N-regioisomers (66% combined yield, not shown above). Treatment of 2 with NaH in DMF affords the sub-
stituted 3-fluoropyrazole 3; control experiments established the need to employ toslyhydrazides in
this reaction. 4-Unsubstituted 3-fluoropyrazoles 5 were accessible from the corresponding 2-silyl al-
lylic hydrazide 4.

Comment: Pyrazoles are among the most meta-
bolically stable unsaturated five-membered het-
erocycles (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 syn-
thetically challenging substituted 3-fluoropyr-
azoles 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 sub-
stitution at C4 was also not explored. Control
experiments suggest that base-mediated ring
closure (2 → 3) proceeds through neither direct
ucleophilic vinylic substitution (SN1V) nor an inter-
mediate nitrene. Instead, an unusual pathway is sug-
gested that features an azomethine imine
intermediate.

Representative examples:

<table>
<thead>
<tr>
<th>R¹</th>
<th>R²</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>4-MeOC₆H₄</td>
<td>88%</td>
</tr>
<tr>
<td>4-BrC₆H₄</td>
<td>85%</td>
<td></td>
</tr>
<tr>
<td>Ph</td>
<td>4-MeOC₆H₄</td>
<td>89%</td>
</tr>
<tr>
<td>2-MeOC₆H₄</td>
<td>86%</td>
<td></td>
</tr>
<tr>
<td>4-F₃CC₆H₄</td>
<td>86%</td>
<td></td>
</tr>
</tbody>
</table>

Representative examples for R² = Boc:

<table>
<thead>
<tr>
<th>R¹</th>
<th>R²</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>Boc</td>
<td>70%</td>
</tr>
<tr>
<td>4-MeOC₆H₄</td>
<td>95%</td>
<td></td>
</tr>
<tr>
<td>4-F₃CC₆H₄</td>
<td>89%</td>
<td></td>
</tr>
</tbody>
</table>

For R² = Boc: 70% yield
For R² = Ph: 95% yield
30–89% yield 55–97% yield

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

**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.
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

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, (2R)-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 co-workers (Bioorg. Med. Chem. Lett., 1999, 9, 2059). This method also circumvents the use of chiral column chromatography, accelerating the drug discovery process even further.
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.
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 FeCl₃-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 (Et₃N) 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.
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 (Cs₂CO₃) in toluene was suited best. The addition of MgSO₄ proved beneficial, presumably by favoring eneamine formation. The reaction failed when Pd(OAc)₂ was used in place of Pd₂dba₃. Both aldehydes and cyclic/acyclic ketones gave moderate yields of indoles. Two examples of azaindoles (Y = N) were also reported. A pyridine derivative (R₃ = 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.


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*IrCl2]2, either NaHCO₃ 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.

**Selected examples:**

```
R¹ = Me, Ph; R² = Alk, Ar
>15 examples; 35–100% yield
```

- 86% yield
- 94% yield
- 69% yield
- 98% yield (dr > 20:1)
- 60% yield (dr = 3:1)
- 81% yield (dr = 3:1)

**Piperazine preparation from two different diols:**

```
2 BnNH₂ + HO-Ph
HHO

[BnNH₂ Ph] + [BnNH₂]

BnNH₂ Ph

90% yield
```

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DOI: 10.1055/s-0032-1317873; Reg-No.: V15712SF
Iron-Catalyzed Synthesis of Pyrazoles from Hydrazones

**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 FeCl₃ 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 \( \text{Ar}^2 = 4\text{-O}_2\text{NC}_6\text{H}_4 \) 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.
Phenyliodine(III) Diacetate-Promoted Synthesis of Benzimidazoles

**Significance:** Reported is the synthesis of 2-substituted benzimidazoles by the reaction of N-aryl amidines 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. Ahmed 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.
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 annihilation 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.

**Category**
- Synthesis of Heterocycles

**Key words**
- benzo[b][1,4]-oxazepines
- domino reaction
- palladium
- bromoalkynes
- isocyanides

**SYNFACS Contributors:** Victor Snieckus, Matthew O. Kitching

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**DOI:** 10.1055/s-0032-1317878; **Reg-No.:** V16212SF


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 Cy3P 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^2 = H, R^4 = Ph). Surprisingly, re-optimization was required in the reaction of 1 with water (eq. 2). Both alkyl- and aryl-substituted alkyynes 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).

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Category
Synthesis of Heterocycles

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

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


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Palladium-Catalyzed Three-Component Synthesis of Oxazolines and Oxazines

**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).

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, 97, 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 SiO₂ 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.