Pd-Catalyzed Synthesis of N-Aryl Indoles

Significance: Reported is a palladium-catalyzed synthesis of N-aryl indoles from the reaction of diaryl amines with olefins by a hydroamination–C–H activation route. In recent years, the traditional methods, for example, the venerable century-old Fischer indole synthesis, among other textbook reactions, have been superceded by a barrage of methodologies based on transition-metal-catalyzed heteroannulation processes originating with Larock, with significant contributions by Buchwald, Ackermann, Glorius, Fagnou, among others (see: Angew. Chem. Int. Ed. 2013, 52, 3434; J. Am. Chem. Soc. 2012, 134, 9098; Angew. Chem. Int. Ed. 2013, 52, 12426). The present methodology takes advantage of the Fujiwara–Moritani reaction (hydroamination of olefins) together with a precededent aryl C–H activation to achieve the N-aryl indole synthesis. Although a comparison to another ruthenium-based photocatalytic method is given, the significance of the present route in assessment to plethora of recently similar established methods is unfortunately not made and would require reading of about 30 references cited in this report.

Comment: The scope of the reaction is defined mainly with styrenes with a few cases of other aliphatic olefins included. The yields of products are modest to good with noticeably lower yields with sterically demanding styryl systems. N-Aryl variation to heterocyclic substituted aryls and pyridyl may be obtained albeit also with lower yields. For unsymmetrical diaryl amines, the regioselectivity of C–H activation–annulations occurs towards the EWG aryl ring. Based on the achieved regioselectivity pattern, a mechanism of initial orthopalladation (for EWG aryls) and initial N-palladation (for EDG aryls) is proposed. The reaction of prototype diphenylamine in the absence of styrene reactant partner in D2O afforded diphenylamine deuterated in all ortho- and para-positions (75–80% d-incorporation), which suggests reversible electrophilic palladation and raises the question of validity to name this a C–H activation process. However, the absence of para-deuterated product in the presence of the styrene co-reactant is good evidence for Pd being trapped by initial N-coordination. Further, putative 2-aminoestilbene and indolenine intermediates were shown to be converted into indole products under the given conditions. This is a useful beginning of a mechanistic study whose elaboration is promised.
H. XIANG, C. YANG* (SHANGHAI INSTITUTE OF MATERIA MEDICA, P. R. OF CHINA)
A Facile and General Approach to 3-[(Trifluoromethyl)thio]-4H-chromen-4-one

**Direct Cyclization–Trifluoromethylthiolation to 4H-Chromen-4-ones**

![Reaction Scheme]

**Significance:** Reported is a general synthesis of 3-[(trifluoromethyl)thio]-4H-chromen-4-ones 2 from 1-[(2'-hydroxyphenyl)-3-dimethylaminoprop-2-enones 1 and the active electrophilic trifluoromethylthio moiety generated from AgSCF₃ and trichloroisocyanuric acid (TCCA). This synthetic approach leads to the direct introduction of the SCF₃ group into chromen-4-ones, which represents a very desirable technique to produce diverse molecules for the medicinal chemist. The screening of reaction conditions showed that the reaction is highly dependent on the solvent; for example, yields in THF were better than in DMF; however, no product was obtained for reactions that were carried out in MeCN, CH₂Cl₂, DMSO, MTBE or toluene. The reaction also showed dependency on the optimized amount of TCCA (1.5 equiv), and remarkable insensitivity to air and moisture. The synthetic utility of this reaction to synthesize other SCF₃-containing heterocycles such as a topopyrone C analogue was also investigated.

**Comment:** The trifluoromethylthio group is incorporated in many bioactive molecules such as the hypotensive agents losartan and nifedipine (L. M. Yagupolskii et al. J. Fluorine Chem. 2001, 109, 87). Classic approaches of introducing this group include an indirect, multistep method (A. E. Feiring J. Org. Chem. 1979, 44, 2907). Herein, an easy and direct synthetic route was used to accomplish the same result. A mechanism was presented without evidence. It includes the possibility of an intramolecular Michael addition–cyclization of 1, followed by enolate nucleophilic attack on the SCF₃ species, then a N,N-dimethylamine elimination process to produce 2.
Rhodium(I)-Catalyzed [4+2]-Cycloaddition Route to 1,2-Dihydropyridines

**Significance:** Piperidine heterocycles are abundant in numerous pharmaceuticals such as oxytocin, plavix, ritalin, and tofacitinib. The piperidine ring can contain multiple stereocenters, quaternary carbons, or be highly substituted. One method to prepare chiral substituted piperidines is the asymmetric hydrogenation of pyridine or tetrahydropyridine precursors; therefore, a robust, scalable route to a diverse range of substituted pyridines or tetrahydropyridines would be of synthetic value to the pharmaceutical industry. The known Diels–Alder approach to substituted pyridines is compromised by significant electronic and steric constraints (J. A. Varela, C. Saá *Chem. Rev.* 2003, 103, 3787; D. L. Boger *Chem. Rev.* 1986, 86, 781; A. Saito et al. *Tetrahedron Lett.* 2007, 48, 6852).

**Comment:** In the presented methodology, a broad scope of 1,2-dihydropyridines was prepared through a rhodium(I)-catalyzed C–H activation–alkenylation–electrocyclization sequence of reactions. Treatment with an electrophile under kinetic or thermodynamic control conditions afforded the corresponding iminiums, which then were treated with nucleophiles to afford the desired tetrahydropyridines with high diastereoselectivity. The 1,2-dihydropyridine intermediates were also shown to react in [3+2] or [4+2] cycloaddition modes to afford bridged bicyclic isoquinuclidines and tropane cores. The catalyst loading was low (<1%), conditions were robust (air-stable), and the tetrahydropyridines were prepared on scale (>100 mmol) in good yield.

**Representative examples:**

<table>
<thead>
<tr>
<th>R1</th>
<th>R2</th>
<th>R3</th>
<th>R4</th>
<th>R5</th>
<th>R6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Et</td>
<td>Et</td>
<td>Et</td>
<td>Me</td>
<td>Ph</td>
<td>Ph</td>
</tr>
<tr>
<td>71% yield</td>
<td>92% yield</td>
<td>88% yield</td>
<td>73% yield</td>
<td>68% yield</td>
<td></td>
</tr>
<tr>
<td>dr &gt; 95%</td>
<td>dr &gt; 95%</td>
<td>dr &gt; 95%</td>
<td>dr &gt; 95%</td>
<td>dr &gt; 95%</td>
<td></td>
</tr>
<tr>
<td>NMe</td>
<td>NPh</td>
<td>NMe</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>67% yield</td>
<td>93% yield</td>
<td>74% yield</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dr &gt; 94%</td>
<td>dr &gt; 95%</td>
<td>dr &gt; 95%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NMe</td>
<td>NPh</td>
<td>NMe</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>89% yield</td>
<td>88% yield</td>
<td>92% yield</td>
<td>74% yield</td>
<td></td>
<td></td>
</tr>
<tr>
<td>dr &gt; 94%</td>
<td>dr &gt; 95%</td>
<td>dr &gt; 95%</td>
<td>dr &gt; 95%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**SYNFACTS Contributors:** Victor Snieckus, Brandon P. Schuff (Pfizer)
One-Pot Diastereoselective Synthesis of Azabicyclo[2.2.2]octanes

**Significance:** Reported is the base-mediated synthesis of azabicyclo[2.2.2]octanes through the reaction of dibenzalacetone and malononitrile. The products were unambiguously identified using NMR and IR spectroscopy as well as mass spectrometry and, for one example, by X-ray diffraction analysis. The starting benzalacetones are easily synthesized from benzaldehyde and acetone (C. R. Conard, M. A. Dolliver Org. Syn. 1932, 12, 22). The method was optimized with respect to solvent, temperature and base, and the substrate scope was modestly examined using electron-rich and electron-poor aromatic substitution. The electronics of the ring had surprisingly little effect on the yield of the reaction; however, ortho-substituted dibenzalacetones did not provide products, probably due to steric hindrance effects. Also unsuccessful were dibenzalacetones with para-hydroxyaryl substituents, possibly due to strong electron-donating effects.

**Comment:** General interest in the azabicyclo[2.2.2]octane (isoquinuclidine) structure is fueled by its presence in many interesting natural products, and also its wide array of both pharmaceutical and synthetic uses. Interestingly, the cinchona alkaloids contain quinuclidine part structures and have many pharmacological properties, such as muscle relaxant, analgesic, and antimalarial. They are also very useful as organocatalysts (see Book below). Of the several methods for the synthesis of azabicyclo[2.2.2]octanes outlined in the introduction to this new work, many suffer from substrate scope issues or poor endo/exo selectivity. The current method should prove useful as it uses easily accessible or readily available starting materials to diastereoselectively provide moderate to good yields of new compounds in an efficient, operationally simple one-pot process.

Aziridine and β-Lactam Synthesis by Amination and Carbonylation Reactions

**Significance:** Although significant progress has been made in the functionalization of unactivated C–H bonds, the transformation of aliphatic C–H bonds remains a challenging endeavor (H. M. L. Davies et al. *Chem. Soc. Rev.*, 2011, 40, 1855). Typically, such transition-metal-catalyzed reactions utilize a directing group within the substrate, which serves to position the metal catalyst in the proximity of a particular C–H bond, and proceed through the kinetically favored five-membered cyclometalated intermediate (L. Ackermann *Chem. Rev.*, 2011, 111, 1315). The current report highlights a different mode of reactivity with the reaction being directed by a simple secondary amine and proceeding through a strained four-membered cyclometalated intermediate (L. Ackermann *Chem. Rev.*, 2011, 111, 1315). The current report highlights a different mode of reactivity with the reaction being directed by a simple secondary amine and proceeding through a strained four-membered cyclometalated intermediate. A broad substrate scope was demonstrated for the efficient syntheses of a series of aziridines. In addition, the ring opening of these products provides a range of secondary amines presenting substitution patterns which would be difficult to access by more conventional methods. The methodology was extended to incorporate a palladium-mediated C–H carbonylation to allow access to potentially biologically active β-lactams.

**Comment:** 3,3,5,5-Tetramethylmorpholin-2-one was initially utilized as the model substrate given that this presents a range of C–H bonds that cannot participate in the classical five-membered cyclopalladation. Treatment with stoichiometric Pd(OAc)$_2$ led to the isolation of the four-membered ring complex (characterized by X-ray) resulting from the amine-directed cyclopalladation. Oxidation of this intermediate with PhI(OAc)$_2$ led to the formation of the corresponding aziridine through reductive elimination from a palladium(IV) intermediate. Optimization enabled the reaction to be carried out in a catalytic manner. A broad substrate scope was shown demonstrating excellent selectivity for the formation of the strained heterocycles and the ability to differentiate between methyl groups based on subtle stereoelectronic effects. Replacement of the oxidant PhI(OAc)$_2$ with CO allowed the development of a carbonylation process proceeding through a palladium(II)–palladium(0) catalytic cycle enabling the synthesis of β-lactams for a range of cyclic and acyclic amines.

**SYNFACTS Contributors:** Victor Snieckus, Paul Richardson (Pfizer)
Tetrahydrofurans and Pyrrolidines from N-Tosylhydrazones via C–H Insertion

**Significance:** Reported is a method for synthesizing substituted tetrahydrofurans and pyrrolidines from acyclic N-tosylhydrazones via an intramolecular ruthenium–porphyrin catalyzed C–H insertion process. Key to the success of this method was the identification of conditions for minimizing decomposition (elimination) of the alkylcarbene or carbenoid intermediate, which was realized through careful optimization of base, solvent and catalyst. The ruthenium–porphyrin catalyst used in this study is not commercially available, but is readily prepared in a single step. A one-pot method for accessing the tetrahydrofuran or pyrrolidine products from the corresponding acyclic ketone was also reported and proceeded with comparable yields. The power of this methodology is demonstrated through a concise synthesis of the alkaloid (±)-pseudoheliotridane from pyrrolidine.

**Comment:** Pyrrolidines and tetrahydrofurans are two of the most prevalent heterocycles found in drugs today. The present method demonstrates good scope for accessing these heterocycles, tolerating both alkenes and free alcohols, and provides access to structurally diverse products including spiro, attached ring, and fused ring systems from easily accessible starting materials. N-Tosylhydrazones derived from either aldehydes or ketones were viable substrates, allowing for flexible substitution at the 3 position of the heterocycle. In those cases in which two or more stereo-centers were introduced, a high level of 2,3-cis-diestereoselectivity was observed, especially in the synthesis of pyrrolidines. Kinetic isotope effect experiments and the observed stereospecificity of the present reaction provide strong support for a concerted C–H insertion process.
Copper(I)-Catalyzed Three-Component Reaction of Terminal Propargyl Alcohols, Aldehydes, and Amines: Synthesis of 3-Amino-2-pyrones and 2,5-Dihydrofurans


**Significance:** Reported is a three-component reaction of propargyl alcohols, aldehydes, and amines under copper(I) catalysis to form 3-amino-2-pyrones and 2,5-dihydrofurans. It follows a previous report from the Ma laboratories in which the same components afforded allylic amines (Nat. Commun. 2014, 5, 3884). The difference appears to be that the aldehyde component is ethyl glyoxylate; there is little if any modification of the reaction conditions or the catalyst. Consideration of the readily derived mechanism of the reaction allows formulation of the 2-pyrone 1 as the expected product resulting from mild (silica gel) acidic treatment of isolated intermediate 2, R = OEt, which in turn results from an allene precursor. A rational consideration that EWG in the aldehyde component would encourage formation of the furan ring was confirmed by using glyoxal and the isolation of dihydrofurans 2, R = Ph. A reasonable mechanism is given which, although proceeding via isolated 2, lacks further definition especially in terms of graphical representation of copper involvement. Both processes were tested with at least ten examples each, thus sufficient to justify giving these new processes general status.

**Comment:** The significance of 2-pyrones and dihydrofurans as units possessing biological activity, selective COX-1 inhibition, and as structural units of bioactive natural and unnatural products, respectively, is noted. Fourteen optimization experiments established the best conditions as shown. Scope for R1 = alkyl, benzyl, aryl, and R2, R3 = substituted pyrrolidinyl, piperidinyl, and one case of dibutyl was established for the 2-pyrone synthesis, while mainly R2, R3 = piperidinyl derivatives for the dihydrofurans were obtained. In the glyoxal study, as expected, EWG = NO2 led to poor yields of product. Experiments were carried out in a flame-dried Schlenk tube under argon atmosphere. Significance of this work would have been increased if further transformation of products 1 and 2 would have been carried out or noted (for example, for 1, use for Diels–Alder chemistry).
Auto-Oxidation–Povarov Annulation Approach to Quinolines

Significance: The reported auto-oxidation of N-aryl glycines 1 afforded a versatile imine intermediate, which underwent the Povarov annulation affording 3; further oxidation led to 4, while nucleophilic addition afforded 5. When 2,3-dihydrofuran was employed in the Povarov reaction, a subsequent ring opening–ring closing sequence was observed, resulting in the isolation of compound 3c. The reported Povarov reaction, in particular, is complementary to existing reactions of anilines with glyoxalates and terminal alkynes under acidic catalysis (for example, see: J. B. Bharate et al. Org. Biomol. Chem. 2014, 12, 6267) and avoids the selectivity issues associated with the functionalization of bishalogenated quinolines.

Comment: Although a more extensive demonstration of substrate scope or functional group tolerance would have been appreciated in the presented synthesis, highlights include the tolerance of N-acyl glycines, allyl esters, and halides. Oxidation side products 4 were always observed in the Povarov annulations, but were minimized when R^2 was an electron-rich substituent. The reaction rates were found to be highly dependent on solvent choice, with a 5:1 mixture of MeCN and DCE required for optimal reactivity. The reaction efficiency was also noted to depend on the use of 3–5 week old DCE or on the addition of a trace quantity of HCl, an observation that will impact the reproducibility of these results without due attention.

Selected examples:

<table>
<thead>
<tr>
<th>R1</th>
<th>R2</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MeO</td>
<td>MeO</td>
<td>3a 47% yield (9% 4)</td>
</tr>
<tr>
<td>MeO</td>
<td>NHMe</td>
<td>3b 28% yield (7% 4)</td>
</tr>
<tr>
<td>OMe</td>
<td>OEt</td>
<td>3c 35% yield (40% 4)</td>
</tr>
<tr>
<td>OEt</td>
<td>OMe</td>
<td>3c 42% yield (2 = 2,3-dihydrofuran)</td>
</tr>
</tbody>
</table>

Other reactions also reported:

- 4 52% yield
- 5 74% yield

SYNFACTS Contributors: Victor Snieckus, Benjamin N. Rocke (Pfizer)
Significance: Reported is a one-pot synthesis of indoles, pyrazoles, and pyridazinones by a variation of the Japp–Klingemann Fischer indole synthesis, involving a trifluoromethylation. The reaction was found to well-tolerate a variety of functionalized arenediazonium salts and aryl allyl ketones. meta-Substituted arenediazonium salts provided mixtures of regioisomeric indoles (A and B). para-Substituted arenediazonium salts were also used with methyl pent-4-enolate to provide dihydropyridazinones in good yields.

Comment: The indole and pyrazole heterocyclic core is found in a number of top-selling drugs, such as sumatriptan, zolmitriptan, rizatriptan, tadalafil, and celecoxib (M. Baumann et al. Beilstein J. Org. Chem. 2011, 7, 442). Therefore, a simple and efficient synthesis of these heterocyclic cores is a worthwhile quest. The developed method gives access to various trifluoromethylated heterocycles. Previously, a similar methodology has been used to synthesize pyrazoles (A. Citterio et al. J. Heterocycl. Chem. 1981, 18, 763). Unexplained is the fact that all examples of dihydropyridazinone synthesis use para-substituted diazonium salt precursors.
NHCs in Rhodium-Catalyzed C–H Activation–Annulation to Fused Imidazolium Salts

Significance: The increasing interest in N-heterocyclic carbenes (NHCs) arises arguably from their unprecedented stereoelectronic properties, strong metal–NHC bonding, and great stability of their metal complexes. NHCs act as both ligands and directing groups. These properties make NHCs useful in C–H functionalization as well as C–C and C–heteroatom bond-forming catalysis (see Review below). Reported here is the first directed intramolecular C–H functionalization–annulation reaction using a NHC–rhodium(III) complex as catalytic system. Thus, reaction of imidazolium salts 1 with internal alkynes 2, bearing different types of substituent groups, furnishes a variety of imidazo[1,2-a]quinolinium derivatives 3 in a one-pot process in 35–93% yield.

Comment: This is the first report of this kind of reaction, which is formally a [4+2]-cycloaddition process. A range of substrates was evaluated and a relationship between the electronic demand of the rings and the alkyne was established. Another pleasant surprise is the mild room-temperature reaction conditions. The NHC–rhodium(III) complex was isolated and characterized, thus supporting strongly the proposed mechanism. The main disadvantage of this methodology is the use of a large amount of AgOTf, which can make its scalability expensive. Further applications are anticipated.

Iron-Mediated Synthesis of Pyrroles from Cyclopropanes

**Significance:** The synthesis of highly substituted pyrroles 3 from cyclopropanes 1 and amines 2 via an iron-mediated sequential ring opening–cyclization–dehydrogenation reaction is reported. The conditions were optimized using different solvents, reaction times, and iron catalysts. The scope was studied and cyclopropanes 1 bearing methyl and aryl substituents at R1 were tested with the latter giving better yields. EWG- and EDG-substituted aryl amines as well as R2 = OEt were well tolerated. Also, a methyl group in the cyclopropane (R4 = Me) was suitable, furnishing 1,2,3,5-substituted pyrrole 3 in good yield. A series of aromatic and aliphatic amines were screened as well: aliphatic amines furnished pyrroles 3 in low yields, while aromatic amines gave better results, although the yields decrease according to the position of the phenyl substituent. A reaction mechanism involving a radical process was suggested based on radical trapping experiments.

**Comment:** Cyclopropane derivatives can be used as precursors to synthesize a variety of useful heterocyclic motifs (C. A. Carson, M. A. Kerr Chem. Soc. Rev. 2009, 38, 3051; J. R. Green, V. Snieckus Synlett 2014, 25, 2258). The present work reports an efficient synthesis of tri- and tetra-substituted pyrroles in moderate to good yields from readily available cyclopropanes and amines. The reaction shows a broad substrate scope; both EWG and EDG in 1 and 2 affording pyrroles 3 in comparable yields. While anilines with different patterns of substitution furnished 3 in good yields, a large excess of amine was required when benzylamines were used. The readily available cyclopropanes can be easily prepared in high yields by the reaction of a dicarbonyl compound with 1,2-dibromoethane (Z. Zhang et al. Angew. Chem. Int. Ed. 2007, 46, 1726).
Significance: Reported is the synthesis of 2-aminothiophenes 3 via a copper-catalyzed addition–oxidative cyclization of alkynoates 2 with thioamides 1. Among a series of tested copper salts, Cu(OAc)$_2$ proved to be the most efficient under aerobic conditions. There was no improvement in yields when the reaction was carried out under an oxygen atmosphere. When the reaction was done under a nitrogen atmosphere, only a trace amount of the product was obtained. Instead, compound 4 was isolated in 46% yield, suggesting that the reaction proceeds through a Michael addition–oxidative cyclization pathway. The reaction also proceeded with catalytic FeCl$_3$, albeit in comparatively lower yield. The reaction failed at 50 °C and a lower yield was observed at 100 °C. A wide variety of EWGs in 1 were tested to synthesize 3 in moderate to good yields. The reaction of N-monosubstituted β-ketothioamide with dimethyl acetylenedicarboxylate gave a mixture of compounds, which were not characterized.

Comment: 2-Aminothiophene is a useful building block for synthetic chemists as well as a key structural unit in biologically active molecules, such as olanzapine which is used for the treatment of schizophrenia and bipolar disorder. Substituted 2-aminothiophenes are generally synthesized by the direct functionalization of thiophenes or by the cyclization of suitable precursors. A number of methods using the latter strategy are known (see Review below). The current method utilizes readily available starting materials and is easy to set up due to its tolerance to aerobic conditions. However, the reaction scope is limited. Also, it would have been interesting to see the reaction carried out with unsymmetrical alkynoates.

An Improved Synthesis of Imidazo[4,5-b]pyridines and Imidazo[4,5-b]pyrazines by Palladium Catalyzed Amidation Using Xantphos in a 1,4-Dioxane:tert-Amyl Alcohol Solvent System


An Improved Procedure for a Pd-Catalyzed Amidation Approach to Imidazopyridines

**Significance:** The present report is a full paper on the previous communication concerned with the synthesis of imidazopyridines using a palladium-catalyzed coupling reaction of amides and 3-amino-2-chloropyridines (A. J. Rosenberg, J. Zhao, D. A. Clark *Org. Lett.* 2012, 14, 1764). The current study aimed to expand the substrate scope, and to find more economical phosphine-based ligands instead of the previously utilized biaryl ligand, Me₄-t-Bu-XPhos. The reaction was tested with the Xantphos ligand, despite the fact that the reaction had previously failed when run in t-BuOH.

**Comment:** The presented procedure is an improvement over the one reported previously. With the current procedure, chlorinated substrates survive the reaction better, and electron-poor substrates afford higher yields. Further, the authors rightly claim economic benefits and a quick comparison of the prices (Sigma-Aldrich website, 10/11/2014) indicates the following prices: Xantphos: 61 CAD$/mmol, and Me₄-t-Bu-XPhos: 135 CAD$/mmol (1 gram quantity). No drawbacks of the procedure are mentioned, but brominated and iodinated substrates are evident in their absence. Furthermore, the scope of pyridine starting materials was not well studied; this is most likely due to poor availability of substituted 3-amino-2-chloropyridines.

**Equation:**

\[
\text{Z = CH, N; CHMe (1 example)}
\]

**R**¹ = i-Pr, c-Pent, Cy, Ph, BN, CH₂(4-MeOC₆H₄), CH₂(2,4-(MeO)₂C₆H₄), CH₂(2,5-(MeO)₂C₆H₄), CH₂(4-Me₃NC₆H₄), CH₂(4-FCH₂CH₂(3-FC₆H₄), CH₂(4-(Cl₃C₆H₃), CH₂(4-(Me₂NC₆H₄), CH₂(4-FC₂H₃(2-ClC₆H₄)), CH₂(4-(Cl₃C₆H₃), CH₂(4-(PhC₆H₄)), CH₂(3,5-(MeO)₂C₆H₄), CH₂(4-F₃CC₆H₃), CH₂(4-NC₂H₄), CH₂(3-O₂NC₆H₄), CH₂Cy, (R)-CHMePh

**R**² = H, Me, Ph, Cy, 2-aryl, furan-2-yl

**Note:**

28 examples
57–97% yield
Enantioselective Synthesis of 3,4-Dihydrothiacarbazol-2(9H)-ones

Significance: Reported is the enantioselective synthesis of 3,4-dihydrothiacarbazol-2(9H)-ones 3 by reaction of indoline-2-thiones 1 with N-alkenoylphthalimides 2 catalyzed by the chiral squaramide 4. Screening of organocatalysts with double hydrogen-bond donor ability led to squaramide 4 derived from L-tert-leucine as the best catalyst for this transformation affording high enantioselectivity. The reaction conditions were optimized in terms of solvent, temperature, and catalyst loadings. Lower temperatures (0 °C) culminated in lengthy reaction time and lower yield but equivalent ee, while higher temperatures (40 °C) provided equivalent reaction yields but loss of stereocontrol. The study of the reaction scope showed that the presence of different substituents on both 1 and 2 were tolerated, but in some cases loss of stereocontrol without following a pattern was observed.

Comment: The indole skeleton is an important class of heterocycles present in many natural products with broad biological activities, and can be synthesized by many well-described methodologies (see Review below). The thiopyran indole 3 was obtained by an activation process promoted by two hydrogen-bonding interactions of 2 with the squaramide organocatalyst, followed by a Michael addition step and a thiolysis reaction. The starting materials 1 and 2 are readily available. Although a mild process, the reported approach has long reaction times and the study of the reaction scope is narrow.

Copper-Catalyzed Amidation of π-Excessive Heterocycles

Significance: Amino-substituted heterocycles are prevalent as subunits in a large number of pharmaceutical drug targets. As a result, transition-metal-catalyzed aryl C–N bond formation has been studied extensively. Traditionally, these compounds are synthesized by coupling heteroaryl halides with amine surrogates. Pan and co-workers report an efficient method for direct amidation of π-electron-rich heterocycles with N-fluorobenzenesulfonimide (NFSI). Interestingly, even though NFSI is typically used as a fluorinating reagent, no fluorinated byproducts are observed in this reaction. The procedure uses mild conditions to provide the desired functionalized products in high yields.

Comment: A variety of electron-deficient and electron-rich thiophenes, furans, and pyrroles undergo regioselective amidation under these reaction conditions. Although the reaction does proceed at ambient temperature, higher yields are obtained at slightly elevated temperature (60 °C). A mechanistic pathway involving copper(I), copper(II), and copper(III) species is proposed, and further studies to investigate the mechanism of this transformation are underway. For a recent method of 2-aminothiophene and other π-excessive heterocycle synthesis, see the copper(II)-catalyzed synthesis of 2-aminothiophenes from alkynoates and thioamides (Org. Biomol. Chem. 2014, 12, 8473; Synfacts 2015, 11, 24).

Representative examples:

- \( \text{R}^1 - \text{X} - \text{H} \quad \overset{\text{PhO}_2\text{PSO}_2\text{Ph}}{\underset{\text{CuI (5 mol%)}}{\text{DCE, 60 °C}}} \quad \text{R}^1 \cdot \text{N(SO}_2\text{Ph)}_2 \)
  - \( X = S, O, NR^2 \)
  - 88% yield
  - 78% yield
  - 89% yield
  - 86% yield

- \( \text{R}^1 - \text{S} - \text{H} \quad \overset{\text{PhO}_2\text{PSO}_2\text{Ph}}{\underset{\text{CuI (5 mol%)}}{\text{DCE, 60 °C}}} \quad \text{R}^1 \cdot \text{N(SO}_2\text{Ph)}_2 \)
  - 79% yield
  - 73% yield
  - 85% yield
  - 89% yield

- \( \text{R}^1 - \text{N(SO}_2\text{Ph)}_2 \quad \overset{\text{PhO}_2\text{PSO}_2\text{Ph}}{\underset{\text{CuI (5 mol%)}}{\text{DCE, 60 °C}}} \quad \text{R}^1 \cdot \text{N(SO}_2\text{Ph)}_2 \)
  - 86% yield
  - 85% yield
  - 83% yield
  - 76% yield

SYNFACTS Contributors: Victor Snieckus, Omar K. Ahmad
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