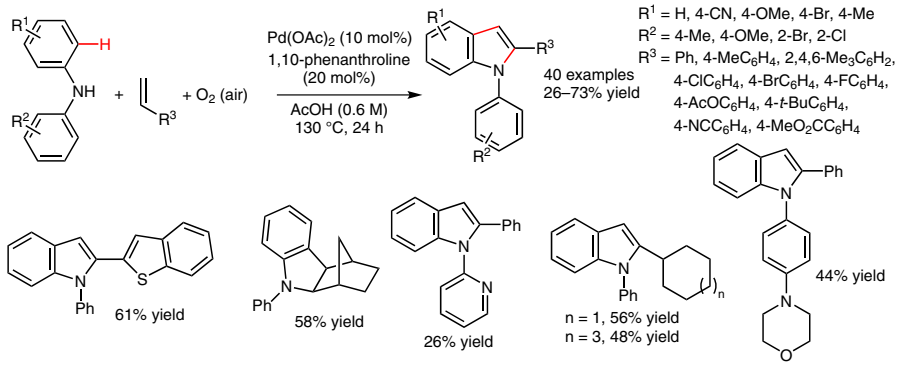
U. SHARMA, R. KANCHERLA, T. NAVEEN, S. AGASTI, D. MAITI* (INDIAN INSTITUTE OF TECHNOLOGY, BOMBAY, INDIA)

Palladium-Catalyzed Annulation of Diarylamines with Olefins through C–H Activation: Direct Access to *N*-Arylindoles

Angew. Chem. Int. Ed. **2014**, *53*, 11895–11899.

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methods, for example, the venerable century-old Fischer indole synthesis, among other textbook reactions, have been superceded by a barrage of methodologies based on transition-metal-catalyzed heteroannulation processes originating with Larock, with significant contributions by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 precedented 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 D_2O 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-aminostilbene 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.

SYNFACTS Contributors: Victor Snieckus
Synfacts 2015, 11(1), 0013 Published online: 15.12.2014
DOI: 10.1055/s-0034-1379706; **Reg-No.:** V15314SF

Category

Synthesis of Heterocycles

Key words

***N*-aryl indoles**

C–H activation

palladium catalysis

heteroannulation

Category

Synthesis of Heterocylces

Key words

trichloroisocyanuric acid

intramolecular cyclization

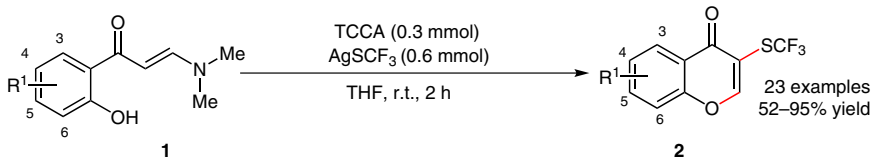
chromenones

H. XIANG, C. YANG* (SHANGHAI INSTITUTE OF MATERIA MEDICA, P. R. OF CHINA)

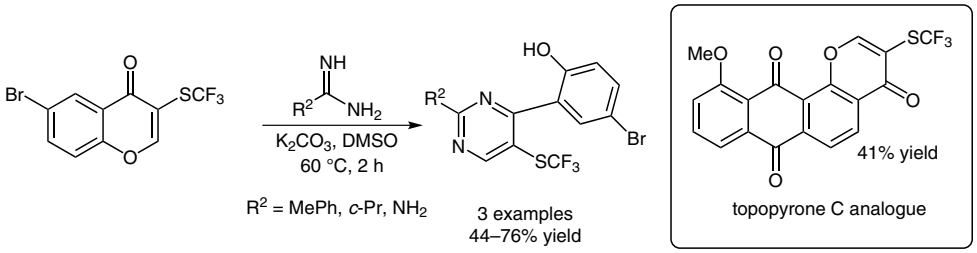
A Facile and General Approach to 3-[(Trifluoromethyl)thio]-4*H*-chromen-4-one

Org. Lett. **2014**, *16*, 5686–5689.

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



R^1 = 4-H, 4-Me, 4-Et, 4-Pr, 4-*i*-Pr, 4-OMe, 4-F, 4-Cl, 4-Br, 4-Ph, 4-(4'-$MeOC_6H_4$), 4-NO_2, 5-OMe, 5-Et, 5-Br, 5-Cl, 4,5-$(OMe)_2$, 4,5-Me_2, 4-Cl-5-Me, 4,6-Me_2, 4-Cl-6-Br, 4-(4'-MeO_2C-C_6H_4-), 4,5-$(CH{=}CH{-})_2$



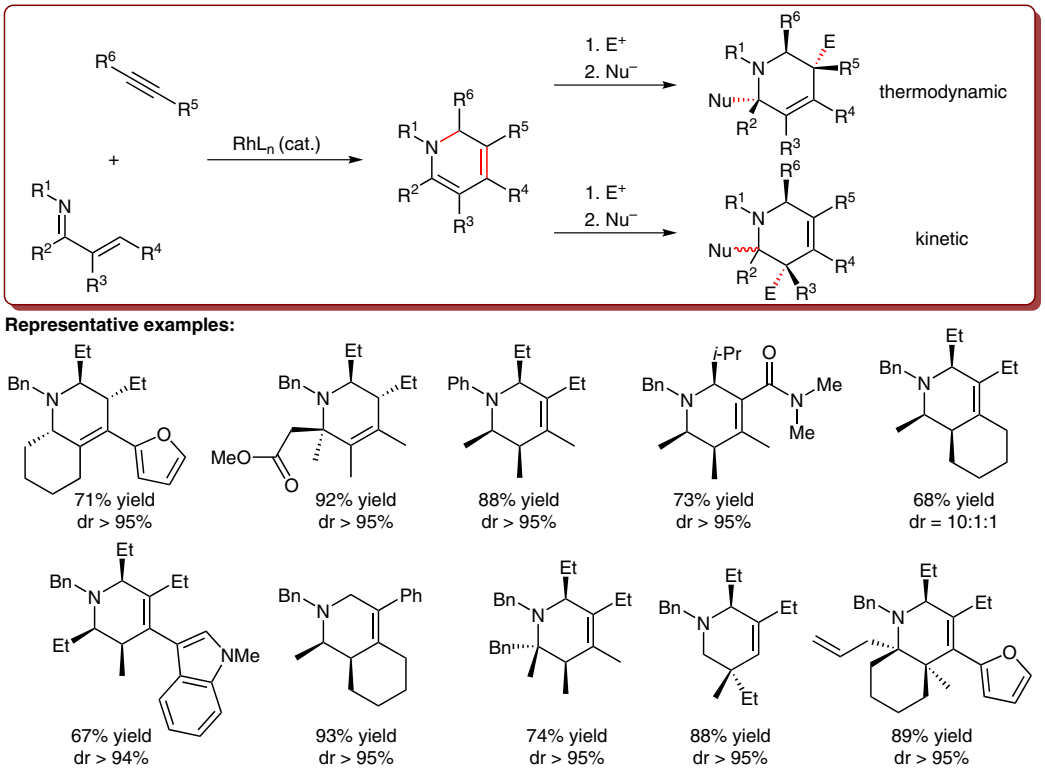
Significance: Reported is a general synthesis of 3-[(trifluoromethyl)thio]-4*H*-chromen-4-ones **2** from 1-(2′-hydroxyphenyl)-3-dimethylaminoprop-2-enones **1** and the active electrophilic trifluoromethylthio moiety generated from $AgSCF_3$and trichloroisocyanuric acid (TCCA). This synthetic approach leads to the direct introduction of the SCF_3 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, CH_2Cl_2, 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 SCF_3-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 $^{+}SCF_3$ species, then a *N*,*N*-dimethylamine elimination process to produce **2**.

SYNFACTS Contributors: Victor Snieckus, Mona Gamal-Eldin (Snieckus Innovations)
Synfacts 2015, 11(1), 0014 Published online: 15.12.2014
DOI: 10.1055/s-0034-1379731; **Reg-No.:** V15714SF

T. MESGANAW, J. A. ELLMAN* (YALE UNIVERSITY, NEW HAVEN, USA)
Convergent Synthesis of Diverse Tetrahydropyridines via Rh(I)-Catalyzed C–H Functionalization Sequences
Org. Process Res. Dev. **2014**, *18*, 1097–1104.

Rhodium(I)-Catalyzed [4+2]-Cycloaddition Route to 1,2-Dihydropyridines



Significance: Piperidine heterocycles are abundant in numerous pharmaceuticals such as oxycotin, plavix, ritalin, and tofacintinib. 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.

SYNFACTS Contributors: Victor Snieckus, Brandon P. Schuff (Pfizer)
Synfacts 2015, 11(1), 0015 Published online: 15.12.2014
DOI: 10.1055/s-0034-1379737; **Reg-No.:** V15914SF

Category

Synthesis of Heterocycles

Key words

bridged bicycles
C–H activation
dihydropyridines
piperidines
rhodium catalysis

Category

Synthesis of Heterocycles

Key words

azabicyclo[2.2.2]-octanes

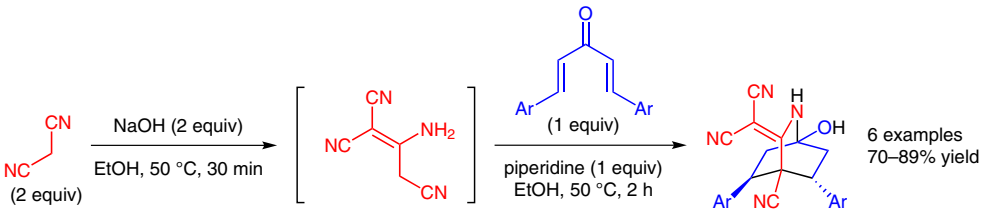
malononitriles

dibenzalacetones

A. ALIZADEH,* V. SADEGHI, F. BAYAT, L.-G. ZHU (TARBIAT MODARES UNIVERSITY, TEHRAN, IRAN AND ZHEJIANG UNIVERSITY, HANGZHOU, P. R. OF CHINA)

Highly Efficient Diastereoselective Synthesis of Azabicyclo[2.2.2]octanes
Synlett **2014**, *25*, 2609–2612.

One-Pot Diastereoselective Synthesis of Azabicyclo[2.2.2]octanes



Ar = Ph, 3-BrC_6H_4, 3-$O_2NC_6H_4$, 4-$MeOC_6H_4$, 4-ClC_6H_4, 3,4-$Me_2OC_6H_3$

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.

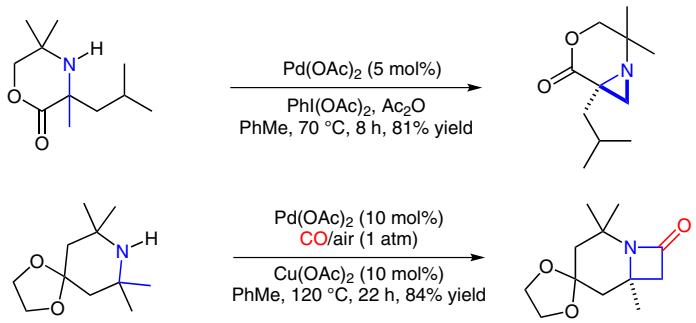
Book: C. E. Song *An Overview of Cinchona Alkaloids in Chemistry*, In *Cinchona Alkaloids in Synthesis and Catalysis: Ligands, Immobilization and Organocatalysis*, C. E. Song, Ed.; Wiley-VCH: Weinheim, Germany, **2009**, 1–10.

SYNFACTS Contributors: Victor Snieckus, Johnathan Board
Synfacts 2015, 11(1), 0016 Published online: 15.12.2014
DOI: 10.1055/s-0034-1379729; **Reg-No.:** V15514SF

A. MCNALLY, B. HAFFEMAYER, B. S. L. COLLINS, M. J. GAUNT* (UNIVERSITY OF CAMBRIDGE, UK)

Palladium-Catalysed C–H Activation of Aliphatic Amines to Give Strained Nitrogen Heterocycles
Nature **2014**, *510*, 129–133.

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. A broad substrate scope is 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)
Synfacts 2015, 11(1), 0017 Published online: 15.12.2014
DOI: 10.1055/s-0034-1379739; **Reg-No.:** V16114SF

Category

Synthesis of Heterocycles

Key words

aziridines

β-lactams

C–H activation

Category

Synthesis of Heterocycles

Key words

tosylhydrazones

carbenes

C–H insertion

pyrrolidines

tetrahydrofurans

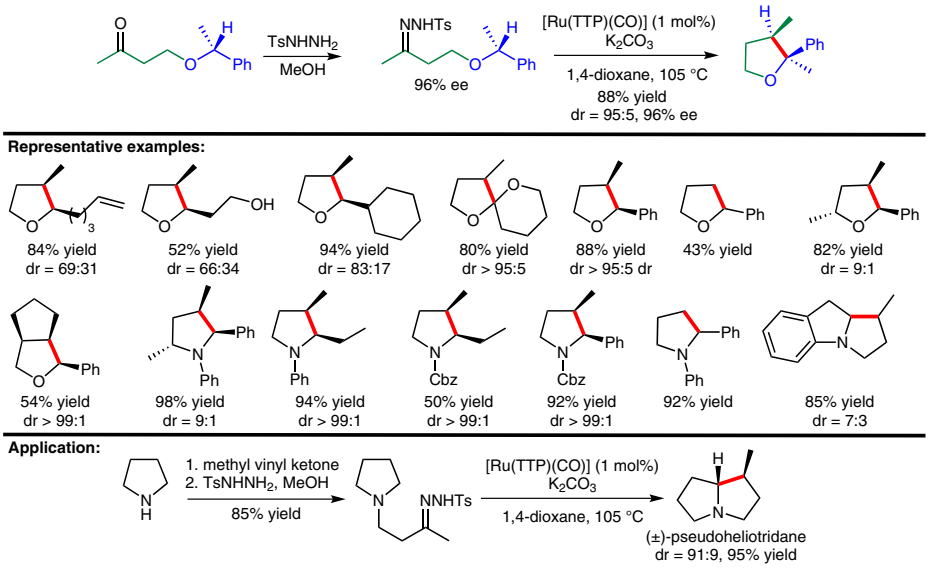
ruthenium

A. R. REDDY, C.-Y. ZHOU, Z. GUO, J. WEI, C.-M. CHE* (HKU SHENZHEN INSTITUTE OF RESEARCH AND INNOVATION AND THE UNIVERSITY OF HONG KONG, P. R. OF CHINA)

Ruthenium–Porphyrin-Catalyzed Diastereoselective Intramolecular Alkyl Carbene Insertion into C–H Bonds of Alkyl Diazomethanes Generated In Situ from *N*-Tosylhydrazones

Angew. Chem. Int. Ed. **2014**, *53*, 14175–14180.

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.

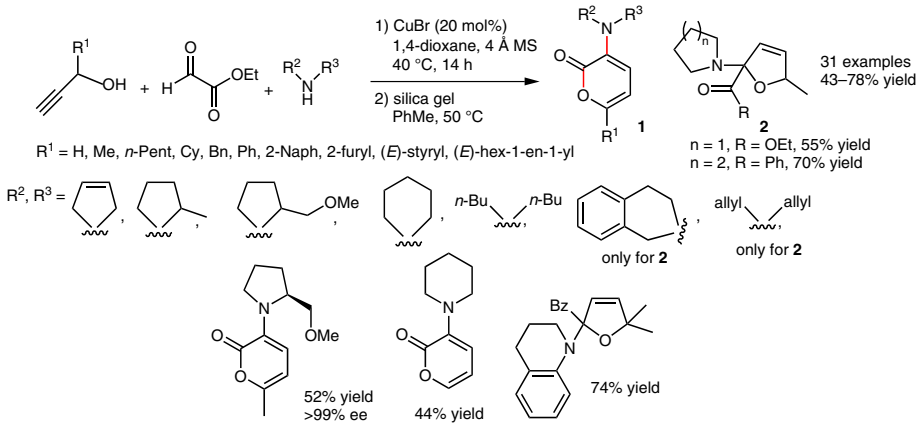
Comment: Pyrrolidines and tetrahydrofurans are two of the most prevalent heterocycles found in drugs today. The present method demonstrates good scope for accessing these heterocycles, tolerating both alkenes and free alcohols, and provides access to structurally diverse products including spiro, attached 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 stereocenters were introduced, a high level of 2,3-*cis* diastereoselectivity 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.

SYNFACTS Contributors: Victor Snieckus, Matt Dowling (Pfizer)
Synfacts 2015, 11(1), 0018 Published online: 15.12.2014
DOI: 10.1055/s-0034-1379701; **Reg-No.:** V14814SF

W. FAN, S. MA* (SHANGHAI INSTITUTE OF ORGANIC CHEMISTRY AND EAST CHINA NORMAL UNIVERSITY, SHANGHAI, P. R. OF CHINA)

Copper(I)-Catalyzed Three-Component Reaction of Terminal Propargyl Alcohols, Aldehydes, and Amines: Synthesis of 3-Amino-2-pyrones and 2,5-Dihydrofurans
Angew. Chem. Int. Ed. **2014**, DOI: 10.1002/anie.201408826.

Copper(I)-Catalyzed 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 R^1 = alkyl, benzyl, aryl, and R^2,R^3 = substituted pyrrolidinyl, piperidinyl, and one case of dibutyl was established for the 2-pyrone synthesis, while mainly R^2,R^3 = piperidinyl derivatives for the dihydrofurans were obtained. In the glyoxal study, as expected, EWG = NO_2 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).

SYNFACTS Contributors: Victor Snieckus
Synfacts 2015, 11(1), 0019 Published online: 15.12.2014
DOI: 10.1055/s-0034-1379705; **Reg-No.:** V15214SF

Category

Synthesis of Heterocycles

Key words

pyrones

dihydrofurans

C–H activation

copper catalysis

multicomponent reaction

Category

Synthesis of Heterocycles

Key words

quinolines

pyranoquinolines

oxidation

Povarov reaction

aromatization

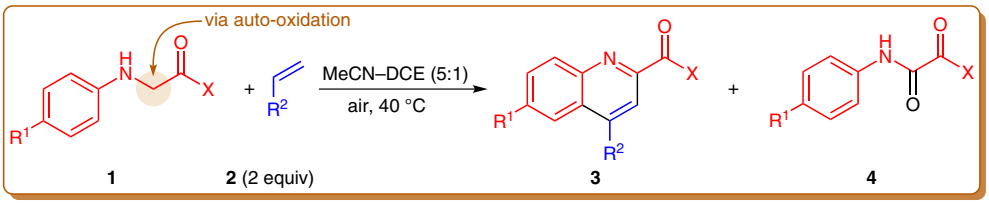
auto-oxidation

C. HUO,* Y. YUAN, M. WU, X. JIA, X. WANG, F. CHEN, J. TANG (NORTHWEST NORMAL UNIVERSITY, LANZHOU, P. R. OF CHINA)

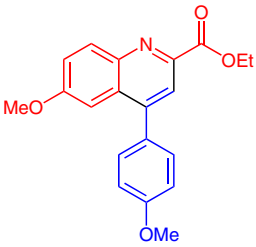
Auto-Oxidative Coupling of Glycine Derivatives

Angew. Chem. Int. Ed. **2014**, *53*, 13544–13547.

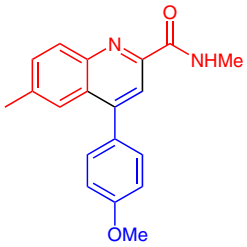
Auto-Oxidation–Povarov Annulation Approach to Quinolines



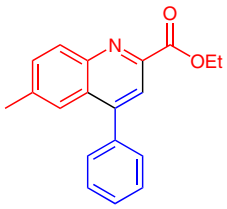
Selected examples:



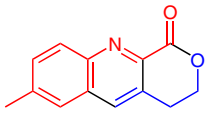
3a 47% yield (9% **4**)



3b 28% yield (7% **4**)

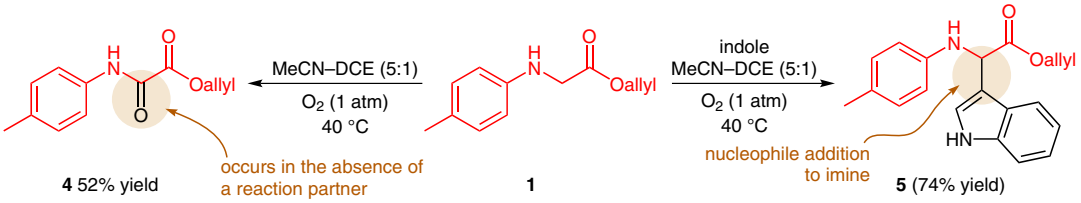


3c 35% yield (40% **4**)



3c 42% yield (**2** = 2,3-dihydrofuran)

Other reactions also reported:



4 52% yield

1

5 (74% yield)

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.

SYNFACTS Contributors: Victor Snieckus, Benjamin N. Rocke (Pfizer)
Synfacts 2015, 11(1), 0020 Published online: 15.12.2014
DOI: 10.1055/s-0034-1379702; **Reg-No.:** V14914SF

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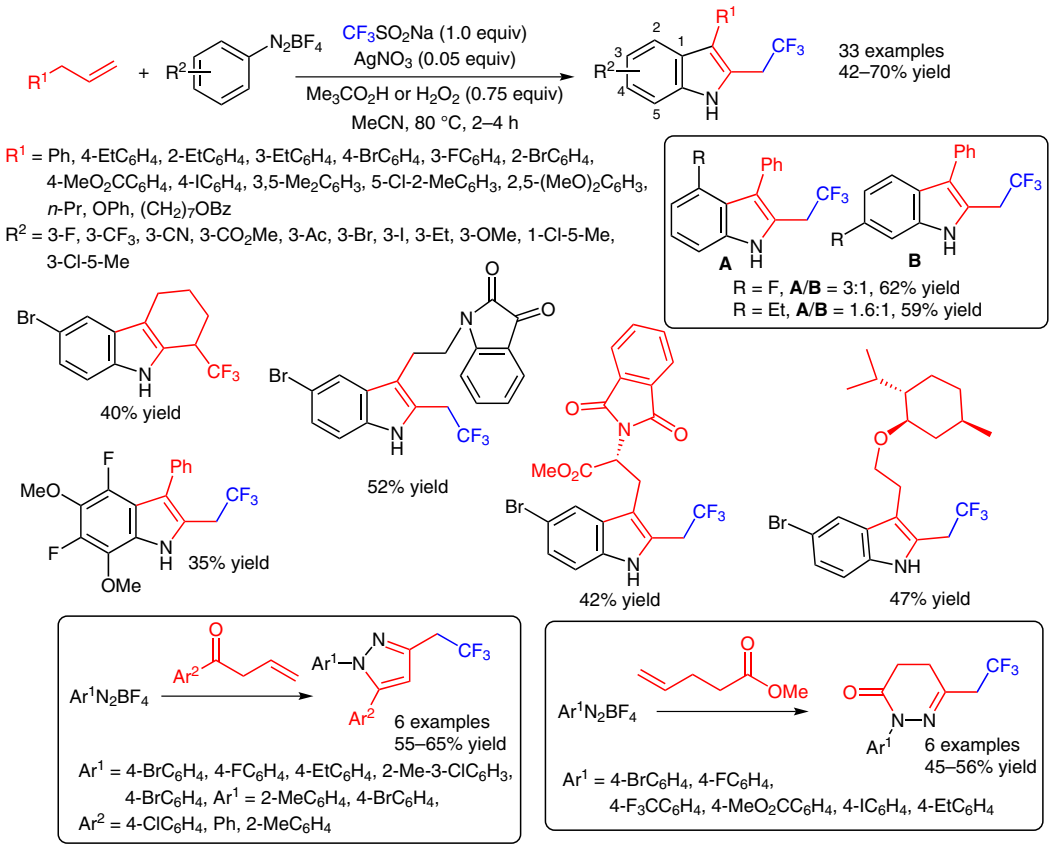
Cascade Multicomponent Synthesis of Indoles, Pyrazoles, and Pyridazinones by Functionalization of Alkenes
Angew. Chem. Int. Ed. **2014**, *53*, 11960–11964.

Synthesis of Indoles, Pyrazoles, and Pyridazinones



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-enoate 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.

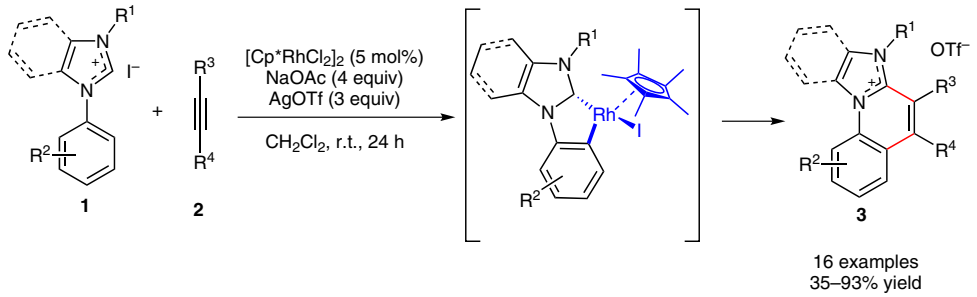
SYNFACTS Contributors: Victor Snieckus, M. Selim Hossain (Snieckus Innovations)
Synfacts 2015, 11(1), 0021 Published online: 15.12.2014
DOI: 10.1055/s-0034-1379730; **Reg-No.:** V15614SF

D. GHORAI, J. CHOUDHURY* (INDIAN INSTITUTE OF SCIENCE EDUCATION AND RESEARCH BHOPAL, INDIA)

Exploring a Unique Reactivity of N-Heterocyclic Carbenes (NHC) in Rhodium(III)-Catalyzed Intermolecular C–H Activation/Annulation

Chem. Commun. **2014**, *50*, 15159–15162.

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.

Review: M. N. Hopkinson, C. Richter, M. Schedler, F. Glorius *Nature* **2014**, *510*, 485–496.

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.

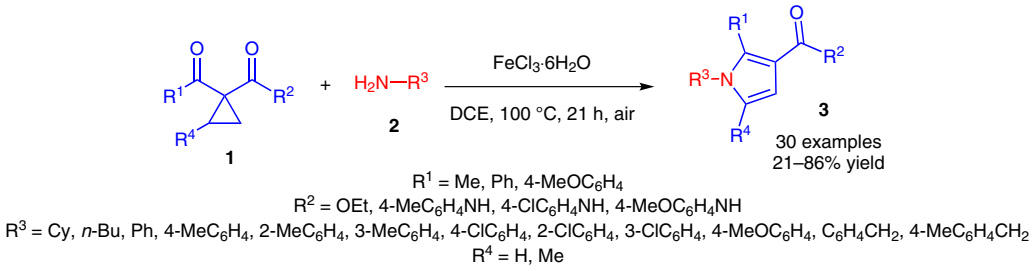
SYNFACTS Contributors: Victor Snieckus, Keller G. Guimarães
Synfacts 2015, 11(1), 0022 Published online: 15.12.2014
DOI: 10.1055/s-0034-1379740; **Reg-No.:** V16214SF

Z. ZHANG,* W. ZHANG, J. LI, Q. LIU, T. LIU, G. ZHANG* (HENAN NORMAL UNIVERSITY, XINXIANG, P. R. OF CHINA)

Synthesis of Multisubstituted Pyrroles from Doubly Activated Cyclopropanes Using an Iron-Mediated Oxidation Domino Reaction

J. Org. Chem. **2014**, *79*, 11226–11233.

Iron-Mediated Synthesis of Pyrroles from Cyclopropanes



R^1 = Me, Ph, 4-$MeOC_6H_4$
R^2 = OEt, 4-MeC_6H_4NH, 4-ClC_6H_4NH, 4-$MeOC_6H_4NH$
R^3 = Cy, *n*-Bu, Ph, 4-MeC_6H_4, 2-MeC_6H_4, 3-MeC_6H_4, 4-ClC_6H_4, 2-ClC_6H_4, 3-ClC_6H_4, 4-$MeOC_6H_4$, $C_6H_4CH_2$, 4-$MeC_6H_4CH_2$
R^4 = H, Me

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 R^1 were tested with the latter giving better yields. EWG- and EDG-substituted aryl amines as well as R^2 = OEt were well tolerated. Also, a methyl group in the cyclopropane (R^4 = 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 tetrasubstituted 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).

SYNFACTS Contributors: Victor Snieckus, Lívia Cristina Frota
Synfacts 2015, 11(1), 0023 Published online: 15.12.2014
DOI: 10.1055/s-0034-1379704; **Reg-No.:** V15114SF

Category

Synthesis of Heterocycles

Key words

alkynoates

thioamides

2-aminothiophenes

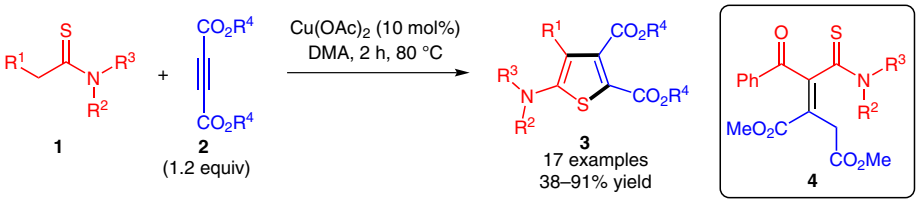
copper catalysis

L.-S. GE, Z.-L. WANG, X.-L. AN, X. LUO,* W.-P. DENG* (EAST CHINA UNIVERSITY OF SCIENCE AND TECHNOLOGY, SHANGHAI, P. R. OF CHINA)

Direct Synthesis of Polysubstituted 2-Aminothiophenes by Cu(II)-Catalyzed Addition/Oxidative Cyclization of Alkynoates with Thioamides

Org. Biomol. Chem. **2014**, *12*, 8473–8479.

Synthesis of 2-Aminothiophenes from Alkynoates and Thioamides



R^1 = PhCO, MeCO, EtCO, *t*-BuCO, 4-*n*-OctC_6H_4CO, MeOCO, EtOCO, *t*-BuOCO, BnOCO, Me_2NCO, Me_2NCS, NC, 4-BrC_6H_4CO

$R^2 = R^3$ = Me, Et, $(CH_2CH_2)_2O$

$R^2 \neq R^3$ = Ph, Me

R^4 = Me, Et

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.

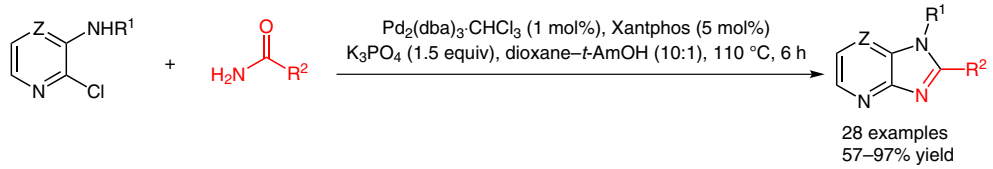
Review: A. El-Mekabaty *Synth. Commun.* **2014**, *44*, 1–31.

SYNFACTS Contributors: Victor Snieckus, Suneel P. Singh (Snieckus Innovations)
Synfacts 2015, 11(1), 0024 Published online: 15.12.2014
DOI: 10.1055/s-0034-1379728; **Reg-No.:** V15414SF

A. J. ROSENBERG, I. AHMED, R. J. WILSON, T. M. WILLIAMS, L. KAMINSKY, D. A. CLARK*
(SYRACUSE UNIVERSITY, USA)

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
Adv. Synth. Catal. **2014**, *356*, 3465–3470.

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



28 examples
57–97% yield

Z = CH, N, CHMe (1 example)
R^1 = *i*-Pr, *c*-Pent, Cy, Ph, Bn, $CH_2(4\text{-}MeOC_6H_4)$, $CH_2(2,4\text{-}(MeO)_2C_6H_3)$, $CH_2(2,5\text{-}(MeO)_2C_6H_3)$, $CH_2(4\text{-}Me_2NC_6H_4)$, $CH_2(4\text{-}FC_6H$ $CH_2(3\text{-}FC_6H_4)$, $CH_2(4\text{-}ClC_6H_4)$, $CH_2(2\text{-}ClC_6H_4)$, $CH_2(4\text{-}PhC_6H_4)$, $CH_2(3,5\text{-}(MeO)_2C_6H_4)$, $CH_2(4\text{-}F_3CC_6H_4)$, $CH_2(4\text{-}NCC_6H_4)$, $CH_2(3\text{-}O_2NC_6H_4)$, CH_2Cy, (*R*)-CHMePh
R^2 = H, Me, Ph, Cy, 2-styryl, furan-2-yl

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, Me_4-*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. Re-examination of the reaction with Xantphos in aprotic solvents led to the desired imidazopyridine together with an unwanted protodehalogenated pyridine byproduct. In order to minimize the formation of this byproduct, a mixed protic–aprotic solvent system using dioxane–*t*-AmOH was devised giving rise to a 93% yield of the desired imidazopyridine. The new reaction conditions improved the yields in some cases, and in others, allowed for product formation, where previously only decomposition had been observed [Z = CH, $R^1 = CH_2(4\text{-}ClC_6H_4)$, R^2 = H; and any substituent containing a nitro group].

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$/mmol, and Me_4-*t*-Bu-XPhos: 135 CAD$/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.

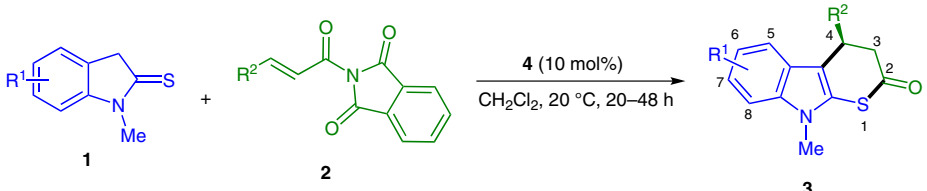
SYNFACTS Contributors: Victor Snieckus, Toni Rantanen
Synfacts 2015, 11(1), 0025 Published online: 15.12.2014
DOI: 10.1055/s-0034-1379736; **Reg-No.:** V15814SF

S. CHEN, J. PAN, Y. WANG, Z. ZHOU* (NANKAI UNIVERSITY, TIANJIN, P. R. OF CHINA)

Stereocontrolled Construction of the 3,4-Dihydrothiacarbazol-2(9*H*)-one Skeleton by Using Bifunctional Squaramide-Catalyzed Cascade Reactions

Eur. J. Org. Chem. **2014**, 7940–7947.

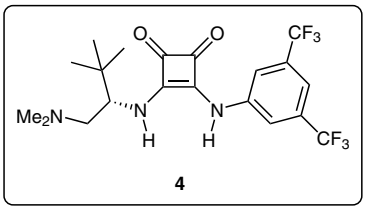
Enantioselective Synthesis of 3,4-Dihydrothiacarbazol-2(9*H*)-ones



R^1 = H, 5-Cl, 6-Me, 6-F, 6-Cl, 6-Br, 7-Cl

R^2 = Me, Ph, 2-furyl, 2-thienyl, 2-BrC_6H_4, 2-ClC_6H_4, 3-$MeOC_6H_4$, 3-$O_2NC_6H_4$, 3-$F_3CC_6H_4$, 3-BrC_6H_4, 3-ClC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-$O_2NC_6H_4$, 4-BrC_6H_4 4-ClC_6H_4, 4-FC_6H_4, (*E*)-styryl

24 examples
37–92% yield
54–98% ee



Significance: Reported is the enantioselective synthesis of 3,4-dihydrothiacarbazol-2(9*H*)-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.

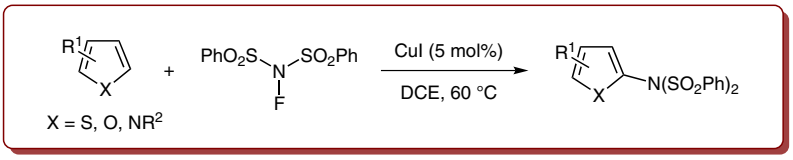
Review: G. R. Humphrey, J. T. Kuethe *Chem. Rev.* **2006**, *106*, 2875–2911.

SYNFACTS Contributors: Victor Snieckus, Sara Gomes
Synfacts 2015, 11(1), 0026 Published online: 15.12.2014
DOI: 10.1055/s-0034-1379703; **Reg-No.:** V15014SF

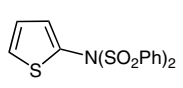
S. WANG, Z. NI, X. HUANG, J. WANG, Y. PAN* (ZHEJIANG UNIVERSITY, HANGZHOU, P. R. OF CHINA)

Copper-Catalyzed Direct Amidation of Heterocycles with *N*-Fluorobenzenesulfonimide
Org. Lett. **2014**, *16*, 5648–5651.

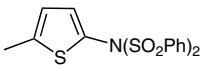
Copper-Catalyzed Amidation of π-Excessive Heterocycles



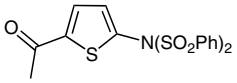
Representative examples:



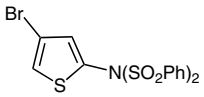
88% yield



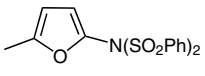
78% yield



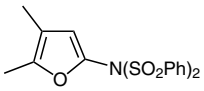
89% yield



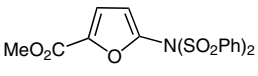
86% yield



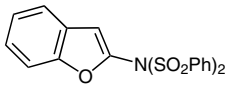
79% yield



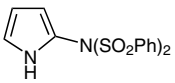
73% yield



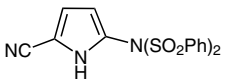
85% yield



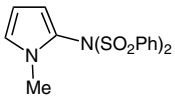
89% yield



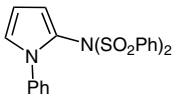
86% yield



85% yield



83% yield



76% yield

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).

SYNFACTS Contributors: Victor Snieckus, Omar K. Ahmad
Synfacts 2015, 11(1), 0027 Published online: 15.12.2014
DOI: 10.1055/s-0034-1379738; **Reg-No.:** V16014SF

Category

Synthesis of Heterocycles

Key words

cuprous iodide
thiophenes
furans
pyrroles
***N*-fluorobenzene-sulfonimide**
amidation