ORGANIC PROCESS RESEARCH & DEVELOPMENT
OPR&D
Highlights from the Literature
Cite This: Org. Process Res. Dev. 2018, 22, 563−573
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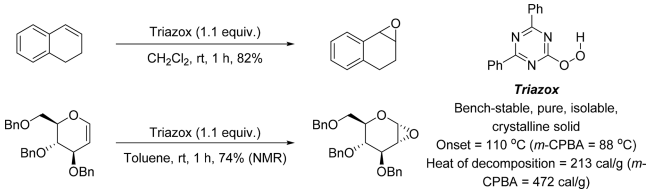
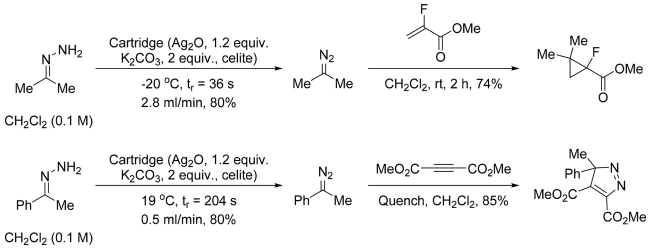
Some Items of Interest to Process R&D Chemists and Engineers

AN ISOLABLE AND BENCH-STABLE EPOXIDIZING REAGENT BASED ON TRIAZINE: TRIAZOX



The epoxidation of olefins using peracid reagents such as m-chloroperoxybenzoic acid (*m*-CPBA) represents a fundamental transformation in organic chemistry. However, issues arise with this class of reagents in terms of their stability (typically available as ∼80% pure hydrate) as well as their performance in reactions with acid-labile substrates. Given this, alternatives such as dimethyldioxirane (DMDO) have been developed, though this is still not ideal because the reagent has to be generated in situ as required. Given this need for further reagents capable of mediating this important transformation, Kunishima and co-workers have extended their previous work on triazine-based reagents, reporting on the bench-stable expoxidizing reagent 2-hydroperoxy-4,6-diphenyl-1,3,5-triazine (Triazox) (*Org. Lett.* **2018**, *20*, 2015). The reagent is easily prepared through treatment of the corresponding chloride with hydrogen peroxide under basic conditions and is isolated as a nonhygroscopic solid that can be stored in the freezer without observable decomposition for over 6 months. The thermal safety evaluation by DSC onset and heat of decomposition compares favorably to those of a range of organic peroxides (in particular *m*-CPBA). Epoxidation reactions were observed to take place under essentially neutral conditions with CH_2Cl_2 as the optimal solvent, with the triazinone byproduct being removed by filtration and easily recycled to the Triazox precursor through treatment with $POCl_3$. Scope-wise, the reagent is capable of successfully epoxidizing a broad range of substrates that had previously been substrates for *m*-CPBA or DMDO, though Triazox did show diminished reactivity compared with the former in mediating the Baeyer−Villiger reaction. The mechanism of epoxidation featuring a "spiro-transition state" is hypothesized to proceed through one similar to that for peracids on the basis of a number of empirical observations, in particular the fact that Triazox reacts faster with electron-rich olefins as well as the solvent-dependent rate of the reaction.

SAFE AND EASY ACCESS TO NONSTABILIZED DIAZOALKANES USING CONTINUOUS FLOW TECHNOLOGY



The full synthetic potential of unstabilized diazo compounds is currently yet to be realized, not only because of their sensitivity, explosivity, and toxicity but also because of their tendency to degrade and the difficulty in obtaining suitably pure material for downstream synthetic purposes. Recognizing these limitations, Charette and co-workers have reported the on-demand synthesis under precisely controlled conditions and facile purification of these highly useful intermediates using continuous flow technology (*Angew. Chem., Int. Ed.* **2018**, DOI: 10.1002/anie.201802092). Despite the ease in handling of the hydrazone precursors for the diazo compounds, their synthesis also introduces problems such as the use of large excesses of hydrazine and high temperatures as well as long reaction times. These issues are shown to be mitigated using continuous flow, wherein the fast heat transfer and the pressurized system allowed the hydrazones to be accessed in sub-20 min reaction times using only a slight excess of hydrazine. After a simple workup, the hydrazones were utilized directly in the oxidation step required to obtain the desired diazo compounds. With the hydrazone derived from acetone as the model substrate, the oxidation was achieved by passing a CH_2Cl_2 solution of the hydrazone through a column packed with silver oxide and potassium carbonate (using Celite as a filler) with careful control of both the residence time and reaction temperature. To avoid dimerization, a concentration of 0.1 M was found to be optimal. These conditions could be applied to a whole range of differentially substituted hydrazones, though tailoring of the residence time and temperature was required for each based on the inherent reactivity of each diazo compound. With the solutions of unstabilized diazo reagents in hand, a range of in-line synthetic transformations of these compounds was demonstrated, including esterification, Michael-induced ring closure, and [3 + 2] cycloadditions as well as the continuous photochemical conversion of these adducts to cyclopropenes. In addition, the safe and convenient large-scale production (and subsequent productive consumption) of an unstabilized diazo compound was demonstrated on an 8.5 mmol scale over a reaction time of 60 min.

FACILE SYNTHESIS OF CHIRAL CYCLIC UREAS VIA HYDROGENATION OF PYRIMIDINES CONTAINING A TAUTOMERIC HYDROXYL GROUP

Cyclic ureas have been established as an important pharmacophore in a range of bioactive molecules, and although a number of asymmetric approaches have recently been developed, typically the classical routes to this structural motif rely on the use of toxic phosgene or related isocyanates. Zhou and co-workers have reported a conceptually simple approach to chiral cyclic ureas through the asymmetric hydrogenation of pyrimidinones that relies on the potential of the nature of the OH group to modulate the hydroxyl−oxo tautomerism and thus weaken the aromatic nature of the system, making it more susceptible to hydrogenation (*Angew. Chem., Int. Ed.* **2018**, DOI: 10.1002/anie.201801485). Using 4-phenylpyrimidin-2-ol as a substrate, model studies

Published: May 8, 2018

DOI: 10.1021/acs.oprd.8b00135
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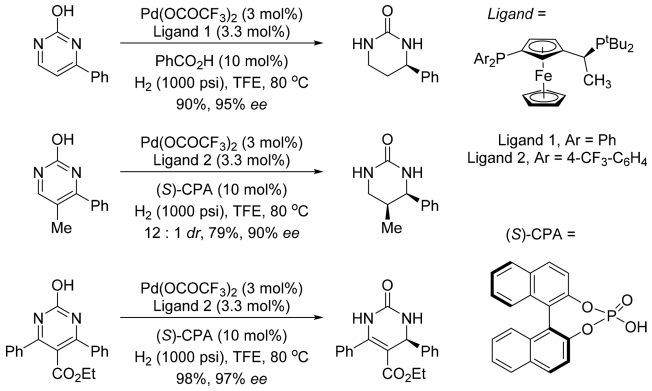
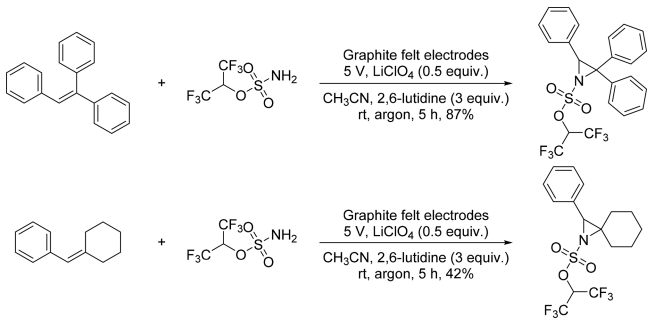


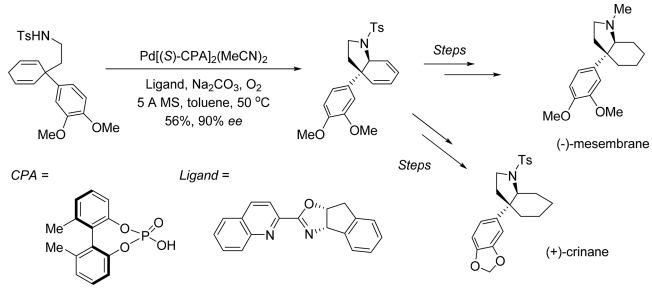
indicated that the reaction showed a remarkable solvent effect with no reaction (1000 psi H_2) taking place in toluene but good conversions being observed in trifluoroethanol (TFE). Optimization of the Brønsted acid (to accelerate the tautomerization in order to activate the substrate), ligand, and palladium source enabled high levels of enantioselectivity (94% ee) to be obtained. A range of 4-substituted pyrimidin-2-ols were successfully hydrogenated under the optimal conditions. Utilizing a stronger Brønsted acid (a chiral phosphoric acid as opposed to benzoic acid—the configuration of the phosphoric acid did not impact the enantioselectivity or absolute configuration of the product) and a slight modification of the ligand enabled disubstituted systems to be effectively hydrogenated, whereas trisubstituted systems furnished the partially hydrogenated 3,4-dihydropyrimidinones. Mechanistic studies involving deuterium labeling suggested that a stepwise process was in operation with hydrogenation of the N1−C6 bond occurring initially, followed by rapid tautomerization and subsequent hydrogenation of the resulting imine. The reaction was further carried out on a gram scale, and conversion of the products to cyclic thioureas and 1,3-diamine derivatives was demonstrated.

ELECTROCHEMICAL AZIRIDINATION VIA ALKENE ACTIVATION WITH A SULFAMATE AS THE NITROGEN SOURCE



Given the versatility of aziridines as reactive building blocks, the direct conversion of olefins to generate this motif under mild conditions is of core interest within organic synthesis. Although significant progress has been made, particularly with the use of nitrenes either under oxidative or electrochemical conditions, triaryl-substituted aziridines remain outside the scope not only because of the need to eliminate the effect of conjugation to obtain the product but also because the steric hindrance of the aryl groups obstructs the approach of the nitrogen source. Inspired by the recent renaissance in the use of electrochemistry, particularly for the formation of C−N bonds, Cheng and co-workers have reported the electrochemical aziridination of triaryl-substituted and multisubstituted styrenes using a sulfamate as the nitrogen source (*Angew. Chem., Int. Ed.* **2018**, DOI: 10.1002/anie.201801106). Model studies on the parent triaryl-substituted alkene using 1,1,1,3,3,3-hexafluoropropan-2-yl sulfamate indicated that the optimal conditions utilized acetonitrile with graphite felt electrodes in an undivided cell with a constant potential of 5 V with $LiClO_4$ as the electrolyte and 2,6-lutidine as the base and provided the aziridine in 87% yield. The conditions were extended to a range of functionalized triaryl substrates as well as tri- and tetrasubstituted styrenes. Mechanistically, the reaction is proposed to proceed through initial electrochemical oxidation of the olefin to provide the radical cation, which is attacked by the sulfamate nucleophile. Base-mediated deprotonation followed by anodic oxidation and ring closure yields the desired aziridine. The reaction was further demonstrated on a gram scale, with the synthetic utility of the aziridine product shown through a series of further transformations.

PALLADIUM-CATALYZED ENANTIOSELECTIVE DESYMMETRIZING AZA-WACKER REACTION: DEVELOPMENT AND APPLICATION TO THE TOTAL SYNTHESIS OF (−)-MESEMBRANE AND (+)-CRINANE



Although the asymmetric Wacker-type cyclization has been developed for the synthesis of chiral nonracemic oxaheterocycles, the corresponding aza-Wacker-type process presents additional challenges, specifically the reversibility and competing nature of the *syn*- and *anti*-aminopalladation steps as well as the incompatibility of many phosphine ligands with the oxidative conditions. Zhu and co-workers have reported the development of an enantioselective desymmetrizing aza-Wacker reaction that exploits a cooperative effect between the catalyst/ligand and a chiral phosphoric acid additive to optimize the yield and enantioselectivity of the process (*Angew. Chem., Int. Ed.* **2018**, *57*, 1995). Initial model studies indicated that a pyrox ligand was the best with an electrophilic source of Pd, though variation of neither the base nor the solvent had much of an effect, and although 81% ee could be obtained, this was offset by a low yield (22%). Evaluation of additives revealed the beneficial effects of chiral phosphoric acids (CPAs), and through a systematic evaluation of counterion effects, the precatalysts with Pd complexed to the CPA were shown to give the optimal results. It is important to note that the configuration of the pyrox ligand determines the absolute configuration, with the matched nature of the CPA leading to an enhancement in both yield and observed ee. A variety of substrates were shown to work well under the optimal conditions, with a range of aryl, functionalized alkyl, and even proton tolerated at C3a. The utility of the transformation was demonstrated by elaboration of one of the reaction products in a divergent fashion to form (−)-mesembrane and (+)-crinane, which are members of the Amaryllidaceae family of alkaloids.

DOI: 10.1021/acs.oprd.8b00135
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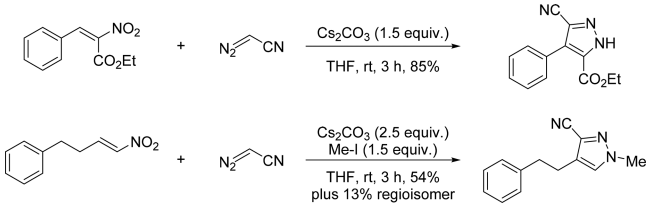
TRANSITION-METAL-FREE [3 + 2] CYCLOADDITION OF NITROOLEFINS AND DIAZOACETONITRILE: A FACILE ACCESS TO MULTISUBSTITUTED CYANOPYRAZOLES



Multisubstituted cyanopyrazoles are not only well-represented in a number of bioactive molecules currently under development but also provide an opportunity for further structural elaboration of a specific molecule through transformation of the nitrile moiety. Although a number of approaches to these molecules have been developed, there are several drawbacks to these, including lengthy synthetic sequences, limited scope, release of toxic substances, or the use of a precious metal. Ma and co-workers have reported a new approach that takes advantage of the [3 + 2] cycloaddition of a nitroolefin (in which the nitro group acts as a traceless directing group) with diazoacetonitrile (*Org. Lett.* **2018**, *20*, 2120). Initial model studies on the reaction between diazoacetonitrile and nitrostyrene demonstrated Cs_2CO_3 to be the optimal base and either THF or DMF to be the best solvent, with the reaction typically proceeding in 1 to 3 h at room temperature. In addition, using 2-aminoacetonitrile hydrochloride/sodium nitrite in a THF/H_2O system allowed the diazo species to be generated in situ. Although this latter protocol used 4 equiv of the hydrochloride salt and led to slightly depressed yields of the cyanopyrazole, this protocol represents a safer approach that mitigates the potential risk associated with the thermally labile diazoacetonitrile. Scope-wise, a range of mono- and disubstituted nitroolefins worked well, and both (hetero)aromatic and aliphatic substituents were well-tolerated. Addition of an alkyl halide to the system enabled a three-component coupling to access predominantly multi-substituted 3-cyanopyrazoles to be realized with modest selectivity (3:1−4:1). Finally, a series of functional group interconversions of the cyano moiety in the products were demonstrated.

OPPORTUNITIES AND CHALLENGES FOR COMBINING CHEMO- AND BIOCATALYSIS

A review of the successes and challenges of combining chemo- and biocatalysis was published by a team from Greifswald University, Novartis, F. Hoffman-La Roche, TU Wien, and Bielefeld University (Rudroff, F.; et al. *Nat. Catal.* **2018**, *1*, 12). The "pros" and "cons" for such possible combinations are presented; the latter include the unavailability of a systematic methodology, high costs, long development timelines, and complicated analytics. Advantages include the possibility of synthesizing molecules that are otherwise difficult or impossible to produce using classical synthetic approaches. Sometimes such advantages can be limited to small-scale synthesis. For current good manufacturing practice operations, an additional challenge is the lack of suitable regulatory guidelines, in particular for biocatalyst impurities (large molecules). Specific technologies are reviewed: transition-metal, organic, and photo/electrochemical catalysis used in combination with biocatalysis. Fit-for-purpose reaction engineering strategies are discussed. This review has 115 references.

NUCLEATION AND GROWTH KINETICS FOR COMBINED COOLING AND ANTISOLVENT CRYSTALLIZATION: ESTIMATING SOLVENT DEPENDENCE

In continuous processing, including continuous crystallization, a gap of a few percentage points between model predictions and actual values for yield and particle size can be significant. The dependence of nucleation and growth phenomena on temperature is better understood than their dependence on solvent composition. This solvent dependence of nucleation and growth kinetics for cooling antisolvent crystallizations was addressed in a recent publication from MIT by the groups of Professors Myerson and Braatz, also associated with the Novartis−MIT Center for Continuous Manufacturing (Schall, J. M.; et al. *Cryst. Growth Des.* **2018**, *18*, 1560). Using population balance modeling, the team was able to describe the growth and nucleation rates as functions of solvent composition, and these models were validated experimentally. The Supporting Information also includes practical comments regarding solubility measurements and FBRM data collection and analysis.

HETEROGENEOUS CRYSTALLIZATION OF FENOFIBRATE ONTO PHARMACEUTICAL EXCIPIENTS

Another interesting example of the use of tablet excipients to control API crystallization was published by a group at the University of Limerick (Bueno, R. A.; et al. *Cryst. Growth Des.* **2018**, *18*, 2151). The model compound was fenofibrate, and the excipients used were α/β-lactose, D-mannitol, microcrystalline cellulose, carboxymethyl cellulose, silica, and polycaprolactone. Nucleation induction times were reduced when fenofibrate crystallization was executed in the presence of such excipients. The mechanistic explanation for such induction time reduction is based on the hydrogen bonds formed between the API and the excipient at stake. Particle size reduction was possible by manipulation of the API loading, temperature, and excipient type and amount. For silica−fenofibrate composites, the dissolution rate achieved was comparable to the dissolution rates of milled commercial fenofibrate. This paper has 53 references.

METHODS FOR DETERMINING CRYSTAL NUCLEATION KINETICS IN SOLUTION

Crystal morphology is determined primarily by the balance between crystal growth and crystal nucleation. Suitable protocols are thus needed for characterizing nucleation and growth kinetics. A team from Tianjin University (Xiao, Y.; et al. *Cryst. Growth Des.* **2018**, *18*, 540) has reviewed five approaches for determining crystal nucleation kinetics in solution: deterministic, droplet, double-pulsed, microfluidic, and stirred small volume methods (as well as certain combinations thereof). Challenges associated with accurate nucleation detection as well as the related metastable zone width measurements are also discussed. The need to account for mixing conditions, especially in nonideally mixed plant reactors, is presented. This review has 98 references.

BATCH, CONTINUOUS, OR "FAKE/FALSE" CONTINUOUS PROCESSES

The ever-increasing amount of attention given to continuous processing by pharmaceutical companies and health authorities has prompted Girish Malhotra to issue a clarification over the use of terminology (*Am. Pharm. Rev.* **2017**, *20* (6), 86). On the basis

DOI: 10.1021/acs.oprd.8b00135
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of chemical engineering principles and his experience of how continuous processing is executed in other industries, the author argues that the term should be reserved for cases where operation is "24/7" with infrequent shutdowns. He uses the descriptor "false" in relation to a "continuous process" where in-process material is held for a significant period of time between unit operations. The processing time required to meet the annual demand for a product is proposed as a yardstick for whether production is better carried out using batch or continuous processing.

ORGANIC ELECTROSYNTHESIS—A ROAD TO GREATER APPLICATION

Derek Pletcher of the University of Southampton has written a mini-review describing what authors contributing to the electrosynthesis literature need to communicate if the potential of "using electrons as reagents" is to be realized by the wider community (*Electrochem. Commun.* **2018**, *88*, 1). Everyone working in the field is implored to provide detailed descriptions of the electrolysis cell used and the associated control parameters, including those that affect the mass transfer regime, so that reported results can be more easily reproduced by others. Authors are asked to highlight why an electrosynthesis is an advantageous way of performing a transformation compared with competing modes of operation. Those working in process-related industries will be pleased by his request for authors to establish whether high conversions actually translate into high yields of isolated product and to demonstrate transformations on polyfunctional substrates that mimic real-world applications rather than simple model compounds. There is also the warning about when an electrosynthetic solution is likely to be the best option: while electrosynthesis can be used to mediate highly selective transformations, it is unlikely to provide selectivity where all viable chemical reagents have failed.

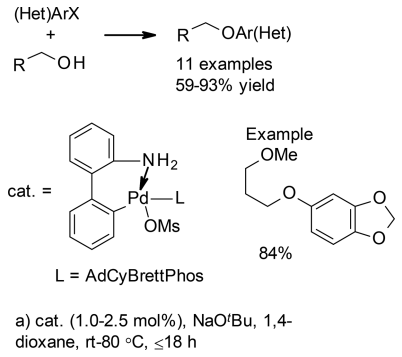
RECOVERY AND RECYCLING OF CHIRAL IRIDIUM(N,P LIGAND) CATALYSTS FROM HYDROGENATION REACTIONS

Catalysts based on iridium continue to prove to be invaluable for the asymmetric hydrogenation of unfunctionalized olefins. The Pfaltz group at the University of Basel have disclosed work on how certain hydrogenation catalysts based on iridium, a platinum-group element with limited availability in the earth's crust, can be recovered and recycled (*Adv. Synth. Catal.* **2018**, *360*, 1340). When the iridium ligand is a phosphinopyridine, the catalyst forms a dimeric Ir(III) dihydride complex once the substrate has been consumed, and the addition of 1,5-cyclooctadiene (COD) regenerates a COD-bearing precatalyst that can be isolated after a filtration through a silica pad and is stable toward oxygen and moisture. While the yield for the recovery is only 60−70%, the recovered catalyst displays the same reactivity and enantioselectivity as the original precatalyst. The procedure does not seem to work, in general, for iridium catalysts that use phosphinooxazoline ligands, as these species irreversibly convert to catalytically inactive iridium clusters once the substrate has been consumed.

IMPURITIES IN OLIGONUCLEOTIDE DRUG SUBSTANCES AND DRUG PRODUCTS

As oligonucleotides are medium-sized molecules, scientific advice for small molecules or biologics is not always appropriate for them. Scientists from a consortium of companies have produced a white paper that argues how impurities in oligonucleotide drug substances (and drug products) arising from side reactions in the manufacturing process and storage should be treated (Capaldi, D.; et al. *Nucleic Acid Ther.* **2017**, DOI: 10.1089/nat.2017.0691). Approaches for impurity reporting, specification limits, impurity identification, and qualification strategies are all proposed. The different structural classes of impurity arising from solid-phase oligonucleotide manufacture, their routes of formation, and examples of each class are tabulated, and the appropriateness of impurity qualification is captured in a decision tree. The authors stress that following their recommendations does not guarantee health authority endorsement.

PALLADIUM-CATALYZED C−O CROSS-COUPLING OF PRIMARY ALCOHOLS



Slow β-hydride elimination as part of the palladium-catalyzed C−O cross-coupling of primary alcohols with (hetero)arene halides means reduction to give the deshalo side product can be problematic. Recent advances in ligand design have gone some way toward addressing this challenge, though electron-rich substrates have hitherto proved a challenge. Now the Buchwald group at MIT have disclosed a method that goes some way to plugging this gap (*Org. Lett.* **2018**, *20*, 1580). The catalyst system provided useful levels of conversion for substrates hindered by the presence of an ortho substituent or primary alcohols with attenuated nucleophilicity. The examples provided do use a 100% molar excess of the alcohol coupling partner: no comment is made as to whether a longer reaction time is the only drawback if a more equimolar ratio of coupling partners is used.

DEOXYFLUORINATION WITH SULFONYL FLUORIDES: NAVIGATING REACTION SPACE WITH MACHINE LEARNING

The combination of a sulfonyl fluoride (e.g., PyFluor) and a base is a common method for the conversion of a primary or secondary alcohol to the corresponding alkyl fluoride. However, because so many reagents have been reported to effect this transformation, a very large number of possible combinations exists. In order to hasten the optimization of these deoxyfluorination reactions, Doyle and co-workers have reported the use of a machine learning approach (*J. Am. Chem. Soc.* **2018**, *140*, 5004). An initial screen of five sulfonyl fluorides with four bases on four alcohol substrates gave a complex data set that defied simple interpretation; no one combination was universally effective, indicating the value in an algorithm with predictive power for these reactions. In order to provide a training set, a diverse set of 32 alcohols was subjected to 20 different deoxyfluorination reaction conditions for a total of 640 data points. A random forest model was then trained using these data along with a number of substrate descriptors such as computed atomic and molecular properties as well as binary categorical identifiers

DOI: 10.1021/acs.oprd.8b00135
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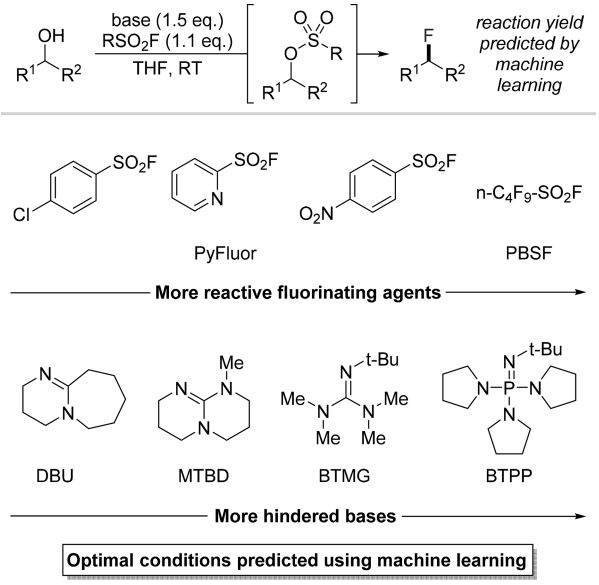
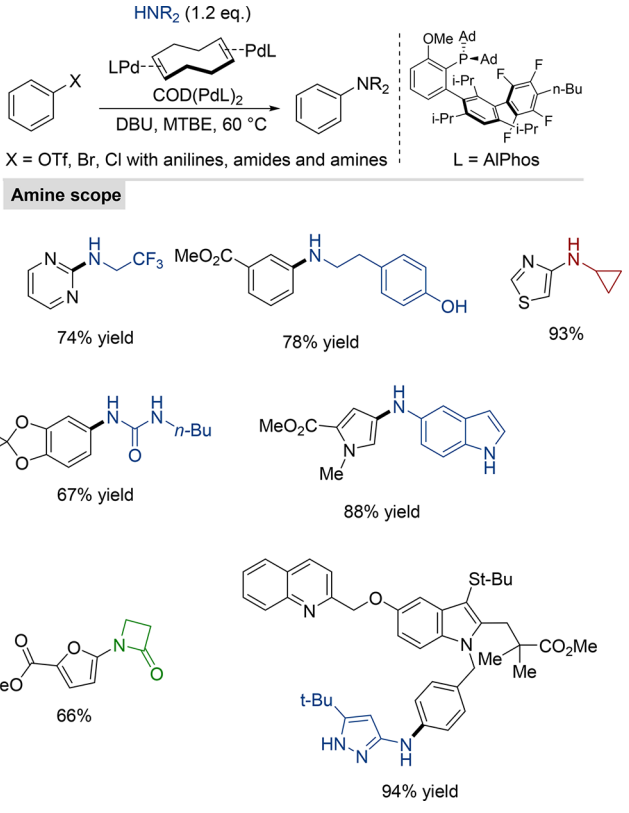
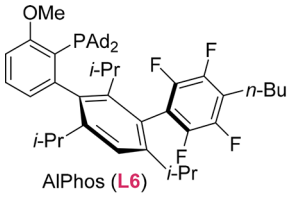


(i.e., primary, secondary, tertiary, cyclic). Despite a relatively small training set, high substrate diversity, and multiple possible reaction mechanisms, good predictive power was observed, even for compounds absent from the original training set. This machine learning approach could have a significant impact on the design of deoxyfluorination reactions, as well as reaction optimization in general, and will no doubt become more common in the future.

BREAKING THE BASE BARRIER: AN ELECTRON-DEFICIENT PALLADIUM CATALYST ENABLES THE USE OF A COMMON SOLUBLE BASE IN C–N COUPLING



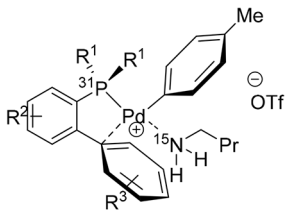
Because of the low acidity of many nitrogen nucleophiles, palladium-mediated amination reactions have often required the use of strong inorganic or insoluble bases, usually under conditions tailored to the specific reaction partners chosen. In contrast, a recent publication from Buchwald and co-workers reports that the use of a palladium precatalyst based on the monophosphine ligand AlPhos enables C–N coupling under mild, general conditions using the common organic base DBU (*J. Am. Chem. Soc.* **2018**, *140*, 4721). The reaction conditions were shown to be highly general, tolerating triflates, bromides, and some chlorides as the electrophilic components and a range of anilines, hetroarylamines, amides, ureas, and even primary amines as the nucleophiles. A number of highly challenging and base-sensitive substrates were also demonstrated as coupling partners, including the volatile and unstable trifluoroethylamine. Furthermore, the reaction can be run at relatively high concentrations (1 M) in MTBE at 60 °C (or lower) using only a small excess of the amine—making it much more attractive for process use than typical Buchwald–Hartwig-type conditions. The team found evidence via heteronuclear NMR studies using ^{15}N-labeled amine complexes that the cationic palladium center increases the acidity of the bound amine, which allows easy deprotonation by a weak amine base:



Precatalyst

[(L6-Pd)$_2$(COD)]

COD = 1,5-cyclooctadiene

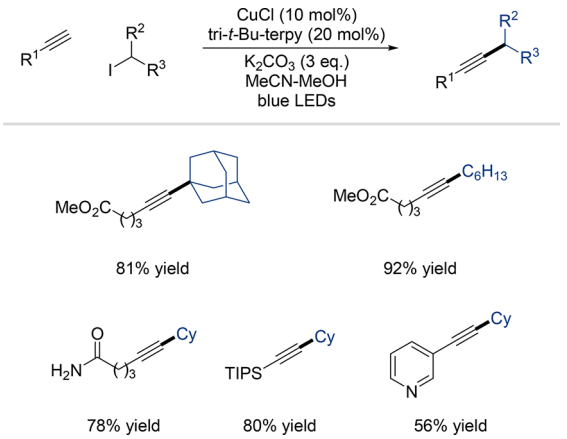


^2J (^{31}P-^{15}N) for L6 = -34.2 Hz

[Indicating that amine-L6-Pd complexes are easily deprotonated]

This report may help provide easy access to Buchwald–Hartwig amination reactions that were unattainable or lower-yielding because of the use of inorganic bases.

PHOTOINDUCED COPPER-CATALYZED COUPLING OF TERMINAL ALKYNES AND ALKYL IODIDES



Although alkynes are far from common in drug molecules, numerous important examples do exist, and the alkyne group itself is a useful intermediate functional group with broad reactivity. Unfortunately, the introduction of this functional group is often not straightforward on scale, as beyond Sonogashira reactions and acetylide additions to carbonyls, few process-friendly options exist. An interesting new methodology that couples simple terminal alkynes with alkyl iodides under copper catalysis with the assistance of visible light was recently reported by Lalic and co-workers (*Angew. Chem., Int. Ed.* **2018**, *57*, 5492).

DOI: 10.1021/acs.oprd.8b00135
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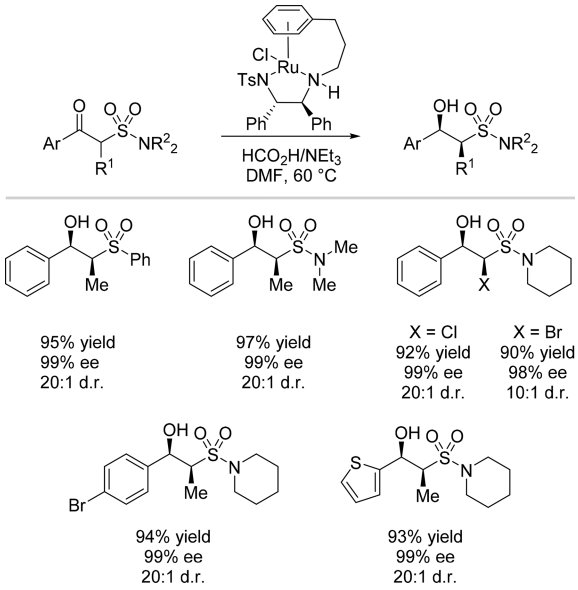
The reaction proceeds at room temperature using simple a Cu(I)−terpyridine catalyst under blue-light irradiation, and primary, secondary, and some tertiary halides are all competent coupling partners. The ability to use common, unfunctionalized alkynes is a clear advantage over many existing methods, although the requirement of an alkyl iodide as the coupling partner may make the reaction unappealing in a process setting.

HIGHLY ENANTIOSELECTIVE TRANSFER HYDROGENATION OF RACEMIC α-SUBSTITUTED β-KETO SULFONAMIDES



A dynamic kinetic resolution approach to β-keto sulfonamides using ruthenium-catalyzed transfer hydrogenation was recently reported by Zhang et al. (*Chem. Commun.* **2018**, *54*, 3883). The reaction proceeds with excellent levels of diastereo- and enantioselectivity at slightly elevated temperatures to deliver the syn products in near-quantitative yield. Although the substrate scope is quite limited and a β-aryl group seems to be required, some variation around the sulfonamide is demonstrated, and the functional group tolerance—including alkyl and aryl halides—is high. The reaction can be performed on a gram scale using as little as a 0.5 mol % loading of a commercially available ruthenium catalyst.

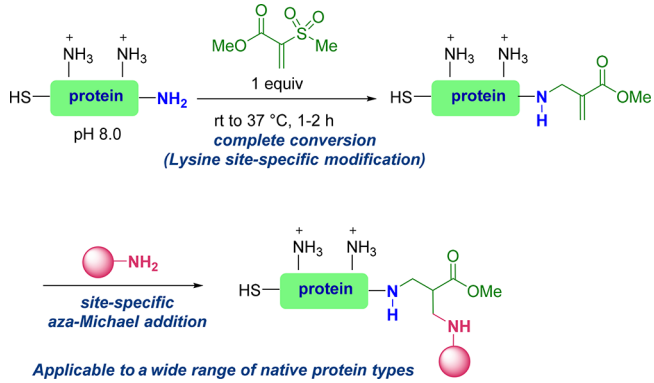
IRON-CATALYZED CROSS-COUPLING IN THE SYNTHESIS OF PHARMACEUTICALS: IN PURSUIT OF SUSTAINABILITY

The use of iron catalysis in the synthesis of pharmaceuticals has obvious advantages over existing methods; the low toxicity, low cost, and high abundance of this metal are almost unequaled. Furthermore, iron is one of the few base metals that has already been used to catalytically effect cross-coupling reactions on a multikilogram scale. A review (Piontek, A.; et al. *Angew. Chem., Int. Ed.* **2018**, DOI: 10.1002/anie.201800364) contains a sizable section on the large-scale use of iron-based cross-coupling reactions in process development (in addition to discussion of the importance of these reactions in medicinal chemistry and sustainable methodology design). The examples chosen from across the pharmaceutical industry will no doubt be of interest to process chemists seeking to learn about the use of base-metal catalysis for API synthesis. This review contains 76 references.

VISIBLE-LIGHT PHOTOCATALYSIS: DOES IT MAKE A DIFFERENCE IN ORGANIC SYNTHESIS?

One of the hottest research topics in organic synthesis in recent years—as indicated by the sheer number of high-impact publications generated by the field—has been photoredox catalysis. As a result, numerous reviews of this area have been published that attempt to summarize new developments. However, because of the difficulties of implementing these reactions on scale, it is important to identify not only what is possible under this paradigm but especially the areas where photoredox catalysis offers a decisive advantage over existing methods. The review from Reiser, König, and colleagues (*Angew. Chem., Int. Ed.* **2018**, DOI: 10.1002/anie.201709766) attempts to answer this question by comparing classic methods for various classes of bond-forming reactions with their newer photoredox alternatives. This will perhaps help chemists engaged in synthesis judge when the use of photoredox methodology over more established alternatives is justified. The review contains 315 references.

CHEMO- AND REGIOSELECTIVE LYSINE MODIFICATION ON NATIVE PROTEINS



Ready access to enzymes and the ability to engineer these enzymes to meet the demands of industrial processes has given rise to remarkable improvements in stereo- and/or regioselectivity, generating large quantities for practical applications, wider substrate scope, and so forth. Jiménez-Osés, Bernardes, and co-workers have disclosed a chemo- and regioselective lysine modification on native proteins that resulted in a simple and robust protocol for accessing diverse, well-defined protein conjugates for possibly a wide range of applications (*J. Am. Chem. Soc.* **2018**, *140*, 4004). In addition, the method does not require any genetic engineering but could potentially be combined with other bioconjugation chemistries to access various functionalities. The team capitalized on the computer-assisted design of a sulfonyl acrylate reagent, which allowed the more abundant lysine residues with ionic character that enables them to be found on protein surfaces, to selectively and completely react with lysine in 1−2 h under mild conditions (room temperature and pH 8.0). Further modification using an amine nucleophile gave an aza-Michael addition product. This report may facilitate the routine use of proteins in basic biological research and industrial applications for a variety of proteins in their native states.

SYSTEMATIC EVALUATION OF 2-ARYLAZOCARBOXYLATES AND 2-ARYLAZOCARBOXAMIDES AS MITSUNOBU REAGENTS

Taniguchi and co-workers have reported the systematic evaluation of novel 2-arylazocarboxylates and 2-arylazocarboxamides as

DOI: 10.1021/acs.oprd.8b00135
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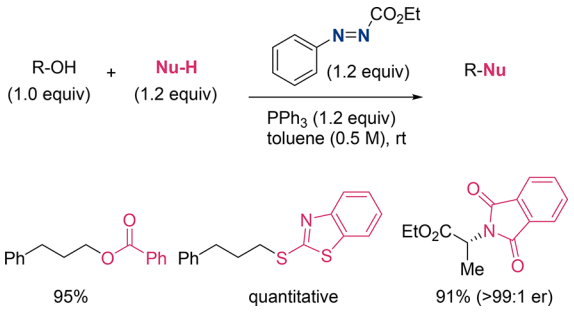
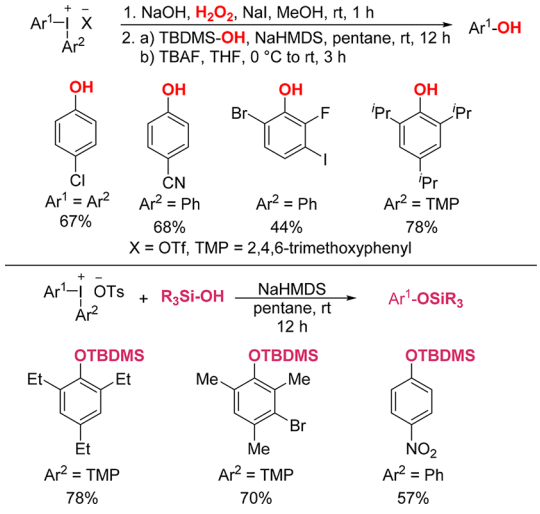


Mitsunobu reagents that showed similar or superior reactivity to the present Mitsunobu reagents such as diethyl azodicarboxylate (*J. Org. Chem.* **2018**, *83*, 4712). The team highlights the thermal stability, reactivity, substrate scope, and recyclability of the disclosed reagents. In addition, the less reactive weakly acidic alcohol substrates gave modest yields of the corresponding products. Although the reported protocol is not compatible with sterically hindered substrates, this report could encourage complementary effort to improve the reactivity and substrate scope of the methodology.

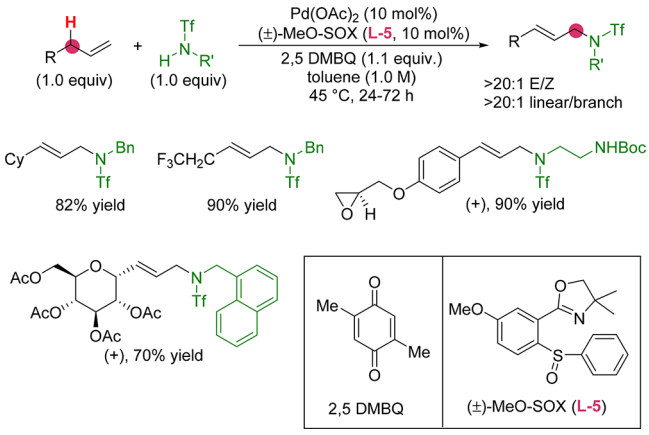
SYNTHESIS OF PHENOLS AND ARYL SILYL ETHERS VIA ARYLATION OF COMPLEMENTARY HYDROXIDE SURROGATES



Phenols and their derivatives are very important building blocks in synthetic, pharmaceutical, and materials sciences. There have been many transition-metal-catalyzed reactions but comparatively few metal-free synthetic protocols. A report by Olofsson and co-workers at the Stockholm University describes two complementary transition-metal-free protocols for the synthesis of substituted phenols that afforded a wide range of phenols with minimal side reactions (*Org. Lett.* **2018**, *20*, 1785). The first protocol involves in situ desilylation using TBAF, which cleaves the Si–O bond and reveals the phenol. The second protocol affords silyl aryl ethers, which help in the stabilization and isolation of very reactive product such as the 4-OMe-substituted one. In addition, both protocols tolerate highly congested substrates and give the corresponding products in good yields. The synthetic utility was demonstrated with the synthesis of propofol, an anesthetic drug.

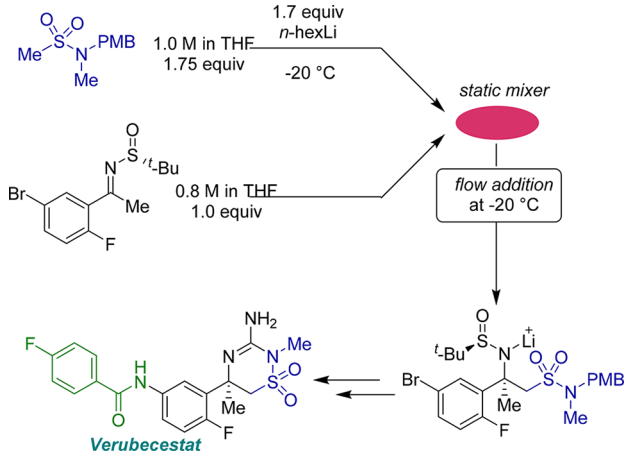
C–H TO C–N CROSS-COUPLING OF SULFONAMIDES WITH OLEFINS

In spite of the ubiquitous nature of aliphatic amines in the pharmaceutical and agrochemical industries, their efficient



synthesis still remains challenging. Ma and White at the University of Illinois (*J. Am. Chem. Soc.* **2018**, *140*, 3202) have reported the discovery of a novel Pd(II)/(±)-MeO-SOX-catalyzed allylic C–H amination reaction that affords allylic amines in good yields with excellent regioselectivities. In addition, the reaction is amenable to electrophilic functionalities such as amides, esters, ketones, terminal epoxides, and so forth. The team also demonstrated late-stage allylic C–H amination for biologically active pharmaceutical compounds in high yields. The report displayed evidence of the unique features of the SOX ligand, which chelates and stabilizes cationic π-allyl–Pd intermediates and facilitates functionalization.

A NEXT-GENERATION SYNTHESIS OF THE BACE1 INHIBITOR VERUBECESTAT (MK-8931)



Alzheimer's disease is one of the formidable diseases in the modern era. Despite tremendous efforts for a cure or symptomatic relief, to date the outcomes have dismal success. However, the synthetic efforts geared toward therapeutic treatments have seen tremendous synthetic successes. In a collaborative work between researchers at Merck & Co. and WuXi AppTec Pharmaceutical Co. (Thaisrivongs, D. A.; et al. *Org. Lett.* **2018**, *20*, 1568), the third-generation commercial manufacturing route for the synthesis of the BACE I inhibitor verubecestat has been developed. Key aspects of this successful synthesis are the use of continuous flow chemistry, the identification of new chiral salt that enables favorable isolation conditions (98.5% yield, 99.9% purity, and 98.8% ee), and the discovery of a novel C–N coupling. In addition, there are cost and waste reductions that add economic value to the developed synthetic route.

DOI: 10.1021/acs.oprd.8b00135
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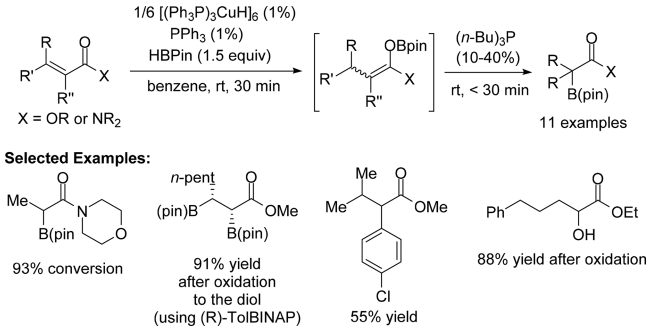
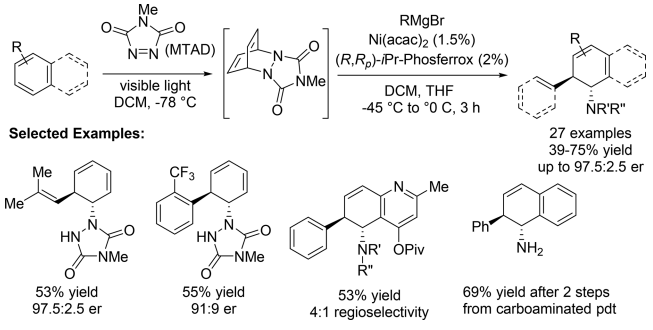
SYNTHESIS AND APPLICATIONS OF UNQUATERNIZED C-BOUND BORON ENOLATES



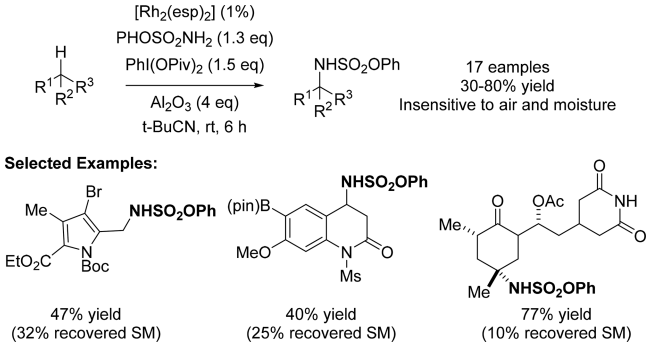
Because of the strength of the B−O bond and the empty p orbital on boron, boron enolates generally exist as the O-bound isomers opposed to the C-bound isomers. Chiu and co-workers at the University of Hong Kong have demonstrated the first general synthesis of unquaternized C-bound boron enolates and their utility as useful synthetic intermediates (*J. Am. Chem. Soc.* **2018**, *140*, 3537). Catalyzed by copper hydride (Stryker's reagent), with pinacolborane as the stoichiometric reductant, the expected O-bound boron enolates are formed from α,β-unsaturated esters and amides. Upon addition of a basic phosphine ($P(n\text{-}Bu)_3$), a Cu-catalyzed O-to-C isomerization occurs to provide the C-bound boron enolate. While C-bound boron enolates are prone to protodeboronation, anhydrous cross-coupling or oxidation conditions can be used to form new α-C−C and α-C−O bonds.

NICKEL-CATALYZED DEAROMATIVE *TRANS*-1,2-CARBOAMINATION



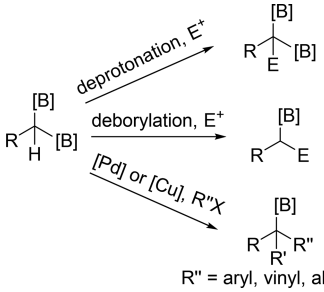
Sarlah and co-workers have described the first general dearomative 1,2-carboamination of arenes, providing an alternative method for the rapid construction of functionalized small molecules (*J. Am. Chem. Soc.* **2018**, *140*, 4503). The strategy first involves a photochemical dearomative cycloaddition of benzene, substituted benzenes, or substituted naphthalenes with *N*-methyl-1,2,4-triazoline-3,5-dione (MTAD) at low temperature. MTAD is a powerful electrophile that can be synthesized in a couple of steps and is the nitrogen source for the carboamination. With low catalyst loadings of cheap, air-stable nickel(II) catalysts, the MTAD−arene cycloadduct can be ring-opened with aryl or vinyl Grignard reagents, providing *trans*-1,2-carboamination products with excellent selectivities. High enantioselectivities for the carboamination of benzene and naphthalene are achieved using *i*Pr-Phosferrox as the ligand. Substituted arenes are not amenable to the enantioselective conditions and require Ni(0) catalysis but provide *trans*-1,2-carboaminated products with generally high site selectivity. The dearomatization products contain several modifiable functional groups for further elaboration. The urazole moiety can be easily converted to amine or oxygen functionality or completely removed via Birch reduction.

INTERMOLECULAR C(SP^3)−H AMINATION OF COMPLEX MOLECULES



Despite the impressive advancements of intermolecular C−H amination methodologies, most of these processes often fail to perform adequately on densely functionalized polar substrates. Du Bois and co-workers at Stanford University have described improvements in previously described reaction conditions for Rh-catalyzed C−H amination of C(sp^3)−H bonds, improving the catalyst efficiency to allow limiting quantities of substrate, low catalyst loadings, and unprecedented reaction scope (*Angew. Chem., Int. Ed.* **2018**, *57*, 4956). To expand this C−H amination to more polar nitrogen-rich substrates, several common polar solvents were screened. The breakthrough occurred when *t*-BuCN or PhCN was used as the solvent. Good conversions were also observed using those solvents as a mixture with IPAc. Studies using deuterated solvents demonstrated that solvent oxidation when MeCN or DCM was used was deleterious to catalyst stability and reaction turnover, explaining the improved results using *t*-BuCN. Phenyl sulfamate was selected as the nitrogen source because of its ease of synthesis and the stability of the sulfonamidated products toward chromatography. The sulfonamidated products can be unmasked to give the primary amines by heating with pyridine in aqueous MeCN. Excellent selectivity is observed for oxidation of benzylic and tertiary C−H bonds, and generally only the product and recovered starting material are observed.

SYNTHESIS AND REACTIVITY OF 1,1-DIBORYLALKANES TOWARD C−C BOND FORMATION AND RELATED MECHANISMS



Fernández and co-workers at Universitat Rovira i Virgili have written an excellent review on the synthesis and reactivity of 1,1-diborylalkanes, which have emerged in the past decade because of their stability, ease of handling, and diverse synthetic utility (*Adv. Synth. Catal.* **2018**, *360*, 1306). The review first discusses the various ways to prepare 1,1-diboryalkanes, including hydroboration, diboration, C−H activation, and carbene insertion.

DOI: 10.1021/acs.oprd.8b00135
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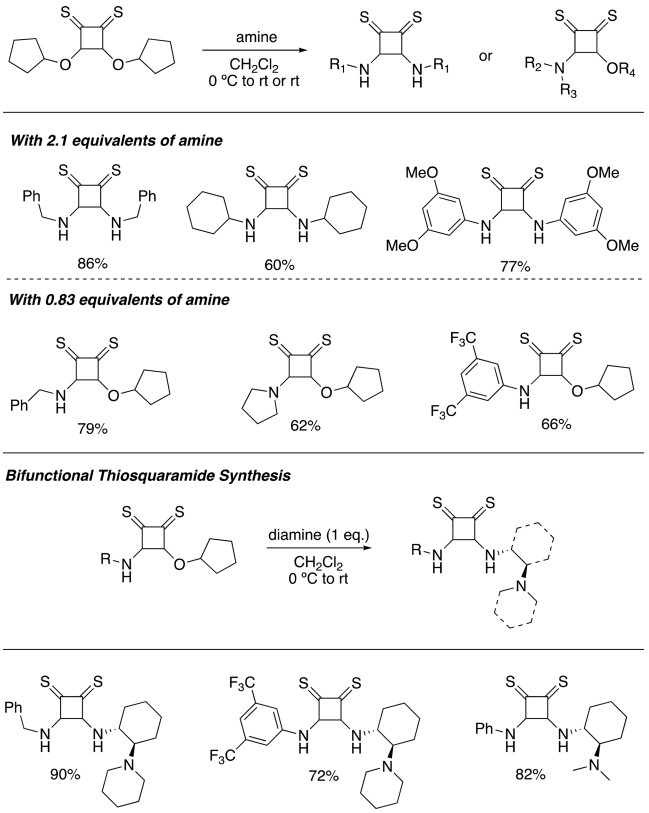
The reactivity of these reagents is then discussed, including activation of 1,1-diborylalkanes with catalysts to form new C−C(B) bonds with chemo-, diastereo-, and enantioselectivity. Additionally, these reagents can generate carbanions with enhanced stability that can react as nucleophiles with carbonyl compounds, imines, and epoxides.

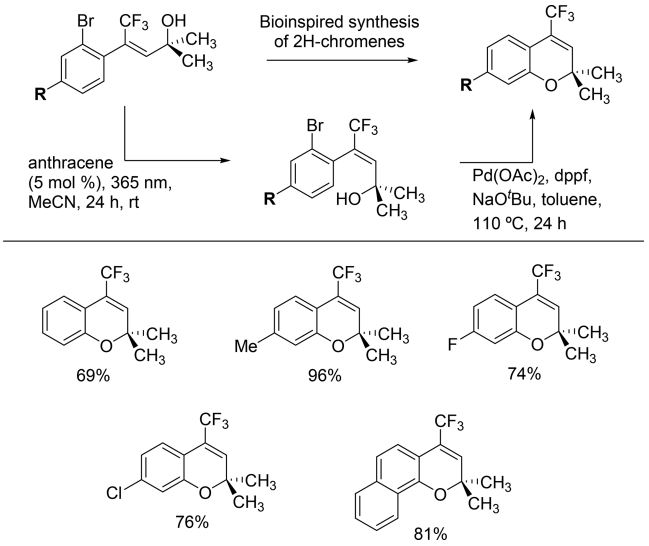
SYNTHESIS OF THIOSQUARAMIDES



The Rawal group (University of Chicago) have recently disclosed their findings on the synthesis of thiosquaramides (*Org. Lett.* **2018**, *20*, 514) via addition−elimination reactions of dicyclopentyl dithiosquarates. The researchers show that under mild reaction conditions, a range of amines can be added to dicyclopentyl dithiosquarates to yield either di- or monodisplaced products depending on the amount of amine added. They show that both primary and secondary amines perform well in the transformation. Isolated yields of monosubstituted squaramides reached 79%, while those of disubstituted products reached 86%. In the later part of the research, the group used the monosubstituted squaramides as intermediates to access chiral bifunctional thiosquaramides—when coupled with 1 equiv of chiral diamine, seven chiral thiosquaramides were accessed in yields of up to 96%. The chiral bifunctional thiosquaramides were evaluated as catalysts in a conjugate addition reaction between lawsone and a β/γ-unsaturated α-keto ester; all of the catalysts were shown to afford higher enantioselectivities than the corresponding oxosquaramide analogues by 10−20% ee.

BIOINSPIRED ROUTE TO 4-TRIFLUOROMETHYL-2*H*-CHROMENES

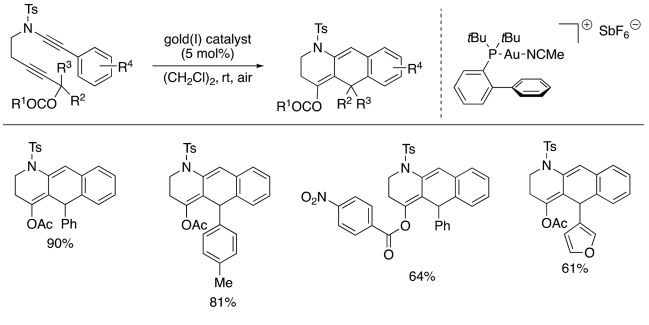
The Gilmour research group (Westfälische Wilhelms-Universität Münster in Germany) have showcased a bioinspired route toward the synthesis of pharmaceutically relevant fluorinated



chromene products (*Org. Lett.* **2018**, *20*, 724). The method utilizes an initial photocatalytic isomerization (5 mol % anthracene, 365 nm, MeCN, 24 h, rt) of the allylic alcohol followed by a palladium-catalyzed intramolecular cyclization ($Pd(OAc)_2$, dppf, NaO^tBu, toluene, 110 °C, 24 h) to afford the desired chromenes. The isomerization step was shown to work exceptionally well (*E*:*Z* > 95:5, up to quantitative yields), while the intramolecular cyclization afforded the final product in yields of up to 96%. The CF_3 moiety was found to suppress the photochemical degradation pathways of allylic alcohols, providing a direct route to desirable fluorinated, medicinally relevant 2*H*-chromenes.

SYNTHESIS OF 1,2,3,5-TETRAHYDROBENZO[*G*]QUINOLINES

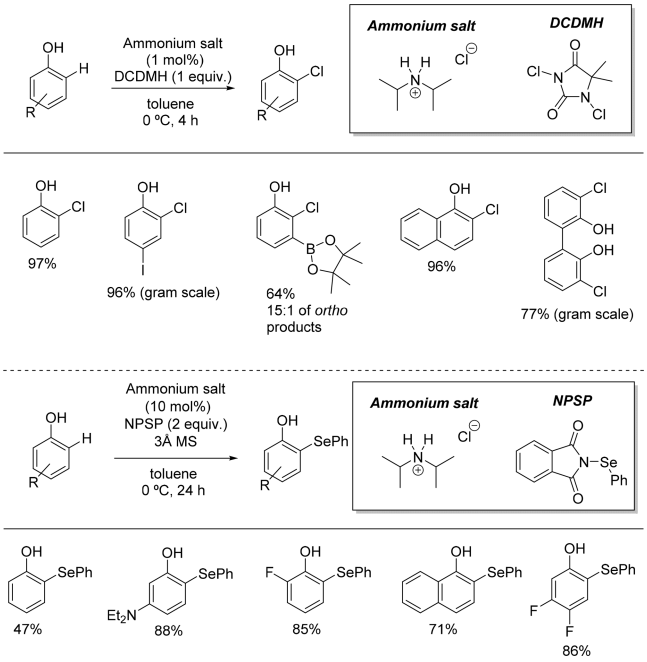
The Chan group (Monash University and the University of Warwick) have recently reported an efficient gold(I)-catalyzed cycloisomerization of 5-(ethynylamino)pent-2-yn-1-yl esters to 1,2,3,5-tetrahydrobenzo[*g*]quinolines (*Org. Lett.* **2018**, *20*, 1542). The transformation benefits from utilizing low catalyst loadings of the gold(I) catalyst while reacting at ambient temperature without requiring inert conditions. Over 20 examples were reported, and yields of up to 90% were achieved. The reaction tolerates modification at three key points in the dialkynyl starting material. First, the OAc migrating group could be replaced with an OPNB or OPMB group without significant erosion in product yield. Next, the substituents R^2 and R^3 at the ester carbon could be modified to incorporate a range of alkyl, aryl, or heteroaryl moieties, and finally, electron-withdrawing or -donating substituents attached to the aryl ring (R^4) were well-tolerated too. The authors provide mechanistic evidence to support a proposed [4 + 2] cycloaddition process between an in situ allenic ester and gold keteniminium species.



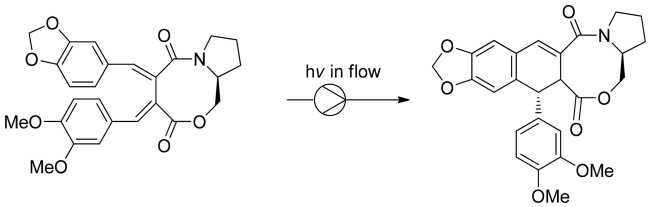
DOI: 10.1021/acs.oprd.8b00135
Org. Process Res. Dev. 2018, 22, 563−573

AMMONIUM-SALT-CATALYZED ORTHO-SELECTIVE MONOHALOGENATION AND PHENYLSELENATION

The Yeung group (The Chinese University of Hong Kong) have used an ammonium salt (at low catalyst loadings) in combination with 1,3-dichloro-5,5-dimethylhydantoin to effect the ortho-selective chlorination of phenols (*ACS Catal.* **2018**, *8*, 4033). In the latter part of the research, the same ammonium salt was utilized in combination with *N*-(phenylseleno)phthalimide to promote ortho-selective selenylation. The ammonium salts work at low catalyst loadings under mild reaction conditions and have been shown to tolerate naphthols and BINOLs as well as phenols containing a range of both electron-withdrawing and -donating substituents at various positions on the ring system (75 examples were reported in total). The methodology is not air-sensitive and affords products with high regioselectivity. A number of key examples were conducted on a gram scale without a noticeable loss in reaction yield.

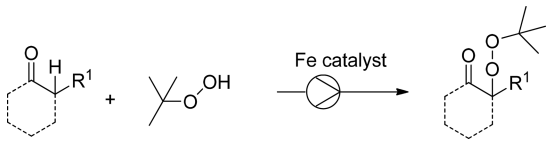


TOTAL SYNTHESIS OF (+)-EPIGALCATIN VIA FLOW PHOTOREACTION



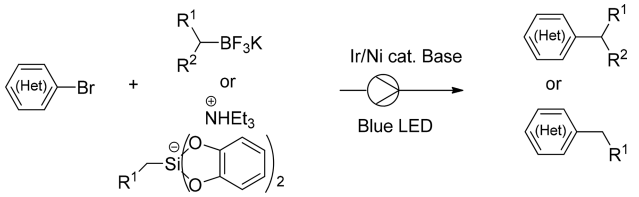
The first highly stereoselective total synthesis of (+)-epigalcatin, from piperonal in 11 steps in 5% overall yield using L-prolinol as the source of chirality, was reported by the Czarnocki group at the University of Warsaw (*Org. Lett.* **2018**, *20*, 605). As shown in the graphic, a continuous photocyclization was a crucial step of the synthesis, constructing the cyclolignan framework starting from a chiral atropisomeric 1,2-bis(benzylidenesuccinate) amide ester. This work also demonstrated that the phenyl group at C1 influenced the configuration at C3 during hydrogenation of the double bond in 1-aryldihydronaphthalene lignans. This methodology highlights two key points: (1) the advantages of a continuous process over batch photoreaction and (2) the commercially cheaper starting material compared with the synthesis of (+)-galcatin from the natural compound chicanine.

IRON-CATALYZED CONTINUOUS C–H FUNCTIONALIZATION TOWARD ANTICANCER PEROXIDES



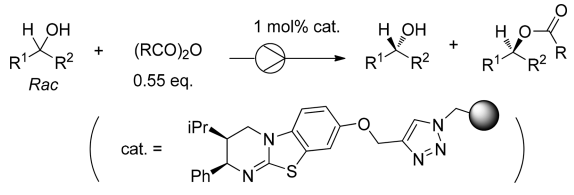
A flow iron-catalyzed dehydrogenative cross-coupling of carbonyl compounds with aliphatic peroxide under mild conditions was developed recently by Gnanaprakasam and co-workers (*J. Org. Chem.* **2018**, *83*, 1358). The methodology gave high selectivity and up to 96% yield of linear alkylated and arylated peroxides (>25 examples), affording a broad scope of biologically important derivatives of 2-oxindole, barbituric acid, and 4-hydroxycoumarin, with good functional group tolerance and without the cleavage of the peroxide bond. This peroxidation reaction was demonstrated at gram scale in continuous flow with increased safety in short duration. According to the mechanism study, Fe(II) underwent a redox-type process to generate radical intermediates, which subsequently recombined selectively to form the stable peroxides. In addition, the Pybox ligand was highly efficient for forming the peroxylated product.

CONTINUOUS PHOTOREDOX COUPLING OF ORGANOTRIFLUOROBORATES AND ORGANOSILICATES WITH HETEROARYL/ARYL BROMIDES



A continuous photoredox $C(sp^3)–C(sp^2)$ coupling of aryl halides with both trifluoroborates and silicate reagents toward the synthesis of diverse product sets was developed by Boyd and co-workers (*J. Org. Chem.* **2018**, *83*, 1551). Both primary and secondary coupling partners could be applied in this transformation, although previously it was inefficient for the coupling of unactivated primary trifluoroborates. This easily scalable procedure proved to be efficient for producing a greater range of analogues bearing a high sp^3 fraction by widening the substrate scope of the coupling reaction compared with the batch process.

A RECYCLABLE POLYMER-SUPPORTED ISOTHIOUREA CATALYST FOR ACYLATIVE KINETIC RESOLUTION OF ALCOHOLS IN FLOW



A flow acylative kinetic resolution of a wide range of secondary alcohols via a polystyrene-supported isothiourea catalyst was

DOI: 10.1021/acs.oprd.8b00135
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successfully developed recently by Pericàs, Smith, and co-workers as the first example of an immobilized Lewis base catalyst used for the kinetic resolution of alcohols, including benzylic, allylic, and propargylic alcohols, cycloalkanol derivatives, and a 1,2-diol (*ACS Catal.* **2018**, *8*, 1067). The heterogeneous catalyst, which was based on its homogeneous counterpart HyperBTM, could resolve 28 examples using either propionic or isobutyric anhydride with good to excellent selectivity factors (*s* values of up to 600). The catalyst could be recovered and reused by a simple filtration and washing sequence, and the recyclability of the catalyst was demonstrated (15 cycles) with no significant loss in either activity or selectivity. In addition, this recyclable catalyst could also be used for the sequential resolution of 10 different alcohols using different anhydrides with no cross-contamination between cycles.

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DOI: 10.1021/acs.oprd.8b00135
Org. Process Res. Dev. 2018, 22, 563−573