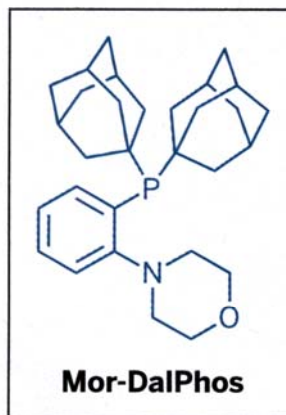


P,N LIGAND ADVANCES AMMONIA COUPLING

Palladium-catalyzed cross-coupling of aryl halides and amines, known as Buchwald-Hartwig amination, is a key tool for constructing arylamines in organic synthesis. In the latest twist on this reaction, Mark Stradiotto and coworkers at Dalhousie University, in Halifax, Nova Scotia, report a new ligand that enables chemists to selectively react ammonia—the simplest and most abundant N–H source—with a broad range of aryl halides and tosylates at room temperature (*Angew. Chem. Int. Ed.*, DOI: 10.1002/anie.201000526). The chelating P,N ligand, which the team calls Mor-DalPhos, consists of an adamantyl-substituted phosphorus and a morpholine-substituted nitrogen bridged by phenylene. The team previously prepared a dimethyl version of the ligand, called Me-DalPhos, which is handy for traditional amine couplings (*Chem. Eur. J.* 2010, 16, 1983). Both Mor-DalPhos and Me-DalPhos are in demand by pharmaceutical companies,



Stradiotto says. His group has made batches of the ligands that are already being sold by Strem Chemicals. The reactivity and selectivity of Mor-DalPhos with ammonia at room temperature “is remarkable,” says John F. Hartwig of the University of Illinois, Urbana-Champaign. Stradiotto’s group has found a ligand “sweet spot” for C–N coupling between tightly bound bidentate bisphosphines and labile hindered monodentate phosphines, Hartwig notes.—SR

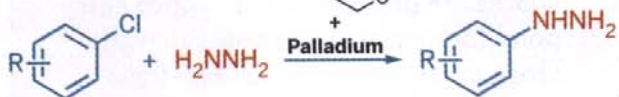
Chemical and Engineering News
2010, 88(21), 32.

COUPLING HYDRAZINE

ORGANIC SYNTHESIS: Palladium-catalyzed reaction offers new route to heterocycles

HYDRAZINE HOOKUP

An electron-rich Mor-DalPhos ligand helps palladium couple aryl chlorides and hydrazine



FOR THE first time, chemists have managed to use palladium cross-coupling chemistry to wed aryl groups with hydrazine (*Angew. Chem. Int. Ed.*, DOI: 10.1002/anie.201003764). The resulting aryl hydrazines are useful intermediates en route to nitrogen-containing heterocycles, such as indoles and pyrazoles.

The coupling reaction, developed by chemistry professor Mark Stradiotto and graduate student Rylan J. Lundgren of Dalhousie University, in Nova Scotia, proceeds in moderate to good yields and short reaction times with mild heating. Because hydrazine is a powerful reductant—and is therefore likely to react with

both the Pd catalyst and the aryl chloride or aryl tosylate substrate—the transformation relies on electron-rich ligands that circumvent these unwanted side reactions, such as the morpholine-based compound Mor-DalPhos.

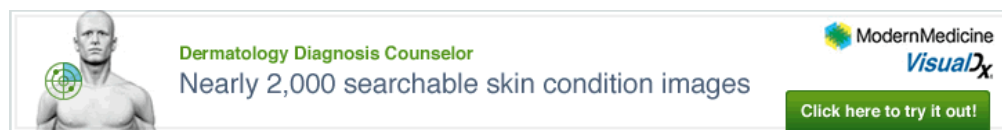
“We are still in the process of understanding what

makes the Mor-DalPhos ligand such a good ligand for hydrazine cross-coupling,” Stradiotto tells C&EN. “It is a sterically demanding, bidentate ligand, which may help the selectivity of the reaction. The bidentate ligand framework may also help in maintaining a monomeric catalyst species, preventing catalyst decomposition steps, as well as in promoting C–N reductive elimination.”

Although some risk of explosion is associated with heating hydrazine and palladium, Stradiotto says that using hydrazine hydrate rather than anhydrous hydrazine can mitigate the hazard. “We didn’t encounter any difficulties on the scales we performed our reactions [50 mg to 2 g],” he adds, “but it is hard to comment on the potential hazards of the reaction on larger scales.”

“It is certainly a surprise that one can conduct the direct coupling of hydrazine, given how commonly this reagent acts as a reducing agent for the synthesis of Pd(0) complexes,” comments University of Illinois, Urbana-Champaign, chemistry professor John F. Hartwig. “I would have thought one would always have to tame this reagent by conducting the synthesis of N-aryl hydrazines indirectly through hydrazone derivatives.”

John P. Wolfe, a chemistry professor at the University of Michigan, adds, “This work further illustrates that heteroatom nucleophilicity plays a key role in selective Pd-catalyzed carbon-heteroatom bond-forming processes and that relatively small perturbations of ligand structure can have a large impact on catalyst reactivity and selectivity.”—BETHANY HALFORD



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Advances in Small-Molecule Synthesis

Approaches in cyclization, palladium-catalyzed cross couplings, fluorination, and natural product synthesis help to optimize routes for select drugs.

Publish date: Dec 2, 2010
By: Patricia Van Arnum

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**Pharmaceutical
Technology**

Coupling reactions

Palladium-catalyzed coupling. Palladium-catalyzed cross-coupling, in which the metal is used to catalyze the formation of carbon-carbon bonds, is an important reaction in organic synthesis, particularly for complex molecules such as pharmaceutical compounds. The importance of these reactions was underscored by the awarding of the 2010 Nobel Prize for Chemistry to Richard F. Heck, Professor Emeritus at the University of Delaware in Newark, Ei-ichi Negishi, the Herbert C. Brown Distinguished Professor of Chemistry at Purdue University in West Lafayette, Indiana, and Akira Suzuki, Distinguished Professor Emeritus at Hokkaido University in Sapporo, Japan, for the development of palladium-catalyzed cross coupling.

The Heck reaction is a palladium-catalyzed cross coupling of organyl halides with olefins. The Negishi reaction is a palladium-catalyzed cross coupling of organozinc compounds with organohalides. Suzuki coupling is a palladium-catalyzed coupling between organoboron compounds and organohalides (2). The legacy of any advance is reflected in how it is applied, and these reactions play an important role in organic synthesis and the development of medicinal compounds.

Christopher W. Jones, a professor of chemical and biomolecular engineering at the Georgia Institute of Technology in Atlanta, was awarded the Ipatieff Prize from Northwest University earlier this year for advancing understanding of the interface between homogeneous and heterogeneous catalysis (3). His work involved elucidating the reaction pathways for palladium-catalyzed carbon-carbon coupling reactions, including Heck and Suzuki coupling reactions, using several Pd(II) pincer complex catalysts. His research showed that these reactions proceed by a Pd(0)-Pd(II) catalytic cycle as opposed to a Pd(II)-Pd(IV) catalytic cycle, which many thought was the case using the purportedly stable Pd(II) pincer complexes. He synthesized Pd(II) pincer complexes supported on solids and used testing based on kinetics, spectroscopy, and catalyst poisoning to show that the reactions proceed via a Pd(0)-Pd(II) catalytic cycle. His research also showed the reactions are mediated by palladium species that are leached from the immobilized (heterogeneous) phase to the solution (homogeneous) phase. From this work, he developed so-called palladium "scavengers" to examine the different roles played by homogeneous and heterogeneous species in these reactions (3-6).

Jones also is part of the Georgia Institute of Technology's Center for Drug Design and Delivery's Pharmaceutical Pipeline Project, which addresses challenges in drug development and manufacturing. The project consists of the three entities within the university: the Drug Design Consortium, the Drug Development Consortium, and the Drug Delivery Consortium. The Drug Development Consortium is involved with improving drug manufacturing. The consortium's work includes using supercritical fluids as a solvent-replacement strategy, crystallization-control methods applied to Crixivan (indinavir), an AIDS drug manufactured by Merck & Co. (Whitehouse Station, NJ), and applying membrane technology for drug isolation. The Drug

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IN Hot Topics in Glaucoma



Drs. Brian Flowers and Henry Perry review the challenges of differentiating and treating glaucoma and dry eye

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Design Consortium focuses on the delivery of novel chemical entities and the optimization of existing chemical entities to generate promising therapies. Some projects include the design of histone deacetylase inhibitors, the biosynthetic engineering of natural products to explore structure–function relationships, and natural product research using marine organisms.

Georgia Tech also is the lead institution in the Center for Pharmaceutical Development, a newly established National Science Foundation Industry/ University Cooperative Research Center. The Georgia Tech site in the center focuses on the development of novel and improved biocatalysis for more selective and environmentally benign manufacturing. It also developed an accelerated assay to detect aggregation in therapeutic proteins.

Although useful, palladium-catalyzed coupling can be costly both because of the palladium and the ligand used with the transition metal in the catalyst. Researchers at the Leibniz Institute for Catalysis at the University of Rostock in Germany have addressed that problem by developing a new family of phosphane ligands, which are recyclable, and therefore could help to bring down the cost of certain palladium-catalyzed coupling reactions. Specifically, the researchers developed recyclable imidazolium phosphanes that work effectively in palladium-catalyzed carbon–oxygen, carbon–nitrogen, and carbon–carbon bond-forming reactions. The homogeneous palladium catalyst can be recycled directly from the reaction without any heterogenization (7).

Palladium-catalyzed cross-coupling of aryl halides and amines, known as Buchwald–Hartwig amination, is a key tool for constructing arylamines in organic synthesis. Researchers at Dalhousie University in Halifax, Nova Scotia, recently reported on a new phosphine ligand, which, when combined with palladium, selectively reacts ammonia or hydrazine with a broad range of aryl halides and tosylates, including reactions at room temperature in the case of ammonia (8, 9). The ligand employed in the chemistry, Mor-DalPhos, consists of an adamantyl-substituted phosphorus and a morpholino fragment bridged by a phenylene unit. The reactivity and selectivity of Mor-DalPhos/Pd with ammonia and hydrazine makes it an attractive choice in carbon–nitrogen couplings in which primary anilines and aryl hydrazines are the desired target compounds. Notably, aryl hydrazines are key intermediates in the preparation of nitrogen-containing heterocycles such as indoles, indazoles, and pyrazoles. Before this work by the Stradiotto group, however, the synthesis of aryl hydrazines directly from hydrazine sources had not been reported (8, 9). Strem Chemicals (Newburyport, MA) is marketing the ligand.

Synthesis of natural products . Researchers at the University of California in Berkeley recently reported on the synthesis of the alkaloid complanadine A, a dimer of another natural product called lycodine. The pseudo-symmetry of this molecule adds to the challenge of its synthesis. Medicinally, complanadine A is thought to aid in the production of nerve growth factors, something of interest for regenerative medicine and Alzheimer's disease research. Complanadine A is isolated from club moss, which grows naturally in the wild. However, the difficulty of isolating significant quantities of complanadine A from this natural source has limited further biological research on the molecule. The Berkeley researchers synthesized complanadine A using a common tetracyclic precursor to the two halves of the dimer. A crucial part of the synthesis was developing an iridium-catalyzed carbon–hydrogen functionalization to produce a boronic ester, which was followed by a Suzuki coupling (10, 11).

Silver-catalyzed coupling. Fluorine-based compounds are important building blocks in pharmaceutical synthesis. Researchers led by Tobias Ritter, associate professor in the Department of Biology and Chemistry at Harvard University, recently reported on a new cross-coupling reaction that attached fluorine atoms onto aromatic substituents. The reaction uses silver oxide to catalyze the fluorination of aryl tin compounds with the electrophilic fluorinating reagent *N*-chloromethyl-*N*-fluorotriethylenediammonium hexafluorophosphate. The researchers asserted that the reaction is the first example of silver catalysis being applied for carbon–heteroatom bond formation by cross-coupling chemistry. Carbon–fluorine bond formation by transition-metal catalysis is difficult, and only a few methods for the synthesis of aryl fluorides have been developed, according to the researchers. Typically, transition metal-catalyzed fluorination reactions for synthesizing functionalized arenes use palladium in the catalyst (12).

An advantage of the silver-catalyzed fluorination reaction is its versatility in terms of the variety of functional groups that can be tolerated and the breadth of the substrate scope. The researchers showed that the cross-coupling reaction can be used to fluorinate polypeptides, polyketides, and alkaloids and can be tolerated by various functional groups, including vinyl ethers, dienones, alcohols, allylic alcohols, ethers, esters, and oxetanes (12).

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New approaches to fluorination are useful for not only producing fluorinated molecules for use in pharmaceuticals, but such approaches also can be applied in imaging techniques. A long-term goal of the research by Ritter and his team is the development of new methods for the synthesis of small-molecule-tracers for positron emission tomography (PET), an imaging technique to study biological processes *in vivo*. PET with the isotope ^{18}F is currently limited by the absence of general chemistry that can introduce fluorine into molecules at a late stage. The approach to carbon–fluorine bond formation using high-valent transition metal fluorides *via* oxidation of aryl transition metal complexes with electrophilic fluorination reagents is one approach to resolve that challenge (12).

Patricia Van Arnum is a senior editor at *Pharmaceutical Technology*, 485 Route One South, Bldg F, First Floor, Iselin, NJ 08830 tel. 732.346.3072, pvanarnum@advanstar.com

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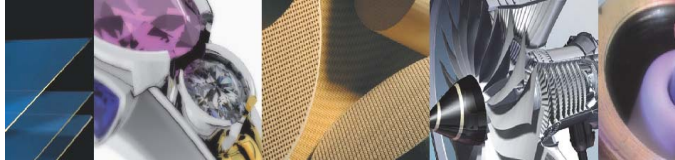
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New Application Developments in PGMs – October 2010

A low-cost catalyst prepares to take on power-plant emissions: Platinum, rhodium

Lehigh University: News: News Article, 01 October 2010

<http://www4.lehigh.edu/news/newsarticle.aspx?Channel=%2fChannels%2fNews%3a+2010&WorkflowItemID=da6b9b50%2f5849%2f47ff%2fb1de%2f282927c1d99c>

A research group led by Charles Lyman, professor of materials science and engineering at Lehigh University, Bethlehem, Pennsylvania, sought first to improve the performance of a platinum-rhodium nanoparticle-based catalyst that uses hydrogen, rather than ammonia, as a reducing agent. This catalyst works at much lower temperatures. To reduce NOx emissions more cheaply, the researchers turned to cobalt. The preparation of cobalt-platinum catalysts is almost identical to that of rhodium-platinum. The researchers substituted metal nitrates for chlorides. The same methodology has now been applied to a nickel-platinum catalyst system.

Use a microreactor for the self-optimization of a Heck reaction: Palladium

Noteworthy Chemistry, 04 October, 2010

http://portal.acs.org/portal/PublicWebSite/noteworthy/archive/CNBP_025820

Image:

http://portal.acs.org/portal/binfetch/consumption?fileUrl=/stellent/groups/web/documents/article/%7Eexport/CNBP_025820%7E2%7EHTML_DC_TEMPLATE%7ESNIPPET_LAYOUT/26699%3.jpg

S. L. Buchwald, K. F. Jensen and co-workers at MIT (Cambridge, MA) have developed a self-optimizing microreactor system that uses previous reaction data to design future experiments. Their process uses the Nelder-Mead simplex method to optimize the reaction conditions. The system consists of three syringe pumps, a micromixer, a microreactor, an inline HPLC analyzer, and a computer to control the system. The reaction between 4-chlorobenzotrifluoride (1) and 2,3-dihydrofuran (2) in the presence of a Pd(OAc)₂, phosphine 3, and dicyclohexylmethylamine in n-BuOH at 90 °C was chosen as a model because it does not produce palladium black or significant amounts of ammonium salts that could clog the system. The first syringe was filled with a mixture of 1, base, phosphine ligand, and Pd(OAc)₂, and the second and third were filled with neat 2 and n-BuOH, respectively. Thus it was possible to change the number of equivalents of 2 by adjusting the flow.

Mimicking nature's solar cells: Ruthenium

Highlights in Chemical Science, 06 October 2010

http://www.rsc.org/Publishing/ChemScience/Volume/2010/10/Mimicking_nature_solar_cells.asp

Plants efficiently use light to initiate reactions that produce energy in a process known as photosynthesis. Now Orlin Velev and colleagues at North Carolina State University, have created a hydrogel device to mimic this process to create electricity. The device uses a 98 per cent water hydrogel doped with two photoactive dyes (9,10-dimethoxy-2-anthracenesulfonic acid and ruthenium trisbipyridine). The gel is layered between a copper foil electrode coated with carbon black and graphite and an indium tin oxide-coated plastic substrate serving as the other electrode. The dyes absorb light exciting the electrons into a higher energy state. Transport of the dyes through the hydrogel allows electrons and electron holes to be transferred to the two electrodes completing the circuit and generating a current.

Degrade polychlorinated biphenyls under ambient conditions: Palladium

Noteworthy Chemistry, 11 October, 2010

http://portal.acs.org/portal/PublicWebSite/noteworthy/archive/CNBP_025874

H. Sajiki and coauthors at Gifu Pharmaceutical University (Japan) and Ogaki Plant Sangyou (Gifu) developed a pilot plant to degrade polychlorinated biphenyls (PCBs) that uses Pd/C-catalyzed hydrogenation at ambient temperature and pressure. The plant consists of tanks for water, heptane, and MeOH; a 50-L stirred tank for the reaction; and other necessary storage and processing equipment.

Water's interaction with platinum demands closer examination, Sandia researchers find.

Sandia News Releases, 13 October, 2010

Unexpected results found at wetting layer could aid future devices

https://share.sandia.gov/news/resources/news_releases/wetplatinum-demands-closer-examination-sandia-researchers-find/

Saving platinum: Monolayer of platinum on tungsten carbide catalyzes electrolytic production of hydrogen.

PhysOrg.com, 15 October, 2010

Hydrogen is one of the most promising fuels of the future. Whether powered by wind or sun energy, electrolysis of water is the method of choice for producing hydrogen without emission of carbon dioxide. The character and properties of the hydrogen-producing catalyst, usually platinum, are of critical importance for the efficiency and cost of the electrocatalytic system.

<http://www.physorg.com/news/2010-10-platinum-monolayer-tungsten-carbide-catalyzes.html>

In the journal *Angewandte Chemie*, Jinguang G. Chen and a team at the University of Delaware (USA) have now introduced a new method for saving on platinum without losing efficiency: they deposit a single layer of platinum atoms onto an inexpensive tungsten carbide support.

Researchers develop alternative to gold in electrical applications: Ruthenium

PhysOrg.com, 13 October, 2010

<http://www.physorg.com/news/2010-10-alternative-gold-electrical-applications.html>

<http://dx.doi.org/10.1063/1.3499369>

Researchers at the University of Connecticut, partnering with United Technologies Research Center (East Hartford, CT) engineers, have modelled and developed new classes of alloy materials for use in electronic applications. Mark Aindow and S. Pamir Alpay, UConn professors of materials science and engineering, and Joseph Mantese, a UTRC Fellow, have developed new classes of materials that behave much like gold and its counterparts when exposed to the oxidizing environments that degrade traditional base metals. They showed that alloying base metals can lead to higher conductivity native scales by: doping to enhance carrier concentration; inducing mixed oxidation states to give electron/polaron hopping; and/or phase separation for conducting pathways. Data from Cu□La, Fe□V, and Ni□Ru alloys demonstrate the viability of these approaches.

Coupling hydrazine: Palladium

Chemical & Engineering News, 18 October, 2010

<http://pubs.acs.org/cen/news/88/i42/8842notw7.html>

Image: Hydrazine Hookup: An electron-rich Mor-DalPhos ligand helps palladium couple aryl chlorides and hydrazine,

http://pubs.acs.org/cen/img/88/i42/8842NOTW7_pg8.gif

For the first time, chemists have managed to use palladium cross-coupling chemistry to wed aryl groups with hydrazine (Angew. Chem. Int. Ed., <http://dx.doi.org/10.1002/anie.201003764>). The resulting aryl hydrazines are useful intermediates en route to nitrogen-containing heterocycles, such as indoles and pyrazoles. The coupling reaction, developed by chemistry professor Mark Stradiotto and graduate student Rylan J. Lundgren of Dalhousie University, in Nova Scotia, proceeds in moderate to good yields and short reaction times with mild heating. The transformation relies on electron-rich ligands such as the morpholine-based compound Mor-DalPhos.

C–H functionalisation at room temperature: Palladium

Chemical Science Blog, 18 Oct 2010

<http://blogs.rsc.org/sc/2010/10/18/c%e2%80%93h-functionalisation-at-room-temperature/>

Image:

<http://pubs.rsc.org/services/images/RSCpubs.ePlatform.Service.FreeContent.ImageService.svc/ImageService/image/GA?id=C0SC00367K>

Matthew Gaunt's group at the University of Cambridge investigated the reactions of β -arylethylamine, a motif commonly found in medicines and natural products. Attempts to catalytically transform the phenylalanine ethyl ester had previously failed but when the group introduced an aryl group onto the amine system, they were able to carbonylate, arylate and aminate the C–H bond.

Oxygen reduction in nanoporous metal-ionic liquid composite electrocatalysts: Platinum

Nature Materials, 2010, 9, (11), 904–907

J. Snyder & J. Erlebacher, Department of Materials Science and Engineering and Department of Chemical and Biomolecular Engineering, Johns Hopkins University, Baltimore, Maryland, USA

T. Fujita & M. W. Chen, WPI Advanced Institute for Materials Research, Tohoku University, Sendai, Japan

<http://www.nature.com/nmat/journal/v9/n11/abs/nmat2878.html>

US and Japanese researchers have shown that a tailored geometric and chemical materials architecture can further improve oxygen reduction reaction catalysis by demonstrating that a composite nanoporous Ni–Pt alloy impregnated with a hydrophobic, high oxygen solubility and protic ionic liquid has extremely high mass activity. The results are consistent with an engineered chemical bias within a catalytically active nanoporous framework that pushes the ORR towards completion.

Catching the sun's heat: Ruthenium

MIT news, October 26, 2010

Storing thermal energy in chemical form has the potential to make it indefinitely storable and transportable.

<http://web.mit.edu/newsoffice/2010/solar-storage-1026.html>

Simple, scalable and aqueous method for synthesising nanoparticles: Palladium

Chemie.DE, 26 Oct 2010

<http://www.chemie.de/news/e/124963/>

Metal nanoparticles that can catalyse organic reactions in water can be made using polyelectrolyte nanoreactors, claim Vy Dong, at the University of Toronto, Canada, and colleagues.



Dear readers,

We all find hopes in the New Year and most of us give thought to the positive things we would like to see the next twelve months bring to us in terms of good health, success and family peace.

Personally I would also love to see more attention for science, research and higher education by politicians and decision makers because it's especially in recession times like these that the three items above must be seen as a key investment rather than an expense. Key discoveries in the fields of Energy, Biomedicine and Materials Science have the potential to act once again as powerful springboards for a future of wellness and economic growth for the humankind, whereas with less science, research and education the future could just be worse, much worse.

Luckily, there is still a lot of great research ongoing and this first 2011 issue of **SYNFORM** reports on two examples of great research in organic chemistry: a new stunning methodology to achieve a biomimetic enantioconvergent transformation of racemic substrates developed by Professor H. Ito (Japan) and the first methodology allowing for the direct use of hydrazine in metal-mediated cross-coupling reactions discovered by Professor M. Stradiotto (Canada). The issue is completed by a profile of Professor M. Malacria (France), member of the **SYNTHESIS/SYNLETT** Advisory Board.

Enjoy your reading!

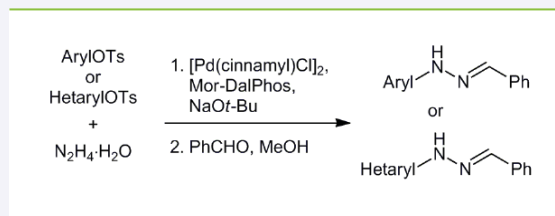
Matteo Zanda

Editor of SYNFORM

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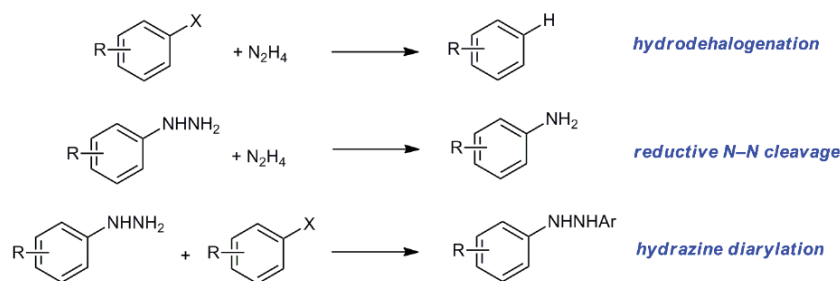
COMING SOON A10

CONTACT + + + +

If you have any questions or wish to send feedback, please write to Matteo Zanda at: Synform@chem.polimi.it

Palladium-Catalyzed Cross-Coupling of Aryl Chlorides and Tosylates with Hydrazine

Angew. Chem. Int. Ed. **2010**, *49*, 8686–8690



Common side reactions accompanying the use of hydrazine in cross-coupling reactions

■ Aryl hydrazines are key intermediates in the preparation of nitrogen-containing heterocycles, such as indoles (Fischer indole synthesis), indazoles and pyrazoles; however, the use of hydrazine in cross-coupling reactions is affected by several problematic metal-mediated side reactions.

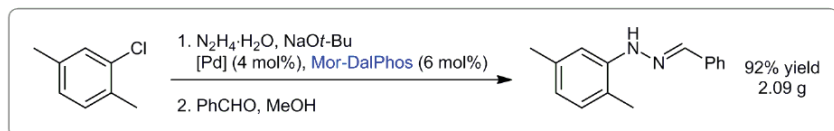
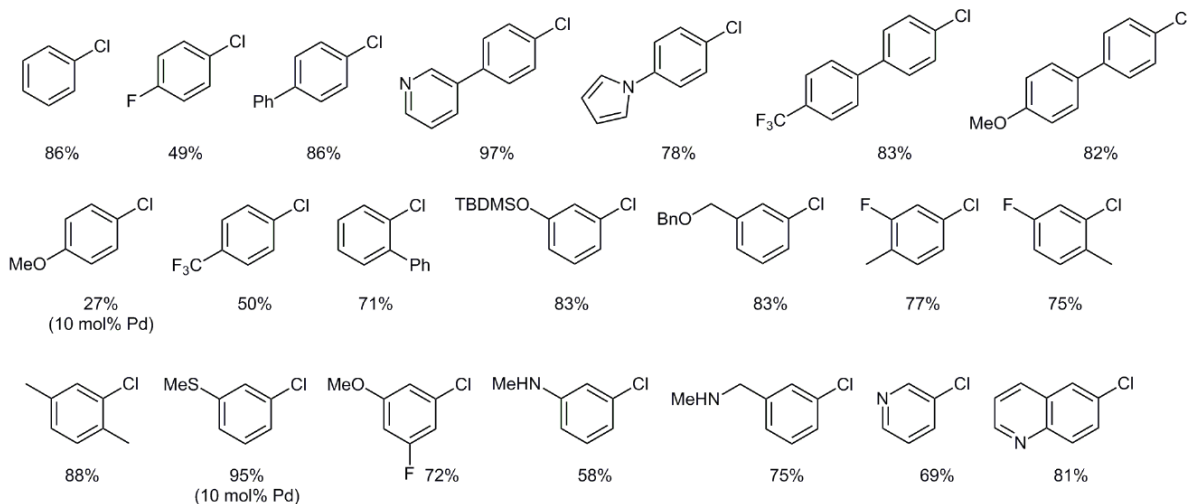
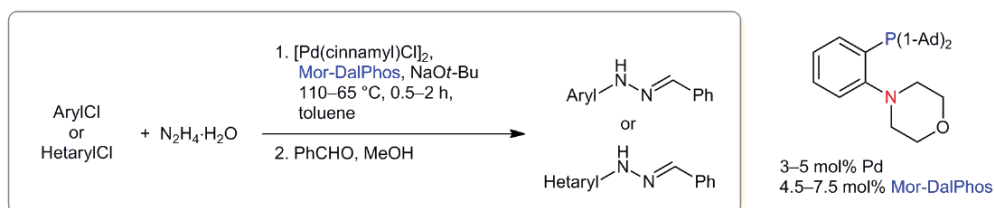
Recently, the group of Professor Mark Stradiotto from Dalhousie University (Halifax, Nova Scotia, Canada) published a novel methodology which promises to open new perspectives for hydrazine in metal-mediated organic synthesis. “Prior to our publication, the synthesis of aryl hydrazines directly from hydrazine sources had not been reported,” said Professor Stradiotto. “While hydrazine surrogates (which require deprotection following the cross-coupling reaction) with attenuated reactivity such as benzophenone hydrazone have been employed previously in cross-coupling chemistry, such strategies are not ideal from atom-efficiency or economic standpoints.” In this context, and given the success of Buchwald–Hartwig amination protocols, Professor Stradiotto and co-worker Rylan Lundgren sought to identify Pd catalysts supported by appropriately designed ancillary ligands that might enable the synthesis of aryl hydrazines directly from aryl halides/pseudohalides and hydrazine. “However, hydrazine is a very good reducing agent,” said Professor Stradiotto, “so side reactions where both the Pd catalyst and the aryl chloride substrate are converted into undesirable products was anticipated to be a major problem. The solution to the problem

that we discovered is found in the implementation of appropriate ancillary ligands to circumvent undesirable reactivity.” The methodology affords very good results and has a broad scope when applied to aromatic and heteroaromatic chlorides.

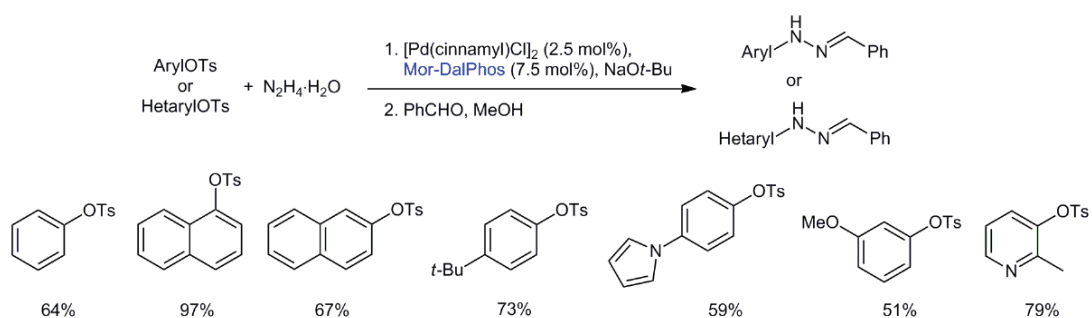
Very interesting results were also achieved with the corresponding tosylates.

“We are still in the process of understanding what makes the Mor-DalPhos ligand such a good ligand for hydrazine (and ammonia – as shown in our previous report in *Angew. Chem. Int. Ed.* **2010**, *49*, 4071) cross-coupling,” continued Professor Stradiotto. “It is a sterically demanding, bidentate ligand which may help the selectivity of the reaction. The bidentate ligand framework may also help in maintaining a monomeric catalyst species, preventing catalyst decomposition steps, as well as in promoting the C–N reductive elimination.”

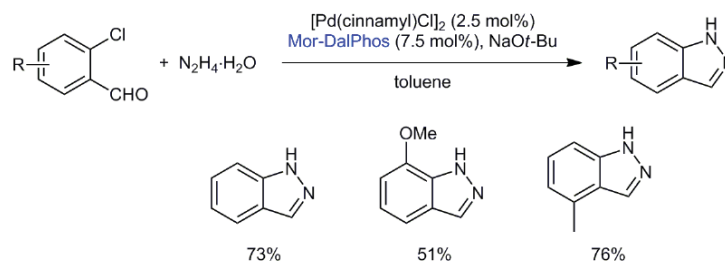
Professor Stradiotto explained that in their paper they also demonstrated that the bidentate bis(phosphine) ligand Josiphos worked well in this hydrazine cross-coupling reaction. “It should be noted that John Hartwig has extensively studied the use of Josiphos in alternative cross-coupling amination chemistry (including reactions involving ammonia) and we drew inspiration from his seminal work,” he acknowledged. “The transformations featured in our report are likely to have applications in pharmaceutical synthesis, including in the preparation of substituted indoles and related heterocyclic



Stradiotto's methodology applied to aromatic and heteroaromatic chlorides



Stradiotto's methodology applied to aromatic and heteroaromatic tosylates



Stradiotto's methodology applied to the synthesis of indoles

molecules, especially if we can continue to improve on the reaction conditions (less Pd, milder bases, lower temperatures) and broaden the substrate scope.”

“We are working on improving these aspects of the reaction as well as on incorporating hydrazine cross-coupling into tandem catalytic reactions,” concluded Professor Stradiotto. ■

Matteo Zanda

About the authors



Dr. R. J. Lundgren

Rylan J. Lundgren was born in Winnipeg (Canada) and received his BSc (Hons.) in chemistry from the University of Manitoba (Winnipeg, Canada) in 2006 where he performed research under the guidance of Professor M. Bieringer. He also conducted research in 2005 with Professor D. Fogg at the University of Ottawa (Canada). In 2006, he began his PhD studies at Dalhousie University (Canada) under the supervision of

Professor Stradiotto, and he successfully defended his PhD thesis in October 2010. Rylan is now a Natural Sciences and Engineering Research Council of Canada Postdoctoral Fellow in the group of Professor Greg Fu at the Massachusetts Institute of Technology (USA).



Prof. M. Stradiotto

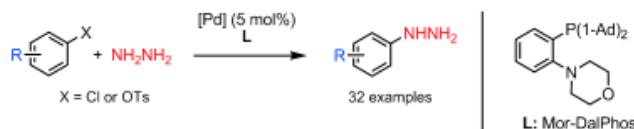
Mark Stradiotto completed his PhD in organometallic chemistry in 1999 at McMaster University (Hamilton, Ontario, Canada) under the supervision of Professors M. A. Brook and M. J. McGlinchey, and then worked at the University of California at Berkeley (USA) as an NSERC Postdoctoral Fellow with Professor T. D. Tilley. In 2001, he moved to the Department of Chemistry at Dalhousie University as an Assistant Professor, and now holds

the rank of Professor with tenure. Mark was awarded the Dalhousie University Undergraduate Chemistry Society Teaching Award in 2002, and again in 2005. In 2005, he was also awarded the Dalhousie University Killam Research Prize, and in 2006 the Dalhousie Innovation Award as well as the Harry Shirreff Research Prize. In 2009, Mark became a member of the editorial board of *Organometallics*, and was a recipient of the Thieme Chemistry Journal Award.

Palladium-Catalyzed Cross-Coupling of Aryl Chlorides and Tosylates with Hydrazine

The introduction of a nitrogen atom via an organometallic coupling has been one of the most active fields in Organic Synthesis in recent years. Two names stand out: Buchwald and Hartwig. The so-called palladium catalyzed amination of aromatic compounds is therefore known as Buchwald-Hartwig reaction. Along the years, many conditions have been developed, allowing the coupling of a broad range of amines and amides with haloaromatic compounds and other suitable partners, as triflates and tosylates. Hydrazine can be introduced using this reaction, but only if you mask it: one of the most used approaches is the use of a hydrazine surrogate with attenuated reactivity, benzophenone hydrazone. Once the surrogate is coupled you must deprotect the hydrazone following a couple of protocols. But those protocols do not work all the time, and of course you are deprotecting. Getting rid of this or other protecting groups and using hydrazine directly would be very welcomed.

That is what Stradiotto et al. (Dalhousie University, Canada) have published now. After their initial success using NH_3 as nitrogen source in the Buchwald-Hartwig reaction, they have tackled the hydrazine problem and developed a working protocol. The protocol involves heating a phenyl chloride or phenyl tosylate, hydrazine monohydrate (ratio 1:2), $[\{\text{Pd}(\text{cinnamyl})\text{Cl}\}_2]$ (3-5 mol% usually), the ligand (5-8 mol%) and NaOtBu (2 eq.) in toluene at 90 °C for 30-60 minutes. The trick? The ligand must be Mor-Dal-Phos, which is not commercially available. The method works with 22 different aryl chlorides, including 4-chloropyridine which is chosen because hydrazine can react with the 2- and 4- isomers through other mechanism, and 7 tosylates. Once you put your hands on the phosphine, really worth to try it !!



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GalChimia, S.L. Cebreiro s/n, 15823 O Pino (A Coruña) - Spain Tel: +34 981 814 506 Fax: +34 981 814 507 www.galchimia.com