



Trip Report for
**“2008 ACS ProSpectives Conference:
Organic Reactions and Syntheses”**
Philadelphia, PA
October 26-28, 2008

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Abstract: *The 2008 ACS ProSpectives Conference “Organic Reactions and Syntheses” was held in Philadelphia, PA from October 26-28, 2008. The two-day conference was divided into four lecture sessions and a poster session dedicated solely to “hardcore” organic synthesis. The ACS brought together top scientists with global expertise from academia and industry, who delivered lectures on the latest chemistries and technologies in the areas of catalysis, heterocyclic chemistry, asymmetric synthesis, methodology, and total synthesis. The conference explored strategies that enable the preparation of new pharmaceutical agents, molecular probes, complex natural products, and organic materials. This report highlights select research material from information presented in seminars.*

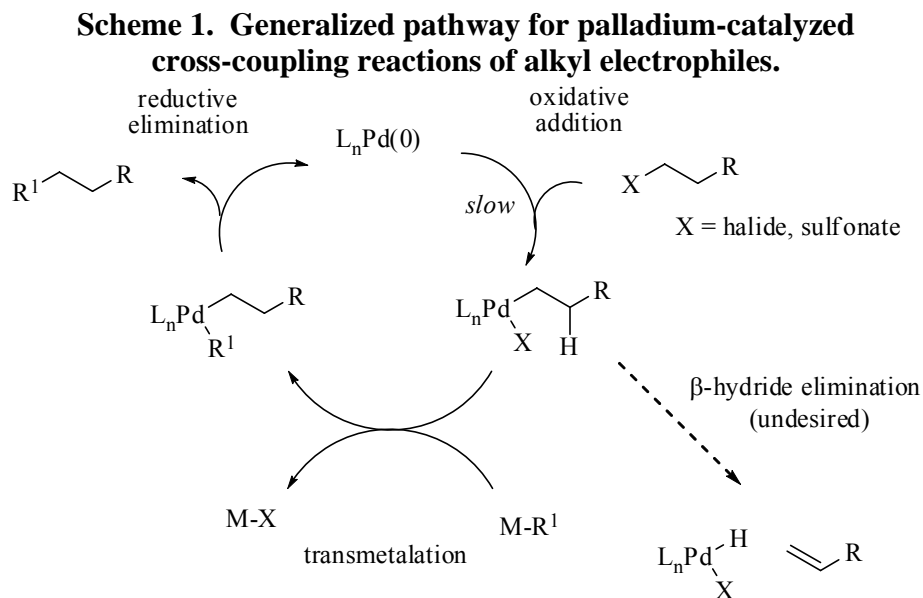
“Palladium- and Nickel-Catalyzed Alkyl-Alkyl Coupling Reactions”

Gregory C. Fu, Massachusetts Institute of Technology, Cambridge, MA

Despite the tremendous accomplishments that have been described in the development of palladium and nickel catalyzed carbon-carbon bond-forming processes, it is nevertheless true that many significant opportunities remain. For example, to date the overwhelming majority of studies have focused on couplings between two sp^2 -hybridized reaction sites (e.g., an aryl metal with an aryl halide).

As of 2001, there were only few examples of palladium or nickel catalyzed coupling reactions of alkyl electrophiles, except for activated compounds that lack β hydrogens (e.g., benzyl halides). During the past several years, Professor Gregory Fu and his team at MIT have pursued the discovery of palladium- and nickel-based catalysts for coupling activated and non-activated primary and secondary alkyl electrophiles that bear β hydrogens. Professor Fu's talk highlighted his group's efforts to develop broadly applicable methods, including enantioselective processes.

It is generally believed that efficient cross-coupling of simple alkyl halides/sulfonates is impeded by slow oxidative addition and by rapid β -hydride elimination (Scheme 1).

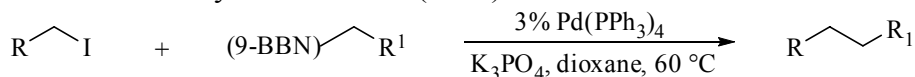


During the past decade, some useful progress toward addressing this challenge has been achieved (Scheme 2). In 1992, Suzuki published a pioneering study of cross-coupling reactions catalyzed by $Pd(PPh_3)_4$ for primary alkyl iodides with 9-BBN derivatives (A. Suzuki, *et al.*, *Chem. Lett.* **1992**, 691-694). In a series of groundbreaking studies beginning in 1995, Knochel demonstrated that nickel complexes can catalyze Negishi reactions of primary alkyl bromides and iodides with a range of organozinc reagents (P. Knochel, *et al.*, *Angew. Chem., Int. Ed. Engl.* **1995**, 34, 2723-2725; P. Knochel, *et al.*, *Angew. Chem., Int. Ed.* **1998**, 37, 2387-2390; R. Giovannini and P. Knochel, *J. Am. Chem. Soc.* **1998**, 120, 11186-11187; P. Knochel, *et al.*, *J. Org. Chem.* **1999**, 64, 3544-

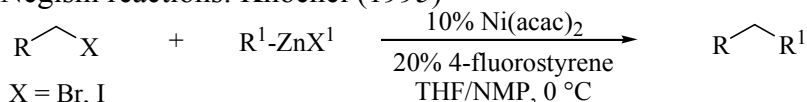
3553; P. Knochel, *et al.*, *Org. Lett.* **1999**, *1*, 1323-1326; A. E. Jensen and P. Knochel, *J. Org. Chem.* **2002**, *67*, 79-85).

Scheme 2. Pd- or Ni-catalyzed coupling of alkyl electrophiles in 2000.

- Suzuki-Miyaura reactions (1992)



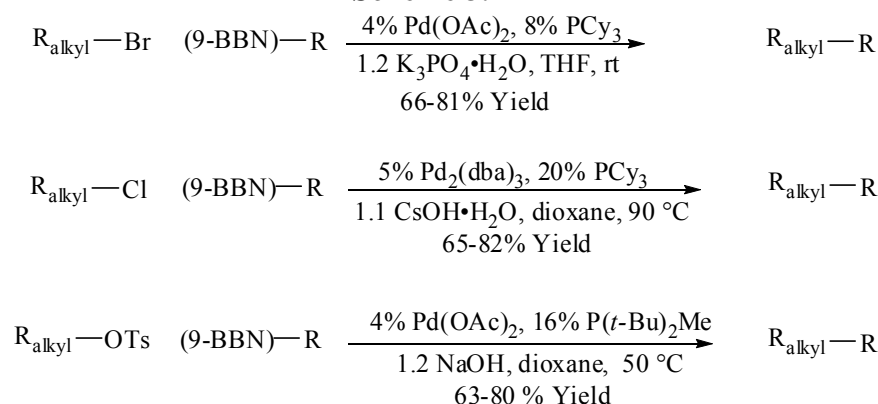
- Negishi reactions: Knochel (1995)



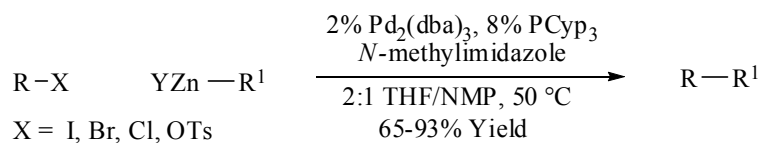
Following this brief introduction on the state of the art of palladium- and nickel-catalyzed coupling reactions during the past decade, Professor Fu summarized the latest discoveries of his research group in this area:

For Suzuki reactions of alkyl bromides, chlorides and tosylates with alkylboranes (Scheme 3), the major limitation of these processes is that they are generally effective only for *primary* alkyl electrophiles (Bromides: G. C. Fu, *et al.*, *J. Am. Chem. Soc.* **2001**, *123*, 10099-10100. Chlorides: G. C. Fu, *et al.*, *Angew. Chem., Int. Ed.* **2002**, *41*, 1945-1947. Tosylates: M. R. Netherton and G. C. Fu, *Angew. Chem., Int. Ed.* **2002**, *41*, 3910-3912).

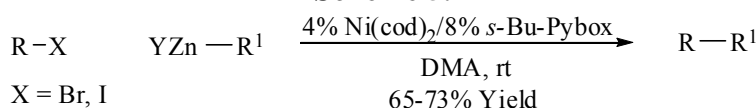
Scheme 3.



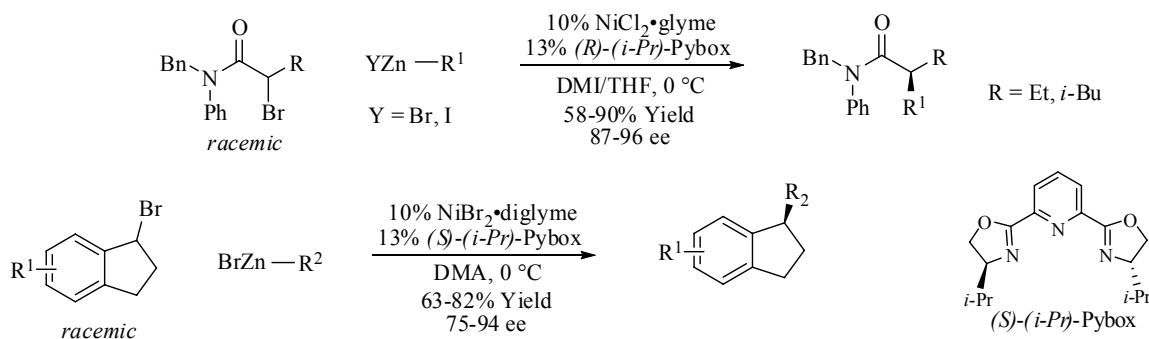
Palladium-catalyzed Negishi coupling reactions can be conducted with alkyl iodides, bromides, chlorides and tosylates (Scheme 4). In terms of versatility, the Pd₂dba₃/PCy₃-based catalyst for Negishi couplings is unique among all of the methods that have been described for coupling alkyl electrophiles – the same catalyst is effective for chlorides, bromides, iodides, and tosylates (J. Zhou and G. C. Fu, *J. Am. Chem. Soc.* **2003**, *125*, 12527-12530).

Scheme 4.

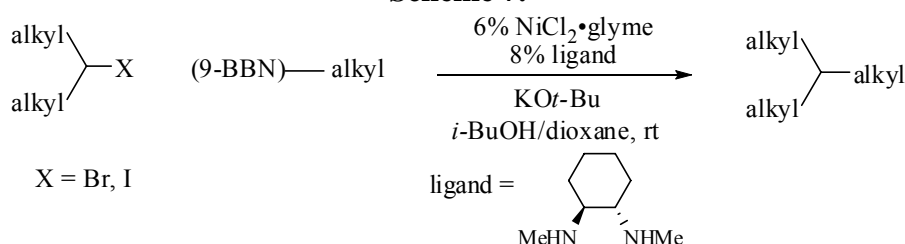
Nickel-catalyzed Negishi reactions can be conducted with secondary and primary alkyl bromides and iodides as shown in Scheme 5 (J. Zhou and G. C. Fu, *J. Am. Chem. Soc.* **2003**, *125*, 14726-14727).

Scheme 5.

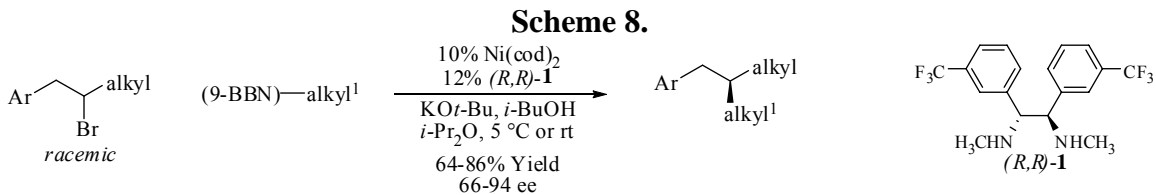
Catalytic asymmetric Negishi reactions can be performed as shown in Scheme 6 (C. Fischer and G. C. Fu, *J. Am. Chem. Soc.* **2005**, *127*, 4594-4595; F. O. Arp and G. C. Fu, *J. Am. Chem. Soc.* **2005**, *127*, 10482-10483).

Scheme 6.

Nickel-catalyzed Suzuki couplings of secondary halides can be run with diamines as ligands as shown in Scheme 7 (B. Saito and G. C. Fu, *J. Am. Chem. Soc.* **2007**, *129*, 9602-9603).

Scheme 7.

Asymmetric Suzuki couplings can be performed with unactivated homobenzylic halides as depicted in Scheme 8 (B. Saito and G. C. Fu, *J. Am. Chem. Soc.* **2008**, *130*, 6694-6695).



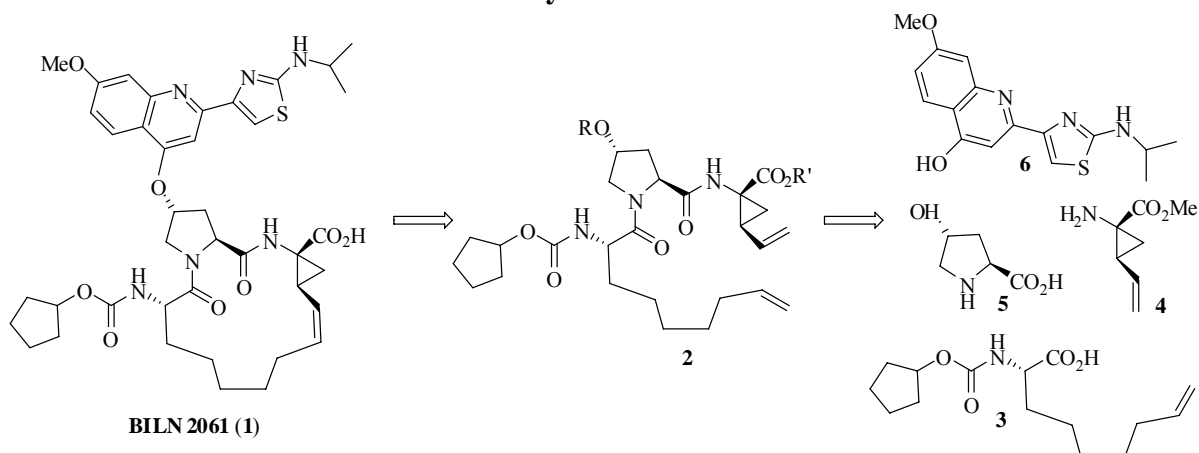
The current efforts in Professor Fu's group are focused on the development of more versatile catalysts for the Pd- and Ni-catalyzed coupling reactions of alkyl electrophiles, improving the mechanistic understanding of these processes as well as the discovery of new asymmetric processes.

“Scale-Up of Ring-Closing Metathesis Reaction: Development of a Highly Practical Process for Macrocyclic HCV Protease Inhibitors”

Nathan Yee, *Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT*

BILN 2061 (1), Scheme 9) is a HCV protease inhibitor, is the first small molecule that was clinically validated for the treatment of hepatitis C infection in human. Its large scale synthesis presented significant challenge for process chemists. Nathan Yee's lecture provided an account of the process research conducted by BIPI's scientists which led to the first highly practical application of ring-closing metathesis (RCM) in the pharmaceutical industry and that allowed for large-scale synthesis of BILN 2061 and closely-related analogues on full production scale (N. K. Yee, *et al.*, *J. Org. Chem.* **2006**, *71*, 7133; T. Nicola, *et al.*, *Org. Process Res. Dev.* **2005**, *9*, 513; X. Zeng, *et al.*, *J. Org. Chem.* **2006**, *71*, 8864; C. Shu, *et al.*, *Org. Lett.* **2008**, *10*, 1303).

Scheme 9. Retrosynthesis of BILN 2061.



The new HCV protease inhibitor BILN 2061(1) features a 15-membered ring bearing a (*Z*)-1,2-disubstituted alkene subunit, as well as five stereocenters. The obvious disconnections involve scission of two amide bonds and an ether function (Scheme 9). Closure of the macrocycle can be effected by a Ru-catalyzed RCM reaction, a synthetic operation that has been widely used in recent years but which still represents a formidable

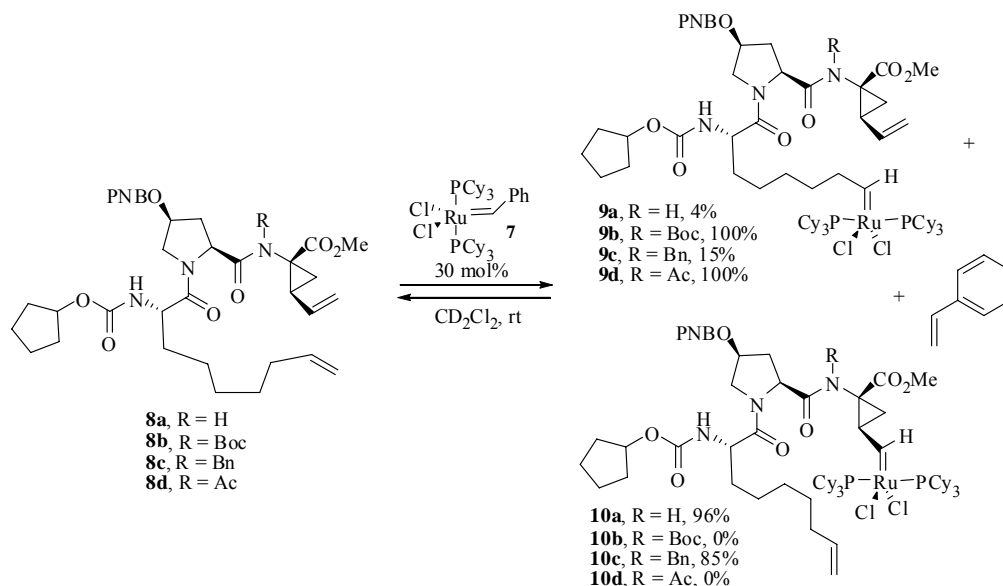
challenge in a manufacturing plant setting, mostly because of the necessity for high-dilution conditions.

A useful concept that has been employed to describe the difficulty of forming large rings is that of “effective molarity” (EM), which depends on the size of the ring to be formed and also on any conformational constraints that may affect the system. In recent years, the RCM reaction has emerged as a very attractive approach to the synthesis of macrocycles, due to its neutral reaction conditions, broad functional group tolerance, and simple reaction procedure (Grubbs, R. H., Ed. *Handbook of Metathesis*; Wiley-VCH: Weinheim, 2003; A. Furstner and K. Langemann, *J. Org. Chem.* **1996**, *61*, 3942; A. Gradillas and J. Perez-Castells, *Angew. Chem., Int. Ed.* **2006**, *45*, 6086; A. Furstner and P. W. Davies, *Chem. Commun.* **2005**, *42*, 2307; A. K. Kulkarni and S. T. Diver, *J. Am. Chem. Soc.* **2004**, *126*, 8110). None the less, implementation of RCM macrocyclizations in an industrial setting is extremely problematic and very uncommon. A recent review highlights the fact that, in the large number of macrocyclizations that have been effected by RCM, the substrate concentration range was 0.2-8.5 mM, and the catalyst loading 2-10 mol %.^{5c} The earlier disclosed process for BILN 2061 which was scaled to >100 kg, suffered from high dilution (10 mM) and large catalyst loading (3-5 mol %), thus rendering the approach unsuitable for production-scale manufacturing.

Nathan Yee reported the solution to the above-mentioned problem, that is, the development of an RCM macrocyclization that can operate at “acceptable” plant concentrations (>0.2 M) and at low catalyst loadings (≤ 0.1 mol %), thus making this the first example of a truly practical RCM macrocyclization. The approach taken stemmed from the following initial observations on the early RCM process: The remote substituent at the C-4 position of the hydroxyproline moiety had a small but detectable effect on the RCM rate and therefore on the EM. This small effect was tentatively ascribed to subtle conformational factors; when the initiation of the reaction was monitored using a stoichiometric amount of Grubbs catalyst (**7**), carbene transfer occurred to a large extent (96%) at the vinylcyclopropane moiety, where the Ru may be stabilized by chelation. Such stabilization, in turn, may reduce the concentration of the active Ru catalyst in the reaction and negatively affect the rate of the RCM step.

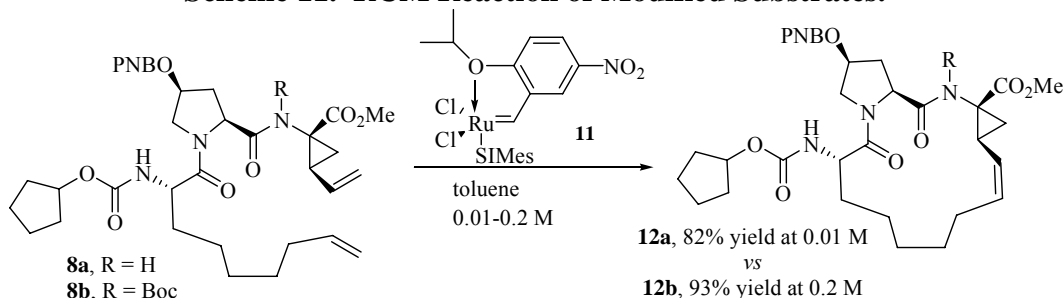
To exploit these clues Nathan Yee and coworkers prepared a number of derivatives in which the amide bond had been protected with various removable groups (Scheme 10). The expectation was that such substitution may interrupt the coordinative stabilization by the ester group through steric interaction ($A^{1,3}$ strain) and therefore lead to initiation at the nonenoic acid moiety, which may be beneficial to the RCM. Indeed, whereas *N*-benzyl substitution (**8c**) had a relatively minor effect on the site of initiation, acylation of the *N*-atom led to inhibition of carbene transfer to that position. Instead, carbene transfer took place completely (>98%) at the nonenoic acid moiety (**9b** and **9d** were produced in >90% conversion).

Scheme 10. RCM Initiation with Modified Substrates.



With these initial observations on hand, Nathan Yee and coworkers proceeded to attempt the RCM of substrates **8a** and **8b** under standard conditions (0.01M, toluene, 60 °C), but employing a second-generation Ru Catalyst **11** (Scheme 11). The desired RCM took place with an initial rate that was 3-4 times faster for substrate **8b** than for substrate **8a** under identical conditions, leading to the desired product in quantitative yield (>98%), without formation of dimers. The yield of the RCM product **12a** was found to decrease as the substrate concentration increased, i.e. a 10-fold increase in the concentration (from 0.01M to 0.10 M) resulted in decrease of the yield from 82% to 35%. In contrast, the yield of **12b** decreased only slightly (from 98% to 80%) under the same conditions.

Scheme 11. RCM Reaction of Modified Substrates.



Furthermore, by running the reaction at higher temperatures (toluene, 110 °C), both the yield of **12b** and the EM increased and the authors were able to lower the catalyst loading from 1 mol % to 0.1 mol %. *In essence, they achieved their goal of operating with ≤ 0.1 mol % catalyst, as well as under standard concentrations (≥ 0.2 M).* At even higher concentrations (0.4 M), up to 20% yield of dimer was detected, therefore limiting the yield of the RCM. Eventually, the RCM reaction was smoothly scaled up to produce >400 kg of cyclized product.

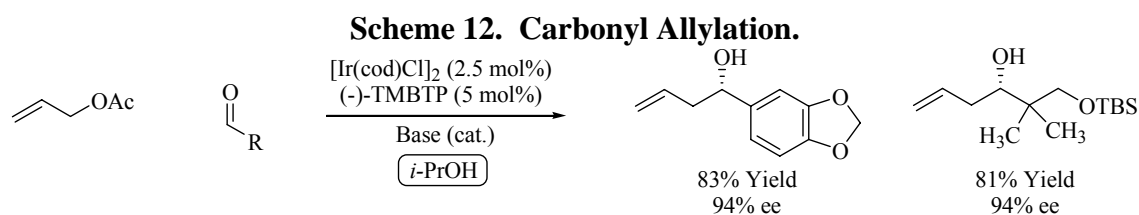
In summary, Nathan Yee and coworkers have developed a practical synthesis of BILN 2061 by introducing the first example of practical RCM macrocyclization. The origins of the “*N*-Boc-effect” seem to be grounded in favorable kinetic and thermodynamic effects. They have shown that strategic introduction of removable groups on the RCM linker can direct the initiation site and have a remarkable effect on the RCM and can also affect the strain content in the product, thus dramatically increasing the thermodynamic EM. Generalization of these important effects could lead to widespread utilization of the RCM and other macrocyclizations in the industrial plant.

“Formation of Carbon-Carbon Bonds *via* Catalytic Hydrogenation and Transfer Hydrogenation”

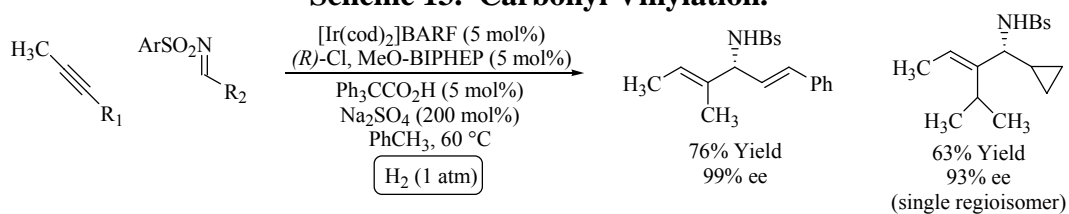
Michael J. Krische, University of Texas at Austin

Whereas conventional hydrogenation involves *C-H bond formation*, research in Professor Krische’s group establishes hydrogenation as a method for *C-C bond formation*. Asymmetric hydrogenation accounts for over half the chiral compounds made by man, withstanding physical or enzymatic resolution. The Krische’s group has shown that the coupling of diverse π -unsaturated reactants to carbonyl compounds, imines and even alcohols is promoted *via* hydrogenation and transfer hydrogenation, offering a byproduct-free alternative to stoichiometrically preformed organometallics in a range of classical $C=X$ ($X = O, NR$) addition processes. These studies represent the first systematic efforts to exploit hydrogenation in C-C couplings beyond hydroformylation and define a departure from the use of preformed organometallic reagents in carbonyl addition.

Representative examples of formation of C-C bonds *via* catalytic and transfer hydrogenation carried out by Krische’s group are outlined Scheme 12 for Carbonyl Allylation (M. J. Krische, *et al.*, *J. Am. Chem. Soc.* **2008**, *130*, 6340), in Scheme 13 for Carbonyl Vinylation (M. J. Krische, *et al.*, *J. Am. Chem. Soc.* **2007**, *129*, 12644) and in Scheme 14 for an Aldol Addition (M. J. Krische, *et al.*, *J. Am. Chem. Soc.* **2008**, *130*, 2747).



Scheme 13. Carbonyl Vinylation.



Scheme 14. Aldol Addition.

