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ALDRICH Chemistry

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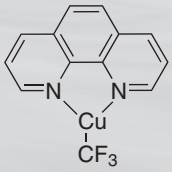

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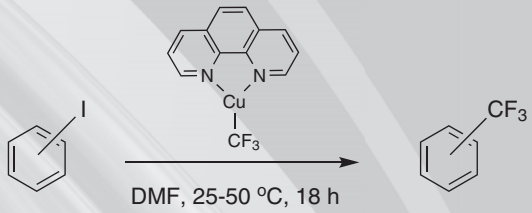
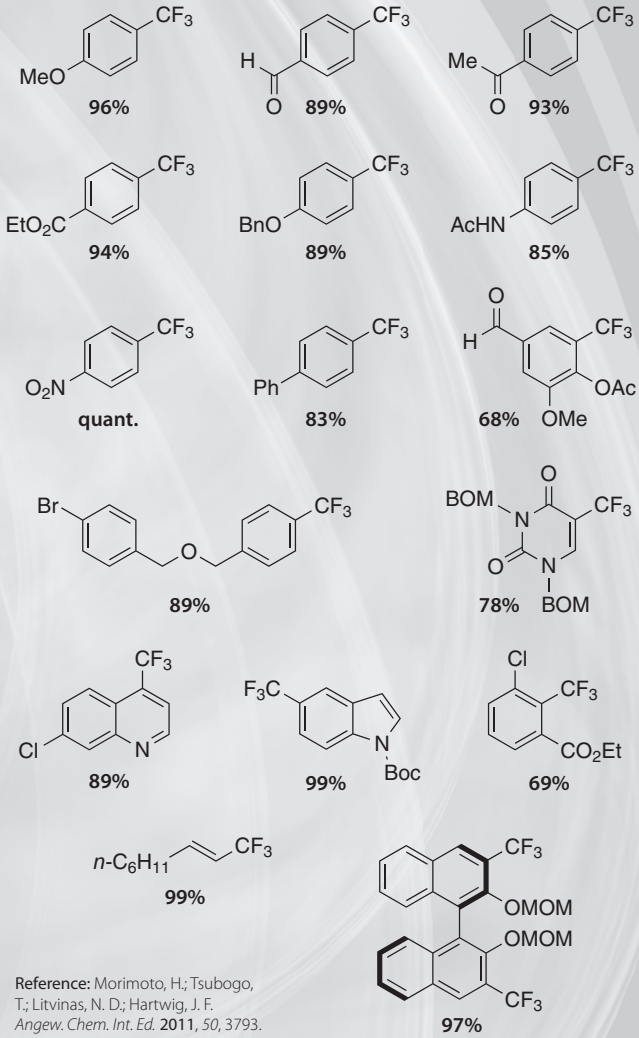


Representative Reaction Scope



Reference: Morimoto, H.; Tsubogo, T.; Litvinas, N. D.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2011**, *50*, 3793.

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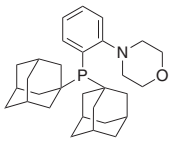
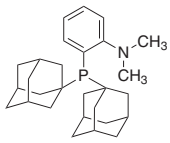
Dear Fellow Chemists,

We have had many suggestions for the DalPhos ligands shown below. These were recently developed by Professor Mark Stradiotto and his group at Dalhousie University. Both are air-stable, chelating N,P ligands that enable the Pd-catalyzed cross-coupling of ammonia. Mor-DalPhos is also effective in coupling hydrazine and acetone, and in the gold–catalyzed hydroamination. The catalysts are used with low loadings and exhibit excellent functional group tolerance and chemoselectivty.

(a) Lundgren, R. J.; Peters, B. D.; Alsabeh, P. G.; Stradiotto, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 4071. (b) Lundgren, R. J.; Stradiotto, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 8686.



751618



751413

751618	Di(1-adamantyl)-2-morpholinophenylphosphine (Mor-DalPhos)	250 mg 1 g
751413	Di(1-adamantyl)-2-dimethylaminophenylphosphine (Me-DalPhos)	250 mg 1 g

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John Radke
Director of Marketing, Chemistry

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Venice: The Dogana and San Giorgio Maggiore (oil on canvas, 91.5 × 122.0 cm) was completed in 1834 by Joseph Mallord William Turner (London, 1775–1851). A prolific British artist and an influential member of the Romantic Movement of the late eighteenth and first half of the nineteenth century, he elevated landscape painting to a level not achieved before and introduced several innovations to the genre. His talent manifested itself very early in life, and he was much admired as an artist in life and death, with institutions, works, and artistic prizes dedicated to preserving his legacy.

Detail from ***Venice: The Dogana and San Giorgio Maggiore***.
Photograph © Board of Trustees, National Gallery of Art, Washington.

This painting depicts a bustling maritime scene in the Grand Canal of Venice, which Turner had visited several times. (Another Venetian cityscape, painted seven years earlier by another British Romantic Movement artist, R. P. Bonington, has graced the cover of *Aldrichimica Acta*, Vol. 43, No. 1.) Turner intended this work as a celebration of commerce, as symbolized by the statue of Fortune atop the Dogana (Customs building) in the foreground. While Turner was not concerned with a faithful depiction of the scene, as evidenced by the apparent widening of the canal and placement of San Giorgio's church, his skill as a draftsman and his mastery of perspective drawing are evident in his precise, linear rendering of the buildings and sharp angles. His color combinations, freely handled layers of paint, and the sparkling water and light sky exemplify his lifelong preoccupation with the effects and significance of light in an awe-inspiring natural world.

This painting is part of the Widener Collection at the National Gallery of Art, Washington, DC.

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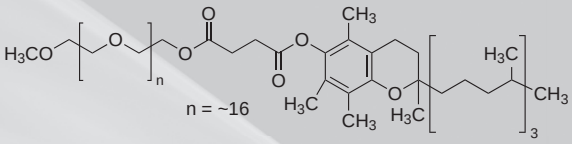

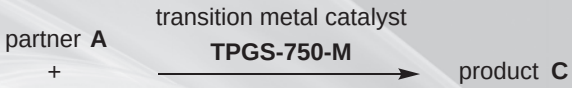

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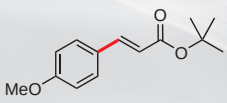

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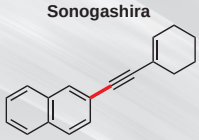

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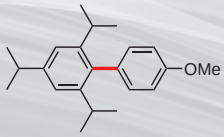

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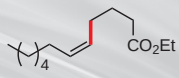

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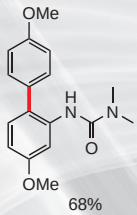

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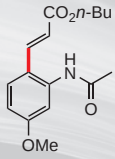
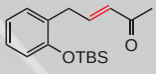


83%

ring-closing metathesis

88%

cross-metathesis



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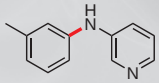

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Lipshutz, B. H. et al. *J. Org. Chem.* **2011**, *76*, 4379.

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"Designer"-Surfactant-Enabled Cross-Couplings in *Water* at Room Temperature

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Keywords. green chemistry; micellar catalysis; designer surfactants; cross-couplings; PTS; TPGS-750-M.

Abstract. New methodologies are discussed that allow for several commonly used transition-metal-catalyzed coupling reactions to be conducted within aqueous micellar nanoparticles at ambient temperatures.

Outline

1. Introduction

Green chemistry recently took a front row seat on the world stage. Unfortunately, it was not associated with any special technological advance; rather, the 200-million-plus gallons (ca. 5 million barrels) of oil that had leaked into the Gulf of Mexico focused attention on methods for dispersing such a huge quantity of localized hydrocarbons.[1] British Petroleum (BP) addressed this catastrophe by injecting dispersants at the site, the key ingredient being a mix of surfactants. While this tactic raised more than a few eyebrows with respect to additional pollutants having been introduced into the ecosphere, the presumption was that sodium dioctylsulfosuccinate (**1**), Span™ 80 (**3**), and a mixture of TWEEN® 80 (**4**) and 85 (**5**)—present in dispersants COREXIT® EC9500 and COREXIT® EC9527[2]—would help to "solubilize" the oil by forming micelles, thereby relocating over time the oil deposited within their lipophilic cores (**Figure 1**). While a disaster of this magnitude needs the tincture of time to assess its full impact on the environment, from a purely chemical perspective, tremendous hope has been placed on these surfactants in anticipation that they will prevent further damage to wildlife and shores.

This micellar chemistry undertaken on a grand scale by the petroleum industry highlights the potential for simple amphiphilic molecules to "solubilize" organic materials in a purely aqueous medium. Many other industries use surfactants routinely; examples include paint, cosmetics, cleaning, leather, carpet, asphalt, and pulp & paper companies.[3] Relatively small amounts have been used for decades in highly controlled environments, e.g., as "excipients" in the pharmaceutical arena, to help increase dissolution of otherwise water-insoluble drugs in aqueous media. But where are the studies on their usage in synthesis? Why not apply the same concepts of solubilization within micelles to reactants and catalysts that become, albeit transiently, the occupants? Of course, some synthetic chemistry can be, and has been, done in micelles.[4] Interestingly, this approach, oftentimes referred to as "micellar catalysis", is technically a misnomer since the micelle is not participating as a catalyst in the reaction itself. Nonetheless, why should these, or thousands of other surfactants created by industry and designed for a narrow range of specialized applications, be the most appropriate for use in state-of-the-art transition-metal-mediated cross-couplings? Since organic reactions are oftentimes very sensitive to solvent effects,[5] and since the lipophilic portions of micelles are functioning as the reaction medium, which surfactant should be used in this capacity to best assist metal-catalyzed reactions in water at room temperature? No one knows. *Perhaps it is time for synthetic chemists to start designing surfactants for synthetic chemistry.*

The situation just a few years ago was not encouraging in that there were virtually no *general* studies of the effect of varying micellar conditions on the most commonly used transition-metal-catalyzed couplings. As green chemistry continues to expand, critical reviews have appeared highlighting micellar media in which the "hydrophobic effect"—the tendency of nonpolar groups to cluster so as to shield themselves from contact with an aqueous environment[6]—assists with organometallic processes in water, such as in oxidation and reduction reactions,[7] as well as in selected C–C-bond forming reactions (e.g., hydroformylations). And so it was in recognition of the potential offered by micellar catalysis, performed in water as the gross reaction medium (and not the solvent), that we set out to develop "designer" surfactants for use in transition-metal-catalyzed cross-coupling reactions.

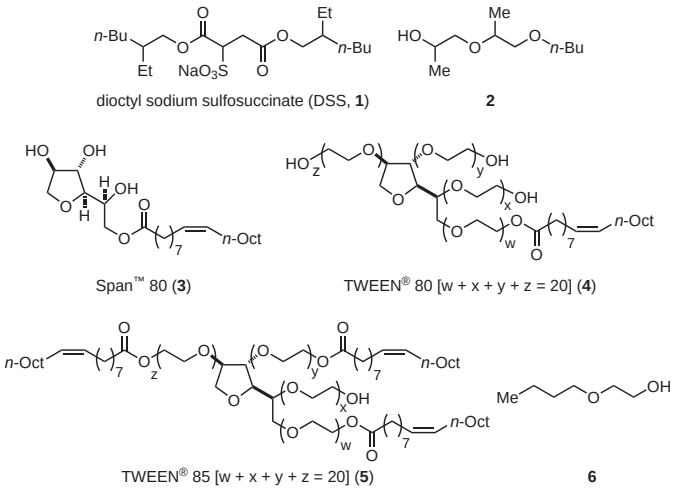


Figure 1. Ingredients of COREXIT® EC9500 (a Mixture of **1–5**) and COREXIT® EC9527 (Includes **1–6**). *(Ref. 2b)*

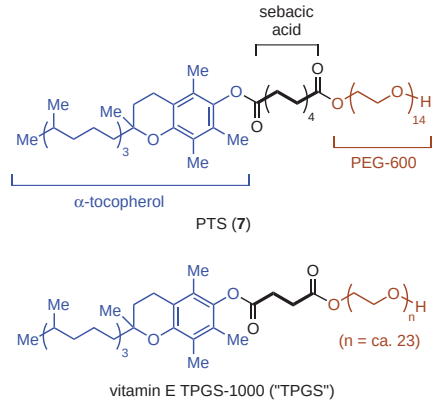


Figure 2. Polyoxyethanyl-α-tocopheryl Sebacate (PTS, **7**) and TPGS-1000. *(Ref. 8,13)*

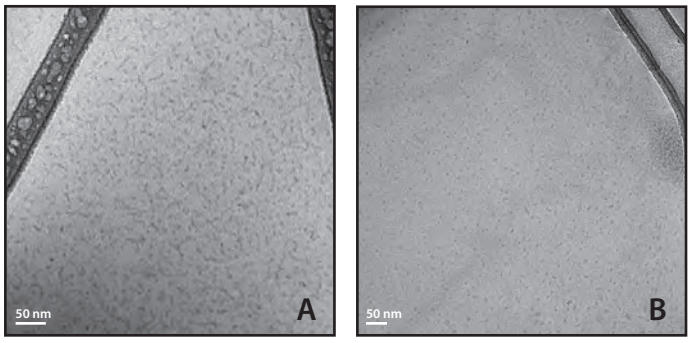


Figure 3. Cryo-TEM Data Comparing Nanoparticles of PTS (A) and TPGS-1000 (B). *(Ref. 8,14)*

2. Background

In our previous review in this journal,[8] we introduced PTS (**7**; **Figure 2**)[9] as a useful (nonionic) surfactant; a nanomicelle-forming species in which a variety of Pd- and Ru-catalyzed couplings took place in water at room temperature. The idea behind the choice of PTS was simple: in the Paul Anastas sense, it follows the "12 Principles of Green Chemistry",[10a] as explained in *Benign by Design*.[10b] That is—in being composed of racemic vitamin E, sebacic acid, and PEG-600—neither PTS nor any of its three components is environmentally of concern. Indeed, PTS is FDA GRAS affirmed for use in dietary supplements.[11] By itself, PTS is a provitamin; a modified version of "ester-E."

By comparison, readily available alternative amphiphiles, such as Triton® X-100 and those in the Brij® series,[12] only on occasion lead to comparable results in cross-coupling reactions. Even the closely structurally related TPGS (TPGS-1000, Figure 2)[13] affords quite different outcomes in cross-couplings under otherwise identical conditions. This seems particularly odd, since both PTS and TPGS-1000 share the same micellar lipophilic interior in the form of α-tocopherol. So what's responsible for the commonly observed greater rates of conversion in PTS? The answer seems to be that both the size and shape of their nanoparticles matter (**Figure 3**).[8,14] For PTS, both 8–10-nm spheres and larger worm- or rod-like particles are present (together averaging ca. 25 nm) according to cryo-TEM analysis (see Section 5). By contrast, TPGS in water forms very sharp 12–13-nm spherical micelles as indicated by microscopy and Dynamic Light Scattering (DLS) measurements.[14]

3. Chemistry in PTS–H_2O, an Update: a 1st-Generation Amphiphile for Transition-Metal-Catalyzed Cross-Couplings

It is not uncommon for synthetic chemistry to advance at a far greater pace than does our understanding of why the chemistry goes as observed. This is certainly true here as well, involving non-ionic surfactants that self-aggregate to form nanoreactors,[15] or what Fujita and co-workers refer to as "functional molecular flasks."[16] Early work focused mainly on a series of Pd-catalyzed "name" reactions (e.g., Heck,[17] Suzuki–Miyaura,[18] and copper-free Sonogashira[19] couplings), as well as olefin cross-[20] and ring-closing metathesis[21] reactions, all of which could be carried out in water at room temperature (**Figure 4**).

Since these initial reports, considerable progress has been made on many related Pd- or Ru-catalyzed couplings. In most cases, the species involved are tolerant of the presence of water as the gross reaction medium.[22] Although these couplings are likely occurring within the lipophilic portions of the micelles, some of a micelle's

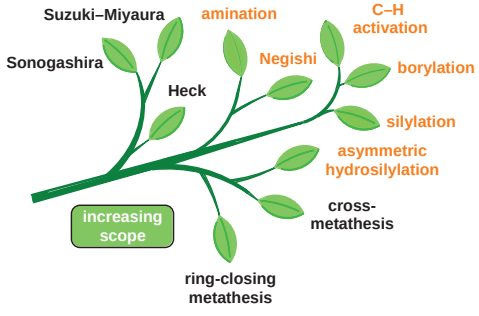


Figure 4. PTS-Enabled Reactions in Water at Room Temperature.

occupants may be exposed at any time to the surrounding water, given its dynamic character.[23] That is, there is constant exchange of monomeric units of surfactant between micellar arrays. This motion creates a mechanism by which educts, catalysts, and reaction product(s) can enter and exit a micelle. But the exchange phenomenon also leads to exposure to an aqueous environment through which they must traverse. This can have major (beneficial) consequences for the desired transformation; that is, the content of the water can be altered to great synthetic advantage. Foreshadowing associated with these effects was noted in the previous *Aldrichimica Acta* review,[8] where couplings run in seawater led, in some cases, to faster reactions than had been observed in pure (HPLC grade) water. Changes in the ionic strength[24] and pH of the aqueous medium have now been studied and, indeed, there are benefits to be had from such perturbations resulting from the simple addition of selected salts to water (vide infra).

3.1. Amination

The use of PTS is an effective enabling technology for two types of amination, both taking place in water at room temperature. Unsymmetrical di- and triarylamines can be constructed using aryl bromides and aniline derivatives. In the presence of $[PdCl(allyl)]_2$, Takasago's ligand, cBRIDP® (**14, Figure 5**), was the most effective among several catalysts (**8–16**) screened. Although these transformations appear to be general in that a variety of reaction partners can be used and yields tend to be good, perhaps the most intriguing aspect of this methodology is the influence of the base (**eq 1**).[25] Thus, while KOH (1.5 equiv) is oftentimes sufficient, reaction times can vary and may take up to a full day to reach completion. That KOH functions well in this capacity is rather interesting, since the coupling is occurring within the lipophilic core of the PTS micelle, where presumably polar species are not to be found. It is certainly possible that KOH remains in the aqueous phase, and that as species exchange between nanoreactors they are exposed to the surrounding water, and it is here when the proton may be abstracted from the participating nitrogen.[26] Likely to be more effective, rate-wise, at finding a protonated amine intermediate would be a more lipophilic base, capable of penetrating the micelle into the hydrophobic pocket (**eq 2**).[25] A switch, therefore, to KO*t*-Bu, made a favorable difference in this regard, notwithstanding the fact that this base in water is mainly KOH. Hence, the same outcome could be achieved by simply adding *tert*-butyl alcohol to the original mixture containing KOH. Even better, was addition of the commercially available potassium trimethylsilanolate ($KOSiMe_3$),[27] which reduced reaction times by almost an order of magnitude. Still more dramatic was inclusion of the far more lipophilic potassium triisopropylsilanolate [$(KOSi(i\text{-}Pr)_3$, or KO-TIPS], readily formed in situ from KOH and TIPS-OH.

Allylic aminations in water at room temperature can also be accomplished using allylic phenyl *ethers* as substrates.[28] These are unconventional partners in Pd-catalyzed couplings, where activation of the hydroxyl group in an allylic alcohol typically takes place in the form of an acetate, carbonate, sulfonate, or phosphate.[29] Nonetheless, under the influence of the hydrophobic effect, and in the presence of excess K_2CO_3 and methyl formate, couplings result in amination predominantly at the least hindered, terminal site and give high *E:Z* ratios (**eq 3**).[28] DPEPhos (**15**)[30] was found to be the ligand of choice, while the more rigid analogue XantPhos (**16**)[31] led to only traces of allylic amines.

Perhaps more intriguing is the same net amination, …but with allylic *alcohols* (**eq 4**).[32] While in situ activation has been achieved previously using a variety of protic or Lewis acids (e.g., $SnCl_2$,[33a] Et_3B,[33b] RCO_2H,[33a] and CO_2[33b]), efforts toward the exclusion of water are common. Those reactions run in pure water typically require harsh conditions.[33c–e] Under similar micellar conditions applied to allylic ethers (above), couplings give highly favored linear rather than

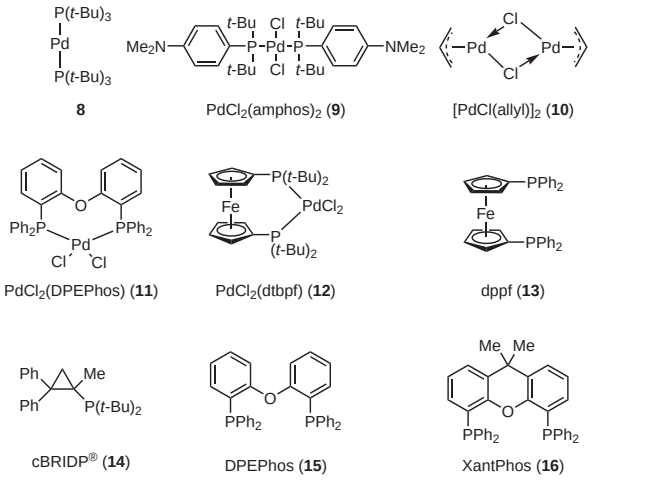
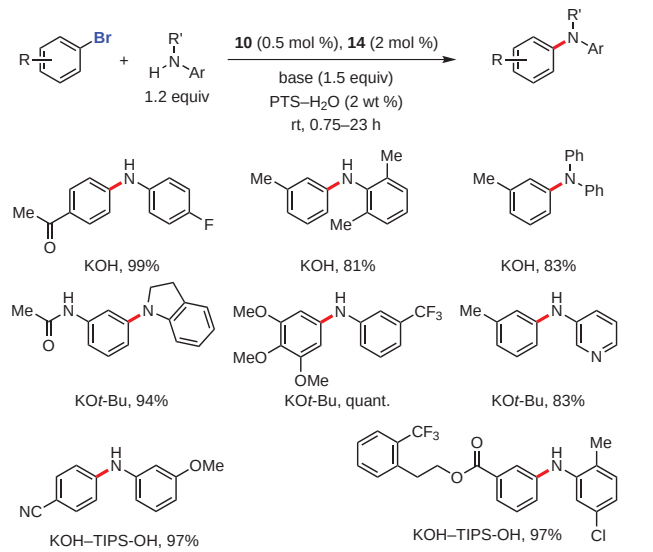
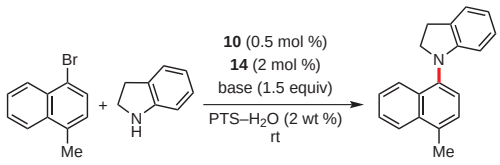


Figure 5. Ligands and/or Catalysts Used in Coupling Reactions. *(Ref. 25)*



Representative Amination in PTS–H_2O. 2′-(Trifluoromethyl)phenethyl 3-(5″-chloro-2″-methylphenyl)aminobenzoate {R = 3-[2-$F_3CC_6H_4(CH_2)_2OC(O)$], R′ = H, Ar = 5-Cl-2-MeC_6H_3}.[25] Inside a dry box, a 5-mL round-bottom flask equipped with a stir bar and fitted with a rubber septum under argon was sequentially charged with **10** (3.0 mg, 0.008 mmol), **14** (8.9 mg, 0.025 mmol), and KOH (89 mg, 1.58 mmol). Outside the dry box, under a positive flow of argon, were sequentially added via syringe to the mixture of **10** and **14**: *degassed* water (0.8 mL) and *degassed* 10 wt % PTS solution (0.2 mL) (to give a *degassed* 2 wt % PTS solution; 1.0 mL), then TIPS-OH (320 µL, 1.61 mmol), 5-chloro-*o*-toluidine (150 µL, 1.25 mmol), and, lastly, 2′-(trifluoromethyl)phenethyl 3-bromobenzoate (380 mg, 1.02 mmol). The milky reaction mixture was stirred under argon at rt for 45 min, after which complete consumption of the aryl bromide was observed by GC analysis. The reaction mixture was diluted with brine and extracted with EtOAc. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated by rotary evaporation to give the crude residue. Purification by silica gel chromatography (gradient from hexanes to 2% EtOAc in hexanes) afforded the product (428 mg, 97%) as a viscous, beige-colored oil.

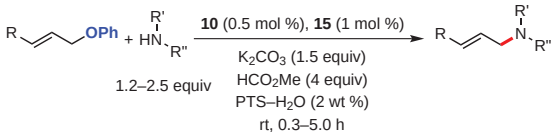
eq 1 *(Ref. 25)*



Base	Time	Conv.
Et_3N	42 h	79%
KOH	44 h	72%
KOH–*t*-BuOH	6 h	100%
$KOSiMe_3$	3 h	100%
KOH–TIPS-OH[a]	0.5 h	100%

[a] TIPS-OH = $(i\text{-Pr})_3SiOH$; in this case, a quantitative yield was obtained.

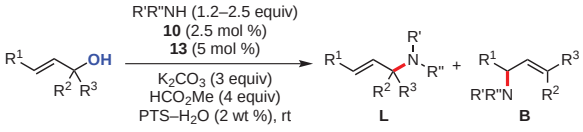
eq 2 *(Ref. 25)*

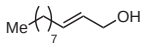
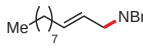
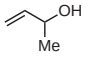
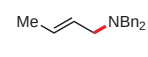
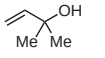
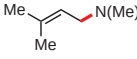
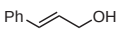
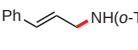
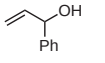
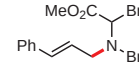


R	R'	R"	Yield
Ph	Me	1-NpCH_2	98%
n-Oct	Me	1-NpCH_2	90%
a	Me	1-NpCH_2	80%
Ph	Bn	4-Br$C_6H_4CH_2$	82%
Ph	H	2-MeC_6H_4	86%
H	EtO_2C(Bn)CH	*b*	85%

[a] RCH=$CHCH_2$ = cyclohexen-3-yl
[b] R" = (*E*)-4-(*t*-BuO_2CCH=CH)$C_6H_4CH_2$.

eq 3 *(Ref. 28)*



Alcohol	Product	Yield	L:B	*E*:*Z*
		84%	>25:1	16:1
		76%	24:1	11:1
		90%	63:1	----
		80%	100:0	all *E*
		80%	100:0	all *E*

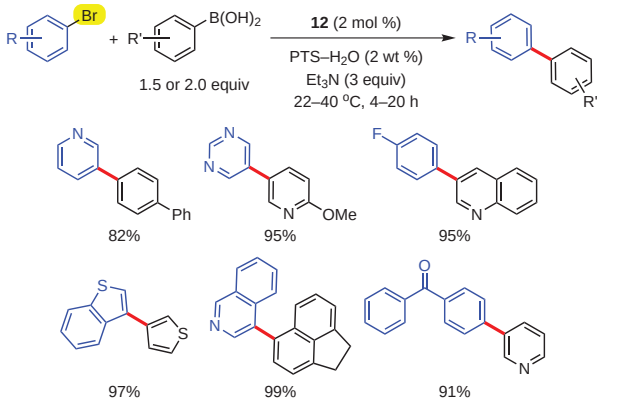
eq 4 *(Ref. 32)*

branched products, also strongly favoring *E* isomers. Here again, K_2CO_3 is the preferred base, while HCO_2Me in excess is required. Since none of the intermediate resulting from transesterification between the alcohol and methyl formate is observed at any point during the reaction, the proposed mechanism involves Pd(0), the educt, and the formate–reasonable given the presumed high concentration of species within the micelles.

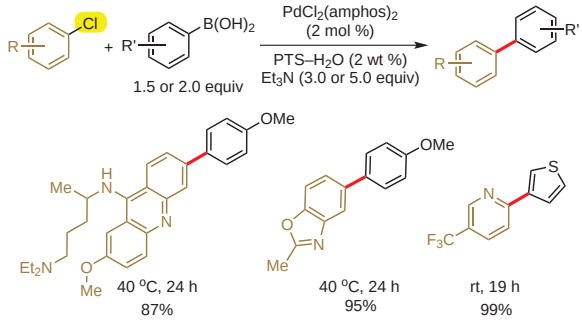
3.2. Suzuki–Miyaura Coupling

As previously described,[18] biaryls can be constructed from precursor aryl halides or pseudo-halides Ar–X (X = I, Br, Cl, OSO_2R) and boronic acids in 1% PTS in water mainly at ambient temperatures. Subsequent to this work, various heteroaromatic halides were also shown to be amenable.[34] Bromide was found to be the preferred leaving group (**eq 5**)[34] and, like chlorides, their reactions occasionally required mild heating to 40 °C (**eq 6**).[34] The choice of catalyst also varied by leaving group: bromides were best accommodated by $PdCl_2$(dtbpf), **12**, while chlorides seemed more responsive to $PdCl_2$(amphos)$_2$, **9**. A direct comparison with a literature case[35] showed the potential for this green chemistry to be highly competitive with traditional organic media (**eq 7**).[34] A review on the Suzuki–Miyaura cross-coupling as an entry to biaryls under green conditions has recently appeared, focusing on water as the reaction medium.[36]

Carbon–carbon bond formation between usually unreactive, acid- and base-stable allylic phenyl ethers and arylboronic acids is



eq 5 *(Ref. 34)*



eq 6 *(Ref. 34)*

also possible under micellar conditions.[37] As with allylic aminations (vide supra), there is a strong tendency to generate linear products where conjugation is maintained. Aliphatic ethers, on the other hand, favor branched products presumably due to the known faster rate of reductive elimination from a more hindered Pd(II) intermediate.[38] In addition to examples **17–19** (**eq 8**),[37] linchpin **20** bearing both acetate and phenyl ether moieties can be sequentially coupled, where, e.g., amination is followed by Suzuki–Miyaura coupling, all in one pot, all in water at room temperature (**eq 9**).[34]

3.3. Silylation

Palladium catalysis in PTS–water can also be extended to the formation of allylic silanes, likewise employing allylic phenyl ethers as substrates, in the presence of Et_3N (**eq 10**).[39] Such reactions do not occur in organic solvents (e.g., MeOH) at room temperature. Moreover, whereas silylations of the corresponding acetates require heating in organic solvents (e.g., DMF) for activation of a disilane ($R_3Si–SiR_3$),[40] cross-couplings in PTS nanoparticles take place at ambient temperatures in ≤20 hours at a global concentration of 0.16 M. The most effective catalyst source is $PdCl_2$(DPEPhos), **11**, as monodentate ligands on the metal (e.g., Ph_3P), or bidentate chelation of palladium by dtppf or dtbpf, afford only moderate levels of conversion (40–60%). Of the various products possible, linear over branched and *E* over *Z* isomers are both favored.[39]

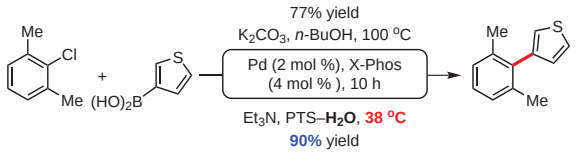
3.4. C–H Activation

With more than a handful of reviews on the topic of aromatic C–H activation reactions in just the past few years,[41] there is now a plethora of methods for introducing C–C bonds mainly ortho- to heteroatom-directing groups….but not in water at room temperature. This can be done, however, employing micellar catalysis.[42] Thus, aryl ureas, especially those bearing electron-donating groups, can be cross-coupled with aryl iodides in an aqueous medium containing any one of several surfactants; including PTS, TPGS, Triton® X-100, Solutol,[43] Brij® 30, and Brij® 35; where yields in optimization studies varied between 65 and 76%. The corresponding "on water" experiment led to only a 35% yield in the same time frame. Since the best results were obtained in nanomicelles containing Brij® 35, several additional examples were studied in this medium, along with ingredients $Pd(OAc)_2$, AgOAc, and HBF_4. Yields were in the 70–97% range (**eq 11**),[42] and products derived from double arylation were rarely observed, presumably reflecting the mild conditions involved.

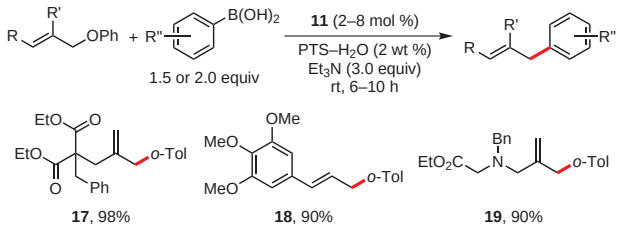
Arylations with $Pd(OAc)_2$ are typically run in highly acidic media; e.g., HBF_4, TFA, TsOH, or HOAc; which facilitate loss of HOAc from the catalyst and lead to electrophilic attack on an aromatic ring.[44] Alternatively, it has been shown that Fujiwara–Moritani coupling reactions with acrylates can be carried out in PTS–water (**eq 12**)[45] by using a *cationic* source of palladium, as in commercially available $[Pd(MeCN)_4](BF_4)_2$,[46] Both benzoquinone (1 equiv) and $AgNO_3$ (2 equiv) are required. Double functionalization ortho to the amide directing group is not observed here as well.

3.5. Negishi-like Couplings on the Fly…in Water

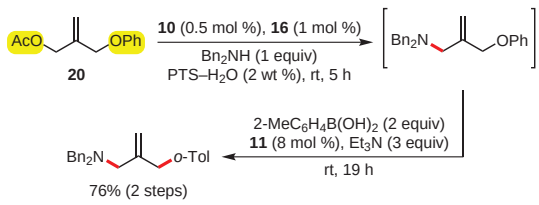
According to reference works on the topic, organozinc halides are not moisture-tolerant.[47] Indeed, Knochel and co-workers have spent, literally, decades elucidating the extent to which RZnX reagents can be used in the presence of protons of varying acidity.[48] Free alcohols, in general, require protection; the presence of even *tert*-butyl alcohol takes its toll on couplings run in the presence of this additive.[48a] Water is nowhere to be found among the various listings; hence, the message



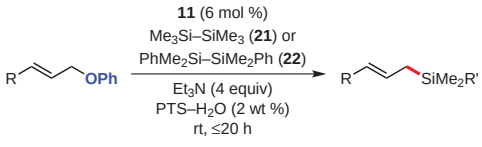
eq 7 *(Ref. 34)*



eq 8 *(Ref. 37)*



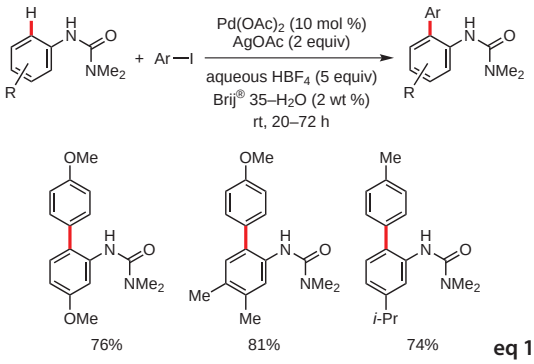
eq 9 *(Ref. 37)*



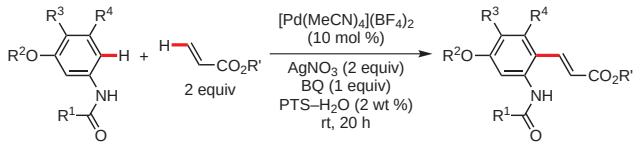
[a] In all cases, linear:branched = 25:1. [b] $PdCl_2(Ph_3P)_2$ (1.5 mol %) and $PdCl_2$(DPEPhos) (1.5 mol %) were used.

R^a	R'	Yield	*E:Z*
Ph	Me	91%	10:1
2-$MeOC_6H_4$	Me	86%	>25:1
3-$MeOC_6H_4$	Me	90%	9:1
n-C_8H_{17}[b]	Me	85%	3:1
Ph	Ph	91%	>25:1
2-$MeOC_6H_4$	Ph	87%	>25:1
3-$MeOC_6H_4$	Ph	91%	24:1
4-$MeOC_6H_4$	Ph	94%	>25:1
4-$EtO_2CC_6H_4$	Ph	95%	>25:1
2-Np	Ph	93%	>25:1

eq 10 *(Ref. 39)*



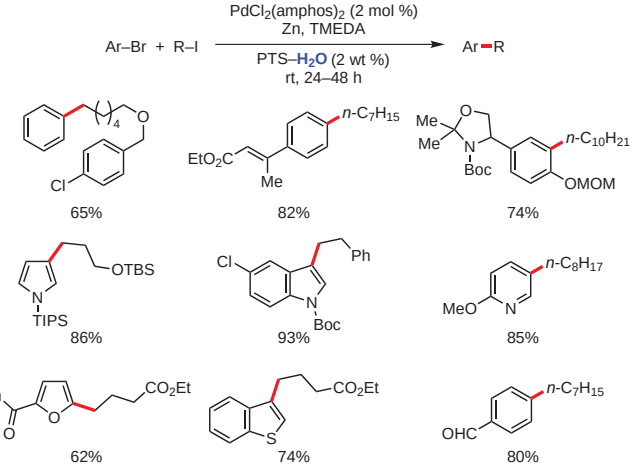
eq 11 *(Ref. 42)*



25	R^1	R^2	R^3	R^4	R'	Yield
a	*i*-Pr	Me	H	H	*n*-$C_{12}H_{25}$	80%
b	Me_2N	Me	H	H	$Me(CH_2)_5CHMe$	76%
c	*n*-Pr	Me	H	H	*n*-BuCH(Et)CH_2	80%
d	Me	*n*-Pr	H	H	*n*-BuCH(Et)CH_2	96%
e	*i*-Pr	Me	Me	H	3,7-$Me_2C_8H_{15}$	81%
f	*i*-Pr	Me	H	H	$Cy(CH_2)_2$	77%
g	*i*-Pr	Me	H	MeO	3,7-$Me_2C_8H_{15}$	80%

Representative Fujiwara–Moritani coupling of 23g and 24g to give cinnamate 25g.[45] Anilide **23g** (56 mg, 0.25 mmol), acrylate ester **24g** (106 mg, 0.5 mmol), 1,4-benzoquinone (27 mg, 0.25 mmol), $AgNO_3$ (85 mg, 0.5 mmol), and $[Pd(MeCN)_4](BF_4)_2$ (11 mg, 0.025 mmol) were sequentially added in air to a reaction tube equipped with a stir bar and a septum. An aqueous solution containing PTS (1.0 mL, 2 wt %) was added by syringe and the resulting mixture vigorously stirred for 20 h. The contents of the flask were then quenched with aqueous $NaHCO_3$ and extracted with EtOAc. The ethyl acetate extracts were combined and filtered through a plug of silica gel and anhydrous $MgSO_4$, and then concentrated by rotary evaporation. The residue was purified by flash chromatography, eluting with hexane–EtOAc to afford analytically pure **25g** (86 mg, 80%). HRMS (ESI) m/z calcd for $C_{25}H_{39}NO_5Na$ (M + Na^+) 456.2726, found 456.2721 (Δ = 1.1 ppm).

eq 12 *(Ref. 45)*



eq 13 *(Ref. 50a)*

is clear: whether it's "on water", "in water", or "with water",[49] the only conditions applicable to zinc reagents involve "no water".[47]

Could the textbooks be "wrong"? Not likely. But in this obvious acid–base chemistry between RZnX and H_2O two assumptions are implied: (i) that RZnX and H_2O find each other, and (ii) that a stoichiometric amount (or more) of RZnX is used; otherwise, with lesser amounts, the anticipated yield must suffer. If both of these conditions are removed; that is, if RZnX could be "insulated" from any water present, and if the amount of RZnX at any given time is minimized and yet, over time, a stoichiometric level of RZnX is formed in the pot, then the desired Pd-catalyzed cross-couplings of organzinc reagents, in water, might be possible. Well, they are, thanks to micellar catalysis.

For both aryl bromides[50] and alkenyl halides,[51] couplings with primary and secondary alkyl halides can now be accomplished in a remarkably straightforward fashion. The recipe calls for the two precursor halides, a specific (commercially available) palladium catalyst, and importantly, TMEDA. These are combined in water (ca. 0.3 M) containing 2 wt % PTS to which is added inexpensive zinc metal in the form of powder or dust; and the whole mixture is then stirred. After a reasonable period of time, which is substrate-dependent, the cross-coupled product is obtained in good yield. Representative examples involving aromatic and heteroaromatic bromides are illustrated in **eq 13**.[50a]

This remarkable process can be envisioned as depending entirely on the precise timing of the various events that need to take place, just like the gears of a fine-tuned pocket watch (**Figure 6**). Within the nanoparticles of PTS are housed the various reaction components, densely packed due to the hydrophobic effect; no organometallic (RZnX) is present. As nanoparticles collide with zinc metal on its surface, preferential insertion of Zn into the sp^3 halide (R–X) takes place in a likely successive one-electron-transfer sequence. The resulting water-sensitive RZnX is insulated from the surrounding water. RZnX is also stabilized by the TMEDA present, which may assist in shuttling it into the micelle where both the Pd catalyst and sp^2 halide await, in relatively high concentrations. If the rate of formation of RZnX is too fast for subsequent passage into the hydrophobic micellar core, the reagent escapes and is rapidly quenched by water, as expected. Thus, while electron transfer en route to RZnX can be controlled for both 1° and 2° alkyl halides, reactions involving 3° precursors are far too rapid; thus, only quenched material (R–H) results.[50]

The corresponding couplings with alkenyl iodides and bromides, rather than aryl bromides, also give the anticipated products with retention of stereochemical integrity (**eq 14**).[51] With both types of educts (aryl and alkenyl), the choice of catalyst is absolutely crucial: $PdCl_2(amphos)_2$ (**9**)[52] is the only species screened to date that affords high levels of conversion and, thus, good isolated yields. Even the parent species; i.e., the bis(des-dimethylamino) analogue, was not nearly as effective. (*Note that the nomenclature for "amphos" as used for this ligand*[52] *is seemingly inconsistent with prior literature.*[53])

4. New Insights into Micellar Catalysis for Organic Synthesis

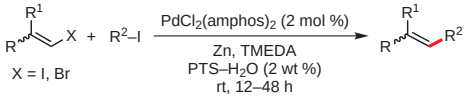
The observation that several of these Pd-catalyzed couplings not only can be run in seawater,[54] but actually take place in this medium at a greater rate than in HPLC grade water, has led to some very exciting developments of potential practical value. The presence of salts in the water can influence the chemistry in two significant ways:[55] (1) the size and shape of the nanoparticles in which these couplings take

place are altered, and (2) the pH of the aqueous medium which can impact the nature of the catalysts involved. With NaCl, a "salting out" effect exists,[56] which removes water from the PEGylated portions of the particles, tending to increase micellar size and/or modify particle shape as the PEG expands into the water. This effect is due to the anion, and several salts examined lead to similar particle changes, although the corresponding coupling chemistry in the presence of each salt has yet to be examined. Particle shape can also be dramatically altered. These effects can be shown by cryo-TEM analysis, e.g., on PTS with and without NaCl (**Figure 7**).[54] The "salting in" effect, which tends to decrease micellar size, is observed, e.g., with iodides NaI and KI.[57]

Changes in pH resulting from addition of small amounts of a salt such as $KHSO_4$ can impact couplings due to the dynamic nature of micelles; i.e., they are constantly in flux.[23] Their amphiphiles traverse a sea of surrounding water for the exchange phenomenon to occur. For catalysts that contain phosphines, e.g., ruthenium carbenes, as used routinely in olefin metathesis,[58] their phosphine ligands can be protonated upon exposure to aqueous acid,[59] and hence, may arrive at the micelle as a coordinatively unsaturated species (and thus, quite "hot"). These phenomena are illustrated below by Heck couplings and olefin metathesis reactions.

4.1. Heck Coupling in PTS–3 M NaCl (aq)

Heck reactions in micellar PTS–H_2O are especially responsive to changes in the ionic strength of the medium.[54] This effect is not to be expected in related reactions that, albeit conducted in water, rely on alternative phenomena. For example, supported catalysts such as



Entry	SM	R	R^1	R^2	X	Yield	*E*:*Z*
1	*Z*	*n*-Hex	H	$TMSCH_2$	I	95%	1:99
2	*Z*	$Cl(CH_2)_4$	H	$BnCH_2$	I	85%	3:97
3	*E*	TMS	H	$EtO_2C(CH_2)_3$	Br	83%	96:4
4		Ph	Me	Cy	Br	66%	----
5	*E*	$BnO(CH_2)_3$	H	*n*-Hex	I	85%	>99:1
6	*E*	Ph	H	*n*-Hex	Br	92%	91:9
7	*Z*	*n*-Hex	H	$EtO_2C(CH_2)_3$[a]	Br	74%	4:96

[a] $EtO_2C(CH_2)_3Br$ used.

Representative Pd-catalyzed, Zn-mediated coupling in PTS–H_2O. Preparation of Ethyl (Z)-5-dodecenoate (entry 7).[51] In a 5-mL, round-bottom flask under argon containing zinc powder (260 mg, 4 mmol) and $PdCl_2(amphos)_2$ (**9**; 7 mg, 0.01 mmol) was added a solution of 2 wt % of PTS (2 mL). *N*,*N*,*N*′,*N*′-Tetramethylethylenediamine (TMEDA) (232 mg, 2 mmol), was added at rt followed by addition of (*Z*)-1-bromooctene (181 mg, 1 mmol; *Z*:*E* = 99:1) and ethyl 4-bromobutanoate (390 mg, 2 mmol). The flask was stirred vigorously at rt for 48 h. The product was extracted with EtOAc. Silica gel (1 g) was added to the combined organic phase and the solvents were removed under reduced pressure. The resulting dry, crude product mixed with SiO_2 was introduced on top of a silica gel chromatography column which was eluted with 5% EtOAc–petroleum ether, affording the analytically pure product (167 mg, 74%; *Z*:*E* = 96:4); HRMS (ESI) *m*/*z* calcd for $C_{14}H_{26}O_2$ (M^+) 226.1933, found 226.1934 (Δ = 0.4 ppm).

eq 14 *(Ref. 51)*

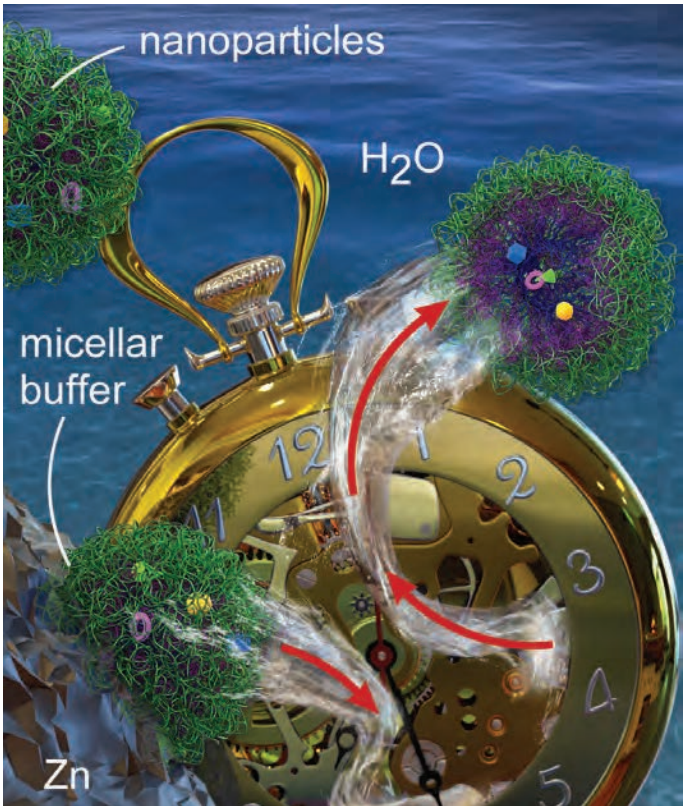


Figure 6. Pictorial Account of Couplings of RZnX in Water: Timing Is Key.

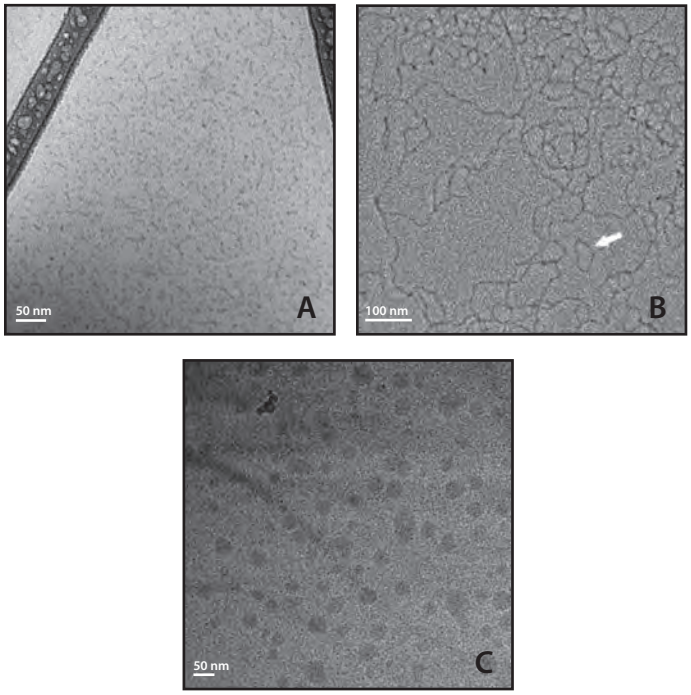
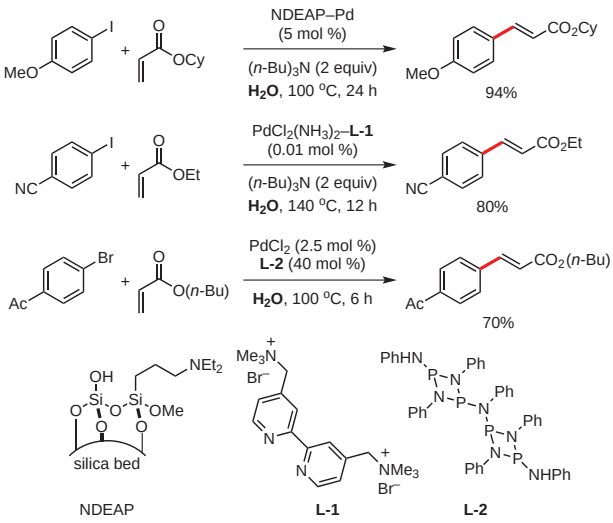
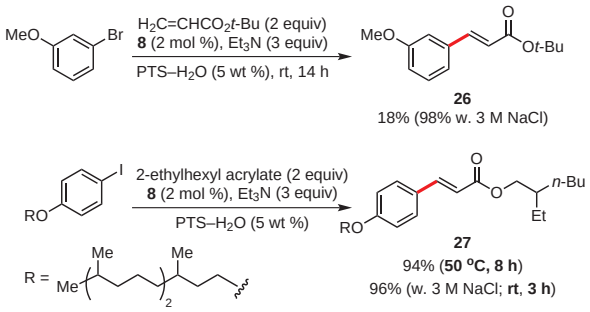


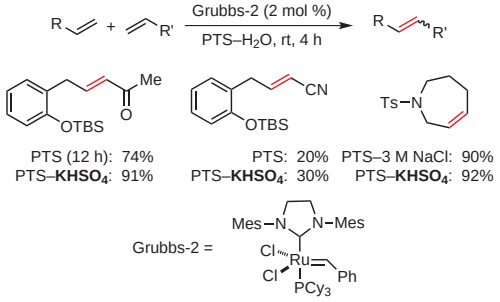
Figure 7. Cryo-TEM Image of (A) Aqueous PTS (50-nm Scale), (B) Aqueous PTS in the Presence of 3 M NaCl (100-nm Scale), and (C) TPGS-750-M. *(Ref. 54)*



Scheme 1. Recent Examples of the Heck Coupling in Water. *(Ref. 60–62)*



Scheme 2. Two Examples of the Influence of Added Salt on the Outcome of the Heck Coupling in PTS–H_2O. *(Ref. 54)*



eq 15 *(Ref. 54)*

$Pd(OAc)_2$ mounted on a reverse-phase *N,N*-diethylaminopropylated (NDEAP) silica gel impregnated with ionic liquid [bmim]PF_6 have been used (**Scheme 1**).[60] Other advances include applications of new Pd-complexed cationic bipyridyl ligands (**L-1**),[61] and new P–N ligands in the form of diazadiphosphetidines (**L-2**).[62] In each case involving an acrylate partner, while water is the reaction solvent, heating is needed to improve conversion.

Two examples of reactions subject to the influence of salts under micellar conditions are worth noting. In the first, cinnamate **26** is formed in PTS–water to a limited extent after 14 hours (**Scheme 2**, top reaction).[54] However, in the presence of NaCl (3 M) and at an identical global concentration (0.50 M), the reaction reaches full conversion in the same time period, with an associated high yield. In the second example, the formation of **27** requires mild heating to 50 °C to reach completion after 8 hours; in PTS–3 M aqueous NaCl, however, the reaction was complete at room temperature in 3 hours (**Scheme 2**, bottom).[54]

4.2. Olefin Metathesis at pH 2–3

In 2006, Hong and Grubbs reported on ring-opening polymerization (ROMP) reactions in aqueous acid, and showed that the 2nd-generation Grubbs catalyst has its phosphine sequestered via protonation.[59] The same protonation is presumably responsible for accelerating cross-metathesis under micellar conditions in water, most visibly in reactions involving tough type-2 olefins such as methyl vinyl ketone (MVK) and acrylonitrile (**eq 15**).[54] For related ring-closing reactions, e.g., forming a 7-membered ring, the net effect of added $KHSO_4$ was equivalent to that seen using 3 M NaCl.

5. Designing a Better Micelle: TPGS-750-M, a 2nd-Generation Amphiphile

Notwithstanding the progress made utilizing the first-generation designer surfactant PTS, the many lessons learned insofar as altering the nature of the surfactant to maximize reaction rates and reagent or catalyst stability encouraged the design of a second-generation amphiphile, TPGS-750-M.[63] Experience had shown that micelle size and shape matter; that improvements in rate in going from TPGS-1000 to PTS, where particle size increases from 13 to (on average) 25 nm,[54] seems to be an important clue. Since differences between the two were best visualized by cryo-TEM (see Figure 3), showing the longer rods or worms present only with PTS, TPGS-750-M (Figure 7C) was engineered to have a higher percentage of larger particles, preferably in the 50–100-nm range. A shorter PEG chain requiring less volume in its coiled state, and hence micelles able to accommodate more molecules per particle, should expand the particle's radius. A structural comparison between TPGS, PTS, and TPGS-750-M is illustrated in **Figure 8**.

From the standpoint of synthesis, a switch to four-carbon succinic acid as found in TPGS-1000,[13] rather than the ten-carbon sebacic acid as in PTS, makes a huge difference in overall efficiency of the two-step sequence (**Scheme 3**). That is, opening of succinic anhydride by vitamin E allows for a virtually quantitative esterification involving the most expensive component in the process. By contrast, PTS relies on sebacoyl chloride, a diacid chloride that reacts at both termini with α-tocopherol, thereby affording mixtures of the mono- and the diester.[8] Conversion of monoester **28** to TPGS-750-M via traditional esterification can be smoothly done in toluene in the presence of catalytic acid (TsOH), another close to quantitative event.[63] Here, use of a mono-methylated polyethylene glycol, or MPEG, rather than PEG (a diol) is the key to avoiding reactions at both ends. This is

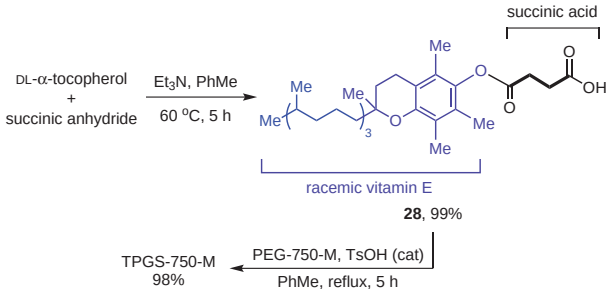
yet another problem in the route to PTS, which uses PEG-600 (and not an MPEG analogue). The 'net-net' of these changes is that the targeted amphiphile can be prepared in an overall yield that exceeds 95%, while the efficiency of making PTS is ca. 45%.

The greatly improved cost implies that couplings enabled by TPGS-750-M–H_2O need only be as good as those done in PTS. Of course, faster reactions might also be anticipated due to larger particle sizes. By virtue of increases in binding constants of the substrates and catalysts within the micellar environment (i.e., longer time spent within a micelle), reactions should reach higher states of conversion more rapidly.[64] What has been found in this regard is that most types of cross-couplings in TPGS-750-M do, in fact, lead to isolated yields that are equal to, or better than, those seen in aqueous PTS. Some direct comparisons are illustrated in **Scheme 4**, with each pair of reactions being run at the identical concentration and time frame.

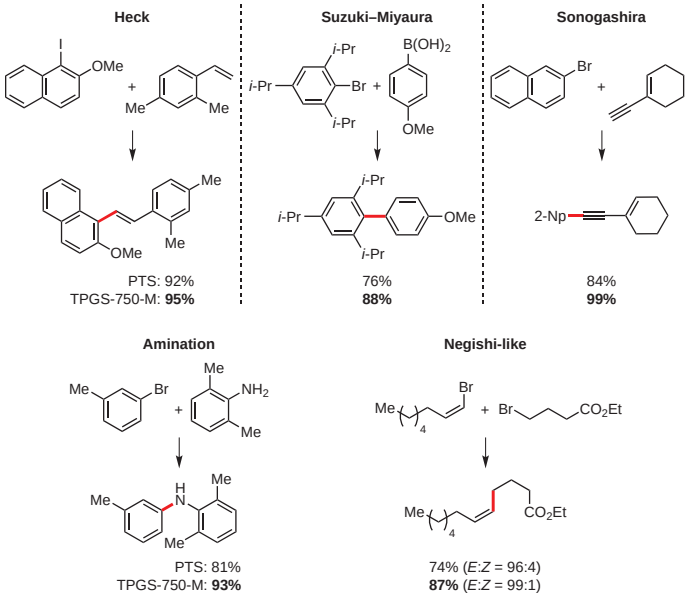
Likewise gold-catalyzed cycloisomerizations of allenols take place readily in both aqueous PTS and TPGS-750-M, where the presence of NaCl was found to shorten reaction times (**eq 16**).[65] In a number of cases, yields were better with the second-generation surfactant, although some substrate dependence was noted.

5.1. CuH-Catalyzed Asymmetric Hydrosilylation

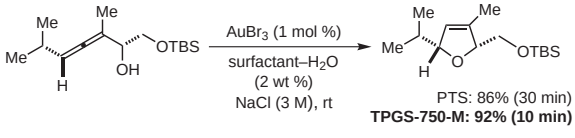
The in situ generation and use of copper hydride, derived from precursors such as CuCl–NaO*t*-Bu, CuF_2, or $Cu(OAc)_2$, routinely takes place in organic media: toluene, THF, etc.[66] Although the reagent is stable to water and, in fact, was used long ago by Stryker to enhance the rate of quenching of copper(I) intermediates (e.g., enolates resulting from 1,4 addition of hydride from $(Ph_3P)CuH$,[67] its use in a strictly aqueous medium is not among the available protocols. It might even be argued that water as "solvent" presents a likely major



Scheme 3. Straightforward, High-Yield Synthesis of TPGS-750-M. *(Ref. 63)*



Scheme 4. Cross-Couplings in PTS–H_2O and in TPGS-750-M–H_2O. *(Ref. 63)*



eq 16 *(Ref. 65)*

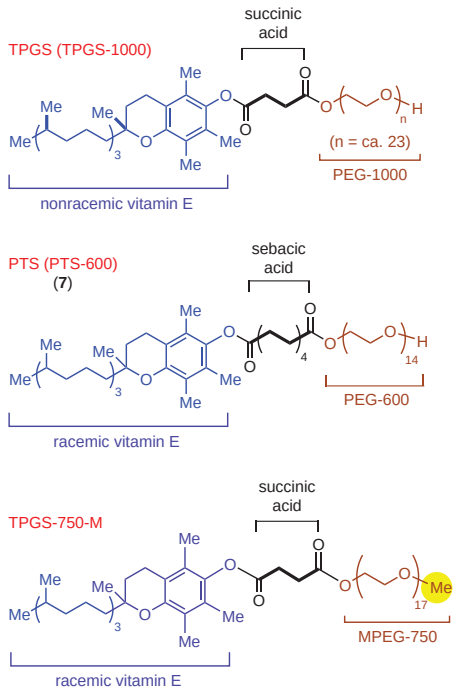


Figure 8. Structures of TPGS, PTS, and the Newly Engineered TPGS-750-M. *(Ref. 63)*

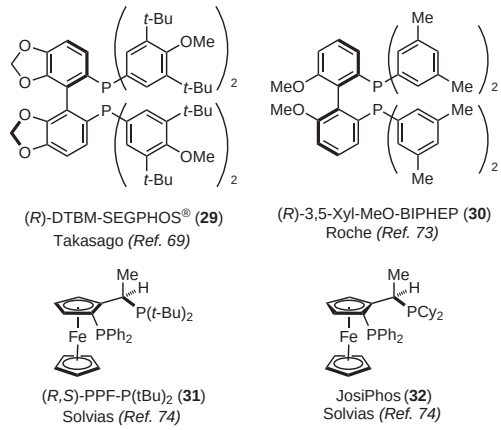
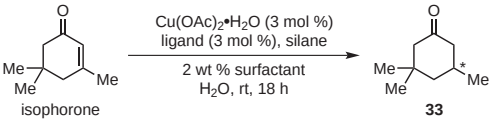
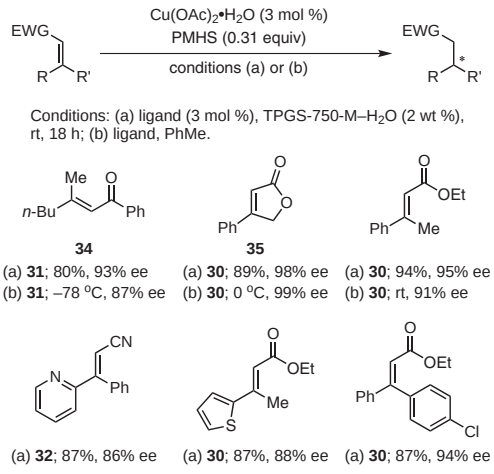


Figure 9. Nonracemic Ligands Used in CuH-Catalyzed Asymmetric Hydrosilylation.



Ligand	Silane	Hydride	Surfactant	Conv. (Yield)	ee
29	$PhSiH_3$	36 equiv	PTS	100% (89%)	99%
30	PMHS	9 equiv	TPGS-750-M	100% (88%)	94%
30	PMHS	9 equiv	none	18%	nd

eq 17 *(Ref. 70)*



eq 18 *(Ref. 70a)*

limitation, since the literature on these conjugate reductions clearly suggests that lower reaction temperatures tend to maximize ee's.[68] Thus, while eliminating organic solvents from these reactions would impart an element of "greenness", the tradeoff in substrate insolubility and potentially lower ee's might not favor a "green" approach. On the other hand, such reactions being run at high concentrations within micelles at room temperature may not follow the same rules, in which case the use of organic solvent and consumption of energy for cooling would both be averted.

It came with some surprise, therefore, that treatment of isophorone with CuH ligated by Takasago's (*R*)-DTBM-SEGPHOS® (**29**)[69] (**Figure 9**) in 2 wt % PTS–H_2O at room temperature afforded the product of 1,4 addition in high yield and in 99% ee (**eq 17**).[70] This result is comparable to the best that has been seen to date, albeit done in toluene at low temperatures.[71] Unfortunately, this conversion required far too much $PhSiH_3$ (12 equiv, or 36 equiv of hydride), as this reagent is competitively decomposed in aqueous solution. Eventually, the best conditions identified focused on the use of polymethylhydrosiloxane (PMHS)[72] as hydride donor (⅓ equiv, 9 equiv of hydride) in 2 wt % TPGS-750-M, giving the same product in 94% ee. By way of comparison, the identical reaction run in water only gave 18% conversion after the same 18-h reaction time.

Other ligands, including Roche's 3,5-Xyl-MeO-BIPHEP (**30**)[73] and Solvias's JosiPhos ligands (**31** and **32**)[74] are also effective, depending upon the nature of the substrate.[70] Particularly interesting is enone **34**, where in combination with ligand **31** and at –78 °C in toluene, an 87% ee was reported.[71] The identical reaction run in water at room temperature gave a comparable yield; however, the ee was *higher*: 93% (**eq 18**).[70a] Likewise, butyrolactone **35** reacted at room temperature and led to a similar yield and ee relative to that seen earlier, where the reaction was run at 0 °C. That ee's can be obtained that are on par with, or even exceed, those normally realized at low temperatures may be a consequence of restricted reagent and/or substrate movement within tightly packed micellar arrays, where energetic differences between diastereomeric transition states are accentuated, and less favorable orientations are minimized. The nature of the micelle interior also plays a crucial role, as documented by these asymmetric hydrosilylations run under otherwise identical conditions using alternative amphiphiles (Brij® 30, Cremophor®, SDS, and Solutol®)–water solutions (**eq 19**).[70] Clearly, the newly designed TPGS-750-M affords the most effective medium for this type of transformation. That high ee's can be realized at room temperature within a micellar array without normal recourse to low temperatures is particularly striking.

5.2. Borylation of Aryl Halides

Aryl boronates, in particular those derived from pinacol using bis(pinacolato)diboron (B_2pin_2), figure prominently as coupling partners in Suzuki–Miyaura reactions.[75] Aryl bromides are common educts, although borylations in organic media (e.g., dioxane, DMSO, or THF) at room temperature are very rare.[76] Couplings "on water" do lead to product, but to a limited and unpredictable extent. However, in water containing 2–3 wt % TPGS-750-M, aryl pinacolatoboranes (**36**) could be smoothly prepared usually within three hours at a global concentration of 0.25 M (**eq 20**).[77] A Pd(0) catalyst, Pd(P*t*-Bu_3)$_2$ (8, 3 mol %), afforded the highest yields over several alternatives examined (e.g., $Pd(OAc)_2$–XPhos, $PdCl_2$(dppf), $Pd_2(dba)_3$–$2PCy_3$, etc.). Given that palladium is already present in the form of Pd(P*t*-Bu_3)$_2$, as well as its known use in Suzuki–Miyaura couplings,[78] introduction of a second aryl bromide into the reaction mixture ultimately leads to biaryl **37**

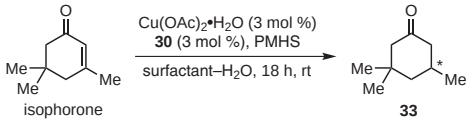
(**eq 21**). Compound **37** is formally the net cross-coupling product of two aryl bromides, achieved in one pot in water at room temperature.[79]

6. Summary and Outlook

Surfactants have an especially rich history of service to many areas of organic chemistry.[3] But most amphiphiles listed in catalogs perused by organic chemists today are from decades ago; they are rarely "green", nor are they matched in any way to the nanoscale environments that maximize the quality of transition-metal-catalyzed reactions. However, starting to appear are newly engineered "designer" surfactants that better accommodate reaction partners, additives, and catalysts characteristic of modern organic synthesis. In the interest of sustainability, the goal in designing new surfactants for synthesis is to develop reproducible and scalable processes that minimize involvement of organic solvents, at least from the standpoint of the reaction medium. Historically, however, "surfactant science & technology as pursued in academia has not overlapped well with the mindset of industrial chemists in this area".[80] That is, while academicians tend to strive for purified, homogeneous materials that are readily subject to analytical techniques (e.g., surfactants such as Triton® X-100 and SDS), industrial researchers oftentimes are faced with a "Make it work and don't worry about why!" approach. As author Drew Meyers unabashedly continues in his monograph,[80] "The sad fact of life is that real surfactant systems are almost always composed of mixed chemical isomers, contaminants, and added materials that can alter the effects of a given surfactant on a system…" This is precisely the current state of affairs surrounding PTS, since, in fact, it is a mix of many components: PEG-600 contains a broad range of polyethylene units, and the many byproducts from its preparation, as discussed earlier, are likely to be present in varying amounts. Its chromatographic purification using peak-shaving techniques led to the unexpected observation that, remarkably, PTS of >95% purity is actually *insoluble* in water![81]

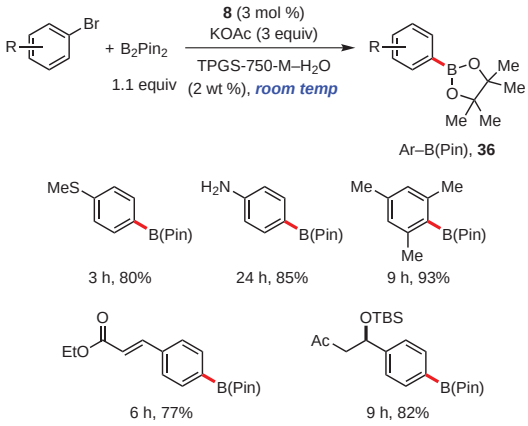
The switch to TPGS-750-M, therefore, provides an amphiphile that avoids many of these contaminants by virtue of its design. While remaining benign, it offers the community a better economic profile, along with enhanced reaction rates for the cross-couplings taking place within its nanomicelles. As with PTS, it also usually leads to a very attractive impurity profile, given the room temperature conditions for the vast majority of reactions in this aqueous medium. For the intended industrial uses, time in the kettle (i.e., throughput) is another virtue, since there is no time (or energy) investment due to heating and/or cooling of these coupling reactions. While this second-generation surfactant has yet to be fully evaluated, it would be naïve to assume that future generations of designed nanomicelles that offer even better matches between reaction ingredients and micellar interiors will not be forthcoming.

Part of the insight yet to be gained will come from just hard work; making and testing surfactants that address variables that may provide additional clues as to how to improve metal-catalyzed couplings. For example, the surfactant "Nok" (**Figure 10**) is currently being studied as an analogue of TPGS-750-M; it relies on a "healthy" phytosterol, β-sitosterol, in keeping with the theme that any newly created surfactant should pose no potential environmental insult regardless of scale of usage. The point to be tested, however, is whether in providing a hydrophobic interior as solvent composed of a cyclic hydrocarbon, as opposed to the linear hydrocarbon found in the vitamin E portion of TPGS-750-M, along with the anticipated control of size in the 50–100-nm range, there are further improvements in any or all of the cross-coupling chemistry of interest. Moreover, let's

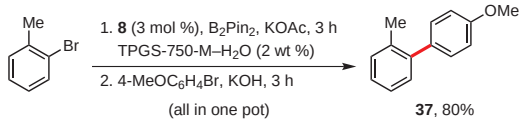


Surfactant	Conv.	ee
Brij® 35	20%	92%
Brij® 30	50%	81%
Cremophor® EL	100%	86%
SDS	6%	95%
Solutol® HS15	21%	92%
TPGS-750-M	**100%**	**94%**

eq 19 *(Ref. 70)*



eq 20 *(Ref. 77)*



eq 21 *(Ref. 77)*

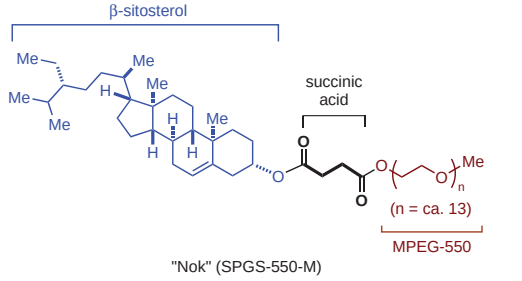


Figure 10. Structure of "Nok" (SPGS-550-M) Currently under Study.

appreciate that micellar catalysis, by virtue of synthetic design and manipulation, de facto offers a virtually unlimited array of potential reaction media tailored to best match a given transformation, each to be used catalytically as a nanoreactor.[82] By contrast, consider just how few the choices of traditional organic solvents there really are.

New discoveries of potential major consequence in synthesis that take advantage of the hydrophobic effect await us; two of these have been discussed herein: organozinc-mediated cross-couplings in water (see Section 3.5),[50,51] and unexpectedly high ee's from asymmetric hydrosilylations with CuH at room temperature (see Section 5.1).[70] More are on the way; e.g., homogeneous catalytic organocopper chemistry that forms *C–C bonds in water* at room temperature.[83] This latter discovery is seemingly difficult to accept, given the many reviews on copper chemistry written by one of the authors. This is especially true in the Schlosser *Manuals*,[84] advising readers to be extremely cautious about the sensitivity of carbon-based copper reagents to moisture! One interpretation of these data could be that the "rules" for doing chemistry at high concentrations in nanoparticles may well be different from those accumulated over the past 40–50 years of modern organic synthesis. This notion was foreshadowed by Lindström and Andersson in their *Angewandte Chemie* article "Hydrophobicity Directed Organic Synthesis",[85] in which these authors suggest that, "The design of stereoselective reactions based on hydrophobic interactions is an area of great potential that is still largely unexplored." After all, Nature does not do chemistry by matching substrates and catalysts to organic solvents as we know them. Nature's macroscopic medium is water, which is used either as a legitimate solvent, or to force molecular organization to create hydrophobic pockets. Isn't that precisely what we call "micellar catalysis"?

7. Acknowledgements

The chemistry discussed herein has been the culmination of tremendous efforts by the PI's graduate students (Ben Taft, Alex Abela, David Chung, Ralph Moser, Karl Voigtritter, Shenlin Huang, and Zarko Boskovic), postdoctoral students (Subir Ghorai, Takashi Nishikata, Christophe Duplais, and Arkady Krasovskiy), and group associates (Wendy Leong, Isabelle Thome, Julian Graff, Paul Konopelski, and Valeria Krasovskaya). These co-workers deserve the credit for the progress we have made in the past few years since our 2008 review in a previous *Aldrichimica Acta* issue.[8] We are also most appreciative of the support extended by the NIH (GM 86485), and the especially generous gifts of both ligands and catalysts used in our studies by Dr. Tom Colacot (Johnson Matthey); Dr. Richard Pedersen (Materia); Ms. Astrid Metzger (Umicore AG & Co.); Drs. Takao Saito and Hideo Shimizu, and Mr. Izuru Nagasaki (Takasago); Dr. Benoit Pugin (Solvias); and Drs. Rudolf Schmid and Michelangelo Scalone (Roche). The author also warmly acknowledges the intellectual contributions of Dr. Volker Berl (Mycell Technologies) toward the creation of TPGS-750-M, and Prof. Norbert Krause, along with several past and present group members for their comments on this manuscript prior to publication.

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About the Authors

Bruce Lipshutz has been on the faculty at UC Santa Barbara for the past 33 years. His training initially as an undergraduate with Howard Alper (SUNY at Binghamton), then Harry Wasserman (Yale), and finally as a postdoctoral student with E. J. Corey (Harvard) set the stage for his interest in organic synthesis and, in particular, organometallics. From his early contributions in the form of reagents such as SEM-Cl and higher order cyanocuprates to heterogeneous catalysts in the form of nickel- and copper-in-charcoal, the focus has been on providing technologies that are broadly applicable to synthetic problems. More recently, he and his co-workers have turned their attention in large measure to "green" chemistry, in appreciation of the major problems now facing society from the standpoint of sustainability, and, more specifically, issues associated with the reduction of organic waste, much of which is solvent-related. Hence, the Lipshutz group has introduced the concept of "designer" surfactants, utilizing micellar catalysis as an environmentally innocuous means of carrying out important transition-metal-catalyzed cross-coupling reactions, as well as several other reaction types (e.g., organocatalysis), in water at room temperature.

Subir Ghorai was born in 1977 in Panskura, West Bengal, India. After receiving his B.S. and M.S. degrees in chemistry from Jadavpur University, India, he joined the Indian Institute of Chemical Biology (IICB), Jadavpur, in 2000 as a CSIR research fellow. He received his Ph.D. degree in 2005 from IICB, working under the supervision of Dr. Anup Bhattacharjya on the synthesis of chiral dendrimers and heterocycles from carbohydrate precursors. From 2005 to 2006, he worked on isonitrile chemistry as a postdoctoral fellow with Professor Michael C. Pirrung at the University of California, Riverside. He then moved to UC Santa Barbara as a postdoctoral fellow working with Professor Bruce H. Lipshutz, where he helped initiate "green" chemistry involving transition-metal-catalyzed reactions in aqueous media. Recently, he has taken a position at Sigma-Aldrich in Sheboygan, Wisconsin, as an R&D scientist in the Catalysis and Organometallics group.

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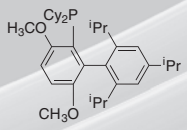

New

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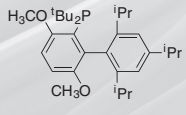

New

t-BuBrettPhos
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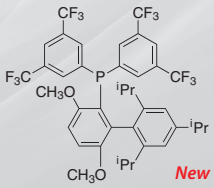

New

JackiePhos
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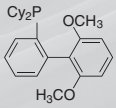

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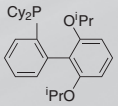

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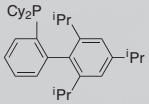

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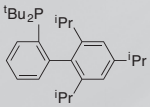

t-BuXPhos
638080

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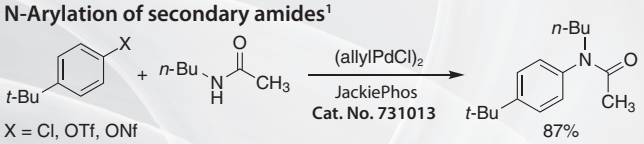
New Applications for Buchwald Ligands

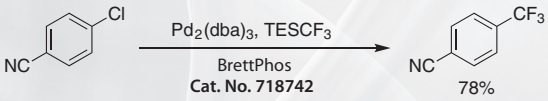
N-Arylation of secondary amides[1]



X = Cl, OTf, ONf

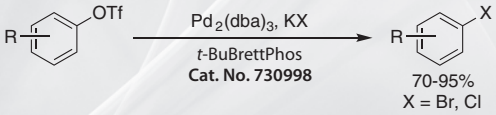
87%

Trifluoromethylation of aryl chlorides[2]



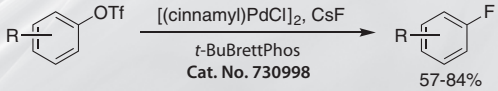
78%

Conversion of aryl and vinyl triflates to bromides and chlorides[3]



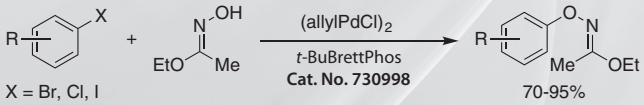
70-95%
X = Br, Cl

Conversion of aryl triflates to aryl fluorides[4]



57-84%

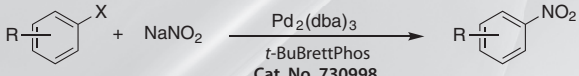
O-Arylation of ethyl acetohydroximate[5]



X = Br, Cl, I

70-95%

Conversion of aryl chlorides and sulfonates to nitroaromatics[6]



X = Cl, OTf, ONf

74-98%

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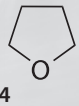
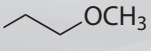
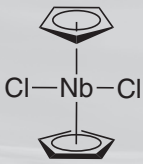
215791	339202	203920
NbO_2	$LiNbO_3$	$NbCl_4 \cdot 2$ 
383163	254290	326364
$NbCl_3 \cdot H_3CO$ 		$NaNbO_3$
326356		400653



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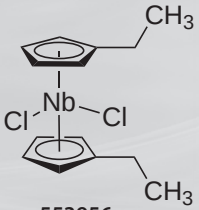
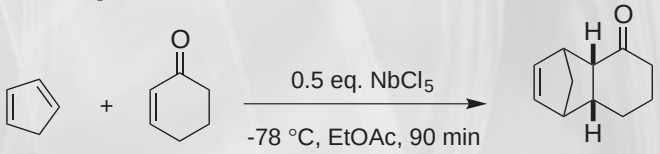


553956

Professor Lacerda's review focuses on applications of niobium compounds in catalysis of:

- Aldol Reactions
- Diels–Alder Reactions
- Friedel–Crafts Reactions
- Epoxide Ring-Openings
- Multicomponent Reactions
- Protection and Deprotection Reactions
- Demethylation Reactions

A representative example employing $NbCl_5$ as a Lewis acid in a Diels–Alder reaction is shown below. The use of $NbCl_5$ ensures formation of the endo stereoisomer. In contrast, the reaction does not take place in the absence of Lewis acids, and gives mixtures of endo and exo products, when the more commonly used $AlCl_3$ is utilized.



74% (endo)

Constantino, M. G.; Lacerda, V., Jr.; da Silva, G. V. J. *Molecules* **2002**, *7*, 456.

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The Growing Impact of Niobium in Organic Synthesis and Catalysis

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Keywords. catalysis; organic synthesis; niobium chlorides; niobium oxides; selectivity; versatility; efficiency.

Abstract. The growing interest in, and applications of, niobium compounds in organic synthesis and catalysis are surveyed, with a focus on their efficiency and versatility in several classical and broad organic reaction types. It is our hope that this review will spur further investigations of this lesser studied, but equally important, member of group 5 transition metals.

Outline

1. Introduction

Being in the same periodic table group as tantalum and vanadium (which is known for its many applications in organic synthesis), niobium is highly oxophilic.[1,2] Niobium can easily accommodate a number of ligands presenting different coordination numbers.[3,4] For this reason, its organometallic chemistry is very rich,[5] and a large number of niobium complexes have been reported.[5,6] Niobium possesses different oxidation states, which range from +5 to –3. Its chemistry, however, is dominated by the higher oxidation states, especially the +5 one.[4] Niobium was originally called columbium (Cb) by Hatchett in 1802,[7] was renamed niobium by Rose in 1844,[8] and then niobe. Finally, over a century later, IUPAC officially adopted the name niobium in 1949–1950.[9] Niobium does not occur in nature in its free metal form,[1c] but as a mixture of metal oxides such as columbites $[(Fe,Mn)(Nb,Ta)_2O_6]$ and pyrochlore $[(Na,Ca)_2Nb_2O_6(OH,F)]$. The most commercially important ore deposits are in Brazil, Canada, Nigeria, and Zaire. About 86% of world reserves are in Brazil, which accounts for roughly 60% of total niobium production.[1b,1c]

Many researchers have focused on the solid-state chemistry of niobium and its compounds, in order to produce catalysts and other materials for industrial applications.[1b,10] Because of its high resistance to corrosion and high electrical conductivity, niobium is ideal for chemical and metallurgical applications such as: (i) heterogeneous catalysis (catalyst components and co-catalysts), (ii) space and aeronautical industries (Nb–Al–Ti alloys), (iii) superconductivity (magnets based on Nb–Sn alloys), and (iv) electronics industry (capacitors, ceramics, bone implants, and internal suturing—since it is completely inert to bodily fluids). Nevertheless, around 85 to 90% of the niobium produced worldwide is used in the steel industry as iron–niobium alloys (ferroniobium), which can contain from 40 to 70% niobium.[11]

The most commonly used niobium compound is undoubtedly commercially available niobium pentachloride ($NbCl_5$), which is highly Lewis acidic and, for this reason, has received increasing attention in recent years. $NbCl_5$ can be prepared in several ways,

but the easiest one is the direct chlorination of metallic niobium at 300–350 °C.[1c] Niobium pentachloride is a yellow solid that is quickly hydrolyzed and transformed into HCl and $NbOCl_3$ or Nb_2O_5•nH_2O (niobic acid). It dissolves into nonaqueous solvents such as alcohols and acetonitrile, and forms stable 1:1 complexes with a number of donor ligands, including ethers, thioethers, tertiary amines, nitriles, etc.[12] $NbCl_5$ exists as dimeric units in the solid state, in which the metal is surrounded by a distorted octahedron of chlorine atoms.[4] This dimer can be seen as two octahedra sharing one edge (**Figure 1**).[4] It is strongly electrophilic and hence is able to catalyze a variety of organic reactions, which is the subject of this review.

The applications of $NbCl_5$ in organic synthesis and the prospects for this promising reagent have been reviewed.[13,14] Interestingly, several reactions mediated by $NbCl_5$ had a different outcome as compared to the same reactions employing other Lewis acids. The main purpose of this article is to highlight the most recent (over the last five years) applications of niobium pentachloride and other niobium compounds in organic synthesis and catalysis, including our own recent results. In this context, $NbCl_5$ offers several benefits such as ease of handling and, generally, low catalyst loadings.

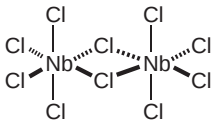
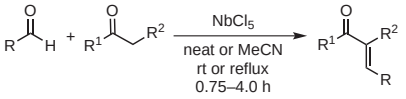
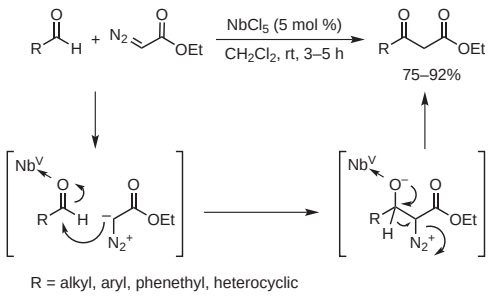


Figure 1. Dimeric Structure of Niobium Pentachloride in the Solid State. *(Ref. 4)*



$NbCl_5$ (mol %)	R	R^1	R^2	Yield
10	Ph	EtO	CN	90%
10	3-Py	EtO	CN	84%
10	2-Fur	EtO	CN	92%
10	*n*-C_7H_{15}	EtO	CN	88%
20	Ph	EtO	CO_2Et	86%
20	2-$O_2NC_6H_4$	Me	Ac	90%
20	*n*-C_7H_{15}	Me	Ac	70%
20	4-ClC_6H_4	Me	CO_2Me	80%

eq 1 *(Ref. 15)*



eq 2 *(Ref. 16)*

2. Catalysis by Niobium Pentachloride ($NbCl_5$)

2.1. Aldol and Related Reactions

Niobium pentachloride effectively catalyzes the Knoevenagel condensation of aromatic and aliphatic aldehydes with active methylene compounds (**eq 1**).[15] This has proven to be an efficient method for preparing α,β-unsaturated carbonyl compounds in good yields, high selectivity, shorter reaction times, and under mild reaction conditions in the presence or absence of solvent. The reaction proceeds presumably through activation of the aldehyde by complexation with Nb(V), followed by nucleophilic addition of the active methylene compound.

Another type of Aldol reaction, described by Yadav et al. involves the $NbCl_5$-catalyzed preparation of β-keto esters through insertion of ethyl diazoacetate (EDA) into the C–H bond of various aldehydes (**eq 2**).[16] These reactions readily occur at room temperature in good yields and high selectivity (no glycidic esters, diethyl maleate, or diethyl fumarate side products are observed), and are believed to take place as shown in equation 2. Of a number of Lewis acid catalysts ($InCl_3$, $CeCl_3$•$7H_2O$, $TaCl_5$, and $GdCl_3$) also tested in this reaction, $NbCl_5$ was found to be the most effective. No reaction was observed between the aldehyde and EDA in the absence of the Lewis acid.

2.2. Diels–Alder Reactions

In the Diels–Alder reaction between dienes and dienophiles, some of the usually sluggish dienophiles (e.g., 2-cycloenones **1–4**) can undergo the cycloaddition at 3 different temperatures (–78 °C, rt, or reflux) with unusually high stereoselectivity in the presence of $NbCl_5$ as a Lewis acid (**eq 3**).[17] $NbCl_5$ induces a decrease in the energy of the LUMO of the carbonyl substrate through complexation with the carbonyl oxygen, thus reducing the electron density of the double bond.

A related study has described the efficient synthesis of biologically important, fused pyrano[3,2-*c*]quinoline derivatives by the aza-Diels–Alder reaction of Schiff bases (**5**) and 3,4-dihydro-2*H*-pyran (**6**) facilitated by niobium(V) chloride (**eq 4**).[18] In this context, $NbCl_5$ is effective, promoting short reaction times and generally improved yields and diastereoselectivities, especially when lower molar concentrations of $NbCl_5$ are employed.

A versatile intermediate in the synthesis of eremophilanes and bakkanes has been prepared by a highly regioselective and stereoselective one-step synthesis that relies on an $NbCl_5$-catalyzed Diels–Alder reaction (**Scheme 1**).[19] The cycloaddition does not take place in the absence of Lewis acids. $NbCl_5$ plays a critical role, since it increases the reactivity to the point that the reaction is carried out at ≤ –50 °C, thus reducing diene polymerization and improving selectivity. The importance of this intermediate was demonstrated in the total synthesis of (±)-bakkenolide A.

2.3. Friedel–Crafts Reactions

Inter- and intramolecular Friedel–Crafts acylations are also highly efficiently catalyzed by $NbCl_5$.[20] In the intermolecular variant, the introduction of additives, such as $AgClO_4$, significantly enhances the catalytic action of the niobium complex. Arai et al. have reported that

$NbCl_5$ smoothly catalyzes the acylation of aromatic compounds with Ac_2O and Bz_2O to form the corresponding ketones in excellent yields (**eq 5**).[20a]

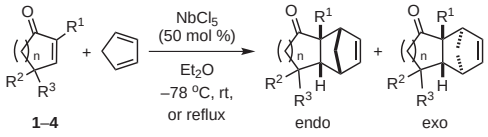
An intramolecular variant was described by Constantino and co-workers, who converted 3-arylpropanoic acids (**11**) into 1-indanones **12** in good yields and under mild conditions in the presence of 1.5–2.5 equivalents of $NbCl_5$ (**eq 6**).[20b] The authors demonstrated through NMR experiments that $NbCl_5$ initially performs the conversion of the 3-arylpropionic acids into acyl chloride and anhydride derivatives. These intermediates are then converted into 1-indanones through a Friedel–Crafts acylation reaction.

2.4. Epoxide Ring-Opening Reactions

The opening of epoxide rings is one of the most studied applications of $NbCl_5$ as catalyst. What this growing number of studies has shown is that small changes in reaction conditions can result in significantly different products being formed. One study reported that a number of cyclohexene oxide derivatives reacted rapidly with 0.13–0.5 equivalents of $NbCl_5$, resulting in good conversions, but led to mixtures of chlorohydrins (products containing solvent residues) and rearrangement products.[21]

In contrast, Oh and Knabe reported that addition of metallic zinc to the epoxide and $NbCl_5$ promoted deoxygenation to the corresponding *E* alkenes under mild conditions and in good yields and relatively short reaction times (**eq 7**).[22]

β-Amino alcohols are versatile intermediates in the synthesis of, among others, a wide variety of biologically active compounds, synthetic amino acids, β-blockers, oxazolines, and chiral auxiliaries. The $NbCl_5$-catalyzed ring-opening of epoxides with aromatic amines leads to the formation of β-amino alcohols in excellent yields and regioselectivity under mild reaction conditions (**eq 8**).[23] The reaction is noteworthy since it does not require anhydrous solvents or stringent reaction conditions and does not proceed in the absence of $NbCl_5$.



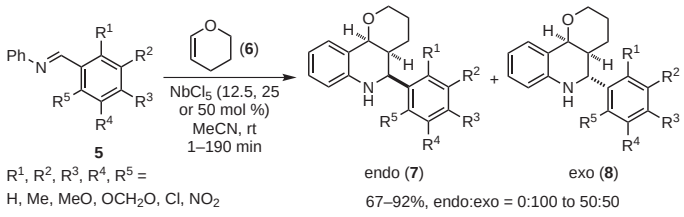
1–4

1; $R^1 = R^2 = R^3$ = H, n = 1; **2**; $R^1 = R^2 = R^3$ = H, n = 2
3; R^1 = Me, $R^2 = R^3$ = H, n = 2; **4**; R^1 = H, $R^2 = R^3$ = Me, n = 2

No.	Temp	Time	Yield	Endo:Exo
1	–78 °C	3 h	61%	89:11
1	rt	0.42 h	58%	78:22
1	reflux	0.08 h	65%	74:24
2	–78 °C[a]	3 h	72%	100:0
2	rt	0.75 h	58%	80:20
2	reflux	0.25 h	62%	78:22
3	–78 °C	8 h	32%	48:52
3	rt	24 h	43%	42:58
3	reflux	12 h	65%	30:70
4	–78 °C	8 h	40%	100:0
4	rt	24 h	34%	100:0
4	reflux	24 h	48%	100:0

[a] With $AlCl_3$ (25 mol %) and 6 equiv of cyclopentadiene at 40 °C, 7 h in PhMe: 80%, endo:exo = 89:11. With $SnCl_4$ (1.0 equiv) and 50 equiv of cyclopentadiene at –20 °C, 14 h: 93%, endo:exo = 92:8.

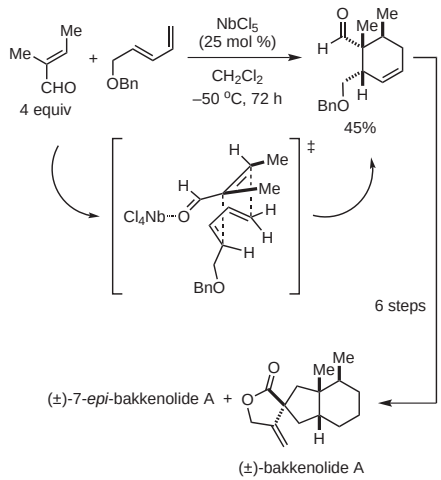
eq 3 *(Ref. 17)*



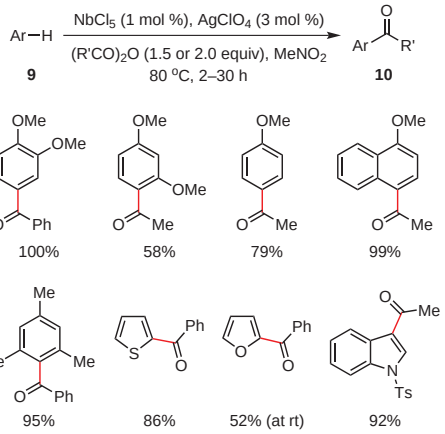
R^1, R^2, R^3, R^4, R^5 =
H, Me, MeO, OCH_2O, Cl, NO_2

67–92%, endo:exo = 0:100 to 50:50

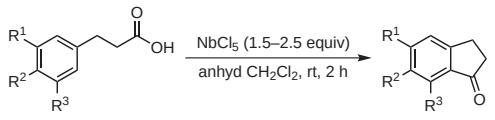
eq 4 *(Ref. 18)*



Scheme 1. The Key, $NbCl_5$-Catalyzed Step in the Synthesis of Eremophilane and Bakkane Systems. *(Ref. 19)*



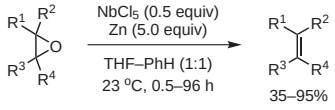
eq 5 *(Ref. 20a)*



11 12

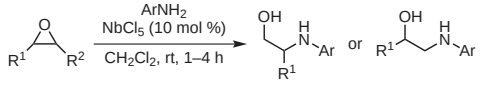
R^1	R^2	R^3	Yield
H	H	H	82%
H	MeO	H	31%
MeO	MeO	H	83%
MeO	MeO	MeO	95%

eq 6 *(Ref. 20b)*



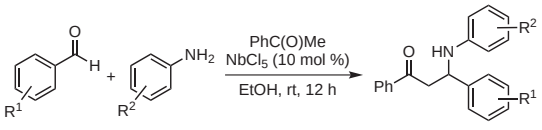
R^x = alkyl, aryl, CO

eq 7 *(Ref. 22)*



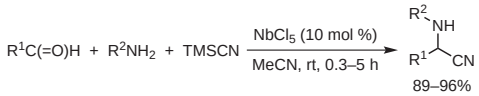
R^1 = Ph, $PhOCH_2$, $ClCH_2$; R^2 = H
R^1,R^2 = $(CH_2)_4$
Ar = mono- or disubstituted benzene

eq 8 *(Ref. 23)*



R^1 = H, 4-Me, 4-NO_2
R^2 = H, 4-Me, 3,4-Me_2, 4-MeO, 3-Cl, 4-Cl, 4-NO_2, 3-CO_2H, 4-CO_2H

eq 9 *(Ref. 24)*



R^1 = alkyl, vinyl, aryl, heteroaryl, and others groups
R^2 = Ph, Bn, 4-$MeC_6H_4CH_2$, 4-$MeOC_6H_4$

eq 10 *(Ref. 25)*

2.5. Multicomponent Reactions

A multicomponent reaction (MCR) is defined as a process in which three or more reactants are combined in one pot to form a structurally complex product that incorporates structural elements from each reactant. Lu and co-workers have described such an MCR in which β-amino carbonyl compounds were synthesized in high yields by an $NbCl_5$-catalyzed Mannich-type reaction between acetophenone, benzaldehydes, and anilines (**eq 9**).[24] Similarly, Kim's group reported a simple and efficient one-pot, $NbCl_5$-catalyzed synthesis of α-aminonitriles through an MCR involving aldehydes, amines, and trimethylsilyl cyanide (**eq 10**).[25]

2.6. Protection and Deprotection Reactions

One of the major challenges in total synthesis is effecting the protection and deprotection of a variety of functional groups. Low concentrations of $NbCl_5$ catalyze the acetylation of alcohols, phenols, amines, and thiols under mild reaction conditions (**eq 11**).[26] These reactions are characterized by short reaction times, cleaner products, and high yields. Based on these conditions and results, the following order of ease of acetylation of OH groups was established: phenolic > benzylic > primary aliphatic > secondary aliphatic > tertiary.

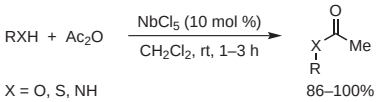
As a homogeneous catalyst, $NbCl_5$ is even more effective in catalyzing the acetylation of the carbonyl group of aldehydes to form acetals. The transformation takes place with acetic anhydride in the absence of solvent, and leads to excellent yields in short reaction times (**eq 12**).[27] The acetals thus formed tend to be stable in neutral, basic, and acidic media and have been employed in synthesis as starting materials, intermediates, and cross-linking reagents for cellulose.

Tetrahydropyrans (THPs) are attractive alcohol protecting groups because they are stable under a variety of reaction conditions, yet can be easily cleaved in dilute acid when needed. Niobium pentachloride catalyzes the smooth tetrahydropyranylation of alcohols and phenols at room temperature, leading to the protected counterparts in high-to-excellent yields (**eq 13**).[28] Some of the advantages of this method, when compared to previously reported hydroxyl-protection methods, are: (i) mild reaction temperature, (ii) shorter reaction times, (iii) lower catalyst loadings, (iv) better yields, (v) greater tolerance of other functional groups, and (vi) easier workup.

It is important to note that, not only does $NbCl_5$ readily promote functional-group-protection reactions, it can also effect the smooth deprotection of functional groups such as methoxy methyl ethers (MOMs) of alkyl, allyl, propargyl, and benzyl alcohols; MOMs of phenols; and the cleavage of MOM esters (**Scheme 2**).[29]

2.7. Demethylation Reactions

Hashimoto and co-workers showed that niobium pentachloride can effect the regioselective demethylation of **13**, a key step in the catalytic asymmetric synthesis of descurainin (**15**), which is widely used as a Chinese traditional medicine to relieve coughing, prevent



X = O, S, NH
R = alkyl, allyl, cycloalkyl, aryl

eq 11 *(Ref. 26)*

asthma, reduce edema, and as a diuretic. Employing the Arai–Nishida protocol, they treated **13** with $NbCl_5$ in 1,2-dichloroethane at 70 °C to effect the regioselective demethylation of the 4-MeO group, affording phenol **14** as the sole product in 79% yield (**Scheme 3**).[30]

3. Other Niobium-Based Catalysts

3.1. Solid-Phase Niobium(V)

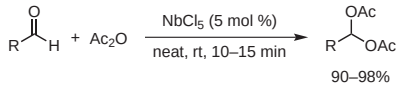
Barbosa's group has demonstrated a clean, efficient, and rapid method for esterifying sterically (biodiesels) or other inactive (aromatic) carboxylic acids by using Lewis acids on solid supports. In all cases investigated, the yields obtained with the mixed catalysts were similar to, or higher than, those reported in the literature. Results for the Nb_2O_5–Zn and Nb_2O_5–Fe are presented in **eq 14**.[31] Trial experiments without the solid-phase Lewis acid did not produce any ester product.

Another study by the same group showed that alcohols and acids can be switched to produce ethers or esters by varying the alcohol-to-catalyst molar ratio in the case of $NbCl_5$–Al_2O_3 under "solvent free" conditions and microwave irradiation. A "two sites" mechanism was proposed for the reaction to explain the tendency of the catalyst effectiveness to be dependent on the steric and electronic characteristics of the alcohol alone during the esterification process.[32]

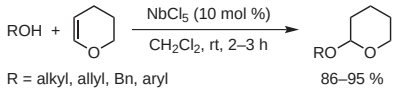
10 wt % Nb_2O_5 supported on silica–alumina catalyzes the liquid-phase esterification of acetic acid with a variety of alcohols at 85–128 °C. After 8 h, and using an acid:alcohol molar ratio of 2:1, 100% selectivity in all cases and good conversions were observed for ethyl (83%), *n*-butyl (87%), and isopentyl (91%) acetates.[33] Following a series of tests, conversions with the supported catalyst were better than those obtained with the isolated oxides, and better yet than those obtained in the absence of catalyst.

Nb_2O_5–SiO_2 mixed-oxide nanocomposites containing 7–37 wt % Nb were synthesized by a new sol–gel route, and their textural and surface acid properties investigated. Their activity as heterogeneous catalysts was tested in the epoxidation of cyclooctene with H_2O_2. The materials containing up to 23.0 wt % Nb were stable and active catalysts for the epoxidation of cyclooctene. The highest activity and selectivity for H_2O_2 was exhibited by the catalyst with the lowest Nb content, which also showed high stability in reuse. The catalytic properties were shown to be related to new acid sites that are different from those that exist in pure Nb and Si oxides, and to the presence of NbO_x species.[34] Niobium(V) oxide efficiently catalyzes the transesterification of β-keto esters with a variety of alcohols. Good conversions and moderate-to-good isolated yields have been obtained at faster rates than those recently reported for various other catalysts (**eq 15**).[35] Gonçalves and co-workers have reported that biodiesel can be obtained from fatty acid raw materials through esterification, and investigated, empirically and theoretically, the reactivity of lauric, palmitic, stearic, oleic, and linoleic fatty acids towards methanol by using powdered niobic acid (niobium oxide solid) as a heterogeneous catalyst.[36]

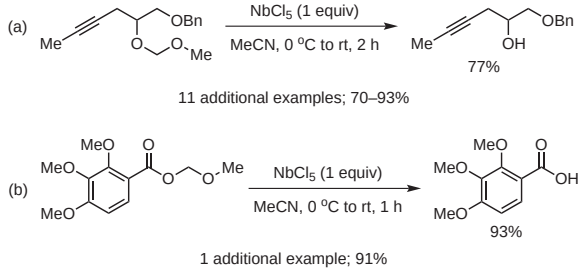
Somma et al. have described the preparation of a series of niobium-based aerogel samples (Nb_2O_5–SiO_2, Nb_2O_5–Al_2O_3, Nb_2O_5–ZrO_2) under acidic and basic conditions, and investigated the effect of the matrix (SiO_2, Al_2O_3, ZrO_2) and of the gelation conditions (acidic or basic) on the surface area, the porosity, and the catalytic activity of the solids in the oxidation of different substrates with hydrogen peroxide. The amount of niobium was constant in all samples tested in the oxidation of unsubstituted (cyclooctene) and substituted (geraniol, nerol, and *trans*-2-pentene-1-ol) olefins. It was found that, even though the catalysts were moderately active, they still produced the epoxides in good yields, and that yields are influenced by the matrix properties



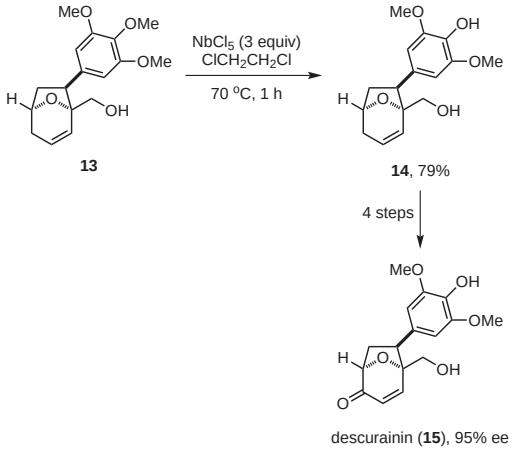
eq 12 *(Ref. 27)*



eq 13 *(Ref. 28)*



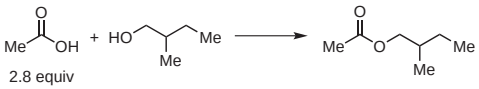
Scheme 2. Deprotection of MOM Ethers and Esters with $NbCl_5$. *(Ref. 29)*



Scheme 3. Regioselective Demethylation with $NbCl_5$. *(Ref. 30a)*

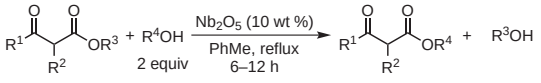
(surface acidity and surface area). The merits of this approach is that it permits the preparation of catalysts that are resistant to leaching and can be recycled several times without appreciable loss of catalytic activity.[37]

A new approach for functionalizing activated and deactivated arenes with iodine, promoted by heterogeneous catalysts, has been reported by Carniti et al. The overarching goal of this study was the development of "greener" iodination processes. Thus, the activity of several different types of solid acid catalysts (acid resins, zeolites, mixed oxides, niobium oxide, and niobium phosphate) was examined in the direct iodination reaction of phenol as a model arene. The mild, eco-friendly conditions (50 °C in methanol in the presence of H_2O_2 as oxidant) led to the efficient introduction of one, two, or three iodines in the arene. Different selectivity distributions of the iodo compounds formed were obtained with the different catalysts, and the latter could be grouped into distinct families on the basis of their ortho or para directing tendencies.[38]



Cat (80 wt %)	360 W μw 70 °C, 1 min	360 W μw 60 °C, 1 h
Nb_2O_5 on $ZnCl_2$	87%	84%
Nb_2O_5 on $FeSO_4$	87%	82%

eq 14 *(Ref. 31)*

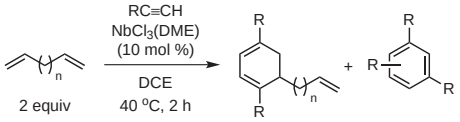


R^1 = Me, MeO_2CCH_2; R^2 = H
R^1,R^2 = $(CH_2)_4$
R^3 = Me, Et
R^4 = *i*-Pr, *n*-Bu, *t*-Bu, Bn, allyl, glycidyl, (–)-menthyl

50–100% conv
33–98% yield

removed by distillation

eq 15 *(Ref. 35)*



16 **17**

n	R	Yield 16	Yield 17
2	*t*-Bu	78%	6%
4	*t*-Bu	84%	trace
6	*t*-Bu	97%	trace
6	TMS	65%	18%
8	*t*-Bu	73%	trace
10	*t*-Bu	56%	nd

eq 16 *(Ref. 40)*

3.2. $NbCl_3$ and Niobium(III) Complexes

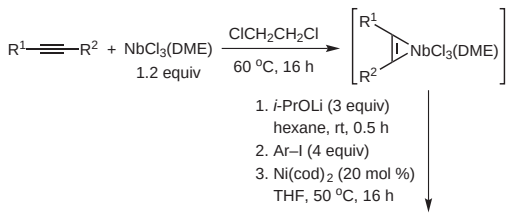
Obora and co-workers have demonstrated that $NbCl_3$(DME) successfully catalyzes the intermolecular [2 + 2 + 2] cycloaddition of alkynes and alkenes, giving 1,4,5-trisubstituted 1,3-cyclohexadiene derivatives in good yields.[39] A year later, the same group reported excellent yields and high chemo- and regioselectivities in the $NbCl_3$(DME)-catalyzed intermolecular [2 + 2 + 2] cycloaddition of *tert*-butylacetylene with α,ω-dienes, affording 5-ω-alkenyl-1,4-disubstituted-1,3-cyclohexadienes (**eq 16**).[40]

Interestingly, Ni(0) catalyzes the cross-coupling of Nb(III)–alkyne complexes with aryl iodides. An excess of lithium alkoxide, as additive, is indispensable for the success of this reaction, which leads to good yields of the corresponding 1,2-diarylalkene products (**Scheme 4**).[41]

$NbCl_3$(DME) mediates the reaction of aliphatic ketones with aryl-substituted alkynes to form a variety of 1,1,2-trisubstituted-1*H*-indenes in good yields (**Scheme 5**).[42] This remarkable transformation is believed to be the first example of a preparative route to the relatively rare 1,1-disubstituted indenes from aliphatic ketones, and is thought to proceed as depicted in Scheme 5.

3.3. $HNbMoO_6$•nH_2O

$HNbMoO_6$ functions as a strong solid-acid catalyst in a number of commonly used reactions. It exhibits high catalytic activity in acetalization, esterification, and hydration reactions, and its activity exceeds those of zeolites and ion-exchange resins in the Friedel–Crafts alkylation. In the first report of successful acid catalysis using a layered transition-metal oxide, the catalytic activity of $HNbMoO_6$ is attributed to the intercalation of reactants into the interlayer and the development of strong acidity. Layered $HNbMoO_6$•nH_2O consists of layers formed of randomly sited MO_6 (M = Nb and Mo) octahedra with H_2O in the interlayer. In one example, the performance of $HNbMoO_6$ was compared with those of niobic acid (Nb_2O_5•nH_2O), zeolites,



R^1	R^2	Ar	Isolated Yield	Isomer Ratio
Ph	Me	Ph	65%	----
Ph	Me	3-MeC_6H_4	63%	59:41
Ph	Me	4-MeC_6H_4	62%	59:41
Ph	Me	4-FC_6H_4	58%	nd
Ph	Me	4-$MeOC_6H_4$	46%	55:45
Ph	Me	4-ClC_6H_4	35%	53:47
Ph	Me	4-$MeO_2CC_6H_4$	53%	55:45
Ph	Ph	Ph	66%	----
3-$F_3CC_6H_4$	Me	Ph	72%	51:49
4-MeC_6H_4	Me	Ph	61%	54:46
n-Pr	Me	Ph	55%	64:36
n-Pr	*n*-Pr	Ph	51%	65:35

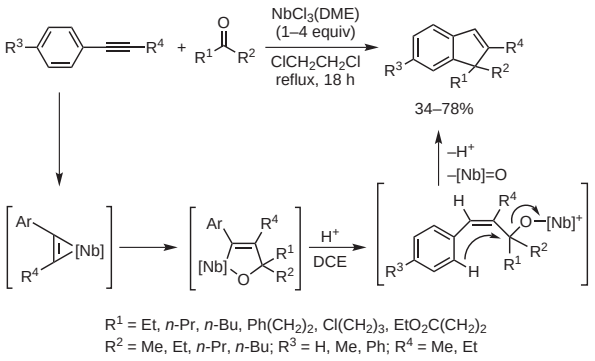
Scheme 4. Ni(0)-Catalyzed Cross-Coupling of Nb(III)–Alkyne Complexes with Aryl Iodides. *(Ref. 41)*

and ion-exchange resins in the Friedel–Crafts alkylation of anisole, toluene, and benzene with benzyl alcohol in the liquid phase over the layered oxide (**eq 17**).[43] The yield of benzyl anisole reached 99% after 30 min, whereas those obtained with the ion-exchange resins reached only ca. 42% even after 1 h. The turnover rate of $HNbMoO_6$ in the alkylation of anisole was more than three times higher than that of Nafion® NR50. It is worth noting that other layered transition-metal oxides such as HNb_3O_8 and $HTiNbO_5$ did not exhibit the activity.

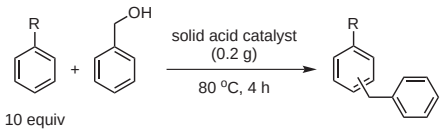
3.4. Niobium Alkoxides

Kobayashi and co-workers have reported the first example of the complementary stereoselective and catalytic desymmetrization of meso epoxides and meso aziridines with anilines as nucleophiles. This approach utilizes an extremely unusual and highly selective niobium catalytic system that promotes closely related reactions with opposite stereochemical outcomes. This Lewis acid system is based on the complex formed from niobium alkoxides and a tetradentate BINOL derivative. The resulting (*R*,*R*)-1,2-amino alcohols and (*S*,*S*)-1,2-diamines are obtained in good-to-excellent yields and very high-to-excellent enantioselectivities (**Scheme 6**).[44] Because of its sensitivity to steric bulk at the β carbon of epoxides, the catalyst displays a remarkable ability to distinguish between different meso epoxides by selectively facilitating the ring-opening of less sterically hindered epoxides in the presence of more sterically hindered ones. In the ring-opening reactions of both epoxides and aziridines, formation of the catalyst in the presence of molecular sieves—which were then filtered off before addition of reactants—was found to be important for the realization of high yields and stereoselectivities.[44]

Katsuki's group discovered a unique asymmetric catalysis by niobium–salan complexes of the epoxidation of allylic alcohols with hydrogen peroxide. It was first shown that a μ-oxo $[Nb(salan)]_2$ complex catalyzes the asymmetric epoxidation of allylic alcohols with the adduct of urea and hydrogen peroxide. Following analysis of the time course of the epoxidation, it was also discovered that in situ prepared Nb(salan) complexes catalyze the epoxidation of allylic alcohols with hydrogen peroxide in aqueous media (**eq 18**).[45] This latter method does not require the troublesome purification of the catalyst, and allows easy tuning of the ligand. It is the first example of a highly enantioselective epoxidation of allylic alcohols with aqueous



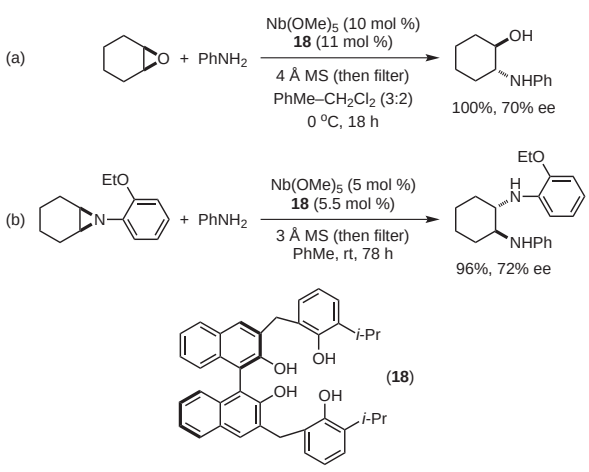
Scheme 5. First Example of a Preparative Route to 1,1-Disubstituted Indenes. *(Ref. 42)*



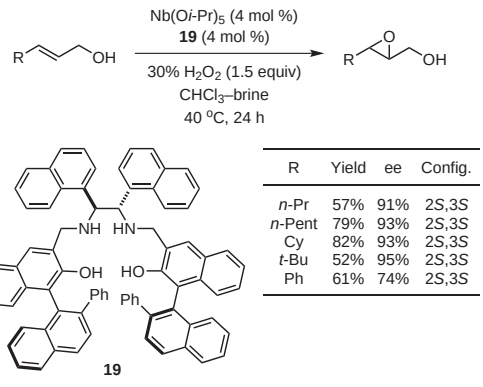
Solid Acid	Amount (mmol•g^{-1})	Yield for R = MeO[a]	Me	H
$HNbMo_6$[b]	1.9	99%	74%	22%
$HNbMo_6$[c]	1.9	94%	22%	8%
Nb_2O_5•nH_2O	0.3	1%	nd	nd
Nafion® NR50	0.9	42%	19%	10%
Amberlyst® 15	4.8	42%	14%	7%
H-ZSM-5 zeolite[d]	0.2	9%	1%	nd
H-Beta zeolite[e]	1.0	31%	1%	nd

[a] At 100 °C for 1 h. [b] Protonated with H_3PO_4. [c] Protonated with HNO_3; reaction time = 0.5 h. [d] SiO_2:Al_2O_3 = 90 (JRC-Z-5-90H). [e] SiO_2:Al_2O_3 = 25 (JRC-Z-HB25).

eq 17 *(Ref. 43)*

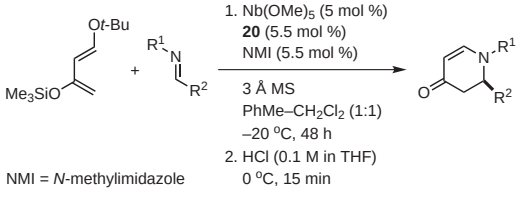


Scheme 6. Nb(V) Catalytic System Promotes the Desymmetrization of Closely Related Systems with Opposite Stereochemical Outcomes. *(Ref. 44)*

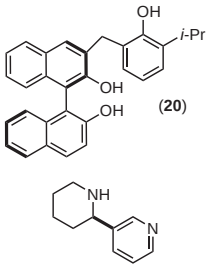


R	Yield	ee	Config.
n-Pr	57%	91%	2*S*,3*S*
n-Pent	79%	93%	2*S*,3*S*
Cy	82%	93%	2*S*,3*S*
t-Bu	52%	95%	2*S*,3*S*
Ph	61%	74%	2*S*,3*S*

eq 18 *(Ref. 45)*



NMI = *N*-methylimidazole

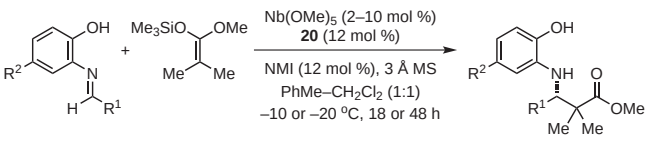


(+)-anabasine

R^1	R^2	Yield	ee
2-HOC$_6$H$_4$	Ph	81%	96%
2-HOC$_6$H$_4$	1-Np	89%	92%
2-HOC$_6$H$_4$	4-MeC$_6$H$_4$	90%	94%
2-HOC$_6$H$_4$	2-F$_3$CC$_6$H$_4$	94%	99%
2-HOC$_6$H$_4$	2-ClC$_6$H$_4$	89%	91%
2-HOC$_6$H$_4$	3-Py	74%	92%
2-HO-5-MeC$_6$H$_3$[a]	Cy	67%	90%
2-HO-5-MeC$_6$H$_3$[b]	*i*-Pr	63%	92%
2-HO-5-MeC$_6$H$_3$[b]	*i*-Bu	47%	90%

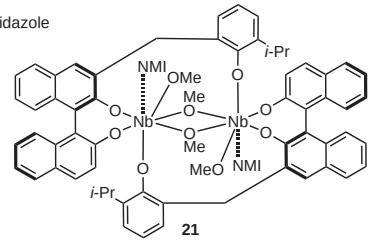
[a] In dichloromethane. [b] In toluene.

eq 19 *(Ref. 46)*



R^1 = Ph, 4-ClC$_6$H$_4$, 4-MeOC$_6$H$_4$, 1-Np, 2-Np, thien-3-yl, 2-Fur
R^2 = H, CF$_3$
NMI = *N*-methylimidazole

40–86%, 91–99% ee



21

eq 20 *(Ref. 47)*

H_2O_2 and of asymmetric catalysis by a niobium complex in aqueous medium.

A chiral, Nb(V)-based Lewis acid effectively catalyzes the aza-Diels–Alder reaction of imines with Danishefsky's diene. The reaction proceeds in high yield and high enantioselectivity for aromatic and aliphatic imines, and has been applied to the total synthesis of (+)-anabasine (**eq 19**).[46]

In an earlier study, Kobayashi's group had identified a novel dinuclear chiral niobium catalyst, **21**, formed from Nb(OMe)$_5$ and **20**. In the presence of a catalytic amount of this complex, asymmetric Mannich-type reactions proceed smoothly to afford the desired adducts in high yields and with high enantioselectivities (**eq 20**).[47]

4. Conclusion

The recently disclosed reactions presented in this review have highlighted the efficiency and versatility of niobium compounds as catalysts and reagents in organic synthesis. Interest in niobium compounds and their applications in chiral catalysis and total synthesis of natural products is growing steadily as evidenced by the increasing number of research groups around the world, who are studying these compounds and developing new applications for them.

5. Acknowledgments

The authors thank the Fundação de Amparo à Pesquisa do Estado do Espírito Santo (FAPES/FUNCITEC), the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), the Coordenadoria de Aperfeiçoamento de Pessoal do Nível Superior (CAPES), the Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP), the Companhia Brasileira de Metalurgia e Mineração (CBMM), and Laboratório Pesquisa e Desenvolvimento de Metodologias para Análise de Petróleos do Departamento de Química da UFES (LabPetro-DQUI/UFES) for financial support. The authors thank all their co-workers whose names appear in the references for their dedication and hard work.

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Valdemar Lacerda, Jr. was born in 1975 in Goiânia, GO, Brazil. He received a B.Sc. degree in chemistry in 1997 from the Federal University of Goiás, where he worked in the laboratory of Professor Pedro Henrique Ferri. He received his M.Sc. degree in 2000 and his Ph.D. degree in 2004 from São Paulo University, Ribeirão Preto, working with Professor Mauricio Gomes Constantino in organic synthesis and NMR studies. In 2004, he began working as a postdoctoral researcher at the NMR laboratory coordinated by Professor Gil Valdo José da Silva. In 2006, he joined the department of chemistry of the Federal University of Espirito Santo (ES State, Brazil) as an associate professor. His current research interests focus on organic synthesis, NMR studies, theoretical calculations, and petroleum studies. He has been Head of the Department of Chemistry since 2007, and is presently also a CNPq level 2 researcher.

Deborah A. dos Santos was born in 1989 in Cachoeiro de Itapemirim, ES, Brazil. She received her B.Sc. degree in chemistry in 2011 from the Federal University of Espírito Santo, where she worked on organic synthesis projects in the research laboratory of Professor Valdemar Lacerda, Jr. Currently, she is studying for her M.Sc. degree, and continues to work in Professor Lacerda's laboratory.

Luiz Carlos da Silva-Filho was born in 1979 in Itapetininga, SP, Brazil. He received his B.S. (2001) and Ph.D. (2006) degrees from São Paulo University, Ribeirão Preto, where he worked in organic synthesis in the laboratory of Professor Mauricio Gomes Constantino. In 2006, he began postdoctoral work in the Laboratory of Structural Biology and Zoochemistry coordinated by Professor Mario Sergio Palma at São Paulo State University, and, in 2008, he was appointed Assistant Professor in the Department of Chemistry at São Paulo State University. His current research interests are focused on organic synthesis and on the development and application of niobium compounds as catalysts for organic reactions.

Sandro J. Greco was born in Rio de Janeiro, RJ, Brazil. He received his B.Sc. degree in chemistry in 1997 and his M.Sc. and Ph.D. degrees in 2001 and 2005 from the Fluminense Federal University (Rio de Janeiro, Brazil), working under the guidance of Professor Sergio Pinheiro on studies of the use of terpenes and terpenoids in the enantioselective synthesis of potential anticholinergic agents, and on the synthesis of amino alcohol based, new chiral phase-transfer catalysts. In 2006, he joined Professor Maria D. Vargas's group at the Fluminense Federal University as a postdoctoral researcher to work on the synthesis and pharmacological evaluation of new anticancer drugs containing the ferrocenyl group. He is currently an associate professor of organic chemistry at the Federal University of Espírito Santo, with research interests in the design and synthesis of potential bioactive compounds and the development of new organocatalysts and chiral phase-transfer catalysts for asymmetric synthesis.

Reginaldo B. dos Santos was born in Matão, Brazil, and obtained his B.Sc. degree in chemistry in 1986 from the Federal University of São Carlos (SP State, Brazil). He then received his M.Sc. and Ph.D. degrees at the same University in 1990 and 1995, working under the supervision of Professor U. Brocksom in the field of organic synthesis. In 1991, he was appointed Assistant Professor in the Department of Chemistry at the Federal University of Espirito Santo (ES State, Brazil), and was promoted to Associate Professor in 1995.

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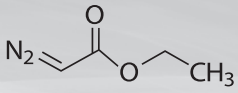

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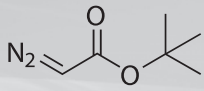

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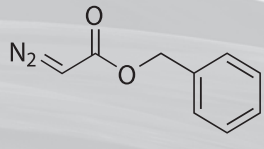

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References: (1) (a) Clark, J. D. et al. *Org. Process Res. Dev.* **2004**, *8*, 176. (b) Anthes, R. et al. *Org. Process Res. Dev.* **2008**, *12*, 168.

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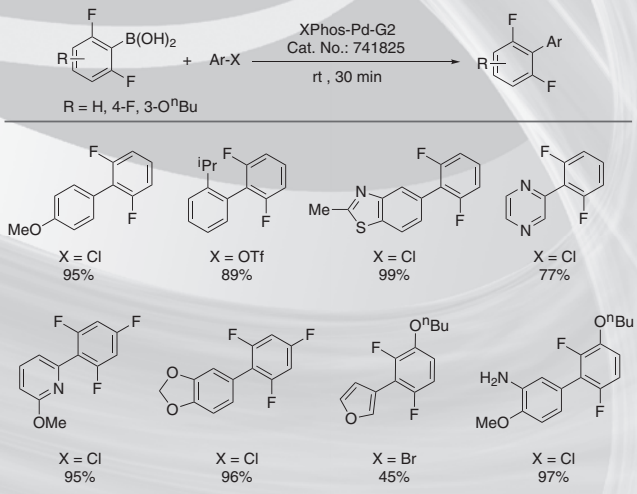

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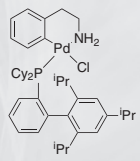
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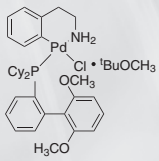
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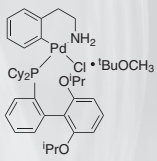
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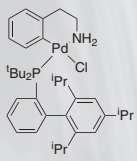
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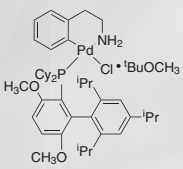
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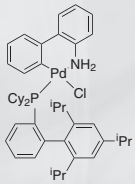
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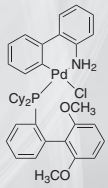
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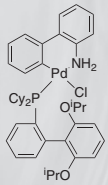
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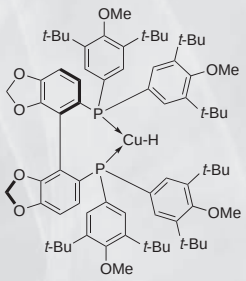

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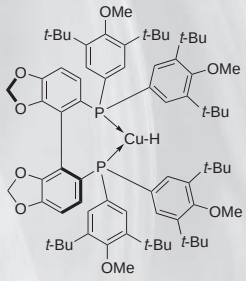

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Cp*Rh-Catalyzed C–H Activations: Versatile Dehydrogenative Cross-Couplings of C_{sp^2} C–H Positions with Olefins, Alkynes, and Arenes

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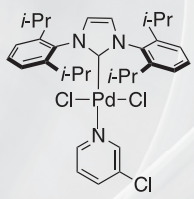

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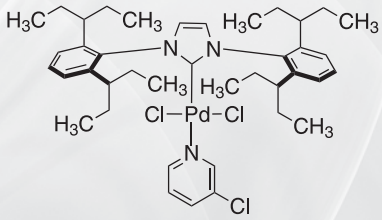

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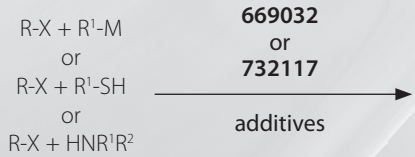

R, R^1, R^2 = C_{sp}, C_{sp^2}, C_{sp^3}

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(1) Valente, C.; Çalimsiz, S.; Hoi, K. H.; Mallik, D.; Sayah, M.; Organ, M. G. *Angew. Chem. Int. Ed.* **2012**, *51*, 3314. (2) Hadei, N.; Achonduh, G. T.; Valente, C.; O'Brien, C. J.; Organ, M. G. *Angew. Chem. Int. Ed.* **2011**, *50*, 276. (3) Çalimsiz, S.; Organ, M. G. *Chem. Commun.* **2011**, *47*, 5181. (4) Hoi, K. H.; Çalimsiz, S.; Froese, R. D. J.; Hopkinson; A. C.; Organ, M. G. *Chem.—Eur. J.* **2011**, *17*, 3086. (5) Çalimsiz, S.; Sayah, M.; Mallik, D.; Organ, M. G. *Angew. Chem. Int. Ed.* **2010**, *49*, 2014. (6) Dowlut, M.; Mallik, D.; Organ, M. G. *Chem.—Eur. J.* **2010**, *15*, 4279. (7) Organ, M. G.; Çalimsiz, S.; Sayah, M.; Hoi, K. H.; Lough, A. J. *Angew. Chem. Int. Ed.* **2009**, *48*, 2383.

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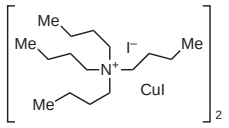

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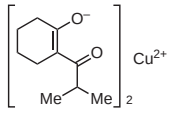

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A View on a High Road (oil on canvas, 93.1 × 127.8 cm) was painted in 1665 by Meindert Hobbema (Amsterdam, 1638–1709), one of the finest Dutch landscape painters. Few details about his personal and professional lives are known, save for the fact that his painting career seems to have lasted about a dozen years, from ca. 1658 to ca. 1669, and that he was an apprentice of another famous Dutch landscape painter, Jacob van Ruisdael. Following his marriage in 1668, he accepted a steady-pay job as a minor customs official gauging imported wines, and, as a consequence, painted infrequently thereafter. He, like several of his contemporary Dutch painters, was not appreciated and did not profit much from his artwork during his lifetime, lived on the edge of poverty, and died destitute. It wasn't until over a century later, chiefly in nineteenth-century England, that his work gained a wide appeal and his talent was finally recognized.

Detail from ***A View on a High Road***. Photograph © Board of Trustees, National Gallery of Art, Washington.

Hobbema specialized in landscape painting, in particular picturesque and serene rural scenes that draw the viewer in, as exemplified by the painting featured here (for another example, see *Aldrichimica Acta*, Vol. 32, No. 1). His landscapes tend to have many elements in common: sky with billowing clouds penetrated by light that illuminates parts of the composition, abundance of trees and foliage rendered with exquisite detail, country roads and buildings, placid waters, and human subjects resting or going about their daily business. His patient attention to detail, the subdued tones and dark greens—prominent in this work and necessitated by the nature of the scene and placement of the viewer—are also characteristic of his painting style.

This painting is part of the Andrew W. Mellon Collection at the National Gallery of Art, Washington, DC.

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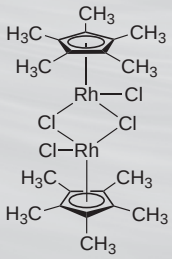
Tools for Rhodium-Catalyzed C–H Activation



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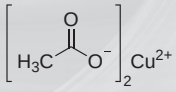

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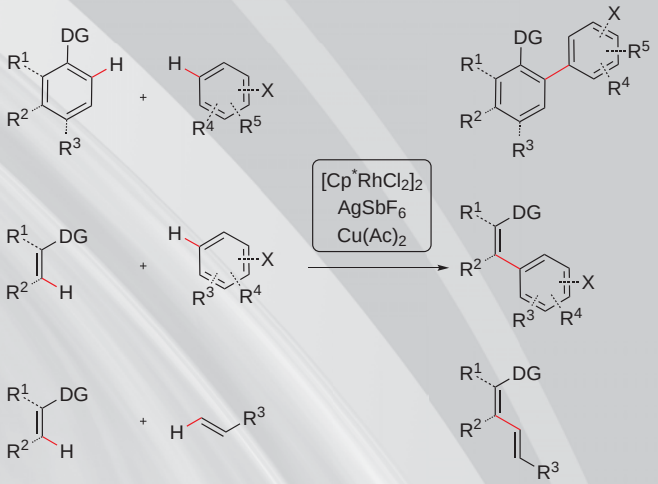

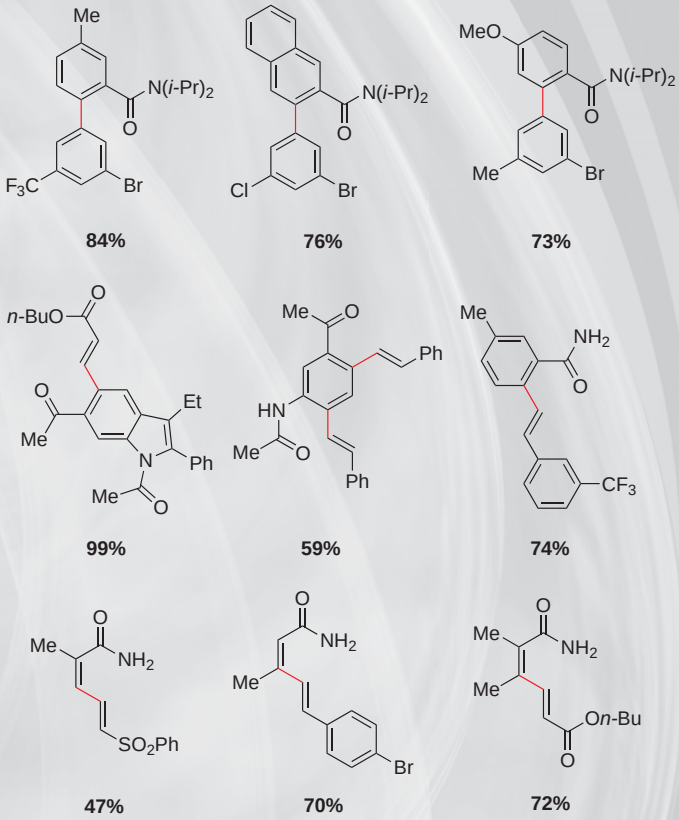

Scheme 1: Rhodium-catalyzed dehydrogenative cross-coupling examples.

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(1) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215. (2) Besset, T.; Kuhl, N.; Patureau, F. W.; Glorius, F. *Chem.—Eur. J.* **2011**, *17*, 7167. (3) Patureau, F. W.; Besset, T.; Glorius, F. *Angew. Chem. Int. Ed.* **2011**, *50*, 1064. (4) Wencel-Delord, J.; Nimphius, C.; Patureau, F. W.; Glorius, F. *Angew. Chem. Int. Ed.* **2012**, *51*, 2247.

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Cp*Rh-Catalyzed C–H Activations: Versatile Dehydrogenative Cross-Couplings of C_{sp^2} C–H Positions with Olefins, Alkynes, and Arenes


Prof. Frederic W. Patureau


Dr. Joanna Wencel-Delord


Prof. Frank Glorius

Frederic W. Patureau,*,[a] Joanna Wencel-Delord,[b] and Frank Glorius*,[b]

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Keywords. C–H activation; rhodium; $[Cp^*RhCl_2]_2$; Cp*Rh; dehydrogenative cross-coupling; cross-dehydrogenative coupling (*cdc*); directing group.

Abstract. The Cp*Rh(III)-catalyzed C_{sp^2} C–H activation and its subsequent cross-coupling with alkenes, alkynes, and arenes is a rapidly evolving research field. Many different directing groups, such as heterocycles, ketones, and carboxylic acid derivatives, can efficiently be used for this transformation; even undirected C–H activations have been reported recently.

Outline

1. Introduction

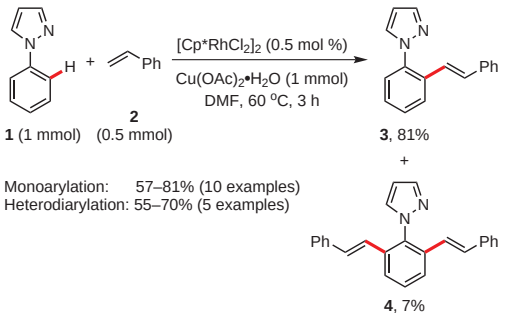
The direct catalytic activation and synthetic utilization of C–H bonds has become an increasingly important synthetic strategy for the atom-economical construction of C–C bonds.[1] Among such transformations, those categorized as "cross-dehydrogenative couplings" (*cdc*) are particularly interesting, because they oxidatively couple two *different* C–H positions, obviating the need for the often-troublesome prefunctionalization of either reaction partner.[2] The field emerged in the late 1960s with the groundbreaking discovery of the Pd-catalyzed dehydrogenative olefination of benzene by Fujiwara and Moritani[3]—a full three years before the discovery of the now famous Mizoroki–Heck reaction.[4] However, it was not until the mid-to-late 1990s, and the key reports by Murai,[5] Miura and Satoh,[6] and Fujiwara[3b,c] himself, that C–H activation was truly accepted as a credible strategy in organic synthesis. Since then, many great contributions have been made to this field, mostly relying on Pd-, Ru-, and Rh-based catalysts.[1] The number of such contributions is growing exponentially, as evidenced by the many excellent reviews that have been written on this topic since 2007. We do not wish to cover here all of these very recent and very well documented results; we propose instead to selectively survey the Rh-catalyzed C–H activation and dehydrogenative cross-coupling reactions, which have been reported very recently by us and others.[7] We wish to provide the reader with an easy-to-understand global perspective on the field of Rh-catalyzed C–H activation dehydrogenative cross-couplings, with the authors' analysis of the associated advantages and disadvantages, and their future impact on the field of organic chemistry.

2. Dehydrogenative Olefination Reactions

2.1. Dehydrogenative Olefination of Aromatic Ortho C–H Bonds

The construction of C–C bonds, especially the coupling of arenes with olefinic building blocks, has kept the scientific community actively involved for the last 50 years. The literature relating to this broad topic is extensive, and it is likely to remain a hot area of research in the future, because it offers such a powerful array of versatile tools for the rapid assembly of complex and relevant organic structures. Pentamethylcyclopentadienylrhodium(III) chloride dimer (CAS Registry Number® 12354-85-7, $[Cp^*RhCl_2]_2$, or simply Cp*Rh) was first (accidentally) prepared by Haszeldine in 1967, by the ring rearrangement of Dewar's hexamethylbenzene in the presence of $RhCl_3 \cdot 3H_2O$ in aqueous methanol.[8] However, the correct structure was

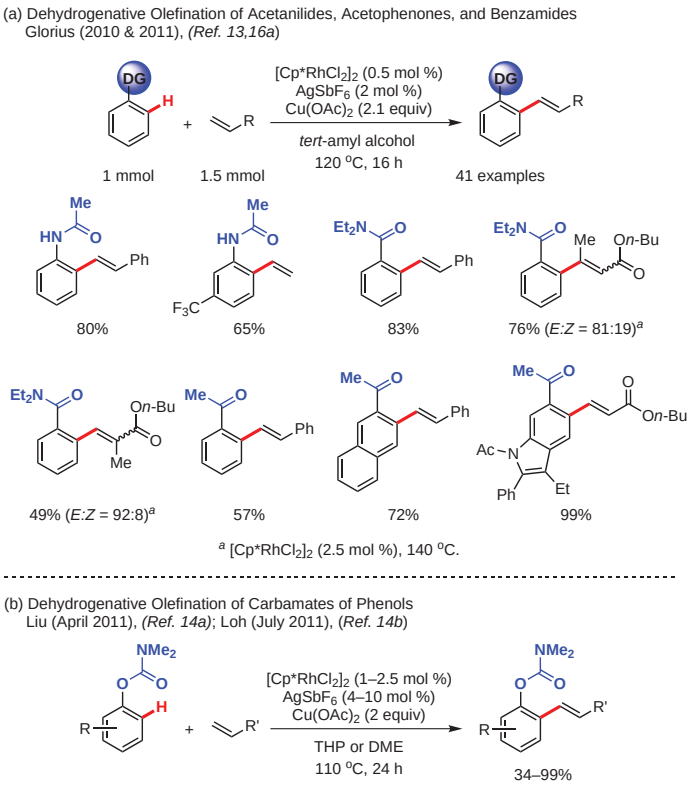
assigned to this compound only when Kang and Maitlis reproduced the experiment in 1968, which is its earliest mention in the literature.[9] The compound remained under-investigated until the last decade or so. Maitlis eventually found out in 1987 that it could cyclometallate benzoic acids under certain conditions.[10] However, its application in catalytic dehydrogenative cross-couplings only started in 2002 with the pioneering report by Matsumoto, Yoshida, and co-workers.[11] Then, between 2007 and 2009, Miura, Satoh, and co-workers showed in four key reports[12] that the Fujiwara–Moritani reaction was not the exclusive domain of the (long-established) $Pd(OAc)_2$ precatalysts, but that $[Cp^*RhCl_2]_2$-derived complexes would also be applicable, and, in some cases, superior to $Pd(OAc)_2$ (**eq 1**).



eq 1 *(Ref. 12d)*

The Rh-catalyzed dehydrogenative olefination of arylpyrazoles (e.g., **1**) described by Satoh and Miura did not immediately catch the attention of the chemistry community because the substrate scope is limited (pyrazoles cannot be easily opened or cleaved), and the selectivity of the reaction is poor, requiring that the loading of the olefin coupling partner be biased in order to limit the formation of the di-olefinated product.[12d] With the benefit of hindsight, it becomes clear without a doubt that this reaction is a considerable breakthrough in terms of reactivity. Shortly afterwards (2010), we reported on the dehydrogenative olefination of aniline derivatives (acetanilides), a very important and broad substrate class since the aniline moiety is ubiquitous in natural and other synthetic targets (**Scheme 1**).[13] It is interesting to note that the structurally analogous phenol derivatives, phenyl acetates, are not reactive at all under these conditions. This problem of lack of reactivity of phenol derivatives was overcome by Lei Liu and, independently, by Teck-Peng Loh, who astutely appended a carbamate to the phenol substrates, thus sufficiently enhancing their planar, as well as electron-rich character, to enable the dehydrogenative olefination to proceed (see Scheme 1).[14]

Fagnou showed, through a series of deuteration experiments, that, when acetanilides are coupled with alkynes, they undergo true C–H activation with Cp*Rh.[15] This reaction mode became obvious when we discovered that versatile benzamides and phenones in general were even more potent *and* selective substrates in the dehydrogenative olefination reaction (see Scheme 1a).[16] This reactivity renders common electrophilic substitution-type mechanisms less likely because of the intrinsic electron-withdrawing character of these classes of substrate (**Scheme 2**).[16a] Therefore, it follows that the reaction should be initiated by a true C–H activation event: The chelate assistance of the directing group guides the Rh intermediate to approach at the proper angle and distance in order to interact with the C–H bond, and, hence, result in its cleavage. While the so-called "base-assisted metallation" transition state, in which a carboxylate moiety participates in the deprotonation–metallation step,[17] could be invoked here, isotopic competition and scrambling experiments in this case tend to favor the idea of high-oxidation-state hydride intermediates being involved (see Fagnou's isotopic experiments, Section 3.1).[15] In the latter scenario, the reductive elimination of hydride with, presumably, a carboxylate ligand occurs subsequently to the C–H activation step and leads to a Rh(III) metallacycle intermediate. Furthermore; as shown recently by Bergman and Ellman, Zhang-Jie Shi, and Chao-Jun Li; carboxylates are not always essential for Cp*Rh C–H activation reactivity,[7c-g] which supports a chronological distinction between the C–H activation and carboxylate protonation steps. In any case, the broad array of suitable substrates, from eletron-rich acetanilides to electron-deficient benzamides and phenones, suggests that the acidity of the ortho C–H bond is only marginally relevant. In addition, we would like to point out here that the mechanistic role of the $Cu(OAc)_2$ salt, besides its obvious oxidizing character, is largely unknown. Its replacement by analogous salts (either acetate-containing or Cu-containing) or organic oxidants usually shuts down the reactivity. It is therefore sensible to assume that this component influences the reactivity through other specific modes of action that have not yet been elucidated. Related to this issue is the observation that substrates bearing an "internal oxidant" such as *N*-methoxybenzamides exhibit the reactivity without $Cu(OAc)_2$, but benefit from a new additive, CsOPiv or CsOAc. The presence of the internal oxidant allows for a somewhat broader olefin



Scheme 1. The Dehydrogenative Olefination of Ubiquitous Benzene Derivatives as Reported by Frank Glorius, Lei Liu, and Teck-Peng Loh.

scope, a lower reaction temperature, and, of course, perfect regio- and chemoselectivity, but is otherwise limited because the substrates have to be pre-functionalized with a reactive N–O bond (**Scheme 3**, right side, R^1 = Me).[18] Control experiments by Fagnou (Guimond et al.) have shown that the C–H activation step occurs first (as opposed to N–O bond activation),[18c] and is even reversible in the absence of a coupling partner. The N–O bond cleavage must occur at a later stage, and is presumably linked to the β-H elimination step. These observations shed some light on the specific role of the external oxidant $Cu(OAc)_2$, whereby the Cu salt is closely linked to the β-H elimination event, partly explaining the narrow specificity of this reaction component. Intriguingly, using an internal oxidant with the ability to chelate (see Scheme 3, left side, R^1 = Piv), β-H elimination seems to get suppressed, providing N-heterocycles presumably by reductive elimination from a 7-membered-ring rhodacycle.[18]

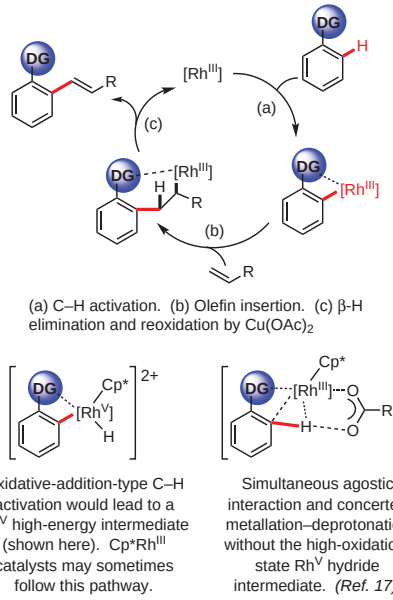
2.2. Dehydrogenative Olefination of Vinylic C–H Bonds

The reactivity discussed in the preceding section transfers well to vinylic C–H activations, and leads efficiently to a broad range of complex, highly functionalized, linear dienes (**eq 2**).[19] Several esteemed specialists have argued that this reactivity is self-evident; however, olefins are very versatile compounds indeed, and their use in such (high-temperature and acidic) coupling reactions is far from trivial. Because of the diverse reactions that can take place at a vinylic C–H position, it is not always obvious how to control the fate of a multiply functionalized reactive olefin. Numerous elegant reports have skillfully covered these topics;[5d,20] thus, we shall only mention the specifics of this particular reaction. The reason acrylates and acrylate-like derivatives are suitable substrates for C–H activation and subsequent exclusively linear dehydrogenative olefination lies mostly in the fact that they react in this catalytic cycle faster than in their decomposition pathways through oligomerization and/or polymerization. It also lies in the fact that the products resulting from dehydrogenative olefination are remarkably resilient under the reaction conditions, given their highly functionalized character. In point of fact, the starting materials are not always detectable at the end of the reaction. Given the breadth of this reaction—preparation of unnatural amino acid precursors, highly functionalized cinnamic derivatives, such as β-substituted cinnamamides, and many different kinds of tri- and tetrasubstituted olefins, all prepared by dehydrogenative cross-coupling in only one step from readily accessible substrates—one quickly realizes its importance in synthesis. The yields and diastereoselectivities are typically moderate to fair, but many of the relevant examples shown would be quite difficult to prepare by any other means. To this we should add that the mechanism is probably similar to the general model (see Scheme 2), especially in the case of electron-poor acrylate derivatives, which are unlikely to proceed to the metallacycle through anything other than a true C–H activation event. This is less obvious, however, in the case of more electron-rich acetamidoacrylate derivatives (amino acid precursors), where an electrophilic attack may not be excluded as initiating the catalytic cycle and otherwise leading to the same classes of highly functionalized linear dienes.

3. Versatile Cyclization Reactions

3.1. Synthesis of Indoles and Pyrroles

The first Cp*Rh-mediated C–H activation that is followed by a condensation or cyclization step was reported as early as 2007 and 2008 by none other than Miura and Satoh.[12a–c] It consists of the oxidative coupling of benzoic acids with internal alkynes to produce

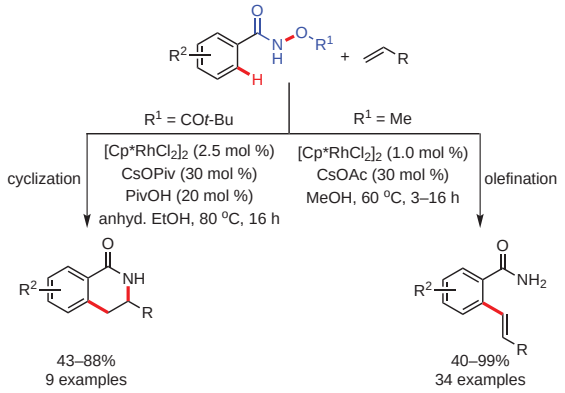


(a) C–H activation. (b) Olefin insertion. (c) β-H elimination and reoxidation by $Cu(OAc)_2$

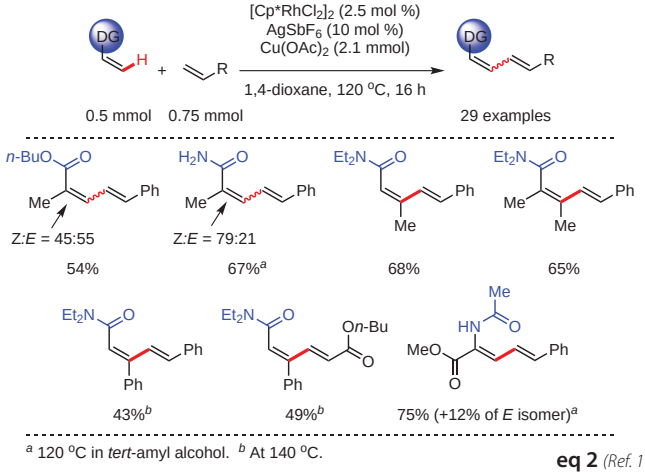
Oxidative-addition-type C–H activation would lead to a Rh^V high-energy intermediate (shown here). Cp*Rh^{III} catalysts may sometimes follow this pathway.

Simultaneous agostic interaction and concerted metallation–deprotonation without the high-oxidation-state Rh^V hydride intermediate. *(Ref. 17)*

Scheme 2. Postulated General Mechanism of the Dehydrogenative Olefination. (Different Modes of C–H Activation Are Possible; Only Two Are Depicted Here.) *(Ref. 16a)*

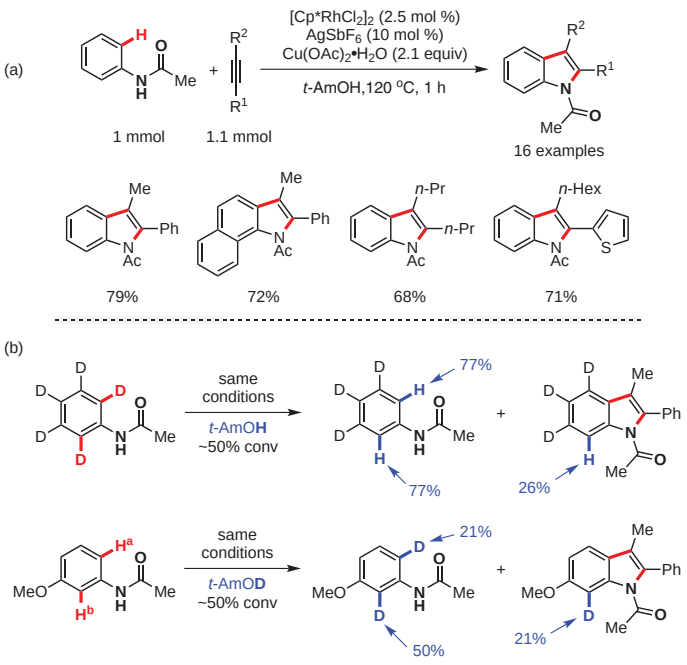


Scheme 3. The "Internal Oxidant Strategy" in Dehydrogenative Olefinations. *(Ref. 18a)*

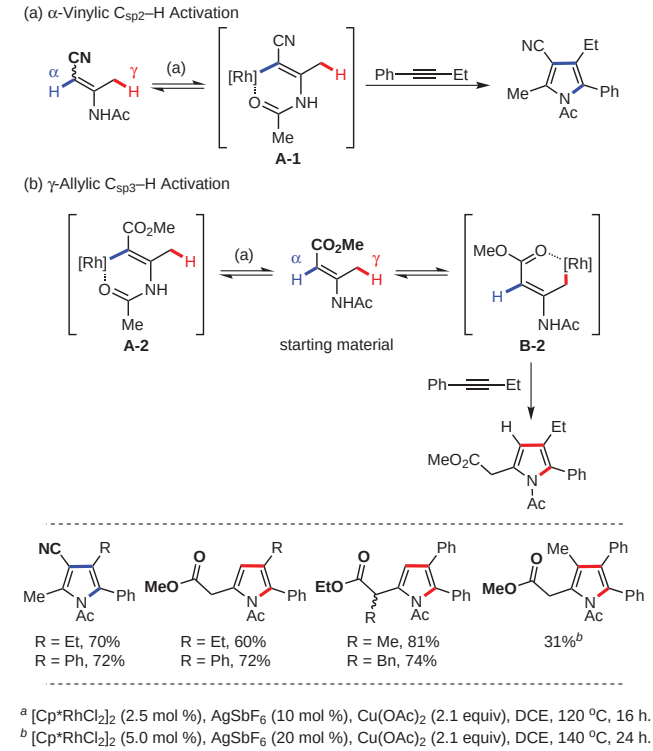


a 120 °C in *tert*-amyl alcohol. b At 140 °C.

eq 2 *(Ref. 19)*



Scheme 4. Fagnou's 2008 Indole Synthesis and the Proof of the Reversibility of the C–H Activation Step under Catalytic Conditions. *(Ref. 15a)*



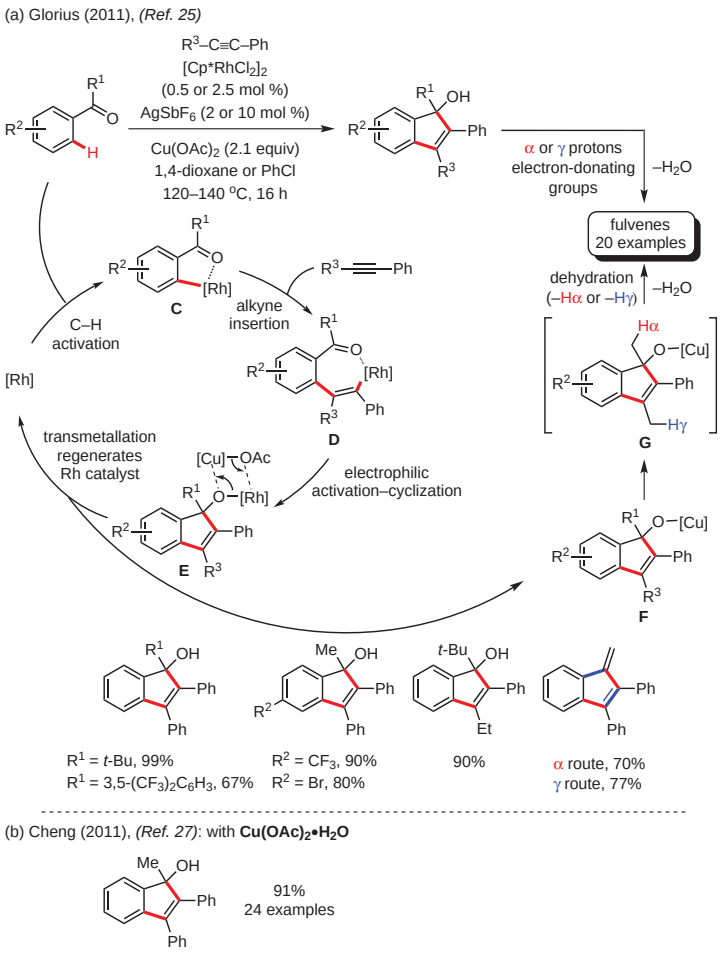
[a] $[Cp^*RhCl_2]_2$ (2.5 mol %), $AgSbF_6$ (10 mol %), $Cu(OAc)_2$ (2.1 equiv), DCE, 120 °C, 16 h.
[b] $[Cp^*RhCl_2]_2$ (5.0 mol %), $AgSbF_6$ (20 mol %), $Cu(OAc)_2$ (2.1 equiv), DCE, 140 °C, 24 h.

Scheme 5. Glorius's 2010 Pyrrole Synthesis. *(Ref. 22)*

mostly a variety of isocoumarin derivatives (see Section 3.3). Not long after, in 2008, Fagnou published his innovative indole synthesis.[15a] These seminal works resulted in a "Rh Rush" in the scientific community. Acetanilides can be C–H activated (see Section 2.1) and undergo insertion of internal alkynes followed by oxidative cyclization to produce a variety of substituted indoles as reported by Fagnou and co-workers (**Scheme 4**).[15a] Through astute H/D scrambling experiments, Fagnou proved that the metallation of C–H is reversible, *even in the presence of the alkyne coupling partner*. This suggests two very important things: (i) that the C–H activation step does indeed go through a high-oxidation-state metal hydride intermediate (presumably Rh^V), hence the scrambling; and (ii) that, in this case, the metallation step is possibly not rate-determining, but rather the subsequent alkyne insertion step is. As the authors point out, the sheer bulk of the doubly substituted internal alkyne may be responsible for this unexpected behavior. While we were investigating analogous Pd-catalyzed transformations, we were impressed by this amazing transformation.[21] We eventually came across a Cp*Rh system that would convert a series of protected β-amino acid precursors into the corresponding tri- and tetrasubstituted pyrroles with amazing simplicity.[22,23] Depending on the substitution pattern and protecting groups, we discovered a way to steer the C–H activation from an α-vinylic (sp^2) C–H one in the case of nitrile-protected amino acids to a γ-allylic (sp^3) C–H activation in the case of methyl ester protected amino acids, followed by coupling of the alkyne to produce the pyrrole (**Scheme 5**).[22] The change of reactivity is exclusive and leads to very high regioselectivities. The key to the selectivity was identified through H/D exchange experiments which showed that both structures (ester and nitrile derivatives) first undergo vinylic C–H activation at the α position to give the initial Rh metallacycle (see Scheme 5, Structures **A-1** and **A-2**). This species then rearranges to a second metallacycle (see Scheme 5, Structure **B-2**) in the case of the ester-substituted unit (γ position). We should mention here that α-amino acid precursors, such as methylacetamidoacrylate (see also Section 2.2) and related substrates, were also found to react with internal alkynes under similar conditions (activation of the β C–H position), leading to a number of analogous, highly substituted pyrroles and substantially broadening the scope and versatility of this reaction. These results were reported by Fagnou's co-authors in a full paper in late 2010 (Stuart et al.)[24] and independently by Glorius's group in the first half of 2011.[19]

3.2. Synthesis of Indenols and Annulated Fulvenes

The idea of combining phenones and internal alkynes came quite naturally to us in late 2010 in light of our findings on dehydrogenative olefination reactions (Section 2). Sure enough, we quickly established that a large array of phenone derivatives would undergo C–H activation, alkyne insertion, and a new step best described as an electrophilic cyclization.[25] The resulting 5-membered-ring closure leads to a series of functionalized indenol derivatives in high yields and regioselectivities (**Scheme 6**). It is worth mentioning that this transformation is redox neutral, that is, no external oxidant is required. However, $Cu(OAc)_2$ is still essential for the reactivity, probably due to its unique and multiple, but still not clearly defined, roles in the mechanisms of these transformations. Probably both phenomena (transmetallation to release the active Rh catalyst and participation in the key intermediates of the cross-coupling reaction) take place, as the $Cu(OAc)_2$ could not be replaced by other analogous Lewis acids. Furthermore, depending on the electronic properties of the substrates, dehydration steps would sometimes follow, mostly in



Scheme 6. Synthesis of Indenols and Annulated Fulvenes.

the presence of electron-donating substituents, leading to the related fulvene derivatives in high yields. The synthesis of these classes of relevant compounds had been described to some degree before, but their preparation typically required systematic prefunctionalization steps.[26] This reaction, described in Scheme 6, is appealing because it is atom-economical, as no waste is formally produced, and allows the rapid buildup of structural complexity through a simple cross-coupling reaction. Shortly after our report appeared, Chien-Hong Cheng and co-workers showed that the use of $Cu(OAc)_2•H_2O$ prevents the dehydration step, thus extending the scope of the reaction to electron-rich indenol derivatives, although in this case the reaction time must be kept short.[27–29]

3.3. Synthesis of Other Heterocycles

As far as Cp*Rh cyclizations are concerned, electrophilic coupling partners (e.g., Michael acceptors, aromatic alkynes, etc.) tend to provoke cyclization steps, especially in the presence of protic or nucleophilic directing groups in the substrate (see indoles and pyrroles in Section 3.1). The tandem C–H oxidative functionalization and cyclization, typically involving the directing group, lead to a variety of 5- and 6-membered-ring systems with backbones as interesting as they are diverse. Many key players have observed this phenomenon, such as for example Miura & Satoh,[12,30] Fagnou,[31] Rovis,[32] Xingwei Li & Zhengyin Du,[33] Chiba,[34] Chen Zhu,[35] and Glorius.[16a,36] These cyclizations are either redox neutral (typical intramolecular Michael addition induced by the nucleophilic character of the directing group) or oxidizing, in which case the ring closure is believed to proceed through a reductive elimination. These two pathways are very case-dependent, and sometimes even occur at the same time. Because each known example is almost a story in itself, we shall only show a selection of them to highlight again the power and versatility of the Cp*Rh catalysts in the construction of such, usually biologically active, cyclic molecules (**Figure 1**).

4. Nonchelate-Assisted C–H Activation Followed by Dehydrogenative Cross-Coupling

4.1. Dehydrogenative Olefination of Aromatic C–H Bonds

C–H activations of benzene derivatives in the absence of a chelating group are very challenging, and only a few methods exist to effect them.[37] In one of their most impressive reports, Miura and Satoh described a method for performing the dehydrogenative olefination of benzoic acids, that involves Cp*Rh-catalyzed C–H activation followed by a directing-group-removing decarboxylation step, yielding unprecedented olefinated products that lack the original

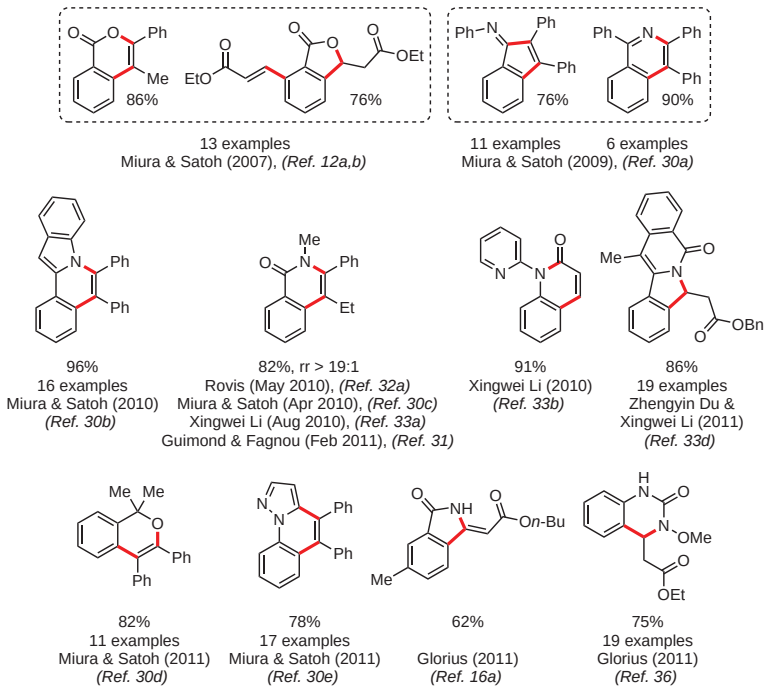
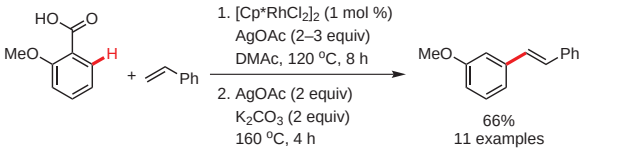
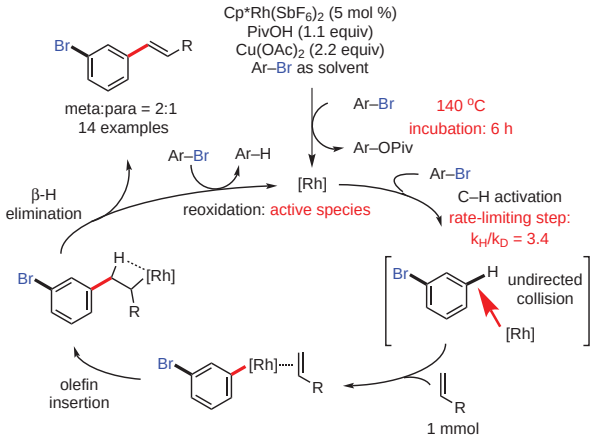


Figure 1. A Selection from 2007 to 2011 of Significant, Mainly Heterocyclic, Fused-Ring Systems That Have Been Accessible through Cp*Rh-Catalyzed C–H Activation–Cyclization.



eq 3 *(Ref. 16e)*



Scheme 7. Nonchelate-Assisted C–H Activation and Dehydrogenative Olefination of Bromoarenes. *(Ref. 40)*

ortho-directing functional groups (**eq 3**).[16e] In the summer of 2011, we stumbled upon what is probably the most significant Cp*Rh-mediated reactivity discovered in our laboratory to date. While the Pd-catalyzed C–H activation of highly biased heterocyclic structures,[38] and usually electron-deficient arenes, was the state of the art in this field,[11b,39] we discovered that bromoarenes could be C–H activated with Cp*Rh without the need for a directing group assisting through chelation.[40] The bromoarene is believed to be the substrate, the terminal oxidant,[41] and possibly a critical catalyst modifier. The lack of a directing group makes the reaction very slow (TOF = 1.3 h^{-1} at best), with the C–H activation step being (predictively) the rate-limiting step (k_H/k_D = 3.4, **Scheme 7**).[40] While the products are typically obtained as poorly useful 2:1 (statistical) mixtures of *meta*- and *para*-bromostilbene derivatives, this breakthrough clearly opens a whole new Cp*Rh era in terms of C–H activation reactivity and selectivity (Sections 4.2 and 4.3), without the structural limitations of a directing group.

4.2. Dehydrogenative Arylation of Aromatic C–H Bonds

Shortly after the discovery of the potential of this Rh(III) catalyst to perform a nonchelate-assisted C–H bond activation of bromoarenes, our group focused its attention on applying this strategy to the development of an unprecedented, Cp*Rh-catalyzed aryl–aryl cross-coupling. The biaryl moiety is one of the key scaffolds in organic chemistry, and its construction by a two-fold C–H bond activation strategy is a highly valuable tool for modern and environmentally friendly chemistry. However, examples of this type of dehydrogenative cross-coupling are still scarce and limited mainly to Pd-catalyzed transformations.[1d,42] Our efforts rapidly turned out to be highly rewarding when the aryl–aryl cross-coupling reaction between benzamides (or phenones) and

aromatic compounds bearing a halide substituent was observed.[43] We feel that this method is attractive and competitive for the formation of regioselectively functionalized biaryls (ortho on one ring, meta on the other). This original transformation displays some very interesting features when compared to the first report on the nonchelate-assisted C–H bond activation (see Section 4.1): (i) This dehydrogenative cross-coupling is compatible not only with bromoarene derivatives, but also iodobenzene and chlorobenzene can be efficiently used as coupling partners. (ii) The undirected C–H bond activation event is more selective: no detectable ortho functionalization (with regard to the halogen or other substituent on the aromatic ring) is observed and, therefore, application of appropriately selected bromo-disubstituted arenes leads to the selective formation of the desired biaryl products. (iii) The nonchelate-assisted insertion of the Rh into the C–H bond seems to be enhanced in the presence of the benzamide substrate;[44] thus the C–H activation/metallation of the benzamide part must occur first and produce a more reactive Rh intermediate (compared to that described in Section 4.1). Studies of the kinetic isotope effect clearly show that true C–H bond activation occurs for both coupling partners [k_H/k_D (with regard to benzamide) ≈ 2.0; k_H/k_D (with regard to bromobenzene) ≈ 3.5]. Moreover, the important H/D scrambling on either benzamide or bromoarene coupling partner suggests the reversibility of both C–H activation events and, again, the probable formation of high-oxidation-state rhodium hydride intermediates (**Scheme 8**).[43]

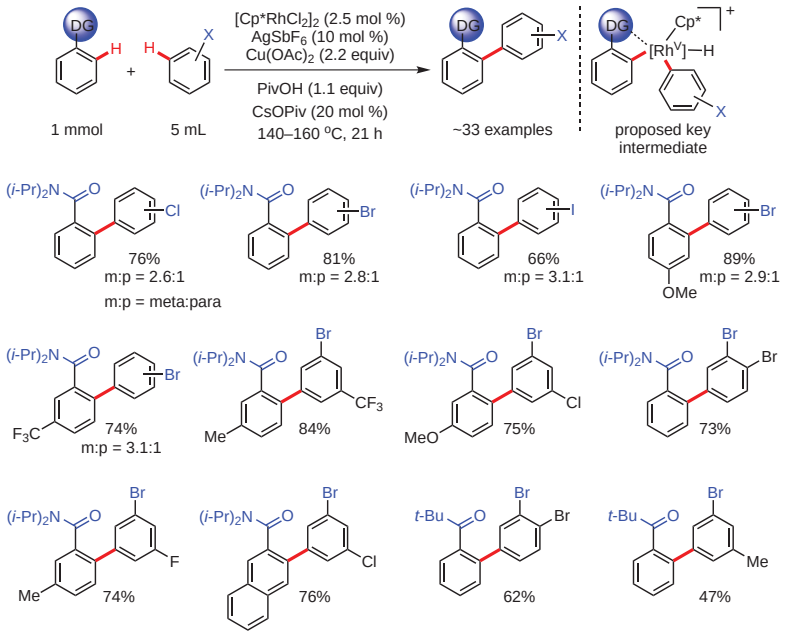
4.3. Dehydrogenative Arylation of Vinylic C–H Bonds

Encouraged by the discovery of the ability of the Cp*Rh catalyst to perform arylation reactions, we extended the scope of this transformation to coupling partners consisting of vinylic substrates bearing a directing group.[45] This novel dehydrogenative alkene–arene coupling reaction is an interesting alternative to the already well-established dehydrogenative olefination reaction (see Section 2). Indeed, due to the directing-group-assisted insertion of the rhodium into the vinylic C–H bond and the formation of a new C–C bond in the reductive elimination step, an exclusive *Z*-selective coupling is observed. Even highly substituted alkenes can be employed as substrates, leading to the formation of tri- and tetrasubstituted olefins. Even though this transformation still suffers from moderate-to-low yields, probably due to the versatility of the alkene starting material under the reaction conditions (see Section 2.2), this is quite a unique and simple way to access highly substituted Z olefins bearing additional sites for further functionalization (**Scheme 9**).[45]

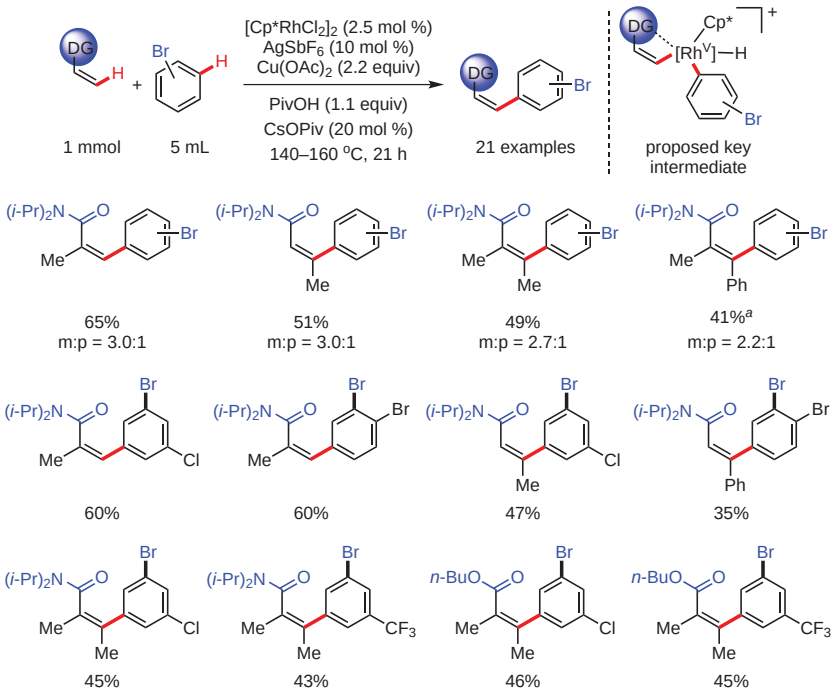
The nonchelate-assisted Rh-catalyzed C–H bond activation is still in its infancy and suffers from important limitations such as the need for halide-substituted arenes, low selectivity (formation of mixtures of meta and para products), and the requirement of a large excess of one of the coupling partners (the haloarene). However, its compatibility with electron-poor arenes clearly indicates its orthogonality with regard to the Pd-catalyzed arene–arene dehydrogenative cross-coupling and other Pd-enabled cross-coupling reactions. The potential of this new reactivity may well lead to important breakthroughs in the near future.[46]

5. Conclusion and Outlook

The versatility of this class of Cp*Rh-catalyzed cross-couplings has already gone, in an incredibly short time, far beyond what we had imagined when we first joined this field (**Figure 2**). The importance and diversity of the products and of the technology itself—improved step by step by research groups from around the world—leave no doubt that dehydrogenative cross-coupling involving Cp*Rh will continue to garner the interest of the chemistry community for a long time. We think this is especially true of the nonchelate-assisted C–H activation cross-couplings that we have just discovered and highlighted here.



Scheme 8. Directed and Undirected Aryl–Aryl Bond Formation. *(Ref. 43)*



Scheme 9. Directed and Undirected Alkene–Arene Bond Formation. *(Ref. 45)*

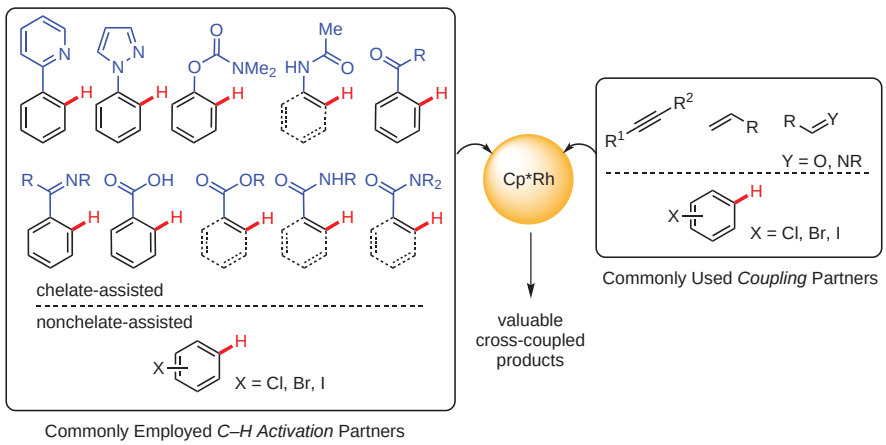


Figure 2. Typical Substrates of the Cp*Rh(III)-Catalyzed Cross-Coupling through C–H Activation.

6. Acknowledgements

We express our gratitude to all the students and professors, who have worked creatively and tirelessly to promote the field of Rh(III)-catalyzed C–H activations. We thank Professor P. M. Maitlis for helpful discussions. F. P. acknowledges support for the writing of this work by the DFG-funded transregional collaborative research center SFB/TRR 88 “Cooperative effects in homo- and heterometallic complexes (3MET)” and the Alexander von Humboldt Foundation. F. G. also acknowledges the support of the European Research Council under the European Community’s Seventh Framework Program, (FP7 2007–2013)/ERC Grant agreement no 25936, and the Alexander von Humboldt Foundation. The research of F. G. has been supported by the Alfried Krupp Prize for Young University Teachers of the Alfried Krupp von Bohlen und Halbach Foundation.

7. References and Notes

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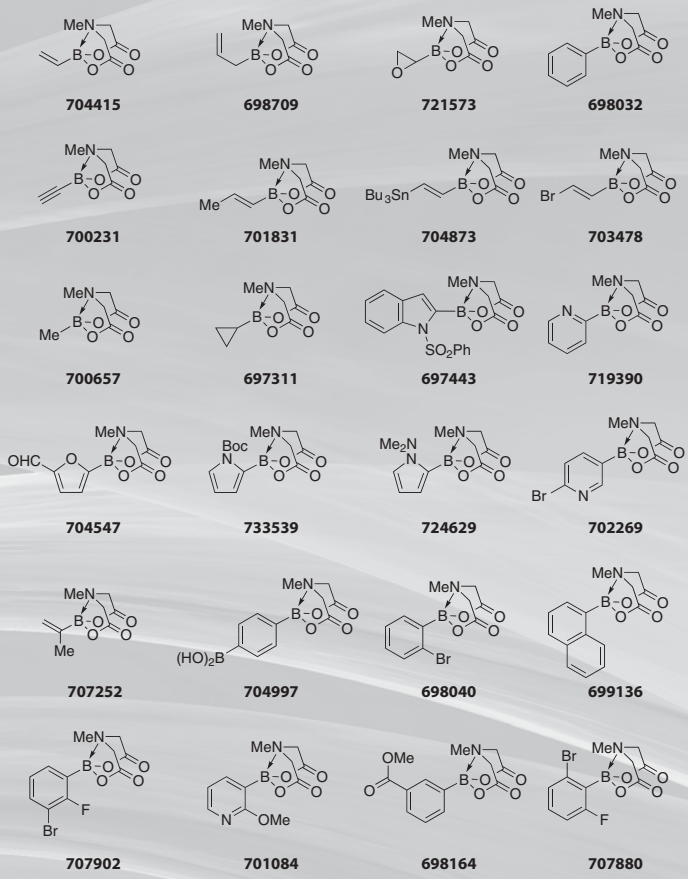

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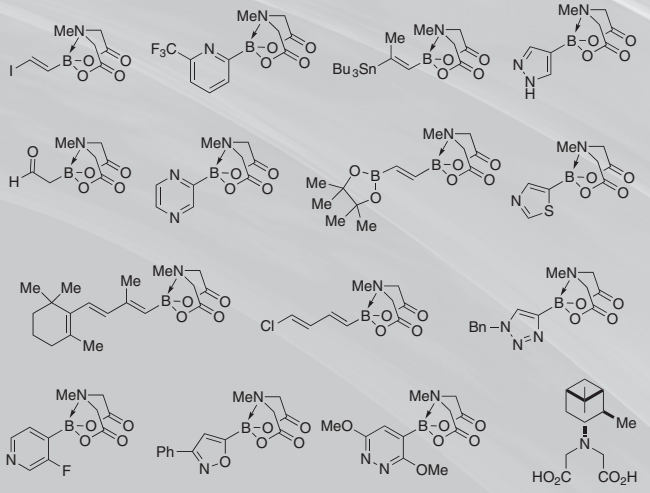

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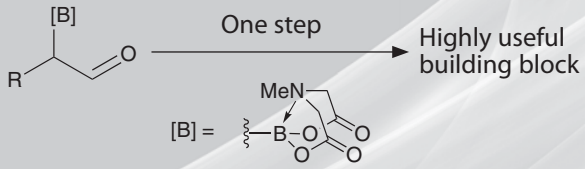

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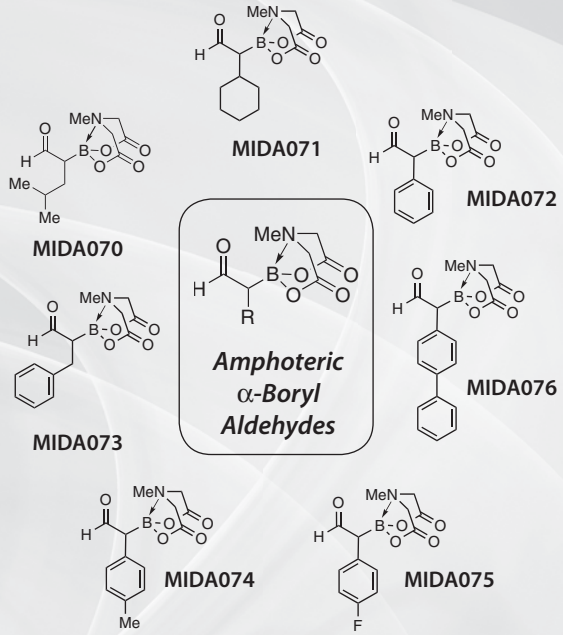

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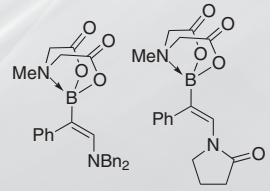

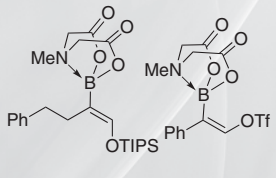

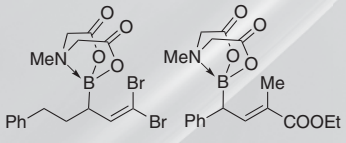

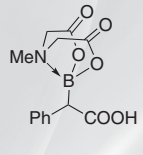

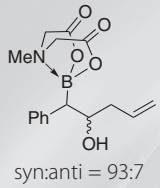

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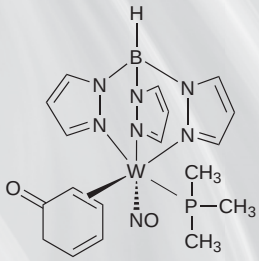

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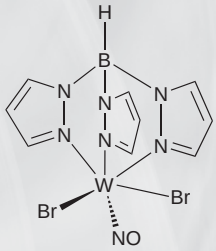

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Welch, K. D.; Harrison, D. P.; Lis, E. C., Jr.; Liu, W.; Salomon, R. J.; Harman, W. D.; Myers, W. H. *Organometallics* **2007**, *26*, 2791

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Opening New Chemical Space through Novel Dearomatization Reactions

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Keywords. tungsten complex; aromatic; dearomatize; arenes; dihapto-coordinated; TpW(NO)(PMe_3)(η^2-C_6H_6).

Abstract. The attachment of a tungsten complex to various aromatic molecules across two carbons localizes the remaining π system in the molecules and renders them highly activated toward electrophilic reagents. As a result, new bonds are formed between the electrophile and the aromatic scaffold, giving rise to stereogenic centers with predictable configurations. Treatment of the resulting adducts with various oxidants frees the organic product from the tungsten fragment. This approach permits the synthesis of a number of small molecules that are difficult to prepare by conventional methods.

Outline

1. Introduction

The reactivity of arenes and aromatic heterocycles is profoundly affected by their coordination to a transition metal. While much is known about the chemistry of η^6-coordinated arenes, the chemistry associated with dihapto-coordinated aromatics has been slow to develop, owing to the relative instability and inaccessibility of such complexes. The arene moiety in complexes such as (η^6-arene)$Cr(CO)_3$,[1,2] $[(\eta^6\text{-arene})Mn(CO)_3]^+$,[3,4] $[(\eta^6\text{-arene})RuCp]^+$,[5–8] and ($\eta^6$-arene)$Mo(CO)_3$[9] is susceptible to nucleophilic substitution, addition, or side-chain activation,[10] leading to the formation of substituted arenes or cyclohexadienes.[11] While the arene ligands of such complexes are more reactive than their uncomplexed counterparts, they nevertheless remain largely aromatic. In the complementary approach of η^2 coordination, the metal–arene bond is stabilized primarily by interaction of a filled metal d_π orbital with a π* orbital of the aromatic ligand. Through this interaction, the aromatic π system becomes both more localized (i.e., dearomatized) and more electron-rich. Hence, the arene is activated toward *electrophilic* addition reactions (**Figure 1**).[12]

Several generations of dihapto-coordinated dearomatization (DCD) agents have been developed. The first complex reported to coordinate benzene in a dihapto fashion and activate it toward organic transformations was $\{Os^{II}(NH_3)_5\}^{2+}$. This was followed by $\{TpRe^{I}(CO)(MeIm)\}^0$ and finally by $\{TpW^0(NO)(PMe_3)\}^0$, where MeIm is methylimidazole and Tp is tris(pyrazolyl)borate (**Figure 2**).[13] As one moves from Os(II) to W(0), the reactivity toward electrophiles increases owing to the increase in π back-bonding associated with the lower oxidation state of the metal.[13]

Herein, we survey the synthesis of tungsten-based transition-metal–arene complexes and the transformation of their aromatic ligands into novel, highly functionalized, alicyclic structures in relatively few steps.

2. Synthesis, Characterization, and Reactivity of Tungsten–Arene Complexes

Complexes have been prepared for a large number of aromatic compounds by ligand substitution of the benzene analogue TpW(NO)(PMe_3)(η^2-benzene). The resulting complexes have been systematically studied in an effort to fundamentally understand the effect that coordination of an extremely π-basic metal has on the aromatic compound. One of the most useful outcomes of the initial studies was revealed when analyzing ^{31}P NMR spectra of the complexes.[14] Tungsten has one spin = ½ isotope of sufficient abundance (^{183}W, 14% abundance) to display W–P coupling. ^{183}W–^{31}P coupling constants are highly sensitive to the coordination environment about the W center (e.g., κ^1-, η^2-, 7-coordinate oxidative insertion complexes; **Figure 3**).[14] As a result, it is possible to utilize ^{31}P NMR data to facilitate the analysis of reactions without the need for deuterated solvents, providing information about (i) the number of products and (ii) the types of complexes (i.e., η^2, κ^1, etc.) that are generated throughout the course of a reaction. Thus, optimization of reaction conditions via ^{31}P NMR is both rapid and economical. In addition to NMR, infrared (NO stretch) and electrochemical (W(I/0): $E_{p,a}$) data also give valuable information regarding the purity and nature of the products.[14]

2.1. Derivatization of Phenol and Aniline

Among their respective three tautomers, phenol and aniline primarily exist in their enolic and enaminic forms due to aromatic stabilization (**Figure 4**).[15–17] The equilibrium is significantly altered when these arenes are coordinated to {TpW(NO)(PMe_3)}. For phenol, only the 2*H*-tautomer complex, **2**, is isolated when phenol is combined with the

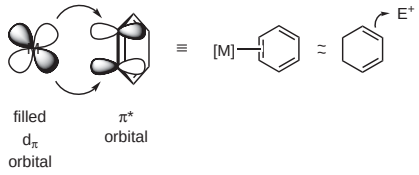


Figure 1. Fundamental Metal–Ligand Interaction and Activation. *(Ref. 12)*

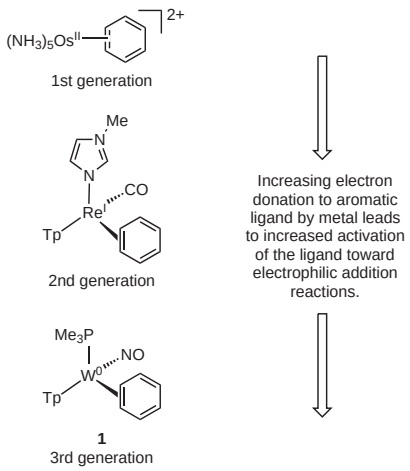


Figure 2. Dearomatization Agents. *(Ref. 13)*

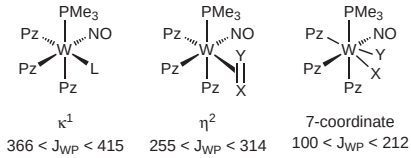


Figure 3. Coordination Environments of Tungsten and Associated Coupling Constant Ranges in Hz. *(Ref. 14)*

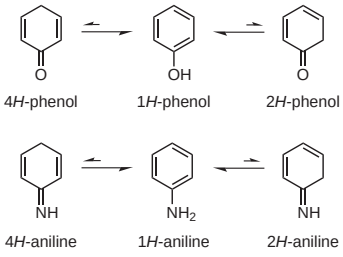


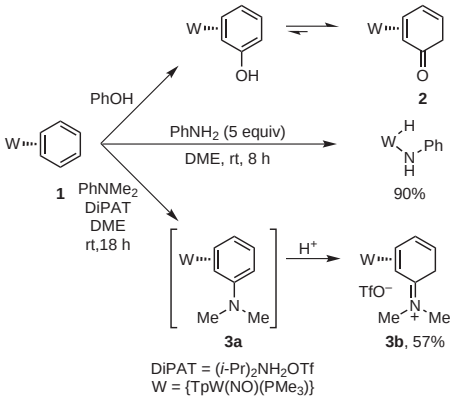
Figure 4. Tautomeric Forms of Phenol and Aniline. *(Ref. 15–17)*

benzene precursor TpW(NO)(PMe_3)(η^2-benzene) (**1**) (**Scheme 1**).[16] In the case of aniline, isolation of a neutral η^2 complex is difficult due to a competing oxidative addition across an N–H bond, which serves to reduce the electron density at the metal center.[17] To avert the N–H insertion, replacement of the amine protons in aniline with alkyl groups is necessary. However, isolation of the neutral η^2-aniline complex **3a** is still difficult, due to its highly electron-rich nature (see the benzene analogue, **1**). This problem is solved by addition of a weak acid to the substitution reaction, which leads to the 2*H*-η^2-anilinium complex, **3b**, that is very stable to both oxidation and substitution. For both **2** and **3b**, selective precipitation procedures have been developed that allow for the isolation of a *single* coordination diastereomer. Also of note, both **2** and **3b** are air-stable, and most of the reactions presented here can be performed in a fume hood without the need for glove boxes or special techniques (i.e., Schlenk techniques).

The C3–C4 alkene bond of the 2*H*-phenol or 2*H*-anilinium ligand is highly activated toward electrophilic addition reactions. Ketenes readily undergo [2 + 2] cycloadditions with alkenes,[18,19] and similar reactivity is found with η^2-phenol complexes. Ketenes, generated in situ via the dehydrohalogenation of acid chlorides, react exclusively at the exposed alkene (C3=C4) to generate a cyclobutanone core, **4a–c** (**Scheme 2**).[16] The reaction is highly stereoselective, with addition occurring at the face of the ligand opposite to that to which the tungsten is coordinated: the metal complex sterically blocks addition syn to the metal. Addition of ketenes is also highly regioselective, with the electrophilic portion of the ketene adding to the meta position of the phenol ring. This is particularly noteworthy for phenol because it represents an umpolung, or reversal, of reactivity that is typically associated with phenol, where electrophiles add to C2 (ortho carbon), C4 (para carbon), or the O atom.[20]

Note that, not only does η^2 coordination increase the electron density of the exposed double bond, it also polarizes the bond such that electrophiles add at the terminal carbon of the bound diene fragment and the resulting allylic cation is stabilized by the metal (see **4ai**–**4ci** in Scheme 2).

The principles outlined above for ketenes may be generalized to other types of electrophiles.[21,22] Addition of *meta*-chloroperoxybenzoic acid (*m*CPBA), a combination of [bis(trifluoroacetoxy)iodo]benzene (PIFA) and methyltriphenylphosphonium bromide (MTPBr), and Selectfluor® (i.e., sources of electrophilic oxygen, bromine, and fluorine,



Scheme 1. Ligand Substitution Reactions of Phenol, Aniline, and *N*,*N*-Dimethylaniline. *(Ref. 16,17)*

respectively) to a methanolic solution of **2** generates 5-substituted 4-methoxycyclohexenones exclusively as their syn isomers (**Scheme 3**).[21]

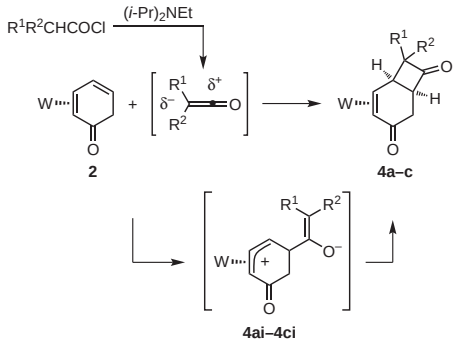
Additionally, when amines or thiols are added to the reaction solution following addition of *m*CPBA, 1,2-amino alcohols and 1,2-hydroxy thioethers are produced. An epoxide intermediate is suspected, but, despite significant efforts, this epoxide has not yet been isolated. However, starting with the *meta*-cresol analogue, **6**, 3,3-dimethyldioxirane (DMDO) oxidation delivers the corresponding epoxide, **7**, in good yield (**Scheme 4**).[22] Subjecting the *meta*-cresol–tungsten complex, **6**, to DMDO in the presence of different nucleophiles produces 4-substituted 5-hydroxy-5-methylcyclohexenone complexes **8**–**11** with high stereofidelity.

The reactivity displayed by the dimethylanilinium analogue, **3b**, closely resembles that of complexed phenol **2** (**Scheme 5**).[17] Electrophiles add to the meta position of the aniline ring, despite such action creating a dicationic intermediate. The more electron-deficient anilinium system, **3b**, offers greater resistance to the competing metal-centered oxidation, compared to its neutral analogue, **3a**, and the phenol analogue, **2**.

2.2. Derivatization of Pyridine

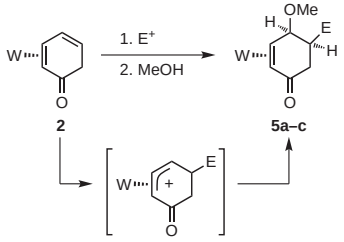
Inorganic and organometallic chemistry has a rich history of using pyridine-based ligands to modify the steric and electronic properties of transition-metal complexes. All of this chemistry is possible because of coordination of the pyridine nitrogen to metal centers. Unfortunately, this is also true for pyridine when combined with {TpW(NO)(PMe_3)}. However, nitrogen coordination may be prevented by substituents at the 2 position, provided they are sufficiently bulky or are good π-electron donors (**Scheme 6**).[23] Furthermore, blocking the nitrogen as in organoborane **12** prevents N coordination and provides access to the parent η^2-pyridine, isolated as its conjugate acid, **13** (**Scheme 7**).[24] The formation of organoborane adduct **12** and its conversion into **13** can be performed in high yield (87% and 92%, respectively) on a >10 g scale. When exposed to acetic anhydride, pyridinium **13** is readily converted into *N*-acetylpyridinium complex **14** (94%; see Scheme 7),[24,25] setting the stage for an extensive range of carbon-centered reactions governed by the metal complex.

Two synthetic pathways may be utilized to convert the bound pyridine into functionalized tetrahydropyridines. The first path involves modification of the exposed alkene followed by nucleophilic



4a: R^1 = H, R^2 = Cl (92%); **4b**: R^1 = H, R^2 = 3-$MeOC_6H_4$ (81%); **4c**: R^1 = R^2 = Cl (57%)

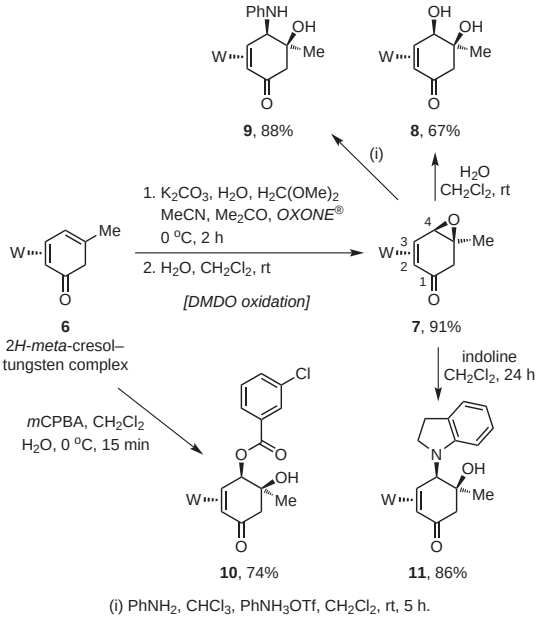
Scheme 2. Ketene [2 + 2] Cycloaddition Reaction with the 2*H*-Phenol Complex. *(Ref. 16)*



5	E	Conditions for Step 1	Yield
a	OH	*m*CPBA, CH_2Cl_2, 0 °C	82%
b	Br	PIFA, MTPBr, CH_2Cl_2, –40 °C	74%
c	F	Selectfluor®	79%

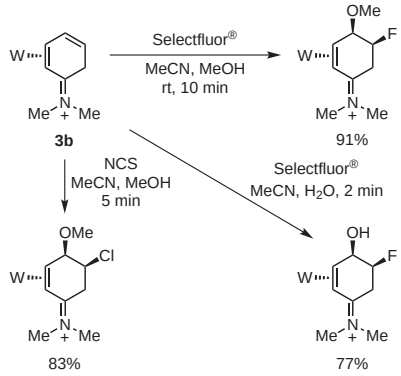
PIFA = $PhI(O_2CCF_3)_2$; MTPBr = Ph_3PMeBr.

Scheme 3. Tandem Electrophilic and Nucleophilic Additions to the 2*H*-Phenol Complex. *(Ref. 21)*

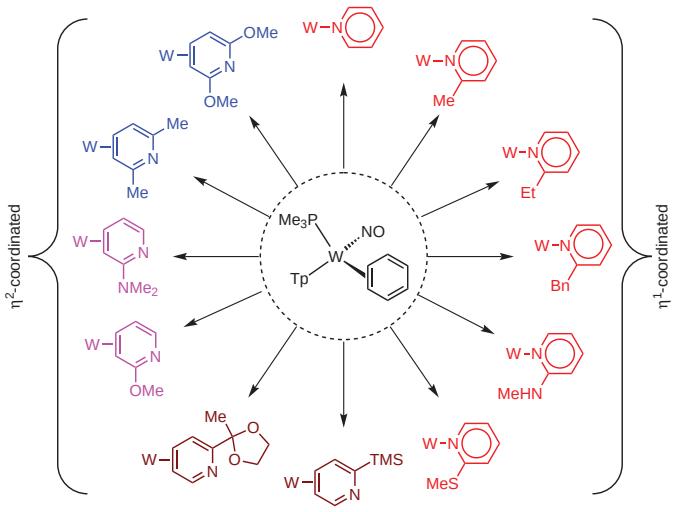


(i) $PhNH_2$, $CHCl_3$, $PhNH_3OTf$, CH_2Cl_2, rt, 5 h.

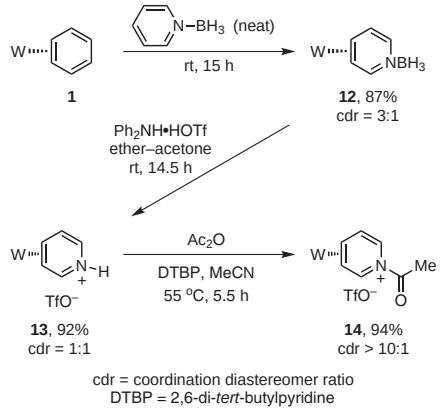
Scheme 4. Isolation of Suspected Epoxide Intermediate and Subsequent Ring-Opening Additions. *(Ref. 22)*



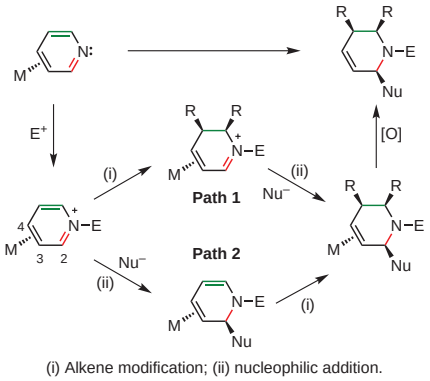
Scheme 5. Tandem Addition Reactions with the 2*H*-Anilinium Complex. The Triflate Counterion Is Omitted for Clarity. *(Ref. 17)*



Scheme 6. Coordination Modes of Pyridines with Different Substituent and Electronic Effects. *(Ref. 23)*



Scheme 7. Synthesis of a Trapped η²-Pyridine: *N*-Acetylpyridinium. *(Ref. 24,25)*



Scheme 8. Divergent Synthetic Pathways for Converting Pyridine into Piperidines. *(Ref. 26)*

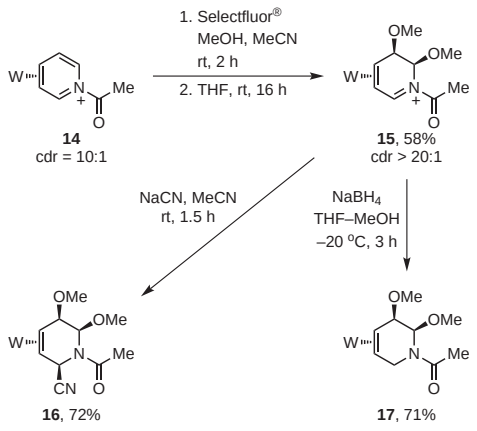
addition to the iminium carbon atom (**Scheme 8**, Path 1).[26] To this end, addition of Selectfluor® or *N*-chlorosuccinimide to **14** in methanol results in the dialkoxylation of the exposed alkene (**Scheme 9**).[27] Addition of nucleophiles to the resulting acyl iminium salt **15** results in tetrahydropyridine complexes **16** and **17** in good yields.

The second pathway reverses the alkene modification and nucleophilic addition steps (see Scheme 8, Path 2). *N*-Acetylpyridinium is invoked as an intermediate in the catalytic acylation of alcohols and amines with acetic anhydride. Conversely, addition of mild nucleophiles to **14** results solely in addition to one position of the pyridine ring and produces η²-1,2-dihydropyridine (DHP) complexes **18**–**28** (**eq 1**).[24,27] As with phenol and aniline complexes, the metal fragment blocks attack from one face of the pyridine ligand, making the addition not only regioselective but also stereoselective.

Functionalization of the C5–C6 double bond via Path 2 in Scheme 8 is also possible.[28] Enamides, like enamines, are polarized such that the β carbon is nucleophilic.[29] This implies that addition of an electrophile should occur at C5, as shown in **Figure 5**, Part (a).[28] However, studies of η²-coordinated 1,3-diene complexes with π-basic metals indicate a clear regiochemical preference for electrophilic addition at the terminal carbon of the uncoordinated double bond.[30,31] By analogy, electrophiles react with dihydropyridine (DHP) complexes at C6.

Addition of a proton to **18**, followed by isolation and characterization of the cationic complex, **29**, reveals that the metal, not the enamide, dictates the placement of the electrophile, representing an umpolung of typical enamide reactivity (**eq 2**).[28] Similar results were obtained upon addition of acid to other DHP complexes. It should be noted here that both rotational isomers of the amide bond are often observed in the NMR spectra of the products.[28]

It is worth noting that the metal–allyl bonds, both in crystallographic data and in solution NMR spectra, are observed to be highly distorted. This type of σ–π or "η²-allyl" distortion has been attributed to the interaction of the allyl π* orbital and the d orbital orthogonal to the nitrosyl, and has significant implications for the reactivity of the complexes (and of other coordinated ligands as well).[28,32] This asymmetry indicates that one of the allylic carbon atoms (C3) is considerably more electrophilic than the other (C5). Nucleophilic reagents react with the pyridine allyl exclusively at the C3 position, thereby desymmetrizing the heterocyclic ring to form Δ³-piperidinamides **31**–**34** (**Scheme 10**).[28] As above, all the tetrahydropyridine (THP) compounds are typically



Scheme 9. Alkene Modification Followed by Nucleophilic Addition. *(Ref. 27)*

observed as mixtures of conformational isomers (i.e., amide rotational isomers).

When nucleophiles are added to a cationic complex containing a 2-ethyl substituent, **30**, they do not add to C3 but rather to the other allylic position, C5, resulting in complexes **35** and **36** (**Scheme 11**).[28] Presumably, the vicinal addition of two nucleophiles creates a steric interaction that overcomes the electronic bias for C3 addition described above.

In a special case, addition of two equivalents of acid to **19** produces a dicationic allylic isoxazolium complex, **37**, often referred to as a Reissert-like salt[33] (**Scheme 12**).[28] Attempts to add nucleophiles compatible with **29** and **30** have resulted in deprotonation to generate a tautomer of the 2-cyano DHP complex. However, 1-methoxy-2-methyl-1-(trimethylsilyloxy)propene reacts as a nucleophile at C3, producing **38**. Addition of $NaBH_4$ or DABCO® to **38** results in the reduction or deprotonation of the isoxazolium to produce the novel structures **39** and **40**.

In the presence of Lewis acids, addition of methyl vinyl ketone or *trans*-cinnamaldehyde to the dihydropyridine complex **18** results in cycloadducts **41** or **42** (**Scheme 13**).[34] Again, the relative stereochemistry and connectivity of the [4 + 2] cycloadducts are consistent with a reversed polarization of the C5–C6 bond.[35-40] Notably, the cycloaddition products are formed with endo stereochemistry. 2-Substituted DHP complexes (e.g., **20**) also appear to be capable of cycloaddition reactions with Michael acceptors, but, to date, have not been explored in detail.

Addition of tosyl isocyanate to DHPs **20**, **22**, **25**, and **27** produces [4 + 2] cycloaddition products **43**–**46** (**eq 3**).[34] X-ray crystallography has confirmed that the polarization imparted by the metal, as described above, is maintained in that the electrophilic portion of the isocyanate (i.e., C=O) adds α-to-N in the DHP ring. Addition of trichloroacetyl isocyanate resulted in a mixture of [4 + 2] cycloadducts, but eventually converted solely to an unproductive electrophilic substitution product.

Addition of acid to the [4 + 2] tosyl isocyanate cycloadducts produced highly asymmetric allyl complexes **47** and **48** (**Scheme 14**).[34] When nucleophiles were added to the ethyl allyl derivative **47**, in an attempt to

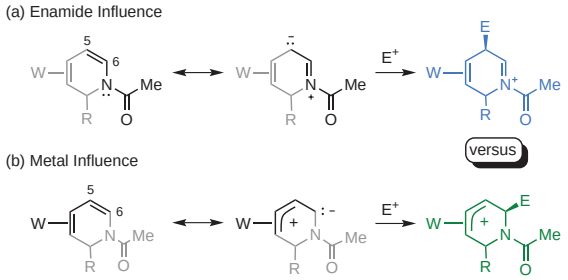
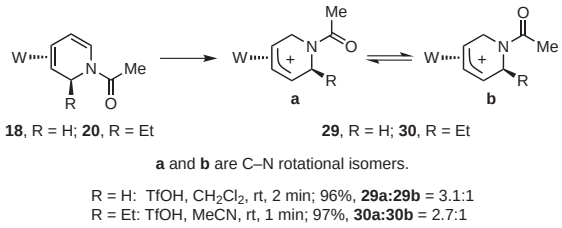
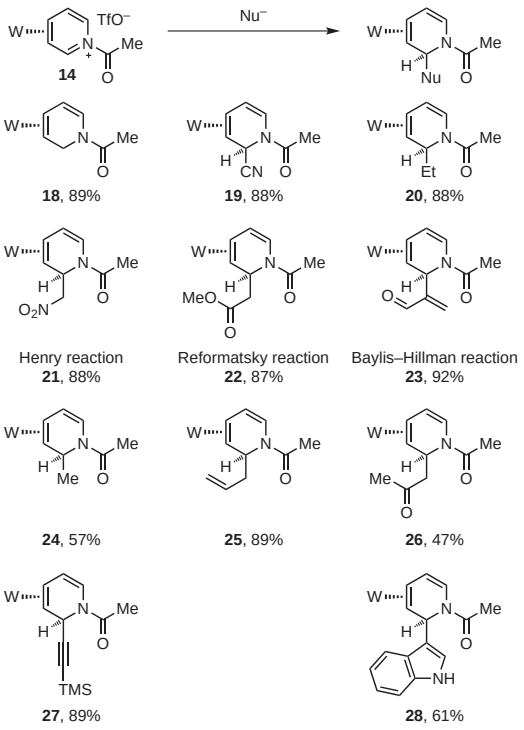


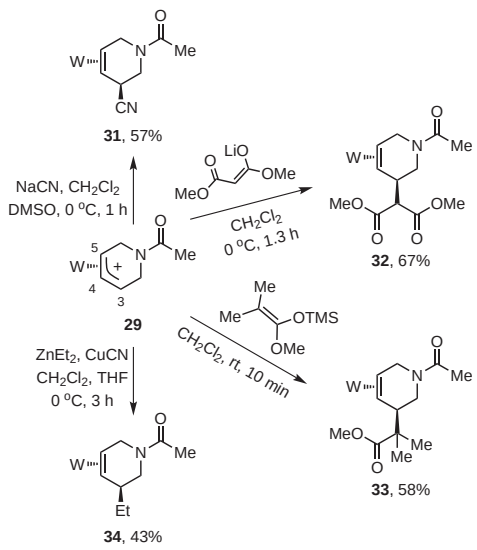
Figure 5. Competing π-Donor Polarizations. *(Ref. 28)*



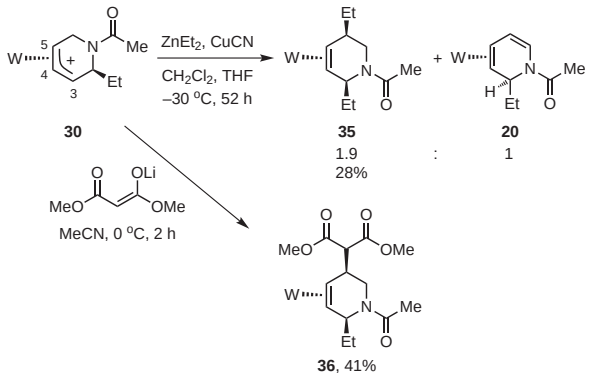
eq 2 *(Ref. 28)*



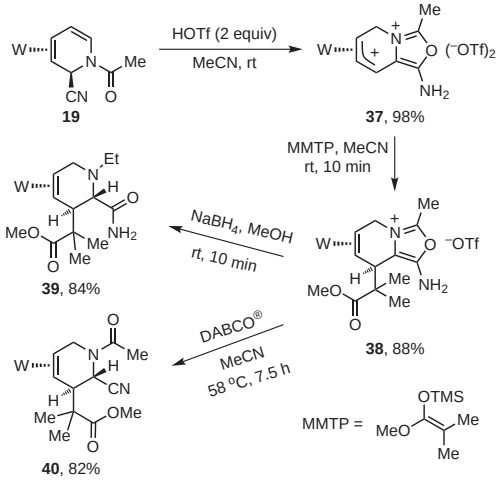
eq 1 *(Ref. 24,27)*



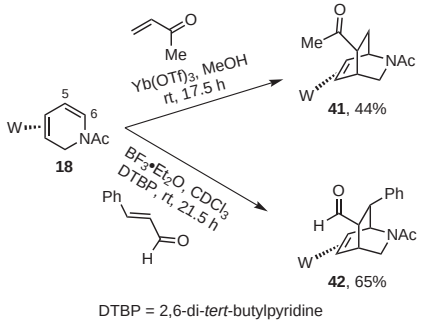
Scheme 10. Stereoselective Nucleophilic Addition to C3 of the Asymmetric η^2-Allyl Group. *(Ref. 28)*



Scheme 11. Stereoselective Nucleophilic Addition to C5, Demonstrating That Steric Interaction of the Ethyl Group at C2 with the Incoming Nucleophile Steers the Latter to the Less Electrophilic C5 Position. *(Ref. 28)*



Scheme 12. Synthesis and Elaboration of a Reissert-like Allyl Salt. *(Ref. 28)*



Scheme 13. Michael Acceptor Additions to a Simple DHP Complex. *(Ref. 34)*

synthesize additional tri- and tetrasubstituted tetrahydropyridine (THP) complexes, deprotonation resulted in regeneration of the [4 + 2] adduct, **43**, or an overall electrophilic substitution product, **48** (see Scheme 14). Substituting a proton for the ethyl group, allows for nucleophilic addition to occur at the allyl regioselectively, producing **50**–**52** from **49** (**Scheme 15**).[34] Apparently, bulky substituents at the C2 and C6 positions lead to deprotonation of the allylic fragment while the lack of one of these substituents allows access to a terminal allylic position.

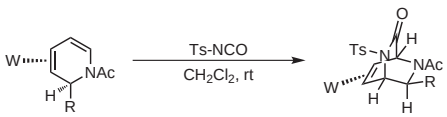
2.3. Derivatization of Other Aromatic Compounds

2.3.1. Substituted η^2-Pyridine Complexes

As noted above, other η^2-pyridine complexes have been isolated in reasonable yields (see Scheme 6; pink, blue, and brown compounds). These coordinated ligands have also been successfully modified under mild conditions. For example, complexes of 2-(*N*,*N*-dimethylamino)-pyridine (**53**), 2,6-dimethoxypyridine (**54**), and 2,6-lutidine (**55**) all undergo concerted [4 + 2] Diels–Alder cycloadditions at the exposed and activated 2-azadiene system to provide complexes **56**–**58**, respectively (**eq 4**).[2] This type of reaction has not been realized in the absence of the dihapto-coordinated metal.[41–44]

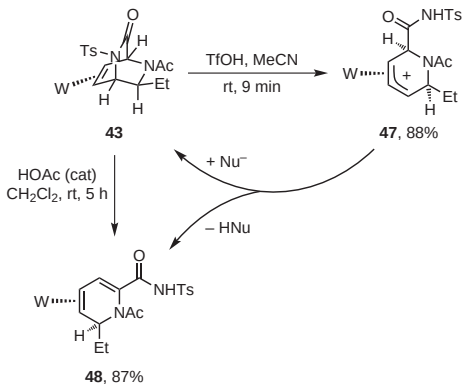
2.3.2. Pyrrole

Much like aniline, when the nitrogen is not sufficiently blocked or substituted, η^2-pyrrole complexes undergo N–H oxidative insertion reactions (**eq 5**).[45,46] Treatment of the benzene complex **1** with 2,5-dimethylpyrrole results in a dihapto-coordinated *3H*-pyrrole, **59**. This unusual tautomer has kinetic access to the 1*H* form, generating an enamine, where addition of carbon electrophiles readily occurs



SM	R	Time	Prod	Yield
20	Et	1.1 h	**43**	84%
22	MeO_2CCH_2	1.8 h	**44**	67%
25	η^1-C_3H_5	1.6 h	**45**	80%
27	TMSC≡C	7.5 h	**46**	38%

eq 3 *(Ref. 34)*



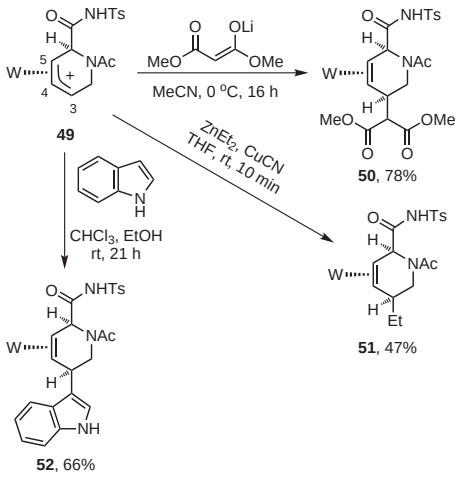
Scheme 14. Allyl Synthesis and Addition of Nucleophiles. *(Ref. 34)*

at C3. For example, α,β-unsaturated ketones, esters, and aldehydes can undergo Michael additions stereo- and regioselectively at C3 to produce **60a–g** (**Scheme 16**).[46] In some cases, the ketones of the Michael addition products (i.e., **61a–c**) undergo stereoselective Aldol reactions with one of the methyl groups of pyrrole to produce bi- (**62**) and tricyclic (**63**) structures (see Scheme 16). This "Michael–aldol–ring-closure" sequence is facilitated by metal coordination, which stops deprotonation at C3 from pre-empting formation of the external enamine. The stereoselectivity of the ring-closure appears to be a result of hydrogen bonding of the ketone with the enamine in the transition state, which favors a synclinal approach.

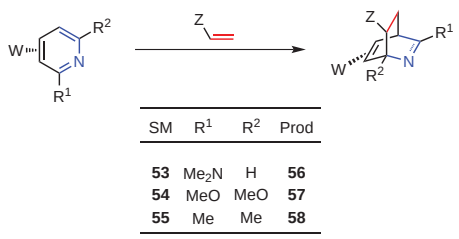
2.3.3. Anisole

When anisole is coordinated to {TpW(NO)(PMe_3)}, either by reduction of TpW(NO)(PMe_3)Br in anisole or by ligand substitution from benzene complex **1**, an equilibrium mixture of the coordination isomers is isolated (**64**).[47] However, addition of acid to the mixture produces a single isomer of a *2H*-anisolium complex, **65**. This anisolium complex may be used as a starting material for other reactions (**Scheme 17**).[47] For example, **65** undergoes Michael addition to produce compounds of type **66** in high de's. Nucleophiles, such as methoxide, cyanide, and the enolate of 2,4-pentanedione, react with these complexes in a cascade reaction to produce 1-oxahexahydronaphthalene complexes of type **67**. Nucleophilic addition to the ketone produces an alkoxide which then undergoes conjugate addition at C3 to produce **67** (**Scheme 18**).[47] It should be noted that mixtures are sometimes observed resulting from a competing nucleophilic addition directly to C3 (**68**). Compounds of type **67** are often most easily isolated as their conjugate acids **69a–c** (see Scheme 18). This feature also allows for the possibility of stereoselectively reducing the resulting methyl enonium to an allyl ether, which can be further modified (e.g., **70**, **71a,b**).

In one unusual example, addition of thiophenolate to **66h** occurs at C3 rather than the carbonyl. The product, **72**, then undergoes an aldol reaction to form **73**, followed by methyl cleavage to generate **74** (**Scheme 19**).[47] This sequence produces a complex *cis*-oxahexahydronaphthalene core and sets three stereocenters.

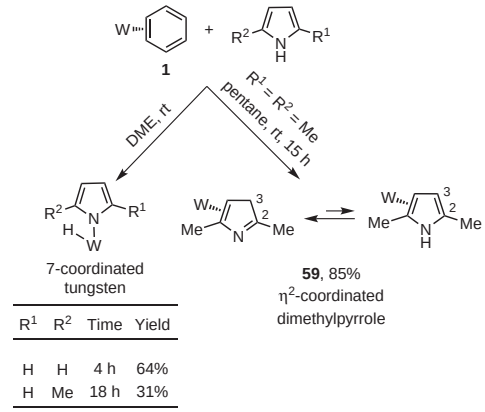


Scheme 15. Nucleophilic Addition to C3. *(Ref. 34)*



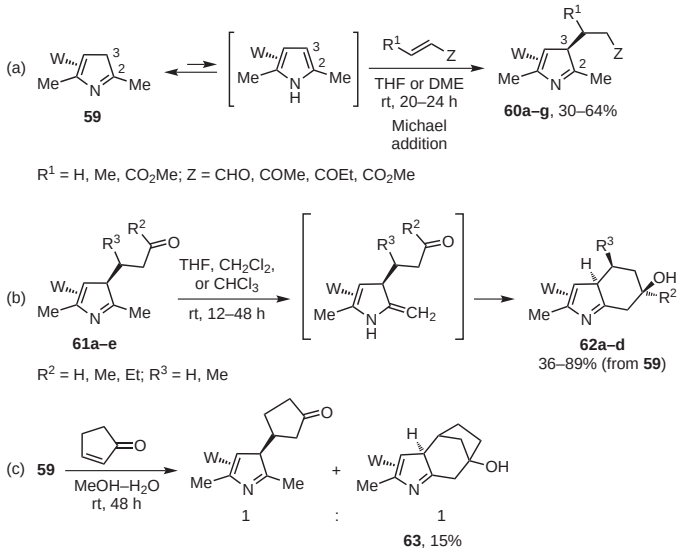
SM	R^1	R^2	Prod
53	Me_2N	H	**56**
54	MeO	MeO	**57**
55	Me	Me	**58**

eq 4 *(Ref. 2)*

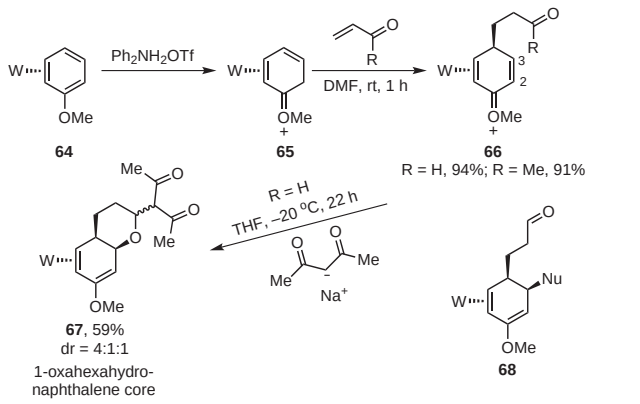


R^1	R^2	Time	Yield
H	H	4 h	64%
H	Me	18 h	31%

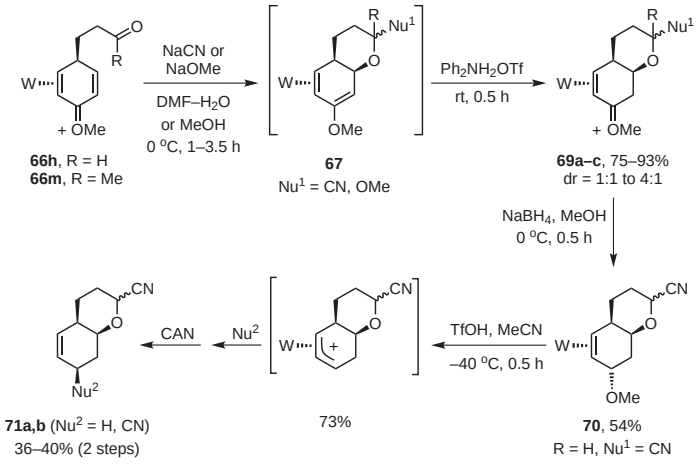
eq 5 *(Ref. 45)*



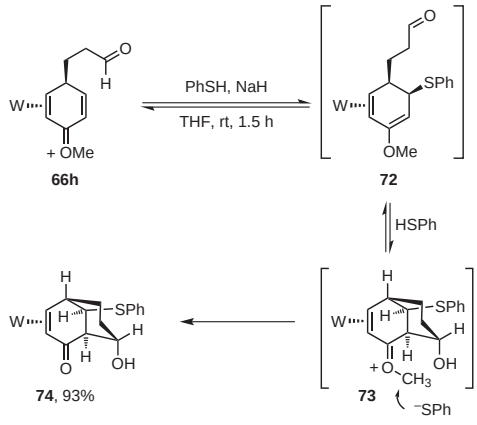
Scheme 16. Michael Additions and Michael–Aldol–Ring-Closures to 2,4-*3H*-Pyrrole Complexes. *(Ref. 46)*



Scheme 17. Synthesis of Anisolium Complexes and Oxahexahydronaphtha–lenes. *(Ref. 47)*



Scheme 18. Modified Procedure for Forming Oxahexahydronaphthalene Cores. (The Final Complexes Were Not Isolated but Were Carried on to the Demetallation Step.) *(Ref. 47)*



Scheme 19. Synthesis of a Bicyclo[3.3.1]nonenone. *(Ref. 47)*

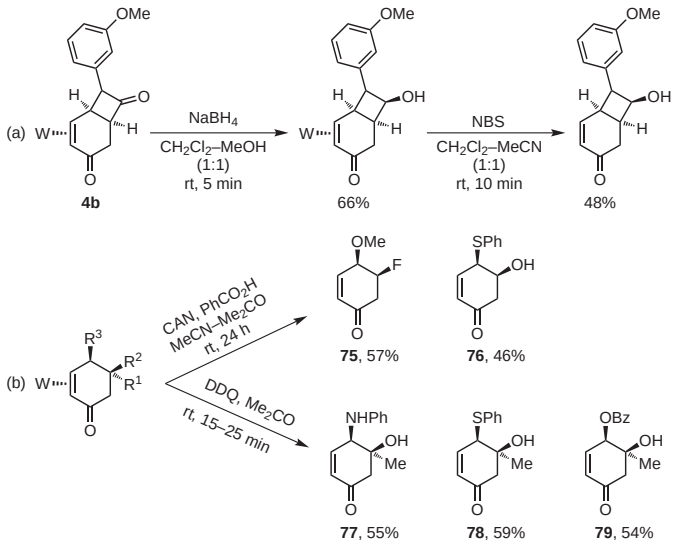
3. Demetallation

The strategy most commonly employed for removing the {TpW(NO)(PMe_3)} fragment involves oxidation of the metal. Metal oxidation reduces the electron density utilized to form stable π bonds with the coordinated ligand, thus weakening the metal's hold on the π-coordinated ligand. After the ligand is released, chromatography is often employed to facilitate the separation of the metal decomposition products from the desired organic compound. Here we provide several examples of the liberation of novel organic compounds.

Reduction of the keto group in **4b** with $NaBH_4$, followed by oxidation with *N*-bromosuccinimide (NBS) allows for the isolation of the corresponding tricyclic cyclobutanol (**Scheme 20**).[16,21] Other tandem addition products (**75–79**) derived from phenol may be isolated through the use of ceric ammonium nitrate (CAN) or 2,3-dichloro-5,6-dicyanoquinone (DDQ).[21,22] Although isolation of organic compounds derived from aniline have not yet been reported, preliminary experiments are promising for their decomplexation and isolation as enones.[48]

Treatment of various Δ^3-piperidine complexes with one equivalent of either CAN, DDQ, or I_2 successfully liberates the heterocyclic ligand.[28] Molecular oxygen can also be used as a decomplexing agent, and the highest recovery of organic compound by this method is usually obtained by stirring MeCN or EtOAc solutions of the complex and silica[49] overnight in a flask under 1 atm of $O_{2(g)}$. As a general rule, complexes with anodic peak potentials ($E_{p,a}$) of more than ~ 0.5 V (vs NHE), are resistant to oxidation with $O_{2(g)}$. In these cases, the use of CAN is indicated. Isolating the tetrahydropyridine (THP) complexes by precipitation is often inefficient. Better yields are obtained if THP complexes are generated in situ (**Scheme 21**),[28] then directly oxidized. The reactions described here constitute a procedure to generate 1,2,5-trisubstituted tetrahydropyridinamides, **80–90**, with a diverse range of substituents, in overall yields from pyridine borane of 21–28% for the five-step process (>75% per step). Derivatives of the [4 + 2] cycloaddition products, **91–99**, may be isolated using DDQ or $O_{2(g)}$, generating 1,2,5-trisubstituted and 1,2,5,6-tetrasubstituted tetrahydropyridinamides (**Scheme 22**).[34]

Metal oxidation yields a variety of new 2-azabicyclo[2.2.2]-

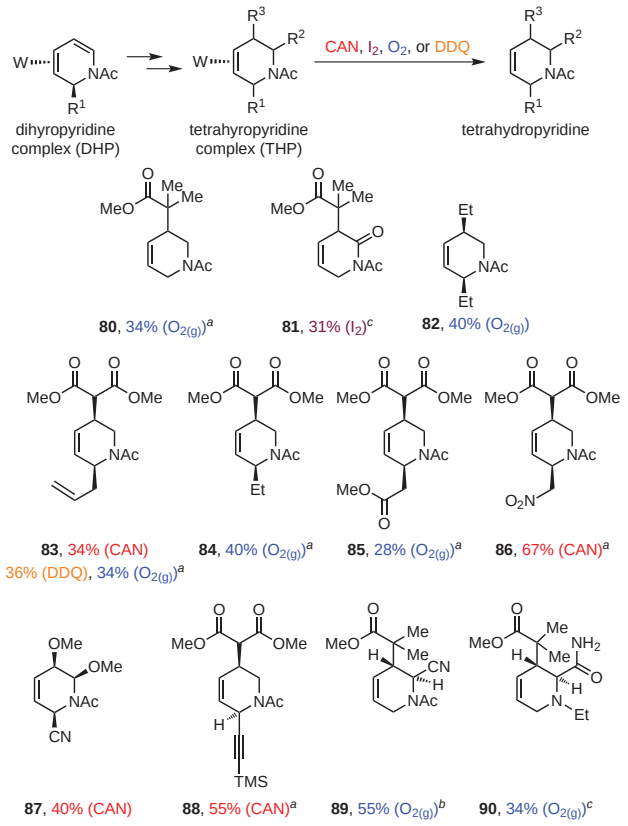


Scheme 20. Demetallation of 2*H*-Phenol Derivatives. *(Ref. 16,21)*

octadienes, **100**–**103**, derived from substituted pyridines (**Scheme 23**).[2,50] Liberation of the *3H*-pyrrole–Michael addition product and Michael–Aldol ring-closure product with CAN is achieved, but such action is accompanied by a rearomatization of the pyrrole portion of the new organic compounds, **104**–**106** (**Scheme 24**).[46]

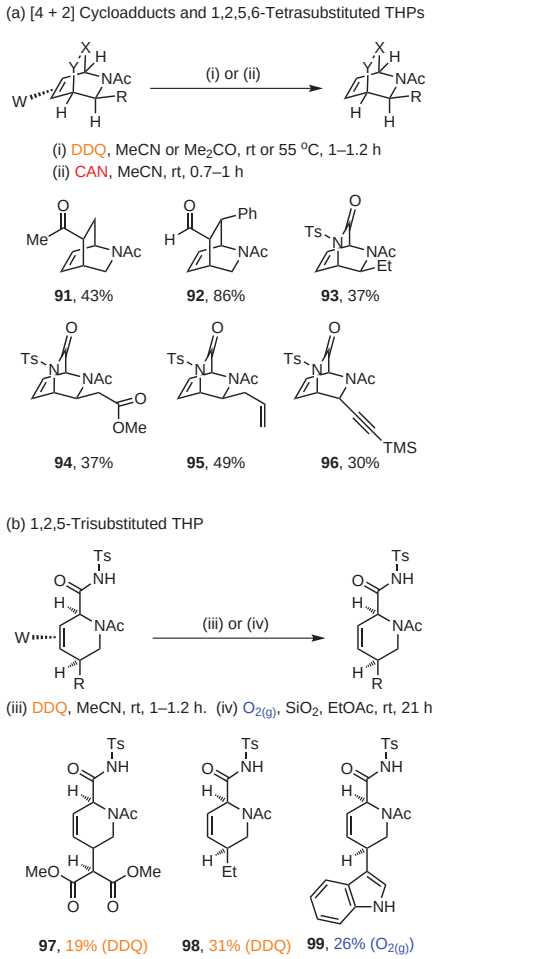
Oxidation of anisole-derived complexes **71a**,**b** with CAN produces new oxadecalin cores, **107a**,**b** (**Scheme 25**).[47] In one interesting case, the action of Cu(II) in the presence of molecular oxygen triggers a conjugate addition of pyrazole (either derived from decomposition of the Tp ligand or independently added) to the enone during the oxidation procedure to form the tricyclic ketone **109**. In the absence of air, the corresponding enone, **108**, is isolated.

As proof of concept that the {TpW(NO)(PMe_3)} metal fragment can produce organic compounds in enantiomeric excess, a procedure was employed in which one enantiomer of the metal irreversibly binds to (*R*)-α-pinene, (*R*)-**110**, and the other coordinates reversibly to (*R*)-α-pinene, (*S*)-**110** (**Scheme 26**).[2] Heating the mixture of diastereomers in a solution of 2,6-lutidine containing some acid, releases the more weakly coordinated (*R*)-α-pinene–tungsten complex, (*S*)-**110**, and allows for the isolation of a cationic η^2-lutidinium complex, (*S*)-**111**, in enantiomeric excess. Addition of base, followed by [4 + 2] cycloaddition with acrylonitrile, and oxidation with AgOTf allows for the isolation of the azabicyclic compound (*S*)-**113**, in an enantiomeric ratio (er) of 9:1 (ee = 80%).[2]

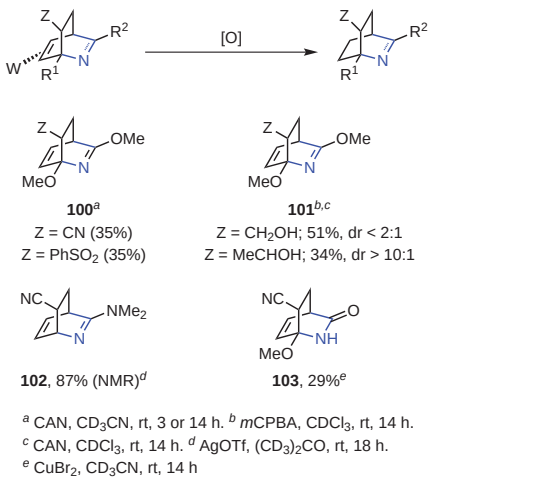


[a] From DHP (3 steps, 1 pot). [b] From THP (1 step). [c] From isoxazolium monocation (2 steps, 1 pot).

Scheme 21. Comparison of Demetallation Methods of Tetrahydropyridine Compounds Derived from the Pyridine–Tungsten Complex. *(Ref. 28)*



Scheme 22. DDQ and CAN Demetallation of Tetrahydropyridine Compounds Derived from the Pyridine–Tungsten Complex. *(Ref. 34)*



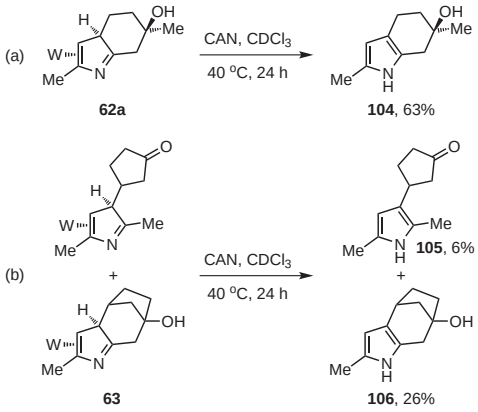
[a] CAN, CD_3CN, rt, 3 or 14 h. [b] *m*CPBA, $CDCl_3$, rt, 14 h. [c] CAN, $CDCl_3$, rt, 14 h. [d] AgOTf, $(CD_3)_2CO$, rt, 18 h. [e] $CuBr_2$, CD_3CN, rt, 14 h

Scheme 23. Liberation of 2-Azabicyclo[2.2.2]octadienes. *(Ref. 2,50)*

4. Conclusion

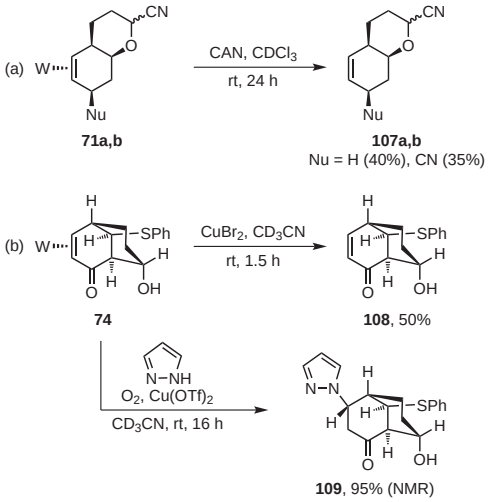
This review surveyed organic transformations that are facilitated by the tungsten complex {TpW(NO)(PMe_3)} and which have no organic or organometallic precedent. The dramatic activation of the aromatic substrates is a direct result of the strong π back-bonding interaction demonstrated by the tungsten. Not only can the metal be thought of as a protecting group for one of the double bonds, as the coordinated double bond is essentially rehybridized to an sp^3 center, but the metal is also an electron-donor group that activates the π system toward electrophilic addition reactions. Often this results in an electronic repolarization of alkene fragments in conjugation with the metal.

Several methodologies have been developed to liberate and isolate the modified ligands from the {TpW(NO)(PMe_3)} fragment. Thus, this tungsten system provides a methodology capable of accessing new chemical space for small molecules derived from aromatic compounds. These new compounds are of potential biological or medicinal significance. To this end, a number of samples have been submitted to the National Institutes of Health Molecular Libraries Small Molecule Repository (MLSMR) for storage and high-throughput biological screening.[51]

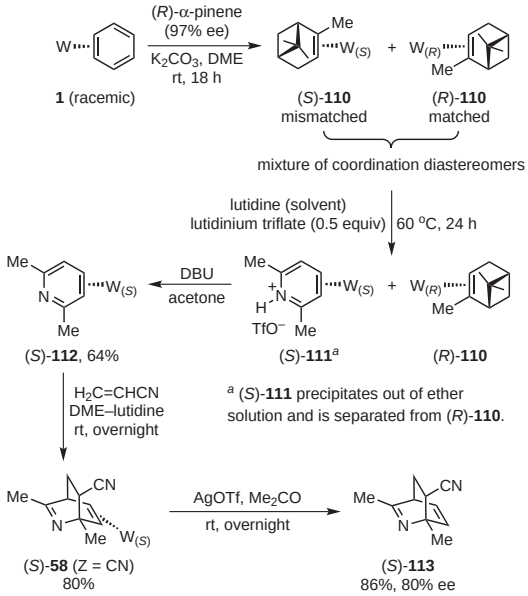


105 and **106** were cleanly separated by column chromatography. Yields of **105** and **106** are of the separated products.

Scheme 24. Demetallation of 3*H*-Pyrrole Derivatives. *(Ref. 46)*



Scheme 25. Demetallation of Anisole Derivatives. *(Ref. 47)*



Scheme 26. Example of the Synthesis and Isolation of an Organic in Enantiomeric Excess. *(Ref. 2)*

5. References and Notes

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About the Authors

Daniel P. Harrison was born in 1983, and received his B.Sc. degree from the Virginia Military Institute in December of 2004. He then worked for the Virginia Institute of Forensic Science and Medicine on a project funded by the FBI designed to develop a database of physical and chemical distinguishing characteristics of polyethylene bags. In January 2006, Dan joined Dean's group at the University of Virginia (UVA) and studied the ability of {TpW(NO)(PMe_3)} to activate pyridine toward mild additions, the isolation of new piperidine small molecules, and the origin of the complexes' ability to produce hyperdistorted allyls. Dan obtained his Ph.D. degree in 2011, and is currently a postdoctoral associate with Prof. Thomas J. Meyer at the U.S. DOE's Center for Solar Fuels at Chapel Hill's Energy Frontier Research Center at the University of North Carolina, where he is studying H_2O oxidation and CO_2 reduction catalysts for application in renewable energy.

W. Dean Harman was born in 1960 in Stanford, California, and received his B.Sc. degree in 1983 from Stanford University. He remained at "The Farm" to attend graduate school under the guidance of Professor Henry Taube. In 1987, he received his Ph.D. degree from Stanford U., and stayed on as a research associate with Taube until 1989, when he joined the faculty at the University of Virginia. In 1997, he was promoted to Full Professor and named the Cavalier Distinguished Teaching Chair. Dean has been named a Camille and Henry Dreyfus Teacher–Scholar (1992–1995), an NSF Young Investigator (1993–1998), an Alfred P. Sloan Research Fellow (1994–1996), and has been the recipient of several UVA teaching awards. He is a coauthor of ca. 150 refereed journal publications that collectively explore the diverse interactions of electron-rich transition-metal complexes with unsaturated organic molecules. Dean currently lives in Earlysville, Virginia, at the edge of the Blue Ridge Mountains with his wife, Lisa, and his children, Alorah and Dustin.

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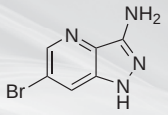

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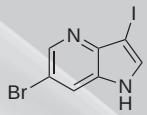

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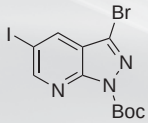

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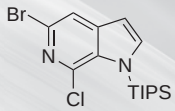

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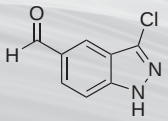

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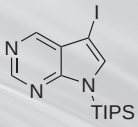

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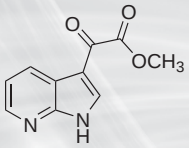

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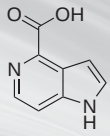

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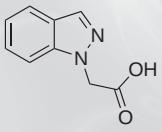

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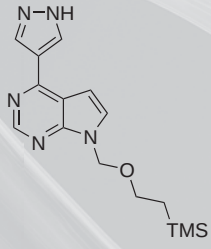

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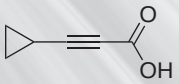

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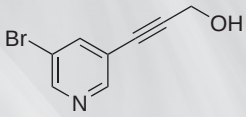

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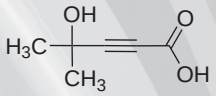

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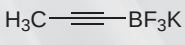

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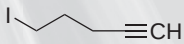

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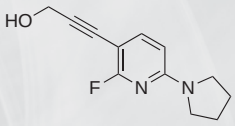

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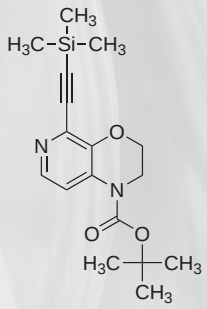

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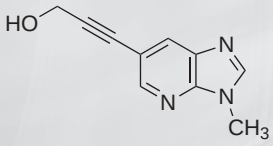

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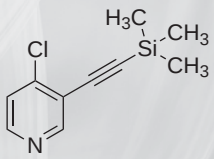

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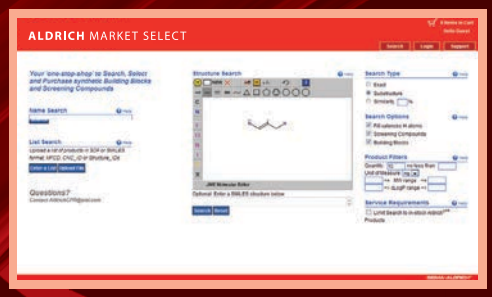

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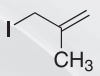
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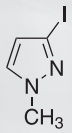
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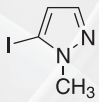
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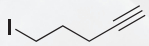
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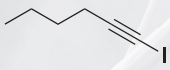
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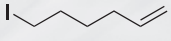
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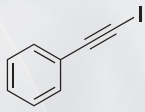
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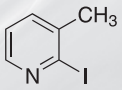
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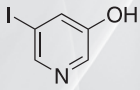
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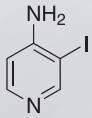
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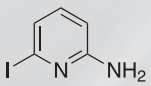
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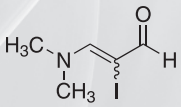
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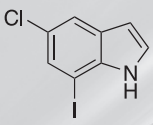
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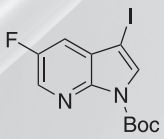
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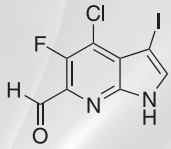
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742937	1,4-Diazabicyclo[2.2.2]octane bis(sulfur dioxide) adduct (DABSO), ≥95% (sulfur, elemental analysis)	1 g 5 g

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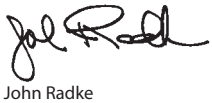

John Radke
Director of Marketing, Chemistry

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ABOUT OUR COVER

Detail from ***Forest of Fontainebleau***. Photograph © Board of Trustees, National Gallery of Art, Washington.

Forest of Fontainebleau (oil on canvas, 175.6 × 242.6 cm) was painted in 1834 by the French artist Jean-Baptiste-Camille Corot (1796–1875). Corot was a prolific painter with a talent that ranged widely from mainly landscapes to portraits, nudes, etchings, and other forms. He even dabbled in photography later on in his life. Unlike a number of his famous contemporaries, his rise to prominence in the artistic world was slow: He did not take up painting until his mid-twenties, and it wasn't until his mid-forties that he began to get the recognition he deserved, first from fellow artists, and then from art critics, official France, collectors, and the public. His artistic training consisted mainly of apprenticeships with Neoclassicist painters Achille-Etna Michallon and Jean-Victor Bertin and three trips a few years apart to Italy where he honed his landscape painting skills. Corot lived his life as a simple and humble man who was a mentor and a philanthropist to many young and struggling artists, and his work is thought to foreshadow the impressionist movement.

Forest of Fontainebleau is a good example of the genre of painting known as "historical" landscape, which Corot excelled at, and in which a historical or biblical theme is incorporated into the painting in order to "elevate" it in the eyes of art critics and gain public attention. In this case, the biblical connection is inferred from several clues* Corot inserted in the painting. Corot's strong naturalist strain, controlled paint strokes, and tendency to favor brown and black colors are reflected in this unpretentious and simply rendered composition depicting a rough forest that stands in sharp contrast to the serene young woman.

This painting is part of the Chester Dale Collection at the National Gallery of Art, Washington, DC.

* *Can you find the clues in the painting? What do the clues reveal about the young woman reading? To find out, visit* ***Aldrich.com/acta/aoc453***

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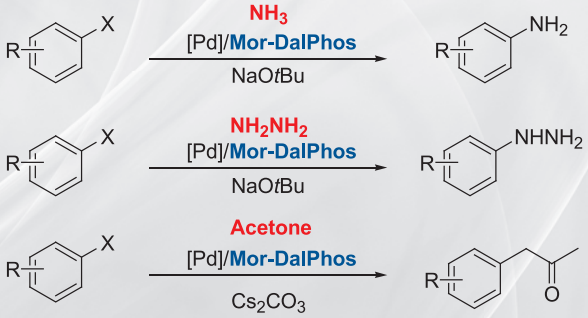
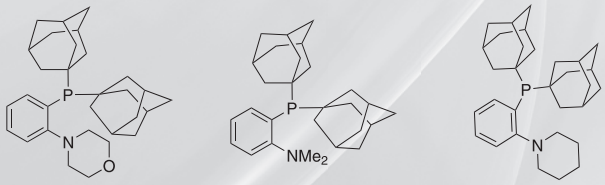
Pd-Catalyzed Monoarylation of Ammonia, Hydrazine and Acetone





751618
Mor-DalPhos

751413
Me-DalPhos

759198
New

References:
(1) Lundgren, R. J.; Peters, B. D.; Alsabeh, P. G.; Stradiotto, M. *Angew. Chem. Int. Ed.* **2010**, *49*, 4071. (2) Lundgren, R. J.; Stradiotto, M. *Angew. Chem. Int. Ed.* **2010**, *49*, 8686. (3) Hesp, K. D.; Lundgren, R. J.; Stradiotto, M. *J. Am. Chem. Soc.* **2011**, *133*, 5194. (4) Lundgren, R. J.; Sappong-Kumankumah, A.; Stradiotto, M. *Chem.—Eur. J.* **2010**, *16*, 1983. (5) Hesp, K. D.; Stradiotto, M. *J. Am. Chem. Soc.* **2010**, *132*, 18026.

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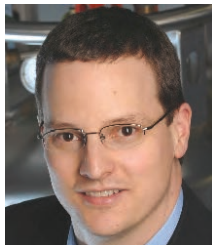
Recent Advances in the Buchwald–Hartwig Amination Reaction Enabled by the Application of Sterically Demanding Phosphine Ancillary Ligands

Dr. Rylan J. Lundgren



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Keywords. amination; catalysis; cross-coupling; ligand design; palladium.

Abstract. This review highlights a selection of important recent developments in the catalysis of the Buchwald–Hartwig amination reaction. These developments have been enabled through the use of sterically demanding phosphine ancillary ligands. Our aim is to inform the reader of recent methodology advances, and to encourage further development and understanding within the field of ancillary ligand design.

Outline

1. Introduction

The palladium-catalyzed cross-coupling of (hetero)aryl (pseudo)halides and N–H containing substrates (i.e., Buchwald–Hartwig amination or BHA) has emerged as a highly effective C–N bond-forming protocol that is employed on both bench-top and industrial scales for the construction of (hetero)arylamines.[1] A prototypical cross-coupling reaction of this type involving 4-chlorotoluene and aniline is depicted in **eq 1**. In the time following the initial development of such catalytic cross-coupling reactions independently by Buchwald's[2] and Hartwig's[3] groups, significant research effort has been directed toward expanding the scope and utility of such methods, including by examining how the choice of solvent, base, palladium precursor, and, perhaps most notably, the ancillary co-ligand influences the course of the BHA reaction.[4] Early studies employed relatively simple triarylphosphine ancillary ligands. However, the subsequent observation that the use of more structurally complex ancillary ligands can enable more challenging substrate pairings, often with excellent functional group tolerance and under milder conditions (e.g., low catalyst loadings, mild reaction temperatures), has given rise to the burgeoning field of ancillary ligand development within the domain of BHA catalysis. Indeed, it is now well-established that the use of sterically demanding and electron-rich phosphine ligands, as well as N-heterocyclic carbenes,[5] serves to facilitate the formation of low-coordinate Pd(0) species that can readily engage in otherwise challenging C_{sp2}–X bond oxidative addition reactions (e.g., X = Cl), as well as to encourage, through the alleviation of steric congestion, C–N bond reductive elimination from requisite $L_nPd(aryl)(NR_2)$ intermediates (R = aryl, alkyl, H, etc.)

The aim of this review is to highlight a selection of important recent developments in the rapidly expanding field of BHA catalysis that have been enabled through the design and/or implementation of sterically demanding phosphine ancillary ligands. In particular, emphasis will be placed on examples from the recent literature in which the novel ligand architecture has played a central role in advancing the state of the art for reaction classes where achieving broad substrate scope, selectivity, and catalytic efficiency has otherwise proven to be particularly challenging. The ancillary ligands that will be discussed in this review include the bisphosphine JosiPhos ligand (**L1**) utilized by Hartwig's group, biaryl monophosphine ligands (**L2–L6**) developed by Buchwald's group, the P,N DalPhos ligands (**L7** and **L8**) developed by our group, and the substituted indole ligand **L9** disclosed by Kwong's group (**Figure 1**).

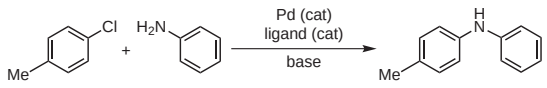
2. Selective Arylation of Challenging Substrates

Notwithstanding the tremendous progress that has been made with regard to expanding the scope of BHA in terms of both the (hetero)aryl (pseudo)halide and amine reaction partners, some transformations have until recently proven to be stubbornly problematic. Notable examples of such challenging transformations include the selective monoarylation of ammonia and hydrazine, the regioselective arylation of imidazoles and 1,2,3-triazoles, and the use of aryl mesylates as coupling partners. In the sections that follow, we discuss in detail the recent advances in ancillary ligand development that have enabled significant progress in addressing these reactivity challenges.

2.1. Selective Monoarylation of Ammonia

The direct preparation of nitrogen-containing molecules from ammonia—an inexpensive commodity chemical—remains an attractive goal in modern chemical synthesis. Unfortunately, many metal-catalyzed chemical transformations, including BHA, that are well-established for other amine classes do not proceed with useful efficiency and selectivity when employing ammonia as a substrate using commonly employed reaction protocols.[6] Challenges associated with the use of ammonia in BHA chemistry include: (i) catalyst deactivation arising from the formation of either Werner-type ammine complexes upon displacement of the ancillary co-ligand, or of amide-bridged polynuclear complexes; (ii) the slow rate of reductive elimination from sterically unencumbered intermediates of the type $L_nPd(aryl)(NH_2)$; and (iii) uncontrolled polyarylation because of the competitive nature of the product (hetero)-aryl amines relative to ammonia in the presence of many commonly employed BHA catalysts. Despite such challenges, the judicious selection of ancillary ligand has recently enabled the development of useful BHA protocols that permit the selective monoarylation of ammonia.

The selective monoarylation of ammonia by use of BHA protocols was first disclosed in 2006 by Shen and Hartwig,[7] who employed the palladium(II) precatalyst [(CyPF-*t*Bu)$PdCl_2$] featuring the JosiPhos ligand, CyPF-*t*Bu (**L1**), which had been developed previously and commercialized by Solvias for use in asymmetric hydrogenation applications.[8] By comparison, it was reported that the use of alternative ancillary ligands including P(*t*Bu)$_3$, XPhos, DPPF, QPhos, IPr, or BINAP did not result in any reaction under the rather forcing conditions employed (80 psi ammonia at 90 ºC), thereby supporting the view that the rigid, sterically demanding, and electron-rich nature of **L1** may serve both to enhance catalyst lifetime and to discourage unwanted polyarylation. A significant improvement to this protocol was published by Vo and Hartwig in 2009, in which the [Pd(P(*o*-Tol)$_3$)$_2$]–**L1** precatalyst mixture was employed (**eq 2**).[9] This catalyst system allowed for the efficient monoarylation of ammonia using aryl bromides, chlorides, iodides, and tosylates, including substrates featuring base-sensitive groups, without the routine need for high ammonia pressures. In a subsequent report by Klinkenberg and Hartwig, the results of stoichiometric reactivity studies were disclosed, which revealed that, in ammonia cross-coupling reactions employing Pd–**L1**, the catalyst resting state is an [(**L1**)Pd(aryl)(NH_2)] complex.[10] More recently, our group successfully applied a Pd–**L1** catalyst system to cascade ammonia arylation–alkyne hydroamination processes employing functionalized 2-bromoarylacetylenes to afford NH-indoles (**eq 3**).[11] Notably, this process represents the first reported synthesis of indoles directly from ammonia through metal-catalyzed cross-coupling.



eq 1 *(Ref. 1)*

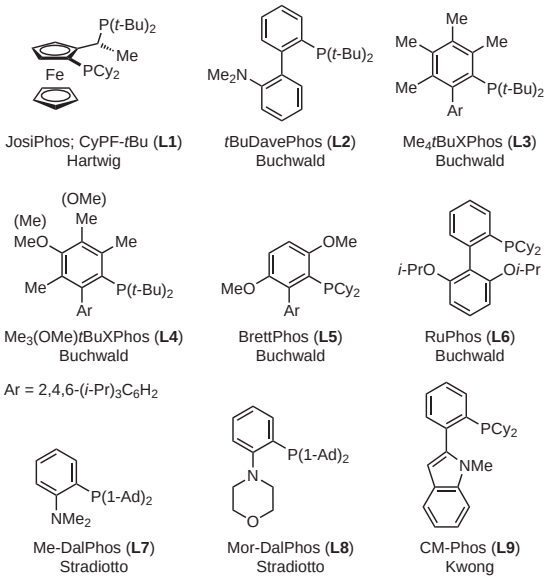


Figure 1. Sterically Demanding and Electron-Rich Phosphine Ligands Featured in this Review.

In a pair of publications, Beller and co-workers[14] reported that imidazole-derived monophosphine ligands are capable of supporting active complexes for the monoarylation of ammonia. Unfortunately, the scope of the reaction with aryl chlorides is somewhat limited, high reaction temperatures are often employed (≥120 ºC), and in some cases high pressures of inert gases (10 bar N_2) are needed to obtain satisfactory results.

In 2010, our group developed structurally simple phenylene-bridged P,N ligands that have proven to be particularly useful in metal-catalyzed C–C and C–N bond-forming reactions, including BHA.[15–17] We initially disclosed the ancillary ligand Me-DalPhos (**L7**), which was shown to be effective for the cross-coupling of a remarkably wide range of amines with structurally diverse (hetero)aryl chlorides.[15] While **L7** provided high conversions and good selectivities in the cross-coupling of ammonia with ortho-substituted aryl chlorides, the use of more challenging aryl chloride substrates resulted in poor monoarylation selectivity.[15] In the quest to circumvent such reactivity issues, further modifications of the DalPhos ligand structure were explored. These studies identified Mor-DalPhos (**L8**) as a highly active and selective

ligand for the cross-coupling of ammonia with aryl chlorides and tosylates (**eq 5**).[17] Reactions employing precatalysts based on **L8** proceeded with high monoarylation selectivity at generally low catalyst loadings and under mild reaction conditions without the need for high pressures of ammonia. The first examples of room-temperature BHA chemistry involving ammonia were also included in this report.[17] When **L8** was used, the substrate scope was found to encompass a diversity of electron-rich and electron-poor (hetero)aryl chlorides and tosylates, and excellent chemoselectivity for ammonia arylation was observed in the presence of potentially competitive aminoaryl chloride substrates.

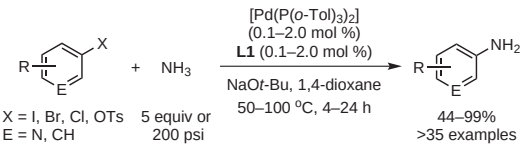
2.2. Selective Monoarylation of Hydrazine

Aryl hydrazines are key intermediates in the synthesis of a number of important nitrogen heterocycles including, most notably, indoles via the Fischer indole synthesis. The most commonly employed protocol for the preparation of aryl hydrazines relies on the stoichiometric oxidation of anilines to their corresponding diazonium salts followed by reduction, which suffers from limited functional-group tolerance and poor atom economy. While hydrazine can, in select cases, react directly with electron-deficient haloarenes in nucleophilic aromatic substitution reactions, the development of effective BHA protocols for the selective monoarylation of hydrazine represents a novel entry point for the preparation of aryl hydrazines. However, the use of hydrazine as a cross-coupling partner in BHA chemistry presents a number of potential problems, including: (i) unwanted reduction of the (hetero)-aryl (pseudo)halide substrate as well as the palladium precatalyst; (ii) metal-mediated N–N bond cleavage resulting in undesired aniline byproducts; and (iii) the inherent susceptibility of the aryl hydrazine product to undergo subsequent C–N cross-coupling leading to polyarylated products.

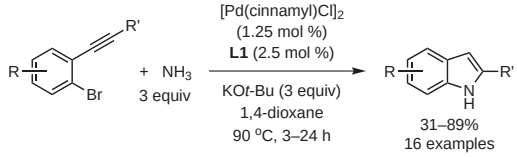
The selective monoarylation of hydrazine by use of BHA protocols was first reported by us in 2010.[18] In the course of this investigation, a broad range of ancillary ligands were surveyed, the vast majority of which afforded either poor conversion of the test substrate 4-phenylchlorobenzene, or exclusive reduction of this substrate to biphenyl by way of metal-catalyzed hydrodehalogenation. However, **L8**, as well as **L1** and **L7**, gave rise to the desired aryl hydrazine as the major product. Optimization of the reaction conditions using **L8** afforded a catalyst system that proved successful in transforming a range of aryl chlorides and tosylates into the corresponding aryl hydrazines with generally excellent monoarylation selectivity (**eq 6**).[18] The synthesis of indazoles via BHA–condensation reactions employing 2-chlorobenzaldehydes and hydrazine was also disclosed in this report. Notwithstanding the significance of this important reactivity breakthrough, some important limitations exist with regard to this **L8**-based catalyst system; notably, a reduced yield (50%) of the target aryl hydrazine was obtained for the electron-poor substrate 4-trifluoromethylchlorobenzene due to competitive hydrodehalogenation, while poor conversion (27% yield) was observed for the electron-rich substrate 4-chloroanisole.[18] The successful application of the [Pd(cinnamyl)Cl]$_2$–**L1** precatalyst mixture in the BHA of hydrazine with 2-alkynylbromoarenes to afford *N*-aminoindoles and indazoles was reported subsequently.[11]

2.3. Regioselective Arylation of Imidazoles and 1,2,3-Triazoles

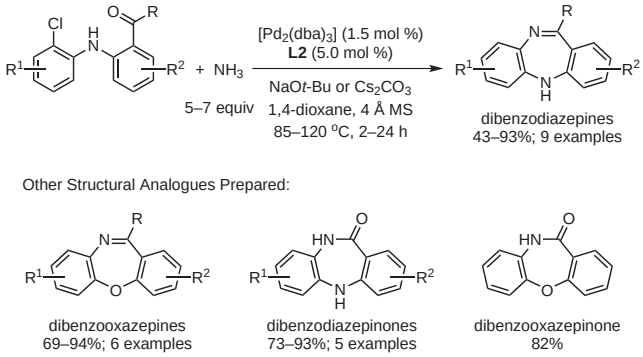
The synthesis of N-arylated heterocycles is of considerable interest, given the widespread application of such compounds in diverse fields ranging from materials science to medicinal chemistry. While a number of synthetic routes to N-arylated heterocycles have been



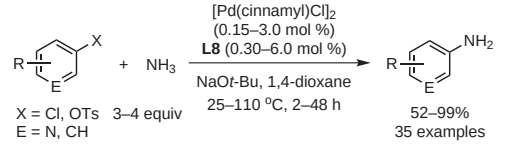
eq 2 *(Ref. 9)*



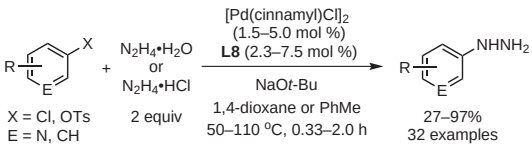
eq 3 *(Ref. 11)*



eq 4 *(Ref. 12b)*



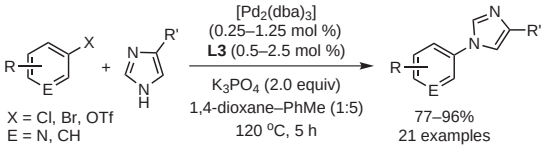
eq 5 *(Ref. 17)*



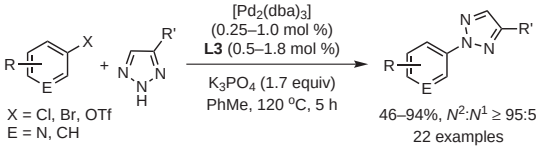
eq 6 *(Ref. 18)*

established, the ability to prepare these target compounds via arylation chemistry (including S_NAr or copper-mediated processes) in a highly regioselective manner and with a useful substrate scope has proven to be particularly challenging. However, recent reports by Buchwald and co-workers[19] demonstrate the utility of BHA chemistry in addressing such reactivity challenges through the judicious selection of ancillary co-ligand and the implementation of appropriate pre-catalyst activation procedures.

The tautomeric nature of unsymmetrical 1*H*-imidazoles presents a challenge with respect to obtaining high levels of regioselectivity in the arylation of such substrates. Given this, and the difficulty associated with separating the product N^1- and N^3-aryl regioisomers, the establishment of efficient and regioselective N-arylation protocols would be of considerable synthetic utility. Building on their earlier work employing Me_4*t*BuXPhos (**L3**) in the palladium-catalyzed N-arylation of imidazole,[20] Buchwald and co-workers developed a completely N^1-selective protocol for the arylation of unsymmetrical 4-substituted imidazoles (**eq 7**).[19b] Activation of the catalyst derived from a mixture of $[Pd_2(dba)_3]$ and **L3** prior to introduction of the imidazole substrate proved crucial in circumventing the inhibitory effect of the heterocyclic substrate during in situ catalyst formation. A variety of (hetero)aryl bromides, chlorides, and triflates were employed successfully in the regioselective arylation of 4-methylimidazole, 4-phenylimidazole, *N*-acetylhistamine, and 4-cyanomethylimidazole (0.5–2.5 mol % each of Pd and **L3**, 120 °C). The utility of their catalytic protocol was further demonstrated through the regiocontrolled synthesis of the glycine transporter inhibitor GSK2137305 (GlaxoSmithKline®) and the anticancer drug nilotinib (TASIGNA®).[19b]



eq 7 *(Ref. 19b)*



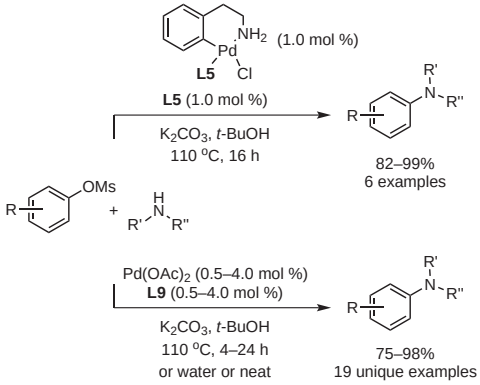
eq 8 *(Ref. 19a)*

Buchwald and co-workers were also successful in applying the $[Pd_2(dba)_3]$–**L3** catalyst system toward the highly N^2-selective arylation of 4,5-unsubstituted and 4-unsubstituted 1,2,3-triazoles with (hetero)-aryl bromides, chlorides, and triflates—a useful class of transformations that to date has not been achieved by use of complementary S_NAr or copper-mediated protocols (**eq 8**).[19a] In keeping with their examination of the arylation of unsymmetrical 4-substituted imidazoles (vide supra), Buchwald and co-workers noted that preactivation of the $[Pd_2(dba)_3]$–**L3** catalyst mixture in the absence of substrates and base was required in order to achieve optimal catalytic performance. Furthermore, studies of the influence of varying the ligand structure confirmed that the substitution pattern on both arene rings in **L3** contributes importantly to the desirable performance of the catalyst system.[19a]

One drawback of **L3** is that it is prepared from the rather costly reagent 1,2,3,4-tetramethylbenzene. In response, Buchwald and co-workers[21] have developed the synthesis of the structurally related ligand Me_3(OMe)*t*BuXPhos ligand (**L4**), which can be prepared in 59% overall yield as a nearly 1:1 mixture of regioisomers from the less costly 2,3,6-trimethylphenol. Comparative catalytic studies established that **L4** can serve as a surrogate for **L3** in the aforementioned regioselective arylation of imidazoles and 1,2,3-triazoles.

2.4. Amination of Aryl Mesylates

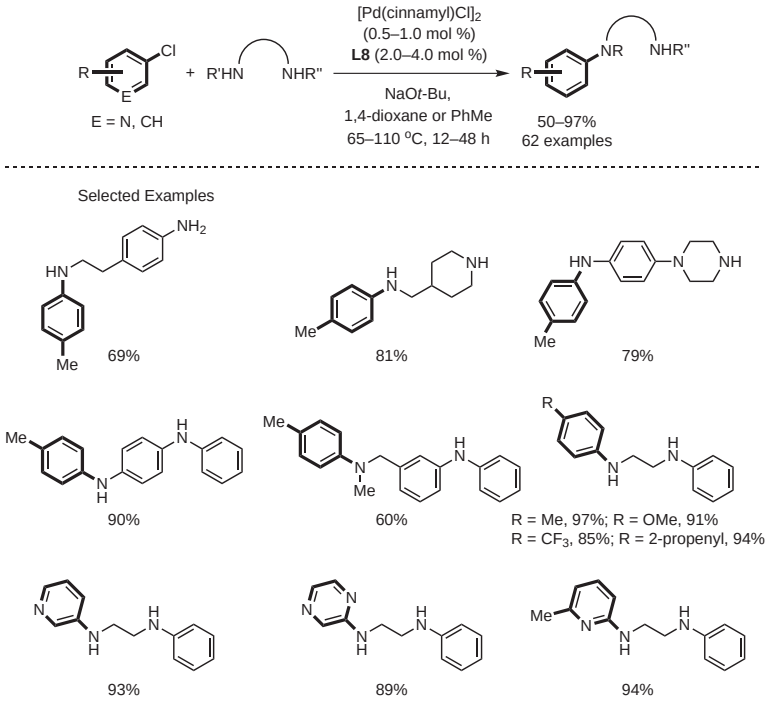
Aryl mesylates are attractive electrophiles for palladium-catalyzed cross-coupling reactions owing to their ease of synthesis from readily available phenols, and the associated waste reduction in comparison to higher-molecular-weight oxygen-based leaving groups, such as tosylates or triflates.[22] However, the sluggish reactivity of aryl mesylates prevented the use of such substrates in BHA until the groups of Kwong[23] and Buchwald[24] independently detailed the first successful protocols in 2008 (**Scheme 1**). It was demonstrated that catalysts featuring either the indole-containing CM-Phos (**L9**)[23] or BrettPhos (**L5**)[24] could mediate the amination of a range of aryl mesylates. Notably, $Pd(OAc)_2$–**L9** mixtures promoted C–N bond-forming reactions that employ *t*-BuOH or water as solvent, as well as those carried out in the absence of solvent. A current limitation of such methodology is the modest substrate scope with respect to the amine component: in the case of **L5**, only primary anilines were coupled; and in the case of **L9**, reactions were generally limited to sterically demanding primary aryl amines or secondary amines.



Scheme 1. The Amination of Aryl Mesylates Employing Catalysts Based on **L5** or **L9**. *(Ref. 23,24)*

3. Chemoselective Arylation of Substrates Featuring Multiple N–H Functionalities

Despite the significant attention that has been given to the application of BHA protocols in organic synthesis, reports documenting chemoselective variants of such reactions involving the preferential arylation of one amine fragment in the presence of multiple, competitive,



eq 9 *(Ref. 28)*

and chemically distinct N–H reactive functional groups are few and include contributions from the groups of Beletskaya,[25] Rouden,[26] and Buchwald,[20,24,27] among others. What is apparent from these reports is that a number of important drawbacks exist, including: (i) a limited demonstrated substrate scope for a given Pd–L catalyst system; (ii) the use of substrates where the statistical bias of amine functional groups can be viewed as contributing directly to the observed product ratio; (iii) low (<50%) isolated yields of isomeric monoarylation and diarylation product mixtures; and/or (iv) the incompatability of synthetically useful (hetero)aryl chloride substrates. In this regard, the identification of effective BHA catalysts for which predictive chemoselectivity models can be developed, and the demonstrated application of such reactivity models with synthetically useful scope, remain important goals in the quest to expand the utility of BHA chemistry. Indeed, the establishment of reliable chemoselective transformations of this type would enable BHA protocols to be applied more broadly toward the arylation of structurally complex substrates featuring multiple N–H functionalities, such as those commonly encountered in the synthesis of biologically active target compounds, thereby circumventing the need for wasteful and sometimes challenging nitrogen protection and deprotection steps.

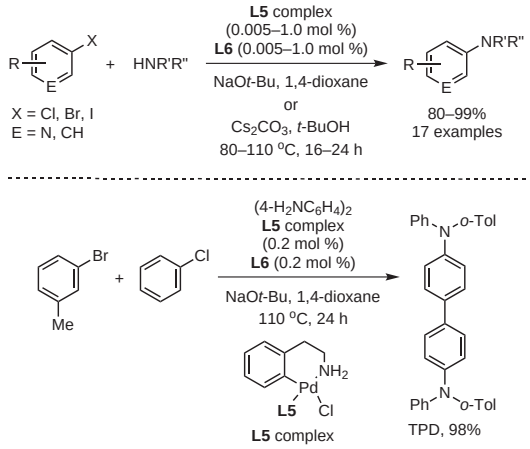
Encouraged by our finding of the distinct preference displayed by the [Pd(cinnamyl)Cl]$_2$–**L8** catalyst system for the selective monoarylation of ammonia or hydrazine when employing aryl chlorides bearing competitor primary amine or secondary amine functionalities,[17,18] our group has recently applied this catalyst system to chemoselective BHA reactions of the type outlined above (**eq 9**).[28] Competition studies confirmed the preference of the [Pd(cinnamyl)Cl]$_2$–**L8** catalyst system for unhindered nucleophilic amine reaction partners, which has enabled a range of structurally diverse di-, tri-, and tetraamines to be arylated in a chemoselective fashion based on this reactivity model. Indeed, this study represents the most extensive compilation of such reactivity reported thus far in the literature.[28] Interestingly, while unhindered nucleophilic amine reaction partners are preferred substrates when employing [Pd(cinnamyl)Cl]$_2$–**L8** mixtures, this catalyst system has also proven useful in the chemoselective arylation of a series of alternative amine functionalities (e.g., linear and α-branched primary alkylamines, imines, primary hydrazones, *N*,*N*-dialkylhydrazines, substituted anilines, and piperidine), while tolerating the presence of a range of potential competitor amine fragments as well as varied substitution within the (hetero)aryl chloride reaction partner. Comparative reactivity studies involving the para isomer of **L8** confirmed that the ortho disposition of phosphorus and nitrogen donors is the key to achieving the distinct chemoselectivity behavior that is observed when employing **L8**.[28]

4. Towards a Universal Catalyst for the Buchwald–Hartwig Amination

While advances in ligand design for use in BHA chemistry have given rise to several distinct classes of catalysts that offer state-of-the-art performance for selected substrates, such "task-specific" ligands often fail when alternative amine classes are employed, or require substantially higher Pd–ligand loadings to achieve reasonable yields of the target compound. This scenario is particularly problematic for practitioners of BHA in both academia and industry, who are faced with the dilemma of choosing an appropriate catalyst system for their particular application.[29] Ideally, the identification of a single "universal" catalyst system that can couple the broad spectrum of potential amine partners with (hetero)aryl (pseudo)halides at modest palladium loadings would serve to advance the utility of BHA protocols in chemical synthesis. While such a "one-catalyst-fits-all" platform has yet to be identified, some broadly useful catalyst systems that meet some of the above-mentioned criteria have been reported.

In 2010, our group reported on the broad applicability of Me-DalPhos (**L7**) in BHA catalysis.[15] The cross-coupling of rather challenging (hetero)aryl chlorides to a diverse range of amines and related substrates was achieved, including large and small primary alkyl- and arylamines, cyclic and acyclic secondary amines, N–H imines, hydrazones, lithium amide, and ammonia. In many cases, the reactions can be performed at low (0.5–0.02 mol %) palladium loadings with excellent functional-group tolerance and chemoselectivity. Subsequent investigations involving Mor-DalPhos **L8** confirm that this ligand variant also offers a similarly broad substrate scope in BHA.[28] However, BHA catalysts based on **L7** or **L8** do have limitations: weakly nucleophilic substrates including indoles, sulfonamides, and Boc-hydroxylamines each proved resistant to coupling under standard conditions.

An alternative approach to the development of more comprehensive catalysts for BHA has recently been disclosed by Fors and Buchwald (**Scheme 2**),[30] who employed a catalyst system based on a combination of the biaryl monophosphine ligands BrettPhos (**L5**) and RuPhos (**L6**). The choice of these two ligands is based on the observation that catalysts featuring **L5** are known to function effectively for the monoarylation of primary amines, but perform poorly in the arylation of secondary amine substrates; the converse is true for **L6**. The result is a complementary catalyst system that not only exhibits the best reactivity properties associated with each of **L5** and **L6**, but that also enables high-yielding transformations that are otherwise inefficient for either of the individual catalyst systems. Using the mixed Pd–**L5**–**L6** precatalyst mixture, anilines, large and small primary alkyl amines, secondary amines, and amides were coupled with (hetero)aryl chlorides, bromides, and iodides in high yields and with Pd loadings ranging from 0.005–1.0 mol %. Furthermore, by exploiting the more facile reactivity of aryl bromides relative to aryl chlorides, Fors and Buchwald were able to apply the Pd–**L5**–**L6** pre-catalyst mixture toward the high-yielding, one-pot synthesis of the hole-transport agent, TPD (see Scheme 2).[30] On the basis of elegant stoichiometric reactivity studies, the authors proposed that, under the catalytic conditions employed (≥100 °C), reversible exchange of **L5** for **L6** on palladium is facile, and can occur involving both Pd(0) and Pd(II) reactive intermediates. Such processes enable the shuttling of palladium between two independent catalytic cycles



Scheme 2. A Multiple-Ligand BHA Catalyst System Employing **L5** and **L6**. *(Ref. 30)*

for primary amine monoarylation (ligated by **L5**) and secondary amine arylation (ligated by **L6**). Notwithstanding the useful scope exhibited by this unusual catalyst system, substrate limitations similar to those noted for the DalPhos system (vide supra) were observed; namely, imidazoles, benzimidazoles, pyrazoles, and secondary cyclic amides were not accommodated. Furthermore, unlike catalysts based on the DalPhos ligands **L7** or **L8**,[15,17] the Pd–**L5**–**L6** precatalyst mixture proved ineffective for the monoarylation of ammonia. More recently, the broad utility of BHA catalysts based either on **L5** or **L6** in the arylation of primary or secondary amines, respectively, has been demonstrated.[31]

5. Conclusions and Outlook

The development and application of sterically demanding phosphine ancillary ligands continues to advance the state of the art in BHA catalysis. As evidenced by the selected examples featured in this review, recently developed ligands of this type have enabled the establishment of catalysts that accommodate previously challenging substrates in a chemoselective fashion, with broad substrate scope and excellent functional-group tolerance. Moreover, from a practical perspective, most of the ancillary ligands featured in this review are both air-stable and commercially available. While it is evident that some ligand structural motifs appear to be privileged, it is noteworthy that no single class has proven superior in all BHA applications. Furthermore, within a ligand class, even subtle structural changes have been shown to profoundly influence the performance of the derived BHA catalyst. In this regard, a more fundamental appreciation of the means by which ancillary ligand structure can direct the course of BHA processes is needed in order to guide the rational development of new catalysts to address the important reactivity goals that remain in the field.

6. Acknowledgements

We thank the NSERC of Canada (including Discovery, CRD, CHRP, Engage, and I2I Grants for M. S., as well as both a Postgraduate Scholarship and a Postdoctoral Fellowship for R. J. L.), the Canada Foundation for Innovation, the Killam Trusts, the Province of Nova Scotia (Springboard, Innovacorp, and the Nova Scotia Research and Innovation Trust), and Dalhousie University for their generous financial support of this work.

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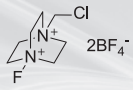

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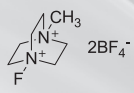

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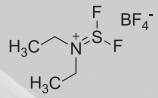

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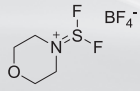

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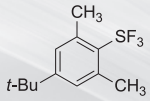

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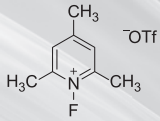

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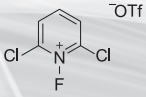

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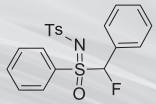

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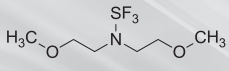

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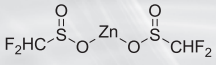

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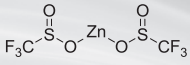

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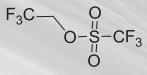

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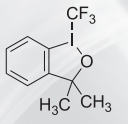

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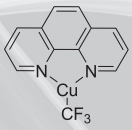

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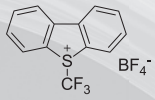

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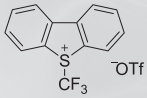

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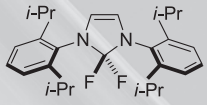

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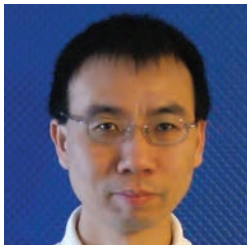
Transition-Metal-Mediated Fluorination, Difluoromethylation, and Trifluoromethylation


Dr. Zhuang Jin


Prof. Gerald B. Hammond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Keywords. transition metal; catalysis; fluorination; difluoromethylation; trifluoromethylation.

Abstract. Introducing fluorine into organic molecules is a proven successful strategy in designing pharmaceuticals with improved therapeutic effects, but has remained a long-standing challenge for synthetic organic chemists. Fortunately, newly developed transition-metal-catalyzed or mediated fluorination, difluoromethylation, and trifluoromethylation reactions are addressing this challenge and facilitating the synthesis of fluorinated compounds. In this review, we have classified and organized the recent developments in fluorination, difluoromethylation, and trifluoromethylation reactions based on the metal catalyst and the underlying mechanism of the C–F, C–CF_2, and C–CF_3 bond formation. We also comment on the limitations of these methods.

Outline

1. Introduction

Extensive research has established that introducing fluorine into a target molecule can effectively modify its physicochemical properties.[1] As a result, up to 20% of pharmaceuticals[2] and approximately 30% of agrochemicals[2b] contain fluorine and/or the trifluoromethyl group. Additionally, fluorine-18 (^{18}F) is regarded as one of the most clinically important radioisotopes for Positron Emission Tomography (PET).[3] Nevertheless, over a century after its discovery, the introduction of fluorine into organic molecules continues to be a long-standing challenge for synthetic organic chemists.

In general, fluorinated compounds can be prepared through the use of molecular-building-block methods or of fluorination reagents.[1g] The former utilizes commercial fluorine-containing building blocks[1f] (functionalized compounds containing F, CF_2, CF_3, and/or OCF_3; e.g., 4-fluorobenzaldehyde). The latter method utilizes fluorinating reagents, most of which are commercially available (**Figure 1**). Their mode of action is to introduce F or CF_3 into target molecules through functional group transformations. If suitable fluorination methods are available, medicinal chemists usually prefer these because they can introduce fluorine where and when they want it.

Fluorination of an aromatic system has been effected most commonly through the Balz–Schiemann reaction (transformation of anilines into

aryl fluorides via diazonium fluoroborates)[4] and the Halex reaction (halogen-exchange reaction),[5] whereas the introduction of fluorine into an aliphatic system has been accomplished through nucleophilic (e.g., the conversion of alcohol into fluoride via DAST) or electrophilic fluorination (e.g., fluorination of the α carbon of a carbonyl group by Selectfluor®).[1g] Moreover, trifluoromethylation has relied heavily on the Swarts reaction[6] and the reaction of carboxylic acid derivatives with SF_4.[7] Although all of these traditional methods employ relatively cheap starting materials or reagents—without the need for expensive metal catalysts—they often require harsh conditions, leading to poor functional-group tolerance.

Transition-metal catalysis plays a major role in organic synthesis (e.g., in coupling and metathesis reactions). In recent years, many transition-metal-catalyzed fluorinations and trifluoromethylations have emerged as powerful methods for synthesizing fluorinated agents[8] as demonstrated by the number of excellent reviews that have appeared on the topic in the past three years.[9]

In this review, we survey ground-breaking research on transition-metal-mediated fluorination, difluoromethylation, and trifluoromethylation reactions that have been reported from 2007 to early 2012. Some transition-metal-catalyzed fluorinations, such as the electrophilic fluorination of metal enolates,[10] are not included, but can be found in other reviews.[9a,b] Some reactions that are not typical for transition metals are also not covered.[11] Moreover, in the case of difluoromethylation and trifluoromethylation methods, we limit the discussion to the use of C-1 fluorine sources, such as $TMSCF_3$.

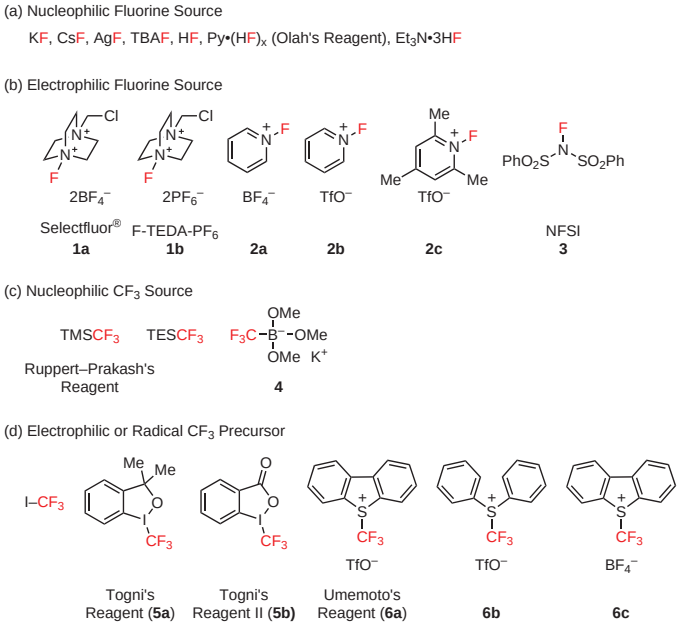
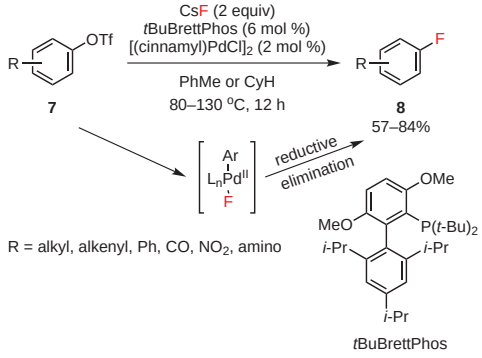


Figure 1. Common Fluorine Sources Covered in this Review.



eq 1 *(Ref. 13)*

2. Transition-Metal-Promoted Fluorination

2.1. Pd-Mediated Fluorination

2.1.1. Fluorinations via Reductive Elimination from R–Pd–F

2.1.1.1. Reductive Elimination from R–Pd(II)–F

Transition metals, such as palladium, have been widely used for carbon–carbon and carbon–heteroatom bond formations via reductive elimination from a R–Pd(II)–X intermediate (X = carbon or heteroatom). However, reductive elimination from R–Pd(II)–F is not an easy task, as demonstrated by the pioneering work of Grushin and co-workers[12] on the reductive elimination from isolated [ArPd(II)F] complexes. It wasn't until 2009 that a successful catalytic C–F bond formation via R–Pd(II)–F was achieved.[13] Buchwald and co-workers found that bulky *t*BuBrettPhos is a suitable ligand for palladium, which enables the fluorination of aryl triflates with CsF (**eq 1**).[13] Increasing the amount of CsF to 6 equivalents and adding 30 mol % of the solubilizing agent poly(ethylene glycol) dimethyl ether significantly shortens the reaction time (one example showed a full conversion in less than 30 min). Although many functional groups can be tolerated in the fluorination protocol, no reaction took place with aryl triflates containing amines or carbonyls in the ortho position. It was proposed that the C–F bond formation proceeds through reductive elimination from an arylpalladium(II) fluoride complex, and DFT calculations by Yandulov and Tran[14] showed that the C–F bond is formed via a concerted reductive elimination from an arylpalladium(II) fluoride complex. The fluorination needed high temperatures and long reaction times, rendering the methodology inapplicable for the introduction of ^{18}F, which is used for Positron Emission Tomography (PET) studies. To solve this problem, Buchwald's group later developed a microflow CsF packed-bed reactor, in which aryl triflates can be fluorinated in a short time (20 min).[15] More specifically, a toluene solution containing aryl triflate, palladium, and ligand was injected into a CsF packed-bed reactor which was heated to 120 °C or 130 °C, and the fluorinated products were collected from the outlet of the reactor.

A more recent mechanistic investigation conducted by Buchwald and co-workers revealed that C–F reductive elimination from an LPd(II)(Ar)F complex (L = *t*BuBrettPhos or RockPhos) does not occur when the aryl group is electron-rich, but rather, a modified phosphine, generated in situ, serves as the actual supporting ligand during catalysis with such substrates.[16]

2.1.1.2. Reductive Elimination from R–Pd(IV)–F

According to the previously mentioned work of Grushin and co-workers,[12] reductive elimination from R–Pd(II)–F is not an easy path for aryl fluoride synthesis. Sanford and others found that reductive elimination from R–Pd(IV)–F could be a more favored process; this may be due to the fact that a Pd(IV) center is possibly more electron-deficient than its Pd(II) counterpart, thus favoring reductive elimination. The

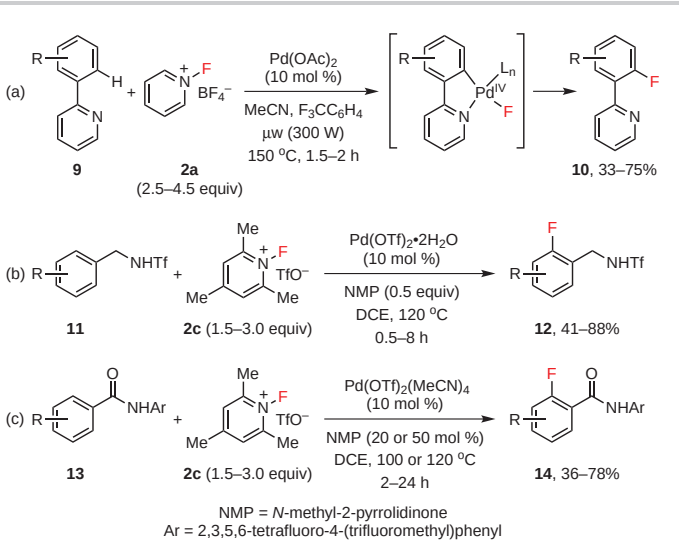
first Pd(II)-catalyzed C–H fluorination through reductive elimination from R–Pd(IV)–F was reported by Sanford in 2006 (**Scheme 1**, Part (a)).[17] Likewise, Yu and co-workers have reported an efficient, Pd(II)-catalyzed synthesis of aryl fluorides using a nitrogen-containing functional group as directing group (Scheme 1, Parts (b) and (c)).[18]

More applications of Pd(IV) reductive eliminations have recently been published. Furuya and Ritter reported direct evidence of carbon–fluorine formation via reductive elimination from a high-valence palladium fluoride complex.[19] Accordingly, palladium(IV) difluoride **15** was carefully prepared and characterized by X-ray crystallography, and led upon heating to the fluorinated product, **16**, through reductive elimination (**Scheme 2**, Part (a)).[19] Further systematic mechanistic analysis showed that the ancillary pyridylsulfonamide ligand played a crucial role in the reductive elimination, probably due to a k^3-coordination mode, in which the oxygen atom of the sulfonyl group coordinates to palladium.[20] Similarly, another palladium(IV) difluoride complex, **17**, isolated by Ball and Sanford, furnished the fluorinated aromatic compound **18** upon heating with electrophilic fluorinating agents (XeF_2, NFSI (**3**)) in nitrobenzene, hinting that C–F reductive elimination is a reasonable pathway (Scheme 2, Part (b)).[21]

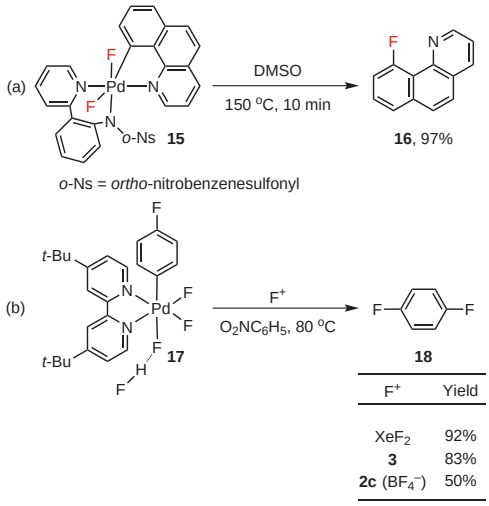
Ritter's group later reported a palladium complex, **19**, that can be readily transmetallated to yield complexes **21**.[22] Both **19** and **21** contain a bidentate ligand possessing a neutral and an anionic nitrogen donor. Complex **21** subsequently reacted with Selectfluor® to yield fluorinated aromatic compounds **8** under mild conditions in a short reaction time (**Scheme 3**).[22] Two possible reaction mechanisms were proposed, namely electrophilic palladium–carbon bond cleavage and carbon–fluorine reductive elimination from a high-valency palladium complex. Compared to the harsh reaction conditions and limited substrate scope of conventional fluorination methodologies, this method seems to be very appropriate for late-stage fluorination, including introducing ^{18}F into organic compounds. ^{18}F is one of the most relevant radioisotopes in Positron Emission Tomography (PET),[3,23] and its incorporation requires not only a fast reaction because of its 110-minute half-life, but also that the reaction be carried out at the end of any synthetic sequence. Ritter's group has recently developed a fluoride-derived, electrophilic late-stage fluorination reagent for PET studies.[24] The authors prepared palladium(IV) complex **22**, which reacted with a nucleophilic fluoride source (KF) to form monofluorinated palladium(IV) complex **23** (confirmed by X-ray crystallography) (**Scheme 4**).[24] Palladium(II) complexes **24** were prepared from arylboronic acids **20** and complex **19´**, and reacted with **23** in acetonitrile at room temperature to produce **25**. The monofluorinated benzene products, **8**, were formed through reductive elimination from complex **25** upon heating at 80 °C for 10 min. The entire procedure, including HPLC purification, took less than 60 min, a time length that is appropriate for ^{18}F PET imaging. Using this protocol, the authors prepared three ^{18}F-containing drug analogues with radiochemical yields of 10–33%.

2.1.2. Pd-Catalyzed Fluorination of Allyl Halides and Allyl Esters

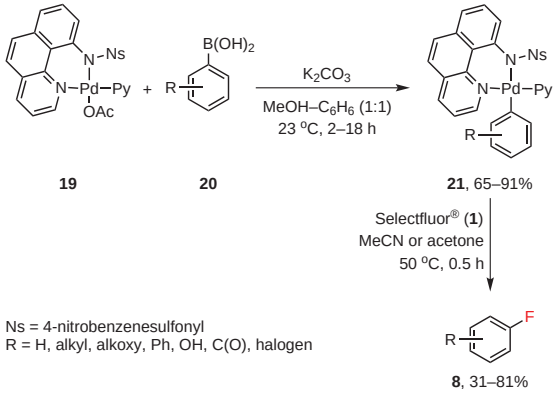
The use of a nucleophilic fluorine source in the Tsuji–Trost reaction, instead of carbon, nitrogen, or oxygen nucleophiles can be a challenge.[25] Recently, though, a palladium-catalyzed asymmetric synthesis of allylic fluoride was reported by Katcher and Doyle.[26] Cyclic allylic chlorides **26** were asymmetrically fluorinated by AgF, in the presence of palladium(0) and Trost's bisphosphine ligand **27**, to form the fluorinated products in moderate-to-high yields and excellent enantioselectivities (**Scheme 5**, Part (a)). The reaction also produced a small amount of the diene elimination products (less than 10 %). The authors proposed that



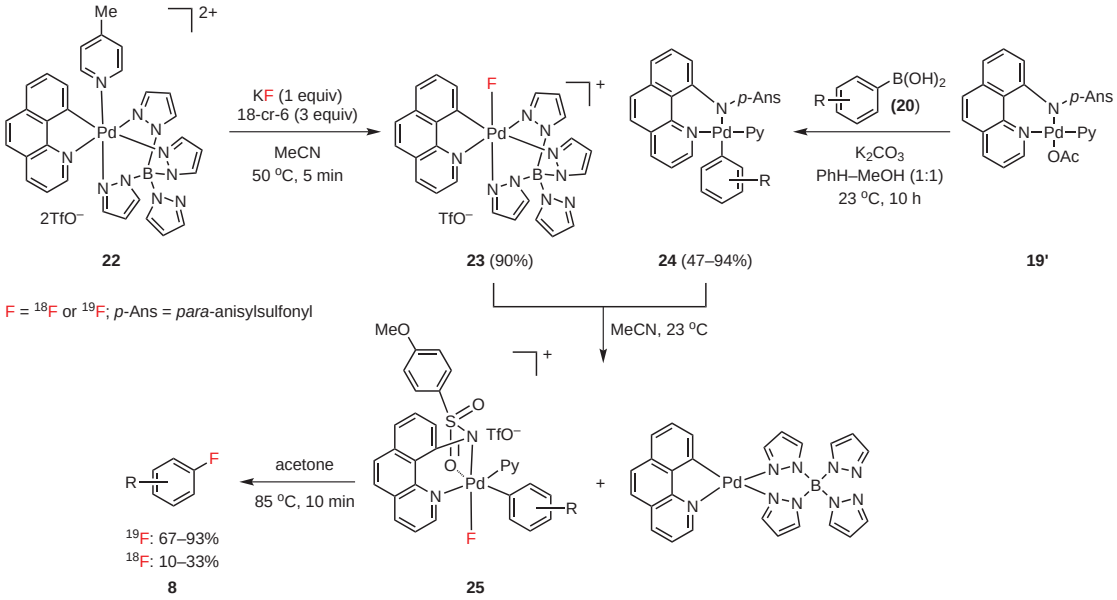
Scheme 1. Synthesis of Aryl Fluorides through Reductive Elimination from a R–Pd(IV)–F Intermediate. *(Ref. 17,18)*



Scheme 2. Evidence of C–F Bond Formation via Reductive Elimination from Pd(IV). *(Ref. 19,21)*



Scheme 3. Palladium-Mediated Fluorination of Boronic Acids. *(Ref. 22)*



Scheme 4. Fluoride-Derived Electrophilic Late-Stage Fluorination Protocol for PET Studies. *(Ref. 24)*

Pd(0) oxidatively adds to **26** with inversion of configuration by an S_N2-type reaction, generating a AgCl precipitate that becomes the driving force for the fluorination. The attack of fluoride on the allylpalladium intermediate gives an overall retention of configuration. Although this fluorination can tolerate functional groups including ethers, amines, esters, and amides, it is not without limitations: (i) the leaving group can only be chloride, and (ii) the synthesis of *acyclic* allyl fluorides is not effective. Later, Doyle's group succeeded in developing an enantioselective fluorination of acyclic allylic halides by employing palladium(0) and Trost's naphthyl ligand **30** in a similar way.[27] Thus, acyclic allylic chlorides (or bromides) **29** were fluorinated with excess AgF to yield branched allylic fluorides **31** in moderate-to-good yields (Scheme 5, Part (b)). While linear allylic chlorides (or bromides) **29** underwent the reaction with only moderate enantioselectivity, α-branched or heteroatom-substituted allylic halides were fluorinated with excellent 90–97% ee's. Substituents and functional groups such as benzyl and silyl ethers, aldehydes, and alkyl bromides are tolerated in this protocol.

Gouverneur's group also developed a palladium-catalyzed allylic fluorination using *para*-nitrobenzoate as leaving group and TBAF•(*t*-BuOH)$_4$ as fluoride source.[28] Phenyl-substituted allylic ester **32** was fluorinated to give allylic fluoride **33** in high yield (Scheme 5, Part (c)). The mild conditions and fast reaction times allowed the authors to prepare an allylic "hot" fluoride. [^{18}F]-Labeled cinnamyl fluoride was obtained in radiochemical yields of 9–42% (n = 12; n being the number of carried-out experiments) for a reaction quenched after 5 min, and no significant improvement was observed after 30 min (10–51%, n = 5). There are some limitations to this method: (i) the double bond in the allyl ester must be attached to an aromatic ring, and (ii) only primary fluorides can be prepared by this protocol.

2.1.3. Pd-Catalyzed Fluorination via Oxidative Addition to C–C Unsaturated Bonds

Another category of Pd-catalyzed fluorinations is the oxidative nucleophilic addition to C–C unsaturated bonds. Palladium-catalyzed intra- and intermolecular aminofluorinations of alkenes were developed by Guosheng Liu and co-workers.[29] AgF and PhI(OPiv)$_2$ were employed as the fluorinating agent and oxidant, respectively, in the intramolecular aminofluorination of unactivated terminal alkenes **34** to vicinal fluoroamines **35** in the presence of palladium catalyst (**Scheme 6**, Part (a)).[29a] The authors found that addition of $MgSO_4$ improves the yield of **35**, and that the C–F bond is probably formed by direct reductive elimination from a Pd(IV) intermediate or through an S_N2-type nucleophilic substitution of fluoride.

Liu also reported on the intermolecular variant, whereby a variety of styrenes **36** were regioselectively aminofluorinated with the electrophilic fluorinating agent *N*-fluorobenzenesulfonimide (NFSI, **3**) to give fluorinated amines **37** in up to 80% yields (Scheme 6, Part (b)).[29b] Both electron-donating and electron-withdrawing groups at different positions of the phenyl ring had no significant effect on this fluoroamination, although the reaction gave small amounts of difluorinated amine as side product. The authors found that the reaction is restricted to activated alkenes, such as styrene, and proposed that Pd(0) is oxidized by NFSI to a Pd(II) intermediate, with the ensuing fluoropalladation of styrene being a key step in the aminofluorination process.

Peng and Liu employed a palladium-catalyzed tandem fluorination–cyclization of enyne **38** to fluorinated lactam **39** in good yield (Scheme 6, Part (c)).[30] Enynes containing branched chains or internal olefins were not suitable, yielding poor-to-trace amounts of the lactam. The authors proposed that *cis*-fluoropalladation (predominant) of the alkyne occurs first, followed by alkene insertion into the vinylpalladium intermediate to form a C_{sp3}–Pd bond, which is then reduced by isopropanol to give fluorinated lactam **39**. Interestingly, the additive 4-nitrophenol was found to slightly increase the yield of the lactam.

2.2. Gold-Catalyzed Fluorination

2.2.1. Using a Nucleophilic Fluorine Source

The discovery by Sadighi's group that an (NHC)gold(I) fluoride complex reacts with excess alkyne to give a β-(fluorovinyl)gold complex prompted them to develop this transformation into a gold-catalyzed hydrofluorination of alkynes to fluoroalkenes.[31] Several types of alkyne, **40**, were effectively *trans*-hydrofluorinated to yield fluoroalkenes **41** in good yields and moderate regioselectivities (**Scheme 7**, Part (a)). The authors reported that (i) good regioselectivities can be achieved only with aryl–alkyl alkynes, (ii) $Et_3N•3HF$ is a suitable nucleophilic fluorinating agent, and (iii) powdered $KHSO_4$ and a co-catalyst, $PhNMe_2•HOTf$, greatly increase the yield of the fluoroalkenes.

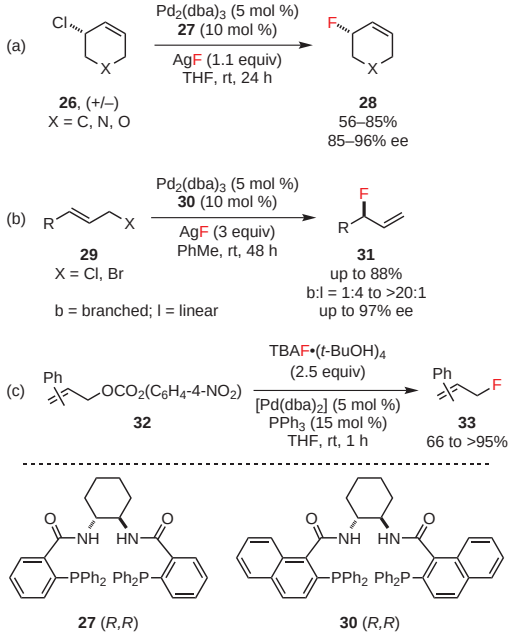
The regioselectivity limitations can be overcome by employing directing groups. Miller and co-workers chose a 2,2,2-trichloroethoxy-carbamate moiety as directing group to successfully hydrofluorinate alkynes **42** stereo- (trans) and regioselectively (rr 49:1 to >50:1) to give predominantly *Z* fluoroalkenes **43** (Scheme 7, Part (b)).[32]

2.2.2. Using an Electrophilic Fluorine Source

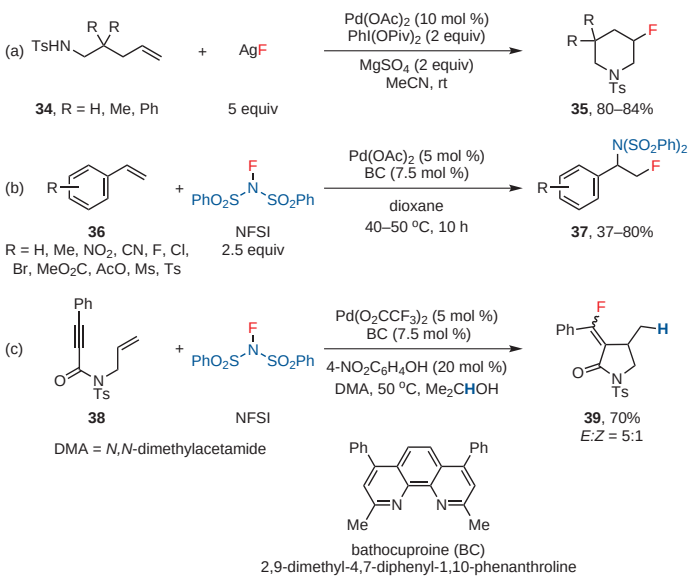
Gouverneur's group developed the first gold-catalyzed oxidative fluorination reaction, by mixing a difluorinated ynone ($PhCH(OH)–CF_2C(O)CCPh$), AuCl, and Selectfluor® in acetonitrile at room temperature for a few days.[33] A trifluorodihydropyranone (20%) was obtained together with a difluorinated pyranone (33%), formed from the competitive protodeauration of the organogold intermediate. A fluorodeauration mechanism was proposed to explain the formation of the fluorinated products observed.

Gold-catalyzed multicomponent transformations are very rare.[34] Our group recently accomplished a truly gold-catalyzed, multicomponent transformation—the functionalized hydration of alkynes (**Scheme 8**).[35] A major shortcoming of traditional metal-catalyzed hydration is that it only adds the elements of H_2O to an alkyne, whereas functionalized hydration combines four intermolecular components (alkyne, nucleophile, electrophile, and coupling reagent) to form a single product, a highly functionalized α-fluoroketone, in good yield and moderate regioselectivity. This one-pot, multicomponent transformation—using readily available starting materials (alkyne, water, organoboronic acid, and Selectfluor®)—has obvious advantages over literature methods that need multiple steps and are not library-friendly.[36] We also detected experimentally (by ^{19}F NMR and X-ray photoelectron spectroscopy) that Au(I) is oxidized by Selectfluor® to give a Au(III) species, which is much more active than Au(I) in hydration and cyclization. In the proposed mechanism, the nucleophile (water) first attacks the gold-activated alkyne to form a vinylgold complex,[37] which can further react with a metal reagent (e.g., $R^3B(OH)_2$) through a transmetallation process.[38] The final C–F formation mechanism is not clear yet; one possibility is that gold actually enhances the nucleophilicity of the vinylgold intermediate, allowing it to react with Selectfluor®.

Nevado's (**Scheme 9**, Part (a))[39] and Gouverneur's groups (Scheme 9, Part (b))[40] have independently developed an efficient gold-catalyzed rearrangement and fluorination of propargyl acetates, leading to α-fluoroenones in good yields and regioselectivities. Later, De Haro and Nevado disclosed the synthesis of α-fluoroketones or α-fluoroacetals, **50**, using similar conditions (Scheme 9, Part (c)).[41] Furthermore, Liu, Xu, and co-workers reported the gold-catalyzed tandem aminofluorination



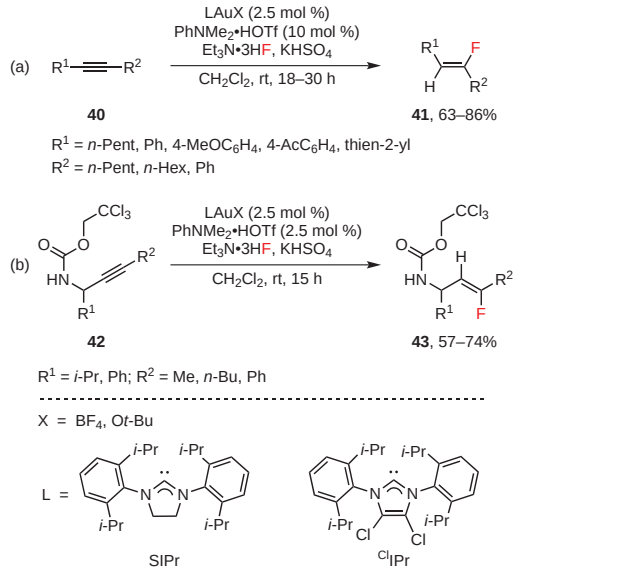
Scheme 5. Fluorination of Allylic Halides and Allylic Acetates. *(Ref. 26–28)*



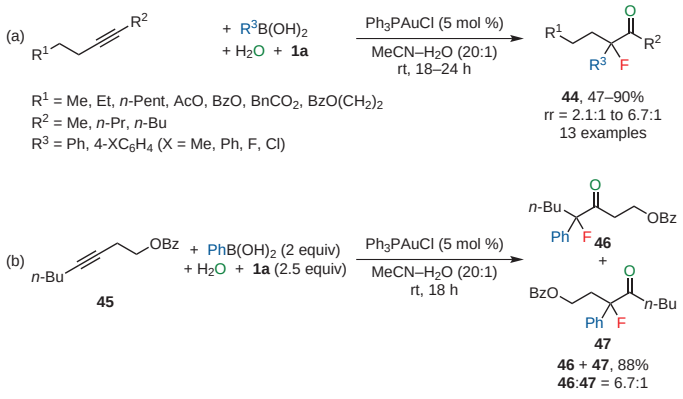
Scheme 6. Palladium-Catalyzed Fluorinations and Cyclizations as Reported by Guosheng Liu and Co-workers. *(Ref. 29,30)*

of propargyl hydrazines **51** to give, after cyclization and fluorination, fluorinated pyrazoles **52** in moderate-to-excellent yields (Scheme 9, Part (d)).[42] However, the reaction also produced significant amounts of nonfluorinated pyrazoles.

Reductive elimination or fluorodeauration has been proposed as a possible mechanism for the formation of the C–F bond in the preceding reactions.[42] There is, however, no direct experimental evidence so far to support these hypotheses, and in all of these cases, the normal protodeauration product (the compound that is obtained in the absence of a fluorination reagent) can react with Selectfluor® to give the corresponding fluorinated product in good yield without the need for a gold catalyst (Scheme 9, Part (e)).[40–42] Therefore, it is most likely that these reactions go through a tandem two-step mechanism. The fluorination step may occur outside of the gold-catalyzed cycle, and gold might not play a significant role in the formation of the C–F bond.



Scheme 7. Gold-Catalyzed Hydrofluorination of Alkynes. *(Ref. 31,32)*



Scheme 8. Functionalized Hydration of Alkynes. *(Ref. 35)*

Direct evidence for the C_{sp3}–F reductive elimination was reported by Mankad and Toste,[43] who prepared an alkyl(IPr)gold complex and readily oxidized it by XeF_2 to give the corresponding difluorinated tetracoordinate gold(III) complex. Reductive elimination from this in situ generated Au(III) complex led to the monofluorinated products in low-to-moderate yields, with the yield being dependent on the nature of the alkyl group. If a β hydrogen (relative to gold) is present in the alkyl group, β-hydride elimination becomes competitive with C–F reductive elimination; while a carbocation-like rearrangement occurs prior to C–F reductive elimination, when the alkyl group bears a strained moiety and lacks a β hydrogen. Density Functional Theory (DFT) calculations supported a C–F reductive elimination occurring through a transient cationic intermediate. Toste's work demonstrates that reductive elimination from R–Au(III)–F may be a feasible process.

2.3. Silver-Mediated Fluorination

The silver-mediated fluorination of arylstannanes and boronic acids was pioneered by Ritter and co-workers, who reported the fluorination of aryl- and alkenylboronic acids with Selectfluor® (**1a**).[44] Arylboronic acids **20** were mixed with stoichiometric amounts of AgOTf and NaOH (a crucial additive) in methanol to give an isolable arylsilver intermediate, which reacted with Selectfluor® to furnish the fluorinated products **8** in good yields (**Scheme 10**, Part (a)). In addition to arylboronic acids, alkenylboronic acids can be fluorinated to give fluoroalkenes (65–85%), in which the alkene stereochemistry is preserved. This methodology can tolerate electron-poor, electron-rich, di-ortho-substituted arenes, and heteroaromatics. The authors also prepared a few fluorinated pharmaceutically active agents, demonstrating the broad functional-group tolerance of their methodology. Preliminary mechanistic investigations hinted that bimetallic oxidation–reductive elimination is a possible pathway for C–F bond formation. There are, however, a couple of limitations to this method: (i) the use of 2 equivalents of a silver salt, and (ii) the formation of 10–20% of hydrodestannylated side products in the case of arylstannane substrates.[45]

Ritter's group also developed a silver-mediated fluorination of arylstannanes **53** using the fluorination agent **1b** (an anion-exchange product of Selectfluor®), obtaining fluorinated arenes in moderate-to-good yields (Scheme 10, Part (b)).[45] **1b** was found to give higher yields of the fluorination products than Selectfluor®. Ritter and co-workers also developed a silver-*catalyzed* fluorination of arylstannanes **54** using **1b**.[46] The key to using only catalytic amounts of silver salt was to employ the additives $NaHCO_3$ and NaOTf (Scheme 10, Part (c)). Carbohydrates, peptides, polyketides, and alkaloids were tolerated by this method, although certain amines, thiol ethers, and carboxyl groups were not tolerated. The proposed fluorination mechanism of the catalytic variant is similar to that proposed for the silver-mediated stoichiometric fluorination and is thought to proceed via intermediate **55** (Scheme 10, Part (d)).

A silver-catalyzed intramolecular oxidative aminofluorination of allenes with NFSI (**3**) has been developed by Liu and co-workers,[47] and represents an efficient method for the synthesis of various 4-fluoro-2,5-dihydropyrroles, which can be elaborated into the corresponding fluorinated pyrroles in good yields.

2.4. Fluorination Mediated by Other Transition Metals

The first platinum-mediated fluorination was reported by Vigalok's group (**Scheme 11**, Part (a)).[48] Platinum(II) complex **56** was prepared and oxidized by XeF_2 to yield the benzylic-fluorinated product **57** in quantitative yield. The authors proposed that platinum(II) is oxidized to

platinum(IV) complex **58**, and fluoride assists in the metallation of the benzyl group to give complex **59** before rendering the product via C–F reductive elimination. Gagné's group has also developed a platinum-mediated fluorination protocol (Scheme 11, Part (b)).[49] For example, complex **60** was reacted with various electrophilic fluorinating agents, such as XeF_2 and N–F salts, to deliver the C–F reductive elimination product **61** in good yield. The fluorination became more efficient as the steric congestion of the platinum complex grew larger. A benzyl group, lacking a β hydrogen, gave high yield of the fluorination product, but other simple acyclic alkyl groups were not fluorinated efficiently owing to competitive β elimination.

A copper-catalyzed, halide-exchange reaction under very mild reaction conditions using a family of model aryl halides has been reported by Ribas and co-workers (Scheme 11, Part (c)).[50] Their work suggests that reductive elimination from R–Cu–F is also a feasible process, although it is still too early to determine the impact of its application in synthesis.

3. Transition-Metal-Promoted Trifluoromethylation

3.1. Copper-Mediated Trifluoromethylation

3.1.1. Trifluoromethylation of Electrophiles (Mainly ArI)

Since the trifluoromethylation of aromatic compounds with metal complexes has been extensively reviewed by Tomashenko and Grushin,[9f] we will limit our discussion to new developments in this rapidly expanding area.

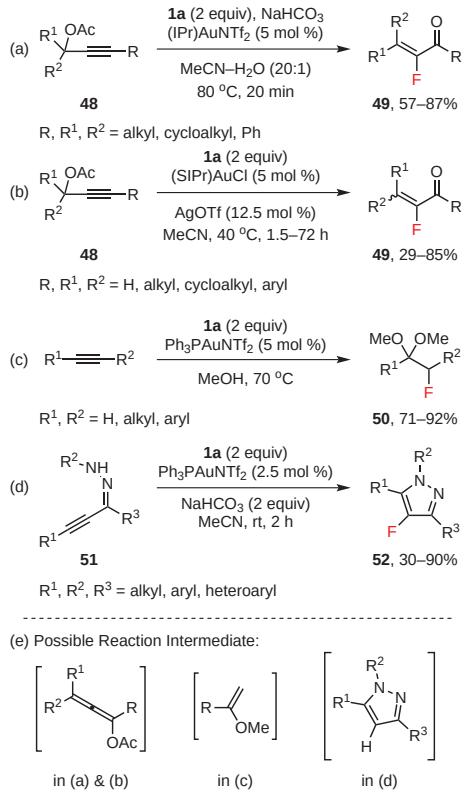
3.1.1.1. Trifluoromethylation via a CF_3Cu Intermediate Generated in Situ

The generation (from CF_2Br_2), spectroscopic detection, and chemical reactivity of CF_3Cu (trifluoromethylcopper) has been revealed through the pioneering work of Burton and co-workers.[51] Another source of CF_3Cu is the CuI–Cu[9f] or CF_3Hg–Cu system.[52] An improved protocol, whereby the transient trifluoromethylcopper species is generated in situ from $TMSCF_3$ (Ruppert–Prakash's reagent, a more convenient source of CF_3) in the presence of cuprous iodide and potassium fluoride, has been advanced.[53] All of the most recent work on trifluoromethylation has been based on Me_3SiCF_3 or reagents derived from it.[54]

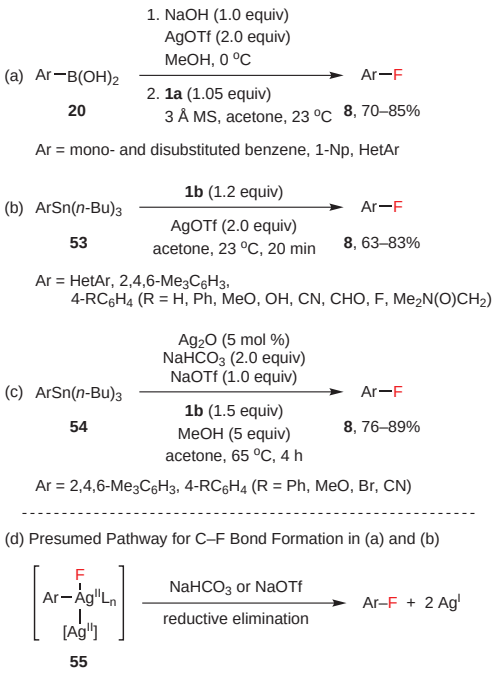
Amii and co-workers reported an improved copper-catalyzed trifluoromethylation of aromatic iodides by (trifluoromethyl)-triethylsilane.[55] They designed their catalytic cycle based on the knowledge that the reaction between the copper catalyst and the trifluoromethylating agent to form the active intermediate $CuCF_3$ is very fast, but that the second step, after delivery of the trifluoromethylated arene, is much slower and cannot resupply sufficient amounts of the copper source for the first reaction. The authors found that adding a diamine ligand such as 1,10-phenanthroline solved the problem. Both electron-rich and electron-poor aromatic iodides can be efficiently trifluoromethylated by Et_3SiCF_3 (**Scheme 12**, Part (a)). Furthermore, heteroaromatic iodides (three examples) were smoothly trifluoromethylated by this protocol.

A collaborative team led by Weng developed a bimetal-mediated [a combination of CuI (10 mol %) and AgF (1.3 equiv)] trifluoromethylation of aryl iodides with Me_3SiCF_3,[56] which is much cheaper than Et_3SiCF_3, to the give trifluoromethylated products in moderate-to-excellent yields (Scheme 12, Part (b)). A mechanistic study revealed that $AgCF_3$ is most probably generated first, and then transfers the CF_3 group to copper to form $CuCF_3$, which is the active catalytic species.

Hafner and Bräse also reported an efficient method for the trifluoromethylation of halogenated double bonds using in situ generated "trifluoromethyl copper". $TMSCF_3$ was converted selectively



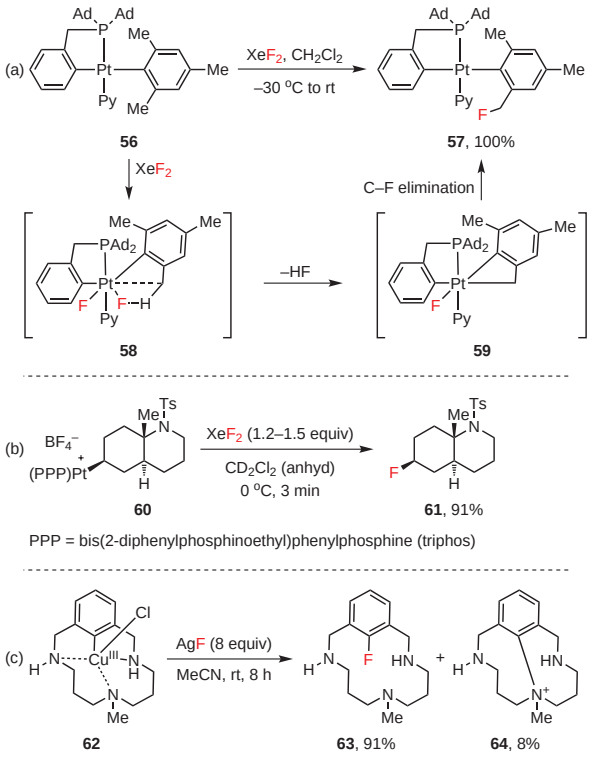
Scheme 9. Gold-Catalyzed Fluorination of Alkynes. *(Ref. 39–42)*



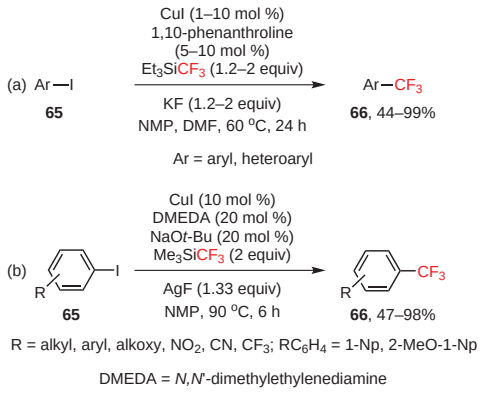
Scheme 10. Ritter's Silver-Mediated Fluorination of Arylstannanes and Arylboronic Acids. *(Ref. 44–46)*

into "trifluoromethyl copper" using CuI as the copper source and KF as promoter; the trifluoromethylation of activated and unactivated alkenyl halides occurred mostly in good-to-excellent yields in up to a gram scale.[57]

In addition to using R_3SiCF_3 directly as the CF_3 source, other reagents have been employed to generate CF_3Cu, although many of these are derived from R_3SiCF_3. Gooßen and co-workers prepared potassium (trifluoromethyl)trimethoxyborate ($F_3CB(OMe)_3K$, **4**) from



Scheme 11. Fluorinations Mediated by Pt and Cu. *(Ref. 48–50)*



Scheme 12. Copper-Catalyzed Trifluoromethylation of Aromatic Iodides by R_3SiCF_3. *(Ref. 55,56)*

Me_3SiCF_3, and introduced it as a stable, easy-to-handle, and efficient trifluoromethylating agent for aryl iodides in the presence of a copper catalyst, giving rise to the trifluoromethylated products in moderate-to-excellent yields (**Scheme 13**, Part (a)).[58] A wide variety of substituents and functional groups, such as cyano, sulfide, halide, ester, amide, and acetal are tolerated in the reaction. More importantly, while Gooßen's protocol allows the trifluoromethylation of heterocyclic iodides, one of its limitations is that the trifluoromethyl moiety can react with ketones and aldehydes.

Xiao's group has reported a copper-mediated trifluoromethylation of heteroaromatic iodides using trifluoromethylsulfonium salt **6b** and Cu (Scheme 13, Part (b)).[59] A large variety of trifluoromethylated heteroaromatics including pyridine, pyridazine, pyrazole, imidazole, indole, and other oxygen- or sulfur-containing heteroaromatics, were prepared in excellent yields. In some cases, the reaction was very sensitive to steric hindrance and did not yield the desired products. As for a possible mechanism, the authors proposed that the likely active intermediate is $CuCF_3$, which is probably generated via a single-electron transfer between Cu and **6b**.

Amii's group also reported a copper-catalyzed trifluoromethylation of aryl iodides using O-silylated trifluoroacetaldehyde hemiaminal **69**, readily prepared from $CF_3CH(OH)(OEt)$ and morpholine. Both electron-rich and electron-poor aryl iodides can be trifluoromethylated in the presence of a complex of copper and ligand, to give trifluoromethylated aromatics in moderate-to-excellent yields (Scheme 13, Part (c)).[60] However, this protocol failed when a ketone or aldehyde group was present in the aryl iodide, due to the nucleophilic trifluoromethylation conditions.

Kremlev, Tyrra, and co-workers reported that $Zn(CF_3)Br•2DMF$ and CuBr act as an alternative trifluoromethylating agent, capable of trifluoromethylating aryl iodides (Scheme 13, Part (d)).[61] For this purpose, $Zn(CF_3)Br•2DMF$ and CuBr were mixed in DMF at room temperature for 3 h, and the in situ generated $CuCF_3$ readily trifluoromethylated electron-poor aryl iodides at 85–90 °C to give moderate yields of trifluoromethylated products. Unfortunately, the reaction with electron-rich aryl iodides was accompanied by formation of a pentafluoroethylation product. Vicic's group disclosed the decarboxylative trifluoromethylation of aryl iodides or bromides by using a copper trifluoroacetate intermediate.[62] Their protocol employed a mixture of CuI and CF_3CO_2Na to trifluoromethylate aryl iodides (and bromides) via a decarboxylative pathway to give trifuoromethylated aromatic compounds in moderate yields after heating at 160 °C for 24 h. Li, Duan, and collaborators discovered that a ligand-free Cu–Ag_2O system facilitated the trifluoromethylation of aryl iodides by CF_3CO_2Na (Scheme 13, Part (e)).[63] CF_3CO_2Na, Cu, and Ag_2O were mixed with a variety of aryl iodides in DMF and heated at 130 °C for 15 h to give the trifluoromethylated arenes in moderate-to-excellent yields. Several functional groups such as nitro, ester, sulfido, amino, and cyano, were tolerated in this protocol. Shibata's group reported using shelf-stable, electrophilic trifluoromethylating reagent **6b** to effect a copper-mediated, chemoselective trifluoromethylation at the benzylic position in good-to-high yields under mild conditions (Scheme 13, Part (f)).[64]

Grushin and co-workers discovered the first direct cupration of fluoroform (HCF_3), the most attractive CF_3 source for the introduction of the trifluoromethyl group into organic molecules. The fluoroform-derived $CuCF_3$ solution can be effectively stabilized with TREAT-HF (triethylamine trihydrofluoride, Franz's Reagent) to produce a $CuCF_3$ reagent that readily trifluoromethylates organic and inorganic electrophiles in the absence of additional ligands such as phenanthroline.[65]

3.1.1.2. Trifluoromethylation via a Preformed CF_3Cu Complex

Vicic's group isolated (NHC)$CuCF_3$ (**72**), characterized it by X-ray crystallography, and reacted it with aromatic and heteroaromatic iodides to give excellent yields of the corresponding trifluoromethylated products, albeit five equivalents of the starting iodide was required (**Scheme 14**, Part (a)).[66] Complex **72** can also trifluoromethylate benzyl bromide in moderate yield (58%). This work provided direct evidence for CF_3Cu's role as the intermediate in the copper-mediated trifluoromethylation of organic iodides.

Hartwig and co-workers prepared and spectroscopically characterized (1,10-phenanthroline)$CuCF_3$ (**73**), and found that it exists in the ionic form [(1,10-phenanthroline)$_2$Cu][Cu$(CF_3)_2$] in DMF (Scheme 14, Part (b)).[67] Complex **73** efficiently trifluoromethylates aromatic iodides containing different functional groups to give the trifluoromethylated products in excellent yields. Additionally, **73** can readily trifluoromethylate heterocyclic iodides; such as quinoline, purine, and indole; and alkenyl iodides (1 example: *trans*-1-iodooctene, 99%); producing the trifluoromethylated derivatives in excellent yields. More importantly, **73** also trifluoromethylates some aromatic bromides to deliver moderate-to-good yields of the corresponding products.

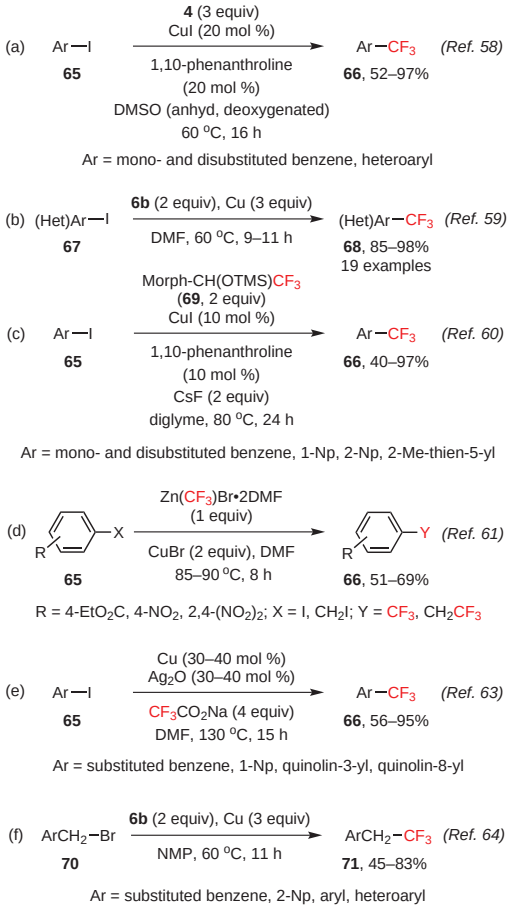
Grushin's group prepared and isolated [$(Ph_3P)_3Cu(CF_3)$] and (1,10-phenanthroline)Cu$(PPh_3)CF_3$ (**74**), and demonstrated that **74** could trifluoromethylate aromatic iodides upon heating at 80 °C, leading to the trifluoromethyl-substituted products in moderate-to-good yields (Scheme 14, Part (c)).[68]

3.1.2. Trifluoromethylation of Nucleophiles through Oxidative Coupling

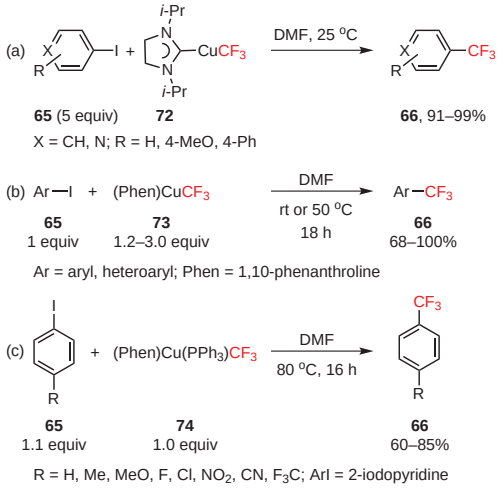
The CF_3Cu intermediate not only can react with electrophiles such as aryl iodides, but it can also participate in oxidative coupling with selected nucleophiles in the presence of a suitable oxidizing reagent. The copper-mediated aerobic oxidative trifluoromethylation of terminal alkynes with Me_3SiCF_3 was first reported by Chu and Qing.[69] Both alkyl- and aryl-substituted terminal alkynes **75** were trifluoromethylated with Me_3SiCF_3 through the mediation of a ligated CuI (**Scheme 15**, Part (a)). A number of functional groups and substituents including alkoxy, amino, ester, nitro, chloro, and bromo were tolerated. Very recently, Fu's group also reported a copper-catalyzed trifluoromethylation of terminal alkynes using Umemoto's reagent,[70] while Weng, Huang, and co-workers reported similar findings by employing Togni's reagent.[71]

The first copper-mediated oxidative cross-coupling of aryl- and alkenylboronic acids **20** with (trifluoromethyl)trimethylsilane was also reported by Qing's group,[72] who employed a copper(I)–ligand complex as catalyst and a silver salt as oxidant. Both electron-rich and electron-poor aromatic rings were efficiently trifluoromethylated with Me_3SiCF_3 (Scheme 15, Part (b)). The same research group also showed that their method is effective for the preparation of trifluoromethylalkenes. Independently, Buchwald's group disclosed the trifluoromethylation of arylboronic acids (Scheme 15, Part (c))[73] by employing a process that is amenable to typical bench-top setups with the reaction typically requiring only 1–4 h under mild conditions. Buchwald's protocol tolerates a range of functional groups, allowing access to a variety of trifluoromethylarenes, and avoids the use of stoichiometric amounts of silver salt.

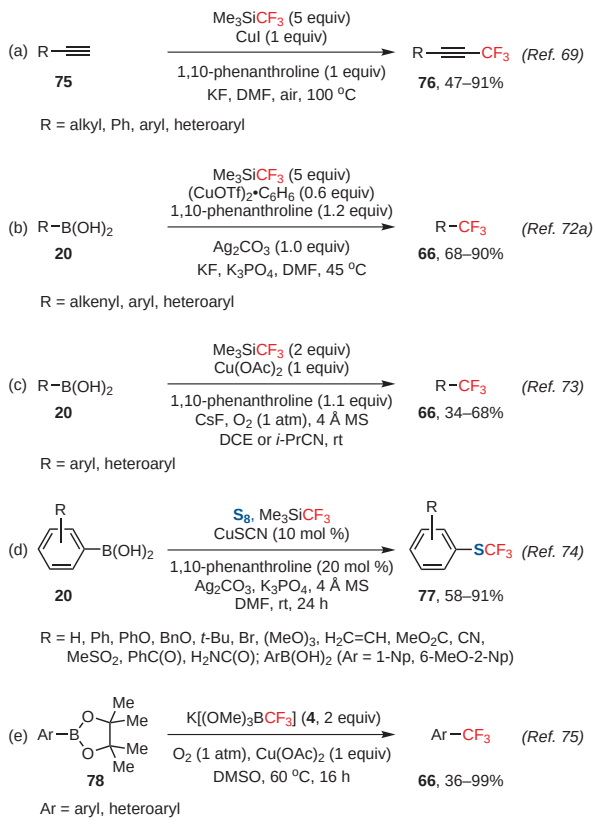
Qing and co-workers reported the copper-catalyzed oxidative trifluoromethyl*thiolation* of arylboronic acids **20** with a combination of Me_3SiCF_3 and elemental sulfur at room temperature. This reaction provides a concise and efficient method for the synthesis of aryl trifluoromethyl thioethers **77** under mild conditions (Scheme 15, Part (d)).[74]



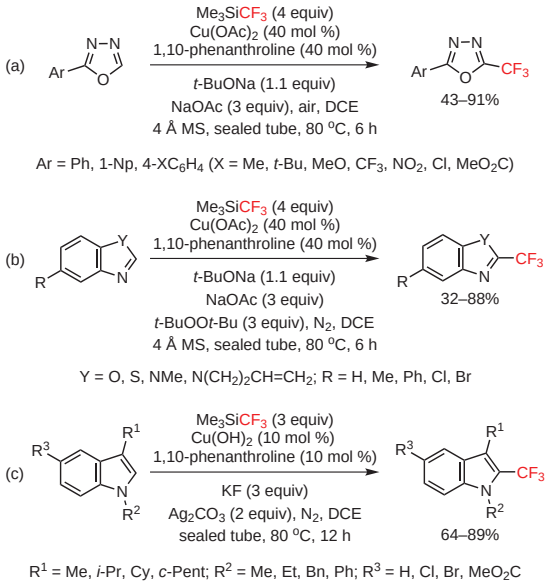
Scheme 13. Copper-Mediated Trifluoromethylation of Aromatic Iodides Employing a Variety of CF_3 Sources.



Scheme 14. Trifluoromethylation of Aryl Iodides with Preformed, Stable CF_3Cu Complexes. *(Ref. 66–68)*



Scheme 15. Oxidative Trifluoromethylation of Terminal Alkynes and Aryl- and Alkenylboronic Acids.



Scheme 16. Copper-Catalyzed, Direct, C–H Oxidative Trifluoromethylation of Heteroarenes Employing Me_3SiCF_3 and Oxidizing Reagents. *(Ref. 77)*

Gooßen and co-workers reported that arylboronic acid pinacol esters can be converted into the corresponding benzotrifluorides with an easy-to-use, one-component trifluoromethylating reagent, potassium (trifluoromethyl)trimethoxyborate (**4**), mediated by copper acetate under an oxygen atmosphere (Scheme 15, Part (e)).[75] Qi, Shen, and Lu reported a Cu-mediated ligandless aerobic fluoroalkylation of arylboronic acids using an R_fI–Cu combination.[76] Although no examples of trifluoromethylation were provided, this method can, at least in theory, be used for trifluoromethylation when ICF_3 is employed.

A copper–catalyzed, direct C–H oxidative trifluoromethylation of heteroarenes has been achieved using Me_3SiCF_3 and a variety of oxidants such as air or *t*-BuOO*t*-Bu (**Scheme 16**).[77] 1,3,4-Oxadiazoles, 1,3-azoles, and indoles were trifluoromethylated in yields ranging from moderate to excellent, and the reaction was compatible with a variety of substituents and functional groups.

The copper-catalyzed oxidative trifluoromethylation approach can also use suitable electrophilic trifluoromethylation reagents. Sodeoka and co-workers have developed a copper-catalyzed C2-selective trifluoromethylation of indoles using **5b**.[78] Substituted indoles were trifluoromethylated by **5b** in the presence of copper catalyst to give low-to-excellent yields of C2-trifluoromethylated indoles (**Scheme 17**, Part (a)). Indoles having electron-withdrawing groups, such as an ester or ketone at R^1 or R^2, resulted in low product yields using this protocol. The proposed reaction mechanism assumes that the copper catalyst increases the electrophilicity of the hypervalent iodine reagent.

Xiao and co-workers have reported a copper(0)-mediated, ligand-free trifluoromethylation of arylboronic acids using **6b** to give moderate-to-satisfactory yields of products (Scheme 17, Part (b)).[79] This methodology tolerates a variety of substituents and functional groups including halo, aldehydo, and cyano. The authors proposed that the reaction might involve a Cu(II) or Cu(III) oxidative pathway. On the other hand, Lei Liu's group discovered that copper(I) triflate (20 mol %), supported by 2 equiv of 2,4,6-trimethylpyridine, catalyzed the trifluoromethylation of aryl-, heteroaryl-, and vinylboronic acids with **6a** at room temperature.[80] Independently, Tianfei Liu and Qilong Shen reported the copper-catalyzed trifluoromethylation of a broad range of aryl- and alkenylboronic acids with Togni's reagent (**5a**), to give trifluoromethylated systems in good-to-excellent yields (Scheme 17, Part (c)).[81]

Sodeoka and co-workers reported the trifluoromethylation of allylsilanes through the use of CuI and **5b** under mild conditions. The reaction of allylsilanes unsubstituted at the 2 position furnished vinylsilanes, while C2-substituted allylsilanes afforded desilylated products (Scheme 17, Part (d)).[82] Hu's group reported that CuF_2•2 H_2O catalyzed the reaction between electrophilic fluoroalkylating agents such as **5b** and α,β-unsaturated carboxylic acids by activating both reactants, affording di- and trifluoromethylalkenes in high yields and excellent *E*/*Z* selectivity (Scheme 17, Part (e)).[83]

Furthermore, Shen and collaborators reported a sequential iridium-catalyzed C–H activation borylation and copper-catalyzed trifluoromethylation of arenes.[84] The reaction is conducted under mild reaction conditions and tolerates a variety of functional groups. The advantage of this tandem procedure was further demonstrated by the late-stage trifluoromethylation of a number of biologically active molecules.

3.1.3. Other Copper-Mediated Trifluoromethylations

The copper-catalyzed trifluoromethylation of unactivated terminal alkenes with **5b** was reported by Parsons and Buchwald to afford linear allylic trifluoromethylated products in good yields and with high *E*/*Z* selectivity (**Scheme 18**, Part (a)).[85] This mild trifluoromethylation

tolerates a wide variety of functional groups including alcohols, protected amines, esters, amides, and alkyl bromides. Epoxide-containing alkenes can be trifluoromethylated using a copper salt of lower Lewis acidity, namely, copper(I) thiophene-2-carboxylate (CuTC). Since the authors were not confident about the actual reaction pathway, they proposed two possibilities, one involving a free radical intermediate and the other an alkylcopper species. Independently, Wang and co-workers developed a similar preparation of allylic trifluoromethylated compounds under mild conditions. Their reaction employs an inexpensive copper chloride as catalyst and a hypervalent iodine(III) reagent as both the oxidant and the CF_3 source.[86]

Alternatively, Fu, Liu, and co-workers used Umemoto's reagent (**6a**) to effect a copper-catalyzed trifluoromethylation of terminal alkenes, leading to linear allylic trifluoromethylated products in low-to-good yields with exclusive *E* selectivity (Scheme 18, Part (b)).[87] As in Buchwald's method, this protocol tolerates many functional groups; such as sulfone, ester, amine, ketal, nitro, ether, amide, ketone, hydroxyl, and epoxide; making this approach attractive to process chemists. Both experimental and theoretical calculations have suggested that a copper(III) intermediate containing CF_3 probably adds onto the double bond, followed by formation of a Heck-like four-membered-ring transition state. The above two methodologies failed to trifluoromethylate internal and branched alkenes. Chu and Qing reported a Cu-catalyzed oxidative trifluoromethylation of terminal alkenes that proceeds under mild conditions, employs the readily available and less expensive Me_3SiCF_3 as the CF_3 source, and leads to efficient formation of C_{sp3}–CF_3 bonds (Scheme 18, Part (c)).[88]

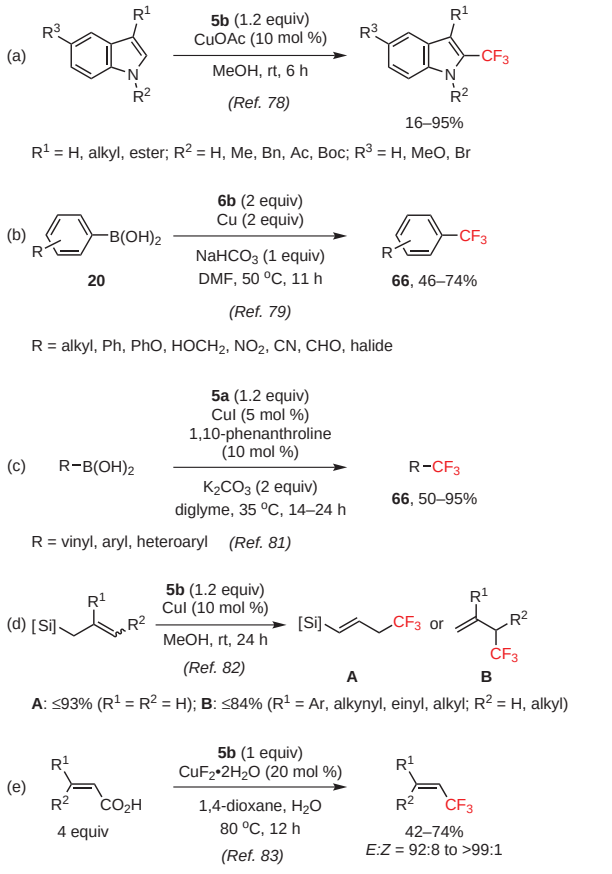
Szabó and co-workers have very recently reported a regio- and stereoselective Cu-catalyzed addition of a hypervalent iodine reagent to alkynes and alkenes. In the presence of CuI, the reaction is suitable for the trifluoromethylbenzoyloxylation and trifluoromethylhalogenation of alkenes and alkynes. Electron-donating substituents accelerate the process, and alkenes react faster than alkynes, emphasizing the electrophilic character of the addition reaction.[89]

3.2. Palladium-Mediated Trifluoromethylation

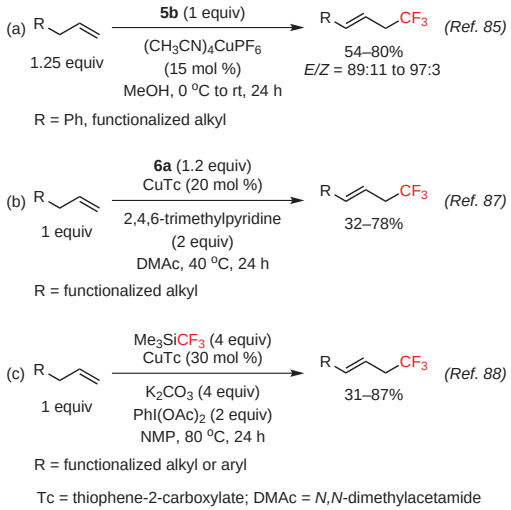
3.2.1. Pd-Catalyzed Trifluoromethylation of Aryl and Alkenyl Halides via a Pd(0)–Pd(II) Cycle

Buchwald's group has developed the first palladium-catalyzed trifluoromethylation of aryl halides using Et_3SiCF_3 as the trifluoromethylating agent.[90] Both electron-rich and electron-poor aromatic chlorides were trifluoromethylated to furnish the desired products in good-to-excellent yields (**Scheme 19**, Part (a)). The reaction is compatible with heteroaromatics; including indoles, carbazoles, quinolines, and benzofurans; and numerous functional groups such as ester, acetal, amide, nitrile, ether, and dialkylamino. Ortho-substituted aryl chlorides gave the corresponding trifluoromethylated products in low yields when the bulky ligand BrettPhos was employed, but RuPhos provided good yields of the products. Unfortunately, this protocol does not tolerate ketones, aldehydes, and unprotected OH and NH groups. A mechanistic study by the authors confirmed that the reaction proceeds through a classical Pd(0)–Pd(II) catalytic cycle.

The palladium-catalyzed trifluoromethylation of cyclohexenyl sulfonates has also been implemented by Cho and Buchwald (Scheme 19, Part (b)).[91] Various cyclohexenyl triflates and nonaflates underwent trifluoromethylation under mild reaction conditions using a catalyst system composed of $Pd(dba)_2$ or $[(allyl)PdCl]_2$ and the monodentate



Scheme 17. Copper-Catalyzed Trifluoromethylation Using Electrophilic Trifluoromethylation Reagents.



Scheme 18. Trifluoromethylation of Terminal Alkenes by Togni's, Umemoto's, or Ruppert–Prakash's Reagent.

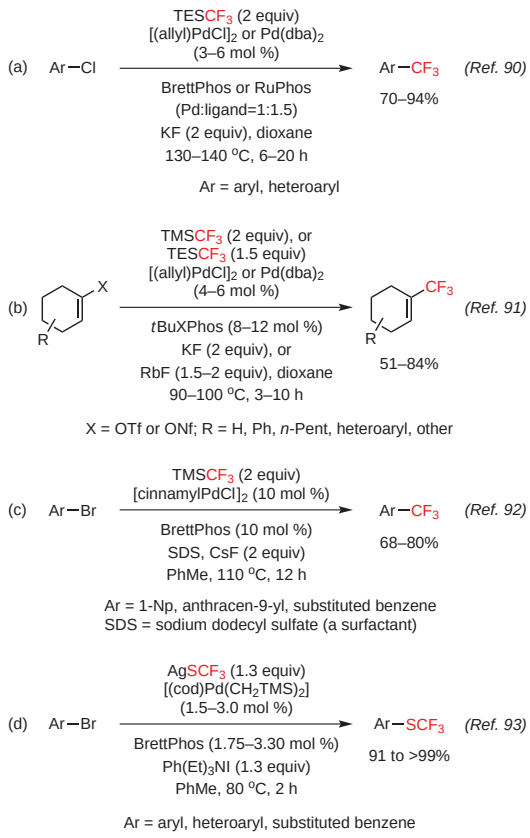
biaryl phosphine ligand *t*BuXPhos. The trifluoromethyl anion (CF_3^-) or its equivalent for the process was generated in situ from $TMSCF_3$ in combination with KF or from $TESCF_3$ with the addition of RbF. Samant and Kabalka developed a highly efficient copper-catalyzed trifluoromethylation of aryl bromides with Me_3SiCF_3 in micellar media (Scheme 19, Part (c)).[92] Owing to the use of the surfactant sodium dodecyl sulfate (SDS), this protocol tolerated ketones, aldehydes, and unprotected alcohols and amines, which were not compatible with Buchwald's process.[90] These authors reasoned that micelles prevent the decomposition of Me_3SiCF_3, and that side products can be avoided in this manner. They also proposed that the spatial orientation of the $ArLPdCF_3$ intermediate, resulting from a hydrophilic CF_3 and a hydrophobic ligand, had a positive effect on the reductive elimination step. Buchwald's team also developed an efficient synthesis of aryl trifluoromethyl sulfides in excellent yields. Aryl trifluoromethyl sulfides are an important class of compounds in both the pharmaceutical and agrochemical areas; their synthesis can be achieved under mild conditions by the Pd-catalyzed reaction of aryl bromides with a trifluoromethylthiolate nucleophile (Scheme 19, Part (d)).[93]

3.2.2. Pd-Catalyzed Trifluoromethylation via a Pd(II)–Pd(IV) Cycle

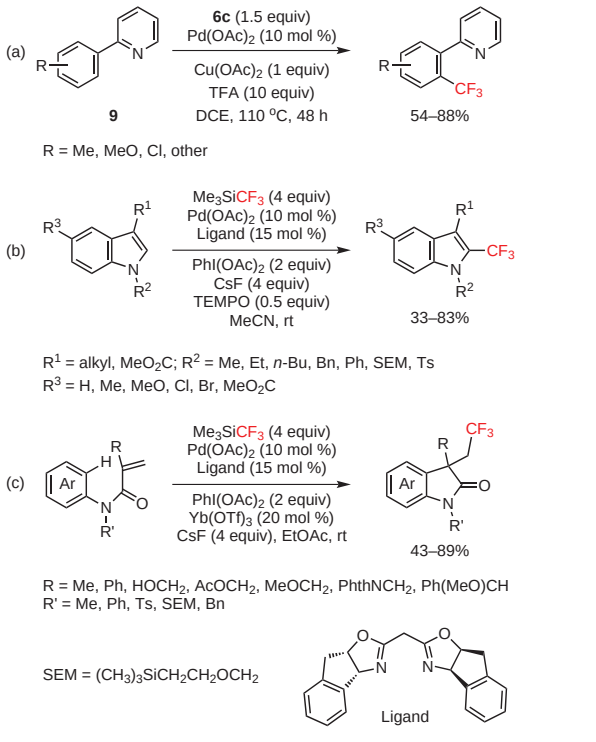
Yu and co-workers developed a palladium-catalyzed, nitrogen-directing-group-assisted, aromatic C–H trifluoromethylation using fluorinating agent **6c** and trifluoroacetic acid as promoter. Numerous 2-arylpyridines were successfully trifluoromethylated to give fluorinated products in good yields (**Scheme 20**, Part (a)).[94] In many cases, pyrimidine, imidazole, and thioazole can also be suitable directing groups in this reaction; however, the detailed roles of copper acetate and TFA are still unknown.

Guosheng Liu and co-workers have reported the oxidative trifluoromethylation of a wide variety of N,3-disubstituted indoles at C2 by Me_3SiCF_3 in the presence of a ligated palladium catalyst to give trifluoromethylated indoles in moderate-to-good yields (Scheme 20, Part (b)).[95] The authors found that: (a) TEMPO can increase the yield of the final product by inhibiting radical side reactions, (b) $PhI(OAc)_2$ is a suitable oxidant in this work, (c) indoles having a tosyl group nitrogen or a free amine group are not suitable substrates for this trifluoromethylation, and (d) when the C2 position of the indole is blocked, trifluoromethylation occurs at the C3 position (3 examples). A preliminary mechanistic study showed that a possible catalytic cycle proceeds through electrophilic palladation, oxidation by $PhI(OAc)_2$–Me_3SiCF_3 to form $ArPd^{IV}CF_3$, followed by reductive elimination to yield the final product. The same research group also reported a palladium-catalyzed intramolecular oxidative aryltrifluoromethylation reaction of activated alkenes (Scheme 20, Part (c)).[96] This reaction allows for the efficient synthesis of a variety of CF_3-containing oxindoles. An initial mechanistic study suggested that the reaction might involve a C_{sp3}–$Pd^{IV}CF_3$ intermediate, which undergoes reductive elimination to afford a C_{sp3}–CF_3 bond.

Sanford and her group uncovered direct evidence for aryl–CF_3 bond formation via reductive elimination from a palladium(IV) complex. $ArPd^{II}CF_3$ complexes were prepared, oxidized by the electrophilic



Scheme 19. Palladium-Catalyzed Trifluoromethylation of Aryl Halides and Vinyl Pseudohalides.



Scheme 20. Pd-Catalyzed, Directing-Group-Assisted C–H Trifluoromethylations. *(Ref. 94–96)*

fluorinating agent **2c**, and the Pd(IV) intermediate reductively eliminated to give trifluoromethylated arenes in low-to-excellent yields (**Scheme 21**, Part (a)).[97] A more detailed mechanistic study showed that reductive elimination from the Pd(IV) intermediate probably proceeds through dissociation of TfO^-, followed by aryl–CF_3 coupling (Scheme 21, Part (b)).[98] DFT calculations indicated that, in this context, CF_3 acts as an electrophile and the aryl ligand as a nucleophile. Sanford and co-workers also reported the preparation and isolation of a related Pd(IV) complex and its characterization by X-ray crystallography. This complex was reductively eliminated in different solvents to give the trifluoromethylated product in moderate yield (Scheme 21, Part (c)).[99]

3.3. Trifluoromethylation Mediated by Other Metals

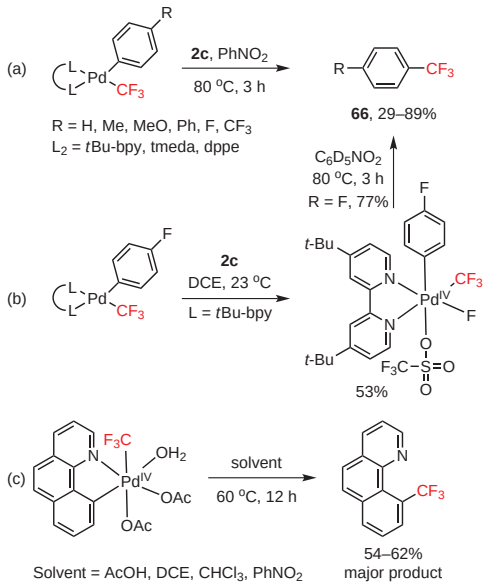
A silver-mediated cross-coupling of trifluoromethoxide with aryl-stannanes and arylboronic acids to give aryl trifluoromethyl ethers was advanced by Ritter and co-workers (**Scheme 22**, Parts (a) and (b)).[100] This is the first report of a transition-metal-mediated C_{aryl}–OCF_3 bond formation.

An iron(II)-catalyzed trifluoromethylation of potassium vinyl-trifluoroborates was developed by Buchwald and co-workers (Scheme 22, Part (c)).[101] 2-Arylvinyl substrates in particular provided flluorinated products in good yields and excellent *E/Z* ratios. The reaction is amenable to a bench-top setup, and proceeds under exceedingly mild reaction conditions. A preliminary mechanistic analysis suggested that the reaction involves a carbocationic intermediate that is promoted by Lewis acid catalysis, but a radical-type mechanism could not be ruled out. The silver-mediated trifluoromethylation of unreactive arenes with Me_3SiCF_3 was reported by Sanford's group to give trifluoromethylated arenes in moderate-to-high yields (Scheme 22, Part (d)).[102] Additionally, heteroaromatics, such as *N*-methylpyrrole, thiophene, and caffeine, were also trifluoromethylated to afford the corresponding products with moderate-to-excellent site selectivity. Initial mechanistic studies showed that a CF_3 radical intermediate is not a likely species in this reaction.

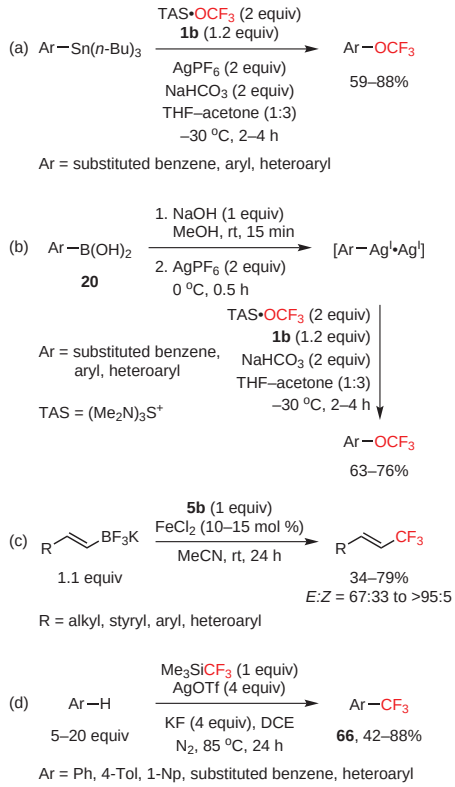
Hafner and Bräse reported the trifluoromethylation of substituted aromatic triazenes ortho to the triazene functionality in the presence of in situ generated $AgCF_3$; selectivity for ortho C–H substitution was high and yields were good.[103] Owing to the possibility of further elaboration of triazenes, a variety of CF_3-substituted building blocks are now accessible. Our group has disclosed an efficient method for preparing α-trifluoromethylated N-heterocycles with medicinally important ring sizes (e.g., 5–7) in a one-pot reaction involving two tandem nucleophilic additions starting from readily available secondary aminoalkynes (**eq 2**).[104]

3.4. Trifluoromethylation Involving Free Radicals

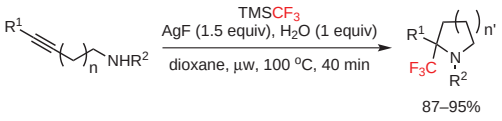
Yamakawa's group disclosed an iron(II)-catalyzed trifluoromethylation of aromatics by ICF_3 in the presence of H_2O_2 in DMSO. Electron-rich arenes and heteroaromatics including pyridines, pyrimidines, pyrroles, indoles, thiophenes, furans, pyrazoles, imidazoles, triazoles, and thiazoles were trifluoromethylated to furnish the desired products in low-to-high yields (**Scheme 23**, Part (a)).[105] The authors proposed that the hydroxyl radical that is formed from the reduction of H_2O_2 by Fe(II) is trapped by DMSO to form a methyl radical, which then reacts with ICF_3 to release a CF_3 radical that is in turn trapped by the arene. Mejía and Togni reported that methyltrioxorhenium acts as a catalyst (5–10 mol %) for the direct electrophilic trifluoromethylation of various aromatic and heteroaromatic compounds with the hypervalent iodine reagent **5b** (Scheme 23, Part (b)). Monitoring of this reaction by EPR demonstrated the involvement of radical species.[106]



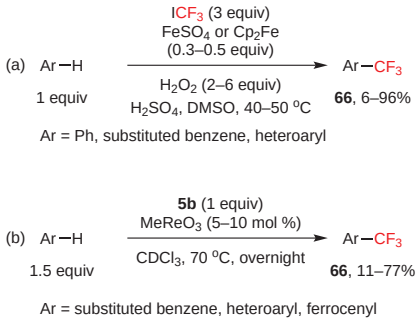
Scheme 21. Direct Evidence for Aryl–CF_3 Bond Formation via Reductive Elimination from a Palladium(IV) Complex. *(Ref. 97,99)*



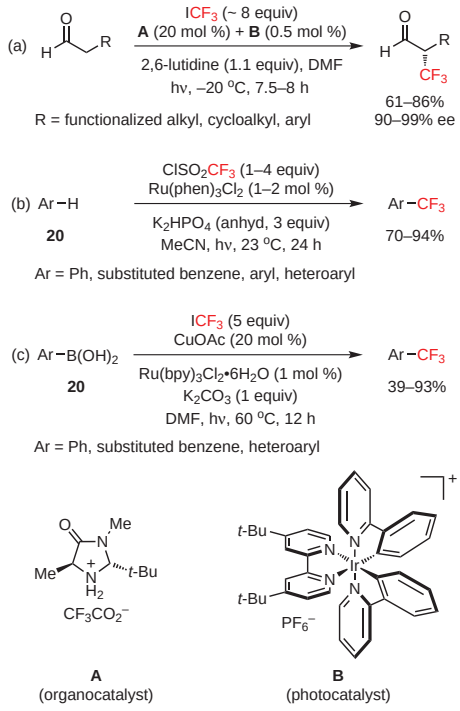
Scheme 22. Silver- and Iron-Mediated Trifluoromethoxylations and Trifluoromethylations. *(Ref. 100–102)*



eq 2 *(Ref. 104)*



Scheme 23. Trifluoromethylation of Aromatics Presumed to Proceed through a Free Radical Mechanism. *(Ref. 105,106)*



Scheme 24. Trifluoromethylation through Photocatalysis. *(Ref. 107,110,111)*

The first enantioselective, organocatalytic α-trifluoromethylation and α-perfluoroalkylation of aldehydes have been accomplished using a readily available iridium photocatalyst and a chiral imidazolidinone catalyst by MacMillan and co-workers (**Scheme 24**, Part (a)).[107] A range of α-trifluoromethyl and α-perfluoroalkyl aldehydes were obtained from commercially available perfluoroalkyl halides in high efficiency and enantioselectivity. The resulting α-trifluoromethyl aldehydes were subsequently shown to be versatile precursors for the construction of a variety of enantioenriched trifluoromethylated building blocks. MacMillan's group also reported an efficient method for the α-trifluoromethylation of carbonyl compounds and enolsilanes through this photoredox catalysis strategy.[108] Ando and co-workers similarly published a rhodium-catalyzed α-trifluoromethylation of ketones via silyl enol ethers.[109]

Nagib and MacMillan were able to generate CF_3 radicals from a light-induced reaction involving a ruthenium photocatalyst and trifluoromethanesulfonyl chloride ($ClSO_2CF_3$), a reagent that can be a useful CF_3 radical precursor (Scheme 24, Part (b)). They demonstrated that their approach can add CF_3 groups to already functionalized aryl groups in molecules such as ibuprofen.[110]

Very recently, Ye and Sanford reported a mild and general approach for the merged Cu-catalyzed–Ru-photocatalyzed trifluoromethylation and perfluoroalkylation of arylboronic acids (Scheme 24, Part (c)). This method also takes advantage of visible-light photoredox catalysis to generate CF_3• under mild conditions, and merges it with copper-catalyzed arylboronic acid functionalization.[111] Baran's team prepared CF_3 radicals using *tert*-butyl hydroperoxide as an oxidant to controllably decompose sodium trifluoromethylsulfinate, $NaSO_2CF_3$. This method can be employed for the trifluoromethylation of pyridines and other nitrogen-based heteroaromatics using CF_3 radicals;[112] but, since a transition metal is not involved in the reaction, it is not covered in this review.

4. Transition-Metal-Promoted Difluoromethylation

Difluoromethylation has received less attention than trifluoromethylation, but in theory, many of the methods employed for trifluoromethylation could also be applied to difluoromethylation.

4.1. Difluoromethylation through an RCF_2Cu Intermediate

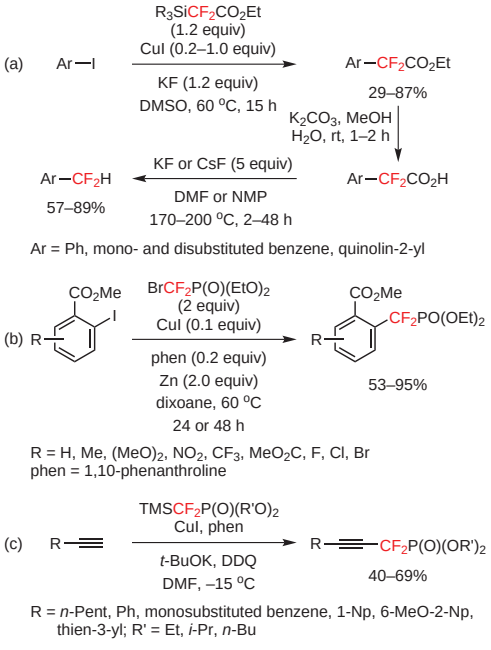
Amii and co-workers have prepared difluoromethylated arenes via copper-mediated cross-coupling followed by decarboxylation.[113] Both electron-rich and electron-deficient aromatic iodides were cross-coupled with α-silyldifluoroacetates to give low-to-high yields of α-aryldifluoroacetates, which were subjected to base hydrolysis and decarboxylation to produce the corresponding difluoromethylated arenes in moderate-to-high yields (**Scheme 25**, Part (a)). However, the intermediate α-aryldifluoroacetic acid that possess an electron-donating group failed to deliver the corresponding difluoromethyated arenes.

Zhang and co-workers reported a copper-catalyzed cross-coupling of 2-iodobenzoates with bromozinc difluorophosphonate (Scheme 25, Part (b)), generated from $BrCF_2P(O)(OEt)_2$ and zinc in dioxane. Notable features of this reaction are its high efficiency, excellent functional-group compatibility, and operational simplicity. This protocol provides a useful and facile access to aryldifluorophosphonates, of interest in life sciences.[114] Qing and co-workers[115] reported a copper-mediated oxidative cross-coupling reaction of terminal alkynes with readily available α-silyldifluoromethylphosphonates under mild conditions (Scheme 25, Part (c)). This method allows for the efficient synthesis of a series of synthetically useful α,α-difluoropropargylphosphonates with excellent functional-group compatibility.

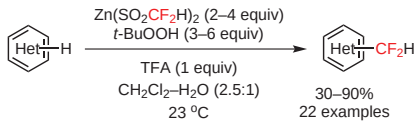
Fier and Hartwig have disclosed a copper-mediated difluoromethylation of electron-neutral or electron-rich, and sterically hindered, aryl and vinyl iodides using Me_3SiCF_2H to give the difluoromethylated products in 30–90% yields.[116] While aryl iodides possessing an electron-withdrawing moiety were not suitable for this methodology, many functional groups including tertiary amines, amides, ethers, esters, bromides, ketals, and protected alcohols were tolerated. More importantly, this methodology can difluoromethylate vinyl iodides to give allylic difluoromethylated alkenes with retention of stereochemistry.

4.2. Difluoromethylation via Radical Species

Baran and co-workers have developed the new difluoromethylation reagent $Zn(SO_2CF_2H)_2$ (DFMS) from $ClSO_2CF_2H$, and demonstrated its ability to difluoromethylate organic substrates in a mild, chemoselective, easy-to-carry-out, and scalable process. Heteroaromatics, such as pyridines, pyrroles, pyrimidines, quinolines, thiadiazoles, and pyridinones, were readily difluoromethylated by $Zn(SO_2CF_2H)_2$ in the presence of *t*-BuOOH as oxidant to give the difluoromethylated products in low-to-excellent yields (**eq 3**).[117] $Zn(SO_2CF_2H)_2$ can also difluoromethylate thiols and enones. The authors proposed that the reaction occurs via a radical process in which the CF_2H radical generated from $Zn(SO_2CF_2H)_2$ possesses a nucleophilic character.



Scheme 25. Copper-Mediated Difluoromethylation of Iodoarenes and Terminal Alkynes. *(Ref. 113–115)*



eq 3 *(Ref. 117)*

5. Summary and Outlook

Newly developed transition-metal-catalyzed or mediated fluorination, difluoromethylation, and trifluoromethylation reactions have contributed to making the synthesis of fluorinated compounds easier than what was possible just a few years ago. Despite the great strides, there are still important limitations to these new approaches. Compared to traditional methodologies, many of the new methods presented in this review use expensive metal and/or ligands, stoichiometric amounts of metal mediators and/or air/water-free conditions. These limitations make many of them impractical in large-scale synthesis or medicinal chemistry venues. We expect that forthcoming research will address these shortcomings. So far, most of the fluorination methods presented are Pd-based, whereas most of the trifluoromethylation and difluoromethylation approaches are Cu- or Ag-based. Recent advances using new metal catalysts such as Fe and Au lift our expectations of possible breakthroughs in the near future. Likewise, it is our hope that there will be further developments in new radical-based approaches.

6. Acknowledgements

We are grateful to the National Science Foundation for financial support (CHE-1111316).

7. References

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About the Authors

Zhuang Jin was born in 1978 in Inner Mongolia, China. He received his undergraduate (2000) and master's (2004) degrees from Inner Mongolia University, where he carried out medicinal chemistry research under the guidance of Professor Gereltu Borjihan. In 2007, Zhuang Jin enrolled in the doctoral program in chemistry at the University of Louisville, where he joined Professor Hammond's research group. His graduate research involved organofluorine chemistry, gold catalysis, green chemistry, and natural product synthesis. He received his Ph.D. degree in 2012, and was awarded The John Richard Binford Memorial Award. Currently, he is a postdoctoral fellow at The Scripps Research Institute in Jupiter, Florida.

Gerald B. Hammond was born in Lima, Perú. He received his undergraduate degree from the Pontificia Universidad Católica del Perú, and obtained his Ph.D. degree in 1985 from the University of Birmingham, England. Following an academic career at the University of Massachusetts Dartmouth, Professor Hammond moved to the University of Louisville in 2004, where he is currently Endowed Chair in Organic Chemistry. His main research interest focuses on the construction of organic molecules, especially fluorine-containing, and natural-product-based drug discovery studies on Peruvian plants.

Bo Xu was born in Hubei province, China. He received his undergraduate degree and master's degree from East China University of Science and Technology, Shanghai, China. He then worked as a research associate at the Shanghai Institute of Organic Chemistry from 2000 to 2003. Bo Xu obtained his Ph.D. degree from the University of Louisville in 2008 (advisor Prof. G. B. Hammond), receiving The Guy Stevenson Award for Excellence. Dr. Xu is currently a research assistant professor at the University of Louisville. His research interests include the development of novel and environmentally friendly synthetic methodologies, especially the synthesis of novel fluorinated building blocks for drugs and advanced materials.

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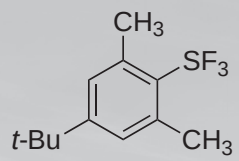

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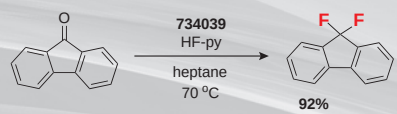

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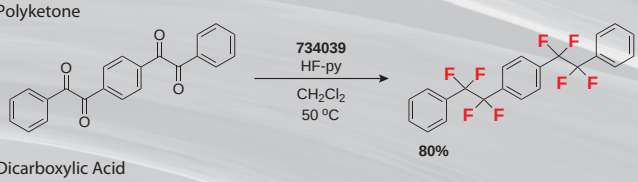

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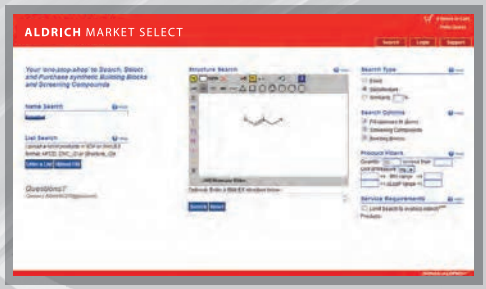

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