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Mini-Review

Palladium Catalysis: Dependence of the Efficiency of C−N Bond Formation on Carboxylate Ligand and Metal Carboxylate or Carboxylic Acid Additive

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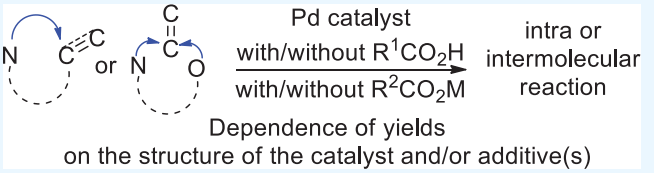
ABSTRACT: The Pd-catalyzed inter- and intramolecular reactions of nitrogen compounds are often carried out with palladium carboxylates, sometimes in the presence of carboxylic acids or alkali metal carboxylates. This Mini-Review highlights the dependence of the reaction efficiency on the nature of the ligand and the carboxylate additives. The proposed reaction mechanisms are presented with, as far as possible, personal comments.



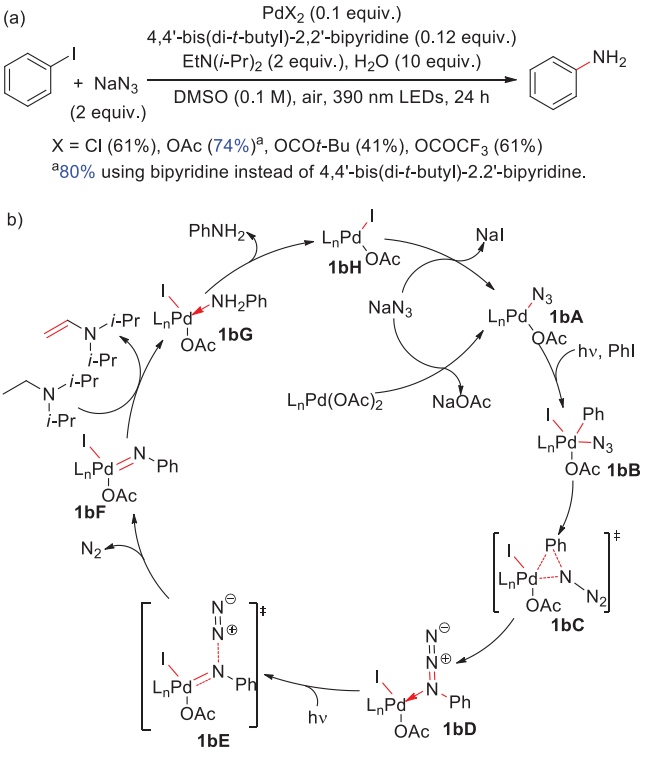
1. INTRODUCTION

The efficiency of the $Pd(OCOR)_2$-catalyzed C−C bond formation may greatly depend on the carboxylate ligand and metal carboxylate or carboxylic acid additive, as highlighted in a number of reports.[1] Such dependences of the C−N bond formation of reactions leading to anilines or oxidative amination, hydroamination, transamidation, and annelation[2] products are the subject of the present Mini-Review, which is not exhaustive and discards the processes with amino acid additives. We will tentatively clarify the role of the carboxylate unit and the effect of its characteristics on the reaction efficiency.

2. SUBSTITUTIVE AMINATIONS

Kancherla and co-workers[3] recently disclosed the efficient aerobic synthesis of aniline from the cross-coupling of phenyl iodide with sodium azide under photochemical conditions and catalysis with the $Pd(OAc_2)$/4,4′-bis(di-*t*-butyl)-2.2′-bipyridine association in the presence of *N*,*N*-diisopropylethylamine in moist DMSO (Scheme 1a). Switching from $Pd(OAc)_2$ to $PdCl_2$, $Pd(OCOCF_3)_2$, or $Pd(OCO$*t*$-Bu)_2$ was prejudicial to the efficiency. Decreases in the yield also arose in changing *N*,*N*-diisopropylethylamine to NEt_3, lowering the concentration, using other solvents, and performing the reaction under anhydrous conditions, while a slight increase occurred with bipyridine as the ligand. No reaction was observed in the absence of either the catalyst or the light. The mechanism proposed by the authors was mainly established from density functional theory studies and is summarized in Scheme 1b. Transmetalation of the Pd^{II} catalyst with sodium azide provides **1bA**. Irradiation at 380 nm of the latter promotes oxidative addition of PhI to provide Pd^{IV} intermediate **1bB**, which undergoes reductive elimination to give **1bD** via transition state **1bC**. Photoexcitation of **1bD** allows N_2 elimination via **1bE** to afford **1bF**. Subsequent reduction with *N*,*N*-diisopropylethyl-

Scheme 1. Cross-Coupling Amination via Photoexcitation of Two Distinct Pd^{II} Complexes



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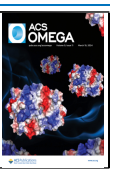
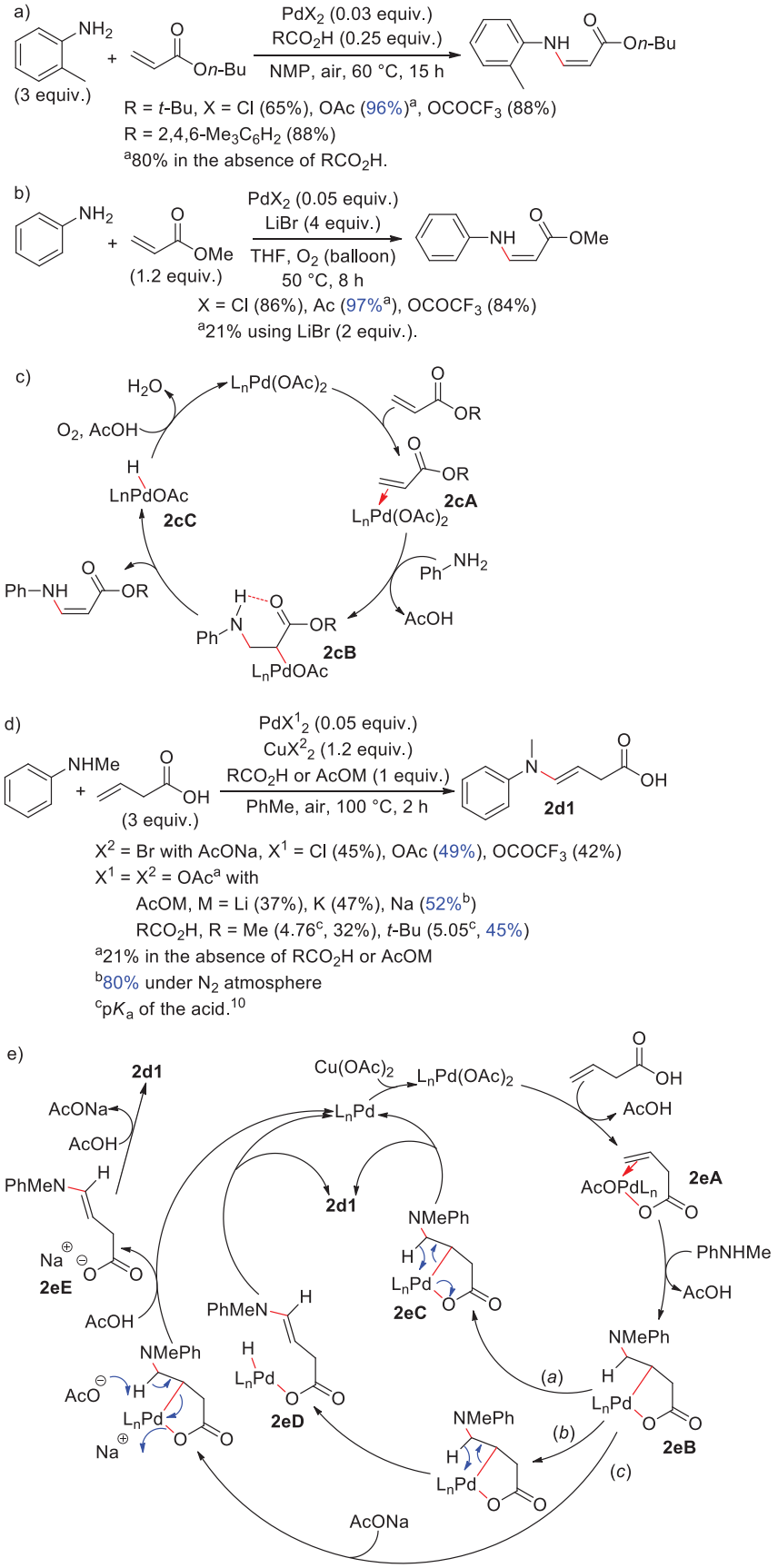


Scheme 2. Oxidative Amination of Methyl Acrylate or 3-Butenoic Acid



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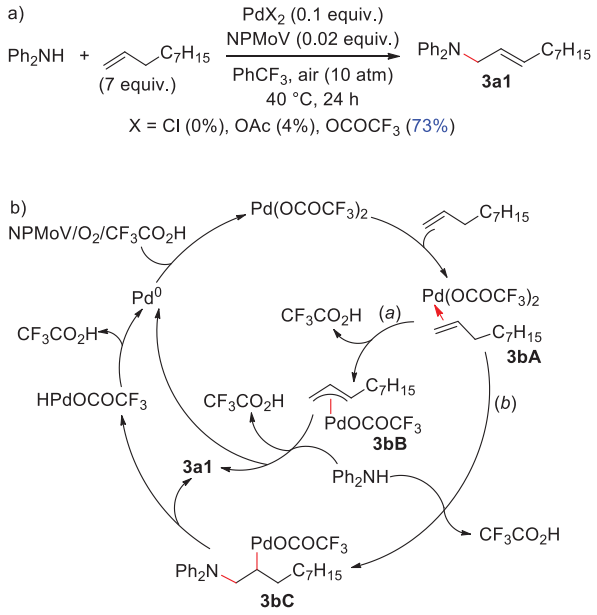
amine produces **1bG**, which releases aniline and **1bH**. Reaction of the latter with NaN_3 starts another catalytic cycle.

3. OXIDATIVE AMINATIONS

Thirty two years after the seminal report of Hegedus and Bozell[4] on the Pd-catalyzed oxidative addition of substituted anilines to

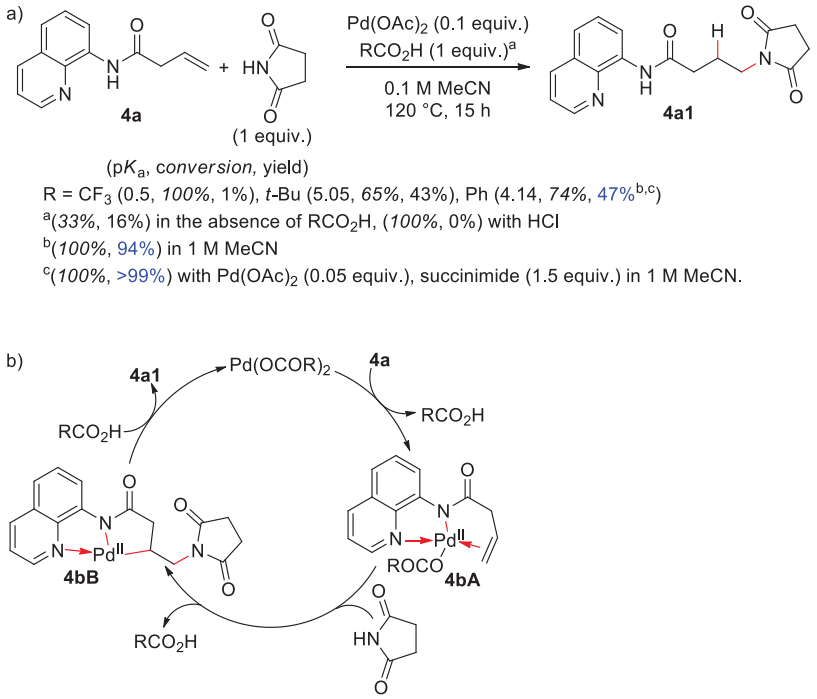
Scheme 3. Allylic Oxidative Amination of 1-Decene



electron-deficient olefins, different experimental conditions have been independently studied by the teams of Obora[5] and Jiang[6] for the reactions of *o*-toluidine with butyl acrylate and aniline with methyl acrylate, respectively. Carried out at 60 °C in *N*-methylpyrrolidone under an air atmosphere, the former reaction provided better yields under catalysis with $Pd(OAc)_2$ than with $PdCl_2$ or $Pd(OCOCF_3)_2$, and a carboxylic acid, preferably *t*-$BuCO_2H$, as additive (Scheme 2a). The second reaction, carried out at 50 °C in the presence of LiBr and molecular oxygen, showed a similar sensitivity of the yield to the nature of the Pd catalyst and an efficiency requiring a large amount of LiBr (Scheme 2b). According to Obora and co-workers, nucleophilic attack of the amine to the η^2-alkenylpalladium complex **2cA** provides η^1-alkylpalladium complex **2cB**, which undergoes β-H elimination to deliver the (*Z*)-enamine and palladium hydride species **2cC** (Scheme 2c). Regeneration of the active catalyst from **2cC** is assumed with the oxygen/carboxylic acid association.[7] The excellent stereoselectivity was attributed to the intramolecular hydrogen bond of **2cB**.[5,6,8] The positive role of the carboxylic acid additive in the reaction of Scheme 2a could be due to its participation in the reoxidation step leading to $Pd(OCO_2R)_2$ (R = *t*-Bu or 2,4,6-$Me_3C_6H_2$), which would be more active than the starting $Pd(OAc)_2$. For the reaction of Scheme 2b, Jiang's team proposed that "the role of excess bromide anion in the reaction system is to prevent Pd^{II} catalyst from deactivation by strong coordination to aromatic primary amines, thus facilitating the catalytic cycle".[6]

Recently, Huang, Zhao, and co-workers[9] disclosed the synthesis of amino acid **2d1** from the Pd^{II}-catalyzed addition of *N*-methylaniline to 3-butenoic acid (Scheme 2d). Preliminary experiments were performed in toluene with Cu^{II} salts and additives, alkali acetates, or carboxylic acids under air. With $CuBr_2$ and AcONa, $Pd(OAc)_2$ was slightly superior to $PdCl_2$ and $Pd(OCOCF_3)_2$. With $Cu(OAc)_2$ and alkali acetates, the efficiency depended on the nature of the alkali cation, with AcONa being superior to AcOK and AcOLi. With $Cu(OAc)_2$ and carboxylic acids, the yield was better with *t*-$BuCO_2H$ than with the more acid AcOH.[10] Lower yields were obtained under additive-free conditions. Finally, the best result arose with $Pd(OAc)_2$, $Cu(OAc)_2$ and AcONa under N_2. The authors assumed that the coordination of 3-butenoic acid generates

Scheme 4. Hydroamination of Unactivated Alkenes



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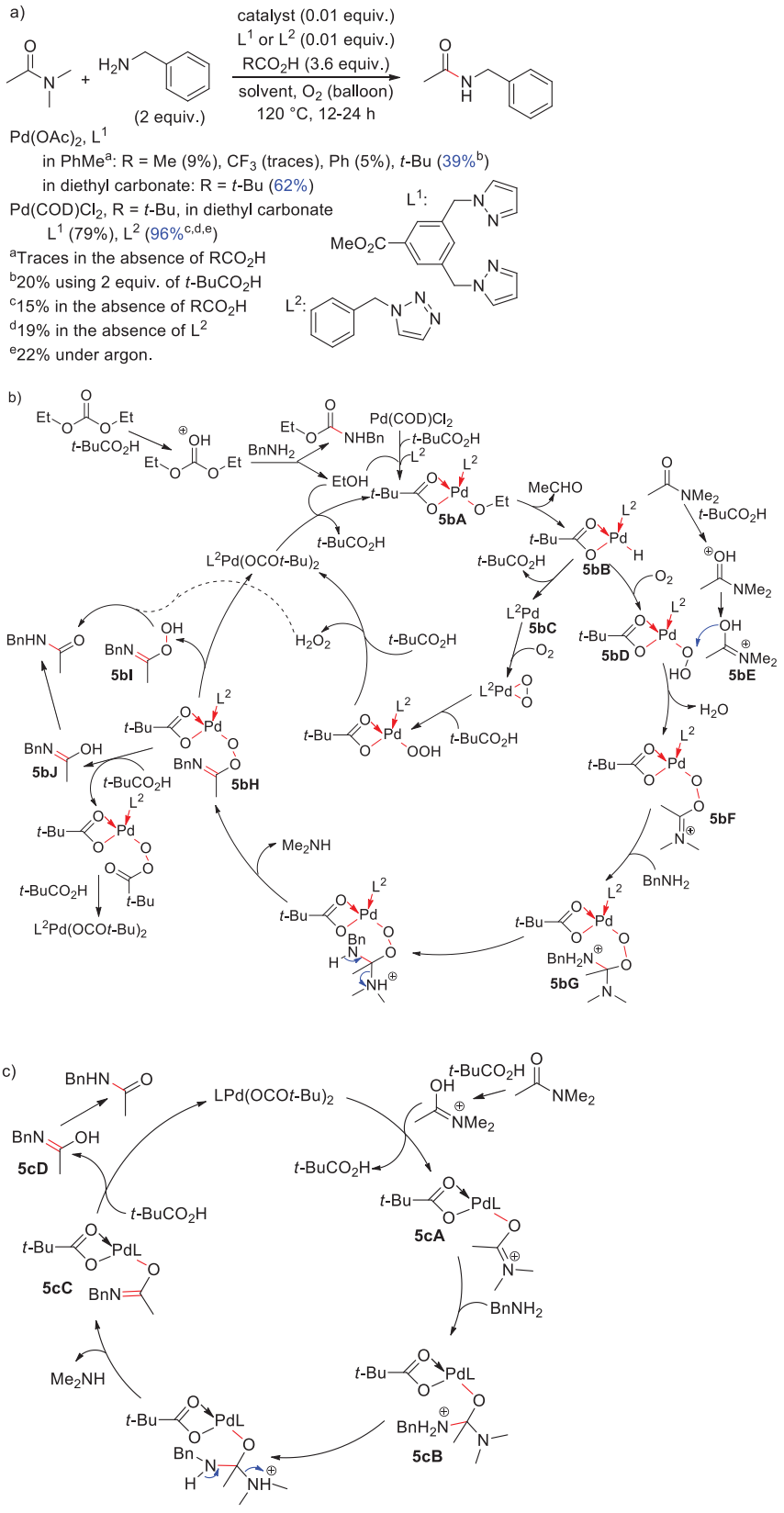
Scheme 5. Pd^{II}-Catalyzed Transamidation



palladacycle **2eA** with the assistance of AcONa (Scheme 2e). Subsequent addition of methylaniline provides palladacycle **2eB**, which, according to the authors, is "followed by β-H elimination and protonation to give product" **2d1** via, without supplementary detail, the rearrangement shown in **2eC** (path a). Instead of this short explanation, we propose that **2eB** evolves via either the usual β-H elimination, which affords hydridopalladium complex **2eD** (path b), or participation of AcONa in H

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abstraction, leading to carboxylate **2eE** (path c). Thus, **2d1** would be obtained from either **2eD** via reductive elimination or **2eE** via acid-mediated hydrolysis. The preferred pathway will depend on the additive: path b uses *t*-$BuCO_2H$, and path c uses AcONa. Regeneration of the catalyst occurs with $Cu(OAc)_2$.

Ishii's team[11] relayed a very different process: the Pd^{II}-catalyzed oxidative allylic amination of 1-decene with diphenylamine (Scheme 3a). In benzotrifluoride with catalytic amounts of $(NH_4)_5H_4PMo_6V_6O_{40}\cdot 23H_2O$ (NPMoV) and air pressure, (*E*)-*N*-(dec-2-en-1-yl)-*N*-phenylaniline **3a1** was obtained in 73% yield under $Pd(OCOCF_3)_2$ catalysis, while $PdCl_2$ and $Pd(OAc)_2$ afforded no more than 4% yield. Two reaction pathways were proposed by the authors (Scheme 3b) who, however, prioritized path a over path b. Coordination of 1-decene to the catalyst afford η^2-alkenylpalladium complex **3bA**, which either leads to η^3-allylpalladium intermediate **3bB** (path a) or undergoes an aza-Wacker process to give alkylpalladium species **3bC** (path b). The allylic amination product **3a1** would be obtained from either **3bB** via nucleophilic addition of diphenylamine or **3bC** via β-H elimination. Both pathways lead to Pd^0, which is oxidized with the NPMoV/O_2/CF_3CO_2H association.

The considerable positive effect of the $Pd(OCOCF_3)_2$ catalyst on the reaction efficiency, which could be in part due to the easier formation of η^3-allylpalladium complexes from olefins and this Pd salt as demonstrated by Trost and Metzner,[12] urges us to also favor path a. Moreover, **3bC** (path b) could be sensitive to the acid, which would result in protodepalladation to give *N*-decyl-*N*-phenylaniline.[13]

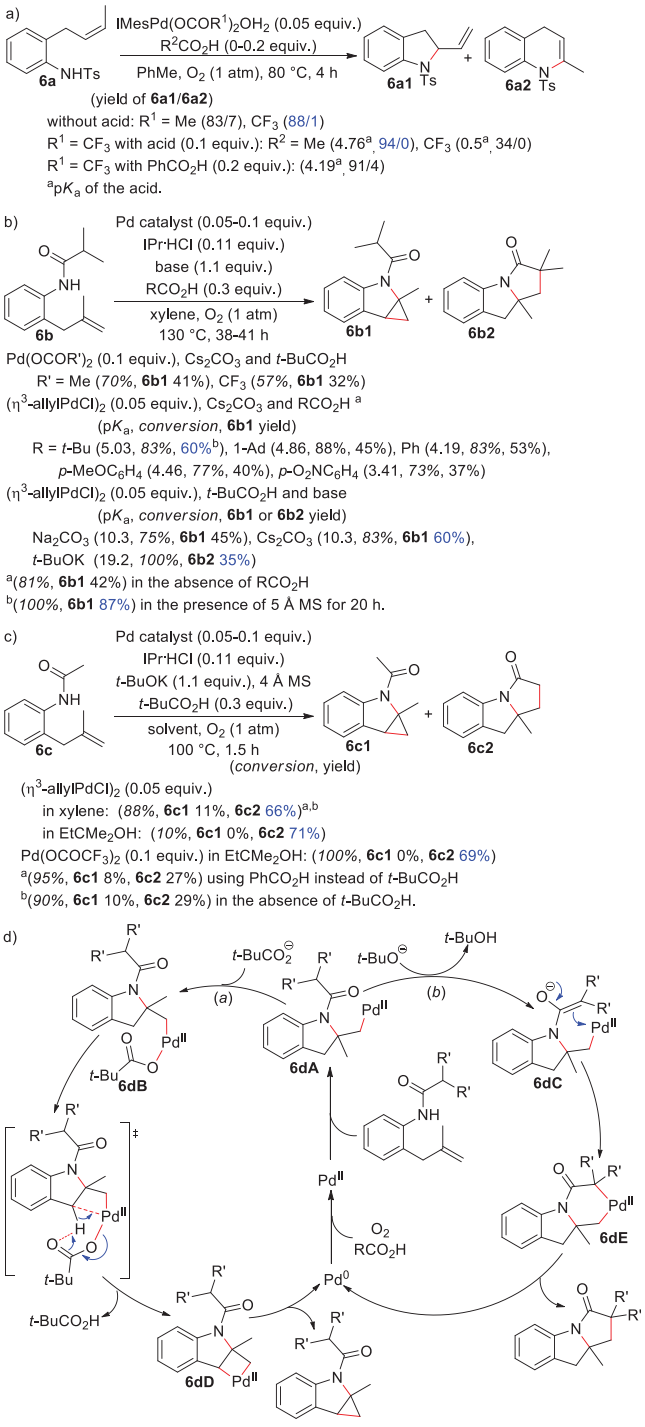
4. HYDROAMINATIONS

Treatment of an equimolecular mixture of *N*-(quinolin-8-yl)but-3-enamide **4a** and succinimide in 0.1 M MeCN at 120 °C with $Pd(OAc)_2$ catalyst provides a low yield of the hydroamination product **4a1** (Scheme 4a).[14] Increased efficiency occurred in the presence of a stoichiometric amount of *t*-$BuCO_2H$ or $PhCO_2H$, while the addition of CF_3CO_2H or HCl led to full consumption of **4a** with a 1% or 0% yield **4a1**, respectively. Supplementary improvement arose from concentrating the reaction solution and increasing the amount of succinimide, even with a reduced amount of the starting catalyst. Coordination of **4a** to **4bA** was proposed by Engle and co-workers. Subsequent nucleophilic addition of succinimide provides palladacycle **4bB**, which undergoes protodepalladation to form **4a1** with regeneration of the catalyst (Scheme 4b). We suspect that the absence of β-H elimination from **4bB** could be due to the large amount of RCO_2H, which helps the protodepalladation step and the regeneration of the catalyst. Given the strong improvement in the presence of RCO_2H (*t*-Bu or Ph), we assume that the active catalytic species is the corresponding $Pd(OCOR)_2$ rather than $Pd(OAc)_2$.

5. TRANSAMIDATIONS

SanMartina's team[15] recently disclosed the Pd^{II}-catalyzed transamidation of dimethylacetamide with benzylamine in the presence of carboxylic acids and azole ligands, notably L^1 and L^2 (Scheme 5a). In toluene with $Pd(OAc)_2/L^1$ and 3.6 equiv of AcOH, CF_3CO_2H, or $PhCO_2H$ under oxygen atmosphere, less than 9% of *N*-benzylacetamide was isolated while 39% yield was obtained with *t*-$BuCO_2H$. Lowering the amount of *t*-$BuCO_2H$ was detrimental to the efficiency, with only traces of *N*-benzylacetamide being produced using this procedure under

Scheme 6. Indole Derivatives from Intramolecular Reactions of Anilines *ortho*-Substituted with an Alkenyl Tether



RCO_2H-free conditions. Switching to diethyl carbonate as the solvent increased the yield from 39% to 62%. Increased efficiency arose using the $Pd(COD)Cl_2$ catalyst, especially with ligand L^2. The low yield obtained under an argon atmosphere led the authors to propose two complementary pathways, namely aerobic and anaerobic. Performing an array of experiments with the $Pd(COD)Cl_2/L^2$ system in diethyl carbonate, they notably observed the in situ formation of ethyl benzylcarbamate and its progressive decay.

A detailed mechanism of the aerobic pathway, summarized in Scheme 5b, with $Pd(OCOt\text{-}Bu)_2/L^2$ and participation of diethyl

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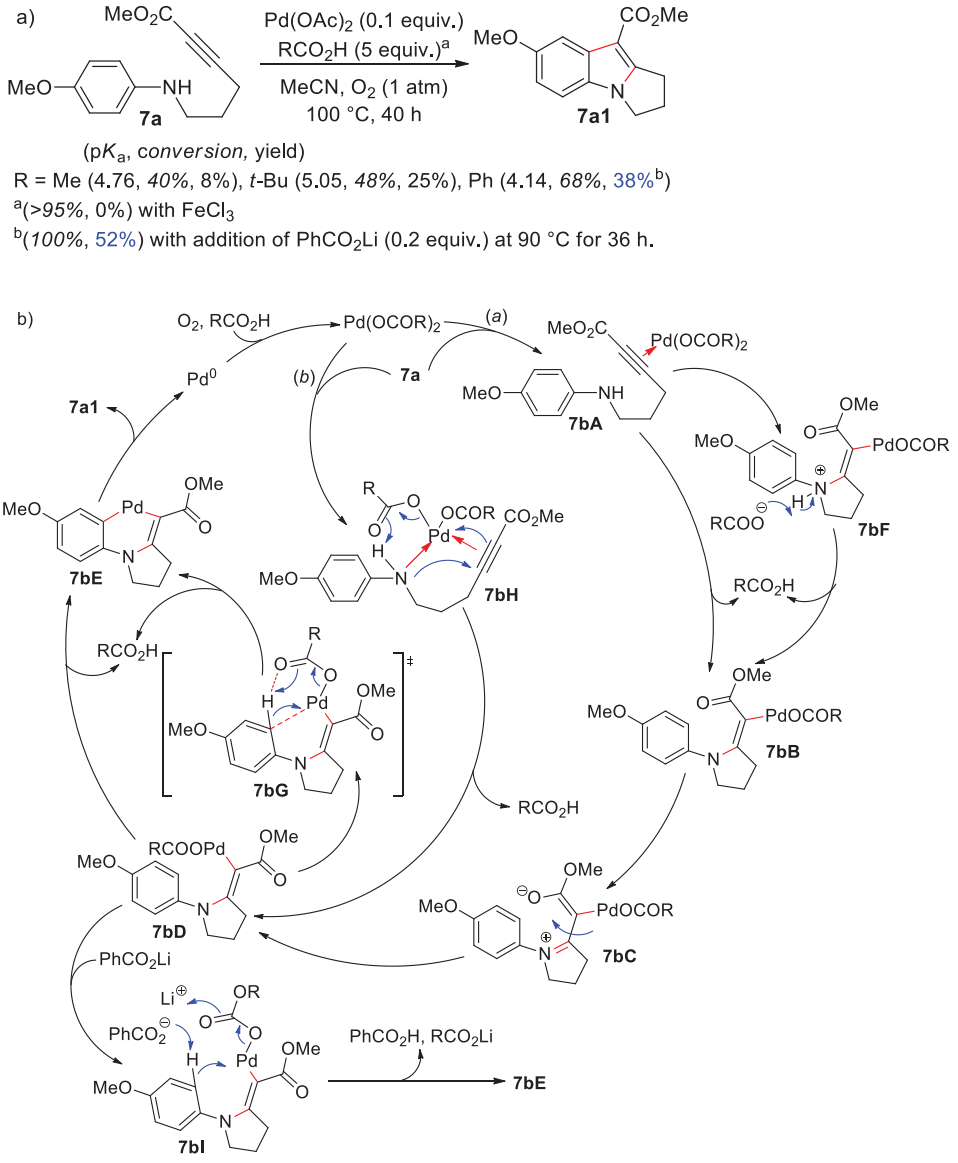
Scheme 7. Indole Derivatives from Intramolecular Reactions of *N*-Alkynyl Anilines



carbonate was thus assumed by the authors. The production of ethyl benzylcarbamate from the *t*-BuCO_2H-mediated reaction of diethyl carbonate with benzylamine releases EtOH. Pd-catalyzed oxidation of the latter via intermediate **5bA** leads to acetaldehyde and hydridopalladium complex **5bB**. The latter suffers either reductive elimination giving Pd^0 complex **5bC** or insertion of oxygen giving palladium hydroperoxide **5bD**. Nucleophilic attack of the hydroxyimine tautomer **5bE** of dimethylacetamide to **5bD** affords **5bF**. Next, nucleophilic addition of benzylamine at the electrophilic azomethine carbon leads to **5bG**, which suffers prototropy and then release of dimethylamine to provide peroxy complex **5bH**. Protonolysis of either the O−Pd or the O−O bond of **5bH** produces peroxidic acid **5bI** or **5bJ**, respectively, the latter rapidly tautomerizing to *N*-benzylacetamide. The Radziszewski-type reaction[16] of **5bI** with H_2O_2, which is produced through the regeneration of the active Pd^{II} species from **5bC** and O_2,[7] is another plausible pathway leading to *N*-benzylacetamide.

Scheme 5c summarizes the catalytic cycle proposed for the aerobic pathway. Exchange of a *tert*-butyl carboxylate of LPd(OCO*t*-Bu)$_2$ for the hydroxyiminic tautomer of dimethylacetamide provides **5cA**, which undergoes benzylamine addition leading to **5cB**. Successive prototropy and release of dimethylamine give **5cC**. Then, protodepalladation regenerates the catalyst with the formation of **5cD**, which tautomerizes to *N*-benzylacetamide.

6. ANNELATIONS

6.1. *N*-Heterocycles. Processes related to the present Mini-Review on the synthesis of *N*-heterocycles via initial formation of the C−C bond have been previously documented.[1c]

6.1.1. Intramolecular Reactions. Stahl's team[17] disclosed in 2006 the use of previously reported *N*-heterocyclic carbene-coordinated Pd^{II} complexes IMesPd(OCOR^1)$_2$OH$_2$ (R^1 = Me or CF_3)[18] to catalyze the annellation of the *cis*-crotyl tosylanilide **6a** under an oxygen atmosphere, leading to a mixture of five- and six-membered *N*-heterocycles **6a1** and **6a2**, with the 5-*exo* cyclization product being the main product (Scheme 6a). The **6a1**/**6a2** ratio depended on the ligand, with the more acidic trifluoroacetate leading to the higher selectivity. With this catalyst, the addition of a catalytic amount of AcOH resulted in the selective formation of **6a1** in high yield. PhCO_2H, which is

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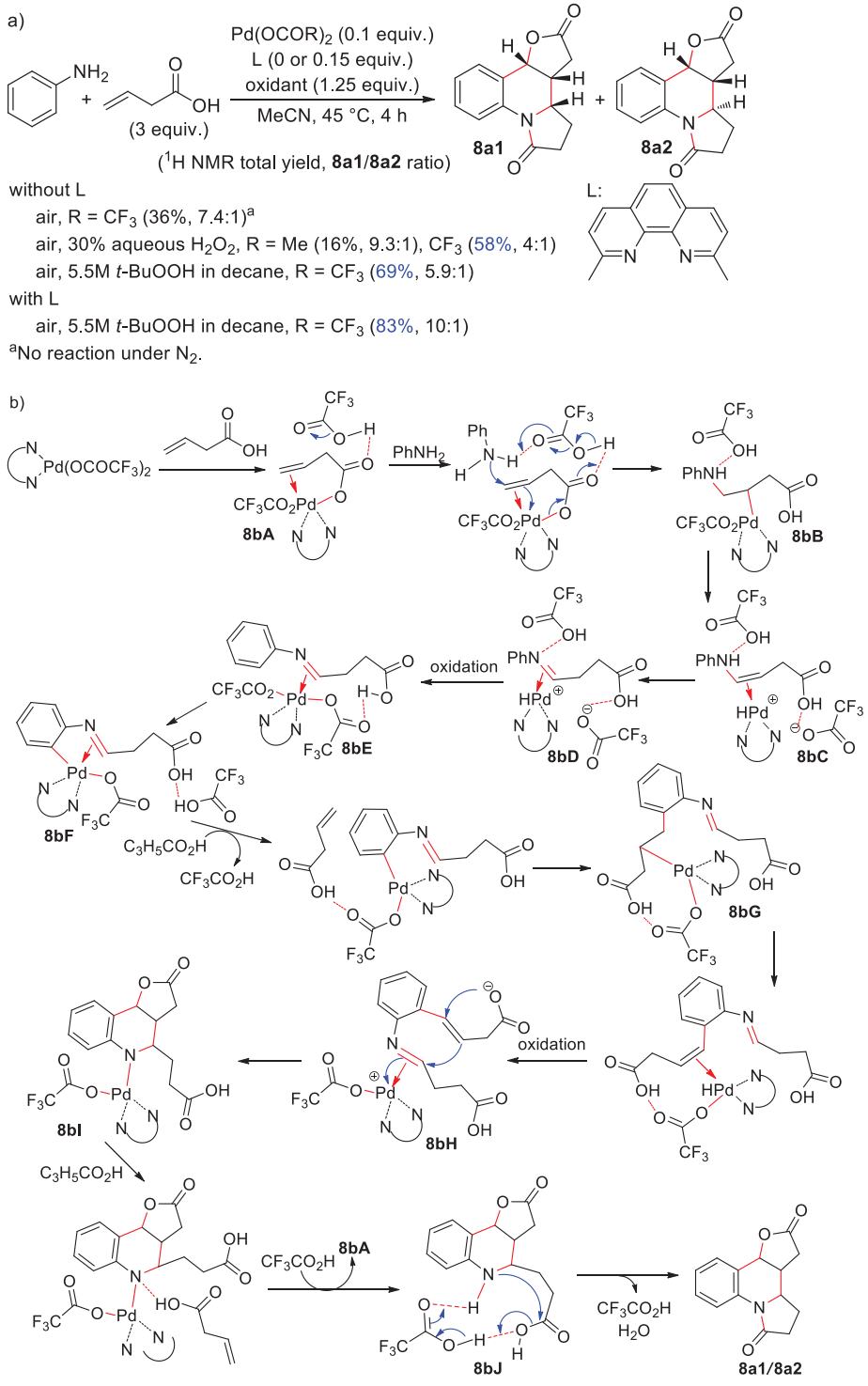
Scheme 8. Fused Benzo-aza-oxa-[5-6-5]tetracycles from the Domino Reaction of Aniline with 3-Butenoic Acid



somewhat more acidic than AcOH, gave slightly inferior results, while the stronger acid CF_3CO_2H was strongly detrimental to the process.

The aerobic $(\eta^3$-allylPdCl$)_2$/IPr·HCl-catalyzed intramolecular reaction of *N*-(2-(2-methylallyl)phenyl)isobutyramide **6b**, which mainly differs from **6a** by the substitution of the alkenyl tether, was subsequently performed by Yang and co-workers[19] in the presence of both a base (1.1 equiv) and a carboxylic acid (0.3 equiv) (Scheme 6b). The three- or five-membered-ring fused indoline **6b1** or **6b2** was isolated as the main compound depending on the used base, Cs_2CO_3 or *t*-BuOK, respectively. Testing a set of carboxylic acids led to the best results with *t*-$BuCO_2H$, and lower conversion and yield were observed in its absence. Exchange of $(\eta^3$-allylPdCl$)_2$ for $Pd(OAc)_2$ or $Pd(OCOCF_3)_2$ was detrimental to the process.

A different substitution of the amide unit may increase the selectivity toward the formation of the five-membered ring, as observed with the reaction of *N*-(2-(2-methylallyl)phenyl)-acetamide **6c**, which afforded **6c2** in 69−71% yields without production of **6c1** using the $(\eta^3$-allylPdCl$)_2$/IPr·HCl or

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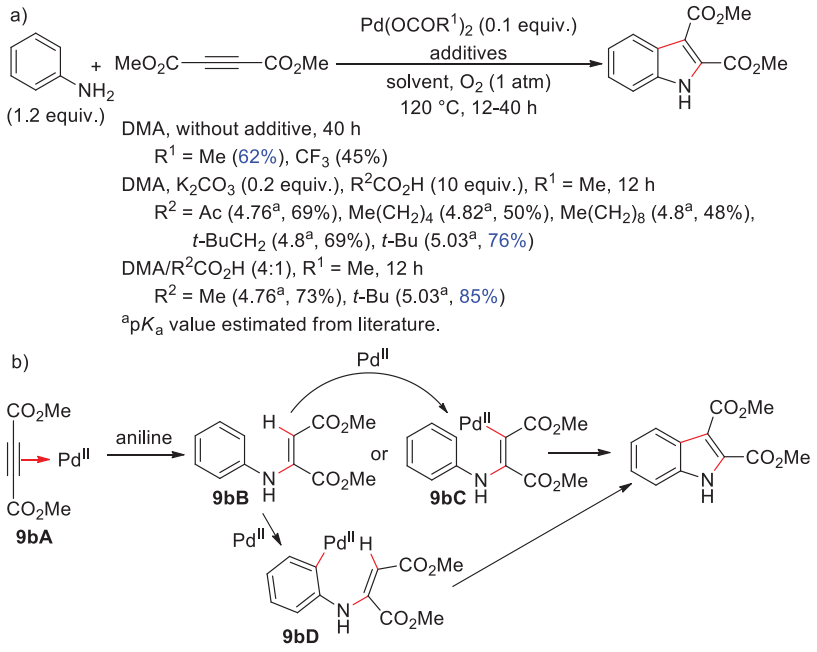
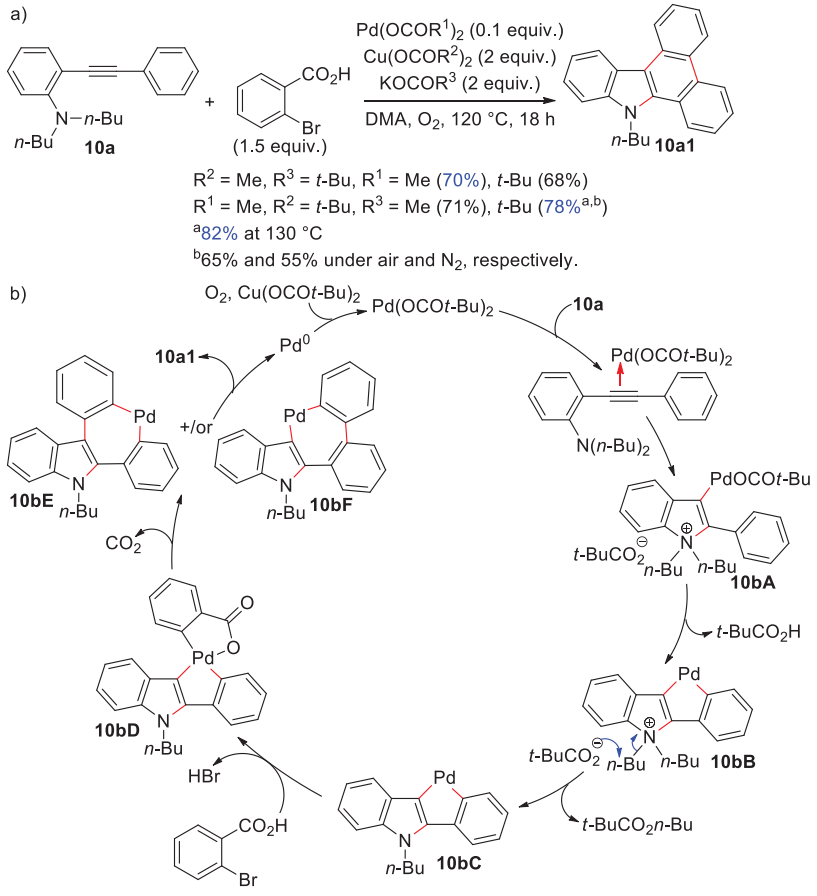
Scheme 9. Aniline/Alkyne Coupling



Scheme 10. Domino Aminopalladation/C−H Activation/Dealkylation/Decarboxylative Cyclization Reaction



$Pd(OCOCF_3)_2$/IPr·HCl catalyst with *t*-BuOK and *t*-$BuCO_2H$ in *tert*-amyl alcohol (Scheme 6c).

According to Yang's team, the alkylpalladium^{II} **6dA**, formed from aminopalladation of the C═C bond of the anilide, reacts with either pivalate formed from *t*-$BuCO_2H$ and Cs_2CO_3 (path a) or *tert*-butoxide (path b) to provide palladium *tert*-butyl carboxylate **6dB** or enolate **6dC**, respectively (Scheme 6d). From **6dB**, a benzylic C(sp^2)−H abstraction, likely via the concerted metalation-deprotonation mechanism (CMD),[20] affords **6dD**, which releases the three-membered-ring fused

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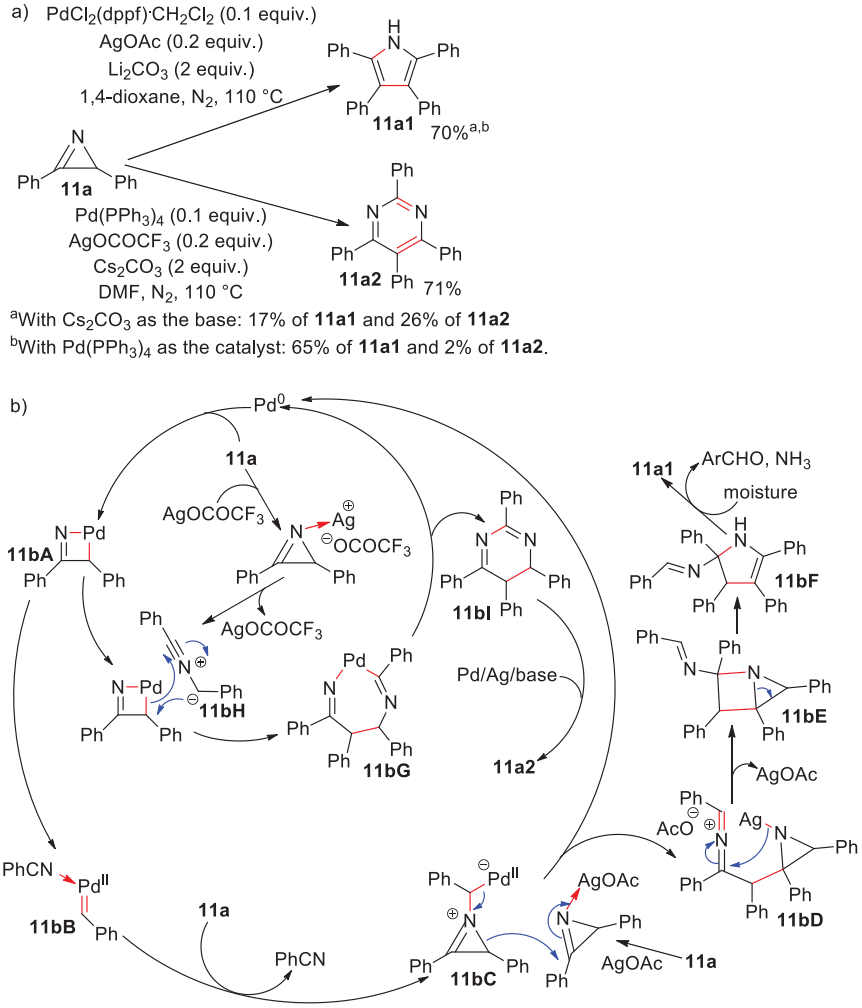
Scheme 11. Silver Carboxylate-Mediated Chemodivergence



indoline via reductive elimination. The formation of the five-membered-ring fused indoline arises from intramolecular addition of enolate amide **6dC** leading to six-membered palladacycle **6dE**, which suffers from reductive elimination. The preferred reactive pathway, path a versus path b, seems dependent on (i) the relative basicity of *t*-BuOCOCs ($pK_a \approx 10$) and *t*-BuOK (pK_a = 19.2)[10] and (ii) the substitution of the amide α-C−H, with the primary amide α-C−H of **6c** making the formation of enolate **6dC** easier and, consequently, favoring path *b*.

In 2013, Jiao's team[21] synthesized the tricyclic compound **7a1** from the aerobic Pd^{II}-catalyzed domino reaction of *N*-alkynyl aniline **7a** in the presence of carboxylic acids (Scheme 7a). $PhCO_2H$ gave the best result, especially in the presence of slight amounts of $PhCO_2Li$, which allowed the reduction of both the reaction temperature and the reaction time. Changing the carboxylic acid to a Lewis acid provoked the consumption of **7a** without producing **7a1**. Coordination of the triple bond of **7a** to $Pd(OAc)_2$ leading to **7bA** and then to *trans*-aminopalladation product **7bB** and its *cis*-form **7bD** via tautomer **7bC** was proposed by the authors (Scheme 7b, R = Me, path a). Subsequent electrophilic aromatic palladation gives the five-membered palladacycle **7bE**, which undergoes reductive elimination to produce **7a1** and Pd^0; recycling of the catalyst occurred with oxygen and AcOH.[7] The formation of **7bE** could arise via transition state **7bG**, which is a CMD pathway.[19]

Given the presence of a large amount of $PhCO_2H$, we propose that the active catalyst is rather the corresponding palladium carboxylate (Scheme 7b, where R = Ph). The *trans*-amino-palladation process of **7bA** is in agreement with other intramolecular aminopalladation reactions of alkynes, which were, however, carried out under acid-free conditions.[22] This reaction could involve the ammonium intermediate **7bF**, whose evolution toward **7bB** would be favored by the $PhCO_2Li$ additive. We considered an alternative pathway (path b) to the one requiring **7bC**: coordination of both nitrogen and the triple bond of **7a1** to the catalyst[23] could afford **7bH**, which would directly provide the required *cis*-aminopalladation intermediate. The lack of annelation when the ester group of **7a** was changed for a phenyl group, however, disfavors path b.

The efficiency of the annelation depends on the structure of the carboxylic acid, but there is no obvious correlation between the efficiency and their acidity or steric hindrance. In contrast, the improvement of the reactivity with $PhCO_2Li$ as an additive leads us to suspect the electrophilic aromatic substitution (S_EAr) mechanism[19] depicted in **7bI** for the formation of **7bE**.

6.1.2. Intermolecular Reactions. Fused tetracycles **8a1** and **8a2** have been synthesized by the teams of Ke and Jiang[24] from the Pd-catalyzed domino reaction of aniline with 3-butenoic acid, which involves the formation of two N−C bonds, two C−C bonds, and one C−O bond (Scheme 8a). Under an air atmosphere at 45 °C in MeCN, catalysis with $Pd(OCOCF_3)_2$

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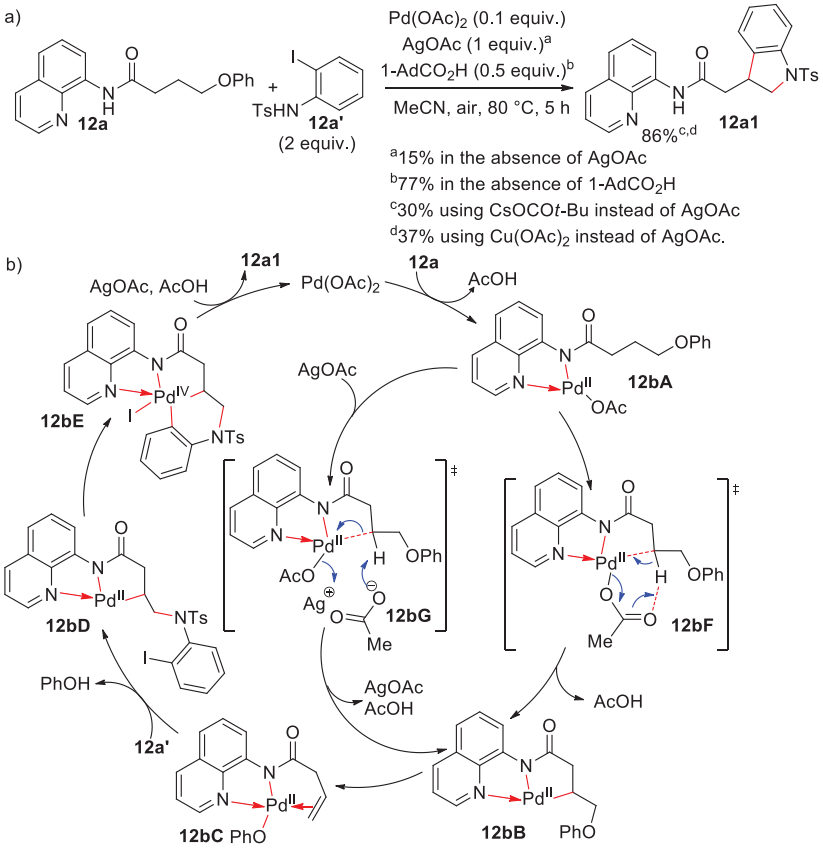
Scheme 12. Annelation via C(sp^3)−H Activation and β-Heteroatom Elimination



provides a low yield, while no reaction occurred under nitrogen. Addition of H_2O_2 or better *t*-BuOOH to the aerobic mixture increased the yield to 69%, while the $Pd(OAc)_2$ catalyst was less efficient. Moreover, further improvement with high diastereoselectivity arose in the presence of a bidentate ligand, the neocuporine. Meticulous studies including deuterium labelling experiments and DFT calculations led the authors to propose a highly detailed mechanism, which is summarized in Scheme 8b. Nucleophilic addition of aniline to η^2-alkenylpalladium carboxylate **8bA** affords η^2-alkylpalladium carboxylate **8bB**, which undergoes β-H elimination leading to cationic hydridopalladium species **8bC**. Isomerization of the latter gives imine complex **8bD**, the oxidation of which produces **8bE**. Then, activation of an Ar−H bond via probably a CMD process provides **8bF**, which undergoes Heck addition to a second molecule of 3-butenoic acid leading to **8bG**. Subsequent β-H elimination followed by oxidation gives the ionic intermediate **8bH**. Next, two successive annellations produce **8bI**. Hydrogen bonding with a third molecule of 3-butenoic acid and subsequent protonolysis of the N−Pd bond with CF_3CO_2H deliver **8bA** and **8bJ**. Finally, CF_3CO_2H-mediated intramolecular amidation provided the fused tetracycles.

It seems of interest to point out the decisive role of the monosubstitution of the amine unit in the formation of the tetracycle as exemplified above with *N*-methylaniline, which, under also Pd^{II}-catalyzed conditions, affords 4-(methyl(phenyl)amino)but-3-enoic acid (Scheme 2d).

The synthesis of dimethyl 1*H*-indole-2,3-dicarboxylate from the reaction of aniline with dimethyl butynedioate in DMA arose in a better yield when $Pd(OAc)_2$ was used as the catalyst instead of $Pd(OCOCF_3)_2$ (Scheme 9a).[25] Performing the $Pd(OAc)_2$-catalyzed reaction with a small amount of K_2CO_3 and a large excess of a carboxylic acid may increase the yield. AcOH, *t*-$BuCH_2CO_2H$, and *t*-$BuCO_2H$ improved the results, while $Me(CH_2)_4CO_2H$ and $Me(CH_2)_8CO_2H$ decreased the efficiency. The reason for such differences cannot be based on their pK_a or their steric hindrance, as AcOH and *t*-$BuCH_2CO_2H$, which have similar pK_a values but different sizes lead to the same yield. Finally, the best conditions were the use of a 4:1 mixture of DMA and *t*-$BuCO_2H$ as the solvent under base-free conditions. Jiao and co-workers assumed that the activation of the alkyne leading to η^2-alkynylpalladium complex **9bA** precedes the reaction with aniline, which leads to either the hydroamination intermediate **9bB** or the aminopalladation complex **9bC** (Scheme 9b). Plausible formation of **9bC** from **9bB** and Pd^{II} via "an acid-promoted electrophilic aromatic palladation and subsequent proton abstraction" was proposed but, under such conditions, we are more confident in the activation of an *ortho*-Ar−H bond resulting in the formation of **9bD**. Both **9bC** and **9bD** may lead to the product.

Using palladium, copper, and potassium acetates or pivalates in DMA under oxygen, Liang, Yang, and co-workers[26] performed the decarboxylative domino reaction of *o*-(phenylethynyl)aniline **10a** with *o*-bromobenzoic acid, which afforded dibenzo[*a*,*c*]carbazole **10a1** (Scheme 10a). The best yield arose using catalytic amounts of $Pd(OAc)_2$ with overstoichiometric amounts of both $Cu(OCOt\text{-}Bu)_2$ and KOCO*t*-Bu. Changing the O_2 atmosphere for air or N_2 was detrimental to the yield. The proposed mechanism involves coordination of the triple bond of **10a** to palladium, followed by intramolecular amination to afford **10bA** (Scheme 10b). Then, formation of five-membered palladacycle **10bB** via C(sp^2)−H bond

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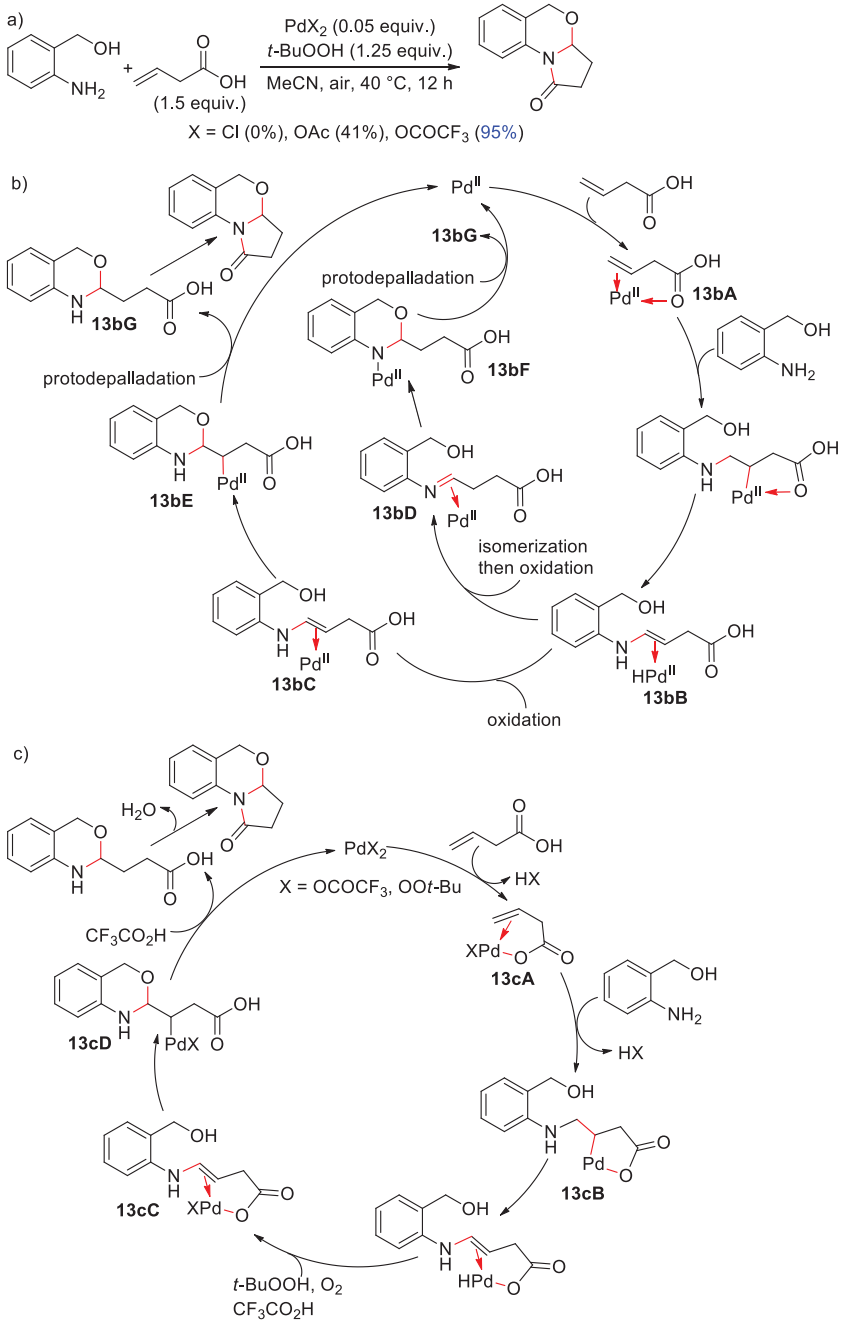
Scheme 13. Domino 1,1-Oxamidation and Amidation



activation is followed by *tert*-butylcarboxylate-mediated dealkylation leading to five-membered palladacycle **10bC**. Subsequent addition of *o*-bromobenzoic acid provides Pd^{IV} complex **10bD**, which undergoes decarboxylation/reductive elimination to give Pd^{II} species **10bE** and/or **10bF**. Finally, reductive elimination furnishes the carbazole and Pd^0, which is oxidized with $O_2/Cu(OCOt\text{-}Bu)_2$.

In the presence of alkali carbonates, the Pd/AgOCOR-catalyzed dimerization of 2,3-diphenyl-2*H*-azirine **11a** selectively provided either pyrrole or pyrimidine derivatives depending on the nature of both the silver carboxylate and the alkali carbonate (Scheme 11a).[27] Catalysis with $PdCl_2(dppf)\cdot CH_2Cl_2$/AgOAc in dioxane with Cs_2CO_3 led to a mixture of pyrrole **11a1** and pyrimidine **11a2**, while **11a1** was exclusively produced when Li_2CO_3 was used instead of Cs_2CO_3. Under the latter conditions, switching to the $Pd(PPh_3)_4$ catalyst provided a similar result, with the **11a1**/**11a2** ratio being 33:1. In contrast, **11a2** was the only product identified when using Cs_2CO_3 and catalysis with $Pd(PPh_3)_4$/$AgOCOCF_3$ in DMF.

According to the mechanism proposed by Yao, Miao, and coworkers,[27] both methods involve Pd^0 catalysis and the chemodivergence results, at least in part, from different reactivities of AgOAc and $AgOCOCF_3$ toward the azirine. The formation of both pyrrole and pyrimidine arises via the four-membered palladacycle **11bA** obtained from insertion of Pd^0 into the N−C bond of **11a** (Scheme 11b). Metathesis of **11bA** affords Pd-carbene intermediate **11bB**, which attacks a second molecule of **11a** to give zwitterionic intermediate **11bC**. The latter leads to nitrile ylide **11bD** via reaction with a third molecule of **11a** that is activated by coordination to AgOAc.

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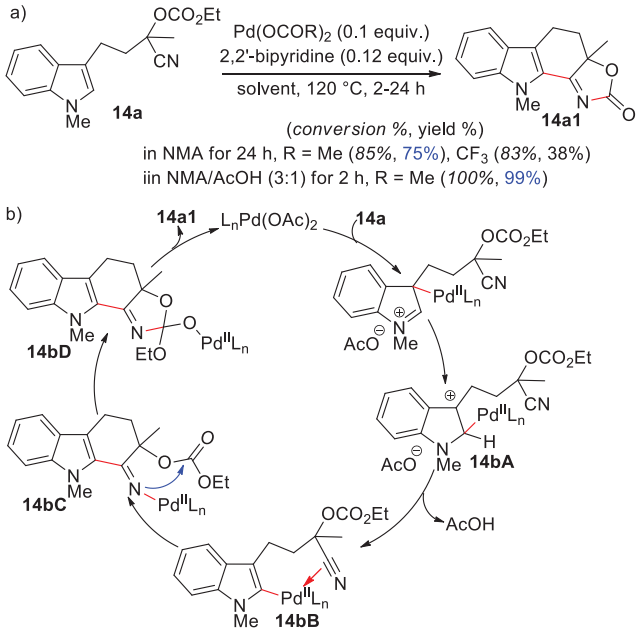
Scheme 14. Pd-Catalyzed Intramolecular C−H Addition to Nitriles



Cyclization of **11bD** furnishes the highly strained intermediate **11bE**, which gives rise to **11bF** via the opening of its cyclopropyl ring. Moisture-mediated hydrolysis of the imine unit of **11bF** followed by loss of NH_3 provides the pyrrole. The other pathway implicates palladacycle **11bG** obtained from regioselective insertion of nitrile ylide **11bH** formed from $AgOCOCF_3$-assisted ring opening of the azirine into the C−Pd bond of **11bA**. Subsequent reductive elimination of Pd^0, which affords dihydropyrimidine **11bI**, is followed by dehydrogenation under the Pd/Ag conditions to produce the pyrimidine. The intensive studies carried out by the authors reveal that the above proposed explanation of the chemodivergence is oversimplified and could be inadequate. Indeed, the careful screening of bases, solvents, temperatures, and silver and palladium catalysts to optimize the selectivity demonstrated its dependence on various more or less identified parameters.

Recently, Engle's team[28] disclosed that the aerobic domino reaction between ether **12a**, which bears the 8-aminoquinoline directing group, and the protected *o*-iodoaniline **12a′** in the presence of catalytic amounts of $Pd(OAc)_2$ associated with AgOAc and 1-adamantanecarboxylic acid in MeCN produced dihydroindole **12a1** in a high yield (Scheme 12a). The absence of 1-$AdCO_2H$, or especially AgOAc, or the replacement of AgOAc by $Cu(OAc)_2$ or CsOCO*t*-Bu was detrimental to the process. A plausible mechanism begins with coordination of **12a**, leading to **12bA** (Scheme 12b). Subsequent $C(sp^3)$−H abstraction provides the alkylpalladacycle **12bB**, which undergoes β-heteroatom elimination rather than β-H elimination[29] to afford the η^2-alkenyl palladium intermediate **12bC**. Then, nucleophilic addition of **12a′** produces **12bD**, which undergoes intramolecular oxidative addition leading to Pd^{IV} complex **12bE**. Finally, reductive elimination and ligand exchange releases **12a1** and regenerates the Pd^{II} active species.

The $C(sp^3)$−H abstraction could arise via either the CMD transition state **12bF** or the electrophilic C−H substitution (S_EC) mechanism depicted with **12bG**. 1-$AdCO_2H$ could be involved via an intermediate corresponding to **12bF** with 1-$AdCO_2$ instead of AcO as the ligand, which could be more reactive than **12bF** for a CMD process; such a role will, however, be minor given the modest yield decrease in the absence of the acid. AgOAc could mediate the S_EC, but the inefficiency of the process using the more basic CsOCO*t*-Bu disfavors this reaction pathway. Consequently, the reaction probably mainly occurs via **12bF**. Scavenging the iodide would be the main role of AgOAc that could also stabilize Pd intermediates via the formation of bimetallic species.

6.2. *N,O*-Heterocycles. Jiang and co-workers[30] recently reported the synthesis of 2,3,3*a*,5-tetrahydro-1*H*-benzo[*d*]-pyrrolo[2,1-*b*][1,3]oxazin-1-one from the coupling of 2-aminobenzyl alcohol with 3-butenoic acid in MeCN using *t*-BuOOH/O_2 as the oxidant and $Pd(OAc)_2$ or preferably $Pd(OCOCF_3)_2$ as the catalyst (Scheme 13a). The catalytic cycle assumed by the authors begins by the coordination of butenoic acid, leading to **13bA** (Scheme 13b). Nucleophilic attack of the amine on the activated C=C bond followed by β-H-elimination provides hydridopalladium intermediate **13bB**, which undergoes either oxidation to give **13bC** or isomerization followed by oxidation to give **13bD**. Subsequent intramolecular Wacker-type reaction of these species affords palladacycles **13bE** and **13bF**, respectively, both releasing **13bG** and the catalyst via protodepalladation. Finally, **13bG** undergoes intramolecular amidation to provide the product.

The effective formation of CF_3CO_2PdOOt-Bu from $Pd(OCOCF_3)_2$ and *t*-BuOOH demonstrated by Mimoun's team[31] urges us to hypothesize a reaction catalyzed by such species. Besides, we suspect that interaction of the catalyst with 3-butenoic acid will give η^2-alkenylpalladium carboxylate complex **13cA** (Scheme 13c) rather than **13bA** (Scheme 13b). Nucleophilic addition of the aminoalcohol to **13cA** would afford five-membered palladacycle **13cB**, which undergoes β-H-elimination followed by oxidation to provide **13cC**. Then, intramolecular Wacker-type addition leads to **13cD**, which evolves as above assumed.

At 120 °C in *N*-methylacetamide (NMA), the efficiency of the Pd-catalyzed activation of the $C(sp^2)$−H, which mediates intramolecular addition to a nitrile unit and leads to fused polycyclic indoles **14a1** from indole **14a** bearing a cyanohydrin tether at the C-3 position, was better with $Pd(OAc)_2$/bpy than with $Pd(OCOCF_3)_2$/bpy (Scheme 14a).[32] Addition of AcOH as a cosolvent led to a dramatic acceleration of the reaction and a quasi-quantitative yield. Liao and co-workers proposed a reaction beginning with the C-3 palladation of the indole core followed by 1,2-migration of palladium, leading to **14bA** (Scheme 14b). Next, elimination of AcOH affords **14bB**, which undergoes insertion into the cyano group to give iminopalladium intermediate **14bC**. Subsequent intramolecular reaction provided palladium alcoholate **14bD**. The authors are very discrete with regard to the transformation of the latter into **14a1**. We hypothesize two pathways: β-OEt elimination or protonation of the O−Pd bond followed by hydrolysis of the resulting hemiacetal. The strong improvement of the reaction rate using AcOH as cosolvent leads us to favor the second possibility.

Two reports from Liao's team[33,34] related the intermolecular C3−H addition of *N*-methylindole to the nitrile group of cyano(aryl)methyl benzoates using palladium carboxylates associated with 2,2′-bipyridine in *N*-methylacetamide. With cyano(phenyl)methyl benzoate, the trisubstituted oxazole **15a1** was selectively produced in a better yield with a carboxylic acid additive, CF_3CO_2H, rather than AcOH and $Pd(OCOCF_3)_2$ instead of $Pd(OAc)_2$ (Scheme 15a).[33] With an oxidant,

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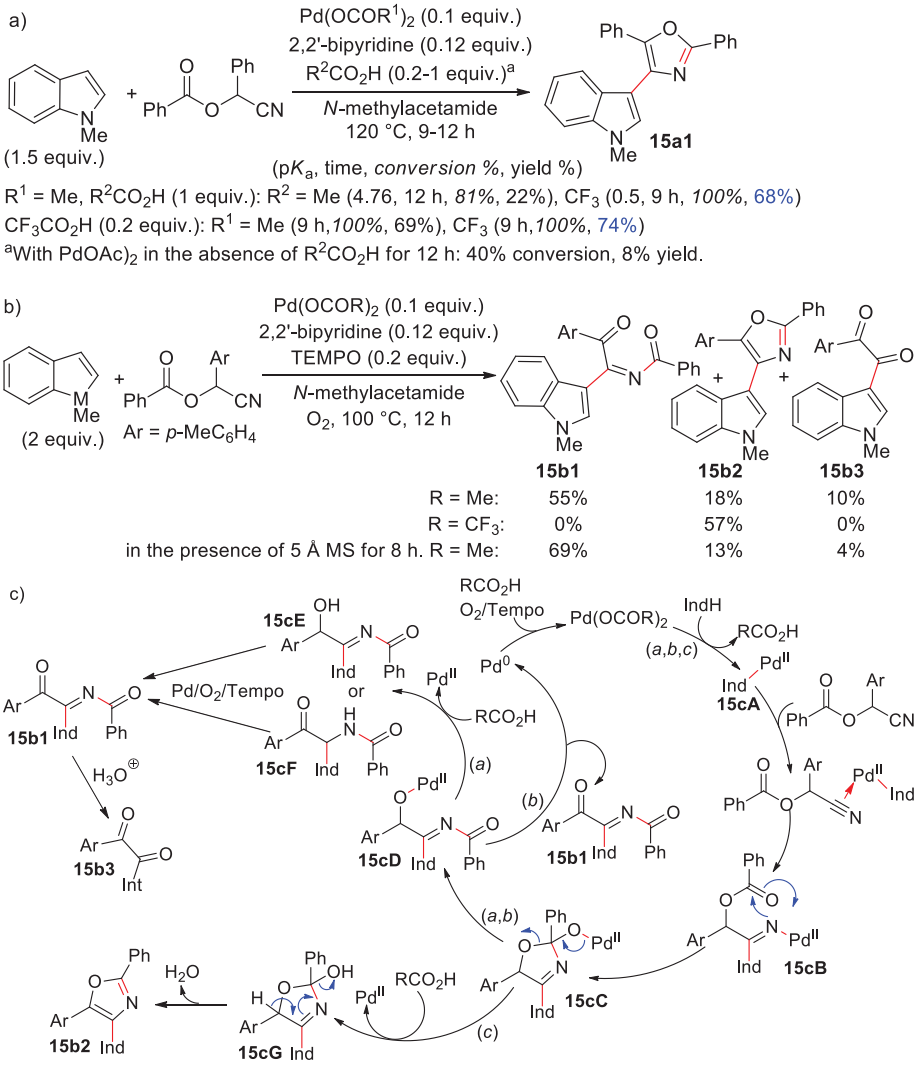
Scheme 15. Dependence of the Reaction Pathway on the Nature of the Carboxylate



especially O_2/TEMPO, and cyano(*p*-tolyl)methyl benzoate under acid additive-free conditions, the selectivity highly depended on the carboxylate (Scheme 15b).[34] $Pd(OAc)_2$ afforded *α*-imino ketone **15b1** as the main compound and low amounts of both oxazole **15b2** and *α*-diketone **15b3**, while only the oxazole was produced with $Pd(OCOCF_3)_2$. This dichotomy may be explained by the plausible mechanism in Scheme 15c. Coordination of the cyano group of *O*-acyl cyanohydrin to C-3 palladated indole **15cA** promotes the insertion leading to ketimine palladium complex **15cB**, which undergoes intramolecular cyclization to afford **15cC** (path a). Then, cleavage of the C−O bond of the heterocycle produces palladium alcoholate **15cD**. Protonolysis of the latter with in situ produced RCO_2H yields **15cE** or **15cF** as the intermediate (path a). The authors assumed the subsequent formation of **15b1** via Pd-catalyzed oxidation. Next, an *α*-diketone is produced from hydrolysis of **15b1**. We hypothesize that **15b1** could be directly obtained from **15cD** via *β*-H elimination (path b). In the presence of catalytic amounts of a carboxylic acid stronger than AcOH such as CF_3CO_2H, **15cC** suffers protonolysis leading to active Pd^{II} species and **15cG**, with the latter affording **15b2** (path c). Under the experimental conditions of Scheme 15a, the larger quantity of CF_3CO_2H due to its use as an additive may promote the selective formation of **15a1**.

7. CONCLUSION

The present review underlines the plausible influence of the nature of the carboxylate ligand and carboxylate additives on the efficiency of the Pd-catalyzed formation of C−N bonds and, in some cases, the other successive bonds. An optimized carboxylate may confer a high yield to the process. Acidity or/and steric hindrance of the carboxylate could be involved in the efficiency change, but the diversity of the results excludes a general rule. Besides, yield and selectivity may depend on the cation of the carboxylate additive.

As seen in this Mini-Review, significant advancement in C−N bond formation has been achieved in the course of the last years. Future research should prioritize a better understanding of the dependence of the reaction efficiency on the different additives.

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Notes

The author declares no competing financial interest.

Biography

Jacques Muzart was born in 1946, in Vienne la Ville, a small village in the Argonne area, 200 km east of Paris. He studied chemistry at l'Université de Reims Champagne-Ardenne and received his degrees (Doctorat de 3ème cycle in 1972, Doctorat d'Etat in 1976) for his work with J.-P. Pète on photochemical rearrangements of α,β-epoxyketones and β-diketones. He spent 15 months as a postdoctoral fellow of National Science Foundation working with Nobel Laureate E. J. Corey at Harvard University. Directeur de Recherche Emérite since 2011, his research interests concentrate on transition metal catalysis.

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