Imines in Stille Reactions

Imines in Stille-Type Cross-Coupling Reactions: A Multicomponent Synthesis of α-Substituted Amides**

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Palladium-catalyzed cross-coupling processes such as the Stille reaction have emerged as some of the more important methods for the construction of carbon–carbon bonds.[1–3] A useful feature of the Stille coupling is its use of nonpolar organostannanes, rather than nucleophilic agents, in reactions with organic halides. Organotin reagents are generally air- and moisture-stable, and they can be prepared with a diverse range of transferrable substituents, many of which are less readily formed, or unavailable, within nucleophilic reagents

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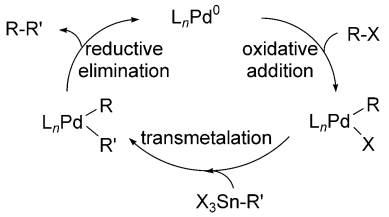
(e.g. Grignard, organozinc, and organolithium reagents). In addition, the lower reactivity of organotin reagents makes them easily handled and compatible with most functional groups, allowing their use on substrates without prior functional-group protection.[1]

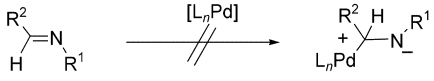
While Stille couplings with organotin reagents have been performed extensively with electrophilic compounds RX (organic halides and triflates, and related σ-bonded substrates),[1] one traditional limitation of this process is its inability to mediate similar reactions with a second important class of electrophiles: multiply bonded substrates $R_2C{=}X$ such as imines.[4] Carbon–carbon bond formation with imines is typically performed with nucleophilic agents and provides a useful method to construct α-substituted amines.[5] However, these reactions lack many of the features detailed above in the complementary Stille cross-coupling reactions. This limitation is of relevance, since α-substituted amines and amides are among the more common units in biologically relevant molecules, including α-amino acids, peptides, peptidomimetics, and β-lactam antibiotics.[6] We report below the development of a method to utilize multiply bonded substrates such as imines in cross-coupling reactions. This provides a palladium-catalyzed alternative to nucleophilic chemistry for the preparation of α-substituted amides, protected amines, and α-amino acid derivatives by a Stille-type coupling of imines with organotin reagents.[7]

Analysis of a generalized mechanism for palladium-catalyzed cross-coupling reactions (Scheme 1) reveals why

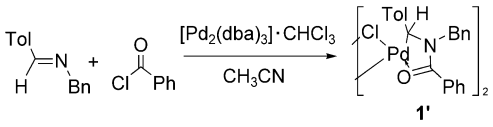


Scheme 1. General mechanism of Stille couplings.

imines and related substrates (aldehydes, ketones) have remained inappropriate as cross-coupling partners: imines have no demonstrated propensity to add directly to palladium to generate a Pd–C bond. This is likely due to the lack of stabilization of either the nitrogen anion or palladium cation shown in Equation (1a). This analysis suggests, however, that the addition of substrates that could neutralize the nitrogen anionic charge might provide a route to activate imines towards this transformation.[8] Indeed, we have recently observed that imines can undergo a catalyzed coupling with carbon monoxide and acid chlorides to generate 1,3-oxazolium-5-oxides (Münchnones),[9] a process that was postulated to proceed by formation of palladium-chelated amides.[10] This indicates that the addition of acid chlorides to imines can convert the latter into a substrate capable of oxidative addition.[11,12] This is clearly demonstrated in stoichiometric control experiments [Eq. (1b)], where the mixing of Tol(H)C=NBn (Tol = 4-$CH_3C_6H_4$), PhCOCl, and $[Pd_2(dba_3)]{\cdot}CHCl_3$ (dba = dibenzylideneacetone) leads to the quantitative formation of chelated product **1′**. Notably,



(1a)



1′

(1b)

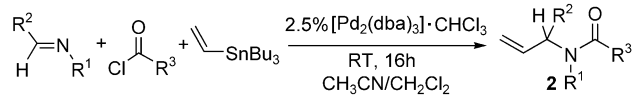
the ^{1}H NMR spectrum reveals reduction of the imine C=N bond upon addition to palladium ($\delta = 5.06$ ppm (s, C*H*Tol)), and ^{13}C NMR data indicates that amide chelation has occurred to form a five-membered metallacycle ($\delta =$ 182.3 ppm (*C*OPh)).[13,14] Mass spectrometric data is consistent with the dimeric structure of **1′**, likely formed through bridging chloro ligands to generate a pseudo-square-planar 16-electron palladium complex.

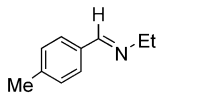
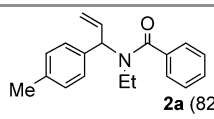
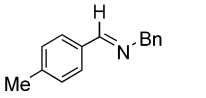
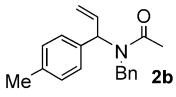
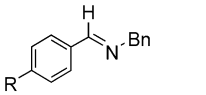
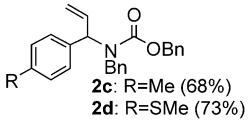
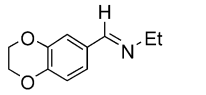
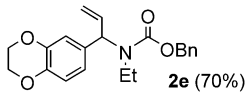
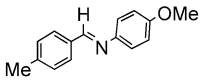
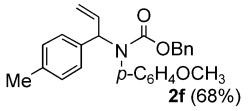
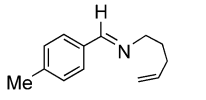
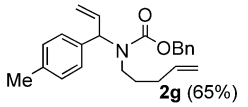
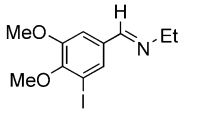
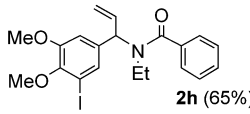
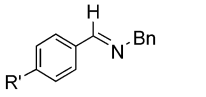
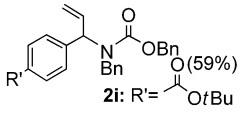
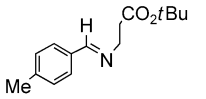
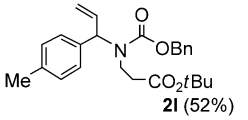
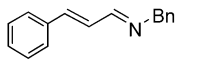
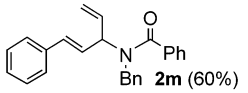
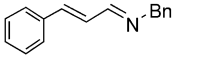
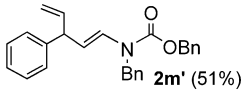
The oxidative addition chemistry in Equation (1b) suggested that this process might also be employed with imines in palladium-catalyzed carbon–carbon bond-forming reactions, provided the palladium–carbon-bonded intermediate **1** can be intercepted with transmetalation. This does turn out to be the case. The reaction of a solution of Tol(H)C=NEt, PhCOCl, and $Bu_3Sn(CH{=}CH_2)$ with 2.5 mol% $[Pd_2(dba_3)]{\cdot}CHCl_3$ results in the rapid disappearance of starting materials at ambient temperature. Workup of the reaction solution reveals that the clean coupling of the three reactants has occurred to form the vinyl-substituted amide **2a** in 82% yield (Table 1, entry 1).

This palladium-catalyzed three-component coupling occurs under mild conditions and with high selectivity, considering that acid chlorides themselves are known to undergo cross-coupling reactions.[1] In examining the plausible mechanism (Scheme 2), we can attribute this selectivity to the equilibrium reaction of imine and acid chloride strongly favoring *N*-acyl iminium salt/α-chloroamide (**3**) formation, which undergoes selective addition to Pd^0.[12] This is facilitated by the ability of **3** to chelate to give **1**, allowing catalysis to proceed in the absence of the ligands often required to aid in oxidative addition.[1] Indeed, the addition of ligands significantly inhibits this coupling,[15] consistent with reports that suggest that an empty coordination site can facilitate transmetalation from tin.[16] As such, reaction with the organotin reagent can occur directly with the three-coordinate complex **1** to form **4**,[17] which yields products by reductive elimination. Overall, these multiple mechanistic steps create what is to our knowledge a unique method to utilize palladium-catalyzed cross-coupling chemistry to convert imines into α-substituted amides.

Further investigation of this catalytic reaction shows it to have a good degree of generality. Thus both aryl and alkyl acid chlorides (Table 1, entry 2) can be employed to generate vinyl-substituted amides. Alternatively, acid chlorides can be replaced with chloroformates. This is somewhat surprising, since the iminium salt of a chloroformate does not oxidatively add to Pd^0 to form a stable product. This provides a catalytic method to convert imines directly into N-protected, α-substituted amine building blocks. As anticipated, the cata-

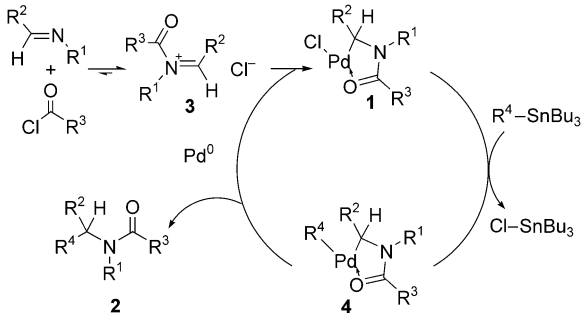
Table 1: Palladium-catalyzed synthesis of amides.[a]



Entry	Imine	Acid chloride	Product (yield)
1		PhCOCl	 **2a** (82%)
2		MeCOCl	 **2b** (78%)
3		BnOCOCl	 **2c**: R=Me (68%) **2d**: R=SMe (73%)
4		BnOCOCl	 **2e** (70%)
5		BnOCOCl	 **2f** (68%)
6		BnOCOCl	 **2g** (65%)
7		PhCOCl	 **2h** (65%)
8		BnOCOCl	 **2i**: R'= (59%)
9		BnOCOCl	 **2l** (52%)
10		PhCOCl	 **2m** (60%)
11[b]		BnOCOCl	 **2m'** (51%)

[a] Reaction conditions: 0.75 mmol imine, 0.75 mmol acid chloride, 0.75 mmol tributylvinyltin, 2.5 mol% $[Pd_2(dba_3)]\cdot CHCl_3$ for 16 h in 20 mL CH_3CN/CH_2Cl_2 (1:1). [b] In the presence of 0.75 mmol Bu_4NBr.

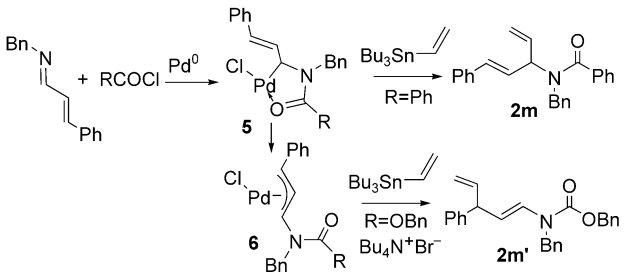
lytic reaction shows tolerance to various functional groups (e.g. ethers, thioethers, and esters; entries 3–5, 8, 9), although enolizable C-alkyl imines are not compatible with these coupling conditions.[18] This process is also amenable to substrates capable of undergoing other palladium-catalyzed reactions. Imines with terminal alkene substituents, which can undergo Heck couplings with acid chlorides,[19] react exclusively at the imine carbon to form α-substituted carbamates



Scheme 2. Postulated mechanism for the palladium-catalyzed three-component coupling.

(entry 6). Similarly, imines containing standard Stille coupling groups such as aryl bromides and electron-rich aryl iodides undergo preferential coupling as the iminium salt (entries 7 and 8). This selectivity can be attributed to the stabilizing effect of amide chelation in the product arising from oxidative addition of the iminium salt, which leads to the favored generation of **1** for transmetalation and coupling.

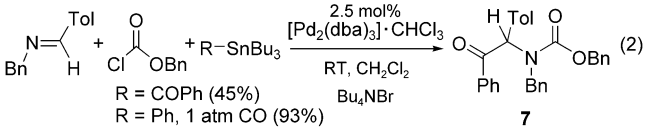
In addition to imines of aromatic aldehydes, α,β-unsaturated imines react with benzoyl chloride and tributylvinyltin to form α-substituted amides (**2m**, entry 10). Interestingly, replacement of the acid chloride with benzylchloroformate results in the generation of the Michael addition product **2m′** as well as **2m** (ca. 1:1 ratio). Based on the mechanism of this reaction, this would appear to result from the rearrangement of a chelated amide intermediate **5** to the π-allylic structure **6**, which can reductively eliminate at the remote carbon (Scheme 3). The addition of a weakly coordinating bromide



Scheme 3. Palladium-catalyzed vinylation of α,β-unsaturated imines.

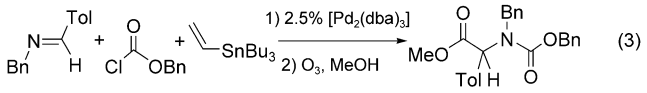
source ($Bu_4N^+Br^-$), which can presumably accelerate an associative rearrangement mechanism relative to transmetalation,[20] results in the favored formation of the 1,4-addition product **2m′** (entry 11). This provides a useful catalyst-based method to control the regioselectivity of the addition to unsaturated imine substrates as opposed to nucleophilic approaches, which typically rely upon variation of the actual vinyl-transfer substrate.[21]

The use of organotin reagents also provides a route to incorporate substrates into the α-position beyond those accessible from nucleophilic sources. This is illustrated in Equation (2), where the palladium-catalyzed reaction of benzoyltributyltin[22] with imine and chloroformate leads to transfer of the benzoyl unit to the imine carbon and formation of **7**. Even more simplified, the intermediacy of Pd–C-bonded



complexes suggests the possibility of incorporating insertion substrates into the overall catalytic process.[1] Thus, the catalytic coupling of Tol(H)C=NBn, BnOCOCl, and phenyltributyltin under one atmosphere of carbon monoxide yields the same product **7** in 51% yield.[10] Examination of the crude mixture revealed that the only starting materials present were free imine and phenyltributyltin. The addition of excess chloroformate (4 equiv) can thus be used to drive conversion of the imine into **7** in 93% yield.[23] This represents a rare example of a selective four-component cross-coupling reaction, in this case from imine, chloroformate, phenyltin, and carbon monoxide, and allows the construction of α-amido ketones. The latter are useful components for the synthesis of heterocycles[24] and as enzyme inhibitors.[25]

In conclusion, this study describes a convenient and general one-pot synthesis of α-substituted amides and N-protected amines by a palladium-catalyzed three-component-coupling of imines, acid chlorides or chloroformates, and organotin reagents. Mechanistically, this process provides an oxidative addition/reductive elimination-based alternative to nucleophilic approaches to C–C bond formation with imines, in which the imines are activated towards addition to palladium by RCOCl. Considering the utility of imine-reduction products, as well as the generality and mild features of tin couplings, this chemistry could prove useful in the preparation of a range of α-substituted amine derivatives. One illustration of this is in Equation (3), where the



palladium-catalyzed reaction of Tol(H)C=NBn, BnOCOCl, and tributylvinyltin followed by ozonolysis of the vinylic group under Marshall conditions[26] provides a simple two-step route to diprotected α-arylglycine derivatives from air-stable reagents and a commercially available catalyst. Studies directed towards the extension of this process to other general classes of cross-coupling reactions, as well as the incorporation of asymmetry into the reaction products, are currently underway.

Experimental Section

All reactions were carried out under an N_2 atmosphere using a Vacuum Atmospheres 553-2 drybox or by standard Schlenk techniques.

Synthesis of **2**: Imine (0.75 mmol) and acid chloride or chloroformate (0.75 mmol) were dissolved in CH_3CN (10 mL) and stirred for 1 h. To this solution was added $[Pd_2(dba)_3]\cdot CHCl_3$ (20 mg, 0.019 mmol). Tributylvinyltin (238 mg, 0.75 mmol) in CH_2Cl_2 (10 mL) was added, and the resulting solution was stirred at ambient temperature for 16 h. The solvent was removed in vacuo, the residue was dissolved in ethyl acetate (50 mL) and added to a saturated KF solution (25 mL). The white precipitate was filtered off and extracted water/ethyl acetate, and the organic layers were dried over $MgSO_4$. Product **2** was isolated by column chromatography (silica gel 60, hexanes/ethyl acetate).

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Keywords: amides · imines · multicomponent reactions · palladium · Stille reaction

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