C−H Activation
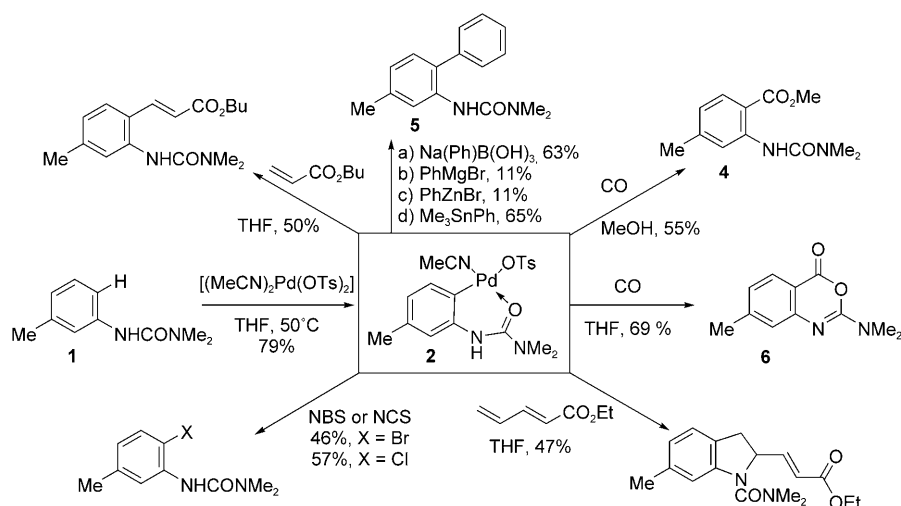
Room-Temperature Palladium-Catalyzed C−H Activation: *ortho*-Carbonylation of Aniline Derivatives**

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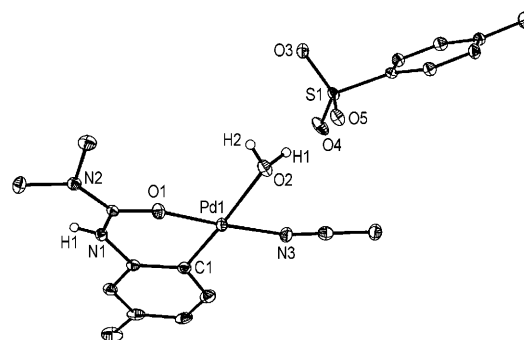
The interconversion of Ar−H and Ar−FG (FG = functional group) is an attractive process for the synthesis of functionalized aromatic rings and the development of transition-metal catalysts for achieving this transformation is currently an area of intense activity. Whilst a range of efficient catalyst systems have recently been reported, it is of note that nearly all of them require high temperatures and/or powerful oxidants.[1] Indeed, the development of an effective catalytic protocol for carbonylation using CO by palladium(II)-mediated C−H activation has long been recognized as being difficult and only recently has the first example been reported.[2] Herein we report a room-temperature, urea-directed, palladium-catalyzed carbonylation that provides access to biologically and synthetically useful anthranilic acid derivatives and heterocycles under mild conditions.

We recently reported the development of a palladium(II)-catalyzed 1,2-carboamination of dienes using aryl urea derivatives.[3] During these investigations, [Pd(OTs)₂-

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Scheme 1. Formation and reactions of Pd^II complex **2**. NBS = *N*-bromosuccinimide, NCS = *N*-chlorosuccinimide.

(MeCN)₂] (Ts = 4-toluenesulfonyl) was identified as a highly efficient precatalyst and we proposed that the reaction proceeded by a urea-directed C−H insertion to give a reactive Pd−Ar complex. In subsequent attempts to isolate Pd−Ar complexes, we found that reaction of the *m*-toluidine urea **1** (Scheme 1) with one equivalent of [Pd(OTs)₂(MeCN)₂] in anhydrous THF led to rapid precipitation of the *ortho*-palladate **2** as a grey amorphous solid, which was readily isolated in analytically pure form (79 %). Crystallization of **2** from CH₂Cl₂/petroleum ether afforded the cationic hydrate complex **3** whose molecular structure was confirmed by X-ray crystallography (Figure 1).

Figure 1. Molecular structure of **3** (thermal ellipsoids shown at 50 % probability).

With a ready supply of **2** in hand we explored its reactivity towards a range of coupling partners and reagents (Scheme 1).[4,5] Methoxycarbonylation[6] (CO/MeOH) and arylation (Ph−M, M = B, Sn, etc.) were found to be effective for the formation of the anthranilic ester **4** and biaryl **5** respectively. Interestingly, carbonylation of **2** in the absence of MeOH led to the instantaneous formation of the cyclic imidate **6** by internal nucleophilic capture of the intermediate acyl palladate.[7]

The ability to selectively convert **2** into either anthranilate **4** or cyclic imidate **6** by stoichiometric reaction with either CO/MeOH or CO, led us to focus on developing these into catalytic processes. After a brief optimization study, it was found that a range of aryl urea derivatives (**7**) underwent rapid carbonylation ([Pd(OTs)$_2$(MeCN)$_2$], 5 mol%), benzoquinone (BQ, 2 equivalents), TsOH (1 equivalent), CO (1 atm), CH$_2$Cl$_2$, reaction time ≤ 5 hours) at ambient temperature (18°C) to afford cyclic imidates[8] (**8**) in moderate to good yields (Table 1). In contrast to the reactions of aniline-derived urea derivatives with dienes,[3] this procedure did not require anhydrous conditions, although TsOH was essential for catalytic turnover. Prolonged reaction times resulted in lower yields, which are presumably a reflection of the acid sensitivity of the imidate products **8**.

Table 1: Room-temperature palladium(II)-catalyzed *ortho*-carbonylation of aryl urea derivatives.

Entry	7	R	R'	8	Yield [%]
1	**7a**	Me	Me	**8a**	67 (75)[a]
2	**7b**	Et	Et	**8b**	50
3	**7c**	iPr	iPr	**8c**	40
4	**7d**	morpholine		**8d**	49
5	**7e**	Me	H	**8e**	34
6	**7f**	Et	H	**8f**	40
7	**7g**	iPr	H	**8g**	66
8	**7h**	tBu	H	**8h**	85

[a] Reaction conducted with 10 mol% precatalyst.

When these palladium(II)-catalyzed reactions were conducted in MeOH as solvent instead of CH$_2$Cl$_2$, methoxycarbonylation gave the desired anthranilate, but yields were compromised by contamination with significant quantities of an unidentified resinous material.[9] After screening a variety of cosolvents, we found that dilution of the MeOH with THF (1:1) gave excellent results with minimal by-product formation. It was also found that the amount of TsOH could be reduced to 0.5 equivalents. These conditions were then applied to a variety of substituted aniline derivatives (Table 2) and generally gave excellent yields of anthranilates **10**. The reaction proceeded readily at room temperature with short reaction times and was unaffected by substitution on the non-aryl urea nitrogen atom. The reaction was generally tolerant of substitution in the aniline ring, although highly electron-withdrawing substituents were troublesome.[10] For

**Table 2:** Room temperature palladium(II)-catalyzed methoxycarbonylation.

Entry	9	R	R'	R''	10	Yield [%]
1	**9a**	Me	Me	H	**10a**	88 (97)[a]
2	**9b**	Et	Et	H	**10b**	76
3	**9c**	iPr	iPr	H	**10c**	55 (75)[b]
4	**9d**	morpholine		H	**10d**	75
5	**9e**	Me	H	H	**10e**	61
6	**9f**	Et	H	H	**10f**	81
7	**9g**	iPr	H	H	**10g**	90
8	**9h**	tBu	H	H	**10h**	88
9	**9i**	Bn	H	H	**10i**	85
10	**9j**	Me	Me	o-Me	**10j**	88
11	**9k**	Me	Me	m-Me	**10k**	84
12	**9l**	Me	Me	p-Me	**10l**	78
13	**9m**	Me	Me	o-MeO	**10m**	15 (40)[c]
14	**9n**	Me	Me	m-MeO	**10n**	26 (60)[c]
15	**9o**	Me	Me	p-MeO	**10o**	31 (80)[c]
16	**9p**	Me	Me	p-CF$_3$	**10p**	5 (30)[c]
17	**9q**	Me	Me	m-Br	**10q**	70
18	**9r**	Me	Me	p-Br	**10r**	40
19	**9s**	Me	Me	o,p-Me	**10s**	56
20	**9t**	Me	Me	p-CO$_2$Me	**10t**	36 (46)[c]
21					**11**	54

[a] Reactions conducted with 10 mol% precatalyst. [b] Reaction conducted in 100% MeOH with 3 equiv BQ. [c] Reactions conducted at 50°C.

example, the *p*-CF$_3$-bearing substrate **9p** gave only traces of anthranilate product (Table 2, entry 16) at ambient temperature, although a 30% yield of **10p** could be obtained at 50°C. The *p*-CO$_2$Me analogue (**9t**) benefited similarly (Table 2, entry 20), which reinforced the conclusion that the palladium(II)-catalyzed C−H activation sequence is electrophilic in nature.[3] Interestingly, all three MeO isomers (Table 2, entries 13–15) reacted inefficiently at 18°C but gave moderate to excellent yields of anthranilates at 50°C. The 1-naphthylamine derivative (Table 2, entry 21) gave only cyclized imidate **11** (see below). Significantly, acetanilide failed to undergo reaction even at 50°C. This latter result highlights the powerful activation effect of the urea moiety with this precatalyst.[3,11]

In certain cases, the transient formation of cyclic imidates (**8**) was observed by TLC, which raised the question of whether ester formation (**10**) proceeds by direct solvolysis of an acyl palladate (**12**→**10**) or by a postcatalytic methanolysis of the imidate (**13**→**10**). Control experiments[12] demonstrated that the imidates are very labile[8] under the methanolic carbonylation conditions and that the likely mechanism for the formation of **10** from **9** is by a C−H insertion, carbonylation, cyclization, and solvolytic ring-opening sequence (Scheme 2).

The synthetic utility of the urea anthranilates was further demonstrated by their cyclization to form quinazolinones, a
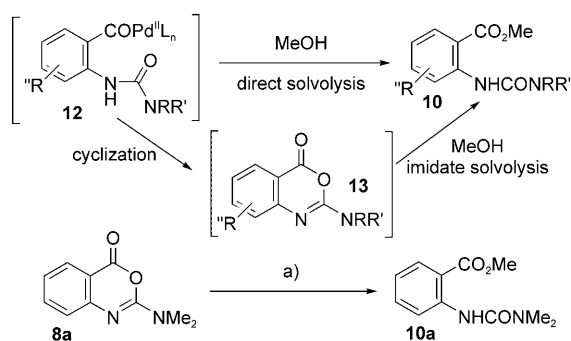
Scheme 2. Mechanism of ester formation: direct solvolysis versus imidate formation. a) For reagents see Table 2, 1.5 h, 95%.

key heterocyclic pharmacophore in numerous drug substances.[13] Indeed, carbonylation of **9i** followed by the addition of potassium carbonate[14] and heating afforded the quinazolinone **14** in 80% overall yield in a one-pot sequence from **9i** (Scheme 3). Both **9e** and **9f** reacted similarly to afford the corresponding quinazolinones in 57 and 70% yields, respectively.
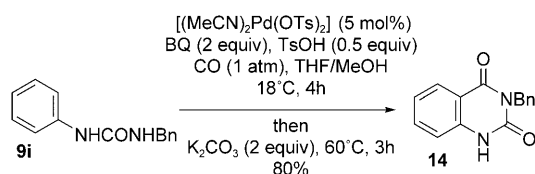
Scheme 3. One-pot carbonylation–cyclization route to quinazolinones.

Finally, we investigated conditions for the selective cleavage of the urea moiety to provide convenient access to the methyl anthranilates and anthranilic acids. During this study we made the observation that aniline diisopropyl urea derivatives undergo an unprecedented facile solvolysis in methanol under neutral conditions.[15] Remarkably, we found that simply heating **10c** in water gave methyl anthranilate **15** in 85% yield with no ester hydrolysis. The unusual reactivity of the diisopropyl urea moiety was further highlighted by the lack of reaction of **10a** and **10b** under identical conditions. Reaction of **10c** with NaOH (1M) gave anthranilic acid **16** in excellent yield, which highlighted the diisopropyl urea moiety as an efficient "traceless" *ortho*-directing C−H activating group for anilines (Scheme 4).

In summary, we have described a highly efficient, palladium(II)-catalyzed, and *ortho*-selective carbonylation
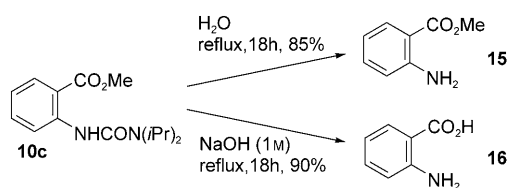
Scheme 4. Facile hydrolysis of an aryl diisopropyl urea.

sequence for aniline derivatives. The reaction proceeds efficiently under CO (1 atm), at room temperature (18°C), and with 5% catalyst loadings. Key features of the reaction are the use of $[Pd(OTs)_2(MeCN)_2]$ as precatalyst and the powerful activating effect of the aniline–urea moiety (compare Table 2, entry 1 (88%) versus acetanilide (0%)). The reaction conditions can be easily manipulated to produce either cyclic imidates (**8**) or methyl anthranilates (**10**). The use of *N*-aryl urea derivatives that bear a terminal N−H moiety allows the generation of quinazolinones by in situ base-mediated cyclization of the methoxycarbonylated products. Finally, we have demonstrated the unique ability of the diisopropyl urea moiety to function as a C−H-activating and -directing group that can be removed under neutral conditions, which represents the selective hydrolysis of a urea group in the presence of an ester group. We anticipate that these reactions will be of substantial utility for the preparation of anthranilic acids, and their derivatives, under mild conditions from the corresponding aniline.

Experimental Section

General procedure for methoxycarbonylation: A Radley's reduced-volume reaction vessel (10 mL) equipped with a stirring bar was charged with the desired urea derivative (1 mmol), benzoquinone (2 mmol), $[Pd(OTs)_2(MeCN)_2]$ (5 mol%), tosic acid monohydrate (0.5 mmol), THF (0.5 mL), and methanol (0.5 mL). The vessel was connected to a Schlenk line and was briefly evacuated and stirred at room temperature (18°C), followed by charging with CO to 1 atm. This cycle was repeated three times and the vessel left open to a dynamic atmosphere of CO (1 atm). The reaction mixture was then stirred at 18°C and monitored by TLC. On completion (2–5 h), the reaction mixture was concentrated in vacuo, the residue dissolved in CH_2Cl_2 and washed with HCl (1M). The organic layer was then washed with water, dried over $MgSO_4$, filtered and concentrated in vacuo. Purification by flash chromatography (10–40% EtOAc/petroleum ether) afforded the pure products.

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[10] The *p*-NO$_2$ derivative failed to react altogether.

[11] We also found that methoxycarbonylation could be achieved with a) PdCl$_2$ (10 mol %), BQ (3 equiv), CO, MeOH/THF (1:1) at 60 °C and b) Pd(OAc)$_2$ (5 mol %), BQ (2 equiv), and TsOH (1 equiv) at 18 °C (see the Supporting Information for full details). However, significantly lower yields were obtained in

these cases, which confirmed the superiority of the [Pd(OTs)$_2$-(MeCN)$_2$] precatalyst system for mild and selective C–H activation (Ref. [3]).

[12] Pure **8a** was subjected to the reaction conditions from Table 2. After 1.5 hours, all of **8a** was consumed and the ester **10a** was isolated in 95 % yield.

[13] For recent reports on synthesis and biological activity of 2,4(1*H*,3*H*)-quinazolinediones see: a) Z. Li, H. H. Huang, H. Sun, H. Jiang, H. Liu, *J. Comb. Chem.* **2008**, *10*, 484; b) C. Larksarp, H. Alper, *J. Org. Chem.* **2000**, *65*, 2773, and references therein.

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[15] To the best of our knowledge, solvolysis of urea derivatives requires relatively harsh conditions, for example, high temperatures, strongly acidic or basic conditions, metal catalysis etc: a) J. Wang, Q. Li, W. Dong, M. Kang, X. Wang, S. Peng, *Appl. Catal.* **2004**, *261*, 191; b) N. V. Kaminskaia, N. M. Kostíc, *Inorg. Chem.* **1998**, *37*, 4302; c) N. R. Ayyanger, A. R. Choudhary, U. R. Kalkote, A. A. Natu, *Chem. Ind.* **1998**, 599. In contrast, we have found that aryl diisopropylamino ureas undergo solvolysis under particularly mild conditions. This is clearly a property imparted by the diisopropylamino group, and not a consequence of (contaminant) palladium catalysis as the following (palladium-free) example demonstrates: Capasso et al have demonstrated

$$\text{PhNHCON}(i\text{Pr})_2 \xrightarrow[\substack{18h, 81\% \\ 48h, 100\%}]{\text{MeOH, reflux}} \text{PhNHCO}_2\text{Me}$$
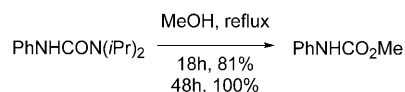
that phenyldimethyl urea derivatives undergo hydrolysis under acidic or basic conditions via phenylisocyanate intermediates: S. Salvestrini, P. DiCerbo, S. Capasso, *J. Chem. Soc. Perkin Trans. 2* **2002**, 1889. We propose that the ease with which phenyldiisopropyl urea derivatives undergo solvolysis may be a result of the leaving group ability of diisopropylamine being enhanced by the steric compression afforded by the isopropyl groups. Further mechanistic investigation is ongoing and will be reported in due course.