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

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C–H activation; carbonylation; heterocycles; heterogeneous catalysis; palladium

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, $[Pd(OTs)_2\text{-}(MeCN)_2]$ (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 CH_2Cl_2/petroleum ether afforded the cationic hydrate complex **3** whose molecular structure was confirmed by X-ray crystallography (Figure 1).

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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_2Cl_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**.

When these palladium(II)-catalyzed reactions were conducted in MeOH as solvent instead of CH_2Cl_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 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_2Me 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 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.

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 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.

References

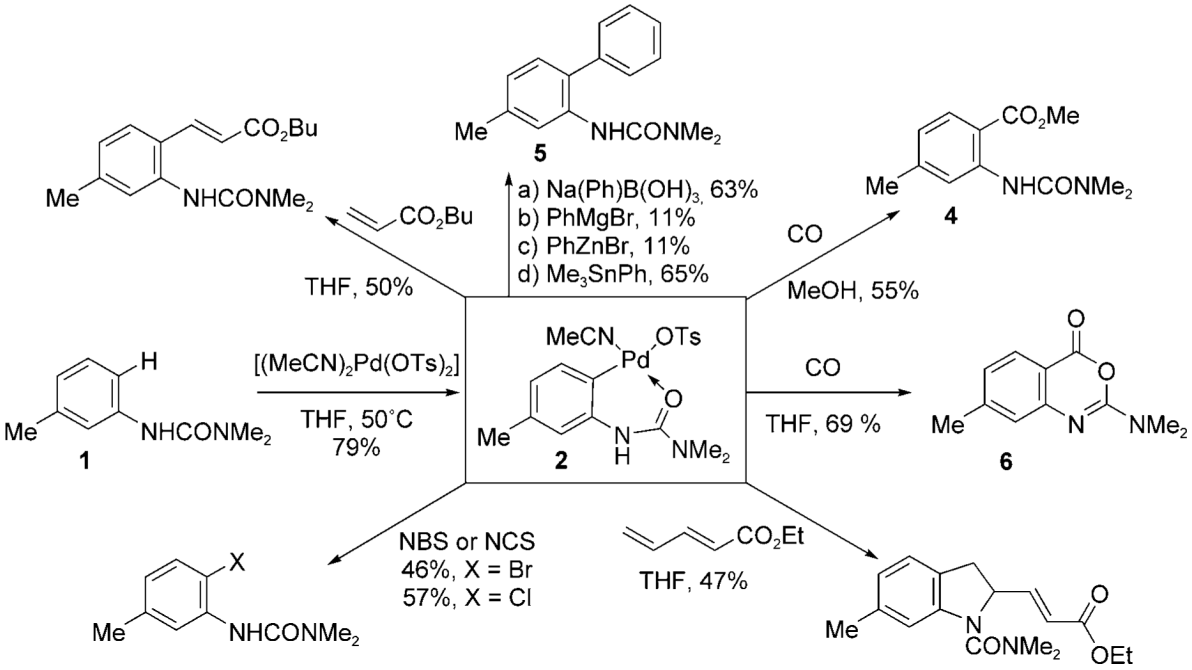
1. a Kakiuchi F, Kochi T. Synthesis 2008:3013–3039. b Alberico D, Scott ME, Lautens M. Chem. Rev 2007;107:174–238. [PubMed: 17212475] c Li BJ, Yang S-D, Shi ZJ. Synlett 2008:949–957. d Campeau L-C, Stuart DR, Fagnou K. Aldrichimica Acta 2007;40:35.
2. During the preparation of this manuscript Yu and Giri reported the first palladium(II)-catalyzed *ortho* carbonylation of benzoic and phenylacetic acids by C-H insertion: Giri R, Yu J-Q. J. Am. Chem. Soc 2008;130:14082. [PubMed: 18834125].
3. Houlden CE, Bailey CD, Ford JG, Gagné MR, Lloyd-Jones GC, Booker-Milburn KI. J. Am. Chem. Soc 2008;130:10066. [PubMed: 18613664]
4. For the stoichiometric reaction of aryl–Pd^{II}–amide complexes, see: Horino H, Inoue N. J. Org. Chem 1981;46:4416..
5. For palladium-catalyzed C-H activation reactions with phenyl amides as directing groups, see: a Boele MDK, van Strijdonck GPF, de Vries AHM, Kamer PCJ, de Vries JG, van Leeuwen PWNM. J. Am. Chem. Soc 2002;124:2002.(vinylation); b Wang J-R, Yang C-T, Liu L, Guo Q-X. Tetrahedron Lett

2007;48:5449.; c Shi Z, Li B, Wan X, Cheng J, Fang Z, Cao B, Qin C, Wang Y. Angew. Chem 2007;119:5650.(arylation with boronic acids);Angew. Chem. Int. Ed 2007;46:5554.;Shi Z, Li B, Wan X, Cheng J, Fang Z, Cao B, Qin C, Wang Y. Angew. Chem 2007;119:7874.;Angew. Chem. Int. Ed 2007;46:7730–7730.; d Brasche G, García-Fortanet J, Buchwald SL. Org. Lett 2008;10:2207. [PubMed: 18465866](arylation without boronic acids); e Yang S, Li B, Wan X, Shi Z. J. Am. Chem. Soc 2007;129:6066. [PubMed: 17455938]; f Daugulis O, Zaitsev VG. Angew. Chem 2005;117:4114.;Angew. Chem. Int. Ed 2005;44:4046.; g Li B-J, Tian S-L, Fang Z, Shi Z-J. Angew. Chem 2008;120:1131–1134.;Angew. Chem. Int. Ed 2008;47:1115–1118.; h Yu W-Y, Sit WN, Lai K-M, Zhou Z, Chan ASC. J. Am. Chem. Soc 2008;130:3304. [PubMed: 18298118] (ethoxycarbonylation); i Wan X, Ma Z, Li B, Zhang K, Cao S, Zhang S, Shi Z. J. Am. Chem. Soc 2006;128:7416. [PubMed: 16756276](chlorination).

6. For CO insertion into palladacycles, see: a Dupont J, Consorti C, Spencer J. Chem. Rev 2005;105:2527. [PubMed: 15941221]; b Ryabov AD. Synthesis 1985:233..
7. For palladium-catalyzed urea *ortho*-carbonylation using thallium intermediates, see: a Larock RC, Fellows CA. J. Am. Chem. Soc 1982;104:1900.;bKrantzASpencerRWTamTFLiakTUS Patent 4,665,0701987; c Krantz A, Spencer RW, Tam TF, Liak TJ, Copp LJ, Thomas EM, Rafferty SP. J. Med. Chem 1990;33:464. [PubMed: 2299617].
8. For the synthesis, biological activity, and reactions of 2-hetero-4*H*-3,1-benzoxazinones see: Coppola GM. J. Heterocycl. Chem 2000;37:1369., and references therein.
9. Pd^{II}/CO has been used for the manufacture of polymers from diols. From NMR studies we suggest that polycarbonate oligomers are formed from hydroquinone repeating units and methanol termini: a Okamoto M, Sugiyama J, Yamamoto T. J Appl. Polym. Sci 2008;110:3902.; b Okuyama K, Sugiyama J, Nagahata R, Asai M, Ueda M, Takeuchi K. Macromolecules 2003;36:6953..
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 Li Z, Huang HH, Sun H, Jiang H, Liu H. J. Comb. Chem 2008;10:484. [PubMed: 18419162]; b Larksarp C, Alper H. J. Org. Chem 2000;65:2773. [PubMed: 10808454], and references therein.
14. For the formation of quinazolinediones from basic condensation of *ortho*-ester aryl urea groups, see: Papadopoulos EP, Torres CD. J. Heterocycl. Chem 1982;19:269..
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 Wang J, Li Q, Dong W, Kang M, Wang X, Peng S. Appl. Catal 2004;261:191.; b Kaminskaia NV, Kostíc NM. Inorg. Chem 1998;37:4302. [PubMed: 11670566]; c Ayyanger NR, Choudhary AR, Kalkote UR, Natu AA. 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

$$\mathrm{PhNHCON(}i\mathrm{Pr)_2} \xrightarrow[\substack{18\mathrm{h},\,18\% \\ 48\mathrm{h},\,100\%}]{\mathrm{MeOH,\ reflux}} \mathrm{PhNHCO_2Me}$$

that phenyldimethyl urea derivatives undergo hydrolysis under acidic or basic conditions via phenylisocyanate intermediates: Salvestrini S, DiCerbo P, Capasso S. 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.



Scheme 1.

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

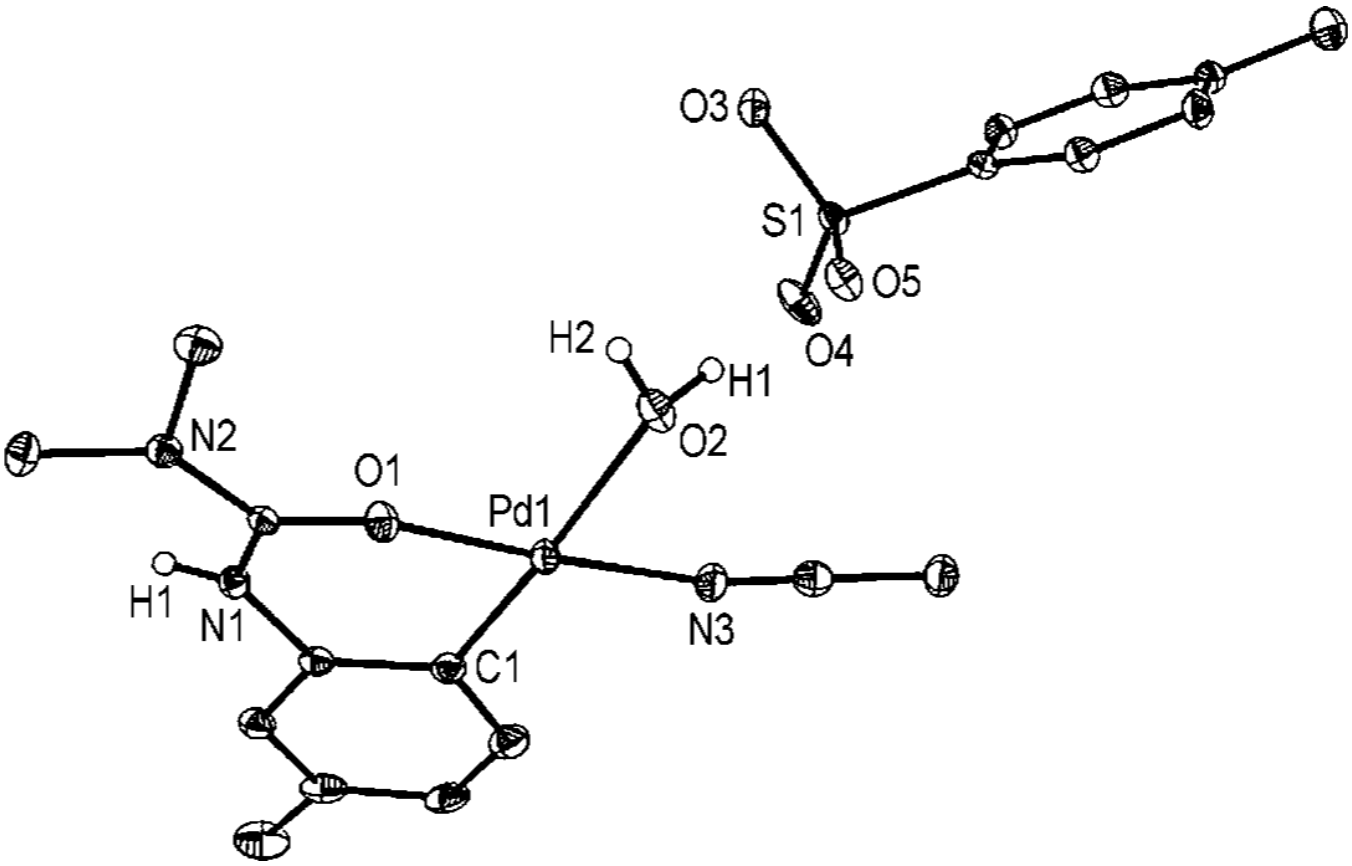
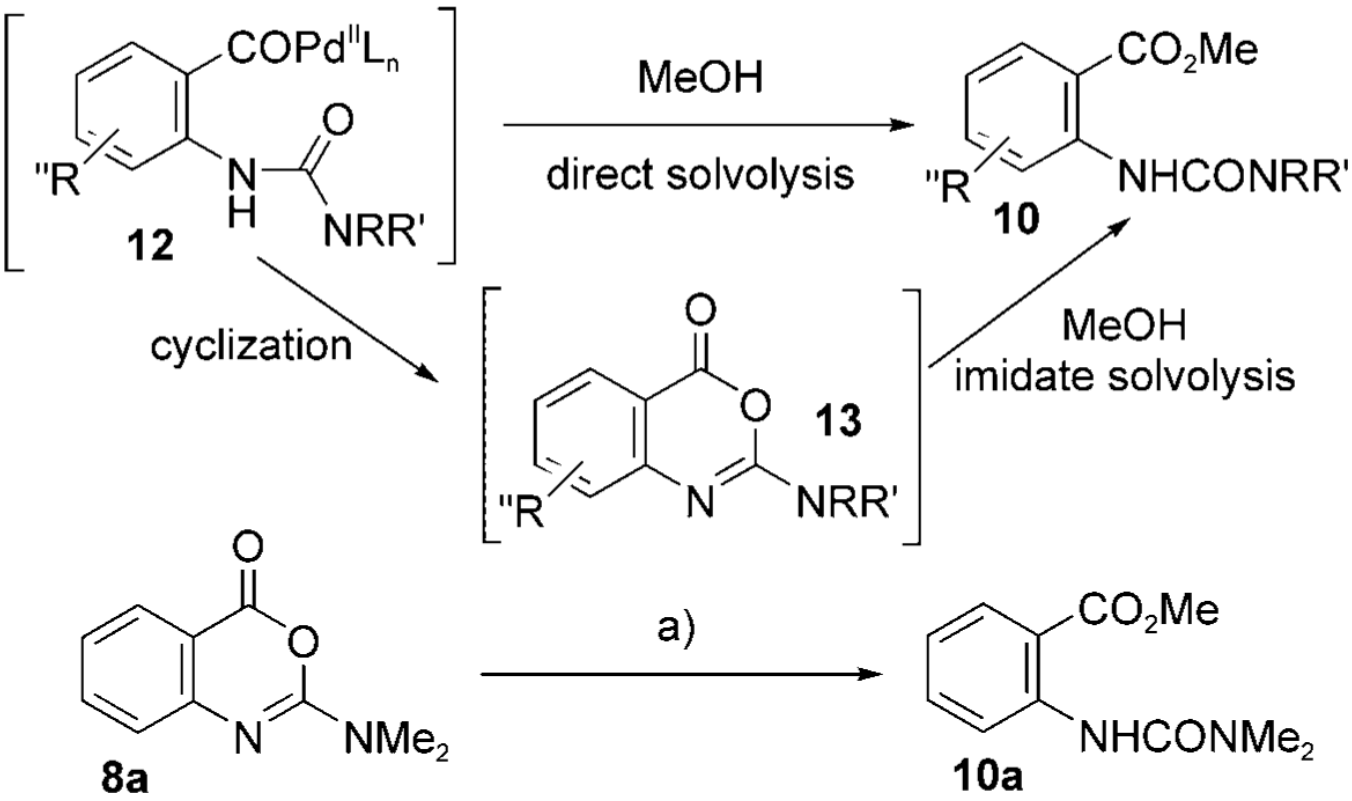
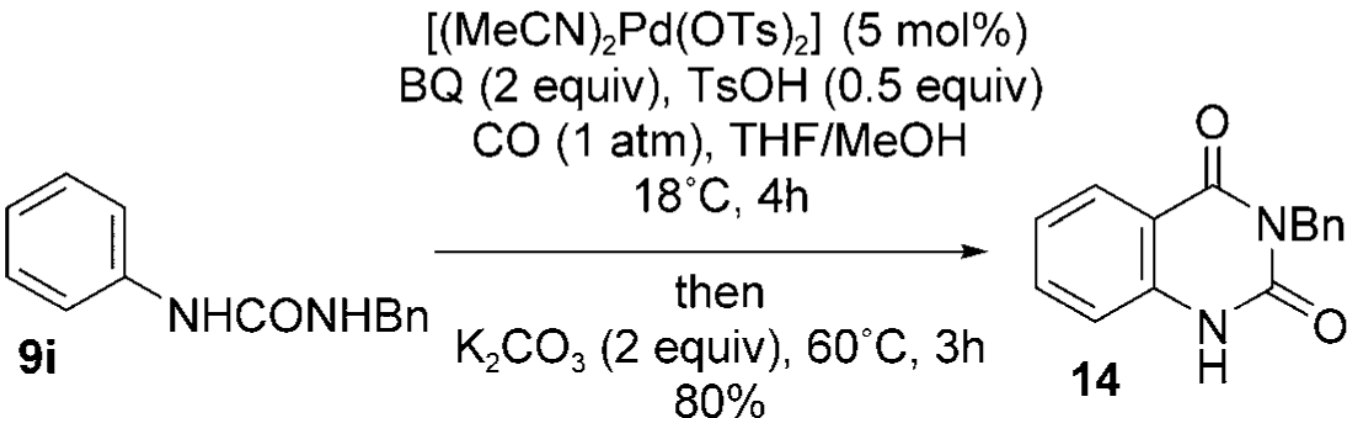


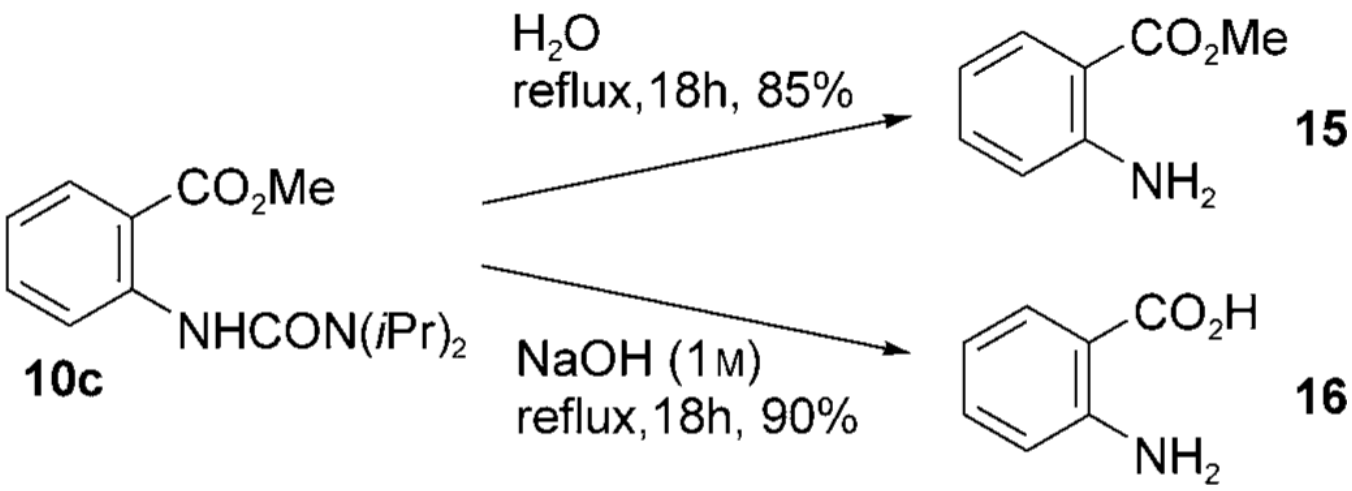
Figure 1.
Molecular structure of **3** (thermal ellipsoids shown at 50% probability).



Scheme 2.
Mechanism of ester formation: direct solvolysis versus imidate formation. a) For reagents see Table 2, 1.5 h, 95%.



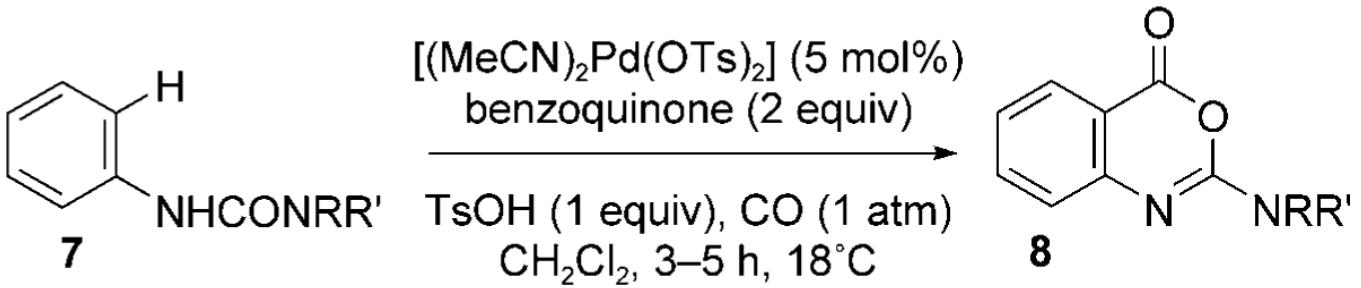
Scheme 3.
One-pot carbonylation—cyclization route to quinazolinones.



Scheme 4.
Facile hydrolysis of an aryl diisopropyl urea.

Table 1

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

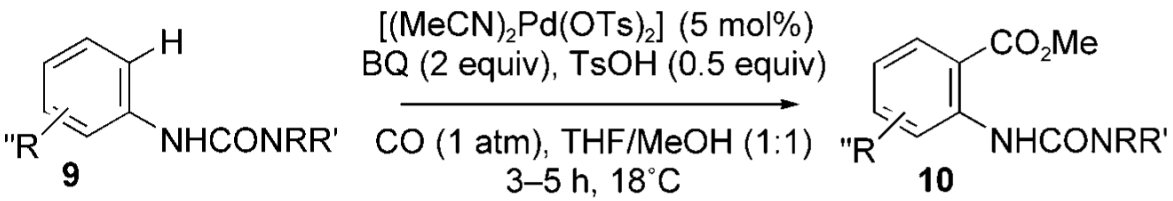


Entry	7	R	R′	8	Yield [%]
1	**7a**	Me	Me	**8a**	67 (75)[a]
2	**7b**	Et	Et	**8b**	50
3	**7c**	*i*Pr	*i*Pr	**8c**	40
4	**7d**		morpholine	**8d**	49
5	**7e**	Me	H	**8e**	34
6	**7f**	Et	H	**8f**	40
7	**7g**	*i*Pr	H	**8g**	66
8	**7h**	*t*Bu	H	**8h**	85

[a] Reaction conducted with 10 mol% precatalyst.

Table 2

Room temperature palladium(II)-catalyzed methoxycarbonylation.



Entry	9	R	R′	R″	10	Yield [%]
	9a	Me	Me	H	**10a**	88 (97)[a]
	9b	Et	Et	H	**10b**	76
	9c	*i*Pr	*i*Pr	H	**10c**	55 (75)[b]
	9d		morpholine	H	**10d**	75
	9e	Me	H	H	**10e**	61
	9f	Et	H	H	**10f**	81
	9g	*i*Pr	H	H	**10g**	90
	9h	*t*Bu	H	H	**10h**	88
	9i	Bn	H	H	**10i**	85
	9j	Me	Me	*o*-Me	**10j**	88
	9k	Me	Me	*m*-Me	**10k**	84
	9l	Me	Me	*p*-Me	**10l**	78
	9m	Me	Me	*o*-MeO	**10m**	15 (40)[c]
	9n	Me	Me	*m*-MeO	**10n**	26 (60)[c]
	9o	Me	Me	*p*-MeO	**10o**	31 (80)[c]
	9p	Me	Me	*p*-CF_3	**10p**	5 (30)[c]
	9q	Me	Me	*m*-Br	**10q**	70
	9r	Me	Me	*p*-Br	**10r**	40
	9 s	Me	Me	*o*,*p*-Me	**10 s**	56
	9t	Me	Me	*p*-CO_2Me	**10t**	36 (46)[c]

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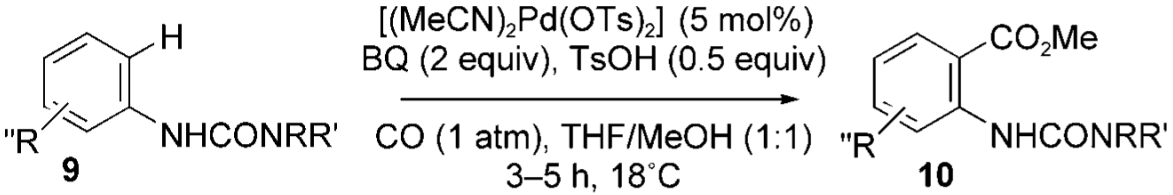
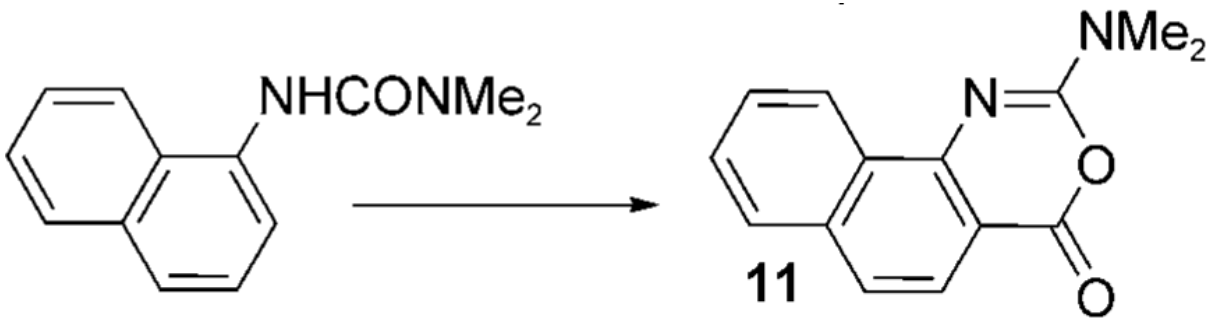


Entry	9	R	R′	R″	10	Yield [%]
1						54

[a] Reactions conducted with 10 mol% precatalyst.

[b] Reaction conducted in 100% MeOH with 3 equiv BQ.

[c] Reactions conducted at 50 °C.

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