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Palladium-Catalyzed Direct Olefination of Urea Derivatives with *n*-Butyl Acrylate by C−H Bond Activation under Mild Reaction Conditions

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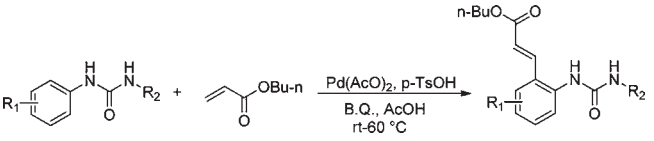
ABSTRACT



Pd^{II}-catalyzed aromatic C−H bond activation using urea as a directing group was achieved in a *p*-TsOH/AcOH medium under mild reaction conditions. The direct olefination products of various urea derivatives were produced from aryl urea derivatives and butyl acrylate in moderate to good yields.

In recent years, C−H bond activation reactions, involving the activation of one of the substrate inert C−H bonds and directly coupling with the other starting material to form the desired product, have been a popular research area in organic synthesis.[1] The advantages for C−H bond activation include the reliance on cheaper readily available starting materials and shorter synthetic routes.[2] Generally, most of the reported C−H bond activation reactions involve, first, a metal catalyst reacting with the substrate directing group to form the precomplex, followed by coupling with the other substrate to give the desired product.[1a,3] Thus, identification of both a suitable metal catalyst and directing groups are the two key factors for these C−H bond activation reactions. Among C−H bond activation reactions, those directed by an ortho directing group are dominant. Typical examples, to name a few, include cobalt-catalyzed ortho-alkylation of secondary benzamide with alkyl chloride or alkyl Grignard reagent,[4] Rh(III)-catalyzed oxidative olefination by the reaction of *N*-methoxybenzamides or aryl carboxamides with alkenes,[5] oxidative palladium(II)-catalyzed cyclization of α,β-unsaturated amides,[6] divergent C−H functionalizations directed by sulfonamide pharmacophores,[7] palladium(II)-catalyzed annulation of benzamides with [60]-fullerene,[8] Pd-catalyzed aerobic olefination of unactivated sp^3 C−H bonds by the nitrogen heterocycles serving as

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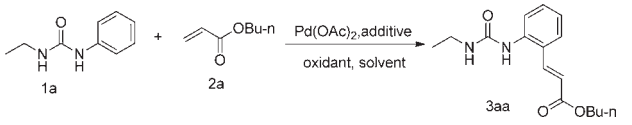
the directing group,[9] Pd(II)-catalyzed C−H alkenylation of phenols directed by silanol,[10] the ortho-silylation of aryl ketone, benzaldehyde, and benzyl alcohol derivatives directed by a hydroxyl group,[11] and rhodium-catalyzed ortho-olefination of benzoates and benzaldehydes directed by ester and carboxaldehyde units.[12] Based on the catalyzed C−H bond activation reactions directed by amide units,[4−6] we postulated that aryl urea derivatives should be an ideal substrate for C−H bond activation; however there are few reports of aryl urea derivatives catalyzed by C−H bond activation. Recently, Glorius and co-workers reported the rhodium-catalyzed oxidative C−H Olefination of *N*-methoxy-*N*′-aryl ureas[13] and Lipshutz and his research group developed the palladium-catalyzed C−H cross-coupling of *N,N*-dimethyl-*N*′-aryl ureas with aryl boronic acid or aryl iodides.[14] Booker-Milburn et al.[14c] and other groups[14d−e] reported a palladium(II)-catalyzed C−H bond olefination reaction on the use of aryl urea derivatives as a directing group. Herein, we report palladium-catalyzed direct olefination of various aryl urea derivatives with *n*-butyl acrylate by C−H bond activation under mild catalyzed conditions. In our experiments, we found that the urea moiety serves as an efficient directing group in the Pd(II)-catalyzed olefination of various aryl urea derivatives.

Ethyl-3-(*p*-tolyl)urea was chosen as a test substrate for the reaction with *n*-butylacrylate and $Pd(OAc)_2$ catalyst under various conditions (Table 1). We were pleased to observe that the $Pd(OAc)_2$ (5 mol %) exhibited notable catalytic activity affording the desired product in high yield in the presence of *p*-TsOH (30 mol %) and 1.0 equiv of *p*-benzoquinone (B.Q.) (entry 3). The generated double bond was almost exclusively in the E-form, and acetic acid was the solvent of choice; other solvents provided limited olefination (entries 1−2, 4−5). Among the selective additives, *p*-TsOH was the best additive (entry 3). By the transition-metal-catalyzed mechanism,[15] Pd(0) should be oxidized by an oxidant and B.Q. had the best catalytic effectiveness. In our tests, addition of more than 1 equiv of B.Q. did not increase the yield significantly. Other oxidants had lower yields than B.Q.

We studied various types of aryl urea derivatives in the reaction with *n*-butylacrylate (see Scheme 1). High

Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst	solvent	additive	oxidant	yield (%)[b]
1	$Pd(AcO)_2$	Toluene	*p*-TsOH	B.Q.	trace
2	$Pd(AcO)_2$	t-BuOH	*p*-TsOH	B.Q.	37
3	$Pd(AcO)_2$	AcOH	*p*-TsOH	B.Q.	72
4	$Pd(AcO)_2$	DMF	*p*-TsOH	B.Q.	trace
5	$Pd(AcO)_2$	DMSO	*p*-TsOH	B.Q.	trace
6	$Pd(AcO)_2$	AcOH	HBF_4	B.Q.	63
7	$Pd(AcO)_2$	AcOH	$B(OCH_3)_3$	B.Q.	68
8	$Pd(AcO)_2$	AcOH	KAcO	B.Q.	trace
9	$Pd(AcO)_2$	AcOH	KOBu-*t*	B.Q.	trace
10	$Pd(AcO)_2$	AcOH	*p*-TsOH	O2	45
11	$Pd(AcO)_2$	AcOH	*p*-TsOH	Air	34
12	$Pd(AcO)_2$	AcOH	*p*-TsOH	$PhI(AcO)_2$	52
13	$Pd(AcO)_2$	AcOH	*p*-TsOH	$K_2S_2O_8$	63
14	$Ni(AcO)_2$	AcOH	*p*-TsOH	B.Q.	trace
15	$Cu(AcO)_2$	AcOH	*p*-TsOH	B.Q.	trace
16	$Co(AcO)_2$	AcOH	*p*-TsOH	B.Q.	trace

[a] Ethyl-3-(*p*-tolyl)urea (0.5 mmol), *n*-butyl acrylate (0.6 mmol), catalyst (0.05 mmol), oxidant (0.5 mmol), and 1.5 mL of solvent. For the detailed reaction procedure, see the Supporting Information. [b] Yields are isolated.

regioselectivity of mono-olefination was observed in all of the aryl urea derivative reactions. For the ethyl aryl urea substrate, it was shown that there was high functional group tolerance as demostrated in the yields aquired from reactions **3a**−**3h**. Substituents on the aromatic moiety of the urea substrate influenced the efficiency of the olefination coupling reaction significantly (see Scheme 1). Due to the steric effect, the yield of the ortho methyl substitution (**3c**) was lower than that of para position substitution (**3a**). The aromatic rings bearing chloro and bromo groups (**3d**−**3e**) had modest yields compared to the corresponding methyl (**3a**) version. The ethyl α-naphthalene urea underwent the olefination smoothly and provided the desired product (**3g**) with a good yield.

In order to investigate the regioselectivity of the urea directing group, benzyl urea derivatives were chosen for the study. A range of benzyl urea derivatives were next examined. Only the methyl substituent on the aromatic moiety of the aryl benzyl urea substrate underwent mono-olefination with acceptable yields (**3j**−**3k**). For other benzyl urea derivatives, debenzyl group reactions may have occurred. Experiments indicated that the benzene ring in the benzyl group did not undergo the olefination and mono-olefination was only located on the ortho position of the aryl ring ortho from the urea directing group (**3j**−**3k**). *N*-Butyl benzyl urea did not effectively undergo olefination (**3l**), providing further evidence that this C−H bond activation of the urea derivative catalyzed by Pd(II) was to the sp^2 carbon atom in the aryl ring.

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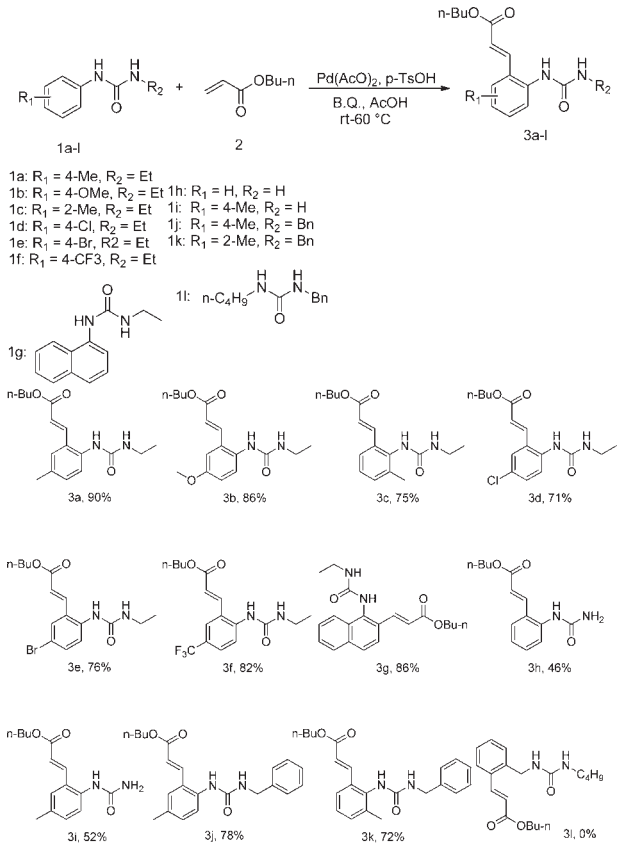
Scheme 1. Highly Regioselective Monoalkenylation of Various Urea Derivatives with *n*-Butyl Acrylate[a]



[a] Aryl urea (1.5 mmol), *n*-butyl acrylate (1.8 mmol), $Pd(OAc)_2$ catalyst (0.15 mmol), oxidant (1.5 mmol), and 3.0 mL of HOAc. The reaction was run in a sealed tube at 60 °C. For the detailed reaction procedure, see the Supporting Information. Yields are isolated.

In addition, to further explore the scope of urea derivative reaction activity, we chose the monoaryl urea derivatives to test the olefination reaction. The experimental results showed that, under the reaction conditions, the reactivity of this type of urea derivative was lower than that of the former types. To improve the yield, trimethyl boroate was added and a moderate yield was obtained (**3h**−**3i**). Among many substrates of this class that were tested, only the two products (**3h**−**3i**) were obtained. These are the first reports of a C−H bond activation olefination reaction utilizing this type of urea derivative. The reason for the low reactivity may be due in part to the amino group in the urea unit chealating with Pd(II), forming a relatively stable intermediate that is difficult to decompose into the desired product.

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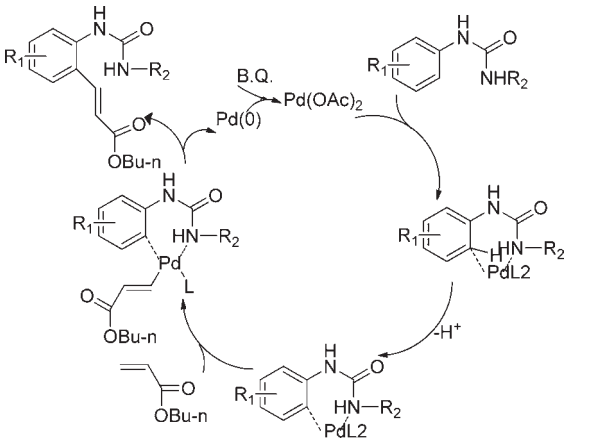
On the basis of the above data and precedent literature,[16] a plausible pathway is proposed in Scheme 2.

Scheme 2. Plausible Catalyic Mechanism for C−H Bond Activation



It is postulated that $Pd(OAc)_2$ was coordinated with the urea substrate; subsequent C−H bond activation at the ortho-position was assumed to take place leading to an aryl Pd metastable complex. Then, olefin insertion takes place followed by β-hydride elimination of the intermediate, producing the E-olefinated products. The reduced Pd(0) was oxidized to the Pd(II) oxidation state by B.Q. The role of additives may be related to coordination with the Pd(II) ion, which decreased the stability of the urea substrate metal ion complex and promoted the intermediate to decompose into olefins.

In summary, a selective and mild oxidative coupling reaction between three types of aryl urea derivatives and *n*-butylacrylate was reported. The reaction occurs through ortho C−H bond activation under $Pd(OAc)_2$ catalyzed reaction conditions. This aspect is noteworthy since various aryl urea derivatives are not only readily available but also easily converted to important aryl amine compounds.[15c]

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Supporting Information Available. Experimental details, and ^1H and ^{13}C NMR spectra of new compounds. This material is available free of charge via the Internetat http://pubs.acs.org.

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