



## Study of Lewis acid accelerated palladium catalyzed C–H activation



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### ABSTRACT

Acceleration of palladium catalyzed C–H activation by various Lewis Acids was demonstrated on the directed *ortho*-alkenylation and acylation of acetanilide and urea derivatives. The universality of this effect was investigated by the study of different palladium catalysts, directing groups in the aromatic substrates and versatile Lewis acids. Experiments were carried out to monitor the reactions and to compare the behavior and activity of different types of Lewis acids. Kinetic investigation revealed a rate determining C–H activation step, and DFT studies were performed for the explanation of Lewis acid effect on C–H activation.

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## 1. Introduction

Over the past decade the palladium catalyzed regioselective direct functionalization of arenes has been extensively utilized in organic chemistry. The mechanistic studies of the transition metal catalyzed C–H bond breaking [1–3] constitute an important part of this research field. Thus, throughout the past decade(s) several theories [4–11] have been elaborated regarding the elementary steps of the key transformation. Some reagents of the reaction mixtures have well-defined role, others are still in the phase of empirical inquiry. Certain substituents and functional groups with heteroatom ensure the proximity of the transition metal to the substrate by coordination and enable the C–H activation [12–16]. In the field of mild transformations [17,18] different additives, mainly inorganic metal salts are generally applied. The exact role of each reactants in the catalytic transformation [19–21] is not always clear. Brønsted acids have proven accelerating effect on the C–H activation reactions via enhancing ligand dissociation/exchange on the transition metal, generating a more electrophilic metal cen-

ter [22–27]. However, the beneficial effect of protic media cannot be omitted. We experienced accelerating effect of Lewis acids on palladium catalyzed *ortho*-acylation of acetanilide derivatives and hypothesize that Lewis acidic triarylboranes may act as effective accelerators in palladium catalyzed C–H activation [28]. In this paper we present the studies of the catalytic system to find out the scope of applicable Lewis acids and their role in the C–H activation processes.

## 2. Experimental

### 2.1. General

Anhydrous dichloromethane was distilled from sodium under N<sub>2</sub> and stored on molecular sieves, 4 Å. Isotope labelled compounds were synthesized. All other solvents and reagents were purchased from commercial sources, including B(C<sub>6</sub>F<sub>5</sub>)<sub>3</sub>. Tris(pentafluorophenyl)borane was stored and handled inside a glove box. BBr<sub>3</sub> was applied in the form of a stock solution: 0.25 M in anh. DCM. BCl<sub>3</sub> was applied in the form of a stock solution: 1 M in anh. DCM. Conversions are determined by gas chromatography: Agilent 5890 Gas Chromatograph (30 m × 0.25 mm column with 0.25 μm HP-5MS coating, He carrier gas) with FID detector

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and mass spectrometry was obtained on an Agilent 6890N Gas Chromatograph (30 m × 0.25 mm column with 0.25 μm HP-5MS coating, He carrier gas) and Agilent HP 5973N Mass Spectrometer (Ion Source: EI+, 70 eV, 230 °C interface 300 °C).

## 2.2. General procedure of the reactions

A screw capped 4 mL vial with a stirring bar was charged with acetanilide (0.1 mmol, 13.5 mg, 1 equiv.) and Pd catalyst (0.005 mmol, 5 mol%). The solids were dissolved in anhydrous dichloromethane (0.2 mL). Lewis acid (0.0072 mmol, 7.2 mol%), 4-fluorobenzaldehyde (0.2 mmol, 21 μL, 2 equiv.) and *t*BuOOH solution (5.5 M in C<sub>10</sub>H<sub>22</sub>, 4 Å M.S.) (0.2 mmol, 40 μL, 2 equiv.) were added and the vial was closed with septum screw cap. The reaction mixture was magnetically stirred at 30 °C for 24 h. During 24 h samples for GC analysis were taken.

A screw capped 4 mL vial with a stirring bar was charged with *N*-aryl, *N,N*-dimethyl urea (0.1 mmol, 1 equiv.) and Pd catalyst (0.005 mmol, 5 mol%). The solids were dissolved in dichloromethane (0.2 mL). Lewis acid (0.0072 mmol, 7.2 mol%), acrylic ester (0.15 mmol, 1.5 equiv.) and *t*BuOOH solution (5.5 M in C<sub>10</sub>H<sub>22</sub>, 4 Å M.S.) (0.15 mmol, 30 μL, 1.5 equiv.) were added and the vial was closed with septum screw cap. The reaction mixture was magnetically stirred at 30 °C for 24 h. During 24 h samples for GC analysis were taken.

## 2.3. Computational protocol

The reaction mechanism has been investigated by density functional theory based calculations employing the M06 exchange-correlation functional [29] as implemented in G09. The Kohn-Sham orbitals have been expanded in a double-zeta basis set (6-31+G\* basis set for main group elements and LANL2DZ basis set with additional set of diffuse and polarization functions). Solvent effects have been introduced by the SMD solvent model using DCM as a solvent [30]. The contributions to the Gibbs free energies have been calculated by assuming 30 °C and 1 mol/L concentration. Kinetic isotope effect has been calculated through the Bigeleisen-Mayer theory [31,32] with the QUIVER code [33]. Scaling factors have been obtained from Ref. [29].

## 3. Results and discussion

Amide moiety is a versatile directing group on aromatic cores. Several examples can be found in recent literature, including mild, palladium catalyzed *ortho*-functionalization of acetanilides. The successfully applied common acylating agents are α-oxocarboxylic acids [34,35] and aldehydes [36–43], but the coupling reaction has already been achieved with benzylic alcohols [44–46] and even from toluene derivatives [47–50].

We have recently identified Lewis acidic triaryl boranes as cocatalyst of palladium(II) compounds in the directed *ortho*-acylation of acetanilide derivatives at ambient temperature by in situ generated acyl radicals. [28] In further investigations we examined the universality of this beneficial effect regarding the types of suitable directing groups, coupling partners, transition metal catalysts and the applicable Lewis acids.

### 3.1. Study of the efficiency of different palladium sources

The *ortho*-acylation of acetanilide by 4-fluorobenzaldehyde was chosen as test reaction. Different kinds of palladium(II) catalysts (5 mol% palladium-acetate, palladium-trifluoroacetate, palladium acetylacetonate) were applied in the presence of boron trifluoride diethyl etherate (7.2 mol%) to see the specific activity of Lewis acidic additive and to compare the reaction rates (Fig. 1).

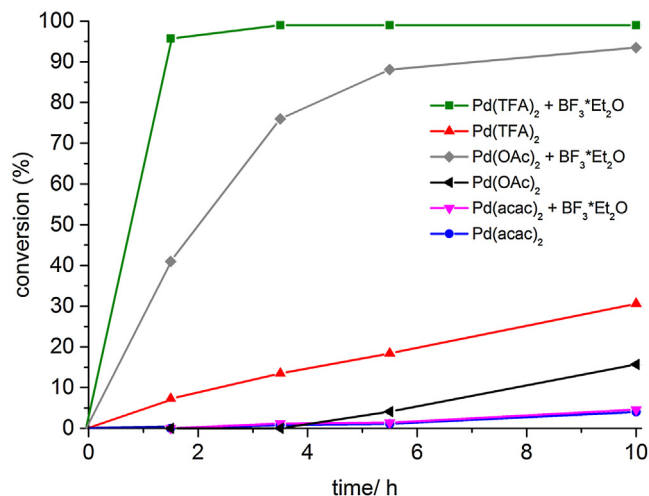
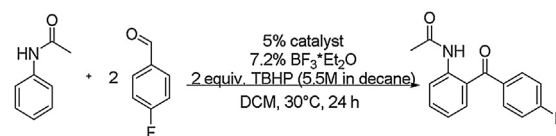


Fig. 1. Accelerating effect of BF<sub>3</sub>·Et<sub>2</sub>O on the palladium catalyzed C–H activation reaction (conversion based on GC FID results).

We found that Pd(acac)<sub>2</sub> itself was not a suitable catalyst for the reaction and the additional Lewis acid did not enhance the transformation. The more electrophilic metal center in palladium-acetate and trifluoroacetate ensured better conversions compared to Pd(acac)<sub>2</sub>. Complete consumption of the starting material was observed in case of both latter palladium catalysts in the presence of 7.2 mol% Lewis acidic BF<sub>3</sub>·Et<sub>2</sub>O. However, in the absence of Lewis acid the conversions were only 50% (Pd(TFA)<sub>2</sub>) and 15% (Pd(OAc)<sub>2</sub>) respectively after 24 h. The reaction rate acceleration was significant in the initial period of the transformation on the basis of the conversions measured after 2 h reaction time. In case of Pd(OAc)<sub>2</sub> the conversion increased from 1% to 41% by the influence of catalytic amount of BF<sub>3</sub>·Et<sub>2</sub>O, while the conversion of Pd(TFA)<sub>2</sub> catalyzed reaction was increased from 7% to 96% when 7.2 mol% Lewis acid was added to the reaction mixture. The results of these comparative studies suggest that the more electrophilic catalyst is more beneficial for the reaction, and the rate acceleration effect of Lewis acidic additive is general for all the studied palladium catalysts.

### 3.2. Scope of Lewis acids

Our earlier studies with electron deficient tris(pentafluorophenyl)borane revealed an unexpected induction period of the palladium acetate catalyzed coupling of anilides and aldehydes [28]. In continuation of our studies, we monitored the same coupling reaction utilizing silver tetrafluoroborate as inorganic Lewis acidic additive (Fig. 2). The aim of the experiments was to explore the generality of the previously observed unusual kinetics of the Lewis acid accelerated coupling reaction. When acetanilide was coupled with 4-fluorobenzaldehyde in the absence of any Lewis acid additive with Pd(OAc)<sub>2</sub> at 30 °C in DCM, we observed only 4% conversion in the reaction. Significant rate acceleration was observed when 7.2 mol% B(C<sub>6</sub>F<sub>5</sub>)<sub>3</sub> or AgBF<sub>4</sub> was added to the reaction mixture. After 24 h, the reaction reached 64% and 94% conversion respectively. In comparison, amongst the studied Lewis acids the silver salt has more pronounced rate

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