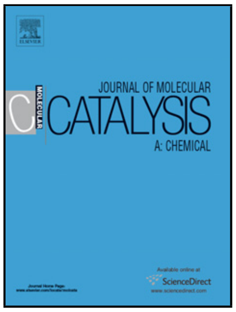

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PII: S1381-1169(16)30390-9
DOI: http://dx.doi.org/doi:10.1016/j.molcata.2016.09.018
Reference: MOLCAA 10042

To appear in: *Journal of Molecular Catalysis A: Chemical*

Received date: 30-5-2016
Revised date: 7-9-2016
Accepted date: 14-9-2016

Please cite this article as: Orsolya Tischler, Szabolcs Kovács, Gábor Érsek, Péter Králln, János Daru, András Stirling, Zoltán Novák, Study of Lewis Acid Accelerated Palladium Catalyzed C-H Activation, Journal of Molecular Catalysis A: Chemical http://dx.doi.org/10.1016/j.molcata.2016.09.018

Study of Lewis Acid Accelerated Palladium Catalyzed C-H Activation

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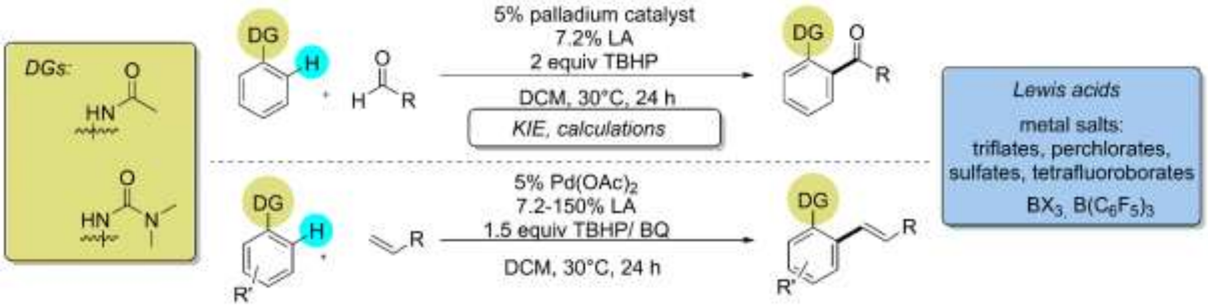
Graphical abstract



Highlights

- Amide and urea directed *ortho*-acylation and *ortho*-olefination on aromatic cores is accelerated by Lewis acidic additives.
- Lewis acidic additives afford more electrophilic transition metal center, favoring C-H activation.
- The efficiency of several palladium(II) catalysts is raised.
- KIE experiments and calculations suggests a rate-determining C-H activation step.

Keywords: C-H activation, palladium, Lewis acid, DFT studies

This paper is dedicated to Professor Georgiy B. Shul'pin on the occasion of his 70th birthday

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.

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 center [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_2 and stored on molecular sieves, 4Å. Isotope labelled compounds were synthesized. All other solvents and reagents were purchased from commercial sources, including $B(C_6F_5)_3$. Tris(pentafluoro)phenyl borane was stored and handled inside a glove box. BBr_3 was applied in the form of a stock solution: 0.25 M in anh. DCM. BCl_3 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 x 0.25 mm column with 0.25 µm HP-5MS coating, He carrier gas) with FID detector and mass spectrometry was obtained on an Agilent 6890N Gas Chromatograph (30 m x 0.25 mm column with 0.25 µm HP-5MS coating, He carrier gas) and Agilent HP 5973N Mass Spectrometer (Ion source: EI+, 70eV, 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 anh. dichloromethane (0.2 mL). Lewis acid (0.0072 mmol, 7.2 mol%), 4-fluoro-benzaldehyde (0.2 mmol, 21 µL, 2 equiv.) and ^{t}BuOOH solution (5.5M in $C_{10}H_{22}$, 4Å 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 hours. During 24 hours 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 (5.5M in $C_{10}H_{22}$, 4Å 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 hours. During 24 hours 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-oxo-carboxylic 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 co-catalyst 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-fluoro-benzaldehyde 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.).

We found that $Pd(acac)_2$ 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 $Pd(acac)_2$. Complete consumption of the starting material was observed in case of both latter palladium catalysts in the presence of 7.2 mol% Lewis acidic $BF_3•Et_2O$. However, in the absence of Lewis acid the conversions were only 50% ($Pd(TFA)_2$) and 15% ($Pd(OAc)_2$) respectively after 24 hours. The reaction rate acceleration was significant in the initial period of the transformation on the basis of the conversions measured after 2 hours reaction time. In case of $Pd(OAc)_2$ the conversion increased from 1% to 41% by the influence of catalytic amount of $BF_3•Et_2O$, while the conversion of $Pd(TFA)_2$ 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(pentafluoro)phenyl 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 $Pd(OAc)_2$ at 30°C in DCM, we observed only 4% conversion in the reaction. Significant rate acceleration was observed when 7.2 mol% $B(C_6F_5)_3$ or $AgBF_4$ was added to the reaction mixture. After 24 hours, the reaction reached 64% and 94% conversion respectively. In comparison, amongst the studied

Lewis acids the silver salt has more pronounced rate acceleration effect, and induction period was observed only in case of the triaryl borane.

Later, we examined the progress of the same reaction catalyzed by the more electrophilic palladium trifluoroacetate in the presence of tris-pentafluorophenyl borane or silver tetrafluoroborate. The monitoring of the reactions showed no induction period of the transformation, and similar conversions were measured to the case of $Pd(OAc)_2$ (Fig. 3.).

Next, we studied the influence of other inorganic Lewis acidic additives on the palladium catalyzed couplings. We have applied halides of aluminium, silver, indium and iron(III) in the palladium catalyzed coupling. The presence of these salts completely inhibited the transformation (not depicted), most likely because of the strong coordination of the halide anions to the palladium center, disabling C-H activation. Zinc and copper sulfate, sodium and iron(II) tetrafluoroborate and ammonium and potassium hexafluorophosphate salts proved to be inert additives and their presence did not change the conversion of the transformation compared to the reactions carried out in the absence of Lewis acid (not depicted). Sulfate salts of iron, aluminum, nickel and lead evolved the conversion 2-2.5 times higher than it was observed in case of Lewis acid free transformations (not depicted). In our further studies we found that the most beneficial additives for the coupling reaction, besides the previously tested $AgBF_4$, are silver zinc and copper salts with weakly coordinating counterions such as triflate or perchlorate. (Fig. 4.). With their application the reaction rate of the transformation can be significantly increased. Boron trifluoride, contrary to the chloro and bromo trihaloborane analogues, also enhances the reaction and almost complete conversion can be reached after 24 hours reaction time.

3.3. Mechanistic studies

Similar transformations are usually explained by catalytic pathways involving palladacycles as intermediates and the corresponding C-H bond breaking is considered to be rate limiting[30, 31]. In order to understand the catalytic effect of the BF_3• Et_2O additive we have performed DFT based calculations for the assumed rate-determining step. Since our experimental evidences suggested the existence of a fast pre equilibrium, the mechanism of the active catalytic complex formation has not been investigated in details (Fig. 5.)

Path A (Fig. 5., blue) represents our lowest energy pathway in the absence of BF_3• Et_2O with the overall activation energy of 23.8 kcal/mol. This path features a neutral transition state. We note that the mechanism where an acetate ion dissociates before the C-H activation requires very high activation energy (50 kcal/mol) therefore it has been excluded from discussion.

Path B (Fig. 5., red) shows that in the presence of Lewis acid, OEt_2 - acetate ligand exchange can be assumed between Pd and the boron center. This mechanism is overall 3.4 kcal/mol more favorable than the previous pathway. Even more favorable path can be obtained if only neutral species are assumed (Path C, Fig. 5., green). Coordination of BF_3 to the *trans* acetate ligand (relative to the aryl ring) can further enhance the reaction by increasing the charge on the Pd atom without providing ionic substances. The overall activation free energy of the path is 14.5 kcal/mol. It is important to note that the presented barrier heights are calculated assuming the presence of $Pd(OAc)_2$ in the solvent. However, its di- and trimerization on nonpolar solvents can be assumed, which may further increase the barrier by the stability of the dimer or trimer. We have calculated the kinetic isotope effect for path C. Our approximate KIE calculation based on the Back-of-an-envelope TST theory yielded k_H/k_D=5.17.

Beside the calculation results, we performed simple experimental kinetic studies. First, coupling reactions of H_5-acetanilide and D_5-acetanilide with 4-fluorobenzaldehyde in the presence of 7.2 % BF_3•Et_2O under the previously used reaction conditions were performed in separate vessels, to determine the time-conversion curves (Fig. 6.). We found difference in the reaction rates: with the replacement of hydrogen atoms to deuterium in the aromatic core the reaction rate decreased, ie. the coupling took place faster in case of H_5-acetanilide. These findings suggest hydrogen atom preference in the C-H activation in perfect accord with the primary kinetic isotope effect predicted by the calculations.

Kinetic isotope effect was also examined by intermolecular competition studies. The palladium catalyzed coupling reactions of the anilides and aldehyde were performed under the previously used catalytic conditions with simultaneous addition of acetanilide and its D_5 analogue into the same reaction mixture in 1:1 ratio (**Error! Reference source not found.** 7.). In these studies strong isotope effect has been experienced by NMR monitoring. The protium isotopomer has been converted to the product significantly faster than the deutero analogue. Based on our experimental estimate, the k_H/k_D is in the range of 3.4 ±1.1 considering the accuracy of integration of the peaks in the NMR spectra.

The measured isotope effect obtained in the intermolecular competition experiment, the results of the parallel reactions of H_5 and D_5-acetanilides in separate vessels and the calculation results suggests that the C-H activation takes place in the rate determining step as it was found earlier for similar systems experimentally [36] and by calculation [37].

3.4. Application of Lewis acids in other C-H activation reactions

In continuation of our studies we wished to expand the Lewis acid acceleration to other palladium catalyzed C-H activation processes. (Fig. 8) Aryl amides and N-aryl ureas are often reported in *ortho*-olefination since the discovery of the Fujiwara-Moritani reaction[51-54]. These transformations usually prefer benzoquinone as oxidant, but there are available examples for mild methods using ^{t}BuOOH instead, which we have applied previously.

Acetanilide was subjected to palladium acetate catalyzed Fujiwara-Moritani type coupling reaction with several alkene reactants in the presence and absence of Lewis acidic $AgBF_4$ additive at 30°C in DCM. Unactivated olefins such as isoprene did not afford any C-H activation product, but the coupling reaction with styrene was accelerated by the silver salt, and 37% conversion was reached after 24 hours. Significant Lewis acid acceleration was observed in case of methyl acrylate. The coupling of acetanilide with methyl acrylate without Lewis acidic additive did not yield the desired product, but in the presence of $AgBF_4$ the conversion increased up to 74%. Butyl acrylate was an effective coupling partner even in the absence of Lewis acid, but together with $AgBF_4$ the conversion was increased from 50% to 82%.

Based on recent literature[25, 55, 56] ureas can be used as directing groups in mild transformations leading to *ortho*-olefinated products. We examined several additives to explore the scope of Lewis acid activation. *N*-(4-methyl)phenyl, *N,N*-dimethyl urea was reacted with methyl and butyl acrylate in the presence of catalytic amount of Lewis acids (see Table 1.). Without any additive (entries 9,18) no product formation was observed. Among the metal salts that were tested, copper and zinc triflate resulted in the highest conversion (entries 3,4), silver triflate and tetrafluoroborate were less efficient (entries 1,2) and the borane derivatives were also ineffective (entries 7,8). Butyl acrylate (entries 10-18.), was more reactive than methyl acrylate but only slight conversion increase was seen in all cases and maximum of 39% conversion was reached with $Zn(OTf)_2$.

For the sake of better conversions, we replaced the TBHP oxidant with benzoquinone, which is a usual, common oxidant utilized in Fujiwara-Moritani type reactions [57, 58]. An elevated amount of the Lewis acids was applied imitating the usual conditions with Brønsted acids as co-catalysts in C-H activation processes (Table 2).

Acrylic esters did not react with N-phenyl, N, N-dimethyl urea under the applied catalytic conditions in the absence of Lewis acid (entries 8,15). If the Lewis acidic additives were added, good to excellent conversions were reached. Silver tetrafluoroborate and perchlorate were the most effective, leading to 91 and 70% conversion (entries 6, 7), boron trifluoride in this case resulted in 45% conversion (entry 3) and copper triflate provided similar results (48%, entry 5). However, zinc triflate did not accelerate the reaction at all. The same substrate with the more reactive butyl acrylate showed similar tendencies. Silver tetrafluoroborate afforded 88%, silver perchlorate 77% conversion (entries 13, 14). Interestingly, copper triflate was inactive but zinc triflate gave 87% conversion (entries 11,12). Boron trifluoride enabled 62% conversion (entry 10). The more electron rich N-(3-MeO)phenyl, N, N-dimethyl urea alone reacted with methyl acrylate in the absence of any additive, and the desired product was formed in 15% conversion (entry 15). In the presence of tris(pentafluoro)phenyl borane, the formation of the coupled product was not observed. Finally, we found that the addition of boron trifluoride, silver tetrafluoroborate, silver perchlorate or copper triflate resulted full conversion of the transformation (entries 17, 19-21). In these experiments we established that the Fujiwara-Moritani reaction can be achieved efficiently in the presence of benzoquinone oxidant in the presence of Lewis acidic additives.

4. Conclusion

In summary, we examined the beneficial effect of different types of Lewis acidic additives on palladium catalyzed C-H activation reactions. *Ortho*-acylation by aldehydes and ketocarboxylic acids and *ortho*-olefination by acrylic esters and styrene was achieved using acetanilide and aromatic urea derivatives as substrates. When anilides were coupled with aldehydes the activity of palladium acetate and trifluoroacetate, was increased with catalytic amount of BF_3•Et_2O additive. We demonstrated that Lewis acidic electron deficient triaryl borane, trihalo boranes and inorganic metal salts are suitable for the acceleration of C-H activation reactions. Amongst the inorganic Lewis acids silver, copper and zinc salts with weakly coordinating anions proved to be applicable additives for rate acceleration of the palladium catalyzed process. With the aid of DFT calculations we explained the catalytic effect of Lewis acids on the direct coupling and determined primary kinetic isotope effect. Additionally, KIE experiments also showed light atom preference in C-H activation and suggest that being the rate determining step. In conclusion, the palladium catalyzed C-H activation reaction of aromatic amide and urea derivatives can be accelerated with catalytic amount of Lewis acidic additives.

Acknowledgements

This work was supported by the “Lendület” Research Scholarship, HAS (LP2012-48/2012).

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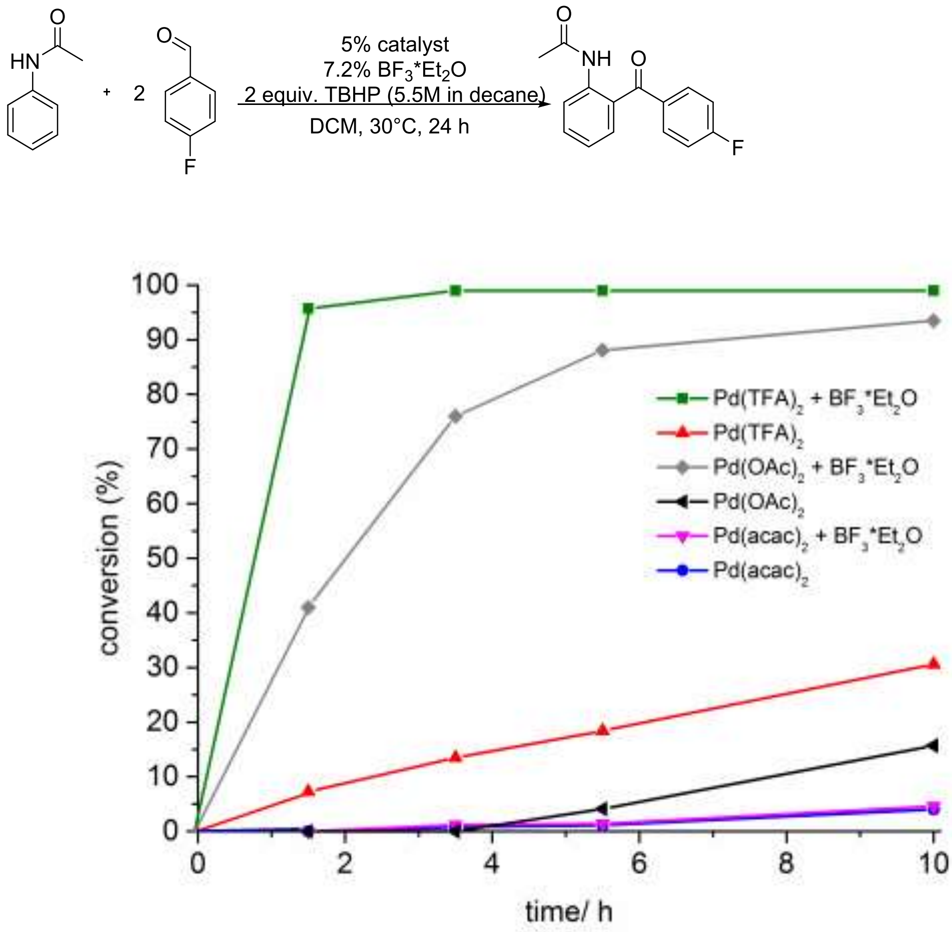


Fig.1. Accelerating effect of BF_3•Et_2O on the palladium catalyzed C-H activation reaction (conversion based on GC FID results).

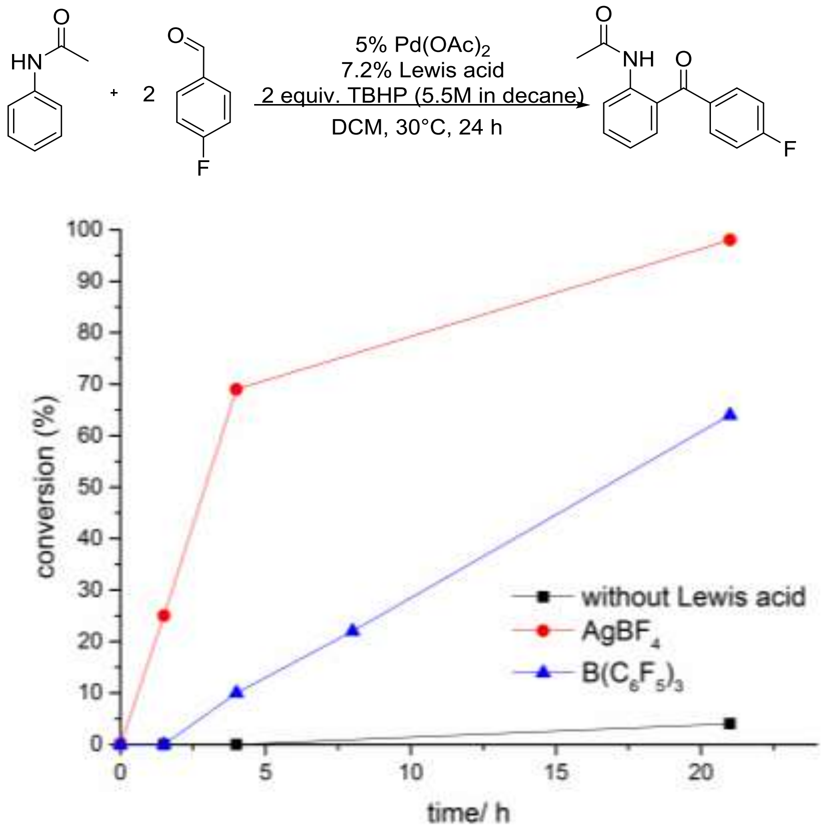


Fig. 2. Monitoring of the coupling reactions catalyzed by $Pd(OAc)_2$ with GC FID analysis.

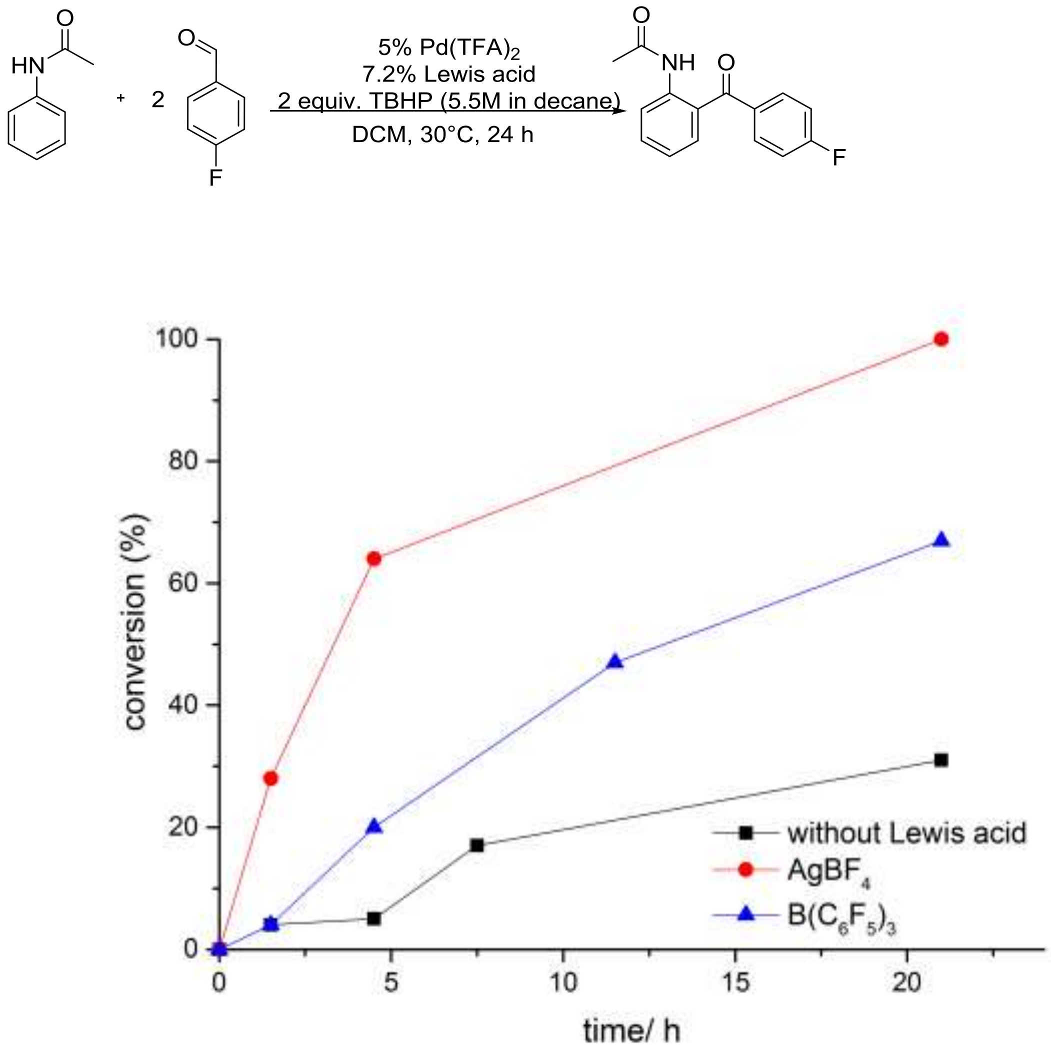


Fig.3. Monitoring of the coupling reactions catalyzed by Pd(TFA)$_2$ with GC FID analysis.

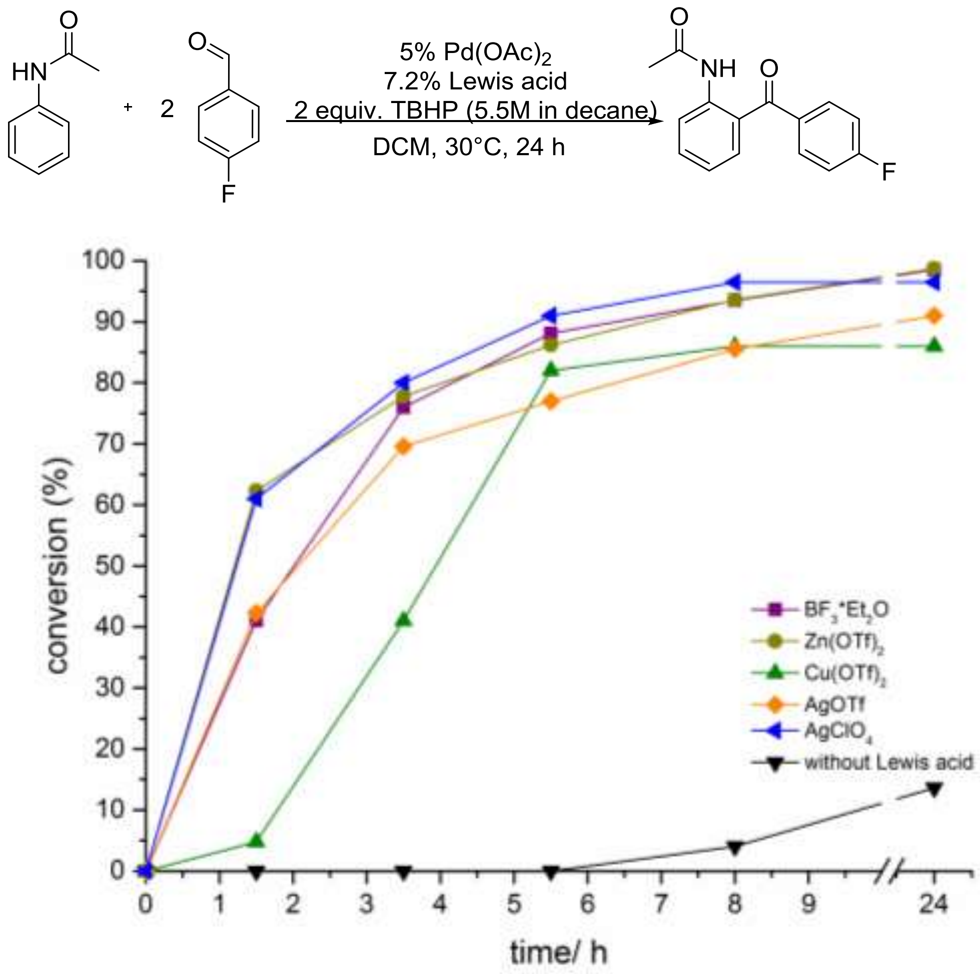


Fig. 4. Profiles of the conversions at the initial stage of the reaction with different Lewis acidic additives.

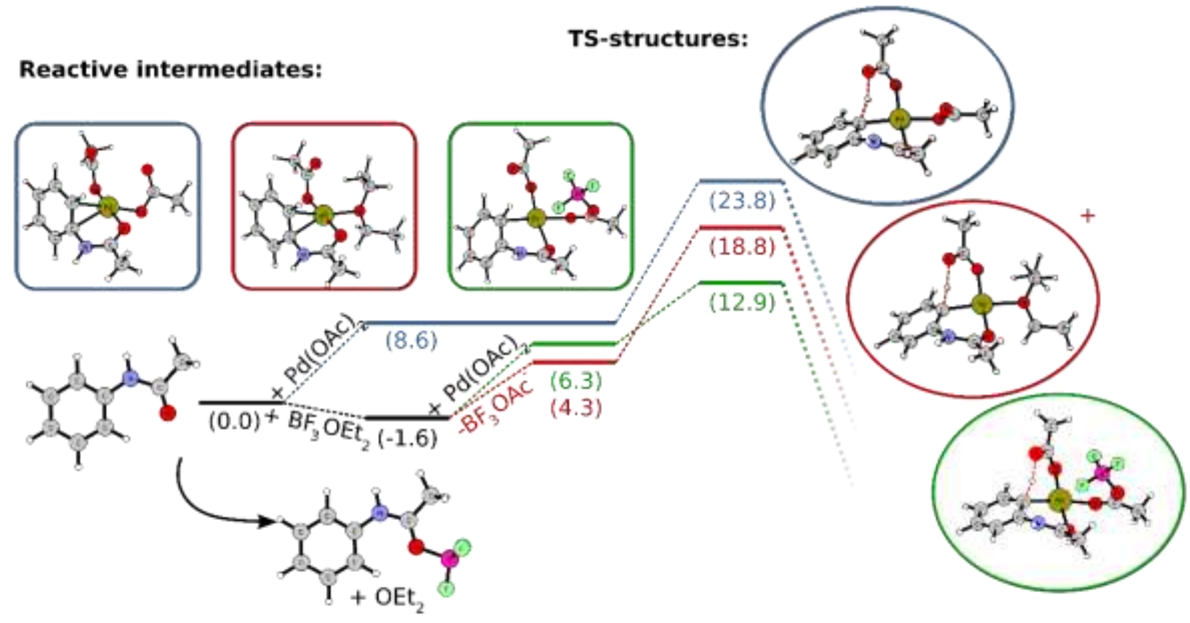


Fig. 5. Free energy profile and relevant structures along three postulated C-H activation mechanisms. Pathways A, B and C are depicted with blue, red and green lines, respectively. Values in parentheses are Gibbs free energies in kcal/mol units.

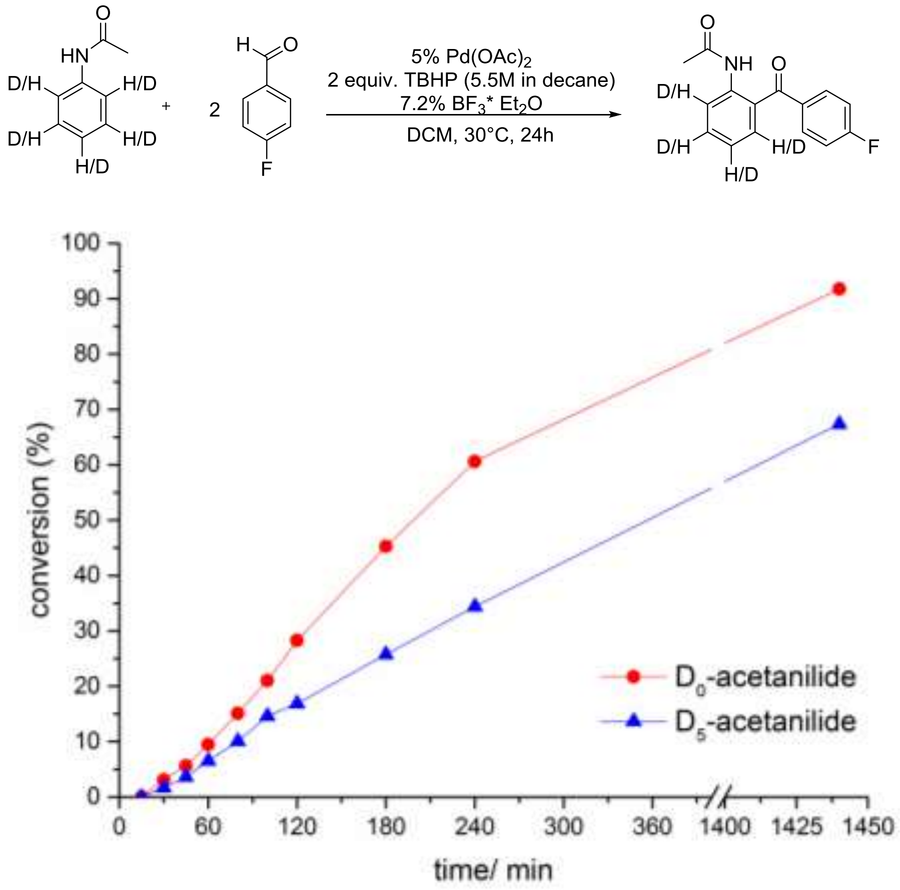


Fig. 6. $Pd(OAc)_2$ catalyzed *ortho*-acylation reactions of H_5 and D_5-acetanilide in the presence of boron trifluoride.

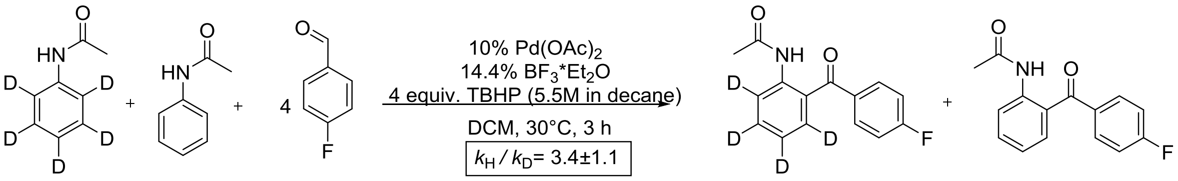


Fig. 7. Intermolecular Kinetic Isotope Effect in the *ortho*-acylation of acetanilides.

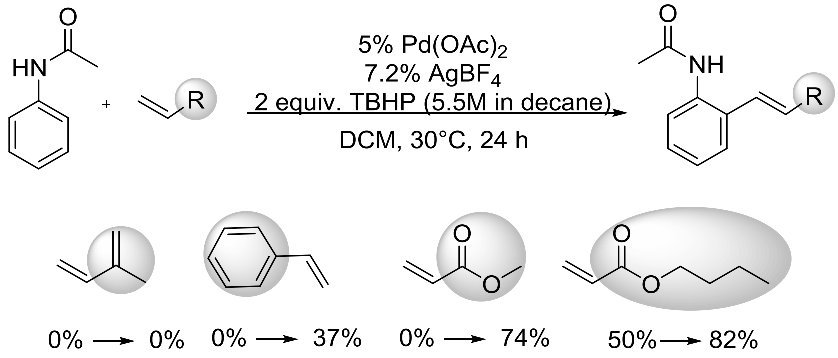
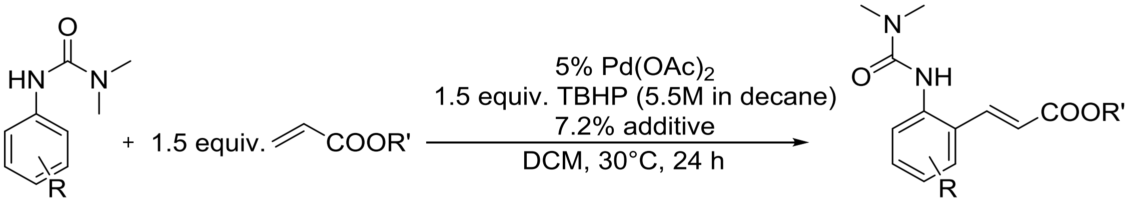


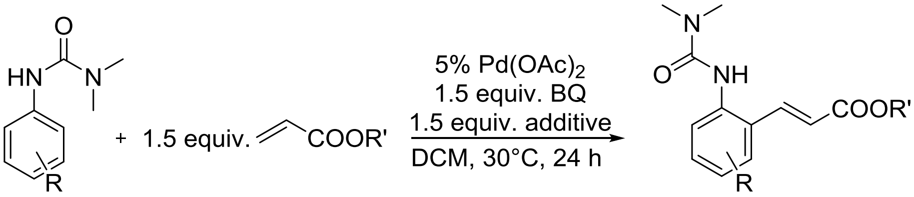
Fig. 8. Silver tetrafluoroborate as activating additive in the catalytic *ortho*-directed olefination of acetanilide. Conversions measured by GC FID analysis.

Table 1. Different Lewis acids in catalytic quantity for the *ortho*-olefination of aryl urea derivatives with acrylic esters



#	R	R’	additive	conversion (24 h)
1	4-Me	Me	$AgBF_4$	7.5%
2	4-Me	Me	AgOTf	11%
3	4-Me	Me	$Cu(OTf)_2$	19%
4	4-Me	Me	$Zn(OTf)_2$	22%
5	4-Me	Me	$Zn(ClO_4)_2$	0%
6	4-Me	Me	BCl_3	0%
7	4-Me	Me	$BF_3•Et_2O$	13%
8	4-Me	Me	$B(C_6F_5)_3$	4%
9	4-Me	Me	-	0%
10	4-Me	Bu	$AgBF_4$	15%
11	4-Me	Bu	AgOTf	18%
12	4-Me	Bu	$Cu(OTf)_2$	22%
13	4-Me	Bu	$Zn(OTf)_2$	39%
14	4-Me	Bu	$Zn(ClO_4)_2$	35%
15	4-Me	Bu	BCl_3	3%
16	4-Me	Bu	$BF_3•Et_2O$	36%
17	4-Me	Bu	$B(C_6F_5)_3$	4%
18	4-Me	Bu	-	0%

Table 2. Different Lewis acids in equimolar quantity in the *ortho*-olefination of aryl urea derivatives with acrylic esters



#	R	R’	additive	conversion (24 h)
1	H	Me	-	0%
2	H	Me	$B(C_6F_5)_3$	0%
3	H	Me	$BF_3 \bullet Et_2O$	45%
4	H	Me	$Zn(OTf)_2$	0%
5	H	Me	$Cu(OTf)_2$	48%
6	H	Me	$AgClO_4$	70%
7	H	Me	$AgBF_4$	91%
8	H	Bu	-	0%
9	H	Bu	$B(C_6F_5)_3$	0%
10	H	Bu	$BF_3 \bullet Et_2O$	62%
11	H	Bu	$Cu(OTf)_2$	4%
12	H	Bu	$Zn(OTf)_2$	87%
13	H	Bu	$AgClO_4$	77%
14	H	Bu	$AgBF_4$	88%
15	3-OMe	Me	-	15%
16	3-OMe	Me	$B(C_6F_5)_3$	0%
17	3-OMe	Me	$BF_3 \bullet Et_2O$	100%
18	3-OMe	Me	$Zn(OTf)_2$	32%
19	3-OMe	Me	$AgBF_4$	100%
20	3-OMe	Me	$AgClO_4$	100%
21	3-OMe	Me	$Cu(OTf)_2$	100%