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C–H Functionalizations by Palladium Carboxylates: The Acid Effect

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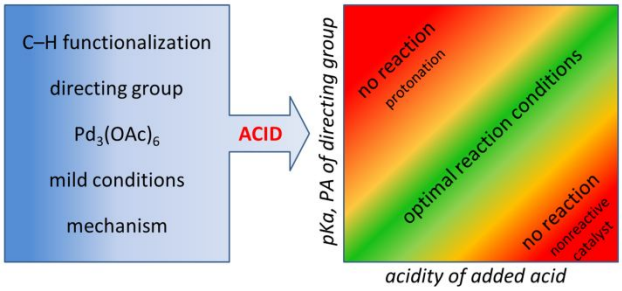


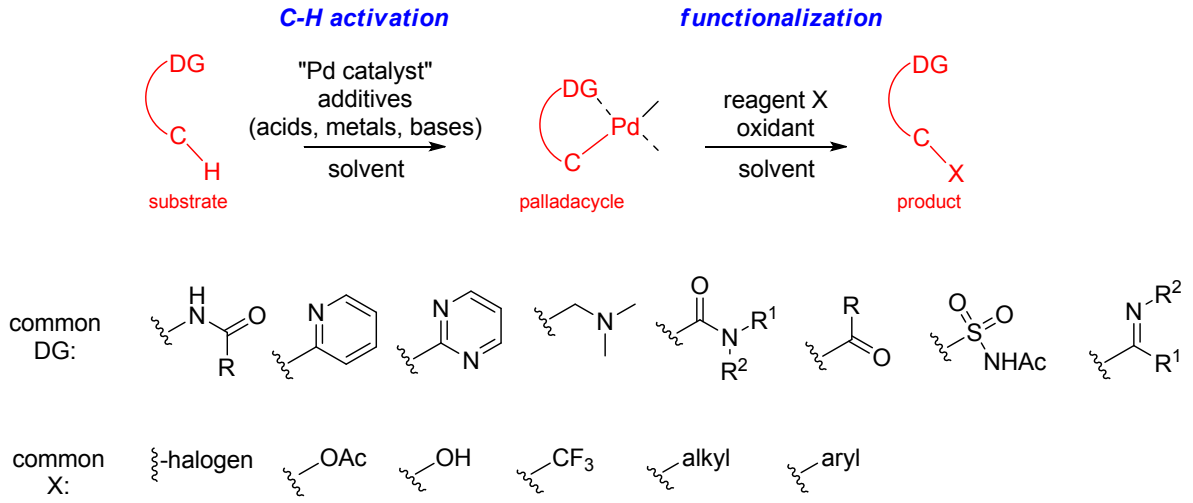
KEYWORDS C–H activation, cyclopalladation, C–H functionalization, reaction mechanism, carboxylic acids, DFT calculations

ABSTRACT Finding optimal reaction conditions is usually complex, requires many experiments and is therefore demanding in terms of human, financial and environmental resources. This work provides a simple workflow for easier design of popular palladium catalyzed C–H functionalization reactions, where the active palladium catalysts contain carboxylate ligands. The key factor for optimizing reaction conditions is to find a balance between two opposing effects of the carboxylic acid in the reaction mixture; generation of more reactive palladium catalyst *vs.* deactivation of substrate by its protonation.

INTRODUCTION

Palladium catalyzed C–H functionalization reactions controlled by directing groups (DG) are used for facile approach to compounds with new C–C and C–heteroatom bonds[1] (Scheme 1) that find application as organic intermediates, pharmaceuticals, agrochemicals or natural products analogues.[2] While this reaction has a broad application scope, the optimal reaction conditions can vary substantially. Therefore, researchers optimize reaction conditions for each individual system. However, the

complexity of the reaction mixtures and incomplete understanding of the reaction mechanism often make the search for optimal reaction conditions a rather elaborate pursuit. A more efficient way is to design reaction conditions based on the given reaction mechanism and recognition of the effects of the individual reaction components on this mechanism.

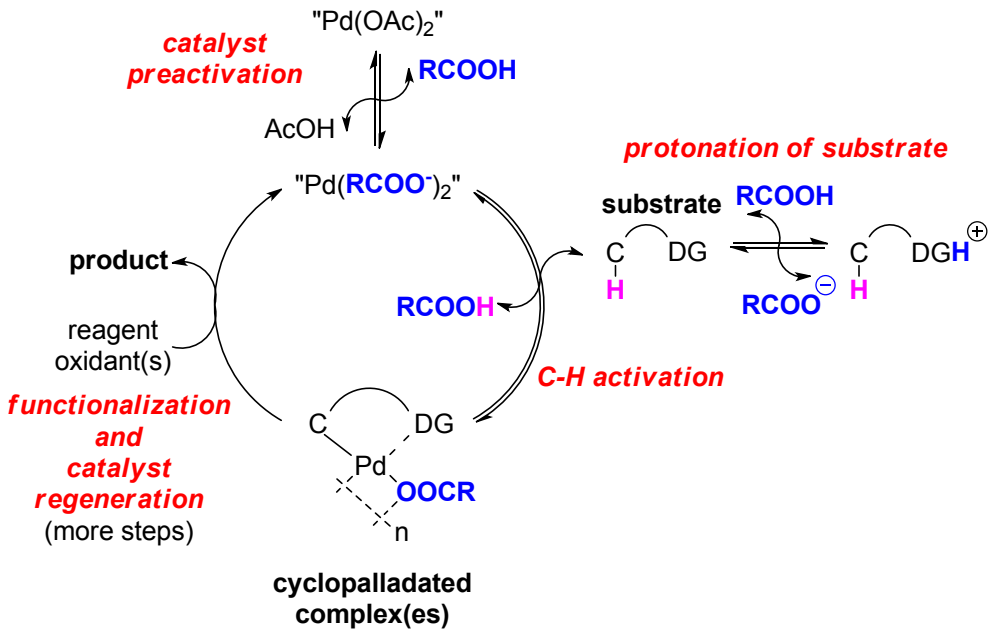


Scheme 1. General scheme for the transition metal assisted C–H functionalization reactions showing examples of typical directing (DG) and functionalizing groups (X).

In general, catalytic C–H functionalization consists of several main steps:[3] First, the formation of a precatalyst, where palladium catalyst reacts with additives (mainly acids or other metal salts) to give the catalytically active species. Second, the C–H activation step where a directing group brings palladium to the proximity of the given C–H bond and subsequently the hydrogen atom is substituted for palladium *via* concerted metalation−deprotonation (CMD) transition state. This leads to the formation of palladacycles mainly existing in monomeric or dimeric forms, although polynuclear species were observed, too.[4] In the third (multiple) step, the reaction of palladacycle

with a reagent leads to the formation of the product. Finally, the palladium precatalyst is regenerated and enters into a new catalytic cycle.

In principle, each reaction component is primarily intended to be responsible for one reaction step. However, it can affect other reaction steps, too. Until now, there has been no all-embracing study on how reaction components affect palladium promoted C–H funcionalizations. However, some dedicated reactivity studies do exist. For example, Sanford[5] investigated effects of the directing groups in C–H bond functionalization. Several groups investigated the effect of added substituted acetic[6] or benzoic acids[7] on functionalization efficiency. Finally, much theoretical work exists to rationalize the reaction mechanisms of carboxylate assisted C–H functionalization as Davies recently summarized.[8]



Scheme 2. Simplified scheme for the palladium carboxylates catalyzed directing group assisted C–H functionalization reactions showing potential places of action of added carboxylic acids.

Deeper insight into the typical reaction scheme (Scheme 2) suggests that added carboxylic acids are the key factor for reactivity control. These acids may influence reaction by at least five different ways: (1) form a precatalyst from palladium acetate; (2) affect the reactivity of palladium in the C–H activation step; (3) protonate substrate; (4) affect oxidation potentials of palladacycles and thus their reactivity in functionalization step;[9] (5) exchange anions in other common reagents; e.g., $PhI(OAc)_2$ or $Cu(OAc)_2$.

Here, we are going to show the effect of added carboxylic acids on key reaction steps and how these findings can be used for simplifying of reaction conditions screening and for facilitating reactions under milder conditions.

RESULTS AND DISCUSSION

Effect of carboxylic acids on rate of precatalyst formation

As was shown in our previous work,[10] addition of trifluoroacetic acid (TFA) to the $Pd_3(OAc)_6$ causes sequential exchange of acetate for trifluoroacetate ligands leading to more reactive $Pd_3(TFA)_6$. This preactivation step is necessary for the C–H activation of acetanilides and is completed within few minutes. In the next series of ^{1}H NMR kinetic experiments, we examined the influence of acid strength on the exchange rate (Fig. S1). We compared rates of the ligand exchange for five different carboxylic acids: trifluoroacetic (pK_a –0.26, (ΔPA_{exp} 25.8),[11,12] trichloroacetic (pK_a 0.77), dichloroacetic (pK_a 1.29, ΔPA_{exp} 20.3), chloroacetic (pK_a 2.86, ΔPA_{exp} 12.4) and tetradeuteroacetic. The half-lives for the individual exchanges are summed in Table 1. Comparison of the results shows that the rate of ligand exchange increases with acidity of carboxylic acid

and is in good correlation with proton affinity (ΔPA_{exp}) values. Especially in the case of weaker acids the catalyst preactivation can be a kinetically significant step.

Table 1. Physical constants of substituted carboxylic acids and measured half-lives of the exchange of acetate ligands in $Pd_3(OAc)_6$ for different carboxylate ligands.

Acid	p*K*a	ΔPA_{exp}	ΔH_D^0 [13]	$t_{1/2}$ (s)[a]
TFA	-0.26	25.8	322.7	16
trichloroacetic	0.77			15
dichloroacetic	1.29	20.3	328.4	30
chloroacetic	2.86	12.4	335.4	91
methoxyacetic	3.53	6.6	341.9	
Ac-Val-OH	≈ 3.7[b]			
acetic	4.76	0	348.5	
CD_3COOD				304

[a]The values are obtained from ^1H NMR monitoring of decrease of overall amount of acetate ligands coordinated to palladium.

[b]Value is expected to be in a similar range as Ac-Gly-OH (pK_a = 3.67) and Ac-Ala-OH (pK_a = 3.70).[14]

Effect of acids on reactivity of starting material

Carboxylic acids in reaction mixture can strongly affect reactivity of substrates by protonation. Shi and coworkers showed that *N*,*N*-dimethylbenzylamines (DMBA) can be C–H activated in the presence of a suitable amount of acetic acid. However, in the presence of more acidic TFA the reaction does not occur.[6a] We studied this effect by NMR titration of different substrates by various carboxylic acids (Figures S1-5). Very illustrative is the comparison of shapes of titration curves in the case of titration of *N*,*N*-dimethylbenzylamine ($pK_a \approx 9$) with acetic, dichloroacetic and trifluoroacetic acids (Fig. 2). The titration curves show that in the case of strong trifluoroacetic and dichloroacetic acids the break occurs at acid/DMBA ratio = 1. This means that *N*,*N*-dimethylbenzylamine is fully protonated after addition of 1 equivalent of acid. Full protonation is further confirmed by the shapes of NMR signals of CH_2 and CH_3 groups of *N*,*N*-dimethylbenzylamine. These signals change from singlets at the beginning of the titration to doublets after protonation (see inset in Figure 1). Contrary to this, titration

curve obtained for acetic acid is relatively smooth without any sharp break, thus indicating a weaker association.

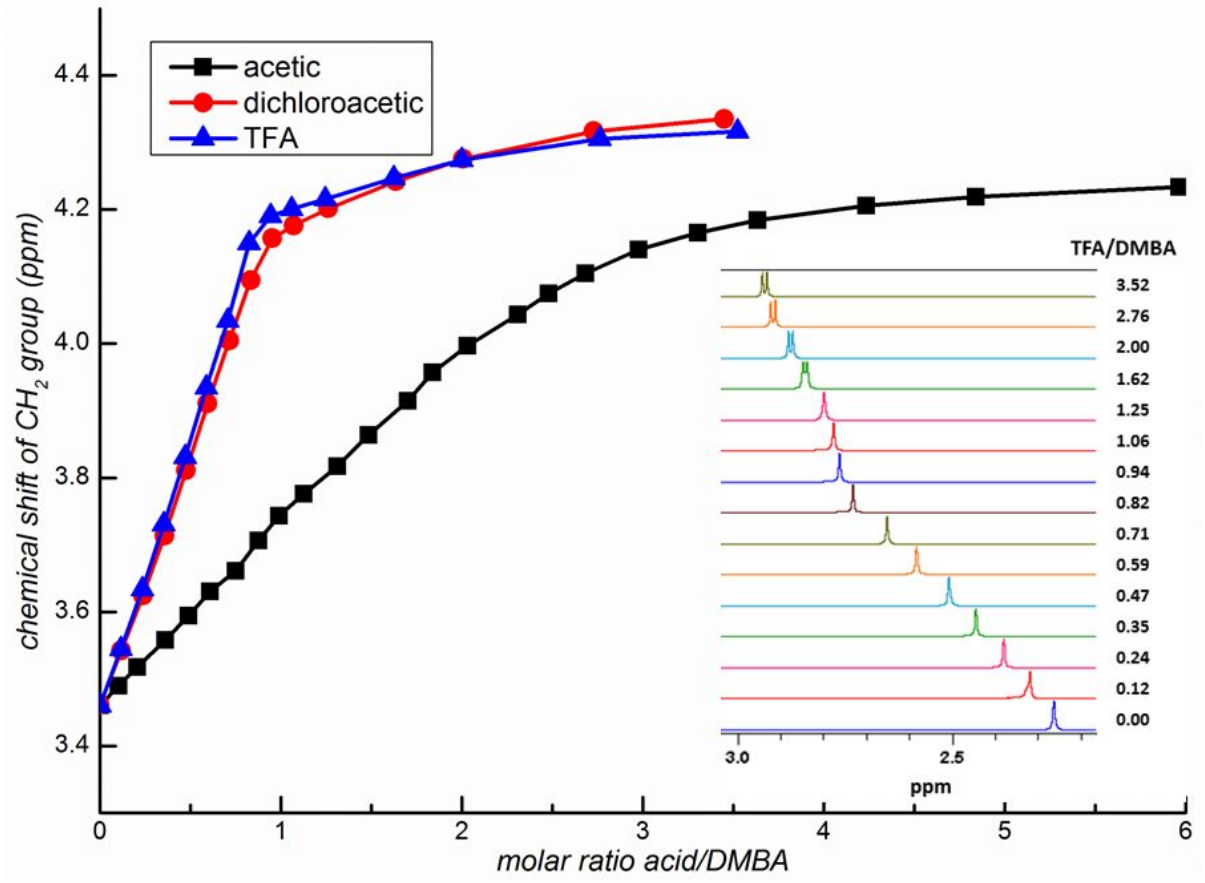


Figure 1. Changes of ^{1}H NMR chemical shifts of benzylic protons caused by titration of *N*,*N*-dimethylbenzylamine (DMBA) by acetic (black squares), dichloroacetic (red circles) and trifluoroacetic (TFA) (blue triangles) acids in CD_2Cl_2. Inset shows changes in chemical shifts and signal shapes in the case of titration by TFA.

To quantify the measured data, we fitted the titration curves using BindFit software.[15] The best match was obtained for substrate/acid ratio 1:2 (Figures. S6-14). The

calculated association constants are summarized in Table 2 and in more detail in Table S1. The data reveal a strong association between the most basic DMBA and stronger acids (TFA and dichloroacetic). In the case of 2-phenylpyridine (Ph-Py) (pK_a ≈ 4.4), the stronger association is observed only in the case of TFA. Finally, there is no strong association in the case of 3-bromoacetanilide (3-Br-acetanilide) (pK_a ≈ – 4.4). These data illustrate why DMBAs are non-reactive in reaction mixtures containing strong acids. More importantly, it can be concluded that addition of a too strong acid to the reaction mixture causes protonation of the substrate and thus retardation of the reaction.

Table 2. Values of first association constants obtained from NMR titrations by BindFit software.

	DMBA	Ph-Py	3-Br-acetanilide
Acid	$K_{1,1}$ (M^{-1})	$K_{1,1}$ (M^{-1})	$K_{1,1}$ (M^{-1})
acetic	0.67±0.03	10±1	6±2
dichloroacetic	238±89	55±8	16±2
TFA	424±361	975±585	10±1

Influence of added acids on C–H activation step

The DFT calculations provide a view on the detailed mechanism of the C–H activation reaction and illustrate the effect of the additional acids on the reactivity of the palladium catalyst. Here we report reaction profiles for two substrates located at the opposite sides of the acidity scale; acetanilide ($pK_a \approx -4.4$) and *N*,*N*-dimethylbenzylamine ($pK_a \approx 9$). For simplification, both models are based on mono-palladium species. However, the reactivity trends should remain identical in the case of polynuclear species that were proposed to be the key species in some cases.[4]

The C–H activation of acetanilide (Fig. 2) begins with *O*-coordinated complex **1**.[16] The first reaction step is an electrophilic attack of palladium cation at the aromatic system and formation of π-complex **2**. Then, palladium slips to the *ortho* position of acetanilide to form σ-complex **3**. Next, proton is transferred *via* agostic **TS** to form palladacycle **4**. This further conformationally relaxes to give palladacycle **5**. The effect of different basicity of carboxylate ligands is illustrated in Figure 2.

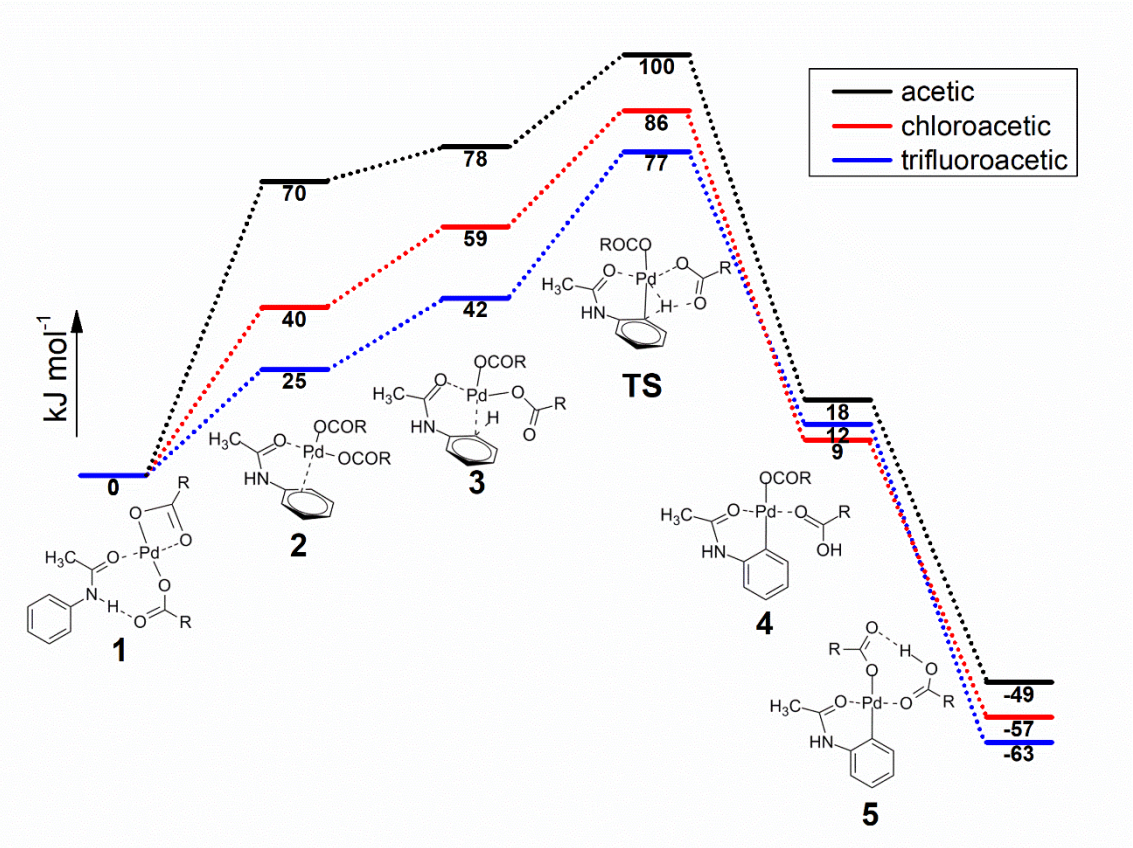


Figure 2. Reaction profile (relative Gibbs energies in DCM at 298 K in kJ mol^{-1}) of C–H activation step calculated for reaction of acetanilide with palladium acetate (black), chloroacetate (red) and trifluoroacetate (blue).

The carboxylate ligand is an electron acceptor and therefore makes palladium more electrophilic.[17] The calculated NPA charges on Pd in monomeric palladium(II) carboxylates are growing in order 0.385 (acetate) 0.392 (chloroacetate) 0.405 (trifluoroacetate). The more electron-withdrawing carboxylate ligands facilitate formation of the π- and σ–complexes and thus make the pathway towards C–H activation more

energy accessible (cf. Figure 2). At the same time, the more electron-withdrawing carboxylate ligand stabilizes better the organopalladium product and makes the C–H activation step more exothermic. Hence overall, the calculations suggest that carboxylate ligands formed from stronger acids favor the C–H activation reactions kinetically as well as thermodynamically.

On the other hand, the larger basicity of less electron-withdrawing carboxylate ligand make the elementary hydrogen atom transfer from carbon to oxygen more exothermic (step 3 → 4). The key interatomic distances in transition structures obtained with different carboxylate ligands nicely illustrate this effect. The less electron-withdrawing carboxylate ligands favor early transition structures with geometries closer to the σ–complexes (Figure 3). Conversely, the more electron withdrawing ligands favor late transition structures with more developed O–H and Pd–C bonds.

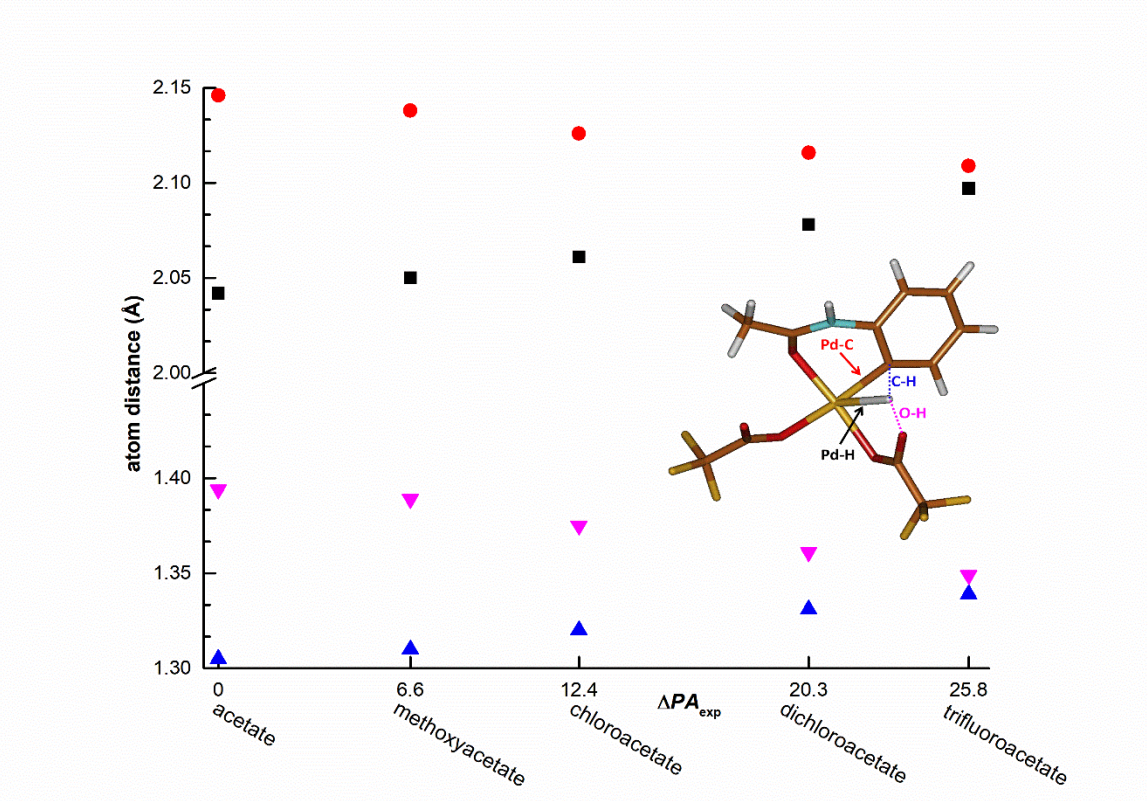


Figure 3. Important atom distances Pd–H (black squares); Pd–C (red circles); C–H (blue triangles); O–H (violet triangles) in agostic transition states calculated with different carboxylate ligands in dependence on ΔPA_{exp}.

Reaction profiles and atom distances calculated for C–H activation of *N,N*-dimethylbenzylamine (Figure S15) show the very same trends as the results for acetanilide.[18] In summary, DFT calculations show that addition of stronger acids to the reaction system facilitates the C–H activation step both, kinetically and thermodynamically. The effect is caused by increased electrophilicity of palladium atom.

Kinetics of C–H activation reactions

Next, we demonstrate the two above-mentioned principles by NMR kinetic measurements. We have studied stoichiometric C–H activation of 3-bromoacetanilide (p*K*a ≈ -4.4) and *N*,*N*-dimethylbenzylamine (p*K*a ≈ 9); two substrates found on the opposite ends of the acidity scale (for details see Experimental section S13). The kinetic profiles of C–H activation of 3-bromoacetanilide are shown in Figures 4a,b. These diagrams illustrate that the rate of C–H activation increases with the increasing acidity strength from dichloroacetic acid to TFA. In the case of weaker chloroacetic or acetic acids the palladium is so unreactive that the reaction does not occur at all. On the other hand, the kinetic profiles of C–H activation of basic *N*,*N*-dimethylbenzylamine (Fig. 4c) show different behavior. With increasing acidity of the additional acid, the conversion of the substrate to the organopalladium complex decreases. The decreased conversion is caused by the added acids that protonate the substrate and thus prevent its coordination to the palladium complex. The protonation is visible in the NMR spectra as the splitting of the signals of CH_2 and CH_3 groups of *N*,*N*-dimethylbenzylamine (Figure

S22) analogous to the splitting in the titration experiments. Furthermore, the amount of unreacted substrate seems to be linearly dependent on PA of the added acids (Figure S24).

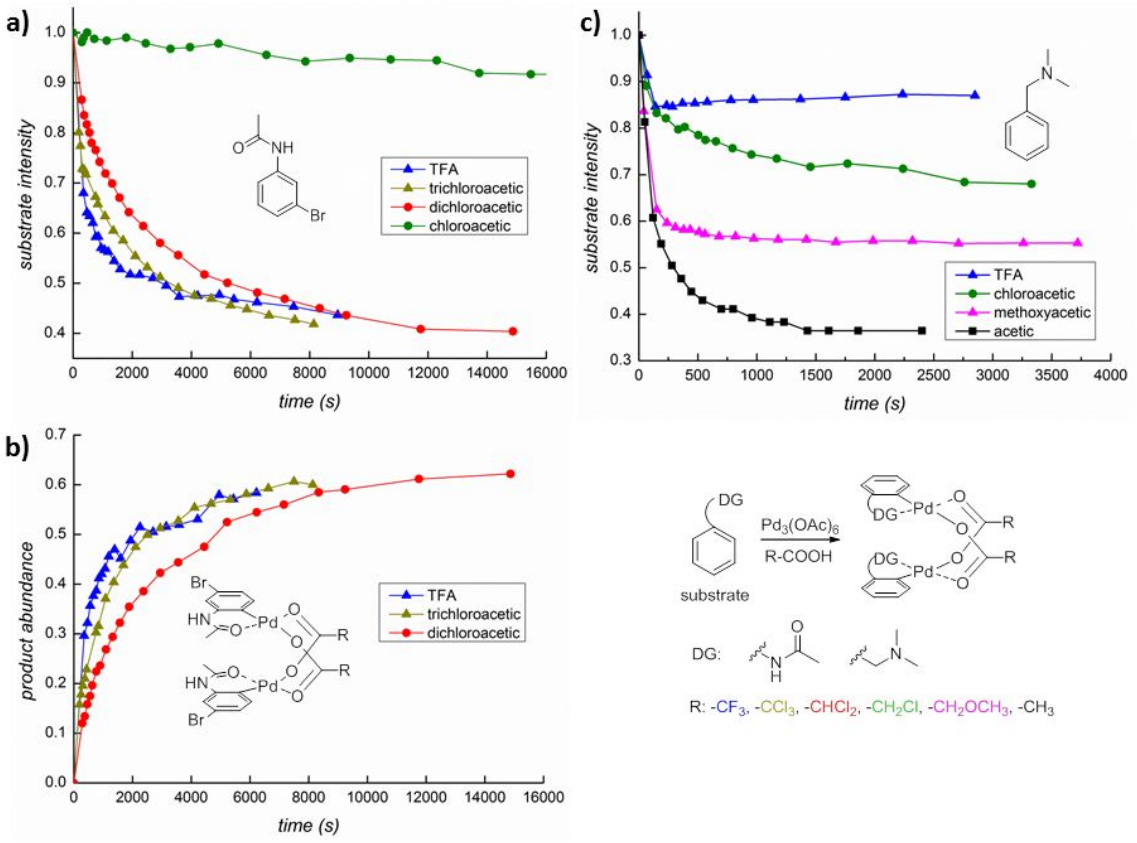


Figure 4. The ^{1}H NMR kinetic profiles of C–H activation of 3-bromoacetanilide (a,b) and *N*,*N*-dimethybenzylamine (c) in presence of palladium(II) acetate (0.66 equiv.) and additional acids (4.4 eq.) in DCM at 25 °C.

Selection of the optimal added acid

The obtained findings illustrate the opposing effects of the added acids. On one hand, addition of strong acids leads to the formation of more active catalyst and thus to acceleration of the reaction. On the other hand, the acid can protonate the substrate which retards the reaction. In other words, optimal added acid should be as strong as possible, but it must not fully protonate the substrate. Finding a balance between these two principles leads to an easier design of optimal reaction conditions.

Good starting point for selecting the optimal additive is to compare acidities of the added acids with acidities of protonated form of the substrate. Obviously, these values should be as close as possible. Using organic solvents for C–H functionalization reactions offers larger selection of suitable acidity parameters. Apart from pK_a known in most cases only in water, these could be for instance PA[11] or ΔH_D^0.[13] We believe that predicted pK_a values from available software like e.g., MarvinSketch[19] provide a sufficient estimate. However, other acidity parameters in solvent of interest can provide more accurate results. For an easier visualization, we will use a tentative diagram in Fig. 5.

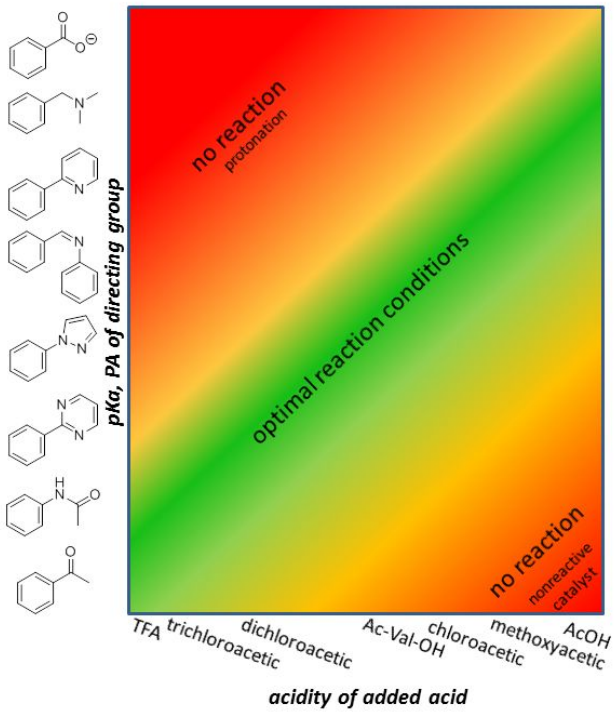


Figure 5. Diagram correlating acidity (in terms of pK_a, PA, ΔH_D^0, etc.) of some typical substrates and added acids with reactivity. The diagram predicts suitable added acids for C–H activation of the substrates.

The diagram correlates acidity parameters for typical substrates with acidity of the added acids. Red areas correspond to the improper substrate/additive combination due to the protonation of the substrate (left upper corner) or not enough reactive catalyst (right bottom corner). The green area corresponds to the optimal substrate/additive combinations enabling reactions to run fast even at lower temperatures.

The idealized workflow for selection is as follows:

1) selection of substrate of interest;
2) selection of the solvent;
3) prediction or measurement of substrate pK_a (or other acidity parameter);
4) selection of appropriate additional acid;
5) final optimization of reaction conditions including other reaction components and temperature.

This workflow can be used under the assumption that the added acid cannot react with substrate, functionalizing reagents or product.

Proof of concept experiments in catalytic arrangement

To validate the concept, we determined yields of several C–H functionalization reactions in dependence of acidities of the added acids. We have chosen two substrates located on the opposite sides of the basicity scale (acetanilide and 2-phenylpyridine). To obtain consistent data with the previous mechanistic experiments, we tried to find reactions proceeding in DCM at room temperature. Even though these are not optimum conditions found in literature and the observed yields are thus reduced.

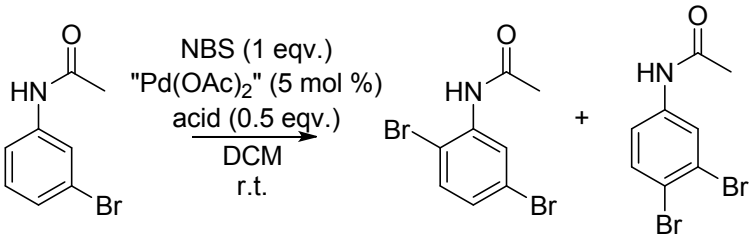
Furthermore, we summarized the effect of the added acids on the yields for some of the typical substrates found in literature (S23-26). We are aware of the complex nature of the reaction mixtures and of the fact that the added acids may affect also other elementary reactions than just C–H activation and substrate protonation. Nevertheless, this is always the case and the selected examples give a hint how the basicity of the substrate affects the acid effect.

Acetanilides ($pK_a \approx -4$)

Literature retrieval shows (Table S7-9) that addition of stronger acids like TFA or *p*-toluenesulfonic acids to the reaction mixtures is either necessary or at least improves the yields.[20] Furthermore Brown et al. showed increasing reaction rate with increasing amount of added *p*-toluenesulfonic acid.[21]

According to Bedford[22] the 3-bromoacetanilide is brominated by NBS to give a mixture of *ortho* and *para* brominated products (Scheme 3). The *para* bromination proceeds *via* classical electrophilic aromatic substitution where electrophile is generated by the reaction of NBS with acid. Table 3 shows that chloroacetic and dichloroacetic acids give

the best yields. The *ortho* bromination product is formed predominantly by the palladium catalyzed directed C–H functionalization. Comparison of the yields in Table 3 shows the predicted decrease of the yields of *ortho* bromination with decreasing acidity strength. The same reactivity trend was observed in the case of oxidative acylation of acetanilides inspired by work of Novak and co-workers (Table S3).[20a]



Scheme 3. Bromination of 3-bromoacetanilide using NBS.

Table 3. Yields of bromination of 3-bromoacetanilide determined after 24 hours.

acid	yield[a] *ortho*	yield[a] *para*
TFA	**33 (36)**[b]	28 (27)[b]
trichloroacetic	30	32

dichloroacetic	16	41
chloroacetic	6	37
methoxyaceti	2	34
c		
Ac-Val-OH	0	29
AcOH	0	15

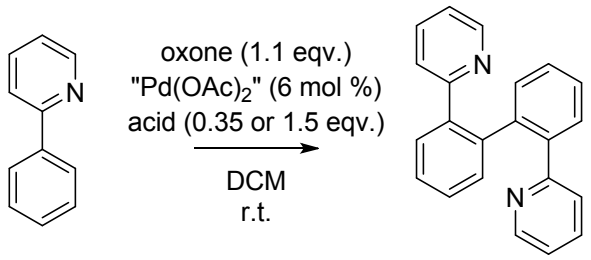
[a] determined by ^{1}H NMR of the crude mixture

[b] isolated yield from independent experiment after 24 hours

2-Phenylpyridines (pK_a ≈ 4.4)

Typical protocols[23] for functionalization of 2-phenylpyridines usually do not use acidic additives. However, some exceptions are known (Table S12).[24] To demonstrate the acidity effect, we followed dimerization of 2-phenylpyridine[25] (Ph-Py) (Scheme 4). The pK_a value of protonated 2-phenylpyridine (4.4 in water) lies between the values of acetic

($pK_a \approx 4.7$) and methoxyacetic ($pK_a \approx 3.4$) acids. In the experiments, we used 0.35 and 1.5 equivalents of acids to see the effects of protonation (Table 4). The results show that in the case of sub-stoichiometric amount of acid, the methoxyacetic acid is the best additive. However, in the case of 1.5 equivalents of the additives, the weaker acetic acid is the most efficient one.



Scheme 4. Dimerization of 2-phenylpyridine.

Table 4. Yields[a] of dimerization of 2-phenylpyridine determined after 4 hours.

Acid	0.35 equiv. acid[c]	1.5 equiv. acid[c]
TFA	9	21

trichloracetic	17	18
dichloroacetic	15	22
chloroacetic	16	23
methoxyaceti c	**47**	20
Ac-Val-OH	35	21
AcOH	21	**54 (50)**[b]
without acid		17

[a] determined by ^{1}H NMR of the crude mixture.

[b] isolated yield from independent experiment after 5 hours

[c] acid equivalents are with respect to 2-phenylpyridine

Further, we followed time dependence of the palladium-catalyzed dimerization with addition of methoxyacetic and acetic acids in detail. In the case of acetic acid, the increasing amount of the acid (from 0 to 1.5 equivalents) correlates with the increasing

yield of the dimerization reaction (Figure S27). Further increase of the amount of acid above 1.5 equiv. does not improve the yield.

In the case of methoxyacetic acid, the best yields were achieved with addition of 0.2–0.4 equivalents of acid with respect to 2-phenylpyridine (Figure S28). The reaction proceeds with 6 mol % of $Pd(OAc)_2$. Hence, for the exchange of acetate ligands by methoxyacetate, we need 0.12 equivalents of the added acid. The results thus suggest that we achieve the best conversion under the conditions that allow ligand exchange, but do not provide a large excess of the free acid in solution. This is in agreement with the presumption that the increasing acidity of the acid facilitates the reaction but reduces amount of available substrate by its protonation. Figure 6 illustrate these observations. At the beginning of the reaction (Figure 6 on the top) the reaction is faster in presence of small amount of methoxyacetic acid. The increasing amount of methoxyacetic acid reduces the yields and acetic acid becomes more efficient additive under such conditions. At long reaction times, acetic acid is the better additive even at the lower concentrations. Finally, in the presence of strong acids, the reaction takes place faster, but with less efficiency.

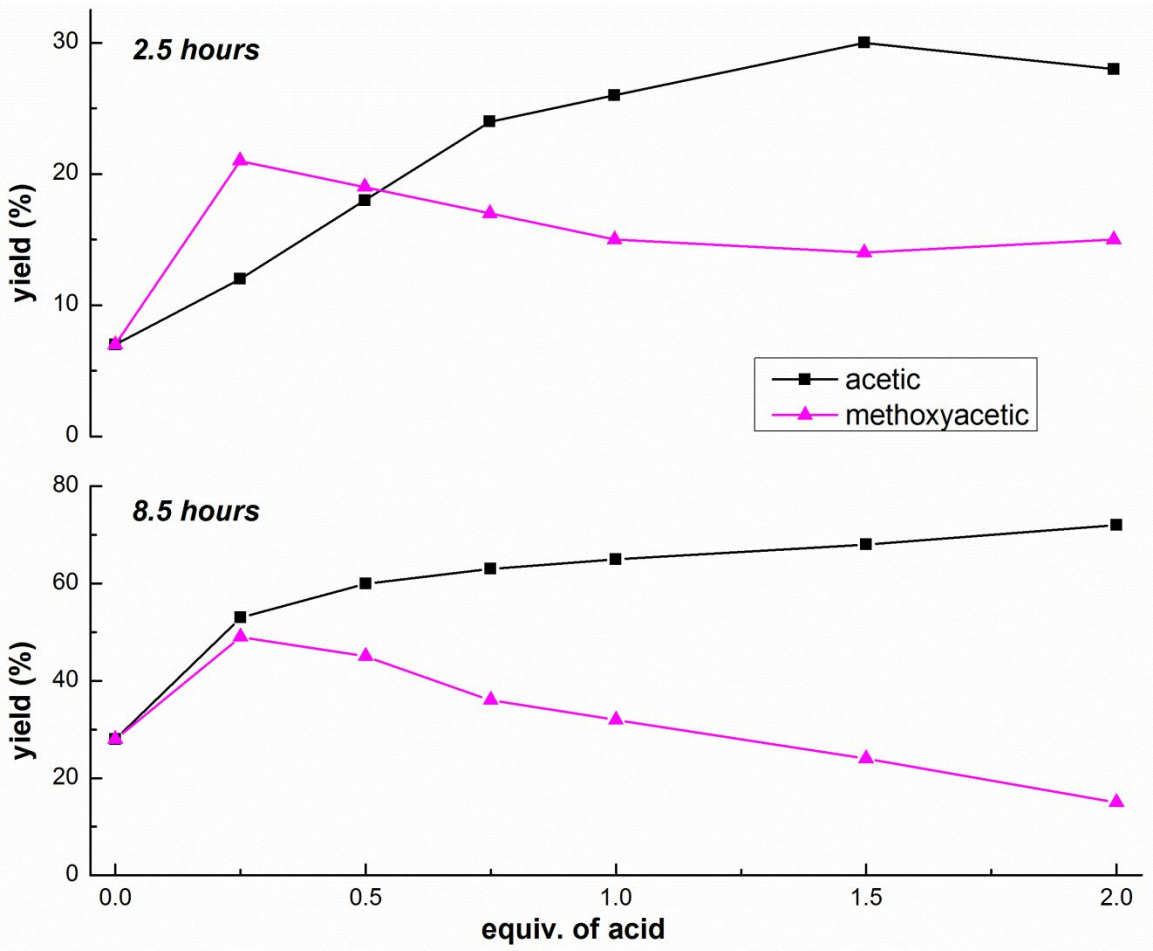


Figure 6. Dependence of yields of dimerization of 2-phenylpyridine determined after 2.5 (top) and 8.5 (bottom) hours on amount of added acetic (black) or methoxyacetic (purple) acids.

The answer to the question "What is the optimal amount of the added acid?" is not straightforward. This depends on the factors such as difference between pK_as of the substrate and expected product or pK_as of the other reaction components. These species can bind the acid more strongly than the substrate and leave it free for the

reaction. Furthermore, the whole reaction system is in equilibrium. Thus non-protonated substrate can be present in the reaction mixture in a small amount even in the presence of strong acids allowing its C–H activation by the reactive catalyst, especially at elevated temperatures.

Recently, mono-*N*-protected amino acids (MPAA) were found to be very efficient additives in this type of reactions.[26] Their role in reaction mechanisms is still a highly discussed topic.[27] Therefore, we included *N*-acetylvaline (Ac-Val-OH) (pK_a ≈ 3.7)[14] into the experiments in order to test, whether part the positive effect of MPAA can originate by their increased pK_a values in comparison to acetic acid. The observed yields in Tables 3,4 suggest that Ac-Val-OH fits into the scale of acids. Thus, its increased ability to activate palladium should be involved in the discussions of the mechanism of action of MPAA.

CONCLUSIONS

This work offers a simple workflow that allows for an easier selection of additional carboxylic acids in palladium carboxylates catalyzed C–H functionalization reactions

assisted by directing groups. The scheme is based on two opposing effects of additional acids; protonation of the substrate and formation of a more active catalyst. The most appropriate additive should have acidity close to the acidity of conjugated acid of the substrate. The comparison of predicted pK_a values has been shown to be sufficient for this approach. Due to the complexity of reaction systems, it is difficult to exactly predict the nature and optimal amount of added acid. However, we illustrated that usage of less common additional acids can help to run reactions with better yields and at lower temperatures. In other words, it helps to improve reaction economy. Furthermore, the positive effect of mono-*N*-protected amino acids is discussed in the context of increased electrophilicity of palladium connected to these ligands. Last but not least, this approach opens up the possibility of protonation driven regioselectivity tuning in substrates containing more directing groups.

EXPERIMENTAL AND COMPUTATIONAL DETAILS

Materials and methods

All the chemicals and solvents were purchased from Acros Organics, Sigma-Aldrich or Fluorochem and used as received. High resolution mass spectra were recorded on a MALDI LTQ Orbitrap XL equipped with nitrogen UV laser (337 nm, 60 Hz, 8-20 μJ) in positive ion mode. The NMR spectra were recorded on a Bruker Avance III 400 MHz or on a Bruker Ascend 500 MHz instruments. Chemical shifts δ are referenced to TMS (δ = 0 ppm) or solvent residual peaks δ(CD_2Cl_2) = 5.35 ppm (^{1}H), δ(DMSO-d_6) = 2.55 ppm (^{1}H).

Ligand exchange experiments In a typical experiment, 10 mg (0.0445 mmol) of palladium(II) acetate was dissolved in 0.7 ml of CD_2Cl_2 in NMR tube and 2 μL trifluoromethylbenzene were added as a standard. The five molar excess (0.223 mmol) of carboxylic acid was added and the ^{1}H NMR kinetics was followed. The rate constants were obtained from the first-order fits of decrease of signals of acetate ligands coordinated to palladium.

Titration experiments In a typical experiment, the carboxylic acids were added in small increments to the solution of 50 μL (0.335 mmol) of DMBA (or other substrates)

dissolved in 0.5 ml of CD_2Cl_2 in NMR tube. The ^1H NMR spectra were recorded after each addition. Chloroacetic and trichloroacetic acids were added in melted form.

Kinetics of C–H activation reactions In a typical experiment, the carboxylic acid (0.3 mmol) was added to the solution of 10 mg (0.045 mmol) of palladium(II)acetate dissolved in 0.4 ml of CD_2Cl_2 (in the case of DMBA containing 5 μL of CH_2Br_2 as a standard) in NMR tube. After 10 minutes the solution of substrate (0.068 mmol) dissolved in 0.1 ml CD_2Cl_2 was added and the ^1H NMR spectra were recorded in increasing time intervals.

DFT calculations All calculations were performed using the B3LYP density functional theory method as implemented in Gaussian09[28] with the D3 dispersion term using the Becke-Johnson damping function.[29] The basis set was a combination of the SDD pseudopotential model for palladium[30] and 6-311++G** for all other atoms. The final energies include solvation free energies in CH_2Cl_2 determined by single-point calculation for the optimized structures using the SMD model.[31]

Characterization of the compounds

2,2'-di(pyridin-2-yl)-1,1'-biphenyl. 2-phenylpyridine (0.275 mmol ,41 μL) was added to the 4 ml vial containing Oxone (0.31 mmol,195 mg), palladium (II)acetate (0.0175 mmol, 3.9 mg,) 2 ml of DCM and 0.41 mmol of acetic acid. The reaction was stirred under air at room temperature for 5 hours. The crude reaction mixture was purified by silica gel column chromatography (ethyl-acetate/hexane). Isolated yield: 21 mg (50 %) of white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.33 (d, ^{3}J 4.8 Hz, 2H,); 7.55-7.51 (m, 2H); 7.46-7.38 (m, 6H); 7.33 (dt, ^{3}J 7.8 and 1.7 Hz, 2H); 7.02 (m, 2H). ^{13}C{1H} NMR (125 MHz, $CDCl_3$): δ 157.9; 148.9; 139.9; 139.8; 135.3; 131.3; 130.0; 128.6; 127.8; 124.5; 121.2. HRMS (MALDI-orbitrap) m/z: $[M + H]^+$ Calcd for $C_{22}H_{17}N_2$ 309.13863; Found: 309.13854.

2,5-dibromoacetanilide. 3-Bromoacetanilide (0.25 mmol, 53.5 mg), NBS (0.251 mmol, 47 mg), palladium (II)acetate (0.0125 mmol, 2.8 mg) and 1 ml of DCM were added to the 4 ml reaction vial, followed by addition of 0.125 mmol of trifluoroacetic acid. The reaction was stirred at room temperature for 24 hours and quenched with 2ml of brine/EtOAc (1:1) solution. Organic layer was evaporated and purified by silica gel column chromatography (ethyl-acetate/hexane). Isolated yield: 26 mg (36 %) of white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.59 (s, 1H,); 7.58 (bs, 1H); 7.39 (d, ^{3}J 8.55 Hz, 1H); 7.11 (dd, ^{3}J 8.55 and 2.29 Hz, 1H); 2.25 (s, 3H). ^{13}C{1H} NMR (125 MHz, $CDCl_3$): δ 168.2; 136.7; 133.1; 128.0; 124.4; 122.1; 111.4; 25.0. HRMS (MALDI-orbitrap) m/z: $[M + H]^+$ Calcd for $C_8H_8Br_2NO$ 291.89672; Found: 291.89704.

N-(2-(4-chlorobenzoyl)phenyl)acetamide Acetanilide (0.25 mmol, 33.7 mg), 4-chlorobenzaldehyde (0.5 mmol,707 mg), palladium (II)acetate (0.0125 mmol, 2.8 mg) and 0.7 ml of DCM were added to the 4 ml reaction vial, followed by addition of 0.125 mmol of trifluoroacetic acid and 100 μL (2.1 eqv.) of TBHP (5.5 M solution in decane). The reaction was stirred for 24 hours at room temperature. The crude reaction mixture was purified by silica gel column chromatography (ethyl-acetate/hexane). Isolated yield: 16 mg (23 %) of white solid ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.71 (s, 1H,); 8.61 (d, ^{3}J 8.38 Hz, 1H); 7.65 (d, ^{3}J 8.53 Hz, 2H); 7.59 (t, ^{3}J 7.42 Hz, 1H); 7.51 (d, ^{3}J 7.79 Hz, 1H); 7.47 (d, ^{3}J 8.50 Hz, 2H); 7.10 (t, ^{3}J 7.75 Hz, 1H); 2.23 (s, 3H). ^{13}C{1H} NMR (125 MHz, $CDCl_3$): δ 198.4; 169.3; 140.4; 139.1; 136.8; 134.5; 133.2; 131.4; 128.7; 123.0; 122.2; 121.7; 25.3.

ASSOCIATED CONTENT

Supporting Information. Ligand exchange experiments, titration experiments, C–H activation experiments, proof of concept experiments, spectra and DFT calculation results together with geometries of all optimized structures.

The following files are available free of charge.

Experimental details (PDF)

Optimized geometries (xyz)

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