Chemistry Letters

Salicylaldehyde-Stabilized Palladium Nanoparticles for Highly Efficient Suzuki-Miyaura Reaction at Room Temperature

Zhen Zhou,* Gao Cao, and Ning Liu

doi:10.1246/cl.190051

Salicylaldehyde−Stabilized Palladium Nanoparticles for Highly Efficient Suzuki-Miyaura Reaction at Room Temperature

Zhen Zhou,*[1,2] Gao Cao,[1,2] and Ning Liu[1,2]
[1]School of Chemistry and Chemical Engineering, Guangdong Pharmaceutical University, Zhongshan, Guangdong 528458, China
[2]Guangdong Cosmetics Engineering & Technology Research Center, Zhongshan, Guangdong 528458, China

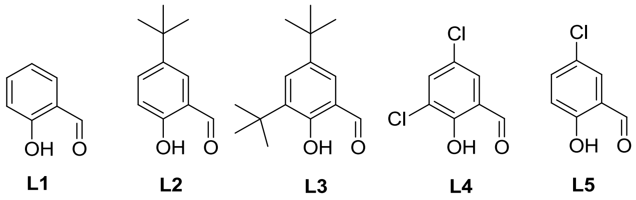
E-mail: zhouzhen@gdpu.edu.cn

Pd-catalyzed Suzuki-Miyaura cross-coupling reactions promoted by simple and commercial salicylaldehyde-based ligands were investigated. The effect of the ligands was evaluated and the reaction conditions were optimized. Moreover, the physical nature of the palladium was determined by TEM analysis and poison tests. It demonstrated that this catalytic system can be reused for ten consecutive runs and showed excellent activities toward the aryl bromides with arylboronic acids at room temperature in air.

Keywords: Salicylaldehydes, Suzuki-Miyaura reaction, Pd nanoparticles

The Pd-catalyzed Suzuki-Miyaura cross-coupling reaction has been received considerable attention in the construction of biaryls, which are common motifs found in natural products, pharmaceuticals and materials.[1,2] Generally, the ligands and precatalysts played significant influence on the catalytic efficiency and selectivity in the homogeneous reaction.[1,2] Over the past decades, the development of well-defined palladium complexes with sterically demanding and strong σ-donor ligands, such as phosphine and N-heterocyclic carbenes (NHCs), have been well established as the most powerful choice in Pd-catalyzed cross-coupling reactions.[1,2]

On the other hand, the involvement of Pd nanoparticles (NPs) has emerged as an alternative strategy in Suzuki-Miyaura cross-coupling reaction over the past few years.[3] Compared with homogenous catalysis with conventional palladium complexes, the physical properties of the nanoscale dimension of palladium particles exhibited intrinsically large surface area, and allowed for highly accessible surface-bound catalytic sites.[3] Nevertheless, the Pd NPs tend to be aggregated with the loss of catalytic activities due to their high surface energy. To prevent the generation of palladium black, the development of ligands for their excellent stabilization of the Pd NPs, has dramatically increased the efficiency of the cross-coupling reactons. As consequence, a variety of ligands, such as amines,[4] thiols,[5,6] palladacycles,[6,7] ionic liquids,[8,9] and bidentate NHCs[10,11,12] have been developed. Despite the impressive recent improvements in this topic, the cross-coupling still suffers from some shortcomings, such as high reaction temperature (80–140 °C), or relative high palladium loading (0.5–2.5 mol%). The reaction took place at room temperature at a low palladium (0.01 mol%) generally led to low reactivity even no conversion.[8,11,13] Furthermore, multiple synthetic steps were necessary for the accessible of the desired ligands, which limited their large scale application.

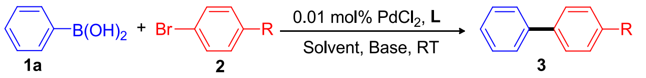


Scheme 1. Salicylaldehyde and its different derivatives as ligand for Suzuki-Miyaura reaction.

Keep this in mind, we were interested in developing catalytic system that could perform the Suzuki-Miyaura cross-coupling at ambient temperature in air. The key to the success was the generation of catalytic Pd(0) species quickly under mild reactions, which required a weak coordinated environment around the palladium. On the contrary, a steric bulk ligand is essential to stabilize the Pd(0) intermediate. Moreover, the electronic nature of the ligand would directly influence the oxidative addition and the reductive elimination processes. With these factors in mind, we envisioned that the weak coordinated oxygen-based salicylaldehydes (Scheme 1) could allow a new modular and systematic way to tune the steric as well as electronic effect onto the Pd NPs. Moreover, salicylaldehydes behave several advantages such as commercial availability and inexpensiveness for applications. Herein, we report salicylaldehydes/$PdCl_2$ catalytic systems for the synthesis of biaryls under mild reaction conditions.

Initially, we have studied the efficiency of salicylaldehyde and its derivatives (Scheme 1, **L1–5**) in Suzuki-Miyaura reaction using 4-bromochlorobenzene (1.0 mmol) and phenylboronic acid (1.2 mmol) as model substrates. The reaction was carried out in the cosolvent of ethanol and water (10:1; 6 mL) utilizing K_2CO_3 as base at room temperature in air. As illustrated in Table 1, all these five catalytic systems showed the almost quantitative yields in the presence of 0.01 mol% of $PdCl_2$ (Table 1, entries 1–5). Subsequently, we chose 4-bromotoluene as a less reactive substrate instead. As summarized in Table 1 (entries 7–11), the steric and electronic ability of the ligands exhibited profound effect on the catalytic efficiency under the same reaction conditions. Among the salicylaldehyde ligands evaluated, the electron rich and bulky 3,5-di-tert-butyl-salicylaldehyde (**L3**) gave the best result (73%, Table 1; entry 9). However, the presence of electron withdrawing group (–Cl) at ortho and para position of the salicylaldehyde significantly diminished the yields of the cross coupling products (Table 1, entries 10–11). The super efficient catalytic systems in this study highlighted that the weak O,O-based ligand would led to a rapid formation of lowvalent active intermediate. These observation also implied that the sterically bulky ligands is indispensible, which might enable the stabilization of the Pd(0) species and favor the reductive elimination.[12,14] In comparison, much lower yields were observed in the absence of ligand, which further demonstrated the stabilization of the palladium center by oxygen-based ligand (Table 1, entries 6 & 12).

Table 1. Optimization of the Suzuki-Miyaura cross-coupling reaction.[a]



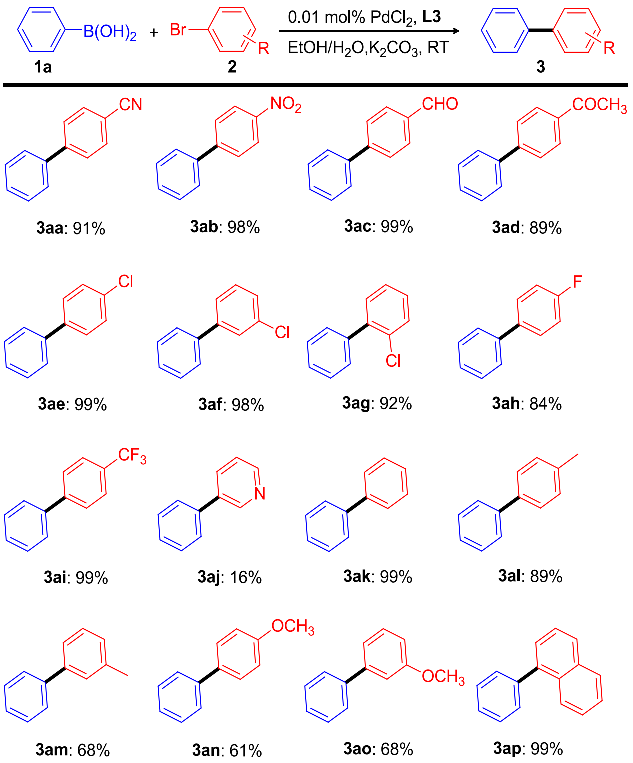
Entry	Ligand	R	Solvent	Base	Yield (%)
1	**L1**	Cl	$EtOH/H_2O$ (10:1)	K_2CO_3	99
2	**L2**	Cl	$EtOH/H_2O$ (10:1)	K_2CO_3	99
3	**L3**	Cl	$EtOH/H_2O$ (10:1)	K_2CO_3	99
4	**L4**	Cl	$EtOH/H_2O$ (10:1)	K_2CO_3	85
5	**L5**	Cl	$EtOH/H_2O$ (10:1)	K_2CO_3	99
6	-	Cl	$EtOH/H_2O$ (10:1)	K_2CO_3	62
7	**L1**	Me	$EtOH/H_2O$ (10:1)	K_2CO_3	65
8	**L2**	Me	$EtOH/H_2O$ (10:1)	K_2CO_3	71
9	**L3**	Me	$EtOH/H_2O$ (10:1)	K_2CO_3	73
10	**L4**	Me	$EtOH/H_2O$ (10:1)	K_2CO_3	52
11	**L5**	Me	$EtOH/H_2O$ (10:1)	K_2CO_3	68
12	-	Me	$EtOH/H_2O$ (10:1)	K_2CO_3	44
13	**L3**	Me	$EtOH/H_2O$ (1:10)	K_2CO_3	20
14	**L3**	Me	$EtOH/H_2O$ (1:5)	K_2CO_3	18
15	**L3**	Me	$EtOH/H_2O$ (1:3)	K_2CO_3	19
16	**L3**	Me	$EtOH/H_2O$ (1:1)	K_2CO_3	82
17	**L3**	Me	$EtOH/H_2O$ (3:1)	K_2CO_3	89
18	**L3**	Me	$EtOH/H_2O$ (5:1)	K_2CO_3	74
19	**L3**	Me	EtOH	K_2CO_3	54
20	**L3**	Me	MeOH	K_2CO_3	38
21	**L3**	Me	H_2O	K_2CO_3	Trace
22	**L3**	Me	EtOAc	K_2CO_3	—
23	**L3**	Me	DMF	K_2CO_3	—
24	**L3**	Me	THF	K_2CO_3	—
25	**L3**	Me	DMA	K_2CO_3	—
26	**L3**	Me	DCM	K_2CO_3	Trace
27	**L3**	Me	$EtOH/H_2O$ (3:1)	Na_2CO_3	33
28	**L3**	Me	$EtOH/H_2O$ (3:1)	$NaHCO_3$	16
29	**L3**	Me	$EtOH/H_2O$ (3:1)	CH_3COONa	12
30	**L3**	Me	$EtOH/H_2O$ (3:1)	NaOH	85
31	**L3**	Me	$EtOH/H_2O$ (3:1)	KOH	35
32	**L3**	Me	$EtOH/H_2O$ (3:1)	NEt_3	12
33	**L3**	Me	$EtOH/H_2O$ (3:1)	—	—

[a] Reaction conditions: aryl bromides (1 mmol), phenylboronic acid (1.2 mmol), base (2.0 mmol), solvent (6 ml); under aerobic atmosphere at room temperature for 2 h. The molar ratio of ligand (0.01 mol%) and $PdCl_2$ (0.01 mol%) is 1:1. Isolated yields.

Encouraged by these results, we ran further optimization of the reaction conditions in the presence of **L3**/$PdCl_2$. The reaction was screened under different solvents using K_2CO_3 as base at room temperature for 2 h (Table 1; entries 9 & 13–26). It was found that the polar protic solvents such as methanol and ethanol gave the coupling product in good yields while the pure water resulted in trace mount of product (Table 1; entries 19–21). To our pleasure, using ethanol and water as co-solvent ($EtOH:H_2O$, 3:1) led to the highest yield of 89% (Table 1, entry 17). Probably, the water would promote the solubility of the inorganic base, which subsequently accelerated the transmetalation of the catalytic process.[15]

With the preliminary results in hand, the effect of base was then explored since the nature of base played significant role on the transmetalation. The results evidently showed that base is essential for the coupling reactions since no coupling product was obtained in the absence of base (Table1, entry 33). Optimization of the base for the reaction was evaluated by using K_2CO_3, Na_2CO_3, $NaHCO_3$, CH_3COONa, NaOH, KOH and NEt_3. It was found that K_2CO_3 was the best choice for this system (Table1, entry 17). Thus, a general condition consisting of 0.01 mol% $PdCl_2$, **L3** as ligand, and K_2CO_3 as base was established for Suzuki-Miyaura cross-coupling in ethanol/water at room temperature under aerobic condition.

Table 2. Suzuki-Miyaura cross-coupling reaction of various aryl bromides with phenylboronic acid.[a]

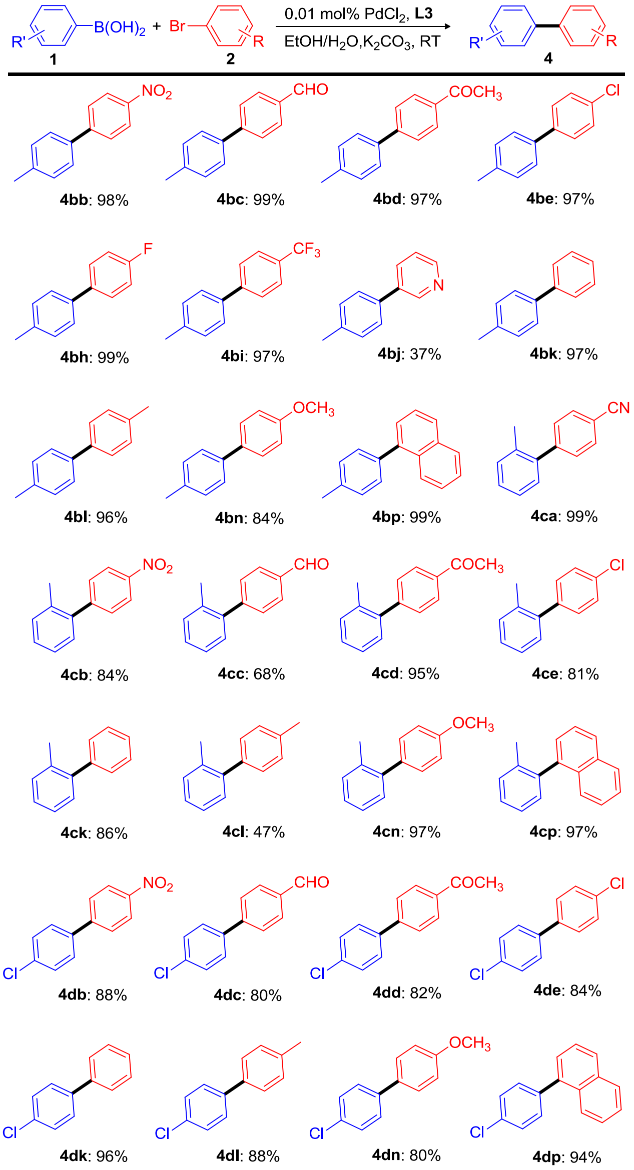


[a] Reaction conditions: aryl bromides (1 mmol), phenylboronic acid (1.2 mmol), K_2CO_3 (2.0 mmol), $EtOH:H_2O$ (6 ml, 3:1); under aerobic atmosphere at room temperature for 2 h. The molar ratio of L3 (0.01 mol%) and $PdCl_2$ (0.01 mol%) is 1:1. Isolated yields.

Under the optimized conditions established, the scopes and limitations of Suzuki-Miyaura cross-coupling were investigated. As list in Table 2 & 3, the catalytic system in this study exhibited that the catalyst system was very efficient for the cross-coupling reaction of a wide range of aryl bromides and different substituted phenylboronic acids.

Various substituted aryl bromides, bearing either electron-deficient groups or electron-rich groups, such as –CN, $–NO_2$, –CHO, $–COCH_3$, –Cl, –F, $–CF_3$, $–CH_3$, $–OCH_3$, were compatible and provided the corresponding products in moderate to excellent yields. Generally, it was observed that aryl bromides with electron withdrawing donating groups were more efficient than that of electron donating groups.

Table 3. Suzuki-Miyaura cross-coupling reaction of various aryl bromides with different arylboronic acids.[a]



4bb: 98% **4bc**: 99% **4bd**: 97% **4be**: 97%

4bh: 99% **4bi**: 97% **4bj**: 37% **4bk**: 97%

4bl: 96% **4bn**: 84% **4bp**: 99% **4ca**: 99%

4cb: 84% **4cc**: 68% **4cd**: 95% **4ce**: 81%

4ck: 86% **4cl**: 47% **4cn**: 97% **4cp**: 97%

4db: 88% **4dc**: 80% **4dd**: 82% **4de**: 84%

4dk: 96% **4dl**: 88% **4dn**: 80% **4dp**: 94%

[a] Reaction conditions: aryl bromides (1 mmol), arylboronic acids (1.2 mmol), K_2CO_3 (2.0 mmol), EtOH:H_2O (6 ml, 3:1); under aerobic atmosphere at room temperature for 2 h. The molar ratio of L3 (0.01 mol%) and $PdCl_2$ (0.01 mol%) is 1:1. Isolated yields.

For instance, the 4-bromobenzaldehyde and 4-bromochlorobenzene afford nearly quantitative yields (Table 2, entries **3ac** & **3ae**). Comparably, the substrates with methyl or methoxy groups resulted in moderate yields (Table 2, entries **3al** – **3ao**). Moreover, the substitutions on para- and meta- position on showed measurable influence on cross-coupling transformation, giving the biaryls in satisfactory yields (Table 2, entries **3ae** vs **3af**, **3al** vs **3am**, **3an** vs **3ao**). Nevertheless, when the heteroaryl bromide of 3-pyridyl bromide was used as substrate, it gave much inferior yields of **3aj** & **4bj** in the yield of 16% & 37% (Table 2 & 3), respectively. Probably, the nitrogen atom on heteroaryl might poison the catalytic center, and make this catalytic procedure less favorable.

To further expand the scope and applicability of this reaction, we continued to investigate the effect of substitution on arylboronic acids. As can be seen in Table 3, it revealed that 4-methylphenylboronic acid underwent reaction smoothly with kinds of activating and deactivating substituted aryl bromides (Table3, entries **4bb** – **4bp**). To our delight, the coupling reaction of 2-tolylboronic acid also gave satisfied yields (Table3, entries **4ca** – **4cp**), which demonstrated that the hemilabile ligand would allow a flexible environment and subsequently promote the transmetalation process when sterically arylboronic acid involvement.[12,14] Moreover, the reactions with less nucleophilic of 4-chlorophenylboronic acid underwent smoothly when the reaction was conducted at room temperature (Table 3, entries **4db** – **4dp**).

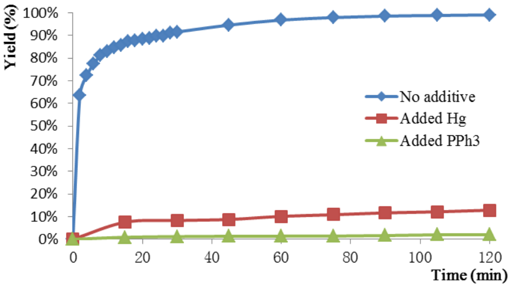


Figure 1. Comparison of the kinetics of this catalytic system in the Suzuki-Miyaura cross-coupling reaction with and without added triphenylphosphine/mercury.

To gain more information, kinetic experiments were then investigated under the standard reaction conditions. As can be seen in the kinetic profile, it is highlighted a rapid initiation process occurred, and a high GC yield of 64% was achieved at the beginning of the first 2 minutes. To probe the physical nature of palladium involvement the reaction, some poison tests were conducted. It is well-known that triphenylphosphine as well as mercury could bind strongly to heterogenous metal centres, thereby blocking access of the substrate to the active site.[10,11,16] Thus, the PPh_3 and Hg poisoning test were performed on representative reactions of 4-bromochlorobenzene (1.0 mmol) and phenylboronic acid (1.2 mmol) under the optimized reaction conditions. As shown in Figure 1, the reaction was thoroughly shut down when 1 equiv (relative to Pd) PPh_3 was added. Besides, the Hg poisoning test was also positive (ca. 10% yield was obtained). In contrast, the kinetics of this catalytic system in Suzuki cross-coupling without added PPh_3 or Hg indicates that the reaction yield up to 90% within 30 min. These tests suggest the involvement of a heterogeneous catalytic process.

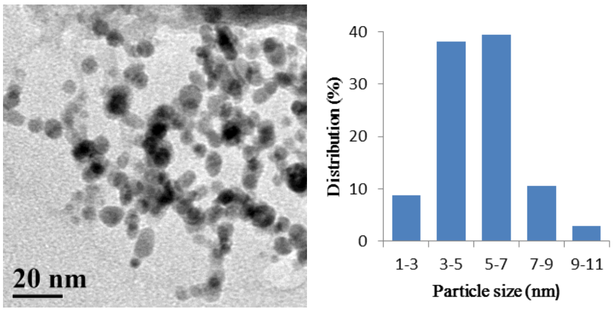


Figure 2. TEM micrograph and size distribution of in-situ generated Pd NPs during Suzuki-Miyaura cross-coupling.

In this circumstance, we considered that Pd(0) NPs are formed from $PdCl_2$ in the presence of **L3**, wherein **L3** acts as both ligand and stabilizer. In order to further clarify the real catalytic species in Suzuki cross-coupling reaction, transmission electron microscope (TEM) was used for the analysis of the distribution and size of Pd NPs. As illustrated in Figure 2, the TEM analysis indicated that nano-Pd particles were generated as dark spherical dots and dispersed well with an average particle sized around of 3–7 nm. These results demonstrated that the in-situ formed Pd NPs are supposed to be the key catalytic species in this catalytic system.

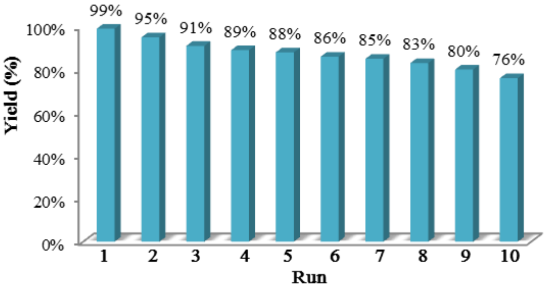


Figure 3. Recycling of **L3**/Pd in Suzuki-Miyaura cross-coupling tested under optimum conditions.

Encouraged by the highly efficient catalytic system depicted in Table 2 & 3, we further explore its ability to perform as a recyclable catalyst for potential industrial applications. For this purpose, the recyclability potential of **L3** stabilized Pd NPs after Suzuki coupling cycle was checked under optimized conditions. A fresh lot of 4-bromochlorobenzene, phenylboronic acid and K_2CO_3 were added to the reaction vessel after completion of a coupling reaction cycle. The respective yields after each run are depicted in Figure 3. Yields of this study by GC indicated that the catalytic system recycled for 10 consecutive runs with only 24% decrease in activity. The TEM image of reused catalyst after the fifth run (ESI, Figure S2) indicates well dispersibility of Pd NPs without detectable size increase. These results imply the distinct advantage of this catalytic system in its good stability and reusability.

In summary, a simple and efficient Suzuki-Miyaura cross-coupling reaction promoted by salicylaldehyde/$PdCl_2$ has been developed. Under the optimized reaction conditions, the present catalytic system demonstrated excellent catalytic activity with very low palladium loading of 0.01 mol% at room temperature in air. Moreover, the TEM analysis and poison tests revealed the heterogenous nature of the palladium species. The catalytic system was recycled up to ten times with small decrease in its activity. This study highlighted that the bulk weak ligands played significant role on the stabilization of the palladium NPs generated in-situ, and rapid initiated the transformation.

This work was supported by the Programs of GDPU (No. 2017KQNCX110, 2014KQNCX144) and Program of TCMBGP (No. 20191196)

Supporting Information is available on http://dx.doi.org/10.1246/cl.******.

References and Notes

1 G. Bringmann, T. Gulder, T. A. M. Gulder, M. Breuning, *Chem. Rev.* **2011**, *32*, 563.

2 a) D. Roy, Y. Uozumi, *Adv. Synth. Catal.* **2017**, *360*, 602. b) J. S. Ouyang, Y. F. Li, F. D. Huang, D. D. Lu, F. S. Liu, *ChemCatChem* **2018**, *10*, 371. c) T. Hoshi, Y. Shishido, A. Suzuki, Y. Sasaki, H. Hagiwara, T. Suzuki, *Chem. Lett.* **2018**, *47*, 780.

3 a) J. D. Scholten, B. C. Leal, J. Dupont, *ACS Catal.* **2012**, *2*, 184. b) B. Karimi, F. Mansouri, H. M. Mirzaei, *ChemCatChem* **2015**, *7*, 1736. c) N. Oger, F. X. Filpin, *ChemCatChem* **2016**, *8*, 1998.

4 a) E. Ramirez, S. Jansat, K. Philippot, P. Lecante, M. Gomez, A. M. Masdeu-Bultó, B. Chaudret, *J. Org. Chem.* **2004**, *689*, 4601. b) R. Bhaskar, H. Joshi, A. K. Sharma, A. K. Singh, *ACS Appl. Mater. Interfaces* **2017**, *9*, 2223.

5 a) P. Singh, A. K. Singh, *Dalton Trans.* **2017**, *46*, 10037. b) R. Bhaskar, A. K. Sharma, M. K. Yadav, A. K. Singh, *Dalton Trans.* **2017**, *46*, 15235.

6 M. P. Singh, F. Saleem, R. S. Pal, A. K. Singh, *New J. Chem.* **2017**, *41*, 11342.

7 V. Sable, K. Maindan, A. R. Kapdi, P. S. Shejwalkar, K. Hara, *ACS Omega* **2017**, *2*, 204.

8 V. Calò, A. Nacci, A. Monopoli, F. Montingelli, *J. Org. Chem.* **2005**, *70*, 6040.

9 J. Xu, X. Zhai, X. Wu, Y. J. Zhang, *Tetrahedron* **2015**, *71*, 1712.

10 E. C. Keske, O. V. Zenkina, R. Wang, C. M. Crudden, *Organometallics* **2012**, *31*, 6215.

11 M. Charbonneau, G. Addoumieh, P. Oguadinma, A. R. Schmitzer, *Organometallics* **2014**, *33*, 6544.

12 a) J. B. Ernst, C. Schwermann, G. Yokota, M. Tada, S. Muratsugu, N. L. Doltsinis, F. Glorius, *J. Am. Chem. Soc.* **2017**, *139*, 9144. b) J. M. Asensio, S. Tricard, Y. Coppel, R. Andrés, B. Chaudret, E. Jesús, *Chem. Eur. J.* **2017**, *23*, 13435. c) A. V. Astakhov, O. V. Khazipov, A. Y. Chernenko, D. V. Pasyukov, A. S. Kashin, E. G. Gordeev, V. N. Khrustalev, V. M. Chernyshev, V. P. Ananikov, *Organometallics* **2017**, *36*, 1981.

13 Z. Du, W. Zhou, F. Wang, J. X. Wang, *Tetrahedron* **2011**, *67*, 4914.

14 a) A. Rühling, K. Schaepe, L. Rakers, B. Vonhören, P. Tegeder, B. J. Ravoo, F. Glorius, *Angew. Chem. Int. Ed.* **2016**, *55*, 5856. b) A. Ferry, K. Schaepe, P. Tegeder, C. Richter, K. M. Chepiga, B. J. Ravoo, F. Glorius, *ACS Catal*. **2015**, *5*, 5414.

15 a) D. D. Lu, X. X. He, F. S. Liu, *J. Org. Chem.* **2017**, *82*, 10898. b) M. Beygzadeh, A. Alizadeh, M. M. Khodaei, D. Kordestani, *Catal. Commun.* **2013**, *32*, 86. c) G. Sarmah,; U. Bora, *Tetrahedron Lett.* **2015**, *56*, 2906.

16 a) S. Tarnowicz, W. Alsalahi, E. Mieczyńska, A. M. Trzeciak, *Tetrahedron* **2017**, *73*, 5605. b) P. Wójcik, L. Sygellou, A. Gniewek, A. Skarżyńska, A. M. Trzeciak, *ChemCatChem* **2017**, *9*, 4397.