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Coumarin based novel ligands in the Suzuki–Miyaura and Mizoroki–Heck cross-couplings under aqueous medium

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ABSTRACT

Coumarin-based novel ligands (benzylidine-bis-(4-hydroxycoumarin)-diethylamines) were easily synthesized using 4-hydroxycoumarin, aromatic aldehydes, and diethylamine. The ionic ligand structure was established by X-ray study. They are air and moisture stable ligands and have shown highly efficient catalytic activity with $Pd(OAc)_2$ (0.1 mol% loading) in the Suzuki–Miyaura and (0.3 mol% loading) in the Mizoroki–Heck cross-coupling reactions in water or water/ethanol mixture. Pd-catalyst was reused efficiently without affecting variety of functional groups in the reaction.

Introduction

Palladium-catalyzed Suzuki–Miyaura and Mizoroki–Heck cross-coupling reactions are extremely useful in the C–C bonds formation.[1,2] Therefore, the methods are widely used in the synthesis of biologically active natural products, pharmaceuticals, and fine chemicals.[3–7] These reactions' efficiency as well as functional group tolerance in the products mostly depend upon the Pd-catalyst and the ligand used. It was found that the sterically hindered biphenyl ligands form a better complex with Pd(0 or II)-catalysts. Thus, the chemists have tried to design new sterically crowded biphenyl phosphines ligands, tertiary phosphines, imidazole, and imidazolium-functionalized phosphines.[8] Nitrogen based ligands such as N,O- and N,N-bidentate ligands,[9] *N*-heterocyclic carbenes,[10] aryloximes or O-aryloxime ether,[11] *N*-acylamidines,[12] simple amines,[13] and pyridine–piperidine bidentate ligands,[14] are effective ligands in the Suzuki–Miyaura and the Mizoroki–Heck reactions. Additionally, significant advances have been made using heterogeneous catalysts,[15] water-soluble ligands,[16] and nucleophilic carbene ligands.[17]

Recently, Aktaş et al. synthesized naphthalenomethyl-substituted imidazolidin-2-ylidene ligands for the Pd-catalyzed Mizoroki–Heck and Suzuki–Miyaura reactions in aqueous media.[18a] After that Guo et al. also reported the use of Pd-complex $[PdCl_2(NH_2CH_2COOH)_2]$ as an efficient catalyst for the Suzuki–Miyaura reaction in aqueous medium.[18b] Further, Li & co-workers and Balakrishna & co-workers have been demonstrated that the ionic adducts are effective ligands in the Suzuki–Miyaura and the Mizoroki–Heck cross-coupling reactions.[19] In metal catalyzed reactions, it is well known that bulky ligand dictates the steric and electronic properties of the metal complexes and thus plays an important role in reactivity and selectivity. It was also observed that ligands with bulky structure around donor atoms are highly efficient in the Suzuki–Miyaura and the Mizoroki–Heck reactions.[20] Based on the literature evidences, we herein designed and synthesized novel coumarin based ligands (**L1**–**L5**) and have shown uses in the Suzuki–Miyaura and the Mizoroki–Heck cross-coupling reactions with Pd(II)-catalyst in aqueous medium under mild reaction conditions.

Results and discussion

Betti bases are generally synthesized using ammonia/amines, benzaldehydes, and 2-naphthols.[21] Under the same reaction condition, we obtained adducts [benzylidine-bis-(4-hydroxycoumarin)-diethylamines (**L1**–**L5**)] as an ionic salt at room temperature. When 4-hydroxycoumarin, diethylamine, and appropriate aldehyde were stirred in absolute ethanol at room temperature for 24 h, it gave ligands as white solids (Scheme 1).[22] The structure of ligands **L1**–**L5** was confirmed by spectroscopic analysis. Further, the structure of ligand **L1** was confirmed by single crystal X-ray analysis (Fig. 1).[23,24] **L1** structure showed that the two molecules of 4-hydroxycoumarin condensed with a molecule of aldehyde and

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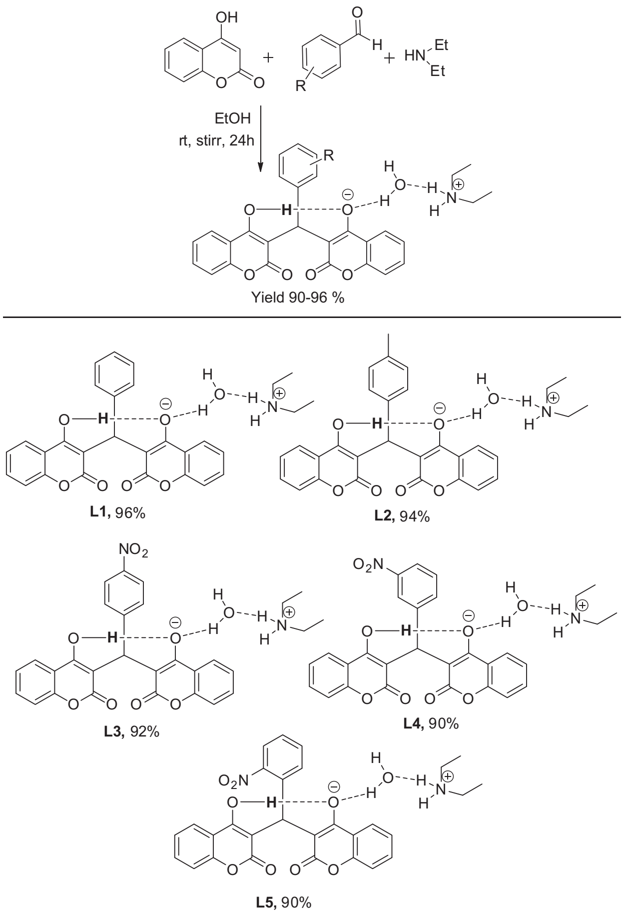


Scheme 1. Benzylidine-bis-(4-hydroxycoumarin)-ethylenediamine.

diethylamine coordinates through hydrogen bonding. The hydrogen atom of 4-hydroxycoumarin abstracted by the diethylamine and form salt with bis-coumarin through water molecule, generated in situ.

On heating in aqueous medium, the hydrogen bonds among the hydroxyl groups, water, and diethyl amine were collapsed which resulted in a neutral ligand which might be the binding sites (two hydroxyl groups) with palladium acetate.[25]

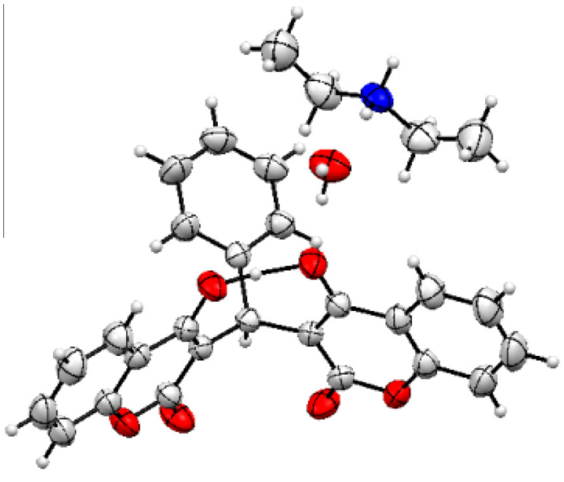


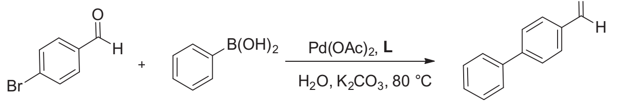
Figure 1. ORTEP diagram of ligand L1 with 40% ellipsoid probability.

Ligands **L1** and **L2** were used in 0.1 mol% which gave the product in excellent yield up to 94% and 92%, respectively, within 1 h (Table 1, entries 1, 2). Ligands **L3**, **L4**, and **L5** gave good yield (91–88%) in 1.5 h. We observed that the yield was slightly decreased with withdrawing group (NO_2) moved from *para*- to *ortho*-position in the ligands, respectively, in the aromatic ring might be due to the steric hindrance of NO_2 group (Table 1, entries 3–5). Without using ligands (**L1**–**L5**), the reaction failed to give products till 10 h. It showed the importance of ligands in the Suzuki–Miyaura cross-coupling reactions (Table 1, entry 6). Similarly, the product yield varied with different ligands (**L1**–**L5**). Ligand **L1** was observed as the better ligand for the coupling reaction between aryl halides and phenylboronic acid as compared to **L2**, **L3**, **L4**, and **L5** (Table 1, entries 2–5).

Bases are known to activate organoboron reagents by enhancing their nucleophilicity. And the use of water, either as additive or solvent, assisted in the solvation of bases.[18b] To examine the effect of bases on Suzuki–Miyaura cross-coupling reactions, we took a series of bases for the coupling reaction between 4-bromobenzaldehyde and phenylboronic acid. A significant development can be made using water along with alkali metal carbonates, as they offer clean and simple work-up procedure with less probable side products as compared to strong base like KO*t*Bu and hydroxide bases such as KOH, and NaOH which gave moderate yield without affecting the functional groups in the substrates. Bases like K_2CO_3 and Na_2CO_3 were found to be more effective and gave good yield under reflux condition (Table 2, entries 1, 3–6). The use of $NaHCO_3$ gave lower cross-coupled products (Table 2, entry 2), as activation of organoboron reagents by enhancing their nucleophilicity are lower than K_2CO_3. However, we have not afforded the cross-coupled products without bases.

For the solvent effects, the reactions were preceded using protic and aprotic solvents. It was observed that the protic polar solvent such as ethanol and methanol gave excellent yields within 1 h (Table 2, entries 4, 5), might be due to the high complex solubility.[1b] A less polar solvent such as acetone or non-polar solvent such as toluene gave moderate yield but these took longer time as compared to the ethanol, methanol, and water (Table 2, entry 3). The polar aprotic such as DMF and dioxane gave poor yields and took more time to complete the reaction (Table 2, entry 2). The optimal yield was obtained by using water as a solvent at 80 °C (Table 2, entry 6). The coupling reactions failed to proceed either in the absence of ligand (**L1**–**L5**), or $Pd(OAc)_2$ till 10 h which showed that the combined ligands and $Pd(OAc)_2$ have a key role in the cross-coupling reactions. Therefore, the combination of $Pd(OAc)_2$ (0.1 mol%), ligand (**L1**) (0.1 mol%), and K_2CO_3 (2 equiv) in water at 80 °C was chosen as the optimal conditions (Table 3).

Table 1
Effect of different ligands on Pd-catalyzed Suzuki–Miyaura reaction

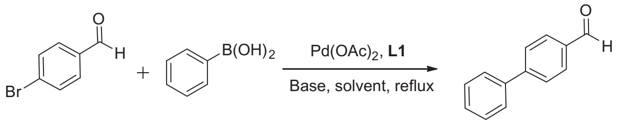


Entry	Ligands	Time (h)	Yield[a] (%)
1	L1	1.0	94
2	L2	1.0	92
3	L3	1.5	91
4	L4	1.5	90
5	L5	1.5	88
6	No ligand	10	–

[a] Isolated yield.

Table 2

Optimization of base and solvents[a]



Entry	Base	Solvent	Time (h)	Yield[b] (%)
1	K_2CO_3	THF	2	60
2	$NaHCO_3$	DMF	2	45
3	Na_2CO_3	Acetone	2	53
4	K_2CO_3	MeOH	1.5	84
5	K_2CO_3	EtOH	2	88
6	K_2CO_3	H_2O	1	94[c]

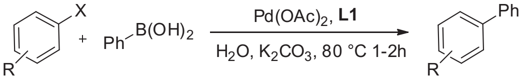
[a] Reagents and conditions: 4-bromobenzaldehyde (1.0 mmol), phenylboronic acid (1.2 mmol), base (2.0 mmol), solvent 5 ml, 0.1 mol% of $Pd(OAc)_2$/**L1**.

[b] Isolated yield,

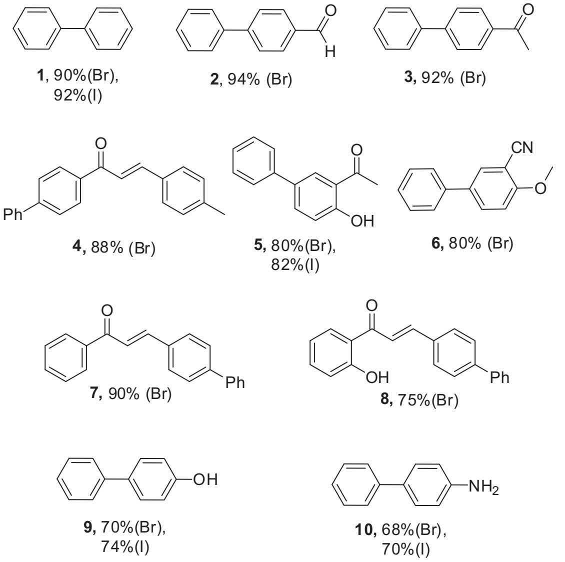
[c] At 80 °C.

Table 3

Suzuki–Miyaura reaction of aryl bromide/iodide with arylboronic acid[a]



R = H, CHO, $COCH_3$, OH, NH_2
OCH_3, CN, and Chalcone
X = Br, I

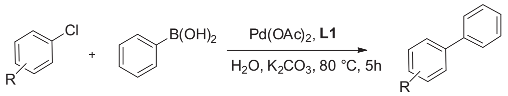


1, 90%(Br), 92%(I)
2, 94% (Br)
3, 92% (Br)
4, 88% (Br)
5, 80%(Br), 82%(I)
6, 80% (Br)
7, 90% (Br)
8, 75%(Br)
9, 70%(Br), 74%(I)
10, 68%(Br), 70%(I)

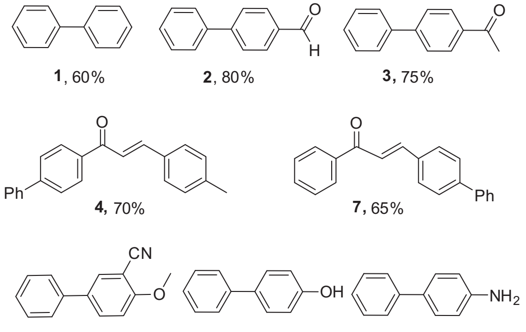
[a] Reagents and conditions: aryl halide (1.0 mmol), phenylboronic acid (1.2 mmol), base (2.0 mmol), water 5 ml, 0.1 mol% of $Pd(OAc)_2$/**L1**.

Table 4

Suzuki–Miyaura reaction of aryl chlorides with arylboronic acid



R = H, CHO, $COCH_3$, OH, NH_2
OCH_3, CN, and Chalcone



1, 60%
2, 80%
3, 75%
4, 70%
7, 65%
6, 60%
9, 55%
10, 50%

[a]Reagents and conditions: aryl chloride (1.0 mmol), phenylboronic acid (1.2 mmol), base (2.0 mmol), water 5 ml, 1 mol% of $Pd(OAc)_2$/**L1**.

Under optimized reaction conditions, we have carried out the reactions using many substrates with arylboronic acid.[26] Generally, it was observed that aryl bromides having electron donating groups were less reactive than aryl bromides having electron withdrawing group in the Suzuki–Miyaura cross-coupling reactions. An excellent yield was obtained for 4-bromobenzaldehyde coupled with phenylboronic acid in the presence of 0.1 mol% $Pd(OAc)_2$/**L1** with two equivalent of K_2CO_3 to give near quantitative yield of biphenyl-4-carbaldehyde **2**. We have also studied the coupling of substituted aryl bromides with arylboronic acid, for example, 5-bromo-2-methoxybenzonitrile, 5-bromo-2-hydroxy acetophenone, and some derivatives of chalcones with phenylboronic acid which gave the corresponding coupled products in good yield (Table 3, compounds **4**–**10**). An excellent yield was obtained when activated electron-poor aryl halides such as 4-bromobenzaldehyde, and 4-bromoacetophenone were treated with phenylboronic acid in water at 80 °C (Table 3, compounds **2**, **3**). And moderate yield was obtained with deactivated electron rich aryl bromide such as 4-bromophenol, 4-bromoaniline, coupled with phenylboronic acid (Table 3, compounds **9**, **10**). Similarly, we have also carried out a series of reactions using aryl chlorides with phenylboronic acid in the presence of $Pd(OAc)_2$/**L1** in water at 80 °C (Table 4).

Under Suzuki–Miyaura reaction condition, novel ligands are equally good for aryl chloride substrate with arylboronic acid under aqueous medium. However, the coupling of aryl chlorides with phenylboronic acid required a long reaction time and more catalyst loading (1.0 mol%) which gave a moderate to good yield at 80 °C in 5 h as compared to the aryl bromide/iodide due to the stability of C–Cl bond.

The scope of our protocol was studied with a diverse range of aryl chlorides. We observed that the deactivated electron rich aryl halide gave moderate yields. However, the activated electron-poor group gave good yield. Activated aryl chlorides such as 4-chlorobenzaldehyde, 4-chloroacetophenone, and chloro-chalcone in water at 80 °C gave good yields (Table 4, compounds **2**, **3**, **4**, and **5**), whereas other inactivated aryl chlorides such as 4-chloroaniline and 4-chlorophenol gave moderate yield (Table 4, compounds **9**, **10**).

We have successfully reused and cycled the catalyst $Pd(OAc)_2$/**L1** system in the cross-coupling of 4-bromobenzaldehyde and phenylboronic acid (Table 5). The reaction was carried out in water at 80 °C. After cooling to room temperature, the organic products were extracted by ethyl acetate, and the aqueous phase was then transferred to a new reaction flask, and the aqueous phase was used for the next reaction. It was observed that the 0.1 mol% Pd $(OAc)_2$/**L1** system could be reused by three cycles and the yield significantly dropped for the fourth cycle.

We also used the ligands in the Mizoroki–Heck cross-coupling reactions under aqueous medium with tetra butyl ammonium bromide as an additive.[27] First, we optimized the reactions conditions using of 4-bromoacetophenone and styrene and 0.3 mol% Pd $(OAc)_2$/**L1** catalyst system (Table 6).

Table 5
Recycling of Catalyst

Entry	Use	Yield (%)[a]
1	1st	90
2	2nd	80
3	3rd	70
4	4th	50

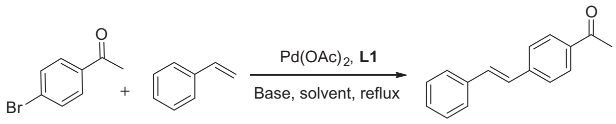
[a] Isolated yield.

In preliminary studies, our goal was to find a good base for the Mizoroki–Heck reaction in water (Table 6). Therefore, we took a series of bases under reflux conditions. Base like Et_3N gave moderate yield (Table 6, entry 4). The common bases such as K_2CO_3, Na_2CO_3 were found to be more effective to afford good yield under reflux condition (Table 6, entries 1–3, 5–6). We have also used some hydroxide bases such as KOH and NaOH which gave moderate to poor yields. Without using bases, no desire product was obtained in the Mizoroki–Heck reactions.

The solvent effects in the Mizoroki–Heck cross-coupling reactions were carried out with a range of solvent systems, mixture of water and organic solvent as well as water alone. We observed that the protic polar solvent like ethanol and methanol gave poor yields up to 45–50% (Table 6, entries 1, 2). A moderate yield was obtained in DMF (Table 6, entries 3–4). However, good yield is obtained in water as a solvent. Further, water/TBAB mixture gave excellent 92% yield at 90 °C and the reaction completed in 8 h (Table 6, entry 6). Here, tetra butyl ammonium bromide (TBAB) was used as a phase transfer catalyst which enhanced the solvation of less polar styrene to obtain better yields. No cross-coupling products were observed without using either any ligands, base or, $Pd(OAc)_2$ heated till 24 h, this showed the ligand, base, and Pd $(OAc)_2$ importance in the Mizoroki–Heck cross-coupling reactions. Therefore, the combination of $Pd(OAc)_2$ (0.3 mo%), ligand (**L1**) (0.3 mol%, and two equivalent of K_2CO_3 in water at 90 °C was chosen as the optimal reaction conditions.

Under optimal condition, Mizoroki–Heck reaction was carried out with a 1:1 mixture of ligand **L1** and palladium acetate as catalyst with 4-bromoacetophenone and styrene. The $Pd(OAc)_2$/**L1** mixture was found to be a highly active catalyst in Mizoroki–Heck cross-coupling of aryl halides with alkenes in water at 90 °C with K_2CO_3. It was observed that aryl bromides with electron donating groups were less reactive than aryl bromides having electron withdrawing group in the Mizoroki–Heck cross-coupling reactions. The coupling of substituted aryl bromides with alkenes, for examples, 5-bromo, 2-hydroxyacetophenone and chalcone derivatives with alkenes in the presence of 0.3 mol% of $Pd(OAc)_2$/**L1** at 90 °C gave the corresponding coupling products in good yield (Table 6, compounds 1**3**, **14**, **17**–**19**). A good product yields was also obtained when activated electron-poor aryl bromide such as 4-bromoacetophenone and chalcone derivatives were treated with alkenes in water/TBAB mixture at 90 °C (Table 7). And a moderate yield was obtained when deactivated electron rich aryl bromide such as 4-bromophenol coupled with alkenes (Table 7, compounds **15**–**16**).

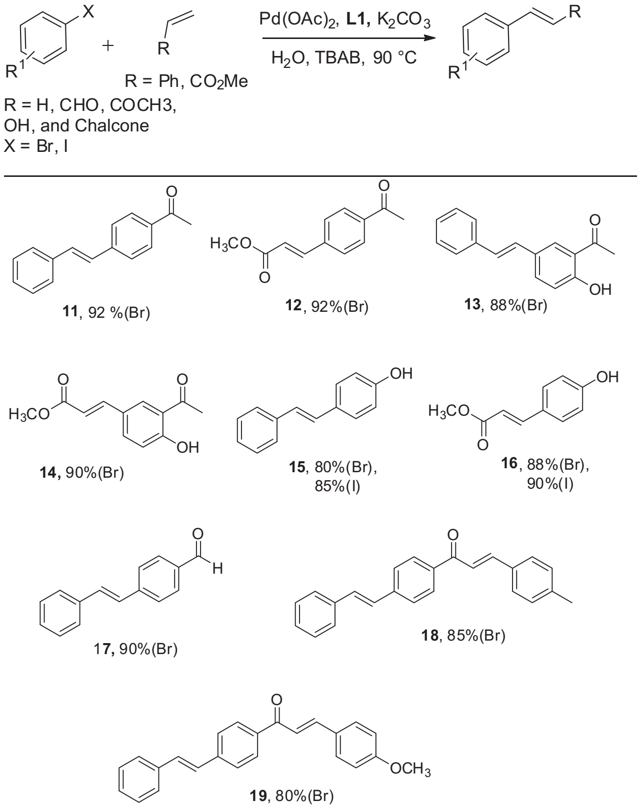
Table 6
Optimization of base and solvents[a]



Entry	Base	Solvent	Time (h)	Yield[b] (%)
1	K_2CO_3	EtOH	24	50
2	K_2CO_3	MeOH	24	45
3	Na_2CO_3	DMF	12	76
4	Et_3N	DMF	15	65
5	K_2CO_3	H_2O	10	80
6	K_2CO_3	H_2O/ TBAB	8	92[c]

[a] Reagent and conditions: 4-bromoacetophenone (1.0 mmol), styrene (1.5 mmol), base (2.0 mmol), TBAB (0.6 mmol) solvent 5 ml, 0.3 mol% of $Pd(OAc)_2$/**L1**.
[b] Isolated yield,
[c] at 90 °C.

Table 7
Mizoroki–Heck cross-coupling reaction of aryl bromide with alkenes[a]



[a] Reagents and conditions: aryl halide (1.0 mmol), alkenes (1.5 mmol), base (2.0 mmol), TBAB (0.6 mmol) water 5 ml, 0.3 mol% of $Pd(OAc)_2$/**L1**.

Table 8
Recycling of catalyst

Entry	Use	Yield[a] (%)
1	1st	92
2	2nd	82
3	3rd	76
4	4th	60

[a] Isolated yield.

We have reused the catalyst $Pd(OAc)_2$/**L1** system in the cross-coupling of 4-bromoacetophenone and styrene (Table 8). The reaction was carried out in water at 90 °C in air. After completions of reaction, reaction mixture was cooled to room temperature. The organic products were extracted by ethyl acetate and the aqueous phase was transferred to a new reaction flask, and used for the next reaction. We have observed that the 0.3 mol% $Pd(OAc)_2$/**L1** system used in Mizoroki–Heck reaction could be reused by three cycles and the yields significantly dropped for the fourth cycle.

Conclusion

In conclusion, we have developed an array of novel and efficient air and moisture stable coumarin ligands (**L1**–**L5**) for the Suzuki–Miyaura and the Mizoroki–Heck cross-coupling reactions. The **L1** with $Pd(OAc)_2$ system was observed to be an efficient catalyst for the cross-coupling reactions in various aryl halides under mild reaction conditions. Our protocol is successfully used in the coupling of aryl chloride with arylboronic acid in high yields.

Acknowledgments

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Supplementary data

Supplementary data (^{1}H and ^{13}C NMR spectra of Ligands **L1**–**L5** and CIF file with CCDC number 1412087) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.07.028.

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22. *Synthesis of bis-coumarin ligands: A General Procedure* ***L1–L5:***
   4-Hydroxylcoumarin (2 mmol) and benzaldehyde (1 mmol) were dissolved in absolute alcohol (5 ml). Amines (1 mmol) were slowly added in the stirred solution. The resulting reaction mixture was further stirred at room temperature for 24 h. TLC monitoring, the solvent was reduced under vacuum to get the solid precipitate. Precipitate was filtered off and washed twice with cold ethyl alcohol (2–3 ml) under vacuum give the pure product **L1**–**L5** in 90–96% yields. **Ligand** (**L1**): White solid, Yield: 96% (0.388 g from 0.405 g); mp 220 °C; IR (KBr): 3455, 3152, 3022, 1676, 1611, 1401 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 8.08 (d, *J* = 7.7 Hz, 2H), 7.47 (t, *J* = 7.8 Hz, 2H), 7.26–7.20 (m, 8H), 7.13 (t, *J* = 7.0 Hz, 1H), 6.21 (s, 1H), 3.08 (q, *J* = 7.3 Hz, 4H), 1.32 (t, *J* = 7.3 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm): 171.0, 167.9, 152.6, 140.4, 131.3, 128.1, 126.5, 125.5, 125.2, 123.5, 120.1, 115.5, 103.5, 43.0, 36.7, 11.4.
23. Crystal data for ligand **L1** were obtained using a Bruker Kappa Apex Four Circle CCD diffractometer, Mo Kα radiation (λ = 0.71073 Å), graphite monochromator, $C_{29}H_{29}NO_7$, monoclinic, space group *P*21/*n*, *a* = 11.5801 (4) Å, *b* = 19.0230 (7) Å, *c* = 11.7616 (4) Å, *V* = 2572.63(16) Å^3, *Z* = 4, Dc = 1.300 mg/m^3, crystal size 0.23 x 0.23 x 0.23 mm, F(000) = 1064, μ = 0.093 mm^{-1}. Data were collected at 293 (2) K using ω-2θ scans in the ranges 1.49–28.35°. A total of 6440 reflections were collected, 3069 were unique (R_{int} = 0.0502). The structure was refined by full-matrix least-squares on F^2. The final refinement [*I* > 2\s (I)] gave R_1 = 0.0504, wR_2 = 0.1087.
24. Crystallographic data for ligand **L1** have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 1412087. This data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
25. Grazul, M.; Budzisz, E. *Chem. Rev.* **2009**, *253*, 2588–2598.
26. *Suzuki cross-coupling reactions: General procedure*
   A mixture of aryl halide (1.0 mmol), phenylboronic acid (1.2 mmol), K_2CO_3 (2.0 mmol), novel ligand (0.1 mol%, 0.5 mg), and $Pd(OAc)_2$ (0.1 mol%, 0.23 mg) was heated in water (5 ml) at 80 °C temperature. The progress of the reaction is monitor by TLC. After the completion of the reaction, ethyl acetate (10 ml) was added to the reaction mixture and extracted with ethyl acetate (3 × 10 ml). The combined organic layer was dried with anhyd. Na_2SO_4 and the solvent were concentrated in vacuum to obtain a light yellow-white solid. The residue was purified by silica gel column chromatography (5–10% EtOAc in hexane) to afford the corresponding pure products **1**–**10** in 94–68% yields. *Biphenyl-4-carbaldehyde* (**2**): White solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 10.06 (s, 1H), 7.96 (d, *J* = 8.2 Hz, 2H), 7.76 (d, *J* = 8.2 Hz, 2H), 7.64 (d, *J* = 7.5 Hz, 2H), 7.48 (t, *J* = 7.3 Hz, 2H), 7.42 (t, *J* = 7.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm): 191.9, 147.1, 139.6, 135.0, 130.2, 128.9, 128.4, 127.6, 127.3.
27. *Mizoroki–Heck cross-coupling reactions: General procedure*
   A mixture of aryl halide (1.0 mmol), alkenes (1.5 mmol), K_2CO_3 (2.0 mmol), novel ligand (0.3 mol%), $Pd(OAc)_2$ (0.25 mol%) and TBAB (0.6 mmol) was heated in water (5 ml) at 90 °C temperature. The progress of the reaction is monitor by TLC. After the completion of the reaction, ethyl acetate (10 ml) was added to the reaction mixture and extracted with ethyl acetate (3 × 10 ml). The combined organic layer was dried with anhyd. Na_2SO_4 and the solvent were concentrated in vacuum to obtain a solid. The residue was purified by silica gel column chromatography (5–10% EtOAc in hexane) to afford the corresponding pure products in 92–80% yields. *(E)-4-Acetylstilbene* (**11**): ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.95 (d, *J* = 8.3 Hz, 2H), 7.58 (d, *J* = 8.3 Hz, 2H), 7.54 (d, *J* = 7.7 Hz, 2H), 7.38 (t, *J* = 7.5 Hz, 2H), 7.30 (t, *J* = 7.4 Hz, 1H), 7.23 (d, *J* = 16.3 Hz, 1H), 7.13 (d, *J* = 16.3 Hz, 1H), 2.60 (s, 3H); ^{13}C NMR (101 MHz,) δ (ppm): 197.4, 141.9, 136.6, 135.9, 131.4, 128.8, 128.7, 128.2, 127.4, 126.7, 126.4, 26.5.