



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 (benzylidene-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.

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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 imidazolide-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 [PdCl₂(NH₂CH₂COOH)₂] as an efficient catalyst for the

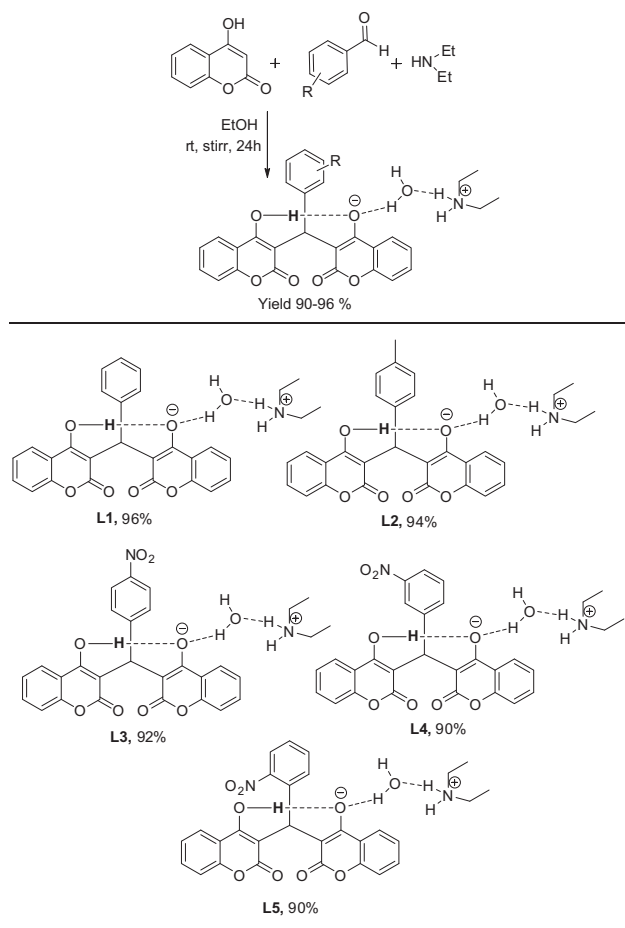
Suzuki–Miyaura reaction in aqueous medium.^{18b} Further, Li & co-workers and Balakrishna & co-workers have been demonstrated that the ionic adducts are effective ligands in the Suzuki–Miyaura and the Mizoroki–Heck cross-coupling reactions.¹⁹ In metal catalyzed reactions, it is well known that bulky 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 [benzylidene-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. Benzylidene-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

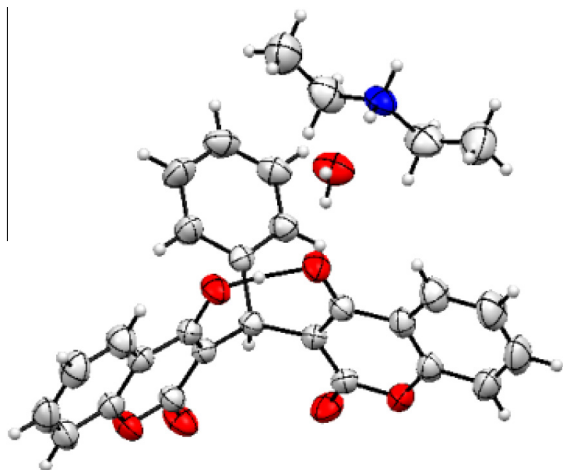


Figure 1. ORTEP diagram of ligand L1 with 40% ellipsoid probability.

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 KOtBu 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 $\text{Pd}(\text{OAc})_2$ till 10 h which showed that the combined ligands and $\text{Pd}(\text{OAc})_2$ have a key role in the cross-coupling reactions. Therefore, the combination of $\text{Pd}(\text{OAc})_2$ (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.

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