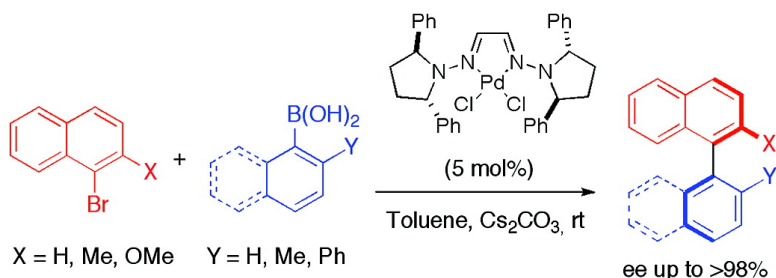


C-Symmetric Bis-Hydrazones as Ligands in the Asymmetric Suzuki#Miyaura Cross-Coupling

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C₂-Symmetric Bis-Hydrazones as Ligands in the Asymmetric Suzuki–Miyaura Cross-Coupling

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The Suzuki–Miyaura cross coupling is growing as one of the most useful C–C bond forming reactions, being the most popular method for the synthesis of biaryls.¹ The development of efficient asymmetric couplings is particularly valuable for the synthesis of configurationally stable derivatives, an important structural motif for its presence in a number of bioactive compounds.² However, a survey of the pertinent literature reveals that, after the pioneering communications by Hayashi (on a related Kumada coupling),³ Buchwald⁴ and Cammidge,⁵ only a few reports on catalytic, enantioselective versions have appeared,⁶ and it can be concluded that there is still need of new catalysts to improve the selectivity and generality of the reaction. In this Communication we wish to report on the use of chiral bis-hydrazones as phosphine-free ligands for the highly enantioselective, room temperature Suzuki–Miyaura coupling of a variety of substrates.

We have recently reported on the development of [Cu(OTf)₂/(bis-hydrazone)] catalysts, in which C₂-symmetric dialkylamino groups, making rotations around N–N bonds inconsequential, are key to achieve high enantioselectivities in asymmetric Diels–Alder reactions⁷ (Figure 1).

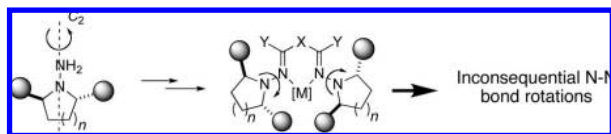


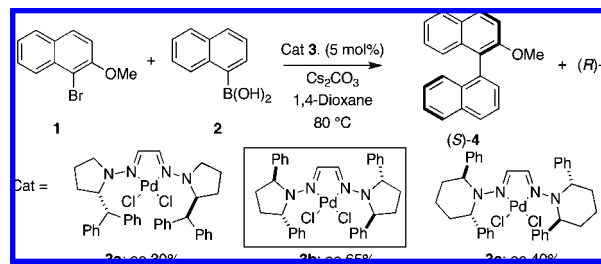
Figure 1. Bis-hydrazone ligand design.

On the other hand, there is experimental⁸ and theoretical⁹ evidence indicating the feasibility of diimine and bis-hydrazone ligands in Suzuki–Miyaura couplings. Stimulated by these precedents, we speculated that the key strategy developed for the bis-hydrazone ligand design would be particularly well suited to control the stereochemical course of the Suzuki cross-coupling reaction. The proposed ligands possess a priori several interesting features: (a) readily accessible in both enantiomeric forms, (b) bidentate structure, avoiding *cis/trans* isomerizations after the initial oxidative addition step, (c) C₂-symmetric structures, simplifying the analysis of the stereochemical outcome, (d) limited flexibility around N–N bonds, providing an adequate chiral environment for square-planar complexes⁷ and a considerable steric crowding beneficial for the formation of the 14e Pd(0) catalysts and the for reductive elimination step, and (e) a high electronic density provided by *n*→*π* conjugation in the bis-hydrazone ligand as compared with the 1,4-diazabutadiene ligands.¹⁰

The reaction of 1-bromo-2-methoxynaphthalene **1** with 1-naphthaleneboronic acid **2** was chosen as a challenging model system.

The preliminary experiments were performed in dioxane at 80 °C, using Cs₂CO₃ as the base, excess (1.5 equiv) of **2**, and 5 mol % of [PdCl₂(bis-hydrazone)] **3a–c** as the catalysts. We were delighted to observe that the desired product **4** was obtained with significant ee's in all cases, reaching a promising 65% ee when (*S,S*)-2,5-diphenyl-pyrrolidine-derived glyoxal bis-hydrazone **3b** was used as the ligand (Scheme 1).

Scheme 1. Chiral bis-Hydrazones as Ligands in a Model Reaction



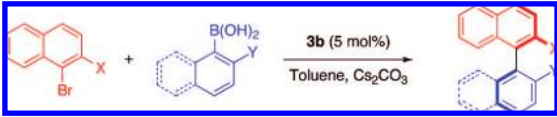
The use of toluene as the solvent provided better results: the product (*S*)-**4** was obtained in near quantitative yield in shorter reaction times and with a higher enantioselectivity (75% ee at 80 °C, Table 1, entry 1). The high catalytic activity of **3b** allowed the reaction to be performed at temperatures as low as 20 °C, affording the product in 90% ee, but in a lower 61% yield (entry 2). As the boronic acid **2** does not suffer significant side reactions (homocoupling and/or deboration) at low temperatures, it was feasible to perform also the reaction with excess of **1**, resulting in a much better yield of product **4** with similar enantioselectivity (entry 3). It is worth mentioning that the stability of the catalyst made it also possible to perform the reaction in the presence of water or oxygen with similar results.¹¹ The procedure was then applied to a variety of systems for the synthesis of functionalized (entries 6, 7, 17, 18) or nonfunctionalized (entries 4, 5, 8–16) 1,1'-binaphthyls, as well as for some hindered naphthyl–phenyl derivatives (entries 19–21), resulting in the isolation of the expected biaryls with good to excellent enantioselectivities.

As a working hypothesis, we assume that the oxidative addition and transmetalation intermediates **I**₁ and **I**₂ possess restricted Pd–C(aryl) bond rotations, particularly at low temperatures. The analysis of the expected geometries in the naphthyl–naphthyl case suggests that only **I**₁(**A**) and the propeller shaped **I**₂(**A**)-*anti* (with an antiparallel arrangement of the two naphthyl moieties) exhibit structures stabilized by one and two cooperative, *π*–stacking interactions, respectively. A reaction path through these intermediates is tentatively proposed to explain the high enantioselections and the absolute configurations observed. Thus, the product derived from **I**₂(**A**)-*anti* is formed by reductive elimination with

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Table 1. Enantioselective Suzuki–Miyaura Cross–Couplings



product	T (°C)	t	ylid. (%) ^a	method ^b	ee ^c
1	80	15 h	99	A	75 (S) ^d
2	20	7 d	61	A	90 (S)
3	20	7 d	97	B	86 (S)
4	80	3.5 h	98	A	90 (R) ^e
5	20	7 d	80	A	95 (R)
6	20	7 d	39	A	89 (S) ^f
7	20	7 d	71	B ^g	80 (S)
8	80	14 h	85	A	89 (R) ^f
9	20	7 d	53	B	>98 (R)
10	80	16 h	99	A	86 (R) ^e
11	20	7 d	71	A	98 (R)
12	80	14 h	64	A	88 (R) ^f
13	20	7 d	67	B	>98 (R)
14	80	14 h	98	A	70 (R) ^f
15	20	7 d	40	A	>98 (R)
16	20	7 d	65	B	93 (R)
17	20	7 d	44	A	92 (S) ^f
18	20	7 d	98	B ^g	81 (S)
19	20	7 d	36	A	84 (R) ^h
20	20	7 d	64	B ^g	77 (R)
21	20	7 d	97	A	84 (S) ^f

^a Isolated yield. ^b Conditions: (A) excess **2** (1.5 equiv); (B) excess **1** (2.5 equiv). ^c Determined by HPLC on chiral stationary phases. ^d The absolute configuration was assigned by comparison with literature data: see ref 6e. ^e The absolute configuration was assigned by comparison with literature data: see ref 6h. ^f The absolute configuration was assigned by analogy. ^g Reaction performed in 1 mL of solvent. ^h The absolute configuration was assigned after demethylation to the 1-(biphenyl-2-yl)naphthalen-2-ol derivative and comparison of the optical rotation with the reported value.¹²

counterclockwise conrotatory Pd–C(aryl) bond rotations, that is favored against the opposite clockwise rotations for steric reasons (Figure 2). A similar model explains also the absolute configurations observed for the naphthyl-phenyl derivatives.

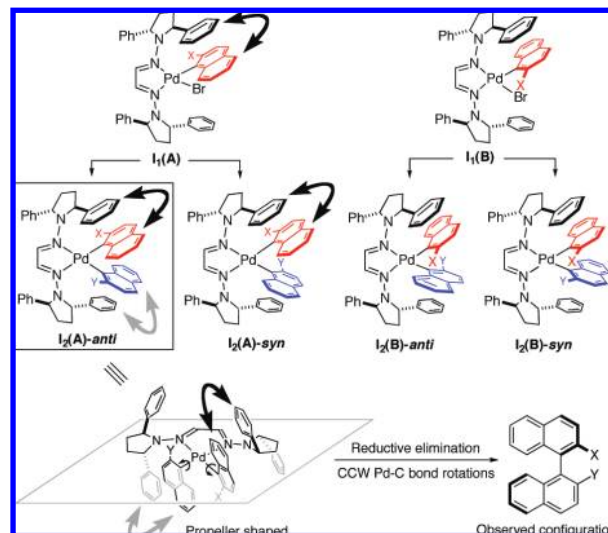


Figure 2. Oxidative addition and transmetalation intermediates to binaphthyls. Arrows indicate stabilizing π -stacking interactions.

In summary, glyoxal bis-hydrazones derived from C_2 -symmetric hydrazines appear as a new class of efficient ligands for the asymmetric Suzuki–Miyaura cross-coupling to biaryls, providing an unprecedented combination of activity and stereochemical control.

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Supporting Information Available: Experimental procedures, characterization data, and ee determinations. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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