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Asymmetric Negishi reaction for sterically hindered couplings: synthesis of chiral binaphthalenes

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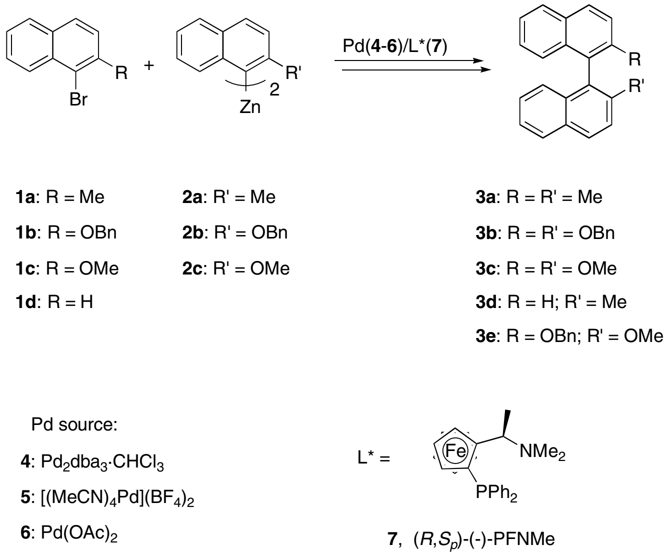
Abstract—A new synthetic approach affording, for the first time chiral binaphthalene derivatives via an asymmetric Negishi reaction, in good yields (55–95%) and good enantioselectivities (49–85% ee), is reported.

1. Introduction

Chiral binaphthalenes are amongst the most useful chiral ligands and auxiliaries employed in asymmetric synthesis.[1–3] Although the Stille and Suzuki–Miyaura reactions are very efficient for aryl–aryl carbon bond formation, sterically congested coupling partners (such as naphthyls) have the problems of poor yields and extensive deboronation in the Suzuki couplings. The naphthyl–naphthyl coupling using organozinc compounds as nucleophiles (Negishi reaction) is a possible alternative to overcome this problem, but has not yet been explored.[4] However, there are interesting precedents. For non-enantioselective couplings, Dai and Fu have developed a general methodology for the coupling of sterically hindered unactivated aryl chlorides with Pd catalysts,[5] and Milne and Buchwald have reported a very efficient new catalytic system for the preparation of hindered biaryls.[6] Very recently, asymmetric Negishi couplings involving secondary α-bromo amides and secondary benzylic halides have been reported by Fu et al. using chiral (*i*-Pr)-Pybox/Ni catalyst.[7,8]

Herein we report our studies on the first Pd catalyzed synthesis of chiral binaphthalenes by an asymmetric Negishi reaction (Scheme 1), as an example of an enantioselective coupling of extended, sterically demanding aromatic systems (such as substituted 1-halonaphthalenes and substituted naphthylzinc compounds) under Negishi conditions.



Scheme 1.

The results are shown in Table 1. The reaction conditions chosen were those giving the best results in our previous studies with Suzuki–Miyaura reactions.[9] After some preliminary experiments, we discovered that a fairly simple and easily accessible chiral ligand, the ferrocenyl monophosphine ligand (R,S_P)-(2-diphenylphosphino-ferrocenyl)-ethyldimethylamine ((R,S_P)-(−)-PFNMe) **7**, which is easily available from commercial (R)-(+)-N,N-dimethyl-1-ferrocenylethylamine,[10] performed better than other more sophisticated and expensive phosphine ligands.

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Table 1. Results from the asymmetric Negishi couplings[a]

Entry	Bromide **1**	Reagent **2**	Product **3**	Pd source	Temperature (°C)	Time (h)	Yield[b] (%)	ee[c] (%) (conf.)
1	**1a**	**2a**	**3a**	**4**	60	24	95	85 (*S*)
2	**1a**	**2a**	**3a**	**5**	60	24	95	85 (*S*)
3	**1b**	**2b**	**3b**	**6**	50	96	60	53 (*S*)
4	**1b**	**2b**	**3b**	**4**	50	96	65	66 (*S*)
5	**1c**	**2c**	**3c**	**6**	50	48	70	49 (*S*)
6	**1c**	**2c**	**3c**	**4**	50	24	70	54 (*S*)
7	**1d**	**2a**	**3d**	**4**	60	72	95	62 (*S*)
8	**1b**	**2c**	**3e**	**4**	60	72	55	60 (n/a)

[a] All reactions were carried out in THF (12.5 ml per 1 mmol of **1**); ratio bromide (**1**)/zinc compound (**2**) = 1/1.5; 5 mol % Pd and 20 mol % ligand were applied.

[b] Isolated yield after column chromatography.

[c] Determined by specific rotation[13–15] and HPLC[9] measurements.

2. Results and discussion

Naphthyl bromides used were obtained commercially **1a** or were synthesized according to literature procedures **1b** and **1c**.[11] The bis(naphthalen-1-yl)zinc compounds **2a–c** were obtained from the corresponding lithium compounds by a modified literature procedure,[12] treating the corresponding lithium organometallic derivative with $ZnCl_2$ solution in THF followed by filtration. The zinc compounds obtained were used as THF solutions in the coupling reactions.[†]

The reactions proceeded smoothly in THF under anhydrous conditions at moderate temperatures (50 and 60 °C). As palladium sources Pd(0) (**4**) and Pd(II) (**5** and **6**) species were used. Applying the Pd catalysts **4–6** in 5 mol % and ligand **7** in 20 mol % we hoped to achieve a high enantiomeric excess. Very good results were obtained, especially for the couplings of **1a** with **2a**. (Table 1, entries 1 and 2). Compared to the results of the corresponding Suzuki reaction,[9] the couplings reported herein proceeded with better yields (almost quantitative), equal enantioselectivities, and in remarkably shorter reaction times (24 h). The same results were obtained with $Pd_2dba_3 \cdot CHCl_3$ **4** or with $[Pd(NCMe)_4](BF_4)_2$ **5**. The coupling of **1b** with **2b** proceeded with lower yields and enantioselectivities, but using **4** instead of $Pd(OAc)_2$ **6** increased the enantioselectivity (Table 1, entry 3 vs 4). Similar results were found for the coupling of **1c** with **2c**, however, for shorter reaction times (Table 1, entry 5 vs 6). The enantioselectivity observed in the reactions decreased in the order Me > OBn > OMe and appears to depend on the steric demand of the coupling partners which, in our examples, is determined by the substituent at the α-position of the Br or B atom respectively of **1** and **2**. Compound **3d** (Table 1, entry 7) has been synthesized with equal enantioselectivity but much better yield than with the corresponding Suzuki reaction.[13]

3. Conclusion

In conclusion we have reported the first synthesis of chiral binaphthalene derivatives using an enantioselective Negishi cross-coupling reaction. This method is superior to the Suzuki equivalent. The protocol is extremely efficient affording up to 85% enantioselectivity and 95% yield in the synthesis of 2,2-dimethyl-1,1′-binaphthalene **3a**. Moreover, preliminary results show that these reaction conditions can be applied to the efficient enantioselective synthesis of a wider range of other naphthalene derivatives, either with **7** or chiral ferrocenyl monophosphine ligands with a similar structure. Looking at the trend of the yields and enantioselectivities observed in Table 1, these results may be even better for binaphthyl derivatives with somewhat bulkier substituents. These studies are currently in progress in our laboratory.

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[†] Typical procedure for the Negishi coupling reactions (see Table 1 and Scheme 1): In a flame dried 50 ml Schlenk flask with a Young's tap and Teflon stirring bar were introduced 0.16 mmol of the desired bromide **1a–c**, the palladium source **4–6** (0.008 mmol Pd), and the chiral ligand **7** (0.032 mmol), which were dissolved in 0.8 ml of THF. Then 1.2 ml of the corresponding 0.2 M solution in THF of zinc compounds **2a–c** were added and the flask sealed and heated at the corresponding temperature. The progress of the reaction was monitored by TLC. After the time indicated in Table 1, the reaction mixture was treated with 10 ml of distilled water, extracted with 3 × 10 ml CH_2Cl_2, dried over $MgSO_4$, and purified by flash chromatography (hexanes for **3a** and **3d** and hexanes/diethyl ether 7/1 for **3b**, **3c** and **3e**) to give the corresponding products **3a–e**.

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