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Microwave assisted asymmetric Suzuki-Miyaura and Negishi cross-coupling reactions: synthesis of chiral binaphthalenes

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Abstract—Microwave assisted asymmetric Suzuki-Miyaura and Negishi enantioselective cross-coupling reactions are reported for the first time, and have been applied to the rapid synthesis of chiral sterically hindered binaphthalene derivatives in reasonable to excellent yields (65–96%) and fair to good enantioselectivities (43–70% ee).

1. Introduction

The biaryl fragment is an important structural motif in many biologically active natural products, and in ligands for homogeneous catalysis.[1] The asymmetric Suzuki-Miyaura cross-coupling reaction has gained popularity as an attractive alternative to the standard methods for the selective control of biaryl axial chirality.[2–5] Very recently we also demonstrated the synthetic potential of the asymmetric Negishi reaction for binaphthalene synthesis.[6] One disadvantage of the Suzuki and Negishi reactions, especially with sterically hindered coupling partners, is the rather long reaction times which are required: they take many hours or even days.

Microwave irradiation has recently become a possible method for improving the reaction yields and shortening the reaction times.[7] It has been already shown that microwave irradiation can significantly promote the Suzuki-Miyaura and the Negishi reactions,[8–18] but to the best of our knowledge, there are no reports on microwave assisted enantioselective versions of the Suzuki and Negishi coupling reactions leading to axially chiral binaphthalenes. This is an important point, as the very small activation energy differences that give rise to stereoselection render the enantioselective catalytic reactions very sensitive to small changes in methodology. Herein we report for the first time asymmetric Suzuki-Miyaura and Negishi cross-couplings with microwave acceleration, and their application to the synthesis of sterically hindered binaphthalenes (Scheme 1).

2. Results and discussion

We decided to check the microwave accelerated couplings under the reaction conditions giving the best results in our previous studies with conventional Suzuki-Miyaura[5] and Negishi[6] reactions. Eventually some adjustment of reaction temperatures was needed. As a chiral ligand we used (R,S_p)-(2-diphenylphosphinoferrocenyl)ethyldimethylamine ((R,S_p)-(−)-PFNMe) (**7**),[5,6,19,20] easily prepared from the commercial (*R*)-(+)-*N*,*N*-dimethyl-1-ferrocenylethyl-amine.[21] The naphthylbromides used were obtained commercially, **1a** and **1d**, or synthesized according to the literature procedures, **1b** and **1c**.[22] The boronic acids **2a**–**c** were obtained and purified according to our previously published procedure.[5] The bis(naphthalen-1-yl)zinc compounds **8a**–**c** were obtained from the corresponding lithium compounds via a modified literature procedure[23] by treatment of the lithium organometallic derivative with $ZnCl_2$ solution in THF followed by filtration. The zinc compounds obtained were used as THF solutions in the Negishi couplings.

The microwave experiments were carried out under an inert atmosphere using sealed vessel irradiation with simultaneous compressed air cooling.[24] We attempted to find a compromise between the yield of the desired products and the enantioselectivity.

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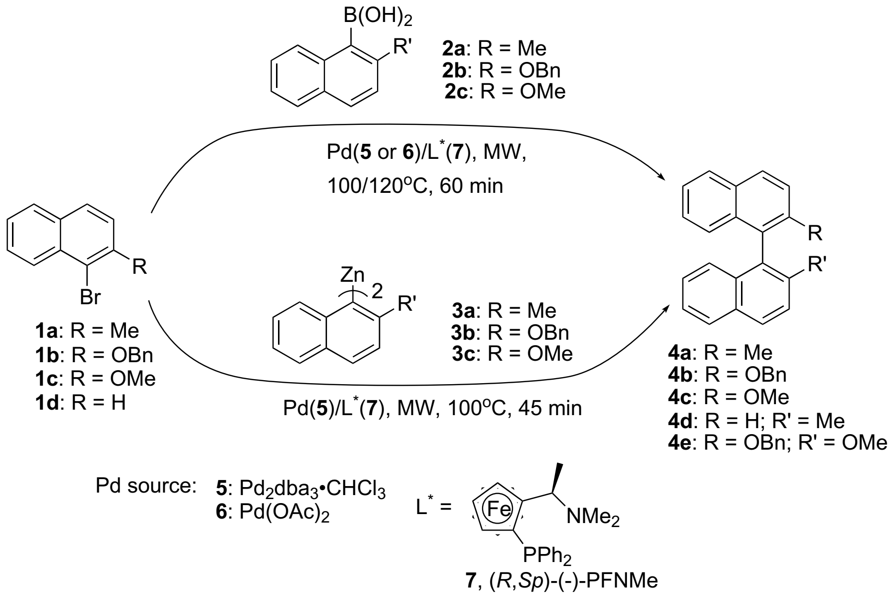

Scheme 1.

The results for the asymmetric Suzuki couplings are shown in Table 1 (entries 1–7).[25] The reactions were carried out under anhydrous conditions. As for the conventionally heated couplings,[5] THF and DME (dimethoxyethane) were used as solvents, with CsF as base. In all cases 5% of Pd and 20% of the chiral ligand were used. $Pd(OAc)_2$ **6** was used for couplings **1b** and **2b**, and **1c** and **2c** (Table 1, entries 4 and 5, respectively), where $Pd_2dba_3 \cdot CHCl_3$ did not afford satisfactory yields. Most reactions work well at 120 °C for 1 h. Except for **4a**, yields were as good as or better than for the conventional oil bath heated reactions, but only required one hour instead of the usual hours or days. The enantioselectivities were somewhat lower but still reasonable. The formation of the most hindered **4a** is a delicate matter (compare entries 1–3). At 120 °C, the reaction is incomplete and the ee is modest. Decreasing the temperature to 100 °C (entry 1) increases the enantiomeric excess but decreases the product yield due to more incomplete reaction. Increasing the temperature to 150 °C (entry 3) mproves the yield but produces deboronation and also decreases the ee. For the rest of the Suzuki couplings (entries 4–7) the yields are almost quantitative while the ee's are usually a bit lower that those obtained in the conventional oil bath heated protocol.

Table 1. Results from the asymmetric Suzuki (entries 1–6)[a] and Negishi (entries 7–11)[b] couplings[a]

Entry	Bromide	Nucleophile	Product	*T* (°C)	Yield[c] (%)	% *S*[d]	ee[d] % (conf.)
1	**1a**	**2a**	**4a**	100	29 (85)	85 (92.5)	70 (*S*) (85)
2	**1a**	**2a**	**4a**	120	36 (85)	79.5 (92.5)	59 (*S*) (85)
3	**1a**	**2a**	**4a**	150	65 (85)	76.5 (92.5)	53 (*S*) (85)
4	**1b**	**2b**	**4b**	120	95 (95)	71.5 (80)	43 (*S*) (60)
5	**1c**	**2c**	**4c**	120	95 (95)	75.5 (75)	51 (*S*) (50)
6	**1d**	**2a**	**4d**	120	95 (95)	75.5 (82)	51 (*S*) (64)
7	**1c**	**2b**	**4e**	120	95 (90)	71.5 (80)	43 (n/a) (60)
8	**1a**	**3a**	**4a**	100	95 (95)	80 (92.5)	60 (*S*) (85)
9	**1b**	**3b**	**4b**	100	20 (65)	74 (83)	48 (*S*) (66)
10	**1c**	**3c**	**4c**	100	78 (70)	70 (77)	40 (*S*) (54)
11	**1d**	**3a**	**4d**	100	95 (95)	72.5 (81)	45 (*S*) (62)
12	**1b**	**3c**	**4e**	100	73 (55)	72 (80)	44 (n/a) (60)

[a] CsF was used as base in all reactions; reaction time: 60 min; 20 mol % of **7** is used; Pd source: $Pd(OAc)_2$ (**6**) for entries 3 and 4, Pd_2dba_3 for entries 1, 2, 5, and 6; reactants ratio: bromide (**1**)/boronic acid (**2**)/CsF = 1/1.8/3; solvents used (12.5 mL per 1 mmol of **1**): THF for entries with Pd_2dba_3 (**5**), DME for entries with $Pd(OAc)_2$ (**6**); power applied: 250 W.

[b] All reactions were carried out in THF (12.5 mL per 1 mmol of **1**); ratio bromide (**1**)/zinc compound (**3**) = 1/1.5; 5 mol % Pd and 20 mol % ligand were used; reaction time: 45 min; power applied 250 W.

[c] Isolated yield after column chromatography; yields of the corresponding oil bath heated reactions in parentheses.

[d] Determined by specific rotation (for **4a** and **4d**)[20] and HPLC measurements (Daicel Chiralpak AD for **4b**, Chiralcel OJ-R for **4e** and Chiralcel OD-H for **4c** columns), using heptane/2-propanol or methanol/water as eluting solvents; major enantiomer is *S* in all cases except for **4e** where the exact configuration was not determined unequivocally; ee of the corresponding oil bath heated reactions is given in parentheses.

The results for the asymmetric Negishi couplings are also shown in Table 1 (entries 8–12).[26] The reactions proceeded smoothly in THF under an inert atmosphere at 100 °C within 45 min, using 5 mol % of $Pd_2dba_3{\cdot}CHCl_3$ **5** as the palladium source and chiral ligand **7** in 20 mol %. Most reaction yields and ee's are good to excellent. Very good results were especially obtained with coupling **1a** and **3a** (entry 8), which is the most sterically demanding and had given problems with the Suzuki reaction (entries 1–3). So, the Negishi reaction is a best choice for the production of **4a**. For the rest of the compounds the yield and ee results are good, but an average the Suzuki reaction worked slightly better. We were unable to provide an explanation for why coupling **1b** + **3b** (entry 9), is particularly bad with the Negishi protocol.

3. Conclusion

In conclusion we report the first microwave assisted enantioselective Suzuki-Miyaura and Negishi coupling reactions and the results in the synthesis of chiral sterically demanding binaphthalenes. Compared with the conventionally heated reactions, the microwave assisted reactions proceed with equal or better yields in dramatically shorter reaction times (1 h vs several days). The enantioselectivity is somewhat lower under our experimental conditions, which were initially focussed onto improve the reaction times and to examine the problem of deboronation in sterically challenging Suzuki reactions. Most of the 'minute-made' microwave accelerated Suzuki-Miyaura couplings reported in the literature involve phenylboronic acid or simple derivatives of it, which are known to react very easily and without noticeable deboronation with a large number of substrates. Suzuki coupling of sterically congested extended aromatics, which is usually accompanied with many difficulties (including extensive deboronation), had not been microwave tested.[5,19,20] With these difficulties in mind, our experimental results can be deemed excellent as far as yields are concerned, proving that the problem of deboronation can be avoided in most cases. Our results also suggested that a better time/ee tradeoff might be achieved using somewhat longer reaction times at lower temperatures. Negishi seems to work less well in general, but it can solve some problematic cases. Studies on both Suzuki and Negishi couplings under microwave acceleration for the enantioselective synthesis of a wide range of sterically demanding fragments are under way in our laboratory.

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25. *General procedure for the Suzuki coupling reactions*: In a dry 10 mL flask with a Teflon stirring bar were introduced 0.16 mmol of the desired bromide **1a**–**d**, palladium source **5** or **6** (0.008 mmol Pd), chiral ligand **7** (0.032 mmol), the relevant boronic acid **2a**–**c** (0.29 mmol), and CsF (0.50 mmol). Anhydrous THF or DME (2 mL) was added, the flask was sealed and the mixture was stirred and irradiated at the corresponding temperature. After 60 min, the reaction mixture was treated with 10 mL of distilled water, extracted with 3 × 10 mL of CH_2Cl_2, dried over $MgSO_4$, and purified by flash chromatography (hexanes for **4a** and **4d**, hexanes/diethyl ether 7/1 for **4b** and **4c** and hexanes/diethyl ether 20/1 for **4e**) to give the corresponding product **4a**–**e**.
26. *General procedure for the Negishi coupling reactions*: In a dry 10 mL flask with a Teflon stirring bar were introduced 0.16 mmol of the desired bromide **1a**–**d**, palladium source **5** (0.008 mmol Pd), and chiral ligand **7** (0.032 mmol), which were dissolved in 0.8 mL of THF. Then 1.2 mL of 0.2 M solution in THF of the corresponding zinc compound (**3a**–**c**) was added, the flask was sealed and irradiated at 100 °C. After 45 min, the reaction mixture was treated with 10 mL of distilled water, extracted with 3 × 10 mL of CH_2Cl_2, dried ($MgSO_4$), and purified by flash chromatography (hexanes for **4a** and **4d**, hexanes/diethyl ether 7/1 for **4b** and **4c** and hexanes/diethyl ether 20/1) to give the corresponding product (**4a**–**e**).