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Tetrahedron Letters 49 (2008) 3204–3207

Tetrahedron Letters

Comparison of monomode and multimode microwave equipment in Suzuki–Miyaura reactions—*en route* to high throughput parallel synthesis under microwave conditions

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Received 2 March 2008; revised 15 March 2008; accepted 19 March 2008

Abstract

The microwave heated Suzuki–Miyaura cross-coupling reaction of boronic acids, boronic esters and organotrifluoroborates served as a model reaction in a singlemode equipment. The reaction conditions were optimized with respect to temperature and reaction time and were transferred to multimode equipment which is well suited for multiparallel synthesis in a larger scale. The source of the Pd species chosen included immobilized Pd complexes and Pd particles. In fact the increased time to reach the required reaction time in multimode chambers suitable for 48 parallel reactions has to be taken into account. The nature of the boronic acid has no impact on the efficiency of the catalytic process. However, heterogenized Pd species perform less well in multimode chambers with larger vial volumes, which we ascribe to diffusion phenomena.

Keywords: Suzuki–Miyaura reaction; Microwave; Monomode; Multimode; Palladium precatalysts

‘Enabling technologies for organic synthesis’ such as microwave, solid-phase assistance, new reactor design or nonconventional solvents have changed organic chemistry in terms of efficiency, work-up and speed. One can only speculate when these laboratory techniques will be incorporated into industrial processes.[1] Since the first reports on the use of microwave heating for accelerating organic reactions by the groups of Gedye[2] and Giguere/Majetich[3] in 1986, the number of publications related to microwave-assisted organic synthesis (MAOS) has increased dramatically. Clearly, this technique leads to a rate enhancement with often excellent reproducibility, improved yields and less side reactions compared to conventional heating.[4] When comparing different reaction techniques, a significant gain in energy efficiency using microwave irradiation has been noted.[5]

With respect to parallel synthesis, compound libraries are commonly prepared sequentially in an automated singlemode instrument with full control of each reaction or in a multimode instrument performing parallel reactions in one irradiation experiment only. Additionally, it has been shown that it is possible to directly scale reaction conditions from singlemode small-scale to multimode larger scale microwave reactors.[6]

Suzuki–Miyaura reaction has emerged as one of the most powerful ways of preparing biaryls.[7] Besides, boronic acids and boronic esters organotrifluoroborates are becoming more and more popular for these cross-coupling reactions.[8]

As some limitations for these different reagents have been discussed (e.g., purification of boronic acids, atom economy of boronic esters or synthetic availability of

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doi:10.1016/j.tetlet.2008.03.094

organofluoroborates), we initiated a research programme for comparing the reactivity of a selected number of aryl boronic derivatives in the microwave-assisted palladium-catalyzed Suzuki–Miyaura cross-coupling reaction.

These studies are in line with our earlier work[9] on homogeneous and heterogeneous palladium precatalysts.

In the present study, it is our intention to investigate the feasibility of a protocol for the rapid optimization of transformations in the microwave field. Is it possible to carry out optimization with a monomode equipment and transfer the knowledge accumulated into a multimode apparatus for the parallel upscaled synthesis of compound libraries? Here, we focus on the comparison of selected Suzuki–Miyaura reactions with different Pd sources under microwave irradiating conditions using singlemode and multimode microwave equipment.[10,11]

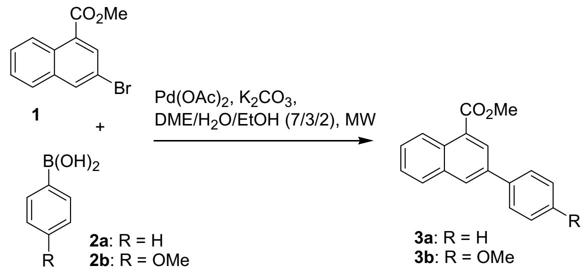
The cross-coupling reaction between two phenyl boronic acids and 3-bromo-naphthalene-1-carboxylic acid methyl ester (Scheme 1) served as a model reaction. First, we investigated the temperature/time profiles under singlemode conditions. Based on the earlier results,[9] we focused on the temperature range between 100 °C and 130 °C (Table 1). Raising the reaction time from 300 to 600 s or increasing the temperature from 100 °C to 130 °C did not result in increased yields and therefore 110 °C was chosen in the following investigations.

In the following, we investigated this model Suzuki–Miyaura reaction with different boron derivatives (acids, esters and fluoroborates) and different palladium sources including heterogeneous (immobilized) precatalysts in a multimode system (Synthos 3000) with parallel setup (Scheme 2).

Besides the commercial $Pd(OAc)_2$ (**A**) and the encapsulated Pd(II)EnCat^{TM} 40 (**C**), we compared a pyridine–aldoxime derivative (**B**),[9a] palladium(0) particles immobilized on an anionic exchange resin (**D**)[12] and a Najera precatalyst immobilized on polyvinyl pyridine (**E**).[9c]

As heating rates are reduced when processing larger volumes compared to small volumes, the reaction time had to be increased from 300 s to 420 s. Temperature and power profiles for a typical Suzuki–Miyaura reaction in the microwave field (in sealed vessel) are depicted below (Fig. 1: monomode; Fig. 2: multimode). For a better comparison, the sample volume per vessel was kept constant (5 mL each).

Obviously, for short reaction times the transfer from mono- to multimode has to be analyzed very carefully. While under singlemode conditions, the reaction temperature of 110 °C was reached within a few seconds, the multimode conditions required more than 200 s. In this special

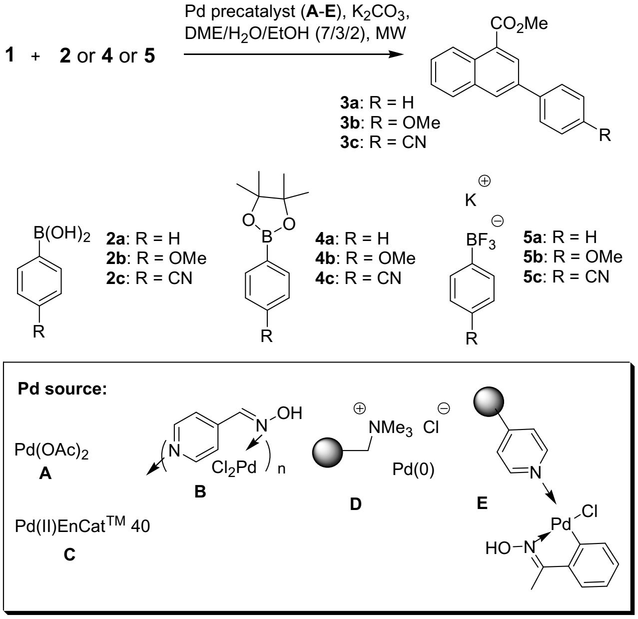


Scheme 1. Model Suzuki–Miyaura cross-coupling reactions. Reagents and conditions: aryl bromide (0.2 mmol), boronic acid (0.4 mmol), K_2CO_3 (0.6 mmol), $Pd(OAc)_2$ (0.02 mmol), $DME/H_2O/EtOH$ (7:3:2; 5 mL).

Table 1
Results of model Suzuki–Miyaura reaction (also refer to Scheme 1)

Product	T (°C)	Time (s)	LC–MS Yield UV[a] (%)
3a	100	600	90
3a	100	300	93
3a	110	300	90
3a	130	300	91
3b	100	600	81
3b	100	300	87
3b	110	300	86
3b	130	300	79

[a] Percentages are based on the product peak area by LC–MS (UV).



Scheme 2. Parallel setup of Suzuki-Miyaura reaction.

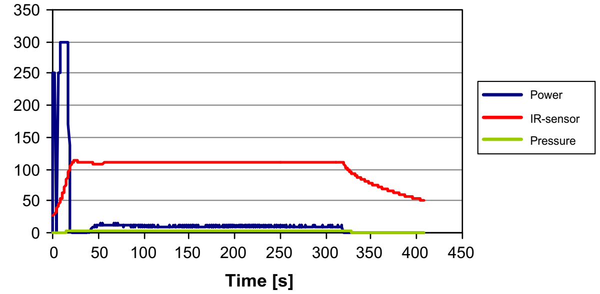


Fig. 1. Microwave heating profile for singlemode irradiation (y axis = temperature [°C], pressure [bar], power [W]); 5 mL sample volume.[10]

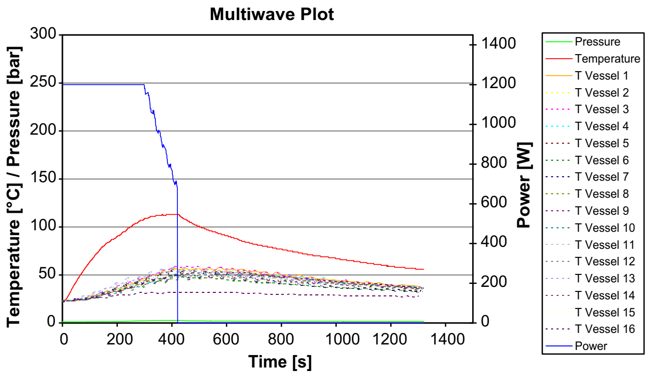


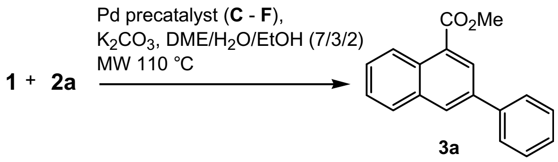
Fig. 2. Microwave heating profiles for multimode irradiation; rotor 48MF50; 48 × 5 mL sample volume; top profile using the internal gas ballon thermometer, bottom profiles with external IR-sensors.[11]

case, the rapid heating and cooling profile cannot be transferred directly but had to be optimized, individually. It has to be noted that Kappe and co-workers recently highlighted the importance of exact measurements of internal and external temperatures using a dedicated reactor setup.[13]

These results set the stage to simultaneously perform 45 Suzuki–Miyaura reactions with a multimode microwave system.[14,15] The results are listed in Table 2.

The data clearly reveal that all the three types of boron derivatives behave in a similar manner irrespective of the aromatic substitution pattern. However, the precatalysts used, differ substantially in their performance. In general, heterogeneous precatalysts showed low or moderate conversions only.

Table 3
Reagents and conditions:[14,15] Aryl bromide (0.2 mmol), boronic acid derivative (0.4 mmol), K_2CO_3 (0.6 mmol), precatalyst (0.02 mmol), DME/H_2O/EtOH (7:3:2; 5 mL)[a]

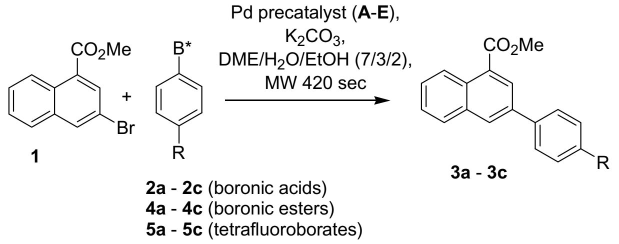


Time (s)	C	D	E	F
180	19	n.p.[b]	n.p.	67
240	30	n.p.	n.p.	83
300	41	13	28	90
600	70	18	47	99
900	73	29	57	n.p.
1200	71	34	97	n.p.

[a] Percentages are based on the product peak area by LC/MS (ELSD).
[b] Not performed.

Returning back to the monomode system, we performed the model reaction with different heterogeneous precatalysts at 110 °C (Table 3). These studies should reveal, whether these differences are caused by a lower reactivity or exclusively by diffusion phenomena. In addition, we used precatalyst Pd(II)EnCat™ 30 (**F**). Based on these data, it can be concluded that the encapsulated catalyst Pd(II)EnCat™ 30 reacts faster and performs more efficiently than Pd(II)EnCat™ 40 (C).[16] With the polymer supported Najera precatalyst (**E**) also complete conversion is achieved. However, the reaction times are extended, whereas the polymeric ionic palladium source (**D**) only afforded moderate results.

Table 2
Reagents and conditions:[14,15] Aryl bromide (0.2 mmol), boronic acid derivative (0.4 mmol), K_2CO_3 (0.6 mmol), precatalyst (0.02 mmol), DME/H_2O/EtOH (7:3:2; 5 mL); 110 °C[a]



	R	B[*]	A	B	C	D	E
2a	H	$B(OH)_2$	99	99	46	29	31
4a	H	$B(OR)_2$	99	99	46	17	37
5a	H	BF_3K	99	99	40	10	0
2b	OCH_3	$B(OH)_2$	99	99	47	16	2
4b	OCH_3	$B(OR)_2$	99	99	50	25	30
5b	OCH_3	BF_3K	99	99	50	35	58
2c	CN	$B(OH)_2$	99	99	82	25	14
4c	CN	$B(OR)_2$	99	99	60	15	0
5c	CN	BF_3K	81	82	54	33	0

[a] Percentages are based on the product peak area by LC–MS (ELSD).

In conclusion the present study is a guideline for transferring reaction conditions initially identified in singlemode equipment onto multimode equipment suitable for multiparallel reactions. Clearly, catalysis under homogeneous conditions can easily be adapted. Still, only slightly longer reaction times were encountered which is associated with a slower heating rate present in the latter equipment. However, for biphasic reactions using solid-phase bound or associated Pd species the situation is more complex, because the larger volume associated with diffusion phenomena lead to substantially reduced reaction rates.

The studies pave the way for the rapid development of compound libraries which includes the optimization of reaction conditions (with monomode equipment) followed by parallel synthesis (in 48 reactors in multimode equipment).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.03.094.

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10. Biotage Emrys Optimizer: A fully automated singlemode (300 W) microwave reactor that incorporates a gripper for robotic vessel transfer. The system is used for the efficient optimization of reaction conditions and for the unattended generation of libraries (sealed vessels, processing volume 0.5–5 mL, max pressure 20 bar, IR temperature sensor on the outside of the reaction vessel). Experimental details: 5 mL sample volume, magnetic stirring, sealed 10 mL reaction vessel (glass); rapid cooling with compressed air.
11. Anton Paar Synthos 3000: A multimode microwave instrument with two magnetrons (1400 W continuously delivered output power) dedicated for batch scale-up that allows processing of volumes of up to 1 L in a variety of different rotor systems (8, 16, 48, 64). Experimental details: 48 × 5 mL sample volume, magnetic stirring; temperature measurement in one reference vessel via an internal gas balloon thermometer, surface temperature monitoring of 16 individual vessels by IR thermography, sealed 50 mL PFA liner; cooling by venting air through cooling gaps.
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14. Yields are based on the product peak areas as compared to total peak area of a LC/MS chromatogram (ELSD). The given yields are calculated from a analysis of filtered reaction mixtures and therefore should be used as an indication of the product yield.
15. Palladium precatalyst (0.02 mmol) was added to a reaction mixture consisting of boronic acid derivative (0.4 mmol), aryl halide (0.2 mmol) and K_2CO_3 (0.6 mmol) in 5 mL DME/H_2O/EtOH (7:3:2). The mixture was subjected to microwave irradiating conditions (Emrys™ Optimizer from Personal Chemistry). The stirred reaction mixture was heated for 300 s at 110 °C and then cooled. The catalyst was removed by filtration over Celite™ and washed with diethyl ether (5 mL). The organic phase was dried with sodium sulfate and concentrated under reduced pressure. The outcome of the reaction was monitored by LC–MS-analysis. In case of the parallel setup (Synthos 3000 from Anton Paar, Rotor 48MF50) the reaction was heated for 420 s at 110 °C. For NMR-characterization the crude product was purified by column chromatography. The isolated yields obtained are **3a** = 90%; **3b** = 95%; **3c** = 85%.
16. Recently, in a mechanistic study on modern palladium catalyst precursors the use of Pd(II)EnCat with microwave heating in cationic Heck reactions was investigated: Svennebring, A.; Sjöberg, P. J. R.; Larhed, M.; Nilsson, P. *Tetrahedron* **2008**, *64*, 1808–1812.