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Microwave-promoted Suzuki–Miyaura coupling reactions in a cycloalkane-based thermomorphic biphasic system

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Abstract—Microwave-promoted Suzuki–Miyaura coupling reaction of aryl halides attached to a cycloalkane-soluble platform was accomplished in a cycloalkane-based thermomorphic biphasic system. Following irradiation and subsequent cooling, the monophasic reaction mixture immediately formed a biphasic solution to allow facile workup and separation of the product.

Suzuki–Miyaura coupling reaction (palladium-catalyzed cross-coupling reaction of aryl halides with boronic acid) is one of the most versatile and utilized reactions for the selective construction of carbon–carbon bonds, in particular for the formation of biaryls. To date, several palladium-catalyzed Suzuki–Miyaura reactions using microwave and conventional heating have been reported.[1] Because of reduced reaction time, increased product yields and allowance of precise control of the reaction parameters, the use of microwave as a tool for synthetic chemistry, especially parallel and combinatorial chemistry, is increasing. In order to facilitate the sequential process, several methods have been developed for the Suzuki–Miyaura coupling reaction. For example, the solid-phase resins possessing aryl halides or boronic acids offer many advantages with regard to compound isolation and ease of handling of corresponding Suzuki–Miyaura coupling.[2] The insoluble nature of the resins has, however, complicated the characterization of compounds attached to them and led to reagent accessibility problems. Solution-phase synthesis methods, including fluorous[3] and ionic liquid[4] strategies, have attracted much interest. In these systems, one of the most important techniques is the relevant phase labelling of the substrate, catalyst reagents and other reaction components. An appropriate phase-labelling system allows purification of the desired products using simple work-up techniques such as evaporation, extraction and filtration. Although the introduction of liquid-phase tags into target compounds which can be isolated from other reaction components represents an attractive methodology compared to solid-phase synthesis, many of the reagents which are currently used for liquid or solid-phase extraction are expensive, and unusual treatments are sometimes required.

To overcome the purification difficulties in general solution-phase reactions, we have decided to explore the use

Table 1. Optimization of solvent combination for Suzuki–Miyaura coupling reaction of aryl halide **1a** with 4-fluorophenylboronic acid[a]

Cycloalkane	Polar solvent	Solvent ratio (v/v)	Phase transition temp (°C)	Yield[b] (%)
c-Hex	DMF	1:1	45	97
c-Hex	DMF	9:1	42	94
MCH	DMF	1:1	50	98
MCH	DMF	9:1	44	95[c]
MCH	DMI[d]	1:1	32	15
MCH	NMP[d]	1:1	18	36
MCH	DMAc[d]	1:1	20	31
MCH	DMSO[d]	1:1	—[e]	34
MCH	NM	1:1	—[e]	66

[a] Reaction conditions: $PdCl_2(dppf)$ (5 mol %), boronic acid (2 equiv), K_3PO_4 (3 equiv), under Argon. Microwave-irradiation 150 W, 110 °C, 5 min.

[b] Isolated yield.

[c] Reusability of the recovered Pd catalyst was also tested; see Supplementary data.

[d] DMI: 1,3-dimethyl-2-imidazolidinone, NMP: 1-methyl-2-pyrrolidone, DMAc: dimethylacetamide, DMSO: dimethylsulfoxide.

[e] Immiscible.

Keywords: Thermomorphic; Cycloalkane; Microwave; Suzuki–Miyaura cross-coupling.

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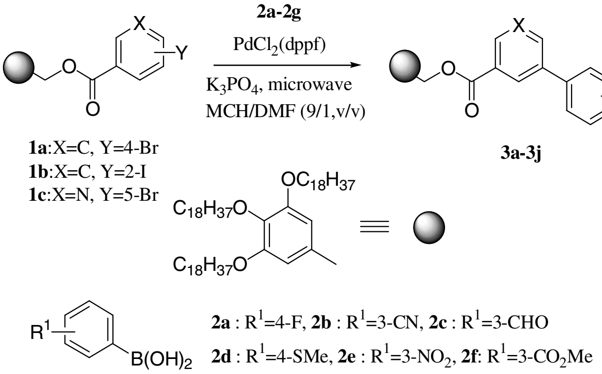
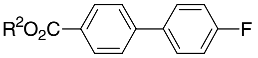
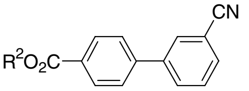
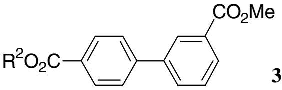
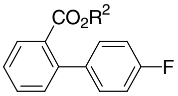
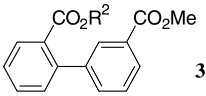
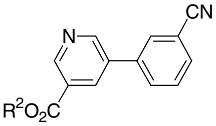
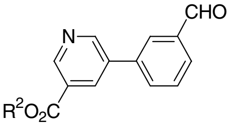
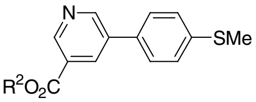
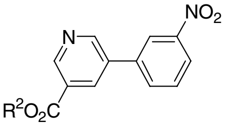
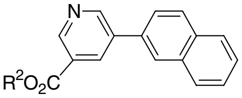
Table 2. Microwave-promoted Suzuki–Miyaura coupling reaction in cycloalkane-based thermomorphic biphasic solution[a]



1a:X=C, Y=4-Br
1b:X=C, Y=2-I
1c:X=N, Y=5-Br

2a : R^1=4-F, **2b** : R^1=3-CN, **2c** : R^1=3-CHO
2d : R^1=4-SMe, **2e** : R^1=3-NO_2, **2f**: R^1=3-CO_2Me
2g : 2-naphthylboronic acid

Entry	Aryl halide	Boronic acid	Product[b]	Yield[c] (%)
1	**1a**	**2a**	 **3a**	98
2	**1a**	**2b**	 **3b**	96
3	**1a**	**2f**	 **3c**	98
4	**1b**	**2a**	 **3d**	97
5	**1b**	**2f**	 **3e**	95
6	**1c**	**2b**	 **3f**	97
7	**1c**	**2c**	 **3g**	98
8	**1c**	**2d**	 **3h**	94
9	**1c**	**2e**	 **3i**	97
10	**1c**	**2g**	 **3j**	79

[a] All reactions were carried out using aryl halide, 2 equiv of boronic acid, 3 equiv of K_3PO_4 and 5 mol % of $PdCl_2(dppf)$ in 4 ml of MCH/DMF (9:1, v/v). The microwave power was 150 W, irradiation time was 5 min.

[b] R^2: 3,4,5-tris-octadecyloxybenzyl.

[c] Isolated yield.

of a thermomorphic biphasic system,[5] which has attractive features for preparative organic synthesis and promising options for liquid-phase combinatorial synthesis. Our studies have previously shown that temperature can control the phase states of a cycloalkane-based biphasic system that is composed of cyclohexane (*c*-Hex) and aprotic polar solvents, such as dimethylformamide (DMF), nitromethane (NM), acetonitrile or methanol.[6] Upon completion of the coupling reaction, the phase separation of cycloalkane and the aprotic polar solvent was employed for product separation and purification.

Although alkanes, because of their low dielectric constants, are not suitable for microwave-irradiated reactions, various polar organic solvents or ionic liquids are known to be effective for acceleration of Suzuki–Miyaura coupling reaction. Even in the conventional heating conditions of biphasic solutions, polar organic solvents accelerated Suzuki–Miyaura coupling reaction. This gave us incentive to construct a thermomorphic reaction system that would enable highly efficient microwave-promoted reactions in a monophasic solutions followed by product isolation upon cooling and phase separation. Herein, we report cycloalkane-based thermomorphic systems for microwave-promoted Suzuki–Miyaura coupling reactions featuring a rapid reaction purification process.

Initially, various solvents were investigated to determine the composition that would give the thermomorphic behaviour necessary for reversible phase transition under microwave-irradiated heating conditions. The thermomorphic properties of various combinations of cycloalkanes and microwave-active organic solvents are listed in Table 1. As an example, the solvent mixture of methylcyclohexane (MCH)/DMF (1:1, v/v), which exists as a monophasic solution at above ca. 45 °C, immediately separates into two phases upon cooling the mixture to below ca. 45 °C. Subsequently, Suzuki–Miyaura coupling reactions were carried out under microwave-irradiated condition using the optimal solvent combination (Table 1). To selectively partition the product into the cycloalkane phase following the reaction, the aryl halides were attached to 3,4,5-tris-octadecyloxybenzyl alcohol (a cycloalkane-soluble platform).[7]

As a model reaction, Suzuki–Miyaura coupling was carried out under microwave-irradiated conditions (150 W, 5 min) using **1a** and two molar equivalents of *p*-fluorophenylboronic acid **2a** in the presence of potassium carbonate and a catalytic amount of $PdCl_2$(dppf) (1,1′-bis(diphenylphosphino)ferrocene). In the presence of a polar solvent, and upon cooling the mixture after the completion of the reaction, the product was recovered from the upper cycloalkane layer almost quantitatively. On the other hand, in the absence of a polar solvent, the coupling reaction afforded the product in less than 20% yield. Microwave-irradiation for the mixture of compound **1a** and **2a** in phase-separated solutions, for example, composed of *n*-tetradecane and DMF (1:1 v/v) gave product **3a** in less than 35% (microwave power: 150 W, 110 °C, 10 min). The mixture of MCH/DMF (9:1, v/v) was chosen as the optimal thermomorphic solvent system. As listed in Table 2, Suzuki–Miyaura couplings of various substituted phenylboronic acids with aryl halides **1a–c** in the presence of potassium carbonate and a catalytic amount of $PdCl_2$(dppf) (5 mol %) in MCH/DMF (9:1, v/v) were carried out (Table 2, Fig. 1). Using microwave dielectric heating (150 W, 110 °C), all reactions were completed in 5 min. Subsequently, after cooling and the phase separation, the cycloalkane-soluble platform-bound substrates **3a–j** were selectively recovered in the upper MCH phase. The purity of the products was verified using TLC analysis, which exhibited a single spot.[8,9] The compounds were readily obtained by evaporation (simple removal of MCH), or by precipitation (addition of methanol in the MCH solution followed by filtration). Finally, the coupled products were cleaved from the cycloalkane-soluble platform by treatment with a catalytic amount of NaOMe in a methanol/MCH solution to afford the corresponding biaryls in excellent yields.

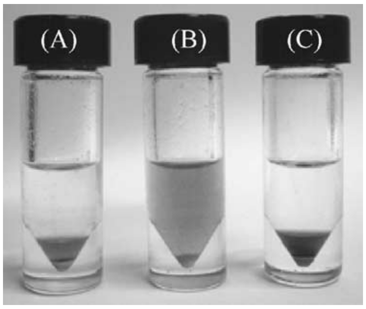


Figure 1. (A) Before heating, with aryl bromide **1a** (MCH phase) and boronic acid **2a**, Pd catalyst, base (DMF phase); (B) homogenous solution after microwave-irradiation (150 W, 110 °C) for 5 min; (C) after the reaction with biphenyls (MCH phase) and boronic acid, Pd catalyst, salts (DMF phase).

It is noteworthy that our thermomorphic biphasic system enables the usage of cycloalkane as a reaction solvent under microwave-irradiation conditions, although alkanes, because of their low dielectric constants, are not suitable for microwave reaction. This result showed a positive effect of miscibility of the cycloalkane-based thermomorphic system for acceleration of reactions. Furthermore, although thermal or microwave-irradiated Suzuki–Miyaura coupling reactions often form small amounts of symmetrical biaryl compounds through self-coupling of the substrates, such biaryl byproducts were not detected in the MCH phase of our biphasic system.

In conclusion, our studies have shown that a cycloalkane-based thermomorphic biphasic system allows for a facile workup and separation in a short reaction time for the microwave-promoted Suzuki–Miyaura coupling reactions. We believe that the rapid reaction-separation methodology using a combination of the microwave-irradiation and heating technique along with the cycloalkane-based thermomorphic biphasic system holds a significant potential for parallel synthesis and for the construction of combinatorial libraries.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.10.161.

References and notes

1. Suzuki, A. *J. Organomet. Chem.* **2002**, *653*, 83; Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147–168; Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483; Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009–3066; Yoon, C. H.; Koo, K. S.; Yi, S. W.; Mishra, R. K.; Jung, K. W. *Org. Lett.* **2004**, *6*, 4037–4039; Datta, A.; Plenio, H. *Chem. Commun.* **2003**, 1504–1505; Selected papers for microwave: Oliver Kappe, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250–6284; Leadbeater, N. E.; Marco, M. *J. Org. Chem.* **2003**, *68*, 888–892; Netherton, M. R.; Dai, C.; Neuschutz, K.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *12*, 10099–10100; Hu, Q.-S.; Lu, Y.; Tang, Z.-Y.; Yu, H.-B. *J. Am. Chem. Soc.* **2003**, *125*, 2856–2857.
2. Selected papers: (a) Li, W.; Burgess, K. *Tetrahedron Lett.* **1999**, *40*, 6527–6530; (b) Brase, S.; Schroen, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 1071–1073; (c) Vanier, Y.; Lorge, F.; Wagner, A.; Mioskowski, C. *Angew. Chem., Int. Ed.* **2000**, *39*, 1679–1683; (d) Pourbaix, C.; Carreaux, F.; Carboni, B. *Org. Lett.* **2001**, *3*, 803–805; (e) Yamada, Y. M. A.; Takeda, K.; Takahashi, H.; Ikegami, S. *Org. Lett.* **2002**, *4*, 3371–3374; (f) Lan, P.; Beta, D.; Porco, J. A.; South, M. S.; Parlow, J. J. *J. Org. Chem.* **2003**, *68*, 9678–9686; (g) Organ, M. G.; Mayer, S. *J. Comb. Chem.* **2003**, *5*, 118–124; (h) Wade, J. V.; Krueger, C. A. *J. Comb. Chem.* **2003**, *5*, 267–272; (i) Zhu, S.; Shi, S.; Gerritz, S. W.; Sofia, M. J. *J. Comb. Chem.* **2003**, *5*, 205–207; (j) Byun, J.-W.; Lee, Y. S. *Tetrahedron Lett.* **2004**, *45*, 1837–1840.
3. Recent reviews: (a) Curran, D. P. *Angew. Chem., Int. Ed.* **1998**, *37*, 1174–1196; (b) Curran, D. P. In *Stimulating Concepts in Chemistry*; Stoddard, F., Reinhoudt, D., Shibasaki, M., Eds.; Wiley-VCH: New York, 2000; pp 25–37; (c) Curran, D. P.; Hadida, S.; Studer, A.; He, M.; Kim, S.-Y.; Luo, Z.; Larhed, M.; Hallberg, A.; Linclau, B.. In *Combinatorial Chemistry: A Practical Approach*; Fenniri, H., Ed.; Oxford University Press: Oxford, 2000; Vol. 2, pp 327–352; (d) Dobbs, A. P.; Kimberley, M. R. *J. Fluorine Chem.* **2002**, *118*, 3–17; (e) Zhang, W. *Tetrahedron* **2003**, *59*, 4475–4489.
4. (a) Fraga-Dubreuil, J.; Bazureau, J.; Bazureau, J. P. *Tetrahedron Lett.* **2001**, *42*, 6097–6100; (b) Fraga-Dubreuil, J.; Bazureau, J. P. *Tetrahedron* **2003**, *59*, 6121–6130.
5. (a) Bergbreiter, D. E. *Chem. Rev.* **2002**, *102*, 3345–3384; (b) Bergbreiter, D. E.; Liu, Y.-S.; Osburn, P. L. *J. Am. Chem. Soc.* **1998**, *120*, 4250–4251; (c) Bergbreiter, D. E.; Osburn, P. L. *J. Am. Chem. Soc.* **2000**, *122*, 9058–9064; (d) Bergbreiter, D. E.; Osburn, P. L.; Frels, J. D. *J. Am. Chem. Soc.* **2001**, *123*, 11105–11106; (e) Bergbreiter, D. E.; Furyk, S. *Green Chem.* **2004**, *6*, 280–285.
6. Chiba, K.; Kono, Y.; Kim, S.; Nishimoto, K.; Kitano, Y.; Tada, M. *Chem. Commun.* **2002**, *16*, 1766–1767.
7. More than 99% of product (**3a**–**j**) was partitioned in the upper cycloalkane phase.
8. Pd catalyst was not detected in products by ^{1}H NMR (less than 0.05 mol %).
9. A typical procedure: A mixture of $PdCl_2$(dppf) (2.0 mg, 5 mol %), K_3PO_4 (32 mg, 0.15 mmol) and phenylboronic acid (0.1 mmol) in 0.4 ml of DMF was treated with aryl halides attached to the cycloalkane-soluble platform (55 mg, 0.05 mmol) dissolved in 3.6 ml of methylcyclohexane. The solution was degassed under Ar and irradiated a microwave (microwave power was 150 W, 110 °C, 5 min). After cooling, methylcyclohexane layer was separated and evaporated under vacuum. Methanol was added to the residue followed by filtration to afford the biaryl product **3a**–**j**. This reaction was achieved in up to 0.1 M scale to give the products in almost the same yields as the above condition.