

# Ligand-Free Suzuki–Miyaura Coupling Using Ruthenium(0) Nanoparticles and a Continuously Irradiating Microwave System

## OVERVIEW

We developed a conceptually and methodologically novel ruthenium(0) nanoparticle catalyst, sulfurmodified gold-supported ruthenium nanoparticles (SARu).

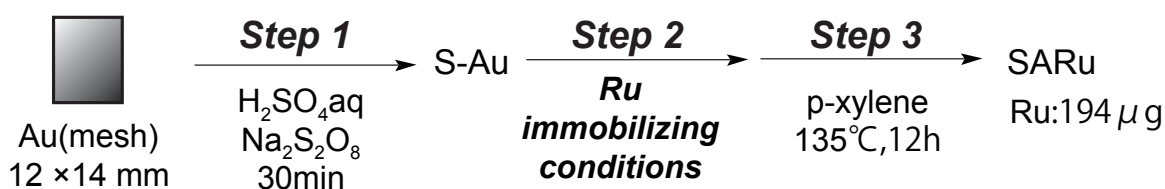
SARu is easily prepared through a three-step procedure involving simultaneous in situ metal nanoparticle and nanospace organization (Scheme 1).

This unique method does not require any conventional preformed template to immobilize and stabilize metal nanoparticles.

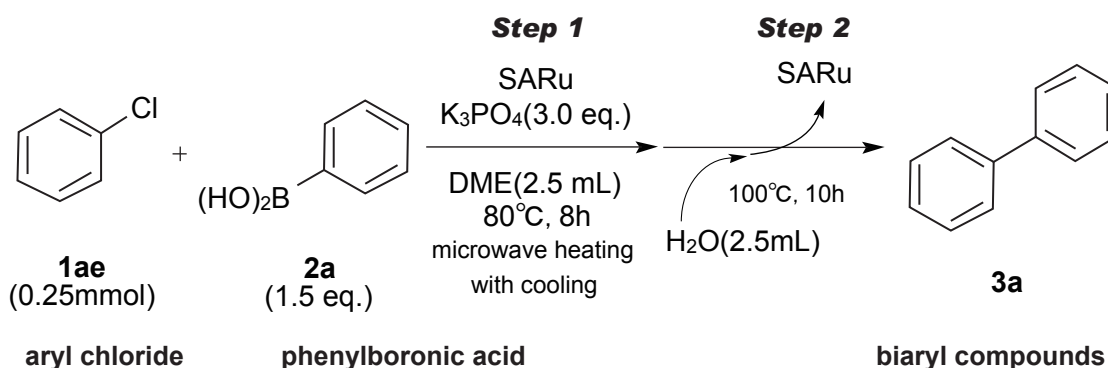
SARu is an ideal ruthenium catalyst for liquid-phase combinatorial synthesis because it repeatedly catalyzes ligand-free Suzuki–Miyaura coupling of aryl halides, including aryl chlorides, with arylboronic acids with low Ru leaching.

Also, we developed a continuously irradiating microwave methodology, which can first time discriminate the heating effect and the microwave effect in microwave experiments (Scheme 2).

Scheme 1. Preparation of SARu.



Scheme 2. Microwave assisted Suzuki–Miyaura coupling of aryl chlorides



## INTRODUCTION

Aryl chlorides, which are economical and readily available substrates, have rarely been used in Suzuki–Miyaura coupling because of their high activation barriers associated with oxidative insertion of ruthenium(0) species into the C–Cl bond.<sup>1,2</sup>

We next investigated the scope of SARu use by performing Suzuki–Miyaura coupling of aryl chloride 1ae with phenylboronic acid 2a. Although we tried various traditional heating conditions, only a trace amount of the corresponding coupling product was obtained. We previously developed a microwave-assisted strategy for Suzuki–Miyaura cross-coupling reactions catalyzed by SAPd, which has very low leaching properties.<sup>3</sup> The combined use of two microwaves with different irradiation approaches made this protocol very efficient, because the leaching induced by microwave-assisted physical etching can be easily controlled during the process. However, irradiation of the reaction mixture containing 1ae and 2a using traditional microwave reactors did not deliver the desired product 3a because the rapid generation of hot spots upon heating the whole reaction vessel caused the irradiation to turn off within a very short period when the temperature limit was reached. Then, we envisioned that the expected reaction might proceed if the whole reaction mixture was continuously irradiated by microwaves.

## SUMMARY OF THE RESULTS

We constructed a special microwave reactor equipped with a cooling unit for this purpose, as shown in Fig. 1,<sup>4</sup> and used it in the first step reaction. The results are summarized in Table 1. The reaction mixture was irradiated at a certain microwave power for 2 h (entries 1–4) as the first step and then the whole reaction mixture was treated in the usual second step. We obtained 3a in 31% yield when we used a microwave irradiation power of 70 W in the first step. Using this novel microwave reactor fitted with a cooling system, we achieved continuous microwave irradiation of SARu (Fig. 2). We observed aggregated Ru in the bottom of the flask (Table 1, entry 4), indicating that stronger irradiation leached more Ru than needed for the reaction, while weaker irradiation did not work. Entries 1–4 reveal that a microwave irradiation power of 70 W is suitable. When we shortened the irradiation time to 1 and 1.5 h, the yield of 3a increased to 41% and 38%, respectively. When the reaction time in the second step was prolonged to 24 h, a quantitative yield of 3a was successfully obtained (entries 7 and 8).

We next investigated the scope of the combined use of SARu and the special microwave reactor by performing liquid phase combinatorial synthesis using various chlorobenzene derivatives; the results are summarized in Table 2. The reactions of chlorobenzene (first cycle) and 4-nitrochlorobenzene (fourth cycle) with phenylboronic acid provided the corresponding biaryl products 3a and 3d in high yields. The reactions of 4-methoxychlorobenzene (second cycle) and 2-methylchlorobenzene (third cycle) with phenylboronic acid gave the corresponding product 3b in 60% yield and 3g in 52% yield, respectively. In the following four cycles, the reactions proceeded smoothly to give the corresponding heterocyclic products 3r, 3o, 3k, and 3n in yields of 65%–83%.

Fig. 1. our microwave reactor with a cooling system.

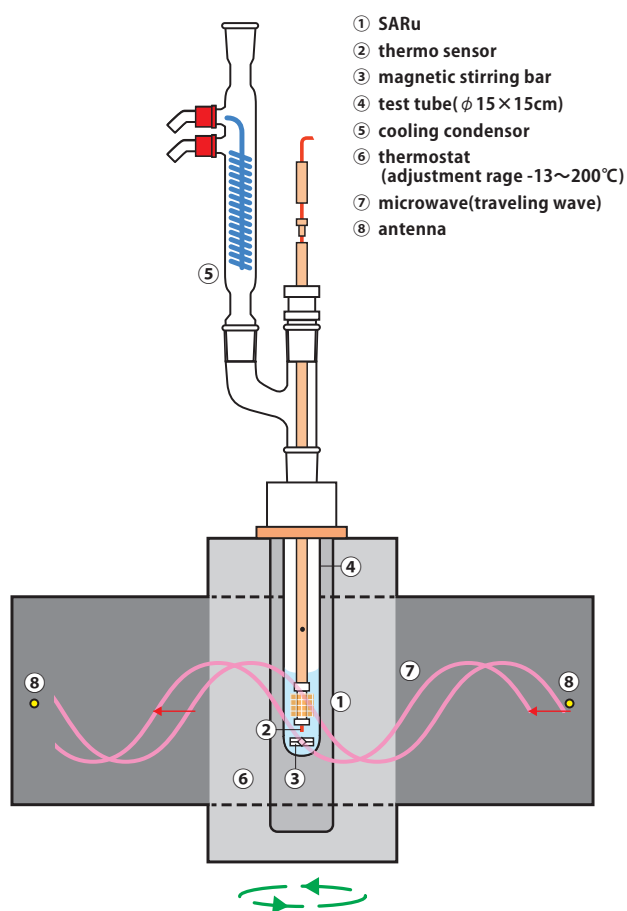


Fig. 2. Our Microwave irradiation data.

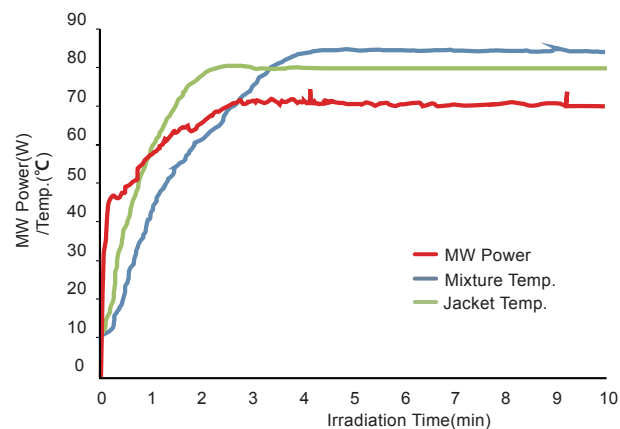
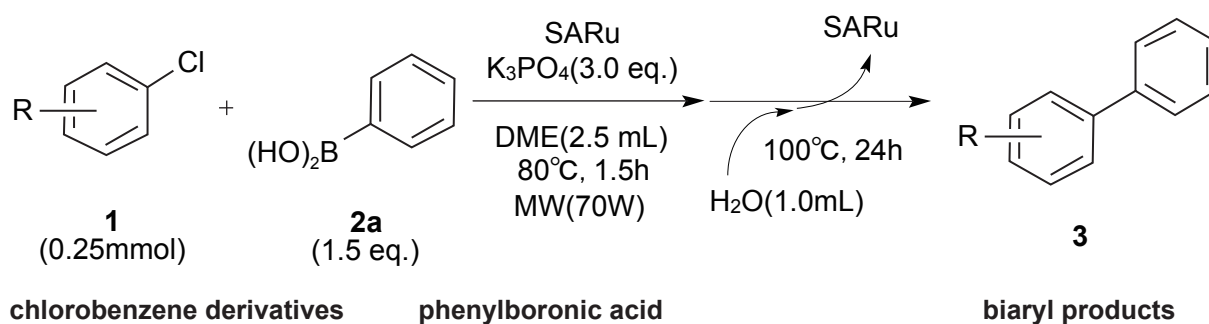


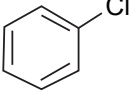
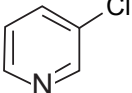
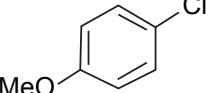
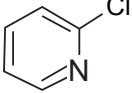
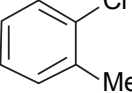
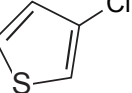
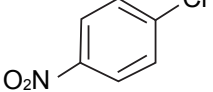
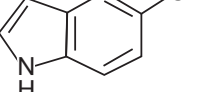
Table 1. Microwave assisted Suzuki–Miyaura coupling.

Entry	Time (h)	MW (W)	Yield (%) <sup>a)</sup>	Entry	Time (h)	MW (W)	Yield (%) <sup>a)</sup>
1	2	10 W	trace	5	1	70 W	41
2	2	50 W	trace	6	1.5	70 W	38
3	2	70 W	31	7 <sup>b)</sup>	1	70 W	96
4	2	100 W	15	8 <sup>b)</sup>	1.5	70 W	97

<sup>a)</sup> Determined by HPLC. <sup>b)</sup> The reaction was conducted for 24 h in the second step.

Table 2. Microwave assisted combinatorial synthesis.



RUN	Ar-Cl	Yield (%)	Run	Ar-Cl	Yield (%)
1		3a (93)	5		3k (76)
2		3b (60)	6		3n (83)
3		3g (52)	7		3o (70)
4		3d (84)	8		3r (65)

## CONCLUSION

This methodology is very useful to make biaryl compounds with heterocycles, because a variety of heterocyclic aryl chlorides are commercially available at reasonable prices.

## REFERENCES

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- Now this microwave machine is commercially available as Tokyorikakikai (brand:EYELA), Wavepro™, GPS-1000.
- For a complete account of this work see: T. Akiyama, T. Taniguchi, N. Saito, R. Doi, T. Honma, Y. Tamenori, Y. Ohki, N. Takahashi, H. Fujioka, Y. Sato, and M. Arisawa, *Green Chem.*, 2017, in press.

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