

# New High Speed Regioselective Heck Coupling Reactions Assisted By Microwave Flash Heating

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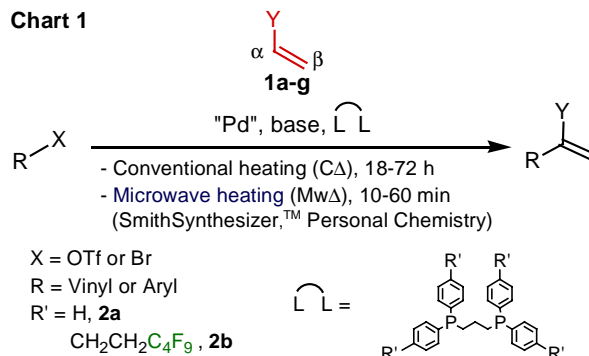
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## Introduction

To increase the ever-growing demand for new organic small molecules for both lead identification and lead optimization, the combinatorial and medicinal chemist require efficient synthesis and purification techniques. New automatic, focused **microwave** synthesizers constitute robust high-speed tools that simplifies and accelerates organic synthesis drastically.<sup>1</sup> In addition the use of innovative **fluorous** techniques facilitates the purification procedure.<sup>2</sup>

Chart 1



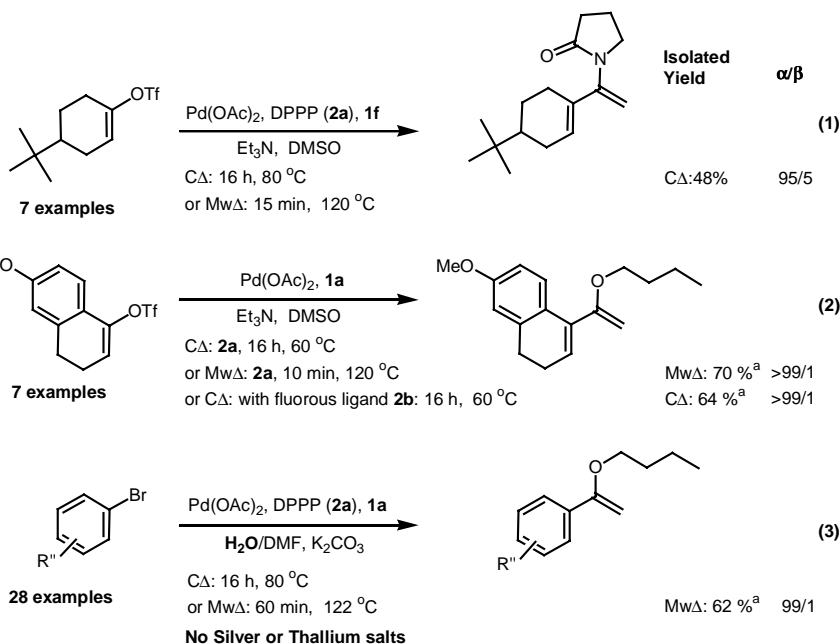
## Results

**New rapid vinylation:** New palladium-catalyzed internal Heck vinylation with unsymmetrical olefins are described (eq 1-2 and chart 1). The regioselectivity for the internal  $\alpha$ -carbon is high with electron-rich vinyl ethers, vinyl amides and allylic alcohol 1a-g (chart 2). Flash heating by microwave irradiation promotes the palladium-catalyzed reactions and the starting materials are fully

converted after reaction times of 10 to 15 minutes.

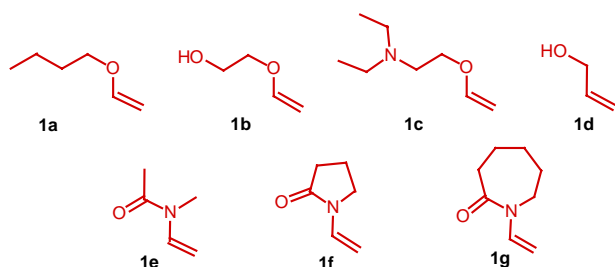
**Fluorous chemistry:** Fluorous synthesis involves tagging an organic substrate with a fluorinated tag for the purposes of fast separation. The tagged bidentate ligand 2b with CH<sub>2</sub>CH<sub>2</sub>C<sub>4</sub>F<sub>9</sub> tails in the para positions preserves the same high regioselectivity as experienced with non-fluorous DPPPP. The fluorous ligand was conveniently separated from the desired product by use of fluorous solid-phase extraction (eq 2).

**“Green” arylations:** Highly selective palladium-catalyzed internal  $\alpha$ -arylations of alkyl vinyl ethers with aryl and heteroaryl bromides were conveniently conducted in aqueous DMF with potassium carbonate.<sup>3</sup> This Heck reaction procedure does not require toxic thallium or expensive silver salt additives (eq 3).



<sup>a</sup> Isolated as the corresponding hydrolyzed methyl keton

Chart 2



## References

<sup>1</sup> Larhed, M.; Hallberg, A. *Drug Discovery Today* **2001**, 6, 385-395.

<sup>2</sup> Luo, Z.; Zhang, Q.; Oderaotoshi, Y.; Curran, D. P. *Science (Washington, DC, U. S.)* **2001**, 291, 1766-1769.

<sup>3</sup> Vallin, K. S. A.; Larhed, M.; Hallberg, A. *J. Org. Chem.* **2001**, 66, 4340-4343.

## Conclusion

We herein report:

- ✓ A new regioselective procedure for internal vinylation of electron-rich olefins.
- ✓ Dramatic accelerations of Heck vinylation and arylation reactions under controlled microwave irradiation.
- ✓ Successful use of new fluorous tagged bidentate ligands for fast separation.
- ✓ An environmentally benign H<sub>2</sub>O/K<sub>2</sub>CO<sub>3</sub> additive as a thallium salt substitute in selective internal arylations.

