

Rapid and Selective Palladium-Catalyzed Asymmetric Allylic Alkylations under Microwave Conditions

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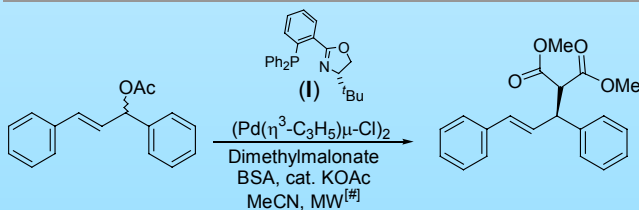
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INTRODUCTION

For high efficiency in parallel synthesis and method development short reaction times are essential. We have examined the possibility of maintaining reported selectivities^[1] in rapid, high temperature palladium-catalyzed asymmetric allylic alkylations. Reactions were promoted by use of single mode microwave heating (*vide infra*),^[2] which opposite to conventional oilbath heating (wall heat transfer) rapidly and almost homogeneously heat large parts of the sample (internal heat transfer).

RESULTS

Employing the standard model substrate, (*rac*)-1,3-diphenylallyl-1-acetate, it was discovered that the allylic alkylations could be performed within a few minutes with maintained stereoselectivity (*vide infra*, Table 1), although reaction temperatures were very high, up to 140 °C (*vide infra*, Figure 1).

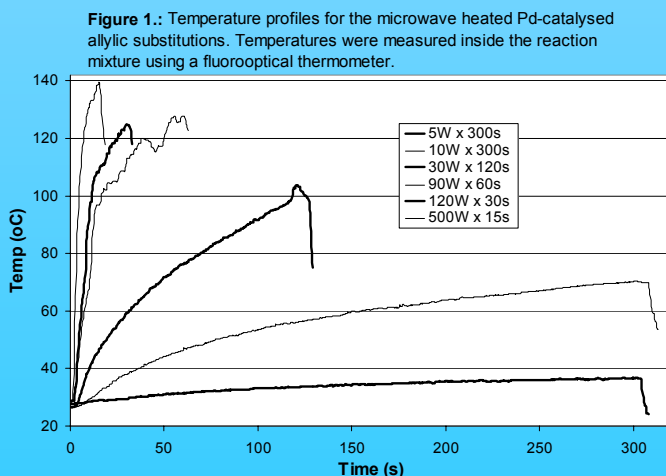


[#]: Focused microwaves at 2.45 GHz. Reaction times from 15 s to 5 min.

Table 1: Comparison between yields and ee's under accelerated and conventional conditions.

Entry	Power	Time	Yield (%) ^[a]	ee (%) ^[b]
1	5 W	× 300 s	15	> 99
2	10 W	× 300 s	99	> 99
3	30 W	× 120 s	99	> 99
4	90 W	× 60 s	> 99	> 99
5	120 W	× 30 s	97	> 99
6	500 W	× 15 s	99	> 99
7	29°C ^[c]	× 6 h (21600 s)	56	> 99

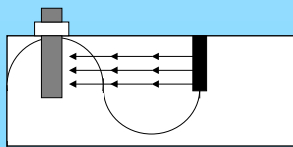
[a]: Measured by HPLC at 254 nm using 4-Methoxybenzotrile as internal standard. [b]: Measured by chiral HPLC. [c]: Reaction performed with internal temperature measurement and stirring at 29 ± 0.5 °C.



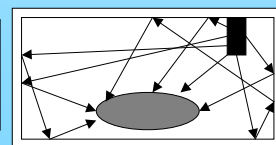
MICROWAVES - A SHORT BACKGROUND^[3]

Microwaves are electromagnetic waves with characteristic wavelengths of 1 cm to 1 m (frequencies: 30 GHz to 300 MHz). Microwaves are used excessively in modern life e.g. as RADAR-waves or for short-wave radio communication. In order not to disturb these important ways of communication the frequency 2.45 GHz has been internationally assigned as free, and is used in different technical applications, e.g. in microwave ovens. As the microwaves runs through the reaction mixture (or food) they force the molecules to agitate. Thus, heat by friction is generated as a bulk phenomenon via internal heat transfer. For high interaction, and energy transfer, the molecules need a large dipolar moment, electric or magnetic. Quick and efficient internal heat transfer facilitates superheating up to 20 °C. The effect of superheating can be even more pronounced if one enables slight pressure build up in closed vessels, up to 200 °C or more.

Two types of microwave reactors are commercially available, multi mode or single mode. Multi mode ovens release an ill-defined distribution of microwaves. The sample heating is therefore inefficient and non-uniform, see figure below. Multi mode is used for large scale chemistry and in domestic microwave ovens. Single mode reactors release the microwaves as focused and planar polarized. Using a wave conductor a standing microwave is produced in the sample. This enables tuning of the power input into the sample and very high internal heat transfer. With the high flexibility and reproducibility of the single mode reactor it has become the preferred technique in research.



Single mode Microwave reactor



Multi mode Microwave reactor

CONCLUSION

The use of microwave flash heating can afford very short reaction times under forced conditions without loss of selectivity. In this work it is demonstrated that this fact also implies to stereochemistry.

REFERENCES

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- 2) We used a microwave reactor named Microwell 10™, manufactured by Labwell AB, Uppsala, Sweden.
- 3) Stone-Erlander, S., Erlander, N., *Appl. Radiat. Isot.*, **1993**, 44(5), 889; Stone-Erlander, S., Erlander, N., *ACS Symposium at 206th National Meeting*, **1993**; Gabriel, C., Gabriel, S., Mingos, D. M. P., *et al*, *Chem. Soc. Rev.*, **1998**, 213; Stuerger, D., Gonon, K., *et al*, *Tetrahedron*, **1993**, 6229; Caddick, S., *Tetrahedron*, **1995**, 10403; Langa, F., de la Cruz, P., *et al*, *Contemporary Organic Synthesis*, **1997**, 373; Loupy, A., Petit, A., *et al*, *Synthesis*, **1998**, 1213; Whittaker, G., <http://www.ed.ac.uk/~ah05/basicintro.html>