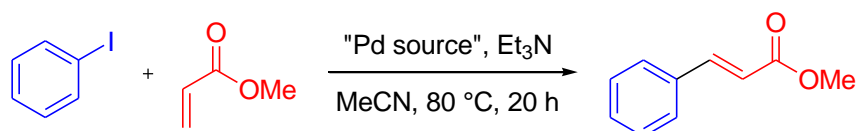




Modification of a Conventional Heating Procedure to Microwave Heating

Transition metal catalyzed couplings have become prominent in organic chemistry over the past 50 years. Of exceptional importance are those reactions which are robust and can be performed under a variety of conditions. One such reaction is the palladium-catalyzed arylation or alkenylation of a double bond known as the Heck reaction.



Scheme 1. Heck coupling of iodobenzene and methyl acrylate

The literature Heck coupling^[1] detailed in Scheme 1 can be readily adapted to a microwave assisted procedure in the CEM Discover. For this study, Pd(OAc)₂ (5 mol %) was used as the palladium source in place of the title catalyst. An initial reaction was performed under literature conditions (1.0 equiv. aryl iodide [0.43 M], 2.0 eq. alkene, 1.2 eq. Et₃N, in MeCN; entry 1, table 1) to first establish the conversion to product at a typical microwave reaction time. Poor conversion (13%) was seen at literature temperature (table 1, entry 1), and no pressure increase was noted as the reaction proceeded.

Table 1. Optimization of reaction temperature for microwave assisted Heck coupling

Entry	Solvent	Temperature [°C]	Time [min]	Conversion [%] ^[a]
1	MeCN	80	10	13
2	MeCN	120	10	44
3	MeCN	160	10	79
4	MeCN	200	10	85 ^[b]
5	MeCN	180	10	85 ^[b]
6	MeCN	170	10	82

^[a]Determined by GC analysis

^[b]Significant by-product formation

Adjustments of 20-40 °C per run provide an efficient way to identify the optimal reaction temperature of a microwave assisted reaction. The percent conversion was seen to increase as higher temperatures were screened (entries 2, 3) until significant amounts of an unidentified by-product appeared in the GC trace of entry 4. Heating the solution at 180 °C (entry 5) yielded similar results to entry 4, but reducing the reaction temperature to 170 °C (entry 6) provided the highest conversion to product while maintaining minimal levels of by-product formation.

Once the optimal temperature was established, additional reaction conditions were surveyed. Using PowerMAX cooling and a fiber optic probe for temperature measurement (table 2, entry 1), a decrease in by-product formation was visible by GC analysis, however this was not accompanied by an increase in conversion. A longer reaction time (entry 2) led to increased by-product formation while 5 minute and 3 minute reactions (entries 3 and 4) maintained comparable yields and purity.



Table 2. Modification of reaction conditions for microwave assisted Heck coupling

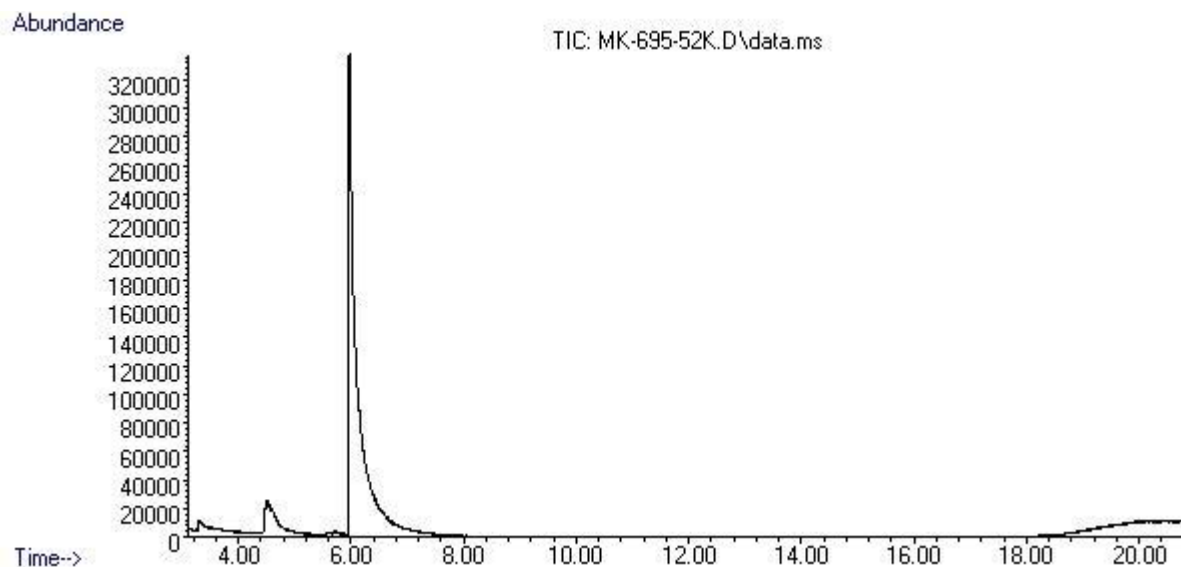
Entry	Solvent	Temperature [°C]	Time [min]	Conversion [%] ^[a]
1	MeCN	170	10	82 ^[b]
2	MeCN	170	15	85
3	MeCN	170	5	82
4	MeCN	170	3	78
5	toluene	170	5	25
6	none	170	5	93 (87) ^[c]

^[a]Determined by GC analysis

^[b]Performed using PowerMAX and fiber optic probe

^[c]Isolated yield

Switching to differentially microwave absorbing solvent can also greatly impact the reaction. The low microwave absorbing toluene did not show any improvement over the moderate absorber acetonitrile (entry 5), and performing the reaction neat (entry 6) resulted in the best conversion while maintaining minimal side reactions (Figure 1). For methodology development, further optimization of solvent, base, reaction stoichiometry, catalyst, and other parameters can be carried out as it would be for a thermal reaction.


Figure 1. GC chromatogram of entry 6, table 2

Taking advantage of the speed and flexibility of microwave heating, this optimization (12 reactions) was performed in about 4 hours. In addition to time savings, the high temperature, high pressure capabilities of the CEM Discover allowed this Heck coupling to be performed solvent-free.

ⁱ Schweizer, S.; Becht, J.-M.; Le Drian, C. Development of Efficient and Reusable Diarylphosphinopolystyrene-Supported Palladium Catalysts for C-C Bond Forming Cross-Coupling Reactions. *Adv. Synth. Catal.* **2007**, 349, 1150–1158. DOI: [10.1002/adsc.200600503](https://doi.org/10.1002/adsc.200600503)