Microwave-Assisted Enantioselective Heck Reactions: Expediting High Reaction Speed and Preparative Convenience

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Abstract: Palladium-catalyzed asymmetric Heck reactions have been performed using high temperature conditions with the aid of controlled microwave dielectric heating. Significant enantioselectivities of up to 92% ee were obtained under non-inert conditions utilizing the previously reported thermostable palladiumphosphineoxazoline catalytic system. With microwave irradiation, reaction times of hours instead of days were obtained. Enantiomeric purities and conversions were found to be strongly dependent on both the choice of the aryl triflate, the reaction temperature, the solvent and the base. Examples of asymmetric arylations of electronrich as well as neutral cyclic alkenes are presented.

Key words: asymmetric catalysis, Heck reaction, arylations, regioselectivity, palladium

In modern medicinal and combinatorial chemistry, reaction optimization and chemical rehearsal rear up as bottlenecks that can severely restrict compound throughput. Despite advances in parallel synthesis, the reaction times can still be rate-limiting.¹ Our research in microwave synthesis is therefore devoted to the discovery and development of high-speed methods of importance for lead generation and lead optimization processes.²

Pfaltz has reported that (R)-2-phenyl-2,5-dihydrofuran (3a) is produced from phenyl triflate (1a) and 2,3-dihydrofuran (2) in the presence of a palladium(0) precursor and phosphineoxazoline A (Figure 1, Scheme 1). The most impressive reaction was carried out in THF with high regioselectivity and an impressive enantiomeric excess of 97%.³ The reaction time for this intermolecular Heck reaction was reported to be 4 days.³ Previous utilization of palladium-(phosphinophenyl)oxazoline based catalytic systems in microwave promoted allylic substitution reactions have afforded up to 97% yield and 99% ee after only 30 seconds of irradiation.⁴ Inspired by these results, we decided to investigate whether the use of controlled microwave heating in combination with thermostable catalytic systems could enable shortening also of the Heck arylation reaction times with high retention of enantioselectivity. This short communication is focused on acceleration of intermolecular asymmetric Heck processes under a non-inert atmosphere.

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Aryl triflates 1 were reacted with olefin 2 in the presence of different palladium precatalysts to furnish the isomeric products 3–5 (Scheme 1). The 0.6 mmol scale one-pot reactions were performed under air, in sealed microwave transparent reaction vessels, using controlled microwave irradiation with a single-mode applicator. The preparative results are summarized in the Table. The best conversions were obtained in these high temperature reactions when proton sponge⁵ was used as the base and benzene as the solvent. To overcome the problem with double bond isomerization, ligand A was first investigated. Increasing the reaction temperature with 2 as olefin to 145 °C, from 70 °C as used originally by Pfaltz, resulted in an isolated yield of 58% and an ee of 90% after only 55 minutes of irradiation (entry 3). At higher reaction temperatures, the catalytic system decomposed before complete conversion was achieved. However, after lowering of the temperature to 140 °C, the isolation of **3a** in 66% yield and with 89% ee was achieved (entry 2). A higher stereoselectivity could be obtained in THF than in benzene, but lower conversions of 1a were experienced in all cases (entries 1–3).⁶



Figure 1 The structures of phosphineoxazoline ligand **A** and diphosphine ligand **B** [(R)-BINAP].

The electronic properties of the aryl triflates were found to be important for the reactivity. In a novel asymmetric reaction, the electron rich **1b** reacted to produce high yields (73–85%) and high ee (88%) of pure **3b** after 1–4 hours (entries 4 and 5) whereas the use of electron-poor 4-cyanophenyl triflate gave only small amounts of an arylated Heck product. The sterically demanding **1c** furnished the highest enantiomeric excess (92%) but also the lowest reaction rate (entry 6). It is noteworthy that small amounts of non-chiral **5a** (Ar = Ph) but no **4a** were formed in all of the reactions between phenyl triflate (**1a**) and 2,3-dihydrofuran (**2**) (entries 1–3). Since the classic (70 °C) phosphinooxazoline controlled arylation of **2** proceeds without



Scheme 1

affording the aryl-conjugated isomer **5**,³ we find it difficult to rationalize the outcome in terms of the accepted cationic Heck-cycle.⁷ Thus, the isomerization to **5a** (Ar = Ph) ought to occur after insertion, β -elimination and subsequent release of the metal from the phenylated product **3a**.^{8,9} The use of the diphosphine ligand **B**, (*R*)-BINAP (2,2'-bis(diphenylphosphino)-1,1'-binaphthyl) (Figure 1), allowed reduction of the reaction times (10–30 min), but significantly lower yields and stereoselectivities were encountered. When Pd₂dba₃ was used as the palladium source, the yield was 66% and the ee 43% (entry 7). The use of Pd(OAc)₂ gave 53% yield and 50% ee (entry 8). These results are in accordance with the literature regarding both reaction rate^{10a} and selectivity.^{10b}

Asymmetric reactions with cyclopentene (6) were included to provide data from reactions of a less electron-rich cyclic olefin. With classical heating (70 °C, 5 d) this valuable extension of the Heck reaction is reported to furnish 80% of 7 in 86% ee in THF (82% ee with benzene as solvent) employing ligand A (Scheme 2).¹¹ Accordingly, microwave arylation of 6 resulted exclusively in the formation of isomer 7 and only trace amounts (1–2%) of isomers 8 and 9 were detected (Scheme 2, Table). The Table reveals that the desired 7 was formed in high yield

Table Palladium-Catalyzed Asymmetric Arylation of the Prochiral Olefins 2 and 6 Using Microwave Irradiation^a

Entry	Main Product	Pd/Ligand	Temp (°C)	Time (h) ^b	Yield (%) ^c	Isomeric Ratio ^d	ee ^e (%)	Optical Rotation
1		Pd ₂ dba ₃ /A	120	3	64	3:5 /90:10	90	
2	3 a	Pd ₂ dba ₃ /A	140	1	66	3:5 /96:4	89	
3		Pd_2dba_3/A	145	55 min	58	3:5 /90:10	90	
4	MeO III. O	Pd_2dba_3/A	120	4	85	3 /100	88	
5	3b	Pd ₂ dba ₃ /A	140	1	73	3 /100	88	
6	J-C	Pd ₂ dba ₃ /A	120	8 ^f	80	3 /100	92	
7		Pd ₂ dba ₃ / B	160	30 min	66	4:3 /83:17	43	
8	4 a	Pd(OAc) ₂ / B	160	10 min	53	4:3 /94:6	50	
9		Pd ₂ dba ₃ /A	120	8	80	7:8+9 /99:1	45 ^g	$[\alpha]_{D}^{23} + 85$
10	7	Pd2dba3/A	140	4	78	7:8+9 /98:2	42 ^g	$[\alpha]_{D}^{23}+90$

^a All reactions were performed in benzene with proton sponge as base.

^b Reactions were irradiated until all of the starting aryl triflate 1 was consumed as deduced by GC/MS.

^c Main product after silica gel column chromatography (>95% pure according to GC/MS).

^d Measured by GC/MS, double bond isomers were assumed to have identical response factors.

^e Ee of major isomer as measured by chiral HPLC.

^f Small amounts of starting 1b remained.

^g Ee of major isomer as measured by optical rotation.

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Scheme 2

(78%), but in moderate stereoselectivity (42%), after only 4 hours of microwave heating at 140 °C (entry 10).

Powerful heating ramps, good temperature control and impressive superheating were readily obtained using the microwave synthesizer despite the use of weakly absorbing solvents (tan $\delta_{THF} = 0.047$, tan $\delta_{benzene} \approx 0$)¹² (Figure 2). The reaction temperatures were recorded with an IR-sensor, positioned outside the reaction vessel.



Figure 2 Temperature (IR-sensor) and pressure profiles for an asymmetric Heck coupling performed in benzene (bp 80 °C, Table, entry 3).

Although reaction times were reduced from days to hours and the preparative procedure simplified, the stereoselectivity for phenylation of 2,3-dihydrofuran (**2**) was reduced from 97% ee (70 °C) to 90% ee (145 °C). In light of this, the high enantioselectivities (99% ee) that have been reported in microwave flash-heated allylic substitutions after only 30 seconds of irradiation are remarkable.⁴

In short, the use of controlled microwave heating expedites metal-catalyzed organic synthesis by increasing the reaction speed and reducing the need for an inert atmosphere. In certain cases the requirement for good yield, high ee (88–92%) and short reaction times can be fulfilled with asymmetric Heck reactions. The preparative utility of the presented microwave-assisted Heck reaction is, however, limited to cases where there is not a strong demand for high enantioselectivity. We believe that an alternative microwave-accelerated auxiliary-controlled stereoselective Heck procedure is worthy of investigation.

Microwave heating was carried out using an automatic Smith single-mode synthesizer from Personal Chemistry AB, Sweden, which produces a radiation frequency of 2450 MHz. Reaction vessels in Pyrex (5 mL, code no 351520, Smith process vial) with silicon septum were supplied by the same company. All reactions were conducted under air. Enantiomerical purities of **3** and **4** were analyzed by HPLC (*Chiracel OD-H*; 0.46 × 25 cm, PS = 5 µm, degassed 2methylpentane–propan-2-ol, flowrate 0.5 mL/min, detection at 220 nm). The chiral HPLC column was protected by a guard column (*Chiralcel* OD 0.46 × 5 cm, PS = 10µm). ¹³C and ¹H NMR spectra were obtained in CDCl₃ at 100 and 400 MHz respectively. Low resolution mass spectra were recorded on a GC/MS instrument equipped with a cross-linked methyl siloxane capillary column (25 m × 0.22 mm × 0.3 µm film) operating at an ionization energy of 70 eV. The oven temperature was 70–315 °C (gradient 30 °C/min). Regioisomers were assumed to have the same (GC/MS) response factor. Optical rotation was measured in CHCl₃ (c = 1, T = 23 °C).

2,8-Bis(dimethylamino)naphthalene; benzene (anhydrous); phenyl trifluoromethanesulfonate (1a); 4-methoxyphenyl trifluoromethanesulfonate (1b); and 2,3-dihydrofuran, were purchased from Aldrich Co and used as received. (R)-(+)-BINAP and cyclopentene: Fluka; Pd₂dba₃ and Pd(OAc)₂: Strem Chemicals. 1-Naphthyl trifluoromethanesulfonate (1c) was prepared from the corresponding naphthol by a standard procedure.¹³ (-)-(4*S*)-4-*tert*-Butyl-4,5-dihydro-2-[2'-(diphenylphosphino)phenyl]oxazole was synthesized according to Koch et al.¹⁴ Flash column chromatography: silica gel 60 0.040–0.063 mm, Merck.

Microwave-Assisted Enantioselective Heck Reaction; General Procedure (Table)

The palladium source (0.03 equiv based on Pd) was stirred together with the chiral ligand (0.06 equiv) in benzene (1 mL) in a Smith process vial at r.t. for 10 min. After subsequent addition of base (3 equiv), olefin **2** or **6** (5 equiv) and aryl triflate **1** (0.60 mmol, 1 equiv) dissolved in benzene (1 mL), the mixture was microwaveheated at the chosen temperature and time. After cooling, the reaction mixture was filtered, evaporated and purified by column chromatography on silica gel (pentane–Et₂O, 95:5). The products were identified by comparison with the literature data for **3a**,¹⁵ **3b**,^{16,17} **3c**,¹⁸ **4a**,¹⁵ **7**,^{18,19} and the configuration was confirmed by optical rotation measurements.

(+)-(*R*)-2-Phenyl-2,5-dihydrofuran (3a)¹⁵

HPLC (2-methylpentane–propan-2-ol, 99:1): t_r 17.7 min (+), t_r 21.0 min (–).

(+)-(*R*)-2-(4-Methoxyphenyl)-2,5-dihydrofuran (3b)¹⁵⁻¹⁷

HPLC (2-methylpentane–propan-2-ol, 95:5): t_r 18.5 min (–), t_r 19.9 min (+).

(+)-2-(1-Naphthyl)-2,5-dihydrofuran (3c)¹⁸

HPLC (2-methylpentane–propan-2-ol, 90:10): $t_r 23.3 \text{ min } (+), t_r 28.3 \text{ min } (-).$

(+)-(*R*)-2-Phenyl-2,3-dihydrofuran (4a)¹⁵

HPLC (2-methylpentane–propan-2-ol, 99.5:0.5): t_r 15.6 min (+), t_r 17.5 min (–).

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 (9) Alternatively product 5a (Ar = Ph) may be formed by a *trans* Pd-β-hydride elimination from the depicted intermediate σcomplex (Figure 3).



Figure 3

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