Rapid and Stereoselective C-C, C-O, C-N and C-S Couplings via Microwave Accelerated Palladium-Catalyzed Allylic Substitutions

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Abstract: Palladium-catalyzed substitution of cyclohex-2-en-1-yl ethyl carbonate with neutral *C*-, *O*-, and *N*-nucleophiles was achieved in 1−2 minutes using microwave flash heating. Enantioselectivities up to 96% were observed. Ionic nucleophiles tended to result in lower ee. With *S*-nucleophiles problems with the stability of the nucleophile were encountered.

Key words: palladium, catalysis, enantioselective, microwave, phosphine, allylation, ligands

Introduction

Chiral transition metal compounds constitute highly efficient tools for asymmetric catalysis.[1] Chiral ligands bound to the metal center are responsible for the chirality transfer to the product, and ligand design is thus a key issue in the development of asymmetric catalytic processes.[2] The palladium-catalyzed allylic substitution reaction has emerged as one of the most versatile and powerful transformations for stereo- and regioselective carbon−carbon as well as carbon−heteroatom bond formation.[3] The methodology has been successfully applied to a variety of substrate types containing enantiotopic faces, leaving groups or electrophilic centers with *P*, *N*, *S*, and *O* based chiral ligands.

In addition to high stereo-, regio- and chemoselectivity, the control of reaction parameters is important in organic synthesis. Reaction conditions resulting in simple and convenient operational procedures are particularly attractive. High reaction rate is often recognized as an important parameter, especially in applications related to high-speed combinatorial chemistry. Microwave heating has been employed during the last 15 years to accelerate a variety of organic reactions, and spectacular increases in rate, yield and purity of products have frequently been noticed, in particular when single mode cavities have been employed.[4] Within the field of achiral homogeneous transition metal catalyzed organic chemistry, a range of high speed coupling reactions have been reported.[5]

It occurred to us that microwave acceleration might be of great significance in asymmetric metal catalysis and therefore such applications were attempted. In preliminary communications we reported on palladium-catalyzed substitution of *rac*-(2*E*)-1,3-diphenylprop-2-enyl acetate with dimethyl malonate as nucleophile.[6] We have now extended the methodology to include a less activated substrate and other nucleophiles.

Requirements for High Selectivity Under Microwave Conditions

In order for a reaction to occur with high enantioselectivity, there must be a high enough difference in activation energy for the processes leading to the two enantiomers. The higher the reaction temperature, the larger the difference in energy required to achieve high selectivity. The enantiomeric ratio, E, a constant introduced for enzymatic kinetic resolutions,[7] is defined as $e^{-\Delta\Delta G^{\#}/RT}$ and thus related to the difference in activation energy for the two competing processes. Occasionally it is convenient to use this constant also for other types of processes, in particular for highly selective processes where a large difference in $\Delta G^{\#}$ results in a minor difference in ee. Applied to asymmetric processes the activation energies represent the formation of two enantiomers. E as a function of $\Delta\Delta G^{\#}$ at three different temperatures (20, 100 and 180 °C) is shown graphically in Figure 1.

Assuming that the selectivity does not change during the reaction, E values are directly related to ee values [E = (1 + ee)/(1 − ee)], as indicated in Figure 1. Comparison of the three curves shows that a difference in activation energy of 15 kJ/mol corresponds to an E value of 472 at 20 °C. With the assumption above, this corresponds to an

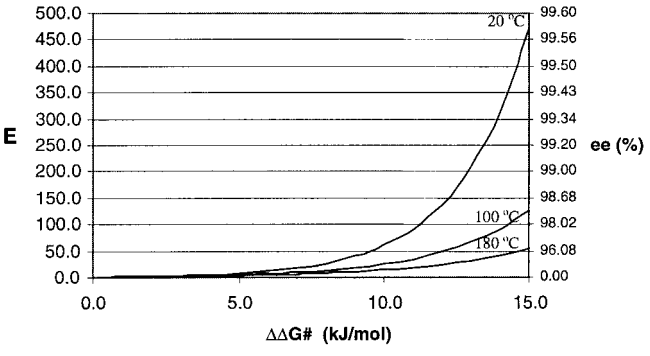
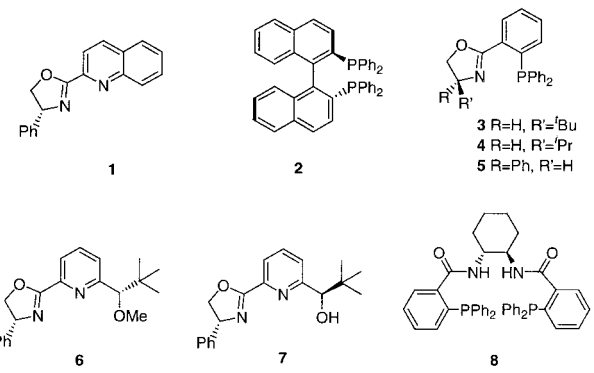


Figure 1 E and ee as functions of $\Delta\Delta G^{\#}$, where $\Delta\Delta G^{\#}$ represents the difference in activation energy for the formation of two enantiomers

ee of 99.6%. Increasing the temperature for this particular reaction results in a minor decrease in selectivity (98.4% ee at 100 °C and 96.3% ee at 180 °C), whereas for a reaction with merely 10 kJ difference in activation energy for the formation of the two enantiomers, a more significant decrease in selectivity is expected. For reactions with high *E* values, the enantioselectivity is thus not expected to be affected to any larger degree upon heating. For microwave applications we have therefore primarily selected reactions where ee values above 98% (*E* ≥100) have been reported at room temperature.

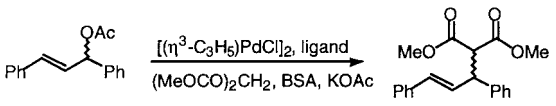
Microwave Heated Palladium-Catalyzed Allylic Substitutions

We started our investigation with palladium complexes containing the *N,N*- and *P,P*-ligands (4'*R*)-2-(4',5'-dihydro-4'-phenyl-2'-oxazolyl)quinoline (**1**) and BINAP (**2**), which catalyze the reaction of *rac*-(2*E*)-1,3-diphenylprop-2-enyl acetate and dimethyl malonate with reasonable selectivity at ambient temperature (73[8] and 90%[9] ee, respectively). With microwave irradiation of the reaction mixtures, the products were obtained with 65% ee after 2 min at 500W magnetron input power and with 83% ee after 1 min at 40W, respectively (Table 1).[6a] As expected, with ligands affording higher ee's under normal conditions, a lower drop in selectivity was observed under microwave irradiation. Thus, microwave conditions were found for ligands **3**–**5**[10] which very rapidly yielded the products in essentially quantitative yield and ee's >99% (Table 1).[6b]



Ligands **6** and **7** have been shown to result in high selectivity (>99% and 95% ee, respectively) when employed in the same process at room temperature, albeit requiring four days reaction time for complete reaction.[11] Surprisingly, little product was obtained upon microwave irradiation. This is probably due to decomposition of the rather weak palladium-ligand complex, as corroborated by the precipitation of palladium black on heating. This process (and in general reactions where the metal complex is thermally unstable) is therefore not feasable for microwave flash heating to high temperatures.

Table 1 Microwave conditions for Ligands **1**–**5** in Palladium-Catalyzed Allylic Couplings



Ligand	Effect[a] (W)	Temp[b] (°C)	Time	Yield[c] (%)	ee (%)
1	35		15.0 min	99	65
	70		7.5 min	99	64
	120		3.5 min	99	63
	250		3.0 min	99	65
	500		2.0 min	99	65
		100	19.0 min	97	62
		140	6.3 min	93	60
		180	4.5 min	93	56
		r.t.	4 d	99	77
2	20		2.0 min	94	83
	20		1.5 min	96	85
	40		1.0 min	95	83
		r.t.	1.0 h	97	87
3	30		2.0 min	99	>99
	90		40 sec	65	>99
	90		1.0 min	>99	>99
	120		30 sec	97	>99
	500		15 sec	98	93
		29	6.0 h	56	>99
4	90		1.0 min	>99	>99
	120		30 s	98	>99
	500		15 sec	85	97
5	90		1.0 min	95	97

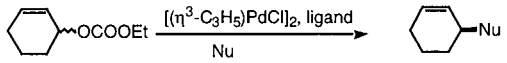
[a] Microwave irradiation effect.
[b] Traditional oil-bath heating.
[c] The yields were determined by GC and verified by isolation of a few samples. The ee's were analyzed by chiral HPLC.

High enantioselectivity has been reported for reactions of several allylic substrates with *C*-, *O*-, *N*- and *S*- nucleophiles in the presence of palladium complexes containing ligand **8**.[12] We selected some processes for investigation under microwave conditions.

We first studied the reaction of *p*-methoxyphenol with cyclohex-2-en-1-yl ethyl carbonate. At 25 °C this process was reported to afford the product in 88% yield and 97% ee after 3 hours.[13] Microwave heating of the reaction mixture under air was safely carried out for 5 min at 35W to afford essentially the same selectivity (91% yield, 95% ee, Table 2), although only 0.23% catalyst was employed instead of 1% as used in the published procedure.[13] At 70W a reaction time of 2.0 min was required to afford a high yield. Optimal conditions were found to be 1 min and 120 W (96% yield and 95% ee). At higher power, a slight drop in ee was observed (Table 2). Prolonged heating at this effect (2 min) did not affect the enantioselectivity or the yield.

Accurate temperature measurements are important for the correlation of temperature and enantioselectivity. To obtain the "true" reaction temperature a microwave-transparent fiber optic probe was utilized. Figure 2 illustrates

Table 2 Microwave Accelarated Palladium-Catalyzed Allylic Substitutions in the Presence of Ligand **8**



Nucleophile	Effect[a] (W)	Temp[b] (°C)	Time	Yield (%)	ee (%)
p-	35		5.0 min	91[c]	95[d]
methoxy	70		40 sec	43[c]	96[d]
phenol	70		2.0 min	92[c]	95[d]
	120		1.0 min	96[c]	95[d]
	150		1.0 min	91[c]	94[d]
	300		45 sec	88[c]	92[d]
	500		30 sec	79[c]	92[d]
		100	5.0 min	91[c]	95[d]
phthal-	30		15 min	40[e]	98[d]
imide	70		2.0 min	57[e]	96[d]
	70		3.0 min	87[e]	95[d]
	70		4.0 min	79[e] (80[c])	97[d]
	100		1.0 min	64[e]	98[d]
	100		1.5 min	87[e]	96[d]
	200		1.0 min	75[e]	96[d]
	500		30 sec	68[e]	94[d]
		20	24 h	18[e]	96[d]
		140	10 min	51[e]	95[d]
dimethyl	50		6.0 min	83[c]	94[f]
malonate	100		3.0 min	69[c]	>95[f]
	100		4.0 min	83[c]	>95[f]
	200		3.0 min	65[c]	>95[f]
	500		1.5 min	83[c]	>95[f]

[a] Microwave irradiation effect.
[b] Traditional oil-bath heating.
[c] Isolated yields.
[d] The ee's were analyzed by chiral HPLC.
[e] Yields determined by GC.
[f] The ee's were analyzed by NMR with the addition of $Eu(hfc)_3$.

temperature/time/power profiles for the reaction with *p*-methoxyphenol.

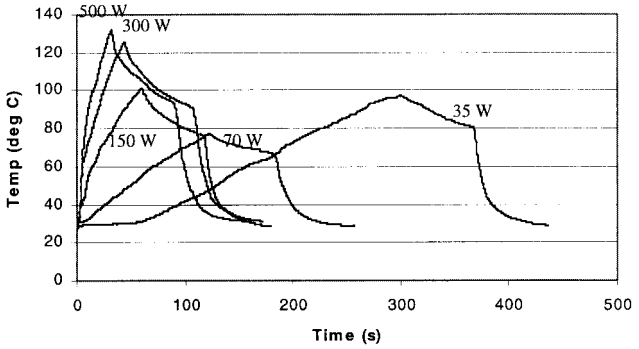


Figure 2 The temperature of the reactions of 4-methoxyphenol in CH_2Cl_2 were measured at the bottom of the reaction vessel

Another example of a highly selective catalyzed process is the reaction of cyclohex-2-en-1-yl ethyl carbonate with potassium phthalimide, yielding up to 98% ee when an excess of tetrahexylammonium bromide was present.[14] These conditions were attempted with microwave heating, but as the high salt concentration led to difficulties in controlling the temperature and subsequent over-pressurization,[15] the amount of salt had to be decreased. With a catalytic amount of ammonium salt the reaction was run under microwave irradiation without complications, but the selectivity dropped to 34% ee. An attempt to substitute the ammonium salt for 18-crown-6 made the reaction much too sluggish and decreased the selectivity to below 10% ee. Using phthalimide as a nucleophile, the reaction proceeded smoothly and with high selectivity (96% ee), although slightly slower and with lower yield than the reported conditions. Under microwave irradiation higher yields were observed, though. The temperature/time/power profile for the reaction is shown in Figure 3. Best results were obtained after 1.5 min at 100W (87% yield, 96% ee) and after 3 min at 70W (87% yield, 95% ee, Table 2). Shorter reaction times led to lower yields and somewhat decreased selectivity.

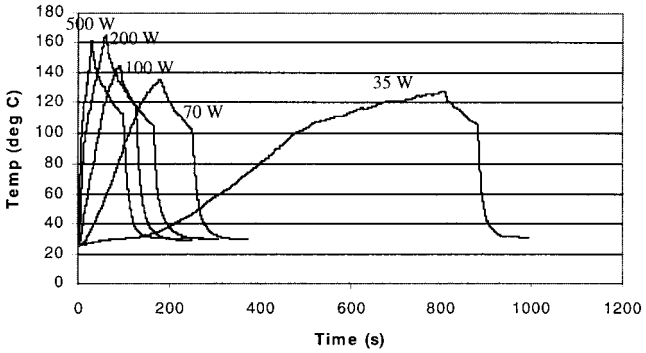


Figure 3 Measured temperatures during irradiation of the reaction in CH_3CN with phthalimide as nucleophile

We next proceeded to dimethyl malonate as nucleophile. The temperature/time/power profile is shown in Figure 4. Highest yields and selectivities (83% yield and 94 to >95% ee) were observed at 50W after 6 min, at 100 W after 4 min, and at 500W after 1.5 min, whereas shorter reaction times at these effects gave lower yields (Table 2).

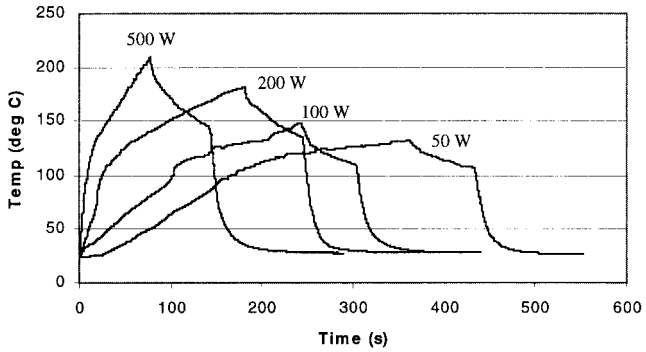


Figure 4 Measured temperatures during irradiation of the reaction in THF with dimethyl malonate as nucleophile

Interesting results were also obtained when sodium benzenesulfinate was employed as a nucleophile in the reaction with cyclohex-2-en-1-yl ethyl carbonate. Reactions in dichloromethane, acetonitrile and trifluorotoluene, in the presence of 0.1 equivalent of ammonium salt, under various microwave conditions afforded essentially racemic products in moderate to good yields. The reaction conditions reported in the literature required the presence of excess hexylammonium bromide to solubilize the starting materials. As high salt concentrations are not appropriate for facile and safe microwave flash heating using our equipment, other conditions had to be found. In methanol the reaction could be performed in the absence of ammonium salt, but a low ee was noted. It has previously been observed that the enantioselectivity is highly dependent on the choice of the counter ion, sodium resulting in low selectivity and tetraalkylammonium in high.[16] With a carbonate as a substrate, the protonated nucleophile could be employed, as a base is generated during the process.[17] Thus, the addition of one equivalent of trifluoroacetic acid resulted in an increased selectivity (70% ee). In the published procedure[16] additional catalyst had to be added to complete the reaction. This was not required using our conditions. Exchange of methanol for acetonitrile was even more successful, affording the product in 88% ee (73% yield), but with acetonitrile as solvent, the results were not always reproducible, probably due to thermal instability of the sulfinic acid.

Effect of Microwave Irradiation

The source and regulation of energy has not normally received proper recognition in synthetic organic chemistry. Microwaves have the capacity to alter that, because of the fact that the energy is directly transferred and concentrated in the reaction mixture and also because of the convenience in performing organic transformations with microwave apparatus.[18]

Occasionally it has been claimed that results different from those obtained by conventional heating can be obtained by microwave irradiation.[19] Slightly lower enantioselectivity and slightly lower yield were obtained when the reaction of *rac*-(2*E*)-1,3-diphenylprop-2-enyl acetate with dimethyl malonate was run in an oil bath instead of with microwave irradiation. In order to study whether the present results were due to some special microwave effect, the reaction of *p*-methoxyphenol with cyclohex-2-en-1-yl ethyl carbonate was run in an oil bath in dichloromethane at 100 °C in a closed vessel. These conditions resulted in the same high enantioselectivity (91% yield, 94% ee after 5 min) as those observed upon microwave irradiation.

Although high yields and high selectivity may equally well result from conventional heating, microwave irradiation offers several advantages. It is energy efficient, only the sample is heated, the heating is fast and flexible, and high temperatures are conveniently reached in a short time. We have also been able to demonstrate that in the reactions under study, lower amounts of catalysts were required than under conventional conditions, and an inert atmosphere was not necessary.

Conclusion

Microwave flash heating has been employed to accelerate enantioselective palladium-catalyzed allylic alkylation, thus extending its use to metal-catalyzed asymmetric processes. When phosphinooxazolines **3**–**5** and bisphosphine **8**, which catalyzes a wide range of reactions with high selectivity, were used as ligands high chemical yields and enantioselectivities were observed.

Microwave heating was performed in a MicroWell 10 single mode microwave cavity from Personal Chemistry AB, Sweden, producing continuous irradiation at 2.45 GHz. The reaction vessel was a round bottomed 100 mm Duran™ glass tube with a Schott GL18 screw cap, provided with teflon septa as a pressure relief device. Temperature profiles were recorded using a NoEMI-TS Reflex™ (NortechFibronic, In. Québec, Canada), utilizing temperature sensitive fluoroptic probes (TPP-01-M2.5A; Nortech Fibronic). The probe was positioned at the bottom of the reaction tube. The sampling rate was 3 Hz. After irradiation was complete, the samples were left in the microwave cavity for 1 min to allow for thermal equilibration before cooling in a water bath at r.t.

Cyclohex-2-en-1-yl ethyl carbonate[20] and ligand **8**[12a] were prepared according to published procedures. THF was freshly distilled over benzophenone/Na. MeCN and CH_2Cl_2 were distilled over P_2O_5 and stored over molecular sieves before use. All other reagents were used as received from Aldrich, Strem and Lancaster. NMR spectra were measured with a Bruker DMX500 at 500 MHZ in $CDCl_3$. The products were identified by comparison with published data.[13,14]

(*S*)-(Cyclohex-2-en-1-yl) 4-Methoxyphenyl Ether

A stock solution A was prepared by dissolving $Pd_2dba_3.CHCl_3$ (26.7 mg, 0.026 mmol), **8** (53.3 mg, 0.077 mmol) and cyclohex-2-en-1-yl ethyl carbonate (1.89 g, 11.10 mmol) in CH_2Cl_2 (10 mL) and stirring at r.t. for 15 min. A stock solution B was prepared by dissolving 4-methoxyphenol (2.00 g, 16.11 mmol) in CH_2Cl_2 (10 mL). These stock solutions could be stored for at least 24 h on dry ice. A reaction sample was prepared by mixing 1 mL each of solutions A and B in a dry reaction vessel suitable for the microwave cavity. The sample was sealed by a septum and irradiated at appropriate time and effect (see Table 2). Alternatively, the sample was heated on an oil-bath. The solvent was evaporated and the residue purified by chromatography (hexanes/Et_2O, 5:1). Enantiopurity was analyzed by HPLC (Chiralcel OD-H, 1 mL/min, 0.7% EtOH in hexanes).

(*S*)-Dimethyl 2-Cyclohex-2-en-1-ylmalonate

$Pd_2Cl_2(C_3H_5)_2$ (3.3 mg, 0.0090 mmol) and **8** (18.6 mg, 0.0269 mmol) were dissolved in THF (0.9 mL) and stirred for 5 min. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) (82 mg, 0.54 mmol) and cyclohex-2-en-1-yl ethyl carbonate (61.3 mg, 0.360 mmol) were added with THF (0.9 mL). This solution could be stored for at least 24 h on dry ice. The solution was transferred to the reaction vessel with the addition of dimethyl malonate (95 mg, 0.072 mmol) immediately before microwave irradiation or immersion in an oil-bath. The product was isolated by chromatography (gradient of 2.5–5% EtOAc in hexanes). The ee was analyzed by ^1H NMR by addition of 1.5 equivalent of $Eu(hfc)_3$.

(*S*)-3-Phthalimidocyclohex1-ene

$Pd_2Cl_2(C_3H_5)_2$ (3.3 mg, 0.0090 mmol), **8** (18.6 mg, 0.0269 mmol), phthalimide (106.0 mg, 0.720 mmol) and cyclohex-2-en-1-yl ethyl carbonate (61.3 mg, 0.360 mmol) were added to a dry reaction vessel, together with MeCN (1.8 mL). The reactants were allowed to mix for 30 sec before the vessel was sealed with a septum and irradiated. After cooling, the reaction mixture was diluted with Et_2O to a total volume of 10 mL and 4-methoxybenzonitrile (29.0 mg, 0.218 mmol) was added as an internal standard for the GC determination of the yield. Alternatively, the product was isolated by diluting with EtOAc (50 mL) and washing with NaOH (2 M, 3 × 50 mL), drying ($MgSO_4$) and evaporation, followed by chromatography (gradient of 5−20% EtOAc in hexanes). HPLC was used to analyze the enantiopurity (Chiralcel OD-H, 1 mL/min, 1.5% *i*-PrOH in hexanes).

(*S*)-3-(Phenylsulfonyl)cyclohex-1-ene

$Pd_2dba_3.CHCl_3$ (4.8 mg, 0.052 mmol) and **8** (10.0 mg, 0.0145 mmol) were stirred together in MeOH (1 mL) for 15 min. A solution of benzenesulfinic acid was prepared by adding CF_3CO_2H (44 mg, 0.39 mmol) to a solution of sodium benzenesulfinate (63.1 mg, 0.384 mmol) in MeOH (1 mL). The two solutions were mixed in the reaction vessel and cyclohex-2-en-1-yl ethyl carbonate (34.0 mg, 0.200 mmol) was added. The reaction vessel was sealed with a septum and irradiated for 2 min at 30 W. Isolation of the product by chromatography (EtOAc/hexanes, 1:8) gave 82% yield. Analysis by NMR and addition of 0.17 equivalent of $Eu(hfc)_3$ showed the enantiopurity to be 70% ee. Performing the reaction in MeCN afforded higher selectivity (88% ee), but the results were not always reproducible.

Caution! *When carrying out microwave heated reactions in closed vessels thermal stress and/or high pressures can be generated. Unless an appropriate pressure release device is used, e. g. a septum, an explosion can result. It is recommended to proceed with caution and keep the microwave reactor in an efficient fume hood.*

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