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Communication

# Microwave-mediated palladium-catalyzed asymmetric allylic alkylation; an example of highly selective fast chemistry

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**Abstract**

Highly enantioselective palladium-catalyzed microwave-mediated fast chemistry has been performed on dimethyl malonate alkylation of (*rac*)-1,3-diphenylallyl-1-acetate (**1**). Utilizing the recently developed palladium–phosphineoxazoline catalytic system, with general stability at elevated temperatures ($\leq 145$°C), quantitative yields of $\geq 97\%$ and ee values of up to $> 99\%$ were obtained after very short irradiation times (15–300 s, TOF up to 7000 $h^{-1}$). © 2000 Elsevier Science S.A. All rights reserved.

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## 1. Introduction

The palladium-catalyzed substitution reaction of allylic substrates has been examined thoroughly during the past 35 years (Fig. 1) [1]. After Tsuji's pioneering work in 1965 [2], Hata, Atkins and co-workers first reported on the catalytic version in 1970 [3], and in 1973 Trost published the first asymmetric version [4]. Today excellent enantiomeric excess can be obtained by the proper choice of catalytic system [1], although long reaction times (hours or even days) are often necessary for complete conversion [1,4]. Unfortunately, for high-speed combinatorial processing, long reaction times constitute a major restriction. The microwave heating technique offers a potential solution to this problem [5]. This prompted us to assess whether the palladium-catalyzed asymmetric allylic alkylation with dimethyl malonate could be significantly accelerated by the use of microwave flash-heating [6]. The commonly used and easily-handled (*rac*)-1,3-diphenylallyl-1-acetate (**1**) [7] was employed as a model substrate. Good results were obtained with palladium–BINAP (*P*,*P*-ligand) as catalyst (complete conversion after 60 s irradiation time, 83% ee). This system decomposed at high power input [8,9]. In contrast, utilizing a quinolineoxazoline ligand (*N*,*N*-ligand) very high thermostability was achieved, but the chiral induction was lower (65% ee). In this preliminary communication we have taken the reaction a step further. We herein report excellent results (30 s irradiation time, 97% yield and $> 99\%$ ee) obtained with phosphineoxazolines (**3**) (*P*,*N*-ligand) [10] as chiral ligands for palladium.

## 2. Results and discussion

It is noteworthy that although the palladium–quinolineoxazoline (*N*,*N*-ligand) mediated allylic alkylation was conducted with very high microwave power (500 W), in our previous investigation [8], no loss of the catalytic activity was observed. Recently, Helmchen, Pfaltz and Williams have independently reported on the ligand class **3** (*P*,*N*-ligands) [11], where the exchange of one *N* to *P* promotes stronger chiral induc-

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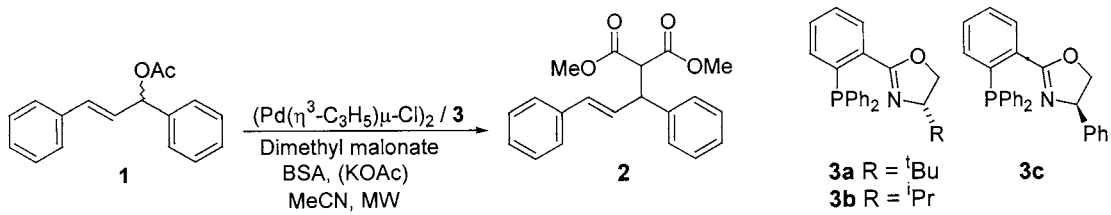


Fig. 1.

tion at the expense of coordinating strength [12], as compared with the previously used quinolineoxazoline [8]. Excellent enantiomeric enrichment and high yields were encountered in palladium-catalyzed asymmetric alkylations under conventional thermal conditions, although the reaction rates were low [11]. Further investigations demonstrated that these ligands were able to chelate palladium [13]. We were therefore inclined to examine the potential use of **3a**–**c**/Pd as stable catalytic systems for selective and very fast allylic dimethyl malonate alkylations under microwave conditions (Fig. 1).

The reactions were performed in acetonitrile, using microwave transparent sealed Pyrex vessels. The microwave heating was conducted with a newly developed microwave technique, which with high reproducibility generates a standing microwave (2.45 GHz), focused in the sample volume (single-mode) [14]. Results from reactions employing selected combinations of microwave irradiation time and power are summarized in Table 1. For the experiments conducted at high power input, the reaction times were proportionally shortened. In Fig. 2 recorded temperature profiles are presented. Control experiments revealed that the temperature profiles were not affected by the choice of catalytic system, but only by the time and microwave power applied. As can be seen in Fig. 2, the reaction mixtures were easily superheated far beyond the normal boiling point of acetonitrile (bp 81–82°C), up to 145°C.

The examples of fast chemistry in Table 1 disclose that with an appropriate choice of microwave power and irradiation time, complete conversions, quantitative yields and excellent ee values could be achieved in seconds (entries 10 and 11). In the absence of microwave irradiation the reaction rate of the asymmetric alkylation was very low (entry 14). Despite high temperatures (up to 130°C) and different temperature profiles the excellent enantiomeric purity of product **2** remained constant up to high power inputs (120 W). At very high power inputs (500 W) the phosphineoxazoline-systems **3a**–**b** behaved differently [15]. The alkylation with **3a** as ligand furnished full conversion but squalemic mixtures with 93% ee were produced (entry 12). The ligand **3b**, on the other hand, did not provide complete conversion but the enantiomeric enrichment was higher than when **3a** was employed, 97% ee (entry 13). We speculate that the catalytic system with ligand

Table 1
Microwave heated palladium-catalyzed asymmetric allylic alkylation with ligands **3a-c**

| Entry | 3 | Power (W) × time (s) | Yield [a] (%) | ee [b] (%) | TOF ($h^{-1}$) |
|---|---|---|---|---|---|
| 1 | **3a** | 5 × 300 | 15 | >99 | 50 |
| 2 | **3a** | 10 × 300 | 99 | >99 | 350 |
| 3 | **3a** | 30 × 120 | 99 | >99 | 900 |
| 4 | **3a** | 90 × 20 | 28 | >99 | 1500 |
| 5 | **3a** | 90 × 40 | 65 | >99 | 1800 |
| 6 | **3a** | 90 × 60 | >99 | >99 | 1800 |
| 7 | **3b** | 90 × 60 | >99 | >99 | 1800 |
| 8 | **3c** | 90 × 60 | 95 [c] | 97 | 1700 |
| 9 | **3a** | 120 × 20 | 66 | >99 | 3500 |
| 10 | **3a** | 120 × 30 | 97 | >99 | 3500 |
| 11 | **3b** | 120 × 30 | 98 | >99 | 3500 |
| 12 | **3a** | 500 × 15 | 98 [d] | 93 | 7000 |
| 13 | **3b** | 500 × 15 | 85 | 97 | 6000 |
| 14 | **3a** | 29°C [e] × 6 h | 56 | >99 | 3 |

[a] Measured by HPLC with detection at 254 nm using 4-methoxybenzonitrile as internal standard. No by-products were observed and conversions were equal to yields.

[b] Values from 2–6 runs measured by repeated chiral HPLC (Daicel Chiralcel OD-H, 99.5:0.5 iso-hexane–2-propanol, 0.5 ml $min^{-1}$).

[c] Isolated yield.

[d] Addition of small amounts of KOAc was necessary for full conversion (~1 mg).

[e] Reaction performed with internal temperature measurement and stirring at 29 ± 0.5°C.

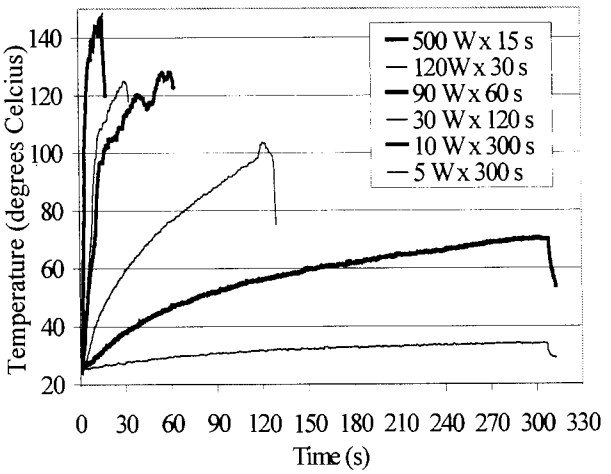


Fig. 2. Selected temperature profiles for the microwave heated palladium-catalyzed asymmetric allylic alkylations. Temperature profiles were recorded using a NoEMI-TS Reflex™ (Nortech Fibronic, Inc. Québec, Canada), utilizing temperature sensitive fluoroptic probe (TPP-01-M2.5-A; Nortech Fibronic). The probe was positioned at the bottom of the reaction tube. Sampling rate was 3 Hz. After appropriate irradiation time the reaction mixtures were efficiently cooled in water at room temperature.

**3b** is deactivated at the very high power input (Fig. 2) [16,17]. In summary, we have demonstrated that palladium-catalyzed allylic alkylation with very high enantiomeric excess ( > 99% ee) can be performed in only 30 s with single-mode standing microwave irradiation, provided suitable ligands are used.

## 3. Experimental

The microwave-mediated alkylations were performed in sealed heavy-walled Pyrex tubes following essentially the procedure given by Sprinz and Helmchen [11b,15], using the *N*,*O*-bis(trimethylsilyl)acetamide (BSA) developed by Trost and Murphy [18] as probase. To a heavy-walled Pyrex tube (8.0–8.5 ml, l = 200 mm) 1000 μl of a substrate solution [BSA (3.830 g, 18.8 mmol), 1,3-diphenylallyl-1-acetate (**1**) (1.600 g, 6.35 mmol) [7] and 4-methoxybenzonitrile (2.196 g, 16.49 mmol) dissolved in 14 ml dry acetonitrile] and 500 μl of a catalyst solution [$(Pd(\eta^3\text{-}C_3H_5)\mu\text{-}Cl)_2$ (41.0 mg, 0.11 mmol) and phosphineoxazoline (**3a**) (108 mg, 0.28 mmol), (**3b**) (105 mg, 0.28 mmol) or (**3c**) (114 mg, 0.28 mmol) [10] dissolved in 11 ml dry acetonitrile, 3%-mol Pd, 4%-mol **3**] were transferred [19]. Dimethyl malonate (75 μl, 86.7 mg, 0.656 mmol) was added and the reaction vessel was sealed with a screw cap. The sample was irradiated at 2.45 GHz with a suitable power for an appropriate time (see Table 1 for details) in a Microwell 10 single-mode cavity (0–500 W, Personal Chemistry AB, Uppsala, Sweden). After irradiation, the reaction was quenched with 75 μl water and 96:4 isohexane–2-propanol (5 ml). The quenched reaction mixture was thereafter diluted and analyzed by HPLC as previously described [8]. Alternatively the product **2** was isolated (entry 8, Table 1) and the enantiomeric excess analyzed by $^1$H-NMR [8].

**Caution!** When carrying out microwave heated reactions in closed vessels thermal stresses and/or high pressures can be generated. This applies in particular to reaction mixtures containing volatile substances or metal complexes (which if precipitated as finely divided metal particles can cause 'thermal runaway'). 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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[15] The omission of the potassium acetate, reported to be needed for decomposition of BSA, did not alter the outcome of the alkylation after conventional heating, nor after microwave irradiation at power input up to 120 W. At a microwave power of 500 W, the addition of very small amounts of potassium acetate allowed for full conversion using **3a** as ligand. An 85% yield was encountered in absence of potassium acetate under otherwise identical conditions. No effect of potassium acetate was observed when using **3b** as ligand. The ee values were not affected by the addition of potassium acetate nor were the temperature profiles.

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