1082 *J. Org. Chem.* **1999,** *64,* 1082−1083

Rapid Microwave-Induced Palladium-Catalyzed Asymmetric Allylic Alkylation

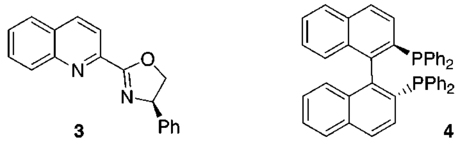
Ulf Bremberg,[†] Mats Larhed,[‡] Christina Moberg,*,[†] and Anders Hallberg*,[‡]

Department of Chemistry, Organic Chemistry,
Royal Institute of Technology, SE-100 44 Stockholm, Sweden,
and Department of Organic Pharmaceutical Chemistry,
Uppsala Biomedical Centre, Uppsala University, Box 574,
SE-751 23 Uppsala, Sweden

Received September 18, 1998

Palladium-catalyzed asymmetric allylic substitution reactions have attracted considerable interest primarily due to their synthetic utility.[1,2] The enantioselectivity is determined either during complex formation or, with substrates yielding *meso*-allyl ligands, during the nucleophilic attack on either of the two diastereotopic π-allyl carbon atoms of the π-allylpalladium(II) intermediate.[2a] The absolute configuration of the starting material is not recognized in the intermediate π-allylpalladium complex, and high asymmetric induction can be achieved by the employment of chiral ligands. A plethora of C_1- and C_2-symmetric chiral ligands are available for this reaction,[3] and among these, bidentate ligands with phosphorus and/or nitrogen as coordinating elements have been most extensively used.[2]

We were encouraged to exploit the potential of microwave irradiation as a nonconventional energy source for promotion of slow asymmetric alkylations. Flash-heating by microwaves for the acceleration of organic reactions is well established,[4] but only during the past few years has the power of the heating methodology been demonstrated in palladium-catalyzed coupling reactions, where the collapse of the catalytic system can be avoided by proper selection of conditions. Thus, selective Heck,[5] Suzuki,[6] and Stille[6] reactions, in solution or on solid phase, were accomplished in 1.5−12 min and in high yields with a variety of reactant combinations.[5a,e,f,6] However, no reports have appeared on the impact of microwave irradiation on asymmetric transition metal catalysis in general or on the reaction rate in such processes where π-allylpalladium(II) complexes constitute the key intermediates in the catalytic cycle. We herein report an example of an enantioselective and very rapid microwave-induced palladium-catalyzed alkylation of an allylic acetate that proceeds via a π-allylpalladium(II) intermediate.



3 **4**

Figure 1.

Racemic 1,3-diphenyl-2-propenyl acetate (**1**), which is a commonly used substrate in asymmetric palladium-catalyzed allylic alkylations, reacts smoothly with dimethyl malonate in catalytic systems where phosphine ligands are employed, while very long reaction times are sometimes needed with dinitrogen ligands.[2,3] The transformation of **1** into **2** was therefore chosen as a suitable model reaction for studies of microwave flash-heating. Two types of ligands with diverse inherent properties were assessed. One of them, (+)-BINAP (**4**) (Figure 1), constitutes an example of an often used C_2-symmetric bis-phosphine ligand.[7] As an example of an N,N-ligand, C_1-symmetric (4′*R*)-2-(4′,5′-dihydro-4′-phenyl-2′-oxazolyl)quinoline (**3**) (Figure 1) was chosen.[8] The alkylations were conducted essentially following the procedure by Trost et al.[9] using *N,O*-bis(trimethylsilyl)acetamide (BSA) as the base, with modifications by Leutenegger et al.[10a] for the nitrogen ligands and by Brown et al.[10b] for BINAP. A π-allylpalladium(II)−ligand complex was prepared in situ, and a low concentration of the nucleophile was generated from dimethyl malonate in the presence of BSA and a catalytic amount of KOAc. The microwave heating was performed with a single-mode cavity[11] in sealed[12] heavy-walled Pyrex tubes.[13] The experiments were conducted without stirring in acetonitrile, which is known to possess a sufficiently high dissipation factor (tan δ) to be efficiently heated under microwave irradiation.[14] The results are summarized in Tables 1 and 2.

Experiments in acetonitrile at room temperature provided high yields with both ligands (Table 1). Neither of them induced extreme enantioselectivities in acetonitrile. The reaction with **4** (entry 5) delivered a slightly higher enantiomeric excess and was considerably faster than the reactions with **3** as ligand (entry 1), which is in agreement with previous findings in dichloromethane.[8,10a] Alkylation with ligand **3** required 3 days for completion at room temperature, a typical rate for N,N-ligands. In Table 2, the microwave irradiation experiments with selected combinations of reaction time and power that result in complete consumption of the starting material are summarized. The microwave-induced alkylations provided excellent yields and high reaction rates, but somewhat lower enantioselectivities were encountered, in particular with the quinolineoxazoline **3** as

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[†] Royal Institute of Technology.

[‡] Uppsala University.

(1) Trost, B. M.; Strege, P. E. *J. Am. Chem. Soc.* **1977**, *99*, 1649.

(2) For reviews, see: (a) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 365. (b) Shibasaki, M. In *Advances in Metal−Organic Chemistry*; Liebeskind, L. S., Ed.; JAI Press: Greenwich, 1996; Vol. 5, p 119. (c) Tsuji, J. *Palladium Reagents and Catalysts*; John Wiley: Chichester, 1995; p 290.

(3) (a) Achiwa, I.; Yamazaki, A.; Achiwa, K. *Synlett* **1998**, 45. (b) Gläser, B.; Kunz, H. *Synlett* **1998**, 53. (c) Ahn, K. H.; Cho, C.-W.; Park, J.; Lee, S. *Tetrahedron: Asymmetry* **1997**, *8*, 1179. (d) Chelucci, G. *Tetrahedron: Asymmetry* **1997**, *8*, 2667. (e) Nordström, K.; Macedo, E.; Moberg, C. *J. Org. Chem.* **1997**, *62*, 1604. (f) Zhang, W.; Hirao, T.; Ikeda, I. *Tetrahedron Lett.* **1996**, *37*, 4545.

(4) For reviews, see: (a) Mingos, D. M. P.; Baghurst, D. R. *Chem. Soc. Rev.* **1991**, *20*, 1. (b) Caddick, S. *Tetrahedron* **1995**, *51*, 10403. (e) Langa, F.; de la Cruz, P.; de la Hoz, A.; Díaz-Ortiz, A.; Díez-Barra, E. *Contemp. Org. Synth.* **1997**, 373. (f) Gabriel, C.; Gabriel, S.; Grant, E. H.; Halstead, B. S. J.; Mingos, D. M. P. *Chem. Soc. Rev.* **1998**, *27*, 213. For www resources devoted to microwave chemistry, see: http://www.ed.ac.uk/~ah05/microwave.html.

(5) (a) Larhed, M.; Hallberg, A. *J. Org. Chem.* **1996**, *61*, 9582. (b) Díaz-Ortiz, A.; Prieto, P.; Vázquez, E. *Synlett* **1997**, 269. (c) Li, J.; Mau, A. W.-H.; Strauss, C. R. *J. Chem. Soc., Chem. Commun.* **1997**, 1275. (d) Wali, A.; Muthukumaru Pillai, S.; Satish, S. *React. Kinet. Catal. Lett.* **1997**, *60*, 189. (e) Garg, N.; Larhed, M.; Hallberg, A. *J. Org. Chem.* **1998**, *63*, 4158. (f) Olofsson, K.; Larhed, M.; Hallberg, A. *J. Org. Chem.*, **1998**, *63*, 5076. (g) Villemin, D. Presented at the International Conference on Microwave Chemistry, Prague, Sep 1998; Paper PL 5.

(6) (a) Larhed, M.; Lindeberg, G.; Hallberg, A. *Tetrahedron Lett.* **1996**, *37*, 8219. (b) Larhed, M.; Hoshino, M.; Hadida, S.; Curran, D. P.; Hallberg, A. *J. Org. Chem.* **1997**, *62*, 5583. See also ref 5a.

(7) 2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl. See: Noyori, R.; Takaya, H. *Acc. Chem. Res.* **1990**, *23*, 345.

(8) Bremberg, U.; Rahm, F.; Moberg, C. *Tetrahedron: Asymmetry*, in press.

(9) Trost, B. M.; Murphy, D. J. *Organometallics* **1985**, *4*, 1143.

(10) (a) Leutenegger, U.; Umbricht, G.; Fahrni, C.; von Matt, P.; Pfaltz, A. *Tetrahedron* **1992**, *48*, 2143. (b) Brown, J. M.; Hulmes, D. I.; Guiry, P. J. *Tetrahedron* **1994**, *50*, 4493.

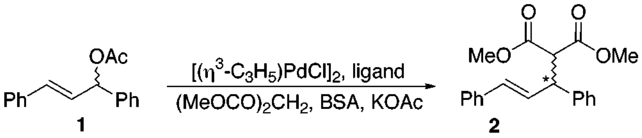
(11) Stone-Elander, S.; Elander, N. *Appl. Radiat. Isot.* **1993**, *44*, 889.

(12) One often overlooked hazard that may become prevalent under microwave irradiation is the formation of electrical arcs. Arcing could result in vessel rupture if air and flammable compounds are involved. We believe the possibility of running reactions in an inert gas atmosphere is a distinct advantage with the sealed reaction vessel strategy.

(13) Baghurst, D. R.; Mingos, D. M. P. *J. Chem. Soc., Dalton Trans.* **1992**, 1151.

10.1021/jo981896h CCC: $18.00

Table 1. Asymmetric Alkylation of 1 with 3 or 4 as Ligand at Room Temperature or with Thermal Heating in Acetonitrile[a]



entry	ligand	temp (°C)	time (min)	yield of **2**[b] (%)	ee (%)	absolute configuration
1	**3**	23	4300	99	77[c] (73[d])	*R*
2	**3**	100	19	97	62[c]	*R*
3	**3**	140	6.3	93	60[c]	*R*
4	**3**	180	4.5	93	56[c]	*R*
5	**4**	23	60	97	87[c] (90[d])	*S*

[a] Reactions were conducted at 23 °C, or in warmed oil baths, in sealed Pyrex tubes under a nitrogen atmosphere. The reaction scale was 0.35 mmol in entries 1−4 and 0.57 mmol in entry 5. [b] Isolated yield. >95% purity by HPLC. [c] Determined by chiral HPLC. [d] Determined by ^{1}H NMR.

Table 2. Microwave-Induced Asymmetric Alkylation of 1 with 3 or 4 as Ligand in Acetonitrile[a]

entry	ligand	time (min)	power (W)	yield of **2**[b] (%)	ee (%)	absolute configuration
1	**3**	15.0	35	99	65[d]	*R*
2	**3**	7.5	70	99	64[d]	*R*
3	**3**	3.5	120	99	63[d]	*R*
4	**3**	3.0	250	99	65[d]	*R*
5	**3**	2.0	500	99 (95[c])	65[d] (63[e])	*R*
6	**4**	2.0	20	94	83[d]	*S*
7	**4**	1.5	20	96	85[d]	*S*
8	**4**	1.0	40	95 (96[c])	83[d] (81[e])	*S*

[a] Reactions were conducted under continuous microwave irradiation (2450 MHz, MicroWell 10) in sealed Pyrex tubes under an atmosphere of nitrogen. The reaction scale was 0.35 mmol in entries 1−5 or 0.57 mmol in entries 6−8. [b] Determined by HPLC. [c] Isolated yield. >95% purity by HPLC. [d] Determined by chiral HPLC. [e] Determined by ^{1}H NMR.

compared to what was observed with this ligand in the reactions performed at room temperature. Despite the reduction in reaction time for the microwave-heated reactions, from 15 min (entry 1) to 2.0 min (entry 5), the enantiomeric purity of **2** was found to be constant. Dichloromethane used in the original protocols[8,10a] has a too low boiling point to be suitable for rapid microwave heating. Solvents with properties similar to those of dichloromethane but with higher boiling points, such as 1,2-dichloroethane and benzotrifluoride,[15] failed to give acceptable enantiomeric excesses and yields.

Attempts to truncate the reaction time by increasing the temperature by classical means (warmed oil baths) did not result in a similarly straightforward success. Three reactions, employing ligand **3**, were performed with traditional heating at 100, 140, and 180 °C (Table 1). Complete conversion of **1** was achieved in 19−4.5 min, and the product was isolated in 97−93% yield (entries 2−4). In contrast to the microwave-assisted reactions (Table 2), the enantiomeric excess decreased with increased reaction rate.

A comparison of entries 1−5 (Table 2) demonstrates that higher microwave power is needed for full conversion of the allyl acetate **1** in the short time reactions. Full conversion was encountered in 2.0 min at 500 W with **3**, while 1.5 min was insufficient and a substantial amount of starting material remained unreacted in the latter case.[16] Furthermore, a comparison of entries 5 and 6 reveals the much higher reactivity of catalytic systems comprising **4** as ligand. A power of 40 W was needed in the 1.0 min reactions with **4** (entry 8) since starting material remained with lower power (30 W). Interestingly, and possibly reflecting a lability of the BINAP (**4**) system as opposed to the quinolineoxazoline (**3**) system, a power of 50 W and above rendered a dramatic decrease in the conversion rate of **1**, which might be attributed to an early collapse of the catalytic system.

Microwave energy transfer to an organic reaction in the liquid state occurs mainly by two mechanisms, namely dipole oscillation and ionic conduction.[4] In the reactions with the Pd−BINAP catalytic system, the contribution from the dipolar oscillation can be expected to be the most predominant since both the final temperature and the ionic strength of the reaction mixture are relatively low.[17] However, because of the very high energy densities employed in the fast reactions with **3** as chiral ligand, it is highly probable that a temperature level is reached where the conductive losses are of great importance.[18] As a high microwave power, and resulting fast heating, gives less time for the sample to react at each given temperature, a decrease in reaction time has to be accompanied by a large increase in power. In addition, microwave absorption efficiency via dipole oscillation for low molecular weight polar organic solvents, e.g. acetonitrile, decreases with increasing temperature.[4,19] These two factors may explain the large increase in power necessary to obtain full conversion with **3** as the reaction time is lowered.

Although we lack appropriate temperature data, we assume that the impact of microwave irradiation, on both the reaction rate and on the asymmetric induction, is a consequence of fast and homogeneous in situ heating without wall effects and sharp temperature gradients.[4,19,20]

We have demonstrated that very fast, small scale, asymmetric palladium-catalyzed allylic alkylation reactions can be accomplished in high yields and with fair enantioselectivity with microwave flash-heating. To the best of our knowledge, this is the first example of an asymmetric transition metal-catalyzed reaction promoted by microwave energy.

Caution! It is unsafe to flash-heat organic reactions in a contained space both by traditional means and with microwave irradiation. Therefore, the reaction vessel must be equipped with an appropriate pressure relief device.

Acknowledgment. We thank the Swedish Natural Science Research Council for financial support.

Supporting Information Available: General experimental procedures and methods.

JO981896H

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(14) (a) Stone-Elander, S.; Elander, N. *Appl. Radiat. Isot.* **1991**, *42*, 885. (b) Mingos, D. M. P.; Whittaker, A. G. *J. Microwave Power Electromag. Energy* **1994**, *29*, 195.

(15) Ogawa, A.; Curran, D. P. *J. Org. Chem.* **1997**, *62*, 450.

(16) The reaction time could probably be reduced below 2.0 min with higher microwave power, but 500 W is the limit of our currently available apparatus (MicroWell 10).

(17) Regarding the bulk of BSA and dimethyl malonate as nonionized and all Pd as $[Pd(II)\text{-}LL\text{-}allyl]^+$, the ion strength of the solution depends only on the Pd-catalyst and dissolved KOAc (partly dissolved). Calculation yields $I = 0.014-0.026$ for **3** and $I = 0.011-0.017$ for **4** (lower limit: no KOAc dissolved, higher limit: all KOAc dissolved).

(18) Zijlstra, S.; de Groot, T. J.; Kok, L. P.; Visser, G. M.; Vaalburg, W. *J. Org. Chem.* **1993**, *58*, 1643.

(19) Strauss, C. R.; Trainor, R. W. *Aust. J. Chem.* **1995**, *48*, 1665.

(20) Hájek, M. *Collect. Czech. Chem. Commun.* **1997**, *62*, 347.