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Microwave-accelerated asymmetric allylations using cysteine derived oxazolidine and thiazolidine palladium complexes

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Abstract

A set of enantiopure oxazolidine–thioether and thiazolidine–alcohol palladium complexes catalyze the microwave-mediated enantioselective allylation of *rac*-1,3-diphenyl-2-propenyl acetate with dimethyl malonate. Good yields and ee's were achieved in reaction times of 2 min instead of hours with conventional heating.

Keywords: Microwave; Palladium; Allylation; Asymmetric catalysis; Oxazolidine; Thiazolidine

1. Introduction

The palladium-catalyzed substitution reaction of allylic substrates has been examined thoroughly during the past three decades [1]. Excellent enantiomeric excess can be obtained by the proper choice of the catalytic system. However, the long reaction times (hours or even days) frequently required for full conversions have limited the exploitation of homogeneous catalysis in high-throughput syntheses. Reaction time is an important issue, especially in combinatorial chemistry, because this considerably influences the sample throughput [2]. A higher throughput results in a faster development of a synthetic method as well as a faster lead optimization in drug discovery [3].

Substitution of traditional heating (oil bath, sand bath, heating jacket, water bath, and hot air) by microwave radiation can diminish the reaction time of many organic reactions from hours and days to seconds and minutes and has been well established as a convenient method to promote rapid reactions [4]. Since then, numerous successful reactions with dramatically enhanced reaction rates have been obtained using only small amounts of energy [4,5]. The possibility of employing milder and less toxic reagents and solvents offers a further advantage of using this heating technology. Often non-inert atmosphere conditions and simple experimental set up of many microwave reactions offers additional convenience in chemical synthesis.

Various homogeneous catalytic reactions with metal ions have been performed successfully under microwave radiation like the Heck reaction [6], Sonogashira coupling [7], Suzuki coupling [7], Stille coupling [8], and palladium-catalyzed phenylation of aryl chlorides [7,9]. Also the asymmetric palladium-catalyzed allylic alkylation has been performed successfully with various, well known bidentate ligands resulting in excellent enantioselectivities [4b,10].

In this context, we recently reported the synthesis of a new set of enantiopure oxazolidine–thioether and thiazolidine–alcohol ligands starting from L-cysteine, S-

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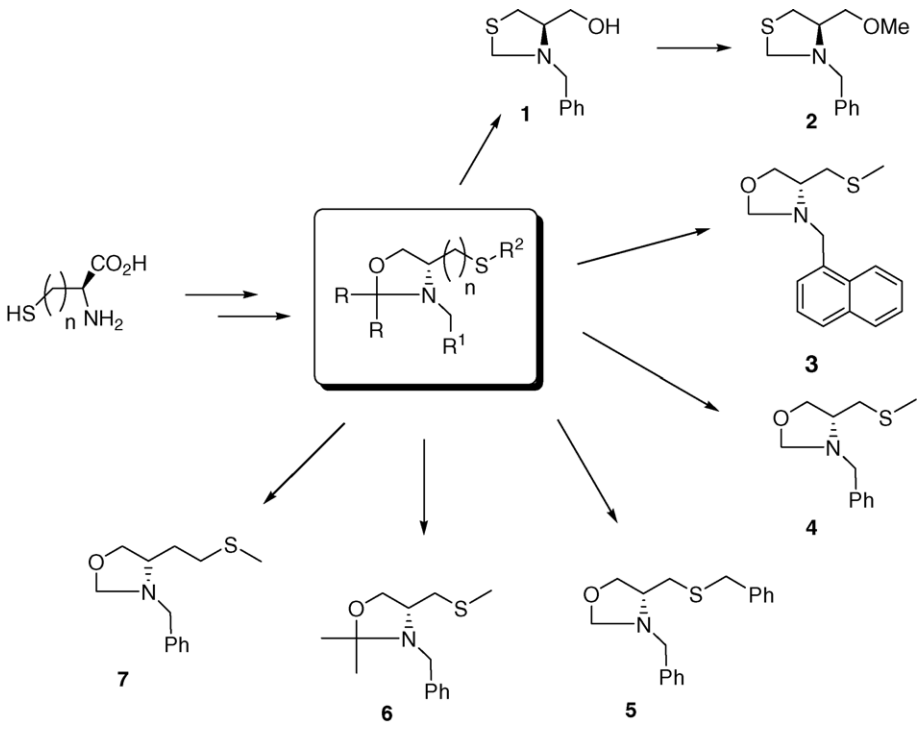


Fig. 1. Oxazolidine and thiazolidine ligands available from cysteine and its homologs.

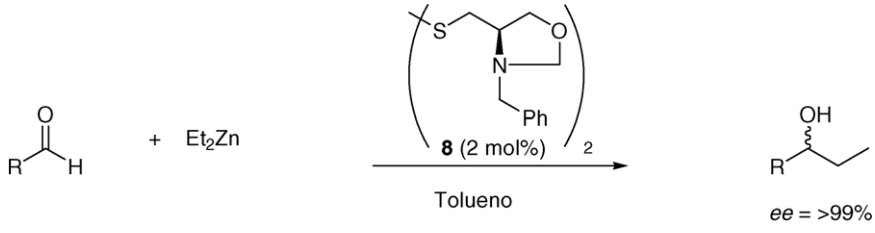
methyl-L-cysteine and L-methionine in a straightforward manner allowing numerous structural variations (Fig. 1). These ligands differ in their properties from the more common phosphane or N/O-based ligands and were explored for asymmetric palladium-catalyzed allylations in the reaction of *rac*-1,3-diphenyl-2-propenyl acetate with dimethyl malonate. The reaction proceeded in excellent yield and enantiomeric excesses of up to 94% [11].

In another series of cysteine-derived ligands we described the synthesis of the chiral disulfide **8** [12]. It was applied for the addition of diethylzinc and alkynylzinc [13] to several aromatic and aliphatic aldehydes and enantioselectivities of up to >99% were achieved when 2 mol% of the catalyst were used (Scheme 1). The basic framework of disulfide **8** forms the basis for a variety of sulfur–oxazolidine ligands in a general combinatorial approach (Fig. 1). Simple variations on its structure led us to new oxazolidine and thiazolidine ligands [11].

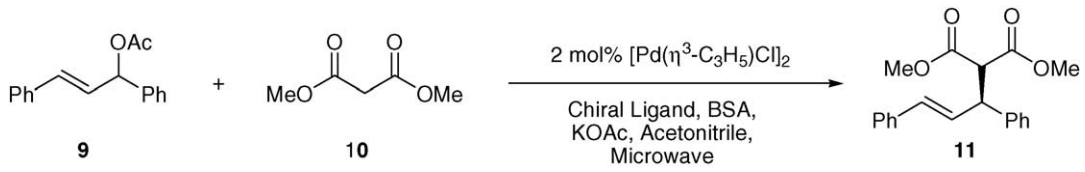
For the best of our knowledge, nitrogen–sulfur bidentate ligands were not screened in the microwave assisted asymmetric palladium-catalyzed allylic alkylations. Since the oxazolidine and thiazolidine ligands, prepared in our previous work [11] promoted the alkylation reactions slowly (12–169 h), we envisioned to perform these reactions under microwave flash heating in order to enhance their speed.

2. Results and discussion

All new ligands were obtained in good yields along the facile synthetic routes described earlier [11]. Transformation of the oxazolidine disulfide **8** into the thioethers **4** and **5** was achieved by $NaBH_4$-reduction under basic conditions, and consecutive alkylation with methyl iodide or benzyl chloride. An analogous procedure can be followed for *N*-(1-naphtylmethyl) derivative giving **3** in 69% yield. However, reduction of bis(oxazolidinylmethyl) disulfide **8** with $NaBH_4$, under neutral conditions, gave the thiazolidine alcohol **1** exclusively in good yields instead of the expected free thiol. Methylation of **1** with methyl iodide resulted in the ether **2**.



Scheme 1.



Scheme 2.

To obtain thioethers with variations of the steric bulk at the oxazolidine ring, as well as variations of the tether length between the two donor atoms of the bidentate ligand, L-Methionine or S-Me-L-Cysteine were used as starting materials. These ligands (**6** and **7**) were obtained by reduction of the amino acid, followed by benzylation and cyclization, in satisfactory yields.

The standard reaction to test the potential of a ligand in the asymmetric palladium catalyzed allylation uses *rac*-1,3-diphenyl-2-propenyl acetate with dimethyl malonate as a nucleophile (Scheme 2).

The alkylations were conduced essentially following the procedure by Moberg and co-workers [14] using *N*,*O*-bis(trimethylsilyl)acetamide (BSA) as the base. A chiral π-allylpalladium (II) – ligand complex was prepared in situ from $Pd_2Cl_2(\eta^3C_3H_3)_2$, and a low concentration of the nucleophile was generated from methyl malonate in the presence of BSA and a catalytic amount of KOAc [15]. The microwave heating was performed with a single-mode cavity in sealed heavy-walled Pyrex tubes. The experiments were conducted with stirring in acetonitrile, which is known to possess a sufficiently high dissipation factor to be efficiently heated under microwave irradiation [16]. Results from reactions employing selected combinations of microwave irradiation times and power are summarized in Table 1.

We started our investigation with palladium complexes containing ligand **4**, which catalyzes the reaction of *rac*-(2*E*)-1,3-diphenyl-prop-2-enyl acetate and dimethyl malonate with reasonable selectivity after 12 h at ambient temperature (Table 1, entry 1) [11]. Microwave heating of the reaction mixture for 2 min at 30 W results in the same selectivity in a little lower yield (70% ee, Table 1, entry 6). Decreasing the catalyst loading from 10 to 2% did not affect the enantioselectivity significantly (Table 1, entries 4–6). When 1 mol% catalyst was used, a significant decrease is observed in both enantioselectivity and yield (Table 1, entry 7). Changing the reaction time from 2 to 4 min does improve neither the yield nor the enantioselectivity (Table 1, entry 8). This catalytic system proved to be very sensitive to high temperature, furnishing only traces of the allylation product in low selectivity (Table 1, entry 9). This is probably due to decomposition of the rather weak palladium-ligand complex, as corroborated by the precipitation of palladium black upon heating. The optimal conditions were found to be 2 min reaction time at 30 W and up to 70 °C. Based on this value, we extended the study to other catalysts. The microwave irradiations were performed under controlled conditions that make the procedure highly safe, reliable and reproducible. Clearly, in the absence of an accurate temperature monitoring, a reaction may not be reproducible between two different

Table 1
Conventional and microwave-heated asymmetric palladium-catalyzed allyylations with ligands **1**–**7** (Scheme 2)[a]

Entry	Ligand	*T* (°C)	*E* (W)	Time	Yield (%)[b]	ee (%)[c]
1[d]	**4** (10 mol%)	r.t.	–	12 h	96	71 (*S*)
2[d]	**1** (10 mol%)	r.t.	–	168 h	52	81 (*S*)
3[d]	**6** (10 mol%)	r.t.	–	12 h	96	81 (*S*)
4	**4** (10 mol%)	70	30	2 min	93	67 (*S*)
5	**4** (5 mol%)	70	30	2 min	92	70 (*S*)
6	**4** (2 mol%)	70	30	2 min	89	70 (*S*)
7	**4** (1 mol%)	70	30	2 min	54	61 (*S*)
8	**4** (2 mol%)	70	30	4 min	82	64 (*S*)
9	**4** (2 mol%)	150	100	2 min	18	7 (*S*)
10	**5** (4 mol%)	70	30	2 min	95	67 (*S*)
11	**1** (2 mol%)	70	30	2 min	12	18 (*S*)
12	**2** (2 mol%)	70	30	2 min	26	6 (*S*)
13	**3** (2 mol%)	70	30	2 min	64	72 (*S*)
14	**5** (2 mol%)	70	30	2 min	97	71 (*S*)
15	**6** (2 mol%)	70	30	2 min	86	34 (*S*)
16[e]	**6** (10 mol%)	82	–	35 min	92	35 (*S*)
17	**7** (2 mol%)	70	30	2 min	47	12 (*S*)

[a] The reaction scale was 0.35 mmol.
[b] Isolated yield.
[c] Determined by HPLC with a chiralcel OD column and the absolute configuration of the product was assigned through comparison of the sign of specific rotations with literature data [17].
[d] NaH (1,5 equiv.), dimethyl malonate (2 equiv.), and 1,3-diphenyl-2-propenyl acetate (1 equiv.).
[e] Reaction was performed with normal heating, without microwave irradiation.

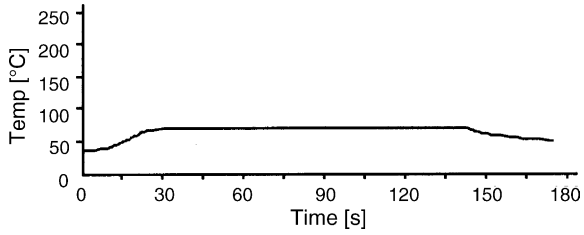


Fig. 2. Representative examples of temperature profile of the microwave accelerated allylations.

microwave systems. Single mode irradiation with monitoring of temperature was used and representative examples of temperature profiles of the microwave accelerated allylations (Fig. 2) favor a temperature of 70–75 °C for the reaction.

Ligands **1** and **6** have been shown to result in high selectivity when employed in the same process at room temperature, albeit requiring hours or even days for a complete reaction (81% ee, Table 1, entries 2 and 3) [11]. Surprisingly, little enantioselectivity was obtained upon microwave irradiation (Table 1, entries 11 and 15). One possible explanation is that these ligand systems have a very low thermostability, as we could observe the precipitation of palladium black during both, conventional heating and microwave irradiation (Table 1, entries 15 and 16). In contrast to this, the reaction with the oxazolidine–thioethers **3** and **5** resulted in high yields and an enantioselectivity comparable to those observed with reactions performed at room temperature (Table 1, entries 13 and 14) [11].

3. Conclusions

In this communication, we have demonstrated that very fast, asymmetric palladium-catalyzed allylic alkylation reactions can be accomplished in high yields and good enantioselectivity with microwave flash heating. The oxazolidine–thioethers **3**, **4** and **5** furnished the alkylation product with the same level of enantioselectivity compared to a non-irradiated reaction at room temperature. Interestingly some ligands gave different results when irradiated, possibly due to faster decomposition—a result that can be seen as a hint to not solely rely on accelerated microwave conditions for catalyst screening.

In general though, microwave irradiation improved the reaction conditions considerably by decreasing the required amount of catalyst from 10 to 2 mol% and the reaction time from 12 h to 2 min, usually without loss of enantioselectivity.

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[15] General procedure for microwave-induced allylation: chiral ligand (2 mol%) and $Pd_2Cl_2(\eta^3\text{-}C_3H_3)_2$ (0.035 mmol, 2 mol%) were dissolved in dry acetonitrile (3.6 mL). The solution was stirred under argon for 30 min. Bis(trimethylsilyl)acetamide and (1.055 g, 5.2 mmol), 1,3-diphenyl-2-propenyl acetate **9** (436 mg, 1.73 mmol) were transferred with 3.6 mL of acetonitrile to the reaction solution. A portion (0.35 mmol, 2 mL for each sample, total volume 9.90 mL) of this solution was transferred to a thick walled Pyrex tube, KOAc (0.006 g, 0.6 mmol) and dimethyl malonate (0.077 mL, 0.630 mmol) were added and the reaction vessel was sealed with a silicon septum under nitrogen atmosphere. The tube was positioned in a MicroWell 10 single mode cavity microwave from Personal Chemistry AB, Sweden, producing continuous irradiation at 2.45 GHz, and the sample was irradiated with suitable power for an appropriate time (Table 1). The solvent was removed and the crude product was flash chromatographed on silica with ethyl acetate:hexane (1:99).
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