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Microwave-Mediated Palladium-Catalyzed Asymmetric Allylic Alkylation Using Chiral β-Seleno Amides

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Keywords: Microwave / Palladium / Allylic alkylation / Selenium

A class of enantiopure β-seleno amide palladium complexes catalyze the microwave-accelerated enantioselective allylic alkylation of *rac*-1,3-diphenyl-2-propenyl acetate with different malonates. Good yields and enantiomeric excess values of up to 94 % *ee* were obtained after irradiation times of 2 or 4 min.
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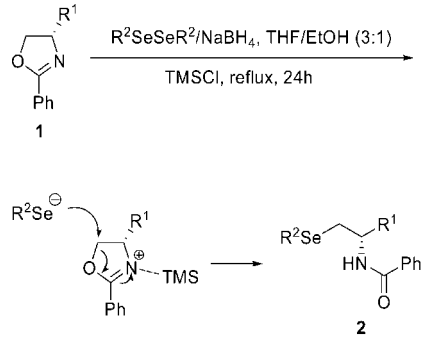
The palladium-catalyzed substitution reaction of allylic substrates has been examined thoroughly during the past three decades.[1] Excellent enantiomeric excess can be obtained by the proper choice of the catalytic system. However, the long reaction time (hours or even days) frequently required for full conversion has limited the exploitation of homogeneous catalysis in high-throughput syntheses. Flash-heating by microwaves for the acceleration of organic reactions is well established as a convenient method,[2] but only during the past few years the power of the heating methodology has been demonstrated in palladium-catalyzed coupling reactions, where often non-inert atmosphere conditions and simple experimental set up of many reactions offers additional convenience in chemical synthesis. Thus, selective Heck,[3] Suzuki,[4] Stille[5] and Sonogashira[6] reactions, in solution or solid phase, were accomplished in short times and in high yields with a variety of combinations. However, few reports concern the impact of microwave irradiation on palladium-catalyzed asymmetric allylic substitutions with π-allylpalladium(II) complexes as the key intermediate in the formation of a new carbon–carbon bond.[7,8]

On the other hand, recent advances in the synthesis of selenium-containing compounds have been driven by the interesting reactivity[9] and potential pharmaceutical significance of these compounds.[10] In particular, chiral selenium-based methods have received special attention from organic chemists in the last decade and are now a very important tool for stereoselective transformations.[11,12] At the same time, catalytic asymmetric reactions to provide enantiomerically enriched compounds have become one of the more exciting research areas using chiral organoselenium compounds, representing a new trend in this field of organometallic chemistry. In this context, chiral selenides and diselenide-containing ligands have been employed as useful catalysts in various asymmetric transformations such as enantioselective addition of diethylzinc to aldehydes,[13,14] 1,4-addition of Grignard reagents to enones[15] and palladium-catalyzed asymmetric allylic substitution.[16,17]

We recently reported the practical synthesis of a new set of chiral β-seleno amides[18] and their derivatives through the ring-opening reaction of inexpensive and easily available 2-oxazolines[19] (Scheme 1). As outlined in the reaction scheme, the preparation of the β-seleno amides proceeds through the formation of an oxazolinium intermediate, followed by regio- and chemoselective nucleophilic attack of the selenide anion at the C(5) position of the ring, leading to the C(5)–O(1) bond cleavage and furnishes the desired products **2a**–**g**,[20] without any loss of enantiomeric purity, as determined by chiral HPLC analysis.



2a: R^1 = *i*Pr; R^2 = Ph; 93%
2b: R^1 = *i*Pr; R^2 = *p*-ClC_6H_4; 82%
2c: R^1 = *i*Pr; R^2 = *p*-$MeOC_6H_4$; 84%
2d: R^1 = *i*Pr; R^2 = 2,4,6-$Me_3C_6H_3$; 79%
2e: R^1 = *i*Pr; R^2 = Bn; 71%
2f: R^1 = Bn; R^2 = Ph; 84%
2g: R^1 = *i*Bu; R^2 = Ph; 82%

Scheme 1.

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These enantiopure organoselenium amides were evaluated as catalysts in palladium-catalyzed asymmetric allylic alkylations and the reactions proceeded in excellent yields and in up to 98% *ee* after 24 h at room temperature.

To the best of our knowledge, selenium-containing ligands have not been screened in microwave-assisted asymmetric palladium-catalyzed allylic alkylations. With this in mind and in connection with our growing interest in the application of organoselenium compounds in asymmetric catalysis,[14,15,17,19] we envisioned to evaluate herein the efficiency of the chiral β-seleno amides **2a**–**g** in palladium-catalyzed asymmetric allylic alkylation (AAA) with use of microwave flash-heating to enhance the reaction rate.

Racemic 1,3-diphenyl-2-propenyl acetate (**3**), which is a commonly used substrate in AAA, and dimethyl malonate (**4a**) were chosen as suitable model reactants to study the influence of microwave-heating on the reaction.

The alkylations were conducted following the procedure of Moberg and co-workers[7a] using *N*,*O*-bis(trimethylsilyl)-acetamide (BSA) as the enolate-forming agent. Chiral π-allylpalladium(II)–ligand complexes were prepared in situ from $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, and a low concentration of the nucleophile was generated from methyl malonate in the presence of BSA and a catalytic amount of KOAc.[21] Microwave-heating was performed with a single-mode cavity in sealed heavy-walled Pyrex tubes. Results from reactions employing selected combinations of microwave irradiation times and power are summarized in Table 1.

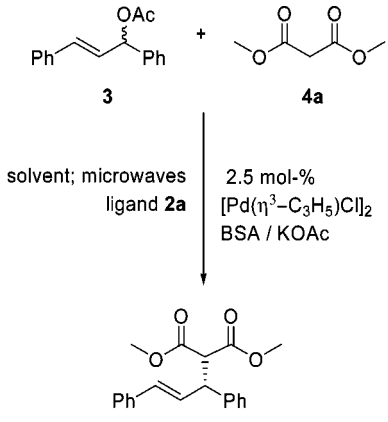
We started our investigation with palladium complexes containing ligand **2a**, which catalyzes the reaction that takes place between *rac*-(2*E*)-1,3-diphenylprop-2-enyl acetate and dimethyl malonate with excellent selectivity in 24 h at room temperature.[19]

We observed that the temperature plays an important role in the microwave-heated allylic substitution reactions when ligand **2a** was used. At high temperatures, the product (*R*)-**5a** was obtained in very low yield and enantioselectivity (Table 1, Entries 1–2). Changing the reaction time from 2 to 4 min improved the yield but decreased the enantioselectivity. This is probably due to decomposition of the rather weak palladium–ligand complex, as corroborated by the precipitation of black palladium upon heating. These results prompted us to further investigate this catalytic system.

When the temperature was decreased to 100 °C, ligand **2a** furnished the alkylated product with reasonable enantioselectivity but low yield (Table 1, Entry 4). Setting the temperature at 70 °C and at the same power to heat the solution, the product **5a** was obtained with good *ee* values but only a slight increase in yield was achieved (Table 1, Entries 5–6). Increasing the reaction time again does not have a significant influence on this catalytic system.

After defining 70 °C as a suitable temperature to run the microwave-heated AAA, we focused our efforts on evaluating the effect of solvents and power input for these reactions. When dichloromethane was used with an input of 300 W, very good enantiomeric excess and yield were achieved in 4 min (Table 1, Entry 8). The change of solvent to THF or toluene at this power, furnished the product **5a** also with very good *ee* values but the yields were lower (Table 1, Entries 9–12). The decrease in power to 100 W leads to the product **5a** with the same level of enantioselectivity (85–91%), but lower yields were obtained (Table 1, Entries 13–20). Based on a recent paper published by our group,[8] we decided to reduce the power input to 30 W. Thus, running the reaction in acetonitrile we could obtain a very good yield and *ee*, even with a short reaction time (Table 1, Entry 21). Other solvents furnished the desired product in lower yields.

Table 1. Microwave-heated asymmetric allylic alkylation with β-seleno amide **2a**.



(*R*)-**5a**

Entry	**2a** [mol-%]	Solvent	Power [W]	Temp. [°C][a]	Time [min]	Yield [%][b]	*ee* [%][c]
1	10	CH_3CN	300	150	2	26	39
2	10	CH_3CN	300	150	4	47	21
3	10	CH_3CN	300	100	2	31	38
4	10	CH_2Cl_2	300	100	4	43	77
5	10	CH_3CN	300	70	2	53	87
6	10	CH_3CN	300	70	4	61	86
7	10	CH_2Cl_2	300	70	2	84	90
8	10	CH_2Cl_2	300	70	4	89	91
9	10	THF	300	70	2	22	88
10	10	THF	300	70	4	19	84
11	10	toluene	300	70	2	30	91
12	10	toluene	300	70	4	53	90
13	10	CH_3CN	100	70	2	61	88
14	10	CH_3CN	100	70	4	70	85
15	10	CH_2Cl_2	100	70	2	58	87
16	10	CH_2Cl_2	100	70	4	40	87
17	10	THF	100	70	2	27	80
18	10	THF	100	70	4	21	80
19	10	toluene	100	70	2	78	91
20	10	toluene	100	70	4	40	88
21	10	CH_3CN	30	70	2	75	91
22	10	CH_3CN	30	70	4	77	89
23	5	CH_2Cl_2	300	70	4	65	90
24	2.5	CH_2Cl_2	300	70	4	36	88
25	5	CH_3CN	30	70	2	15	80
26	2.5	CH_3CN	30	70	2	15	85

[a] Limit temperature. [b] Isolated yield. [c] Determined by HPLC with Chiralcel OD column; hexane/2-propanol, 99:1; 0.5 mL/min; 254 nm.

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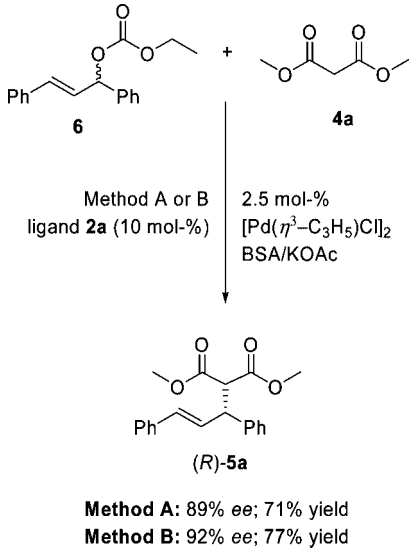
On the basis of these results, we decided to evaluate the influence of two different methods in our catalytic system: method A (CH_2Cl_2, 300 W, 70 °C, 4 min) and method B (CH_3CN, 30 W, 70 °C, 2 min). With this in mind, a reduction of the amount of catalyst was also evaluated for both methods using 5 and 2.5 mol-%. The alkylated products were still obtained with good *ee* values (80–90%) but in a very low yield (Table 1, Entries 23–26).

In addition, we evaluated the effect of the leaving group (Scheme 2). A change from acetate to the ethyl carbonate **6** furnished the alkylated product in slightly lower yield; however, it did not affect the enantioselectivity of the AAA.



Scheme 2.

The microwave irradiations were performed under controlled conditions that make the procedure very safe, reliable and reproducible. Single mode irradiation with monitoring of temperature was used. Representative examples of temperature profiles of the microwave accelerated alkylations show the similarity of the two methods in this respect, as depicted in Figure 1.

After determining the best conditions to perform the microwave-accelerated AAA reactions by methods A and B, we decide to extend our studies and evaluate the behavior of the ligands **2a**–**g** in the catalytic system, as shown in Table 2.

We observed that the nature of the groups R^1 and especially R^2 attached the selenium atom plays an essential role in terms of yield and enantioselectivity. Only the β-seleno amides **2a**–**c** furnished the alkylated product (*R*)-**5a** in satisfactory results. Ligands containing an electron-withdrawing group as in **2b** (R^2 = *p*-ClC_6H_4) and an electron-donating group as in **2c** (R^2 = *p*-$MeOC_6H_4$) furnished the respective product in good yields and excellent enantioselectivities ranging from 85–94% (Table 2, Entries 1–6), evidencing that electronic effects do not reduce the ability of the selenium to coordinate to palladium. We also noted that the method employed does not have a strong influence on this catalytic system.

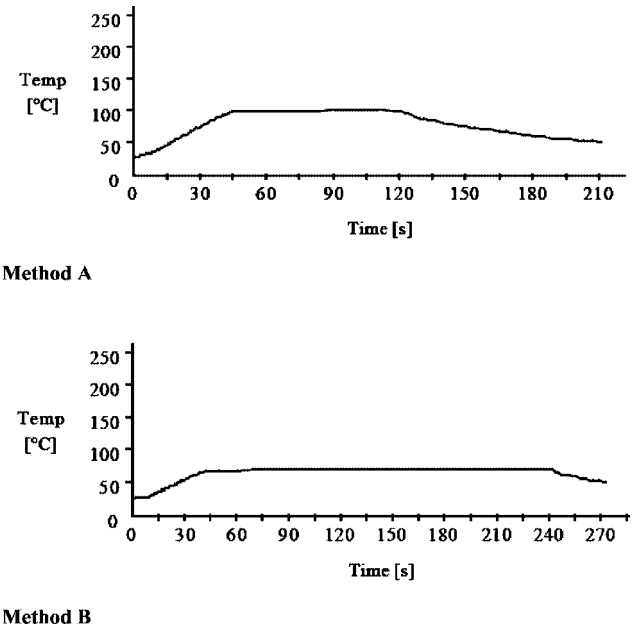
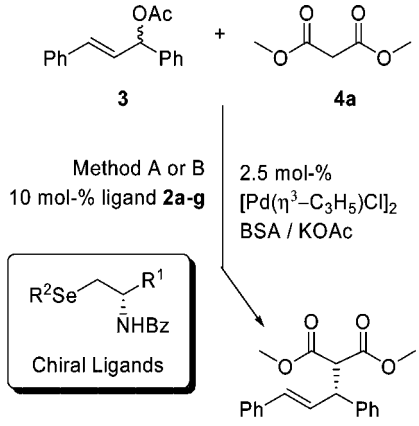


Figure 1. Representative examples of temperature profile of the microwave-accelerated alkylations by methods **A** and **B**.

Table 2. Microwave-heated asymmetric allylic alkylations with chiral β-seleno amides **2a**–**g**.



Entry	Ligand	R^1	R^2	Method[a]	Yield [%][b]	*ee* [%][c]
1	**2a**	*i*Pr	Ph	A	75	91
2	**2a**	*i*Pr	Ph	B	90	90
3	**2b**	*i*Pr	*p*-ClC_6H_4	A	93	93
4	**2b**	*i*Pr	*p*-ClC_6H_4	B	89	85
5	**2c**	*i*Pr	*p*-$MeOC_6H_4$	A	89	93
6	**2c**	*i*Pr	*p*-$MeOC_6H_4$	B	91	94
7	**2d**	*i*Pr	2,4,6-$Me_3C_6H_2$	A	40	50
8	**2d**	*i*Pr	2,4,6-$Me_3C_6H_2$	B	47	38
9	**2e**	*i*Pr	Bn	A	30	24
10	**2e**	*i*Pr	Bn	B	23	06
11	**2f**	Bn	Ph	A	80	67
12	**2f**	Bn	Ph	B	55	47
13	**2 g**	*i*Bu	Ph	A	40	61
14	**2 g**	*i*Bu	Ph	B	35	38

[a] Method A: CH_2Cl_2, 300 W, 70 °C, 4 min. Method B: CH_3CN, 30 W, 70 °C, 2 min. [b] Isolated yield. [c] Determined by HPLC with Chiralcel OD column; hexane/2-propanol, 99:1; 0.5 mL/min; 254 nm.

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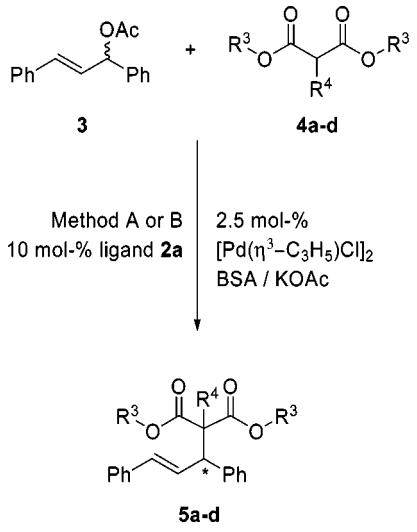
On the other hand, ligands **2d**–**e** lead to the desired products with lower yields and *ee* values, probably due to their unfavorable steric effect (too bulky or too small) and their higher thermal instability (Table 2, Entries 7–10). For the ligands **2f**–**g** the heating method has a strong influence. When method A was employed better *ee* values were achieved (Table 2, Entries 11 and 13). However, when method B was used, the respective alkylated products were obtained in lower yields and in up to 47% *ee*.

We also examined the microwave AAA reaction of various dialkyl malonates, as showed in Table 3 using reference ligand **2a**.[19] Thus, the alkylated products **5b**–**d** were obtained with different levels of enantioselectivity and in good yields. We observed that the method employed to accelerate the reaction showed a significant influence, because different results in the enantioselection can be obtained with the methods A and B (Table 3, compare Entries 5–6 and Entries 7–8).

Table 3. Microwave accelerated palladium-catalyzed asymmetric allylic alkylation with β-seleno amide **2a**.



5a: R^3 = Me; R^4 = H **5c:** R^3 = Et; R^4 = Et
5b: R^3 = Et; R^4 = H **5d:** R^3 = Et; R^4 = Ph

Entry	R^3	R^4	Method[a]	Yield [%][b]	*ee* [%][c,d]
1	Me	H	A	75	91
2	Me	H	B	89	90
3	Et	H	A	50	46
4	Et	H	B	70	44
5	Et	Et	A	59	81
6	Et	Et	B	55	69
7	Et	Ph	A	51	69
8	Et	Ph	B	57	85

[a] Method A: CH_2Cl_2, 300 W, 70 °C, 4 min. Method B: CH_3CN, 30 W, 70 °C, 2 min. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] For Entries 1–4, the product has an *R* configuration. For Entries 5–8, the absolute configuration of the product was not determined.

In summary, we have demonstrated an efficient and very fast asymmetric palladium-catalyzed allylic alkylation under microwave flash-heating using chiral β-seleno amides as ligands. The organoselenium compounds **2a**–**c** furnished the respective alkylated products in good yields and in up to 94% *ee*. The major advantage of microwave irradiation is the considerable reduction in reaction times from 24 h to 2 min with only a minimal loss of enantioselectivity when compared to a non-irradiated reaction at room temperature. This is a crucial factor to consider when developing reaction protocols for both routine synthetic transformations and parallel synthesis.

Acknowledgments

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[18] **General Procedure for the Synthesis of Chiral β-Seleno Amides 2:** Under argon, freshly distilled TMSCl (1 mmol) was added to a solution of the appropriate oxazoline **1** (1 mmol) in dry THF (4 mL). The mixture was stirred for at least 30 min. The selenide anion was generated by reaction of the corresponding diselenide (0.6 mmol) with $NaBH_4$ (1.5 mmol) in a mixture of THF (1.5 mL) and EtOH (0.5 mL) and transferred to the flask containing the oxazolium intermediate. The resulting solution was stirred for 24 h under reflux. The mixture was quenched with a saturated NH_4Cl solution, extracted with CH_2Cl_2 and the combined organic fractions were collected, dried with $MgSO_4$ and filtered. The solvent was removed in vacuo yielding the cruded products **2a**–**g** which were purified by flash chromatography.
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[20] **Selected Spectral and Analytical Data for 2a:** The enantiomeric purity was determined by HPLC analysis (column Chiralcel-OD, eluent hexane/2-propanol, 90:10, flow rate 1.0 mL/min), *R* isomer (t_R = 9.33 min), *S* isomer (t_R = 13.47 min) and found to be >99.9%: yield 0.322 g (93%); white solid; m. p. 101–103 °C. $[\alpha]_D^{20}$ = +210 (*c* = 1.0, CH_2Cl_2). IR (KBr): $\tilde{\nu}$ = 3313, 2965, 1633, 1533, 1470, 1178, 733, 693 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.60–7.35 (m, 7 H), 7.25–7.19 (m, 3 H), 6.29 (d, *J* = 8.4, 1 H), 4.22 (m, 1 H), 3.25–3.23 (m, 2 H), 2.05–2.00 (m, 1 H), 0.98–0.96 (m, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 167.0, 134.5, 132.7, 131.1, 129.9, 129.1, 128.3, 126.9, 126.7, 54.7, 31.7, 31.6, 19.3, 18.5 ppm. ^{77}Se NMR ($CDCl_3$): δ = 251.5 ppm. HRMS-ESI: *m*/*z* calcd. for $C_{18}H_{21}NOSe + Na^+$ 370.0680, found 370.0677.
[21] **General Procedure for Microwave-Induced Allylic Alkylation:** Chiral ligand **2a**–**g** (10 mol-%) and $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2.5 mol-%) were dissolved in appropriated solvent (3.6 mL). The solution was stirred under argon for 30 min. Bis(trimethylsilyl)acetamide (5.2 mmol) and 1,3-diphenyl-2-propenyl acetate (**3**) (1.73 mmol) were transferred with 3.6 mL of appropriated solvent 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 (0.6 mmol) and the respective malonate **4a**–**d** (0.630 mmol) were added and the reaction vessel was sealed with a silicon septum under nitrogen. 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 **5a**–**d** was flash chromatographed on silica with hexane/ethyl acetate (99:1).

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