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Communication

Chalcogen-Containing Oxazolines in the Palladium-Catalyzed Asymmetric Allylic Alkylation

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Nesse trabalho descreve-se, pela primeira vez, um estudo comparativo sobre a atuação de oxazolinas quirais contendo calcogênio em suas estruturas em reação de alquilação alílica assimétrica, catalisada por paládio, do acetato de 1,3-difenil-2-propenila com malonato de dimetila. Diferenças no desempenho entre os análogos de enxofre, selênio e telúrio são observadas.

A comparative study about the ability of chiral chalcogen-containing oxazolines to act as chiral ligands in the palladium-catalyzed allylic alkylation of rac-1,3-diphenyl-2-propenyl acetate with dimethyl malonate is reported. Differences in the catalytic performance are observed with sulfur, selenium and tellurium analogues.

Keywords: selenium, oxazolines, palladium, asymmetric allylic alkylation, tellurium

Introduction

The search for new ligands in asymmetric catalysis is a field of continuing interest. To facilitate practical applications, new ligands should be easy to prepare from simple and easily available starting materials.

In this context, the use of chiral nitrogen compounds bearing an organochalcogen moiety and their metal complexes have gained increased importance in the field of asymmetric catalysis due to their novel and unprecedented properties. For example, they have been reported to be efficient chiral catalysts[1] in several different enantioselective reactions, such as the asymmetric hydrosilylation[2] and hydrogenation[3] of ketones, enantioselective diethylzinc[4,5] and alkynylzinc[6] addition to aldehydes, and conjugate addition of organocopper reagents to to enones.[7]

Among the transition metal-catalyzed reactions known to form carbon-carbon and carbon-heteroatom bonds, the palladium-catalyzed allylic substitution stands out as one of the most valuable synthetic tools available.[8] Many sulfur-containing ligands have been described to catalyze this transformation in an asymmetric fashion.[9] On the other hand, the parent selenium-containing ligands for asymmetric allylations have been largely overlooked.[10] Furthermore, to the best of our knowledge, tellurium-containing analogues have never been tested in such transformation.

In this paper we report about the examination on the behavior of a series of sulfur- selenium- and tellurium-containing oxazolines as chiral catalysts for the asymmetric alkylation of racemic 1,3-diphenyl-2-propenyl acetate with dimethylmalonate, catalyzed by palladium.[11]

Results and Discussion

The chiral chalcogeno-oxazolines were synthesized in two different approaches. The first one starts from amino acids S-benzyl-*L*-Cysteine and *L*-methionine. Initially, both amino acids were cleanly reduced with the $NaBH_4/I_2$ method,[12] to afford thioether amino alcohol **1** and **3** in good yields. The amino alcohol moiety was then cyclized in good yields to their corresponding oxazolines **2** and **4** by reaction with ethyl chlorobenzimidate in boiling 1,2-dichloroethane, with K_2CO_3 as base (Scheme 1).

The second approach employs *L*-aspartic acid as the chiral source. Ligands **8a-c** were obtained by esterification of both carboxyl groups of *L*-aspartic acid, followed by acylation at nitrogen with benzoyl chloride. The diester was cleanly reduced to the diol **6**[13] which was treated, without further purification, with TsCl in dichloromethane using triethylamine as base. The ditosylated intermediate immediately cyclizes to the entropically favored oxazoline **7**. The organochalcogen functionalization took place by nucleophilic displacement of the tosylate leaving group

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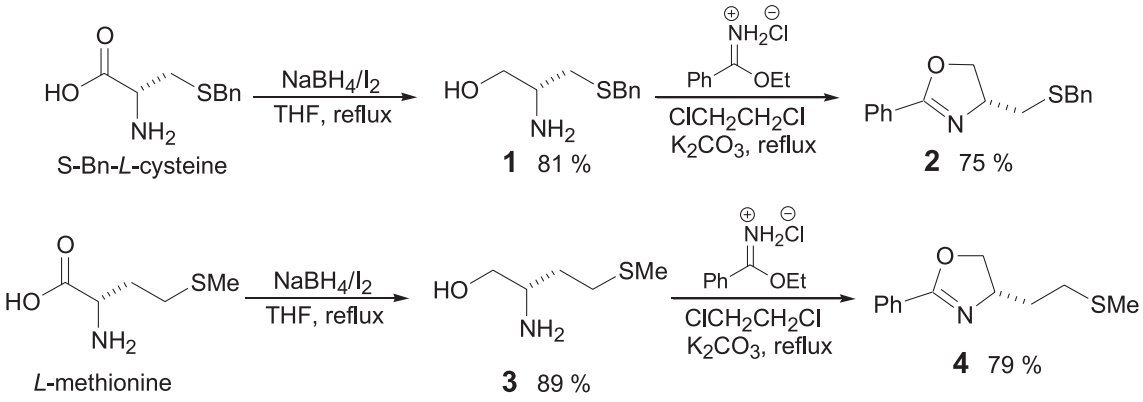


Scheme 1.

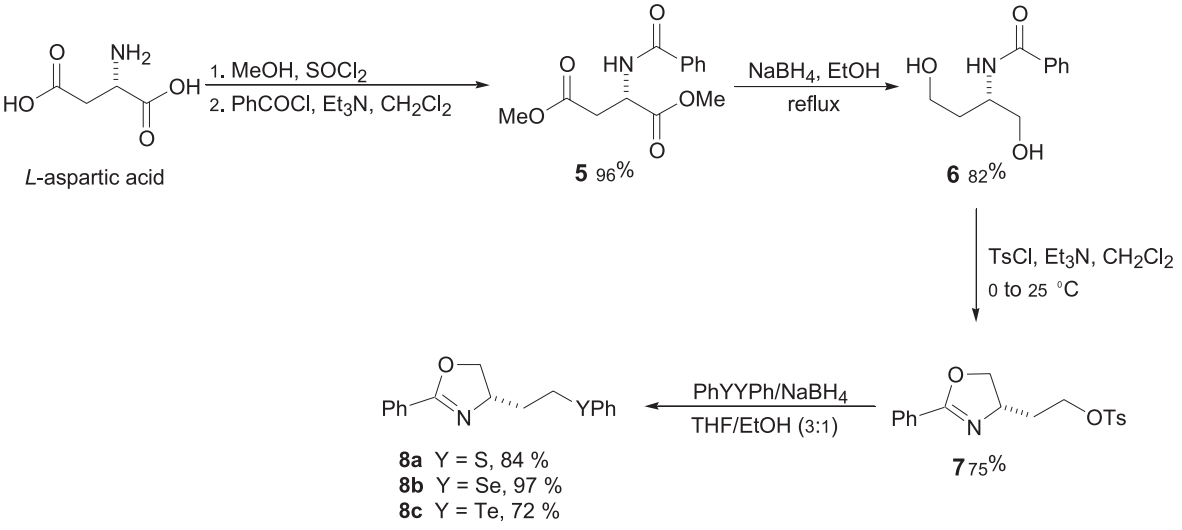
by a phenyl chalcogenide anion generated by reduction of the corresponding diphenyl dichalcogenide with $NaBH_4$ in a 3:1 mixture of THF and ethanol. The desired chalcogeno-oxazolines **8a**-**c** were obtained with yields ranging from 72-97% (Scheme 2).[14]

With ligands **2**, **4** and **8a**-**c** in hands, we turned our attention to investigate their potential in the palladium-catalyzed asymmetric allylic alkylation.

It is worth to mention that ligand **8b** has already been reported by our group to act as efficient chiral catalyst for this asymmetric allylation reaction.[15] We the carried out a comparative study on the alkylation reaction of racemic 1,3-diphenyl-2-propenyl acetate with dimethyl malonate, using the chiral chalcogen-containing oxazolines as chiral ligands (10 mol%) in the presence of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2.5 mol%). Several different conditions were screened, and variations were made in the base, solvent and temperature. The results of these studies are summarized in Table 1.

We have first evaluated ligand **2** and **4** as catalysts in the asymmetric allylation, under conditions first described by Williams and coworkers,[16] that uses NaH/THF as the base/solvent system. Moderate enantioselection was achieved with ligand **2**, while ligand **4** furnished the product in higher level of enantioselection. We then decided to study further variations in the reaction setup, especially concerning the base/solvent combination and the temperature of the reaction. Initially, temperature was decreased to 0 °C and the product was obtained in the same *ee* compared to the room temperature reaction. Changing the base to BSA/KOAc and the solvent to dichloromethane did not result in any improvement in the ee, not even when the reaction was carried out at lower temperatures. At -78 °C no reaction at all was observed (See entries 4-6).

We then decided to evaluate the behavior of catalysts **4** and **8a**-**c** under conditions previously developed by us for seleno-oxazoline **8b** (Cs_2CO_3/CH_2Cl_2).[17] This would allow us to make a direct comparison of the ability of sulfur, selenium and tellurium to complexate with palladium and to catalyze the asymmetric allylation reactions. Selenium-containing oxazoline **8b** has proven to be the more efficient



Scheme 2.

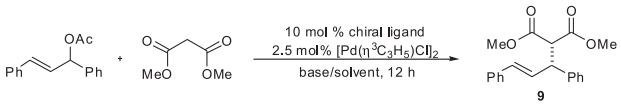
of the series, delivering the product **9** in 91% *ee*, when the reaction was carried out at 0 °C (Entry 10). The sulfur derivatives **4** and **8a** furnished the alkylated product in 82 and 83% *ee*, respectively, under the optimal conditions (Entries 7 and 8). This observation of difference in the behavior between sulfur and selenium donors gives an evidence of the higher ability of selenium to complexate with palladium and thus to form a tighten complex that would lead to a superior level of enantioselection.

To the best of our knowledge, a chiral organic telluride was never evaluated as a chiral ligand for this kind of transformation. We then tested the telluro-oxazoline **8c** as catalyst in the alkylation reaction, but unfortunately, no reaction was observed and the decomposition of the palladium complex was observed, which could be evidenced by the formation of palladium black in the reaction medium. A possible explanation for this could be that the palladium could be inserted into the Csp^2-Te bond, leading to the decomposition of the catalyst. This proposal is supported by the fact that unsaturated organic tellurides can undergo cross-coupling reactions with several nucleophiles, in the presence of palladium catalysts.[18]

In order to propose a plausible explanation of the stereoselectivity observed, a schematic reaction pathway is shown in Scheme 3.

The attack of the nucleophile in a π-allylpalladium complex is believed to take place *trans* to the better π-acceptor. Supported by the work of Anderson where he proposes that the attack of the nucleophile occurs *trans* to a nitrogen donor[9] in a nitrogen-sulfur chelate complex, we assumed that our system behaves in a similar way,

Table 1.

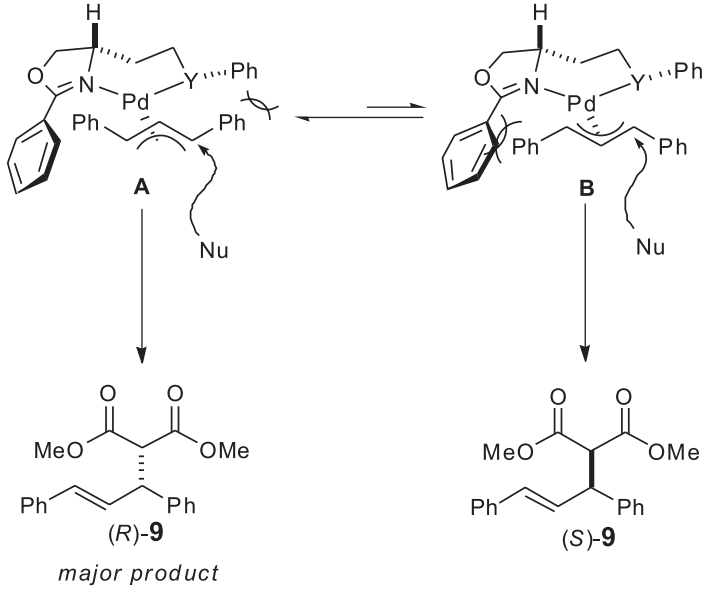


Entry	Ligand	Base	Solvent	Temp. (°C)	Yield (%)[a]	*ee* (%)[b]
1	**2**	NaH	THF	rt	90	76
2	**4**	NaH	THF	rt	93	84
3	**4**	NaH	THF	0	87	84
4	**4**	BSA/KOAc	CH_2Cl_2	rt	93	75
5	**4**	BSA/KOAc	CH_2Cl_2	0	65	77
6	**4**	BSA/KOAc	CH_2Cl_2	-78	nr	nr
7	**4**	Cs_2CO_3	CH_2Cl_2	0	95	83
8	**8a**	Cs_2CO_3	CH_2Cl_2	0	88	82
9	**8b**	Cs_2CO_3	CH_2Cl_2	rt	99	85
10	**8b**	Cs_2CO_3	CH_2Cl_2	0	99	91
11	**8c**	Cs_2CO_3	CH_2Cl_2	rt	nr	nr

[a] Isolated yields. [b] Determined by HPLC with a Daicel Chiralcel OD column, hexane:isopropanol 99:1; 0.5 mL min^{-1}; 254 nm.

i.e., the nucleophile attacks preferentially at the allylic position *trans* to the Pd-N bond in the π-allylpalladium complex.

Since the major product obtained is the (*R*)-**9**, the reaction appears to proceed preferentially via the intermediate **(A)** in the equilibrium depicted in Scheme 3. Intermediate **(A)**, where the allyl group is disposed in a "W" orientation, seems to be more stable than intermediate **(B)**, where the allyl moiety is arranged in a "M" conformation. The major interaction that accounts for the difference in the stability of both intermediates would be the steric repulsion between the phenyl terminus of the allylic substrate and the phenyl group of the 2-oxazoline ring, in intermediate **(B)**. This disfavoring interaction would



Scheme 3.

explain the predominance of intermediate **(A)** in the equilibrium.

Indeed, attack of the nucleophile at the allyl moiety *trans* to the nitrogen atom in structure **(A)** would lead to the (*R*)-**9** product, which is in full agreement with the observed in the reaction.

Conclusions

In summary, we have described a study were a set of chalcogeno-oxazolines have been synthesized in a short, high yielding synthetic route and with a modular character. Furthermore, these compounds were tested as chiral ligands for the palladium-catalyzed allylation of racemic 1,3-diphenyl-2-propenyl acetate with dimethylmalonate. Good to high *ee*s of up to 91% of the product were achieved. The best result was obtained with the seleno-oxazoline **8b**, compared to the sulfur and tellurium analog. This result demonstrates the higher ability of selenium to complexate with palladium and thus, is an interesting feature that should be taken into consideration for the design of new ligands containing the chalcogen atom.

Acknowledgments

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14. *General procedure for the preparation of **8**:* Under an argon atmosphere, sodium borohydride was added to a solution of the diphenyl dichalcogenide (0.55 mmol) in THF (4 mL). Ethanol (2 mL) was then dropwise added and the clear solution formed was stirred at room temperature for 10 minutes. After this time a THF (1 mL) solution of the appropriate oxazolinyl tosylate (1 mmol) was added dropwise. After stirring for 24 h at room temperature, the reaction mixture was quenched with aqueous saturated NH4Cl (10 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography first eluting with hexanes and then with a mixture of hexanes/ethyl acetate (80:20). Selected spectral and analytical data for (*S*)-2-phenyl-4-(2-(phenylthio)ethyl)-4,5-dihydrooxazol (**8a**). Yield: 84 %; $[\alpha]_D^{20}$ = -26 (*c*=0.55, CH_2Cl_2); 1H NMR ($CDCl_3$, 400 MHz): δ 7.95-7.93 (m, 2H), 7.41-7.11 (m, 8H), 4.42-4.36 (m, 2H), 3.95-3.92 (m, 1H), 3.13-3.11 (m, 1H), 3.05-3.02 (m, 1H), 1.5-1.87 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.47, 136.07, 131.06, 128.75, 128.65, 128.02, 128.00, 127.47, 125.62, 72.03, 65.44, 35.26, 29.80; HRMS *m/z* Calc. for $C_{17}H_{18}ONS^+$ H^+ 284.1107, Found 284.1103.
*(S)-2-phenyl-4-(2-(phenylselanyl)ethyl)-4,5-dihydrooxazole (**8b**).* Yield: 97 %; $[\alpha]_D^{20}$ = -57 (*c*=0.55, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.93 (d, *J* 7.16 Hz, 2H), 7.52-7.37 (m, 5H), 7.26-7.20 (m, 3H), 4.48-4.37 (m, 2H), 4.02-3.98 (m, 1H), 3.14-2.99 (m, 2H), 2.10-2.01 (m, 1H), 2.00-1.94 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.88, 132.48, 131.24, 130.04, 129.14, 128.21, 128.17, 127.99, 126.74, 72.12, 66.46, 36.45, 24.04; HRMS *m/z* Calc. for $C_{17}H_{17}ONSe^+$ Na^+ 354.0366; Found 354.0367.
*(S)-2-phenyl-4-(2-(phenyltelanyl)ethyl)-4,5-dihydrooxazol (**8c**).* Yield: 72 %; $[\alpha]_D^{20}$= -63 (*c*=0.5, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.93 (d, *J* 7.2 Hz, 2H), 7.72 (d, *J* 6.9 Hz, 2H); 7.45-7.36 (m, 3H), 7.25-7.16 (m, 3H), 4.45-4.35 (m, 1H), 4.33-4.31 (m, 1H), 4.00-3.96 (m, 1H), 3.12-3.05 (m, 1H), 2.98-2.91 (m, 1H), 2.17-2.11 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.71, 138.05, 131.26, 129.10, 128.22, 127.63, 127.48, 126.79, 112.44, 71.98, 68.14, 38.05, 4.44; HRMS *m/z* Calc. for $C_{17}H_{17}ONTe^+$ H^+ 398.0392; Found 398.0394.
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17. *General Procedure for the Asymmetric Allylic Alkylation with Cs_2CO_3/CH_2Cl_2:* A solution of $[Pd(h_3\text{-}C_3H_5)Cl]_2$ (10 mg, 2.5 mol%), catalyst (10 mol%) in dichloromethane (2.5 mL) was stirred for 1 h under an argon atmosphere, at room temperature, and then cooled to 0 °C, when 1,3-diphenyl-2-propenyl acetate (126 mg, 0.5 mmol) was added. The mixture was stirred for 10 minutes at this temperature and dimethyl malonate (173 mg, 1.5 mmol), and cesium carbonate (489 mg, 1.5 mmol) were sequentially added. The reaction mixture was then stirred for 10 h at 0 °C. After this time, saturated $NH_4Cl_{(aq)}$ was added and the aqueous solution was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were dried with $MgSO_4$, the solvent was evaporated and the crude product was purified by flash chromatography eluting with hexane/ethyl acetate (98/2). Enantiomeric excess was determined by chiral HPLC (Chiralcel OD column, 0.5 mL min-1, hexane:2-propanol 99:1, 254 nm). The optical rotation of the product was compared with literature data to assign the absolute configuration (*R*).
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