New Aziridine Sulfide Ligands for Palladium-Catalyzed Asymmetric Allylic Alkylation

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Abstract: Aziridine sulfides, a new type of chiral *S,N*-ligand, have been easily synthesized in a straightforward synthetic route, from an inexpensive and easily available chiral pool. They were used in the Pd-catalyzed asymmetric allylic alkylation of 1,3-diphenyl-2-propenyl acetate with dimethymalonate anion, furnishing the alkylated product in excellent yields and stereoselectivity up to 99%.

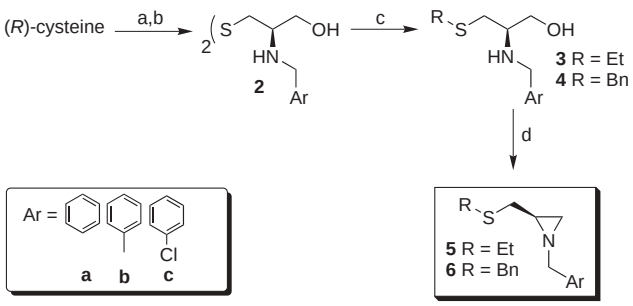
Key words: asymmetric allylic alkylation, asymmetric catalyst, palladium, chiral pool, aziridine, *S,N*-ligands

The palladium-catalyzed allylic alkylation reaction is without a doubt one of the most important protocols in organic chemistry for the formation of carbon-carbon bonds, and the topic has been the subject of several recent high profile reports.[1] The enantioselectivity of this process may be influenced by the base, the counter-cation and the concentration of the nucleophile, but is mainly influenced by the chiral ligand coordinated to the palladium atom.[2]

Several efficient enantioselective catalysts such as C_2- and C_1-symmetric bidentate chiral ligands[1b] and non-C_2-symmetric ligands such as phosphineoxazolines[3] have been explored for these reactions. Heterobidentate sulfur-nitrogen ligands have found less attention in the search for an effective catalyst.[4] Although asymmetric bidentate ligands with an oxazoline unit as chiral modifier have been investigated extensively,[4a–e] applications in asymmetric palladium-catalyzed allylic alkylation of heterobidentate ligands with an aziridine moiety are scarcely described.[5]

As part of a broader program to explore the preparation and use of chiral organochalcogen compounds in asymmetric catalysis,[6] we wish to describe herein the application of aziridine sulfides as efficient ligands for the palladium-catalyzed asymmetric allylic alkylation.

The chiral aziridine sulfides are readily prepared from (*R*)-cysteine in a straightforward three steps synthetic route. Initially, (*R*)-cysteine was converted into disulfide amino alcohols **2** by treatment with different aldehydes followed by $NaBH_4/I_2$ reduction and air oxidation.[7] Disulfides **2** were reduced with $NaBH_4$ and alkylated, to give thioethers **3** and **4** in good yields.[6d] Treatment of **3** or **4** with DEAD and triphenylphosphine in THF afforded the desired aziridine sulfides **5a** and **6a**–**c**[8] in 69% and 61% yield, respectively (Scheme 1).



Scheme 1 *Reagents and conditions*: a) EtOH, ArCHO; b) THF, $NaBH_4/I_2$ then O_2; c) EtOH, NaOH, $NaBH_4$, RX; d) THF, PPh_3, DEAD.

The optical purity of these ligands has been verified by HPLC analyses.

With this sterically and electronically varied set of enantiopure *S,N*-ligands in hand, we examined the efficacy of these compounds as chiral catalysts in the palladium-catalyzed asymmetric allylic alkylation reaction. First, asymmetric allylic substitution of *rac*-1,3-diphenyl-2-propenyl acetate was examined using chiral aziridine **6a**. These results are summarized in Table 1.

The reaction with dimethyl malonate under standard conditions: 2.5 mol% of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, 2.5 mol% of chiral aziridine **6a**, and a mixture of *N,O*-bis-(trimethysilyl)acetamide (BSA) and a catalytic amount of KOAc in CH_2Cl_2,[9] proceeded smoothly to give a quantitative yield but unsatisfactory ee (entry 1). We decided to find other reaction conditions to conduct the alkylation reaction. By changing the base, an important improvement of the level of enantioselectivity was observed. Preparing the nucleophile from the previous reaction of dimethyl malonate with NaH and using THF as solvent (entry 2), the alkylated product was obtained with a satisfactory level of enantiomeric excess in quantitative yield.

Variations of ligand-to-metal ratio had a small influence in this work (entries 2–4). Using 2.5 mol% loading of **6a**, which corresponds to a 1:1 ratio of bidentade ligand to palladium, proved to be the best condition (entry 2). An increased ratio in our system apparently had only a small

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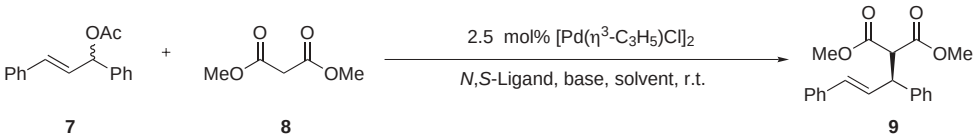
Table 1 Asymmetric Palladium-Catalyzed Allylic Alkylation of **7** with Dimethyl Malonate **8**[a,b]



7 **8** **9**

Entry	Ligand	Base	Solvent	Temp (°C)	Time (h)	Yield (%)[c]	Ee (%)[d]
1	**6a** (2.5 mol%)	BSA/KOAc	CH_2Cl_2	r.t.	24	100	64 (*S*)
2	**6a** (2.5 mol%)	NaH	THF	r.t.	24	100	75 (*S*)
3	**6a** (5 mol%)	NaH	THF	r.t.	24	100	74 (*S*)
4	**6a** (10 mol%)	NaH	THF	r.t.	24	100	70 (*S*)
5	**5a** (2.5 mol%)	NaH	THF	r.t.	24	100	72 (*S*)
6	**6a** (2.5 mol%)	NaH	CH_2Cl_2	r.t.	24	87	56 (*S*)
7	**6a** (2.5 mol%)	NaH	Toluene	r.t.	24	93	80 (*S*)
8	**6a** (2.5 mol%)	NaH	Toluene	0	48	89	85 (*S*)
9	**6b** (2.5 mol%)	NaH	Toluene	0	48	90	81 (*S*)
10	**6c** (2.5 mol%)	NaH	Toluene	0	48	87	99 (*S*)

[a] Entries 1–7: NaH (1.5 equiv), dimethyl malonate (2 equiv), and acetate (1 equiv).
[b] Entries 8–12: *N*,*O*-bis(trimethylsilyl)acetamide (BSA, 3 equiv), dimethyl malonate (3 equiv), KOAc (cat. quantity), and acetate (1 equiv).
[c] Determined by GC.
[d] Determined by HPLC with a chiralcel OD-H column. The absolute configuration of the product was assigned by comparison of the sign of specific rotations with literature data.

influence, resulting in an enantiomeric excess of 74% in the case of a 2:1 ratio (entry 3).

A decrease in the enantioselectivity when a 4:1 ratio (entry 4) was used might be caused by a change in the coordination of the ligand to palladium. The coordination of two monodentate ligands to the Pd center, instead of one bidentate ligand, can be considered as a possible explanation to the lower level of enantioselectivity observed.[10,11]

The effect of solvent on the reaction was also examined. When the reaction was carried out in toluene, the enantioselectivity obtained was higher than with THF or CH_2Cl_2 (entry 7 vs. entries 2 and 6).

Performing the allylation at 0 °C led to a further improvement of the enantioselectivity providing diester **9** with 85% ee and 89% yield (entry 8).

Thus, the best results were obtained by performing the reaction with 2.5 mol% of the chiral ligand, 2.5 mol% of the palladium catalyst and toluene as solvent at 0 °C.[12]

With all the conditions optimized, we decided to extend this reaction to other chiral aziridine-sulfide ligands synthesized. The electronic and steric properties of the N-aromatic group have been briefly investigated. It would appear that an electron-donating substituent has little effect (entries 8 vs. 9), whereas an electron-withdrawing substituent gives higher enantiomeric excess (entries 8 vs. 10). The lone pairs of halogens are known to overlap with aromatic π-systems, but at the same time halogens deactivate the aromatic nucleus.[13] The chloro substituent in this ligand system has a complex mixture of steric and electronic properties and further studies are underway to understand them.

These results suggest that the influence of the benzyl group attached to nitrogen is important in obtaining high asymmetric induction (the dominant stereocontrol element) and the substituent at the sulfur atom has a small effect in the conversion of the alkylation reaction (entries 2 vs. 5).

In the present runs, the absolute configuration of the major enantiomer was determined to be *S* in all cases by the optical rotation and the comparision of peaks in chiral HPLC analysis.

In summary, we described in this paper, the use of new aziridine containing sulfides as chiral ligands in palladium catalyzed asymmetric allylic alkylation, furnishing the product in high yields as well as excellent levels of stereoselectivity. Besides, it should be mentioned that the preparation of our catalysts begins from inexpensive and easily available (*R*)-cysteine. Although this first generation of new sulfur/aziridines based catalyst is not yet developed as the more traditional phosphine[1b] we are confident that they will prove to be a useful alternative to existing methods as has already shown in other allylic substitutions.[1d,g,3d] Further studies dealing with their improvement and application in asymmetric synthesis are in progress.

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(8) **General Procedure for the Synthesis of Compound 6a.** To a suspension of PPh_3 (1.048 g, 4 mmol) in THF (10 mL), DEAD (0.696 g, 4 mmol) was added at –78 °C under argon atmosphere. After 2 h, sulfide aminoalcohol **4a** (1.148 g, 4 mmol) was added and the mixture was stirred for 12 h at r.t. Then, the solvent was evaporated and the residue was partitioned between H_2O and CH_2Cl_2. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography (hexane–EtOAc 8:2). **Analytical data for 6a:** Yield: 61%; $[\alpha]_D^{20}$ –42 (*c* 0.56, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.18 (m, 10 H), 3.67 (d, 1 H, *J* = 13.2 Hz), 3.63 (d, 1 H, *J* = 13.2 Hz), 3.41 (d, 1 H, *J* = 13.2 Hz), 3.35 (d, 1 H, *J* = 13.2 Hz), 2.51 (dd, 1 H, *J* = 13.8 Hz, *J* = 5.8 Hz), 2.39 (dd, 1 H, *J* = 13.8 Hz, *J* = 5.8 Hz), 1.68–1.63 (m, 2 H), 1.39 (d, 1 H, *J* = 6.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.79, 138.33, 128.75, 128.26, 128.22, 128.07, 126.98, 126.74, 64.44, 39.24, 36.03, 34.14, 33.73. HRMS-ESI: *m/z* calcd for $C_{17}H_{19}NS + H^+$: 270.1309; found: $C_{17}H_{19}NS + H^+$: 270.1310.

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(12) **General Procedure for the Allylic Alkylation of 1,3-Diphenyl-2-propenyl Acetate with Sodium Dimethyl Malonate:** A toluene (1 mL) solution of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (9.1 mg, 25 μmol, 2.5 mol%) and the ligand (2.5 mol%) was stirred for 30 min under an argon atmosphere and then *racemic* 1,3-diphenyl-2-propenyl acetate (252 mg, 1.0 mmol) was added. The mixture was stirred for 10 min and a solution of sodium dimethyl malonate, prepared from dimethyl malonate (264 mg, 2.0 mmol) and NaH (48 mg, 2.0 mmol) in toluene (5 mL) was added at 0 °C. The mixture was stirred at 0 °C for the time given in Table 1. The reaction was quenched with sat. NH_4Cl (aq) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried over $MgSO_4$. The solvent was evaporated and the crude product was purified by flash chromatography on silica gel (230-400 mesh) eluting with hexane–EtOAc (98:2). The ee was determined by HPLC (Chiralcel OD, 2-propanol/ hexane = 1:99 flow rate 0.5 mL/min, λ = 254 nm).

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