Seleno-Imine: A New Class of Versatile, Modular N,Se Ligands for Asymmetric Palladium-Catalyzed Allylic Alkylation

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Abstract: The palladium-catalyzed asymmetric allylic alkylation of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate in the presence of chiral seleno-imine ligands derived from an inexpensive and easily available chiral pool was investigated. Excellent yield and enantioselectivity (up to 97% ee) was achieved when ligand **4a** was used.

Key words: seleno-imines, allylic alkylations, palladium-catalyzed

Asymmetric catalysis of organic reactions to provide enantiomerically enriched products is of central importance to modern synthetic chemistry.[1] Within this field palladium-catalyzed allylic nucleophilic substitution is one of the most important tools for the enantioselective formation of carbon–carbon and carbon–heteroatom bonds. The reaction mechanism is well understood and the process has already found numerous applications in the synthesis of natural products.[2]

Development of new chiral ligands is an important challenge of current research in this area. Various C_2- and C_1-symmetric bidentate chiral ligands have been applied to this process to provide high enantioselectivities.[2c,3]

Recently, some reports exploring imines containing β-phosphines[4] or sulfides[5] as effective chiral ligands have been successfully applied to the palladium-catalyzed asymmetric allylic substitution. Furthermore, the efficient use of chiral organoselenium ligands has been recently reported for this reaction.[6] For example, Hou and co-workers have evaluated the planar chiral [2,2]-paracyclophane ligands for the palladium-catalyzed allylic substitution, obtaining good to excellent enantioselectivities.[6a] Other groups also showed that high enantioselectivity was obtained with this type of N,Se-bidentate ligand (Figure 1).

As part of our broader program to explore the preparation and use of chiral organochalcogen compounds in asymmetric catalysis,[7] we now give a preliminary account of our efforts towards the synthesis of a focused library of chiral seleno-imine ligands as a new class of sterically and electronically adjustable chiral ligands and their application for the palladium-catalyzed asymmetric allylic alkylation.

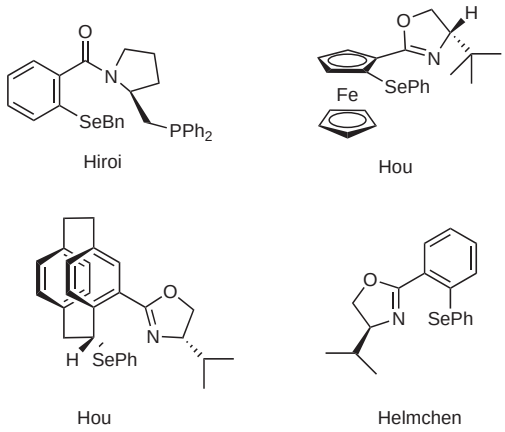
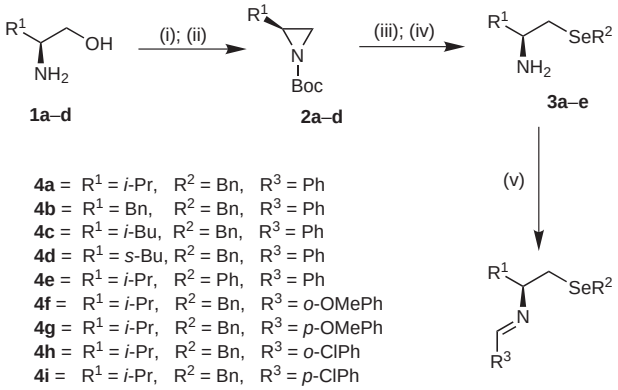


Figure 1

The modular structure of seleno-imines in general allows the preparation of a ligand library with enormous diversity (Scheme 1).

The chiral imino-selenides **4a**–**i** were easily prepared from the corresponding, commercially available α-amino alcohols or readily prepared[8] precursors **1a**–**d**, which were further quantitatively converted into the Boc-protected derivatives by reaction with di-*tert*-butyl dicarbonate in acetonitrile. The chiral aziridines **2a**–**d** was obtained in good yields by treatment of *N*-Boc aminoalcohols with *p*-toluenesulfonyl chloride and potassium hydroxide in boiling THF. Finally, the selenium moieties were efficiently



Scheme 1 Synthesis of a seleno-imine ligand library. *Reagents and conditions*: (i) Boc_2O, CH_3CN, r.t., 3 h; (ii) KOH, TsCl, THF, reflux, 4 h; (iii) $R^2SeSeR^2/NaBH_4$, THF, r.t., 24 h; (iv) TFA, CH_2Cl_2, r.t., 1 h; (v) R^3CHO, EtOH, $MgSO_4$, r.t., 12 h.

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introduced by regioselective nucleophilic ring-opening by attack of $R^2SeSeR^2/NaBH_4$[9] at the less hindered carbon of the aziridines **2a**–**d**,[10] furnishing the aliphatic chiral amino selenide. Deprotection of the chiral selenide **3a**–**e** using TFA proceeded smoothly at room temperature to give the free amino-selenide. Subsequently, imines **4a**–**i** were synthesized by condensation with the requisite aromatic aldehyde in the presence of magnesium sulfate. After filtration, and removal of solvent and excess aldehyde in high vacuum at elevated temperature, compounds **4a**–**i** were obtained as practically pure materials and single stereoisomers. The imines were unstable towards moisture as well as SiO_2, thus, no further attempts at purification were undertaken (Scheme 1).[11]

With the target ligands in hand, we focused our attention on investigating their potential in asymmetric catalysis. As a starting point, we chose to explore the enantioselective palladium-catalyzed allylic alkylation.

In order to optimize the reaction conditions, the amount of catalyst, base, and solvents were varied for ligand **4a** (Table 1). Varying the ligand-to-metal ratio had a small influence (Table 1, entries 1– 4); using 5 mol% of **4a**, which corresponds to a 1:1 ratio of bidentate ligand/palladium, gave the best results (Table 1, entry 2). In terms of base, some differences in the asymmetric induction between the use of dimethyl malonate/BSA and dimethyl sodiomalonate (Table 1, entries 2 vs 5) were observed.[12] Recently, the majority of substitution reactions have been conducted according to Trost's procedure[13] using BSA in the presence of metal acetate salts. Under these conditions and using dichloromethane as solvent, the alkylated product was obtained with an excellent level of enantiomeric excess in quantitative yield (Table 1, entry 2).

Other solvents were also tested, however it was found that dichloromethane gave the highest selectivity.[14]

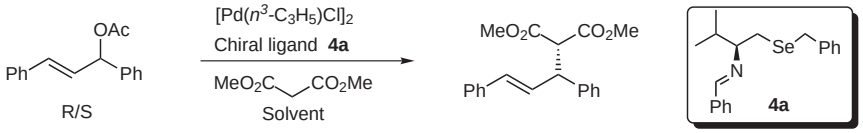
Under the same conditions, we have examined the steric and the electronic effect based on the different structures of ligand **4** derived from different chiral resources (Table 2).

Table 2 shows that the more bulky selenenyl substituents (R^1) in **4a** and **4e** provided a higher degree of asymmetric induction in proportion to the steric bulk (Table 2, entries 1 vs 5).

In the next stage we examined how the amino acid side chain (R^1) of the ligands influences the stereoselectivity of the alkylation reaction. We found that *i*-Pr (Table 2, entry 1) is superior to Bn, *i*-Bu, or *s*-Bu (Table 2, entries 2, 3, and 4).

With both the substituent at the selenium atom and the amino acid side chain determined, we finally examined the effect of the imine group on the stereoselectivity (Table 2, entries 6–9). Varying the electronic and steric properties resulted in a remarkable change in the enantioselectivity. Reactions with *o*- and *p*-methoxy on the phenyl group were employed; in this case we observed decreased ees of the corresponding products (Table 2, entries 6 and 7). An electron-withdrawing group present on the phenyl group also lowers the enantioselectivity when compared with an unsubstituted phenyl group.

Table 1 Optimization of the Allylic Alkylation Using Ligand **4a**



Entry[a]	Loading of **4a** (mol%)	Solvent	Yield (%)[c]	ee (%)[d]
1	10	CH_2Cl_2	100	90
2	5	CH_2Cl_2	100	97
3	2.5	CH_2Cl_2	92	85
4	1	CH_2Cl_2	72	82
5[b]	5	CH_2Cl_2	55	35
6	5	Toluene	74	82
7	5	CH_3CN	92	73
8	5	THF	75	78

[a] *N*,*O*-bis(trimethylsilyl)acetamide (BSA, 3 equiv), dimethyl malonate (3 equiv), KOAc (0.06 mmol), and acetate (1 equiv).
[b] NaH (1.5 equiv), dimethyl malonate (2 equiv), and acetate (1 equiv).
[c] Isolated yield.
[d] Determined by HPLC with a chiralcel OD column and the absolute configuration of the product was assigned through comparison of the sign of specific rotation with literature data.

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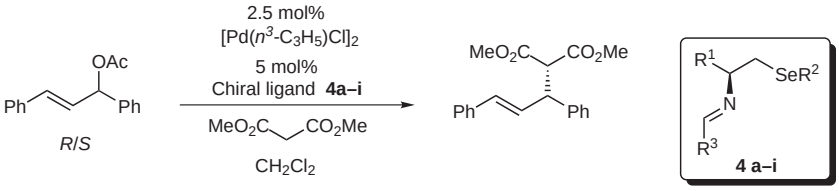
Table 2 Asymmetric Palladium-Catalyzed Allylic Alkylation with Dimethyl Malonate



Entry[a]	Ligand	R^1	R^2	R^3	Yield (%)[b]	ee (%)[c]
1	**4a**	*i*-Pr	Bn	Ph	93	97
2	**4b**	Bn	Bn	Ph	89	78
3	**4c**	*i*-Bu	Bn	Ph	86	75
4	**4d**	*s*-Bu	Bn	Ph	94	80
5	**4e**	*i*-Pr	Ph	Ph	92	75
6	**4f**	*i*-Pr	Bn	*o*-OMePh	95	87
7	**4g**	*i*-Pr	Bn	*p*-OMePh	94	85
8	**4h**	*i*-Pr	Bn	*o*-ClPh	100	85
9	**4i**	*i*-Pr	Bn	*p*-ClPh	99	84

[a] BSA (3 equiv), dimethyl malonate (3 equiv), KOAc (0.06 mmol), and acetate (1 equiv).
[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 rotation with literature data.

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

In summary, we have developed a new class of modular ligands that are derived from amino acids for the palladium-catalyzed asymmetric allylic alkylation, the products were obtained in high yields and enantiomeric excess. This work paves the way for the synthesis and evaluation of larger libraries of ligands based upon the same general structure. Further studies are in progress in our laboratories concerning new metal-catalyzed asymmetric reactions and will be reported in due course.

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(11) **General Procedure for the Synthesis of Seleno-Imine Ligands 4a–i:** An equimolar mixture of **3** (1 mmol) and the requisite aromatic aldehyde (1 mmol) with $MgSO_4$ (0.54 g/mmol) was stirred in EtOH (2.5 mL/mmol) for 24 h. Filtration and concentration in vacuo gave ligands **4a–i** as oils, which were unstable to chromatography, the compounds were obtained as practically pure materials.
4a: Yield: 90%; $[\alpha]_D^{20}$ +54 (*c* 0.6, CH_2Cl_2). ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.14 (s, 1 H), 7.76–7.71 (m, 2 H), 7.37–7.04 (m, 8 H), 3.69 (dd, 2 H, *J* = 12, *J* = 19), 2.97–2.76 (m, 3 H), 1.92–1.90 (m, 1 H), 0.88 (d, 6 H, *J* = 5.8). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 160.36, 139.55, 136.18, 130.44, 129.66, 128.93, 128.88, 128.50, 128.25, 77.93, 33.17, 28.98, 28.32, 22.63, 19.70. HRMS-ESI: *m*/*z* calcd for $C_{19}H_{23}NSe + H^+$: 346.1073; found: 346.1063.
4b: Yield: 65%; $[\alpha]_D^{20}$ –29 (*c* 0.276, CH_2Cl_2). ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.88 (s, 1 H), 7.67–7.64 (m, 2 H), 7.39–6.93 (m, 13 H), 3.75 (dd, 2 H, *J* = 12, *J* = 21), 3.46–3.44 (m, 1 H), 3.04–2.80 (m, 4 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 160.81, 139.41, 138.55, 135.84, 130.50, 129.60, 129.22, 128.80, 128.59, 128.42, 128.31, 126.46, 126.03, 76.68, 42.95, 30.99, 27.50. HRMS-ESI: *m*/*z* calcd for $C_{23}H_{23}NSe + H^+$: 394.1074; found: 394.1084.
4c: Yield: 72%; $[\alpha]_D^{20}$ +21 (*c* 1.13, CH_2Cl_2). ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.16 (s, 1 H), 7.76–7.74 (m, 2 H), 7.42–7.40 (m, 3 H), 7.28–7.17 (m, 5 H), 3.77–3.73 (m, 2 H), 3.31–3.29 (m, 1 H), 2.77–2.61 (m, 2 H), 1.69–1.63 (m, 1 H), 1.48–1.39 (m, 2 H), 0.89–0.81 (m, 6 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 160.40, 139.57, 136.05, 130.60, 129.72, 128.57, 128.40, 128.25, 126.57, 69.91, 45.35, 31.20, 27.70, 24.67, 23.55, 21.38. HRMS-ESI: *m*/*z* calcd for $C_{20}H_{25}NSe + H^+$: 360.1230; found: 360.1224.
4d: Yield: 70%; $[\alpha]_D^{20}$ +13 (*c* 1.08, CH_2Cl_2). ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.16 (s, 1 H), 7.77–7.75 (m, 2 H), 7.41–7.39 (m, 3 H), 7.26–7.17 (m, 5 H), 3.74–3.66 (m, 2 H), 3.07–3.03 (m, 1 H), 2.88–2.75 (m, 2 H), 1.70–1.68 (m, 1 H), 1.50–1.47 (m, 1 H), 1.11–1.09 (m, 1 H), 0.90–0.83 (m, 6 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 160.31, 138.51, 136.14, 130.46, 128.53, 128.33, 128.25, 126.87, 126.50, 76.69, 40.04, 28.38, 27.50, 25.41, 15.63, 11.51. HRMS-ESI: *m*/*z* calcd for $C_{20}H_{25}NSe + H^+$: 360.1230; found: 360.1224.
4e: Yield: 76%; $[\alpha]_D^{20}$ +52 (*c* 0.7, CH_2Cl_2). ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.16 (s, 1 H), 7.72–7.71 (m, 2 H), 7.47–7.15 (m, 8 H), 3.34–2.96 (m, 3 H), 2.04–1.99 (m, 1 H), 0.95–0.91 (m, 6 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 160.68, 136.07, 133.55, 132.30, 130.82, 130.43, 129.34, 128.87, 126.46, 77.00, 32.74, 32.42, 19.71, 18.57. HRMS-ESI: *m*/*z* calcd for $C_{18}H_{21}NSe + H^+$: 332.0911; found: 332.0915.
4f: Yield: 78%; $[\alpha]_D^{20}$ = +23 (*c* 0.6, CH_2Cl_2). ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.60 (s, 1 H), 7.99–7.97 (m, 1 H), 7.35–7.16 (m, 6 H), 6.97–6.88 (m, 2 H), 3.88 (s, 3 H), 3.76–3.69 (m, 2 H), 3.01–2.99 (m, 1 H), 2.87–2.77 (m, 2 H), 1.95–1.90 (m, 1 H), 0.89 (d, 6 H, *J* = 6,72). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 158.80, 156.24, 139.60, 131.60, 128.90, 128.27, 127.52, 126.42, 124.68, 120.70, 111.56, 77.87, 55.50, 33.26, 28.32, 27.37, 19.71, 18.81. HRMS-ESI: *m*/*z* calcd for $C_{20}H_{25}NOSe + H^+$: 376.1179; found: 376.1189.
4g: Yield: 90%; $[\alpha]_D^{20}$ +71 (*c* 0.58, CH_2Cl_2). ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.09 (s, 1 H), 7.71–7.69 (m, 2 H), 7.29–7.16 (m, 5 H), 7.00–6.91 (m, 2 H), 3.81 (s, 3 H), 3.75–3.67 (m, 2 H), 2.95–2.76 (m, 3 H), 1.93–1.89 (m, 1 H), 0.94–0.81 (m, 6 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 161.51, 159.61, 139.62, 131.91, 129.95, 129.80, 129.17, 128.31, 126.47, 114.30, 113.93, 77.91, 55.50, 33.37, 28.80, 28.48, 19.72, 18.72. HRMS-ESI: *m*/*z* calcd for $C_{20}H_{25}NOSe + H^+$: 376.1179; found: 376.1193.
4h: Yield: 88%; $[\alpha]_D^{20}$ +52 (*c* 0.75, CH_2Cl_2). ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.57 (s, 1 H), 8.03–8.01 (m, 1 H), 7.37–7.19 (m, 8 H), 3.85 (s, 2 H), 3.01–2.97 (m, 1 H), 2.89–2.74 (m, 2 H), 1.94–1.92 (m, 1 H), 0.94–0.88 (m, 6 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 157.05, 139.41, 134.99, 133.25, 131.22, 129.61, 128.87, 128.60, 128.50, 126.85, 126.50, 77.32, 33.15, 28.43, 27.40, 19.62, 18.53. HRMS-ESI: *m*/*z* calcd for $C_{19}H_{22}NClSe + H^+$: 380.070; found: 380.0856.
4i: Yield: 80%; $[\alpha]_D^{20}$ +61 (*c* 0.9, CH_2Cl_2). ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.10 (s, 1 H), 7.70–7.67 (m, 3 H), 7.38–7.21 (m, 6 H), 3.70 (dd, 2 H, *J* = 12, *J* = 16), 2.95–2.73 (m, 3 H), 1.94–1.86 (m, 1 H), 0.89–0.86 (m, 6 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 158.98, 139.47, 136.40, 134.63, 129.42, 128.90, 128.78, 128.71, 128.54, 128.35, 126.56, 77.85, 33.36, 28.60, 27.81, 19.66, 19.61. HRMS-ESI: *m*/*z* calcd for $C_{19}H_{22}NClSe + H^+$: 380.0684; found: 380.0673.

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(14) **General Procedure for the Allylic Alkylation of 1,3-Diphenyl-2-propenyl Acetate with Dimethyl Malonate:** A solution of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (50 μmol) and chiral ligand (5 mmol%) in dichloromethane (1.5 mL) was stirred for 30 min at r.t. Subsequently, a solution of *rac*-1,3-diphenyl-2-propenyl acetate (1.0 mmol), dimethyl malonate (3.0 mmol), BSA (3.0 mmol), and KOAc (3 mg, cat. quantity) in dichloromethane (0.8 mL) were added. The reaction mixture was stirred for 48 h. After this time, sat. NH_4Cl (aq) was added to quench the reaction, followed by extraction with dichloromethane (3 × 15 mL). The combined organic layers were dried over $MgSO_4$. The solvent was removed in vacuo. The yield was determined by isolated product and the ee by HPLC (Chiralcel OD, 0.5% 2-propanol–hexane, flow 0.5 mL/min, λ = 254nm).

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