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Synthesis and application of new iminopyridine ligands in the enantioselective palladium-catalyzed allylic alkylation

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ABSTRACT

A variety of iminopyridines were obtained by condensation of chiral amines with pyridine-2-carboxaldehyde and quinoline-8-carbaldehyde, or of aminoalkylpyridine derivatives with chiral ketones. These ligands were assessed in the enantioselective palladium catalyzed allylic substitution of 1,3-diphenylprop-2-enyl acetate with dimethyl malonate affording the product dimethyl 1,3-diphenylprop-2-enylmalonate in good yields and moderate enantioselectivities (up to 62% ee). Catalytic activity and enantioselectivity were found to be highly dependent upon the steric properties of the ligands. The best enantioselectivity (62% ee) was obtained by an iminopyridine based on a camphane skeleton.

1. Introduction

Transition-metal-catalyzed asymmetric allylic substitutions [1], particularly those employing palladium- [2], copper- [3], iridium- [4] or molybdenum-complexes [5] have become some of the most powerful tools for asymmetric C—C and C—heteroatom bond formation, finding wide application in the synthesis of valuable molecules and complex natural products [6].

In the past few decades, a plethora of efficient chiral ligands has been developed for this asymmetric process. Most of them are mixed bidentate donor ligands with *P*–*P* or *P*–*N* chelating mode [1–6], although several interesting examples of *N*,*N*-chelating ligands such as diamines [7], pyridine-based ligands (2,2′-bipyridines, 1,10-phenanthrolines, pyridyl amines, pyridyl oxazolines, etc.) [8] and oxazoline-containing ligands [9] have also proven their efficiency.

Notwithstanding chiral *N*,*N*-ligands based on imino and pyridine moieties have become a large and important topic in asymmetric synthesis, they have been barely applied in allylic substitution reactions [10]. Hoveyda and co-workers developed readily modular peptide-based iminopyridine ligands **1** (Fig. 1), which led to an interesting level of regio- and enantioselectivity in the Cu-catalyzed allylic substitution of cinnamyl phosphates with diethylzinc [11]. Lacour and co-workers reported that the combination of unsymmetrical iminopyridine ligands **L2** (Fig. 1) and the ruthenium complex $[CpRu(MeCN)_3]PF_6$ afforded highly regio- and enantioselective Carroll rearrangements, this being the first example of Ru-catalyzed asymmetric C—C bond-forming allylic substitution [12]. Finally, the tridentate *PNN* ligands **L3a–c** (Fig. 1) were compared by Zheng and co-workers in the palladium-catalyzed allylic alkylation of 1,3-diphenylprop-2-enyl pivalate and cyclohexenyl acetate with dimethyl malonate in the presence of BSA-KOAc, but as a result, it was found that the ligand **L3a** with a 2-pyridine *N*-atom surprisingly showed no activity, thus indicating that this type of ligand works well only in a *P*–*N* chelating fashion [13].

We have recently reported the synthesis and application in the copper(II)-catalyzed Henry reaction of iminopyridine ligands obtained by condensation of chiral amines with pyridine-2-carboxaldehyde **L2** or (5*S*,7*R*)-6,6-dimethyl-2-phenyl-5,7-methanoquinolin-8(5*H*)-one **L4** [14], or by reaction of aminoalkylpyridines with naturally occurring chiral ketones **L5** [15]. Since, as mentioned-above, these type of chiral ligands have been never applied in Pd-catalyzed allylic substitutions, in line with our ongoing efforts to explore highly enantioselective reactions using simple and cheap chiral catalytic systems [16], we have investigated the potential of this type of chiral ligands in asymmetric Pd-catalyzed allylic substitutions. Herein we report the comparative results obtained in the Pd-catalyzed allylic alkylation of 1,3-diphenylprop-2-enyl acetate with dimethyl malonate

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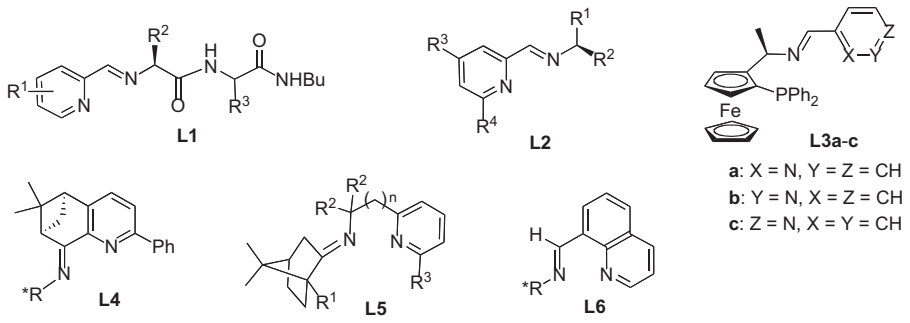

Fig. 1. Ligands applied in allylic substitution reactions.

using the known iminopyridines of the type **L2** and **L5**, and the new iminopyridines **L6** (Fig. 1). It should be noted that all the examined ligands share the imino and pyridine moieties, but differ from their chelating properties. In fact, both ligands **L2** and **L5** ($n = 0$) form a five-membered chelate ring with palladium, but differ from the orientation of the N=C double bond, which is directed forward the pyridine ring in ligands **L2** and in the opposite side in ligands **L5**. On the other hand, ligands **L5** ($n = 1$) and **L6** form a six-membered chelate ring in a rather rigid structure.

2. Experimental

2.1. General remarks

Ligand syntheses were carried out under nitrogen atmosphere in oven-dried glassware with magnetic stirring, while catalytic allylic alkylation reactions were performed without air or moisture exclusion. Unless otherwise noted, all materials were obtained from commercial suppliers and were used without further purification. All solvents were HPLC grade. THF was distilled from sodium-benzophenone ketyl and degassed thoroughly with dry nitrogen directly before use. Unless otherwise noted, organic extracts were dried with Na_2SO_4, filtered through a fritted glass funnel, and concentrated with a rotary evaporator (20–30 mmHg). Flash chromatography was performed with silica gel (200–300 mesh) using the mobile phase indicated. Melting points are collected using a BÜCHI B-540 and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury (^{1}H 400.1 MHz, ^{13}C 100.6 MHz) with tetramethylsilane (TMS) as reference. Chemical shifts (δ) are reported in ppm and multiplicity is indicated as follow: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, bs = broad signal. Coupling constants (J) are indicated in hertz. Ligands **2a**–**e** [15], **2f** [17], and **4a**,**c**–**g** [14] were prepared according to reported procedures.

2.1.1. (1R,4R)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-ylidene)quinolin-8-amine (**2f**)

This compound was prepared according to our procedure [17]: mp 110–112 °C; $[\alpha]_D^{25} = -5.8$ (c 1.0, $CHCl_3$); ^{1}H NMR (400.1 MHz, $CDCl_3$): $\delta = 8.10$ (d, $J = 4.4$ Hz, 1*H*, ArH), 8.08 (d, $J = 8.4$ Hz, 1*H*, ArH), 7.50–7.41 (m, 2*H*, ArH), 7.32 (dd, $J = 8.8$, 4.4 Hz, 1*H*, ArH), 7.06 (d, $J = 6.8$ Hz, 1*H*, ArH), 2.06 (dt, $J = 17.2$, 4.0 Hz, 1*H*), 1.92–1.74 (m, 4*H*), 1.50 (d, $J = 17.2$ Hz, 1*H*), 1.27–122 (m, 1*H*), overlapped with 1.25 (s, 3H, CH3), 1.04 (s, 3H, CH3), 1.00 (s, 3*H*, CH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 185.2$, 148.8, 148.2, 139.3, 134.8, 128.0, 125.6, 121.3, 119.8, 116.9, 53.3, 46.6, 42.8, 36.1, 31.3, 26.4, 18.8, 18.2, 10.3. Anal. Calcd. for $C_{19}H_{22}N_2$: C, 81.97; H, 7.97; N, 10.06. Found: C, 82.33; H, 7.85; N, 10.01.

2.2. General procedure for the synthesis of imines **5a**–**d**,**f**,**g**

The proper amine (1.8 mmol) was added dropwise to a stirred mixture of quinoline-8-carbaldehyde (0.28 g, 1.8 mmol) and anhydrous K_2CO_3 (0.5 g) in anhydrous diethyl ether (10 mL). The resulting mixture was stirred at room temperature overnight and then filtered. The organic phase was evaporated and the residue was purified by flash chromatography eluting with petroleum ether/EtOAc = 9:1.

2.2.1. (S,E)-N-(1-Phenylethyl)-1-(quinolin-8-yl)methanimine (**5a**)

Yield 82%; Pale yellow oil; $[\alpha]_D^{25} = -94.5$ (c 0.5, $CHCl_3$); ^{1}H NMR (400.1 MHz, $CDCl_3$): $\delta = 9.78$ (s, 1*H*, NCH), 8.96 (dd, $J = 4.2$, 1.8 Hz, 1*H*, ArH), 8.52 (dd, $J = 7.3$, 1.5 Hz, 1*H*, ArH), 8.19 (dd, $J = 8.3$, 1.8 Hz, 1*H*, ArH), 7.89 (dd, $J = 8.1$, 1.5 Hz, 1*H*, ArH), 7.60 (t, $J = 7.6$ Hz, 1*H*, ArH), 7.51 (d, $J = 7.5$ Hz, 2*H*, ArH), 7.44 (dd, $J = 8.3$, 4.2 Hz, 1*H*, ArH), 7.35 (t, $J = 7.5$ Hz, 2*H*, ArH), 7.24 (t, $J = 7.5$ Hz, 1*H*, ArH), 4.77 (q, $J = 6.6$ Hz, 1*H*), 1.67 (d, $J = 6.6$ Hz, 3*H*, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 157.3$, 150.1, 146.8, 145.6, 136.4, 133.3, 128.5 (2C), 128.3, 127.9, 126.9 (2C), 126.8, 126.6, 126.4, 121.3, 70.4, 25.0; Anal. Calcd. for $C_{18}H_{16}N_2$: C, 83.04; H, 6.19; N, 10.76. Found: C, 83.22; H, 6.20; N, 10.53.

2.2.2. (R,E)-N-(1-(Naphthalen-1-yl)ethyl)-1-(quinolin-8-yl)methanimine (**5b**)

Yield 84%; white solid mp 92–94 °C; $[\alpha]_D^{25} = -97.6$ (c 1.1, $CHCl_3$); ^{1}H NMR (400.1 MHz, $CDCl_3$): $\delta = 9.89$ (s, 1*H*, NCH), 8.96 (dd, $J = 4.2$, 1.7 Hz, 1*H*, ArH), 8.59 (dd, $J = 7.3$, 1.5 Hz, 1*H*, ArH), 8.36 (d, $J = 8.4$ Hz, 1*H*, ArH), 8.19 (dd, $J = 8.3$, 1.7 Hz, 1*H*, ArH), 7.94–7.87 (m, 3*H*, ArH), 7.76 (d, $J = 8.2$ Hz, 1*H*, ArH), 7.64 (t, $J = 7.1$ Hz, 1*H*, ArH), 7.57–7.43 (m, 4*H*, ArH), 5.58 (q, $J = 6.6$ Hz, 1*H*), 1.81 (d, $J = 6.6$ Hz, 3*H*, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 157.5$, 149.9, 146.6, 141.6, 136.3, 133.9, 133.2, 130.6, 130.3, 128.8, 128.1, 127.7, 127.1, 126.5, 125.7, 125.6, 125.2, 123.9, 123.6, 121.2, 66.3, 24.8; Anal. Calcd. for $C_{22}H_{18}N_2$: C, 85.13; H, 5.85; N, 9.03. Found: C, 85.65; H, 5.90; N, 9.53.

2.2.3. (R,E)-N-(1-Cyclohexylethyl)-1-(quinolin-8-yl)methanimine (**5c**)

Yield 81%; pale yellow oil; $[\alpha]_D^{25} = -38.0$ (c 1.4, $CHCl_3$); ^{1}H NMR (400.1 MHz, $CDCl_3$): $\delta = 9.56$ (s, 1*H*, NCH), 8.96 (dd, $J = 4.2$, 1.8 Hz, 1*H*, ArH), 8.44 (dd, $J = 7.7$, 1.5 Hz, 1*H*, ArH), 8.16 (dd, $J = 8.3$, 1.8 Hz, 1*H*, ArH), 7.86 (dd, $J = 8.1$, 1.5 Hz, 1*H*, ArH), 7.59 (t, $J = 7.7$ Hz, 1*H*, ArH), 7.43 (dd, $J = 8.3$, 4.2 Hz, 1*H*, ArH), 3.27 (quin, $J = 6.5$ Hz, 1*H*, CH), 1.89–1.84 (m, 1*H*), 1.79–1.61 (m, 4*H*), 1.56–1.54 (m, 1*H*), 1.29 (d, $J = 6.5$ Hz, 3*H*, CH_3), overlapped with 1.34–1.12 (m, 3*H*), 0.98–0.94 (m, 2*H*); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 156.5$, 150.7, 146.8, 136.4, 133.6, 130.1, 128.4, 127.8, 126.7, 121.3, 72.3, 44.1, 30.2, 30.0, 26.8, 26.6, 26.5, 20.2; Anal. Calcd. for $C_{18}H_{22}N_2$: C, 81.16; H, 8.32; N, 10.52. Found: C, 81.66; H, 8.55; N, 10.76.