Synthesis of New Chiral N-Heterocyclic Carbene−Imine Ligands and Their Application to an Asymmetric Allylic Alkylation Reaction

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Summary: Silver(I) and palladium(II) complexes of new chiral N-heterocyclic carbene (NHC)−imine ligands derived from trans-1,2-diaminocyclohexane have been prepared. These ligands have been applied to a palladium(II)-catalyzed asymmetric allylic alkylation reaction giving a maximum ee of 92%.

Over the past decade N-heterocyclic carbenes (NHC) have emerged as one of the most important classes of compound used as ancillary ligands for a number of late transition metal mediated catalytic reactions.[1] In comparison to ubiquitous tertiary phosphine ancillary ligands, advantages of using NHC include increased thermal stability and that excess ligand is not required.[2] More recently a concurrent development has been the investigation of chiral NHC derivatives for asymmetric catalysis.[3] In comparison to tertiary phosphine chemistry, reported examples where chiral NHC complexes give good enantioselectivity are rare. However the recent reports of >99% ee for an iridium-catalyzed asymmetric hydrogenation of aryl alkenes[4] and ruthenium-catalyzed symmetry-breaking metathesis[5] exemplify the potential of chiral NHC ligands, indicating that further investigation is warranted. Even though the vast majority of reactions studied to date use NHC precatalysts of group 10 metals,[1] the highest enantioselective reaction to date by far is 76% ee for a palladium(II)-catalyzed intramolecular cyclization.[6]

Here we wish to report the synthesis of new chiral NHC−imine ligands derived from *trans*-1,2-diaminocyclohexane and initial work on their application to a palladium(II)-catalyzed intermolecular asymmetric allylic alkylation reaction.

We wished to prepare chiral chelating NHC precursors including imidazoles and imidazolium salts derived from chiral diamines such as *trans*-1,2-diaminocyclohexane, in part because of the success of ligand sets based on chiral diamines in several metal-mediated enantioselective catalytic reactions.[7] The most common method for the preparation of an imidazole or imidazolium salt is co-condensation between amines, paraformaldehyde, and a dione.[8] Initial attempts to prepare imidazoles from (1*R*,2*R*)-1,2-diaminocyclohexane using co-condensation routes led to the formation of oligomeric mixtures, and therefore an alternative strategy was sought. The base-induced 1,3-cycloaddition of tosylmethylisocyanide (TosMIC) to imines has sporadically been used for the preparation of imidazoles,[9] and therefore we investigated the reaction between TosMIC and diimine (**1**) shown in Scheme 1.

Reaction between 1 equiv of TosMIC and **1** did give the imidazole−imine (**2**) in 95% yield as shown in Scheme 1. As noted by other workers, we found that the preparation of imidazoles from imines and TosMIC

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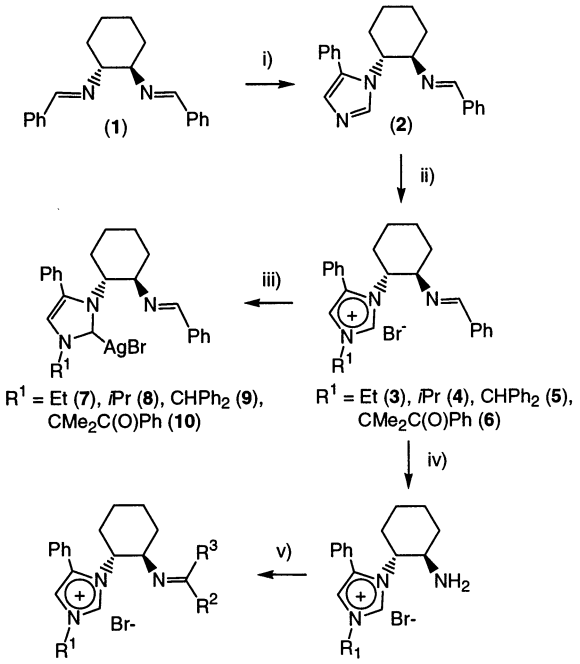
Scheme 1[a]



[a] (i) TosMIC, K_2CO_3, MeCN, 70 °C; (ii) R^1Br, MeCN, 60 °C; (iii) Ag_2O, CH_2Cl_2, 25 °C; (iv) CH_2Cl_2/H_2O, 40 °C; (v) R^2R^3CO, CH_2Cl_2, 25 °C.

is very sensitive to solvent, base, and reaction temperature.[9a] Several reactions between **1** and 2 equiv of TosMIC under various conditions did not yield a significant quantity of the corresponding diimidazole, and ^{1}H NMR spectroscopy indicated thermal decomposition products of excess TosMIC.

Imidazolium salts are common precursors to NHC ligands, and reaction between **2** and organic bromides gave the imidazolium−imines (**3**−**6**). Transfer of imidazolium salt derived ligands to group 10 metals has been shown to be conveniently achieved via silver(I) halide complexes of NHC,[10] and therefore complexes (**7**−**10**) were prepared from reaction between Ag_2O and the corresponding imidazolium salt.

To probe the coordination mode and conformations of these ligands, a palladium(II) dichloride complex (**11**) was prepared from reaction between **8** and $[PdCl_2(MeCN)_2]$ and studied by single-crystal X-ray diffraction[11] and variable-temperature ^{1}H NMR spectroscopy. The molecular structure in Figure 1 shows that the ligand in complex **11** is chelating and that the six-atom metallocycle adopts a boatlike conformation.

In addition the Pd−Cl bond length *trans* to the NHC ligand (Pd(1)−Cl(2) = 2.3695(7) Å) is significantly longer

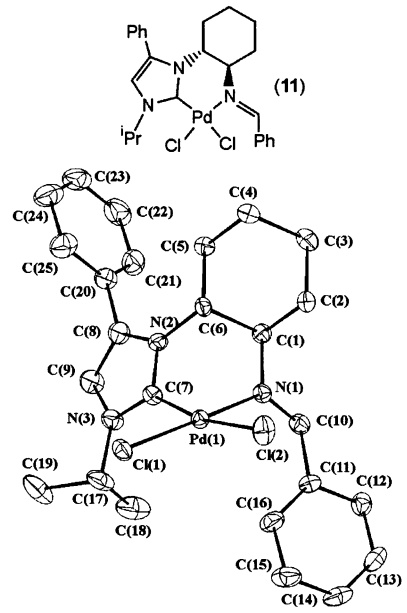


Figure 1. Molecular structure of complex **11**. Hydrogen atoms have been removed for clarity. Thermal ellipsoids are set at 50% probability. Selected bond lengths (Å) and angles (deg): Pd(1)−C(7) = 1.958(3), Pd(1)−N(1) = 2.013(2), Pd(1)−Cl(1) = 2.3185(7), Pd(1)−Cl(2) = 2.3695(7), C(7)−Pd(1)−N(1) = 82.09(10), C(7)−Pd(1)−Cl(1) = 91.58(8), Cl(1)−Pd(1)−Cl(2) = 94.33(3), N(1)−Pd(1)−Cl(2) = 92.35(6).

than the Pd−Cl bond *trans* to the imine (Pd(1)−Cl(1) = 2.3185(7) Å), demonstrating the greater *trans* influence of the strongly σ-donating NHC ligand.[12] Variable-temperature ^{1}H NMR spectroscopy of **11** in CD_3CN in the presence of 10 equiv of water shows that in this complex the ligand is conformationally robust and stable to hydrolysis at 80 °C for at least one week.

Further ligand modification of the imine group can also be readily achieved via hydrolysis to the corresponding imidazolium−amines **12** and **13** to give **14**−**17** as shown in Scheme 1. However to date we have been unable to prepare compounds where $R^3 \neq$ H or Me presumably due to steric constraints.

The potential application of this new class of chiral ligand was tested on the asymmetric allylic alkylation of (*E*)-1,3-diphenylprop-3-en-1-yl acetate with dimethylmalonate as shown in eq 1, and results are given in Table 1. There are several examples of phosphine-based ligands giving ee's > 99% for this reaction,[13] but to the best of our knowledge, to date there are no reports describing the use of NHC complexes for any asymmetric allylic alkylation, although a recent report has for the first time demonstrated an achiral variant.[14] Palladium(II) allyl complexes of NHC have also been used as precatalysts for cross-coupling reactions.[15]

Entries 1−16 in Table 1 show that in all cases the *S* enantiomer is favored using (1*R*,2*R*)-1,2-diaminocyclohexane as the ligand motif, and entry 17 shows that

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(11) X-ray structure for **11**. Yellow crystals, $C_{25}H_{29}N_3Cl_2Pd$, dimensions 0.18 × 0.16 × 0.10 mm; M_r = 548.81; orthorhombic $P2_12_12_1$, a = 11.0731(6) Å, b = 18.2240(10) Å, c = 12.0902(6) Å, V = 2439.8(2) Å^3, Z = 4, λ(Cu Kα) = 1.54178 Å, ρ_{calc} = 1.494 g cm^{-3}, T = 195(2) K, F(000) = 1120, θ range for data collection 4.39−70.92°, limiting indices −12 ≤ h ≤ 13, −21 ≤ k ≤ 22, −14 ≤ l ≤ 14 14532/4532 collected/unique reflections (R(int) = 0.0365), absolute structure parameter 0.042(7), goodness of fit on F^2 = 1.061, $\Delta\rho_{max/min}$ = 0.396/−0.800 e Å^{-3}, final R indices ($I > 2\sigma(I)$) R1 = 0.0235, wR2 = 0.0577. The structure was solved using SHELXS-97 and refined using SHELXL-97. G. M. Sheldrick, University of Göttingen, Germany, 1997.

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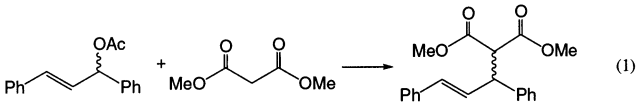
Table 1. Asymmetric Allylic Alkylation between (*E*)-1,3-diphenylprop-3-en-1-yl Acetate and Dimethylmalonate[a]



(1)

entry	ligand	*t* (h)	conversion (%)[b]	ee *S* (%)[c]
1	**7**	15	40	20
2	**7**	90	>99	20
3	**8**	15	>99	40
4	**9**	15	>99	55
5	**10**	15	>99	0
6	**14**[d]	15	69	36
7	**14**[d]	90	>99	36
8	**15**[d]	15	60	12
9	**15**[d]	90	>99	12
10	**16**[d]	15	>99	92
11	**17**[d]	15	>99	90
12	**8**	10	95	40
13	**8**	10	50	38[e]
14	**8**	10	26	26[f]
15	**16**	15	>99	92[g]
16	**16**	15	>99	90[h]
17	(1*S*,2*S*)-**16**	15	>99	92*R*

[a] 2.5 mol % $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, 5 mol % ligand, 1,3-diphenylacetate, 3.0 equiv of dimethylmalonate, 2.9 equiv of NaH, THF, 50 °C. $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ and ligand are stirred for 1 h, filtered, and injected into the reaction mixture. [b] Measured by HLPC. [c] ^{1}H NMR using $Eu(hfc)_3$ as the chiral shift agent. [d] Transfer of NHC ligands derived from **14**−**17** was achieved via silver(I) complexes in an manner analogous to **7**−**10**. [e] **8**:Pd = 0.5:1. [f] **8**:Pd = 2.0:1. [g] 40 °C. [h] 70 °C.

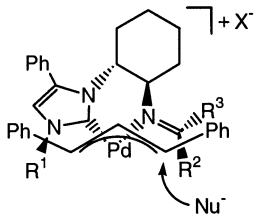


Figure 2. Proposed allyl complex intermediate.

the stereochemistry is reversed when the (1*S*,2*S*)-enantiomer is used. The dependence of enantioselectivity on ligand modification is shown in entries 1−11. In general the data indicate that increasing the steric bulk of the imidazolium substituent and decreasing the steric bulk of the imine appear to increase selectivity for the *S* enantiomer.

Altering the ligand-to-metal ratio (12−14) shows that the yield is optimized for a L:Pd ratio of 1:1 and the ee decreases on addition of greater than 1 equiv of ligand. Entries 10, 15, and 16 also show that the enantioselectivity is not strongly temperature dependent over the range studied.

Most of the data in Table 1 can be rationalized on the basis of the allyl intermediate shown in Figure 2 and that Curtin−Hammett conditions are operative during the reaction and that there is no memory effect.[16] It has been shown that in the absence of overriding steric factors, addition of soft nucleophiles to allyl complexes is regioselective, occurring *trans* to the ligand that is the strongest σ-donor.[17] As indicated by the structure of **11**, nucleophilic attack would therefore occur *trans* to the NHC group.[12] For nucleophilic attack *trans* to the NHC to give the *S* product, orientation of the allyl moiety as shown in Figure 2 is required, which is in accord with increasing bulk of the NHC and imine groups.

With the exception of **10**, entries 1−4 show that increasing the bulk of the NHC substituent increases the ee. In contrast to **7**−**9**, reaction between **10** and $[PdCl_2(MeCN)_2]$ did not give a tractable palladium(II) complex analogous to **11**, and therefore it is likely that the catalytic species derived from **10** is distinct from that of the other ligands investigated. Modification of the imine substituent shows that ligands **16** and **17** derived from acetone give the highest ee of 92%, whereas larger substituents at the R^2 position are detrimental to the enantioselectivity. A likely explanation is that steric bulk at the imine position reduces the relative rate of nuclephilic attack *trans* to the NHC moiety. A hemilabile imine group also cannot be discounted at this time.[18]

In conclusion, we have prepared a new class of chiral NHC ligands derived from reaction between a chiral imine and TosMIC. Modification of the ligand is straightforward, and in particular, use of the amine moiety in **12** and **13** for the preparation of a range of chiral ligands can be envisaged. We have shown that NHC−imine ligands can be used for an intermolecular asymmetric allylic alkylation reaction giving excellent conversion and have elucidated some structural features that determine enantioselectivity.

Currently the enantioselectivity and rates of reaction for the reaction studied are relatively poor compared to many chiral phosphine ligands. However, we are investigating the synthesis and solution dynamics of allyl complexes incorporating this new class of ligand, and its derivatives, to determine in more detail the origin of the observed enantioselectivity in an attempt to improve catalytic performance.

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Supporting Information Available: Experimental procedures and data for all compounds and tables of crystal data, fractional atomic coordinates, bond distances, bond angles, anisotropic thermal parameters and CIF file for **11** are available free of charge via the Internet at http://pubs.acs.org.

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(18) See ref 14 for a structurally characterized (NHC)Pd(allyl)Cl complex.