Pergamon

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Tetrahedron: *Asymmetry* 14 (2003) 2331–2333

TETRAHEDRON: *ASYMMETRY*

Asymmetric exchange of cyclopalladated ligands with a high level of asymmetric induction: a new route to optically active phosphapalladacycles

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Received 14 May 2003; accepted 23 June 2003

Abstract—The first example of an asymmetric C–H bond activation with chirality transfer (up to 91% ee) from an enantiopure *CN*-palladacycle is described. This asymmetric version of cyclopalladated ligand exchange was elaborated in an aprotic medium using prochiral phosphines as substrates and an enantiopure benzylaminate palladacycle bearing a primary amino group and a bulky *tert*-Bu substituent on the side chain as the palladation agent.

Asymmetric activation of the C–H bonds in prochiral substrates seems to be an intriguing task. Only one successful solution to this problem in the framework of intramolecular palladation has been reported previously[1,2] based on the use of optically active bases (*N*-acylated amino acidates) as the source of chiral information. Recent attempts to achieve asymmetric induction of planar chirality from enantiopure sulfoxide ligand inserted into the metallation agent during the cyclopalladation of *N*,*N*-dimethylaminomethylferrocene ligand have failed.[3]

Herein we report the first example of a highly efficient asymmetric cyclopalladation of a prochiral phosphine ligand based on the chirality transfer from an enantiopure *CN*-palladacycle (which serves here as both palladation agent and stereoselector) to the *CP*-palladacycle formed in the framework of cyclopalladated ligand exchange (CLE). Our choice of palladacycle as chirality inducer was motivated by excellent recent achievements in their application for chiral recognition: in resolution,[4,5] for spectral discrimination of enantiomers,[6,7] as matrices for asymmetric synthesis,[8,9] and as enantioselective catalysts.[10,11]

It was clear from the outset that the standard conditions used for the CLE processes[12,13] (including the indispensable presence of acetic acid in the reaction mixture) can't be used for the development of an asymmetric version of this process. For example, complete absence of any asymmetric induction was reported previously for the reaction of 8-ethylquinoline with optically active cyclopalladated *N*,*N*-dimethyl-α-methylbenzylamine under protic conditions (AcOH/$CHCl_3$ mixture, 50°C, 24 h).[14]

The following points were crucial for the elaboration of our asymmetric version of the cyclopalladated ligand exchange: (i) an aprotic medium was necessary for the retention of the starting homochiral palladacycle in the chelated state during the stage of C–H bond activation; (ii) *P*-donor ligands were involved in this process to provide tight bonding of the substrate with the chirality inducer; (iii) the choice of the starting *CN*-palladacycle was aimed at the efficient shift of the equilibrium between two palladacycles to the target molecule under mild conditions.

For the prochiral ligands we selected the monophosphines with enantiotopic *ortho*-tolyl groups (**HL**[1]), or with enantiotopic C-H bonds of the cyclopentadienyl ring (**HL**[2]), which are precursors of known palladacycles **1** and **2**, containing a *P**-stereocenter[15] and a chiral plane,[16] respectively (Scheme 1).

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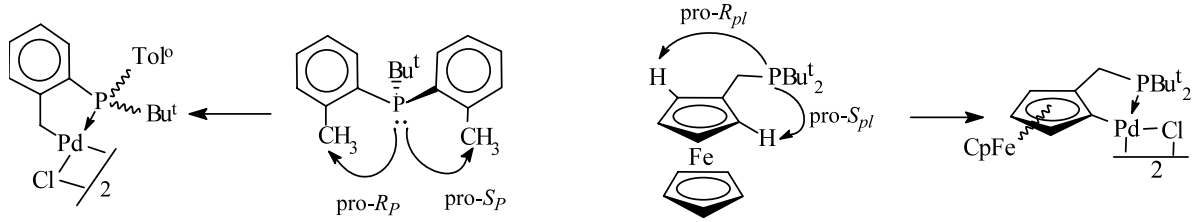
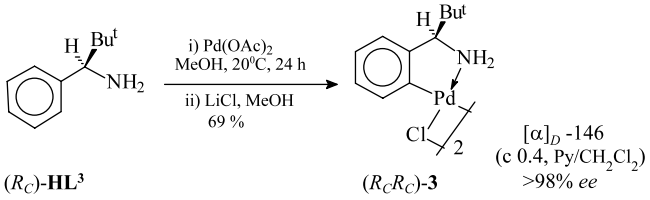
doi:10.1016/S0957-4166(03)00496-8



Scheme 1.

For the chirality inducer we chose the α-*tert*-Bu substituted cyclopalladated complex (R_CR_C)-**3** since (i) its conformational stability provides good potential for the chiral recognition, and (ii) it is known that derivatives of primary amines usually have a rather low tendency to be palladated.[17] This complex (described previously as the racemate[18]) was prepared by direct *ortho*-palladation of the primary benzylamine (R_C)-**HL^3** preresolved by a known procedure (Scheme 2).[19]



Scheme 2.

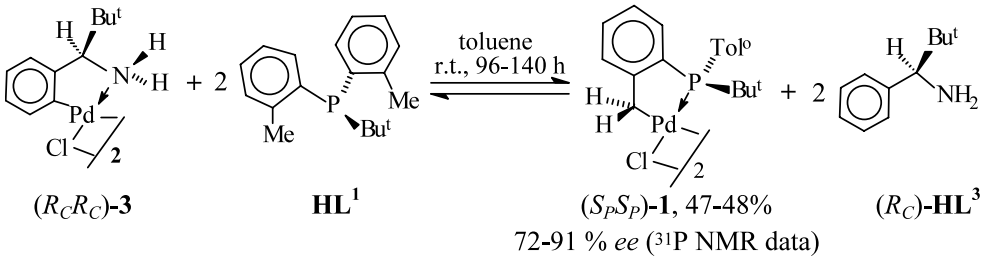
Our preliminary experiments on the CLE reaction of this reagent with the phosphine **HL^1** performed in the protic medium (toluene/AcOH, 60°C, 1 h) gave a good chemical result: the *CP*-dimer **1** was isolated in a high yield of 71% considerably exceeding that found in the only previously reported reaction of this kind with participation of a phosphine ligand in the presence of acetic acid (21%[20]). However, under these conditions reaction occurs without any selectivity and complex **1** was isolated as the racemate (<2% ee). This result may be considered as indirect stereochemical evidence in support of a dissociative mechanism of the CLE processes in the protic medium[12,13] including destruction of the starting palladacycle (via protonolysis of the Pd–C bond) before the stage of a new C-H bond activation. Monodentate *N*-bonded benzylamine (R_C)-**HL^3** thus formed cannot provide any noticeable asymmetric induction owing to its rotameric mobility.

In contrast, the CLE reaction of the *CN*-palladacycle (R_CR_C)-**3** with the phosphine **HL^1** performed in an aprotic medium at rt was both chemically and stereochemically successful: *CP*-dimer (S_PS_P)-**1** of high enantiomeric purity (72–91% ee depending on the reaction duration) was isolated in the moderate chemical yields of ca. 50% (Scheme 3).

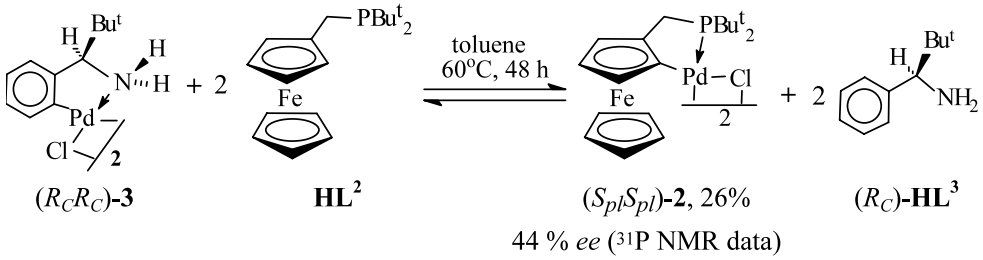
The isolation of the *CP*-dimer (S_PS_P)-**1** and recovery of the starting *CN*-dimer (R_CR_C)-**3** from their intermediate mononuclear amine and phosphine adducts was performed using known methodology involving the phosphine displacement by the auxiliary ethane-1,2-diamine ligand.[21] The enantiomeric composition of the phosphapalladacycle thus formed was determined by means of ^{31}P NMR spectroscopy after chiral derivatizing in situ with the readily available auxiliary (*S*)-prolinate ligand (cf. [7]).

Strong chemical and stereochemical advantages of the reagent (R_CR_C)-**3** are evident from its comparison with related benzylaminate palladacycles: (i) negligible low asymmetric induction (ca. 13% *ee*) was found in the phosphine **HL^1** reaction with the related α-Me-substituted analogue despite a good chemical yield of 66% provided by the primary amino group; (ii) the similar reaction with the *N*-Me-α-Bu^t-substituted analogue was possible only on heating (132 h at 60°C) resulting in extremely low chemical yields and enantiomeric excesses of dimer **1** (8%, <9% *ee*), while with the dimer (R_C,R_C)-**3** this process may be realized even at −13°C (165 days, 13% yield, >86% ee).

Unfortunately, even the optimal reagent (R_C,R_C)-**3** proved to be less efficient for induction of planar chirality in the reaction with the ferrocenylmethylphosphine **HL^2**; owing to a rather low activity of this phosphine substrate CLE reaction becomes possible



Scheme 3.



(R_CR_C)-**3** **HL**^{2} $(S_{pl}S_{pl})$-**2**, 26% (R_C)-**HL**^{3}

Scheme 4.

only on heating, and planar chiral *CP*-dimer $(S_{pl}S_{pl})$-**2** may be isolated with only a moderate enantiomeric excess of 44% (Scheme 4).

In this case decreased activity in the CLE processes of other α-Bu^t-substituted benzylaminate palladacycles bearing secondary (NHMe) or tertiary amino group (NMe_2) became more pronounced: only traces of the target *CP*-palladacycle **2** were observed by TLC after very long heating (420 h at 60°C).

In conclusion, we have elaborated a new version of asymmetric C-H bond activation based on the chirality transfer from the enantiomerically pure *CN*-palladacycle in the course of CLE reaction. The success was achieved due to the use of an aprotic medium, with the benzylaminate palladacycle containing a primary amino group and the bulky *tert*-Bu substituent on the side chain as the chirality inducer. To the best of our knowledge, this is the first example of the cyclopalladated ligand exchange in the absence of any acid; mechanistic aspects of this new process are now under investigation.

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