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Asymmetric Pd-NHC*-catalyzed coupling reactions*

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Abstract: Very high asymmetric inductions result in the Pd-catalyzed intramolecular arylation of amides to give 3,3-disubstituted oxindoles when new in situ-generated chiral *N*-heterocyclic carbene (NHC*) ligands are employed. Structural studies show that conformational locking to minimize allylic strain is the key to understanding the function of these ligands.

New applications of these ligands in the frontier area of asymmetric coupling reactions involving C(sp^3)–H bonds are detailed. Highly enantioenriched fused indolines are accessible using either preformed- or in situ-generated Pd-NHC* catalysts. Remarkably, this occurs at high temperature (140–160 °C) via excellent asymmetric recognition of an enantiotopic C–H bond in an unactivated methylene unit.

Keywords: asymmetry; C–H bond reactivity; coupling reactions; *N*-heterocyclic carbenes; palladium.

INTRODUCTION

Chiral bidentate phosphorous ligands are ubiquitous in asymmetric transition-metal catalysis. In most cases, the chiral ligand backbone orients the stereocontrol elements—often aryl substituents—on phosphorus, such as to generate the appropriate chiral environment for the catalytic reaction [1]. We have used this ourselves extensively in the design of chiral Fe- and Ru-Lewis acids for [4 + 2] and [3 + 2] cycloaddition reactions as shown in Scheme 1 [2].

Interestingly, in these reactions the ground-state coordination of the carbonyl substrate shows an *anti-s-trans* arrangement for both enals and enones. With enals, this is also the reactive conformation, whereas α,β-unsaturated ketones react via a *syn-s-trans* transition state [2g,l].

anti-s-trans *syn-s-trans*

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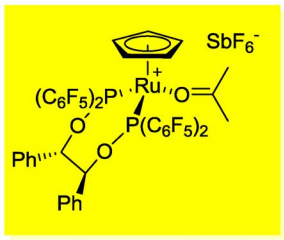
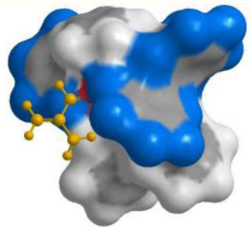
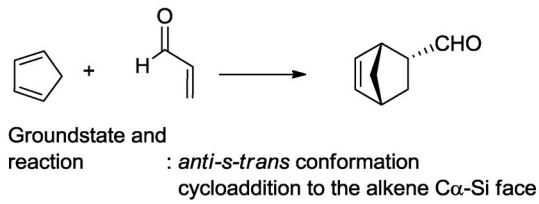
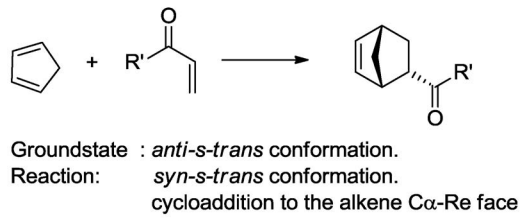








Scheme 1 One-point binding transition-metal Lewis acid catalysts for cycloaddition reactions.

Recent developments in catalysis include the use of monodentate rather than bidentate ligands. Bulky monodentate ligands are very promising because the availability of an additional coordination site enables new transformations. An impressive example is the family of monodentate ligands reported by the Buchwald group [3]. Asymmetric induction with chiral monodentate ligands is difficult, however, because they lack the stereodirecting chiral backbone that has proven so successful in generating a well-defined chiral environment. The design and use of chiral monodentate ligands is still in its early stage, and when compared to the vast arsenal of chiral bidentate ligands, chiral monodentate phosphines that have found successful applications are scarce, even if one includes ligands that can temporarily act as bidentates by weak coordination, such as phosphoramidates [4]. Lacking the chiral backbones and the rigidity of bidentate ligands, different stereodirecting elements must be built in for the application of chiral monodentate ligands in asymmetric catalysis [5].

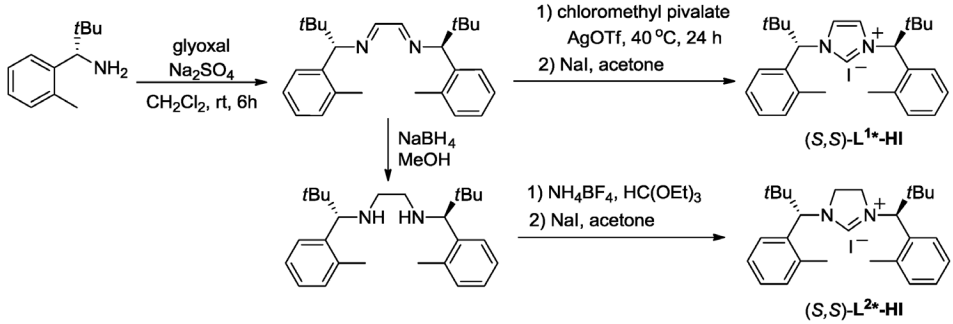
We focused on *N*-heterocyclic carbene (NHC) ligands [6], and in this presentation we will show that the concept of minimization of the $A^{1,3}$-strain [7] offers a powerful method to achieve the goal of high asymmetric induction with chiral monodentate NHCs.

RESULTS AND DISCUSSION

New chiral monodentate *N*-heterocyclic carbene ligands

C_2-symmetric *NHC*-ligands L^1 and L^2 derived from (*S*)-2,2-dimethyl-1-(*o*-tolyl)propan-1-amine and analogs are readily prepared in enantiopure form [8] (Scheme 2).

An X-ray structure of the complex [Pd(allyl)L^1I] revealed that large groups at the stereogenic centers C* enforce coplanarity of the C(ligand)–Pd and C*–H bonds [8a,9]. Rotation around the N–C* bond would lead to a sharp increase in allylic strain. This fixes the aryl groups in space. Their orientation is determined by the aryl *o*-substituent. Again, minimization of $A^{1,3}$-strain is at play and as can be seen in Fig 1: the C(Ar)–CH_3 bond is coplanar with the C*–H bond. The place and orientation of the ligand aryl groups are thus determined by the minimization of $A^{1,3}$ strain.



Scheme 2 Synthesis of ligand precursor immidazolium and dihydroimidazolium salts.

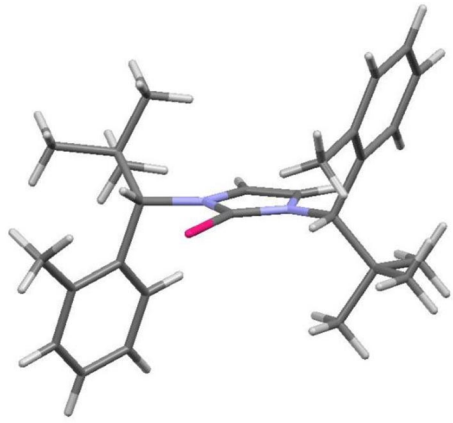
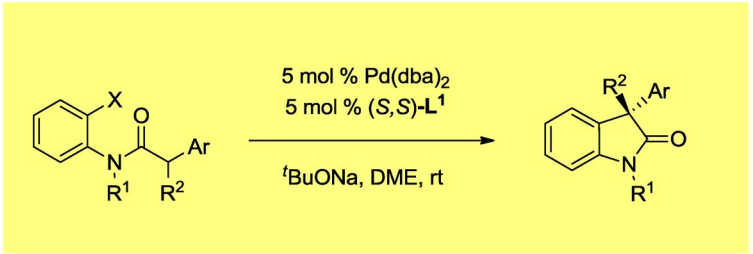


Fig. 1 X-ray structure of fragment [PdL^1] in the complex [Pd(allyl)L^{1}I]. For clarity, the allyl and iodide ligands were removed.

Pd-catalyzed asymmetric intramolecular arylation of anilides

Our first application of these ligands was in the asymmetric intramolecular arylation of amides to give 3-aryl, 3-alkyl oxindoles and 3-aryl, 3-alkoxy (or amino) oxindoles. Pioneered by Hartwig and his group some years earlier [10], we reported the first efficient asymmetric version of this elegant route to 3,3-disubstituted oxindoles [8,11]. A selection of results is shown in Scheme 3.



R	Y %	Ee %
5-Me	98	95
5-iPr	99	92
6-F	99	95
6-CF_3	96	94
6-MeO	99	95
7-F	98	70

R	Y %	Ee %
5-Me	98	95
5-iPr	99	92
6-F	99	95
6-CF_3	96	94
6-MeO	99	95
7-F	98	70

87 % yield
94 % ee

86 % yield
87 % ee

The results below were obtained with (*R,R*)-**L**^{3} :

(*R,R*)-**L**^{3}

R	Y %	Ee %
4-Me	99	91
4-MeO	90	91
4-CF_3	45	82
3,5-Me_2	89	96

94 % yield
80 % ee (80 °C)

88 % yield
85 % ee (50 °C)

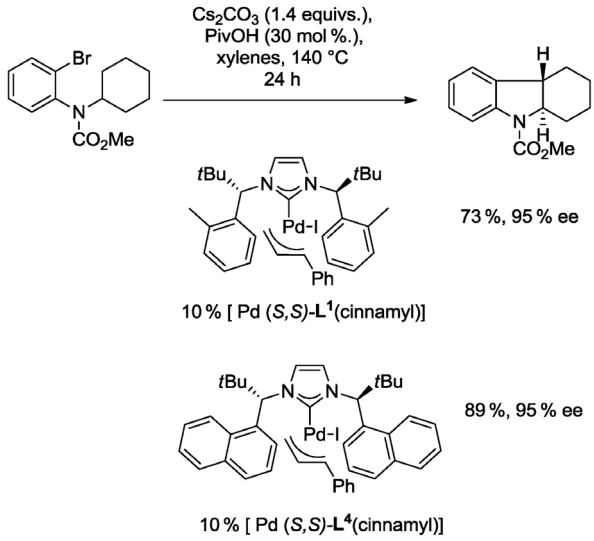
96 % yield
90 % ee (50 °C)

Scheme 3 Enantioenriched 3,3-disubstituted oxindoles via asymmetric arylation of anilides.

Indolines via Pd-catalyzed asymmetric C–C coupling involving an unactivated methylene group

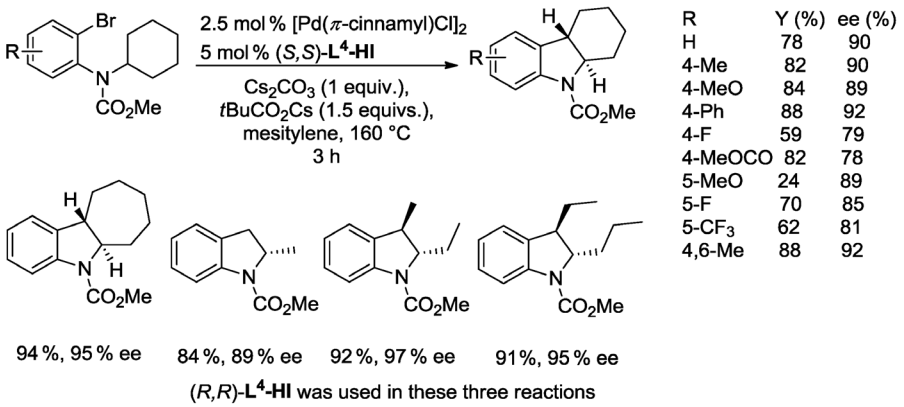
The direct functionalization of unactivated C(sp^3)–H bonds remains a major challenge in organic synthesis [12]. Mechanistic and theoretical studies indicate metalation of C–H bonds to occur via an inner sphere carboxylate-assisted concerted deprotonation pathway [13]. In Pd-catalyzed intramolecular reactions, the coordination of an internal base, the substrate, and the agostic C–H–Pd interaction leave only one coordination site open. Monodentate ligands are thus required for this transformation. Indeed, literature examples show electron-rich phosphines such as P(cyclohexyl)$_3$ to be best [12,14]. An efficient asymmetric C–H activation in which the catalyst selects one of the two enantiotopic hydrogens of a methylene group remained to be uncovered [5,15]. This was a crucial test for the chiral carbene Pd catalyst because it not only required a high stereocontrol, but in addition the catalyst needed to be stable at the high temperatures required for this transformation. We therefore started with preformed Pd carbene complexes. Optimization of initial results showed that the reaction could be realized in high yield

and high asymmetric induction (Scheme 4) [15c]. Complexes incorporating the dihydroimidazolium-derived ligands, such as L^2, afforded the product in low yield due to lack of stability of the Pd-NHC unit above 120 °C. This was manifested by the precipitation of Pd black. The increased yield with L^4 is ascribed to the higher thermal stability of its Pd complex compared to that containing L^1.



Scheme 4 Indoline synthesis via asymmetric intramolecular C(Ar)–C(sp^3)–H coupling.

The next step consisted in finding conditions whereby the Pd-carbene catalyst was generated in situ. A reduction of catalyst loading and of reaction time was also achieved by raising the temperature to 160 °C. A selection of results is shown in Scheme 5.

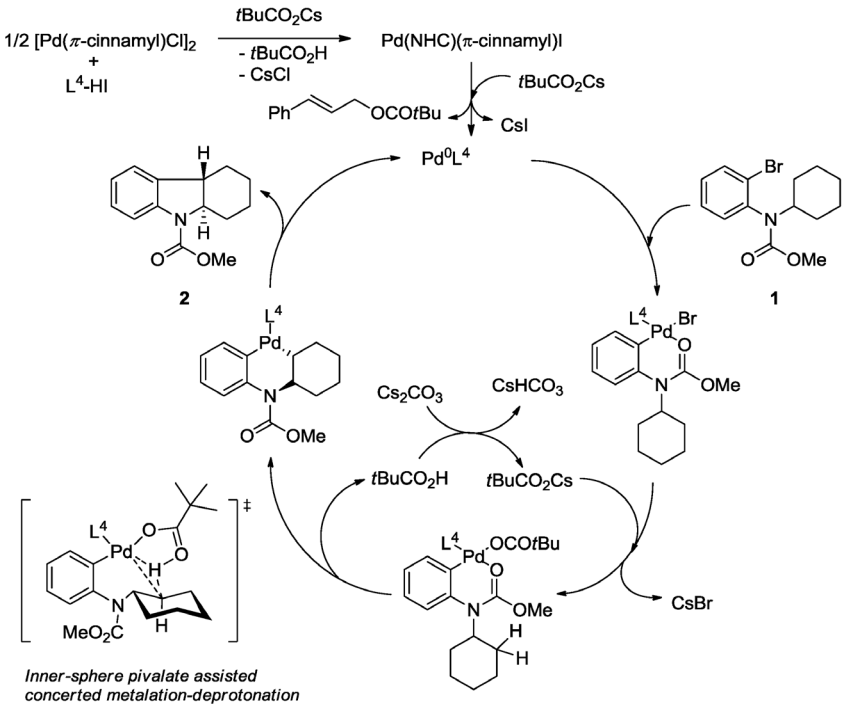


R	Y (%)	ee (%)
H	78	90
4-Me	82	90
4-MeO	84	89
4-Ph	88	92
4-F	59	79
4-MeOCO	82	78
5-MeO	24	89
5-F	70	85
5-CF_3	62	81
4,6-Me	88	92

Scheme 5 Indoline synthesis via asymmetric intramolecular C(Ar)–C(sp^3)–H coupling: In situ generation of the chiral catalyst.

We propose the reaction mechanism as shown in Scheme 6. The $[Pd(\pi\text{-cinnamyl})Cl]_2$ dimer is cleaved with the NHC ligand. The latter is generated in situ from L^4-HI and cesium pivalate.

Nucleophilic addition of pivalate to the cinnamyl ligand followed by alkene dissociation generates the Pd(0)-L^4 catalyst [16]. Oxidative addition of carbamate **1** and bromide/pivalate exchange is fol-



Scheme 6 Proposed catalytic cycle for the formation of enantioenriched fused indolines.

lowed by C–H bond activation and reductive elimination to produce the fused indoline **2** and regeneration of the catalyst. Excellent mechanistic analyses of the C–H bond activation step in the base assisted concerted metalation deprotonation mechanism of C(sp^3)–H activation of Me groups has been reported, and an adaption to the reaction leading to the fused enantioenriched indolines is shown in Scheme 6 [13].

CONCLUSION

Chiral readily synthesized NHC ligands derived from chiral 2,2-dimethyl-1-arylpropane-1-amines were successfully applied to the intramolecular α-arylation of anilides to give 3,3-disubstituted oxindoles with high asymmetric induction. More spectacular, the same ligands find application in the synthesis of highly enantioenriched indolines via Pd-catalyzed C–H activation. This reaction requires temperatures of 140–160 °C. It is extraordinary that, despite the high temperature, this transformation occurs via high asymmetric recognition of an enantiotopic C–H bond in an unactivated methylene unit. The concept of placing stereocontrol elements at the appropriate place by using minimization of allylic strain is shown to be viable and promising for future applications.

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