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Palladium-NHC Catalyzed Enantioselective Synthesis of Fused Indolines *via* Inert C(sp^3)-H Activation

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Abstract: New sterically hindered chiral *N*-heterocyclic carbene (NHC) ligands were used in palladium catalysis to bring about a highly enantioselective C(sp^3)-H activation on the methylene site of a cycloalkane moiety. The intramolecular coupling reaction of a prochiral *N*-aryl-*N*-cycloalkyl methyl carbamate required high temperatures (140–160 °C) and afforded highly enantioenriched *trans*-2,3-fused indolines.

Keywords: Asymmetric catalysis · C–H Activation · Chiral NHC · Indoline · Palladium

Introduction

Palladium-catalyzed cross-coupling reactions are powerful tools in modern chemical synthesis and they have profoundly changed synthesis protocols.[1] Following pioneering work in catalytic C–C bond forming reactions between aryl halides and Grignard reagents (Corriu, Kochi and Kumada), aryl halides and alkanes (Mizoroki-Heck), and arylhalides and alkynes (Sonogashira), a series of reactions involving C–C coupling reactions between Ar–X (X = halides, triflates) and Ar–M reactions were developed. These are closely related reactions named after their discoverers and differing in the C–M precursors: Migita-Kosugi-Stille (M = Sn), Suzuki-Miyaura (M = B), Negishi (M = Zn) and Hiyama (M = Si). More recent important extensions include the C(sp^2)–N and C(sp^2)–O bond formation (Buchwald-Hartwig) and reactions involving the more accessible aryl chloride and also alkyl halides (Beller, Buchwald, Hartwig and Fu). Direct insertion of metal complex into a C(sp^2)–H bond alleviates the need for prefunctionalization and provides a welcome shortcut that has received increasing attention over the past two decades.[2] In these reactions, the preparation of starting material can be dramatically simplified. However, C–C bond formation reactions involving C(sp^3)–H bonds in general and those of unactivated alkyl groups in particular still remain a major challenge. This notwithstanding, impressive progress has been made.[3] Methylene groups having two different substituents bear enantiotopic (or diastereotopic) hydrogens. We have taken up the challenge to direct the coupling of such fragments in an enantioselective fashion *via* the use of a palladium catalyst incorporating a bulky chiral NHC ligand.[4]

Indoles, oxindoles, and indoline form one of the most important classes of nitrogen heterocycles. Palladium-catalyzed cross-coupling reactions have figured prominently in modern indole and oxindole synthesis.[5] The indoline (2,3-dihydroindole) nucleus is present in numerous biologically active natural substances[6] and pharmaceuticals,[7] but the methods of asymmetric syntheses of substituted derivatives remains quite restricted.[8]

Fujii, Ohno and co-workers, using a palladium-phosphine catalytic system, constructed the indoline frame work by C(3)–C(3a) bond formation, involving a direct C(sp^3)–H arylation.[9] We reasoned that given a chiral catalyst, capable of withstanding the high temperatures (140 °C) required for this reaction, might result in a successful asymmetric version of this reaction.

For this project we chose C_2-symmetric NHC-ligands derived from chiral *ortho*-substituted α-alkyl-phenyl amines. The preparation of these ligands was previously reported from our research laboratory.[10] These ligands had performed outstandingly in asymmetric intramolecular α-arylation of amides to give 3-aryl, 3-alkyl oxindoles and 3-aryl, 3-alkoxy (or amino) oxindoles.[11] We applied the principle of minimization of A^{1,3}-strain to place the stereocontrol elements in the appropriate sectors of the catalyst (Fig. 1). Using this approach, we now succeeded in the highly enantioselective synthesis of 2,3-fused indolines (Scheme 1).[4a]

Results and Discussion

We started studies toward the asymmetric synthesis of indolines using

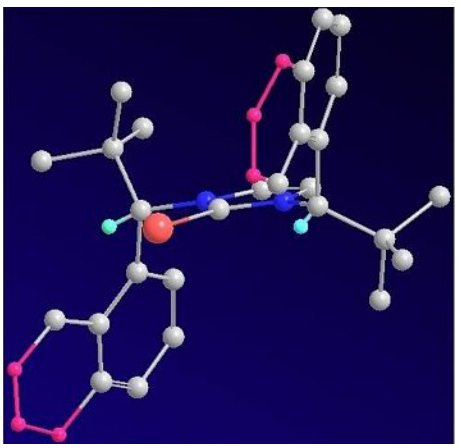

Fig. 1. Partial X-ray structure of (*S,S*)-**3** showing the arrangement of Pd-NHC ligand. In pink, the modeled modification by naphthyl fragment to extend the aryl plane.

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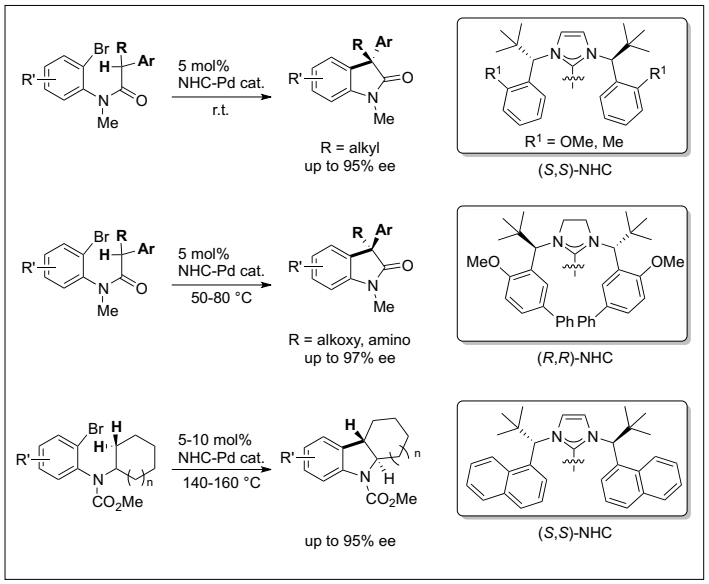
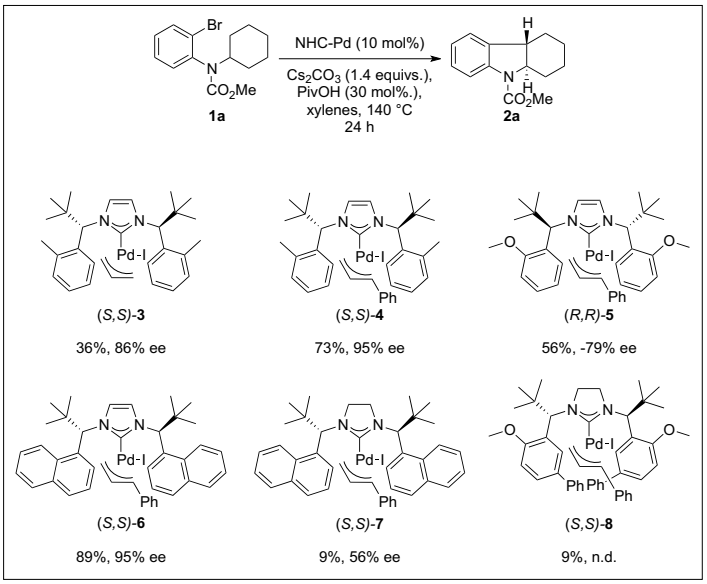


Scheme 1. Asymmetric synthesis of 3,3-disubstituted oxindoles and 2,3-fused indolines by Pd-NHC catalysis.



Scheme 2. Screening of chiral Pd-NHC catalysts.

N-cyclohexyl substituted carbamate **1a** as an initial substrate. A first promising result was obtained by applying Fujii and Ohno's protocol with NHC-Pd complex **3** (Scheme 2).[8a] Further significant improvement of both yield and enantiomeric excess was found, when η^3-allyl complex **3** was replaced by the more reactive η^3-cinnamyl complex **4**.[12] Pd-NHC complex **5**, incorporating the chiral NHC ligand with *ortho*-methoxy phenyl groups, was less efficient in terms of reactivity and enantioselectivity. Finally, 1-naphthyl substituted Pd-NHC complex **6** improved stability at higher temperatures and gave better yield. In contrast, we note that 4,5-dihydroimidazolium derived Pd-NHC catalysts lacked stability at high temperature. Thus, complexes **7** and **8** gave product **2a** only in very poor yields. This was also indicated by the observation that Pd-NHC complex **7** decomposed with precipitation of palladium black when heated in xylenes at 140 °C for 30 min, while Pd-NHC complex **6** was recovered unchanged under the same conditions.

Substrate Scope

Based on the results from ligand screening, the optimum NHC ligand precursor **9** was selected for generating the Pd-NHC catalyst *in situ*. The conditions using an *in situ* generated catalyst in the presence of cesium pivalate as additive and cesium carbonate as base in dry xylenes as solvent afforded the fused indoline **2a** in good yield with high enantioselectivity (Scheme 3). This result fits closely to the one obtained with the preformed Pd-NHC complex as catalyst. We succeeded in reducing the catalyst loading and reaction time to 5% and 3 hours by raising the reaction temperature to 160 °C using mesitylene as solvent instead of xylenes. Gratifyingly, the level of yields and asymmetric induction remained unchanged under these conditions with most of the substrates (Scheme 3). The ring size of the cycloalkane moiety is important in this system. For instance, C–H activation of the *N*-cyclopentyl carbamate derivative did not proceed at all (Scheme 4). On the contrary, *N*-cycloheptyl group gave a better yield with higher asymmetric induction than the *N*-cyclohexyl one.

The absolute configuration of indolines **2** was determined through an X-ray crystallographic analysis of indoline **10**.[4a] The X-ray structure of indoline **10** shows the (5a*S*,10a*R*) configuration (Fig. 2). Thus, the absolute configuration of all indolines **2** was assigned by comparison of the circular dichroism (CD) spectra with that of **2o**.

Mechanism

The mechanism proposed for this transformation is shown in Scheme 5. First, a Pd(II)-NHC complex is formed by reaction with NHC-HI and [Pd(η^3-cinnamyl)Cl]$_2$ in the presence of cesium pivalate. The generated Pd(NHC)(η^3-cinnamyl)I

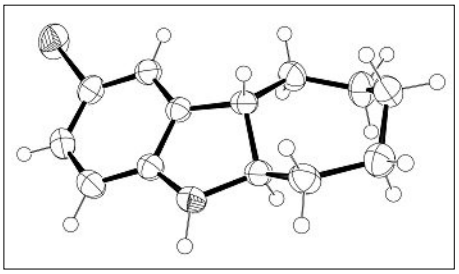
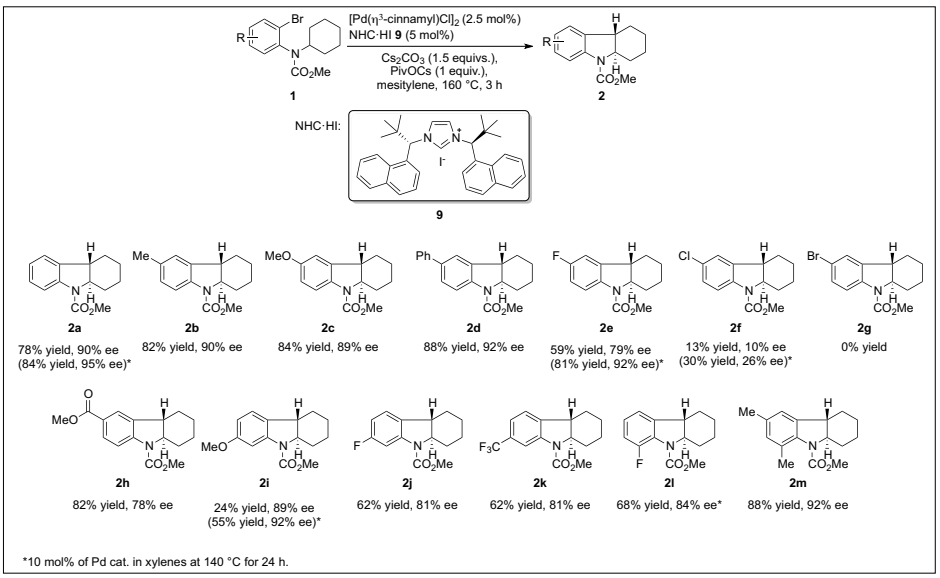
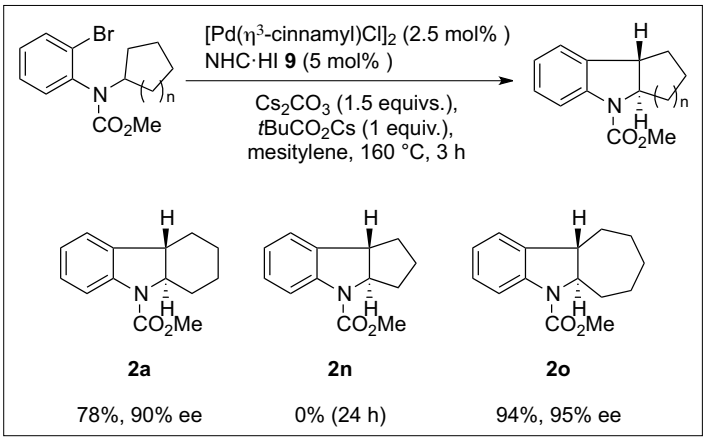


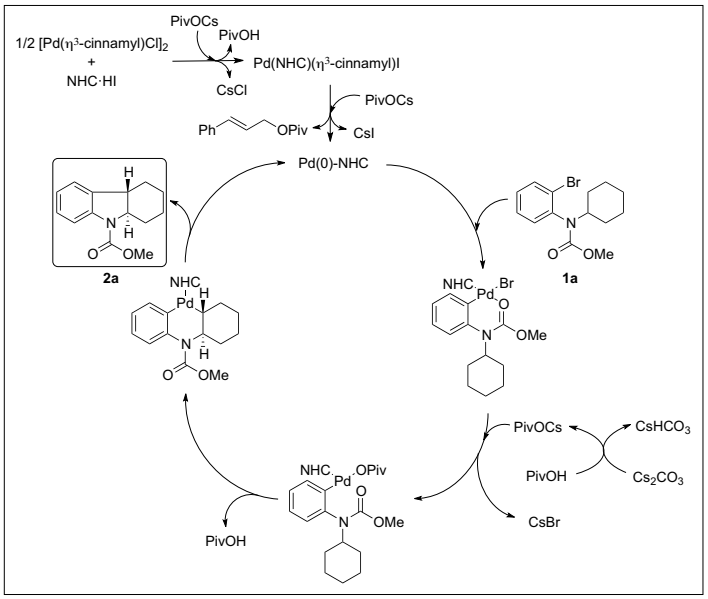
Fig. 2. X-ray structure of 2-bromo-fused indoline **10**.



Scheme 3. Substrate scope in asymmetric 2,3-fused indoline synthesis with NHC precursor **9**.



Scheme 4. Effect of alkane ring size in asymmetric synthesis of fused indolines.



Scheme 5. Plausible catalytic cycle in asymmetric fused indoline synthesis

complex is reduced by nucleophilic attack of pivalate anion onto the cinnamyl group to generate the Pd(0)-NHC species.[12] Oxidative addition of carbamate **1a** forms the palladacycle intermediate followed by bromide ligand exchange for pivalate.[13] The key C(sp^3)–H activation step consists in an inner-sphere pivalate-assisted concerted metalation-deprotonation (CMD) pathway.[3f] On the methylene site, one only of the two enantiotopic C(sp^3)–H enters the reaction to give the *trans*-fused product selectively and regeneration of a Pd(0)-NHC species.

Conclusion

We successfully applied a library of sterically-bulky chiral NHC ligands to the straightforward synthesis of 2,3-fused indolines in a highly enantioselective fashion. This impressive methodology created a new direct pathway to access a variety of highly enantioenriched indolines involving the activation of the inert C(sp^3)–H bond. Currently, the expansion of this reaction to the nonfused 2- and 2,3-substituted chiral indolines is in progress.

Acknowledgements

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