C–H Activation

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Fused Indolines by Palladium-Catalyzed Asymmetric C–C Coupling Involving an Unactivated Methylene Group**

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In memory of Keith Fagnou

The field of palladium-catalyzed cross-coupling reactions was honored by the 2010 Nobel Prize in Chemistry which was awarded to the pioneers R. Heck, E. Negishi, and A. Suzuki. This thus reflected the tremendous importance of this family of reactions in organic synthesis. Initially focused on C–C bond formation between C(sp) and C(sp^2) centers, cross-coupling reactions subsequently evolved to include the formation of C(sp^2)–N and C(sp^2)–O bonds and most recently the formation of C–C bonds involving C(sp^3) centers. C–C bond formation typically requires the activation of the coupling partners either in the form of a C–X and/or a C–M precursor. The past decade has seen the emergence of coupling reactions with C–H centers, which thus bypasses the preparation of functionalized substrates.[1] The use of unactivated C(sp^3)–H alkyl groups remains a major challenge, however, even though some progress has been made recently in this area.[2] Asymmetric reactions would be an additional exceptionally powerful tool in this area, but to our knowledge efficient coupling reactions that distinguish between two enantiotopic C–H bonds in an unactivated methylene group have not been reported.[3] Herein we describe a successful approach to this transformation.

The indoline motif is found in a large number of natural products and pharmaceuticals, and diverse strategies for their synthesis have been developed.[4] The important subgroup of fused indoline-containing natural products has received much attention.[5] New routes of access to indolines by palladium-catalyzed functionalization of unactivated C(sp^3)–H alkyl groups are detailed in very recent literature reports.[6]

N-heterocyclic carbenes (NHCs) are outstanding nucleophilic catalysts in organic synthesis and electron-rich ligands in transition-metal-catalyzed transformations.[7] Conversely, chiral NHC ligands that lead to high asymmetric induction are still scarce.[8] The wedge shape of NHC ligands, the absence of a chiral backbone (which controls chiral induction in chelating ligands), and the difficulty of placing stereocontrol elements in a monodentate ligand at appropriate positions near the metal center represent major challenges. We have reported new chiral NHC ligands derived from chiral *o*-substituted α-alkylphenethyl amines. They perform very well in the intramolecular arylation of amides[9] to give highly enantioenriched 3-aryl-3-alkyl-, 3-aryl-3-alkoxy-, and 3-aryl-3-amino-oxindoles.[10] We report here on the highly enantioselective synthesis of fused indolines using members of the same family of chiral NHC ligands.

We started our study with the *N*-cyclohexyl-substituted carbamate **1a**. Under the conditions we used previously for reactions of oxindoles ($Pd(dba)_2$/NaO*t*Bu/DME/RT) indoline **2a** was formed in traces only. The first encouraging result was obtained using the protocol developed by Fujii, Ohno, and coworkers[6a] (Table 1, entry 1). *trans* Fusion in product **2a** was indicated by the 12 Hz coupling constant in the ^{1}H NMR spectrum, confirming the previous assignment.[6a,11] Both the yield and enantiomeric ratio of products increased strongly when, in place of the η^3-allyl complex **3**, the more reactive η^3-cinnamyl palladium complex (*S*,*S*)-**4** was used (Table 1, entry 2). It is noteworthy that in the absence of pivalic acid as an additive, only traces of product were observed.[12] The reaction did not proceed at lower temperature (110 °C). Complex (*R*,*R*)-**5**, incorporating the enantiomeric NHC ligand with *o*-OMe aryl groups, afforded *ent*-**2a** as the major product (Table 1, entry 3).

In a previous paper, we reported the X-ray structure of complex **3**. The arrangement of the Pd–carbene ligand fragment is shown in Figure 1. The minimization of allylic ($A^{1,3}$) strain, both in the Pd-C-N-C-H part and in the H-$C_{benzylic}$-C_{Ar}-C_{ortho}-CH_3 parts of the ligand, position the stereocontrol elements of the NHC ligand in the complex (Figure 1).[10c] We hypothesized that the substitution of the *ortho*-Me group by a fused aromatic ring could make the ligand even better. Indeed the naphthyl-NHC complex showed improved stability at elevated temperatures, and this had a beneficial effect on the yield of the coupling reaction (Table 1, entry 4). Conversely, we found that 4,5-dihydroimidazolium-derived NHC–palladium complexes **7** and **8** lacked robustness at high temperature and gave product **2a** in very poor yield (Table 1, entries 5 and 6).[13]

Consequently, compound **9**, the precursor of the most efficient NHC ligand, was chosen for the in situ generation of a palladium–NHC catalyst. This protocol was investigated because it would simplify the operational procedure. Experimentation showed that using an in situ generated catalyst in the presence of cesium pivalate and cesium carbonate in xylenes as solvent gave **2a** in good yield with high asymmetric

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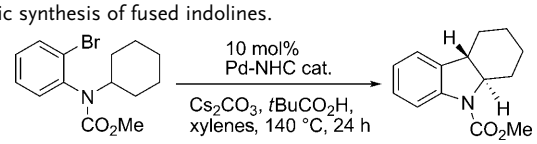
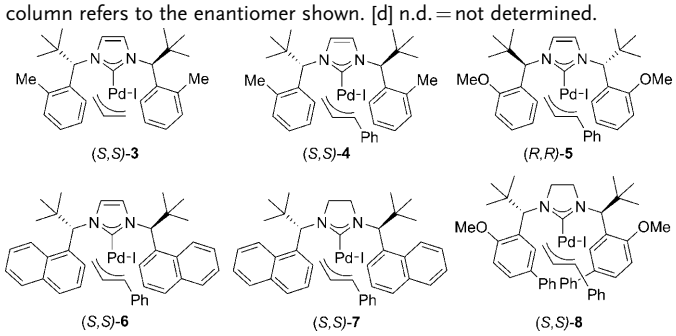
Table 1: Screening of chiral NHC–palladium precursors in the asymmetric synthesis of fused indolines.



1a **2a**

Entry[a]	Pd–NHC	Yield [%][b]	e.r.[c]
1	(*S*,*S*)- **3**	36	93:7
2	(*S*,*S*)- **4**	73	97.5:2.5
3	(*R*,*R*)- **5**	56	10:90
4	(*S*,*S*)- **6**	89	97.5:2.5
5	(*S*,*S*)- **7**	9	78:22
6	(*S*,*S*)- **8**	9	n.d.[d]

[a] Reaction conditions: **1a** (0.2 mmol), Pd–NHC complex (0.02 mmol), pivalic acid (0.06 mmol), cesium carbonate (0.3 mmol), dry xylenes (2 mL). [b] Yield of product isolated after flash column chromatography. [c] The enantiomeric ratio was determined by HPLC on a chiral stationary phase (Chiralcel OD-H, *n*-hexane/*i*PrOH 99:1, 0.5 mL min^{-1}). The left column refers to the enantiomer shown. [d] n.d. = not determined.



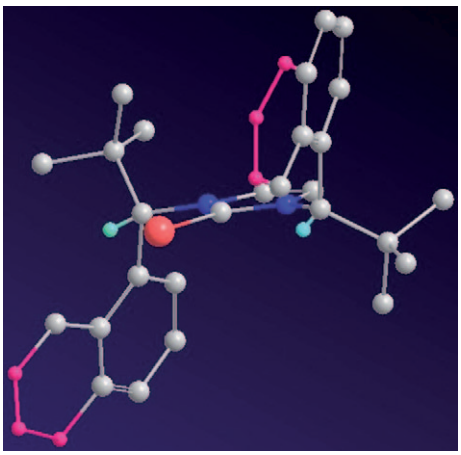
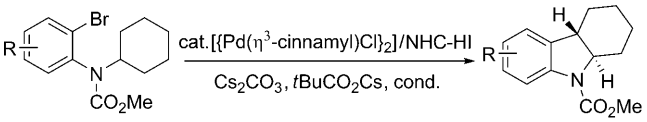


Figure 1. Part of the X-ray structure of (*S*,*S*)-**3** showing the Pd–NHC ligand arrangement. In pink, the modeled modification of the ligand in which a naphthyl fragment is used to extend the aryl plane.

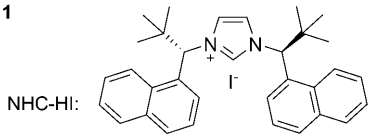
induction (Table 2, entry 1). The results closely match those obtained with the pre-assembled NHC–Pd catalyst (Table 1, entry 6). The yield dropped when catalyst loading was reduced (entry 2).

Extension to substituted aniline precursors showed that under these reaction conditions a fluoro group (Table 2,

Table 2: Chiral palladium–NHC catalyzed asymmetric synthesis of fused indolines **2** from carbamates **1**.



1 **2**



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Entry	Substr.	R	Cond.[a] *T* [°C]/*t* [h]	Prod.	Yield [%][b]	e.r.[c]
1	**1a**	H	140/24	**2a**	84	97.5:2.5
2	**1a**	H[d]	140/24	**2a**	39	96:4
3	**1a**	H	160/3	**2a**	78	95:5
4	**1b**	4-Me	160/3	**2b**	82	95:5
5	**1c**	4-MeO	160/3	**2c**	84	94.5:5.5
6	**1d**	4-Ph	160/3	**2d**	88	96:4
7	**1e**	4-F	140/24	**2e**	81	96:4
8	**1e**	4-F	160/3	**2e**	59	90:10
9	**1f**	4-Cl	140/24	**2f**	30	63:37
10	**1f**	4-Cl	160/3	**2f**	13	55:45
11	**1g**	4-Br	140/24	**2g**	0[e]	n.d.
12	**1h**	4-CO_2Me	160/3	**2h**	82	89:11
13	**1i**	5-MeO	140/24	**2i**	55	96:4
14	**1i**	5-MeO	160/3	**2i**	24	90:10
15	**1j**	5-F	160/3	**2j**	70	93:7
16	**1k**	5-CF_3	160/3	**2k**	62	90:10
17	**1l**	6-F	140/24	**2l**	68	92:8
18	**1m**	4,6-Me_2	160/3	**2m**	88	96:4

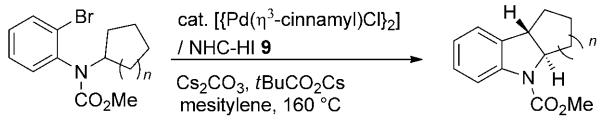
[a] Conditions for reaction carried out at 140 °C : **1** (0.2 mmol), [{Pd(η^3-cinnamyl)Cl}$_2$] (0.01 mmol), NHC-HI (0.02 mmol), cesium pivalate (0.2 mmol), cesium carbonate (0.3 mmol), dry xylenes; conditions for reactions carried out at 160 °C: **1** (0.2 mmol), [{Pd(η^3-cinnamyl)Cl}$_2$] (0.005 mmol), NHC-HI (0.01 mmol), cesium pivalate (0.2 mmol), cesium carbonate (0.3 mmol), dry mesitylene. [b] Yield of product isolated after flash column chromatography. [c] Enantiomeric ratios were determined by HPLC on a chiral stationary phase. The left column refers to the enantiomer shown. [d] [{Pd(η^3-cinnamyl)Cl}$_2$] (2.5 mol%), NHC-HI (5 mol%). [e] 0.1 mmol scale.

entry 8) is tolerated, but, not surprisingly, chloro and bromo groups are not (Table 2, entries 9 and 11). Before extending this study further, we reduced the catalyst loading and reaction time to 5% and 3 h, respectively, and increased the reaction temperature to 160 °C (mesitylene as solvent). Gratifyingly, the yields and asymmetric induction remained high (Table 2, entries 3–6).

Substrates with donor substituents at C4 gave improved product yields (Table 2, entries 4–6). In contrast, electron-withdrawing groups at C4 decreased both product yields and enantioselectivities (Table 2, entries 7–12). A methoxy group at C5 reduced the product yield (Table 2, entries 13 and 14). Fluoro and trifluoromethyl groups are reasonably well tolerated (Table 2, entries 15 and 16). Finally, entries 17 and 18 show that the reaction can be performed with 6-substituted carbamates.

The size of the cycloalkyl ring is crucially important in this system. Thus, C–H activation of the *N*-cyclopentyl carbamate derivative did not proceed at all (Table 3, entry 2). By

Table 3: Asymmetric synthesis of fused indolines **2** from carbamates **1**.



1a,n,o **2a,n,o**

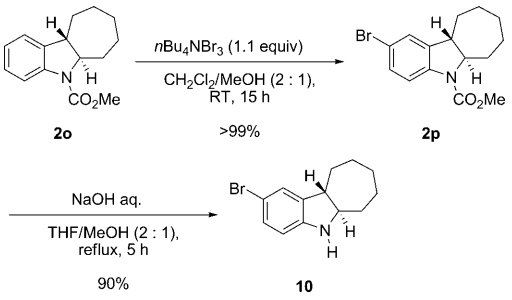
Entry[a]	Substr.	*n*	*t* [h]	Product (yield %)[b]	e.r.[c]
1	**1a**	2	3	**2a** (78)	95:5
2	**1n**	1	24	**2n** (0)	–
3	**1o**	3	3	**2o** (94)	97.5:2.5
4[d]	**1o**	3	3	**2o** (88)	97.5:2.5

[a] Reaction conditions: **1** (0.2 mmol), [{Pd(η³-cinnamyl)Cl}$_2$] (0.005 mol%), NHC-HI (0.01 mol%), cesium pivalate (0.2 mmol), cesium carbonate (0.3 mmol), mesitylene. [b] Yield of isolated product. [c] Enantiomeric ratios were determined by HPLC on a chiral stationary phase. The left column refers to the enantiomer shown. [d] 1 mmol scale.

contrast, *N*-cycloheptyl-substituted substrates gave better yields and an even higher asymmetric induction than the *N*-cyclohexyl (Table 3, entries 3 and 4).

The absolute configuration of the fused indolines was determined by an X-ray structural analysis of **10**, which was obtained by hydrolysis of carbamate **2p**. All other indolines were assigned configurations by analogy. As **2p** was not accessible directly, it was formed from **2o** by reaction with tetra-*n*-butylammonium tribromide (Scheme 1). The X-ray structure shows **10** to have the 5a*S*,10a*R* configuration (Figure 2).[14]

We propose the reaction mechanism shown in Scheme 2. The palladium dimer, [{Pd(η³-cinnamyl)Cl}$_2$, is cleaved by the NHC ligand. The latter is generated in situ from NHC-HI and



Scheme 1. Bromination of fused indoline **2o**.

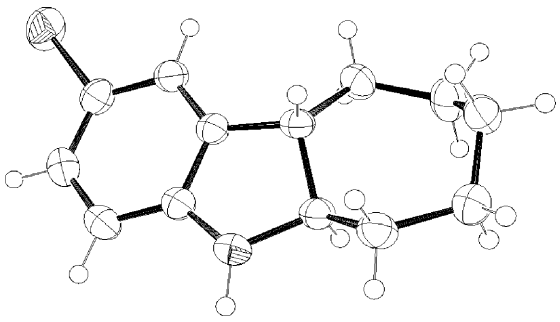
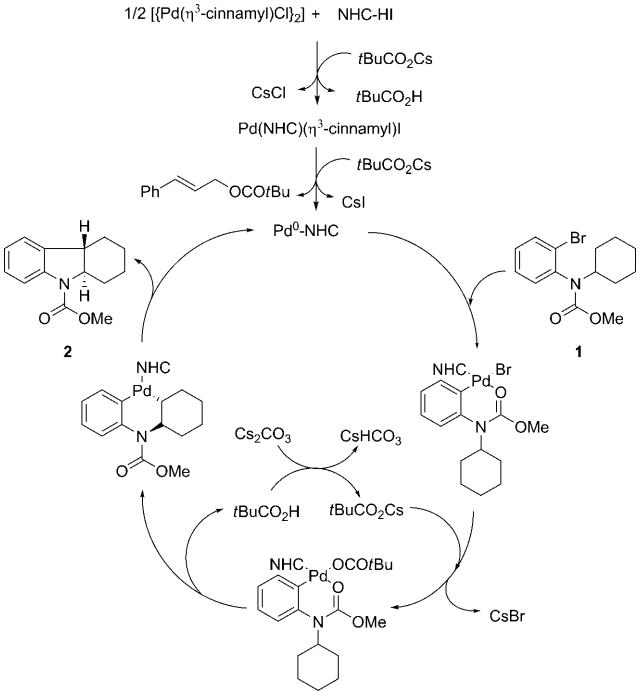


Figure 2. X-ray structure of fused indoline (−)-(5a*R*,10a*S*)-**10**.[15]



Scheme 2. Proposed catalytic cycle for the synthesis of fused indolines **2**.

cesium pivalate. Nucleophilic addition of pivalate to the cinnamyl ligand followed by alkene dissociation generates the Pd^0–NHC catalyst.[15] Oxidative addition of carbamate **1** and bromide/pivalate exchange is followed by C–H bond activation and reductive elimination to produce the fused indoline **2** and regenerate the catalyst. An excellent mechanistic analysis of the C–H bond-activation step has been reported by Rousseaux et al.[2f]

In summary, chiral NHC ligands derived from chiral 2,2-dimethyl-1-arylpropane-1-amines were successfully applied to the synthesis of highly enantioenriched *trans*-fused indolines by palladium-catalyzed C–H activation. The reaction requires temperatures of 140–160 °C. It is extraordinary that despite the high temperature, this transformation occurs through high asymmetric recognition of an enantiotopic C–H bond in an unactivated methylene unit.

Experimental Section

Representative procedure for the asymmetric synthesis of indoline **2**: [{Pd(η³-cinnamyl)Cl}$_2$] (2.5 mol%), cesium pivalate (0.2 mmol), and NHC-HI (5 mol%) were introduced to a Schlenk tube. After evacuation of the tube and backfilling with nitrogen, anhydrous mesitylene (2 mL) was added and the mixture was stirred for 30 min. Methyl carbamate **1** (0.2 mmol) and cesium carbonate (0.3 mmol) were added next and the reaction mixture was heated to 160 °C and stirred at this temperature for 3 h. The reaction mixture was cooled to room temperature, diluted with dichloromethane (2 mL), and then filtered through a pad of celite. Volatiles were removed in vacuo and the crude product was purified by flash column chromatography (eluent: ethyl acetate/pentane) to afford the fused indoline **2**.

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[14] CCDC 821885 ((−)-(5a*R*,10a*S*)-**10**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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