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Enantioselective synthesis of 2-methyl indolines by palladium catalysed asymmetric C(sp^3)–H activation/cyclisation†

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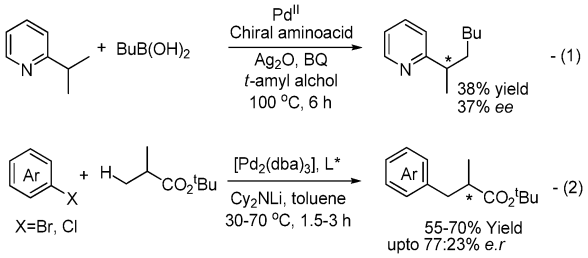
The first example of the enantioselective methyl C–H activation by an intramolecular ArPdX species and subsequent cyclisation was developed. Palladium catalysts using commercially available chiral diphosphines yield good ee's (up to 93% ee) in the synthesis of 2-methyl indolines from 2-halo *N*-isopropyl anilides. This approach was also employed for the synthesis of enantioenriched cyclohexyl fused indolines with moderate enantioselectivities.

Chiral 2-substituted indolines are common structural subunits found in numerous natural products and biologically active compounds.[1] The various routes for the synthesis of this class of compounds have been recently summarized.[2] The general and effective methods for the catalytic asymmetric synthesis of 2-substituted indolines are rare, and mainly used the asymmetric hydrogenation of 2-alkyl indoles[3] as well as the intramolecular amination reactions.[4] We wish to describe a new approach where a chiral palladium catalyst controls the enantioselective C(sp^3)–H activation of a methyl group and a subsequent aryl cyclisation.

Among the various classes of palladium catalysed C–H activation reactions,[5] the transformation of C(sp^3)–H bonds has received significant attention in past several years.[6] In this context, Ohno *et al.* recently described an interesting strategy towards the synthesis of an indoline skeleton *via* a palladium catalysed C(sp^3)–H bond activation and subsequent cyclisation in the presence of caesium carbonate as a base and pivalic acid as an additive.[7] It was discussed earlier by Fagnou *et al.* who proposed that coordinated pivalic acid is involved in the key step for the removal of hydrogen from the methyl group in a similar class of reactions.[8] More studies were reported on related processes depicting various kinds of intramolecular cyclisation reactions on substrates devoid of nitrogen in the absence of pivalic acid.[9]



Scheme 1 Enantioselective intermolecular methyl C–H activation.

The enantioselective version of such palladium catalysed alkyl C–H activation processes was unknown when we started our investigation. However, the asymmetric transformations involving the insertion of metal bound carbenes/nitrenes into C(sp^3)–H bonds have been well documented.[10] In 2008, Yu *et al.* described the first example of the palladium catalysed asymmetric C(sp^3)–H activation involving the methyl group of 2-propylpyridine to yield the butylated product in 37% ee (Scheme 1, eqn (1)).[11] Recently, Baudoin and co-workers reported a Pd(0) catalysed asymmetric β-arylation of methyl C–H bonds of carboxylic esters with aryl halides in the presence of a chiral ligand related to davephos (Scheme 1, eqn (2)).[12]

To the best of our knowledge, there are no reports available on the enantioselective methyl C–H activation by an intramolecular ArPdX species. While preparing this manuscript, Kündig *et al.* reported an interesting palladium catalysed asymmetric activation of methylene C(sp^3)–H bonds for the synthesis of fused indolines by using chiral NHC ligands.[13] The main hurdle associated with palladium catalysed C(sp^3)–H activation processes is the relatively high reaction temperature under which most of the chiral ligands fail to promote the favored reaction pathway.[6b] Herein we report a palladium catalysed intramolecular enantioselective activation of methyl C–H bonds using commercially available chiral diphosphines leading to the synthesis of chiral 2-methyl indolines (Scheme 2).

We started our experiments with the synthesis of *rac*-2-methyl indoline **2a** from **1a** as described by Ohno *et al.* using PCy·HBF$_4$ as the achiral ligand.[7] Then the attempts for asymmetric cyclisations were performed using a number of chiral ligands and the initial trials delivered slight enantioselectivities.[14] We were delighted to observe a significant enantiomeric excess in some cyclisations using chiral diphosphines (*S*,*S*)-DIOP and

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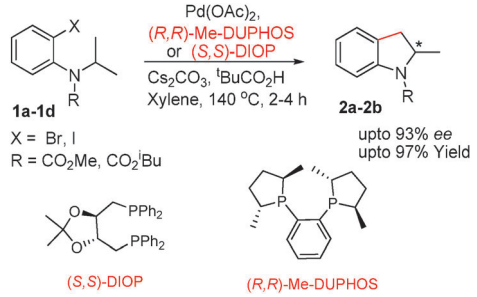
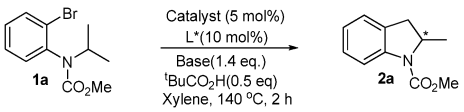


Scheme 2 Enantioselective intramolecular methyl C–H activation.

Table 1 Screening studies on **1a** as a substrate with various Pd catalysts/ligands/bases[a]



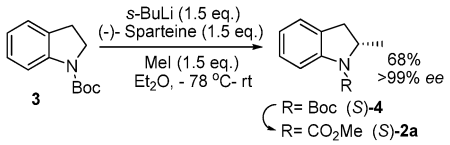
Entry	Catalyst	Ligand (L*)	Base	Yield%[b]	ee[b] (%)
1	$Pd_2(dba)_3$	(*R*,*R*)-DIOP	Cs_2CO_3	> 99	47
2	$Pd_2(dba)_3$	(*S*,*S*)-Me-DUPHOS	Cs_2CO_3	80	84
3	$Pd(OAc)_2$	(*S*,*S*)-DIOP	Cs_2CO_3	> 99	48
4	$Pd(OAc)_2$	(*R*,*R*)-DIOP	Cs_2CO_3	97	44[c]
5	**$Pd(OAc)_2$**	**(*R*,*R*)-Me-DUPHOS**	**Cs_2CO_3**	**> 99**	**93**
6	**$Pd(OAc)_2$**	**(*S*,*S*)-Me-DUPHOS**	**Cs_2CO_3**	**> 99**	**93**[c]
7	$Pd(Oac)_2$	(*R*,*R*)-Me-DUPHOS	Et_3N	6	80
8	$Pd(OAc)_2$	(*R*,*R*)-Me-DUPHOS	K_2CO_3	61	58
9	$Pd(OAc)_2$	(*R*,*R*)-Me-DUPHOS	Na_2CO_3	No reaction	
10	$Pd(OAc)_2$	(*R*,*R*)-Me-DUPHOS	Cs_2CO_3	6	90[d]

[a] Procedure: ref. 15 [b] Determined by HPLC analysis. [c] Enantioselectivity reversed. [d] In toluene at 100 °C.

(*R*,*R*)-Me-DUPHOS. However the lack of reproducibility of these results prompted us for further optimization studies with $Pd(OAc)_2$/DIOP or Me-DUPHOS combination. After a series of experiments[14] we found effective conditions for the enantioselective methyl C–H activation and cyclisation. During our studies, it was observed that argon is not necessary for this reaction. Using this modified procedure,[15] the reaction of **1a** was repeated with various catalysts, ligands and bases. These results are summarized in Table 1. Best results were obtained with $Pd(OAc)_2$/Me-DUPHOS/Cs_2CO_3 combinations (entries 5 and 6). The effort to lower the reaction temperature by carrying out the reaction in toluene (100 °C) resulted in poor yield (entry 10). The scale up reaction using 1 g of the substrate **1a** and (*S*,*S*)-DIOP as a ligand also gave substantially good results.[14]

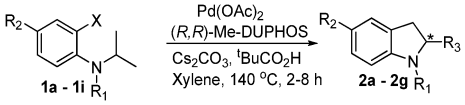
The absolute configuration of the product **2a** was assigned by correlation with the known compound (*S*)-**4**. The compound (*S*)-**4** was prepared by Beak's procedure of asymmetric deprotonation/methylation of *N*-Boc indoline **3** in the presence of *s*-BuLi/Sparteine.[16] The original procedure was slightly modified by replacing cumene by diethyl ether as solvent and dimethyl sulfate by methyl iodide. Hydrolysis of (*S*)-**4** followed by treatment with methyl chloroformate gave (*S*)-**2a** (Scheme 3).

We briefly investigated the scope of the palladium catalysed methyl C–H activation/cyclisation reaction with various 2-halo-*N*-alkyl anilide derivatives (Table 2). The iodide **1b** delivered the indoline **2a** in 82% yield and 90% ee (entry 2),



Scheme 3 Synthesis of (*S*)-2-methyl indolines.[16]

Table 2 Asymmetric cyclisation of various substrates[a]



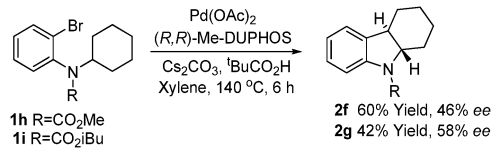
Entry	Substrate	Time/h	Product	Yield%[b]	ee[c] (%)
1	**1a** X=Br, R=CO_2Me	2	(*S*)-**2a**	97	93
2	**1b** X=I, R=CO_2Me	4	(*S*)-**2a**	82	90
3	**1c** X=Cl, R=CO_2Me	16	(*S*)-**2a**	nr[d]	—
4	**1d** X=Br, R=$CO_2{}^iBu$	2	(*S*)-**2b**	80	55
5	rac-**1e**	3	(**S**)-**2c**	65	23
6	**1f**	3	(**S**)-**2d**	84	85
7	**1g**	16	**2e**	nr[d]	—

[a] Under optimized conditions (ref. 15). [b] Isolated yields. [c] Determined by HPLC analysis. [d] No reaction, starting material recovered.

while the reaction of chloro substrate **1c** resulted in complete recovery of the starting material (entry 3). The isobutylcarbamate **1d** and the fluoroaniline derivative **1f** also afforded the expected products (*S*)-**2b** and (*S*)-**2d**, respectively, with good yields and reasonable enantioselectivities (entries 4 and 6). Interestingly, the C–H activation of the *N*-*sec*-butylaniline derivative (*rac*)-**1e** regioselectively proceeded at the methyl group to afford 2-ethylindoline (*S*)-**2c** with 23% ee (entry 5). The unreactivity of *N*-propyl substrate **1g** (entry 7) to afford 3-methyl indoline **2e** *via* C(sp^3)–H activation at the secondary carbon was correlating with Fagnou's observations for a similar kind of reaction.[8b]

We have also examined the possibility of the palladium catalysed C(sp^3)H–activation/cyclisation reaction involving a methylene group leading towards the synthesis of fused indolines. Upon treatment of *N*-cyclohexyl derived substrates **1h** and **1i** under similar reaction conditions,[15] the expected C–H activation/cyclization proceeded smoothly to yield the corresponding *trans*-fused products **2f** and **2g** in moderate ee's (Scheme 4).

In conclusion, we have developed a novel methodology for palladium catalysed asymmetric activation of methyl C–H



Scheme 4 Asymmetric cyclisation towards fused indolines.[17]

bonds by using commercially available chiral diphosphine ligands and subsequent cyclisation leading to the synthesis of chiral 2-methyl indolines with ee's up to 93%. This is the first example of the enantioselective methyl C–H activation by an intramolecular ArPdX species. We have also successfully employed this approach for the synthesis of enantioenriched cyclohexyl fused indolines with moderate enantioselectivities. More studies to explore the scope of the reaction over a range of substrates and the use of chiral carboxylic acids as ligands and/or additives in this kind of reactions are in progress.[18]

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14 For more details, see ESI†.

15 Optimized procedure: 0.2 mmol of substrate, 5 mol% catalyst, 10 mol% ligand, 1.4 eq. base and 0.5 eq. $^tBuCO_2H$ were taken in a 10 mL RB flask equipped with a reflux condenser. To this, xylene (2.0 mL) was added in an open atmosphere and mixed well under stirring at room temperature. The reaction mixture was stirred further for 2 h at 140 °C. After cooling, the reaction mixture was concentrated *in vacuo* and crude material was purified by silica gel chromatography with the pentane/ethyl acetate mixture to afford the corresponding indolines.

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17 *trans*-Stereochemistry assigned by comparing with the compound in ref. 7.

18 When the reaction depicted in entry 1 (Table 2) was repeated with (0.5 eq.) *N*-Boc-L-Valine instead of pivalic acid, we observed traces of formation of **2a** with 30% ee even in the absence of a phosphine ligand. This experiment provided further evidence for the involvement of carboxylic acid additive in the catalytic cycle.