Asymmetric C(sp³)-H/C(Ar) coupling reactions. Highly enantio-enriched indolines via regiodivergent reaction of a racemic mixture†

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Received 26th January 2012, Accepted 21st February 2012
DOI: 10.1039/c2sc20111a

N-Aryl, N-branched alkyl carbamates react with in situ generated chiral Pd-NHC catalysts by coupling a Pd-Ar moiety with an aliphatic C–H bond at high temperature to give enantioenriched 2-substituted and 2,3-disubstituted indolines. Prochiral precursors give single products with very high asymmetric induction. Chiral racemic precursors react in a regiodivergent reaction of a racemic mixture to yield enantioenriched indolines resulting from either methyl C–H activation or asymmetric methylene C–H activation. In favorable cases this can result in a complete separation of an enantiomeric mixture into two different highly enantioenriched indolines.

Introduction
Numerous natural products and biologically active compounds incorporate the indoline heterocyclic ring system and the literature abounds with approaches to its synthesis.1,2 In this field, one frontier route receiving much attention focuses on the asymmetric synthesis of 2- and 3-substituted indolines.2,3 In pioneering work, the group of Ohno and Watanabe reported an indoline synthesis via Pd catalyzed intramolecular coupling of N-aryl, N-alkyl carbamates.4 We subsequently developed the first highly asymmetric coupling reaction involving an unactivated methylene C–H bond (Scheme 1).5–7

Asymmetric induction in this coupling relied on either preformed- or in situ generated Pd-catalysts incorporating chiral N-heterocyclic carbene (NHC) ligands where the stereodirecting elements were judiciously placed by the avoidance of A1,3-strain.8 The high thermal stability of the catalysts, the role of the Pd-bound pivalate as internal base in the C–H activation step,9

Table 1 Asymmetric synthesis of 2- and 2,3-substituted indolines 2

<table>
<thead>
<tr>
<th>Entry</th>
<th>S.M.</th>
<th>R</th>
<th>Product</th>
<th>Yield (%)</th>
<th>ee°</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>H</td>
<td>2a</td>
<td>84</td>
<td>89</td>
</tr>
<tr>
<td>2</td>
<td>1a</td>
<td>H</td>
<td>2a</td>
<td>86</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>1b</td>
<td>Me</td>
<td>2b</td>
<td>92</td>
<td>97</td>
</tr>
<tr>
<td>4</td>
<td>1c</td>
<td>Et</td>
<td>2c</td>
<td>91</td>
<td>95</td>
</tr>
<tr>
<td>5°</td>
<td>1d</td>
<td>Ph</td>
<td>2d</td>
<td>96</td>
<td>98</td>
</tr>
</tbody>
</table>

+ Reaction conditions: [Pd(n-cinnamyl)Cl]2 (2.5 mol%), NHC-HI (5 mol%), carbamate 1a (0.2 mmol), cesium pivalate (0.2 mmol), C2H5CO3 (0.3 mmol), dry mesitylene (2 mL). † Isolated yield of pure material. ‡ Enantiomeric excess (ee) was determined by chiral HPLC, see ESI. ‡ These authors contributed equally.
and the region- and stereo-control exercised by the monodentate NHC-ligands were crucial for success.

In the present article we focus our attention on the synthesis of enantoenriched 2-substituted and 2,3-disubstituted indolines. While this work was in progress, the asymmetric synthesis of 2-methylindoline via the same sequence but using chiral phosphine ligands was reported by Kagan and co-workers. Highly enantoenriched 2-methylindoline was obtained with a Pd/((R),R) Me-DUPHOS catalyst. Attempts to extend the reaction to other members of this class of compounds met with very limited success. After submission of this manuscript, a communication by Cramer and coworkers appeared which detailed a more extensive study to a wide range of highly enantoenriched indolines. The authors used new, sterically demanding monodentate phosphines, bulky carboxylic acids, and Na3PO4 as base in the Pd-catalyzed C(sp3-H) activation to give indolines.

Results and discussion

Substrates 1a–1d and 6a–6k for the coupling reactions detailed below were prepared readily by either reductive amination of ketones with o-bromoaniline or Pd-catalyzed amination of 1,2-dibromobenzene (see ESI†). Table 1 summarizes the results of our reactions with the prochiral substrates 1a–1d. 2-Methylindoline (2a) was obtained in high yield with good enantioselectivity (Table 1, entry 1). Higher catalyst loading did not improve the yield and enantioselectivity in this system (entry 2). Product yield increased and asymmetric induction strongly increased with the N-3-isopentyl carbamate 1b and N-3-isooctyl carbamate 1c where the cyclization engaged not a methyl group but a C–H bond of a methylene unit (entries 3 and 4). We note that Me activation in 1b would have led to the formation of a 6-membered ring product (a 2-ethyl-1,2,3,4-tetrahydroquinoline derivative). This was completely absent in the crude product.

Table 2 Pd-catalyzed synthesis of indolines from rac-6a

<table>
<thead>
<tr>
<th>Entry</th>
<th>L</th>
<th>Ratio 7a : 8a (ee)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>PCy3·HBF&lt;sub&gt;4&lt;/sub&gt;</td>
<td>100 : 0</td>
<td>90</td>
</tr>
<tr>
<td>2&lt;sup&gt;d&lt;/sup&gt;</td>
<td>IPr·HCl</td>
<td>100 : 0</td>
<td>90</td>
</tr>
<tr>
<td>3&lt;sup&gt;10&lt;/sup&gt;</td>
<td>(R,R) Me-DUPHOS</td>
<td>100 (~23) : 0</td>
<td>65</td>
</tr>
<tr>
<td>4&lt;sup&gt;e&lt;/sup&gt;</td>
<td>(S,S)-3</td>
<td>59 (68) : 35 (&gt;99)</td>
<td>94</td>
</tr>
<tr>
<td>5&lt;sup&gt;e&lt;/sup&gt;</td>
<td>(S,S)-4</td>
<td>57 (77) : 38 (&gt;99)</td>
<td>95</td>
</tr>
</tbody>
</table>

<sup>a</sup> The ratio of products (R)-7a and (2R,3S)-8a was determined by 1H-NMR. Enantiomeric excess (ee) was determined by chiral HPLC (AD-H column, n-hexane/i-PrOH = 99 : 1, 0.5 mL min<sup>−1</sup>), see ESI.†

<sup>b</sup> Isolated yield of the mixture of 7a and 8a.

<sup>c</sup> Reaction conditions: [Pd(OAc)<sub>2</sub> (10 mol%), PCy<sub>3</sub>·HBF<sub>4</sub> (20 mol%), carbamate 6a (0.2 mmol), pivalic acid (0.06 mmol), Cs<sub>2</sub>CO<sub>3</sub> (0.3 mmol), dry xylenes (2 mL).

<sup>d</sup> Reaction conditions: [Pd(η<sup>6</sup>–cinnamyl)Cl<sub>2</sub>] (5 mol%), IPr·HCl (10 mol%), carbamate 6a (0.2 mmol), cesium pivalate (0.2 mmol), Cs<sub>2</sub>CO<sub>3</sub> (0.3 mmol), dry xylenes (2 mL).

<sup>e</sup> Reaction conditions: [Pd(η<sup>6</sup>–cinnamyl)Cl<sub>2</sub>] (5 mol%), NHC·HCl (10 mol%), cesium pivalate (0.2 mmol), cesium pivalate (0.2 mmol), Cs<sub>2</sub>CO<sub>3</sub> (0.3 mmol), dry xylenes (2 mL).

As shown, and in accordance with the results obtained for fused indolines, the trans products 2b–2d were obtained exclusively. The stereochemical assignment in 2a was made by comparison with literature data and that in 2b and 2c was tentatively made on the basis of the similarity of the CD spectra with the trans-fused indolines. Differences in the CD spectrum of 2d initially
Table 3  Chiral NHC-palladium catalyzed regiodivergent RRM of carbamates 6 to give 2- and 2,3-substituted indolines 7 and 8

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2-substituted indolines to be the sole products. However, if the CH$_2$ group participates, two additional pairs of diastereomers of enantiomeric indolines may form (Fig. 1).

Initial results were sought for the reaction of 6a with triscyclohexylphosphine (Table 2, entry 1) and with an achiral NHC ligand (entry 2). In both cases methyl C–H activation was the exclusive reaction pathway. This was also observed by Anas, Cordi and Kagan with Me-DUPHOS (entry 3). It was expected since precedents show that C$_{sp3}$-H activation is easier in methyl groups than in methylene groups.

Interestingly, the chiral NHC ligands 3 and 4 generate two products, corresponding to both methyl- as well as methylene–C–H activation. In 6a, the former occurred with enantioselectivities around 70%, whereas the latter afforded trans-8a as an enantioomerically pure diastereomer (entries 4 and 5). The products of the reactions of 6a with the chiral NHC-Pd catalysts are the result of a regiodivergent reaction of a racemic mixture (regiodivergent RRM). No cis-products are formed in this reaction.

Product (R)-7a arises from the matched case of the reaction of substrate (S)-6a and catalyst Pd(S,S)-3 (or Pd(S,S)-4). It is formed in higher yield but lower enantioselectivity because the reaction of (R)-6a/Pd(S,S)-3 (or (R)-6a/Pd(S,S)-4), the mismatched pair, produces not only (2R,3S)-8a (catalyst control, excellent enantioselectivity), but also some (S)-7a. Fig. 2 shows a plot of the progress of the reaction. The ee values for (R)-7a and (R,3S)-8a are invariant over the course of the reaction.

The ligand precursors 3 and 4 were then applied to reactions with differently substituted substrates. This data is shown in Table 3.

The coupling reactions proceeded in high yields (81–99%). The 2,3-disubstituted indolines 8, when formed, were generated with excellent enantiomeric purity. As shown in entries 3–10,
functional groups in the chain are tolerated. Interestingly, substrate 6g (entries 11 and 12) reacts with very high selectivity. Both pairs, (R)-6g/PdL* and (S)-6g/PdL* providing products in high yield and asymmetric induction. The effect is that up to 93% of the engaged racemic starting material (6g) is transformed into close to equal portions of separable highly enantioenriched indolines having different substitution patterns (7g and 8g).

It follows from the above that starting with highly enantioenriched substrates, highly enantioenriched products may be obtained. This is demonstrated in Scheme 2. The reaction of (S)-6f with the (S,S)-3/Pd catalyst gives (S)-7f exclusively (matched case), whereas the reaction of (S)-6f with (R,R)-3/Pd gives a mixture of products thereby confirming our interpretation of the data in Table 3 that this is the mismatched pair and it is responsible for the modest ee of 7f in the reactions of rac-6f (Table 3, entries 9 and 10). An exception in this series is 6g. Here (S)-6g reacts to give (R)-7g selectively and (R)-6g reacts to give (2R,3S)-8g selectively.

A plausible catalytic cycle for this reaction has been proposed previously.4 The divergent regio- and diastereoselectivity takes place in the inner-sphere pivalate assisted concerted metatation-deprotonation (CMD) step,5 leading, after reductive elimination, to either the 2-substituted or the trans-2,3-disubstituted indolines. The N-protecting group in the enantioenriched carbamate 8g (98% ee) was successfully cleaved producing (2R,3S)-2-methyl-3-phenylindoline 9 in 92% yield without loss of enantiomeric purity (for details see Supporting Information†).

Conclusions

In summary, we have successfully applied bulky chiral monodentate NHC ligands to the conversion of readily accessible acyclic precursors into 2-substituted and 2,3-disubstituted indolines via palladium-catalyzed Ar-Br/unactivated C(sp 3)-H coupling. In substrates with symmetrical NCHR 2 groups, very highly asymmetric induction was obtained in those reactions where the catalyst had to distinguish between two enantiotopic methylene hydrogens. In substrates with NCHRR' groups, Pd phosphine and Pd-IPr catalysts showed strong preference for activation of a Me group. It was therefore unexpected to find that the bulky chiral Pd-NHC catalysts directed this transformation to a regiodivergent reaction of the racemic mixture. In the ideal case where competition was between C–H activation of a Me group versus C–H activation in a benzyl fragment the catalyst transformed one enantiomer of the racemic mixture into a highly enantioenriched indoline via CMe-H activation and the other enantiomer into an equally highly enantioenriched indoline via highly asymmetric C methylene-H activation. The inductions found for these homogenous catalytic reactions are all the more remarkable as they take place at high temperature. To our knowledge this also are the first examples of a direct synthesis of highly enantioenriched 2,3-trans-disubstituted indolines and of that of regiodivergent reactions of racemic mixtures involving C–H activation.

Acknowledgements

This study was supported by a grant from the Swiss National Science Foundation (200020_134682/1).

Notes and references