A Divergent Duo: Palladium Catalyzed Carboamination in Enantioselective Desymmetrization and Regiodivergent Catalysis

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We describe a regiodivergent synthesis of pseudo-C₂-symmetric and pseudo-meso bis-indoline scaffolds from norbornadiene and substituted α-iodo-anilines. The Pd(0)/Josiphos system enables the highly regioselective catalyst controlled carboaminations required for the two step synthesis of the scaffolds.

The design of catalytic sequences that enable access to small molecules with high chemoselectivity is a central topic in chemistry. This is especially so if specific classes of compounds can be obtained and branching points for diversity-oriented synthesis (DOS) are provided.[1] To this end, regiodivergent catalysis is an excellent tool.[2] The basic idea of this approach is the highly selective synthesis of regioisomeric products from one enantiomer of a substrate by the action of the enantiomers of a catalyst. This allows not only a highly selective preparation of particular synthetic targets but also the generation of structural diversity from a single compound by changing the absolute configuration of a catalyst.

In this publication, we highlight these points by adding catalyst controlled Pd-catalyzed regioselective carboamination reactions to the repertoire of enantioselective catalysis in a synthesis of bis-indoline scaffolds[3] (Scheme 1). Syntheses of indolines are of particular interest, because of the heterocycle’s presence in about 4% of all commercial drugs.[4]

Norbornadiene with its two double bonds that can be functionalized in subsequent steps is an ideal starting material for regiodivergent catalysis if two critical conditions can be met.

The first condition is that the initial desymmetrizing carboamination proceeds with high enantioselectivity. To the best of our knowledge such a method has not yet been described. Catellani and others have described the achiral version of this reaction.[5] The desired selectivity can be realized if the carboamination proceeds with high regioselectivity (C–C bond formation at one of the homotopic C₁ positions and C–N bond formation at the corresponding homotopic C² position as shown for the example in Scheme 1) in the presence of a Pd catalyst and an enantiomerically pure ligand L. In this manner, indoline scaffolds 1 that constitute the pivotal branching points for bis-indoline synthesis are obtained.

The second critical aspect for efficient regiodivergent catalysis is that the carboamination of 1, a substituted norborne, also has to proceed with catalyst-controlled selectivity. Using ligand L should lead to C–C bond formation at C¹ and C–N bond formation at C² to provide the pseudo-C₂-symmetrical product 2. Employing the enantiomer of the ligand ent-L will result in the synthesis of the pseudo-meso product 3. Since norbornenes are less strained and less reactive than norbornadienes, it may be necessary to employ a different catalyst system for the second carboamination.

From the analysis of Scheme 1, it is clear that in order to generate molecular diversity in a general way, the synthesis of the bis-indolines needs to be carried out stepwise. In one-pot reactions, only products with C₂-symmetry and, hence, identical substitution patterns of the amines can be obtained.

We started our investigations with a screening of Pd-precatalysts, ligands and reaction conditions for the mono-carboamination to yield 1a from norbornadiene (Table 1, see Supporting Information for details of the optimization).
The Josiphos ligands (a) L1–L3 showed a strong influence of the substitution pattern on the enantioselectivity. While L1 gave only moderate selectivity, the sterically demanding RBU groups in L2 prevented a reaction. Gratifyingly, the Josiphos ligand L3 gave 1a in high enantioselectivity (95:5) as a single diastereoisomer (see Supporting Information for structural assignments) despite the harsh reaction conditions (100 °C). However, we note that the enantioselectivity of the carboamination is sensitive to the purity of L3 that should be stored under Ar. With samples of L3 containing phosphate oxides, lower e.r. values in the range of 91:9 were obtained. We recommend that L3 is occasionally checked for the presence of phosphate oxides by 31P-NMR spectroscopy. These impurities should be removed by crystallization. (R)-BINAP (a) L4 and (R)-Segphos (a) L5 gave only very low enantioselectivity.

The carboamination of norbornadiene is broad in scope and tolerates a number of substituents on the aniline and works well with N-alkylated substrates as summarized in Table 2. The enantioselectivity of the reaction (e.r. = 93:7–96:4) is largely independent of the substrates’ substitution. Methyl and fluorine substituents in S1 are tolerated (entries 1–5). An o-Methyl substituent does not affect the outcome of the reaction (entry 6). Moreover, S1 may be N-alkylated (entry 6). All products were obtained as the single diastereoisomer shown (see Supporting Information for details).

As pointed out above, the second critical condition for the regiodivergent synthesis of the bis-indolines is that the norbornene derivatives 1 also undergo highly selective carboamination reactions.

We did not want to optimize the reaction conditions with the valuable indolines 1 and chose to investigate reactions with norbornene as a simple model substrate for 1 in the carboamination reaction because it should display a similar reactivity. As summarized in Table 3, norbornene is indeed a suitable substrate for the carboamination. The catalytic system is identical to the norbornadiene reactions with the sole difference that the use of H2O as an additive becomes redundant. Importantly, the enantioselectivities of the carboamination are in the range of 93:7–96:4 and do not differ significantly from those observed in the reaction with norbornadiene. Products 4 are obtained as single diastereoisomers (see Supporting Information for details of compound characterization). The reaction tolerates a number of substituents on the arenne (–Me, entry 3; –F, entry 2; –Cl, entry 5) and the aniline (S1) may be N-alkylated (entry 4).

The suggested mechanism (Figure 1) rationalizes the results. The intermolecular carbopalladation of norbornadiene or norbornene leading to 1A is the enantioselective C–C bond-forming event of the reaction. The generation of the palladaheterocycle B by deprotonation of the pending N–H is essential for C–N bond formation through reductive elimination.

To the best of our knowledge, there is only one intermolecular carboamination reported, in a synthesis of furoindolines from 2,3-dihydrofuran enantioselectivities ranging from 87:13 to 82:18 were obtained with MOP-type ligands. N-Sulfonylated anilines were employed and it seems that N-alkylated anilines or anilines mainly give products of Heck reactions rather than carboaminations.

Table 1. Identification of suitable conditions for the desymmetrizing enantioselective carboamination of norbornadiene.

| Entry | R1 | R2 | Yield [%] | e.r. |
|-------|----|----|-----------|------|
| 1     | R1 = H; R2 = H | 94 | 20:80 |
| 2     | R1 = H; R2 = H | 80 | 95:5 |
| 3     | R1 = H; R2 = H | 92 | 45:55 |

[a] Norbornadiene (1.5 mmol), S1 (0.5 mmol), entries 6–10 with 40 mol% H2O, [b] No product detected in crude NMR, [c] Determined by HPLC (see Supporting Information for details).

Table 2. Examples of the enantioselective carboamination of norbornadiene.

| Entry | R1 | R2 | Yield [%] | e.r. |
|-------|----|----|-----------|------|
| 1     | R1 = 4-F; R2 = H | 81 | 95:5 |
| 2     | R1 = 5-F; R2 = H | 77 | 94:6 |
| 3     | R1 = 4-Me; R2 = H | 75 | 6:94 |
| 4     | R1 = 5-Me; R2 = H | 80 | 5:95 |
| 5     | R1 = 4,6-Me; R2 = H | 71 | 93:7 |
| 6     | R1 = H; R2 = Me | 84 | 4:96 |

[a] Norbornadiene (3 eq.), S1 (1 eq.), H2O (4 eq.). Reactions were performed overnight (16 h) at 110 °C, [b] Reaction conditions: norbornadiene (5 eq.), S1 (1 eq.), H2O (4 eq.), [c] L3, [d] L3-ent-L3.

Table 3. Examples of the enantioselective carboamination of norbornene.

| Entry | R1 | R2 | Yield [%] | e.r. |
|-------|----|----|-----------|------|
| 1     | R1 = H; R2 = H | 72 | 4:96 |
| 2     | R1 = 5-F; R2 = H | 71 | 5:95 |
| 3     | R1 = 4-Me; R2 = H | 59 | 7:93 |
| 4     | R1 = H; R2 = Me | 70 | 6:94 |

[a] Norbornene (3.0 eq.), S1 (1.0 eq.). Reactions were performed over night at 100 °C, [b] Reaction was performed with 10 mol% catalyst loading and 2 eq. NaOtfBu.
selectivities have been obtained in intramolecular carboamination where the attack of an N-atom on a pending Pd-complexed olefin is the selectivity determining step.\textsuperscript{[11]}

The enantioselective carboamination of norbornadiene and norborne have set the scene for the regiodivergent bis-indoline synthesis. As shown in Scheme 1, the (pseudo)-C\textsubscript{2}-symmetrical products or the (pseudo)-meso products can be obtained by choice of L with the appropriate absolute configuration.

Accordingly, the (pseudo)-C\textsubscript{2}-symmetrical bis-indolines can be obtained from 1 in the presence of L3 (Table 4). They were obtained with excellent (>99.5%: <0.5% except for entry 4) enantiomeric ratios and as single diastereoisomers (see Supporting Information for details of characterization). The pseudo-meso-side products are significantly more polar and can be easily removed by chromatography.

A highly beneficial side effect of these reactions is the improvement of the enantiomeric ratio from substrate to product. Thus, they can be used to remove the minor, unwanted enantiomer by converting it to an easy to separate regioisomer. The selectivity is caused by the formation of the major enantiomer of 2 through by the favored pathway of the major enantiomer of 1 and the disfavored pathway of the minor enantiomer of 1. This implies that the ratio of 2:3 is lower than the e.r. of 1 as was indeed verified for the cases when 2 could be isolated in pure form (2b: 2:3 = 89:11 (68:8) vs. e.r. (1a) = 9:91, entry 2) and 2e: (2:3 = 83:17 (60:12) vs. e.r. (1a) = 6:94, entry 5). This increase in e.r. is practically especially valuable when the enantiomeric purity of the substrate is relatively low. Therefore, we employed 1a with an e.r. of only 9:91 that had been prepared with L3 of lower quality.

A synthetically important aspect of the products 2 is their potential for further functionalization. When derivatives of 2 are obtained with two N-H groups, it is difficult to regioselectively functionalize one N-H bond. Therefore, it is important to note that with our method, N-methylated bis-indolines can be readily prepared in excellent enantioreselectivities (R\textsubscript{e.r.} = Me, entries 2, 3, 5–8). These compounds can be readily functionalized further by reactions with the remaining N-H bond.

To fully explore and exploit the scope of the regiodivergent carboamination, we used ent-L3 in synthesis of the pseudo-meso compounds 3. If the second carboamination proceeds under catalyst control, these compounds will be obtained with high selectivities similar to those observed for 2.

As envisioned the pseudo-meso indolines 3 (see Supporting Information for details of structural characterization) were obtained almost as single enantiomers (e.r. = 99.5:0.5 or higher in all cases) and as single diastereoisomers (Table 5). The reactions leading to 3 in the presence of ent-L3 closely parallel those of the syntheses of the (pseudo)-C\textsubscript{2}-symmetrical bis-indolines 2 in the presence of L3. Thus, essentially the same degree of catalyst control is exerted in both sets of reactions. Hence, the influence of the substrate on the regioselectivity of the carboamination of 1 can be overruled by the enantiomerically pure catalyst.

In order to provide bis-indoline 3 building blocks that are amenable to straightforward functionalization, we mainly prepared products with one of the N-atoms methylated (R\textsubscript{1} = Me). However, products with two N-H bonds (R\textsubscript{1} = H) can also be accessed (entries 3 and 4). Substituents on the arené are readily tolerated.

Recently, it has been shown that ligands based on selectively functionalized meso-compounds can be used with excellent success as substitutes for C\textsubscript{2}-symmetrical salen ligands in organocatalysis and metal catalyzed epoxidations.\textsuperscript{[12]} This exciting finding suggests that such pseudo-meso compounds in enantioselectively pure form have been neglected in applications in stereoselective synthesis.

Our sequence of reactions provides a synthetic entry to such compounds in very high enantioselectivity and complete

\[\text{Figure 1. Proposed mechanism of the enantioselective carboamination of norbornadiene or norborne.}\]
Table 5. Preparation of pseudo-meso bis-indolines 3 by regiodivergent carboamination in the presence of ent-L3 and L3.

| entry | R' | R'' | [e.r.] (%) | [e.r.] (%) |
|-------|----|-----|------------|------------|
| 1     | Me | Me | 3a, 80    | 0.2:99.8   |
| 2     | Me | Me | 3b, 73    | 99.6:0.4   |
| 3     | 4-f | Me | 3c, 73    | 99.6:0.4   |
| 4     | 4-f | Me | 3d, 54    | 99.5:0.5   |
| 5     | 4-f | Me | 3e, 64    | 99.8:0.2   |
| 6     | Me | Me | 3f, 65    | 0.4:99.6   |
| 7     | Me | Me | 3g, 69    | 0.5:99.5   |
| 8     | Me | Me | 3h, 70    | 0.5:99.5   |
| 9     | Me | Me | 3i, 75    | 99.7:0.3   |
| 10    | Me | Me | 3j, 69    | 99.9:0.1   |

[a] 1 (2.0 eq), S1 (1.0 eq). Reactions were performed overnight (16 h) at 110 °C. [b] L3. [c] ent-L3.

Conflict of Interest

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The authors declare no conflict of interest.