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# Catalytic enantioselective synthesis of $\alpha$ -aryl $\alpha$ -hydrazino esters and amides

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thereof.

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peptidomimetics

Catalysts generated by combinations of  $Pd(TFA)_2$  and pyridinehydrazone ligands have allowed the asymmetric 1,2-addition of aryl boronic acids to *N*-carbamoyl (Cbz and Fmoc) protected glyoxylate-derived hydrazones, yielding  $\alpha$ -aryl  $\alpha$ -hydrazino esters/amides in high enantioselectivities. Subsequent removal of the carbamoyl moiety affords key building blocks en route to

hydrazinopeptides, N-aminopeptides and

 $\alpha$ -Hydrazino acids I are an important family of compounds in bioorganic and medicinal chemistry (Scheme 1).<sup>1</sup> For example, L-Carbidopa, acting as inhibitor of the peripheral aromatic Lamino acid decarboxylase (DDC), has been shown to improve the efficiency of Parkinson's treatment in combination with L-Dopa.<sup>2</sup> Additionally,  $\alpha$ -hydrazino acids are essential building blocks for the synthesis of artificial peptides, in which the presence of a NH-NH-C-CO motif induces conformational restrictions (hydrazino turns) through intramolecular Hbonds,<sup>3</sup> and hence modify their biological activities. Hydrazinopeptides II,<sup>4</sup> N-aminopeptides (NAP) III,<sup>5</sup> hydrazoneligated bioconjugates<sup>6</sup> and other non-proteogenic amino acid derivatives have attracted increasing interest as proteaseresistant peptidomimetics at the forefront of pharmaceutical research. Traditional routes to enantioenriched  $\alpha$ -hydrazino acid derivatives,<sup>1</sup> basically  $\alpha$ -alkyl substituted ones,<sup>7</sup> rely on some transformations of amino acids from the chiral pool,<sup>8</sup> electrophilic amination of enolates with azodicarboxylates and diverse reactions using hydrazones (hydrogenation,<sup>9</sup> cyanation,<sup>10</sup> or introduction of side-chains<sup>11</sup>).



Scheme 1. Synthetic design to  $\alpha$ -aryl  $\alpha$ -hydrazino acid derivatives IV.

However, direct methodologies for accessing  $\alpha$ -aryl substituted  $\alpha$ -hydrazino acids are scarce.<sup>12</sup>

In this communication, we report on a straightforward approach based on Pd(II)-catalyzed enantioselective 1,2addition of aryl boronic acids to *N*-carbamoyl protected glyoxylate-derived hydrazones. Effective removal of the carbamoyl moiety provides an appealing entry to *ad hoc* deprotected  $\alpha$ -aryl  $\alpha$ -hydrazino acid derivatives **IV** which might serve to expand the repertoire of the above-mentioned pharmacophores (Scheme 1).

Preliminary experiments were performed with phthaloylprotected hydrazone **1a** and phenylboronic acid (**2a**) as model reagents. The behavior of catalysts prepared in situ from bipyridine (bipy, 11 mol%) and different Pd(II) sources (10 mol%) in trifluoroethanol (TFE) at 60 °C was analyzed (See S1 in the ESI<sup>‡</sup>). From this screening, Pd(TFA)<sub>2</sub> was identified as the best precatalyst, affording the desired product **3aa** in 87% yield after 24 h.

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#### Table 1. Optimization of reaction conditions<sup>a</sup> HN<sup>NR<sup>1</sup>R<sup>2</sup></sup> L\* (11 mol%) NR<sup>1</sup>R<sup>2</sup> Pd(TFA)<sub>2</sub> (10 mol%) PhB(OH)<sub>2</sub> Solvent, 60 °C EtO<sub>2</sub>C EtO<sub>2</sub>C 2a Ph 24 h 1a.1b 3aa, 3ab NR<sup>1</sup>R<sup>2</sup> Compound 1a, 3aa 1b, 3ab Ph ∕tBu L1 L2: X = H P L3: X = CO<sub>2</sub>Me L\* Yield (%)<sup>b</sup> Entry Solvent 3 ee (%)<sup>c</sup> 1 1 1a TFE L1 52 (R)-3aa 55 2 1a TFE L2 82 (S)-3aa 58 3 1a TFE L3 86 (80)d (S)-3aa 62 TFE 4 (E)-1b L1 21 (R)-3ab 60 TFE 75 5 (E)-1b L2 56 (S)-3ab (S)-3ab (E)-1b DCE L2 83 (75)d 93 6 DCE 87 (79)<sup>d</sup> 7 (E)-1b L3 (S)-3ab 93 8 (Z)-1b DCE L2 82 (S)-3ab 86

<sup>a</sup> Reactions were performed under air on a 0.2 mmol scale. <sup>b</sup> Yields were determined by <sup>1</sup>H NMR analysis of the crude reaction mixture using 1,3,5trimethoxybenzene as an internal standard. <sup>c</sup> Determined by HPLC on chiral stationary phases. <sup>d</sup> In parenthesis, isolated yield after column chromatography.

Diverse N,N-ligands<sup>13</sup> bearing chiral oxazolines<sup>13b,c</sup> or  $C_2$ symmetric hydrazones<sup>14</sup> were evaluated (See S2 in the ESI<sup>‡</sup>). As representative examples, pyridine-oxazoline L1 furnished 3aa in 52% yield and 55% ee (entry 1, Table 1) while pyridinehydrazone L2 provided 3aa in better yield (82%), albeit in yet moderate enantioselectivity (58% ee, entry 2). Structural variations of the pyridine-hydrazone ligand were also investigated without any improvement (See S3 in the ESI<sup>‡</sup>). Only the introduction of an electron-withdrawing group  $(CO_2Me)$  at C5 of the pyridine ring (L3) led to similar or slightly better results than those provided by L2 (entry 3). Next, benzyloxycarbonyl (Cbz)-protected hydrazone (E)-1b was selected as a model mono-carbamoyl substituted substrate. Lower yields but better enantioselectivities were observed (entries 4 and 5): 3ab was obtained in 56% yield and 75% ee with L2. To our delight, a significant improvement was observed by using dichloroethane (DCE) as the solvent (entries 6 and 7), affording 3ab in high yields (83-87%) and excellent enantioselectivities (93% ee with both L2 or L3). A similar level of reactivity, slightly lower enantioselectivity and the same stereochemical outcome was observed in an additional experiment employing (Z)-1b (entry 8), suggesting the intervention of a common intermediate.

The influence of the structure of the ester moiety in the glyoxylate hydrazone 1 was also investigated (Scheme 2).

ester derivative 1c afforded Methyl 3acviewingrticle owner enantioselectivity (74% ee), while the introduction of Odd Kier ester moieties (1d, R = Bn; 1e, R =  ${}^{i}$ Pr; 1f, R =  ${}^{t}$ Bu) had a detrimental effect in reactivity, leading to products 3ad-af in lower yields than 3ab, although with similar levels of enantioselectivity (83-94% ee). It was therefore decided to retain the ethyl ester scaffold and explore other alternative removable N-protecting groups. Fmoc-derived hydrazone 1g provided competitive results (70% yield, 87% ee), while Bocderived hydrazone **1h** gave **3ah** in high enantioselectivity (92% ee), albeit in low yield (26%). Finally, the introduction of an additional N-benzyl group in Cbz-protected hydrazone 1i totally inhibited the reactivity, while PMP-protected hydrazone 1j reacted sluggishly to afford oxidized hydrazone 3aj' instead of the expected hydrazine 3aj.



Scheme 2. Screening for optimal hydrazone structure. Reactions were performed under air on a 0.2 mmol scale. Isolated yields after column chromatography. Enantiomeric excess (ee) determined by HPLC on chiral stationary phases.

During the scaling-up at 0.4 mmol, we observed that the presence of water had a strong impact in both yield and enantioselectivity and was also possibly the origin of some erratic data. Therefore, the remaining optimization studies were performed in dry DCE with controlled amounts of water (See S5 in the ESI<sup>‡</sup>). 0.6 Equiv. was found to be the optimal amount, affording **3ab** in good yield and without erosion of the enantioselectivity [61%, 93% ee (L2); 69%, 94% ee (L3)].

Successive studies were aimed at analyzing the scope of the reaction (Scheme 3). Thus, under optimized conditions, either using L2 or L3 as the best option, Cbz- 1b and Fmoc-protected **1g** reacted with a variety of arylboronic acids **2**, affording  $\alpha$ aryl  $\alpha$ -hydrazino esters **3ab-hg** in good yields (47-92%) and good to excellent enantioselectivities (82-96% ee).

Electron-rich aryl boronic acids (p-Me-C<sub>6</sub>H<sub>4</sub> and p-MeO-C<sub>6</sub>H<sub>4</sub>) were suitable reagents. More challenging ortho-substituted boronic acids, exemplified by 2d (o-Me-C<sub>6</sub>H<sub>4</sub>), also provided the corresponding products 3db and 3dg in excellent enantioselectivities (93-96% ee) and good yields (69-77%). Electron-poor p-chlorophenylboronic acid 2e reacted slower (<30% conversion to 3eb in 24 h) and prolonged reaction times were required to increase conversions (up to 72% in 96 h).§

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Scheme 3. Reactions were performed under air on a 0.4 mmol scale. Isolated yields after column chromatography. Enantiomeric excesses (ee's) were determined by HPLC on chiral stationary phases.

Therefore, stopping the reaction at half conversion afforded 3eb (48 h) and 3eg (36 h) in 82% and 87% ee, respectively; consequently, in moderate yields (47-48%). Electron-rich disubstituted boron reagents 2f,g were well tolerated, leading to 3fb,fg and 3gb,gg in good yields (70-89%) and enantioselectivities (85-93% ee). Remarkably, a challenging 1naphthyl boronic acid derivative **2h** afforded  $\alpha$ -hydrazino esters 3hb,hg in good yields and enantioselectivities (92-96% ee). We next investigated the asymmetric arylation of some Cbz-protected hydrazones bearing amides. Gratifying, employing optimized conditions and L3 as the best ligand, simple  $\alpha$ -hydrazino amides **3ck** and **3cl** were obtained in moderate to good yields (52-86%) and excellent enantioselectivities (93-95% ee). Glycine derivative 3cm was also synthesized in 73% yield, albeit in slightly lower enantioselectivity (84% ee). In order to evaluate the practical applicabbility of the developed methodology, the syntheses of 3ab (82%, 92% ee) and 3ag (85%, 92% ee) were performed on 1 mmol scale under slightly optimized reaction conditions [H<sub>2</sub>O (0.27 Equiv.), iterative addition of 2a (0.5-0.75 mmol/12 h)].

To demonstrate the suitability of the carbamoyl protecting groups in the developed strategy, complementary deprotection conditions were applied to Cbz- and Fmocprotected hydrazino esters **3ab** and **3ag** (Scheme 4). Applying standard hydrogenolysis [Pd(C) /  $H_2$  (1 atm), rt] **3ab** was transformed into deprotected  $\alpha$ -aryl  $\alpha$ -hydrazino ester **4a** which was isolated as its hydrochloride salt in 71% yield and 93% ee. Alternatively, a 2-step protection/base-promoted deprotection protocol allowed to convert 3ag into Naminopeptide precursor 5a in good overall yield (78%) and without erosion of enantioselectivity (93% ee). 5a was also fully deprotected to 4a employing acidic conditions. Additionally, hydrolysis of the ester moiety of 3cb was efficiently performed under basic conditions to get free acid 6a in 85% yield. This compound is another key building block for the synthesis of hydrazinopeptides. For example, a direct coupling with glycine methyl ester hydrochloride afforded  $\alpha$ tolyl  $\alpha$ -hydrazino amide **3cm** in 81% yield and 93% ee. Importantly this transformation proceeds without significant erosion of the chiral integrity during amide bond formation.§§ The absolute configuration of **3ab** was determined to be (S) by

X-ray diffraction analysis. The absolute *S* configuration of products **3ag**, **5a** and **3cm** were assigned by chemical correlation.<sup>555</sup> Assuming a uniform reaction pathway, the absolute configurations of all other hydrazino esters and amides **3** were assigned by analogy.

In summary, catalysts generated by combinations of  $Pd(TFA)_2$ and pyridine-hydrazone ligands **L2/L3** have shown excellent activities and enantioselectivities in the 1,2-addition of aryl boronic acids to *N*-carbamoyl (Cbz and Fmoc) protected glyoxylate-derived hydrazones, yielding  $\alpha$ -aryl  $\alpha$ -hydrazino

#### COMMUNICATION

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esters/amides, key hydrazino acid derivatives. Moreover. the orthogonal reactivity of the different carbamoyl groups offers a versatile tool for the synthesis of hydrazinopeptides and *N*-aminopeptides.



**Scheme 4**. ORTEP drawing of (*S*)-**3ab** and representative deprotections and transformations

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## Notes and references

§ A decrease of the enantiomeric purity over reaction time was observed independently of the nature of the aryl boronic acid employed. Control experiments suggests that this fact is not due to a racemization process of the products under the reaction conditions and might instead be a consequence of the hemilabile performance of the ligand (hydrazone fragment), leading to conversion by less-selective catalytic species (see *ref* 14d).

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see the ESI<sup>‡</sup>). (b) The absolute *S* configuration of **3cm** where assigned by comparing HPLC traces of **3cm** obtained from direct arylation of amide (*S*)-**6a** with HPLC of **3cm** obtained from direct arylation of amide **1m**.

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