COMMUNICATION

Catalytic enantioselective synthesis of α-aryl α-hydrazino esters and amides

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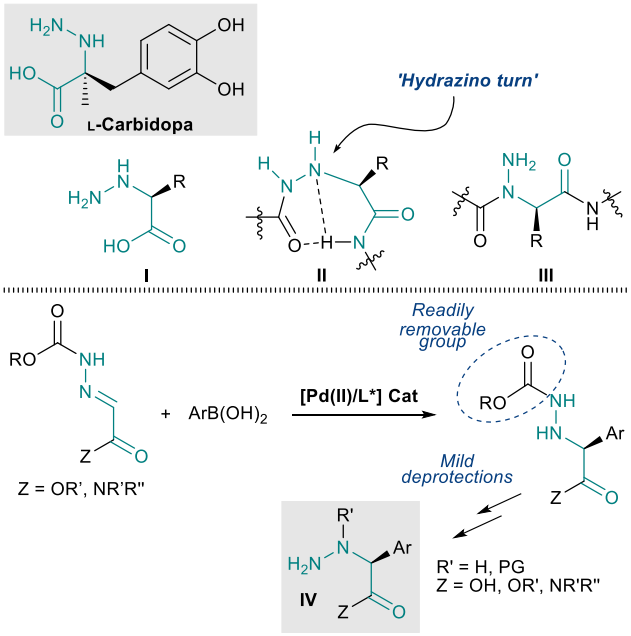
Catalysts generated by combinations of $Pd(TFA)_2$ and pyridine-hydrazone ligands have allowed the asymmetric 1,2-addition of aryl boronic acids to *N*-carbamoyl (Cbz and Fmoc) protected glyoxylate-derived hydrazones, yielding α-aryl α-hydrazino esters/amides in high enantioselectivities. Subsequent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

α-Hydrazino acids **I** are important molecules in bioorganic and medicinal chemistry (Scheme 1).[1] For example, L-Carbidopa, acting as inhibitor of the peripheral aromatic L-amino acid decarboxylase (DDC), has been able to improve the efficiency of Parkinson's treatment in combination with L-Dopa.[2] Additionally, α-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 H-bonds,[3] and hence modify their biological activities. Hydrazinopeptides **II**,[4] *N*-aminopeptides (NAP) **III**,[5] hydrazone-ligated bioconjugates[6] and other non-proteogenic amino acid derivatives have attracted increasing interest as protease-resistant peptidomimetics at the forefront of pharmaceutical research. Traditional routes to enantioenriched α-hydrazino acid derivatives,[1] basically α-alkyl substituted ones,[7] rely on some transformations of amino acids from chiral pool,[8] electrophilic amination of enolates with azodicarboxylates and diverse reactions using hydrazones (hydrogenation,[9] cyanation,[10] or introduction of side-chain[11]), among others. However, direct methodologies for accesing α-aryl substituted α-hydrazino acids are scarce.[12]



Scheme 1. Synthetic design to α-aryl α-hydrazino acid derivatives **IV**.

In this communication, we report on a straightforward approach based on Pd(II)-catalyzed enantioselective 1,2-addition 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 α-aryl α-hydrazino acid derivatives **IV** which might serve to expand the repertoire of the above-mentioned pharmacophores (Scheme 1).

Preliminary experiments were performed with phthaloyl-protected 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‡). From this screening, $Pd(TFA)_2$ was identified as the best precatalyst, affording the desired product **3aa** in 87% yield after 24 h.

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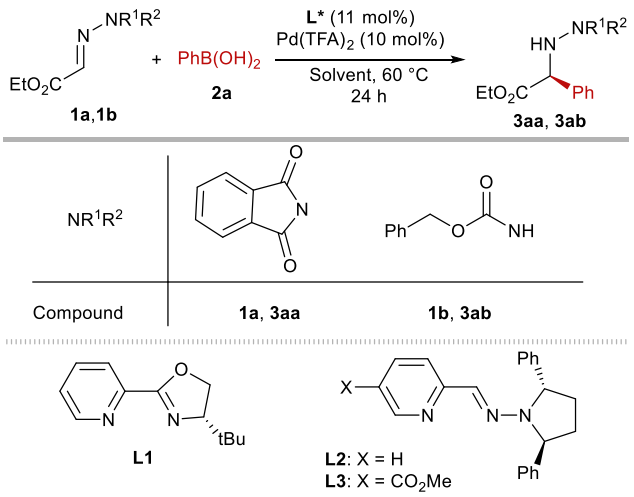
Table 1. Optimization of reaction conditions[a]

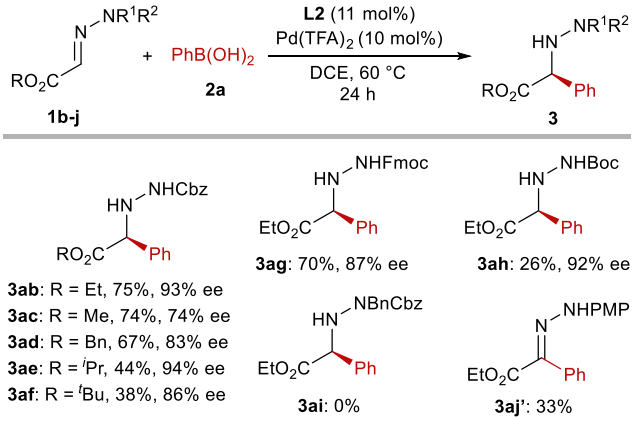


Entry	1	Solvent	L*	Yield (%)[b]	3	ee (%)[c]
1	**1a**	TFE	**L1**	52	(***R***)-**3aa**	55
2	**1a**	TFE	**L2**	82	(***S***)-**3aa**	58
3	**1a**	TFE	**L3**	86 (80)[d]	(***S***)-**3aa**	62
4	(*E*)-**1b**	TFE	**L1**	21	(***R***)-**3ab**	60
5	(*E*)-**1b**	TFE	**L2**	56	(***S***)-**3ab**	75
6	(*E*)-**1b**	DCE	**L2**	83 (75)[d]	(***S***)-**3ab**	93
7	(*E*)-**1b**	DCE	**L3**	87 (79)[d]	(***S***)-**3ab**	93
8	(*Z*)-**1b**	DCE	**L2**	82	(***S***)-**3ab**	86

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

Diverse *N*,*N*-ligands[13] bearing chiral oxazolines[13b,c] or C_2-symmetric hydrazones[14] were evaluated (See S2 in the ESI‡). As representative examples, pyridine-oxazoline **L1** furnished **3aa** in 52% yield and 55% ee (entry 1, Table 1) while pyridine-hydrazone **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‡). 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). Methyl ester derivative **1c** afforded **3ac** in lower enantioselectivity (74% ee), while the introduction of bulkier 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 Boc-derived 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**.

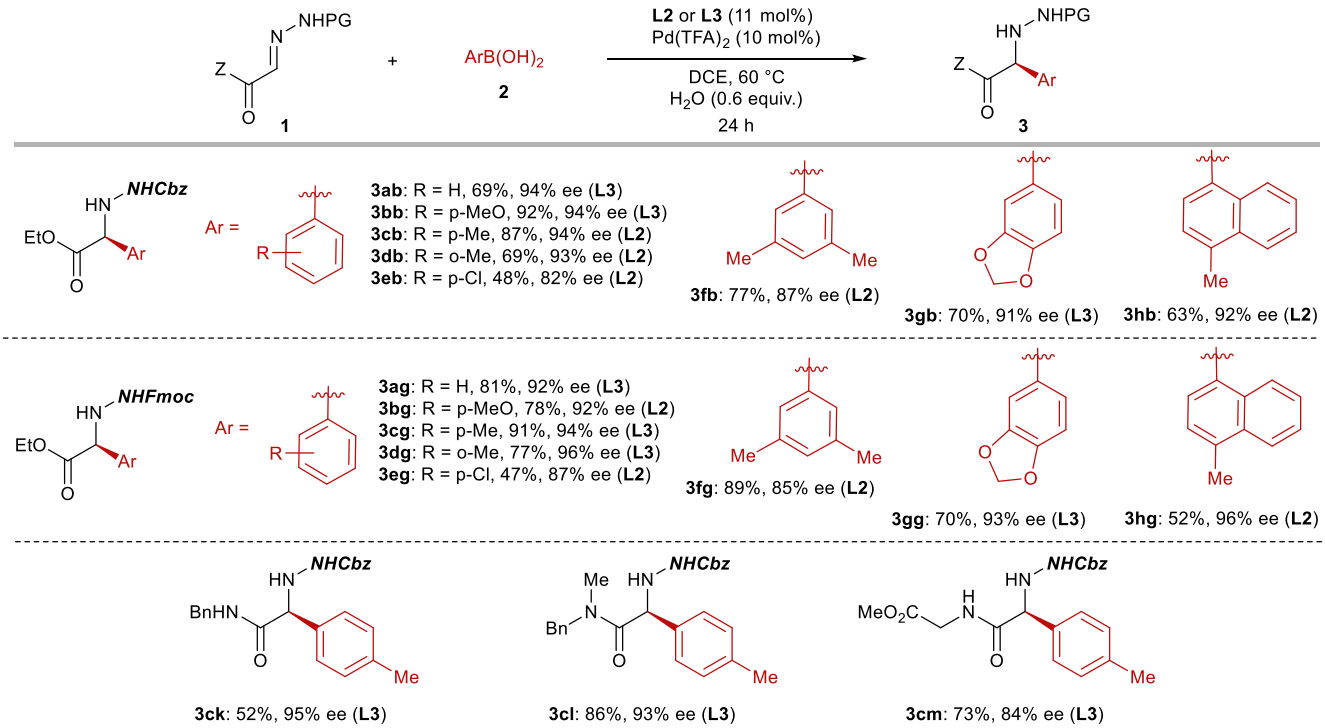


Scheme 2. Screening for optimal hydrazone structure. Reactions were performed under air on a 0.2 mmol scale. Isolated yields after column chromatography. Enantiomeric excess (ee) determined by HPLC on chiral stationary phases.

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‡). 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 α-aryl α-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_6H_4 and *p*-MeO-C_6H_4) were suitable reagents. More challenging *ortho*-substituted boronic acids, exemplified by **2d** (*o*-Me-C_6H_4), 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).

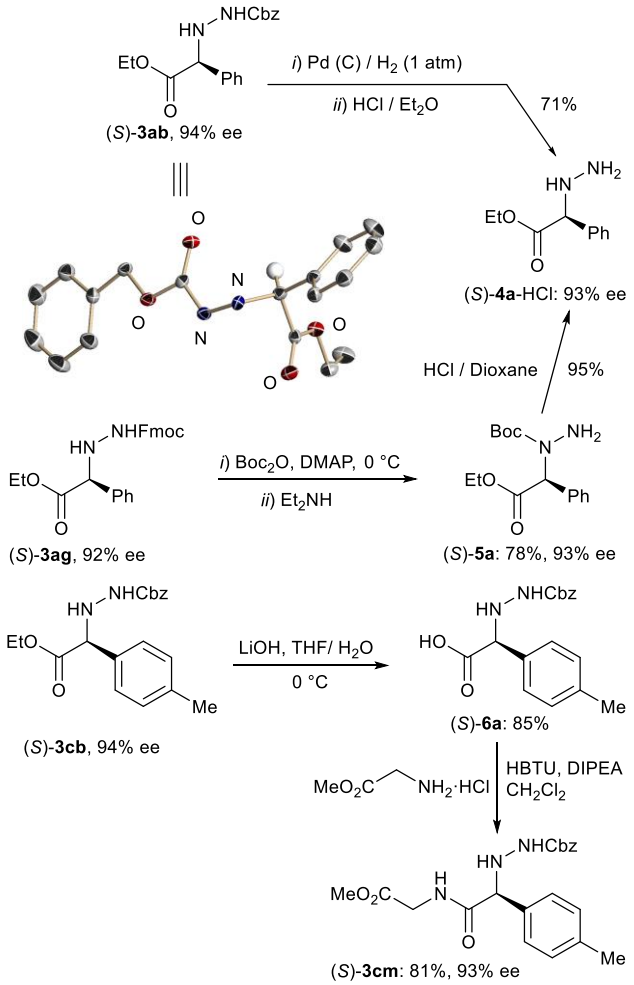


Scheme 3. Reactions were performed under air on a 0.4 mmol scale. Isolated yields after column chromatography. Enantiomeric excesses (ee's) were determined by HPLC on chiral stationary phases.

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 di-substituted 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 1-naphthyl boronic acid derivative **2h** afforded α-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 α-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_2O (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 Fmoc-protected hydrazino esters **3ab** and **3ag** (Scheme 4). Applying standard hydrogenolysis [Pd(C) / H_2 (1 atm), rt] **3ab** was transformed into deprotected α-aryl α-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 *N*-aminopeptide 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 α-tolyl α-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.[§§§] Assuming a uniform reaction pathway, the absolute configurations of all other hydrazino esters and amides **3** were assigned by analogy.



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

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 α-aryl α-hydrazino 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.

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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).

§§ Carbamoyl-protected L-arylglycines are extremely prone to epimerization/racemization during the activation of carboxylic acid by standard coupling reagents in peptide synthesis. See: (a) G. G. Smith and T. Sivakua, *J. Org. Chem.* 1983, **48**, 627; (b) W. Muramatsu, T. Hattori and H. Yamamoto, *J. Am. Chem. Soc.* 2019, **141**, 12288, and references therein.

§§§ (a) The absolute *S* configurations of **3ag** and **5a** were assigned by deprotection of **5a** and subsequent transformation of hydrochloride salt (*S*)-**4a**-HCl into (*S*)-**3ab** (for HPLC analysis, see the ESI‡). (b) The absolute *S* configuration of **3cm** was assigned by comparing HPLC traces of **3cm** obtained from acid (*S*)-**6a** with HPLC of **3cm** obtained from direct arylation of amide **1m**.

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