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Pd-Catalysed oxidative carbonylation of α -amino amides to hydantoins under mild conditions†‡

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The first example of palladium-catalysed oxidative carbonylation of unprotected α -amino amides to hydantoins is described here. The selective synthesis of the target compounds was achieved under mild conditions (1 atm of CO), without ligands and bases. The catalytic system overrode the common reaction pathway that usually leads instead to the formation of symmetrical ureas.

Imidazolidine-2,4-dione (hydantoin) is a privileged structural unit in natural products and pharmaceuticals,¹ such as Phenytoin, Ethotoin and Enzalutamide.² Hydantoins display an array of utilities that include their usage as ligands,³ directing groups,⁴ organocatalysts,⁵ intermediates in organic synthesis,⁶ and functional moieties in specialty polymers.⁷ Traditional routes to this scaffold include the Bucherer–Bergs reaction,⁸ the Urech⁹ and the Read¹⁰ syntheses, and the Biltz reaction.¹¹ Enantiopure hydantoins can provide additional key properties, which can be exploited in medicinal chemistry¹² and organic chemistry.¹³ Besides the well-established Urech and Read syntheses, the most common strategy to chiral imidazolidine-2,4-diones relies on the use of optically pure building blocks.¹⁴ In this context, α -amino acid derivatives are converted into the corresponding ureido compounds and then annulated by reacting with isocyanates or other unfriendly acylating agents (*i.e.* phosgene, triphosgene and 1,1-carbonyldiimidazole (CDI)) and an amine.^{1a} These stoichiometric strategies, despite their efficiency, suffer from limited

atom-economy, and low generality and functional group tolerance. Alternatively, the optically enriched hydantoins can be accessed by elegant enantioselective transformations.¹⁵ Their general applicability is however weakened by the high cost of these catalytic systems, the limited availability of reagents or low enantioselectivity values. Therefore, catalytic protocols for the synthesis of chiral hydantoins featuring improved efficiency, atom-economy and versatility are still in high demand.¹⁶

Catalytic carbonylative approaches to hydantoins are highly attractive because they merge all of the above-mentioned issues. However, only a few examples have been reported so far.¹⁷ In 1994, Beller and co-workers reported a simple but remarkable synthesis of hydantoins by palladium-catalysed high-pressure carbonylation of aldehydes with urea derivatives (Scheme 1a).^{17a} More recently, McElwee-White *et al.* reported the first example of carbonylation of primary amino amides to hydantoins by means of the W(CO)₆ catalyst (Scheme 1b).^{17b} Meanwhile, a high pressure of CO (80 atm) and a stoichiometric amount of the base (DBU) were essential. This is a unique example of the catalytic carbonylative synthesis of hydantoins from amino amides. This challenging goal is indeed usually inaccessible because the palladium catalysed carbonylation of primary amino acids *via* catalytic CO insertion leads exclusively to the formation of urea¹⁸ or benzolactam derivatives.¹⁹

Here, we describe the first example of palladium-catalysed carbonylative transformation of α -amino amides to hydantoins under mild conditions and low CO pressure (1 atm) (Scheme 1c). Competitive pathways to urea and benzolactam derivatives are successfully circumvented, and carbonylation takes place without racemisation of the chiral centre.

Firstly, in the context of our work on the carbonylation of amines to ureas²⁰ in the presence of the PdI₂/KI catalytic system,²¹ we examined to what extent amino amides can be used as hydantoin precursors under palladium catalysis. The easily accessible amide of L-phenylalanine (*S*)-**1a** was selected as a model substrate.²² The initial attempts to direct the carbonylation of (*S*)-**1a** to imidazolidine-2,4-dione **2a** were completely unsuccessful. In fact, the PdI₂/KI catalytic system turned out to

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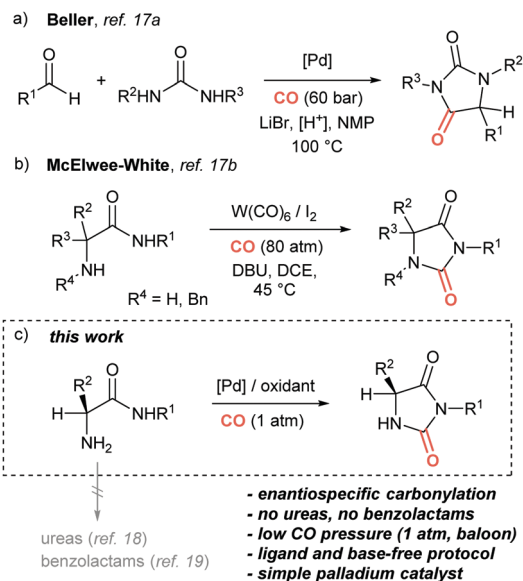
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† The authors dedicate this manuscript to Prof. Mirco Costa on the occasion of his 80th birthday.

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Scheme 1 Carbonylative approaches to hydantoins.

be as efficient in the synthesis of ureas as ineffective in the formation of hydantoins. Many experiments performed under various conditions, using different solvents and concentrations, afforded urea **3a** in quantitative yields and no traces of hydantoin **2a** were retrieved (see Table S1 in the ESI†).

The formation of urea derivatives is also the most preferred pathway when primary amines, including unprotected amino esters, are carbonylated under milder palladium-based conditions.¹⁸ Exceptions to this behaviour include the palladium-catalysed oxidative carbonylation of *N*-protected amino acids to 3,4-dihydroisoquinolinones²³ and the synthesis of benzolactams by the palladium-catalysed carbonylation of *N*-unprotected amino esters.^{19a}

Inspired by the work of Garcia and Granell,^{19a} who were successful in preventing the formation of urea in favour of benzolactam derivatives, we decided to test the model substrate (*S*)-**1a** under similar carbonylative conditions. The use of Pd(OAc)₂ and benzoquinone (BQ) as oxidants, 1 atm of carbon monoxide (CO) and acetic acid as the solvent (Table 1) gratifyingly hindered the formation of both urea **3a** and acetylamide **4a**. Similarly, the formation of a benzolactam derivative *via* C–H activation^{19a} was not detected, and hydantoin **2a** was obtained in 74% NMR yield (Table 1, entry 1). Importantly, the absolute configuration of the chiral centre of **2a** was found to be *S* (Fig. S1 and S2 of the ESI†).²⁴ Unfortunately, the ultimate purification of the target product was unsatisfactory due to the presence of traces of BQ derivatives. A possible adduct of BQ and the product²⁵ were difficult to remove by chromatography. We were pleased to find that the yield increased on lowering the reaction temperature to 80 °C (Table 1, entry 2). Nonetheless, the purification issues persisted even though BQ was employed in a near stoichiometric amount (Table 1, entry 3). This led us to consider alternative oxidants. Methyl-*p*-benzoquinone (MBQ) and 2,6-dimethyl-*p*-benzoquinone (DMBQ) were however less efficient (Table 1, entries 4 and 5).

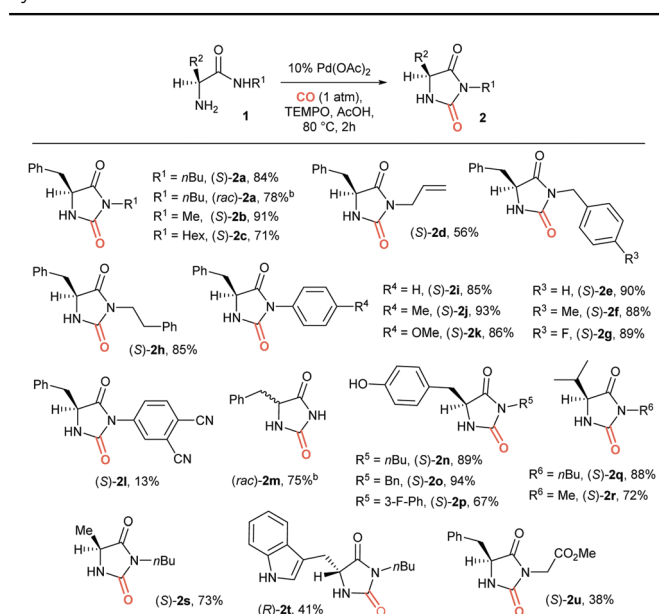
Table 1 Optimization study for the palladium-catalysed carbonylation to hydantoins^a

Entry	Pd (mol%)	Oxidant (equiv.)	T (°C)	t (h)	Yield 2a (%)
1	Pd(OAc) ₂ (10)	BQ (2.0)	120	6	74, ^c 70 ^{bd}
2	Pd(OAc) ₂ (10)	BQ (2.0)	80	6	86, ^c 83 ^{bd}
3	Pd(OAc) ₂ (10)	BQ (1.2)	80	6	80, ^c 76 ^{bd}
4	Pd(OAc) ₂ (10)	MBQ (1.2)	80	6	19 ^{bd}
5	Pd(OAc) ₂ (10)	DMBQ (1.2)	80	6	23 ^{bd}
6	Pd(OAc) ₂ (10)	Cu(OAc) ₂ (2.2)	80	6	16 ^{be}
7	Pd(OAc) ₂ (10)	Cu(OAc) ₂ (1.0) ^f	80	6	64 ^{bg}
8	Pd(OAc) ₂ (10)	AgOAc (2.2)	80	6	81 ^b
9	Pd(OAc) ₂ (10)	TEMPO (2.2)	80	2	84 ^b
10	Pd(MeCN) ₂ Cl ₂ (10)	TEMPO (2.2)	80	2	77 ^b
11	Pd(TFA) ₂ (10)	TEMPO (2.2)	80	2	60 ^b
12	Pd ₂ (dba) ₃ (10)	TEMPO (2.2)	80	2	68 ^b
13	Pd(OAc) ₂ (5)	TEMPO (2.2)	80	3	81 ^b
14	Pd(OAc) ₂ (2)	TEMPO (2.2)	80	5	74 ^b
15	Pd(OAc) ₂ (10)	TEMPO (2.2)	60	3	65 ^b

^a Reaction conditions: (*S*)-**1a** (0.3 mmol), CO (balloon, 1 atm), Pd catalyst, oxidant, and acetic acid (0.1 M). ^b Isolated yields. ^c NMR yields. ^d Impure of quinone. ^e Compounds **3a** and **4a** were isolated in 15% and 27% yields, respectively. ^f An atmosphere of CO and air (3 : 1) were employed. ^g Compound **4a** was isolated in 11% yield and traces of **3a** were detected.

Copper(II) acetate, a common oxidant in palladium-catalysed reactions, gave satisfactory results only in combination with air (Table 1, entries 6 and 7). The purification of the final product was much easier, but compound **4a** was formed in a higher amount, suggesting that the competitive acetylation of (*S*)-**1a** might be accelerated by a copper(II) species.²⁶ High yield and selectivity were achieved when 2.2 equivalents of silver acetate were used (Table 1, entry 8). However, we aimed to find a more sustainable oxidation system despite its high efficiency. Pleasingly, TEMPO provided the highest yield of (*S*)-**2a**, which could be easily isolated in this case (Table 1, entry 9). Remarkably, the use of 2.2 equiv. of TEMPO (see Table S2 in the ESI†) caused a significant reduction of the reaction time (from 6 to 2 hours), too. Moreover, the acetylated compound **4a** was no longer observed. In all reactions carried out with TEMPO, the selectivity reached values close to 99%, as only a reduced amount of the starting material was recovered. Other palladium precursors behaved well but were less efficient (Table 1, entries 10–12). The reduction of Pd(OAc)₂ from 10% to 5% and 2% was still acceptable in terms of yield, but longer reaction times were required (Table 1, entries 13 and 14). The optimal reaction temperature was 80 °C since at 60 °C lower performance was observed (Table 1, entry 15). Alternative polar solvents, such as MeCN and DMF, provided less satisfactory results and still required the combination with acetic acid (see Table S2 in the ESI†).²⁴ Then, to explore the reaction scope (Table 2), an array of α -amino amides were smoothly prepared from the

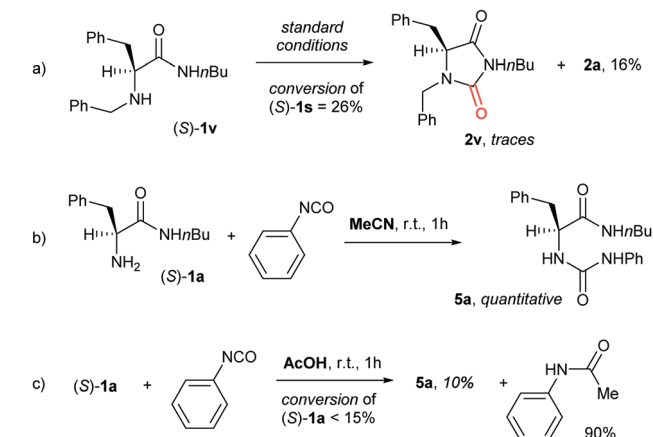


Table 2 Scope of the Pd-catalysed carbonylation of α -amino amides to hydantoin^a

^a Reaction conditions: **1a** (0.3 mmol), CO (balloon, 1 atm), Pd(OAc)₂ (10 mol%), TEMPO (2.2 equiv.), AcOH (3 mL, 0.1 M), 80 °C, and 2 h. Isolated yields. ^b From the corresponding (rac)-aminoamides.

corresponding esters (see the ESI†) and submitted under the optimised reaction conditions (Table 1, entry 9).

Firstly, the catalytic process was successfully extended to the racemic phenylalanine amide (rac)-**1a** that was converted to (rac)-**2a** in 78% yield. Different R^1 substituents were then explored. The methyl group on the amide nitrogen ($R^1 = \text{Me}$) provided an excellent yield of compound **2b**, while a longer alkyl chain ($R^1 = \text{Hex}$) seems to decrease the efficiency of the reaction (**2c**, 71%). The allyl substituent is only partially tolerated with the corresponding hydantoin **2d** being obtained in 56% yield. The benzyl moiety was particularly beneficial to this transformation and nearly 90% yield was achieved with both electron withdrawing and electron releasing groups (**2e–g**, 88–90%). Substrate **1h**, bearing a phenylethyl unit, afforded the desired product **2h** in 85% yield. Aryl amides were also compatible with this process and allowed 2-arylhydantoin **2i–k** to be prepared in excellent yields (85–93%). However, two strong EWGs at the ring (CN group) were detrimental to the process (**2l**, 13%). The unsubstituted amide of (rac)-phenylalanine **1m** was successfully converted to the hydantoin scaffold in a good yield (**2m**, 75%). Different natural amino acids were then considered. The hydroxyl function of tyrosine amides was well tolerated, delivering the expected carbonylated products **2n–p** in good yields. A comparable outcome was observed for valine derivatives (**2q–r**, 72–88%) and alanine amide **1s** (**2s**, 73%), while the *N*-butyl amide of tryptophan led to the desired product **2t** in a poor 41% yield as the C–H activation at the C2 position of indole turned out to be a competitive pathway.²⁷ Finally, dipeptide **1u** gave the corresponding hydantoin **2u** in 38% yield.

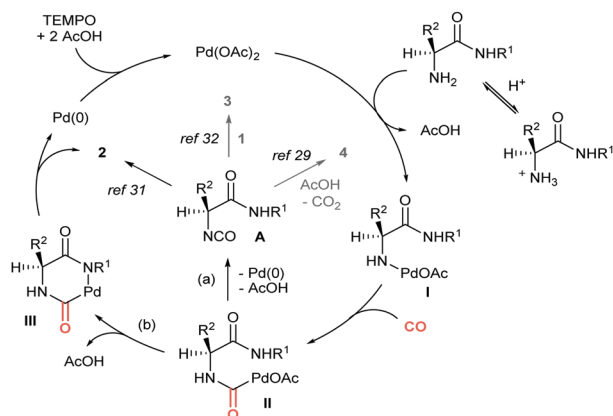
**Scheme 2** Control experiments.

A few control experiments were performed (Scheme 2) to gain preliminary insights into the reaction mechanism. Firstly, an attempt to carbonylate the secondary amino amide (S)-**1v** was performed under the standard conditions. Surprisingly, the expected product (S)-**2v** was detected in traces only and hydantoin (S)-**2a** was isolated in a limited amount (Scheme 2a). This would suggest the intermediacy in the sequence of an isocyanate, which, in turn, could be generated from primary amines only.^{20c,28} Keeping this in mind, the reaction of (S)-**1a** with phenyl isocyanate was performed in MeCN and AcOH (Scheme 2b and c). Urea **5a** was quantitatively obtained in MeCN. In contrast, 10% of **5a** was observed in AcOH together with *N*-phenylacetamide in 90% yield.²⁹ This is consistent with the complete suppression of urea **3** in reactions performed in acetic acid. Similarly, it could correlate with the formation of traces of acetamide **4**, due to the reaction of an isocyanate intermediate with acetic acid,²⁹ under suboptimal conditions (Table 1).

Summarising, two reaction pathways are in principle possible. The first one involves an isocyanate intermediate (Scheme 3, pathway a) and the other a palladacycle one (Scheme 3, pathway b). Initially, Pd(OAc)₂ coordinates the free amino group leading to complex **I**. Insertion of CO leads to intermediate **II**, which can evolve to isocyanate **A** (pathway a). Compound **4** can be generated by the reaction of intermediate **A** with acetic acid.²⁹ Alternatively, it can derive directly from the free amino group³⁰ under acetate/acetic acid conditions. Product **2** can be formed from **A** by an intramolecular attack of the amide moiety to isocyanate.³¹ The formation of **3**, which is usually the preferred product in conventional reaction media (Scheme 2b),^{1a,32} is completely prevented here mainly thanks to the acidic medium (Scheme 2c). Furthermore, the reaction of the amine with the isocyanate to afford **3** might be disfavoured in acidic media because **1** should be mostly in its protonated form. The alternative pathway b, where **II** leads to palladacycle **III**, which then undergoes reductive elimination to hydantoin **2**, cannot be ruled out. In both pathways a and b, the Pd(0) species are promptly re-oxidised by TEMPO to Pd(OAc)₂.

In conclusion, we have developed a new palladium-catalysed carbonylative protocol to access hydantoin from α -amino





Scheme 3 Possible reaction pathways.

amides with excellent yields under very mild conditions. Importantly, the common formation of urea derivatives under palladium catalysis is completely circumvented here. The key features of the method include the use of largely available starting materials (α -amino amides and CO) and acetic acid as an environmentally friendly and cheap chemical. Moreover, the catalytic method does not require bases and ligands. Target compounds retain the chiral information of the reagent.

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Conflicts of interest

There are no conflicts to declare.

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