ChemPubSoc Europe

DOI: 10.1002/chem.201500773

CHEMISTRY A European Journal Full Paper

Asymmetric Synthesis

Asymmetric Synthesis of Fluorinated Isoindolinones through Palladium-Catalyzed Carbonylative Amination of Enantioenriched Benzylic Carbamates

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Abstract: The asymmetric synthesis of fluorinated isoindolinones has been achieved by a palladium-catalyzed aminocarbonylation reaction of the corresponding α-fluoroalkyl *o*-iodobenzylamines. A base-mediated *anti* β-hydride elimination process was suggested to explain the partial erosion of the optical purity observed in some cases. This mechanistic rationale enabled the minimization of this partial racemization by fine-tuning the pK_a of the base.

Introduction

The isoindolinone ring system constitutes an important motif found in numerous bioactive molecules, pharmaceuticals and natural products with interesting therapeutic activities.[1] They are considered to be privileged structures because of their widespread use as building blocks in total synthesis of natural products as well as a common motif for drug-discovery. In particular, the chiral 3-substituted isoindolinone scaffold has emerged as an attractive lead in medicinal chemistry. Examples containing this benzolactam system are (*S*)-pagoclone,[2a,b] (*R*)-pazinaclone (anxiolytic agents),[2c,d] or (+)-lennoxamine,[2e] a natural isoindolobenzazepine alkaloid (Figure 1).

Although the synthesis of racemic 3-alkylisoindolinones has been thoroughly explored,[3] only a few enantioselective approaches have been described, mainly including diastereoselective reactions by using: 1) chiral auxiliaries,[4] including *N-tert*-butanesulfinyl imines,[4c] 2) catalytic asymmetric processes,[5] or 3) organocatalytic approaches.[6] Surprisingly, only a few examples of racemic fluorinated isoindolinones have been reported,[7] despite the fact that the inclusion of fluorinated fragments, such as the trifluoromethyl group, in organic molecules has contributed significantly to the development of new drugs.[8] To the best of our knowledge, there has been no report on enantiomerically pure fluorinated analogues.

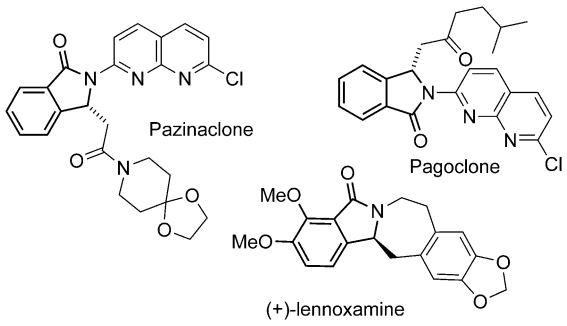

Figure 1. Representative 3-substituted isoindolinone natural products and pharmaceuticals.

Previously, we reported, within the context of diversity-oriented synthesis (DOS), the use of *ortho*-substituted aromatic *tert*-butylsulfinyl imines for the asymmetric synthesis of a variety of benzo-fused carbo- and heterocycles such as fluorinated and non-fluorinated isoindolines and isoquinolines,[9a–c] indanones[9d] or, more recently, the antidepressant sertraline[9e] and aminoesteroid derivatives[9g] (Scheme 1). We have now extended our work based on DOS to the preparation of enantiomerically pure fluorinated γ-lactam derivatives by using palladium-catalyzed carbonylative amination as the key step.[10] In this case, carbon monoxide was used as an inexpensive and readily available C1 source.

Results and Discussion

Preliminary results

First, condensation with Ellman's reagent[11] and then diastereoselective nucleophilic addition of the Ruppert–Prakash reagents[12] (CF_3TMS, C_2F_5TMS) proceeded uneventfully, consistent with previous results.[9a] In a first approach, the carbonylative amination reaction was performed on the starting sulfinyl

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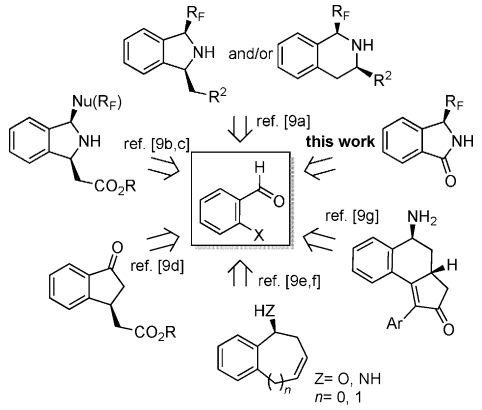
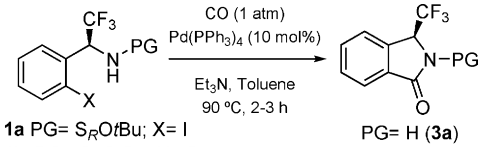
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201500733.



Scheme 1. Diversity-oriented synthesis (DOS) strategy on 2-halobenzaldehyde.

amine **1a/1′a** (X = I, Br), being unsuccessful under different reaction conditions (Table 1, entries 1 and 2). In contrast, we found that subjecting unprotected *ortho*-iodo derivative **2a** to the carbonylation protocol provided the desired isoindolinone scaffold **3a** in good yield but with partial erosion of optical purity (Table 1, entry 3). Surprisingly, no reaction was obtained with the unprotected *ortho*-bromo derivative **2′a** (Table 1, entry 4).[9a]

Table 1. Preliminary results.



1a PG= S_RO*t*Bu; X= I
1'a PG= S_RO*t*Bu; X= Br
2a PG= H; X= I
2'a PG= H; X= Br

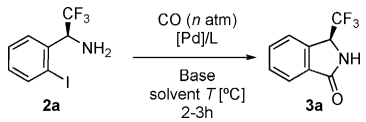
Entry	Compound (e.r.)	Compound ([%])[a]	e.r.[b]
1	**1a**	n.r.[c]	
2	**1′a**	n.r.[c]	
3	**2a** (98:2)	**3a** (67)	83:17
4	**2′a**	n.r.[c]	

[a] Yield of the isolated product. [b] Determined by chiral HPLC analysis. [c] n.r. = no reaction.

Optimization

In view of these results, we first evaluated the influence of the base (Table 2, entries 2–8), employing $[Pd(PPh_3)_4]$ as the catalyst (10 mol%)[13] at 90 °C. Whereas strong bases such as *t*BuOK or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) gave complex mixtures and decomposition of the starting material (Table 2, entries 2 and 3), milder bases such as Li_2CO_3, K_2CO_3, Cs_2CO_3, or AcOK provided high enantioselectivity (an enantiomeric ratio (e.r.) of up to 94:6) to the detriment of chemical yield (21–53%; Table 2, entries 4–7). Finally, Et_3N was mild enough to give a good yield and preserve the enantioselectivity (85% yield; e.r. 92:8; Table 2, entry 8). We further explored different catalytic systems (Table 2, entries 9–13) consisting of $[Pd(OAc)_2]$ or $[PdCl_2(PPh_3)_2]$ and phosphine-based ligands (PPh_3, 1,4-bis(diphenylphosphino)butane (dppb), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (XantPhos)) but none was as good as $[Pd(PPh_3)_4]$ (10 mol%). Toluene turned out to be the best solvent, whereas the use of other solvents such as MeCN, DMF, or dioxane led to unfavorable results (Table 2, entries 14–16). To minimize the racemization, the reaction was carried out at lower temperature (50 °C, Table 2, entry 17), but very low conversion was achieved. Conversion at this temperature could be improved by increasing the pressure of CO to 10 atm (Table 2, entry 18); however, under these conditions epimerization took place to a slightly higher extent than when using 1 atm of CO at 90 °C (Table 2, entry 18 vs. entry 8). Finally, the reaction conditions shown in entry 8 (CO (1 atm), $[Pd(PPh_3)_4]$ (10 mol%), 90 °C, toluene, Et_3N (4 equiv)) were selected for studying the scope and limitations of this transformation.

Table 2. Optimization of the reaction conditions for the intramolecular aminocarbonylation.

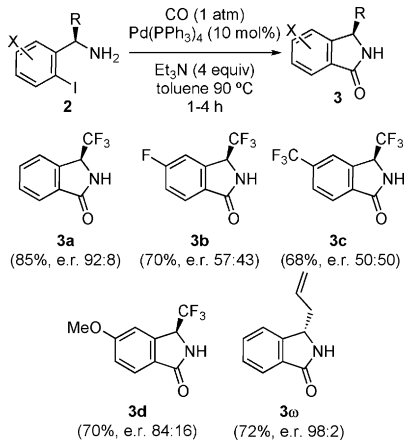


Entry	[Pd]/L	Base	Solvent	**3a** [%][a]	e.r.[b]
1	$[Pd(PPh_3)_4]$	K_3PO_4	TolH	67	83:17
2	$[Pd(PPh_3)_4]$	*t*BuOK	TolH	c.m.	–
3	$[Pd(PPh_3)_4]$	DBU	TolH	c.m.	–
4	$[Pd(PPh_3)_4]$	Li_2CO_3	TolH	21	83:17
5	$[Pd(PPh_3)_4]$	K_2CO_3	TolH	42	94:6
6	$Pd(PPh_3)_4$	Cs_2CO_3	TolH	30	92:8
7	$[Pd(PPh_3)_4]$	AcOK	TolH	53	93:7
8	$[Pd(PPh_3)_4]$	Et_3N	TolH	85	92:8
9	$[(Ph_3P)_2PdCl_2]/PPh_3$	Et_3N	TolH	n.r.	–
10	$[Pd(OAc)_2]$/XantPhos	Et_3N	TolH	74	75:25
11	$[Pd(OAc)_2]/PPh_3$	Et_3N	TolH	63	60:40
12	$[Pd(OAc)_2]$/dppb	Et_3N	TolH	37	80:20
13	$[Pd(OAc)_2]$	Et_3N	TolH	26	88:12
14	$[Pd(PPh_3)_4]$	Et_3N	MeCN	50	80:20
15	$[Pd(PPh_3)_4]$	Et_3N	DMF	90	65:35
16	$[Pd(PPh_3)_4]$	Et_3N	1,4-dioxane	73	78:22
17[c]	$[Pd(PPh_3)_4]$	Et_3N	TolH	28	n.d.
18[c,d]	$[Pd(PPh_3)_4]$	Et_3N	TolH	67	88:12

[a] Yields of the isolated products (c.m. = complex mixture; n.d. = not determined; n.r. = no reaction). [b] Determined by chiral HPLC. [c] Reaction conducted at 50 °C. [d] Reaction conducted under 10 atm of CO.

Scope and limitations

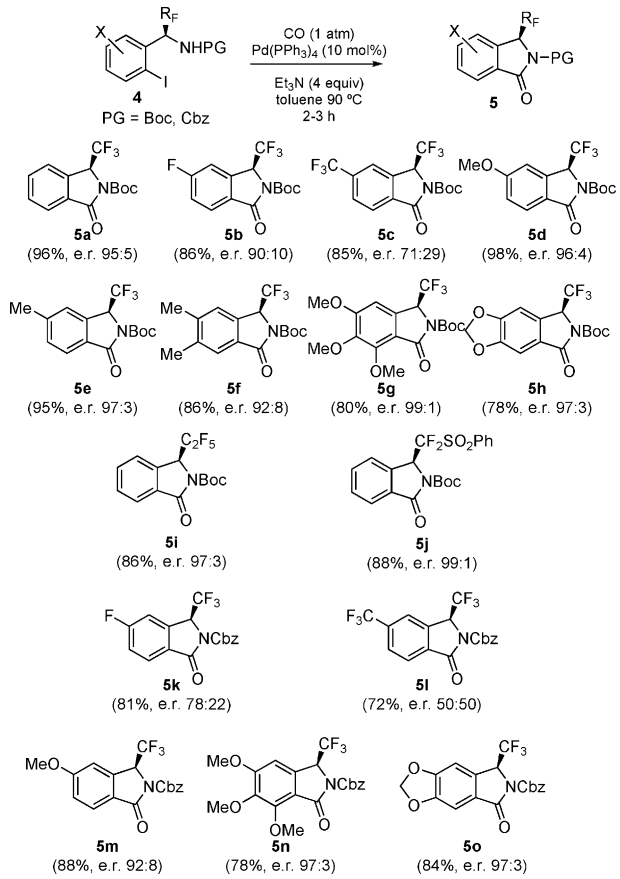
With the optimized reaction conditions in hand (Table 2, entry 8), the scope of this transformation was studied next (Scheme 2). Unfortunately, a noticeable loss of optical purity was observed in all cases during carbonylation, this behavior being particularly pronounced for substrates bearing electron-withdrawing groups, such as F or CF_3, at the aromatic ring (Scheme 2, **3b,c**). Actually, complete racemization was observed for the CF_3 derivative **3c** (Scheme 2, **3c**). It should also be mentioned that the non-fluorinated substrate **2ω** (X = H,



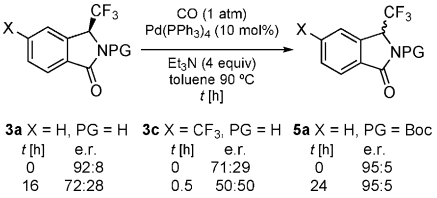
Scheme 2. Intramolecular aminocarbonylation on unprotected benzylamines **2**.

R = allyl) did not undergo racemization under the reaction conditions (Scheme 2, **3ω**).[14]

In view of the observed loss of optical purity, we shifted our attention to N-protected derivatives, in particular, *ortho*-iodobenzyl carbamates **4**, as the fluorinated building block of choice (Scheme 3). To our delight, *tert*-butoxycarbonyl (Boc)-protected substrate **4a** was successfully cyclized under the established conditions with no racemization, apart from certain substrates, especially those containing strong electron-withdrawing groups at the aromatic ring (Scheme 3, **5b,c**). In addition to trifluoromethyl analogues, products bearing higher or lower fluorine loading at the substituent at position 3 could also be synthesized (Scheme 3, **5i,j**). These latter results are remarkable, since they allow fine tuning important physicochemical properties of potential drugs such as pK_a, lipophilicity, or shape. The benzyloxycarbonyl (Cbz) group can be used as alternative nitrogen protecting group, providing comparable results (Scheme 3, **5k**–**o**).



Scheme 3. Intramolecular aminocarbonylation on carbamate protected benzylamines **4**.



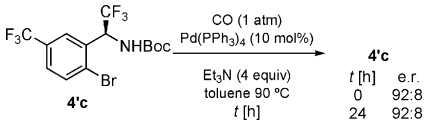
Scheme 4. Studies on the epimerization.

Mechanistic studies

At this point, the question about the partial erosion of optical purity upon carbonylation remained obscure. Racemization might take place by the formation of a flat carbon–nitrogen double bond. To shed some light on this issue, a few experiments were carried out to determine the step when the racemization occurs. In a first set of experiments, the protected and unprotected final products were subjected to the reaction conditions to check their configurational stability. Hence, partial racemization was observed when the free NH isoindolinone **3a** was treated with [Pd(PPh$_3$)$_4$] and Et$_3$N under the reaction conditions. As expected, racemization was much faster for **3c**, which completely racemizes in just half an hour (Scheme 4). On the other hand, Boc-protected product **5a** maintained its optical purity even after prolonged periods (24 h) under the reaction conditions (Scheme 4).

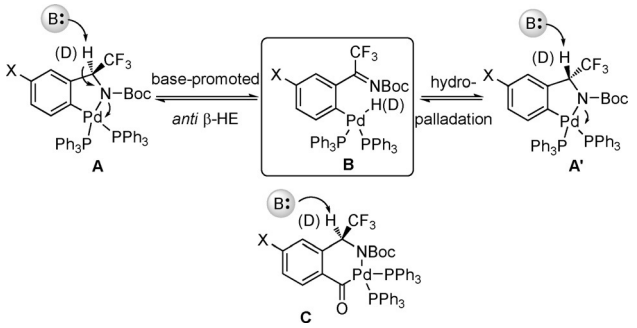
From these experiments, we suggest that the origin of the partial racemization observed upon aminocarbonylation of unprotected benzylamines might be attributed to the presence of an acidic NH. This reaction pathway would be completely suppressed for Boc-protected isoindolines. However, a noticeable loss of enantiomeric purity was still observed for some protected amines (Scheme 3, **5b,c,k,l**). In this case, racemization on the final product was ruled out and, therefore, we examined the configurational stability of the starting carbamate **4** as it contains an NH of similar pK_a of those unprotected isoindolinones **3** and thus, susceptible to deprotonation. To this end, we used the Boc-protected 5-trifluoromethyl-2-bromobenzaldehyde derivative **4′c** (X = Br), which does not give rise to carbonylation under our reaction conditions. Thus, the e.r. of the starting material was monitored upon heating under the reaction conditions. To our surprise, no erosion of the optical purity was observed even after 24 h (Scheme 5).

All these data suggest that for the unprotected amines **2**, the partial racemization observed may be explained by the



Scheme 5. Studies on the epimerization.

configurational instability of the final products under the reaction conditions; whereas for the carbamate-protected derivatives **4**, racemization occurs neither on the final product nor on the starting material. Therefore, we suggest that this partial racemization takes place by reversible β-hydride elimination (β-HE)/hydropalladation (HP) on one of the intermediates after oxidative addition (Scheme 6).



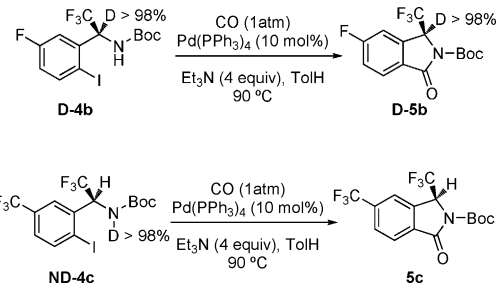
Scheme 6. Mechanistic proposal for the epimerization.

The geometrical restrictions imposed by the cyclic structure of intermediate **A**[15] (the same argument may be applied to intermediate **C**) require the β-hydride elimination step to take place in an *anti*-fashion rendering planar intermediate **B** (Scheme 6). Although several authors have proposed processes of this kind, little mechanistic support has been reported to date.[16,17] Again, this proposal would explain the greater extension of the racemization when electro-withdrawing substituents are present by increasing the acidity of the benzylic proton.

In a further effort to find experimental support for the intramolecular nature of the racemization process, the aminocarbonylation reaction was tested on deuterium-labeled derivatives D-**4b** and **ND-4c** (Scheme 7). In agreement with our hypothesis, neither H- nor D-incorporation was observed upon aminocarbonylation of **D-4b** and **ND-4c**, respectively (Scheme 7). The lack of H/D scrambling seems to rule out that a simple acid–base reaction is responsible for the observed partial epimerization.

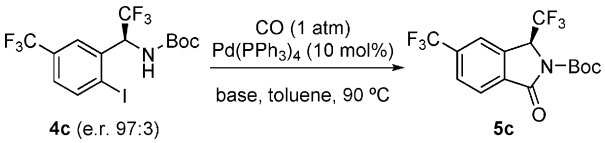
Assuming that the *anti* β-hydride elimination is a base-promoted E2-type process,[18] the degree of epimerization should display a pronounced dependence on the pK_a of the base. Therefore, fine-tuning of the basicity made it possible to overcome the partial racemization on substrates bearing fluorinated residues at the aromatic ring (Table 3).

From Table 3, a nice correlation between the pK_a of the base and the e.r. of the final products may be inferred: the weaker the base, the higher the optical purity of the product (Table 3, entries 1–4).[19] In this way, the use of a milder base, such as AcONa, allowed us to obtain product **5c** with complete preservation of the optical purity (Table 3, entry 4). A few features deserve mentioning: 1) To date, most examples of *anti* β-hydride elimination mechanisms have been reported on Heck or allylic acetate elimination reactions;[16] 2) In most of those examples, isomerization of the palladium intermediate to one featuring hydrogen in a *syn* disposition cannot be excluded,[20] therefore, they would only be formally *anti*; 3) To the best of our knowledge, this is the first report on erosion of optical purity by a reversible *anti* β-hydride elimination/hydrometalation mechanism; 4) Identification of such undesired reaction pathway has allowed us to suppress the racemization by fine-tuning the pK_a of the base used.



Scheme 7. Aminocarbonylation reaction on deuterium-labeled derivatives D-**4b** and **ND-4c**.

Table 3. Dependence of the e.r. with the pK_a of the base.



4c (e.r. 97:3) **5c**

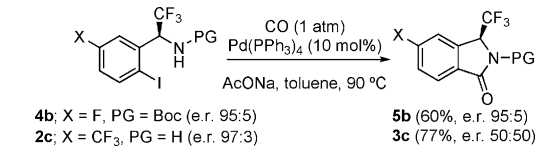
Entry	Base	pK_a	**5c** [%][a]	e.r.[b]
1	Et_3N	10.75	85	71:29
2	collidine	7.4	88	76:24
3	NH_2OH	5.96	95	90:10
4	AcONa	4.76	70	98:2

[a] Yield of the isolated product. [b] Determined by chiral HPLC analysis.

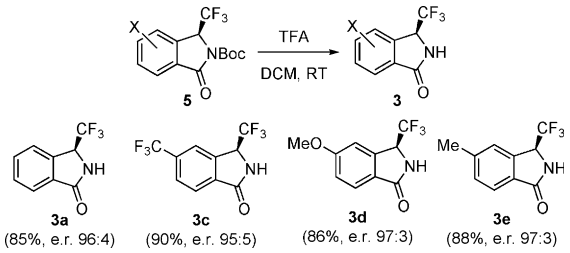
With the optimal base (AcONa, Table 3, entry 4), other reactions for which a higher degree of racemization was observed under our initial reaction conditions were repeated (Scheme 8). As expected, carbamate derivative **4b** underwent smooth aminocarbonylation with complete preservation of optical purity. On the other hand, the most challenging substrate, the unprotected 5-CF_3 derivative **2c**, led to complete racemization because of the configurational instability of the free NH isoindolinone under the reaction conditions. However, the corresponding product **3c** was achieved in excellent optical purity by trifluoroacetic acid (TFA) deprotection of **5c** (see below).

Deprotection

Finally, free NH isoindolines **3** may be obtained in high optical purity by TFA deprotection of the corresponding NBoc deriva-



Scheme 8. Application of the re-optimized reaction conditions to other challenging substrates.



Scheme 9. TFA deprotection of *N*-Boc-protected isoindolinones **5**.

tives **5** (Scheme 9). In this way, product **3c**, which is obtained as a racemate by direct carbonylation of the corresponding unprotected amine, could be achieved with an e.r. of 95:5.

Conclusion

We have described a palladium-catalyzed aminocarbonylation strategy for the asymmetric synthesis of fluorinated isoindolinones starting from the corresponding *ortho*-iodofluoroalkyl benzylamines. The observation of an unexpected erosion of the optical purity upon reaction led us to re-optimize the reaction conditions keeping in mind the possible intermediacy of a reversible *anti* β-hydride elimination/hydrometalation mechanism. The identification of such a reaction pathway allowed us to fine-tune the pK_a of the base, resulting in improved non-racemating reaction conditions. Further mechanistic studies to highlight the intermediacy of such a process are currently underway in our laboratories and will be reported in due course.

Experimental Section

General procedure for the intramolecular aminocarbonylation

CO was bubbled for 10 min into a suspension of the corresponding free amine **2** or carbamate **4**, [Pd(PPh$_3$)$_4$] (10 mol%) and the appropriate base (4 equiv) in toluene (0.1 M). Then, the reaction mixture was heated at 90 °C under an atmosphere of CO (1 atm) until TLC revealed disappearance of the starting material. The reaction mixture was filtered through a short pad of Celite, concentrated under reduced pressure, and purified by means of column chromatography on silica gel using mixtures of hexane and ethyl acetate as eluent.

Acknowledgements

The authors are grateful to the Spanish MINECO (CTQ2013-43310-P) and Generalitat Valenciana (PROMETEOII/2014/073) for their financial support. S.C. expresses her thanks for a Juan de la Cierva contract and L.H. for a predoctoral fellowship.

Keywords: asymmetric synthesis · carbonylation · fluorine · heterocycles · palladium

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Received: February 23, 2015
Revised: May 13, 2015
Published online on June 29, 2015