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Dynamic Kinetic Resolution of 1,3-Dihydro-2*H*-isoindole-1-carboxylic Acid Methyl Ester: Asymmetric Transformations toward Isoindoline Carbamates

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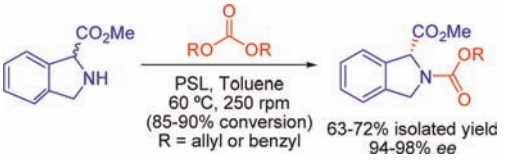
ABSTRACT



Asymmetric syntheses of isoindoline carbamates have been successfully achieved through enzyme-mediated dynamic kinetic resolution processes and without requirement of metal or acid−base catalyst for the substrate racemization. Optically active carbamates were obtained in good yields and an excellent degree of stereoselectivity when *Pseudomonas cepacia* lipase (PSL) was used as biocatalyst, with diallyl or dibenzyl carbonates being both adequate reagents in alkoxycarbonylation reactions.

The isoindoline core is an attractive target in organic and medicinal chemistry because of its presence in the structure of some biologically active compounds.[1] Among isoindoline derivatives, isoindoline-1-carboxylic acid has attracted special attention due to its usefulness as scaffold in the preparation of biologically active compounds.[2] More concretely, isoindoline-1-carboxylic acid is present in the structure of diuretic agents[2a] or angiotensin converting enzyme inhibitors[2b] used in SAR studies. This proline analogue is also included in the structure of organophosphorus compounds showing antioxidant activity.[2e] Furthermore, it constitutes the core skeleton of molecules with potential use in the treatment of diabetes, obesity, dyslipidemia, and atherosclerosis,[2f] the prevention of tissue damage in inflammatory diseases,[2c] or against cancer.[2d]

Even though there is potential interest in the preparation of new drugs, only a few synthetic procedures have been described in the literature (Scheme 1). Thus, isoindoline-1-carboxylic acid or different esters have been synthesized by the addition and further intramolecular cyclization of an amine to alkyl 2-bromo-2-(*o*-bromomethyl)-acetates (path a) and in turn were obtained from commercially available *o*-tolylacetic acid after treatment with thionyl chloride and subsequent bromination and esterification.[2b,3] On the other hand, as depicted in path b, protected isoindoline-

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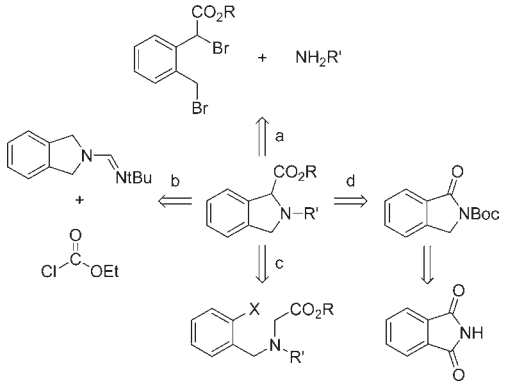
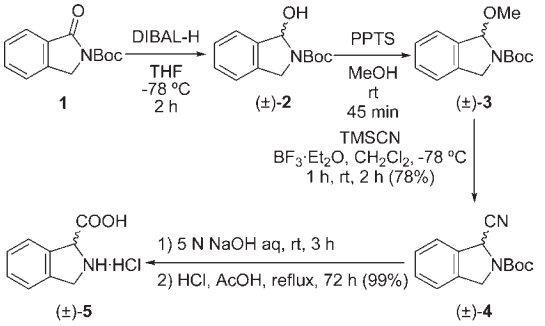
Scheme 1. Synthetic Methods Described in the Literature for the Preparation of Isoindoline-1-carboxylic Acid Derivatives



1-carboxylic acid derivatives can also be prepared via metalation and acylation of the formamidinio derivative of isoindoline[4] (Meyers' methodology). Recently, the synthesis of many isoindoline-1-carboxylic acid derivatives has been achieved by Pd(0)-catalyzed enolate arylation of aryl halides derived from glycine (path c).[5] Herein, we have synthesized racemic isoindoline-1-carboxylic acid in a high yield starting from phthalimide (path d), which provided the suitable *N*-acyl lactam **1** following the procedure previously reported by our research group.[6] The *N*-Boc protected isoindolin-1-one (**1**) was converted into nitrile **4** by a three-step procedure that involved the reduction of the lactam carbonyl group with diisobutylaluminium hydride to obtain an intermediate hemiaminal, which was immediately transformed into the corresponding methoxyaminal. Subsequent addition of trimethylsilyl cyanide in the presence of boron trifluoride etherate yielded compound **4** in 78% yield. Hydrolysis of nitrile **4** furnished the isoindoline-1-carboxylic acid (**5**) as a hydrochloride salt (Scheme 2).

Interestingly, and despite the importance of using enantiomerically pure compounds in biological tests, to the best of our knowledge all reported synthetic procedures only provide isoindoline derivatives in racemic form; therefore, the development of methodologies that provide enantiomerically pure isoindoline-1-carboxylic acid derivatives is an outstanding research field. Biocatalysis provides a wide toolbox for the asymmetric synthesis of optically

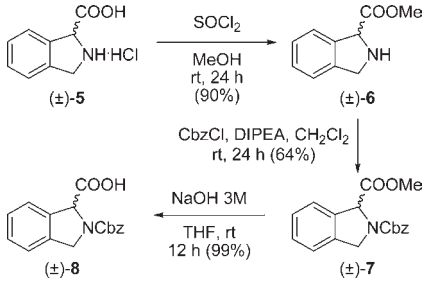
Scheme 2. Synthesis of α-Amino Acid Hydrochloride Salt **5**



active coumpounds in aqueous medium but also in organic or neoteric solvents.[7] In particular, amino acid derivatives are extremely versatile substrates because of their intrinsic bifunctionality.[8] Within this context, we have focused on the study of biocatalytic methods for the enzymatic resolution of suitably protected isoindoline-1-carboxylic acid derivatives. With that aim, the use of hydrolases[9] has been deeply analyzed because of their excellent properties in the asymmetric synthesis of *N*-heterocyclic compounds.[10]

Different experiments were planned, looking for chemoselectively controlled reactivity of the ester moiety or the amino group. The results have been summarized depending on the moiety part susceptible to be transformed: hydrolysis or transesterification reactions were considered when modifying the ester, while alkoxycarbonylation processes were studied when the free amino group was altered.

Scheme 3. Synthesis of Compounds for Use in Lipase-Catalyzed Hydrolysis, Esterification, or Alkoxycarbonylation Reactions



For that reason, a series of racemic amino acid derivatives were prepared from readily available isoindoline-1-carboxylic acid (**5**): α-amino ester **6** for alkoxycarbonylation processes, *N*-Cbz methyl amino ester **7** with hydrolytic purposes and *N*-Cbz protected amino acid **8** for esterification reactions (Scheme 3). Then, **5** was esterified with thionyl chloride ($SOCl_2$) in MeOH forming the racemic

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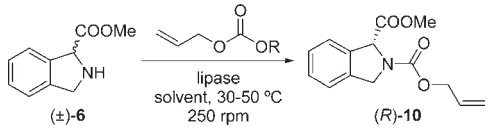
amino ester **6** in high yield (Scheme 2), and then conveniently protected as the *N*-Cbz methyl amino ester **7** with benzyloxycarbonyl chloride (CbzCl) in the presence of (*N*, *N*)-diisopropylethylamine (DIPEA). Before carrying out the hydrolase-catalyzed hydrolysis reactions, *N*-Cbz protected amino acid **8** was prepared by saponification of **7** in quantitative yield.

Enzymatic hydrolysis reactions of the methyl ester **7** in either aqueous medium (phosphate buffer) or organic solvent (THF) using a 20-fold excess of water were unsuccessful, recovering the starting material in all cases when *Candida antarctica* lipase type A (CAL-A), *Candida antarctica* lipase type B (CAL-B), or *Pseudomonas cepacia* lipase (also known as *Burkholderia cepacia* lipase, PSL-C I) were used at 28 °C and 200 rpm.

Esterification processes with the racemic amino acid **8** were attempted in a similar manner to that described by Pietruszka and co-workers in structurally related compounds;[11] however, neither of the lipases tested displayed activity using 5 equiv of MeOH or BuOH in dry THF, or alternatively a biphasic toluene/phosphate buffer system.

Once we explored the unsuccessful modification of the carboxylic group, we decided to study the lipase-catalyzed alkoxycarbonylation reaction of racemic methyl 1,3-dihydro-2*H*-isoindole-1-carboxylate (**6**).[12] Initially 3-methoxyphenyl allyl carbonate (**9a**) was selected as alkoxycarbonylating agent because of the good results shown in the lipase mediated kinetic resolution of indoline[13] or isoquinoline derivatives.[14] Unfortunately CAL-A, CAL-B, or *Candida cycindracea* lipase (CCL) did not display any activity with 2.5 equiv of carbonate (Scheme 4). On the other hand, PSL-C I allowed the formation of the desired enantioenriched allyl carbamate **10** in 28% conversion after 19 h, although surprisingly the starting amino ester was recovered in racemic form, which means that racemization is occurring during the process. Therefore we propose that the racemization equilibrium consists in a deprotonation–protonation process through an achiral intermediate, a stabilized enolate. Amino ester racemization occurs without the addition of an acid–base catalyst, a metal or an oxidation agent, which is typical in DKR processes, and gives an added value to this methodology.[15]

Scheme 4. Lipase-Catalyzed Alkoxycarbonylation of Racemic **6** Using Allyl Carbonates **9a**–**b** in Dynamic Kinetic Resolutions



R = 3-MeO-C_6H_4- (**9a**); R = CH_2=$CHCH_2$- (**9b**)

Coming back to the description of the enzymatic alkoxycarbonylation, it is worth noting that the reaction with 3-methoxyphenyl allyl carbonate (**9a**) released 3-methoxyphenol to the reaction medium, making monitoring the enzymatic processes difficult. Therefore, we decided to attempt the stereoselective alkoxycarbonylation of racemic **6** using the commercially available diallyl carbonate (**9b**) that produced volatile allylic alcohol as byproduct. Initial assays using THF as solvent and variable temperatures and amounts of carbonate led us to fix 10 equiv of **9b** and 50 °C as optimal values to start the process optimization. In these conditions, a 72% conversion was achieved, recovering the carbamate (*R*)-**10** with very high selectivity and substrate with low enantiomeric excess (entry 1, Table 1).

Table 1. DKR of Racemic **6** (0.1 M) Using Diallyl Carbonate and PSL-C I at 50 °C during 48 h at 250 rpm

entry	solvent	carbonate **9b**	*c* (%)[a]	ee_P (%)[b]	ee_S (%)[b]
1	THF	10 equiv	72	96	15
2	1,4-dioxane	10 equiv	29	>99	8
3	MeCN	10 equiv	0		
4	toluene	10 equiv	83	95	65
5	TBME	10 equiv	87	94	78
6	**9b**	0.1 M	85	91	nd[c]

[a] Conversion values determined by ^{1}H NMR of the reaction crude. [b] Enantiomeric excesses determined by HPLC. [c] Not determined.

In order to increase the conversion values, different solvents were tested, finding a remarkable influence depending on the reaction medium, yielding enantiopure (*R*)-**10** and the remaining substrate in very low enantiomeric excess with 1,4-dioxane (entry 2, Table 1), while a more polar solvent such as acetonitrile provokes the inactivation of the enzyme (entry 3, Table 1). Solvents with a lower polaritiy such as *tert*-butyl methyl ether (TBME) or toluene led to higher conversions (83–87%), yielding (*R*)-**10** with high stereoselectivities (94–95% *ee*, entries 4 and 5, Table 1), while racemization failed at longer reaction times. The use of diallyl carbonate as both solvent and alkoxycarbonylating agent did not improve the results previously obtained. Additionally, other PSL preparations were also employed, but while no conversion was found for PSL-SD (supported on diatomite mainly active only in aqueous systems), lower conversions and similar selectivities were found for PSL-IM (crude preparation stabilized with cyclodextrins).

Biocatalytic reactions were finally examined in terms of enzyme loading and temperature by adding double the amount of enzyme in weight or heating at 60 °C (Table 2); however, in all cases doubling the amount of enzyme led to similar results as the ones previously obtained (entries 3

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(12) Amino ester **6** was highly unstable, leading to the corresponding aromatic heterocycle in short reaction times. Therefore, it was used immediately after its preparation or stored as a dichloromethane stock solution previously to be enzymatically reacted with allyl carbonates.

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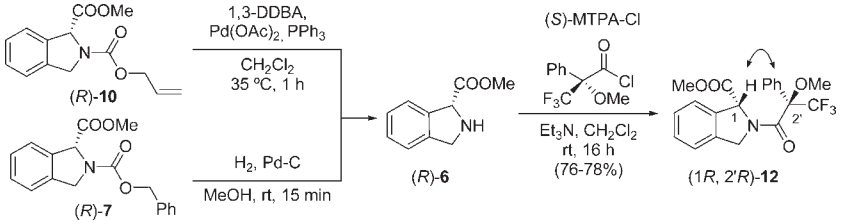
Scheme 6. Synthesis of Mosher Derivative for ^{1}H NMR Analysis in the Assignment of Carbamates (*R*)-**7** and (*R*)-**10** Absolute Configurations



and 4, Table 2). On the other hand, higher temperatures led to a significant increase in the conversion value from 83 to 90% with toluene, yielding the desired carbamate in 94% *ee* (entry 5, Table 2).

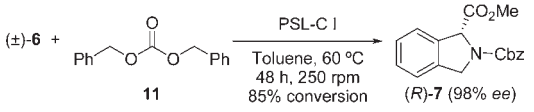
Table 2. DKR of Racemic **6** (0.1 M) Using **9b** during 48 h at 250 rpm and Different Amounts of PSL-C I

entry	solvent	*t* (°C)	PSL-C I[a]	*c* (%)[b]	ee_P (%)[c]	ee_S (%)[c]
1	toluene	50	1:1	83	95 (66)	65
2	TBME	50	1:1	87	94 (68)	78
3	toluene	50	2:1	85	92 (71)	82
4	TBME	50	2:1	87	90 (70)	81
5	toluene	60	2:1	90	94 (72)	72

[a] Ratio (enzyme:substrate) in weight. [b] Conversion values determined by ^{1}H NMR of the reaction crude. Isolated yields of carbamate **10** in parentheses. [c] Enantiomeric excesses determined by HPLC.

Probing the flexibility of our system and although dibenzyl carbonate (**11**) is traditionally considered as a poor reactive reagent,[14,16] the introduction of the Cbz group was possible, gratifyingly yielding the *N*-Cbz aminoester (*R*)-**7** in 85% conversion (63% isolated yield and 98% *ee*, Scheme 5) when using identical conditions as the ones employed with diallyl carbonate (entry 5 in Table 2). Introduction of different *N*-protective groups is a highly demanding task because of the versatility of selective functionalization in peptide coupling.

Scheme 5. Use of Dibenzyl Carbonate (**11**) in PSL-C I catalyzed DKR Process of Racemic Amino Ester **6**



To confirm the absolute configurations for enantioenriched products obtained by means of lipase-catalyzed processes, hydrochloride and hydrobromide salts were prepared, but unfortunately none of them were suitable for X-ray diffraction analysis. For that reason, the corresponding Mosher derivative was synthesized from the already obtained carbamates **7** and **10** through DKR processes. For allyl carbamate **10**, the allyloxycarbonyl group was deprotected by reaction with 1,3-dimethylbarbituric acid (DMBA), palladium(II) acetate, and triphenylphosphine, while for **7**, cleavage of the benzyloxycarbonyl rest was achieved through conventional palladium-catalyzed hydrogenation. Then, subsequent protection of the free amino ester acid **6** using (*S*)-(+)-α-methoxy-α-trifluoromethylphenylacetic acid chloride (MTPA-Cl) in the presence of triethylamine led to the formation of the Mosher amide (1*R*,2′*R*)-**12** in good yields (Scheme 6).[17] This relative stereochemistry defines the *R* configuration for the chiral center C-1, and then a (1*R*,2′*R*) for the Mosher derivative. It must be noticed that partial epimerization was observed after the deprotection−protection sequence, highlighting the lability of this type of compound (see Figure S1, Supporting Information). This aspect is not surprising because the intermediate of the transformation is the free amino ester **6**, which has a high tendency to racemize.

In summary, we have developed for the first time a chemoenzymatic access to isoindoline carbamates in high optical purity by means of an efficient dynamic kinetic resolution strategy without using metal, acid, or basic catalyst for the racemization of the slow reacting amine enantiomer, yielding carbamates in very high optical purities and good yields. The scope of the reaction has been expanded using not only diallyl carbonate but also dibenzyl carbonate, in order to selectively modify the *N*-protection of amino acid derivatives with synthetic purposes.

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Supporting Information Available. General methods, experimental procedures, characterization data for new compounds, and copies of ^{1}H, ^{13}C, and DEPT NMR experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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(17) After registering the ^{1}H NMR spectra for both racemic (1*RS*, 2′*R*) and optically active (1*R*, 2′*R*)-**12**, we compared their H-1 signal, hydrogen atom in α to the carboxylic rest (5.75−5.90 ppm), observing that the proton corresponding to the major diastereoisomer appears at higher fields and therefore is in the opposite side to the Ph group bearing the MTPA rest (it is not affected by ring anisotropy of the Ph group).