RSC Advances

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Cascade reactions of glycine Schiff bases and chiral phase transfer catalysts in the synthesis of α-amino acids 3-substituted phthalides or isoindolinones†

Cite this: *RSC Adv.*, 2014, **4**, 4239

Received 30th October 2013
Accepted 2nd December 2013

DOI: 10.1039/c3ra46268d

www.rsc.org/advances

Milena Perillo, Antonia Di Mola, Rosanna Filosa, Laura Palombi and Antonio Massa*

The tuning of aldol/cyclization cascade reactions of glycine Schiff bases with 2-cyano benzaldehydes provides access to non-natural α-amino acid derivatives substituted alternatively with phthalides or isoindolinones, depending on the strength of the used base. Moreover, a preliminary screening of catalysts and conditions for development of asymmetric versions identified chiral bifunctional phase transfer catalysts as particularly promising, leading to the α-amino esters 3-substituted phthalides in high yields and good diastereo- and enantioselectivity.

Introduction

The interest from academia and chemical industries in α-substituted-α-amino acids has been increasing in the last few years because of their continuing new applications in health care, food production and organocatalysis.[1] Accordingly, the progress in this area is mostly related to the development of truly efficient methods for their preparation, especially in an enantiomerically enriched form.

In this context, α-amino acids linked to important heterocyclic nucleus, like phthalides[2] or isoindolinones,[3] in α-position can be particularly relevant since the combination in a single scaffold of different biologically active groups can confer additional properties. For example, in the past, racemic non-natural α-amino acids substituted with phthalides have been recognized as potential GABA antagonists.[4a] Moreover, similar related scaffolds have been employed in synthesis of other heterocycles like isoquinolines.[4b,c] However, several steps, harsh conditions and a series of intermediate purifications were necessary, with consequent rather low overall yields.[4a] In addition, the reported synthetic strategies are not suitable for asymmetric synthesis.[4] These drawbacks limit their applications in further drug discovery and synthetic transformations.

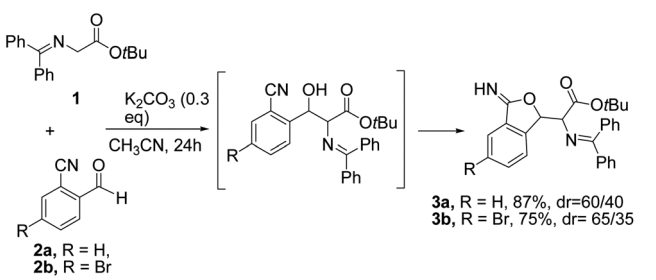
Thus, possible direct accesses to non-natural α-amino acids substituted with heterocyclic groups can be envisioned on the basis of our recent studies about the challenging aldol addition of active methylene compounds.[5] The use of glycine Schiff bases as nucleophiles in tandem addition/cyclization reactions with 2-cyano- or 2-carbomethoxybenzaldehyde could give the advantage of the construction of the heterocyclic core and of the introduction of protected α-amino acid group in the same synthetic step.

In the last years a wide range of reactions of glycine Schiff bases have been reported in the synthesis of natural or non-natural α-substituted amino acids.[6] However, very few studies regard aldol reactions of aromatic aldehydes,[6a] giving to this investigation a further added value.

Results and discussion

Cascade aldol/cyclization reactions of glycine Schiff bases with suitable 2-substituted benzaldehydes

In a preliminary investigation, we examined the reactivity of the *t*-butyl ester of glycine Schiff base **1** with 2-cyano benzaldehyde **2a**, in the presence of a catalytic amount of K_2CO_3. Under the conditions described in Scheme 1, after 24 h, we were pleased to



Scheme 1 Tandem *aldol/cyclization* approaches to α-amino acids substituted with phthalides.

Dipartimento di Chimica e Biologia, Università di Salerno, Via Giovanni Paolo II, 132, 84084-Fisciano, SA, Italy. E-mail: amassa@unisa.it; Fax: +39-089-969-603; Tel: +39-089-969565

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c3ra46268d

‡ Dedicated to professor Adolfo Zambelli on the occasion of his 80th birthday.

observe the formation of a single product in high yield, even if in a rather low diastereomeric ratio.

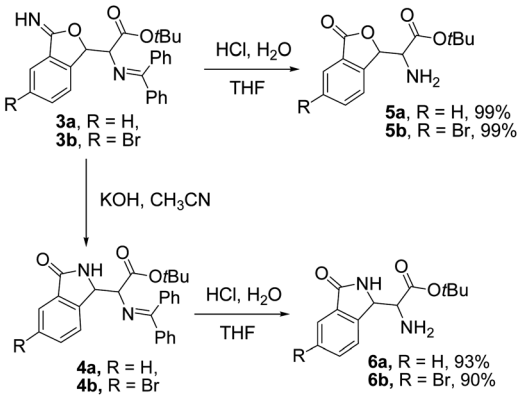
A similar outcome was observed with the aldehyde **2b**, bearing a further bromine substituent on the aromatic ring.

Unexpectedly, the cascade reactions stopped at the cyclic imidates **3**, for both the aldehydes **2a** and **2b** (see Scheme 1). In the presence of other nucleophiles like malonates and β-ketoesters, a different behaviour was observed in the reaction with **2**.[7] The corresponding cyclic imidates have never been isolated, but a rearrangement, a further elimination/intra-molecular conjugated addition, led directly to isoindolinone analogues.[7]

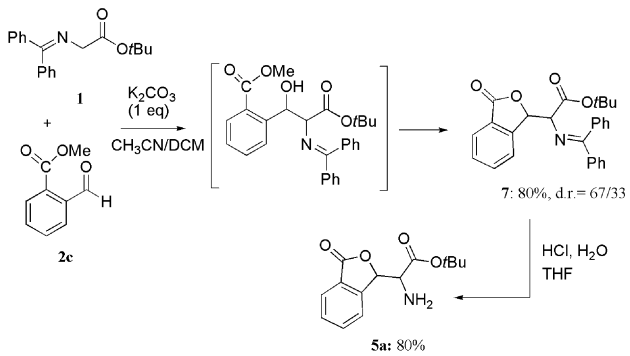
The high stability of **3** is reasonably due to the lower acidity of the CH proton of the glycine Schiff base residual. Glycine Schiff bases are reported to be less acidic than β-ketoesters.[8] A notable consequence of this behaviour is the success of asymmetric alkylation reactions of glycine Schiff bases that is probably related to the scarce capability of racemization of the alkylated products.[6a–d]

Thus, we thought to use a stronger base, eventually to force the deprotonation of **3** and the subsequent rearrangement toward the isoindolinone analogue. Following this idea, when 1 eq. of KOH was used, **3** was obtained in high yield in less than 0.5 h (Table 1, entry 1). Very nicely, under these new conditions, longer reaction time favored the deprotonation of **3**, and the subsequent steps of elimination/intra-molecular conjugated addition, leading to the protected isoindolinones **4** in good conversion.[9] However, only moderate isolated yields of **4** were obtained (entries 2 and 3) because of some decomposition on column.

Then, both **3** and **4**, submitted to mild hydrolysis (Scheme 2), were selectively converted into the phthalides **5** or isoindolinones **6** respectively, substituted with α-amino ester, as

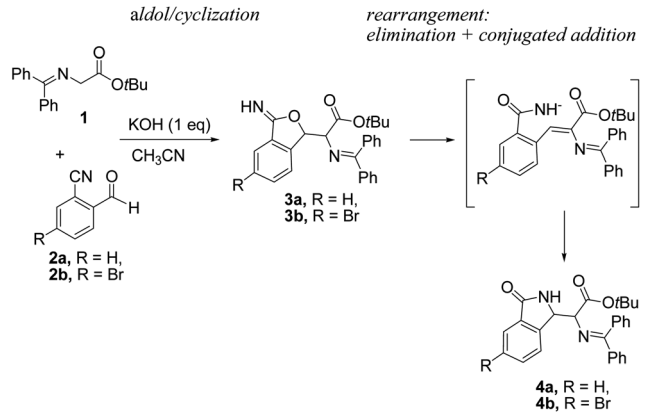


Scheme 2 Mild hydrolysis of protected derivatives to give α-amino ester 3-substituted phthalides or isoindolinones.



Scheme 3 An alternative route to α-amino ester 3-substituted phthalide based on 2-carbomethoxy benzaldehyde as starting material.

Table 1 Cascade reaction of glycine Schiff base under KOH condition enabling the synthesis of α-amino ester 3-substituted isoindolinone



Entry	R	t (h)	Yield **3**[a]	Yield **4**[a]	d.r.
1	H	0.5	85	0	62/38
2	H	16	0	55	60/40
3	Br	24	0	57	62/38

[a] Isolated yield.

characterized by MS and NMR spectroscopy, in high yields. The two diastereomers of **5** were easily separated by chromatography, an aspect particularly important from a synthetic point of view, while a rather less efficient separation was achieved with **6**, probably due to the high polarity of the these compounds (see ESI† for details).

We also evaluated the possibility to obtain the related phthalide **7** in a conceptually similar tandem *aldol/lactonization* process of glycine Schiff base **1** with the 2-carbomethoxy benzaldehyde **2c** (Scheme 3). Pleasingly, after optimization of the reaction conditions, the desired heterocyclic compound **7** was obtained in good yield but moderate diastereoselectivity. Then, submitting **7** to the previously described mild hydrolysis, we obtained **5a** in high yield, providing another direct access to this non-natural α-amino acid derivative (Scheme 3).

Toward an asymmetric version

The study of asymmetric versions of these methodologies is particularly intriguing, also because little attention has been paid to aldol and cascade reactions involving aromatic aldehydes.[6,10,11]

Keeping in mind that both organocatalysed[12] and phase transfer conditions[6a–d,10,13] have been applied to asymmetric

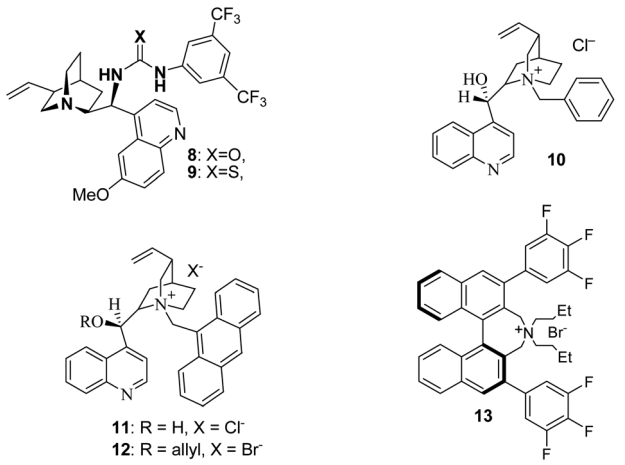


Fig. 1 Common chiral organocatalysts and phase transfer catalysts.

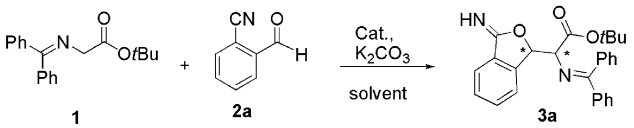
Table 2 Chiral catalysts screening

Entry	Cat.	t (h)	Yield **3a**[a] (%)	d.r.[b]	ee_{mayor}[c] (%)	ee_{minor}[c] (%)
1	**8**[d]	24	—			
2	**9**[d]	24	—			
3	**10**	16	80	67/33	28	8
4	—	24	—			
5	**11**	19	61	65/35	−12	−53
6	**12**	72	46	59/41	30	30
7	**13**	22	40	45/55	21	11

[a] Isolated yield. [b] Determined by ^{1}H-NMR on the crude mixtures. [c] Determined by HPLC on chiral column. [d] Reactions performed with and without K_2CO_3.

transformations of glycine Schiff bases, we began our investigation exploring the well-known bifunctional urea-[12a] and thiourea-quinine[12b] organocatalysts **8** and **9** (Fig. 1). We performed several experiments using 0.15 eq. of the organocatalysts in DCM reacting both **2a** and **2b**, but we observed low conversions and decomposition products (Table 2, entries 1 and 2). Several other reaction conditions were tested as the combination of **8** or **9** with K_2CO_3, but similar disappointing results were obtained. This outcome is in contrast with what is obtained with malonates and β-ketoesters in asymmetric reaction with 2-cyano benzaldehydes leading to the corresponding 3-substituted isoindolinones in high yields and good ees,[7d,e] highlighting the particular behavior of **1** with respect to other active methylene compounds.

Then, we tried a different approach, considering the series of the chiral ammonium salts **10–13** (Fig. 1) in combination with inorganic bases as in asymmetric phase transfer conditions.



Scheme 4 Enantioselective synthesis of cyclic imidates through tandem aldol/cyclization reaction.

We began this further investigation, employing the cinchoninium benzylic salt **10** at 5 mol% in combination with K_2CO_3 in DCM (Scheme 4 and Table 2, entry 3). This system revealed particularly effective, leading to the 3-substituted iminophthalane **3a** in high yield and in a reasonable reaction time (Scheme 4 and Table 2, entry 3). However, despite the effectiveness of the PTC **10** in several asymmetric transformations,[6a–d,10a] a very poor enantioselectivity was observed. Thus, in a control experiment, reacting 2-cyano benzaldehyde **2a** with **1** in DCM in the presence of the only K_2CO_3, we recovered the starting materials non-reacted (Table 2, entry 4), excluding the concomitant background non-asymmetric reaction.

Then, an interesting outcome was observed with the related chiral PTCs **11** and **12** derived from cinchonidine. In the case of **11**, a higher ee was obtained for the minor diastereomer (entry 5), while its O-allyl protected analogue **12** showed a lower reactivity (entry 6). These outcomes probably highlights the importance of two aspects, of both the steric hindrance of ammonium substituent and the necessity of the hydrogen bond donor in the PTC. A similar explanation can be given to justify the disappointing outcome in the presence of **13**, belonging to another class of particularly effective chiral PTC, widely employed in glycine Schiff bases asymmetric reactions.[6a,13] The observed low yield, the formation of decomposition products and the low level of enantioselectivity are probably due to the lacking of a suitable hydrogen bond donor (entry 7).

Based on these considerations, the linking in a chiral molecule of a strong hydrogen bond donor, as an urea group, together with an ammonium ion, could bring to a better efficiency through a more ordered transition state, favoring the

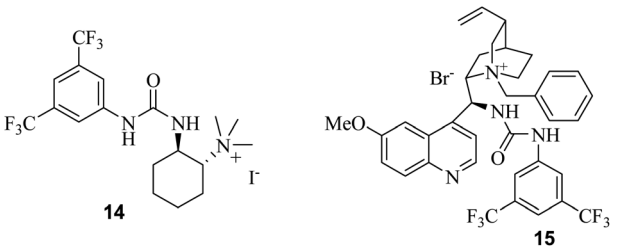
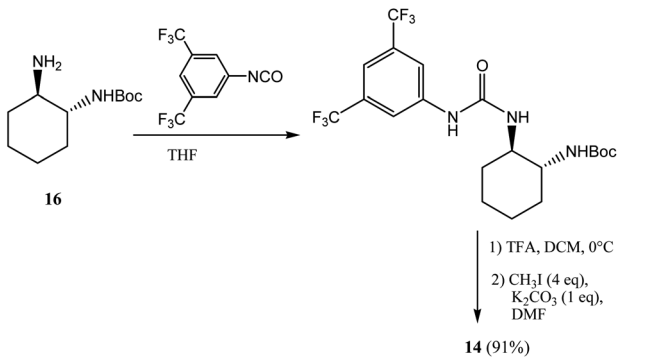


Fig. 2 Bifunctional phase-transfer catalysts.



Scheme 5 Synthesis of bifunctional chiral ammonium salt from (*R*,*R*)-diaminocyclohexane.

proximity of both the aldehyde and the nucleophilic species. Thus, we focused on two structurally different bifunctional ammonium salts: firstly on **14** designed by us and then on **15**, recently reported by Dixon[14] (Fig. 2).

The ammonium salt **14** was easily obtained in a very straightforward synthesis, consisting of three simple steps (reaction with the aryl isocyanate, deprotection and alkylation) using the *N*-Boc protected (*R*,*R*)-diaminocyclohexane **16** as commercially available starting material. Thus, the final product **14** was obtained in the very high total yield of 91%, without intermediate purifications (see Scheme 5 and ESI† for details). On the contrary, as also reported by the authors,[14] even if **15** derives from the alkylation of the urea-quinine derivative **8**, its purification requires much more efforts. Consequently, **15** was obtained in a lower total yield of 40%, considering also the synthesis of **8** from the commercially available quinine.

Nevertheless, both **14** and **15** were tested under the same reaction conditions of Scheme 4, leading to **3a** in high yields (Table 3). In particular, a moderate level of enantioselectivity was observed with **14** (Entry 1, Table 3), while **15** revealed more effective both in terms of diastereo- and enantio-selectivity leading to the good value of 70% ee for the major diastereomer (entry 2).

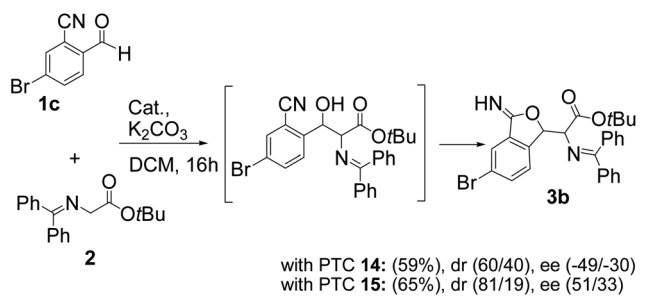
Different solvents were also tested in the presence of **15**, giving worse results than DCM, even if a higher d.r. was detected with $CHCl_3$ (Table 3, entry 3).

Then, the combination $KOH_{(S)}$/**15** was also considered in the reaction of Scheme 4. However, the outcomes were not encouraging since we observed decomposition products (Table 3, entry 5), leaving the possibility or the problem to obtain isoindolinones **4** asymmetrically to future studies.

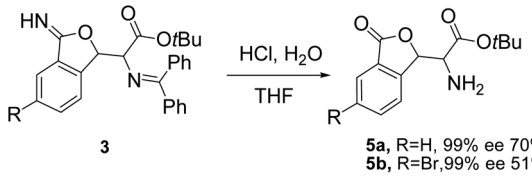
Table 3 Asymmetric reaction in the presence of bifunctional chiral PTCs

Entry	Cat.	Solv.	*t* (h)	Yield **3a**[a] (%)	d.r.[b]	ee_{mayor}[c] (%)	ee_{minor}[c] (%)
1	**14**	DCM	18	82	60/40	−55	−20
2	**15**	DCM	16	89	80/20	70	45
3	**15**	$CHCl_3$	6	72	86/14	63	50
4	**15**	Toluene	6	80	75/25	42	44
5[d]	**15**	DCM	24	—			

[a] Isolated yield. [b] Determined by ^{1}H-NMR on the crudes **3a**. [c] Determined by HPLC on chiral column. [d] 1 eq. of KOH was used instead of K_2CO_3.



Scheme 6 Reaction of 4-bromo-2-cyanobenzaldehyde.



Scheme 7 Synthesis of enantioenriched α-amino esters 3-substituted phthalides.

The aldehyde **2b**, with a further bromine substituent in 4 position on the aromatic ring, was employed under the previous conditions of Table 3, entries 1 and 2. In the presence of both **14** and **15**, **2b** revealed less effective than **2a** in terms of yields and enantioselectivity, while, **15** led to a slightly higher ee than **14** (see Scheme 6).

At the end of this explorative investigation, it is worthy to analyze our results in the literature context. If we consider the surprising lack of studies about aldol reactions of glycine Schiff bases with aromatic aldehydes under organocatalytic or PTC conditions,[6a] the described results are particularly encouraging. Chiral PTCs are widely reported to be particularly effective in aldol reactions of aliphatic aldehydes.[6a,10,13b,c] Conversely, reactions of aromatic aldehydes with **1** have been reported under strongly basic conditions using *n*-BuLi,[11] in which the use of chiral amines as additives leads to only moderate levels of enantioselectivity (<60% ee for β-hydroxy-α-amino acid derivatives).[11] Nevertheless, the observations of rapid decomposition of the aldol adducts of benzaldehyde with glycine Schiff bases reported by Castle *et al.*[10b] are noteworthy. This suggests that the success of the aldol reaction of the 2-cyanobenzaldehydes is probably due to the intramolecular entrapping of aldol intermediate at the cyano group, leading to the stable cyclic imidates **3**.

Also the 2-carbomethoxy benzaldehyde **1c** was tested under organocatalytic or phase transfer conditions employing **8**, **9** or the chiral PTCs **10**, **14** and **15**, respectively. Unfortunately, in all the cases we observed a very low reactivity, recovering the starting materials unreacted. This outcome parallels our previous studies about the reaction of **2c** with other active methylene compounds, like malonates and β-ketoesters, for which we have been able to develop only an efficient non asymmetric reaction to 3-substituted phthalides.[15] In contrast, the use of 2-cyano benzaldehydes, under asymmetric PTC, yields a promising route to chiral 3-substituted phthalides, submitting **3** to the mild hydrolysis described in Scheme 7. In this way, after the removing of both the imino groups, we obtained the α-amino acid derivatives **5** in quantitative yields and, most importantly, with unchanged enantiomeric purity with respect to **3** (Scheme 7).

Conclusions

In summary, we have developed the synthesis of α-amino ester derivatives of 3-substituted phthalides or isoindolinones through cascade reactions of a glycine Schiff base with 2-cyano benzaldehydes and 2-carbomethoxy benzaldehyde. In the presence of 2-cyano benzaldehydes as starting materials, we

have demonstrated that the type of the used base tunes the cascade process toward the synthesis of cyclic imidates or, after their rearrangement, to isoindolinone derivatives.

Then, in a preliminary investigation, an asymmetric version to give chiral phthalides has been developed. Good results in terms of yield, diastereo- and enantio-selectivity have been obtained in the presence of bifunctional chiral PTCs.

Based on the reported results, other studies can be envisioned not only in the improvement and expanding the scope of the described methodologies, but also in the development of an asymmetric rearrangement of imidates into isoindolinones or in other modifications and applications of the new PTC.

Experimental part

General remarks

All reactions were performed using commercially available compounds without further purification. Column chromatographic purification of products was carried out using silica gel 60 (70–230 mesh, Merck). The NMR spectra were recorded on Bruker DRX 400, 300, 250 spectrometers (400 MHz, 300 MHz, 250 MHz, ^{1}H; 100 MHz, 75 MHz, 62,5 MHz ^{13}C). Spectra were referenced to residual $CHCl_3$ (7.26 ppm, ^{1}H, 77.23 ppm, ^{13}C). Coupling constants J are reported in Hz. Yields are given for isolated products showing one spot on a TLC plate and no impurities detectable in the NMR spectrum. Mass spectral analyses were carried out using an electrospray spectrometer, Waters 4 micro quadrupole. Elemental analyses were performed with FLASHEA 1112 series-Thermo Scientific for CHNS-O apparatus.

Procedure for the synthesis of cyclic imidates 3 from 2-cyano benzaldehydes under K_2CO_3 condition

In a round-bottom flask, K_2CO_3 (0.5 eq.) was added at room temperature to a stirred solution of 2-cyanobenzaldehydes **2a** or **2b** (0.20 mmol) and *N*-(diphenylmethylene)glycine *tert*-butyl ester **1** (1.1 eq., 0.22 mmol), in CH_3CN (1.2 mL). The mixture was stirred until starting material disappeared, then the solvent was evaporated and the crude mixture was purified without further work-up directly by flash chromatography on silica gel with hexane/ethyl acetate 1/1 mixtures to give the products **3**.

tert-Butyl-2-(diphenylmethyleneamino)-2-(3-iminoisoindolin-1-yl)acetate (3a)

Chromatography: hexane/ethyl acetate 8 : 2; amorphous solid. Major diastereomer: ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.85 (bs, 1H), 7.52–7.48 (m, 4H), 7.39–7.30 (m, 8H), 6.91 (d, J = 6.5 Hz, 2H), 6.06 (d, J = 5.8 Hz, 1H), 4.22 (d, J = 5.9 Hz, 1H) 1.47 (s, 9H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 172.9, 168.1, 144.9, 138.9, 135.6, 131.8, 130.7, 128.9, 128.8, 128.7, 128.5, 128.3, 128.1, 128.0, 127.7, 123.6, 123.1, 82.8, 82.3, 69.8, 27.9. MS (ESI): m/z = 427 (M + H$^+$). Anal. calcd for $C_{27}H_{26}N_2O_3$: C, 76.03; H, 6.14; N, 6.57. Found: C, 76.23; H, 6.04; N, 6.50%. Minor diastereomer has been obtained in mixture with the major diastereomer. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.85 (m, 1H), 7.52–7.48 (m, 4H), 7.39–7.30 (m, 7H), 6.91 (d, J = 6.5 Hz, 2H), 5.90 (d, J = 3.7 1H), 4.37 (d, J = 3.7 Hz, 1H) 1.36 (s, 9H).

tert-Butyl-2-(5-bromo-3-imino-1,3-dihydroisobenzofuran-1-yl)-2-(diphenylmethyleneamino)acetate (3b)

Chromatography: hexane/ethyl acetate 8 : 2; amorphous solid. Major diastereomer: ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.01 (bs, 1H), 7.63–7.60 (m, 1H), 7.53–7.50 (m, 2H) 7.44–7.37 (m, 4H), 7.32–7.27 (m, 4H), 7.10–7.09 (m, 2H), 5.83 (d, J = 4.4 Hz, 1H) 4.34 (d, J = 4.3 Hz, 1H) 1.36 (s, 9H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 172.7, 167.6, 143.1, 138.8, 135.8, 134.8, 130.6, 128.8, 128.7, 128.5, 127.9, 127.6, 127.5, 126.7, 124.1, 122.9, 82.9, 82.3, 68.2, 27.7. MS (ESI): m/z = 505 (M + H$^+$). Anal. calcd for $C_{27}H_{25}BrN_2O_3$: C, 64.16; H, 4.99; N, 5.54. Found: C, 64.02; H, 4.85; N, 5.64%. Minor diastereomer has been obtained in mixture with the major diastereomer, aromatic region overlaps. The main peaks are: ^{1}H-NMR peaks (250 MHz, $CDCl_3$) are: δ 6.01 (d, J = 6.1 Hz, 1H), 4.26 (d, J = 6.1 Hz, 1H), 1.47 (s, 9H).

Procedure for the synthesis of protected isoindolinones 4 from 2-cyano benzaldehydes under KOH condition

In a round-bottom flask, KOH (1.0 eq.) was added at room temperature to a stirred solution of 2-cyanobenzaldehydes **2a** or **2b** (0.20 mmol) and *N*-(diphenylmethylene)glycine *tert*-butyl ester **1** (1.1 eq., 0.22 mmol), in CH_3CN (1.5 mL). The mixture was stirred until starting material disappeared, then the mixture was purified without intermediate work-up directly by flash chromatography on silica gel with hexane/ethyl acetate 1/1 mixtures to give the products **4**. Alternatively the solvent was evaporated and the crude was submitted to hydrolysis without purification.

tert-Butyl-2-(diphenylmethyleneamino)-2-(1-oxoisoindolin-3-yl)acetate (4a)

Chromatography: hexane/ethyl acetate 7/3; amorphous solid, mixtures of diastereomers 1.3/1. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.78 (d, J = 7.8 Hz, 2H), 7.68 (d, J = 7.8 Hz, 2H), 7.46–7.40 (m, 19H), 7.27–7.25 (m, 5H), 7.05 (m, 2H), 6.75 (d, J = 7.2 Hz, 2H), 6.70 (bs 1H), 6.50 (bs, 1H), 5.19–5.16 (m, 2H), 4.24 (d, J = 5.36 Hz, 1H), 3.93 (d, J = 8 Hz, 1H), 1.47 (s, 9H), 1.40 (s, 9H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 172.7, 172.3, 170.4, 170.1, 168.9, 168.8, 144.8, 144.1, 139.1, 138.9, 135.6, 135.5, 132.6, 132.4, 131.6, 131.4, 130.8, 130.7, 128.9, 128.8, 128.7, 128.5, 128.4, 128.3, 128.2, 128.0, 127.7, 127.6, 127.5, 124.5, 123.8, 123.7, 123.4, 123.1, 82.7, 82.4, 70.3, 68.5, 58.4, 57.8, 27.9, 27.7. MS (ESI): m/z = 427 (M + H$^+$). Anal. calcd for $C_{27}H_{26}N_2O_3$: C, 76.03; H, 6.14; N, 6.57. Found: C, 76.39; H, 6.32; N, 6.23%.

tert-Butyl-2-(6-bromo-1-oxoisoindolin-3-yl)-2-(diphenylmethyleneamino)acetate (4b)

Chromatography: hexane/ethyl acetate 8/2; amorphous solid, mixtures of diastereomers 1.4/1. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.88 (d, J = 7.6 Hz, 1H), 7.68 (d, J = 7.6 Hz, 1H), 7.55 (m, 2H), 7.46 (m, 2H), 7.42–7.27 (m, 15H), 7.14 (d, J = 8.0 Hz 1H), 7.07 (m, 2H), 7.05 (m, 2H), 6.75 (d, J = 7.2 Hz, 1H), 6.75 (bs 1H), 6.58 (bs, 1H), 5.14–5.12 (m, 2H), 4.22 (d, J = 5.2 Hz, 1H), 3.94 (d, J = 8.0 Hz, 1H), 1.46 (s, 9H), 1.41 (s, 9H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 173.0, 172.6, 168.7, 168.6, 168.5, 167.7, 143.4, 142.8, 138.9, 138.7, 135.5, 134.7, 134.5, 134.4, 134.3, 131.0, 130.8, 130.0, 128.9, 128.8,

128.5, 128.4, 128.3, 128.2, 128.1, 127.5, 127.0, 126.1, 125.0, 122.7, 82.9, 82.8, 69.9, 68.2, 58.2, 57.7, 27.9, 27.7. MS (ESI): $m/z = 505$ ($M + H^+$). Anal. calcd for $C_{27}H_{25}BrN_2O_3$: C, 64.16; H, 4.99; N, 5.54. Found: C, 64.28; H, 5.09; N, 5.42%.

Procedure for the synthesis of protected phthalides 7 from 2-carbomethoxy benzaldehyde 2c

In a round-bottom flask, K_2CO_3 (1 eq.) was added at room temperature to a stirred solution of 2-carbomethoxy benzaldehyde **2c** (0.20 mmol) and *N*-(diphenylmethylene)glycine *tert*-butyl ester **1** (1.1 eq., 0.22 mmol), in CH_3CN (0.2 mL) and DCM (0.2 mL). The mixture was stirred until starting material disappeared, then the mixture was purified without intermediate work-up directly by flash chromatography on silica gel with hexane/ethyl acetate 1/1 mixtures to give the product **7**.

tert-Butyl-2-(diphenylmethyleneamino)-2-(3-oxo-1,3-dihydroisobenzofuran-1-yl)acetate (7)

Chromatography: hexane/ethyl acetate 8 : 2; amorphous solid. Mixture of diastereoisomers. ^{1}H-NMR and ^{13}C-NMR is given for the major diastereomer (400 MHz, $CDCl_3$): δ 7.90 (d, J = 7.6 Hz, 1H), 7.64–7.61 (m, 2H), 7.57–7.53 (m, 3H), 7.45–7.43 (m, 2H), 7.40–7–37 (m, 2H), 7.33–7.29 (m, 2H), 7.14–7.13 (m, 2H), 5.88 (d, $J = 4.4$ Hz, 1H) 4.43 (d, $J = 4.4$ Hz, 1H), 1.31 (s, 9H, major). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 174.0, 168.7, 148.4, 140.1, 137.1, 135.1, 131.9, 130.6, 130.1, 129.6, 129.3, 129.2, 129.0, 128.8, 128.4, 126.6, 124.3, 83.7, 82.3, 69.0, 28.9. MS (ESI): m/z = 428 ($M + H^+$). Anal. calcd for $C_{27}H_{25}NO_4$: C, 75.86; H, 5.89; N, 3.28. Found: C, 75.62; H, 5.75; N, 3.54%.

Procedure for the synthesis of amino esters phthalides 5 and isoindolinone 6 by hydrolysis

The purified products **3**, **4** or **7** was dissolved at 0 °C in a solution of 0.5 M HCl (1 mL) and THF (3 mL). The mixture was stirred at the same temperature for 2 h and THF was evaporated under vacuum. Then, two work-up procedures can be applied: (1) the resulting solution was treated with saturated $NaHCO_3$ (20 mL) and extracted with CH_2Cl_2 (4 × 30 mL). Alternatively: (2) the acidic solution is firstly extracted with 30 mL CH_2Cl_2 to separate the benzophenone, then treated with saturated $NaHCO_3$ (20 mL) and extracted with CH_2Cl_2 (4 × 30 mL). For both the cases the organic extracts were treated with anhydrous Na_2SO_4, filtered and evaporated under vacuum. The crude product was purified by flash chromatography on silica gel with hexane/ethyl acetate 1/1 mixture for **5** or only ethyl acetate for **6** to give the title products.

tert-Butyl-2-amino-2-(3-oxo-1,3-dihydroisobenzofuran-1-yl)-acetate (5a)

Chromatography: hexane/ethyl acetate from 8/2 to 6/4 mixtures; amorphous solid. Mayor diastereomer ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.92 (d, $J = 7.6$ Hz, 1H), 7.68 (t, $J = 6.48$ Hz, 1H), 7.58 (t, $J = 7.42$ Hz, 1H), 7.44 (d, $J = 7.6$ Hz, 1H), 5.77 (d, $J = 3.5$ Hz, 1H), 4.04 (d, J = 3.6 Hz, 1H), 1.61 (br s, 2H), 1.40 (s, 9H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 171.5, 171.3, 147.5, 135.2, 130.8, 128.3, 126.9, 123.8, 83.9, 83.3, 58.7, 29.1. MS (ESI): $m/z = 264$ ($M + H^+$). Anal. calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.97; H, 6.41; N, 5.37%. Minor diastereomer ^{1}H-NMR (250 MHz, $CDCl_3$): δ 7.92 (d, $J = 7.6$ Hz, 1H) 7.70–7.53 (m, 3H), 5.83 (d, $J = 2.4$ Hz, 1H) 3.93 (d, $J = 2.7$ Hz, 1H) 1.45 (s, 9H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 171.7, 171.4, 148.2, 135.3, 130.8, 128.2, 126.7, 123.2, 84.0, 83.1, 58.3, 29.1. MS (ESI): $m/z = 264$ ($M + H^+$). Anal. calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.79; H, 6.62; N, 5.43%.

tert-Butyl-2-amino-2-(6-bromo-1,3-dihydro-1-oxoisobenzofuran-3-yl)acetate (5b)

Chromatography: hexane/ethyl acetate from 9/1 to 7/3 mixtures; amorphous solid. Major diastereomer ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.04 (d, $J_1 = 1.7$ Hz, 1H), 7.78 (dd, $J_1 = 8.1$ Hz, $J_2 = 1.7$ Hz, 1H), 7.33 (d, $J = 8.1$ Hz, 1H), 5.70 (d, $J = 3.8$ Hz, 1H) 3.99 (d, J = 3.7 Hz, 1H) 1.44 (s, 9H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 170.1, 168.3, 144.8, 136.9, 129.1, 128.5, 124.1, 123.4, 82.9, 81.7, 57.2, 27.8. MS (ESI): $m/z = 343$ ($M + H^+$). Anal. calcd for $C_{14}H_{16}BrNO_4$: C, 43.14; H, 4.71; N, 4.09. Found: C, 43.39; H, 4.62; N, 4.23%. Minor diastereomer ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.04 (s, 1H) 7.80 (dd, $J_1 = 6.7$ Hz, $J_2 = 1.5$ Hz, 1H) 7.44 (d, $J = 8$ Hz, 1H) 5.78 (d, $J = 2.3$ Hz, 1H) 3.90 (d, $J = 2.7$ Hz, 1H) 1.45 (s, 9H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 170.3, 168.6, 145.7, 137.2, 129.0, 128.6, 123.5, 82.9, 81.7, 56.7, 27.8. MS (ESI): $m/z = 343$ ($M + H^+$). Anal. calcd for $C_{14}H_{16}BrNO_4$: C, 43.14; H, 4.71; N, 4.09. Found: C, 43.29; H, 4.82; N, 3.98%.

tert-Butyl-2-amino-2-(1-oxoisoindolin-3-yl)acetate (6a)

Chromatography: ethyl acetate; amorphous solid. Major diastereomer. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.86 (d, $J = 7.5$ Hz, 1H), 7.59–7.46 (m, 3H), 6.52 (br s, 1H), 4.91 (d, $J = 3.5$ Hz, 1H), 3.77 (d, J = 3.5 Hz, 1H), 1.88 (br s, 2H), 1.50 (s, 9H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 172.2, 170.9, 143.9, 132.2, 128.8, 124.1, 123.6, 122.5, 82.7, 58.8, 57.3, 27.9. MS (ESI): $m/z = 263$ ($M + H^+$). Anal. calcd for $C_{14}H_{18}N_2O_3$: C, 64.10; H, 6.92; N, 10.68. Found: C, 64.39; H, 6.81; N, 10.43%. Mixtures of diastereomers ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.86–778 (m, 2H major + minor), 7.58–7.46 (m, 6H major + minor), 7.04 (br s, 1H minor), 6.58 (br s, 1H major), 4.91 (d, $J = 3.5$ Hz, 1H major), 4.84 (d, $J = 3.5$ Hz, 1H minor), 3.79 (d, $J = 3.5$ Hz, 1H minor), 3.77 (d, $J = 3.5$ Hz, 1H major), 1.50 (s, 9H major), 1.32 (s, 9H minor). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 172.2, 171.2, 170.9, 170.7, 144.1, 139.3, 132.4, 132.2, 131.7, 130.3, 130.0, 128.8, 128.6, 128.4, 128.3, 124.0, 123.8, 123.6, 122.5, 82.6, 82.4, 59.9, 58.9, 57.7, 57.4, 27.9, 27.7. MS (ESI): $m/z = 263$ ($M + H^+$). Anal. calcd for $C_{14}H_{18}N_2O_3$: C, 64.10; H, 6.92; N, 10.68. Found: C, 64.31; H, 7.10; N, 10.83%.

tert-Butyl-2-amino-2-(1-oxoisoindolin-3-yl)acetate (6b)

Chromatography: ethyl acetate; amorphous solid. Major diastereomer. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.99 (d, $J = 2.5$ Hz, 1H), 7.72–7.67 (m, 1H), 7.36 (d, $J = 9.1$ Hz, 1H), 6.67 (bs, 1H), 4.87 (d, J = 3.2 Hz, 1H), 3.75 (d, J = 3.2 Hz, 1H), 1.90 (bs, 2H), 1.50 (s, 9H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 171.8, 169.3, 142.6, 135.1, 134.5, 127.2, 124.1, 122.9, 82.9, 58.5, 57.1, 27.9. MS (ESI):

$m/z = 341$ ($M + H^+$). Anal. calcd for $C_{14}H_{17}BrN_2O_3$: C, 49.28; H, 5.02; N, 8.21. Found: C, 49.37; H, 5.13; N, 8.29%. Mixtures of diastereomers ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.88 (bs, 2H major + minor), 7.72–7.67 (m, 2H major + minor), 7.47 (d, $J = 6.0$ Hz), 7.35 (d, $J = 6.0$ Hz), 6.92 (bs, 1H minor), 6.58 (bs, 1H major), 4.86 (d, $J = 3.5$ Hz, 1H major), 4.79 (d, $J = 5.8$ Hz, 1H minor), 3.71 (m, 2H major + minor), 1.50 (s, 9H major), 1.35 (s, 9H minor). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 172.0, 170.7, 169.2, 168.9, 142.8, 142.7, 135.1, 134.7, 134.5, 127.3, 127.0, 125.5, 124.1, 123.0, 122.8, 82.8, 82.7, 59.5, 58.6, 57.7, 57.2, 28.0, 27.8. MS (ESI): $m/z = 341$ ($M + H^+$). Anal. calcd for $C_{14}H_{17}BrN_2O_3$: C, 49.28; H, 5.02; N, 8.21. Found: C, 49.17; H, 5.20; N, 8.09%.

Synthesis of 1-(3,5-bis(trifluoromethyl)phenyl)-3-((1*R*,2*R*)-2-(trimethylamonium)cyclohexyl)urea-iodide (14)

N-Boc protected (*R*,*R*)-diaminocyclohexane **14** (0.2 mmol) were dissolved in 1.0 mL of dry THF. Then a solution of 3,5-bis(trifluoromethyl)phenylisocyanate (0.25 mmol) in 1.0 mL of dry THF was added dropwise. The mixture was stirred overnight at room temperature. Then the solvent was evaporated and the crude product was dissolved in DCM (5 mL) and treated at 0 °C with a solution of TFA (1 mL) in 2 mL of DCM. After 2 h stirring, 5 mL of saturated $NaHCO_3$ solution was added and additional solid $NaHCO_3$ until the end of the effervescence. Then the resulting mixture was extracted with 4 × 30 mL of DCM, treated with anhydrous Na_2SO_4, filtered and the solvent evaporated under vacuum to give deprotected crude **15**. The crude product **15** was dissolved in 1 mL of dry DMF. Then 1.1 eq. of K_2CO_3 and 4 eq. of CH_3 were added at room temperature. The reaction was allowed to stir at room temperature for 6 h. Then DMF was evaporated under vacuum and the crude product was purified by a short chromatography with a mixture 95/5 of DCM/MeOH to give the pure compound **16** (98 mg, 0.182 mmol). Yellow solid. M.p.: 121–122 °C ^{1}H-NMR (300 MHz, $CDCl_3$): δ 9.04 (s, 1H), 8.05 (s, 2H), 7.46 (s, 1H), 7.36 (d, $J = 9$ Hz, 1H), 4.24–4.13 (m, 2H), 3.41 (s, 9H), 2.45 (m, 1H), 2.12 (d, 1H), 1.94–1.32 (m, 8H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 154.5, 140.7, 131.9 (q, $J = 30$ Hz), 124.6, 118.1, 115.5, 76.1, 54.5, 50.2, 35.5, 27.1, 24.6, 24.3. MS (ESI): $m/z = 412$ ($M - I^-$). Anal. calcd for $C_{18}H_{24}F_6IN_3O$: C, 40.09; H, 4.49; N, 7.79. Found: C, 40.25; H, 4.61; N, 7.63%. $[\alpha]_D = +2.0$ (c 1.0, $CHCl_3$).

Procedure for asymmetric cascade reactions under phase transfer catalyzed conditions

In a round-bottom flask, 2-cyanbenzaldehydes **2a** or **2b** (0.10 mmol) were added at room temperature to a stirred solution of glycine Schiff base **1** (1.1 eq., 0.11 mmol), K_2CO_3 (1 eq.) and PTC (5% mol) in CH_2Cl_2 (3 mL). The mixture was reacted under the condition described in Scheme 4 and Tables 2 and 3. At the end of the reaction, the mixture was purified directly by flash chromatography on silica gel with hexane/ethyl acetate 8/2 mixtures to give the product **3a** or **3b**.

3a, major diastereomer: $[\alpha]_D = +47.0$ (c 1.0, $CHCl_3$), ee = 70%. HPLC chiral separation: Chiralpack AS-H column, 9/1 hexane/iPrOH, 0.6 mL min^{-1} $\lambda = 254$ ($t_{minor} = 16.27$ min, $t_{major} = 21.76$ min).

The products **3a** and **3b**, submitted to the previousdescribed hydrolysis, gave **5a** and **5b**.

5a, major diastereomer: $[\alpha]_D = -1.8$ (c 1.0, $CHCl_3$), ee = 70%. HPLC chiral separation major diastereomer: OD-H column, 9/1 hexane/iPrOH, 0.7 mL min^{-1}, $\lambda = 220$ nm, ($t_{minor} = 26.35$, $t_{major} = 32.61$). Minor diastereomer HPLC separation OD-H column, 9/1 hexane/iPrOH, 0.7 mL min^{-1}, $\lambda = 220$ nm, ($t_{minor} = 24.99$, $t_{major} = 40.01$), ee = 40%.

5b, major diastereomer: $[\alpha]_D = -2.5$ (c 1.0, $CHCl_3$), ee = 51%. HPLC chiral separation major diastereomer: OD-H column, 9/1 hexane/iPrOH, 0.7 mL min^{-1}, $\lambda = 220$ nm, ($t_{minor} = 27.3$, $t_{major} = 35.4$).

Acknowledgements

MIUR and University of Salerno for their financial support.

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