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Cinchona Alkaloid-Catalyzed Enantioselective Direct Aldol Reaction of *N*-Boc-Oxindoles with Polymeric Ethyl Glyoxylate

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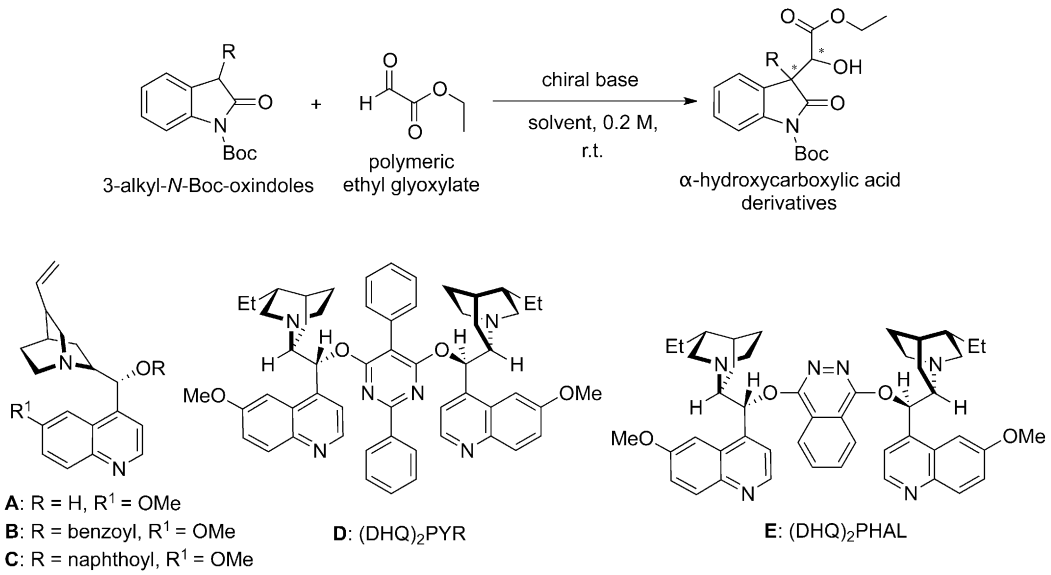
Abstract: The first enantioselective direct aldol addition of *N*-Boc-oxindoles to polymeric ethyl glyoxylate is presented. The reaction is performed by using as low as 0.1 mol% $(DHQ)_2PHAL$ and gives access to α-hydroxycarboxylate derivatives bearing adjacent secondary alcohol and quaternary stereocenters with high levels of diastereo- and enantiocontrol. The use of ethyl glyoxylate in its polymeric form represents an important advantage for synthetic applications and allows us to directly install a C_2 unit ready to be converted in useful building blocks. A further one-pot protection/deprotection sequence catalyzed by $Zn(ClO_4)_2{\cdot}6H_2O$ preserved the α-hydroxycarboxylates from racemization by means of a parasitic alcohol-catalyzed retroaldol reaction.

Keywords: acid derivatives; aldol reaction; asymmetric catalysis; *Cinchona* alkaloids; hydrogen bonding

In the last years, asymmetric organocatalysis has proved to be amongst the most powerful approaches for the direct enantioselective construction of optically active frameworks, starting from commercial or readily available compounds.[1] However, the need of always more efficient processes able to address most of the principles of *green chemistry*[2] opens up new scenarios and challenges for organocatalysis. In this field the realization of organocatalyzed enantioselective transformations that give access to important chiral building blocks with relevant synthetic applications or remarkable biological activities by means of new efficient activation modes and under a low catalyst loading are highly desirable. Indeed, the realization of new chemical transformations carried out by forming several bonds in a single operation in order to reduce many purification steps, to minimize the generation of chemical wastes and to save time are necessary requirements for modern chemistry.[2]

Recently, oxindole derivatives containing a quaternary stereocenter at the C-3 position became the targets of several intriguing asymmetric transformations because of their well documented importance as effective biologically active compounds.[3] Thus many efforts have been devoted in the realization of organocatalyzed enantioselective Mannich, Michael addition, amination, hydroxylation, alkylation and cascade reactions with the aim to install the oxindole scaffold in the final products.[4] Although the aldol reaction represents one of the most powerful tools for the realization of C–C bonds, the direct organocatalytic aldol reaction of oxindoles with aldehydes for the stereocontrolled generation of adjacent quaternary and secondary alcohol stereocenters remains unexplored.[5] Herein we report the efficient direct aldol addition of 3-substituted alkyloxindoles with a commercially available toluene solution of polymeric ethyl glyoxylate for the synthesis of α-hydroxycarboxylate derivatives.[6] The reaction furnishes new oxindole derivatives (Scheme 1) with almost total stereocontrol of the newly forged adjacent quaternary and secondary alcohol stereocenters and is performed using a loading as low as 0.1 mol% of commercially available *Cinchona* alkaloid catalyst. Moreover, the direct use of polymeric ethyl glyoxylate represents an important advantage for synthetic applications because it avoids the need to prepare and use the extremely reactive monomer form that rapidly polymerizes and reacts with water to generate the hydrated form.[8] Moreover the use of ethyl glyoxylate allows one to directly install a C_2 unit ready to be converted into useful building blocks.

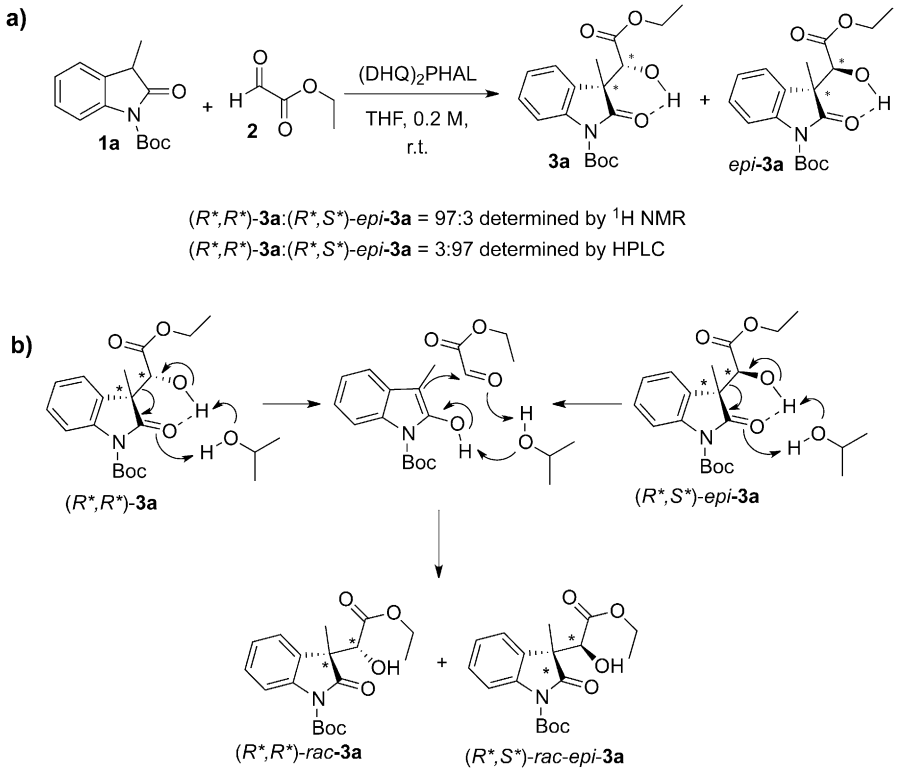
In a preliminary stage of the project we began to study the reaction of *tert*-butyl 3-methyl-2-oxoindo-



Scheme 1. Direct aldol reaction of 3-alkyl-*N*-Boc-oxindoles with polymeric ethyl glyoxylate.

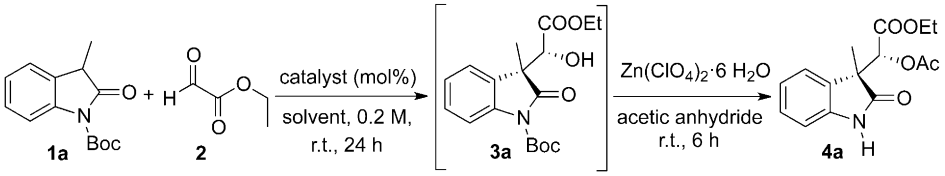
line-1-carboxylate (**1a**)[9] with polymeric ethyl glyoxylate (**2**) in THF 0.2 M in the presence of 10 mol% of commercially available or readily prepared *Cinchona* alkaloid derivatives as catalyst at room temperature (Scheme 2).

We found that hydroquinine 1,4-phthalazinediyl diether (DHQ)$_2$PHAL **E** was extremely efficient, providing the desired α-hydroxycarboxylate with a diastereomeric ratio of 97:3 [Scheme 2 **a)**] as determined by ^{1}H NMR in favour of **3a**.[10] However, the same sample analyzed by HPLC on a chiral stationary



Scheme 2. a) Observed diastereoisomers and relative ratio after and before HPLC analysis. **b)** Hypothesized mechanism for the racemization pathway.

Table 1. Optimization studies for the direct aldol reaction of *N*-Boc-3-methyloxindole **1a** and toluene solution of polymeric ethyl glyoxylate **2**.[a]



Entry[a]	Catalyst (mol%)	Solvent	Conversion [%][b]	*dr*[b]	*ee* [%][c]
1	**A** (10)	THF	full	66:34	30
2	**B** (10)	THF	full	92:8	77
3	**C** (10)	THF	full	95:5	80
4	**D** (10)	THF	full	88:12	66
5	**E** (10)	THF	full	95:5	85
6	**E** (10)	Et_2O	full	95:5	80
7	**E** (10)	CH_2Cl_2	full	85:15	67
8	**E** (10)	1,4-dioxane	full	93:7	84
9	**E** (10)	AcOEt	full	91:9	83
10	**E** (10)	dry THF	full	92:8	82
11[d]	**E** (10)	THF	full	95:5	74
12	**E** (5)	THF	full	95:5	87
13	**E** (1)	THF	full	97:3	90
14	**E** (0.5)	THF	full	97:3	90
15	no catalyst	THF	–	–	–

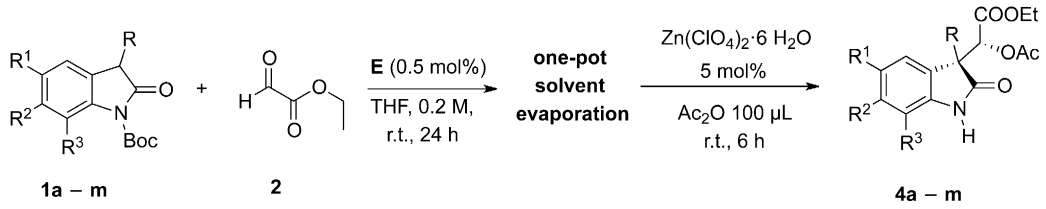
[a] Unless otherwise noted all reactions were performed at room temperature with **1a** (0.1 mmol), **2** (50% in toluene, 0.1 mmol), catalyst (10 mol%), solvent (500 μL), $Zn(ClO_4)_2{\cdot}6H_2O$ (5 mol%), Ac_2O (50 μL).
[b] Determined by ^1H NMR analysis of the crude mixture.
[c] Determined by HPLC analysis on a chiral stationary phase.
[d] Reaction performed at 0 °C.

phase showed a much lower diastereomeric ratio, inconsistent with the one determined by NMR. In the attempt to gain more insight into this discrepancy, further NMR measurements showed that the purified product as such or as a $CDCl_3$ solution maintains indefinitely the 97:3 **3a**:*epi*-**3a** diastereomeric ratio over time. Then, a sample of the isolated crude product was dissolved in a hexane-isopropyl alcohol mixture and this solution was analyzed as such by HPLC on a chiral stationary phase at regular intervals over 48 h. During this time, the **3a**:*epi*-**3a** diastereoisomer ratio initially observed by NMR underwent a complete inversion and at the end it was 3:97. This phenomenon was also accompanied by a rapid racemization of both diastereoisomers **3a** and *epi*-**3a**.[11] [Scheme 2 **a)**]. Based on the above findings and on the fact that using either Dabco or K_2CO_3 as the catalyst furnished *epi*-**3a** as the major diastereoisomer, we suppose that the chiral *Cinchona* alkaloid-catalyzed reaction is under catalyst control forming the kinetic diastereoisomer **3a** which in hexane-isopropyl alcohol solution undergoes a conversion to the thermodynamic diastereoisomer *epi*-**3a**. Since this conversion is also accompanied by racemization, as depicted in Scheme 2 **b)**, we think that isopropyl alcohol may promote two consecutive reaction pathways: the retroaldol reaction and the racemic C–C bond formation between the 2-hydroxy-3-methylindole and the ethyl glyoxylate.[12] Moreover, as established by NMR analysis,[10] the presence of a hydrogen bond between the secondary OH and the oxygen of the amidic carbonyl group of the oxindole moiety enhances the acidity of the hydroxy proton, thus promoting the action of the alcohol.

In order to avoid the racemization, we decided to protect the alcoholic moiety of compound **3a** by acetylation. Thus, after evaporation of the solvent, treatment of the crude reaction mixture with $Zn(ClO_4)_2{\cdot}6H_2O$ (5 mol%) and acetic anhydride at room temperature gave compound **4a** in which the *tert*-butyloxycarbonyl group was removed, thus providing a one-pot easy and highly efficient protection-deprotection sequence.[13] Neither diastereomeric conversion nor racemization was observed when compound **4a** was exposed to isopropyl alcohol and the diastereomeric ratio of **4a** determined by HPLC exactly matched the value obtained by NMR.

The real efficiency of the proposed catalysts was evaluated on the protected compound **4a**. The results outlined in Table 1 show that commercially available bis-*Cinchona* alkaloid $(DHQ)_2PHAL$ (**E**) was the best catalyst providing the best result with *dr* = 95:5 and 85% *ee* (Table 1, entries 1–5). Tetrahydrofuran (THF) revealed to be the solvent of choice and inter-

Table 2. Direct aldol reaction of *N*-Boc-3-alkyloxindoles and polymeric ethyl glyoxylate.[a]



Entry[a]	**4**	R	R^1	R^2	R^3	Yield [%][b]	*dr*[c]	*ee* [%][d]
1	**a**	Me	H	H	H	71	97:3	90
2	**b**	*n*-butyl	H	H	H	75	98:2	94
3	**c**	*i*-butyl	H	H	H	65	97:3	80
4	**d**	Bn	H	H	H	83	99:1	96
5	**e**	*p*-Cl-$C_6H_4CH_2$	H	H	H	80	98:2	96
6	**f**	*p*-CF_3-$C_6H_4CH_2$	H	H	H	84	97:3	96
7	**g**	*p*-MeO-$C_6H_4CH_2$	H	H	H	82	99:1	96
8	**h**	*m*-MeO-$C_6H_4CH_2$	H	H	H	87	99:1	98
9	**i**	Bn	Me	H	H	85	98:2	95
10	**j**	Bn	Me	H	Me	76	97:3	96
11	**k**	Bn	F	H	H	75	97:3	90
12	**l**	Bn	H	H	F	78	98:2	94
13	**m**	Bn	H	Cl	H	65	98:2	95
14[e]	**a**	Me	H	H	H	77	95:5	93
15[f]	**d**	Bn	H	H	H	70	97:3	95

[a] Unless otherwise noted all reactions were performed at room temperature with **1a–m** (0.2 mmol), **2** (50% in toluene, 0.2 mmol), $(DHQ)_2PHAL$ (0.5 mol%, 100 μL of 0.01 M THF solution), THF (900 μL), $Zn(ClO_4)_2{\cdot}6H_2O$ (5 mol%), Ac_2O (100 μL).
[b] Sum of diastereoisomers.
[c] Determined by ^1H NMR analysis of the crude mixture.
[d] Determined by HPLC analysis on chiral stationary phase.
[e] Reaction performed using 0.5 mol% of $(DHQD)_2PHAL$.
[f] Reaction performed on 2 mmol scale using 0.1 mol% of **E**.

estingly the reaction performed in dry THF caused a loss of diastereo- and enantioselectivity (Table 1, entry 10). In order to improve the enantioselectivity the reaction was conducted at 0 °C and, whilst a good level of diastereoselectivity was maintained, the enantiomeric excess dramatically dropped to 74% (Table 1, entry 11). The decision to run the reaction with a minor amount of catalyst led to an increment in the stereocontrol without a detectable loss of reactivity (Table 1, entries 12–14). Moreover without organocatalyst no traces of product could be detected (Table 1, entry 15). The reaction proceeded smoothly with catalyst **E** (0.5 mol%) at room temperature for 24 h and then for further 6 h hours with $Zn(ClO_4)_2{\cdot}6H_2O$ (5 mol%) and acetic anhydride to give **4a** in 71% yield, with a *dr* = 97:3 and an *ee* value of 90%.

The scope of the direct aldol reaction of various *N*-Boc-oxindoles **1a–m**, with polymeric ethyl glyoxylate **2** was then investigated using the optimized conditions (Table 2). The reaction perfectly maintained the high level of efficiency as regards all the substituents of the oxindolic structure despite the very low amount of catalyst and the synthesis of compounds **4a–m** was realized through a one-pot protection and deprotection protocol without any precaution to exclude water and air. As shown in Table 2, less hindered linear substituents at the C-3 position gave good results in term of yields and stereocontrol (Table 2, entries 1 and 2). Interestingly, the reaction proceeded smoothly also in the case of the more encumbered oxindole **3c** and compound **4c** was isolated in 65% yield with a *dr* = 97:3, albeit with a lower value of enantiomeric excess. (Table 2, entry 3). More sterically demanding oxindoles bearing a benzyl substituent at the C-3 position maintained high levels of diastereo- and enantiocontrol (Table 2, entries 4–13) even when the stereoelectronic nature and the position of the various substituents changed. For example, both electron-withdrawing chlorine and trifluoromethyl groups in the *para* position of the aromatic ring (Table 2, entries 5 and 6) and electron-releasing methoxy substituents in *para* or *meta* positions (Table 2, entries 7 and 8), furnished the corresponding products in excellent yields, essentially as a single diastereoisomer and with *ee* values ranging from 96 to 98%. Except for the methyl group (Table 2, entry 9), the substitution on the aromatic ring of the oxindole

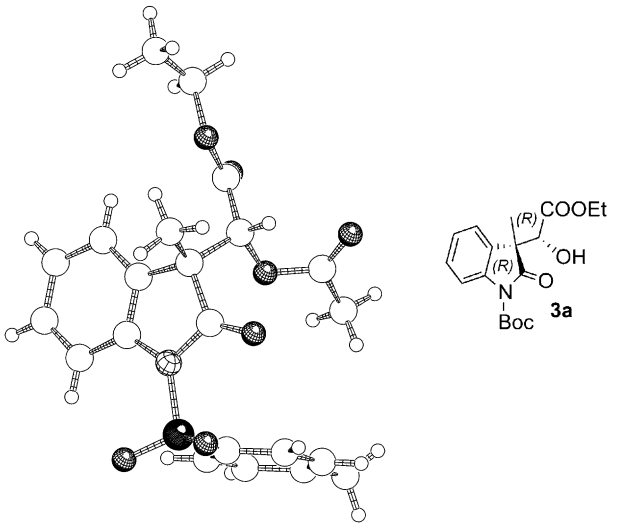


Figure 1. X-ray structure of the *N*-tosyl derivative (2*R*,3′*R*)-**5** (*left*) and absolute configuration of the corresponding precursor alcohol **3a** (*right*).

proved to influence negatively the catalyst activity, leading to a general decrease of isolated product yield (Table 2, entries 10–13). Indeed, the presence of a second methyl substituent at the C-7 of the oxindole moiety gave compound **4j** in 76% yield and with very high enantioselectivity (Table 2, entry 10). Also strongly electron-withdrawing fluorine and chlorine atoms did not change the stereochemical outcome of the reaction and the corresponding products **4k**, **4l** and **4m** were isolated as almost single diastereoisomers with 90%, 94% and 95% *ee* respectively (Table 2, entries 11–13).

Interestingly, the reaction performed using oxindole **1a** with 0.5 mol% of $(DHQD)_2PHAL$, the pseudoenantiomer of **E**, gave access to the enantiomer of compound **4a** (***ent*-4a**) in 77% yield but with high diastereo- and enantioselectivity: $dr = 95{:}5$ and 93% *ee* (Table 2, entry 14). Notably, when the catalyst loading was further diminished to 0.1 mol% the reaction of *tert*-butyl 3-benzyl-2-oxoindoline-1-carboxylate **1d** performed on a 2-mmol scale, maintained the same level of enantioselectivity (95% *ee*) and furnished the desired α-hydroxycarboxylate derivative in good yield as single diastereoisomer (Table 2, entry 15). The absolute configuration has been determined to be 2*R*,3′*R* by X-ray crystallographic analysis[14] of the corresponding *N*-tosylated oxindole derivative **5** obtained by simple reaction of **4a** with TsCl and NaH in THF[11] (Figure 1). The same absolute configuration could be assigned by analogy to the corresponding alcohol **3a** thus suggesting that the *Si* face of the indole enolate species generated by the interaction between the oxindole **1a** and $(DHQ)_2PHAL$[5b], approaches the *Re* face of the ethyl glyoxylate.

In conclusion, we have realized the first enantioselective direct aldol addition of *N*-Boc-3-alkyloxindoles to polymeric ethyl glyoxylate using $(DHQ)_2PHAL$ as catalyst. The reaction gives access to both enantiomers of oxindole-containing α-hydroxycarboxylate derivatives bearing adjacent secondary alcohol and quaternary stereocenters with excellent optical purity and relevant diastereoselectivity using directly the commercially available toluene solution of polymeric ethyl glyoxylate. The present synthesis features some important aspects which represent significant breakthroughs for the realization of always more efficient routes for the synthesis of chiral building blocks. The high efficiency of the reaction allows the use of as low as 0.1 mol% of the catalyst at room temperature maintaining an elevated level of stereocontrol. In addition, three reactions: aldol addition, *O*-acetylation and *N*-deprotection can be performed in a one-pot process without any need to exclude water, thus saving energy, time and costly separation and purification procedures. In particular, the protection/deprotection process, that has proved to be necessary to prevent the racemization pathway, is realized using the same catalyst and this aspect represents a great advantage from an economical point of view.

Experimental Section

Typical Procedure

In an ordinary vial equipped with a Teflon-coated stir bar, *tert*-butyl 3-methyl-2-oxoindoline-1-carboxylate **1a** (0.2 mmol, 49.4 mg) was dissolved in 900 μL of THF and 100 μL of a 0.01 M solution of $(DHQ)_2PHAL$ (**E**) in THF (0.001 mmol, 0.78 mg, 0.5 mol%) were added. After 5 min ethyl glyoxylate **2** (0.2 mmol, 40 μL of a 50% toluene solution, 1.0 equiv.) was added. The resulting solution was stirred at room temperature for 24 h then solvent was removed under reduced pressure without heating and Ac_2O was added (1.06 mmol, 100 μL, 5.3 equiv.) followed by $Zn(ClO_4)_2{\cdot}6H_2O$ (5 mol%, 3.74 mg) and 2 drops of diethyl ether. The resulting mixture was stirred for 6 h then diluted with 2 mL of dichloromethane and flushed through a short plug of silica gel, using dichloromethane/ethyl acetate 1:1 as the eluent (100 mL). The solvent was removed under vacuum and crude **4a** ($dr = 97{:}3$) was purified by flash column chromatography using hexane/diethyl ether 2:3 as the eluent mixture. Pure **4a** was obtained in 71% yield as sum of diastereoisomers and 90% *ee* on the major diastereoisomer. HPLC (Daicel Chiralpak AD-H column: 90/10 hexane/*i*-PrOH, flow rate 0.75 mL min^{-1}, $\lambda = 214$, 254 nm): $t_{minor} = 17.03$ min, $t_{major} = 23.47$ min.

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[7] For a comprehensive review on the *Cinchona* alkaloids as organocatalysts, see: T. Marcelli, H. Hiemstra *Synthesis* **2010**, 1229–1279.

[8] a) T. Urushima, Y. Yasui, H. Ishikawa, Y. Hayashi, *Org. Lett.* **2010**, *12*, 2966–2969; b) D. A. Evans, S. W. Tregay, C. S. Burgey, N. A. Paras, T. Vojkovsky, *J. Am. Chem. Soc.* **2000**, *122*, 7936–7943; c) D. A. Evans, L. Kvarno, T. B. Dunn, A. Beauchemin, B. Raymer, J. A. Mulder, E. J. Olhava, M. Juhl, K. Kagechika, D. A. Favor, *J. Am. Chem. Soc.* **2008**, *130*, 16295–16309; d) R. Matsubara, Y. Nakamura, S. Kobayashi, *Angew. Chem.* **2004**, *116*, 3320–3322; *Angew. Chem. Int. Ed.* **2004**, *43*, 3258–3260.

[9] Attempts to perform the reaction using 3-non-substituted *N*-Boc-alkyloxindole did not gave any traces of the corresponding α-hydroxycarboxylate derivative.

[10] ^{1}H NMR spectra recorded in $CDCl_3$ show the OH proton as a doublet with a 9.4 Hz coupling constant, whereas the spectrum taken in a polar solvent like CD_3CN does not show this coupling. This strong hydrogen bond between the OH group and the oxindole carbonyl group allowed us to establish by NOE experiments that the major diastereoisomer has the relative configuration shown in the structure **3a**.
[11] See the Supporting Information for more details.
[12] A similar retro-aldol process was reported to be working under basic conditions, see ref.[5b] There, exposure of the compounds to 2-propanol for HPLC analysis under neutral conditions had no effect on both diastereo- and enantioselectivity.
[13] a) R. Dalpozzo, G. Bartoli, L. Sambri, P. Melchiorre, *Chem. Rev.* **2010**, *110*, 3501–3551; b) G. Bartoli, M. Bosco, R. Dalpozzo, E. Marcantoni, M. Massaccesi, L. Sambri, *Eur. J. Org. Chem.* **2003**, 4611–4617; c) G. Bartoli, M. Bosco, R. Dalpozzo, E. Marcantoni, M. Massaccesi, S. Rinaldi, L. Sambri, *Synlett* **2003**, 39–42.
[14] CCDC 828981 (**5**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

