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Asymmetric organocatalytic α-amination of 2-oxindoles with bis(2,2,2-trichloroethyl)azo-dicarboxylate

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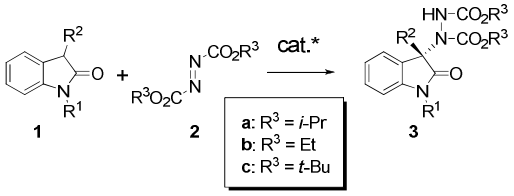
ABSTRACT

An enantioselective electrophilic amination of 3-substituted-2-oxindoles is reported, using bis(2,2,2-trichloroethyl)azo-dicarboxylate and commercially available *Cinchona* alkaloid organocatalysts. The best results were obtained in the reaction of 3-aryl substrates, with high to excellent yields (75% to quantitative) and good stereoselectivity (64-77% *ee*). Facile reductive conversion of the protected 3-hydrazino fragment into the corresponding primary amine was also demonstrated, to expand the synthetic flexibility of asymmetric electrophilic amination with azo-dicarboxylic esters *en route* to enantioenriched 3-amino-2-oxindoles. The absolute configuration of 3-amino-3-phenyl-2-oxindole was independently established by electronic circular dichroism (ECD), combined with time-dependent density functional theory (TDDFT).

Several chiral 2-oxindole derivatives with an amino-substituted stereocenter at C3 display strong bio-activity and useful pharmacological properties.[1] Amongst the methods reported for their enantioselective synthesis,[2] significant efforts have been devoted to metal-free electrophilic asymmetric α-amination reactions (AαA) with azo-dicarboxylic esters (Scheme 1). In 2009, the groups of Liu and Chen,[3] Zhou,[4] and Barbas III[5] independently reported the AαA of 3-alkyl-2-oxindole substrates **1** under the action of commercially available *Cinchona* alkaloid organocatalysts. In the former two protocols, the best results were obtained for the reaction of diisopropyl azo-dicarboxylate (**2a**) with oxindoles devoid of substituents at the nitrogen atom. On the contrary, efforts of the latter team disclosed conditions for the AαA of *N*-substituted substrates (*N*-Boc or *N*-benzyl) with diethyl azo-dicarboxylate (**2b**), which were also applied by our group to test the performance of polymer-supported alkaloid organocatalysts.[6] Further advancements came with the introduction of procedures for the AαA with di-*tert*-butyl azo-dicarboxylate (**2c**) of 3-aryl-2-oxindole substrates not protected at the nitrogen atom[8] or provided with a *N*-Boc group.[7] Even though these methods allow the attainment of high *ee* values, their practical usage appears nonetheless hampered by the requirement for very low temperatures (*e.g.* -70 °C),[7] long reaction times (1-6 d)[8] and on-purpose synthesized,[7] or rather expensive,[8] organocatalysts. Similar considerations can be made for the recent report from the groups of Zou and Zhao on novel amidophosphane catalysis in the AαA of 3-aryl-2-oxindoles.[9] ~~Despite~~ good *ee* values and astonishingly fast reactions (<5 min), the oxygen sensitivity of the catalysts[10] and the need of temperatures as low as -78 °C render the method less appealing for large-scale applications.



Cheng and Liu:[3]
R^1 = H, R^2 = alkyl, R^3 = *i*-Pr, r.t, 24-48 h, 78-97% *ee*

Zhou:[4, 8]
R^1 = H, R^2 = alkyl, R^3 = *i*-Pr, -10°C or 0°C, 4-6 d, 81-98% *ee*
R^1 = H, R^2 = aryl, R^3 = *t*-Bu, -10°C, 2-5 d, 81-94% *ee*

Barbas III:[5, 7]
R^1 = Boc or Bn, R^2 = alkyl, R^3 = Et, r.t., 24-48 h, 76-99% *ee*
R^1 = Boc , R^2 = aryl, R^3 = *t*-Bu, -78°C., 24-48 h, 73-98% *ee*

Zou and Zhao:[9]
R^1 = Boc , R^2 = aryl, R^3 = Et or *i*-Pr, -30°C, 5 min, 81-90% *ee*
R^1 = Boc , R^2 = aryl, R^3 = *t*-Bu, -78°C., 5 min, 73-98% *ee*

Scheme 1. Literature protocols for AαA of 2-oxindoles

As noted by Zhou and co-workers,[8] and also observed in our laboratory, a second major drawback of some of the available AαA protocols is deprotection of the aminated products. In particular, when the R^3 group is *iso*-propyl (**3a**) or ethyl (**3b**) the conditions required are so harsh that the step becomes practically unfeasible due to extensive substrate decomposition.

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Considering that bis(2,2,2-trichloroethyl)azo-dicarboxylate (**2d**) is much more electrophilic than ordinary dicarboxylic esters,[11] we became interested in exploring its use in the AαA reaction.[12] A further prompt in this direction came from the fact that 2,2,2-trichloroethoxycarbonyl (Troc) protecting groups are easily removed under mild reducing conditions; and that, if desired, cleavage of N-N bond can be attained in the same synthetic step.[13] Moreover, even if **2d** is rather expensive when obtained from commercial sources, a cheap and scalable synthesis of the compound is well detailed in the literature.[14]

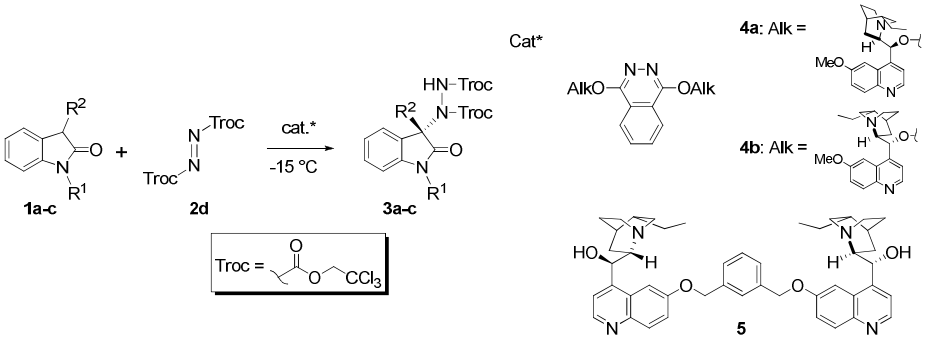
Our investigation began by screening a number of commercially available *Cinchona* alkaloid derivatives and chiral phosphanes, as well as other organocatalysts from the literature (for a complete listing and results, see the ESI).[7,8,9] With this aim, **1a**, **1b**, and **1c** were selected as prototypes of the 3-alkyl and 3-aryl substrate classes, the choice of **1a** being dictated by the fact that a similar starting material had been used in a formal synthesis (based on metal-catalyzed AαA) of the bio-active compound AG-041R.[15] These preliminary runs showed that none of the examined chiral phosphanes, including that of choice in the work of Zou and Zhao,[9] was capable to induce > 33% *ee* in the reaction of **1b** with **2d** at 0 °C. Similar results were obtained for a number of monomeric and dimeric alkaloid derivatives, as well as a Takemoto-type catalyst (ESI).

Gratifyingly, higher levels of enantioselectivity were observed using the commercially available phthalazine ethers **4a** and **4b** and with the dimeric quinine derivative **5**. The former type of organocatalysts performed better in the AαA of substrates devoid of substituents at the nitrogen atom (Table 1, entries 1-8) than for *N*-Boc oxindole **1c** (Table 1, entry 10), whereas the opposite outcome was observed with the xylyl-linked dimeric derivative **5** (Table 1, entries 9 and 11). These latter results were not totally unexpected, as **5** had been specifically designed to deal with the AαA of *N*-Boc substrates like **1c**.[7] Instead, at least for **1b** the attainment of appreciable *ee* values with the phthalazine ethers was rather surprising, as **4b** affords essentially racemic product in the AαA of the same oxindole substrate with *tert*-butyl ester **2c**.[8] As expected, but not always observed in the organocatalytic applications of dimeric alkaloid derivatives,[16] switching between the pseudo-enantiomeric organocatalyst **4a** and **4b** (Table 1, entry 6 and entry 5, respectively) caused nearly perfect inversion of the sense of asymmetric induction.

Encouraged by these results, some optimization of the reaction solvent was carried out for the reaction of **2d** with **1a** (Table 1, entries 1-4) or **1b** (Table 1, entries 6-8). Eventually, this led to identify diethyl ether (Table 1, entry 2 and entry 7) as the solvent of choice for maximizing the stereoselectivity. Curiously, these conditions are very similar to those identified by Barbas III and co-workers in their initial study,[5] apart for the fact that protected oxindole substrates were definitively required in that investigation in order to obtain useful *ee's*. Together with other results disclosed so far in the literature,[3-9] these observations point to the difficulty of predicting the best organocatalyst and solvent for any new combination of R^1, R^2, and R^3 groups in the AαA reaction partners.

Even if the data in Table 1 might suggest a very large difference in reactivity between 3-alkyl (**1a**) and 3-aryl oxindoles (**1b** and **1c**), control experiments demonstrated this was not the case. In particular, the addition of further aliquots of **2d** to mixtures containing partially converted **1a** led to the prompt formation of more product **3a**. Reasoning that limitation in the amount of electrophilic reagent, as opposed to unexpectedly low reaction rate, was the likely cause of incomplete conversion of **1a**, the evolution of a mixture of **1a**, **2d**, and **4a** (1:1:0.1 initial molar ratio) in $CDCl_3$ was followed in time by NMR.

Table 1. Best results in the catalyst and solvent screening for substrates **1a**-**c**.



Entry[a]	Substrate (R^1, R^2)	Catalyst	Solvent	*t* (h)	Conversion (%)[b]	*ee* (%)[c]
1	**1a** (H, CH_2CO_2Et)	**4a**	CH_2Cl_2	48	82	19
2	**1a** (H, CH_2CO_2Et)	**4a**	Et_2O	48	57	61
3	**1a** (H, CH_2CO_2Et)	**4a**	AcOEt	48	74	27
4	**1a** (H, CH_2CO_2Et)	**4a**	toluene	48	83	51
5[d]	**1b** (H, Ph)	**4b**	CH_2Cl_2	1	quant.	-47
6	**1b** (H, Ph)	**4a**	CH_2Cl_2	1	quant.	48
7	**1b** (H, Ph)	**4a**	Et_2O	1	quant.	69
8	**1b** (H, Ph)	**4a**	toluene	1	quant.	61
9	**1b** (H, Ph)	**5**	Et_2O	1	quant.	27
10	**1c** (Boc, Ph)	**4a**	Et_2O	1	quant.	-24
11	**1c** (Boc, Ph)	**5**	Et_2O	1	quant.	-55

[a]Reactions carried out with 10 mol% of the organocatalyst, 1.1-1.3 equiv. of **2d**, and [**1**] = 170 mM

[b]Evaluated by ^{1}H NMR after evaporation of the volatiles.

[c]By chiral HPLC (Lux Cellulose-1 column); for **3b**: direct analysis; for **3a**: after conversion to the corresponding 3-acetamido derivative **7** (see text); for **3c**: after removal of Boc group with trifluoroacetic acid. Positive values indicate an excess of the second eluting enantiomer that, in the case of **3b** and **3c**, had (*S*) configuration (see text).

[d]At -10°C.

As shown in Figure 1, the experiment revealed that the azodicarboxylic ester **2d** was consumed at much faster rate than the oxindole substrate **1a**. This led to recognize the existence of a competitive process, later identified (ESI) as the decomposition of **2d** into 2,2,2-trichloroethanol and the corresponding bis-carbonate, under the action of **4a**. Because this side reaction was found to proceed with $t_{1/2} \approx 5.5$ h, its effects become apparent in the AαA of **1a** ($t_{1/2} \approx 2$ h) but not in that of **1b** or **1c** ($t_{1/2} < 1$ h).

In consideration of better results obtained in the AαA of **1b** with **4a** in Et_2O, this combination was kept constant while optimizing temperature, substrate concentration, and catalyst loading (Table 2, entries 1-10).

Cooling the reaction mixture to -78 °C did not increase the enantiomeric purity of **3b** which, in fact, reached its maximum value at room temperature (Table 2, entries 1-4). This trend is in sharp contrast with the findings in the AαA of **1c** with **2c**, where a strong positive effect of cooling well below -20 °C had been observed.[7] On the contrary, the low sensitivity to temperature variations evidenced by data in Table 2 looks similar to that reported for the reaction of **1c** with **2b** under chiral phosphane catalysis.[9]

In much the same way, changing the concentration of reactants over an order of magnitude (Table 2, entries 5-7) or the catalyst loading in the 5-20 mol% range (Table 2, entries 6 and 8-10) did not cause any dramatic change in either the isolated yield of **3b** or in its enantiomeric purity. In fact, because the use of 5 mol% of organocatalyst at room temperature led to even slightly higher *ee*, these conditions were selected in the final examination of the substrate scope (Table 2, entries 11-14). In this case, runs were performed and 25 mM substrate concentration in order to avoid solubility problems with some of the starting materials. Under these conditions, the AαA of oxindoles **1d-f**, bearing unhindered aryl groups at C3 (Table 2, entries 11-13), afforded the corresponding aminated products **3d-f** in high isolated yields and with enantiomeric composition close to that noted above for **1b**. On the contrary, the reaction of oxindole **1g**, containing an *o*-substituted phenyl ring at C3, was found to be far less enantioselective (< 20% *ee*, Table 2, entry 14). In this regard, we speculate that the *ortho* substituent in the phenyl moiety may lead to hindered rotation around the C3-C1' bond upon conversion of **1g** to the corresponding enolate (Fig. 2). In this event, the bulk provided by the methoxy group together with the high reactivity of **2d** could largely override the influence of the chiral catalyst in determining the asymmetric induction extent.

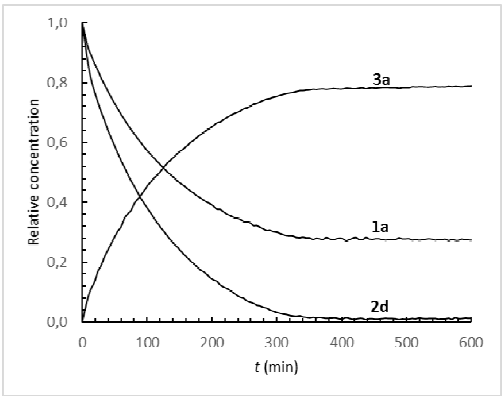
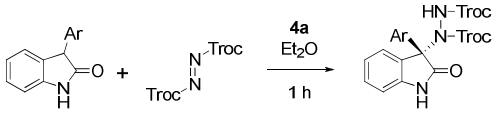


Figure 1. ^{1}H NMR kinetic profiles for reactants **1a** and **2d** and product **3a**, in the reaction catalyzed by **4a** (25 °C, $CDCl_3$).

Table 2. AαA of 3-aryl substituted 2-oxindoles.



Entry[a]	Substrate (Ar)	[**1**] (mM)	**4a** (mol%)	*T* (°C)	Yield (%)[a]	*ee* (%)[b]
1[c]	**1b** (Ph)	170	10	-78	75	67
2[c]	**1b** (Ph)	170	10	-15	>95	69
3	**1b** (Ph)	170	10	23	>95	74
4[d]	**1b** (Ph)	170	10	40	94	73
5	**1b** (Ph)	10	10	0	85	71
6	**1b** (Ph)	50	10	0	>95	70
7	**1b** (Ph)	100	10	0	>95	69
8	**1b** (Ph)	50	5	0	>95	73
9	**1b** (Ph)	50	20	0	>95	67
10	**1b** (Ph)	50	5	23	90	75
11	**1d** (4-$MeOC_6H_4$)	25	5	23	85	64
12	**1e** (4-FC_6H_4)	25	5	23	>95	76
13	**1f** (2-naphthyl)	25	5	23	92	77
14	**1g** (2-$MeOC_6H_4$)	25	5	23	>95	< 20

[a]Reactions carried out with 1.2 equiv of **2d**; complete conversion was observed in all cases (TLC), except for entry 1.

[b]After flash chromatography.

[b]By chiral HPLC analysis; the major enantiomer of **3d** had (*S*) configuration (see text).

[c]Reaction time 2 h.

[d]Carried out in a screw-cap vial.

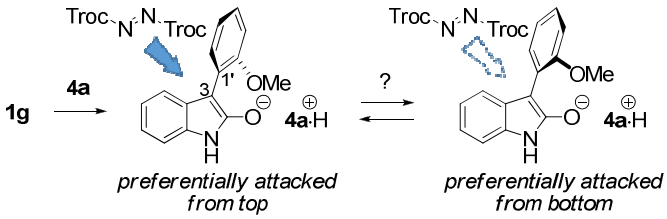
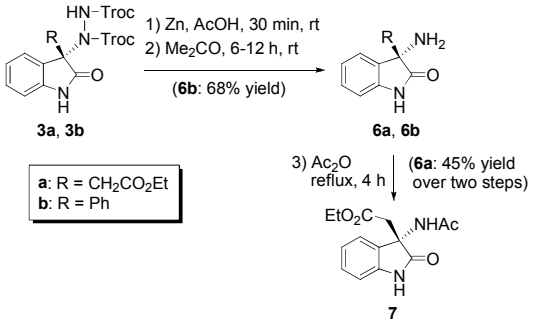


Figure 2. Possible cause of the low enantioselectivity in the AαA of **1g**.

For the purpose of demonstrating the synthetic versatility of the aminated products prepared by the approach describe herein, **3a** and **3b** were subjected to deprotection and cleavage of N-N (Scheme 2) under the conditions originally introduced by Leblanc and Fitzsimmons for Troc-protected carbohydrate hydrazines.[13a] The method worked also for the selected AαA products of this study and gave the corresponding amines **6a** and **6b**, which were isolated as such (**6b**) or as the corresponding acetamide (**7**). Because the acetylation of primary amines has been reported to proceed in AcOH, in the presence of $Zn(OAc)_2$,[17] the transformation of **6a** into **7** (45% overall yield) could be attained in a simple two-pot sequence, by adding acetic anhydride to the filtrate from the deprotection/N-N cleavage step.

As observed for other AαA products,[4,6b] recrystallization of a sample of **3b** having 32% *ee* afforded nearly racemic crystals and

a solution containing the product with >98.5% *ee* (31% yield). When the enantio-enriched fraction was subjected to the procedure of Scheme 2, the amine was obtained with >98.5% *ee* (HPLC) and $[\alpha]_D^{25}$ = -30.8. Although negative optical rotation had been reported in the literature for (*S*)-**6b**,[8] such assignment relied on the tentative comparison between the $[\alpha]_D$ values of structurally different AαA products.



Scheme 2. Elaboration of the Troc-protected hydrazine unit of **3a** and **3b**.

For this reason we sought independent proof of the configuration of the sample in our hands, by comparing the electronic circular dichroism (ECD) spectrum of **6b** in methanol with the theoretical spectrum calculated on (*S*)-**6b**. Using a consolidated computational protocol (ESI)[18] we calculated the ECD spectrum of (*S*)-**6b** with the time-dependent density functional theory (TDDFT) using MP2-optmized geometries selected after a thorough conformational search, which revealed the presence of three energy minima. The Boltzmann-weighted average reproduces well the experimental spectrum (Fig. 3), thus allowing a definitive configurational assignment. It should be noted that despite the presence of two aromatic chromophores with almost fixed reciprocal arrangement, only a faint positive exciton couplet appears in the 230-260 nm region, therefore the application of the exciton chirality rule[19] is questionable in the present case.

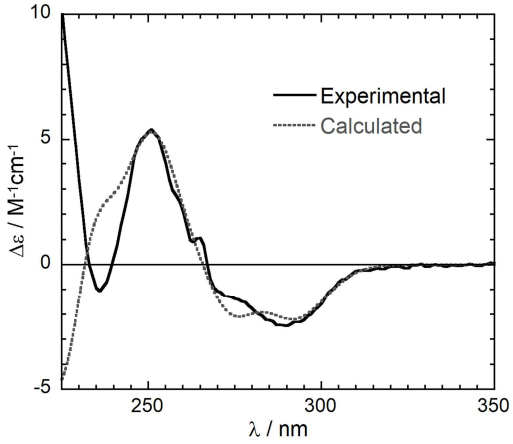


Figure 3. Experimental (solid line) and calculated (dotted line) ECD spectra of (*S*)-**6b**. Experimental conditions: 0.69 mM in methanol, cell 0.1 cm. Level of calculation: TDB3LYP/def2-TZVP//MP2/6-311+G(d,p) with PCM solvent model for methanol; Boltzmann average over 3 energy minima. Spectrum plotted as sum of Gaussians with 0.2 eV exponential width, shifted by 20 nm and scaled by a factor 10.

In summary, conditions were developed for the asymmetric electrophilic amination of 2-oxindoles with the highly electrophilic reagent **2d**. Even though the enantioselectivity reached so far (up to 61% *ee* and 77% *ee* for 3-alkyl and 3-aryl substrates, respectively) is lower compared with other azo-dicarboxylic esters from the literature,[3-9] the protocol disclosed herein has the merits of requiring low loadings of a relatively inexpensive and air-insensitive alkaloid organocatalysts, afford useful *ee* values near room temperature, and allow reactions completeness in a matter of hours rather than days.

Further investigation aimed to improve the stereoselectivity of the reaction, as well as to apply the use of **2d** to the synthesis of pharmaceutically relevant products, are currently underway.

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