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Graphical Abstract

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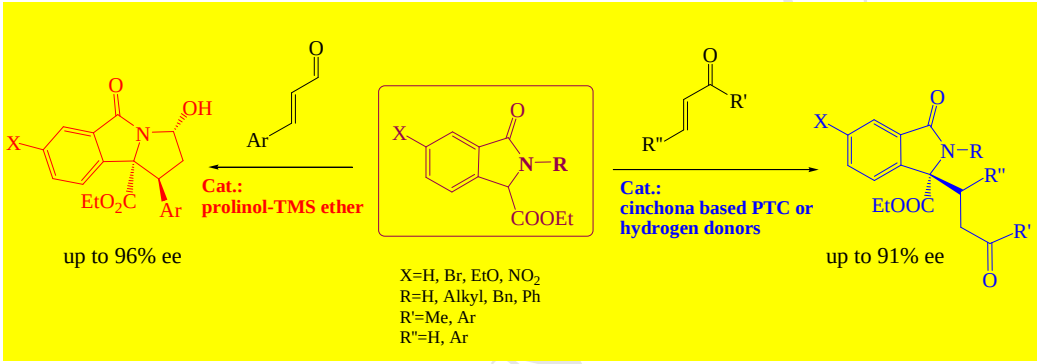

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ABSTRACT

In this article we describe a series of new asymmetric Michael reactions of carboxylate-3-substituted isoindolinones used as nucleophiles in the synthesis of valuable chiral tetrasubstituted derivatives. It has been shown that the reactivity and enantioselectivity strongly depend on the substitution pattern of the isoindolinone, requiring either cinchona-alkaloid based phase transfer catalysts or chiral hydrogen donors. Moreover, prolinol-TMS ether-based secondary amine catalysts permitted the development of Michael/cyclization tandem reaction with cynnamaldehyde for the synthesis of aza-polycyclic derivatives.

1. Introduction

In recent years chiral 3,3-disubstituted isoindolinones have become increasingly attractive because of the wide range of different biological activities that are associated with this structural motif.[1] For example, a series of compounds like **1**, a potential drug for the treatment of cardiac arrhythmias,[1a] or the derivative **2**, useful for the treatment of atherosclerosis[1b] and the urea-containing isoindolinone **3**, a blood pressure regulator[1c] (Figure 1) have been the subject of extensive investigations. However, the isolation of enantioenriched examples of these targets has so far largely been achieved *via* chromatographic separation of the racemates using chiral stationary phases[1a,b] or by the use of chiral auxiliaries.[1c] Until recently only a few catalytic asymmetric methodologies have been developed to access 3,3-disubstituted isoindolinones using either chiral metal complexes[2] or chiral phosphoric acids[3]. This is in contrast with the larger number of asymmetric methodologies that are available for the synthesis of chiral 3-substituted isoindolinones.[4] This prompted us to develop a more general route towards 3,3-disubstituted isoindolinones *via* asymmetric catalysis mediated by chiral small molecules (organocatalysis) oriented towards derivatives which could be employed for the synthesis of bioactive compounds.

Our attention focused on compounds of general structure **4**[5] (Figure 1) that are surprisingly unprecedented as intermediates in asymmetric reactions. As recently reported for analogous isobenzofuranones,[6] these compounds, activated by an ester group, can be successfully employed as nucleophiles in a number of asymmetric transformations. In addition, the presence of a further nucleophilic moiety, i.e. the free NH group of **4** when R=H, can be particularly useful for the synthesis of aza-polycyclic compounds **5**. This is of particular interest as asymmetric methodologies for the synthesis of targets **5** are rare.[7]

We initially focused on asymmetric Michael reactions utilizing methyl vinyl ketone and thus obtained products that serve as valuable intermediates for further transformations. Initial results were encouraging with high yields (95%) and moderate to good enantioselectivities (up to 76% ee) obtained in the presence of chiral ammonium salts under phase transfer conditions although neutral bifunctional organocatalysts were less effective.[8] However, only a very limited number of isoindolinones (three in total) and catalysts were tested leaving substantial room for further improvement.

Considering the novel nature of using nucleophilic esterification and radical bromination and then into the target isoindolinones in asymmetric catalysis, we felt it would be particularly useful to expand the scope of this work by focusing on, *i*) a wider screening of chiral ammonium salts and organocatalysts and *ii*) a detailed analysis of the substrate scope by changing both the nucleophilic part and the Michael acceptor. Alongside focusing on the use of compounds **4** in asymmetric C-C bond forming reactions, we also addressed the synthesis of new isoindolinones **4** with different substituents on both the lactam and the aromatic ring by introducing either new synthetic strategies or by modifying and optimizing known routes to these compounds.

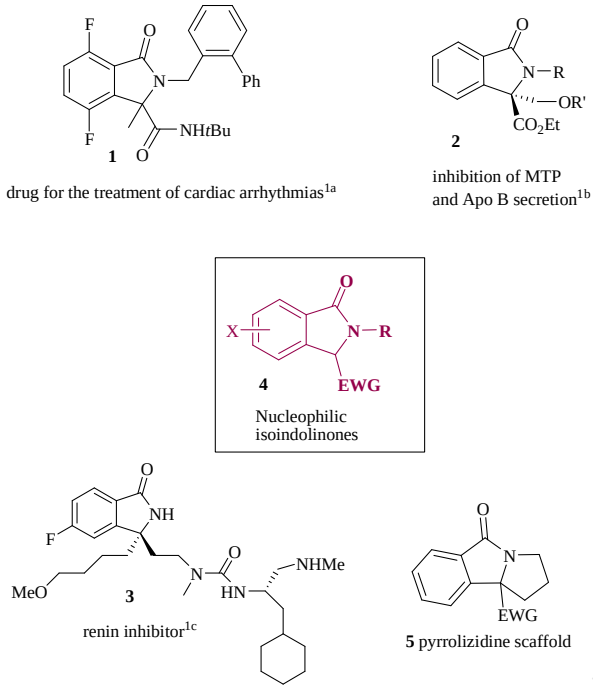
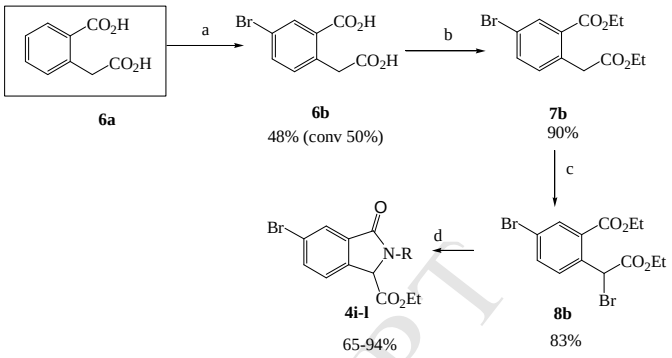


Figure 1. Examples of pharmacologically active 3,3-disubstituted isoindolinone derivatives and pyrrolozidines and the general structure of nucleophilic isoindolinones **4** used in this study.

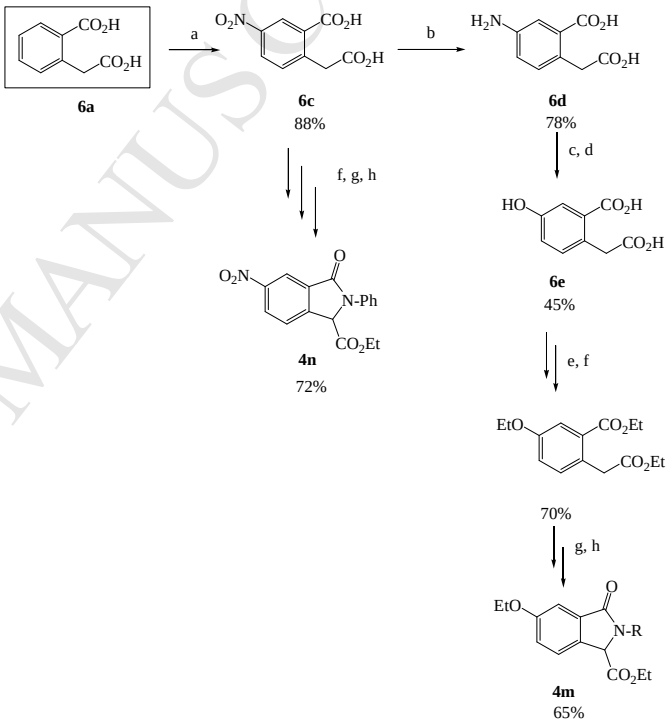
2. Results and discussion

*2.1 Synthesis of nucleophilic isoindolinones **4**.*

Our initial efforts were directed towards the synthesis of a series of isoindolinones **4** with a focus on the functionalization of the aryl moiety. Reported strategies describe the synthesis of isoindolinones **4** through two routes: 1) reaction of 3-unsubstituted isoindolinones with CO_2 under strongly basic conditions[9] or 2) displacement/lactamization of diethyl α-bromohomophthalate with primary amines.[5] However, only a few derivatives have been reported so far with no examples bearing substituents on the aryl ring. Thus, we considered the latter approach, focusing on the elaboration of the homophthalic acid **6a** that was successfully used for the synthesis of diversely substituted isoindolinones **4** according to Schemes 1 and 2. Bromination[10a] utilising $KBrO_3$ or nitration[10b] of **6a** led to intermediates that were smoothly transformed into the substituted α-bromohomophthalates **8** by



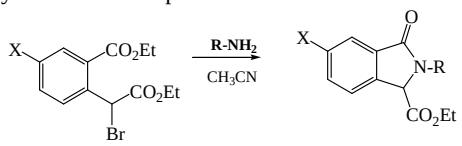
Scheme 1. Synthetic pathway to 5-bromoisoindolinones **4i-4l**: a) $KBrO_3$, H_2SO_4, 90 °C, 2 h; b) H_2SO_4, EtOH reflux, 24 h; c) NBS, AIBN, CCl_4, 85 °C, 20 h; d) RNH_2, CH_3CN.



Scheme 2. Synthetic pathways to 5-ethoxy and 5-nitroisoindolinones **4n** and **4m**: a) HNO_3, H_2SO_4, 0 °C, 2 h; b) H_2, Pd/C 5%, MeOH; c) $NaNO_2$, H_2SO_4, 0 °C, 2 h; d) H_2SO_4, H_2O, reflux; e) K_2CO_3, CH_3CH_2I, DMF, 48 h; f) H_2SO_4, EtOH reflux, 24 h; g) NBS, AIBN, CCl_4, 85 °C, 20 h; h) RNH_2, CH_3CN.

Interestingly the lactamization of the diethyl α-bromohomophthalates **8** required careful fine-tuning depending on the nature of the amine (the details are summarized in Table 1). Unsurprisingly, aniline was less reactive than the other amines and higher temperature was required (Entries 8, 12, 14). The reaction of **4k** with $BnNH_2$ was also problematic at room temperature because of the formation of undesired byproducts. Gratifyingly the reaction proceeded smoothly *via* lowering the temperature to 0 °C (Entry 11). In contrast, the more activated *p*-NO_2 derivative **4n** gave satisfactory yield from reaction with aniline (Entry 14), while other amines led to decomposition products.

Table 1. Synthesis of nuclophilic isoindolinones **4**.

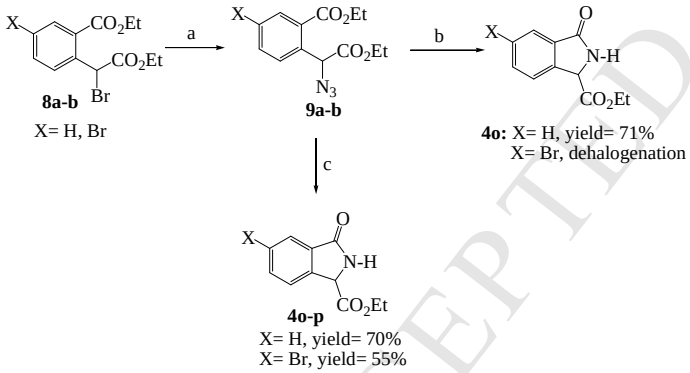


8a-d **4a-n**

Entry	X	R	4	T (°C)	t (h)	Yield[a] %
1[5]	H	Bn	**4a**	R.T.	5	76
2	H	*n*-Bu	**4b**	R.T.	4	85
3	H	*n*-hexyl	**4c**	R.T.	6	83
4[11]	H	Me	**4d**	R.T.	18	65
5[5]	H	propargyl	**4e**	R.T.	5	90
6	H	3,5-$(CF_3)_2$-$C_6H_3CH_2$	**4f**	R.T.	24	57
7	H	4-$EtOC_6H_4CH_2$	**4g**	R.T.	24	66
8	H	Ph	**4h**	70	96	80
9	Br	*n*-Bu	**4i**	R.T.	24	94
10	Br	*n*-hexyl	**4j**	R.T.	8	75
11	Br	Bn	**4k**	0	24	89
12	Br	Ph	**4l**	70	72	90
13	EtO	*n*-Bu	**4m**	R.T.	93	65
14	NO_2	Ph	**4n**	70	97	72

[a]Isolated yields

The synthesis of free NH-isoindolinone was particularly challenging. The previously reported[11] method based on the use of Pd/C and cyclohexadiene or hydrogen for the reduction of azide **9a** (X=H), was found to be not applicable to **9b** (X=Br) where de-halogenation was the mainly observed (Scheme 3).



8a-b X= H, Br

9a-b

4o: X= H, yield= 71%
X= Br, dehalogenation

4o-p
X= H, yield= 70%
X= Br, yield= 55%

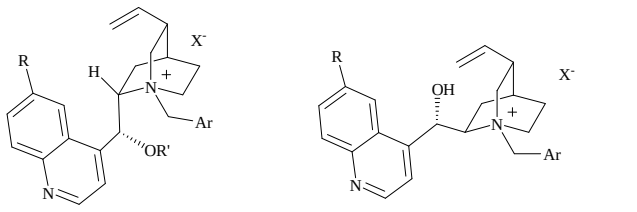
Scheme 3. Synthetic pathway to free NH isoindolinones. a) NaN_3, CH_3CN, 24 h; d) 1,4-cyclohexadiene, Pd/C 10%, EtOH, 2 h, 70 °C; c) $P(Me)_3$, THF/H_2O (4/1), dry THF.

Other reducing agents like $CeCl_3$[12a] or $NaBH_4$[12b] were also not effective. To our delight the Staudinger methodology[12c] allowed us to overcome this obstacle and led to the target compounds in reasonable yields when $P(Me)_3$ was used under nitrogen in THF/H_2O mixture (PPh_3 gave low yields and more complex mixtures that were difficult to purify).

2.2 Chiral phase transfer catalysts.

Our preliminary screening performed on **4a**[8] showed that cinchonidinium salt **11a** (Figure 2) with an anthracenyl group on the ammonium side gave the highest selectivity, leading to 74% ee in the Michael reaction of **4a** with methyl vinyl ketone (compound **10**, Table 2, entries 1-4). The optimal reaction conditions were identified as using of DCM as solvent and K_2CO_3 as base at -40 °C (Table 2, entry 4) where other solvents and bases were less effective. The other catalysts that were tested highlighted the importance of maintaining a free -OH group at the C-9 position of the catalyst, since O-allyl derivative (**11b**, see Table 2, entry 2) showed less satisfying catalytic activity (low yield and low selectivity).

At this point, we reasoned that it would be useful to further undertake a systematic investigation regarding the structural key-features of the catalysts, testing all the cinchona diastereomers bearing different substituents on the ammonium portion (Figure 2, Table 2). The anthracenyl quininium salt **11c** showed comparable results with respect to the analogue **11a** (entry 5), while other diastereomeric catalysts **12a, 12b** and **12c** that gave to the opposite product enantiomer led to a slightly lower selectivity (entries 3, 6 and 7). It should be noted that it is a common phenomenon where the use of pseudoenantiomeric cinchona alkaloid derivatives does not always give identical selectivities for both enantiomers,[13a] and thus it came as no surprise that similar challenges were observed in this study. The derivative **11d** with a benzotriazole group installed on the cinchonidinium salt was comparable to **11a** (entry 8), while also in this case, its diastereomeric counterpart **12d** gave slightly lower enantioselectivity and reactivity (entries 9 and 10). Other catalysts with hindered aromatic groups on the ammonium side[14] (**11e-11j** and **12e**, entries 11-16), were less effective than **11a** and **11d**. Only **12e** with a 3-Ph-C_6H_4 substituent reversed the trend, giving higher ee than **11e** (entries 11 and 12). The presence of an additional -OH group on quinoline ring in **11j**, despite the possibility of hydrogen bond network,[15] gave disappointing results (entry 17). Other catalysts like Maruoka's axially chiral binaphthyl-based ammonioum salts,[16] bifunctional urea-cinchona ammonium salts (Dixon's catalyst),[17] cinchona derived sulfonamides[18] or dimers[19] or salts derived from trans-cyclohexyl diamine recently described by our group[20] proved to be less effective and no further structural changes thereafter were investigated (these data can be found in Table S1 in the on line supporting information). Despite the moderate enantio-enrichment, the absolute configuration (AC) of (-)-**10a** was determined to be *S* by Vibrational Circular Dichroism (VCD).[21]

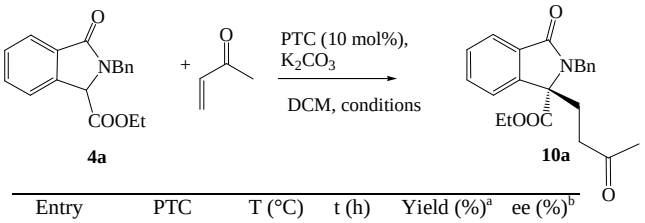


11a: R=H, R' = H, Ar = 9-anthracenyl, X^- = Cl^-
11b: R=H, R' = allyl, Ar = 9-anthracenyl, X^- = Br^-
11c: R=OMe, R' = H, Ar = 9-anthracenyl, X^- = Cl^-
11d: R=H, R' = H, Ar = 1-benzotriazole, X^- = Cl^-
11e: R=H, R' = H, Ar = 3-Ph-C_6H_4-, X^- = Br^-
11f: R=H, R' = H, Ar = phenyl, X^- = Br^-
11g: R=H, Ar = 3,5-diMe-phenyl, X^- = Br^-
11h R=H, Ar = 3,5-di*t*Bu-phenyl, X^- = Br^-
11i: R=H, Ar = b-Np, X^- = Br^-
11j: R=OH, R' = H, Ar = phenyl, X^- = Br^-

12a: R=H, Ar=Ph, X^- = Cl^-
12b: R=H, Ar = 9-anthracenyl, X^- = Cl^-
12c: R=OMe, Ar = 9-anthracenyl, X^- = Cl^-
12d: R=H, R' = H, Ar = 1-benzotriazole, X^- = Cl^-
12e: R=OMe, Ar = 3-Ph-C_6H_4-, X^- = Br^-

Figure 2. Some of the chiral phase transfer catalysts used. The structures and the results obtained with other catalysts are reported in the online supporting information.

Table 2. Asymmetric Michael reaction of *N*-benzyl isoindolinone **4a** with methyl vinyl ketone under phase transfer conditions

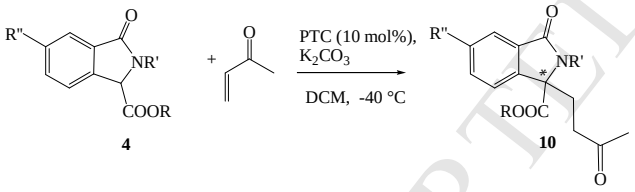


Entry	PTC (10 mol %)	T (°C)	t (h)	Yield (%)[a]	ee (%)[b]
1[8]	**11a**	r.t.	2	90	56
2[8]	**11b**	r.t.	24	95	11
3[8]	**12a**	r.t.	2	89	-55[c]
4[8]	**11a**	-40	24	97	74
5	**12c**	-40	24	91	70
6	**12b**	-40	24	45	-59[c]
7	**12c**	-40	24	93	-65[c]
8	**11d**	-40	24	97	72
9	**12d**	-20	8	95	-64[c]
10	**12d**	-40	40	90	-54[c]
11	**11e**	-20	24	92	48
12	**12e**	-20	24	97	-64[c]
13	**11f**	-40	24	94	66
14	**11g**	-20	24	96	57
15	**11h**	-20	24	94	50
16	**11i**	-20	24	95	48
17	**11j**	-40	48	93	15

[a]Isolated yield. [b]Determined by HPLC using a chiral stationary phase. [c]The opposite enantiomer was obtained, as given by HPLC analysis.

With data so far collected in hand, we investigated the effects of structural modifications on the isoindolinone scaffold at ester and lactam group and on the phenyl ring on the outcome of this reaction in the presence of the best performing catalysts. Interestingly, all these efforts soon revealed a rather complex picture that justified the previous exhaustive catalyst screening and analysis of conditions. Modifications of the ester position showed that hindered substituents like a *t*-butyl group in **4ac** give less satisfactory results in terms of yield and enantioselectivity compared to methyl and ethyl groups (Table 3, entries 1-3).[8] When we investigated the effect of different substituents on the lactam moiety, like H, substituted benzyl, alkyl and phenyl groups, we observed a very interesting phenomenon. It turned out that for isoindolinone **4b**, bearing a *n*-butyl substituent on the nitrogen, catalyst **11d** gave better results than **11a** which allowed us to obtain **10b** with a good enantioselectivity of 81% ee at -40 °C in very high yield (entries 4-6). Notably, with some of the other isoindolinones, catalyst **11d** gave less satisfactory results than **11a** illustrating again the need for a comparative screening of different ammonium salts for different substrates. Good levels of enantioselectivity were reached with the isoindolinones **4c** and **4e**, bearing propargyl and *n*-hexyl substituents (78% and 84% ee respectively, entries 7 and 9), while decreasing the size of the substituent group in **4d** had a detrimental effect on the observed selectivity (entry 8). Other isoindolinones with substituted benzylamines gave slightly lower enantioselectivity than **4a**, an effect that was more pronounced with the electron-donating ethoxy substituent (entries 10-11 *vs* entry 1). Good yields and enantioselectivities were also obtained with the isoindolinone **4h** bearing a phenyl group on the lactam ring (entry 12).

Table 3. Different isoindolinones in phase transfer catalyzed asymmetric Michael reactions



Entry	**4**	R	R'	R"	PTC (10 mol %)	T (°C)	t (h)	**10**	Yield (%)[a]	ee (%)[b]
1[8]	**4a**	Et	Bn	H	**11a**	-40	24	**10a**	97	74
2[8]	**4ab**	Me	Bn	H	**11a**	-40	24	**10ab**	98	70
3[8]	**4ac**	*t*-Bu	Bn	H	**11a**	-40	48	**10ac**	60	45
4	**4b**	Et	*n*-Bu	H	**11a**	-20	18	**10b**	95	76
5	**4b**	Et	*n*-Bu	H	**11a**	-40	40	**10b**	96	71
6	**4b**	Et	*n*-Bu	H	**11d**	-40	48	**10b**	93	81
7	**4c**	Et	*n*-hexyl	H	**11d**	-20	24	**10c**	92	84
8	**4d**	Et	Me	H	**11a**	-20	24	**10d**	96	60
9	**4e**	Et	CH_2CCH	H	**11a**	-40	50	**10e**	95	78
10	**4f**	Et	3,5-$(CF_3)_2$-$C_6H_3CH_2$	H	**11a**	-40	5	**10f**	90	70
11	**4g**	Et	4-$EtOC_6H_4CH_2$	H	**11a**	-40	17	**10g**	98	67
12	**4h**	Et	Ph	H	**11d**	-40	20	**10h**	97	74
13	**4i**	Et	*n*-Bu	Br	**11d**	-40	6	**10i**	92	91
14	**4j**	Et	*n*-hexyl	Br	**11a**	-40	10	**10j**	95	90
15	**4k**	Et	Bn	Br	**11a**	-40	18	**10k**	97	79
16	**4l**	Et	Ph	Br	**11a**	-40	6	**10l**	88	72
17	**4m**	Et	*n*-Bu	EtO	**11d**	-40	15	**10m**	88	55
18	**4o**	Et	H	H	**11a**	-40	8	**10n**	97	20
19	**4o**	Et	H	H	**11d**	-40	3	**10n**	98	50

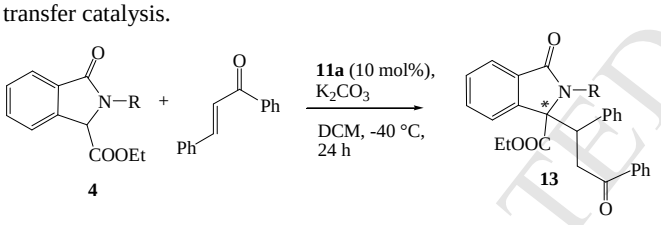
[a]Isolated yield. [b]Determined by HPLC using a chiral stationary phase

Then, the effect of substituents on the aromatic ring of the isoindolinones was investigated using catalysts **11a** and **11d** (entries 13-19, Table 3 reports the best result for each nucleophile). The presence of bromine in **4i** and **4j** was beneficial in comparison to the parent unsubstituted isoindolinone giving high ees of 91% and 90% (Entries 13 and 14). On the other hand nucleophiles **4k** and **4l** bearing a benzyl or a phenyl *N*-substituent performed less selectively (Entries 15 and 16). In addition, the isoindolinone **4m** with a strong electron-donating group gave only moderate enantioselectivity (Entry 17), while **4n** with a nitro group was not reactive at all. A significantly lower enantioselectivity was observed reacting the NH-free isoindolinone **4o**, even if the catalyst **11d** led to significantly higher ee in comparison with **11a** (entries 18 and 19).

After variation of the isoindolinone nucleophiles, other enone and enal-based Michael acceptors were tested. We focused on chalcone and cinnamaldehyde to study the diastereoselectivity of the reaction and the possibility of the formation of tricylic derivatives.

Surprisingly, the *N*-substituted isoindolinones **4a** and **4b** did not react with chalcone possibly due to the increased steric hindrance at the nucleophilic carbon (Table 4, entries 1 and 2). On the other hand, **4o** reacted smoothly with chalcone giving the acyclic derivative **13** in high yield, high diastereoselectivity but with no enantioselectivity (entry 3). Surprisingly, this issue could not be resolved by testing alternative catalysts and conditions and it has to be admitted that a rational for this striking difference is still missing.

Table 4. Michael reaction of the chalcone under asymmetric phase-transfer catalysis.



Entry	**4**	R	Yield **13** (%)[a]	d.r.[b]	ee (%)
1	**4a**	Bn	--	--	
2	**4b**	*n*-Bu	--	--	
3	**4o**	H	96	95/5	2

[a]Isolated yield. [b]Determined by HPLC on chiral column.

2.3 Bifunctional tertiary amine-based organocatalysts.

The limitations observed when using chalcones under chiral phase-transfer conditions in the presence of the free NH isoindolinone **4o** (Table 4) prompted us to continue our investigations by focusing on chiral tertiary amine-based organocatalytic systems instead. Starting from the results described in Table 4, we focused on the bifunctional organocatalysts derived from cinchona alkaloids and trans-cyclohexane diamine, which are widely used in asymmetric conjugated additions[22] (Figure 3).

These catalysts were first tested for comparison in the reactions of **4a** and **4o** with both methyl vinyl ketone and chalcone (Table 5). Under these new conditions, both quinine and bifunctional *epi*-quinine **14** were less effective than chiral phase transfer catalysts for reactions of methyl vinyl ketone (compare entries 1-3 of Table 5 with data of Table 2). In sharp contrast, when using chalcone as an acceptor (entry 5, Table 5) we observed an appreciable increase of the enantiomeric excess by using catalyst **14** (73% ee), with good yield and very good diastereoselectivity (compare also with entry 3 of Table 3 and Table 4). In contrast, quinine itself was less efficient as a catalyst for this reaction (entry 4 of Table 5). Interestingly, this outcome is somewhat comparable with a recently described diastereo- and enantioselective aldol initiated cascade reaction of free NH isoindolinones **4o** with 2-cyano benzaldehydes.[23] We were then able to improve the selectivity further in the presence of 20 mol% of squaramide derivative **15**, which gave the product **13a** in 80% ee and 96/4 dr (entry 7).

Other bifunctional organocatalysts as well as pseudoenantiomeric cinchona alkaloid derivatives were also tested but gave lower selectivities than **15**, while DCM proved to be the most effective solvent (see Table S2 of the supporting information for these additional data). Under the conditions of entry 7, other chalcones were tested next. A higher reactivity was observed with 4-nitro-chalcone, leading to the final product **13b** in high yields in shorter reaction times, with high diastereoselectivity (>99/1) and good enantioselectivity (entries 8 and 9). Good results were also obtained with 4-chloro-, 2-chloro- and 4-methoxy-chalcones (entries 10-13) and with the introduction of the new Br-substituted nucleophile **4p** (entry 14). Only in the presence of a CF_3–aryl substituent a lower enantioselectivity was obtained (entry 15).

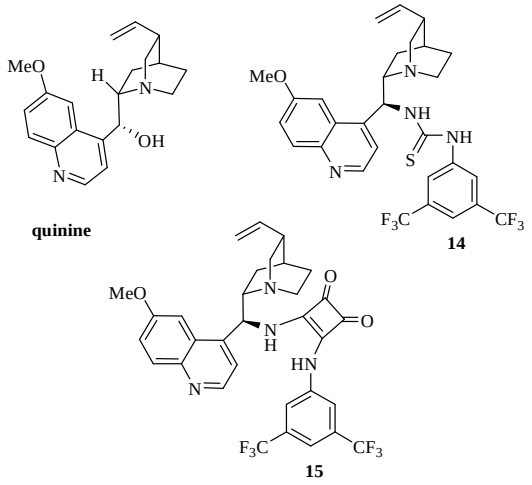
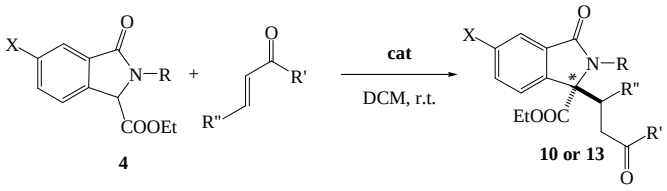


Figure 3. Some of the bifunctional organocatalysts used in this study.

Finally, by slow evaporation of a chloroform/hexane solution of *rac*-**13c** we were able to obtain diffraction quality single crystals (Figure 4) which allowed us to determine the relative configuration being (*RR-SS*)[24] and the other derivatives were assigned by analogy (unfortunately enantioenriched products could not be crystallized in satisfying quality).

Table 5. Michael reactions of chalcones in the presence of bifunctional organocatalysts



Entry[a]	Cat. (mol %)	R	X	R'	R''	t (d)	Yield (%)[b]	d.r.[c]	ee (%)[c]
1	**Quinine** (10)	**4a:** Bn	H	Me	H	5	**10a:** 60	--	48
2	**14** (10)	**4a:** Bn	H	Me	H	5	**10a:** 65	--	45
3	**14** (10)	**4o:** H	H	Me	H	5	**10o:** 90	--	13
4	**Quinine** (10)	**4o:** H	H	Ph	Ph	5	**13a:** 94	93:7	50
5	**14** (10)	**4o:** H	H	Ph	Ph	5	**13a:** 75	91:9	73
6	**15** (10)	**4o:** H	H	Ph	Ph	5	**13a:** 51	93/7	77
7	**15** (20)	**4o:** H	H	Ph	Ph	5	**13a:** 72	96/4	80
8[d]	**15** (10)	**4o:** H	H	Ph	4-$NO_2C_6H_4$	2	**13b:** 92	>99/1	81
9[d]	**15** (5)	**4o:** H	H	Ph	4-$NO_2C_6H_4$	6	**13b:** 91	>99/1	80
10	**15** (20)	**4o:** H	H	Ph	4-ClC_6H_4	2	**13c:** 96	>99/1	83
11	**15** (10)	**4o:** H	H	Ph	4-ClC_6H_4	5	**13c:** 85	>99/1	77
12	**15** (10)	**4o:** H	H	Ph	2-ClC_6H_4	4	**13d:** 93	>99/1	75
13	**15** (20)	**4o:** H	H	Ph	4-$MeOC_6H_4$	7	**13e:** 86	>99/1	70
14	**14** (10)	**4p:** H	Br	Ph	Ph	2	**13f:** 95	93/7	70
15	**15** (20)	**4o:** H	H	2-$CF_3C_6H_4$	Ph	3	**13g:** 91	96/4	52

[a]Reaction performed at [**4**] = 25 mM
[b]Isolated yield.
[c]Determined by HPLC using a chiral stationary phase.
[d]Reaction performed at [**4**] = 10 mM.

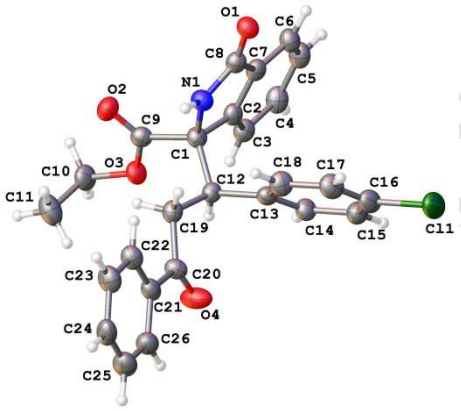


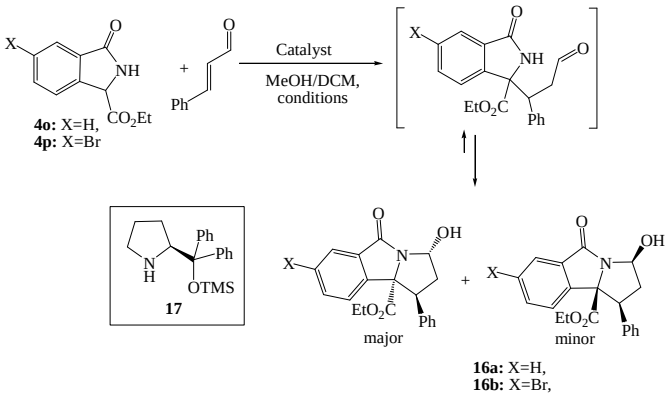
Figure 4. X-ray molecular structure of *rac*-**13c**. Thermal ellipsoids are drawn at 50% probability level.[24]

2.4 Asymmetric synthesis of aza-tricyclic derivatives via organocatalytic cascade/hemi-aminalization reaction.

The reaction of **4o** with cinnamaldehyde in the presence of catalysts **11a** or **11d** led to the tricyclic derivative **16a** in high yield (Table 6, entries 1-3). Even if we obtained only two diastereomers, rather low dr and ee were observed confirming the already previously reported challenges of controlling this acceptor under chiral phase transfer conditions.

In comparison H-donor catalyst **15** gave a higher dr with moderate enantioselectivity, but the low reactivity was not promising enough for further optimization (entry 4).

Table 6. Michael reactions of cinnamaldehyde.



Entry	**4**	Cat.	T (°C)	t (h)	**16:** Yield (%)[a]	d.r.[b]	ee (%)[b]
1	**4o**	**11a**/K_2CO_3	r.t.	4	**16a:** 85	55/45	10/25
2	**4o**	**11a**/K_2CO_3	-40	18	**16a:** 91	66/34	20/40
3	**4o**	**11d**/K_2CO_3	-40	24	**16a:** 95	60/40	12/15
4	**4o**	**15**	r.t.	96	**16a:** 90	80/20	60/20
5[26]	**4o**	**17**	-15	18	**16a:** 85	53/47	**87/96**
6	**4p**	**17**	-15	18	**16b:** 85	60/40	61/30

[a]Isolated yield. [b]Determined by HPLC on chiral column.

Nevertheless, this type of aza-tricyclic compounds, the benzopyrrolizidinones, are known for their biological activity[7] and consequently new asymmetric methodologies were investigated. We then focused on the covalent activation of the electrophile *via* iminium ion catalysis, using proline based organocatalysts.[25] To our delight, an impressive increase of the enantioselectivity was observed using the TMS-ether of diphenylprolinol **17** giving the product with up to 96% ee and in good yield (entry 5).[26] Several substituted cinnamaldehydes were reacted with similar efficiency,[26] while the introduction of the new Br-substituted nucleophile **4p** gave an unexpected lower ee (entry 6). The relative and absolute configuration of the tricyclic derivatives was addressed by X-ray analysis and by mechanistic investigations as disclosed previously.[25b,26]

3. Conclusions

We have demonstrated that 3-carboxylate substituted isoindolinones **4** are effective nucleophiles in asymmetric Michael reactions to access valuable chiral derivatives containing a tetra-substituted carbon stereocenter. A comparative study of different catalytic systems and conditions was necessary to establish structure-activity relationships and for the development of efficient asymmetric versions of the reaction. Good results in terms of yield and enantioselectivity (up to 91% ee), were obtained in the reaction of *N*-substituted isoindolinones with methyl vinyl ketone in the presence of chiral ammonium salts, while the free-NH-containing **4o** performed more sluggishly. On the other hand, **4o** was better suited for reactions with chalcones in the presence of bifunctional amine-H-bonding donor containing organocatalysts and in reactions with cinnamaldehyde in the presence of diphenylprolinol trimethylsilyl (TMS) ether. In this latter case, valuable tricyclic pyrrolo-isoindolinones were obtained *via* a cascade Michael/hemi-aminalization reaction, in good yields and with enantioselectivities up to 96% ee. Notably, these studies showed that seemingly small changes in the substrate structure may require a totally different catalytic activation mode to obtain the target product with high levels of stereoselectivity. These strict requirements may be useful in future studies about new applications in other asymmetric reactions and in the synthesis of bioactive compounds.

4. Acknowledgement

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5. Experimental

For detailed experimental information, spectra and chromatograms of all the new compounds and procedures and for the preparation of 3-Carboethoxy-isoindolinones **4** see supporting information.

Procedure for enantioselective Michael reaction with methyl vinyl ketone. The Michael acceptor (1.5 eq) was added at -40 °C to a stirred solution of **4** (0.1 mmol, 1 eq.), K_2CO_3 (0.1 mmol, 1 eq.) and **11a** (10 mol%) in CH_2Cl_2 (1.5 mL). The reaction was monitored by TLC until the disappearance of **4**. Then, the mixture was purified directly by flash chromatography affording **10** in the range of 60-97% yields.

Adducts **10a**, **10ab**, **10ac**, **10b**, **10o** have been already described in ref. 8, **16a** in ref. 26.

10c. Ethyl -2-hexyl-3-oxo-1-(3-oxobutyl)isoindoline-1-carboxylate. Purification by chromatography (hexane/ethyl acetate 7/3) gave a pale oil. Yield: 92%. $[\alpha]_D^{20}$: -7.2 (c = 0.6, $CHCl_3$). IR (KBr) ν: 2960, 2932, 1750, 1700, 1206, 1187, 734 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.85 (d, 1H, *J*= 7.2 Hz), 7.57-7.48 (m, 2H), 7.41 (d, 1H, *J*= 7.2 Hz), 4.22-4.04 (m, 2H), 3.49-3.27 (m, 2H), 2.82 (ddd, 1H, J_3= 5.4 Hz, J_2= 10.8 Hz, J_1= 15.0 Hz), 2.51 (ddd, 1H, J_3= 4.5 Hz, J_2= 10.5 Hz, J_1= 15.0 Hz), 2.01 (ddd, 1H, J_3= 4.5 Hz, J_2= 10.8 Hz, J_1= 15.0 Hz), 1.75 (ddd, 2H, J_3= 5.4 Hz, J_2= 10.5 Hz, J_1= 15.0 Hz), 1.57 (ddd, 1H, J_3= 6.0 Hz, J_2= 12.3 Hz, J_1= 15.0 Hz), 1.38-1.25 (m, 6H), 1.17 (t, 3H, *J*= 7.2 Hz), 0.89 (t, 3H, *J*= 6.3 Hz). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 206.9, 170.6, 169.4, 143.1, 132.4, 132.3, 129.5, 124.0, 121.9, 71.6, 62.5, 42.0, 36.7, 31.7, 30.6, 28.5, 27.3, 26.2, 22.8, 14.2, 14.1. MS (ESI): m/z = 360 $(M+H)^+$. Anal. calcd for: $C_{21}H_{29}NO_4$: C, 70.17; H, 8.13; N, 3.90. Found: C, 70.45; H, 8.38; N, 3.66. Chiral HPLC: OD-H column, hexane/*i*PrOH (9:1), flow: 0.6 ml/min, t: 13.3 min (minor) and 14.6 min (major); ee 84%.

10d. Ethyl 2-methyl-3-oxo-1-(3-oxobutyl)isoindoline-1-carboxylate. Purification by chromatography (hexane/ethyl acetate 7/3) gave a yellow oil. Yield: 93%. $[\alpha]_D^{20}$: - 8.7 (c = +0.5, $CHCl_3$). IR (KBr) ν: 2962, 2931, 1748, 1702, 1205, 1186, 731 cm-^{1}. ^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 7.84 (d, 1H, *J*= 7.2 Hz), 7.53-7.51 (m, 3H), 4.25-4.04 (m, 2H), 3.02 (s, 3H), 2.78 (ddd, 1H, J_3= 5.5 Hz, J_2= 10.0 Hz, J_1= 15.0 Hz), 2.50 (ddd, 1H, J_3= 5.5 Hz, J_2=10.0 Hz, J_1=15.0 Hz), 1.92-1.89 (m, 4H), 1.70 (ddd, 1H, J_3= 5.5 Hz, J_2=10.0 Hz, J_1=15.0 Hz), 1.20 (t, 3H, *J*= 7.2 Hz). ^{13}C-NMR ($CDCl_3$,75 MHz) δ: 206.4, 169.7, 168.5, 142.4, 131.9, 131.8, 129.3, 123.6, 121.9, 70.7, 62.2, 42.7, 36.1, 29.9, 25.9, 13.9. MS (ESI): *m/z* = 290 $(M+H)^+$. Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.52; H, 6.51; N, 4.67. Chiral HPLC: IA-3 column, hexane/*i*PrOH (8:2), flow: 0.8 ml/min, t: 13.3 min (major) and 15.5. min (minor); ee 60%.

10e. Ethyl 3-oxo-1-(3-oxobutyl)-2-(prop-2-ynyl)isoindoline-1-carboxylate. Purification by chromatography (hexane/ethyl acetate 7/3) gave a yellow oil. Yield: 92%. $[\alpha]_D^{20}$: - 4.6 (c= 1, $CHCl_3$). IR (KBr) ν: 3448, 3274,1732,1696, 1636, 1386, 1248 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 7.86 (d, 1H, *J*= 7.0 Hz), 7.58-7.48 (m, 3H), 4.74 (dd, 1H, J_2= 2.5 Hz, J_1= 18.0 Hz), 4.23-4.03 (m, 3H), 2.85 (ddd, 1H, J_3= 5.3 Hz, J_2= 11.0 Hz, J_1= 15.0 Hz), 2.68 (ddd, 1H, J_3= 4.5 Hz, J_2= 11.0 Hz, J_1= 15.0 Hz), 2.32 (ddd, 1H, J_3= 4.5 Hz, J_2= 11.0 Hz, J_1= 15.0 Hz), 2.17 (t, 1H, *J*= 2.5 Hz), 1.92 (s, 3H), 1.73 (ddd, 1H, J_3= 5.3 Hz, J_2=11.0 Hz, J_1= 15.0Hz), 1.21 (t, 3H, *J*= 7.1 Hz). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 207, 169.9, 168.3, 142.9, 132.8, 131.3, 129.7, 124.3, 122.3, 78.4, 71.9, 71.5, 62.7, 37.1, 30.2, 30.1, 27.1, 14.2. MS (ESI): *m/z* = 314 $(M+H)^+$. Anal. Calcd for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47. Found: 69.19; H, 5.98; N, 4.57. Chiral HPLC: IA-3 column, hexane/*i*PrOH (8:2), flow: 0.6ml/min, t: 16.5 min (major) and 20.7 min (minor); ee 78%.

10f. Ethyl 2-(3,5-bis(trifluoromethyl)benzyl)-3-oxo-1-(3-oxobutyl)isoindoline-1-carboxylate. Purification by chromatography (hexane/ethyl acetate 8/2) gave a white solid (52 mg). Yield: 81%. Mp. 94-95 °C (ethyl acetate/hexane). $[\alpha]_D^{20}$: -16.7 (c = 0.5, $CHCl_3$). IR (KBr) ν: 2988, 2926, 1735, 1714, 1699, 1278, 1180, 1121 $cm^{-1.}$ ^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 7.93-7.77 (m, 3H), 7.61 (s, 1H), 7.60-7.52 (m, 2H), 7.45 (dd, 1H, J_2= 4.0 Hz, J_1= 6.5 Hz), 4.91 (d, 1H, *J*= 15.6 Hz), 4.65 (d, 1H, *J*= 15.8Hz), 3.99-3.91 (m, 2H), 2.80-2.77 (m, 1H), 2.46-2.38 (m, 1H), 1.75 (s, 3H), 1.61 (dd, 2H, J_2= 7.0 Hz, J_1= 12.0 Hz), 1.04 (t, 3H, *J*= 7.1 Hz). ^{13}C-NMR ($CDCl_3$, 150 MHz) δ: 205.9, 169.7, 168.8, 143.1, 139.9, 132.8, 131.8

(q, J_{C-F} = 33.0 Hz), 131.0, 129.2, 128.6, 124.3, 123.6 (q, J_{C-F} = 264.0 Hz), 122.2, 122.1, 71.7, 62.7, 44.4, 36.3, 29.8, 26.5, 13.9. MS (ESI): *m/z*= 402 $(M + H)^+$. Anal. Calcd for $C_{24}H_{21}F_6NO_4$: C, 57.49; H, 4.22; N, 2.79. Found: C, 57.55; H, 4.37; N, 2.91. Chiral HPLC: OD-H column, hexane/*i*PrOH (9:1), flow: 0.6 ml/min, t: 13.1 min (major) and 15.4 min (minor); ee 70%.

10g. Ethyl 2-(4-ethoxybenzyl)-3-oxo-1-(3-oxobutyl)isoindoline-1-carboxylate. Purification by chromatography (hexane/ethyl acetate 7/3) gave a slightly yellow waxy solid. Yield: 97%. $[\alpha]_D^{20}$: -5.5 (c = 0.22, $CHCl_3$). IR (KBr) ν: 2984, 1725, 1691, 1397, 1384, 1244 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.89 (dd, 1H, J_2= 2.7 Hz, J_1= 6.6 Hz), 7.54-7.50 (m, 2H), 7.38 (d, 3H, *J*= 8.4 Hz), 6.79 (d, 2H, *J*= 8.7 Hz), 5.02 (d, 1H, *J*= 15.3 Hz), 4.26 (d, 1H, *J*= 15.3 Hz), 4.00-3.93 (m, 4H), 2.70 (ddd, 1H, J_3= 5.5 Hz, J_2= 9.7 Hz, J_1= 15.2 Hz), 2.39 (ddd, 1H, J_3= 4.7 Hz, J_2= 9.7 Hz, J_1= 15.3 Hz), 1.64 (s, 3H), 1.51-1.45 (m, 2H), 1.37 (t, 3H, *J*= 6.9 Hz), 1.09 (t, 3H, *J*= 7.2 Hz). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 206.7, 170.0, 169.1, 158.3, 143.7, 132.2, 131.7, 130.4, 129.2, 123.9, 121.5, 114.3, 71.6, 63.3, 62.2, 44.2, 36.0, 29.5, 26.3, 14.7, 13.7. MS (ESI): *m/z* = 410 $(M + H)^+$. Anal. Calcd for $C_{24}H_{27}NO_5$: C, 70.40; H, 6.65; N, 3.42. Found: C, 70.30; H, 6.57; N, 3.22. Chiral HPLC: OD-H column, hexane/*i*PrOH (9:1), flow: 0.6 ml/min, t: 36.1 min (major) and 42.7 min (minor); ee 67%.

10h. Ethyl 3-oxo-1-(3-oxobutyl)-2-phenylisoindoline-1-carboxylate. Purification by chromatography (hexane/ethyl acetate 8/2) gave a yellow waxy solid. Yield: 80%. $[\alpha]_D^{20}$: +6.4 (c = 0.3, $CHCl_3$). IR (KBr) ν: 2961, 2922, 1730, 1702, 1384, 1351 cm-^{1}. ^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 7.97 (d, 1H, *J*= 6.8 Hz), 7.59-7.56 (m, 2H), 7.45-7.29 (m, 4H), 7.60-7.52 (m, 2H), 7.25 (s, 1H), 4.19-4.11 (m, 2H), 2.91 (ddd, 1H, J_3= 4.7 Hz, J_2= 11.0 Hz, J_1= 15.3 Hz), 2.49 (ddd, 1H, J_3= 4.9 Hz, J_2= 10.7 Hz, J_1= 15.2 Hz), 2.05 (ddd, 1H, J_3= 5.0 Hz, J_2= 10.7 Hz, J_1= 15.1 Hz), 1.86 (s, 3H), 1.78-1.72 (m, 2H), 1.12 (t, 3H, *J*= 6.4 Hz). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 206.6, 170.5, 168.8, 143.1, 136.1, 133.2, 131.8, 126.8, 125.1, 121.9, 72.5, 63.0, 43.1, 36.7, 30.3, 26.3, 14.2. MS (ESI): *m/z* = 352 $(M + H)^+$. Anal. Calcd for $C_{21}H_{21}NO_4$: C, 71.78; H, 6.02; N, 3.99. Found: C, 71.58; H, 6.22; N, 4.08. Chiral HPLC: IA-3 column, hexane/ *i*PrOH (8:2), flow: 0.8 ml/min, t: 18.8 min (major) and 26.9 min (minor); ee 74%.

10i. Ethyl 5-bromo-2-butyl-3-oxo-1-(3-oxobutyl)isoindoline-1-carboxylate. Purification by chromatography (hexane/ethyl acetate 7/3) gave a white solid. Yield: 92%. Mp. 44-45°C (ethyl acetate/hexane). $[\alpha]_D^{20}$: -31.4 (c= 0.4, $CHCl_3$). IR (KBr) ν: 2965, 2933, 1741, 1701, 1240 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 7.96 (d, 1H, *J*= 1.7 Hz), 7.65 (dd, 1H, J_2= 1.8 Hz, J_1= 8.1 Hz), 7.28 (d, 1H, *J*= 8.0 Hz), 4.20-4.05 (m, 2H), 2.85-2.72 (m, 2H), 2.52 (ddd, 1H, J_3= 4.5 Hz, J_2= 10.6 Hz, J_1= 15.3 Hz), 2.46 (ddd, 1H, J_3= 4.5 Hz, J_2= 10.5 Hz, J_1= 15.3 Hz), 1.98 (s, 3H), 1.95-1.92 (m, 2H), 1.30 (q, 4H, *J*= 7.4 Hz), 1.17 (t, 3H, *J*= 7.2 Hz), 0.94 (t, 3H, *J*= 7.1 Hz). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 206.1, 169.6, 167.6, 141.4, 135.3, 134.9, 127.1, 123.4, 123.3, 71.1, 62.9, 42.0, 36.3, 29.9, 29.6, 25.5, 20.5, 13.8, 13.4. MS (ESI): *m/z*= 411 $(M + H)^+$. Anal. Calcd for $C_{19}H_{24}BrNO_4$: C, 55.62; H, 5.90; N, 3.41. Found: C, 55.46; H, 6.10; N, 3.22. Chiral HPLC: IA-3 column, hexane/*i*PrOH (7:3), flow: 0.6 ml/min, t: 10.8 min (major) and 19.5 min (minor); ee 91%.

10j. Ethyl 5-bromo-2-hexyl-3-oxo-1-(3-oxobutyl)isoindoline-1-carboxylate. Purification by chromatography (hexane/ethyl acetate 7/3) gave a waxy solid. Yield: 95%. $[\alpha]_D^{20}$: -18.8 (c = 0.83, $CHCl_3$). IR (KBr) ν: 2975, 2935, 1740, 1702, 1242 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 75 MHz) δ: 7.98 (d, 1H, *J*= 1.5Hz), 7.67 (dd, 1H, J_2= 1.5 Hz, J_1= 8.1 Hz), 7.30 (d, 1H, *J*= 8.1 Hz), 4.21-4.08 (m, 2H), 3.43-3.32 (m, 2H), 2.79 (ddd, 1H, J_3= 5.4 Hz, J_2= 10.5 Hz, J_1= 15.0 Hz), 2.51 (ddd, 1H, J_3= 5.4 Hz, J_2= 10.5 Hz, J_1= 15.0 Hz), 2.04-1.92 (m, 4H), 1.81-1.70 (m, 1H), 1.63-1.52 (m, 1H), 1.42-1.26 (m, 5H), 1.19 (t, 3H, *J*= 6.9 Hz), 0.90 (t, 3H, *J*= 6.6 Hz).^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 206.5, 170.0, 167.8, 141.8, 135.2, 134.4, 127.2, 123.8, 123.6, 71.4, 62.7, 42.2, 36.6, 31.6, 30.2, 28.4, 27.2, 26.1, 22.7, 14.2, 14.0. MS (ESI): *m/z* = 439 $(M+ H)^+$. Anal. calcd for: $C_{21}H_{28}BrNO_4$: C, 57.54; H, 6.64; N, 3.20. Found: C, 57.35; H, 6.41; N, 3.46. Chiral HPLC: OD-H column, hexane/ *i*PrOH (9:1), flow: 0.6 ml/min, t: 13.8 min (minor) and 15.4 min (major); ee 91%.

10k. Ethyl 2-benzyl-5-bromo-3-oxo-1-(3-oxobutyl)isoindoline-1-carboxylate. Purification by chromatography (hexane/ethyl acetate 8/2) gave a waxy solid. Yield: 97%. $[\alpha]_D^{20}$: + 22.6 (c = 0.5, $CHCl_3$). IR (KBr) ν: 2958, 2925, 1733, 1699, 1238 cm-^{1}. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 8.03 (d, 1H, *J*= 1.5 Hz), 7.61 (s, 1H), 7.66 (d, 1H, J_2= 1.8 Hz, J_1= 8.1 Hz), 7.27 (d, 2H, *J*= 8.1 Hz), 7.28- 7.21 (m, 4H), 5.07 (d, 1H, *J*= 15.0 Hz), 4.34 (d, 1H, *J*= 15.0 Hz), 4.01-3.95 (m, 2H), 2.66 (ddd, 1H, J_3= 5.1 Hz, J_2= 10.2 Hz, J_1= 15.6 Hz), 2.38 (ddd, 1H, J_3= 5.4 Hz, J_2= 10.8 Hz, J_1= 15.7 Hz), 1.64 (s, 3H), 1.47-1.41 (m, 2H), 1.09 (t, 3H, *J*= 6.9 Hz). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 206.2, 169.3, 167.6, 141.6, 136.9, 135.2, 133.6, 129.1, 127.7, 127.2, 123.5, 123.2, 71.6, 62.4, 44.9, 35.9, 29.4, 26.1, 13.7. MS (ESI): *m/z* = 443 $(M + H)^+$. Anal. Calcd for $C_{22}H_{22}BrNO_4$: C, 59.47; H, 4.99; N, 3.15. Found: C, 59.71; H, 5.11; N, 2.99. Chiral HPLC: OD-H column, hexane/*i*PrOH (9:1), flow: 0.8 ml/min, t: 17.7 min (major) and 21.5 min.(minor); ee 79%.

10l. Ethyl 5-bromo-3-oxo-1-(3-oxobutyl)-2-phenylisoindoline-1-carboxylate. Purification by chromatography (hexane/ethyl acetate 7/3) gave a pale oil. Yield: 88%. $[\alpha]_D^{20}$: +17.8 (c = 0.4 $CHCl_3$). IR (KBr) ν: 2969, 2927, 1742, 1714, 1360, 1240 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 8.10 (d, 1H, *J*= 1.5 Hz), 7.74 (dd, 1H, J_2= 1.75 Hz, J_1= 8 Hz), 7.43-7.29 (m, 6H), 4.26-4.05 (m, 2H), 2.87 (ddd, 1H, J_3= 4.7 Hz, J_2= 10.7 Hz, J_1= 13.7 Hz), 2.49 (ddd, 1H, J_3= 5.1 Hz, J_2= 11.0 Hz, J_1= 15.7 Hz), 2.08 (ddd, 1H, J_3= 4.7 Hz, J_2= 10.7 Hz, J_1= 13.7 Hz), 1.90 (s, 3H), 1.74 (ddd, 1H, J_3= 5.1 Hz, J_2= 11.0 Hz, J_1= 15.7 Hz), 1.14 (t, 3H, *J*= 7.1 Hz). ^{13}C-NMR ($CDCl_3$, 62.5 MHz) δ: 206.4, 170.1, 167.1, 141.8, 136.1, 135.8, 134.0, 129.6, 128.0, 127.2, 125, 124.1, 123.3, 72.5, 63.0, 36.6, 30.2, 25.6, 14.1. MS (ESI): *m/z* = 431 $(M+ H)^+$. Anal. calcd for:$C_{21}H_{20}BrNO_4$: C, 58.62; H, 4.68; N, 3.26. Found: C, 58.35; H, 4.28; N, 3.66. Chiral HPLC: OD-H column , hexane/*i*PrOH (9:1), flow: 0.8 ml/min, t: 18.2 min (major) and 22.6 min. (minor); ee 72%.

10m. Ethyl 2-butyl-5-ethoxy-3-oxo-1-(3-oxobutyl)isoindoline-1-carboxylate . Purification by chromatography (hexane/ethyl acetate 8/2) gave a yellow waxy solid. Yield: 88%. $[\alpha]_D^{20}$: -8.9 (c= 0.6, $CHCl_3$). IR (KBr) ν: 2958, 2927, 1742, 1696, 1258, 1237 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 7.28 (s, 2H), 7.06 (dd, 1H, J_2= 2.4 Hz, J_1= 8.4 Hz), 4.18-4.04 (m, 4H), 3.45-3.28 (m, 2H), 2.78 (ddd, 1H, J_3= 5.5 Hz, J_2= 10.8 Hz, J_1= 15.0 Hz), 2.46 (ddd, 1H, J_3= 4.7 Hz, J_2= 9.2 Hz, J_1= 15.1 Hz), 2.05-1.93 (m+ s, 4H), 1.80-1.70 (m, 4H), 1.45-1.36 (m, 4H), 1.16 (t, 3H, *J*= 7.1 Hz), 0.93 (t, 3H, *J*= 7.2 Hz). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 206.8, 170.5, 169.1, 160.1, 134.7, 133.5, 122.6, 120.5, 107, 70.9, 63.9, 62.1, 41.6, 36.4, 30.3, 30.0, 25.9, 20.5, 14.6, 13.8, 13.7. MS (ESI): *m/z* = 376 $(M + H)^+$. Anal. Calcd for $C_{17}H_{23}NO_4$: C, 66.86; H, 7.59; N,4.59. Found: C, 66.76; H, 7.34; N, 4.71. Chiral HPLC: IE-3 column , hexane/*i*PrOH (8:2), flow: 0.6 ml/min, t: 40.6 min (major) and 51.5 min.(minor); ee 55%.

Procedure for asymmetric organocatalytic Michael reaction of chalcones.

A solution of isoindolinone **4o** or **4p** (0.048mmol) in DCM (2 mL), chalcone (1.5 equiv.) and squaramide epiquinine **15** (20 mol%) was stirred at room temperature for the required time. The solvent was evaporated and the diastereoisomeric ratio (dr) was determined by ^{1}H-NMR of crude product. Purification of the crude mixture by flash chromatography (hexane/ethyl acetate 1:1) afforded the required compounds.

13a. Ethyl 3-oxo-1-(3-oxo-1,3-diphenylpropyl)isoindoline-1-carboxylate. Yield: 72 %, waxy solid; d.r. 96/4, $[\alpha]_D^{20}$: + 49.5 (c= 0.44, $CHCl_3$). IR (KBr) ν: 3441, 3431, 1726, 1690, 1241 cm^{-1}.^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.95 (d, *J*= 7.4 Hz, 2H, Ar) 7.93 (d, *J*=

7.7 Hz, 1H, Ar), 7.56-7.53 (m, 3H, Ar) 7.44-7.35 (m, 3H, Ar) 7.10 (d, *J* = 7.3 Hz, 2H, Ar), 6.99 (d, 3H, *J*= 6.7 Hz, Ar), 4.56 (dd, 1H, J_2= 4.2 Hz, J_1= 9.9 Hz), 4.23 (q, 2H, *J* =7.2 Hz), 3.93 (dd, J_2= 9.9 Hz, J_1 = 17.0 Hz, 1H), 3.36 (dd, 1H, J_2= 3.9 Hz, J_1= 17.0 Hz), 1.10 (t, *J* =7.2 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 62.5 MHz) δ: 196.8, 170.9, 170.2, 143.9, 136.6, 136.5, 133.1, 131.8, 131.3, 128.9, 128.4, 128.3, 128.1, 127.6, 127.0, 124.1, 123.3, 71.5, 62.6, 47.2, 40.0, 13.8. MS (ESI): *m/z* = 414 $(M + H)^+$. Anal. calcd for $C_{26}H_{23}NO_4$: C, 75.53; H, 5.61; N, 3.39. Found: C, 75.40; H, 5.75; N, 3.25. Chiral HPLC: IA-3 column, hexane/*i*PrOH (8:2), flow: 0.6 ml/min, t: 17.38 min (minor), 20.92 min (major); ee 80%.

13b. Ethyl 1-(1-(4-nitrophenyl)-3-oxo-3-phenylpropyl)-3-oxoisoindoline-1-carboxylate. Yield: 92%, waxy solid; d.r. >99:1, $[\alpha]_D^{20}$: + 61.8 (c = 0.17, $CHCl_3$). IR (KBr) ν: 3443, 3436, 1596, 1390 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 9.20 (br s, 1H), 8.02 (d, *J*= 6.0 Hz, 2H), 7.86 (t, *J*= 8.1 Hz, 3H), 7.69-7.58 (m, 3H), 7.46-7.38 (m, 3H), 7.34 (d, 2H, *J* = 8.1 Hz), 4.77 (dd, J_2= 2.7 Hz, J_1=10.7 Hz, 1H), 4.34-4.19 (m, 3H), 3.41 (dd, J_2= 2.4 Hz, J_1= 10.7 Hz, 1H), 1.31 (t, *J*= 6.5 Hz, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 196.46, 172.0, 169.9, 147.0, 144.7, 143.8, 136.3, 133.9, 132.8, 131.2, 130.1, 129.8, 128.9, 128.4, 123.9, 123.1, 71.8, 63.4, 46.9, 40.1, 14.3. MS (ESI): *m/z* = 459 $(M + H)^+$. Anal. calcd for $C_{26}H_{22}N_2O_4$: C, 68.11; H, 4.84; N, 6.11. Found: C, 68.30; H, 4.62; N, 6.25. Chiral HPLC: IC column, hexane/*i*PrOH (8:2), flow: 0.6 ml/min, t: 37.9 (major) min and 48.5 min (minor); ee 81%.

13c. Ethyl 1-(1-(4-chlorophenyl)-3-oxo-3-phenylpropyl)-3-oxoisoindoline-1-carboxylate. Yield: 96%, waxy solid; d.r. >99:1, $[\alpha]_D^{20}$: +6.3 (c = 1, $CHCl_3$). IR (KBr) ν: 3441, 3433, 1644, 1637, 1389, 1364 cm^{-1}. ^{1}H -NMR ($CDCl_3$, 300 MHz) δ: 8.59 (br s, 1H), 7.98 (t, *J*= 7.1 Hz, 2H), 7.80 (d, *J*= 7.7 Hz, 1H), 7.62-7.54 (m, 3H), 7.47-7.37 (m, 3H), 7.07 (d, *J*= 8.5 Hz, 2H), 6.96 (d, *J*= 8.8 Hz, 2H), 4.60 (dd, J_2= 3.9 Hz, J_1= 10 Hz, 1H), 4.32-4.21 (m, 2H), 4.04 (dd, J_2=10 Hz, J_1=17.2 Hz, 1H), 3.33 (dd, J_2= 3.9 Hz, J_1= 17.2 Hz, 1H), 1.29 (t, *J*= 7.1 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 196.9, 171.7, 170.4, 144.1, 136.6, 135.4, 133.6, 133.1, 132.4, 131.4, 130.5, 129.4, 128.8, 128.5, 128.1, 124.0, 123.8, 71.9, 63.0, 46.7, 40.2, 14.2. MS (ESI): *m/z* = 448 $(M + H)^+$. Anal. calcd for $C_{26}H_{22}ClN_2O_4$: C, 69.72; H, 4.95; N, 3.13. Found: C, 69.51; H, 4.74; N, 3.27. Chiral HPLC: IA-3 column, hexane/*i*PrOH (8:2), flow: 0.6 ml/min, t: 19.41 min (minor) and 23.76 min (major); ee 83%.

13d. Ethyl 1-(1-(2-chlorophenyl)-3-oxo-3-phenylpropyl)-3-oxoisoindoline-1-carboxylate. Yield: 93%, waxy solid; d.r. >99:1, $[\alpha]_D^{20}$: + 5.4 (c = 0.21,$CHCl_3$). IR (KBr) ν: 3433, 3431, 1725, 1690, 1242 cm^{-1}. ^{1}H -NMR ($CDCl_3$, 400 MHz) δ: 8.43 (br s, 1H), 7.99 (d, *J*= 8.1 Hz, 2H), 7.93 (d, *J*= 7.8 Hz, 1H), 7.59-7.32 (m, 7H), 7.08 (d, *J*= 7.9 Hz, 1H), 6.97 (t, *J*= 7.5 Hz, 1H), 6.89 (t, *J*= 7.8 Hz, 1H), 5.38 (dd, J_2= 4.5 Hz, J_1= 10.0 Hz, 1H), 4.31-4.18 (m, 2H), 3.95 (dd, J_2= 10 Hz, J_1= 16.0 Hz, 1H), 3.43 (dd, J_2= 4.5 Hz, J_1= 16.0 Hz, 1H), 1.28 (t, *J*= 7.1 Hz, 3H).^{13}C -NMR ($CDCl_3$, 100 MHz) δ: 196.9, 171.9, 170.4, 143.6, 136.6, 135.6, 135.0, 133.5, 132.0, 131.2, 129.6, 129.4, 128.8, 128.5, 127.9, 126.8, 124.6, 123.2, 72.0, 63.1, 41.6, 41.4, 14.2. MS (ESI): *m/z* = 448 $(M + H)^+$. Anal. calcd for $C_{26}H_{22}ClN_2O_4$: C, 69.72; H,4.95; N, 3.13. Found: C, 69.41; H, 4.65; N, 3.43. Chiral HPLC: IA-3 column, hexane/*i*PrOH (8:2), flow: 0.6 ml/min, t: 15.7 min (minor) and 21.83 min (major); ee 75%.

13e. Ethyl 1-(1-(4-methoxyphenyl)-3-oxo-3-phenylpropyl)-3-oxoisoindoline-1-carboxylate. Yield: 86%, waxy solid; d.r. >99:1, $[\alpha]_D^{20}$: + 43.1 (c= +0.4, $CHCl_3$). IR (KBr) ν: 3433, 3419, 1649, 1389, 1365 cm^{-1}. ^{1}H -NMR (300 MHz, $CDCl_3$) δ: 8.16 (brs, 1H), 7.97 (d, *J*= 9.0 Hz, 2H), 7.79 (d, *J*= 9.0 Hz, 1H), 7.60-7.42 (m, 3H), 7.27-7.39 (m, 3H), 7.02 (d, *J*= 6.0 Hz, 2H), 6.53 (d, *J*= 9.0 Hz, 2H), 4.51 (dd, J_2= 3.1 Hz, J_1= 9.3 Hz, 1H), 4.29-4.20 (m, 2H), 3.94 (dd, J_2= 9.9 Hz, J_1= 16.5 Hz, 1H), 3.77 (s, 3H, minor diast), 3.58 (s, 3H), 3.31 (dd, J_2= 3.1 Hz, J_1= 16.8 Hz, 1H), 1.28 (t, 3H, *J*= 7.1 Hz). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 197.3, 171.9, 170.6, 158.6, 144.3, 136.8, 133.5, 133.3, 132.1, 131.5, 130.7, 130.1, 129.2, 128.8, 128.6, 128.4, 124.3, 124.1, 123.7, 122.8, 113.3, 85.4, 71.9, 63.7, 62.9, 55.1, 46.8, 40.4, 29.9, 14.2. MS (ESI): *m/z* = 444 $(M + H)^+$. Anal. calcd for $C_{27}H_{25}NO_5$: C, 73.12; H, 5.68; N, 3.16. Found: C, 73.32; H, 5.55; N, 3.19. Chiral HPLC: IA-3 column, hexane/*i*PrOH (9:1), flow: 0.7 ml/min, t: 45.21 min (minor) and 55.32 min (major); ee 70%.

13f. Ethyl 5-bromo-3-oxo-1-(3-oxo-1,3-diphenylpropyl) isoindoline-1-carboxylate. Yield: 95%, white solid; mp. 208-209 °C (ethyl acetate/hexane); d.r. 93/7; $[\alpha]_D^{20}$: +14.8 (c = 1, $CHCl_3$). IR (KBr) ν: 3202, 1742, 1704, 1680, 1235, 1219 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.93 (dt, 3H, J_2= 6.0 Hz, J_1= 10.0 Hz), 7.70-7.55 (m, 3H), 7.45 (t, 2H, *J*= 6.0 Hz), 7.11-7.04 (m, 5H), 4.53 (dd, 1 H, J_2= 6.0 Hz, J_1= 9.0 Hz), 4.31-4.21 (m, 2H), 3.88 (dd, 1H, J_2= 6.0 Hz, J_1= 15.0 Hz), 3.33 (dd, 1H, J_2= 6.0 Hz, J_1= 15.0 Hz), 1.27 (t, 3H, *J* = 9.0 Hz). ^{13}C-NMR ($CDCl_3$, 150 MHz) δ: 198.2, 171.2, 170.7, 144.1, 138.0, 136.9, 136.3, 134.7, 130.3, 130.1, 129.6, 129.4, 128.9, 128.1, 127.3, 124.7, 72.8, 64.3, 48.5, 41.5, 31.1, 15.4. MS (ESI): *m/z* = 493 $(M+ H)^+$. Anal. calcd for:$C_{26}H_{22}BrNO_4$: C, 63.42; H, 4.50; N, 2.84. Found: C, 63.25; H, 4.28; N, 2.59. Chiral HPLC: IA-3 column, hexane/*i*PrOH (8:2), flow: 0.6 ml/min, t: 19.5 min (minor) and 26.8 min (major); ee 70%.

13g. Ethyl 1-(3-(2-(trifluoromethyl)phenyl)-3-oxo-1-phenylpropyl)-3-oxoisoindoline-1-carboxylate. Yield: 91% , waxy solid; d.r. 96/4 ; $[\alpha]_D^{20}$: +38.6 (c = 1, $CHCl_3$). IR (KBr) ν: 3441, 3419, 1649, 1610, 1420, 1389 cm^{-1}. ^{1}H -NMR ($CDCl_3$, 300 MHz) δ: 8.72 (br s, 1H), 8.21 (d, *J*= 6.5 Hz, 2H), 7.83-7.78 (m, 2H), 7.59-7.52 (m, 3H), 7.39-7.31 (m, 1H), 7.14 (d, *J*= 6.5 Hz, 2H), 7.04-6.94 (m, 3H), 4.59 (dd, J_2= 3.8 Hz, J_1= 10.0 Hz, 1H), 4.32-4.21 (m, 2H), 4.10 (dd, J_2= 10.0 Hz, J_1= 16.0 Hz, 1H), 3.41 (dd, J_2= 3.8 Hz, J_1=16.0 Hz, 1H), 1.27 (t, *J*= 7.1 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 150 MHz) δ: 195.8, 171.4, 170.4, 144.0, 137.1, 136.5, 132.0, 131.5, 131.4, 129.7, 129.3, 129.1, 129.0, 128.9, 127.8, 127.4, 125.0, 124.1, 123.7 (q, J_{C-F} = 270.0 Hz),123.5, 71.7, 62.8, 47.2, 40.4, 14.0. MS (ESI): *m/z* = 482 $(M+ H)^+$. Anal. calcd for $C_{27}H_{22}F_3N_2O_4$: C, 67.35; H, 4.61; N, 2.91. Found: C, 67.61; H, 4.81; N, 2.68. Chiral HPLC: AD column, hexane/*i*PrOH (9:1), flow: 0.6 ml/min, t: 28.52 min (minor) and 34.22 min (major); ee 52%.

Procedure for organocatalytic enantioselective cascade Michael/cyclization reaction.[26]

To a solution of (*S*)-(–)-α,α-Diphenyl-2-pyrrolidinemethanol trimethylsilyl ether **17** (15 mol %, 0.015 mmol) and benzoic acid (15 mol %, 0.015 mmol) in MeOH (0.40 mL) was added cinnamaldehyde (1.5 equiv, 0.15 mmol). After the resulting mixture was stirred at room temperature for 15 min, a previously prepared solution of the isoindolinone **4p** (0.10 mmol) in MeOH (0.6 mL) and DCM (0.05 mL) was added dropwise at -15 °C, and the reaction mixture was stirred for the required time. The solvent was then evaporated and the diastereomeric ratio (dr) was determined by ^{1}H-NMR of the crude product. The crude mixture was purified by flash chromatography (Hexane/Ethyl acetate 1/1) to afford the pure adduct as a mixture of diastereoisomers.

16b. Ethyl 7-bromo-2,3,5,9b-tetrahydro-3-hydroxy-5-oxo-1-phenyl-1H-pyrrolo[2,1-a] isoindole carboxylate. Yield: 97%, waxy solid; d.r = 40/60; IR (KBr) ν: 2958, 2927, 1739,1717, 1703, 1092, 1070 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.97 (d, 1H, *J*= 6.0 Hz, minor diast), 7.71-7.66 (m, 2H), 7.42-7.39 (m, 4H), 7.30-7.19 (m, 5H), 7.11-7.05 (m, 4H), 6.80 (dd, 2H, J_2= 3.0 Hz, J_1= 9.0 Hz), 6.11 (dd, 1H, J_2= 6.0 Hz, J_1= 12.0 Hz), 5.81 (dd, 1H, J_2= 3.0 Hz, J_1= 6.1 Hz, minor diast.), 4.36-4.22 (m, 3H), 4.02 (dd, 1H, J_2= 6.0 Hz, J_1= 12.0 Hz, minor diast.), 3.90 (ddd, 1H, J_3= 6.0 Hz, J_2= 12.0 Hz, J_1= 16.0 Hz, minor diast.), 3.12 (ddd, 1H, J_3= 6.0 Hz, J_2=12.0 Hz, J_1= 16.0 Hz minor diast), 2.89 (m, 1H), 2.70 (m, 1H),1.34 (t, 3H, J_1= 6.0 Hz), 0.93 (t, 3H, *J*= 6.0 Hz, minor diast). ^{13}C-NMR ($CDCl_3$, 150 MHz) δ: 172.8, 170.6, 169.9, 169.6, 143.5, 142.2, 139.4, 136.9, 136.5, 135.8, 135.7, 134.9, 130.2, 130.1, 130.0, 129.8, 129.5, 129.4, 129.1, 128.9, 128.6, 128.4, 127.4, 125.3, 124.8, 81.0, 80.7, 64.5, 64.0, 56.1, 51.4, 46.0, 44.6, 15.5, 14.8. MS (ESI): *m/z* = 416.2 (M+

H)$^+$. Anal. calcd for: $C_{20}H_{18}BrNO_4$: C, 57.71; H, 4.36; N, 3.36. Found: C, 57.55; H, 3.48; N, 3.26. Chiral HPLC: IA-3 column, hexane-ethanol (8:2), flow: 0.6 ml/min, minor diastereomer: 23.5 min and 25.2 min. Major diastereomer: 35.1 min and 57.7 min; ee minor 30%; ee major 61%.

6.Notes and references

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