

Communication

Isoindolinones as Michael Donors under Phase Transfer Catalysis: Enantioselective Synthesis of Phthalimidines Containing a Tetrasubstituted Carbon Stereocenter

Francesco Scorzelli, Antonia Di Mola, Laura Palombi and Antonio Massa *

Dipartimento di Chimica e Biologia, Università di Salerno, Via Giovanni Paolo II, 132, 84084-Fisciano, SA, Italy; E-Mails: scorzelli.francesco@tiscali.it (F.S.); toniadimola@libero.it (A.D.M.); lpalombi@unisa.it (L.P.)

* Author to whom correspondence should be addressed; E-Mail: amassa@unisa.it; Tel: +39-089-969-565; Fax: +39-089-969-603.

Academic Editor: Diego A. Alonso

Received: 14 April 2015 / Accepted: 6 May 2015 / Published: 12 May 2015

Abstract: Readily available chiral ammonium salts derived from cinchona alkaloids have proven to be effective phase transfer catalysts in the asymmetric Michael reaction of 3-substituted isoindolinones. This protocol provides a convenient method for the construction of valuable asymmetric 3,3-disubstituted isoindolinones in high yields and moderate to good enantioselectivity. Diastereoselectivity was also investigated in the construction of contiguous tertiary and quaternary stereocenters. The use of acrolein as Michael acceptor led to an interesting tricyclic derivative, a pyrroloisoindolinone analogue, via a tandem conjugated addition/cyclization reaction.

Keywords: synthetic methods; asymmetric catalysis; nitrogen heterocycles; conjugate addition; chiral phase transfer catalysts

1. Introduction

The construction of chiral tetrasubstituted carbons represents one of the most challenging and demanding topics in the synthesis of natural products and chiral drugs [1–5]. The development of such a new catalytic enantioselective synthesis of isoindolinones with this feature appeared to be of great value. Besides unsubstituted [6,7] and monosubstituted isoindolinones [7], many asymmetric

3,3-disubstituted isoindolinones show a wide spectra of biological activities as represented by the general structure **1**, a family of inhibitors of phosphatidylinositol 3-kinase [8]; by **2**, a drug for the treatment of cardiac arrhythmias [9]; by **3**, which is a HIV-reverse transcriptase inhibitor [10]; and by **4**, which is a renin inhibitor [11] (Figure 1).

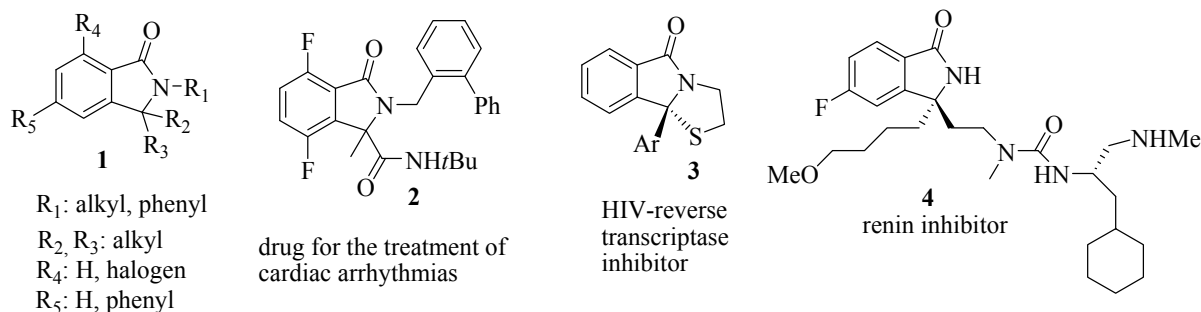


Figure 1. Examples of synthetic pharmacologically active chiral 3,3-disubstituted isoindolinones.

The preparation of these compounds in enantioenriched form has traditionally been pursued by kinetic resolution of racemates or with chiral acids or bases [12–14] or by the use of chiral auxiliaries [15–17], while few catalytic asymmetric methodologies have been reported [18–25]. In particular, the construction of tetrasubstituted stereocenters in the heterocyclic ring in the presence of a chiral Pd(II) complex in an aerobic aza-Wacker-type cyclization performed on alkylidene *ortho*-substituted benzamides has been reported in 2012 by Zhang *et al.* [19]. In 2013 Nishimura *et al.* found that a chiral hydroxorhodium complex was effective in the synthesis of 3,3-diaryl substituted isoindolinones [20]. Only one organocatalytic method for the asymmetric Friedel–Crafts alkylation of indoles with 3-alkyl-3-hydroxyisoindolin-1-ones, showing good enantioselectivity has been described by Zhou *et al.* in 2011 [21]. The limited number of catalytic methodologies for the construction of quaternary stereocenters on the isoindolinone ring prompted us to tackle this challenge, considering the possible use of compounds of general structure **5** as nucleophiles in asymmetric reactions (Figure 2).

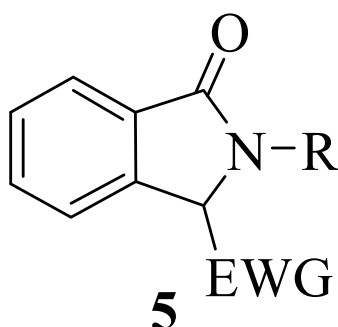


Figure 2. General structure of potentially nucleophilic 3-substituted isoindolinones

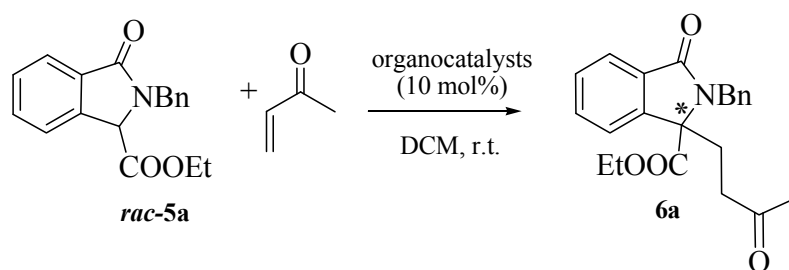
The electron-withdrawing group should activate the benzylic carbon in the 3 position of **5** for asymmetric transformations in the presence of chiral organocatalysts or chiral phase transfer catalysts. As part of our ongoing studies on the asymmetric synthesis of isoindolinones and related compounds [24–28], we report herein the first example of an enantioselective Michael reaction of

rac-3-substituted isoindolinones in the presence of chiral phase transfer catalysts for the construction of 3,3-disubstituted chiral derivatives, highlighting the scope and the limitations of the procedure.

2. Results and Discussion

In order to prove the synthetic utility of compounds of general structure **5** in asymmetric transformations, we started our investigation by testing the reactivity of the readily available isoindolinone **5a** [29] taken as model compound. The choice to study the asymmetric Michael reaction has been inspired by the number of asymmetric methodologies using cyclic β -keto esters and activated phthalides, which can be performed under both organocatalytic [30–32] or chiral phase transfer conditions [33–35]. Accordingly, we firstly tested quinine and bifunctional organocatalyst **7** (Figure 3), under the conditions of Table 1. Pleasingly, the reaction of **5a** with methyl vinyl ketone in DCM led to the adduct **6a** in moderate ee. However, rather low yields, very long reaction times and incomplete conversions were observed (Table 1).

Table 1. Chinchona based organocatalysts in the and identified Michael reaction of 3-substituted isoindolinones.



Entry	Cat. (10 mol %)	t (h)	Yield (%) ^a	ee (%) ^b
1	quinine	96	51	48
2	7	96	55	45

^a Isolated yield. ^b Determined by HPLC on chiral column.

Then, for comparison, we turned our attention to the use of the chiral phase transfer catalyst **8a** (Figure 3) in combination with the inorganic base K_2CO_3 , a catalytic system also employed in Michael reaction of cyclic β -keto esters with good results [33–35]. Nicely enough, the expected Michael adduct **6a** was obtained in high yield and with higher enantioselectivity (56% ee) than when quinine and **7** were used and in a shorter reaction time (compare Entry 1 of Table 2 with the data of Table 1). Considering the promising results obtained under asymmetric phase transfer conditions, we tested other readily available chiral ammonium salts, widely used in asymmetric reactions [33–39]. The *O*-allyl ether derivative **8b** was less effective in terms of yield and enantioselectivity, emphasizing the importance of maintaining free the -OH group at the C-9 position of the catalyst (Entry 2). The *quasi*-enantiomer cinchoninium salt **9a** showed a comparable efficiency with respect to **8a**, giving *ent*-**6a** with a -55% ee (Entry 3), while **8c** had a negative effect on the enantioselectivity (entry 4).

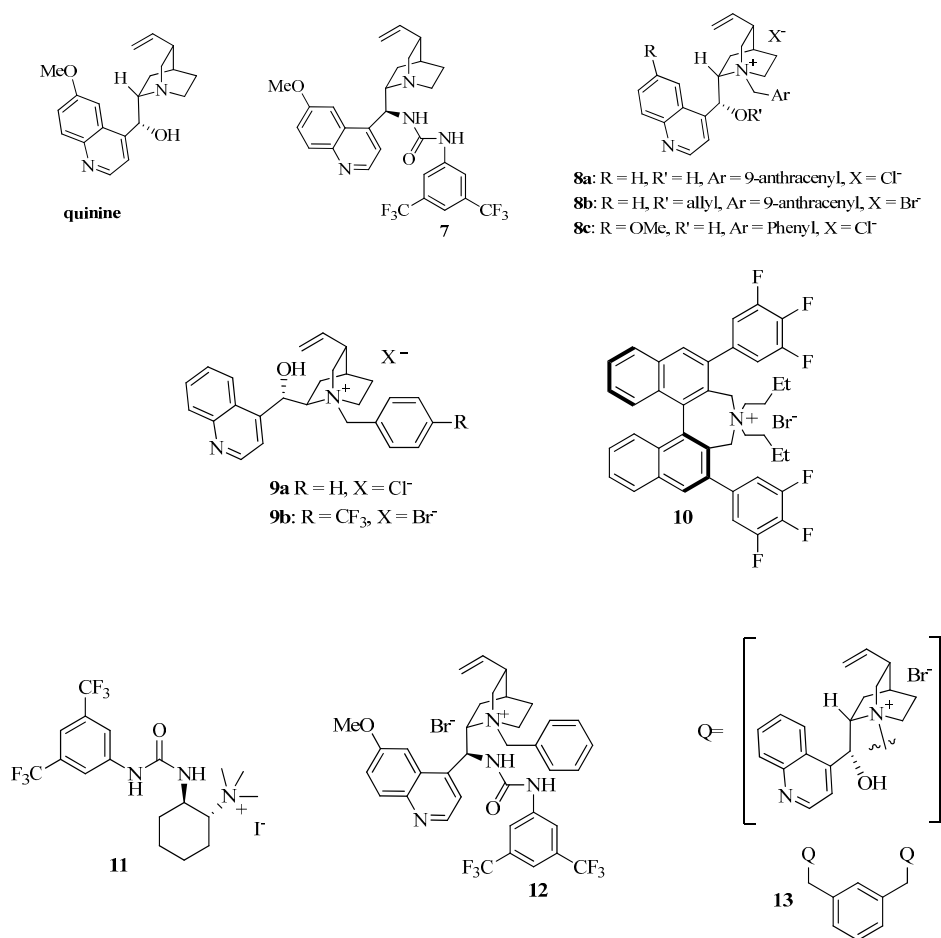
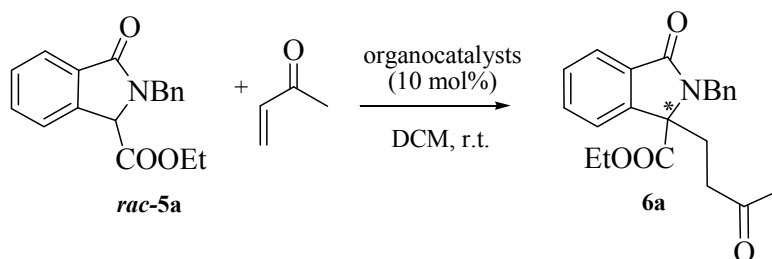


Figure 3. A survey of chiral phase transfer catalysts and organocatalysts.

Table 2. Phase transfer catalyzed asymmetric Michael reactions.



Entry	PTC (10 mol %)	Solvent	T (°C)	t (h)	Yield (%) ^a	ee (%) ^b
1	8a	CH ₂ Cl ₂	r.t.	2	90	56
2	8b	CH ₂ Cl ₂	r.t.	24	95	11
3	9a	CH ₂ Cl ₂	r.t.	2	89	-55
4	8c	CH ₂ Cl ₂	r.t.	48	92	38
5	10	CH ₂ Cl ₂	r.t.	30	91	10
6	11	CH ₂ Cl ₂	r.t.	8	83	rac.
7	12	CH ₂ Cl ₂	r.t.	8	96	-11
8 ^c	8a	CH ₂ Cl ₂	r.t.	3	96	56
9 ^d	8a	CH ₂ Cl ₂	r.t.	24	93	54
10	8a	CH ₂ Cl ₂ /H ₂ O	r.t.	1	92	40

Table 2. Cont.

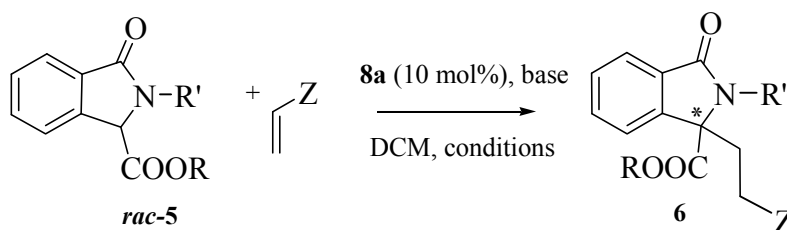
Entry	PTC (10 mol %)	Solvent	T (°C)	t (h)	Yield (%) ^a	ee (%) ^b
11	8a	CH ₂ Cl ₂	−20	3	91	60
12	8a	CH ₂ Cl ₂	−40	24	97	73
13	8a	CH ₂ Cl ₂	−50	48	97	68
14	9b	CH ₂ Cl ₂	−50	48	97	−25
15 ^e	8a	CH ₂ Cl ₂	−40	48	97	65
16 ^f	8a	CH ₂ Cl ₂	−40	48	62	33
17	8a	CHCl ₃	−40	72	96	68
18	8a	1,2-DCE	r.t.	24	97	51
19	8a	Toluene	−40	72	87	61
20 ^g	8a	CH ₂ Cl ₂	−40	36	95	68
21 ^h	8a	CH ₂ Cl ₂	−40	7	94	63

^a Isolated yield. ^b Determined by HPLC on chiral column. ^c **8a** was used at 5 mol %. ^d **8a** was used at 2 mol %.

^e Cs₂CO₃ was used. ^f *i*Pr₂NEt was used. ^g [**5a**] = 7 mM instead of 14 mM of entry 12. ^h [**5a**] = 28 mM.

The structurally different Maruoka's catalyst **10** [33] also employed in a number of asymmetric transformations, gave almost a racemic compound (entry 5). We also investigated the bifunctional chiral ammonium salts **11** [36,37] and **12** [38] derived from (*R,R*)-diamino cyclohexane and from quinine, respectively. Despite the possibility of giving a more ordered TS with the additional hydrogen bonds of the urea group [39], unsatisfactory results were obtained (Entries 6 and 7). Thus, focusing on **8a**, we were able to perform the reaction even at 2 mol % with only a slight decrease in the ee (Entries 8 and 9). The DCM/H₂O system was less effective in terms of enantioselectivity (entry 10). Only with the decreasing of the temperature we observed an increase of the enantioselectivity with a maximum of 73% ee at −40 °C (Entries 11–13). Under these conditions, the PTC **9b** was less effective (entry 14). Other combinations of bases like Cs₂CO₃ or *i*Pr₂NEt with DCM and solvents like CHCl₃, 1,2-DCE or toluene with K₂CO₃, gave less satisfactory results, even if in some cases they have positive effects on asymmetric Michael reactions of methyl vinyl ketone (Entries 15–19) [34]. Also the effect of the molar concentration was analyzed: the best result is represented by Entry 12 in comparison with those of Entries 20 and 21. Then, the scope of the reaction was analyzed by screening several Michael acceptors and isoindolinones, in the presence of **8a**, under different conditions (Table 3).

Table 3. Scope of phase transfer catalyzed asymmetric Michael reaction.



Entry	5	R	R'	Z	T (°C)	t (h)	6	Yield (%) ^a	ee (%) ^b
1	5a	Et	Bn	COMe	−40	24	6a	97	73
2	5b	Me	Bn	COMe	−40	24	6b	98	70
3	5c	<i>t</i> -Bu	Bn	COMe	−40	48	6c	60	45

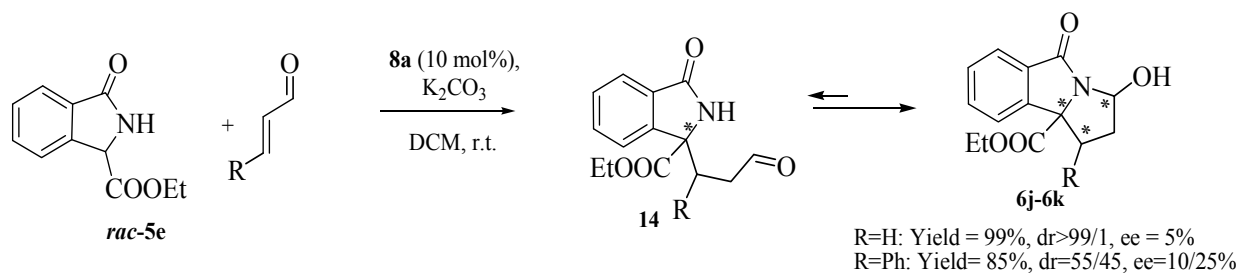
Table 3. Cont.

Entry	5	R	R'	Z	T (°C)	t (h)	6	Yield (%) ^a	ee (%) ^b
4	5a	Et	Bn	COEt	−40	24	6d	95	58
5	5a	Et	Bn	CHO	−40	18	6e	90	33
6	5a	Et	Bn	CO ₂ Me	r.t.	24	-	No reac.	-
7	5d	Et	<i>n</i> -Bu	CO ₂ Me	r.t.	24	6f	75	50
8	5d	Et	<i>n</i> -Bu	CO ₂ Me	−20	48	6f	75	21
9	5d	Et	<i>n</i> -Bu	COMe	r.t.	1	6g	90	61
10 ^c	5d	Et	<i>n</i> -Bu	COMe	r.t.	24	6g	95	59
11	5d	Et	<i>n</i> -Bu	COMe	−20	8	6g	95	76
12	5d	Et	<i>n</i> -Bu	COMe	−40	24	6g	96	71
13 ^d	5d	Et	<i>n</i> -Bu	COMe	r.t.	4	6g	96	38
14	5d	Et	<i>n</i> -Bu	CN	−20	18	6h	97	13
15	5d	Et	<i>n</i> -Bu	CN	r.t.	5	6h	94	36
16	5e	Et	H	COMe	−40	8	6i	97	20

^a Isolated yield. ^b Determined by HPLC on chiral column. ^c Reaction performed in the presence of Na₂CO₃.

^d Reaction performed with 10 mol % of PTC **13** instead of **8a**.

Isoindolinone **5c** with the hindered *t*-butyl ester group was less effective in terms of reactivity and enantioselectivity than the analogues with ethyl and methyl groups **5a** and **5b**, respectively (Table 3, Entries 1–3). Other Michael acceptors were tested. Ethyl vinyl ketone and acrolein gave the expected adducts in very good yields, but with progressively lower ees than methyl vinyl ketone (Entries 4 and 5). Methyl acrylate did not react with **5a** (Entry 6) and a structural change of the isoindolinone scaffold was necessary to guarantee a higher reactivity. In this case, in the presence of the *n*-butyl substituent on the amide in **5d** instead of a benzyl group, the final adduct was obtained in good yield and moderate ee in a reasonable reaction time (Entries 7 and 8). The isoindolinone **5d**, in the presence of methyl vinyl ketone, slightly affected the enantioselectivity in a positive manner, giving the good value of 76% at −20 °C in very high yield (Entries 9–12). Under these new conditions, Na₂CO₃ was slightly less effective than K₂CO₃ (entry 10), while the dimeric cinchonidinium salt **13**, synthesized according to reported procedures [40] was less satisfactory than **8a** (entry 13). Acrylonitrile also showed a very good reactivity, with higher enantioselectivity being observed at r.t. (entries 14 and 15). We also tested the isoindolinone **5e** synthesized according to reported procedures [41] in order to investigate the effect of a further structural change on the reactivity and enantioselectivity. Despite the high reactivity toward methyl vinyl ketone, the free NH group was not beneficial for the enantioselectivity of the process, (entry 16). On the other hand the presence of the NH in **5e** was particularly useful because a further cyclization reaction with the acrolein led to the tricyclic derivative **6j** in high yield (Scheme 1). As observed by ¹H-NMR analysis only one diastereomer was detected, but with very low enantioselectivity. A similar reactivity was observed with cinnamaldehyde, leading to the tricyclic derivative in high yield, but with low enantioselectivity, confirming the negative trend of **5e** with this type of catalysis [42].

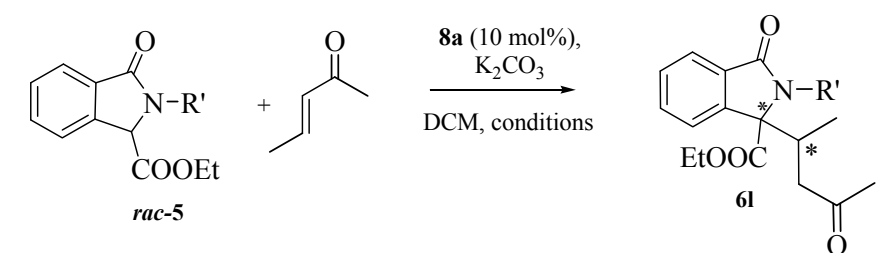


Scheme 1. Synthesis of pyrroloisindolinone analogue.

Nevertheless, this outcome is particularly promising. The obtained compound is an analog of the pyrroloisindolinone scaffold found, for example, in the cyclin dependent kinase 1,2,4,6 inhibitor [43]. Other studies are in course to improve the enantioselectivity and to enlarge the scope of this class of heterocyclic compounds, also considering eventual transformations of the existing functional groups [42].

In the last part of the discussion we focused on reactions of the Michael acceptor 3-penten-2-one in order to study the diastereoselectivity and possibly to obtain adducts with contiguous tertiary and quaternary stereocenters (Table 4). Also in this case the behavior was rather unexpected. According to the data reported in Table 3, the reactivity was strongly dependent on the isoindolinone structure. Probably due to the congested steric situation at the nucleophilic carbon, *N*-substituted isoindolinones **5a** and **5d** did not react at all, while the substrate **5e** gave smoothly the expected product **6l** with the contiguous quaternary and tertiary stereocenters in high yield and with good diastereoselectivity. Unfortunately, also in this case, a very low enantioselectivity was observed, leaving this challenge to future investigations.

Table 4. Reactivity of 3-penten-2-one.



Entry	5	R'	t (h)	T (°C)	Yield (%) ^a	d.r. ^b	ee (%) ^c
1	5a	Bn	24	r.t.	-	-	-
2	5d	<i>n</i> -Bu	24	r.t.	-	-	-
3	5e	H	4	r.t.	95	9/1	4
4	5e	H	24	-40	92	92/8	8

^a Isolated yield. ^b Determined by ¹H-NMR on the crude. ^c Determined by HPLC on chiral column.

3. Experimental Section

3.1. General Information

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, Darmstadt, Germany). The NMR spectra were recorded on Bruker (Rheinstetten, Germany)

DRX 400, 300, 250 spectrometers (400 MHz, 300 MHz, 250 MHz, ^1H ; 100 MHz, 75 MHz, 62.5 MHz ^{13}C). Spectra were referenced to residual CHCl_3 (7.26 ppm, ^1H , 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 a Waters 4 micro quadrupole electrospray spectrometer (Waters, Milford, MA, USA). Elemental analyses were performed with a FLASHEA 1112 series for CHNS-O apparatus (Thermo Scientific, Waltham, MA, USA). Polarimeter Jasco P-2000 (Tokio, Japan), HPLC Waters dual 1485 (Waters).

3.2. Synthesis

The isoindolinones **5a–e** were synthesized according to reported procedures and spectroscopic were in agreement with literature [29,41,44]. Only **5c** and **5d** have never been described and the corresponding spectroscopic data are given below.

tert-Butyl-2-benzyl-3-oxoisoindoline-1-carboxylate (5c). To a solution of compound **5b** (56 mg, 0.2 mmol) in absolute EtOH (1 mL), NaOH 0.5 M (1 mL) was added and the mixture was stirred for 2 h at room temperature. The solvent was removed and the residue was taken up with water, acidified to pH 1 and extracted twice with dichloromethane. The organic layers were combined and evaporated to give a white solid (52 mg, 0.18 mmol) which was resolubilized in dichloromethane (1 mL). Then EDC (40 mg, 0.204 mmol), DMAP (2 mg, 0.02 mmol) and *tert*-butanol (30 μL , 0.670 mmol, in excess) were added to the solution and the mixture was allowed to stir at room temperature for 3 h. Purification by chromatography (ethyl acetate–hexane 1:4) gave a waxy solid. Yield: 52%. $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 7.89 (d, 1H, $J = 6.5$ Hz), 7.35–7.52 (m, 4H), 7.34–7.27 (m, 4H), 5.49 (d, 1H, $J = 16$ Hz), 4.76 (s, 1H), 4.27 (d, 1H, $J = 16$ Hz), 1.47 (s, 9H). MS (ESI): $m/z = 324$ ($\text{M}+\text{H}$) $^+$. Anal. Calcd. for $\text{C}_{20}\text{H}_{21}\text{NO}_3$ C, 74.28; H, 6.55; N, 4.33; found C, 74.33; H, 6.46; N, 4.30.

Ethyl 2-butyl-3-oxoisoindoline-1-carboxylate (5d). Yield 85%; oil. $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 7.99–7.95 (m, 1H), 7.74–7.45 (m, 3H), 5.31 (s, 1H), 4.47–4.24 (m, 2H), 4.23–4.15 (m, 1H), 3.43–3.32 (m, 1H), 1.79–1.69 (m, 2H), 1.54–1.35 (m, 5H), 1.07 (t, 3H, $J = 7.2$ Hz). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ : 168.7, 168.5, 139.5, 132.2, 131.9, 129.3, 124.0, 122.7, 62.3, 62.2, 41.3, 30.2, 20.3, 14.3, 13.9. MS (ESI): $m/z = 262$ ($\text{M}+\text{H}$) $^+$. Anal. calcd for $\text{C}_{15}\text{H}_{19}\text{NO}_3$ C, 68.94; H, 7.33; N, 5.36; found C, 68.83; H, 7.46; N, 5.30.

3.3. Procedure for Preparation of *rac*-6

The Michael acceptor (1.5 eq) was added at r.t. to a solution of isoindolinones **5** (0.05 mmol) and K_2CO_3 (0.5 eq) in CH_3CN (1 mL). The reaction was stirred overnight, the solvent was evaporated and the mixture purified directly on a chromatographic column eluting with 4:1 hexane–ethyl acetate, to afford *rac*-**6** in yields ranging from 70%–90% [45].

3.4. Procedure for Enantioselective Michael Reactions of **5** to Afford **6**

The Michael acceptor (1.5 eq) was added at -40 °C to a stirred solution of **5** (0.1 mmol, 1 eq.), K_2CO_3 (0.1 mmol, 1 eq.) and **8a** (10% mol) in CH_2Cl_2 (1.5 mL). The reaction was monitored by TLC until the

disappearance of **5**. Then, the mixture was purified directly by flash chromatography eluting with 4:1 hexane–ethyl acetate to affording compounds **6** as waxy solids in yields ranging from 60%–99%.

Ethyl 2-benzyl-3-oxo-1-(3-oxobutyl)isoindoline-1-carboxylate (6a). Yield: 35 mg (97%); $[\alpha]_D^{20} = -2.0$ (c = 0.1 M CHCl₃); ee: 73%; ¹H-NMR (400 MHz, CDCl₃) δ: 7.91 (d, 1H, *J* = 8 Hz), 7.55–7.46 (m, 2H), 7.4–7.36 (m, 3H), 7.27 (q, 3H, *J* = 7.6 Hz), 5.1 (d, 1H, *J* = 15.2 Hz), 4.3 (d, 1H, *J* = 15.2 Hz), 4.0 (q, 2H, *J* = 7.2 Hz), 2.74–2.67 (m, 1H), 2.39–2.35 (m, 1H), 1.61 (s, 3H), 1.48–1.41 (m, 2H), 1.09 (t, 3H, *J* = 7.0 Hz); ¹³C-NMR (100 MHz, CDCl₃) δ: 206.5, 169.8, 169.1, 142.9, 137.2, 132.2, 131.5, 129.2, 129.0, 128.4, 127.6, 123.9, 121.4, 71.6, 62.1, 44.7, 35.9, 29.4, 26.2, 13.7; MS (ESI): *m/z* = 366 (M+H)⁺. Anal. calcd for C₂₂H₂₃NO₄ C, 72.31; H, 6.34; N, 3.83; found C, 72.20; H, 6.45; N, 3.70. Chiral HPLC: ODH column, hexane–*i*PrOH (4:1), flow: 0.6 mL/min, t: 15.6 min and 17.5 min.

Methyl 2-benzyl-3-oxo-1-(3-oxobutyl)isoindoline-1-carboxylate (6b). Yield: 34 mg (98%); $[\alpha]_D^{20} = -2.7$ (c = 0.7 M CHCl₃); ee: 70%; ¹H-NMR (400 MHz, CDCl₃) δ: 7.91 (d, 1H, *J* = 7.4 Hz), 7.54–7.36 (m, 3H), 7.28–7.22 (m, 5H), 4.98 (d, 1H, *J* = 14.9 Hz), 4.42 (d, 1H, *J* = 15.1 Hz), 3.46 (s, 3H), 2.77–2.65 (m, 1H), 2.48–2.42 (m, 1H), 1.65 (s, 3H), 1.53–1.43 (m, 2H); ¹³C-NMR (100 MHz, CDCl₃) δ: 206.7, 170.7, 169.3, 143.2, 137.4, 132.6, 131.9, 129.5, 129.4, 128.8, 127.9, 124.3, 121.8, 71.6, 53.1, 44.9, 36.2, 29.7, 26.4; MS (ESI): *m/z* = 352 (M+H)⁺. Anal. calcd for C₂₁H₂₁NO₄ C, 71.78; H, 6.02; N, 3.99; found C, 71.60; H, 6.11; N, 3.87; Chiral HPLC: ODH column, hexane–*i*PrOH (4:1), flow: 0.6 mL/min, t: 19.2 min and 22.6 min.

tert-Butyl 2-benzyl-3-oxo-1-(3-oxobutyl)isoindoline-1-carboxylate (6c). Yield: 24 mg (60%); $[\alpha]_D^{20} = -56.0$ (c = 0.8 M CHCl₃); ee: 45%; ¹H-NMR (400 MHz, CDCl₃) δ: 7.87 (d, 1H, *J* = 6.7 Hz), 7.85–7.35 (m, 3H), 7.28–7.18 (m, 5H), 5.18 (d, 1H, *J* = 15.5 Hz), 4.23 (d, 1H, *J* = 15.0 Hz), 2.66–2.30 (m, 1H), 2.29–2.14 (m, 1H), 1.5 (m, 5H), 1.28 (s, 9H); ¹³C-NMR (100 MHz, CDCl₃) δ: 206.7, 169.3, 168.7, 143.3, 137.5, 132.1, 131.6, 129.1, 128.5, 127.5, 123.9, 121.4, 83.1, 72.5, 44.9, 36.2, 29.6, 27.5, 26.3; MS (ESI): *m/z* = 394 (M+H)⁺. Anal. calcd for C₂₄H₂₇NO₄ C, 73.26; H, 6.92; N, 3.56; found C, 73.40; H, 6.80; N, 3.65; Chiral HPLC: ODH column, hexane–*i*PrOH (4:1), flow: 0.6 mL/min. t: 13.9 min and 14.8 min.

Ethyl 2-benzyl-3-oxo-1-(3-oxopentyl)isoindoline-1-carboxylate (6d). Yield: 36 mg (95%); $[\alpha]_D^{20} = -1.8$ (0.1 M, CHCl₃); ee: 58%; ¹H-NMR (400 MHz, CDCl₃) δ: 7.89 (d, 1H, *J* = 1.5 Hz), 7.87–7.43 (m, 3H), 7.38–7.35 (m, 1H), 7.27–7.20 (m, 4H), 5.06 (d, 1H, *J* = 15.3 Hz), 4.31 (d, 1H, *J* = 15.3 Hz), 3.97–3.92 (m, 2H), 2.72–2.67 (m, 1H), 2.44–2.33 (m, 1H), 1.80–1.76 (m, 2H), 1.45–1.36 (m, 2H), 1.08–1.02 (m, 3H), 0.72 (t, 3H, *J* = 7.3 Hz); ¹³C-NMR (100 MHz, CDCl₃) δ: 209.6, 170.2, 169.5, 143.7, 137.9, 132.5, 131.9, 129.5, 129.4, 128.7, 127.8, 124.2, 121.9, 72.0, 62.4, 45.1, 35.7, 35.0, 26.5, 14.0, 8.2; MS (ESI): *m/z* = 380 (M+H)⁺. Anal. calcd for C₂₃H₂₅NO₄ C, 72.80; H, 6.64; N, 3.69; found C, 72.95; H, 6.60; N, 3.59; Chiral HPLC: ODH column, hexane–*i*PrOH (4:1), flow: 0.6 mL/min, t: 13.1 min and 14.5 min.

Ethyl 2-benzyl-3-oxo-1-(3-oxopropyl)isoindoline-1-carboxylate (6e). Yield: 32 mg (90%); $[\alpha]_D^{20} = +0.52$ (0.9 M, CHCl₃); ee: 33%; ¹H-NMR (300 MHz, CDCl₃) δ: 9.10 (s, 1H), 7.89–7.86 (m, 1H), 7.88–7.41 (m, 6H), 7.37–7.20 (m, 2H), 5.07 (d, 1H, *J* = 15.2 Hz), 4.31 (d, 1H, *J* = 15.2 Hz), 4.01–3.88 (m, 2H), 2.75–2.65 (m, 1H), 2.44–2.34 (m, 1H), 1.48 (t, 2H, *J* = 7.7 Hz), 1.05 (t, 3H, *J* = 7.1 Hz); ¹³C-NMR

(75 MHz, CDCl₃) δ : 200.0, 170.1, 169.4, 143.0, 137.4, 132.6, 131.9, 129.7, 129.3, 128.8, 128.0, 124.4, 121.6, 71.7, 62.5, 45.1, 37.2, 24.8, 14.0; MS (ESI): $m/z = 352$ (M+H)⁺. Anal. calcd for C₂₁H₂₁NO₄ C, 71.78; H, 6.02; N, 3.99, found C, 71.90; H, 6.12; N, 3.87; Chiral HPLC: ODH column, hexane-*i*PrOH (4:1), f: 0.6 mL/min., t: 21.4 min and 23.6 min.

Ethyl 2-butyl-1-(3-methoxy-3-oxopropyl)-3-oxoisindoline-1-carboxylate (6f). Yield: 26 mg (75%); $[\alpha]_D^{20} = -25.3$ (0.7 M, CHCl₃); ee: 50%; ¹H-NMR (250 MHz, CDCl₃) δ : 7.82 (d, 1H, $J = 6.5$ Hz), 7.54–7.40 (m, 3H), 4.19–4.08 (m, 2H), 3.55 (s, 3H), 3.47–3.32 (m, 2H), 2.94–2.84 (m, 1H), 2.62–2.51 (m, 1H), 1.95–1.83 (m, 1H), 1.73–1.62 (m, 3H), 1.4 (q, 2H, $J = 7.3$ Hz), 1.15 (t, 3H, $J = 7.1$ Hz). 0.92 (t, 3H, $J = 7.1$ Hz); ¹³C-NMR (60 MHz, CDCl₃) δ : 172.6, 170.2, 169.1, 142.5, 132.1, 131.9, 129.2, 123.7, 121.4, 71.3, 62.2, 51.6, 41.5, 30.3, 27.5, 27.4, 20.5, 13.7, 13.6; MS (ESI): $m/z = 348$ (M+H)⁺. Anal. calcd for C₁₉H₂₅NO₅ C, 65.69; H, 7.25; N, 4.03; found C, 65.80; H, 7.40; N, 4.09; Chiral HPLC: ODH column, hexane-*i*PrOH (4:1), flow: 0.6 mL/min, t: 29.2 min and 33.7 min.

Ethyl 2-butyl-3-oxo-1-(3-oxobutyl)isoindoline-1-carboxylate (6g). Yield: 31 mg (95%); $[\alpha]_D^{20} = -1.4$ (0.1 M CHCl₃); ee: 76%; ¹H-NMR (400 MHz, CDCl₃) δ : 7.84 (d, 1H, $J = 7.4$ Hz), 7.56–7.47 (m, 2H), 7.40 (d, 1H, $J = 7.1$ Hz), 4.18–4.09 (m, 2H), 3.44–3.36 (m, 1H), 3.34–3.31 (m, 1H), 2.86–2.78 (m, 1H), 2.54–2.47 (m, 1H), 2.03–1.94 (m, 1H), 1.75 (s, 3H), 1.73–1.68 (m, 2H), 1.61–1.55 (m, 1H), 1.39 (q, 2H, $J = 7.5$ Hz), 1.16 (t, 3H, $J = 7.1$ Hz), 0.94 (t, 3H, $J = 7.3$ Hz); ¹³C-NMR (100 MHz, CDCl₃) δ : 206.6, 170.2, 169.1, 142.8, 132.1, 132.0, 129.2, 123.6, 121.6, 71.3, 62.1, 41.5, 36.4, 30.3, 29.9, 25.9, 20.5, 13.8, 13.6; MS (ESI): $m/z = 332$ (M+H)⁺. Anal. calcd for C₁₉H₂₅NO₄ C, 68.86; H, 7.60; N, 4.23; C, 68.94; H, 7.75; N, 4.15; Chiral HPLC: IA-3 column, hexane-*i*PrOH (4:1), f: 0.6 mL/min, t: 11.3 min and 15.9 min.

Ethyl 2-butyl-1-(2-cyanoethyl)-3-oxoisindoline-1-carboxylate (6h). Yield: 29 mg (97%); $[\alpha]_D^{20} = -10.1$ (1.6 M CHCl₃); ee: 36%; ¹H-NMR (250 MHz, CDCl₃) δ : 7.86–7.83 (m, 1H), 7.84–7.50 (m, 2H), 7.44–7.41 (m, 1H), 4.20–4.05 (m, 2H), 3.51–3.42 (m, 1H), 3.37–3.27 (m, 1H), 2.98–2.86 (m, 1H), 2.65–2.53 (m, 1H), 1.99–1.86 (m, 1H), 1.73–1.65 (m, 2H), 1.41 (q, 2H, $J = 7.2$ Hz), 1.25 (m, 1H), 1.15 (t, 3H, $J = 7.1$ Hz), 0.92 (t, 3H, $J = 7.1$ Hz); ¹³C-NMR (60 MHz, CDCl₃) δ : 169.6, 168.9, 141.4, 132.5, 132.2, 129.9, 124.2, 121.2, 118.1, 70.7, 62.6, 60.3, 41.6, 30.5, 28.5, 20.5, 13.7, 11.0; MS (ESI): $m/z = 315$ (M+H)⁺. Anal. calcd for C₁₈H₂₂N₂O₃ C, 68.77; H, 7.05; N, 8.91; C, 68.90; H, 7.14; N, 8.82; Chiral HPLC: IE-3 column, hexane-*i*PrOH (4:1), f: 0.6 mL/min. t: 10.0 min and 11.4 min.

Ethyl 3-oxo-1-(3-oxobutyl)isoindoline-1-carboxylate (6i). Yield: 25 mg (97%); $[\alpha]_D^{20} = -0.3$ (0.5 M CHCl₃); ee: 20%; ¹H-NMR (400 MHz, CDCl₃) δ : 7.82 (d, 1H, $J = 7.28$ Hz), 7.63–7.51 (m, 3H), 6.68 (brs, 1H), 4.22 (q, 2H, $J = 6.6$ Hz), 2.56–2.25 (m, 2H), 2.19–2.12 (m, 2H), 2.03 (s, 3H), 1.26 (t, 3H, $J = 7.1$ Hz); ¹³C-NMR (100 MHz, CDCl₃) δ : 206.8, 170.3, 169.8, 144.1, 132.6, 131.0, 129.3, 123.8, 123.3, 67.0, 62.4, 37.1, 30.9, 29.9, 13.9; MS (ESI): $m/z = 276$ (M+H)⁺. Anal. calcd for C₁₅H₁₇NO₄ C, 65.44; H, 6.22; N, 5.09; C, 65.54; H, 6.34; N, 5.15; Chiral HPLC: IA3 column, hexane-*i*PrOH (4:1), flow 0.6 mL/min. t: 19.2 min and 29.4 min.

Ethyl 2,3,5,9b-tetrahydro-3-hydroxy-5-oxo-1H-pyrrolo[2,1-a]isoindole-9b-carboxylate (6j). Yield: 26 mg (99%); $[\alpha]_D^{20} = -0.1$ (1 M CHCl₃); ee: 5%; ¹H-NMR (300 MHz, CDCl₃) δ : 7.77 (d, 1H, $J = 7.1$ Hz),

7.61–7.45 (m, 3H), 5.71 (q, 1H, $J = 6.3$ Hz), 4.26–4.21 (m, 2H), 3.63 (d, 1H, $J = 6.1$ Hz), 2.80–2.75 (m, 1H), 2.68–2.63 (m, 1H), 2.24–2.18 (m, 1H), 1.72–1.67 (m, 1H), 1.25 (t, 3H, $J = 6.9$ Hz); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ : 171.4, 171.0, 145.1, 133.2, 131.9, 129.7, 124.9, 123.3, 80.2, 75.5, 62.7, 37.9, 34.2, 14.2; MS (ESI): $m/z = 262$ (M+H) $^+$. Anal. calcd for $\text{C}_{14}\text{H}_{15}\text{NO}_4$: C, 64.36; H, 5.79; N, 5.36; found: C, 64.51; H, 5.65; N, 5.43; Chiral HPLC: colonna IE-3 column, hexane-*i*PrOH (4:1) flow: 0.6 mL/min. t: 32.2 min and 37.6 min.

Ethyl 2,3,5,9b-tetrahydro-3-hydroxy-5-oxo-1-phenyl-1H-pyrrolo[2,1-a]isoindole-9b-carboxylate (6k). The title compound was obtained as a mixture of two diastereomers. Yield: 29 mg (85%). ee: 10/25%. $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 7.85–7.82 (m, 1H, minor diast.), 7.59–7.55 (m, 1H), 7.43–7.40 (m, minor diast), 7.29–7.22 (m, 3H), 7.10–6.98 (m, 3H), 6.79 (dd, 2H, $J_2 = 1.5$ Hz, $J_1 = 6.2$ Hz), 6.12 (q, 1H, $J = 6.4$ Hz), 5.82 (t, 1H, $J = 5.3$ Hz, minor diast.), 4.39–4.20 (m, 3H), 3.99 (m, minor diast.), 3.64 (d, 1H, $J = 6.3$ Hz), 3.13 (q, $J = 7.0$ Hz, minor diast.), 2.90 (ddd, 1H, $J_3 = 2.6$ Hz, $J_2 = 6.7$ Hz, $J_1 = 12$ Hz), 2.70 (ddd, 1H, $J_3 = 4.7$ Hz, $J_2 = 7.7$ Hz, $J_1 = 13$ Hz), 1.35 (t, 3H, $J = 7.1$ Hz) 0.93 (t, 3H, $J = 7.1$ Hz, minor diast.); $^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ : 171.7, 170.0, 143.3, 141.9, 138.2, 134.7, 132.2, 132.0, 129.5, 129.0, 128.6, 128.2, 127.9, 127.7, 127.0, 125.4, 124.3, 124.0, 79.4, 79.0, 62.7, 62.3, 54.5, 50.0, 44.5, 43.2, 14.0, 13.2; MS (ESI): $m/z = 338$ (M+H) $^+$. Anal. calcd for $\text{C}_{20}\text{H}_{19}\text{NO}_4$: C, 71.20; H, 5.68; N, 4.15; found: C, 71.32; H, 5.77; N, 4.02; Chiral HPLC: IA-3 column, hexane-*i*PrOH (9:1), flow: 0.6 mL/min. Major diast. t: 12.5 min and 14.2 min. Minor diast. t: 16 min and 19.4 min.

Ethyl 3-oxo-1-(4-oxopentan-2-yl)isoindoline-1-carboxylate (6l). Yield: 27 mg (95%); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 7.81 (d, 1H, $J = 7.5$ Hz), 7.69 (d, 1H, $J = 7.7$ Hz), 7.60 (t, 1H, $J = 7.5$ Hz), 7.53 (t, 1H, $J = 7.5$ Hz), 7.18 (brs, 1H), 7.07 (brs, 1H, minor diastereomer), 4.22–4.16 (m, 2H), 3.19–3.14 (m, 1H), 2.50 (dd, $J = 16.8$ Hz, 3.6 Hz, 1H), 2.41 (dd, $J = 16.8$ Hz, 9.2 Hz, 1H), 2.17 (s, 3H), 1.87 (s, 1H, minor diastereomer), 1.26–1.19 (m, 3H), 1.08 (d, 2H, $J = 9.2$ Hz), 0.59 (d, 3H, $J = 6.7$ Hz); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ : 206.6, 170.9, 170.8, 144.4, 132.7, 131.6, 129.5, 123.8, 123.7, 71.5, 62.6, 46.3, 35.7, 30.9, 14.2, 13.6; MS (ESI): $m/z = 290$ (M+H) $^+$. Anal. calcd for $\text{C}_{16}\text{H}_{19}\text{NO}_4$: C, 64.42; H, 6.62; N, 4.84; found: 64.55; H, 6.52; N, 4.71; Chiral HPLC: IE-3 column, hexane-*i*PrOH (4:1), f: 0.8 mL/min. Major diast. t: 8.9.5 min and 13.0 min. Minor diast. t: 9.7 min and 16.4 min.

4. Conclusions

In conclusion, 3-substituted isoindolinones have been used for the first time as nucleophiles in asymmetric Michael reactions under phase transfer catalyzed conditions in the synthesis of adducts with tetrasubstituted stereocenters. Several electron-deficient olefins were tested. Excellent chemical yields were obtained in the presence of chiral phase transfer catalysts, while organocatalysts were less effective. However, variable enantioselectivities were observed, with good values only occurring in the presence of methyl vinyl ketone. Other studies are in course with the aim to enlarge the substrate scope and field of application of these isoindolinone-based nucleophiles in different asymmetric reactions.

Acknowledgments

MIUR and University of Salerno for their financial support.

Supplementary Materials

Supplementary materials are available at: <http://www.mdpi.com/1420-3049/20/05/8484/s1>.

Author Contributions

FS performed the synthetic work, spectral data analysis and collected data. ADM contributed with literature research and with the synthetic work. LP and AM analysed and discussed results. AM assisted with overall planning, planned the synthetic route, designed the new derivatives, discussed results, wrote and reviewed the manuscript. All authors contributed to the paper and approved the manuscript.

Conflicts of Interest

The authors declare no conflict of interest

References

1. Corey, E.J.; Guzman-Perez, A. The Catalytic Enantioselective Construction of Molecules with Quaternary Carbon Stereocenters. *Angew. Chem. Int. Ed.* **1998**, *37*, 388–401.
2. Christoffers, J.; Mann, A. Enantioselective Construction of Quaternary Stereocenters. *Angew. Chem. Int. Ed.* **2001**, *40*, 4591–4597.
3. Cozzi, P.G.; Hilgraf, R.; Zimmermann, N. Enantioselective Catalytic Formation of Quaternary Stereogenic Centers. *Eur. J. Org. Chem.* **2007**, 5969–5994.
4. Christoffers, J.; Baro, A. *Quaternary Stereocenters: Challenges and Solution for Organic Synthesis*; Christoffers, J., Baro, A., Eds.; Wiley-VCH: Weinheim, Germany, 2005; pp. 83–115.
5. Bella, M.; Gasperi, T. Organocatalytic Formation of Quaternary Stereocenters. *Synthesis* **2009**, *10*, 1583–1614.
6. Shi, L.; Hu, L.; Wang, J.; Cao, X.; Gu, H. Highly Efficient Synthesis of *N*-Substituted Isoindolinones and Phthalazinones Using Pt Nanowires as Catalysts. *Org. Lett.* **2012**, *14*, 1876–1879.
7. Di Mola, A.; Palombi, L.; Massa, A. Active Methylene Compounds in the Synthesis of 3-substituted Isobenzofuranones, Isoindolinones and Related Compounds. *Curr. Org. Chem.* **2012**, *16*, 2302–2320.
8. Aronov, A.; Come, J.H.; Davies, R.J.; Pierce, A.C.; Collier, P.N.; Grey, R.L.; O'Dowd, H.; Henderson, J.A.; Krueger, E.B.; Le Tiran, A.; *et al.* Isoindolinone Inhibitors of Phosphatidylinositol 3-kinase. U.S. Patent 2012/0202784 A1, 9 August 2012.
9. Bjoere, A.; Bostroem, J.; Davidsson, O.; Emtenaes, H.; Gran, H.; Iliefski, T.; Kajanus, J.; Olsson, R.; Sandberg, L.; Strandlund, G.; *et al.* Isoindoline Derivatives for the Treatment of Arrhythmias. WO2008008022, 17 January 2008.
10. Mertens, A.; Zilch, J.H.; Konig, B.; Schafer, W.; Poll, T.; Kampe, W.; Seidel, S.; Leser, U.; Leinert, H. Selective Non-Nucleoside HIV-1 Reverse Transcriptase Inhibitors. New 2,3-Dihydrothiazolo[2,3-*a*]isoindol-5(9*bH*)-ones and Related Compounds with Anti-HIV-1 Activity. *J. Med. Chem.* **1993**, *36*, 2526–2535.

11. Baldwin, J.J.; Claremon, D.A.; Tice, C.M.; Cacatian, S.; Dillard, L.H.; Ishchenko, A.V.; Yuan, J.; Xu, Z.; Mcgeehan, G.; Zhao, W.; *et al.* Renin Inhibitors. WO2008156816, 27 March 2008.
12. Yagishita, F.; Ishikawa, H.; Onuki, T.; Hachiya, S.; Mino, T.; Sakamoto, M. Total spontaneous resolution by deracemization of isoindolinones. *Angew. Chem. Int. Ed.* **2012**, *51*, 13023–13025.
13. Belliotti, T.R.; Brink, W.A.; Kestern, S.R.; Rubin, J.R.; Wistrow, D.J.; Zoski, K.T.; Whetzel, S.Z.; Corbin, A.E.; Pugsley, A.T.; Heffner, T.G.; *et al.* Isoindolinone enantiomers having affinity for the dopamine D4 receptor. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1499–1502.
14. Kanamitsu, N.; Osaki, T.; Itsuji, Y.; Yoshimura, M.; Tsujimoto, H.; Soga, M. Novel water-soluble sedative-hypnotic agents: Isoindolin-1-one derivatives. *Chem. Pharm. Bull.* **2007**, *55*, 1682–1688.
15. Lamblin, M.; Couture, A.; Deniau, E.; Grandclaoudon, P. Alternative and complementary approaches to the asymmetric synthesis of C3 substituted NH free or N-substituted isoindolin-1-one. *Tetrahedron: Asymmetry* **2008**, *19*, 111–123.
16. Nieto, S.; Sayago, F.J.; Laborda, P.; Soler, T.; Cativiela, C.; Urriolabeitia, E.P. Efficient access to (1*H*)-isoindolin-1-one-3-carboxylic acid derivatives by orthopalladation and carbonylation of methyl arylglycinate substrates. *Tetrahedron* **2011**, *67*, 4185–4191.
17. Lorion, M.; Couture, A.; Deniau, E.; Grandclaoudon, P. Complementary synthetic approaches to constitutionally diverse N-amino-alkylated isoindolinones: Application to the synthesis of falipamil and 5-HT_{1A} receptor ligand analogues. *Synthesis* **2009**, *2009*, 1897–1903.
18. Guo, S.; Xie, Y.; Hu, X.; Xia, C.; Huang, H. Diastereo- and Enantioselective Catalytic Tandem Michael Addition/Mannich Reaction: Access to Chiral Isoindolinones and Azetidines with Multiple Stereocenters. *Angew. Chem. Int. Ed.* **2010**, *49*, 2728–2731.
19. Yang, G.; Shen, C.; Zhang, W. An Asymmetric Aerobic Aza-Wacker-Type Cyclization: Synthesis of Isoindolinones Bearing Tetrasubstituted Carbon Stereocenters. *Angew. Chem. Int. Ed.* **2012**, *51*, 9141–9145.
20. Nishimura, T.; Noishiki, A.; Ebe, Y.; Hayashi, T. Hydroxorhodium/Chiral Diene Complexes as Effective Catalysts for the Asymmetric Arylation of 3-Aryl-3-hydroxyisoindolin-1-ones. *Angew. Chem. Int. Ed.* **2013**, *52*, 1777–1780.
21. Yu, X.; Lu, A.; Wang, Y.; Wu, G.; Song, H.; Zhou, Z.; Tang, C. Organocatalyzed Enantioselective Synthesis of Quaternary Carbon-Containing Isoindolin-1-ones. *Eur. J. Org. Chem.* **2011**, *16*, 3060–3066.
22. Mirabal-Gallardo, Y.; Piérola, J.; Shankaraiah, N.; Santos, L.S. Enantioselective total synthesis of (S)-(+)-lennoxamine through asymmetric hydrogenation mediated by L-proline-tetrazole ruthenium catalyst. *Tetrahedron Lett.* **2012**, *53*, 3672–3675.
23. Chen, M.W.; Chen, Q.A.; Duan, Y.; Ye, Z.S.; Zhou, Y.G. Asymmetric hydrogenolysis of racemic tertiary alcohols, 3-substituted 3-hydroxyisoindolin-1-ones. *Chem. Commun.* **2012**, *48*, 1698–1700.
24. More, V.; Rohlmann, R.; García Mancheño, O.; Petronzi, C.; Palombi, L.; de Rosa, A.; di Mola, A.; Massa, A. The first organocatalytic asymmetric synthesis of 3-substituted isoindolinones. *RSC Adv.* **2012**, *2*, 3592–3595.
25. Tiso, S.; Palombi, L.; Vignes, C.; di Mola, A.; Massa, A. Organocatalysts and sequential asymmetric cascade reactions in the synthesis of functionalized isoindolinones and benzoindolizidinones. *RSC Adv.* **2013**, *3*, 19380–19387.

26. Petronzi, C.; Collarile, S.; Croce, G.; Filosa, R.; de Caprariis, P.; Peduto, A.; Palombi, L.; Intintoli, V.; Di Mola, A.; Massa, A. Synthesis and Reactivity of the 3-Substituted Isoindolinone Framework to Assemble Highly Functionalized Related Structures. *Eur. J. Org. Chem.* **2012**, *27*, 5357–5365.
27. Antico, P.; Capaccio, V.; Di Mola, A.; Massa, A.; Palombi, L. Electrochemically Initiated Tandem and Sequential Conjugate Addition Processes: One-Pot Synthesis of Diverse Functionalized Isoindolinones. *Adv. Synth. Catal.* **2012**, *354*, 1717–1724.
28. Massa, A.; Rizzo, P.; Monaco, G.; Zanasi, R. Absolute configuration assignment made easier by the VCD of coupled oscillating carbonyls: the case of (–)-propanedioic acids, 2-(2,3)-dihydro-3-oxo-1*H*-isoindol-1-yl)-1,3-dimethyl ester. *Tetrahedron Lett.* **2013**, *54*, 6242–6246.
29. Rammah, M.M.; Othman, M.; Ciamala, K.; Strohmam, C.; Rammah, M.B. Silver-catalyzed spiro-lactonization: First synthesis of spiroisoindole- γ -methylene- γ -butyrolactones. *Tetrahedron* **2008**, *64*, 3505–3516.
30. Almasi, D.; Alonso, D.A.; Najera, C. Organocatalytic asymmetric conjugate additions. *Tetrahedron: Asymmetry* **2007**, *18*, 299–365.
31. Luo, J.; Jiang, C.; Wang, H.; Xu, L.W.; Lu, Y. Direct asymmetric Michael addition of phthalide derivatives to chalcones. *Tetrahedron Lett.* **2013**, *54*, 5261–5265.
32. Tan, B.; Hernandez-Torres, G.; Barbas, C.F. Rationally Designed Amide Donors for Organocatalytic Asymmetric Michael Reactions. *Angew. Chem. Int. Ed.* **2012**, *51*, 5381–5385.
33. Shirakawa, S.; Maruoka, K. Recent Developments in Asymmetric Phase-Transfer Reactions. *Angew. Chem. Int. Ed.* **2013**, *52*, 4312–4348.
34. Tarí, S.; Chinchilla, R.; Nájera, C. Enantioselective Michael reaction of β -keto esters organocatalyzed by recoverable Cinchona-derived dimeric ammonium salts. *Tetrahedron: Asymmetry* **2009**, *20*, 2651–2654.
35. Elsner, P.; Bernardi, L.; Salla, G.D.; Overgaard, J.; Jørgensen, K.A. Organocatalytic Asymmetric Conjugate Addition to Allenic Esters and Ketones. *J. Am. Chem. Soc.* **2008**, *130*, 4897–4905.
36. Perillo, M.; Di Mola, A.; Filosa, R.; Palombi, L.; Massa, A. Cascade reactions of glycine Schiff bases and chiral phase transfer catalysts in the synthesis of alpha-amino acids 3-substituted phthalides or isoindolinones. *RSC Adv.* **2014**, *4*, 4239–4246.
37. Novacek, J.; Waser, M. Syntheses and Applications of (Thio)Urea-Containing Chiral Quaternary Ammonium Salt Catalysts. *Eur. J. Org. Chem.* **2014**, *4*, 802–809.
38. Johnson, K.M.; Rattley, M.S.; Sladojevich, F.; Barber, D.M.; Nunez, M.G.; Goldys, A.M.; Dixon, D.J. A New Family of Cinchona-Derived Bifunctional Asymmetric Phase-Transfer Catalysts: Application to the Enantio- and Diastereoselective Nitro-Mannich Reaction of Amidosulfones. *Org. Lett.* **2012**, *10*, 2492–2495.
39. Novacek, J.; Waser, M. Bifunctional Chiral Quaternary Ammonium Salt Catalysts: A Rapidly Emerging Class of Powerful Asymmetric Catalysts. *Eur. J. Org. Chem.* **2013**, 637–648.
40. Jew, S.S.; Jeong, B.S.; Yoo, M.S.; Huh, H.; Park, H.G. Synthesis and application of dimeric Cinchona alkaloid phase-transfer catalysts: -bis[O(9)-allylcinchonidinium]-o,m or p-xylene dibromide. *Chem. Commun.* **2001**, 1244–1245, doi:10.1039/B102584H.
41. Conn, E.L.; Hepworth, D.; Qi, Y.; Rocke, B.N.; Ruggeri, R.B.; Zhang, Y. 2-Phenyl Benzoylamides. PCT WO 2011/145022 A1, 24 November 2011.

42. Scorzelli, F.; Di Mola, A.; Croce, G.; Palombi, L.; Massa, A. Organocatalytic asymmetric synthesis of highly functionalized pyrrolizidines via cascade Michael/hemi-aminalization reactions of isoindolinones. *Tetrahedron Lett.* **2015**, *56*, 2787–2790.
43. Kawanishi, N.; Sugimoto, T.; Shibata, J.; Nakamura, K.; Masutani, K.; Ikuta, M.; Hirai, H. Structure-based drug design of a highly potent CDK1,2,4,6 inhibitor with novel macrocyclic quinoxalin-2-one structure. *Bioorg. Chem. Lett.* **2006**, *16*, 5122–5126.
44. Cho, C.S.; Jiang, L.H.; Lee, D.Y.; Shim, S.C. Facile synthesis of isoindolin-1-ones via Palladium Catalyzed Carbonylative Cyclization of 2-bromobenzaldehyde with Primary Amines. *Bull. Korean Chem. Soc.* **1996**, *17*, 1095–1096.
45. Scorzelli, F.; Di Mola, A.; Palombi, L.; Filosa, R.; Massa, A. 3-Carboxylate-Substituted Isoindolinones in K_2CO_3 -Catalyzed Michael Reactions. *Synth. Commun.* **2015**, doi:10.1080/00397911.2015.1033063.

Samples Availability: All samples available from the authors.

© 2015 by the authors; licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution license (<http://creativecommons.org/licenses/by/4.0/>).