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Synthesis and Organocatalytic Asymmetric Nitro-aldol Initiated Cascade Reactions of 2-Acylbenzonitriles Leading to 3,3-Disubstituted Isoindolinones

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Abstract: In this work, we investigated two strategies for the synthesis of the challenging ketones 2-acylbenzonitriles and we report their use as electrophiles in asymmetric organocatalytic cascade reactions with nitromethane. Promising results were obtained in the presence of chiral bifunctional ammonium salts under phase transfer conditions, which led to novel 3,3-disubstituted isoindolinones in quantitative yields and moderate enantioselectivity.

Keywords: cascade reactions; Henry-reactions; asymmetric organocatalysis; isoindolinone; heterocycles; ketones as electrophiles

1. Introduction

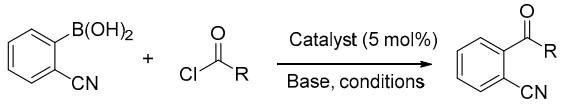
In recent years, cascade reactions have been one of the main topics in organic chemistry because of the convenient construction of complex scaffolds in one-pot procedures without the isolation of the intermediates [1–4]. The electrophilic additions to ketones are particularly challenging because of the poor reactivity of this functional group when compared to the aldehydes despite the great potential in the construction of quaternary carbons [5–7]. Accordingly, the applications of ketones as electrophiles in nitro-aldol cascade type reactions are very limited [1–4]. Therefore, one of our research interests stems from the investigation of the reactivity of ketones bearing further reactive groups in a suitable position, which enhances the poor reactivity of the ketone group. In this context, we have developed efficient cascade reactions of 2-acetylbenzonitriles, which react with a range of nucleophiles to afford useful 3,3-disubstituted isoindolinones in the presence of K_2CO_3 [8]. The difficult accessibility to 2-acylbenzonitriles is also a limitation, from which results few synthetic applications [8–10]. Hence, the aim of the present work is to develop viable synthesis of these compounds and preliminary investigation of the reactivity of 2-acylbenzonitriles with nitromethane in the presence of chiral organocatalytic systems.

2. Results

2.1. Synthesis of 2-acylbenzonitriles by Suzuki-Miyaura Type Cross-Coupling Reactions

In order to develop a direct access to 2-acylbenzonitriles, the first efforts were focused on palladium catalyzed cross-coupling reactions of the commercially available 2-cyanophenylboronic acid **1** with hexanoyl chloride **2**. [11–17]. The use of 2-cyanophenylboronic acid is reported to be an issue [14–17]. The modification of established protocols for the synthesis of ketones can be useful, even though the desired products were isolated in rather low yields (Table 1). Several catalysts and reaction conditions were tested. The best results were obtained with a combination of $Pd(PPh_3)_4$, Cs_2CO_3 (5 eq) in toluene (Entry 2) or $PdCl_2(PPh_3)_2$, and K_3PO_4 (5 eq) in THF (Entry 5). However, the reaction proved to be rather problematic because of the necessity to use an excess of the heptanoyl chloride (5 eq) and because a high temperature and/or a prolonged reaction time led to decomposition of the ketone and of the starting materials (Entries 1–3). This gives complex mixtures of products that are rather difficult to purify. Similar results were obtained with other acyl chlorides (Entries 7 and 8).

Table 1. Suzuki–Miyaura type cross-coupling reactions.



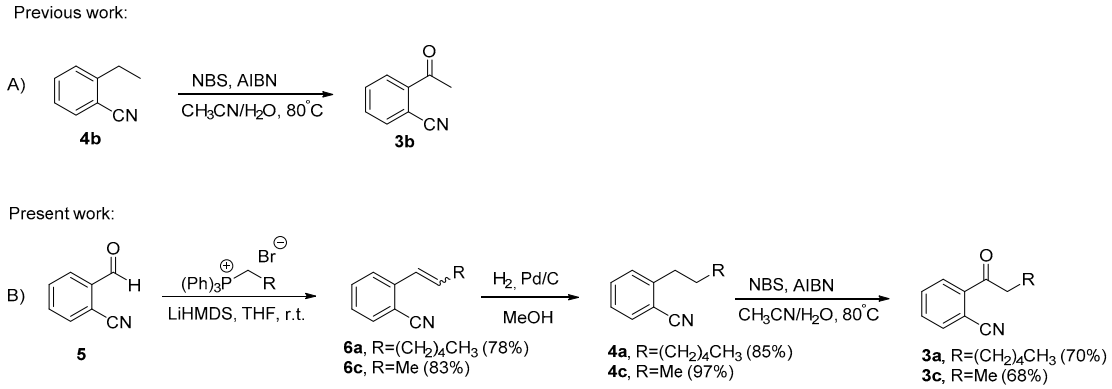
1 **2** **3**

Entry	R (eq)	Solvent	catalyst	Base (eq)	T (°C)	Time(h)	Yield 3 (%) [a]
1	Hexyl, (3 eq)	Toluene	$Pd(PPh_3)_4$	Cs_2CO_3 (5 eq)	100	2.5	**3a,** 20%
2	Hexyl, (5 eq)	Toluene	$Pd(PPh_3)_4$	Cs_2CO_3 (5 eq)	100	2.5	**3a,** 42%
3	Hexyl, (5 eq)	Toluene	$Pd(PPh_3)_4$	Cs_2CO_3 (5 eq)	100	18	**3a,** 16%
4	Hexyl, (5 eq)	Toluene	$Pd(PPh_3)_4$	Cs_2CO_3 (3 eq)	100	2.5	**3a,** 26%
5	Hexyl, (5 eq)	THF	$PdCl_2(PPh_3)_2$	K_3PO_4 (5 eq)	60	24	**3a,** 42%
6	Hexyl, (5 eq)	THF	$Pd(PPh_3)_4$	Cs_2CO_3 (5 eq)	60	24	**3a,** 16%
7	Methyl, (5 eq)	Toluene	$Pd(PPh_3)_4$	Cs_2CO_3 (5 eq)	100	24	**3b,** 35%
8	Ethyl, (5 eq)	Toluene	$Pd(PPh_3)_4$	Cs_2CO_3 (5 eq)	100	24	**3c,** 36%

[a] Yields refer to chromatographically pure compounds.

2.2. Wittig/Oxidation Strategy in the Synthesis of 2-acylbenzonitriles

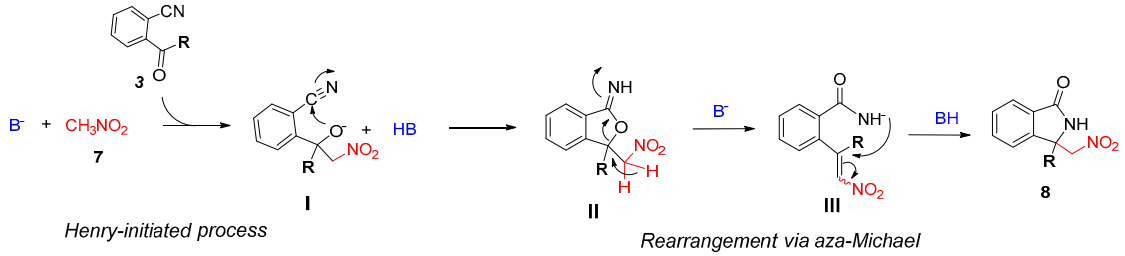
In order to develop more efficient and flexible synthesis of 2-acylbenzonitriles (Scheme 1), we investigated the possibility to obtain the target ketones by selective benzylic oxidation of 2-alkylbenzonitriles with catalytic amount of AIBN [8]. However, 2-alkylbenzonitriles **4** are not easily accessible and few inefficient protocols are reported in literature for their synthesis. Instead of the difficult homologation of 2-methylbenzonitrile in the presence of LDA [18–20], we propose a new approach via reduction of 2-alkylidenebenzonitriles **6**. A feature of this sequence of reactions relies on the selectivity of the Wittig reaction of the readily available 2-cyanobenzaldehyde **5** (Scheme 1), in which the cyano group in the 2 position is left non-reacted, while 2-cyanobenzaldehyde is reported to give efficient cascade reactions involving both the aldehyde and the cyano group. This leads to valuable 3-monosubstituted isoindolinones in the presence of a number of carbon- and hetero-nucleophiles [21–30]. The cis/trans olefin mixture **6** was, then, hydrogenated under heterogeneous conditions and, taking advantage from our previous work [8], the obtained 2-alkylbenzonitriles **4** were selectively oxidized at the benzylic position with NBS/AIBN/H_2O to afford the desired ketones **3** in good yields (Scheme 1).



Scheme 1. Multi-step synthesis of 2-acylbenzonitriles.

2.3. Asymmetric Henry-Initiated Cascade Reactions

The use of ketones as electrophiles in asymmetric organocatalytic reactions is challenging mainly because of the attenuated reactivity in relation to aldehydes and very few examples have been reported [1–4]. We have recently demonstrated that the presence of the cyano group in the 2-position of aromatic ketones, like 2-acetylbenzonitriles, triggers an efficient cascade reaction with a variety of nucleophiles in the presence of K_2CO_3 [8]. In this way, a number of interesting 3,3-disubstituted isoindolinones were obtained as racemates via a carbonyl addition step followed by a Dimroth type rearrangement of the immediate intermediate (Scheme 2) [8].



Scheme 2. Proposed mechanism of cascade reactions of 2-acylbenzonitriles with nitromethane.

It is worthy to note that the number of methodologies for the asymmetric synthesis of 3,3-disubstituted isoindolinones is limited [31–33] and the reported strategies are mainly based on racemate resolution [31–33] or on the use of chiral auxiliaries [31–33], while asymmetric catalytic procedures are relatively rare [34–39]. Therefore, we were interested to investigate the reactivity of 2-acylbenzonitriles with common nucleophiles employing chiral organocatalytic systems in order to achieve a direct construction of chiral 3,3-disubstituted isoindolinones. In particular, we have investigated asymmetric Henry-initiated cascade reactions in the presence of nitromethane because of the importance to introduce a nitromethyl moiety in natural compound analogs and active pharmaceutical ingredients [40], which is an aspect particularly challenging with 2-cyanobenzaldehyde in the synthesis of 3-substituted isoindolinones [22–24].

In a preliminary screening, performed on the model 2-acetylbenzonitrile **4b** in DCM (Table 2 and Figure 1), it immediately emerged that the combination of the chiral ammonium salts **A** or **C1** and an inorganic base under phase transfer conditions furnishes the final isoindolinone in a very efficient manner (Entries 1, 3). Furthermore, bifunctional chiral tertiary amines based organocatalysts **B** or **D** were not effective (Entries 2, 4). The best results in terms of enantioselectivity were obtained in the presence of the bifunctional ammonium salt **C1** derived from *trans*-1,2-cyclohexyldiamine recently developed by our group [41,42], which gave a quantitative yield and moderate enantioselectivity (41% ee). On the other hand, (di)azepino based PTC **E1** (Maruoka's catalyst) [43] and **E2** (Lygo's catalyst) [43] were not effective (Entries 5, 6), which highlights the importance to use bifunctional

ammonium salts with an effective hydrogen donor group to promote the reaction for having sufficient enantiofacial differentiation in the last step of the mechanism (Scheme 2).

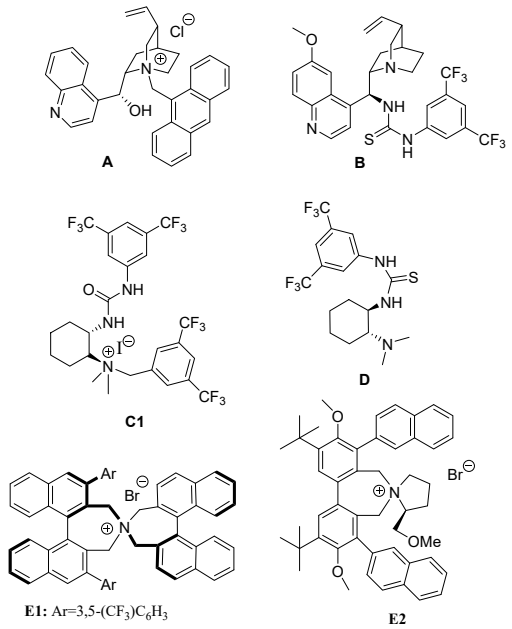


Figure 1. Organocatalysts used in this screening.

Table 2. Asymmetric organocatalytic cascade reaction of nitromethane.

4b **7a** **8a**

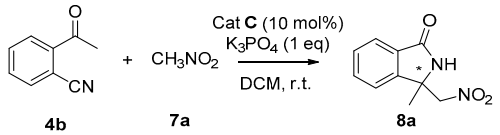
Entry	Catalyst (mol%)	Base (1 eq)	Time (Days)	Yield (%) [a]	ee (%) [b]
1	**A** (20)	K_2CO_3	3d	99	6
2	**B** (20)	–	7d	Traces	–
3	**C1** (20)	K_2CO_3	3d	99	41
4	**D** (20)	–	7d	Traces	–
5	**E1** (20)	K_2CO_3	7d	Traces	–
6	**E2** (20)	K_2CO_3	7d	Traces	–

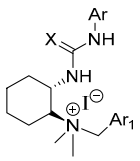
[a] Yields refer to chromatographically pure compounds. [b] Enantiomeric excesses were determined by HPLC on a chiral stationary phase column.

However, the enantioselectivity was not improved by the modification of the substituents on catalyst **C** (Table 3). The best results were obtained with **C1** bearing strong electron-withdrawing groups installed on both aromatic rings. This catalyst was then tested under different reaction conditions (See also s.i. for details), changing solvent (DCM, toluene, THF, $CHCl_3$), base (Cs_2CO_3, K_3PO_4, LiOH, KOH), and equivalents of the base (5, 1, 0.2 eq), temperature (35 °C, r.t., 5 °C), concentration (0.18, 0.092, 0.061 M), and equivalents of the catalyst (0.2, 0.1). A slight improvement of the enantioselectivity was observed using K_3PO_4 as a base in a solid/liquid heterogeneous system (Entries 1 *vs* 2). $CHCl_3$ gave similar results with respect to DCM (Entry 9), while other solvents were less effective (See Supplementary Materials). The reactions perform better at room temperature and in more diluted solutions (see Supplementary Materials). It was possible to decrease the amount of the K_3PO_4 at 0.2 eq only with a slight erosion of the ee (43%), but at the expense of the reaction time (Entry 10). Despite the moderate enantio-enrichment, the enantiopurity of **8a** was improved by a single reverse crystallization (**8a** crystallizes as racemate) in a solvent/non-solvent mixture (Entry 2).

The enantio-enriched product was easily isolated from the solution by filtration with 87% ee and an acceptable 42% yield.

Table 3. Screening of different *trans*-1,2-cyclohexyldiamine based PTC.





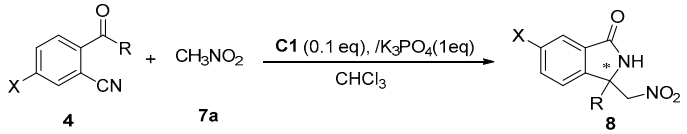
C1: X=O, Ar=Ar$_1$=3,5-(CF$_3$)C$_6$H$_3$
C2: X=O, Ar=3-NO$_2$C$_6$H$_4$, Ar$_1$=3,5-(CF$_3$)C$_6$H$_3$
C3: X=O, Ar=4-NO$_2$C$_6$H$_4$, Ar$_1$=3,5-(CF$_3$)C$_6$H$_3$
C4: X=O, Ar=Et, Ar$_1$=3,5-(CF$_3$)C$_6$H$_3$
C5: X=O, Ar=Ar$_1$=3-NO$_2$C$_6$H$_4$
C6: X=O, Ar=Ar$_1$=Ph
C7: X=S, Ar=Ar$_1$=3,5-(CF$_3$)C$_6$H$_3$

Entry	Catalyst (10 mol%)	Time (Days)	Yield (%) [a]	ee (%) [b]
1 [c]	**C1**	3d	99	41
2	**C1**	3d	99 (42) [d]	45 (87) [d]
3	**C2**	3d	95	39
4	**C3**	3d	93	38
5	**C4**	7d	15	20
6	**C5**	3d	95	40
7	**C6**	7d	99	7
8	**C7**	7d	50	39
9 [e]	**C1**	3d	99	45
10 [f,g]	**C1**	3d	99	43

[a] Yields refer to chromatographically pure compounds. [b] Enantiomeric excesses were determined by HPLC on the chiral stationary phase column. [c] 1.0 eq of K_2CO_3 were used. [d] Yield and ee after crystallization. [e] Reactions performed in $CHCl_3$. [f] 0.2 eq of K_3PO_4 were used.

Then, we analyzed the scope of the reaction under the best conditions, which varied the chain R and the type of the substituent X on the aromatic ring of the ketone (Table 4). In the presence of both electro-withdrawing or donating groups, we obtained the final products in quantitative yields in a shorter reaction time than the parent 2-acetylbenzonitrile, but the enantioselectivity was significantly lower with both strong electro-withdrawing and -donating groups (Entries 4, 5).

Table 4. Scope of asymmetric organocatalytic cascade reaction.



Entry	X	R	Time (Days)	Yield (8) (%) [a]	ee (%) [b]
1	H	Me	3d	99 **(8a)**	45
2	Cl	Me	2d	99 **(8b)**	30
3	Br	Me	2d	99 **(8c)**	26
4		Me	1d	99 **(8d)**	4
5	NO_2	Me	2d	95 **(8e)**	4
6	H	Et	3d	99 **(8f)**	36
7	H	Hexyl	3d	99 **(8g)**	36

[a] Yields refer to chromatographically pure compounds. [b] Enantiomeric excesses were determined by HPLC on the chiral stationary phase column.

Increasing the length of the R group of the ketone, we obtained the same yields and enantioselectivities for the two ketones bearing an ethyl or hexyl group, but lower ee than **4b** (Entries 6-7 *vs* entry 1).

These results should not be surprising because of the low stereo-differentiation usually observed in asymmetric Michael and aza-Michael reactions of α-nitroolefins, which bears a further substituent on β-carbon (see Scheme 2) [40,44]. However, it is noteworthy that both asymmetric nitro-aldol reactions of nitromethane with ketones and asymmetric conjugated additions of α-nitroolefins bearing a further substituent on β-carbon are very rare [40,44].

3. Materials and Methods

Experimental Details. Reactions were performed using commercially available compounds without further purification and analytical grade solvents. All the reactions were monitored by thin layer chromatography (TLC) on precoated silica gel plates (0.25 mm) and visualized by fluorescence quenching at 254 nm. Flash chromatography was carried out using silica gel 60 (70–230 mesh, Merck, Darmastdt, Germany). The NMR spectra were recorded on Bruker (Rheinstetten, Germany) DRX 600, 400, and 300 spectrometers (600 MHz, ^{1}H, 125 MHz, ^{13}C, 400 MHz, ^{1}H, 100 MHz, ^{13}C, 300 MHz, ^{1}H, 75 MHz, ^{13}C). Spectra were referenced to residual $CHCl_3$ (7.26 ppm, ^{1}H, 77.00 ppm, ^{13}C). The following abbreviations are used to indicate the multiplicity in NMR spectra: s—singlet, d—doublet, t—triplet, q—quartet, dd—double doublet, ddd—doublet of doublet of doublet, m—multiplet, bs—broad signal. Coupling constants (*J*) are quoted in hertz. Yields are given for isolated products showing one spot on a TLC plate and no impurities detectable in the NMR spectrum. FTIR spectra were recorded as thin films on KBr plates using Bruker (Rheinstetten, Germany) VERTEX 70 spectrometer and absorption maxima are reported in wavenumber (cm^{-1}). High resolution mass spectra (HRMS) were acquired using a Bruker solariX XR Fourier transform ion cyclotron resonance mass spectrometer (Bruker Daltonik GmbH, Bremen, Germany) equipped with a 7T refrigerated actively-shielded superconducting magnet. The samples were ionized in a positive ion mode using an electrospray (ESI) ionization source. Specific rotation $[\alpha]^{20}_{D}$ was recorded using the Polarimeter Jasco P-2000 (Tokio, Japan). Analytical HPLC was performed on HPLC Waters dual 1485 (Waters, Milford, MA, USA). Phosphonium salts were prepared by following a modified reported procedure [45]. 2-Acetylbenzonitriles and racemic isoindolinones obtained from 2-acylbenzonitriles were prepared as described in the literature [8].

General procedure for 2-acylbenzonitriles synthesis by cross coupling the palladium reaction between 2-cyanophenylboronic acid and acyl chlorides. To a solution of 2-cyano phenylboronic acid (0.34 mmol), catalyst (3 mol%), and base (1.5 mmol) in solvent (2 mL) under nitrogen added freshly prepared acyl chloride (1.5 mmol). The reaction mixture was heated for the required time. After evaporation of the solvent, the crude was taken up with ethyl acetate and washed with a saturated solution of sodium bicarbonate, water, and brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The resulting material was purified by column chromatography on silica gel to give the ketones.

2-heptanoylbenzonitrile 3a. Purified by flash chromatography (Hexane/Ethyl acetate from 98:2 to 90:10). Waxy solid (30 mg). Yield: 42%. FT-IR (KBr): 2222, 1689 cm^{-1}. HR-MS (ESI) *m/z*: calcd for $C_{14}H_{17}NNaO$ $[M+Na]^+$: 238.1202. Found: 238.1209. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 7.7 Hz, 1H), 7.83 (d, *J* = 7.5 Hz, 1H), 7.74–7.66 (m, 2H), 3.03 (t, *J* = 7.2 Hz, 2H), 1.79–1.74 (m, 2H), 1.41–1.27 (m, 6H), 0.91 (t, *J* = 6.2 Hz, 3H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 198.9, 140.1, 135.1, 132.5, 132.1, 129.8, 118.1, 110.8, 39.8, 31.5, 28.7, 23.8, 22.4, 13.9.

2-acetylbenzonitrile 3b. Purified by flash chromatography (Hexane/ethyl acetate, 80:20). White solid (17 mg). Yield: 35 %. Mp. 47–48 °C. *Data in accordance with literature* [3,4]. HR-MS (ESI) *m/z*: calcd for C_9H_7NNaO $[M+Na]^+$: 168.0420. Found: 168.0417.

2-propionylbenzonitrile 3c. Purified by flash chromatography (Hexane/Ethyl acetate from 95:5 to 85:15). White solid (19 mg). Mp. 42–43 °C (lit. 45-46 °C) [7c]. Yield: 36%. FT-IR (KBr): 2224, 1685 cm^{-1}. HR-MS (ESI) *m/z*: calcd for $C_{10}H_9NNaO$ $[M+Na]^+$: 182.0576. Found: 182.0582. ^{1}H NMR (300 MHz,

$CDCl_3$) δ 7.92 (d, *J* = 7.7 Hz, 1H), 7.83-7.80 (m, 1H), 7.74–7.54 (m, 2H), 3.04 (q, *J* = 7.1 Hz, 2H), 1.27–1.18 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 198.8, 140.1, 135.1, 132.5, 132.2, 129.1, 118.1, 110.9, 28.9, 13.9.

General procedure for the 2-alkylbenzonitriles synthesis. To a solution of phosphonium salt (1.2 eq.) in dry THF (28 mL), LiHMDS 1M in THF (7 mmol, 2.3 eq) was added and the orange solution was stirred for 10 minutes before adding 2-formylbenzonitrile (270 mg, 2.06 mmol, 1 eq). The mixture was stirred at room temperature until starting material disappeared by TLC (Hexane/Ethyl acetate 95:5). The solvent was removed under reduced pressure and the residue take up with diethyl ether was washed with water. The organic layers were dried on Na_2SO_4 and concentrated in vacuo to give a brown oil, which was purified by flash chromatography (Hexane/Diethyl ether 99.5:0.5). This afforded alkene compounds to appear as a *cis/trans* mixture. After solubilized (10 mL) in methanol under nitrogen atmosphere, the stirred mixture Pd/C 10% (25 mg) was added. The reaction was allowed to stir at room temperature for 4 h, was diluted with hexane, filtered on celite, and then concentrated.

2-heptylbenzonitrile 4a. Yellow liquid (250 mg). Yield: 85%. *Data in accordance with literature* [18]. HR-MS (ESI) *m/z:* calcd for $C_{14}H_{20}N$ $[M+H]^+$: 202.1590. Found: 202.1587. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.8 Hz, 1H), 7.48 (dt, *J* = 7.7 Hz, 1.3 Hz, 1H), 7.30–7.23 (m, 2H), 2.82 (t, *J* = 7.6 Hz, 3H), 1.67–1.54 (m, 2H), 1.33–1.27 (m, 7H), and 0.86 (t, *J* = 6.7 Hz, 3H).

2-propylbenzonitrile 4c. Yellow liquid (190 mg). Yield: 97%. *Data in accordance with literature* [19]. HR-MS (ESI) *m/z:* calcd. for $C_{10}H_{12}N$ $[M+H]^+$: 146.0964. Found: 146.0971. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 7.6 Hz, 1H), 7.49 (dt *J* = 7.7 Hz, 1.32 Hz, 1H), 7.32–7.27 (m, 2H), 2.81 (t, *J* = 7.5 Hz, 2H), 1.74–1.68 (m, 2H), and 0.98 (t, *J* = 7.4 Hz, 3H).

General procedure for the oxidation/hydrolysis of 2-alkylbenzonitriles [8] A mixture of 2-alkylbenzonitrile (0.76 mmol), *N*-Bromosuccinimide (3.5 eq.) and AIBN (0.1 eq.) in CH_3CN/H_2O 4/1 (3.5 mL) was heated at 80 °C under stirring until starting material disappeared. After cooling to room temperature, the solvent was removed under reduced pressure and the residue taken up with dichloromethane was washed with water. The organic phase was dried over Na_2SO_4 and concentrated in vacuo.

2-heptanoylbenzonitrile 3a. Reaction time 8 h. Purified by flash chromatography (Hexane/Ethyl acetate from 98:2 to 90:10). Waxy solid (114 mg). Yield: 70%.

2-propionylbenzonitrile 3b. Reaction time 9 h. Purified by flash chromatography (Hexane/Ethyl acetate from 95:5 to 85:15). White solid (82 mg). Yield: 68%.

General Procedure for the enantioselective Tandem Reaction of 2-Acylbenzonitriles. A mixture of 2-acylbenzonitrile (0.1 mmol) in $CHCl_3$ or CH_2Cl_2 (1.8 mL), catalyst (10%), anhydrous K_3PO_4 (1 eq.) and nucleophile (3 eq.) was stirred at room temperature until the starting material disappeared (TLC, Hexane/Ethyl acetate, 3:7). The solution was filtered and purified on silica gel (Hexane/Ethyl acetate, 60:40).

3-methyl-3-(nitromethyl)isoindolin-1-one. Waxy white solid (21 mg). Yield: 99%. *Data in accordance with literature* [8]. Ee: 45%, Chiralpak IA3, Hex/IPA 80:20, 0.6 mL/min, 254 nm, t: 16.92 min and 23.69 min. HR-MS (ESI) *m/z*: calcd for $C_{10}H_{11}N_2O_3$ $[M+H]^+$: 207.0764. Found: 207.0769.

Procedure for reverse crystallization: The sample (21 mg) was dissolved in a mixture of $CHCl_3$ (400 µL) and hexane (600 µL) at room temperature and then left at −20 °C for 24 h. The enantio-enriched product was recovered by filtration and evaporation of the solution, which gave 8 mg of **8a** with 87% ee $[\alpha]^{20}_D$: +21.7 (c 0.20, $CHCl_3$).

6-chloro-3-methyl-3-(nitromethyl)isoindolin-1-one. Waxy white solid (24 mg). Yield: 99%. *Data in accordance with literature* [8]. Ee: 30%, Chiralpak IA3, Hex/IPA 80:20, 0.6 mL/min, 254 nm, t: 16.78 min and 19.61 min. $[\alpha]^{20}_D$: +34.1 (c 0.46, $CHCl_3$). HR-MS (ESI) *m/z*: calcd for $C_{10}H_{10}ClN_2O_3$ $[M+H]^+$: 241.0374. Found: 241.0377.

6-bromo-3-methyl-3-(nitromethyl)isoindolin-1-one. Waxy white solid (28 mg). Yield: 99%. FT-IR (KBr): 3392, 1717, 1552 cm^{-1}. Ee: 26%, Chiralpak IA3, Hex/IPA 80:20, 0.6 mL/min, 254 nm, t: 17.43 min and 22.03 min. $[\alpha]^{20}_D$: +24.74 (c 0.56, $CHCl_3$). HR-MS (ESI) *m/z*: calcd for $C_{10}H_{10}BrN_2O_3$ $[M+H]^+$:

284.9869. Found: 284.9874. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, *J* = 1.5 Hz, 1H), 7.76 (dd, *J* = 8.1 Hz, 1.8Hz, 1H), 7.30 (d, *J* = 8.1 Hz, 1H), 7.04 (bs, 1H), 4.82 (d, *J* = 12.8 Hz, 1H), 4.40 (d, *J* = 12.8 Hz, 1H), 1.67 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1, 145.2, 135.7, 132.9, 127.9, 124.0, 122.9, 82.2, 59.4, 23.1.

***N*-methyl-*N*-(1-methyl-1-(nitromethyl)-3-oxoisoindolin-5-yl)acetamide.** Purified by flash chromatography (Ethyl acetate). Waxy white solid (27 mg). Yield: 99%. FT-IR (KBr): 3260, 1712, 1608, 1552 cm^{-1}. Ee: 4%, Chiralpak IE-3, Hex/IPA 70:30, 0.5 mL/min, 254 nm, t: 76.81 min, and 90.76 min. $[\alpha]^{20}_{D}$: +11.93 (c 0.56, $CHCl_3$). HR-MS (ESI) *m/z*: calcd for $C_{13}H_{16}BrN_3O_4$ $[M+H]^+$: 278.1135. Found: 278.1131. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (s, 1H), 7.50 (s, 2H), 7.3 (s, 1H), 4.84 (d, *J* = 12.8 Hz, 1H), 4.46 (d, *J* = 12.8 Hz, 1H), 3.30 (s, 3H), 1.90 (s, 3H), 1.71 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1, 167.6, 146.1, 145.5, 132.8, 131.6, 123.1, 122.7, 82.2, 59.5, 29.6, 23.2, 22.5.

3-methyl-6-nitro-3-(nitromethyl)isoindolin-1-one. Waxy white solid (24 mg). Yield: 95%. FT-IR (KBr): 3269, 1699, 1554 cm^{-1}. Ee: 4%, Chiralpack IA-3, Hex/IPA 70:30, 0.6 mL/min, λ= 254 nm, t: 16.49 min and 22.53 min. HR-MS (ESI) *m/z*: calcd for $C_9H_{10}N_3O_5$ $[M+H]^+$: 252.0615. Found: 252.0621. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (s, 1H), 8.53 (d, *J* = 8.0 Hz, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.07 (s, 1H), 4.88 (d, *J* = 12.8 Hz, 1H), 4.49 (d, *J* = 12.8 Hz, 1H), 1.75 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 151.9, 149.4, 132.9, 127.8, 122.8, 120.4, 81.6, 59.9, 23.4.

3-ethyl-3-(nitromethyl)isoindolin-1-one. Waxy white solid (22 mg). Yield: 99%. FT-IR (KBr): 3280, 1722, 1554 cm^{-1}. Ee: 36%, Chiralpack IA-3, Hex/IPA 80: 20, 0.6 mL/min, λ= 254 nm, t: 16.49 min and 22.53 min. $[\alpha]^{20}_{D}$: +18.4 (c 0.4, $CHCl_3$). HR-MS (ESI) *m/z*: calcd for $C_{11}H_{13}N_2O_3$ $[M+H]^+$: 221.0921. Found: 221.0926. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 7.4 Hz, 1H), 7.68 (t, *J* = 7.5 Hz, 1 H), 7.63 (t, *J* = 7.5 Hz, 1H), 7.42 (d, *J* = 7.6 Hz, 1H), 7.40 (s, 1H), 4.92 (d, *J* = 12.8 Hz, 1H), 4.48 (d, *J* = 12.8 Hz, 1H), 2.08 (q, *J* = 7.3 Hz, 2H), 0.70 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 144.7, 132.7, 132.0, 129.7, 124.7, 121.4, 82.23, 62.9, 28.1, 7.2.

3-hexyl-3-(nitromethyl)isoindolin-1-one. Waxy white solid (27 mg). Yield: 99%. FT-IR (KBr): 3261, 1729, 1550 cm^{-1}. Ee: 36%, Chiralpack IA-3, Hex/IPA 80: 20, 0.6 mL/min, λ= 254 nm, t: 10.97 min and 14.75 min. $[\alpha]^{20}_{D}$: +18.9 (c 0.4, $CHCl_3$). HR-MS (ESI) *m/z*: calcd for $C_{15}H_{21}N_2O_3$ $[M+H]^+$: 277.1547. Found: 277.1552. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 7.4 Hz, 1H), 7.66 (t, *J* = 7.4 Hz, 1H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.41 (d, *J* = 7.5 Hz, 1H), 7.11 (s, 1H), 4.89 (d, *J* = 12.6 Hz, 1H), 4.50 (d, *J* = 12.6 Hz, 1H), 2.01 (t, *J* = 7.6 Hz, 2H), 1.28–1.17 (m, 8H), 0.83 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 145.2, 132.6, 131.9, 129.6, 124.7, 121.4, 82.3, 62.7, 35.0, 31.3, 28.9, 22.8, 22.4, 13.8.

4. Conclusions

We report the synthesis of 2-acylbenzonitriles by selective oxidation of the respective 2-alkylbenzonitriles. The obtained ketones have been used in asymmetric nitro-aldol initiated cascade reaction leading to unprecedented 3,3-disubstituted isoindolinones bearing a nitro group in the side chain in quantitative yields by the use of a chiral bifunctional ammonium salt derived from *trans*-1,2-cyclohexyldiamine. Even though moderate enantioselectivity was obtained, it is possible to increase the enantiopurity of the final product by an efficient process of reverse crystallization.

Supplementary Materials: The following are available online at http://www.mdpi.com/2073-4344/9/4/327/s1. 1. Screening with $MeNO_2$; 2. ^{1}HNMR and ^{13}CNMR spectra of compounds; 3. HPLC traces of compounds.

Author Contributions: F.R. and A.D.M. contributed equally in performing asymmetric screening and synthesis of ketones respectively and in the editing of the supplementary materials; L.P. editing the manuscript and data analysis; M.T. synthesized the catalysts; M.W. designed the catalysts, data analysis and manuscript editing; A.M. designed the reaction, planned the experiments, wrote the manuscript.

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