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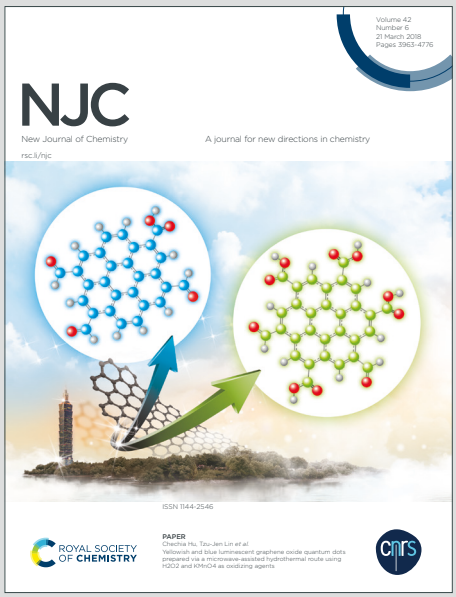

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COMMUNICATION

Enantioselective organocatalytic formal [3+2]-cycloaddition of isatin-derived ketimines with benzylidenemalononitriles and benzylidineindanones

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The biological and medicinal importance of oxindole-derived spirocycles is now well-established, and has inspired the development of numerous creative synthetic strategies. Here we report an efficient formal [3+2]-cycloaddition of isatin-derived *N*-trifluoroethyl ketimines with a series of cinnamonitrile and benzylidineindandione dipolarophiles catalysed by a cinchona-derived thiourea catalyst. The reaction affords a series of functionalized spiro-pyrrolidinoxindole products with up to four contiguous stereocentres in excellent yields, *ee* and d.r. (up to 98% yield, 97% *ee*, and 49:1 d.r.). These products share a common core scaffold with compounds previously found to have anti-tumour, anti-microbial and anti-inflammatory activities.

Spiro-oxindole alkaloids are a common motif found in a variety of naturally occurring products and biologically active species,[1] which in recent years have garnered a lot of interest due to their rigidity, potency, and target specificity.[2] In particular, spiro[pyrrolidin-3,2'-oxindoles] have become a framework of interest due to their diverse therapeutic effects such as anti-microbial,[3] anti-tumour,[4] anti-viral,[5] and anti-inflammatory activities[6] (**Figure 1a**). One of the most common synthetic approaches to these structures is the catalytic asymmetric 1,3-dipolar cycloaddition between azomethine ylides and activated alkenes,[2a, 7] first reported by Gong *et al.* under chiral phosphoric acid catalysis (**Figure 1b**).[8] This methodology has since been extended to incorporate a range of oxindoles and 1,3-dipolarophiles using chiral Lewis acid,[9] chiral phosphoric acid,[7f, 10] and bifunctional organocatalysts.[11] One such extension that has seen widespread interest is the synthesis of the optically active 5'-CF_3 spiro[pyrrolidin-3,2'-oxindole].[12] Incorporation of CF_3 is known to reduce the basicity of adjacent amines, enhance binding interactions and improve metabolic stability and bioavailability.[13] Synthesis of this motif was first realised by Wang *et al.* who developed a proline-based organocatalysed 1,3-dipolar cycloaddition between trifluoroethyl isatin ketimines and cinnamaldehydes.[14] Subsequently *N*-2,2,2-trifluoroethyl isatin ketimines have been utilised in conjunction with a variety of dipolarophiles and organocatalysts,[15] such as Wang *et al.*'s use of nitroalkenes (**Figure 1b**),[16] Yuan *et al.*'s β-trifluoromethyl electron deficient alkenes,[17] or more recently Du *et al.*'s use of barbituric acid derivatives.[18]

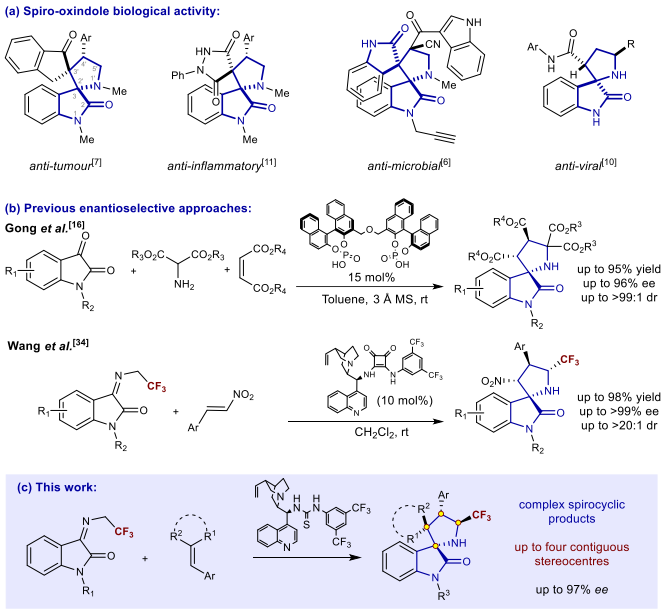

Figure 1. Biological significance and selected extant synthetic approaches to the pyrrolidinoxindole spirocyclic core. Inset: an overview of this research.

We set out to expand the use of the trifluoroethyl ketimine 1,3-dipole and examine new novel dipolarophiles. Benzylidenemalononitriles were first considered, since the geminal dinitrile renders the alkene highly electrophilic and may provide a bidentate binding site for the catalyst.

The [3+2]-cycloaddition of N-2,2,2-trifluoroethylisatin ketimine **1a** and benzylidenemalononitrile **2a** to generate spirocycle **3a** was examined against a variety of organocatalysts in CD_2Cl_2 at room temperature using NMR to profile the reaction (**Table 1**, entries 1-5, see supplementary information for further discussion). Chen's cinchonidine-derived thiourea catalyst (**C1**) gave the greatest conversion and highest enantio- and

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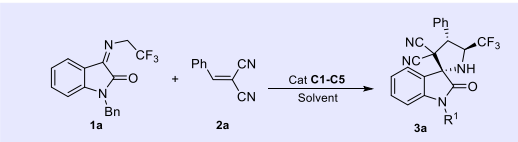
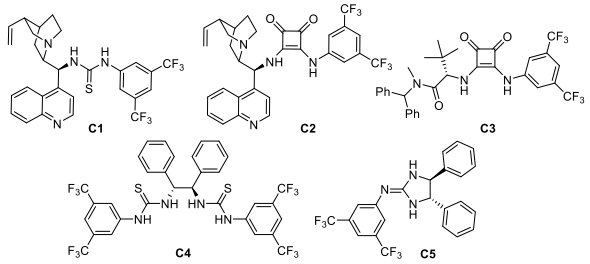
diastereoselectivities (>99% ,92% *ee*, 12:1 d.r.),[19] whilst squaramide (**C2**,**C3**), bis(thiourea) (**C4**), and **novel** guanidine (**C5**) catalysts all gave inferior results. The superiority of thiourea **C1** over squaramide **C2** is surprising, given **C2**'s better performance in the related 1,3-dipolar cycloaddition involving nitroolefins reported by Wang *et al.* Novel guanidine **C5** provided moderate selectivity (43% *ee*) suggesting it may find future applications in asymmetric catalysis. CH_2Cl_2 proved to be the optimal solvent in terms of both enantio- and diastereoselectivity (entries 6-10). Reducing the temperature to 0 or –30 °C had no significant effect on the reaction outcome (entries 11-12). A reduction in catalyst loading maintained high levels of stereoselectivity, but led to slower conversion, so subsequent reactions were conducted with a loading of 10 mol% (entries 13-14).

Table 1. Screening of organocatalysts and optimization of reaction conditions.[a]

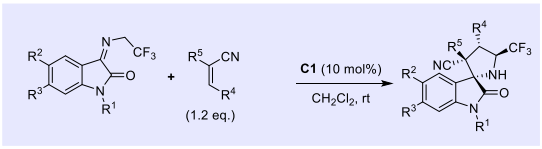


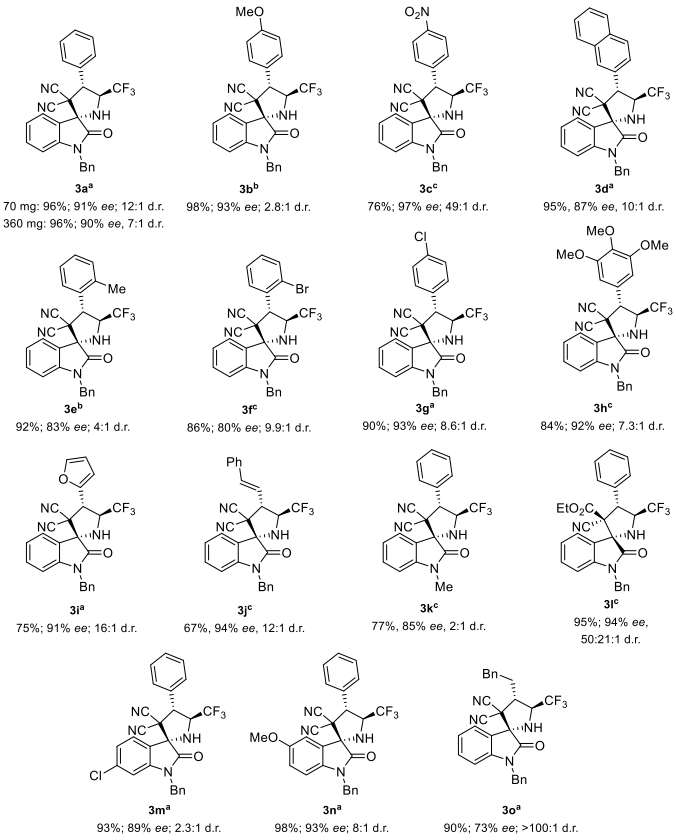
Entry	Solvent	Catalyst	t (h)	Yield[b] (%)	d.r.	*ee*[c] (%)
1	CD_2Cl_2	**C1**	6	>99	12:1	92
2	CD_2Cl_2	**C2**	25	79	7:1	39
3	CD_2Cl_2	**C3**	6	n.r.	n.r.	n.r.
4	CD_2Cl_2	**C4**[d]	6	54	3:2	-41
5	CD_2Cl_2	**C5**	24	28	1.2:1	43
6	CH_2Cl_2	**C1**	3.5	>99	14:1	92
7	PhMe	**C1**	3.5	-[e,f]	13:1	89
8	$PhCF_3$	**C1**	3.5	-[e,g]	9:1	91
9	Et_2O	**C1**	3.5	-[e,f]	4:1	89
10	EtOH	**C1**	3.5	-[e,g]	-[e]	-13
11[h]	CH_2Cl_2	**C1**	2	-[e,f]	-[e]	90
12[i]	CH_2Cl_2	**C1**	19	-[e,g]	-[e]	91
13[j]	CD_2Cl_2	**C1**	12	67	11:1	91
14[k]	CD_2Cl_2	**C1**	12	39	6:1	90



[a] The reactions were performed using catalyst (10 mol%), **1a** (0.1 mmol), and **2a** (0.15 mmol) in solvent (1.0 mL) at room temperature for the time indicated; [b] unless stated otherwise, yields were calculated from ^{1}H NMR spectra with an internal standard [c] determined by small-scale preparative TLC on the crude reaction mixture and HPLC on a chiral stationary phase; [d] NEt_3 (10 mol%) added as co-catalyst; [e] not determined; [f] TLC indicated incomplete conversion; [g] TLC indicated complete conversion; [h] reaction run at 0 °C; [i] reaction run at −30 °C; [j] 5 mol% catalyst; [k] 2.5 mol% catalyst; n.r. = no reaction;

With the optimised conditions in hand (10 mol% **C1**, 0.1 M, CH_2Cl_2, room temperature) the scope of the asymmetric reaction was examined (Scheme 1). The cycloaddition proceeded smoothly affording the spirocycles **3a-l** in high yields and enantioselectivity irrespective of the electronic effect of aryl substituents, with both electron-withdrawing and donating groups being readily tolerated. A range of diastereomeric ratios were observed, from 2.8:1 up to 49:1 (**3b** and **3k** respectively), with electron-withdrawing substituents generally giving the highest diastereoselectivities. In terms of enantioselectivity, *ortho*-substituents on the dipolarophile (**3e,f**) led to a slight decrease in enantioselectivity (~10% reduction) compared to *para*- or non-substituted. Non-benzenoid dipolarophiles were also tolerated, with 2-naphthyl and 2-furanyl products **3d** and **3i** formed in high yields, d.r. and *ee*. A cinnamaldehyde derived malononitrile derivative regioselectively formed **3j** in good yield and excellent stereoselectivity (67%, 94% *ee*, 12:1 d.r.), with no indication of the alternative [4+3]-cycloaddition occurring. *N*-Methylated oxindole **3k** was also formed, with a slight decrease in *ee* and yield compared to **3a**; the d.r. was significantly reduced to 2:1. Replacing one of the cyano groups with an ethyl ester (**3l**) allowed for the generation of spirocycles possessing four-contiguous stereocenters including two congested quaternary centres.





Scheme 1. Scope of the catalytic reaction. Reaction conditions: ketimine (1 eq., 0.1 M), benzylidene (1.2 eq.), catalyst **C1** (10 mol%), CH_2Cl_2, RT, a=24 h, b=48 h, c=72 h. Yields are for isolated material. d.r. determined by ^{1}H or ^{19}F NMR analysis of the crude reaction mixture. Enantioselectivities are given for the major diastereomer, and were determined by HPLC on a chiral stationary phase by comparison to a racemic standard.

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The product **3l** was obtained in 95% yield and 94% *ee* (of the major diastereomer), with modest control over the ester-bearing quaternary stereocentre (~5:2 d.r.). The reaction was tolerant of electron-withdrawing (Cl) and donating (OMe) groups at the isatin 5- and 6-positions respectively, forming spirocyclic products **3m** and **3n** in high yield and *ee*, though **3m** was formed in a modest 2.3:1 diastereomeric ratio. Lastly, it was demonstrated that alkylidenemalononitriles are also reactive under the optimized conditions: dihydrocinnamaldehyde-derived **3o** was formed with outstanding diastereoselectivity (90% yield, >100:1 d.r.), but with a reduced *ee* (73%) relative to the benzylidinemalononitrile-derived products. The relative and absolute configuration of the major diastereomeric components of **3d** and **3l** were determined by single crystal X-ray diffraction, and other products are assumed to be analogous (Figure 2).‡ The stereochemical relationship between the spirocyclic centre and the pyrrolidine substituents is different from that obtained by Wang in the related nitroolefin study.[16,20]

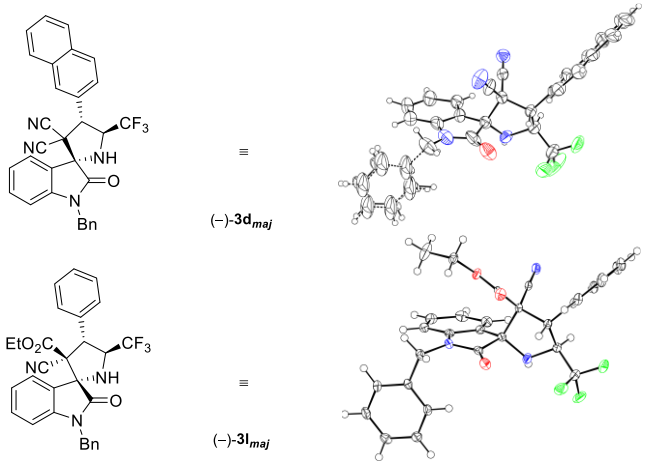
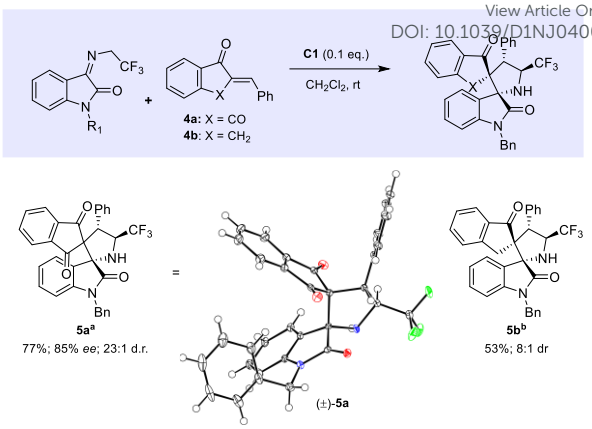


Figure 2. Single crystal X-ray structures of (–)-**3d**$_{maj}$ (CCDC 2103731) and (–)-**3l**$_{maj}$ (CCDC 2114148). Thermal ellipsoids are displayed at the 50% probability level. The *N*-benzyl fragment of (–)-**3d**$_{maj}$ displayed some disorder so is modelled over two positions.

The generality of the reaction conditions for other dipolarophiles was further explored using benzylidene-indanediones **4a** and **4b**. These dipolarophiles were chosen due to the presence of the indanone moiety in biologically active spiro-oxindoles (see **Figure 1**), and therefore would offer a simple, stereoselective route to related architectures. Under the standard conditions both indanone species could readily be incorporated into the spiro-oxindole in moderate yield and diastereoselectivity (**Scheme 2**). 1,3-Indandione product **5a** was obtained in 85% *ee*, 77% yield and 23:1 d.r. while indanone **5b** was obtained in a lower 53% yield (likely due to the reduced electrophilicity of the dipolarophile) and 8:1 d.r., showing good control over the indanone stereocentre. The *ee* of **5b** could not be determined despite exhaustive attempts to resolve it by chiral HPLC.



Scheme 2. Synthesis of indanone-containing dispirocyclic oxindoles **5a** and **5b**. Reaction conditions: ketimine (1 eq., 0.1 M), benzylidene (1.2 eq.), catalyst **C1** (10 mol%), CH_2Cl_2, RT, a=24 h, b= 72 h. Yields are for isolated material. d.r. determined by ^{1}H or ^{19}F NMR analysis of the crude reaction mixture. Enantioselectivities are given for the major diastereomer and were determined by HPLC on a chiral stationary phase by comparison to a racemic standard. A racemic single crystal was obtained of the major diastereomer of **5a** (CCDC 2103730); thermal ellipsoids are displayed at the 50% probability level. The relative stereochemistry of **5b** is inferred from the X-ray structure of **5a**, and presence of nOe enhancements between the indanone C$\underline{H}_2$ signals and the C$\underline{H}$-CF_3.

The relative stereochemistry of **5a** was determined by single crystal X-ray diffraction, revealing an *anti*-relationship between the CF_3 and aryl substituents, with the oxindole lactam linkage *syn*- to the former (**Scheme 2**). The indanone motif appears in spiro-oxindoles previously shown to have anti-tumour activity (see **Figure 1a**) and **5a** and **5b** bear a close structural similarity to these compounds. This similarity and the expectation that the CF_3 will improve metabolic stability make these promising candidates for further biological study.

The relative and absolute configuration of the major stereoisomeric products is consistent with the putative transition state (**3a-TS1**) depicted in **Figure 3**. We propose that the benzylidenemalononitrile coordinates to the thiourea through hydrogen bonding, with the aryl substituent oriented away from the bulk of the catalyst. Deprotonation of the ketimine **1a** by the quinuclidine generates an *aza*-allyl anion, which binds the protonated catalyst through a bifurcated hydrogen bond. The reaction then proceeds with bond formation on the *re*-face of C(1) and the *si*-face of C(3), the latter bonding to the *si*-face of C(4). The formation of the minor diastereomer is consistent with **2a** instead binding the thiourea in a manner that instead exposes its *re*-face to attack. Prior to the reaction imine **1a** adopts a (*Z*)-configuration so **3a-TS1** requires rotation around the C(1)-N(2) bond, which could occur by reversible base-catalysed imine isomerisation. An alternative conformation and configuration of the *aza*-allyl anion would also expose the C(3) *re*-face and generate the observed product, without the requirement for imine isomerisation (**3a-TS2**), but requires the molecule to adopt a highly strained conformation that precludes bifurcated hydrogen bonding to the quinuclidine. **3a-TS1** is consistent with the transition state proposed by Wang for nitroolefin cycloadditions.[16]

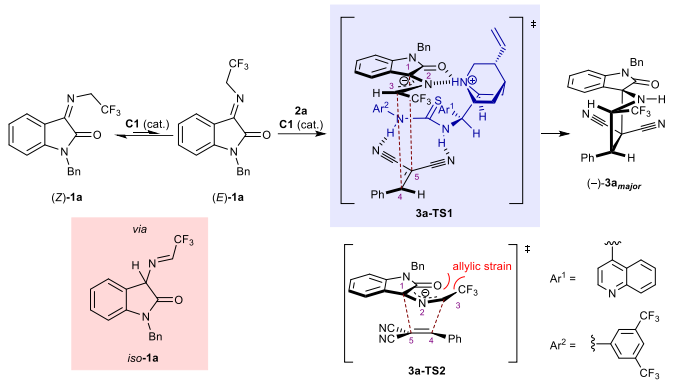


Figure 3. Proposed mechanism and transition state (**3a-TS1**) consistent with the formation of (−)-**3a**$_{major}$ as the major stereoisomeric product. **3a-TS2** is presented as an alternative product-forming transition state, but is unlikely to be favoured due to allylic strain. The cycloaddition is depicted as fully concerted for brevity. The catalyst has been omitted from **3a-TS2** for clarity.

In summary, simple achiral starting materials are rapidly converted into architecturally complex, three-dimensional chiral spirocycles *via* an asymmetric [3+2] cycloaddition approach. This method enables access to a library of spirocyclic oxindole derivatives from *N*-trifluoroethyl isatin ketimines and a range of activated alkene dipolarophiles, mediated by a bifunctional thiourea organocatalyst. The reaction yielded a series of 5′-CF_3 spiro[pyrrolidin-3,2′]-oxindoles containing up to four contiguous stereocentres in high yields and stereoselectivities (up to 98% yield, 97% *ee*, and 48:1 d.r.). The method was extended to benzylidene-indandione dipolarophiles, generating a bi-spirocyclic framework in good yield and stereoselectivity. The compounds formed may find applications in medicinal chemistry, where related materials have previously exhibited strong biological activities against cancer, inflammation and infection.

Author Contributions

Author contributions are itemised using the CRediT system below. CD: data curation; formal analysis; investigation; methodology; validation; writing – review & editing. SR: data curation; formal analysis; investigation. WER: data curation; formal analysis; investigation; methodology; validation; visualization; writing – original draft; writing – review & editing. AMH: investigation; methodology; writing – review & editing. RM: investigation; methodology; writing – review & editing. PCK: conceptualization; data curation; formal analysis; funding acquisition; methodology; project administration; resources; supervision; visualization; writing – original draft; writing – review & editing.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

‡ The absolute stereochemistry of products at the spirocyclic centre is identical to that obtained using a related squaramide catalyst in the [3+2]-cycloaddition of nitroolefins.

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20. We note that in the study by Wang (ref. 16) the authors state that the trifluoroethyl imine possesses (*E*)-stereochemistry. However, their NMR data for this compound match identically the data reported by the same authors earlier that year (ref. 14). In the earlier study, an X-ray crystal analysis of a brominated analogue revealed (*Z*)-stereochemistry, and it is reasonably stated by extension that all the related imines are (*Z*)-configured. We therefore suggest that the (*E*)-stereochemistry of imines depicted in ref. 16 is erroneous.