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Highly diastereoselective entry to chiral spirooxindole-based 4-methyleneazetidines via formal [2+2] annulation reaction†

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A diastereoselective, DABCO-catalyzed reaction of isatin-derived ketimines and allenoates is described. Exploiting the stereodirecting effect of the bulky *tert*-butanesulfinyl chiral auxiliary, the method provides an efficient access to single diastereoisomers of unprecedented spirocyclic oxindoles, bearing a 4-methyleneazetidine ring at the spiro junction. The versatility of the method is fully demonstrated by further transformations including the conversion to relevant spirocyclic oxindolo-β-lactams.

The strained four-membered ring system of azetidines[1] is present as a partial structure of a number of natural products[2] and pharmaceutical agents[3] (Figure 1). Owing to their strong molecular rigidity and, at the same time, to their reasonable stability, azetidines are of special interest, being able to potentially provide improved physicochemical properties in their interaction with biological systems.

They have had enormous application in medicinal chemistry in the form of azetidin-2-ones (β-lactams), that are the key components of many biologically active compounds showing antibacterial, antifungal, and anti-inflammatory properties.[4] Various multifunctional spiro β-lactam derivatives have also been reported recently,[5] among which spirooxindolyl β-lactams are particularly relevant.[6] Despite this interest for azetidin-2-ones, in general azetidines have received much less attention with respect to their lower and higher small-ring homologues, and their application in the context of drug discovery is not so common. In particular, only few novel spirocyclic azetidine scaffolds have been recently proposed,[7] able to access unexplored chemical space and to act as potential new lead compounds.[8]

Our long-standing interest in the asymmetric synthesis of 3,3-disubstituted oxindoles derivatives and related spiro

Figure 1 Examples of biologically relevant compounds containing azetidines and azetidin-2-ones moieties.
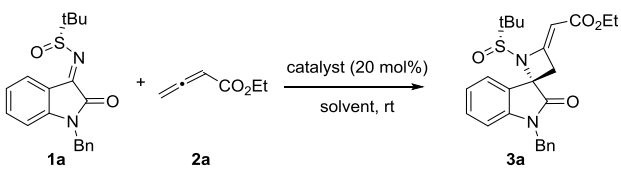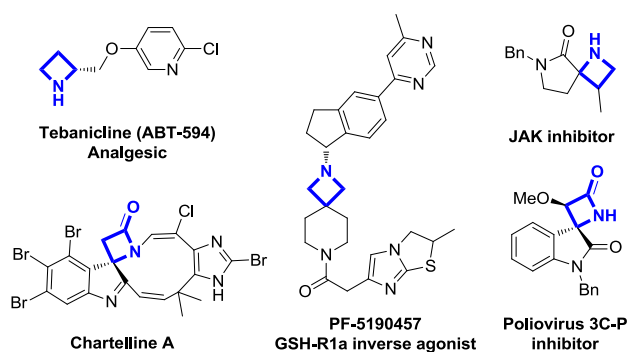

compounds,[9] unitely to the growing interest towards hybrid drugs as therapeutic agents, inspired us to combine the two biologically active oxindole and azetidine moieties, by means of a spiro arrangement of the two ring systems.[10] We conceived the synthesis of chiral spirooxindole-based 4-methyleneazetidines, as an unprecedented, intriguing combination of pharmacologically relevant motifs. Such methyleneazetidines can be also seen as key intermediates for the synthesis of particularly relevant spirooxindolyl β-lactams derivatives.

Relying on our previous experience with isatin-derived ketimines, we looked at the formal [2+2] annulation reactions of such compounds with allenoates, as a practical and direct strategy to obtain highly functionalized target compounds, with a good level of atom-economy. Since Shi's pioneer work[11] disclosing an abnormal Aza-Baylis-Hillman reaction of *N*-tosylated imines with allenoates to give azetidine derivatives in the presence of the strong Lewis base DABCO (1,4-diazabicyclo[2.2.2]octane), additional examples of such [2+2] annulation were reported, both on electron-deficient aldimines and ketimines. A detailed investigation on the effect of different Lewis bases in the reaction of allenoates with cyclic trifluoromethyl ketimines was accomplished by Ma and co-workers.[12]

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Table 1 Survey of the reaction conditions for the formal [2+2] annulation reaction of isatin ketimine **1a** with ethyl buta-2,3-dienoate **2a**.[a]

entry	catalyst	solvent	equiv 2a	conc [M]	time [h]	yield (%)[b]
1	DABCO	THF	1.5	0.1	24	76
2	DBU	THF	1.5	0.1	24	nr
3	DMAP	THF	1.5	0.1	24	-
4	Pyridine	THF	1.5	0.1	24	-
5	DABCO	toluene	1.5	0.1	24	67
6	DABCO	dioxane	1.5	0.1	24	57
7	DABCO	CH_2Cl_2	1.5	0.1	24	72
8	DABCO	THF	2.0	0.1	8	83
9	DABCO	THF	2.5	0.1	8	69
10	DABCO	THF	2.0	0.05	24	48
11	DABCO	THF	2.0	0.2	8	79

[a]All reactions were performed with 0.15 mmol of **1a**. [b]Isolated yields. nr = no reaction.

Remarkable is also the application of this strategy from Ye and co-workers,[13] affording functionalized biologically relevant sultam-fused azetidines. The asymmetric approach to this [2+2] annulation is more challenging, with only two reports reporting enantioselective, organocatalytic versions employing Cinchona alkaloid-derived catalysts.[14] Finally, a diastereoselective synthesis of 2-azetidines was exploited by Santos and co-workers,[15] based on allenoates bearing a chiral auxiliary on the ester moiety.

At the best of our knowledge, no diastereoselective [2+2] annulation-based strategies employing chiral imines have been described for the preparation of methyleneazetidines. Herein we first demonstrate the suitability of chiral, isatin-derived *tert*-butanesulfinyl ketimines for reaction with allenoates, applying this reaction to the synthesis of unprecedented, enantiopure spirooxindole-based 4-methyleneazetidines.

We began our investigation by catalyst screening and reaction optimization using the known 1-benzyl-isatin-derived *N-tert*-butanesulfinyl ketimine **1a** and ethyl buta-2,3-dienoate **2a** (Table 1). A number of amines as diazabicyclo[2.2.2]octane (DABCO), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), *N,N*-dimethyl-4-aminopyridine (DMAP) and pyridine were screened at room temperature in THF for 24 hours (entries 1-4). Only DABCO promoted efficiently the reaction to give the desired azetidine **3a**. DBU proved to be quite ineffective, instead with pyridine or DMAP the reaction afforded complex mixtures, from which only traces of the probable aza-Morita-Baylis-Hillman adduct could be tentatively identified by NMR. Next, solvent screening revealed that the reaction with DABCO worked also in toluene, dioxane and dichloromethane, but in slightly lower yields with respect to THF (entries 5-7). Using a greater excess of ethyl buta-2,3-dienoate **2a** had positive effects on the chemical yields, with the value of 2.0

equivalents performing at the best (entries 8-9). Finally, lowering the substrate concentration elongated the reaction time reducing the conversion, while increasing the concentration gave a less clean reaction, however with a good isolated yield for **3a** (entries 10-11). With respect to the stereochemical outcome, we were delighted to realize that, in all reactions, only the *E*-double bond isomer was formed, bearing, at the best of ^{1}H NMR sensitivity, only a single C-3 relative configuration with respect to the chiral auxiliary.

With the optimized reaction conditions in hand, a variety of *N*-tert-butanesulfinyl ketimines **1** were next explored, to investigate the substrate scope of this novel, DABCO-catalyzed formal [2+2] annulation reaction. The generality was also evaluated with respect to allenoates **2** (Table 2). The protecting group on oxindole nitrogen atom was found to have a moderate effect on the reactivity, with best yields obtained with R^1= Bn, Me, Trt and *p*-Br-Bn (entries 1-9). Surprisingly, ketimine **1c**, bearing the *N*-trityl protecting group, afforded the corresponding azetidine **3c** with the highest yield, but definitely lower stereocontrol, probably due to a steric mismatching effect of the bulky trityl group with the chiral auxiliary *tert*-butanesulfinyl moiety (entry 3). Unprotected ketimine **1d** also gave the reaction, affording the unexpected compound **3d**, deriving from both the [2+2] annulation and the competitive *NH* partecipation with allenoate (entry 4).

Table 2 Diastereoselective formal [2+2] annulation reaction of various isatin ketimines **1** with allenoates **2**, catalyzed by DABCO.[a]
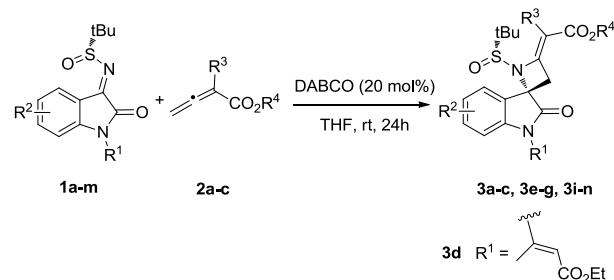
entry	compound 1 (R^1/R^2)	compound 2 (R^3/R^4)	% yield[b]	dr[c]
1	**1a** (Bn/H)	**2a** (H/Et)	**3a**, 83	>99:1
2	**1b** (Me/H)	**2a** (H/Et)	**3b**, 85	>99:1
3	**1c** (Trt/H)	**2a** (H/Et)	**3c**, 97	74:26
4	**1d** (H/H)	**2a** (H/Et)	**3d**, 38 (75)[d]	>99:1
5	**1e** (*p*-NO$_2$-Bn /H)	**2a** (H/Et)	**3e**, 36	>99:1
6	**1f** (*p*-OMe-Bn /H)	**2a** (H/Et)	**3f**, 51	>99:1
7	**1g** (*p*-Br-Bn/H)	**2a** (H/Et)	**3g**, 95	>99:1
8	**1h** (Ac/H)	**2a** (H/Et)	**3d**, 31 (68)[d]	>99:1
9	**1i** (Allyl/H)	**2a** (H/Et)	**3i**, 66	>99:1
10	**1j** (Bn/5-OMe)	**2a** (H/Et)	**3j**, 81	>99:1
11	**1k** (Bn/5-Cl)	**2a** (H/Et)	**3k**, 59	>99:1
12	**1l** (Bn/5-F)	**2a** (H/Et)	**3l**, 47	>99:1
13	**1m** (Bn/6-Br)	**2a** (H/Et)	**3m**, 71	>99:1
14	**1a** (Bn/H)	**2b**(H/Bn)	**3n**, 52	>99:1
15	**1a** (Bn/H)	**2c** (Me/Et)	nd	-

[a]Reactions were performed with 0.15 mmol of **1** and 0.30 mmol of **2**. [b]Isolated yields. [c]Determined by ^{1}H NMR analysis of crude mixture. [d]Reaction performed with 4 equiv of **2a**. Trt = Trityl; nd = not detected.

The same compound **3d** could be also recovered from reaction of ketimine **1h** (entry 8), probably for the great lability of the acetyl protecting group.

Next, *N*-benzylisatin ketimines with various substituents on the aromatic ring were explored. Moderate to good yields of the corresponding azetidines were obtained in the presence of a variety of substituents including electron-donating groups (entry 10), and halogen substituents (entries 11-13) at the 5- or 6-position on the oxindole aromatic ring.

Finally, we investigated the formal [2+2] annulation with two different allenoates, namely benzyl buta-2,3-dienoate **2b** and ethyl 2-methylbuta-2,3-dienoate **2c**. Employing **2b**, the corresponding azetidine **3n** could be easily obtained, albeit in moderate yield (entry 14). On the other hand, α-substituted allenoate **2c** proved to be completely unreactive under the reaction conditions and the corresponding azetidine could not be detected, also after a longer reaction time (entry 15). This result can be ascribed both to the stereoelectronic influence of the methyl group on the allenoate **2c**, than to the high steric challenge inherent in the formation of the tetrasubstituted double bond, jointed to the spiroazetidine ring.

As usual for such kinds of studies, we also proceeded to an experiment of scale-up, employing 1 mmol of ketimine **1a** (reaction conditions as reported in Table 2). After 24 hours, the desired azetidine **3a** could be obtained in yield quite similar to that obtained on the small scale, still as a single diastereoisomer (yield 80%, dr >99:1).

To determine the absolute stereochemistry of the oxindole C-3 spiro center, a single crystal of 4-methyleneazetidine **3a** was subjected to X-ray crystallographic analysis. The experiment unambiguously confirms the *E*-double bond configuration and assigns the stereochemistry of the spiro center as (*S*)-configuration, derived from (*R*)-*tert*-butanesulfinyl ketimine **1a** (Figure 2).

In order to explain this stereochemical outcome, we refer to the established mechanism of Lewis base-catalysed similar formal [2+2] annulations.[11] Accordingly, the nitrogen base DABCO acts as a nucleophile activator, producing a zwitterionic allylic carbanion from the allenoate reagent. Such intermediate undergoes a γ-addition to the ketimine, followed
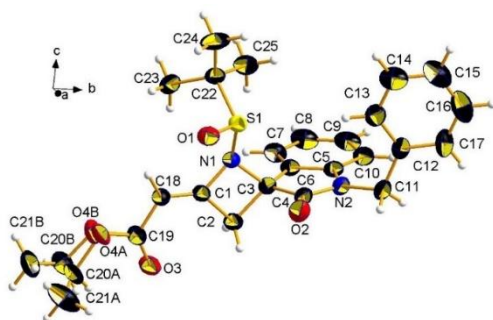
Figure 3 Plausible explanation of the stereochemical outcome.

favored TS

by intramolecular nucleophilic attack to give the azetidine ring with regeneration of DABCO. On this basis, a plausible transition state for the formation of (3,*S*)-**3a** is illustrated in Figure 3. In the working model, the sterochemical outcome can be explained assuming a *syn*-periplanar relationship between the imine and the S=O double bond,[16] which favours the shown conformation for starting ketimine **1a**. The excellent diastereoselectivity observed in the azetidine formation may be due to the high stereodirecting effect of the bulky *tert*-butanesulfinyl group. According to what, the delivery of the DABCO-activated nucleophile would occur from the less hindered *re*-face, resulting in the formation of the (3,*S*)-azetidine.

To demonstrate the synthetic utility of highly functionalized azetidines, we subjected compound **3a** to cleavage of *N*-*tert*-butanesulfinyl chiral auxiliary, to sulfur oxidation and to ozonolysis (Scheme 1). Treatment of sulfinyl amide **3a** with anhydrous HCl in dioxane at room temperature afforded the secondary amine **4** in acceptable yield. Whereas, by action of *m*-chloroperbenzoic acid at room temperature, the sulfinyl amide **3a** was readily oxidized to the corresponding solfonamide **5**. Finally, β-lactam **6** was obtained in quantitative yield by treatment with ozone. This last result can be considered particularly relevant, given the interest in the spirocyclic oxindolo-β-lactam skeleton, which, combining two privileged heterocycles such as indole and β-lactam, is a motif strictly related to natural products and synthetic compounds with significant biological activities.[17]

In conclusion, an efficient asymmetric approach for the

Figure 2 ORTEP view of compound **3a**, with the atom-numbering scheme and the crystallographic reference system. Thermal ellipsoids of non-H atoms were drawn at the 25 % probability level. The two equiprobable conformations of the disordered ethoxy chain of the ester moiety are shown (see ESI).
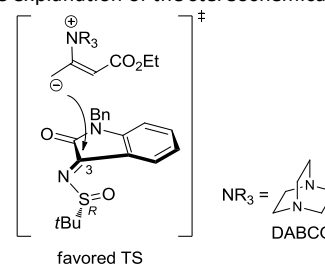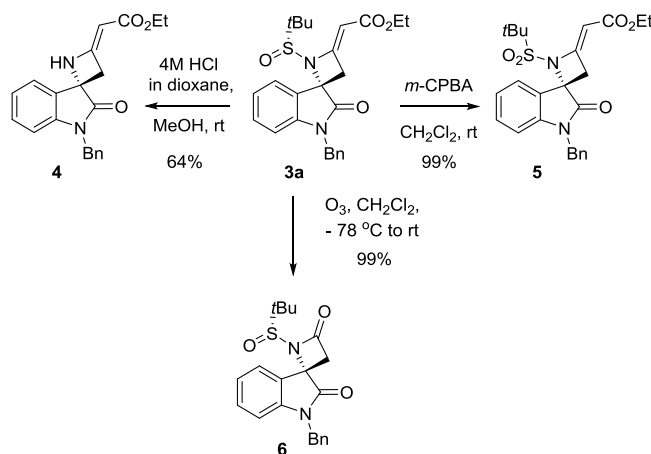
Scheme 1 Further transformations of azetidine **3a**.

preparation of unprecedented, chiral spirooxindole-fused 4-methyleneazetidines has been developed, based on a diastereoselective, DABCO-catalysed formal [2+2] annulation reaction. The method provides easy access to a range of highly functionalized compounds, which are obtained as single diastereoisomers, under mild conditions. By taking advantage of the functional groups transformations, a rapid asymmetric construction of the relevant spirocyclic oxindolo-β-lactam has been also achieved.

Further work is current underway, aimed to establish spirooxindole-fused 4-methyleneazetidines as possible lead compounds for drug discovery programs.

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