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Lewis acid catalyzed annulation of spirocyclic donor–acceptor cyclopropanes with *exo*-heterocyclic olefins: access to highly functionalized bis-spirocyclopentane oxindole frameworks†

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Lewis acid catalyzed highly efficient [3+2] annulation of spirocyclic Donor–Acceptor cyclopropanes (DACs) with *exo*-heterocyclic olefins is reported to furnish various biologically relevant dispiro-2,3-dioxopyrrolidine[cyclopentane]oxindole and dispiropyrazolone-[cyclopentane]oxindole frameworks. This report highlights the use of oxindole-activated spiro-DACs as potential synthons to access complex dispirocarbocyclic oxindoles *via* ring-enlargement of the former, with high yields and diastereoselectivity.

The synthesis of spirocycle containing, all-carbon quaternary centres, has received growing attention in the context of both organic synthesis and medicinal chemistry.[1] Spiro-ring fusion imposes conformational constraints in these compounds and often elicits improved biological activities.

Donor–Acceptor cyclopropanes (DACs), particularly the 2-substituted cyclopropane-1,1-dicarboxylates, have emerged as important building blocks in organic synthesis for the preparation of numerous carbocyclic and heterocyclic compounds.[2] The notion of uniting a DAC and exocyclic olefin or spirocyclic DAC with an olefin may offer a powerful tactic to generate a range of mono or bis-spirocarbocyclic systems through ring-enlargement of the cyclopropane unit. Surprisingly, such a strategy is largely under-developed in the realm of spirocycle forming transformations. A few such examples are reported to date and most rely on the use of DACs with geminal substituted ester or ketone groups for effective activation.[3] In this regard, use of spirocyclopropyl oxindoles as another subclass of monoactivated spiro-DAC system for the

preparation of mono or bis-spirocycles is attractive due to the high biological relevance of the resulting spirooxindole architectures.

In fact, to ascertain the full prospective utility of this subclass of DAC for the assembly of important spirocycles, development of new strategies that can induce facile activation and engage a broad range of reaction partners is needed. This facet, however, has remained challenging and largely unexplored.

Seminal work of Carreira *et al.* on spirocyclopropyl oxindoles demonstrated their facile activation to a ring-opened amphoteric intermediate which subsequently underwent [3+2] annulations with imines and isocyanates leading to bioactive spiro[pyrrolidin-3,3′-oxindole] and spiro[pyrrolidone-3,3′-oxindole] scaffolds.[4] More recently, Melnikov, Budynina and Zhou reported on the development of nucleophilic ring-opening-annulation processes and [3+3] and [3+2] cycloadditions with aryl (donor) substituted DAC of this class, which furnished heterocyclic mono-spirooxindoles (Scheme 1b).[5] Conceptually, similar ring-enlargement of this spiro-DAC can be applied for the synthesis of various spirocarbocyclic oxindole systems upon development of suitable methods.

Spirocyclopentane oxindoles or bis-oxindoles with one or two spirocenters belongs to another class of highly sought after structures that are featured in many natural products and bioactive compounds (Fig. 1).[6] Several catalytic strategies are available in the literature for the synthesis of spirocyclopentane oxindoles with a single spirocenter.[7] Synthesis of the related spirocyclopentane bis-oxindole variant, where the middle cyclo-pentane ring is flanked by two oxindole moieties, is more synthetically challenging but has been a subject of intense research.[8] In this context, development of a method which enables the flexible incorporation of various heterocyclic phar-macophores along with an oxindole nucleus at the two edges of the core cyclopentane ring would be highly desirable for exploring new biologically relevant chemical space (Scheme 1c).[8d,9]

In continuation of our investigations to develop new methodol-ogies with DAC,[10] we now demonstrate the utility of oxindole-activated spiro-DAC for the *de novo* construction of analogous assembly of spirocyclopentane bis-oxindole systems, for the

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† Electronic supplementary information (ESI) available. CCDC 1911435–1911437. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c9cc03393a

(a) Representative approaches to spirocycles with Donor-Acceptor Cyclopropanes(DAC)[ref 3]

(b) Use of oxindole-activated spiro-DACs in heterocyclic spirooxindole synthesis [ref 4-5]

(c) **This Study**: Access to bis-spirocyclopentane oxindole frameworks from spiro-DAC

- bis-heterocyclic-spirocyclopentane framework
- two quaternary all-carbon sp³ centres
- broad substrate scope
- > 40 examples (30-98% yield)
- scalable

Scheme 1 Prior reports and our strategy.

Fig. 1 Natural products containing spirocyclopentane oxindole frameworks.
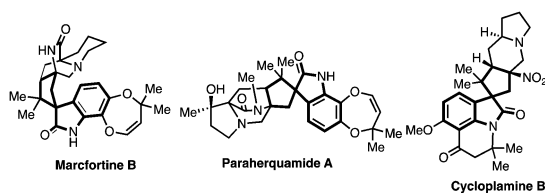
first time, by successfully developing an efficient [3+2] annulation with challenging *exo*-heterocyclic alkene partners (Scheme 1c).

With **1a** (DAC) and MgI_2 (Lewis acid), we commenced the search for a suitable olefin partner for the reaction. Initial screening with a chalcone and *exo*-heterocyclic olefins such as *N*-Boc-protected 3-benzylidenepyrrolidine-2-one or methyleneindolinone proved unsuccessful.[11] Anticipating that the activated DAC could trigger the reaction from its nucleophilic enolate site,[4a] we next evaluated 4-benzylidenepyrrolidine-2,3-dione, **2a**, considering its improved electrophilicity profile and uses in Diels–Alder reactions for accessing biologically active spiropyrrolidone scaffolds.[12] Although the undesired annulation through C3 carbonyl group was of a concern with this substrate,[12a] gratifyingly, the transformation resulted in the formation of desired dispiro-2,3-dioxopyrrolidine[cyclopentane]oxindole (**3aa**), which after optimization (Table 1, entry 1) afforded high yield (96%) and good selectivity (dr = 8 : 1 : 1).

Key results on the optimization of this reaction are illustrated in Table 1. Lewis acids such as $Sc(OTf)_3$, $In(OTf)_3$, or $Mg(OTf)_2$ were unable to furnish the desired product (entries 2–4), whereas $MgBr_2$ afforded the product in high selectivity, albeit in low yield (entry 5). Decreasing the concentration or changing the solvent of the reaction both had a detrimental effect on reaction efficiency (entries 6 and 7).

With the optimized reaction conditions in hand, we next focused on the substrate scope (Table 2). *N*-Alkylated oxindoles

Table 1 Optimization of reaction conditions[a]

Entry	Deviations from standard conditions	Yield[b] [%]	Ratio of stereoisomers[c]
1	None	96	8 : 1 : 1
2[d]	$Sc(OTf)_3/CH_2Cl_2$	NR	0
3[d]	$In(OTf)_3/CH_2Cl_2$	NR	0
4	$Mg(OTf)_2$	NR	0
5	$MgBr_2$	55	20 : 1
6	Use of 10 mol% MgI_2	58	12 : 3 : 2 : 1
7	1,4-Dioxane as solvent	50	7 : 1 : 1

[a] Reaction conditions: **1a** (1.5 equiv.), **2a** (1.0 equiv.), 12–15 h. [b] Combined isolated yield of all diastereomers. [c] Determined by crude NMR. [d] Temperature = 50 °C.

were found to be better substrates in the reaction (**3aa–3ba**, entries 1 and 2) compared to those with free NH or *N*-acetyl protection (entries 3 and 4). Likewise, the *N*-alkylated 2,3-dioxopyrrolidines (**2**) were found to be viable reaction partner (R^3 in entries 1–5). X-Ray crystal structure analysis of **3ba** (major diastereomer) unambiguously proved the connectivity and stereochemistry at the spirocentres.

Next, we evaluated the effect of substituents on the benzylidene aromatic ring of **2**. Functional groups having different electronic and steric properties (*e.g.*, 2-Me, 4-Me, 3 or 4-OMe, 4-F *etc.*) were well tolerated and afforded smooth conversion to final compounds **3ac–3aj** (entries 6–13). Larger aromatic rings such as naphthyl and heterocyclic thiophene nucleus are also accommodated in the

Table 2 Substrate scope

| Entry	3	$R^1/R^2/R^3$	Yield[a,b] [%]	dr[c]
1	**3aa**	Me/Ph/Bn	68	8 : 1 : 1
2	**3ba**	Bn/Ph/Bn	65[d]	n.d.[e]
3	**3ca**	H/Ph/Bn	38	n.d.
4	**3da**	Ac/Ph/Bn	36	8 : 1
5	**3ab**	Me/Ph/cyclohexyl	65	8 : 1 : 1
6	**3ac**	Me/4-Me-C$_6$H$_4$/Bn	57	8 : 1.5 : 1
7	**3ad**	Me/4-^{i}Pr-C$_6$H$_4$/Bn	61	7 : 1.3 : 1
8	**3ae**	Me/4-OMe-C$_6$H$_4$/Bn	66	7 : 1 : 1
9	**3af**	Me/3,4-di-OMe-C$_6$H$_3$/Bn	54	7 : 1.7 : 1
10	**3ag**	Me/3-OMe-C$_6$H$_4$/Bn	58	3 : 1
11	**3ah**	Me/2-Me-C$_6$H$_4$/Bn	53	9 : 2 : 1 : 1
12	**3ai**	Me/4-Cl-C$_6$H$_4$/Bn	62	5 : 1.4 : 1
13	**3aj**	Me/4-F-C$_6$H$_4$/Bn	54	5.2 : 1.5 : 1
14	**3ak**	Me/1-naphthyl/Bn	55[f]	7 : 1.4 : 1
15	**3al**	Me/2-thiophenyl/Bn	56	9 : 2 : 1

[a] Isolated yields of major diastereomer. [b] Minor diastereomers were obtained as inseparable mixture (impure form). In most cases, compound **1** was recovered from the reaction mixture (*ca.* 5–15%). [c] Determined by crude NMR. [d] 62% yield (1 g scale reaction). [e] n.d. = not determined. [f] Isolated as diastereomeric mixture.

spirocyclic products (entries 14 and 15). Interestingly, with 9-anthracenyl derivative (**2m**, not shown in Table 2), the annulation proceeded with C3 carbonyl group (Scheme S2 in ESI†). This switch in site selectivity can be attributed to the steric bulk of the 9-anthracenyl group.

Intrigued by the success of compound **2a**, we next focused on alkylidine pyrazolone derivatives. These substrates are powerful Michael acceptor and moreover, 4-spiro-5-pyrazolone moieties exhibit diverse biological activities as agrochemicals and pharmaceuticals.[13] We surmised that integration of this pharmacophore to oxindole within the bis-spirocyclopentane skeleton could lead to potential bioactivities.

To our delight, by subjecting **1a** and (Z)-unsaturated pyrazolone **4a** to the optimized reaction condition afforded the formation of unprecedented dispiropyrazolone[cyclopentane]oxindoles **5aa** in high yield (82%) and excellent diastereoselectivity (>20:1). Compounds **5ba**, **5ab**, and **5bb** were also formed with similar high yields and selectivity. In order to explore the broader scope and introduce additional complexity and diversity in the resulting products, we next employed phenyl substituted spiro-DAC, **1e**. Pleasingly, the reaction of **1e** with **4a** proceeded smoothly and afforded product **5ea** in excellent yield (98%). Importantly, only two diastereomers of **5ea** (dr = 1.5:1) out of several possibilities, were formed in the reaction. X-ray structural analysis of each diastereomers of **5ea** revealed that two phenyl groups on the cyclopentane moiety are present in a *cis* and *trans* configuration (*vide infra*), and the *cis*-isomer is formed in excess to the other.

Curiously, we next employed N-diethoxyphosphoryl oxindole-activated DAC (**1f**). This DAC was reported to undergo facile activation and cycloadditions with heteroatom containing partners in presence of Sc(OTf)$_3$ or In(OTf)$_3$.[5c] However, the reported
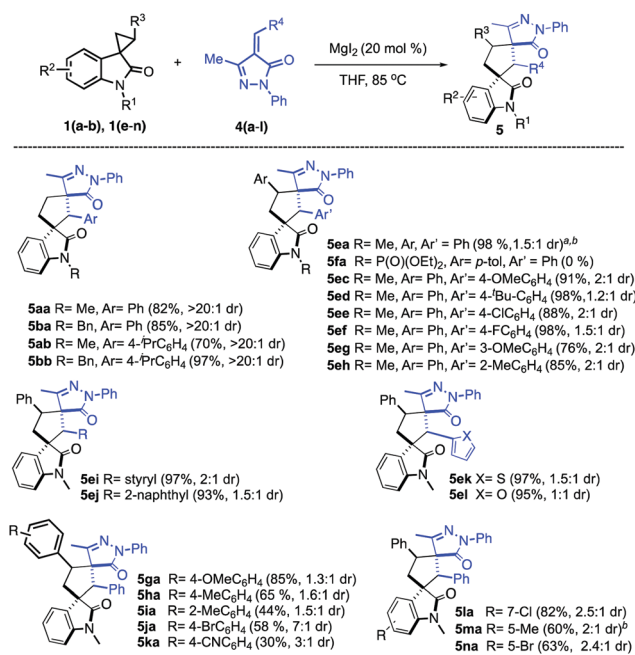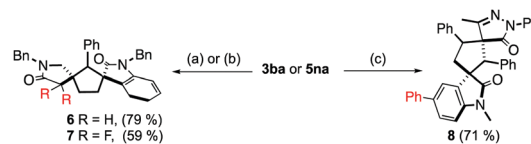
Scheme 3 Follow up chemistry. Reaction conditions: (a) NH$_2$NH$_2$·H$_2$O (30 equiv.), KOH, EtOH–H$_2$O, reflux, 6 h; (b) DAST (3 equiv.), DCM, 40 °C, 12 h; (c) PhB(OH)$_2$ (1.5 equiv.), Pd(PPh$_3$)$_4$ (5 mol%), K$_3$PO$_4$ (2.5 equiv.), toluene–H$_2$O, 80 °C, 12 h.
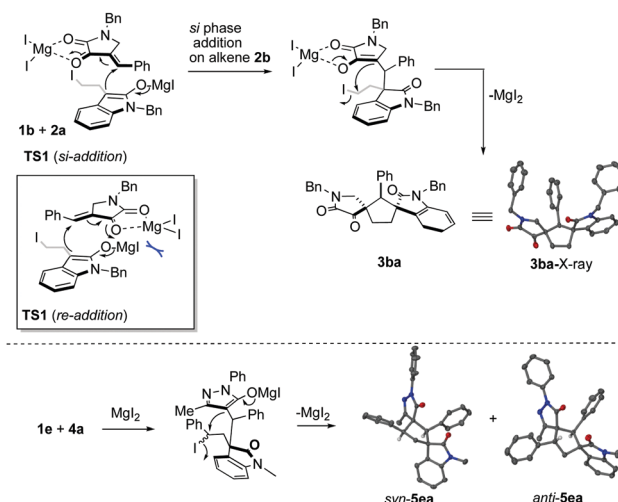
reaction conditions of **1f** fall short of engaging alkene **4a** for any productive interactions and didn't work under our optimized conditions as well, inferring that the activation sphere of reactants in the reported transformations[5c] differs significantly to that of ours.

A broad substrate scope of alkene **4** with regards to β-substitution in alkylidene pyrazolone substrates was observed (**5ec–5el**). While probing the effect of substituents on the cyclopropane aryl fragment, it appeared that electron donating groups (**5ga–5ha**), in general, worked better in comparison to electron withdrawing substituents (**5ja–5ka**). *ortho*-Substitution, however, led to lower yield (**5ia**) due to steric effects.

Variation of substituents on oxindole ring was also well tolerated (**5la–5na**). Stereochemistry of the products in Scheme 2 was tentatively assigned based on the X-ray crystal structure of **5ea**, considering structural and reactive similarities of intermediates involved in the process.

Some useful synthetic elaboration of the spirocyclopentane oxindole products is shown in Scheme 3. The keto functional group in **3ba** was converted into methylene (**6**) or difluoro-methylene unit (**7**) under the Wolff–Kishner reduction conditions or by using the fluorinating agent, DAST. Compound **5na** (major diastereomer), on the other hand, was transformed into **8** via a Suzuki–Miyaura coupling, indicating the feasibility to introduce many such groups at C-5.

A plausible mechanism linking to the observed stereochemical preference for the formation of **3ba**-major diastereomer is illustrated in Scheme 4. In the course of the reaction, addition

Scheme 2 Scope of reaction for spirocyclopropyl oxindoles (**1**) with alkylidene pyrazolones (**4**). Products were isolated as mixture of diastereomers. [a] 92% yield (1 g scale reaction). [b] Diastreomers were separated by column chromatography.

Scheme 4 Plausible mechanism.

to the *si*-face of the MgI$_2$-activated alkene partner (**2a**) occurs preferentially by the *in situ* generated magnesium enolate from DAC **1b**. Final intramolecular ring-closure with iodide displacement also occurs from the same face, which keeps the carbonyls of the two participating units at a distance in the major diastereomer. Density functional theory (DFT) calculations were performed to rationalize the observed facial selectivity using model substrates that are similar to **1b** and **2a** (see ESI† for details).[14] The corresponding pathways for the *re* and *si* face addition were calculated. From Scheme S5 (see ESI†), it is clear that both reaction steps for *si* face addition are associated with lower barriers, which is consistent with experiment. A similar preference for addition could be speculated for **5ea** as well; however in this case, the iodide displacement during ring-closure occurs at a secondary racemic carbon-centre and leads to the formation of two diastereomers of **5ea**.

In conclusion, we have developed an efficient approach to construct structurally diverse 2,3-dioxopyrrolidine and pyrazolone appended bis-spirocyclopentane oxindole frameworks in good to excellent yields using oxindole-activated spiro-DACs and *exo*-heterocyclic olefins. This method highlights the potential of this subclass of DAC as a useful synthon for the assembly of complex spirocyclopentane oxindole systems, featuring two all-carbon spirocenters and two different heterocycles present within the backbone. DFT calculations were performed to provide support for the proposed mechanism of the transformation. Formation of the experimentally observed *si*-adduct is associated with lower barriers and more favourable reaction energies. Additional studies to develop novel applications of this oxindole-activated spiro-DAC are currently ongoing in our laboratory.

Conflicts of interest

There are no conflicts to declare.

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