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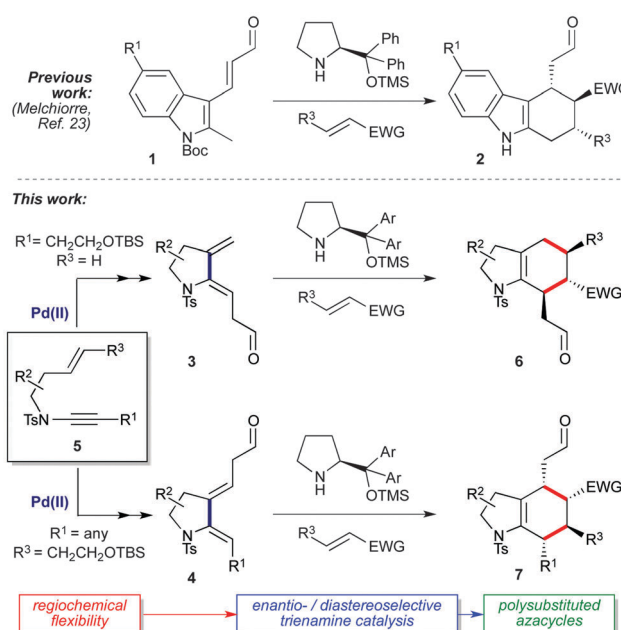
# Combining cycloisomerization with trienamine catalysis: a regiochemically flexible enantio- and diastereoselective synthesis of hexahydroindoles†

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The synthesis of polysubstituted hexahydroindoles through trienamine-organocatalyzed cycloadditions of pyrrolidinyl dienals, prepared by palladium-catalyzed cycloisomerization, is reported. The cycloadditions of this novel class of dienals proceed with excellent levels of enantio- and diastereoselectivity, with the regioselectivity of cycloaddition with respect to the tethering ring readily tuned through design of the cycloisomerization substrate. This work culminates in the first examples of double-stereodifferentiating trienamine catalysis, where catalyst stereocontrol dominates facial selectivity in the cycloaddition, affording azacyclic products that are specifically functionalized at every position.

Trienamine organocatalysis represents a frontier of asymmetric synthesis,<sup>1–6</sup> with trienamine-catalyzed cycloadditions of acyclic dienals<sup>7–16</sup> and dienones<sup>17,18</sup> enabling efficient syntheses of enantioenriched monocyclic cyclohexenes. In contrast, the use of exocyclic dienals in trienamine catalysis is comparatively rare, being limited mainly to elegant work on dearomatized aromatics such as indole-2,3-quinodimethane trienes (1 → 2 Scheme 1).<sup>19–23</sup> Furthermore, this chemistry has to date accessed only one of two possible cycloaddition regioisomers with respect to the tethering ring, presumably due to synthetic constraints in the positioning of the aldehyde. The wider extension of trienamine chemistry to cyclic substrates thus depends on the availability of suitable ring-tethered dienals, and methods that streamline dienal synthesis whilst simultaneously expanding reaction scope would offer a valuable entry to densely functionalized chiral (hetero)cyclic scaffolds.

Here we report a flexible and atom-efficient synthesis of a new class of azacyclic dienals (3 and 4) from enynamides (5) *via* palladium-catalyzed cycloisomerization,<sup>24–26</sup> where the relative positioning of the aldehyde on the dienal framework is dictated by simple variation of the enynamide starting material. The enantio- and diastereoselective cycloadditions of these dienals



Scheme 1 Trienamine-organocatalyzed cycloadditions of exocyclic dienals.

give a range of regioisomeric hexahydroindole cycloadducts (6, 7), including spirooxindoles and azactams which are of significant interest as medicinal chemistry scaffolds.<sup>27–29</sup> These investigations culminate with the first examples of double stereodifferentiation in trienamine catalysis, which afford fully-functionalized hexahydroindole frameworks with precise control over the stereochemistry of all ring substituents, and thus expand the field of trienamine catalysis to access products of unprecedented complexity.

Our work began with the preparation of the regioisomeric ring-constrained dienals 3a and 4a (Scheme 2) by high-yielding palladium-catalyzed cycloisomerization<sup>24</sup> of enynamides 5a and 5b,<sup>30</sup> followed by desilylation and oxidation. In the case of 5b, either the partially- (4a) or fully-conjugated (8a) dienal could be accessed, depending on the oxidation conditions. As the success of trienamine catalysis can depend crucially on the

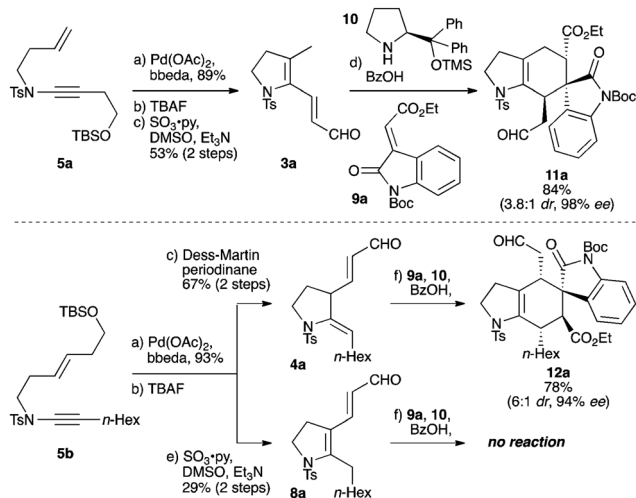
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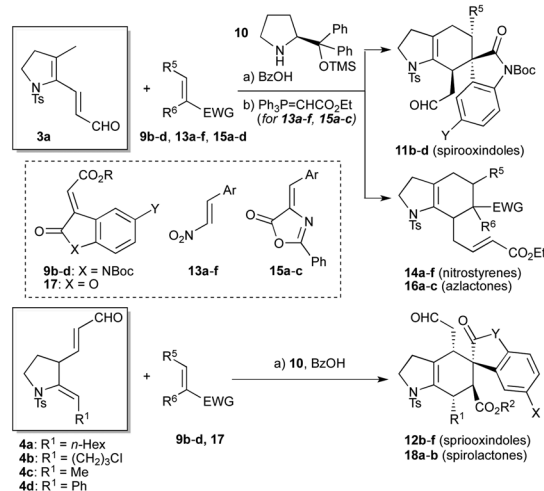


**Scheme 2** Palladium-catalyzed synthesis of regioisomeric dienals **3a**, **4a** and **8a**, and initial study of trienamine-organocatalyzed cycloadditions. *Reagents and conditions:* (a) Pd(OAc)<sub>2</sub> (5 mol%), bis-benzylidene ethylenediamine (bbeda) (5 mol%), toluene, 60 °C, 30 min; (b) TBAF, THF, rt, 2 h; (c) Dess–Martin periodinane, CH<sub>2</sub>Cl<sub>2</sub>, rt, 1.5 h; (d) **10** (20 mol%), BzOH (20 mol%), **9a** (1.0 equiv.), **3a** (1.5 equiv.), toluene, rt, 2 h; (e) SO<sub>3</sub>·py, Et<sub>3</sub>N, DMSO, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 2 h; (f) **10** (20 mol%), BzOH (20 mol%), **9a** (1.0 equiv.), **4a** (1.5 equiv.), toluene, rt, 6 h.

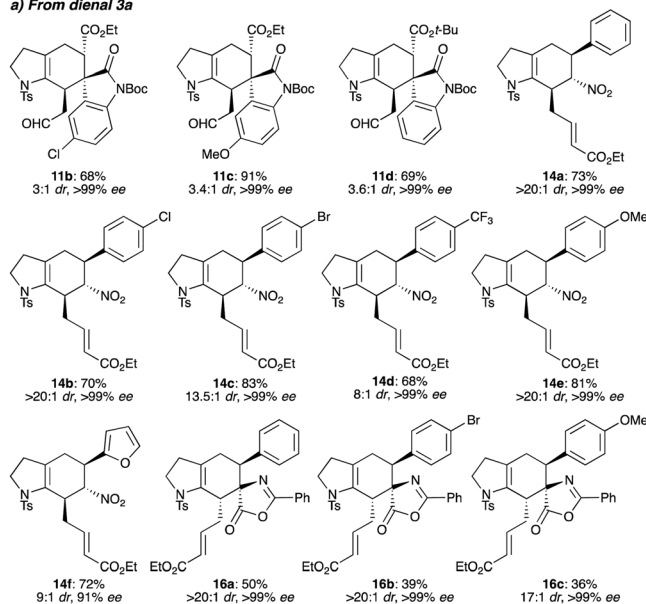
degree of conjugation of the carbonyl substrate,<sup>16–18</sup> it is notable that this cycloisomerization/oxidation approach permits such regiocontrol in dienal synthesis; in the event this indeed proved important. We were pleased to find that **3a** underwent smooth cycloaddition with oxindole **9a**, promoted by the Jørgensen–Hayashi catalyst **10**, giving cycloadduct **11a** in high yield and enantioselectivity after just 2 h at room temperature (84%, 98% ee, 3.8 : 1 dr). Reaction of **4a** was similarly successful, giving the regioisomeric product **12a** (78%, 94% ee, 6 : 1 dr). In contrast, no reaction was observed between **8a** and **9a**, even under heating, emphasizing the importance of the deconjugated nature of dienal **4a**.<sup>16–18</sup>

With conditions to effect organocatalyzed Diels–Alder reactions established, we next evaluated the scope of the enantioselective cycloadditions (Table 1). The reactions of **3a** with various oxindoles were first examined, which afforded spirooxindoles **11b–d** with high enantioselectivity. A selection of electron-deficient and electron-rich nitroalkenes were next tested, which pleasingly also underwent high yielding cycloadditions, giving cycloadducts **14a–f** with excellent enantio- and diastereoselectivities.<sup>31</sup> Azlactone cycloadditions provide a useful route to masked quaternary amino acids;<sup>32</sup> for dienal **3a**, these reactions were again found to be exceptionally diastereoselective and enantioselective (**16a–d**, >99% ee, >20 : 1 dr), albeit moderate yielding. Collectively, these reactions show a marked increase in rate compared to related acyclic<sup>1,2,16</sup> or aromatic substrates,<sup>19</sup> which may be due to the intrinsic *s-cis* constraint of the reacting diene in the trienamine intermediate, an effect that appears to override any electron-withdrawing effects from the sulfonamide group. It is also notable that formation of the presumed trienamine intermediate from **3a** is regioselective for the formation of an exocyclic, rather than endocyclic double bond.

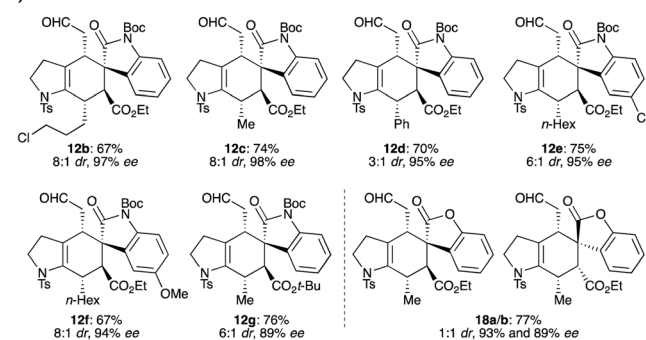
**Table 1** Enantioselective cycloaddition reactions of dienals **3a** and **4a–d**. Reaction conditions: dienophile (1.0 equiv.), aldehyde (1.4 equiv. for oxindoles, 1.5 equiv. for azlactones and nitrostyrenes), **10** (20 mol%), BzOH (20 mol%), toluene, rt, 2–6 h. The products from reaction of **3a** with **13a–f** and **15a–c** were derivatized via Wittig reaction to aid analysis by chiral HPLC. Yields are isolated yields; dr determined by <sup>1</sup>H NMR spectroscopic analysis of the crude reaction mixture; ee determined by chiral HPLC



**a) From dienal 3a**



**b) From dienals 4a–d**



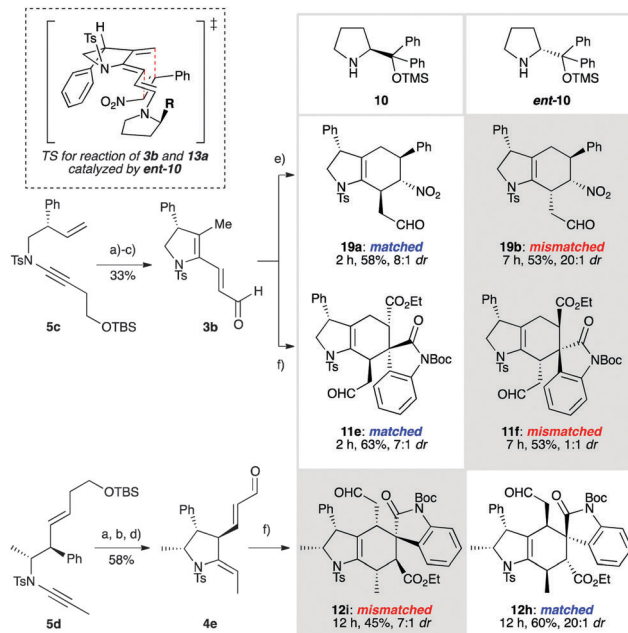
A similar exploration of reactivity was now conducted with the regioisomeric aldehyde system (**4**), which provided an



opportunity to vary the enamide substituent ( $R^1$  in **4a–d**, Table 1); these cycloadditions afford products that are substituted at all positions of the cyclohexene ring. We first tested oxindole dienophile cycloadditions, where variation of the enamide sidechain (**12b–d**) and oxindole (**12e–g**) led to high yields and excellent enantioselectivities. Notably, the diastereoselectivities of these 'regio-complementary' cycloadditions were enhanced compared to those of dienal **3a**, and showed some influence from the enamide substituent  $R^1$ . Although cycloadditions with nitrostyrenes and azlactones proved ineffective, use of the more reactive lactone **17** successfully delivered cycloadducts **18a/b** in high enantioselectivity, but without *endo/exo* preference.<sup>33</sup>

The cycloisomerization approach to these dienals provides the opportunity to functionalize the tethering pyrrolidine scaffold. This raised a question in trienamine catalysis that has not been addressed in previous studies: what levels of catalyst stereocontrol could be achieved in a double stereo-differentiating setting, where a chiral, single enantiomer substrate is reacted under the influence of enantiomeric catalysts?<sup>34–41</sup> To investigate this, we prepared ynamides **5c** and **5d** (Scheme 3) as single enantiomers.<sup>30</sup> These were subjected to palladium-catalyzed cycloisomerization, followed by desilylation and oxidation, to give dienals **3b** and **4e** respectively. Reaction of monosubstituted dienal **3b** with nitrostyrene, under the influence of catalyst **10**, afforded cycloadduct **19a** in short reaction time (2 h at rt) with high diastereoselectivity (58%, 8:1 dr). This matched combination of substrate and catalyst reflects a preference of both components for approach of the dienophile to the top face of the molecule (as drawn). The corresponding mismatched reaction of **3b** with nitrostyrene and catalyst **ent-10** proceeded at a reduced reaction rate (7 h at rt), but pleasingly with a complete reversal of facial selectivity. To our surprise, an increased level of diastereoselectivity was observed (**19b**, 53%, 20:1 dr), interestingly in favour of the *endo* isomer with respect to the nitro group<sup>30</sup> – an unprecedented observation in trienamine-organocatalyzed nitrostyrene Diels–Alder reactions.<sup>42</sup> This suggests that although the catalyst completely controls the facial selectivity of cycloaddition, the substrate has a significant, and in this case dominant influence over *endo/exo* selectivity, such that steric interactions between the phenyl groups are minimized, irrespective of electronic<sup>2,19</sup> or other stereocontrolling effects (see TS in Scheme 3).<sup>43</sup>

We next examined the reactions of **3b** with oxindole **9a**, which generated spirooxindoles **11e** and **11f**. In the matched case (giving **11e**), we were delighted to find that previously observed levels of diastereoselectivity for oxindole cycloadditions (see Scheme 2) were increased (63%, 7:1 dr), illustrating a reinforcing influence of the conformation of the substrate on reaction diastereoselectivity. The mismatched combination gave a moderate yield of the cycloadducts **11f**, arising from exclusive addition to the opposite face, but with poor selectivity. Finally, we addressed the challenge of the stereochemical influence of the doubly-substituted backbone in dienal **4e**. To our delight, the reactions of **4e** with **9a**, which generate hexahydroindole spirooxindoles featuring a stereogenic centre at every position on the indole skeleton, proceeded with excellent yield and stereoselectivity in both the matched (**12h**, 60%, 20:1 dr) and mismatched (**12i**, 45%, 7:1 dr) settings; both reactions again



**Scheme 3** Double stereodifferentiating cycloadditions of dienals **3b** and **4e**. Diastereomer ratios reflect *endo/exo* selectivity; in all cases only a single face of the diene reacts. Cycloadditions were conducted using the dienophile (3.0 equiv.), aldehyde (1.0 equiv.), catalyst (**10** or **ent-10**, 20 mol%) and BzOH (20 mol%) in toluene at rt under Ar (18 h). Other reagents and conditions: (a) Pd(OAc)<sub>2</sub> (5 mol%), bbed (5 mol%), toluene, 60 °C, 30 min, 85% from **5c**, 95% from **5d**; (b) TBAF, THF, rt, 2 h, 97% from **5c**, 93% from **5d**; (c) SO<sub>3</sub>·py, Et<sub>3</sub>N, DMSO, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 2 h, 40%; (d) Dess–Martin periodinane, CH<sub>2</sub>Cl<sub>2</sub>, rt, 1.5 h, 66%; (e) reaction with **13a**; (f) reaction with **9a**. See the ESI† for structural assignment.

illustrate strong substrate conformational effects that enhance diastereoselectivity.<sup>30</sup>

In conclusion, palladium-catalyzed cycloisomerization provides a powerful and efficient entry to regioisomeric azacycle-tethered exocyclic dienals, which undergo enantio- and diastereoselective trienamine-organocatalyzed cycloadditions. These represent the first examples of exocyclic dienes to engage in such chemistry that arise from non-aromatic precursors. In addition to exploring the relative reactivity of these regioisomeric substrates across a range of dienophiles, we show that double stereodifferentiating cycloadditions proceed under high levels of catalyst stereocontrol for both regioisomers, thus permitting the tuneable synthesis of fully-functionalized hexahydroindole frameworks, including complex spirooxindoles.

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- 43 A question arises as to whether the terms ‘matched’ and ‘mismatched’ should refer to the rate of reaction (where **19a** would be the ‘matched’ product), or its selectivity (where **19b** would be the ‘matched’ product). For the purposes of this work, we use the former definition; as the reactions of **3b** to generate **11e** or **11f** proceed with the same trend in facial selectivity and rate as those to give **19a** and **19b**, we feel the superior (inverse) diastereoselectivity arising in the case of **13c** is a result solely of steric interactions imparted by the substrate. In other words, we propose that this reaction is ‘mismatched’ with respect to the dienophile, and an overturn in *endo/exo* selectivity for **19b** is a consequence of the enforced approach of this dienophile to the more hindered face of the molecule.

