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Stereo-controlled synthesis of polyheterocycles via diene-transmissive hetero-Diels–Alder reaction of $\beta,\gamma$-unsaturated $\alpha$-keto esters

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We describe the stereoselective synthesis of polyyring-fused heterocyclic compounds based on diene-transmissive hetero-Diels–Alder reactions utilizing $\beta,\gamma$-unsaturated $\alpha$-keto esters. This protocol involves initial endo- or exo-selective Diels–Alder (DA) reactions with electron-rich dienophiles, methylenation of the ester carbonyl groups with Tebbe reagent, and a second stereoselective DA reaction with electron-deficient dienophiles. The use of enantioselective DA reactions in the initial reaction enables access to chiral polyyring-fused heterocyclic compounds with multiple chiral centres.

Synthetic methods that can be used to assemble fused rings bearing multiple contiguous stereocentres are being pursued because of the abundance of such moieties in complex natural products and pharmaceutically active compounds. In particular, the development of new protocols that are applicable to diverse ring systems and that are also compatible with enantioselective synthesis has been greatly needed.

The diene-transmissive Diels–Alder (DTDA) reaction, which is a sequence of DA reactions of $\alpha,\beta$-divinylpoly(vinylidene) or [n]dendralenes (Scheme 1a), has begun to emerge as a potential method for the stereoselective construction of 6,6-fused carbocycles. The simplest and most typical examples of the DTDA reaction employ a cross-conjugated triene ($n=3$) ([3]dendrale) as substrate. Scheme 1b illustrates a typical example in which a cross-conjugated triene A undergoes initial DA reaction on either diene unit with an initial dienophile D to form the mono-cycloadduct, vinyl cyclohexene B, which then reacts further with a second dienophile E on the transmitted diene unit of B, leading to the 6,6-fused ring C. A single DA reaction forms a six-membered ring with up to four stereogenic centres with high stereoselectivity (also known as the endo-rule). Accordingly, if the second DA reaction occurs with high endo/exo and $\pi$-facial selectivity, the DTDA reaction of cross-conjugated trienes can be used to assemble 6,6-fused rings with up to eight stereogenic centres. Indeed, the research groups of Tsuge, Fallis, Schreiber, Sherburn, Brummond, and others have developed this DTDA methodology by using cross-conjugated carbotrienes and their equivalents. Fallis et al. demonstrated the utility of this method by applying it to the construction of oxygenated nor-steroid and triterpenoid skeletons, and to the tricyclic core of vinigrol.

The diene-transmissive hetero-DA (DTHDA) reaction, in which one or more heteroatoms are incorporated in either a triene framework or a dienophile skeleton or both, has also been explored for the stereoselective synthesis of ring-fused heterocyclic compounds. Our group introduced for the first time the DTHDA reaction in which a heteroatom was involved in a triene framework using a cross-conjugated thiatriene for synthesis of sulfur-containing bi- or tricyclic compounds. Subsequently, Tsuge, Spino, and Carboni employed oxygen-containing trienes in the DTHDA reaction. Notably, Spino and co-workers have applied this method to the stereoselective construction of quassinoids having the pircasane framework. We have also developed variations on our own DTHDA reaction by using dioxa.

Scheme 1 a) Structure of $\alpha,\beta$-divinylpoly(vinylidene) or [n]dendralenes. b) A diene-transmissive Diels–Alder reaction of cross-conjugated triene.
and aza-trienes, leading to the construction of a range of ring-fused compounds. To expand the breadth of this strategy, we have demonstrated that imination or thionation of the resulting enone moiety formed by the initial DA reaction facilitates the second DA reaction, even if the initial mono-cycloadduct does not participate in the second DA reaction. If the initial DA reaction is rendered enantioselective through the use of a chiral catalyst, this DTHDA reaction creates enantiomerically pure ring-fused compounds with contiguous, multiple stereogenic centres, thus enhancing the value of this protocol. However, to our knowledge, only one successful example of an intramolecular version of the DTHDA reaction has been reported. Chi et al. employed a chiral phosphine-catalysed intramolecular HDA reaction of a cross-conjugated aza- triene as an initial DA reaction, and they synthesized multicyclic N-heterocycles with exceptionally high diastereoselectivities with up to 99% enantiomeric excess (ee). In this context, we became interested in cross-conjugated heterotrienes that are suitable for enantioselective intermolecular DA reactions.

\[ \text{Yb(OTf)}_3 \]

In particular, the asymmetric inverse-electron-demand hetero-DA reaction that produces chiral 2,3-dihydro-1,4-oxazines is one of the most valuable transformations available. They demonstrated endo-selective HDA reactions that delivered chiral 2,4-cis-disubstituted-5,6-dihydropyranys with up to 99% ee by employing chiral bis(oxazoline) copper(II) complexes. Meanwhile, Blay and co-workers reported exo-selective reactions that afforded the corresponding 2,4-trans-derivatives with up to 88% ee by using copper(II) complexes of hydroxy oxazolines derived from (S)-ketonic acid. Given the availability of enantiomerically enriched 2,4-cis- and 2,4-trans-disubstituted-5,6-dihydropyranys, we envisioned that if their ester carbonyl group could be alkylated, the resultant carbodiene would participate in DA reactions that could be used to construct chiral 6,6-fused rings containing up to six stereogenic centres. As a preliminary study, we investigated racemic and enantioselective DTHDA reactions based on this strategy.

Table 1 Initial Diels–Alder reaction under thermal and Lewis acid conditions.

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<th>Entry</th>
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<th>Time (h)</th>
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<td>S</td>
<td>1.5</td>
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<td>3</td>
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</table>

In the second DA reaction, we examined four typical electron-deficient dienophiles (Scheme 2). The reaction of endo-5 with 1.2 equiv of tetracyanoethylene (TCNE) proceeded smoothly at room temperature to furnish 3,4,4a,5,6,7-hexahydro-2H-chromene derivative 7, exclusively. Cycloaddition of TCNE took place from the less hindered C4-side to the diene, which is consistent with the selectivity of the reaction of 2-ethoxy-3,4-dihydro-6-styryl-2H-pyran. Similarly, the cycloaddition of TCNE to endo-6 also occurred with the same \( \pi \)-diastereofacial selectivity to produce 8 in high yield.

We then employed 4-phenyl-1,2,4-triazole-3,5-dione (PTAD) as a diaza-dienophile for the construction of a pyran[3,2-c]pyrazidine skeleton. When endo-6 was treated with 1.2 equiv of PTAD, the expected DA adducts 9 and 10 was obtained. For the latter case, bis-cycloadduct 11 as a single diastereomer was accompanied. In both the \([4+2]\) and \([2+2]\) cycloadditions, PTAD cycloaddicted also from the less hindered C4-side of the diene exclusively.

A heterocumulenic dienophile, N-tosyl isocyanate, underwent the second DA reaction at room temperature to afford pyran[3,2-d]pyridazines 12 and 13 in good yields. However, the cycloadducts 12 and 13 were formed as if the N-tosyl isocyanate attacked the diene moiety of endo-5 and endo-6 from the more hindered phenyl group side at C-4. For the opposite \( \pi \)-diastereofacial selectivity, we assume that a stepwise addition mechanism via the twitter ion intermediate \( \text{A} \) occurred rather than a concerted mechanism because of the electronically highly polarized character of N-tosyl isocyanate to give preferable formation of \( \text{H}^+\)-\( \text{H}^+\) cis product 12.

Less reactive N-phenylmaleimide, compared to the dienophiles PTAD and N-tosyl isocyanate, participated in the DA reaction with endo-5 and endo-6 under heating conditions (80 °C) to produce 14 and
with complete π-diastereofacial and endo selectivities probably through transition state B. The structure of 14 was unambiguously established by the X-ray crystal analysis. It is noteworthy that endo-5 and 6 are easily hydrolyzed under heating conditions and thus rigorously anhydrous conditions are required to obtain the adducts in high yield.

![Diagram](image_url)

Scheme 2 Methylenation of endo-3,4 and subsequent DA reaction of endo-5,6. 

a) Tebbe reagent (1.2 equiv), THF, 0 °C, 1 h, endo-5: 81%, endo-6: 97%; b) TCNE (1.2 equiv), CH₂Cl₂, rt, 4 h; c) PTAD (1.0 equiv for endo-5, 1.2 equiv for endo-6), CH₂Cl₂, rt, 4 h; d) TsNCO (1.5 equiv), CH₂Cl₂, rt, 4 h; e) N-Phenylmaleimide (1.5 equiv), toluene, 80 °C, 48 h

We continued with the second DA reactions of exo-5 (Scheme 3). Tebbe methylation of exo-3 and the DA reactions of exo-5 with TCNE, PTAD, and N-tosyl isocyanate delivered the corresponding cycloadducts 16-18 as single diastereomers in good to high yields. With N-phenylmaleimide, however, exo-5 showed substantially lower reactivity than endo-5 under the same reaction conditions (at 80 °C for 48 h in toluene); the [4 + 2] cycloadduct 19 was obtained in 23% yield with recovery of considerable amounts of exo-5. The ethoxy group at C-2 in exo-5 would somewhat interrupt the attacking of N-phenylmaleimide in the endo arrangement in transition state C. When the reaction was conducted under harsher conditions (100 °C, 82 h), adduct 19′, which would be a formal 1,3-H migration product of 19, was obtained in 47% yield. The obstruction by the phenyl group at the C-4 atom, not the ethoxy group at C-2 in 5 is largely responsible for the π-diastereofacial selectivity observed in the second concerted DA reactions.

![Diagram](image_url)

Scheme 3 Methylenation of exo-3 and subsequent DA reaction of exo-5.

a) Tebbe reagent (1.2 equiv), THF, 0 °C, 1 h; b) TCNE (1.2 equiv), CH₂Cl₂, rt, 1.5 h; c) PTAD (1.0 equiv), CH₂Cl₂, rt, 0.5 h; d) TsNCO (1.5 equiv), CH₂Cl₂, rt, 4 h; e,f) N-Phenylmaleimide (1.5 equiv); e) toluene, 80 °C, 48 h; f) 100 °C, 82 h.

With the above results in hand, we performed enantioselective versions of the above DTHDA reaction by applying Evans’ enantioselective protocols to the initial oxadiene-DA reaction (Scheme 4). First, enantiopure (2R,4R)-endo-3 (>98% ee) was prepared from the Hetero-Diels–Alder reaction of 1 with ethyl vinyl ether (2a) in the presence of 2 mol% of chiral C₂-symmetric bis(oxazoline)–Cu(II) complex 20. Treatment of (2R,4R)-endo-3 with Tebbe reagent followed by the second DA reaction with the selected dienophiles used above, afforded the corresponding cycloadducts (-)-7, (-)-12, and (-)-14 with...
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herein constitutes the first example of an enantioselective reaction of polyheterocycles with multiple stereogenic centres.

Conclusions

We have demonstrated a diene-transmissive hetero-Diels–Alder protocol employing β,γ-unsaturated α-keto esters I. In the racemic initial DA reactions of I with ethyl vinyl ether and sulfide, Yb(OTf)₃ promoted predominantly endo-cycloaddition at a lower temperature and exo-cycloaddition at a higher temperature. Treatment of the cycloaducts with Tebbe reagent followed by a second DA reaction with electron-deficient dienophiles proceeded in a highly π-facial and endo-selective manner to produce polyring- and N-heterocycles with up to six multiple, contiguous stereogenic centres. Notably, their asymmetric variants were also achieved by applying Evans’ protocol for the initial HDA reactions. The reaction described herein constitutes the first example of an enantioselective intermolecular DTHDA reaction.

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20 The reversal of the endo- to exo- selectivity may be attributed to the alteration of a chelation structure of Yb(OTf)₃ with the two carbonyl oxygen atoms to a mono-dentate one in the TS and/or switching to a concerted or a stepwise mechanism. Switching of a chelation structure to a mono-dentate one in the TS for the Yb(OTf)₃-catalyzed HDA reactions, see for example, (a) T. Saito, M. Kawamura and J.-i. Nishimura, Tetrahedron Lett., 1997, 38, 3231. Selective endo- or exo- approach and discussion on concerted and stepwise mechanisms in the HDA reaction of β,γ-unsaturated α keto esters with vinyl ethers, see for example, (b) A. Martel, S. Leconte, G. Dujardin, E. Brown, V. Maisonneuve and R. Retoux, Eur. J. Org. Chem. 2002, 514.


22 CCDC 1050668.

23 The structure of 19′ was determined by NMR spectroscopic analysis and by X-ray crystallographic analysis of a co-crystal of 19′ with N phenylmaleimide. CCDC 1050667.

24 Relief of the distortion present in the 5-6-6 ring fused tetrahydropyran with an exo methylene bond and of electronic repulsion of the proximate oxygen atoms in 19 would facilitate the rearrangement to 19′ at a high temperature.

‡ Electronic supplementary information (ESI) available: Experimental details, characterization data and NMR spectra. CCDC 1050668 (14) and 1050667 (19′). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b000000xs.

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