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Stereo-controlled synthesis of polyheterocycles via diene-transmissive hetero-Diels–Alder reaction of β,γ-unsaturated α-keto esters

Cite this: DOI: 10.1039/x0xx00000x

Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

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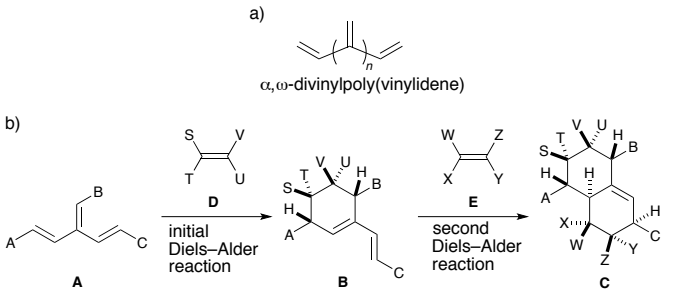
We describe the stereoselective synthesis of polyring-fused heterocyclic compounds based on diene-transmissive hetero-Diels–Alder reactions utilizing β,γ-unsaturated α-keto esters. This protocol involves initial *endo*- or *exo*-selective Diels–Alder (DA) reactions with electron-rich dienophiles, methylenation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

Synthetic methods that can be used to assemble fused rings bearing multiple contiguous stereocentres efficiently 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 α,ω-divinylpoly(vinylidene) or [n]dendralenes (Scheme 1a), has begun to emerge as a potential method for the stereoselective construction of 6,6-fused carbocycles.[1] The simplest and most typical examples of the DTDA reaction employ a cross-conjugated triene (n = 3) ([3]dendralene) 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 π-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,[2] Fallis,[3] Schreiber,[4] Sherburn,[5] Brummond,[6] and others[7] 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,[3b] and to the tricyclic core of vinigrol.[3d]



Scheme 1 a) Structure of α,ω-divinylpoly(vinylidenes) or [n]dendralenes. b) A diene-transmissive Diels–Alder reaction of cross-conjugated triene.

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.[8] Subsequently, Tsuge,[9] Spino,[10] and Carboni[11] 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 picrasane framework.[10] We have also developed variations on our own DTHDA reaction by using dioxa-[12]

and aza-trienes,[13] 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.[12]

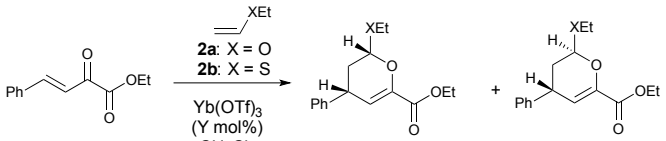
If the initial DA reaction is rendered enantioselective through the use of a chiral catalyst, this DTHDA reaction creates enantiomerically pure ring-fused compounds with contiguous, multiple stereogenic centres, thus enhancing the value of this protocol. However, to our knowledge, only one successful example of an *intramolecular* version of the DTHDA reaction has been reported.[14] 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 diastereo- and enantioselectivities with up to 99% enantiomeric excess (ee).[14] In this context, we became interested in cross-conjugated heterotrienes that are suitable for enantioselective *intermolecular* DA reactions.

β,γ-Unsaturated α-keto esters are known to participate in various types of reactions and they are useful building blocks in organic synthesis.[15,16] In particular, the asymmetric inverse-electron-demand hetero-DA reaction that produces chiral 2,3-dihydropyrans pioneered by Evans and co-workers is one of the most valuable transformations available.[16a,b,17] They demonstrated *endo*-selective HDA reactions that delivered chiral 2,4-*cis*-disubstituted-5,6-dihydropyrans 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*)-ketopinic acid.[16d] Given the availability of enantiomerically enriched 2,4-*cis*- and 2,4-*trans*-disubstituted-5,6-dihydropyrans, we envisioned that if their ester carbonyl group could be alkenylated, 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.[18] As a preliminary study, we investigated racemic and enantioselective DTHDA reactions based on this strategy.

Hetero-Diels–Alder reactions of 2-oxo-4-phenyl-3-butenoic acid ethyl ester (**1**) with ethyl vinyl ether (**2a**) or ethyl vinyl sulfide (**2b**) have been reported in enantioselective versions exclusively; thus, the results of their racemic reactions would be worthy of note (Table 1). When the reaction of **1** and **2a** was carried out in 1,2-dichloroethane at 80 ºC without catalyst, the [4 + 2] adduct, ethyl 2-ethoxy-3,4-dihydro-4-phenyl-2*H*-pyran-6-carboxylate (**3**), was obtained in 95% yield with high *endo*/*exo* selectivity of 88:12 (entry 1). We then examined the effects on the reaction of the Lewis acid ytterbium(III) trifluoromethanesulfonate ($Yb(OTf)_3$).[19] In the presence of 20 mol% $Yb(OTf)_3$, the reaction at –40 °C for 1h gave **3** with improved *endo*/*exo* selectivity of 95:5 in 93% yield (entry 2). Interestingly, the *endo*/*exo* selectivity depends strongly on the temperature, and the ratio was reversed to 5:95 when the reaction was conducted at 40 °C (entry 2 vs. entry 4).[20] A similar reversal of *endo*/*exo* selectivity was observed in the reaction with **2b** leading to **4** (entries 5–8).

We employed Tebbe reagent {μ-chloro[di(cyclopenta-2,4-dien-1-yl)]dimethyl(μ-methylene)titanium-aluminium} for the direct alkenylation of *endo*-**3**,**4**. The methylenation was conducted with 1.2 of equiv of Tebbe reagent at 0 °C and reached completion within 1 h; quick work-up, including chromatography with a short basic alumina column, afforded almost pure *endo*-**5**,**6**, 6-(1-ethoxyethenyl)-3,4-dihydro-2*H*-pyranes, which were used in the second DA reaction without further purification.

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



Entry	X	Molar ratio[a]	Y (mol%)	Temp (ºC)	Time (h)	Yield[b] (%)	*endo*/*exo*[c]
1[d]	O	20	0	80	39	95	88:12
2	O	4	20	–40	1	93	95:5
3	O	4	20	0	0.5	99	14:86
4[e]	O	4	20	40		92	5:95
5[d]	S	1.5	0	80	55	82	89:11
6	S	1.5	20	–40	1	99	99:1
7	S	1.5	20	0	1.5	99	59:41
8[e]	S	1.5	20	40	3	99	22:78

[a] **2a**/**1** or **2b**/**1**. [b] Yield of isolated, purified product. [c] Determined by ^{1}H NMR spectroscopic analysis (integration). [d] $(CH_2Cl)_2$ was used as the solvent. [e] **2a** or **2b** was added by a syringe pump. [f] Addition period..

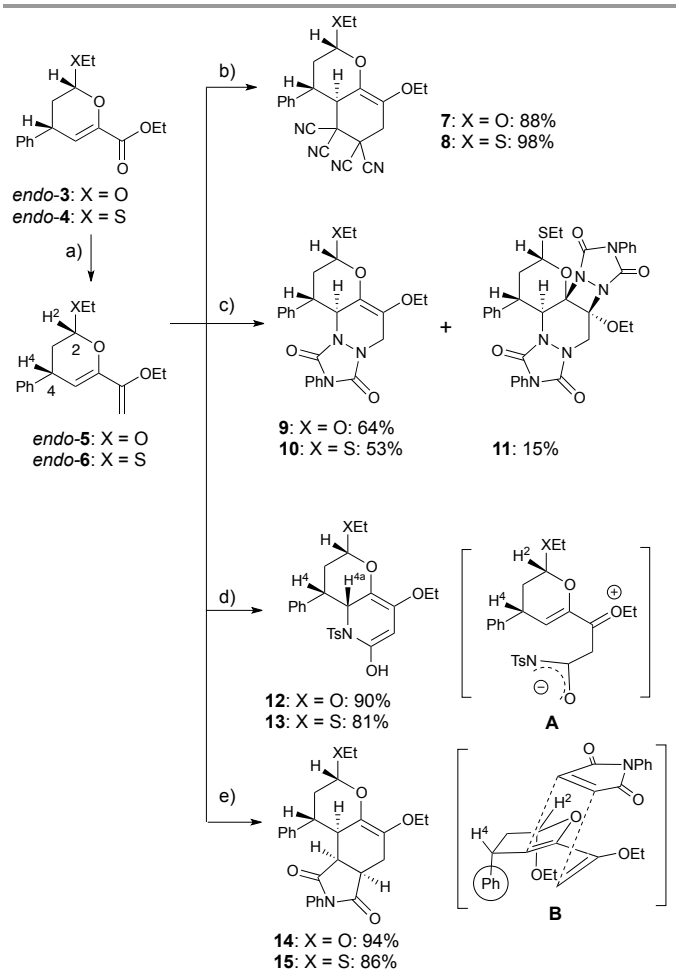
In the second DA reaction, we examined four typical electron-deficient dienophiles (Scheme 2). The reaction of *endo*-**5** with 1.2 equiv of tetracyanoethylene (TCNE) proceeded smoothly at room temperature to furnish 3,4,4a,5,6,7-hexahydro-2*H*-chromene derivative **7**, exclusively. Cycloaddition of TCNE took place from the less hindered H^4-side to the diene, which is consistent with the selectivity of the reaction of 2-ethoxy-3,4-dihydro-6-styryl-2*H*-pyran.[9b] Similarly, the cycloaddition of TCNE to *endo*-**6** also occurred with the same π-diastereofacial selectivity to produce **8** in high yield.

We then employed 4-phenyl-1,2,4-triazole-3,5-dione[9,21] (PTAD) as a diaza-dienophile for the construction of a pyrano[3,2-*c*]pyridazine 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 cycloadded also from the less hindered H^4-side of the diene exclusively.

A heterocumulenic dienophile, *N*-tosyl isocyanate, underwent the second DA reaction at room temperature to afford pyrano[3,2-*b*]pyridines **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 π-diastereofacial selectivity, we assume that a stepwise addition mechanism via the twitter ionic intermediate **A** occurred rather than a concerted mechanism because of the electronically highly polarized character of *N*-tosyl isocyanate to give preferable formation of H^4–H^{4a} *cis* product **12**.

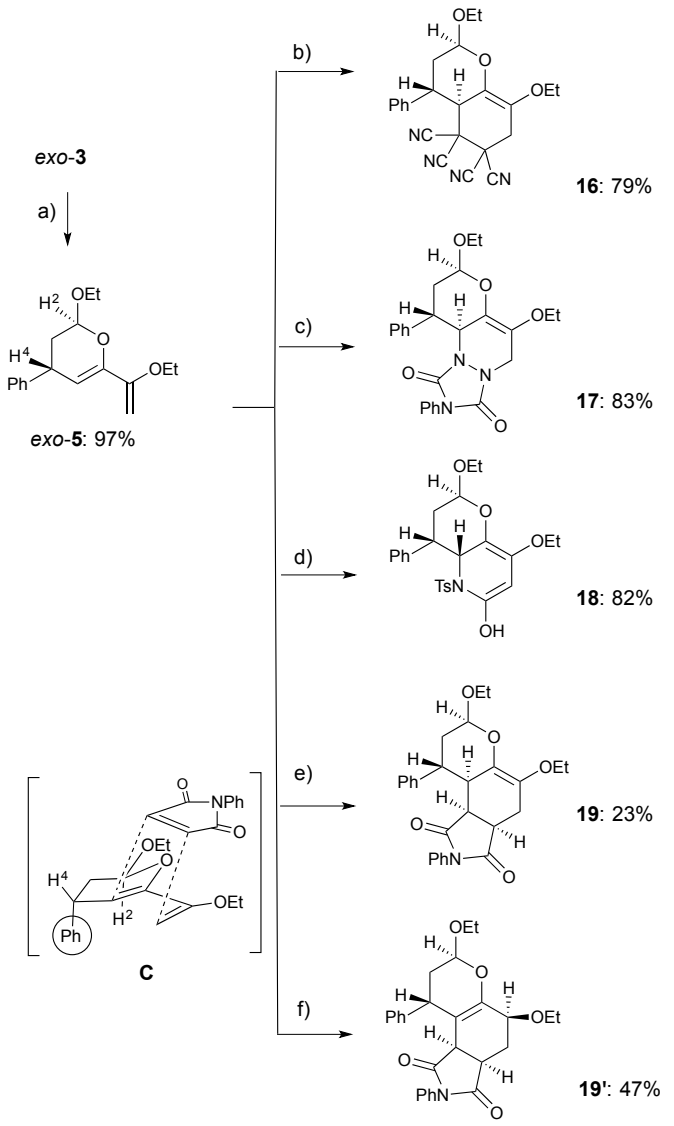
Less reactive *N*-phenylmaleimide, compared to the dienophiles PTAD and *N*-tosyl isocyanate, participated in the DA reaction with *endo*-**5** and *endo*-**6** under heating conditions (80 ºC) to produce **14** and

15 with complete π-diasereofacial and *endo* selectivities probably through transition state **B**. The structure of **14** was unambiguously established by the X-ray crystal analysis.[22] 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.



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), CH_2Cl_2, rt, 4 h; c) PTAD (1.0 equiv for *endo*-**5**; 1.2 equiv for *endo*-**6**), CH_2Cl_2, rt, 3 h; d) TsNCO (1.5 equiv), CH_2Cl_2, rt, 4 h; e) *N*-Phenylmaleimide (1.5 equiv), toluene, 80 °C, 48 h

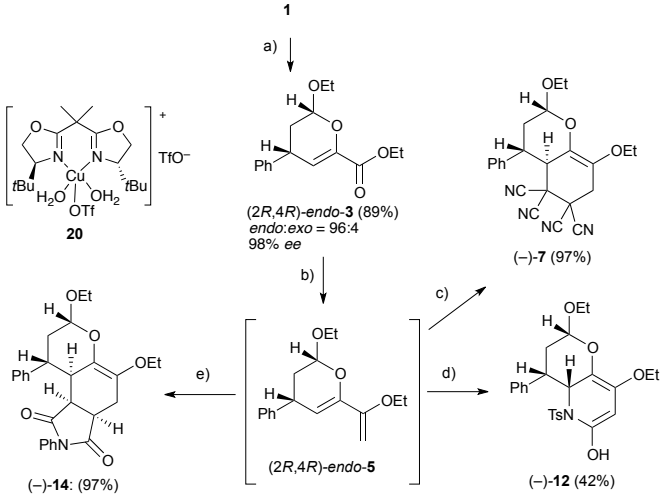
We continued with the second DA reactions of *exo*-**5** (Scheme 3). Tebbe methylenation of *exo*-**3** and the DA reactions of *exo*-**5** with TCNE, PTAD, and *N*-tosyl isocyanate delivered the corresponding cycloadducts **16**–**18** as single diastereomers in good to high yields. With *N*-phenylmaleimide, 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'**,[23] which would be a formal 1,3-H migration product of **19**, was obtained in 47% yield.[24] 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.



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), CH_2Cl_2, rt, 1.5 h; c) PTAD (1.0 equiv), CH_2Cl_2, rt, 0.5 h; d) TsNCO (1.5 equiv), CH_2Cl_2, 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 (2*R*,4*R*)-*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 C_2-symmetric bis(oxazoline)−Cu(II) complex **20**. Treatment of (2*R*,4*R*)-*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

extremely high enantioselectivity in moderate to excellent yields. We affirm that this DTHDA strategy is applicable to asymmetric synthesis of other polyheterocycles with multiple stereogenic centres.



Scheme 4 Enantioselective diene-transmissive Diels–Alder type reaction.
a) Ethyl vinyl ether, **20** (2 mol%)[16b]; b) Tebbe reagent (1.2 equiv), THF, 0 °C, 1 h; c) TCNE (1.5 equiv), CH_2Cl_2, rt, 18 h; d) TsNCO (1.5 equiv), CH_2Cl_2, rt, 15 h; e) *N*-Phenylmaleimide (1.5 equiv), toluene, 80 °C, 48 h.

Conclusions

We have demonstrated a diene-transmissive hetero–Diels–Alder protocol employing β,γ-unsaturated α-keto esters **1**. In the racemic initial DA reactions of **1** 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 cycloadducts 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-fused *O*- and *N*-heterocycles with up to six multiple, contiguous stereogenic centres. Notably, their asymmetric variants ware 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.

Notes and references

1 For a review, H. Hopf and M. S. Sherburn, *Angew. Chemie, Int. Ed.*, 2012, **51**, 2298.

2 (*a*) O. Tsuge, E. Wada and S. Kanemasa, *Chem. Lett.,* 1983, **12**, 239; (*b*) O. Tsuge, S. Kanemasa, E. Wada and H. Sakoh, *J. Synth. Org. Chem. Jpn.*, 1986, **44**, 756 and references cited therein; (*c*) O. Tsuge, T. Hatta, K. Yakata and H. Maeda, *Chem. Lett.*, 1994, **23**, 1833.

3 (*a*) S. Woo, N. Squire and A.G. Fallis, *Org. Lett*., 1999, **1**, 573; b) S. Woo, S. Legoupy, S. Parra and A. G. Fallis, *Org. Lett*., 1999, **1**, 1013; (*c*) M. S. Souweha, A. Arab, M. ApSimon and A. G. Fallis, *Org. Lett*., 2007, **9**, 615; (*d*) M. S. Souweha, G. D. Enright and A. G. Fallis, *Org. Lett*., 2007, **9**, 5163

4 O. Kwon, S. B. Park and S. L. Schreiber, *J. Am. Chem. Soc*., 2002, **124**, 13402.

5 (*a*) T. A. Bradford, A. D. Payne, A. C. Willis, M. N. Paddon-Row and M. S. Sherburn, *Org. Lett*., 2007, **9**, 4861; (*b*) N. A. Miller, A. C. Willis, M. N. Paddon-Row and M. S. Sherburn, *Angew. Chem., Int. Ed*., 2007, **46**, 937; (*c*) K. M. Cergol, C. G. Newton, A. L. Lawrence, A. C. Willis, M. N. Paddon-Row, M. S. Sherburn, *Angew. Chem. Int. Ed.*, 2011, **50**, 10425; (*d*) S. V. Pronin and R. A. Shenvi, *J. Am. Chem. Soc.*, 2012, **134**, 19604; (*e*) T. Fallon, A. C. Willis, M. N. Paddon-Row and M. S. Sherburn, *J. Org. Chem.*, 2014, **79**, 3185. (*f*) C. G. Newton, S.L. Drew, A. L. Lawrence, A. C. Willis, M. N. Paddon-Row and M. S. Sherburn, *Nat. Chem.,* 2015, **7**, 82.

6 (*a*) K. M. Brummond and L. You, *Tetrahedron*, 2005, **61**, 6180; (*b*) B. Mitasev, B. Yan and K. M. Brummond, *Heterocycles*, 2006, **70**, 367.

7 (*a*) A. T. Blomquist and J. A. Verdol, *J. Am. Chem. Soc*., 1955, **77**, 81; (*b*) W. J. Bailey and J. Economy, *J. Am. Chem. Soc*., 1955, **77**, 1133; (*c*) A. Hosomi, T. Masunari, Y. Tominaga, T. Yanagi and M. Hojo, *Tetrahedron Lett*., 1990, **31**, 6201; (*d*) W. Adam, T. Deufel, R. Finzel, A. G. Griesbeck and J. Hirt, *J. Org. Chem*., 1992, **57**, 3991. (*e*) H. Hopf and S. Yildizhan, *Eur. J. Org. Chem.*, 2011, 2029; (*f*) R. Singh and S. K. Ghosh, *Chem. Commun.*, 2011, **47**, 10809.

8 (*a*) S. Motoki, Y. Matsuo and Y. Terauchi, *Bull. Chem. Soc. Jpn*., 1990, **63**, 284; (*b*) T. Saito, H. Kimura, K. Sakamaki, T. Karakasa and S. Moriyama, *Chem. Commun*., 1996, 811.

9 (*a*) O. Tsuge, T. Hatta, H. Yoshitomi, K. Kurosaka, T. Fujiwara, H. Maeda and A. Kakehi, *Heterocycles,* 1995, **41**, 225; (*b*) O. Tsuge, T. Hatta, T. Fujiwara, T. Yokohari and A. Tsuge, *Heterocycles*, 1999, **50**, 661.

10 (*a*) C. Spino and G. Liu, *J. Org. Chem*., 1993, **58**, 817; (*b*) C. Spino, G. Liu, N. Tu and S. Girard, *J. Org. Chem*., 1994, **59**, 5596; (*c*) C. Spino, B. Hill, P. Dubé and S. Gingras, *Can. J. Chem*., 2003, **81**, 81; (*d*) A. Dion, P. Dubé and C. Spino, *Org. Lett*., 2005, **7**, 5601. For an account (*e*) C. Spino, *Synlett*, 2006, 23; (*f*) S. Perreault, C. Spino, *Org. Lett*., 2006, **8**, 4385.

11 F. Tripoteau, T. Verdelet, A. Hercouet, F. Carreaux and B. Carboni, *Chem. - Eur. J*., 2011, **17**, 13670.

12 T. Saito, S. Kobayashi, T. Otani, H. Iwanami and T. Soda, *Heterocycles*, 2008, **76**, 227.

13 T. Saito, H. Kimura, T. Chonan, T. Soda and T. Karakasa, *Chem. Commun.*, 1997, 1013; (*b*) T. Saito, S. Kobayashi, M. Ohgaki, M. Wada, C. Nagahiro, *Tetrahedron Lett*., 2002, **43**, 2627; (*c*) S. Kobayashi, T. Furuya, T. Otani and T. Saito, *Tetrahedron Lett.*, 2008, **49**, 4513; (*d*) S. Kobayashi, T. Furuya, T. Otani and T. Saito, *Tetrahedron*, 2008, **64**, 9705; (*e*) S. Kobayashi, T. Semba, T. Takahashi, S. Yoshida, K. Dai, T. Otani and T. Saito, *Tetrahedron*, 2009, **65**, 920.

14 Z. Jin, R. Yang, Y. Du, B. Tiwari, R. Ganguly, Y. R. Chi, *Org. Lett*. **2012**, *14*, 3226.

15 (*a*) S. R. Wang and A. T. Radosevich, *Org. Lett*., 2013, **15**, 1926-1929; (*b*) J. Qi, X. Xie, R. Han, D. Ma, J. Yang and X. She, *Chem. - Eur. J*., 2013, **19**, 4146; (*c*) J. Feng, X. Fu, Z. Chen, L. Lin, X. Liu and X. Feng, *Org. Lett*., 2013, **15**, 2640; (*d*) H.-G. Cheng, L.-Q. Lu, T. Wang, Q.-Q. Yang, X.-P. Liu, Y. Li, Q.-H. Deng, J.-R. Chen and W.-J. Xiao, *Angew. Chem., Int. Ed*., 2013, **52**, 3250; (*e*) P. Xing, W.

Zang, Z.-g. Huang, Y.-x. Zhan, C.-j. Zhu and B. Jiang, *Synlett*, 2012, **23**, 2269; (*f*) L.-y. Mei, Y. Wei, Q. Xu and M. Shi, *Organometallics*, 2012, **31**, 7591; (*g*) T.-R. Kang, Y. Cheng, L. He, J. Ye and Q.-Z. Liu, *Tetrahedron Lett*., 2012, **53**, 2552; (*h*) X. Jiang, L. Wu, Y. Xing, L. Wang, S. Wang, Z. Chen and R. Wang, *Chem. Commun*., 2012, **48**, 446; (*i*) L. Gremaud and A. Alexakis, *Angew. Chem., Int. Ed*., 2012, **51**, 794.

16 HDA reaction of β,χ-unsaturated α-keto ester with vinyl ether: (*a*) D. A. Evans, E. J. Olhava, J. S. Johnson and J. M. Janey, *Angew. Chem., Int. Ed.*, 1999, **37**, 3372; (*b*) D. A. Evans, J. S. Johnson and E. J. Olhava, *J. Am. Chem. Soc.*, 2000, **122**, 1635; (*c*) Y. J. Shin, C.-E. Yeom, M. J. Kim and B. M. Kim, *Synlett*, 2008, 89; (*d*) A. Barba, S. Barroso, G. Blay, L. Cardona, M. Melegari and J. R. Pedro, *Synlett*, 2011, 1592. With stylenes (*e*) J. Lv, L. Zhang, S. Luo and J.-P. Cheng, *Angew. Chem. Int. Ed.,* 2013, **52**, 9786.

17 R. M. Giuliano, A. D. Jordan, A. D. Gauthier and K. Hoogsteen, *J. Org. Chem.*, 1993, **58**, 4979.

18 (*a*) S. Kobayashi, I. Hachiya, H. Ishitani and M. Araki, *Tetrahedron Lett*., 1993, **34**, 4535; (*b*) A. Kawada, S. Mitamura and S. Kobayashi, *J. Chem. Soc., Chem. Commun*., 1993, 1157; (*c*) S. Kobayashi, *Chem. Lett*., 1991, 2187.

19 DA reactions of other vinyl-appended 1,2-dicarbonyl compounds with electron-rich dienophiles, for a review; (*a*) L. F. Tietze and G. Kettschau, *Top. Curr. Chem.*, 1997, **189**, 12120. Asymmetric versions using chiral Lewis acids, see for examples; (*b*) D. A. Evans and J. S. Johnson, *J. Am. Chem. Soc.*, 1998, **120**, 4895. (*c*) H. Audrain, J. Thorhauge, R. G. Hazell and K. A. Jørgensen, *J. Org. Chem.*, 2000, **65**, 4487. (*d*) D. A. Evans, J. S. Johnson, C. S. Burgey and K. R. Campos, *Tetrahedron Lett.*, 1999, **40**, 2879.

20 The reversal of the *endo*- to *exo*- selectivity may be attributed to the alteration of a chelation structure of Yb^{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.

21 (*a*) T. Kobayashi, K. Miki, B. Nikaeen and H. Baba, *Tetrahedron*, 1999, **55**, 13179; (*b*) I. Smonou, M. Orfanopoulos and C. S. Foote, *Tetrahedron Lett.*, 1988, **29**, 2769; (*c*) H. Wamhoff, F. J. Fassbender, G. Hendrikx, H. Puff and P. Woller, *Chem. Ber.*, 1986, **119**, 2114; (*d*) P. Eisenbarth and M. Regitz, *Chem. Ber.*, 1982, **115**, 3796.

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.

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† 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/b000000x//

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