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Chiral 1,3-butadiene-2-carboxylates for an efficient asymmetric Diels–Alder reaction

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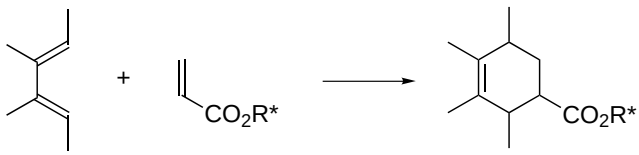
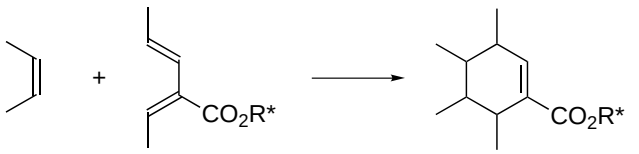
Abstract—1,3-Butadiene-2-carboxylates derived from certain chiral alcohols are good substrates for a highly efficient asymmetric Diels–Alder reaction, which permits the preparation of optically active heterocyclic, cyclohexane and hydrindane systems.

An asymmetric Diels–Alder reaction of a diene and dienophile having a chiral auxiliary constitutes a potential method to prepare optically active cyclic compounds.[1] Among many possible combinations of chiral reactants, reactions between achiral dienes and chiral dienophiles such as optically active acrylates, maleates and fumarates have been extensively studied and have become a well-established synthetic protocol (Eq. (1)).[1] A reversed combination between a chiral 1,3-butadiene-2-carboxylate and an achiral dienophile as shown in Eq. (2) provides an alternative way to give a similar six-membered framework. Nonetheless, this latter process has not been well studied and, accordingly, little is known about its latent efficiency.[2] As we recently reported a facile preparation of 1,3-butadiene-2-carboxylates via a titanium-mediated coupling of acetylenes,[3] we prepared several optically active dienes by this method and investigated the aforementioned reaction. In fact, the asymmetric Diels–Alder reaction formulated in Eq. (2) turned out to be quite promising, some preliminary results of which will be reported herein.



(1)



(2)

Three similar 1,3-butadiene-2-carboxylates **1a**–**c**, yet having a different chiral auxiliary,[4] were prepared by the aforementioned method in good yields.[3] Their ability to effect the chiral induction was assessed by the Diels–Alder reaction with *N*-phenyl-1,2,4-triazoline-3,5-dione (PTAD),[5] because this hetero-dienophile does not involve any issue regarding the selectivities (i.e. regio- and *endo*/*exo*) other than the chiral induction itself (Eq. (3)). While diene **1a** derived from *trans*-2-phenylcyclohexanol[6] showed diastereoselectivity (d.s.) in as high as 90:10 ratio, dienes **1b** and **1c** from 8-phenylmenthol[7] and (diphenylmethyl)isoborneol[8] far exceeded this level to give virtually single adducts **2b**[9] and **2c**, achieving a highly efficient asymmetric synthesis.[10] The depicted structures of products **2a**–**c** were deduced based on a model proposed in the following discussion.

Keywords: asymmetric synthesis; camphor; Diels–Alder reaction; dienes; dienophiles; Lewis acid.

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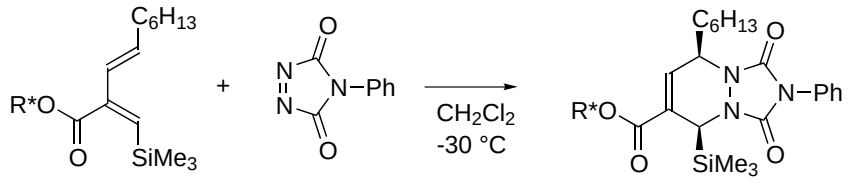
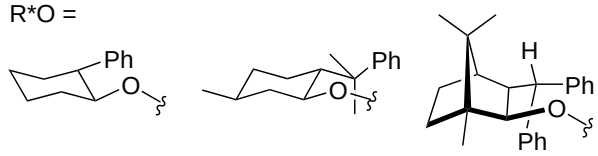


1a-c PTAD

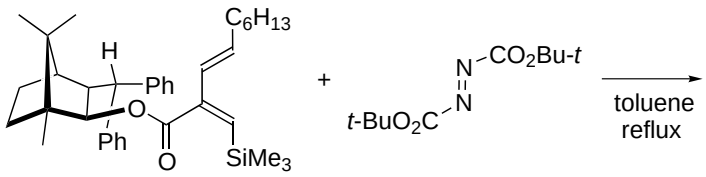
2a 77% d.s. = 90:10
2b 90% single adduct
2c 80% single adduct

(3)

R*O =

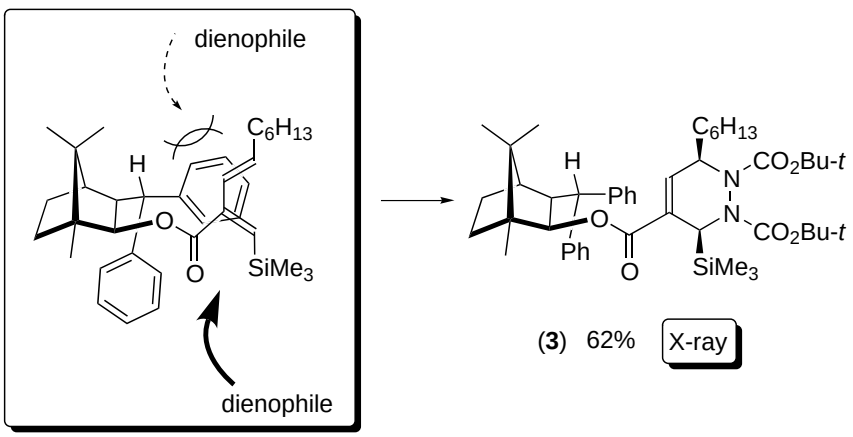


a **b** **c**



(**1c**)

(4)



(**3**) 62% X-ray

Model **A** for chiral induction

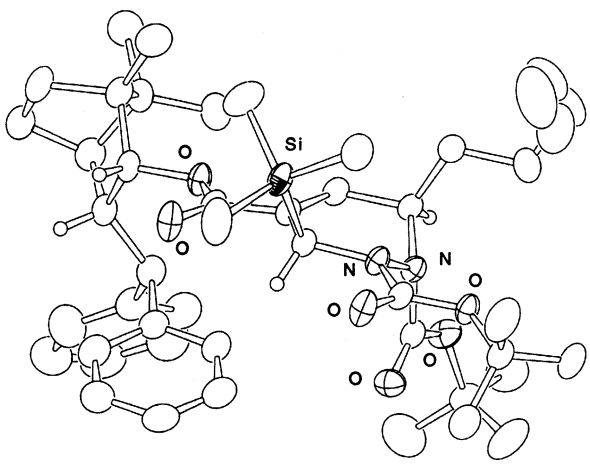
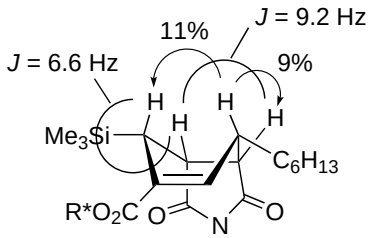


Figure 1. ORTEP drawing of the crystal structure of **3**.

Diene **1c** and di(*tert*-butyl) azodicarboxylate, an analog of PTAD, afforded again a single adduct (Eq. (4)), which crystallized from heptane. The X-ray crystallography of this sample unambiguously determined the structure of the adduct **3** (Fig. 1).[11] This stereochemical outcome is well rationalized by model **A** in Eq. (4) involving the approach of the dienophile to the chiral diene as follows: (i) the 1,3-diene-2-carboxylate moiety is placed in the shown orientation, and (ii) a dienophile approaches the diene plane from the less hindered side.[12]

The above reaction could be readily extended to a carbon dienophile, where an additional stereochemical issue of *endo*/*exo* selectivity arises (Eq. (5)). Upon reaction with *N*-phenylmaleimide, diene **1b**[7] afforded adduct **4** in excellent yield. ^{1}H NMR analysis of crude **4** revealed that high selectivities were attained for both

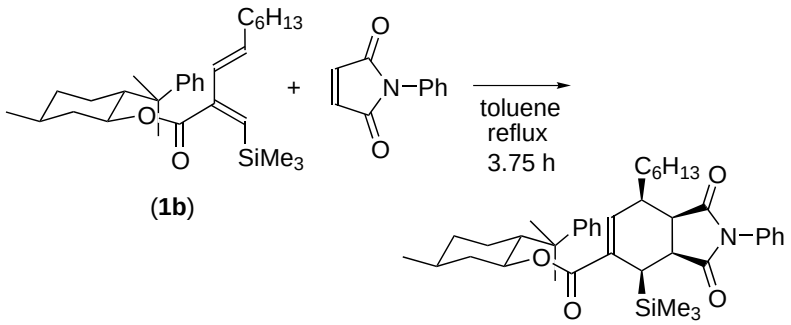
the asymmetric induction and the *endo*/*exo* stereocontrol. The structure of the major *endo* adduct was established by NOE study and coupling constants of the ^{1}H NMR spectroscopy (Fig. 2) and its asymmetric induction was determined on the basis of model **A** in Eq. (4).



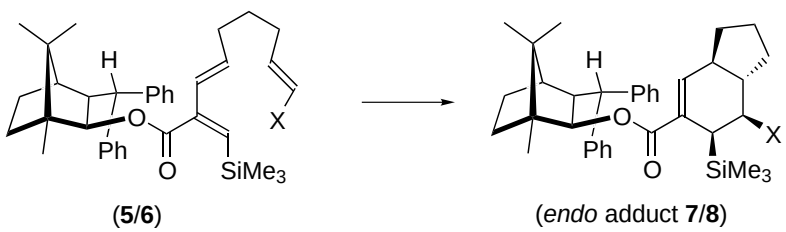
(**4**)

Figure 2. Values in % refer to NOE enhancements.

Having disclosed the asymmetric intermolecular Diels–Alder reaction of 1,3-diene-2-carboxylates, we then turned our attention to an intramolecular version,[1f] furnishing a hydrindane system[13] as shown in Eq. (6).[14] The thermal Diels–Alder reaction of **5** again afforded an *endo*/*exo* mixture (entry 1 in Table 1), the structures of which were assigned based on the observation of Eq. (5). However, the Lewis acid-assisted reaction completely diminished the minor (*exo*) product found in entry 1 to give a virtually single isomer **7** (entry 2).[15] On the other hand, unsaturated acyloxazolidinone **6**, even under thermal conditions, produced a nearly single isomer **8** accompanied with small amounts of two additional constituents, which are attributable to an *exo*-isomer and another *endo*-diastereoisomer. The relative structure of the major adduct **8** was assigned by NOE study and coupling constants of the ^{1}H NMR spectroscopy, and its absolute stereochemistry was deduced based on model **A** in Eq. (4).

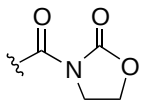


(5)



(6)

Table 1. Intramolecular asymmetric Diels–Alder reaction of **5** and **6** (Eq. (6))

Entry	X		Conditions	*Endo*/*exo*	*Endo* adduct		
						Yield (%)	D.s.[a]
1	CO_2Et	(**5**)	toluene reflux,10 h	61:39		(72[b])	nd[c]
2	CO_2Et	(**5**)	$EtAlCl_2$ (1 equiv) CH_2Cl_2, r.t., 21 h	*ca*.100: 0	(**7**)	41	>97:<3
3		(**6**)	toluene reflux, 5 h	95: 5	(**8**)	71	94: 6

[a]Chiral induction in *endo* adduct. [b]Yield of a mixture of *endo* and *exo* isomers.
[c]Not determined.

In conclusion, the chiral 1,3-diene-2-carboxylates[16] now readily available served as substrates for a new class of highly efficient asymmetric Diels–Alder reaction. As the intramolecular reaction should be useful for the concise construction of optically active bicyclic frameworks with a functional group(s) at an appropriate position,[17] the generality of the methodology will be reported in due course.

Acknowledgements

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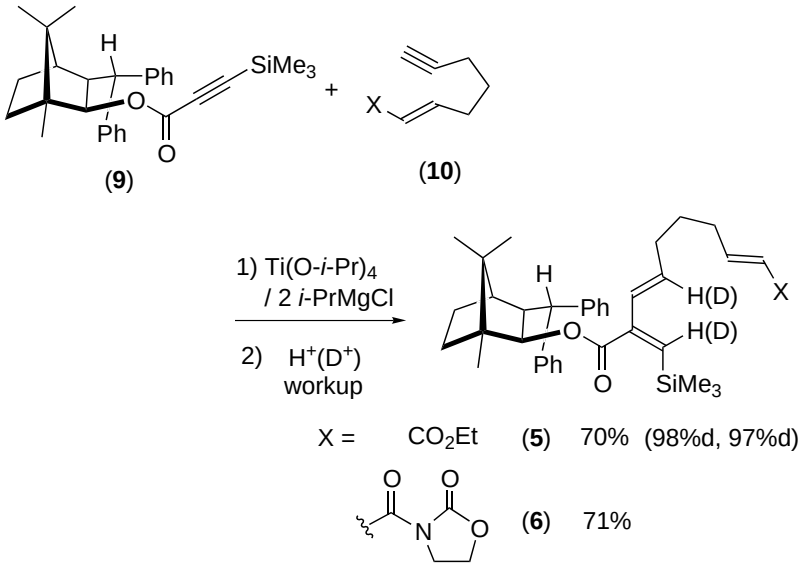
2. Homo-dimerization of a chiral 1,3-butadiene-2-carboxylate has been reported: Basavaiah, D.; Pandiaraju, S.; Sarma, P. K. S. *Tetrahedron Lett*. **1994**, *35*, 4227–4230; cf. for Diels–Alder reaction of chiral 1,3-butadiene-1-carboxylates, see: Sheradsky, T.; Milvitskaya, J.; Pollak, I. E. *Tetrahedron Lett*. **1991**, *32*, 133–136; Markó, I. E.; Evans, G. R. *Tetrahedron Lett*. **1994**, *35*, 2767–2770; Posner, G. H.; Ishihara, Y. *Tetrahedron Lett*. **1994**, *35*, 7545–7548.
3. Hamada, T.; Suzuki, D.; Urabe, H.; Sato, F. *J. Am. Chem. Soc*. **1999**, *121*, 7342–7344.
4. For a review on these chiral auxiliaries, see: Oppolzer, W. *Tetrahedron* **1987**, *43*, 1969–2004; Whitesell, J. K. *Chem. Rev*. **1992**, *92*, 953–964; Jones, G. B.; Chapman, B. J. *Synthesis* **1995**, 475–497; Seyden-Penne, J. *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*; Wiley: New York, 1995; pp. 513–592; Regan, A. C. *J. Chem. Soc., Perkin Trans. 1* **1999**, 357–373.
5. *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: Chichester, 1995; Vol. 6, pp. 4087–4090; Ref. 1e, pp. 426–430.
6. In practice, we performed this reaction using a racemic sample of **1a**.
7. The actual experiment was carried out with the antipode of **1b** prepared from commercially available (−)-8-phenylmenthol. The structure **1b** was adopted in order to align the molecules **1a–c** (and also products **2a–c** or **4**) consistently to enable easy comparison with each other.
8. The chiral auxiliary of **1c**, (diphenylmethyl)isoborneol, was readily prepared from *d*-camphor by a reported method: Hakam, K.; Thielmann, M.; Thielmann, T.; Winterfeldt, E. *Tetrahedron* **1987**, *43*, 2035–2044; Suzuki, D.; Urabe, H.; Sato, F. *Angew. Chem., Int. Ed*. **2000**, *39*, 3290–3292; Pearson, A. J.; Gontcharov, A. V. *J. Org. Chem*. **1998**, *63*, 152–162. For the original procedure, see: Oppolzer, W.; Kurth, M.; Reichlin, D.; Chapuis, C.; Mohanhaupt, M.; Moffatt, F. *Helv. Chim. Acta* **1981**, *64*, 2802–2807. For an alternative preparation, see: Binger, P.; Brinkmann, A.; Roefke, P.; Schäfer, B. *Liebigs Ann. Chem*. **1989**, 739–750.
9. The conversion from **1b** to **2b** was briefly mentioned in our earlier report (Ref. 3).
10. For synthetic applications of hydrogenated pyridazines, see: Liang, X.; Bols, M. *J. Org. Chem*. **1999**, *64*, 8485–8488; Aspinall, I. H., Cowley, P. M.; Mitchell, G.; Raynor, C. M.; Stoodley, R. J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2591–2599; Arakawa, Y.; Goto, T.; Kawase, K.; Yoshifuji, S. *Chem. Pharm. Bull*. **1998**, *46*, 674–680.
11. The data for **3** have been deposited at the Cambridge Crystallographic Data Centre (file no. CCDC 150590).
12. To our best knowledge, this is the first model for the Diels–Alder reaction of a chiral 1,3-butadiene-2-carboxylate, while a relevant model for chiral acrylates (i.e. the reaction of Eq. (1)) has been well documented.[4] In model **A**, all atoms of the ester moiety, CH–O–C(=O), are placed on the same plane and, at the same time, the C–H bond parallels the C=O bond. This conformation of esters of secondary alcohol was also accepted in other study. Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc*. **1991**, *113*, 4092–4096; Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. P. *J. Org. Chem*. **1986**, *51*, 2370–2374. The shown partial structure of CH–O–C(=O) and the orientation of two phenyl groups coincide with the crystal structure of **3** (Fig. 1).
13. For a review on the construction of hydrindane systems, see: Hong, B.; Sarshar, S. *Org. Prep. Proc. Int*. **1999**, *31*, 1–86; Jankowski, P.; Marczak, S.; Wicha, J. *Tetrahedron* **1998**, *54*, 12071–12150; Hudlicky, T.; Price, J. D. *Chem. Rev*. **1989**, *89*, 1467–1486; Ramaiah, M. *Synthesis* **1984**, 529–570.
14. In order to carry out this process, we needed trienes **5** and **6**. Gratifyingly, the titanium-mediated, chemoselective coupling of enyne **10** with acetylene **9** proceeded without any complication to give the desired Diels–Alder substrates in good yields as shown below. Deuteriolysis of the intermediate titanacycle in place of simple hydrolytic workup afforded the bis-deuterated diene, a possible precursor for D-labeled carbocycles.



15. That a Lewis acid enhances the *endo* preference of certain Diels–Alder reactions is mentioned in Ref. 1d, p. 340 and in the following: Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; Wiley: London, 1976; pp. 161–163.
16. In contrast to the high chirality induction with 1,3-butadiene-2-carboxylates, a corresponding 1,3-butadiene-1-carboxylate such as **11**[3] provided an inferior result (d.s. of **12**) as shown below.
17. The chiral auxiliary could be removed by basic hydrolysis or hydride reduction of the ester at an appropriate stage of subsequent transformations. See Ref. 8.