Chiral 2-Alkoxy-1,3-butadienes: Synthesis and Face-selectivity in Diels–Alder Reactions

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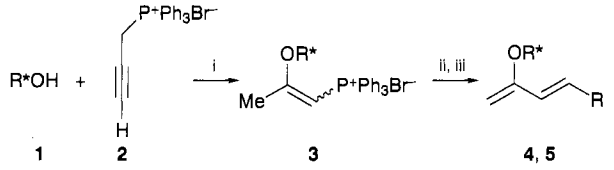
Chiral 2-alkoxy-1,3-butadienes are prepared from chiral alcohols, prop-2-ynyltriphenylphosphonium bromide and aldehydes; they undergo [4 + 2] cycloadditions to carbo- and hetero-dienophiles with moderate to high face-selectivity.

The development of enantioselective Diels–Alder reactions are currently a major goal in selective organic synthesis.[1] In this respect, the use of chiral auxiliaries containing dienophiles[1,2] and the development of efficient chiral catalysts[1,3] have received much attention. Comparatively, few enantioselective Diels–Alder reactions involving dienes with an appended chiral auxiliary have been reported;[1,4] for instance, a number of dienes with chiral substituents placed at C-1 exhibit moderate enantioselectivities.[5] Although 2-substituted dienes appear to be more attractive (for instance, in terms of the removal of the chiral auxiliary) only a few examples are known up to date.[6,7] Among them, 2-aminodienes have proved to be highly useful towards some dienophiles;[7] however, their inherent strong enamine character makes these dienes of limited generality.[8] Surprisingly, the chiral version of the most popular hetero-substituted dienes, 2-alkoxy-1,3-butadiene derivatives, has not been investigated. Reported herein is the synthesis of chiral, racemic and non-racemic 2-alkoxy substituted dienes as well as their [4 + 2] cycloaddition to hetero- and carbo-dienophiles.

The synthesis of alkoxydienes is based on the previous procedure reported for aminodienes[9] (Scheme 1). Accordingly, phosphonium salts **3** were first prepared by heating alcohols **1**[5e,10] and prop-2-ynyltriphenylphosphonium bromide **2** in toluene at 110 °C. Compounds **3** were not isolated but washed with diethyl ether–THF (5 : 1) and subjected to the Wittig reaction [potassium hexamethyldisilazide (KHMDS), −60 °C, THF; then RCHO]; the resulting mixture was stirred overnight (20 °C for R = alkyl; 60 °C for R = aryl, H) furnishing high yields of racemic and enantiomerically pure dienes **4** (R* = *trans*-2-phenylcyclohexyl) and **5** (R* = *trans*-2-mesitylcyclohexyl) as single *E* stereoisomers [$^3J_{H(3)-H(4)}$ 15–16 Hz] after column chromatography (Table 1).†‡



Scheme 1 *Reagents and conditions*: i, toluene, 110 °C, 48 h; ii, KHMDS, THF, −60 °C, 4 h, iii, RCHO, THF, 20–60 °C, 14 h

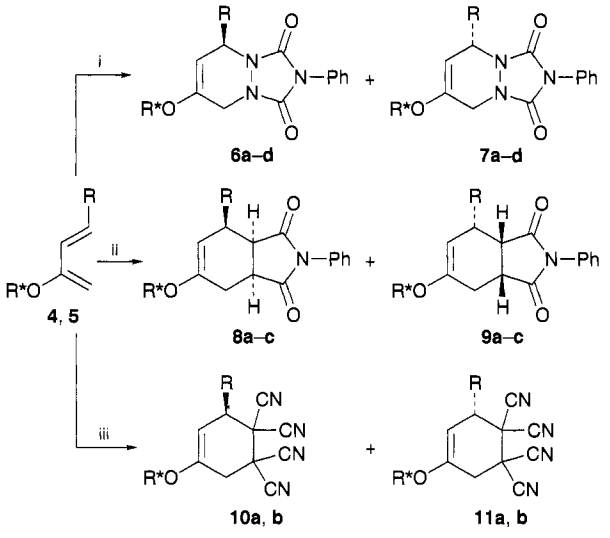
Table 1 Preparation of 2-alkoxy-1,3-butadienes **4** and **5**

Diene	R	R*[a]	Yield[b] (%)
(±)-**4a**	2-Furyl	(1*R*, 2*S*/1*S*, 2*R*)-PC	90
(±)-**4b**	Propyl	(1*R*, 2*S*/1*S*, 2*R*)-PC	76
(±)-**4c**	Phenyl	(1*R*, 2*S*/1*S*, 2*R*)-PC	93
(+)-**4c**[c]	Phenyl	(1*S*, 2*R*)-PC	93
(−)-**4c**[c]	Phenyl	(1*R*, 2*S*)-PC	93
(−)-**4d**[c]	H	(1*R*, 2*S*)-PC	92
(±)-**5**	Phenyl	(1*R*, 2*S*/1*S*, 2*R*)-MSC	86

[a] PC = *trans*-2-phenylcyclohexyl, MSC = *trans*-2-mesitylcyclohexyl. [b] Isolated yields after chromatographic purification (deactivated SiO_2; diethyl ether). All the reported dienes are oils. [c] $[\alpha]_{20}^{D}$ in CH_2Cl_2 (*c*/mg cm^{-3}): (+)-**4c** +97.5 (*c* = 5.9); (−)-**4c** −100.7 (*c* = 6.5); (−)-**4d** −17.3 (*c* = 6.2).

Phenyltriazolinedione (PTAD) was selected as reactive dienophile (Scheme 2). Thus, it was slowly added at −100 °C to dienes **4a–c** (molar ratio 1 : 1) in THF and the mixture warmed to 20 °C during 12 h; removal of the solvent gave high yields of a mixture of diastereoisomeric cycloadducts **6a–d** and **7a–d** with excellent facial selectivity [d.e. (diastereoisomeric excess) = 87–91%; Table 2, entries 1–4]. Enantiomerically pure cycloadducts (+)-**6c** and (−)-**7d** were available from dienes (+)-**4c** and (−)-**4c** (entries 3,4), respectively, after crystallization of the resulting mixture from methanol.‡§

Then the carbodienophiles *N*-phenylmaleimide (NPM) and tetracyanoethylene (TCNE) were subjected to cycloaddition (Scheme 2, Table 2, entries 5–9). Dienes (−)-**4c** and (−)-**4d** were mixed at −10 °C with NPM and $ZnCl_2$ (molar ratio

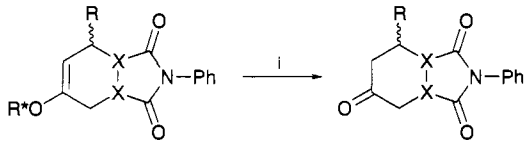


Scheme 2 *Reagents and conditions*: i, PTAD, THF, −100 °C to room temp., 12 h; ii, NPM, $ZnCl_2$, THF, −10 °C to room temp., 12 h; iii, TCNE, THF, −100 °C to room temp., 12 h

Table 2 [4 + 2] Cycloadditions of dienes **4** and **5**

Entry	Diene	Dienophile	Cyclo-adduct	Yield[a] (%)	D.e.[b]/Major
1	(±)-**4a**	PTAD	**6a + 7a**	87	87
2	(±)-**4b**	PTAD	**6b + 7b**	90	92
3	(+)-**4c**	PTAD	**6c + 7c**	91	89/**6c**[d]
4	(−)-**4c**	PTAD	**6d + 7d**	91	89/**7d**[d]
5	(−)-**4c**	NPM[c]	**8a + 9a**	82	60/**9a**
6	(−)-**4d**	NPM[c]	**8b + 9b**	82	60/**9b**[d]
7	(±)-**5**	NPM[c]	**8c + 9c**	80	71
8	(±)-**4c**	TCNE	**10a + 11a**	91	90
9	(±)-**5**	TCNE	**10b + 11b**	86	89

[a] Isolated yield after careful elution of both diastereoisomers on column chromatography (SiO_2; hexane : ethyl acetate, 3 : 1). [b] The diastereoisomeric excess was determined by ^{1}H NMR spectroscopy by integration over the vinylic resonances. [c] Only the *endo* isomer observed. [d] Mp and $[\alpha]_{20}^{D}$ in CH_2Cl_2 (*c*/mg cm^{-3}) for pure cycloadducts: (+)-**6c** 171–172 °C, + 134.2 (*c* = 4.4); (−)-**7d** 171–172 °C, −132.0 (*c* = 5.3); (−)-**9b** 166–167 °C, −34.9 (*c* = 4.3).



Scheme 3 *Reagents and conditions*: i, 12 mol dm^{-3} HCl, CH_2Cl_2, 20 °C, 6h

1 : 1 : 1) in THF, stirred at room temp. for 12 h and worked up with water; analysis of the crude revealed the cycloaddition to show complete *endo*-selectivity (entry 5) giving cycloadducts **8a,b** and **9a,b** with moderate face-selectivity (80 : 20) (entries 5, 6). The major diastereoisomer (−)-**9b** (entry 6) was obtained in enantiomerically pure form after crystallization of the diastereoisomeric mixture from methanol.‡ The cycloaddition of (±)-**4c** with TCNE showed great selectivity; thus, running the reaction as described above for PTAD led to a 95 : 5 mixture of **10a** and **11a** (entry 8). Diene **5** derived from (±)-mesitylcyclohexanol allowed to slightly improve the facial selectivity in the cycloaddition with NPM (**8c** and **9c**, entry 7); on the contrary, there were no noticiable differences in the cycloaddition of dienes **5** and **4c** (R = Ph) with TCNE (as compared entries 8 and 9).¶

The hydrolysis of the crude cycloadducts **6c/7c** [from (+)-**4c** and PTAD] and **8a/9a** [from (−)-**4c** and NPM] was accomplished without racemization with 12 mol dm^{-3} HCl (CH_2Cl_2, 20 °C, 6 h); the mixture was diluted (water), extracted and purified by flash chromatography to yield ketones **12** (80%) and **13** (90%), respectively, and unalterated chiral auxiliary (> 85% recovered) (Scheme 3).‡‖**

In summary, an easy stereoselective synthesis of new chiral 2-alkoxydienes is outlined. Dienes derived from *trans*-phenylcyclohexanol appears to be promising reagents for Diels–Alder cycloadditions in terms of *endo*- and *diastereo facial*-selectivity, chemical yield and availability of both enantiomers.

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Footnotes

† When LHMDS was employed variable amounts (10–15%) of the Z isomer were produced.

‡ All compounds gave satisfactory spectroscopic (IR, ^1H and ^{13}C NMR) data and HRMS data or elemental analyses. *Selected spectroscopic data* for **4c**: ^1H NMR ($DCCl_3$, 300 MHz) δ 1.3–2.3 (m, 8H), 2.9 (m, 1H), 4.2 (m, 1H), 4.25 (d, *J* 1.8 Hz, 1H), 4.3 (d, *J* 1.8, 1H), 6.4 (d, *J* 15.8 Hz, 1H), 6.7 (d, *J* 15.8 Hz, 1H), 7.2–7.5 (m, 10H). For **6c**: ^{13}C NMR ($DCCl_3$, 75 MHz) δ 152.31 (s), 150.96 (s), 148.08 (s), 143.23 (s), 137.03 (s), 130.88 (s), 128.85 (d), 128.60 (d), 128.25 (d), 127.83 (d), 127.32 (d), 126.51 (d), 125.08 (d), 93.43 (d), 80.17 (d), 56.11 (d), 50.28 (d), 44.55 (t), 33.34 (t), 31.36 (t), 25.67 (t), 24.69 (t).

§ The stereochemical assignment of the cycloadducts **6** and **7**, as well as that of **8–11**, was ascertained by an X-ray structure analysis of **7d**.[11]

¶ Mesitylcyclohexanol has been reported to be superior to phenylcyclohexanol.[5e] Poor diastereoselectivities (d.e. < 43%) were achieved when using dienes derived from either (−)-menthol or (−)-8-phenylmenthol.

‖ We were unable to perform the hydrolysis of **10** and **11**, since either they withstand the reaction conditions or formation of intractable products occurred.

** The enantiomeric purity of **12** was determined by ^1H and ^{13}C NMR analysis of the acetal derived from (*R,R*)-butane-2,3-diol,[12] while that of **13** was deduced from HPLC (Chiralcell OD-H, ethanol : hexane 3 : 1).

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