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Desymmetrization of 1,4-Pentadien-3-ol by the Asymmetric 1,3-Dipolar Cycloaddition of Azomethine Imines

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This paper is dedicated to Professor Teruaki Mukaiyama in celebration of the 40th anniversary of the Mukaiyama aldol reaction.

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Abstract: Desymmetrization of the divinyl carbinol, 1,4-pentadien-3-ol, was accomplished by the asymmetric 1,3-dipolar cycloaddition of azomethine imines based on a magnesium-mediated, multi-nucleating chiral reaction system utilizing diisopropyl (*R*,*R*)-tartrate as the chiral auxiliary. The corresponding optically active *trans*-pyrazolidines, each with three contiguous stereogenic centers, were obtained with excellent regio-, diastereo-, and enantioselectivity, with results as high as 99% ee. This reaction was shown to be applicable to both aryl- and aliphatic-substituted azomethine imines. The use of a catalytic amount of diisopropyl (*R*,*R*)-tartrate was also effective when accompanied by the addition of $MgBr_2$.

Introduction

The desymmetrization of achiral or *meso* compounds has proved to be a powerful technique in asymmetric synthesis, since it allows the formation of multiple stereogenic centers in one symmetry-breaking operation. This strategy has therefore attracted considerable attention with regard to the synthesis of optically active natural products or biologically active substances.[1] Group selective desymmetrization of divinyl carbinols and their derivatives is one of the most promising strategies for the production of new optically active alcohol derivatives containing an unreacted olefinic moiety, which could be a useful functional group during further transformations. The Katsuki-Sharpless epoxidation of 1,4-pentadien-3-ols results in desymmetrization to yield epoxy alcohols which are versatile synthetic intermediates for the preparation of oxygen-functionalized biologically active compounds.[2,3] However, techniques which allow the desymmetrization of divinyl carbinols as a means of forming multiple stereocenters along with the formation of new C–C bonds are quite limited.

Pyrazolidines are biologically active[4] and are versatile synthetic intermediates for the synthesis of nitrogen-containing chemicals, and various enatioselective syntheses of pyrazolidines by asymmetric 1,3-dipolar cycloaddtions have been reported.[5] Recently, we developed the asymmetric 1,3-dipolar cycloaddition of azomethine imines to allyl and homoallyllic alcohols, utilizing either stoichiometric or catalytic amounts of diisopropyl (*R*,*R*)-tartrate [(*R*,*R*)-DIPT] to furnish *trans*-pyrazolidines with high regio-, diastereo-, and enantioselectivity.[6] In order to construct multi-chiral centers via our 1,3-dipolar cycloaddition of azomethine imines, enantiotopic differentiation of the two vinyl groups of prochiral divinyl carbinols is required, which is challenging. Herein we describe the desymmetrization of a divinyl carbinol, 1,4-pentadien-3-ol, by the asymmetric 1,3-dipolar cycloaddition of azomethine imines, utilizing (*R*,*R*)-DIPT as the chiral auxiliary.

Results and Discussion

We initially investigated the 1,3-dipolar cycloaddition of 1-benzylidene-3-oxopyrazolidin-1-ium-2-ide (**2a**) to 1,4-pentadien-3-ol (**1**), based on a magnesium-mediated, multi-nucleating chiral reaction system of our own design, as depicted in Figure 1.[6-8]

Figure 1.

In this process, a mixture of 1.0 equiv of **1** and 1.0 equiv of (*R*,*R*)-DIPT is treated with 3.0 equiv of MeMgBr in MeCN, followed by the addition of 1.0 equiv of azomethine imine **2a**, after which the reaction mixture is held at 80 °C for 2 d. It was gratifying to observe that the desymmetrization proceeded under these conditions to give only one diastereomer of the corresponding pyrazolidine **3a** with excellent enantioselectivity (Table 1, Entry 1).[9] The use of the alternate solvent EtCN further enhanced the reaction yield (Entry 2). The halogen in the Grignard reagent also had an effect;[10] when *n*BuMgCl was used, the yield of the cycloadduct **3a** was significantly improved (Entry 3).

The desymmetrization of 1,4-pentadiene-3-ol (**1**) by the asymmetric cycloaddition of several azomethine imines **2b**-**2f** was subsequently investigated in EtCN at 80 °C. The aryl-substituted azomethine imines **2b** and **2c** afforded the corresponding cycloadducts **3b** and **3c** with excellent enantioselectivity and complete regio- and diastereoselectivity in each case (Entries 4 and 5). The cycloaddition of the pentyl-substituted azomethine imine **2d** proceeded in an enantioselective manner, although a significant quantity of the by-product **4** (Figure 2) was obtained (Entry 6). The use of an excess of the carbinol **1** slightly improved the reaction yield (Entry 7). The cycloaddition of the cyclohexyl-substituted and *t*-butyl-substituted azomethine imines **2e** and **2f** also afforded the cycloadducts **3e** and **3f** with enantioselectivities of 99% and 98% ee, respectively (Entries 8 and 9).

Table 1.

Figure 2.

To increase the efficiency of the procedure, we subsequently employed only a catalytic amount of (*R*,*R*)-DIPT as the chiral auxiliary.[6c] In this revised procedure, 1.5 equiv of *n*BuMgCl and the azomethine imine **2a** were added successively to a mixture of 1.1 equiv of **1**, 0.2 equiv of (*R*,*R*)-DIPT, and 1.0 equiv of $MgBr_2$ in EtCN and the reaction mixture was held at 80 °C for 5 d. Although the corresponding pyrazolidine **3a** was obtained with 84% ee, the reaction proceeded quite slowly and yield was insufficient (Table 2, Entry 1). When MeMgBr was used in place of *n*BuMgCl, both enantioselectivity and chemical yield were increased (Entry 2). The addition of the magnesium salt was confirmed to be effective by comparing the enantioselectivity shown in Entry 2 with the result obtained in the absence of $MgBr_2$ (Entry 3).

The catalytic asymmetric cycloadditions of a number of other azomethine imines **2b**-**2f** to the divinyl carbinol **1** were attempted in EtCN at 80 °C. The aryl-substituted azomethine imines **2b** and **2c** once again resulted in excellent enantioselectivity, even when applied in this modified catalytic process (Entries 4 and 5). The cycloaddition of pentyl-substituted azomethine imine **2d** proceeded quite slowly to give the desired cycloadduct **3d** in low yield in addition to the dimerized by-product **4** (Entries 6 and 7). The cycloaddition of cyclohexyl- and *t*-butyl-substituted azomethine imines **2e** and **2f** still afforded the corresponding pyrazolidines in good chemical yields with excellent enantioselectivity (Entries 8 and 9).

Table 2.

The absolute configuration of the enantiomerically rich **3a** (98% ee) was determined by treating this product with (1*S*)-camphanic chloride and Et_3N in the presence of a catalytic amount of 4-(*N*,*N*-dimethylamino)pyridine (DMAP) in CH_2Cl_2 to generate the corresponding ester **5** (99%) (Equation 1). Recrystallization gave diastereomerically pure **5** and the absolute stereochemistry at each of its three chiral centers was determined to be *R*,*R*,*R* by X-ray crystallographic analysis of a single crystal (Figure 3). From this result, the absolute configuration of **3a** was confirmed as 5*R*,7*R*,1'*R*. The absolute configurations tentatively assigned to the other products were 5*R*,7*R*,1'*R* in the case of **3b**, **3c**, **3e**, and **3f** and 5*S*,7*R*,1'*R* in the case of **3d**, which has the same configurational arrangement of the substituents at the 5- and 7-positions as the other products.

Equation 1.

Figure 3.

We have previously reported that the 1,3-dipolar cycloaddition of **2a** to homoallylic alcohols proceeded with excellent enantioselectivity.[6c] In this study, we also examined the desymmetrization of the homoallylic-type dialkenyl carbinol, 1,6-heptadien-4-ol (**6**). The corresponding cycloadduct **7** was obtained with moderate enantioselectivity and the diastereoselectivity was low (Equation 2).

Equation 2.

While the precise mechanism by which this reaction proceeds is not yet clear, we propose the following transition state model. In this model, the carbonyl oxygen of **2**, rather than the imine nitrogen, coordinates with the magnesium salt of DIPT (Figure 4). In the case of the T_2 transition state, steric repulsion between the pro-*R* vinyl group and the azomethine imine skeleton disturbs the cycloaddition to the pro-*S* vinyl group. As a result, it is more likely that the T_1 state actually occurs, since in this state it is primarily the pro-*R* olefin which approaches the azomethine imine, giving the *R*,*R*,*R* product. During the reaction of the homoallylic-type alcohol **6**, the extension of the side chains by one carbon compared to the divinyl carbinol **1** makes these chains more flexible, especially around C4, and reduces steric hindrance effects. The diastereoselection between the T_3 and T_4 states is therefore less than that between the T_1 and T_2 states, although the exact stereochemistry of the major product of this reaction has not yet been determined.

Figure 4.

The pyrazolidines could be transformed to the 1,3-diamine derivatives.[11] We simply demonstrated the reduction of **3a** by the use of Raney nickel. Although only the double bond was reduced under the ordinary atmosphere, N–N bond was successfully cleaved to give **8** under a pressured hydrogen atmosphere. Furthermore, the attractive reductive or oxidative transformation of **3a** was realized. The reduction of amide moiety with $LiAlH_4$ afforded a one-of-a-kind tricyclic hexahydro-1-oxa-2a^1,4a-diazacyclopentapentalene skeleton **9** in good yield. The use of large excess amount of $LiAlH_4$ induced reductive ring opening of oxazolidine moiety to give a bicyclic hydrazine derivative **10**. In addition, the hydrazide moiety in **3a** was chemoselectively oxidized by treatment with *m*CPBA to furnish a unique *N*-oxide **11** while olefinic moiety remained intact (Scheme 1). The novel structures of **9**, **10**, and **11** might have potential as new types of organocatalysts, for example.

Scheme 1.

Conclusion

An attractive and unique reaction scheme allowing the desymmetrization of 1,4-pentadien-3-ol by the asymmetric 1,3-dipolar cycloaddition of azomethine imines has been developed. This process generates highly enantiomerically pure pyrazolidines possessing three contiguous stereogenic centers as single diastereomers. The obtained pyrazolidines contain a double bond and a hydroxyl group on the side chain, both of which might allow further functionalization. The present method would be useful for the preparation of optically active nitrogen and oxygen containing chemicals.[12]

Experimental Section

General Remarks

^{1}H NMR spectroscopy was performed in $CDCl_3$ using a JEOL ECS 400 NMR (400 MHz) spectrometer. Chemical shifts (δ) were determined relative to TMS (δ = 0 ppm) as an internal standard. ^{13}C NMR spectroscopy was performed in $CDCl_3$ on a JEOL ECS 400 NMR (100 MHz) spectrometer and chemical shifts (δ) were determined relative to $CDCl_3$ (δ = 77.0 ppm) as an internal standard. IR spectra were acquired on a JASCO FT/IR-230 spectrometer. Melting points were determined on a micro-melting apparatus (Yanagimoto–Seisakusho) and were uncorrected. The specific optical rotations were recorded on a JASCO DIP-370 spectrometer. HPLC was performed using chiral column with JASCO PU980 plus JASCO UV970. X-ray crystallography was performed on a Rigaku/MSC Mercury diffractometer with graphite-monochromated Mo-Kα radiation. Elemental analysis was performed on a Yanaco CHN Corder MT-5 elemental analyzer. Mass spectra were obtained using JMS-700 and JMS-T100TD mass spectrometers. All solvents were distilled prior to use and stored over drying agents. Merck silica gel 60 PF254 (Art. 7749), Cica silica gel 60N spherical neutral (37563-84), and JAIGL-SIL (s-043-15) were used for thin-layer chromatography (TLC), flash column chromatography, and recycle HPLC, respectively. The retention factors (R_f) of various compounds were determined by TLC.

The following is a representative procedure for the stoichiometric asymmetric 1,3-dipolar cycloaddition of azomethine imine **2e** (Table 1, Entry 8):

To a EtCN (3 mL) solution of 1,4-pentadien-3-ol (**1**) (42 mg, 0.50 mmol) and (*R*,*R*)-DIPT (117 mg, 0.50 mmol) was added butylmagnesium chloride (1.50 mmol, 1.70 mL of 0.91 M solution in THF) at 0 °C under an argon atmosphere and the mixture was stirred for 1 h. Azomethine imine **2e** (90 mg, 0.50 mmol) was added to the resulting solution and the mixture was stirred for 0.5 h at rt and then 3 d at 80 °C. The reaction was quenched by the addition of a sat. aqueous solution of NH_4Cl and the mixture was subsequently extracted with $CHCl_3$. The combined extracts were dried over Na_2SO_4 and condensed under reduced pressure. The residue was purified by column chromatography (SiO_2, hexane/AcOEt = 1:1 to 0:1) to give the corresponding pyrazolidine **3e** (106 mg, 80%) with a selectivity of 99% ee.

In a similar manner, the pyrazolidines **3a**–**3d**, **3f**, and **7** were prepared from azomethine imines **2a**–**2d**, **2f**.

(5*R*,7*R*)-7-((*R*)-1-Hydroxyallyl)-5-phenyltetrahydropyrazolo[1,2-a]pyrazol-1(5*H*)-one (**3a**)

3a (120 mg, 93%) was obtained as a solid. R_f = 0.65 (AcOEt); $[\alpha]^{25}_D$ +55 (*c* 1.2, EtOH); The ee was determined to be 99% by HPLC (Daicel CHIRALCEL OD-H, hexane/EtOH = 10:1, 0.5 mL/min, 254 nm, major 33 min and minor 25 min); m.p. 76–77 °C (recrystallized from EtOH); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.40 (dt, 1H, *J* = 13.3, 9.6 Hz), 2.49 (ddd, 1H, *J* = 13.3, 7.8, 5.0 Hz), 2.74–2.86 (m, 2H), 2.91–3.01 (m, 1H), 3.38 (dd, 1H, *J* = 9.2, 7.8 Hz), 3.55 (dd, 1H, *J* = 9.2, 6.4 Hz), 3.89 (ddd, 1H, *J* = 9.6, 8.7, 5.0 Hz), 4.31–4.36 (m, 1H), 5.29 (d, 1H, *J* = 10.5 Hz), 5.46 (d, 1H, *J* = 17.0 Hz), 5.82 (ddd, 1H, *J* = 17.0, 10.5, 7.3 Hz), 6.54 (br, 1H), 7.31–7.39 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 36.4, 41.2, 50.3, 59.8, 68.5, 75.0, 118.7, 127.1, 128.2, 128.7, 136.1, 137.3, 165.9; IR (KBr) 3189, 3063, 3033, 2978, 2931, 2865, 1649, 1455, 1421, 1366, 1339, 1315, 1146, 1067, 1001, 929, 760, 700 cm^{-1}; elemental analysis calcd (%) for $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02; N, 10.85; found: C, 69.75; H, 7.11; N, 10.79.

(5*R*, 7*R*)-7-((*R*)-1-Hydroxyallyl)-5-(4-methoxyphenyl)tetrahydropyrazolo[1,2-a]pyrazol-1(5*H*)-one (**3b**)

3b (141 mg, 98%) was obtained as an oil; R_f = 0.60 (AcOEt) ; $[\alpha]^{25}_D$ +53 (*c* 1.4, EtOH); The ee was determined to be 99% by HPLC (Daicel CHIRALCEL OD-H, hexane/EtOH = 10:1, 0.5 mL/min, 254 nm, major 36 min and minor 29 min); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.37 (dt, 1H, *J* = 13.3, 9.2 Hz), 2.45 (ddd, 1H, *J* = 13.3, 7.8, 5.0 Hz), 2.73–2.84 (m, 2H), 2.86–2.99 (m, 1H), 3.33–3.37 (m, 1H), 3.48–3.53 (m, 1H), 3.81 (s, 3H), 3.88 (ddd, 1H, *J* = 9.2, 8.7, 5.0 Hz), 4.32 (dd, 1H, *J* = 8.7, 7.4 Hz), 5.28 (d, 1H, *J* = 10.5 Hz), 5.45 (d, 1H, *J* = 17.0 Hz), 5.82 (ddd, 1H, *J* = 17.0, 10.5, 7.4 Hz), 6.50 (br, 1H), 6.89 (d, 2H, *J* = 8.7 Hz), 7.25 (d, 2H, *J* = 8.7 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 36.5, 41.2, 50.2, 55.3, 60.0, 68.2, 75.3, 114.1, 118.8, 128.4, 129.0, 136.2, 159.6, 166.1; IR (neat) 3271, 2838 1651, 1612, 1514, 1444, 1420, 1359, 1302, 1248, 1176, 1151, 1033, 997, 833, 767 cm^{-1}; HRMS (FAB$^+$): *m*/*z* calcd for $C_{16}H_{21}N_2O_3$: 289.1552: [*M*+H]$^+$; found: 289.1555.

(5*R*, 7*R*)-5-(4-Chlorophenyl)-7-((*R*)-1-hydroxyallyl)tetrahydropyrazolo[1,2-a]pyrazol-1(5*H*)-one (**3c**)

3c (144 mg, 97%) was obtained as an oil. R_f = 0.65 (AcOEt); $[\alpha]^{25}_D$ +58 (*c* 1.4, EtOH); The ee was determined to be 99% by HPLC (Daicel CHIRALCEL OD-H, hexane/EtOH = 10:1, 0.5 mL/min, 254 nm, major 35 min and minor 27 min); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.34 (dt, 1H, *J* = 13.3, 9.2 Hz), 2.48 (ddd, 1H, *J* = 13.3, 7.3, 4.6 Hz), 2.75–2.84 (m, 2H), 2.91–3.02 (m, 1H), 3.35–3.40 (m, 1H), 3.52 (dd, 1H, *J* = 9.2, 7.8 Hz), 3.87 (ddd, 1H, *J* = 9.2, 8.7, 4.6 Hz), 4.33 (dd, 1H, *J* = 8.7, 7.3 Hz), 5.29 (d, 1H, *J* = 10.6 Hz), 5.45 (d, 1H, *J* = 17.4 Hz), 5.81 (ddd, 1H, *J* = 17.4, 10.6, 7.3 Hz), 6.49 (br, 1H), 7.28 (d, 2H, *J* = 8.2 Hz), 7.34 (d, 2H, *J* = 8.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 36.4, 41.3, 50.3, 59.8, 67.8, 74.7, 118.7, 128.4, 128.8, 133.9, 135.96, 136.03, 165.7; IR (KBr) 3404, 3049, 2977, 2920, 2834, 1657, 1496, 1446, 1421, 1305, 1264, 1234, 1135, 1091, 1028, 937, 849, 731, 711 cm^{-1}; elemental analysis calcd (%) for $C_{15}H_{17}N_2O_2Cl$: C, 61.54; H, 5.85; N, 9.57; found: C, 61.28; H, 6.01; N, 9.38.

(5*S*,7*R*)-7-((*R*)-1-Hydroxyallyl)-5-pentyltetrahydropyrazolo[1,2-a]pyrazol-1(5*H*)-one (**3d**)

3d (33 mg, 33%) was obtained as an oil. R_f = 0.60 (AcOEt) ; $[\alpha]^{25}_D$ +36 (*c* 0.3, EtOH); The ee was determined to be 97% by HPLC (Daicel CHIRALCEL OD-H, hexane/EtOH = 20:1, 0.5 mL/min, 254 nm, major 34 min and minor 24 min); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.89 (t, 3H, *J* = 6.4 Hz), 1.28–1.36 (m, 7H), 1.50–1.60 (m, 1H), 2.03 (ddd, 1H, *J* = 12.8, 9.6, 9.2 Hz), 2.19 (ddd, 1H, *J* = 12.8, 7.3, 5.0 Hz), 2.44–2.51 (m, 1H), 2.72–2.82 (m, 2H), 2.92–3.04 (m, 1H), 3.53–3.59 (m, 1H), 3.65 (ddd, 1H, *J* = 9.2, 8.7, 5.0 Hz), 4.22 (dd, 1H, *J* = 8.7, 7.3 Hz), 5.28 (d, 1H, *J* = 10.6 Hz), 5.42 (d, 1H, *J* = 17.4 Hz), 5.80 (ddd, 1H, *J* = 17.4, 10.6, 7.3 Hz), 6.67 (br, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.9, 22.4, 25.7, 31.8, 32.0, 36.6, 38.0. 51.5, 59.7, 65.0, 75.0, 118.5, 136.3, 165.1; IR (neat) 3431, 2980, 2931, 1741, 1660, 1453, 1376, 1263, 1131, 1105, 1031, 701 cm^{-1}; HRMS (FAB$^+$): *m*/*z* calcd for $C_{14}H_{25}N_2O_2$: 253.1916: [*M*+H]$^+$; found: 253.1920.

(5*R**,6*R**,7*R**)-6-Butyl-7-(3-oxopyrazolidine-1-yl)-5-pentyltetrahydropyrazolo[1,2-a]pyrazol-1(5*H*)-one (**4**)

R_f = 0.30 (AcOEt); m.p. 153–154 °C (recrystallized from AcOEt); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.88–0.92 (m, 6H), 1.24–1.43 (m, 11H), 1.51-1.69 (m, 3H), 2.05–2.11 (m, 1H), 2.36–2.52 (m, 3H), 2.63–2.73 (m, 2H), 3.05–3.14 (m, 1H), 3.56 (dt, *J* = 11.0, 7.8 Hz, 1H), 3.64–3.76 (m, 2H), 4.48 (d, *J* = 5.0 Hz, 1H), 7.80 (br, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.9, 14.0, 22.4, 22.8, 25.7, 29.4, 30.2, 31.0, 31.1, 31.8, 32.2, 47.9, 49.7, 50.8, 72.5, 81.0, 174.1, 175.6; IR (KBr): 3154, 3070, 2954, 2930, 2898, 2858, 1682, 1471, 1420, 1344, 1313, 1289, 1273, 1179, 1095, 1081, 966, 767, 663 cm^{-1}; elemental analysis calcd (%) for $C_{18}H_{32}N_4O_2$: C, 64.24; H, 9.60; N, 16.65; found: C, 63.94; H, 9.66; N, 16.49. Crystal data: $C_{18}H_{32}N_4O_2$, *FW*. 336.48, monoclinic, $P2_1/n$, *a* = 10.0073(8), *b* = 8.1555(6), *c* = 23.033(2) Å, *V* = 1845.6(3) Å^3, β = 100.960(2)°, *Z* = 4. D_{calc} = 1.211 g/cm^3. *R* = 0.037 (R_w = 0.046) for 2936 reflections with $I > 3.00\sigma(I)$ and 217 variable parameters.

CCDC 951615 (**4**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(5*R*,7*R*)-5-Cyclohexyl-7-((*R*)-1-hydroxyallyl)tetrahydropyrazolo[1,2-a]pyrazol-1(5*H*)-one (**3e**)

3e (106 mg, 80%) was obtained as an oil. R_f = 0.65 (AcOEt); $[\alpha]^{25}_D$ +16 (*c* 1.1, EtOH); The ee was determined to be 99% by HPLC (Daicel CHIRALCEL OD-H, hexane/EtOH = 20:1, 0.5 mL/min, 254 nm, major 37 min and minor 28 min); ^{1}H NMR ($CDCl_3$, 400

MHz): δ = 0.88–1.02 (m, 2H), 1.08–1.25 (m, 3H), 1.36–1.43 (m, 1H), 1.66–1.77 (m, 5H), 2.06–2.11 (m, 2H), 2.35 (dd, 1H, *J* = 8.2, 6.9 Hz), 2.70–2.82 (m, 2H), 2.92–2.59 (m, 1H), 3.53–3.62 (m, 2H), 4.23 (dd, 1H, *J* = 8.7, 6.9 Hz), 5.26 (d, 1H, *J* = 10.1 Hz), 5.42 (d, 1H, *J* = 17.0 Hz), 5.80 (ddd, 1H, *J* = 17.0, 10.1, 6.9 Hz), 6.82 (br, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 25.7, 25.8, 26.1, 28.6, 30.0, 35.3, 36.5, 40.5, 53.3, 59.5, 69.8, 74.2, 118.2, 136.1, 164.3; IR (neat) 3258, 2925, 2852, 1658, 1449, 1421, 1353, 1297, 1285, 1158, 1049, 997, 929, 894, 714 cm^{-1}; HRMS (FAB$^+$): *m*/*z* calcd for $C_{15}H_{25}N_2O_2$: 265.1916: [*M*+H]$^+$; found: 265.1911.

(5*R*,7*R*)-5-*tert*-Butyl-7-((*R*)-1-hydroxyallyl)tetrahydropyrazolo[1,2-a]pyrazol-1(5*H*)-one (**3f**)

3f (67 mg, 56%) was obtained as an oil. R_f = 0.75 (AcOEt) ; $[\alpha]^{25}_D$ –13 (*c* 0.9, EtOH); The ee was determined to be 99% by HPLC (Daicel CHIRALCEL OD-H, hexane/EtOH = 20:1, 0.5 mL/min, 254 nm, major 34 min and minor 27 min); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.90 (s, 9H), 1.94–2.06 (m, 2H), 2.36 (dd, 1H, *J* = 8.7, 6.9 Hz), 2.72 (dd, 1H, *J* = 15.1, 7.8 Hz), 2.83 (dt, 1H, *J* = 13.3, 8.2 Hz), 2.93–3.02 (m, 1H), 3.45 (td, 1H, *J* = 8.7, 8.2 Hz), 3.60 (t, 1H, *J* = 8.7 Hz), 4.23 (dd, 1H, *J* = 8.7, 6.9 Hz), 5.27 (d, 1H, *J* = 10.5 Hz), 5.44 (d, 1H, *J* = 16.9 Hz), 5.82 (ddd, 1H, *J* = 16.9, 10.1, 6.9 Hz), 6.96 (br, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 26.3, 26.9, 33.2, 33.9, 36.7, 55.0, 60.1, 73.7, 118.1, 135.9, 163.9; IR (neat) 3237, 2958, 2870, 1657, 1452, 1422, 1299, 1252, 1152, 1132, 1052, 994, 929 cm^{-1}; HRMS (FAB$^+$): *m*/*z* calcd for $C_{13}H_{23}N_2O_2$: 239.1760: [*M*+H]$^+$; found: 239.1754.

7-(2-Hydroxy-4-penten-1-yl)-5-phenyltetrahydropyrazolo[1,2-a]pyrazol-1(5*H*)-one (**7**)

A 16:9 mixture of diastereomers (40 mg, 28%) was obtained as an oil. The mixture was further separated by recycle HPLC (AcOEt/EtOH = 15:1) to give the major and minor products: Major diastereomer: R_f = 0.50 (AcOEt); $[\alpha]^{25}_D$ +41 (c 0.22, EtOH); The ee was determined to be 78% by HPLC (Daicel CHIRALPAK IA, hexane/EtOH = 10:1, 0.5 mL/min, 254 nm, major enantiomer of the major diastereomer 35 min and its minor enantiomer 27 min); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.77 (dd, 1H, *J* = 14.6, 6.9 Hz), 2.25–2.35 (m, 3H), 2.42 (ddd, 1H, *J* = 12.8, 6.4, 3.7 Hz), 2.52–2.68 (m, 3H), 2.87 (td, 1H, *J* = 10.1, 9.6 Hz), 3.68–3.75 (m, 1H), 3.75–3.83 (m, 1H), 3.98 (br, 1H), 4.16–4.23 (m, 1H), 5.00–5.04 (m, 1H), 5.12 (d, 1H, *J* = 10.1 Hz), 5.13 (d, 1H, *J* = 17.0 Hz), 5.87 (ddt, 1H, *J* = 17.0, 10.1, 7.3 Hz), 7.13–7.39 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 36.1, 40.9, 42.6, 44.4, 48.9, 51.0, 67.3, 68.9, 117.7, 127.5, 128.3, 128.8, 134.7, 137.3, 166.1; IR (KBr): 3387, 3069, 2978, 2924, 2845, 1662, 1495, 1370, 1342, 1305, 1146, 1072, 1034, 996, 915, 755, 703 cm^{-1}; HRMS (FAB$^+$): *m*/*z* calcd for $C_{17}H_{23}N_2O_2$: 287.1760: [*M*+H]$^+$; found: 287.1756. Minor diastereomer: R_f = 0.60 (AcOEt); $[\alpha]^{25}_D$ +13 (c 0.13, EtOH); The ee was determined to be 68% by HPLC (Daicel CHIRALCEL OD-H, hexane/EtOH = 10:1, 0.5 mL/min, 254 nm, major enantiomer of the minor diastereomer 27 min and its minor enantiomer 20 min); ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.74 (ddd, 1H, *J* = 13.7, 10.1, 4.6 Hz), 1.90 (ddd, 1H, *J* = 13.7, 10.1, 3.2 Hz), 2.22–2.37 (m, 3H), 2.39–2.50 (m, 2H), 2.66 (ddd, 1H, *J* = 12.8, 8.7, 6.0 Hz), 3.05 (q, 1H, *J* = 10.1 Hz), 3.16 (td, 1H, *J* = 10.1, 3.2 Hz), 3.85–3.94 (m, 2H), 4.31–4.40 (m, 1H), 4.46 (br, 1H), 5.09 (d, 1H, *J* = 10.1, Hz), 5.11 (d, 1H, *J* = 17.0 Hz), 5.89 (ddt, 1H, *J* = 17.0, 10.1, 7.4 Hz), 7.21–7.28 (m, 2H), 7.32–7.40 (m, 3H) ; ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 34.8, 41.6, 42.9, 43.0, 46.2, 50.4, 66.1, 67.7, 117.1, 127.8, 128.3, 128.9, 135.1, 137.1, 169.6; IR (neat) : 3385, 3068, 2962, 2921, 2849, 1663, 1604, 1495, 1418, 1368, 1302, 1261, 1141, 1087, 1031, 915, 802, 756, 703 cm^{-1}; HRMS (FAB$^+$): *m*/*z* calcd for $C_{17}H_{23}N_2O_2$: 287.1760: [*M*+H]$^+$; found: 287.1757.

The following is a representative procedure for the catalytic asymmetric 1,3-dipolar cycloaddition of azomethine imine **2e** (Table 2, Entry 8):

To a suspension of Mg turning (12 mg, 0.50 mmol) in THF (3 mL), 1,2-dibromoethane (144 mg, 0.50 mmol) was added at rt under an argon atmosphere and the mixture was stirred for 3 h until all Mg turning was converted to $MgBr_2$. To the solution, a EtCN (3 mL) solution of 1,4-pentadien-3-ol (**1**) (47 mg, 0.55 mmol) and (*R*,*R*)-DIPT (24 mg, 0.10 mmol) was added. After the addition of methylmagnesium bromide (0.75 mmol, 0.76 ml of 0.99 M solution in THF) at 0 °C, the mixture was stirred for 1 h. Azomethine imine **2e** (90 mg, 0.50 mmol) was added to the resulting solution and the mixture was stirred for 0.5 h at rt and then 2 d at 80 °C. The reaction was quenched by the addition of a sat. aqueous solution of NH_4Cl and the mixture was subsequently extracted with $CHCl_3$. The combined extracts were dried over Na_2SO_4 and condensed under reduced pressure. The residue was purified by column chromatography (SiO_2, hexane/AcOEt = 1:1 to 0:1) to give the corresponding pyrazolidine **3e** (91 mg, 69%) with a selectivity of 95% ee.

(*R*)-1-((1*R*,3*R*)-7-Oxo-3-phenylhexahydropyrazolo[1,2-*a*]pyrazol-1-yl)allyl (1*S*,4*R*)-4,7,7-trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carboxylate (**5**)

A CH_2Cl_2 (1 mL) solution of the pyrazolidine **3a** (85 mg, 0.33 mmol, 98% ee) was added to a mixture of (*S*)-camphanic chloride (217 mg, 1.00 mmol), triethylamine (0.14 mL, 1.00 mmol), and 4-(dimethylamino)pyridine (16 mg) in CH_2Cl_2 (1 mL) at rt under a nitrogen atmosphere and the mixture was stirred for 3 d at rt. Solvent was evaporated and the residue was partitioned between AcOEt and water, followed by extraction with AcOEt. The combined extracts were dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by TLC on SiO_2 (hexane/AcOEt = 1:1) to afford **5** (143 mg, 99%) as a solid. Diastereomerically pure **5** was obtained by recrystallization (Et_2O/hexane). R_f = 0.40 (hexane/AcOEt = 1:1); $[\alpha]_D^{25}$ +49 (*c* 1.43, $CHCl_3$); m.p. 164–165 °C (recrystallized from Et_2O/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.95 (s, 3H), 1.08 (s, 3H), 1.11 (s, 3H), 1.67 (ddd, 1H, *J* = 13.7, 9.6, 4.6 Hz), 1.90–2.02 (m, 1H), 1.92 (ddd, 1H, *J* = 13.3, 10.5, 4.6 Hz), 2.02 (ddd, 1H, *J* = 13.7, 9.2, 4.6 Hz), 2.38–2.53 (m, 3H), 2.60–2.67 (m, 1H), 2.95–3.05 (m, 1H), 3.21–3.27 (m, 1H), 3.77–3.84 (m, 1H), 4.25–4.32 (m, 1H), 5.48 (d, 1H, *J* = 10.5 Hz), 5.57 (d, 1H, *J* = 16.0 Hz), 5.90–5.99 (m, 2H), 7.22–7.25 (m, 2H), 7.32–7.38 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 9.4, 16.4, 16.6, 28.7, 30.4, 34.7, 38.3, 47.2, 54.0, 54.6, 67.1, 73.7, 77.2, 90.8, 121.1, 127.5, 128.2, 128.6, 131.0, 136.9, 165.8, 168.4, 177.8; IR (KBr) 2968, 2841, 1779, 1755, 1666, 1431, 1415, 1320, 1258, 1168, 1110, 1062 cm^{-1}; elemental analysis calcd (%) for $C_{25}H_{30}N_2O_5$: C 68.47, H 6.90, N 6.39; found: C 68.14, H 6.88, N 6.39. Crystal data: $C_{25}H_{30}N_2O_5$, *FW*. 438.52, monoclinic, *C*2, *a* = 28.417(2), *b* = 8.1392(7), *c* = 9.7820(7) Å, *V* = 2262.3(3) Å^3, β = 90.608(1)°, *Z* = 4. D_{calc} = 1.287 g/cm^3. *R* = 0.035 (R_w = 0.046) for 4763 reflections with $I > 3.00\sigma(I)$ and 290 variable parameters.

CCDC 948017 (**5**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(5*R*,7*R*)-7-((*R*)-1-Hydroxypropyl)-5-phenyltetrahydropyrazolo[1,2-*a*]pyrazol-1(5*H*)-one

To a MeOH (1.4 mL) solution of **3a** (99% ee, 52 mg, 0.20 mmol), potassium hydroxide (27 mg, 0.50 mmol) in H_2O and nickel/aluminum alloy (421 mg) were subsequently added at room temperature.[13] The mixture was stirred at room temperature for 3 d and filtered through a bed of Celite and the filtrate was condensed under reduced pressure. The residue was purified by column chromatography (SiO_2, AcOEt only) to give (5*R*,7*R*)-7-((*R*)-1-hydroxypropyl)-5-phenyltetrahydropyrazolo[1,2-*a*]pyrazol-1(5*H*)-one (18 mg, 35%) as an oil. R_f = 0.70 (AcOEt only); $[\alpha]_D^{25}$ +117 (*c* 0.18, EtOH); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.05 (t, *J* = 7.3 Hz, 3H), 1.41–1.52 (m, 1H), 1.57–1.64 (m, 1H), 2.39–2.51 (m, 2H), 2.76–2.91 (m, 3H), 3.35–3.39 (m, 1H), 3.61–3.65 (m, 1H), 3.76 (td, *J* = 8.7, 2.8 Hz, 1H), 3.83–3.89 (m, 1H), 6.29 (brs, 1H), 7.26–7.29 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 9.4, 26.6, 36.3, 41.1, 49.9, 61.0, 68.7, 73.3, 127.2, 128.3, 128.8, 138.0, 166.3; IR (neat) 3270, 2930, 1650, 1460, 1420, 1160, 980 cm^{-1}; HRMS (DART): *m*/*z* calcd for $C_{15}H_{21}N_2O_2$: 261.1603: [*M*+H]$^+$; found: 261.1593.

(6*S*,8*S*)-8-((*R*)-1-Hydroxypropyl)-6-phenyl-1,5-diazocan-2-one (**8**)

A EtOH (2 mL) solution of **3a** (99% ee, 52 mg, 0.20 mmol) was combined with Raney nickel (W-2) (100 mg, wet weight). The mixture was stirred at room temperature under 50 atm of hydrogen for 3 d.[11b] The mixture was filtered through a bed of Celite and condensed under reduced pressure. The residue was purified by column chromatography (SiO_2, AcOEt only ~ AcOEt/MeOH = 10:1) to give **8** as a solid. R_f = 0.30 (AcOEt/MeOH = 5:1); $[\alpha]_D^{25}$ –19 (*c* 0.27, $CHCl_3$); m.p. 97.5–99.0 °C (recrystallized from AcOEt); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.97 (t, *J* = 7.4 Hz, 3H), 1.41–1.48 (m, 2H), 1.92–1.99 (m, 1H), 2.22–2.34 (m, 2H), 2.36–2.43 (m, 1H), 2.54–2.62 (m, 1H), 2.76–2.83 (m, 1H), 3.08–3.15 (m, 1H), 3.21–3.27 (m, 1H), 3.52–3.56 (m, 1H), 3.55 (br, 1H), 4.08 (td, *J* = 4.1, 10.5 Hz, 1H), 7.17–7.32 (m, 5H). Signal of one OH or NH proton was not observed clearly; ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 10.2, 28.3, 30.3, 32.8 (2C), 43.6, 56.6, 75.8, 126.0, 128.2, 128.5, 141.6, 172.7; IR (KBr) 3310, 2960, 1640, 1440, 1300, 1100, 1000 cm^{-1}; HRMS (DART): *m*/*z* calcd for $C_{15}H_{23}N_2O_2$: 263.1760: [*M*+H]$^+$; found: 263.1771.

(2*R*,2a*R*,4*R*)-4-Phenyl-2-vinylhexahydro-2*H*-1-oxa-2a^1,4a-diazacyclopenta[*cd*]pentalene (**9**)

To a suspension of $LiAlH_4$ (12 mg, 0.30 mmol) in THF (1.0 mL) was added a THF (0.5 mL) solution of **3a** (99% ee, 39 mg, 0.15 mmol) at 0 °C and the resultant suspension was stirred for 2 h under refluxing. After the reaction was cooled to 0 °C, H_2O (0.01 mL), 30% NaOH aq (0.01 mL), and H_2O (0.03 mL) were subsequently added, followed by stirring for 30 min at rt. The mixture was filtered through a bed of Celite and the filtrate was condensed under reduced pressure. The residue was purified by TLC on SiO_2 (hexane/AcOEt = 1:1) to afford **9** (32 mg, 88%) as an oil. R_f = 0.40 (hexane/AcOEt = 2:1); $[\alpha]_D^{25}$ +117 (*c* 0.39, EtOH); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.29–2.33 (m, 3H), 2.39–2.46 (m, 1H), 2.88–2.94 (m, 1H), 3.10–3.16 (m, 1H), 3.64–3.66 (m, 1H), 3.92 (dd, *J* = 11.0, 5.9 Hz, 1H), 4.32–4.33 (m, 1H), 5.11–5.15 (m, 2H), 5.25 (d, *J* = 15.5 Hz, 1H), 5.84 (ddd, *J* = 15.5, 11.0, 5.9 Hz, 1H), 7.17–7.21 (m, 1H), 7.27 (t, *J* = 7.1 Hz, 2H), 7.36 (d, *J* = 7.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 32.9, 44.5, 50.5, 67.8, 68.1, 86.3, 97.6, 116.1, 127.2, 127.4, 128.4, 136.3, 140.9; IR (KBr) 2940, 1640, 1490, 1450, 1300, 1090 cm^{-1}; HRMS (FAB$^+$): *m*/*z* calcd for $C_{15}H_{19}N_2O$: 243.1497: [*M*+H]$^+$; found: 243.1501.

(*R*)-1-((1*R*,3*R*)-3-Phenylhexahydropyrazolo[1,2-*a*]pyrazol-1-yl)prop-2-en-1-ol (**10**)

To a suspension of $LiAlH_4$ (151 mg, 4.0 mmol) in THF (8.0 mL) was added a THF (2.0 mL) solution of **3a** (99% ee, 103 mg, 0.40 mmol) at 0 °C and the resultant suspension was stirred for 1 h under refluxing. After the reaction was cooled to 0 °C, H_2O (0.15 mL), 30% NaOH aq (0.15 mL), and H_2O (0.45 mL) were subsequently added, followed by stirring for 30 min at rt. The mixture was filtered through a bed of Celite and the filtrate was condensed under reduced pressure. The residue was purified by column chromatography (SiO_2, AcOEt only ~ AcOEt/MeOH = 10:1~5:1) to afford **10** (60 mg, 61%) as a solid. R_f = 0.35 (AcOEt/MeOH = 5:1); $[\alpha]_D^{25}$ +3 (*c* 0.61, EtOH); m.p. 122.0–125.0 °C (recrystallized from AcOEt); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.02–2.14 (m, 2H), 2.24–2.31 (m, 1H), 2.43–2.54 (m, 3H), 2.94–3.01 (m, 1H), 3.12 (brs, 1H), 3.17–3.24 (m, 1H), 3.60 (br, 1H), 4.08–4.12 (m, 1H), 4.36 (brs, 1H), 5.19 (dd, *J* = 10.5, 1.4 Hz, 1H), 5.37 (dd, *J* = 17.0, 1.4 Hz, 1H), 5.90 (ddd, *J* = 17.0, 10.5, 5.5 Hz, 1H), 7.24–7.28 (m, 1H), 7.30 (t, *J* = 7.1 Hz, 2H), 7.39 (d, *J* = 7.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 25.9, 35.3, 46.7, 51.0, 65.1, 67.1, 74.6, 115.5, 127.2, 127.7, 128.3, 139.0, 139.6; IR (KBr) 3086, 2974, 1641, 1603, 1494, 1449, 1361, 1286, 1140, 1061, 932, 766 cm^{-1}; HRMS (DART): *m*/*z* calcd for $C_{15}H_{21}N_2O$: 245.1654: $[M+H]^+$; found: 245.1650.

(1*R*,3*R*)-1-((*R*)-1-Hydroxyallyl)-7-oxo-3-phenylhexahydro-1*H*-pyrazolo[1,2-*a*]pyrazole 4-oxide (**11**)

To a CH_2Cl_2 (2 mL) solution of **3a** (99% ee, 52 mg, 0.20 mmol), *m*CPBA (70%, 48 mg, 0.19 mmol) was added at 0 °C and the resulting solution was stirred at rt for 1 h. A sat. aqueous solution of $NaHCO_3$ was added and the mixture was subsequently extracted with $CHCl_3$. The aqueous layer was separated and extracted with $CHCl_3$. The combined organic layers were dried over Na_2SO_4 and condensed under reduced pressure. The mixture was filtered through a bed of Celite and condensed under reduced pressure. The residue was purified by column chromatography (SiO_2, hexane/AcOEt = 1:1 ~ AcOEt only ~ AcOEt/MeOH = 5:1~1:1) to give **11** as an oil. R_f = 0.30 (AcOEt/MeOH = 5:1); $[\alpha]_D^{25}$ +30 (*c* 0.45, EtOH); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.44–1.53 (m, 1H), 2.10 (br, 1H), 2.77–2.87 (m, 2H), 3.65–3.71 (m, 1H), 3.96–4.03 (m, 1H), 4.14–4.21 (m, 1H), 4.24–4.26 (m, 1H), 4.90 (tt, *J* = 7.4, 1.4 Hz, 1H), 5.04 (d, *J* = 8.2 Hz, 1H), 5.24 (dt, *J* = 10.5, 1.4 Hz, 1H), 5.49 (dt, *J* = 16.9, 1.4 Hz, 1H), 5.97 (ddd, *J* = 16.9, 10.5, 5.0 Hz, 1H), 7.28–7.29 (m, 2H), 7.45–7.42 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 32.1, 33.2, 61.4, 63.0, 71.4, 88.4, 116.0, 129.4, 129.9, 131.0, 132.9, 138.9, 169.3; IR (KBr) 3400, 2930, 1730, 1645, 1450, 1350, 1280, 1200, 980 cm^{-1}; HRMS (DART): *m*/*z* calcd for $C_{15}H_{19}N_2O_3$: 275.1396: $[M+H]^+$; found: 275.1395.

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[9] In the ^{1}H NMR spectrum of the crude products, production of other diastereomers was not observed.

[10] The reaction was designed on the assumption that Grignard reagent (R'MgX) used was consumed by equiamount of hydroxyl groups in both **1** and DIPT to initially form the corresponding halomagnesium alkoxides accompanied with generation of alkene (R'H). Therefore, the kind of alkyl group (R') in Grignard reagent did not affect the reaction.

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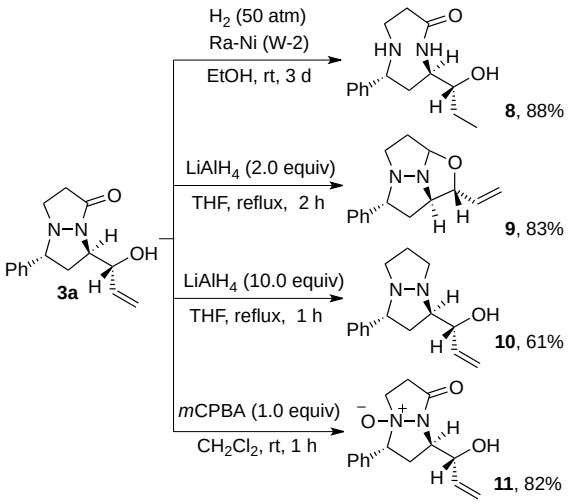
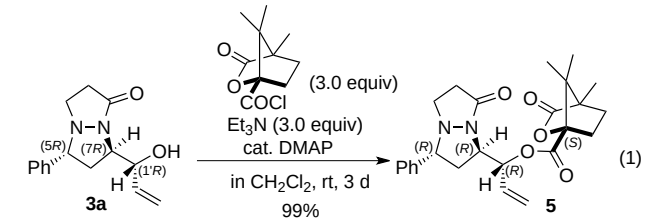
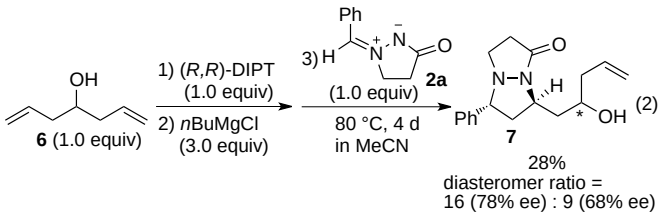


Scheme 1. Transformation of **3a**.



Equation 1. Derivatization of **3a** to **5**



Equation 2. Desymmetrization of the homoallylic-type dialkenyl carbinol, 1,6-heptadien-4-ol (**6**)

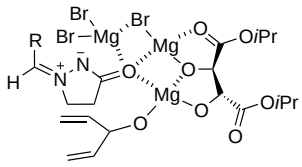


Figure 1. Intended asymmetric 1,3-dipolar cycloaddition of an azomethine imine to 1,4-pentadien-3-ol.

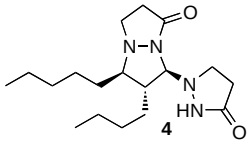


Figure 2. By-product **4**.

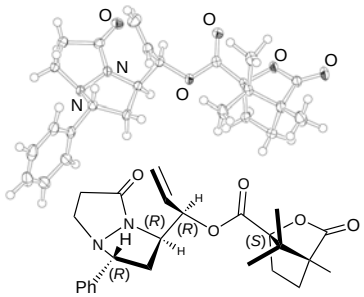


Figure 3. X-ray structure of compound **5**.

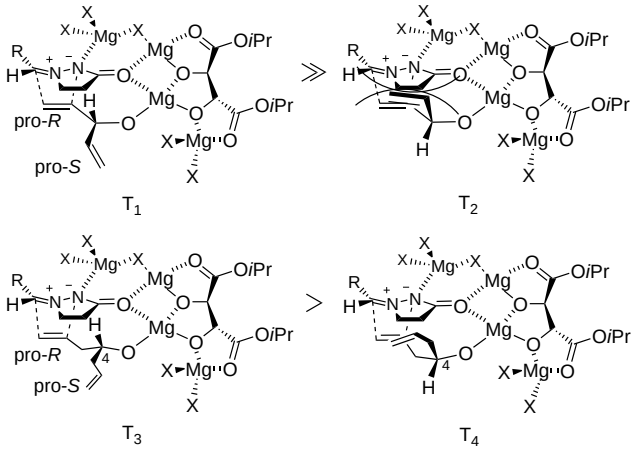
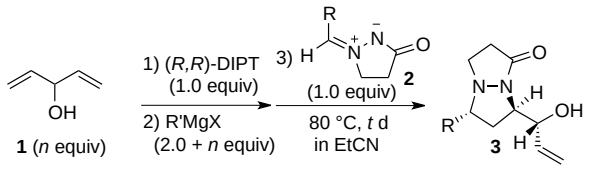


Figure 4. Proposed transition states during the 1,3-dipolar cycloaddition of an azomethine imine to **1** (T_1) and **6** (T_3).

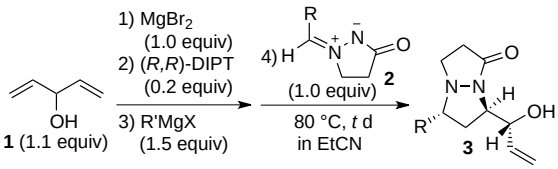
Table 1. Desymmetrization of 1,4-pentadiene-3-ol (**1**) by the stoichiometric asymmetric 1,3-dipolar cycloaddition of azomethine imines **2**



Entry	R'MgX	*n*	R		*t*/d	Yield/%	ee/%[a]
1[b]	MeMgBr	1.0	Ph	**a**	2	50	98
2	MeMgBr	1.0			2	57	99
3	*n*BuMgCl	1.0			2	93	99
4	*n*BuMgCl	1.0	*p*MeOC$_6$H$_4$	**b**	2	98	99
5	*n*BuMgCl	1.0	*p*ClC$_6$H$_4$	**c**	2	97	99
6	*n*BuMgCl	1.0	*n*C$_5$H$_{11}$	**d**	2	14[c]	63
7	*n*BuMgCl	3.0			2	33[c]	97
8	*n*BuMgCl	1.0	*c*C$_6$H$_{11}$	**e**	3	80	99
9	*n*BuMgCl	1.0	*t*Bu	**f**	3	56	98

[a] Enantioselectivities were determined by HPLC analysis (Daicel CHIRALCEL OD-H). [b] Solvent was MeCN instead of EtCN. [c] By-product **4**, produced via rearrangement of **2d** to an enamine intermediate, was obtained in 33% (Entry 6) and 27% (Entry 7) yields, respectively.

Table 2. Desymmetrization of 1,4-pentadiene-3-ol (**1**) by the catalytic asymmetric 1,3-dipolar cycloaddition of azomethine imines **2**



Entry	R'MgX	R		*t*/d	Yield/%	ee/%[a]
1	*n*BuMgCl	Ph	**a**	5	30	84
2	MeMgBr			2	68	95
3[b]	MeMgBr			2	64	91
4	MeMgBr	*p*MeOC$_6$H$_4$	**b**	5.5	40	93
5	MeMgBr	*p*ClC$_6$H$_4$	**c**	5.5	60	96
6	MeMgBr	*n*C$_5$H$_{11}$	**d**	2	13[c]	79
7[d]	MeMgBr			2	10[c]	85
8	MeMgBr	*c*C$_6$H$_{11}$	**e**	2	69	95
9	MeMgBr	*t*Bu	**f**	5.5	75	98

[a] Enantioselectivities were determined by HPLC analysis (Daicel CHIRALCEL OD-H). [b] $MgBr_2$ was not added in step 1. [c] By-product **4** was obtained in 24% (Entry 6) and 27% (Entry 7) yields, respectively. [d] 2.2 Equiv of **1** and 2.6 equiv of MeMgBr were employed.

Entry for the Table of Contents (Please choose one layout only)

Layout 2:

Desymmetrization
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Mari Yoshida, Naotaro Sassa, Tomomitsu Kato, Shuhei Fujinami, Takahiro Soeta, Katsuhiko Inomata, and Yutaka Ukaji *
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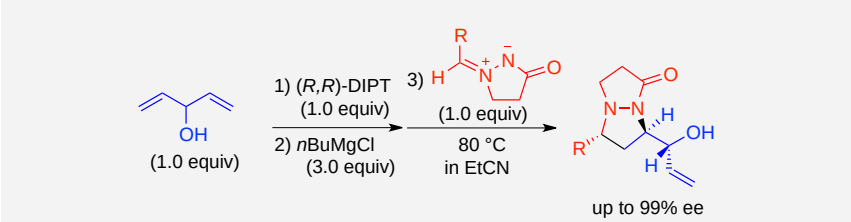
Desymmetrization of 1,4-Pentadien-3-ol by the Asymmetric 1,3-Dipolar Cycloaddition of Azomethine Imines



Desymmetrization of the divinyl carbinol, 1,4-pentadien-3-ol, was achieved by the asymmetric 1,3-dipolar cycloaddition of azomethine imines, using diisopropyl (*R*,*R*)-tartrate as the chiral auxiliary, to afford the corresponding optically active *trans*-pyrazolidines with excellent regio-, diastereo-, and enantioselectivity.

Keywords:

desymmetrization • 1,3-dipolar cycloaddition • azomethine imine • pyrazolidine • diisopropyl (*R*,*R*)-tartrate

core keyword list