Regioselective Formation of Optically Active Cycloheptatrienes by Chiral Tethered Büchner Reaction

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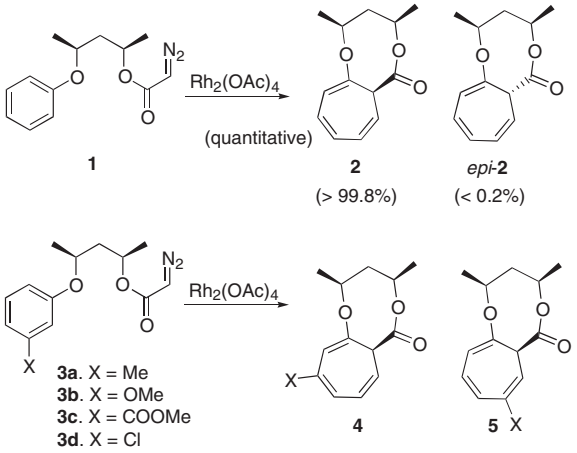
Optically active cycloheptatrienes were prepared by addition of the rhodium carbenoid to polysubstituted phenyl rings connected by a 2,4-pentanediol tether in sufficient regio- and stereoselectivity.

The chiral tethered reaction is a versatile reaction design for asymmetric synthesis where strict stereocontrol can be achieved during the reaction between reagent and substrate elements connected by a chiral 2,4-pentanediol (PD) tether.[1] Chiral cycloheptatrienes in optically active forms became available by applying this reaction design to the Büchner reaction.[2,3] The PD-tethered carbenoid addition with **1** is highly stereocontrolled to result in a quantitative yield of **2** with no trace formation of *epi*-**2** (<0.2%).[4] In addition to the high stereoselectivity, reactions with substrates, **3a**[4] and **3b**,[5] having a substituent at the 3-position (*m*-position) proceed regioselectively to give **4** exclusive of **5**.

Regioselectivity in the Büchner reaction is generally poor for the intermolecular addition to substituted benzenes,[6] but intramolecular reactions of some *m*-methoxy derivatives showed high regioselectivity.[7,8] However, the selectivity is dependent on the substituents, and the *m*-methyl or 3,4-dimethoxy analogue showed poorer selectivity even in the same intramolecular conditions. In this sense, the high regioselectivity observed with both **3a** and **3b** is remarkable, and the extension of this PD-tethered reaction to other *m*-substituted substrates is worthy of examination. The high regioselectivity of the PD-tethered reaction is now confirmed for substrates with the electron-withdrawing *m*-substituents, and more challenging selectivity with unsymmetrically 3,5-disubstituted substrates are further achieved with manipulation of the rhodium catalyst. Various optically active cycloheptatrienes are generally available from the reaction using proper phenol derivatives as starting materials.



Scheme 1.

The first two substrates, **3c** and **3d**,[9] have electron-withdrawing *m*-substituents, the directing effects of which on electrophilic additions are different. When **3c** was treated with $Rh_2(OAc)_4$ in dichloromethane (1.5 M) at room temperature (30 min), intramolecular addition did not proceed quantitatively as did with **1** and **3a–b**, and gave **4c** only in 26% yield after silica gel chromatography. The obtained **4c** was regio- and stereochemically pure, and its regio- and stereoisomers were not detected in the reaction mixture. The low reactivity due to the electron deficiency at the aromatic ring was overcome by using a $Rh_2(OCOCF_3)_4$ catalyst. The product yield was improved to 78%, while a mixture of **4c** and **5c** was produced in a ratio of 95:5 (Table 1).[10]

The treatment of **3d** with $Rh_2(OAc)_4$ catalyst produced **4d** in 50% yield. The yield for the intramolecular addition can be improved again with $Rh_2(OCOCF_3)_4$ to 90%, but in this reaction, the loss in the regiocontrol is obvious because it gives a mixture of **4d** and **5d** in a ratio of 65:35. The high product yield (80%) and the strict regiocontrol (>98%) as well as the stereocontrol could be achieved with **3d** when $Rh_2(OCOCPh_3)_4$[11] was employed as a catalyst. Through the reaction with the *m*-substituted substrates **3a–d**, the regioselectivity of the intramolecular addition is generally high, and is not much affected by the electronic nature of *m*-substituent. It was also disclosed that optically active cycloheptatrienes having electron-withdrawing groups can also be obtained in a good yield by using $Rh_2(OCOCPh_3)_4$.

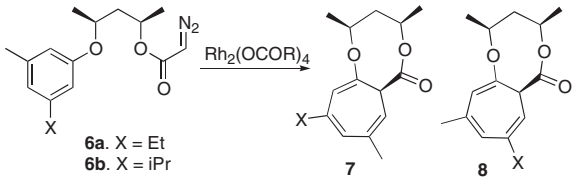
The regiocontrol with **3a–d** must be due to the relative geometry of the rhodium carbenoid to the internal reaction sites of the aromatic ring by the tethering. The differentiation of the two *m*-positions, substituted vs unsubstituted (X vs H in **3** to lead to **4** vs **5**) was extended to the differentiation of two different *m*-substituents, X vs methyl. For the sake of simplicity in analysis of the steric factors, two substrates **6a** and **6b** were employed to compare the methyl group with ethyl and isopropyl; the former is more challenging than the latter in their differentiation.

The 3,5-disubstituted substrates **6a** and **6b** were synthesized according to the procedure for the other substrates.[12,13] When they were treated with $Rh_2(OAc)_4$ in dichloromethane at room temperature, mixtures of regioisomers **7** and **8** were produced in ratios of 55:45 from **6a** and 74:26 from **6b**. The $Rh_2(OCOCF_3)_4$ catalyst reduced the regioselectivity to give approximately equal amounts of **7** and **8**. Improvement of the regioselectivity with **6b** was achieved by using catalysts having bulkier ligands, and the observed regioselectivity increased with their bulkiness; acetate < octanoate < pivalate < triphenlyacetate (Table 1). As a result, **7b** was obtained in over 98% regio-

Table 1. Regioisomeric ratios of **4** vs **5** and **7** vs **8** for the reaction of **3c–d** and **6a–b**, respectively, with varied rhodium catalysts[a]

Substrate	$Rh_2(OAc)_4$	$Rh_2(OCOCF_3)_4$	$Rh_2(OCOC_7H_{15})_4$	$Rh_2(OCOt\text{-}Bu)_4$	$Rh_2(OCOCPh_3)_4$
3c	>98:<2	95: 5	—	—	>98:<2
3d	>98:<2	65:35	—	—	>98:<2
6a[b]	55:45	50:50	58:42	69:31	81:19
6b[b]	74:26	50:50	82:18	86:14	>98:<2

[a] The reaction was carried out at room temperature, and the isomeric retios were determined by ^{1}H NMR of the reaction mixture.
[b] The reaction mixture contained only **7** and **8** except for the adduct with contaminated water.

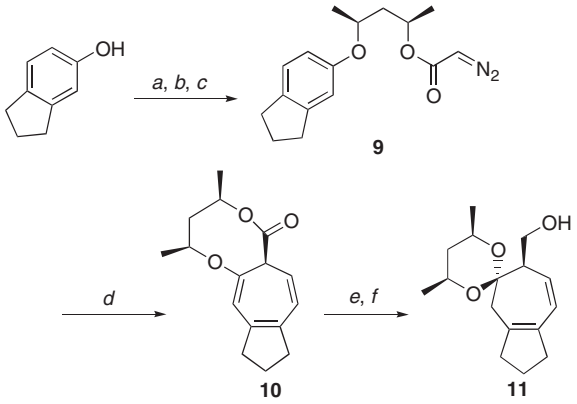


Scheme 2.

chemical purity from the reaction of **6b** with $Rh_2(OCOCPh_3)_4$. The reaction of **6a** differentiating methyl and ethyl groups was more difficult to control. The selectivity with $Rh_2(OAc)_4$ could be improved with bulkier catalysts though the regioselectivity was not high enough even with very bulky $Rh_2(OCOCPh_3)_4$ (up to **7a**:**8a** = 4:1).

Generality of the regiocontrol by *m*-substituent was then demonstrated with a 3,4-disubstituted substrate **9**. Starting with 5-hydroxyindane, four-step conversion proceeded under strict regiocontrol (>98%) as well as stereocontrol to give a single isomer of ring-fused cycloheptatriene **10** (Scheme 3). Although **10** is not fully stable for epimerization or olefinic isomerization,[14] its two-step conversion gave a stable and stereochemically pure compound **11**, a potent chiral synthon for polyquinane terpenoids.[15]

The regioselectivity of the PD-tethered Büchner reaction was found to be controlled and enhanced by the steric bulkiness of the ligands of the catalyst. The results display an additional advantage of the PD-tethered reaction inaccessible with conventional inter- and intramolecular reactions.



Scheme 3. Reagents and conditions. a: (2*R*,4*R*)-2,4-pentanediol/diisopropyl azodicarboxylate/PPh_3 (74.3%), b: diketene/triethylamine (91.2%), c: TsN_3/triethylamine, then 1 M NaOH aq (87.3%), d: $Rh_2(OAc)_4$ (82.8%), e: $LiAlH_4$/−78 °C (quant.), f: TsOH·Py/THF/rt (70.6%).

References and Notes

1 T. Sugimura, in "Recent Research Developments in Organic Chemistry," ed. by S. G. Pandalai, Transworld Research Network, Trivandrum (1998), Vol. 2, pp 47–53.
2 T. Sugimura, S. Nagano, and A. Tai, *Chem. Lett.*, **1998**, 45.
3 For Büchner reaction, see: H. M. L. Davies, in "Comprehensive Organic Synthesis," ed. by B. M. Trost, Pergamon, Oxford (1991), Vol. 4, pp 1031–1067; G. Mass, in "Topics in Current Chemistry," Springer-Verlag, Berlin (1987), Vol. 137, pp 75–253; M. P. Doyle, M. A. McKervey, and T. Ye, "Modern Catalytic Methods for Organic Synthesis with Diazo Compounds," Wiley, New York (1998), Chap. 6.
4 T. Sugimura, K. Hagiya, Y. Sato, T. Tei, A. Tai, and T. Okuyama, *Org. Lett.*, **3**, 37 (2001).
5 T. Sugimura, M. Kagawa, K. Hagiya, and T. Okuyama, *Chem. Lett.*, **2002**, 260.
6 A. J. Anciaux, A. Demonceau, A. F. Noels, A. J. Hubert, R. Warin, and P. Teyssie, *J. Org. Chem.*, **46**, 873 (1981).
7 M. P. Doyle, M. S. Shanklin, and H. Q. Pho, *Tetrahedron Lett.*, **29**, 2639 (1988).
8 M. Kennedy, M. A. McKervey, A. R. Maguire, S. M. Tuladhar, and M. F. Twohig, *J. Chem. Soc., Perkin Trans. 1*, **1990**, 1047.
9 The substrates **3c** and **3d** were prepared by applying the reported method[2] as follows: a) Mitsunobu reaction of (2*R*,4*R*)-2,4-pentanediol with 3-chlorophenol or 3-methoxycarbonylphenol (79.6 and 86.5% yields, respectively), b) formation of acetoacetate ester with diketene and triethylamine (89.3 and 88.3%), treatment with *p*-tosyl azide and triethylamine, and then c) reaction with aqueous sodium hydroxide (85.1 and 79.5%). Stereochemical purities of **3** were confirmed as over 99% pure by GLC analysis after necessary conversions.
10 This catalyst was also effective for *p*-methoxycarbonyl substrate. The product yield by $Rh_2(OAc)_4$ (31.7%) was improved to 68.7%.
11 S. Hashimoto, N. Watanabe, and S. Ikegami, *Tetrahedron Lett.*, **33**, 2709 (1992); S. Hashimoto, N. Watanabe, and S. Ikegami, *J. Chem. Soc., Chem. Commun.*, **1992**, 1508.
12 5-Ethyl-3-methylphenol was prepared from 5-methylresorcinol by the sequence of *i*-PrBr/K_2CO_3 (46.9%), Tf_2O/Et_3N (96.5%), EtMgBr/$NiCl_2$dppe (58.7%), and BBr_3 (quant).
13 Isolated yields for the three-steps preparation procedure shown in the Ref. 9: For **6a**, a) ca. 70%, b) 84.8%, c) 76.4%. For **6b**, a) 67.5%, b) 95.2%, c) 63.4%.
14 T. Sugimura, W. H. Kim, M. Kagawa, and T. Okuyama, *Org. Lett.*, **4**, 2059 (2002).
15 L. A. Paquette and A. M. Doherty, "Polyquinane Chemistry," Springer-Verlag, New York (1987).

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