Asymmetric Cycloadditions

Asymmetric Induction in Ruthenium-Catalyzed [2+2] Cycloadditions between Bicyclic Alkenes and a Chiral Acetylenic Acyl Sultam**

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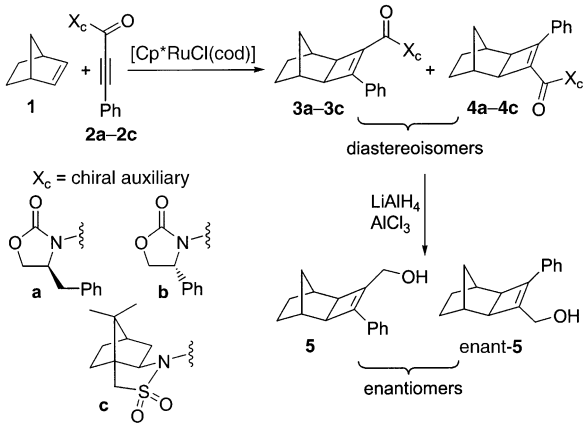
Cycloaddition reactions of unactivated alkenes, alkynes, and dienes usually require extreme reaction conditions, such as high temperature and high pressure, for the cycloadducts to be formed in good yields. Transition-metal catalysts provide new opportunities for highly selective cycloaddition reactions, as the complexation of the metal to an alkene, alkyne, or diene significantly modifies the reactivity of this moiety, thus opening up possibilities for enhanced reactivity and novel reactions.[1] One of the most important consequences of complexation to a transition metal is the temporary polarization and activation of an otherwise unreactive species. The rate enhancements observed in the presence of the metal catalyst, and the potential to carry out asymmetric transformations by the use of chiral ligands or chiral auxiliaries are among the most attractive features of this strategy.

Recent developments in transition-metal-catalyzed [2+2+1],[2] [4+2],[3] [5+2],[4] [4+4],[5] and [6+2][6] cycloadditions have provided efficient methods for the construction of five- to eight-membered rings. We and others have studied various aspects of transition-metal-catalyzed [2+2] cycloadditions between alkenes and alkynes for the synthesis of cyclobutene rings, including the development of novel catalysts, studies on the reactivity of the reaction partners, and investigations into regioselectivity with unsymmetrical substrates.[7–10] However, to the best of our knowledge, no asymmetric version of transition-metal-catalyzed [2+2] cycloadditions between alkenes and alkynes has been reported in the literature. Herein, we report our first results of studies on asymmetric induction in ruthenium-catalyzed [2+2] cycloadditions of bicyclic alkenes with alkynes that bear a chiral auxiliary (Scheme 1). The cycloaddition of a bicyclic alkene



Scheme 1. Ruthenium-catalyzed [2+2] cycloaddition of norbornene (**1**) with chiral alkynes.

with an alkyne could give rise to two stereoisomers (*exo* or *endo* cycloadducts). However, based on our previous studies on ruthenium-catalyzed [2+2] cycloadditions of bicylic alkenes with alkynes[10] we anticipated that only *exo* cycloadducts would be formed. The cycloaddition of norbornene (**1**) with a chiral alkyne **2** could result in the formation of two *exo* diastereoisomers **3** and **4**. Removal of the chiral auxiliary would provide **5** and its enantiomer.

We first prepared the chiral acetylenic acyl carbamates **2a** and **2b** and the chiral acetylenic acyl sultam **2c** from the oxazolidinones of Evans and the sultam of Oppolzer.[11b] These chiral alkynes showed a high level of asymmetric

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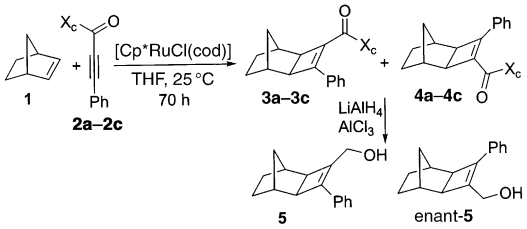
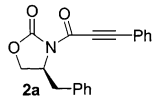
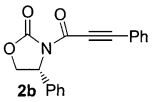
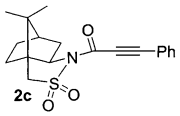
induction in cobalt-mediated Pauson–Khand [2+2+1] cycloadditions.[11] The results of our ruthenium-catalyzed [2+2] cycloadditions of **2a–c** with **1** are shown in Table 1. As observed previously,[10] these cycloadditions were found to be

Table 1: Ruthenium-catalyzed [2+2] cycloadditions between **1** and alkynes with different chiral auxiliaries.[a]



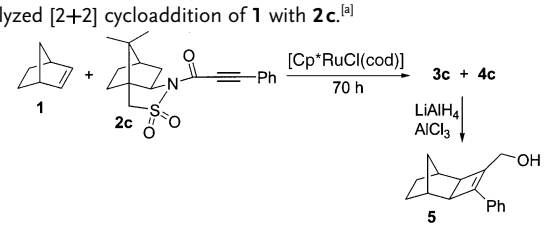
Entry	Alkyne	Yield[b] [%]	d.r.[c] (**3**/**4**)	*ee* (**5**)[d] [%]
1	 **2a**	97	1.3:1	nd[e]
2	 **2b**	80	1.3:1	nd[e]
3	 **2c**	94	131:1	98.5

[a] All reactions were carried out with 3 equivalents of **1** (with respect to the alkyne) and 5–10 mol% of [Cp*RuCl(cod)]. [b] Yield of isolated products (**3c+4c**). [c] The diastereomeric ratio was determined by NMR (400 MHz) or HPLC. [d] The *ee* value of **5** was determined by HPLC on a chiral phase (Chiralcel OJ-H column); see Supporting Information for details. [e] Not determined.

completely stereoselective for the *exo* cycloadducts, but high yielding only in the presence of excess norbornene (**1**; 3 equiv). Although the chiral alkynes **2a** and **2b**, which bear Evans oxazolidinones, gave a low level of asymmetric induction in the cycloadditions, the ruthenium-catalyzed [2+2] cycloadditions of **1** with the chiral acetylenic acyl sultam **2c** were found to be highly diastereoselective and to give the two diastereoisomers **3c** and **4c** in a 131:1 ratio. Upon removal of the recoverable chiral auxiliary (the camphorsultam of Oppolzer), compound **5** was formed with 98.5% *ee*. We believe that the exceptionally high level of asymmetric induction observed in the ruthenium-catalyzed [2+2] cycloadditions of **1** with **2c** (but not with the chiral acetylenic acyl carbamates **2a** and **2b**) may arise from coordination of the sulfone oxygen atom of the sultam with the ruthenium metal center.[12]

The effect of the temperature and the solvent on the asymmetric induction in the ruthenium-catalyzed [2+2] cycloadditions of **1** with **2c** was studied (Table 2). When the cycloadditions were carried out in THF, an increase in the temperature from 25 to 50 °C led to a decrease in the diastereoselectivity from d.r. 131:1 to 64:1. No further decrease in the diastereoselectivity was observed when the

Table 2: Effect of the temperature and of the solvent in the ruthenium-catalyzed [2+2] cycloaddition of **1** with **2c**.[a]



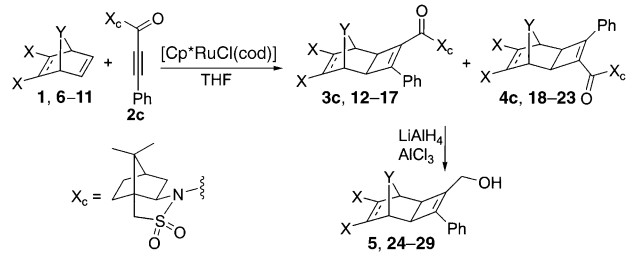
Entry	Solvent[b]	*T* [°C]	Yield [%][c]	d.r. (**3c**/**4c**)[d]	*ee* (**5**) [%][e]
1	THF	25	95	131:1	98.5
2	THF	50	95	64:1	nd[f]
3	THF	80	99	64:1	nd[f]
4	THF/Et_3N (1:1)	25	95	114:1	98
5	DME	25	76	132:1	nd[f]
6	diglyme	25	90	126:1	nd[f]

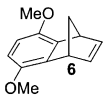
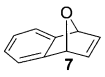
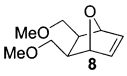
[a] All reactions were carried out with 3 equivalents of **1** (with respect to the alkyne) and 5–10 mol% of [Cp*RuCl(cod)]. [b] The use of other solvents, such as DMSO, DMF, toluene, hexanes, and 1,2-dichloroethane, led to very low yields. [c] Yield of isolated products (**3c+4c**). [d] The diastereomeric ratio was determined by HPLC. [e] The *ee* value of **5** was determined by HPLC on a chiral phase (Chiralcel OJ-H column; see Supporting Information for details). [f] Not determined.

temperature was increased to 80 °C (Table 2, entries 1–3). Ethereal solvents (THF, 1,2-dimethoxyethane (DME), and diglyme) were found to be the most effective in the cycloadditions in terms of the yields and levels of asymmetric induction observed. The use of other solvents, such as dimethyl sulfoxide (DMSO), dimethyl formamide (DMF), toluene, hexanes, and 1,2-dichloroethane, led to very low yields ($<20\%$).[10a]

To test the generality of the asymmetric induction in the ruthenium-catalyzed [2+2] cycloaddition, we studied the reactions of various bicyclic alkenes (**6–11**) with **2c** (Table 3; for detailed experimental procedures, compound characterization data, and HPLC traces, see Supporting Information). All the bicyclic alkenes were found to undergo completely stereoselective cycloaddition reactions to give only the *exo* cycloadducts. The cycloadditions of 2,3-dibromonorbornadiene (**10**) and 7-phenylnorbornadiene (**11**) were also completely regioselective (Table 3, entries 6 and 7) and only occurred at the less-hindered, less-substituted double bond. Similar to with norbornene (**1**) (Table 3, entry 1), both the yield and the diastereoselectivity observed in the cycloaddition of **6** with **2c** were very high (98% yield, d.r. 163:1; Table 3, entry 2). Removal of the chiral auxiliary provided compound **24** with 98.8% *ee*. This is the highest *ee* value we have observed in ruthenium-catalyzed [2+2] cycloadditions with **2c**. High levels of asymmetric induction were also observed with the 7-oxanorbornenes **7** and **8** (94 and 95% *ee* after removal of the chiral auxiliary), although the yields were only moderate (78% and 73%, respectively; Table 3, entries 3 and 4). The levels of asymmetric induction observed in the cycloadditions of norbornadiene (**9**) and its derivatives **10** and **11** were significantly lower (Table 3, entries 5–7) than those observed for **1** and its derivatives (usually $>94\%$ *ee*; Table 3, entries 1–4). Whereas **9** reacted with **2c** to give the diastereomeric cycloadducts with d.r. 8:1 at 25 °C and d.r. 5:1

Table 3: Ruthenium-catalyzed [2+2] cycloadditions of **2c** with alkenes.[a]



Entry	Alkene	T [°C]	t [h]	Yield[b] [%]	d.r.	ee[c] [%]
1	 **1**	25	70	94	131:1[d]	98.5
2	 **6**	25	70	98	163:1[e]	98.8
3	 **7**	25	70	78	33:1[f]	94
4	 **8**	25	168	73	35:1[f]	95
5	 **9**	25	168	27[g]	8:1[f]	75
		65	168	89	5:1[e]	67
6	 **10**	25	70	85	10:1[f]	83
7	 **11**	25	168	44[g]	24:1[f]	90

[a] All reactions were carried out with 3 equivalents of the alkene (with respect to the alkyne) and 5–10 mol% of [Cp*RuCl(cod)]. [b] Yield of isolated cycloadducts. [c] The *ee* values of **5** and **24**–**29** were determined by HPLC on a chiral phase (Chiralcel OJ-H column; see Supporting Information for details). [d] The diastereomeric ratio of the cycloadducts was determined by HPLC. [e] The diastereomeric ratio of the cycloadducts was determined indirectly from the *ee* value of the product obtained upon removal of the auxiliary. [f] The diastereomeric ratio of the cycloadducts was determined by ^{1}H NMR spectroscopy (400 MHz). [g] The cycloaddition did not proceed to completion and starting materials were recovered.

at 65 °C, 2,3-dibromonorbornadiene (**10**) and 7-phenylnorbornadiene (**11**) reacted with **2c** to provide the corresponding diastereomeric cycloadducts with d.r. 10:1 and 24:1, respectively.

In conclusion, we have demonstrated asymmetric induction in ruthenium-catalyzed [2+2] cycloadditions between alkenes and alkynes. The cycloadditions were found to be highly stereo- and regioselective, and excellent levels of asymmetric induction (up to 98.8% *ee* after removal of the recoverable chiral auxiliary) were observed. This method is a mild and simple procedure for the asymmetric construction of cyclobutene ring systems. Further investigations into the source of the asymmetric induction in the cycloadditions, the scope of the reaction, and the application of this method to the asymmetric synthesis of four-membered-ring-containing natural products are currently in progress in our laboratory.

Experimental Section

Typical procedure: A mixture of **1** (27.1 mg, 0.288 mmol), **2c** (30.6 mg, 0.089 mmol), and THF (0.4 mL) in an oven-dried vial was added through a cannula to an oven-dried screw-cap vial containing [Cp*RuCl(cod)] (weighed out from a dry box, 4.4 mg, 0.012 mmol; Cp* = 1,2,3,4,5-pentamethylcyclopentadiene) under nitrogen. The residue in the first vial was then dissolved in THF (0.1 mL) and added through a cannula to the reaction mixture. The reaction mixture was stirred in the dark at 25 °C for 70 h. The crude product was purified by column chromatography (EtOAc/hexanes 1:9) to give an inseparable mixture of the cycloadducts **3c** and **4c** (14.8 mg, 0.052 mmol, 95%, d.r. 131:1 (determined by HPLC)) as a white solid (m.p. 155–158 °C, hexanes/CH_2Cl_2). $R_f = 0.44$ (EtOAc/hexanes 3:7); HPLC (C-18 column, 1 mL min^{-1}, 20% acetonitrile/water, 254 nm): t_R (major diastereomer): 11.85 min, t_R (minor diastereomer): 8.59 min; IR (CH_2Cl_2): $\tilde{\nu} = 3054$ s, 2987 m, 2966 m, 2875 w, 1669 w, 1422 m, 1266 vs, 1167 w, 1059 cm^{-1} w; ^{1}H NMR ($CDCl_3$, 400 MHz, major diastereomer): $\delta = 7.84$–7.86 (m, 2H), 7.26–7.36 (m, 3H), 4.11 (m, 1H), 3.50 (d, $J = 13.6$ Hz, 1H), 3.43 (d, $J = 13.6$ Hz, 1H), 3.29 (br d, $J = 2.9$ Hz, 1H), 2.85 (br d, $J = 3.1$ Hz, 1H), 2.28 (br s, 1H), 2.19 (br s, 1H), 2.06–2.14 (m, 2H), 1.87–1.96 (m, 3H), 1.60–1.62 (m, 2H), 1.36–1.48 (m, 3H), 1.26 (s, 3H), 1.19–1.26 (m, 2H), 1.03 (d, $J = 10.9$ Hz, 1H), 1.00 ppm (s, 3H); ^{13}C NMR (APT, $CDCl_3$, 100 MHz, major diastereomer): $\delta = 162.9$, 157.0, 132.7, 129.91, 129.86, 128.5, 128.2, 65.8, 53.7, 48.2, 48.1, 47.7, 47.0, 45.2, 38.8, 35.6, 34.4, 33.3, 30.8, 28.2, 28.1, 26.4, 21.3, 19.9 ppm; elemental analysis calcd (%) for $C_{26}H_{31}NO_3S$: C 71.36, H 7.14; found: C 71.48, H 7.01.

A solution of a mixture of **3c** and **4c** (20.0 mg, 0.0457 mmol) in THF (0.7 mL) was added through a cannula to an oven-dried vial containing a suspension of $LiAlH_4$ (2.5 mg, 0.065 mmol) and $AlCl_3$ (1.8 mg, 0.014 mmol) in THF (0.3 mL) under nitrogen at 0 °C. The reaction mixture was stirred at 0 °C for 45 min, then quenched with water. Ethyl acetate was added, and the layers were separated. The aqueous phase was extracted twice with ethyl acetate, and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated to dryness. The crude product was purified by column chromatography (EtOAc/hexanes 1:7) to give **5** (9.1 mg, 0.040 mmol, 88%) as a white solid (m.p. 57–60 °C, hexanes/CH_2Cl_2). $R_f = 0.30$ (EtOAc/hexanes 3:7); $[\alpha]_D^{23} = -20.3$ ($c = 0.35$, $CHCl_3$, 98.5% *ee*); HPLC (OJ-H column, 1 mL min^{-1}, 10% *i*PrOH/hexane, 254 nm): t_R (major enantiomer): 5.69 min, t_R (minor enantiomer): 7.84 min; IR (CH_2Cl_2): $\tilde{\nu} = 3445$ br, s, 3060 w, 3028 w, 2947 s, 2871 s, 1448 m, 737 m, 696 cm^{-1} m; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta =$ 7.31–7.36 (m, 4H), 7.21–7.25 (m, 1H), 4.48 (d, $J = 14.0$ Hz, 1H), 4.40 (d, $J = 14.0$ Hz, 1H), 2.73 (br d, $J = 3.2$ Hz, 1H), 2.59 (br d, $J = 3.3$ Hz, 1H), 2.20 (br s, 1H), 2.14 (br s, 1H), 1.58–1.66 (m, 2H), 1.44 (d, $J =$ 10.2 Hz, 1H), 1.37 (br s, 1H), 1.12–1.22 (m, 2H), 1.02 ppm (d, $J =$ 10.2 Hz, 1H); ^{13}C NMR (APT, $CDCl_3$, 100 MHz): $\delta = 140.6$, 140.1, 134.3, 128.4, 127.2, 126.5, 59.0, 46.4, 46.3, 34.5, 34.2, 30.6, 28.5, 28.1 ppm; HRMS calcd for $C_{16}H_{18}O$: *m/z* 226.1358; found: *m/z* 226.1345.

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