Asymmetric Transfer Hydrogenation of α,β-Acetylenic Ketones

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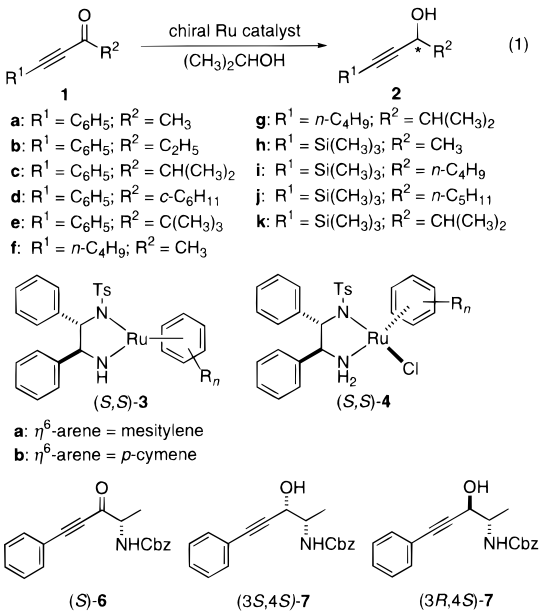
Chiral propargylic alcohols are useful building blocks for the synthesis of various biologically active[1] and structurally interesting compounds.[2] Compounds of this important class had been prepared by stoichiometric asymmetric reduction of acetylenic ketones with chirally modified metal hydrides,[3] reductive cleavage of chiral acetylenic acetals,[4] enantioselective alkynylation of aldehydes,[5] or enzymatic transformations[6] until Corey and Parker developed the catalytic asymmetric hydroboration of α,β-ynones with chiral oxazaborolidines.[7] Although asymmetric hydrogenation would be the most straightforward approach, none of the currently available catalyst systems can convert α,β-acetylenic ketones to propargylic alcohols in a chemoselective and enantioselective manner.[8] Here, we describe the first asymmetric *transfer hydrogenation* of acetylenic ketones using chiral Ru(II) catalysts and 2-propanol as the hydrogen donor.[9] This method allows highly selective reduction of structurally diverse acetylenic ketones to propargylic alcohols of high enantiomeric purity leaving the C≡C bond intact (eq 1).



A search for the appropriate conditions using **1a**, known as a difficult substrate,[10] revealed that the chiral 16-electron Ru complexes **3**[11] are excellent catalysts for the carbonyl-selective asymmetric reduction with 2-propanol (method A). The asymmetric reaction, normally with a 0.1 to 1 M 2-propanol solution of the ketone, proceeds under neutral conditions at room temperature with a substrate/catalyst molar ratio (S/C) of 100−200, or even 1000 in certain cases, giving **2a** in up to 98% ee (enantiomeric excess) and in >99% yield. The Ru catalysts **3** can be conveniently generated *in situ* by mixing the 18-electron precursors **4** and KOH in a 1:1.2 molar ratio (method B)[12] or simply $[RuCl_2(\eta^6\text{-arene})]_2$ (**5**), (1*S*,2*S*)- or (1*R*,2*R*)-*N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine, and KOH in 2-propanol (Ru:diamine:KOH = 1:1:2.5) (method C), only if a ketonic substrate is insensitive to the KOH treatment. The mesitylene and *p*-cymene complexes **3a** and **3b** worked equally well, while the former was somewhat more reactive. A combined catalyst system consisting of $[RuCl_2(\eta^6\text{-}C_6(CH_3)_6)]_2$, (1*S*,2*S*)-2-(methylamino)-1,2-diphenylethanol, and KOH (Ru:amino alcohol:KOH = 1:1:2.5) is also usable (method D).[13]

Various achiral acetylenic ketones **1** can be reduced to chiral propargylic alcohols **2** in good yields.[14] Table 1 lists some examples. The ee values are consistently high regardless of the bulkiness of R^2 substituents from methyl[10] to *tert*-butyl. Both

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(10) The methyl ketone was converted to the alcohol in 96% ee and in 80% yield only with neat *B*-(iso-2-*n*-propylapopinocampheyl)-9-borabicyclo-[3.3.1]nonane (Prapine-Borane) (Brown, H. C.; Ramachandran, P. V.; Weissman, S. A.; Swaminathan, S. *J. Org. Chem.* **1990**, *55*, 6328−6333), whereas the Corey method afforded quantitatively the product in 87% ee.[7b]

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Table 1. Asymmetric Transfer Hydrogenation of α,β-Acetylenic Ketones Catalyzed by Chiral Ruthenium(II) Complexes[a]

	Ru catalyst			product **2**		
substrate	complex	method[b]	time (h)	yield (%)[c]	ee (%)[d]	config[e]
1a	(*S*,*S*)-**3a**	A	20	87	98	*S*
1a	(*S*,*S*)-**3b**	A	20	>99	97	*S*
1a (1 M)	(*S*,*S*)-**3b**	A	20	94	96	*S*
1a (5 M)	(*S*,*S*)-**3b**	A	41	58	94	*S*
1a	(*S*,*S*)-**4a**	B	4	>99	97	*S*
1a (1 M)	(*S*,*S*)-**4a**	B	63	99	95	*S*
1a	(*S*,*S*)-**4b**	B	18	94	96	*S*
1a	**5**[f]	C	18	>99	98	*S*
1a	**5**[g]	C	18	90	97	*S*
1a	**5**[h]	D	18	93	90	*S*
1b	(*S*,*S*)-**4a**	B	12	97	97	*S*
1c	(*S*,*S*)-**4a**	B	5	98	99	*S*[i]
1d	(*S*,*S*)-**4a**	B	13	>99	98	*S*[j]
1e	(*S*,*S*)-**4a**	B[k]	13	84	98	*S*
1f	(*S*,*S*)-**4a**	B	6	70	98[l]	*S*
1g	(*S*,*S*)-**4a**	B	6	90	>99[l]	*S*
1g (1 M)	(*S*,*S*)-**4a**	B[k]	13	85	99[l]	*S*
1h	(*S*,*S*)-**3b**	A	12	>99	98[m]	*S*
1h	(*S*,*S*)-**3b**	A[n]	27	86	98[m]	*S*
1i	(*S*,*S*)-**3b**	A	12	>99	97[o]	*S*
1j (1 M)	(*S*,*S*)-**3b**	A[k]	12	99	94[o]	*S*[p]
1j	(*R*,*R*)-**3b**	A	15	98	99[o]	*R*[p]
1k	(*S*,*S*)-**3b**	A	12	>99	99[q]	*S*[i]

[a] Unless otherwise specified, the reaction was carried out at 28 °C using a 0.1 M solution of the ketone in 2-propanol with S/C = 200. [b] Method A, **1**:**3** = 200:1; method B, **1**:**4**:KOH = 200:1:1.2; method C, **1**:**5**:(1*S*,2*S*)-*N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine:KOH = 200:0.5:1:2.5; method D, **1**:**5**:(1*S*,2*S*)-2-(methylamino)-1,2-diphenylethanol:KOH = 200:0.5:1:2.5. [c] Isolated yield after flash chromatography on silica gel. [d] HPLC analysis using a Daicel Chiralcel OD column unless otherwise specified. [e] Determined by the sign of rotation of the isolated product. [f] η^6-arene = mesitylene. [g] η^6-arene = *p*-cymene. [h] η^6-arene = hexamethylbenzene. [i] Determined after conversion to the methyl (*S*)-2-(benzoyloxy)-3-methylbutyrate. [j] Determined after conversion to the methyl (*S*)-*O*-benzoylhexahydromandelate. [k] S/C = 100. [l] Capillary GLC using a Chrompack Cp-Cyclodextrin-β-236-M-19 column. [m] HPLC analysis of the corresponding 3,5-dinitrobenzoate using a Chiralcel OD-H column. [n] S/C = 1000. [o] HPLC analysis of the corresponding benzoate using a Chiralcel OJ-R column. [p] Determined after hydrolysis to (*S*)- or (*R*)-1-octyn-3-ol. [q] HPLC using two Chiralpak AD columns.

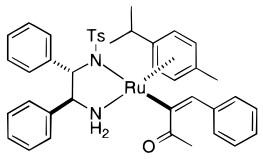
aryl- and alkylethynyl ketones serve as good substrates. Although unsubstituted ethynyl ketones are not usable, the silylated compounds are reduced easily under neutral conditions with the preformed catalysts **3**.[11] The precursor of the lower side chain unit of prostaglandins, (*S*)- or (*R*)-**2j**,[15] of high enantiomeric purity can be prepared by this method. However, the starting materials should be carefully purified, because terminal acetylenes are strong inhibitors of this catalytic reaction.

The asymmetric transfer hydrogenation of acetylenic ketones with a preexisting stereogenic center leads to diastereomeric propargylic alcohols. When the chiral ketone (*S*)-**6** with 98% ee was reduced with 2-propanol containing (*R*,*R*)-**3b** (S/C = 100, [ketone] = 0.1 M, 28 °C, 2 h), (3*S*,4*S*)-**7** with >99% ee was produced in >97% yield together with small amounts of other stereoisomers. In a similar manner, reduction of (*S*)-**6** with the enantiomeric catalyst (*S*,*S*)-**3b** (S/C = 50, 5 h) gave (3*R*,4*S*)-**7** in >99% ee and >97% yield. Thus, the carbonyl diastereofaces in (*S*)-**6** are efficiently differentiated by the chirality of the Ru template, while the adjacent nitrogen-substituted stereogenic center does not play any significant role. The reaction of racemic **6** in 2-propanol containing (*R*,*R*)-**3b** (S/C = 100) indicated that the *S* enantiomer is four times more reactive than the *R* isomer.

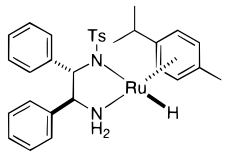
2-Propanol is the best hydrogen donor. Attempted reduction using a 2 M solution of **1a** in a 1:1 formic acid/triethylamine mixture[16] containing (*S*,*S*)-**4b** (S/C = 200, THF, 28 °C, 20 h) gave (*S*)-**2a** in 91% ee but only 55% yield. Similarly, reaction of **1g** (S/C = 100) afforded (*S*)-**2g** in 97% ee and 60% yield.

The success of the asymmetric reaction in 2-propanol relies on the appropriate chiral structures of the Ru complexes, mechanism-based functional group discrimination[11a] allowing the selective saturation of the carbonyl group, and suitable thermodynamic and kinetic parameters. Hydrogen transfer between secondary alcohols and ketones is reversible. Fortunately, in comparison to the reduction of aromatic ketones,[12] the ynone/ynol thermodynamic balance that limits the product yield favors the reduced form more. Thus, the reaction using a 1 M (not 0.1 M) 2-propanol solution of **1a** catalyzed by (*S*,*S*)-**4a** (method B, S/C = 200) gave **2a** in up to 99% yield. Furthermore, reduction of **1a** catalyzed by (*S*,*S*)-**3b** afforded (*S*)-**2a** in 94% ee, even when the reaction was conducted with a substrate concentration as high as 5 M (S/C = 200). This ee value is lower than 97% obtained with a 0.1 M solution but is still synthetically useful.

A separate structural study revealed the cause of the catalyst deactivation. Treatment of (*S*,*S*)-**3b** with a 1 M solution of **1a** in 2-propanol (ketone/Ru = 10, 28 °C, 12 h) produced the orange-yellow complex (*S*,*S*)-**8**, mp 160−162 °C dec, in 88% isolated yield. The structure of (*S*,*S*)-**8** posessing the *R* configuration at Ru was confirmed by X-ray crystallographic analysis. The 16-electron complex (*S*,*S*)-**3b**[11a] dehydrogenates 2-propanol, giving the 18-electron Ru hydride intermediate (*S*,*S*)-**9**, which is responsible for carbonyl reduction of the ynone. The hydride complex, however, partly undergoes irreversible addition across the triple bond to result in the catalytically inactive alkenyl complex (*S*,*S*)-**8**. This side reaction becomes serious with a high substrate concentration. Overall, the high catalytic efficiency, enantioselectivity, and operational convenience are obtained with 0.1 (S/C = 200) to 1 M (S/C = 100) concentrations of an ynone in 2-propanol.



(*S*,*S*)-**8**



(*S*,*S*)-**9**

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Supporting Information Available: Experimental procedures for the transfer hydrogenation, HPLC or GLC behavior, and $[\alpha]_D$ values of the products and data of single-crystal X-ray analysis of (*S*,*S*)-**8** (34 pages). See any current masthead page for ordering and Internet access instructions.

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(14) A mixture of **1a** (721 mg, 5 mmol) and (*S*,*S*)-**3b**[11a] (15 mg, 0.025 mmol) in 2-propanol (50 mL) was stirred under argon at 28 °C for 20 h. The reaction mixture was then concentrated under reduced pressure. The residue was subjected to flash chromatography on silica gel (3:1 hexane/ethyl acetate) to afford (*S*)-**2b** (731 mg, 100% yield) in 97% ee. $[\alpha]_D^{23}$ −50.0 (*c* 1.50, ether) (lit.[6c] $[\alpha]_D^{25}$ −50.6 (*c* 1.475, ether), >95% ee (*S*)). The ee value was determined by HPLC analysis (Chiralcel OD, 20% 2-propanol in hexane, 0.5 mL/min, λ = 254 nm, t_R = 19.5 min, *S* isomer, 11.8 min, *R* isomer).

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