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Highly Enantioselective Copper-Catalyzed Ring Opening of Oxabicyclic Alkenes with Grignard Reagents

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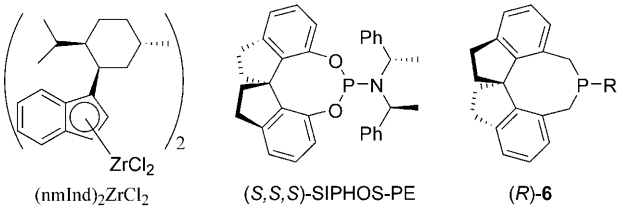
Abstract: A highly efficient copper-catalyzed enantioselective ring opening of oxabicylic alkenes with Grignard reagents has been developed by using chiral spiro phosphine ligands. Excellent *trans* selectivities, good yields, and high enantioselectivities are obtained for a broad range of Grignard reagents under mild reaction conditions. The catalyst system shows an extraordinary activity and the TON of the reaction reaches 9000.

Keywords: asymmetric catalysis · copper · enantioselectivity · Grignard reaction · spiro compounds

Introduction

The transition-metal-catalyzed enantioselective C–C bond-formation reaction, which employs organometallic reagents, is one of the most useful methods in organic synthesis. With the development of chiral ligands and catalysts, a broad range of organometallic compounds including organozinc, organoboron, organoaluminum, organosilane, and organostannane reagents have been applied successfully in a variety of enantioselective reactions.[1] In sharp contrast, the Grignard reagent, which is the most accessible organometallic reagent, has limited applications in catalytic asymmetric reactions. The main limitations of the Grignard reagent are its high reactivity, which results in a rapid, uncatalyzed background reaction, and its sensitivity to reaction conditions.[2] In the past several decades, only a few transition metal-catalyzed enantioselective transformations with a Grignard reagent have been reported. In 1988, Hayashi and Ito described a Ni-catalyzed, asymmetric cross-coupling reaction with Grignard reagents to produce chiral binaphthyl compounds in up to 95% *ee*,[3] which represented the first catalytic, highly enantioselective reaction with Grignard reagents. In 1993, Hoveyda and co-workers reported a zirconium-catalyzed, asymmetric allylic alkylation with Grignard reagents in excellent enantioselectivities.[4] Recently, Cu-catalyzed, highly enantioselective conjugate addition and allylic-alkylation reactions with Grignard reagents were developed by Feringa[5] and Alexakis,[6] respectively. Although impressive progress has been made in those reactions,[7] the application of Grignard reagents in other catalytic asymmetric reactions is scarce.[8] Therefore, the development of highly enantioselective catalytic reactions with the Grignard reagent remains a challenge and has a great impact on asymmetric synthesis from both conceptual and practical points of view.

The enantioselective ring-opening reaction of *meso*-oxabicyclic alkenes with organometallic reagents is a powerful method to construct cyclic compounds with multiple chiral centers while simultaneously generating a new C–C bond.[9] Investigated by Lautens et al., this asymmetric reaction has been accomplished successfully with various organometallic reagents, such as organozinc,[10] organoaluminum,[11] and organoboron[12] in the presence of palladium, nickel, rhodium, copper, and zirconium catalysts (see Figure 1). Although Grignard reagents have been used as nucleophiles in non-asymmetric ring-opening reactions,[13] there is only one example of the asymmetric ring-opening reaction of bicyclic



$(nmInd)_2ZrCl_2$ (*S,S,S*)-SIPHOS-PE (*R*)-**6**

Figure 1. Catalyst and ligands for asymmetric ring opening of oxabicylic alkenes with Grignard reagents.

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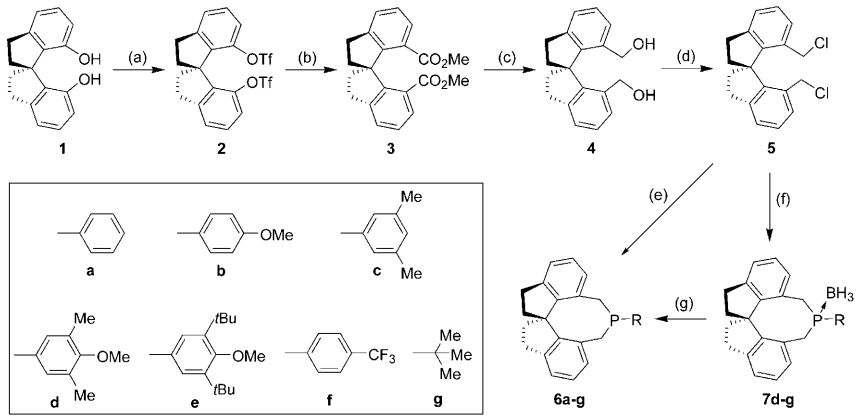
alkene with Grignard reagents: the reaction of 2,4-dimethyl-3-(benzyloxy)-8-oxabicyclo-6-octene and ethyl magnesium bromide catalyzed by chiral zirconium catalyst ($(nmInd)_2ZrCl_2$) gave the ring-opening product in 27% yield with 48% *ee*.[11d] In our study of catalytic enantioselective reactions of the Grignard reagent, we reported copper-catalyzed enantioselective ring opening of *meso*-oxabicyclic alkenes with Grignard reagents using chiral spiro phosphoramidite ligand (SIPHOS-PE) in enantioselectivities of up to 88% *ee*.[14] Although this result is an improvement over previous data, it is still far removed from the practical demands of organic synthesis. Therefore, a more efficient catalyst system is desirable. In the present study, we describe a highly efficient catalyst system composed of a copper salt and electron-rich chiral monodentate phosphine ligands **6**. This catalyst offers superb catalytic activity, broad substrate generality, mild reaction conditions, and excellent selectivities in the enantioselective ring-opening reaction of oxabenzonorbornadienes with Grignard reagents.



Scheme 1. Synthesis of chiral spiro phosphine ligands **6**. Reagents and conditions: a) Tf_2O, pyridine, CH_2Cl_2, −10°C–RT, 98%; b) 15 mol% $Pd(OAc)_2$, 15 mol% dppp, Et_3N, MeOH, CO (1 atm), DMSO, 80°C, 98%; c) $LiAlH_4$, Et_2O, −15°C-reflux, 95%; d) $SOCl_2$, pyridine, $CHCl_3$, 0°C-RT, 88%; e) RPH_2 (**8a–c**), NaH, THF, −78°C-reflux, 72–84%; f) RPH_2 (**8d–g**), NaH, DMSO, 15°C–40°C and then BH_3•Me_2S, 65–83%; g) DABCO, toluene, 55°C, 61–85%.

Results and Discussion

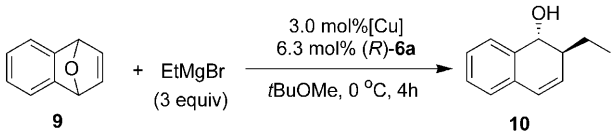
Synthesis of Chiral Spiro Phosphine Ligands 6

The phosphine ligands **6** with different R groups on the phosphorous atom were prepared according to our previously reported strategy[15] with some modifications (Scheme 1). Thus, optically pure diol (*R*)-**1** was first converted to the ditriflate (*R*)-**2** in high yield. Compound (*R*)-**2** was then directly subjected to an esterification with methanol and carbon monoxide in the presence of a palladium catalyst to produce compound (*R*)-**3** in high yield.[16] Reduction of diester (*R*)-**3** with $LiAlH_4$ to diol (*R*)-**4** followed by chlorination with $SOCl_2$ afforded the dichloride (*R*)-**5**. Finally, dichloride (*R*)-**5** was condensed with different phosphines **8** to afford the ligands **6**. For the synthesis of ligands **6a–c**, the condensation was performed directly in THF in good yields. However, for ligands **6d–g**, the condensation of dichloride (*R*)-**5** with phosphines proceeded very slowly in THF because of the high steric hindrance (for **8d**, **8e**, **8g**) and the reduced nucleophilicity (for **8f**) of the corresponding phosphines. Therefore, we changed the solvent from THF to DMSO, which greatly improved the rate and yield of condensation. Because ligands **6d–6g** are sensitive to air and are partially decomposed during purification, BH_3•Me_2S was added after condensation to form phosphine-boron complexes, which were sufficiently stable to be purified by column chromatography. The phosphine-boron complexes were deprotected with 1,4-diazabicyclo[2.2.2]octane (DABCO) in toluene to provide pure ligands **6d–g** in good yields.[17]

Ring Opening of Oxabenzonorbornadienes with Grignard Reagents

In our studies of the ring-opening reaction of oxabicyclic alkenes and Grignard reagents, we found that the electron-rich monodentate spiro phosphine ligand **6a** has high reactivity. By using (*R*)-**6a** as the ligand, the $Cu(OTf)_2$-catalyzed reaction of EtMgBr with oxabenzonorbornadiene **9** was completed in 4 h with high diastereoselectivity and moderate enantioselectivity (Table 1, entry 1). The reaction rate was much faster than that obtained previously with the SIPHOS-PE ligand under its optimal conditions, and the *de* and *ee* values of the ring-opening product were comparable.[18] To attain higher enantioselectivity and reactivity, a broad survey of reaction conditions was undertaken with

Table 1. Cu-Catalyzed asymmetric ring opening of **9** with EtMgBr: The influence of the copper salts.



Entry	Copper salt	Yield [%][a]	*trans*/*cis*[b]	*ee* [%][c]
1	$Cu(OTf)_2$	83	>99/1	54
2	$CuBr_2$	90	>99/1	39
3	CuCl	84	>99/1	57
4	CuBr·Me_2S	82	>99/1	45
5	CuI	83	>99/1	29
6	CuTc[d]	80	>99/1	45
7	$[Cu(OTf)]_2$·Tol	83	>99/1	37

[a] Isolated yield. [b] Determined by HPLC. [c] *ee* of the *trans* product, as determined by HPLC. The absolute configuration is (1*R*, 2*S*).[19] [d] CuTc: copper thiophene-2-carboxylate.

ligand **6a**. A variety of copper salts can be applied as catalyst precursors in the reaction, and good yields and excellent diastereoselectivities were obtained in all cases. Among the copper precursors tested, $Cu(OTf)_2$ (54% *ee*, Table 1, entry 1) and CuCl (57% *ee*, Table 1, entry 3) gave the highest enantioselectivities.

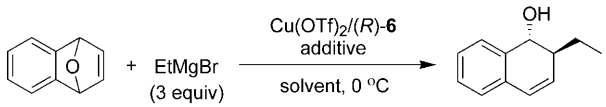
It has been reported that catalytic additives could play a crucial role in improving reactivities and enantioselectivities in asymmetric reactions.[20] Moreover, it has also been shown that the catalyst activity could be increased remarkably by changing the counterion of the catalyst in the copper-catalyzed asymmetric Diels–Alder reaction.[21] Accordingly, we studied a number of additives such as $AgBF_4$, $AgSbF_6$, $AgPF_4$, and sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]-borate (NaBArF) in our reaction to improve the activity and selectivity of the catalysts. The addition of silver salts had a positive effect on enantioselectivity but retarded the reaction rate and yield (Table 2, entries 1–3). The activity of catalyst was enhanced significantly by the addition of NaBArF, which provides a noncoordinating anion.[22] The reaction was completed in 1 h and gave the ring-opening product **10** in 93% yield and 74% *ee* (Table 2, entry 4). The high activity of catalyst may be rationalized by the generation of more active cationic copper species through the exchange of the counterion of the catalyst to the noncoordinating anion $BArF^-$. In solvent experiments, better reactivity and enantioselectivity were achieved in chlorinated solvent, and CH_2ClCH_2Cl (DCE) was found to be the best choice of solvent (Table 2, entries 5–10). Further study revealed that the catalyst system was so active that the catalyst loading could be reduced to 0.5 mol% at 0°C without deterioration of yield, diastereoselectivity, or enantioselectivity (Table 2, entry 11).

To search for the most effective ligand, the chiral spiro phosphines **6** were surveyed in the reaction. With all tested ligands **6**, the reaction proceeded smoothly and afforded the desired ring-opening product in high yields and almost complete *trans* selectivities. The electronic and steric properties of the R group on the phosphorous atom of ligands **6** distinctly influenced the enantioselectivity. The aryl group with electron-donating alkyl and alkoxy substituents is beneficial to higher enantioselectivity; for instance, the ligands **6b**, **6c**, and **6d** afforded *trans* ring-opening products in 87%, 89%, and 91% *ee*, respectively (Table 2, entries 12–14). However, the ligands with an aryl group bearing bulky 3,5-di-*tert*-butyl groups (**6e**) and an electron-withdrawing CF_3 group (**6f**) showed lower enantioselectivities and activities. The reaction required 4 h for complete conversion, and the product **10** was obtained in 81% *ee* (Table 2, entries 15 and 16). Ligand **6g**, with a *tert*-butyl group directly on the P-atom, caused the lowest enantioselectivity (63% *ee*, Table 2, entry 17). Decreasing the reaction temperature from 0°C to −20°C enhanced the enantiomeric excess of product from 91% to 93% in the reaction employing ligand **6d** (Table 2, entry 18).

To evaluate the scope of the reaction, we examined various Grignard reagents under the optimal reaction conditions, and the results are summarized in Table 3. The ring opening of **9** was consummated in high yields, and excellent enantio- and diastereoselectivities with a broad range of alkyl Grignard reagents. The Grignard reagent with a small Me group gave the ring-opening product in a slightly lower *ee* (Table 3, entry 2). However, the reaction of the aromatic Grignard reagent PhMgBr with **9** provided an almost racemic product in the presence of 1.0 mol% catalyst at 15°C (Table 3, entry 9). The functionalized Grignard reagents including allylic magnesium bromide and vinyl magnesium chloride did not show activities under the optimal reaction conditions.

When catalyzed by Cu–**6d**–NaBArF, oxabenzonorbornadienes **18**–**22** reacted successfully with typical alkyl Grignard reagents (Table 4). The reactions proceeded very efficiently and afforded the ring-opening products in good yields and excellent diastereo- and enantioselectivities. The electronic property of the oxabenzonorbornadiene substrates had an apparent effect on the

Table 2. Cu-Catalyzed asymmetric ring opening of **9** with EtMgBr: Optimizing reaction conditions.

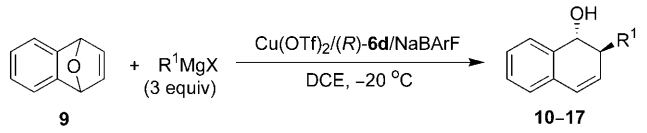


9 **10**

Entry	[Cu] [mol%]	Ligand	Additive[a]	Solvent	Time [h]	Yield [%][b]	*trans*/*cis*[c]	*ee* [%][d]
1	3	(*R*)-**6a**	$AgBF_4$	*t*BuOMe	24	11[e]	99/1	71
2	3	(*R*)-**6a**	$AgPF_6$	*t*BuOMe	24	22[e]	99/1	73
3	3	(*R*)-**6a**	$AgSbF_6$	*t*BuOMe	24	13[e]	99/1	71
4	3	(*R*)-**6a**	NaBArF	*t*BuOMe	1	93	>99/1	74
5	3	(*R*)-**6a**	NaBArF	Et_2O	24	65[e]	99/1	40
6	3	(*R*)-**6a**	NaBArF	THF	24	trace[e]	ND[f]	ND[f]
7	3	(*R*)-**6a**	NaBArF	Toluene	1	88	99/1	60
8	3	(*R*)-**6a**	NaBArF	*n*-Hexane	4	83	98/2	70
9	3	(*R*)-**6a**	NaBArF	CH_2Cl_2	0.5	86	>99/1	80
10	3	(*R*)-**6a**	NaBArF	DCE	0.5	92	>99/1	83
11	0.5	(*R*)-**6a**	NaBArF	DCE	2	90	>99/1	83
12	0.5	(*R*)-**6b**	NaBArF	DCE	2	94	>99/1	87
13	0.5	(*R*)-**6c**	NaBArF	DCE	2	94	>99/1	89
14	0.5	(*R*)-**6d**	NaBArF	DCE	2	94	>99/1	91
15	0.5	(*R*)-**6e**	NaBArF	DCE	4	91	>99/1	81
16	0.5	(*R*)-**6f**	NaBArF	DCE	4	85	99/1	81
17	0.5	(*R*)-**6g**	NaBArF	DCE	4	89	99/1	63
18[g]	0.5	(*R*)-**6d**	NaBArF	DCE	6	93	>99/1	93

[a] Additive/$Cu(OTf)_2$) is 2.5/1. [b] Isolated yield. [c] Determined by HPLC. [d] *ee* of the *trans* product, as determined by HPLC. The absolute configuration is (1*R*, 2*S*). [e] Compound **9** could not be completely converted. [f] Not determined. [g] At −20°C.

Table 3. Asymmetric ring opening of **9** with various Grignard reagents.[a]



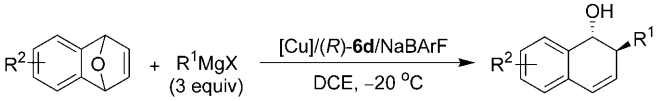
Entry	R^1MgX.	Product	Time [h]	Yield [%][b]	*trans*/*cis*[c]	*ee* [%][d]
1	EtMgBr	**10**	4	94	>99/1	93[e]
2[f]	MeMgBr	**11**	12	88	99/1	80
3	*n*BuMgBr	**12**	4	87	>99/1	95
4	*n*BuMgCl	**12**	6	89	>99/1	89
5	*i*BuMgBr	**13**	6	92	>99/1	93
6	*i*PrMgBr	**14**	6	95	>99/1	93
7	*t*BuMgCl	**15**	1	76	>99/1	90
8	BnMgCl	**16**	8	71	99/1	87
9[f]	PhMgBr	**17**	12	78	99/1	5

[a] Reaction conditions: 0.5 mol% $Cu(OTf)_2$, 1.1 mol% (*R*)-**6d**, 1.25 mol% NaBArF, DCE, −20°C. [b] Isolated yield. [c] Determined by HPLC. [d] *ee* of the *trans* product, as determined by HPLC. [e] The absolute configuration is (1*R*, 2*S*). [f] The reaction was carried out at 15°C in the presence of 1.0 mol% catalyst.

reactivity and enantioselectivity of the reaction. The reactions of substrates **18** and **19**, which contain methoxy groups on the 5,8-positions, with R^1MgX proceeded at −20°C in the presence of 1.0 mol% $Cu(OTf)_2$, 2.1 mol% (*R*)-**6d**, and 2.5 mol% NaBArF (Method A) to provide ring-opening products **23**–**32** in 78–94% yields with 90–99.6% *ee* (Table 4, entries 1–10). The ring-opening reaction of 6,7-dibromo-substituted oxabenzonorbornadiene **20** needed to be carried out at 0°C, and the enantioselectivities (86–92% *ee*) were slightly lower than for other oxabenzonorbornadiene substrates (Table 4, entries 11–15). For the substrates **21** and **22**, which bear two methyl groups, the use of CuCl instead of $Cu(OTf)_2$ improved the reactivity. Under the optimal reaction conditions, oxabenzonorbornadienes **21** and **22** reacted smoothly with R^1MgX in the presence of catalyst generated from 1.0 mol% CuCl, 2.1 mol% (*R*)-**6d**, and 1.1 mol% NaBArF (Method B). The corresponding ring-opening products **38**–**47** were obtained in 76–91% yields with 86–97% *ee* (Table 4, entries 16–25).

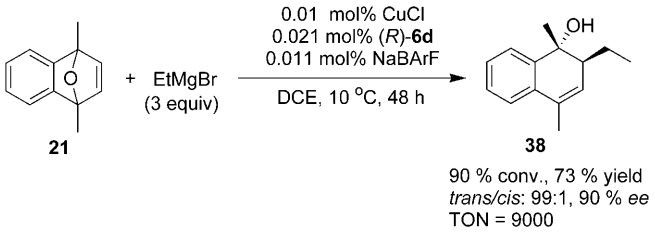
The high efficiency of the present copper catalyst with ligand (*R*)-**6d** is highlighted by the reaction of substrate **21** at a low catalyst loading (Scheme 2). The ring opening of **21** with EtMgBr proceeded in the presence of only 0.01 mol% of the catalyst at 10°C to give product **38** with 90% conversion, 75% yield, and 90% *ee*. The turnover number (TON) of the reaction reached 9000, which to our knowledge repre-

Table 4. Asymmetric ring opening of oxabenzonorbornadienes **18**–**22** with alkyl Grignard reagents.[a]



Entry	X	Method	Substrate	Product	R1	Yield [%][b]	*ee* [%][c]
1	Br				Et (**23**)	94	94
2	Br				*n*Bu (**24**)	93	91
3	Br				*i*Bu (**25**)	93	92
4	Br	**A**			*i*Pr (**26**)	93	96
5	Cl		**18**		*t*Bu (**27**)	78	98
6	Br				Et (**28**)	85	96
7	Br				*n*Bu (**29**)	91	94
8	Br				*i*Bu (**30**)	85	90
9	Br	**A**			*i*Pr (**31**)	79	98
10	Cl		**19**		*t*Bu (**32**)	80	99.6
11[d]	Br				Et (**33**)	83	86
12[d]	Br				*n*Bu (**34**)	95	87
13[d]	Br	**A**			*i*Bu (**35**)	83	88
14[d]	Br				*i*Pr (**36**)	89	88
15[d]	Cl		**20**		*t*Bu (**37**)	72	92
16	Br				Et (**38**)	83	93
17	Br				*n*Bu (**39**)	82	91
18	Br	**B**			*i*Bu (**40**)	78	86
19	Br				*i*Pr (**41**)	82	92
20	Cl		**21**		*t*Bu (**42**)	76	97
21	Br				Et (**43**)	86	91
22	Br				*n*Bu (**44**)	89	90
23	Br	**B**			*i*Bu (**45**)	91	91
24	Br				*i*Pr (**46**)	77	93
25	Cl		**22**		*t*Bu (**47**)	76	97

[a] Experiment conditions: Method A: for substrates **18**, **19**, and **20**, 1.0 mol% $Cu(OTf)_2$, 2.1 mol% (*R*)-**6d**, 2.5 mol% NaBArF, 1–12 h. Method B: for substrates **21** and **22**, 1.0 mol% CuCl, 2.1 mol% (*R*)-**6d**, 1.1 mol% NaBArF, 0.5–12 h. [b] Isolated yield. In all cases *trans*/*cis* are ≥99/1. [c] *ee* of *trans* product, as determined by HPLC (see Supporting Information). [d] At 0°C.

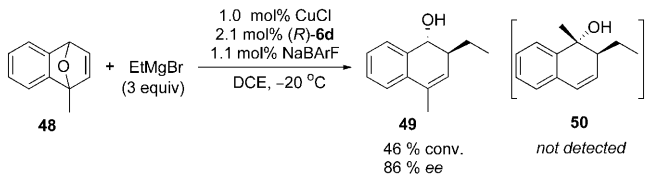


Scheme 2. High activity of the catalyst in ring-opening reaction of substrate **21** with EtMgBr.

sents one of the highest TONs reported in the asymmetric C–C bond-formation reaction employing Grignard reagents.

Ring Opening of Unsymmetrical Oxabenzonorbornadienes

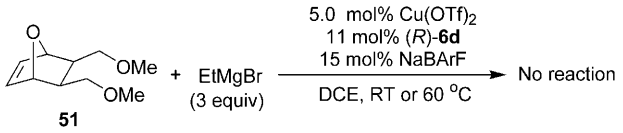
Under standard reaction conditions, the kinetic resolution of racemic unsymmetrical substrate **48** with EtMgBr afforded the *trans* ring-opening product **49** with 86% *ee* at 46% conversion and the unreacted **48** with 60% *ee* (Scheme 3). No *regio* isomer **50** was obtained, indicating that the reaction has excellent regioselectivity.



Scheme 3. The kinetic resolution of *rac*-**48** with EtMgBr.

Ring Opening of Nonaromatic Oxabicyclic Alkenes with EtMgBr

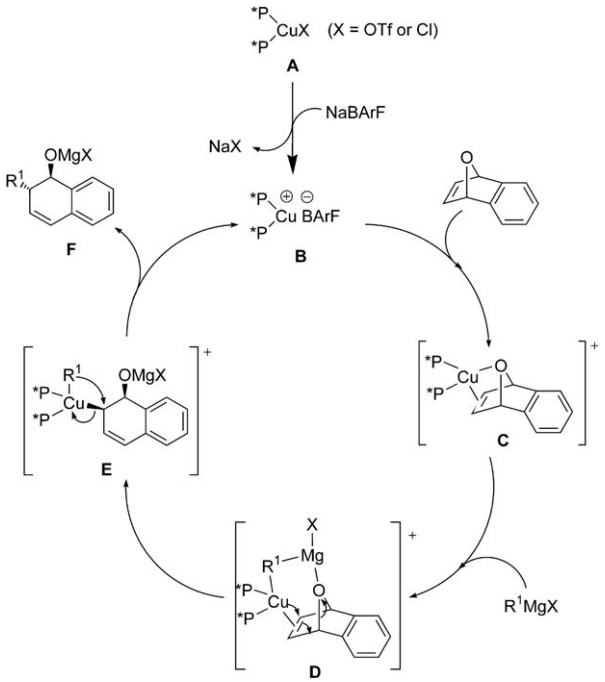
We also examined the less reactive nonaromatic oxabicyclic alkene, 5,6-bismethoxymethyl-7-oxa-bicyclo[2.2.1]-2-heptene (**51**) in the reaction with EtMgBr (Scheme 4). However, only the starting substrate was recovered under our reaction conditions. Raising the reaction temperature from room temperature to 60 °C did not result in ring opening.



Scheme 4. Ring opening of oxabicyclic alkene **51** with EtMgBr.

Mechanism Hypothesis

A proposed mechanism for the copper-catalyzed ring opening of oxabenzonorbornadienes is summarized in Scheme 5. Though the exact effect of NaBArF is unclear, we speculate that it will exchange the counterion of complex **A** to form an active catalyst **B**. The cationic copper catalyst **B** approaches the substrate from the *exo* direction to form the π-complex **C**. The complex **C** reacts with Grignard reagent



Scheme 5. Proposed mechanism of the ring opening of oxabenzonorbornadienes with Grignard reagents.

quickly to generate intermediate **D**, in which the magnesium atom coordinates with oxygen to activate the C–O bond of substrate. The formation of π-complex **D** is possibly followed by an intramolecular rearrangement to σ-complex **E** with an oxa-ring opening. This step is irreversible because of the release of ring strain, and it is also an enantiodiscriminating step. The R^1 group attacks the carbon 2 from the backside of copper in the intermediate **E**, which explains the *trans* selection of the reaction.

Conclusions

In summary, we have developed a highly efficient catalyst consisting of copper, chiral spiro phosphine ligand, and NaBArF for the enantioselective ring opening of oxabicyclic alkenes with Grignard reagents. In the presence of the catalyst, the ring-opening reaction is consummated under mild conditions with various Grignard reagents. The ring-opening products, cyclic alcohols with two chiral centers, are obtained in high yields and excellent *trans* diastereoselectivities and enantioselectivities. The remarkable efficiency of the catalyst suggests potential widespread applications in other copper-catalyzed asymmetric transformations.

Experimental Section

General

All the manipulations which are sensitive to moisture or air were performed in an Argon-filled glove box (VAC DRI-LAB HE 493 or

MBRAUN labstar) or by using standard Schlenk techniques unless otherwise noted. NMR spectra were recorded on a Varian Mercury Plus-400 spectrometer at 400 MHz (^{1}H NMR), 100 MHz (^{13}C NMR), and 162 MHz (^{31}P NMR), or a Bruker AV-300 spectrometer at 300 MHz (^{1}H NMR), 75 MHz (^{13}C NMR), and 121.5 MHz (^{31}P NMR). Chemical shifts (δ) were reported in ppm downfield from internal Me_4Si and external 85% H_3PO4, respectively. Melting points were measured on an RY-I apparatus and uncorrected. Optical rotations were recorded on a Perkin–Elmer Model-341 polarimeter in a 10 cm cell. HPLC analyses were performed using a Hewlett–Packard Model HP-1100 Series, and supercritical fluid chromatography (SFC) analyses were performed on a Berger Analytix SFC instrument. High resolution mass spectra were recorded on a Bruker APEX II spectrometer or VG ZAB-HS mass spectrometer.

Syntheses

Representative procedure for the preparation of the ligand (*R*)-**6a** from (*R*)-**5**[15]: To a solution of (*R*)-**5** (400 mg, 1.6 mmol) and NaH (116 mg, 4.8 mmol) in anhydrous THF (40 mL) was added phenylphosphine (**8a**, 180 mg, 1.6 mmol) dropwise at −78 °C under N_2 atmosphere. The mixture was returned to room temperature spontaneously and stirred for 24 h. After additional phenylphosphine (18 mg, 0.16 mmol) was added, the mixture was heated at reflux for 24 h. The solvent was removed under vacuum and the residue was purified by flash column chromatography on silica gel with petroleum ether/ethyl acetate (15:1) to afford (*R*)-**6a** as a white solid (472 mg, 84% yield). M.p.: 148–149 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.30$–7.07 (m, 7H), 7.00–6.93 (m, 2H), 6.70 (t, $J = 7.2$ Hz, 1H), 5.71 (d, $J = 7.6$ Hz, 1H), 3.11–2.82 (m, 6H), 2.74 (t, $J = 10.8$, 1H), 2.54 (dd, $J = 14.0$, 8.4 Hz, 1H), 2.30–2.19 (m, 2H), 2.05–1.83 ppm (m, 2H).

Representative procedure for the preparation of (*R*)-**7d** from (*R*)-**5**: To a solution of (*R*)-**5** (400 mg, 1.6 mmol) and NaH (96 mg, 4.0 mmol) in anhydrous DMSO (50 mL) was added (3,5-dimethyl-4-methoxyphenyl)-phosphine (**8d**, 303 mg, 1.8 mmol) dropwise at room temperature under N_2 atmosphere. The mixture was heated to 50 °C and stirred at this temperature. $BH_3{\cdot}Me_2S$ (2.0 M in THF, 1.6 mL, 3.2 mmol) was added to the solution at 0 °C after the dichloride compound disappeared (monitored by TLC). The mixture was left to react at room temperature overnight. Water (30 mL) was added and the mixture was extracted with ethyl acetate (50 mL, 3 times), and washed with brine solution (25 mL). The organic phase was dried, filtered, and concentrated. The residue was purified by column chromatography on silica gel with petroleum ether/ethyl acetate (6:1) to afford (*R*)-**7d** (580 mg, 85% yield) as a white solid. M.p.: 161–162 °C; $[\alpha]_D^{20} = +82.1$ ($c = 1.0$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.25$–7.15 (m, 4H), 6.88 (t, $J = 7.2$ Hz, 1H), 6.72 (d, $J = 9.6$ Hz, 2H), 6.06 (d, $J = 7.2$ Hz, 1H), 3.71 (s, 3H), 3.54 (dd, $J = 16.4$ and 13.2 Hz, 1H), 3.26 (dd, $J = 14.4$ and 8.4 Hz, 1H), 3.05–2.85 (m, 4H), 2.73 (dd, $J = 12.8$ and 5.2 Hz, 1H), 2.56 (dd, $J = 14.0$ and 6.0 Hz, 1H), 2.31–1.85 (m, 4H), 2.18 (s, 6H), 0.87–0.47 ppm (br, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 160.1, 147.8, 147.7, 147.5, 147.4, 143.8, 143.4, 133.9, 133.8, 131.3, 131.0, 130.9, 130.3, 130.2, 128.0, 127.9, 127.4, 127.3, 126.7, 124.5, 124.4, 124.0, 121.4, 120.9, 62.1, 59.9, 38.3, 38.1, 30.5, 30.1, 29.8, 26.2, 25.9, 16.2 ppm; ^{31}P NMR (162 MHz, $CDCl_3$): $\delta = 16.0$–15.7 ppm (m); HRMS (EI): *m/z* (%) calcd for [$C_{28}H_{32}$BOP-BH_3]: 412.1956; found: 412.1957.

Representative procedure for the preparation of the ligand (*R*)-**6d** from (*R*)-**7d**: In a flame-dried flask (*R*)-**7d** (200 mg, 0.47 mmol), DABCO (350 mg, 3.12 mmol) and anhydrous toluene (15 mL) were added. The solution was heated to 50 °C and stirred for 12 h. Solvent was removed under vacuum and the residue was purified by flash column chromatography on neutral Al_2O_3 with petroleum ether/ethyl acetate (20:1) to afford (*R*)-**6d** (164 mg, 85% yield) as viscous oil and was solidified slowly by standing. $[\alpha]_D^{20} = +50.9$ ($c = 1.0$, benzene); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.21$–7.01 (m, 4H), 6.76 (t, $J = 7.5$ Hz, 1H), 6.51 (d, $J = 6.9$ Hz, 2H), 5.75 (d, $J = 7.5$ Hz, 1H), 3.71 (s, 3H), 3.08–2.81 (m, 6H), 2.63 (t, $J =$ 11.1 Hz, 1H), 2.44 (dd, $J = 13.8$ and 8.7 Hz, 1H), 2.31–1.82 (m, 4H), 2.18 ppm (s, 6H); ^{13}C NMR (75 MHz, [D_6]benzene): $\delta = 158.5$, 148.2, 148.1, 147.0, 143.0, 142.5, 134.1, 133.9, 133.0, 132.9, 131.8, 131.5, 130.3, 130.2, 130.0, 129.9, 129.4, 129.1, 127.8, 126.1, 123.1, 123.0, 122.4, 61.7, 59.3, 38.8, 37.9, 30.7, 30.6, 30.1, 29.7, 27.0, 26.8, 16.0 ppm; ^{31}P NMR (162 MHz, [D_6]benzene): $\delta = -20.0$ (s); HRMS (ESI): *m/z* (%) calcd for [$C_{28}H_{29}OP+H$]: 413.2029; found: 413.2023.

General procedure for the asymmetric ring opening of oxabicylic alkenes **9** with Grignard reagents: A solution of $Cu(OTf)_2$ (1.0 mg, 0.0028 mmol), (*R*)-**6d** (2.4 mg, 0.0058 mmol), and NaBArF (6.3 mg, 0.0069 mmol) in anhydrous DCE (4 mL) was stirred at room temperature for 3 h. Oxabenzonorbornadiene **9** (80 mg, 0.56 mmol) was added to this colorless solution. After being stirred for 5 min at room temperature, the solution was cooled to −20 °C, and Grignard reagent was added dropwise to the mixture. The solution was stirred at −20 °C until the end of the reaction (monitored by TLC). After quenching with an aqueous solution of Na_2CO_3 (1.0 M, 3 mL), the reaction mixture was extracted with ether (3× 10 mL). The organic phase was dried, filtered, and concentrated to give a crude product, which was subjected to flash chromatography on silica gel with petroleum ether/ethyl acetate/triethyl amine (75:15:1) to afford product **10** as a white solid (91 mg, 94% yield). HPLC condition: Chiralcel OD-H column, *n*-hexane/*i*PrOH = 98:2, 1.0 mL min^{-1}, UV detector (254 nm); retention time: $t_R = 15.9$ min and $t_R = 18.2$ min (major); m.p.: 64–65 °C; 93% *ee*; $[\alpha]_D^{20} = +361$ ($c = 1.0$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.35$ (d, $J = 6.8$ Hz, 1H), 7.29–7.22 (m, 2H), 7.10 (d, $J =$ 6.8 Hz, 1H), 6.49 (d, $J = 9.6$ Hz, 1H), 6.00 (dd, $J = 9.6$, 4.8 Hz, 1H), 4.51 (s, 1H), 2.47–2.26 (m, 2H), 1.51–1.29 (m, 2H), 0.97 ppm (t, $J = 7.6$ Hz, 3H).

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