SimplePhos as Efficient Ligand for the Copper-Catalyzed Kinetic Resolution of Cyclic Vinyloxiranes with Grignard Reagents

Renaud Millet, Alexandre Alexakis*

Department of Organic Chemistry, University of Geneva, 30 Quai Ernest Ansermet, 1211 Geneva, Switzerland
Fax +41(22)3793215; E-mail: alexandre.alexakis@chiorg.unige.ch

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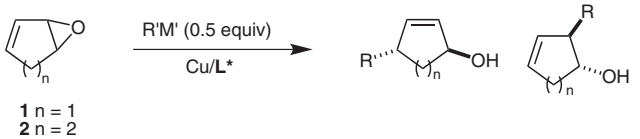
Abstract: Cyclic vinyloxiranes react with Grignard reagents under copper catalysis. Highly efficient kinetic resolution is achieved with the new SimplePhos family of chiral phosphorus ligands. Stereodivergence could be exploited to get either the S_N2 or S_N2' product with up to 96% ee.

Key words: epoxides, asymmetric synthesis, Grignard reagents, catalysis, copper

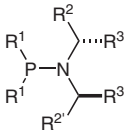
Asymmetric carbon–carbon bond formation is an important issue in modern organic chemistry. Copper catalysis is a well-documented method to achieve this goal.[1] Among all the different methodologies to produce enantiomerically pure chiral centers, kinetic resolution is the oldest but still a very useful and successful one.[2] Chiral allylic alcohol can be easily prepared by kinetic resolution of racemic vinyloxiranes (Scheme 1). Copper-catalyzed kinetic resolution of such racemic compound with hard nucleophile is not very well documented. Dialkylzinc reagents have been successfully used in combination with a chiral copper complex based on phosphoramidite.[3] Similar complexes can also promote the kinetic resolution of vinyloxiranes with trimethylaluminium.[4] We also recently showed that more easily and commercialy available Grignard reagents are able to perform this kinetic resolution in the presence of chiral ferrocenyl-based ligand and copper.[5] However, all these methodologies have several drawbacks, zinc and aluminum reagents lead to good to excellent enantioselectivities (up to 96% ee) but only the transfer of commercially available methyl and ethyl group has been reported. With Grignard reagents both primary and secondary alkyl groups can be transferred, but with lower enantioselectivities (up to 90% ee with primary one and up to 74% ee with secondary one). More recently, our group described the synthesis and the applications of a new class of phosphorus ligand SimplePhos and their application in copper-catalyzed allylic substitution.[6]



1 n = 1
2 n = 2

Scheme 1

In this communication we report our results on the copper-catalyzed kinetic resolution of cyclic vinyloxiranes with Grignard reagents with SimplePhos ligands. From a mechanistic point of view this reaction is a copper-catalyzed allylic substitution.[7a,b]



L1 R^1 = Ph, R^2 = $R^{2'}$ = Ph, R^3 = Me
L2 R^1 = Ph, R^2 = $R^{2'}$ = 2-naphthyl, R^3 = Me
L3 R^1 = Ph, R^2 = $R^{2'}$ = 2-MeC_6H_4, R^3 = Me
L4 R^1 = 2-naphthyl, R^2 = $R^{2'}$ = Ph, R^3 = Me
L5 R^1 = 3,5-$Me_2C_6H_3$, R^2 = $R^{2'}$ = Ph, R^3 = Me
L6 R^1 = 3-$CF_3C_6H_4$, R^2 = $R^{2'}$ = Ph, R^3 = Me
L7 R^1 = 4-MeC_6H_4, R^2 = $R^{2'}$ = Ph, R^3 = Me
L8 R^1 = Ph, R^2 = $R^{2'}$ = 2-MeOC_6H_4, R^3 = Me
L9 R^1 = R^2 = Ph, $R^{2'}$ = 2-naphthyl, R^3 = Me
L10 R^1 = Ph, R^2 = $R^{2'}$ = Ph, R^3 = Et

Figure 1 Ligands used for this study

Different SimplePhos ligands were tested (Scheme 1) and the simplest **L1** was used to perform a screening of experimental conditions (Scheme 2, Table 1). The nature of the copper salt and the solvent are known to be crucial for both regioselectivity and enantioselectivity.[8,9] First of all, the reaction was performed in a mixture of CH_2Cl_2 and the Et_2O content of the Grignard reagent, with CuTC (copper 2-thiophene carboxylate) as the best conditions described for the allylic substitution with Grignard reagents and this family of ligand.[6,7c,d]

Table 1 Screening of Experimental Conditions

Entry	Copper salt	Solvent	Conversion[a] (yield,[b] %)	S_N2'/S_N2[c]	ee S_N2' (%)[d]
1	CuTC	CH_2Cl_2[e]	50 (47)	95:5	88
2	CuCN	CH_2Cl_2[e]	17	92:8	14
3	CuOAc·H_2O	CH_2Cl_2[e]	20 (17)	96:4	62
4	$Cu(OTf)_2$	CH_2Cl_2[e]	18 (15)	90:10	48
5	CuBr	CH_2Cl_2[e]	15	96:4	88
6	CuTC	Et_2O	45	97:3	40
7	CuTC	PhMe	50	96:4	46

[a] Determined by GC-MS with undecane as internal standard.
[b] Isolated yield.
[c] Determined by ^1H NMR.
[d] Determined by chiral GC.
[e] Mixture of CH_2Cl_2 and the Et_2O content of the Grignard reagent.

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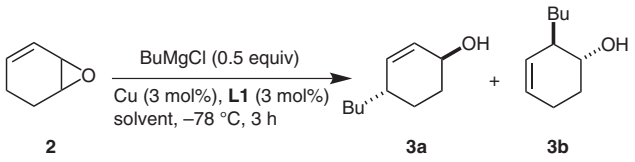


Scheme 2 Test reaction

Full conversion was obtained (50% maximum conversion) with a very good S_N2'/S_N2 ratio and a good enantiomeric excess (Table 1, entry 1). Then, different copper salts were tested and all showed good regioselectivities, but a dramatic effect on the conversion was observed: none of them led to more than 20% conversion (Table 1, entries 2–5). And only CuBr led to a good enantioselectivity (88% ee, Table 1, entry 5).

The choice of the solvent is very important in terms of enantiomeric excess. When more polar solvent, such as Et_2O, was used the enantiomeric excess decreases down to 40% (Table 1, entry 6) and aromatic solvent had the same effect on the reaction (Table 1, entry 7). Our investigations continued by modifying the structure of the ligand (Figure 1).

We first studied the effect of the bulkiness of the ligand by changing the aromatic ring of the amine part from a phenyl to a 2-naphthyl (Table 2, entry 2) or *o*-tolyl (Table 2, entry 3). In both cases a decrease of the enantioselectivity was observed (70% for the 2-naphthyl and only 22% for the *o*-tolyl). An increase of the bulkiness on the phosphorus part **L4** led to an impressive lost of conversion and enantioselectivity (Table 2, entry 4).

Then, we tried to increase the bulkiness of the two aryl groups on the phosphorus by changing the two phenyl group for two xylyl **L5**, but no improvement was observed on the reaction (Table 2, entry 5).

Then we decided to study the electronic effect of the aromatic part on the phosphorus atom. Ligands bearing electron-deficient aryl group ($3\text{-}F_3CC_6H_4$) **L6** gave a bad result with moderate conversion, regioselectivity, and low enantiomeric excess (Table 2, entry 6). A small increase of the electronic density on the aromatic was also detrimental to the reaction with a decrease of the enantiomeric excess down to 66% (Table 2, entry 7).

Table 2 Ligand Study[a]

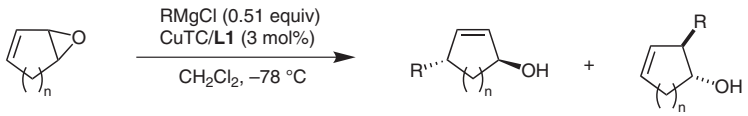
Entry	Ligand	Conversion (%)[b]	S_N2'/S_N2[c]	ee S_N2' (%)[d]
1	**L1**	47	95:5	88
2	**L2**	50	94:6	70
3	**L3**	45	90:10	22
4	**L4**	20	93:7	12
5	**L5**	50	97:3	88
6	**L6**	30	90:10	52
7	**L7**	45	97:3	66
8	**L8**	43	92:8	38
9	**L9**	42	98:2	84
10	**L10**	43	83:17	34

[a] Reaction conditions: **2** (1 mmol), CuTC (3 mol%), ligand (3 mol%), BuMgCl in Et_2O (0.5 equiv.), CH_2Cl_2, –78 °C.
[b] Determined by GC-MS with undecane as internal standard.
[c] Determined by ^1H NMR.
[d] Determined by chiral GC.

Finally, other modifications were studied such as the introduction of a chelating group on the aromatic part of the amine **L8**, C_1-symmetrical ligand **L9** and the replacement of a methyl group by an ethyl one on the amine part (Table 2, entries 8–10). But none of these modifications led to any improvement (38%, 84%, and 34% ee, respectively).

With this set of conditions in hand we tested the scope of the substrate and Grignard reagents (Scheme 3).

The very reactive five-membered ring **1** led to very good selectivities with simple primary Grignard reagents (Table 3, entries 1 and 2) with respectively 90% ee and 92% ee, with ethyl and butyl Grignard, and more than 90:10 regioselectivity. However, isolated yield remains low around 20%. Nevertheless, these results remain better than the one obtained previously on this substrate.[3] Moving to a secondary Grignard reagent had a positive effect



1 n = 1
2 n = 2

3a n = 2 R = Bu
4a n = 1 R = Et
5a n = 1 R = Bu
6a n = 1 R = *i*-Pr
7a n = 1 R = CH_2TMS
8a n = 2 R = Et
9a n = 2 R = CH_2CH_2Ph
10a n = 2 R = *i*-Bu
11a n = 2 R = *i*-Pr
12a n = 2 R = *c*-Hex
13a n = 2 R = *c*-C_5H_9
14a n = 2 R = CH_2TMS

3b n = 2 R = Bu
4b n = 1 R = Et
5b n = 1 R = Bu
6b n = 1 R = *i*-Pr
7b n = 1 R = CH_2TMS
8b n = 2 R = Et
9b n = 2 R = CH_2CH_2Ph
10b n = 2 R = *i*-Bu
11b n = 2 R = *i*-Pr
12b n = 2 R = *c*-Hex
13b n = 2 R = *c*-C_5H_9
14b n = 2 R = CH_2TMS

Scheme 3

on the yield, but the enantiomeric excess decreases somewhat while regioselectivity remained at the same level (Table 3, entry 3). Finally, the highly hindered and functionalized $TMSCH_2MgCl$ gave a poor S_N2'/S_N2 ratio of 58:42 but an interesting 72% ee with a good yield. This is the first successful result with this Grignard reagent.

The six-membered ring was then investigated. Simple primary Grignard reagents showed good reactivities with almost perfect regioselectivities and good enantioselectivities (80% ee for ethyl and 88% ee for butyl) with good conversion and yield (Table 3, entries 5 and 6). Optical rotation of the acetate derivative of **3a** allowed us to determine the absolute configuration 1*S*,4*S* {$[\alpha]_D^{20}$ –155 (*c* 0.76 $CHCl_3$), ee = 88%].[5] Increasing the bulkiness of the Grignard reagent in β-position induces a slight decrease in the enantioselectivity of the process 73% ee with $PhCH_2CH_2$ and 79% ee for *i*-Bu (Table 3, entries 7 and 8). The ee can be increased above the 80's by decreasing the conversion to 25% (Table 3, entry 9).

Using secondary Grignard reagents allowed a good enantioselectivity for the kinetic-resolution process and especially when the reaction was stopped below 50% conversion with ee above 90% and good regioselectivities (Table 3, entries 11 and 13). When the reaction was allowed to reach 50% conversion the ee decreased slightly below 90% (Table 3, entries 10, 12, and 14).

Finally, the highly hindered and functionalized $TMSCH_2MgCl$ gave a moderate regioselectivity and a good yield. Interestingly, even if the ee of the S_N2' is not high (45%) the S_N2 product is obtained in good enantioselectivity (70%, Table 3, entry 15).

It has already been shown that in some cases a regiodivergent kinetic resolution of such vinyloxiranes can be performed.[10] We tried to perform such resolution with our system by adding 1.5 equivalents of *i*-PrMgCl (Scheme 4). We were delighted to see that we managed to obtain the S_N2' product **11a** with still a moderate ee (54% ee) but the S_N2 product in enantiomerically pure form (>99% ee). No traces of the other enantiomer were detected.

In conclusion we have shown that SimplePhos ligands are able to perform the kinetic resolution of racemic cyclic vinyloxirane with moderate to good regio- and enantioselectivities and from low-to-good yields. We were also able to perform a regiodivergent kinetic resolution with secondary Grignard reagents yielding the homoallylic alcohol in moderate yield but in very high enantioselectivity. Furthermore, SimplePhos ligands gave access to a wider range of Grignard reagents (functionalized Grignard reagents) with the same or higher enantioselectivities than the ferrocenes-based ligands.[5] Reactions were also cleaner with this new methodology. Additional studies are in progress with other substrates and especially on the regiodivergent kinetic resolution process.

Table 3 Scope of Substrate and Grignard Reagents[a]

Entry	n	R	Product	Conversion[b] (yield,[c] %)	S_N2'/S_N2[d]	ee S_N2' (%)[e]
1	1	Et	**4a**	18	91:9	90
2	1	Bu	**5a**	20	90:10	92
3	1	*i*-Pr	**6a**	32	92:8	76
4	1	CH_2TMS	**7a**	41[f]	58:42	72[g]
5	2	Et	**8a**	48 (42)	95:5	82
6	2	Bu	**3a**	47	95:5	88 (–)
7	2	CH_2CH_2Ph	**9a**	42	>95:5	73
8	2	*i*-Bu	**10a**	46 (42)	97:3	79
9[h]	2	*i*-Bu	**10a**	25 (20)	97:3	83
10	2	*i*-Pr	**11a**	49 (45)	96:4	84
11[i]	2	*i*-Pr	**11a**	18 (15)	95:5	93
12	2	*c*-Hex[11]	**12a**	55 (44)	83:17	88
13[j]	2	*c*-Hex	**12a**	37 (32)	95:5	96
14	2	*c*-C_5H_9	**13a**	38 (35)	95:5	88
15	2	CH_2TMS	**14a**	36 (30[f])	87:13	45[k]

[a] Reaction conditions see Scheme 3.
[b] Determined by GC-MS with undecane as internal standard.
[c] Isolated yield of allylic alcohol.
[d] Determined by ^1H NMR.
[e] Determined by chiral GC.
[f] Isolated yield of the mixture.
[g] The ee of S_N2 product was not determined.
[h] Grignard: 0.3 equiv.
[i] Grignard: 0.25 equiv.
[j] Grignard: 0.4 equiv.
[k] Enantiomeric excess of S_N2 product: 70%.

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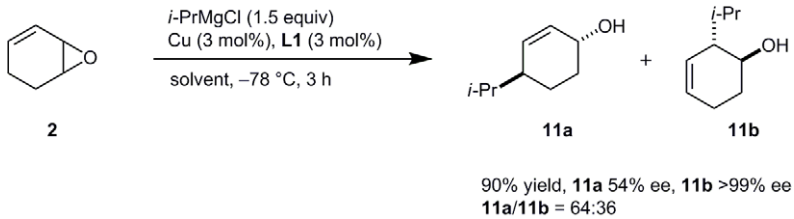

Scheme 4 Regiodivergent kinetic resolution of **2** with *i*-PrMgCl

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(11) **Typical Procedure**
In a dried Schlenk tube under N_2 atmosphere were placed CuTC (5.7 mg, 0.03 mmol) and (*S*,*S*)-**L1** (13.5 mg, 0.03 mmol). Then, CH_2Cl_2 was added (6 mL) and the mixture was stirred at r.t. for 20 min. The tube was cooled down to –78 °C and 1,3-cyclohexadiene monoepoxide **1** (100 μL, 1 mmol) was added. *c*-HexMgCl (250 μL, 2.0 M in Et_2O, 0.5 mmol) was added dropwise over a period of 3 min. The reaction was stirred for 3 h and quenched with MeOH and $(NH_4)_2SO_4$ before being allowed to reach r.t. The aqueous phase was extracted with CH_2Cl_2 and the organic layer was dried over $MgSO_4$ and the solvent removed on rotary evaporator (55% conversion, 88% ee). The crude product was purified by flash chromatography on SiO_2 (pentane then pentane–Et_2O, 75:25) yielding 79 mg (44% yield) of a white solid. $[\alpha]_D^{20}$ –128.2 (*c* 0.87, $CHCl_3$, ee = 88%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.68 (m, 2 H), 4.20 (br, 1 H), 2.09 (m, 1 H), 1.97 (m, 1 H), 1.74–1.60 (m, 6 H), 1.45–1.35 (m, 3 H), 1.22–1.12 (m, 4 H), 1.07–0.97 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 133.3, 130.1, 67.5, 42.4, 41.1, 32.7, 30.2, 29.7, 26.7, 23.7.