ORGANIC LETTERS

2002
Vol. 4, No. 23
4147−4149

Tandem Copper-Catalyzed Enantioselective Allylation–Metathesis

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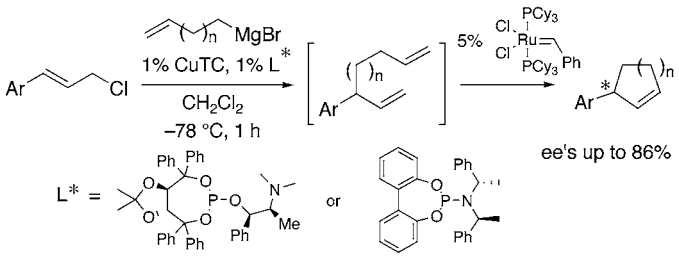
Received September 18, 2002

ABSTRACT

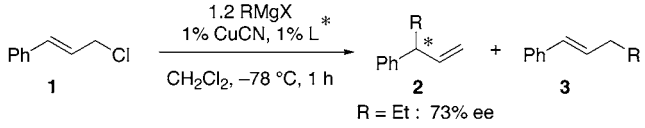


Grignard reagents undergo enantioselective (up to 86% ee) copper-catalyzed S_N2' substitution on achiral allylic chlorides. The reaction is wide in scope for both the Grignard reagent and the allylic substrate. The resulting terminal alkene could be submitted to intra- or intermolecular metathesis to afford new chiral synthons. The experimental conditions are compatible with a one-pot overall substitution–metathesis procedure without loss of enantioselectivity.

The allylic substitution reaction is a useful organic transformation, provided the regio-, stereo-, and chemoselectivities could be controlled. This control is usually provided by the type of metal catalyst, by the nucleophile, and by the leaving group.[1] In the field of asymmetric synthesis, although spectacular results have been achieved with Pd,[2] only recent attention has been paid to Cu, despite the fact that it allows the best γ-regioselectivity.[3] In addition, Cu allows the use of Grignard or organozinc reagents as nucleophiles.

Enantioselective copper-catalyzed γ-allylations have been disclosed, with R_2Zn, by Knochel,[4] Hoveyda,[5] and Feringa,[6] and with RMgX, by us[7] and by Van Koten and Bäckvall.[8] The latter authors have worked with a chiral Cu thiolate, as chiral source, whereas all other authors have used an external chiral ligand (Scheme 1).

Scheme 1



In our first report,[7] we showed that Grignard reagents can afford high enantioselectivity only with aryl-substituted (cinnamyl-type) allylic chlorides. CuCN was essential for the control of the γ-regioselectivity, and the best ligand was **4** (Figure 1). Since that report, we have disclosed new chiral ligands, **5**−**7**, with induced atropoisomerism,[9] and we have

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(3) Karlström, A. S. E.; Bäckvall, J.-E. In *Modern Organocopper Chemistry*; Krause, N., Ed.; Wiley-VCH: Weinheim, 2001; p 259.
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10.1021/ol0269244 CCC: $22.00
Published on Web 10/16/2002

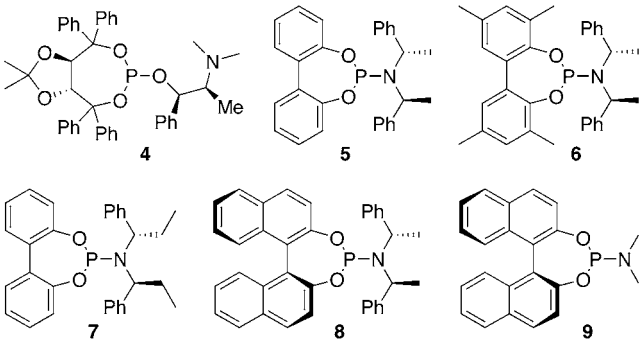

Figure 1. Chiral ligands used in this work.

found that other experimental conditions were more appropriate (Cu carboxylates, Et_2O) for the conjugate addition with phosphorus ligands.[10] We expected that these new conditions, together with new ligands, could afford much better enantioselectivities, and wider substrate and RMgX tolerance.

Keeping our previous best ligand **4** but changing the copper salt to CuTC (copper thiophene 2-carboxylate) improved the enantioselectivity on cinnamyl chloride to 82%, instead of 73% (Table 1, entries 1 and 2). Shifting to the

Table 1. Allylic Substitution of Cinnamyl Chloride with EtMgBr and Various Chiral Ligands, According to Scheme 1

entry	ligand	Cu salt	solvent	T (°C)	% convn	γ/α	% ee
1	**4**	CuCN	CH_2Cl_2	−78	100	96/4	73, *R*
2	**4**	CuTC	CH_2Cl_2	−78	100	96/4	82, *R*
3	**5**	CuCN	CH_2Cl_2	−78	100	100/0	6, *S*
4	**5**	CuTC	CH_2Cl_2	−78	100	91/9	79, *S*
5[a]	**5**	CuTC	CH_2Cl_2	−78	100	84/16	75, *S*
6	**5**	CuTC	CH_2Cl_2	−55[b]	100	90/10	68, *S*
7	**5**	CuTC	Et_2O	−55[b]	47	2/92	
8	**5**	CuTC	toluene	−55[b]	50	34/66	58, *S*
9	**5**	CuTC	$CHCl_3$	−55[b]	100	92/8	70, *S*
10	**5**	$CuOAc_2$	CH_2Cl_2	−55[b]	100	94/6	70, *S*
11	**5**	CuNaphth	CH_2Cl_2	−55[b]	100	68/32	60, *S*
12	**6**	CuTC	CH_2Cl_2	−55[b]	100	38/62	54, *S*
13	**7**	CuTC	CH_2Cl_2	−55[b]	100	89/11	68, *S*
14	**8**	CuTC	CH_2Cl_2	−55[b]	100	90/10	49, *R*
15	**9**	CuTC	CH_2Cl_2	−55[b]	100	85/15	7, *R*

[a] With cinnamyl bromide instead of chloride. [b] 5% of Cu salt and ligand.

new ligand **5** showed a dramatic difference between the use of CuCN (6% ee) and CuTC (79% ee). In this case, cinnamyl bromide (entry 5) affords results similar to those with the chloride. Et_2O and toluene (entries 7 and 8) are not good solvents, whereas chloroform (entry 9) is similar to dichloromethane. $CuOAc_2$ (entry 10) is as efficient as CuTC, whereas copper naphthenate gives a diminished regioselectivity. The other biphenol-type ligands **6** and **7** gave slightly lower enantioselectivities. Finally, the known ligands **8** and **9**[11] were also screened and gave moderate or very low ee's.

It should be pointed out that, in the absence of ligand, CuTC alone gave 90% of α-substituted product, whereas the presence of a phosphorus ligand reverses the trend toward γ-regioselectivity (Scheme 2). This effect of a donor ligand on the regioselectivity is unprecedented in the Cu literature.[12]

Scheme 2

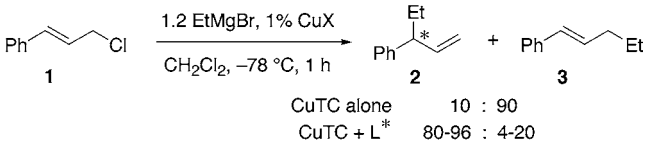

Table 2 shows the results obtained with various Grignard reagents. It should be recalled that in all these examples

Table 2. Allylic Substitution of Cinnamyl Chloride with Various Grignard Reagents[a]

entry	ligand	Grignard	% convn[b]	γ/α	% ee
1	**4**	EtMgBr	100 (97%)	96/4	82, *R*
2	**5**		100 (96%)	92/8	79, *S*
3	**4**	MeMgBr	95	31/69	61, *R*
4	**5**		83	12/88	62, *S*
5	**4**	*n*-PrMgBr	100 (96%)	80/20	75, *R*
6	**5**		100	59/41	69, *S*
7	**4**	3-butenyl-MgBr	100	91/9	61, *R*
8	**5**		100 (94%)	71/29	48, *S*
9	**4**	4-pentenyl-MgBr	100	90/10	72, *R*
10	**5**		100 (92%)	73/27	64, *S*
11	**4**	*i*-PrMgBr	100	88/12	46, *R*
12	**5**		100 (98%)	90/10	83, *S*

[a] All reactions were done with 1% CuTC + 1% ligand, in CH_2Cl_2, at −78 °C. [b] In parentheses: isolated yield of the mixture of regioisomers.

CuCN does not allow high enantioselectivities, whereas CuTC does. Cinnamyl chloride reacts with *n*-propyl, 3-butenyl, and 4-pentenyl Grignard reagents in a similar way than EtMgBr. The regio- and the enantioselectivity are usually better with the TADDOL-derived ligand **4** than with **5**. Only with a secondary Grignard, *i*-PrMgBr, ligand **5** is clearly superior, giving the best ee's (83%, entry 12).

As shown in Scheme 3, the results obtained with *i*-PrMgBr are steadily high (up to 86% ee) with a range of cinnamyl-type chlorides. This is a clear improvement over our previous results.[7]

The use of CuTC and the new ligands allow extension to alkyl substituents on the allylic substrate. Thus, the saturated analogue of cinnamyl chloride **10** could be enantioselectively substituted (Table 3, entry 8) with up to 74% ee. This is the first time that a catalytic system, with Grignard reagents, is

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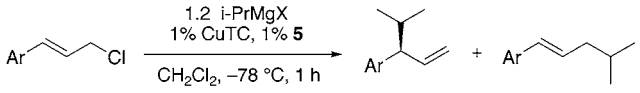
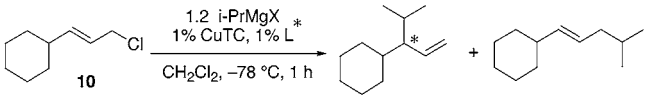
Scheme 3



Ar	yield %	γ : α	ee %
Ph	98	90 : 10	83
2-Naphth	97	92 : 8	85
4-Cl-C_6H_4	92	87 : 13	79
3,4-diCl-C_6H_3	93	89 : 11	80
4-Me-C_6H_4	93	91 : 9	83
4-MeO-C_6H_4	98	90 : 10	77
3-MeO-C_6H_4	98	91 : 9	86
3,5-CH_2O_2-C_6H_3	96	92 : 8	82

equally effective with both aromatic and aliphatic substituents on the allylic substrate. Table 3 summarizes our results with several ligands. As seen previously, TADDOL-derived ligand **4** is not efficient in this series. Biphenol ligands **5** and **7** work equally well with high ee's (68%). Similarly, ligand **8** and its diastereomer **8′** afford high ee's but show a match/mismatch effect,[11] as for the conjugate addition.

Table 3. Allylic Substitution of (3-Chloropropenyl)cyclohexane by *i*-PrMgBr and 1% CuTC as Catalyst[a]



entry	ligand	Cu salt	% convn[b]	γ/α	% ee
1	**4**	CuCN	100	96/4	2, *R*
2	**4**	CuTC	100	83/17	13, *R*
3	**5**	CuCN	100	99/1	51, *S*
4	**5**	CuTC	100 (95%)	99/1	68, *S*
5	**6**	CuTC	100	18/82	18, *S*
6	**7**	CuTC	100	98/2	68, *S*
7	**8**	CuCN	100	99/1	49, *R*
8	**8**	CuTC	100	99/1	74, *R*
9	**8′**[a]	CuTC	100	97/3	63, *S*
10	**9**	CuTC	100	96/4	12, *R*

[a] **8′** is the (S_a,*SS*) diastereomer of ligand **8**. [b] In parentheses: isolated yield of the mixture of regioisomers.

All the above allylic substitution reactions end up with a terminal vinyl group. This group is usually further transformed in a second step, by cleavage of the double bond or hydroborated and oxidized. Another possibility, not yet explored, could be the metathesis reaction. Accordingly, the intermolecular reaction was attempted, according to Grubbs,[13] without loss of optical purity, giving **11**, a useful new chiral synthon (Scheme 4).

An interesting aspect would be to be able to perform the whole procedure in one pot. However, nothing was known about the compatibility of Grubbs catalyst with excess Grignard reagent and copper salts. Accordingly, 3 equiv of

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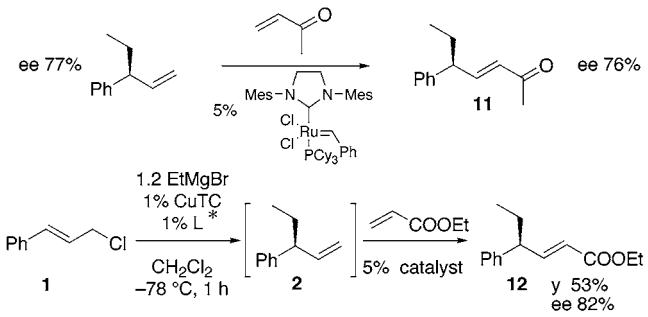
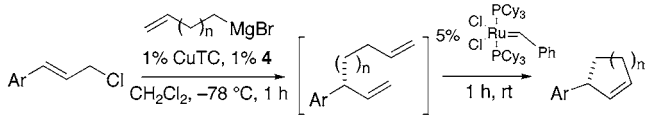
Scheme 4



ethyl acrylate and 5% Grubbs catalyst were added to the reaction mixture, after completion of the allylic substitution (Scheme 4). After 24 h at 40 °C, the reaction was completed, and **12** was obtained in 53% isolated yield and an ee of 82%, identical to intermediate **2**.

The intramolecular version was equally successful with the 4-pentenyl- and 3-butenyl-substituted substrates affording, quantitatively, the cyclized product in just 1 h at room temperature. The RCM compounds could be easily separated from the S_N2 regioisomer and obtained in good isolated yield with the same enantioselectivity as the intermediate diene (Scheme 5).

Scheme 5



Ar =	n =	isolated yield % =	ee % =
Ph	1	68	61
p-Tol	1	64	64
Ph	2	79	72
p-Tol	2	66	76

In conclusion, thanks to new Cu salts and new ligands, we have extended the enantioselective Cu-catalyzed γ-allylic substitution with Grignard reagents to several aryl- and alkyl-substituted substrates. The ee values are the best known for Grignard reagents, which are cheaper and more available commercially than diorganozinc reagents. We have also pointed out the unknown effect of the ligand on the regioselectivity. Finally, we have demonstrated the synthetic versatility of the method by carrying out a tandem substitution-metathesis reaction in a one pot procedure.

Acknowledgment. We thank Stephane Rosset and Gaëlle Lisci for help and the Swiss National Research Foundation No. 20-61891.00 and COST action D12/0022/99 for financial support.

Supporting Information Available: Experimental details and spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0269244