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γ-Selective allylic substitution reaction with Grignard reagents catalyzed by copper *N*-heterocyclic carbene complexes and its application to enantioselective synthesis

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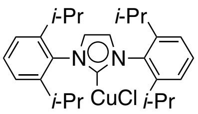
Abstract—The reaction of allylic compounds with alkyl Grignard reagents in the presence of a catalytic amount of copper *N*-heterocyclic carbene (NHC) complexes proceeded predominantly in an S_N2' reaction pathway to give γ-substituted product in excellent yield. The method was applied to asymmetric reaction by using optically active NHC ligands.

Copper-catalyzed allylic substitution reactions have received widespread acceptance as valuable methods in organic synthesis.[1,2] Among various organometallic counterparts in these reactions, Grignard reagents have been widely used due to their variety and accessibility. The regioselectivity of the substitution is dependent upon the structure of the allylic substrates and the Grignard reagents and is also influenced by the reaction conditions including copper salt, solvent(s), temperature and the addition order of reagents.[1] Protocols have been developed to effect clean γ-substitution (S_N2' reaction), where CuCN (or its salts) has been utilized in general. However, further development of the reaction with copper catalysts *having a modifiable organic ligand* other than simple inorganic salts is desired because it would enable catalyst-based control of the reaction including enantioselection.[3] Herein reported is a novel procedure for S_N2'-selective reaction with a Grignard reagent catalyzed by copper *N*-heterocyclic carbene (NHC) complexes and its application to enantioselective substitution by using chiral modified NHC ligands.[4,5]

Table 1 shows the feasibility of CuCl–NHC complexes **4**[6] as a catalyst for Grignard substitution of allylic substrates **1**. Thus, (*E*)-2-nonenol derivatives **1** ($R = n\text{-}C_6H_{13}$) were treated with *i*-PrMgCl (1.5 equiv) in the presence of a catalytic amount of **4** (1 mol %) at 0 °C.[7] As revealed from Table 1, high γ-selectivity was observed in the reaction with **1** having a variety of leaving groups (X) such as carbonate, acetate, phosphate and chloride when the reaction was carried out in diethyl ether. It was observed that the reaction with **4a** was slower than that with **4b** and the regioselectivity with **4a** was somewhat lower than that with **4b** (entries 1 and 2),[8] probably due to steric bulkiness of the ligated NHC part in **4a**. The reaction could be effectively catalyzed by a reduced amount of catalyst (0.1 mol %) (entry 3). While allylic carbonate gave α-product **3** predominantly in THF (entry 4), allylic chloride afforded γ-product **2** nearly exclusively in both ether and THF (entries 7 and 8). These results suggest that coordination of the leaving group in the substrate to the metal may be important in the reaction of ester allylic substrates. On the basis of the fact that a CuCl-catalyzed reaction gave α-product exclusively (entry 9), the high γ-selectivity attained in the **4**-catalyzed reactions indicates that the NHC-copper bond (coordination) is stable and was not cleaved during the catalysis.

4a:



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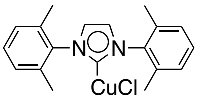

Keywords: Allylic substitution; Organocopper; *N*-Heterocyclic carbene; Asymmetric reaction.

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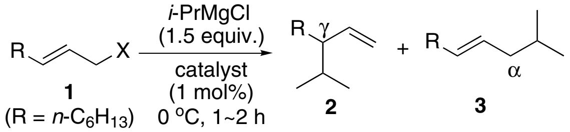
Table 1.

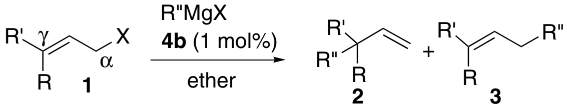


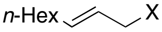
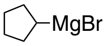
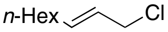
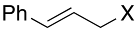
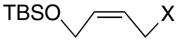
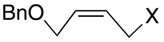
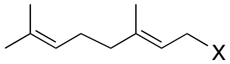
Entry	X	Catalyst	Solvent	2:3[a]	Total yield %
1	OCO_2Et	**4a**	Ether	95:5	Quant.
2	OCO_2Et	**4b**	Ether	>99:1	Quant.
3	OCO_2Et	**4b** (0.1 mol%)	Ether	>99:1	Quant.
4	OCO_2Et	**4b**	THF	24:76	50[b]
5	OAc	**4b**	Ether	94:6	Quant.
6	$OP(O)(OEt)_2$	**4b**	Ether	>99:1	Quant.
7	Cl	**4b**	Ether	>99:1	Quant.
8	Cl	**4b**	THF	96:4	96
9	OCO_2Et	CuCl	Ether	1:99	90

[a] Determined by 500 MHz ^{1}H NMR analysis.

[b] Reaction was performed for 48 h. 50% of **1** was recovered.

Table 2.

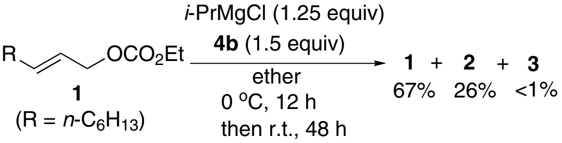


Entry	1 (X = OCO_2 Et)	R″MgX	2:3	Total yield %
1		MeMgI	97:3	88
2		n-Hex·MgBr	99:1	Quant.
3			99:1	Quant.
4		PhMgBr[a]	2:98	Quant.
5		PhMgBr[a]	3:97	82
6		i-PrMgCl	95:5	82
7		i-PrMgCl	>99:1	Quant.
8		i-PrMgCl	>99:1	Quant.
9[b]		MeMgI	>99:1	84

[a] PhMgBr was prepared in THF.

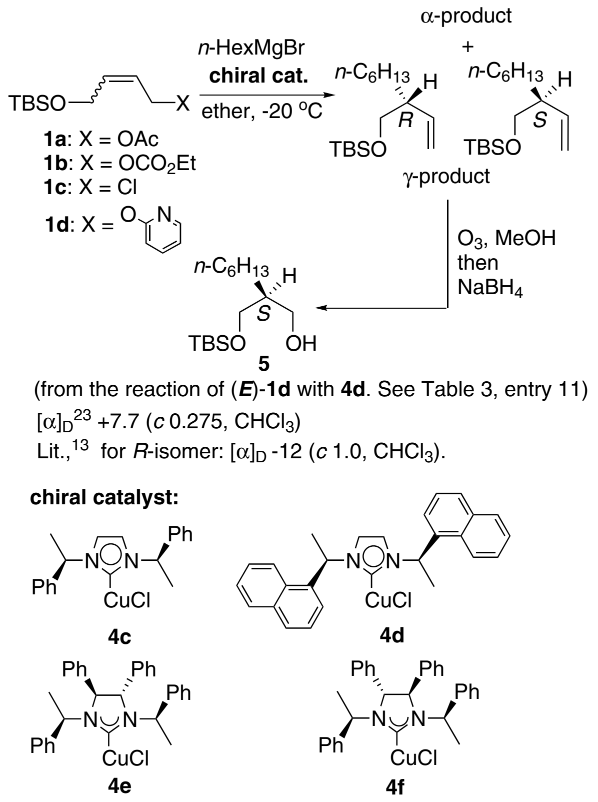
[b] 5 mol% of **4b** was used.

Table 2 summarizes representative examples of this reaction using a variety of allylic substrates and Grignard reagents. These results show the following features of this substitution reaction: (i) Primary alkyl including methyl and secondary alkyl Grignard reagents could provide **2** in excellent yield and regioselectivity. (ii) But aryl Grignard reagents gave α-product **3** predominantly (entries 4 and 5). (iii) Regarding allylic substrates, the reaction with disubstituted and trisubstituted **1** having a variety of substituents such as alkyl, aryl, siloxy- and alkoxymethyl groups with *E*- or *Z*-geometry proceeded in a highly γ-selective way.



Scheme 1.

As shown in Scheme 1, the reaction of allylic carbonate **1** and *i*-PrMgCl with a stoichiometric amount of **4b** was found to be much slower than that with a catalytic amount of **4b** mentioned above. On this basis, the major active catalyst in the present reaction can be postulated to be an ate-complex (higher order cuprate) such as the type $[(NHC)CuR_2]^-(MgX)^+$ but not a complex of the type (NHC)CuR[9] although confirmation of the reaction mechanism and explanation of a high regioselectivity must await further study.



(from the reaction of (*E*)-**1d** with **4d**. See Table 3, entry 11)
$[\alpha]_D^{23}$ +7.7 (*c* 0.275, $CHCl_3$)
Lit.,[13] for *R*-isomer: $[\alpha]_D$ -12 (*c* 1.0, $CHCl_3$).

Scheme 2.

With these results in hand, we turned our attention to perform the reaction in an asymmetric way by using copper complexes with chiral modified NHC ligands. Scheme 2 and Table 3 summarize preliminary results. Thus, 4-siloxy-2-buten-1-ol derivatives **1a**–**d** were treated with *n*-$C_6H_{13}MgBr$ in the presence of copper complexes with enantiomerically pure C_2-symmetric NHC ligands, **4c**–**f**[10] (5 mol %), in ether at −20 °C (Scheme 2). The resulting γ-product[11] was isolated and converted to the corresponding MTPA-esters,[12] 500 MHz ^1H NMR analyses of which confirmed the enantiomeric excess (ee) of the γ-product. The γ-product obtained by the reaction of (*E*)-**1d** with **4d** catalyst (entry 11) was converted to the known alcohol **5**[13] by ozonolysis and the following reduction, and comparison of its optical rotation with that reported determined the absolute configuration as illustrated in Scheme 2.

As can be seen from Table 3, the reactions proceeded quantitatively in S_N2'-selective fashion to give optically active γ-substituted product with low to moderate enantiomeric purity. As revealed from the results in entries 1–4, the catalyst with sterically demanding *N*-substituents (**4d**) gave the highest ee. Interestingly, introduction of additional C_2-chirality into the heterocyclic part of NHC resulted in inversion or decrease of the enantioselectivity (entries 3 and 4). Allylic acetate and 2-pyridyl ether[14] were good substrates but carbonate and chloride gave low ee. Inversion of the product configuration was observed when *E*-allylic substrates were used instead of *Z*-isomers, and the ee of the products from *E*-substrates was somewhat lower than that from the corresponding *Z*-isomers (entries 5 and 11). The highest enantiomeric ratio of 85:15 was attained by the reaction of 2-pyridyl ether (*Z*)-**1d** with catalyst **4d** (entry 10).

In summary, we have demonstrated that copper *N*-heterocyclic carbene (NHC) complexes are a useful catalyst for the highly S_N2'-selective allylic substitution reaction with Grignard reagents and the method can be applied to asymmetric reaction by using chiral modified NHC ligands although the preliminary results presented here reached moderate level of ee. Further investigation on the scope of the present reaction and its synthetic utilization including development of method to attain more efficient enantioselection is underway in our laboratory.

Table 3.[a]

Entry	Allylic substrate	Catalyst		γ-Product		
			γ:α	% Ee[b]	Config.[c]	$[\alpha]_D$[d]
1	(*Z*)-**1a**	**4c**	87:13	40	*R*	+6.6
2		**4d**	95:5	60	*R*	+10.0
3		**4e**	88:12	38[e]	*S*	−6.1
4		**4f**	84:16	6[e]	*R*	+1.0
5	(*E*)-**1a**	**4d**	97:3	38[e]	*S*	−6.1
6	(*Z*)-**1b**	**4c**	96:4	5[e]	*R*	+0.9
7	(*Z*)-**1c**	**4c**	77:23	8[e]	*S*	−1.3
8		**4d**	84:16	16[e]	*R*	+2.5
9	(*Z*)-**1d**	**4c**	91:9	36	*R*	+6.3
10		**4d**	98:2	70	*R*	+11.0
11	(*E*)-**1d**	**4d**	86:14	60	*S*	−9.8

[a] Total yield of the reaction was 93–100%.
[b] Determined by 500 MHz ^1H NMR analyses of the corresponding MTPA-esters, unless otherwise indicated.
[c] Confirmed for entry 11 (see text).
[d] *c* in 1.0 $CHCl_3$, at 23 °C.
[e] Based on $[\alpha]_D$ value.

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2. For organocopper chemistry, see: *Organocopper Reagents*; Taylor, R. J. K., Ed.; Oxford University Press: Oxford, 1994; Lipshutz, B. H. In *Organometallics in Synthesis*; Schlosser, M., Ed.; Wiley: Chichester, 2002; p 665; *Modern Organocopper Chemistry*; Krause, N., Ed.; Wiley-VHC: Weinheim, 2001.
3. Chiral copper complex-catalyzed enantioselective allylic substitution reactions: with Grignard reagents: van Klaveren, M.; Persson, E. S. M.; del Villar, A.; Grove, D. M.; Bäckvall, J.-E.; van Koten, G. *Tetrahedron Lett.* **1995**, *36*, 3059; Karlström, A. S. E.; Huerta, F. F.; Meuzelaar, G. J.; Bäckvall, J.-E. *Synlett* **2001**, 923; Meuzelaar, G. J.; Karlström, A. S. E.; van Klaveren, M.; Persson, E. S. M.; del Villar, S.; van Koten, G.; Bäckvall, J.-E. *Tetrahedron* **2000**, *56*, 2895; Alexakis, A.; Malan, C.; Lea, L.; Benhaim, C.; Fournioux, X. *Synlett* **2001**, 927; Alexakis, A.; Croset, K. *Org. Lett.* **2002**, *4*, 4147; Croset, K.; Polet, D.; Alexakis, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 2426; With dialkylzinc compounds, Dübner, F.; Knochel, P. *Angew. Chem., Int. Ed.* **1999**, *38*, 379; Dübner, F.; Knochel, P. *Tetrahedron Lett.* **2000**, *41*, 9233; Malda, H.; van Zijl, A. W.; Arnold, L. A.; Feringa, B. L. *Org. Lett.* **2001**, *3*, 1169; Luchaco-Cullis, C. A.; Mizutani, H.; Muphy, K. E.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2001**, *40*, 1456.
4. Asymmetric conjugate addition reactions catalyzed by copper imidazolium carbene complexes: (a) Guillen, F.; Winn, C. L.; Alexakis, A. *Tetrahedron: Asymmetry* **2001**, *12*, 2083; (b) Fraser, P. K.; Woodward, S. *Tetrahedron Lett.* **2001**, *42*, 2747; (c) Alexakis, A.; Winn, C. L.; Guillen, F.; Pytkowicz, J.; Roland, S.; Mangeney, P. *Adv. Synth. Catal.* **2003**, *345*, 345.
5. Other catalyses with copper imidazolium carbene complexes in organic synthesis: (a) Jurkauskas, V.; Sadighi, J. P.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 2417; (b) Kaur, H.; Zinn, F. K.; Stevens, E. D.; Nolan, S. P. *Organometallics* **2004**, *23*, 1157, and references for recent structural studies of *N*-heterocyclic carbene copper complexes cited therein.
6. Compounds **4a**[5] and **4b** were prepared by the reaction of CuCl, *t*-BuONa and the corresponding imidazolium chloride in THF according to the reported procedure.[5] The isolated **4a** and **4b** were used. **4b**: Mp 268 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.31 (t, $J = 7.5$ Hz, 2H), 7.21 (d, $J = 8.0$ Hz, 4H), 7.10 (s, 2H), 2.17 (s, 12H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 137.4, 134.9, 129.6, 128.8, 122.1, 17.8 (one carbon could not be detected); IR (neat) 3166, 1695, 1599, 1557, 1479, 1443, 1404, 1335, 1290, 1230, 1161, 1110, 1038, 948, 786, 735, 693, 609 cm^{-1}. Elemental analysis, calcd for $C_{19}H_2N_2OClCu$: C, 60.79; H, 5.37; N, 7.46. Found: C, 60.95; H, 5.54; N, 7.47.
7. To a suspension of CuCl–NHC complex **4** (0.02 mmol) in ether (1 mL) was added Grignard reagent (0.7–1.5 M in ether, 3.0 mmol) at 0 °C and the mixture was stirred for 0.5 h at this temperature. To this was added a solution of allylic substrate **1** (2.0 mmol) in ether (2 mL) and the mixture was stirred at 0 °C. After confirming the completion of the reaction by TLC analysis, saturated aqueous NH_4Cl was added. Usual extractive work-up and passing through a short silica gel column yielded a mixture of α- and γ-products.
8. TLC analysis of the reaction mixture indicated that for complete consumption of **1a** it needed 2 h for the reaction with **4a** and 30 min for the reaction with **4b**.
9. Synthesis and structural study of (NHC)Cu(I) methyl complex were reported: Mankad, N. P.; Gray, T. G.; Laitar, D. S.; Sadighi, J. P. *Organometallics* **2004**, *23*, 1191.
10. Compounds **4c–f** were prepared from the corresponding imidazolium salts,[4c] *t*-BuONa and CuCl in THF. The resulting mixture was filtered through a pad of Celite and the filtrate was stored under Ar. The THF-solution containing **4c–f**, respectively, thus obtained was charged into the reaction vessel and THF was removed under reduced pressure prior to use.
11. *tert*-Butyldimethyl(2-hexylbut-3-enyloxy)silane: ^{1}H NMR ($CDCl_3$, 270 MHz): δ 5.62 (ddd, $J = 8.4$, 9.7, 17.8 Hz, 1H), 4.97–5.07 (m, 2H), 3.52 (dd, $J = 6.3$, 11.2 Hz, 1H), 3.49 (dd, $J = 6.3$, 11.2 Hz, 1H), 2.07–2.23 (m, 1H), 1.10–1.60 (m, 10H), 0.89 (s, 9H), 0.88 (t, $J = 7.1$ Hz, 3H), 0.07 and 0.04 (2s, each 3H); ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 140.6, 115.2, 66.7, 31.8, 30.8, 29.4, 27.0, 26.0, 22.7, 18.4, 14.1, −5.3, −5.4; IR (neat) 3076, 2926, 2854, 1644, 1470, 1383, 1365, 1254, 1101, 1008, 942, 915, 837, 777 cm^{-1}. Elemental analysis, calcd for $C_{16}H_{34}OSi$: C, 71.04; H, 12.67. Found: C, 70.64; H, 13.00.
12. Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1971**, *95*, 512.
13. Gurjar, M. K.; Bhaket, P. *Heterocycles* **2000**, *53*, 143.
14. We found that the reaction of allylic 2-pyridyl ethers with alkyl Grignard reagents in the presence of a catalytic amount of CuCN in ether proceeded highly predominantly in an S_N2' fashion (unpublished results).