Title
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**Graphical Abstract**

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\begin{align*}
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\end{align*}
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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. © 2011 Elsevier Science. All rights reserved

Copper-catalyzed allylic substitution reactions have received widespread acceptance as valuable methods in organic synthesis. 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. 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. 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.

Table 1 shows the feasibility of CuCl-NHC complexes as a catalyst for Grignard substitution of allylic substrates. Thus, (E)-2-nonenol derivatives (R = n-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

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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), 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 give 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.

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).
(ii) 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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>R'</th>
<th>R''</th>
<th>γ-product 2</th>
<th>α-product 3</th>
<th>Total yield</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>n-Hex</td>
<td>X</td>
<td>OOCOEt</td>
<td>MeMgl</td>
<td>97 : 3</td>
<td>88</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>n-Hex</td>
<td>MgBr</td>
<td></td>
<td>99 : 1</td>
<td>quant.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>n-Pr</td>
<td>Br</td>
<td></td>
<td>99 : 1</td>
<td>quant.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Ph</td>
<td></td>
<td></td>
<td>2 : 98</td>
<td>quant.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>n-Hex</td>
<td>Cl</td>
<td>PhMgl</td>
<td>3 : 97</td>
<td>82</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Ph</td>
<td></td>
<td>i-PrMgl</td>
<td>95 : 5</td>
<td>82</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>TBSO</td>
<td></td>
<td>i-PrMgl</td>
<td>&gt;99 : 1</td>
<td>quant.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Ph</td>
<td></td>
<td></td>
<td>MeMgl</td>
<td>&gt;99 : 1</td>
<td>84</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Ph</td>
<td></td>
<td></td>
<td></td>
<td>75 mol% of 4b was used.</td>
<td></td>
<td></td>
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</tbody>
</table>

As shown in Scheme 1, the reaction of allylic
carbonate 1 and i-PrMglCl 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 although confirmation of the reaction
mechanism and explanation of a high regioselectivity must
await further study.

Scheme 1

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-siloxa-
2-buten-1-ol derivatives 1a-1d were treated with n-
C6H13MgBr in the presence of copper complexes with
enantiomerically pure C2-symmetric NHC ligands, 4c-4f
(5 mol%), in ether at ~20 °C (Scheme 2). The resulting γ-
product11 was isolated and converted to the corresponding
MTPA-esters,12 500 MHz 1H NMR analyses of which
confirmed the enantiomeric excess (e.e.) 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 513
by ozonolysis and the following reduction, and comparison
of its optical rotation with that reported determined the
absolute configuration as illustrated in Scheme 2.

Scheme 2
As can be seen from Table 3, the reactions proceeded quantitatively in S$_2$2'-selective fashion to give optically active $\gamma$-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 e.e. Interestingly, introduction of additional C$_7$-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 were good substrates but carbonate and chloride gave low e.e. Inversion of the product configuration was observed when E-allylic substrates were used instead of Z-isomers, and the e.e. 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).

<table>
<thead>
<tr>
<th>entry</th>
<th>allylic</th>
<th>catalyst</th>
<th>$\gamma$:</th>
<th>$\gamma$-product</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>substrate</td>
<td></td>
<td></td>
<td>%</td>
</tr>
<tr>
<td>1</td>
<td>(Z)-1a</td>
<td>4c</td>
<td>87:13</td>
<td>40</td>
</tr>
<tr>
<td>2</td>
<td>4d</td>
<td>95:5</td>
<td>60</td>
<td>R</td>
</tr>
<tr>
<td>3</td>
<td>4e</td>
<td>88:12</td>
<td>38°</td>
<td>S</td>
</tr>
<tr>
<td>4</td>
<td>4f</td>
<td>84:16</td>
<td>6°</td>
<td>R</td>
</tr>
<tr>
<td>5</td>
<td>(E)-1a</td>
<td>4d</td>
<td>97:3</td>
<td>38°</td>
</tr>
<tr>
<td>6</td>
<td>(Z)-1b</td>
<td>4c</td>
<td>96:4</td>
<td>5°</td>
</tr>
<tr>
<td>7</td>
<td>(Z)-1c</td>
<td>4c</td>
<td>77:23</td>
<td>8°</td>
</tr>
<tr>
<td>8</td>
<td>4d</td>
<td>84:16</td>
<td>16°</td>
<td>R</td>
</tr>
<tr>
<td>9</td>
<td>(Z)-1d</td>
<td>4c</td>
<td>91:9</td>
<td>36</td>
</tr>
<tr>
<td>10</td>
<td>4b</td>
<td>98:2</td>
<td>70</td>
<td>R</td>
</tr>
<tr>
<td>11</td>
<td>(E)-1d</td>
<td>4d</td>
<td>86:14</td>
<td>60</td>
</tr>
</tbody>
</table>

Table 3

aTotal yield of the reaction was 93-100%. bDetermined by 500 MHz $^1$H NMR analyses of the corresponding MTPA-esters, unless otherwise indicated. cConfirmed for entry 11 (see text). dBased on $\delta_{10}$ value.

In summary, we have demonstrated that copper N-heterocyclic carbene (NHC) complexes are a useful catalyst for the highly S$_2$2'-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 e.e. 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.

References

6. Compounds 4a and 4b were prepared by the reaction of CuCl-t-BuONa and the corresponding imidazolidine chloride in THF according to the reported procedure. The isolated 4a and 4b were used: 4b: Mp 268 °C; $^1$H NMR (CDC$_1$_1, 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 (CDC$_1$_1, 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, 1443, 1404, 1335, 1290, 1230, 1161, 1110, 1038, 948, 786, 735, 693, 609 cm$^{-1}$. Elemental analysis, Calcd. for C$_{24}$H$_{28}$N$_{2}$O$_{2}$C$_{1}$; 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$_{4}$Cl was added. Usual extractive work-up and washing through a short silica gel column yielded a mixture of $\alpha$- and $\gamma$-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 30min for the reaction with 4b.
10. Compounds 4c-4f were prepared from the corresponding imidazolidine salts, 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-4f, 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) $\delta$ 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) $\delta$ 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$_{34}$O$_2$Si; C, 71.04; H, 12.67. Found; C, 70.64; H, 13.00.


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$\text{N}_2$' fashion (unpublished results).