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Generation and asymmetric Michael addition reaction of chirally *N*-protected α-aminoalkyl cyanocuprates

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Abstract

Enantio-enriched α-aminopropylcyanocuprates, generated from the chirally *N*-protected α-aminopropylstannane (racemic at the Sn-bearing stereocenter) via Pearson's Sn/Li transmetalation protocol followed by treatment with copper cyanide, is shown to undergo an addition reaction to α,β-unsaturated aldehydes and ketones to give the γ-amino carbonyl compounds in higher stereoselective fashion. Of special interest is the reaction with acrolein and 2-cyclohexenone which affords the adducts as a single stereoisomer.

Keywords: asymmetric synthesis; amino ketones; copper reagents; transmetalation; Michael reaction.

The Michael reaction of organocopper reagents to α,β-unsaturated carbonyl compounds is a useful C–C bond-forming reaction, and hence the development of its asymmetric versions is a subject of current extensive studies.[1] While two types of asymmetric versions have been developed which employ either a Michael acceptor having a chiral auxiliary or a copper reagent having a chiral but nontransferable ligand, little is known about another type of asymmetric version which employs a copper reagent having an enantio-enriched transferable ligand. Recently, Linderman et al. have shown the feasibility of this approach in the Michael addition reactions of enantio-enriched α-alkoxy organocopper reagents.[2] However, no example of the successful generation of enantio-enriched α-amino alkylcuprates from chiral organolithium precursors has been reported,[3–5] mainly due to the considerable difficulty encountered in the enantioselective generation of α-amino organolithiums and their configurational instability.[6] To overcome these difficulties, we were interested in the use of Pearson's chirally *N*-protected chiral α-aminoalkyllithiums (**B**) as cuprate precursors which can be generated diastereoselectively from the chirally *N*-protected α-aminoalkylstannanes (**A**) in which the Sn-bearing stereocenter is racemic (Eq. (1)).[7,8] Herein disclosed are the preliminary results on the generation of the chirally *N*-protected chiral

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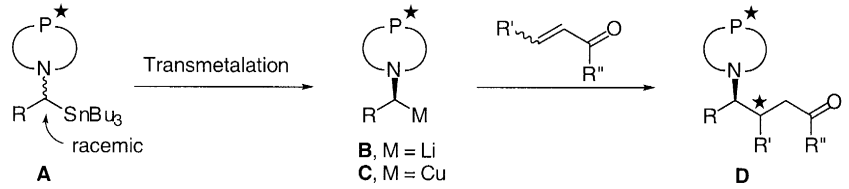
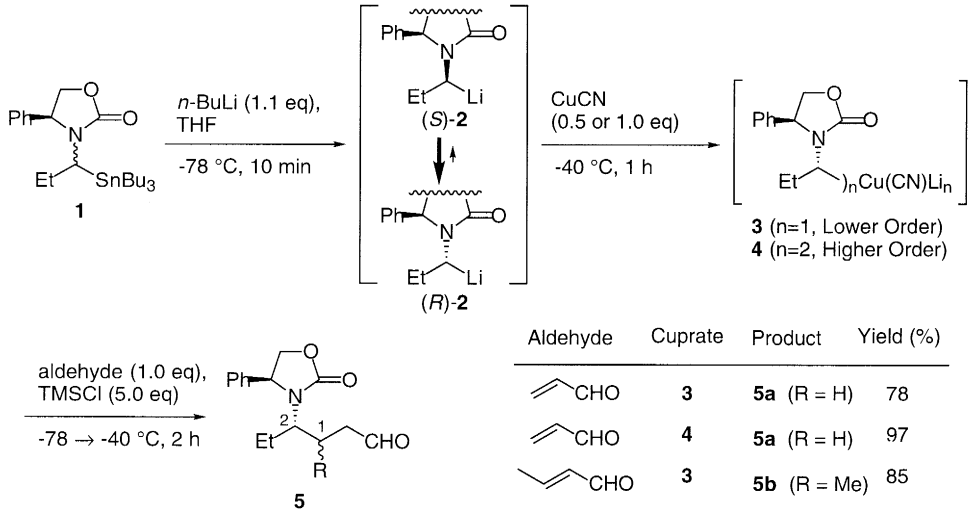
α-aminoalkyl cyanocuprates (**C**) and their Michael reactions to α,β-unsaturated aldehydes and ketones to afford the γ-amino carbonyl compounds (**D**) in enantio-enriched form.



(1)

The enantio-enriched α-aminoalkyl cyanocuprates **3** and **4** required for this study were generated from the corresponding α-aminopropylstannane **1** which was prepared as a racemic form at the Sn-bearing stereocenter from the racemic α-hydroxy propylstannane according to our reported procedure.[8] Transmetalation of **1** with *n*-BuLi at −78°C occurred, to lead initially to an epimeric mixture of α-amino alkyllithiums **2**, which quickly equilibrated to the thermodynamically more stable (*R*)-**2**.[7,8] The doubly chiral lithium species thus formed was then added to a suspension of CuCN (1.0 or 0.5 equiv.) in THF to generate the chiral 'lower-order' cyanocuprates **3** or 'higher-order' cyanocuprates **4**, respectively, as homogeneous solutions. The chiral cyanocuprates **3** and **4** thus generated were reacted with α,β-unsaturated aldehydes in the presence of TMSCl at −78°C (Scheme 1).[9] In the reaction with acrolein, both of the cuprates **3** and **4** provided 1,4-adduct **5a** as a single diastereomer in 78 and 97% yields, respectively.[10,11] The reaction of **3** with *trans*-crotonaldehyde was found to afford the 1,4-adducts **5b** as a 71:29 mixture of the two epimers due to the C-1 chiral center.[12] These results reveal that the present double transmetalation protocol permits ready access to enantio-enriched α-amino alkylcyanocuprates which are otherwise difficult to generate.



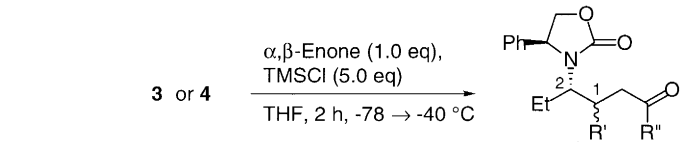
Aldehyde	Cuprate	Product	Yield (%)
CHO	3	**5a** (R = H)	78
CHO	4	**5a** (R = H)	97
CHO	3	**5b** (R = Me)	85

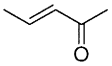
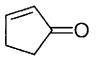
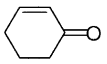
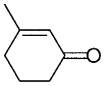
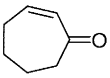
Scheme 1.

We next examined the reaction of chiral cuprates **3** and **4** to α,β-unsaturated ketones (Table 1). The results reveal that the reactions with cyclic ketones (entry 2–4, 6) proceed with higher diastereoselectivities at the C-1 chiral center as compared with the reaction with 3-penten-2-one (entry 1). The highest diastereoselectivity was obtained in the reaction of higher-order cuprate **4** with 2-cyclohexenone (entry 4). Adduct **8** was obtained in a stereochemically pure form (>95% de) in 95% yield.[10] The absolute configuration of **8** was confirmed to be (*S*,*S*,*S*) by X-ray analysis of a crystal obtained from a diethyl ether solution (Fig. 1).[13] Based on these results, it is safe to conclude that both the Li→Cu transmetalation

concerned and the Michael addition reaction proceed with complete retention of configuration at the carbanion center.[14,15]

Table 1
Conjugate addition reaction of α-amino alkylcyanocuprate with α,β-unsaturated ketones



Entry	Substrate	Cuprate	Product	R'	R"	Yield (%) [a]	d.r. [b, c]
1		**4**	**6**	CH_3	CH_3	47	56 : 44
2		**4**	**7**	$-(CH_2)_2-$		66	77 : 23
3		**3**	**8**	$-(CH_2)_3-$		71	83 : 17
4		**4**	**8**	$-(CH_2)_3-$		95	>98 : <2
5		**4**				No Reaction [d]	
6		**4**	**9**	$-(CH_2)_4-$		78	75 : 25

[a] No 1,2-adducts were detected in the crude reaction mixture by ^{1}H NMR assay.
[b] Refers to the ratio of the C-1 epimers determined by ^{1}H NMR assay.
[c] All products were of >98% de at C-2. [d] The destannylated derivative of **1** was formed.

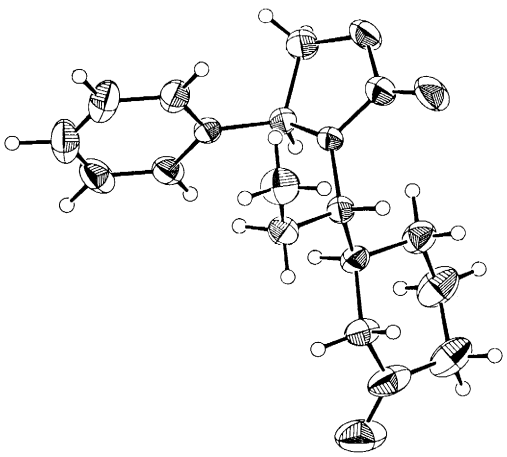
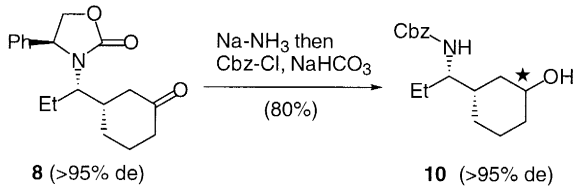


Fig. 1. X-Ray crystal structure of (*S*,*S*,*S*)-**8**

The oxazolidinone moiety of **8** was successfully deprotected by using the Birch condition.[8] Thus, **8** was treated with sodium in liquid ammonia followed by reprotection of the liberated primary amine with benzyloxycarbonyl chloride (Cbz–Cl) to afford the Cbz-protected amino alcohol **10** as a single stereoisomer in good yield (Eq. (2)).[10,16]



8 (>95% de) **10** (>95% de) (2)

In conclusion, we have shown that the enantio-enriched α-aminoalkyl cyanocuprate generated from Pearson's doubly chiral α-amino alkyllithium undergoes asymmetric Michael addition reactions with overall retention of configuration at the carbanionic stereocenter. Of particular interest is the finding that the reaction of the chiral higher-order cuprate with 2-cyclohexenone afforded the 1,4-adduct as a single stereoisomer. Thus, the present type of asymmetric reaction provides an efficient method for asymmetric synthesis of γ-amino carbonyl compounds. Further investigation to expand the scope of this approach is in progress.

Acknowledgements

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9. The presence of TMSCl is essential for this reaction. In the absence of TMSCl, only a destannylated product was obtained. For a TMSCl effect on the conjugate addition, see: Bertz, S. H.; Miao, G.; Rossiter, B. E.; Snyder, J. P. *J. Am. Chem. Soc.* **1995**, *117*, 11023–11024, and references cited therein.
10. All the compounds were characterized by ^{1}H and ^{13}C NMR. Data for selected products are as follows. Compound **5a**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.84 (t, J=7.4 Hz, 3H), 1.23–1.45 (m, 2H), 1.79–1.90 (m, 1H), 2.02–2.15 (m, 1H), 2.38 (ddd,

J=1.2, 6.8, 14.5 Hz, 2H), 3.24–3.25 (m, 1H), 4.24 (dd, *J*=6.3, 8.7 Hz, 1H), 4.61 (dd, *J*=8.7, 8.9 Hz, 1H), 4.72 (dd, *J*=6.3, 8.9 Hz, 1H), 7.35–7.45 (m, 5H), 9.62 (t, *J*=1.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.2, 23.2, 25.9, 40.8, 56.5, 59.8, 69.9, 127.6, 129.1, 129.2, 139.0, 158.0, 201.2. Compound **8**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.82 (t, *J*=7.3 Hz, 3H), 1.00–1.26 (m, 2H), 1.34–1.48 (m, 1H), 1.50–1.66 (m, 1H), 1.79–2.07 (m, 3H), 2.12–2.43 (m, 3H), 3.19 (dt, *J*=3.3, 10.1 Hz, 1H), 4.29 (dd, *J*=6.0, 8.2 Hz, 1H), 4.65 (dd, *J*=8.2, 9.0 Hz, 1H), 4.68 (dd, *J*=6.0, 9.0 Hz, 1H), 7.31–7.43 (m, 5H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 10.8, 22.0, 24.4, 28.5, 40.0, 40.9, 45.3, 60.1, 61.1, 69.8, 127.9, 129.1, 129.4, 138.6, 158.5, 210.7. **10**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.08–2.00 (m, 12H), 0.91 (t, *J*=7.3 Hz, 3H), 3.41 (m, 2H), 4.57 (d, 1H), 5.08 (dd, *J*=12.2, 16.8 Hz, 2H), 7.26–7.40 (m, 5H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 10.6, 23.8, 25.1, 27.0, 35.6, 38.8, 40.6, 56.8, 66.6, 70.7, 127.9, 128.0, 128.4, 136.5, 156.3.

11. In the absence of CuCN, the reaction of alkyllithium (*R*)-**2** with acrolein was found to afford 71% yield of the 1,2-adduct as a mixture of the two epimers due to the α-hydroxy chiral center.
12. The stereochemistry of the diastereomers have not been determined yet; however, it is quite reasonable that these have opposite configurations over C1 and C2, but the identical relative configuration at C2, because the similar reaction with acrolein provides a single diastereomer. The diastereomers are easily distinguishable by ^{1}H NMR ($CDCl_3$): δ value for C*H*O of **5b**: 9.65 for the major isomer and 9.68 for the minor isomer; δ value for COCH_3 of **6**: 2.04 for the major isomer and 2.13 for the minor isomer.
13. Crystal date for (*S*,*S*,*S*)-**8** ($C_{18}H_{23}NO_3$): monoclinic, $P2_1$ (#4), *a*=9.117(2) Å, *b*=7.311(1) Å, *c*=12.417(3) Å, β=97.07(2)°, *V*=821.3(3) Å^3, *Z*=2. A total of 1673 reflections (*h*,*k*,±*l*) were collected in the range 6°<2θ<50° with 1189 having *I*>3.00σ(*I*) being used in the structural refinement by full-matrix least-squares techniques (198 variables) using the TEXSAN crystallographic package from Molecular Structures Corporation.
14. Linderman et al. have reported that the addition reaction of enantio-defined α-alkoxyalkylcopper reagents with α,β-enones occurs predominantly with retention of configuration at the carbanionic stereocenter (Ref. 2).
15. It is still hard to propose a transition-state model to rationalize the high diastereoselectivity over the double bond, because the mechanism of the cuprate addition reaction itself remains unsettled.
16. The assignment of the configuration of the newly-formed chiral center of **10** has not been made yet, although *R*-configuration is highly expected.