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The first example of enantioselective isocyanosilylation of *meso* epoxides with TMSCN catalyzed by novel chiral organogallium and indium complexes†

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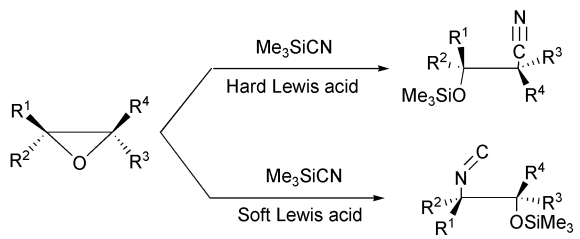
The desymmetrization ring opening of *meso* epoxides using trimethylsilyl cyanide catalyzed by organogallium and indium complexes with binaphthol monoether derivatives as chiral ligands gave β-isocyanohydrins with moderate to excellent enantioselectivities of up to 95% ee.

The desymmetrization of *meso* epoxides *via* the enantioselective addition of nucleophiles is an efficient strategy for asymmetric synthesis since it simultaneously establishes two contiguous stereogenic centers.[1] This type of reaction has been successfully accomplished with various nucleophiles.[2] The reaction of epoxide with trimethylsilyl cyanide (TMSCN) leads to formation of either β-trimethylsilyloxy nitrile or β-trimethylsiloxy isocyanide depending on the kind of catalyst, due to the ambident nucleophilic character of TMSCN (Scheme 1).[3] The enantioselective addition of TMSCN to *meso* epoxides catalyzed by hard Lewis acid (chiral Ti catalyst), first reported by Hoveyda, gave β-trimethylsilyloxy nitriles with moderate to high enantiomeric excess.[4] We envisioned that the catalytic asymmetric isocyanosilylation could be realized using soft chiral Lewis acid as catalyst. In the course of our continuing study on the synthesis and application of organogallium and indium complexes,[5] here we present the first enantioselective isocyanosilylation achieved by the asymmetric opening of *meso* epoxides using novel chiral organogallium and indium complexes as catalysts.

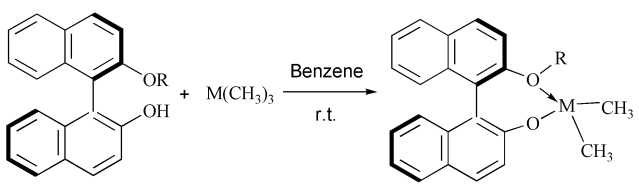
The use of C_2 symmetry as a chiral ligand design element is a well-recognized strategy in metal-catalyzed enantioselective process. However there is no fundamental reason why a C_2-symmetric ligand should necessarily be superior to a non-symmetric counterpart.[6] In fact, chiral nonsymmetric ligands have also proven to afford excellent stereochemical control in some processes.[7] Considering that only one of methyl groups of $GaMe_3$ can be easily removed,[8] we chose C_1-symmetric binaphthol monoether derivatives as chiral ligands in our research. We supposed that the coordination between the oxygen atom of the ether group and the metal not only help the formation of the desired monomeric metal complex, but also be beneficial to produce a favorable steric environment in asymmetric catalytic process. The ligands (*R*)-2-hydroxy-2′-methoxy-1,1′-binaphthyl (BINOL-Me) and (*R*)-2-hydroxy-2′-phenylmethoxy-1,1′-binaphthyl (BINOL-Bn) were conveniently synthesized according to a literature procedure from (*R*)-binaphthol,[9] and (*R*)-2-hydroxy-2′-*tert*-butoxy-1,1′-binaphthyl (BINOL-^{t}Bu) was synthesized by adapting a literature report of similar compounds.[10]

Treatment of the binaphthol monoethers (*R*)-BINOL-Me, (*R*)-BINOL-Bn and (*R*)-BINOL-^{t}Bu with one equivalent of trimethylgallium in benzene at ambient temperature gave chiral organogallium complexes **I**, **III**, **V**, respectively, as shown in Scheme 2.‡ The complexes have been characterized by ^{1}H NMR, IR, MS and element analysis. The mass spectra revealed the molecular ion $[M]^+$ or more commonly, the mass peak $[M - CH_3]^+$ resulting from monodemethylation at the gallium center. No fragment greater than $[M]^+$ was detected, thus suggesting those complexes are monomeric. Reflecting the electropositive character of the metal center, ^{1}H NMR spectra of the compounds consistently exhibited the dimethylgallium hydrogens (δ −0.92 ~ −0.98 ppm) at significantly upfield of TMS. As a typical example, the resonance of the –OCH_3 group (δ 3.64 ppm) in complex **I** appeared at upper field in comparing with that of free ligand (δ 3.86 ppm), this demonstrated that the coordination bond was formed between the oxygen atom in the ether group and the central metal.[11] As a congener of gallium, indium is similar in properties to gallium. For exploring the application of organoindium compound as asymmetric catalyst, we also synthesized chiral organoindium complexes **II**, **IV**, **VI**, which showed similar spectra and structure features with those of gallium complexes.

The reaction of TMSCN with cyclohexene oxide catalyzed by complex **I** was initially examined in dichloromethane.§ The reaction was started at −78 °C and then raised to room temperature and stirred for 10 h, followed by treatment with a methanolic solution of potassium fluoride, we found that, as envisioned, the reaction gave the product of β-isocyanocyclohexanol, which was identified by IR and ^{1}H NMR analysis, with 54% yield and 52 ee%. After many attempts, we were pleased to find that the addition of MS 4A (0.2 g $mmol^{-1}$ of substrate), was extremely effective in increasing the enantioselectivity (75% ee) and enhancing the reaction yield to 62%. In the case



Scheme 1



Scheme 2

† Electronic supplementary information (ESI) available: Characterization data, chiral analysis and determination of absolute configuration. See http://www.rsc.org/suppdata/cc/b2/b212511k/

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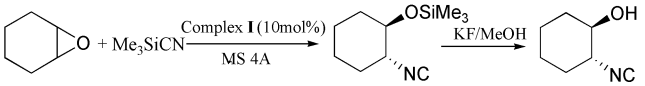
of prolonging the reaction time, no significant increase of yield was found (entry 3 in Table 1). The reaction was also examined in other solvents under identical experimental conditions. From the results, we could see that polar solvents such as CH_3CN and THF showed higher reactivity but lower selectivity (entries 4 and 5), while the lower polar solvent toluene showed better selectivity but lower reactivity (entry 6). Among the solvents tested, dichloromethane proved to be the most favourable solvent for the enantioselectivity of the reaction (Scheme 3).

Table 1 Asymmetric ring opening of cyclohexene oxide with TMSCN catalyzed by complex **I** under various conditions

Entry	Solvent	Time (h)	Yield (%)[a]	Ee (%)[b]
1[c]	CH_2Cl_2	10	54	52
2	CH_2Cl_2	10	62	75
3	CH_2Cl_2	20	64	75
4	THF	10	65	56
5	CH_3CN	10	68	60
6	Toluene	10	50	71

[a] Isolated yield of β-isocyanocyclohexanol based on cyclohexene oxide. [b] Enantioselectivity excess values were determined by HPLC analysis using a DAICEL CHIRAL OD-H column. [c] Without MS 4A.



Scheme 3

Asymmetric ring openings of cyclohexene oxide (**a**), norbonylene oxide (**b**), and cyclooctene oxide (**c**) with TMSCN were investigated in the presence of various kinds of chiral gallium and indium catalysts under optimized reaction conditions. As summarized in Table 2, the expected β-isocyanohydrins have been obtained in yields varying from 45% to 80%, with the enantioselectivity varying from 10% to 95% depending on the nature of the epoxide and the catalyst used. The isocyanosilylation of *meso* cyclohexene oxide catalyzed by catalyst **III** gave the best selectivity, up to 95% ee, with a yield of 70% (entry 3). We found that gallium complexes gave better enantioselectivities but lower yields than indium complexes. By the way, to the best of our knowledge, this is the first example of asymmetric indium catalysts. It is particularly noteworthy that the substituents in the ether group of catalysts had a significant effect on the enantioselectivity of the asymmetric ring opening of epoxides. This is exemplified by a comparison of catalysts **I**, **III**, **V**. Sterically hindered ligand (*R*)-BINOL-^{t}Bu (entries 5 and 6) produced β-isocyanohydrins with lower enantioselectivity, maybe due to steric factors decreasing the coordinative ability between the oxygen atom in the ether group and the central metal. A higher degree of enantioselectivity was obtained using (*R*)-BINOL-Bn as ligand (entries 3, 9, 13), in which the benzyl group might provide the most suitable steric and electronic effects.

Table 2 Asymmetric ring openings of various *meso* epoxides with TMSCN catalyzed by different catalysts

Entry	Epoxide	Catalyst	Yield(%)[a]	Ee (%)[b] (config.)[c]
1	**a**	**I**	62	75 (1*R*, 2*R*)
2	**a**	**II**	72	41 (1*R*, 2*R*)
3	**a**	**III**	70	95 (1*R*, 2*R*)
4	**a**	**IV**	80	47 (1*R*, 2*R*)
5	**a**	**V**	45	47 (1*R*, 2*R*)
6	**a**	**VI**	58	10 (1*R*, 2*R*)
7	**b**	**I**	55	54
8	**b**	**II**	68	21
9	**b**	**III**	61	69
10	**b**	**IV**	69	42
11	**c**	**I**	52	55 (1*R*, 2*R*)
12	**c**	**II**	65	49 (1*R*, 2*R*)
13	**c**	**III**	58	72 (1*R*, 2*R*)
14	**c**	**IV**	72	68 (1*R*, 2*R*)

[a] Isolated yields of β-isocyanohydrins based on epoxides. [b] Enantioselectivity excess values were determined by HPLC analysis using a DAICEL CHIRAL OD-H column. [c] The absolute configurations of entries 1–6 and 11–14 were determined by converting β-isocyanohydrins to corresponding β-aminohydrins and then comparing the optical rotations with literature values.[12,13] The configurations of entries 7–10 were not determined.

In conclusion, we put forth the first example of a catalytic and enantioselective method for isocyanosilylation of *meso* epoxides with TMSCN. This reaction, promoted by a new catalytic system consisting of novel chiral organogallium or indium complexes, can give β-isocyanohydrins with moderate to high enantiomeric excess. Further studies for improving the enantioselecvitity of this reaction are currently under investigation.

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Notes and references

‡ General procedure for the synthesis of the complexes: Trimethylgallium (1.5 mmol in 2 cm³ benzene) was added dropwise to a stirred solution of the binaphthol monoether (1 mmol) in benzene (2 cm³) at room temperature (*ca*. 15 min). During the addition of trimethylgallium, a vigorous evolution of gas was observed. The solution was stirred for another half an hour. Volatiles were removed *in vacuo* and the residue was recrystallized from benzene and petroleum ether to give a white solid complex.

§ General procedure for the ring opening of *meso* epoxides with TMSCN: A mixture of catalyst (0.2 mmol) and 0.4 g molecular sieve (4A) in dichloromethane (15 cm³) was stirred at −78 °C. After 15 min, *meso* epoxide (2 mmol) and trimethylsilyl cyanide (2.4 mmol) were added and the resulting mixture was gradually increased to room temperature and stirred for another 10 h, followed by treatment with a methanolic solution of potassium fluoride (0.8 g in 10 cm³ methanol) for 5 h. The reaction mixture was filtered, concentrated and separated by flash chromatography (petroleum ether and ethyl acetate as the eluent) to give the β-isocyanohydrin.

1 M. C. Wills, *J. Chem. Soc., Perkin Trans. 1*, 1999, 1765.
2 H. Y. Zhou, E. J. Campbell and S. T. Nguyen, *Org. Lett.*, 2001, **3**, 2229; S. Matsunaga, J. Das, J. Roels, E. M. Vogl, N. Yamamoto, T. Iida, K. Yamaguchi and M. Shibasaki, *J. Am. Chem. Soc.*, 2000, **122**, 2252; X. L. Hou, J. Wu, L. X. Dai, L. J. Xia and M. H. Tang, *Tetrahedron: Asymmetry*, 1998, **9**, 1747; E. N. Jacobsen, *Acc. Chem. Res.*, 2000, **33**, 421.
3 P. G. Gasman and T. L. Guggenheim, *J. Am. Chem. Soc.*, 1982, **104**, 5850; K. Imi, N. Yanagihara and K. Utimoto, *J. Org. Chem.*, 1987, **52**, 1013.
4 B. M. Cole, K. D. Shimizu, C. A. Krueger, J. Harrity, M. L. Snapper and A. M. Hoveyda, *Angew. Chem., Int. Ed. Engl*, 1996, **35**, 1668; S. E. Schaus and E. N. Jacobsen, *Org. Lett.*, 2000, **2**, 1001.
5 Y. Z. Shen, H. W. Gu, Y. Pan, G. Dong, T. Wu and H. W. Hu, *J. Organomet. Chem.*, 2000, **605**, 234.
6 G. Helmchen and A. Pfaltz, *Acc. Chem. Res.*, 2000, **33**, 336.
7 D. A. Evans, K. R. Campos, J. S. Tedrow, F. E. Michael and M. R. Gagne, *J. Am. Chem. Soc.*, 2000, **122**, 7905; Y. Yamada and M. Shibasaki, *Tetrahedron Lett.*, 1998, **39**, 5561.
8 D. A. Atwood and M. J. Harvey, *Chem. Rev.*, 2001, **101**, 37.
9 M. Amano, M. Watanebe, N. Baba, J. Oda and Y. Inouye, *Bull. Chem. Soc. Jpn.*, 1983, **56**, 3672.
10 W. H. Pirkle and J. C. Schreiner, *J. Org. Chem.*, 1981, **46**, 4988.
11 R. W. Chesnut, R. R. Cesati, C. S. Cutler, S. L. Pluth and J. A. Katzenellenbogen, *Organometallics*, 1998, **17**, 4889.
12 U. Schollkopf and P. Bohme, *Angew. Chem., Int. Ed. Engl.*, 1971, **10**, 491.
13 H. Yamashita, *Bull. Chem. Soc. Jpn.*, 1988, **61**, 1213; J. Aube, M. S. Wolfe, R. K. Yantiss, S. M. Cook and F. Takusagawa, *Synth. Commun.*, 1992, **22**, 3003.