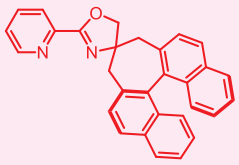
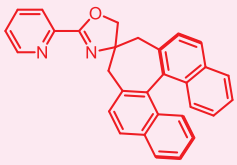
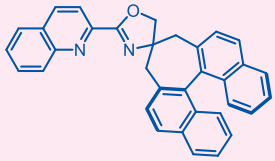
Chiral spirodiamine ligands
– SPYMOX, SQUMOX -

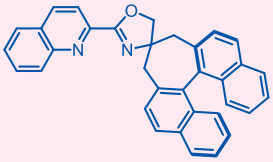
Enantioselective halogenation reactions of active methine compound

For the introduction of asymmetric fluorination into the active methine group of β-ketoester compounds.

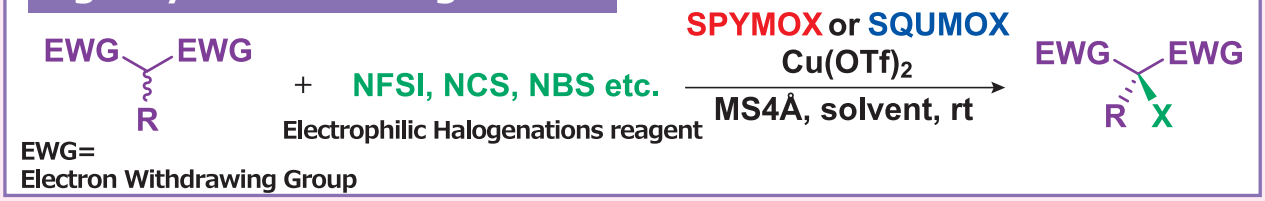

(*R*)-SPYMOX


(*S*)-SPYMOX


(*R*)-SQUMOX


(*S*)-SQUMOX

e.g. Asymmetric Halogenation



EWG=
Electron Withdrawing Group

Organohalogen compounds has been widely applied in organic synthesis.
Recently, organofluorine compounds are becoming increasingly important in pharmaceutical, agricultural and functional material chemistry.
Shibatomi 's group (Toyohashi University of Technology) has developed chiral spirodiamine ligands, **SPYMOX**[1] and **SQUMOX**[2], and reported enantioselective halogenation reactions.
Using a copper complex with **SPYMOX**, and **SQUMOX**, a variety of β-ketoesters were halogenated to α-halogen-β-ketoesters in good to excellent yields with overall good ee's.
Furthermore, **SPYMOX** and **SQUMOX** can complexation various metals and can be used as chiral diamine ligand.

Characteristic

- **Good substrate scope and limitation, excellent enantioselectivity for activated methine compounds.**
- **Copper of Ubiquitous metal without using other rare metals.**
- **Active methine group can be asymmetric fluorinated [3] and asymmetric chlorinated [2] with high enantioselectivity.**
- **Asymmetric gem-chlorofluorination can be carried out in a one-pot sequence by using different halogenation reagent (e.g. chlorinating agent and other halogenating agent) in sequence on the active methylene group [4].**

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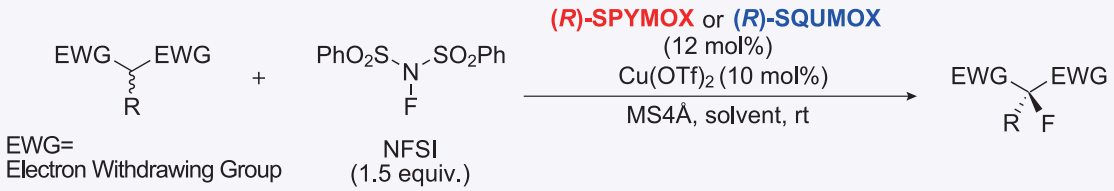
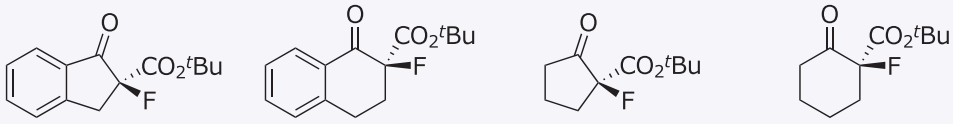
Examples

Asymmetric fluorination [3)]

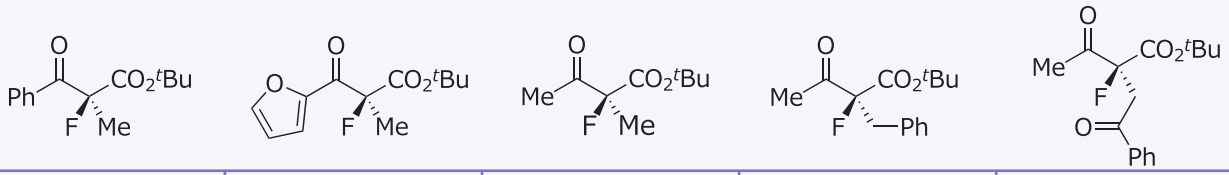
- It provides optically active fluorinated compounds with high enantioselectivity for activated methine compounds.



Example of fluorination of an activated methine compound



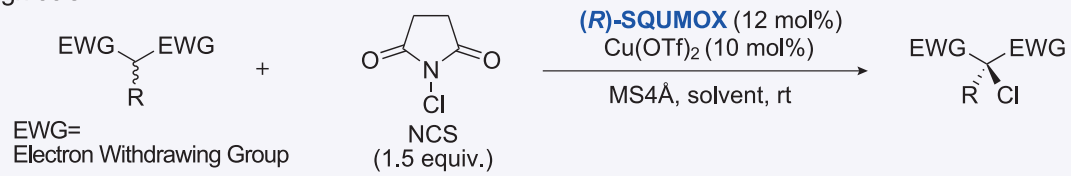
(*R*)-SPYMOX	95% yield, 95% ee	94% yield, 89% ee	77% yield, 75% ee	76% yield, 86% ee
(*R*)-SQUMOX	94% yield, 93% ee	93% yield, 87% ee	82% yield, 99% ee	86% yield, 99% ee



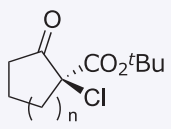
83% yield, 92% ee	83% yield, 88% ee	76% yield, 85% ee	—	—
81% yield, 90% ee	—	81% yield, 99% ee	93% yield, 90% ee	90% yield, 90% ee

Asymmetric chlorination [2)]

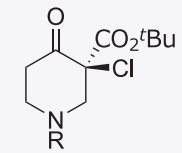
- Cu-SPYMOX or Cu-SQUMOX complex catalyzed asymmetric chlorination reaction for activate methine compound with high ee's.



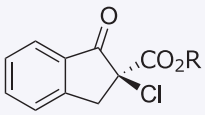
Example of chlorination of an activated methine compound



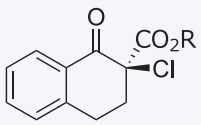
(n = 1) 90% yield, 95% ee
(n = 2) 92% yield, 98% ee
(n = 3) 92% yield, 98% ee



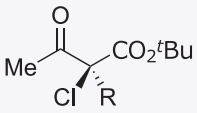
(R = Cbz) 90% yield, 90% ee
(R = Boc) 93% yield, 88% ee



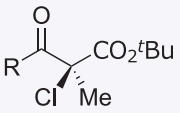
(R = ^{t}Bu) 94% yield, 96% ee
(R = Me) 97% yield, 63% ee



(R = ^{t}Bu) 98% yield, 90% ee
(R = *l*-mentyl) 99% yield, 84% ee
(R = *d*-mentyl) 96% yield, 89% ee



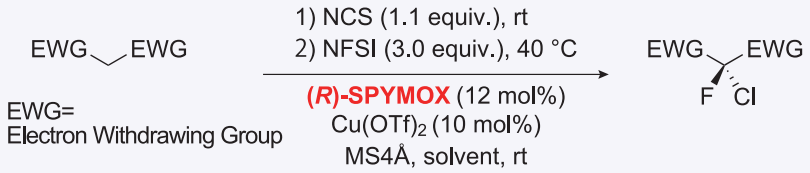
(R = Me) 99% yield, 95% ee
(R = Bn) 94% yield, 92% ee
(R = allyl) 96% yield, 94% ee
(R = CH_2CN) 84% yield, 95% ee
(R = CH_2COPh) 90% yield, 91% ee



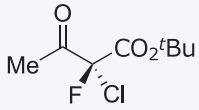
(R = Et) 72% yield, 90% ee
(R = $(CH_2)_2Ph$) 92% yield, 86% ee
(R = Ph) 78% yield, 96% ee

Asymmetric *gem*-chlorofluorination [4)]

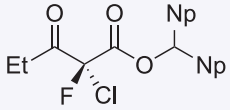
- Asymmetric chlorination and fluorination can be carried out in one pot by adding halogenation reagents in sequence to the activated methylene compound to give the corresponding *gem*-chlorofluorine compound.



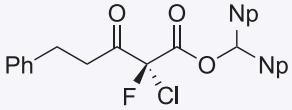
Example of asymmetric *gem*-chlorofluorination



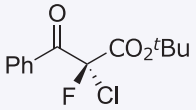
70% yield, 90% ee



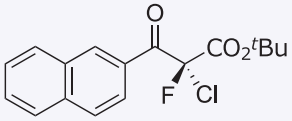
67% yield, 87% ee



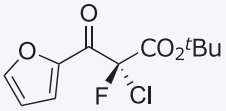
63% yield, 79% ee



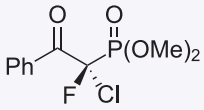
67% yield, 92% ee



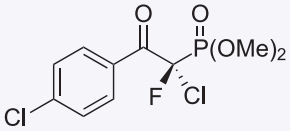
71% yield, 92% ee



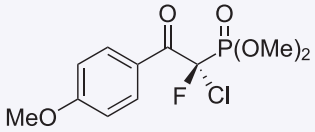
73% yield, 82% ee [a]



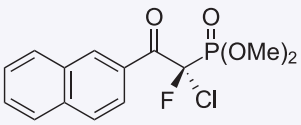
73% yield, 92% ee [a]



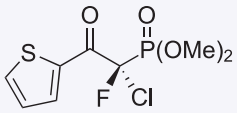
55% yield, 90% ee [a]



52% yield, 92% ee [a]



64% yield, 90% ee [a]

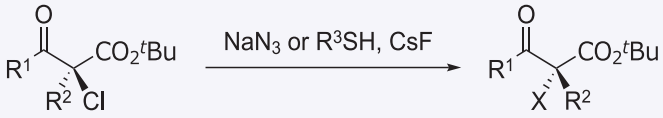


69% yield, 86% ee [a]

[a] 1) at -30 °C, 2) at 0 °C

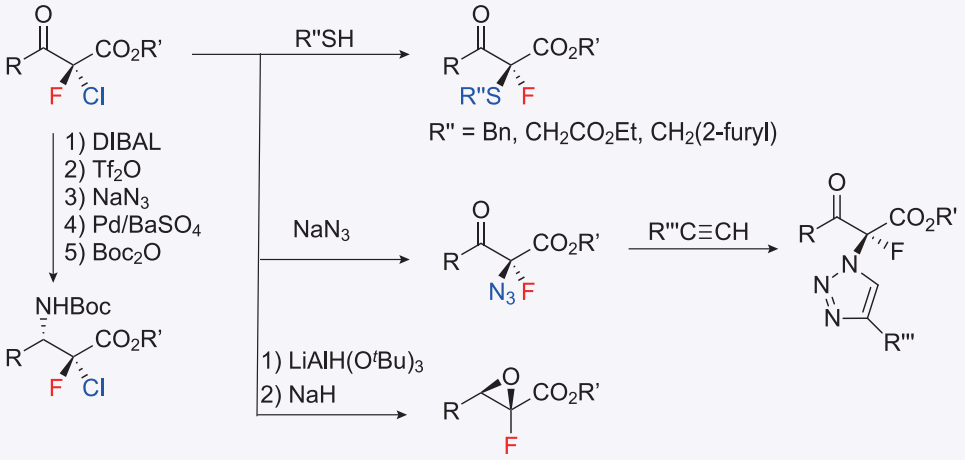
S_N2 reaction of optically active halogen compounds without decreasing of enantiopurity [2,4)]

- Chiral Halogen compounds obtained by asymmetric chlorination can be applied on β-amino acid derivatives and Click reactions without loss of optical purity.

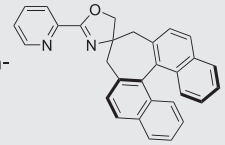
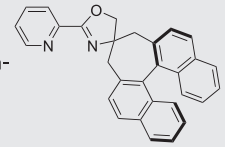
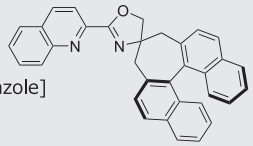
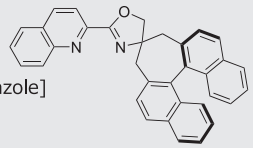


X = N_3, SR^3, F

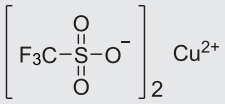
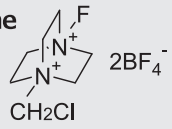
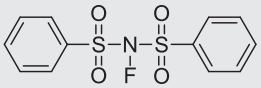
Example of S_N2 reaction of optically active halogen compounds without decreasing of enantiopurity



Product List

Product Name	Product Code	Package
(*R*)-SPYMOX (11b*R*)-3,5-Dihydro-2'-(2-pyridinyl)spiro[4H-cyclohepta-[2,1-a:3,4-a']dinaphthalene-4,4'(5'H)-oxazole] CAS RN® : 1138157-05-7 	37417-68	100 mg
(*S*)-SPYMOX (11b*S*)-3,5-Dihydro-2'-(2-pyridinyl)spiro[4H-cyclohepta-[2,1-a:3,4-a']dinaphthalene-4,4'(5'H)-oxazole] CAS RN® : – 	37418-68	100 mg
(*R*)-SQUMOX (11b*R*)-3,5-Dihydro-2'-(2-quinolinyl)spiro[4H-cycloheptа[2,1-a:3,4-a']dinaphthalene-4,4'(5'H)-oxazole] CAS RN® : 1381879-49-7 	37419-68	100 mg
(*S*)-SQUMOX (11b*S*)-3,5-Dihydro-2'-(2-quinolinyl)spiro[4H-cycloheptа[2,1-a:3,4-a']dinaphthalene-4,4'(5'H)-oxazole] CAS RN® : – 	37420-68	100 mg

Related reagents

Product Name	Product Code	Package
Copper(II) trifluoromethanesulfonate CAS RN® : 34946-82-2 	07704-35	25 g
***N*-Fluoro-*N'*-(chloromethyl)triethylenediamine bis(tetrafluoroborate)** CAS RN® : 140681-55-6 	16185-35	25 g
N-Fluorodibenzenesulfonimide CAS RN® : 133745-75-2 	16081-35	25 g

References

1) Shibatomi, K.; Muto, T.; Sumikawa, Y.; Narayama, A.; Iwasa, S. *Synlett*, **2009**, *2*, 241.
2) Shibatomi, K.; Soga, Y.; Narayama, A.; Fujisawa, I.; Iwasa, S. *J. Am. Chem. Soc.* **2012**, *134*, 9836.
3) Narayama, A.; Shibatomi, K.; Soga, Y.; Muto, T.; Iwasa, S. *Synlett*, **2013**, *24*, 375.
4) Shibatomi, K.; Narayama, A.; Soga, Y.; Muto, T.; Iwasa, S. *Org. Lett.* **2011**, *13*, 2944.

Review Shibatomi, K. ; *J. Synth. Org. Chem. Jpn.*, **2014**, 72, 232.

- Please use the products listed in the catalog as reagents (chemicals used for testing or research purpose).
- Product information is subject to change without notice. For the latest information, please have a look at our website "Cica-Web".

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