Catalysis Science & Technology

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: K. Masukawa, A. Kojima, T. Sato, M. Terada and I. Nakamura, *Catal. Sci. Technol.*, 2025, DOI: 10.1039/D5CY00106D.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/catalysis

View Article Online
DOI: 10.1039/D5CY00106D

COMMUNICATION

Cu-catalyzed [1,3]-Asymmetric Methoxy Rearrangement of *N*-Methoxyanilines: Mechanistic Insight

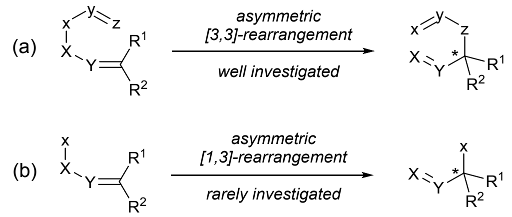
Kazuki Masukawa,[b] Amu Kojima,[b] Takuma Sato,[b] Masahiro Terada,[b] Itaru Nakamura*[a,b]

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

Cu-catalyzed reactions of *N*-methoxy-2,6-dimethylanilines in the presence of a cationic Cu catalyst ligated to a chiral NHC ligand, which has an (*ortho*-carbamoyl)phenyl group on the nitrogen atom of (*S,S*)-diphenylimidazolidinylidene, furnished chiral *ortho*-quinol imines with good enantioselectivity. In addition, a cascade reaction involving the [1,3]-methoxy rearrangement followed by the Diels-Alder reaction yielded the corresponding three-dimensional molecules in a diastereo- and enantioselective manner.

Asymmetric rearrangements have received much attention for constructing sterically congested structures with a tetrasubstituted carbon as an asymmetric center by changing the connectivity of the starting materials.[1] Asymmetric [3,3]-rearrangement, such as the Claisen rearrangement and the Cope rearrangement, have been intensively investigated for the synthesis of enantio-enriched organic molecules (Scheme 1a).[2] In contrast, asymmetric [1,3]-rearrangement reactions have received much less attention, because the process inherently proceeds via a strained transition state, making the stereo control of the enantio-determining process difficult (Scheme 1b).[3-7] Recent studies have indicated that transition metal catalysts, nucleophilic catalysts, and Brønsted acid catalysts promote asymmetric [1,3]-rearrangements with excellent enantioselectivity. However, these processes are still limited to the migration of the carbon group from the oxygen atom to the carbon atom, such as the aza-Petasis-Ferrier rearrangement[3-5] and the Steglich rearrangement,[6] involving C–C bond formation (X = O, Y = CR, x = CR'$_3$).

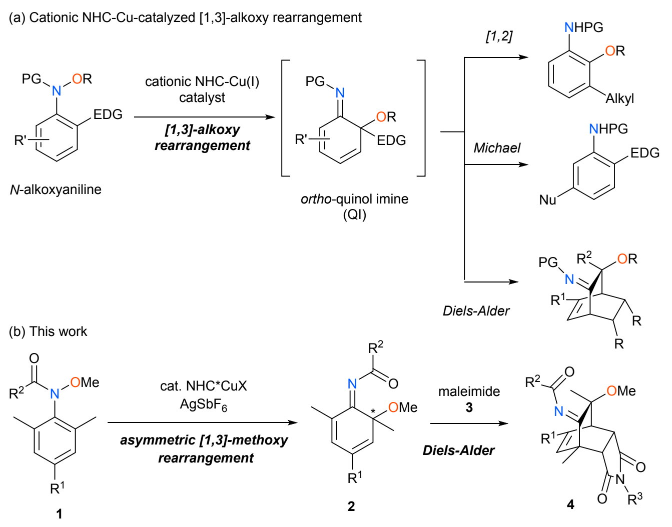


Scheme 1. Asymmetric [3,3]- and [1,3]-rearrangements

In this context, we focus on the [1,3]-alkoxy rearrangement of *N*-alkoxyanilines, which involve N–O bond cleavage and C–O bond formation (Scheme 2a).[8-15] We recently found that cationic Cu catalysts ligated to an *N*-heterocyclic carbene (NHC) ligand effectively promote the [1,3]-alkoxy rearrangement. In particular, in substrates having an electron-donating substituent, such as an alkyl, a *p*-anisyl, or a methoxy group, at the *ortho* position, the migration of the alkoxy group preferentially to the substituted *ortho* position takes place.[11-14] Because the resulting *ortho*-quinol imines function as a versatile intermediate for further transformations, such as the [1,2]-rearrangement,[11] the Michael addition,[12,13] or the Diels-Alder reaction,[14] the [1,3]-alkoxy rearrangements are useful for the synthesis of elaborate organic molecules. Accordingly, we envisioned that properly designed chiral NHC ligands would induce the enantioselective C–O bond formation, realizing a new class of asymmetric [1,3]-rearrangement. Specifically, the reactions of 2,6-disubstituted *N*-alkoxyanilines would proceed via the differentiation of the two prochiral *ortho* positions by employing chiral NHC ligands (Scheme 2b). Herein, we report that the Cu-catalyzed reaction of 2,6-disubstituted *N*-methoxyanilines **1** in the presence of cationic Cu catalysts ligated to a chiral NHC ligand proceeds through an asymmetric [1,3]-methoxy rearrangement to yield chiral *ortho*-quinol imines **2** with high enantioselectivity. In addition, the cascade reaction of **1** with maleimides **3** produces three-dimensional compounds **4** with good diastereo- and enantioselectivities.

[a] Institute for Excellence in Higher Education, Tohoku University, 980-8576, Japan,
[b] Department of Chemistry, Graduate School of Science, Tohoku University, 980-8578, Japan

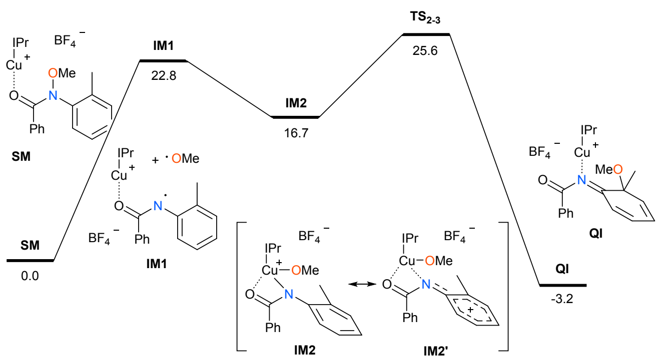
Supplementary Information available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x



Scheme 2. Cu-catalyzed [1,3]-alkoxy rearrangement

Prior to performing experiments aimed at designing the chiral NHC ligand, we conducted a theoretical investigation of the [1,3]-methoxy rearrangement using a computational approach to elucidate the C–O bond forming process that leads to an *ortho*-quinol imine-copper complex (Schemes S1 and 3, Figures 1 and 2).[§] First, we calculated an achiral reaction of an *ortho*-toluidine derivative using $IPrCuBF_4$ catalyst as a model system (Schemes S1 and 3). In the first stage of the reaction, we assumed that the N–O bond, which has a relatively low bond dissociation energy,[15] is cleaved to form the corresponding methoxycopper species through either ionic cleavage, which we proposed based on Lewis acid-mediated [1,3]-rearrangement (Scheme S1a), or concerted oxidative addition calculated by Dang (Scheme S1b). However, despite conducting an exhaustive search, we were unable to find a structurally reasonable transition state for this rearrangement process via these mechanisms.[16] Therefore, given that the N–O bond has a relatively low bond dissociation energy, we hypothesized that the first stage of this reaction proceeds through homolytic cleavage of the N–O bond to generate radical pair **IM1** (Scheme S1c).[17-19] In fact, the calculated bond dissociation energy of the N–O bond in *ortho*-toluidine **SM**, of which the carbonyl is coordinated to the copper catalyst, is 22.8 kcal/mol. Then, the generated methoxy radical binds again to the copper atom, forming methoxycopper(III) intermediate **IM2** with square planar geometry. Although this intermediate has a character of the nitrenium species **IM2'**, the NBO analysis suggested that contribution of the methoxycopper(III) **IM2** is larger than Cu(I) **IM2'** with the nitrenium moiety (see SI). In addition, the calculations suggest that the C–O bond-forming process through $\mathbf{TS_{2\text{-}3}}$ is the rate-determining process, the activation energy of which is calculated to be 25.6 kcal/mol. It should be noted that the methoxy group preferentially migrates to the methyl-bound *ortho* position, where the nucleophilic attack on the *ortho* carbon with a methyl substituent is energetically favored over that on a non-substituted *ortho* carbon, as evidenced by previously reported experimental results (See SI).[7-9] This is because the methyl-bound carbon atom is more positively charged according to the NBO analysis. Moreover, the calculations suggest that the electron-withdrawing group on the *N*-methoxyaniline substrate decelerates the rearrangement. According to NBO analysis, the C-O bond forming process involves decrease of electrons at the *ortho* position forming the C-O bond to facilitate interaction with a lone pair of the migrating methoxy group. In other words, contribution of the nitrenium character like **IM2'** in the transition state $\mathbf{TS_{2\text{-}3}}$ is larger than in the intermediate **IM2** (See SI).

View Article Online
DOI: 10.1039/D5CY00106D



Scheme 3. Reaction coordinates for the Cu-catalyzed [1,3]-rearrangement of *N*-methoxy-*ortho*-toluidine.

According to these computational results, we envisioned that an NHC ligand with a coordinative group would induce the enantio-recognition of 2,6-dimethylaniline through desymmtrizative C–O bond formation through methoxycopper(III) intermediate, with square pyramidal geometry. From the perspective of structural simplicity and synthetic accessibility, we selected chiral (*S*,*S*)-diphenylimidazolidinylidene ligand **L1**, which has *ortho*-(*N*,*N*-dimethylcarbamoyl)phenyl and 2,4,6-triisopropylphenyl (Trip) groups as substituents on the nitrogen atoms of NHC. As a result of structural exploration, the transition states for the C–O bond formation were classified into eight states based on the attack of the methoxy group on either the *si*- or *re*-face of the four conformational isomers of methoxycopper(III) intermediate **IM2***, originated from (1) the C–N axial chirality of the *ortho*-(*N*,*N*-dimethylcarbamoyl)phenyl group on NHC (R_a and S_a) and (2) the relative orientation of the NHC ligand and the substrate molecule (distal and proximal; the conformation in which the methoxy ligand is located close to the *ortho*-carbamoyl group is named proximal, Figure 1). From the energy diagram of the eight transition states shown in Figure 2, we predict that designed NHC ligand **L1** has the potential to induce the enantio-differentiation of the two prochiral *ortho* positions, with the *S* enantiomer as the main product. It should be noted that interconversion between the conformational isomers occurs through homolytic cleavage of the Cu-O bond in **IM2***, generating a radical pair corresponding to **IM1** in Scheme 3. In other words, interconversion via rotation of the C-N bond between the nitrogen atom on the imidazolidinylidene ring and the carbon atom on the aryl ring substituted by *ortho*-carbamoylaryl group, as well as the Cu-N bond in **IM2*** is unlikely due to the bulkiness of the chiral NHC ligand.

View Article Online
DOI: 10.1039/D5CY00106D

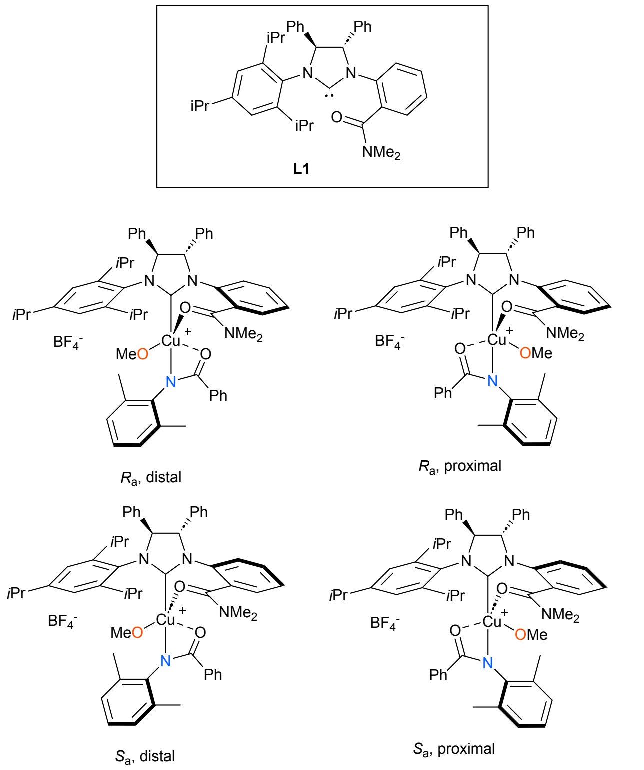


Figure 1. Design of chiral NHC ligand **L1** and conformational isomers of methoxycopper (III) intermediate **IM2***

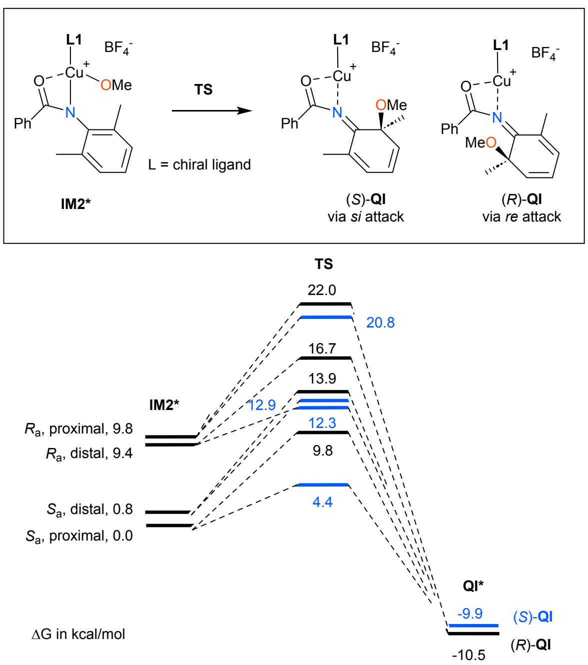
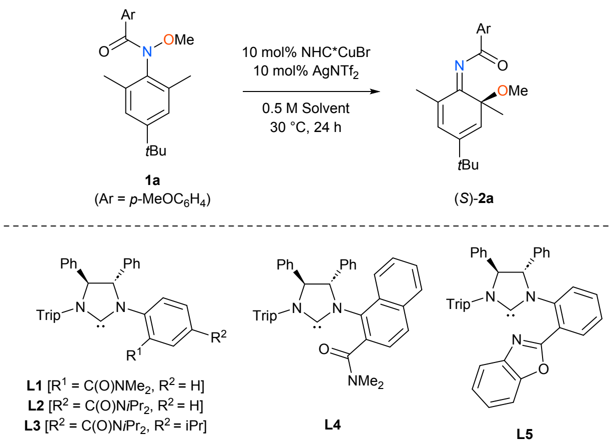


Figure 2. Reaction coordinates for the C–O bond-forming process

Based on these computational results, we examined the applicability of chiral NHC (NHC*) ligands **L1** to **L5** to the Cu-catalyzed reactions of 2,6-dimethyl-*N*-methoxyaniline **1a.** The results are summarized in Table 1. Chiral ligands **L1** and **L2**, which have an *N,N*-dimethylcarbamoyl group and an *N,N*-diisopropylcarbamoyl group, respectively, at the *ortho* position of the phenyl ring attached to the nitrogen atom, induced the enantio-differentiation of the *ortho* position of the aniline ring, yielding *S* product (*S*)-**2a** as a major stereoisomer, as predicted (Table 1, entries 1 and 2).§§ In contrast, chiral ligand **L4**, the *N,N*-dimethylcarbamoyl group of which is located at the 2 position of the 1-naphthyl group yielded (*R*)-**2a** as a major stereoisomer with low enantioselectivity (entry 4). In chiral ligand **L5**, the 2-benzoxazolyl group (**L5**) was an effective substituent in place of the carbamoyl group (entry 5), whereas other functional groups, such as benzoyl and methoxy groups, were much less efficient (see SI).† Among the reaction conditions tested, the combination of chiral ligand **L3**, which has an isopropyl group at the *para* position of the benzene ring with *ortho*-carbamoyl group, and ethyl acetate as a solvent led to good enantioselectivity, albeit a low chemical yield (entry 6).¶ Because a considerable amount of starting material **1a** was recovered, we examined the effect of increasing the loading amount of the chiral NHC*-Cu catalyst (entry 7). However, we found that the use of 30 mol% of **L3**CuBr and $AgNTf_2$ resulted in a decrease in enantioselectivity, presumably owing to the partial racemization of obtained product **2a** (See SI).

Table 1. Optimization of chiral NHC ligand



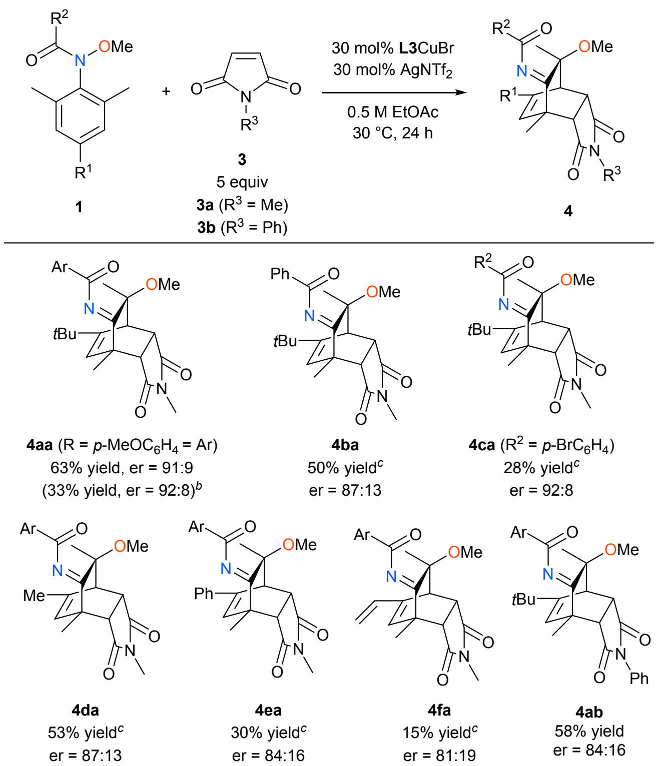
Entry	NHC*	Solvent	Yield / %[a]	Er[b]	Recovery / %[a]
1	**L1**	DCE	27	82:18	70
2	**L2**	DCE	33	80:20	65
3	**L3**	DCE	31	74:26	60
4	**L4**	DCE	49	34:66	50
5	**L5**	DCE	13	82:18	85
6	**L3**	EtOAc	24	89:11	51
7[c]	**L3**	EtOAc	58	83:17	18

[a] Yields were determined by ^1H NMR analysis using CH_2Br_2 as an internal standard. [b] Enantiomeric ratio was determined by chiral HPLC analysis. [c] 30 mol% each of **L3**CuBr and $AgNTf_2$ was used.

To solve the racemization problem of the *ortho*-quinol imine **2a**, we carried out a cascade reaction involving the [1,3]-alkoxy rearrangement followed by the Diels-Alder reaction with maleimides **3** (Scheme 4). To our delight, excellent enantioselectivity was maintained even in the reaction of **1a** with *N*-methylmaleimide **3a** (5 equiv) using 30 mol% of the chiral NHC catalyst, affording desired product **4aa** in 63% yield

View Article Online
DOI: 10.1039/D5CY00106D

with 91:9 er. It should be noted that the reactions yielded a single diastereomer derived from the approach of maleimides **3** to *ortho*-quinol imine **2** from the side of the methoxy group in an *endo* manner.[14] As expected, substrate **1c** having an electron-withdrawing bromo group in the aroyl group on the nitrogen atom exhibited lower reactivity than **1a**, which has a methoxy group, although the enantioselectivity was maintained. Similarly, the substrates **1e** and **1f**, which have a phenyl group and a vinyl group, respectively, at the *para* position of the aniline ring, underwent the cascade reaction to yield products **4ea** and **4fa**, respectively, with good enantioselectivity but in low chemical yields. The low chemical yields are presumably due to the inhibition of the catalyst turnover through the formation of a homoleptic $[(\mathbf{L3})_2Cu]^+$ complex, which is inactive in the [1,3]-rearrangement reactions.[‡] In addition, the result that the opposite enantiomer was obtained as a major product when **L4** was used indicates that the transition state for the C-O bond-forming process is very sensitive to trivial changes in the chemical structure. Further development of chiral NHC ligands for the catalytic [1,3]-alkoxy rearrangement to solve these problems is underway in our laboratory. Nevertheless, the present cascade reaction involving the asymmetric [1,3]-methoxy rearrangement is efficient for the synthesis of three-dimensional molecules in a highly stereoselective and enantioselective manner. In addition, it should be noted that stereocontrol of alkoxy group is still limited to oxy-Michael addition reactions of alcohols, due to low nucleophilicity or high pKa.[20] In this context, we realized enantio-control of the alkoxy group by a total different approach based on rearrangement in this investigation.



Scheme 4. Cu-catalyzed asymmetric [1,3]-rearrangement and Diels-Alder reaction of **1** with **3**

[a] The reactions of **1** (0.1 mmol) with **3** (0.5 mmol) were carried out in the presence of **L3**CuBr (30 mol%) and $AgNTf_2$ (30 mol%) in EtOAc (0.2 mL) at 30 °C for 24 h. Isolated yield. The enantiomeric ratio was determined by chiral HPLC analysis. [b] 10 mol% each of **L3**CuBr and $AgNTf_2$ was used. [c] At 50 °C.

In conclusion, we have developed a chiral NHC ligand for the catalytic asymmetric [1,3]-methoxy rearrangement of *N*-methoxyaniline derivatives. Because *ortho*-quinol imines can be further manipulated to furnish favourable compounds, the present method is useful for the synthesis of chiral building blocks in a unique manner.

Author contributions

Conceptualization: IN; methodology: KM and IN; investigation: KM and AK, and YS; formal analysis: TS and IN, writing: TS, MT and IN; supervision: MT. All authors have given approval to the final version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

Data availability

The exploratory investigation, experimental procedures, computational data, and characterization data are available. The data supporting this article have been included as part of the Supplementary Information. Crystallographic data for **2c** has been deposited at the CCDC under 2415308.

Acknowledgements

The computation was performed using Research Centre for Computational Science, Okazaki, Japan (Project: 22-IMS-C127, 23-IMS-C116, and 24-IMS-C110). This work was supported by JSPS KAKENHI Grant Number JP20H02731, Grant-in-Aid for Scientific Research (B) from MEXT, Japan.

Notes and references

§ Quantum chemical calculations were performed using Gaussian 16 program package. Structure optimizations based on density functional theory (DFT) were carried out using B3LYP functional including Grimme's D3 dispersion correction with Becke-Johnson dumping and def2-SVP basis set. Intrinsic reaction coordinate (IRC) calculations were performed to verify the connectivity between the transition state and the corresponding intermediates. All structures of the intermediates (no imaginary frequency) and the transition states (a single imaginary frequency) were verified by vibrational analysis.

§§ The absolute configuration of the product was deduced from the reaction of **1c** using **L2** as a chiral ligand. See SI.

† The use of previously reported chiral NHC ligands was not effective for the present reaction. See SI.

View Article Online
DOI: 10.1039/D5CY00106D

¶ We found that the use of ethyl acetate provided the best enantioselectivity for the cascade reaction between **1** and maleimide **2a** (Table S2). Moreover, it was observed that **L3** performed better than **L2** in ethyl acetate (Table S2, entry 4 versus 7).

‡ A molecular ion peak, which corresponded to $[(\mathbf{L2})_2Cu]^+$ was observed by HRMS. Additionally, $[(IMes)_2Cu]NTf_2$ did not promote the [1,3]-rearrangement reaction. See SI.

1 X.-L. Liu, M.-L. Gong, X. Yang, P. Tian, Q.-H. Li, *Org. Chem. Front.*, 2024, **11**, 4934.
2 H. Ren, W. D. Wulff, *J. Am. Chem. Soc.* 2011, **133**, 5656.
3 Y. Zhang, Y. Chen, *Org. Chem. Front.*, 2022, **9**, 4744.
4 M. Terada, Y. Toda, *J. Am. Chem. Soc.* 2009, **131**, 6354.
5 M. Terada, T. Komuro, Y. Toda, T. Korenaga, *J. Am. Chem. Soc.* 2014, **136**, 7044.
6 J. Zhang, X. Han, X. Wu, Y. Liu, Y. Cui, Y. *ACS Sustainable Chem. Eng.* 2019, **7**, 5065.
7 L. Yao, K. Ishihara, *Chem. Sci.*, 2019, **10**, 2259.
8 I. Nakamura, T. Jo, Y. Ishida, H. Tashiro, M. Terada, *Org. Lett.* 2017, **19**, 3059.
9 I. Nakamura, S. Nozawa, Y. Ishida, I. Muranushi, A. Mayerweg, M. Terada, *Org. Chem. Front.* 2021, **8**, 6390.
10 I. Nakamura, R. Konta, Y. Ishida, M. Tachibana, M. Terada, *Adv. Synth. Catal.* 2023, **365**, 4677.
11 Y. Ishida, I. Nakamura, M. Terada, *J. Am. Chem. Soc.* 2018, **140**, 8629.
12 I. Nakamura, H. Tashiro, Y. Ishida, M. Terada, *Org. Lett.* 2020, **22**, 3794.
13 I. Nakamura, M. Tachibana, R. Konta, H. Tashiro, M. Terada, *Molecules*, 2023, **28**, 4251.
14 I. Nakamura, K. Masukawa, Y. Ishida, M. Terada, *Org. Lett.* 2021, **23**, 4127.
15 O. Mó, M. Yáñez, M. Eckert-Maksić, Z. B. Maksić, I. Alkorta, J. Elguero, *J. Phys. Chem. A* 2005, **109**, 4359.
16 Y.-Q. Fang, L. Dang, *Org. Lett.* 2020, **22**, 9178.
17 Y.-N. Zheng, H. Zheng, T. Li, W.-T. Wei *ChemSusChem* 2021, **14**, 5340.
18 H.-M. Jiang, Y.-L. Zhao, Q. Sun, X.-H. Ouyang, J.-H. Li, *Molecules* 2023, **28**, 1775.
19 X. Tang, Z. Zhu, C. Qi, W. Wu, H. Jiang, *Org. Lett.* 2016, **18**, 180.
20 G. Su, M. Formica, K. Yamazaki, T. A. Hamlin, D. J. Dixon, *J. Am. Chem. Soc.* 2023, **145**, 23, 12771.

View Article Online
DOI: 10.1039/D5CY00106D

Institute for Excellence in Higher Education,
Tohoku University
Sendai 980-8576, Japan

Prof. Itaru Nakamura

Tel: (+81)-22-795-3370, E-mail: itaru-n@tohoku.ac.jp

January 27, 2025

41 Kawauchi
Sendai 980-8576
Japan

Catalysis Science & Technology

Dear Professor Bert Weckhuysen,

Data Availability Statements for my manuscript entitled "Cu-catalyzed [1,3]-Asymmetric Methoxy Rearrangement of *N*-Methoxyanilines: Mechanistic Insight"

The exploratory investigation, experimental procedures, computational data, and characterization data are available. The data supporting this article have been included as part of the Supplementary Information. Crystallographic data for 2c has been deposited at the CCDC under 2415308.

Sincerely yours,

Itaru Nakamura