# Ruthenium-Catalyzed Isomerization of *ortho*-Silylanilines to Their *para* Isomers

Wataru Ishiga, Masaya Ohta, Takuya Kodama, and Mamoru Tobisu\*



The substitution pattern of polysubstituted arenes has a critical impact on their chemical, physical, and biological properties, and therefore, the development of methods for the selective synthesis of polysubstituted arenes with the desired arrangement of substituents is now one of the most important subjects in the field of synthetic organic chemistry. In this context, a number of methods that allow for the site-selective introduction of a functional group to an aromatic compound have been reported.<sup>1</sup> Another approach to this end would be the selective interconversion of positional isomers of polysubstituted arenes, such as that between ortho, meta, and para isomers of disubstituted arenes. This approach is potentially powerful, because it would permit a positional isomer that is difficult to access by direct introduction methods to be synthesized. Reported transposition reactions of substituents on a benzene ring are summarized in Scheme 1. It would be possible to cause an alkyl group to migrate around an aromatic ring with the aid of Brønsted or Lewis acids via a reversible Friedel-Crafts-type reaction, which would result in the formation of a mixture of positional isomers (Scheme 1a). The isomerization of ortho- or para-bromophenol to a meta isomer was reported to be mediated by a superacid (SbF<sub>5</sub>-HF) via an arenium cation intermediate (Scheme 1b, top).<sup>3</sup> The 1,2-transposition of a halide group could also occur via an anionic mechanism, a reaction that is known as the halogen dance reaction (Scheme 1b, bottom).<sup>4</sup> A silyl group of 1,2bis(silyl)arenes can migrate in a 1,2-fashion to form a *meta* isomer with the aid of  $CF_3CO_2H$  (Scheme 1c).<sup>5</sup> The reversible transposition of an ester group is catalyzed by a palladium complex, presumably via the oxidative addition of a C(acyl)-O bond and decarbonylation (Scheme 1d).<sup>6</sup> Herein, we report on the ruthenium-catalyzed isomerization of ortho-silylaniline derivatives to the corresponding *para* isomers (Scheme 1e). Unlike the acid-catalyzed reaction (Scheme 1c),<sup>5</sup> the exclusive 1,3-migration of a silyl group is possible by the use of a transition metal catalyst.

During the course of our studies on catalytic carbon–silicon bond activation reactions,<sup>7</sup> we examined annulation reactions

using the o-silylaniline derivative 1a in the presence of a series of transition metal catalysts. Although the expected product was not observed, the corresponding para isomer 2a was unexpectedly formed. Given that no catalytic 1,3-silicon migration reactions have been reported to date, we focused our attention on optimizing this catalytic isomerization reaction. Finally, compound 2a was obtained in 73% isolated yield when compound 1a was reacted in the presence of  $[RuCl_2(p-cymene)]_2$  (10 mol %), (±)-BINAP (20 mol %), and Cu(OAc)<sub>2</sub> (1.2 equiv) in toluene at 180 °C for 15 h (entry 1 in Table 1). Although no product was formed in the absence of a ruthenium catalyst (entry 2), several other transition metal complexes exhibited some levels of catalytic activity: [RhCl-(cod)]<sub>2</sub> (75%),  $[Cp*RhCl_2]_2$  (18%),  $[Cp*IrCl_2]_2$  (45%),  $Ni(OAc)_2$  (7%), and  $Pd(OAc)_2$  (44%). The yield of compound 2a was significantly lowered in the absence of an added ligand (32%, entry 3), and  $(\pm)$ -BINAP proved to be an optimal ligand among the ligands that were examined: dppm (47%), dppe (57%), dppp (59%), dppb (69%), Xantphos (28%), PCy<sub>3</sub> (65%), and P(*p*-tolyl)<sub>3</sub> (41%).<sup>8</sup> The addition of  $Cu(OAc)_2$  is required for the formation of compound 2a (entry 4), and the yield was diminished to 34%, with 13% of compound 1a being recovered and 24% of a protodesilylated product being formed when the amount of  $Cu(OAc)_2$  was reduced to 20 mol % (entry 5). Other copper salts, such as CuCl (13%), CuI (10%), and CuBr<sub>2</sub> (0%), were much less effective. It is important to note that, when compound 1a was exposed to CF<sub>3</sub>CO<sub>2</sub>H-catalyzed conditions,<sup>5</sup> which were used for the isomerization of bis(silyl)arenes (Scheme 1c), compound 2a was obtained in only 14% yield, with a

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# Scheme 1. Transposition of Functional Groups on a Benzene Ring



Table 1. Ru-Catalyzed Isomerization of *ortho*-Silylaniline 1a to Its *para* Isomer  $2a^{a}$ 



<sup>*a*</sup>Reaction conditions: compound 1a (0.20 mmol),  $[RuCl_2(p-cymene)]_2$  (0.020 mmol), (±)-BINAP (0.040 mmol),  $Cu(OAc)_2$  (0.20 mmol), and toluene (1.0 mL) in a screw-capped pressure-proof vial under an atmosphere of N<sub>2</sub> for 15 h. <sup>*b*</sup>GC yield. <sup>*c*</sup>Isolated yield with 1.2 equiv of  $Cu(OAc)_2$ .

protodesilylated compound (i.e., *N*,*N*-dimethylaniline) being the major product (48%). The corresponding *m*-silylaniline derivative did not isomerize into compound **2a**, indicating that sequential double 1,2-silicon migration is unlikely to be involved in this 1,3-silicon transposition reaction.

Under the optimized conditions identified above, we subsequently explored the scope of this catalytic silicon transposition reaction (Scheme 2). With regard to the silyl

# Scheme 2. Scope of the Ru-Catalyzed Isomerization of *ortho*-Silylanilines to Their *para* Isomers<sup>*a*</sup>



<sup>*a*</sup>Reaction conditions: compound 1 (0.50 mmol),  $[RuCl_2(p-cymene)]_2$  (0.050 mmol), (±)-BINAP (0.10 mmol),  $Cu(OAc)_2$  (0.60 mmol), and toluene (2.5 mL) in a screw-capped pressure-proof vial under N<sub>2</sub> at 180 °C for 15 h. <sup>*b*</sup>[RhCl(cod)]<sub>2</sub> (0.050 mmol) was used instead of  $[RuCl_2(p-cymene)]_2$ . The yield was determined by GC analysis. <sup>*c*</sup>Run for 9 h. <sup>*d*</sup>[RuCl\_2(*p*-cymene)]<sub>2</sub> (0.10 mmol) was used.

group, both <sup>t</sup>BuMe<sub>2</sub>Si (i.e., compound 1a) and <sup>t</sup>Pr<sub>3</sub>Si (i.e., compound 1b) groups can be translocated from the ortho to the para position of an aniline framework in an efficient manner, but Et<sub>3</sub>Si and Me<sub>3</sub>Si groups were not suitable as a result of the formation of a protodesilylation product as the major product (48% for compound 1d and 99% for compound 1e). In the case of a substrate bearing a Ph<sub>3</sub>Si group (i.e., compound 1c), the yield of compound 2c was increased from 8 to 23% by changing the catalyst to  $[RhCl(cod)]_2$ . These results indicate that the use of bulky 'BuMe<sub>2</sub>Si or 'Pr<sub>3</sub>Si groups is essential for maximizing the yield of the silicon transposition product by suppressing a competing protodesilylation pathway. In addition to simple 2-silylaniline derivatives, substrates bearing an additional substituent, including Me, F, Cl, and OMe groups, at the 5 position also underwent this 1,3-silicon migration to form the corresponding 4-silylanilines 2f-2j, despite the increased steric congestion that is generated in the products. This isomerization reaction was successfully applied to a 1-aminonaphthalene-based substrate 1k, of which a silyl

group was translocated exclusively to the 4 position. A silyl group in the 2-aminopyridine derivative 11 also underwent this catalytic 1,3-silicon migration to form the corresponding product 21 in 41% yield. A NMe<sub>2</sub> group in the substrate is currently essential for this silicon transposition reaction, and substrates bearing NEt<sub>2</sub>, OMe, and CH<sub>2</sub>NMe<sub>2</sub> groups instead were completely unreactive under these conditions.

This catalytic system also allows for the transposition of a silyl group on five-membered heteroarenes (Scheme 3). For





example, the 2-silylindoles 1m and 1n could be isomerized to the corresponding 3-silylindoles 2m and 2n, respectively, by applying the standard conditions. Unlike the six-membered arene substrates shown in Scheme 2, a neighboring NMe<sub>2</sub> group is not needed for the indole substrates to be isomerized, and even an electron-withdrawing sulfamoyl group can be used as a N-protecting group. Similarly, a silyl group at the 2 position of a pyrrole ring was translocated to the 3 position, which indicates that the site selectivity is different from that observed for typical S<sub>E</sub>Ar reactions of pyrroles.<sup>1,9</sup> This site selectivity allows for readily accessible 2,5-bis(silyl)pyrrole 10<sup>10</sup> to be isomerized to the 2,4-bis(silyl) isomer 20, which is otherwise difficult to synthesize from the parent pyrrole.

Several preliminary mechanistic experiments were conducted to shed light on the mechanism of this catalytic isomerization reaction (Scheme 4). A crossover experiment using compounds 1b and 1h revealed that the silicon transposition occurs in an intramolecular manner (Scheme 4a). When 2-silylaniline 1a-d, which contains deuterium at the para position, was reacted under the standard conditions, compound 2a was formed in 67% yield, with no deuterium incorporation (Scheme 4b), suggesting that an intermolecular proton exchange process is involved. A kinetic isotope effect of 1.17 was observed in parallel kinetic experiments using compounds 1a and 1a-d, indicating that the cleavage of a C-H bond is not the turnover-limiting step in this catalytic reaction. Although we identified a Ru(II) complex as the most effective catalyst precursor, a Ru(III) complex (i.e., [Cp\*Ru- $(III)Cl_2]_n$  can also be used to mediate the silicon transposition reaction (Scheme 4c). Importantly, with this Ru(III) precatalyst, the effect of  $Cu(OAc)_2$  additive is not quite as profound [45% yield with Cu(OAc)<sub>2</sub> and 39% yield without  $Cu(OAc)_2$ , which is in sharp contrast to the use of a  $[RuCl_2(p-cymene)]_2$  catalyst, where no reaction occurs in the absence of  $Cu(OAc)_2$  (entry 4 in Table 1). These observations can be rationalized by assuming that one of the roles of  $Cu(OAc)_2$  in this reaction is to oxidize Ru(II) to Ru(III),

#### Scheme 4. Mechanistic Studies

(a) Crossover experiment



which presumably serves as the catalytically active species, although the role of  $Cu(OAc)_2$  is not completely understood at this stage. With regard to the silicon migration step, Li and co-workers recently reported on an intriguing reaction between 3-silylarynes and allyl solfoxides that involves 1,3-silicon migration.<sup>11</sup> In their study, the electrophilic bromination of 2-silylphenol was reported to afford 2-bromophenol with a silyl group at the 4 position. Prompted by this report, we examined electrophilic bromination of compound 1a to investigate whether 1,3-silicon migration is induced in the case of the 2silylanilne derivatives. As a result, 2-bromoaniline with the silyl group having migrated to the 4 position (i.e., compound 3) was formed in 21% yield, along with the 4-brominated product 4 (25%) (Scheme 4d). Similarly, the bromination of 2,5bis(silyl)pyrrole 10 underwent 2-bromination with a 1,2silicon shift to form compound 5 as a sole product. These results indicate that an attack of an electrophile at the ipso position of silyl(hetero)arenes appears to induce the migration of a silvl group.

On the basis of the mechanistic studies described above, a proposed mechanism is depicted in Scheme 5.  $RuX_3$ , which is generated *in situ* by the oxidation of  $RuX_2$  with Cu(II), serves as the catalytically active species. Coordination of a  $NMe_2$  group in compound 1a to  $RuX_3$  forms intermediate A, which

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# Scheme 5. Proposed Mechanism



facilitates the electrophilic attack of RuX<sub>3</sub> at the *ipso* position of a silvl group, providing the cationic intermediate **B**. The silvl group in intermediate B subsequently migrates to the para position, likely driven by the relief of steric congestion, to form the intermediate  $C_{i}$  as was observed in the reaction of compound 1a with a bromonium cation (Scheme 4d).<sup>12</sup> The deprotonation of intermediate  $C^{13}$  affords the aromatized intermediate D, which undergoes protodemetalation to furnish compound 2a with the regeneration of RuX<sub>3</sub>. Although the formation of compound 2a directly from intermediate C via the 1,3-migration of a proton could be an alternative pathway, we currently exclude this possibility based on the results of a labeling experiment (Scheme 4b). Arenium cation intermediates B and C are prone to desilvlation by attack of an external nucleophile, such as AcO<sup>-</sup>, when the size of a silvl group is small, leading to the formation of the protodesilylation product.<sup>14</sup> A NMe<sub>2</sub> group plays three roles in the catalytic cycle: as an ortho directing group to facilitate the electrophilic addition, imposition of steric repulsion on the ortho silyl group to promote its migration, and as an electron-donating group that stabilizes the cationic intermediates B and C.

Although the use of a NMe<sub>2</sub> group is essential for this silicon transposition reaction, this group can be transformed into other substituents by cross-coupling via the cleavage of C(aryl)-N bonds. For example, the NMe<sub>2</sub> group in compound **2k** can be converted into an alkyl or other amino groups by iron-catalyzed cross-coupling with RMgX<sup>15a</sup> or nickel-catalyzed amination<sup>15b</sup> through the conversion to the corresponding ammonium salt (Scheme 6).

In summary, we report on the development of a catalytic transposition reaction of a silyl group on an aromatic ring, which allowed *ortho*-silylaniline derivatives to isomerize to the corresponding *para* isomers with the aid of a ruthenium catalyst. This transposition reaction is also applicable to 2-silylpyrroles and 2-silylindoles, which undergo 1,2-silicon migration. The findings reported herein will stimulate further development of transition-metal-catalyzed transposition reactions, which serve as potential methods for the synthesis of positional isomers of multi-substituted (hetero)arenes that are

Scheme 6. Transformation of a NMe<sub>2</sub> Group in the Isomerized Product



difficult to access by direct aromatic functionalization. Studies along this line are currently underway in our laboratory.

### ASSOCIATED CONTENT

#### **9** Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c02280.

Detailed experimental procedures and characterization of new compounds (PDF)

#### **Accession Codes**

CCDC 2090589 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data\_request/cif, or by emailing data\_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

# AUTHOR INFORMATION

## **Corresponding Author**

Mamoru Tobisu – Department of Applied Chemistry, Graduate School of Engineering and Innovative Catalysis Science Division, Institute for Open and Transdisciplinary Research Initiatives (ICS–OTRI), Osaka University, Suita, Osaka 565-0871, Japan; ocid.org/0000-0002-8415-2225; Email: tobisu@chem.eng.osaka-u.ac.jp

#### Authors

- Wataru Ishiga Department of Applied Chemistry, Graduate School of Engineering, Osaka University, Suita, Osaka 565-0871, Japan
- Masaya Ohta Department of Applied Chemistry, Graduate School of Engineering, Osaka University, Suita, Osaka 565-0871, Japan
- Takuya Kodama Department of Applied Chemistry, Graduate School of Engineering and Innovative Catalysis Science Division, Institute for Open and Transdisciplinary Research Initiatives (ICS–OTRI), Osaka University, Suita, Osaka 565-0871, Japan; orcid.org/0000-0001-8275-2393

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.1c02280

## Notes

The authors declare no competing financial interest.

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