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# Base-Catalyzed Aryl Halide Isomerization Enables the 4-Selective Substitution of 3-Bromopyridines

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The base-catalyzed isomerization of simple aryl halides is presented and utilized to achieve the 4-selective etherification, hydroxylation and amination of 3-bromopyridines. Mechanistic studies support isomerization of 3-bromopyridines to 4-bromopyridines proceeds via pyridyne intermediates and that 4-substitution selectivity is driven by a facile aromatic substitution reaction. Useful features of a tandem aryl halide isomerization/selective interception approach to aromatic functionalization are demonstrated. Example benefits include the use of readily available and stable 3-bromopyridines in place of less available and stable 4-halogenated congeners and the ability to converge mixtures of 3- and 5-bromopyridines to a single 4-substituted product.

#### Introduction

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The synthetic value of aryl halides derives from their thoroughly studied reactivity that allows reliable and predictable access to functionalized aromatic compounds.<sup>1</sup> The utility of these widely available substrates can be significantly increased as new reactivity modes are discovered and applied. In this regard, catalytic aryl halide isomerization drew our attention as a relatively underdeveloped yet potentially useful process (Scheme 1).<sup>2</sup>



Scheme 1. Concept of catalytic aryl halide isomerization.

The rearrangement of halogenated arenes under basic conditions has been extensively studied in the context of "halogen dance" chemistry.<sup>3</sup> Early studies by Bunnett on the base-catalyzed isomerization of 1,2,4-tribromobenzene into 1,3,5-tribromobenzene revealed rearrangement occurs via intermolecular halogen transfer, resulting in regioisomeric mixtures and disproportionated side products.<sup>4</sup> This catalytic rearrangement requires an acidic arene that can generate electrophilic halogen transfer intermediates (e.g. tetrabromobenzenes); thus, isomerization is observed for tribromobenzenes but not for simple aryl halides.<sup>5</sup> This insight guided decades of development of modern "halogen dance" methodology, wherein stoichiometric and irreversible

metalation of haloarenes can lead to rearrangement through intermolecular metal-halogen transposition.<sup>6</sup> In addition to typically requiring stoichiometric lithium bases under cryogenic conditions, a synthetically useful dance requires a thermodynamic gradient in order to drive a selective rearrangement.<sup>3</sup> In this regard, important achievements have been made in identifying specific classes of metalated haloarenes that rearrange as a strategy for electrophilic functionalization.<sup>7</sup>

We sought to identify more mild and general conditions for aryl halide isomerization as an entry to developing new arene functionalization methods. Inspired by sporadic reports of rearranged aryl halide side products<sup>8</sup> in reactions involving aryne<sup>9,10</sup> intermediates, we hypothesized that non-nucleophilic bases could enable reversible HX elimination/addition as an additional isomerization pathway (Figure 1a). We further proposed that pairing isomerization with a tandem substitution reaction could provide a driving force for nontraditional selectivity in aromatic substitution reactions (Figure 1b).<sup>11</sup> We herein describe initial studies on a general approach to catalytic aryl halide isomerization and demonstrate its utility as a new route to 4-functionalized pyridines.<sup>12</sup>

(a) A potential elimination/addition pathway to catalytic ArX isomerization



(b) Proposal: selective substitution via tandem isomerization/substitution



**Figure 1.** A general approach to aryl halide isomerization and its application to a new selective substitution reaction.

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#### **Results and Discussion**

We speculated bases that reversibly deprotonate aryl C-H bonds may create conditions capable of isomerizing aryl halides.<sup>13</sup> This led us to investigate the non-nucleophilic organic superbase P<sub>4</sub>-t-Bu (pK<sub>BH+</sub> 30.2 in DMSO) as a potential isomerization catalyst.<sup>14</sup> In 1,4-dioxane, we discovered P<sub>4</sub>-t-Bu catalyzes the isomerization of 2-bromobenzotrifluoride (1) into all possible regioisomers (Scheme 2a). Under these conditions, 3-bromobenzotrifluoride (2) and 4-bromobenzotrifluoride (3) interconvert but do not form 2-bromobenzotrifluoride (Scheme 2b). No protodehalogenated or polyhalogenated side products are observed, and we note isomerization occurs to a lesser extent for 4-iodobenzotrifluoride (4).15 A variety of other bromoarenes (5, 6 and 7) also isomerize, including the formation of 4-bromopyridine from 3-bromopyridine (8).<sup>16</sup> Although further studies on the scope of this process are ongoing, these observations suggest P<sub>4</sub>-t-Bu-catalyzed aryl halide isomerization is a general and reversible process.



**Scheme 2.**  $P_4$ -*t*-Bu-catalyzed aryl halide isomerization. <sup>*a*</sup> Yields determined by <sup>1</sup>H NMR spectroscopy; the mass balance is less than 100% with no observed haloarene side products; conditions for Scheme 2b are as shown in Scheme 2a. <sup>*b*</sup> Reaction performed in cyclohexane for 14 h.

As a broader objective, we questioned if aryl halide isomerization could be utilized to address current challenges in aromatic functionalization. As a halogen migrates around an arene, we reasoned that differing electronic properties of isomeric C–X bonds could provide a source to differentiate interconverting isomers and drive an overall selective transformation.<sup>17</sup> A mechanistic outline for the application of this concept to the 4-substitution of 3-bromopyridines is shown

in Scheme 3. This pathway exploits the inherent preference for 4-bromopyridines to undergo nucleophilic/ $D^{0}$  aromatic substitution (S<sub>N</sub>Ar) over 3-bromopyridines.<sup>18</sup> However, a likely challenge is avoiding nucleophilic addition to the proposed 3,4pyridyne intermediate, as this could decrease the desired reaction's yield and regioselectivity.<sup>19</sup> Successful development of this protocol would offer an attractive route to 4functionalized pyridines from 3-bromopyridines, which are more commercially available<sup>20</sup> and stable<sup>21</sup> than 4-halogenated congeners. This method would also complement other recently developed methods for 4-selective nucleophilic pyridine C–H functionalization, including McNally's powerful heterocyclic phosphonium salt approach.<sup>22,23</sup>



**Scheme 3.** Proposed pathway for the 4-selective substitution of 3bromopyridine (B = base, NuH = nucleophile).

As the proposed process requires stoichiometric base, we first investigated the use of hydroxide bases as more practical reagents for promoting aryl halide isomerization. Hydroxide bases are known to generate and be compatible with aryne intermediates, and we identified that 3-bromopyridines isomerize in the presence of 18-crown-6-ligated KOH in N,Ndimethylacetamide (see Supporting Information).<sup>24</sup> Using these conditions, we then employed two separate strategies for optimizing a 4-selective etherification reaction of 3bromopyridine (Table 1). When 1 equivalent of 3bromopyridine (8) reacts with 4 equivalents of alcohol 9, a 2.4:1 ratio of 4:3-substituted product (10:11) is obtained in 54% overall yield (Entry 1). This ratio is comparable to reported selectivities for nucleophilic additions to 3,4-pyridyne, which typically range from 1:1 to 3:1 for 4:3 addition selectivity.<sup>25</sup> The 4-selectivity increases as higher ratios of pyridine: alcohol (8:9) are used, a result perhaps explainable by less alcohol intercepting a 3,4-pyridyne intermediate (Entries 2-5). Based on this observation, we hypothesized that added bromide salts may enable more efficient isomerization and prevent undesired side reactions.<sup>26</sup> When 50% KBr is added to a reaction using a 1.5:1 pyridine: alcohol (8:9) ratio, the yield increases to 76% with >14:1 4-selectivity compared to 67% yield and 8.6:1 4selectivity in the absence of bromide salt (Entries 6-10).

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**Table 1.** Optimization of 4-selective etherification of 3-bromopyridine.<sup>a</sup>



effect of pyridine:alcohol ratio				effect of bromide salt additive <sup>b</sup>			
Entry	8:9	Yield	10:11	Entry	KBr	Yield	10:11
1	1:4	54%	2.4	6	0%	67%	8.6
2	1:2	65%	5.5	7	10%	69%	8.9
3	1:1	64%	8.1	8	20%	73%	11.1
4	2:1	95%	12.6	9	50%	76%	14.2
5	4:1	90%	11.9	10	100%	77%	14.2

<sup>*a*</sup> Yields and selectivities determined by <sup>1</sup>H NMR spectroscopy of the crude reaction mixtures; yields represent total amount of both isomeric products **10** and **11**. <sup>*b*</sup> 2.0 equiv of KOH used with a 1:1 ratio of **8:9**.

A reaction profile with the optimized conditions shows the rapid formation of a low concentration of 4-bromopyridine (approximately 5%) that decreases as the reaction reaches completion (Scheme 4a). Subjection of the 3-substituted ether product (11) to the reaction conditions does not result in mass balance loss, indicating the high 4-selectivity is not a result of selective decomposition or product rearrangement.<sup>27</sup> To test for the generation of 3,4-pyridyne under these conditions, when the alcohol is replaced with an excess of furan (12) the corresponding cycloadduct 13 forms in 42% yield (Scheme 4b).<sup>28</sup> We also subjected 3-iodopyridine (14) to the reaction conditions in the absence of alcohol; in the presence of furan (12) cycloadduct 13 forms and in the presence of KBr a mixture of 3- and 4-bromopyridine form (8 and 15, Scheme 4c). The observed mixture of 3- and 4-bromopyridine supports the proposal of bromide addition to 3,4-pyridyne. Overall, these results are consistent with an isomerization pathway via 3,4pyridyne and 4-substitution selectivity driven by a facile S<sub>N</sub>Ar reaction.



(c) Addition of KBr to 3-iodopyridine under reaction conditions



**Scheme 4.** Mechanistic studies on the 4-selective etherification of 3bromopyridine. <sup>*a*</sup> Conditions as shown in Table 1 using 1.5:1 ratio of **8:9** with 50 mol% KBr additive; see Supporting Information for details.

A substrate scope for the 4-selective etherification of 3bromopyridines is provided in Table 2.29 A range of primary and secondary alcohols are first shown using 1.5 equiv of simple bromopyridines. Sterically hindered alcohols (16) and those containing amino groups (17, 23, and 24), a terminal alkene (18) and a protected sugar (22) are suitable nucleophiles. Pyridines methylated in all positions react in high yield and selectivity (19, 20, 21 and 24), indicating that steric hindrance and acidic C-H bonds are tolerated on the arene. Pyridine biaryl substrates also selectively couple in the 4-position (25 and 26). Both 2-alkoxy (23) and 2-amino (28) substituents on the pyridine are tolerated, although we note the high selectivity observed for these substrates could originate from alcohol addition to a distorted 3,4-pyridyne intermediate.<sup>19</sup> Pyridine substrates with more electron-withdrawing groups undergo direct 3substitution under the current reaction conditions (e.g. 3bromo-2-(trifluoromethyl)pyridine).30



bromination in the 3- and 5-positions (**35a** and **35b**), Application of conditions from Table 2 provides access to the 2



Scheme 5. 4-selective etherification of a 2,6-disubstituted pyridine.

We next examined if other nucleophiles can participate in the 4-selective substitution of 3-bromopyridines. We found that indolines are effective coupling partners and this route provides straightforward access to 4-aminopyridines from readily available 3-bromopyridines (**37-40**, Scheme 6a). The 4amination of 3-bromopyridine with indoline proceeds on gram scale with excellent selectivity (**37**). A single isomer of the 5bromoindoline product **38** is obtained, demonstrating the chemoselectivity of aryl halide isomerization.



**Scheme 6.** The 4-substitution of 3-bromopyridines with additional nucleophiles. <sup>*a*</sup> Isolated yield of purified 4-substituted products; selectivities determined by <sup>1</sup>H NMR spectroscopy of crude reaction mixtures; <sup>*b*</sup> 1.5 equiv of 3-bromopyridine used; <sup>*c*</sup> Selectivity 9:1.

It is interesting to note that 4-hydroxypyridine side products are not typically observed for the reactions in Table 2 even though KOH is used as a base.<sup>32</sup> To develop a 4-hydroxylation protocol, we instead hypothesized tandem isomerization/substitution could be further sequenced with a base-promoted elimination step. This is demonstrated in



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<sup>*o*</sup> Yields are of purified 4-ether product; regioselectivities determined by <sup>1</sup>H NMR spectroscopy of the crude reaction mixture; <sup>*b*</sup> Selectivity >6:1; see Supporting Information for details; <sup>*c*</sup>  $P_{a}$ -*t*-Bu (1.3 equiv) used as base in place of KOH.

An advantage of this functionalization strategy is demonstrated with substrates **29-33** in Table 2, where the bromopyridine substrate is obtained from commercial pyridines while a 4-halogenated isomer is either not available or significantly more expensive (see Supporting Information for a discussion). Using 1-1.2 equiv of these bromopyridines, 4-substituted products featuring a carbamate (**29**), an acidic amide (**30**), a 2,6-disubstituted pyridine (**31**), a nicotine isomer (**32**) and a ketal (**33**) can be rapidly accessed.

This strategy can also utilize an arene's innate halogenation position as an entry to functionalizing more difficult to access C–H bonds. This is demonstrated in Scheme 5, where the 2,6disubstituted pyridine **34** undergoes facile but unselective

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Scheme 6b, where the use of  $\beta$ -hydroxyamide **42** as a nucleophile directly delivers the 4-hydroxylated product **43** in 50% yield with >10:1 selectivity. We speculate this reaction proceeds through the standard 4-substitution pathway followed by a facile base-promoted acrylamide elimination reaction.<sup>33</sup>

#### Conclusions

This work demonstrates base-catalyzed aryl halide isomerization can be paired with  $S_NAr$  reactivity to achieve unconventional substitution selectivity. In contrast, established "halogen dance" methodology relies on the controlled rearrangement of specific classes of stoichiometrically metalated haloarenes prior to treatment with electrophiles.<sup>3</sup> Thus, tandem isomerization/selective interception may be a complementary and general strategy for achieving nontraditional selectivities in aryl halide functionalization chemistry.

#### **Conflicts of interest**

There are no conflicts to declare.

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involvement of aryl halide isomerization; see Supporting Information for details. DOI: 10.1039/D0SC02689A

- 30 For a similar S<sub>N</sub>Ar reaction, see: Basséne, C. E.; Suzenet, F.; Hennuyer, N.; Staels, B.; Caignard, D.-H.; Dacquet, C.; Renard, P.; Guillaumet, G. Bioorg. Med. Chem. Lett. 2006, 16, 4528-2532.
- 31 See reference 12c for a similar convergence example in a Pd/norbornene co-catalyzed 4-selective amination reaction using N-hydroxylamine ester electrophiles.
- 32 In the reactions reported in Table 2, less than 5% of 4hydroxypyridine side products are typically observed. Attempts to perform the reaction in the absence of alcohol did not significantly increase the yield of hydroxylation products.
- 33 N,N-Dibenzyl acrylamide is observed as the major byproduct in this reaction. For related hydroxylation strategies, see: (a) Revuelto, A.; Ruiz-Santaquiteria, M.; de Lucio, H.; Gamo, A.; Carriles, A. A.; Gutiérrez, K. J.; Sánchez-Murcia, P. A.; Hermoso, J. A.; Gago, F.; Camarasa, M.-J.; Jiménez-Ruiz, A.; Velázquez, S. ACS Infect. Dis. 2019, 5, 873-891. (b) Rogers, J. F.; Green, D. M. Tetrahedron Lett. 2002, 43, 3585-3587.

# **TOC Image and Text**

### Image:



## Text:

The base-catalyzed isomerization of simple aryl halides is described, including its application to the tandem isomerization/4-substitution of 3-bromopyridines as a new strategy for achieving unconventional selectivity in nucleophilic aromatic substitution reactions.