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Diversification of Bipyridines and Azaheterocycles via Nucleophilic Displacement of Trimethylammoniums

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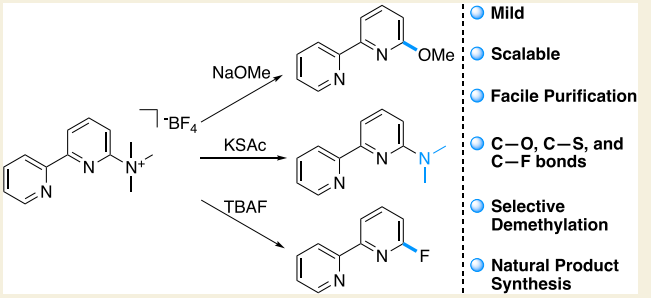
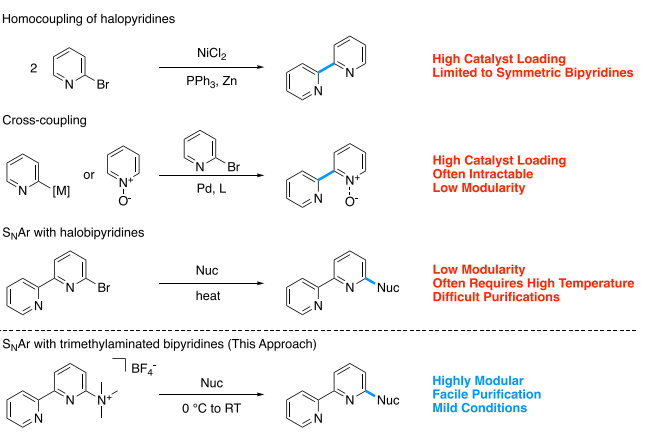
ABSTRACT: Bipyridines and azaarenes are an important class of ligands that impart unique and tunable properties to transition metal complexes and catalysts. While some derivatives are commercially available, noncommercial analogues are often challenging to prepare and purify. Herein, we report a general nucleophilic aromatic substitution reaction that converts cationic trimethylaminated bipyridines into a series of functionalized bipyridines. Our method showcases a series of C−O, C−S, and C−F bond-forming reactions as well as a selective monodemethylation that converts the electron-deficient trimethylammonium to an electron-rich dimethylamine. The approach was further applied to diversification of pharmaceuticals and natural products and was applied to the total synthesis of Graveolinine and the preparation of Graveolinine derivatives.



KEYWORDS: *S_NAr, nucleophilic aromatic substitution, bipyridines, 2,2′-bipyridyl, trimethylammonium, cations*

Nucleophilic aromatic substitution (S_NAr) reactions are powerful transformations prevalent in all areas of organic synthesis.[1] First used in the 1800s to prepare small molecules,[2] and S_NAr reactions have since seen significant incorporation in the preparation of natural products,[3,4] pharmaceuticals,[5] and agrochemicals,[6] and for the modification and diversification of biomolecules[7] and functional materials.[8,9] While classic S_NAr reactions involve nucleophilic displacement of halides on strongly electron-deficient arenes,[10] recent investigations have advanced the transformation by developing milder conditions and expanding the scope of accessible arene electrophiles. Notably, Knowles and co-workers developed a homolysis-enabled aromatic substitution reaction that proceeds on an electron-rich arene via stepwise proton and electron transfers that transiently make the arene electron-deficient.[11] Another important advance is the use of trimethylaminated arenes as the electrophile in these reactions.[12,13] Because the starting electrophile is charged and the products are often neutral, isolation and purification are particularly facile. This feature is noteworthy because S_NAr and other halogen exchange reactions performed on complex or polar molecules often do not appreciably change the molecules' interaction with stationary phases used for isolation, resulting in more challenging purification.[14] The reactivity and ease of purification have allowed trimethylaminated (hetero)arenes to be maintstays in (radio)fluorination reactions,[14−17] along with C−O and some C−N bond-forming reactions on azaarenes.[18−21] We were particularly interested in applying the S_NAr reaction involving cationic electrophiles to trimethylamonium-substituted 2,2′-bipyridines. 2,2′-bipyridine is a ubiquitous ancillary ligand for transition metals.[22] Substitution around the pyridyl rings tunes the properties of the transition metal it is bound to, including accessible oxidation and electronic states,[23,24] thermochemical properties,[25] and the metals' reactivity toward organic molecules.[26]

Scheme 1. Approaches to Synthesize Bipyridines



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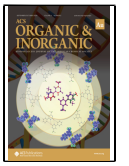


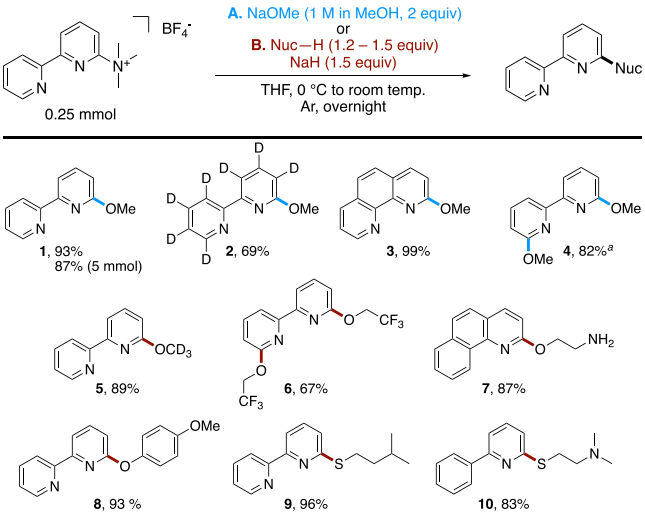
While bipyridines are very important small molecules and numerous derivatives are commercially available, synthesis of novel or noncommercial bipyridines is often limited to three different approaches: reductive homocoupling of halopyridines with a nickel catalyst,[27] cross-coupling of halopyridines and either 2-pyridyl nucleophiles or pyridine N-oxides with a palladium catalyst,[28,29] or nucleophilic substitution of halobipyridines with strong nucleophiles (Scheme 1).[30] Each approach has its shortcomings. As bipyridines are competent ligands for transition metal catalysts, large catalyst loadings are often required due to product binding and catalyst inhibition.[27,31] Further, cross-couplings involving 2-pyridyl nucleophiles are not always tractable due to the instability of the 2-pyridyl analogues of most common cross-coupling nucleophiles.[32,33] More recent bipyridine syntheses involving S(IV)- or P(V)-mediated couplings have been reported; however, these approaches require multistep manipulations to install the requisite sulfur or phosphorus center and often require the use of unstable magnesio- or lithio-pyridines.[34−37] The final approach, S_NAr with halobipyridines, is the most general way to access unsymmetrical bipyridines. Unfortunately, few substituted halobipyridines are commercially available and their preparation can be challenging.[38,39] Additionally, separation of S_NAr products from unreacted starting material by silica gel column chromatography can be difficult.[14] Since we previously reported a general, modular, and scalable approach to accessing trimethylammonium-substituted 2,2′-bipyridines and azaarenes,[40] we wondered if they could also function as precursors to a variety of substituted bipyridines. If successful, their application would have numerous benefits over using 6-halobipyridines as electrophiles, including ease of access to more highly functionalized ligands, and more facile purification from unreacted trimethylammonium bipyridine. Further, as pyridines are the most common aromatic azaheterocycle in pharmaceutical molecules[41] and as S_NAr is one of the most common transformations in all levels of pharmaceutical development,[5] advances in substitution of trimethylaminated pyridines impacts drug discovery.

RESULTS AND DISCUSSION

We began our investigation with the reaction of 6-trimethylammonium 2,2′-bipyridine tetrafluoroborate with 1.5 equiv of a methanolic solution of sodium methoxide in tetrahydrofuran (THF) at room temperature. Under these conditions, there is quantitative conversion to the desired product, 6-methoxy-2,2′-bipyridine **1**, as determined by ^{1}H NMR spectroscopic analysis (Table 1). These are mild conditions, as most S_NAr require elevated temperatures to proceed. Further, when the reaction was performed on a 0.25 mmol scale, **1** could be isolated in 93% yield. This process is scalable, and the product is obtained in 87% isolated yield on a 5 mmol scale.

To determine the generality of this method, we looked into other trimethylaminated azaarenes and a series of relatively simple nucleophiles (Table 1). Using sodium methoxide as the nucleophile, the perdeuterated analogue of 6-methoxy-2,2′-bipyridine **2** was accessible in 69% yield. Further, ammonium-substituted phenanthrolines and 2,2′-bipyridyl bearing two trimethylammoniums are tolerated, as **3** and **4** could be obtained in 99 and 82% yields, respectively. However, in the case of **4**, full conversion required the reaction to be performed

Table 1. Scope of Accessible C−O and C−S Bonds Using Simple Nucleophiles[a]



[a]Reaction conditions: (A) Trimethylammonium (0.25 mmol, 1 equiv), NaOMe (1 M in MeOH, 0.50 mL, 0.50 mmol, 2 equiv) and THF (5 mL). (B) Trimethylammonium (0.25 mmol, 1 equiv), nucleophiles (0.30−0.375 mmol, 1.2−1.5 equiv), sodium hydride (60% in mineral oil, 0.375 mmol, 1.5 equiv), and THF (5 mL). [b]Reaction was performed at reflux. See the Supporting information for specific conditions.

at reflux, as the starting dication was insufficiently soluble in THF for the reaction to proceed at ambient temperature.

The method was expanded by investigating other nucleophiles. Namely, we targeted neutral nucleophiles that would necessitate deprotonation with an exogenous base to proceed. To this end, the use of sodium hydride as the base was effective, as the reaction of 6-trimethylammonium 2,2′-bipyridine tetrafluoroborate with 1.2 equiv of methanol-d_4 proceeds smoothly in the presence of 1.5 equiv of sodium hydride (Table 1). The product, **5**, was isolated in 89% yield using this approach. Longer alkyl chains and other functional groups on the nucleophile were also successful, as the bis-trifluoroethoxy **6** and ethanolamine-substituted **7** could be accessed in 67 and 87%, respectively. The chemoselectivity of **7** is noteworthy, as C−O bond formation was exclusively observed even in the presence of a primary amine.[42] Phenols could also be used as nucleophiles, as diarylether **8** was obtained in 93% isolated yield.

An interesting change in reactivity occurs when heavier chalcogens, namely thiolates, are used as nucleophiles. While alkylthiolates such as isoamylthiol and *N*,*N*-dimethylaminoethanethiol work well to afford **9** and **10** in 96 and 83% yields, respectively (Table 1), arylthiols have drastically different reactivities. Here, the use of 2-mercaptopyridine or 4-*tert*-butylthiophenol as the nucleophile did not lead to nucleophilic displacement of the trimethylammonium. Instead, monodemethylation of the trimethylammonium proceeded in 100% conversion (Scheme 2). This reactivity is particularly noteworthy because it allows for a trimethylammonium group, a very strong electron-withdrawing group, to be rapidly converted into a dimethylamino group, a very strong electron-donating group, in one reaction.[43] While this reaction has been reported in the literature,[44−46] it typically occurs on more electron-rich aryltrimethylammoniums, it has not been

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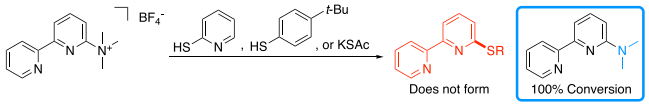
Scheme 2. Reaction of Trimethylammoniums with Arylthiols and Potassium Thioacetate as Nucleophiles Yields Demethylation Instead of Aryl Substitution

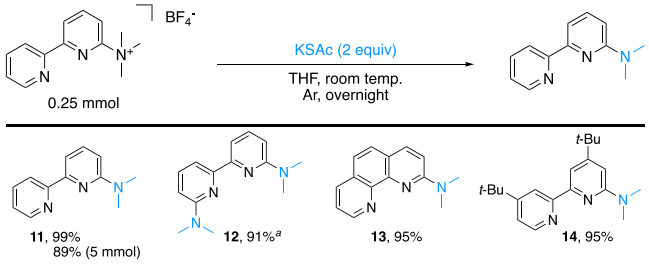


made general, and, in some cases, it is considered an undesired transformation.

Intrigued by this result, we endeavored to find an air-stable thiolate analogue with similar reactivity. The use of 2 equiv of potassium thioacetate (KSAc) readily demethylates the trimethylammonium into a dimethylamino group at room temperature. Not only is KSAc air-stable, commercial, and less noxious than other thiolate, but it also obviates the need for sodium hydride, and the side product, *S*-methylthioacetate, is volatile and easily removable by concentration in vacuo.

To explore the scope of this demethylation reaction, we first found that 6-trimethylammonium 2,2′-bipyridine tetrafluoroborate reacts with KSAc to form 6-dimethylamino-2,2′-bipyridine **11** in 99% isolated yield (Table 2). As with the

Table 2. Scope of Demethylation Using KSAc as a Nucleophile[a]



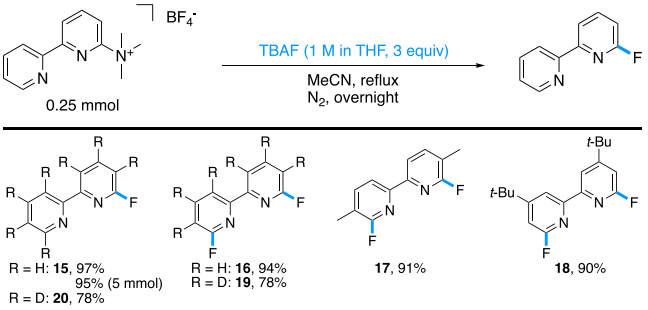
[a]Reaction conditions: Trimethylammonium (0.25 mmol, 1 equiv), KSAc (0.50 mmol, 2 equiv), and THF (5 mL). [b]Reaction was performed at reflux. See the Supporting information for specific conditions.

reactions involving sodium methoxide as the nucleophile, the demethylation was scalable, affording **11** in 89% isolated yield on a 5 mmol scale. If two trimethylammoniums are present in the substrate, both are selectively monodemethylated to afford **12** in 91% isolated yield. Much like **4**, elevated temperatures were required to reach full conversion as the starting dication has poor solubility in THF. Demethylation of trimethylaminated phenanthroline and 4,4′-di-*tert*-butyl-2,2′-bipyridine proceed smoothly at room temperature, allowing for access to **13** and **14**, both in 95% isolated yield.

We were also interested in probing whether the trimethylammonium could be displaced by fluorides. Formation of aryl C−F bonds is of significant interest to pharmaceutical development, as more than 25% of pharmaceuticals have C−F bonds.[47,48] Further, installing fluorides on bipyridines allows for functional handles to further diversify bipyridines and imparts the ability to use ^{19}F NMR to probe different forms of reactivity and host−guest binding studies.[49,50] While fluoride salts can displace electron-deficient aryl-chlorides, these aromatic Finkelstein reactions require very high temperatures, and the product aryl-fluoride is often inseparable from unreacted aryl-chloride.[51] In an informative report by Xiong and Hoye,[52] tetrabutylammonium fluoride (TBAF) was used as a fluoride source to displace trimethylammonium groups on pyridines. Under their optimized conditions (3 equiv of TBAF in DMF at 90 °C), Xiong and Hoye reported that the nucleophilic displacement with fluorides could proceed in 1 h.

Using their conditions with our trimethylaminated bipyridines, the displacement of trimethylammoniums was slow and led to incomplete conversion after 1 h. Upon further optimization, the reaction reached full conversion in acetonitrile (MeCN) after refluxing overnight. Under our optimized conditions, 6-trimethylammonium 2,2′-bipyridine tetrafluoroborate was readily fluorinated to form 6-fluoro-2,2′-bipyridine **15** in 97% yield on a 0.25 mmol scale and 95% on a 5 mmol scale (Table 3). Difluorination was also facile, as 6,6′-

Table 3. Scope of Accessible C−F Bonds[a]



[a]Reaction Conditions: Trimethylammonium (0.25 mmol, 1 equiv), TBAF (1 M in THF, 0.75 mL, 3 equiv), and MeCN (4 mL). See the Supporting information for specific conditions.

difluoro-2,2′-bipyridine **16** was accessible in 94% isolated yield. Deuteration did not significantly impact the reaction, as the d_7-bipyridyl fluoride **20** and d_6-bipyridyl difluoride **19** could be formed in 78% yield. Substituted azaarenes were also suitable, as 5,5′-dimethyl-bearing **17** and 4,4′-di-*tert*-butyl-functionalized **18** were isolated in 91 and 90% yields, respectively.

To get a better understanding of the nucleophile tolerance of this reaction, we next evaluated more complex alcohol nucleophiles. These nucleophiles impart new characteristics to the bipyridine, including additional transition metal-binding modes,[53] chirality,[54] and functional handles to bind to surfaces.[55] As more decorated nucleophiles are less abundant than our timethylaminated bipyridines and are more likely to greatly impact the polarity of the product, an excess of the ammonium electrophile was used. To increase metal-binding motifs to the bipyridine, alcohols tethered to bipyridylmethane, bis(diphenylphosphino)propane, and imidazole were attempted, successfully forming **21**, **22**, and **23** in 85, 82, and 99% yields, respectively (Table 4). To create products that could bind to surfaces through π-stacking interactions, 1-pyrenemethanol was also a successful nucleophile, forming **24** in 91% yield. Finally, we were interested in investigating if natural product and pharmaceutical-derived nucleophiles were accessible, as this would create chiral bipyridines for asymmetric catalysis,[54] metal-drug conjugates,[56,57] and showcase the possibility of our method's application to pharmaceutical development. With this in mind, quinine was used as a nucleophile, forming bipyridine **25** in 87% isolated yield. Of note, previous approaches to prepare this bipyridine required high temperatures that resulted in stereoablation of the benzylic secondary alcohol.[54] Using the pharmaceutical

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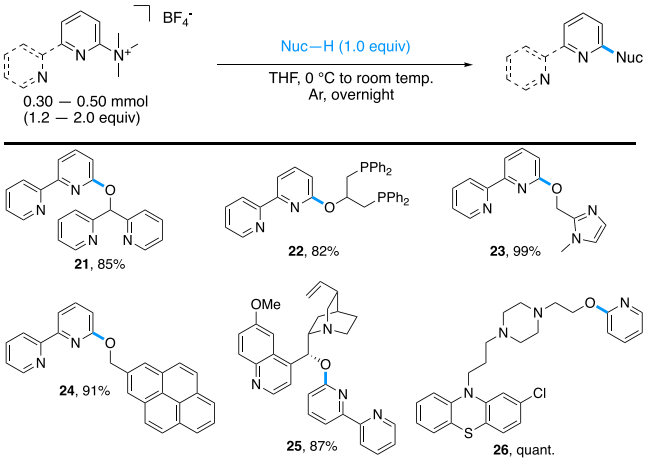
Table 4. Scope of C−O Bonds Accessible Using More Complex Nucleophiles[a]

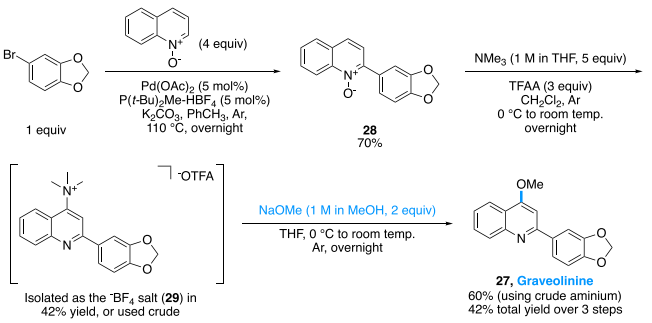


[a]Reaction conditions: Trimethylammonium (0.30−0.50 mmol, 1.2−2 equiv), nucleophile (0.25 mmol, 1 equiv), sodium hydride (60% in mineral oil, 0.375 mmol, 1.5 equiv), and THF (5 mL). See the Supporting information for specific conditions.

perphenazine as the nucleophile and 2-trimethylaminated pyridine, **26** was accessible in quantitative yield.

Informed by the broad scope of successful nucleophiles, we wondered if we could install the trimethylammonium on a complex molecule. This approach would make the electrophile the complex fragment of the S_NAr reaction. Making small modifications to a complex molecular scaffold is a common approach to building libraries of molecules in the early stages of drug discovery and medicinal chemistry.[58] Thus, if successful, our method could be incorporated in pharmaceutical development campaigns. With this goal in mind, we targeted Graveolinine (**27**), a quinoline natural product that has been investigated as an anti-Alzheimer and antiangiogenesis agent.[59,60] As Graveolinine has a methoxy group in the 4-position of the quinoline, we attempted to selectively install a trimethylammonium in the 4-position of the corresponding quinoline *N*-oxide (**28**). *N*-oxide **28** was accessible in 70% isolated yield using a Pd-catalyzed Fagnou-type cross-coupling of 1-bromo-3,4-(methylenedioxy)benzene and quinoline *N*-oxide (Scheme 3). Using our modification to Xiong and Hoye's C−H trimethylamination conditions,[40,52] we accessed spectroscopically pure 4-trimethylaminated quinoline **29** in 42% isolated yield following salt metathesis with sodium tetrafluoroborate. Isolated **29** can subsequently react with

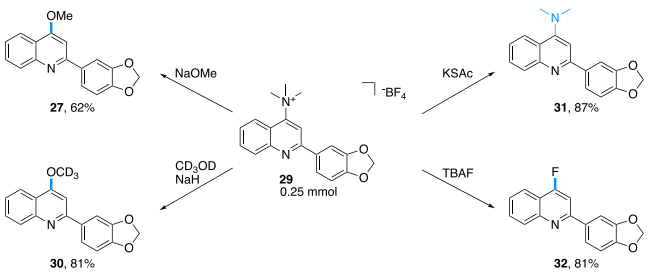
Scheme 3. Synthesis of Graveolinine Using the Trimethylammonium S_NAr Reaction



sodium methoxide to form Graveolinine (**27**) in 62% isolated yield. However, these two reactions can be telescoped, where crude **29** can be used directly in the methoxylation step to access **27** in 60% over two steps, as compared to 25% using isolated **29**. Taken together, we have developed a two-pot, three-step total synthesis of Graveolinine to access the natural product in 42% yield from commercial chemicals.

To build a representative small library of Graveolinine derivates, we performed the reaction of isolated trimethylammonium **S4** with a series of nucleophiles. As stated above, Graveolinine (**27**) could be obtained in 62% yield from pure **S4**. The use of methanol-d_4 as a nucleophile with sodium hydride as a base allowed for access to Graveolinine-d_3 (**28**) in 81% isolated yield (Table 5). Selective incorporation of

Table 5. Graveolinine Derivatives Prepared through This Method[a]

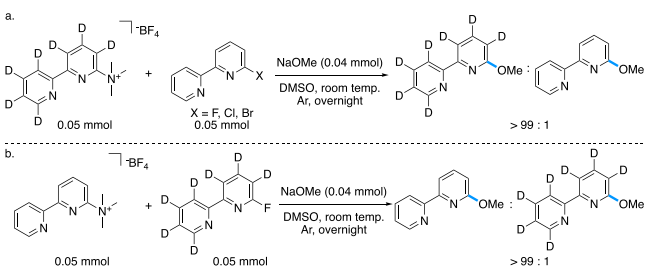


[a]See the SI for specific conditions.

deuterons in pharmaceutical molecules, such as on aryl-methyl-ethers, can greatly impact pharmacokinetic properties, as these positions can readily be oxidized in vivo, and installation of deuterons slows this often undesirable or deleterious decomposition pathway.[61,62] Our KSAc-mediated monodemethylation and nucleophilic fluorination also readily proceed, allowing for access to dimethylaminoquinoline **29** and fluoroquinoline **30** in 87 and 81% yields, respectively. These transformations showcase the utility of this S_NAr method.

With a better understanding of the generality of using trimethylammoniums as leaving groups in nucleophilic aromatic substitution reactions, we compared their reactivity to the more commonly used halogen-leaving groups. To do so, we dissolved an equimolar mixture of d_7-6-trimethylammonium 2,2′-bipyridine tetrafluoroborate and 6-halo-2,2′-bipyridine (halo = fluoro, chloro, or bromo) in dimethyl sulfoxide and subjected them to 0.4 equiv of sodium methoxide (Scheme 4a). In each case, we observed >99:1 selectivity for d_7- to h_7-6-methoxy-2,2′-bipyridine, showing that the nucleophilic displacement of trimethylammoniums is much faster

Scheme 4. Competition Experiments between Trimethylaminated Bipyridines and Halobipyridines



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than those using the more commonly used halogens.[63] This reactivity even holds in solvents like THF, where d_7-6-trimethylammonium 2,2′-bipyridine tetrafluoroborate is not fully soluble. To confirm that the deuterons do not influence the reactivity at all, we also repeated the same experiment using 6-trimethylammonium 2,2′-bipyridine tetrafluoroborate and d_7-6-fluoro-2,2′-bipyridine (Scheme 4b). Here, the selectivity is now 1:>99 d_7- to h_7-6-methoxy-2,2′-bipyridine, further exemplifying the noteworthy reactivity of trimethylammoniums. These results are in agreement with previous reports by Barlin and co-workers that show that trimethylaminated azaarenes react faster with hydroxide ions than the corresponding chlorinated analogues.[64−66]

CONCLUSIONS

In summary, a nucleophilic aromatic substitution reaction to access a diverse array of C−O, C−S, and C−F bonds on bipyridines and azaarenes is described. The method capitalizes on using cationically charged trimethylammonium groups the allow for ease of synthesis and purification and for the reactions to proceed under mild conditions. Further, the potassium thioacetate can be used to selectively monodemethylate the trimethylammonium, converting it from the electron-deficient trimethylammonium to the very electron-donating dimethylamino group. This approach is scalable and tolerates complex molecules, including natural products and pharmaceutically relevant alcohols. Further, the method was utilized in the 2-pot, 3-step, total synthesis of Graveolinine and used the trimethylaminated intermediate to prepare a series of Graveolinine derivatives. Finally, competition experiments between our trimethylaminated bipyridines and analogous halogenated bipyridines showed that the trimethylammonium reacts much faster than the halogens commonly utilized in S_NAr reactions. Taken together, this method is a useful tool for the synthesis of functionalized bipyridines and azaarenes for purposes ranging from ligand synthesis to complex molecule derivatization. We are currently investigating how our novel bipyridines bind metals and the reactivity these complexes enable.

EXPERIMENTAL SECTION

General Procedure A: S_NAR Using Sodium Methoxide as the Nucleophile

A flame-dried 20 mL scintillation vial equipped with a magnetic stir bar and a septum cap was allowed to cool to room temperature under vacuum before being backfilled with nitrogen. At this point, the cap was removed and the vial was charged with trimethylammonium salt (0.25 mmol, 1 equiv). The cap was returned, and the vial was placed under a balloon of argon before being charged with THF (4 mL). The vial was placed in an ice/water bath, and the contents were allowed to cool to 0 °C. The reaction was initiated by adding NaOMe (0.5 M in MeOH, 1 mL, 0.5 mmol, 2 equiv). The ice/water bath was removed, and the reaction mixture was allowed to stir overnight at room temperature. At this point, the vial was opened to air, and the reaction mixture was quenched with water (10 mL). The contents of the flask were transferred to a 60 mL separatory funnel with the assistance of water (10 mL) and CH_2Cl_2 (10 mL). The mixture was extracted with CH_2Cl_2 (3 × 20 mL). The organic layers were combined, dried with $MgSO_4$, filtered, and concentrated. The resulting residue was purified by column chromatography to afford the desired product.

General Procedure B: S_NAR Using Neutral Nucleophiles and Sodium Hydride as a Base

A flame-dried 20 mL scintillation vial equipped with a magnetic stir bar, and a septum cap was allowed to cool to room temperature under vacuum before being backfilled with nitrogen. At this point, the cap was removed, and the vial was charged with trimethylammonium salt (0.25 mmol, 1 equiv) and the nucleophile (if solid, 0.3−0.375 mmol, 1.2−1.5 equiv). The cap was returned, and the vial was placed under a balloon of argon before being charged with THF (5 mL) and the nucleophile (if liquid, 0.3−0.375 mmol, 1.2−1.5 equiv). The vial was placed in an ice/water bath, and the contents were allowed to cool to 0 °C. At 0 °C, the cap was quickly removed and the reaction was initiated by adding NaH (60% in mineral oil, 15 mg, 0.375 mmol, 1.5 equiv). The cap was quickly returned, the ice/water bath was removed and the reaction mixture was allowed to stir overnight at room temperature under argon. At this point, the vial was opened to air and the reaction mixture was quenched with water (10 mL). The contents of the flask were transferred to a 60 mL separatory funnel with the assistance of water (10 mL) and CH_2Cl_2 (10 mL). The mixture was extracted with CH_2Cl_2 (3 × 20 mL). The organic layers were combined, dried with $MgSO_4$, filtered, and concentrated. The resulting residue was purified by column chromatography to afford the desired product.

General Procedure C: Demethylation Using Potassium Thioacetate

A flame-dried 20 mL scintillation vial equipped with a magnetic stir bar and a septum cap was allowed to cool to room temperature under vacuum before being backfilled with nitrogen. At this point, the cap was removed and the vial was charged with trimethylammonium salt (0.25 mmol, 1 equiv) and KSAc (0.5 mmol, 2 equiv). The cap was returned and the vial was placed under a balloon of argon before being charged with THF (5 mL). The reaction mixture was allowed to stir overnight at room temperature. At this point, the vial was opened to air and the reaction mixture was quenched with water (10 mL). The contents of the flask were transferred to a 60 mL separatory funnel with the assistance of water (10 mL) and CH_2Cl_2 (10 mL). The mixture was extracted with CH_2Cl_2 (3 × 20 mL). The organic layers were combined, dried with $MgSO_4$, filtered, and concentrated. The resulting residue was purified by column chromatography to afford the desired product.

General Procedure D: S_NAR Using Tetrabutylammonium Fluoride as the Nucleophile

A flame-dried 25 mL round-bottom flask equipped with a magnetic stir bar, an oven-dried reflux condenser, and a rubber septum was allowed to cool to room temperature under vacuum before being backfilled with nitrogen. At this point, the reflux condenser was removed and the flask was charged with trimethylammonium salt (0.25 mmol, 1 equiv). The condenser was returned and the flask was evacuated and backfilled with N_2 3 times. Under N_2, the flask was charged with MeCN (5 mL) followed by TBAF (1 M in THF, 750 μL, 0.75 mmol, 3 equiv). The flask was placed in a preheated oil bath, and the reaction was allowed to reflux overnight under N_2. At this point, the oil bath was removed and the reaction mixture was allowed to cool to room temperature under N_2. At room temperature, the flask was opened to air and the reaction mixture was quenched with water (10 mL). The contents of the flask were transferred to a 60 mL separatory funnel with the assistance of water (10 mL) and CH_2Cl_2 (10 mL). The mixture was extracted with CH_2Cl_2 (3 × 20 mL). The organic layers were combined, dried with $MgSO_4$, filtered, and concentrated. The resulting residue was purified by column chromatography to afford the desired product.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study is available in the published article and Supporting Information

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsorginorgau.4c00031.

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Experimental details, characterization data, and copies of LCMS traces (Figures S1−S5) and NMR spectra (PDF)

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Author Contributions

R.P.K. conceived the method, performed all of the syntheses and NMR spectroscopic analyses, and prepared the manuscript. J.Y.Y. gave feedback on the manuscript and substrate scope. CRediT: **Jenny Y. Yang** conceptualization, funding acquisition, investigation, project administration, supervision, writing-review & editing; **Ryan P. King** conceptualization, formal analysis, methodology, writing-original draft.

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Notes

The authors declare no competing financial interest.

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