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Site-Selective Silver-Catalyzed C–H Bond Deuteration of Five-Membered Aromatic Heterocycles and Pharmaceuticals

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Abstract

Catalytic methods for the direct introduction of hydrogen isotopes into organic molecules are essential to the development of improved pharmaceuticals and to the alteration of their absorption, distribution, metabolism, and excretion (ADME) properties. However, the development of homogeneous catalysts for selective incorporation of isotopes in the absence of directing groups under practical conditions remains a long-standing challenge. Here, we show that a phosphine-ligated, silver-carbonate complex catalyzes the site-selective deuteration of C–H bonds in five-membered aromatic heterocycles and active pharmaceutical ingredients that have been resistant to catalytic H/D exchange. The reactions occur with CH₃OD as a low-cost source of the isotope. The silver catalysts react with five-membered heteroarenes lacking directing groups, tolerate a wide range of functional groups, and react in both polar and nonpolar solvents. Mechanistic experiments, including deuterium kinetic isotope effects, determination of kinetic orders, and identification of the catalyst resting state, support C–H bond cleavage from a phosphine-ligated, silver-carbonate intermediate as the rate-determining step of the catalytic cycle.

Graphical Abstract

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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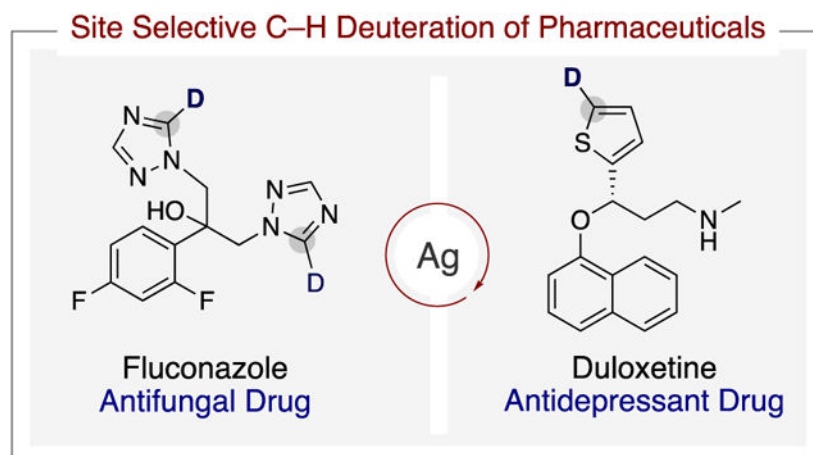
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Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acscatal.0c04917>.

Experimental procedures and spectroscopic data on the reaction products (PDF)

Crystallographic data (CIF)



Keywords

hydrogen isotope exchange; silver catalyst; C–H activation; heteroarenes; deuteration

INTRODUCTION

Synthetic methods to incorporate hydrogen isotopes selectively into organic molecules have attracted considerable interest, due to the widespread application of isotopically labeled compounds in chemical and pharmaceutical research. For example, the selective replacement of hydrogen for deuterium at C–H bonds prone to metabolic degradation is a useful approach for the development of new pharmaceuticals with improved pharmacokinetic and pharmacodynamic properties (Scheme 1a).¹ Deuterated and tritiated biologically active compounds and pharmaceuticals are also employed in absorption, distribution, metabolism, and excretion (ADME) studies, which are pivotal for the understanding of their mode of action and toxicology.² In addition, deuterated molecules are used to investigate reaction mechanisms and are used as standards for mass spectrometry and nuclear magnetic resonance.³

Classical methods to synthesize deuterated and tritiated compounds require prefunctionalized starting materials, which are subjected to reductive or dehalogenative processes during the installation of the desired hydrogen isotope.^{1b,4} However, hydrogen isotope exchange (HIE) catalyzed by homogeneous transition metals has become a widely applicable method for the late-stage introduction of hydrogen isotopes directly into C–H bonds.⁵ Thus, this method, which can be conducted with commercially available sources of deuterium or tritium, is employed in industry for the isotopic labeling of complex pharmaceuticals.

Ir catalysts, including Crabtree's catalyst and variants developed by Kerr, are the most used catalyst for H/D exchange because they catalyze the selective isotopic labeling of sp^3 and sp^2 C–H bonds with the tolerance of many functional groups.⁶ However, these catalysts require directing groups, and binding of other Lewis basic functional groups to the catalyst

reduces the level of isotopic incorporation, presumably because these functional groups bind and poison the catalyst (Scheme 1b).^{6a,f}

Recently, research by Chirik⁷ and MacMillan⁸ on base-metal and photoredox catalysts has enabled reactivity and site selectivity that are complementary to those of the Ir-catalyzed methods. As a result, these studies have provided new methods for the selective deuteration and tritiation of sp^3 and sp^2 C–H bonds in complex pharmaceuticals without the need for directing groups. In spite of these recent advances, common, medically relevant molecular scaffolds, such as those based on five-membered ring heteroarenes, remain resistant to HIE under practical conditions with any type of catalyst.

Five-membered aromatic heterocycles are prevalent in pharmaceuticals, agrochemicals, and natural products.⁹ The introduction of these heterocycles into biologically active agents is a widely used approach for the optimization of their toxicology properties¹⁰ because they can alter lipophilicity, polarity, and hydrogen-bonding capacity.^{10a} Five-membered aromatic heterocycles are also used in drug discovery as bioisosteres of benzene rings, carboxylic acids, and esters.^{10b,11} Despite the value of such heteroarenes, homogeneous catalysts for the selective incorporation of hydrogen isotopes in a broad range of five-membered aromatic heterocycles embedded in complex pharmaceuticals without the assistance of directing groups have been elusive. Base-induced H/D exchange under stoichiometric conditions has been employed for the isotopic labeling of a handful of five-membered heterocycles at multiple positions with limited tolerance of functional groups; however, these methods require high reaction temperatures (over 120 °C) and in some cases supercritical conditions (high temperatures combined with high pressures).¹²

Our group¹³ recently reported the activation of C–H bonds in arenes by silver complexes as part of a study of the mechanism of the direct allylation of arenes catalyzed by palladium complexes with silver additives. The groups of Larrosa,¹⁴ Sanford,¹⁵ and Zhu¹⁶ have reported that related silver complexes cleave the C–H bonds of arenes bound to $Cr(CO)_3$, activated arenes containing multiple fluorine substituents, thiophene, and benzothiophene. The reactions of less activated arenes and heteroarenes have not occurred.

These previous studies suggested that silver salts and phosphine-ligated silver complexes bearing carboxylate ligands were the species in palladium-catalyzed couplings that cleaved C–H bonds, presumably by a carboxylate-assisted concerted metalation deprotonation step.^{14–16} However, characterization of a silver carboxylate species that effects C–H bond cleavage, particularly cleavage of the C–H bonds in heteroarenes, has not been conducted,^{14a} and ligands that accelerate the rate of the C–H activation step were not identified. Thus, high concentrations of silver catalysts and stoichiometric amounts of bases were needed to activate the C–H bonds, even of these more reactive arenes, and moderate degrees of isotopic incorporation were observed during mechanistic experiments.

We considered that this C–H activation chemistry could be applied to unsolved problems in H/D exchange by creating silver complexes that cleave the C–H bonds of medically important five-membered heteroarenes and enable H/D exchange under practical conditions. This goal would require the development of discrete silver catalysts that cleave C–H bonds

at faster reaction rates and with greater tolerance of functional groups than prior silver systems that were part of catalytic C–C bond-forming processes.

Herein, we describe the identification of a catalytic system based on silver for such site-selective deuteration of C–H bonds in medically relevant five-membered aromatic heterocycles, including imidazole, thiazole, triazole, thiophene, and indole. The developed method proceeds in the absence of directing groups, and it uses commercially available silver catalysts, phosphine ligands, and CH₃OD as a low-cost source of deuterium (Scheme 1c). Moreover, we demonstrate that the functional group compatibility of this silver-catalyzed method is broad, and this property enables the isotopic labeling of complex pharmaceutical ingredients to produce new isotopologues.

RESULTS AND DISCUSSION

Development of Silver-Catalyzed C–H Deuteration.

We began our studies to achieve mild, silver-catalyzed HIE with 2-methylthiophene (**1**) as a model substrate for an electron-rich, five-membered heterocycle (Table 1). Initial experiments showed that the deuterated thiophene [²H]**1** formed with moderate isotopic incorporation and perfect site selectivity toward the most acidic sp² C–H bond in the presence of Ag₂CO₃ (2.5 mol %) and PPh₃ (5 mol %) in CH₃OD solvent after 8 h at 40 °C (Table 1, entry 1). A series of experiments with a range of commercially available phosphines demonstrated that [²H]**1** formed in high isotopic incorporation (up to 95%) when the silver catalyst contained the electron-rich 2-(biphenyl)di-*tert*-butylphosphine (JohnPhos) ligand (Table 1, entry 5). Catalysts containing related electron-rich dialkylbiaryl phosphines, namely, 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (SPhos) and 2-(dicyclohexylphosphino)biphenyl (Cy-JohnPhos), led to lower degrees of isotope exchange. A notable feature of the silver catalyst ligated by JohnPhos is its high activity in the presence of atmospheric oxygen, which allowed the synthesis of [²H]**1** in air with high isotopic composition (Table 1, entry 8) and with rates that were identical to those measured under nitrogen (see SI for details). Silver catalysts containing other anionic ligands were also tested. The analogues containing acetate and pivalate ligands were not active toward the deuteration of **1** (Table 1, entries 9–10). Control experiments in the absence of JohnPhos or Ag₂CO₃ showed the necessity of both components for the C–H bond deuteration reaction to proceed (Table 1, entries 11–12). Other commercially available sources of deuterium, including CH₃CH₂OD and D₂O, in different organic solvents were also investigated, but reactions with these sources led to lower degrees of deuterium incorporation into **1** than did reactions conducted in CH₃OD (see SI for further details).

Scope of the Silver-Catalyzed C–H Deuteration.

The functional group compatibility of the silver-catalyzed C–H deuteration was first examined with mono- and disubstituted thiophenes.¹⁷ During the course of these experiments, we observed that a high degree of isotopic incorporation (up to 99%) was obtained after two cycles of C–H deuteration in air after 10–48 h at temperatures between 50 and 80 °C (see SI for details). After the first reaction cycle, purification of the intermediate deuterated product was not required, although addition of further silver catalyst

was necessary in a few cases to obtain high isotopic incorporation (see SI for complete experimental details).

As shown in Scheme 2, thiophene **2**, containing the electron-donating 3,4-ethylenedioxy moiety, underwent high deuterium incorporation at the position α to the sulfur atom. The thiophene in **3** was more reactive toward C–H bond deuteration than the phenyl unit, giving [^2H]**3** selectively in high yield. Reactions of thiophenes containing ester, benzoyl, carboxamide, and carbamate moieties showed that these coordinating functionalities did not direct C–H activation; selective deuteration at the C5-position of the thiophenes provided [^2H]**4**–[^2H]**7** in high yield. The lack of directing effect of the pyridine in 2-(2-pyridyl)thiophene **8** is particularly noteworthy. The major site of incorporation of deuterium was the C–H bond distal to, rather than adjacent to, the basic nitrogen.

Thiophenes bearing an unprotected alcohol or containing amines (**9**–**11**) underwent this HIE process, but the latter reactions required higher concentrations of silver catalysts and reaction temperatures to achieve high levels of isotopic incorporation. Accordingly, the deuterated [^2H]**10** product was formed from a reaction with 10 mol % of Ag_2CO_3 and 20 mol % of JohnPhos at 80 °C for 48 h under nitrogen to suppress partial decomposition of the starting material. Under the same reaction conditions, the thienopyridine **11**, a secondary amine scaffold present in antiplatelet drugs,¹⁸ underwent deuteration at the two C–H bonds of the thiophene ring.

Finally, the broad functional group tolerance of the silver-catalyzed deuteration was further highlighted by the deuteration of **12** and **13**. Existing homogeneous Ir catalysts for HIE do not tolerate unsaturated C–C bonds and nitriles, due to the sensitivity of the former toward reduction in the presence of deuterium or tritium gas and the irreversible binding of nitriles to Ir catalysts.^{6a,f} Our developed method tolerated the aforementioned functionalities, as shown for [^2H]**12** and [^2H]**13**. The synthesis of [^2H]**12** and [^2H]**13** also inspired further experiments on the use of cosolvents for catalytic HIE due to the insolubilities of **12** and **13** in CH_3OD . We found that the developed silver catalyst is active for exchange of the C–H bonds with CH_3OD in a range of polar and nonpolar solvents, including dimethylformamide, dimethyl sulfoxide, tetrahydrofuran, and dichloromethane (see SI for further details). Thus, the syntheses of [^2H]**12**–[^2H]**13** were performed with THF or CH_2Cl_2 as cosolvent, respectively.

The scope of the silver-catalyzed method with a series of different classes of five-membered aromatic heterocycles is shown in Scheme 3. Thiazoles, imidazoles, and 1,2,4-triazoles are electron-poor five-membered heterocycles found in modern antibiotics, antifungal drugs, and agrochemicals.^{9a} Despite this prevalence, homogeneous catalysts for isotopic exchange with these heterocycles without directing groups are lacking.^{7a,c} Our data show that methyl thiazole-4-carboxylate (**14**) undergoes high deuterium incorporation at the 2- and 5-positions, and *N*-benzyl-1,2,4-triazole (**15**) undergoes selective deuteration at its most acidic C–H bond under the conditions we developed with the silver catalyst.

N-Benzyl-imidazole (**16**) proved less reactive than other heteroarenes under the standard conditions. However, **16** underwent C–H deuteration at faster reaction rates when di-*tert*-

butylphenylphosphine was used as ligand in place of JohnPhos (see SI for details). Therefore, the deuteration of **16** was performed after two reaction cycles over a period of 48 h at 65 °C under nitrogen in the presence of 10 and 20 mol % of Ag₂CO₃ and di-*tert*-butylphenylphosphine, respectively. This protocol led to deuteration of **16**, with relative rates of reaction at the 2-, 4-, and 5-positions that follow the trend C2 > C4 > C5.

Indoles and pyrroles are important electron-rich heterocycles. However, isotopic labeling of these nitrogen heterocycles to high levels has required directing groups that enable C–H activation.¹⁹ In contrast, our silver-catalyzed method enabled high levels of incorporation of deuterium into **17** and **18** at the positions α and β to the nitrogen atom with the silver complex of JohnPhos as catalyst in air at 80 °C. Other fused heterocycles including benzofuran (**19**), benzothiophene (**20**), benzoxazole (**21**), benzothiazole (**22**), and caffeine (**23**) also underwent deuteration with a high level of deuterium incorporation at the most acidic C–H bond with the silver complex of JohnPhos as catalyst in air.

Deuteration of Pharmaceuticals.

The broad functional group tolerance and the site selectivity of the silver-catalyzed method complementary to that of existing methodologies²⁰ prompted us to examine its applicability to the deuteration of C–H bonds in pharmaceuticals by conducting reactions with a series of active pharmaceutical ingredients. As shown in Scheme 4, pharmaceuticals containing xanthine heterocycles, namely, doxofylline (**24**) and pentoxifylline (**25**), underwent high levels of incorporation of deuterium at the most acidic sp² and sp³ C–H bonds at 50 °C after 24 h. The labeling of sp³ C–H bonds in **25** resulted from the facile enolization of the hydrogen atoms α to the carbonyl group. Etomidate (**26**), an anesthetic agent, and flumazenil (**27**), a GABA-antagonist, developed by Roche underwent deuteration at the imidazole core, while trace amounts of isotopic incorporation also were observed at the sp³ C–H bonds of the benzodiazepine ring of **27**. It is important to note that **26** and **27** were deuterated with commercially available CH₃CH₂OD to avoid transesterification with CH₃OD.

Antifungal drugs, such as clotrimazole (**28**) and tioconazole (**29**), which contain imidazole and thiophene, underwent C–H bond deuteration in these heterocycles at 65 °C after 48 h. In addition, partial isotopic incorporation at one position of the benzene ring of **29** was observed, which presumably resulted from the moderate acidity of the labeled C–H bond. The antidepressant (*S*)-duloxetine (**30**) and the antiplatelet drug ticlopidine (**31**) both underwent selective deuteration at the thiophene heterocycle. Finally, fluconazole (**32**) and tebuconazole (**33**), an antifungal and agrochemical agent, respectively, underwent selective deuteration at the most acidic position of their triazole units in excellent yield and isotopic incorporation.

Mechanistic Investigation.

Having demonstrated the synthetic applications of the silver-catalyzed HIE, we performed a series of experiments to gain insight into the reaction mechanism. We first examined whether C–H bond cleavage was involved in the rate-determining step of the reaction. To do so, we measured the initial rates of deuterium and protium incorporation in parallel

reactions of **34** and [^2H]**34** in separate vessels. As shown in Scheme 5a, a large primary kinetic isotope effect (KIE) of 4.8 ± 0.3 was measured from experiments with 2.5 mol % of Ag_2CO_3 and 5 mol % of JohnPhos at 40 °C under air. The large value of the measured KIE strongly suggested that C–H cleavage occurs during the rate-determining step.

To gain additional kinetic data on the silver-catalyzed C–H deuteration, we measured the dependence of the reaction rate on the concentration of benzothiophene (**34**), silver catalyst, and CH_3OD under air at 40 °C by the method of initial rates (Scheme 5b). The obtained data showed a first-order dependence on the concentration of **34** and on the concentration of the silver catalyst, and a zero-order dependence on the concentration of CH_3OD (determined in THF).²¹ These kinetic data are consistent with the primary KIE and suggest a mechanism in which the phosphine-ligated silver catalyst cleaves the C–H bond during the rate-determining step of the reaction.

To help interpret the kinetic data, we conducted experiments to determine the resting state of the silver catalyst. We monitored the course of the deuteration of the C–H bond of 2-methylthiophene (**1**) by ^{31}P NMR at 40 °C in CD_3OD under air in the presence of Ag_2CO_3 (2.5 mol %) and JohnPhos (5 mol %). An examination of the ^{31}P NMR spectra after different amounts of isotopic incorporation into the thiophene revealed the presence of a single species containing phosphorus in the reaction medium. This signal was observed at 44.0 ppm and comprises two superimposed doublets with large $^1J^{107}\text{Ag} - ^{31}\text{P}$ and $^1J^{109}\text{Ag} - ^{31}\text{P}$ coupling constants (657 and 758 Hz, respectively). The large $^1J_{\text{Ag}-\text{P}}$ coupling constants indicate that the resting state of the silver catalyst consists of a metal species bearing a single coordinated phosphine per silver atom with a tricoordinated (JohnPhos) AgX_2 (X = oxygen) coordination environment (Figure 1).²²

We also isolated and structurally characterized the phosphine-ligated silver complex involved in the C–H bond activation step. To isolate the observed complex, we investigated the coordination chemistry of Ag_2CO_3 (1 equiv) with JohnPhos (2 equiv). After allowing the two catalyst components to react under conditions of the catalytic reaction (30 min in CH_3OH at 50 °C under air, Scheme 6) and appropriate workup, an air-stable, light-brown solid was isolated in 69% yield. The ^{31}P NMR spectrum of the isolated solid in CD_3OD at room temperature revealed the same set of phosphorus resonances centered at 44.0 ppm, as observed during the catalytic reaction (Figure 1). Moreover, the isolated complex catalyzed the C–H deuteration of **1** with rates that were identical to those with the catalyst formed in situ from Ag_2CO_3 and JohnPhos (see SI for details).

An analysis by solid-state IR spectroscopy of the isolated solid revealed two strong absorption bands at 1338 and 1416 cm^{-1} , respectively, which were assigned to the $\text{E}' \nu(\text{CO}) \nu^3$ mode of the silver-coordinated CO_3^{2-} ligand. Previously characterized metal-carbonato complexes have $\text{E}' \nu(\text{CO})$ absorption bands in the range of 1200–1600 cm^{-1} .²³ The small separation of the observed $\text{E}' \nu(\text{CO})$ absorption bands in **36** ($\nu = 78 \text{ cm}^{-1}$) is characteristic of a metal complex containing a bridging carbonate ligand and is indicative of a minimal distortion around the O–C–O angles. The ν values of the $\text{E}' \nu(\text{CO})$ absorption bands in metal complexes containing bridging carbonate ligands are smaller than 250 cm^{-1} , a difference in frequency that has been associated with small distortions of the angles

around the carbonate moiety in this coordination mode.²³ Solution molecular weight data indicate that the phosphine-ligated silver-carbonate complex contains two silver ions, two phosphines, and one carbonate.

The molecular weight determined by the Sigmer method²⁴ was 717 g/mol in CH₃OH at 24 °C. Although this measured value is lower than that for complex **36** (872 g/mol), it is clearly smaller than that expected for higher aggregates of **36** and larger than values for potential mononuclear silver compounds (e.g., 466 g/mol for LAgCO₃H, L = JohnPhos). Together, the recorded characterization data suggest that a binuclear, phosphine-ligated silver-carbonate complex (**36**) is the resting state of the catalyst for the C–H bond deuteration. Only two phosphine-ligated silver-carbonate complexes have been isolated previously and characterized by single-crystal X-ray diffraction; their solution chemistry has not been investigated.²⁵

Although we were unable to obtain suitable crystals of compound **36** for X-ray diffraction, we isolated and characterized an analogue **37** containing *t*BuXPhos (2-di-*tert*-butylphosphino-2',4',6'-triisopropylbiphenyl) by X-ray diffraction, solution NMR, and solid-state IR spectroscopy (Scheme 7a and Figure 1). The relevance of the structural studies of **37** to the C–H deuteration reaction is demonstrated by the reaction of 2-methylthiophene (**1**) catalyzed by **37**. This reaction led to the formation of [¹H]**1** with 91% deuterium incorporation at the 5-position after 6 h in CH₃OD (Scheme 7b).

An examination of the ³¹P NMR spectra of **37** in CH₃OH-*d*₄ revealed two superimposed doublets centered at 43.5 ppm, with ¹J¹⁰⁷_{Ag–³¹P} and ¹J¹⁰⁹_{Ag–³¹P} coupling constants of 649 and 748 Hz, respectively. The solid-state IR spectrum of **37** showed bands for the E' ν(CO) ν³ mode of the silver-coordinated CO₃²⁻ ligand at 1315 and 1440 cm⁻¹. These NMR and IR data are comparable to the analogous data recorded for the isolated complex **36** (*vide supra*).

An ORTEP diagram of the solid-state structure of silver complex **37** is depicted in Figure 2 and consists of a binuclear *t*BuXPhos-ligated silver carbonate structure, in which both silver atoms are tricoordinated with slightly distorted trigonal PAgO₂ environments. The CO₃²⁻ ligand in **37** bridges the two silver atoms in a highly symmetric κ²:κ² coordination mode.^{25b} The symmetric coordination environment around the CO₃²⁻ ligand is reflected in its O–C–O angles, which are close to 120°.

To gain information on the elementary C–H bond cleavage step, we conducted reactions with a series of thiophenes containing electron-donating and electron-withdrawing substituents (Figure 3). These studies showed that 2-bromo- and 2-methoxy-substituted thiophene underwent deuteration with comparable rates (*k*_{OMe}/*k*_{Br} = 0.9). However, both substrates reacted faster than 2-methylthiophene (*k*_{Br}/*k*_{Me} = 2.6, *k*_{OMe}/*k*_{Me} = 2.4). The faster rates for reaction of the more electron-rich and electron-poor thiophenes are inconsistent with an S_EAr pathway for the rate-determining, C–H bond cleavage step.²⁶ Moreover, the general selectivity of the silver-catalyzed method for H/D exchange at the most acidic C–H bonds in the five-membered heterocycles strongly suggests that the C–H bond cleavage step occurs by a concerted metalation-deprotonation mechanism.

Although more research is needed to fully understand the mechanism of the silver-catalyzed deuteration of C–H bonds, an initial hypothesis that is consistent with all of our data is depicted in Scheme 8. The phosphine-ligated silver catalyst **I** undergoes rate-determining C–H bond activation with the heterocyclic substrate by a carbonate-assisted, concerted metalation-deprotonation step. This reaction would form one heteroarylsilver complex and one bicarbonate complex. Rapid H/D exchange between CH₃OD and the bicarbonate O–H bond, followed by demetalation of the (hetero)aryl phosphine-ligated silver intermediate **II** by reaction with the isotopically enriched bicarbonate complex **III**, regenerates the starting silver complex and forms the labeled product.

CONCLUSIONS

In summary, we have developed a silver-catalyzed method to conduct the previously elusive, catalytic, site-selective deuteration of C–H bonds in medicinally relevant five-membered aromatic heterocycles, including thiazole, imidazole, triazole, thiophene, and indole. These results hold promise for the synthesis of deuterated heterocyclic building blocks, an approach that can be applied for the development of pharmaceuticals with improved pharmacodynamic and pharmacokinetic properties. The developed method occurs in the absence of directing groups, under mild reaction conditions, and in the presence of a diverse array of potentially reactive functional groups, such as alcohols, amines, alkenes, alkynes, and nitriles. These attributes enable the deuterium labeling of complex pharmaceutical ingredients,²⁷ a result that can be extended to the incorporation of tritium because sources of this isotope in the form of T₂O and CH₃OT have been reported in the literature.^{8,28} Mechanistic experiments support turnover-limiting C–H bond activation by a new phosphine-ligated, silver-carbonate catalyst, which presumably occurs by a carbonate-assisted concerted metalation deprotonation step. The unique C–H bond activation chemistry by the herein reported phosphine-ligated, silver-carbonate complex lays the foundation for the development of a new class of catalysts that are currently being developed in our laboratory for previously elusive C–H functionalization reactions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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34 approached 15% conversion, the rate began to decrease at lower concentrations of CH₃OD (see S12 in the SI). We hypothesized that partial decomposition of the silver catalyst occurred at lower concentrations of CH₃OD on the basis of the observation of a black precipitate in these experiments.

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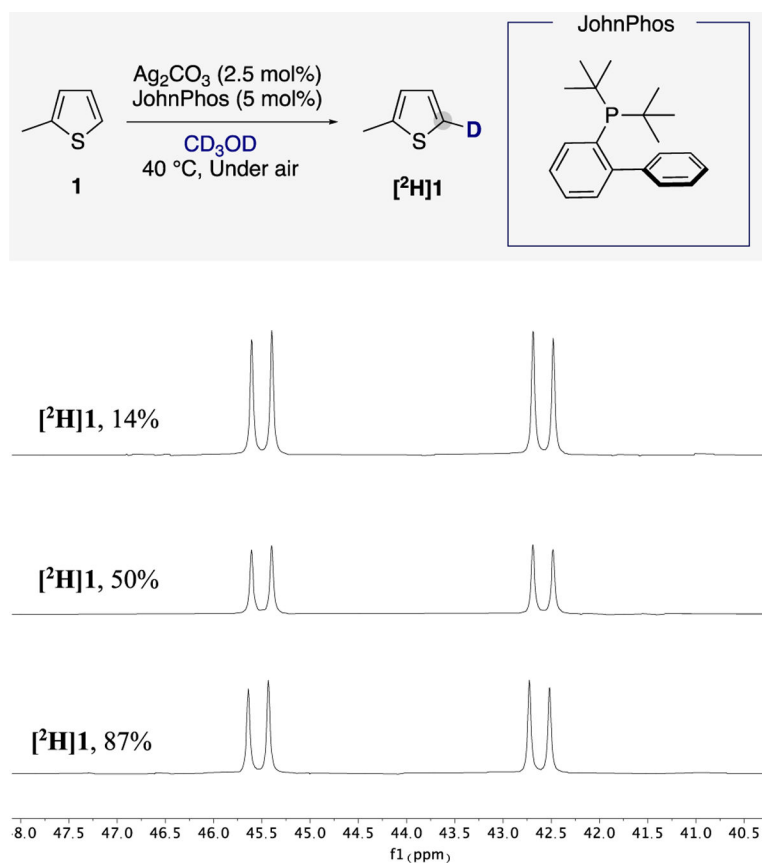


Figure 1. ^{31}P NMR spectra of the reaction mixture of 2-methylthiophene, Ag_2CO_3 , and JohnPhos in CD_3OD at different amounts of deuterium incorporation.

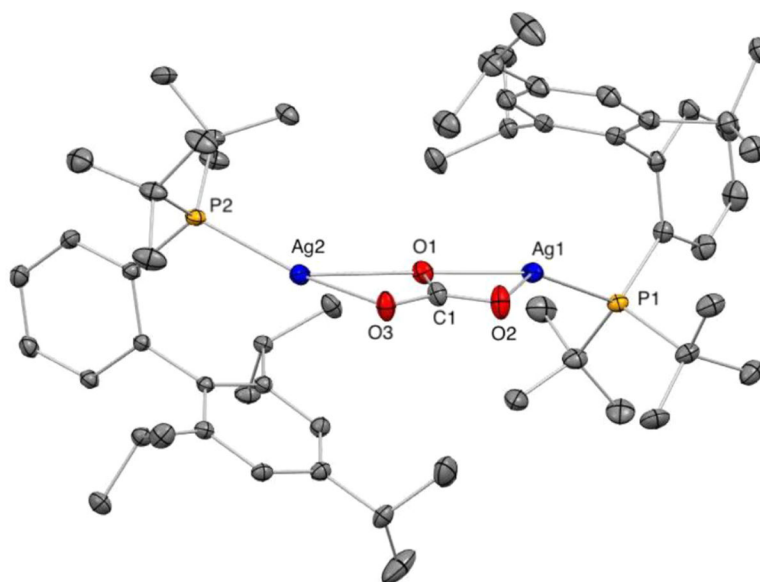


Figure 2. ORTEP diagram of *t*BuXPhos-ligated silver-carbonate complex **37**. Bonds (Å): Ag1–P1, 2.3465(4); Ag1–O1, 2.2337(12); Ag1–O2, 2.4227(14); C1–O1, 1.295(2); C1–O2, 1.274(2); C1–O3, 1.2904(19); Ag2–O1, 2.4651(12); Ag2–O3, 2.1912(12); Ag2–P2, 2.3415(4). Angles (deg): O3–C1–O2, 122.49(16); O2–C1–O1, 119.51(15); O3–C1–O1, 118.00(15). Ellipsoids are shown at 50% probability. Hydrogen atoms, THF, and water within the crystal structure are omitted for clarity.

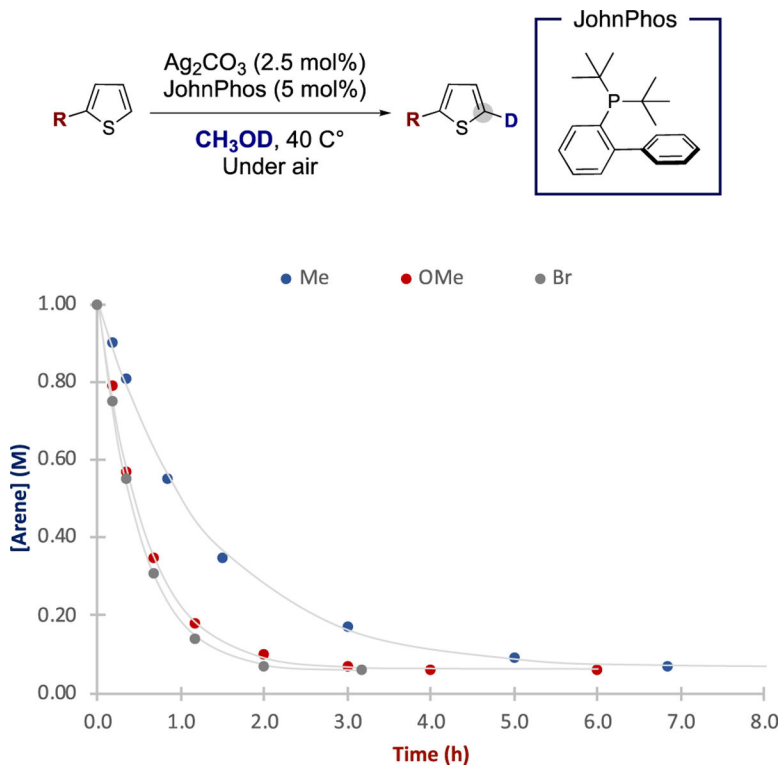
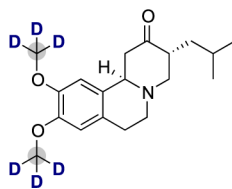
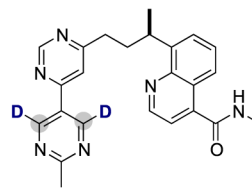


Figure 3. C–H Bond deuteration of 2-substituted thiophenes. C–H Deuteration of 2-substituted thiophenes. Rate constants (h^{-1}): Me, 0.76; OMe, 1.8; Br, 2.0.

A. Application of Deuterium for Drug Development



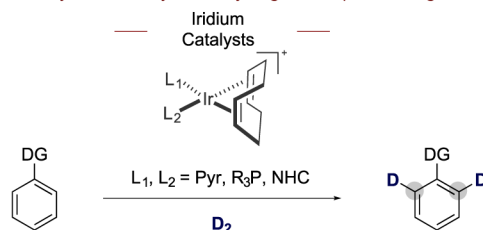
Deutetrabenazine (Teva)
Treatment of chorea



VX-984 (Vertex)
Anticancer Agent (Phase I)

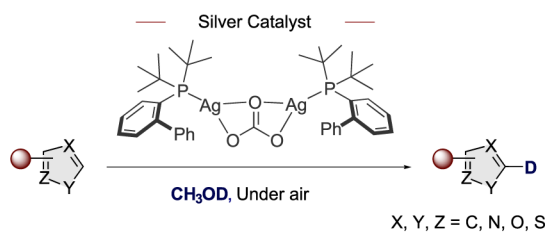
- Selective Deuteration Enables Superior Metabolic Stability

B. Commonly Used Catalysts for Hydrogen Isotope Exchange



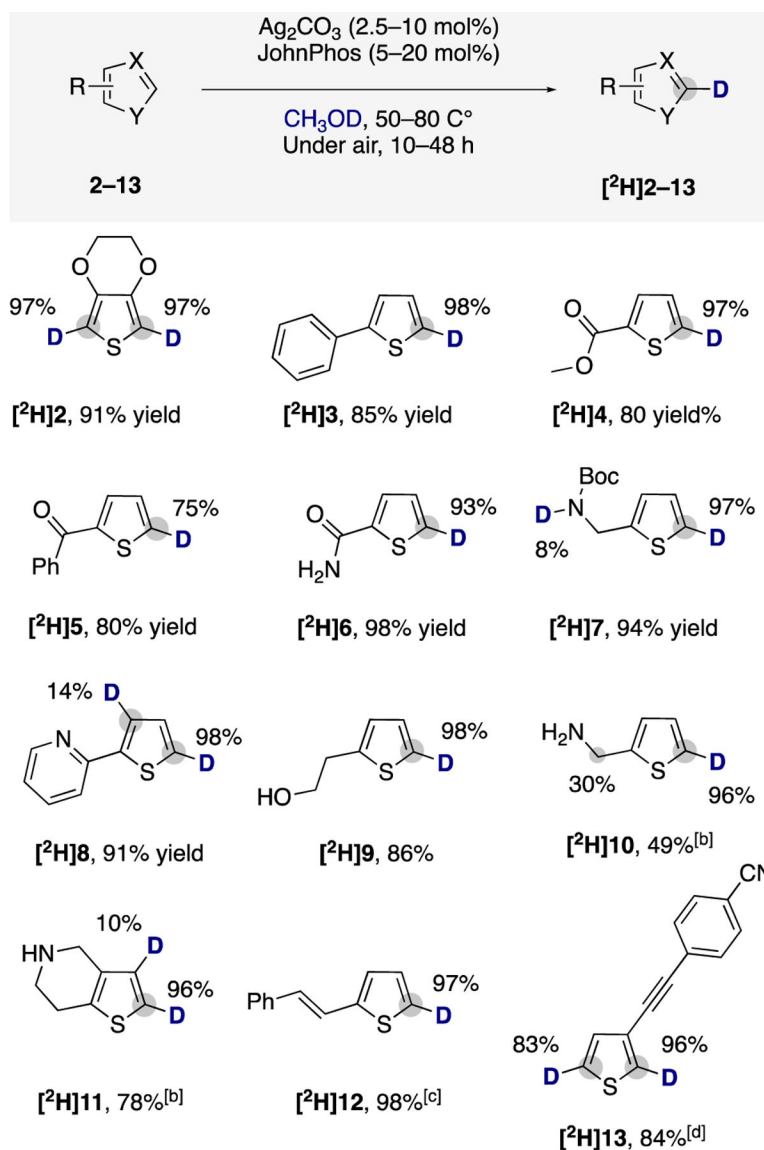
- Requires Directing Groups (DG)

C. This work: Site Selective Undirected C–H Deuteration



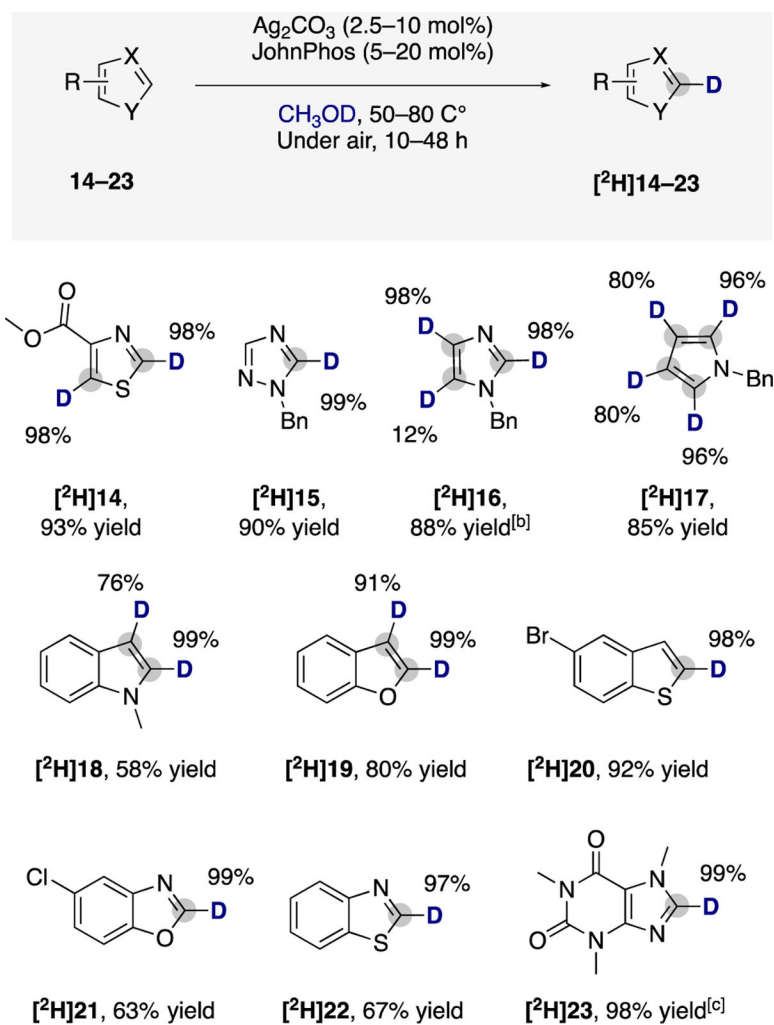
- Does not Require Directing Groups
- Broad Functional Group Tolerance
- Applicable to Elusive Five-membered Heterocycles in Pharmaceuticals

Scheme 1.
Applications of Deuterium and Recent Developments in Catalytic Hydrogen Isotope



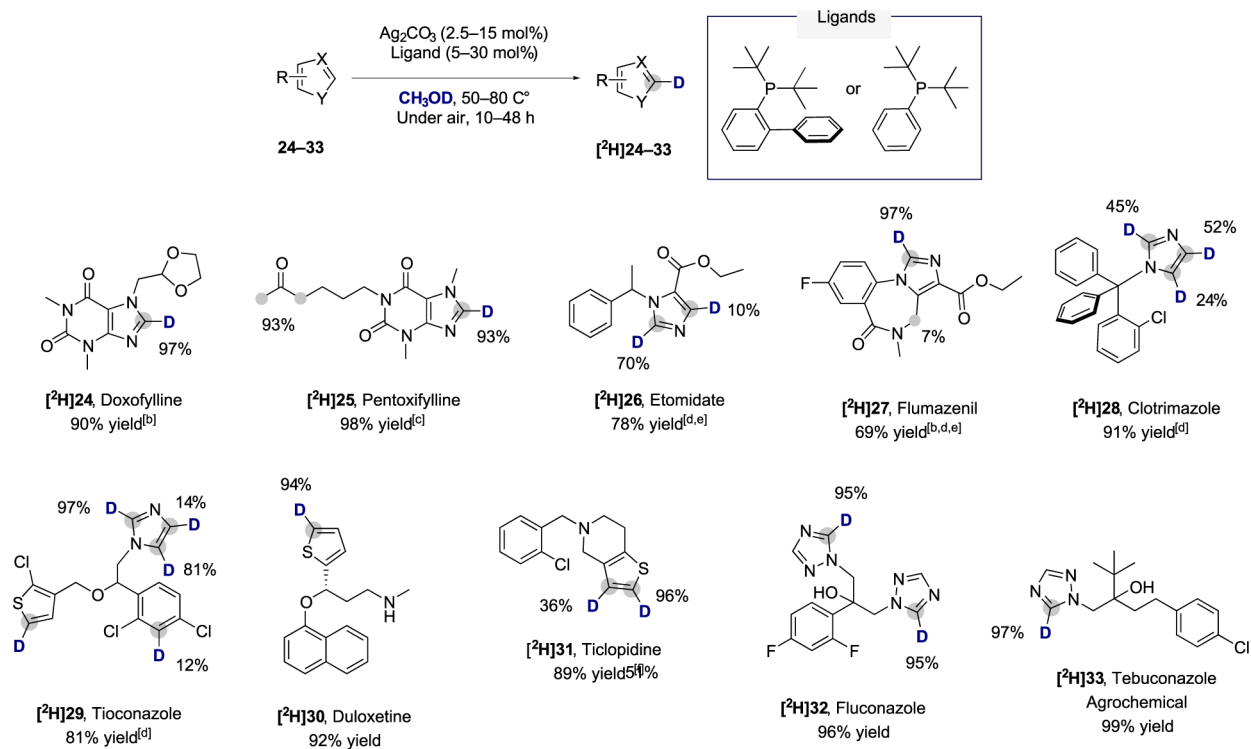
Scheme 2. Scope of Thiophenes That Undergo Selective C–H Deuteration^a

^aPerformed over two reaction cycles (see SI for details). ^bUnder nitrogen and isolated as the hydrochloride salt. ^cWith THF as cosolvent. ^dWith CH_2Cl_2 as cosolvent.



Scheme 3. Scope of Five-Membered Heterocycles That Undergo Selective C–H Deuteration^a

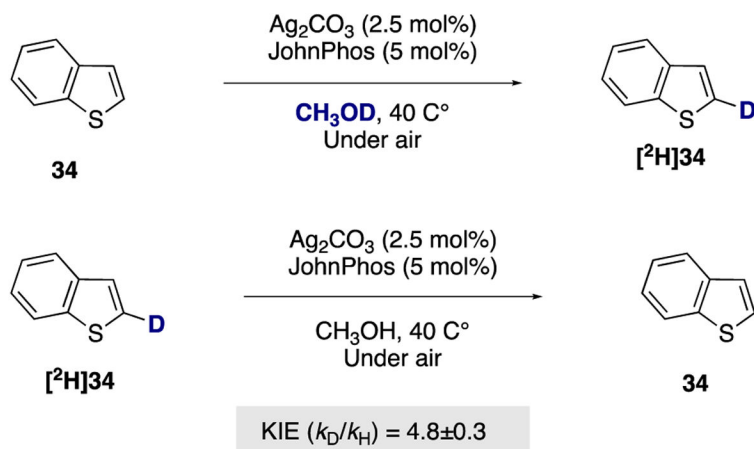
^aPerformed over two reaction cycles (see SI for details). ^bWith di-*tert*-butylphenylphosphine under nitrogen. ^cWith CH₂Cl₂ as cosolvent.



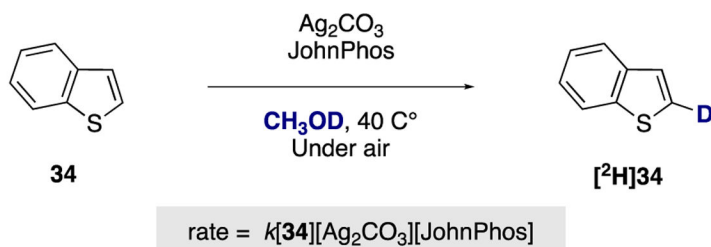
Scheme 4. Scope of Pharmaceuticals That Undergo Selective C–H Deuteration^a

^aPerformed over two reaction cycles (see SI for details), 50 equiv of deuterium was used for each of the 2 reaction cycles. For results with selected heterocycles and pharmaceuticals after one single cycle of deuteration, see Section 3 of the Supporting Information. ^bWith CH_2Cl_2 as cosolvent. ^cWith THF as cosolvent. ^dWith di-*tert*-butylphenylphosphine under nitrogen. ^eWith $\text{CH}_3\text{CH}_2\text{OD}$ as deuterium source. ^fIsolated as the hydrochloride salt.

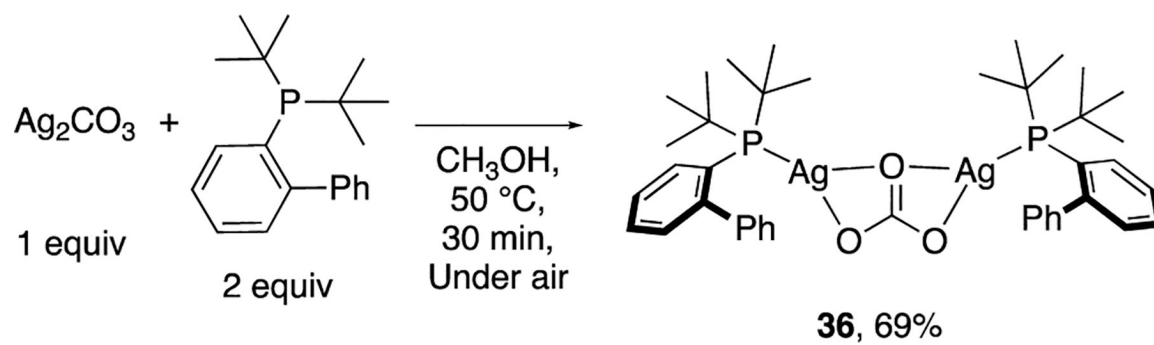
A. Determination of KIE



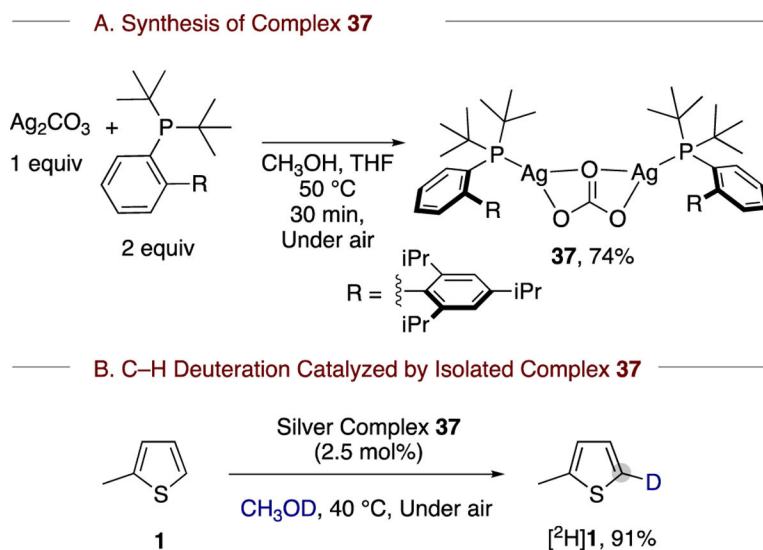
B. Kinetic Orders

**Scheme 5.**

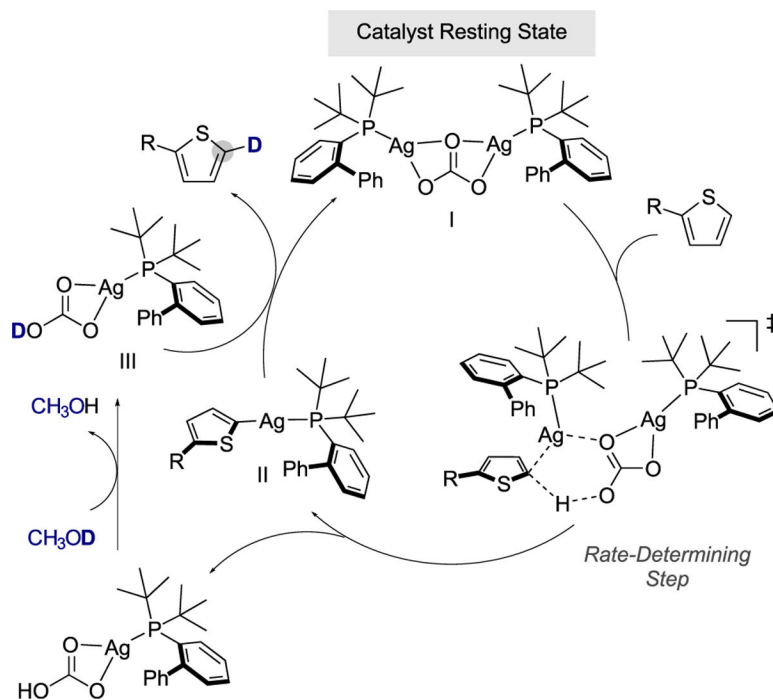
Determination of KIE and Reaction Orders of the Silver-Catalyzed C–H Deuteration: (A) Determination of KIE and (B) Kinetic Orders



Scheme 6.
Synthesis of a Phosphine-Ligated Silver–Carbonate Complex



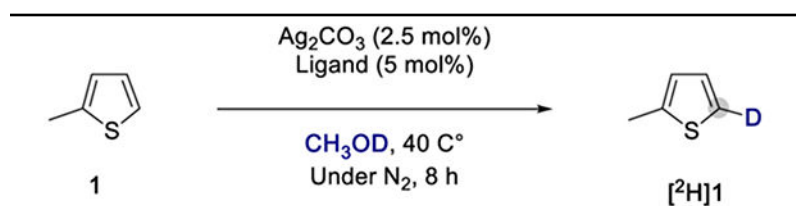
Scheme 7.
Synthesis of *t*BuXPhos-Ligated Silver Carbonate Complex **37** and Evaluation of Its Competence as a Catalyst for C–H Deuteration



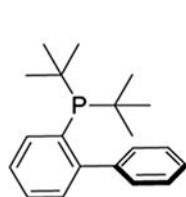
Scheme 8.
Mechanistic Hypothesis for the Site-Selective C-H Deuteration of Five-Membered Heterocycles

Table 1.

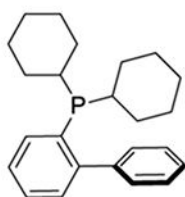
Evaluation of Reaction Conditions for the Site Selective C–H Deuteration of 2-methylthiophene (1)



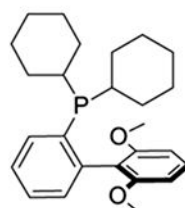
Ligands Evaluated:



JohnPhos



CyJohnPhos



SPhos

entry	silver catalyst	ligand	%D ^a
1	Ag_2CO_3	Ph_3P	29
2	Ag_2CO_3	Cy_3P	39
3	Ag_2CO_3	tBu_3P	52
4	Ag_2CO_3	tBu_2PPh	77
5	Ag_2CO_3	JohnPhos	95
6	Ag_2CO_3	CyJohnPhos	92
7	Ag_2CO_3	SPhos	90
8 ^b	Ag_2CO_3	JohnPhos	95
9 ^{b,c}	AgOAc	JohnPhos	0
10 ^{b,d}	AgOPiv	JohnPhos	0
11 ^b		JohnPhos	0
12 ^b	Ag_2CO_3		0

^aDetermined by ^1H NMR in CDCl_3 .^bUnder air.^cWith 5 mol % of AgOAc .^dWith 5 mol % of AgOAc .