Heterocycle Synthesis

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Palladium(0)-Catalyzed Iminohalogenation of Alkenes: Synthesis of 2-Halomethyl Dihydropyrroles and Mechanistic Insights into the Alkyl Halide Bond Formation**

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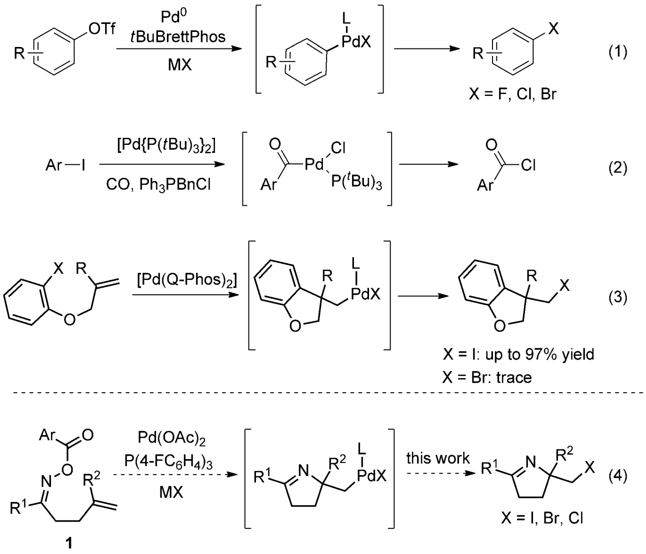
Abstract: *Although the advances on carbon halide reductive elimination have been made, the alkyl bromide and chloride analogues remain a challenge. Here, a palladium(0)-catalyzed iminohalogenation of γ,δ-unsaturated oxime esters is described, and the use of electron-poor phosphine ligands proved to be crucial to promoting alkyl bromide and chloride reductive elimination. Furthermore, S_N2-type alkyl bromide and chloride reductive elimination has also been established.*



Scheme 1. Palladium(0)-catalyzed synthesis of organic halides. Tf = trifluoromethanesulfonyl.

Organic halides serve as extremely valuable materials in organic synthesis. They are also present in a wide variety of natural products, pharmaceuticals, and agrochemicals.[1] Therefore, the development of efficient and general accesses to functionalized organic halides is of great interest. Recently, the advances on palladium(0)-catalyzed synthesis of organic halides provide a new conceptual alternative, which enables the formation of carbon–halide bonds by the highly endothermic carbon halide reductive elimination (RE) from a palladium(II) species.[2] Since 2009, the group of Buchwald has developed elegant palladium(0)-catalyzed systems to realize the conversion of aryl triflates into aryl halides, including ArBr and ArCl, as well as ArF [Scheme 1, Eq. (1)].[3] These results clearly indicate the crucial role of the bulky and electron-rich phosphine ligand on the aryl halide RE, and is consistent with the finding by Hartwig and co-workers, a finding based on the stoichiometric variant.[4] Interestingly, Arndtsen and co-workers have found that even the energetically disfavored reductive elimination of an acyl-Pd^{II}-Cl can also smoothly occur with the help of a P(tBu)$_3$ ligand, and thus provides a powerfully catalytic method towards acyl chlorides [Scheme 1, Eq. (2)].[5] In sharp contrast to these achievements on the sp^2-carbon halide RE, only the alkyl iodide RE has been realized to date, and the alkyl bromide and chloride RE have met with very limited success (Scheme 1).[6] Lautens and co-workers have shown that the catalytic systems,[7] which are highly efficient for alkyl iodide RE, furnished the corresponding alkyl bromide RE product in less than 10 % yield [Scheme 1, Eq. (3)].[8] Very recently, Xi and co-workers developed an elegant palladium(0)-catalyzed transformation of an aryl halide into an alkyl halide. However, only one example relating to alkyl bromide RE was presented and the corresponding yield was as low as 38 %.[9] These results strongly demonstrate that the alkyl bromide and chloride RE are much more challenging and cannot be promoted by bulky phosphine ligand.[10] To address these issues, we envisioned that the electron-poor phosphine ligands might be valid because of their capability of reducing the electron density on the metal, thus facilitating the reductive elimination.[11] A computational study conducted by Houk and co-workers also disclosed a similar effect of an electron-poor ligand on alkyl halide RE.[10] Given this unique role of an electron-poor phosphine ligand and our continued interest in the palladium(0)-catalyzed synthesis of organic halides,[12] we explored the iminohalogenation[13] of the γ,δ-unsaturated oxime ester **1** with the help of halide salts and found the ligand P(4-FC$_6$H$_4$)$_3$ to be highly effective for the formation of the C–X bond (X = I, Br, Cl) [Scheme 1, Eq. (4)]. Herein we present our preliminary results.

Our investigations firstly focused on the oxime ester **1a** because of the facile oxidative addition of its N–O bond to the palladium(0) catalyst (Table 1).[14] Additionally, the introduction of a methyl group on the alkene ensured the formation of an alkyl-Pd^{II}-X species without a β-hydrogen atom. Upon

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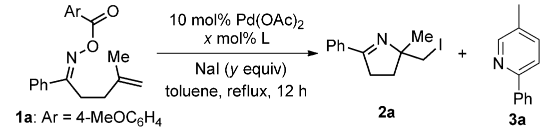
Table 1: Optimization of the reaction conditions.[a]



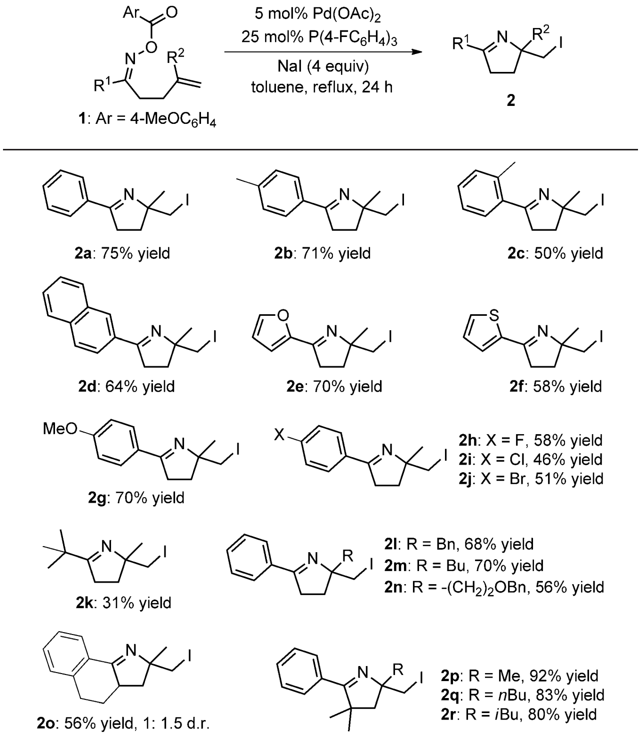
Entry	L (*x*)	NaI (*y*)	Yield [%][b] 2a	Yield [%][b] 3a
1	$P(4-FC_6H_4)_3$ (20)	NaI (2)	15	35
2	$P[3,5-(CF_3)_2C_6H_3]_3$ (20)	NaI (2)	15	29
3	$P(4-FC_6H_4)_3$ (50)	NaI (2)	62	8
4	$P[3,5-(CF_3)_2C_6H_3]_3$ (50)	NaI (2)	37	14
5	$P(4-FC_6H_4)_3$ (50)	NaI (4)	77	<5
6	$P(4-FC_6H_4)_3$ (50)	NaI (6)	78	<5
7[c]	$P(4-FC_6H_4)_3$ (25)	NaI (4)	75	<5

[a] For reaction conditions, see the Supporting Information. [b] Yield of isolated product. [c] 5 mol% $Pd(OAc)_2$ and 25 mol% ligand were used. The reaction was run for 24 h.

treatment with $Pd(OAc)_2$ (10 mol%), $P(4-FC_6H_4)_3$ (20 mol%), and NaI (2 equiv) in refluxing toluene, the reaction of **1a** afforded the desired product **2a** in 15% yield and the aza-Heck product **3a** was isolated in 35% yield (entry 1). The ligand $P(3,5-(CF_3)_2C_6H_3)_3$ delivered similar results (entry 2).[15] The yield of **2a** was improved to 62% when the loading of $P(4-FC_6H_4)_3$ was increased to 50 mol% (entry 3). However, 50 mol% $P(3,5-(CF_3)_2C_6H_3)_3$ resulted in 37% yield of **2a** (entry 4). On the basis of these results, we thoroughly examined several reaction parameters, such as phosphine ligands and halide salt additives (see the Supporting Information), none of which exhibited superior performance to the combination of $P(4-FC_6H_4)_3$ and NaI. It should be mentioned that significant quantities of **3a** were isolated in all cases. To facilitate the desired iminohalogenation, an increase in the loading of NaI was thought to be potentially useful. Indeed, the use of 4 equivalents of NaI provided **2a** in 77% yield and suppressed the formation of **3a** (entry 5). In the presence of 4 equivalents of NaI, **2a** was obtained, without erosion of the yield, even when using 5 mol% $Pd(OAc)_2$, although a prolonged reaction time and more strict reaction conditions were required (entry 7).[16]

The scope of the iminoiodination was further examined and the results are shown in Table 2. In general, the palladium(0)-catalyzed iminoiodination can be effectively achieved with a wide range of oxime esters (**1**), thus delivering the 2-iodomethyl dihydropyrroles **2** in moderate to high yields. Various electron-rich aryl oxime esters can participate in this process (**1a–g**) and the yield is adversely affected by steric hindrance. For an example, the reaction of the *o*-tolyl oxime ester **1c** gives **2c** in relatively low yield. The electron-poor aryl oxime esters **1h–j** exhibit reduced efficiency, thus delivering the corresponding products **2h–j** in moderate yields. Alkyl oxime esters are more challenging and only the *tert*-butyl substrate **1k** was found to be suitable and gave **2k** in 31% yield. Substitution on the alkene seems to have no deleterious effects and the reactions of **1l–n** with various alkyl substituents proceed, thus affording the corresponding products in high yields. The reaction of **1o**, which is derived from dihydronaphthalenone, delivers the product **2o** in 56% yield and as a 1.5:1 mixture of diastereomers. As a result of the Thorpe–Ingold effect, the α-trisubstituted oxime esters **1p–r** can be converted into the corresponding dihydropyrroles **2p–r** in excellent yields.

Table 2: The reaction scope of the iminoiodination.[a]

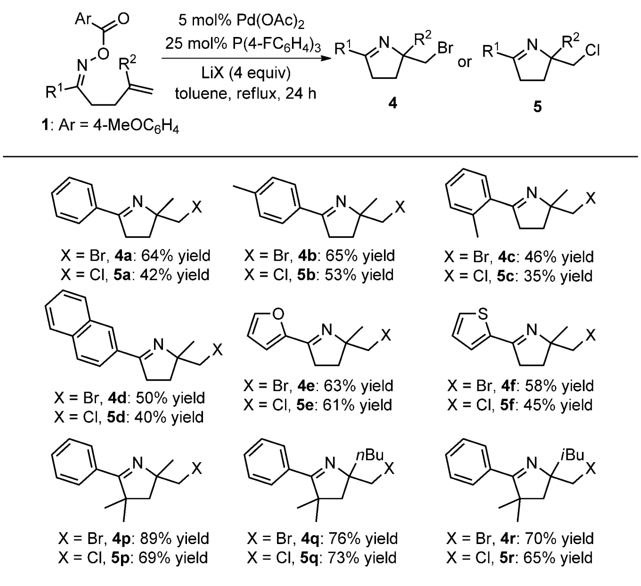


[a] For reaction conditions, see the Supporting Information. Yields of isolated products.

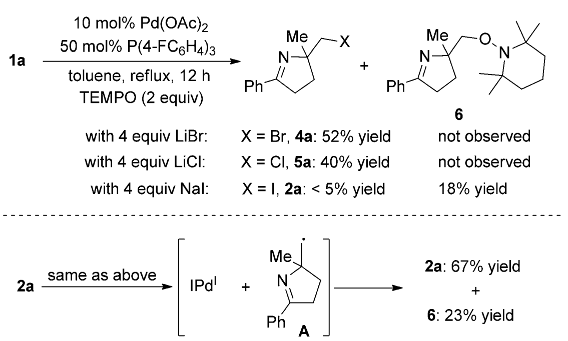
After our investigation of iminoiodination, we moved on to determine whether the $Pd(OAc)_2/P(4-FC_6H_4)_3$ catalytic system was applicable to iminobromination and iminochlorination. Finally, we were delighted to find that LiX (X = Br or Cl) was a proper additive to promote the corresponding iminohalogenation under otherwise identical reaction conditions. As shown in Table 3, the iminobromination products **4** were isolated in somewhat lower yield than those of the corresponding iminoiodination products. The iminochlorination also proceeded to give products **5** in synthetically useful yields albeit with less efficiency compared to iminoiodination and iminobromination. These results suggest that the trend of formation of carbon–halide bonds follows I > Br > Cl, which is opposite to that obtained as a result of thermodynamic control.[4,10]

Cyclizations involving the γ,δ-unsaturated oxime ester have been reported to proceed through a radical process.[17] In our iminobromination and iminochlorination, addition of TEMPO did not show a remarkable effect. In the presence of 2 equivalents of TEMPO, the products **4a** and **5a** were still isolated in the yield of 52% and 40%, respectively (Scheme 2). These results indicated that a radical process could be excluded. In contrast, a TEMPO additive strongly affected the iminoiodination. When 2 equivalents of TEMPO

Table 3: The reaction scope of the iminobromination and iminochlorination.[a]

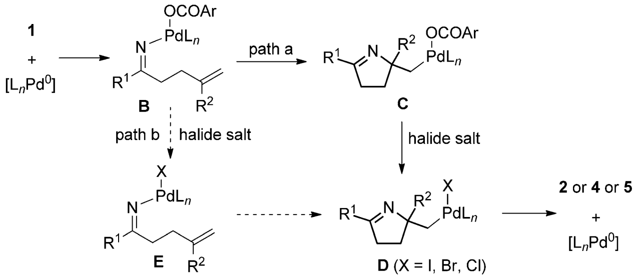


[a] For reaction conditions, see the Supporting Information. Yields of the isolated products.



Scheme 2. Reaction employing 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO).

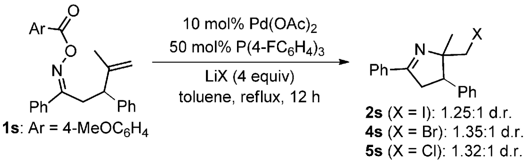
were added to the iminoiodination reaction, only trace amounts of **2a** were observed, and the TEMPO adduct **6** was instead isolated in 18% yield. Furthermore, it was found that iminoiodination product **2a** could be converted into **6** under the same reaction conditions, an outcome consistent with the primary iodide studied previously.[18] As a result of much higher reactivity of alkyl iodides than bromide and chloride analogues, the interaction of **2a** and the palladium(0) catalyst could generate a IPd^{I} species and the carbon radical intermediate **A** which can be trapped by TEMPO to form **6** (Scheme 2).



Scheme 3. A plausible reaction mechanism.

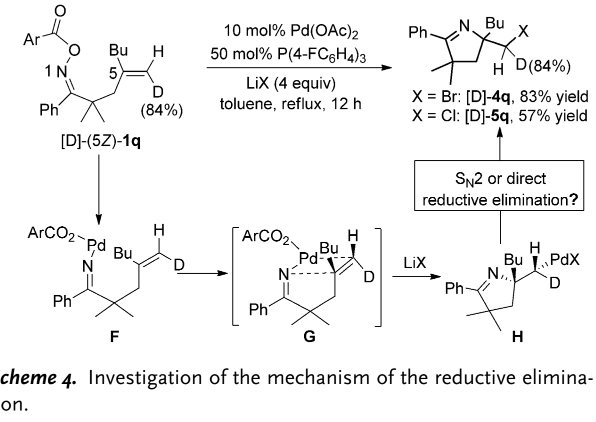
On the basis of the results obtained using TEMPO, a radical process can be ruled out for the iminohalogenation. Thus, a classical transition-metal-catalyzed pathway is alternatively proposed (Scheme 3). Firstly, the oxidative addition of **1** to the Pd^{0} catalyst leads to the imino-Pd^{II} intermediate **B**, and is followed by alkene insertion to generate the alkyl-Pd^{II} intermediate **C** (Scheme 3, path a). After ligand exchange from benzoate to halide, **C** is converted into the alkyl-Pd^{II}-X intermediate **D** which might also be generated via the intermediate **E** (Scheme 3, path b). Finally, **D** undergoes alkyl halide RE to deliver alkyl halide product. Although the conversion of alkyl-Pd^{II} into an alkyl halide can be realized by a Pd^{II}/Pd^{IV} cycle, an additional oxidant is always required.[19]

To distinguish between the paths a and b shown in Scheme 3, the iminohalogenation of **1s** was conducted in the presence of LiX (X = I, Br or Cl) [Eq. (5)]. It was found that these three reactions delivered the corresponding products with very similar diastereoselectivity, thus indicating that the alkene insertion, the diastereoselectivity determining step, would not involve the halide ligand. Thus, path a (Scheme 3) seems to be more reasonable, although path b (Scheme 3) cannot be excluded completely.



(5)

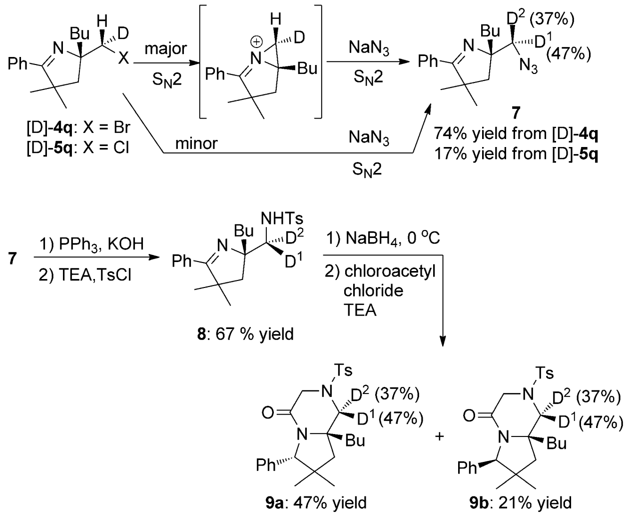
To get more insight on the mechanism of the alkyl halide RE, two control experiments were conducted using substrate [D]-(5*Z*)-**1q** (Scheme 4). Under the optimal reaction conditions, both the products [D]-**4q** and [D]-**5q** were isolated without deuterium erosion and scrambling. Thus, we concluded that the alkyl bromide and chloride RE are a stereospecific process.



Scheme 4. Investigation of the mechanism of the reductive elimination.

For the iminobromination and iminochlorination of [D]-(5*Z*)-**1q** (Scheme 4), the stereospecific intramolecular alkene insertion via the transition state **G** would generate intermediate **H** with well-defined stereochemistry, and is followed by alkyl bromination and chloridation RE to deliver the products [D]-**4q** and [D]-**5q**, respectively. Thus, the stereochemical information of [D]-**4q** and [D]-**5q** in turn provides a trustworthy way in which to explore the mechanism of the reductive elimination.

Fortunately, both imine and alkyl halide functional groups in [D]-**4q** and [D]-**5q** provide an opportunity to determine their relative stereochemistry. Thus, upon treatment with NaN_3, [D]-**4q** was transformed into the 2-(azidomethyl)-dihydropyrrole **7** with 47% D^1 and 37% D^2 (Scheme 5). The reaction of [D]-**5q** gave similar results. For this substitution reaction, both the double S_N2 and S_N2 processes were believed to be possible and the former was supposed to be favorable,[20] thus affording **7** with configuration retention. After a four-step synthetic manipulation, two separable diastereomers, **9a** and **9b**, were obtained (Scheme 5). The nOe experiments on **9a** and **9b** clearly indicated that the butyl group and D^1 were located in a *syn* arrangement. Because of the reliable stereoselective reactions employed in these synthetic transformations, it was sufficient to determine the relative stereochemistry of [D]-**4q** and [D]-**5q** to be that depicted in Scheme 5. Thus, on the basis of the stereochemical outcome of [D]-**4q** and [D]-**5q**, S_N2-type alkyl bromide and chloride RE of the intermediate **H** could be concluded, and is consistent with microscopic reversibility in the oxidative addition of alkyl halide to Pd^0 species.[21]



Scheme 5. Determination of the stereochemistry of [D]-**4q** and [D]-**5q**. TEA = triethylamine.

In summary, we have developed the palladium(0)-catalyzed iminohalogenations of alkenes with the assistance of halide salts, and thus provided facile access to synthetically useful 2-halomethyl dihydropyrroles. The reaction features the use of an electron-poor phosphine as the ligand, which proved to be essential for promoting alkyl bromide and chloride RE. The catalytic systems described provide a complementary solution for the highly endothermic carbon halide reductive elimination. Furthermore, a plausible S_N2-type alkyl bromide and chloride RE has been established on the basis of the results from deuterated substrate.

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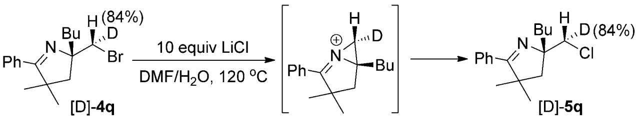
[20] As a result of discussions with Professor Mark Lautens concerning the mechanism, the double S_N2 process was proposed and confirmed by the transformation shown below.



Under the same reaction conditions as NaN_3 substitution, the reaction of [D]-**4q** with 10 equiv of LiCl afforded [D]-**5q**, thus strongly demonstrating that the double S_N2 process should dominate the substitution reaction of [D]-**4q**.

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