Asymmetric Catalysis

Palladium-Catalyzed Asymmetric Iodination of Unactivated C–H Bonds under Mild Conditions**

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Dedicated to Professor E. J. Corey

The catalytic activation of $C(sp^3)$–H and $C(sp^2)$–H bonds in readily available, inexpensive starting materials would provide a valuable array of new transformations for organic chemistry research and the fine chemical industry.[1] Activation of $C(sp^2)$–H bonds in benzene and *ortho*-substituted arenes has been successfully exploited in the development of catalytic C–C bond-forming reactions by coupling to olefins.[2,3] The selective activation of $C(sp^3)$–H bonds under mild conditions could be an attractive strategy for the development of catalytic reactions with wide applicability. Despite extensive efforts that have focused mainly on carbene and nitrene insertions, metathesis, Shilov chemistry, and biomimetic approaches, the catalytic and asymmetric functionalization of $C(sp^3)$–H bonds remains a significant challenge.[4]

We report herein an auxiliary approach for the chemoselective and asymmetric room-temperature iodination of

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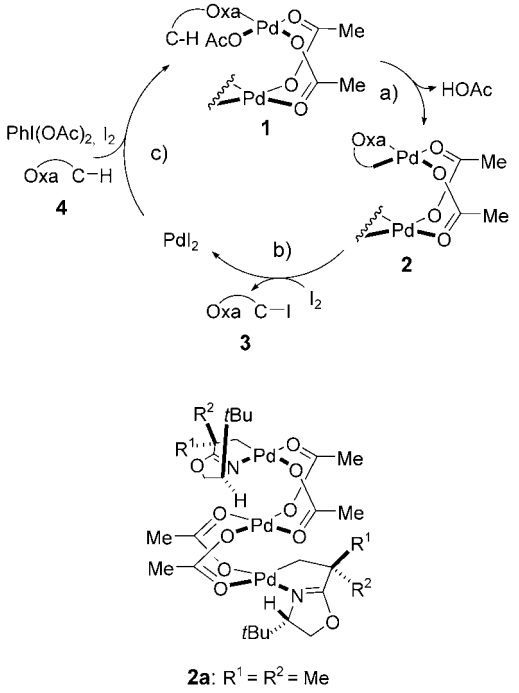
methyl groups located at the α position of saturated aliphatic acids.[5] This protocol also applies to the activation of cyclopropanes (C–H bond β to the carboxy group) and arenes (C–H bond γ to the carboxy group). Our strategy involves the installation of a σ-chelating auxiliary, such as oxazoline,[6] to facilitate the assembly of the pre-transition state for cyclometallation through a square-planar complex as illustrated by compound **1** (Scheme 1). One of the earliest observed



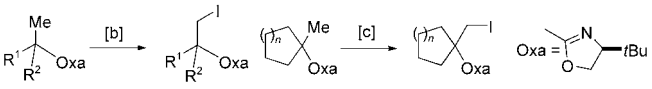
2a: $R^1 = R^2 = Me$

Scheme 1. Proposed catalytic cycle of C–H-bond activation.

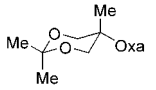
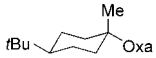
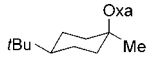
examples of C–H bond activation was cyclometallation promoted by agostic interactions or sigma chelation.[7] The activation of *ortho* aryl C–H bonds to give cyclopalladation by the pre-coordination of a nitrogen atom has been reviewed extensively.[8] Inspired by the remarkable discovery of, and recent progress in the Shilov oxidation cycle,[9] we searched for an oxidation system that would render the cyclopalladation reaction catalytic in a similar manner. Notably, Sanford and co-workers recently reported an efficient Pd^{II}-catalyzed acetoxylation reaction with *O*-methyl oxime as a directing group at the time our work was in progress.[10]

Trimethylacetic acid was selected for an initial test, owing to its structural simplicity. Oxazoline **5a** and other substrates were readily prepared from their corresponding carboxylic acids and (*S*)-*tert*-leucinol (Table 1). We found that $Pd(OAc)_2$/I_2 was an effective stoichiometric reagent for the iodination of a methyl group in **5a**. Stirring **5a** with $Pd(OAc)_2$ and I_2 (1 equivalent each) in CH_2Cl_2 at 24 °C for 24 h gave exclusive iodination of the methyl group to provide the monoiodide in 80 % yield. Reactions of other oxazolines that were prepared from trimethylacetic acid and ethanolamine, 2-methyl-2-aminopropanol, or valinol were either very slow or did not proceed under the same conditions.

Table 1: Monoiodination of methyl groups catalyzed by $Pd(OAc)_2$.[a]



5a–7a **5b–7b** **8a–10a** **8b–10b**

Entry		Substrate	Yield [%]
1	**5a**	$R^1 = R^2 = Me$	92
2	**6a**	$R^1 = Me$; $R^2 = Et$	91[d]
3	**7a**	$R^1 = R^2 = Et$	88[e]
4	**8a**	$n = 1$	90[e]
5	**9a**	$n = 2$	97[e]
6	**10a**	$n = 3$	81
7	**11a**		67[f]
8	**12a**		98
9	**13a**		32

[a] Reaction conditions: $Pd(OAc)_2$ (10 mol %), I_2 (1 equiv), $PhI(OAc)_2$ (1 equiv), CH_2Cl_2, 24 °C, 48–72 h. [b] Entries 1–3. [c] Entries 4–6. [d] 63:37 d.r. (NMR spectroscopy). [e] PdI_2 precipitated at 36–48 h, $PhI(OAc)_2$ (1 equiv) was added, and stirring continued for another 48 h. [f] $PhI(OAc)_2$ (2 equiv), 50 °C, 48 h.

A single isomer of the trinuclear palladium alkyl species **2a** (Scheme 1) was obtained in 60 % yield (determined by Pd recovery) by simply stirring substrate **5a** with $Pd(OAc)_2$ (1 equiv) in CH_2Cl_2 at 24 °C for 36 h (Supporting Information).[11] The *syn* geometry of **2a** was tentatively assigned by a steric argument: the bulky *tert*-butyl group must avoid the concave face. This complex was instantly converted into the iodinated product **5b** when I_2 was added.

Following these experimental observations, we proposed a stoichiometric C–H bond-activation pathway that involves steps a) and b) shown in Scheme 1. From the known structure of the cyclic trimer $Pd_3(OAc)_6$ crystallized from CH_2Cl_2[12] and the isolated complex **2a**, we assumed the trinuclear bis-μ-acetatopalladium complex **1** is formed as the reactive precursor. First, electrophilic cleavage of the C–H bond occurs to give the trinuclear square-planar Pd^{II} complex **2**. Next, I_2 reacts with complex **2**, presumably by oxidative addition[13] and reductive elimination, to form the iodinated product **3** and PdI_2 (isolated as a powder in quantitative yield and characterized by X-ray powder diffraction).[14] The kinetic isotope effect (KIE) of the iodination reaction of substrate **9a** into **9b**, in which the methyl group was deuterated ($k_H/k_D = 4.7$), is also consistent with C–H bond cleavage as the rate-limiting step.[15]

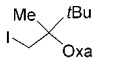
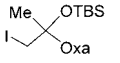
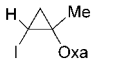
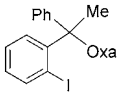
PdI_2 was unreactive with substrate **5a**. Therefore, IOAc generated[16] in situ from AgOAc and I_2 was used to convert PdI_2 into $Pd(OAc)_2$ to close the catalytic cycle, as shown in step c) (Scheme 1). $PhI(OAc)_2$ was more effective for this catalytic reaction.[17] Control experiments showed that $PhI(OAc)_2$ alone does not react directly with PdI_2. However, PdI_2 was converted into $Pd(OAc)_2$ by stirring with $PhI(OAc)_2$ and I_2 (1 equiv each) in CH_2Cl_2 at 24 °C for 1 h (Supporting Information). Thus, substrate **5a** was stirred with I_2, $PhI(OAc)_2$ (1 equiv each), and $Pd(OAc)_2$ (10 mol %) in CH_2Cl_2 at

24 °C for 64 h to afford the iodination product in 92 % yield (Table 1).

The highly selective activation of primary over secondary C–H bonds was conclusively demonstrated with substrates **6a** and **7a**. The oxazoline prepared from triethylacetic acid does not react under the same conditions. These observations are consistent with the unfavorable steric interactions between coordinated ligands and branched alkyl groups in a cyclometalation step. Cyclic substrates (**8a**–**10a**) were also examined, and the methyl C–H bonds were consistently selectively iodinated in high yields. Substrate **11a**, which bears a polar ketal group, was also iodinated in 67 % yield at 50 °C (Table 1). The striking rate difference ($k_{trans}/k_{cis} = 5.7$) between isomeric substrates **12a** and **13a** is particularly intriguing. A detailed understanding of this observation requires further mechanistic exploration of the C–H bond-cleavage processes.

The moderate diastereoselectivity (63:37 d.r.) observed with substrate **6a** prompted us to test asymmetric iodination with various prochiral substrates. Iodination of substrate **14a** exhibited drastically improved diastereoselectivity relative to the reaction of **6a**. The two diastereomers were isolated as a mixture (d.r. = 91:9) (Table 2). We were pleased to find that the reaction conditions were also compatible with a TBS-protected hydroxy group in substrate **15a**.

Table 2: Asymmetric iodination.[a]

Entry	Substrate		Product		Yield [%]	d.r.
1	**14a**		**14b**		83[b]	91:9
2	**15a**		**15b**		62[c]	93:7
3	**16a**		**16b**		65[d]	99:1
4	**17a**		**17b**		98[e]	99:1

[a] Reaction conditions: $Pd(OAc)_2$ (10 mol %), I_2 (1 equiv), $PhI(OAc)_2$ (1 equiv), CH_2Cl_2. [b] 24 °C, 30 h. [c] 50 °C, 48 h. [d] 24 °C, 96 h. [e] 24 °C, 13 h. TBS = *tert*-butyldimethylsilyl.

The well-documented amide-directed lithiation reactions of cyclopropanes[18] prompted us to determine if this newly developed catalytic system could functionalize the secondary cyclopropyl C–H bond in the presence of a methyl group. Cyclopropane substrate **16a** was subjected to the same conditions as described. Indeed, the selectivity was completely reversed from primary to secondary C–H bonds. Of particular importance is the excellent stereochemical control in the exclusive iodination of the cyclopropyl C–H bond. Reaction of **16a** afforded iodinated product **16b** as a single isomer in 65 % yield. The *cis* geometry of **16b** was established by NOE experiments. The enantiomer of **16b** was also obtained with oxazoline substrate prepared from (*R*)-*tert*-leucinol. Both **16b** and its enantiomer were hydrolyzed by treatment with H_2SO_4/dioxane (1:1, 4 M) at reflux for 8 h to give the corresponding carboxylic acids with > 99 % *ee* as determined by HPLC analysis.

The scope of this C–H bond-activation reaction was further examined with the arene-containing substrate **17a**. Interestingly, the arene C–H bond was iodinated with high selectivity in the presence of a methyl group. The monoiodinated product **17b** was isolated in 98 % yield (> 99:1 d.r.; NMR spectroscopy, GC–MS, Table 2).[19] We reasoned that if the reaction proceeds by cyclometallation of the trinuclear complex **1**, the hydrogen atom cleaved from the methyl group is the one that affords **2** with the larger group on the convex face (R^2) (Scheme 1*)*. This model explains the high diastereoselectivity attained, even though the stereogenic center in the oxazoline ring is far removed from the reaction site. Unfortunately, confirmation of this model through the assignment of the absolute configuration of the products has proven difficult, and is still in progress.

A clear advantage of this catalytic system is the ease with which the palladium catalyst can be recycled (Table 3). As PdI_2 precipitates from solution toward the completion of the reaction, it can be isolated by centrifugation. After decanting the supernatant, PdI_2 is recycled with a fresh supply of I_2 and $PhI(OAc)_2$. With **17a**, five reaction cycles starting with only 22.4 mg (0.1 mmol) of $Pd(OAc)_2$ produced 1.99 g (4.6 mmol) of the iodinated product **17b** with high diastereoselectivity (> 99:1 d.r.).

Table 3: Catalyst recycling experiments with substrate **17a**.[a]

Run	1	2	3	4	5
Yield [%]	98	97	93	88	84

[a] Reaction conditions: $Pd(OAc)_2$ (10 mol %), I_2 (1 equiv), $PhI(OAc)_2$ (1 equiv), CH_2Cl_2, 24 °C, 13–20 h.

In summary, the combination of a hindered oxazoline auxiliary, $Pd(OAc)_2$, I_2, and $PhI(OAc)_2$ was shown to be a powerful protocol for the catalytic and asymmetric iodination of inactivated C–H bonds of methyl, cyclopropyl and aryl groups under mild conditions.

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