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Studies on Selective Hydroxylation of Aliphatic C-H Bonds Using Tridentate NHC-Amidate-Alkoxide Pd(II) Complexes†

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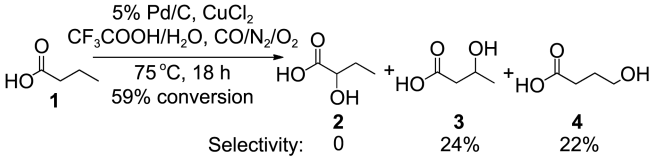
Catalytic functionalization of unreactive sp^3 C-H bonds under mild conditions is a highly desirable prospect that has generated a considerable amount of interest in recent years.[1] Numerous studies have been carried out in an effort to develop efficient methods; nonetheless, controlling selectivities in these reactions remains a challenge. The chemo-, stereo-, and/or enantioselectivity of these reactions have been particularly difficult to control, especially in those intended to produce hydroxylated products, as overoxidation to ketones and even C-C bond cleavage products are prevalent.

Under relatively mild conditions, overoxidation can be reduced significantly to offer hydroxylation products somewhat selectively while some starting material usually remains. As shown in Scheme 1, Sen developed relatively mild conditions using oxygen instead of other reactive oxidants, which converted 59% of the starting acid **1** to produce an equimolar mixture of β- and γ-hydroxylated products.[2] Surprisingly, α-hydroxylation was not observed whereas remote C-H functionalization was efficient. Recently, we introduced a unique tridentate NHC-amidate Pd catalyst which showed surprising reactivity toward unreactive C-H bonds under mild conditions.[3] We wondered if our new Pd catalysts with a unique architecture of tridentated ligands would be able to effect improved regioselectivity and furthermore promote asymmetric functionalization. This report describes initial results on regioselectivity and enantioselectivity using new catalysts **5** and **6** depicted in Figure 1.



Scheme 1. A recent successful example of remote C-H functionalization.

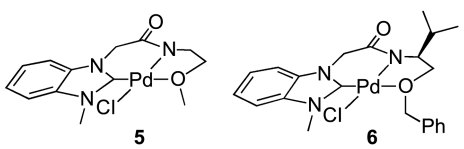
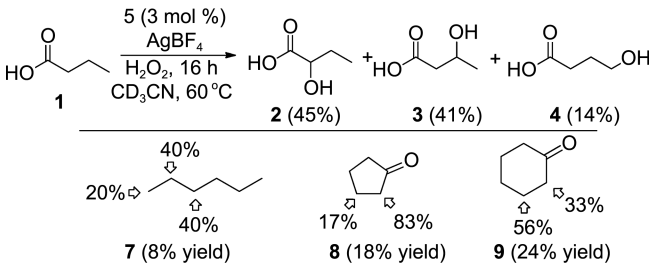


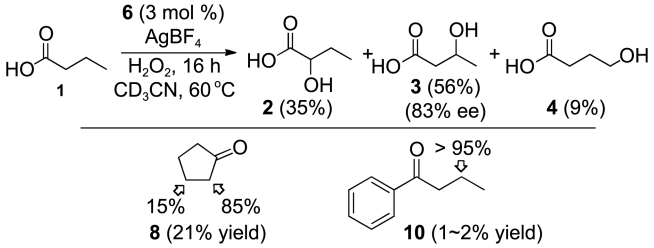
Figure 1. Novel tridentate NHC-amidate-alkoxide Pd(II) catalysts.

We examined hydroxylation of butyric acid using catalyst **5** and hydrogen peroxide (Scheme 2).[4] Contrary to Sen's conditions, we observed hydroxylation on all three possible centers with poor regioselectivity, which was also observed from *n*-hexane (**7**) in a very similar way. Using cyclic substrates, we found that cyclopentane (**8**) and cyclohexane (**9**) furnished mixed selectivities, which might imply relocation of reaction centers during the course of the reactions.

Catalyst **6** gave rise to similar results on acyclic and cyclic substrates, **1** and **8**, respectively (Scheme 3). We also learned that this enantiopure catalyst induced high enantioselection on the β-hydroxylation product **3** which could be due to direct C-H activation by Pd.[5] Although we did not pursue identification of the absolute configuration, we conducted an NMR study with a chiral shift reagent to confirm the optical purity of 83% ee.[6] It is evident that this type of catalyst can facilitate chiral induction at an unreactive C-H site. In addition, we found that ketone **10** provided high β-selectivity in the beginning of the oxidation, thus we hypothesized that the incipient reaction center would be β-center to the carbonyl,



Scheme 2. Regioselectivity in hydroxylation using catalyst **5**.



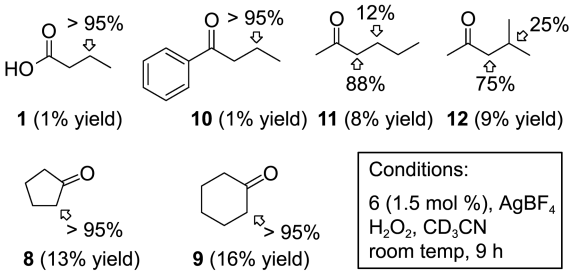
Scheme 3. Regioselectivity in hydroxylation using catalyst **6**.

†This paper is dedicated to Professor Eun Lee on the occasion of his honourable retirement.

prompting us to study hydroxylation at room temperature.

As shown in Scheme 4, we conducted hydroxylation using various substrates under milder conditions such as reduced loading of catalyst **6**, room temperature instead of 60 °C, and shorter reaction time to maximize the chance of observing incipient results. With the same substrate **1** as before, we observed the β-hydroxylation product without any other products. Similarly, ketone **10** offered the same regioselectivity. However, other ketones including **11** and **12** produced α-hydroxylation products as the major and β-alcohols as the minor. Cyclic ketones furnished α-hydroxylation products exclusively. This observed α-selectivity of **11**, **12**, and cyclic ketones could be due to the formation of enols from ketones when they coordinate to Pd.[7] In addition, α-hydroxylation of **12** could be caused by steric hindrance of β-carbon. These results implied that hydroxylation using our catalysts could take place initially in a kinetic manner for higher regioselectiviy before relocation of reaction centers, and further studies on optimizing conditions are underway.

Before relocation of reaction centers, hydroxylations seemed to occur at the β-centers for acyclic carbonyls whereas α-centers would be the site of hydroxylation for cyclic carbonyls. Moreover, asymmetric catalysis was possible, indicating that there would be a certain rigid binding between the catalyst and the substrate. We currently speculate a lone pair of electrons or π electrons from the carbonyls would interact with the Pd metal, which would dictate the closest carbon C-H bonds as the reaction center (Figure 2). For acyclic substrates, both α- and β-centers are possible as illustrated in the complex **13** which has a lone pair electron interaction. In contrast, α-centers are significantly more proximal to the metal than β-centers as depicted in the complex **14** for cyclic



Scheme 4. Incipient regioselectivity in hydroxylation using catalyst **6**.

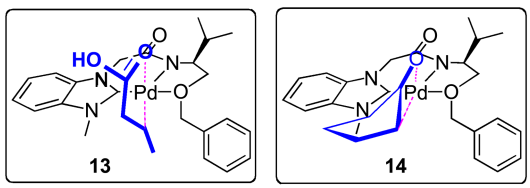


Figure 2. Potential binding mode of carbonyls to **6**.

substrates which could have π electron interaction. At high temperatures, both α and β C-H bonds could be activated directly by Pd complexes with less contribution from the coordinated forms, which could explain the different results for cyclic systems in Schemes 2 and 3. In summary, we believe that the C-H activation would take place preferentially *via* carbonyl-coordinated intermediates in the beginning of the reaction and at a low temperature. As the reaction progresses and also at high temperatures, reaction centers would be relocated and significant direct activation without coordination would occur. Based on these binding modes and observed regioselectivities, we are developing revised conditions to improve chemoselectivity, regioselectivity, and potential enantioselectivity while endeavoring to further understand the mechanism, which could be either a radical reaction or more typical C-H activation.

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4. For a representative experimental for the Scheme 2; 3 mg of **5** and $AgBF_4$ were placed in a 1 dram vial with 0.5 mL CD_3CN. After stirring 5 minutes, 30 equivalents of substrates and 40 μL of H_2O_2 solution (30% w/w) were added. The reaction mixture was stirred in a 60 °C oil bath. After 16 hours, the mixture was cooled to room temperature and NMR spectra were directly taken. For the Scheme 3, complex **6** was used instead of **5**. For the Scheme 4, reactions were run at room temperature without an oil bath.
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6. 3 mg of **6** and $AgBF_4$ were placed in a 1 dram vial with 0.5 mL CD_3CN. After stirring 5 minutes, 30 equivalents of butyric acid and 40 μL of H_2O_2 solution (30% w/w) were added. After stirring in a 60 °C oil bath for 16 hours, the mixture was cooled to room temperature and 10 mg of a chiral shift reagent (europium tris[3-(heptafluoropropylhydroxylemethylene)-(+)-camphorate]) was added. δ-CH_3 peaks (1.18 : 1.24 ppm = 1 : 10.5 by integration) were used to calculate the *ee* value (*ee* = 83%).
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