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 sp³ C-H bonds under mild conditions is a highly desirable prospect that has generated a considerable amount of interest in recent years. 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. 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. 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.

We examined hydroxylation of butyric acid using catalyst 5 and hydrogen peroxide (Scheme 2). 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 enantioselectivity on the β-hydroxylation product 3 which could be due to direct C-H activation by Pd. 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. 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 1. A recent successful example of remote C-H functionalization.

Scheme 2. Regioselectivity in hydroxylation using catalyst 5.


This paper is dedicated to Professor Eun Lee on the occasion of his honourable retirement.
ketones could be due to the formation of enols from ketones exclusively. This observed minor. Cyclic ketones furnished hydroxylation products as the major and β-products. Similarly, ketone loading of catalysts both could be caused by steric hindrance of ketones when they coordinate to Pd. In addition, α-hydroxylation of 12 could be explained by the formation of enols from ketones. These results implied that hydroxylation using our catalysts could take place initially in a kinetic manner for higher regioselectivity before relocation of reaction centers, and further studies on optimizing conditions are underway.

Before relocation of reaction centers, hydroxylation 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 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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References

1. For recent reviews, see: (a) Herrera, C.; Yao, X.; Li, Z.; Li, C. Chem. Rev. 2007, 107, 2546. (b) Shul’pin, G. Mini-Reviews in Organic Chemistry 2009, 6, 95.
4. For a representative experimental for the Scheme 2; 3 mg of 5 and AgBF₄ were placed in a 1 dram vial with 0.5 mL CD₂CN. After stirring 5 minutes, 30 equivalents of substrates and 40 μl of H₂O₂ solution (30% w/w) were added. The reaction mixture was stirred for 24 h 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.
6. 3 mg of 6 and AgBF₄ were placed in a 1 dram vial with 0.5 mL CD₂CN. After stirring 5 minutes, 30 equivalents of butyric acid and 40 μl of H₂O₂ 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-CH₃ peaks (1.18 : 1.24 ppm = 1 : 10.5 by integration) were used to calculate the ee value (ee = 83%).