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Regioselectivity of sp^3 C−H borylation of N-hetrocycles catalyzed by cooperation of iridium(III) boryl complex and Lewis acid.

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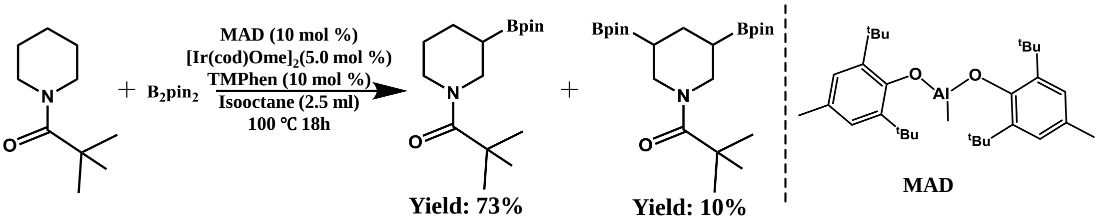
[Abstract] Borylation of *β* sp^3 C−H bond of N-hetrocycles catalyzed by the cooperation of iridium(III) boryl complex and Lewis acid was experimentally succeeded. DFT calculation reveals that B−C reductive elimination is the rate-determining step and the activation energy of *β* C−H borylation is lower than these of *α* and *γ* C−H bond borylations. This regioselectivity arises from that carbon sp^3 orbital is lower in energy at the *β* position than that at the *α* and *γ* position, which leads to a larger stabilization energy in *β*-TS of B−C reductive elimination. Lewis acid accelerates the reaction because Lewis acid lowers the sp^3 orbital energy to increase the stabilization energy in the TS of B−C reductive elimination.

[Introduction] Recently, sp^3 C−H borylation of N-hetrocycles catalyzed by the cooperation of iridium(III) boryl complex and Lewis acid was experimentally succeeded.[1] In this reaction, the weaker *α* C−H borylation did not occur but the only *β* C−H borylation occurred. It is also interesting that the similar *γ* C−H borylation did not occur. A bulky Lewis acid MAD (see Scheme 1) accelerated the reaction more effectively than $AlMe_3$. Up to now, the fundamental understanding of *β*-selectivity and the role of Lewis acid have not been presented yet. In this theoretical study, we elucidated the reason of the *β*-selectivity and the effect of Lewis acid.



Scheme 1. Regioselectivity of C−H borylation of N-hetrocylce.

[Methods]

All geometry optimizations were performed by B3PW91-D3 functional, where the Stuttgart-Dresden-Bonn basis set was employed for Ir with the effective core potentials for core electron of Ir and the 6-31G(d) basis sets for other atoms. Single-point calculations were performed using ωB97XD, and better basis set system, in which two f polarization functions were added to Ir and 6-311+(d, p) basis sets were used for other atoms. Solvation effect (isooctane) was evaluated with polarizable continuum model (PCM), where the geometries optimized in gas phase were employed. All discussions were presented based on the Gibbs energy, where the translation entropy in solution was corrected by the method of Whiteside et al. [2]

[Results and Discussion]

The Gibbs energy profile of the full catalytic cycle of *β* C−H borylation was presented in Figure 1. Four elementary steps are involved in the catalytic cycle; *α* C−H bond coordinated Ir(III)tris(boryl) complex **3A** is the resting state. The C−H activation step starts from *β* C−H interacting adduct **β-4A$_{eq}$** through transition state **β-TS$_{4/5}$A$_{eq}$**; the Gibbs activation energy ($\Delta G^{o\ddagger}$) of this step is 28.3 kcal mol^{-1}. The B−C reductive elimination occurs through **β-TS$_{6/7}$A$_{eq}$**; the $\Delta G^{o\ddagger}$ is 29.6 kcal mol^{-1}. Compared with equatorial β C−H bond borylation, axial β C−H bond (see the parentheses in Figure 1) is less reactive with a higher $\Delta G^{o\ddagger}$ (38.3 kcal mol^{-1}). Catalytic cycle completed by the regeneration of active catalyst, which consists of two steps, namely the oxidative addition of B_2pin_2 and reductive elimination of HBpin. These two steps would occur easily though two lower energy barriers. The ΔG^{o} of the full catalytic cycle is -6.8 kcal mol^{-1} and the rate-determining step is the B−C reductive elimination. On the other hand, the $\Delta G^{o\ddagger}$ of B−C reductive elimination step of α and γ C−H borylation is 37.7 kcal mol^{-1} and 34.8 kcal mol^{-1}, respectively, which is higher than that of β C−H borylation. These results are consistent with the experimental results that the β C−H borylation was successfully performed but α and γ C−H borylation were not. The β carbon sp^3 orbital is lower in energy than that at α and γ carbon sp^3 orbital, which leads to a larger stabilization energy in TS of B−C reductive elimination. $AlMe_3$ and MAD lowers the sp^3 orbital energy by 0.7 eV and 1.01 eV, respectively to increase the stabilization energy in TS of B−C reductive elimination and decrease the barrier by 2.9 kcal mol^{-1} and 5.6 kcal mol^{-1}, respectively. These results suggest that Lewis acid can accelerate the reaction and MAD is better than $AlMe_3$, which is consistent with experimental results.

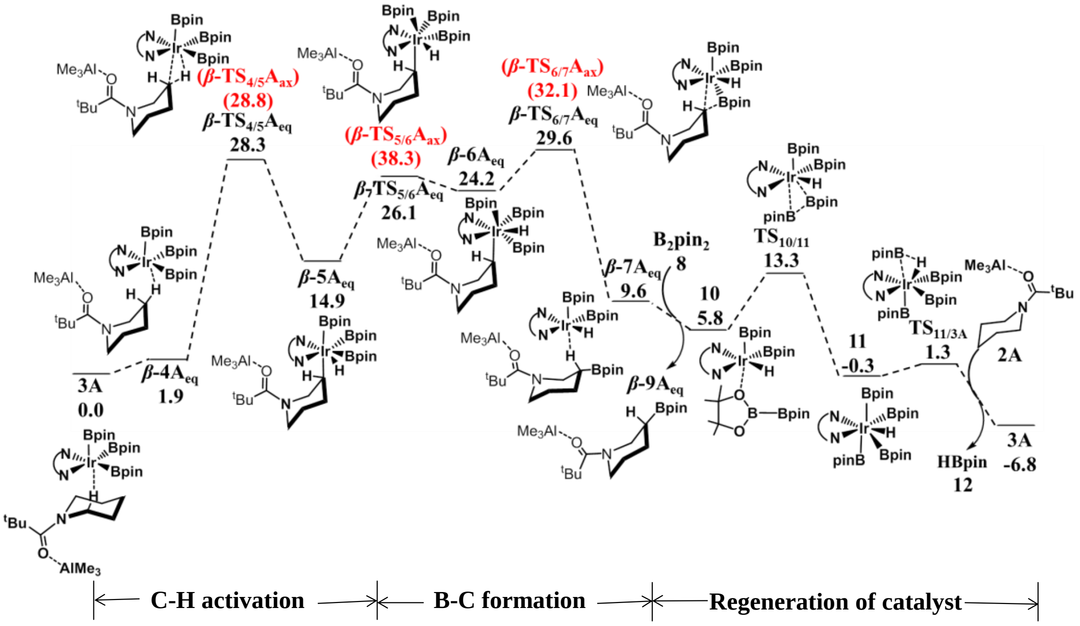


Figure 1. Full catalytic cycle of β equatorial (axial is shown in parentheses) C−H borylation with $AlMe_3$.

[References]

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