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Ir-Catalyzed C–H Amidation of Aldehydes with Stoichiometric/Catalytic Directing Group

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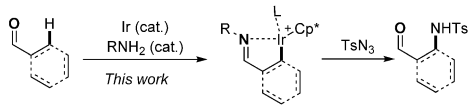
Abstract: Ir-catalyzed sp^2 C–H amidation of aldehydes with various anilines as stoichiometric or catalytic directing groups was accomplished. A wide range of substrates were selectively amidated in good to excellent yields with broad functional group tolerance. The iridacycle complexes were isolated, characterized, and proved as key intermediates. Kinetic studies and Hammett plots provided detailed understandings of this amidation. According to the mechanism, the electron-rich $ArSO_2N_3$ was proved effective for intermolecular sp^3 C–H amidation.

Introduction

Transition-metal-catalyzed C–H activation with directing strategy is one of the most reliable pathways to form C–C and C–X bonds (X = heteroatom) with both efficiency and selectivity.[1] Due to the easy preparation and simple removal ability, the imine derivative is considered as an ideal directing group of aldehydes/ketones for direct C–H functionalization.[2] Compared to the prepared directing group in substrates, using a catalytic amount of amine as transient directing group for aldehydes/ketones is much more desirable. An early example was reported by Jun and co-workers using 2-amino pyridine as a transient directing group for Rh-catalyzed activation of aldehydic C–H bonds.[3] Dong and co-workers used an enamine intermediate with a pyridine moiety as a transient directing group to realize α-C–H functionalization of ketone.[4] Seayad and co-workers used 4-trifluoromethylaniline as transient directing group to realize the oxidative coupling of aldehydes.[5] Very recently, Yu and co-workers reported another successful example on direct functionalization of C(sp^3)–H bonds using amino acid as a transient directing group.[6] Considering the importance of such processes, it is still highly appealing to develop new transformations based on this strategy.

Aldehydes are readily available and easily transformable. Due to the weak coordinating ability and instability of the produced intermediates, direct β-C–H functionalization of aldehydes is far behind, with limited reaction classes and substrate scopes.[7c] To date, C–C and C–O formation were successfully resolved with different nucleophiles.[7] Due to step- and atom-economy, much attention has recently been paid to transition-metal-catalyzed C–H amination/amidation.[8] Indeed, both nucleophilic and electrophilic aminating/amidating reagents have been applied.[9] Recently, Chang,[10] Jiao,[11] Bolm[12] and others[13] made significant contributions in transition-metal-catalyzed C–H amidation using organic azides as amidating reagents. Herein we report the successful iridium-catalyzed intermolecular C–H amidation of aldehydes through stoichiometric and catalytic directing strategy (Scheme 1).



Scheme 1. Direct C–H amidation of aldehyde through stoichiometric and catalytic directing strategy.

Results and Discussion

We initially tried the desirable *ortho*-amidation of 2-bromobenzaldehyde with TsN_3 in the presence of $[Cp^*IrCl_2]_2$ (5 mol%) and $AgPF_6$ (20 mol%) as catalyst [Eq. (1)]. No reaction occurred as expected. To our delight, when using the imine **1a** as substrate, C–H amidation took place smoothly and the amidated aldehyde **3a** was isolated in 91% yield after a simple workup, indicating the vital role of iminyl group. After the systematic optimization we found that both the catalyst loading and the amount of TsN_3 could be reduced and the desired aldehyde was obtained in a 92% yield [Eq. (2), method A; for details, see the Supporting Information]. Based on this result, we envisaged that the presence of catalytic amounts of proper amines might also enhance the reactivity mediated by imine. Indeed, the results indicated that, by using a catalytic amount of 3-trifluomethylaniline, the desired product was obtained in 84%

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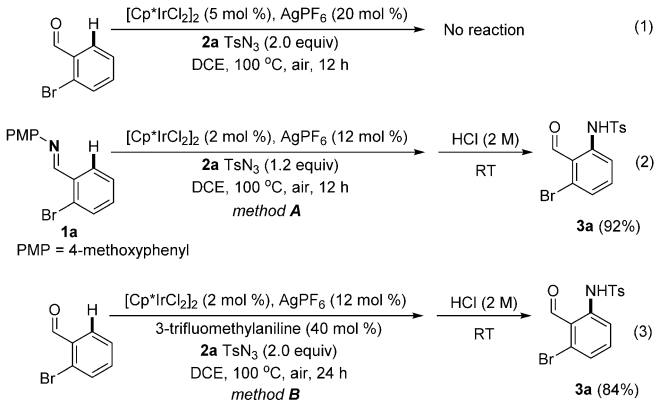
isolated yield [Eq. (3), method B; for details, see the Supporting Information).



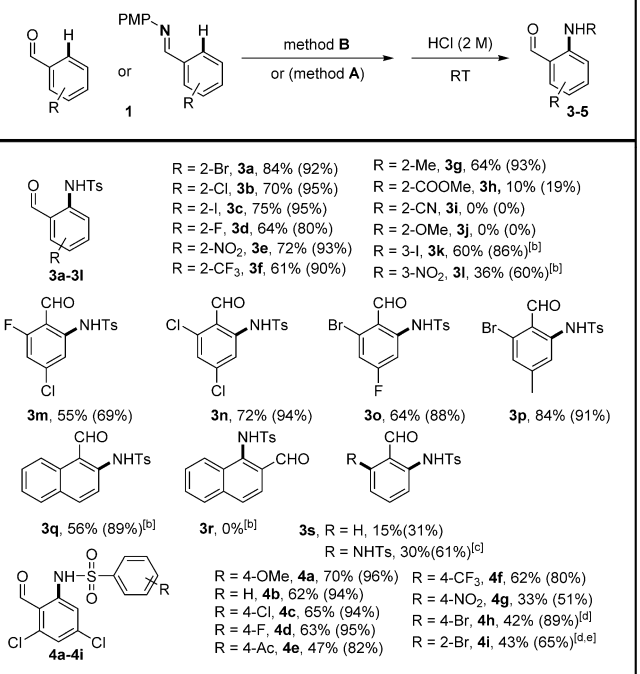
With the optimal conditions in hand, a variety of imines and organic azides were tested based on methods A and B and representative data are shown in Table 1. Generally, the yields with catalytic amount of aniline derivatives gave good to acceptable yields, albeit lower than those from the corresponding imines. Different halo-substituents, including Br (**3a**), Cl (**3b**) ad I (**3c**) survived well and comparable efficacy was obtained. While F (**3d**) was present, a relatively lower yield was obtained. Other functional groups, such as nitro- (**3e**), trifluoromethyl- (**3f**), and methyl- (**3g**), equipped at the *ortho* position, also gave good results. However, the ester group (**3h**) at the *ortho* position gave much lower efficiency while *ortho*-cyano- (**3i**) and methoxy- (**3j**) substituents terminated the reaction; this probably arises from the chelating effect of heteroatoms of substituents and iminyl groups to cationic Ir-complexes to prevent C–H activation. The *meta* substituents were also tested and we found that 3-I (**3k**) gave a good yield while 3-NO_2 (**3l**) gave lower efficiency.

Disubstituted imines containing different functional groups also reacted well. Dihalo-substituted imines showed great reactivity to produce the multisubstituted products (**3m**–**3o**) and the methyl substituted **3p** was also workable. Interestingly, the 1-naphthaldehyde derivative **3q** gave a credible reactivity while the 2-naphthaldehyde **3r** completely failed. *N*-Phenyl benzaldimine **1s** was also suitable and both mono- and diamidated products were obtained in good yield in the presence of 5 mol% of Ir catalyst (**3s**). This result also indicates that the amide substituent is compatible for the additional amidation.

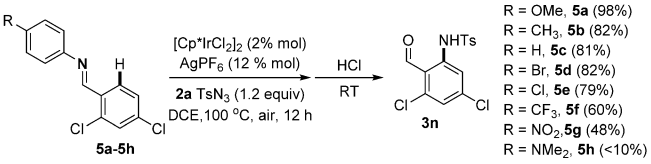
We further examined the scope of organic azides (Table 1). A variety of functional groups, such as methoxy (**4a**), chloro (**4c**), fluoro (**4d**), acetyl (**4e**), trifluoromethyl (**4f**), nitro (**4g**) and bromo (**4h**) moieties, were compatible. Probably owing to steric effects, the 2-Br substituted substrate **4i** only gave a modest yield at a higher temperature with a higher catalyst loading. At this stage, acyl azides, phosphoryl azides and aryl azides were not applicable (see the Supporting Information).

Moreover, the directing ability of imines with different substituents of aryl group was investigated and the results are shown in Scheme 2. Probably due to the competitive coordination with the iridium catalyst center, NMe_2 substituted imine gave a very poor yield. Imines bearing other substituents gave good results while showing an obvious electronic effect.

Table 1. Iridium-catalyzed sp^2 amidation of aldehydes or imines **1** with organic azides **2**.[a]



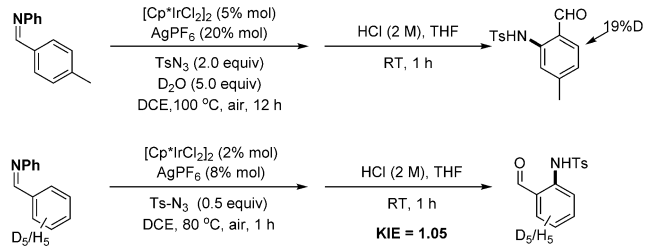
[a] Conditions: yields based on method B are shown outside of parentheses; yields based on method A are shown in parentheses. PMP = 4-methoxylphenyl. [b] $[Cp^*IrCl_2]_2$ (4 mol%) and $AgPF_6$ (24 mol%). [c] $[Cp^*IrCl_2]_2$ (5 mol%), $AgPF_6$ (20 mol%) and TsN_3 (2.0 equiv). [d] 120 °C. [e] $[Cp^*IrCl_2]_2$ (5 mol%) and $AgPF_6$ (20 mol%).



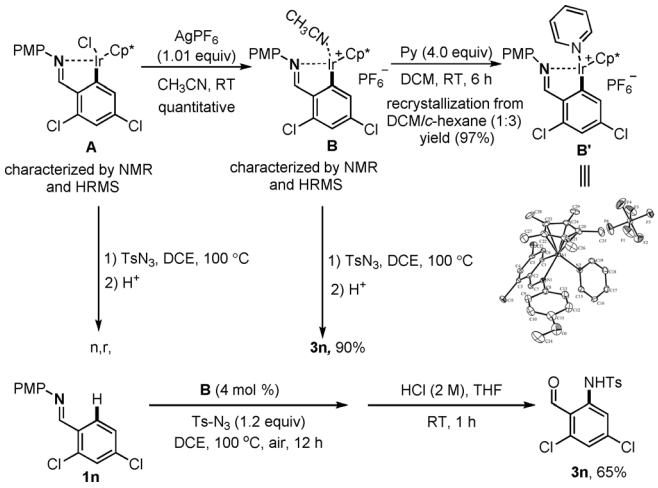
Scheme 2. Comparison of the directing ability of imines with different substituents.

To obtain mechanistic insights into this amidation, a series of experiments were conducted.[14] First, a remarkable H/D exchange of 19% in the product was found upon addition of D_2O, thereby implying C–H activation was reversible under this condition. Further, an intermolecular kinetic isotope effect (KIE) of $k_H/k_D = 1.05$, indicates that the C–H cleavage is not involved in the turnover-limiting step of the catalytic cycle (Scheme 3). We further synthesized the iridacycle **A** and cationic species **B** according to reported methods.[15] **B** was fully characterized by ^1H NMR spectroscopy and ESI-HRMS. To further confirm the structure of **B**, the complex **B′** was prepared through ligand exchange with pyridine from **B**. The structure was confirmed by its single-crystal X-ray diffraction. The successful conversion of iridacycle **B** to **3n** indicated the crucial role of $AgPF_6$ to gener-

ate activated species since neutral complex **A** completely failed. The iridacycle **B** also successfully catalyzed the C–H amidation albeit at a lower efficiency (Scheme 4). Compared to standard condition, lower efficiency might imply that **B** was probably the resting state of catalyst.



Scheme 3. Deuterium-labeling experiments.



Scheme 4. Experimental analysis of iridacycles. PMP = 4-methoxyphenyl.

To understand the kinetic behavior of the reactants and catalyst in this catalytic cycle, the kinetic characterization of this amidation was then surveyed. To simplify the transformation, the reaction was carried out with imine **1n** and azide **2a** in the presence of cationic iridacycle **B** as catalyst (see the Supporting Information). A plot of k_{obs} versus imine **1n** clearly showed an inverse first-order dependence (Figure 1a), however, the plot of k_{obs} versus azide **2a** (Figure 1b) and catalyst **B** (Figure 1c) clearly showed a first-order dependence. These results suggest that the formation of a C–N bond was probably involved in the rate-limiting step.[16]

Since most sulfonyl azide and aryl amines showed credible while diverse reactivity (Table 1 and Scheme 2), we further conducted the Hammett plots to support our conclusion. The effect of different substituents of arenesulfonyl azides on the reactivity of amidation was investigated. The initial competitive experiments of different electronic arenesulfonyl azides indicated that the effect on the reactivity of the substituent followed the sequence: OMe > H > CF_3 (Scheme 5).

Based on these results, the relative rates of imines and arenesulfonyl azides bearing different electronic substituents (R = OMe, CH_3, H, Cl, CF_3, NO_2) were tested and Hammett plots were prepared (Figure 2a and b). Both ρ values of −0.640 and −1.396 were obtained. These results clearly demonstrate that electron-donating substituents at the *para*-position of the imines and arenesulfonyl azides had an accelerating effect on the rate of reaction, which probably arises from the better coordinating ability toward the Ir center.

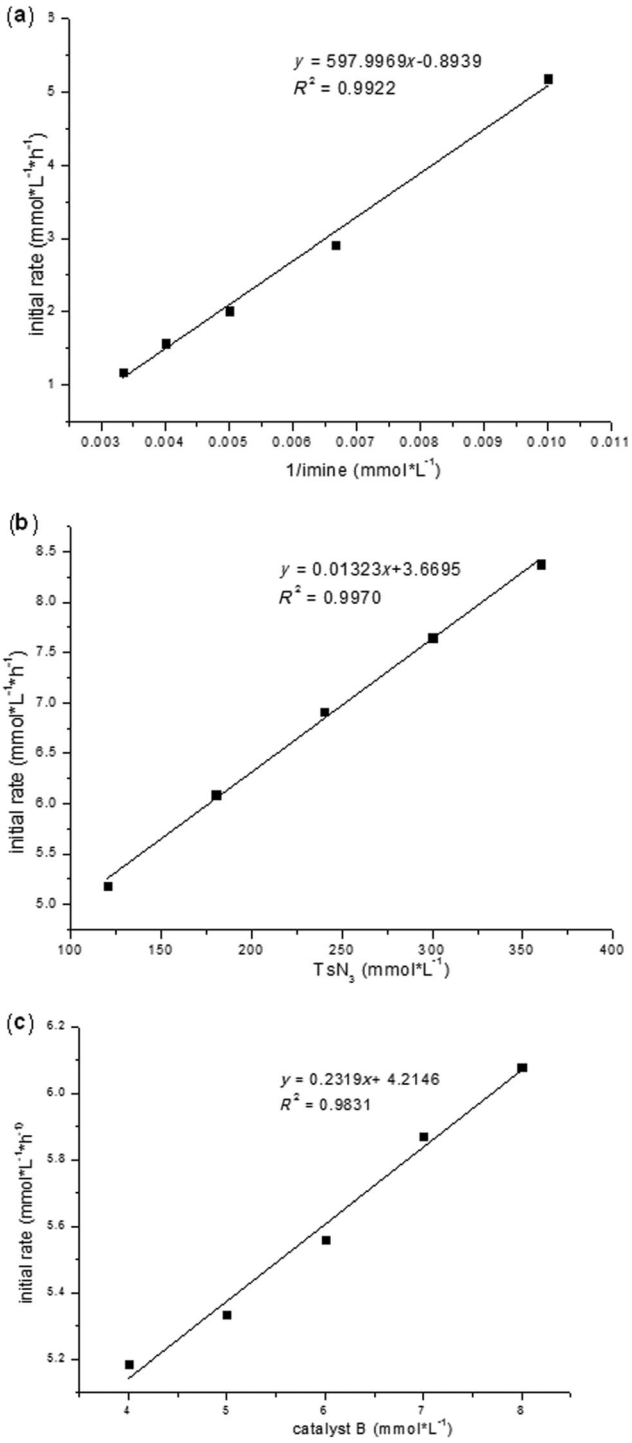
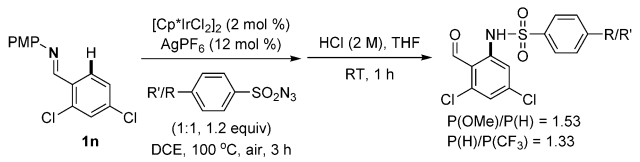


Figure 1. a) Plot of initial rate versus **1**/imine **1n**. b) Plot of initial rate versus TsN_3 **2a**. c) Plot of initial rate versus catalyst **B**.



Scheme 5. Intermolecular competitive experiment of different arenesulfonyl azides.

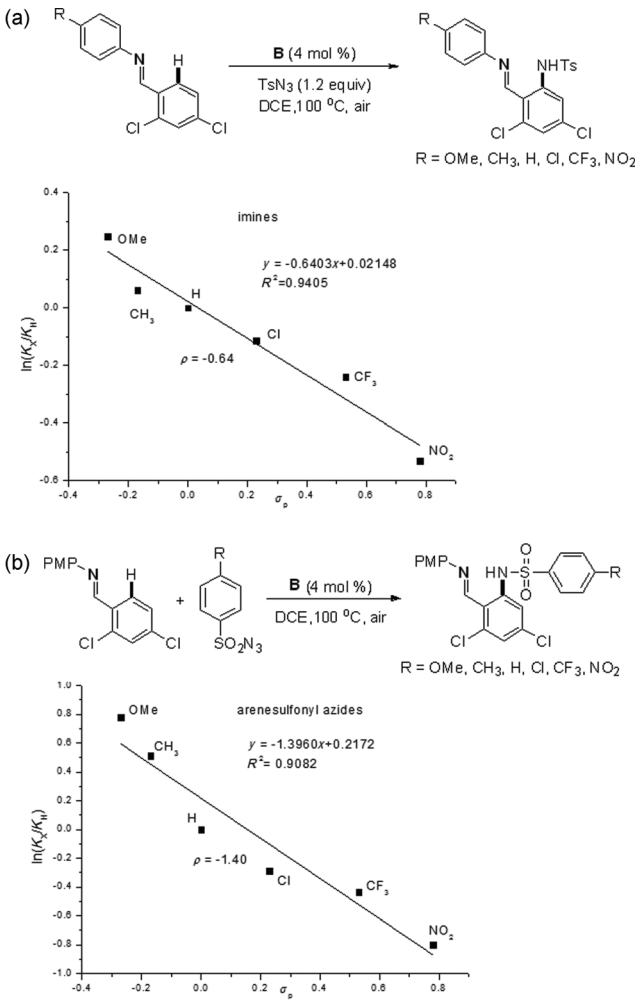
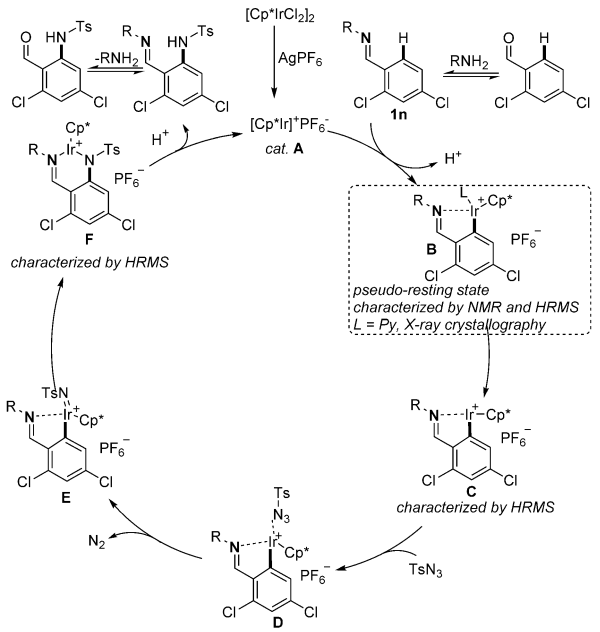


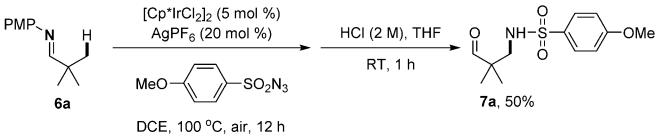
Figure 2. a) Hammett plot of different imines. b) Hammett plot of different arenesulfonyl azides.

Based on the results and previous reports,[10–13,16c] the mechanism is proposed in Scheme 6. Initially, an active cationic Cp^*Ir^+ species from $[Cp^*IrCl_2]_2$ is produced with $AgPF_6$, which facilitates C–H activation to generate the five-membered iridacycle **C**. The coordination of **C** with organic azide leads to **D**. Subsequent extrusion of one molecular N_2 generates **E**. Insertion of an amido moiety to **E** generates the six-membered iridacyclic species **F**, followed by protonation to deliver the amidated product and to regenerate the catalyst to facilitate the catalytic cycle. Notably, **C** was a possible resting state, which was characterized by ESI-HRMS. Intermediate **B** was one synthetic pseudo-resting state stabilized by the ligand. Fortunately, intermediate **F** was also confirmed by HRMS.



Scheme 6. Proposed mechanism for iridium-catalyzed amidation of imine **1n**.

Compared to intermolecular sp^2 C–H amidation, intermolecular amidation at unreactive sp^3 C–H bonds still remains a great challenges.[17] Moreover, catalytic β-functionalization of aliphatic aldehyde or ketone directed by imines is far behind.[6] Encouraged by the efficient sp^2 C–N formation, we intended to expand such an amidation to the sp^3 C–H bond. However, we found that the frequently used TsN_3 shows a very low efficiency. According to the Hammett plot, electron-donating arenesulfonyl azide should be promising. Indeed, the β-amidation of aliphatic aldehydes was achieved, albeit in a moderate yield at this stage (Scheme 7). Further optimization of this synthetic methodology is underway.



Scheme 7. Iridium-catalyzed sp^3 C–H amidation of imine with azide.

Conclusions

In conclusion, we demonstrate a successful example of Ir-catalyzed sp^2 C–H amidation of aldehydes with amine as stoichiometric and catalytic directing group. This chemistry showed broad functional group tolerance. Cycloiridation complexes as key intermediates were characterized by X-ray crystallography and other analytical methods. Kinetic study of the reactants and catalyst in a catalytic cycle were also conducted and led to the conclusion that the formation of the C–N bond was involved in the turnover-limiting step through an inner sphere pathway. Hammett plot of both imines and arenesulfonyl

azides provided further evidence to support the catalytic cycle. Moreover, Ir-catalyzed sp^3 C–H amidation directed by imine was developed based on the understanding of the mechanism. Further efforts to expand this chemistry are under way.

Experimental Section

General procedure for iridium-catalyzed sp^2 amidation of imine 1a

To a 50 mL reaction tube (sealed tube), $[CpIrCl_2]_2$ (3.2 mg, 0.004 mmol) and the imine **1a** (58.0 mg, 0.2 mmol) were added under air atmosphere. $AgPF_6$ (6.0 mg, 0.024 mmol) was added in a glovebox. TsN_3 (42 μL, 0.24 mmol) was added and DCE (1,2-dichloorethane, 2.0 mL) was injected into the system. The tube was sealed and connected to a Wattecs parallel reactor at 100 °C for 12 h. After cooling to room temperature, the solution was removed to a 50 mL flask with 10 mL of THF, 5 mL of hydrochloric acid (2 M) was added, the mixture was stirred at RT for 1 h, and extracted with DCM (3×15 mL). The combined organic phase was dried over anhydrous Na_2SO_4, concentrated and crude product was purified by flash chromatography on silica gel with petroleum ether/EtOAc (10:1 to 5:1) as an eluent to give the product (65.2 mg, 92%).

General procedure for iridium-trifluomethylaniline catalyzed sp^2 amidation of 2-bromobenzaldehyde

To a 50 mL reaction tube (sealed tube), $[CpIrCl_2]_2$ (3.2 mg, 0.004 mmol) and 2-bromobenzaldehyde (37.0 mg, 0.2 mmol) were added under air atmosphere. $AgPF_6$ (6.0 mg, 0.024 mmol) was added in a glovebox. Then TsN_3 (70 μL, 0.40 mmol), 3-trifluomethylaniline (10 μL, 0.08 mmol) were added and DCE (1,2-dichloroethane, 2.0 mL) was injected into the system. The tube was sealed and connected to a Wattecs parallel reactor at 100 °C for 24 h. After cooling to room temperature, the solution was removed to a 50 mL flask with 10 mL of THF, 5 mL of hydrochloric acid (2 M) was added, the mixture was stirred at RT for 3 h, and extracted with DCM (3×15 mL). The combined organic phase was dried over anhydrous Na_2SO_4, concentrated and crude product was purified by flash chromatography on silica gel with petroleum ether/EtOAc (10:1 to 5:1) as an eluent to give the product (59.5 mg, 84%).

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Keywords: aldehydes · C–H amidation · imines · iridium · transient directing group

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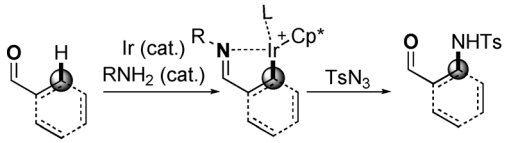
Ir-Catalyzed C–H Amidation of Aldehydes with Stoichiometric/Catalytic Directing Group



dual catalysis
high functional group tolerance
kinetic and ESI-MS study
Hammett plot study
sp^3 C-H amidation

Cat power: Ir-catalyzed C–H amidation of aldehydes with various anilines as stoichiometric or catalytic directing groups was accomplished (see scheme). A wide range of substrates were selectively amidated in good to excellent yields with broad functional group tolerance. The iridacycle complexes were isolated, characterized, and proved as key intermediates. Kinetic studies and Hammett plots provided detailed understandings of this amidation.