Communication

Modular Tuning of Electrophilic Reactivity of Iridium Nitrenoids for the Intermolecular Selective #-Amidation of #-Keto Esters

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Modular Tuning of Electrophilic Reactivity of Iridium Nitrenoids for the Intermolecular Selective α-Amidation of β-Keto Esters

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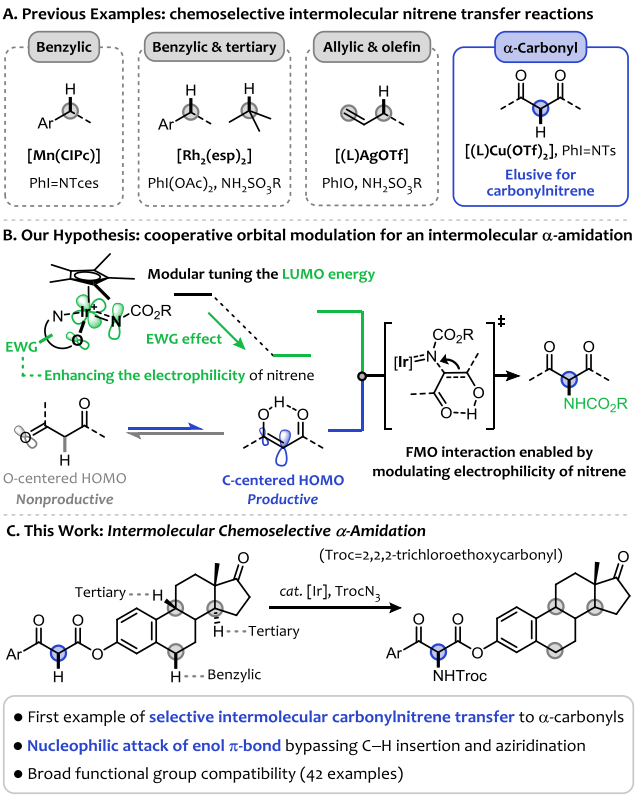
Supporting Information Placeholder

ABSTRACT: We report herein an Ir-catalyzed intermolecular amino group transfer to β-keto esters (amides) to access α-aminocarbonyl products with excellent chemoselectivity. The key strategy was to engineer electrophilicity of the putative Ir-nitrenoids by tuning electronic property of the κ^2-*N,O* chelating ligands, thus facilitating nucleophilic addition of enol π-bonds of 1,3-dicarbonyl substrates.

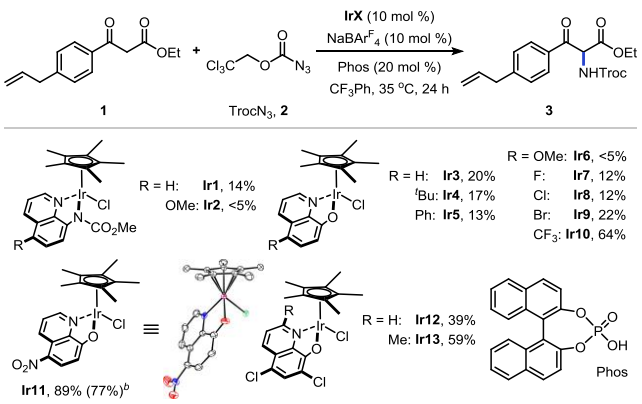
The α-amination of carbonyl compounds has received great interest in synthetic and medicinal chemistry as a straightforward route to versatile building units widely present in natural products and pharmaceuticals.[1] Since the α-carbonyl carbon and amine reactants are electronically mismatched,[2] a polarity reversal of reaction components is required to enable a C–N bond formation at this α-position.[3,4] In this context, while electrophilic amination has been well-established,[5] the currently available α-amination relies on the use of pre-generated enolates, enamines, or β-keto carbonyls bearing activated methylene sites to react with contrived *N*-electrophiles such as azodicarboxylates, nitroso reactants, or sulfonyliminoiodinane.[6–8] Meanwhile, a direct amino group transfer to the α-position of carbonyls via metal-nitrenoid intermediacy can also be considered as an attractive alternative.[9] In recent advances on the nitrene transfer reactions,[10] several elegant examples of sulfonylamination were revealed to showcase notable selectivity toward a specific site among benzylic, tertiary or allylic C–H bonds by designing a new catalyst system or tuning the reaction parameters (Scheme 1A). For instance, White explored benzylic C–H amidation by virtue of electron-deficient Mn-porphyrin catalyst.[11] Du Bois achieved a selective amidation at the tertiary or benzylic C–H bonds by the use of $Rh_2(esp)_2$ catalyst.[12] Schomaker elegantly showcased a ligand-controlled divergent selectivity in Ag catalysis, leading to allylic amidation or aziridination.[13] Despite these notable advances enabling selective amination at the electron-rich C–H bonds, nitrene transfer at the α-carbonyl site remains less explored.[14] A rare example of an intermolecular sulfonylamidation at the α-carbonyl site was revealed by Chan and Ohshima independently, wherein stepwise pathway was proposed to involve a Cu-nitrenoid radical species to form a transient aziridine intermediate.[15] However, this type of open-shell catalysis is known to often hamper a selective amidation of multifunctional carbonyl substrates.[9,16]

Continuing our efforts on utilizing the reactivity of metal-nitrenoids toward challenging C–N bond-forming processes,[17] we envisioned to achieve selective α-amidation of 1,3-dicarbonyl compounds via an intermolecular carbonylnitrene transfer by modulating electrophilicity of the key intermediate. To this end, we hypothesized that LUMO energy of the presupposed Cp*Ir-nitrenoid can be tuned to enhance its electrophilicity through the bidentate chelating ligand (Scheme 1B).[18] In particular, when β-keto esters (amides) are of interest, we envisaged that HOMO located at the C=C π-bond of an enol tautomer would efficiently interact with the engineered LUMO of metal-nitrenoid to facilitate an intermolecular C–N bond formation. This closed-shell platform was projected to offer distinctive chemoselectivity toward the α-carbonyl amidation even in the presence of competing reactive sites (Scheme 1C). Herein, we describe a mechanistic approach to access α-amino-1,3-dicarbonyl products.

Scheme 1. Selective Intermolecular Nitrene Transfer Reactions



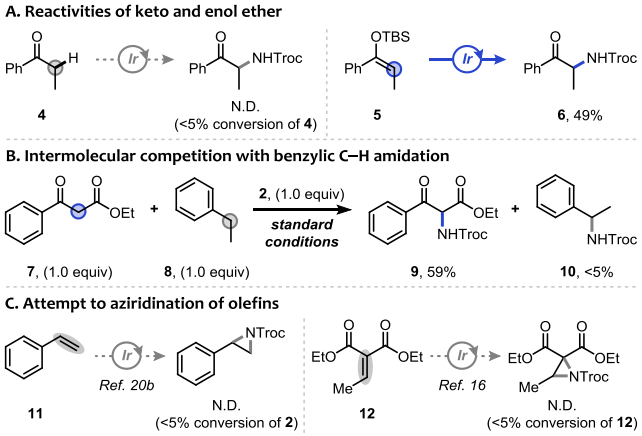
Scheme 2. Catalyst Evaluation for Intermolecular α-Amidation[a]



[a]**1** (0.05 mmol), **2** (0.15 mmol), **Ir** catalysts (10 mol %), $NaBAr^F_4$ (10 mol %), and Phos (20 mol %) in CF_3Ph (0.14 M) at 35 °C for 24 h. ^1H NMR yields are indicated. [b]Isolated yield in parenthesis.

We commenced our study with an intermolecular model reaction by examining a range of tailored iridium catalysts (Scheme 2). β-Keto ester **1** was chosen as a test substrate given that it contains potentially competing reactive sites (benzylic, allylic, and olefinic) in addition to the targeted α-carbonyl C–H bond, thus serving as a chemoselectivity probe. The amidation was attempted with 2,2,2-trichloroethoxycarbonyl azide **2** ($TrocN_3$, 3.0 equiv), known as an efficient alkoxycarbonylnitrene precursor.[19,20] A catalytic amount of Brønsted acid additive (e.g., Phos) was found to promote the tautomerization of 1,3-dicarbonyl substrate more significantly (see Table S3 for NMR analysis). A parent iridium catalyst $[Cp^*IrCl_2]_2$ was totally ineffective in the presence of $NaBAr^F_4$ (see Table S1). While a catalyst **Ir1** bearing κ^2-*N,N'*-chelator gave 14% of the α-amidated product **3**, **Ir2** bearing a 5-methoxy substituent, the most optimal catalyst in our previous intramolecular lactam formation,[17c] was totally ineffective.

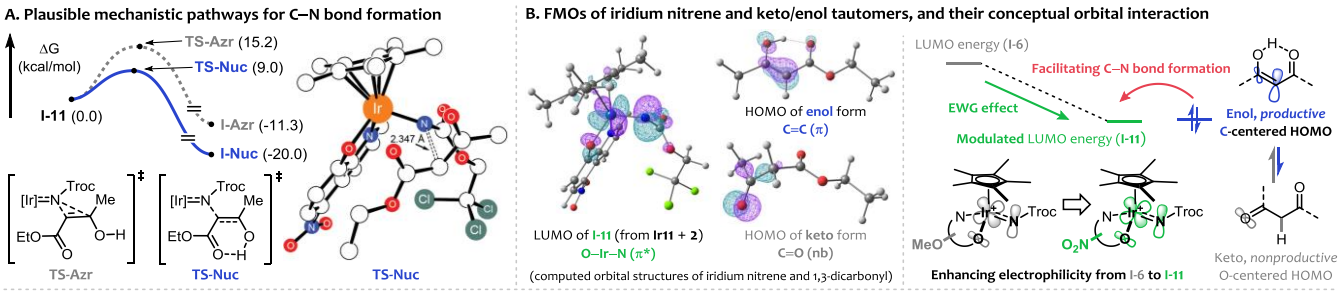
Scheme 3. Tests of Chemoselective Nitrenoid Transfer[a]



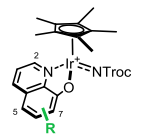
[a]See the Supporting Information for experimental details.

With these initial results in hand, we turned our attention to another catalyst system bearing κ^2-*N,O*-ligands where electronically and/or sterically modulating substituents can be easily introduced.[21] A wide range of Ir complexes bearing 8-hydroxyquinoline derivatives were prepared (**Ir3**–**Ir13**, see SI) and examined for the α-amidation of **1**. The reactivity of these catalysts was found to be dependent on the electronic variation at the κ^2-*N,O*-ligands; complexes bearing electron-withdrawing substituents exhibited higher catalytic activity. Among those, **Ir11** having a 5-nitro moiety was especially effective to afford **3** in high yield. Moderate reactivity was observed with **Ir12** having 5,7-dichloro substituents, which was previously employed in an intramolecular spirocyclization.[17d] Additional 2-methyl substituent improved the amidation performance (**Ir13**).[22] On the other hand, the reaction proceeded with slightly decreased efficiency in the absence of phosphoric acid additive (66% with **Ir11**), and acids other than Phos were less effective (see Table S2). It should be emphasized that the reaction occurred exclusively at the α-carbonyl site while benzylic C–H bond and olefinic double bond were completely intact.

Figure 1. Computational Analysis of the Catalytic System

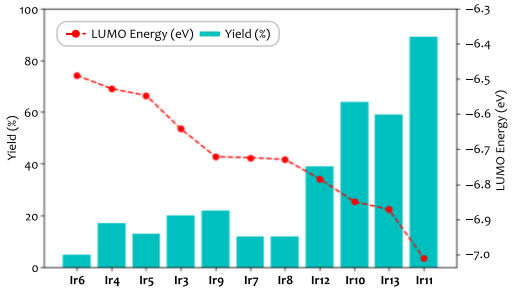


C. Qualitative trend between the amidation yields and LUMO energies for various iridium-nitrenoids



IrX	R	LUMO Energy (eV)	Yield (%)[a]	IrX	R	LUMO Energy (eV)	Yield (%)[a]
Ir6	5-OMe	-6.490	<5	Ir8	5-Cl	-6.729	12
Ir4	5-^{t}Bu	-6.528	17	Ir12	5,7-di-Cl	-6.784	39
Ir5	5-Ph	-6.547	13	Ir10	5-CF_3	-6.849	64
Ir3	5-H	-6.642	20	Ir13	2-Me-5,7-di-Cl	-6.871	59
Ir9	5-Br	-6.721	22	Ir11	5-NO_2	-7.010	89
Ir7	5-F	-6.724	12				

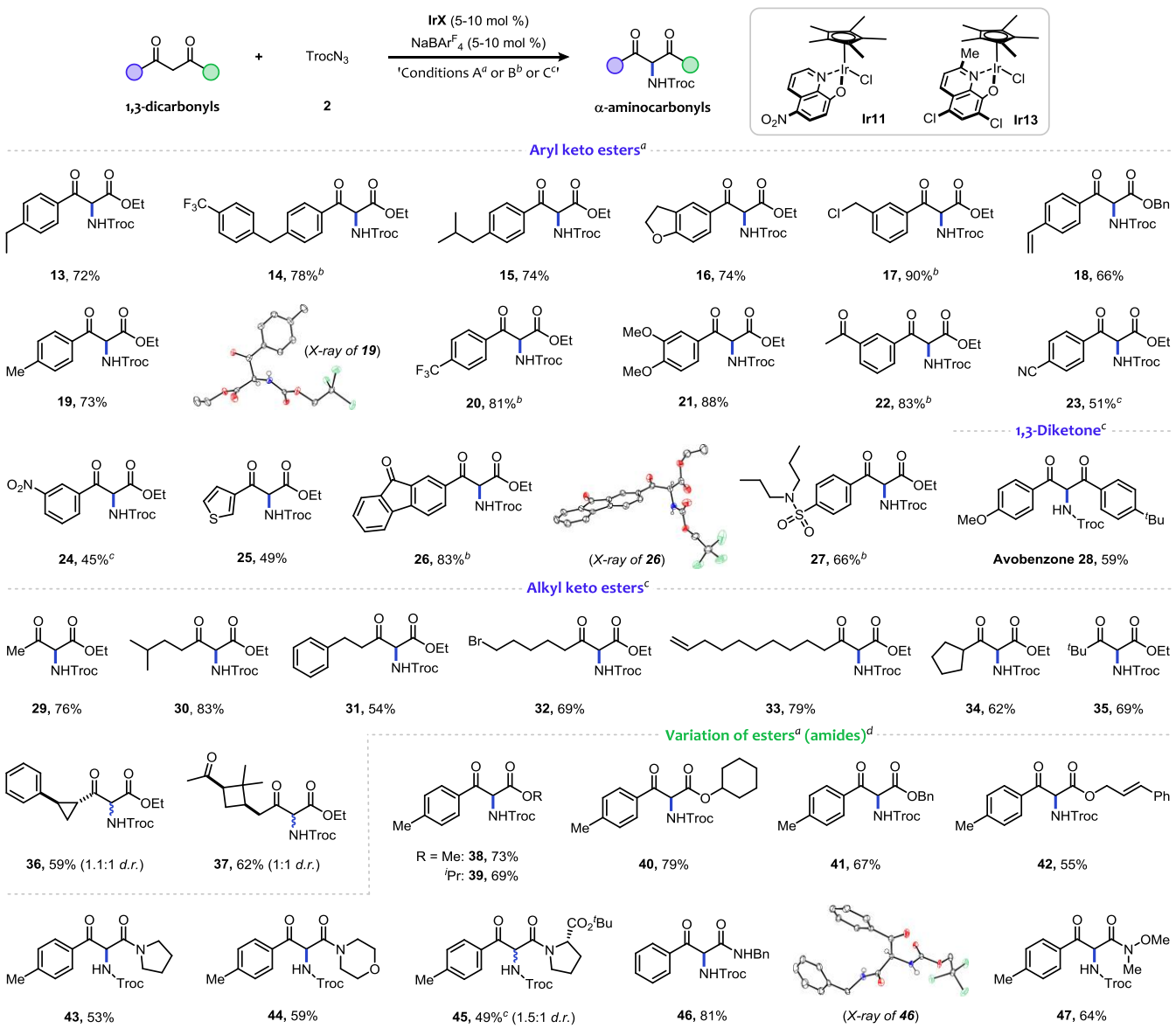
[a]Yield of **3** from α-amidation of **1** (Scheme 2)



To rationalize the observed chemoselectivity, a series of control experiments were conducted. Since 1,3-dicarbonyls equilibrate with their enol tautomers (evidenced by ^{1}H NMR spectroscopy and X-ray crystallographic analysis; see the SI), we first examined respective amidation reactivity of keto and enol ether compounds. Whereas propiophenone (**4**) was unreactive under the optimal conditions, its silyl enol ether **5** underwent the amidation to give **6** (Scheme 3A). This result suggests that the reaction proceeds via an electrophilic interaction of the putative iridium nitrene with enol double bond. Along with this line, an amidation occurred almost exclusively at β-keto ester **7** in the presence of ethylbenzene (**8**) (Scheme 3B).[23] In addition, the current protocol was not effective in rendering aziridination when isolated olefins such as styrene (**11**) and α,β-unsaturated carbonyl **12** were subjected to the amidation conditions (Scheme 3C). This outcome is in stark contrast to the previous reports on the amino group transfer to olefins leading to aziridines.[20b,24–26]

To obtain further mechanistic information, we interrogated the reaction system with density functional theory (DFT) studies. As illustrated in Figure 1A, the nucleophilic attack of enol π-bond to the putative Ir-nitrenoid intermediate was calculated to be kinetically feasible with a barrier of 9.0 kcal/mol traversing the transition state **TS-Nuc**. In comparison, an alternative pathway involving an aziridine intermediate requires higher barrier (**TS-Azr**, $\Delta G^{\ddagger}$ = 15.2 kcal/mol, see Figure S9).

Scheme 4. Substrate Scope in the α-Amidation of 1,3-Dicarbonyl Compounds



^{a}Conditions A: **Ir11** (5-10 mol %), NaBAr$^F_4$ (5-10 mol %), and Phos (20 mol %) in CF_3Ph at 35 °C for 24-72 h. ^{b}Conditions B: **Ir11** (5-10 mol %), NaBAr$^F_4$ (5-10 mol %), HOAc (20 mol %), and Zn(OTf)$_2$ (20 mol %) in CF_3Ph at 30 °C for 24 h. ^{c}Conditions C: **Ir13** (10 mol %), NaBAr$^F_4$ (10 mol %), and Zn(OTf)$_2$ (5-15 mol %) in CF_3Ph at 10~30 °C for 24-72 h. ^{d}**Ir13** (5-10 mol %), NaBAr$^F_4$ (5-10 mol %), and HOAc (20 mol %) in CF_3Ph at 35~50 °C for 24-72 h. Diastereomeric ratio was determined by ^{1}H NMR spectroscopy.

We next conducted frontier molecular orbital (FMO) analysis of two key components, β-keto ester and Ir-nitrenoid, to rationale the origin of the current α-amidation reactivity (Figure 1B, left). In β-keto ester, while HOMO of the keto form is located at the ketone moiety, that of enol tautomer resides at the C=C bond, thus endowing the enol to serve as a π-nucleophile. Next, FMO analysis on the iridium-nitrenoid intermediate **I-11** (from the reaction of **Ir11** and **2**) revealed that the *p*-orbital of the oxygen atom of the κ^2-*N,O* ligand effectively participates in constructing the three-centered, four-electron bonding system.[18,27] For all iridium-nitrenoids examined, these O–Ir–N(π^*) orbitals were found to be LUMOs, thus receiving a direct influence from the electronic perturbation of the 8-hydroxyquinoline ligand (see Figure S8).

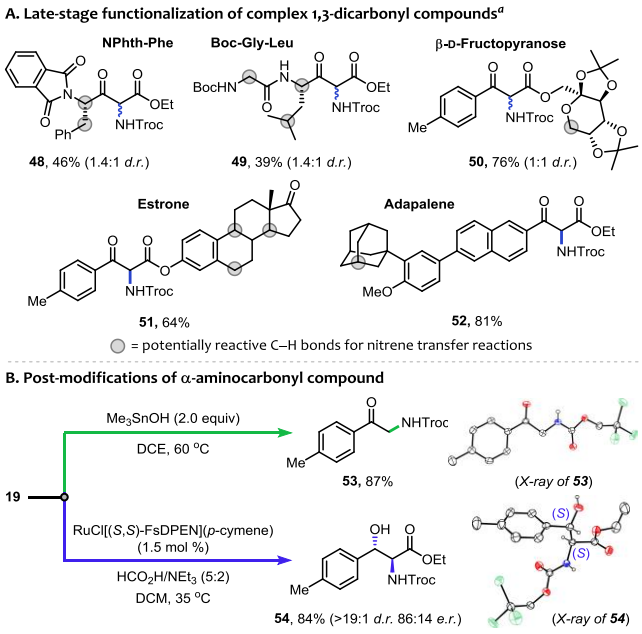
Our observation that electron-withdrawing substituents at the κ^2-*N,O* ligand led to higher catalytic activity can be rationalized by assuming that thus lowering LUMO energy enhances the electrophilicity of the Ir-nitrenoid to react with enolizable β-keto esters (Figure 1B, right). This FMO interaction between C-centered enol π-orbital and LUMO of Ir-nitrenoid is believed to be the key for the present intermolecular C–N bond formation. Indeed, as illustrated in Figure 1C, the observed amidation yields (cyan bar) correlates qualitatively with the LUMO level of the presumed iridium-nitrenoids (red dash). Since the computational studies suggest that the generation of iridium-nitrenoid via N_2 extrusion is kinetically competent, we premised that subsequent interaction of iridium-nitrenoid with enol would be the major factor to affect the overall amidation efficiency (see Figure S9). It is worth mentioning that while a strategy to control FMO was previously utilized to facilitate cycloaddition reactions by Lewis acids,[28] its application for the nitrenoid transfer has been unexplored to our best knowledge.

Given the above promising chemoselectivity toward the α-carbonyl amidation with theoretical rationale, the generality of our catalyst system was next investigated for various types of 1,3-dicarbonyl compounds by using **Ir11** catalyst (5~10 mol %, Scheme 4). The reaction was carried out at ambient temperature (30~35 °C) in α,α,α-trifluorotoluene solvent (24~72 h), and good to high product yields were obtained in the presence of catalytic amounts of acid additives. First, we evaluated aryl β-keto esters that contain potentially reactive multiple C–H bonds, and the reaction was highly selective for the desired α-carbonyl amidation leaving other C–H bonds at the benzylic (**13**–**17**) and tertiary (**15**) position intact. Significantly, the styrenyl group was tolerated and no aziridine side product was observed (**18**). Phenyl β-keto esters bearing electron-neutral (**19**), withdrawing (**20**) and donating (**21**) substituents smoothly underwent the desired amidation. While the reaction of a substrate bearing an acetyl group was facile (**22**), product yields were slightly decreased by the presence of cyano or nitro substituents (**23**–**24**). β-Keto esters having thienyl (**25**) and fluorenonyl (**26**) moieties were also amenable. A substrate derived from biorelevant probenecid was successfully amidated (**27**). In addition, 1,3-diketone was applicable as demonstrated in a reaction of Avobenzone (**28**).

When alkyl β-keto esters were examined, the reaction took place smoothly even at 10 °C by **Ir13** catalyst in the presence of $Zn(OTf)_2$ additive (5~15 mol %).[29] Substrates having primary, secondary, or tertiary alkyl moieties all underwent the desired α-amidation (**29**–**35**). It is noteworthy that bromide and olefinic double bond were compatible with the current conditions (**32**–**33**). Substrates having stereodefined cyclopropyl or cyclobutyl substituent were successfully applied (**36**–**37**). Subsequently, it was observed that an array of esters such as methyl (**38**), isopropyl (**39**), cyclohexyl (**40**), secondary benzyl (**41**) and allyl (**42**) were all applicable. Moreover, β-keto amides derived from pyrrolidine (**43**), morpholine (**44**), and Boc-protected proline (**45**) were smoothly reacted. A substrate containing acidic N–H bond was viable to give **46** in high yield. Amidation of an analogue bearing *N*-methyl-*N*-methoxy group (Weinreb amide) proceeded without difficulty (**47**).

To further see whether the current amidation protocol could be applied to the late-stage functionalization, we tested complex β-keto esters (Scheme 5A). Compounds derived from amino acid (NPhth-Phe) and dipeptide (Boc-Gly-Leu) were selectively amidated at the targeted α-position to give **48** and **49**, respectively. β-Keto esters having ketal-protected β-D-ribofuranose or estrone reacted to afford **50** and **51**, respectively. A substrate derived from Adapalene also underwent the α-amidation to form **52** in 81% yield. Finally, synthetic utility of the obtained product was briefly examined (Scheme 5B). α-Amino-β-keto ester **19** was readily decarboxylated by Me_3SnOH to furnish α-aminoketone **53**. Asymmetric transfer hydrogenation of **19** took place to provide α-amino-β-hydroxy ester **54** stereoselectively (X-ray structure of a major diastereomer is shown).[30]

Scheme 5. Synthetic Applications



[a]See the Supporting Information for detailed procedures.

In summary, we have presented the first example of an intermolecular α-amidation of 1,3-dicarbonyl compounds using $TrocN_3$ as the amino source under mild conditions. Electrophilic nature of the key iridium-nitrenoid intermediate was modulated by the electronic tuning of the κ^2-*N,O* ligand, thus enabling a concerted C–N bond formation by nucleophilic addition of enol π-bonds. It is anticipated that the current mechanistic approach to enhance the reaction efficiency as well as chemoselectivity in a nitrene transfer process would provide a platform for the future development of amination reactions of high synthetic utility.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures; characterization data; spectra for all new compounds; crystallographic data; Cartesian coordinates

of all computed structures (PDF)
Crystallographic data for **Ir11**
Crystallographic data for **Ir13**
Crystallographic data for **S3**
Crystallographic data for **19**
Crystallographic data for **26**
Crystallographic data for **46**
Crystallographic data for **53**
Crystallographic data for **54**

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Notes

The authors declare no competing financial interests.

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