Amidation Reactions

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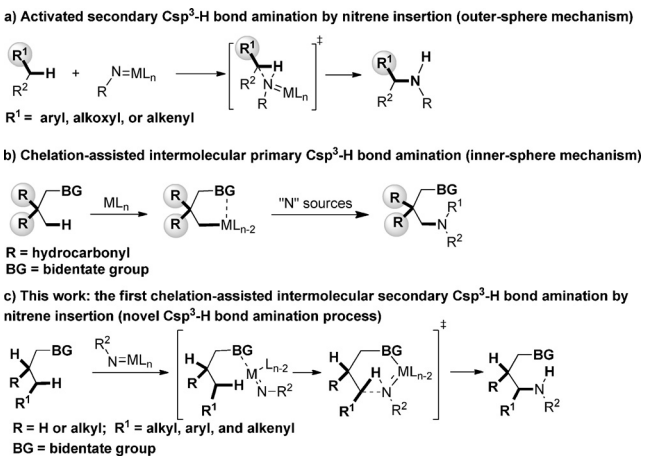
Iridium(III)-Catalyzed Regioselective Intermolecular Unactivated Secondary Csp^3–H Bond Amidation

Xinsheng Xiao, Cheng Hou, Zhenhui Zhang, Zhuofeng Ke, Jianyong Lan, Huanfeng Jiang, and Wei Zeng**

Abstract: *For the first time, a highly regioselective intermolecular sulfonylamidation unactivated secondary Csp^3–H bond has been achieved using Ir^{III} catalysts. The introduced N,N'-bichelating ligand plays a crucial role in enabling iridium–nitrene insertion into a secondary Csp^3–H bond via an outer-sphere pathway. Mechanistic studies and density functional theory (DFT) calculations demonstrated that a two-electron concerted nitrene insertion was involved in this Csp^3–H amidation process. This method tolerates a broad range of linear and branched-chain N-alkylamides, and provides efficient access to diverse γ-sulfonamido-substituted aliphatic amines.*

Metal-catalyzed direct amination of unactivated Csp^3–H remains one of the most challenging topics in synthetic chemistry, owing to the low reactivities and high thermodynamic stabilities of such bonds.[1] Over the past decades, various amination strategies have been extensively investigated for atom-economic construction of C–N bonds.[2] However, the intermolecular amination between nitrogen sources and unactivated alkyl Csp^3–H bonds has yet to be well-demonstrated. In this context, although transition-metal-mediated nitrene insertion into C–H via an outer-sphere mechanism is one of the most general approaches for secondary Csp^3–H amination, the reactive sites are basically limited to the activated Csp^3–H bonds (Scheme 1 a).[3] Consequently, developing intermolecular amination methods for the unactivated secondary Csp^3–H bond of alkanes with nitrogen sources in high regioselectivity, remains highly challenging.

Recently, research into monodentate ligand-assisted intermolecular primary Csp^3–H amination has undergone a breakthrough via the inner-sphere mechanism.[4] For example, Chang et al. reported that a ketoxime-directed catalytic system could efficiently enable methyl Csp^3–H amidation.[4d] Meanwhile, a number of research groups took advantage of the directing character of bidentate ligands to enable metal-catalyzed intramolecular Csp^3–H amination when assembling heterocycles.[5] In comparison, an intermolecular version of this process, involving unactivated secondary alkyl Csp^3–H amination, has not been reported. To date, Ge et al. and Qin et al. have demonstrated that bichelate-ligand-directed intermolecular Csp^3–H amination of alkanes could occur by a Csp^3–H activation process,[6] but these two transformations were still only limited to primary Csp^3–H bonds of alkanes by the Thorpe–Ingold effect (Scheme 1 b). Therefore, a general intermolecular amination of unactivated secondary Csp^3–H bonds is in high demand. Given that transition-metal-catalyzed nitrene insertion into unactivated Csp^3–H bonds generally suffers from poor regioselectivity,[3d,i,7] and bidentate-chelation catalytic tactics could regioselectively enable secondary Csp^3–H arylation,[8] We postulated that a bidentate-assisted unactivated Csp^3–H amination involving an outer-sphere mechanism could surmount the above-mentioned limits. Herein, we report invention of an Ir^{III}-catalyzed site-selective intermolecular nitrene insertion of unactivated secondary Csp^3–H bonds with the aid of bidentate chelation. Moreover, the versatile method could allow for secondary, even tertiary, Csp^3–H bond amination of a broad range of linear or branched-chain alkanes (Scheme 1 c).



Scheme 1. Transition-metal-catalyzed intermolecular Csp^3–H bond amination.

To achieve this reaction, *N,N'*-bidentate chelating sites containing *N*-butylpyridine-2-carboxylic acid amide (**1a**) was initially used as a test substrate for screening of the various nitrogen sources (**A**–**D**) by employing $[Cp^*IrCl_2]_2$ (5 mol%) as a catalyst in combination with $AgSbF_6$ (20 mol%) in $CHCl_3$ under Ar atmosphere at 60 °C for 24 h (Table 1,

[*] Dr. X. Xiao, Z. Zhang, J. Lan, Prof. H. Jiang, Prof. W. Zeng
Key Laboratory of Functional Molecular Engineering of Guangdong Province, School of Chemistry and Chemical Engineering
South China University of Technology
Guangzhou 510641 (China)
E-mail: zengwei@scut.edu.cn
Dr. C. Hou, Prof. Z. Ke
School of Materials Science and Engineering, Sun Yat-sen University
Guangzhou 510275 (China)
E-mail: kezhf3@mail.sysu.edu.cn

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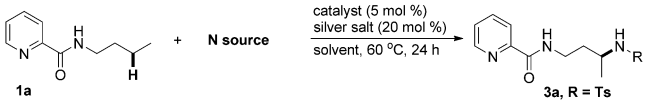
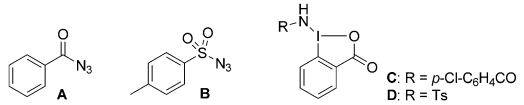
Table 1: Reaction development.[a]



Entry	Catalyst	N source	Ag salts	Solvent	Yield [%][b]
1	$[Cp^*IrCl_2]_2$	A	$AgSbF_6$	$CHCl_3$	0
2	$[Cp^*IrCl_2]_2$	B	$AgSbF_6$	$CHCl_3$	13
3	$[Cp^*IrCl_2]_2$	C	$AgSbF_6$	$CHCl_3$	0
4	$[Cp^*IrCl_2]_2$	D	$AgSbF_6$	$CHCl_3$	0
5	$Ir_2(COD)_2Cl_2$	B	$AgSbF_6$	$CHCl_3$	0
6	$[Cp^*RhCl_2]_2$	B	$AgSbF_6$	$CHCl_3$	0
7	$Rh_2(OAc)_4$	B	$AgSbF_6$	$CHCl_3$	0
8	$RhCl_3$	B	$AgSbF_6$	$CHCl_3$	0
9	$Pd(OAc)_2$	B	$AgSbF_6$	$CHCl_3$	0
10	$[Cp^*IrCl_2]_2$	B	$AgClO_4$	$CHCl_3$	9
11	$[Cp^*IrCl_2]_2$	B	$AgNTf_2$	$CHCl_3$	37
12	$[Cp^*IrCl_2]_2$	B	$AgBF_4$	$CHCl_3$	40
13	$[Cp^*IrCl_2]_2$	B	$AgBF_4$	TCE[c]	68
14	$[Cp^*IrCl_2]_2$	B	$AgBF_4$	acetone	22
15	$[Cp^*IrCl_2]_2$	B	$AgBF_4$	TFE[d]	12
16	$[Cp^*IrCl_2]_2$	B	$AgBF_4$	toluene	33
17	$[Cp^*IrCl_2]_2$	B	$AgBF_4$	DCE	74
18	$[Cp^*IrCl_2]_2$	B	$AgBF_4$	DCE	72[e]
19	$[Cp^*IrCl_2]_2$	B	$AgBF_4$	DCE	62[f]
20	$[Cp^*IrCl_2]_2$	B	$AgBF_4$	DCE	38[g]
21	$[Cp^*IrCl_2]_2$	B	$AgBF_4$	DCE	72[h]
22	$[Cp^*IrCl_2]_2$	B	$AgBF_4$	DCE	67[i]

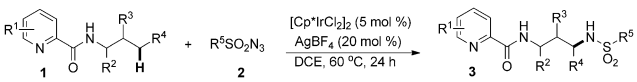


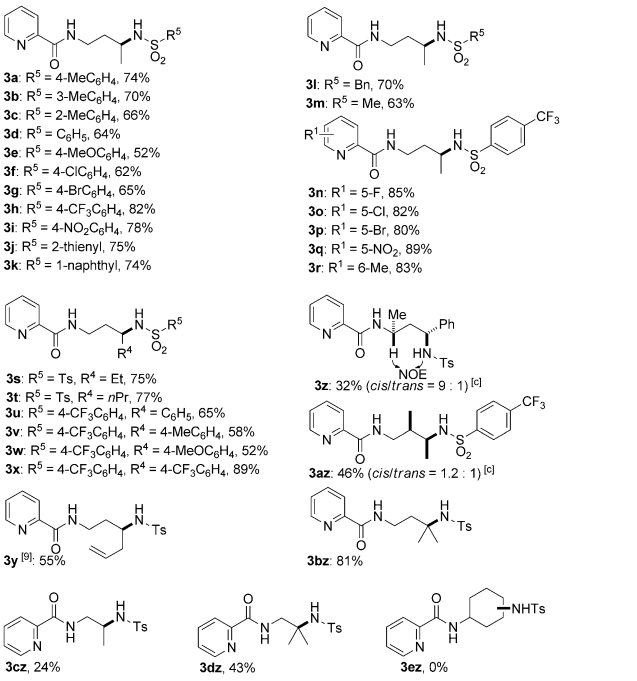
[a] Unless otherwise noted, all the reactions were carried out using amide (**1a**; 0.10 mmol) and nitrogen sources (**2a**; 0.20 mmol) with catalysts (5 mol%) in the presence of silver salts (20 mol%) in solvent (1.0 mL) at 60°C for 24 h under Ar in a sealed reaction tube, followed by flash chromatography on SiO_2. [b] Yield of isolated products. [c] 1,1,2,2-tetrachloroethane (TCE). [d] 2,2,2-trifluoroethanol (TFE). [e] Ag_2O (10 mol%) used. [f] AgOAc (10 mol%) added. [g] Reaction temperature 50°C. [h] Reaction temperature 80°C. [i] **1a** (1.0 mmol) and tosyl azide (**B**; 2.0 mmol) used.

entries 1–4). To our delight, we soon found tosyl azide (**B**) could produce the desired Csp^3–H amidation product **3a** in 13% yield, in which the intermolecular sulfonylamidation had occurred highly regioselectively at the γ-secondary Csp^3–H bond of alkyl amine moiety (Table 1, entry 2). Notably, Ir^I, Rh^{II}, or Pd^{II} catalysts did not furnish the corresponding Csp^3–H sulfonylamidation product **3a** in the presence of tosyl azide (**B**) as a nitrogen source (Table 1, entries 5–9). Subsequently, we continued to evaluate various silver salts to further improve the reaction conversion of **1a** (Table 1, entries 10–12). Among the investigated silver additives, $AgBF_4$ was identified as the optimal additive that could significantly improve the reaction yield from 13% to 40% (Table 1; compare entries 2, 10, and 11, with 12). Additionally, solvent screening demonstrated that 1,2-dichloroethane (DCE) is the most suitable solvent for this reaction, and could moderately increase the yield of **3a** to 74% (Table 1; compare entries 12–16 with 17). It should be noted that employing combinations of silver additives (such as $AgBF_4$/Ag_2O or $AgBF_4$/AgOAc), and lowering or increasing the reaction temperature, led to worse results (Table 1; entries 18–21 vs. 17). Finally, when a large-scale reaction was performed under the conditions listed in entry 17, we could still obtain a 67% yield of **3a** (Table 1, entry 22).

With this method in hand, the optimal reaction conditions were then applied to various *N*-alkyl-substituted amides (**1**) and sulfonyl azides (**2**), as summarized in Table 2. As expected, the Ir^{III}-catalyzed intermolecular sulfonylamidation of unactivated secondary Csp^3–H bonds of pyridine-2-carboxylic acid butylamide (**1a**) proceeded well with various arylsulfonyl azides and alkylsulfonyl azides at the γ-position of the amidoalkanes. First, we evaluated the substitution effects on the phenyl rings from arylsulfonyl azides. This transformation was compatible with electronically diverse functional groups, and 4-substitution on the phenyl rings with electron-donating groups (methyl, methoxy) and electron-withdrawing groups (including halide, nitro, and trifluoromethyl), afforded good to excellent yields of the desired secondary Csp^3–H sulfonylamidation products **3a**–**3i** (52–82%). Among them, the structure of **3h** was unambiguously assigned by single crystal X-ray crystallographic analysis (Supporting Information). Notably, introducing a methyl group to the *ortho*- or *meta*-position of the phenyl ring still lead to good yields of **3b** and **3c** (70 and 66%, respectively),

Table 2: Substrate scope.[a,b]





[a] All the reactions were carried out using amides (**1**; (0.10 mmol) and sulfonyl azides (**2**; 0.2 mmol) with $[Cp^*IrCl_2]_2$ (5.0 mol%) in the presence of $AgBF_4$ (20 mol%) in DCE (1.0 mL) at 60°C for 24 h under Ar in a sealed reaction tube, followed by flash chromatography on SiO_2. [b] Yield of isolated products. [c] Determined by ^1H NMR spectroscopy (Supporting Information).

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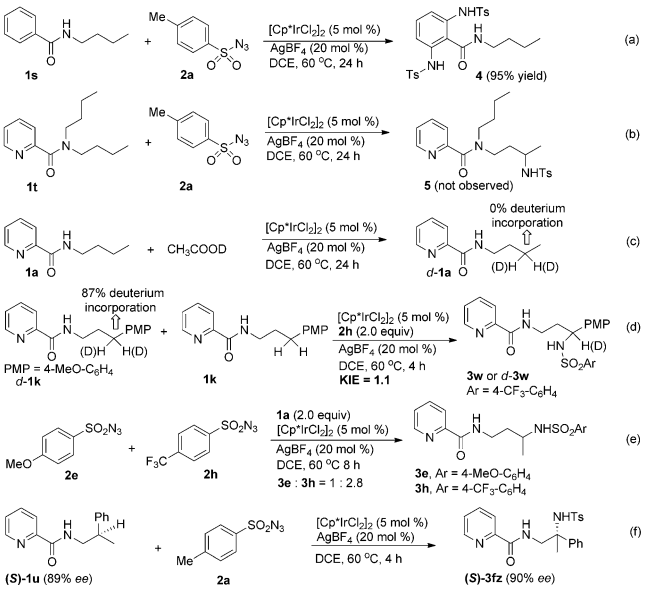
regardless of the steric hindrance. Moreover, heteroarylsulfonyl azides, 1-naphthylsulfonyl azides, and alkylsulfonyl azides were also amenable to this transformation and produced the corresponding sulfonylamidation products **3j**–**3m** in 63–75% yields.

Subsequently, we prepared the 5- and 6-substituted pyridine-2-carboxylic acid butylamides, and found their corresponding secondary Csp^3–H sulfonylamidation efficiencies were still maintained, irrespective of the type of substituents and the substituent positions on the pyridyl rings (**3n**–**3r**). For example, 5-chloropyridine-2-carboxylic acid butylamide and 5-nitropyridine-2-carboxylic acid butylamide furnished the corresponding sulfonylamidation products **3o** and **3q** in 82% and 89% yields, respectively.

Finally, the scope of the present procedure with regard to different types of *N*-amido alkanes has also been established systematically. Compared with the *N*-*n*-butyl-substituted amide (**1a**), the longer straight chain *n*-amyl amine-based amide and *N*-*n*-hexyl amide was amenable to regioselective installation of a secondary C–N bond into the γ-position of the alkylamine moiety in 75% and 77% yields (**3s** and **3t**), respectively. We also observed that the intermolecular secondary Csp^3–H amidation of 3-aryl-propylamine amides proceeded well to give yields of 52–89%, but an electron rich phenyl ring from 3-(4-methoxylphenyl)-propylamine amide made the reaction a little sluggish, possibly because the lower p*K*a of the Csp^3–H bonds benefits the nitrene insertion (compare **3w** with **3x**). We further performed Hammett correlation studies with compounds **3u**–**3x**, which showed a linear free energy relationship ($R = 0.99$); the Hammett constant σ_I and the value ρ_I was found to be $+0.28$ (Supporting Information, Figure S-14). This result is remarkably different to those described for Rh^{II}-catalyzed nitrene insertion into activated Csp^3–H bonds, in which the yields decrease with the electron deficiency of the substituents.[10] To our surprise, the present reaction was also applicable to an alkenyl functional group containing amidoalkane, in which the C=C double bond could be kept intact (**3y**, 55% yield).[11] More importantly, in addition to the linear *N*-alkylamides, the branched-chain *N*-alkylamides were also amenable to the reaction, and furnished the desired γ-sulfonylamido substituted alkanes in 32–81% yields (**3z**, **3az** and **3bz**), in which 1,3-*cis*-**3z** (*cis*/*trans* = 9:1) and 1,2-*cis*-**3az** (*cis*/*trans* = 1.2:1) belong to the major products based on the combined NOE NMR and DFT calculations.[12] Furthermore, the scope of the present procedure with regard to shorter carbon chains substituted with *N*-alkylamide has also been evaluated, and we were pleased to find that the unactivated Csp^3–H bond amidation could also occur at the beta-position on the amidoalkanes in acceptable yields (**3cz** and **3dz**). Unfortunately, *N*-cyclohexylamide was not allowed for this transformation, possibly because of steric hindrance (**3ez**).

Further removal of the directing group and the newly introduced sulfonyl group from the Csp^3–H amidation product **3s** allowed the construction of pentane-1,3-diamine in a one-pot procedure, and the corresponding diamine could be easily cyclized with glyoxylic acid and arylaldehyde to afford good yields of 2-carboxyl- and 2-aryl-substituted hexahydro-pyrimidines (Supporting Information), which are versatile synthetic units for assembling biologically active molecules.[13]

Several control experiments, as well as DFT studies (Supporting Information), were designed to elucidate the plausible reaction mechanism for this Ir^{III}-catalyzed γ-sulfonylamidation of amidoalkanes (Scheme 2). It was found that the treatment of *N*-butyl-benzamide (**1s**) with tosyl azide (**2a**) under our standard conditions only provided the *ortho*-phenyl Csp^2–H bond sulfonylamidation product (**4**) in 95% yield,[14] and no alkyl Csp^3–H bond amidation product was observed [Eq. (a)]. Moreover, the reaction of the amido *N*-blocked pyridine-2-carboxylic acid dibutylamide (**1t**) with **2a** did not produce the corresponding alkyl Csp^3–H bond amidation product **5** [Eq. (b)]. These results clearly demonstrate that the pyridyl group and amide nitrogen played a significant bichelate-directing role in forming the remote secondary Csp^3–N bond.



Scheme 2. Preliminary mechanistic studies.

On the other hand, when the H/D exchange of amide (**1a**) was conducted in a Ir^{III}-CH_3CO_2D system at 60 °C for 24 h in the absence of **2a**, the degree of deuterium incorporation into the alkyl chain of **1a** was 0% [Eq. (c)]. Therefore, the possibility of a bichelate-directed Csp^3–H activation process could be ruled out. DFT study also excluded the C–H activation pathway, which has a high activation free energy of 31.7 kcal mol^{-1} (Supporting Information, Figure S-10). Subsequently, the competitive sulfonamidation of *d*-**1k** and **1k** with tosyl azide did not exhibit a kinetic isotope effect ([Eq. (d)]; $k_H/k_D = 1.1$).[15] Furthermore, a competitive intermolecular Csp^3–H sulfonamidation between tosyl azides differing in electronic effects implied that an electron-poor azide tended to easily form iridium nitrene at a higher rate [Eq. (e)]. Meanwhile, the kinetic experiments also indicated that the concentration of tosyl azide governed the reaction rate of the intermolecular amidation of *N*-alkyl amides with azides (Supporting Information, Table S-7 and S-8). These experiments further suggest that the formation of the metal-

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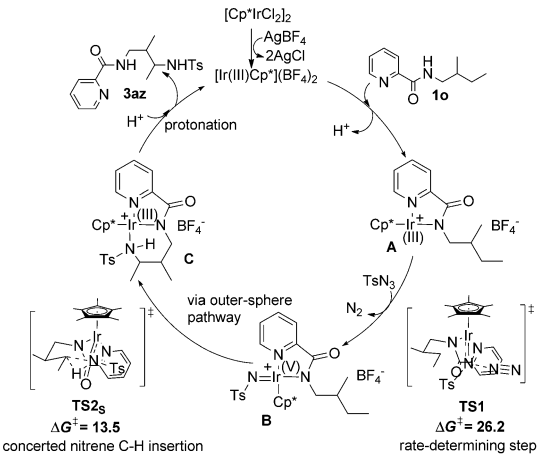
lonitrene complexes, instead of metal nitrene insertion into the alkyl Csp^3–H bond, is involved in the rate-determining step.[16]

This denitrogenation step is suggested by DFT studies to be the rate-determining step of the whole catalytic cycle (Figure 1) with an activation free energy of 26.2 kcal mol^{-1} (**TS1**). Finally, both the singlet concerted nitrene insertion mechanism and the triplet H-abstraction mechanism for the sulfonylamidation step were evaluated by DFT study, which indicates that the sulfonylamidation step is a two-electron concerted singlet nitrene insertion process ($\Delta G^{\neq} = 13.5$ kcal mol^{-1}, $\mathbf{B_S} \rightarrow \mathbf{TS2_S}$). In contrast, the triplet H-abstraction mechanism via radical intermediate is less possible ($\Delta G^{\neq} =$ 24.9 kcal mol^{-1}, $\mathbf{TS2_T}$-**b** relative to $\mathbf{B_S}$). To further demonstrate this possibility, a chiral substrate (*S*)-**1u** (89% *ee*) bearing a stereodefined tertiary center at the beta-position was subjected to standard reaction conditions; we obtained the highly enantiomerically enriched product (*S*)-**3fz**[17] (90% *ee*) in which racemization did not occur (Scheme 2, [Eq. (f)]).

On the basis of the above-mentioned experiments and the known Ir^{III}-catalyzed Csp^2–H bond amination process,[18] the proposed mechanistic pathway for this intermolecular sulfonylamidation process, involving unactivated secondary Csp^3–H bonds, is shown in Scheme 3. First, $[Cp^*IrCl_2]_2$ dimers break apart and coordinate to the pyridine nitrogen and amide nitrogen of **1o** to produce an Ir^{III} complex (**A**). Subsequently, coordination of tosyl azide (**2a**) to the iridium center is followed by denitrogenation to form cyclic iridium(V) nitrene complex (**B**). Finally, the iridium nitrene complex **B** undergoes a bichelate-assisted intramolecular nitrene insertion into a γ-secondary Csp^3–H bond via an outer-sphere pathway[19] and is further protonated to furnish the desired Csp^3–H bond sulfonylamidation product **3az**, with regeneration of Ir^{III} catalyst.



Scheme 3. Proposed reaction mechanism.

Cis*/*trans selectivity can be well-rationalized by the proposed two-electron concerted singlet nitrene insertion mechanism, where the six-membered ring transition state adopts a chair conformation. The located *cis* and *trans* transition states derived from **1n** are depicted in Figure 2 (***cis*-$\mathbf{TS2_{ph}}$** and ***trans*-$\mathbf{TS2_{ph}}$**). As a result of the 1,3-diaxial repulsion, the activation free energy of the *trans* transition state ***trans*-$\mathbf{TS2_{ph}}$** is 4.0 kcal mol^{-1}, higher than that of ***cis*-$\mathbf{TS2_{ph}}$**, which explains our experimental observations well (Table 2, **3z**).

In summary, a novel Ir^{III}-catalyzed intermolecular sulfonylamidation of unactivated secondary Csp^3–H bonds with azides was developed. This transformation proceeds regioselectively by

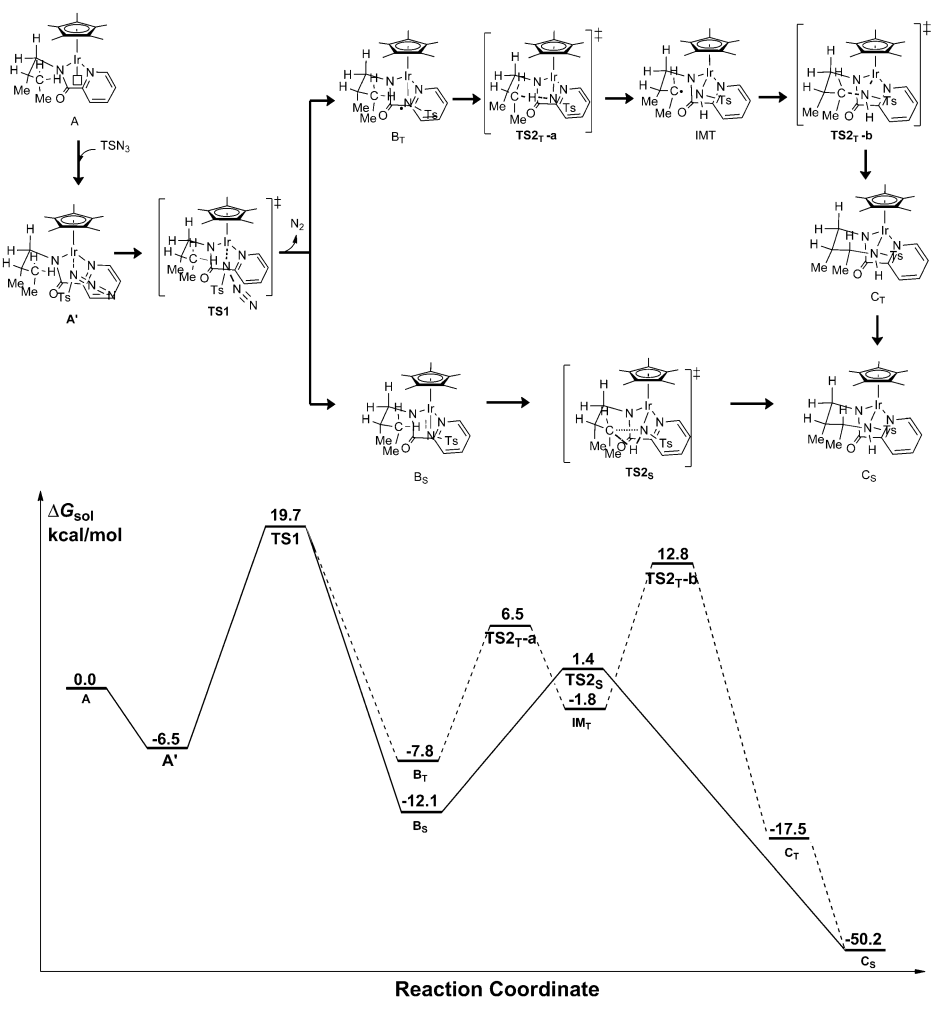


Figure 1. The free energy profiles for the Ir^{III}-catalyzed remote intermolecular unactivated secondary Csp^3–H bond sulfonylamidation of **1o**. The free energies are reported in kcal mol^{-1} at the M06-L/BSII/SMD(dichloroethane)//M06-L/BSI level of theory (Supporting Information).

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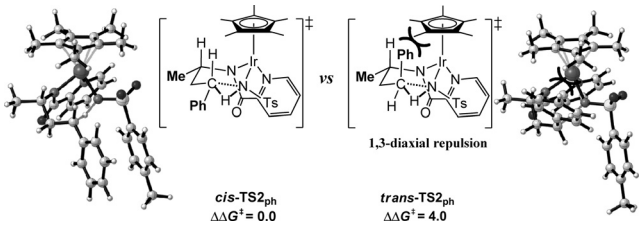

Figure 2. Transition state models for the *cis/trans* selectivity of **3z**. The free energies are reported in kcal mol^{-1} at the M06-L/BSII/SMD(dichloroethane)//M06-L/BSI level of theory (Supporting Information).

bichelate-assisted iridium nitrene insertion into the Csp^3–H bond, followed by protonolysis to give the remote γ-sulfonylamidation products. The broad compatibility of this sulfonylamidation with linear- and branched-chain amidoalkanes renders this reaction highly valuable for rapid construction of structurally diverse 1,3-diamines. Our current efforts are focused on achieving an asymmetric version of this new reaction.

Acknowledgements

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Keywords: C(sp^3)–H activation · iridium catalysis · nitrene insertion · sulfonylamidation · tosyl azides

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