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Iron-Catalyzed Intramolecular C–H Amination of α-Azidyl Amides

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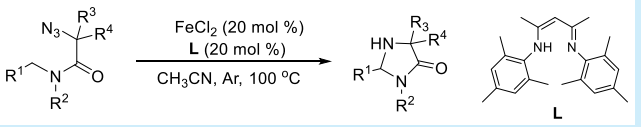
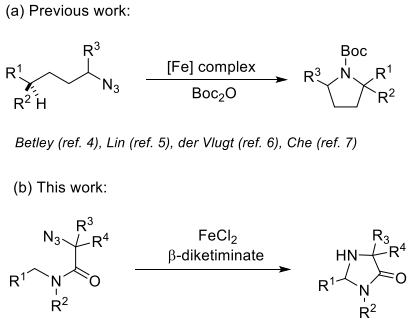
Supporting Information

ABSTRACT: Iron-catalyzed intramolecular C–H amination of aliphatic azides has recently emerged as a powerful tool for the preparation of nitrogen heterocycles. This paper reports that α-azidyl amides can be converted in high efficacy to imidazolinone compounds via intramolecular C(sp^3)–H amination by the action of a simple catalytic system composed of $FeCl_2$ and a β-diketiminate ligand. The reactions provide a simple and atom-economical approach toward polysubstituted imidazolinones.



Transition-metal-catalyzed C–H amination reactions provide highly effective and atom-economical means for the synthesis of nitrogen-containing compounds.[1] Azides are commonly used nitrogen sources for this purpose because they are not only readily available but also of minimal environmental impact as only nitrogen gas is released as reaction waste.[2] Previous studies demonstrate that the azide-involved C–H amination can be enabled by complexes of late first row transition metals such as iron,[3−7] cobalt,[8] and copper.[9] From a modern synthetic point of view, using iron as catalyst is particularly attractive because it is earth-abundant, cheap, and relatively nontoxic,[10] and thus it is highly desirable to apply iron catalysis to C–H amination reactions. It has been proven that iron complexes can react with the azidyl group to form iron-imido or iron-iminyl species,[11] which can insert into the aliphatic C–H bond.[12] The importance of this chemistry has recently been demonstrated by Betley et al., who developed a highly efficient protocol to convert aliphatic azides to saturated N-heterocycles via intramolecular C(sp^3)–H amination by using a high-spin iron dipyrrinato complex as catalyst.[4] Similar results were achieved with other iron complexes, as reported by Lin,[5] der Vlugt and de Bruin,[6] and Che[7] (Scheme 1, (a)). Inspired by these elegant studies, we explored the iron-catalyzed intramolecular C(sp^3)–H amination of α-azidyl amides following our recent studies on iron-catalyzed acyl migration of α-azidyl tertiary ketones.[13] It was found that by using a catalytic system of $FeCl_2$ and a β-diketiminate ligand the insertion of the azidyl nitrogen into the C(sp^3)–H bond attached to the amidyl group took place effectively, affording polysubstituted imidazolinones in good yields. Herein we report this result (Scheme 1, (b)).

Scheme 1. Iron-Catalyzed Intramolecular C(sp^3)–H Amination of Azides



Imidazolinone is an important heterocyclic motif that appears in some biologically and pharmaceutically significant compounds (Figure 1). Commonly used methods to gain access to these structure motifs involve reactions of cyanide or nitrile compounds with ketones, followed by hydrolysis and oxidative cyclization.[14] Although these methods are highly effective and of general applicability, the use of cyanide or nitrile precursors, as well as generation of waste over multistep operations, is a matter of concern from the point of view of green chemistry. We envisioned that the iron-promoted C–H

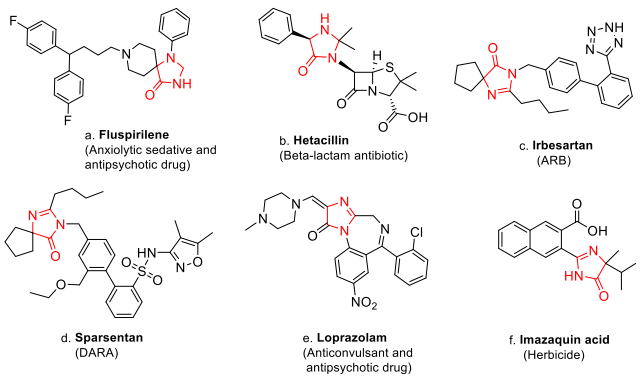


Figure 1. Representative imidazolinone derivatives.

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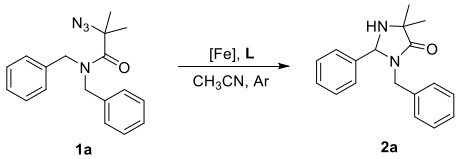
amination might provide an efficient and atom-economical approach toward the imidazolinone ring system. In this view, the conditions developed previously by us for the acyl migration of α-azidyl tertiary ketones[13] were applied to compound **1a**, and the result is illustrated in Table 1.

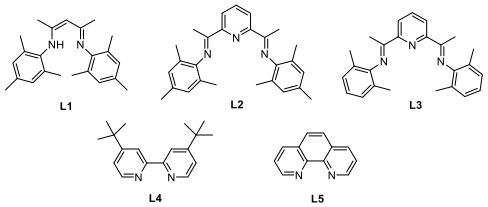
As shown in Table 1, when *N*-benzyl α-azidyl amide **1a** was subjected to 1.0 equiv of $FeBr_2$ at elevated temperature in CH_3CN, compound **2a** was obtained in moderate yield (Table 1, entry 2). The structure of **2a** was confirmed by X-ray crystallographic analysis (CCDC No. 1872309). However, the reaction did not take place when the amount of iron salt was reduced to 0.2 equiv (Table 1, entry 1). A similar result was obtained when $FeCl_2$ or FeI_2 was used as catalyst (Table 1, entries 3−5). The reaction was greatly facilitated when $FeCl_2$ or $FeBr_2$ was used together with β-diketiminate L1 (entries 6−11). The conversion was almost quantitative at 100 °C by using 20 mol % of $FeCl_2$ (or $FeBr_2$) and L1 (entries 6 and 8). The reaction was less efficient at lower temperatures or with less amount of catalysts (entries 7, 8, 10, and 11). The effect of several other ligands (L2−L5) was also tested, but they were all inferior to L1 (entries 13−16). Besides acetonitrile, several other solvents, such as THF, dichloroethane, DMSO, and toluene, were tested for their efficacy, and the result is also listed in Table 1 (entries 17−20).

Table 1. Screening of Reaction Conditions for the Reaction of 1a[a]



1a 2a

entry	iron salt (mol %)	ligand (mol %)	temp (°C)	yield (%)
1	$FeBr_2$ (20)	none	100	trace[b]
2	$FeBr_2$ (100)	none	100	36
3	$FeCl_2$ (20)	none	100	trace[b]
4	$FeCl_2$ (100)	none	100	26
5	FeI_2 (100)	none	100	48
6	$FeCl_2$ (20)	L1 (20)	100	99
7	$FeCl_2$ (10)	L1 (10)	100	89
8	$FeCl_2$ (20)	L1 (10)	100	88
9	$FeBr_2$ (20)	L1 (20)	100	99
10	$FeBr_2$ (10)	L1 (10)	100	77
11	$FeCl_2$ (10)	L1 (10)	80	50
12	FeI_2 (20)	L1 (20)	100	N.R.[c]
13	$FeCl_2$ (20)	L2 (20)	100	73
14	$FeCl_2$ (20)	L3 (20)	100	46
15	$FeCl_2$ (20)	L4 (20)	100	61
16	$FeCl_2$ (20)	L5 (20)	100	trace[b]
17	$FeCl_2$ (20)	L1 (20)	100	91[d]
18	$FeCl_2$ (20)	L1(20)	100	98[e]
19	$FeCl_2$ (20)	L1 (20)	100	95[f]
20	$FeCl_2$ (20)	L1 (20)	100	37[g]



[a]The reactions were conducted on a 0.2 mmol scale in 2 mL of solvent under an argon atmosphere. The reaction time was 12 h. The yields are isolated yields. [b]Most of **1a** was recovered, with trace of **2a** detected by GC-MS. [c]No reaction took place. [d]Dichloroethane was used as solvent. [e]THF was used as solvent. [f]DMSO was used as solvent. [g]Toluene was used as solvent.

The optimized conditions (Table 1, entry 6) were then applied to a variety of differently substituted α-azidyl amides, and the result is summarized in Scheme 2. The reaction proceeded smoothly for a variety of 2-azido-*N*,*N*-diarylmethyl-2-methylpropanamides, with the cyclization products **2b**−**2i** being formed in high yields. The substituent at the phenyl ring exhibited a small effect on the reaction but did not influence much the selectivity (**2h**). Compounds **2j**−**2l** can also be prepared with this method, albeit in lower yields. For compound **1m** which bears a benzyl group and a methyl group at the amidyl nitrogen atom, the reaction afforded two products (**2m-1** and **2m-2**) in a ratio of 2:1, with the insertion at the benzyl position being more favored. When 2-azido-*N*-benzyl-2-methyl-*N*-(1-phenylethyl) propanamide was subjected to the standard conditions, on the other hand, **2n** was generated exclusively in a yield of 89%. This protocol is also suitable for amination of the unactivated methylene group, as demonstrated in the case of **2o**. However, when 2-azido-2-methyl-1-(piperidin-1-yl) propan-1-one (**1p**) and 2-azido-2-methyl-1-(pyrrolidin-1-yl) propan-1-one (**1q**) were used as the substrates, no desired reaction took place. Subsequent experiments showed that by adding Boc_2O into the reaction vessel **1p** and **1q** can be converted to the Boc-protected C−H insertion product **2p′** and **2q′** in yields of 84% and 33%, respectively (Scheme 3). Variation of substitution pattern at the α-position was found to have a big influence on the reaction. As such, while compounds **2r** and **2s** as well as monosubstituted **2t** and **2u** were prepared in good to excellent yields, we failed to obtain compound **2v** by using the same protocol. It is noteworthy that in most cases illustrated in Scheme 2 Boc_2O was not required to guarantee a complete conversion and a good yield. Moreover, the reaction can be realized on gram scales, with no significant loss of efficiency (see footnote a in Scheme 2; experimental details can be found in Supporting Information (SI)).

To further explore the scope of this protocol, the standard conditions were then applied to compounds **3** and **4**, which are the chosen precursors for the previously reported iron-based catalytic systems.[4−7] Unfortunately, we did not obtain the desired cyclization products (a complex mixture was generated). However, by adding Boc_2O to the reaction system, the *N*-Boc-protected heterocycles **5** and **6** can be obtained in high yields (Scheme 4).

β-Diketiminates (NacNac) are commonly used ligands which can coordinate with a variety of metals.[15] The studies by Holland et al. show that iron(I) coordinated with β-diketiminate can react with an azide to form iron(III)−imido complexes which are capable of effecting hydrogen atom transfer[16] or nitrene transfer.[17] The capacity of NacNac−Fe complexes for C−H amination was recently explored by Lin et

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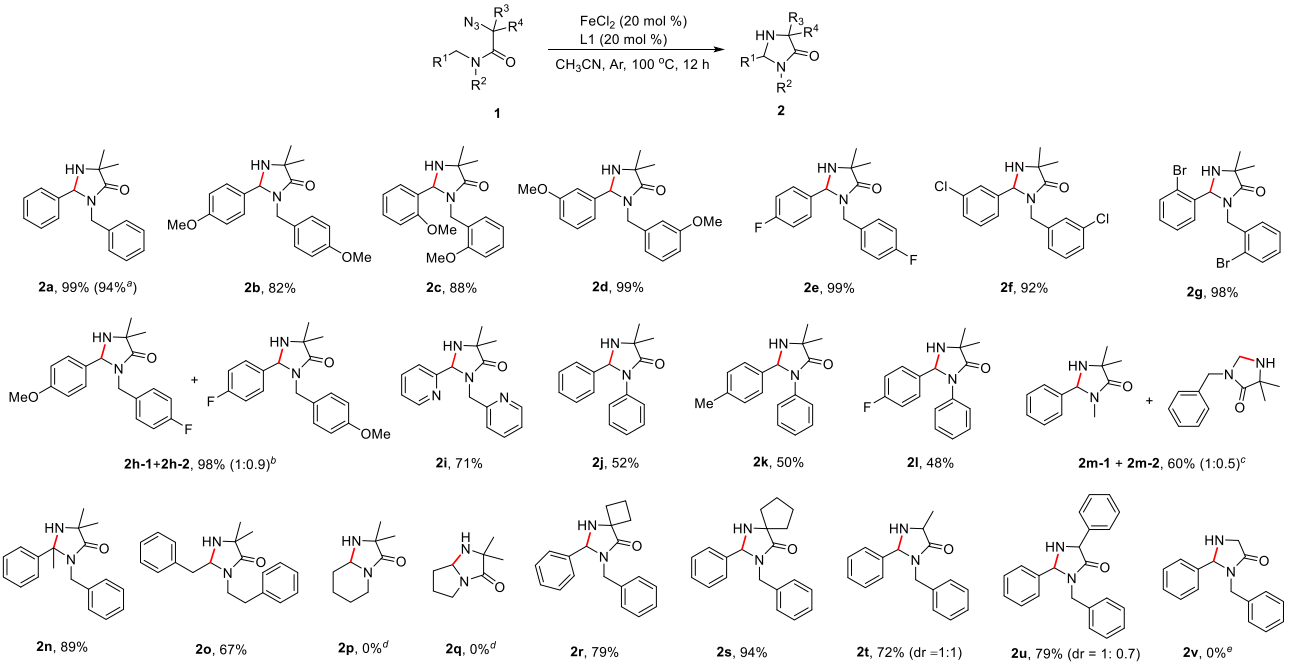
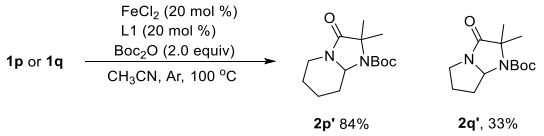
Scheme 2. Scope of the Method for the Synthesis of Imidazolinones*

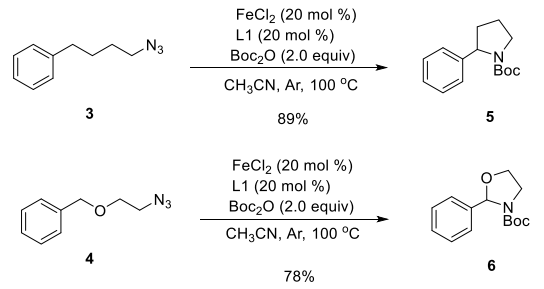


*The reactions were conducted on a 0.2 mmol scale. The yields are isolated yields. [a]The reaction was conducted on a 4.0 mmol scale. [b]The ratio was determined by ^{1}H NMR. [c]The ratio was based on the isolated yields. [d]S. M. decomposed. [e]With most of the reactant recovered.

Scheme 3. Reactions of 1p and 1q in the Presence of Boc_2O



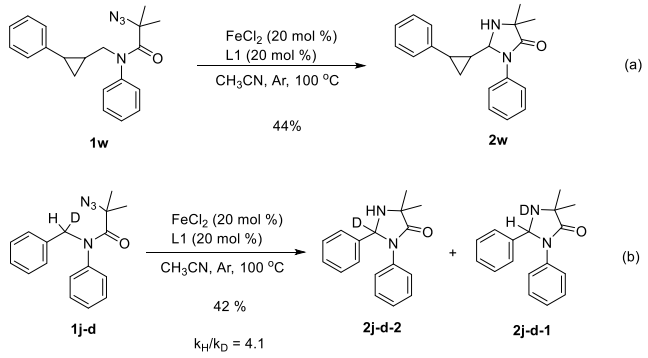
Scheme 4. Reactions of 3 and 4



al., who realized the cyclization of aliphatic organic azides by using a MOF-supported NacNac−Fe(II) complex bound with a methyl group.[5a] Compared with the NacNac−Fe complexes employed by Holland and Lin, the present catalytic system is readily accessible by mixing $FeCl_2$ and L1 in the reaction vessel and thus is much simpler to operate when applied to synthesis.

The iron-catalyzed C(sp^3)−H amination of azides has been investigated intensively by Betley's group by using iron dipyrrinato complexes as catalyst.[4,11] Their studies demonstrate that the reaction of a high-spin iron(II) dipyrrinato complex with an azide could form a high-spin ferric iminyl radical complex, which is highly effective for C(sp^3)−H amination. In the present reactions, the active catalyst is believed to be an iron(II) complex generated in situ from $FeCl_2$ and a β-diketiminate ligand. This complex should also be in a high-spin quintet state (S = 2),[18] like the iron(II) dipyrrinato complexes. To shed light on the reaction mechanism, compound **1w** was prepared and subjected to the standard reaction conditions. It was found that the reaction gave compound **2w** in a yield of 44% (Scheme 5, (a)),

Scheme 5. Mechanistic Studies



comparable to those of **2j** to **2l**, with no ring-opening products being obtained. Subsequent kinetic isotopic experiment with **1j−d** as substrate gave a k_H/k_D value of 4.1 (Scheme 5, (b)), similar to that reported by Betley's group.[4a] Thus, on the basis of the mechanistic studies by Betley's group, a possible mechanism is proposed in Scheme 6 to rationalize the present reactions: The in situ formed NacNac−Fe(II) complex **A** first reacts with the substrate to afford ferric iminyl radical complex **B**, which then undergoes intramolecular hydrogen atom abstraction (HAT) to give intermediate **D**. The latter is converted to product **2** via a fast radical recombination. Apart from this mechanism, it is also possible that the reactions proceed via intermediacy of ferric-imido intermediate **C** through direct C−H insertion (Scheme 6, path (b)). These

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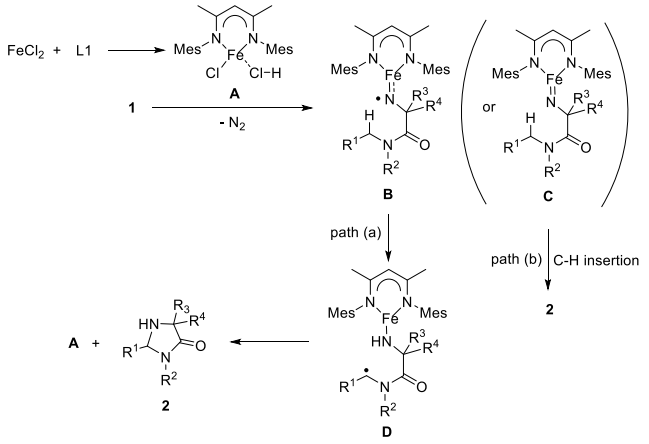
Scheme 6. Proposed Mechanism



two mechanisms cannot be distinguished at this stage as no intermediates could be isolated and characterized.

In summary, we have developed a simple effective protocol for the intramolecular C−H amination of organic azides. This protocol features the use of cheap, readily available $FeCl_2$ and β-diketiminate as catalyst and is highly effective for the denitrogenative cyclization of α-azidyl amides. In this way, polysubstituted imidazolinones can be prepared efficiently in an atom-economical way. We hope that the present method might find applications in the synthesis of medicinally important compounds. Further work is being done in this laboratory to search for more efficient iron-based catalytic systems for the azide-involved C−H amination reactions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03927.

General experimental procedures, characterization data for the substrates and products, and copies of ^{1}H NMR and ^{13}C NMR spectra (PDF)

Accession Codes

CCDC 1872309 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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