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Fe(III)/L-Valine-Catalyzed One-Pot Synthesis of *N*-Sulfinyl- and *N*-Sulfonylimines via Oxidative Cascade Reaction of Alcohols with Sulfinamides or Sulfonamides

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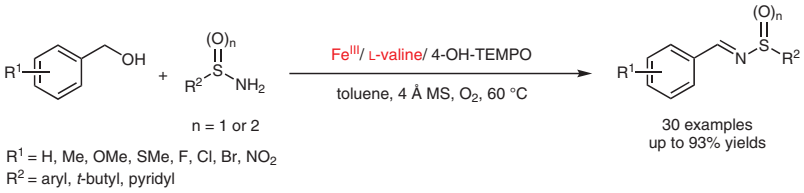

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Abstract An efficient Fe(III), L-valine, and 4-OH-TEMPO catalytic system was found for the oxidation of alcohols followed by condensation with sulfinamide or sulfonamide in one pot for the synthesis of *N*-sulfinyl- and *N*-sulfonylimines compounds under mild conditions. This transformation accommodates a variety of substrates, shows high functional-group tolerance, and affords the corresponding products in good to excellent yields.

Key words Fe catalysis, one-pot, *N*-sulfinylimines, *N*-sulfonylimines, oxidative cascade, alcohols

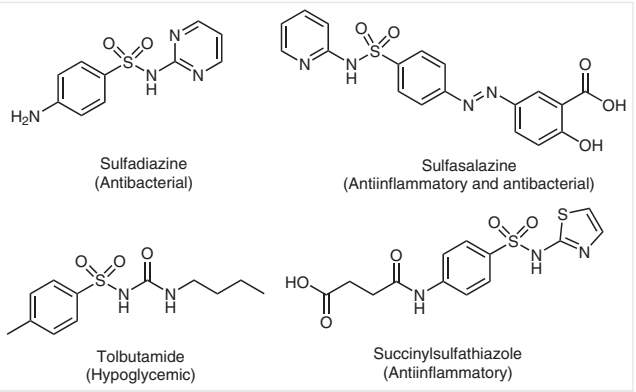

Figure 1 Pharmaceuticals containing the sulfonamide scaffold

The formation of imine compounds has been a priority in organic synthesis because of the properties of the C=N bond and the diversity of the substituents,[1] but imines are less stable and difficult to separate.[2] In the last two decades, *N*-sulfinylimines and *N*-sulfonylimines have received significant attention as they are the few types of electron-deficient imines that are stable enough to be isolated,[3] and ubiquitous in organic transformations.[4] They can undergo various nucleophilic additions,[5] reductions,[6] radical reactions,[7] and hetero-Diels–Alder reactions[8] to afford *N*-sulfinamide and *N*-sulfonamide compounds, which are frequently encountered as core structural motifs in pharmaceuticals (Figure 1).[9]

Thus, various synthetic routes to *N*-sulfonylimines have been developed. The best known method of the synthesis of *N*-sulfinylimines and *N*-sulfonylimines is condensation of sulfinamides or sulfonamides with aldehyde agents mediated by Lewis acid (Scheme 1a).[10] However, these methods usually require harsh acidic condition and high temperature, which limit the range of substrate and produce large amounts of inorganic salt.[11] Another synthetic strategy makes use of nitrile reactions with organometallic reagents and methylsulfonate; the poor commercial availability and toxicity of the product limit the scope of this transformation.[12]

In terms of sustainability, the choice of alcohols as substrates is highly desirable as they are inexpensive, relatively nontoxic, more stable than the corresponding aldehydes,[13] and alcohols are readily oxidized to aldehydes.[14] In 2010, R. Patel et al. reported a saccharin-LiBr catalytic system to access *N*-tosyl imines directly from alcohols (Scheme 1b).[15] In 2017, we reported that copper/L-proline efficiently catalyzed the reaction of alcohols with sulfinamides or sulfonamides to obtain *N*-sulfinylimines or *N*-sulfonylimines (Scheme 1c).[16] Recently, our group has developed a new method for using Fe(III)/TEMPO as catalyst to oxidize alcohols to the corresponding aldehydes.[17] Inspired by these recent discoveries, we report herein a simple, economical, base-free, Fe(III)/L-valine-catalyzed one-pot reaction system for the synthesis of *N*-sulfinyl- and *N*-sulfonylimines via oxidative cascade reaction of alcohols with sulfinamides or sulfonamides.

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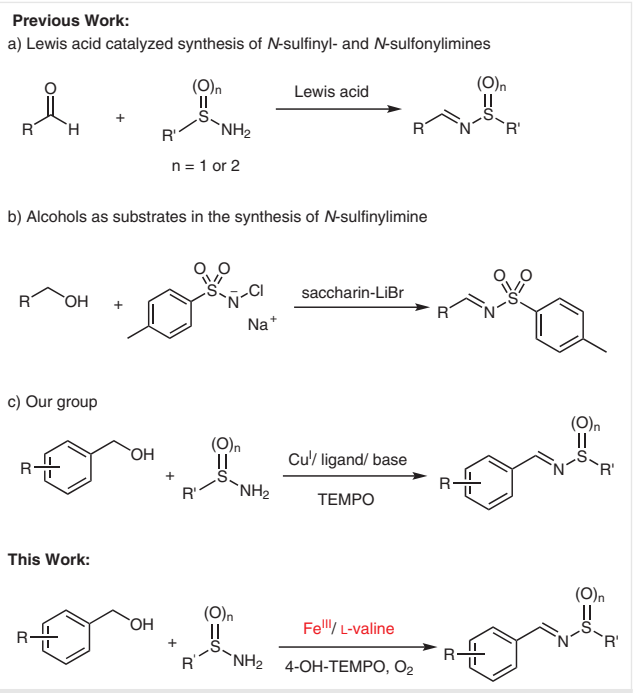
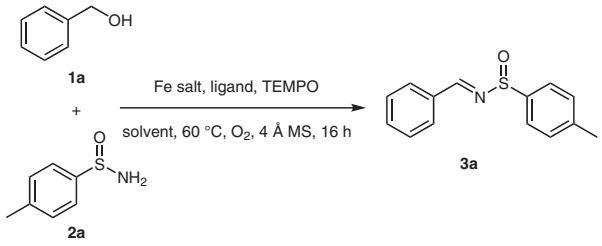


Scheme 1 Methods for the preparation of *N*-sulfinyl- and *N*-sulfonylimines

The reaction of unsubstituted benzyl alcohol (**1a**) with 4-toluenesulfinamide (**2a**) was selected as the model reaction to establish the best reaction conditions. Initially, the reaction was catalyzed by $Fe(NO_3)_3$, L-valine as the ligand, TEMPO as the co-oxidant and 4 Å MS under O_2 in toluene at 60 °C for 16 hours to obtained the desired product **3aa** in 56% yield (Table 1, entry 1). Encouraged by this result, different solvents were screened and toluene was found to be the most effective solvent for this reaction. Other solvents like CH_2Cl_2, DMF and THF led to moderate conversions of the substrates (Table 1, entries 2–6). Next, various iron catalysts including iron(II) and iron(III) were further screened. When $FeCl_3$was used as the catalyst, the desired product **3aa** was obtained in 71% yield (Table 1, entry 12). Then, a variety of bases were added to the reaction system and we found that the reaction proceeded when no base was present (Table1, entries 13–15). Replacement of L-valine with other common ligands, such as L-proline, *N*-Ac-Val, pyrrolidine and imidazole also reduced the reactivity (Table 1, entries 16–20). Interestingly, when 4-OH-TEMPO was used as co-oxidant instead of TEMPO, the reaction rate was significantly improved (Table 1, entry 21). Further improvement was achieved by adjusting the amount of 4-OH-TEMPO and the reaction time, thus affording **3aa** in 93% yield (Table 1, entry 24). Finally, the control experiments showed that 4-OH-TEMPO, $FeCl_3$, L-valine and O_2 are essential for the alcohol oxidation system (Table 1, entries 25–28). Hence, the

Table 1 Optimization of Reaction Conditions[a]



Entry	Fe salt	Solvent	Ligand	Yield (%)[b]
1	$Fe(NO_3)_3$	toluene	L-valine	56
2	$Fe(NO_3)_3$	CH_2Cl_2	L-valine	50
3	$Fe(NO_3)_3$	DMF	L-valine	14
4	$Fe(NO_3)_3$	THF	L-valine	7
5	$Fe(NO_3)_3$	DCE	L-valine	10
6	$Fe(NO_3)_3$	MeOH	L-valine	36
7	$Fe_2(SO_4)_3$	toluene	L-valine	12
8	$Fe(acac)_3$	toluene	L-valine	18
9	FeF_3	toluene	L-valine	trace
10	$Fe(OTf)_3$	toluene	L-valine	41
11	$Fe(OAc)_2$	toluene	L-valine	49
12	$FeCl_3$	toluene	L-valine	71
13[c]	$FeCl_3$	toluene	L-valine	57
14[d]	$FeCl_3$	toluene	L-valine	52
15[e]	$FeCl_3$	toluene	L-valine	34
16	$FeCl_3$	toluene	L-proline	60
17	$FeCl_3$	toluene	*N*-Ac-Val	51
18	$FeCl_3$	toluene	pyrrolidine	49
19	$FeCl_3$	toluene	imidazole	52
20	$FeCl_3$	toluene	glycine	47
21[f]	$FeCl_3$	toluene	L-valine	81
22[g,f]	$FeCl_3$	toluene	L-valine	85
23[h,f]	$FeCl_3$	toluene	L-valine	92
24[i]	**$FeCl_3$**	**toluene**	**L-valine**	**93 (90[l])**
25[j]	$FeCl_3$	toluene	L-valine	9
26[i]	–	toluene	L-valine	10
27[i]	$FeCl_3$	toluene	–	15
28[k,i]	$FeCl_3$	toluene	L-valine	0

[a] Reaction conditions: **1a** (0.4 mmol), **2a** (0.2 mmol), iron salt (10 mol%), TEMPO (10 mol%), ligand (10 mol%), solvent (2.5 mL), 4 Å MS (500 mg), O_2 (1 atm), 60 °C, 16 h.
[b] Determined by HPLC.
[c] K_2CO_3 (0.5 equiv).
[d] Na_2CO_3 (0.5 equiv).
[e] $MgSO_4$ (0.5 equiv).
[f] We used 4-OH-TEMPO instead of TEMPO.
[g] Reaction time was 24 h.
[h] **1a** (0.6 mmol).
[i] 4-OH-TEMPO (20 mol%).
[j] 4-OH-TEMPO was omitted.
[k] Reaction was carried out under N_2.
[l] Isolated yields.

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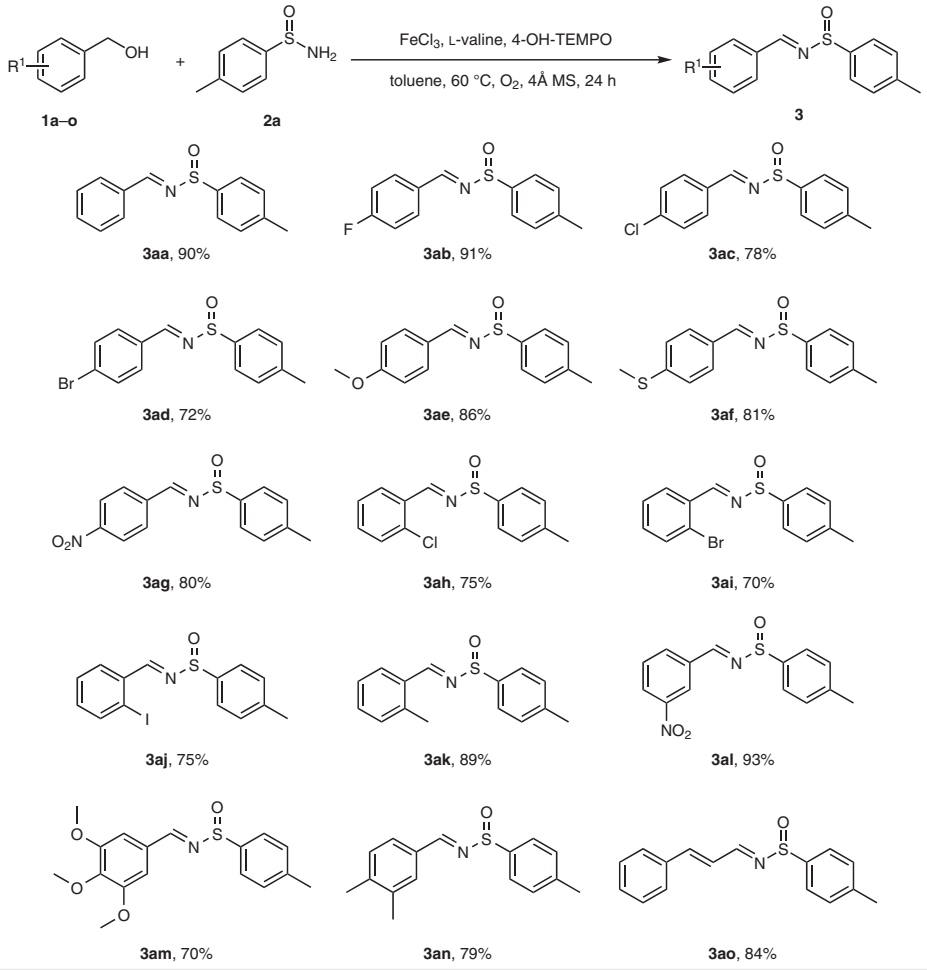
optimized reaction conditions were obtained (Table 1, entry 24): $FeCl_3$ (10 mol%), L-valine (10 mol%), 4-OH-TEMPO (20 mol%), 4 Å MS, under O_2 in toluene at 60 °C.

Based on the optimized reaction conditions, we first investigated the reactions of 4-toluenesulfinamide (**2a**) with various aromatic alcohols to study the scope of this novel system. As shown in Scheme 2, under suitable conditions, both electron-rich and electron-deficient benzylic alcohols could be smoothly reacted with 4-toluenesulfinamide into the desired products. The *para*-substituted aromatic alcohols bearing halogen, methoxy, methylthio, and nitro groups were compatible with the optimized reaction conditions, thus affording the corresponding products with good to excellent isolated yields (**3ab**–**3ag**). The *ortho*-substituted aromatic alcohols, bearing an electron-withdrawing group such as chloro, fluoro, bromo or an electron-donating group such as a methyl group were converted into the desired products in 70–93% yields (**3ah**–**3ak**). The *meta*-substituted aromatic alcohol could also be converted into the corresponding *N*-sulfinylimines with excellent isolated yields (**3al**). Additionally, other alcohols with electron-donating groups were compatible with the transformation and afforded the target products in 70–79% yields (**3am**–**3an**). Gratifyingly, under the optimal conditions the cinnamyl alcohol also reacted to form the imine in 84% isolated yield (**3ao**).

To expand the scope of this oxidative cascade reaction, a variety of other sulfinamides were investigated in the reaction. As shown in Scheme 3, various sulfinamides (**2b**–**d**) were successfully coupled with aromatic alcohols providing the resulting sulfinylimines in moderate to excellent yields (72–93%). Various aromatic alcohols bearing electron-withdrawing groups such as halogen (**3cb**, **3cc**, **3cd**, **3cj**, **3db**), nitro (**3cg**) or electron-donating groups including methoxy (**3bm**, **3cm**) were compatible with the reaction conditions. Gratifyingly, **2c** could also react with allyl alcohols and be obtained in good isolated yields under these conditions (91%, **3co**). In general, the results showed that electron-



Scheme 2 Substrate scope of aromatic alcohols. *Reagents and conditions*: **1** (0.4 mmol), **2a** (0.2 mmol), $FeCl_3$ (10 mol%), 4-OH-TEMPO (20 mol%), L-valine (10 mol%), toluene (2.5 mL), 4 Å MS (500 mg), O_2 (1 atm), 60 °C, 24 h; isolated yields are shown.

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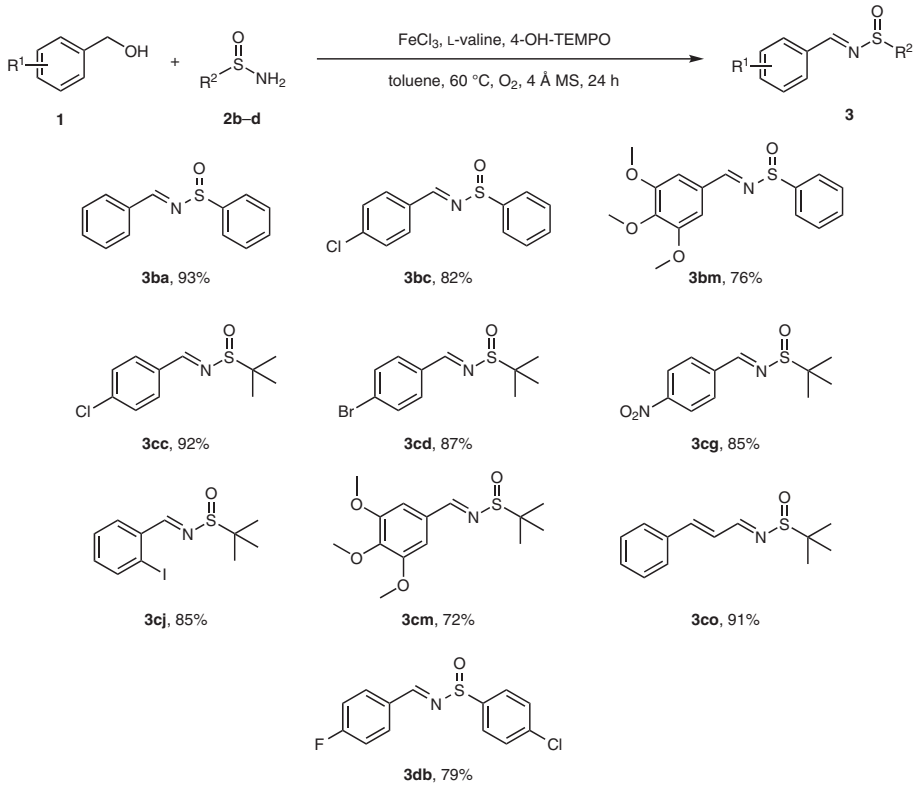
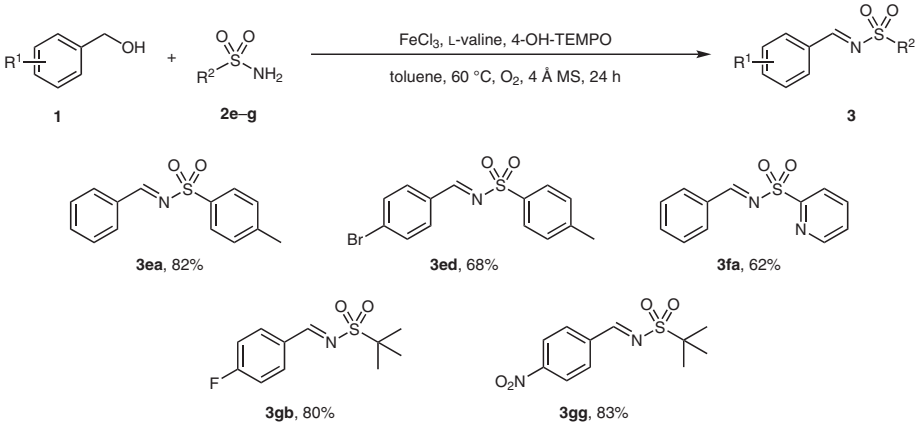


Scheme 3 Substrate scope of sulfinamides. *Reagents and conditions*: **1** (0.4 mmol), **2** (0.2 mmol), $FeCl_3$ (10 mol%), 4-OH-TEMPO (20 mol%), L-valine (10 mol%), toluene (2.5 mL), 4 Å MS (500 mg), O_2 (1 atm), 60 °C, 24 h; isolated yields are shown.

releasing substituents had no significant effect on the yields. Unfortunately, heteroaryl alcohols and less active aliphatic alcohols were not compatible in the reaction.

Subsequently, we probed whether aromatic alcohols could also be reacted with sulfonamides. A variety of sulfonamides such as 4-toluenesulfonamide, *tert*-butanesulfonamide and 2-pyridinesulfonamide were employed successfully in this process even though the nucleophilicity of the nitrogen atom of sulfonamides is much lower than that of sulfinamides. As shown in Scheme 4, all the examined substrates provided medium to good yields (62–83%). We discovered that the use of electron-withdrawing aryl alcohols bearing halogen (**3ed**, **3gb**) and nitro (**3gg**) groups also



Scheme 4 Substrate scope of sulfonamides. *Reagents and conditions*: **1** (0.4 mmol), **2** (0.2 mmol), $FeCl_3$ (10 mol%), 4-OH-TEMPO (20 mol%), L-valine (10 mol%), toluene (2.5 mL), 4 Å MS (500 mg), O_2 (1 atm), 60 °C, 24 h; isolated yields are shown.

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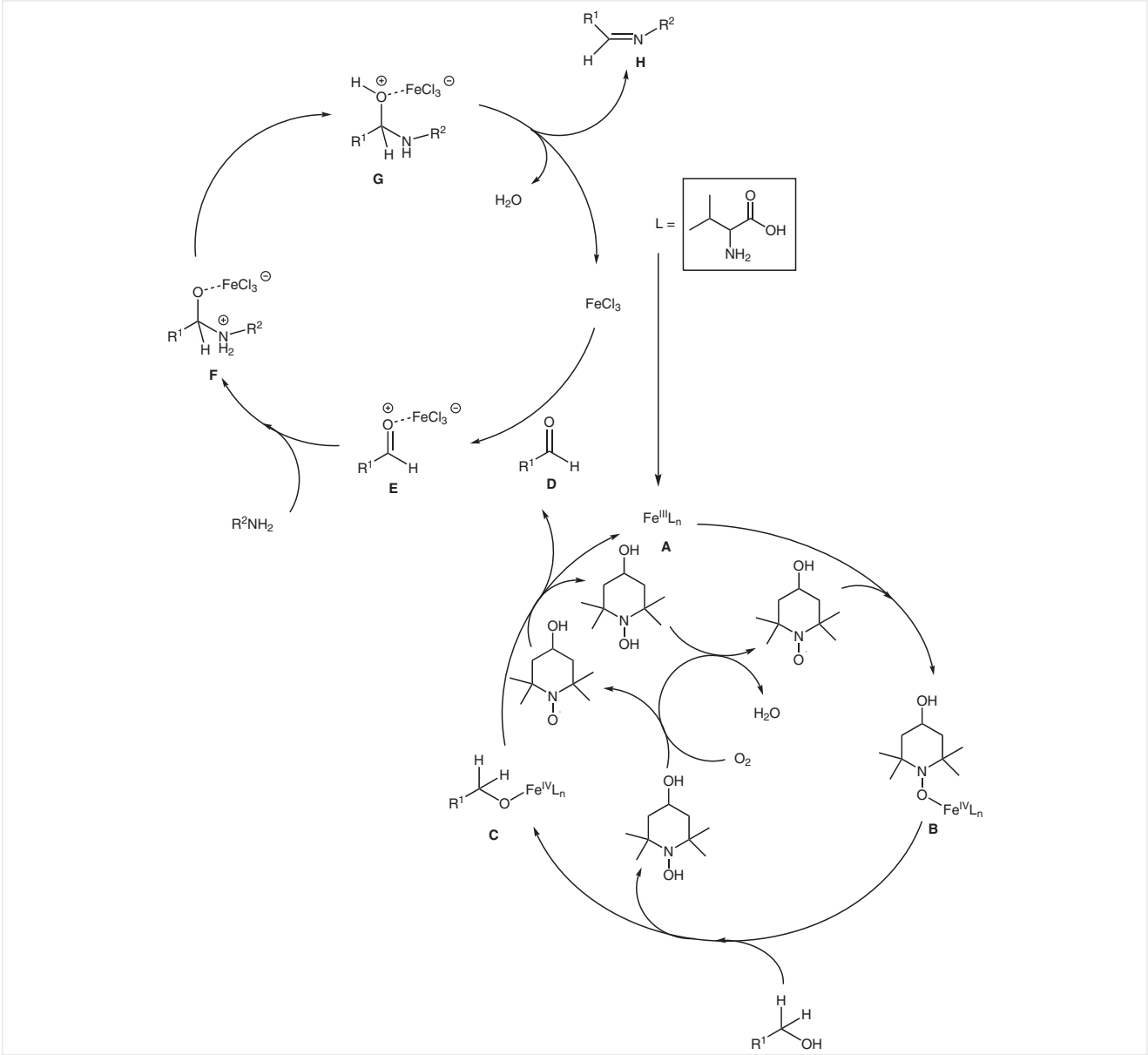
provided the desired products in good yields. It is worth noting that 2-pyridinesulfonamide was also compatible with the conditions and obtained in satisfying results (**3fa**).

Considering the potential biological activities of *N*-sulfinylimine and to show the synthetic utility of this method, the gram-scale synthesis of **3aa** was performed. Compounds **1a** (1.404 g, 13.0 mmol) and **2a** (1.008 g, 6.5 mmol) reacted well under the standard reaction conditions, affording the desired product **3aa** in 77% yield (1.211 g).

Amino acids as building blocks of protein have been reported to greatly improve the activity of the catalyst.[17,14a,14c] Based on the above results and relevant literature,[16,10c,18] a plausible mechanism for the iron/L-valine-catalyzed aerobic oxidative cascade reaction is illustrated in Scheme 5. L-Valine as a ligand combines with $FeCl_3$ to form compound **A**. The active Fe(IV) species B is generated via a one-electron oxidation of **A** by TEMPO. Alkoxy replacement, followed by coordination of a second molecule of TEMPO and intramolecular β-hydrogen abstraction affords the desired carbonyl compound **D**, Fe(III) and TEMPOH. Finally TEMPO is regenerated by rapid air oxidation of TEMPOH. In the second catalytic cycle, $FeCl_3$, as Lewis acid catalyst, participates in the catalytic cycle. Catalyst $FeCl_3$ and carbonyl product **D** initially react to form iron-coordinated carbonyl species **E**, which increases its electrophilicity to trigger the nucleophilic attack by the sulfinamide or sulfonamide. Intermedi-



Scheme 5 Possible mechanism

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ate **F** obtained by the nucleophilic addition reaction, which takes place via intramolecular hydrogen to give the species **G**. Subsequently, liberation of water from **G** delivers the product **H** along with the generation of $FeCl_3$ for entry into the subsequent catalytic cycles.

In conclusion, we have demonstrated a first example of Fe-catalyzed aerobic oxidative one-pot synthesis of *N*-sulfinyl and *N*-sulfonylimines directly from alcohols.[19,20] The protocol is highly efficient and has a broad substrate scope. Further studies to more clearly understand the reaction mechanism and the synthetic applications are currently underway in our laboratory.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1609320.

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(19) **Typical Procedure for the Synthesis of *N*-Sulfinylimine [(±)-*N*-Benzylidene-*p*-toluenesulfinamide]**: A mixture of *p*-toluenesulfinamide (0.0621 g, 0.4 mmol), phenylmethanol (0.0648 g, 0.6 mmol), L-valine (0.0047 g, 0.04 mmol), $FeCl_3$ (0.0065 g, 0.04 mmol), 4-OH-TEMPO (0.0138 g, 0.08 mmol), toluene (2.5 mL), and 4 Å MS (0.7000 g) were added to a 100-mL Schlenk tube. Then the resulting mixture was vigorously stirred under O_2 (1 atm) at 60 °C for 24 h. After the reaction was complete, the residue was filtered off, and the solvent was removed under vacuum to give the crude product, which was purified by

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column chromatography on silica gel to give the pure product **3aa**. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.77 (s, 1 H), 7.82–7.90 (m, 2 H), 7.65 (d, *J* = 8.2 Hz, 2 H), 7.51 (t, *J* = 8.6 Hz, 1 H), 7.46 (t, *J* = 7.3 Hz, 2 H), 7.32 (d, *J* = 8.0 Hz, 2 H), 2.40 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.67, 141.84, 141.73, 133.93, 132.59, 129.85, 129.60, 128.90, 124.82, 21.43.

(20) **Typical Procedure for the Synthesis of *N*-Sulfonylimine [(*E*)-*N*-Benzylidene-*p*-toluenesulfonamide]**: A mixture of *p*-toluenesulfonamide (0.0685 g, 0.4 mmol), phenylmethanol (0.0648 g, 0.6 mmol), L-valine (0.0047 g, 0.04 mmol), $FeCl_3$ (0.0065 g, 0.04 mmol), 4-OH-TEMPO (0.0138 g, 0.08 mmol), toluene (2.5 mL), and 4 Å MS (0.7000 g) were added to a 100-mL Schlenk tube. Then the resulting mixture was vigorously stirred under O_2 (1 atm) at 60 °C for 24 h. After the reaction was complete, the residue was filtered off, and the solvent was removed under vacuum to give the crude product, which was purified by flash column chromatography or purified by precipitation from CH_2Cl_2–pentane to give the pure product **3ea**. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.05 (s, 1 H), 7.93 (ddd, *J* = 17.4, 7.4, 1.6 Hz, 4 H), 7.60–7.67 (m, 1 H), 7.50 (t, *J* = 7.8 Hz, 2 H), 7.36 (d, *J* = 8.1 Hz, 2 H), 2.45 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.13, 144.60, 134.92, 132.42, 131.30, 129.81, 129.14, 128.11, 126.48, 21.66.

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