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A C–H functionalization approach to diverse nitrogenous scaffolds through conjugate addition of catalytic allyliron nucleophiles†

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Cyclopentadienyliron(II) dicarbonyl complexes capable of coordinating to and enhancing the acidity of a range of unsaturated substrates have emerged as a new class of base-metal derived catalysts for C–H functionalization. In this manuscript, the iron-catalyzed C–H functionalization of allylic C(sp^3)–H bonds using nitrogen containing α,β-unsaturated carbonyl compounds as coupling partners is reported. Employing a cationic cyclopentadienyliron dicarbonyl complex, this redox neutral process converts simple alkenes into allylic anion equivalents for 1,4-addition into maleimides, acyclic α,β-unsaturated imides, and vinylogous amides. The judicious pairing of pyridine and alkylamine bases with Lewis acid additives allowed each of these classes of substrates to be successfully employed, allowing for the formation of a diverse collection of cyclic and acyclic nitrogen-containing compounds featuring C–C unsaturation. The resulting Michael adducts can be further transformed into a variety of useful scaffolds such as allylated pyrroles, pyrrolidines, and carbocyclic acids.

Introduction

Nitrogen-containing building blocks, including heterocyclic scaffolds, are highly sought after targets of chemical synthesis, owing to their applicability as precursors toward the synthesis of pharmaceutical candidates and other bioactive compounds.[1,2] Thus, the identification and investigation of general and modular approaches to access nitrogen-containing compounds endowed with commonly applicable synthetic handles represent important goals for the development of new synthetic methods. Approaches that provide access to nitrogenous compounds containing rapidly diversifiable olefin and carbonyl groups are especially valuable in this context.

Succinimide derivatives in particular not only have independent bioactivity[1–4] but also serve as versatile intermediates toward the synthesis of other five-membered nitrogen-containing heterocycles, including γ-lactams, pyrrolidines, and pyrroles, that feature prominently in drug candidates.[5–7] In addition to providing a useful functional group that allows for further derivatization, the installation of allylic groups on to these azacycles can lead to bioactive compounds of interest in their own right (Scheme 1).[1,3] Conjugate addition of carbon nucleophiles (Michael addition) to the readily available maleimide scaffold constitutes a straightforward and attractive route for quickly accessing 3-alkylated succinimides.[8–11] However, there is a distinct lack of suitable nucleophiles for the C=C bond allylation of maleimide derivatives. Common organometallic allyl nucleophiles such as magnesium,[12] silicon,[13] boron,[14] indium,[15] and tin[16] reagents all selectively provide the 1,2-adduct of direct carbonyl addition, rather than 3-allylated succinimide derivative resulting from 1,4-addition.[17] The installation of an allylic substructure at the 3-position by conjugate addition has only been successful in the context of additions by extended enolate species (Scheme 2).[18]

Although 1,4-addition of allylic radicals to maleimides has been demonstrated using allylic sulfones as radical sources, the synthesis of the allylic sulfone precursors is often a nontrivial endeavour, and only the installation of the parent allyl group and a narrow range of 2-substituted derivatives have been demonstrated.[19–21] Maleimides are also known to react with allylbenzene derivatives through the Alder-ene reaction[22] to give 3-cinnamylated succinimides at very high reaction temperatures. Practically speaking, the current state-of-the-art for accessing allylated succinimide derivatives still relies on the reaction of succinimide-derived enolates with allylic bromides.[23–25] However, highly reactive allylic bromides may be difficult to purify or handle and can give side products, including bis-allylated or regioisomeric adducts.[23] In addition, they require additional steps to synthesize, creating hurdles when a functional group-rich allylic fragment is needed. A protocol for the regioselective addition of a nucleophilic allylic fragment to maleimide under catalytic conditions, particularly one employing simple hydrocarbon-based precursors (*i.e.*, by C–H functionalization), would be

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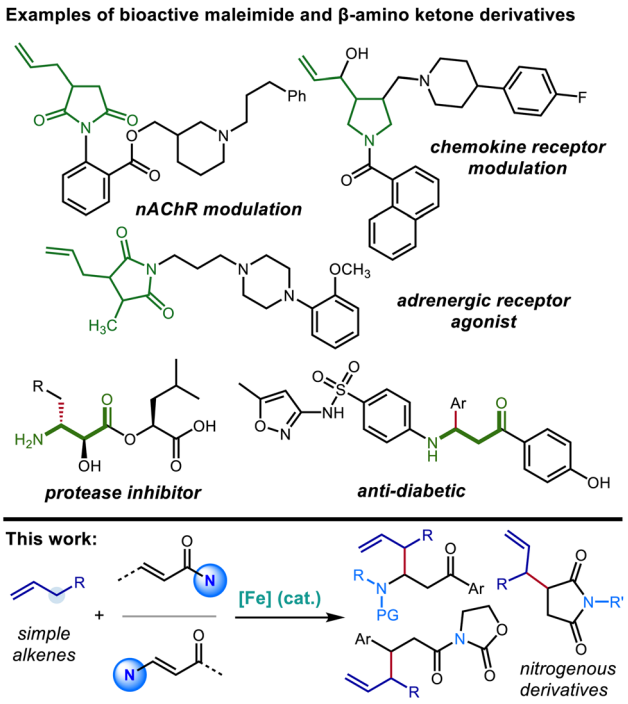
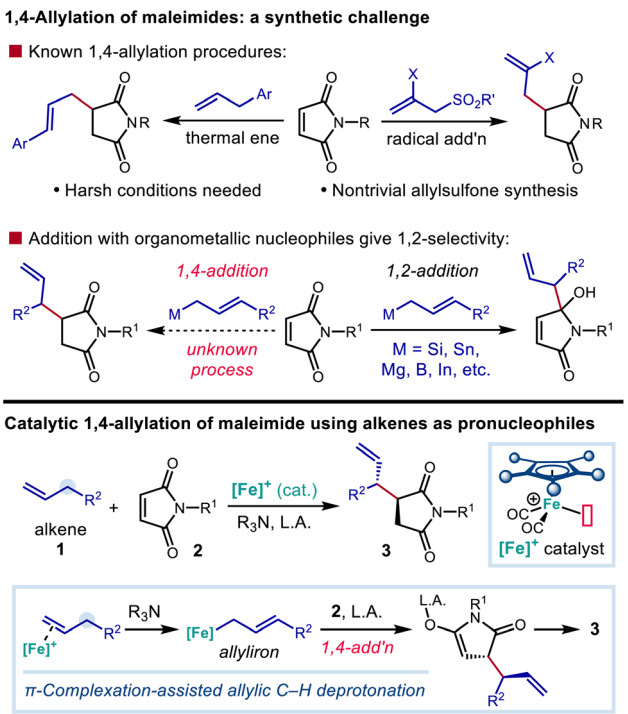


Scheme 1 Examples of biologically active 3-allylated succinimides, β-substituted β-amino ketones (top) and overview of the transformations reported in this manuscript (bottom).

a valuable tool for the synthesis of 3-allylated succinimides and other functionalized five-membered nitrogen-containing heterocycles.



Scheme 2 Allylation of maleimide derivatives as an unmet synthetic challenge and an approach to the synthesis of 3-allylated five-membered azacycles.

Our group and others have shown that coordination of a cationic late transition metal complex to a C–C π-bond can greatly enhance the C–H acidity of the neighboring allylic, propargylic, or allenic protons.[26,27] In particular, through the use of cyclopentadienyliron(II) dicarbonyl derivatives as catalysts,[28] this acidity enhancement enables the use of weak, functional group-tolerant amine bases to effect the allylic deprotonation of olefins to generate nucleophilic allyliron intermediates that react with electrophiles with S_E2' selectivity.[29–35] We further discovered that these nucleophilic organoiron species will undergo electrophilic functionalization with chalcone derivatives through a 1,4-addition process.[36]

In this article we report the development of a series of C–H functionalization methods for the coupling of alkenes with maleimides and other synthetically versatile nitrogen-containing α,β-unsaturated carbonyl compounds. These processes allow for the synthesis of high value nitrogen-containing building blocks using simple, readily available precursors. Moreover, these procedures can be used for the elaboration of complex scaffolds derived from known pharmaceuticals and bioactive compounds.

Results and discussion

Maleimide electrophiles

We hypothesized that this π-coordination-assisted deprotonation approach to allylic C–H functionalization could allow for conjugate addition into maleimides, delivering functionalized succinimide products in a highly regioselective manner. Exploring these electrophiles, we immediately found that silyl Lewis acids such as TIPSOTf (Table 1, entry 1) and TMSOTf (entry 2) provided no desired product. However, the boron Lewis acid $BF_3 \cdot Et_2O$ (entry 3) did provide the desired coupling product, though with poor mass balance in part due to product decomposition. An increase in yield was observed upon inclusion of lithium bistriflimide as a co-Lewis acid additive (entry 4), as well as by decreasing base strength (entries 5–7). Stronger amine bases such as 2,2,6,6-tetramethylpiperidine (TMPH) appeared to be incompatible with the highly electrophilic starting material and the readily enolizable product, while weak and hindered bases like 4-chloro-2,6-lutidine (4-Cl-lutidine) were found to be optimal (entry 7). Reflecting the sensitivity of the starting material and product, lowering the temperature to 40 °C and reducing the amount of Lewis acid used likewise improved yield (entries 8 and 9). Gratifyingly, extensive screening of additives demonstrated that employing substoichiometric $AgNTf_2$ as the co-Lewis acid and toluene as a solvent resulted in an 89% isolated yield while increasing the diastereomeric ratio (d.r.) from 3.7 : 1 to 7.6 : 1 (entry 11). The addition of $Mg(NTf_2)_2$ was nearly as effective for this purpose and may be a more economical alternative on larger scale (entry 10). The major regioisomer obtained was ascertained by X-ray crystallographic analysis and is consistent with an open transition state model (see the ESI†). Under all conditions evaluated, ^{1}H NMR analysis of the

Table 1 Optimization for maleimide electrophiles

Entry	L.A. + additive[a]	Base	Temp.	Ratio (LA/base)	Yield[b] (%)	dr
1	TIPSOTf	Collidine	60	3/4	0	—
2	TMSOTf	Collidine	60	3/4	0	—
3	$BF_3 \cdot Et_2O$	Collidine	60	3/4	30	—
4	$BF_3 \cdot Et_2O$ + $LiNTf_2$	Collidine	60	3/4	37	—
5	$BF_3 \cdot Et_2O$ + $LiNTf_2$	TMPH	60	3/4	0	—
6	$BF_3 \cdot Et_2O$ + $LiNTf_2$	Lutidine	60	3/4	40	—
7	$BF_3 \cdot Et_2O$ + $LiNTf_2$	4-Cl-lutidine	60	3/4	47	—
8	$BF_3 \cdot Et_2O$ + $LiNTf_2$	4-Cl-lutidine	40	3/4	64	—
9	$BF_3 \cdot Et_2O$ + $LiNTf_2$	4-Cl-lutidine	40	1.5/4	83	3.7 : 1
10	$BF_3 \cdot Et_2O$ + $Mg(NTf_2)_2$	4-Cl-lutidine	40	1.5/4	75	6.4 : 1
11	$BF_3 \cdot Et_2O$ + $AgNTf_2$	4-Cl-lutidine	40	1.5/4	89[c]	7.6 : 1
12	$BF_3 \cdot Et_2O$	4-Cl-lutidine	40	1.5/4	9	6.3 : 1

[a] Bistriflimide additive (0.35 equiv.) used for entries 4–11. [b] Yields determined by ^{1}H NMR using 2,4-dinitrotoluene as the internal standard. [c] Isolated yield. Conditions: **1a** (3.0 equiv.), **2a** (0.2 mmol), $[Cp^*Fe(CO)_2(thf)]^+[BF4]^-$ (20 mol%), $BF_3 \cdot Et_2O$ (1.5 equiv.), 4-chlorolutidine (4.0 equiv.), $AgNTf_2$ (0.35 equiv.), toluene [1.5 M], 40 °C, 24 h.

crude material indicated that the branched regioisomer was formed exclusively (>20:1 r. r.).

With these reaction conditions in hand, we explored a variety of nitrogen substituents and alkene coupling partners. The scope of well tolerated *N*-substituents was broad: alkyl groups spanning a range of steric profiles (Scheme 3, **3ba** and **3ca**) were tolerated, as well as cycloalkyl groups (**3da**, **3ea**), as was a maleimide derived from a pharmaceutical fragment (**3ga**). The reaction performed well with *N*-benzylic substituents (**3aa** and **3ha**), giving good yields and good diastereoselectivity. Although *N*-aryl maleimides furnished products with somewhat reduced diastereoselectivity, succinimide products were nonetheless obtained in good to excellent yields for both electron-donating (**3ka**) and electron-withdrawing (**3ia**) aryl substituents. This reaction provided good to excellent yields for a range of alkene substrates, including electron-rich (**3ab**, **3ae**) and electron-poor (**3ad**) allylbenzene derivatives. Unfortunately, unactivated olefins (without an additional aryl group at the α-position) were unsuccessful (<5% yield), presumably because the weakly basic 4-chlorolutidine ($pK_{aH} = 5.4$) and lower reaction temperatures (40 °C) needed in this protocol are insufficient for deprotonation of these substrates.[30]

A slightly modified protocol could be performed on gram scale while maintaining synthetic efficiency, giving the aryl bromide **3ja** in excellent yield. Notably, both aromatic and saturated five-membered azacycles can be obtained as derivatives of the succinimide products. For example, reduction of **3fc** using $LiAlH_4$ selectively provided either the 3-allylic pyrrole or the 3-allylic pyrrolidine depending on the level of vigor of the reaction conditions (Scheme 4).

N-Acyl oxazolidinone electrophiles

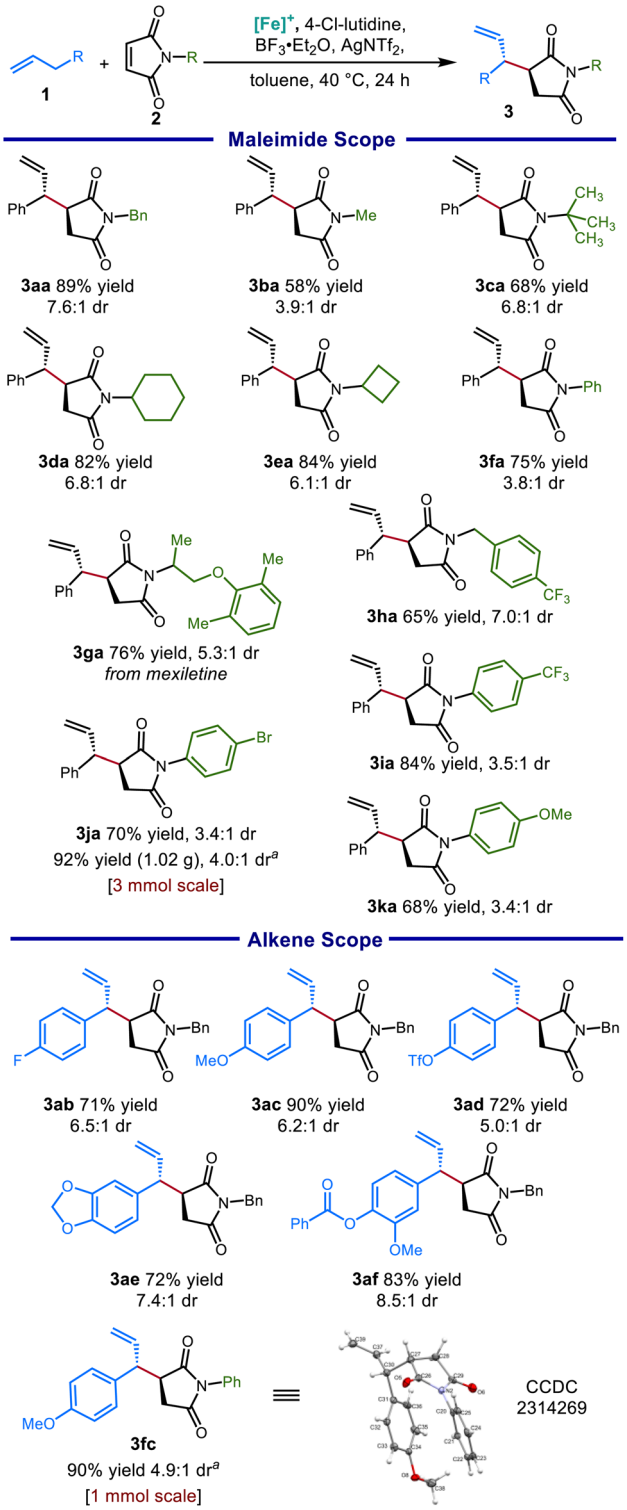
Having unlocked a strategy for conjugate addition of alkenes into maleimides, we further hypothesized that alkene addition to acyclic α,β-unsaturated imides would also be possible. α,β-Unsaturated *N*-acyl oxazolidinones were chosen due to their ease of synthesis and synthetic utility as precursors to a variety of functional groups, including alcohols, aldehydes, carboxylic acids,[37] hydroxamic acids,[38] esters, and amides.[39]

This reaction was found to require elevated temperatures relative to the maleimide coupling partners, in addition to a larger amount of the Lewis acids $BF_3 \cdot Et_2O$ and $LiNTf_2$. These reaction conditions reflect the decreased reactivity of the acyclic system, as well as the presence of additional Lewis basic sites on the oxazolidinone substrate. Although diastereoselectivities remained modest after optimization, the identity and stoichiometry of the co-Lewis acid additive nonetheless proved important for this reaction (Table 2).

Optimized reaction conditions allowed for the coupling of α,β-unsaturated *N*-acyl oxazolidinone electrophiles with alkenes bearing synthetic handles such as aryl halides (**5bg**), and an alkene derived from a pharmaceutical fragment (**5ah**). Hydrolysis of the oxazolidinone with lithium hydroperoxide provided the δ,ε-unsaturated carboxylic acid **12** in excellent yield (Scheme 5). Moreover, ytterbium-catalyzed alcoholysis using propargyl alcohol afforded ester **13** bearing an additional terminal alkyne function in excellent yields.[40]

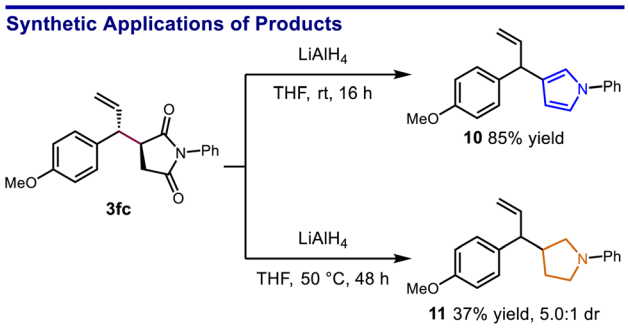
Phthalimide-protected vinylogous amide electrophiles

Encouraged by the results from α,β-unsaturated imides, we hypothesized that our system could also provide allylation products by nucleophilic addition to vinylogous amides (β-



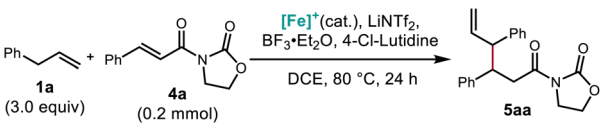
Scheme 3 Scope of 3-allylic pyrrolidine-2,5-dione products obtained from catalytic C–H allylic functionalization. Conditions: **1** (3.0 equiv.), **2** (0.2 mmol), $[Cp^*Fe(CO)_2(thf)]^+[BF_4]^-$ (20 mol%), $BF_3{\cdot}Et_2O$ (1.5 equiv.), 4-chlorolutidine (4.0 equiv.), $AgNTf_2$ (0.35 equiv.), toluene [1.5 M], 40 °C, 24 h. Isolated yields reported. [a]Conditions: $Mg(NTf_2)_2$ (0.35 equiv.).

enaminones), another challenging class of Michael acceptor susbtrates. Conjugate addition to the β-position of these substrates represents a straightforward and attractive route for



Scheme 4 Diversification of five-membered nitrogen heterocycles.

Table 2 Optimization for *N*-acyl oxazolidinone electrophiles

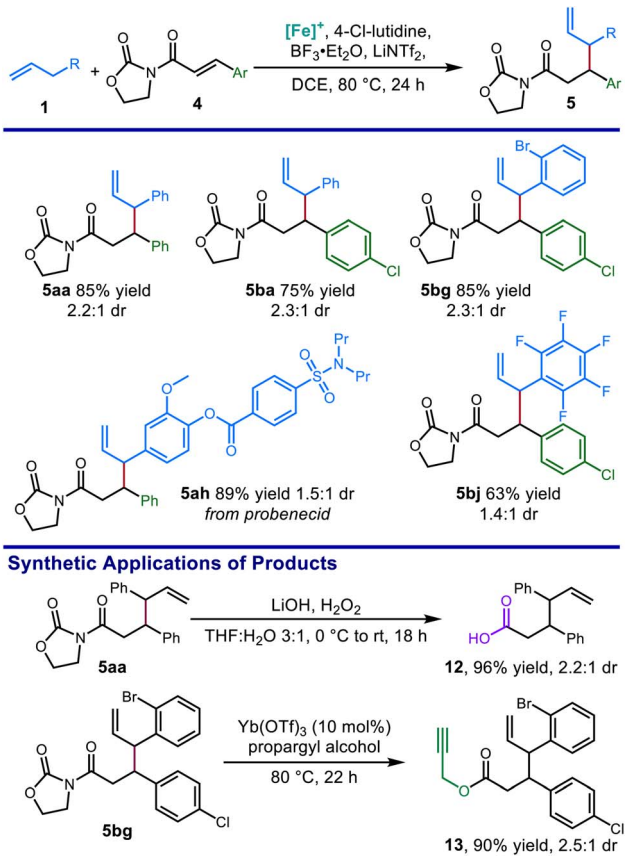


Entry	Ratio (LA/base/add.)	Additive	Yield[a] (%)
1	1.5/4/0.2	$AgNTf_2$	Trace
2	5/3/0.2	$AgNTf_2$	19
3	5/3/0.2	$Cu(NTf_2)_2$	42
4	5/3/0.2	$Yb(OTf)_3$	54
5	5/3/0.2	$Zn(OTf)_2$	57
6	5/3/0.2	$LiNTf_2$	67
7	5/3/1.0	$LiNTf_2$	85 (88)[b]

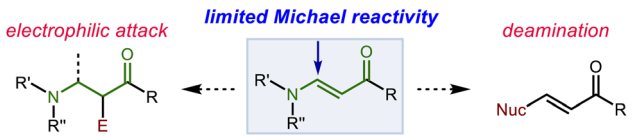
[a] Yields determined by ^1H NMR using 2,4-dinitrotoluene as the internal standard. [b] Isolated yield. Conditions: **1a** (3.0 equiv.), **4a** (0.2 mmol), $[Cp^*Fe(CO)_2(thf)]^+[BF_4]^-$ (20 mol%), $BF_3{\cdot}Et_2O$ (5.0 equiv.), 4-chlorolutidine (3.0 equiv.), $LiNTf_2$ (1.0 equiv.), DCE [1.5 M], 80 °C, 24 h.

quickly accessing β-substituted β-amino carbonyl compounds. However, this process faces two significant hurdles. First, the nitrogen substituent confers potentially undesirable nucleophilic character to the α-position. Moreover, electrophilicity of the β-position is attenuated by its unfavorable steric and electronic influence. Vinylogous amides thus tend to be sluggish Michael acceptors.[41–46] Additionally, when addition does occur at the β-position, E1cb elimination of the nitrogen substituent readily occurs. While some processes have capitalized on this phenomenon to produce new β-substituted α,β-unsaturated ketones, attempts to prepare β-amino ketones through conjugate addition are often plagued by formation of these compounds as side products.[47–52] Thus, the successful implementation of this strategy requires carbanion equivalents of high nucleophilicity while simultaneously demanding relatively mild conditions to ensure that the desired adduct survives the reaction conditions (Scheme 6).

We began our investigation with the addition of allylbenzene to the phthalimido enaminone **6a**. In contrast to the α,β-unsaturated imides explored earlier, $BF_3{\cdot}Et_2O$ was ineffective as the Lewis acid activator. Instead, we turned to silyl triflates as strong Lewis acids that irreversibly trap the incipient enolate



Scheme 5 Scope of allylic *N*-acyl oxazolidinone products obtained from catalytic C–H allylic functionalization and their synthetic applications. Conditions: **1** (3.0 equiv.), **4** (0.2 mmol), $[Cp^*Fe(CO)_2(thf)]^+[BF_4]^-$ (20 mol%), $BF_3{\cdot}Et_2O$ (5.0 equiv.), 4-Cl-lutidine (3.0 equiv.), $LiNTf_2$ (1.0 equiv.), DCE [1.5 M], 80 °C, 24 h. Isolated yields reported.

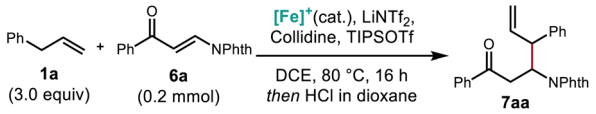


Scheme 6 Side reactions in competition with 1,4-addition to enaminones.

ion intermediates as silyl enol ethers, which could be cleaved in a subsequent workup step to reveal the β-phthalimido ketone.[36] We posited that this initial trapping as the silyl enol ether could also prevent the occurrence of deamination as a side reaction. In preliminary experiments, we found that an acidic workup (in contrast to fluoride-mediated or base-mediated desilylation) led to good yields of the ketone and minimal formation of the deaminated product.

Optimization of this reaction was carried out with careful attention to reagent stoichiometry. An increase of the reagents provided a corresponding increase in yield (Table 3, entry 2). The selection of TIPSOTf over TMSOTf was found to be highly beneficial to the reaction (entry 3). Other changes to the

Table 3 Optimization for phthalimido enaminones substrates



Entry	Ratio (LA/base/$LiNTf_2$)	Lewis acid	Temp.	Yield[a] (%)
1	1.5/2.0/0.6	TMSOTf	80	18
2	2.5/3.0/0.6	TMSOTf	80	37
3	2.5/3.0/0.6	TIPSOTf	80	90 (93)[b]
4	2.5/3.0/0.3	TIPSOTf	80	73
5	2.5/3.0/0.6	TIPSOTf	60	85

[a] Yields determined by ^1H NMR using 2,4-dinitrotoluene as the internal standard. [b] Isolated yield. Conditions: **1a** (3.0 equiv.), **6a** (0.2 mmol), $[Cp^*Fe(CO)_2(thf)]^+[BF_4]^-$ (20 mol%), TIPSOTf (2.5 equiv.), collidine (3.0 equiv.), $LiNTf_2$ (0.6 equiv.), DCE [1.5 M], 80 °C, 16 h. Then 4 N HCl in dioxane.

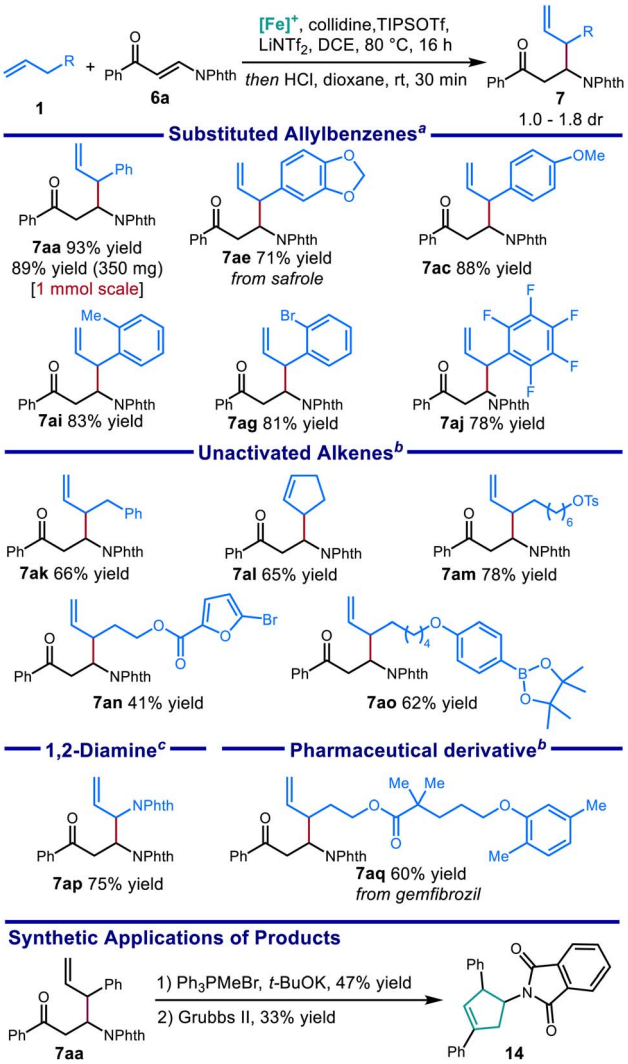
conditions, like decreasing the amount of $LiNTf_2$ additive or the reaction temperature, led to decreased yields (entries 4 and 5).

Using the optimized protocol, we investigated the scope of the alkene nucleophile. Allylbenzene coupling partners with a variety of substitution patterns provided excellent yields under the optimized conditions, including safrole (Scheme 7, **7ae**) and allylpentafluorobenzene (**7aj**). Changing the conditions by using TMPH (4 equiv.) in place of 2,4,6-collidine (3 equiv.) allowed a variety of electronically unactivated alkenes to be utilized, including cyclopentene (**7al**) and a terminal alkene incorporating a pharmaceutical fragment (**7aq**). The improved yields using the stronger base TMPH over weaker pyridine bases is consistent with the decreased C–H acidity of the electronically unactivated substrates in relation to allylbenzene derivatives, further validating the importance of correctly identifying suitable combinations of base and Lewis acid for each pairing of alkene and electrophile. Alkenes bearing functional groups such as an alkyl *p*-toluenesulfonate ester (**7am**), a boronic acid pinacol ester (**7ao**), and a five membered heterocycle (**7an**), were also good coupling partners in this reaction. Finally, with slightly modified conditions, coupling with a phthalimide-protected allylic amine (**7ap**) provided the protected allylic 1,2-diamine in good yield.

The synthetic value of this method was further demonstrated through the elaboration of the product into a new scaffold: under Wittig conditions, the phthalimido protected β-amino ketone provided the β-amino-δ,ε-unsaturated diene, which was then cyclized through ring closing olefin metathesis to give 3-aminocyclopentene **14**.[53]

Sulfonamide-protected vinylogous amide electrophiles

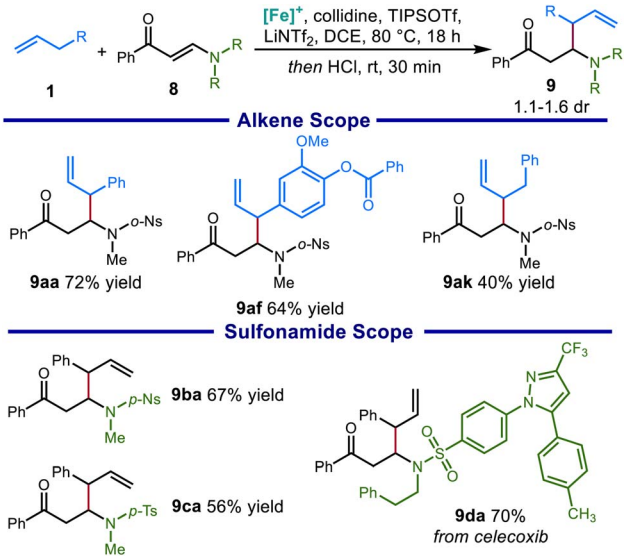
We then sought to expand this system to access β-substituted β-amino carbonyl compounds bearing a sulfonamide group on the nitrogen. Sulfonamide-bearing enaminones are a challenging substrate for this reaction due to the strong tendency toward deamination side reactions. This is reflected by the



Scheme 7 Scope of β-substituted β-phthalimido carbonyl compounds obtained from catalytic C–H allylic functionalization and synthetic applications of products. [a]Conditions 1: **1** (3.0 equiv.), **6a** (0.2 mmol), $[Cp^*Fe(CO)_2(thf)]^+[BF_4]^-$ (20 mol%), TIPSOTf (2.5 equiv.), collidine (3.0 equiv.), $LiNTf_2$ (0.6 equiv.), DCE [1.5 M], 80 °C, 16 h. Then 4 N HCl in dioxane. [b]Conditions 2: Base = 2,2,6,6-tetramethylpiperidine (4.0 equiv.). [c]Conditions 3: $LiNTf_2$ (0.8 equiv.). Isolated yields reported.

current lack of reported protocols to directly produce β-substituted β-amino ketones through 1,4-conjugate addition to sulfonyl-protected vinylogous amides. Optimizing the reaction conditions, we found that even milder conditions were necessary to avoid decomposition of the sensitive starting materials and products, including reduced reaction temperature and fewer equivalents of base (see the ESI for details†).

These modifications allowed us to prepare a range of β-substituted β-sulfonamido ketones, including products derived from allylbenzene (**9aa**), an ester-containing eugenol derivative (**9af**), and an unactivated alkene (**9ak**). The protocol was also found to tolerate a wide variety of sulfonamides, including a *p*-nitrobenzenesulfonamide (**9ba**) and a sulfonamide derived from celecoxib (**9da**) (Scheme 8).



Scheme 8 Scope of β-substituted β-sulfonamido carbonyl compounds obtained from catalytic C–H allylic functionalization. Conditions: **1** (3.0 equiv.), **8** (0.2 mmol), $[Cp^*Fe(CO)_2(thf)]^+[BF_4]^-$ (20 mol%), TIPSOTf (2.5 equiv.), collidine (2.5 equiv.), $LiNTf_2$ (0.6 equiv.), DCE [1.5 M], 60 °C, 16 h. Then 4 N HCl in dioxane. Isolated yields reported.

Conclusions

In summary, we have developed a series of iron-catalyzed allylic C–H functionalization reactions that provide allylated derivatives of nitrogen-containing carbonyl compounds in a general and modular approach. These diverse products were formed through the deprotonative generation of catalytic allyliron intermediates from allylbenzenes and other olefin derivatives which then undergo regiospecific addition to α,β-unsaturated carbonyl electrophiles. Further explorations of this strategy towards improved stereocontrol are ongoing in our laboratory and will be reported in due course.

Data availability

The data that support the findings of this study are available in the ESI† of this article.

Author contributions

S. G. S. designed and performed the experiments, analyzed the data, and wrote the manuscript. Y.-M. W. conceptualized the project, analyzed the data, and revised the manuscript.

Conflicts of interest

There are no conflicts to declare.

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