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Iron-Catalyzed C–H/N–H Activation by Triazole Guidance: Versatile Alkyne Annulation

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Iron-catalyzed C–H/N–H functionalizations were achieved by the aid of modular triazole amides. The alkyne annulation allowed for the expedient synthesis of valuable isoquinolone scaffolds with high levels of chemo-, site- and regio-selectivities.

Isoquinolones represent a privileged structural motif that occurs in biological active molecules, as well as antitumor, anti-malaria and anti-inflammatory compounds.[1] Traditional methods for their syntheses, including the Bischler-Napieralski and the Pictet-Spengler reaction, often suffer from the need for pre-activated substrates and harsh reaction conditions, among others.[2] However, over the last decade, transition-metal catalyzed C–H functionalizations[3] have emerged as a powerful alternative for conventional isoquinolone syntheses. Thus, toxic and/or precious 4d and 5d transition metals were exploited,[4] while the use of cost-effective and environmentally-benign 3d metals offered a viable option with bidentate directing groups.[5,6] Very recently, our group established a novel family of triazolylamine (TAM) directing groups,[7] which emerged as a powerful and modular alternative to the frequently employed 8-aminoquinoline directing group, particularly highlighting the prospect of establishing novel iron-catalyzed C–H activations.[8,9]

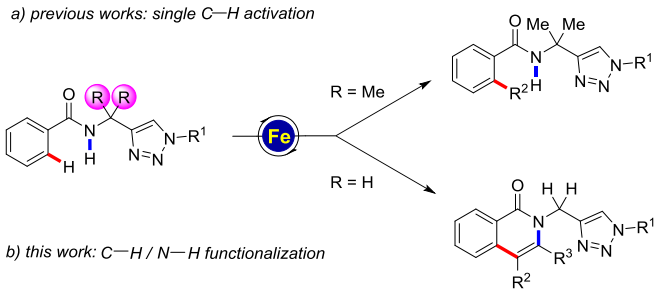
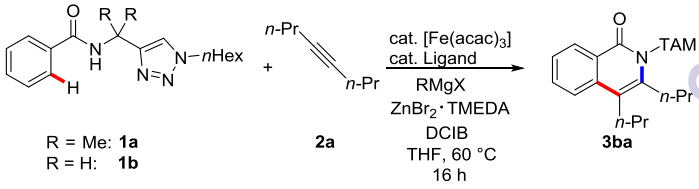


Figure 1 Chemo-divergent iron-catalyzed C–H functionalizations by modular triazole guidance.

Despite considerable advances, all triazole-assisted C–H activations were thus far limited to single C–H functionalization. In this context, we have very recently disclosed an iron-catalyzed C–H alkynylation, enabling a C–H alkynylation/deprotection sequence for the assembly of 3,4-unsubstituted isoquinolones.[9c] In contrast, we now probed the first TAM-assisted C–H/N–H functionalization for an iron-catalyzed alkyne annulation strategy. Indeed, the modular nature of the TAM group facilitated the iron-catalyzed C–H/N–H activation for the synthesis of 3,4-decorated isoquinolones, on which we report herein (Figure 1).[10,11]

Preliminary orienting reactions with alkyne **2a** highlighted the importance of the Thorpe-Ingold effect in controlling the chemo-selectivity of the triazole-guided C–H/N–H activation.[12] Hence, while the previously used *gem*-disubstitution on the methylene backbone resulted in a lack of reactivity (Table1, entry 1), triazolyl amide **1b** being devoid of the *gem*-disubstitution enabled the synthesis of isoquinolone **3ba** (entry 2).

Table 1 Optimization of the iron-catalyzed C–H annulation



R = Me: **1a**
R = H: **1b**

2a

3ba

Entry	R	Ligand	RMgX	Yield (%)[a]
1	Me (**1a**)	dppen	$TMS(CH_2)MgCl$	---
2	H (**1b**)	dppen	$TMS(CH_2)MgCl$	74
3	H	dppen	$TMS(CH_2)MgCl$	---[b]
4	H	dppen	$TMS(CH_2)MgCl$	16[c]
5	H	dppen	PhMgCl	5
6	H	dppen	CyMgCl	---
7	H	dppen	*i*-PrMgBr	57
8	H	d*t*B-bipy	$TMS(CH_2)MgCl$	---
9	H	dppf	$TMS(CH_2)MgCl$	---
11	H	phen	$TMS(CH_2)MgCl$	---
12	H	dppe	$TMS(CH_2)MgCl$	51
13	H	dppe	---	---
14	H	dppe	*i*PrMgBr	16[c]
15	**H**	**dppe**	***i*PrMgBr**	**81**

[a] Reaction conditions: **1a** (0.30 mmol), $Fe(acac)_3$ (10 mol %), ligand

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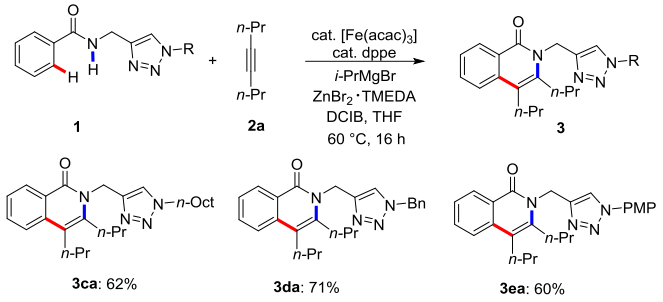
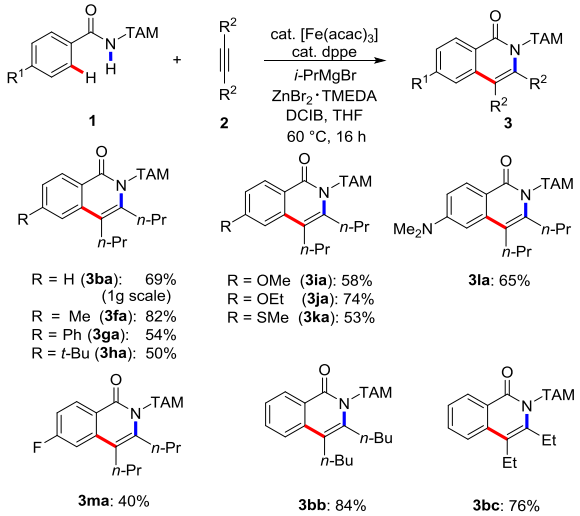
(15 mol %), RMgX (1.50 mmol), $ZnBr_2$·TMEDA (0.45 mmol), DCIB (0.60 mmol), THF (0.50 ml), 50 °C, 16 h; yields of isolated product. [b] Reaction without DCIB. [c] Reaction without $ZnBr_2$·TMEDA. DCIB=1,2-dichloro-2-methylpropane.

It is noteworthy that zinc salts and 1,2-dichloroisobutane[13] proved to be mandatory for promoting the C–H functionalization (entries 3-4), whereas among a variety of ligands, dppe was identified as being optimal (entries 5-11).
The optimized catalyst was found to be broadly applicable to the step-economical C–H/N–H transformation of different *N*-triazole-substituted benzamides **1** (Scheme 1).



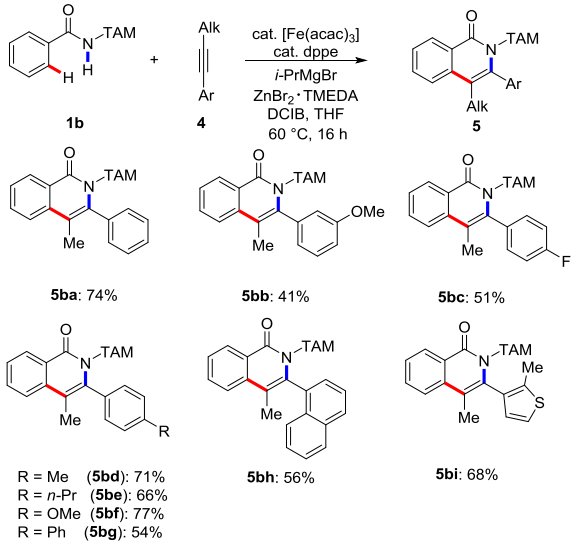
Scheme 1 Impact of the TAM substitution pattern

Furthermore, a representative set of isoquinolones **3** was accessed by the versatile iron-catalyzed C–H/N–H functionalization strategy (Scheme 2). Thus, amides **1** displaying alkyl- or aryl-substituents were found competent substrates, site-selectively delivering the corresponding isoquinolones **3fa**-**3ha**. The catalytic system was found tolerant to ethers, thioethers and even amines (**3ia**-**3la**). Electron-withdrawing groups on the arene led to somewhat lower yields, highlighting the importance of electronic effects on the C–H/N–H functionalization regime. Further, different symmetrical alkynes could be used likewise, thereby delivering the corresponding isoquinolones **3bb**-**bc**.



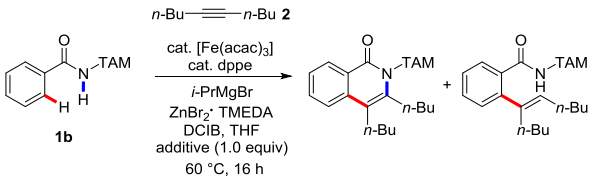
Scheme 2 Scope of iron-catalyzed C–H/N–H functionalization of benzamides 1.

The selectivity of C–H/N–H functionalizations with unsymmetrical alkynes **4** was subsequently investigated. To this end, several aryl-1-butyne derivatives were submitted to the iron-catalyzed C–H/N–H activation. To our delight, the synthesis of isoquinolones **5** proceeded with complete regio-selectivity,[13] which can be rationalized by the compact nature of the iron catalyst (Scheme 3). Thereby, diversely decorated arenes bearing electron-donating or electron-withdrawing groups were efficiently converted, delivering the corresponding isoquinolones **5ba**-**bg**. The protocol was also found to be competent in the presence of extended aromatic systems, such as naphthalene derivatives and heteroarenes, providing isoquinolones **5bh** and **5bi** with complete regio-selectivity.



Scheme 3 Regio-selective iron-catalyzed C–H/N–H activation

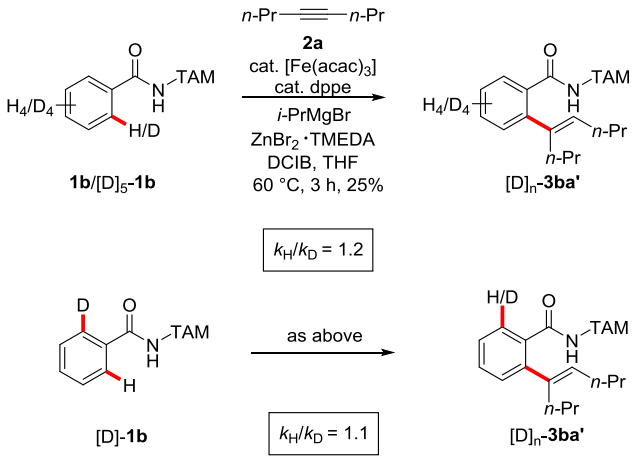
Given the outstanding selectivity features of the triazole-guided iron-catalyzed C–H/N–H activation, we became intrigued to elucidate its mode of action. Indeed, reactions conducted in the presence of typical radical scavengers, led to only a slight decrease in catalytic efficacy. Notably, the hydroarylation product **3bb´** was isolated here as a by-product (Scheme 4).



additive	**3bb** (%)	**3bb'** (%)
none	84	--
TEMPO	58	15
BHT	46	24
galvinoxyl	43	20

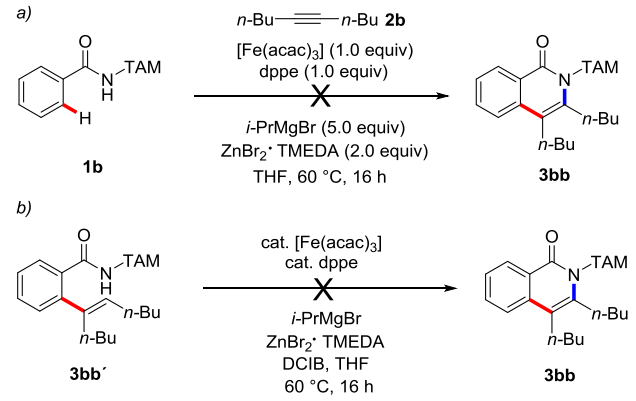
Scheme 4 Probing SET-type mechanism

These findings render a radical-based C–H functionalization less likely to be operative, and indicate an initial migratory alkyne insertion as the key step. Furthermore, by performing inter- and intramolecular kinetic experiments we observed a lack of primary isotopic effect within the initial formation of the hydroarylation product **3ba'**, which suggests the C–H metalation step not to be kinetically-relevant (Scheme 5).



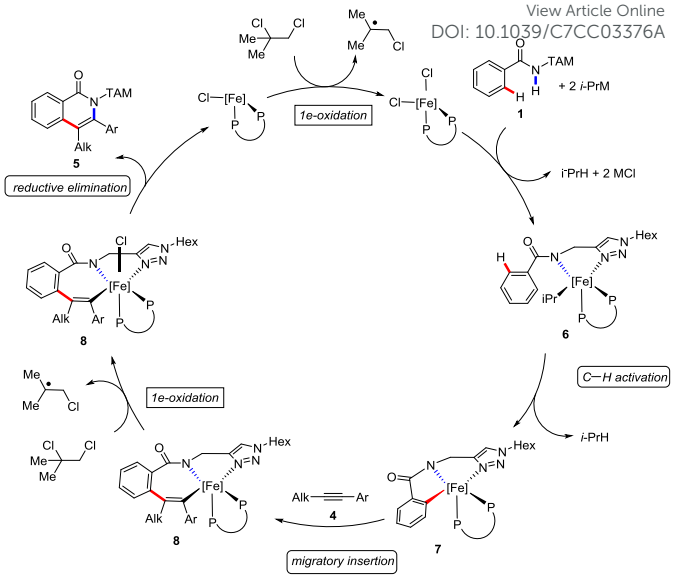
Scheme 5 Inter- and intramolecular KIE studies

Moreover, a stoichiometric reaction in the absence of the oxidant failed to deliver any product, thus rendering a low-valent iron catalysis regime unlikely to be operative (Scheme 6, a).[14] Finally, when submitting intermediate **3bb´** to otherwise identical reaction conditions (Scheme 6, b), a conversion to the isoquinolone **3bb** was not viable, suggesting a 7-membered metallacycle as the key intermediate for the C–N formation.



Scheme 6 Mechanistic experiments

Based on our mechanistic studies, we propose a plausible catalytic cycle for the alkyne annulation to initiate by the facile C–H metalation to generate metallacyle **7**. Subsequently, a migratory insertion of alkyne **2** occurs, delivering the key intermediate **8**, while a single electron oxidation and the subsequent reductive elimination provides the final product **3** (Scheme 7).



Scheme 7 Plausible catalytic cycle

Conclusions

In conclusion, we have developed the unprecedented iron-catalyzed C–H/N–H functionalization by triazole[15] assistance. The modular nature of the TAM motif set the stage for a facile C–H activation within an oxidative C–H/N–H functionalization manifold. Thereby, a versatile iron catalyst enabled alkyne annulations for the synthesis of synthetically meaningful 3,4-substituted isoquinolones with ample scope.

Acknowledgements

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