Iron Catalysis

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Expedient Iron-Catalyzed C–H Allylation/Alkylation by Triazole Assistance with Ample Scope

*Gianpiero Cera, Tobias Haven, and Lutz Ackermann**

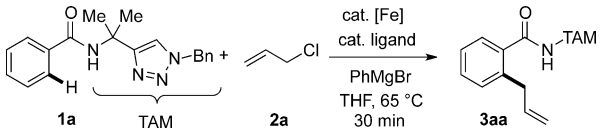
Abstract: *Triazole assistance set the stage for a unified strategy for the iron-catalyzed C–H allylation of arenes, heteroarenes, and alkenes with ample scope. The versatile catalyst also proved competent for site-selective methylation, benzylation, and alkylation with challenging primary and secondary halides. Triazole-assisted C–H activation proceeded chemo-, site-, and diastereo-selectively, and the modular TAM directing group was readily removed in a traceless fashion under exceedingly mild reaction conditions.*

The selective *ortho*-functionalization of carboxylic acid derivatives is a major challenge in organic synthesis. In contrast to established strategies,[1] transition-metal-catalyzed C–H alkylation has emerged as a particularly versatile approach for step-economical C–C bond formation.[2] C–H alkylation and allylation reactions have mostly involved catalysts based on precious 4d transition metals; however, these protocols often suffer from long reaction times, high reaction temperatures, and/or moderate selectivities.[3,4] Very recently, considerable progress has been made with inexpensive iron complexes to establish novel C–C forming processes.[5] A particularly powerful approach involves the use of a bidentate directing group developed by Daugulis and co-workers.[6] This directing group derived from 8-aminoquinoline (8-AQ) enables *ortho*-selective C–H allylation and alkylation reactions, as were devised by Nakamura and co-workers, with important contributions by Cook and co-workers.[7] These transformations were restricted to the AQ motif, the structural modification of which is challenging. More importantly, the removal of the bidentate directing group generally called for harsh reaction conditions, namely, concentrated HCl at 130 °C.[6,7] To address these limitations, our research group has recently established a novel family of highly modular bidentate directing groups,[8] which are particularly effective in promoting iron-catalyzed C–H transformations.[8a,c]

Within our program on sustainable C–H functionalization, we have now devised a unified strategy for iron-catalyzed C–H allylation/alkylation through triazole assistance. Notable features of our approach include 1) the use of inexpensive iron compounds for challenging C–H activation reactions, 2) a versatile catalyst that enabled a plethora of C–H allylation and alkylation reactions of arenes and alkenes, and 3) a novel protocol for the removal of the TAM auxiliary under exceedingly mild reaction conditions.

At the outset of our studies, we probed the unprecedented use of inexpensive and readily available allyl chlorides **2** in the iron-catalyzed C–H functionalization of triazolyldimethyl (TAM) amide **1a** (Table 1, see also Tables S1–S4 in the Supporting Information).[9] The iron-catalyzed C–H allylation with substrate **2a** proceeded most efficiently with catalysts derived from $FeCl_3$ or $Fe(acac)_3$ and the ligand dppe (Table 1; entries 1–5). A test reaction verified that the iron catalyst was essential. Notably, the AQ-derived auxiliary was found to be ineffective under otherwise identical reaction conditions (Table 1; entry 7), thus illustrating the unique features of the TAM directing group. Besides allyl chlorides **2**, allylic phosphonates, sulfonates, carbonates, and acetates proved to be viable electrophiles for the C–H allylation.[9]

Table 1: Optimization of the iron-catalyzed C–H allylation.[a]



1a TAM **2a** **3aa**

Entry	[Fe]	Ligand	**3aa** [%][b]
1	$[Fe(acac)_3]$	dppen	17
2	$[Fe(acac)_3]$	dppbz	14
3	$FeCl_2$	dppe	75
4	**$FeCl_3$**	**dppe**	**85**
5	**$[Fe(acac)_3]$**	**dppe**	**84**
6	–	–	–
7	$[Fe(acac)_3]$	dppe	12[c]

[a] Reaction conditions: **1a** (0.20 mmol), [Fe] (10 mol%), ligand (15 mol%), PhMgBr (0.75 mmol), **2a** (0.75 mmol), THF (0.1 M), 65 °C, 30 min. [b] Yield of the isolated product. [c] The AQ-derived auxiliary was used instead of the TAM group. acac = acetylacetonate, Bn = benzyl, dppen = *cis*-1,2-bis(diphenylphosphino)ethylene, dppe = 1,2-bis(diphenylphosphino)ethane, dppbz = 1,2-bisdiphenylphosphinobenzene.

The optimized catalyst proved amenable to the transformation of various triazole-functionalized benzamides **1** (Table 2). The spiro substitution pattern in the amide backbone of substrate **1b** did not diminish the yield (Table 2, entry 1), and also *N*-alkylated or *N*-arylated triazoles provided the desired products **3ca** and **3da** efficiently (entries 2 and 3). Notably, our triazolylmethylamide (TAH)[8b,d] directing group (in **1e**) was found to be unsuitable for the C–H transformation (Table 2, entry 4).

[*] Dr. G. Cera, T. Haven, Prof. Dr. L. Ackermann
Institut für Organische und Biomolekulare Chemie
Georg-August-Universität
Tammannstrasse 2, 37077 Göttingen (Germany)
E-mail: Lutz.Ackermann@chemie.uni-goettingen.de
Homepage: http://www.ackermann.chemie.uni-goettingen.de

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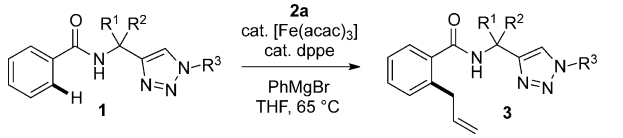
Table 2: Influence of the substitution pattern.[a]

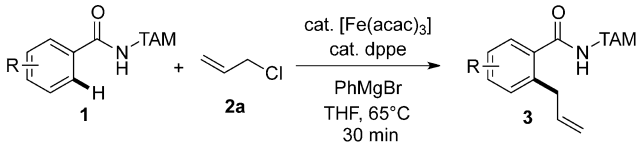


Entry	R^1	R^2	R^3	3
1	-$(CH_2)_5$-		Bn	**3ba**: 64%
2	Me	Me	*n*Pr	**3ca**: 77%
3	Me	Me	PMP	**3da**: 78%
4	H	H	*n*Hex	**3ea**: –

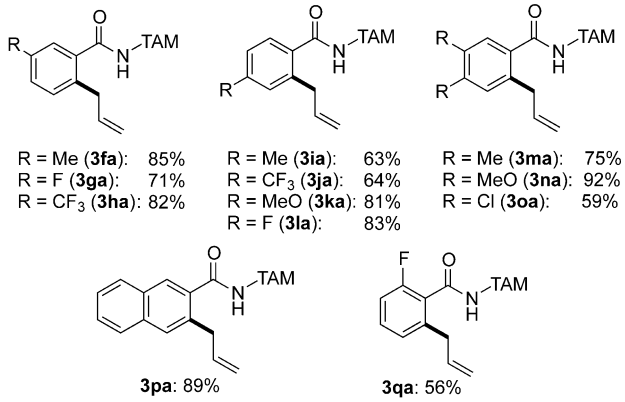
[a] Reaction conditions: **1** (0.20 mmol), $[Fe(acac)_3]$ (10 mol%), dppe (15 mol%), PhMgBr (0.75 mmol), **2a** (0.75 mmol), THF (0.2 M), 65 °C, 30 min. Yields are for the isolated products. PMP = *p*-methoxyphenyl.

In terms of the substrate scope, benzamides **1** with *ortho*-, *meta*-, or *para*-substituents were smoothly converted into the desired products **3fa–qa** (Scheme 1). The allylation of heteroaromatic thiophene and pyrrole derivatives to give products **3sa** and **3ta** occurred site-selectively, and the unprecedented synthesis of ferrocenyl derivative **3ra** was also possible. Notably, the optimized catalyst was also applicable to the first iron-catalyzed C–H allylation of alkenes. Thus, products **3ua–za** were accessible in good yields with excellent diastereoselectivity.[9]

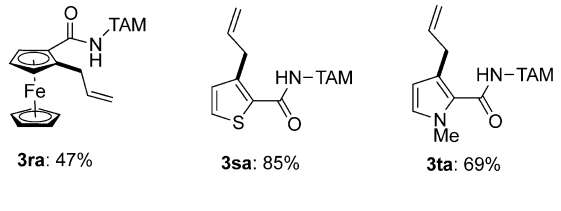
Subsequently, we explored the versatility of the optimized catalytic system with differently substituted allyl chlorides **2** (Scheme 2). Thus, with (*E*)-crotyl chloride (**2b**), the branched



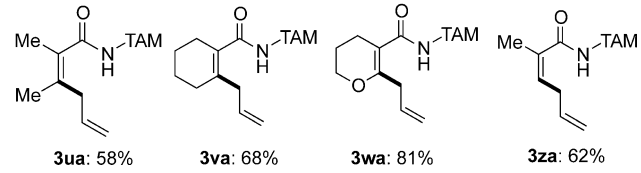
a) arenes



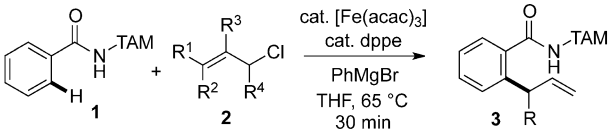
b) ferrocene and heteroarenes



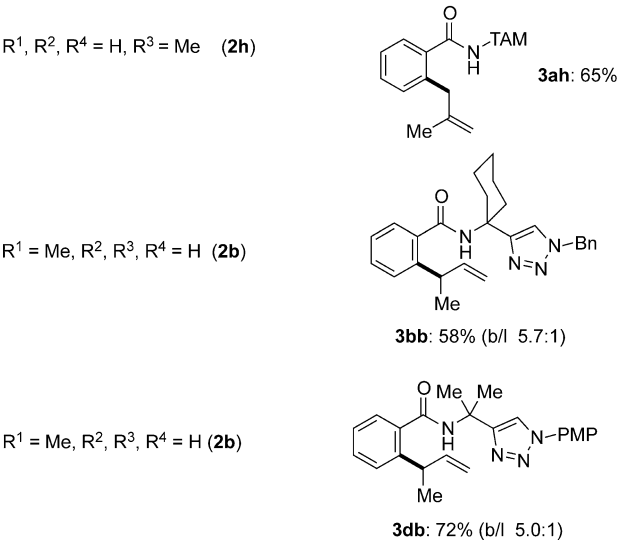
c) alkenes



Scheme 1. Iron-catalyzed C–H allylation with allyl chloride (**2a**).



R^1 = Me, R^2, R^3, R^4 = H (**2b**) — **3ab**: R = Me, 80% (b/l 4.2:1)
R^1, R^2, R^3 = H, R^4 = Me (**2c**) — **3ac**: R = Me, 75% (b/l 2.5:1)
R^1 = *n*Pr, R^2, R^3, R^4 = H (**2d**) — **3ad**: R = *n*Pr, 71% (b/l 3.1:1)
R^1 = *n*Bu, R^2, R^3, R^4 = H (**2e**) — **3ae**: R = *n*Bu, 65% (b/l 3.2:1)
R^1 = *i*Pr, R^2, R^3, R^4 = H (**2f**) — **3af**: R = *i*Pr, 62% (b/l 2.0:1)
R^1, R^3, R^4 = H, R^2 = Et (**2g**) — **3ag**: R = Et, 58% (b/l 5.5:1)



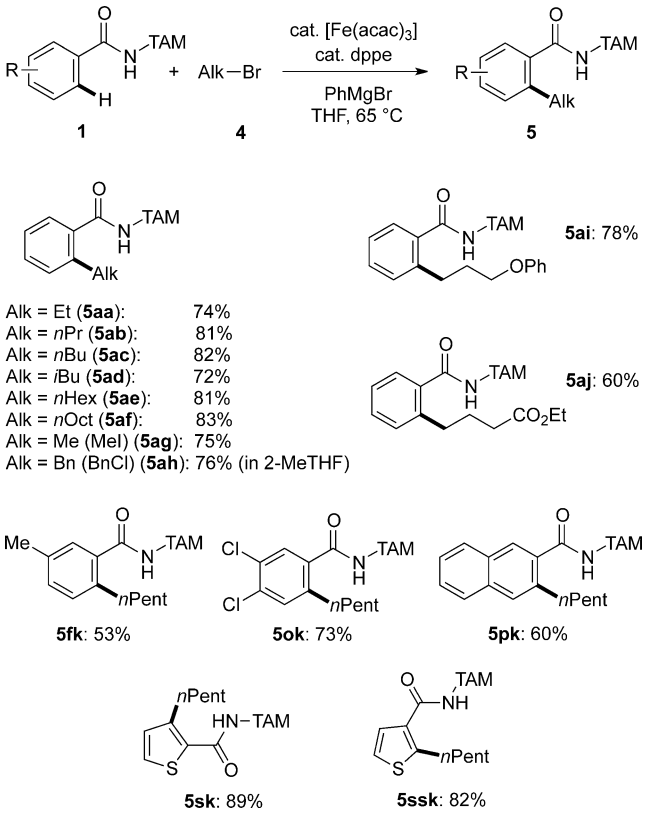
Scheme 2. Iron-catalyzed C–H allylation with substituted allyl chlorides **2**.

allylated benzamide **3ab** was obtained in good yield with moderate regioselectivity.[10] To gain insight into the reaction mechanism, we next used the secondary allyl chloride **2c**, which furnished the product **3ac** with a comparable regioselectivity. These findings provided strong support for the formation of an η^3-allyl intermediate, whereby the regioselectivity is dominated by the nature of the phosphine ligand, in resemblance of Plietker's observations on iron-catalyzed coupling reactions.[11] Thereafter, several *E*-configured allyl chlorides were tested. For instance, substrates **2d–f** furnished the corresponding branched allylated benzamides **3ad–af** by chelation assistance. Furthermore, the use of a *Z*-allyl chloride, **2g**, resulted in the formation of product **3ag** with good selectivity for the branched product. The β-substituted allyl chloride **2h** also proved to be a viable substrate for the

iron-catalyzed C–H activation. Finally, we explored the influence of the triazole auxiliary in the synthesis of arenes **3bb** and **3db**, which were obtained in high yields and with good selectivity for the branched isomers.

We investigated the reaction mechanism by carrying out competition experiments with isotopically labeled substrates and found considerable intra- and intermolecular kinetic isotopic effects (KIEs) of $k_H/k_D \approx 1.8$ and 2.1, respectively,[9] thus suggesting that C–H cleavage occurs as or prior to the turnover-limiting step. Moreover, the use of the radical scavenger 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) in stoichiometric amounts led only to a slight decrease in the yield to 65%, which indicates that a radical-based reaction mechanism is less likely to be operativehere.

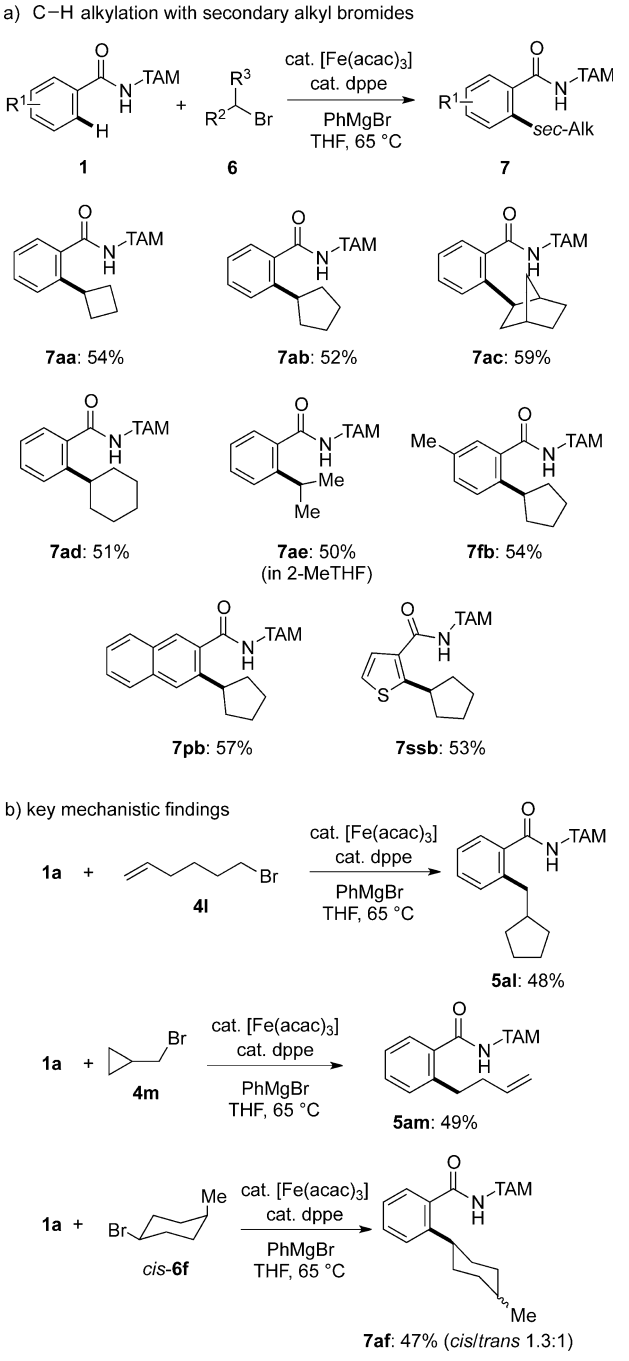
In consideration of the unique catalytic activity of our TAM-assisted iron-catalyzed C–H allylation, we tested the feasibility of challenging C–H alkylation reactions (Scheme 3). To our delight, the direct alkylation of benzamide



Scheme 3. TAM-assisted iron-catalyzed C–H alkylation with primary alkyl halides **4**.

1 proceeded well with various alkyl bromides **4a–f** to deliver compounds **5aa–af** under our standard reaction conditions. Furthermore, methyl iodide (**4g**) was identified as a suitable organic electrophile. With this reagent, benzamide **5ag** was formed in good yield with excellent monoalkylation selectivity.[12] Furthermore, C–H benzylation was observed with benzyl chloride (**4h**). The robustness of the iron catalyst was reflected by its tolerance of ether and ester functionalities, among others. Benzamides **1f,o,p** bearing *meta*-substituents were alkylated at the less congested C–H bond, and thiophenes **5sk** and **5ssk** were also accessible.

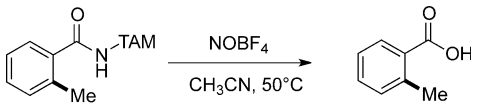
Intriguingly, more challenging secondary alkyl bromides **6a–e** also proved to be competent substrates under the optimized reaction conditions (Scheme 4a). A variety of *sec*-alkylated benzamides **7aa–ae** were thus synthesized in a site-selective fashion. The *exo*-norbornyl bromide **6c** gave selectively the *exo* product **7ac**. Also, acyclic 2-bromopropane (**6e**) was identified as a suitable substrate. The protocol proved to be widely applicable, and hence allowed for the C–H activation of *meta*-substituted benzamides to furnish products



Scheme 4. Iron-catalyzed C–H alkylation with secondary alkyl halides **6** and mechanistic findings.

7fb and **7pb**, as well as thiophene **7ssb**. To unravel the working mode of the catalyst (Scheme 4b), we first submitted 6-bromohex-1-ene (**4l**) to the optimized reaction conditions and observed the formation of the cyclized product **5al**. Second, the use of cyclopropylmethyl bromide (**4m**) afforded the homoallylated product **5am**. Next, the presence of radical inhibitors, such as TEMPO, led in this case to a significantly decreased conversion of 20%.[9] Furthermore, the reaction of diastereomerically pure *cis*-1-bromo-4-methylcyclohexane (**6f**) with **1a** delivered the alkylated benzamide **7af** with almost complete erosion of the stereochemical information. All of these observations can be rationalized in terms of a single-electron-transfer-type reaction mechanism.[13]

Finally, we devised a novel protocol for the facile removal of the TAM directing group under mild reaction conditions (Scheme 5).[14] Thus, $NOBF_4$[15] promoted TAM cleavage at a reaction temperature of only 50°C to furnish the desired carboxylic acid **8ag** in high yield.



5ag **8ag**: 87%

Scheme 5. Mild removal of the TAM directing group.

In summary, we have developed a unified strategy for iron-catalyzed C–H allylation, benzylation, methylation, and alkylation with primary as well as secondary alkyl halides. Thus, triazole assistance enables the site-selective C–H functionalization of arenes, heteroarenes, and alkenes. Our strategy features the use of a removable directing group, which was cleaved in a traceless fashion under exceedingly mild reaction conditions.

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Keywords: alkylation · allylation · C–H activation · iron · triazoles

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[9] For details, see the Supporting Information.

[10] A reaction run with $Fe(acac)_3$ (20 mol %), (*S*,*S*)-dipamp (30 mol %), crotyl chloride (**2b**; 0.75 mmol), and PhMgBr (4.5 equiv) in THF (0.2 M) at ambient temperature afforded **4a** in 58 % yield (b/l 4.5:1, 7 % *ee*; see the Supporting Information).

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[12] For advances with rhodium and palladium catalysts, see: a) F. Pan, Z.-Q. Lei, H. Wang, H. Li, J. Sun, Z.-J. Shi, *Angew. Chem. Int. Ed.* **2013**, *52*, 2063 – 2067; *Angew. Chem.* **2013**, *125*, 2117 – 2121; b) S. R. Neufeldt, C. K. Seigerman, M. S. Sanford, *Org. Lett.* **2013**, *15*, 2302 – 2305; c) H.-X. Dai, A. F. Stepan, M. S. Plummer, Y.-H. Zhang, J.-Q. Yu, *J. Am. Chem. Soc.* **2011**, *133*, 7222 – 7228; d) Ref. [3c]; e) Y. Zhang, J. Feng, C.-J. Li, *J. Am. Chem. Soc.* **2008**, *130*, 2900 – 2901; f) R. Giri, N. Maugel, J. Li, D. Wang, S. P. Breazzano, L. B. Saunders, J.-Q. Yu, *J. Am. Chem. Soc.* **2007**, *129*, 3510 – 3511; g) X. Chen, J. Li, X. Hao, C. E. Goodhue, J.-Q. Yu, *J. Am. Chem. Soc.* **2006**, *128*, 78 – 79; for a low-valent cobalt catalyst, see: h) Q. Chen, L. Ilies, N. Yoshikai, E. Nakamura, *Org. Lett.* **2011**, *13*, 3232 – 3234.

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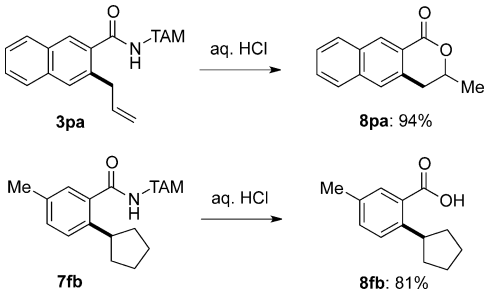
[14] The TAM group could also be removed under acidic reaction conditions that we have described previously; see Ref. [8c].



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