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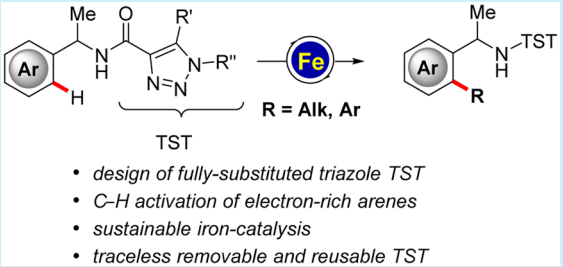
Tri-Substituted Triazole-Enabled C−H Activation of Benzyl and Aryl Amines by Iron Catalysis

Zhigao Shen,[†] Gianpiero Cera,[†] Tobias Haven, and Lutz Ackermann*

Institut für Organische und Biomolekulare Chemie, Georg-August-Universität, Tammannstraße 2, 37077 Göttingen, Germany

Supporting Information

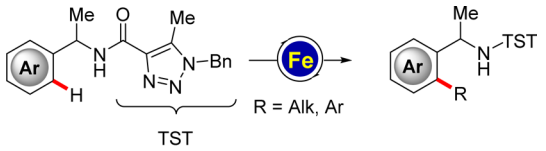
ABSTRACT: The design of trisubstituted triazoles set the stage for proximity-induced iron-catalyzed C−H activation of benzyl and aryl amines with ample scope. Thereby, C−H alkylations and C−H arylations proved viable with high levels of chemo and positional selectivities by means of racemization-free iron catalysis with the reusable triazole being removed in a traceless fashion.



Benzylamines represent the key molecular motif of various natural products and bioactive compounds.[1] As a consequence, the development of flexible strategies for their selective functionalization continues to be in high demand. A step-economical approach toward this goal exploits the activation of otherwise inert C−H bonds.[2] In this context, major advances have been achieved by means of precious, toxic transition metals.[3] In sharp contrast, the use of inexpensive, environmentally benign base metals[4] only recently emerged as a viable alternative for selective C−H activation chemistry. Despite considerable progress,[5] the direct functionalization of benzylamines remains particularly challenging because of their electron-rich nature and their geometrical flexibility within the chelation-assisted C−H metalation. In recent years, iron catalysis has been identified as an increasingly powerful tool in C−H activation chemistry.[6] However, the potential of iron-catalyzed C−H activation has thus far been largely limited to the modification of electron-deficient benzamides.[7,8] Contrastingly, we became attracted to developing an unprecedented iron-catalyzed C−H functionalization by triazole[9] assistance on inherently electron-rich benzylamines. To this end, we designed a set of novel tri-substituted 1,2,3-triazoles (TST), which set the stage for versatile iron-catalyzed C−H activations on electron-rich benzylamines including the direct installation of the medicinally relevant[10] methyl group (Scheme 1).

At the outset of our studies, we probed the TST benzylamide **1a** for the envisioned iron-catalyzed C−H methylation manifold.[11] Preliminary results revealed that nitrogen or NHC ligands fell short in enabling the desired C−H methylation (Table 1, entries 1−3). The bidentate dppe ligand gave only unsatisfactory results, which could be rationalized with the need for a more rigid coordination environment on iron (entry 4). In good agreement with this hypothesis, dppz and dppen led to the formation of the desired compound **2a** in synthetically useful yields (entries 5 and 6), particularly when

Scheme 1. Iron-Catalyzed C−H Activations on Electron-Rich Benzylamines by Fully-Substituted Triazoles



2,3-dichlorobutane[7b] was used as a mild oxidizing agent (entry 7).

With the optimized reaction conditions in hand, we explored the influence exerted by the TST substitution pattern on the catalytic efficacy. Thus, the iron catalysts tolerated various benzylamines, with the sterically congested *gem*-disubstituted benzylamine **1b** being efficiently converted (Scheme 2). The iron-catalyzed C−H activation proved amenable to differently *N*-substituted triazoles including alkyl and aryl-decorated derivatives **1c,d**. The tertiary amide **1e** failed to undergo C−H methylation, probably due to an anionic bidentate coordination mode on iron. It is particularly noteworthy that the frequently used, powerful picolinic acid-derived[12] benzylamine **1f** was significantly less effective under otherwise identical reaction conditions.

Thereafter, we probed the versatility of our iron-catalyzed C−H activation with differently substituted benzylamines **1**. To our delight, *ortho*-functionalized substrates furnished the products **2g−l** in good-to-excellent yields while tolerating both electron-donating and electron-withdrawing groups (Scheme 3). Also, the aromatic naphthalene-derivative **1m**

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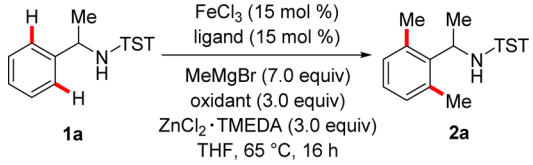
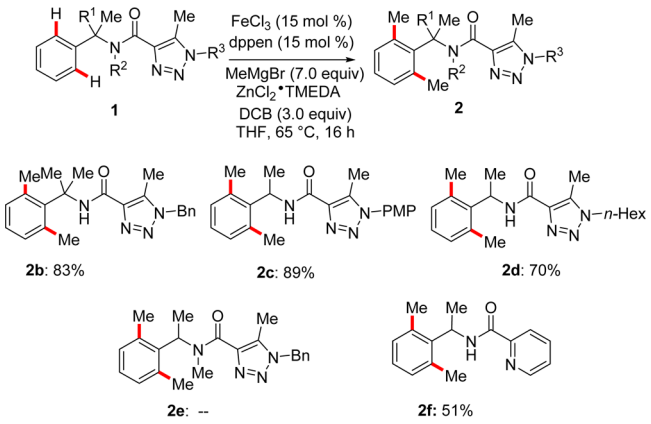
Table 1. Iron-Catalyzed C−H Methylations of Benzylamine 1a[a]



entry	ligand	oxidant	2a [%]
1	–	DCB	–
2	dtbpy	DCB	–
3	IPrHCl	DCB	–
4	dppe	DCB	21
5	dppbz	DCB	45
6	dppen	DCIB	53
7	dppen	DCB	86

[a]Reaction conditions: **1a** (0.20 mmol), $FeCl_3$ (15 mol %), ligand (15 mol %), MeMgBr (1.40 mmol), $ZnCl_2$·TMEDA (0.60 mmol), oxidant (0.60 mmol), THF (0.5 M), 65 °C, 16 h. Isolated yields. dppe = 1,2-bis(diphenylphosphino)ethane; dppbz = 1,2-bis(diphenylphosphino)-benzene; dppen = 1,2-bis(diphenylphosphino)ethene. DCB = 2,3-dichlorobutane. DCIB = 1,2-dichloro-2-methylpropane.

Scheme 2. Influence of the TST Substitution Pattern

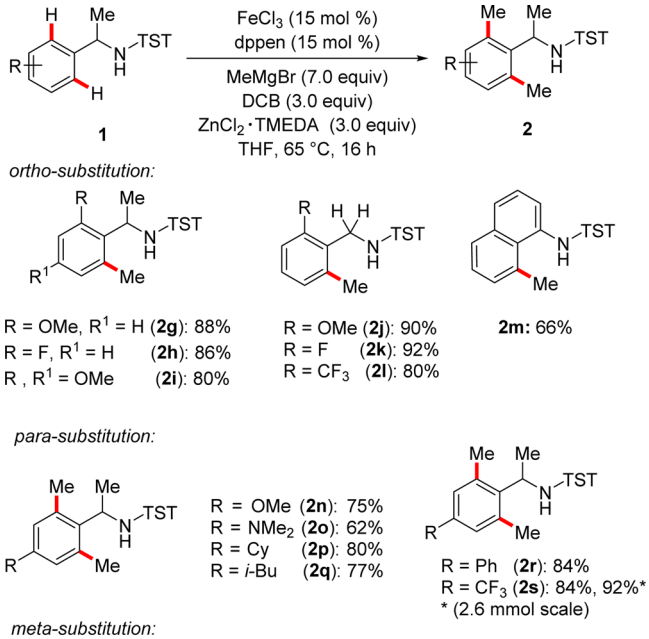


underwent a rather unusual *peri*-C−H methylation, which thereby furnished the product **2m** with excellent positional selectivity. *Para*- and *meta*-substituted substrates directly delivered the two-fold methylated products **2n−u**. Importantly, the robustness of this sustainable iron catalyst was highlighted by synthesizing product **2s** on a gram-scale with comparable levels of efficacy. Given the practical importance of nitrogen-containing heterocycles, it is noteworthy that pyridine **2v** could be obtained in synthetically useful yields as well. Likewise, bicyclic substrate **1w** delivered the desired product **2w** featuring the sertraline motif−an important pharmacophore in medicinal chemistry.[13]

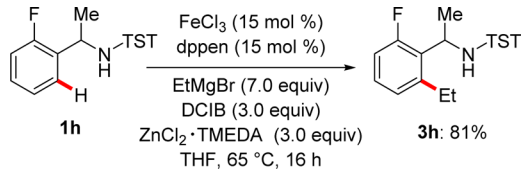
Our iron-catalyzed C−H activation strategy was not limited to direct methylation reactions. Indeed, the versatility of our approach was reflected by the high-yielding C−H ethylation[14] of benzylamine **1h**, with the best results being achieved by the action of DCIB as the oxidant (Scheme 4).

Moreover, the robust nature of our iron catalyst also set the stage for effective C−H arylations on benzylamines **1** under otherwise identical reaction conditions (Scheme 5). Again, DCIB proved to be the optimal oxidant, as was previously found for iron-catalyzed C−H arylations.[8e] The observed monoselectivity[8e] is likely due to increased steric interactions.

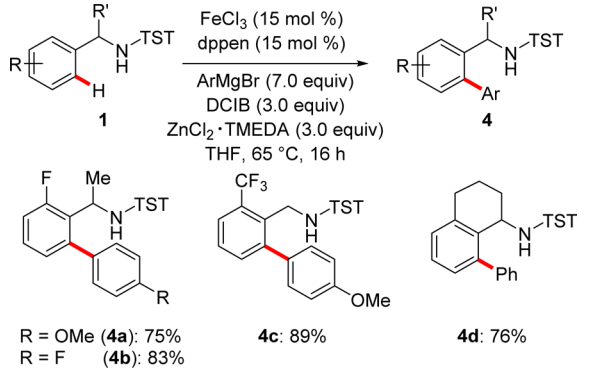
Scheme 3. TST-Assisted Iron-Catalyzed C−H Methylation



Scheme 4. TST-Assisted Iron-Catalyzed C−H Ethylation



Scheme 5. TST-Assisted Iron-Catalyzed C−H Arylation



As to the catalyst mode of action, we conducted kinetic studies through independent experiments. To this end, we unraveled a kinetic isotope effect (KIE) of k_H/k_D = 1.7, which

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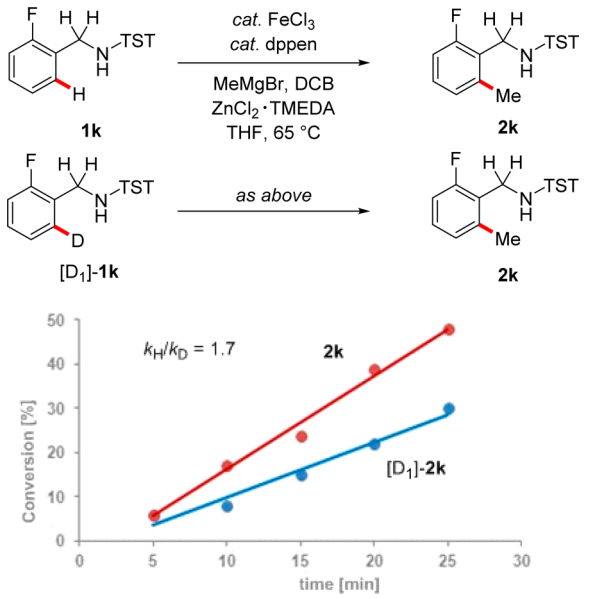
was suggestive of a kinetically relevant C−H activation step (Scheme 6) likely leading to two-state reactivity.[15] The

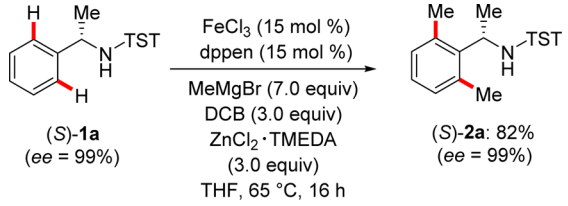
Scheme 6. KIE Studies by Independent Experiments



outstanding efficacy of this iron-catalyzed C−H activation was further reflected by a 48% conversion of substrate **1k** within only 25 min reaction time.

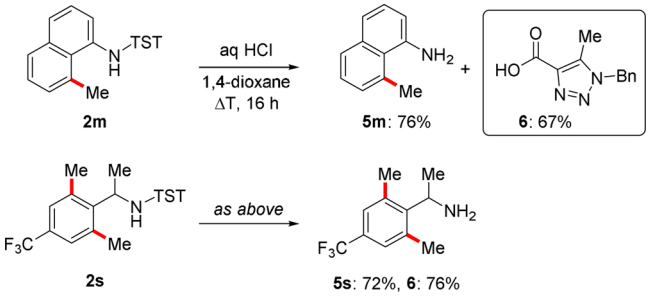
The synthetic utility of our iron-catalyzed C−H activation strategy was among others mirrored by the racemization-free modification of the enantiomerically enriched benzylamine (*S*)-**1a** (Scheme 7).[16]

Scheme 7. Racemization-Free C−H Methylation of Benzylamine (*S*)-1a



Finally, the TST group could be removed in a traceless fashion, which furnished the free primary aryl and benzyl amines **5m** and **5s**, while the reusable[17] TST **6** could be recovered in high yields (Scheme 8).

Scheme 8. Removal of TST Group



In summary, we have reported on the design of a fully trisubstituted triazole TST that has enabled the expedient C−H functionalization of electron-rich benzyl and aryl amines by sustainable iron-catalysis. Thus, hitherto unprecedented triazole-assisted C−H methylations, alkylations, and arylations are now viable with excellent positional selectivity under racemization-free conditions, exploiting the versatile TST group, which could be removed in a traceless fashion.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01672.

Experimental methods and data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: Lutz.Ackermann@chemie.uni-goettingen.de.

ORCID

Lutz Ackermann: 0000-0001-7034-8772

Author Contributions

†These authors contributed equally.

Notes

The authors declare no competing financial interest.

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