Iron-catalyzed C—H insertions: organometallic and enzymatic carbene transfer reactions

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Abstract

C—H insertion reactions with organometallic and enzymatic catalysts based on earth-abundant iron complexes remain one of the major challenges in organic synthesis. In this report, we describe the development and application of these iron-based catalysts in the reaction of two different carbene precursors with *N*-heterocycles for the first time. While FeTPPCl showed excellent reactivity in the Fe(III) state with diazoacetonitrile, the highest activities of the YfeX enzyme could be achieved upon heme-iron reduction to Fe(II) with both diazoacetonitrile and ethyl diazoacetate. This highlights unexpected and subtle differences in reactivity of both iron catalysts. Deuterium labeling studies indicated a C—H insertion pathway and a marked kinetic isotope effect. This transformation features mild reaction conditions, excellent yields or turnover numbers with broad functional group tolerance, including gram-scale applications giving a unique access to functionalized *N*-heterocycles.

Main

The C—H bond belongs to the most common groups in organic molecules and is typically considered unreactive towards functionalization reactions. Its direct modification would allow the most atom-economic and streamlined synthesis of functional molecules. C—H insertion reactions of diazo compounds are a modern strategy to construct highly functionalized molecules from simple and readily available precursors.[1-3] While state-of-the-art C—H functionalization reactions with diazoalkanes greatly depend on the application of precious metals such as rhodium, iridium, palladium or ruthenium, the application of earth-abundant non-precious metals, like cobalt, manganese or iron, in C—H functionalization reactions is still in its infancy.[4-6]

In recent years, iron-heme based catalysts – organometallic and enzymatic – have been employed for a diverse set of transformations of diazo compounds such as cyclopropanations, N—H, S—H, O—H, Si—H and B—H insertions as well as carbonyl-olefinations.[4-7] The C—H insertion reactions of iron-heme containing organometallic and enzymatic catalysts, have only been reported with azides in amination reactions.[7] To the best of our knowledge these catalysts have not been reported in C—H insertion reactions with diazo alkanes.

The major research focus on C—H insertion reactions with the diazoalkanes is on donor-acceptor substituted derivatives that allow simple handling and access to a broad variety of available precious metal catalysts.[8] Diazoacetonitrile was never considered being an appropriate synthon in C—H functionalization reactions although it would pave the way to prepare substituted acetonitriles in a single step. This can be attributed to lack of procedures for handling of this highly explosive diazo compound.[9,10] In particular, the insertion reaction of diazoacetonitrile into indole derivatives would enable a two-step synthesis of valuable tryptamine and alkaloid precursors.

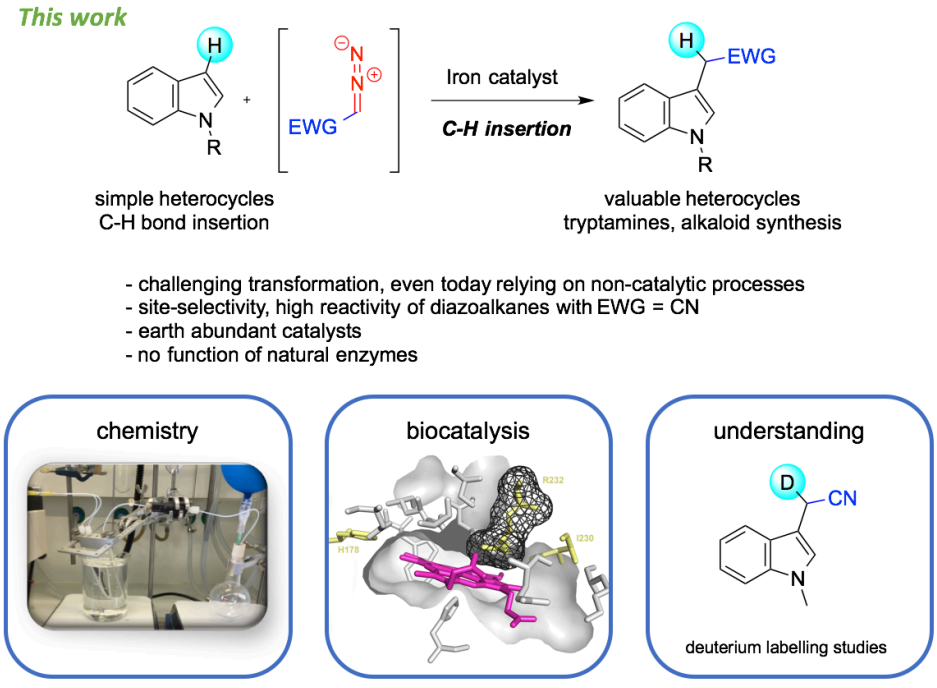
In classic organic synthesis, tryptamines can be most readily prepared either by decarboxylation of tryptophan and its derivatives[11,12] or in a three-step synthesis starting with the Mannich reaction of indole followed by quaternization of the amine and final nucleophilic

substitution with cyanide to yield 1*H*-Indole-3-acetonitrile (41% yield over 3 steps).[13,14] This key building block can be readily reduced to yield tryptamines in high yields.

The reaction of indole heterocycles with acceptor-only diazo compounds has only been studied with Rh(II) or Cu(I) catalysts and ethyl diazoacetate (EDA).[15-19] Currently available catalysts either suffer from low yielding reactions or provide – as in the case of Cu(I) catalysts – the cyclopropanation product of indole, which delivers the 3-substituted indole upon ring-opening.[17] Approaches by Woo and co-workers with FeTPPCl[20] as catalyst for the C—H insertion reaction of EDA and indole resulted in no product formation.[21]

While the biocatalytic construction of C—C bonds with diazo compounds via C—H activation has been shown with Mn-, Co- or Ir-substituted heme-proteins, naturally occurring iron-heme containing enzymes could not catalyze this reaction-type yet.[22-24]

As part of our ongoing studies towards highly reactive diazo alkanes,[25,26] we envisioned the C—H insertion reactions of diazoacetonitrile with non-precious metal catalysts. In this work, we describe iron-catalyzed C—H insertion reactions with bio- and organometallic catalysts, showcase the efficiency in 38 examples – including gram-scale synthesis – and investigate the reaction mechanism by deuterium labeling studies.



Scheme 1. C—H functionalization of indole heterocycles.

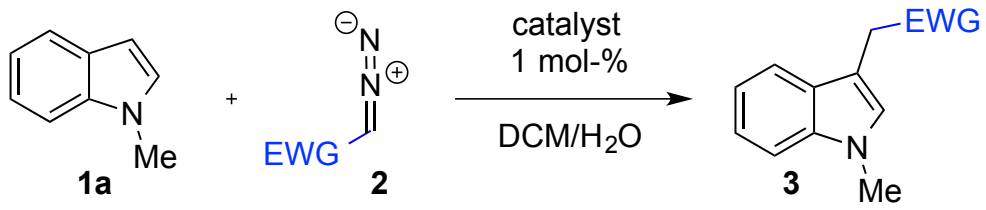
Results and discussion

Organometallic C—H insertion. We initiated our investigations towards C—H activation reactions of diazoalkanes by studying a range of organometallic iron catalysts in the reaction of *N*-methyl indole with diazo acetonitrile. The latter was generated in continuous-flow to reduce safety hazards associated to this diazo compound.[27] To our surprise, the reaction of *N*-methyl indole with diazoacetonitrile was highly efficient with different organometallic iron catalysts (table 1, entry 1-7). FeTPPCl showed the best isolated yields of 92% and performed much better than the respective Fe(II) catalyst. The reduction of FeTPPCl by addition of $Na_2S_2O_4$ also resulted in significantly reduced product yield.

We subsequently investigated different alternative routes relying on the *in situ* generation of diazoacetonitrile. However, neither in a one-pot protocol nor a slow release protocol the desired product could be isolated in satisfactory yield and purity (yields for: slow release reaction: 43%, one-pot: 57%).[28] The reactivity of diazoacetonitrile is in striking contrast to the reaction of EDA, which provided only trace amounts of the desired reaction product (table 1, entry 8-12).

The natural iron containing prosthetic group hemin was tested thereafter for its activity in C—H insertion reactions; yet, the desired reaction product could only be isolated in reduced yield in the case of diazoacetonitrile.

Table 1. Reaction optimization.



#	catalyst	additive	EWG	diazoalkane	product	% yield
1	FeTPP (1 mol-%)		CN	**2a**	**3aa**	54%
2	FePC (1 mol-%)		CN	**2a**	**3aa**	41%
3	FeTPPCl (1 mol-%)		CN	**2a**	**3aa**	92%
4	FeTPPCl (1 mol-%)	10 mol-% $Na_2S_2O_4$	CN	**2a**	**3aa**	51%
5	FeTPPCl (1 mol-%)	1 eq $Na_2S_2O_4$	CN	**2a**	**3aa**	10%
6	Hemin-Cl (1 mol-%)		CN	**2a**	**3aa**	47%
7	Hemin-Cl (1 mol-%)	10 mol-% $Na_2S_2O_4$	CN	**2a**	**3aa**	19%
8	FeTPP (1 mol-%)		CO_2Et	**2b**	**3ab**	no rct.
9	FeTPPCl (1 mol-%)		CO_2Et	**2b**	**3ab**	*traces*
10	FeTPPCl (1 mol-%)	10 mol-% $Na_2S_2O_4$	CO_2Et	**2b**	**3ab**	no rct.
11	Hemin-Cl (1 mol-%)		CO_2Et	**2b**	**3ab**	no rct.
12	Hemin-Cl (1 mol-%)	10 mol-% $Na_2S_2O_4$	CO_2Et	**2b**	**3ab**	no rct.

reaction conditions: a solution of amino acetonitrile hydrochloride (0.8 M, 4 eq) in water, and a solution of $NaNO_2$ (0.96 M, 4.8 eq) in water are added via syringe pump at a flow rate of 50 µL/min for each syringe into a microreactor (LTF-MRT MX, 200µL volume) heated to 55 °C. The outlet of the reactor is added to a reaction vessel containing 0.4 mmol **1a**, 1 mol-% catalyst in 0.1 mL DCM and stirred for 2h. Isolated yields are reported.

Biocatalytic C—H insertion. Encouraged by the observed reactivity of organometallic iron-heme complexes and in particular by the activity of the natural cofactor hemin, we decided to investigate heme-containing enzymes that could serve as a biocatalytic alternative in this C—H functionalization reaction.

In initial studies, we had shown that $P450_{BM3}$ (from *Bacillus megaterium*) or $P450_{NOR}$ ((from *Histoplasma capsulatum*) had lower activities toward C—H insertions than the *E. coli* enzyme YfeX.[28] YfeX had been used in previous studies to perform carbonyl olefination reactions in the absence of triphenylphosphine or arsine – though with modest turnovers.[29] Due to its *E. coli* origin YfeX shows remarkable expression rates and possesses a high stability at room temperature. YfeX wildtype showed TON of 37 at four hours reaction time in the reaction of diazoacetonitrile and *N*-methyl indole in the absence of oxygen. In striking difference to the organometallic experiments, we found the best reactivity by adding 5 mM of the reducing

agent $Na_2S_2O_4$. This indicates that the biocatalytic reactions are catalyzed by Fe(II) rather than Fe(III).

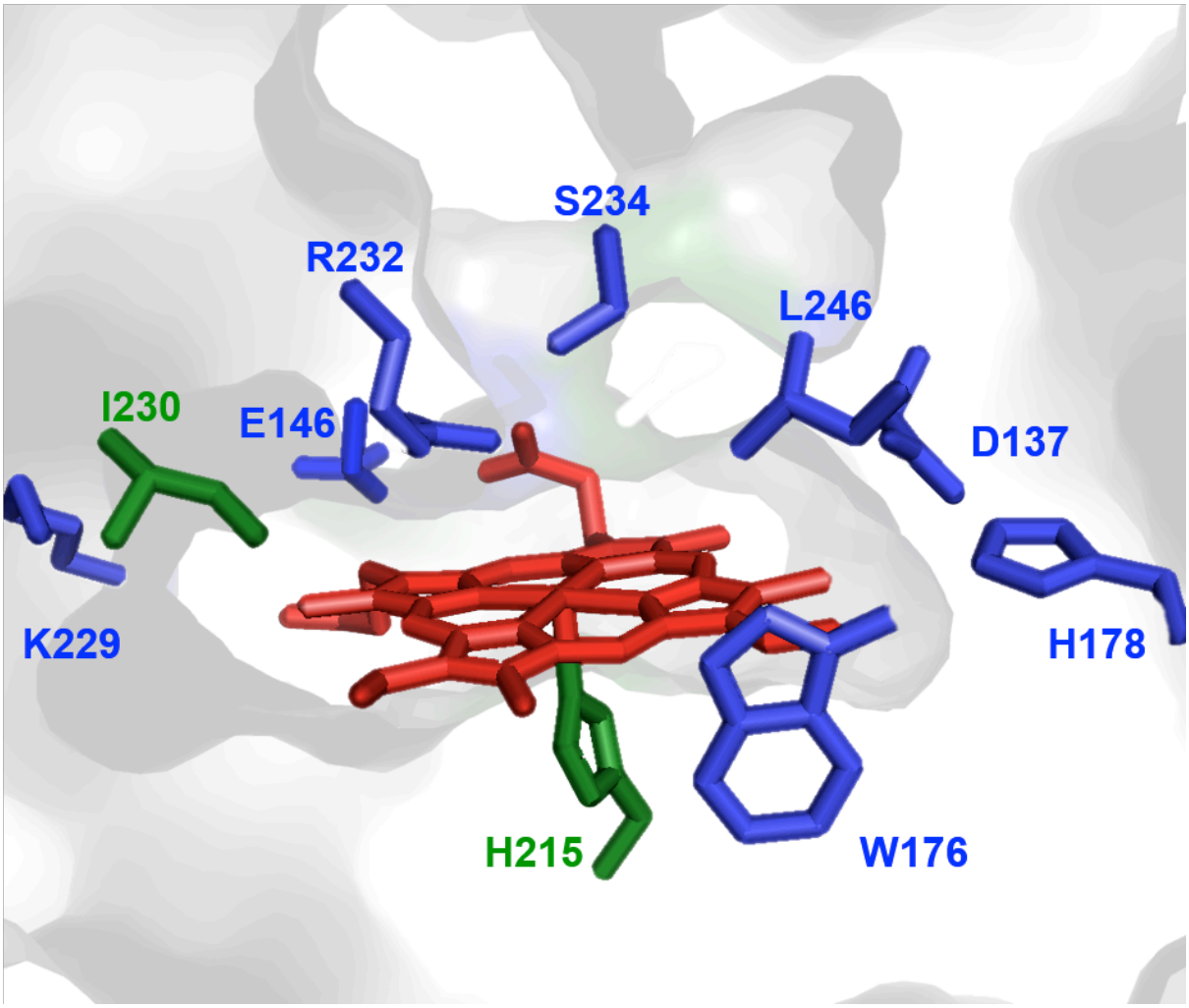


Figure 2. Active site residues of YfeX that were investigated in a focused mutant library. The green amino acids showed the most dominant effects. PDB: 5GT2.

As a proof of principle, we next tested a focused library of eleven YfeX variants. Active site residues from the distal site in proximity to the iron have been picked and changed for alanine.[30] The best variant I230A improved the TON twofold from 37 to more than 80, thereby clearly demonstrating the influence of the protein scaffold as well as its ability to be engineered. The mutation of the proximal axial ligand H215A caused the expected decrease in activity. Removal of the anionic aspartic acid D143 to alanine resulted in a substantial loss in activity.

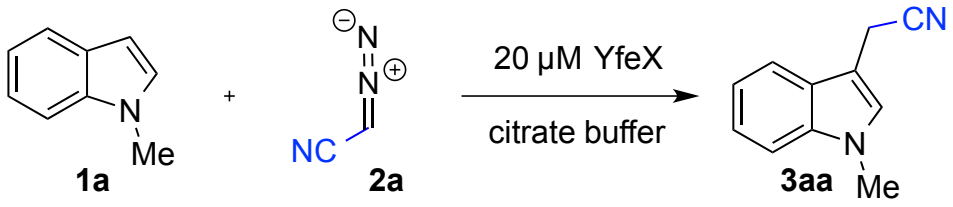


Table 2. Enzymatic activity of YfeX variants in C—H insertion reactions with *N*-methyl indole **1a** and diazo acetonitrile.

#	catalyst	3aa [µM][a]	TON[c]
1	YfeX WT	748	37 (51)
2	YfeX R232A	941	47 (66)
3	YfeX D143A	337	17 (20)
4	YfeX D137A	957[b]	48 (56)
5	YfeX H178A	1232[b]	62 (69)
6	YfeX H215A[e]	278	14 [e]
7	YfeX I230A	1607	80 (94)
8	YfeX S234A	995	50 (50)
9	YfeX L246A	898	45 (106)
10	YfeX E146A	601[b]	30 (39)
11	YfeX K229A	1263	63 (68)

reaction conditions: Reactions were performed in an anaerobic 100 mM citrate buffer (pH = 7) with 50 mM *N*-methyl indole, 50 mM diazo acetonitrile, 5 mM $Na_2S_2O_4$ and 20 µM catalyst for 4 h at 30 °C. [a] Mean values from three replicates ± 17 % standard deviation, conversions were based on GC analysis [b] 26 – 29 % standard deviation. [c] TON = **3aa** µM/20 µM YfeX variant. In brackets the extrapolation to 100 % heme loading. [e] apoYfeX.

Further investigations focused on the insertion reaction of *N*-methyl indole with EDA. In striking contrast to the organometallic iron porphyrine catalysts, YfeX proved to be an excellent catalyst for this transformation under reductive conditions (50 mM $Na_2S_2O_4$). The best variant showed 211 TON under optimized conditions. These observations are in sharp contrast to the reaction with diazoacetonitrile and highlights differences in the reactivity of both diazo compounds as well as their catalysts. In additional experiments, we could demonstrate this C—H insertion reaction in a whole-cell setup with YfeX WT enzyme and could achieve a high TON of 236.

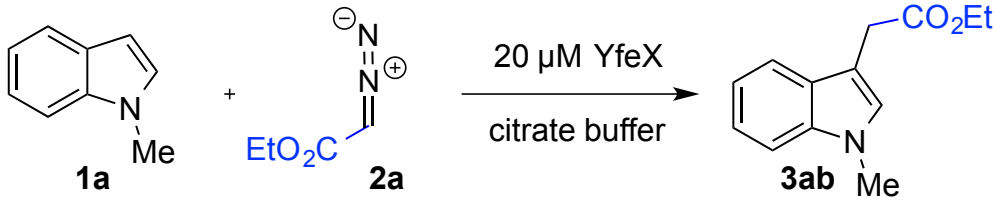
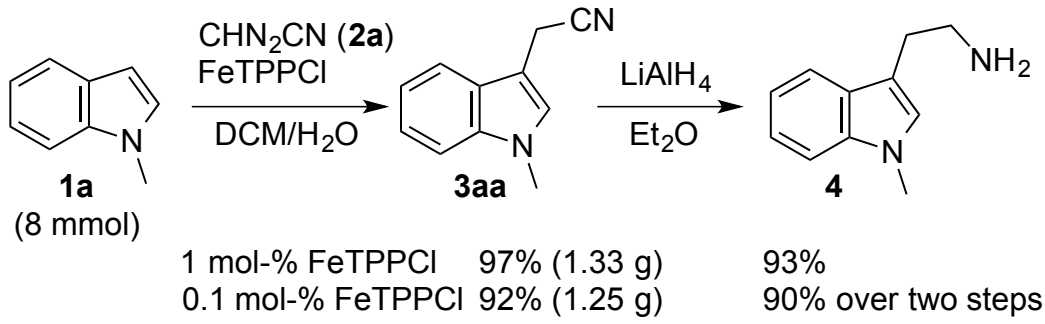


Table 3. Enzymatic activity of purified YfeX variants and the whole cell system in the C—H insertion reaction of *N*-methyl indole and ethyl diazoacetate.

#	catalyst	3ab [µM][d]	TON[e]
1	YfeX WT	1208	60 (82)
2	YfeX R232A	1243	62 (87)
3	YfeX D143A	1397	70 (83)
4	YfeX I230A	1699	85 (100)
5	YfeX I230A [a]	211	211 (248)
6	*E. coli* (BL21) pCA24N-YfeX WT [b]	1652	236 (320) [f]
7	*E. coli* (BL21) pCA24N[b, c]	33	-

reaction conditions: Reactions were performed in an anaerobic 100 mM citrate buffer (pH = 7) with 50 mM *N*-methyl indole, 50 mM diazo acetonitrile, 50 mM $Na_2S_2O_4$ and 20 µM catalyst for 4 h at 30 °C. [a] 1 µM YfeX WT concentration. [b] Whole cell biocatalyst, OD = 30. [c] Empty pCA24N vector (control). [d] Mean values from three replicates ± 12 % standard deviation, conversions were based on GC analysis. [e] TON = **3ab** µM/20 µM [or 1 µM] YfeX variant. In brackets the extrapolation to 100 % heme loading. [f] TON = **3ab** µM/7 µM.

Application of the organometallic C—H insertion reaction. We probed the organometallic protocol in a short synthesis of a tryptamine derivative, which would enable a streamlined synthesis of indole alkaloids. Starting with 8 mmol of *N*-methyl indole (**1a**), we could demonstrate that this protocol can be readily applied to the gram-scale synthesis of **3aa** in excellent yield and catalyst loadings as low as 0.1 mol-%. Reduction with $LiAlH_4$ provides the tryptamine derivative (**4**) in a two-step synthesis and total yield of 90% over two steps, which is superior over classical routes (scheme 2).



Scheme 2. Gram-scale reaction and application in the synthesis of tryptamine.

This process thus allows the rapid synthesis of valuable tryptamines that are a privileged motif in biological and pharmaceutical research (figure 3);[31-34] an example is Cysmethynil (**8**), which is an inhibitor of isoprenylcysteine methyl transferase.[32,33] Their closely related analogues, the indazol-3-yl ethane amines, are privileged scaffolds in many drugs, such as DY-9760e (**9**), which is used for the treatment of ischemia.[34]

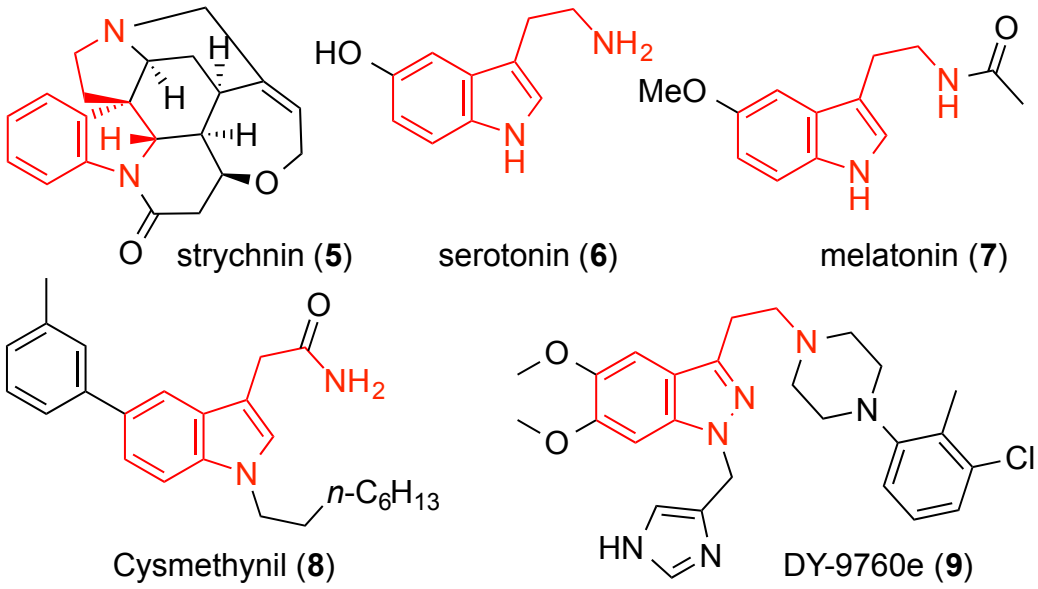


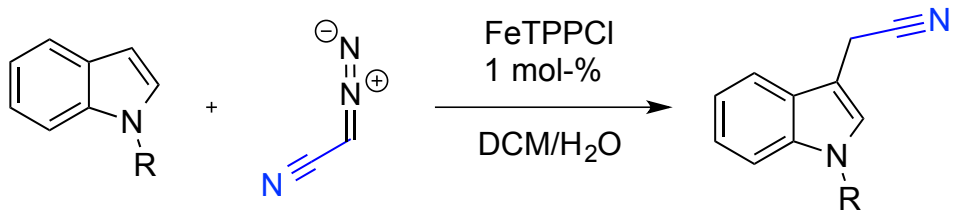
Figure 3. Occurrence of tryptamines in natural products and biologically active compounds.

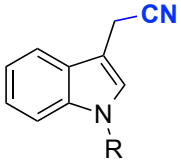
In further studies, we examined the applicability of this newly developed method and probed different *N*-alkylated indoles. To our delight these indoles reacted smoothly under the present reaction conditions, providing the desired reaction products in very good to excellent yields. A broad variety of functional groups were well tolerated such as double and triple bonds, nitriles or ethers; no cyclopropanation or cyclopropenation byproducts were observed (table 4, **3ga-ia**). Further investigations focused on *N*-aryl substituted indoles, which reacted to the desired 1-aryl-3-acetonitrile indoles (table 4, **3ja**-**3ta**) with yields of up to 99%. We examined a range of substituents to probe the influence of electronic and steric effects. Electron-withdrawing, electron-donating and halogen substituents in the *para*-, *meta*- and *ortho*-position of the aromatic ring were tolerated and only a negligible effect on the reaction with diazoacetonitrile was observed. Sulfur containing heterocycles also proved compatible providing the 3-substituted indole in moderate yields (**3ta**). It should be noted that *N*-

heterocyclic substrates (*e.g. N*-(pyrimidin-2-yl)-indole) did not react under the present reaction conditions. We also investigated *Boc*-protected indole, however, we did not observe the formation of the desired product.

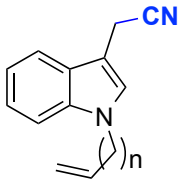
We then decided to investigate unprotected indoles, which would give a direct one-step access to building blocks that allow simple functionalization. These investigations would reveal insight into the reaction mechanism and show, whether C—H or N—H insertion is preferred. To our delight, unprotected indole reacted to the desired 1*H*- 3- acetonitrile indole in 62% yield, without formation of the *N*-alkylation product. Even with a large excess of diazoacetonitrile (8 eq.), no N—H insertion was observed. Increasing the addition time of diazoacetonitrile from 10 to 20 min improved the reaction and the product was isolated in 75 % yield. Encouraged by these observations, we investigated a variety of core-substituted indoles, both without a masking group at the indole nitrogen and with the corresponding *N*-substituted derivatives. Aliphatic substituents at the indole core were well tolerated and the corresponding alkyl-substituted 3-acetonitrile indoles were isolated in good yields. Electron withdrawing groups, such as esters or fluorine, are tolerated, though the products were obtained only in moderate yields (table 4, entries **10** and **11**). Remarkably, indazole readily underwent the C—H insertion reaction and the desired product **12** was isolated in good yield, which marks the first example of C—H functionalization reactions of indazole with diazo compounds. It should be noted that 7-aza-indole did not provide the desired reaction product. Blocking the 3-position of indole as in 3-methyl-1-phenyl indole resulted in no reaction, which indicates that the C—H insertion takes place in the 3-position of indole exclusively.

Table 4. Reaction scope of substituted *N*-alkyl and *N*-aryl indoles.

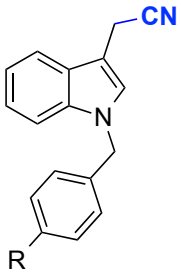




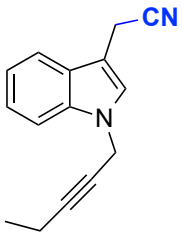
3aa, R = Me, 92%
3ba, R = n-Pentyl, 96%
3ca, R = -$(CH_2)_3$-CN, 89%
3da, R = -$(CH_2)_2$-OPh, 90%



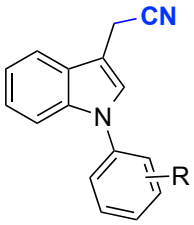
3ga, n = 1, 80%
3ha, n = 3, 95%



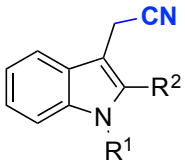
3ea, R = H, 86%
3fa, R = Cl, 83%



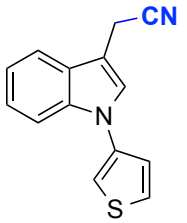
3ia, 87%



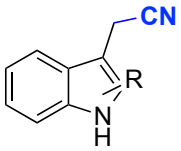
3ja, R = H, 86%
3ka, R = 4-Methyl, 99%
3la, R = 4-Ethyl, 89%
3ma, R = 4-*tert.*-Butyl, 92%
3na, R = 4-Chloro, 73%
3oa, R = 4-Methoxy, 85%
3pa, R = 2-Methyl, 99%
3qa, R = 3-Methyl, 99%
3ra, R = 3-Methoxy, 67%
3sa, R = 3,5-Dimethyl, 92%



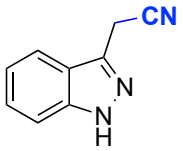
10a, R^1 = Me, R^2 = 2-Ph, 56%
10b, R^1 = Ph, R^2 = 2-Me, 80%
10c, R^1 = Me, R^2 = 2-Me, 93%
10d, R^1 = Ph, R^2 = 5-Me, 88%
10e, R^1 = Ph, R^2 = 6-Me, 88%
10f, R^1 = Ph, R^2 = 7-Me, 94%
10g, R^1 = Ph, R^2 = 6-F, 48%
10h, R^1 = Ph, R^2 = 5-MeO, 91%
10i, R^1 = Ph, R^2 = 6-MeO, 78%



3ta, 78%



11a, R = H, 75%[a]
11b, R = 2-Me, 41%[a]
11c, R = 5-Me, 75%[a]
11d, R = 6-Me, 71%[a]
11e, R = 7-Me, 71%[a]
11f, R = 6-CO_2Me, 71%[a]
11g, R = 5-MeO, 54%[a]
11h, R = 6-MeO, 51%[a]

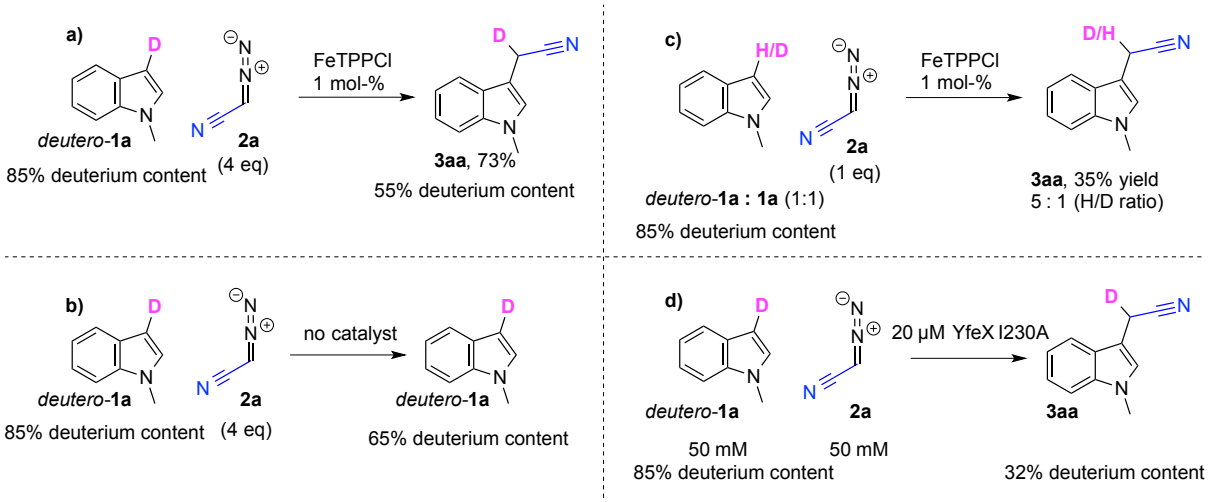


12, 64%

Reaction conditions: diazoacetonitrile (0.8 M, 4 eq) in water was added at a flow over a period of 10 minutes to a solution of indole derivative (0.4 mmol), 1 mol-% FeTPPCl in 0.1 mL DCM and stirred for 2h. Isolated yields are reported. [a] addition of diazoacetonitrile over a period of 20 minutes.

Mechanistic studies. We decided to study the reaction mechanism of the C—H insertion reaction for a better understanding of the observed reactivity. We tested FeTPPCl with 3-deutero-*N*-methyl indole (*deutero*-**1a**) under standard reaction conditions and were able to isolate *deutero*-**3aa** with good yields. NMR analysis revealed a 55 % incorporation of deuterium in the benzylic position (Scheme 3a). To further elucidate the drop of deuterium label during the reaction, we suggested a D/H exchange reaction in the slightly acidic reaction mixture (pH = 6.5) prior to the insertion reaction. We conducted the experiment under otherwise identical conditions without catalyst and examined the crude mixture by NMR spectroscopy. This experiment revealed an erosion of deuterium label to 65% under the present reaction conditions. This indicates, that the loss of deuterium label can indeed be driven by a D/H exchange reaction prior to the insertion reaction (Scheme 3b). Finally, we investigated a competition reaction of *N*-methyl indole (**1a**) and 3-deutero-*N*-methyl indole (*deutero*-**1a**) using only 1 eq. of diazoacetonitrile and could observe a ratio of 5 : 1 of **3aa** : *deutero*-**3aa** (Scheme 3c), which indicates that a proton transfer is the rate-limiting step. This observation is in striking contrast to previously reported copper catalyzed reactions of indole with EDA, in which a) no deuterium is incorporated in the reaction product and b) no kinetic isotope effect was observed.[17] To investigate, whether the biocatalyst behaves in a similar manner, we tested the enzymatic reaction with 3-deutero-*N*-methyl indole (*deutero*-**1a**), which revealed a deuterium incorporation of 32%. In absence of a enzyme, the deuterium label eroded to be 80% under neutral reaction conditions (pH = 7.0).

The above observations are indicating at an insertion reaction mechanism into the C-H/C-D bond at the C3-position of indole, which marks the first example of iron-catalyzed C-H insertion reactions of diazo compounds from both the organometallic and enzymatic perspective.



Scheme 3. Deuterium labelling experiments of the iron catalyzed reaction of indole with diazoacetonitrile: a) organometallic transformation with 3-deutero-*N*-methyl indole; b) background reaction in the absence of catalyst; c) competition experiment for the determination of the kinetic isotope effect; d) enzymatic transformation with 3-deutero-*N*-methyl indole using the most active YfeX variant I230A.

Conclusion.

We have discovered a novel reactivity of organometallic and enzymatic iron porphyrin catalysts, which enables the insertion reaction of diazoalkanes into the C—H bond of *N*-heterocycles. This work demonstrates that diazoacetonitrile can be regarded as a "cyanomethyl" transfer reagent for the selective introduction of an acetonitrile moiety into the C3 position of indole and indazole heterocycles in up to 99% yield with broad functional group tolerance in a single step. This reaction was showcased in 38 examples and proved reliable on gram-scale to prepare tryptamine analogues with broad general applicability ranging from drug discovery and approved drugs to total synthesis. Besides the organometallic studies, we herein show the first example of iron-protein catalyzed C—H insertions of diazoalkanes utilizing a focused mutant library of the heme-protein YfeX. The reaction was also demonstrated in whole cells overexpressing YfeX with turnonver numbers as high as 236. In contrast to the organometallic catalyst, YfeX was able to convert both, diazoacetonitrile and ethyl diazoacetate, respectively, to the C—H insertion product.

Mechanistic investigations with deuterium labelled indole revealed a marked kinetic isotope effect and suggest a C—H insertion mechanism.

Methods

FeTPPCl catalyzed C—H insertion reaction

Two stock solutions were prepared in thoroughly degassed water: a) aqueous solution of amino acetonitrile hydrochloride (1.6 M) b) aqueous solution of sodium nitrite (1.92 M). The stock solutions were transferred into two syringes and placed in a syringe pump. The syringes were connected via PTFE tubing to a microreactor (LTF-MRT MX, 200 µL volume) heated to 55 °C with an internal volume of 0.2 mL. Then, the tubing was passed through an ice bath to cool down the reaction mixture and the cold solution of diazoacetonitrile was added over a period of ten minutes to a mixture of FeTPPCl (1 mol-%) and indole derivative (0.4 mmol, 1 eq) that were dissolved in 0.1 mL of thoroughly degassed DCM. The resulting mixture was stirred an additional 2 h at room temperature. The aqueous phase was extracted with DCM (three times) and the combined organic layers were dried with Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (pentane: diethyl ether 20:1 -> 1:1) to afford the desired product.

YfeX catalyzed C—H insertion reactions

Diazoacetonitrile: Diazoacetonitrile was freshly prepared for each experiment. A degassed aqueous solution of amino acetonitrile hydrochloride (1 M) was stirred at 0 °C. Sodium nitrite was added to obtain a 1.2 M reaction mixture. After 5 min the reaction mixture was stirred for 10 min at room temperature, followed by further 5 min on ice cooling for an easier handling and a direct addition of the diazo acetonitrile component to the C—H insertion reaction mixture. C—H insertion reactions with the YfeX variants were performed in 2.5 ml Rotilabo® sample vials (Carl Roth, Karlsruhe, DE) with a final volume of 400 µl in 100 mM citrate buffer (pH = 7). The reaction mixture consisted of 20 µM YfeX, freshly prepared 50 mM diazo

acetonitrile, 50 mM *N*-methyl indole, 5 mM $Na_2S_2O_4$ and 5 % DMSO as degassed cosolvent and was saturated with N_2. After a reaction time of 4 h at 30 °C and 600 rpm the products were extracted using 400 µL MTBE with 0,005 % ethyl benzoate and centrifuged at 8400 rpm for 3 min. The organic phase was analyzed by GC/MS.

Ethyl diazoacetate: C–H insertion reactions with the YfeX variants were performed in 2.5 ml Rotilabo® sample vials (Carl Roth, Karlsruhe, DE) with a final volume of 400 µl in 100 mM citrate buffer (pH = 7). The reaction mixture consisted of 20 µM/1 µM YfeX, 50 mM ethyl diazoacetate, 50 mM *N*-methyl indole, 50 mM $Na_2S_2O_4$ and 10 % DMSO as degassed cosolvent and was saturated with N_2. After a reaction time of 4 h at 30 °C and 600 rpm, the products were extracted using 400 µL MTBE with 0,005 % ethyl benzoate and centrifuged at 8400 rpm for 3 min. The organic phase was analyzed by GC/MS.

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Acknowledgements

R.M.K. thanks for support from the Excellence Initiative of the German federal and state governments and the Fonds der Chemischen Industrie (Sachkostenbeihilfe) for financial support. M.J.W and A.K. thank the BMBF („Biotechnologie 2020+ Strukturvorhaben: Leibniz Research Cluster“, 031A360B) for generous funding. The authors thank Niels Borlinghaus who performed the YfeX mutagenesis. J.H. thanks the Australian Research Council for financial support (Grant DE160100807) and the Australia National Computational Infrastructure (NCI) and Intersect Australia Ltd. for generous allocation of computational resources.

Author Contributions

K.J.H, A.K. and R. H. performed the experiments. K.J.H., J. H., M.J.W. and R.M.K. participated in the discussions, supervised the project and wrote the manuscript. K.J.H. and R. M. K. conceived the idea of iron catalyzed C-H insertion reactions. R.M.K. organized the research.

Additional Information

Supplementary information and chemical compound information are available.

Competing Financial Interests statement

The authors declare no competing financial interest.