How to cite: *Angew. Chem. Int. Ed.* **2024**, *63*, e202407003
doi.org/10.1002/anie.202407003

Photocatalysis **Hot Paper**

Intermolecular Enantioselective Amination Reactions Mediated by Visible Light and a Chiral Iron Porphyrin Complex

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Abstract: In the presence of 1 mol % of a chiral iron porphyrin catalyst, various 3-arylmethyl-substituted 2-quinolones and 2-pyridones underwent an enantioselective amination reaction (20 examples; 93–99 % *ee*). The substrates were used as the limiting reagents, and fluorinated aryl azides (1.5 equivalents) served as nitrene precursors. The reaction is triggered by visible light which allows a facile dediazotation at ambient temperature. The selectivity of the reaction is governed by a two-point hydrogen bond interaction between the ligand of the iron catalyst and the substrate. Hydrogen bonding directs the amination to a specific hydrogen atom within the substrate that is displaced by the nitrogen substituent either in a concerted fashion or by a rebound mechanism.

The importance and relevance of amines for a multitude of applications is reflected by the large number of methods which allow for the introduction of a nitrogen atom into a carbon skeleton. Arguably, one of the most efficient methods for this purpose is the direct amination of carbon–hydrogen bonds.[1] An array of ingenious reactions have been invented over the years which not only address the site-selectivity of the C–H insertion but also its enantioselectivity.[2–4] Typically, a nitrene precursor is combined with a suitable transition metal complex, the metal atom of which serves as vehicle for the amination process. The quest for sustainable catalysts has shifted the attention in recent years to transition metals which are abundant in the earth's crust, and which are considered non-toxic. Iron represents the prototypical example for a metal which fulfills all criteria of sustainability[5] and which plays an essential role in enzymatic catalysis.[6] Nature undertakes a remarkable synthetic effort to provide iron with a suitable ligand, i.e. a porphyrin, enabling the metal to play its critical role in oxygen transport and oxygenation chemistry.[7]

Given the prevalence of iron porphyrin complexes and their high importance for oxidative C–H activation,[8] it seems appropriate to interrogate their suitability for selective amination reactions. In a series of papers, the group of Arnold[9] has shown how naturally occurring cytochrome P450 can be repurposed to achieve this goal.[10] A key modification involves the coordination of serine (Ser) instead of cysteine to the iron core which leads to a shift of the Soret band from 450 nm to 411 nm. Directed evolution delivered a variety of P411 enzymes which were competent to perform an array of amination reactions. By employing a hydroxylamine derivative, the Arnold group achieved highly enantioselective amination reactions leading to primary amines such as **1** with high enantioselectivity and high turnover numbers (Scheme 1). Attempts to devise similarly efficient iron porphyrin catalysts with low molecular weight, have seen limited success.[11] A key finding by Che and coworkers[11d] relates to the use of azides,[12] such as **2**, in a light-mediated amination reaction promoted by catalyst **3**. Product *rac*-**4**, however, was isolated in high yield only if the azide was used as the limiting reagent. Although a successful enantioselective intramolecular variant of the reaction has been recently reported,[13,14] the challenge to tame the reactive nitrene intermediate in an intermolecular reaction has not yet been met.

A critical issue with intermolecular amination reactions is the high reactivity of the short-lived nitrene intermediate. Rapid consecutive reactions are required which can only be guaranteed for the reaction to *rac*-**4** if the substrate is used in excess. While the enzyme in the reaction to product **1** accommodates a proximity of reactive intermediate and substrate, typical chiral catalysts fail to do so. Only if the catalyst displays an explicit substrate binding motif, an enzyme-like reactivity can be achieved. We have now found that a chiral iron porphyrin complex, which displays a lactam as two-point hydrogen bonding site,[15] is competent to catalyze the intermolecular amination of various heterocyclic substrates in an enantioselective fashion. Exquisite enantiomeric excesses (>90 % *ee*) were achieved and the

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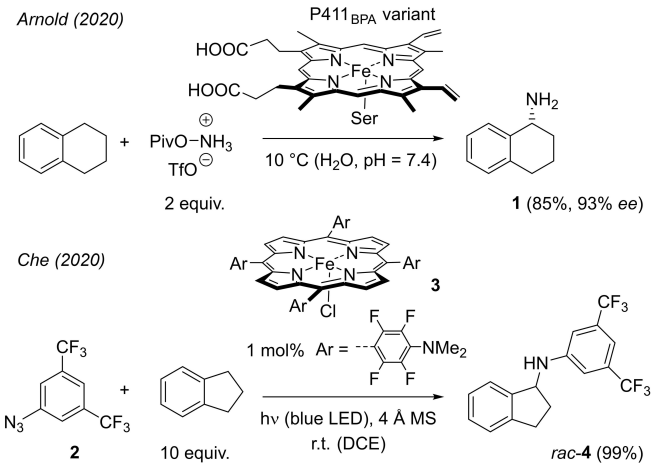
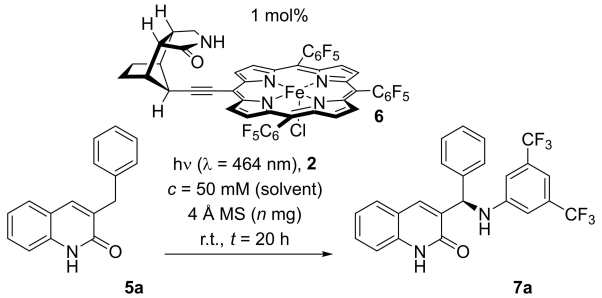


Scheme 1. Successful repurposing of iron porphyrin complexes for nitrene transfer: Modifications of cytochrome P450 led to a powerful benzylic C–H primary aminase (BPA) which facilitates the amination of tetralin to 1-aminotetralin (**1**) with high enantioselectivity (top, equiv. = equivalents, Piv = pivaloyl; Tf = trifluoromethanesulfonyl).[9c] Azide **2** serves as an aryl nitrene precursor for the amination of indane to product *rac*-**4**. The reaction was triggered by visible light and catalyzed by iron porphyrin complex **3**. The azide was employed as the limiting reagent (bottom).[11d]

hydrogen bonding event was shown to be crucial for the success of the reaction.

In initial experiments, we aimed to find proper conditions for the application of a catalyst, which displays a hydrogen bonding motif, to the amination protocol reported by Che and co-workers.[11d] In this context, the recently reported[16] iron porphyrin complex **6** seemed particularly well suited. Optimization experiments (Table 1) were performed with 3-benzyl-2-quinolone (**5a**) as the substrate, which had so far not been employed in enantioselective amination reactions. To our delight, already the first attempt (entry 1) with substrate **5a** as the limiting reagent gave a 26 % conversion and more importantly delivered product **7a** in very high enantioselectivity (> 99 % *ee*). It was shown that the reaction does not proceed in the absence of light (entry 2), and it was found that the achiral, electronically related iron porphyrin catalyst with four pentafluorophenyl groups was not suited as catalyst (entry 3). An increase of the amount of molecular sieves (MS) in the reaction mixture led to an increase in conversion indicating that the exclusion of water is crucial for the success of the reaction. After optimizing the required quantity of molecular sieves (entries 4–7), we turned our attention to the influence of the solvent. It was found that among several options (see the Supporting Information for a complete list of optimization experiments) 1,2-dichloroethane (DCE)[17] was slightly superior to dichloromethane (entry 8 vs. entry 6). An increase in the substrate concentration to 100 mM led to an improvement in conversion and yield (entry 9) while an increase in catalyst loading had only a minor impact on the outcome of the reaction (entry 10). Monitoring of the azide consumption by in situ IR measurements (see the Supporting Information) revealed that the reagent was completely consumed

Table 1: Reaction optimization of the enantioselective, visible light-induced amination **5a** →**7a** catalyzed by chiral iron porphyrin complex **6**.



entry[a]	n [mg]	solvent	2 [equiv.]	conv.[b] [%]	yield[c] [%]	ee[d] [%]
1	30	CH_2Cl_2	1.0	26	10	> 99
2[e]	30	CH_2Cl_2	1.0	–	–	–
3[f]	30	CH_2Cl_2	1.0	–	–	–
4	60	CH_2Cl_2	1.0	38	21	> 99
5	120	CH_2Cl_2	1.0	48	33	> 99
6	180	CH_2Cl_2	1.0	49	43	> 99
7	240	CH_2Cl_2	1.0	46	42	> 99
8	180	DCE	1.0	62	48	> 99
9[g]	180	DCE	1.0	63	55	> 99
10[h]	180	DCE	1.0	65	60	> 99
11[g]	180	DCE	1.5[i]	81	67	> 99
12[g]	180	DCE	2.0[j]	75	58	> 99

[a] Reactions were carried out on a scale of 50–100 µmol in the given solvent at room temperature (r.t.). Irradiation was performed at λ_{em} = 464 nm (maximum of emission) with a set of light emitting diodes (LEDs). [b] The conversion (conv.) was calculated from re-isolated starting material (conv. = 100 %–yield (%) of re-isolated starting material). [c] Yield of isolated product after column chromatography. [d] The enantiomeric excess (*ee*) was calculated from the enantiomeric ratio (**7a**/*ent*-**7a**) as determined by chiral HPLC analysis. [e] The reaction was performed without light. [f] The reaction was performed with 5,10,15,20-tetrakis(pentafluorophenyl)-21*H*,23*H*-porphyrin iron chloride as the catalyst. [g] The reaction was performed at a concentration of *c* = 100 mM. [h] The reaction was performed with 2 mol % of catalyst **6**. [i] 0.5 equiv. of azide **2** were added after a reaction time of 14 hours. [j] 1.0 equiv. of azide **2** were added after a reaction time of 14 hours.

after 12 hours while unreacted starting material was still present in the reaction mixture (63–65 % conversion). In fact, addition of azide (0.5 equiv.) to the reaction mixture after 14 hours triggered a re-start of the reaction and led to a conversion of 81 % after 20 hours (entry 11). An addition of larger quantities of azide turned out to have a less significant effect (entry 12). While it might be possible to further increase the conversion upon adding additional equivalents of azide after 20 hours, we felt that the method was most practical with the conditions of entry 11. It delivered reproducibly yields over 80 % based on conversion, i.e. products **7a** were isolated in > 65 % yield in enantiomerically pure form (> 99 % *ee*). It was shown that the reaction is amenable to scale-up. When performed on 1 mmol scale, product **7a** was isolated in 68 % yield with > 99 % *ee*. In addition, 15 % of recovered starting material **5a** were isolated (85 % conversion). Furthermore, an imine

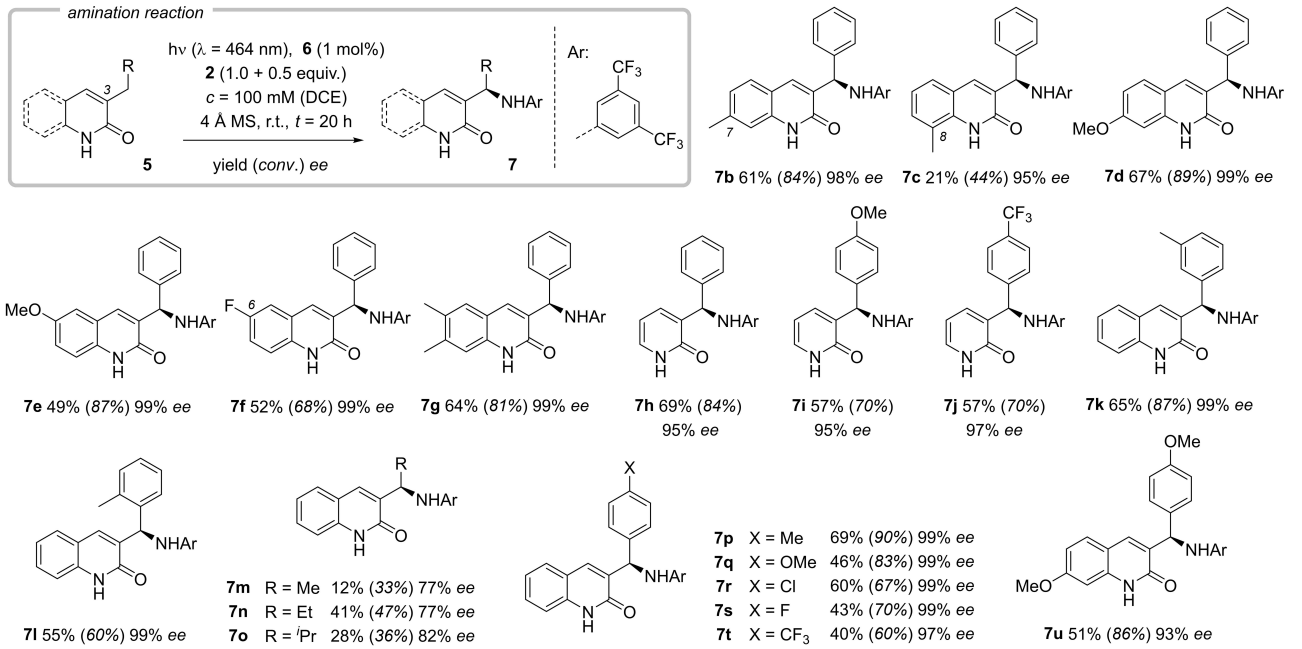
product was identified and quantified as the resulting ketone (6 % yield, see below).

Under the optimized conditions of Table 1 (entry 11), a broad variety of 3-substituted 2-quinolones and 3-arylmethyl-2-pyridones were subjected to the enantioselective amination conditions (Scheme 2). All reactions were performed with 3,5-bis(trifluoromethyl)phenyl azide (**2**) as the aminating reagent. In the first set of experiments (products **7b**–**7g**), the substituent within the benzo ring of 2-quinolones was varied. Methyl, methoxy, and fluoro groups in positions C6 and C7 were fully compatible with the conditions, and products **7b**, **7d**–**7g** were formed in similar yields and enantioselectivities as **7a**. In several instances, the minor enantiomer was not even detectable by chiral HPLC. The C8 substituent (product **7c**) seems to interfere with the binding to the catalyst and the conversion remained low. Remarkably, the enantioselectivity was retained. Like quinolones, pyridone substrates reacted smoothly and yielded the aminated products **7h**–**7j** in moderate to good yields and with excellent enantioselectivity.

Substrates with substituents in the *ortho*- and *meta*-position of the benzylic phenyl group (products **7k** and **7l**) delivered similar results as the unsubstituted compound (product **7a**). Although the site-selectivity of the reaction is high (see below), the methylene group at position C3 of the heterocycle benefits from electronic activation by an adjacent aryl group to proceed smoothly. 3-Alkyl-2-quinolones (products **7m**–**7o**) did not undergo the amination as efficiently and as selectively as the 3-arylmethyl-substituted substrates. Conversions remained lower and product yields varied between 12 % and 41 %. Despite the lack of activation, the enantioselectivity was notable (77–82 % *ee*). If there is an aryl group adjacent to the methylene group, its electronic influence is inconsequential for the success of the reaction. Aryl groups displaying methyl, methoxy, chloro, fluoro, or trifluoromethyl substituents in *para*-position were shown to be compatible with the conditions of the amination reactions and delivered products **7p**–**7t** in high yields and with excellent enantioselectivity. A two-fold methoxy substitution at the aryl group and within the benzo ring was well tolerated and product **7u** was produced with high enantioselectivity.

The absolute configuration of the major enantiomer **7a** obtained under optimized conditions (Table 1, entry 11) was determined as (*R*) at the newly formed stereogenic center by vibrational circular dichroism (VCD) spectroscopy (see the Supporting Information for details).[18] The absolute configuration of all other products was assigned based on analogy.

Although the focus of the current study was on the substrate and its catalyst interaction, the influence of the aminating reagent was briefly addressed. An electron deficient aryl azide was required for high conversion reflecting (a) the need for a suitable chromophore to induce dediazotation and (b) the electrophilic nature of the formed nitrene intermediate. Pentafluorophenyl azide delivered, when reacted with quinolone **5a**, the expected product **8** in a useful conversion and with 94 % *ee* (Figure 1). The respective 3,5-dichlorophenyl azide, however, reacted only sluggishly (13 % yield), yet in 97 % *ee*. Other azides such as 4-nitrobenzenesulfonyl azide (NsN_3), toluenesulfonyl azide (TsN_3) or 2,2,2-trichloroethoxycarbonyl azide ($TrocN_3$) did



Scheme 2. Scope and limitations of the enantioselective, visible light-induced amination of 3-substituted quinolones and pyridones. Aryl azide **2** was employed as the aminating reagent (1.5 equiv.) which was added in two portions at $t = 0$ h and $t = 14$ h. All yields refer to isolated compounds. The conversion (*conv.*) is defined as conv. = 100 %–yield (%) of re-isolated starting material. The enantiomeric excess (*ee*) was determined by chiral HPLC analyses.

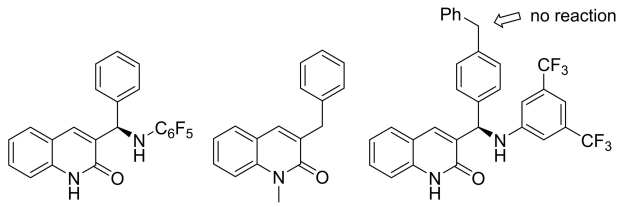


Figure 1. Structures of compounds **8**, **9**, and **7v** showcasing the use of a different aminating reagent (**8**), the relevance of hydrogen bonding for the success of the amination reaction (substrate **9**), and the exquisite site-selectivity (**7v**) of the enantioselective amination.

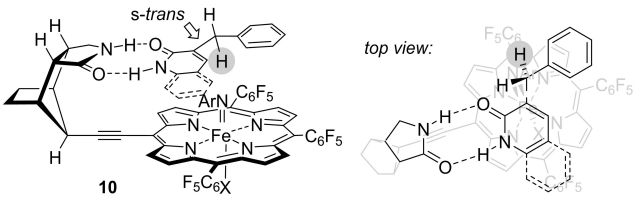


Figure 2. Model for the enantioselective iron-catalyzed amination of 2-quinolones and 2-pyridones: The pro-*R* hydrogen atom is directed towards the reactive nitrene species within complex **10** (X = ligand).

not lead to a notable substrate conversion (see the Supporting Information for further details).

The most remarkable feature seen in the amination reaction of 2-quinolones and 2-pyridones is the enormous directing power of the hydrogen bonding motif within catalyst **6**. If achiral 5,10,15,20-tetrakis(pentafluorophenyl)-21*H*,23*H*-porphyrin iron chloride, which is electronically comparable to catalyst **6**, was employed in the attempted racemic reaction **5a**→*rac*-**7a**, not even traces of product could be detected (Table 1, entry 3). Likewise, if quinolone **9**, which does not display a two-point hydrogen bonding motif was probed as substrate in the amination reaction, there was no reaction under the conditions of entry 11 (Table 1). Indane (cf. Scheme 1) was more reactive and showed conversion to the respective product **4**. The reaction proceeded in 50 % yield (conv. not determined due to volatility of the starting material) but the product was racemic (< 2 % *ee*) underpinning the requirement for a two-point hydrogen bonding interaction to direct the attack of the aminating intermediate. In perfect agreement with these data, the reaction proceeds exclusively at the methylene group adjacent to the quinolone core. If a second benzylic position is available, it is not attacked. Product **7v** was isolated as a single regioisomer with high enantioselectivity.

Due to the critical importance of hydrogen bonding for site- and enantioselectivity it appears sensible to assume that the amination occurs in a 1:1 complex of the reactive porphyrin complex and the substrate. Formation of a nitrene intermediate is triggered by excitation of the azide-metal complex[19] and likely leads to the formation of an iron imido complex. The latter is competent to undergo the amination reaction provided that the substrate is properly accommodated in its binding site (Figure 2). Turnover numbers (TONs) are in most cases above 50 but do not reach the efficiency of biocatalytic amination.[9,10] The catalyst can be recovered from the reaction mixture after column chromatography and retains its activity (for further details see the Supporting Information). Based on previous work with substrates **5**[20] and on the product configuration established for **7a**, we assume their reactive conformation to involve an s-*trans* orientation between the aryl group at the reactive methylene position and the carbonyl group of the quinolone. The amination reaction thus addresses the indicated (gray circle) pro-*R* hydrogen atom leading to the respective (*R*)-configured products. The reaction mode of the formal C–H insertion was interrogated by kinetic isotope experiments which delivered a value of $k_H/k_D = 2.3$ (± 0.2). The value indicates C–H bond cleavage to occur in the turnover-limiting step[21] but varies significantly from the value (6.5) Che and co-workers have previously obtained for the racemic reaction (cf. Scheme 1).[11d] It is conceivable that the proximity of the C–H bond facilitates a direct insertion into the C–H bond.[22] Alternatively, if a rebound mechanism is operative, it could be argued that the trajectory of the hydrogen abstraction step was bent[23] but not as linear as it is possible in a less confined transition state. The narrow pocket within complex **10** is likely responsible for steric restrictions regarding the nitrene source but enables beneficial ππ interactions to the substrate.

In any case, it is apparent from the model for the amination reaction **10** that the nitrene delivery will occur with excellent enantiocontrol and that any substrate displaying a *pro*-R hydrogen atom will be processed. In line with this notion, we found over-oxidation to imines to occur in some of the reactions. The phenomenon was further studied with the racemic amination product *rac*-**7t** (see the Supporting Information for further details). for which the imine could be isolated. A notable kinetic resolution was achieved under the reaction conditions favoring product **7t** over its enantiomer *ent*-**7t**. The absence of enantiomers *ent*-**7** in some of the reactions with > 99 % *ee* is therefore likely due to kinetic resolution. Since most imines hydrolyze upon work-up to the ketone, the ketone was taken as evidence of consecutive oxidation. Under the optimized reaction conditions (Table 1, entry 11), the ratio of imine to product **7a** was ca. 1:10 in the crude product mixture and a ketone yield of 6 % was recorded. Even if imine formation was not observed (e.g. for products **7l** or **8**), the enantioselectivity remained far above 90 % *ee* indicating the high stereochemical fidelity of the amination catalyst.

In summary, it has been shown that a two-point hydrogen interaction between an iron porphyrin catalyst and an amination substrate are sufficient to overcome the insufficient reactivity in intermolecular amination reactions via nitrene intermediates. The spatial proximity of the substrate and the reagent enable a high control over the site- and enantioselectivity of the reaction. A remarkable observation relates to the nature of the transition metal within the porphyrin backbone. It was found that the manganese porphyrin complex[20b,24] corresponding to **6** was completely inactive in the amination reaction (see the Supporting

Information), although it had previously turned out to be the superior catalyst for oxygenation reactions. The current study emphasizes that porphyrins attached to a chiral octahydro-1*H*-4,7-methanoisoindol-1-one scaffold hold great promise for the development of earth-abundant metal catalysts.

Acknowledgements

Financial support by the *Deutsche Forschungsgemeinschaft* (Ba 1372/23) is gratefully acknowledged. BG thanks the Alexander von Humboldt foundation for a research fellowship. CM acknowledges support by the DFG through the Heisenberg programme (ME 4267/5-1, project number 418661145) and the Cluster of Excellence "Ruhr Explores Solvation" (RESOLV, EXC-2033, project number 390677874). We thank Olaf Ackermann and Philip Freund (TUM) for HPLC measurements. Dr. C. Troll, Wacker Chair of Macromolecular Chemistry (TUM), is acknowledged for his help with the in situ IR experiments. We thank the following students for experimental assistance: Veronika Maria Stotter, Ji Won Lee and Paul Josef Ehrenreich. Open Access funding enabled and organized by Projekt DEAL.

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: amination · C–H activation · enantioselectivity · iron · porphyrinoids

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Manuscript received: April 12, 2024
Accepted manuscript online: May 2, 2024
Version of record online: June 14, 2024