An Enantioconvergent Benzylic Hydroxylation Using a Chiral Aryl Iodide in a Dual Activation Mode

Ayham Abazid,[a] Nils Clamor[a] and Boris J. Nachtsheim[a]*

University of Bremen, Institute of Organic and Analytical Chemistry, Leobener Straße 7, 28359 Bremen, Germany
nachtsheim@uni-bremen.de

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ABSTRACT: We report the application of a chiral triazole-substituted iodoarene in a direct enantioselective hydroxylation of alkyl arenes. This method allows the rapid synthesis of chiral benzyl alcohols in high yields and exceptional stereocontrol despite its non-templated nature. In a unique cascade activation comprising of an initial irradiation-induced radical C-H-bromination and a consecutive enantioconvergent hydroxylation, the iodoarene catalyst has a dual role. It initiates the radical bromination in its oxidized state through an in situ formed bromoiodane and in the second, Cu-catalyzed step, it acts as a chiral ligand. To the best of our knowledge this the first example demonstrating the ability of a chiral aryl iodide catalyst acting both, as an oxidant and as a chiral ligand in a highly enantioselective C-H-activating transformation. Furthermore, this is the first example for an enantioconvergent hydroxylation.

INTRODUCTION

The direct hydroxylation of C(sp^3)–H bonds is one of the most efficient reactions to introduce molecular complexity into unfunctionalized bulk chemicals.[1,2] Once introduced, the resulting alcohols are either a fundamental part of the desired target molecule or they can be readily transformed into other useful functionalities. Hydroxylations of benzylic C(sp^3)–H bonds are of particular interest due to the intrinsic reactivity of the benzylic C-H bond allowing a highly regioselective C-H activation in the presence of other aliphatic C-H bonds.[3,4] Based on cytochrome P-450 oxygenases as natural blueprint,[5] a variety of chiral metal-porphyrine complexes were developed for enantioselective hydroxylations.[6] In a first report in 1989 by Groves and co-workers chiral iron porphyrins could be applied in combination with iodosobenzene as oxygen-donor to hydroxylate ethyl benzene in 40% yield and 41% ee.[7] Template-directed procedures give excellent selectivities although only well-selected substrates that can non-covalently interact with the chiral catalyst through hydrogen-bonding patterns can be addressed efficiently.[8,9] It is surprising, that even more than three decades after the initial finding of Groves, simple alkyl benzenes are still difficult to hydroxylate in good yields and enantioselectivities through purely synthetic catalysts.[10,11] Hypervalent iodine reagents are commonly used oxidants for oxidative coupling reagents and in group and oxygen transfer reactions.[12,13,14] They can be also applied in benzylic hydroxylations as demonstrated by Groves in his early report as well as in high valent transition metal chemistry[15] and in photoredox catalysis.[16] The use of chiral iodanes or their aryl iodide precursors in catalytic enantioselective benzylic hydroxylations is so far unknown.[17] During our systematic studies of *N*-heterocycle-stabilized iodanes (NHIs),[18] we recently introduced triazole-substituted aryl iodides **1** (Figure 1) as chiral iodane-precursors and successfully verified their excellent performance in a plethora of enantioselective oxidative transformations.[19] In a new approach we herein demonstrate their unique ability to act in a dual way, initially as a iodane-based halogen donor for a non-stereoselective radical-mediated halogenation and as a chiral ligand in a so far undescribed enantioconvergent hydroxylation.[20,21]

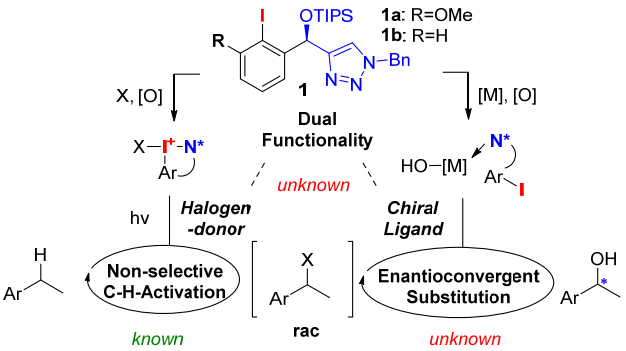


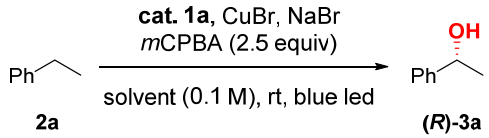
Figure 1. Working model for the dual activation of alkyl arenes using catalysts of type **1**

Combining **1** with a co-oxidant and a halogen anion-should initially form a stabilized halogen(aryl)-λ^3-iodane, to initiate the C-H-activation and then ligate a transition metal during the second, enantioconvergent, reaction step. The combination of bromide sources and aryl-λ^3-iodanes is known to activate benzylic C-H-bonds through *in situ* formation of bromo-iodanes followed by a light-induced homolytic cleavage of the labile I-Br-bond.[22]

RESULTS AND DISCUSSION

Based on the fact that many radical-mediated enantioconvergent substitutions, in particular alkylations of secondary alkyl halides, can be catalyzed by Cu(I)-salts,[23,24] We initially focused on CuBr acting as the bromide donor and the transition metal-catalyst. To test our hypothesis, the direct hydroxylation of ethyl benzene **2a** was investigated (Table 1). As expected, under thermodynamic conditions in DCM no reaction was observed (entry 1). To our delight, irradiation with a blue LED gave the desired product **(*R*)-3a** in 68% yield and 71% ee using 150 mol% CuBr (entry 2). While aromatic solvents such as toluene give a diminished yield and selectivity (entry 3) using acetonitrile gave **(*R*)-3a** in 75% yield and 90% ee (entry 4). Since the Cu-salt should initially only act as an activator for I-Br-bond activation, we were surprised by the observed high amounts that were needed for this additive and wondered whether it would be sufficient to add catalytic amounts of Cu(I)Br and another, cheaper, bromide source in stoichiometric quantities. Indeed, if only 20 mol% of CuBr in combination with 1.5 equiv. of NaBr as additive were used, the reaction still proceeds with almost the same outcome (entry 5). Under these conditions we could even decrease catalyst loading of **1a** to 15 mol% without affecting yield and selectivity (entry 6). In agreement with our recent findings, catalyst **1b** not bearing the important *ortho*-substituent in the aryl iodide, performs worse (see ESI, Scheme S1)

Table 1. Optimization of the reaction conditions.



2a **(*R*)-3a**

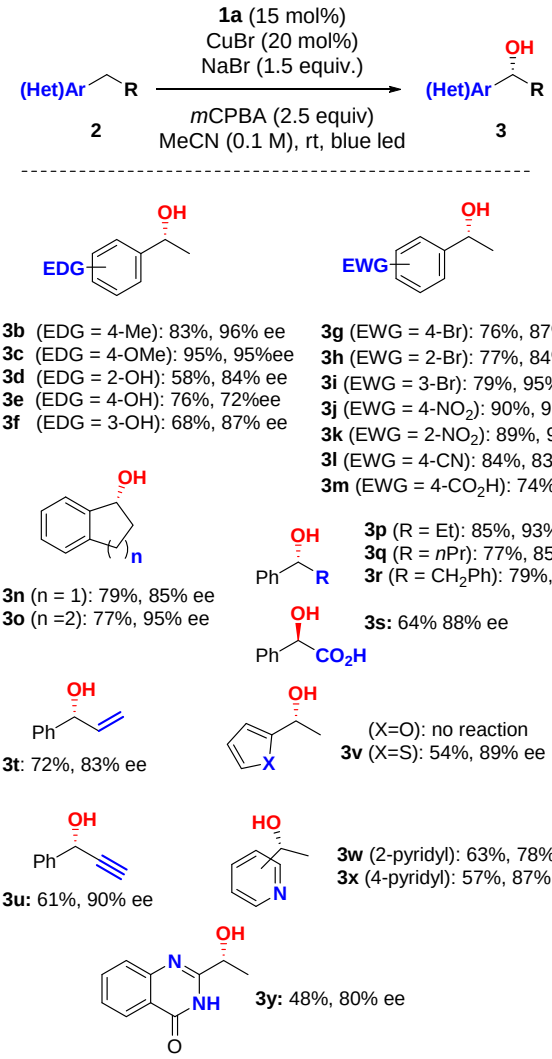
entry	1a	CuBr	NaBr	solvent	t [h]	yield [%]	ee [%]
1[a]	20	150	0	DCM	12	0	-
2	20	150	0	DCM	20	68	71
3	20	150	0	PhMe	30	25	40
4	20	150	0	CH_3CN	14	75	90
5	20	20	150	CH_3CN	14	74	90
6[b]	**15**	**20**	**150**	**CH_3CN**	**14**	**74**	**90**

[a]The reaction was performed at 60°C for 12 hr. [b] These conditions will be further referred as "optimized conditions".

Under these optimized conditions, we examined the applicable substrate scope (Scheme 1). Initially, we investigated simple electron rich ethyl arenes. 4-Methyl- and 4-methoxy-substituted derivatives reacted superior giving the desired benzyl alcohols **3b** and **3c** in high yields and 96% and 95% ee. Free hydroxy groups are tolerated as well giving **3d-3f** in still good yields and 72%-87% ee.

We then examined the effect of electron withdrawing groups at the arene. All possible bromo-substituted isomers reacted well giving **3g-3i** in throughout good yields of 76-79% with the best enantioselectivity being observed for the 3-Br-derivative (95%). Ethyl-substituted nitro arenes gave compounds **3j** and **3k** in even better yields (90 and 89%) and excellent 93% and 95% ee. Synthetically versatile nitriles and free carboxylic acids are also well tolerated yielding benzyl alcohols **3l** and **3m** in good yields and 83% and 95% ee. Indane and tetrahydronaphthalene give **3n** and **3o** in 79% and 77% yield with 85% and 95% ee. For these substrates, small amounts of dihydroxylation products (<10% were observed). Next, the aliphatic side chain of the ethyl benzene was varied. *n*Propyl- and *n*butyl benzene gave **3p** and **3q** in yields and selectivities comparable to the model substrate. The same was observed for 1,2-diphenylethane giving **3r** in 79% and 93% ee. 2-Phenyl acetic yielded (*R*)-mandelic acid **3s** in 64% and 88% ee. We then examined multiple bond substitution in the benzylic side chain. Once again, the method showed a high robustness among those substrates. Allyl benzene was directly hydroxylated to yield the allyl alcohol **3t** in 83% ee. Propargyl alcohol **3u** was isolated with even higher selectivities of 90% ee, although the yield was lower (61%), probably due to a slight decomposition of the delicate propargylic alcohol. Finally, we investigated a variety of ethyl-substituted heterocycles as substrates.

Scheme 1. Substrate Scope



3b (EDG = 4-Me): 83%, 96% ee
3c (EDG = 4-OMe): 95%, 95%ee
3d (EDG = 2-OH): 58%, 84% ee
3e (EDG = 4-OH): 76%, 72%ee
3f (EDG = 3-OH): 68%, 87% ee

3g (EWG = 4-Br): 76%, 87%ee
3h (EWG = 2-Br): 77%, 84% ee
3i (EWG = 3-Br): 79%, 95% ee
3j (EWG = 4-NO_2): 90%, 93% ee
3k (EWG = 2-NO_2): 89%, 95% ee
3l (EWG = 4-CN): 84%, 83% ee
3m (EWG = 4-CO_2H): 74%, 95% ee

3n (n = 1): 79%, 85% ee
3o (n =2): 77%, 95% ee

3p (R = Et): 85%, 93%ee
3q (R = *n*Pr): 77%, 85% ee
3r (R = CH_2Ph): 79%, 93% ee

3s: 64% 88% ee

3t: 72%, 83% ee

(X=O): no reaction
3v (X=S): 54%, 89% ee

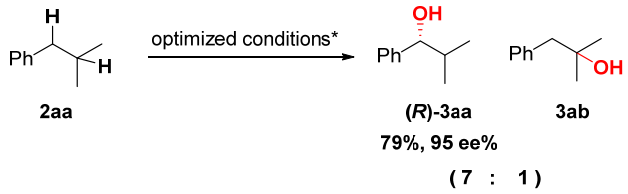
3u: 61%, 90% ee

3w (2-pyridyl): 63%, 78% ee
3x (4-pyridyl): 57%, 87% ee

3y: 48%, 80% ee

While 2-ethyl furane did not react at all, the corresponding thiophene gave **3v** in 89% ee and 54% yield. Even ethyl pyridines were tolerated under the applied oxidative conditions, despite potential oxygenations of the ring nitrogen. giving 2- and 4-pyridyl-substituted alcohols **3w** and **3x** in moderate yields and 78% and 87% ee. Even 4-ethyl quinazolinone could be directly hydroxylated to **3y** with 80% ee.

Scheme 2. Investigating the regioselectivity.

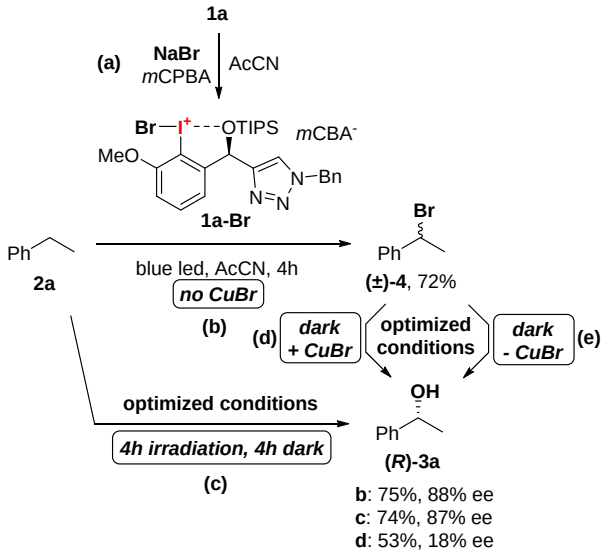


[a]After 4 h the reaction temperature was decreased to 0 °C

We were also interested whether the applied reaction conditions allow the regioselective C-H-activation of the benzyl C-H-bond in the presence of tertiary C-H-bonds - also potential hot spots for the initial radical-mediated halogenation. Therefore, we submitted substrate **2aa** to our optimized reaction conditions and indeed found a mixture of regioisomers **3aa** and **3ab** in a ratio of 7:1 and 95% ee for **3aa**. (Scheme 2). Thus, the regioselective activation of the benzylic C-H is strongly favored.

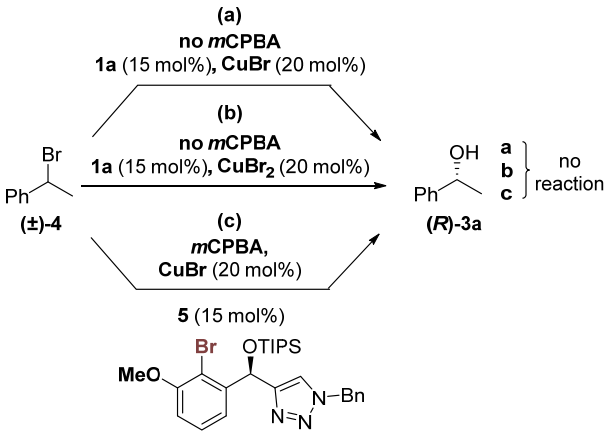
After this comprehensive elaboration of the substrate scope we were intended to get a deeper understanding of the underlying reaction mechanism and in particular, proof the initially proposed dual role of the catalyst in this process and the unique enantioconvergent hydroxylation. For the first step, the radical-mediated halogenation, a brominated catalyst must be formed with a labile I-Br bond that easily breaks homolytic to induce the radical-mediated benzyl C-H-abstraction.

Scheme 3. Bromination with isolated catalyst 1a-Br to prove the first step of the dual activation mechanism.



Treatment of **1a** with NaBr and *m*CPBA allowed us to isolate a white solid which we identified via NMR and MS as being the brominated derivative **1a-Br** (Scheme 3 – a). Treatment of **2a** with this compound without a Cu-source under light irradiation yielded the benzyl bromide **4** in a very clean reaction and 72% yield as a racemate (b). Even if benzyl bromide would be formed enantioenriched its known tendency to racemize in polar solvents would yield the racemate under the given reaction conditions.[25] This experiment implies, that once the benzyl bromide is formed, the second step of the transformation must be an enantioconvergent substitution in which irradiation should not be essential anymore. To verify this hypothesis, we reacted **2a** again using the optimized conditions, but with only 4h of light irradiation followed by further stirring for 4h in the dark (c). Under these conditions the desired benzyl alcohol was observed in nearly the same yield and enantioselectivity as under full-time irradiation. We then treated **4** under the optimized conditions, without irradiation (d) and isolated **3a** in almost the same quantities and ee-values as in the previous experiments. We then questioned the necessity of CuBr as additive which was intended to catalyze exclusively the second step. When the reaction was repeated, without adding CuBr (e), **3a** could still be isolated in 53% yield, however, nearly as a racemate (18% ee). From these experiments we conclude that Cu is not necessary for the initial C-H activation but plays a fundamental role in the enantioconvergent hydroxylation. Here, **1a** must act as a *N*-ligand coordinating through its triazole functionality, and therefore no oxidative conditions should be necessary. We therefore performed further control experiments starting from racemic **4** under our optimized conditions, without the addition of *m*CPBA, but adding either CuBr or $CuBr_2$ (Scheme 4 – a and b). In both experiments no conversion to **3a** was observed. Thus, even in the second step the oxidant is necessary, but not just to oxidize the Cu(I)-species. Obviously a hypervalent iodine compound must be important as well in the enantioconvergent step.

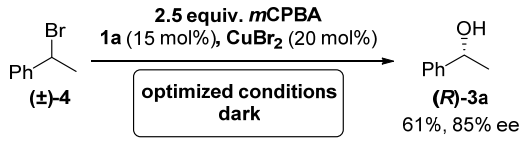
Scheme 4. Control experiments to elucidate the stereoconvergent substitution.



To proof this claim, we prepared catalyst derivative **5** bearing an aryl bromide instead of an aryl iodide. Aryl bromides cannot be oxidized with *m*CPBA into a hypervalent state and therefore, as we observed, no reaction should occur (c). For gaining more insights about the potential active oxidation state of the involved Cu-species, we repeated the

experiment starting from benzyl bromide under oxidative conditions but now adding $CuBr_2$ instead of CuBr (Scheme 5). Under these conditions **3a** was isolated in slightly lower yields (61%) but in similar enantioselectivity (85% ee), again implying that the co-oxidant is necessary for the formation of a hydroxy iodane.

Scheme 5. Enantioconvergent substitution with $CuBr_2$[a]



[a]Reaction conditions: **(±)-4** (0.11 mmol), MeCN (0.1 M),

A hydroxylated catalyst **1a-OH** could also not be isolated as a pure substrate for further control experiment due to its high reactivity based on the *ortho*-effect of the methoxy group and the induced hypervalent twist.[26] However, NMR-experiments strongly support a hydroxylation under reductive collapse of the iodane as exemplified by 13C chemical shifts of the characteristic iodine-bound aryl signal (Figure 2). This ipso-carbon in **1a** (blue) and the meta-carbon (green) have typical chemical shifts of approx. 90 and 110 ppm (a). Upon addition of *m*CPBA to yield **1a-OH** as a mixture of different isomers, both signals clearly disappear and shift downfield to > 115 ppm (b). Addition of CuBr regenerates **1a** demonstrated by the reappearance of both signals (c). A significant line broadening of the signals in the corresponding proton NMR implies the existence of paramagnetic Cu(II) in the reaction mixture (see ESI). The transient formation of Cu(III)-species cannot be ruled out and should be considered as well. Unfortunately, we were not able to isolate or characterize a Cu-triazole complex therefore in depth understanding of the enantioconvergent step remains elusive.

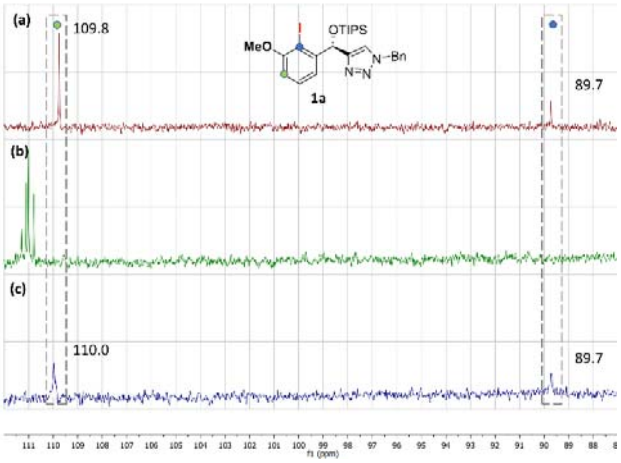
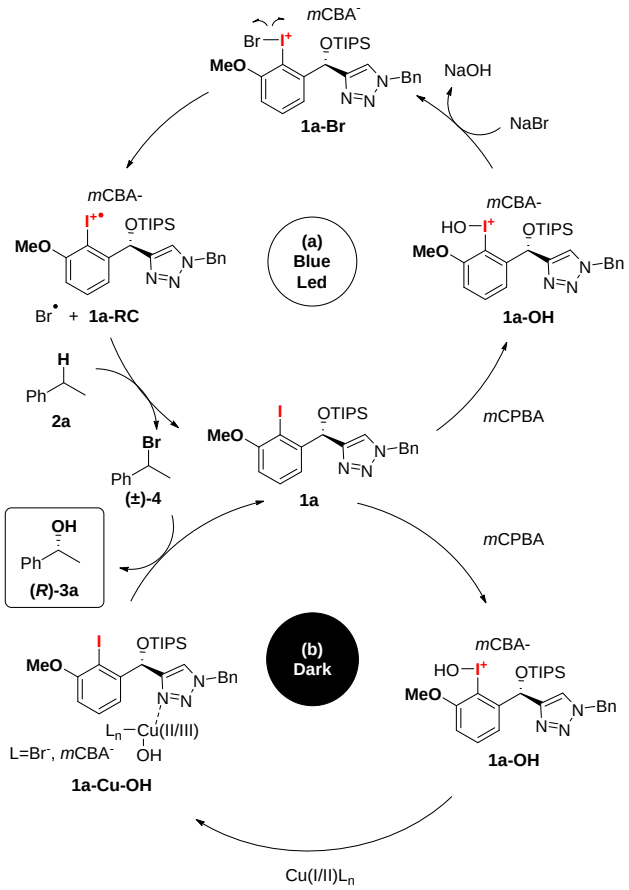


Figure 2. 13C-NMR-shifts for *in situ* oxidation of **1a** between 85-112 ppm. **(a) 1a** alone**. (b) 1a**+*m*CPBA**. (c) 1a** + *m*CPBA + CuBr.

However, based on these control experiments we want to propose a catalytic cycle shown in Scheme 6. In the initial irradiation-mediated cycle (Scheme 6 - a) **1a** is first oxidized into the hydroxyiodobenzene **1a-OH**. Ligand exchange with NaBr gives the bromoiodobenze **1a-Br** which underlies rapid I-Br bond cleavage under irradiation yielding a bromine radical and the radical cation **1a-RC**. Radical benzylic bromination initiated by either of both species converts the alkyl benzene into the benzyl bromide as a racemate. In the second cycle (Scheme 6 - b) **1a** is oxidized again in the initial-step to **1a-OH**. The iodane then hydroxylates the Cu-salt either yielding a chiral Cu(II) or a Cu(III)-hydroxy complex **1a-Cu-OH**.

Scheme 6. Mechanistic proposal



Depending on the oxidation state of the active Cu-complex, either a radical or a S_N-type enantioconvergent substitution with the emerging benzyl bromide from cycle (a) yields **(*R*)-3a**. Due to the high racemization tendency of **4** we suggest this overall reaction to be a stereomutative enantioconvergent reaction with significantly different reaction rates for both enantiomers.

CONCLUSIONS

In conclusion this work demonstrates the ability of chiral aryl iodides substituted with *N*-heterocycles to be used in enantioselective benzylic hydroxylations through a double role, acting as oxidant and as a chiral ligand in a consecutive reaction sequence consisting of a benzyl bromination and a Cu-mediated substitution. The verification of (±)-benzyl bromide as a reaction intermediate verifies that the second, Cu-mediated reaction, is a unique enantioconvergent hydroxylation. The reaction tolerates a wide variety of substrates including electron rich and electron poor alkyl benzenes, exocyclic π-bonds as well as alkyl-substituted *N*-heterocycles. Furthermore, a high regioselectivity for the ben-

zylic C-H-bond in the presence tertiary C-H-bonds was observed. This unique reaction cascade offers great potential for other enantioselective oxidative benzylic C-H-activations, although the mechanism of the enantioconvergent step still needs to be further elaborated.

ASSOCIATED CONTENT

Supporting Information. The Supporting Information is available free of charge on the ACS Publications website at DOI: XXX. Including all experimental procedures and characterization data.

AUTHOR INFORMATION

Corresponding Author

* nachtsheim@uni-bremen.de

Author Contributions

The manuscript was written by BJN. All authors have given approval to the final version of the manuscript. / ‡These authors contributed equally. (match statement to author names with a symbol)

Orcid

Boris J. Nachtsheim: 0000-0002-3759-2770

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Notes

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ABBREVIATIONS

*m*CPBA: *meta*-Chloroperbenzoic acid; *m*CBA: *meta*-Chlorobenzoic acid; DCM: Dichloromethane

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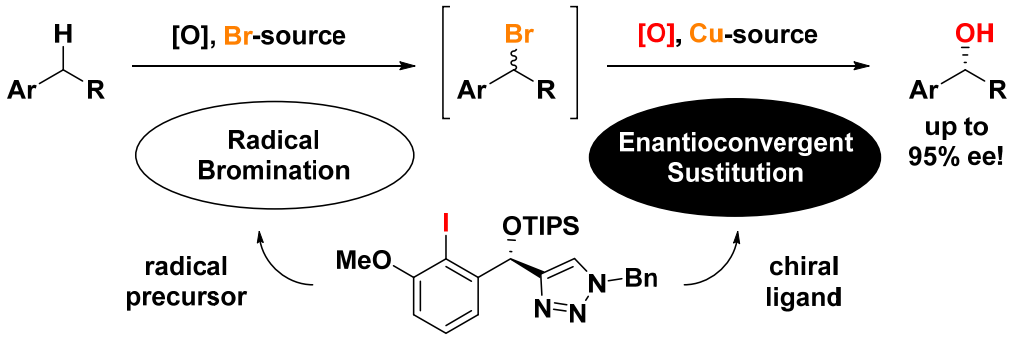
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