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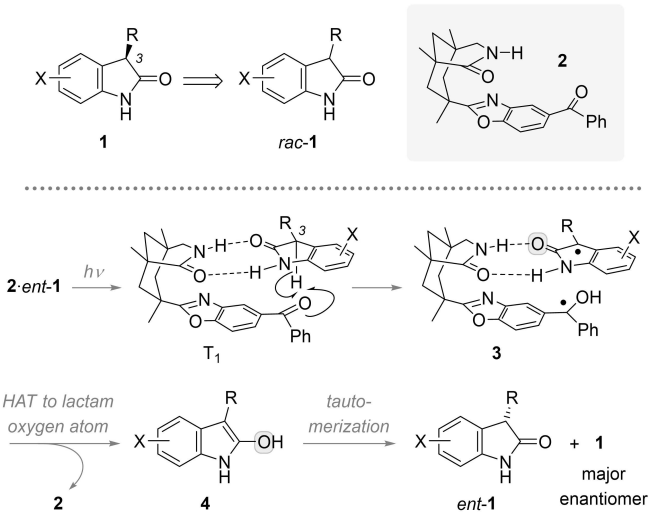
Photochemistry

Photochemical Deracemization of 3-Substituted Oxindoles

*Johannes Großkopf, Alexandra A. Heidecker, and Thorsten Bach**

Abstract: Racemic 3-substituted oxindoles were successfully converted into enantiomerically pure or enriched material (up to 99 % *ee*) upon irradiation at $\lambda = 366$ nm in the presence of a chiral benzophenone catalyst (10 mol %). The photochemical deracemization process allows predictable editing of the stereogenic center at carbon atom C3. Light energy compensates for the associated loss of entropy and enables the decoupling of potentially reversible reactions, i.e. a hydrogen atom transfer to (photochemical) and from (thermal) the carbonyl group of the catalyst. The major enantiomer is continuously enriched in several catalytic cycles. The obtained oxindoles were shown to be valuable intermediates for further transformations, which proceeded with complete retention at the stereogenic center.



Scheme 1. Enantiomerically pure oxindoles **1** by stereochemical editing of the respective racemates *rac*-**1** with catalyst **2** (top). Possible reaction course of a deracemization with enantiomer *ent*-**1** being continuously processed by catalyst **2** and enantiomer **1** being enriched due to the inaccessibility of its hydrogen atom in position C3. Enantiomer **1** is not processed by catalyst **2** while enantiomer *ent*-**1** re-enters the catalytic cycle (bottom).

2-Indolinones (oxindoles) represent one of the most important classes of condensed heterocyclic compounds. They have attracted considerable attention, mainly due to their wide range of biological activities.[1] Extensive efforts have been undertaken towards their synthesis and their consecutive use as synthetic building blocks.[2] The existence of a stereogenic center at position C3 renders many oxindoles chiral and there is a wide array of 3,3-disubstituted oxindoles known, which can be prepared enantioselectively.[3] In contrast to the latter compound class which is configurationally stable, 3-(mono)substituted oxindoles **1** (Scheme 1) display a more fragile stereogenic center. Their enantioselective synthesis is hampered by possible racemization which in turn has impeded an access to the compounds in enantiomerically pure form.[4] Since catalytic photochemical deracemization occurs under very mild conditions, we envisioned this new technique[5–7] to be a suitable tool to prepare 3-substituted oxindoles in enantiomerically pure or enriched form from a racemic mixture *rac*-**1**. Photochemical deracemization reactions can be performed by a single chiral catalyst that distinguishes between enantiomers,[8] or by multi-catalytic systems, in which the chiral catalyst is responsible for the enantioselective transformation of a transient intermediate,[9] or by combinations thereof.[10] Our group has taken the first approach and we have recently shown that a chiral benzophenone catalyst **2** enables the deracemization of hydantoins by a reversible hydrogen atom transfer (HAT).[11] When applied to oxindoles, we expected the chiral catalyst **2** to selectively induce a HAT from oxindole enantiomer *ent*-**1** in the hydrogen-bonded complex **2**·*ent*-**1**. Upon excitation and intersystem crossing to the triplet state T_1, the carbonyl group of the benzophenone would abstract the hydrogen atom at carbon atom C3, forming two carbon-centered radicals associated within complex **3**. While it was shown for hydantoins that the hydrogen atom is transferred from the protonated ketyl radical to an oxygen atom *not* involved in the hydrogen bonding event,[11b] it is required for the oxindoles that the hydrogen atom is returned unselectively to the carbon atom or—more likely—to the hydrogen-bonded lactam oxygen atom. The latter process would form intermediate **4**, which was expected to tautomerize statistically to oxindoles *ent*-**1** and **1**. Since the C3 hydrogen atom of enantiomer **1** is not accessible in a putative complex **2**·**1**, this enantiomer would be enriched, while enantiomer *ent*-**1** would re-enter the photocatalytic cycle.

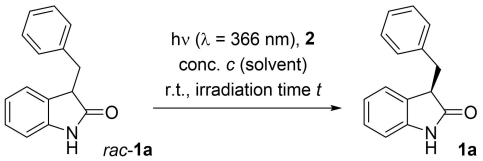
[*] Dr. J. Großkopf, A. A. Heidecker, Prof. Dr. T. Bach
Technische Universität München, School of Natural Sciences, Department of Chemistry and Catalysis Research Center
Lichtenbergstrasse 4, 85747 Garching (Germany)
E-mail: thorsten.bach@ch.tum.de
Homepage: https://www.ch.nat.tum.de/en/oc1/home/

Based on the described hypothesis, we have now studied 3-substituted oxindoles in a photochemical deracemization reaction. We found the process to be extremely efficient and we were able to prepare a wide range of chiral oxindoles enantioselectively. Our preliminary results, which include consecutive reactions of chiral oxindoles, are presented in this communication.

Optimization experiments (Table 1) were performed with 3-benzyl-2-indolinone (*rac*-**1a**) as the substrate. Excitation of benzophenone **2** was achieved with fluorescent lamps displaying an emission maximum at $\lambda = 366$ nm. Following irradiation, the products were isolated by removing the solvent and subjecting the resulting slurry to reverse phase column chromatography. The initial irradiation time was chosen to be 13 hours ($t = 13$ h) and the study commenced with a screening of possible solvents (entries 1–3), from which trifluorotoluene emerged as clearly superior. Lowering the catalyst concentration from 10 mol % to 5 mol % led to a decrease in enantioselectivity (entries 4 and 7). The substrate concentration could be increased to 5 mM without a change in performance (entry 5). At a higher concentration (entry 6), the yield and enantioselectivity dropped, even if the irradiation time was shortened (entry 8). A reaction time of nine hours was found to be optimal (entries 9, 10), and it was shown that the reactions can be run on larger scale (entry 11).

Under the optimized conditions of Table 1 (entry 9), a large variety of oxindoles was subjected to a photochemical deracemization (Figure 1). 3-Arylmethyl substituted oxindoles *rac*-**1b**–**1l** reacted consistently in high yield and delivered the desired products with high *ee*. Functional groups were compatible (ether, ester, halogen substituents) with the deracemization protocol as was the heterocyclic pyridine ring (**1k**, **1l**). In the aliphatic series (**1m**–**1x**), a size effect of the alkyl group was not notable and even 3-ethyl-2-indolinone (**1u**) was obtained with excellent *ee* (97 % *ee*). Oxindole **1m** contains the side chain of the lipid lowering agent clofibrate, which was fully compatible with the reaction conditions, as was the ester group in strained bicyclo[1.1.1]pentane **1n** and in **1v**. Several other branched aliphatic substrates were used successfully (**1o**–**1u**) and a substitution of the aromatic core was also tolerated (**1w**, **1x**). A full list of all oxindoles subjected to the deracemization protocol can be found in the Supporting Information. An issue with deracemization by HAT is the stability of the catalyst. If back HAT from the protonated ketyl radical is delayed and the two radicals of complex **3** (Scheme 1) diffuse in solution, decomposition products will be formed. In cases where a very high *ee* is required, another 10 mol % of catalyst can be added, and the irradiation can be continued for another nine hours. As an example, the *ee* of

Table 1: Reaction optimization of the photochemical deracemization *rac*-**1a**→**1a** catalyzed by chiral benzophenone **2**.



Entry[a]	*c* [mm]	Solvent [equiv.]	**2** [mol %]	*t* [h]	Yield[b] [%]	ee[c] [%]
1	2.5	CH_2Cl_2	10	13	45	12
2	2.5	MeCN	10	13	81	51
3	2.5	$PhCF_3$	10	13	79	90
4	2.5	$PhCF_3$	5	13	81	80
5	5	$PhCF_3$	10	13	78	90
6	10	$PhCF_3$	10	13	75	86
7	5	$PhCF_3$	5	13	78	83
8	10	$PhCF_3$	10	8	84	86
9	5	$PhCF_3$	10	9	91	90
10	5	$PhCF_3$	10	11	86	90
11[d]	5	$PhCF_3$	10	11	85	90

[a] Reactions were carried out on a scale of 25 µmol in the given solvent at room temperature. Irradiation was performed at $\lambda_{exc} = 366$ nm with a set of 16 fluorescent lamps[12] (maximum of emission). [b] Yield of isolated product after column chromatography. [c] The enantiomeric excess was calculated from the enantiomeric ratio (**1a**/*ent*–**1a**) as determined by chiral HPLC analysis. [d] The reaction was performed on a scale of 1.0 mmol.

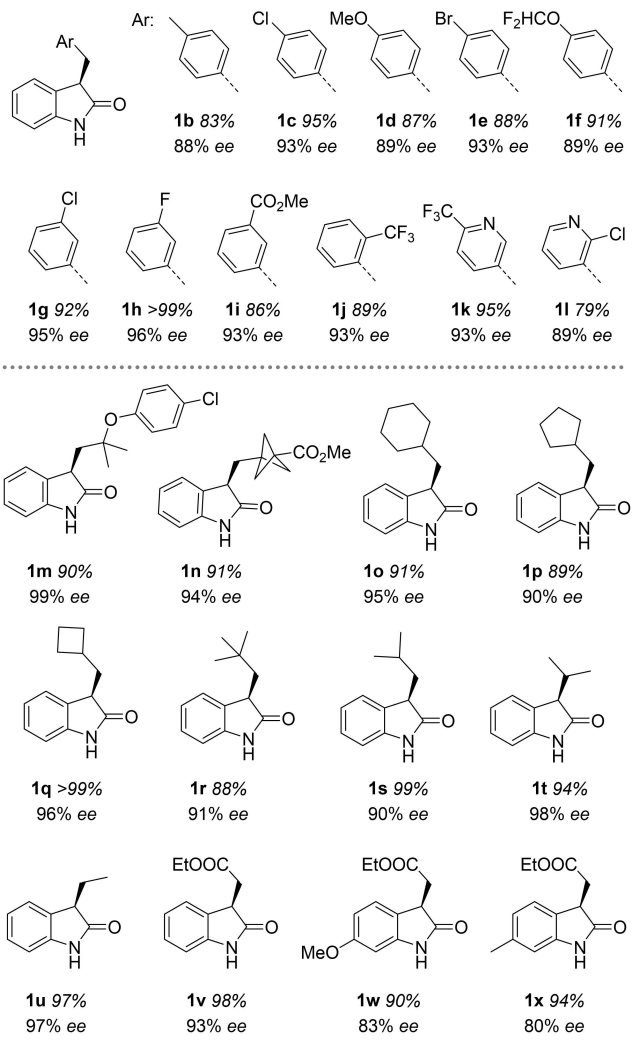
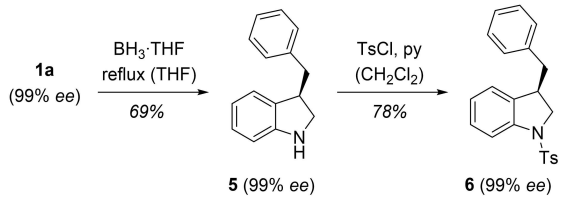


Figure 1. Representative products **1b**–**1x** obtained by photochemical deracemization of oxindoles *rac*-**1** under optimized conditions ($\lambda = 366$ nm, 10 mol % **2**, $t = 9$ h, $c = 5$ mM in $PhCF_3$).

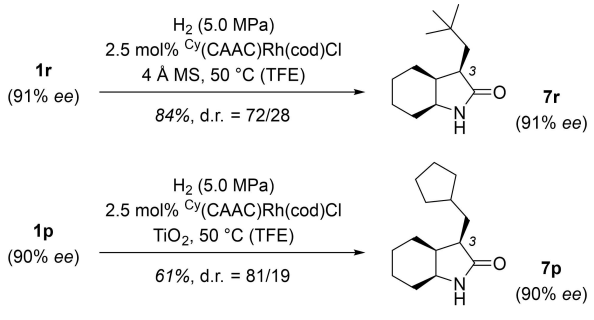
product **1a** increased to 99 % (82 % yield) when employing the latter protocol.

Apart from the stability issue, two other factors limit the scope. (a) With very bulky groups, e.g. adamantyl, in proximity to carbon atom C3, a HAT seems to be completely impossible. (b) If oxindole substitution leads to a decrease in triplet energy E_T, energy transfer (sensitization) might occur, thus also prohibiting HAT. Benzophenone **2** has a triplet energy of $E_T = 291\ kJ\,mol^{-1}$ (77 K, pentane/isopentane)[13] which is much lower than that of typical oxindoles, such as compound **1s** ($E_T = 321\ kJ\,mol^{-1}$, 77 K, EtOH). Substitution at the indole lowers the value as seen for the 5-bromo analogue of **1s** with $E_T = 309\ kJ\,mol^{-1}$ (77 K, EtOH). The latter compound cannot be involved in a photochemical deracemization reaction with catalyst **2** (see the Supporting Information for details).

The enantiomerically pure or enriched oxindoles serve as versatile starting materials for consecutive reactions. It was shown for some selected transformations that they proceed without compromising the optical purity of the material. 3-Benzyl-2-indolinone (**1a**, 99 % *ee*) was reduced to the respective amine, 3-benzylindoline (**5**), upon treatment with borane-THF complex under reflux (Scheme 2).[14] The compound (99 % *ee*) was levorotatory which is in line with the expected (*R*)-configuration of the compound.[4b] To obtain further evidence for the absolute configuration, indoline **5** was tosylated (Ts = *para*-toluenesulfonyl, py = pyridine) and the resulting product **6** (99 % *ee*) was subjected to single crystal X-ray crystallography. Anomalous diffraction confirmed the compound to be (*R*)-configured at



Scheme 2. Reduction of oxindole **1a** to 3-benzylindoline (**5**) and subsequent tosylation. The reactions occurred with complete retention of configuration.



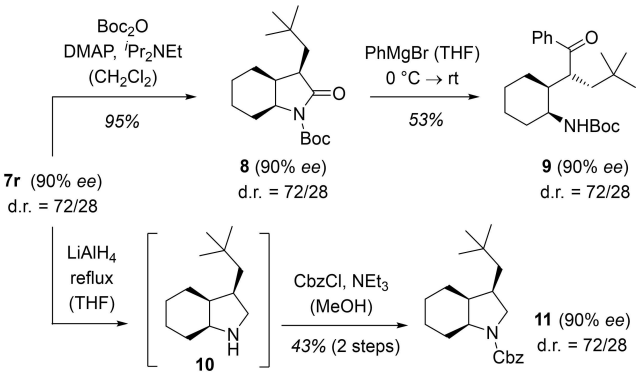
Scheme 3. The configurational integrity of the stereogenic center at position C3 during hydrogenation was proven by subjecting oxindoles **1r** and **1p** to typical reaction conditions. ^{Cy}(CAAC) = cyclic (alkyl)-(amino)carbene; cod = 1,5-cyclooctadiene; TFE = trifluoroethanol.

the stereogenic center[15] and supported our mechanistic hypothesis regarding the deracemization (Scheme 1).

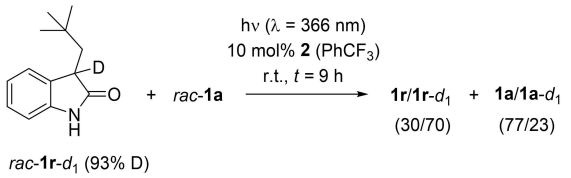
Attempts to completely hydrogenate the benzo ring of oxindoles resulted in low diastereoselectivities when Rh/C[16] was employed as catalyst. The known carbene complex ^{Cy}(CAAC)Rh(cod)Cl[17] gave better results and enabled the conversion[18] of oxindoles **1r** and **1p** with a notable diastereoselectivity (Scheme 3). In the former case, molecular sieves (4 Å MS) were used as solid support, in the latter case titanium dioxide. Although it is remarkable that the larger substituents at C3 produced a lower d.r. than the small methyl group,[18b] it was beyond the scope of the present study to investigate the diastereoselectivity in greater detail. The more relevant observation is that the enantiopurity of the material was consistently retained.

It was possible to perform the deracemization and arene hydrogenation in two consecutive steps without purification. Compound **7r** was thereby obtained in 76 % yield (90 % *ee*). In order to allow for its ring opening, the lactam was *N-tert*-butyloxycarbonyl(Boc)-protected [DMAP = 4-(dimethylamino)pyridine]. The resulting product **8** was subsequently treated with phenyl magnesium bromide[19] furnishing the desired ketone **9** with three contiguous stereogenic centers (Scheme 4). An alternative reaction sequence included reduction[20] of the lactam to amine **10**, which was difficult to isolate and was therefore benzyloxycarbonyl(Cbz)-protected. Product **11** was obtained in 43 % yield over two steps. All transformations proceeded without notable epimerization at any stereogenic center and the *ee* values remained unchanged.

As depicted in Scheme 1, the hypothetical reaction mechanism involves the intermediacy of an enol **4**, which undergoes tautomerization by intermolecular proton transfer.[21] This process typically leads to deuterium scrambling.[11b] When deuterated substrate *rac*-**1r**-d_1 and non-deuterated substrate *rac*-**1a** were subjected to the standard reaction conditions of the photochemical deracemization (Scheme 5), it was found that ca. 25 % of deuterium was incorporated into **1a** while ca. 25 % of hydrogen was



Scheme 4. Further transformations of product **7r**, which was obtained in a telescoped deracemization-hydrogenation reaction (76 % yield overall). After nitrogen protection the lactam ring was opened to provide ketone **9**. Reduction to octahydro-1*H*-indole **10** was followed by *N*-protection to provide product **11**. In all reactions, the absolute and relative configuration was retained.



Scheme 5. Deuterium scrambling in the deracemization of deuterated substrate *rac*-**1r**-d_1 and non-deuterated substrate *rac*-**1a**. Since only enantiomer *ent*-**1**, i.e. 50% of the racemate, is assumed to be processed in the reaction (cf. Scheme 1), the result indicates statistical scrambling.

found in **1r**-d_1. The result is in line with the expectation that only one enantiomer (*ent*-**1**) is processed, corresponding to 50% of the racemate, and that the subsequent tautomerization causes statistical 1:1 scrambling.

In summary, our study has revealed that 3-substituted oxindoles are amenable to a catalytic photochemical deracemization which enables a general enantioselective access to this compound class for the first time. The reaction occurs likely by a reversible HAT within the substrate–catalyst complex. The efficiency of the process is surprising given that oxindoles require both the N–H bond and the carbonyl group of the lactam for hydrogen bonding to the catalyst. The forward HAT is easy to visualize for enantiomer *ent*-**1** of the oxindole, but the back HAT requires the hydrogen-bonded carbonyl group to serve as hydrogen atom acceptor and to leave its binding partner. This intriguing process warrants further studies with oxindoles or related substrates. Work along these lines is ongoing in our laboratories.

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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 Supporting Information of this article.

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