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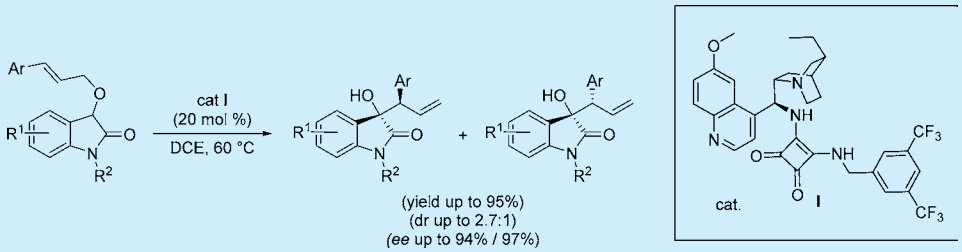
Asymmetric Organocatalytic Wittig [2,3]-Rearrangement of Oxindoles

Maksim Ošeka,[†] Mariliis Kimm,[†] Sandra Kaabel,[†,‡] Ivar Järving,[†] Kari Rissanen,[‡] and Tõnis Kanger*[,†]

[†]Department of Chemistry, Tallinn University of Technology, Akadeemia tee 15, 12618 Tallinn, Estonia

[‡]University of Jyvaskyla, Department of Chemistry, Nanoscience Center, P.O. Box 35, FI-40014 Jyvaskyla, Finland

Supporting Information

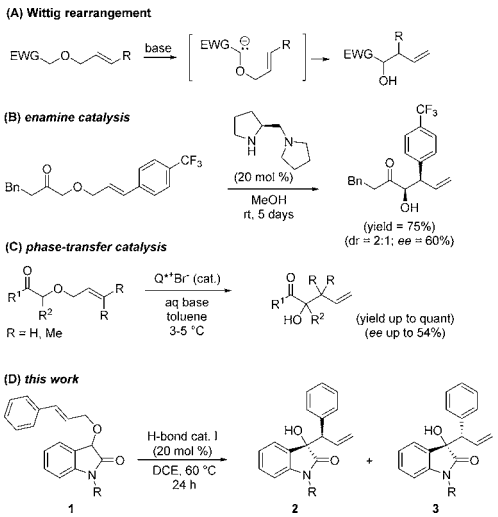


ABSTRACT: A highly enantioselective organocatalytic [2,3]-rearrangement of oxindole derivatives is presented. The reaction was catalyzed by squaramide, and this provides access to 3-hydroxy 3-substituted oxindoles in high enantiomeric purities.

An asymmetric [2,3]-sigmatropic rearrangement is an efficient tool for the creation of C−C or C−heteroatom bonds and the insertion of stereocomplexity into organic compounds. The rearrangement of allylic or propargylic ethers is called a Wittig rearrangement[1] (Scheme 1A), and it has been applied as a key step for the total synthesis of various natural products.[2] An anionic Wittig rearrangement involves the formation of an α-oxycarbanion, followed by a 2,3 allylic shift.[3] The anion formation is the promoter of the reaction. The use of strong Brønsted bases, such as BuLi or tBuLi, with chiral ligands is the most common strategy for acquiring asymmetric products in a [2,3]-rearrangement.[2,4] In addition, boron enolates have been used to achieve the goal.[5] Approaches based on chiral auxiliaries have also been used.[6] In all cases the oxyanion is obtained via enolization. However, the above-mentioned methods require a stoichiometric amount of a chiral ligand or chiral starting material and are very moisture sensitive, which has made scientists turn their attention to more efficient catalytic systems. This century has witnessed remarkable achievements in asymmetric organocatalysis, which has become a powerful methodology in organic synthesis.[7] In addition to the experimental simplicity (mild conditions; no need for an inert atmosphere or anhydrous conditions), organocatalytic reactions provide a wide range of activation types via covalent or noncovalent interactions. Bifunctional catalysts derived from *Cinchona* alkaloids simultaneously activate both the electro- and nucleophilic counterparts of the reaction, allowing for the implementation of various reactions.[8] To the best of our knowledge, only two examples of an asymmetric organocatalytic Wittig [2,3]-rearrangement have been published so far. In 2006, Gaunt et al. described an aminocatalytic Wittig rearrangement of α-allyloxy substituted ketones in the presence of a proline derivative (Scheme 1B).[9] The authors demonstrated the asymmetric reaction with moderate yield and selectivity for only one substrate, which makes the field relatively unexplored. Very recently, Denmark described a [2,3]-sigmatropic rearrangement under phase-transfer catalysis conditions (Scheme 1C).[10] However, the highest enantioselectivity obtained was moderate (*ee* 54%).

We previously demonstrated that 3-halogen substituted oxindoles can be easily and efficiently activated as nucleophiles via hydrogen bonds for various asymmetric organocatalytic

Scheme 1. Wittig [2,3]-Rearrangement



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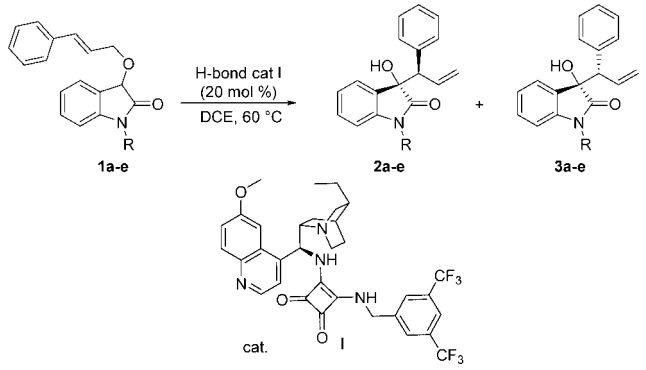
transformations.[11] We assumed that a similar activation of 3-substituted oxindoles could act as a trigger for the following Wittig rearrangement. Indeed, it was found that 3-cinnamyloxyoxindoles **1** afforded rearranged products in the presence of various H-bonding catalysts. Herein, we represent our results of the first hydrogen bond mediated asymmetric organocatalytic Wittig [2,3]-rearrangement (Scheme 1D). The obtained chiral 3-substituted 3-hydroxyoxindoles **2** and **3** are of great importance because they can be used as building blocks for the synthesis of biologically active compounds and natural products.[12]

Of the various chiral H-bonding catalysts screened (*Cinchona* alkaloids, *Cinchona* alkaloid derived thioureas and squaramides) the most efficient catalyst for the H-bond mediated Wittig [2,3]-rearrangement was squaramide **I**. According to our solvent and conditions optimization studies the reaction was performed in 1,2-dichloroethane at 60 °C (Scheme 1D) (see Supporting Information for the optimization details).

With optimal conditions in hand, the influence of various *N*-protecting groups of oxindoles was investigated (Table 1). In the model reaction with *N*-benzyl protected 3-cinnamyloxyoxindole **1a**, products were isolated in high yields and enantiomeric purities of both diastereoisomers (Table 1, entry 1). From the synthetic point of view, the use of unprotected NH-oxindole is preferred.[13] However, 3-cinnamyloxyoxindole **1b** reacted slowly and enantioselectivity decreased considerably for the major isomer (Table 1, entry 2). Protecting 3-cinnamyloxyoxindole with either a methyl or isopropyl group also did not increase the reaction rate and selectivity (Table 1, entries 3 and 4). As benzyl remained the best protective group in terms of reactivity and selectivity, we decided to slightly modify it with an additional methyl group in the *para*-position of the phenyl ring for more convenient determination of the conversion and diastereoisomeric ratio by ^{1}H NMR analysis of the crude mixture (Table 1, entry 5). Although the diastereoselectivity of the reaction was rather moderate, the formed diastereoisomers were separable by column chromatography on silica gel. This may be an advantage in terms of biological studies, as enantiomerically enriched diastereoisomers may have different activities.

The effect of various substituents in the aromatic ring of oxindole was studied. The obtained results are summarized in Table 2 (entries 2−10). The substitution with a halogen atom or electron-donating methoxy group at the fifth and seventh positions resulted in a slight decrease in diastereoselectivity while the overall yield and enantioselectivity remained very high compared to the unsubstituted 3-cinnamyloxyoxindole **1e** (Table 2, entries 2−7). When the aromatic ring of the oxindole was substituted with a strongly electronegative trifluoromethoxy group, reversed diastereoselectivity was observed (Table 2, entry 8). However, the diastereoselectivity remained low. Although substitution with the electron-withdrawing nitro group at position 7 did not remarkably affect the yield and selectivity, 5-nitro-substituted products were isolated in slightly lower yield and enantiomeric purity of the major diastereoisomer (Table 2,

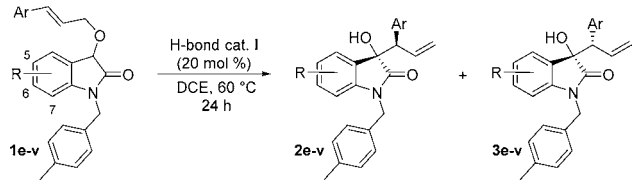
Table 1. Screening of Protective Groups[a]

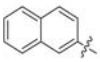
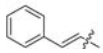


entry	R	time (h)	yield (%)[b]	dr **2**:**3**[c]	*ee* (%)[d]
1	**a**: Bn	24	87	2.5:1[e]	90 / 93
2	**b**: H	48	79	1.8:1	71 / 90
3	**c**: Me	48	79	2.5:1	80 / 86
4	**d**: *i*-Pr	72	36	1.8:1	82 / 85
5	**e**: 4-MeBn	24	91[f]	2.2:1	94 / 97

[a]Reaction conditions: 0.1 mmol scale, 20 mol % of cat. **I**, DCE (0.5 mL), 60 °C. [b]Overall isolated yield of the separated diastereoisomers. [c]Determined by ^{1}H NMR analysis of the crude mixture. [d]Determined by chiral HPLC analysis of the isolated products. [e]Determined by RP HPLC analysis of the crude mixture. [f]Reaction in 1.0 mmol scale.

Table 2. Scope of the Reaction[a]



entry	R	Ar	yield (%)[b]	dr **2**:**3**[c]	*ee* (%)[d]
1	H	Ph	(**e**) 91	2.2:1	94 / 97
2	5-F	Ph	(**f**) 83[e]	1.6:1	91 / 92
3	5-Cl	Ph	(**g**) 82	1.4:1	90 / 94
4	5-Br	Ph	(**h**) 86	1.3:1	90 / 95
5	7-F	Ph	(**i**) 92	1.4:1	92 / 93
6	7-Cl	Ph	(**j**) 89[e]	1.3:1	91 / 95
7	5-MeO	Ph	(**k**) 92	2.0:1	93 / 95
8	5-CF_3O	Ph	(**l**) 82[e]	1:1.4	91 / 95
9	5-NO_2	Ph	(**m**) 71	1.3:1	80 / 90
10	7-NO_2	Ph	(**n**) 85[e]	1.1:1	89 / 93
11	H	4-ClPh	(**o**) 90	2.0:1	94 / 95
12	H	3-ClPh	(**p**) >95	1.9:1	93 / 95
13	H	2-ClPh	(**q**) 87[f]	1:1.1	88 / 93
14	H	4-MeOPh	(**r**) 95	1.8:1	91 / 97
15	H	4-NO_2Ph	(**s**) 77[g]	1.6:1	80 / 30
16	H		(**t**) 88	2.7:1	93 / 95
17	H		(**u**) 93	2.0:1	92 / 95
18	H		(**v**) 63	1.7:1	86 / 91

[a]Reaction conditions: 0.1 mmol scale, 20 mol % of cat. **I**, DCE (0.5 mL), 60 °C. [b]Overall isolated yield of the separated diastereoisomers. [c]Determined by ^{1}H NMR analysis of the crude mixture. [d]Determined by chiral HPLC analysis of the isolated products. [e]Reaction was finished after 5 h. [f]Reaction was finished after 48 h. [g]Reaction was finished after stirring at rt for 48 h.

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entries 9 and 10). It can be concluded that the electronic effects of the substituents in oxindole on the selectivity of the reaction are not substantial.

Next, the influence of substituents at the cinnamyl phenyl ring was investigated. *para*- and *meta*-chloro substituted 3-cinnamyloxyoxindole **1o** and **1p** underwent [2,3]-rearrangement smoothly affording corresponding products in excellent yields and enantioselectivities (Table 2, entries 11 and 12). In the reaction with *ortho*-chloro substituted substrate **1q**, full conversion was observed only after 48 h (Table 2, entry 13). Moreover, the diastereoselectivity of the reaction was the lowest in the scope and was reversed, while the enantioselectivity remained very high. The low reactivity and diastereoselectivity of 3-cinnamyloxyoxindole **1q** may be explained by steric hindrance between the chlorine atom and the catalyst. Substitution with an electron-donating methoxy group provided products in excellent yield, and the minor diastereoisomer was isolated in the highest enantiomeric purity (Table 2, entry 14). A strong electron-withdrawing group in the *para*-position caused a dramatic decrease in the enantioselectivity of the minor diastereoisomer, while the enantioselectivity of the major diastereoisomer remained relatively high. Due to the formation of side products the yield of the reaction was lower than that when using other compounds (Table 2, entry 15).

The reaction scope was then further broadened with different aromatic substituents (Table 2, entries 16−18). A [2,3]-rearrangement with 2-thienyl (**1t**) and 2-naphtyl (**1u**) analogs of cinnamyloxyoxindole proceeded very efficiently under the same conditions with slightly better diastereoselectivities and very high enantioselectivities (Table 2, entries 16 and 17). The formation of unidentified side product was observed in the case of the analog **1v** with an extended double bond sequence. The reaction resulted in a lower, but still reasonable, isolated yield of [2,3]-rearranged products **2v** and **3v** (Table 2, entry 18). Finally, our study revealed that the scope of the reaction was limited to *trans*-3-cinnamyloxyoxindoles and their aromatic analogs. No reaction was observed under standard conditions when *cis*-3-cinnamyl, 3-allyloxy-, or crotyloxyoxindole was used as starting material. Moreover, an additional substituent at the double bond almost completely suppressed the [2,3]-rearrangement due to the sterical hindrance (see Supporting Information for additional details).

The relative and absolute stereochemistry of Wittig [2,3]-rearrangement products **2o** and **3i** were unambiguously assigned by single crystal X-ray diffraction (Figure 1).[14]

The configurations of other compounds in the series were assigned by analogy. According to the observed geometries of the products, the following transition states for Wittig [2,3]-rearrangement of 3-cinnamyloxyoxindole **1e** are proposed (Figure 2).

It can be assumed that 3-cinnamyloxyoxindole **1** was deprotonated at the third position and enolized by the tertiary amine moiety of the catalyst. The formed intermediate was activated by the multiple hydrogen bond interactions by squaramide and the protonated amine of the catalyst. The attack of enolate to the *Re*-face of the cinnamyl led to the formation of the *unlike* diastereoisomer **2**, whereas the attack to the *Si*-face gave the *like* diastereoisomer **3**. Transition states leading to different diastereoisomers do not differentiate from each other substantially causing the low diastereoselectivity of the reaction. As only aromatic or heteroaromatic allyloxy substrates were efficient substrates for the rearrangement, it is expected that the

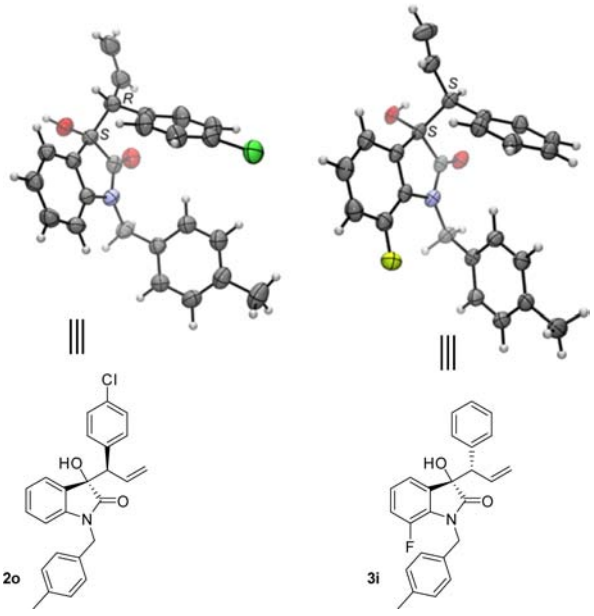

Figure 1. X-ray structures of [2,3]-rearranged products **2o** (major diastereoisomer) and **3i** (minor diastereoisomer).

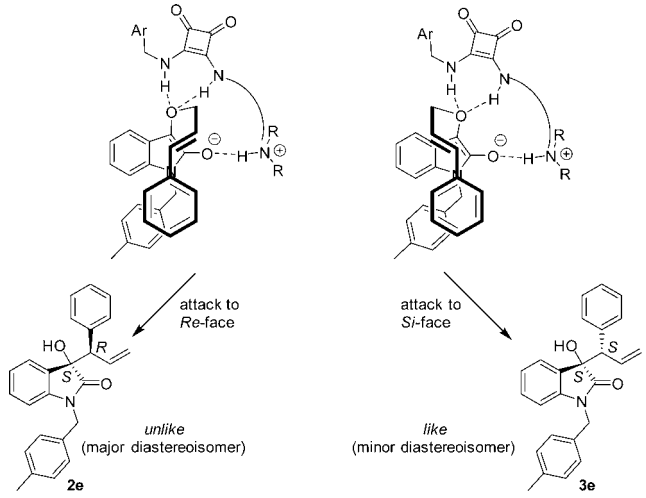

Figure 2. Proposed transition state for Wittig [2,3]-rearrangement of 3-cinnamyloxyoxindole **1e**.

$\pi-\pi$ attractive interaction played an important role in the stabilization of the transition state.

In order to further investigate the mechanism of the Wittig [2,3]-rearrangement of 3-cinnamyloxyoxindole **1k**, a kinetic study was performed (Figure 3). The reaction was carried out in deuterated chloroform, and crude samples were taken over time. ^{1}H NMR measurements revealed that the ratio between the two diastereomeric products, **2k** and **3k**, remained the same (2:1) throughout the entire reaction. It can be assumed that no isomerization of the products took place, and the diastereoselectivity was defined by the thermodynamic control.

In conclusion, we have developed the first highly selective asymmetric organocatalytic hydrogen bond mediated Wittig [2,3]-rearrangement. The rearrangement of 3-cinnamyloxyoxindole **1** was efficiently catalyzed by chiral squaramide **I** to provide 3-substituted 3-hydroxyoxindoles **2** and **3** in very high yields (up to 95%) and enantioselectivities (up to 97%). Although the diastereoselectivity of the reaction was low (dr

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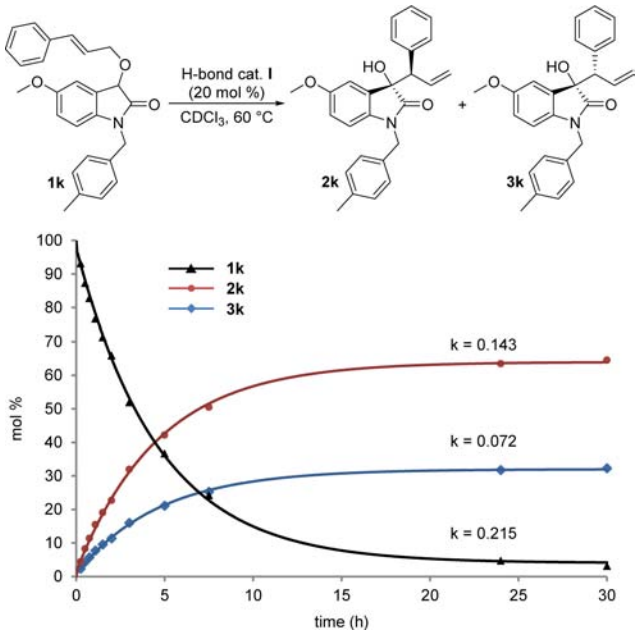

Figure 3. Kinetic study of Wittig [2,3]-rearrangement of 3-cinnamyloxyoxindole **1k**.

up to 2.7:1), the isomers were chromatographically separable. Both electron-donating and -withdrawing groups were well tolerated at the aromatic ring of the oxindole and phenyl group in the allyl chain as well as the aromatic analogs of the cinnamyl derivative.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00291.

Synthesis of starting compounds, optimization of the procedures, copies of ^{1}H and ^{13}C NMR spectra, HPLC chromatograms (PDF)

Crystallographic data of compound **2o** (CIF)

Crystallographic data of compound **3i** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: tonis.kanger@ttu.ee.

Notes

The authors declare no competing financial interest.

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(14) CCDC 1447017−1447018 contains the supplementary data for this structure. These data can be obtained via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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