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Biomimetic Asymmetric Reduction of Tetrasubstituted Olefin 2,3-Disubstituted Inden-1-ones with Chiral and Regenerable NAD(P)H Model CYNAM

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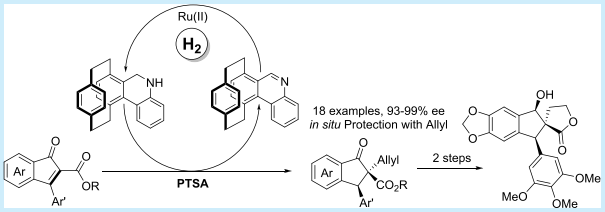
ABSTRACT: Because of the formidable development of the asymmetric reduction of tetrasubstituted olefins, an effective method is in urgent demand. Herein, through the biomimetic protocol of the coenzyme NAD(P)H, the reduction of tetrasubstituted olefin 2,3-substituted 1*H*-inden-1-ones has been successfully realized with the catalytic chiral NAD(P)H model CYNAM, which is hard to bring about via the common rhodium or iridium-based catalytic system, producing the corresponding products in good yield (up to 98%) with good enantioselectivity (up to 99% ee). Furthermore, the chiral bioactive molecule can be concisely synthesized from the reduced product.



Over the past few decades, the asymmetric hydrogenation of unsaturated double bonds[1] has matured and, on the one hand, become one of the chief methods for installing stereocenters in organic molecules, especially in industrial processes.[2] On the other hand, with the rapid development of the pharmaceutical industry, the optical purity, safety, and efficiency of drugs have been paid more and more attention.[3] Therefore, it is particularly important to develop a method that can facilitate the synthesis of unavailable 1,2-continuous stereocenters. Fortunately, with the emergence of the direct asymmetric hydrogenation of tetrasubstituted olefins, it is possible to construct synthons and bioactive molecules containing 1,2-continuous chiral centers.[4] However, owing to the limitations of the catalysts and the substrates, there are still many challenges in the asymmetric hydrogenation of tetrasubstituted olefins (AHTOs).

Although many substrates of tetrasubstituted olefins still present challenges, remarkable achievements have been made in the past decade (Scheme 1a).[1d−j,5] For rhodium catalysts, as early as 1995, outstanding progress was made by Burk and coworkers. With the use of the chiral rhodium-diphosphine catalyst, the asymmetric hydrogenation of the tetrasubstituted enamides was successfully realized.[1a] With the development of various diphosphine ligands in the following decade, gratifying results were obtained with the rhodium-catalyzed AHTOs.[6−12] For the ruthenium catalytic system, there were only a few examples. For instance, the catalytic enantioselective reduction of cyclic β-(acylamino)acrylates was achieved with the use of a ruthenium catalyst by Zhang and coworkers.[13] In addition, Christensen and coworkers utilized the ruthenium−JosiPhos complex to synthesize the α-methyl-β-cyclopropylcinnamate derivatives with excellent enantioselectivities in 2016.[14]

Another catalytic system, iridium, has been rapidly established over the past decades. It originated from Buchwald's preliminary report[15] that used a highly electrophilic but sensitive *ansa*-zirconocene catalyst in the asymmetric hydrogenation of unfunctionalized tetrasubstituted olefins as far back as 1999. Iridium complexes with chiral N,P ligands were used for the first time by Pfaltz and coworkers in 2007.[16] Eventually, the employment of iridium/N,P ligand catalysts contributed to the further development of the AHTOs.[17−20] Although we can list many achievements of the AHTOs, in general, the scope of the substrates is still very limited. Therefore, it is particularly important and urgent to develop other reduction methods that are different from the traditional AHTOs to construct multiple chiral centers at the same time.

Inspired by the success of the AHTOs, in the first stage, we used the previously mentioned representative catalytic systems (Rh-diphosphine and Ir-PHOX) to carry out the initial attempts to direct the asymmetric hydrogenation of the tetrasubstituted olefin 2,3-disubstituted 1*H*-inden-1-one **1a**, which is an important synthetic intermediate that possesses a skeleton with biological activity potential. Unfortunately, neither the rhodium nor the iridium catalytic system could provide the target product (Scheme 1b) owing to the challenges of controlling the formation of continuous stereo-

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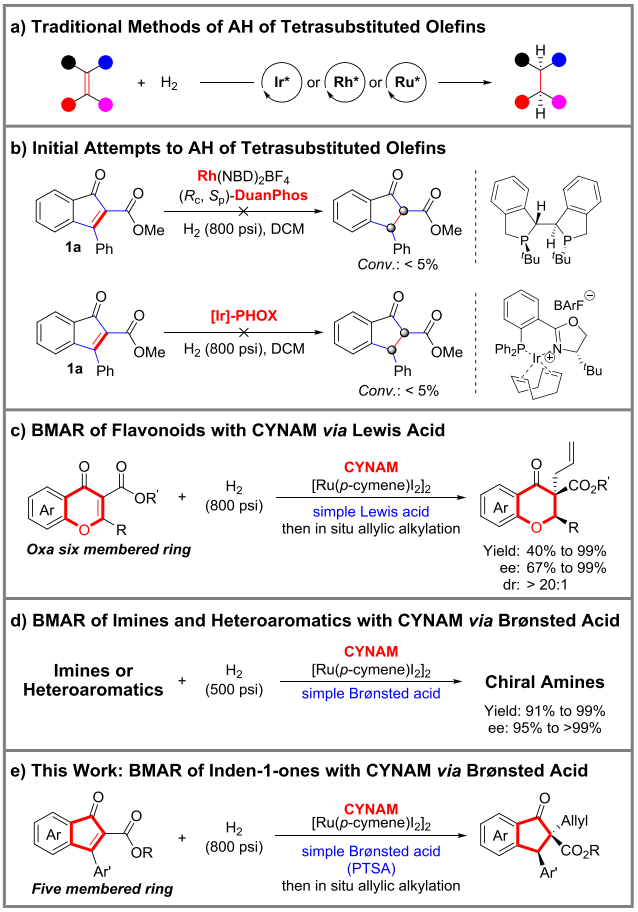
Scheme 1. Advances in the Reduction of Tetrasubstituted Olefins, Initial Attempts, and Previous Works of Biomimetic Asymmetric Reduction (BMAR)

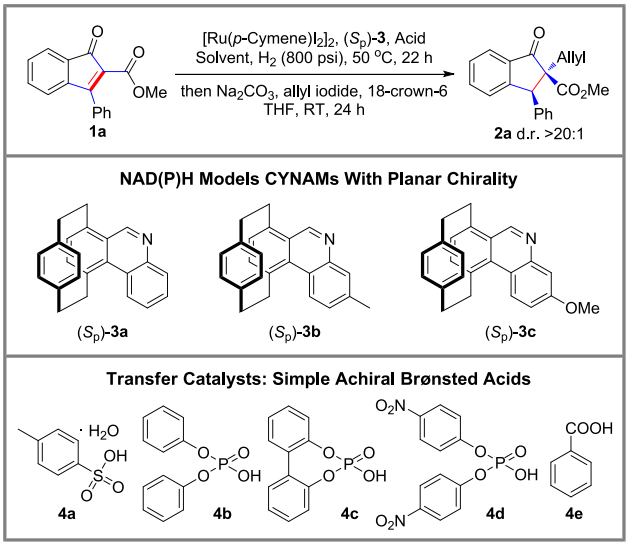


centers, the steric hindrance, or the firm binding affinity between the chelating group and the catalyst.[21]

As a special and powerful unconventional reduction method, biomimetic asymmetric reduction (BMAR) on the basis of the coenzyme NAD(P)H has attracted much attention. To date, there are three generations.[22,23] Inspired by the third-generation BMAR system previously developed by our group, which has successfully realized the reduction of alkenes, heteroaromatics, and imines using chiral and regenerable NAD(P)H models with readily available Lewis acids, Brønsted acids, or organocatalysts ureas as achiral transfer catalysts,[23] we tried to apply this efficient and potential catalytic system to the asymmetric reduction of tetrasubstituted olefin 2,3-disubstituted inden-1-ones. First, according to the good results of the BMAR of oxa six-membered-ring flavonoids with CYNAM via Lewis acids (Scheme 1c), the BMAR of five-membered-ring tetrasubstituted olefin 2,3-disubstituted inden-1-ones was tested.[23a] However, the use of different Lewis acids could not achieve satisfactory results. Considering that the Brønsted acid is also an effective transfer catalyst (Scheme 1d),[23b] herein we report the enantio- and diastereoselective BMAR of tetrasubstituted olefin 2,3-disubstituted inden-1-ones with the regenerable and chiral [2.2]paracyclophane-based NAD(P)H CYNAM model via Brønsted acids (Scheme 1e).

At the outset, we chose the tetrasubstituted olefin 2,3-disubstituted 1*H*-inden-1-one **1a** as the model substrate (Table 1). When the CYNAM and the Brønsted acid were not added,

Table 1. Optimization of the Reaction Conditions



entry[a]	acid	solvent	model	yield (%)[b]	ee (%)[c]
1		mesitylene		<5	
2	**4a**	mesitylene		<5	
3		mesitylene	(S_p)-**3a**	35	74.8
4	**4a**	mesitylene	(S_p)-**3a**	93	93.8
5	**4a**	THF	(S_p)-**3a**	93	85.1
6	**4a**	$CHCl_3$	(S_p)-**3a**	47	67.6
7	**4a**	1,4-dioxane	(S_p)-**3a**	16	51.2
8	**4a**	EtOAc	(S_p)-**3a**	89	87.0
9	**4a**	toluene	(S_p)-**3a**	92	93.1
10	**4b**	mesitylene	(S_p)-**3a**	92	77.2
11	**4c**	mesitylene	(S_p)-**3a**	89	80.5
12	**4d**	mesitylene	(S_p)-**3a**	91	77.1
13	**4e**	mesitylene	(S_p)-**3a**	61	79.2
14	**4a**	mesitylene	(S_p)-**3b**	90	94.2
15	**4a**	mesitylene	(S_p)-**3c**	91	94.0
16	**4a**	mesitylene	(S_p)-**3c**	98[d]	94.1
17[e]	**4a**	mesitylene	(S_p)-**3c**	89	92.0

[a]Reactions were carried out with **1a** (0.10 mmol), $[Ru(p\text{-cymene})I_2]_2$ (0.5 mol %), (S_p)-**3** (10 mol %), acid (4 mol %), solvent (2 mL), H_2 (800 psi), 50 °C, 22 h; Na_2CO_3 (2.0 equiv), allyl iodide (2.0 equiv), 18-*crown*-6 (15 mol %), THF (2 mL), RT, 24 h. [b]Yield and diastereoselectivity were measured by the analysis of ^1H NMR spectra using 1,3,5-trimethoxybenzene as an internal standard. [c]Determined by chiral HPLC. [d]Isolated yield for the reaction with a 0.15 mmol scale and 24 h in the first step. [e]Isolated yield and ee value for the reaction with a 0.15 mmol scale, 5 mol % (S_p)-**3c**, and 24 h in the first step.

the reduction was carried out in mesitylene using the ruthenium complex. As a result, the reaction did not occur (<5% *conv.*, entry 1). With the addition of the Brønsted acid **4a**, the desired product still could not be obtained (<5% *conv.*, entry 2). Obviously, the direct hydrogenation could not take place in this system. To our surprise, after adding CYNAM (S_p)-**3a** but without any Brønsted acid as the transfer catalyst, there was a small amount of reduced product with moderate enantioselectivity. Because the reduced products would undergo keto−enol tautomerism, for a more accurate characterization, the *in situ* alkylation with allyl delivered **2a** bearing a quaternary stereogenic center with excellent diastereoselectivity (d.r. > 20:1) in excellent yield (entry 3). Gratifyingly, when the strong Brønsted acid **4a** was added as

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Org. Lett. 2021, 23, 7166−7170

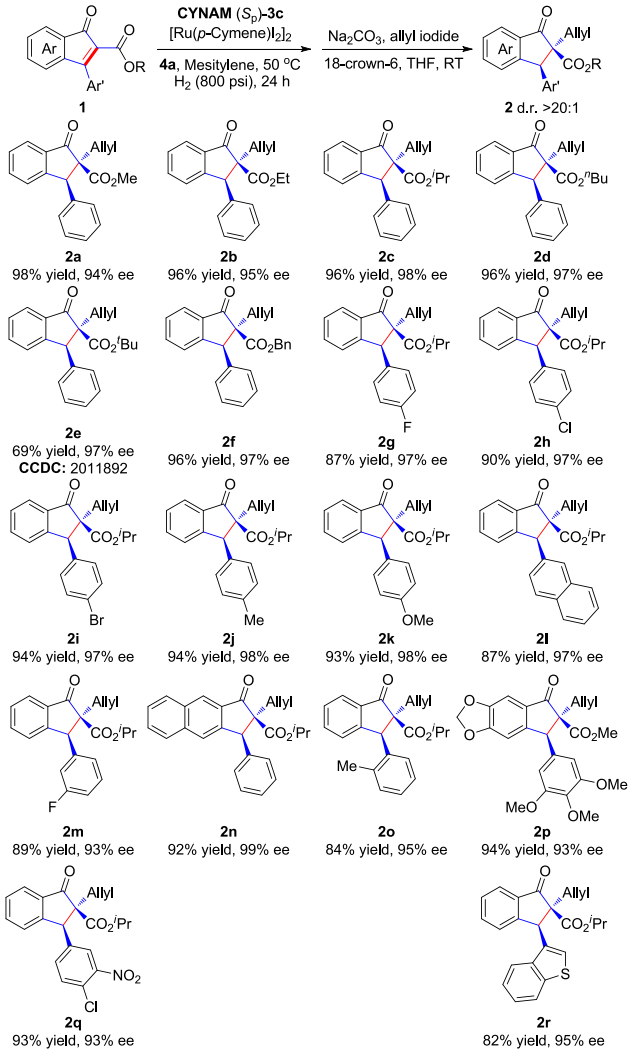
the transfer catalyst, the desired product could be obtained in 93% yield with 93.8% ee, documenting that a suitable transfer catalyst can help to suppress the background reaction (entry 4). With the preliminary result in hand, we began to optimize the reaction condition. First of all, the evaluation of solvents suggested that mesitylene was optimum according to the enantioselectivity and reactivity (entries 4−9). Subsequently, further optimization of Brønsted acids was conducted. Although the reactivity was improved to varying degrees, the enantioselectivity was not significantly improved (entries 10−13). Therefore, the strong Brønsted acid *p*-TsOH·H_2O (**4a**) was appropriate. Last but not least, the use of different kinds of CYNAMs had little effect on the reactivity or enantioselectivity (entries 14 and 15), so that CYNAM (S_p)-**3c** with a gentle result was selected as the optimal NAD(P)H model. After the reaction time was extended from 22 to 24 h, a good isolated yield (0.15 mmol, 98% yield) could be obtained (entry 16). However, both the yield and the ee value were decreased with a lower loading of CYNAM (S_p)-**3c** (10 to 5 mol %, entry 17). Eventually, the optimal reaction conditions were confirmed: substrate **1** (0.15 mmol), [Ru(*p*-cymene)I_2]$_2$ (0.5 mol %), CYNAM (S_p)-**3c** (10 mol %), **4a** (4 mol %), H_2 (800 psi), mesitylene (3 mL), 50 °C, and 24 h; Na_2CO_3 (2.0 equiv), allyl iodide (2.0 equiv), 18-*crown*-6 (15 mol %), THF (3 mL), RT, and 24 h.

Having optimized the reaction, we proceeded to investigate the substrate scope (Scheme 2). As expected, all inden-1-ones **1** performed well. As usual, different ester moieties of substrates were examined preferentially. Among them, the greater the steric hindrance of the ester group, the better the enantioselectivity. Because of the excessive steric hindrance of **2e**, a certain amount of alkoxylation products was formed. The best result was obtained for the ester with an isopropyl group (**2c**). The electronic properties of the substituent on the aryl group had little effect on the reaction (**2g−2o**). As for the more complicated substrates **2p** and **2q**, the reduction reaction could also proceed smoothly. It should be noted that the substituents on the aryl group in the para position rarely affected the enantioselectivity or reactivity, whereas those in the meta or ortho position (**2m** and **2o−2q**) showed more evident spatial effects, which slightly reduced the enantioselectivity. In addition, the reaction was also compatible with the substrate containing the heterocycle, thianaphthene (**2r**). The absolute configuration of **2e** was assigned as (2S,3S) by X-ray diffraction analysis. (For the details, see the Supporting Information.)

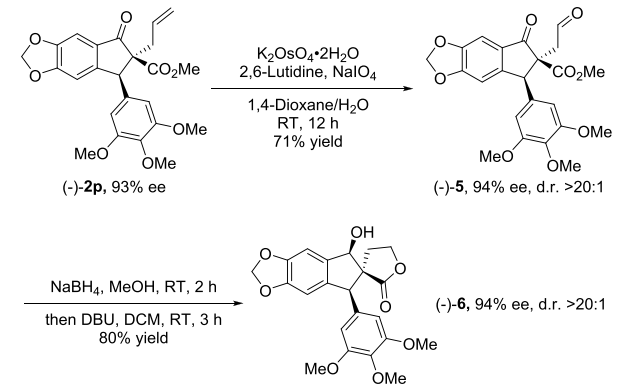
As a semisynthetic compound, the antitumor agent etoposide is prepared by several steps from the naturally occurring lignan podophyllotoxin, both of which exhibit potent antitumor activity. As an analogue of etoposide and podophyllotoxin and having a modified ring system, the racemic bioactive molecule **6** shows good in vitro antitumor activities against the A549, HT-29, and P388-D1 tumor cell lines.[24] Fortunately, with the use of the chiral reductive product (−)-**2p** (93% ee, d.r. > 20:1) as a starting material, the chiral biologically active molecule (−)-**6** (94% ee, d.r. > 20:1) could be efficiently and concisely synthesized via the osmium-catalyzed oxidation of olefin (71% yield) and a cascade reduction and lactonization (80% yield) in good overall yield with excellent enantio- and diastereoselectivity for the first time (Scheme 3).

In summary, the BMAR of tetrasubstituted olefin 2,3-disubstituted 1*H*-inden-1-ones with the regenerable and chiral

Scheme 2. Substrate Scope



Scheme 3. Asymmetric Synthesis of Bioactive Molecule



[2.2]paracyclophane-based NAD(P)H model CYNAM has been successfully realized; it was tough to reduce by the currently mature and commonly used rhodium or iridium catalytic system. Employing the simple achiral Brønsted acid as the transfer catalyst, the substrate range was markedly broadened. An array of tetrasubstituted olefin 2,3-disubstituted 1*H*-inden-1-ones could be reduced and *in situ* alkylated with allyl in up to 98% yield with 99% ee. Furthermore, utilizing the chiral product as the important starting material, the chiral

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bioactive molecule could be concisely synthesized for the first time. By mixing and matching the NAD(P)H model CYNAM and the transfer catalyst, it is expected that this method can be utilized in many systems. Efforts to expand the BMAR to other types of substrates are currently in progress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c02568.

General information, general experimental procedures, characterization data, spectra, and X-ray data (PDF)

Accession Codes

CCDC 2011892 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge 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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Notes

The authors declare no competing financial interest.

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