Molecular transformation from monocyclic to chiral tricyclic scaffold by using organonickel catalyst

Waste-free (or -minimized) molecular transformations from chemical feedstocks to complex structures is a state of the art, as it provides a cost-effective, environmentally benign and practical route to natural products as well as active pharmaceutical candidates (API). Furthermore, synthesis of a single enantiomer of these molecules is essential for their specific biomedical properties, as biological receptor sites are chiral in general (usually proteins). Tricyclic scaffolds including a chiral hydronaphtho[1,8-*bc*]furan moiety are ubiquitous in natural products. For example, morphine, azadirachtin, teucvidin and momilacton include the chiral hydronaphtho[1,8-*bc*]furan moieties, and they show a range of biological activities such as analgesic, anti-tumor, insecticides, and allelochemicals (Fig. 1). Such tricyclic structures are also reported as key synthetic intermediates for the synthesis of sesquiterpenoids. These molecules are featured by their complex architectures and multiple chiral centers, which was accessed by a stepwise ring construction in stereoselective manner so far. Furthermore, one should always concern an inherent stereoselectivity problem since a number of possible isomers (2^n; n = number of chiral centers) increases exponentially with an increase of n. It is thus long-awaited to develop a straightforward strategy to afford such multifunctional chiral tricyclic scaffolds with complete control of stereoselectivity from feedstock materials.

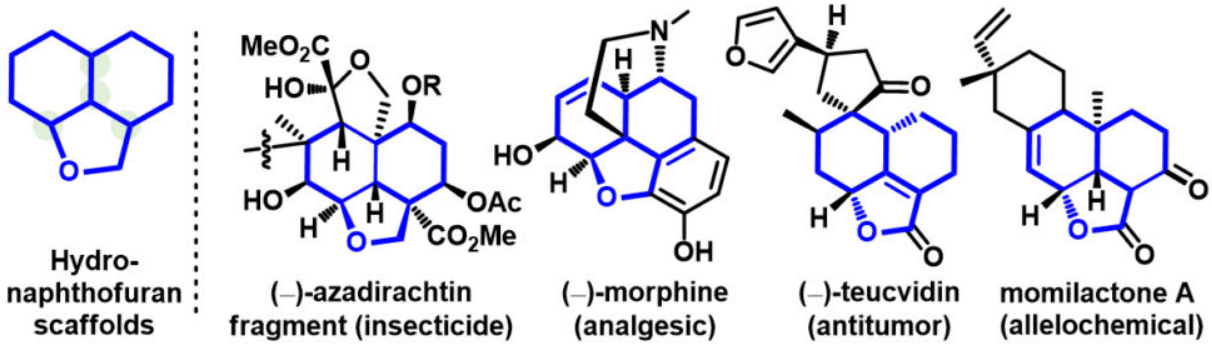

Fig. 1. Representative examples of bioactive molecules.

Given a high efficiency in forming carbon?carbon bond between an alkene and an alkyne by oxidative cyclization on organonickel complexes, we envisioned the single-step construction of tricyclic scaffold **3** from alkynyl-cyclohexadienones **1** (Fig. 2). Note that the starting material **1** was very easily accessible from a cheap raw materials, phenols, generally by a single-step preparation. We used an organometallic nickel-based enantio-pure catalyst to construct tricyclic nickelacycle **2** with three chiral centers though the oxidative cyclization of one of the alkene (asymmetric desymmetrization) of dienone and the tethered alkyne. *In situ* displacement of nickel moiety in the

intermediate **2** with another reactive molecule of desired substituents afforded a variety of hydronaphthofurans **3** with the generation of two more chiral centers. The enantio-pure ligand **L*** attached to nickel center is the key to control in enantioselectivity, and a number of ligands were thus explored to achieve the optimal enantioselectivity. With the optimal catalyst comprising nickel and **L*1** in hand, more than twenty compounds were synthesized as a single isomer (out of sixteen possible diastereomers) in good yields and with excellent enantioselectivity (up to 99% *ee*, where *ee* means enantiomeric excess, showing the degree to which one enantiomer in greater amounts than the other). The overall two step transformation from phenol (monocyclic) to hydronaphtho[1,8-bc]furans (tricyclic scaffolds) involves oxidative dearomatization and catalytic tandem desymmetrization of **1** and a formal [4+2] cycloaddition of **2** with an alkene (Fig. 2).

We rationalized the putative mechanistic pathway by the isolation of a tricyclic nickelacycle (**2**; using **L** = IPr, where IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene) from a stoichiometric reaction, which confirmed that desymmetrization via oxidative cyclization on nickel plays a key role in the above transformation. Enantioselectivity should be determined by facial-selective coordination of an alkene with tethered alkyne to the nickel complex bearing the enantio-pure ligand **L***.

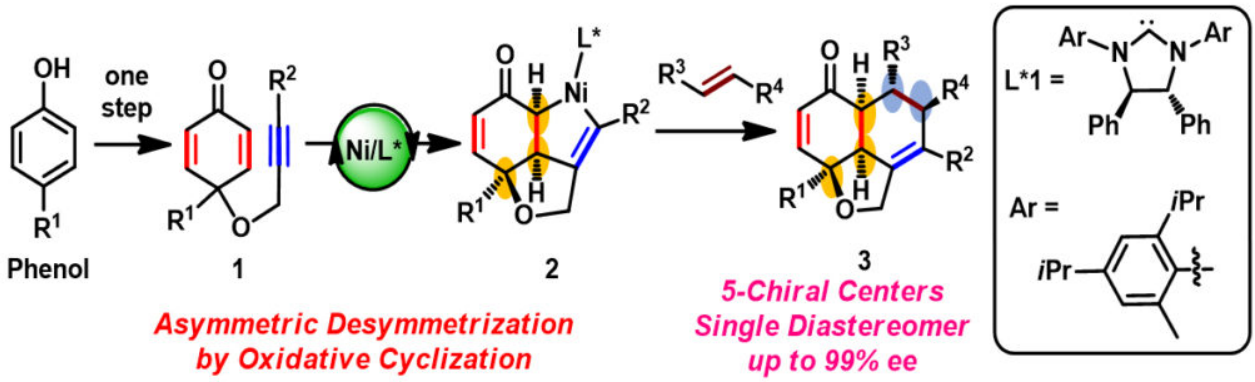

Fig. 2. Two step enantioselective synthesis of hydronaphthofurans scaffolds.

A wide range of substituents (R^{1-4} = halogens, benzene rings and esters) were tolerated in the present method. In addition, further transformation is enabled by the derivatization of the conventional functional groups such as C=O and C=C, which should expand the synthetic potential of the tricyclic products to bioactive molecules. This work demonstrated a novel strategy that offers a rapid, cost-, and step- economical synthesis of tricyclic fused rings with excellent enantioselectivity. This should be crucial requirements for scaling up the research from laboratory to industrial production. Moreover, such strategy would provide a rapid production of key tricyclic scaffolds of candidates for high-throughput screening of new bioactive compounds in the drug discovery.

Publication

Two-step synthesis of chiral fused tricyclic scaffolds from phenols via desymmetrization on nickel.
Kumar R, Hoshimoto Y, Tamai E, Ohashi M, Ogoshi S
Nat Commun. 2017 Jun