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Stereoselective synthesis of a *Podophyllum* lignan core by intramolecular reductive nickel-catalysis†

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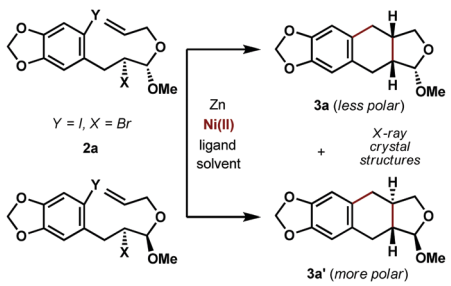
A Ni-catalyzed reductive cascade to a diastereocontrolled construction of THN[2,3-c]furan, is developed. The mild reaction conditions led to the tolerance of broad functional groups that can be placed in almost every position of this skeleton with good yields. The conformational control for the observed *trans*- or *cis*-fused selectivity during this tandem cyclization-coupling is also proposed.

Over the past decade, the renaissance of nickel catalysis in cross-coupling reactions especially with alkyl partners, has appeared and received considerable attention[1,2] from synthetic chemists due to the earth-abundance and unique properties of this transition-metal. In particular, nickel-catalyzed reductive coupling,[3,4] featuring direct use of electrophiles instead of organometallic reagents, has already evolved into a practical method for the formation of carbon–carbon bonds under mild conditions. However, research progress in this promising field has mainly focused on various intermolecular couplings[5] while our interest was intramolecular reactions[6] and stereocontrolled tandem cyclizations.[7] Further applications in the synthesis of bioactive natural products and pharmaceuticals remain elusive and thus in high demand. In this communication, we devised a new synthetic route to the core of the natural product podophyllotoxin (**1**), a typical aryltetralin lignan[8] for the treatment of anogenital warts which also serves as the key starting material for cancer chemotherapy drugs like etoposide and teniposide.[9] Ni-catalyzed reductive cyclization of a dihalide A invented by us will lead to the generation of a tetrahydronaphtho[2,3-*c*]furan (tetrahydronaphtho = THN) core B embedded in this kind of lignan in one step. And the formation of two C–C bonds was diastereodivergent in this tandem process, therefore enabling access to any members of the *podophyllum* family with *trans*- or *cis*-fused stereochemistry.

First of all, model studies with the β-bromo acetal **2a** as two diastereomers for the above designed tandem reductive coupling were performed as shown in Table 1. This cyclization precursor was conveniently synthesized using commercially available allyl alcohol and enol methyl ether derived from 6-bromopiperonal according to general procedure A-1 in the ESI.† Ethyl crotonate[10] (EC) as a ligand was chosen to run this reaction in DMA at 24 °C using a stoichiometric Ni(0) complex, and the expected transformation occurred smoothly, providing

Table 1 Optimization of conditions for reductive tandem cyclization[a]



Entry	Ni salt (equiv.)	Ligand[c]	Solvent	Isolated yield [%] 3a	3a′
1	$NiCl_2$ (1.0)	EC	DMA	54	26
2	$NiCl_2$·DME (1.0)	EC	DMA	57	28
3	$NiCl_2$·DME (0.5)	EC	DMA	56	28
4	$NiCl_2$·DME (0.2)	EC	DMA	56	28
5[b]	$NiCl_2$·DME (0.1)	EC	DMA	7	2
6	$NiBr_2$ (0.2)	EC	DMA	35	13
7	NiI_2 (0.2)	EC	DMA	25	9
8	$NiCl_2$·DME (0.2)	2,2′-bpy	DMA	35	18
9	$NiCl_2$·DME (0.2)	dtbbpy	DMA	29	14
10	$NiCl_2$·DME (0.2)	dMeobpy	DMA	27	13
11	$NiCl_2$·DME (0.2)	EC	CH_3CN	50	24
12	$NiCl_2$·DME (0.2)	EC	DMF	38	13
13	$NiCl_2$·DME (0.2)	EC	DMPU	38	15

[a] The reaction was run on a 0.6 mmol scale. [b] 3 mmol scale. [c] 0.72 mmol for EC and 0.24 mmol for other nitrogen ligands.

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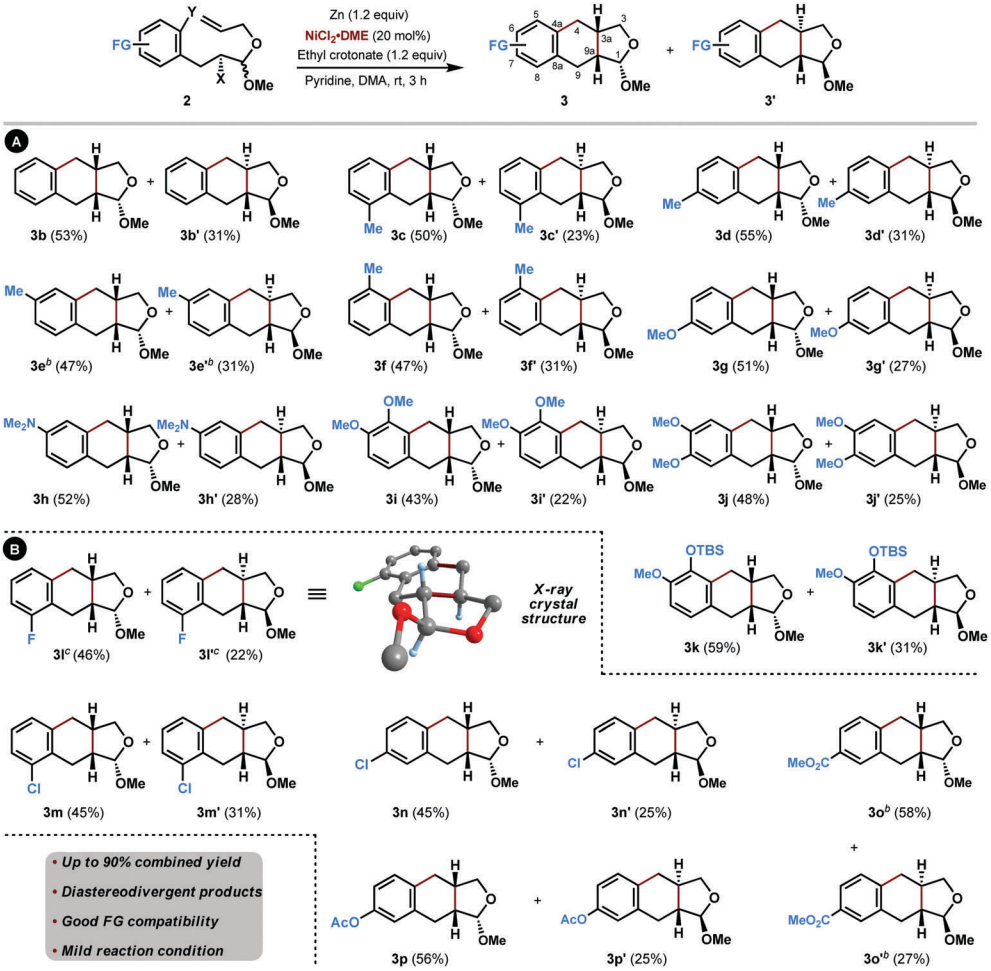
separable THN[2,3-*c*]furans **3a** and **3a′** in 80% combined yield (entry 1). The less polar isomer was identified as **3a** through its single-crystal structure,[11] where *cis*-fused stereochemistry and the pseudo-axial orientation of the methoxy group could be observed clearly. The more polar product was also isolated and assigned as **3a′** by its single-crystal analysis.[11] In comparison to **3a**, the latter demonstrated a *trans*-fused stereochemistry relationship in the newly-formed bicyclic moiety. The desired diastereodivergent cyclization results (**3a** *vs.* **3a′**) during this reductive cascade have thus been achieved. The better yields of tetracyclic acetals **3a** and **3a′** were obtained when the *in situ* generated complex from $NiCl_2$·DME was employed (entry 2). To our delight, the loading of this stable Ni(II) salt could be lowered to 20 mol% and almost same yields of **3a** and **3a′** were maintained (entries 3 and 4). Further decrease in the Ni catalyst afforded a detrimental result (entry 5). Screening of other nickel halides did not give superior outcomes (entries 6 and 7). Evaluation of some nitrogen ligands[12] such as bipyridine resulted in yield decrease of this tandem cyclization event (entries 8–10), suggesting the importance of olefin EC as π ligands.[13] Investigation of solvents proved that DMA is the best choice, and both acetals **3a** and **3a′** could be isolated in 84% combined yield (entries 11–13 *vs.* entry 4). The addition of TBABr or TBAI (ref. 5*n*) led to a decrease (10–15%) in yields. The detailed screening of reaction parameters is summarized in the ESI† (Tables S1–S4). The corresponding precursor dibromide **2aa** (X = Y = Br) and β-iodo acetal **2ab** (X = I, Y = Br), whose preparation can be found the ESI,† resulted in lower yields of **3a** and **3a′** (65% and 70%, respectively) under the identical conditions of entry 1. Its cost cannot compete with **2a** although the diiodide **2ac** (X = Y = I) provided the same yield as that of **2a**.

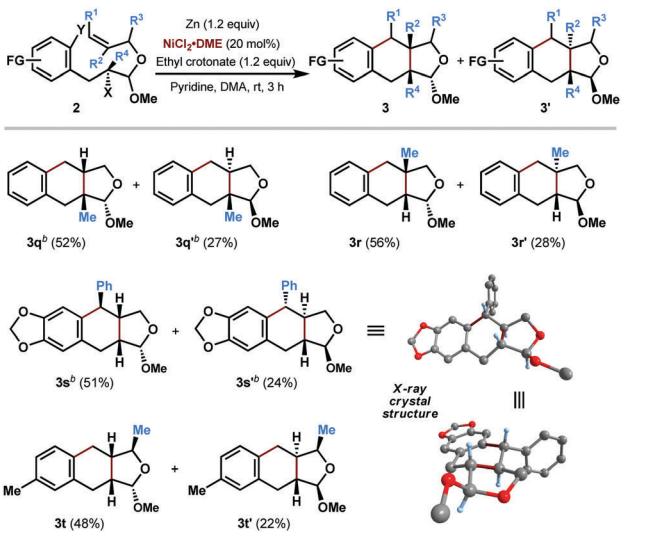
With the above optimized conditions in hand, the scope of this cascade catalyzed by nickel was then investigated. We first replaced the methylenedioxy group on the benzene ring in **2a** with hydrogens, the corresponding products **3b** and **3b′** could be isolated in 53% and 31% yields, respectively (Scheme 1A). Reductive tandem cyclization of other β-bromo acetals tethered to the electron-rich iodobenzene moiety all produced stereodefined THN[2,3-*c*]furans **3c**(**c′**)–**3k**(**k′**) in good combined yields. As demonstrated in the cases of tricyclic acetals **3c**(**c′**)–**3f**(**f′**), a methyl group can be placed at any of the remaining positions of the benzene ring (C5–C8), with an



Scheme 1 Stereoselective synthesis of THN[2,3-*c*]furan: investigation of functional groups at the benzene ring. [a] Substrate **2** (X = Br, Y = I) was used generally unless otherwise stated, and isolated yields of **3** were reported. [b] **2e** and **2o** (X = Br, Y = Br) were used. [c] $NiCl_2$·DME (30 mol%) was used.

average yield of 79%. More electron-rich substrate **2g** can also tolerate the mild reaction conditions, generating **3g**(**g**′) in almost equal yields. The reaction of phenyl iodides bearing two methoxy groups still worked well under the identical conditions, affording the tetrasubstituted benzene derivatives **3i**(**i**′) and **3j**(**j**′) in 65% and 73% yields, respectively. In particular, a precursor with a –OTBS moiety, a typical protecting-group for hydroxyl, participated in this reductive cyclization as well, affording **3k** and **3k**′ in a surprising 90% yield since this silyl group with steric hindrance is oriented at the *ortho*-position of the reaction site. As shown in Scheme 1B, the extension of this tandem cyclization to electron-deficient benzene-derived substrates also afforded good results. The reaction of phenyl iodides bearing typical electron-withdrawing groups like F and Cl proceeded smoothly to provide the expected products **3l**(**l**′)–**3n**(**n**′) in serviceable yields. A single-crystal of **3l**′ was obtained, whose structure clearly demonstrated that all three tertiary hydrogen atoms at C3a, C9a and C1 adopt a *trans*-orientation (Scheme 1B inset; selected H atoms have been omitted for clarity).[11] The chlorine atom in THN[2,3-*c*]furans **3n**(**n**′) could serve as a handle for further elaboration. Notably, the ester group as exemplified by the case of tricyclic acetal **3o**(**o**′) was also feasible under the mild reductive conditions; in contrast, this kind of electrophilic functional group is generally incompatible in classical cross-coupling reactions because of the organometallic reagents involved. The acetates **3p**(**p**′) that were obtained in combined 81% yield, showed another example which is difficult to produce in the traditional coupling reactions with nucleophilic reagents.

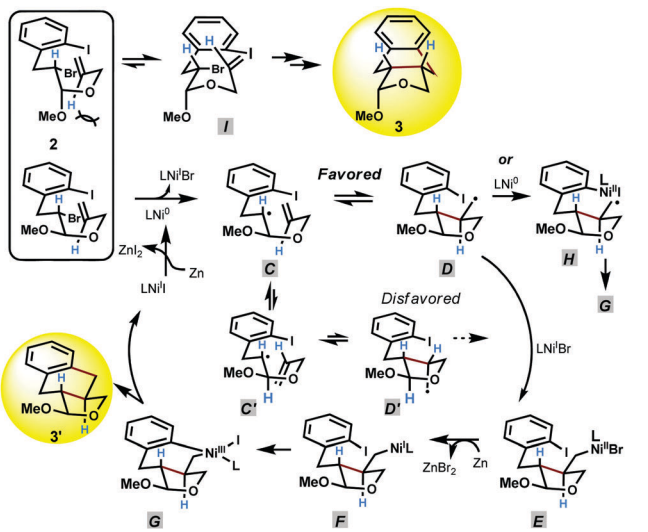
The tolerance of substituents at some positions of two other rings in THN[2,3-*c*]furans **3** was evaluated next (Scheme 2). As shown in tricyclic acetals **3q**(**q**′) and **3r**(**r**′), angular-methyl and an all-carbon quaternary stereocenter at C9a or C3a could be efficiently incorporated in 79% and 84% combined yields, respectively.



Scheme 2 Investigation of substituents at the aliphatic rings. [a] Substrate **2** (X = Br, Y = I) was used generally unless otherwise stated, and isolated yields of **3** were reported. [b] **2q** and **2s** (X = Br, Y = Br) were used.

Besides terminal alkenes as suitable substrates, β-bromo acetal **2s** derived from cinnamyl alcohol was also compatible with the reaction conditions same as those in Scheme 1, furnishing C4-phenyl substituted THN[2,3-*c*]furan in 75% combined yield. An all *trans*-relationship among continuous stereogenic centers (C4–C3a–C9a–C1) in more polar diastereomer **3s**′ was unambiguously established by its single-crystal analysis (Scheme 2, selected H atoms have been omitted for clarity).[11] Finally, the reductive cascade of β-bromo acetal **2t** derived from a secondary allyl alcohol triggered by nickel catalysis here proceeded uneventfully to generate stereodivergent tetrasubstituted tetrahydrofurans **3t**(**t**′) in 70% combined yield.

As shown in Scheme 3, a mechanistic hypothesis and rationalization of stereoselectivities for this intramolecular cross-electrophile coupling catalyzed by nickel is proposed. One of the diastereomeric β-bromo acetals **2** proceeds to produce radical **C** by a single-electron-transfer (SET) process with the Ni^0 complex being *in situ* generated under reduction conditions. This secondary radical would adopt a pseudo-half-chair conformation, and provide a primary radical species **D** upon cyclization. In this favored step, two labeled hydrogens are oriented at the *trans*-position of the formed tetrahydrofuran ring in **D**. The remaining steps would follow the known Ni^I–Ni^{III} redox process[14] *via* intermediates **E**, **F**, and **G**. The expected THN[2,3-*c*]furan **3**′ with a half-chair conformation and *trans*-fused stereochemistry was thus obtained after the formation of the second carbon–carbon bond. The first 5-*exo*-*trig* type cyclization can also occur to give *cis*-isomer **D**′, but the subsequent cyclization is difficult therefore this pathway (**C**′–**D**′) is disfavored. The interception of **D** with Ni^0 is also plausible, and the generated Ni^{II} species[15] **H** could be converted to **G** directly. The axially disposed –OMe group in the other β-bromo acetal isomer (top) of **2** causes huge steric repulsion thus severe destabilization. After rotation of the allylic C–O single bond, it would equilibrate to conformer **I**, which adopts a pseudo-boat conformation. Following the similar steps as those for **3**′,



Scheme 3 Proposed mechanism.

cis-THN[2,3-*c*]furan **3** was generated. The whole mechanistic scenario is an interplay process between nickel and radical species.[16]

In summary, we have developed a nickel-catalyzed intramolecular reductive coupling method for the sequential construction of C–C bonds in THN[2,3-*c*]furan[17] scaffolds in antineoplastic aryltetralin lignan lactones. In particular, this tandem cyclization is stereodivergent, and can be seen as an intramolecular version[18] of intermolecular hydroarylations or 1,2-dicarbofunctionalizations of olefin.[19]

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Conflicts of interest

There are no conflicts to declare.

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11 CCDC 1811053 (**3a**), 1811054 (**3a′**), 1811055 (**3l′**) and 1811056 (**3s′**)†.

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