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Highly Enantioselective Nickel-Catalyzed Oxa-[3+3]-annulation of Phenols with Benzylidene Pyruvates for Chiral Chromans

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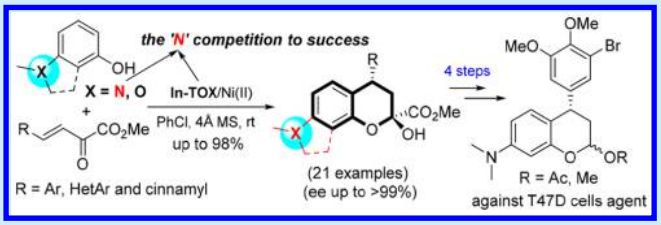
Supporting Information

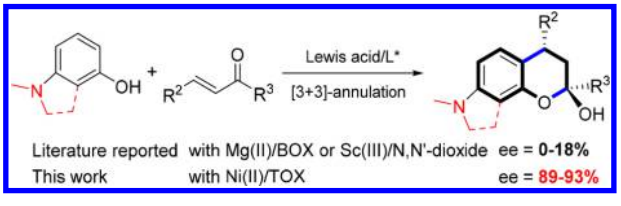
ABSTRACT: Nickel-catalyzed asymmetric annulation of oxygenated phenols and previously challenging 3-aminophenols with β,γ-unsaturated α-ketoesters is described, leading to rapid access to a variety of oxygenated and 7-aminated chromans in excellent yields with excellent diastereoselectivities and enantioselectivities under mild conditions. This method was readily scaled-up to gram scale and applied for a concise synthesis of two potential anticancer agents 7-aminated 4-arylchromans.



Since the Food and Drug Administration (FDA) announced its policy statement on the development of stereoisomeric drugs in 1992, asymmetric synthesis of chiral molecules that are biologically active and potentially useful has become a significant issue in drug research and development.[1] Chroman is an important heterocyclic motif that is found as a core structure of numerous biologically active natural products and pharmaceutical molecules.[2,3] For instance, Cai et al. have reported a series of 7-amino-4-arylchromans with significant potency as apoptosis inducers and cell growth inhibitors over a variety of tumor cells (EC_{50} < 10 nM).[4] Thus, synthetic methods for optically active functionalized chromans have received continued attention in asymmetric synthesis.[5−8]

Since the pioneering report by Jørgensen and co-workers in 2003,[8a] asymmetric oxa-[3+3]-annulation between electron-rich phenols and α,β-unsaturated carbonyl compounds has emerged as an efficient direct method for synthesizing chiral chromans from readily available reagents (Scheme 1).[8] Very recently, Feng et al. described an elegant enantioselective annulation between the oxygenated phenols and β,γ-unsaturated α-ketoesters catalyzed by a chiral *N,N′*-dioxide-scandium(III) complex, affording 4-arylchromans in excellent yields with 80−95% ee and high dr values.[8d] Similar to Jørgensen's pioneering report,[8a] the enantioselection for the aminated phenols was, however, found to be problematic, giving almost racemic products, even though the yields were excellent (Scheme 1).[8d] Given the importance of the aminated chromans in drug discovery, effective catalysts for these challenging nitrogen-containing substrates are highly desirable, which is likely to be a common challenge in synthetic organic chemistry from the perspective of the pharmaceutical industry.[9] Herein, we report highly enantioselective oxa-[3+3]-annulation of aminated phenols with β,γ-unsaturated α-ketoesters[10] by the use of a Ni(II)/TOX catalyst (Scheme 1), wherein the oxazoline side arm probably interferes with the coordination of the amino group to the catalyst for the improved functionality tolerance.[11,12]

Scheme 1. Lewis-Acid Catalyzed Asymmetric Oxa-[3+3]-Annulation of Aminated Phenols with Unsaturated Ketones



Preliminary studies showed that a strong background reaction of 3-(dimethylamino)phenol (**1a**) with β,γ-unsaturated α-ketoester **2a** proceeded in the absence of a Lewis acid catalyst at rt, giving the cycloadduct **3a** in 29% yield with 64/36 dr after 23 h (Table 1, entry 1), which may inherently account for the challenging enantioselection of such annulation with aminated phenols.[8a,d] Under catalysis of 10 mol % of $Ni(ClO_4)_2{\cdot}6H_2O$, the yield was improved to 81% with a better diastereoselectivity of 86:14 (Table 1, entry 2). Furthermore, in the presence of 4 Å molecular sieves (MS) or chiral indane-BOX ligands **L1** and **L2**, the reaction was significantly accelerated and was completed in 1−2 h with the same catalyst (Table 1, entries 3−5). However, the enantioselection was rather low with **L1** and **L2**. A similar outcome with the reversed enantioselection was obtained when chiral indane-TOX ligand **L3** was employed (Table 1, entry 6). A better enantioselectivity was achieved by using indane-TOX **L4** with the unified chiral centers for both the side arm and the BOX framework oxazolines (35% ee)

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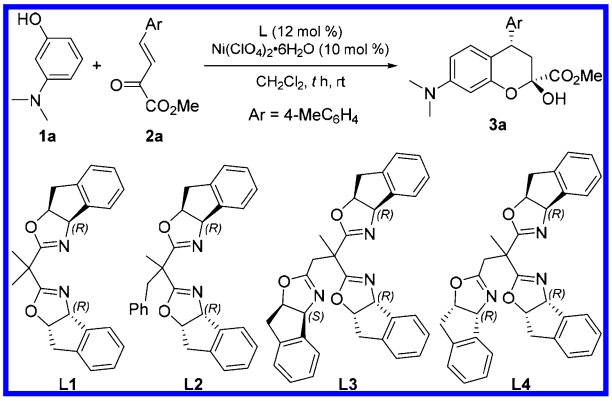
Table 1. Optimization of Reaction Conditions[a]



entry	L	4 Å MS	t (h)	yield (%)[b]	dr[c]	ee[d]
1[e]	–	–	23	29	64:36	–
2	–	–	21	81	86:14	–
3[f]	–	400 mg	2	92	90:10	–
4	L1	–	1	95	92:8	9[g]
5	L2	–	1	98	90:10	5[g]
6	L3	–	1	98	90:10	10
7	L4	–	1	96	92:8	35
8	L4	400 mg	1	96	90:10	73
9[f]	L4	400 mg	1	97 (94)	92:8	90

[a]Carried out at rt under nitrogen atmosphere: $Ni(ClO_4)_2·6H_2O$ (0.02 mmol), **L** (0.024 mmol), **1a**/**2a** = 1:1.5 (**1a**, 0.2 mmol), CH_2Cl_2 (4.0 mL). [b]NMR yields with 1,1,2,2-tetrachloroethane (TTCE) as the internal standard, the yield in parentheses was the isolated yield. [c]The dr values were determined by ^1H NMR spectra of the crude reaction mixtures. [d]The ee values were determined by HPLC with a chiral stationary phase. [e]Without $Ni(ClO_4)_2·6H_2O$ in PhCl. [f]PhCl as the solvent. [g]Reversed ee.

(Table 1, entry 7). Interestingly, the 4 Å MS additive was found to remarkably improve the enantioselectivity to 73% ee with unaffected efficiency and diastereoselectivity (Table 1, entry 8). A solvent effect also plays an important role in the enantioselection. When chlorobenzene was used as solvent, excellent enantioselection was achieved (94%, dr = 92:8, ee = 90%) (Table 1, entry 9).

With the optimal conditions in hand, we next investigated the substrate scope with respect to 3-aminophenols **1** and β,γ-unsaturated α-ketoesters **2**. As shown in Figure 1, a variety of 7-amino-4-arylchromans were obtained in excellent yields with excellent diastereo- and enantioselectivities under mild reaction conditions. The use of various ketoesters containing different substituents at the aryl group, regardless of their electronic characters, such as methyl (**2a**), methoxy (**2b**), fluoro (**2d**), chloro (**2e**), and bromo (**2f**) groups, led to the corresponding products in 87–97% yields with 91:9 to 92:8 dr and 89–91% ee. Ketoester **2g** bearing multisubstituents on the benzene ring, also survived the reaction, affording the product (**2g**) in 98% yield with 91:9 dr and 91% ee. To our delight, 2-thienyl (**2h**) and cinnamyl (**2i**) substituted β,γ-unsaturated α-ketoesters are compatible as well, providing 7-amino-chromans **3h** and **3i** in 93–96% yields with 85:15–91:9 dr and 90–93% ee. Notably, 3-aminophenol (**1b**) bearing two benzyl groups was also tolerated, furnishing the desired product (**3j**) in 97% yield with 89:11 dr and 93% ee. More importantly, 4-hydroxy-*N*-methylindoline (**1c**) is also a suitable substrate for this reaction, giving products **3k** and **3l** with the key potential antitumor motifs in 90–96% yields with 88:12 to 91:9 dr and 90–92% ee.

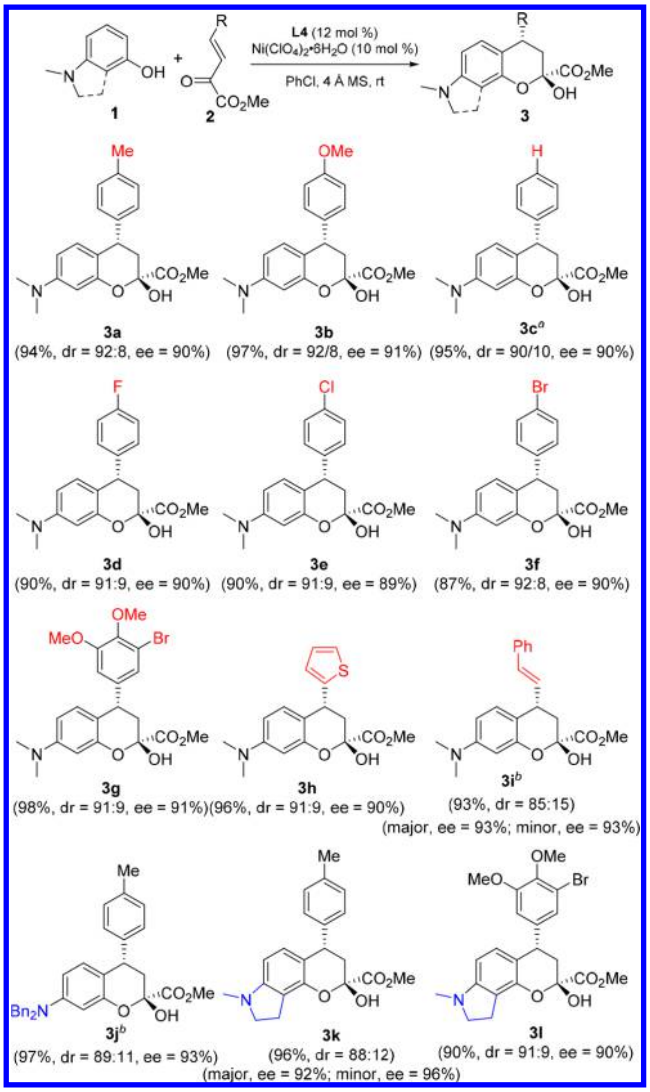


Figure 1. Substrate scope with respect to 3-aminophenols **1**: [a]24 mol % of **L4**; [b]20 mol % of $Ni(ClO_4)_2·6H_2O$ and 24 mol % of **L4**.

Gratifyingly, oxygenated phenols are also effective substrates for the current enantioselective annulation (Figure 2). For example, under the same reaction conditions, reactions of 3,4-dimethoxy phenol **4a** with various benzylidene pyruvate esters led to the corresponding products **3m**–**4s** in 97–98% yields with 90:10–92:8 dr and 93–98% ee. Sesamol **4b** was also a suitable substrate, and the corresponding product (**3t**) was obtained in 94% yield with 91:9 dr and 95% ee. When 3,4,5-trimethoxyphenol was employed, the almost enantiopure product (**3u**) was afforded in high yield. Catalytic asymmetric synthesis of **3o**, **3s**, and **3t** were previously reported with 84–87% ee,[8d] which could be improved up to 95% ee by the current method. The absolute configuration of **3p** was determined to be 2*R*,4*S* by comparing its optical rotation value with that of the literature.[8d]

The synthetic utility of this enantioselective method for the preparation of pharmaceutically valuable compounds was demonstrated by a concise synthesis of potential antitumor drug candidates **5a** and **5b** (Scheme 2).[4] The synthesis began with the nickel-catalyzed asymmetric tandem cyclization of commercially available 3-dimethylaminophenol **1a** with **2g** on the gram scale, which provided 2.16 g of enantioenriched chroman **3g** in 93% yield with 91:9 dr and 90% ee.

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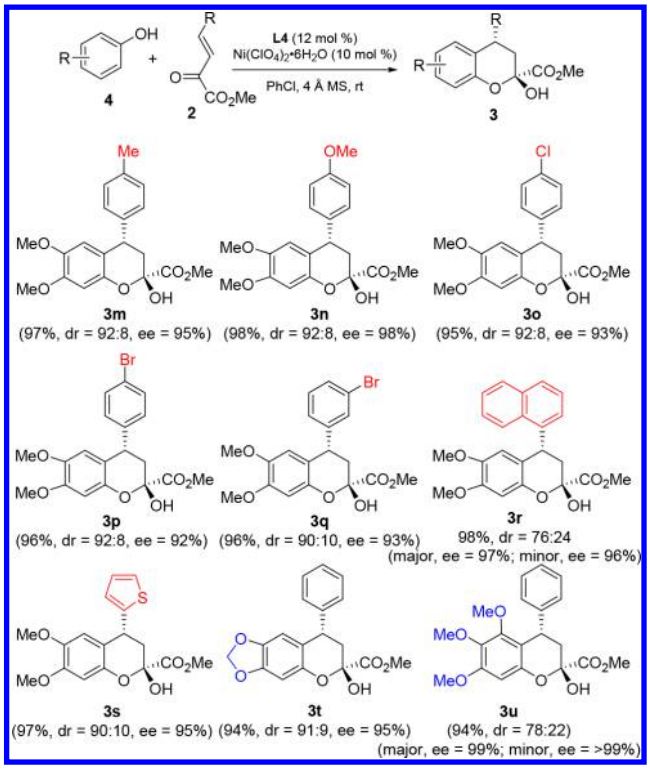
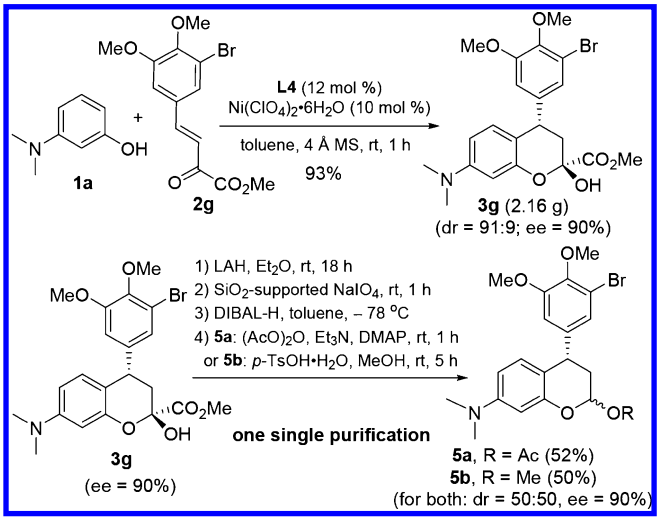


Figure 2. Substrate scope with respect to oxygenated phenols **4**.

Scheme 2. Scaled-Up Reaction and Applications



Subsequently, **3g** was reduced with lithium aluminum hydride (LAH),[13] followed by successive transformations, including an oxidation with silica gel-supported $NaIO_4$,[14] reduction with DIBAL-H, and protection of the hydroxyl group. The resulting products **5a** and **5b** were obtained in 50−52% overall yields without loss of enantiopurity by one single purification of the four-step transformation.

In summary, a Ni(II)/TOX-catalyzed asymmetric cascade annulation of 3-aminophenols with β,γ-unsaturated α-ketoesters in high yields with excellent diastereo- and enantioselectivities under very mild conditions has been reported for the first time. The reaction was further extended to the oxygenated phenols, leading to the chiral chromans in 94−98% yields with up to 92:8 dr and 93 → 99% ee, which reveals the broad tolerance of the developed catalyst toward the structurally diverged electron-rich phenols. Moreover, the concise synthesis of potential anticancer agents by this method may demonstrate its synthetic potentials in the discovery of chroman-based medicines. Our work also demonstrates that a side arm strategy[11] for chiral ligand design may provide a promising way to conquer the challenges arising from the fact that drug molecules generally contain the coordinative groups, such as amines and *N*-heterocycles.[9]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01442.

Experimental procedures and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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