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Organocatalysis

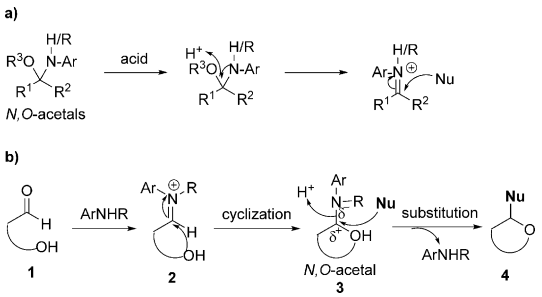
Aniline-Promoted Cyclization–Replacement Cascade Reactions of 2-Hydroxycinnamaldehydes with Various Carbonic Nucleophiles through In Situ Formed *N,O*-Acetals

Chenguang Yu,[a] He Huang,[a] Xiangmin Li,[a, b] Yueteng Zhang,[a] Hao Li,*[b] and Wei Wang*[a, b]

Abstract: In this study, we report the harnessing of new reactivity of *N,O*-acetals in an aminocatalytic fashion for organic synthesis. Unlike widely used strategies requiring the use of acids and/or elevated temperatures, direct replacement of the amine component of the *N,O*-acetals by carbon-centered nucleophiles for C–C bond formation is realized under mild reaction conditions. Furthermore, without necessary preformation of the *N,O*-acetals, an amine-catalyzed in situ formation of *N,O*-acetals is developed. Coupling both reactions into a one-pot operation enables the achievement of a catalytic process. We demonstrate the employment of simple anilines as promoters for the cyclization–substitution cascade reactions of *trans*-2-hydroxycinnamaldehydes with various carbonic nucleophiles including indoles, pyrroles, naphthols, phenols, and silyl enol ethers. The process offers an alternative approach to structurally diverse, "privileged" 2-substituted 2*H*-chromenes. The synthetic power of the new process is furthermore shown by its application in a 2-step synthesis of the natural product candenatenin E and for the facile installation of 2-substituted 2*H*-chromene moieties into biologically active indoles.

Introduction

N,O-Acetals (also called hemiaminal ethers) are useful building blocks in organic synthesis (Scheme 1a).[1] They are widely used for the formation of C–C bonds by carbon-centered nucleophilic-substitution reactions. It is observed that the extrusion of the "O" moiety in *N,O*-acetals is generally favored, because of the poorer leaving tendency of "N" and/or higher stability of the formed iminium ions (Scheme 1a).[2] Furthermore, the processes generally require a Brønsted or Lewis acid and/or elevated temperature.[2] Although cyclic *N,O*-acetals are also widely used in these processes, still the extrusion of "O" moieties is often seen with "N" moieties embedded in the ring structures.[3] Furthermore, to make O-containing heterocycles, cyclic acetals or hemiacetals are generally used.[4] These precedent studies reflect the challenge in the replacement of "N" moieties in *N,O*-acetals by a nucleophile. In addition, *N,O*-acetals are often required to be preformed.



Scheme 1. a) Well-studied *N,O*-acetals in "O"-involved nucleophilic substitution reactions. b) Proposed amine-catalyzed "N"-involved cyclization–substitution cascade reaction through in situ formed *N,O*-acetals in this study.

We recently challenged this dogma by developing a new and mild approach capable of a direct substitution of the "N" components in *N,O*-acetals by carbon nucleophiles. Moreover, we proposed a method for the in situ formation of *N,O*-acetal precursors (Scheme 1b). Therefore, it is expected that the amine shall bestow a twofold function; being a leaving group and a promoter for the formation of *N,O*-acetals. This cascade process would produce an unprecedentedly powerful catalytic approach in *N,O*-acetal-involved synthesis.[5]

Our working hypothesis was inspired by our previous study of an iminium-ion-initiated Michael–Michael cascade reaction that serves as a one-pot protocol for the generation of chiral chromanes.[6] The interesting *N,O*-acetal intermediates **8** were

[a] C. Yu, H. Huang, X. Li, Prof. Dr. Y. Zhang, Prof. Dr. W. Wang
Department of Chemistry & Chemical Biology
University of New Mexico
MSC03 2060, Albuquerque, NM 87131-0001 (USA)
Fax: (+1) 505 277 2609
E-mail: wwang@unm.edu

[b] X. Li, H. Li, Prof. Dr. W. Wang
School of Pharmacy
East University of Science and Technology
130 Mei-Long Road, Shanghai 200237 (P. R. China)
E-mail: hli77@ecust.edu.cn

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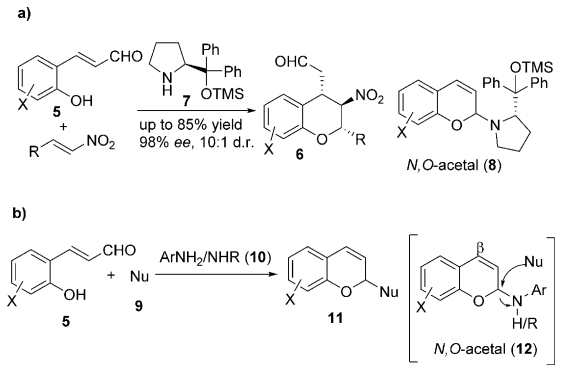


Scheme 2. a) Amine-catalyzed Michael–Michael cascade. b) Proposed arylamine-catalyzed cyclization–substitution cascade reaction.

observed in this process by reaction of 2-hydroxy-*trans*-cinnamaldehydes **5** with chiral amine **7** (Scheme 2a). Subsequent reaction of the *N*,*O*-acetals **8** with a *trans*-nitroolefin led to the formation of chromanes **6** and the concurrent regeneration of the amine catalyst. Analysis of this observation led us to question if the hemiaminal intermediates **8** or **12** could undergo a direct substitution reaction with nucleophiles. The realization of this process could offer an alternative approach to 2-substituted 2*H*-chromenes **11**,[7] a class of "privileged" structures with a broad range of interesting biological activities.[8] Additionally, they have served as targets for a number of synthetic studies.[6,7,9,10]

Herein we wish to disclose a conceptually novel amine-catalyzed formation of *N*,*O*-acetals from α,β-unsaturated aldehydes, followed by subsequent substitution by a nucleophile in an efficient catalytic-cascade fashion. In this investigation, we uncovered that simple aromatic amines promote cyclization–substitution cascade reactions of 2-hydroxy-*trans*-cinnamaldehydes **5** with various nucleophiles **9**, including indoles, pyrroles, naphthols, phenols, and silyl enol ethers (Scheme 2b). Notably, it is found that aromatic amines **10** with balanced nucleophilicity and leaving tendency are critical for the cascade processes through in situ generated *N*,*O*-acetals **12**. These processes produce structurally diverse 2-substituted 2*H*-chromenes **11** with high chemo- and regioselectively. Moreover, the mild reaction conditions enable the process to tolerate the use of a broad range of sensitive functional groups.

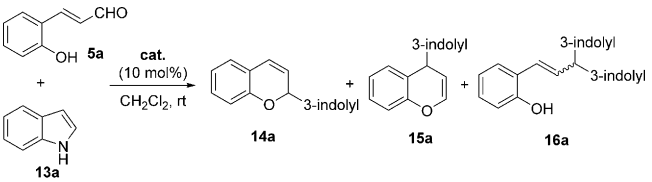
Results and Discussion

Amine-catalyzed cyclization–substitution cascade reaction of 2-hydroxylcinnamaldehydes with electron-rich arenes

Exploration and optimization of the reaction conditions

As discussed above, the extrusion of the amines from the *N*,*O*-acetal intermediates **8** or **12** is notoriously difficult. We conceived that an amine with a good leaving tendency might be replaced by a nucleophile. Nonetheless, this property would also need to be balanced by the requirement that the amine serves as a good nucleophile to ensure effective addition to the aldehyde in the route for the formation of the iminium ion. We believed that aromatic amines **10** would fulfill these requirements. Accordingly, in an exploratory study, 2-hydroxylcinnamaldehyde **5a** and the indole **13a** were used as the respective aldehyde and nucleophile reactants in the presence of an aromatic amine **10** (Table 1). To our delight, the reaction of the these substrates in the presence of aniline (**10a**) gave rise to the formation of 2-(3-indolyl)chromene **14a**, albeit in low yield (26%) along with its regioisomer **15a** and an interesting by-product **16a** (entry 1). Encouraged by the results, we surveyed other anilines that contained various electron-donating and -withdrawing substituents (entries 1–5). The results show that, although, 4-fluoroaniline (**10b**) is superior to 4-methoxylaniline (**10c**) (entries 2 and 3) as a catalyst for the double substitution reaction, the more electron-deficient analogues like 3,4-difluoroaniline (**10d**) and 4-nitroaniline (**10e**) are less effective (entries 4 and 5). Increasing the steric bulkiness of the aniline compounds, as in 2-methylaniline (**10f**) and 2,4-dimethylaniline (**10g**), leads to a deterioration of the catalytic potency (entries 6 and 7). It was found that 2-hydroxylaniline (**10h**) serves as an ideal catalyst for the process that generates **14a** in modest yield (59%) and selectivity (entry 8, 3.5:1.3:1 for **14a**:**15a**:**16a**). In contrast, 4-hydroxylaniline (**10k**; entry 11, 18% yield, 2.0:0.7:1 for **14a**:**15a**:**16a**) and 2-methoxylaniline (**10l**; entry 12, 30%, 1.1:0.6:1 for **14a**:**15a**:**16a**) are

Table 1. Optimization of the reaction conditions.[a]



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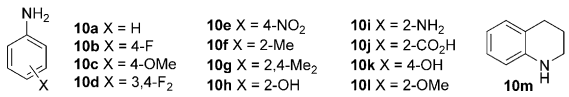


Entry	Cat.	*t* [h]	Yield [%][b]	Ratio of **14a**:**15a**:**16a**[c]
1	**10a**	24	26	0.9:0.5:1.0
2	**10b**	24	34	1.6:0.6:1.0
3	**10c**	24	11	0.3:0.4:1.0
4	**10d**	24	12	0.2:0.4:1.0
5	**10e**	24	0	–
6	**10f**	24	11	1.2:0.5:1.0
7	**10g**	24	<5	–
8	**10h**	24	59	3.5:1.3:1.0
9	**10i**	24	24	0.8:0.4:1.0
10	**10j**	24	28	1.2:0.8:1.0
11	**10k**	24	18	2.0:0.7:1.0
12	**10l**	24	30	1.1:0.6:1.0
13	**10m**	24	49	2.9:0.3:1.0
14[d]	**10h**	24	63	17.0:1.3:1.0
15[d,e]	**10h**	24	56	11.0:1.0:1.0
16[d,f]	**10h**	24	70	12.0:1.0:0.0
17[d,f,g]	**10h**	22	86	10.0:1.0:0.0

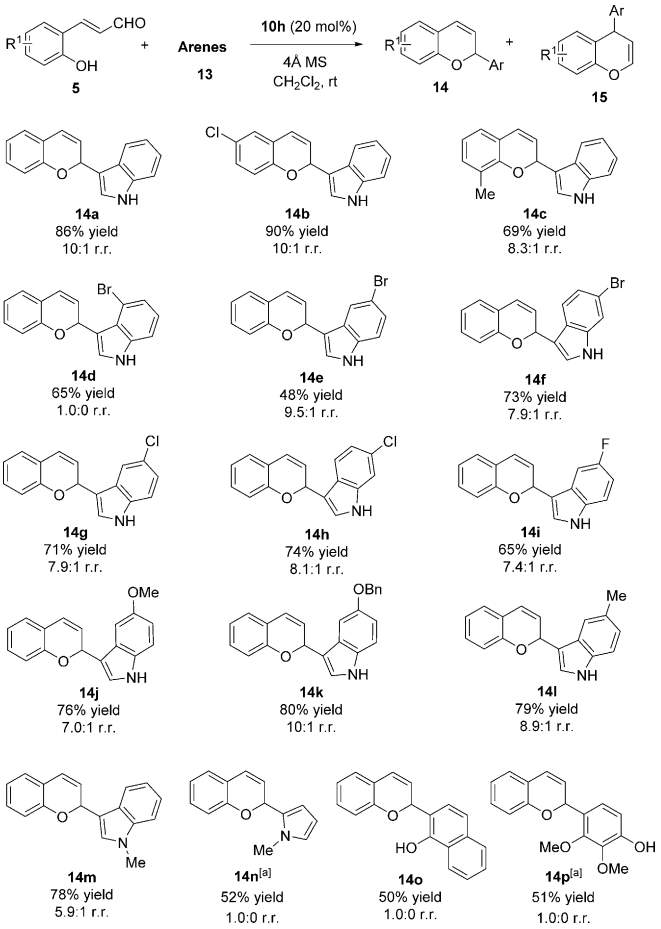
[a] Reaction conditions unless specified; a mixture of **5a** (0.1 mmol), **13a** (0.12 mmol), and catalyst (**10**, 0.01 mmol) in CH_2Cl_2 (0.5 mL) was stirred at rt. [b] Isolated yields. [c] Determined by using ^1H NMR spectroscopy. [d] 4 Å molecular sieves (MS) were added. [e] Ratio of **5a**:**13a** is 1:1.5. [f] Ratio of **5a**:**13a** is 1.2:1. [g] 20 mol% cat. **10h**.

not effective catalysts. Moreover, anilines containing other *ortho*-hydrogen-bonding donor groups such as amines (e.g., **10i**) and carboxylic acids (e.g., **10j**) promote only low-yielding processes (entries 9 and 10).

Further studies were carried out accordingly to optimize the reaction of 2-hydroxylcinnamaldehyde (**5a**) with the indole **13a** promoted by the aniline **10h**. Unexpectedly, the addition of 4 Å molecular sieves (MS) to the reaction mixture led to a slight increase in the yield (63%) and a dramatic increase in regioselectivity (17:1.3:1) (entry 14). Furthermore, increasing the ratio of **5a**:**13a** to 1.2:1 further enhanced the efficiency (70%) and regioselectivity (12:1:0) for the formation of the adduct **14a** (entry 16). Raising the catalyst loading to 20 mol% further improved the yield (86%) while maintaining the regioselectivity (10:1.0:0) of the process (entry 17). Of the solvents screened, CH_2Cl_2 was found to be optimal (Table S1 in the Supporting Information). Therefore, the ideal reaction conditions for the formation of **14a** involve the use of 0.12 mmol of **5a** (1.2 equiv), 0.1 mmol of **13a** (1 equiv) and 20 mol% of **10h** (0.2 equiv) in 0.5 mL of CH_2Cl_2 with 4 Å MS.

Reaction scope

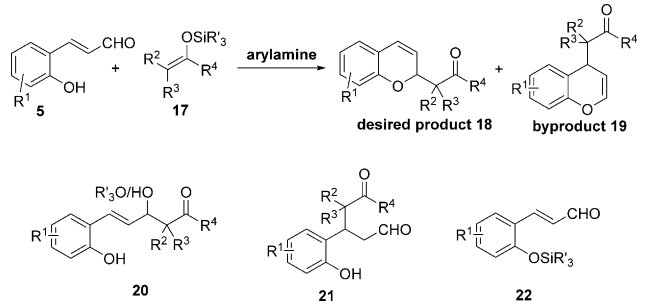
An exploratory study was carried out to probe the scope of the cyclization–substitution cascade reactions of the arene nucleophiles and *trans*-2-hydroxycinnamaldehyde catalyzed by2-hydroxyaniline (**10h**) (Scheme 3). We first examined potential electronic effects in the *trans*-2-hydroxycinnamaldehyde reactants using analogues containing electron-neutral (H, **14a**), -withdrawing (Cl, **14b**) and -donating (Me, **14c**) aromatic substituents. Reactions of these substrates with indole under optimal conditions were found to proceed smoothly to produce the corresponding 2*H*-chromenes **14a**–**c** in high yields (69–90% yields) and with high regioselectivities (8.3:1 to 10:1 r.r.). A variety of electron-rich arenes were then explored as potential nucleophiles in this process. The results demonstrate that indoles containing a wide variety of electronically different substituents react with the aldehyde **5a** under optimal conditions to generate the corresponding adducts **14e**–**l**. Furthermore, *N*-methyl indole also serves as a substrate for this reaction, which forms the adduct **14m** in high yield and with good regioselectivity (78% yield, 5.9:1 r.r.). *N*-Methyl pyrrole undergoes this reaction to exclusively generate the 2-pyrrole adduct **14n** in 52% yield. In this case, as well as in others in which less reactive nucleophiles are employed, tetrahydroquinoline (**10m**) was found to be superior to **10h** as a catalyst (Scheme 3). In addition to indoles and pyrrole, naphthols and phenols are also applicable for this protocol, as exemplified by the observations that 1-naphthol and 2,3-dimethoxylphenol react smoothly with **5a** in the presence of aniline **10m** to form **14o** (50%) and **14p** (51%), respectively.



Scheme 3. Substrate scope of the aniline-catalyzed cyclization–substitution cascade reaction of **5** with electron-rich arenes **13** (unless specified, see experimental section and SI). [a] 20 mol% cat. **10m**.

Aniline-catalyzed cyclization–substitution cascade reaction of 2-hydroxylcinnamaldehydes with silyl enol ethers

To further demonstrate the versatility of the new strategy, reactions employing silyl enol ethers as nucleophiles were explored next. This effort was stimulated by the thought that cyclization–substitution cascade processes of this type would serve as a new method for C_{sp^3}–C_{sp^3} bond formation. Unlike the case of the electron-rich arenes shown above, we were concerned about complications associated with the high reactivity/lability of silyl enol ethers under the conditions employed and the potential lack of regioselectivity of the processes associated with the possible generation of competitive 1,2- and 1,4-additions (e.g., **20** and **21**) (Scheme 4). Finally, we were also concerned



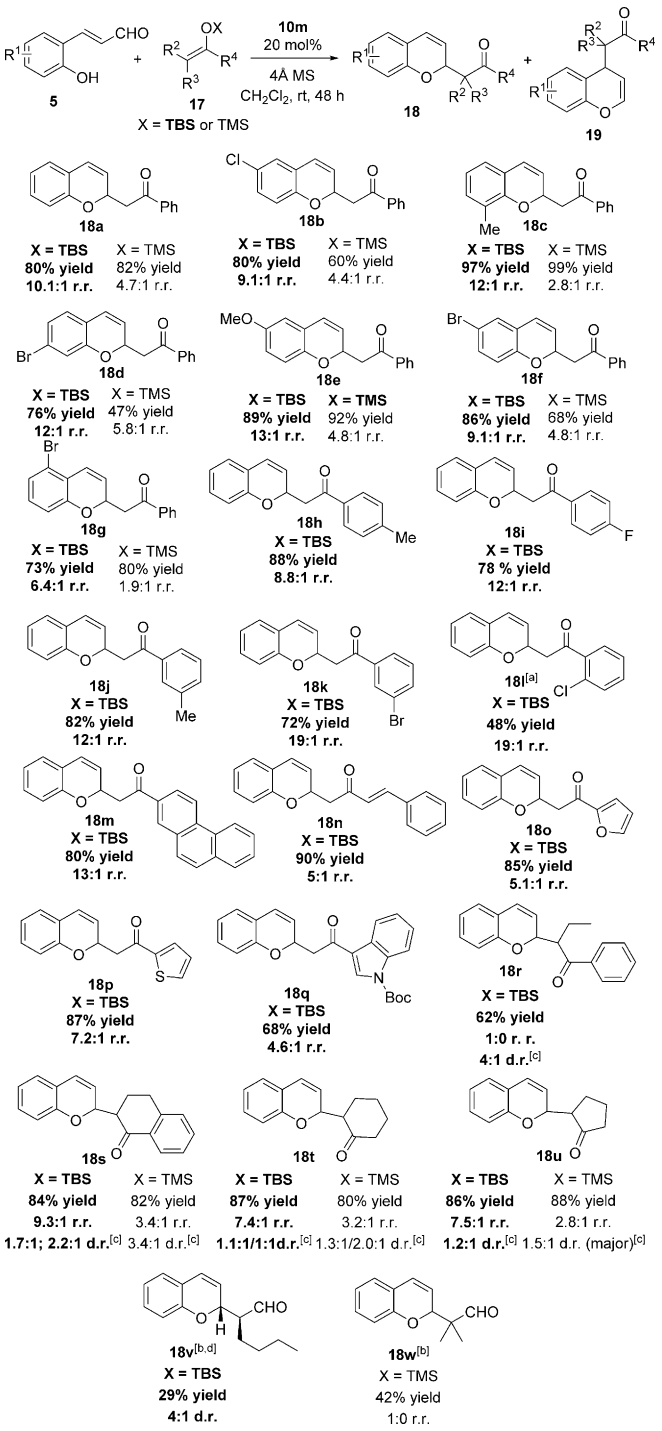
Scheme 4. Arylamine-catalyzed cyclization–substitution cascade reactions of *trans*-hydroxycinnamaldehydes **5** with silyl enol ethers **17**.

about the possible transilylation between the 2-hydroxy moiety of the cinnamaldehyde substrates and the silyl enol ether (e.g., **22**), an occurrence that could complicate this process.

To explore the features of the proposed silyl enol ether addition process, 2-hydroxycinnamaldehyde (**5a**) and the TMS (trimethylsilyl)-derived silyl enol ether of acetophenone **17a** were used as reactants and 2-hydroxyaniline (**10h**) as catalyst (Scheme 5). We observed that the reaction of these substrates in a respective molar ratio of 1:1.5, under the optimized conditions described above, generates the expected chromene **18a** in 68% yield and a r.r. of 4.3:1 (see details of the optimization of the reaction conditions, Supporting Information Table S2). Except for the production of a trace amount of the conjugate addition product and acetophenone, this process is not complicated by the formation of side products. In an attempt to improve the efficiency of the process, other arylamine catalysts were explored. The findings showed that tetrahydroquinoline (**10m**) is an ideal promoter for this reaction, which generates **18a** in 82% yield and a r.r. of 4.7:1; The yield was lowered to 74% when the ratio of **5a** and **17a** was changed to 1.0:1.2.

Studies probing the substrate scope of the reaction showed that some of the 2-hydroxycinnamaldehydes (e.g., **5b**, **5d**, **5f** and **5v**) participate in low-yielding reactions with the TMS-derived silyl enol ether **17a** (Scheme 5). Analysis of these reactions reveals that the transfer of the TMS moiety from **17a** to the 2-hydroxy group in the *trans*-2-hydroxycinnamaldehydes **5** is the major reason for the diminished efficiencies of these reactions. To overcome this problem, the bulkier *tert*-butyldimethylsilyl (TBS) ether of acetophenone was employed as the substrate. Indeed, in reactions with this silyl enol ether, the silyl-transfer process is less competitive and the yields of the respective chromene-forming reactions with **5b**, **5d**, **5f** and **5v** increased dramatically (80% vs. 60% for **18b**, 76% vs. 47% for **18d**, 86% for vs. 68% for **18f**, and 29% vs. 0% for **18v**; Scheme 5). Furthermore, the regioselectivities of all reactions of the TBS adducts are significantly improved and the amount of the silyl enol ether reactant can be decreased to 1.1 equivalents.

An examination of the TBS-enol-ether scope of the addition reactions of the aldehyde **5a** showed that sterically demanding, *ortho*-substituted acetophenone-derived enol ethers only inefficiently participate in this process (e.g., 48% yield for the formation of **18l**). Nonetheless, both unhindered *para*- and *meta*-analogues efficiently generated the corresponding adducts (e.g., **18h**–**k**). Moreover, TBS enol ethers of polycyclic-aromatic-containing methyl ketones, such as that derived from 2-acetylphenanthrene, also reacted with **5a** to form the adduct **18m** in high yield and regioselectivity (e.g., 80%, 13:1 r.r.). The benzylideneacetone-derived TBS enol ether also reacted to form chromene **18n** in 90% yield and r.r. of 5:1, in addition to those reactants arising from heteroaryl methyl ketones like 2-acetylfuran (85%, **18o**), 2-acetylthiophene (87%, **18p**), and 3-acetylindole (68%, **18q**). Non-terminal TBS enol ethers were also found to be effective substrates, each of them producing mixtures of the diastereomeric chromenes containing two stereogenic centers as exemplified by the conversion of



Scheme 5. Arylamine **10m** catalyzed cyclization–substitution cascade reaction of cinnamaldehyde derivatives **15** and silyl enol ethers **17** with isolated yields (unless specified, see experimental section and SI). [a] 72 h. [b] 96 h. [c] The relative stereochemistry was not assigned for this product mixture. [d] Relative configuration is determined by comparison with known compounds in reference [4f].

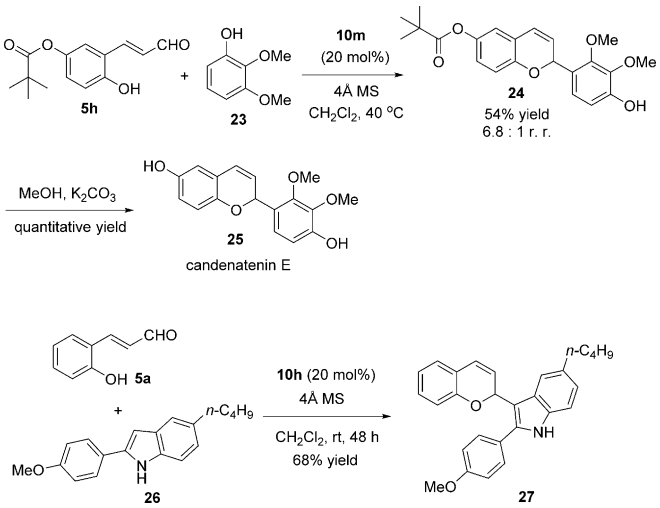
the (*E*)-TBS enol ether of butyrophenone to **18r** in 62% yield and with a d.r. of 4:1. Similarly, endocyclic TBS enol ethers of cyclic ketones also reacted with **5a**. For example, the silyl enol ether of 1-tetralone reacted to form **18s** with a high degree of regioselecitivity, but only modest diastereoselectivity. Similar

trends were followed in reactions of the TBS enol ethers of cyclohexanone and cyclopentanone. Although, we originally believed that aldehyde-derived silyl enol ethers might be more challenging substrates for this process, we found that the TBS enol ether of hexnal reacts with **5a** to produce the desired product **18v**, albeit in low yield. It is worth noting that the TMS enol ether of hexanal failed to generate the chromene **18v**, but the TMS enol ether of isobutyraldehyde reacted with **5a** to form the quaternary carbon-containing product **18w** in 42% yield and with a r. r of 1:0. In contrast, the TBS analogue of this aldehyde did not undergo this reaction.

Synthetic applications

As discussed above, chromenes and chromanes are scaffolds widely present in a number of natural products and bioactive compounds. The new method that we have developed can serve as a powerful tool to construct interestingly substituted members of these heterocyclic families. To demonstrate the synthetic utility of the new protocol, we designed a two-step route for the preparation of the chromene-containing natural product candenatenin E (**25**), isolated from the heartwood of the Thai medicinal plant *D. candenatensis* (Scheme 6).[11] (*E*)-4-Hydroxy-3-(3-oxoprop-1-en-1-yl)phenyl pivalate (**5h**), a readily available starting material, undergoes efficient reaction with 2,3-dimethoxyphenol (**23**) in the presence of 20 mol% amine catalyst **10m** at 40 °C to give the desired product **24** in 54% yield and a r.r. of 6.8:1. Racemic candenatenin E (**25**) is then generated in nearly quantitative yield by simple base promoted saponification of the pivalate ester moiety in **24**.

We also used the new method to install a chromene group at the C-3 position of 5-butyl-2-(4-methoxyphenyl)-1*H*-indole (**26**). Specifically, reaction of **26** with the cinnamaldehyde derivative **5a**, catalyzed by the aniline **10h**, produces the potentially bioactive indole-chromene derivative **27** in 68% yield (Scheme 6).[12]

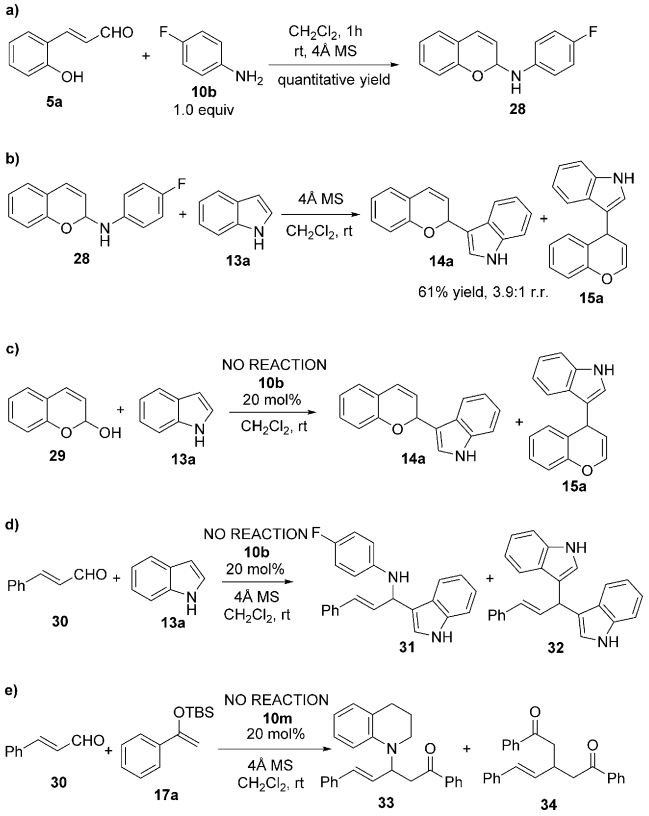


Scheme 6. Two-step synthesis of candenatenin E and functionalization of bioactive indole-containing compounds.

Mechanistic study

The studies described above have produced new amine-catalyzed cyclization–nucleophilic-substitution cascade reactions. These processes, which do not require the use of acid additives or elevated temperatures to activate *N*,*O*-acetals in a catalytic manner, take place under mild reaction conditions in high yields and with high degrees of chemo- and regioselectivity. The key to the success of these processes is the identification of aniline derivatives as catalysts that have properly balanced nucleophilicities and leaving abilities. The nucleophilicity is essential for the effective formation of an iminium ion with the aldehyde in the initial cyclization step. However, a good leaving propensity is essential for the catalyst regeneration. For example, we observed that the more nucleophilic Jørgensen–Hayashi diphenylpyrrolinol TMS catalyst **7** in reaction between the cinnamaldehyde **5a** and the indole **13a** is sufficiently nucleophilic to promote the formation of the iminium intermediate, which then undergoes cyclization to form the *N*,*O*-acetal **8** (Scheme 2).[6] However, its poor leaving tendency prevents the subsequent nucleophilic-substitution process even with an acid additive (e.g., CF_3CO_2H).

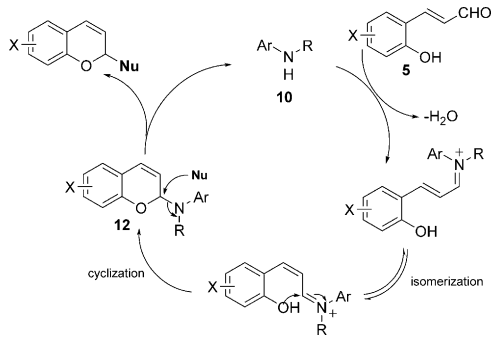
To understand the new aminocatalytic cyclization–substitution process, we carried out a more detailed investigation. In this effort, we observed that treatment of the aldehyde **5a** with a stoichiometric amount of the 4-fluoroaniline **10b** leads to the generation of the *N*,*O*-acetal **28** in quantitative yield within 1 h (Scheme 7a). The *N*,*O*-acetal is stable and can be pu-



Scheme 7. Results of the preliminary experiments designed to gain understanding of the mechanism of the cyclization–substitution cascade process.

rified and characterized (see Supporting Information). Moreover, **28** was found to react with the indole **13a** to form the substitution products **14a** and **15a** in a combined 61% yield and a r.r. of 3.9:1 (Scheme 7b). Furthermore, the preformed hemiacetal **29** does not react with the indole **13a** under the standard reaction conditions in the presence of **10b**, which suggests that the route does not undergo through hemiacetal formation (Scheme 7c). In addition, we found that *trans*-cinnamaldehyde **30** does not react with the indole **13a** in the presence of **10b** under the standard reaction conditions. This outcome shows that the cascade process does not take place by a pathway involving the initial addition of indole to the iminium ion formed between the aldehyde and the aniline catalyst (Scheme 7d). In a similar manner, *trans*-cinnamaldehyde **30** does not react with *tert*-butyldimethyl[(1-phenylvinyl)oxy]silane (**17a**) in the presence of **10m** (Scheme 7e).

Based on these experiments, a possible catalytic cycle is proposed (Scheme 8). The formation of the key *N*,*O*-acetal **12** from an aniline and a *trans*-2-hydroxycinnamaldehyde **5** is an essential step. It is noted that two possible pathways exist for the substitution reaction between the *N*,*O*-acetal **12** and a nucleophile; the first involving direct displacement of the amine by the nucleophile in a concerted process and the second involving the initial stepwise loss of the amine followed by the addition of the nucleophile to the formed oxonium ion (structure not shown). At the current time, we have no evidence that enables distinction between these two possibilities.



Scheme 8. Proposed catalytic cycle.

Conclusion

In the study described above, we developed an unprecedented, arylamine-catalyzed cyclization–substitution cascade reaction for the one-pot synthesis of 2-substituted 2*H*-chromenes. Unlike widely used strategies, the protocol employs simple amines as activators for the formation of *N*,*O*-acetals and subsequent direct substitution by nucleophiles under mild conditions without requirement of acids or elevated temperatures. Notably, the process leads to high yields with high degrees of chemo- and regioselectivity, and it shows a broad nucleophilic-substrate scope including indoles, pyroles, phenols, and silyl enol ethers. Furthermore, the synthetical value of the new method is demonstrated by its use in a two-step synthesis of the natural product candenatenin E and the facile installation of 2-substituted 2*H*-chromene moieties in biologically active indoles. Importantly, the process developed in this study represents the first example of a direct germinal functionalization of aldehydes in a catalytic fashion. Further exploration of the utilization of the aminocatalytic mode in the design of new organic transformations and useful enantioselective processes is underway in our laboratories.

Experimental Section

General procedure for the arylamine-catalyzed cyclization–substitution cascade reaction of 2-hydroxycinnamaldehydes with electron-rich arenes (Scheme 3)

An electron-rich arene **13** (0.1 mmol) was added to a solution of a 2-hydroxycinnamaldehyde **5** (0.12 mmol) in anhydrous dichloromethane (0.5 mL) in the presence of **10h** (20 mol%) and 4 Å molecular sieves (100 mg). The resulting solution was stirred for a specified time (22–72 h) at room temperature and filtered through a short microcolumn of celite. Concentration of the filtrate gave a residue that was subjected to ^{1}H NMR analysis. Isolation of the product was conducted by subjecting the residue to silica gel chromatography.

General procedure for the arylamine-catalyzed cyclization–substitution cascade reaction of 2-hydroxycinnamaldehydes with silyl enol ethers (Scheme 5)

A specified silyl enol ether **17** (0.11 mmol) was added to a solution of hydroxycinnamaldehyde **5** (0.1 mmol) in anhydrous dichloromethane (0.5 mL) in the presence of **10m** (20 mol%) and 4 Å molecular sieves (100 mg). The resulting solution was stirred for 48 h at room temperature and filtered through a short microcolumn of celite. Concentration of the filtrate in vacuo gave a residue that was subjected to ^{1}H NMR analysis. Isolation of the product was conducted by subjecting the residue to silica gel chromatography.

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