Organic LETTERS

Letter

pubs.acs.org/OrgLett

Asymmetric Roadmap to Diverse Polycyclic Benzopyrans via Phosphine-Catalyzed Enantioselective [4 + 2]-Annulation Reaction

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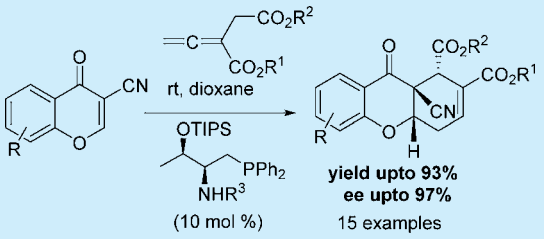
Supporting Information

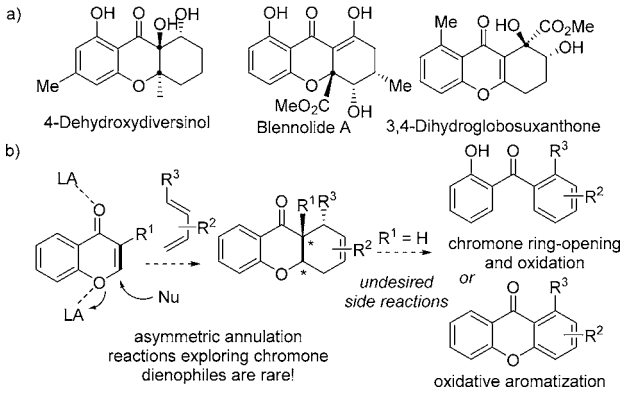
ABSTRACT: The catalytic addition of the amino acid derived bifunctional *N*-acylaminophosphine to an α-substituted allene ester generated a zwitterionic dipole that engaged the vinylogous ester function of 3-cyano-chromones in a [4 + 2] annulation reaction to deliver tetrahydroxanthones embodying three consecutive chiral centers in high yields and with excellent enantioselectivities. The established asymmetric synthesis further paves the way to two different classes of complex, sp^3-rich tetracyclic benzopyrans via efficient cascade reactions.



Small molecules based on privileged molecular frameworks and rich in three-dimensional complexity are in high demand in modern drug and probe discovery research.[1] Consequently, synthesis routes that build up novel and complex natural product based scaffolds in an asymmetric fashion remain highly desired.[2] 4-Benzopyrone or chromone is a privileged ring system that has inspired organic as well as medicinal chemists to explore chemical space around this scaffold.[3] The field has witnessed a large number of syntheses that have focused either on adding further aromatic rings to chromone, for instance in the synthesis of xanthone derivatives, or on decoration of the chromone ring with appended aryl, heteroaryl, or alkyl substituents, *i.e.* the synthesis of substituted flavones or isoflavone derivatives.[4] In some other cases, a vinylogous ester appended with additional functionalities, often at the 3-position of chromone in the form of a diene or a heterodiene, has been employed in cycloaddition reactions.[5] Despite the commercial availability of a large number of chromone derivatives, their scant application as dieno- or dipolarophiles in asymmetric cycloaddition or annulation reactions to afford higher order benzopyrones is disconcerting.[6] To the best of our knowledge, the trienamine mediated asymmetric [4 + 2] annulation reaction reported recently by Jørgensen group is the only asymmetric annulation reaction known to utilize the vinylogous ester function of chromone as a dipolarophile.[7] Herein we present a phosphine catalyzed asymmetric [4 + 2] annulation of α-substituted allene esters with electron-poor chromones, which provides a facile access to polycyclic and three-dimensionally complex benzopyrones and related frameworks that embody a number of consecutive chiral centers.

The dearth of catalytic tools that steer the enantioselective annulation or cycloaddition reactions that can engage the vinylogous ester of chromone substrates, is a prime reason for the lack of small molecules based on sp^3-rich tetrahydroxanthones and related natural product cores (Scheme 1a).[8]

Scheme 1. (a) Natural Products Embodying Tricyclic Benzopyrone Scaffold; (b) Rarely Addressed Asymmetric Annulation Reactions of Chromone Substrates



This has led chemists to design strategies that either build hetero- or carbocycles appended to an untouched chromone ring or generate a chromone ring at a later stage.[6b,9] Among other challenges, oxidative aromatization, as well as the facile opening of a pyrone ring can remove the stereoinformation induced by key annulation reactions (Scheme 1b).[10] Also, the ability of the keto moiety, as well as the phenolic ether of the chromone ring to engage Lewis acids in catalytic cycloaddition reactions, makes the design of facially discriminating annulation reactions a rather precarious exercise.

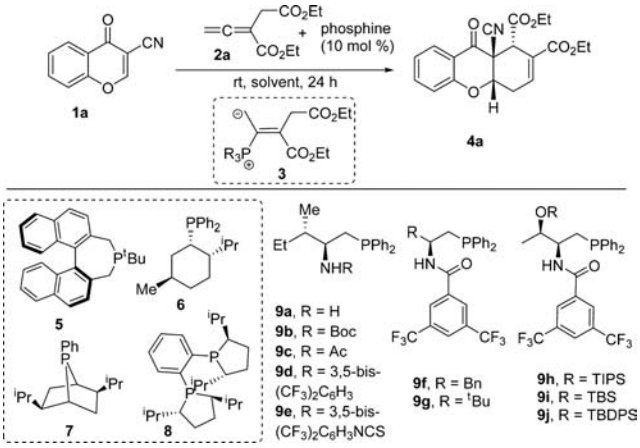
Lewis base catalyzed dipolar annulation reactions of allene derived zwitterions are important transformations for building hetero- and carbocycles.[11] We envisaged that C-3 substituted chromones (**1**) might serve as dipolarophiles in asymmetric [4 + 2] annulation reactions with α-substituted allene (**2**) if the

Received: April 12, 2016
Published: May 17, 2016

DOI: 10.1021/acs.orglett.6b01030
Org. Lett. 2016, 18, 2632–2635

latter was converted to the phospho-zwitterion (**3**). If successful, this would afford tetrahydroxanthones (**4**, Table 1)[12] with an all-carbon-quaternary center, which could avoid chromone ring opening as well as oxidative aromatization.

Table 1. Catalyst Screening for Asymmetric [4 + 2] Annulation of 1a and Allene Ester 2a Affording Tetrahydroxanthone 4a



entry	catalyst	solvent	yield[a,b] (%)	dr[c] (maj:min)	ee[d] (%)
1	**9a**	DCM	NR	–	–
2	**9b**	DCM	30	1.2:1	72
3	**9c**	DCM	29	1.7:1	87
4	**9d**	DCM	52	3.6:1	93
5	**9e**	DCM	NR	–	–
6	**9f**	DCM	32	2:1	89
7	**9g**	DCM	55	3:1	93
8	**9h**	DCM	83	3.5:1	95
9	**9h**	toluene	43	4.5:1	96
10	**9h**	THF	51	5.6:1	93
11	**9h**	dioxane	81	11:1	96
12	**9i**	dioxane	83	10:1	95
13	**9j**	dioxane	84	10:1	95
14[e]	**9h**	**dioxane**	**93**	**11:1**	**96**

[a]Isolated yield of the [4 + 2] adduct (both diastereoisomers). [b]1 M solution of **1a** was used for the reactions (see Supporting Information, Table 2). [c]Determined via ^{1}H NMR analysis of the crude product. [d]Ee of the major isomer was determined by chiral HPLC. [e]3 Å molecular sieves were added to the reaction mixture. NR = no reaction. dioxane = 1,4-dioxane.

We initiated our study by treating 3-cyanochromone **1a** with an allene ester (**2a**) and various chiral phosphines (Table 1). Fu et al. have successfully used a binepine monophosphine catalyst (**5**) for an enantioselective [4 + 2] annulation reaction of allene esters **2** with aldimines.[13] However, in our hands, binepine (**5**) as well as some other complex chiral phosphines **6**–**8** did not mediate any reaction between the intermediary zwitterion and the chromone **1a** (Supporting Information, Table 1). We and others have recently successfully employed amino acid derived chiral and bifunctional alkyldiphenylphosphines **9** in various annulation reactions of allenoates with olefins.[14] We wondered if the H-bond donating ability of these phosphines would positively influence the chemoreactivity and stereoselectivity of the [4 + 2] annulation reaction of chromone **1a** with the allene ester **2a**. Although L-isoleucine based-aminophosphine **9a** with a free amino group did not promote any reaction between chromone **1a** and allene ester **2a** (entry 1), 10 mol % of **9b**–**c** afforded the desired adduct **4a** in moderate yields and with good enantiomeric excess, *albeit* with low diastereoselectivities (entries 2–3). The hydrogen bonding effect induced by the Brønsted acid part of the phosphine and the influence of the chiral backbone of the amino acid derived phosphines on the stereocontrol of the reaction were nevertheless apparent. Therefore, a small collection of different amino acid derived aminophosphine catalysts (**9a**–**j**) were synthesized, where both parts of the catalyst were varied, and a reaction screening was performed. Phosphine **9d**, supporting a bulky protecting group, provided adduct **4a** with enhanced diastereo- and enantioselectivity (entry 4). Aminophosphine **9e**, supporting a strong hydrogen bond donating thiourea moiety, failed to provide sufficient activation for the reaction and no adduct **4a** was formed (entry 5).

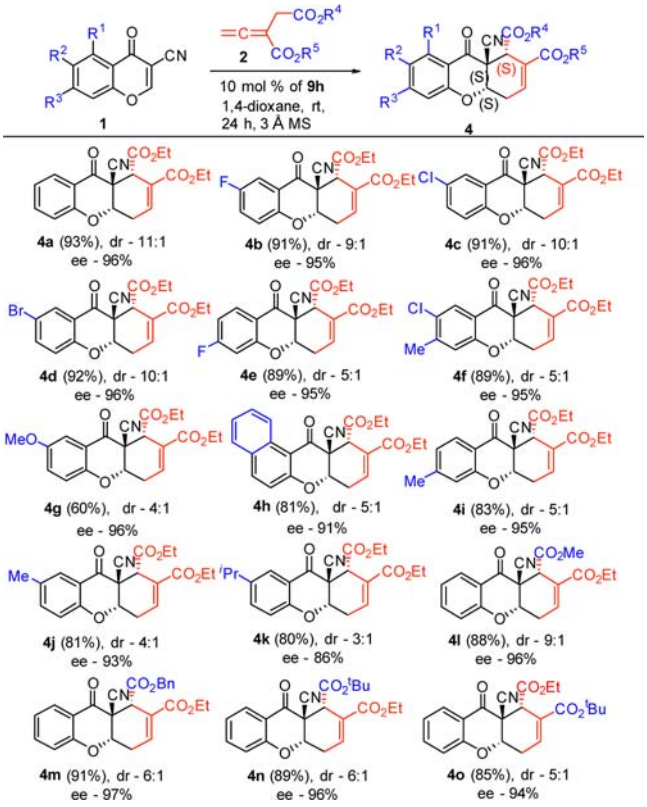
L-Phenyl alanine and L-*tert*-leucine derived aminophosphines **9f** and **9g** respectively did not improve the outcome significantly over **9d** (entries 6–7). However, highly encouraging results were obtained with L-threonine based catalysts **9h**–**j** (entries 8–13). Triisopropylsilyl protected aminophosphine **9h** in dichloromethane (DCM) afforded the [4 + 2] adduct in 83% yield and with excellent enantioselectivity (95%) for the major diastereoisomer (entry 8). A solvent screen with this catalyst revealed 1,4-dioxane as the best among tested solvents (entries 8–11) affording **4a** with high diastereoselectivity (11:1) and excellent enantioselectivity (96% ee, entry 11). Phosphines **9i**–**j** with a similar bulky silyl protecting group were equally efficient in the reaction (entries 12–13). Therefore, under the optimized conditions for this asymmetric [4 + 2] annulation reaction between the 3-cyanochromone **1** and the allene esters (**2**), 10 mol % of aminophosphine **9h** was used as the catalyst in dioxane in the presence of 3 Å molecular sieves to build the tricyclic benzopyrones **4** (entry 14, Table 1 and Scheme 2).

By employing the optimal reaction conditions for the asymmetric [4 + 2] annulation reaction, the scope of the methodology was explored. To this end, diversely substituted 3-cyano-chromones (**1**) and allene esters (**2**) were utilized. 3-Cyanochromones with electron-poor aromatic rings reacted with allene ester **2a**, successfully affording the tricyclic benzopyrones **4b**–**f** in excellent yields and with excellent enantioselectivity (Scheme 2); for the single crystal X-ray analysis of **4c**, please see the Supporting Information. In the case of 3-cyanochromones with electron-rich aromatic rings, a higher loading of catalyst (15–20 mol%) and a longer reaction time (48 h) provided good yields of the adducts **4g**–**h** (Scheme 2). Appreciable diastereoselectivity and excellent enantioselectivity remained the highlight of adducts **4g**–**k** (Scheme 2). Importantly, different ester groups on the allenes were well tolerated, delivering benzopyrones **4l**–**o** with similar efficiency and stereoselectivities (Scheme 2), thereby rendering the selective modification of different ester moieties on the periphery of scaffold plausible for further synthetic elaboration. Overall, the established asymmetric methodology delivered a set of small natural product-like molecules embodying three consecutive chiral centers including an-all-carbon-quaternary center in high yield and with excellent enantiomeric excess.

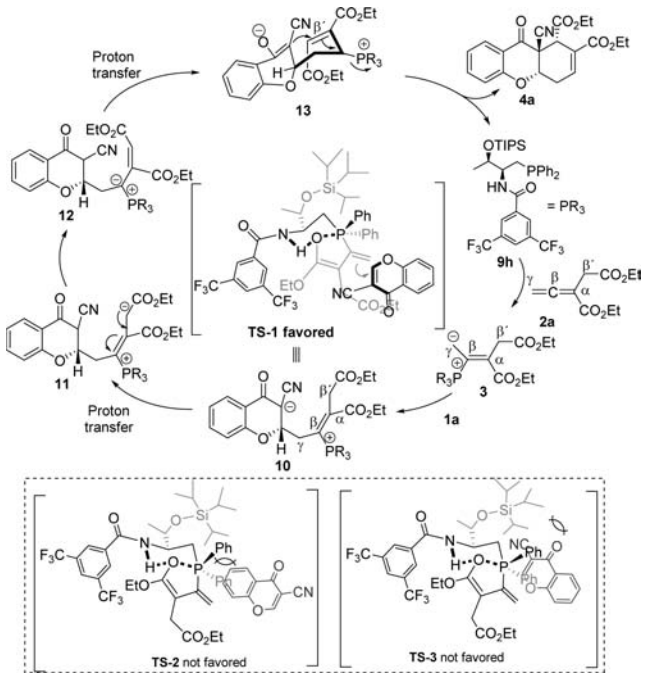
The aforementioned enantioselective [4 + 2] annulation reaction to give benzopyrone **4a** involves a γ-addition of the phosphonium enolate **3** to the electrophilic C-2 position of the chromone **1a**. The stabilization of the nucleophilic zwitterionic species is assisted by the hydrogen bonding interaction between the amide NH of the catalyst and the enolate as well as a P–O interaction (**TS-1** in Scheme 3).[14a−c] A *si*-face attack by the

DOI: 10.1021/acs.orglett.6b01030
Org. Lett. 2016, 18, 2632–2635

Scheme 2. Enantioselective [4 + 2]-Annulation Reaction between 3-Cyanochromones 1 and Allene Esters 2



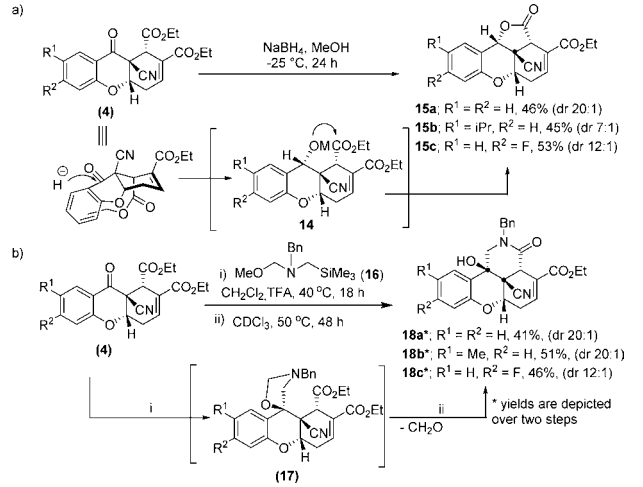
Scheme 3. Proposed Reaction Mechanism of the [4 + 2]-Annulation Reaction between Zwitterion 3 and Chromone 1a



phosphonium enolate on the chromone is preferred (**TS-1**, Scheme 3) since this avoids the steric bulk of the triisopropyl group (catalyst backbone) as well as the two phenyl rings of the phosphine (**TS-2** and **TS-3**). Two consecutive proton transfers shuffle the proton from the β'-carbon to the β-carbon and generate the allylic phosphonium zwitterionic intermediate **13**, supporting a relatively stable *Z*-olefin to avoid the proximity of the β'-ester and cyano function (Scheme 3). A conjugated addition of the chromonyl enolate followed by β-elimination of the aminophosphine (**9h**) furnishes the [4 + 2] cycloadduct **4a** with excellent enantiomeric excess.

We anticipated that the axial orientation of the ester function would drive the stereoselective reduction of the ketone (*re*-face addition of hydride). After some experiments, we identified that using $NaBH_4$ at low temperature (−25 °C) in methanol formed the tetracyclic benzopyran scaffold **15**. The latter was presumably formed through a metal alkoxide **14** that added on to the proximal ester to yield the lactone **15**. Some representative tetracyclic benzopyrans **15a−c** were prepared supporting different substitutions on the chromone ring in good yield and with high diastereoselectivities (Scheme 4a).

Scheme 4. Building Diverse and Complex Benzopyran Scaffolds 15 and 18 from Enantiopure Tricyclic Benzopyrones 4



In another molecular complexity building transformation, we attempted a 1,3-dipolar cycloaddition reaction of an *in situ* generated azomethine ylide from commercial *N*-(methoxymethyl)-*N*-(trimethylsilylmethyl)benzylamine (**16**, Scheme 4b) under mild acidic conditions. The reaction led to the formation of an unstable spirooxazolidine compound (**17**), and surprisingly, no reaction with α,β-unsaturated ester was observed. We optimized the reaction conditions that induced a tandem cleavage of the hemiaminal in the spirooxazolidine **17** and which led to an amine that concomitantly underwent lactamization to yield novel and complex tetracyclic benzopyrans **18a−c** in very high overall yields (Scheme 4b). The assignment of the relative stereochemistry of **18** stems from the recognition that only an equatorially placed alkyl amine generated *in situ* from **17** can form a lactam ring. The complex enantiopure compounds **18a−c** embody a δ-lactam fused to a tricyclic benzopyran supporting *four chiral centers* with *two consecutive quaternary carbons*, including *an all-carbon-quaternary center*. It represents a highly complex sp^3-rich natural product based molecular framework.

In summary, we have disclosed the first asymmetric [4 + 2] annulation reaction of α-substituted allenoates (**2**) via the zwitterionic trapping of the vinylogous ester function of

DOI: 10.1021/acs.orglett.6b01030
Org. Lett. 2016, 18, 2632−2635

chromone (**1**) as a dipolarophile. L-Threonine-derived chiral phosphine **9h** catalyzed the annulation reaction to afford the tricyclic benzopyrones **4** in excellent yields and with excellent enantioselectivities. The potential of this asymmetric methodology to provide access to a range of complex molecular frameworks has been demonstrated by establishing two novel cascade reactions that transformed the common substrate **4** into two diverse classes of tetracyclic benzopyran compounds (**15** and **18**). Further applications of the methodology to provide asymmetric access to a range of natural product scaffolds will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01030.

Experimental procedures, product characterization, crystallographic data, and ^{1}H and ^{13}C NMR spectra (PDF)
X-ray crystallographic data for **4c** (CIF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This research was supported by funds from Max-Planck-Gesellschaft.

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DOI: 10.1021/acs.orglett.6b01030
Org. Lett. 2016, 18, 2632−2635