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$AlCl_3$-Catalyzed Annulations of Ynamides Involving a Torquoselective Process for the Simultaneous Control of Central and Axial Chirality

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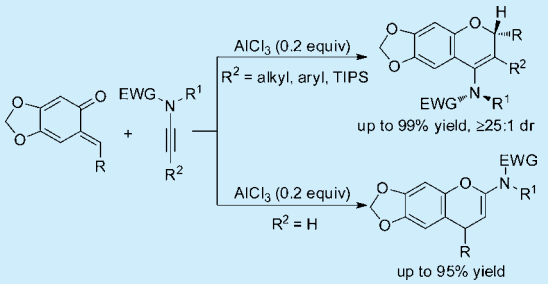
Supporting Information

ABSTRACT: A highly torquoselective process for simultaneous control of central and axial chirality by the annulation of terminally substituted ynamides with *o*-quinone methides is reported. In the presence of $AlCl_3$, a sequence comprising a [2 + 2] cycloaddition followed by the torquoselective 4π-electrocyclic ring opening and 6π-electrocyclic ring closure leads to highly stereoselective formation of diastereoisomeric 4-amino-2*H*-chromenes. Terminally unsubstituted ynamides undergo $AlCl_3$-catalyzed [4 + 2] cycloaddition with *o*-quinone methides providing 2-amino-4*H*-chromenes.



Atropisomers, compounds in which chirality originates from restricted rotation along a chiral axis, have received much attention due to their widespread appearance in naturally occurring biologically active compounds and artificial chiral ligands for asymmetric catalysis.[1] In most of the known structures, the chiral axis is between two aromatic moieties, but there are examples of non-biaryl atropisomers. Among different types of non-biaryl atropisomeric systems, those around a C−N bond are important in areas as diverse as enzyme/substrate binding,[2] molecular torsional balances,[3] and asymmetric synthesis.[4a]

Several reports followed the pioneering work on atropisomeric anilides.[4a] Some compounds of type **I**, such as atropisomeric anilides, carbamates, imides, and ureas, emerged afterward (Figure 1). Compounds of class **II** (naphthamides)

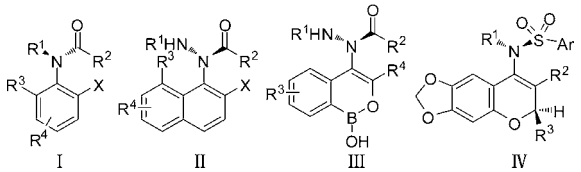


Figure 1. Nonbiaryl atropisomers around a C−N chiral axis.

were also investigated.[4b] Recently, it was demonstrated that a heteroaryl atropisomer **III** traditional carbonyl group was involved in all three types of non-biaryl atropisomers around a C−N chiral axis.[4c] There is no reported data about the corresponding compounds of *N*-sulfonyl-substituted heteroaryl atropisomers **IV**, such as 4-amino-2*H*-chromenes.

Amino-substituted chromenes are important because they belong to privileged medicinal scaffolds to generate small-molecule ligands with highly pronounced biological activities.[5,6] Although various cyclic systems, such as indoles,[7] pyridines,[8] 2-aminochromones,[9a] and 3-aminoisocoumarins,[9b] were successfully synthesized via the reactions of ynamides,[10,11] construction of amino-substituted chromenes from ynamides has not been achieved. To the best of our knowledge, only two examples have been reported to construct the amino-substituted 4*H*-pyran skeleton via [4 + 2] cycloaddition of α,β-unsaturated carbonyl compounds with ynamides.[12] Herein, we report the highly stereoselective synthesis of atropisomers of class **IV**, namely, 4-amino-2*H*-chromenes. The strategy of forming this new class is based on $AlCl_3$-catalyzed annulation of terminally substituted ynamides with *o*-quinone methides, while terminally unsubstituted ynamides undergo [4 + 2] cycloaddition, providing 2-amino-4*H*-chromenes (Scheme 1).

First, we tested the reaction of *o*-quinone methide **1a** with ynamide **2a** (Table 1). We isolated two diastereoisomeric 4-amino-2*H*-chromene **3a** in excellent yield but with low diastereoselectivity with ZnI_2 catalyst (entry 1). Similar results were obtained when the other two bidentate Lewis acids $ZnCl_2$ and $SnCl_4$ were used (entries 2 and 3). Another bidentate Lewis acid, $Zn(OTf)_2$, improved the selectivity but decreased yield (entry 4). AgOTf, $FeCl_3$, $BF_3{\cdot}OEt_2$, and $AlCl_3$ catalyzed the reaction to give **3a** in good to high yields with moderate diastereoselectivities (entries 5−8). With the optimized catalyst $AlCl_3$, solvent screening revealed that etheric solvents such as

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Scheme 1. Annulations of *o*-Quinone Methides with Ynamides

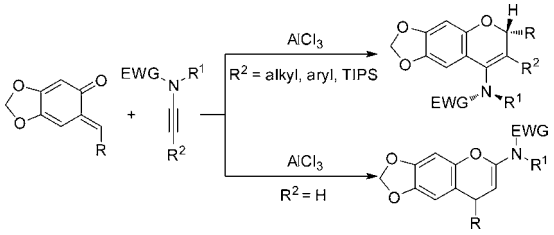
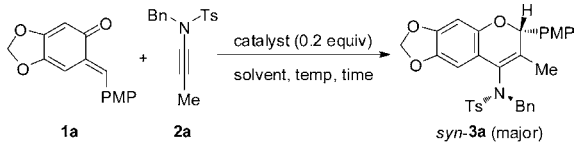


Table 1. Optimization of the Annulation of *o*-Quinone Methide 1a with Ynamide 2a



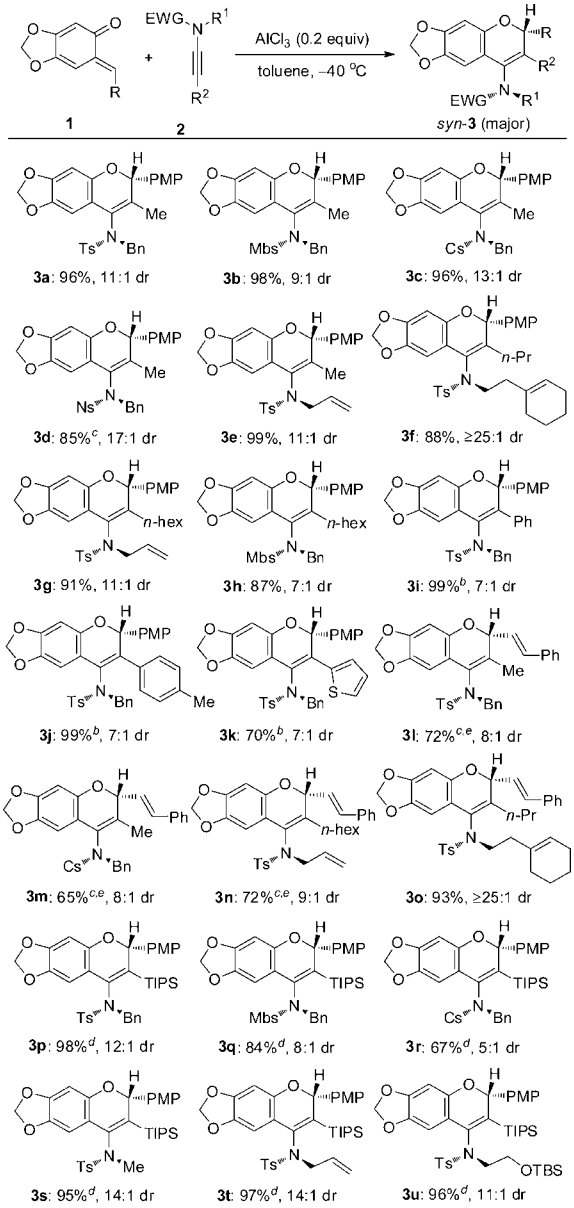
entry[a]	catalyst	solvent	temp (°C)	time (h)	yield[b] (%)	dr[c]
1	ZnI_2	DCM	60	0.5	93	1:1
2	$ZnCl_2$	DCM	60	1.0	99	1:1
3	$SnCl_4$	DCM	0	0.3	99	2:1
4	$Zn(OTf)_2$	DCM	0 to rt	2.5	54	5:1
5	AgOTf	DCM	0	0.3	62	5:1
6	$FeCl_3$	DCM	0	0.3	73	5:1
7	$BF_3{\cdot}OEt_2$	DCM	0	0.3	78	4:1
8	$AlCl_3$	DCM	0	0.2	84	5:1
9	$AlCl_3$	THF	0	2.0	85	4:1
10	$AlCl_3$	Et_2O	0	0.2	83	6:1
11	$AlCl_3$	toluene	0	0.2	95	9:1
12	$AlCl_3$	toluene	rt	0.2	99	9:1
13	$AlCl_3$	toluene	50	0.2	98	9:1
14	$AlCl_3$	toluene	−10	0.2	99	9:1
15	$AlCl_3$	toluene	−20	0.2	99	9:1
16	$AlCl_3$	toluene	−30	0.5	95	9:1
17	$AlCl_3$	toluene	−40	2.0	96	11:1
18	$AlCl_3$	toluene	−50	8.0	29	6:1

[a]Reactions were carried out using **1a** (0.24 mmol) and **2a** (0.20 mmol) with catalyst (0.04 mmol) in solvent (2.67 mL). [b]Combined yield of isolated diastereomers. [c]Diastereoselectivity determined by HPLC analysis of unpurified reaction mixture. PMP = *p*-methoxyphenyl.

THF and ether did not provide better results (entries 9, 10 vs 8), but toluene led to **3a** in excellent yield with high regioselectivity (entry 11). Further investigation showed that there was no noticeable temperature effect when the reaction was carried out at 50 to −30 °C, but −40 °C resulted in quantitative yield with higher selectivity (entries 11−17); further temperature decrease led to a poor result (entry 18).

The scope and generality of this annulation are shown in Scheme 2. Ynamides with electron-donating and electron-withdrawing sulfonyl systems were examined, and reactions proceeded smoothly to give **3a**−**3c** in excellent yields with high diastereoselectivities, and low reactivity of *N*-Ns-substituted ynamide **2d** led to a high yield of **3d**. These examples revealed that ynamides with electron-withdrawing sulfonyl groups had slightly better selectivities. Other alkyl- and aryl-terminated ynamides or *N*-alkenyl-substituted ynamides afforded **3e**−**3j** with excellent yields and high diastereoselectivities even for bulkier *n*-hexyl- and phenyl-substituted ynamides. For hetero-

Scheme 2. Annulation of *o*-Quinone Methides with Terminally Substituted Ynamides[a]



[a]Unless otherwise specified, reactions were carried out using **1** (0.24 mmol) and **2** (0.20 mmol) with $AlCl_3$ (0.04 mmol) in toluene (2.67 mL) at −40 °C. [b]At 0 °C. [c]At rt. [d]At 50 °C. [e]With 0.4 equiv of $AlCl_3$. Mbs = *p*-methoxybenzenesulfonyl; Ns = *p*-nitrobenzenesulfonyl; Cs = *p*-chlorobenzenesulfonyl.

aromatic-substituted ynamide, thienyl-terminated ynamide **2k** gave **3k** in 70% yield with 7:1 dr. Reactions of aryl-terminated ynamides **2i**−**2k** were smoother at 0 °C than at −40 °C. *o*-Quinone methide with a cinnamyl substituent worked well, affording **3l**−**3o** in good to excellent yields with high diastereoselectivities. TIPS-terminated ynamides, with low reactivity, gave good to excellent yields of **3p**−**3u** with high diastereoselectivities at 50 °C. The stereochemistry of the major isomers *syn*-**3** is based on analogy to *syn*-**3a** and *anti*-**3a**, verified by X-ray structure analysis.

Having uncovered this novel annulation reaction, we were intrigued by its mechanism. We propose that formation of **3** follows the pathway shown in Scheme 3. Stepwise [2 + 2]

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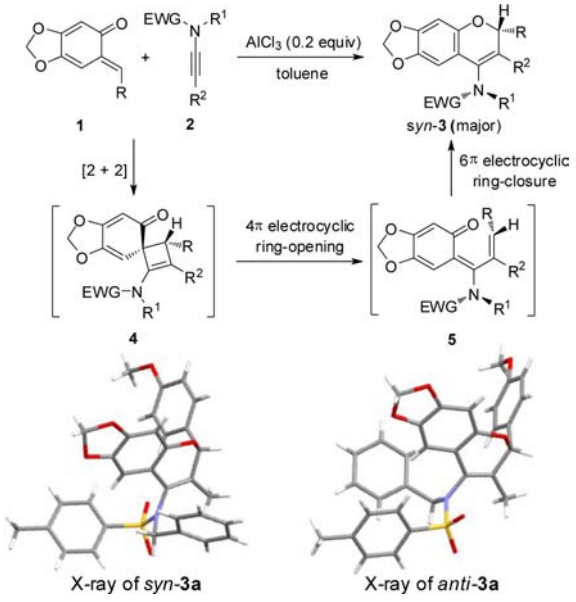
Scheme 3. Possible Pathway for the Annulation of *o*-Quinone Methide 1a with Ynamide 2a



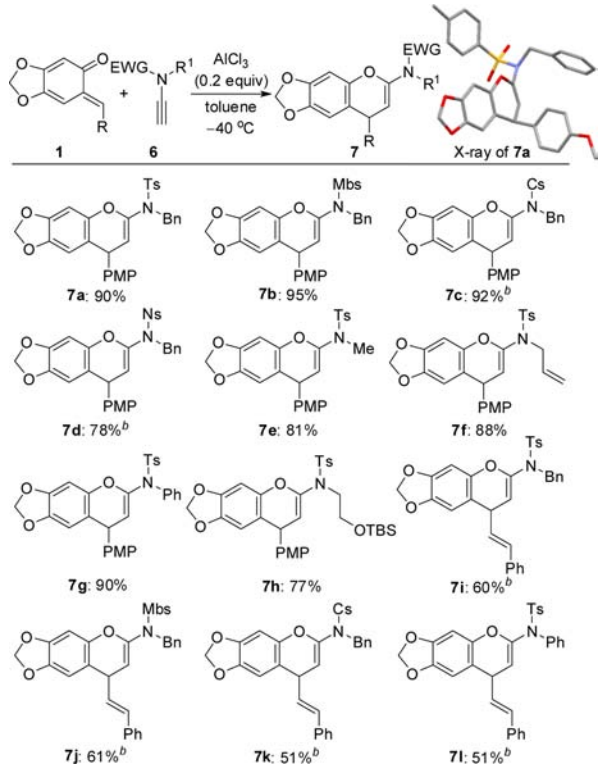
cycloaddition followed by torquoselective 4π-electrocyclic ring opening[13] of spirocyclic intermediate **4** with the electron-withdrawing carbonyl group rotating inward[13] led to 1-oxatriene **5**. 6π-Electrocyclic ring closure[14] of **5** provides **3**, achieving highly stereoselective formation of C−N axial chirality. Geometrical structures for *syn*- and *anti*-**3a** were optimized with Gaussian 09.[15] Based on the calculated results at the M06-2X/6-311++G(d,p)//6-31G(d,p) level[16] in toluene using the IEFPCM solvation model,[17] *anti*-**3a** is 3.0 kcal/mol less stable than *syn*-**3a** and the barrier for epimerization is low,[18] indicating that the torquoselective process is thermodynamically controlled. From single-crystal X-ray structures of *syn*- and *anti*-**3a**,[19] we see the benzene ring of the benzyl group in *syn*-**3a** is roughly parallel to the plane of the tricyclic ring, and there must be a π-stack packing effect between them that makes the *syn* geometry more stable than *anti* geometry and leads to high regioselectivity of the annulation.

We assessed how terminally unsubstituted ynamides **6** behave under the reaction conditions. When **6** was employed, **7** was isolated from the hetero[4 + 2] cycloaddition (Scheme 4), which may be caused by decreasing steric effect of ynamides, making [4 + 2] cycloaddition easier. Variation of substituents on the nitrogen atom of the starting ynamides led to **7a**−**7h** with high to excellent yields. *o*-Quinone methide with a cinnamyl substituent was also tolerated, giving **7i**−**7l** in moderate yields. Unlike **3**, there is no atropisomers of **7** due to lower steric hindrance around the C−N bond.

To further expand the diversity in the aromatic core of the amino-substituted chromene rings, TIPS-substituted **3p** and **3t** were modified to generate benzofurans **8** and **9** (Scheme 5). **3** could be converted into methoxybenzyl-substituted **8**[19] when the reactions were carried out under N_2, while reactions run under O_2 obtained high yields of methoxybenzoyl-substituted **9**,[19] which are used for treatment of hyper-proliferative disorders.[20] **9p** was further reduced by Grignard reagent to give tertiary alcohol **10p** in high yield with good diastereoselectivity.

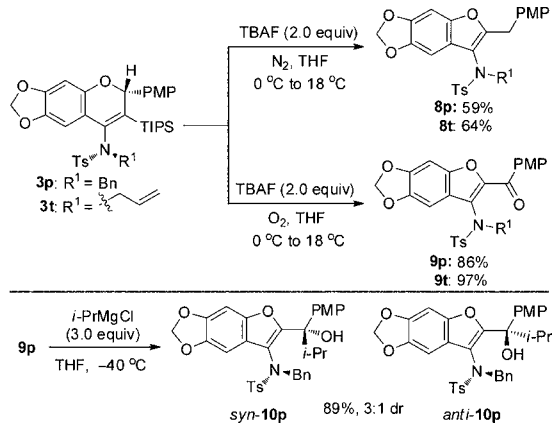
We have shown a highly torquoselective process for simultaneous control of central and axial chirality via an $AlCl_3$-catalyzed annulation reaction of *o*-quinone methides with

Scheme 4. Annulation of *o*-Quinone Methides with Terminally Unsubstituted Ynamides[a]



[a]Unless otherwise specified, reactions were carried out using **1** (0.24 mmol) and **5** (0.20 mmol) with $AlCl_3$ (0.04 mmol) in toluene (2.67 mL) at −40 °C. [b]Reaction was carried out at 0 °C with 0.4 equiv of $AlCl_3$.

Scheme 5. Chemical Transformations of TIPS-Substituted 4-Amino-2*H*-Chromenes



terminally substituted ynamides. The reaction represents easy access to non-biaryl atropisomers, which can be further elaborated to several new atropisomers. Terminal substitution pattern played an imminent role in favoring either the [2 + 2] cycloaddition followed by the electrocyclic ring opening and closure reactions or the [4 + 2] cycloaddition pathway, leading to 4-amino-2*H*-chromenes in generally excellent yields with high regioselectivities or 2-amino-4*H*-chromenes with good to high yields.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02480.

Detailed experimental procedures (PDF)
Characterization data for the new compounds (PDF)
Crystallographic data for *syn*-**3a** (CIF)
Crystallographic data for *anti*-**3a** (CIF)
Crystallographic data for **7a** (CIF)
Crystallographic data for **8p** (CIF)
Crystallographic data for **9p** (CIF)

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Notes

The authors declare no competing financial interest.

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(18) Though the pure *syn*- and *anti*-**3a** are stable, both of them in $CDCl_3$ (0.036 M) isomerized into a 3:1 (*syn*/*anti*) mixture at rt after 25 days. For further discussions, see the Supporting Information.

(19) For details concerning the crystal structure of *syn*-**3a**, *anti*-**3a**, **7a**, **8p**, and **9p** see the Supporting Information.

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