BTL NEDERLAND

Insights

Scientific Literature Review

ISSN 2590-0811

September/October 2021 | volume 4 | number 6

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Development of Synthetic Methodology

Specific focus was placed on topic strategies relevant to recent advances in synthetic methodology.

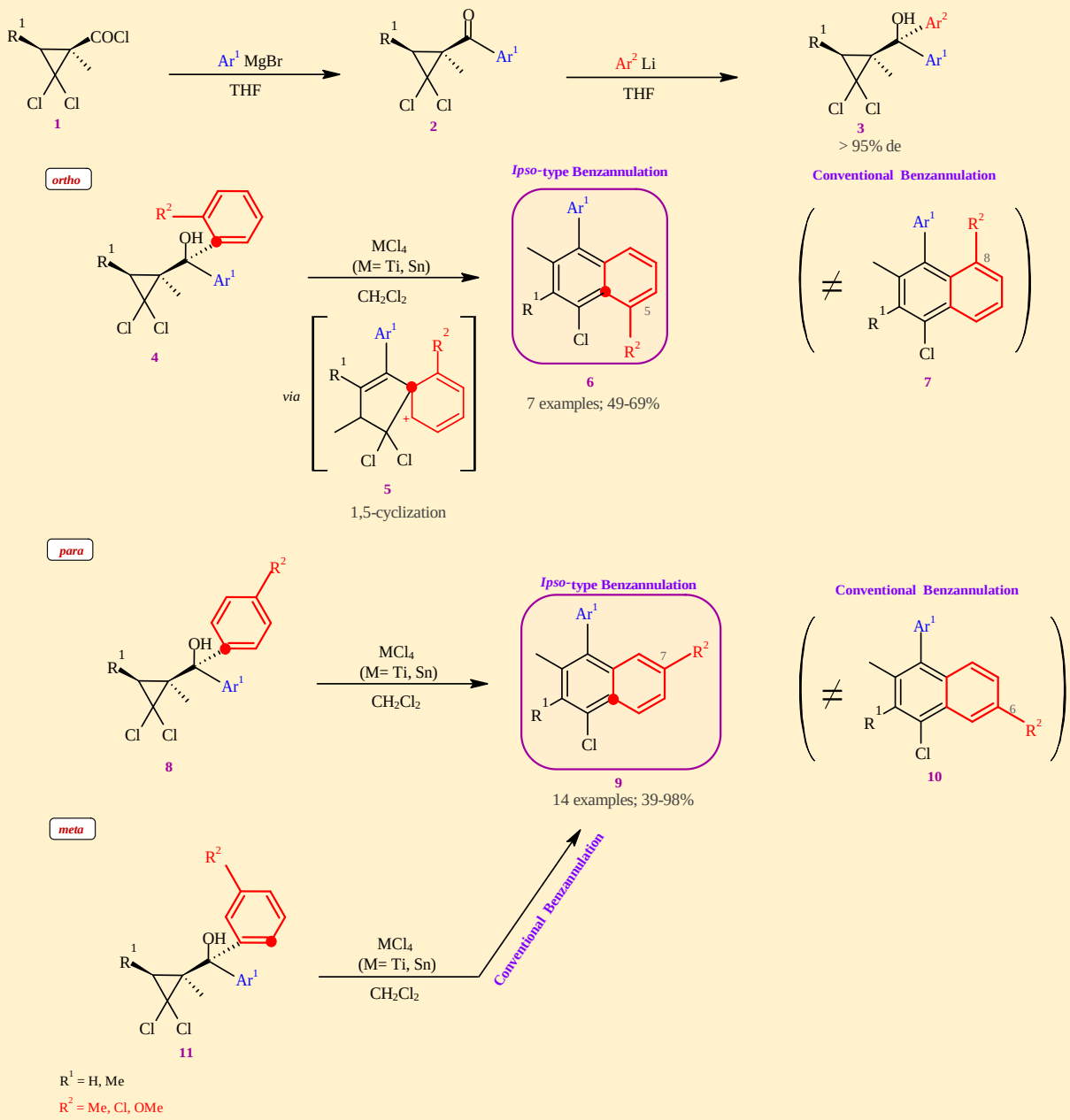
KEYWORDS: Benzannulation, Thioxanthone, Total synthesis of natural products, Synthetic polymers.

Introduction

Developing synthetic methodology constitutes a key element to create new compounds or procedures with a new dimension of versatility and selectivity. Such success of many of these reactions indicates the progress that has been made in understanding the chemistry operative in nature as well as in our daily life. This snapshot presents a blend of few advances and selected topics to stress the important strategies underlying these topics; to catalyze discussions around the scope and generality of such processes in chemical synthesis; and to inspire future improvements and new applications.

1- A distinctive approach for synthesizing multisubstituted α-arylnaphthalenes

Due to the uniquely core structural scaffolds of substituted α-arylnaphthalenes (cyclolignolides), these compounds have a wide range of applications. Moriguchi *et al.* reported a new admirable tactic for the synthesis of multisubstituted α-arylnaphthalenes.[1] Unlike the reported conventional benzannulation mode, *ortho*- and *para*-substituted 1,1-diaryl-2,2-dichlorocyclopropyl methanols (AACM) (**4** & **8**) were transformed to the corresponding *ipso*-type α-arylnaphthalenes (**6** & **9**), while the *meta*-substituted AACM (**11**) underwent the reaction in the expected conventional way (Scheme 1).



Scheme 1. Preparation of *Ipso*-type regiocontrolled benzannulations.

The distinguishing features of this approach are that: i) the reaction of AACM using $TiCl_4$ or $SnCl_4$ proceeds smoothly to yield *ipso*-type products with almost exclusive regioselectivity; ii) the desired product is obtained without any detection of those compounds resulting from the conventional benzanuulation; and iii) no specific correlation of either reactivity or yield between EDG or EWG groups in aryl compounds can be observed.

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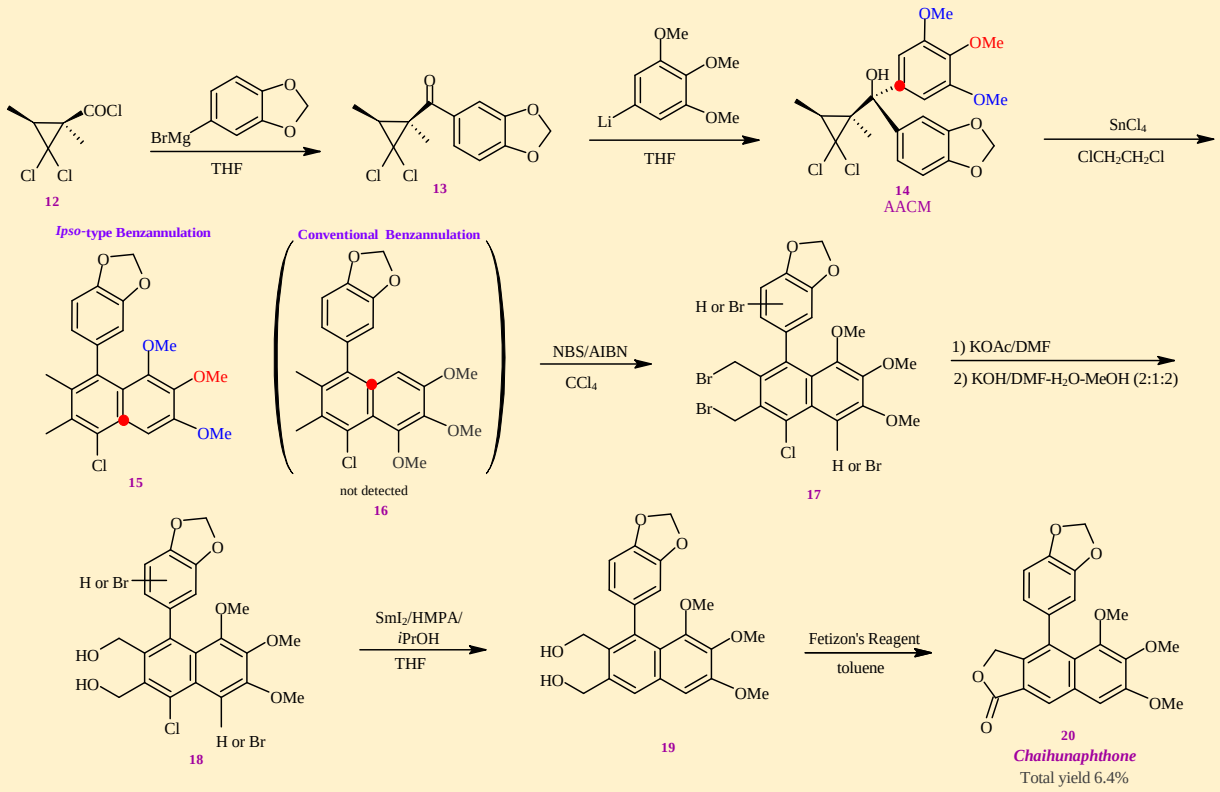
In such a variant, the *ipso*-type is expected to form radical intermediates. In sharp contrast, the *ipso*-type mode of **4** (similarly **8**) led to form benzenonium cationic intermediate **5** through 1,5-cyclization, followed by reversal conversion to tricyclic carbenium intermediate; ring fission and aromatization to furnish α-arylnaphthalenes **6**.

An application of such reaction was achieved for the first total synthesis of chaihunaphthone, that exhibits immunosuppressive effects and a stereo-congested and less accessible natural lignan lactone with three contiguous trimethoxy substituents (Scheme 2).



Scheme 2. Total synthesis of chaihunaphthone.

This methodology provides diverse syntheses for highly substituted and less accessible arylnaphthalenes.

2- Thioxanthone synthesis

Another interesting class of compounds are thioxanthones, which exist in a wide variety of natural compounds that exhibit extraordinary pharmacological activities. An efficient pathway to synthesize various derivatives of thioxanthones has been reported by Kobayashi *et al.* utilizing 3-halobenzoic esters as starting building block.[2] The strategy of this route is based on directed *ortho*-lithiation of 3-halobenzoic acid esters **21** followed by

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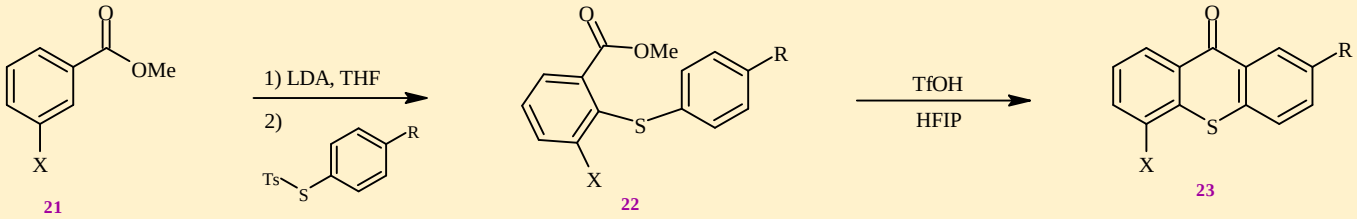
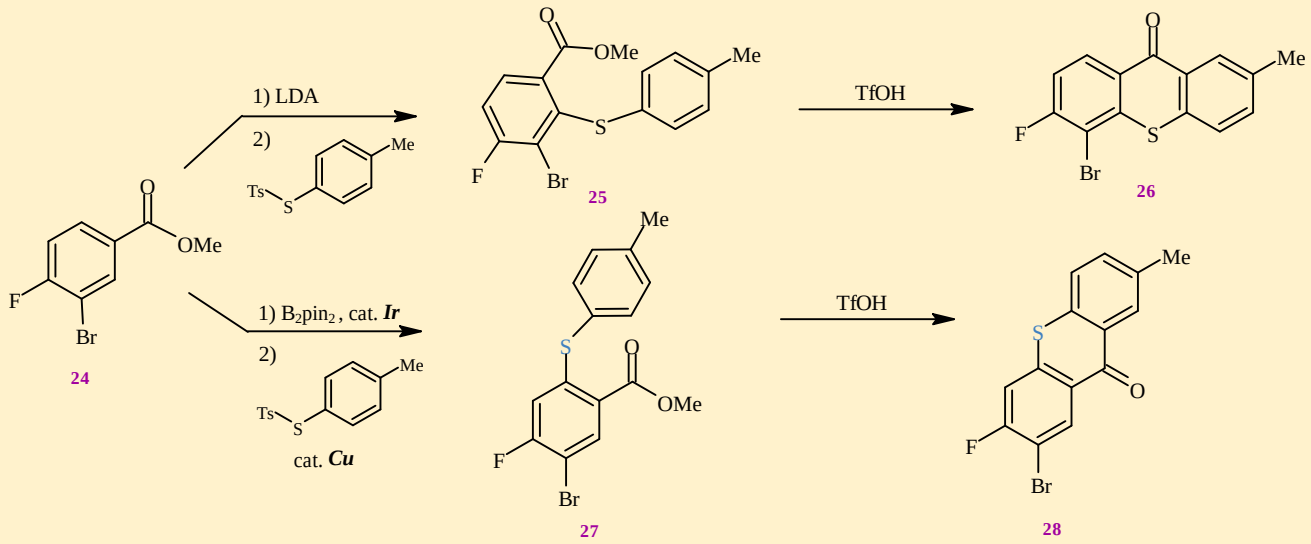
arylthiolation, resulting in sterically congested 2-(arylthio)-3-halobenzoic acid esters **22**, which were subsequently afforded diverse thioxanthones **23** by TfOH-promoted cyclization in HFIP (Scheme 3).



Scheme 3. Synthesis of various thioxanthones.

The authors described facile syntheses of two thioxanthone rigioisomers from benzoic acid esters **24** *via* two-types of the *ortho*-thiolation procedures (Scheme 4). The thioxanthone **28** was selectively prepared by employing iridium-promoted *ortho*-borylation of **24** at less sterically hindered site followed by copper-catalyzed thiolation furnished **28** and TfOH-facilitated ring-closure.

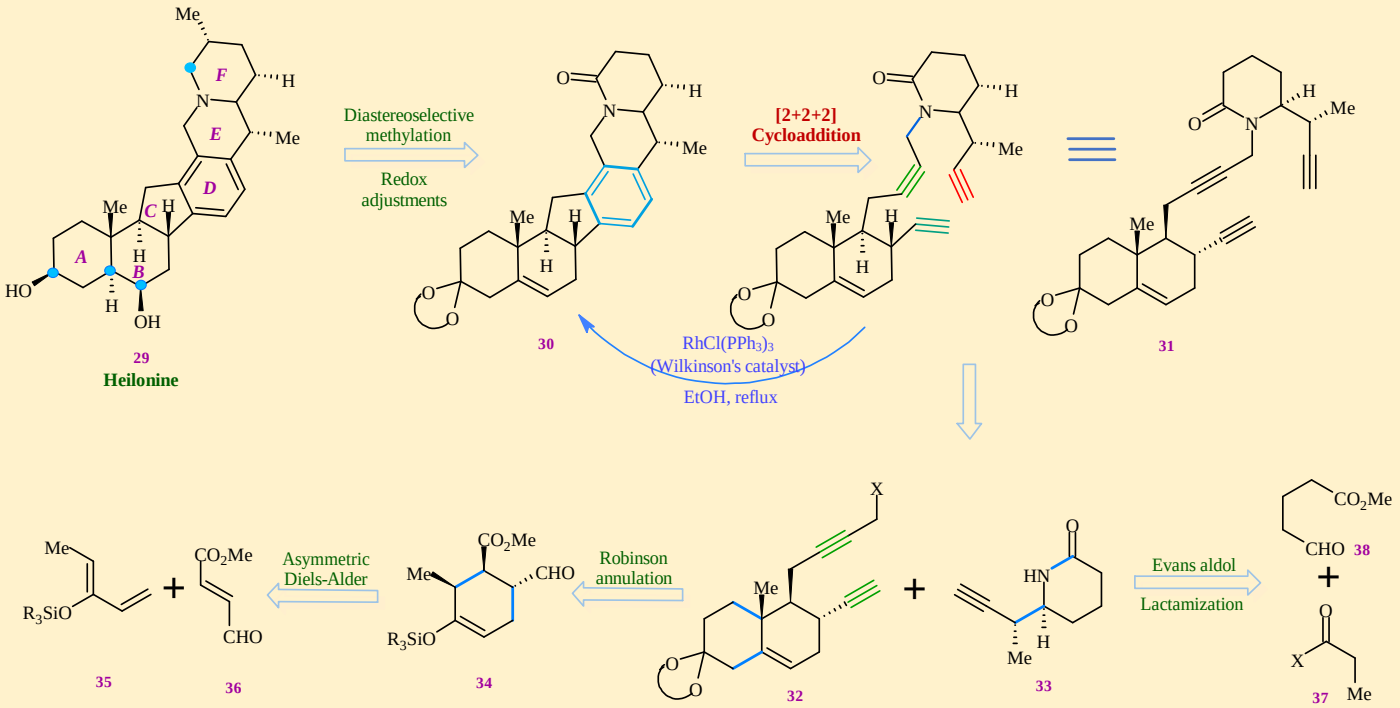


Scheme 4. Synthesis of regioisomeric thioxanthones **26** and **28**.

3- Total synthesis of (+)-Heionine

As a most stringent test, total synthesis often serves as a measure of the power of a given reaction. Cassaidy and Rawal have developed the first total synthesis of heilonine **29**, as a model of the first *de novo* synthesis of a cevanine-type alkaloid.[3] The key step to accomplish the synthesis of the complex hexacyclic structure of

heilonine along with its nine stereogenic centers was the utilization of a transition metal catalyzed intramolecular [2 + 2 + 2] cycloisomerization to forge the central aromatic D ring, along with C and E rings in a single synthetic operation (Scheme 5). The Wilkinson's catalyst in refluxing ethanol smoothly effected the alkyne trimerization, affording the desired cevanine framework in 89% yield. A polar solvent plays a key role in obtaining a high yield of the cycloisomerized product.



Scheme 5. The retrosynthesis of Heilonine.

4- Synthesis of efficient antiplatelet adhesive surfaces

When the materials composed of synthetic polymers are implanted and come in contact with blood, their surface is immediately covered by plasma proteins, affecting their adhesion to cells, and causing thrombus formation. To overcome this problem, Jikei *et al.* have developed bioabsorbable copolymers with good antiplatelet adhesion behavior characterized by the different orientations of fibrinogen on their surface.[4] These bioabsorbable copolymers composed of poly(L-lactide-co-glycolide) (PLGA) and poly(1,5-dioxepan-2-one) (PDXO). The synthetic pathway is depicted in Scheme 6. Compared to other antiplatelet adhesive materials, PLGA−PDXO MBC **40** showed good tensile properties and biodegradation behavior.

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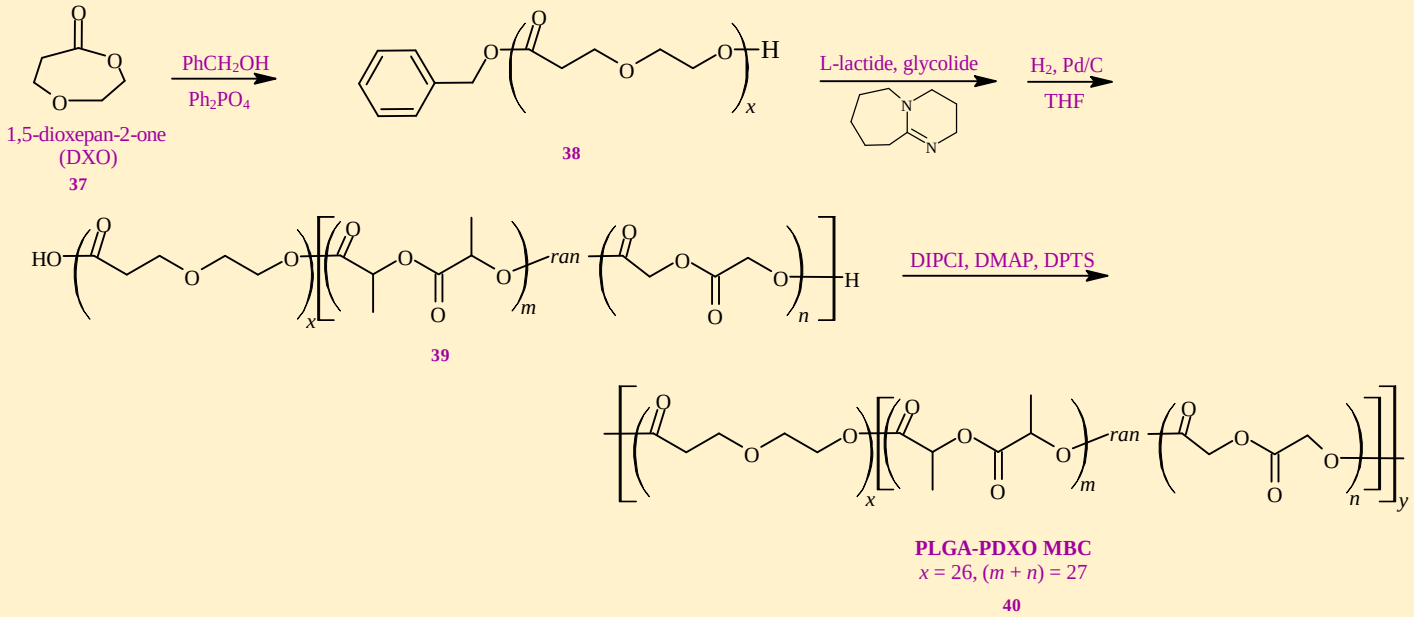

Scheme 6. Preparation of PLGA−PDXO MBC. DIPCI: *N*,*N*′-diisopropylcarbodiimide; DMAP: 4-(dimethylamino)pyridine; DPTS: 4-(dimethylamino)pyridinium *p*-toluenesulfonate.

Conclusion

The focal point of this snapshot is to reflect the growing interest in developing new synthetic strategies. These new topics are not only practically attractive as step-economical synthetic routes and improving reaction selectivity, but are also fundamentally interesting and show the latest innovations in synthetic methodology. New scenarios and creative applications of synthetic methods continue to emerge.

References

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