ISOCOUMARINS IN SKELETAL EDITING: A SYNTHETIC APPROACH TO MULTI-SUBSTITUTED POLYCYCLIC AROMATICS

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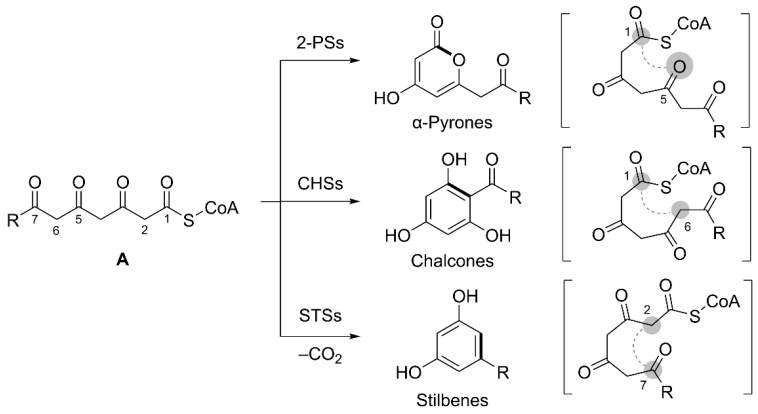
Abstract. *Isocoumarins are widely found in Nature. Their biosynthesis is closely linked with that of naphthalene natural products. Replacing oxygen atom in the isocoumarin ring system to carbon atom offers an attractive approach for the synthesis of multiply substituted naphthalenes.*

Contents

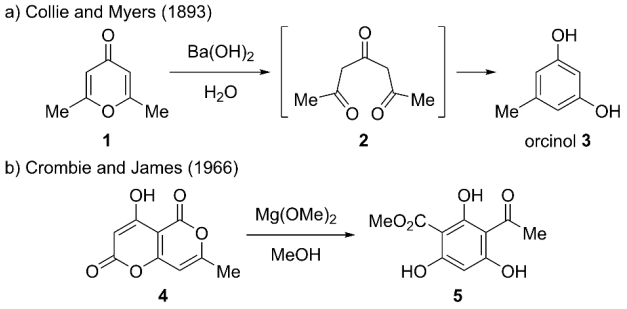
1. Introduction

Multi-substituted polycyclic aromatic skeletons are widely found as core structures of natural aromatic compounds, exemplified by aromatic polyketides. Such highly oxygenated polycyclic aromatic compounds have been a rich source of biologically active agents. Structural diversity in polyketide natural products is caused by means of polyketide synthases (PKSs).[1] As shown in Scheme 1, even just with the biosynthetic reactions of tetraketide motifs **A** giving rise to simple monocyclic products, the cyclisation modes on multifunctional type III PKSs can be classified into three types: 1) lactonisation through nucleophilic attack of the oxygen atom catalysed by plant-specific 2-pyrone synthases (2-PSs); 2) Claisen-type condensation through the C1–C6 bond formation by chalcone synthases (CHSs); 3) decarboxylative aldol type condensation catalysed by plant stilbene synthases (STSs). These cyclisation modes are strictly regulated by cavity sizes and active site structures in catalyst domain on the PKSs.[2]



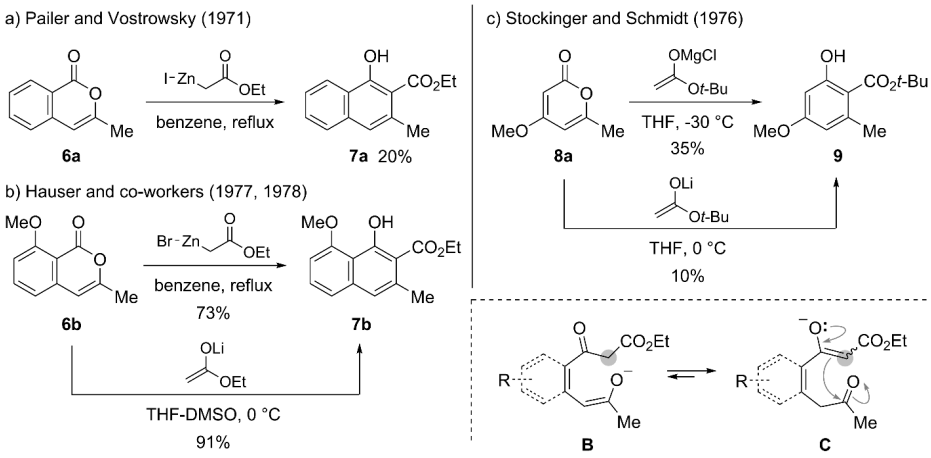
Scheme 1. Biosynthetic cyclisation modes in tetraketide motifs.

Reproducing such selective cyclisation reactions of acyclic polyketide chains in a flask has been a focus of research for over 100 years.[3] For the same purpose, γ- or α-pyrones have been utilised as masked polyketide equivalents. As early example, in 1893, Collie and Myers reported that orcinol **3** could be obtained by treating γ-pyrone **1** with barium hydroxide (Scheme 2a).[4] Here, the reaction should include intramolecular aldol reaction of triketone intermediate **2**. In 1966, Crombie and James reported a formation of phloroglucinol **5** from bispyrone **4** by means of $Mg(OMe)_2$ (Scheme 2b).[5]



Scheme 2. Pioneering works of multi-substituted arene synthesis from pyrenes.

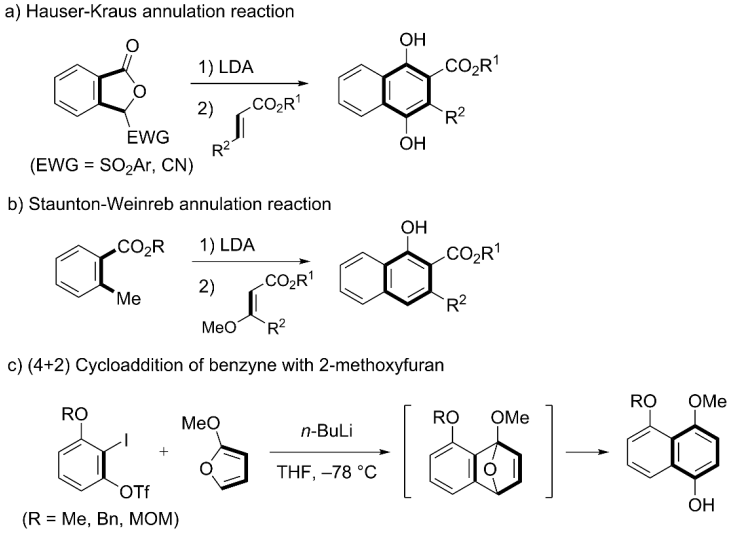
The latter means that the vinyl ester functionality in α-pyrone skeleton provides both pro-nucleophilic and pro-electrophilic carbon atoms for the ring construction. Considering structural variety of α-pyrone natural products and their significant importance in drug discovery, the value of such chemical imitations of biosynthetic reactions should be renewed. Especially, specific replacement of inner (ethereal) oxygen atom in bio-relevant isocoumarins with bicyclic structures to carbon atom ('carbon swap') would provide a powerful synthetic strategy for multi-substituted polycyclic aromatic compounds.[6] In this context, the reactivity of isocoumarins in traditional enolate chemistry is notable. For example, in 1971, Pailer and Vostrowsky reported that the reaction of isocoumarin **6a** with ethyl iodoacetate in the presence of zinc produced 1-hydroxy-2-naphthoate **7a** in 20% yields (Scheme 3a).[7] Hauser found that a slow addition of ethyl bromoacetate caused a significant improvement of the reaction to produce 2-naththoate product **7b** in 73% yield (Scheme 3b).[8,9] They also reported that the use of lithium enolates, instead of zinc enolates, improved the yield of 1-hydroy-2-naphthoates **7**.[10] On the other hand, in a report of similar reactions from α-pyrone **8** by Stockinger and Schmidt,[11,12] orsellinic acid ester derivative **9** was obtained in low yields (Scheme 3c).



Scheme 3. Pioneering works in isocoumarin skeletal editing.

From a mechanistic point of view, these reactions should include thermodynamically controlled isomerisation from primary enolate **B** to more stable enolate **C**, which underwent the intramolecular aldol condensation reaction. Such classical findings also reveal clear differences in the reactivity between isocoumarin and α-pyrone substrates. In a nucleophilic attack of enolates on isocoumarins, the carbonyl carbon is only reaction site. On the other hand, not only the carbonyl carbon but also the β- and δ-carbon atoms can serve as electrophilic sites for monocyclic α-pyrones.

In chemical synthesis of multi-substituted polycyclic aromatic compounds, chemists usually face two issues to be solved; 1) construction of polycyclic ring systems and 2) regioselective introduction of substituents. Therefore, multi-substituted polycyclic aromatic compounds has been considered as challenging synthetic targets.[13] From late 1970ies to 1980ies, Hauser,[14] Kraus[15] and others[16] successfully developed the [4+2]-benzannulation strategies through sequential Michael-Dieckmann type reaction, where phthalides and *ortho*-toluates served four carbon unit partners, towards total synthesis of tetracyclin antibiotics (Schemes 4a and 4b). Benzyne also participates as the two carbon source in the [4+2]-benzannulation with furan derivatives (Scheme 4c).[17] On the other hand, despite such long history, the isocoumarin skeletal editing with the *O*→*C* atom replacement, which corresponds to the [5+1]-annulation approach, has less attention and the reaction examples have been limited.



Scheme 4. Conventional [4+2]-approaches for multi-substituted naphthalene synthesis.

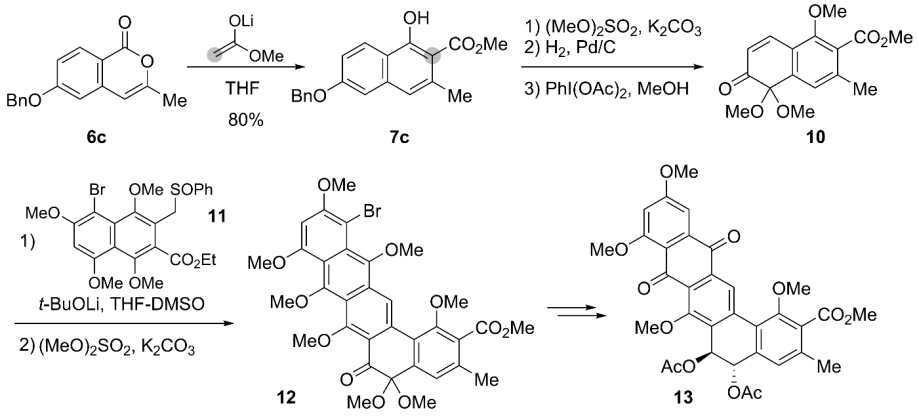
In this chapter, we provide an overview of the skeletal editing reactions using isocoumarin platforms including recent progress by the authors. In the most cases, the reaction examples of isocoumarins or further π-extended lactone substrates are selected in relation to the construction of polycyclic systems. However, some remarkable reactions of monocyclic α-pyrones are also included. For comprehensive information of the monocyclic α-pyrone chemistry, recent reviews in both chemical[18] and biological[19] aspects will be useful.

2. Synthesis of multi-substituted polycycles through isocoumarin skeletal editing

2.1. Reactions with enolates and related *C*-centred nucleophiles

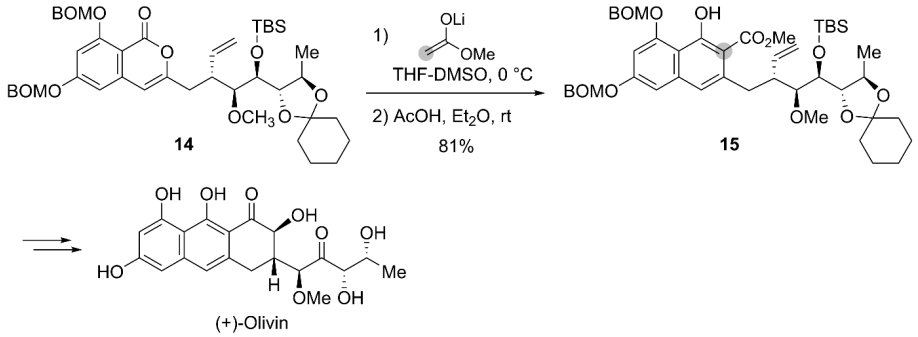
As mentioned above, the reactions of isocoumarins with enolates can be regarded as a prototype of isocoumarin skeletal editing with the *O*→*C* atom replacement. Nowadays, Hauser's modified conditions have been adopted for selective synthesis of substituted 1-hydroxy-2-naphthoates, which are useful building blocks for polycyclic aromatic natural products such as aromatic polyketides.[20] For example, a synthesis of antibiotic benanomicin-pradimicin analogue **13**, which has the benzo[*a*]naphthacene-8,13-quinone skeleton, by Hauser's research group would be a good example to follow the synthetic utility of the skeletal editing.[21] They

began the synthesis from the skeletal editing reaction of isocoumarin **6c** with a lithium enolate derived from methyl acetate to give multi-substituted naphthalene **7c** (Scheme 5). After methylation and debenzylation, $PhI(OAc)_2$-mediated dearomatic ketalisation successfully yielded an *ortho*-quinone mono-ketal **10**, which served as a reaction partner in the subsequent [4+2]-annulation. In the presence of *t*-BuOLi, the annulation reaction between **10** and phenylsulfinyl naphthoate **11** well proceeded and the desired benzo[*a*]tetracen-6(5*H*)-one **12** was isolated in a good yield after methyl etherification.



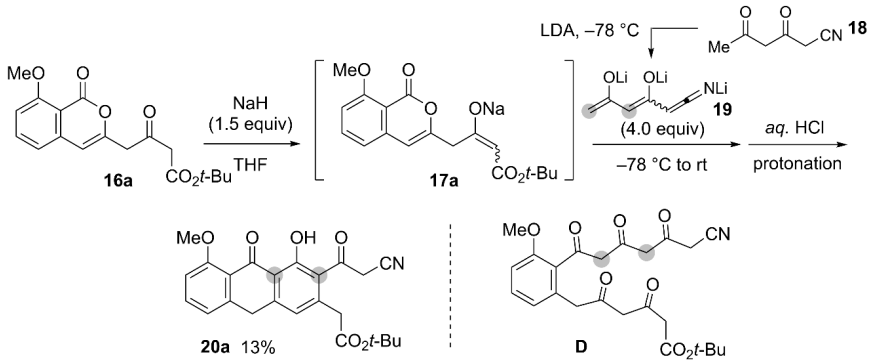
Scheme 5. Hauser's synthesis of a benanomicinone/pradimicinone aglycon analogue **13**.

The lithium enolate-mediated conditions sometimes require acidic work-up with acetic acid to achieve an improved yield of the desired naphthalene products. The acid treatment contributes smooth dehydration of aldol adducts. One of the leading works is found in Roush's total synthesis of (+)-olivin, an aglycon of olivomycine A. In 1992, they applied the isocoumarin ring editing reaction to the substrate **14** to obtain the product **15**, which was converted to olivine (Scheme 6).[22] Gimbert and co-workers reported similar conditions in his synthesis of hypoxyxylerone derivatives.[23]



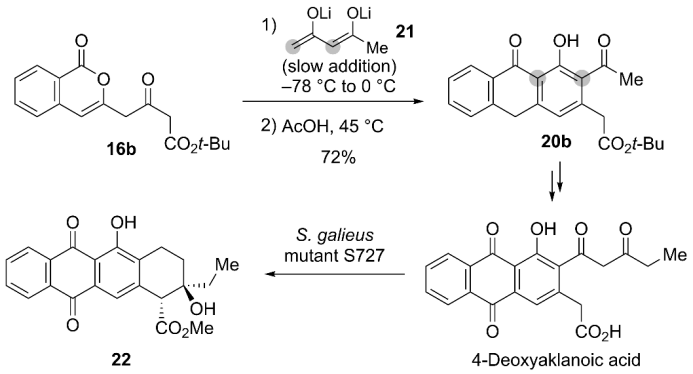
Scheme 6. Roush's total synthesis of (+)-olivin.

Not only simple enolates derived from acetic acid esters, but also di- and trianionic species of polyketones or ketoesters, were utilised in the isocoumarin skeletal editing along with further ring formations. In a pioneering work, Harris and co-workers reported the reaction of isocoumarin **16a** bearing an acetoacetate moiety at the 3-position with trianionic species **19** derived from 3,5-dioxohexanenitrile **18** and 3 equiv of LDA (Scheme 7).[24] In this case, pre-formation of mono-sodium salt **17a** by the treatment with NaH was essential and it slowly reacted with trianion **19** to give the desired anthrone **20a** in 13% yield after acidic workup and careful chromatographic purification. This transformation corresponds to the cyclisation of pentaketone **D**.



Scheme 7. Reaction of a trianion equivalent.

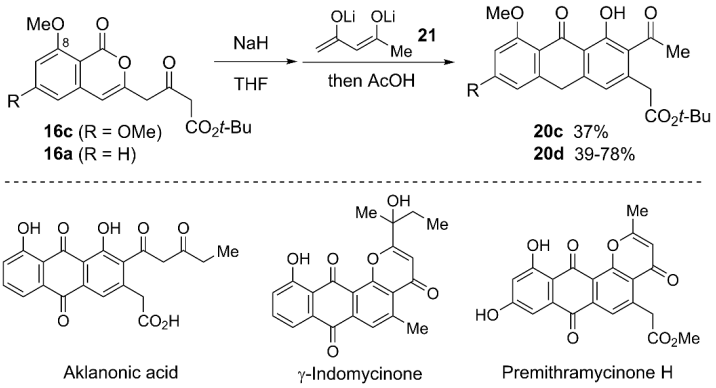
Krohn and co-workers have provided a series of systematic works.[25] For example, they reported that isocoumarin **16b** was effectively converted to the corresponding anthrone product **20b** (72% yield) through slow addition of acetylacetone dianion **21** followed by acid treatment (Scheme 8). According to conventional ways, the obtained anthrone **20b** was transformed to 4-deoxyaklanoic acid, which served as a substrate for fermentation by *Streptomyces galieus* mutant S727 to afford anthracyclinone **22** after one-day incubation in the culture medium.



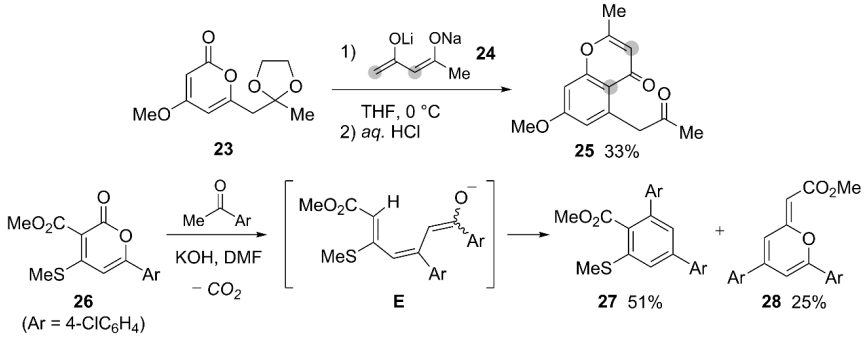
Scheme 8. Krohn's 'hybrid' synthesis of anthracyclinone **22**.

In the case of 8-methoxyisocoumarins **16a**, and **16c**, which could be regarded as useful synthetic intermediates for natural anthraquinones, pre-treatment of **16** with NaH was essential to obtain the desired anthrones **20** in acceptable yields (Scheme 9). Based on this methodology, the Krohn research group achieved the total syntheses of aklanonic acid,[25b] γ-indomycinone,[25c] and premithramycinone H.[25d]

As mentioned above, similar reactions of α-pyrone substrates are problematic because the nucleophilic attack of enolates usually occur at δ-position. Indeed, 1,2-addition required for the *O*→*C* atom replacement process are not favourable. Despite such difficulty, Stockinger and Schmidt[11] found that bimetallic dienolate **24**, which was generated from acetylacetone under the Yamaguchi conditions using NaH and *n*-BuLi, is relatively effective for the desired molecular tranformation.[26] This protocol was also applied in the synthesis of chromenone **25** from α-pyrone **23** by Tobinaga and co-workers (Scheme 10).[27] Tanyeli and Tarhan also examined that several carbanions derived from β-ketoesters, ethyl acetate, acetonitrile, and dimethyl sulfoxide were applicable for the *O*→*C* replacement.[12a] In this context, the reactions of 4-sulfanylpyrones by Ram and co-workers provide interesting aspects;[18c] the reaction of α-pyrone **26** with a methylketone enolate yielded terphenyl **27** and divinyl ether **28** (Scheme 10).[28] The reaction proceeded *via* acyclic intermediate **E**, which generated by 1,6-addition-tiggered ring opening followed by decarboxylation.



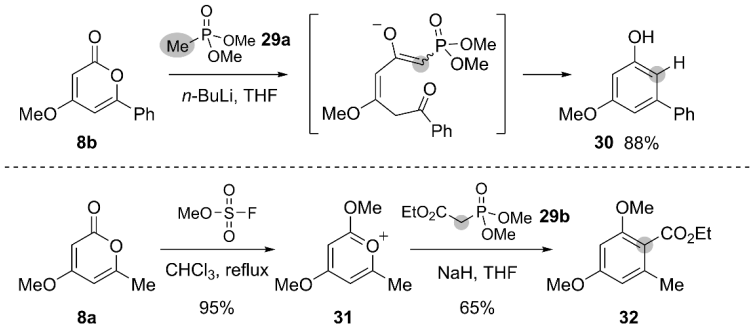
Scheme 9. Reactions of 8-methoxyisocoumarins with dienolates.



Scheme 10. Reaction of α-pyrone with enolates.

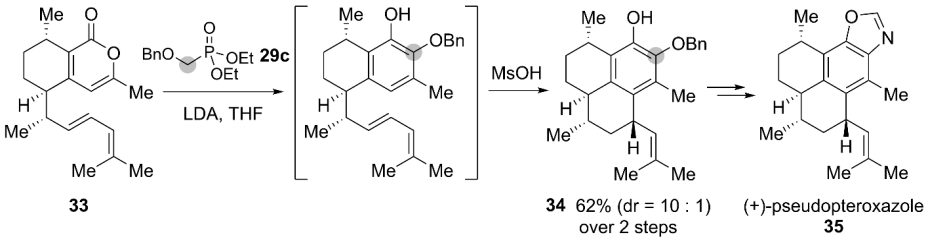
2.2. Reactions with α-carbanion of methylphosphonates

In the above work by Tanyeli and Tarhan, it was mentioned that a carbanion generated from dimethyl methylphosphonate **29a** and *n*-BuLi did not produce 2-phosphorylphenol, but 2-unsubstituted phenol **30** in good yield (Scheme 11).[12a] This implies that the reaction sequence includes intramolecular Horner-Wadsworth-Emmons (HWE) reaction as the ring closure step. Staunton and Griffin found that 2-methoxypyrylium ion **31**, which was generated by *O*-methylation of α-pyrone **8a**, was successfully converted to orsellinic acid derivative **32** in a good overall yield by reaction with phosphonoacetate **29b**.[29] In fact, similar reactivity of pyryliums with phosphorous ylides was reported in early 1960's by Märkl.[30]



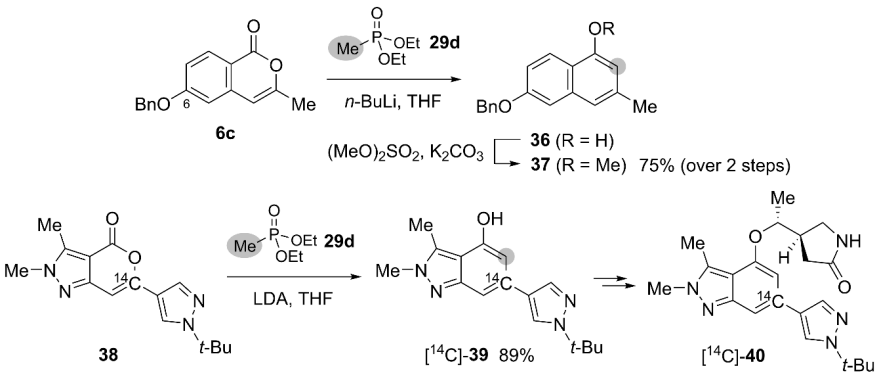
Scheme 11. Reactions of α-pyrones with α-carbanions of methylphosphonates.

Recently, Luo and co-workers extended this chemistry to replace the inner oxygen atom with carbon (Scheme 12).[31] The reaction of bicyclic pyrone **33** with (α-benzyloxy)methylphosphonate **29c** afforded **34** after acid-mediated cyclisation reaction. From this product, the syntheses of (+)-pseudopetroxazole **35** and related natural products were successfully achieved. This procedure is an effective protocol to construct less accessible 1,2,3-trisubstituted benzene systems.



Scheme 12. Luo's synthesis of (+)-pseudopetroxazole.

Although similar reactions of isocoumarins have not been studied well, Hauser and co-workers reported one example using 6-benzyloxyisocoumarin **6c** to give 2-unsubstituted naphthalene **36**, which was isolated as methyl ether **37** in a good overall yield (Scheme 13).[32] Moreover, Latli and co-workers reported the synthesis of ^{14}C-labelled BI 1342561 ([^{14}C]-**40**),[33] which was a potent inhibitor towards the spleen tyrosine kinase[34] from naphthol **39** prepared by the reaction of ^{14}C-labelled lactone **38** with **29d**.



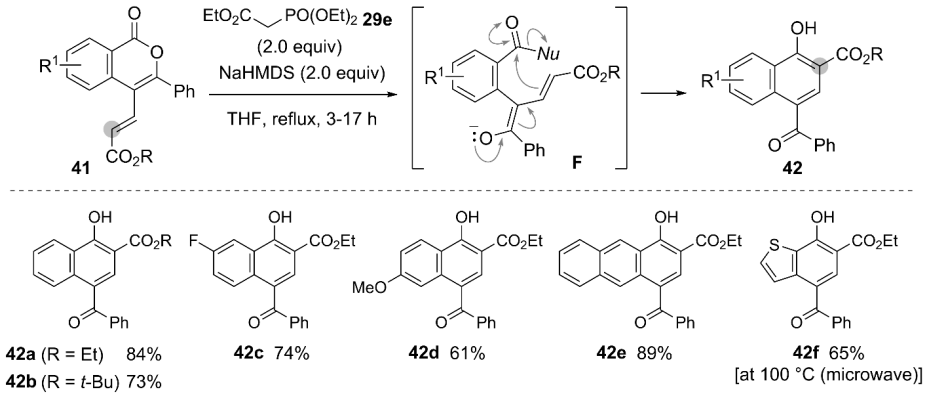
Scheme 13. Reactions of isocoumarins with phosphorous ylides.

The authors recently reported that isocoumarins **41** bearing acrylate moiety as 3-substituent underwent intramolecular vinylogous aldol condensation after nucleophilic ring-opening process (Scheme 14).[35] The anionic species derived from α-phosphonoacetate **29e** and sodium bis(trimethylsilyl)amide (NaHMDS) was found as an effective nucleophilic promotor for the ring rearrangement reaction to give 1-hydroxy-2-naphthoates **42**, which included intramolecular nucleophilic acyl substitution step of **F**. Here, dienoate moieties in the isocoumarin substrates served as latent dienolates during the cascade process. In this reaction system, products deriving from intramolecular HWE reaction were not formed at all. Unfortunately, the use of a catalytic amount of **29e** and NaHMDS was less effective to obtain the products in good yields.

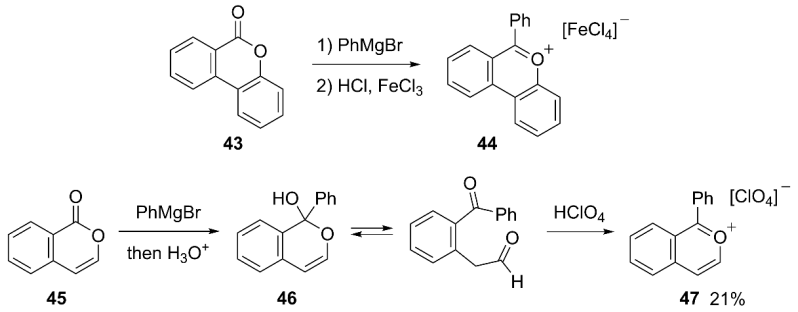
2.3. Reactions with organometallic reagents

In 1908, Decker and Felser reported a synthesis of pyrylium species **44** through the reactions of lactone **43** with PhMgBr followed by acid-mediated dehydration of the lactone intermediate (Scheme 15).[36] After this work, the same protocol with aryl Grignard reagents was widely utilised for the synthesis of several pyrylium salts. For instance, Shriner and co-workers applied this chemistry to isocoumarin **45**, and pyrylium species **47**

was obtained in 21% yield.[37] It was also mentioned that lactol **46** generated by aqueous work-up was in equilibrium with 1,5-ketoaldehyde form.

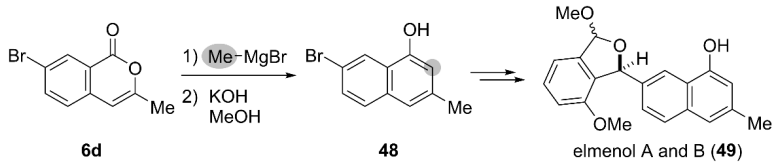


Scheme 14. Ring rearrangement reaction of 4-alkynylisocoumarins **41** promoted by phosphorous ylides.



Scheme 15. Reactions of lactones with Grignard reagents.

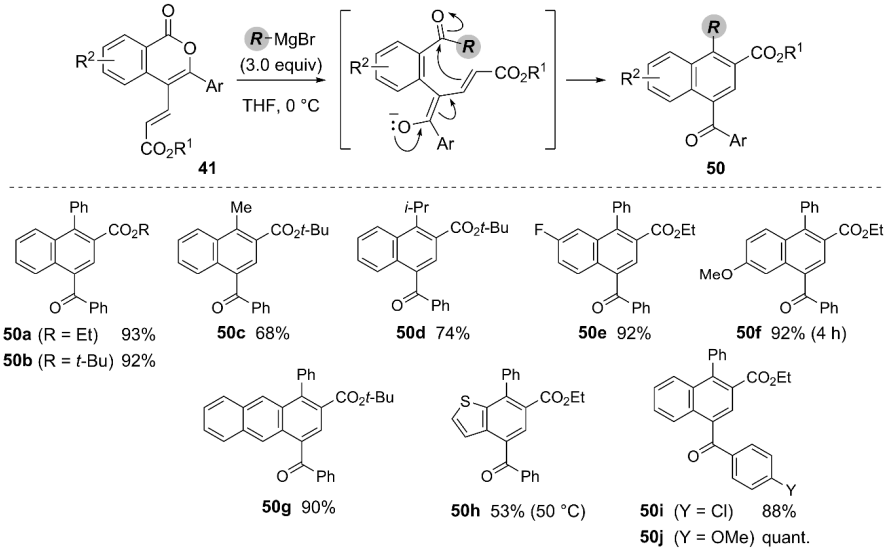
On the other hand, Aycard and co-workers reported the reactions of isocoumarins with alkyl Grignard reagents brought about the skeletal editing with the *O*→*C* atom replacement.[38] Recently, Mikhaylov applied the reaction of isocoumarin **6d** with MeMgBr to synthesise a key intermediate **48** for total synthesis of elmenols A and B **49** (Scheme 16).[39]



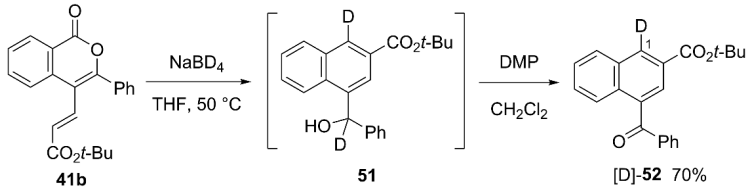
Scheme 16. Mikhaylov's synthesis of elmenols A and B **49**.

In 2024, the authors reported that 4-alkenylisocoumarins **41** reacted with several Grignard reagents to give the naphthalene products **50** in good yields (Scheme 17).[35] Again, the dienyl ester moieties embedded in the isocoumarin substrates worked as latent dienolates, therefore, anionic carbon atom of the Grignard reagent was incorporated as 1-substituent. Likewise, $NaBH_4$ was found to be used as suitable nucleophiles in similar reaction ring rearrangement reaction.[35] In particular, the reaction using $NaBD_4$ was useful for regioselective incorporation of deuterium atom on the 1-position of the naphthalene skeleton (Scheme 18). For example, the

reaction of **41b** with $NaBD_4$ yielded secondary alcohol **51**, which was oxidized to yield 1-deuterionaphthalene [D]-**52.**



Scheme 17. Ring rearrangement reaction of 4-alkynylisocoumarins **41** using Grignard reagents.



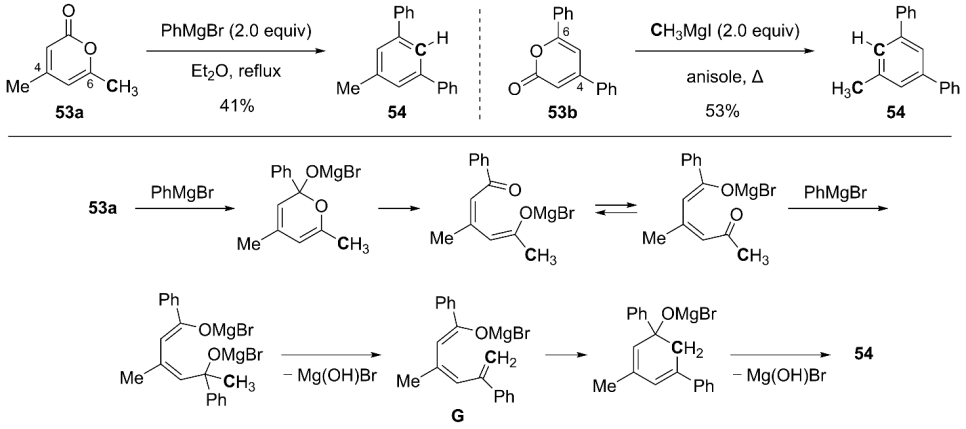
Scheme 18. Reaction of 4-alkynylisocoumarin **41b** using $NaBD_4$.

A publication by Gompper and Chritmann in 1961 brings our attention to the unique reactivity of α-pyrones in the Grignard reactions (Scheme 19).[40] When α-pyrones were slowly added to a solution of aryl Grignard reagents, 1,1-diaryl-α-pyranes was mainly formed.[41] By contrast, quick addition or reverse addition of aryl Grignard reagents (α-pyrones are always present in excess) resulted in a selective formation of multi-substituted benzenes as the products. For example, 4,6-dimethyl-α-pyrone **53a** was converted to 3,5-diphenyltoluene **54** in 41% yield. Interestingly, the same product was obtained by slow addition of MeMgI to 4,6-diphenyl-α-pyrone **53b**. The proposed reaction paths from **53a** to **54** included the 6π-electrocyclic ring closure of triene intermediate **G**, which generated *via* nucleophilic ring-opening and the second addition of PhMgBr followed by elimination of Mg(OH)Br. The mechanistic discussions were also provided by other groups.[42]

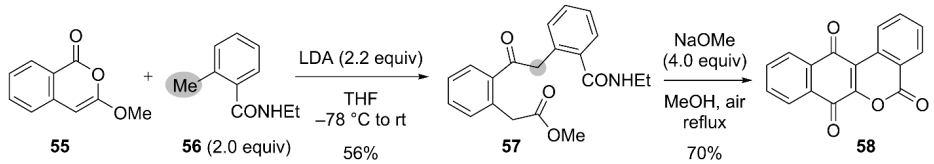
Benzylmetallic species are also useful reagent for the 'carbon swap' of isocoumarin skeleton. For example, Watanabe and co-workers described that the reaction of 3-methoxyisocoumarin **55** with benzyl carbanion derived from *o*-toluamide **56** and LDA gave the ring-opening product **57**, which was easily converted to tetracyclic compound **58** by heating in a NaOMe/MeOH solution under air atmosphere (Scheme 20).[43] This reaction was also applied to the synthesis of antibiotic WS-5995A.

Similar molecular transformation was achieved in Trauner's synthetic study toward 2',5'-oligoadenylate phosphodiesterase (2'-PDE) inhibitor A-74528, which was isolated from *Steptomyces* sp. SANK 61196 (Scheme 21).[44] In this synthesis, naphthol **61** was synthesised in 70% yield by the reaction of isocoumarin **59** with benzyl anion derived from orsellinic acid derivative **60** and the following treatment of diketone

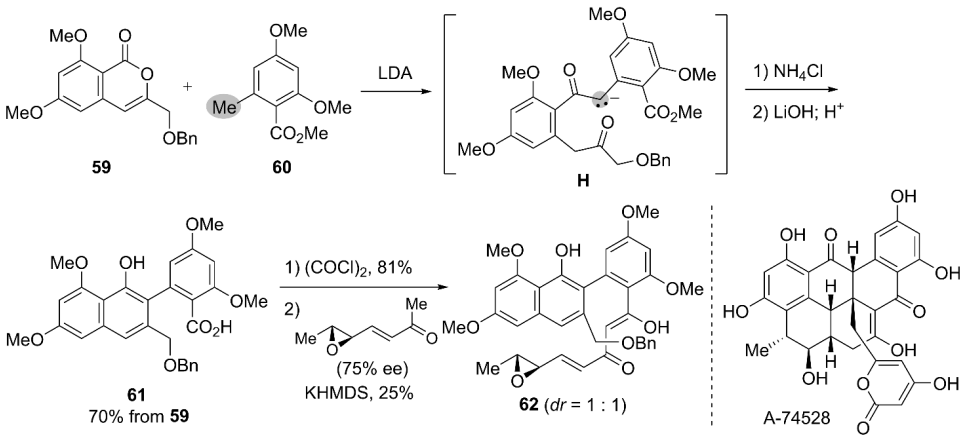
intermediate **H** with NH_4Cl and LiOH. After installing a chiral epoxide side chain, biaryl product **62** was obtained in a low yield as a mixture of two diastereomers.



Scheme 19. Reactions of α-pyrones with Grignard reagents.



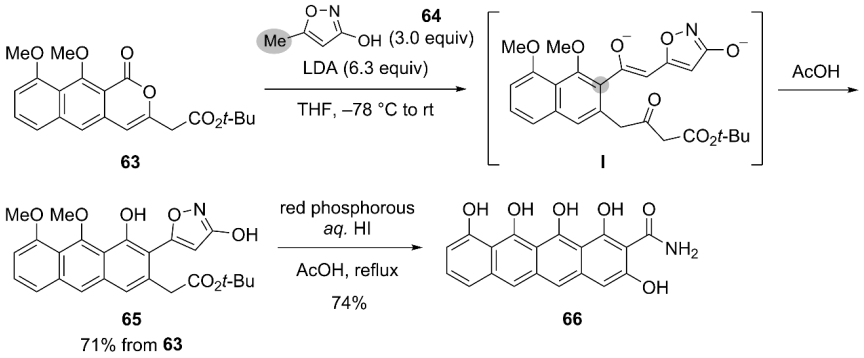
Scheme 20. Reaction of 3-methoxyisocoumarin **57** with toluamide.



Scheme 21. Trauner's synthetic study of 2'-PDE inhibitor A-74528.

3-Hydroxy-5-methylisoxazole **64**, which was introduced by Harris and coworkers in 1988, is a unique synthetic equivalent for β-ketoamide structures (Scheme 22).[45] The π-extended benzo-isocoumarin **63** bearing *tert*-butyl acetate pendant as the 3-substitutent reacted with the dianion species generated *in situ* by premixing of **64** and *ca.* 2 equiv of LDA to produce the *C*-acylation intermediate **I**, which easily cyclised by subsequent stirring in AcOH to give anthracene-isoxazole **65** in 71% yield. Further ring closure between substituents on the anthracene skeleton was enabled by heating in acetic acid-hydroiodic acid containing red phosphorous to

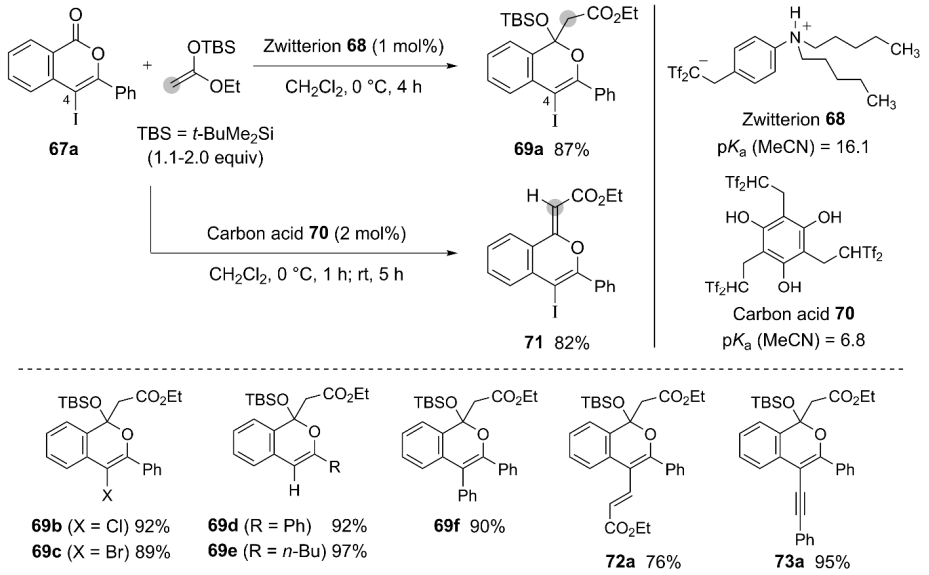
give pretetramide **66** in 74% yield.



Scheme 22. Reaction using 3-hydroxy-5-methylisoxazole as a β-ketoamide equivalent.

3. Isocoumarin-based lactol silyl ethers as potent platforms for 'carbon swap'

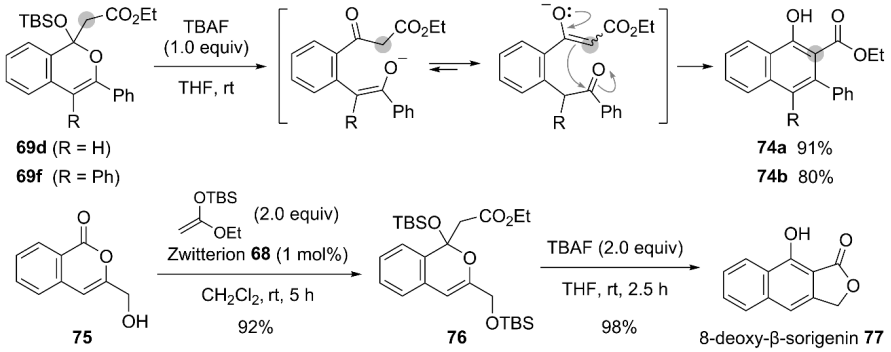
In 2013, it was reported that the reaction of isocoumarins **67** with a ketene silyl acetal derived from ethyl acetate nicely promoted by anilinium type zwitterion **68** to give the corresponding adducts **69** in good to excellent yields (Scheme 23).[46] By contrast, the same reaction using superacidic carbon (C–H) acid **70**[47] instead of zwitterion **68** caused selective formation of divinyl ether **71**, which is the E1 product of the adduct.[48] Notably, in the zwitterion-mediated case, acid sensitive functionalities including the silyl ketal and vinyl ether moieties in the products **69** were totally tolerated and a wide range of lactol silyl ethers **69**, **72**, and **73** were obtained in good to excellent yields. The significantly higher pK_a value of zwitterion **68** (16.1) in acetonitrile,[49] compared to the values of carbon acid **70** (6.8) and sulfuric acid (7.2),[50] accounts for the specific activation of the lactonic carbonyl group.



Scheme 23. Divergent synthesis of lactol silyl ether **67a** and divinyl ether **71**.

The lactol silyl ethers (LSEs) thereby obtained can be regarded to be isolable forms of the tetrahedral intermediates in the nucleophilic acyl substitution chemistry. Therefore, we predicted that fluoride-induced

desilylative activation of the LSEs brought about naphthalene formation similar to the reaction of isocoumarins with enolates (Scheme 24). Upon treatment with tetrabutylammonium fluoride (TBAF) at room temperature, LSEs **69d**, **69f** were converted to 1-hydroxy-2-naphthoate products **74** in excellent yields. This protocol was also applied to a short-step synthesis of 8-deoxy-β-sorigenin **77**.[46] Here, zwitterion-mediated reaction of isocoumarin **75** with 2.0 equiv of a ketene silyl acetal yield LSE **76**, which gave **77** by means of TBAF.



Scheme 24. The '*O*→*C*' ring rearrangement reaction.

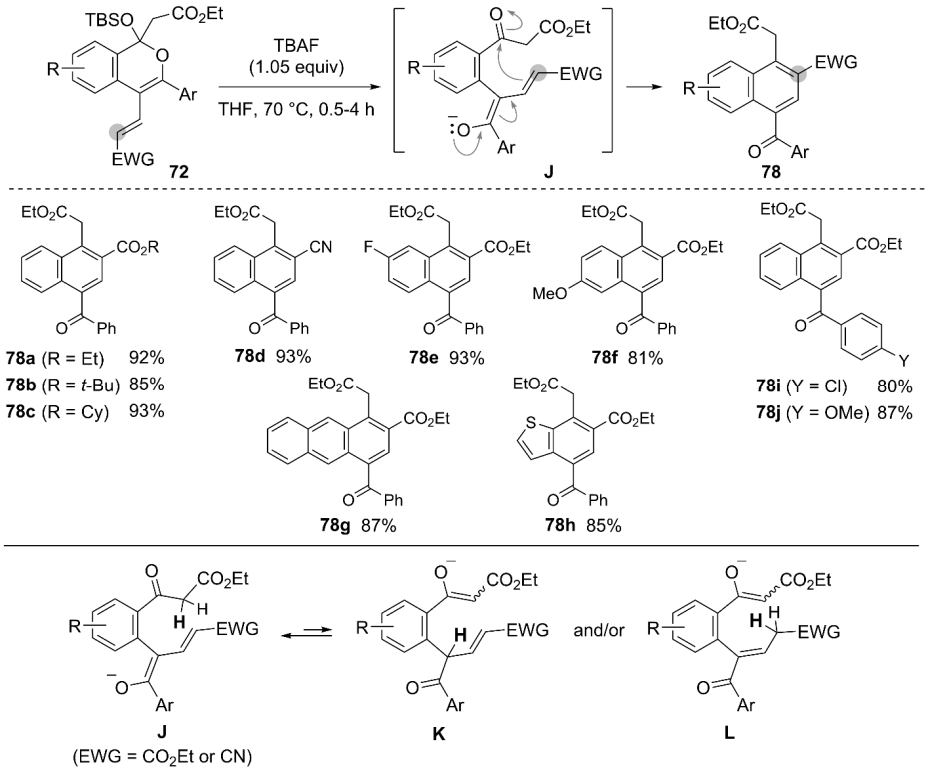
3.1. Ring rearrangement reactions of isocoumarin-based lactol silyl ethers

Considering high accessibility of 4-substituted isocoumarins[51,52] and a broad substrate scope of the zwitterion-induced addition reaction of KSAs, the LSE framework were an attractive platform for the selective synthesis of multiply substituted naphthalenes and related polycyclic compounds. In this context, the authors recently reported that similar reaction from LSEs **72** bearing electron-deficient alkene moiety as the 4-substituents gave benzo-homophthalates **78** in a totally different cyclisation mode (Scheme 25).[35] For example, several acrylates **72a-c** (EWG=CO_2R) and acrylonitrile **72d** (EWG=CN) were converted into the corresponding benzo-homophthalates **78a-d** without formation of other products. Likewise, substituted naphthalenes **78e**, **78f**, anthracene **78g**, and benzothiophene **78h** were obtained in good to excellent yields. The dienyl ether moieties in the LSE substrates served as potential dienolate equivalents because elongated π-conjugation in initial intermediate **J** made it more stable than possible isomers **K** and **L**, in which the acidity of the vinylogous β-ketoester moieties were stronger than that of the β-ketoester moiety in **J**.

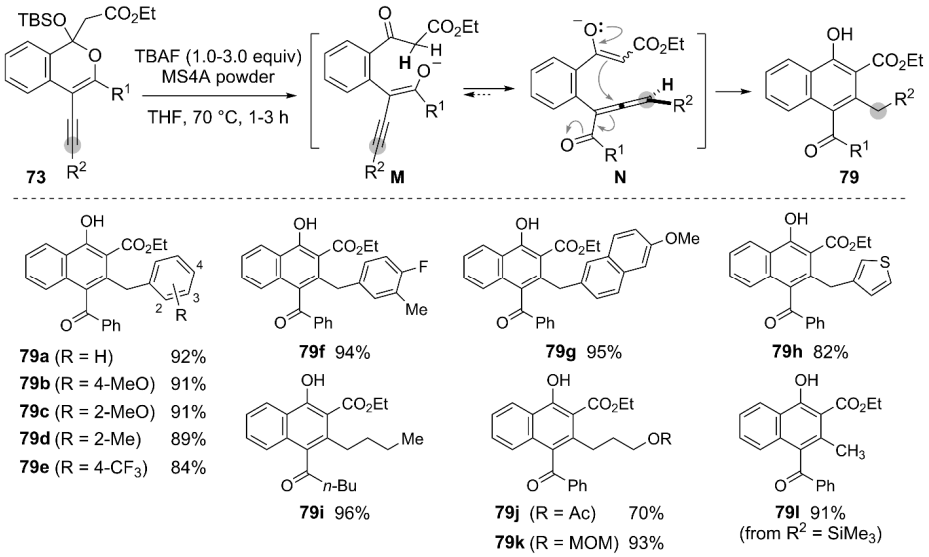
The reaction outcome of 4-alkynyl LSEs **73** also needs special notice. In this case, the treatment of **73** with TBAF in the presence of molecular sieves (MS) 4A cleanly yielded 1,2,3,4-tetrasubstituted naphthalenes **79** (Scheme 26).[53] The substitution pattern in the products implied that the ring closure proceeded *via* intramolecular Michael reaction of allenone intermediate **N**, which was formed by thermodynamically favourable proton transfer from primary enolate intermediate **M**. This reaction was successfully applied to a wide range of reaction substrates and yielded less accessible naphthalene products **79**, which have totally different substituents on each carbon atom in the naphthalene skeleton.

Interestingly, a careful design of the reaction substrate enabled more complex cascade reaction. Specifically, LSE **80** bearing an enyne pendant as a 4-substitutent afforded tetracyclic product **81** under gentle heating conditions (Scheme 27). The reaction includes 6π-electrocyclisation followed by dehydrative aromatisation.

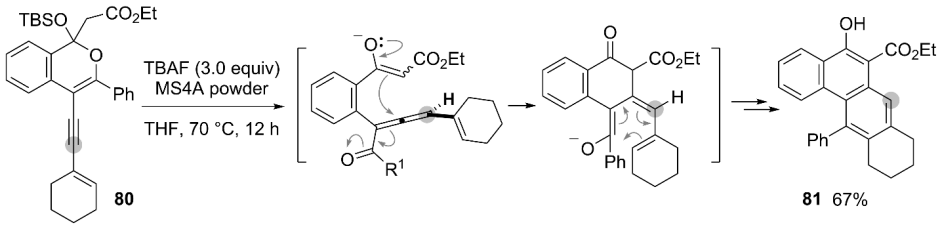
Several 4-halogenated LSEs also exhibited slightly different reactivity, yielding only a messy mixture under conventional TBAF-mediated conditions.[54] On the other hand, when a series of 4-brominated LSEs **69** was heated in acetic acid containing sodium acetate, 4-aryl-1,3-dihydroxy-2-naphthoates **82** were obtained (Scheme 28). It was found that such LSE substrates were rapidly converted to the corresponding divinyl ether **71** under the present conditions. Therefore, the addition-elimination reaction of **71** with acetate ion and the following nucleophilic acyl substitution were proposed as a most likely reaction path for the formation of α-bromoketone intermediate **O**. The subsequent aldol reaction probably produces intermediate **Q**, which underwent the semipinacol rearrangement as the 1,2-Ar migration step.[55]



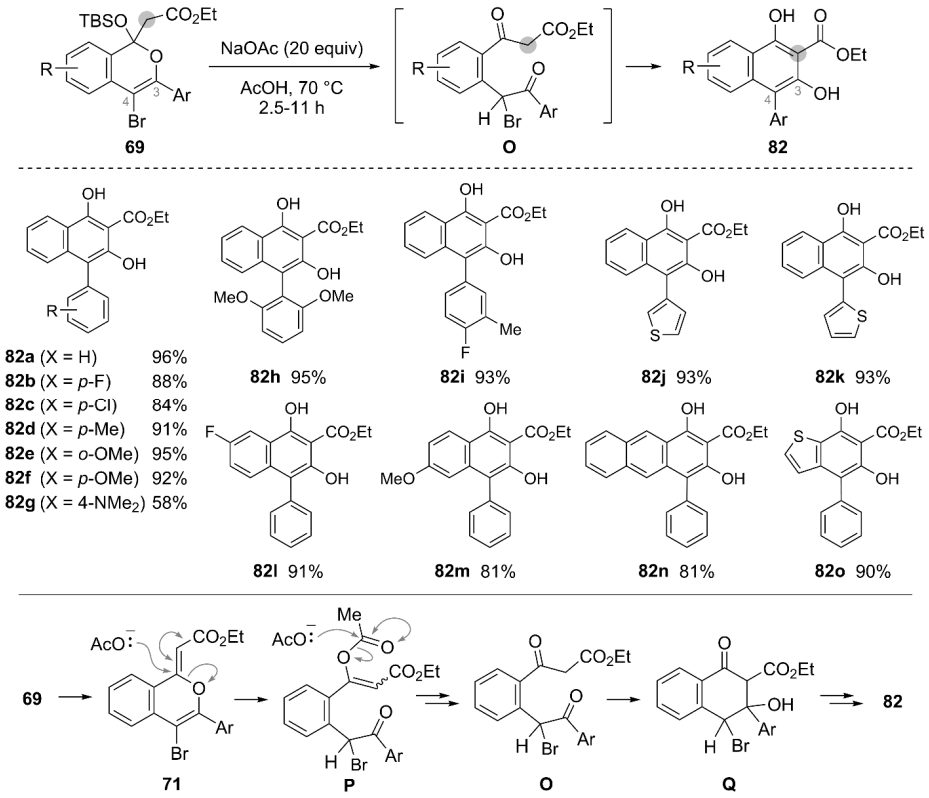
Scheme 25. The '*O*→*C*' ring rearrangement reaction including intramolecular vinylogous aldol reaction.



Scheme 26. The '*O*→*C*/*C*→*C*' ring rearrangement reaction.



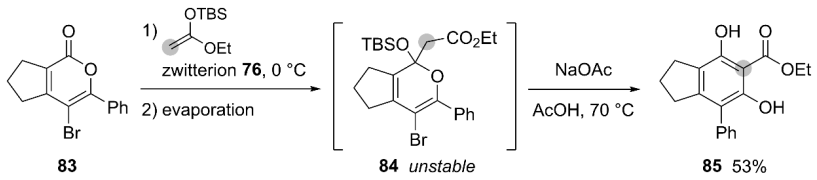
Scheme 27. TBAF-mediated ring rearrangement reaction of 4-alkynyl derivatives.



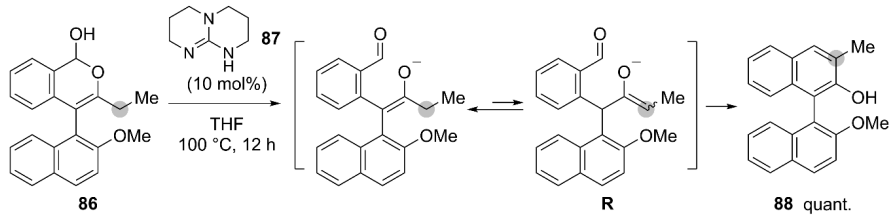
Scheme 28. 1,2-Ar Migrative ring rearrangement reaction of 4-bromined LSEs.

One-pot protocol containing the zwitterion-induced addition reaction and the 1,2-Ar migrative ring rearrangement reaction enabled to avoid isolation of less stable LSEs derived from α-pyrones (Scheme 29). For example, all substituted benzene **85** was obtained in 53% yield from α-pyrone **83** by heating the crude material containing **84** in NaOAc-AcOH.

As the related reaction, Terada and Dan reported a ring rearrangement reaction of isocoumarin-based LSE **86** (Scheme 30).[56] The reaction was catalysed by 10 mol% of a strong organic base **87**, 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD), to give binaphthyl **88** through intramolecular aldol condensation of thermodynamically less favourable enolate **R** as the ring closing step. Regrettably, the asymmetric version with chiral organic bases yielded the product in a low yield with poor enantioselectivity.



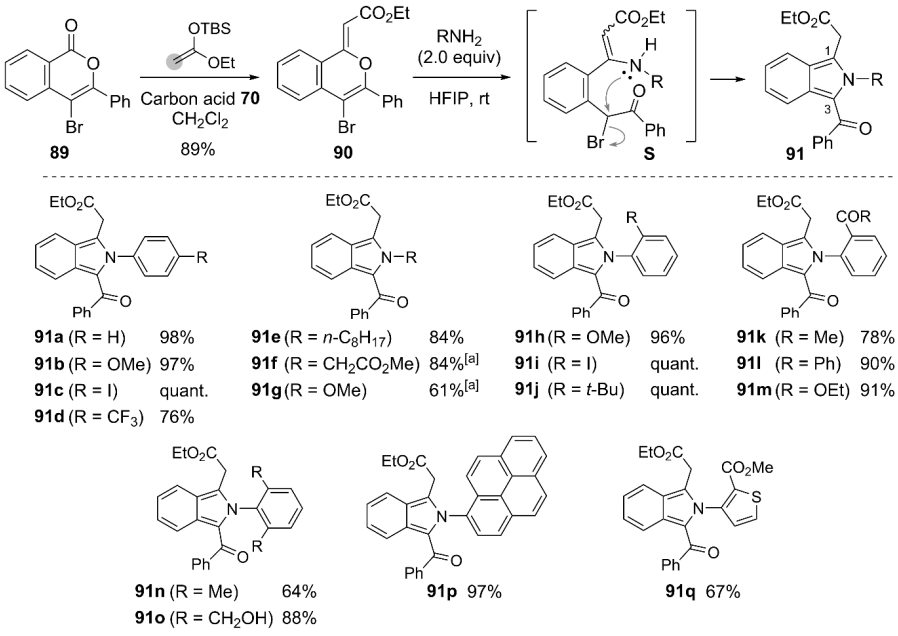
Scheme 29. One-pot synthesis of all substituted benezene.



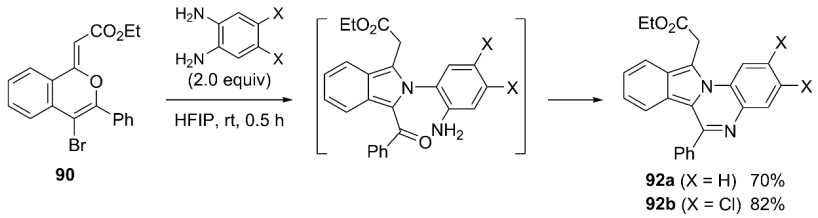
Scheme 30. TBD-Catalysed formation of binaphthyl.

3.2. Synthesis of π-extended heterocycles through ring rearrangement strategy

The reaction of isocoumarins with ammonia is a well established protocol for the synthesis of isoquinolin-1(2*H*)-ones (*O*→*N* replacement). On the other hand, the authors reported a new two-step skeletal editing of pyrane ring to pyrrole ring in 2023.[57] Brominated divinyl ether **90**, which was obtained by the reaction of isocoumarin **89** with a ketene silyl acetal in the presence of carbon acid catalyst **70**, underwent with several primary amines in 1,1,1,3,3,3-hexafluoroisopropyl alcohol (HFIP) to produce enamine intermediates. This reactivity was successfully applied to a selective synthesis of multi-substituted 2*H*-isoindoles **91** *via* 5-*exo*-*tet* cyclisation of intermediate **S** (Scheme 31). Under similar conditions, the reaction of **90** with 1,2-phenylenediamines afforded isoindolo[2,1-*a*]quinoxaline derivatives **92** through the isoindole-forming reaction followed by intramolecular imine formation (Scheme 32).

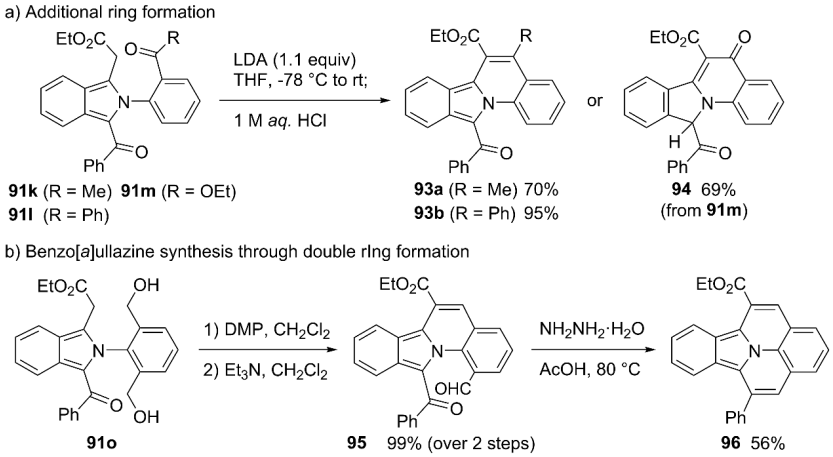


Scheme 31. Selective synthesis of 2*H*-isoindoles **91**.



Scheme 32. Isoindolo[2,1-*a*]quinoxaline synthesis through the reaction with 1,2-phenylenediamines.

Fortunately, our isoindole-forming reaction proceeded smoothly even with sterically and/or electronically less nucleophilic *ortho*-substituted anilines as the reaction partner. This represented an advantage for further ring formation between the isoindole and benzene moieties. For example, 2-arylisoindoles bearing electrophilic carbonyl functionalities at the *ortho*-position of the benzene pendant easily afforded the corresponding tetracyclic compounds **93a**, **93b**, and **94** using LDA (Scheme 33a). Likewise, the dialdehyde derived from 2,6-bis(hydroxymethyl)benzene **91o** underwent intramolecular aldol condensation reaction to give tetracycle **95** in the presence of Et_3N (Scheme 33b). Moreover, this product was successfully converted into the novel nitrogen-doped π-system **96**, namely benzo[*a*]ullazine, by hydrazine-mediated reductive cyclisation.[58]



Scheme 33. Conversions to several 2*H*-isoindole-based polycyclic systems.

This synthesis of isoindole-based polycycles allowed strict comparisons of molecular geometries among *N*-arylisoindole **91j**, isoindolo[2,1-a]quinolone **93b**, and benzo[*a*]ullazine **96**. As shown in Figure 1a, the X-ray crystallographic structure of *N*-(2-*tert*-butylphenly)isoindole **91j** revealed large torsion around the N–C_{Ar} bond axis (twisting angle τ=84.4°). By contrast, isoindolo[2,1-*a*]quinolone **93** presented a near planar geometry of the π-system (τ=10.4°) and two-fold bridging in benzo[*a*]ullazine **96** resulted in completely planer π-structure (τ≈0°) (Figures 1b and 1c). Interestingly, by decreasing the twist angle, the lengths of the central N–C_{Ar} bond were significantly shorten. Such highly shorten N–C_{Ar} bond in **96** well supported its enhanced double bond nature and peripheral 18π aromaticity in the benzo[*a*]ullazine skeleton.[59] The isocoumarin skeletal editing opens the door to new chemistry of nitrogen-doped polycyclic aromatic hydrocarbons.

As an interesting example of ring rearrangement reaction yielding nitrogen-containing heterocycles, in 2021, Sarpong and co-workers reported a rearrangement reaction of 3-indolyl-α-pyrone **97a** to yield pyrido[1,2-*a*]indole **98**, which enabled an *O*⟶*N* ring rearrangement initiated by nucleophilic ring opening step with NaOMe (Scheme 34).[60] Interestingly, under similar conditions, *N*-methylindole **97b** and aniline **100** yielded the corresponding carbazole **99** and naphthalene **101**, respectively. These reactions proceeded *via*

C-alkylation step as the ring closing step. Recently, they also reported a unique synthesis of anilines from 3-alkynyl-α-pyrone with amines.[61]

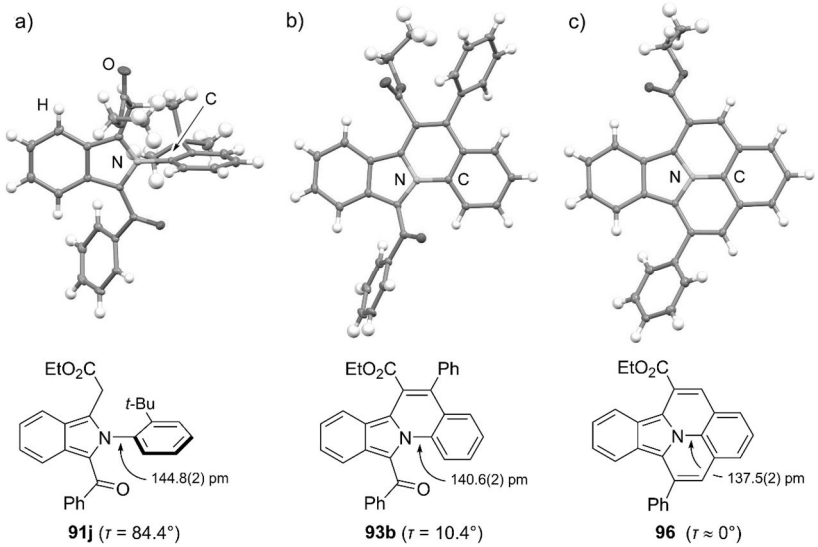
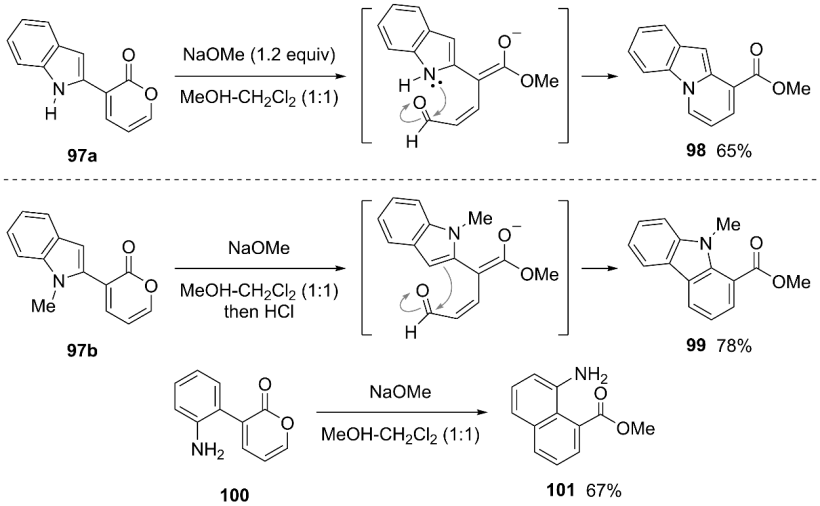


Figure 1. X-ray structures of polycyclic isoindoles and their key geometric parameters.



Scheme 34. Sarpong's ring remodeling of α-pyrone skeleton.

4. Conclusion

In this chapter, we have provided an overview of isocoumarin skeletal editing with *O*→*C* atom replacement, namely 'carbon swap'. Many reactions are triggered by a well-established nucleophilic acyl substitution process as the ring opening of α-pyrone motif embedded in the bicyclic structure. It should be noted that much higher reactivity of the conformationally restricted, cyclic vinyl ester functionality in nucleophilic acyl substitution reactions favours the formation of the ring opening intermediates, which usually underwent intramolecular aldol condensation reaction as a ring closing step. The synthesis of multi-substituted

polycyclic aromatic compounds based on such [5+1]-approach has attracted less attention, compared to the widely used [4+2]-benzannulation approach. However, they should be re-evaluated as pioneering works in the modern context of skeletal editing.

As illustrated in the latter part, we have shown that a careful choice of the latent reactive substituents on the isocoumarin skeleton provides a powerful strategy for ensuring diversity of cyclisation modes. Using LSE substrates programmed fundamental reaction processes, reprogramming of the ring structure triggered by chemical treatments has been achieved. In addition to such new 'carbon swap' reactions, the development of olefination reactions of lactonic carbonyl functionalities, enabled by the superacidic carbon acid catalyst, is important because the reaction realised to introduce a pro-nucleophilic carbon atom into the isocoumarin 1-position. This finding caused that the isocoumarin ring editing was expanded from the simple *O→C* atom replacement reaction to more complex variations such as our isoindole forming reaction.

Isocoumarins are structurally simple and easily preparable. In addition, a number of simple isocoumarins exhibit diverse bioactivities including antibacterial, antiviral, and anti-cancer activities. Therefore, the isocoumarin skeletal editing with *O→C* atom replacement enables not only the 'salvage' synthesis of multi-substituted polycyclic compounds, but also the direct and rapid derivatisation of such interesting isocoumarin natural products. The authors are ongoing in the way to find new aspects and applications of the isocoumarin skeletal editing.

Acknowledgement

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