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REVIEW ARTICLE

The Petasis-Ferrier rearrangement: developments and applications

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In the mid-1990s, Petasis reexamined a promising but infrequently used rearrangement strategy, the so-called Ferrier-type-II reaction, and provided it with a modern update. Previously, Ferrier had developed a strategy where carbohydrate derivatives would undergo a fragmentation/aldol-type recombination sequence, generating a carbocycle, albeit under the promotion of stoichiometric mercury salts. Petasis' new variant showed the promise to effectively and stereoselectively convert a range of cyclic vinyl acetals to useful tetrahydrofurans and tetrahydropyrans, using less toxic promoters. Since these first reports, the 'Petasis-Ferrier rearrangement' has represented a vibrant area of research and innovation for organic chemists. With numerous applications in complex natural product total synthesis, the utility of the reaction has been resoundingly established. Recent developments have extended the reaction to a broader synthetic context, allowing for *in situ* generation of rearrangement substrates and more liberal interpretation of what fragmentation/recombination reactions warrant the designation of a Petasis-Ferrier rearrangement.
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INTRODUCTION—ORIGINS AND DEVELOPMENT OF THE PETASIS-FERRIER REARRANGEMENT

In modern organic synthesis, value is placed on reactions that significantly increase structural complexity and/or utility. Molecular rearrangements can be premier examples of such reactions; radical, ionic and pericyclic rearrangements challenge the creativity of the organic chemist with the promise of elegant and efficient synthetic routes. One of the pioneers in this field was carbohydrate chemist Robert J (Robin) Ferrier, who disclosed two distinct and widely recognized oxocarbenium-based rearrangement strategies that now bear his name. In 1962, Ferrier *et al.*[1] published the preparation of C2–3 glycals from readily available C1–2 glycals, as shown in Figure 1a. This reaction has gained widespread use in the carbohydrate field, and is often referred to as a Ferrier-type-I reaction.

In 1979, Ferrier disclosed a convenient procedure for the assembly of carbocyclic intermediates from carbohydrate analogs, in a reaction that became known as a Ferrier-type-ll reaction (Figure 1b).[2,3] In this 'type-ll' reaction, Ferrier found that heating C5–6 unsaturated pyranose **3** to reflux in aqueous acetone, with the promotion of stoichiometric $HgCI_2$, furnished ketone **4** in 83% yield as a single isomer. The mechanism Ferrier presented for this rearrangement is presented in Figure 1c. First, the alkene of **3** is hydroxymercurated in a Markovnikov sense, furnishing unstable hemiketal intermediate **5**. After fragmentation, which leads to two carbonyls and expulsion of methanol, the liberated mercury enolate **6** undergoes an intramolecular aldol reaction, affording cyclohexanone **4**. In subsequent optimization studies, mercury trifluoroacetate was recognized as the promoter of choice, capable of affecting similar rearrangements in catalytic amounts (<10 mol %) at room temperature in a matter of hours, as well as tolerating a variety of substituents on the molecule.[4] A notable feature of the Ferrier-type-II reaction is the observed stereoselectivity in formation of the free hydroxyl center; a single diastereomer is commonly observed as the sole reaction product. Stereochemical rationalizations invoked a chelation effect (**6B**) of the C3 substituent, suggested by the observed correlation of C3 configuration with the stereochemistry of the installed hydroxyl group.

In 1995 and 1996, Petasis and Lu[5,6] reported modifications of the Ferrier-type-ll reaction, whereby *cis*-fused tetrahydrofurans and tetrahydropyrans could be assembled from vinyl acetals (that is, **7**; Figure 2)—note that the exo-methylene group in **7** matched the substrate of Ferrier (**3**), but the acetal functionality is held entirely within the ring. Petasis recognized that an *endo*-cyclization onto an oxocarbenium ion would afford heterocycles in close analogy to the Ferrier-type-ll *exo*-mercury enolate attack of aldehydes (boxed intermediates **9B** and **11**). Petasis postulated that the Lewis acid activation of each of the ether oxygens in **7** would be reversible, but that the only productive pathway would be activation of the enol ether oxygen (that is, **8**). Subsequent electron flow from the second oxygen would liberate an aluminum enolate (**9A**), and permit reclosure through a chair-like conformation (**9C**), furnishing tetrahydropyranone **10**. This reaction has been dubbed the Petasis-Ferrier rearrangement, in light of the analogous fragmentation–recombination sequence originally documented in the Ferrier-type-II reaction.

This type of rearrangement was also applied to the preparation of five-membered rings, although this reaction has received less attention in the literature; the synthetic routes devised by Petasis to prepare both

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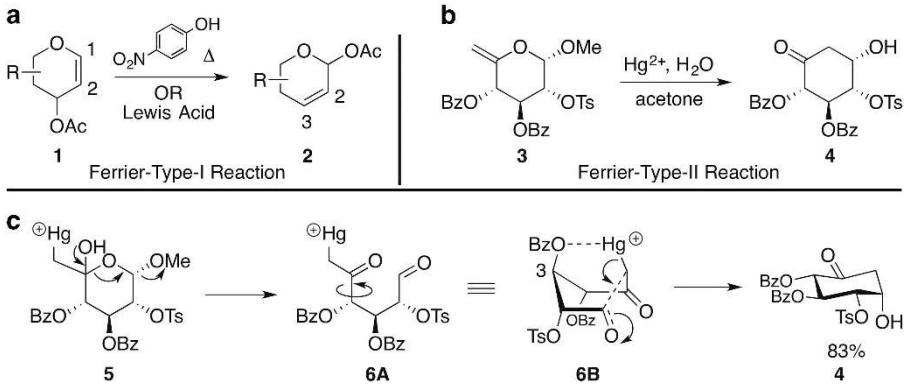

Figure 1 (**a**) Ferrier-type-I reaction. (**b**) Ferrier-type-II reaction. (**c**) Ferrier-type-II reaction mechanism.

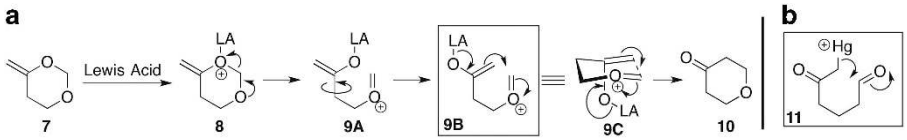

Figure 2 (**a**) Initially-proposed Petasis-Ferrier mechanism for tetrahydropyranone assembly. (**b**) Analogous Ferrier-type-II reaction cyclization intermediate.

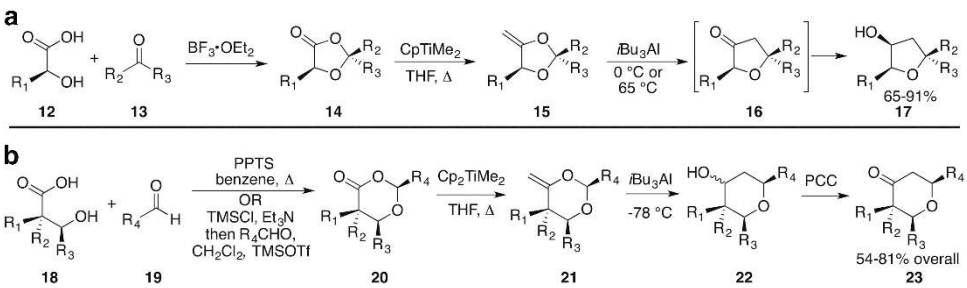

Figure 3 Synthetic strategy for Petasis-Ferrier reaction for (**a**) tetrahydrofuran, and (**b**) tetrahydropyran synthesis.

tetrahydrofurans and tetrahydropyrans are illustrated in Figure 3. Each assembly launches from readily available starting materials—a hydroxy carboxylic acid (**12** or **18**) and a carbonyl (**13** or **19**), the latter limited to an aldehyde in the formation of the larger ring. Coupling under acidic (pyridinium p-toluenesulfonic acid (PPTS)) or Lewis acidic (trimethylsilyl trifluoromethanesulfonate (TMSOTf)) conditions affords a cyclic acetal (dioxalanone **14** or dioxanone **20**). The relative stereochemistry in the cyclic acetal is set by the existing chirality centers in the hydroxyl acid; for example, in **20**, R_3 and R_4 adopt a *cis*-configuration. This substrate can then be methylenated with Cp_2TiMe_2 (also developed by Petasis, and known as the Petasis-Tebbe reagent[7]), furnishing a cyclic vinyl acetal (**15** or **21**), the substrate for rearrangement. Exposure of this acetal to a Lewis acid leads to rearrangement, at low temperature for the 6-membered ring, and either at 0 °C or at reflux for the tetrahydrofuran. Rearrangement, however, is followed by *in situ* Meerwein-Ponndorf-Verley reduction of the ketone (when using iBu$_3$Al) or methyl attack on the carbonyl (when using Me_3Al). Although the five-membered ring displays a sterically driven selective reduction, forming tetrahydrofuranol **17**, a mixture of epimeric alcohols (**22**) is provided in the pyran case; the diastereomeric ratio of the hydroxyl center ranges from 1:1 to >20:1, and thus reoxidation with pyridinium chlorochromate was reported by Petasis. Stereoselectivity at the R_4 center in **22** was initially postulated to arise from a chair-like transition state of reclosure (that is, **9C**).

Thus by 1996, a rearrangement-based route for the rapid assembly of tetrahydrofurans and tetrahydropyrans was devised, presenting both significant upsides and shortcomings. Although the reaction showed great promise in selectivity and efficiency, particularly in the convergency of the approach and the easy access to the two starting partners, a non-specific reduction of the nascent ketone required a reoxidation step for the six-membered ring variant. Further, there was a necessary installation of a rather delicate cyclic vinyl acetal moiety. In the two decades since the advent of this reaction, numerous applications and extensions have been developed, and will be detailed in this review. The reader is first pointed toward two excellent previous overviews of this work; the Kurti/Czako[8] name reactions text provided in 2005 a concise description of the reaction, and in 2008, Smith *et al.*[9] reported a review of their group's contribution toward the adaptation of this reaction, forming the cornerstone of no fewer than seven natural product total syntheses.[9] This review will briefly detail such overviews, but place greater emphasis on newer developments and inquiries into the mechanistic details of the Petasis-Ferrier rearrangement.

METHODOLOGICAL ADVANCES AND MECHANISTIC INSIGHTS

In 1999, the Smith group[10,11] became the first to report the utilization and extension of the Petasis-Ferrier reaction, developed in support of a total synthesis campaign toward phorboxazole A. To this end,

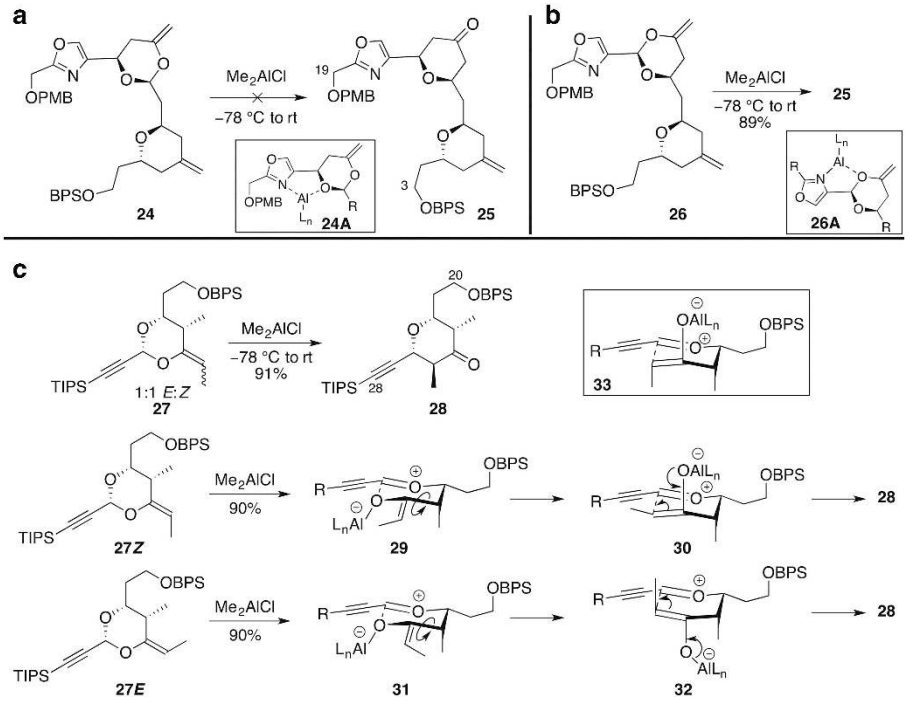

Figure 4 Petasis-Ferrier reactions used in the Smith total synthesis of phorboxazole A. (**a**) Failed rearrangement attempt to prepare the C3–19 subtarget of phorboxazole A. (**b**) Successful rearrangement in the same subunit, illustrating the flexibility of the rearrangement. (**c**) Proposed mechanism of the convergent rearrangement to prepare the C20–28 subtarget either by a chair or boat transition state.

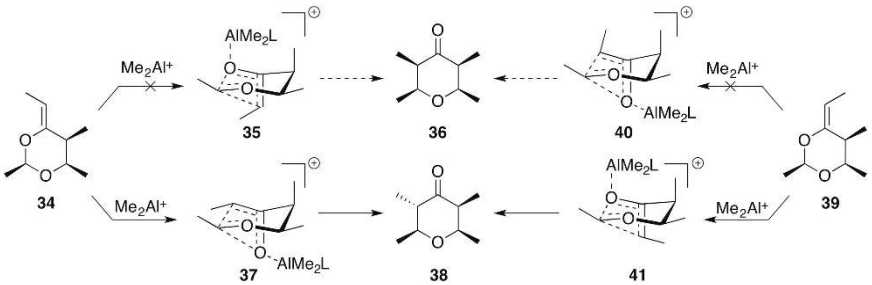

Figure 5 Rationalization of stereochemistry of the Petasis-Ferrier rearrangement, using DFT analysis, by Yu *et al.*

a number of Lewis acid promoters of the reaction were investigated as potential alternatives to iBu$_3$Al or Me$_3$Al, to avoid superfluous reduction or addition reactions, respectively, after rearrangement. After experimentation with BF_3•OEt_2, $ZnCl_2$, $TiCl_2(OiPr)_2$ and $MeAlCl_2$, each of which promoted some level of rearrangement, Me_2AlCl was identified as an ideal promoter, leading to reaction in high yield and without compromising the carbonyl formed in the reaction. Two Petasis-Ferrier rearrangements ultimately used in the Smith phorboxazole A total synthesis are illustrated in Figure 4, leading to the phorboxazole A C3–19 and C20–28 subunits. For the assembly of the C3–19 segment **25**, rearrangement was initially unsuccessful, as vinyl acetal **24** suffered from an unproductive chelation event (**24A**) with the oxazole nitrogen. Fortunately, owing to the inherent pseudosymmetry in the Petasis-Ferrier rearrangement, alternative vinyl acetal **26** was rearranged in high yield, as the oxazole nitrogen allowed for simultaneous activation of the key enol ether oxygen (**26A**). An interesting extension of the rearrangement was noted in the other phorboxazole subunit, where a fully substituted tetrahydropyran was required (that is, **28**). Accordingly, vinyl acetal **27** was extended to include an ethylidene moiety, which led to a first mechanistic variation of the rearrangement. As shown in the proposed mechanism in Figure 4c, two different enol ethers (**27*Z*** and **27*E***) were rearranged to furnish the same tetrahydrapyranone product **28**, either as a mixture or as pure isomers, in equally high yield. This was rationalized by invoking a Zimmerman-Traxler[12] transition state (**30**) for the cyclization of **27*Z***, as suggested by Petasis; this allows for maximal disposition of equatorial groups during the cyclization. However, the *E*-enol ether **27*E*** presumably proceeded through a boat-like transition state **32** to afford the same product **28**; this was rationalized to be preferred over chair-like cyclization mode **33**, wherein unfavorable 1,3-diaxial interactions between the methyl groups are present.

Although the mechanisms proposed by Smith were consistent with the observed reaction outcomes, no mechanistic corroboration was reported until 2013, when a computational report by Yu and co-workers[13] provided additional insights into the Petasis-Ferrier rearrangement. By using a density functional theory analysis of the reaction mechanism, the Yu group first asserted that the active

promoter in the reaction was actually R_2Al^+, with calculations indicating that the use of a neutral aluminum Lewis acid in the reaction would be prohibitively high in energy. Also, while their work supported the initially proposed mechanism for the tetrahydrofuran formation, modifications of the six-membered ring reaction mechanism were suggested. Yu asserted that the five-membered ring formation is indeed stepwise, reflecting a fragmentation step followed by a recombination step to reform a ring, but the tetrahydropyran synthesis was found to proceed through a concerted and asynchronous rearrangement. Although the boat and chair conformations invoked by Smith were supported, such conformations were suggested to be a part of a larger, concerted, rearrangement event, as illustrated by calculations for the two ethylidene acetals in Figure 5. Accordingly, exposure of either starting vinyl acetal to Me_2Al^+ leads to a bicyclic coordinated intermediate, favoring a chair-like assembly under 'normal' circumstances (that is, **34** to **37** to **38**). Diaxial repulsions were invoked for the inability of the *E*-ethylidene **39** to rearrange through a chair-like transition state (**40**), and a boat-like conformation (**41**) was supported, similarly to the suggestion of Smith.[10]

APPLICATION OF THE PETASIS-FERRIER REARRANGEMENT TO TOTAL SYNTHESIS

The Petasis-Ferrier reaction has been installed as a cornerstone reaction in no fewer than seven natural product total syntheses in the group of Amos Smith III: (+)-phorboxazole A (**42**),[14] (+)-zampanolide (**43**),[15] (+)-dactylolide (**44**),[14] (+)-spongistatin 1 (**45**),[16] (−)-kendomycin (**46**),[17] (−)-clavosolide A (**47**)[18] and (−)-okilactomycin (**48**).[19] Although an excellent recap of these syntheses appears in an *Accounts of Chemical Research* review, Figure 6 highlights the Petasis-Ferrier-derived substructures incorporated into the natural products. From their synthetic campaigns, the Smith group noted some significant take-home points. As indicated above in Figure 4, the (+)-phorboxazole A synthesis led to insights about the mechanism and optimal promoter of the Petasis-Ferrier rearrangement, as well as identified the inherent pseudosymmetry of the 2,6-*cis*-substituted tetrahydropyranone product. In the synthetic campaigns toward (+)-zampanolide and (+)-dactylolide, added trifluoromethanesulfonic acid (TfOH) was found to enhance the efficiency of the initial β-hydroxy acid/aldehyde condensation reaction, particularly on larger scale. The Smith group's preparation of (−)-kendomycin further improved the condensation via the addition of *i*PrOTMS and TMSOTf. The syntheses of (−)-clavosolide A and (−)-okilactomycin demonstrated the utility of the Petasis-Ferrier rearrangement in the presence of a highly acid-labile cyclopropylcarbinyl moiety and a neighboring alkene functionality, respectively. Finally, the large-scale synthesis of (+)-spongistatin 1 was aided in a 15-g scale Petasis-Ferrier-based assembly of the highlighted F ring.

EXTENSIONS OF THE PETASIS-FERRIER REACTION: THE HOMO-PETASIS-FERRIER REARRANGEMENT

In 2005, Minbiole and co-workers reported an extension of the Petasis-Ferrier rearrangement, wherein cyclopropanes were shown to serve as effective surrogates for the alkene in the vinyl acetal, leading to a homologous reaction. This led to the preparation of seven-membered oxygenated heterocycles, oxepanones (**53**), as shown in Figure 7.[20] An advantage of this development was the one-pot nature of the condensation and rearrangement; in the case where benzylic stabilization was present (that is, $R_2 = Ph$), this could be accomplished using a single Lewis acid, which could be any of the three metal (III) triflate species (Al, Bi or In). Otherwise, for alkyl substituents at the R_2 position, the sequential use of two different Lewis acids affected the reaction sequence. Interestingly, a stronger Lewis acid ($TiCl_4$) was required to promote the rearrangement step; Me_2AlCl was ineffective. The mechanism was proposed to proceed through a pseudo-Zimmerman-Traxler transition state (**52**), supported by observation of the product in strictly the *cis*-relative stereochemistry. A related cycloheptanone formation strategy was later reported by Cha and co-workers.[21]

EXTENSIONS OF THE PETASIS-FERRIER REACTION: GOLD CATALYSIS AND *IN SITU* VINYL ACETAL/AMINAL FORMATION

A significant advance in the Petasis-Ferrier rearrangement was reported by Rhee and co-workers[22] in 2009, where they presented an elegant gold-catalyzed reaction they categorized as an aza-Prins reaction. In this report, Rhee described the activation of an alkyne in the presence of an aminal functionality; as illustrated in Figure 8a, this leads to a cyclization cascade that fits squarely in the description of a Petasis-Ferrier rearrangement. Accordingly, aminal **54** is exposed to gold (I) catalysis and generates cyclic enol ether intermediate **55**; this in turn fragments, liberating pseudo-enolate **56**, which re-cyclizes in an aldol/Mannich-type reaction to generate piperidinone **59** after acidolysis. This strategy represents a significant advance for the

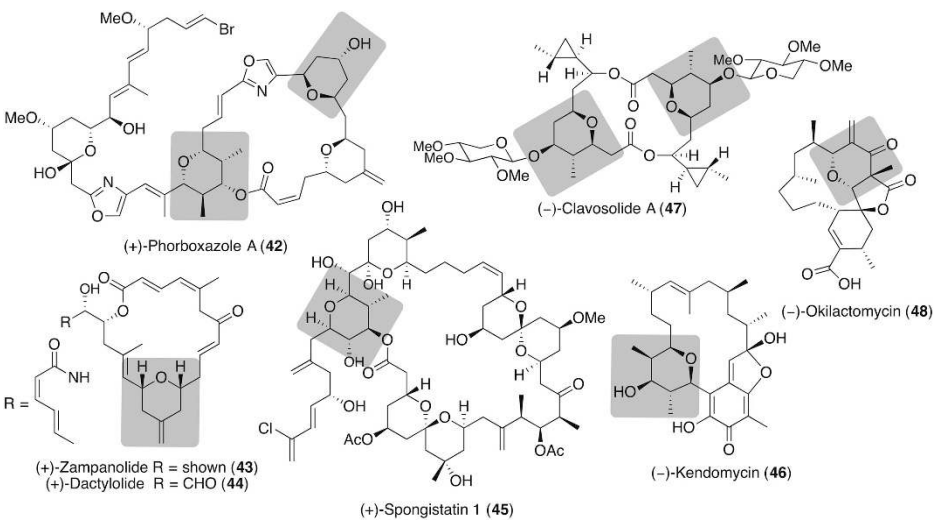

Figure 6 Total syntheses by the Smith group using Petasis-Ferrier rearrangements; products of rearrangements are shaded.

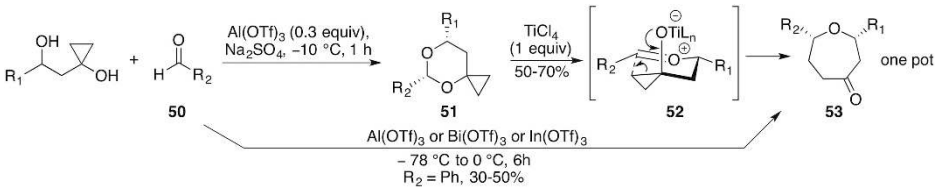

Figure 7 A homologous variant of the Petasis-Ferrier rearrangement reported by Minbiole *et al.*

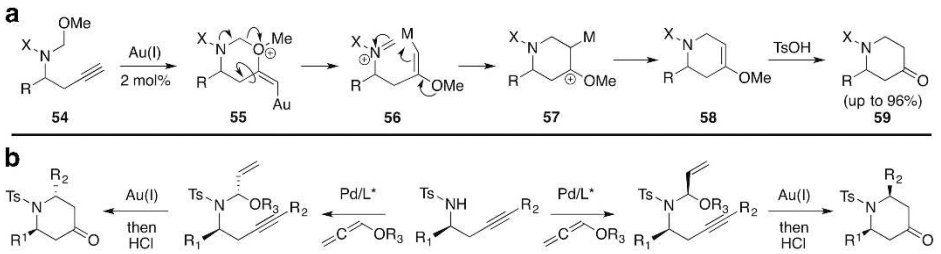

Figure 8 (**a**) Rhee's extension of the Petasis-Ferrier rearrangement, utilizing gold (I) catalysis of an alkynyl aminal. (**b**) Rhee's route to *cis*- and *trans*-fused 2,6-disubstituted piperidines.

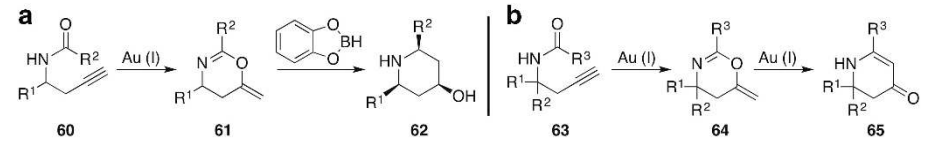

Figure 9 Extensions of the gold (I) promoted Petasis-Ferrier rearrangement reported by (**a**) Zhang and (**b**) Fustero.

Petasis-Ferrier reaction, as it serves to streamline the construction of the challenging vinyl acetal (or here, aminal) moiety. Low catalyst loadings (2 mol %) and high yields (up to 96%) also add to the attractiveness of this route. Rhee and Kim[23] later developed a strategy for the chiral installation of the aminal moiety, allowing for the selective preparation of either *cis*- or *trans*-2,6-disubstituted piperidines, as shown in Figure 8b.

Gold catalysis has since been used in a number of nitrogenous variants of the Petasis-Ferrier reaction, with each improving the scope and utility of this strategy, including those reactions in Figure 9. For example, Zhang and co-workers[24] effected rearrangement with a substrate that tethered an alkyne to an amide, which formed an enol ether/imine *in situ* (Figure 9a); this was reduced in the presence of catecholborane, forming a vinyl aminal which rearranged, furnishing piperidinol **62** after ketone reduction. A later development by Zhang and Liu[25] employed nucleophilic attack instead of reduction, leading to a cyclization cascade. Fustero *et al.*[26] has developed analogous reactions that are based on a tandem sequence, where a simple $AuPPh_3Cl/AgOTf$ combination catalyzes the rearrangement step in addition to the precursor formation (Figure 9b).

Back-to-back papers published in 2011 by Rhee and co-workers[27] and by Chan and co-workers[28] extended these developments to the facile production of oxygenated heterocycles, using acetal or hemiacetal-bearing precursors, respectively. As developed in the nitrogenous versions, the rearrangement substrate can be formed *in situ*, and from an easily available alkyne–aldehyde precursor, thanks to the activation of the alkyne by a gold (I) catalyst. Accordingly, as shown in Figure 10a, an ether oxygen of the generated acetal in **66** is able to bond to an activated alkyne, forming an activated enol ether **67**, which can then undergo the fragmentation–recondensation, that is, the hallmark of the Petasis-Ferrier rearrangement, furnishing **70**. A final step involves the acidic hydrolysis of the resulting cyclic enol ether, furnishing tetrahydropyranone **71**. Optimal selectivity was observed by Rhee when using the gold (I) catalyst $[Au\{P(tBu)_2(o\text{-biphenyl})\}(CH_3CN)]^+ X^-$. At the same time, Chan and co-workers reported a quite similar reaction of an alkynyl aldehyde, in this case, under the promotion of gold (I) catalyst **76**. In this case, attachment of the functional groups to a benzene ring led to the rapid assembly of fused heterocycles, including benzo[b]oxepin-3-ones **75A** (X = O), as well as nitrogenous analogs benzo[b]azepin-3-ones (**75B**, X = NTs).[29]

Further variants on this theme were developed shortly thereafter in the laboratories of Pati and Alabugin[30] and Fiksdahl and co-workers[31] (Figure 11). Pati was the first to report a carbocyclic variant of the Petasis-Ferrier reaction, using additional aromatic substitution (shown as Ar in **77**) to allow for a cationic cascade, resulting in substituted naphthalene **78** in high yields. Fiksdahl used a similar strategy to that outlined by Rhee, but incorporated an optional halogenation step, resulting in halogenated pyran **81** (or its tetrahydropyranone analog after acidic hydrolysis). This was extended[32] to introduce a fluorine atom, in an impressive single step from alkynyl acetal **79**, due to the promotion of a gold (I) catalyst in the presence of Selectfluor (Sigma-Aldrich, St Louis, MO, USA).

EXTENSIONS OF THE PETASIS-FERRIER REACTION: NITROGENOUS VARIANTS (ACYCLIC)

There are a number of other reactions that are billed as 'aza-Petasis Ferrier,' or APF, reactions in the literature.[33,34] Although these reactions are based on acyclic precursors, they still bear the hallmark of a fragmentation/recombination of the original Petasis-Ferrier rearrangement. Such reactions are perhaps best viewed as extensions of work reported in 1993, where Frauenrath *et al.*[35] pioneered a diastereoselective rearrangement of hemiaminal vinyl ethers **83** promoted by a substoichiometric amount of TMSOTf an achiral Lewis acid (Figure 12a). It seems reasonable to categorize such a reaction as a

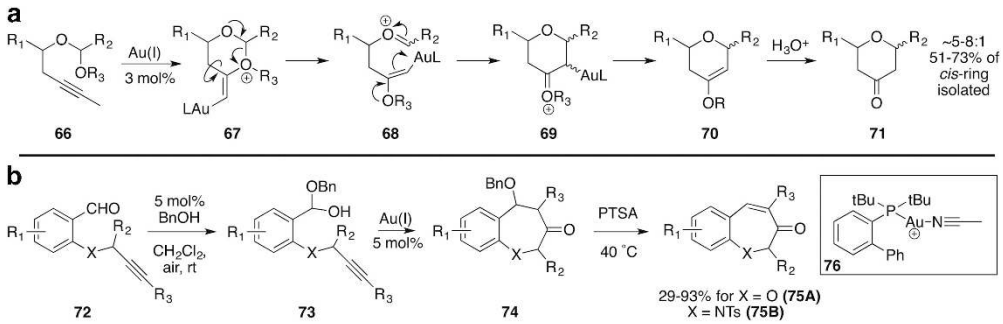

Figure 10 (**a**) Rhee's alternative to the Petasis-Ferrier rearrangement, resulting in tetrahydropyranones. (**b**) Chan's analog of the Petasis-Ferrier reaction, preparing benzo[b]oxepin-3-ones (X = O) as well as nitrogenous analogs benzo[b]azepin-3-ones (X = NTs).

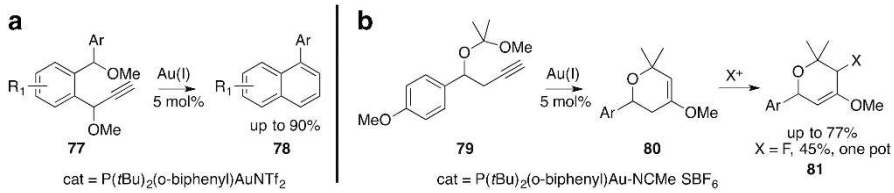

Figure 11 Gold (I) catalyzed Petasis-Ferrier reactions, as developed by (**a**) Pati and (**b**) Fiksdahl.

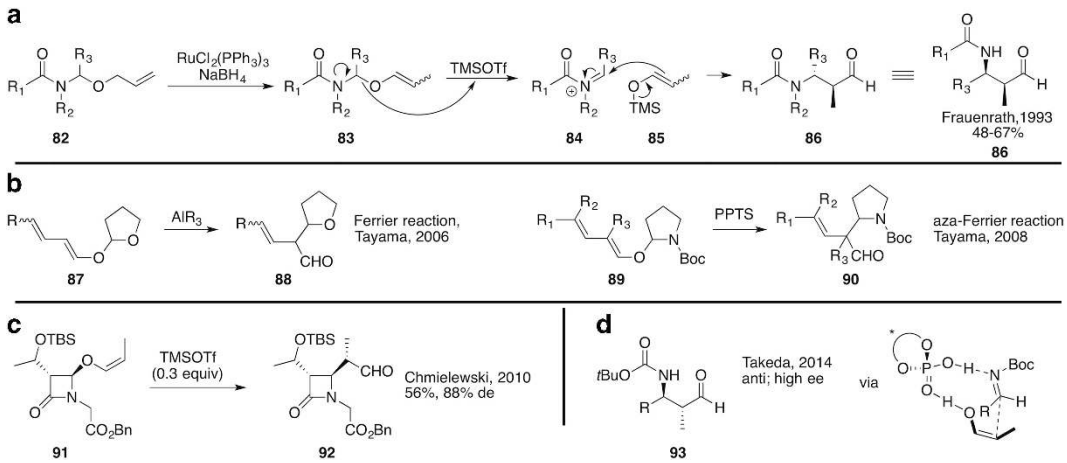

Figure 12 (**a**) Frauenrath's precedent for a Petasis-Ferrier-like fragmentation/recombination sequence. (**b**) Ferrier and aza-Ferrier rearrangements reported by Tayama. (**c**) β-Lactam fragmentation/recombination by Chmielewski. (**d**) Enantioconvergent modification by Takeda, using chiral Brønsted acid catalysis.

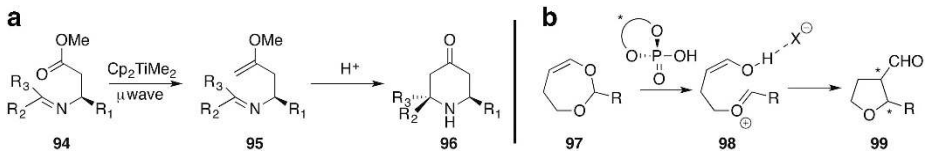

Figure 13 Other acid-catalyzed variants of the Petasis-Ferrier rearrangement using (**a**) microwave or (**b**) chiral Bronsted acid promotion.

Petasis-Ferrier rearrangement, as it depends on a fragmentation/Mannich/aldol-type recondensation sequence, even though this work in fact predates the reports of Petasis. After Frauenrath's initial disclosure, however, no report by other researchers followed until 2008,[36] when the group of Tayama and Isaka[37] reported an 'aza-Ferrier' rearrangement, in extension of their previous Ferrier-type rearrangements (Figure 12b). Tayama's work represented a close analog of that of Frauenrath, although the acyliminium intermediate was cyclic. Shortly thereafter, a fragmentation/recombination of β-lactam **91** (Figure 12c) was reported by Chmielewski and co-workers,[38] presumably operating via liberated silyl enol ether, as suggested by the promotion of TMSOTf. Finally, since this system serves as an ideal ground for enantioselective reaction development promoted by chiral Brønsted acids, Takeda used a binaphthyl-based chiral phosphoric acid to this end, as shown in Figure 12d.

EXTENSIONS OF THE PETASIS-FERRIER REACTION: OTHER ACIDIC EXTENSIONS

The reader is pointed toward two additional examples of modified Petasis-Ferrier reactions that arise from acid catalysis; these reactions

perhaps indicate that there are a wealth of as-yet undiscovered reactions in this arena that may require only simple promotion. Accordingly, an aza-Petasis reaction was published in 2007,[39] wherein an enol ether was prepared from the microwave-assisted methylidenation of ester **94**, prepared in the presence of an imine (Figure 13a). Such an arrangement allowed for simple acid catalysis to generate piperidine ring **96**. Finally, in 2014, Terada and co-workers reported an acid-catalyzed ring contraction that also fits the Petasis-Ferrier paradigm. Therein, preassembled cyclic enol ether **97** was exposed to a chiral phosphoric acid, leading to preparation of tetrahydrofuran **99**,[40] finally representing an extension of the original Petasis rearrangement to form tetrahydrofurans.

CONCLUSION

In the mid-1990s, the laboratory of Nicos Petasis reexamined a useful rearrangement developed by Robin Ferrier nearly two decades earlier, and reported key improvements in a reaction now termed the Petasis-Ferrier reaction. In the two decades since, there has been significant interest in this reaction, with its utility demonstrated in total syntheses and its flexibility uncovered through elegant synthetic variations. The totality of this set of reactions indeed embody the ideal of molecular rearrangements—clever, efficient and widely applicable reactions that are indeed useful to the modern synthetic organic chemist.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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