Abstract
In the presence of a suitable acid or base, α-hydroxyaldehydes, ketones, and imines can undergo isomerization that features the 1,2-shift of one of the α-substituents to the adjacent unsaturated carbon, with a concomitant proton transfer to form compounds of type 2 (Figure 1) [1]. Differing from the related Wagner–Meerwein and pinacol/semipinacol rearrangements, the 1,2-shift does not require a leaving group or carbocation intermediate, as the neighboring π system is capable of accepting the migrating group. While the reaction is generally reversible, the product can be favored through four common strategies: (1) the use of aldehydes (R’ = H), which are usually less stable than their ketone counterparts; (2) ring expansion (Z, R = cyclic) or contraction (Z, R’ = cyclic) of strained cyclic α-ketols; (3) the use of α-dicarbonyl compounds (R’ = acyl, ester, amide, etc.), which lead to more stable β-dicarbonyl compounds; or (4) the use of imines (X = NR”), which lead to more stable α-amino ketones.
The α-ketol or α-iminol rearrangement is a synthetic organic tool used for ring expansions and contractions and other isomerizations that is also used in some biological pathways [2,3]. Works featuring these reactions through mid-2002 have been thoroughly discussed in a past review by Paquette [1]. The current review expands on that work by providing an updated account from mid-2002 through early 2021, including the following recently developed applications: asymmetric synthesis, total synthesis, tandem reactions, and enzymatic rearrangements.

**Review**

**Asymmetric α-ketol rearrangements**

One major advancement in the field of α-ketol rearrangements is the development of methods for performing the reaction asymmetrically. This is possible by two approaches: (1) stereoselectively through the use of a chiral catalyst in the presence of a substrate possessing a prochiral migrating group or (2) stereospecifically by means of a chiral α-ketol.

As an example of an enantioselective rearrangement, complexes of nickel(II) with a series of chiral 1,2-diaminopropane or pyridineoxazoline ligands were evaluated for their conversion of 3 into the cyclohexanone product 4 (Figure 2) [4]. The best results were obtained with 2-[4-(S)-tert-butyloxazolin-2-yl]pyridine ((S)-5), which gave >90% yield of (S)-4 in 46% ee.

In a similar investigation except with copper(II) and β-hydroxy-α-diketone 6 as the substrate, the catalyst containing the chiral bisoxazoline ligand (S,S)-8 led to the α-ketol rearrangement product 7 in 70% yield and 68% ee (Figure 3) [5]. The study further demonstrated the effectiveness of the catalyst for a series of analogues of 6 bearing various replacements for the phenyl group, often proceeding with greater than 80% ee.

As a third example of an enantioselective α-ketol rearrangement, Dai et al. used a chiral Al(III) catalyst to induce the rearrangement of 3 (Ar = Ph) and several aryl derivatives 9 (Figure 4) [6]. Among the N,N'-dioxide ligands explored, 11, which was derived from L-pipeolinic acid, was the most effective. Optimized conditions for substrate 3 (11, m = 1; Ar = 2,6-iPr2C6H3) led to yields approaching 99% with 91% ee. Addition of substituents on the phenyl group maintained excellent enantioselectivity, with 84% to 92% ee. Most of the twelve derivatives tested also had excellent yields (>85%), but the two most strongly electron-withdrawing, para-CF3 and meta-CH3, had lower yields (59% and 67%, respectively).

Instead of a ring expansion driving the rearrangement, the authors also tested a series of α,α-diaryl-α-hydroxyaldehydes 12 and their corresponding aldimines 14 (Figure 4). These reactions required small adjustments to ligand 11, with m = 1 and Ar = 2,6-Me2C6H3 working best for 12 and m = 0 and Ar = 2,4,6-iPr3C6H2 best for 14. Sc(III) proved to be superior for rearrangement of α-hydroxylamines. Under these conditions, products 13 were obtained in poor-to-moderate yields but with ≥74% ee, while the α-amino ketone products 15 could be obtained in nearly quantitative yields and variable ee, from 53% to 98% [6].

A fifth example of an enantioselective α-ketol rearrangement provides a twist by demonstrating the ability to function on substrates protected as silyl ethers. Ooi et al. utilized an axially...
Figure 4: Enantioselective rearrangement of ketols 9 and 12 and hydroxyaldimine 14 catalyzed by Al(III) or Sc(III) liganded by 11. Ligand 11: for 9, \(m = 1\) and \(Ar = 2,6-iPr_2C_6H_3\); for 12, \(m = 1\) and \(Ar = 2,6-Me_2C_6H_3\); and for 14, \(m = 0\) and \(Ar = 2,4,6-iPr_3C_6H_2\).

Figure 5: Asymmetric rearrangement of \(\alpha,\alpha\)-dialkyl-\(\alpha\)-siloxyaldehydes 16 to \(\alpha\)-siloxyketones 17 catalyzed by chiral organoaluminum Lewis acid 18. The catalyst is also capable of kinetic resolution of a mixture of enantiomeric substrates. \(Al^* = 18\).
The final example of asymmetric α-ketol rearrangements utilizes asymmetric induction arising from the chiral alcohol. When the ketol’s carbonyl is located at the α position to an amide, as in β-hydroxy-α-ketoamide 21, the difluoroalkoxyborane intermediate 22 that results from BF₃-promoted α-ketol rearrangement can be isolated chromatographically. Subsequent methanolysis yields β-hydroxy-α-ketoamide 23 (Figure 6). The overall reaction occurs diastereospecifically, with greater than 80% yield across each of 5 distinct amide derivatives [8].

**Tandem α-ketol rearrangements**

Because α-ketol rearrangements can be initiated by simple reagents like a Brønsted base or Lewis acid, the possibility exists to couple the rearrangement to other compatible reactions without any intervention. Such tandem reactions are attractive synthetic “tricks” that can allow for complex modifications with efficiency and often high selectivity. This short section introduces this concept by application to isolated reactions, while in the following section, examples of tandem reactions in total syntheses are given.

Inspired by the direct ring expansion of 1-alkynylcyclobutanols to α-methylene cyclopentanones catalyzed by gold reported by Toste and co-workers [9], Kim et al. hypothesized that by conducting the reaction in the presence of water, the reaction would be diverted to an initial hydration followed by an α-ketol rearrangement [10]. First, it was determined with model 1-alkynylcyclobutanol derivative 24 that in anhydrous conditions, the major product was 25, resulting from the expected direct ring expansion (Figure 7). When the reaction was repeated in the presence of a single drop of water, however, only product 26 was observed, presumably by the hydration-rearrangement sequence. The intermediacy of the cyclobutyl α-ketol 27 was indirectly confirmed using diphenyl derivative 28, which has a lower tendency for ring expansion. At room temperature, this substrate stopped at the hydrated intermediate 29, which could be isolated and remained intact when heated to 80 °C alone in 1,4-dioxane. Inclusion of the gold catalyst while heating, however, initiated the rearrangement to 30, confirming the importance of Au(I) in catalyzing both steps in the tandem reaction. Notably, this is the first time in the literature that α-ketol rear-

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**Figure 6:** BF₃-promoted diastereospecific rearrangement of α-ketol 21 to difluoroalkoxyborane 22.

**Figure 7:** In the presence of a gold catalyst and water in 1,4-dioxane, 1-alkynylbutanol derivatives undergo tandem hydration and α-ketol rearrangement to give the corresponding ring-expanded cyclopentanones. IPr = N,N′-bis(2,6-diisopropylphenyl)imidazole-2-ylidene.
rangements have been initiated by a gold catalyst. Optimization revealed that the tandem reaction is best performed with Au(JohnPhos)SbF₆ in 1,4-dioxane with a single drop of water.

**α-Ketol rearrangements implemented in total syntheses**

Although rare, α-ketol rearrangements have been included in the total syntheses of some natural products with high success. In the first total synthesis of periconianone A (31), an α-ketol rearrangement was used to shift a four-carbon chain one position on the bicyclic molecule 32 using the base calcium methoxide with a yield of 70% of 33 and a diastereomeric ratio of 3:1 (14:1 after separation) (Figure 8) [11]. Note that 33 bears an enone moiety, and therefore, this reaction is apparently the first example of the use of conjugation to drive an α-ketol rearrangement. This study elegantly illustrates the synthetic power of α-ketol rearrangements, whose suprafacial migration ensured that the α-ketol moiety present in the target product 31 was installed with correct stereochemistry. Taking inspiration from the above work from the Gademann group, Kalmode et al. incorporated the same synthetic strategy into their total synthesis of racemic periconianone A [12]. Interestingly, these authors not only tested the natural product for neural anti-inflammatory activity but also the two immediate synthetic precursors containing simpler decalin systems (identical to 32 and 33 but with an additional conjugated double bond) and found the α-ketol rearranged product superior to periconianone A.

Another example of an α-ketol rearrangement in a total synthesis is in the preparation of silvestrol (34) and episilvestrol (35), natural products with potent anticancer properties. The step prior to the rearrangement involved a photoinduced [3 + 2] cycloaddition between hydroxyflavone 36 and methyl cinnamate (37), resulting in the bicyclic α-ketol 38 as a mixture of diastereomers (Ph and CO₂Me groups trans) (Figure 9) [13]. Interestingly, when this mixture was subjected to silica gel chromatography, not only could the isomers of 38 not be separated, they also underwent silica-catalyzed α-ketol rearrangement to cyclobutane 39. This rearrangement, however, was of no consequence because addition of sodium methoxide to the mixture of 38 and 39 induced a second α-ketol rearrangement to 40 as a tautomeric mixture. The same research group later utilized the same [3 + 2] cycloaddition and α-ketol rearrangement approach to prepare the 2″-epimer of 35, which bears an inverted methyl acetal in the dioxane ring, but this compound was less active at inhibiting protein translation [14].

![Figure 8: The diastereospecific α-ketol rearrangement of 32 to 33, part of the total synthesis of periconianone A (31).](image)

![Figure 9: Two α-ketol rearrangements, one catalyzed by silica gel on 38 and the other by NaOMe on both 38 and 39, part of the total synthesis of silvestrol (34) and episilvestrol (35). PMP = p-methoxy phenyl.](image)
Triumphalone (41) and isotriumphalone (42) represent a class of oxidized phloroglucinol natural products isolated from the Australian plant *Melaleuca triumphalis*. In their total synthesis of these two compounds in racemic form, Nishimura et al. discovered that 41 spontaneously undergoes an α-ketol rearrangement to form 42 in protic solvents (Figure 10) [15]. NMR solvent screening revealed that among CDCl₃, DMSO-d₆, C₆D₆, and CD₃OD, 41 only isomerized at room temperature into 42 when dissolved in CD₃OD (60% conversion over ≈5 days, as determined by ¹H NMR). Additionally, purified 42 was not observed to undergo any α-ketol rearrangement reaction, although the authors did not discuss why the reverse reaction did not occur.

As was alluded to earlier, tandem reactions that include an α-ketol rearrangement have been incorporated into some total synthesis schemes. In the total synthesis of strophasterol A, a member of a structurally unprecedented class of secosterols, when intermediate 43 was treated with base, it was quantitatively converted to 44 (Figure 11) [2]. The proposed mechanism for the tandem reaction involves three hydroxide-promoted steps, beginning with a vinylogous α-ketol rearrangement to 46. Following protonation of the enolate and addition of hydroxide to the carbonyl on the D ring, 47 rearranges with loss of chloride to give enedione 48. Base-catalyzed isomerization yields 44, which is apparently more stable despite the reduction in conjugation.

Another example of a tandem α-ketol rearrangement was used in the total synthesis of delitschiapyrone A (49), a cytotoxic natural product with previously demonstrated efficacy against several cancer cell lines. The final steps of the synthesis include a Diels–Alder reaction between 50 and 51, an α-ketol rearrangement of 52, and a hemiketal-forming cyclization of 53, all of which occurred as a cascade (Figure 12) [16]. Over a series of optimizations, it was found that performing this cascade in a solution of water at 35 °C over the course of 2.5 days produced a 75% yield of 49 and a 22% yield of the Diels–Alder adduct, showing that the first step of the cascade had near-quantitative yield, diastereoselectively and regioselectively. The authors speculated that it is possible, considering their own reaction efficiency in conditions reminiscent of natural ones, that the biosynthesis of delitschiapyrone A could occur non-enzymatically in nature by a similar process.
The final example of a tandem reaction involving an α-ketol rearrangement in a total synthesis was employed by Chen et al. in the preparation of (±)-securinine (54) and (±)-allosecurinine (55), biological alkaloids with diverse biological activities [17]. The key step first involved the rhodium carbenoid-mediated OH insertion/Claisen rearrangement following complexation of diazoester 56 and allylic alcohol 57 to produce intermediate 58 (Figure 13). Addition of BF$_3$·OEt$_2$ to the reaction mixture then catalyzed the α-ketol rearrangement to 59. Note that this reaction took advantage of the thermodynamically preferred conversion of an α-ketoester to a β-ketoester seen in other examples in this review. Although not technically a tandem reaction due to the need to add a reagent to continue the cascade, the sequence of reactions nevertheless accomplishes the same goal of connecting two carbon-skeleton alterations conveniently in one pot with a combined yield of 45%.

**α-Ketol rearrangements in biosynthetic reactions**

At the time of this review, only two enzymes have been identified that catalyze an α-ketol rearrangement as part of their mechanism. Ketol-acid reductoisomerase (KAR), which is involved in the biosynthesis of branched-chain amino acids, takes as its substrate either (2S)-acetolactate (60, R = Me), which is ultimately converted into valine or leucine, or (2S)-acetohydroxybutyrate (60, R = Et), which eventually becomes...
isoleucine (Figure 14a). The enzyme catalyzes two consecutive reactions: an $\alpha$-ketol rearrangement to generate a 3-hydroxy-2-ketoacid intermediate 61, followed by NADPH-dependent reduction to the dihydroxylated product 62 [18]. Interestingly, another reductoisomerase known as 1-deoxy-$\alpha$-xylulose-5-phosphate reductoisomerase (DXR), uses a different mechanism to accomplish the carbon-skeleton rearrangement of its substrate 63 [19]; kinetic isotope effect experiments have excluded an $\alpha$-ketol rearrangement and instead support a stepwise retro-aldol/aldol sequence for formation of intermediate 64 (Figure 14b) [20,21]. The other enzyme believed to catalyze an $\alpha$-ketol rearrangement is AuaG, which is a monoxygenase that uses FAD and molecular oxygen to convert aurachin C (66) to 69 (Figure 14c) [22]. Subsequent reduction and dehydration by AuaH produces aurachin B (71).

While the above are the only identified enzymes that catalyze $\alpha$-ketol rearrangements so far, there is little doubt additional examples are to be discovered. The remainder of this section provides cases of biological pathways and reactions that have been hypothesized to involve $\alpha$-ketol rearrangements.

In a study proposing a biosynthetic pathway for the novel steroid asperflotone (72), it was suggested that its source was asperfloroid (73), a similar steroid isolated from the same source fungus, Aspergillus flocculosus [23]. First, reduction of the C8–C9 double bond and oxidation at C15 would provide $\alpha$-ketol 74 (Figure 15). Next, ring-expanding rearrangement is proposed to form 75. Finally, the C7 ketone is reduced, the C8–C9 bond is oxidized back to an alkene, the C5–C6 double bond is oxidized to an epoxide, and C15 is oxidized to a tertiary alcohol to yield 72. The authors not only structurally characterized asperflotone and asperfloroid but also demonstrated their immunosuppressive activity against IL-6 production in induced THP-1 cells. Thus, as they noted, these two steroids may be attractive targets for total synthesis, perhaps incorporating the

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**Figure 14:** Enzyme-catalyzed $\alpha$-ketol rearrangements. a) Ketol-acid reductoisomerase (KAR) catalyzes the rearrangement of (2S)-acetolactate (65, $R = \text{Me}$) or (2S)-acetohydroxybutyrate (65, $R = \text{Et}$) to 66, followed by reduction by NADPH to 67. b) Despite the similarity in reaction, 1-deoxy-$\alpha$-xylulose-5-phosphate reductoisomerase (DXR) instead uses a retro-aldol/aldol sequence to accomplish its rearrangement of 68 to 69. c) The secondary metabolite aurachin C (71) is oxidized by the FAD-dependent monoxygenase AuaG to epoxide 72, which upon deprotonation by an enzymatic base (B), ring opens and subsequently rearranges to 74. AuaH uses NADH to reduce the ketone to diol 75, which undergoes dehydration to give aurachin B (76).
Prekinamycin (76) and isoprekinamycin (77) are diazo compounds isolated from *Streptomyces murayamensis* that differ in their ring system, with the former containing a fused 6-6-5-6 skeleton and the latter containing a 6-5-6-6 skeleton. Due to their similarity and common source, it had been hypothesized by several groups that one could be the biological precursor of the other by means of a reversible hydration–rearrangement–dehydration sequence (Figure 16a) [24-26]. The presence of the diazo group in intermediates 78 and 79 is noteworthy in that this functional group has not yet been demonstrated to be compatible with an α-ketol rearrangement. To test the feasibility of their hypothesis, Kawamura et al. subjected 80 to basic (Cs$_2$CO$_3$ or K$_2$CO$_3$) and acidic (TsOH) conditions [27]. While TsOH led only to dehydration product 81, the bases exclusively generated 82 as the result of an α-ketol rearrangement (Figure 16b). While 6-6-5-6 ring systems were not explored, Cs$_2$CO$_3$ was tested on several other fused multi-ring α-ketols, leading to the expected rearranged products in moderate to quantitative yields in all cases where competing dehydration was not possible (Figure 16c). The authors concluded that further studies of this type of rearrangement in a biological system are currently being attempted.

As a final example of natural products believed to form as a result of an α-ketol rearrangement, Li et al. isolated and characterized eight novel acylphloroglucinol meroterpenoids, known as elodeoidins, from the herb *Hypericum elodeoides* [28]. The authors proposed that these molecules derived from common acylflicinic acid precursors 87 through two distinct pathways based on the regiochemistry of an oxidation–α-ketol rearrangement sequence (Figure 17). If oxidation occurs at C3, then a subsequent ring-contracting α-ketol rearrangement would form 89. From here, a series of oxidation, cyclization, methylation, and/or reduction steps yield 92 and 93 (each representing two isolated products, one with R = Me and the other with R = Et). Oxidation at C1 and α-ketol rearrangement to 91, on the other hand, is proposed to give rise to isolated products 94 (R = Me, Et), 95, and 96. Interestingly, 94 showed anti-inflammatory activity.

**α-Iminol rearrangements**

Whereas α-ketol rearrangements must be driven thermodynamically by the presence of a destabilizing feature in the reactant (e.g., aldehyde, ring strain, or α-carbonyl group), α-iminols are typically less stable than their α-amino ketone products. In the presence of a Bronsted acid, protonation of the amine product can be used to drive the rearrangement to completion. Thus, favorable yields and stereoselectivities can be realized by first converting the α-ketol to an α-iminol by condensation with a suitable amine, provided that the amino group resulting from the rearrangement is compatible with the planned synthesis.

In recent years, the Wulff group has made significant progress in the development of catalysts for asymmetric α-iminol rearrangements. Inspired by the use of a BOROX catalyst in a series of asymmetric imine reactions, the group performed a catalyst screen for the conversion of 97 to 98 (Figure 18) [3]. Out of nearly twenty catalysts tested, (R)-VANOL Zr (99) produced the best results, with 5 mol % in toluene at 80 °C for 1 hour giving 96% yield of (S)-98 with 97% ee. Impressively, raising the temperature to 160 °C for only 30 s gave 95% yield with
Figure 16: Hypothetical interconversion of natural products prekinamycin (76) and isoprekinamycin (77) and chemical models of their proposed α-ketol intermediates. a) The natural products are believed to interconvert biologically by a reversible sequence of hydration–rearrangement–dehydration. b) α-Ketol rearrangement of 80, an analogue of proposed intermediate 78, occurs with base (M = K or Cs), but dehydration to 81 occurs with acid. c) Substrate scope of similar Cs₂CO₃-catalyzed α-ketol rearrangements.

89% ee. The substrate scope revealed broad tolerance for aryl (except for p-trifluoromethyl) and aliphatic R groups, with yields and ee in excess of 90% in most cases.

The Wulff group later explored alternative Brønsted and Lewis acids that could effectively catalyze the rearrangement of symmetric α-hydroxy aldimes [29]. A catalyst screen was performed on the model substrate 97a (R = Ph; Figure 19a) using three different Brønsted acids (acetic acid, sulfuric acid, and p-toluene sulfonic acid), five different Lewis acids (Zn(OTf)₂, Cu(OTf)₂, Sc(OTf)₂, silica gel, and montmorillonite K 10), and one base (NaOEt). Of these, silica gel and
Figure 17: Proposed biosynthetic pathway converting acylphloroglucinol (87) to isolated elodeoidins A–H 92–96. Oxidation at C3 followed by α-ketol rearrangement is believed to give rise to 92 and 93, while a similar sequence at C1 is proposed to yield 94–96. R = Me or Et.

Figure 18: α-Iminol rearrangements catalyzed by VANOL Zr (99). The rearrangement can be conducted with preformed iminol 97 or from a mixture of aldehyde 100 and aniline.

Montmorillonite K 10 had the best yields (95% and 100%, respectively). A substrate scope was then determined for 97 using aryl, n-hexyl, and cyclohexyl R groups in the presence of silica gel at 80 °C (Figure 19b). The rearrangements proceeded well with electron-rich aryl groups, regardless of the position of substitution, but the reaction was especially slow for the electron-withdrawing para-trifluoromethyl derivative.

A major advantage of the use of silica gel and montmorillonite K 10 as catalysts is that they function under neutral conditions, permitting the use of acid-sensitive groups, such as silyl ethers. For example, 101 was converted to 102 in 70% and 96% yield, respectively, with silica gel and montmorillonite K 10, but with sulfuric acid, no 102 was formed, only the free alcohol (103) in 56% yield (Figure 19c). As an extension of this method, the
Figure 19: α-iminol rearrangements catalyzed by silica gel and montmorillonite K 10. a) For 102a (102 with R = Ph), silica gel and montmorillonite K 10 gave ≥95% yields, while Brønsted acids, other Lewis acids, and NaOEt generally performed much more poorly. b) Electron-rich R groups rearrange efficiently in the presence of silica gel but not the electron-deficient p-trifluoromethylphenyl derivative. c) In the presence of silica gel or montmorillonite K 10, TBS-protected 101 is converted to 102 without any side products, but when sulfuric acid is used, only the deprotected product 103 is detected. d) Silica gel-catalyzed rearrangement of 104 provided 105, an analogue of the anesthetic ketamine (106).

Figure 20: Synthesis of tryptamines 110 via a ring-contracting α-iminol rearrangement. A mechanism for the final step has been proposed to occur through cyclobutyl intermediates 112 and 114 (some steps have been added/modified from the original source).

authors demonstrated the formation of 105, an analogue of the anesthetic ketamine (106), in 83% yield using silica gel (Figure 19d) [29].

An α-iminol rearrangement was utilized by Serusi et al. in a tandem reaction to synthesize functionalized tryptamines from 2-hydroxycyclobutanones 107 with a primary aniline [30]. Notably, the α-iminol rearrangement results in a ring contraction to give the 2-aminocyclopropyl ketone intermediate 109, which upon condensation with a second equivalent of aniline in the presence of a Brønsted acid undergoes a multistep rearrangement to form the indole group as part of the target tryptamine 110 (Figure 20). The one-pot conversions occurred successfully over a wide range of monosubstituted anilines, including various para-alkyl groups (65–72% yield), para-alkoxy and para-halogen substituents (45–69%), ortho-methyl (74%), and...
meta-methyl (80% as a 65:35 mixture of regioisomers). Electron-withdrawing groups (nitro, cyano, and methyl ester) stopped at the ketone intermediate.

Interestingly, another tandem sequence that exploits the relief of ring strain from cyclobutane derivatives has been developed by Cheng et al. to prepare functionalized α-amino cyclopentanones [31]. In the presence of a palladium catalyst, an electron-rich heteroarene 115 first adds to the nitrile group in a 1-cyanocyclobutyl ester 116 to give a tetrahedral imine intermediate 117. C–O bond cleavage produces an α-iminol intermediate 118, which proceeds to rearrange by ring expansion to ultimately yield 119 (Figure 21a). Using the benzoate ester of 118 (R = Ph; X = CH₂) as the substrate and N-methylindole as the heteroarene, optimal reaction conditions (95% yield) were found with Pd(OAc)₂/bpy as the catalyst, N-methylacetamide as the solvent, and a temperature of 80 °C. Variously substituted indoles as well as esters of 118 (R = aryl, alkyl, vinyl) were generally well tolerated, but oxa- (X = O) and azo- (X = NR) cyclobutanes met with limited success. Alternative heteroarenes were much poorer, with pyroles and thiophenes giving yields of ≈20% or less and benzofuran and benzothiophene failing to produce any product. Interestingly, a cyclopentanone-derived substrate (120) failed to yield the corresponding α-amino cyclohexanone 121 under the standard conditions used for cyclobutane derivatives (Figure 21b), highlighting the importance of the relief of ring strain in driving the rearrangement [31].

Like their α-ketol counterparts, rearrangements of α-iminols have also been used in total syntheses. In their total synthesis of four eburnane-type alkaloid natural products 122–125, Li et al. utilized a ring-contracting α-iminol rearrangement to diastereoselectively install the spiroindolinone moiety that served as a key common intermediate (Figure 22) [32]. The rearrangement was triggered by saponification of the benzoyl ester in 126, resulting in a 90% yield of 127.

Conclusion

Although α-ketol and α-iminol rearrangements are a somewhat specialized synthetic tool, they are steadily seeing increased use in organic chemistry. In particular, great progress has been made in asymmetric synthesis and tandem reactions, as illustrated in several examples in this review, and continued development in these areas can be expected in the coming years. It is becoming apparent that nature also utilizes these rearrangements in natural product biosynthesis, and one might expect to see an increase in the discovery of enzymes governing these reactions.

![Figure 21: Tandem synthesis of functionalized α-amino cyclopentanones 119 from heteroarenes 115 and cyclobutane-derived cyanohydrins 116.](image-url)

a) Pd-catalyzed C–H addition of 115 to the nitrile group of 116 produces intermediates 117 and 118. An α-iminol rearrangement with ring expansion subsequently produces 119. b) Cyclopentanone-based substrates (120) do not react under the same conditions.
Figure 22: Four eburnane-type alkaloid natural products 122–125 were synthesized from common intermediate 127, which was produced from known precursor 126 by an α-iminol rearrangement.

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References
1. Paquette, L. A.; Hofferberth, J. E. Chapter 3: The α-Hydroxy Ketone (α-Ketol) and Related Rearrangements. In Organic Reactions; Overman, L. E., Ed.; American Cancer Society, 2004; Vol. 62, pp 477–567. doi:10.1002/0471264180.or062.03
2. Heinze, R. C.; Lentz, D.; Heretsch, P. Angew. Chem., Int. Ed. 2016, 55, 11656–11659. doi:10.1002/anie.201605752
3. Zhang, X.; Staples, R. J.; Rheingold, A. L.; Wulf, W. D. J. Am. Chem. Soc. 2014, 136, 13971–13974. doi:10.1021/ja5065685
4. Brunner, H.; Kagan, H. B.; Kreutzer, G. Tetrahedron: Asymmetry 2003, 14, 2177–2187. doi:10.1016/s0957-4166(03)00433-6
5. Wu, H.; Andres, R.; Wang, Q.; Zhu, J. Angew. Chem., Int. Ed. 2019, 58, 499–503. doi:10.1002/anie.201812244
6. Dai, L.; Li, X.; Zeng, Z.; Dong, S.; Zhou, Y.; Liu, X.; Feng, X. Org. Lett. 2020, 22, 5041–5045. doi:10.1021/acs.orglett.0c01626
7. Ooi, T.; Ohmatsu, K.; Maruoka, K. J. Am. Chem. Soc. 2007, 129, 2410–2411. doi:10.1021/ja063051q
8. Rossbach, J.; Harms, K.; Koert, U. Org. Lett. 2015, 17, 3122–3125. doi:10.1021/acs.orglett.5b03066
9. Markham, J. P.; Staben, S. T.; Toste, F. D. J. Am. Chem. Soc. 2005, 127, 9708–9709. doi:10.1021/ja052831g
10. Kim, K.-D.; Yeom, H.-S.; Shin, S.; Shin, S. Tetrahedron 2012, 68, 5241–5247. doi:10.1016/j.tet.2012.03.018
11. Löffert, R.; Linden, A.; Gademann, K. J. Am. Chem. Soc. 2017, 139, 16996–16999. doi:10.1021/acs.jacs.7b01053
12. Kalmode, H. P.; Patil, S. S.; Handore, K. L.; Athawale, P. R.; Dandera, R.; Verma, A. K.; Basu, A.; Reddy, D. S. Eur. J. Org. Chem. 2019, 2376–2381. doi:10.1002/ejoc.201900048
13. Adams, T. E.; El Souls, M.; Hawkins, B. C.; Hiner, S.; Holloway, G.; Khoo, M. L.; Owen, D. J.; Savage, G. P.; Scammells, P. J.; Rizzacasa, M. A. J. Am. Chem. Soc. 2009, 131, 1607–1616. doi:10.1021/ja808402e
14. Chambers, J. M.; Huang, D. C. S.; Lindqvist, L. M.; Savage, G. P.; White, J. M.; Rizzacasa, M. A. J. Nat. Prod. 2012, 75, 1500–1504. doi:10.1021/ic300376f
15. Nishimura, E.; Ohhune, Y.; Shinada, T. Tetrahedron Lett. 2015, 56, 539–541. doi:10.1016/j.tetlet.2014.12.005
16. Kurasawa, K.; Kwon, E.; Kuwahara, S.; Enomoto, M. Org. Lett. 2016, 20, 4645–4648. doi:10.1021/acs.orglett.6b01932
17. Chen, J.-H.; Levine, S. R.; Buergler, J. F.; McMahon, T. G.; Medeiros, M. R.; Wood, J. L. Org. Lett. 2012, 14, 4531–4533. doi:10.1021/ol202072z
18. Chunduru, S. K.; Mrachko, G. T.; Calvo, K. C. Biochemistry 1989, 28, 486–493. doi:10.1021/bi00428a012
19. Murkin, A. S.; Manning, K. A.; Kholidar, S. A. Bioorg. Chem. 2014, 57, 171–185. doi:10.1016/j.bioorg.2014.06.001
20. Manning, K. A.; Sathyamooorthy, B.; Eleitsky, A.; Szyperski, T.; Murkin, A. S. J. Am. Chem. Soc. 2012, 134, 20589–20592. doi:10.1021/ja310353c
21. Munos, J. W.; Pu, X.; Mansoorabadi, S. O.; Kim, H. J.; Liu, H.-w. J. Am. Chem. Soc. 2009, 131, 2048–2049. doi:10.1021/ja807987h
22. Katsuyama, Y.; Harmolffs, K.; Pistorius, D.; Li, Y.; Müller, R. Angew. Chem., Int. Ed. 2012, 51, 9437–9440. doi:10.1002/anie.201204138
23. Gu, B.-B.; Wu, W.; Jiao, F.-R.; Jiao, W.-h.; Li, L.; Sun, F.; Wang, S.-P.; Yang, F.; Lin, H.-W. J. Org. Chem. 2019, 84, 300–306. doi:10.1021/acs.joc.8b02679
24. Janso, J. E.; Hatli, B. A.; Eustáquio, A. S.; Kukowski, K.; Waldman, A. J.; Zha, L.; Nakamura, H.; Bernan, V. S.; He, H.; Carter, G. T.; Koehn, F. E.; Balskus, E. P. Tetrahedron 2014, 70, 4156–4164. doi:10.1016/j.tet.2014.03.009
25. Wang, B.; Guo, F.; Ren, J.; Ai, G.; Aigle, B.; Fan, K.; Yang, K. Nat. Commun. 2015, 6, 7674. doi:10.1038/ncomms8674
26. Proteau, P. J.; Li, Y.; Chen, J.; Williamson, R. T.; Gould, S. J.; Laufer, R. S.; Dmitrenko, G. I. J. Am. Chem. Soc. 2000, 122, 8325–8326. doi:10.1021/ja001631w
27. Kawamura, M.; Kamo, S.; Azuma, S.; Kubo, K.; Sasamori, T.; Tokitoh, N.; Kurasocho, K.; Tsukuba, K. Org. Lett. 2017, 19, 301–303. doi:10.1021/acs.orglett.6b03541
28. Li, Q.-J.; Tang, P.-F.; Zhou, X.; Lu, W.-J.; Xu, W.-J.; Luo, J.; Kong, L.-Y. Org. Chem. Front. 2021, 8, 1409–1414. doi:10.1039/d0qo01118e
29. Zhang, X.; Dai, Y.; Wulf, W. D. Synlett 2018, 29, 2015–2018. doi:10.1055/s-0037-1610262

Beilstein J. Org. Chem. 2021, 17, 2570–2584.
30. Serusi, L.; Cuccu, F.; Secci, F.; Aitken, D. J.; Frongia, A. Synthesis 2021, 53, 673–681. doi:10.1055/s-0040-1705587
31. Cheng, N.; Cui, S.-Q.; Ma, Q.-Q.; Wei, Z.-L.; Liao, W.-W. Org. Lett. 2021, 23, 1021–1025. doi:10.1021/acs.orglett.0c04214
32. Li, G.; Piemontesi, C.; Wang, Q.; Zhu, J. Angew. Chem., Int. Ed. 2019, 58, 2870–2874. doi:10.1002/anie.201813920