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Synthesis of 2-phenyl-2-cycloalkenones via palladium-catalyzed tandem epoxide isomerizationintramolecular aldol condensation

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Abstract: We have extended the scope of our palladium-catalyzed tandem epoxide isomerization/aldol condensation reaction to encompass intramolecular condensations, which provide facile access to conjugated cycloalkenones from epoxy aldehydes or diepoxides. For example, reaction of 5,6-epoxy-6-phenylhexanal with Pd(OAc)₂-PBu₃ catalyst in the presence of NaHCO₃ and 3Å molecular sieves forms 2-phenyl-2-cyclopentenone (80%). Similarly, 1,2;5,6-diepoxy-1-phenylhexane affords 3-methyl-2-phenyl-2-cyclopentenone (72%). The observation of dicarbonyl intermediates (e.g., 1-phenyl-2,5-hexanedione in the latter case) demonstrates that the reaction proceeds via Pd-catalyzed isomerization of the diepoxide to the diketone, followed by base-catalyzed aldol condensation. © 1998 Elsevier Science Ltd. All rights reserved.

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A major theme in modern chemical synthesis is the development of innovative strategies for increasing synthetic efficiency in organic reactions [1 - 3]. Noteworthy among these strategies are tandem (or domino) reactions, in which two or more distinct bond-forming reactions occur sequentially in a single synthetic process, without the isolation of reaction intermediates [4 - 6]. Tandem reaction sequences initiated by a transition metal-mediated step are increasing in number and importance [7]. Our research program is directed toward the development of synthetically useful transformations of small-ring heterocycles catalyzed by transition metal complexes [8 - 10]. To that end, we recently reported that the Pd(0) catalyst generated *in situ* from Pd(OAc)₂ and PBu₃ catalyzes a tandem process, in which aryl-substituted epoxides undergo sequential isomerization to arylacetaldehydes, followed by self- or crossed-aldol condensation (eq 1), to form α,β -unsaturated aldehydes [10]. We wondered whether it would be possible to increase the scope of this novel reaction sequence to include the formation of rings via *intramolecular* aldol condensation. In this Letter, we report that aryl-substituted epoxides bearing either an

aldehyde moiety or another isomerizable epoxide group do indeed undergo the title reaction, providing five- and six-membered cyclic conjugated enones in good yields, in a single synthetic operation.



The syntheses of our cyclization substrates are shown below. Epoxy aldehydes 1 and 2 were prepared from dihydropyran as illustrated in eq 2 [11], and diepoxides 3 - 6 were synthesized as depicted in eqs 3 - 5 [12, 13].



Our first attempts at tandem epoxide isomerization-intramolecular aldol condensation focused on epoxy aldehydes 1 and 2, in which the acceptor carbonyl group is already present. We employed our previously identified catalyst conditions [10, 14], generating the Pd(0) catalyst by reduction of $Pd(OAc)_2$ with PBu₃ (3 equiv) in t-BuOH. As we have noted that the addition of weak bases and dehydrating agents improves the yields of intermolecular tandem isomerization-condensation reactions [15], we investigated a series of such additives, and found that sodium bicarbonate and 3Å molecular sieves (or MgSO₄, in some cases) gave the best yields of cycloalkenones 7 and 8 (eq 6). Low substrate concentrations (0.15 - 0.25 M) provided optimal yields within reasonable time periods (12 - 16 h).

$$\begin{array}{c} \begin{array}{c} \begin{array}{c} Ph & \begin{array}{c} Pd(OAc)_{2} (6\%), PBu_{3} (18\%) \\ \end{array} \\ \begin{array}{c} Ph & \begin{array}{c} Pd(OAc)_{2} (6\%), PBu_{3} (18\%) \\ \end{array} \\ \begin{array}{c} NaHCO_{3} (1-4 \ eq), 3Å \ MS \\ \end{array} \\ \begin{array}{c} 1 & (n = 1) \\ \begin{array}{c} 2 & (n = 2) \end{array} \end{array} \end{array} \begin{array}{c} \begin{array}{c} Ph \\ \end{array} \\ \begin{array}{c} T & (n = 1, 80\%) \\ \end{array} \\ \begin{array}{c} NaHCO_{3} (1-4 \ eq), 3Å \ MS \end{array} \end{array} \begin{array}{c} \begin{array}{c} Ph \\ \end{array} \\ \begin{array}{c} Ph & \begin{array}{c} T & (n = 1, 80\%) \\ \end{array} \\ \begin{array}{c} R & (n = 2, 78\%) \end{array} \end{array} (6) \end{array}$$

We next turned our attention to diepoxide substrates, in which *both* carbonyl functionalities necessary for the aldol condensation are "masked" as epoxides. In substrates **3** and **4**, the two epoxy groups differ in the regiochemical outcome of palladium-catalyzed isomerization: the aryl-substituted epoxide selectively forms only the benzylic ketone [9], while the terminal alkyl-substituted epoxide rearranges to provide only the methyl ketone [16]. Under the optimal conditions described above, diepoxide **3** underwent tandem isomerization-cyclization (0.07 M, 48 h) to form the conjugated, disubstituted cyclopentenone **9** in good yield (eq 7). However, the homologous substrate **4** provided

cyclohexenone 10 in much lower yields (0.11 M, 72 h), due in part to slower cyclization (as evidenced by the observation of 6,7-epoxy-1-phenyl-2-heptanone and 1-phenyl-2,6-heptanedione, products of incomplete isomerization and cyclization, respectively). With symmetrical diepoxides 5 and 6, in which both epoxide termini bear a single aryl substituent, tandem epoxide isomerization-aldol cyclization provided the 3-benzyl-2-phenyl-2-cycloalkenones, as shown in eq 8. Again, while cyclopentenone 11 was obtained in quite

good yield (0.11 M, 72 h), the corresponding cyclohexenone 12 was formed in much lower yield (0.17 M, 84 h); 20% of the acyclic dione intermediate (1,7-diphenyl-2,6-heptanedione) was also isolated. The longer reaction times required with diepoxide substrates 3 - 6 undoubtedly reflect the fact that aldol condensations are normally slower with ketone acceptors than with aldehydes.

A typical procedure is as follows: To a solution of Pd(0) catalyst (generated from Pd(OAc)₂ (7.1 mg, 32 μ mol) and PBu₃ (24 μ L, 95 μ mol) in 5 mL t-BuOH under N₂ [14]) was added diepoxide **3** (66 mg, 0.35 mmol), NaHCO₃ (29.4 mg, 0.35 mmol) and 3Å molecular sieves (0.88 g), and the mixture was refluxed under N₂. After 24 h, additional

NaHCO₃ (1 equiv) was added; after 48 h, GC showed no further conversion, and enone 9 [17] was obtained as a yellowish oil (43.5 mg, 72%; $R_f = 0.36$) by flash chromatography on silica gel (3:1 hexane-ethyl acetate). ¹H NMR (270 MHz): δ 7.60-7.30 (m, 5H), 2.64-2.59 (m, 4H), 2.17 (s, 3H). IR (film): 3062, 3036, 2930, 2864, 1702, 1641, 1609, 1503, 1443, 1384, 1299.

In conclusion, this work demonstrates the application of an aryl-substituted epoxide as a synthon for a benzylic ketone enolate, in an *intra*molecular extension of our previously reported tandem epoxide isomerization-aldol condensation reaction [10]. This process provides five- and six-membered conjugated cycloalkenones, which are themselves useful substrates for further elaboration, in moderate to good yields, in a single synthetic operation. We are currently attempting to expand the epoxide isomerization-*in situ* enolization process to encompass other enolate reactions, such as Michael additions [7].

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