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LETTERS

Synthesis of 2-phenyl-2-cycloalkenones via palladium-catalyzed tandem epoxide isomerization-intramolecular 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 $Pd(OAc)_2$-PBu_3 catalyst in the presence of $NaHCO_3$ 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.

Keywords: aldol reactions, epoxides, isomerization, palladium

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 PBu_3 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

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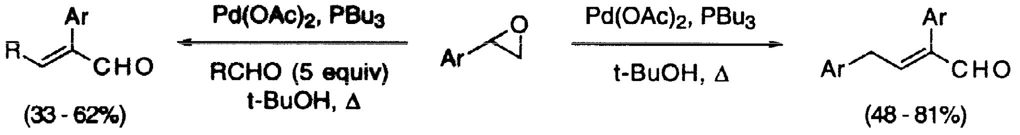
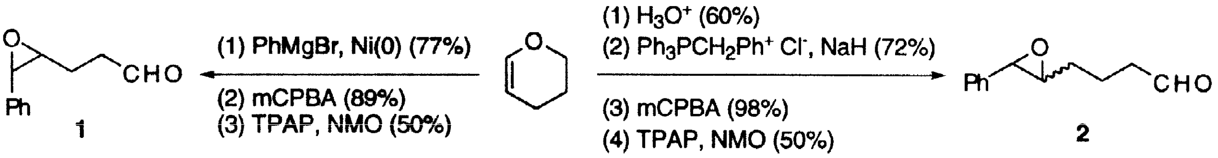
aldehyde moiety or another isomerizable epoxide group do indeed undergo the title reaction, providing five- and six-membered cyclic conjugated enones in good yields, in a single synthetic operation.



(1)

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].



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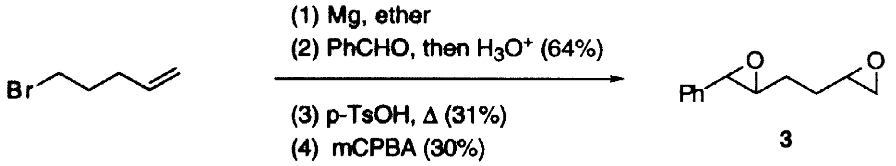

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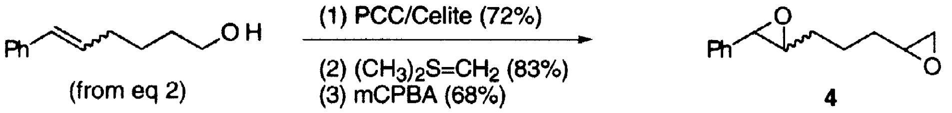

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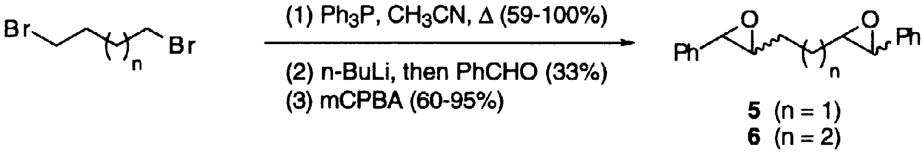
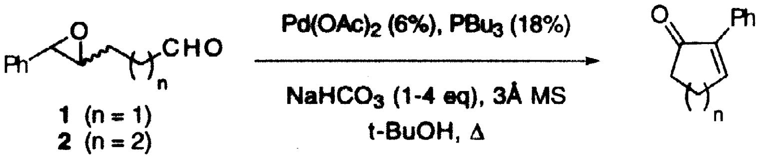


(5)

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 PBu_3 (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 $MgSO_4$, 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).

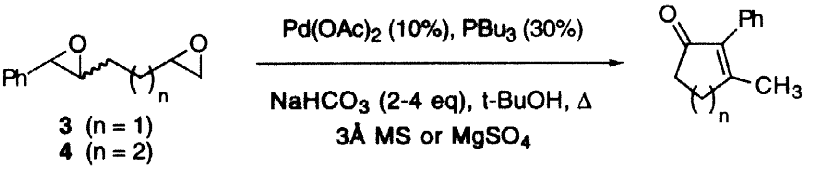


1 (n = 1)
2 (n = 2)

7 (n = 1, 80%)
8 (n = 2, 78%)

(6)

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

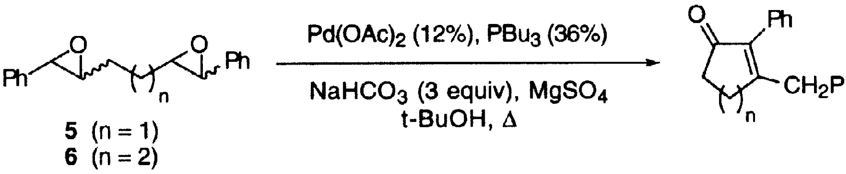


3 (n = 1)
4 (n = 2)

9 (n = 1, 72%)
10 (n = 2, 33%)

(7)

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



5 (n = 1)
6 (n = 2)

11 (n = 1, 84%)
12 (n = 2, 35%)

(8)

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 μmol) and PBu_3 (24 μL, 95 μmol) in 5 mL t-BuOH under N_2 [14]) was added diepoxide **3** (66 mg, 0.35 mmol), $NaHCO_3$ (29.4 mg, 0.35 mmol) and 3Å molecular sieves (0.88 g), and the mixture was refluxed under N_2. After 24 h, additional

$NaHCO_3$ (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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