A Tandem Epoxide Isomerization−Aldol Condensation Process Catalyzed by Palladium Acetate−Tributylphosphine

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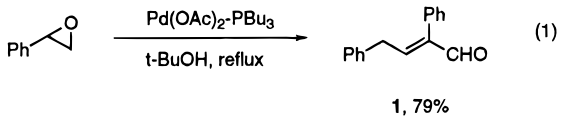
The importance of developing new strategies designed to increase synthetic efficiency in organic chemistry continues to increase.[2] One particular strategy that has received a great deal of attention in recent years is the development of sequential reactions[3] (also known as tandem or domino reactions), in which two or more distinct bond-forming processes are carried out in a single synthetic operation, without requiring isolation of intermediates. While most cases of sequential reactions documented in the recent literature involve ionic, radical, and/or pericyclic reactions, the number of transition-metal-mediated tandem reactions, many of which involve Pd-catalyzed combinations of π-bonds, is increasing rapidly.[4] We have initiated a research program directed toward the discovery and development of synthetically useful reactions of small-ring heterocycles catalyzed by transition metal complexes and now report a novel palladium-catalyzed synthesis of α,β-unsaturated aldehydes under mild conditions, via a tandem isomerization−aldol condensation reaction of aryl-substituted epoxides.[5]

We recently described the application of electron-rich palladium(0) complexes, generated *in situ* from $Pd(OAc)_2$ and PR_3 (R = *n*-Bu, Ph),[6] as catalysts for the chemo- and regioselective isomerization of epoxides to carbonyl compounds.[7] During the course of these studies, we noticed that prolonged reaction of 2-aryloxiranes with $Pd(OAc)_2$−PBu_3 afforded, in addition to the expected arylacetaldehyde, an α,β-unsaturated aldehyde apparently arising via aldol self-condensation of the primary isomerization product. Thus, reaction of styrene oxide with $Pd(OAc)_2$ (3 mol %) and PBu_3 (3 equiv/Pd) in *t*-BuOH (reflux, 10 h) yielded (*E*)-2,4-diphenyl-2-butenal (**1**) in 79% isolated yield (eq 1).[8,9] Monitoring the reaction by capillary GC clearly demonstrates that the overall process involves initial rapid isomerization of the epoxide to phenylacetaldehyde, followed by slower aldol condensation. We saw no evidence for an initial aldol addition product (i.e., 3-hydroxy-2,4-diphenylbutanal).



(1)

1, 79%

The isomerization−condensation reaction proceeds in modest to good yield in a variety of solvents, with best yields in polar media; we chose 2-methyl-2-propanol as our standard solvent because of its superior yields and moderate reflux temperature. This observation is in accord with our recent discovery that the isomerization of aryl-substituted epoxides proceeds much faster and in higher yields in polar, protic solvents than in aromatic hydrocarbons.[10] Preliminary catalyst studies show that 3−12 mol % $Pd(OAc)_2$ and a Pd:PBu_3 ratio of 1:3 provides satisfactory reaction time and yield. Using $Pd(OAc)_2$−PPh_3 (1:3) as catalyst, rapid epoxide isomerization occurs,[10] but subsequent aldol condensation proceeds more slowly than with PBu_3, providing the enal in lower overall yield (65% in 24 h).

Reaction of a variety of aryl-substituted epoxides under these conditions produces the analogous (*E*)-2,4-diaryl-2-butenals in moderate to good yields (Table 1, eq 2).[11,12] In each case, the reaction mixture was refluxed until GC indicated no further conversion of arylacetaldehyde to enal, and the yields refer to isolated products, purified by column chromatography. In the presence of 5 equiv of another aldehyde, styrene oxide undergoes a tandem isomerization−*crossed* aldol condensation reaction to afford the corresponding (*E*)-3-substituted 2-phenylpropenal, as shown in eq 3 (Table 2).[12,13] Under these conditions, the reaction is completely chemoselective for the crossed-condensation product; no self-condensation (i.e., formation of enal **1**) is observed. The stereochem-

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(2) (a) Hudlicky, T. *Chem. Rev.* **1996**, *96*, 3−30. (b) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259−281. (c) Wender, P. A.; Miller, B. L. In *Organic Synthesis: Theory and Applications*; Hudlicky, T., Ed.; JAI Press: Greenwich, CT, 1993; Vol. 2, pp 27−66.

(3) (a) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115−136. (b) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131−163. (c) Ho, T.-L. *Tandem Organic Reactions*; Wiley: New York, 1992.

(4) For leading examples, see: (a) Carpenter, N. E.; Kucera, D. J.; Overman, L. E. *J. Org. Chem.* **1989**, *54*, 5846−5848. (b) Grigg, R.; Dorrity, M. J.; Malone, J. F.; Sridharan, V.; Sukirthalingam, S. *Tetrahedron Lett.* **1990**, *31*, 1343−1346. (c) Zhang, Y.; Wu, G.; Agnel, G.; Negishi, E. *J. Am. Chem. Soc.* **1990**, *112*, 8590−8592. (d) Oppolzer, W.; De Vita, R. J. *J. Org. Chem.* **1991**, *56*, 6256−6257. (e) Trost, B. M.; Shi, Y. *J. Am. Chem. Soc.* **1993**, *115*, 9421−9438. (f) Padwa, A.; Weingarten, M. D. *Chem. Rev.* **1996**, *96*, 223−269.

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(7) Kulasegaram, S.; Kulawiec, R. J. *J. Org. Chem.* **1994**, *59*, 7195−7196.

(8) A representative experimental procedure is as follows: A suspension of $Pd(OAc)_2$ (10 mg, 45 μmol, 3 mol %) in deoxygenated *t*-BuOH (1.0 mL) was treated with tributylphosphine (33 μL, 0.13 mmol, 9 mol %) under N_2, resulting in rapid formation of the yellow Pd(0) catalyst. Styrene oxide (170 μL, 1.49 mmol) was added, and the homogeneous solution was refluxed under N_2 for 10 h. The mixture was chromatographed directly on silica gel (6:1 hexane−ethyl acetate) to afford (*E*)-2,4-diphenyl-2-butenal[9] (**1**, 130.5 mg, 79%, R_f = 0.43). ^{1}H NMR (270 MHz, $CDCl_3$): δ 9.66 (s, 1H), 7.44−7.15 (m, 10H), 6.87 (t, J = 7.3 Hz, 1H), 3.70 (d, J = 7.3 Hz, 2H). IR (neat): 3085, 2925, 2849, 2712, 1687, 1633, 1520, 1494, 1453, 1369, 1232.

(9) (*E*)-2,4-Diphenyl-2-butenal was previously prepared via aldol self-condensation of phenylacetaldehyde and characterized by X-ray crystallography; see: Axelsson, O.; Becker, H. D.; Skelton, B. W.; Sørenson, H.; White, A. H. *Aust. J. Chem.* **1988**, *41*, 727−733.

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(11) Product stereochemistry is assigned by analogy to compound **1**, the double-bond geometry of which was determined unambiguously; see ref 9.

(12) All new compounds have been fully characterized by spectroscopic techniques.

(13) A representative experimental procedure is as follows: The Pd(0) catalyst was generated from $Pd(OAc)_2$ (20 mg, 89 μmol, 12 mol %) and tributylphosphine (66 μL, 0.27 mmol, 36 mol %) in deoxygenated *t*-BuOH (1.0 mL). After addition of benzaldehyde (377 μL, 3.73 mmol, 5 equiv), the mixture was stirred at room temperature for 20 min, and styrene oxide (85 μL, 0.75 mmol) was added. After the mixture was refluxed for 48 h, only benzaldehyde, phenylacetaldehyde, and the crossed-aldol condensation product were observed by GC; the latter, (*E*)-2,3-diphenylpropenal (**2**, 51 mg; 33% based on epoxide), was isolated by chromatography (silica gel, 6:1 hexane−ethyl acetate, R_f = 0.48). ^{1}H NMR (270 MHz, $CDCl_3$): δ 9.78 (s, 1H), 7.40−7.18 (m, 11H). IR (neat): 3061, 2891, 2717, 1695, 1628, 1544, 1461, 1419, 1218, 1095. For a previous synthesis, see: Nerdel, F.; Weyerstahl, P.; Kühne, D.; Lengert, H.-J. *Liebigs Ann. Chem.* **1968**, *718*, 115−119.

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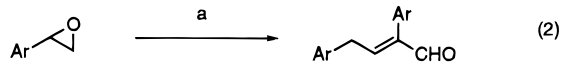
Table 1

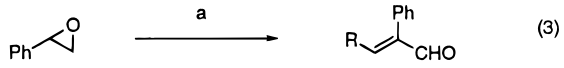


(2)

Ar	time[b] (h)	yield[c] (%)
C_6H_5	10	79 (**1**)
p-MeC_6H_4	22	81
p-FC_6H_4	23	60
p-$MeOC_6H_4$	23	48
2-naphthyl	50	48

[a] $Pd(OAc)_2$ (3−5 mol %), PBu_3 (3 equiv/Pd), *t*-BuOH, reflux. [b] Time after which no further conversion to enal was observed. [c] All yields refer to isolated, purified compounds and are unoptimized.

Table 2



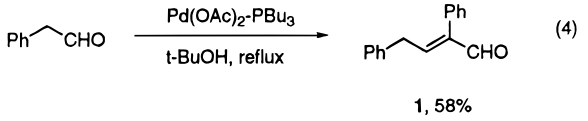
(3)

R	time (h)	yield[b] (%)
C_6H_5	48	33 (**2**)
2-furyl	24	62
p-FC_6H_4	48	43
p-$MeOC_6H_4$	26	11
$CH_3CH_2CH_2$	48	33

[a] $Pd(OAc)_2$ (12 mol %), PBu_3 (3 equiv/Pd), 5 equiv of RCHO per styrene oxide, *t*-BuOH, reflux. [b] Time after which no further conversion to enal was observed. [c] All yields (unoptimized) are based on epoxide and refer to isolated, purified compounds.

istry of one of the aldol condensation products ((*E*)-2,3-diphenylpropenal, **2**) was determined unambiguously by a single-crystal X-ray diffraction study.[14] The tandem isomerization−condensation process also occurs with alkanals; thus, reaction of styrene oxide with butanal (eq 3) produced (*E*)-2-phenyl-2-hexenal in 33% yield.[12] However, in the presence of 2-butanone (5 equiv) we isolated only enal **1** in 40% yield, with no trace of ketone-derived condensation products, demonstrating chemoselectivity for condensation with aldehydes over ketones.

In a control experiment, treatment of phenylacetaldehyde under the same conditions employed in eq 2 ($Pd(OAc)_2$−PBu_3, reflux, 10 h) also yielded the aldol condensation product **1**, albeit in considerably lower yield (eq 4). The epoxide isomerization reaction is thought to



(4)

1, 58%

proceed via a metal hydrido−enolate complex intermediate,[15] which may undergo an aldol addition reaction with free aldehyde; however, the result depicted in eq 4 demonstrates that direct enolization of the arylacetaldehyde must also occur under these reaction conditions.

(14) See the supporting information for details of the crystallographic study. The indicated stereochemistry of the crossed-condensation products is supported by molecular mechanics calculations (MM+). In all cases, optimization using the Polak-Ribiere algorithm with a root mean square gradient of 0.4 kcal/[Å mol] gave the (*E*) stereoisomer as the stable configuration; see the supporting information for details.

Although a number of reports describe the direct enolization of activated carbonyl compounds by low-valent metal catalysts,[16] suggesting the possible relevance of a Pd−enolate intermediate in the present case, we believe that traces of base (most likely acetate[17]) present in the reaction mixture may also be responsible in part for the aldol condensation. This hypothesis is supported by our observation that the yield of enal formed in the tandem isomerization−aldol condensation of *p*-fluorostyrene oxide is increased from 60% to 66% upon addition of 6 mol % NaOAc. Similarly, addition of tributylamine (1 equiv) improves the yield of **2** formed via isomerization−crossed condensation of styrene oxide with benzaldehyde from 33% to 57%.

In summary, this report demonstrates the novel concept that 2-aryloxiranes can serve as synthons for arylacetaldehyde enolates in a novel tandem epoxide isomerization−aldol condensation process, in which both self- and crossed-condensations are possible. Although yields are sometimes moderate, they represent *overall* yields for both steps in the reaction sequence and in many cases are comparable to those obtained in classical crossed-aldol condensation reactions.[18] We have also shown that relatively unactivated carbonyl compounds can undergo direct enolization under mild conditions in the presence of $Pd(OAc)_2$−PBu_3 and are continuing to explore the implications of these findings for other palladium-mediated enolate reactions.

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Supporting Information Available: Experimental procedures, including characterization data for all new compounds, preliminary X-ray data on compound **2**, and details of the molecular mechanics study (17 pages).

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(16) For representative examples, see: (a) Ito, Y.; Sawamura, M.; Hayashi, T. *J. Am. Chem. Soc.* **1986**, *108*, 6405−6406. (b) Paganelli, S.; Schionato, A.; Botteghi, C. *Tetrahedron Lett.* **1991**, *32*, 2807−2810. (c) Lin, Y.; Zhu, X.; Xiang, M. *J. Organomet. Chem.* **1993**, *448*, 215−218. (d) Murahashi, S.-I.; Naota, T.; Taki, H.; Mizuno, M.; Takaya, H.; Komiya, S.; Mizuho, Y.; Oyasato, N.; Hiraoka, M.; Hirano, M.; Fukuoka, A. *J. Am. Chem. Soc.* **1995**, *117*, 12436−12451.

(17) (a) Amatore and co-workers have shown[17b] that reduction of $Pd(OAc)_2$ by PR_3 generates $Pd(OAc)(PR_3)_n^-$, HOAc, and $R_3P{=}O$; thus, acetate is likely to be present in our reactions. (b) Amatore, C.; Carré, E.; Jutand, A.; M'Barki, M. A.; Meyer, G. *Organometallics* **1995**, *14*, 5605−5614. (c) We also find that NaOAc (5 mol %) catalyzes the aldol self-condensation of phenylacetaldehyde to **1**; however, other likely impurities ($Pd(OAc)_2$, PBu_3, HOAc) do not. See the supporting information for details.

(18) Nielsen A. T.; Houlihan, W. J. *Org. React.* **1968**, *16*, 1−438.