A Simple Divergence from Asymmetric Cyclopropane to Lactone Annulation

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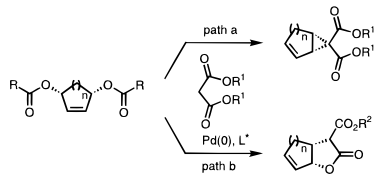
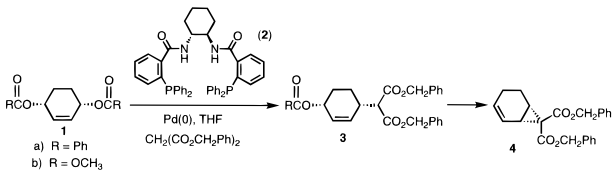
The widespread occurrence of lactones and their utility as building blocks makes a simple protocol for their asymmetric introduction desirable. The few existent protocols for an annulation equivalent do not lend themselves readily for catalytic asymmetric introduction.[1] In addition, asymmetric syntheses of cyclopropanecarboxylic acids almost invariably involve transition metal catalyzed cyclopropanations of alkenes with diazo compounds. While the copper-[2] and rhodium-[3]catalyzed asymmetric cyclopropanations have shown spectacular successes, these reactions have limitations.[4,5] An appealing alternative paradigm makes use of the ability to desymmetrize meso diesters as shown in eq 1, path a, using an asymmetric palladium catalyzed allylic alkylation.[6] In the course of these studies, we discovered that the asymmetric cyclopropanation[7,8] was not straightforward and that simple choice of malonate derivative allowed either an asymmetric lactone annulation (eq 1, path b) or an asymmetric cyclopropane annulation (eq 1, path a).



(1)

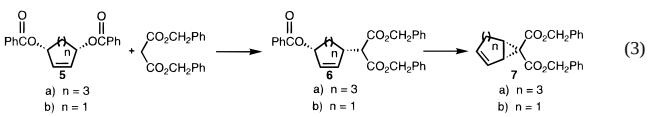
Initial studies examined the reaction of the dibenzoate **1a** with dibenzyl malonate[9] (eq 2). When 2.5 mol % $[\eta^3\text{-}C_3H_5PdCl]_2$ and 10 mol % **2** are utilized with DBU (1,8-diazabicyclo[5.4.0.]-undec-7-ene) as base at 0 °C, the monoalkylation product **3** was isolated in 63% yield and the cyclopropane in 22% yield.



(2)

Raising the temperature to reflux under otherwise identical conditions allowed complete conversion of scalemic **3** to its cyclopropane **4**. The sluggishness of the cyclization of **3** stemmed from a slow ionization since the chirality of the ligand and the remaining allylic benzoate represented a mismatch. Proof for this contention arose by using racemic ligand **2** wherein cyclization now proceeded at room temperature. Decreasing the amount of catalyst to 1 mol % of $[\eta^3\text{-}C_3H_5PdCl]_2$ and 2.5 mol % **2** with 2 equiv of DBU at 0 °C to room temperature overnight gave a 77% yield of **3**[10] whose ee of 96% was determined by HPLC (Chiralcel AD, 5% 2-propanol/heptane). Better results were obtained by using sodium hydride as the base at 0 °C to room temperature with the reaction requiring only 2.5 h to give **3** in 81% yield and 99% ee.

Applying this last set of reaction conditions to the seven-membered ring substrate **5a** gave the monalkylated product **6a**[10] in 71% yield and >99% ee[9] at −20 °C to room temperature (eq 3). Initiating the reaction at 0 °C caused a diminishment in ee to 86%. The five-membered ring substrate **4b** showed the greatest sensitivity to temperature. Initiating the reaction at −20 °C under otherwise identical reaction conditions gave **6b**[10] in 75% yield and 92% ee.



(3)

Cyclization to the cyclopropanes proved surprising. Using triphenylphosphine as ligand, $(\eta^3\text{-}C_3H_5PdCl)_2$, and DBU as base, cyclization proceeded moderately but significant racemization accompanied ring closure. For example, **3** of 99% ee gave **4** of 42% ee in THF and 64% ee in CH_2Cl_2. On the other hand, use of cesium carbonate with a catalyst formed from $(\eta^3\text{-}C_3H_5\text{-}PdCl)_2$ and dppp (1,3-diphenylphosphinopropane) in THF at 0 °C to room temperature to reflux gave **4**[10,11] in 90% yield and 94% ee.[9] Control experiments demonstrated that the source of the surprising racemization did not derive from racemization of the cyclopropane. The improved conditions obtained for the final cyclization with minimal racemization were applied to the seven-membered (i.e., **6a**) and five-membered (i.e., **6b**) ring substrates to give the cyclopropanes **7a**[10,11] and **7b**[10,12] in 95% yield (96% ee[9]) and 58% yield (89% ee[9]), respectively.

Switching to Meldrum's acid as the pronucleophile, as shown in eq 4, gave similar results wherein the monoalkylation product **8a**,[10] mp 154 °C, was isolated in 60% yield and 98% ee.[9] Resubjection of **8a** to the same conditions, with the exception being the use of a racemic mixture of ligand **2**, gave none of the cyclopropane **9** and only lactone **10a**[13] in 75% yield. Use of achiral ligands, such as triphenylphosphine and triisopropyl

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(9) All ee values were determined by HPLC (Daicel Chiracel AD or OD). The dibenzyl esters were utilized prefentially because of ease of analysis using a chiral HPLC column for determination of ee.

(10) This compound has been fully characterized spectrally and elemental composition established by high-resolution mass spectrometry and/or combustion analysis.

(11) Cf. the dimethyl ester in ref 7b.

(12) For methyl ester, see: Burgess, K. *J. Org. Chem.* **1987**, *52*, 2046.

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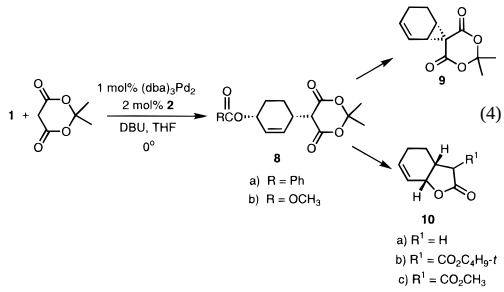
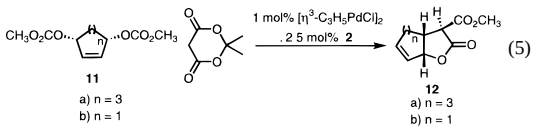
phosphite, in the same reaction also gave **10a** in comparable yields. Adding *tert*-butyl alcohol to the reaction mixture produces the *tert*-butyl ester **10b** instead in 52% yield.



(4)

Switching to the dicarbonate **1b** in the absence of base led directly to the lactone **10c** but only in 30% yield (83% ee). Use of $(\eta^3\text{-}C_3H_5PdCl)_2$ as catalyst precursor gave a slightly improved ee to 90%, but still only in 43% yield. The reaction consists of two stages—asymmetric alkylation and cyclization. For the first step, use of potassium carbonate as base proved beneficial to maximize ee; however, it did not appear to be satisfactory for the cyclization step. The latter was improved by using a tertiary amine base in the presence of methanol. The best conditions involved performing the alkylation with 1 mol % $(\eta^3\text{-}C_3H_5PdCl)_2$, 2.5 mol % **2**, and 0.5 equiv of potassium carbonate with 3 equiv of methanol in THF at 0 °C. After 1 h, 0.5 equiv of (diisopropylethyl)amine was added, the reaction was allowed to warm to room temperature and subsequently heated to 55 °C. By this method, crystalline lactone **10a**,[10,14] mp 98−99 °C was obtained in 70% yield and >99% ee.[9]

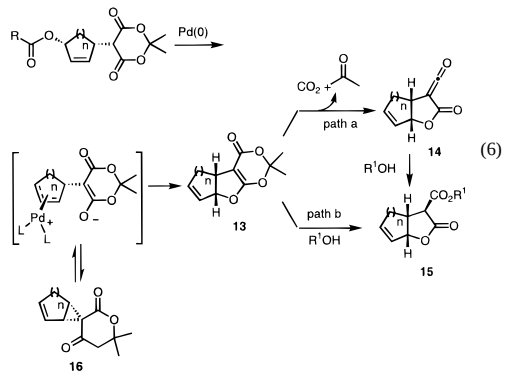
The sluggishness of the reaction for the seven-membered substrate **11b** required the alkylation to be performed at 50 °C (eq 5). At this temperature, use of 0.5 equiv of potassium carbonate as base even in the absence of methanol generated the lactone **13a**[10] in satisfactory yield (70%) and ee (96%[9]).



(5)

The five-membered ring substrate **11b** (eq 5) proved to be exceptionally reactive. When the reaction was performed as for **1b**, **11b** produced the lactone **12b** having only 76% ee. Lowering the temperature improved the ee. The insolubility of potassium carbonate made it impractical to employ it at low temperature. Switching to methanolic sodium methoxide allowed the reaction to be performed at −20 °C. After warming to room temperature, (diisopropylethyl)amine was added, and the reaction was allowed to proceed to completion. The bicyclic lactone **12b**[10] was obtained in 54% yield and 96% ee.[9]

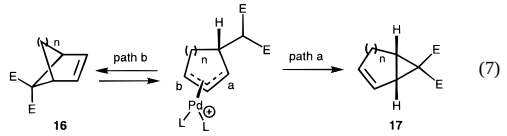
The formation of the lactone in the reactions with Meldrum's acid is unexpected.[15] It presumably arose from an unprecedented O-alkylation as shown in eq 6. Formation of the O-alkylated product **13** may trigger a retro-Diels−Alder reaction to form the acyl ketene **14** which may then be trapped by alcohol to give the observed lactone **15** (path a). Alternatively, the O-alkylated product **13** may react directly with the alcohol to give **15** (path b). The mildness of the reaction conditions and precedent with related systems suggest path a to be less likely. Either pathway suggests that any R^1 group may be introduced. Indeed, as shown in eq 4, adding *tert*-butyl alcohol to the cyclization of benzoate **8a** gave the *tert*-butyl ester. Addition of no alcohol led to trapping by water ($R^1OH = H_2O$) followed by decarboxylation to give the parent lactone. The sensitivity of **13** toward alcoholysis was illustrated by the fact that methanol released from the carbonate leaving group was sufficient to



(6)

effectively hydrolyze it. Formation of the O-alkylated product **13** may derive from an isomerization of the initial C-alkylated product **16**. The known reactivity of these vinylcyclopropanes toward Pd(0)[12,16] and the special activation toward ring opening of cyclopropanes provided by Meldrum's acid[17] make this scenario quite reasonable.

The racemization accompanying formation of the cyclopropane indicates this seemingly straightforward reaction is much more complex. The simplest explanation invokes reversible cyclization to a symmetrically bridged bicyclic system **16** (eq 7, path b) by attack at C_b competitive with formation of cyclopropane **17** (path a) by attack at C_a. For $n = 2$, the



(7)

considerably higher strain of **17** compared to that of **16**, according to molecular mechanics, would suggest the reverse scenario (i.e., equilibration will favor **16** not **17**). Vinylcyclopropanes such as **17** are known to be substrates for Pd(0).[16] Furthermore, these calculations suggest that bridged bicycles like **16** ($n = 2$ or 3) should be observable, but they have not been detected. Thus, a much more complicated mechanism must be involved. The speculative nature of any such suggestions leads us to postpone any further comment at this time.

Thus, we have established a very simple protocol for facile formation of either a cyclopropane or a lactone both with exceptionally high ee. This sequence constitutes a new paradigm for asymmetric cyclopropanation that complements the traditional carbenoid additions to alkenes. Lactone annulations are usually multistep processes and require chiral scalemic starting materials to be asymmetric. Thus, this one-pot protocol from readily available achiral starting materials in a catalytic asymmetric reaction makes these valuable building blocks much more accessible. The widespread presence of lactones in target molecules and their importance as building blocks (e.g., recently for carbanucleoside synthesis)[18] imparts special significance to this new reaction.

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Supporting Information Available: Sample experimental procedures and characterization data for **3**, **4**, **6a**,**b**, **7a**,**b**, **10c**, **12a**,**b** (4 pages). See any current masthead for ordering and Intenet access instructions.

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