Cyclic 1,2-Diketones as Building Blocks for Asymmetric Synthesis of Cycloalkenones

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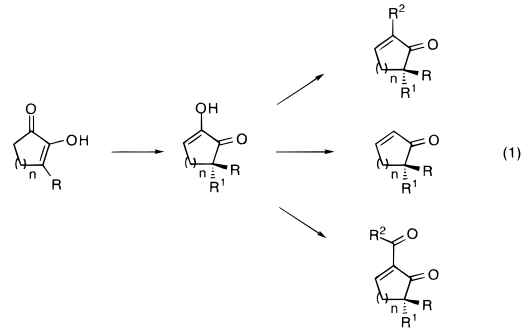
Received January 25, 2000

Cyclic 1,2-diketones[1] have found little use in organic synthesis. However, their functionality offers much flexibility for further structural variations. The fact that 3-substituted cyclic 1,2-diketones exist as single tautomeric species raised the prospect of an asymmetric synthesis of cycloalkenones as shown in eq 1.



(1)

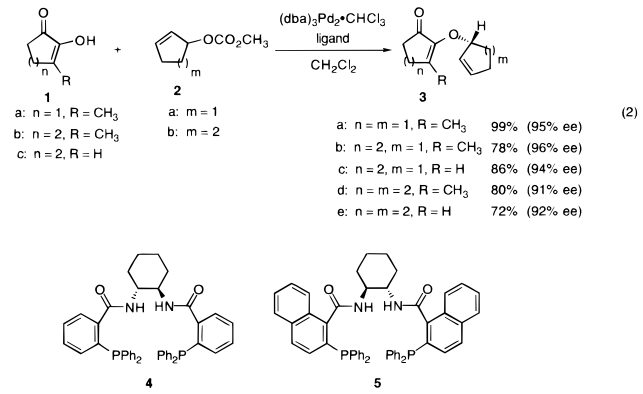
For such a scheme, nucleophiles must be shown to be capable of participating in palladium-catalyzed allylic alkylations.[2] Furthermore, the anticipated O-alkylated products must be capable of good transfer of chirality to the C-alkylated products. We report the realization of such a scheme based upon an asymmetric allylic alkylation (AAA)-Claisen rearrangement[3,4] protocol and the development of a new lanthanide catalyst for the rearrangement.[5]

The first stage of the sequence requires the development of an asymmetric O-alkylation. For this purpose, commercially available 3-methylcyclopentane-1,2-dione **1a** was alkylated with 3-cyclopentenyl methyl carbonate (**2a**) to give the allylated product **3** using our standard ligand **4**[6a] (eq 2 and Table 1). While the yield was fine, the ee was only 34% (entry 1). Tightening the pocket by switching to the naphtho linker as in ligand **5**[6b] dramatically increased the enantioselectivity to 84% ee (entry 2). Two additional optimization experiments proved quite interesting. In the first, removal of any exogeneous base further increased the selectivity to 92% ee. In the second, lowering the catalyst loading to 1% (no attempt to reduce this loading further was made) also increased the selectivity to 95%.[6] In this way, a nearly quantitative yield of the O-alkylated product **3** of 95% ee was isolated. Switching to the six-membered ring nucleophile **1b** led to a more sluggish reaction and required 40 °C but still gave an excellent ee (96%). The six-membered ring electrophile **2b** showed a parallel trend (see eq 2).[7]

Table 1. Selected Optimization Experiments[a]

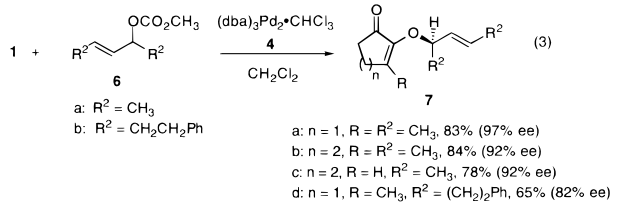
entry	base	catalyst mol %	ligand	% yield[b]	% ee (er)[c]
1	NaH	5	4	77	−34[d] (33:67)
2	NaH	5	5	55	84 (92:8)
3	None	5	5	76	92 (96:4)
4	None	1	5	99	95 (97.5:2.5)

[a] All reactions were performed in methylene chloride (0.2 M in nucleophile) at room temperature using 1.1 equiv of **2a**. [b] Isolated yield. [c] Determined by chiral HPLC. [d] The negative sign indicates the opposite chirality of product from the other entries.



(2)

Symmetrical acyclic substrates also behaved well as shown in eq 3.[8] In these cases, the more standard ligand **4** proved to be satisfactory. The simple 1,3-dimethylallyl system, which fails to give useful enantioselectivity with most chiral ligands, gives excellent (92−97% ee) results. Increasing the steric size of the substituents to phenethyl decreased the enantioselectivity some-



(3)

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(3) For reviews of the Claisen rearrangement, see: (a) Ito, H.; Taguchi, T. *Chem. Soc. Rev.* **1999**, *28*, 43. (b) Gaweski, J. J. *Acc. Chem. Res.* **1997**, *30*, 219. (c) Ganem, B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 936. (d) P. Wipf in, *Comprehensive Organic Synthesis* ed. B. M. Trost and I. Fleming, Pergamon Press: Oxford, 1991, vol 5, 827. (e) Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423. (f) Rhoads, S. J.; Rawlins, N. R. *Org. React.* **1975**, *22*, 1.

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(5) The palladium-catalyzed asymmetric O-alkylation of phenols and Claisen rearrangement of the resulting allyl aryl ethers was recently reported. (a) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1998**, *120*, 815. (b) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1998**, *120*, 9074.

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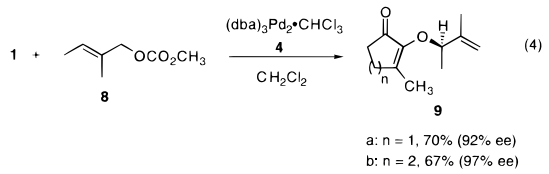
(7) The absolute configuration shown in eq 2 was assigned by applying the mnemonic developed in the group for the palladium-catalyzed asymmetric allylic alkylation reaction using ligands **4** and **5** (see ref 2a and 6a).

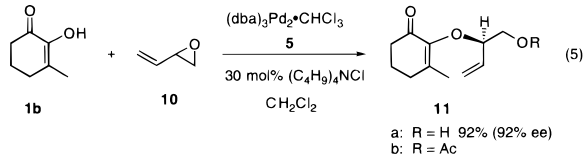
(8) The absolute configuration shown in eqs 3 and 4 was assigned by comparison of the optical rotation of a derivative to that reported in the literature.

10.1021/ja000274m CCC: $19.00
Published on Web 03/31/2000

what. The unsymmetrical tiglyl system raises the question of both regio- and enantioselectivity (eq 4).[9] The intrinsic propensity of



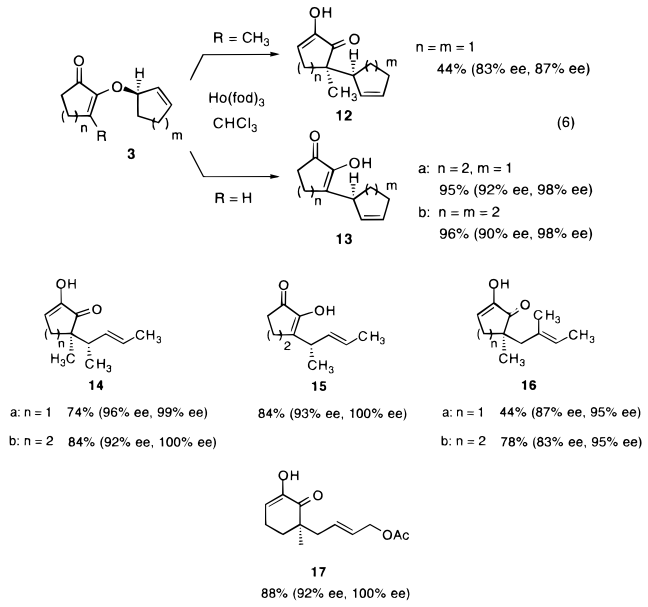
the ligand to favor nucleophilic attack at the more substituted allyl terminus with sterically nondemanding nucleophiles is observed.[10] The regioselectivity favoring **9a** and **9b** over attack at the less substituted allyl terminus was 14:1 and 7:1, respectively. Finally, butadiene monoepoxide gave excellent regio- (only one) and enantioselectivity (92% ee) using the naphtho ligand **5** as appears to be required in all the reactions of this electrophile (eq 5).[11,12] No boron cocatalysts were required for good regioselectivity in contrast to simple alcohol nucleophiles. On the other hand, best ee's required chloride ion, low palladium loading (0.2 mol %), and slightly elevated temperatures (50 °C).

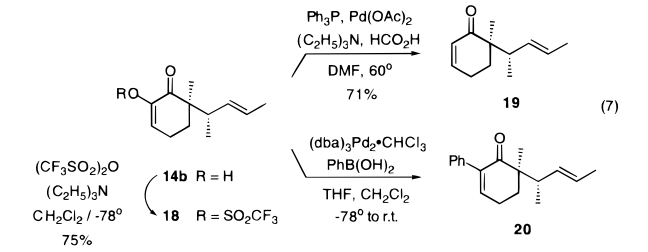


With the viability of a broad diversity of enantioselective O-alkylations established, the chirality transfer in a Claisen rearrangement was examined in the case of the cyclic substrate **3a**. The classical thermal process required temperatures >110° and gave a great deal of ionization competing with rearrangement. Classical Lewis acids such as mercuric acetate and dimethylaluminum chloride as well as bis(acetonitrile)dichloropalladium(II) resulted in no reaction or cleavage of the allylic ether bond. Lanthanide triflates such as lanthanum and europium triflate proved too reactive.[13] On the other hand, the FOD complexes of the lanthanides did prove to be effective. Among Pr, Eu, Ho, Er, and Yb, the most effective in maintaining kinetic reactivity but minimizing dissociation recombination that leads to racemization were Eu and Ho, with the latter being slightly more effective. Thus, use of 10 mol % $Ho(fod)_3$ in a minimal amount of chloroform at 50−80 °C was adopted as our standard protocol. The rearrangement of **3a** and **3b** proved to be the worst cases. The former required 75° which resulted in 87% chirality transfer in forming **12a** (eq 6).[14] Reducing the steric hindrance as in **3c** and **3e** allowed the rearrangement to proceed to give **13a** and **b** respectively at 50−60° with 98% chirality transfer.

The acyclic substrates **7a**−**c**, **9a,b**, and **11b** rearranged more smoothly to give **14**−**17** with excellent chirality transfer (95−100%). In each case, the alkene geometry is only *E*. The facility of the rearrangement in these cases is indicated by the fact that only 1 mol % of $Ho(fod)_3$ was required to form **14b**.[6]

In cases where there is the prospect of forming diastereomers (**12a**, **14a**, and **14b**), only one diastereomer, as determined by NMR spectroscopy and hplc, was observed. The excellent chirality transfer from the side chain to the ring in forming **16** and **17** represents the equivalent of an asymmetric C-alkylation. The latter product is particularly interesting since an allyl acetate, which can be used for further metal catalyzed, as well as noncatalyzed (such as Ireland−Claisen rearrangement) transformations are readily available. The holmium catalyst appears to be a quite useful catalyst generally for aromatic as well as aliphatic Claisen rearrangements. The utility of the α-diketone products for asymmetric synthesis of cycloalkenones is illustrated in eq 7.





Thus, subjecting the triflate[15] **18** to palladium-catalyzed cross-coupling allows access to the unsubstituted (i.e., **19**) or substituted (i.e., **20**) cyclohexenones.

Acknowledgment. We thank the National Science Foundation and the National Institutes of Health, General Medical Sciences, for their generous support of our programs and NSF for a predoctoral fellowship to G.M.S.. Mass spectra were provided by the Mass Spectrometry Regional Center of the University of California-San Francisco supported by the NIH Division of Research Resources. We thank Chirotech and NSC Technologies for their generous gifts of ligands.

Supporting Information Available: Experimental details (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) For recent papers on controlling the regiochemistry of Pd-catalyzed allylic alkylations, see: (a) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1999**, *121*, 4545. (b) Pretot, R.; Pfaltz, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 323. (c) Hayashi, T.; Kawatsura, H.; Uozumi, Y. *J. Am. Chem. Soc.* **1998**, *120*, 1681.

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(12) The absolute stereochemistry was assigned in analogy to previous work, see: ref 6b.

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(14) Chirality transfer is defined as (% ee product/% ee starting material) × 100%. In reporting ee's, the first number in parentheses is the observed ee of the product and the second represents this number corrected for the ee of the starting material.

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