Asymmetric O- and C-Alkylation of Phenols

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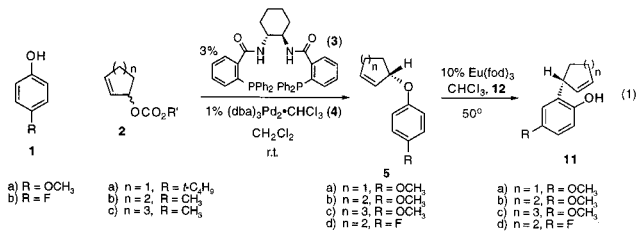
While the aliphatic Claisen rearrangement has proven to be a major synthetic tool for controlling stereochemistry in C−C bond formation, the aromatic Claisen rearrangement has not been exploited as an asymmetric aryl alkylation protocol.[1,2] The high temperatures required for the thermal process make a catalytic version desirable. However, the reported Lewis acid-catalyzed versions have led to significant racemization as well as fragmentation accompanying rearrangement.[3,4] The utility of a catalytic Claisen reaction that occurs with excellent chirality transfer also requires a facile asymmetric O-alkylation of phenols.[5,6] We report the accomplishment of both goals.

For the asymmetric O-alkylation, we examined the use of asymmetric Pd-catalyzed allylic alkylation. Whereas, standard allylic carboxylates fail as substrates due to the propensity for acyl shift to form phenyl esters, carbonates proved efficacious as shown in the alkylation of *p*-methoxyphenol (**1a**) with *tert*-butyl-3-cyclopentenyl carbonate (**2a**, eq 1). Using the ligand **3**[7,8] with



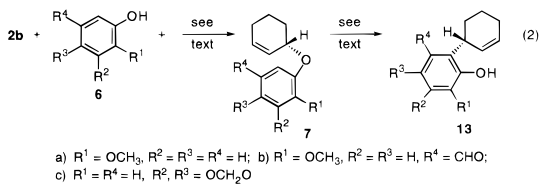
the palladium complex **4** gave **5a**[9] in good yield but with a modest enantioselectivity (see Table 1, entry 1). Lowering the temperature improved the enantioselectivity, but there clearly is an optimal temperature below which no further improvement pertains (entries 2 and 3). It should be noted that one recrystallization from cold pentanes raises the ee from 85% to 94%.

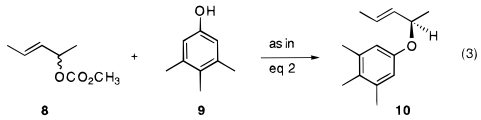
Table 1. Enantioselective Phenol Alkylations[a]

entry	phenol	allyl carb.	O-alk. temp (°C)	allyl ether (isol yield, %)	% ee[b]	rearr. temp (°C)	C-alk. (isol yield, %)	product ee (%)
1	**1**	**2a**	25	**5a** (96)	60			
2	**1**	**2a**	−40	**5a** (85)	85			
					94[c]	50	**11a** (86)	93
3	**1**	**2a**	−78	**5a** (82)	78			
4	**1**	**2b**	25	**5b** (88)	97	50	**11b** (79)	97
5	**1**	**2c**	25	**5c** (89)	92			
6	**1**	**2c**	0	**5c** (85)	93	50	**11c** (77)	96
7	**1b**	**2b**	25	**5d** (88)		80	**11d** (83)	94[h]
8	**6a**	**2b**	25	**7a** (89)	94	50	**13a** (81)	93
9	**6b**	**2b**	25	**7b** (90)	77			
10	**6b**	**2b**	0	**7b** (83)	85	80	**13b** (84)	80
11	**6c**	**2b**	25	**7c** (90)	95	50[d]	**13c**[e] (91)	93
12	**9**	**8**	25	**10** (89)	85	50	**14** (97)[f]	91[g]

[a] For reaction conditions, see text. [b] Determined by chiral HPLC using a Chiracel OD or Chirapak AD column eluting with heptane−2-propanol mixtures. [c] After recrystallization from cold pentanes. [d] Rearrangement performed with 1 mol % $Eu(fod)_3$. [e] The ee was determined by NMR analysis of the corresponding *O*-methylmandelate ester. [f] The yield corresponds to the 6:1 *E:Z* isomers. [g] For the major *E* isomer **14**. [h] The ee was determined by HPLC of the corresponding O-methylmandelate ester.

Switching from the five-membered ring allyl carbonate to either the six- or seven-membered analogue led to reactions that proved to be more straightforward. Even at room temperature, under the standard conditions, excellent ee's of products **5b**[6,9] and **5c**[10] were obtained (entries 4−6). Changing the phenol to **6a**, **6b**, or **6c** led to equally gratifying results (eq 2 and Table 1, entries





8−11) with formation of ethers **7a**,[13] **7b**,[14] and **7c**.[10] In the synthesis of adduct **7c**, the catalyst loading was reduced to 0.25 mol % of palladium precursor **4** and 0.75 mol % of ligand

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(10) All new compounds have been satisfactorily characterized spectroscopically.

(11) After stirring a solution of the allylic carbonate **2b** (261 mg, 1.67 mmol), Pd_2dba_3•$CHCl_3$ (4 mg, 0.004 mmol), and the ligand **3** (8 mg, 0.012 mmol) in degassed CH_2Cl_2 (3.0 mL) at room temperature, under argon, for 15 min, a solution of sesamol **6c** (235 mg, 1.70 mmol) in CH_2Cl_2 was added. The resulting purple solution became orange and finally yellow after stirring at room temperature for 4 h. Flash chromatography eluting with 5:1 petroleum ether:ether afforded the aryl ether **7c** (335 mg, 90% yield) as a colorless liquid. A solution of the aryl ether **7c** (175 mg, 0.803 mmol) and $Eu(fod)_3$ (8 mg, 0.008 mmol) in minimal dry chloroform (0.1 mL), under nitrogen, was placed into a preheated 50 °C oil bath for 8 h. After cooling, direct flash chromatography, eluting with 5:1 petroleum ether:ether, afforded **13c** (160 mg, 91% yield) as a colorless liquid. For larger scale reactions, better results were obtained by diluting the reaction mixture with ether and washing with water to remove the europium catalyst prior to chromatography.

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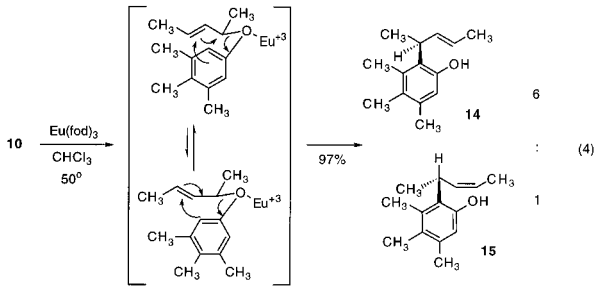
3.[12] With the less electron rich phenol **6b**, a lower temperature was required to improve the ee whereas the *p*-fluorophenol **1b** was allylated with 94% ee even at room temperature (entry 7 vs 10). The reaction of an acyclic allylic carbonate[15] **8** with phenol **9**[4b] was also examined wherein the results paralleled those seen in the cyclic case (eq 3 and Table 1, entry 12).

With the availability of the allyl aryl ethers of high enantiopurity, attention focused on the Claisen rearrangement to convert C−O to C−C stereochemistry. Initial studies examined classical Lewis acids. Treatment of **5a** with boron trichloride (PhH, −40 °C) or diethylaluminum chloride (hexanes, 25 °C) led to the rearranged product **11a** with significant racemization. A lanthanide triflate[15,16] proved too reactive—again leading to racemization. On the other hand, the common europium complex **12**[15a] in chloroform at 50 °C proved effective wherein the chirality of **5a** (94% ee) was faithfully transferred to **11a**[9] (eq 2) in 86% yield (93% ee). As summarized in Table 1, similar results were obtained in the other cases. In the case of **6c**, performing the rearrangement with minimal solvent to maintain homogeneity allowed the use of only 1 mol % of Eu(fod)$_3$.[11] The less electron rich analogues **5d**[6] and **7b** (85% ee) required slightly more elevated temperatures (80 °C, DCE) but proceeded satisfactorily to give **11d** (83% yield, 94% ee) and **13b**[13] (84% yield, 80% ee), respectively. The increased steric hindrance (in the latter case) and/or the decreased electron richness of the aromatic ring may account for the slower reaction.

The acyclic system proved to be more complicated. Rearrangement proceeded quite well under the standard conditions (97% yield) but produced a 6:1 mixture of the *E* and *Z* alkene isomers, **14** and **15**, respectively.[4b] On the basis of chairlike and boatlike transition states, respectively (eq 4),[5,17] the stereochem-

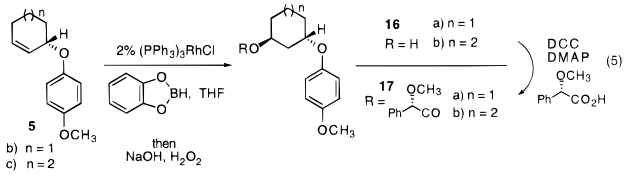


(4)

istry of the two products should be as depicted in **14** and **15**. The ee of **14** was 91%, which indicated excellent chirality transfer in the acyclic case as well.

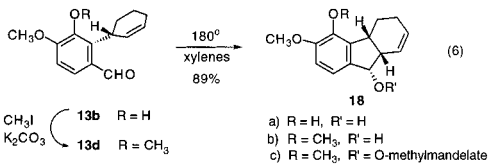
The stereochemistries of **10** and **14** have been previously established,[4b] and the stereochemistry of the former also follows from our previously established mnemonic.[6] Further evidence for this stereochemistry was obtained by hydrogenating **10** and comparing the saturated product to an authentic sample prepared by the Mitsonobu reaction of **9** with (*S*)-2-pentanol.

The absolute stereochemistry of the cyclic aryl ethers was established by regio- and diastereoselective rhodium-catalyzed hydroboration of **5b**,**c**.[18] Hydroboration proceeded smoothly in the case of the six-membered ring, producing almost exclusively the 3-alcohol **16a**. In the seven-membered-ring compound **5c**, however, a separable 1:1.7 mixture of the 2- and 3-alcohols was formed. The alcohols **16a**,**b** were converted into their mandelate esters **17a,b**, which allowed for the determination of the stereochemistry in agreement with the established mnemonic (eq 5).[19]



(5)

Asymmetric O-alkylation followed by diastereoselective Claisen rearrangement constitutes a useful protocol for asymmetric C-alkylation of phenols. The importance of the lanthanide-catalyzed Claisen rearrangement is highlighted by (1) the failure of the thermal reactions in some cases, (2) racemization occurring in some instances, and (3) subsequent reactions of the initial products. For example, the thermal reaction of **7b** leads solely to **18a** (eq 6) which, for these authors, was undesired since **13b**



(6)

was needed for morphane synthesis.[13] In our hands, reaction with the aldehyde proved more efficient after methylation of the tricyclic phenol **13b**. The product alcohol **18b** was converted into its mandelate ester **18c**, used for determining its stereochemistry.[19] The presence of the double bond in both the O- and C-alkylation products becomes a focus for further modifications.[13,20] Since rearrangements to the para position of phenols are also documented,[1,3c] this process may also consititute asymmetric para as well as ortho alkylation.[5] Such a protocol may be envisioned for other aryl heteroatom systems (e.g., anilines) and thus become a more general approach for asymmetric alkylations of aromatic (including heteroaromatic) rings.[1c] The prospect of asymmetric catalysis in the lanthanide-catalyzed rearrangement with achiral allyl aryl ethers is also suggested.[21]

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Supporting Information Available: Characterization data and copies of ^{1}H NMR and ^{13}C NMR spectra for **5a**−**d**, **7a,b**, **9**, **12**, **14**, **16a**−**d**, **17a**−**c**, **18**, **20,** and **24b** (49 pages). See any current masthead page for ordering and Internet access instructions.

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