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Regioselective palladium-catalyzed allylic alkylations

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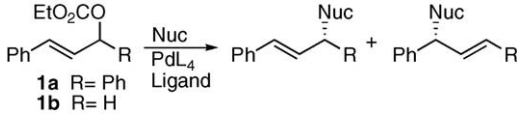
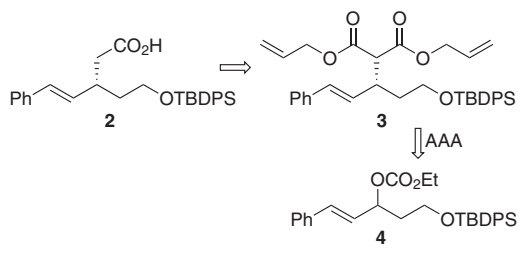
Abstract—Palladium-catalyzed allylic alkylations on asymmetrical allylic carbonates using a variety of chiral ligands gave good to excellent ee's and poor to excellent regioselectivity depending on the nucleophile used.

The search for chiral ligands for asymmetric allylic alkylation (AAA) reactions with Pd catalysts have led to numerous designs and types.[1–9] Although the majority of these studies have used allylic substrates such as **1a**, Eq. 1 that lead to symmetric π-allyls,[10,11] several studies have addressed the question of regioselectivity in asymmetric systems similar to **1b**.[12–18]



(1)

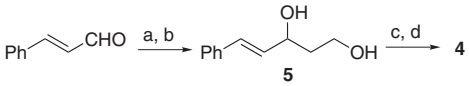
Recently, we required acid **2** that we envisioned could arise from a palladium catalyzed dealloxycarbonylation[19] of **3**, which would be assembled in a stereoselective manner using an AAA reaction and **4**, Scheme 1. Given that the use of **4** in the AAA reaction is novel in terms of regiochemistry, we present herein its use in the AAA thus providing further information on the scope of this reaction.



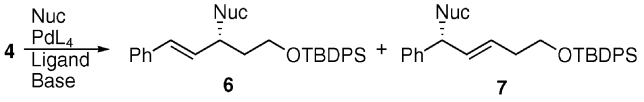
Scheme 1.

Formation of **4** involves a straightforward synthesis involving the known diol **5**, Scheme 2. Thus, modified reduction of the aldol product[20] of cinnamaldehyde and ethyl acetate gives **5** in an overall 86% yield. Standard protection of the primary alcohol followed by reaction with ethyl chloroformate gives the desired carbonate **4** in an excellent overall yield. This synthesis can be performed on the large scale providing gram quantities of **4**.

Treatment of **4** under AAA conditions could potentially result in the formation of either **6** or **7**, presumably with **6** in abundance, Eq. 2. Prior to the formation of **4**, we



Scheme 2. Reagents: (a) EtOAc, LDA then PhCH=CHCHO, 94%; (b) NABH4, I_2, 91%; (c) TBDPSCl, imidazole, 95%; (d) $ClCO_2Et$, Py, 87%.



(2)

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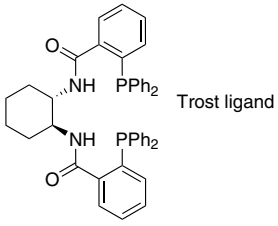
Table 1. AAA reactions with chiral ligands[a]

Entry	Nucleophile	Chiral ligand[b]	Base	Reaction condition	Yield (%)	Ratio **6**:**7**	ee[c] (%)
1	$CH_2(CO_2Me)_2$	*s*-Binap	NaH	THF, reflux 3 h	88	1.5:1	[d]
2	$CH_2(CO_2Me)_2$	*s*-Binap	Cs_2CO_3	THF, reflux 2 h	93	2.2:1	[d]
3	$CH_2(CO_2Me)_2$	*s*-Binap	BSA	THF, reflux, 4 h	90	0.8:1	[d]
4	$CH_2(CO_2Me)_2$	*s*-Binap	NaH	CH_2Cl_2, reflux, 2 h	69	0.8:1	[d]
5	$CH_2(CO_2Me)_2$	*s*-*p*-Tolbinap	Cs_2CO_3	THF, reflux, 3 h	91	1.6:1	[d]
6	$CH_2(CO_2Me)_2$	*s*,*s*-Trost	Cs_2CO_3	THF, reflux, 1 h	81	4.8:1	[d]
7	4-Methoxyphenol	*s*-Binap	Cs_2CO_3	THF, reflux, 12 h	88	>99:1	88
8	4-Methoxyphenol	*s*-Binap	NaH	THF, reflux 12 h	87	>99:1	89
9	4-Methoxyphenol	*s*-*p*-Tolbinap	Cs_2CO_3	THF, reflux 12 h	89	>99:1	87
10	4-Methoxyphenol	*s*,*s*-Trost	nBu$_4$NCl	THF, reflux 24 h	92	>99:1	94
11	Phenol	*s*-Binap	Cs_2CO_3	THF, reflux 12 h	94	>99:1	92
12	Phenol	*s*,*s*-Trost	nBu$_4$NCl	THF, reflux 48 h	90	>99:1	93
13	4-*tert*-Butylphenol	*s*-Binap	Cs_2CO_3	THF, reflux 12 h	94	>99:1	94
14	4-*tert*-Butylphenol	*s*,*s*-Trost	nBu$_4$NCl	THF, reflux 24 h	88	>99:1	98
15	4-Methoxyaniline	*s*-Binap	Cs_2CO_3	THF, reflux 12 h	50	>99:1	92
16	Aniline	*s*-Binap	Cs_2CO_3	THF, reflux 12 h	52	>1:99	98

[a] 3 mol% $Pd_2dba_3{\cdot}CHCl_3$ used in all reactions.
[b] 8 mol%.
[c] Determined by chiral GC on crude samples.
[d] Not determined due to overlapping peaks in the GC.

felt that control of the regiochemistry would be governed by retention of conjugation to the alkene/aromatic ring and that the large TBDPS group was remote enough to produce limited steric interactions. As diallyl malonate is not commercially available,[21] we initially tested dimethyl malonate to determine the feasibility of the concept. Using a loading of 3 and 8 mol% palladium and BINAP ligand, respectively, we observed a disappointing ratio of 1.5:1, entry 1 Table 1.[22–24] Conversely, the olefin geometry remained as the *E* isomer in all cases as expected.[16] The use of caerium carbonate as a base, entry 2, improved this ratio only slightly while bis(trimethylsilyl)acetamide (BSA) reversed the level of selectivity, entry 3. One attempt was made at changing the solvent (entry 4), which resulted in reduced yields. With an indication of conditions in hand, we next screened alternative ligands. Toluene binap proved to be no better then binap, however Trost's ligand (1*S*,2*S*-(−)-1,2,-diaminocyclohexane-*N*,*N*′-bis(2′-diphenylphosphinobenzoyl)), did show moderate improvement with only slightly diminished yields, entries 5 and 6.



Trost ligand

We then turned to alternative nucleophiles that had literature precedence for more selective attack. As seen in entries 7–14, excellent regioselectivity is observed for these nucleophiles with concurrent high ee's and yields. Noticeable is that the Trost ligand in entries 10 and 14 does give improved ee's. Finally, we also tested two amine nucleophiles that both gave excellent ee's but poor yields, however we were surprised to see a complete reversal of selectivity with aniline as the nucleophile.

The regioselectivity of metal catalyzed allylic alkylation is comprised of both steric and electronic effects, with steric effects usually dominating in palladium catalyzed reactions.[25] Furthermore, Cook et al. have shown that hydrogen bonding also plays a role in regioselectivity in specific substrates.[26] Two possible explanations for the change in selectivity in these reactions are the slight change in the size of the incoming nucleophile, or more probable, the change in the hardness/softness of the nucleophile. Given that palladium π-allyls are relatively soft, the change from a softer malonate carbanion to a hard phenoxide could result in the observed selectivity. Similar observations have been observed in nucleophilic attack on iron complexes.[27] However, surprisingly a remarkable change in the selectivity is observed when using aniline, a presumed hard nucleophile. Thus, in employing asymmetrical allylic carbonates, the use of the appropriate nucleophile can lead to excellent regio- and enantioselectivity. However, in view of the modest to poor selectivity of the malonate products **6**/**7** and the inability to separate these, we our pursuing alternative routes to the synthesis of **2**.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.09.190. Spectral data and experimental conditions available.

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