Palladium-catalysed Arylation of α-Methoxyketene Methyl Silyl Acetals

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Methyl α-methoxyarylacetates **3** have been synthesized by the palladium-catalysed reaction of iodobenzenes **1** with α-methoxyketene methyl silyl acetals **2**. The diastereoselective and enantioselective synthesis of the arylacetates has also been examined.

Palladium catalysed cross-coupling of organometallic compounds with aryl halides has been widely used for functionalization of aromatic compounds.[1] Although an acetate moiety has been introduced into an aromatic ring by palladium-catalysed reaction with a Reformatsky reagent[2a] or organotin reagents,[2b,c] these reagents were unsuited to the synthesis of α-substituted arylacetates. Recently, Carfagna *et al.* reported the palladium-catalysed reaction of ketene silyl acetals with aryl halides or triflates, which allows the introduction of α-alkyl- or α-aryl acetates into aromatic nuclei.[3] We have already found the reaction useful for heteroaromatic iodides.[4]

In order to evaluate both the scope and limitations of the palladium-catalysed reaction, we have investigated the reaction of heteroatom-substituted ketene silyl acetals, which is the subject of this paper.

First, the α-methoxyketene methyl silyl acetal **2** was employed as a reagent. The reaction of iodobenzene **1a** with **2** proceeded smoothly in the presence of a palladium catalyst and thallium(I) acetate in THF under reflux to give the methyl α-methoxyarylacetates **3** (see Table 1). In contrast to Carfagna's report, triphenylphosphine seemed to be somewhat better than diphenylphosphinoferrocene (DPPF) as a ligand on the palladium catalyst of this reaction. Whilst the reaction was little affected by the presence of various functional groups at the 4-position, a nitro substituent slowed the reaction. In addition, attempted palladium-catalysed reactions of methylthio **4a** or dimethylamino substituted ketene silyl acetals **4b** resulted in recovery of aryl halides.

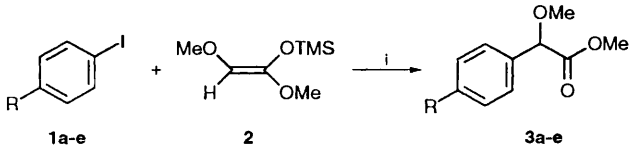
Chiral α-methoxyphenylacetic acid has been used as the reagent for NMR analysis of absolute configuration and for the preparation of chiral phosphine ligands. A practical preparative method has been reported by Takano *et al.*,[5] although no example of asymmetric carbon–carbon bond formation was reported. Therefore, we have investigated the asymmetric palladium-catalysed reaction using both diastereoselective and enantioselective methods.

The diastereoselective palladium-catalysed reaction was examined with the ketene silyl acetal of menthyl **5a** or 2-phenylcyclohexyl ester **5b** as a substrate.[6] The reaction proceeded smoothly under the reaction conditions described above, to give the phenylated products **6a** and **6b** in 54 and 52%, respectively. Diastereoisomeric excesses were determined as 22 and 15% by analysis of the ^{1}H NMR spectra, and the absolute configuration of enriched enantiomers was determined by comparison with authentic diastereoisomers obtained from optical pure α-methoxyphenylacetic acid.

The enantioselective reaction was investigated using (*S*)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl [(*S*)-BINAP]† or (*S*)-*N*,*N*-dimethyl-1-[(*R*)-1′,2-bis(diphenylphosphino)ferrocenyl]-ethylamine [(*S*)-(*R*)-BPPFA]† as a chiral ligand. With (*S*)-BINAP as a ligand, the reaction was slow, the product being obtained in only 19% yield with no asymmetric induction as determined from the specific optical rotation of the product. A low level of asymmetric induction was observed with (*S*)-(*R*)-BPPFA as a ligand, the palladium-catalysed reaction proceeding smoothly to give 67% of the product of which the enantiomer excess was estimated as 7.1% by comparing the value $[\alpha]_D$ −6.30 (*c* 3.36 acetone) with that reported {lit.,[7] $[\alpha]_D$ −89.1 (*c* 1.11 acetone)}. Further studies for obtaining greater asymmetric induction are in progress.

† These chiral ligands were purchased from Kanto Chemical Co. Ltd.

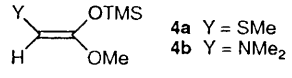
Table 1 Palladium-catalysed arylation of the ketene acetal **2**



1a-e **2** **3a-e**

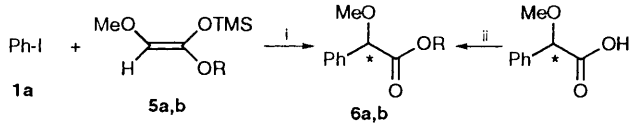
i, $[Pd(PPh_3)_4]$, TlOAc, THF, reflux, 24 h

No.	R	X	Palladium catalyst	Yield (%)
1a	H	I	$[Pd(dppf)_2]$	57
1a	H	I	$[Pd(PPh_3)_4]$	89
	H	Br	$[Pd(PPh_3)_4]$	Recovery
1b	Me	I	$[Pd(PPh_3)_4]$	82
1c	OMe	I	$[Pd(PPh_3)_4]$	89
1d	CO_2Et	I	$[Pd(PPh_3)_4]$	74
1e	NO_2	I	$[Pd(PPh_3)_4]$	13



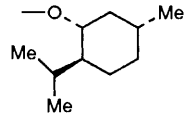
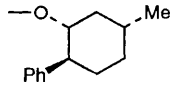
4a Y = SMe
4b Y = NMe_2

Table 2 Diastereoselective arylation of the ketene acetals **5a,b**



1a **5a,b** **6a,b**

i, $[Pd(PPh_3)_4]$, TlOAc, THF, reflux, 16 h; ii, ROH, DCC, DMAP

No.	OR	Yield (%)	D.e. (major)
5a		54	22 (*S*)
5b		52	15 (*S*)

Experimental

Methyl α-Methoxyphenylacetate **3a**.—All operations were performed under an argon atmosphere. To a mixture of TlOAc (1.78 g, 6 mmol) and THF (20 cm^3) was added a THF solution of $[Pd(PPh_3)_4]$ (0.15 mmol) and a THF solution of iodobenzene (0.61 g, 3 mmol). The mixture was stirred for 5 min, after which the α-methoxyketene methyl silyl acetal **2a** (1.06 g, 6 mmol) was added to it, and the whole refluxed for 24 h. After removal of the solvent under reduced pressure, the residue was diluted with water and extracted with Et_2O (70 cm^3 × 3). The ethereal extract was dried ($MgSO_4$) and concentrated under reduced pressure and the residue was purified by silica gel column chromatography using hexane–AcOEt (19:1) as eluent to give the crude material. This was distilled *in vacuo* to give a colourless liquid (0.48 g, 89%), b.p. 95 °C at 3 mmHg; $\nu_{max}(CHCl_3)/cm^{-1}$ 1752; δ_H(300 MHz; $CDCl_3$) 3.41 (3 H, s), 3.71 (3 H, s), 4.78 (1 H, s) and 7.53 (5 H, s); *m/z* 180 (M^+, 1.46%).

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