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ACID-MEDIATED, CHROMIUM-CATALYZED ALLYLATION OF ALDEHYDES

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ABSTRACT

Allyl bromides are efficiently coupled with aryl and aliphatic aldehydes in the presence of manganese metal, collidine hydrochloride, *bis*(diisopropylphosphino)ethane and chromium dichloride. Homoallylic alcohols are isolated in good to excellent yields directly from the reaction mixture.

Key Words: Chromium; Catalytic; Allylation; Acid-mediated

Chromium mediated addition of organic halides to aldehydes has become an important synthetic methodology due to the high functional group tolerance of organochromium species (Eq. 1).^[1,2] A drawback of the early work by Nozaki and Hiyama,^[3] and later Kishi,^[4] was the need to use large excesses of chromium(II) salts (4–100 equivalents) to obtain the desired products. The recent development of chromium-catalyzed Nozaki– Hiyama–Kishi (NHK) reactions has greatly increased the utility of this methodology.^[5,6] While catalytic in chromium, these systems require a

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stoichiometric amount of reductant and trimethylsilyl chloride (TMSCl), neither of which can be easily recovered. These features limit the large-scale application of this methodology. Therefore as part of our interest in developing more efficient versions of this methodology, we report the chromium-catalyzed allylation of aldehydes mediated by collidine-hydrochloride.

$$\begin{array}{c} O \\ H \\ H \end{array} + R'X \xrightarrow{1) C I'} O \\ H \\ 2) H^{*} \\ R \\ R \\ R \\ R \\ R \\ R \end{array}$$
 (1)

The role of TMSCl in the catalytic systems is to cleave the Cr–O bond facilitating the reduction of the Cr(III) intermediate to the catalytically active Cr(II) species.^[2,7] Upon hydrolysis of the TMS-ether products of this reaction, hexamethylsiloxane is produced, which cannot be readily recovered or converted back to TMSCl. We reasoned that the use of an acid to cleave the Cr–O bond would directly provide the desired alcohol product and the conjugate base of the acid, which could potentially be recycled. Gansäuer^[8] has reported the use of pyridinium acids in titanium-catalyzed pinacolizations in place of TMSCl to facilitate cleavage of titanium–alkoxide intermediates. Since organochromium compounds react slowly with protic acids,^[9] it seemed likely that the coupling reaction could take place under acidic conditions to directly give the desired alcohol products.

Collidine-hydrochloride, which had successfully been used by Gansäuer,^[8] was tested initially in a series of small scale reactions using manganese metal as reductant (Table 1).^[5] Reactions mediated by collidine-HCl proceeded slowly in the absence of ligands (Entry 1), but occurred rapidly and in high yield in the presence of chelating diphosphines (Entries 2-4). Both alkyl (R=Me, i-Pr) and aryl (R=Ph) diphosphines ligands gave similar yields, although catalysts derived from 1,2-bis(diisopropylphosphino)ethane (dippe) appeared to be more active. An N, N, N', N'tetramethylethylenediamine (TMEDA) chromium(II) complex was no more active than (THF)CrCl₂. Both authentic [(dippe)CrCl₂]₂ and the complex formed in situ from dippe and (THF)CrCl₂ gave similar yields and activities (Entries 2 and 7). As expected for this catalytic system, the active catalyst could also be formed from an air stable chromium(III) salt—(THF)₃CrCl₃ (Entry 8), although $CrCl_3$ formed a less active catalyst apparently due to its low solubility. Replacement of collidine-HCl with pyridine-HCl or acetic acid completely inhibited the reaction.

Collidine-HCl-mediated coupling reactions gave good to excellent yields of homoallylic alcohols for a range of allylic bromides with both

Time Conversion Yield (%)^{b,c} $(\%)^{b}$ Entry Ligand (h) THF 7 75 60 1 2 *i*-Pr₂PCH₂CH₂P*i*-Pr₂^d 100 79 1 3 Ph₂PCH₂CH₂PPh₂ 3 98 80 79 4 Me2PCH2CH2PMe2 3 98 5 63 t-Bu₃P (2 eq/Cr) 3 46 6 **TMEDA**^e 7 76 59 7 *i*-Pr₂PCH₂CH₂P*i*-Pr₂ 100 84 1 8 i-Pr2PCH2CH2Pi-Pr2 100 79 1 9 *i*-Pr₂PCH₂CH₂P*i*-Pr₂^g 4.5 97 69

Table 1. Ligands Effects in Collidine-HCl-Mediated Allylation of Benzaldehyde^a

^aReactions carried out using 0.2 mmol benzaldehyde, 0.4 mmol allylbromide, 0.02 mmol (THF)CrCl₂, the indicated ligand (0.02 mmol), 0.4 mmol. Mn, and 0.24 mmol collidine-HCl in THF at room temperature. ^bGC yields. ^cBenzaldehyde conversion. ^d0.01 mmol [(dippe)CrCl₂]₂. ^e0.01 mmol [(TMEDA)CrCl₂]₂. ^fCrCl₃(THF)₃. ^gCrCl₃.

aryl and alkyl aldehydes (Eq. 2, Table 2). Upon completion of the reaction, GC analysis of the reaction mixture shows only the desired alcohol product and collidine. The sterically demanding dippe ligand gave lower levels of diastereoselectivity in the crotylation of benzaldehyde (3:1) than was observed in the absence of ligand (>9:1).^[5] Use of the less sterically demanding ligands dmpe or dppe resulted in a 9:1 mixture of diastereomers in similar yield to dippe as determined by GC analysis. Addition of geranyl bromide to benzaldehyde or octyl aldehyde catalyzed by (dippe)CrCl₂ gave the homoallylic alcohol as a 9:1 ratio of diastereomers in excellent yield. Allylation of electron-rich 4-methoxybenzaldehyde occurred in moderate yield, but the reaction was unsuccessful with electron-poor 4-cyanobenzal-dehyde due to competing pinacolization.

$$O = R^{1} H^{2} H^{2}$$

In summary, in situ formed (dippe) $CrCl_2$ efficiently catalyzes the allylation of aldehydes in the presence of manganese powder and collidine-HCl. The active catalyst can be conveniently formed from (THF) $CrCl_2$, or

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Yield^a d.r.^b **RCHO** RBr Product Entry OH 1 PhCHO Allyl bromide 86 Ρh OH └__Ph 2 PhCHO Benzyl bromide 72 97 3 PhCHO Prenyl bromide 4 PhCHO Crotyl bromide 78 3:1 5 PhCHO Geranyl bromide 99 9:1 94 6 n-C7H15CHO Allyl bromide 7 96 n-C7H15CHO Prenyl bromide 8 n-C7H15CHO Geranyl bromide 98 9:1 9 4-MeOC₆H₅CHO Allyl bromide ŌН 64 MeO

Table 2. Scope of the Collidine-HCl-Mediated Allylation of Aldehydes

^aAverage isolated yield from 2 runs. Products characterized by ¹H and ¹³C NMR, which were consistent with literature values.

^bDiastereomeric ratio determined by GC and/or ¹H NMR.

air-stable $(THF)_3CrCl_3$. A range of allylic bromides can be coupled with both aryl and alkyl aldehydes in good to excellent yield. The alcohol product can be isolated directly from the reaction mixture without the need for deprotection. In principle, the collidine base could be recovered and recycled to its conjugate acid.

EXPERIMENTAL

General Procedure

In a drybox, a flask was charged with (THF)CrCl₂ (0.2 mmol), dippe (0.2 mmol), manganese powder (4 mmol), and collidine-HCl (2.2 mmol). The flask was sealed with a septum and attached to a nitrogen line. THF (10 mL) was added followed by the allyl bromide (4.0 mmol) and aldehyde (2.0 mmol). Addition of the allyl bromide and aldehyde gave a deep sky blue colored mixture, which faded to green upon completion of the reaction. When TLC or GC analysis showed the aldehyde had been consumed, the reaction mixture was quenched in 10% HCl and extracted with ether. The crude material was purified by flash chromatography eluting with 5-10% ethyl acetate in hexanes.

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