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Direct Formylation and Acylation of Pyridine via Pentacarbonyliron

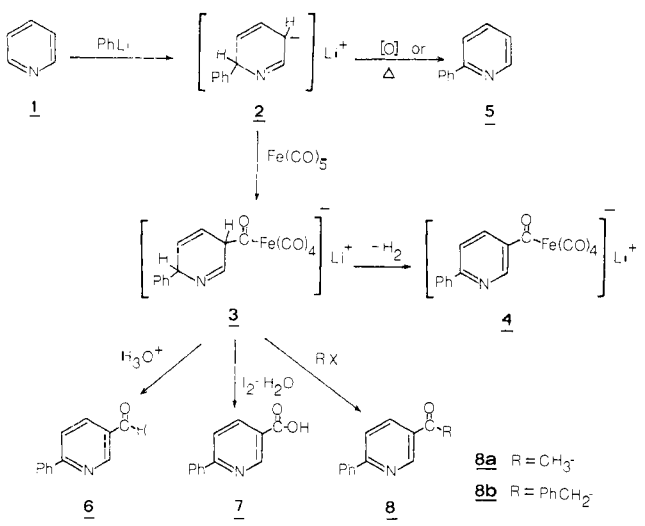
Sir:

A wide variety of β-substituted pyridines and their derivatives have found important uses, e.g., in biological studies,[1] mechanistic investigations,[2] as insecticides,[3] anticorrosion formulations,[4] intermediates in organic and pharmaceutical synthesis, and as potentially useful drugs. Some aryl pyridine-2-carboxaldehydes and their derivatives have been investigated for their potential antitumor activity,[5] but aryl 3-(or 5-)pyridinecarboxaldehydes have not been evaluated because their preparation, like other β-substituted derivatives,[6] has been a problem. In fact, Friedel–Crafts acylation, which is so facile in benzene, has to date *not* been successfully carried out with pyridine. While there have been recent reports of formylation and acylation procedures to prepare 2,3-disubstituted pyridines via [2,3]-sigmatropic rearrangements of α-pyrrolidinyl-2-alkylpyridines,[7] and via the rearrangement of azasulphonium salts of 2-aminopyridines,[8] there have been no reports of a direct formylation or acylation of the β-position of pyridine using pentacarbonyliron. Pentacarbonyliron has been used for formylation and acylation in benzenoid systems.

Thus, it is known that aryl- and alkyllithium compounds react with pentacarbonyliron at low temperature to give unstable lithium acylcarbonylferrates, which are useful precursors for the synthesis of aromatic aldehydes[9] and ketones.[10] Acyltetracarbonylferrates, which can also be obtained from other reactions (e.g., between acid chlorides and $Na_2Fe(CO)_4$), were used for the preparation of aldehydes, ketones, and carboxylic acid derivatives.[11] While benzene derivatives have been prepared via such reactions, the preparation of pyridine aldehydes using pentacarbonyliron is unknown.

We now wish to report the first direct formylation (and other carbonylation reactions) of pyridine via pentacarbonyliron; in particular, the "one-flask" synthesis of 2-aryl-5-pyridinecarboxaldehyde and other carbonyl derivatives from pyridine. Pyridine was carefully added to an ethereal solution of phenyllithium at room temperature and under an atmosphere of argon. The resulting suspension of solids **2**[6c] was taken up in dry tetrahydrofuran (THF) and cooled to −65 °C. After addition of an equimolar amount of pentacarbonyliron in THF, the mixture (containing intermediate **3** or **4**) was allowed to gradually warm to room temperature. Hydrolysis with saturated, aqueous ammonium chloride gave after purification 2-phenylpyridine (**5**) (18%) and 2-phenyl-5-pyridinecarboxaldehyde (**6**) (46%). When acetic acid was used for the hydrolysis, 73% yield of **6** was obtained. **6:** mp 58–59 °C; NMR ($CDCl_3$) δ 7.72 (complex multiplet, pyridine C-3, C-4 and phenyl 7 H), 9.15 (singlet, pyridine C-6 1 H), 10.13 (singlet, aldehydic 1 H). Anal. ($C_{12}H_9NO$) C, H, N.[12] If the mixture (containing **3** or **4**) was oxidized with iodine, 2-phenylpyridine-5-carboxylic acid (**7**) (50%) was isolated; the use of methyl iodide (RX = CH_3I) or benzyl bromide (RX = $PhCH_2Br$) instead of iodine resulted in the production of 2-phenyl-5-acetylpyridine[13] (**8a**) (32%) or 2-phenyl-1-(6-phenyl-3-pyridinyl)ethanone (**8b**) (24%), respectively. **8b:** mp 122–123 °C; NMR ($CDCl_3$) δ 4.31 (singlet, benzyl 2 H), 7.90 (complex multiplet, pyridine C-3, C-4 and phenyl 12 H), 9.29 (singlet, pyridine C-6 1 H). Anal. ($C_{19}H_{15}NO$) C, H, N.[12] In addition to the acid and ketones, 2-phenylpyridine was also isolated. 2-Phenylpyridine has been found in other reactions involving **2**. Dihydropyridinyl structures such as **2** are easily aromatized via thermolysis or oxidation.[6c]

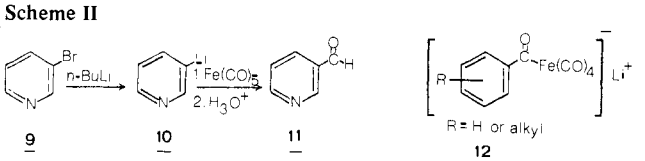
Scheme I



We have isolated 3-pyridinecarboxaldehyde (**11**) from the reaction of 3-pyridinyllithium (**10**) and pentacarbonyliron, but preliminary experiments gave a poor yield (5%). 3-Pyridinyllithium was prepared from 3-bromopyridine and *n*-butyllithium.[15] Thus, this reaction is feasible but under these conditions it is not a useful synthetic procedure. In fact, if 3-bromopyridine (instead of pyridine) were to be used as a starting compound, other higher yield synthetic methods have been reported.[16]

We have not been able to characterize the intermediate **3** (or **4**) responsible for the formation of the aldehyde, ketones, and carboxylic acid. However, the infrared spectrum of the reaction mixture after adding pentacarbonyliron to a solution of phenyllithium–pyridine intermediate **2** gave a characteristic R–C(=O)Fe absorption at 1635 cm^{-1} which is not associated with either the reagents or products. **4** is a more likely immediate precursor, because the related lithium benzoyltetracarbonylferrates (**12**) give aromatic aldehydes[9] and ketones[10] on treatment with aqueous acid and benzylbromide, respectively. Irrespective of the actual structure of the intermediate, we have provided a direct formylation and acylation of pyridine using pentacarbonyliron.

Scheme II



The scope and applicability of the above reaction to other heterocyclic substrates (substituted pyridines, quinolines, isoquinolines, and naphthyridines), and other metal carbonyls are being investigated.

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Hydrogen vs. Deuterium Transfer in Asymmetric Reductions: Reduction of Phenyl Trifluoromethyl Ketone by the Chiral Grignard Reagent from (*S*)-2-Phenyl-1-bromoethane-*1,1,2-d*$_3$

Sir:

We wish to report on an asymmetric reduction by a Grignard reagent that is chiral by virtue of a hydrogen and deuterium disparity at the asymmetric β-carbon. We find that (*S*)-PhCHDCD$_2$MgBr(**5**) not only reduces a prochiral ketone asymmetrically, but shows a higher asymmetric induction for deuterium transfer than for hydrogen transfer.

The chiral Grignard reagent **5** was synthesized[1] from (*R*)-(−)-mandelic acid **1** according to Scheme I, and used to reduce phenyl trifluoromethyl ketone, **6**, to the mixture of chiral carbinols, **8**.

Composition of 8:

S_H-**8**	R_H-**8**	S_D-**8**	R_D-**8**
45.8 ± 0.8%	16.5 ± 0.5%	8.6 ± 0.5%	29.1 ± 0.6%
62.3 ± 0.6% H transfer		37.7 ± 0.6% D transfer	
47.1 ± 1.6% ee S_H-**8**		54.4 ± 2.2% ee R_D-**8**	

Product analysis of the enantiomeric and isotopic four-component carbinol mixture **8** was achieved by conversion to the mixture of the α-methoxy-α-trifluoromethyl phenylacetates **9** (MTPA derivatives).[2] At 254 MHz, the ^{19}F NMR spectrum[3] of the diasteromeric esters **9** showed completely resolved resonance signals of the carbinyl CF_3 group for the four components, shown in Figure 1.

This difference in stereoselectivity between hydrogen vs. deuterium transfer cannot be ascribed to any differences in reagents or conditions in contrast to previous incidental studies[5,6] since the competing reactions are taking place simultaneously and internally within the same mixture. Reduction by a single electron transfer process (SET) or by a magnesium hydride species giving rise to only S_H-**8** and R_H-**8** seems remote.[4]

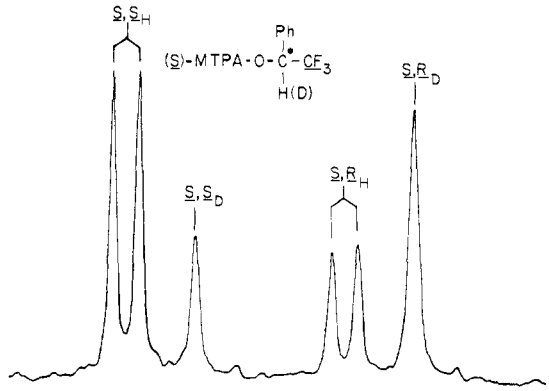
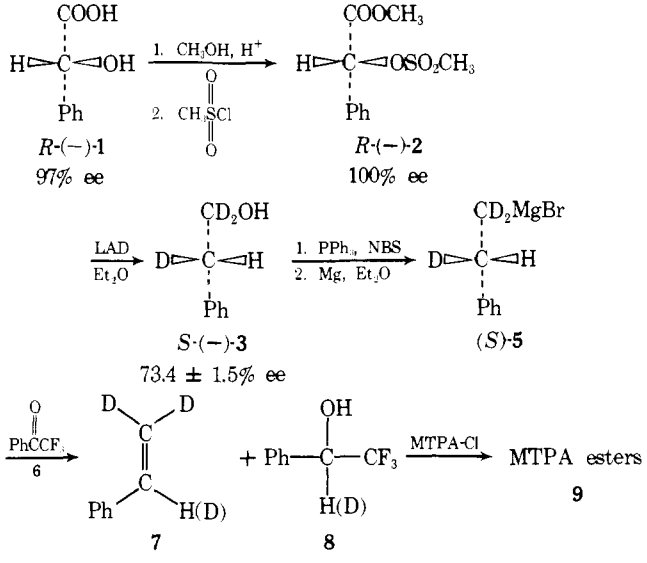
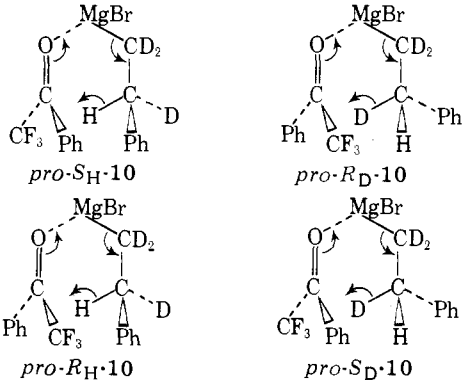


Figure 1. A 254-MHz ^{19}F NMR spectrum in the carbinyl CF_3 region of **9**.

Scheme I



Scheme II



The mechanistic situation can be conceptualized in terms of four models for the competing transition states (Scheme II). Two of these models (*pro*-S_H-**10** and *pro*-R_D-**10**) involve transfer of hydrogen from the reagent **5** to the prochiral faces of the ketone **6** to give enantiomeric protio carbinols (S_H-**8** and R_H-**8**) and two (*pro*-S_D-**10** and *pro*-R_D-**10**) involve transfer of deuterium to give enantiomeric deuteriocarbinols (S_D-**8** and R_D-**8**). The preferred transition state for hydrogen transfer is represented by *pro*-S_H-**10** and that for deuterium transfer by *pro*-R_D-**10** as anticipated.[7] The differences in stereoselectivity can be viewed as the sum of at least two effects—namely, the differences associated with the transfer of hydrogen vs. deu-