

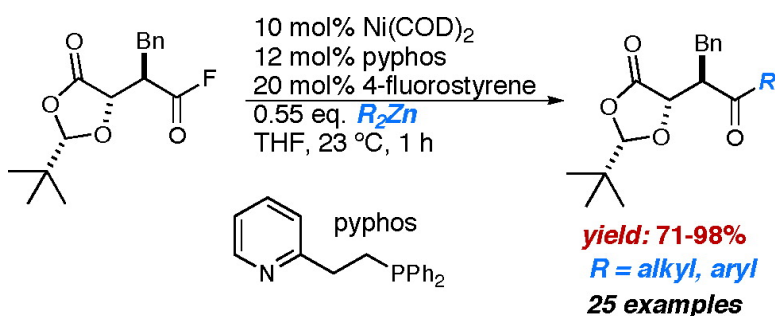
Communication

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J. Am. Chem. Soc., **2004**, 126 (49), 15964-15965 • DOI: 10.1021/ja044113k • Publication Date (Web): 18 November 2004

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A Unique Catalyst Effects the Rapid Room-Temperature Cross-Coupling of Organozinc Reagents with Carboxylic Acid Fluorides, Chlorides, Anhydrides, and Thioesters

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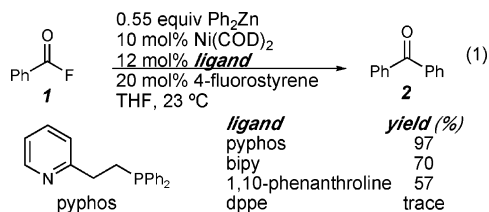
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In view of the paramount importance of ketones in the synthesis of a wide variety of pharmaceutical and material-science target molecules,¹ extensive efforts have been made for efficient synthesis of this fundamental functionality.² Transition metal-catalyzed cross-coupling reactions of organometallic reagents with carboxylic acid derivatives present a powerful and convergent approach to ketone synthesis.³ These new approaches have the advantage of avoiding strongly basic and nucleophilic reaction conditions typically associated with protocols such as the Weinreb amide approach.⁴ However, the current state of the art, although enabling in fundamental reaction design, is typically limited to simple electrophilic partners devoid of eliminatable groups and epimerizable stereocenters.⁵ A handful of exceptions to this generalization have appeared, with Fukuyama's thioester cross-coupling being perhaps the most versatile protocol, although it requires the use of excess nucleophile.⁶ Herein we report the rapid cross-coupling of acid fluorides with organozinc reagents tolerating epimerizable stereocenters and transferring both groups from zinc in the presence of a versatile catalyst.

We identified acid fluorides as potentially versatile acid derivatives since they are widely used in peptide coupling under conditions that do not lead to epimerization.⁷ Acyl fluorides are easily prepared from carboxylic acids,⁸ acid anhydrides,⁹ and acid chlorides^{9a} in good yields and typically exhibit greater stability toward water and neutral oxygen nucleophiles than corresponding acid chlorides.⁷ This allows for their isolation through organic extraction and flash silica gel chromatography.

We applied reaction conditions previously developed for anhydride monoalkylation to the coupling reaction of benzoyl fluoride and Ph₂Zn in the presence of Ni(COD)₂ and bipy.^{10–12} The coupling reaction proceeds smoothly at room temperature with only 0.55 equiv of Ph₂Zn, affording **2** in 70% yield after 0.5 h, indicating that both groups are transferred from zinc.¹³



We have found that the reaction is very sensitive to ligand (eq 1), with pyphos [(2-diphenylphosphinoethyl)pyridine]¹⁴ being superior. With this ligand, in situ IR spectroscopy indicates the acyl fluoride band at 1845 cm⁻¹ disappears in 3 min.¹⁵ In the absence of Ni(COD)₂, no product is observed on TLC even after a mixture of PhCOF, Ph₂Zn, pyphos, and 4-fluorostyrene in THF is stirred overnight at room temperature. Without 4-fluorostyrene, the isolated yield of benzophenone is only 18% after 16 h, consistent with previous observations about the beneficial effect of these additives.¹⁶

Our optimized reaction conditions, 10 mol % Ni(COD)₂, 12 mol

Table 1. Ni-Catalyzed Coupling of Acyl Fluorides and Ph₂Zn

Entry ^a	Acyl Fluoride ^b	Reaction Time	Product	Yield(%) ^c
1		10 min		97 77 ^d
2		22 h		77
3		10 min		98
4		10 min		71
5		10 min		83
6		10 min		92
7		10 min		97
8		30 min		92
9		30 min		93

^a All reactions were conducted in the presence of 10 mol % Ni(COD)₂, 12 mol % pyphos, 20 mol % 4-fluorostyrene, and 0.55 equiv of Ph₂Zn in THF for 10–30 min at 23 °C, unless otherwise stated. ^b Acyl fluorides are prepared by treatment of acids with DAST or Deoxo-Fluor at 0 °C for 30 min. ^c Isolated yield. ^d Reaction was conducted in the presence of 5 mol % benzoic acid.

% pyphos, and 20 mol % 4-fluorostyrene at room temperature, afford coupling products between Ph₂Zn and a variety of acyl fluorides in good to excellent yields (Table 1). In most cases, the reaction proceeds to completion in 10 min. It is worth noting that the reaction proceeds well albeit much slower with an extremely bulky acyl fluoride such as **3**, providing the ketone in 77% yield. A range of functionality is tolerated, including thiophene, alkenes, and acetals. Significantly, β-alkoxides are well tolerated, with substrates **13** and **15** providing high yield of ketones, entries 7 and 8. Amino acids may be converted into the corresponding ketones without epimerization, entry 9.¹⁷

Treatment of benzoyl fluoride with Me₂Zn as a nucleophile using standard reaction conditions affords the corresponding methyl ketone in 92% yield (entry 1, Table 2). When Et₂Zn is used, no aldehyde is observed¹⁸ and the ethyl ketone may be isolated in 90% yield.¹⁹ An isopropyl group can be transferred without concomitant isomerization (entry 3). In the case of functionalized organozinc reagent derived from [(1-ethoxycyclopropyl)oxy]trimethylsilane,²⁰

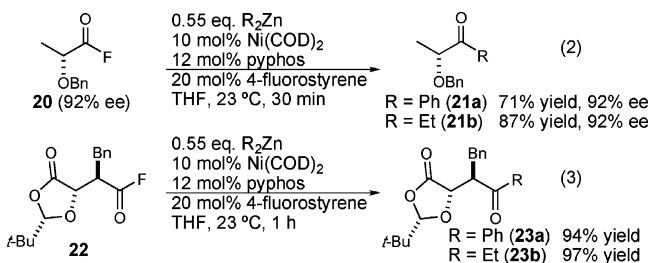
Table 2. Alkylzinc Nucleophiles

entry ^a	R ₂ Zn	R	yield (%) ^b
1	Me ₂ Zn	Me (19a)	92
2	Et ₂ Zn	Et (19b)	90
3	<i>i</i> -Pr ₂ Zn	<i>i</i> -Pr (19c)	91
4	(EtO ₂ CCH ₂ CH ₂) ₂ Zn	CH ₂ CH ₂ CO ₂ Et (19d)	95

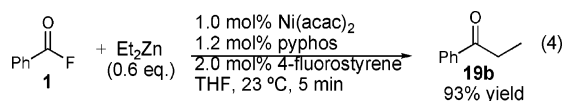
^a See Table 1. ^b Isolated yield.

the desired coupling product may be isolated in 95% yield without formation of O-acylation product.²¹

One of the current shortcomings of metal-catalyzed ketone synthesis is that epimerizable functionality has not been extensively illustrated to participate.^{6a,22} The use of acyl fluorides allows this to occur. Lactate-derived acyl fluoride **20** undergoes the reaction in good yield without loss of stereochemical integrity, while **22** also participates well with no elimination or epimerization (eqs 2 and 3).¹⁵



In order to render this reaction more practical, we have found that air-stable Ni(acac)₂ may be used as a precatalyst in place of the air-sensitive Ni(COD)₂. As a further testament to the practicality of this protocol, we have conducted this reaction using 1.0 mol % Ni(acac)₂, 1.2 mol % pyphos, and 2.0 mol % 4-fluorostyrene on a 40 mmol scale to afford **19b** in 93% yield after 5 min at 23 °C (eq 4).²³



We have extended this protocol to other acid derivatives. Impressively, acid chlorides, anhydrides, acyl cyanides, thioesters, and even pyridyl and aryl esters are good reaction partners with this catalyst (Table 3), providing the coupling product in excellent yields with slightly longer reaction times.

Table 3. Other Acid Derivatives as Coupling Partners

entry ^a	RCOX	reaction time	yield (%) ^b
1	PhCOCl	10 min	97
2	PhCOCN	30 min	93
3 ^d	PhCOSEt	2 h	92
4	PhCOOCO ₂ <i>i</i> -Bu	1 h	91
5 ^d	(PhCO) ₂ O	30 min	95
6 ^d	(PhCO) ₂ O	30 min	68 ^c
7	PhCOO-2-Py	6 h	95
8	PhCOS-2-Py	10 min	95
9 ^e	PhCOOPh	5 h	50

^a See Table 1. ^b Isolated yield. ^c Technical grade (PhCO)₂O (90%) was used. ^d Performed with 1.1 equiv of Ph₂Zn. ^e Reaction was conducted at 60 °C.

In summary, an efficient ketone synthesis protocol has been developed by Ni-catalyzed cross-coupling of acid fluorides and

organozinc reagents. The procedure can be applied to a variety of acid derivatives, including pyridyl esters and tolerates epimerizable stereocenters.

Acknowledgment. We thank the National Institute of General Medical Sciences (GM65407) for support of this research. T.R. thanks Merck, GlaxoSmithKline, Amgen, and Eli Lilly for support.

Supporting Information Available: Experimental procedures and characterization data of all new compounds (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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JA044113K