Tetrahedron 70 (2014) 3259–3265

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Pd-catalyzed Fukuyama cross-coupling of secondary organozinc reagents for the direct synthesis of unsymmetrical ketones

Alan H. Cherney, Sarah E. Reisman *

The Warren and Katharine Schlinger Laboratory of Chemistry and Chemical Engineering, California Institute of Technology, Division of Chemistry, 1200 E. California Blvd, MC 101-20, Pasadena, CA 91125, United States

ARTICLE INFO

Article history:
Received 26 August 2013
Received in revised form 21 November 2013
Accepted 29 November 2013
Available online 7 December 2013

Keywords:
Palladium
Cross-coupling
Organozinc

ABSTRACT

The coupling of acyl electrophiles with organometallic reagents represents a convergent route toward complex and versatile ketone products. Despite the mild conditions and high functional group tolerance, the cross-coupling of carboxylic acid derivatives, such as thioesters, and secondary organometallic reagents is an underdeveloped transformation. Herein, we disclose a convenient and efficient protocol for the Pd-catalyzed Fukuyama cross-coupling of secondary organozinc reagents with thioester electrophiles. Under these mild conditions, a range of thioesters possessing sensitive functional groups can be coupled with either activated or unactivated secondary organozinc halides in good yields. This method was expanded to include an acid chloride substrate, generating an aryl alkyl ketone in high yield. In addition, a modest dynamic kinetic resolution of the organozinc reagent can be achieved using chiral phosphoramidite ligands to furnish enantioenriched ketone products.

1. Introduction

Transition metal-catalyzed cross-coupling reactions have emerged as a transformative methodology in the field of organic synthesis, enabling the rapid generation of complex molecules under mild, selective, and catalytic conditions. While initial reports focused on C(sp^2)–C(sp^2) couplings, the burgeoning field of C(sp^3) bond-forming processes has rapidly expanded in the past decade.[1] In a seminal report, Hayashi and co-workers found that Pd complexes supported by bulky, bidentate phosphines with large bite angles (e.g., 1,1′-bis(diphenylphosphino)ferrocene) (dppf) can catalyze the cross-coupling between aryl or vinyl halides and primary or secondary organomagnesium and organozinc reagents.[2] In 2003, Fu and co-workers demonstrated that similar bulky, electron-rich phosphines enable a general Pd-catalyzed Negishi coupling of sp^3-hybridized electrophiles with alkyl, alkenyl, and aryl nucleophiles.[3] In the decade that has followed, steady advances have been made in Pd- and Ni-catalyzed cross-coupling reactions of both secondary C(sp^3) organometallic reagents and secondary C(sp^3) electrophiles, giving rise to a wide variety of products now accessible via simple alkyl building blocks.[4–6]

One transformation that remains underdeveloped is the transition metal-catalyzed cross-coupling reaction between carboxylic acid derivatives and C(sp^3) organometallic reagents to prepare ketones, despite the fact that the Pd-catalyzed reaction between acid chlorides and alkyl tin reagents was first reported over thirty years ago.[7] In 1998, Fukuyama and co-workers reported the Pd-catalyzed coupling of thioesters and primary alkyl organozinc or hydride reagents, generating ketone or aldehyde products, respectively.[8] A number of functional groups are tolerated due to the relative stability of both coupling components. Seki and co-workers[9] have since developed both heterogeneous and phosphine-free Pd-catalyzed Fukuyama couplings, as well as a Ni-catalyzed Fukuyama coupling. Despite these advances, the use of secondary C(sp^3) organometallic reagents still proves challenging. While α,α-disubstituted ketones can be prepared by direct attack of a variety of strongly nucleophilic organometal species onto acyl electrophiles, such protocols are frequently accompanied by over-addition products due to the electrophilicity of the newly formed ketone.[10] Specialized acyl derivatives, such as Weinreb amides, can minimize over-addition; however, these electrophiles require the use of organolithium or Grignard reagents, which suffer from poor functional group tolerance.[11] Recent strategies to eliminate the need for alkyl organometallic reagents in ketone synthesis include reverse-polarity cross-couplings[12] and reductive cross-couplings.[13]

Although substantial progress has been made on the transition metal-catalyzed cross-coupling between acyl electrophiles and primary alkyl organometallic reagents, there are far fewer reports describing the coupling of secondary alkyl organometallics. In an early study, Harada and Oku disclosed the coupling of secondary organozinc reagents with acid chlorides and obtained moderate to good yields of ketone product, although the functional group tolerance of the reaction was not further explored (Fig. 1).[14] Zhang and

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* Corresponding author. Tel.: +1 626 395 6044; e-mail address: reisman@caltech.edu (S.E. Reisman).

0040-4020/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2013.11.104

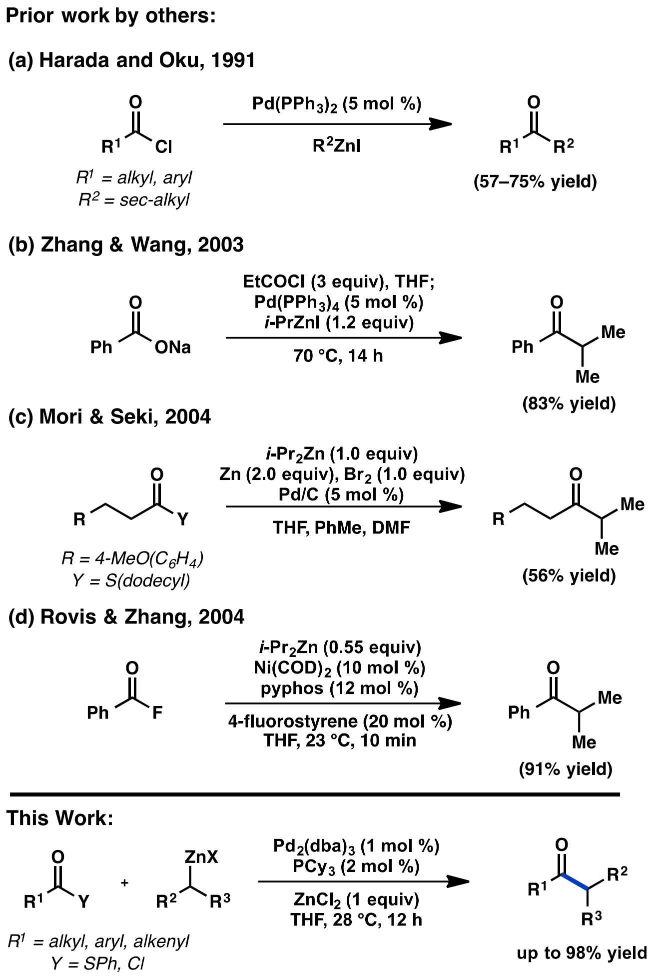


Fig. 1. Acyl cross-coupling reactions of secondary organozinc reagents.

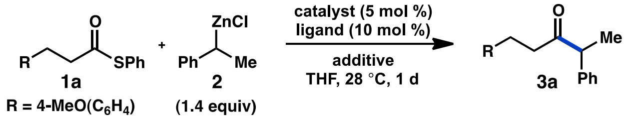
Wang reported a high-yielding reaction between *i*-PrZnI and the mixed anhydride generated from sodium benzoate, however additional substrate scope was not disclosed.[15] Subsequently, Mori and Seki reported a Pd-catalyzed coupling of *i*-Pr_2Zn that proceeds in moderate yield.[16] Rovis and Zhang have also reported a single case of a high-yielding coupling between an acid fluoride and *i*-Pr_2Zn.[17] Finally, the related Liebeskind–Srogl coupling of thioesters and organoboron nucleophiles proceeds only with primary organoboron reagents despite efforts to extend the reaction to secondary reagents.[18] With the objective of expanding the synthetic utility of metal-catalyzed acyl cross-coupling reactions, herein we report a general method for the cross-coupling of secondary organozinc reagents and thioesters.

2. Results and discussion

The scarcity of *sec*-alkylmetal couplings with acyl derivatives is indicative of the inherent difficulties of transition metal-catalyzed reactions involving C(sp^3)-hybridized coupling partners.[1d] In general, alkyl organometallic reagents are prone to β-hydride elimination as well as proto-demetalation under typical cross-coupling reaction conditions. Additionally, many alkyl organometallics suffer from slow transmetalation to the transition metal catalyst. Furthermore, not only is transmetalation troublesome for *sec*-alkylmetals, but reductive elimination from a transition metal is also slow due to σ-donation of the alkyl group to the metal. The sluggishness of reductive elimination enhances side reactions, such as β-hydride elimination and isomerization. Acceleration of the reductive elimination pathway, either through catalyst and ligand tuning or through the use of additives, can prevent this undesired isomerization. Significantly, alkylzinc reagents display relatively broad use in C(sp^3) cross-couplings because of their ability to undergo a facile transmetalation with Pd as compared to other organometallic partners used in cross-coupling chemistry.

We therefore began our studies by evaluating the cross-coupling between thioester **1a** and organozinc **2**. An analysis of metal catalysts revealed that Ni sources performed poorly (Table 1, entries 1 and 2), whereas $PdCl_2$(dppf) was more promising (Table 1, entry 5). A screen of several phosphine ligands revealed that the bulky, monodentate, electron-rich ligand PCy_3 furnished ketone **3a** in 34% yield (entries 6–9). Despite their success in a number of Negishi couplings, the Buchwald ligands SPhos and XPhos showed low reactivity.[19] On the other hand, use of 10 vol % DMF as a polar cosolvent further increased the yield to 52% (entry 10), although additional DMF had no effect on the reaction. Other trialkylphosphines resulted in lower yields of **3a** (entries 11–14). Interestingly, these conditions of $Pd_2(dba)_3/PCy_3$/DMF closely resemble Fu's general conditions ($Pd_2(dba)_3/PCyp_3$/NMI) for Negishi cross-couplings of alkyl electrophiles.[3] Notably, no isomerized linear product was observed.

Table 1
Optimization of reaction conditions



Entry	Catalyst	Ligand[a]	Additive	Conversion (%)[b]	Yield[b] (%)
1	$Ni(acac)_2$[c]	—	—	75	10
2	$NiCl_2$(glyme)[c]	—	—	83	14
3	$Pd_2(dba)_3$	—	—	94	13
4	$Pd(OAc)_2$[c]	—	—	75	15
5	$PdCl_2$(dppf)[c]	—	—	88	20
6	$Pd_2(dba)_3$	PPh_3	—	92	16
7	$Pd_2(dba)_3$	PCy_3	—	89	34
8	$Pd_2(dba)_3$	SPhos	—	93	16
9	$Pd_2(dba)_3$	XPhos	—	82	14
10	$Pd_2(dba)_3$	PCy_3	DMF[e]	78	52
11	$Pd_2(dba)_3$	PMe_3	DMF[e]	100	23
12	$Pd_2(dba)_3$	PEt_3	DMF[e]	80	35
13	$Pd_2(dba)_3$	P^nBu_3	DMF[e]	90	32
14	$Pd_2(dba)_3$	P^tBu_3	DMF[e]	88	22
15	$Pd_2(dba)_3$[d]	PCy_3	DMF[e]/$ZnCl_2$[f]	100	83
16	$Pd_2(dba)_3$[d]	PCy_3	$ZnCl_2$f	93	89
17	$Pd_2(dba)_3$[d]	dCyb	$ZnCl_2$[f]	49	44

[a] 1:1 Pd:phosphine was used.
[b] Conversion of **1a** and yield of **3a** were calculated by ^1H NMR analysis with internal standard.
[c] 10 mol % was used.
[d] 1 mol % was used.
[e] 10 vol % was added.
[f] 1 equiv was added.

Previous studies of the Fukuyama coupling have noted that addition of inorganic zinc salts may shift the Schlenk equilibrium of the organozinc reagent toward a more reactive organozinc halide and may also activate Pd toward oxidative addition.[9] Gratifyingly, addition of $ZnCl_2$ increased both the conversion and yield of the reaction, while allowing the catalyst loading to be reduced to 1 mol % $Pd_2(dba)_3$ without an appreciable decrease in yield (entry 15). Use of $ZnCl_2$ as the sole additive also obviated the need for DMF, delivering **3a** in 89% yield (entry 16). Replacement of PCy_3 for a bidentate phosphine analog, 1,4-bis(dicyclohexylphosphino)butane (dCyb), resulted in both a lower conversion of **1a** and a lower yield of **3a**.