Organic LETTERS

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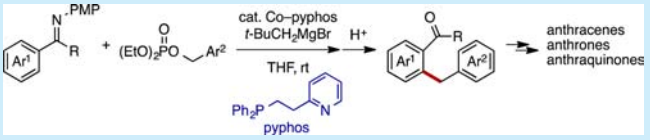
Ortho-C−H Benzylation of Aryl Imines with Benzyl Phosphates under Cobalt−Pyphos Catalysis

Wengang Xu, Rupankar Paira, and Naohiko Yoshikai*

Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore 637371, Singapore

Supporting Information

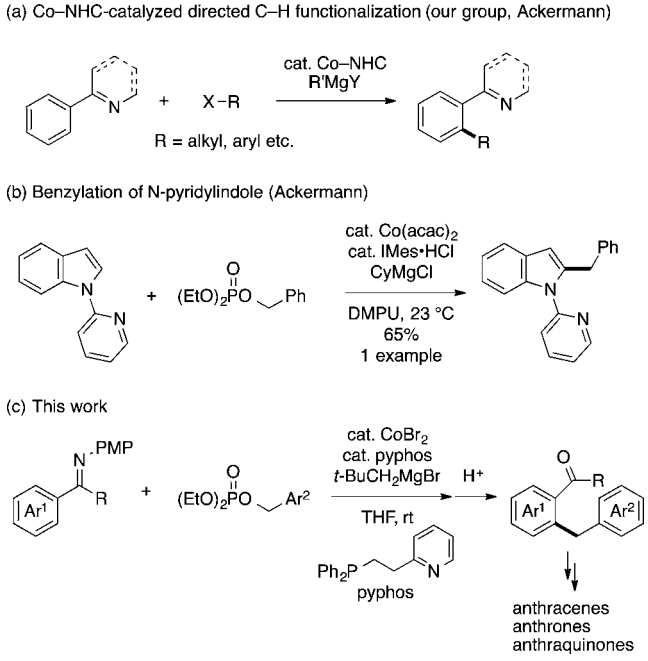
ABSTRACT: Ortho-C−H benzylation of aryl ketimines with benzyl phosphates is achieved with the aid of a catalytic system consisting of a cobalt(II) salt, a phosphine/pyridine bidentate ligand, and a Grignard reagent under room-temperature conditions, affording a variety of diarylmethanes bearing *o*-acetyl or -acyl groups in moderate to good yields. Owing to the versatility of the *o*-acetyl group, the reaction opens useful synthetic routes to polycyclic compounds such as unsymmetrical anthracene, anthracenone, and anthraquinone derivatives.



Diarylmethane moieties are present in many pharmacologically active compounds[1] as well as in several approved drugs and agrochemicals such as papaverin, trimethoprim, and piritrexim. Established synthetic approaches to the diarylmethane moiety include Friedel−Crafts-type benzylation of electron-rich arenes with benzylic electrophiles[2,3] and transition-metal-catalyzed cross-coupling between arylmetal reagents and benzylic electrophiles or between benzylmetal reagents and aryl electrophiles.[4,5] These approaches, however, have their own drawbacks. The Friedel−Crafts reaction often produces a mixture of regioisomers, while the cross-coupling reaction a priori requires two prefunctionalized starting materials. Therefore, it is attractive to develop alternative aryl−benzyl bond-forming methods such as those based on heteroatom-directed aromatic C−H activation.[6] However, directed C−H benzylation reactions developed thus far are somewhat limited, particularly in terms of the scope, the cost, and the versatility of the directing group.[7] For example, a directed benzylation reaction using a Ru catalyst employs less transformable N-heterocyclic directing groups,[8] while those achieved with Pd,[9] Ni,[10] or Fe[11] catalysts require an expensive 8-aminoquinoline-based bidentate directing group.[6d,g,12]

Recently, our group and Ackermann et al. independently developed low-valent cobalt−N-heterocyclic carbene (NHC) catalytic systems for nitrogen-directed aromatic C−H functionalization with organic electrophiles such as alkyl and aryl halides and pseudohalides (Scheme 1a).[13−16] While Ackermann demonstrated the applicability of their catalytic system to the benzylation of *N*-pyridylindole with benzyl phosphate (Scheme 1b), the generality of this benzylation reaction remains unclear.[14a] Here, we report on a directed C−H benzylation reaction of an aryl imine with a benzyl phosphate that is efficiently promoted by a cobalt catalyst complexed with 2-[2-(diphenylphosphino)ethyl]pyridine (pyphos) at room temperature (Scheme 1c).[17,18] The diarylmethane product serves as a versatile starting material for the synthesis of anthracene, anthrone, and anthraquinone derivatives.

Scheme 1. Cobalt-Catalyzed Directed Aromatic C−H Alkylation and Benzylation

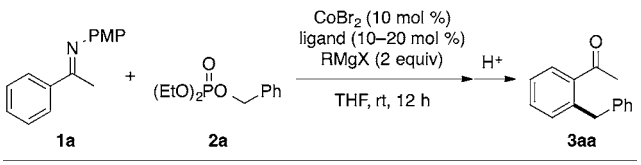


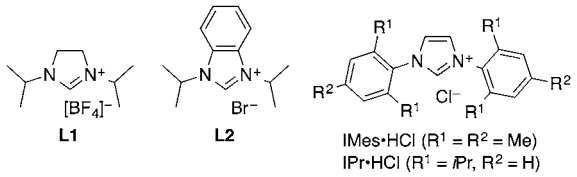
The present study commenced with attempted application of our previous Co−NHC catalytic systems for the ortho-alkylation (Scheme 1a)[13b,c] and related reactions[19] to the reaction of acetophenone imine **1a** with benzyl diethyl phosphate **2a** (Table 1). A combination of $CoBr_2$ (10 mol %), imidazoli(ni)um salt **L1** or **L2** (10 mol %), and *t*-$BuCH_2MgBr$ (2 equiv) promoted the desired reaction to afford

Received: July 8, 2015
Published: August 25, 2015

DOI: 10.1021/acs.orglett.5b01955
Org. Lett. 2015, 17, 4192−4195

Table 1. Screening of Ligands for the Ortho-Benzylation of Imine 1a with Benzyl Phosphate 2a[a]





entry	ligand (mol %)	RMgX	yield[b] (%)
1	**L1** (10)	*t*-BuCH$_2$MgBr	19
2	**L2** (10)	*t*-BuCH$_2$MgBr	32
3	IMes·HCl (10)	*t*-BuCH$_2$MgBr	5
4	IPr·HCl (10)	*t*-BuCH$_2$MgBr	6
5	IMes·HCl (20)	CyMgCl	<1
6	P(3-ClC$_6$H$_4$)$_3$ (20)	*t*-BuCH$_2$MgBr	18
7	P(4-FC$_6$H$_4$)$_3$ (20)	*t*-BuCH$_2$MgBr	14
8	1,10-phenanthroline (10)	*t*-BuCH$_2$MgBr	10
9	pyphos (10)	*t*-BuCH$_2$MgBr	40
10	dppp (10)	*t*-BuCH$_2$MgBr	4
11	pyphos (15)	*t*-BuCH$_2$MgBr	83[c]
12	pyphos (20)	*t*-BuCH$_2$MgBr	54
13	pyphos (10) + PPh$_3$ (5)	*t*-BuCH$_2$MgBr	72
14	pyphos (10) + pyridine (20)	*t*-BuCH$_2$MgBr	42

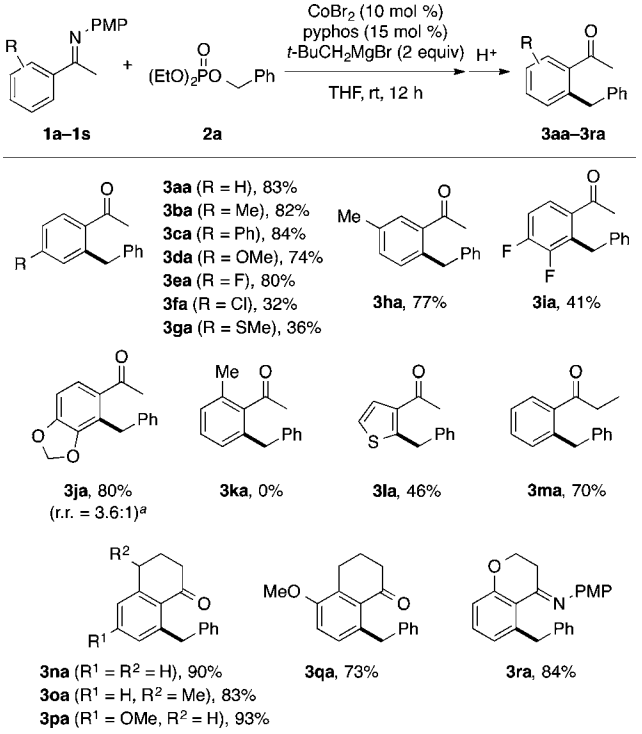
[a]The reaction was performed using 0.3 mmol of **1a** and 0.6 mmol of **2a**. [b]Determined by GC using *n*-tridecane as an internal standard. [c]Isolated yield.

the desired diarylmethane **3aa**, but the yield was unsatisfactorily modest (ca. 20−30%; entries 1 and 2). The use of other NHC preligands such as IMes·HCl and IPr·HCl gave even poorer results (entries 3 and 4). Likewise, Ackermann's Co−IMes catalytic system (Scheme 1b) was ineffective (entry 5). Triarylphosphines and 1,10-phenanthroline also exhibited poor performances (entries 6−8).[20] Upon further ligand screening, we identified P,N-bidentate pyphos as a promising ligand that afforded **3aa** in 40% yield (entry 9). By contrast, bidentate phosphines such as dppp interfered with the desired reaction (entry 10). In all these reactions, unreacted imine **1a** was largely recovered, whereas **2a** was fully consumed to afford bibenzyl and (3,3-dimethylbutyl)benzene as major byproducts arising from homocoupling of **2a** and cross-coupling between **2a** and *t*-BuCH$_2$MgBr, respectively.

In a subsequent optimization study using pyphos as the supporting ligand, we observed a significant impact of the metal/ligand ratio on the benzylation reaction. An increase of the loading of pyphos to 15 mol % dramatically improved the yield of **3aa** (83% isolated yield) while suppressing the homo- and cross-coupling byproducts (entry 11), whereas a further increase to 20 mol % caused only a marginal improvement (entry 12). The positive effect of the excess pyphos ligand may be attributed to its phosphine moiety rather than to the pyridine moiety, as judged from control experiments using pyphos (10 mol %) in combination with PPh$_3$ (5 mol %) or pyridine (20 mol %) as the additional ligand (entries 9, 13, and 14). Note that the use of benzyl bromide or benzyl chloride in place of **2a** resulted in predominant formation of the homo- and the cross-coupling products while affording only a trace amount of **3aa**.

Having established the Co−pyphos catalytic system (Table 1, entry 11), we explored the scope of aryl imines using benzyl phosphate **2a** as the reaction partner (Scheme 2). Imines

Scheme 2. Ortho-Benzylation of Various Imines with Benzyl Phosphate 2a



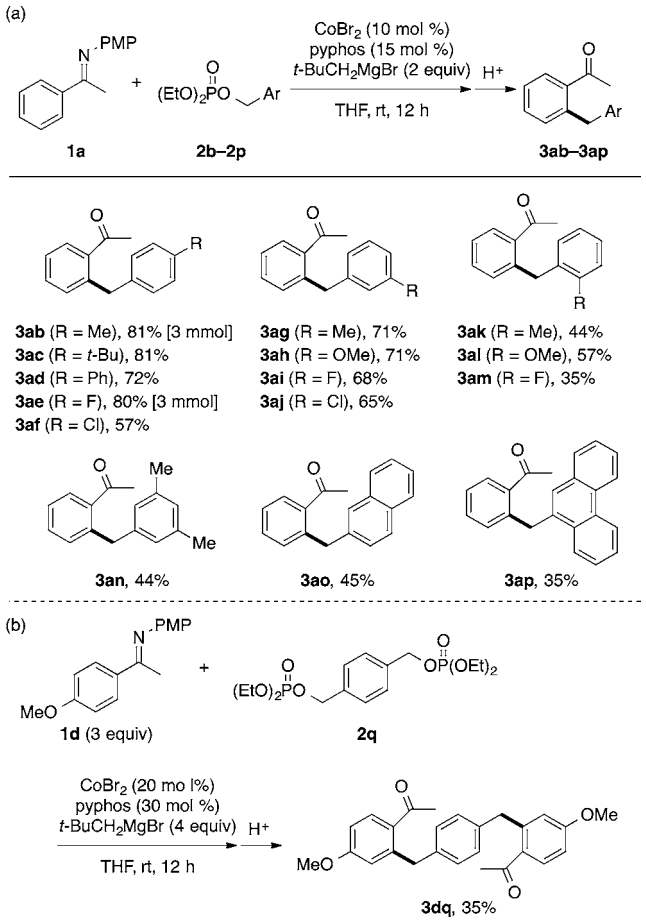
[a]The major regioisomer is shown (r.r = regioisomer ratio).

derived from various para- and/or meta-substituted acetophenone derivatives afforded the desired benzylation products **3aa**−**ja** in moderate to good yields, whereas the one derived from *o*-methylacetophenone failed to participate in the reaction (see **3ka**). Aryl chloride and sulfide moieties could be tolerated albeit in modest yields (**3fa** and **3ga**), while in the former case a partial cross-coupling between the C−Cl bond and *t*-BuCH$_2$MgBr was observed.[13a−c,14b] An imine derived from 4-bromoacetophenone failed to participate in the reaction. While a *m*-methyl group directed the reaction to take place at the less hindered ortho position (**3ha**), meta−fluorine and −ether substituents caused preferential benzylation of their proximity (**3ia** and **3ja**), as was the case with other cobalt-catalyzed C−H functionalization reactions.[13a−c,14a,b,20] Imines derived from heteroaryl methyl ketones, propiophenone, tetralones, and chromanone were also amenable to the present benzylation, affording the products **3la**−**ra** in moderate to high yields.

Next, we examined the reaction of imine **1a** with various benzyl phosphates (Scheme 3a). Benzyl phosphates derived from a series of para-, meta-, and ortho-substituted benzyl alcohols participated in the benzylation of **1a** to afford the products **3ab**−**an** in moderate to good yields, among which **3ab** and **3ae** could be prepared on a 3 mmol scale. Again, aryl chloride moieties on the benzylic substrate could be tolerated (**3af** and **3aj**). Phosphates derived from 2-naphthylmethyl alcohol and 9-phenanthrenylmethyl alcohol also served as viable coupling partners for imine **1a**, affording diarylmethanes

DOI: 10.1021/acs.orglett.5b01955
Org. Lett. 2015, 17, 4192−4195

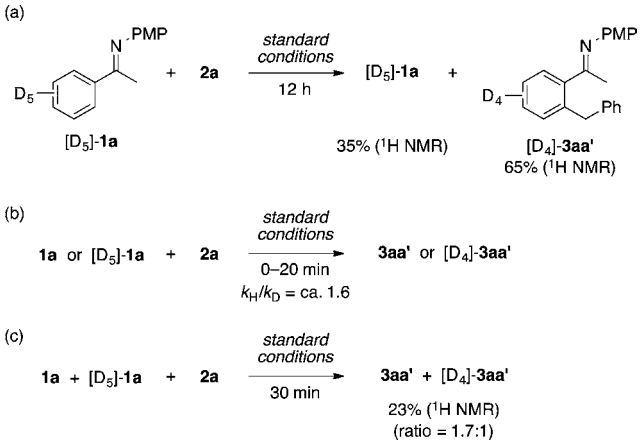
Scheme 3. (a) Ortho-Benzylation of Imine 1a with Various Benzyl Phosphates and (b) 2-fold Benzylation of Imine 1d with Bis-phosphate 2q



3ao and **3ap** in moderate yields. The present catalytic system was also applicable to a 2-fold benzylation reaction using a bis-phosphate **2q** derived from 1,4-phenylenedimethanol (Scheme 3b). Thus, with an excess amount of imine **1d** and increased loadings of the precatalyst and the Grignard reagent, the 1,4-bisbenzylbenzene derivative **3dq** was successfully obtained albeit in a moderate yield. Note that a primary alkyl phosphate such as triethyl phosphate was completely inert as an electrophile under the present conditions.

We consider that the present reaction involves imine-directed aromatic C−H metalation with an organocobalt species,[21] electrophilic trapping of the resulting cobaltacycle with benzyl phosphate to produce the benzylation product, and regeneration of the organocobalt species through transmetalation with the Grignard reagent.[15] In order to gain insight into the C−H cleavage process, we performed a series of experiments using pentadeuterated imine **1a**-d_5 (Scheme 4). The reaction of **1a**-d_5 with **2a** under the standard conditions afforded the expected benzylation product **3aa**-d_4 but with substantial recovery of **1a**-d_5 (ca. 35%; Scheme 4a). GCMS and ^{1}H NMR analysis of the crude product showed no significant loss of ortho-D atoms of the recovered **1a**-d_5. Parallel individual reactions of **1a** and **1a**-d_5 showed a modest but noticeable difference in the initial conversion, giving an approximate KIE value of 1.6 (Scheme 4b). We also performed a competition reaction of **1a** and **1a**-d_5, which afforded a mixture of the products **3aa** and **3aa**-d_4 in a ratio of 1.7:1 (Scheme 4c). These

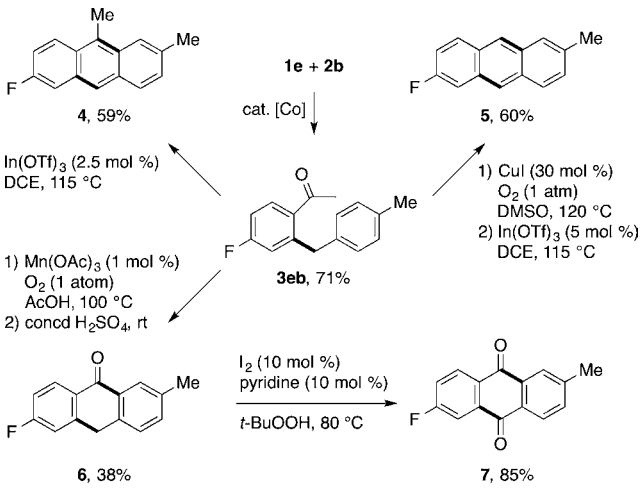
Scheme 4. Deuterium-Labeling Experiments



observations demonstrate that the C−H metalation step occurs irreversibly and influences the reaction rate, while the moderate magnitude of the KIE values may suggest that the C−H metalation step is not distinctly slower than the catalyst−substrate association/dissociation processes.[22,23] Note that the addition of TEMPO (1 equiv) completely shut down the C−H benzylation as well as the formation of the homo- and the cross-coupling products, suggesting a radical character of the active catalyst.

The acetyl group of the present benzylation products makes them versatile precursors to polycyclic compounds, as demonstrated by a series of transformations illustrated in Scheme 5. Diarylmethane **3eb**, prepared in a decent yield on a

Scheme 5. . Transformation of Diarylmethane 3eb into Polycyclic Compounds[a]



preparatively useful scale (3 mmol), was readily converted into an anthracene **4** through In(OTf)$_3$-catalyzed dehydrative cyclization.[24] Another anthracene **5** was obtained through Cu-catalyzed oxidative conversion of the acetyl group to a formyl group[25] followed by In(OTf)$_3$-catalyzed dehydrative cyclization. The acetyl group could also be oxidized to a carboxylic acid under aerobic Mn catalysis,[26] and subsequent intramolecuar Friedel−Crafts acylation afforded an anthrone **6**. The anthrone **6** was further converted into an anthraquinone **7** by an I_2/pyridine-catalyzed oxidation protocol.[27] Note that exposure of the 2-fold benzylation product **3dq** to the

DOI: 10.1021/acs.orglett.5b01955
Org. Lett. 2015, 17, 4192−4195

$In(OTf)_3$-catalyzed conditions turned the color of the reaction mixture dark blue, which implied the formation of a pentacene derivative. Nevertheless, the reaction actually caused substantial deacetylation, and the desired pentacene could not be identified (see the Supporting Information).

In summary, we have developed a cobalt−pyphos catalytic system for the ortho C−H benzylation of aryl imines with benzyl phosphates, affording diarylmethanes bearing *o*-acyl groups under room-temperature conditions. The present benzylation reaction, owing to the versatility of the acetyl group, has opened a route to facile synthesis of unsymmetrically substituted anthracenes, anthrones, and anthraquinones, which are nontrivial to access by the existing methods. Further expansion of the scope of electrophiles for cobalt-catalyzed C−H functionalization is currently underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01955.

Experimental procedures and characterization data for new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: nyoshikai@ntu.edu.sg.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by Nanyang Technological University/Singapore Ministry of Education (Academic Research Fund Tier 1: RG5/14) and JST, CREST.

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DOI: 10.1021/acs.orglett.5b01955
Org. Lett. 2015, 17, 4192−4195