Graphical Abstract

Arylation of diethyl malonate and ethyl cyanoacetate catalyzed by palladium/di-*tert*-butylneopentylphosphine

Jeffrey G. Semmes, Stephanie L. Bevans, C. Haddon Mullins, and Kevin H. Shaughnessy*

Arylation of diethyl malonate and ethyl cyanoacetate catalyzed by palladium/di-*tert*-butylneopentylphosphine

Jeffrey G. Semmes, Stephanie L. Bevens, C. Haddon Mullins, and Kevin H. Shaughnessy*

Department of Chemistry, The University of Alabama, Box 870336, Tuscaloosa, Alabama 35487-0336, United States

*Corresponding author: Tel.: +1-205-348-4435; fax: +1 205-348-9104

E-mail: kshaughn@ua.edu

We dedicate this article to the memory of professor Harry H. Wasserman.

Abstract

α -Arylated carbonyl derivatives are important structural motifs in many natural products and pharmaceutically active compounds. Although arylation of simple monocarbonyl compounds is a well-established methodology, metal-catalyzed arylation of β -dicarbonyl derivatives is significantly more challenging. The ability of β -dicarbonyl anions to bind to palladium in a κ^2 -*O,O* mode, rather than the κ^1 -*C*-bound mode required for bond formation, often results in the deactivation of catalyst systems. The *C*-bound form of the enolate can be favored through the use of sterically demanding ligands. Herein, we report that the sterically demanding di-*tert*-butylneopentylphosphine (DTBNpP) ligand in combination with Pd(dba)₂ provides an effective catalyst for the coupling of aryl bromides and chlorides with diethyl malonate. The Pd/DTBNpP system also catalyzes the coupling of aryl bromides with ethyl cyanoacetate.

Keywords: Cross-coupling; palladium; phosphine; enolate

1. Introduction

In recent years there has been significant interest in the development of efficient methods for the α -arylation of carbonyl compounds due to the importance of these structures in

biologically active compounds. Metal-catalyzed coupling of aryl halides with enolate nucleophiles has been developed into a highly general method for preparing these important compounds.¹ The coupling of aryl halides with enolates derived from ketones, aldehydes, and carboxylic acid derivatives catalyzed by palladium and copper is well preceded. In contrast, β -dicarbonyls have proven to be more challenging substrates and have received significantly less attention than monocarbonyls. This trend is opposite to that seen in classical enolate chemistry, where the more acidic β -dicarbonyl enolates are widely used nucleophiles. The resulting substituted β -dicarbonyl enolates are widely used intermediates in organic synthetic methodologies. Therefore, routes to α -aryl- β -dicarbonyls are of significant interest.

The relative lack of catalyst systems for the arylation of β -dicarbonyls likely results from specific challenges presented by β -dicarbonyls compared to monocarbonyl compounds in the catalytic cycle (Scheme 1). Monocarbonyl enolates can exist in both κ^1 -C- and κ^1 -O-bound forms with the preferred coordination mode depending on the structure of the enolate and the metal complex.² For bond formation to occur between a palladium bound aryl group and an enolate, the C-bound form is presumably required. In contrast, for β -dicarbonyl enolate anions, the κ^2 -O,O-bound complex would be expected to be strongly favored in most cases over the κ^1 -C-bound form. If the κ^2 -O,O-bound is strongly favored, reductive elimination would not be expected to occur and the catalyst would become inactivated. In addition, the less nucleophilic β -dicarbonyl enolate would be expected to undergo reductive elimination more slowly than more nucleophilic monocarbonyl enolates.³ Both of these challenges must be overcome to achieve successful coupling.

Scheme 1. Catalytic cycle for coupling of aryl halides with dialkyl malonates.

The initial couplings of β -dicarbonyl enolates with aryl iodides were achieved using stoichiometric amounts of copper.⁴ Catalytic systems for these couplings were first reported by Miura and provided moderate yields using aryl iodides at high temperatures.⁵ Ligand-supported copper catalysts effect these couplings under milder conditions, but are still limited to aryl iodide and bromide substrates.⁶ Palladium-catalyzed coupling of aryl halides and enolates were initially reported concurrently by the Hartwig,⁷ Buchwald,⁸ and Miura⁹ groups. Palladium-catalyzed methodologies have been developed into highly general routes for the coupling of aryl bromides, chlorides, and sulfonates with a wide range of stabilized carbanions.^{1b,1c} Despite these advances, palladium-catalyzed arylation of β -dicarbonyl enolates still represents a synthetic challenge. Initial reports by Hartwig and Buchwald demonstrated that palladium catalysts were able to couple aryl bromides and chlorides with β -dicarbonyl derivatives.¹⁰ A range of sterically demanding, electron-rich phosphine and NHC ligands have been shown to provide effective catalysts for coupling of aryl bromides, chlorides, and sulfonates with β -dicarbonyl derivatives.¹¹ At elevated temperatures, arylation of malonate or cyanoacetate esters is accompanied by

decarboxylation to provide α -arylacetonitrile or α -arylacetic acid derivatives directly in analogy to the malonic ester synthesis.¹²

Sterically demanding, electron-rich ligands have generally been found to be most effective for arylation of β -dicarbonyl derivatives. Sterically demanding ligands are expected to overcome the particular challenges faced in coupling with β -dicarbonyl. The bulky ligand can disfavor the κ^2 -*O,O*-binding mode, while also promoting reductive elimination. Electron-rich ligands promote oxidative addition, allowing less reactive aryl chloride and aryl sulfonate substrates to be used.

Our group has previously reported the use of di-*tert*-butylneopentylphosphine (DTBNpP), *tert*-butyldineopentylphosphine (TBDNpP) and trineopentylphosphine (TNpP) in C–C bond-forming reactions,¹³ amine arylations,¹⁴ and arylation of ketone enolates.¹⁵ Calculated cone angles suggest that DTBNpP is more sterically demanding than tri-*tert*-butylphosphine (TTBP) and has similar electronic properties.^{14a} Additional neopentyl groups further increase the calculated cone angle, but also provide additional conformational flexibility. As a result, TNpP appears to be effectively less sterically demanding than DTBNpP or TTBP and provides effective catalysts for cross-coupling of highly sterically demanding substrates.^{14b,15} Given the steric and electronic properties of DTBNpP and its successful application in the arylation of ketones, we hypothesized that it might provide an effective ligand for the arylation of dialkyl malonates and other active methylene compounds.

2. Results and Discussion

Reaction conditions were optimized for the coupling of 4-bromoanisole and diethyl malonate using DTBNpP in combination with Pd(dba)₂. A range of inorganic and organic bases were

explored. Complete conversion to product was obtained with NaH (Table 1, entry 1) in toluene.^{10c} More coordinating solvents, such as THF and DMF, gave lower yields using NaH as the base (entries 2-3). In contrast to NaH, KH gave only a 53% yield under the same conditions in toluene (entry 4). Weaker bases, such as sodium carbonate, sodium phosphate, and potassium phosphate gave yields ranging from 45–73% (entries 5-7). Interestingly, the cation effect with phosphate was opposite to that observed with the hydride bases. Sodium *tert*-butoxide and amine bases gave no conversion to product (entries 8-10). Base strength does not directly correlate with conversion. Both hydride and *tert*-butoxide fully deprotonate the malonate anion, yet only NaH results in conversion to product. Weaker bases that would not fully deprotonate malonate give moderate yields in some cases (Na₂CO₃), but no conversion in others (amine bases). The reasons for these trends are unclear. Notably, good yields were obtained with diethyl malonate, rather than the more hindered di-*tert*-butyl malonate needed for some systems.^{11c}

Table 1. Base screening in coupling of 4-bromoanisole and diethyl malonate

entry	base	solvent	yield (%) ^a
1	NaH	toluene	100
2	NaH	THF	45
3	NaH	DMF	33
4	KH	toluene	53
5	Na ₂ CO ₃	toluene	45
6	Na ₃ PO ₄	toluene	52
7	K ₃ PO ₄	toluene	73
8	NaO <i>t</i> -Bu	toluene	0
9	Et ₃ N	toluene	0

10	<i>i</i> Pr ₂ NEt	toluene	0
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^aDetermined by GC

Using NaH in toluene at 70 °C, high conversion could be achieved for a variety of electron-deficient and electron-rich aryl and heteroaryl bromides with 1 mol % Pd(dba)₂ and 2 mol % DTBNpP (Table 2). Aryl bromides with electron-donating substituents in the 3- or 4-positions were successfully coupled to diethyl malonate with yields ranging from 85-92% (entries 1-5). In contrast, the more sterically demanding 2-bromoanisole gave only a 29% conversion to product (entry 6). In the arylation of propiophenone with the DTBNpP/Pd system, *ortho*-substituted aryl halides were tolerated, but low yields were obtained with di-*ortho*-substituted aryl halides.¹⁵ Switching to the more flexible TNpP ligand provided high yields with di-*ortho*-substituted aryl bromides. Use of TNpP in the coupling of 2-bromoanisole with diethyl malonate gave minimal conversion to product, however. Reductive elimination of the more hindered and less nucleophilic malonate anion may be more sensitive to steric effects than ketone enolates. The smaller steric demand of the conformationally flexible TNpP ligand may be unable to sufficiently disfavor the κ^2 -O,O-coordination mode of the malonate anion resulting in catalyst deactivation. High yields were obtained with 4-bromophenol and 6-bromo-2-naphthol using 2.2 equivalents of NaH despite the presence of the strongly electron donating phenoxide anion (entries 7 and 8).

Table 2. Coupling of diethyl malonate with aryl bromides.^a

entry	ArBr	yield (%)	entry	ArBr	yield (%)
1		86	12		91
2		88	13		87
3		85	14		71
4		92	15		90
5		90	16		69
6		29 ^b trace ^c	17		77
7		85 ^d	18		82
8		89 ^d	19		72 84 ^e
9		89	20		0
10		85	21		82
11		0	22		70

^a Aryl bromide (1 mmol), diethyl malonate (1.2 mmol), NaH (1.2 mmol), Pd(dba)₂ (1 mol %), DTBNpP (2 mol %), in toluene at 70 °C, 24 h. Yields are average isolated yields for two attempts.

^b Yield determined by GC.

^c TNpP (2 mol %) used as ligand.

^d 2.2 equivalents of NaH

^e 3.0 equivalents of K₃PO₄ used as base

Unfunctionalized aryl bromides gave comparable yields to those with electron-donating substituents (entries 9, 10, 12, and 13). The one exception to this was 1-bromonaphthalene, which gave no conversion, likely due to steric interactions with H8. Mixed results were obtained

with electron-deficient aryl halides. 1-Bromo-4-trifluoromethylbenzene and methyl 3-bromobenzoate gave good yields of coupled product (90% and 82%, respectively, entries 15 and 18). 1-Bromo-4-fluorobenzene, 1-bromo-3,5-di(trifluoromethyl)benzene, and 4-bromobenzonitrile gave slightly lower yields ranging from 69–77% (entries 14, 16, and 17). 4-Bromoacetophenone gave a 72% yield using the standard conditions (entry 19). The yield could be improved to 84% using K_3PO_4 as the base. Similar improvements were not observed for other electron-deficient aryl bromides, however.

Heteroaryl halides are often challenging substrates, but are highly desirable in the synthesis of pharmaceuticals and agricultural compounds. No conversion was obtained with 2-bromopyridine (entry 20). The lack of reactivity may be due to coordination of pyridine to the active catalyst and the electron-deficient nature of this compound. In contrast, electron-rich thiophene derivatives gave good yields. 3-Bromothiophene afforded an 82% yield (entry 21) and 3-bromobenzo[*b*]thiophene provided the coupled product in 70% yield (entry 22). The lower yield with 3-bromobenzo[*b*]thiophene may be due to steric congestion from the fused benzene ring as was seen with 1-bromonaphthalene. The DTBNpP/Pd system is the first example of palladium-catalyzed coupling of bromothiophene derivatives with malonate anions, although the copper-promoted coupling of iodothiophenes with malonate anions is known.^{6d,16}

Aryl chlorides could be efficiently coupled with diethyl malonate using the DTBNpP/Pd(dba)₂ system by doubling the catalyst loading (2 mol % Pd, 4 mol % DTBNpP) and increasing the reaction temperature to 100 °C. When using NaH as the base, 60–70% conversion to product was achieved. Switching to anhydrous potassium phosphate gave yields above 80%. Both electron-rich (entries 1-5) and electron-poor substrates (entries 6-8) were found to be suitable coupling partners with observed yields ranging from 81-86%. Although coupling of 4-

bromobenzonitrile to diethyl malonate resulted in a good yield, 4-chlorobenzonitrile gave low conversion under these conditions. As seen with aryl bromides, *ortho*-substituted aryl bromides gave low conversion with both DTBNpP and TNpP.

Table 3. Coupling of diethyl malonate with aryl chlorides.^a

entry	ArCl	yield (%)	entry	ArCl	yield (%)
1		83	5		85
2		81	6		85
3		86	7		84
4		86	8		82

^aConditions: aryl chloride (1 mmol), diethyl malonate (1.2 mmol), and K₃PO₄ (3 mmol), Pd(dba)₂ (2 mol %), and DTBNpP (4 mol %) in toluene at 100 °C for 24 h.

The DTBNpP/Pd catalyst is effective for the coupling of aryl bromides and chlorides with diethyl malonate. The DTBNpP system provides higher yields than are achieved with the Mor-Dal-phos ligand^{11c} and are comparable to the results reported with TTBP.^{10c} The TTBP catalyst tolerates *ortho*-substituted aryl halides, whereas these substrates afford low yields with the DTBNpP-derived catalyst. Calculated cone angles suggest that DTBNpP (198°) is more sterically demanding than TTBP (194°),^{14a} which may account for the low yields with hindered aryl bromides using DTBNpP.

Ethyl cyanoacetate was explored as the nucleophile with the DTBNpP/Pd system. Examples of palladium-^{10c,17} and copper-catalyzed^{6b} arylation of cyanoacetate esters are limited.

Cyanoacetate esters are more acidic than malonate esters, which would be expected to make reductive elimination more challenging than with malonate anions. The cyanoacetate is not capable of the same type of strong chelation coordination available to malonate anions, although coordination through the nitrile could have a similar inhibitory effect.

A moderate scope of aryl bromides were successfully coupled to ethyl cyanoacetate using $\text{Pd}(\text{dba})_2$ (2 mol %) and DTBNpP (4 mol %) with NaH as the base (Table 4). Good to excellent yields were observed with unsubstituted aryl bromides (entries 1 and 2) and aryl bromides with electron-donating substituents (entries 3-5). The electron rich substrates 3- and 4-bromoanisole gave yields of 92% and 91%, respectively. As previously observed in the reactions of diethyl malonate, 2-bromoanisole resulted in almost no conversion of starting material. The more electron-rich 4-bromo-*N,N*-dimethylaniline afforded a lower 72% yield compared to the bromoanisoles, whereas similar yields were observed with these substrates with diethyl malonate.

Table 4. Coupling of diethyl malonate with aryl chlorides.^a

$\text{ArBr} + \text{EtO}-\text{C}(=\text{O})-\text{CH}_2-\text{CN} \xrightarrow[\text{NaH, toluene, 70 } ^\circ\text{C, 24 h}]{\text{Pd}(\text{dba})_2 \text{ (2 mol \%), DTBNpP (4 mol \%)}} \text{EtO}-\text{C}(=\text{O})-\text{CH}(\text{Ar})-\text{CN}$					
entry	ArBr	yield (%)	entry	ArBr	yield (%)
1		91	5		92
2		84	6		47
3		91	7		37
4		72			

^a Aryl bromide (1 mmol), ethyl cyanoacetate (1.2 mmol), NaH (1.2 mmol), $\text{Pd}(\text{dba})_2$ (2 mol %), DTBNpP (4 mol %), in toluene at 70 °C, 24 h.

Electron-withdrawing substituents had a significant negative effect on the yield in these reactions. Low conversions were obtained for reactions involving 4-bromoacetophenone (37%) and methyl 3-bromobenzoate (47%, entries 6 and 7). Attempts at coupling other electron-deficient substrates, such as 1-bromo-4-trifluoromethylbenzene, 4-bromobenzonitrile, and 1-bromo-4-fluorobenzene, were unsuccessful. Aryl chlorides could not be coupled with ethyl cyanoacetate using the DTBNpP/Pd system.

The performance of the DTBNpP/Pd system with neutral and electron-rich aryl bromides is comparable to results reported with TTBP and Q-Phos^{10c} and is achieved with lower catalyst loading and lower temperature than Verkade's^{17b} bicyclic proazaphosphatranes ligand. The DTBNpP/Pd system is less effective with electron-deficient aryl bromides, however. The reason for the poor performance of the electron-deficient aryl bromides is unclear. The poor conversion may be due to a difference in the preferred coordination mode of the cyanoacetate anion to disfavor the *C*-bound mode.

In conclusion we have shown that DTBNpP provides an efficient catalyst system for the α -arylation of diethyl malonate using aryl bromides and chlorides as well as for the α -arylation of ethyl cyanoacetate with electron-rich and electron-neutral aryl bromides. The Pd/DTBNpP catalyst system provides high yields for a range of sterically unhindered substrates, but is unable to couple sterically hindered substrates. The Pd/TNpP system, which was useful for reactions coupling sterically hindered substrates to ketone enolates, was ineffective with diethyl malonate and ethyl cyanoacetate. Attempts at coupling various electron-poor aryl bromides as well as all aryl chlorides to ethyl cyanoacetate were also unsuccessful.

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