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Palladium-catalyzed cross-coupling of cyclopropanolderived ketone homoenolates with aryl bromides[†]

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David Rosa and Arturo Orellana*

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The cross-coupling reaction of cyclopropanol-derived ketone homoenolates bearing β -hydrogens with aryl and hetaryl bromides has been achieved for the first time. This reaction is high yielding, is broad in scope and uses a simple catalytic system. Notably, the proposed palladium homoenolates do not undergo β -hydride elimination to the corresponding α , β -unsaturated ketones.

Homoenolates constitute an important class of umpolung¹ synthons that bear a charge affinity pattern complementary to that of enolate anions (Fig. 1). Owing to their synthetic potential and the difficulties associated with their direct preparation from ketones,² significant effort has been devoted to the development of new methods to access and use homoenolates and homoenolate equivalents over the years.^{3,4} N-Heterocyclic carbenes have enabled the catalytic generation of homoenolates from α , β -unsaturated aldehydes.⁵ These reactions, however, are not amenable to forging C-C bonds between homoenolates and aryl electrophiles (i.e. aryl halides). One approach to this transformation involves the palladium-catalyzed cross-coupling reaction of *preformed* homoenolates⁶ with aryl electrophiles. These reactions, however, suffer from the need to synthesize these homoenolates by activation of simpler substrates, which often requires multiple steps.⁷ The catalytic formation and cross-coupling of ester homoenolates with any electrophiles developed by Baudoin et al.⁸ and the formation and cross-coupling of amide homoenolates using Pd(0)/ Pd(II) and Pd(II)/Pd(IV) catalysis developed by Yu *et al.*⁹ represent more

$$\begin{array}{c} O \\ H \\ R \\ (+)_{(-)} \end{array} M \qquad \begin{array}{c} O \\ H \\ R \\ (+)_{(-)} \end{array} H \xrightarrow{O'} M \\ R \\ (+)_{(-)} \end{array}$$

enolate homoenolate cyclopropanol

Fig. 1 Charge affinity patterns of enolates and homoenolates, and equilibrium between a metal homoenolate and metallated cyclopropanol.

direct approaches to this transformation. Unfortunately, these catalytic methods are restricted to the use of amides or esters, and can suffer from the generation of product mixtures.

In the 1970s Kuwajima recognized the potential of the cyclopropanol ring to act as a homoenolate precursor (Fig. 1), and subsequently developed a number of related synthetic methods,¹⁰ including the first palladium-catalyzed cross-coupling reaction of cyclopropanol derivatives.¹¹ These cross-coupling reactions, however, were severely limited in scope and required very electron-rich cyclopropane acetals, very electron-poor palladium intermediates (derived from oxidative addition of Pd(0) to aryl triflates or acyl halides), or both. In addition, the preparation of the cyclopropanol derivatives was not straightforward. Since then, the development of the Kulinkovich reaction¹² has made cyclopropanols readily available. In this light, it is surprising that little work related to the catalytic cross-coupling reactions of cyclopropanol-derived homoenolates with any electrophiles has been performed. This is perhaps due to limitations shown in Kuwajima's early work, and to the propensity of palladium homoenolates to undergo decomposition to the corresponding α,β -unsaturated ketones via β-hydride elimination.¹³ Our group reported the first palladiumcatalyzed cross-coupling of aryl halides with cyclopropanol-derived homoenolates,¹⁴ and the first direct arylation reaction using cyclopropanol-derived homoenolates.¹⁵ These reactions were limited by the need to use homoenolates that were incapable of undergoing β -hydride elimination. Here we report the first palladium-catalyzed cross-coupling reaction of aryl bromides with catalytically generated ketone homoenolates bearing β -hydrogens.

Our working mechanistic proposal for these cross-coupling reactions invokes (i) oxidative addition of a Pd(0) catalyst to the aryl halide, (ii) ligand exchange on palladium and deprotonation of the cyclopropanol (not necessarily in that order), (iii) β -carbon elimination leading to a palladium homoenolate, and (iv) reductive elimination (Scheme 1). The development of this palladiumcatalyzed cross-coupling reaction must circumvent the propensity of cyclopropanol rings to undergo base-mediated ring-opening to the corresponding ketone,¹⁶ and the more problematic tendency of palladium homoenolates to undergo facile β -hydride elimination¹⁷ to the corresponding α , β -unsaturated ketone. Therefore the choice

Department of Chemistry, York University, 4700 Keele Street, Toronto, ON M3J 1P3, Canada. E-mail: aorellan@yorku.ca; Fax: +1 416 736 5936; Tel: +1 416 736 2100 ext 70760

¹el: +1 416 /36 2100 ext /0/60

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Scheme 1 Mechanistic proposal for the cross-coupling of aryl halides with ketone homoenolates and competing side reactions.

of base and catalyst system would be expected to have a significant impact on the product distribution.

A 1,1-disubstituted cyclopropanol (1) and 4-bromoanisole were chosen to optimize this reaction (Table 1). The use of monodentate ligands provided the coupled product (1a) in modest yields along with significant amounts of the ring-opened product (1b, entries 1 and 2). The use of monodentate biaryl phosphine ligands (Buchwald ligands) resulted in increased product yields, however significant amounts of ring-opened product were still observed (entries 3–5). A further increase in yield was observed when bidentate ligands were used (entries 6–10). Note that the yield of the coupled product does not vary significantly with the bite angle or the nature of the phosphine (trialkyl *vs.* alkyldiaryl *vs.* triaryl). These results suggest that the increased yield of the reaction is due the bidentate phosphine occupying two coordination sites on palladium, thereby retarding β -hydride elimination relative to reductive elimination.¹⁸

Having developed satisfactory conditions for the cross-coupling of cyclopropanol-derived homoenolates, we explored the scope of the

Table 1	Reaction develop	oment (selected result	s) ^{a,b}	
t-Bu	ОН	4-bromoanisole base (2.0 equiv.) Pd(OAc) ₂ (10 mol%)	t-Bu O 1a	
		toluene, 80 °C	t-Bu O 1b	
Entry	Base	Ligand	Yield $(1a:1b)^c$	
1	Cs_2CO_3	PPh ₃	53:18	
2	Cs_2CO_3	PtBu ₃	46:36	
3	Cs_2CO_3	$XPhos^d$	49:36	
4	Cs_2CO_3	$SPhos^d$	64:18	
5	Cs_2CO_3	DavePhos ^d	62:15	
6	Cs_2CO_3	dppf ^d	77:0	
7	Cs_2CO_3	$dppe^d$	73:0	
8	Cs_2CO_3	$dppp^d$	79:0	
9	K ₃ PO ₄	$dppb^d$	83:0	
10	K_3PO_4	$dcpb^d$	86:5	

^{*a*} See ESI for complete optimization results. ^{*b*} All reactions were conducted using 0.24 mmol of cyclopropanol (0.1 M) and 20 mol% of bidentate or 40 mol% of monodentate ligand. ^{*c*} Isolated yields. ^{*d*} XPhos = 2-dicyclohexylphosphino-2',4',6'-triisopropyl-biphenyl, SPhos = 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl, DavePhos = 2-dicyclohexylphosphino)ferrocene, dimethylamino)biphenyl, dppf = 1,1'-bis(diphenylphosphino)ferrocene, dppe = ethylenebis(diphenylphosphine), dppp = 1,3-bis(diphenylphosphino)propane, dppb = 1,4-bis(diphenylphosphino)butane, dcpb = 1,4-bis(dicyclohexylphosphino)butane.



 a Isolated yields. b Cs₂CO₃ was used instead of K₃PO₄. c All reactions were conducted using 0.24 mmol of cyclopropanol (0.1 M).

reaction with respect to the oxidative addition partner (Table 2). Aryl halides bearing electron-withdrawing (entries 2–7) and electrondonating (entries 8–12) functional groups provide the coupled products in good yields. Aryl halides bearing one *ortho*-substituent couple well (entry 8), however, a di-*ortho*-substituted aryl halide provides a moderate yield of the product (entry 9). The latter result likely reflects a difficult oxidative addition step. A selection of electron-poor and electron-rich heterocycles was also shown to couple effectively (entries 13–16). In some instances (entries 3, 6, 9, 11, 12, 14 and 16), the coupled product was obtained in lower than expected yield and was sometimes (entries 3c, 9c and 11c) accompanied by the corresponding α_{β} -unsaturated ketone.^{19,20} Fortunately, switching from K₃PO₄ to the weaker Cs₂CO₃ base improved the yield of the coupled product, and prevented the formation of the unsaturated ketone in all but one instance (entry 9).

We have also investigated the scope of the reaction with respect to the cyclopropanol partner (Table 3). Monocyclic cyclopropanols bearing alkyl (entries 17–19), allyl (entry 20), benzyl (entry 21) and aryl (entry 22) substituents at the 1-position couple effectively. Notably, monocyclic 1,2-disubstituted cyclopropanols couple selectively, giving the product arising from cleavage of the least substituted cyclopropane bond (entries 21 and 22). Fused bicyclic cyclopropanols also couple selectively to give the product arising from scission of the least substituted cyclopropane bond (entries 23a, 24a and 25a/25c), however appreciable amounts of the products arising from cleavage of the ring fusion bonds are also observed in some instances (entries 23d and 24d). HO

0

 $R^2 R^3$

4-bromoanisole

Pd(OAc)₂, dppb



 a Isolated yields. b Cs₂CO₃ was used instead of K₃PO₄. c All reactions were conducted using 0.24 mmol of cyclopropanol (0.1 M).

In conclusion, we have developed the first palladium-catalyzed cross-coupling reaction of aryl bromides with cyclopropanolderived homoenolates capable of undergoing β -hydride elimination. This reaction proceeds with good yields, uses a simple catalyst system, and tolerates a wide range of aryl bromides and cyclopropanols.

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