Pergamon

Tetrahedron Letters 43 (2002) 7091–7094

TETRAHEDRON
LETTERS

Palladium-catalyzed carbon–carbon coupling reactions using aryl Grignards

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Received 28 June 2002; accepted 22 July 2002

Abstract—Coupling reactions using $Pd(PPh_3)_4$ were investigated with a number of electron donating and electron withdrawing substituents. High yields were obtained with both types of substituents. In competitive reactions the electron-withdrawing group $-NO_2$ reacted preferentially over the electron donating groups. When the starting halides were converted to Grignard reagents, high yields were obtained for some hindered electron-withdrawing groups. © 2002 Elsevier Science Ltd. All rights reserved.

Preparations of aryl alkynes have been described in the literature using the Sonogashira coupling reaction.[1] These coupling reactions have been used in natural product synthesis[2] and materials chemistry.[3] As these types of reactions have become an integral part of the synthetic toolbox, and the number of reports of their use have increased,[2,3] variations in reaction conditions have also been introduced in the literature. The initial report of Sonogashira et al. with the palladium catalyst[1] described the requirement for a base and cuprous iodide. The nature of the base,[4] the solvent[5] and the palladium catalyst have been investigated, with changes in these resulting in improved yields and decreased reaction times.

Previous cross-coupling reactions reported by Stephens and Castro,[6] using cuprous acetylides, indicate that electron withdrawing groups in the *para* position increase the ease of substitution relative to electron-donating groups in the following manner: *p*-nitro>H>*p*-methoxy. Subsequent reports that have described improved yields, focused on electron withdrawing substituents such as carboxyaldehydes, nitro groups and esters.[5,7]

We prepared a number of substituted trimethyl silyl ethynyl benzenes using Sonogashira coupling (Table 1, Method A), and then compared these results to a novel method of coupling aryl iodides to terminal alkynes developed in our laboratory. All of the reactions were completed with $Pd(PPh_3)_4$ as the catalyst using identical reaction conditions, i.e. the reactions have not been optimized. The compounds investigated were chosen due to the availability of all three isomers, with the exception of the ethyliodobenzenes.

For most substituents, substitution in the *para* position provided the highest yield. The reactivity pattern that Stephens and Castro[6] first noted for electron withdrawing versus electron rich groups is not evident from the yields for the trifluoromethyl and ethyl groups, with exceptional yields in both cases. To determine if the electron withdrawing substituents were indeed the most reactive, competitive reactions were run between 4-iodonitrobenzene and both 4-iodotoluene and 4-iodoanisole.[8] The competitive reaction of toluene and nitrobenzene was monitored by GC; it was found that after 1 h there was no remaining 4-iodonitrobenzene, and no disappearance of 4-iodotoluene. Over a prolonged reaction time (2 h) the corresponding coupled nitro-product was obtained with no evidence of the coupled toluene product. The competitive reaction between 4-iodonitrobenzene and 4-iodoanisole resulted in a similar pattern of reactivity with the disappearance of the 4-iodonitrobenzene and no reaction of the substituted anisole. The reactivity pattern originally described by Castro and Stephens[6] is also seen in these palladium-catalyzed, cross-coupling reactions.

Many of the carbon–carbon bond forming reactions that use a palladium catalyst, such as Stille coupling[9] or the Heck reaction of aryl mercury compounds,[10] resulting in the formation of an alkenyl aryl compound, involve a transmetallation reaction. This type of transmetallation has not been extended to the forma-

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Keywords: Sonogashira; coupling; Grignard reagent.

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PII: S0040-4039(02)01538-1

Table 1. Palladium-catalyzed cross-coupling reactions

Entry	R		Yield (%)[a]		
			2-	3-	4-
1	CF_3	A[b]	>99	>99	>99
		B[b]	18	88	97
2	CO_2Me	A[c]	73	87	89
		B[c]	9	65	43
3	NO_2	A[c]	90	62	94
		B[c]	7	97	41
4	CH_3	A[c]	37	30	54
		B[c]	94	92	69
5	CH_2CH_3	A[b]	>99	–	>99
		B[b]	75	–	75
6	OH	A[c]	91	87	78
		B[c]	59	49	20
7	OCH_3	A[c]	74	48	99
		B[c]	59	49	20
8	NH_2	A[c]	61	65	42
		B[c]	56	73	38

[a] Reaction conditions: Method A: $Pd(PPh_3)_4$ (46 mg, 0.04 mmol), CuI (15 mg, 0.08 mmol) and Et_3N (303 mg, 3.0 mmol) were combined in THF (5.0 mL) under a N_2 atmosphere. Substituted iodobenzene (2.0 mmol) was added and the reaction mixture was cooled to 0°C. After stirring for 10 min, trimethylsilylacetylene (206 mg, 2.1 mmol) was added dropwise over 30 min. The reaction mixture stirred at room temperature overnight and was filtered through Celite to remove Pd and Cu catalysts; Method B: Magnesium (2.0 mmol), the substituted iodide (2.0 mmol) and I_2 (catalytic) were combined in dry THF (4.0 mL) and heated to 40°C overnight to generate the Grignard. $Pd(PPh_3)_4$ (46 mg, 0.04 mmol), CuI (15 mg, 0.08 mmol) and Et_3N (0.42 mL, 3.0 mmol) were added. After stirring for 10 min, TMS–acetylene (0.30 mL, 2.0 mmol) was added dropwise over 10 min. The reaction mixture was reacted for 4 h, under N_2, quenched with water, saturated NaCl and dried over $MgSO_4$.

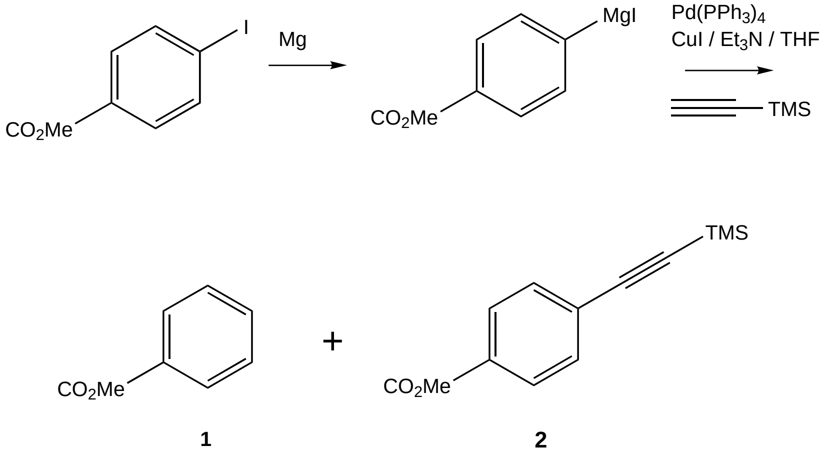
[b] Isolated yields from an average of two runs.

[c] Yield obtained by GC from an average of two or more runs.

tion of alkynyl aryl compounds and we were interested in investigating this type of chemistry. We chose to convert the starting iodides to Grignard reagents, before addition of the palladium and copper catalysts and alkyne, and compared these coupling reactions to our standard conditions. Since it is known that the acidic nature of acetylenic hydrogens (pK_a's from 20–25) interferes with Grignard reactions, it was anticipated that only **1** would form (Scheme 1). When the reaction was attempted using methyl 4-iodobenzoate, a trace amount of **1** was obtained and a 43% yield of **2** was also obtained.

This surprising result was further investigated to determine the effects of different substituents (Table 1, Method B) and the reaction mechanism. With the electron-donating methyl group, significantly higher yields were obtained than those from the corresponding reaction using standard Sonogashira conditions (Table 1, entry 4). In particular, neither the steric nor electronic effects that result from the presence of the *ortho*-methyl group seem to hinder reactivity in this Grignard modified reaction, with a high yield being obtained in comparison to the standard Sonogashira conditions. This high yield is in direct contrast with many reported yields, using different starting reagents and alkynes. For example, the preparation of trimethyl [(2-methylphenyl)ethynyl]silane from the aryl cuprate and haloacetylene proceeded in a 48% yield.[11] A recent report using 2-bromotoluene does show the preparation of 2-tolylalkynes in high yields (94% and 84%) using a catalyst optimized for aryl bromides.[12] Our methodology shares the same mild (room temperature) conditions reported therein.[12] Another surprising aspect of our investigations was that functional groups which usually interfere with Grignard reagents (NO_2, OH, CO_2CH_3) still resulted in the formation of product, albeit at lower yields than those obtained for the standard conditions.

A series of reactions using 2-iodotoluene was run to determine which reagents were necessary for the coupling reaction to proceed. In the absence of $Pd(PPh_3)_4$ the coupling does not proceed.[13] In the absence of the CuI co-catalyst the reaction also does not proceed.[14] With neither catalyst present the reaction does not proceed. When Mg, $Pd(PPh_3)_4$ and CuI are added simultaneously to the reaction mixture, the yield of trimethyl[(2-methylphenyl)ethynyl]silane decreased with respect to that obtained under standard Sonogashira conditions. It has been postulated that Grignard



Scheme 1.

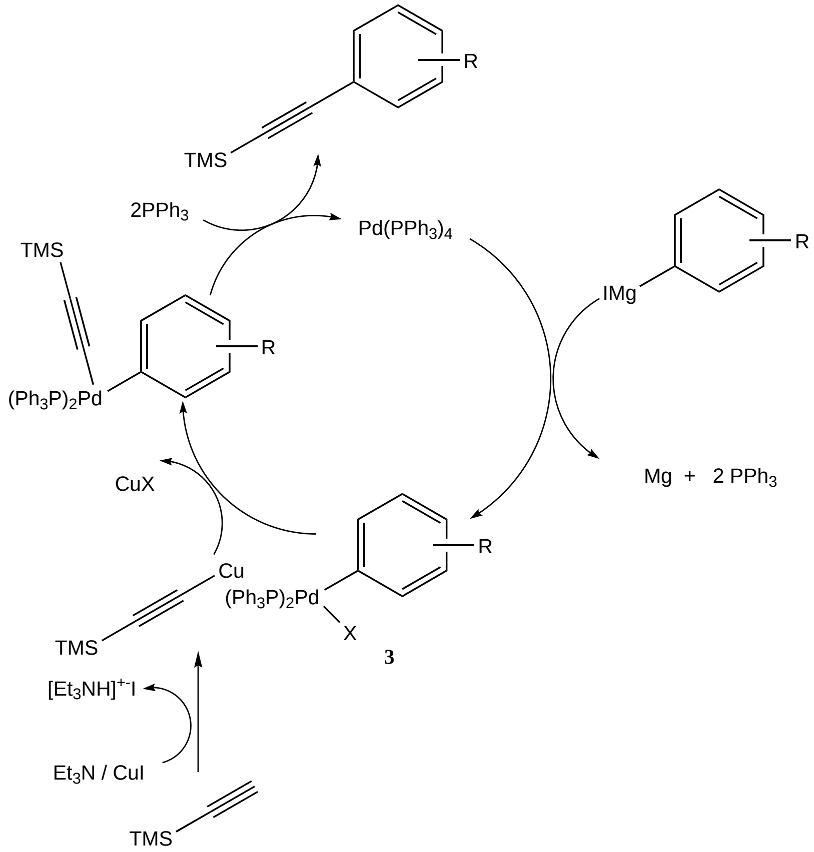


Figure 1.

reagents have radical behavior but the presence of a radical trap (TEMPO) did not interfere in the progress of the reaction.

We propose that our coupling reactions are indeed undergoing a transmetallation reaction (Fig. 1). The more reactive carbon–magnesium bond, relative to the carbon–halogen bond, can exchange with palladium. This carbon–magnesium bond shows a higher degree of polarization that assists with the Pd insertion. The insertion of Pd^0 occurs with an oxidation state change to Pd^{2+} and we propose that this oxidation is coupled to a reduction of the Mg^{2+} to Mg^0. In ^{31}P NMR studies[15] we observed identical intermediates in both the standard Sonogashira reaction and our Grignard modified reaction. An observed ^{31}P NMR signal (relative to H_3PO_4 as the internal standard) at 23.8 ppm is indicative of a *trans*-$ArPdX(PPh_3)_2$ species (**3**).[16] Due to the aqueous work-up in the reaction we have been unable to determine the nature of the magnesium by-product in the reaction, to date. We are continuing to investigate the mechanism of this Mg–Pd exchange.

In summary, we have demonstrated a modified set of Pd-coupling reaction conditions that use Grignard reagents as the source of the aryl compounds that react with an alkyne to give coupled products in good to exceptional yields. It is particularly significant to note that the mild reaction conditions do not result in the alkyne reacting with the Grignard to give the acetylide and that functional groups such as the nitro-substituent still give high yields of the coupled compound. This modified Grignard–Sonogashira reaction provides a facile and moderate method for the formation of carbon–carbon bonds.

Acknowledgements

Financial support by the Natural Sciences and Engineering Research Council of Canada is gratefully acknowledged.

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