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Preparation of 4-Allylisoindoline via a Kumada Coupling with Allylmagnesium Chloride

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Abstract:

A practical, cost-effective Kumada coupling for the preparation of 4-allylisoindoline has been developed. The first catalyst screen for this reaction with allylmagnesium reagents is described. The challenges associated with product isomerization have been minimized by a thorough understanding of the reaction parameters. Additionally, a novel workup protocol has been developed to render Mg salts soluble in aqueous media at pH 10.

Introduction

4-Allylisoindoline (**1**) is a key component of a drug candidate currently being developed. We envisioned that **1** should be accessible from **2** *via* a Pd-catalyzed coupling reaction (Scheme 1). **2•HCl** is available from either commercial sources or from 1-bromo-2,3-dimethylbenzene via a multistep sequence.[1]

Commercial availability of allyl Grignard reagents made a Kumada coupling an attractive approach for allyl installation; however, we would need to develop a procedure without *N*-H protection for optimal step efficiency.[2] Additionally Kumada coupling was preferable to the corresponding Suzuki or Negishi reactions, for which the requisite allyl-metal reagents are not available at reasonable prices on scale. A review of the literature showed limited precedent for this coupling reaction using an allylmagnesium reagent as the nucleophile.[3] In order to render the process cost-effective, we required an inexpensive Pd source and ligand. Furthermore, isolation of the basic amine product in the presence of excess Mg salts proved nontrivial. Since the product was highly water-soluble at low pH, a novel protocol was needed to solubilize Mg salts at pH ≥ 10 (suitable for product extraction). In this paper, we describe a successful solution to each of these challenges and detail the execution of this chemistry.

Scheme 1

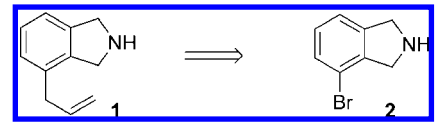
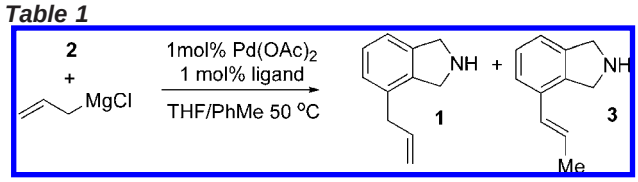


Table 1



entry	ligand	assay yield (%)[a]	**1:3** (area %)[b]
1	XPhos	82	94:6
2	Cy2P[(*o*-tol)indole]	72	94:6
3	(neopentyl)(*t*-Bu)$_2$P•HBF$_4$	91	96:4
4	dippf	85	94:6
5	(*t*-Bu)$_2$P(Ph)HBF$_4$	87	97:3
6	Cy$_2$P(Mes)	33	96:4
7	(*t*-Bu)$_3$PHBF$_4$	74	96:4

[a] Determined by dilution of the reaction with THF (to homogeneity) and comparison of the concentration to that of a standard solution of known concentration using HPLC. [b] Area % refers to HPLC area percent, in this case as a relative ratio. Due to different response factors, a 1:1 area percent ratio of **1:3** corresponds to a quantitative molar ratio of 1:0.48.

Results and Discussion

Kumada Coupling of 4-Bromo-isoindoline. A comprehensive high throughput screen of Pd sources and readily available ligands yielded numerous combinations that catalyzed the desired reaction.[4] A selection of results is presented in Table 1.[5] Among the possibilities we selected (neopentyl)(*t*-Bu)$_2$P•HBF$_4$ (entry 3) for development due to cost and availability on scale.[6] All reactions were contaminated with styrene **3** (derived from isomerization of **1**).[7]

During screening with 1 mol % Pd(OAc)$_2$, no significant difference was seen by modification of the metal/ligand ratio from 1:1 to 1:2. However, reaction conversion depended greatly upon this ratio (Table 2) when the reaction was scaled outside of the glovebox using 0.5 mol % Pd(OAc)$_2$. Ultimately, we

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(1) (a) Commercially available on kg scale from ASW MedChem, Inc. (New Jersey, USA). (b) For a representative procedure, see: Woodhead, A. J.; Angove, H.; Carr, M. G.; Chessari, G.; Congreve, M.; Coyle, J. E.; Cosme, J.; Graham, B.; Day, P. J.; Downham, R.; Fazal, L.; Feltell, R.; Figueroa, E.; Frederickson, M.; Lewis, J.; McMenamin, R.; Murray, C. W.; O'Brien, M. A.; Parra, L.; Patel, S.; Phillips, T.; Rees, D. C.; Rich, S.; Smith, D.-M.; Trewartha, G.; Vinkovic, M.; Williams, B.; Woolford, A. J.-A. *J. Med. Chem.* **2010**, *53*, 5956. (c) Zhang, L.; Song, J.; Zhouhong, T. CN 101560180 (Oct. 21, 2009), CAN 151:528607.

(2) For a recent review of the Kumada coupling with heteroarenes, see: Slagt, V. F.; de Vries, A. H. M.; de Vries, J. G.; Kellogg, R. M. *Org. Process Res. Dev.* **2010**, *14*, 30.

(3) (a) Doherty, S.; Knight, J. G.; Smyth, C. H.; Harrington, R. W.; Clegg, W. *Organometallics* **2007**, *26*, 6453. (b) Ackermann, L.; Kapdi, A. R.; Schulzke, C. *Org. Lett.* **2010**, *12*, 2298.

(4) In each case of ref 2, the metal/ligand combinations were expensive or not available from commercial sources on scale at reasonable cost.

(5) The combination of solvents was determined from toluene as the reaction solvent and THF as the solvent of the Grignard solution.

(6) For a recent review of the use of (neopentyl)(*t*-Bu)$_2$P in Pd catalyzed reactions, see: Hill, L. L.; Smith, J. M.; Brown, W. S.; Moore, L. S.; Guevera, P.; Pair, E. S.; Porter, J.; Chou, J.; Wolterman, C. J.; Craciun, R.; Dixon, D. A.; Shaughnessy, K. H. *Tetrahedron* **2008**, *64*, 6920. To the best of our knowledge this ligand has not been used for a Kumada coupling.

(7) For a possible mechanism, see: Lim, H. J.; Smith, C. R.; RajanBabu, T. V. *J. Org. Chem.* **2009**, *74*, 4565.

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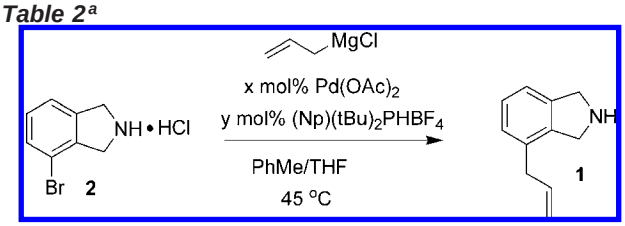
10.1021/op1002837

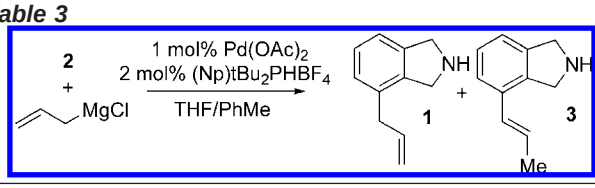
Table 2[a]



entry	*x* (mol %)	*y* (mol %)	AY% of **1**	**1:2** (area %)[b]
1	1.0	1.0	88	98:2
2	0.5	0.5	51	50:50
3	0.5	0.75	63	61:39
4	0.5	1.0	92	99:1

[a] The abbreviation "Np" in the catalyst refers to "neopentyl.". [b] Area % refers to HPLC Area Percent, in this case as a relative ratio. A 1:1 area percent ratio (of 1:2) corresponds to a quantitative molar ratio of 1.22:1.

Table 3



entry	PhMe/THF (vol)	T_i (°C)	AY of **1** (%)[a]	**1:3**[a]
1	0:1	45	31.8	97:3
2	1:1	45	86.0	90:10
3	1.5:1	40	88.9	96:4
4	1.5:1	50	87.7	93:7
5	2:1	45	91.0	97:3
6	2.5:1	40	90.8	98:2
7	2.5:1	50	90.3	96:4

[a] The yield and ratio of **1:3** were determined by HPLC analysis: Agilent Eclipse Plus C18 column, 4.6 mm × 150 mm, 2.7 μm particle size, 40 °C, mobile phase: 0.1% aq H_3PO_4/MeCN; flow rate: 1.5 mL/min.

adopted a ratio of 1:2 in order to maintain reaction efficacy and robustness.

We next investigated the effect of temperature and solvent composition (Table 3). The results demonstrated the beneficial role of toluene in terms of yield (entries 1−3, 5) and suppressing olefin isomerization (entries 2−6). Reaction temperature also impacted both the assay yield of **1** and the levels of **3** observed (entries 3−4, 6−7). Although lower temperatures tended to improve the selectivity for **1**, the reaction rate was slow at $T_i \leq 40$ °C. Although higher toluene/THF ratios were beneficial, the reaction volume efficiency (which is limited by the availability of allyl-MgCl as 1.5−2 M solutions in THF) became too low for practical scale up at levels higher than 2.5:1.[8] Further examination[9] of the data from entries 3−7 suggested that temperature and solvent composition in this narrow operational range exhibit an independent effect on the amount of styrene observed (Figure 1).[10] Balancing these considerations, the conditions in entry 5 (Table 3) were deemed optimal.

(8) Removal of THF by distillation prior to the introduction of catalyst was examined but found to be inefficient. The Mg-amide and the Grignard reagent form insoluble precipitates that do not react.
(9) The data set was analyzed using Design Expert software, applying best fit equations.
(10) The lack of curvature suggested no interaction between these parameters. Analysis of this limited data set was intended to apply only to the experimentally defined optimal operational window.

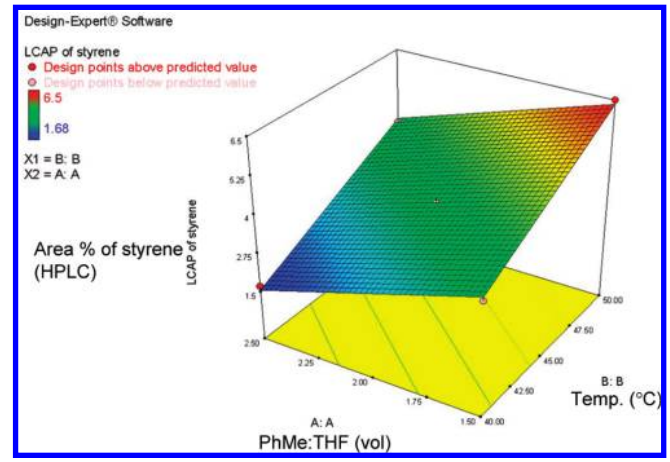


Figure 1

As **2** was available as its HCl salt (for purity upgrade), a third equivalent of base was required in the overall process. Although **2•HCl** could be treated with 5 N NaOH and the resulting toluene stream used successfully in the coupling step, we preferred to avoid these additional operations. Thus, ≥3 equiv of Grignard were required in order to break the HCl salt, deprotonate the amine *N*-H, and participate in the coupling reaction. Using this stoichiometry we developed a convenient and robust procedure. A N_2-purged vessel was charged with **2•HCl**, 0.5 mol % $Pd(OAc)_2$, and 1 mol % (neopentyl)(t-Bu)$_2$P•HBF_4 as a mixture of solids, followed by air-free toluene. Allylmagnesium chloride was then added slowly, and the resulting solution was heated to $T_i = 45$ °C (*Note: evolution of propene occurs during the exothermic addition of allylmagnesium chloride at a rate proportional to the rate of addition. Mild effervescence was observed upon heating, which was likely due in part to evolution of dissolved propene. This was removed efficiently by a mild N_2 sweep*).

Workup. A homogeneous aqueous phase was desirable to minimize losses due to poor phase cuts caused by insoluble, amphoteric Mg^{2+} salts.[11] Filtration of these salts would add to operational costs, and unfiltered salts could clog drain valves.[12] After extensive experimentation,[13] we developed a quench that rendered Mg salts soluble at pH ≥ 10.[14] Inverse addition of the reaction mixture into 10 volumes of saturated aqueous NH_4Cl, followed by pH adjustment with 5 volumes of NH_4OH, allowed for >98% extraction of the product into the organic phase. An intriguing and subtle feature of this workup was the presence of chloride counterions. Whereas this aqueous solution

(11) Complications arising from the difficulty of extracting unsaturated amines from reactions with Grignard reagents can be ascertained from an unrelated study: Richey, H. G., Jr.; Moses, M.; Domalski, M. S.; Erickson, W. F.; Heyn, A. S. *J. Org. Chem.* **1981**, *46*, 3773.
(12) Application of various literature procedures resulted in thick aqueous slurries that required either filtration or large volumes in order to be practical. For the use of sat. NH_4Cl, see: Bonnet, V.; Mongin, F.; Trécourt, F.; Quéguiner, G.; Knochel, P. *Tetrahedron Lett.* **2001**, *42*, 5717. For brine, see: Martin, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 3844. For 1 M Na citrate, see: Miller, J. A.; Dankwardt, J. W.; Penney, J. M. *Synthesis* **2003**, 1643.
(13) Including the quenching procedures described in ref 12 as well as the following aqueous solutions: H_2O, sat. NH_4Cl followed by NaOH pH adjustment, 4:4:1 sat. $NH_4Cl/NH_4OH/H_2O$ pH 10 buffer, 1 N Rochelle's salt, 10% aq. Na_2CO_3, and 10% aq. K_2CO_3. All of these procedures resulted in heterogeneous aqueous phases.
(14) Product extraction was inefficient at pH ≤ 9.5.

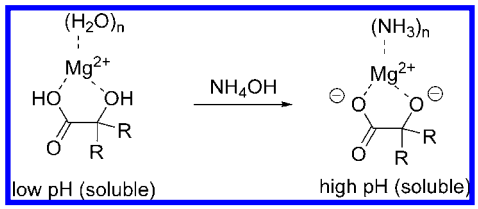


Figure 2

was homogeneous, the use of NH_4OH alone resulted in thick aqueous slurries.[15]

Although promising, this protocol suffered from the retention of dark color in the organic phase, which translated to high levels of residual Pd metal in the isolated product (≥500 ppm, from ICP analysis). To avoid a separate step for Pd removal, we examined alternative workups which took advantage of Pd catalyst solubility in the organic phase. The ultimate solution was the adoption of a "pH swing" workup using an α-hydroxy carboxylic acid. The presence of a chelate, in combination with ammonia, is believed to be responsible for the solubility of the Mg^{2+} complex at pH 10 (Figure 2).[16] We found both citric acid and glycolic acid capable of providing the desired homogeneous aqueous solutions.

The optimized workup involved an inverse quench of the reaction mixture into 10 volumes of aq. 15% citric acid[17] to afford a lightly colored, product-rich, aqueous solution, along with a dark organic phase that contained several low level impurities and <1 g/L of product. After rejection of the organic PhMe/THF phase, fresh PhMe was added, followed by 5 volumes of NH_4OH (28−30% in water). The resulting homogeneous aqueous phase (pH 10) contained <1 g/L of product. Furthermore, the aqueous phase remained homogeneous when aged for 3 days. Citric acid could be replaced with glycolic acid, but aqueous homogeneity was only possible at twice the aqueous volume achieved with citric acid.[18] Further support for the chelation model was secured when the use of AcOH or HCl instead of citric acid resulted in thick heterogeneous slurries after pH adjustment. Furthermore, pH adjustment with LiOH, NaOH, KOH, Na_2CO_3, or K_2CO_3 afforded thick aqueous slurries.

Isolation. Allyl-isoindoline **1** was conveniently isolated as its HCl salt. The toluene extract of free base was dried *via* distillation with toluene and then concentrated. Controlling the KF of this solution to ≤2000 ppm of H_2O was important, since supernatant losses increased with increasing water content. The slow addition of HCl in *i*PrOH afforded a slurry of **1•HCl**.[19] Cooling of the slurry to T_i = 0 °C reduced supernatant loss without detriment to the product purity. Under these conditions, the styrene isomer **3** is rejected to ≤1%.[20] The desired product was obtained as $a \geq 97$ area % solid containing ≤25 ppm of residual Pd.

Conclusion

We have described a practical, cost-effective Kumada coupling for the preparation of 4-allylisoindoline. An examination of reaction parameters has revealed the factors crucial for the suppression of olefin isomerization. The reaction conditions for this challenging substrate are milder and require lower catalyst loadings than existing protocols. Additionally, a scalable workup has been developed that renders Mg^{2+} soluble at pH 10. This novel workup protocol will be useful where an amine product is formed in the presence of Mg^{2+} salts.

Experimental Section[21]

4-Allylisoindoline•HCl. Using standard Schlenk techniques, **2•HCl** (100 g, 0.426 mol), $Pd(OAc)_2$ (0.48 g, 2.13 mmol), (neopentyl)tBu$_2$P•HBF_4 (1.3 g, 4.3 mmol), and toluene (1.8 L) were treated with allylmagnesium chloride (800 mL, 1.36 mol, 1.7 M in THF) over 1 h at $T_i \leq 25$ °C.[22] The resulting solution was then heated to and maintained at T_i = 45−50 °C for 16 h. After cooling to ambient temperature, the reaction was inverse-quenched into a stirring solution of 15 wt % citric acid (1.1 L) at T_i < 35 °C. The aqueous phase was assayed for 61.3 g of **1** (90% yield in organic phase, corresponding to a 92% end of reaction assay yield, along with 2.6% AY of **3**). The aqueous phase was transferred to an extractor, to which was charged fresh toluene (650 mL), and the resulting biphasic mixture was stirred. Ammonium hydroxide (28−30% in water, 650 mL) was added at $T_i \leq 30$ °C, resulting in a pH 10 aqueous phase. The phases were separated, and the aqueous phase (which contained 1.8 g of **1** by assay, 1.0 g/L) was extracted with toluene (200 mL). 0.3 g of **1** remained in the aqueous phase after extraction, or 0.18 g/L. The combined organic phases were washed with 15 wt % aqueous NaCl (160 mL). The toluene solution was dried via azeotropic distillation with toluene under "constant volume" conditions (11−12 volumes at 50 mmHg partial pressure and T = 40−45 °C) and then concentrated to a 650 mL total volume solution (KF = 500 ppm H_2O). The solution was assayed by wt/wt% to contain 59.4 g of **1**.

A solution of HCl in *i*PrOH (5.1 M) was added to the solution of **1** over 1 h at $T_i \leq 40$ °C. The resulting slurry

(15) The use of chloride sources NaCl and $MgCl_2$ were not as effective as NH_4Cl.

(16) (a) This model is conceptually similar to that of the routine water "hardness" test, wherein a homogeneous solution of Mg(EDTA) forms in a dilute pH 10 NH_4Cl/NH_4OH buffer. See: Houlihan, J. E. *Analyst* **1952**, *77*, 158. for early development studies. The volumes (>1000 vol), however, are impractical for large scale use. (b) For a discussion of equilibria data for Mg^{2+} with various counterions including NH_3, see: Kofina, A. N.; Koutsoukos, P. G. *Cryst. Growth Des.* **2005**, *5*, 489.

(17) Citric acid has been used to prepare homogeneous Mg^{2+} solutions at pH 6.5. See: Inaba, T. JP2004091442 (March 25, 2004), CAN 140: 287104. To the best of our knowledge this has not been extended to higher pH levels.

(18) The success of this acid (R = H in Figure 2) was consistent with the chelation model. Potential chelates such as tartaric acid and EDTA afforded heterogeneous aqueous streams upon addition of NH_4OH (without further dilution).

(19) The internal temperature during the addition of HCl was controlled by the addition rate. The addition occurred at a rate such that $T_i \leq 40$ °C.

(20) Attempted formation of other salts, including *p*-TsOH, MsOH, and AcOH, resulted in inefficient rejection of **3**.

(21) See Supporting Information for further details.

(22) Evolution of propene occurs during the exothermic addition of allylmagnesium chloride at a rate proportional to the rate of addition. A mild N_2 sweep efficiently removed any residual propene that was observed to evolve upon heating to T_i = 45 °C.

was aged for 6 h, with gradual cooling to ambient temperature. The slurry was cooled to $T_i = 0$ °C over 1 h and then maintained at this temperature for an additional hour. The slurry was filtered, with loss to the supernatant assayed at 7.6 g/L of **1•HCl** (4.12 g total, along with 1.6 g of **3•HCl**). The cake was washed with 9:1 toluene/IPA (175 mL, $T = 0$ °C) and then dried with vacuum/N_2 sweep. **1•HCl** was isolated as an off white solid (69.5 g) that was assayed at 96 wt % (97.6 area % by HPLC), corresponding to an isolated yield of 80%. ^{1}H NMR (400 MHz, d_6-dmso) δ 9.95 (br s, 2H), 7.32 (t, $J = 7.4$ Hz, 1H), 7.25 (d, $J = 7.4$ Hz, 1H), 7.16 (d, $J = 7.4$ Hz, 1H), 5.96−5.84 (m, 1H), 5.10−5.04 (om, 2H), 4.48 (s, 2H), 4.45 (s, 2H), 3.37 (d, $J = 6.5$ Hz, 2H); ^{13}C NMR (100 MHz, d_6-dmso) δ 135.6, 135.1, 134.6, 133.8, 128.7, 128.3, 120.8, 116.4, 49.8, 48.7, 36.9; HRMS $[M+H]^+$ for $C_{11}H_{13}N$ calcd 160.1126, found 160.1128.

Acknowledgment

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Supporting Information Available

Characterization data for **3•HCl**, ^{1}H and ^{13}C spectra for **1•HCl** and **3•HCl**. This material is available free of charge via the Internet at http://pubs.acs.org.

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