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Cost-Effective Cyanotetralone Chemical Development to Support Casdatifan (AB521) DS Manufacturing Process

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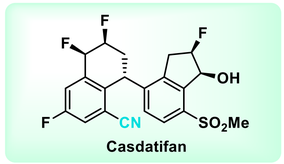
OVERVIEW

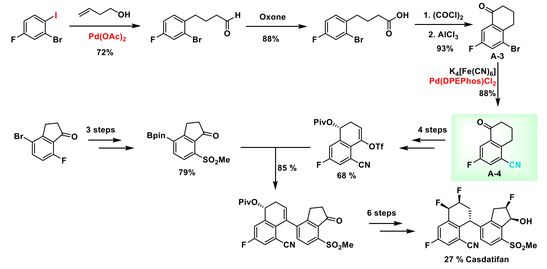
- Casdatifan (**AB521**)[1] is a hypoxia-inducible factor (HIF)-2α inhibitor under investigation for the treatment of renal cell carcinoma.
- A new, palladium-free approach to synthesize one of the key intermediates in the casdatifan manufacturing process, 5-cyano-7-fluorotetralone (**A-4**), was developed.
- A scalable copper-catalyzed ring opening reaction of dimethyl cyclopropane-1,1-dicarboxylate by a functionalized aryl Grignard reagent containing a chloride handle was developed.
- Subsequent elaboration to produce the chlorotetralone was followed by development of a novel, process friendly nickel-catalyzed cyanation protocol, optimized to >95% isolated yield.
- Applicability of the new cyanation process was demonstrated on a diverse set of chloroarenes.



Casdatifan

CASDATIFAN MANUFACTURING PROCESS

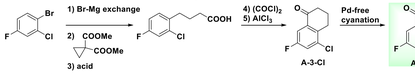
Currently, **A-4** is manufactured following the steps presented in Scheme 1,[2] utilizing the intermediate bromotetralone **A-3** as substrate for a palladium-catalyzed cyanation.



Scheme 1. Casdatifan manufacturing process

DESIRED IMPROVEMENTS

High yielding and developed to multi-kilo scale, current 5-step sequence to **A-4** contains two palladium-catalyzed steps and an iodo substituent on the starting material. Eliminating these could afford significant savings. A new sequence was proposed for development (Scheme 2)



Scheme 2. Proposed improved route to **A-4**

OPTIMIZATION, SCALE-UP OF THE KEY STEPS and CYANATION SUBSTRATE SCOPE

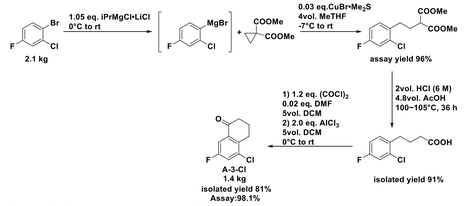
Optimization of the cuprate addition and kilo-scale preparation of tetralone A-3-Cl

A strategy analogous to a previously reported catalytic cuprate ring-opening of an electron-poor cyclopropane ring opening[3] was utilized to introduce the required 4-carbon unit (Scheme 2, steps 1-3). The aryl Grignard reagent was prepared by a magnesium-bromine exchange and charged directly to the mixture of the CuCl and dimethyl cyclopropane-1,1-dicarboxylate in MeTHF at 0 °C to generate the desired adduct in good yield (Table 1, Entry 1).

Entry (scale)	Catalyst (mol%)	iPrMgCl·LiCl equiv.	Cyclopropane equiv.	Solvent (Vol)	LCAP
1 (1 g)	CuCl(50)	1.2	1	MeTHF (4)	77
2 (5 g)	CuCl(5)	1.1	1	MeTHF (4)	79
3 (5 g)		1.1	1	THF (4)	56
4 (5 g)		1.1	1	Toluene (4)	74
5 (5 g)		1.1	1	DCM (4)	64
6 (5 g)		1.1	1	MTBE (4)	62
7 (10 g)	CuCl(3)	1.1	1.3	MeTHF (4)	76
8 (10 g)	CuI(3)	1.1	1.3		59
9 (10 g)	CuCN(3)	1.1	1.3		71
10 (10 g)	CuCl·2LiCl(3)	1.1	1.3		72
11 (10 g)	CuBr·SMe$_2$(3)	1.1	1.3		80
12 (50 g)		1.05	1.3		79

Table 1. Optimization of the catalytic process

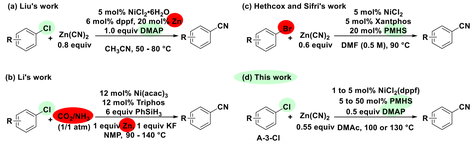
The CuCl load could be reduced to 5%. Several other solvents were investigated, but provided no improvement. In a copper salt screen, **copper bromide dimethyl sulfide complex** gave the best yield with even lower loading (3%, Entry 11). Scaling up to 50 grams, provided a result deemed acceptable for further scale-up (Entry 12). The optimized cyclopropane opening reaction was employed as part of the sequence to produce intermediate **A-3-Cl** in excellent isolated yield and purity on kilogram scale (Scheme 3).



Scheme 3. Kilo-scale demonstration of A-3-Cl manufacturing process

Relevant cyanation methods

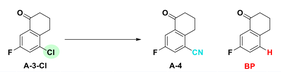
While more established for aryl bromide and iodide substrates, cyanations of aryl chlorides often require palladium catalysis or conditions that pose challenges for large-scale processing. Although Pd usually provides outstanding conversion and yield, due to their cost, developing catalysts based on more abundant metals such as Ni , Cu , and Co received increasing attention in recent years.



Scheme 4. Selected examples of methods of making (hetero)aryl cyanides

Liu *et al*[4] reported a process where DMAP proved to be a beneficial additive (Scheme 4a). Subsequently, Li's group[5] proposed a reductive cyanation of aryl chlorides using CO_2/NH_3 and $PhSiH_3$ (Scheme 4b). While these strategies generally work well for cyanation of aryl chlorides, disadvantages related to heterogeneous reactants (gas, Zn dust) usually limit their application in manufacturing, particularly upon scale up. Inspired by the aryl bromide cyanation protocol using polymethylhydrosiloxane (PMHS) as Ni(II) reductant, reported by Sifri and Hethcox[6] (Scheme 4c), a protocol was optimized for the cyanation of tetralone **A-4** (Scheme 4d).

Development of the cyanation process for A-3-Cl



Entry (scale)	Metal catalyst (mol%)	Ligand (mol%)	Reductant (equiv.)	Cyanide source (equiv.)	Additive (equiv.)	Solvent (Vol)	Temp (°C)	Reaction time (h)	A-4 LCAP (assay yield%)	BP4 wt%
1 (0.2 g) [a]	Pd(OAc)$_2$ (2)	XPhos (4)	Zn (0.04)	Zn(CN)$_2$ (0.6)	H_2SO_4	DMAc (20)	120	16	6.7	
2 (0.2 g) [a]	-	-	-	CuCN (2)	-	DMF (20)	120	16	<1	
3 (0.2 g) [a]	NiCl$_2$•6H$_2$O (10)	dppf (12)	Zn (0.4)	Zn(CN)$_2$ (1.6)	DMAP (2)	CH$_3$CN (10)	90	16	8.3	
4 (0.2 g) [a]	NiCl$_2$•6H$_2$O (50)	dppf (60)		Zn(CN)$_2$ (1.6)			90	16	93.5	
5 (0.2 g) [a]	NiCl$_2$•6H$_2$O (20)	dppf (24)		K$_4$[Fe(CN)$_6$]•3H$_2$O (0.5)			90	16	<1	
6 (0.2 g) [a]	NiCl$_2$•6H$_2$O (50)	dppf (60)	PMHS (0.74)	Zn(CN)$_2$ (1.6)			90	16	88	
7 (0.2 g) [a]	NiCl$_2$•6H$_2$O (30)	dppf (12)		Zn(CN)$_2$ (1.2)			90	16	95.3	
8 (0.2 g) [a]	NiCl$_2$•6H$_2$O (30)	dppf (12)		Zn(CN)$_2$ (1.2)			90	16	96.5	
9 (0.2 g) [a]		dppf (10)					90	16	93.1	
10 (1 g) [a]	NiCl$_2$•6H$_2$O (10)	dppf (10)					90	16	27	
11 (1 g) [a]	NiCl$_2$(dppf) (3)	-		Zn(CN)$_2$ (0.55)		DMAc (10)	100	6	97.8 (88.4)	4.7
12 (1 g) [a]		-	PMHS (0.05)				100	6	99.7 (93.0)	0.9
13 (1 g) [a]		-	-				100	6	(0)	
14 (1 g) [a, b]		-	PMHS (0.05)		DMAP (1)	DMAc (5)	100	12	13	
15 (1 g) [a]		-			DMAP (0.5)		100	6	98.8 (92.2)	2.1
16 (1 g) [a]		-			DMAP (0.5)		100	6	98.9 (92.2)	2.6
17 (1 g) [a]		-			-		100	6	98.9 (90.5)	2.4
18 (1 g) [c]		-			DMAP (0.5)		100	6	63.4 (55.3)	
19 (1 g) [a]		-			DMAP (1)		130	2	98.6 (92.1)	3.6
20 (1 g) [a]		-			DMAP (0.3)		120	4	98.7 (93.2)	3.8
21 (1 g) [a]		-			DMAP (0.5)		120	6	98.7 (90.8)	3.4
22 (1 g) [c]		-					120	3	99.6 (93.9)	1.2
23 (1 g) [c]	NiCl$_2$(dppf) (1)	-					120	3	99.7 (97.5)	0.9
24 (1 g) [c]	NiCl$_2$(dppf) (0.3)	-					120	16	39.6	
25 (50 g) [c, d]	NiCl$_2$(dppf) (1)	-	PMHS (0.05)	Zn(CN)$_2$ (0.55)	DMAP (0.5)	DMAc (5)	100	12	99.8 (98.0)	1.6

[a] Tetralone **A-3-Cl**, metal catalyst, ligand, reductant, cyanide source, additive and solvent were mixed, heated to the target temperature and stirred for 16 h; [b] no nitrogen atmosphere; [c] **A-3-Cl**, metal catalyst, ligand, cyanide source, additive and solvent were mixed, heated to the target temperature, and then PMHS was charged; [d] PHMS was charged over 10 h.

Table 2. Optimization of the cyanation process

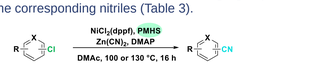
Initially, Pd and Cu based-catalysts were tested, but neither provided promising results. A process following Liu's paper[4] gave good yield only with large catalyst loadings in superheated acetonitrile (Table 2, Entry 4). Using a less toxic cyanide K$_4$[Fe(CN)$_6$] did not lead to a promising result. Considering the challenges of mass transfer and workup during scale-up, a homogeneous reductant, poly(methylhydrosiloxane) (PMHS), was successfully tried instead of Zn (88 LCAP, Entry 6), however the catalyst loading had to remain very high to maintain acceptable turnover (Entry 7). Among solvents screened (DMF, *n*-butanol and DMAc) DMAc afforded the highest conversion after adjusting process temperature to 100 °C, lowering the Zn(CN)$_2$ charge to 0.55 equiv. and catalyst to 3 mol% (97.8 LCAP, Entry 11). A discrepancy between LCAP and assay yield was noted due to the presence of poorly UV-absorbing **BP**. It was found in Entry 11 at 4.7 wt%, and was difficult to remove in the subsequent isolation steps. To minimize dechlorination, lower amount of PMHS (down to 5 mol%) was successfully used, lowering the **BP** level to 0.9%.

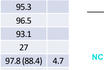
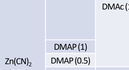
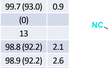
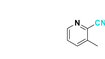
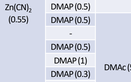
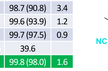
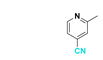
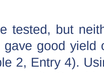
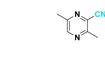
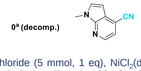
The process is oxygen and/or water sensitive and requires thorough inertization to keep the activity of the catalyst (Entry 14). Further optimization by decreasing the equivalents of DMAP and volume of DMAc did not show any impact on the yield and purity, but provided a nearly homogeneous reaction mixture, and would also simplify the following workup steps. Tests probing increasing the process temperature up to 130 °C could somewhat improve the conversion LCAP and shorten the reaction time to 2 h, but at the expense of additional **BP** formation, so this direction was abandoned.

Best strategy for mitigating **BP** formation, while promoting the desired process is to charge 1 mol% PMHS in one portion to initiate the reaction, followed 4 mol% of PMHS over 10 h. The process was successfully demonstrated at 50 g scale.

Substrate scope for the new cyanation process

The optimized Ni-catalyzed cyanation protocol was subsequently tested on a wide variety of (hetero)aryl chlorides with varying degrees of success. Generally, substrates possessing electron-withdrawing groups afforded excellent yields of the corresponding nitriles (Table 3).



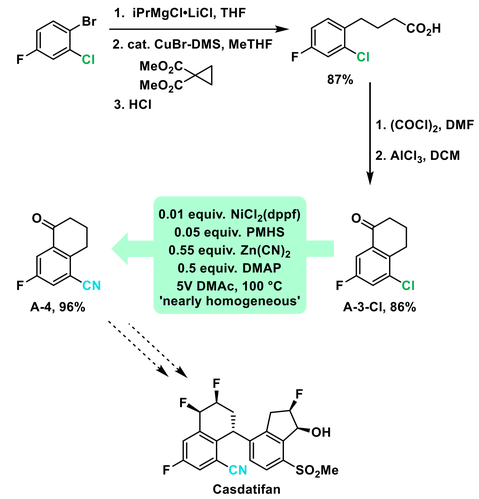
Product	Yield[c] (%)	Product	Yield[c] (%)	Product	Yield[c] (%)
	96[a]		99[b,d]		99[b]
	97[a]		99[b]		95[b]
	25[b]		94[b]		0[b]
	0[b]		0[b]		53[b]
	96[a]		94[b]		91[b]
	99[a]		97[b]		6[b]
	0[a] (decomp.)		0[b]		10[b]

[a] Conditions A: Chloride (5 mmol, 1 eq), NiCl$_2$(dppf) (0.01 eq), DMAP (0.5 eq), Zn(CN)$_2$ (0.55 eq), PMHS (0.2 eq), DMAc (5 mL), 100 °C, 16 h; [b] Conditions B: Chloride (2 mmol, 1 eq), NiCl$_2$(dppf) (0.05 eq), DMAP (0.5 eq), Zn(CN)$_2$ (0.55 eq), PMHS (0.5 eq), DMAc (2 mL), 130 °C, 16 h; [c] QNMR yield with 1,3,5-trimethoxybenzene as internal standard; [d] 24 h

Table 3. Scope of the newly-developed cyanation process

Set of reaction Conditions A (Table 3 legend) originally optimized for the **A-3-Cl** substrate turned out to be insufficiently forceful for many of the starting materials. Set of reaction Conditions B was employed in such cases. This broadened the reaction scope (for example some of the *o*-methyl substituents were tolerated).

SUMMARY



- A copper-catalyzed ring opening reaction of dimethyl cyclopropane-1,1-dicarboxylate by a functionalized aryl Grignard reagent containing a chloride handle was developed.
- Subsequent elaboration to produce the chlorotetralone **A-3-Cl** was followed by development of a novel, process friendly nickel-catalyzed cyanation protocol, optimized to >95% isolated yield. The key feature of this protocol is the use of cheap NiCl$_2$(dppf) precatalyst, Zn(CN)$_2$ as cyanide source, DMAP additive to accelerate reaction rate and improve homogeneity of the reaction mixture, and use of PMHS in place of the typical Zn dust as a reducing agent. Avoiding the use of Zn dust provides nearly homogeneous reaction conditions that are projected to be easily scalable to multikilogram batch sizes.
- The estimated cost savings for the target cyanotetralone **A-4** is about 30% on 500 kg scale compared to the previous generation process.
- The cyanation procedure proved applicable to certain other aryl chlorides that were subsequently examined

REFERENCES

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