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Continuous-Flow Suzuki−Miyaura Reaction in Supercritical Carbon Dioxide

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Abstract:

The Suzuki−Miyaura cross-coupling of *p*-tolylboronic acid 1 and iodobenzene 2 to form 4-phenyltoluene 3 in the presence of tetrabutylammonium methoxide 4 and the immobilized catalyst PdEnCat as stationary phase has been carried out in continuous-flow mode using conventional organic and supercritical carbon dioxide solvent systems between temperatures of 55 to 120 °C and pressures up to of 250 bar. Laboratory-scale reaction studies have been undertaken on a 5 cm × 4.5 mm i.d. column packed with Pd(II)EnCat 40 catalyst [Lee et al., *Chem Commun*. 2005, 2175] using conventional organic solvents in continuous flow. We now report exploratory commercial-scale continuous flow using a 14.5 cm × 25.4 mm i.d. ModCol column with toluene/methanol solvent and, most significantly, continuous flow using a 48.5 cm × 25.4 mm i.d. high-pressure column using supercritical CO_2 solvent + MeOH cosolvent. Conversion to 4-phenyltoluene 3 was found to be 81% in the supercritical CO_2 system and 74% in the organic solvent system after a single pass through the continuous-flow reactor. The conversion in the organic solvent system was increased to quantitative after adopting pH control and further recycling. Experimental design included variation in temperature, supercritical pressure, the residence time, and the number of passes, and for each experiment the product conversion is reported. System hydrodynamics are interpreted in terms of Reynolds, Schmidt, Sherwood, and Peclet numbers. The work demonstrates the application of continuous-flow mode reactions in supercritical carbon dioxide as a potentially benign manufacturing process.

Introduction

Supercritical carbon dioxide ($scCO_2$) offers real potential as an alternative, environmentally benign reaction medium for the synthesis of organic molecules because it is cheap, nontoxic, and easily separable from reactants and products.[1,2] Several workers have reported batch-mode homogeneous and heterogeneous catalysed reactions in $scCO_2$,[3−8]and others have reported these reactions in a mini-continuous-flow reactor system using conventional solvents.[9] In chemical manufacturing processes the operation costs and labour required for continuous-flow processes are generally lower than those required for batch processes. Recently, there has been considerable interest in developing continuous-flow heterogeneous catalytic processes in supercritical fluids to reduce the use of organic solvents and to alleviate the process issues associated with homogeneous catalysis, such as the recycling and reuse of ligated and unligated metal catalyst, catalyst contamination of products, catalyst contamination of reactor vessels (leading to high cleaning costs), and catalyst contamination of the intermediate which can interfere with downstream chemistry. Among these developments is the heterogeneous hydrogenation process pioneered by the Nottingham group[10,11]in collaboration with Swan-SCF.[12] In this paper we report for the first time a metal-mediated C−C bond-forming reaction under continuous-flow conditions in $scCO_2$. As shown by the Nottingham group, the advantage of continuous-flow conditions is that reactions can be conducted under pressure in small-bore reactor tubing, rather than in batch mode in large pressure vessels.

The Suzuki−Miyaura Pd-mediated C−C bond formation reaction is industrially important and plays a crucial part in discovery-based chemistry practised in the fine chemical, agrochemical, and pharmaceutical industries.[13] Following our preliminary exemplification of efficient batch processes for

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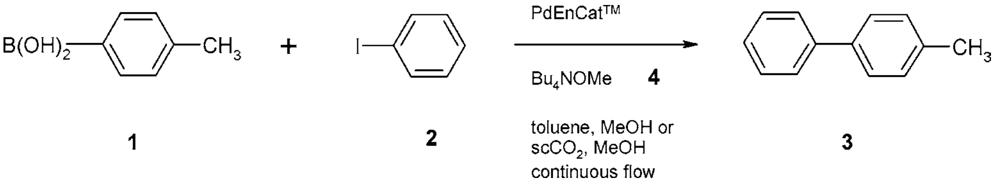

Figure 1. **Suzuki−Miyaura preparation of 4-phenyltoluene 3 under continuous-flow conditions.**

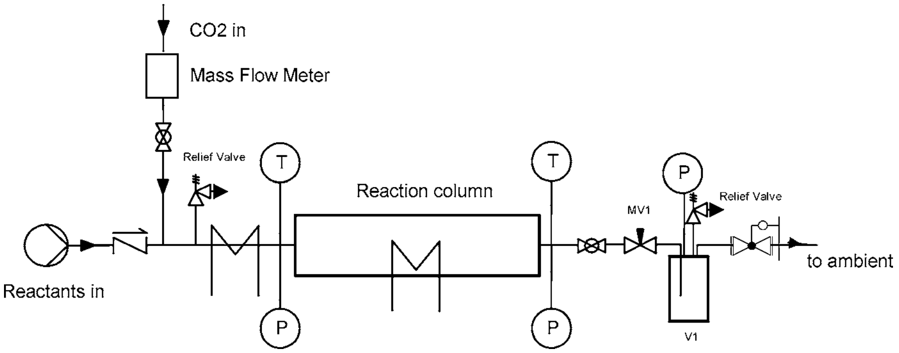

Figure 2. **Schematic of continuous-flow apparatus for Suzuki−Miyaura reaction in scCO$_2$.**

the Suzuki−Miyaura reactions using the immobilized catalyst PdEnCat 40[14] in both conventional and scCO$_2$ solvents,[15] we have initiated a comprehensive research and development programme to translate these results from batch to a continuous-flow fixed-bed reactor. The Suzuki−Miyaura coupling reaction of *p*-tolylboronic acid **1** and iodobenzene **2** to produce 4-phenyltoluene **3** in the presence of tetrabutylammonium methoxide **4** is shown in Figure 1 and was investigated up to pressures of 250 bar at temperatures between 55 and 120 °C in both conventional solvent and scCO$_2$. In general, the reactants were pumped in a solution of either toluene/methanol or scCO$_2$ + MeOH through a column packed with PdEnCat catalyst. The eluate was analyzed by gas chromatography (GC), and the percentage conversions of product are reported.

Experimental Methods

p-Tolylboronic acid **1** [5720-05-8] and iodobenzene **2** [591-50-4] were obtained from Sigma-Aldrich. Tetrabutylammonium methoxide **4** (1 M in methanol) [34851-41-7] was obtained from Fluka. All were used without further purification. PdEnCat was obtained from AstraZeneca, Process Research, Macclesfield, through Avecia. The catalyst used in the experiments was Pd(II)EnCat 40 and is the original form of the catalyst containing 0.4 mmol/g Pd(II)-acetate (4.6 %w/w Pd). Newer forms of the catalyst such as Pd(II)EnCat 30 are now available, having higher porosity and demonstrating improved kinetics in use and better accessibility of higher-molecular weight species.[16] Liquid carbon dioxide was obtained from BOC, CP grade, and had a given purity of 99.995%. HPLC grade toluene and methanol were dried over molecular sieve number 3A and degassed before use.

Continuous-Flow Synthesis Using Toluene/Methanol. Continuous-flow synthesis using toluene/methanol was undertaken on a ModCol column. The column was packed with 45 g of PdEnCat to give an initial bed length of 14.5 cm × 25.4 mm i.d. This length was later reduced to 10 cm for experiments undertaken at $\geq$70 °C. The column was heated to the desired temperature by an oil jacket. A heated precolumn consisting of 2 m of coiled SS tubing (i.d.: 1.05 mm) was employed to ensure the upstream reactant/solvent mixture entered the column at the process temperature. Two thermocouples recorded the temperature up- and downstream of the column. Similarly, two pressure transducers recorded any pressure differential and gave an indication of blocking within the column. The reactants were dissolved in toluene/methanol (9:1 v/v) to the desired concentration. An HPLC pump was used to pump this reactant mixture through the column to give a range of residence times. Upon leaving the column, samples of the mixture were periodically collected for GC analysis.

Before any experiment the solvent flow was equilibrated before the reactant solution was introduced. Following the experiment, a solvent wash removed any components from the catalyst bed. In preliminary tests, it was found that there was no significant change in product conversion from carrying out the reaction for longer than 60 min and the results are reported accordingly.

Continuous-Flow Synthesis Using Carbon Dioxide. A similar experimental procedure for continuous-flow synthesis in scCO$_2$ was used as indicated in the schematic in Figure 2. A packed high-pressure column containing 123 g og Pd(II) EnCat to give a bed length of 48.5 cm × 25.4 mm (i.d.) was initially used. This length was reduced to 22.5 cm in later tests as indicated by superscript *e* in Table 3. The column was heated by thermostatically controlled electric heaters to the desired process condition. CO$_2$ was delivered to the process at the desired pressure and temperature by

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(16) For information on PdEnCatTM, see http:// www.reaxa.co.uk/pd_encat.pdf.

the use of a liquid piston pump and an electrically heated precolumn, respectively; details of the CO_2 delivery are given elsewhere.[17] The reactants were introduced in solution in a small amount of methanol by an HPLC pump into a mixing chamber located 1 cm upstream from the reactor column. Here they were contacted with, and solubilized by the carbon dioxide and carried into the column. Methanol was employed to assist in solubilizing the tetrabutylammonium methoxide. In previous studies tetrabutylammonium methoxide was determined to be the optimum base for Suzuki reaction in batch mode in $scCO_2$.[15] The phase behaviour of the reactants and product in carbon dioxide have been previously determined.[18,19] At the CO_2 flow rates and conditions used, iodobenzene **2** is completely miscible in CO_2. *p*-Tolylboronic acid **1** has comparatively low solubility and is always in excess in the CO_2, and 4-phenyltoluene **3** has high solubility. Methanol acts as a cosolvent and increases the solubilities of all the components.

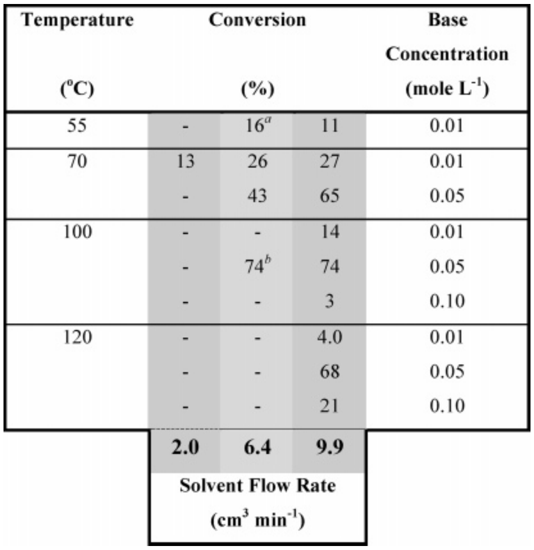
The flow of CO_2 through the column was controlled by the micrometering valve (MV1) situated downstream of the column (see Figure 2) and was verified by an on-line mass flow meter (Rheonik RHE 08). Samples were collected at 10 bar in the methanol that had passed through the column, which was advantageous for their recovery and subsequent GC analysis. The experimental arrangement enabled switching of the CO_2 flow through two parallel collectors, which minimized the disruption to the continuous process. Pre-experimental and post-experimental procedures were undertaken in a manner similar to those for the conventional organic solvent runs above.

GC Analysis of the Product Mixture. GC analysis was conducted using an Ai Cambridge GC-94 gas chromatograph fitted with a Varian FactorFour (VF-1ms) capillary column (15 m, i.d. 0.25 mm, film thickness 0.1 μm) and FID detector. A split flow of 11 $cm^3\ min^{-1}$ was used. Temperature gradient: 50 °C for 4 min; 50 to 200 °C at 10 °C min^{-1}; hold 200 °C for 1 min. The mass of an individual component was calculated from a predetermined peak area response factor. Injection errors were minimized by comparing the peak area of an internal standard with a predetermined set value and applying any necessary corrections.

Results and Discussion

Continuous-Flow Suzuki−Miyaura Coupling in Toluene/Methanol. Experiments were carried out at 55, 70, 100, and 120 °C using a toluene/methanol (9:1 v/v) solvent system at various flow rates and concentrations of Bu_4NOMe base **4**. The concentration of reactants in the solvent stream was 0.05 M and was based on our previously described batch studies.[15] Table 1 shows the maximum percentage conversions to the product 4-phenyltoluene **3**. Using Modde experimental design software[20] it was shown that the reaction temperature is important and that there is a weak temperature−flow interaction. The effect of solvent flow rate on product yield was small. In all tests the homocoupled product biphenyl did not exceed 1.8%, and in most cases the yield was less than 0.2%.

Table 1. **Conversions for Suzuki−Miyaura coupling in toluene/methanol (9:1 v/v) under continuous-flow conditions; concentration of 1 and 2 = 0.05 M**



Temperature (°C)	Conversion (%)			Base Concentration (mole L^{-1})
55	-	16[a]	11	0.01
70	13	26	27	0.01
	-	43	65	0.05
100	-	-	14	0.01
	-	74[b]	74	0.05
	-	-	3	0.10
120	-	-	4.0	0.01
	-	-	68	0.05
	-	-	21	0.10
	2.0	**6.4**	**9.9**	
	Solvent Flow Rate ($cm^3\ min^{-1}$)			

[a] 17% conversion for triple pass. [b] 75% conversion for triple pass.

It is clear that the amount of base has a marked effect on the conversion yield. It is inferred in the Suzuki catalytic cycle[13] that the base catalyzes the transmetallation of the aryl substituent from boron to palladium. Higher temperatures led to higher conversions although this trend began to diminish above 100 °C. In addition, a flow rate of 6.4 $cm^3\ min^{-1}$ and above was favourable. A lower flow rate would have resulted in a higher residence time for the reactants in the column but led to a lower conversion owing to a lower liquid/solid ratio and poorer mixing. A measure of the mixing and mass transfer within the process was quantified by undertaking hydrodynamic analysis in terms of Reynolds (*Re*), Schmidt (*Sc*) and Peclet (*Pe*) numbers. *Re* numbers were typical for that of a packed column and did not exceed 0.53. The values decreased at lower flow rates and lower temperatures, which indicated poorer mixing at such conditions. *Sc* numbers did not exceed 107 and were greatest at

Table 2. **Continuous-flow Suzuki−Miyaura reaction in toluene/methanol (9:1 v/v) at flow rate 6.4 $cm^3\ min^{-1}$; temperature 100 °C, [1] = [2] = [4] = 0.05 M; showing pH of reaction mixture before reaction and after repeated passage of the same reaction through the column**

	pH	conversion after pH correction (%)
reactants before reaction	13.4	−
first pass	7.3	74
second pass	10.1	100
third pass	11.1	100

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Table 3. **Continuous-flow Suzuki−Miyaura reaction in $scCO_2$ containing MeOH; in all runs except runs 4 and 5 the concentrations of tolylboronic acid 1, iodobenzene 2, and Bu_4NOMe 4 were identical**

run	*P* (bar)	*T* (°C)	reaction phase	flow rate (g min^{-1})	[**1**, **2**, **4**] in CO_2 (mol L^{-1})	[**1**, **2**, **4**] in MeOH (mol L^{-1})	CO_2:MeOH ratio	conv (%)
1	150	80	sc	4.5	2.0×10^{-4}	0.72	15:1	21
2	150	80	sc	2.5	2.1×10^{-5}	0.15	29:1	38
3	166	100	sc	2.0	2.1×10^{-5}	0.15	24:1	39
4	150	80	sc	4.8	*a*	*b*	7:1	9
5	150	80	sc	4.5	*c*	*d*	6:1	6
6[e]	102	100	L−V[f]	5.5	0.05	0.48	10:1	65
7[e]	110	100	L−V[f]	5.5	0.05	0.48	10:1	74
8[e]	166	100	sc	5.5	0.05	0.48	10:1	81
9[e]	168	100	sc	5.5	5×10^{-3}	0.35	70:1	21
10[e]	167	100	sc	5.5	3.4×10^{-4}	0.05	145:1	20
11[e]	186	100	sc	5.5	0.05	0.48	10:1	75
12[e]	208	100	sc	5.5	0.05	0.48	10:1	73
13[e]	250	100	sc	5.5	0.05	0.48	10:1	70

[a] Run 4 [**1**] = [**4**] 9.5×10^{-5} M, [**2**] 1.3×10^{-4} M in CO_2. [b] Run 4 [**1**] = [**4**] 0.15 M, [**2**] 0.21 M in MeOH. [c] Run 5 [**1**] 9.5×10^{-5} M, [**2**] 1.3×10^{-4}, [**4**] 1.9×10^{-5} M in CO_2. [d] Run 5 [**1**] 0.15 M, [**2**] 0.21 M, [**4**] 0.03 M in MeOH. [e] Column length reduced from 48.5 to 22.5 cm. [f] L−V: Two-phase liquid−vapor system.

low flow rates and low temperatures. Larger values imply poorer molecular momentum and mass transfer of the reactants. *Pe* numbers indicate the degree of axial mixing and were found to fluctuate between 2.1 and 2.2. These values indicated that the conditions within the column tended towards plug flow where each molecule had an equal opportunity for reaction.

All data are for a single pass of the reaction mixture through the column, and the highest conversion obtained was 74%. Passage of the same reaction mixture three times over the column resulted in a slight increase in conversion as indicated by the *a* and *b* superscripts in Table 1. However, correcting the pH of the reaction mixture by the addition of Bu_4NOMe **4** from 7.3 back to 13.4 after the first passage through the column resulted in quantitative conversion after the second pass. Table 2 shows the pH of the reaction mixture and the percent conversions after each pass at a flow rate of 6.4 cm^3 min^{-1} at 100 °C using [Bu_4NOMe] = 0.05 M (initially). The observed fall in pH was due to the acidic nature of PdEnCat 40, which was measured to be 3.9 to 4.1 at 100 °C in the solvent/catalyst slurry. In conclusion, pH control and recycling over the column can produce effective conversions of reactants to products for Suzuki−Miyaura coupling processes under continuous-flow conditions in conventional organic solvents.

Continuous-Flow Suzuki−Miyaura Coupling in Carbon Dioxide. The successful coupling observed in toluene/methanol showed the way for the optimum conditions to be explored in carbon dioxide. Experiments were carried out at 80 °C and 100 °C over pressure ranges up to 250 bar using $scCO_2$ as solvent with additional methanol cosolvent to assist in solubilizing the base. The results are shown in Table 3. The concentrations of the reactants and base have been expressed in the methanol feed solution ([**1**, **2**, **4**] in MeOH) and also once they have become solubilised in the carbon dioxide stream ([**1**, **2**, **4**] in CO_2). Two column lengths (48.5 and 22.5 cm) were used as indicated by the *e* superscript. An additional amount of MeOH (other than that present in the base) was added to the reactant mixture in all runs, except run 1 to provide a range of reactant concentrations and CO_2:MeOH ratios. The importance of this ratio on the conversion to 4-phenyltoluene **3** can clearly be seen in runs 8−10; in particular the highest conversion was obtained in run 8 with a CO_2:MeOH ratio of 10:1, whereas a large excess of MeOH as used in runs 4 and 5 had a detrimental effect on conversion. The phase of the reacting system is important to the success of the reaction. The highest conversion of 81% occurred at 166 bar and 100 °C (run 8) where the reactant mixture was monophasic in the supercritical state.

Runs 6−8 and 11−13 were based on the optimum conditions determined for the methanol/toluene continuous-flow conditions, namely a flow rate of 6.4 cm^3 min^{-1} at 100 °C, with [Bu_4NOMe] = [**1**] = [**2**] = 0.05 M. This volumetric flow rate is equivalent to 5.5 g min^{-1} at the pressure−temperature conditions. It can be seen that for the Suzuki−Miyaura reaction a higher pressure leads to poorer conversion. Lin and Akgerman[21] have correlated lower yields at increased pressures with a positive activation volume of the transition state. A reduction in pressure (runs 6 and 7) resulted in a two-phase liquid−vapor system and a satisfactory conversion. This indicates that the reaction can be carried out at lower pressures, which is advantageous for process economics. However, it should be pointed out that as the density of CO_2 is also lower it will have an increased volume and a larger volume of methanol would be required to realize the required concentrations/ratios. A decrease in reactant concentration (by increasing the CO_2 ratio) in runs 9 and 10 significantly affected the conversion. In fact in run 10, the reactant loading was based on the maximum solubility of *p*-tolylboronic acid **1** in CO_2. Its poor solubility limits the concentrations of reactants that can be maintained at stoichiometric ratios in solution and hence limits their availability for conversion. Runs 1−5 showed poor conversion, largely owing to the low temperature and high dilution of reactants in CO_2, although a decrease in flow rate led to an increase in productivity. An excess of iodobenzene **2** in runs 4 and 5 did not improve conversions. The importance of base

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concentration is also demonstrated here. A mole equivalent of base is required for each mole of reactant. The maximum conversion of homocoupled product was found to be 2.5% on the longer column; however, this was reduced to <0.8% on the shorter column.

In comparison to the toluene/methanol system, *Re* numbers were higher (1.4−3.2) owing to the lower viscosity of the supercritical fluid. *Sc* numbers were significantly lower (2.4−2.9) due to the enhanced diffusivity, much reduced viscosity and comparable density of the supercritical system. This clearly highlights the advantage of a supercritical fluid in improving mass-transfer properties in reaction systems, providing higher diffusivities and therefore better pore accessibility of the catalyst, and this is reflected in the higher conversion from a single pass through the column: 81% in comparison to 74% in the organic solvent system. This can be quantified by calculating the rate of material transfer from the Sh number and packed bed area, A ($A = 6(1 - \epsilon)/d_p$, where ϵ is the void volume and d_p the particle diameter). A value of 5.82×10^{-4} mol dm^{-3} s^{-1} was obtained for the organic solvent system in comparison to a value of 1.46×10^{-3} mol dm^{-3} s^{-1} for the scCO$_2$ system.

Process Issues. An issue for the application of this procedure in a future manufacturing process is the low solubility of tetrabutylammonium methoxide **4** in scCO$_2$. Carbon dioxide has been observed to act as an antisolvent and to deposit the base out of methanol solution. The by-products of the reaction, Bu_4NI and $B(OH)_2OMe$[13] (as well as *p*-tolylboronic acid **1**), also have low solubility in CO$_2$. These compounds are believed to be capable of blocking the column during operation. In contrast, where the CO$_2$:MeOH ratio was ≤10:1 *o*r when the reactant concentration in scCO$_2$ was dilute, blockages did not occur. Methanol is required to improve productivity, but excessive amounts can decrease the conversion to 4-phenyltoluene. In runs 6−13, a reduction in the column length also helped to alleviate the blockage problem. In most cases the blockages could be removed by backwashing the column with methanol at ambient conditions.

Blockages were also encountered with the organic solvent system, especially at base concentrations of 0.1 M and at temperatures of 120 °C. Issues in catalyst design remain to be optimized. The reduction of Pd(II) to Pd(0) during the reaction, and the subsequent leaching of Pd particles can lead to blockages. ICP analysis of samples collected showed that the Pd content was no greater than 0.8 ppm in solution.[22] The target for the catalyst system is to reduce the level of metal contamination in the final organic product to ≤5 ppm and is therefore not an issue here. In both solvent systems it was evident that PdEnCat had a defined lifetime. The appearance of the catalyst after the tests had changed from discrete, free-flowing brown particles into a solid, black cake. A portion of the used catalyst was tested in a batch experiment for activity, and this was found to have decreased to 52% for the toluene/methanol runs and 41% for the scCO$_2$ runs, indicating that a loss in catalyst activity occurred with increasing passage of reactants.

Conclusion

The results obtained from the continuous-flow organic and supercritical experiments are encouraging. By taking into account the environmental and disposal costs of the organic solvents the prospect of conducting the Suzuki−Miyaura synthesis using scCO$_2$ and PdEnCat is favourable. The scale-up factor of approximately 25 based on column internal diameter has been achieved with results comparable to those achieved in the preliminary laboratory experiments.[15] Based on the optimum condition this would enable 0.06 g min^{-1} of product to be produced from a single column Furthermore, by avoiding the incineration of reactant liquor for catalyst recovery, CO$_2$ emissions of 20 kg/kg of product would be typically prevented. Scale-up could be achieved by increasing the number of columns. On industrial scale, CO$_2$ would be scrubbed and recycled, and its loss would be small. In summary, we have described the first continuous-flow metal-catalysed C−C bond-forming process in scCO$_2$, and these results demonstrate considerable promise for adaptation as a manufacturing process.

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[22] NAMAS accredited analysis.