

The Effect of Added Ligands on the Reactions of [Ni(COD)(dppf)] with Alkyl Halides: Halide Abstraction can be Reversible

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ABSTRACT: The reactions of dppf-nickel(0) with alkyl halides proceed *via* three-coordinate nickel(0) intermediates of the form [Ni(dppf)(L)]. The effect of the identity of the added ligand (L) on catalyst speciation and the rates of reactions of [Ni(COD)(dppf)] with alkyl halides has been investigated using kinetic experiments and DFT calculations. A series of monodentate ligands have been investigated in attempts to identify trends in reactivity. Sterically bulky and electron donating ligands are found to decrease the reaction rate. It was found that (i) the halide abstraction step is not always irreversible, and the subsequent recombination of a nickel(I) complex with an alkyl halide can have a significant effect on the overall rate of the reaction; and (ii) some ligands lead to very stable [Ni(dppf)(L)₂] species. The yields of prototypical (dppf)nickel-catalysed Kumada cross-coupling reactions of alkyl halides are significantly improved by the addition of free ligand, which provides another important variable to consider when optimizing nickel-catalysed reactions of alkyl halides.

INTRODUCTION

The importance of molecules that contain a large number of *sp*³ centers in industries such as pharmaceuticals and agrochemicals is driving much of the reaction discovery and development in the field of nickel catalysis.^{1,2} However, despite recent advances in our mechanistic understanding of nickel catalysis,^{3,4} gaps in this understanding still remain. This is apparent for the case of the reactions of nickel(0) complexes with alkyl halides, which are quite different from the reactions of nickel(0) complexes with *sp*² organohalides.⁵ The reactions of alkyl halides have a greater propensity to involve radical intermediates, and deleterious β -hydride elimination presents further challenges. We have recently focused our attention on the reactions of alkyl halides with nickel(0), with the aim of developing a better understanding of these reactions and thereby underpinning future reaction discovery, development, and understanding.

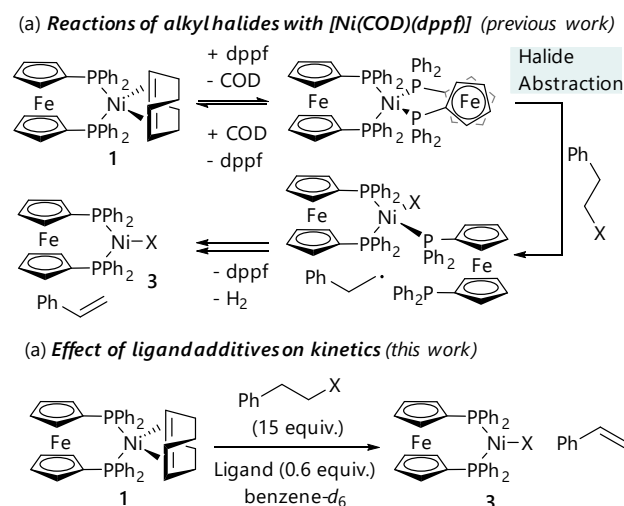
The outcomes of nickel-catalysed reactions can be extremely sensitive to the structure(s) of the ligand(s). For example, Liu *et al.* found that [Ni(COD)₂]/dppf was not a competent catalyst for the cross-coupling of phenyl triflate and aniline, but that a modified ligand (1,1'-bis(di(3,5-trifluoromethylphenyl)phosphino)ferrocene) enabled the reaction to achieve almost quantitative conversion.⁶ There are many examples of situations where the mechanisms of nickel-catalysed reactions can also be very sensitive to ligand structure. If the nickel-catalysed Suzuki-Miyaura coupling of benzylic esters is carried out using tricyclohexylphosphine as the ligand the stereochemistry at the benzylic position is retained; however, the use of SIMes produces the stereoinverted product *via* a different mechanistic pathway.⁷ The size of the NHC ligand in [Ni(NHC)₂] complexes determines whether [Ni(Ar)X(NHC)₂] or [NiX(NHC)₂] products result from their reactions with aryl halides.^{8,9} The choice

of ligand type – bisphosphine or bipyridine – is crucial in the trifluoromethylthiolation reactions of aryl halides.¹⁰

The reactions of alkyl halides with nickel(0) have received relatively little attention compared to reactions of aryl halides and other aryl electrophiles.^{11–15} Baird has studied the reactions of various alkyl halides with [Ni(PPh₃)₄] *via* variable temperature ¹H and ³¹P NMR spectroscopic analyses of reactions *in situ*.¹⁶ The major products from the reactions of iodoalkanes are alkanes and alkenes, with a nickel hydride species obtained as a minor product; this suggests that formal oxidative addition was followed by β -hydride elimination. The alkanes were proposed to arise from the generation of alkyl radicals by halide abstraction, which then abstract the hydride ligand from a nickel hydride complex. The trends observed in the reactivity of alkyl halides followed the stability of the corresponding radicals, consistent with an operative radical mechanism.

We recently published a detailed study of the reactions of the model complex [Ni(COD)(dppf)]¹⁷ (**1**) with alkyl halides.¹⁸ The experimental and computational evidence that was gathered supported a mechanism in which [Ni(COD)(dppf)] was in equilibrium with [Ni(dppf)₂] (**2**) (with the additional dppf being a trace impurity in **1**), and that [Ni(κ^2 -dppf)(κ^1 -dppf)] performed a halide abstraction step to produce [Ni(X)(κ^2 -dppf)(κ^1 -dppf)] plus an alkyl radical (Scheme 1(a)); subsequent dppf dissociation and the recombination of the alkyl radical and nickel(I) complex yielded the formal oxidative addition product [Ni(X)(R)(dppf)], which underwent rapid β -hydride elimination. The final products were [Ni(X)(dppf)] (**3**) and alkene, with no alkane product observed.

The reaction of [Ni(COD)(dppf)] with alkyl halides relies upon the presence of additional dppf in order to form the three-coordinate species necessary for the halide abstraction step. However, the bidentate nature of dppf means that [Ni(dppf)₂] is



Scheme 1. (a) Our previous study of the reactions of [Ni(COD)(dppf)] with alkyl halides. (b) This work.

lower in energy than the desired [Ni(κ^2 -dppf)(κ^1 -dppf)] intermediate. Here, we have examined the use of a range of alternative monodentate ligands and their effects on the rate of stoichiometric and catalytic reactions of alkyl halides (Scheme 1 (b)).

RESULTS AND DISCUSSION

Kinetic Studies of Stoichiometric Reactions with Alternative Ligands

Our previous study¹⁸ established that the rate of reaction between [Ni(COD)(dppf)] (**1**) and alkyl halides was significantly increased by the addition of free dppf ligand, as this shifted the equilibrium between **1** and [Ni(dppf)₂] towards the latter species. For this study, a selection of monodentate group 15 ligands was assembled with a diverse range of steric and electronic properties, and where the Lewis basic atom was nitrogen, phosphorus, arsenic, or antimony. These were all used as additives in the stoichiometric reaction between **1** and (2-bromoethyl)benzene (**4-Br**) which was monitored by ³¹P NMR spectroscopy. All experiments were pseudo-first order in **1**, and the ³¹P NMR spectra confirmed that dppf remained bound to the nickel center throughout, with no free dppf ligand detected ($\delta_p = -17$ ppm). Data were collected at one or two of three temperatures (263 K, 273 K, or 293 K) depending on how fast the reaction proceeded; the results for reactions with fifteen monodentate ligands, along with previous data for the reaction with added dppf,¹⁸ are recorded in Scheme 2. Pseudo-first order constants are listed in order of largest to smallest. Data span a *ca.* 200-fold range of rate constants.

A series of reactions were carried out with different concentrations of triphenylphosphine, confirming that the reaction is first order in added triphenylphosphine (Figure 1(a) and (b)); our previous work noted that the reaction was first order in dppf when this was the added ligand.¹⁸

The use of diphenylphosphinoferrocene (FcPPh₂) as an additive led to a higher rate of reaction than the corresponding experiment with dppf. This can be rationalized by considering the requirement for (bidentate) dppf to dissociate one phosphine atom from the nickel center to enable the reaction to occur; the binding of a second FcPPh₂ ligand does not benefit from the chelate effect.

Ligand	$k_{obs} \times 10^3 \text{ s}^{-1}$	263 K	273 K	293 K	k_{rel}
P(<i>p</i> -C ₆ H ₄ CF ₃) ₃	2.8(1)				1.00
P(<i>m</i> -C ₆ H ₄ Me) ₃	2.4(1)				0.89
P(<i>p</i> -C ₆ H ₄ F) ₃	2.4(1)				0.89
P(<i>p</i> -C ₆ H ₄ Me) ₃	1.7(1)				0.63
PPh ₃	1.40(3)				0.52
P(<i>p</i> -C ₆ H ₄ OMe) ₃	1.3(1)		4.4(1)		0.48
FcPPh ₂			1.80(6)		0.20
P(<i>n</i> -Bu) ₃			0.87(1)		0.091
dppf			0.50(1)		0.055
PMe ₃				3.3(1)	0.030
AsPh ₃				2.7(1)	0.026
SbPh ₃				1.8(1)	0.019
PCy ₃				0.94(3)	0.008
P(<i>o</i> -C ₆ H ₄ Me) ₃			0.04(1)	0.49(2)	0.004
P(OPh) ₃				0.45(2)	0.004
NEt ₃				0.45(2)	0.004

Scheme 2. Kinetic studies of the reactions between [Ni(COD)(dppf)] (**1**) (0.022 mol L⁻¹) and (2-bromoethyl)benzene (**4-Br**) (0.33 mol L⁻¹) in toluene-*d*₈ in the presence of various added ligands (0.0132 mol L⁻¹).

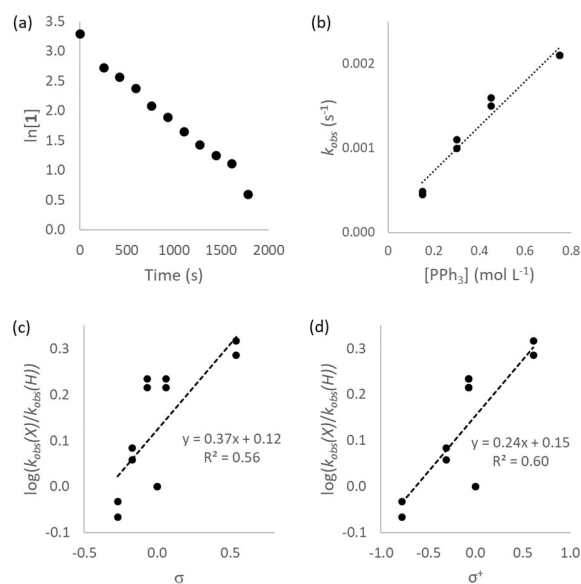


Figure 1. (a) Kinetic data for the reaction between [Ni(COD)(dppf)] (**1**) (0.022 mol L⁻¹) and (2-bromoethyl)benzene (**4-Br**) (0.33 mol L⁻¹) at 263 K in toluene-*d*₈ in the presence of triphenylphosphine (0.0132 mol L⁻¹). (b) Plot of k_{obs} versus [PPh₃]. (c) Hammett plot (using substituent constants σ) for the reactions in the presence of substituted triarylphosphines. (d) Hammett plot (using substituent constants σ^+).

It is apparent that neither the steric nor the electronic properties of the ligand dominate the observed effects on reaction rates; Tolman electronic parameter (TEP) and cone angle data are gathered for some of the ligands deployed in this study (Table 1).¹⁹ It was initially anticipated that electron-rich ligands would generate a more reactive nickel(0) complex, and therefore accelerate halide abstraction. However, the use of tricyclohexylphosphine leads to a very slow reaction with no conversion after 45 min at 273 K ($k_{rel} = 0.008$); reactions in the presence of trimethylphosphine ($k_{rel} = 0.030$) or tri(*n*-butyl)phosphine ($k_{rel} = 0.091$) are faster. The reaction with triphenylphosphine as an additive led to a reaction that was faster still ($k_{rel} = 0.52$), despite being less electron rich.

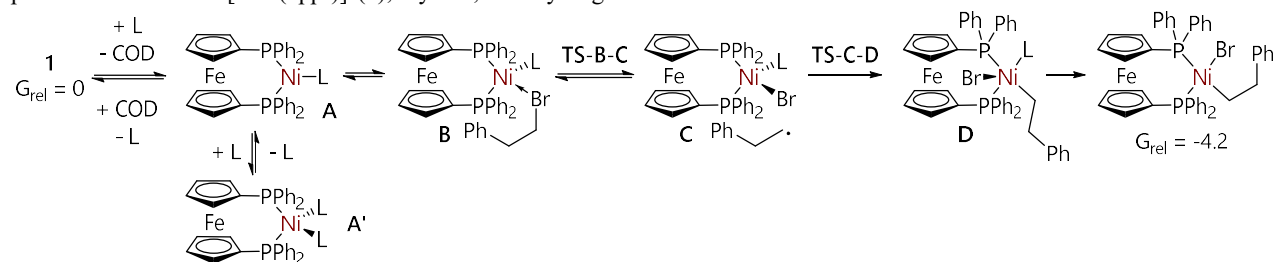
Table 1. Relative rate constants for selected reactions where TEP and cone angle are known¹⁹ for the corresponding ligand.

Ligand	TEP (cm ⁻¹)	Cone Angle (°)	k_{rel}
P(<i>m</i> -C ₆ H ₄ Me) ₃	2067.2	-	0.89
P(<i>p</i> -C ₆ H ₄ F) ₃	2071.3	-	0.89
P(<i>p</i> -C ₆ H ₄ Me) ₃	2066.7	145	0.63
PPh ₃	2068.9	145	0.52
P(<i>p</i> -C ₆ H ₄ OMe) ₃	2066.7	-	0.48
P(<i>n</i> -Bu) ₃	2060.3	132	0.31
PMe ₃	2064.1	118	0.030
PCy ₃	2056.4	170	0.008
P(<i>o</i> -C ₆ H ₄ Me) ₃	2066.6	194	0.004
P(OPh) ₃	2085.3	128	0.004

A Hammett plot²⁰ of $\log(k_{obs(X)}/k_{obs(H)})$ versus σ for a set of five triarylphosphines gave a relatively shallow gradient of $\rho = 0.37$ (Figure 1(c)).²¹ A slightly better correlation with $\rho = 0.24$ is obtained using σ^+ parameters for the *para*-substituted triarylphosphines (Figure 1(d)),²² but in both cases these show that the reaction is promoted by *electron-poor* triarylphosphines. The relatively simple reaction mechanism that we had initially anticipated – i.e. ligand binding, halide abstraction, ligand dissociation – is too simple to explain the observed trends, and so we turned to computational chemistry for additional insight.

DFT Calculations of the Reaction Mechanism

DFT calculations carried out during our earlier study¹⁸ supported the proposal that the reaction occurs *via* formation of a three-coordinate nickel(0) complex, halide abstraction to form nickel(I) plus a radical, and recombination of these species to form a nickel(II) complex. The nickel(II) complex is then proposed to undergo β -hydride elimination followed by comproportionation to form [NiX(dppf)] (3), styrene, and hydrogen.



Scheme 3. Mechanism for the reactions of **1** plus added ligand (L) with (2-bromoethyl)benzene **4-Br**.

For details of the level of theory used in this study please see the experimental section. Trimethylamine was used as a conformationally less complicated model for triethylamine; we have previously used trimethylphosphine as a model for triethylphosphine.²³

The reactions of [Ni(COD)(dppf)] (**1**) with (2-bromoethyl)benzene (**4-Br**) in the presence of added ligands were systematically studied. Scheme 3 outlines the mechanism, while Table 2 records the corresponding data and the overall barrier for the halide abstraction transition state *versus* the lowest energy preceding intermediate. For simplicity, the reactions with the corresponding alkyl chloride and alkyl iodide were not studied here.

In most cases, [Ni(dppf)(L)] had $G_{rel} = -0.6$ to 1.6 kcal/mol, with the exceptions of trimethylamine ($G_{rel} = 14.3$ kcal/mol) and triphenylphosphite ($G_{rel} = -6.1$ kcal/mol). The strong binding of the π -accepting phosphite to the dppf-nickel(0) fragment is not unexpected, given the important role of π -backbonding in the coordination chemistry of organometallic complexes of nickel(0).^{24–26} The steric profile of each coordinated ligand in a selection of the corresponding [Ni(dppf)(L)] complexes was evaluated using the percent buried volume (% V_{bur}) metric (see the Supporting Information for the full dataset).^{27–29} This metric has been widely applied across organometallic chemistry and catalysis.^{30,31} The % V_{bur} value did not vary as much as was anticipated. For example, tricyclohexylphosphine and triphenylphosphine have % V_{bur} that vary by less than one unit (31.9 and 31.2, respectively), despite their vastly different cone angles (170° and 145°, respectively). Trimethylphosphine (24.0), triphenylarsine (22.7), and triphenylstibene (27.7) have a lower % V_{bur} than triarylphosphines (*ca.* 31) in this environment.

It is possible for two monodentate ligands to coordinate the [Ni(dppf)] fragment in most cases; [Ni(dppf)(PMe₃)₂]³² and [Ni(dppf)(P(OPh)₃)₂]³³ are known species that have been fully characterized using methods including single crystal X-ray diffraction. The possible formation of these species was also investigated computationally. In the case of trimethylamine and tricyclohexylphosphine, geometry optimization led to the spontaneous decoordination of the second ligand. In all other cases, [Ni(dppf)(L)₂] complexes could be optimised as minima on the free energy surface. For triphenylarsine, triphenylstibene, trimethylphosphine, and triphenylphosphite the binding of a second ligand is very favourable, and so this increases the barrier to halide abstraction by [Ni(dppf)(L)]; this explains the rather poor performance of these four ligands in the kinetic experiments. The binding of a second diphenylphosphinoferrocene or triarylphosphine ligand is endergonic by a few kcal/mol.

The next step is the formation of [Ni(BrCH₂CH₂Ph)(dppf)(L)], although in many cases the steric environment around nickel precludes short Ni...Br distances. These are

Table 2. Free energies for the complexes considered during this study, obtained at the M06/6-311+G(d,p), LANL2DZ(d,p)[Sb], SMD(benzene)//B3LYP-D3/6-31G(d), LANL2TZ(f)[Ni,Fe], LANL2DZ(d,p)[Br,As,Sb] level of theory, and quoted relative to [Ni(COD)(dppf)] (1).

Ligand	k_{rel}	G_{rel} (kcal/mol)								ΔG^\ddagger (HA)	ΔG^\ddagger (recomb.)
		A	A'	B	TS-B-C	C	TS-C-D	D			
P(<i>p</i> -C ₆ H ₄ CF ₃) ₃	1.00	0.0	4.1	4.3	23.8	20.5				23.8	
P(<i>p</i> -C ₆ H ₄ F) ₃	0.89	1.0	2.9	2.8	22.5	4.5				22.5	
P(<i>p</i> -C ₆ H ₄ Me) ₃	0.63	1.6	5.8	3.8	22.7	18.9				22.7	
PPh ₃	0.52	1.4	5.3	2.5	24.6	17.7	26.4	10.8		24.6	26.4
P(<i>p</i> -C ₆ H ₄ OMe) ₃	0.48	1.0	3.2	4.2	21.4	3.5				21.4	
FcPPh ₂	0.20	0.3	8.0	3.0	24.7	7.2				24.7	
dppf	0.055	-0.2 ^a	- ^b	2.9	24.6	10.1				26.1	
PMe ₃	0.030	0.0	-12.2	5.5	22.2	5.9	4.5	4.1		34.4	16.7
AsPh ₃	0.026	1.4	-5.3	12.1	22.0	9.4				27.3	
SbPh ₃	0.019	0.9	-14.6	9.3	19.0	11.2				33.6	
PCy ₃	0.008	-0.2	- ^c	4.5	26.3	-0.2	31.7	14.6		26.3	31.9
P(OPh) ₃	0.004	-6.1	-21.6	-3.3	18.8	- 13.1				40.4	
NMe ₃	0.004	14.3	- ^c	21.1	32.8	15.1				32.8	

^a [Ni(dppf)₂] has $G_{\text{rel}} = -1.5$ kcal/mol. ^b [Ni(dppf)(κ^1 -dppf)₂] is unlikely to be competitive with [Ni(dppf)₂]; note that [Ni(dppf)(FcPPh₂)₂] has $G_{\text{rel}} = 8.0$ kcal/mol. ^c Attempts to locate structures for [Ni(dppf)(PCy₃)₂] and [Ni(dppf)(NMe₃)₂] led to spontaneous dissociation of one of the ligands during geometry optimization.

typically slightly higher in energy than [Ni(dppf)(L)], presumably due to the entropic cost of bringing two molecules together. Halide abstraction takes place subsequently, and forms [NiBr(dppf)(L)] plus an alkyl radical. Our initial treatment of the data assumed facile ligand dissociation and radical recombination to form [NiBr(CH₂CH₂Ph)(dppf)] (5) ($G_{\text{rel}} = -4.2$ kcal/mol) which transpired to be an over-simplification of the reaction mechanism;¹⁸ the events after halide abstraction but before the formation of 5 will be discussed subsequently.

An initial analysis of the data revealed limited agreement between experimentally-determined rate constants and computationally-determined halide abstraction barriers. FcPPh₂ is a more effective ligand than dppf, and this is reflected in the 1.4 kcal/mol decrease in ΔG^\ddagger . However, the DFT data for triarylphosphines ligands are at odds with the experimental observations, and instead suggest that the reactions with more *electron-rich* ligands should proceed more quickly.

We next considered the possibility that the halide abstraction is in fact reversible, and that a subsequent step in the mechanism might be rate-determining in some or all cases. Experimental evidence suggests that the alkyl radical exists for long enough to undergo unimolecular rearrangement reactions, but the lack of any corresponding alkane or dimerized product suggests that it is captured by the nickel complex relatively quickly.¹⁸ However, the radical might be captured by the formation of a nickel(II) complex (formation of a C-Ni bond) or by the abstraction of the halide from the nickel center (C-X reformation), especially within the relatively crowded environment of the nickel center.

Further calculations identified transition states for the combination of the alkyl radical with [NiBr(dppf)(L)], where L is trimethylphosphine, tricyclohexylphosphine, or triphenylphosphine. In the case of trimethylphosphine, two transition states were characterized: one with approximately

trigonal bipyramidal geometry, and one (of lower energy) with distorted square-based pyramidal geometry. For tricyclohexylphosphine and triphenylphosphine pathways only the latter geometry of transition state was located; attempts to locate trigonal bipyramidal transition states were unsuccessful. Geometry optimizations of structures along the reaction coordinate confirmed that the transition states linked the nickel(I) complex and a square-based pyramidal nickel(II) species.

The barrier to recombination varies considerably depending on the identity of the ligand. For tricyclohexylphosphine, the radical capture transition state is significantly higher in energy than the halide abstraction transition state (31.7 *versus* 26.3 kcal/mol), which explains the poor performance of this ligand in the stoichiometric reactions. In contrast, the recombination of the radical with the trimethylphosphine complex presents no significant barrier.

Figure 2 displays the free energy profiles for the reactions where trimethylphosphine, tricyclohexylphosphine, and triphenylphosphine are used as additives; these illustrate the three types of behavior that are observed in these reactions. These are discussed in turn.

In the case of trimethylphosphine, the formation of [Ni(dppf)(PMe₃)₂] inhibits the reaction because one of the trimethylphosphine ligands must dissociate before halide abstraction can occur, and this carries a significant energetic penalty. Similar behavior is observed for triphenylphosphite, triphenylarsine, and triphenylstibene.

The reaction in the presence of tricyclohexylphosphine suffers from a large barrier to radical recombination with the nickel(I) intermediate. A structure for [Ni(dppf)(PCy₃)₂] could not be obtained because one of the tricyclohexylphosphine ligands dissociated during geometry optimization, and so the barrier to halide abstraction is reasonable. However, the radical

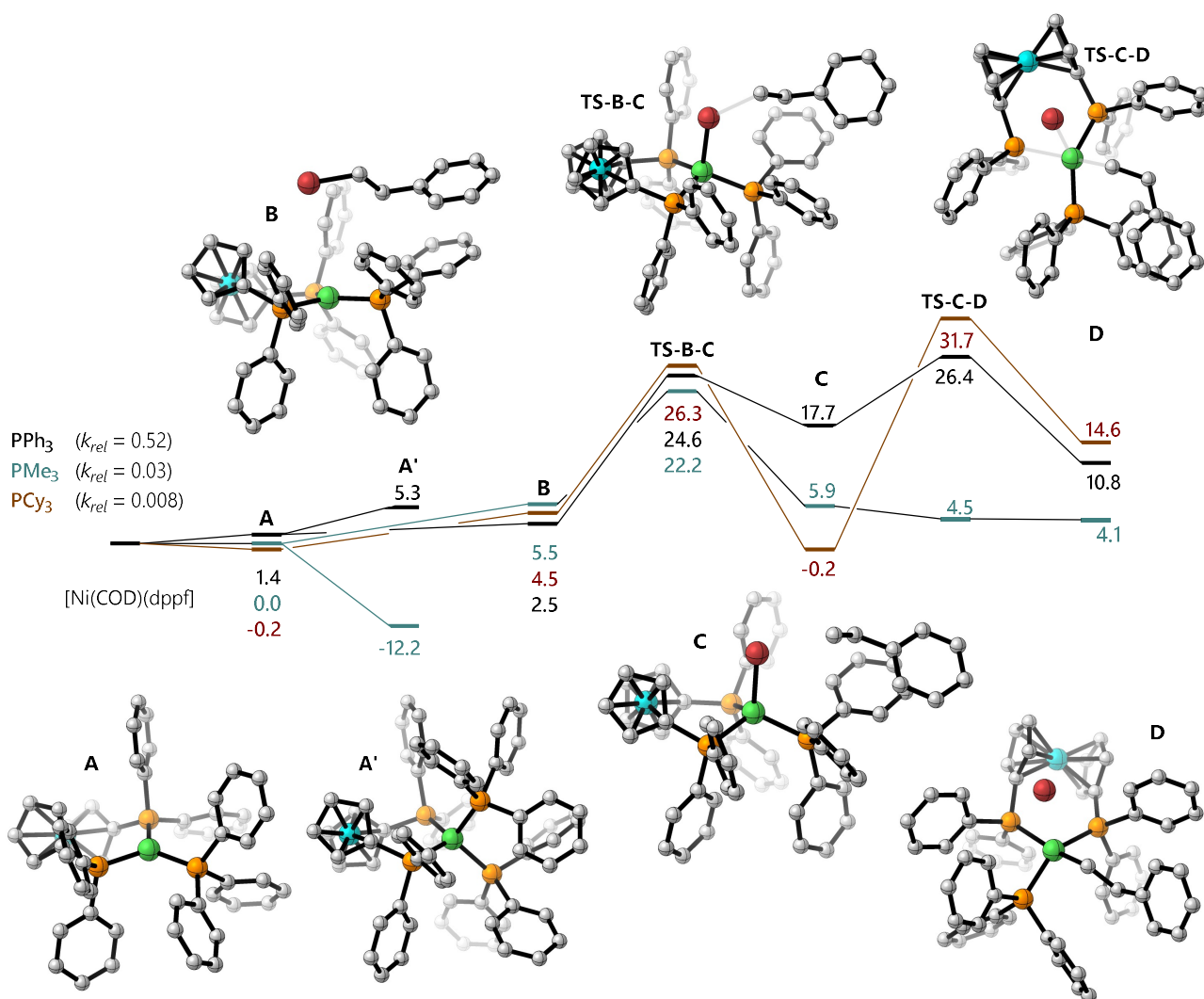


Figure 2. Free energy profiles for the reactions of [Ni(COD)(dppf)] (1) with (2-bromoethyl)benzene (4-Br) in the presence of triphenylphosphine (black), trimethylphosphine (teal), or tricyclohexylphosphine (red). Images represent DFT-derived structures of the relevant intermediates with triphenylphosphine as the added ligand (Ni green, Fe blue, P orange, Br red, C grey) with H atoms omitted for clarity.

formed during halide abstraction (**D**) faces a smaller barrier to re-form the C-Br bond (26.5 kcal/mol) than to form a C-Ni bond (31.9 kcal/mol) and so the halide abstraction is reversible.

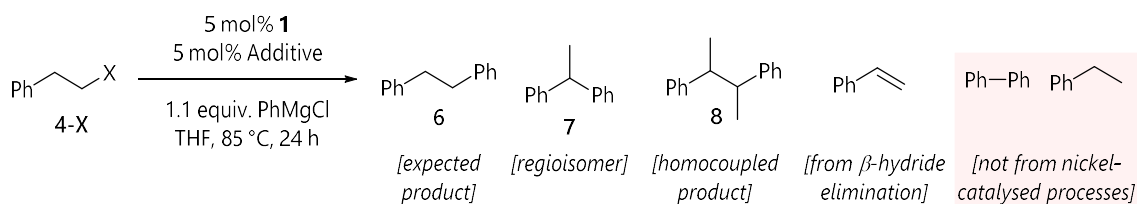
The reaction in which triphenylphosphine is present faces neither of these issues. The coordination of a second phosphine ($\Delta G = 3.9$ kcal/mol) is less favorable than coordination of the substrate ($\Delta G = 1.1$ kcal/mol) and the transition states for C-Br formation and C-Ni formation are close in energy ($G_{\text{rel}} = 24.6$ and 26.4 kcal/mol), respectively.

The ‘ideal’ added ligand for this process is therefore a ligand that coordinates only once, but that is not sufficiently bulky to interfere with the recombination of the radical with nickel(I).

Relevance to Catalysis

We sought to link our new understanding of the effects of ligands on the halide abstraction step to the outcomes of catalytic reactions of importance to synthetic chemistry. A series of

prototypical Kumada-Tamao-Corriu cross-coupling reactions were carried out using (2-haloethyl)benzene substrates (**4-Cl**, **4-Br**, **4-I**) to understand the effects of additives on catalytic reactions (Scheme 4). All reactions were catalysed by 5 mol% [Ni(COD)(dppf)] in the presence of 5 mol% of an additional ligand; the same conditions were used in our previous study.¹⁸ These reactions produced the expected 1,2-diphenylethane product (**6**), the 1,1-diphenylethane regioisomer (**7**), styrene, ethylbenzene, and biphenyl (Figure 3). We have shown previously, through the use of control reactions, that ethylbenzene and biphenyl do not arise from nickel-catalysed reactions.¹⁸ The regioisomer is likely formed from β -hydride elimination followed by migratory insertion to generate the [NiX(C(Me)Ph)(dppf)].¹⁸ The alkyl halide homocoupling product 2,3-diphenylbutane (**8**) was observed in some reactions, particularly when **4-Cl** was used as the substrate. All reaction outcomes were quantified using GC-FID analysis with an internal standard; the GC-FID was calibrated using authentic pure samples of each analyte. These model reactions proceed poorly in



Scheme 4. Model Kumada-Tamao-Corriu reactions.

the absence of an added ligand. The reactions of **4-I** are relatively insensitive to the choice of added ligand, although triphenylstibene and triethylamine perform quite poorly. It is likely that the relatively weak carbon-iodine bond strength means that the halide abstraction step is unlikely to be rate-determining in the reactions of alkyl iodides. These reactions significantly favor the expected (linear) product (**6**) over the branched side-product (**7**). The reactions of **4-Br** show more diverse outcomes, and produce mixtures of **6** and **7**. Here, the most effective ligands appear to be trimethylphosphine, tri(*meta*-tolyl)phosphine, and triphenylphosphite. The reactions of **4-Cl** are evidently more challenging, and most reactions had rather poor mass balance and/or did not achieve complete substrate conversion. Once again, tri(*meta*-tolyl)phosphine appears to be the best ligand in terms of enabling complete conversion of the alkyl halide substrate, although the major product is regioisomer **7**.

Despite the 200-fold spread of reaction rates in the stoichiometric halide abstraction reactions, the outcomes of catalysis are generally rather less variable. Tri(*meta*-tolyl)phosphine emerges as a ligand that is a good choice for the reactions of any of the three of these substrates. It must be noted that a full optimization of this reaction has not been carried out, but the choice of added ligand represents an important factor that should be considered in these reactions. This added ligand can of course affect steps other than halide abstraction, but an examination of the full catalytic cycle for this reaction is beyond the scope of the present study.

CONCLUSION

This study has established that a range of different added ligands increase the rate of the reaction between [Ni(COD)(dppf)] (**1**) and a model alkyl bromide (**4-Br**), with a *ca.* 200-fold range of rate constants. This is consistent with our current mechanistic model which requires a three coordinate nickel(0) complex that can abstract the halide atom from the alkyl halide substrate. DFT studies have provided further insight into the reaction, identifying that the rate-determining step in the stoichiometric reactions between **1** and **4-Br** can be either the halide abstraction step *or* the recombination of the alkyl halide with the nickel(I) complex formed during halide abstraction.

Studies of a prototypical Kumada-Tamao-Corriu reaction have established that the choice of ligand has relatively little effect for the reactions of **4-I**, but that the reactions in the absence of an added ligand give poor outcomes. The outcomes of the reactions of **4-Br** and **4-Cl** show a more complicated dependence on the structure of the added ligand, but this certainly presents a useful vector for the optimization of these types of cross-coupling reactions.

Further studies of the complex reactions between nickel(0) and alkyl halides, and of the related catalytic cross-coupling reactions are currently underway within our laboratories.

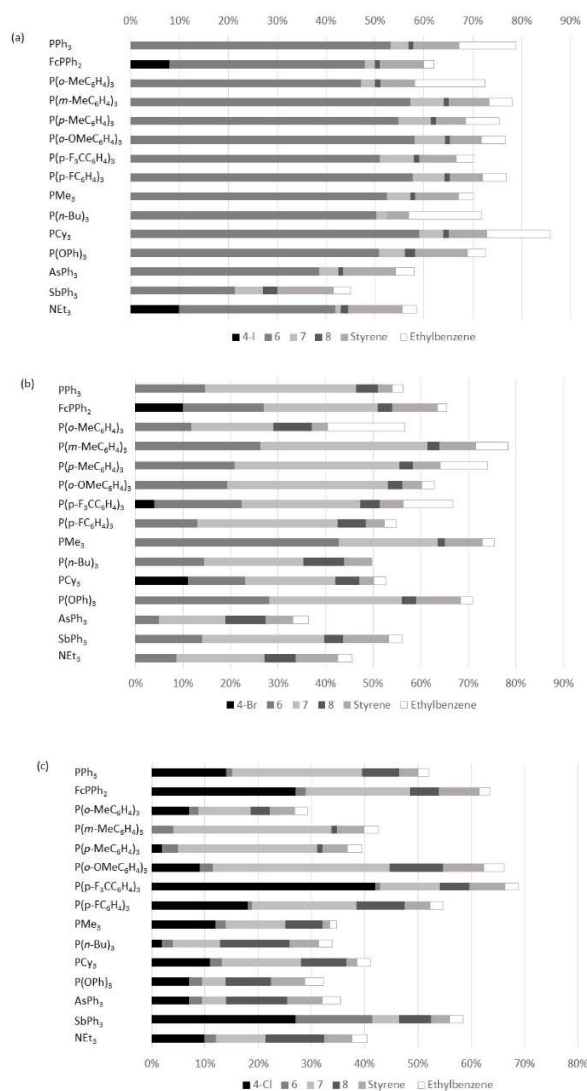


Figure 3. Product distributions in model Kumada-Tamao-Corriu cross-coupling reactions using different added ligands. Reactions were conducted with three substrates: (a) (2-iodoethyl)benzene, (b) (2-bromoethyl)benzene, and (c) (2-chloroethyl)benzene.

The raw data underpinning the experimental parts of this study can be downloaded from the University of Strathclyde Knowledgebase at [http://dx.doi.org/\[TBA\]](http://dx.doi.org/[TBA]). Computational chemistry data underpinning this study can be accessed via the IOChem-BD data repository³⁴ at [http://dx.doi.org/\[TBA\]](http://dx.doi.org/[TBA]).

EXPERIMENTAL SECTION

Materials. Anhydrous toluene, THF, and hexane were obtained from an Inert Technologies PureSolv apparatus (< 10 ppm water by Karl-Fischer titration). Any manipulations of air-sensitive nickel complexes were carried out under argon using Schlenk techniques or in a glovebox. Substrates used for kinetic experiments and cross-coupling reactions were obtained from commercial sources and used as supplied. The synthesis of FcPPh_2 and some of the reaction side products are detailed below; characterization data for the remaining products can be found in our previous manuscript.¹⁸ $[\text{Ni}(\text{COD})_2]$ (96% purity) was purchased from Alfa Aesar and stored at -35°C in the glovebox freezer. 1,1'-Bis(diphenylphosphino)ferrocene was purchased from Fluorochem and stored in the glovebox. $[\text{Ni}(\text{COD})(\text{dppf})]$ was prepared according to the literature method.¹⁷ Deuterated solvents were obtained from commercial sources and dried overnight on 4 Å molecular sieves before use.

Analysis. NMR spectroscopy was performed using Bruker AV3-400 (liquid nitrogen cryoprobe), Bruker AV3-400 Nano (BBFO-z-ATMA probe), or Bruker AVII-600 (BBO-z-ATMA) instruments. All kinetic experiments were performed using the latter instrument. ^1H NMR spectra are referenced to residual solvent signals, $^{13}\text{C}\{^1\text{H}\}$ NMR spectra are referenced to the deuterated solvent signal, and $^{31}\text{P}\{^1\text{H}\}$ NMR spectra are externally referenced.³⁵ Chemical shifts are given in ppm and coupling constants in Hertz. GC-MS analyses were carried out using an Agilent 7890A gas chromatograph fitted with a RESTEK-RXi-5Sil column (30 m x 0.32 mm I.D. x 0.25 µm) connected to an Agilent 5975C MSD running in EI mode. GC-FID analyses were carried out using an Agilent 7890A gas chromatograph fitted with an Agilent HP5 column (30 m x 0.25 mm I.D. x 0.25 µm).

1,4-Diphenylbutane. 1,4-Diphenyl-1,3-butadiene (1 g, 4.8 mmol) was added to a flask with Pd/C (0.1 g, 10 wt%), which was then sealed with a septum and evacuated and backfilled with nitrogen. Propan-2-ol (20 mL) was added and the flask was evacuated and backfilled again. A balloon of hydrogen was attached to the flask *via* a needle. The reaction was stirred at room temperature for 24 h. The balloon was removed, the Pd/C was filtered off and the solvent was removed under reduced pressure to give 1,3-diphenylbutane as a white solid (0.7 g, 73%). ^1H NMR (400 MHz, CDCl_3): δ 1.71 (dt, 4H, $^3J_{\text{H-H}} = 7.0$, ArCH_2), 2.67 (t, 4H, $^3J_{\text{H-H}} = 7.1$, ArCH_2CH_2), 7.19 – 7.22 (m, 6H, aryl C-H), 7.28 – 7.32 (m, 4H, aryl C-H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3): δ 30.6, 35.3, 125.1, 127.8, 127.9, 142.2. GC-MS ($\text{C}_{16}\text{H}_{18}$) m/z : 210.2. NMR data are consistent with the literature.³⁶

2,3-Diphenylbutane. Benzil (2 g, 9.5 mmol) was dissolved in anhydrous THF (20 mL) under a nitrogen atmosphere. MeMgCl (12.6 mL, 3 M in THF, 37.8 mmol) was added dropwise and the mixture was stirred at room temperature for 16 h. The reaction mixture was quenched (HCl , 1 M, 100 mL) and extracted with DCM (3 x 20 mL). The organic layers were combined, dried over MgSO_4 , filtered and concentrated to give 2,3-diphenylbutane-2,3-diol which was used in the next step without purification. Following a literature preparation,³⁷ 2,3-diphenylbutane-2,3-diol (1.5 g) was dissolved in hexamethylphosphoramide (20 mL) and stirred at room temperature for 2 h. The mixture was then heated to reflux for 90 min. After cooling, Et_2O (25 mL) was added and the reaction mixture was washed with water (100 mL). The aqueous layer was extracted with Et_2O (15 mL). The combined organic layers were then washed with water (2 x 50 mL) and brine (25 mL), dried over MgSO_4 , filtered and concentrated to give a brown/red oil. Column chromatography on silica gel (petroleum ether) gave 2,3-diphenylbuta-1,3-diene as a white solid. 2,3-Diphenylbuta-1,3-diene (150 mg) was added to a RBF with Pd/C (15 mg, 10 wt%), which was then sealed with a septum and evacuated and backfilled with nitrogen. Propan-2-ol (20 mL) was added and the flask was evacuated

and backfilled again. A balloon of hydrogen was attached to the flask *via* a needle. The reaction was then stirred at room temperature for 24 h. The balloon was removed, the Pd/C was filtered off and the solvent was removed under reduced pressure to give 2,3-diphenylbutane (95 mg, 5% over three steps) as a white solid. ^1H NMR (400 MHz, CDCl_3): δ 1.05 (dd, 6H, $^3J_{\text{H-H}} = 2.2$, 6.7), 1.31 (dd, 4H, $^3J_{\text{H-H}} = 1.9$, 6.7), 2.80 – 2.84 (m, 2H), 2.93 – 3.00 (m, 1.3H), 7.02 – 7.04 (m, 2.5H), 7.09 – 7.14 (m, 1.3H), 7.17 – 7.26 (m, 8.2H), 7.32 – 7.36 (m, 3.8H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3): δ 17.4, 20.5, 45.9, 46.8, 125.2, 125.5, 127.1, 127.2, 127.3, 127.8, 145.9. GC-MS ($\text{C}_{16}\text{H}_{18}$) m/z : 210.2. NMR data are consistent with the literature.³⁸

Diphenylphosphinoferrocene. Prepared according to a literature procedure.³⁹ Ferrocene (1.9 g, 0.1 mmol) and aluminium chloride (1.3 g, 0.1 mmol) were dissolved in hexane (20 mL). Chlorodiphenylphosphine was added and the solution was heated at reflux for 16 h. The hexane was decanted and solids were extracted with fresh hexane (50 mL). This was repeated with water (50 mL). The hexane and water were discarded, and the remaining solids were extracted with hot toluene (50 mL). The toluene was dried over MgSO_4 , filtered, and concentrated to dryness. The residue was extracted with hexane (100 mL) and this was concentrated to yield the product as a yellow powder (92 mg, 3%). ^1H NMR (400 MHz, CDCl_3): δ 4.12 (q, 4H, $^3J_{\text{H-H}} = 1.8$ Hz), 4.39 (t, 4H, $^3J_{\text{H-H}} = 1.8$ Hz), 7.33 – 7.41 (m, 20H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3): δ 68.6, 70.2 (d, $J_{\text{P-C}} = 3.9$), 72.4 (d, $J_{\text{P-C}} = 14.9$), 127.6 (d, $J_{\text{P-C}} = 14.9$), 127.9, 132.9, 133.1, 138.6 (d, $J_{\text{P-C}} = 9.6$). $^{31}\text{P}\{^1\text{H}\}$ NMR (162 MHz, CDCl_3): δ -17.0.

Kinetic Experiments. Kinetic data was obtained using the same methodology that has been deployed previously, by monitoring the decay of the concentration of $[\text{Ni}(\text{COD})(\text{dppf})]$ over time by ^{31}P or $^{31}\text{P}\{^1\text{H}\}$ NMR spectroscopy.^{11,18,26} For a typical experiment, in an argon-filled glovebox, a septum-fitted NMR tube was charged with a benzene- d_6 or toluene- d_8 solution containing $[\text{Ni}(\text{COD})(\text{dppf})]$ (8 mg, 0.011 mmol) and any solid additives. Any liquid additives – or stock solutions of additives – were then added. The total volume of the reaction was 0.5 mL. This sample was used to tune, match, lock, and shim the spectrometer. The alkyl halide was then added *via* syringe through the septum to start the reaction, and $^{31}\text{P}\{^1\text{H}\}$ NMR spectra were acquired at intervals until *ca.* 87% conversion (16 scans, 2 s between scans). All experiments were performed in duplicate. In all reactions, pseudo-first order rate constants (k_{obs}) were obtained from a linear plot of the natural log of the integral of the signal for $[\text{Ni}(\text{COD})(\text{dppf})]$ *versus* time. The rate constants from each experiment are tabulated in the supporting information.

Cross-coupling Reactions. In an argon-filled glovebox, $[\text{Ni}(\text{COD})(\text{dppf})]$ (0.0125 mmol, 5 mol%) and any solid additives were added to a microwave vial equipped with a stirrer bar. The vial was sealed with a septum-fitted cap and removed from the glovebox. On the Schlenk line, anhydrous THF (1 mL) was added, followed by phenylmagnesium chloride (0.28 mmol, 1.1 equiv.). The vial was then heated (with rapid stirring) to 85°C . When at the desired temperature, any liquid additives and the aryl halide (0.25 mmol) were added *via* microsyringe. The reactions were stirred at 85°C for 24 h, then cooled to room temperature and pierced with a needle. Each vial was opened, an accurately known amount of *n*-tetradecane was added, and a sample was taken for GC-FID analysis. All reactions were performed in duplicate; average conversions are reported in the manuscript, and the result of each individual cross-coupling reaction is tabulated in the supporting information. The GC-FID was calibrated for each substrate and product using authentic samples of each compound.

Computational Methodology. DFT calculations were carried out using Gaussian16 Rev. A.03.⁴⁰ DLPNO-CCSD(T) calculations⁴¹⁻⁴³ were carried out using Orca 4.2.1.^{44,45} Geometry optimizations were carried out without symmetry constraints using the B3LYP functional⁴⁶⁻⁴⁹ with the Grimme D3 empirical dispersion correction.⁵⁰ The LANL2TZ(f) pseudopotential/ECP was used for nickel

and iron, while LANL2DZ(d,p) was used for bromine, arsenic, and antimony.⁵¹⁻⁵³ The 6-31G(d) basis set was used for all other atoms. Frequency calculations verified the nature of stationary points. Transition states were checked using IRC calculations or by optimizing structures along the reaction coordinate. The energies of all structures were refined using single point calculations with the M06 functional,⁵⁴ the LANL2DZ(d,p) pseudopotential/ECP on antimony, and the 6-311+G(d,p) basis set on all other atoms. Solvation was included for the single point calculations using the SMD model (in benzene).⁵⁵ This level of theory was decided upon by benchmarking calculations for the formation of [Ni(dppf)₂] plus COD from [Ni(COD)(dppf)] plus dppf: ΔG (experiment) = -1.2 kcal/mol; ΔG (DLPNO-CCSD(T)/cc-pVTZ) = -1.6 kcal/mol; ΔG (M06/6-311+G(d,p)) = -1.5 kcal/mol (see the Supporting Information for full details). A correction of +1.89 kcal/mol was applied to the free energy of each species to consider a 1 mol/L reference state for the calculations rather than the ideal gas concentration.⁵⁶ Yamaguchi's approach was used to correct the electronic energies of open shell singlets for triplet contamination.⁵⁷ The images of DFT-derived structures in Figure 2 were prepared using CYLView 2.0.⁵⁸

ASSOCIATED CONTENT

Supporting Information. Kinetic data, computational data (methods, coordinates, energies), and data regarding the outcomes of catalytic reactions. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

There are no conflicts of interest to declare.

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ABBREVIATIONS

DPPE, 1,1'-bis(diphenylphosphino)ferrocene; SIMes, 1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene; NHC, *N*-heterocyclic carbene.

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