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A Structure–Activity Study of Ni-Catalyzed Alkyl–Alkyl Kumada Coupling. Improved Catalysts for Coupling of Secondary Alkyl Halides

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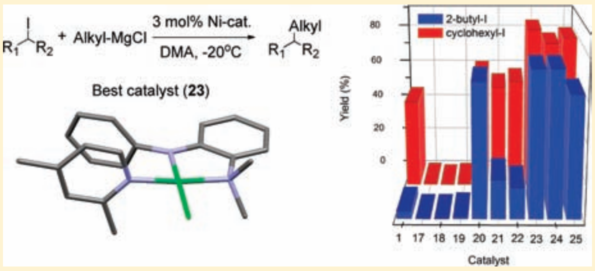
S *Supporting Information*

ABSTRACT: A structure–activity study was carried out for Ni catalyzed alkyl–alkyl Kumada-type cross coupling reactions. A series of new nickel(II) complexes including those with tridentate pincer bis(amino)amide ligands ($^{R}N_2N$) and those with bidentate mixed amino-amide ligands (^{R}NN) were synthesized and structurally characterized. The coordination geometries of these complexes range from square planar, tetrahedral, to square pyramidal. The complexes had been examined as precatalysts for cross coupling of nonactivated alkyl halides, particularly secondary alkyl iodides, with alkyl Grignard reagents. Comparison was made to the results obtained with the previously reported Ni pincer complex [($^{Me}N_2N$)NiCl]. A transmetalation site in the precatalysts is necessary for the catalysis. The coordination geometries and spin-states of the precatalysts have a small or no influence. The work led to the discovery of several well-defined Ni catalysts that are significantly more active and efficient than the pincer complex [($^{Me}N_2N$)NiCl] for the coupling of secondary alkyl halides. The best two catalysts are [(^{H}NN)Ni(PPh_3)Cl] and [(^{H}NN)Ni(2,4-lutidine)Cl]. The improved activity and efficiency was attributed to the fact that phosphine and lutidine ligands in these complexes can dissociate from the Ni center during catalysis. The activation of alkyl halides was shown to proceed via a radical mechanism.



INTRODUCTION

C–C cross coupling of nonactivated alkyl halides and pseudohalides is one of the most actively pursued reactions in homogeneous catalysis.[1–6] The main challenge has been to develop metal catalysts that overcome two significant barriers in cross coupling, namely, the oxidative addition of relatively electron-rich alkyl electrophiles (compared to aryl and vinyl electrophiles), and the unproductive β-H elimination. Since the pioneering work of Suzuki[7] and Knochel,[8] impressive progress has been made in the last years, resulting in many active catalytic systems.[1–6,9–12] However, the majority of reported methods are only applicable for the coupling of alkyl electrophiles with aryl nucleophiles. There are much fewer catalysts for alkyl–alkyl coupling.[4,7,8,12–41]

The coupling of secondary alkyl halides is particularly interesting because it creates a tertiary carbon center that might be otherwise difficult to access.[3] An asymmetric process would produce a stereogenic center. Pioneering and remarkable work of Fu et al. demonstrated that this type of asymmetric catalysis could indeed be achieved starting from racemic activated and nonactivated alkyl halides.[25,27,42–46] However, nonactivated secondary alkyl halides are very difficult to couple because of the increased steric hindrance of the substrates and the tendency of secondary alkyl halides to undergo base-mediated HX elimination (X = halide).[3] Consequently, there are only a handful of catalysts known for alkyl–alkyl coupling of nonactivated secondary alkyl electrophiles.[21,23–27,29,31,33,34,37] And to the best of our knowledge, there are only two preformed and defined catalysts, including the one developed by our group.[29,33,34]

We have focused on the development of well-defined (pre) catalysts for cross coupling reactions.[11] We recently reported a Ni^{II} pincer complex, [($^{Me}N_2N$)NiCl] (**1**),[33,47] that was an efficient catalyst for Kumada–Corriu-Tamao (Kumada) coupling of nonactivated alkyl halides with Grignard reagents.[33,34,48] Mechanistic study suggested that the alkyl-alkyl coupling catalysis started with the transmetalation of the Ni halide complex with an alkyl Grignard reagent to form a Ni alkyl species, which reacted with the alkyl halide to form the coupling product and regenerated the catalyst (Scheme 1).[33,49] The catalysis has a wide substrate scope and a high functional group tolerance.[34,48] As Grignard reagents are relatively cheap, easy to synthesize or purchase, and atom-economic, this Ni-catalyzed Kumada coupling method is attractive for the synthesis of highly functionalized organic molecules. The scope of the coupling method, especially for secondary alkyl halides, however, remained to be expanded.[33,34,48] Here we describe a structure–activity study of the Ni-catalyzed alkyl–alkyl Kumada coupling employing a series of isolated Ni complexes. We were able to identify some main factors governing the efficiency of the catalysis. Furthermore, catalysts much more efficient than complex **1** had been developed for the coupling of secondary alkyl halides.

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Scheme 1. The Proposed Catalytic Cycle for Alkyl−Alkyl Kumada Coupling by the Pincer Complex 1

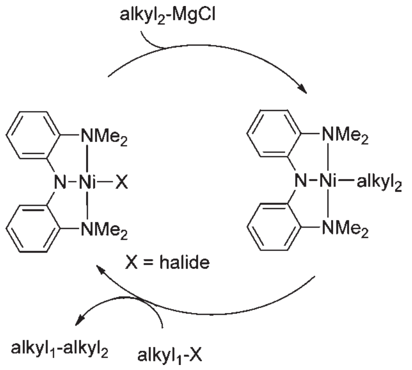
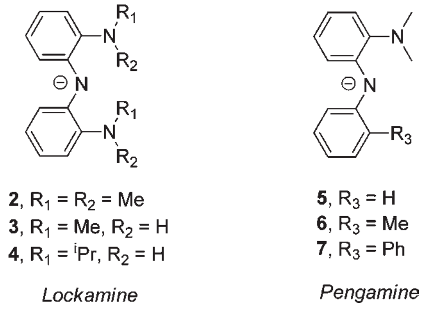


Chart 1



RESULTS

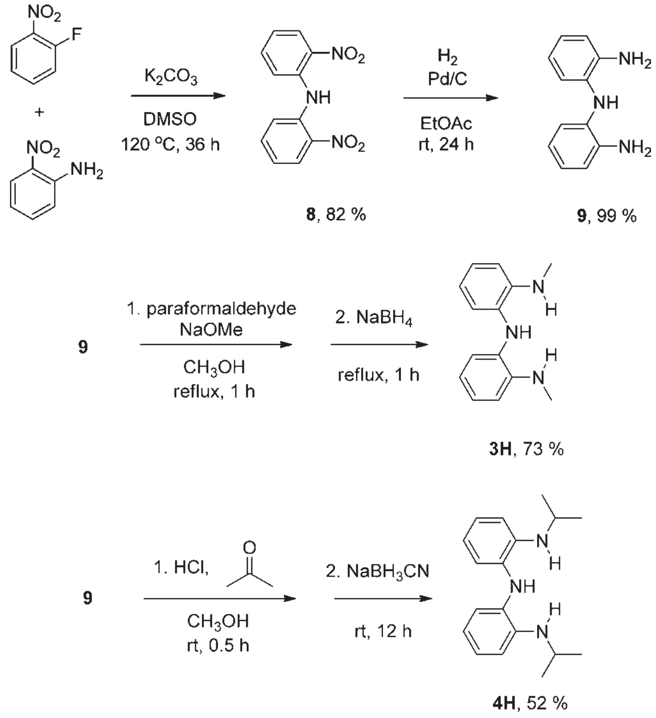
1. Synthesis and Structure of Ni Catalysts. *1.1. Ligand Synthesis.* In addition to the pincer ligand $^{Me}N_2N$ (**2**) in complex **1**,[47] a few new ligands (**3**−**7**) were employed in this study (Chart 1). For convenience of bookkeeping, we propose to name tridentate **2**−**4** "Lockamine" ligands and bidentate **5**−**7** "Pengamine" ligands.[50] An analogue of ligand **4** with electron-donating methoxy substituents was recently reported by Heyduk et al.[51] Protonated, neutral forms of these ligands were first prepared. Scheme 2 shows the synthesis of **3H** and **4H**. The overall synthetic sequence is similar to those employed for the preparation of pincer and tripodal triamido ligands.[51,52] Scheme 3 shows the synthesis of **5H**, **6H**, and **7H**. These compounds were prepared in high yields using the Pd-catalyzed Buchwald-Hartwig C−N coupling method.[53,54] Ligand **5H** was previously made by a different method.[55]

1.2. Metalation Using Organo-lithium and Magnesium Reagents. Lithiation occurred readily with ^{n}BuLi to give complexes **10**−**15** (Scheme 4). The crystal structures of **11**, **13**, and **15** have been determined (Figures S1−S3, Supporting Information). Because of the similarity of ligands **5**−**7**, complexes **12** and **14** might have similar structures as **13**.

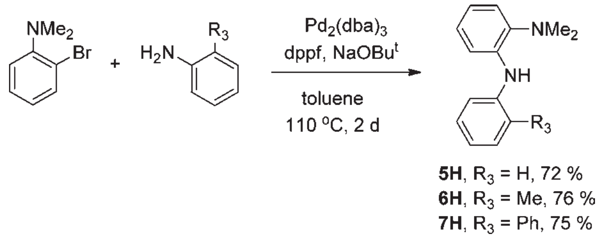
When the dimeric complex **14** was treated with THF, it was converted to monomeric and THF coordinated complex **15**. Thus, the solution structures of these Li complexes depend on the solvents in which they were dissolved. Donor solvents such as THF should favor monomeric forms.

A magnesium complex was also synthesized as a potential transmetalation reagent. The reaction of **7H** with EtMgCl in THF produced the dimeric compound **16** (Scheme 5). The structure of **16** was revealed by crystallography (Figure S4, Supporting Information).

Scheme 2. Synthesis of Pro-ligands 3H and 4H



Scheme 3. Synthesis of Pro-ligands 5H−7H

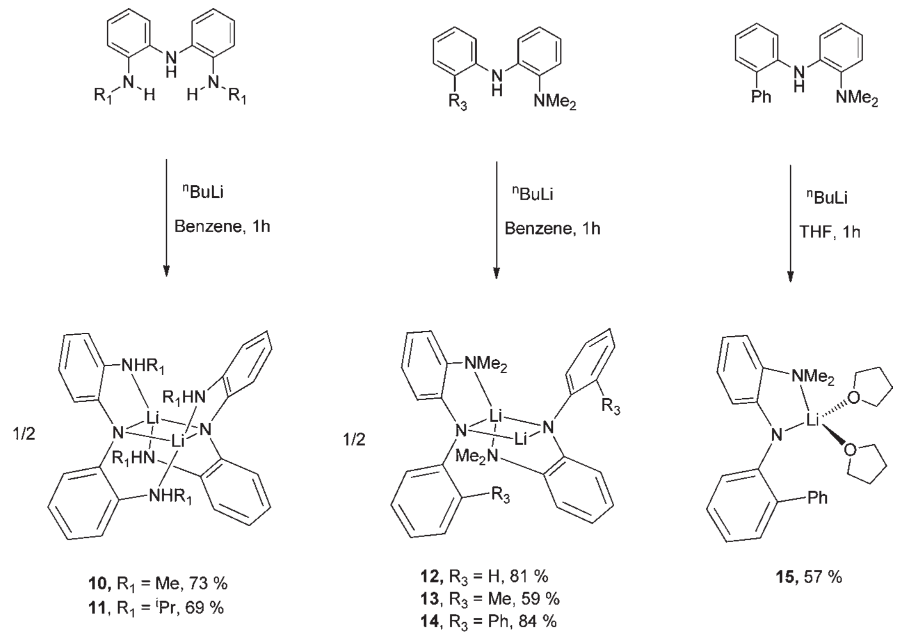


*1.3. Synthesis of Ni Complexes of Ligands **3**−**7**.* For tridentate Lockamine ligands **3** and **4**, their Ni complexes could be easily prepared by reactions of the Li complexes with $NiCl_2$(dme) (dme = dimethoxyethane) in THF (Scheme 6). The resulting Ni complexes (**17** and **18**) are diamagnetic. Only the *rac*-isomer was observed in the solid state (vide infra). However, in the solution, both *rac* and *meso* isomers exist, as indicated by the ^{1}H and ^{13}C NMR spectra. The ratios of isomers are 1:1 for **17** and 1:3 for **18**.

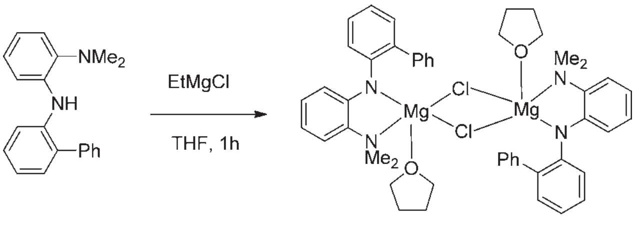
The synthesis of Ni complexes with bidentate Pengamine ligands **5**−**7** proved to be more challenging (see Supporting Information). Fortunately after many struggles, we were able to prepare a series of Ni complexes with these ligands by judicious choice of Ni precursors and reaction conditions.

Reaction of Li complex **13** with anhydrous $NiCl_2$ in THF led to the formation of complex **19**, in which two molecules of ligand **6** coordinate to one Ni ion (Scheme 7). The complex is paramagnetic and its ^{1}H NMR spectrum shows chemical shifts from −40 to +40 ppm. Changing the stoichiometry of the

Scheme 4. Lithiation of Ligands 3−7



Scheme 5. Synthesis of Mg Complex 16



16, 71 %

reagents did not affect the outcome of this reaction. Reaction of Li complex **12** with $NiCl_2(PPh_3)_2$ in THF led to the four-coordinate paramagnetic complex **20** (Scheme 7).

Reactions of Li complex **14** with $NiCl_2(py)_2$ and $NiCl_2$-(4-picoline)$_4$ yielded five-coordinate Ni complexes **21** and **22** (Scheme 8). Both compounds are paramagnetic. Finally, four coordinate and diamagnetic Ni complexes were prepared by the reaction of **12**−**14** with $NiCl_2$(2,4-lutidine)$_2$ (Scheme 8). The resulting complexes (**23**−**25**) have the formula of [(^{R}NN)Ni(2,4-lutidine)(Cl)]. The diamagnetism suggests that these compounds have square-planar structures which were confirmed by crystallography (vide infra).

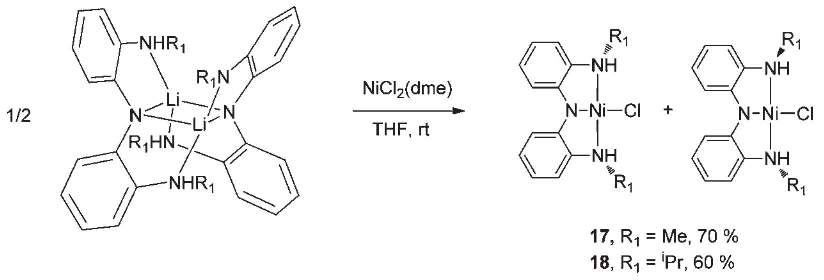
1.4. Structures of Ni Complexes. The solid-state structures of complexes **17**−**25** were determined by X-ray crystallography. The results confirmed the structural formulas depicted in Schemes 6−8. Complexes **17**, **18**, **23**−**25** are square planar, complexes **19** and **20** are distorted tetrahedral, and complexes **21** and **22** are distorted square pyramidal. The solid state molecular structures of **20** and **23** are shown in Figure 1, and the structure of the others are shown in the Supporting Information (Figures S5−S11).

2. Kumada Coupling of Secondary Alkyl Halides Using Ni Complexes As Precatalysts. *2.1. Test Reactions.* We chose the coupling of 2-iodobutane with octylMgCl (Table 1, eq 1) and cyclohexyl iodide with butylMgCl (Table 1, eq 2) as the model reactions to test the performance of Ni complexes **17**−**25**. The catalysis with complex **1** was used as a reference. The screening of reaction conditions showed that these reactions were best run at −20 °C and in DMA (DMA = dimethylacetamide), and using 1 equiv of Grignard reagent diluted in THF. Slow addition of Grignard reagents was sometimes beneficial and, in the best cases, gave 5 to 10% better yields (see Table S1, Supporting Information). The improvement is due to a decrease of olefinic side product, for example, octene from octylMgCl.

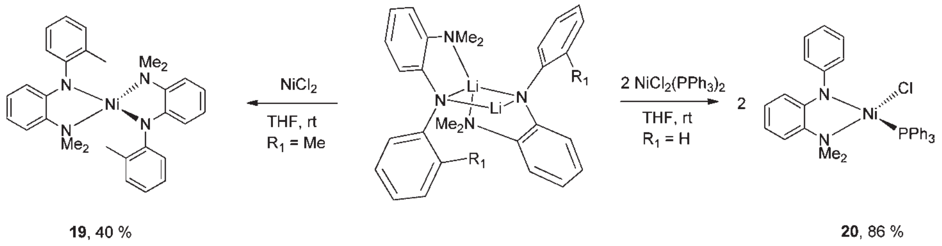
Figure 2 and Table 2 summarize the results. The pincer catalyst **1** was not efficient for coupling of 2-iodobutane (entry 1, Table 2), giving a 4% coupling yield for eq 1. It gave a modest yield for the coupling of cyclohexyl iodide. Analogous pincer complexes **17** and **18** did not give any coupling products (entries 2 and 3, Table 2). [(^{H}NN)$_2$Ni] complex (**19**) was also inefficient (entry 4, Table 2). As shown in Table S2, Supporting Information, most of the starting alkyl halides remained after the reactions using these precatalysts, and thus their inefficiency was due to the inability to activate alkyl halides. More encouraging results were obtained with [(^{H}NN)Ni(PPh_3)Cl] (**20**). It was active for the coupling of both acyclic and cyclic secondary iodides, giving a yield of 68% and 61% for 2-butyl and cyclohexyl iodide, respectively (entry 5, Table 2). The five-coordinate complexes **21** and **22** were also active (entries 6 and 7, Table 2). The coupling yields for 2-butyl iodide were low, and for cyclohexyl iodide were modest. The square-planar complexes **23**−**25** were the most efficient catalysts (entries 8−10, Table 2). Coupling yields between 62% and 84% were obtained. Complex [(^{H}NN)Ni(2,4-lutidine)Cl] (**23**) was the best catalyst, giving yields of 74% and 84% for the coupling of 2-butyl and cyclohexyl iodide, respectively (entry 8, Table 2). For precatalysts **20**−**25**, the major side products are due to homocoupling of Grignard reagents and alkyl electrophiles.

2.2. Ranking of Catalysts. Complexes **1**, **20**, and **22**−**25** showed certain activity for reactions 1 and 2 (Table 1). They were further tested for the coupling of additional cyclic and acyclic secondary alkyl iodides. The results were summarized in

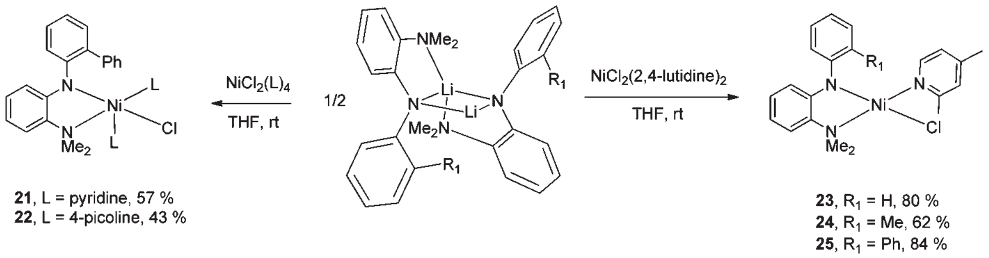
Scheme 6. Synthesis of Ni Pincer Complexes 17 and 18



Scheme 7. Synthesis of Complexes 19 and 20



Scheme 8. Synthesis of Complexes 21–25



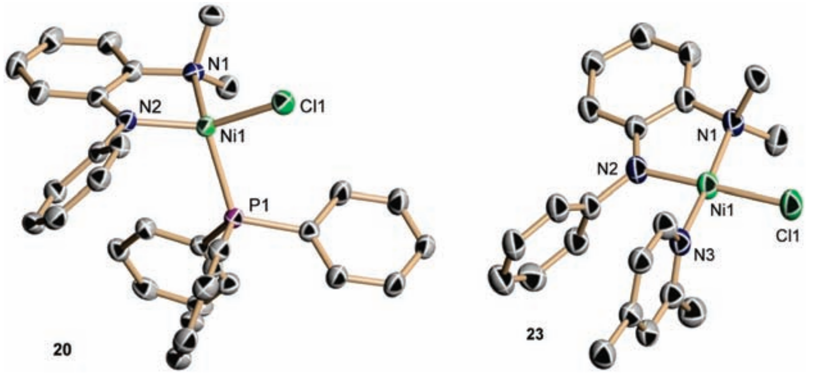


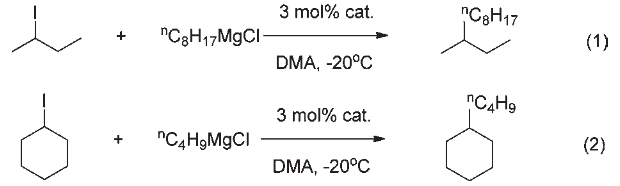
Figure 1. Solid-state molecular structures of complexes **20** and **23**. The thermal ellipsoids are displayed in 30% probability.

Table 3, and their graphical representations are shown in Figures S12, Supporting Information. .

The pincer complex **1** had no or low efficiency for the coupling. The 5-coordinate complex **22** performed better than **1**, but the overall efficiency remained low. The results were consistent with those shown in Table 2, and together, ranked complexes **1** and **22** as poor catalysts for coupling of secondary iodides. Table S3, Supporting Information, showed that the low efficiency was largely due to the inability to activate secondary alkyl halides.

Four-coordinate complexes **20** and **23**–**25** were much more efficient catalysts. Alkyl halides were readily activated (Supporting Information Table S3), and modest to high yields were obtained for

Table 1. Reactions 1 and 2



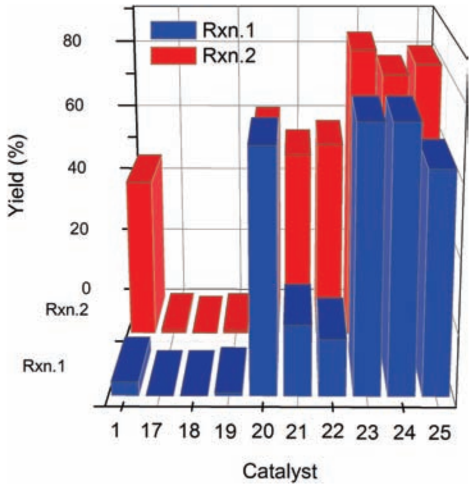
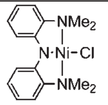
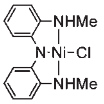
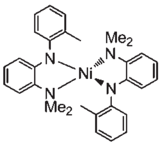
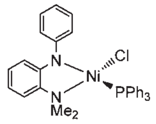
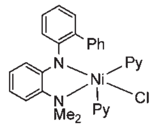
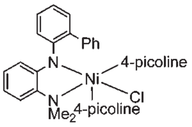
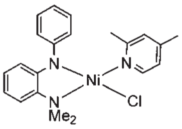
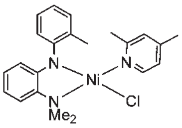
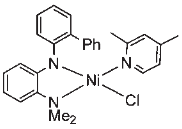


Figure 2. A graphical representation of the efficiency of various Ni catalysts for the test coupling reactions.

Table 2. Kumada Coupling of Secondary Alkyl Halides, Test Reactions[a]

Entry	Catalyst	formula	Yield (%) for reaction (1)	Yield (%) for reaction (2)
1	**1**		4	46
2	**17**		trace	1
3	**18**		trace	trace
4	**19**		1	1
5	**20**		68	61
6	**21**		20	54
7	**22**		16	57
8	**23**		74	84
9	**24**		74	77
10	**25**		62	80

[a] RMgCl (0.5 mmol (1 equiv.)) was diluted in THF (3 mL), and then was added dropwise via a syringe pump during 1 h to a DMA solution containing the nickel catalyst (0.015 mmol, 3%) and alkyl iodide (0.5 mmol) at −20 °C . After addition, the reaction mixture was further stirred for 1 h at −20 °C, and then the solution was taken out from the cooling system and stirred for 1 h to warm up to room temperature.

the coupling of all substrates. Except for coupling of 2-pentyl iodide, catalyst **20** is less efficient than **23**−**25**. Table S4, Supporting Information showed that more elimination products were produced using **20** as precatalyst. For the coupling of isopropyl and cyclopentyl iodide, complexes **23**−**25** were similarly efficient, having yields of about 70%. However, for the coupling of 3-pentyl, cycloheptyl, and cyclooctyl iodide, the performance of **23**−**25** was noticeably different. Complex **23** with the least bulky ligand **5**, was clearly the best catalyst. It gave yields of 53%, 87%, and 82% for those substrates. The efficiency dropped with **24**, and lowered furthermore with **25**. Table S4, showed that the efficiency of these precatalysts correlates with the amounts of elimination products, and complex **23** is more efficient because it suppresses elimination processes.

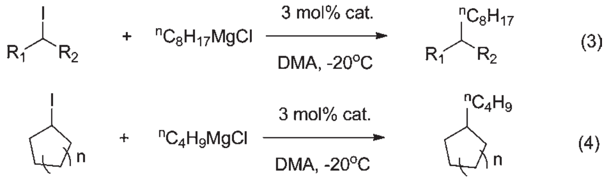
As complexes **20** and **23** gave a similar coupling yield for 3-pentyl iodide, they were further tested for the coupling of acyclic secondary alkyl iodides that are bulkier than 3-pentyl iodide. Modest yields of 42−65% were obtained (Table 4). Complex **20** was slightly more efficient than **23**, but the difference in yields was small, ranging from 2−11%.

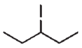
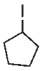
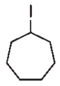
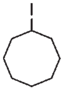
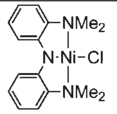
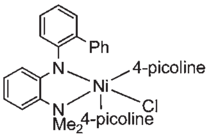
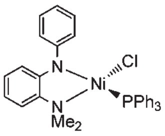
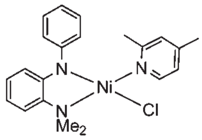
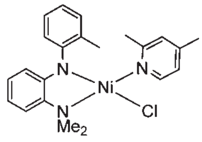
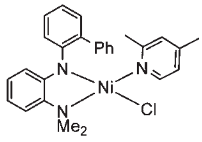
Overall, the results in Tables 3 and 4 indicate that complex **23** is the best catalyst for the coupling of cyclic and nonbulky acyclic secondary alkyl iodides, and complex **20** is the best catalyst for the coupling of bulky acyclic secondary alkyl iodides.

The coupling with secondary alkyl Grignard reagents[56,57] was also attempted (Table 5). A very low yield was obtained for coupling of secondary alkyl iodide with a secondary alkyl Grignard reagent (entry 1, Table 5). The yields for coupling of primary alkyl iodides with secondary alkyl Grignard reagents were modest, and similar efficiencies were obtained for complexes **23**−**25**. Unlike pincer complex **1**,[49] no significant isomerization products were formed using these catalysts.

*2.3. Further Probing the Origin of the Activity and Efficiency for Catalysts **1**, **20**, and **23**.* In addition to the desired products, various compounds originated from elimination, homocoupling, Grignard exchange, and reduction processes can form during a coupling reaction. To further probe the origin of the activity and

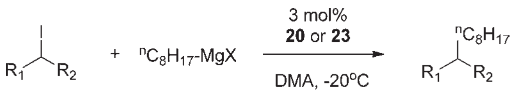
Table 3. Kumada Coupling of Secondary Alkyl Iodides, Continued[a]

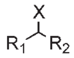
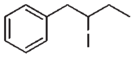
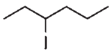
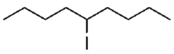
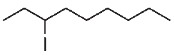


					
 **(1)**	8	trace	38	trace	0
 **(22)**	43	3	47	13	7
 **(20)**	58	50	43	65	52
 **(23)**	69	53	69	87	82
 **(24)**	75	38	68	81	61
 **(25)**	68	31	69	65	54

[a] Same conditions as in Table 2.

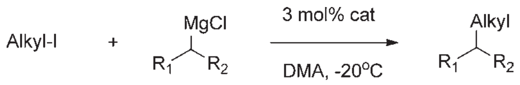
Table 4. Kumada Coupling of Bulky Acyclic Secondary Alkyl Iodides[a]

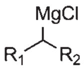
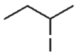
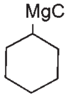
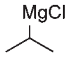
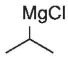
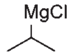
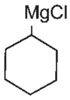


Entry		Yield with **20** (%)	Yield with **23** (%)
1		65	54
2		51	45
3		46	44
4		51	42

[a] Same conditions as in Table 2.

Table 5. Kumada Coupling of Secondary Alkyl Griganrd Reagents[a]



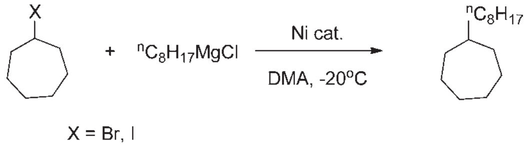
Entry	Alkyl-I		cat	Yield (%)
1			**25**	7
2	n-C_8H_{17}		**23**	43
3	n-C_8H_{17}		**24**	51
4	n-C_8H_{17}		**25**	42
5	n-C_4H_9		**23**	45

[a] Same conditions as in Table 2.

efficiency of representative precatalysts **1**, **20**, and **23**, we chose to study in detail the coupling of cycloheptyl-I and cycloheptyl-Br with octylMgCl. These two reactions were chosen because the potential products could be readily determined by GC or GC−MS. The reaction time was set to 1 h (addition of Grignard reagent) + 1 h (further reaction) at −20 °C.

The results are shown in Table 6. Catalyst **1** was not an active catalyst, and most of the starting cycloheptyl halides remained (entries 1 and 5, Table 6). For coupling of cycloheptyl-I, a high yield of 74% was obtained with **23**; with **20**, the yield was 53%, and the main side product was cycloheptene (entries 2 and 3, Table 6). The conversion was more than 90% in both cases. For coupling of cycloheptyl-Br, yields of about 30% were obtained with **20** or **23** (entries 6 and 7, Table 6). The conversions were about 60−70%, indicating that activation of alkyl bromide is slower than that of alkyl iodide. For coupling of both alkyl bromide and iodide, more olefinic products were formed with catalyst **20**. When no catalyst

Table 6. Kumada Coupling of Secondary Alkyl Halides[a]



entry	X/catalyst	octane	octene	cyclo-C_7H_{14}	cyclo-heptene	$C_7H_{13}I$ or $C_7H_{13}Br$	oct−oct	$C_7H_{13}-C_7H_{13}$	C_7H_{13}−Oct
1	I/1	99	0	0	7	76	<1	<1	<1
2	I/20	8	2	8	36	1	8	1	53
3	I/23	9	4	7	8	8	5	8	74
4	I/no	>99	0	0	4	77	0	0	0
5	Br/1	95	0	0	6	97	<1	0	<1
6	Br/20	52	3	1	32	31	2	<1	38
7	Br/23	49	5	1	12	43	2	6	34
8	Br/no	86	0	0	2	92	0	0	0

[a] Same conditions as in Table 2.

was used, most alkyl halides remained, and a small amount of olefins were produced (entries 4 and 8, Table 6). Thus, the olefins observed in the coupling reactions should originate from metal mediated β-H elimination.

According to entry 7, Table 6, coupling of secondary alkyl bromide was fairly selective using **23** as the catalyst, although the conversion was low within the chosen reaction time. The coupling yields could be increased if a longer reaction time (2 h) was applied. Table 7 shows the results for some secondary alkyl bromides. Modest to good yields were obtained.

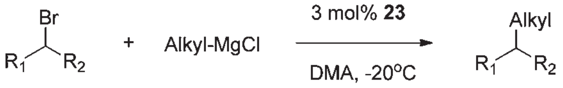
2.4. Coupling of Primary Alkyl Iodides. We showed earlier that for catalyst **1**, the coupling of primary alkyl halides was faster than secondary alkyl halides.[33] To determine whether this preference also holds for catalysts **20** and **23**, competition experiments were conducted using equal amounts of cyclohexyl and octyl iodides (eq 5, Scheme 9). Multiple trials were conducted in which the reaction time was set to 10 s, 1, 2, and 5 min (Table S5, Supporting Information). It appeared that after 10 s, the reactions already reached completion, making it difficult to determine the rates of the reactions.

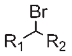
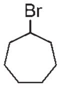
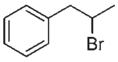
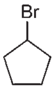
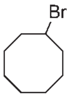
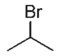
Nevertheless, according to Scheme 9 and Table S5, with both catalysts **20** and **23**, the coupling of octyl iodide was faster than cyclohexyl iodide. The difference in reaction rate is modest. These results suggest that activation of primary alkyl halides is also faster than secondary alkyl halides with the new catalysts.

Catalysts **20** and **23** were further studied for the coupling of primary alkyl halides. Unfortunately the yields were modest and generally lower than with catalyst **1**. Further experiments were conducted to probe the origin of this lowered efficiency for coupling of primary alkyl electrophiles (Table 8).

When the coupling was conducted without a catalyst, we found that 97% of β-phenylethyl-I reacted (entry 1, Table 8). The main product was β-phenylethyl-Cl, possibly formed via a I/Cl exchange reaction with octyl-MgCl. Base-mediated elimination was severe, and 27% of styrene was formed. These background reactions needed to be overcome for a successful cross coupling. With catalyst **1**, the productive cross coupling was rapid and efficient, and out-competed the noncatalytic side reactions (entry 2, Table 8). An 85% coupling yield was achieved. With catalyst **20**, the cross coupling was not sufficiently rapid, and the noncatalytic side reactions were significant (entry 3, Table 8). The I/Cl exchange reaction was only partially attenuated, giving β-phenylethyl-Cl in a 23% yield. Base-mediated elimination was also severe, and 20% of styrene was formed. In addition, homocoupling was noticeable. The yield of cross coupling was a low 29%. With catalyst **23**, the cross coupling was fast enough to suppress the noncatalytic side reactions (entry 4, Table 8). However, homocoupling marred the efficiency of cross coupling (41%).

Table 7. Kumada Coupling of Secondary Alkyl Bromides[a]

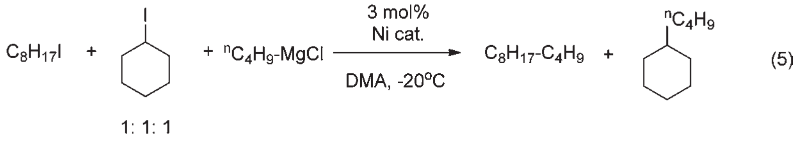


Entry		Alkyl	Yield (%)
1		n-C_8H_{17}	69
2		n-C_8H_{17}	52
3		n-C_4H_9	75
4		n-C_4H_9	60
5		n-C_8H_{17}	64

[a] RMgCl (0.6 mmol (1.2 equiv)) was diluted in THF (3 mL), and then was added dropwise via a syringe pump during 1 h to a DMA solution containing the nickel catalyst (0.015 mmol, 3%) and alkyl bromide (0.5 mmol) at −20 °C . After addition, the reaction mixture was further stirred for 2 h at −20 °C and then the solution was taken out from the cooling system and stirred for 10 min to warm up to room temperature.

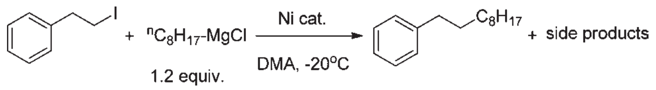
The results in Table 8 show that for coupling of primary alkyl iodides, the activity has the order of **1** > **23** > **20**. Complex **20** was not

Scheme 9. Competition Experiment for Primary and Secondary Alkyl Iodides; The Reaction Time Was 10 Seconds



	Conversion:		Yields:	
catalyst **20** :	60 %	40 %	38 %	23 %
catalyst **23** :	60 %	44 %	35 %	14 %

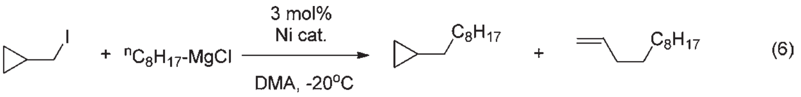
Table 8. Kumada Coupling of Primary Alkyl Iodides[a]



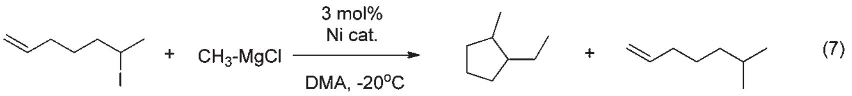
entry	catalyst	octene	ethyl−benzene	styrene	phenyl−ethyl−I	phenyl−ethyl−Cl	oct−oct	(phenyl−ethyl)$_2$	$C_6H_5C_2H_4$−oct
1	no	0	0	27	3	58	0	0	0
2	1	7	2	2	0	0	4	7	85
3	20	5	0	20	0	23	13	16	29
4	23	12	3	7	0	<1	18	24	41

[a] Octyl-MgCl (0.6 mmol (1.2 equiv)) in THF (2 M) was added dropwise to a DMA (0.75 mL) solution of Ni Cat. (3 mol %) and the alkyl halide (0.5 mmol) at −20 °C. After addition, the reaction mixture was further stirred for 30 min at −20 °C and then the solution was taken out from the cooling system and stirred for 10 min to warm up to room temperature.

Scheme 10. Alkyl−Alkyl Kumada Coupling Reactions Using Radical Clocks



	Yields:	
catalyst **20** :	8 %	32 %
catalyst **23** :	12 %	30 %

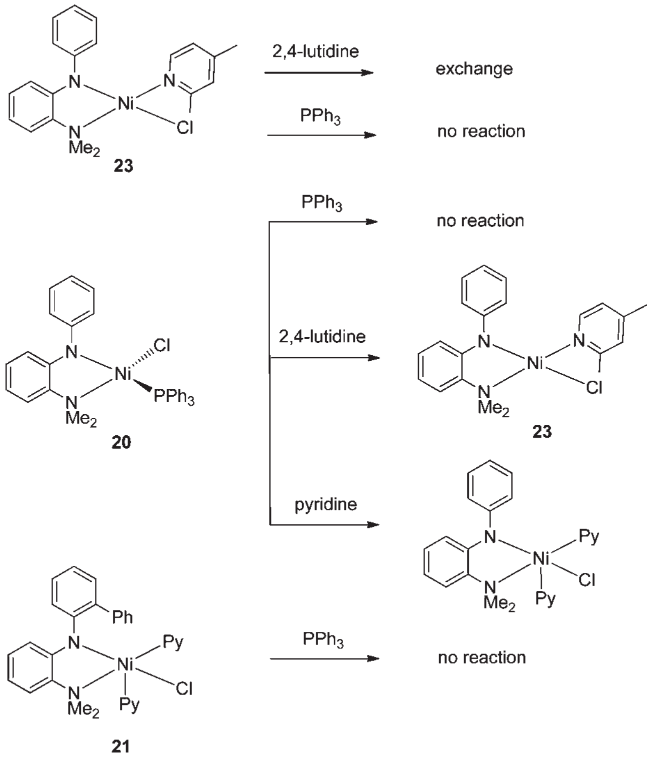


	Yields:	
catalyst **20** :	38 %	trace
catalyst **23** :	30 %	trace

active enough so noncatalytic side reactions prevailed. Complex **23** was sufficiently active, but its efficiency suffers from significant homocoupling. As a result, neither **20** nor **23** is a good catalyst for the coupling of primary alkyl halides. These two catalysts are thus best suited for coupling of secondary alkyl electrophiles. Fortunately, complex **1** is an excellent catalyst for the coupling of primary substrates. A combination of these three catalysts can cover a wide range of substrates.

2.5. Radical Clock. We reported earlier that activation of alkyl halides using catalyst **1** occurred via a radical mechanism. To ascertain that this is the case for catalysis using complexes **20** and **23**, we carried out coupling reactions using a radical clock, cyclopropylmethyl iodide (eq 6, Scheme 10). Despite that the overall coupling yields for this primary alkyl iodide were again modest (vide supra), the distribution of coupling product gave insight into the activation process of the substrates. Both ring-closed and ring-opened products were observed with both catalysts, and the ring-opened products dominated. These results confirmed that the activation of primary alkyl halide takes place via

Scheme 11. Ligand Substitution Reactions of Complexes 20, 21, and 23



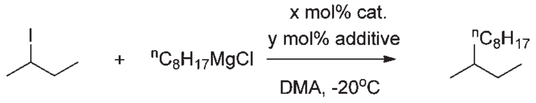
an alkyl radical intermediate. The recombination of the primary carbon radical with the catalyst has the rate that is slightly slower than the ring-opening rearrangement of cyclopropyl-methyl radical, which has a first-order rate constant of about 10^8 s^{-1}.[58]

A similar reaction was carried out with a radical clock that is a secondary alkyl halide, 6-iodohept-1-ene (eq 7, Scheme 10). Using **20** or **23** as the catalyst, the coupling with CH_3MgCl yielded the ring-closed product, 1-ethyl-2-methylcyclopentane, in yield of about 30%. The direct coupling product, 6-methylhept-1-ene, was produced in trace. Thus, the recombination of this acyclic secondary carbon radical with the catalyst is slower than the ring-closing rearrangement of the hept-6-en-2-radical, which has a first-order rate constant of about 10^5 s^{-1}.[58]

2.6. Substitution Reactions for Complexes ***20****,* ***21****, and* ***23****.* Precatalysts **20**, **21**, and **23** have tetrahedral, square-pyramidal, and square-planar structures, respectively. Unlike the pincer complex **1**, the pyridine, PPh_3, and lutidine ligands in these complexes might be subject to dissociation and ligand substitution during catalysis. To probe the stability of these complexes toward external donor ligands, substitution reactions were carried out.

The lutidine ligand in complex **23** could not be substituted by PPh_3, and the complex did not react with extra lutidine to form a 5-coordinate species (Scheme 11). However, the lutidine ligand could exchange with external lutidine. On the contrary, the PPh_3 ligand in **20** was prone to substitution (Scheme 11). It reacted with 2,4-lutidine to form **23** quantitatively. It also reacted with pyridine to form probably a 5-coordinate complex like **21**, according to NMR. It either did not undergo exchange reaction with PPh_3 or the exchange was too slow to be observed by NMR. Complex **21**, on the other hand, did not react with PPh_3.

Table 9. Inhibition Study for Catalysis by 20 and 23[a]



entry	cat	x	additive	y	conversion (%)	yield (%)
1	20	3			100	77
2	20	3	PPh_3	15	96	42
3	20	3	PPh_3	30	60	37
4	20	0.6			41	12
5	23	3			100	62
6	23	3	2,4-lutidine	15	83	36
7	23	3	2,4-lutidine	30	60	18
8	23	0.6			92	18

[a] Same conditions as in Table 2, except that the Grignard reagent was added at once.

The substitution reactions showed that pyridine and lutidine ligands bind more strongly than PPh_3 for the Ni−Pengamine system. Because ligand substitution can occur either via associate or dissociate mechanism, the formation of 3-coordinate species from **20** and **23** in the substitution and exchanges reactions could not be definitely confirmed.

2.7. Inhibition Study for Precatalysts ***20*** *and* ***23****.* To probe whether the PPh_3 and lutidine ligands in **20** and **23** dissociate from the Ni centers during catalysis, the effect of additional PPh_3 and lutidine on a representative coupling reaction (Table 9) was investigated.

As shown in Table 9, the addition of an excess amount of PPh_3 or 2,4-lutidine decreased both the conversions and the coupling yields for precatalyst **20** and **23**. The more PPh_3 or 2,4-lutidine added, the lower the conversions and yields (compare entries 2 and 3, and 6 and 7, Table 9). These results suggest that PPh_3 and 2,4-lutidine ligands in **20** and **23** dissociate from the Ni centers to form species with lower coordination numbers during catalysis. The addition of external of PPh_3 or 2,4-lutidine decreases the concentrations of these species, and thus diminishes the efficiency of catalysis. The effect of this addition should be similar to that of decreasing the loading of the catalysts. Indeed, a lower loading of catalysts led to lower conversions and yields as well (entries 4 and 8, Table 9).

DISCUSSION

1. Synthesis of Ni Complexes. The earlier reported pincer complex **1** was not very efficient for the coupling of secondary alkyl halides. We hypothesized that it was due to the steric encumbrance of the pincer ligand **2** on a square-planar Ni(II) ion. Ligands **3** and **4** were therefore synthesized in aim to reduce the steric hindrance of the ligands.

We thought that in Lockamine ligands **2**−**4**, the electronic property was dictated by both amino and amido donors. Bidentate Pengamine ligands **5**−**7** were then prepared as a new class of mixed amine−amide ligands. The combination of them with another monodentate ligand could lead to a wider control in the steric and electronic properties of ligands, while mimicking the main characters of pincer ligands **2**−**4**. It turned out that metalation of Pengamine ligands was not trivial, and the originally targeted products, square-planar Ni(II) complexes, could only be accessed employing $NiCl_2$(2,4-lutidine)$_2$ as the Ni precursor. The use of other

Ni salts resulted in various Ni complexes with tetrahedral or square pyramidal geometries.

2. Alkyl−Alkyl Kumada Coupling Using Preformed Ni Complexes. Having many defined and structurally characterized Ni complexes in hand, we carried out a structure−activity study for alkyl−alkyl Kumada coupling reactions. As complex **1** was efficient for the coupling of primary but not secondary alkyl halides, we focused on the coupling of secondary alkyl iodides.

Two representative reactions, that is, coupling of 2-butyl iodide with octylMgCl (Table 1, eq 1) and coupling of cyclohexyl iodide with butylMgCl (Table 1, eq 2) were used as test reactions for Ni complexes **1**, **17**−**25**. Pincer complex **1** had a low efficiency, and **17** and **18** had no efficiency. Most of the substrates remained intact after the reactions. Complexes **17** and **18** have protons as substituents on the amino donors which might be cleaved upon addition of basic Grignard reagents, leading to decomposition of the complexes. This might explain why they were completely inactive. Complex **19** is tetrahedral and has a Ni center coordinated by two molecules of bidentate ligand **6**. It was not catalytically active. We showed earlier that transmetalation of an alkyl group from the Grignard reagent to the Ni-halide was a key step in alkyl−alkyl coupling by catalyst **1** (Scheme 1). The inactivity of **19** might be attributed to the lack of a site for transmetalation. Complexes **20**−**25** all have such a site and they were indeed active for the cross coupling reactions. As shown in Table 2 and Figure 2, they performed better than complex **1** in the test reactions.

Selected catalysts (**1**, **20**, **22**−**25**) were further tested for the coupling of a wide range of secondary alkyl halides (Tables 2−4, 7). Analysis of the results shown in Tables 2 and 3 indicates that coordination number has a noticeable influence on the performance of these catalysts. Five-coordinate complexes **21** and **22** were less efficient than four-coordinate complexes **20** and **23**−**25**, due to lower conversions of the substrates. This could be explained considering that even if one pyridine ligand in **21** and **22** dissociates, the resulting 4-coordinate species are still less active than the 3-coordinate species from **23**−**25**. On the other hand, spin-state of the precatalysts has at most a small influence. Paramagnetic catalyst **20** is only slightly inferior to the diamagnetic catalysts **23**−**25** and is significantly more active than diamagnetic **1**.

Complexes **23**−**25** differ only in the substituents on the Pengamine ligands. It was then possible to examine the electrosteric effects of the ligands using these complexes. The bulk of the ligands is in the order of **23** < **24** < **25**, but the efficiency of the catalysis follows the opposite order, **23** > **24** > **25**. Thus, a less bulky ligand is better for the coupling of secondary alkyl halides. Considering on the other hand the donor property of ligands, the Ni center in **24** is more electron rich than in **23** which is more electron rich than in **25**. This is not the order of catalytic efficiency. Therefore, steric instead of electronic factor dictates the performance of catalysts **23**−**25**. The efficiency of the catalysts correlates inversely with the yields of elimination products (Tables S2−S4). Assuming that such products arise from metal-mediated β-H elimination, the results suggest that a bulkier ligand favors β-H elimination through steric pressure.

Precatalysts **20** and **23** differ in one ligand (PPh_3 versus 2,4-lutidine), coordination geometry (tetrahedral versus square-planar), and spin state (paramagnetic versus diamagnetic). Despite these differences, their catalytic efficiencies are similar. The ligand substitution reactions, and particularly the inhibition studies, showed that the PPh_3 and lutidine ligands dissociated from the Ni centers to form same species during catalysis. The small difference in catalytic performance is then attributed to the different reaction rates and equilibrium constants for ligand dissociation.

Compared to pincer complex **1**, complexes **20** and **23** are less efficient for coupling of primary alkyl halides, but much more efficient for coupling of secondary alkyl halides. The origin of this contrast in efficiency is probably related to the fact that with complex **1**, no ligand dissociates from the Ni center; with complexes **20** and **23**, the PPh_3 and lutidine ligands dissociate readily during catalysis.

For primary alkyl iodides, a main challenge for cross coupling is the noncatalytic side reactions such as I/Cl exchange and base-mediated elimination (Table 8). These side reactions are rapid so that to be efficient, a catalyst needs to activate the substrate quickly. The 4-coordinate catalytically active species from **1** is electron-rich, and has a high activity toward primary alkyl halides. For complexes **20** and **23**, the in situ generated 3-coordinate active species are less electron-rich, and react more slowly with primary alkyl halides. Using precatalyst **20**, the activation of alkyl halides is not fast enough to compete with noncatalytic side reactions. For catalyst **23**, the activation of alkyl halides is sufficiently fast, but homocoupling is severe and the overall efficiency drops. As the coupling takes place via an alkyl radical, the homocoupling products probably originate from bimolecular combination of the radicals.

The situation is different for the coupling of secondary alkyl halides. Activation of secondary substrates is slower than primary ones due to steric constraints. However, noncatalytic side reactions are no longer a problem (Table 6). Furthermore, bimolecular combination of secondary alkyl radicals is slow so homocoupling does not represent a trouble. Likely for steric reason, complex **1** has a very low activity for secondary substrates. It is therefore not a good catalyst. For complexes **20** and **23**, after the PPh_3 and 2,4-lutidine ligands dissociate, the resulting 3-coordinate species can activate secondary substrates in an appreciable rate (albeit slower than with primary substrates). The various Ni alkyl species involved in the coupling now suffer more from β-H elimination due to a more open Ni center. Indeed some olefinic products were formed. For precatalyst **20**, β-H elimination appears to be more facile and a substantial amount of olefin is produced. For this reason, **20** gives normally a cross-coupling yield of 50−70% for secondary substrates. Fortunately a good compromise was found for precatalyst **23** so that only a small amount of olefin is produced in the coupling reactions. It thus becomes a very good catalyst.

Dissociation of PPh_3 and lutidine from precatalysts **20** and **23** gives the same 3-coordinate Ni−Cl species. Yet, the catalytic performance of **20** and **23** is sometimes quite different. This difference might be attributed to the different reaction rates and equilibrium constants for ligand dissociation. Similar observations have been made in a series of Pd-PEPPSI complexes.[41] Some of the complexes differ only in the fourth pyridinyl ligand, which is shown to dissociate during catalysis. The catalytic performance of these complexes is often different.[41]

The overall catalytic cycle for reactions catalyzed by **20** and **23** should be similar to the one shown in Scheme 1. Transmetalation of a 3-coordinate Ni-halide species produces the corresponding Ni alkyl species, which reacts with an alkyl halide to give the coupling product. The results from coupling reactions of radical-probe type substrates indicate that the activation of alkyl halide occurs via a radical mechanism.

CONCLUSION

We describe here a structure−activity study for Ni-catalyzed alkyl−alkyl Kumada coupling. A large number of Ni(II) complexes with tridentate (Lockamine) and bidentate (Pengamine) mixed amino-amide ligands were prepared and structurally characterized. The complexes of the bidentate ligands span a wide range of coordination numbers, geometries, and spin states. The rich coordination chemistry of Ni with these bidentate ligands points to the difficulty in identifying catalytic active species in many Ni catalyzed cross coupling reactions, where the catalysts are mixtures of Ni salts and ligands. Such a problem can be alleviated by using preformed and well-defined coordination compounds as catalysts.

Compared to the previously reported pincer complex, $[(^{Me}N_2N)NiCl]$ (**1**), the newly prepared Ni complexes with the bidentate Pengamine ligands are better catalysts for the coupling of secondary alkyl halides, as long as they contain one transmetalation site. Four-coordinate compounds are more efficient than five-coordinate compounds. Coordination geometry and spin state of the precatalysts seem to have little influence.

For Kumada coupling of secondary alkyl halides, two excellent catalysts have been developed. Tetrahedral complex $[(^{H}NN)Ni(PPh_3)Cl]$ (**20**) is the best catalyst for coupling of bulky acyclic secondary alkyl iodides, with yields of 46−65%. Square-planar complex $[(^{H}NN)Ni(2,4\text{-lutidine})Cl]$ (**23**) is the best catalyst for coupling of cyclic and less bulky acyclic secondary alkyl iodides and bromides. A wide scope has been achieved using this catalyst, with typical yields of 60−87%. The origin of the efficiency was thoroughly probed and was related to the dissociation of the PPh_3 and 2,4-lutidine ligands during catalysis to form 3-coordinate active species. To the best of our knowledge, these two complexes are the most efficient catalysts for alkyl−alkyl Kumada coupling of nonactivated secondary alkyl halides.

ASSOCIATED CONTENT

Ⓢ Supporting Information. Experimental and crystallographic details, preparation procedures for substrates, detailed coupling procedures, all crystallographic files (cif). This material is available free of charge via the Internet at http://pubs.acs.org.

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