

Nickel-Catalyzed Diastereoselective
Alkyl–Alkyl Kumada Coupling Reactions

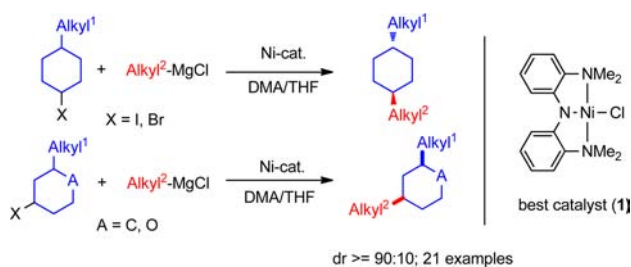
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ABSTRACT



A nickel pincer complex is found to catalyze alkyl–alkyl Kumada coupling reactions of 1,3- and 1,4-substituted cyclohexyl halides and tetrahydropyrans with an excellent diastereoselectivity. The mechanistic investigation of the coupling reactions provides evidence that the activation of alkyl halides is reversible.

Current advances in transition metal catalysis have transformed the challenging alkyl–alkyl cross-coupling into a synthetically applicable method for constructing new C–C bonds.^{1–3} The value of this method can be greatly enhanced if the reactions are rendered stereoselective. While remarkable progress has been made in enantioselective alkyl–alkyl coupling,² diastereoselective cross-coupling of

this type is largely unexplored. Until now, high diastereoselectivity was observed primarily for the coupling of 1,2-substituted cyclic substrates.³ Herein we report the nickel-catalyzed cross-coupling of 1,3- and 1,4-substituted cyclohexyl halides and tetrahydropyrans with alkyl Grignard reagents. High diastereoselectivity is achieved using a bulky catalyst and conformational control.

Knochel and co-workers recently developed highly diastereoselective Negishi coupling of 1,3- and 1,4-substituted cyclohexylzinc reagents with aryl, heteroaryl, and alkynyl halides.^{4,5} These pioneering studies demonstrated powerful diastereocontrol using the conformational preference of Pd-cyclohexyl intermediates, which were produced by transmetalation of a Pd catalyst with cyclohexyl zinc reagents. We reasoned that analogous nickel cyclohexyl intermediates might be generated through oxidative addition of cyclohexyl halides on a nickel catalyst. If the activation of cyclohexyl halides occurs via a radical process (which is often the case), then diastereoselective alkyl–alkyl

(1) (a) Netherton, M. R.; Fu, G. C. *Adv. Synth. Catal.* **2004**, *346*, 1525–1532. (b) Frisch, A. C.; Beller, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 674–688. (c) Hu, X. L. *Chem. Sci.* **2011**, *2*, 1867–1886. (d) Terao, J.; Kambe, N. *Acc. Chem. Res.* **2008**, *41*, 1545–1554. (e) Devasagayaraj, A.; Studemann, T.; Knochel, P. *Angew. Chem., Int. Ed.* **1995**, *34*, 2723–2725. (f) Giovannini, R.; Studemann, T.; Dussin, G.; Knochel, P. *Angew. Chem., Int. Ed.* **1998**, *37*, 2387–2390. (g) Netherton, M. R.; Dai, C. Y.; Neuschütz, K.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 10099–10100. (h) Valente, C.; Baglione, S.; Candito, D.; O'Brien, C. J.; Organ, M. G. *Chem. Commun.* **2008**, 735–737. (i) Keaton, K. A.; Phillips, A. J. *Org. Lett.* **2007**, *9*, 2717–2719.

(2) (a) Rudolph, A.; Lautens, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 2656–2670. (b) Glorius, F. *Angew. Chem., Int. Ed.* **2008**, *47*, 8347–8349. (c) Saito, B.; Fu, G. C. *J. Am. Chem. Soc.* **2008**, *130*, 6694–6695. (d) Lundin, P. M.; Fu, G. C. *J. Am. Chem. Soc.* **2010**, *132*, 11027–11029. (e) Owston, N. A.; Fu, G. C. *J. Am. Chem. Soc.* **2010**, *132*, 11908–11909. (f) Lu, Z.; Wilsily, A.; Fu, G. C. *J. Am. Chem. Soc.* **2011**, *133*, 8154–8157. (g) Zultanski, S. L.; Fu, G. C. *J. Am. Chem. Soc.* **2011**, *133*, 15362–15364.

(3) (a) Saito, B.; Fu, G. C. *J. Am. Chem. Soc.* **2007**, *129*, 9602–9603. (b) Lu, Z.; Fu, G. C. *Angew. Chem., Int. Ed.* **2010**, *49*, 6676–6678. (c) Gong, H. G.; Gagne, M. R. *J. Am. Chem. Soc.* **2008**, *130*, 12177–12183. (d) Yu, X. L.; Yang, T.; Wang, S. L.; Xu, H. L.; Gong, H. G. *Org. Lett.* **2011**, *13*, 2138–2141.

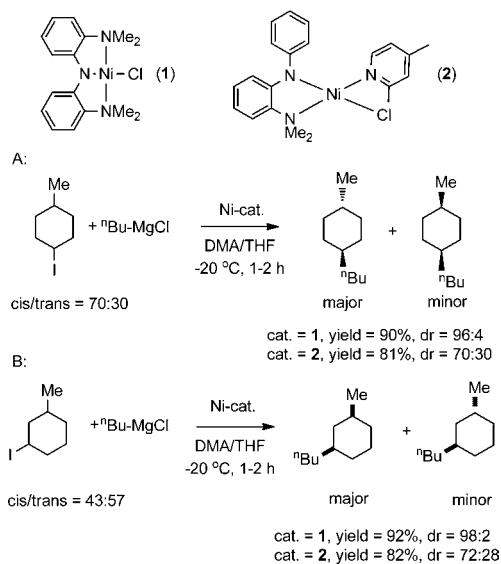
(4) Thaler, T.; Guo, L. N.; Mayer, P.; Knochel, P. *Angew. Chem., Int. Ed.* **2011**, *50*, 2174–2177.

(5) (a) Thaler, T.; Haag, B.; Gavryushin, A.; Schober, K.; Hartmann, E.; Gschwind, R. M.; Zipse, H.; Mayer, P.; Knochel, P. *Nat. Chem.* **2010**, *2*, 125–130. (b) Seel, S.; Thaler, T.; Takatsu, K.; Zhang, C.; Zipse, H.; Straub, B. F.; Mayer, P.; Knochel, P. *J. Am. Chem. Soc.* **2011**, *133*, 4774–4777.

coupling might be achieved by nickel catalysis (Scheme S1, Supporting Information).

Complexes **1** and **2** (Scheme 1) were chosen as catalysts after we previously showed them to be efficient for alkyl–alkyl Kumada coupling reactions.^{6–8} The coupling of 4-methylcyclohexyl iodide with ⁿBuMgCl was examined using the previously published protocols (Scheme 1A). Catalyst **2** was more efficient for the coupling of secondary alkyl halides, and a 3 mol % loading was sufficient for a high coupling yield. Comparatively, a 9 mol % loading of **1** was required for a similar coupling yield. *trans*-1-Butyl-4-methylcyclohexane was produced as the major isomer using either catalyst. The diastereoselectivity of the reaction was excellent using **1** as the catalyst (dr = 96:4) but was modest with **2** as the catalyst (dr = 70:30). The pincer N₂N ligand in **1** seems to be sufficiently bulky to induce high diastereoselectivity, while it was shown that the lutidine ligand dissociated from **2** during catalysis.⁸ The ligand environment of the nickel center might be considered less sterically hindered in **2** than in **1**, which could lead to a lower diastereoselectivity. The coupling of 3-methylcyclohexyl iodide with ⁿBuMgCl was also examined (Scheme 1B). *cis*-1-Butyl-3-methylcyclohexane was the major isomer using either catalyst. Catalyst **1** again enabled excellent diastereoselectivity (dr = 98:2), while catalyst **2** resulted in modest diastereoselectivity (dr = 72:28).

Scheme 1. Test Reactions in Diastereoselective Alkyl–Alkyl Kumada Coupling



(6) (a) Csok, Z.; Vechorkin, O.; Harkins, S. B.; Scopelliti, R.; Hu, X. L. *J. Am. Chem. Soc.* **2008**, *130*, 8156–8157. (b) Breitenfeld, J.; Vechorkin, O.; Corminboeuf, C.; Scopelliti, R.; Hu, X. L. *Organometallics* **2010**, *29*, 3686–3689.

(7) (a) Vechorkin, O.; Csok, Z.; Scopelliti, R.; Hu, X. L. *Chem.—Eur. J.* **2009**, *15*, 3889–3899. (b) Vechorkin, O.; Hu, X. L. *Angew. Chem., Int. Ed.* **2009**, *48*, 2937–2940.

(8) Ren, P.; Vechorkin, O.; von Allmen, K.; Scopelliti, R.; Hu, X. L. *J. Am. Chem. Soc.* **2011**, *133*, 7084–7095.

Table 1. Scope of Nickel-Catalyzed Diastereoselective Kumada Coupling of Alkyl Halides^a

| entry | alkyl-x | product | yield (%) ^b | dr |
|-------|---------|---------|------------------------|--------------------|
| 1 | 3a | | 80 ^b | 96:4 |
| 2 | 3a | | 80 ^b | 96:4 |
| 3 | 3a | | 87 ^b | 96:4 |
| 4 | 3a | | 65 ^{cd} | 94:6 |
| 5 | 3a | | 81 ^{cd} | 94:6 |
| 6 | 3b | | 77 ^b | 98:2 |
| 7 | 3b | | 93 ^b | 98:2 |
| 8 | 3b | | 87 ^b | 97:3 |
| 9 | 3b | | 79 ^{cd} | >99:1 ^e |
| 10 | 3b | | 69 ^{cd} | 96:4 |
| 11 | | | 74 ^c | 90:10 |
| 12 | | | 52 ^c | 90:10 |
| 13 | 3c | | 80 ^c | >99:1 ^e |
| 14 | 3c | | 65 ^c | >99:1 ^e |
| 15 | | | 77 ^{bf} | 94:6 |
| 16 | | | 79 ^{bf} | 95:5 |
| 17 | 3d | | 83 ^{bf} | 95:5 |
| 18 | 3d | | 88 ^b | 95:5 |
| 19 | 3a | | 62 ^{be} | 94:6 |
| 20 | 3b | | 91 ^{be} | 95:5 |
| 21 | 3e | | 87 ^b | 55:45 |

^aStandard conditions: The Grignard reagent (0.6 mmol) in THF (3.5 mL) was added by Syringe pump over 2 h to a solution of **1** (15 mg, 9 mol %) and alkyl halide (5 mmol) in DMA (0.75 mL) at -20°C . Reaction time: 30 min. ^bGC yield. ^cIsolated yield. ^dModified conditions: The Grignard reagent was added to a solution of **1** (15 mg, 9 mol %), TMEDA (25 μL), and alkyl halide (5 mmol) in THF (1 mL) at -20°C . ^eThe other isomer was not observed by NMR. ^fStandard conditions except at rt. ^gModified conditions except at rt.

The scope of the diastereoselective alkyl–alkyl Kumada coupling was explored using **1** as the catalyst (Table 1). A large number of alkyl Grignard reagents could be used, with generally high yields. For 1,4-substituted substrates, the major product is always the *trans*-isomer; for 1,3-substituted substrates, the major product is always the *cis*-isomer. The dr was nearly independent of the nature of the Grignard reagent. The coupling of ⁿPentylMgCl and ⁿOctylMgCl compared to the coupling of ⁿBuMgCl gave identical dr values, that is, 96:4 with 4-methylcyclohexyl iodide (entries 1–2, Table 1) and 98:2 with 3-methylcyclohexyl iodide (entries 6–7, Table 1). ^tBuMgCl was coupled with similar dr values (entries 3 and 8, Table 1). Grignard reagents with an aryl group were successfully coupled, although a modification of experimental conditions was required to obtain reasonable isolated yields (entries 4, 5, 9, 10, Table 1). An ester group was able to control the conformation of the nickel-cyclohexyl intermediates as well. Thus, coupling of ethyl 4-iodocyclohexanecarboxylate and ethyl 3-iodocyclohexanecarboxylate gave a dr of 90:10 (entries 11 and 12, Table 1). The lower dr compared to those of methyl-substituted derivatives is consistent with a lower *A* value for ester (*A* = 1.2–1.3) than for CH₃ (*A* = 1.74).⁹ This result confirms that the diastereoselectivity of the coupling reactions is linked to the conformational preference of the remote substituents. Gratifyingly, the coupling of tetrahydropyran derivatives was also successful (entries 13, 14, 17, 18, Table 1). The dr reached >99:1 for the coupling of **3c**, which is consistent with the high *A* value of the C₆H₅ group (*A* = 2.8 on cyclohexane and even larger on tetrahydropyran).⁹ Alkyl bromides could be coupled with high dr values (≥94:6, entries 15–18, Table 1). These reactions were conducted at rt to ensure high yields, and as a result, the dr values are slightly lower than those from the corresponding alkyl iodides at –20 °C. While this work focuses on alkyl–alkyl coupling, the method described here could be modified¹⁰ for diastereoselective alkyl–aryl coupling^{5,11} as well. Coupling of **3a** and **3b** with PhMgCl was achieved in good yields and high dr (entries 19 and 20, Table 1). When 3-methyl-1-iodocyclopentane (**3e**) was coupled to ⁿBuMgCl, the yield was 87%, but the dr was only 55:45 (entry 21, Table 1). The low diastereoselectivity is consistent with the similar energies of different conformers for cyclopentane derivatives.⁹

The origin of the diastereoselectivity was probed by several experiments. The diastereoselectivity was independent of the dr ratio of the substrates. When a 80:20 *cis/trans* mixture of 4-methylcyclohexyl iodide was coupled to ⁿBuMgCl, the dr of the product was 96:4, the same as that of the coupling of an 70:30 *cis/trans* mixture of 4-methylcyclohexyl iodide (Scheme 1A). Likewise, when a 20:80 *cis/trans* mixture of 3-methylcyclohexyl iodide was coupled

to ⁿBuMgCl, the dr of the product was the same (98:2) as that of the coupling of a 43:57 *cis/trans* mixture of 3-methylcyclohexyl iodide (Scheme 1B).

The coupling of 3-methylcyclohexyl iodide with ⁿBuMgCl was followed at partial conversions. ⁿBuMgCl was slowly added by a syringe pump over 1 h to the reaction mixture, and the quantities of the substrates and products were determined by GC (Figure 1, top). The dr of the product was 98:2 throughout the reaction. Interestingly, the amount of *cis*-3-methylcyclohexyl iodide increased initially before the eventual decrease to give the coupling product. The initial increase, albeit small, was always observed in multiple reaction trails. The amount of *trans*-3-methylcyclohexyl iodide decreased at all times.

To further confirm the initial increase of the amount of *cis*-3-methylcyclohexyl iodide, the kinetic profile of the coupling of 3-methylcyclohexyl iodide with ⁿBuMgCl was followed in the first 5 min. Because the coupling was fast and completed quickly after the addition of the Grignard

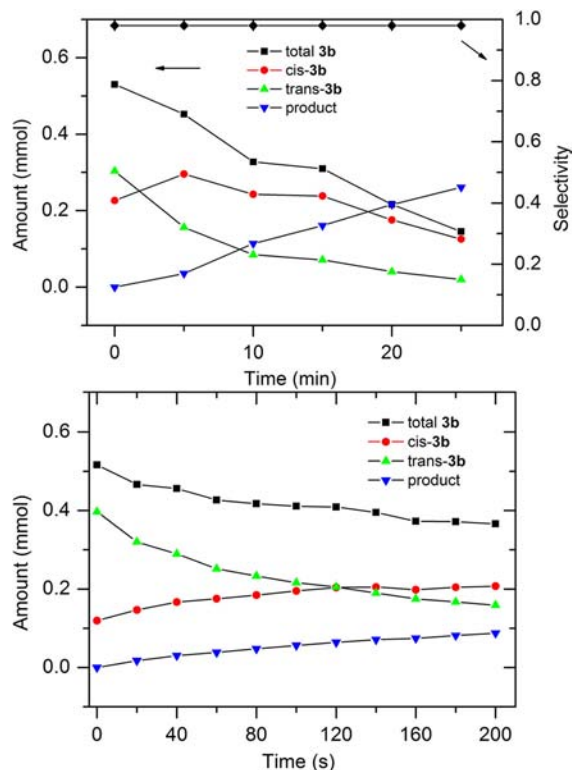


Figure 1. (Top) Reaction profile of the coupling of 3-methylcyclohexyl iodide with ⁿBuMgCl. (Bottom) Kinetic profile of the coupling of 3-methylcyclohexyl iodide with ⁿBuMgCl.

reagent, a 3-fold dilution in the initial concentrations of the reagents was necessary to enable the measurements. Again, the amount of *cis*-3-methylcyclohexyl iodide was found to increase during this time (Figure 1, bottom). Control experiments showed that MgBr₂ and NaI do not mediate the isomerization, pointing to an essential role of the nickel catalyst in the isomerization.

(9) Anslyn, E. V.; Dougherty, D. A. *Modern Physical Organic Chemistry*; University Science Books: Sausalito, CA, 2006.

(10) Vechorkin, O.; Proust, V.; Hu, X. L. *J. Am. Chem. Soc.* **2009**, *131*, 9756–9766.

(11) (a) Steib, A. K.; Thaler, T.; Komeyama, K.; Mayer, P.; Knochel, P. *Angew. Chem., Int. Ed.* **2011**, *50*, 3303–3307. (b) Nakamura, M.; Matsuo, K.; Ito, S.; Nakamura, B. *J. Am. Chem. Soc.* **2004**, *126*, 3686–3687.

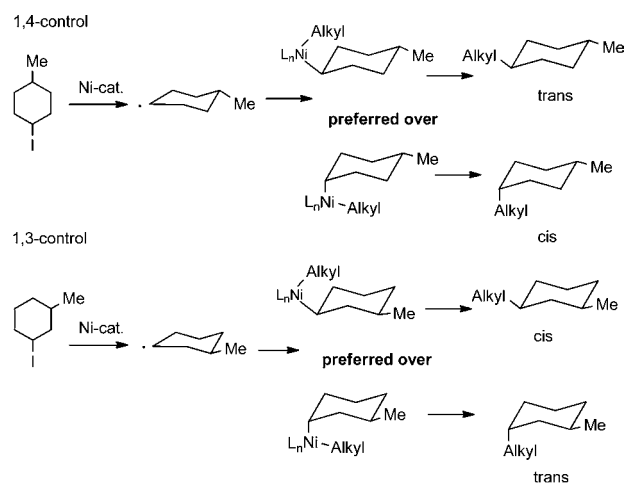


Figure 2. A rationale for observed diastereoselectivity.

These observations suggested that the activation of 3-methylcyclohexyl iodide was reversible in the current catalytic system. The reverse reaction, however, gave *cis*-3-methylcyclohexyl iodide as the major product because it is thermodynamically more stable. Therefore, at a low conversion, an increase in the quantity of *cis*-3-methylcyclohexyl iodide could be observed.

The aforementioned observations all point to the independence of the diastereoselectivity on the dr ratio of the substrates. We have reported evidence that the alkyl–alkyl Kumada coupling reactions catalyzed by **1** and **2** occurred via a radical process.^{7,8} A radical-based mechanism would be consistent with the results described here. It is noted that in the presence of a radical inhibitor, TEMPO, the yields of the coupling of 4-methylcyclohexyl iodide and 3-methylcyclohexyl iodide with ⁷BuMgCl catalyzed by **1** decreased to ca. 46%, but the dr remained the same.¹² Figure 2

(12) This result is only consistent with, but does not prove, that the reaction occurs via a radical process.

(13) (a) Hartwig, J. F. *Organotransition Metal Chemistry - From Bonding to Catalysis*; University Science Books: Sausalito, CA, 2010. (b) Taylor, B. L. H.; Jarvo, E. R. *J. Org. Chem.* **2011**, *76*, 7573–7576. (c) Wilsily, A.; Tramutola, F.; Owston, N. A.; Fu, G. C. *J. Am. Chem. Soc.* **2012**, *2012*, 5794–5797.

depicts a rationale for the diastereoselectivity of the coupling reactions, using **3a** and **3b** as examples. The activation of cyclohexyl halides by a nickel catalyst generated a cyclohexyl radical. The substituents would prefer an equatorial position. When the carbon radical recombines with a nickel center, the nickel-ligand fragment might take either the axial or the equatorial position. In general, the equatorial position is preferred, and the ratio of axially and equatorially bound nickel intermediates depends on the steric property of the catalyst. A concerted C–C reductive elimination is known to be stereo-conservative¹³ and would lead to the enrichment of the *trans* product in the 1,4-substituted substrates and the *cis*-product in the 1,3-substituted substrates.¹⁴

In conclusion, we have developed a nickel-catalyzed diastereoselective alkyl–alkyl Kumada coupling method for 1,3- and 1,4-substituted cyclohexyl halides and tetrahydropyrans. Excellent diastereoselectivity is achieved using the nickel pincer catalyst **1**. The diastereoselectivity is controlled by the conformational preference of the nickel-alkyl intermediates. Fortunately, we have also obtained evidence for the reversible activation of alkyl halide in the nickel catalysis, which provides significant information for mechanistic considerations of the nickel-catalyzed cross-coupling of nonactivated alkyl halides.¹⁵

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Supporting Information Available. Experimental details, additional entries, and characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

(14) Figure 2 explains the formation of the major isomer; the minor isomer might also be produced from a cyclohexyl radical where the methyl substituent is at an axial position.

(15) The details of the reversible activation of alkyl halides are subject to a following study.

The authors declare no competing financial interest.