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Nickel-Catalyzed C(sp²)–C(sp³) Kumada Cross-Coupling of Aryl Tosylates with Alkyl Grignard Reagents

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Abstract. Aryl tosylates are an attractive class of electrophiles for cross-coupling reactions due to ease of synthesis, low price, and the employment of C-O electrophiles, however, the reactivity of aryl tosylates is low. Herein, we report the Ni-catalyzed $C(sp^2)-C(sp^3)$ Kumada cross-coupling of aryl tosylates with primary and secondary alkyl Grignard reagents. The method delivers valuable alkyl arenes by cross-coupling with challenging alkyl organometallics possessing \beta-hydrogens that are prone to β -hydride elimination and homo-coupling. The reaction is catalyzed by an air- and moisture stable-Ni(II) precatalyst. A broad range of electronically-varied aryl including bis-tosylates, underwent tosylates, this transformation, and many examples are suitable at mild room temperature conditions. The combination of Ar-X cross-coupling with the facile Ar-OH activation/crosscoupling strategy permits for orthogonal cross-coupling with challenging alkyl organometallics. Furthermore, we demonstrate that the method operates with TON reaching 2000, which is one of the highest turnovers observed to date in Ni-catalyzed cross-couplings.

Keywords: nickel; cross-coupling; alkylation; C(sp²)– C(sp³) cross-coupling; Kumada cross-coupling

Introduction

Transition-metal-catalyzed cross-couplings have become a central method for the construction of C-C bonds in organic synthesis in both academic and settings.^[1–3] industrial While high level of sophistication has been achieved in methods that lead to the synthesis of biaryls,^[4] the cross-coupling using alkyl organometallics has been much less developed.^[5] The key challenges presented by alkylorganometallic reagents involve facile decomposition by β -hydride elimination and/or protodemetallation and slow transmetallation, which effectively limit the practicality of this transformation.^[6]

Simultaneously, the engagement of C–O electrophiles provides a powerful alternative to aryl halides in cross-coupling reactions.^[7,8] In particular, aryl tosylates are an attractive class of C–O

electrophiles for cross-coupling due to ease of synthesis, low price, high stability and the possibility for orthogonal employment of prevalent phenols, however, the reactivity of aryl tosylates is low.^[9]

Recently, considerable progress has been made in the use of C-O electrophiles as attractive coupling partners using sustainable and more economically viable Ni catalysts^[10] in combination with the lowand broadly available organomagnesium cost reagents, with the majority of methods focused on the synthesis of biaryls (Figure 1A).[11-13] By contrast, Ni-catalyzed $C(sp^2)$ – $C(sp^3)$ cross-coupling of C–O electrophiles has proven more challenging with only few reports existing in this arena (Figure 1B).^[14] To our knowledge, there are no examples which employ aryl tosylates in the Ni-catalyzed C(sp²)-C(sp³) crosscoupling with alkylmagnesium reagents,^[9-17] a notable deficiency in the cross-coupling toolbox, which underlines the challenge of developing $C(sp^2)$ -C(sp³) cross-couplings of aryl tosylates.

Herein, we report the Ni-catalyzed $C(sp^2)-C(sp^3)$ Kumada cross-coupling of aryl tosylates with primary and secondary alkyl Grignard reagents (Figure 2). Notable features of our study include: (1) The method delivers valuable alkyl arenes by cross-coupling with challenging alkyl organometallics possessing βhydrogens that are prone to β -hydride elimination and homo-coupling using C-O electrophiles. (2) The reaction is catalyzed by an air- and moisture stable-Ni(II) precatalyst under conditions that do not lead to hydrolysis, which is the main side reaction in the cross-coupling of C-O electrophiles.^[18] (3) A broad range of electronically-varied aryl tosvlates. including bis-tosylates, underwent this transformation, and many examples are suitable at mild room temperature conditions. (4) We demonstrate that the combination of Ar-X cross-coupling with the facile Ar-OH activation/cross-coupling strategy permits for orthogonal cross-coupling with challenging alkyl organometallics. The practical utility has been additionally demonstrated in the synthesis of liquid crystals and pharmaceutical intermediates. (5) We demonstrate that the method operates with TON reaching 2000, which is one of the highest turnovers

observed to date in Ni-catalyzed cross-couplings.

Further, it is worthwhile to note major cross-coupling advantages of the of C-0 electrophiles.^[7a-g] Specifically, bench-stable C-O electrophiles represent orthogonal precursors in organic synthesis to aryl halides. Furthermore, the use of oxygen-based electrophiles allows for reducing the amount of toxic halide waste produced during the cross-coupling. Moreover, phenols are more abundant that aryl halides, and often are derived from a different pool of precursors than aryl halides. Finally, C–O electrophiles allow for complementary strategies in organic synthesis, which altogether is particularly important from an industrial standpoint. In this context, the cross-coupling of C-O electrophiles with possessing β-hydrogens organometallics is particularly challenging and very few methods have been reported.^[5a,14] Base-metal catalysis^[14] holds promise for the cross-coupling of C–O electrophiles with alkyl organometallics; however, the use of iron has been less effective to date. In this respect, the use of well-defined Ni(II) precatalysts that are benchstable, operate with high process economy and obviate the use of excess of ancillary ligands is particularly attractive.^[2a,b,18] Since hydrolysis of C-O electrophiles is the major side-reaction in the crosscoupling, facile activation of Ni(II) precatalysts enabling the cross-coupling under mild conditions could lead to the benefits of using base-metal catalysts in this cross-coupling platform.



Figure 1. Nickel-Catalyzed Kumada Cross-Coupling of O-Electrophiles with Aryl and Alkylmagnesium Reagents.



Figure 2. Nickel-Catalyzed $C(sp^2)$ – $C(sp^3)$ Cross-Coupling of Aryl Tosylates with Alkyl Grignard Reagents (this study).

Results and Discussion

We began our studies by examining the proposed cross-coupling using 1-naphthyl tosylate as an electrophilic component and *n*-butylmagnesium chloride as a nucleophile in the presence of various

Table 1. Optimization of Ni-Catalyzed C(sp²)–C(sp³)Cross-Coupling with Alkyl Grignard Reagents.^[a]

| | OTs | | | | | C₄H ₉ |
|---------------------------------------|--|--------|--------------|------|-------|------------------|
| | | | [Ni], ligand | | | |
| + C ₄ H ₉ -MgCl | | | conditio | ns | | |
| Entry | Catalyst | Ligand | Ligand | Т | time | Viald |
| Enuy | Catalyst | Liganu | Liganu | 1 | ume | Tielu |
| | | | [equiv] | [°C] | | [%][b] |
| 1 | Ni(dppe)Cl ₂ | - | - | 23 | 3 h | 94 |
| 2 | Ni(acac) ₃ | - | - | 23 | 3 h | 5 |
| 3 | Ni(acac) ₃ | - | - | 65 | 3 h | 6 |
| 4 | Ni(acac)3 | IMes | 0.10 | 23 | 3 h | 7 |
| 5 | NiCl ₂ | IMes | 0.10 | 23 | 3 h | <5 |
| 6 | Ni(acac)3 | ICy | 0.10 | 23 | 3 h | <5 |
| 7 | NiCl ₂ | ICy | 0.10 | 23 | 3 h | <5 |
| 8 | Ni(acac) ₃ | IPr | 0.20 | 65 | 3 h | 23 |
| 9 | Ni(PPh ₃) ₂ Cl ₂ | - | - | 23 | 3 h | 9 |
| 10 | Ni(PCy ₃) ₂ Cl ₂ | - | - | 23 | 3 h | 8 |
| 11 | Ni(dppf)Cl ₂ | - | - | 23 | 3 h | 38 |
| 12 | Ni(dppp)Cl ₂ | - | - | 23 | 3 h | 91 |
| 13 ^[c] | Ni(dppe)Cl ₂ | - | - | 23 | 3 h | 95 |
| 14 ^[d] | Ni(dppe)Cl ₂ | - | - | 23 | 3 h | 92 |
| 15 ^[e] | Ni(dppe)Cl ₂ | - | - | 23 | 3 h | 93 |
| 16 | Ni(dppe)Cl ₂ | - | - | 23 | 5 min | 90 |
| $17^{[f]}$ | Ni(dppe)Cl ₂ | - | - | 23 | 3 h | 88 |
| 18 | - | - | - | 65 | 3 h | - |

^[a]Conditions: **1a** (0.25 mmol), [Ni] (10 mol%), THF (0.15 M), C₄H₉MgCl (2.0 equiv, 2.0 M, THF), *T*, 3 h, RMgCl added dropwise over 2-3 s. ^[b]Determined by ¹H NMR and/or GC-MS. ^[c]Et₂O as solvent. ^[d]PhMe as solvent ^[e]Dioxane as solvent. ^[f]C₄H₉MgCl (1.20 equiv). IMes = 1,3-bis(2,4,6-trimethylphenyl)imidazolium; ICy = 1,3-bis(2,6-diisopropylphenyl)imidazolium.

Ni-based catalytic systems (Table 1). After extensive optimization, we were delighted to find that the desired cross-coupling product could be obtained in 94% yield using commercially-available, bench- and air-stable Ni(dppp)Cl₂ (entry 1).^[18] Under the optimized conditions, <2% of hydrolysis and <2% of reduction products is observed. Starting material and homocoupling products are not detected. At the initial stage of reaction development, various catalytic systems based on [Ni]-NHC were tested (entries 2-8).^[19] However, these catalysts resulted in very low reaction efficiency (typically, <10%) with the hydrolysis (1-naphthol) and reduction (naphthalene) products as the major reaction products. WC discovered that under these conditions, [Ni]phosphane catalytic systems showed much better reaction efficiency (entries 9-12). Interestingly, bidentate phosphines afforded the desired coupling significantly higher yields product in than monodentate (PPh₃, PCy₃) (entries 9-10), with dppe and dppp as the preferred ligands for the crosscoupling (entry 1 and entry 12). Using monodentate ligands, hydrolysis and reduction were found to be the major reaction pathways, indicating inefficient stabilization of the Ar-[Ni]-alkyl intermediate under these conditions.^[5a] A brief investigation of solvents

indicated that the reaction can be readily performed in various solvents (entries 13-15). Control experiments revealed that the reaction is complete (>95% conversion) after 5 minutes at room temperature (entry 16) (48% conversion after 1 min, <5% at 0 °C) (*vide infra*). Importantly, high reaction efficiency was observed using close to equimolar ratio of the reagents (entry 17). Finally, no reaction was observed in the absence of the Ni-catalyst with the mass balance corresponding to the hydrolysis product (entry 18).

Table 2. Nickel-Catalyzed C(sp²)–C(sp³) Cross-Coupling of Aryl Tosylates with Alkyl Grignard Reagents.^[a]

| Ar- | C ₄ H ₉ —MgC (entries 1-6 | | CI 6) | Ni(dppe)Cl ₂ | Ar — C | ₄ <mark>H</mark> 9 1-6) |
|-------------------|--|---|----------|---|----------------------------------|---------------------------------------|
| 1 | | C ₁₄ H ₂₉ —MgCl (entries 7-10) | | THF, 23 °C Ar — C ₁₄ + (entries 7- 2 | | ₄ H ₂₉ 7-10) |
| Entry | Sub | strate | 2 | Produ | ct | Yield (%) |
| 1 ^[a] | | OTs | 2a | C | ₄H ₉ | 92 |
| 2 ^[a] | | OTs | 2b | | C₄H ₉ | 94 |
| 3 ^[a] | | OTs | 2c | | C₄H ₉ | 87 |
| 4 ^[b] | MeO ₂ C | ТО | s 2d | MeO ₂ C | C ₄ H ₉ | 64 |
| 5 ^[b] | NC | OTs | 2e | NC | C ₄ H ₉ | 66 |
| 6 ^[c] | Ph | OTs | 2f | Ph | ,C₄H ₉ | 80 |
| 7 ^[d] | F ₃ C | OTs | 2g | F ₃ C | ,C ₁₄ H ₂₉ | 93 |
| 8 ^[e] | MeO | OTs | 2h | МеО | C ₁₄ H ₂₉ | 62 |
| 9 ^[f] | F ₃ C | OTs CF ₃ | 2i | F ₃ C | ,C ₁₄ H ₂₉ | 70 |
| 10 ^[f] | MeO | OTs | 2j | MeO | C ₁₄ H ₂₉ | 70 |

[a] Conditions: **1** (0.25 mmol), Ni(dppe)Cl₂ (10 mol%), THF (0.15 M), C₄H₉MgCl (2.0 equiv, 2.0 M, THF), 23 °C, 3-24 h, RMgCl added dropwise over 2-3 s. [b] C₄H₉MgCl (1.05 equiv). [c] 65 °C. [d] Et₂O. [e] C₁₄H₂₉MgCl (4.0 equiv), 65 °C. [f] C₁₄H₂₉MgCl (2.0 equiv), Et₂O. See SI for details.

With the optimized reaction conditions in hand, we examined the preparative scope of the Nicatalyzed alkylative cross-coupling of aryl tosylates (Table 2). As shown, we found that a broad range of electronically-varied aryl tosylates serves as suitable cross-coupling partners in this protocol. Notably,

Table 3. Nickel-Catalyzed C(sp²)–C(sp³) Cross-Coupling of Aryl Tosylates with Alkyl Grignard Reagents.^[a]

| OTs | | | | R | |
|-------------------|-------------------------------------|------------|--|-------------------|--|
| | | | Ni(dppe)Cl ₂ | | |
| | | | THF, 23 °C | 2 | |
| Entry | RMgX | 2 | Product | Yield (%) | |
| 1 ^[a] | C ₄ H ₉ MgBr | 2a | $R=C_4H_9$ | 92 | |
| 2 ^[a] | EtMgBr | 2k | $\mathbf{R} = \mathbf{E}\mathbf{t}$ | 81 | |
| 3 ^[a] | C ₆ H ₁₃ MgBr | 21 | $R=C_6H_{13}$ | 88 | |
| 4 ^[a] | C ₆ H ₁₃ MgCl | 21 | $R=C_6H_{13}$ | 84 | |
| 5 ^[a] | $C_{14}H_{29}MgBr$ | 2m | $R = C_{14}H_{29}$ | 95 | |
| 6 ^[a] | CyMgBr | 2n | $\mathbf{R} = \mathbf{C}\mathbf{y}$ | 82 | |
| 7 ^[a] | ^c PentylMgBr | 20 | $R = ^{c}Pentyl$ | 92 | |
| 8 ^[a] | ⁱ PrMgBr | 2p | $\mathbf{R} = {}^{i}\mathbf{P}\mathbf{r}$ | 75 | |
| 9 ^[a] | ⁱ PrMgCl | 2p | $\mathbf{R} = {}^{\mathrm{i}}\mathbf{P}\mathbf{r}$ | 75 | |
| $10^{[b]}$ | BnMgBr | 2q | $\mathbf{R} = \mathbf{B}\mathbf{n}$ | 61 | |
| 11 ^[a] | PhenethylMgBr | 2r | R = Phenethyl | 91 | |
| 12 ^[a] | ⁱ BuMgBr | 2s | $\mathbf{R} = {}^{i}\mathbf{B}\mathbf{u}$ | 87 | |
| 13 ^[c] | MeMgBr | 2t | $\mathbf{R} = \mathbf{M}\mathbf{e}$ | 87 | |
| 14 ^[a] | Np-MgBr | 2u | $\mathbf{R} = \mathbf{N}\mathbf{p}$ | 94 | |
| 15 ^[a] | ^t BuMgBr | 2 v | $\mathbf{R} = \mathbf{H}$ | 74 ^[d] | |

[a] Conditions: **1** (0.25 mmol), Ni(dppe)Cl₂ (10 mol%), THF (0.15 M), RMgX (2.0 equiv, THF), 23 °C, 3 h, RMgX added dropwise over 2-3 s. [b] 65 °C. [c] 65 °C, 24 h. [d] Napthahlene. See SI for details. Np = neopentyl.

various naphthyl (entries 1-2) and phenanthrenyl (entry 3) tosylates, including substitution with electrophilic carboxylic-acid derived functional groups, such as nitriles and esters (entries 4-5) proved highly effective for the cross-coupling.^[20] The alkyl products of these reactions constitute common motifs in electronic, pharmaceutical and liquid crystal applications (vide infra). Pleasingly, unactivated arenes are readily accommodated as coupling partners (entry 6), demonstrating that the reaction is not limited to naphthyl electrophiles, which is a of Ni-catalyzed common limitation C-O activation/cross-coupling methods.^[7c] Furthermore, both electron-withdrawing (entry 7) and even electron-donating (entry 8) groups are tolerated on the electrophilic component. Full selectivity for the OTs cross-coupling has been observed in the latter case. Importantly, 3,5-disubstitution with electronwithdrawing (entry 9) and electron-donating (entry 10) groups is also compatible, thus demonstrating the versatility and potential applications of the protocol.

We further note that the cross-coupling of phenyl tosylate proceeds in 62% yield. The use of Ni(II) salts is also possible. For example, the cross-coupling of **2a** using Ni(acac)₂ (10 mol%)/dppe (10 mol%) proceeds in 91% yield. The use of NiCl₂/dppe is inefficient due to low solubility. It is worthwhile to note that preformed, bench-stable Ni(II) precatalysts such as NiCl₂(dppe) are highly advantageous in cross-coupling because they favor cross-coupling

economy and obviate the need for excess of ancillary ligands which may hinder the catalysis.^[2a,b,18] The alkylbenzene products of these reactions are important intermediates in agrochemical and pharmaceutical industries.^[21]

Next, we examined the scope with respect to the Grignard reagent (Table 3). Variation in the *n*-alkyl group (entries 1-5) is possible without detrimental loss of reactivity due to β -hydride elimination and protodemetallation.^[5a] Both alkylmagnesium chlorides and alkylmagnesium bromides (entries 3-4) are effective cross-coupling partners.^[22] Pleasingly, incorporation of the secondary Grignard reagents (R = cyclohexyl, cyclopentyl, isopropyl) (entries 6-9) results in regioselective cross-coupling without isomerization, which is a major side reaction in related protocols.^[14a] Furthermore, challenging benzyl (entry 10) as well as prone to β -hydride elimination phenethyl (entry 11) and isobutyl (entry 12) Grignard reagents are feasible cross-coupling partners. The scope was further extended to include methyl (entry 13) and sterically-demanding neopentyl (entry 14) Grignard reagents. These examples demonstrate that β -hydride elimination is not required to activate the catalyst. However, the attempted cross-coupling of a tert-butyl Grignard resulted in the reduction to afford naphthalene, as expected. The most reliable method to afford *tert*-alkyl-benzenes at present is the elegant protocol reported by Biscoe and co-workers.^[19]

Reactions of these tosylates readily afford bisalkylated products when two electrophilic groups are present in the electrophile structure (Scheme 1). This cross-coupling includes deactivating 2,6- as well as 2,7-substitution using bis-naphthols as starting materials (Scheme 1A-B). Alternatively, readily available chlorinated naphthols are feasible crosscoupling precursors (Scheme 1C). Polyalkylated naphthalenes, such as **2w-2y** are an important class of products in organic semiconductors.^[23]

Pleasingly, the combination of Ar-X crosscoupling with the facile Ar–OH activation/crosscoupling permits for orthogonal cross-coupling with challenging alkyl organometallics (Scheme 2). This orthogonal strategy underlines the potential of C–O electrophiles in combination with the availability and ready synthesis of tosylates in cross-coupling.



Scheme 1. Double Nickel-Catalyzed C(sp²)–C(sp³) Cross-Coupling of Aryl Tosylates with Alkyl Grignard Reagents.



Scheme 2. Sequential Nickel-Catalyzed C(sp²)–C(sp³) Cross-Coupling with Alkyl Grignard Reagents.



liquid crystals





Scheme 4. Synthesis of S1P₁ Antagonists.

The synthetic utility of this Ni-catalyzed crosscoupling with alkyl organometallics has been further demonstrated in the rapid synthesis of a liquid crystal (Scheme 3)^[24] and an intermediate in the synthesis of S1P1 antagonists (Scheme 4).^[25] The approach using C–O electrophiles is distinguished from current methods by the orthogonal availability of phenols,

Table 4. Ni-Catalyzed C(sp²)–C(sp³) Cross-Coupling atLow Catalyst Loading.^[a]

| $\begin{array}{c} \text{OTs} \\ \hline \\ \hline \\ 1 \end{array} + C_4H_9 - MgCl \hline \\ \hline \\ \text{conditions} \end{array}$ | | | | • | C ₄ H ₉ 2 |
|---|-------------------------|-------|------|------|------------------------------------|
| Entry | Catalyst | Mol% | Т | time | Yield |
| | | | [°C] | | [%] ^[b] |
| 1 | Ni(dppp)Cl ₂ | 1 | 23 | 3 h | 82 |
| 2 | Ni(dppe)Cl ₂ | 1 | 23 | 3 h | 96 |
| 3 | Ni(dppe)Cl ₂ | 0.10 | 23 | 3 h | 36 |
| 4 | Ni(dppe)Cl ₂ | 0.10 | 65 | 24 h | 62 |
| 5 ^[c] | Ni(dppe)Cl ₂ | 0.10 | 23 | 24 h | 98 |
| 6 ^[c] | Ni(dppe)Cl ₂ | 0.050 | 23 | 24 h | 98 |

| 7 ^[c] | Ni(dppe)Cl ₂ | 0.050 | 23 | 10 min | 21 |
|-------------------|-------------------------|-------|----|--------|----|
| 8 ^[c] | Ni(dppe)Cl ₂ | 0.050 | 23 | 1 h | 91 |
| 9 ^[c] | Ni(dppe)Cl ₂ | 0.010 | 23 | 24 h | 17 |
| 10 ^[c] | Ni(dppe)Cl ₂ | 0.010 | 65 | 24 h | 27 |
| () | | | | | |

^[a]Conditions: **1a** (1.0 equiv), [Ni] (0.010-1.0 mol%), THF (0.15 M), C₄H₉MgCl (2.0 equiv, 2.0 M, THF), *T*, 1-24 h, RMgCl added dropwise over 2-3 s. ^[b]Determined by ¹H NMR and/or GC-MS. ^[c]THF (1.0 M).



Scheme 5. Large Scale Cross-Coupling.



Scheme 6. Mechanistic Studies.

and should be of significant utility in implementing synthetic sequences. $\ensuremath{^{[26]}}$

Intrigued by the remarkable versatility of the Nicatalyzed cross-coupling, we were interested in testing TON of this novel method. At present, one of the major limitations of Ni-catalyzed cross-couplings is the requirement for high catalyst loading, which prevents broad industrial use.^[27] Remarkably, we found that the method operates with TON reaching 2000 (Table 4, entries 1-6), which is one of the highest turnovers observed to date in Ni-catalyzed cross-couplings.^[1–3,7,10,11] Furthermore, TOF of 2500 h⁻¹ was determined under these conditions (entries 7-8), consistent with efficient catalysis.

To demonstrate the preparative utility, gram scale reaction was performed at low catalyst loading (0.10 mol%), affording the cross-coupling product in 98% yield.

Preliminary mechanistic studies were conducted (Scheme 6). Competition between aryl tosylates and chlorides established that tosylates and chlorides show similar reactivity (Scheme 6A), which bodes well for future applications using the developed catalyst system. Control experiments using TEMPO as a radical scavenger gave the desired product without decrease in catalytic efficiency under standard conditions, suggesting that the reaction does not involve a radical process (Figure 6B). Further studies to elucidate the mechanism are ongoing.

Additional competition experiments were conducted to determine the order of reactivity between I, Br, Cl vs. OTs. We found that in THF the cross-coupling reactivity order is as follows: OTs \approx Cl < Br < I (1a:1-Np-Cl = 50:50; 1a:1-Np-Br = 48:52; 1a:1-Np-I = 40:60). The selectivity is independent on the solvent used: toluene: 1a:1-Np-Cl = 49:51; 1a:1-Np-Br = 43:57; 1a:1-Np-I = 42:58; Et₂O: 1a:1-Np-Cl = 49:51; 1a:1-Np-Br = 45:55; 1a:1-Np-I = 42:58. Based on the experimental data and literature precedents,^[5a,10a,18] we propose that a Ni(0)/(II) cycle is involved in the reaction.

Conclusion

In conclusion, we have developed a novel protoco¹ for Ni-catalyzed $C(sp^2)$ – $C(sp^3)$ Kumada crosscoupling of aryl tosylates with primary and secondary alkyl Grignard reagents. This transformation gives access to valuable alkyl-arenes using challenging alkyl organometallics possessing β -hydrogens that are prone to β -hydride elimination and homocoupling. A variety of aryl tosylates, including bistosylates, underwent this transformation. The practical value of this method is highlighted by the use of air- and moisture stable-Ni(II) precatalyst. The advantages of the method include the ease of synthesis, low price and high stability of C-O electrophiles as well as low-cost and broad availability of organomagnesium reagents. The synthetic potential of this transformation has been demonstrated in orthogonal Ar-X cross-coupling/Ar-OH activation/cross-coupling with challenging alkyl organometallics as well as in the synthesis of liquid crystals and pharmaceutical intermediates. The TON demonstrated in this reaction represents one of the highest turnovers observed to date in Ni-catalyzed cross-couplings. Ongoing work is focused on expanding the scope of this cross-coupling and further extension to broad classes of coupling partners. These studies will be reported in due course.

Experimental Section

General Information. General methods have been published.^[14d]

General Procedure for Nickel-Catalyzed $C(sp^2)-C(sp^3)$ Cross-Coupling. An oven-dried vial equipped with a stir bar was charged with an aryl tosylate substrate (neat, typically, 0.25 mmol, 1.0 equiv) and Ni(dppe)Cl₂ (typically, 10 mol%), placed under a positive pressure of argon and subjected to three evacuation/backfilling cycles under vacuum. Tetrahydrofuran (0.15 M) and a solution of Grignard reagent (typically, 2.0 equiv) were sequentially added with vigorous stirring at room temperature, and the reaction mixture was stirred for the indicated time at 23 °C. After the indicated time, the reaction mixture was diluted with HCl (1.0 N, 1.0 mL) and Et₂O (1 x 20 mL), the organic layer was extracted with HCl (1.0 N, 2 x 5 mL) and NaOH (1.0 N, 2 x 5 mL), the organic layers were combined, dried and concentrated. A sample was analyzed by ¹H NMR (CDCl₃, 400 MHz) and/or GC-MS to obtain conversion, yield and selectivity using internal standard and comparison with authentic samples. Purification by chromatography on silica gel (EtOAc/hexanes) afforded the title product.

Representative Procedure for Nickel-Catalyzed C(sp²)– **C(sp³) Cross-Coupling. 1.0 g Scale.** An oven-dried, twonecked flask (100 mL) equipped with a stir bar was charged with naphthalen-1-yl 4-methylbenzenesulfonate (1.00 g, 3.35 mmol, 1.0 equiv) and Ni(dppe)Cl₂ (1.77 mg, 0.10 mol%). A solution of n-C₄H₉MgCl (2.0 M in THF, 3.35 mL, 2.0 equiv) was added dropwise with vigorous stirring at room temperature and the reaction mixture was stirred for 24 h at 23 °C. After the indicated time, the reaction mixture was diluted with HCl (1.0 N, 10 mL) and Et₂O (1 x 100 mL), the organic layer was extracted with HCl (1.0 N, 2 x 15 mL) and NaOH (1.0 N, 2 x 15 mL), the organic layers were combined, dried and concentrated. A sample was analyzed by ¹H NMR (CDCl₃, 400 MHz) and GC-MS to obtain conversion, yield and selectivity using internal standard and comparison with authentic samples. Purification by chromatography on silica gel (EtOAc/hexanes) afforded the title product; 98% (0.603 g).

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FULL PAPER

Nickel-Catalyzed C(sp²)–C(sp³) Kumada Cross-Coupling of Aryl Tosylates with Alkyl Grignard Reagents

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[■ challenging alkyl nucleophiles] [■ up to 98% yield] [■ practical & mild conditions] [■ broad scope] [■ base metal catalysis] [■ high TON]