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Ni/Co-Catalyzed Homo-Coupling of Alkyl Tosylates

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Abstract: A direct reductive homo-coupling of alkyl tosylates has been developed by employing a combination of nickel and nucleophilic cobalt catalysts. A single-electron-transfer-type oxidative addition is a pivotal process in the well-established nickel-catalyzed coupling of alkyl halides. However, the method cannot be applied to the homo-coupling of ubiquitous alkyl tosylates due to the high-lying σ*(C–O) orbital of the tosylates. This paper describes a Ni/Co-catalyzed protocol for the activation of alkyl tosylates on the construction of alkyl dimers under mild conditions.

Keywords: homo-coupling; S_N2-type oxidative addition; transalkylation; alkyl tosylates; cobalt catalyst; nickel catalyst

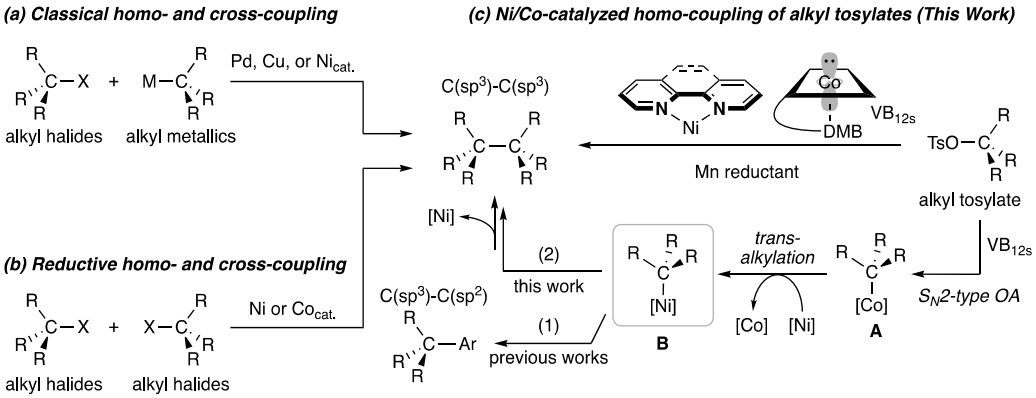
1. Introduction

The development of synthetic methods for carbon–carbon bonds is one of the central challenges in organic synthesis. Particularly, C(sp^3)–C(sp^3) linkages are the most abundant carbon skeleton rather than C(sp^3)–C(sp^2) and C(sp^2)–C(sp^2) linkages in naturally occurring products and pharmaceuticals [1]. In the past few decades, a great advance has been made in the transition-metal-catalyzed C(sp^3)–C(sp^3) coupling between alkyl halides and alkyl metallic reagents (alkyl-MgX, -ZnX, and -BR_2) by Pd [2–4], Cu [5,6], and Ni [7–13] catalysts (Scheme 1a). However, alkyl metallic reagents are generally prepared from the corresponding alkyl halides and are sensitive to polar functional groups. Although alkyl-BR_2 is stable and available in numerous cross-couplings, they require basic additives to activate for the transmetalation of Alkyl-BR_2. These inherent reactivities place limitations on synthesizable C(sp^3)–C(sp^3) linkages. Therefore, the development of more tractable and practical protocols for the formation of C(sp^3)–C(sp^3) linkages without alkyl metallic reagents is still in high demand.

In contrast to the above traditional approaches for the C(sp^3)–C(sp^3) linkages, the nickel or cobalt-catalyzed reductive cross- [14–19] and homo-coupling [20–23] between two alkyl halides have been intensively studied over the past decade (Scheme 1b). In these transformations, a single-electron-transfer (SET) process has been adopted for the initial activation step of alkyl halides, enabling a generation of high-valent dialkyl transition-metal intermediates to lead to C(sp^3)–C(sp^3) linkages via a rapid reductive elimination without a competitive β-H elimination. Despite recent significant progress on such reductive couplings, their alkyl sources have been limited to alkyl halides. Thereby, accessible C(sp^3)–C(sp^3) linkages utilizing the reductive coupling intrinsically depend on the availability of alkyl halides. Compared with alkyl halides, alkyl alcohols are present in a diverse set of natural products and medicines and are upstream raw materials for many alkyl halides. Although the transformation of alcohols via a direct cleavage of the robust C(sp^3)–O bonds is quite tricky due to their high bond dissociation energy, alcohols can be easily converted into stable but highly electrophilic alkyl tosylates, which work as competent carbon-electrophiles in the copper

or nickel-catalyzed couplings with Grignard reagents [24]. However, the C(sp^3)–C(sp^3) reductive coupling directly utilizing alkyl tosylates is still challenging [17,21] because alkyl tosylates are inert for the SET process due to the high-lying σ*(C–O) orbital of the tosylates, as demonstrated in numerous Ni-catalyzed couplings [25–31].

Recently, we developed a C(sp^2)–C(sp^3) reductive cross-coupling between aryl halides and alkyl tosylates using a combination of nickel and nucleophilic vitamin B_{12s}, VB_{12s} (Scheme 1c-1) [32,33]. In the cross-coupling, the cobalt played a crucial role in the activation of alkyl tosylates. Thus, an S_N2-type oxidative addition of the tosylate to VB_{12s} affords alkyl-cobalt **A**, which could perform a transalkylation with nickel to give an alkyl-nickel **B**, leading to C(sp^3)–C(sp^2) linkages in our previous works. It is noteworthy that the alkyl-nickel **B** would also be an intermediate in the homo-coupling. Based on the unique performance of the Ni/Co-hybrid catalyst system, we assumed that the catalyst system might enable a direct homo-coupling of alkyl tosylates to form C(sp^3)–C(sp^3) linkages (Scheme 1c-2) without the in situ halogen-OTs exchange [21,34].



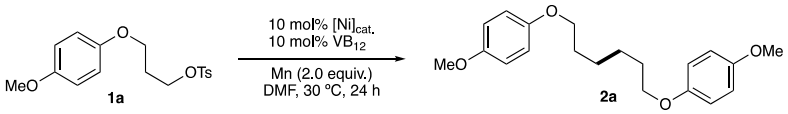
Scheme 1. The transition metal-catalyzed C(sp^3)–C(sp^3) bond construction.

2. Results and Discussion

2.1. Screening of Reaction Conditions

To test our hypothesis, we carried out the reaction of 3-(4-anisyl)propyl tosylate (**1a**) as a model substrate using the combination of nickel and cyanocobalamine, VB_{12}, catalysts (Table 1). When **1a** was treated with $NibpyCl_2$ (10 mol%, bpy = 2,2′-bipyridine, Figure 1) and VB_{12} (10 mol%) in the presence of Mn powder (2.0 equiv.) and DMF (*N*,*N*-dimethylformamide) at 30 °C for 24 h, the alkyl dimer **2a** was obtained in a 72% yield with a complete consumption of the tosylate **1a** (entry 1, Table 1). In the transformation, no detectable amount of β-hydride eliminated and proto-detosylated products of **1a** were obtained (see Supplementary Materials). We carefully confirmed that the lack of nickel and cobalt catalysts did not lead to the dimer **2a** at all (entries 2 and 3), in which most of **1a** remained unchanged after the reaction. These results indicated that alkyl tosylates are not reduced with Mn in the presence or absence of Ni and Co catalysts [35–37]. Mn powder is also crucial for efficient homo-coupling; that is, the absence of Mn (entry 4) or the use of Zn instead of Mn (entry 5) caused no reaction or a diminished yield of **2a**, respectively. Additionally, the coupling highly depended on the nickel-ligand. 4,4′-(MeO_2C)bpy, 4,4′-^{t}Bu_2bpy, 4,4′-Mes_2bpy, 4,4′-$(MeO)_2$bpy, 6-Mebpy, and 6,6′-Me_2bpy (Figure 1) provided **2a** in low yields (entries 6–11). In contrast, phenanthroline-type ligands were effective (entries 12 and 13), particularly 1,10-phen afforded **2a** in a 75% yield (entry 12). Furthermore, we found that the present reaction was sensitive to the solvent; thus DMF (entry 12) and DMSO (dimethyl sulfoxide, entry 14) were superior to THF (tetrahydrofuran), 1,4-dioxane, and acetonitrile (entry 15). The best result (93% yield of **2a**) was accomplished using a $NiphenBr_2$ catalyst in DMSO (entry 16). Furthermore, other cobalt complexes like $CoCl(dmg)_2L$ could also be utilized in the homo-coupling, but these reactions were slow (entry 17).

Table 1. The screening of the reaction conditions in the homo-coupling of **1a**.



Entry	Ni catalysts	Yield of 2a (%) [a]	Conversion of 1a (%) [a]
1	$NibpyCl_2$	72	100
2 [b]	$NibpyCl_2$	0	20
3	None	0	32
4 [c]	$NibpyCl_2$	0	0
5 [d]	$NibpyCl_2$	38	65
6	$Ni(4,4'\text{-}(MeO_2C)_2bpy)Cl_2$	38	76
7	$Ni(4,4'\text{-}^tBu_2bpy)Cl_2$	18	67
8	$Ni(4,4'\text{-}Mes_2bpy)Cl_2$ [e]	38	78
9	$Ni[4,4'\text{-}(MeO)_2bpy]Cl_2$	10	66
10	$Ni(6\text{-}Mebpy)Cl_2$	42	92
11	$Ni(6,6'\text{-}Me_2bpy)Cl_2$	17	95
12	$Ni(1,10\text{-}phen)Cl_2$	75	100
13	$Ni(4,7\text{-}Ph_2phen)Cl_2$	60	100
14 [f]	$NiphenCl_2$	82	100
15 [g]	$NiphenCl_2$	0	0
16 [f]	$NiphenBr_2$	93	100
17 [h]	$NiphenBr_2$	21–28	51–59

[a] Determined by GC. [b] Without VB_{12}. [c] Without Mn. [d] Zn instead of Mn. [e] Mes = 2,4,6-Trimethylphenyl. [f] DMSO was used instead of DMF. [g] THF, 1,4-dioxane, or acetonitrile were used instead of DMF. [h] $CoCl(dmg)_2L$ (dmg = dimethylglyoximato, L = pyridine derivatives) were used instead of VB_{12}.

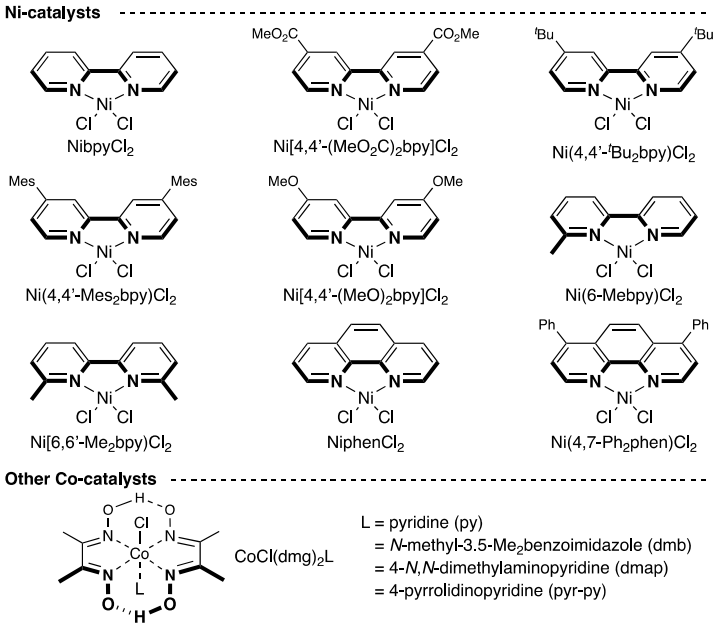


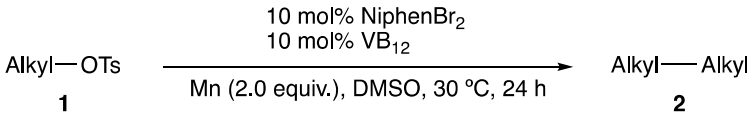
Figure 1. The list of nickel and cobalt catalysts.

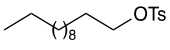
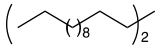
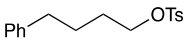
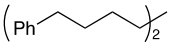
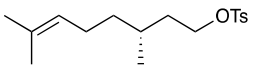
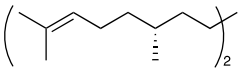
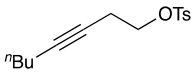
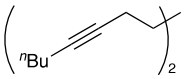
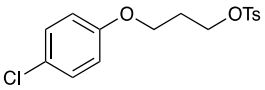
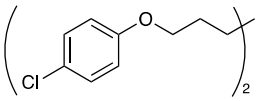
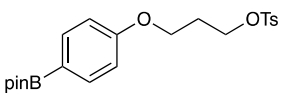
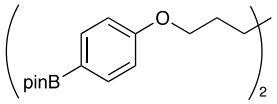
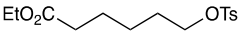
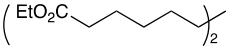
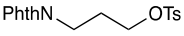
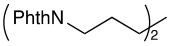
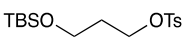
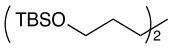
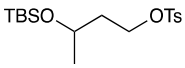
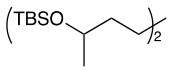
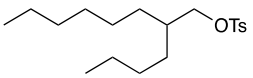
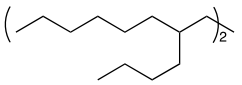
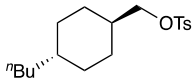
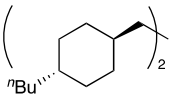
2.2. Substrate Scope

With optimized conditions in hand (entry 16 in Table 1), we next explored the substrate scope in the Ni/Co-catalyzed homo-coupling of alkyl tosylates (Table 2). The homo-coupling tolerated well not only simple alkyl groups (**1b** and **1c**, entries 1 and 2) but also alkenyl and alkynyl substituents (**1d** and **1e**, entries 3 and 4); the corresponding homodimers **2b**–**2e** were provided in good yields. The chloro and pinacolboryl groups on the aryl ring (**1f** and **1g**, entries 5 and 6) did not interfere with the transformation, highlighting the potential of the present coupling in combination with further conventional cross-coupling sequences. Additionally, useful functional groups such as ester (**1h**,

entry 7), phthalimide (**1i**, entry 8), and silyl ether (**1j** and **1k**, entries 9 and 10) were compatible in the transformation, giving rise to the corresponding C(sp^3)–C(sp^3) linkages in 60–90% yields. Especially, **1k** can be easily synthesized through a regioselective mono-tosylation of the corresponding diol [38–40]. Therefore, the homo-coupling **1k** is thought to be of assistance in constructing complex alkyl dimers from polyols. Incidentally, a key step in the homo-coupling would be considered the S_N2-type oxidative addition of alkyl tosylates to nucleophilic Co(I) to generate alkyl-Co(III) species as shown in Scheme 1 (the formation of the alkyl-cobalt intermediate **A**). Indeed, neighboring substituents at the 2-position of primary alkyl tosylate **1l** and **1m** inhibited the homo-coupling due to the steric repulsion between the substituent and the cobalt center in the transition state in the S_N2 reaction (entries 11 and 12). Although these couplings required longer reaction time (48–74 h) in a DMF solvent, the corresponding alkyl dimers **2l** and **2m** were obtained in 80% and 65% yield, respectively.

Table 2. The substrate scope in the Ni/Co-catalyzed homo-coupling.

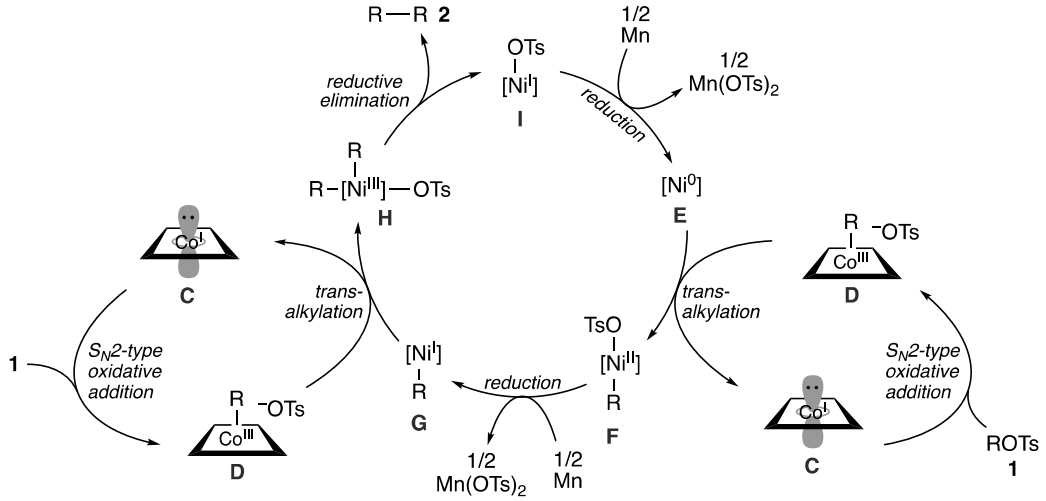


Entry	Alkyl Tosylates 1		Product 2 and Yield (%) [a]		
1		**1b**		**2b**	86
2		**1c**		**2c**	70
3		**1d**		**2d**	67
4		**1e**		**2e**	63
5		**1f**		**2f**	65
6		**1g**		**2g**	75
7		**1h**		**2h**	70
8 [b]		**1i**		**2i**	60
9		**1j**		**2j**	73
10		**1k**		**2k**	90 [1:1] [c]
11 [d,e]		**1l**		**2l**	80 [1:1] [c]
12 [e,f]		**1m**		**2m**	65

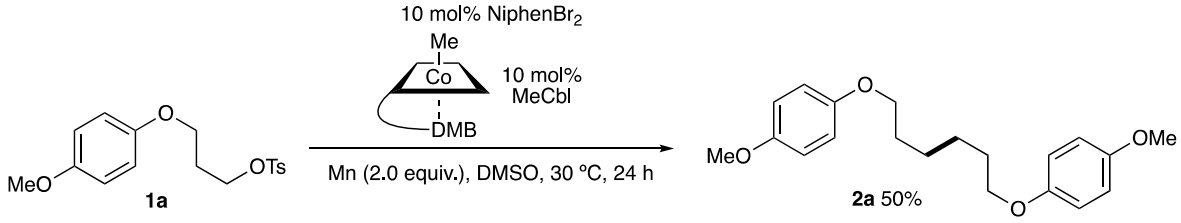
[a] Isolated yields. [b] PhthN = Phthalimidyl. [c] The bracket value indicates a ratio of the *dl*- and *memo*-dimers estimated by NMR spectra. [d] Reaction times: 48 h. [e] DMF was used instead of DMSO. [f] Reaction times: 74 h.

2.3. Plausible Reaction Mechanism

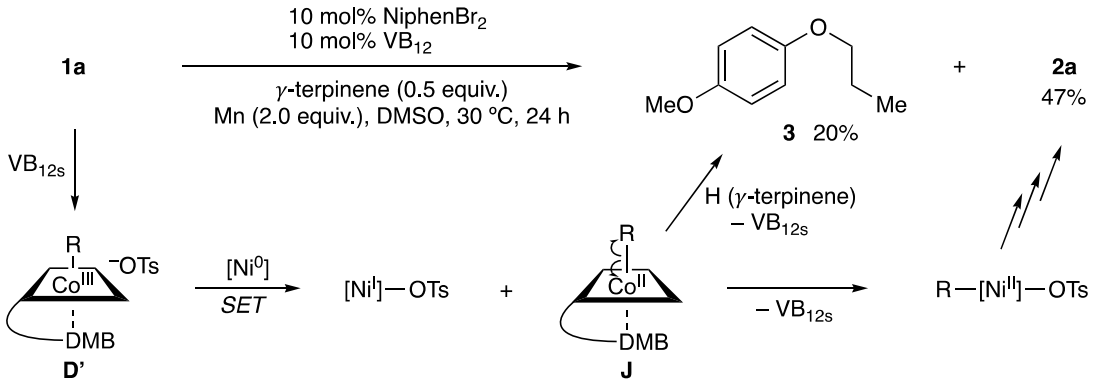
Although further mechanistic studies would be needed to understand the present homo-coupling in detail, we propose a plausible reaction mechanism as depicted in Scheme 2. Initially, an S_N2-type oxidative addition of the alkyl tosylate **1** to the in situ-generated nucleophilic Co(I) species **C** could provide the alkyl-cobalt(III) **D**, followed by transalkylation with the zerovalent nickel **E** to afford alkyl-nickel intermediate **F** [41,42]. The reduction of **F** with Mn gives the monovalent alkyl-nickel intermediate **G**. A second transalkylation between **G** and the alkyl-cobalt(III) **D** provides dialkyl-nickel(III) **H**, which undergoes a rapid reductive elimination to produce the alkyl dimer **2** and the monovalent nickel species **I**. Finally, the catalytic cycle would be closed by a reduction of **I** with Mn to regenerate **E**. As a corroboration of the expected mechanism, the methylcobalamin (MeCbl) catalyst participated in the homo-coupling, leading to the alkyl dimer **2a** in a 50% yield (Scheme 3). The result might imply the formation of the alkyl-cobalt(III) during the reaction. Additionally, the homo-coupling in the presence of hydrogen-atom donor, γ-terpinene (0.5 equiv.), [43] provided the detosyloxylated product **3** in a 20% yield along with the alkyl dimer **2a** in a 47% yield (Scheme 4), indicating the formation of the alkyl radical during the reaction. Thus, a cleavage of the generated alkyl-cobalt(III) **D′** could be induced by an electron transfer from nickel to give the alkyl-cobalt(II) intermediate **J** [41]. Thermodynamically unstable **J** was rapidly converted into alkyl radical and VB_{12s} [44,45]. Most of the radicals were captured by Ni(I)–OTs to produce alkyl dimer **2a**; a part of the alkyl radical could react with γ-terpinene to form the reduction product **3**.



Scheme 2. A plausible reaction mechanism of the Ni/Co-catalyzed $C(sp^3)$–$C(sp^3)$ homo-coupling.



Scheme 3. The homo-coupling of **1a** using a combination of $NiphenBr_2$ and MeCbl catalysts.



Scheme 4. The Ni/Co-catalyzed homo-coupling of **1a** in the presence of γ-terpinene.

3. Materials and Methods

3.1. General Information

All reactions were performed on oven- and flame-dried glassware under argon using standard Schlenk techniques. Flash column chromatography was performed with 40–80 nm silica gel 60 (KANTO Chemical Co. Inc., Tokyo, Japan). Analytical thin layer chromatography (TLC) monitoring was carried out with type 60 F_{254} silica gel aluminum sheets (Merck KGaA, Darmstadt, Germany). Gas chromatography (GC) monitoring was carried out on GC-2014 (Shimadzu, Kyoto, Japan) with a 0.25 mm × 60 m TC-1 capillary column (GL Science Co., Torrance, CA, USA). The nuclear magnetic resonance (NMR) spectra were recorded with a Varian-400 (^{1}H NMR: 400 MHz; ^{13}C NMR: 101 MHz) spectrometer or Varian-500 (^{1}H NMR: 500 MHz; ^{13}C NMR: 126 MHz) spectrometers (Agilent, Santa Clara, CA, USA), calibrated from residual chloroform and deuterated chloroform as internal standards at 7.26 ppm for ^{1}H NMR spectra and at 77.0 ppm for ^{13}C NMR spectra, respectively. The high-resolution mass spectrum (HRMS) was performed by the Natural Science Center for Basic Research and Development (N-BARD) of Hiroshima University (Higashi-Hiroshima, Japan) using LTQ Orbitrap XL from (Thermo Fisher Scientific, Waltham, MA, USA). All nickel catalysts were synthesized based on the literature [46]. $CoCl(dmgH)_2L$ were prepared according to the literature [47]. All solvents and TMSCl were dried over activated Molecular Sieves (MS) 4Å and distilled and stored with activated MS 4Å under argon. All alkyl tosylates were prepared from the corresponding alcohols by the reported methods [48]. Unless otherwise noted, commercially available reagents were used as received without further purification.

3.2. General Procedure of the $NiBr_2$phen/VB_{12}-Catalyzed Homo-Coupling of Alkyl Tosylates

In an oven-dried Pyrex-Schlenk tube, Mn powder (27.5 mg, 0.5 mmol) was added and heated at 400 °C for 5 min under a vacuum to activate the manganese. After cooling, the Schlenk tube was filled with argon. $NiphenBr_2$ (10.0 mg, 0.025 mmol). Then, VB_{12} (33.9 mg, 0.025 mmol), DMSO (1.0 mL) and TMSCl (6.4 µL) were added into the tube. After stirring for 10 min at room temperature, the color of the reaction mixture changed from red to black. Alkyl tosylate (0.25 mmol) was added to the reaction mixture and stirred at 30 °C for an appropriate time. The obtained mixture was diluted with ethyl acetate and quenched with saturated aqueous ammonium chloride. At this time, the GC yield was measured using dodecane as an internal standard. The aqueous phase was extracted with ethyl acetate. The combined organic phase was dried over $MgSO_4$. After filtration and the removal of the solvent, the residue was purified by a silica-gel column chromatography to get the corresponding alkyl dimer.

3.3. Product Characterization

1,6-Di(4-anisyloxy)hexane (**2a**) was isolated as a white solid (Mp.: 78–79 °C) by a silica-gel column chromatography using chloroform as an eluent; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83 (s, 8H), 3.92 (t,

J = 6.5 Hz, 4H), 3.77 (s, 6H), 1.85–1.74 (m, 4H), 1.59–1.46 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.68, 153.24, 115.42, 114.61, 68.48, 55.72, 29.32, 25.87; HRMS (ESI) calcd for $C_{20}H_{27}O_4$ $[M+H]^+$: 331.1909, found: 331.1907.

Tetracosane (**2b**) was isolated as a white solid (Mp.: 45–46 °C) by silica-gel column chromatography using hexane as an eluent; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32–1.23 (m, 44H), 0.88 (t, *J* = 6.7 Hz, 6H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 31.92, 29.70, 29.36, 22.69, 14.14, 14.10; all peaks were broad or multiplet; HRMS (ESI) calcd for $C_{24}H_{50}$: 338.3913, found: 338.3920.

1,8-Diphenyloctane (**2c**) was isolated as a colorless oil by silica-gel column chromatography using a mixture of Hexane and EtOAc (5:1) as an eluent; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.22 (m, 6H), 7.21–7.12 (m, 4H), 2.63–2.55 (m, 4H), 1.60 (dt, *J* = 15.1, 7.4 Hz, 4H), 1.37–1.27 (m, 8H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 142.90, 128.38, 128.20, 125.53, 35.96, 31.49, 29.41, 29.29; HRMS (ESI) calcd for $C_{24}H_{50}$: 266.2035, found: 266.2035.

2,6,11,15-Tetramethylhexadeca-2,14-diene (**2d**) was isolated as a colorless oil by silica-gel column chromatography using hexane as an eluent; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.10 (t, *J* = 7.2 Hz, 2H), 2.04–1.87 (m, 4H), 1.68 (s, 6H), 1.60 (s, 6H), 1.44–1.18 (m, 10H), 1.17–1.03 (m, 4H), 0.85 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 130.94, 125.10, 37.15, 36.99, 32.39, 27.34, 25.72, 25.57, 19.60, 17.62; HRMS (ESI) calcd for $C_{20}H_{38}$: 278.2974, found: 278.2973.

5,11-Hexadecadiyne (**2e**) was isolated as a colorless oil by silica-gel column chromatography using hexane as an eluent; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.20–2.10 (m, 8H), 1.62–1.34 (m, 12H), 0.90 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 80.44, 79.78, 31.23, 28.24, 21.93, 18.42, 18.32, 13.63; HRMS (ESI) calcd for $C_{16}H_{26}$: 218.2035, found: 218.2025.

1,4-Di(4-chlorophenyloxy)hexane (**2f**) was isolated as a white solid (Mp.: 78–79 °C) by silica-gel column chromatography using chloroform as an eluent; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (d, *J* = 9.0 Hz, 4H), 6.81 (d, *J* = 9.0 Hz, 4H), 3.93 (t, *J* = 6.4 Hz, 4H), 1.80 (p, *J* = 6.3 Hz, 4H), 1.52 (dd, *J* = 7.2, 3.8 Hz, 4H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 157.65, 129.26, 125.34, 115.71, 68.08, 29.10, 25.80; HRMS (ESI) calcd for $C_{24}H_{50}$: 338.0840, found: 338.0840.

1,6-Di(4-pinacolborylphenyloxy)hexane (**2g**) [49] was isolated as a white solid (Mp.: 139–140 °C) by silica-gel column chromatography using chloroform as an eluent; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.56 Hz, 4H), 6.89 (d, *J* = 8.60 Hz, 4H), 3.99 (t, *J* = 7.5 Hz, 4H), 1.82 (t, *J* = 6.25 Hz, 4H) 1.54 (quin, *J* = 3.75 Hz, 4H), 1.34 (s, 24H); ^{13}C NMR (500 MHz, $CDCl_3$) δ161.68, 136.50, 113.85, 83.51, 67.58, 29.15, 25.85, 24.86.

Diethyl dodecanedioate (**2h**) was isolated as a colorless oil by silica-gel column chromatography using a mixture of hexane and EtOAc (3:1) as an eluent; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.12 (t, *J* = 7.1 Hz, 4H), 2.32–2.25 (m, 4H), 1.66–1.54 (m, 8H), 1.33–1.21 (m, 14H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 173.93, 60.14, 60.06, 34.37, 29.22, 29.11, 24.94, 14.22; HRMS (ESI) calcd for $C_{16}H_{31}O_4$ $[M+H]^+$: 287.2222, found: 287.2221.

1,6-Diphthalimidylhexane (**2i**) [22] was isolated as a white solid (Mp.: 180–181 °C) by silica-gel column chromatography using a mixture of hexane and EtOAc (3:1) as an eluent; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (dd, *J* = 5.4, 3.0 Hz, 4H), 7.70 (dd, *J* = 5.5, 3.0 Hz, 4H), 3.67 (t, *J* = 7.3 Hz, 4H), 1.67 (quint, *J* = 7.1 Hz, 4H), 1.38 (quint, *J* = 3.5 Hz, 4H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 168.42, 133.83, 132.14, 123.16, 37.87, 28.44, 26.41.

1,6-Di(tert-butyldimethylsilyloxy)hexane (**2j**) was isolated as a colorless oil by silica-gel column chromatography using a mixture of hexane and EtOAc (10:1) as an eluent; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.60 (t, *J* = 6.6 Hz, 4H), 1.51 (q, *J* = 6.7 Hz, 4H), 1.32 (ddd, *J* = 7.3, 4.5, 3.3 Hz, 4H), 0.89 (s, 18H), 0.04 (s, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 63.24, 32.86, 25.98, 25.61, 18.37, −5.27; HRMS (ESI) calcd for $C_{18}H_{43}O_2Si_2$ $[M+H]^+$: 347.2802, found: 347.2802.

2,7-Di(tert-butyldimethylsilyloxy)octane (**2k**) was isolated as a 1:1 mixture of *dl*- and *meso*-form (colorless oil) by silica-gel column chromatography using a mixture of hexane and EtOAc (10:1) as an eluent; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.76 (dq, *J* = 11.8, 6.0 Hz, 2H), 1.49–1.18 (m, 8H), 1.11 (d, *J* = 6.1 Hz, 6H), 0.88 (s, 18H), 0.042 and 0.040 (s, 12H); all signals were obscured except for the peaks at 0.04 ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 68.61, 39.76, 25.91, 25.87, 23.80, 18.17, −4.72, assignable signals for another isomer: 68.57, 25.85, 23.82, 18.17, −4.42; HRMS (ESI) calcd for $C_{20}H_{47}O_2Si_2$ $[M+H]^+$: 375.3115, found: 375.3109.

7,10-Dibutylhexadecane (**2l**) was isolated as a 1:1 mixture of *dl*- and *meso*-form (colorless oil) by silica-gel column chromatography using hexane as an eluent; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.34–1.16 (m, 38H), 0.93–0.84 (m, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 37.71, 33.69, 33.39, 31.98, 30.28, 29.84, 29.00, 26.69, 23.18, 22.72, 14.19, 14.13; HRMS (ESI) calcd for $C_{24}H_{50}$: 338.3913, found: 338.3906.

1,2-Bis(*trans*-4-butylcyclohexyl)ethane (**2m**) was isolated as a white solid (Mp.: 89–90 °C) by silica-gel column chromatography using hexane as an eluent; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.76–1.67 (m, 8H), 1.32–1.20 (m, 8H), 1.19–1.10 (m, 12H), 0.91–0.80 (m, 14H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 38.20, 37.87, 37.23, 34.83, 33.43, 33.40, 29.26, 23.03, 14.16; HRMS (ESI) calcd for $C_{22}H_{42}$: 306.3287, found: 306.3290.

4. Conclusions

In summary, we have established a direct homo-coupling of alkyl tosylates using a combination of nickel and the nucleophilic cobalt-hybrid catalyst system in the presence of an Mn reductant. A diverse set of functional groups on alkyl tosylates can be tolerated in the homo-coupling, giving rise to the corresponding alkyl dimers in good yields under mild conditions. Although the homo-coupling was sensitive to the bulkiness of alkyl tosylates, a longer reaction time gave the corresponding homodimer. Mechanistic studies using a MeCbl catalyst strongly suggested a formation of the alkyl-Co(III) intermediate in the homo-coupling. Moreover, the addition of the hydrogen-atom donor, γ-terpinene, into the reaction revealed a generation of alkyl radicals during the reaction. Further mechanistic studies and synthetic applications of this Ni/Co-hybrid catalyst system are underway in our laboratory.

Supplementary Materials: The ^{1}H and ^{13}C NMR spectra of homo-coupling products are available online.

Author Contributions: R.T. carried out all the experiments and analyzed the data with technical support and advice from T.M., H.Y., and I.O. K.K. supervised the project, designed the experiments to develop this homo-coupling, and wrote the paper.

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References

1. Tasker, S.Z.; Standley, E.A.; Jamison, T.F. Recent advances in homogeneous nickel catalysis. *Nature* **2014**, *509*, 299–309. [CrossRef]
2. Netherton, M.R.; Dai, C.Y.; Neuschütz, K.; Fu, G.C. Room-temperature alkyl-alkyl Suzuki cross-coupling of alkyl bromides that possess beta hydrogens. *J. Am. Chem. Soc.* **2001**, *123*, 10099–10100. [CrossRef] [PubMed]
3. Zhou, J.; Fu, G.C. Palladium-Catalyzed Negishi Cross-Coupling Reactions of Unactivated Alkyl Iodides, Bromides, Chlorides, and Tosylates. *J. Am. Chem. Soc.* **2003**, *125*, 12527–12530. [CrossRef]
4. Hadei, N.; Kantchev, E.A.B.; O'Brien, C.J.; Organ, M.G. Room-temperature Negishi cross-coupling of unactivated alkyl bromides with alkyl organozinc reagents utilizing a Pd/N-heterocyclic carbene catalyst. *J. Org. Chem.* **2005**, *70*, 8503–8507. [CrossRef] [PubMed]
5. Burns, D.H.; Miller, J.D.; Chan, H.-K.; Delaney, M.O. Scope and Utility of a New Soluble Copper Catalyst [CuBr−LiSPh−LiBr−THF]: A Comparison with Other Copper Catalysts in Their Ability to Couple One Equivalent of a Grignard Reagent with an Alkyl Sulfonate. *J. Am. Chem. Soc.* **1997**, *119*, 2125–2133. [CrossRef]

6. Terao, J.; Todo, H.; Begum, S.A.; Kuniyasu, H.; Kambe, N. Copper-catalyzed cross-coupling reaction of grignard reagents with primary-alkyl halides: Remarkable effect of 1-phenylpropyne. *Angew. Chem. Int. Ed.* **2007**, *46*, 2086–2089. [CrossRef] [PubMed]
7. Devasagayaraj, A.; Stüdemann, T.; Knochel, P. A New Nickel-Catalyzed Cross-Coupling Reaction between sp^3 Carbon Centers. *Angew. Chem. Int. Ed.* **1995**, *34*, 2723–2725. [CrossRef]
8. Terao, J.; Ikumi, A.; Kuniyasu, H.; Kambe, N. Ni- or Cu-catalyzed cross-coupling reaction of alkyl fluorides with Grignard reagents. *J. Am. Chem. Soc.* **2003**, *125*, 5646–5647. [CrossRef]
9. Saito, B.; Fu, G.C. Alkyl-alkyl suzuki cross-couplings of unactivated secondary alkyl halides at room temperature. *J. Am. Chem. Soc.* **2007**, *129*, 9602–9603. [CrossRef] [PubMed]
10. Gong, H.; Gagné, M.R. Diastereoselective Ni-Catalyzed Negishi Cross-Coupling Approach to Saturated, Fully Oxygenated C-Alkyl and C-Aryl Glycosides. *J. Am. Chem. Soc.* **2008**, *130*, 12177–12183. [CrossRef]
11. Vechorkin, O.; Hu, X. Nickel-catalyzed cross-coupling of non-activated and functionalized alkyl halides with alkyl Grignard reagents. *Angew. Chem. Int. Ed.* **2009**, *48*, 2937–2940. [CrossRef] [PubMed]
12. Qin, T.; Cornella, J.; Li, C.; Malins, L.R.; Edwards, J.T.; Kawamura, S.; Maxwell, B.D.; Eastgate, M.D.; Baran, P.S. A general alkyl-alkyl cross-coupling enabled by redox-active esters and alkylzinc reagents. *Science* **2016**, *352*, 801–805. [CrossRef] [PubMed]
13. Schmidt, J.; Choi, J.; Liu, A.T.; Slusarczyk, M.; Fu, G.C. A general, modular method for the catalytic asymmetric synthesis of alkylboronate esters. *Science* **2016**, *354*, 1265–1269. [CrossRef] [PubMed]
14. Qian, X.; Auffrant, A.; Felouat, A.; Gosmini, C. Cobalt-Catalyzed Reductive Allylation of Alkyl Halides with Allylic Acetates or Carbonates. *Angew. Chem. Int. Ed.* **2011**, *50*, 10402–10405. [CrossRef]
15. Yu, X.; Yang, T.; Wang, S.; Xu, H.; Gong, H. Nickel-catalyzed reductive cross-coupling of unactivated alkyl halides. *Org. Lett.* **2011**, *13*, 2138–2141. [CrossRef]
16. Dai, Y.; Wu, F.; Zang, Z.; You, H.; Gong, H. Ni-Catalyzed Reductive Allylation of Unactivated Alkyl Halides with Allylic Carbonates. *Chem. Eur. J.* **2012**, *18*, 808–812. [CrossRef]
17. Xu, H.; Zhao, C.; Qian, Q.; Deng, W.; Gong, H. Nickel-catalyzed cross-coupling of unactivated alkyl halides using bis(pinacolato)diboron as reductant. *Chem. Sci.* **2013**, *4*, 4022. [CrossRef]
18. Chen, H.; Jia, X.; Yu, Y.; Qian, Q.; Gong, H. Nickel-Catalyzed Reductive Allylation of Tertiary Alkyl Halides with Allylic Carbonates. *Angew. Chem. Int. Ed.* **2017**, *129*, 13283–13286. [CrossRef]
19. Smith, R.T.; Zhang, X.; Rincon, J.A.; Agejas, J.; Mateos, C.; Barberis, M.; García-Cerrada, S.; de Frutos, O.; MacMillan, D.W.C. Metallaphotoredox-Catalyzed Cross-Electrophile Csp^3-Csp^3 Coupling of Aliphatic Bromides. *J. Am. Chem. Soc.* **2018**, *140*, 17433–17438. [CrossRef]
20. Goldup, S.M.; Leigh, D.A.; McBurney, R.T.; McGonigal, P.R.; Plant, A. Ligand-assisted nickel-catalysed sp^3–sp^3 homocoupling of unactivated alkyl bromides and its application to the active template synthesis of rotaxanes. *Chem. Sci.* **2010**, *1*, 383. [CrossRef]
21. Prinsell, M.R.; Everson, D.A.; Weix, D.J. Nickel-catalyzed, sodium iodide-promoted reductive dimerization of alkyl halides, alkyl pseudohalides, and allylic acetates. *Chem. Commun.* **2010**, *46*, 5743–5745. [CrossRef]
22. Peng, Y.; Luo, L.; Yan, C.S.; Zhang, J.-J.; Wang, Y.W. Ni-Catalyzed Reductive Homocoupling of Unactivated Alkyl Bromides at Room Temperature and Its Synthetic Application. *J. Org. Chem.* **2013**, *78*, 10960–10967. [CrossRef] [PubMed]
23. Cai, Y.; Qian, X.; Gosmini, C. Cobalt-Catalyzed Csp^3–Csp^3 Homocoupling. *Adv. Synth. Catal.* **2016**, *358*, 2427–2430. [CrossRef]
24. Yang, C.-T.; Zhang, Z.-Q.; Liang, J.; Liu, J.-H.; Lu, X.-Y.; Chen, H.-H.; Liu, L. Copper-catalyzed cross-coupling of nonactivated secondary alkyl halides and tosylates with secondary alkyl Grignard reagents. *J. Am. Chem. Soc.* **2012**, *134*, 11124–11127. [CrossRef]
25. Powell, D.A.; Fu, G.C. Nickel-Catalyzed Cross-Couplings of Organosilicon Reagents with Unactivated Secondary Alkyl Bromides. *J. Am. Chem. Soc.* **2004**, *126*, 7788–7789. [CrossRef] [PubMed]
26. Powell, D.A.; Maki, T.; Fu, G.C. Stille cross-couplings of unactivated secondary alkyl halides using monoorganotin reagents. *J. Am. Chem. Soc.* **2005**, *127*, 510–511. [CrossRef] [PubMed]
27. González-Bobes, F.; Fu, G.C. Amino Alcohols as Ligands for Nickel-Catalyzed Suzuki Reactions of Unactivated Alkyl Halides, Including Secondary Alkyl Chlorides, with Arylboronic Acids. *J. Am. Chem. Soc.* **2006**, *128*, 5360–5361. [CrossRef]

28. Dudnik, A.S.; Fu, G.C. Nickel-catalyzed coupling reactions of alkyl electrophiles, including unactivated tertiary halides, to generate carbon-boron bonds. *J. Am. Chem. Soc.* **2012**, *134*, 10693–10697. [CrossRef] [PubMed]
29. Liang, Y.; Fu, G.C. Nickel-Catalyzed Alkyl-Alkyl Cross-Couplings of Fluorinated Secondary Electrophiles: A General Approach to the Synthesis of Compounds having a Perfluoroalkyl Substituent. *Angew. Chem. Int. Ed.* **2015**, *54*, 9047–9051. [CrossRef]
30. Lévêque, C.; Corcé, V.; Chenneberg, L.; Ollivier, C.; Fensterbank, L. Photoredox/Nickel Dual Catalysis for the C(sp^3)–C(sp^3) Cross-Coupling of Alkylsilicates with Alkyl Halides. *Eur. J. Org. Chem.* **2017**, *2017*, 2118–2121. [CrossRef]
31. Lu, X.; Wang, Y.; Zhang, B.; Pi, J.-J.; Wang, X.-X.; Gong, T.-J.; Xiao, B.; Fu, Y. Nickel-Catalyzed Defluorinative Reductive Cross-Coupling of gem-Difluoroalkenes with Unactivated Secondary and Tertiary Alkyl Halides. *J. Am. Chem. Soc.* **2017**, *139*, 12632–12637. [CrossRef] [PubMed]
32. Komeyama, K.; Ohata, R.; Kiguchi, S.; Osaka, I. Highly nucleophilic vitamin B_{12}-assisted nickel-catalysed reductive coupling of aryl halides and non-activated alkyl tosylates. *Chem. Commun.* **2017**, *53*, 6401–6404. [CrossRef] [PubMed]
33. Komeyama, K.; Yamahata, Y.; Osaka, I. Nickel and Nucleophilic Cobalt-Catalyzed Trideuteriomethylation of Aryl Halides Using Trideuteriomethyl p-Toluenesulfonate. *Org. Lett.* **2018**, *20*, 4375–4378. [CrossRef]
34. Ito, S.; Fujiwara, Y.-I.; Nakamura, E.; Nakamura, M. Iron-Catalyzed Cross-Coupling of Alkyl Sulfonates with Arylzinc Reagents. *Org. Lett.* **2009**, *11*, 4306–4309. [CrossRef] [PubMed]
35. Closson, W.D.; Wriede, P.; Bank, S. Reductive Cleavage of Toluenesulfonates with Sodium Naphthalene 1. *J. Am. Chem. Soc.* **1966**, *88*, 1581–1583. [CrossRef]
36. Lipshutz, B.H.; Wilhelm, R.S.; Nugent, S.T.; Little, R.D.; Baizer, M.M. Electrochemical peak potentials of typical substrates used for coupling reactions with organocuprates: Effects of solvent. *J. Org. Chem.* **1983**, *48*, 3306–3308. [CrossRef]
37. Sridhar, M.; Kumar, B.A.; Narender, R. Expedient and simple method for regeneration of alcohols from toluenesulfonates using Mg-MeOH. *Tetrahedron Lett.* **1998**, *39*, 2847–2850. [CrossRef]
38. Kotsuki, H.; Kadota, I.; Ochi, M. A new expeditious synthesis of (+)-exo-brevicomin via efficient C-C bond formation of triflates. *Tetrahedron Lett.* **1989**, *30*, 3999–4000. [CrossRef]
39. O'Donnel, C.J.; Burke, S.D. Selective Mesylation of Vicinal Diols: A Systematic Case Study. *J. Org. Chem.* **1998**, *63*, 8614–8616. [CrossRef]
40. Bouzide, A.; Sauvé, G. Silver(I) Oxide Mediated Highly Selective Monotosylation of Symmetrical Diols. Application to the Synthesis of Polysubstituted Cyclic Ethers. *Org. Lett.* **2002**, *4*, 2329–2332. [CrossRef] [PubMed]
41. Ram, M.S.; Riordan, C.G. Methyl transfer from a cobalt complex to Ni(tmc)+ yielding Ni(tmc)Me+: A model for methylcobalamin alkylation of CO dehydrogenase. *J. Am. Chem. Soc.* **1995**, *117*, 2365–2366. [CrossRef]
42. Eckert, N.A.; Dougherty, W.G.; Yap, G.P.A.; Riordan, C.G. Methyl Transfer from Methylcobaloxime to (Triphos)Ni(PPh_3): Relevance to the Mechanism of Acetyl Coenzyme A Synthase. *J. Am. Chem. Soc.* **2007**, *129*, 9286–9287. [CrossRef]
43. Gansäuer, A.; Fleckhaus, A.; Lafont, M.A.; Okkel, A.; Kotsis, K.; Anoop, A.; Neese, F. Catalysis via Homolytic Substitutions with C−O and Ti−O Bonds: Oxidative Additions and Reductive Eliminations in Single Electron Steps. *J. Am. Chem. Soc.* **2009**, *131*, 16989–16999. [CrossRef]
44. Martin, B.D.; Finke, R.G. Cobalt-carbon homolysis and bond dissociation energy studies of biological alkylcobalamins: Methylcobalamin, including a > 10^{15} Co-CH_3 homolysis rate enhancement at 25 °C following one-electron reduction. *J. Am. Chem. Soc.* **1990**, *112*, 2419–2420. [CrossRef]
45. Birke, R.L.; Huang, Q.; Spataru, T.; Gosser, D.K. Electroreduction of a Series of Alkylcobalamins: Mechanism of Stepwise Reductive Cleavage of the Co−C Bond. *J. Am. Chem. Soc.* **2006**, *128*, 1922–1936. [CrossRef]
46. Bialek, M.; Cramail, H.; Deffieux, A.; Guillaume, S.M. Styrene polymerization using nickel(II) complexes as catalysts. *Eur. Polym. J.* **2005**, *41*, 2678–2684. [CrossRef]
47. Panagiotopoulos, A.; Ladomenou, K.; Sun, D.; Artero, V.; Coutsolelos, A.G. Photochemical hydrogen production and cobaloximes: The influence of the cobalt axial N-ligand on the system stability. *Dalton Trans.* **2016**, *45*, 6732–6738. [CrossRef]

48. Bissember, A.C.; Levina, A.; Fu, G.C. A Mild, Palladium-Catalyzed Method for the Dehydrohalogenation of Alkyl Bromides: Synthetic and Mechanistic Studies. *J. Am. Chem. Soc.* **2012**, *134*, 14232–14237. [CrossRef]
49. Komber, H.; Müllers, S.; Lombeck, F.; Held, A.; Walter, M.; Sommer, M. Soluble and stable alternating main-chain merocyanine copolymers through quantitative spiropyran–merocyanine conversion. *Polym. Chem.* **2013**, *5*, 443–453. [CrossRef]

Sample Availability: Samples of the compounds are not available from the authors.