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Nickel-Catalyzed Cross-Coupling between Functionalized Primary or Secondary Alkylzinc Halides and Primary Alkyl Halides

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In the presence of Bu_4NI (3 equiv) and 4-fluorostyrene (20 mol %), unreactive primary and secondary alkylzinc iodides undergo nickel-catalyzed cross-couplings with various primary alkyl iodides or bromides. More reactive secondary dialkylzincs and the mixed zinc organometallics RZnTMSM undergo the cross-coupling reaction in the absence of Bu_4NI. The bicyclic secondary diorganozinc **6** prepared via boron−zinc exchange reacts with high retention of configuration. Free NH-groups are tolerated in the cross-coupling allowing the synthesis of aminated products.

Introduction

Transition metal catalyzed cross-coupling reactions are important methods for forming new C−C bonds.[1] Especially, Pd(0) catalysis[2] and Cu(I)-mediated reactions[3] have occupied a central role. Other transition metals such as nickel-[4] and iron-complexes[5] have found less general applications. Recently, we have reported a new cross-coupling between functionalized diorganozincs and primary alkyl iodides in the presence of catalytic amounts of $Ni(acac)_2$ (7.5−10 mol %) and a reaction promotor such as *m*- or *p*-trifluoromethylstyrene.[6] Although various diorganozincs react well under these conditions with a range of primary alkyl iodides, the reaction does not proceed with alkylzinc halides. Recently, we have also found that the presence of Bu_4NI (3 equiv) considerably improves the rate of Ni(0)-catalyzed cross-coupling reactions between functionalized *benzylic* zinc halides and primary alkyl iodides.[7] Herein, we wish to report that the presence of Bu_4NI allows the cross-coupling between various functionalized primary alkyl iodides and primary or secondary alkylzinc iodides. Since a broad range of polyfunctional alkylzinc iodides are available[8] from the corresponding alkyl iodides by insertion of zinc foil, this modification significantly expands the scope of the cross-coupling reaction. The limitations of the reaction as well as applications to the preparation of nitrogen-containing products are reported.

Results and Discussion

Primary or secondary alkyl iodides readily react with zinc foil or zinc dust in THF, furnishing alkyzinc iodides of type **1** in good yields.[4h−i,8] These alkylzinc iodides of type **1** react with functionalized primary alkyl iodides of type **3** in the presence of Bu_4NI (3 equiv), *p*-fluorostyrene (**2**, 20 mol %), and $Ni(acac)_2$ (10 mol %) in a 2:1 THF/NMP (*N*-methylpyrrolidinone) mixture at −5 °C within a few hours, providing the expected cross-coupling products of type **4** in 48−82% yields (Scheme 1 and Table 1). The role of 4-fluorostyrene is to facilitate the reductive elimination step by removing electron density from the metal center.[6] The presence of Bu_4NI is essential for the reaction. In its absence, no product was formed.

Both keto and ester groups (entries 1 and 3−6 of Table 1) as well as an amido function (entry 2) are well tolerated in the alkyl iodides. The presence of a functional group reduces the reactivity of the organozinc reagent through intramolecular complexation of zinc with the functional group. However, by increasing the amount of zinc reagent from 3 to 5 equiv, the cross-coupling product (**1b**, entry 6 of Table 1) can be obtained in good yield. The use of a larger excess of the alkylzinc iodide (5 equiv) allows, in all cases, an improvement of the reaction yield (entries 1, 2, and 6). Diorganozinc reagents (R_2Zn) are more reactive than organozinc iodides; however, only one alkyl group is transferred, leading to the waste of one alkyl group.[4h−i,8] The use of mixed diorganozincs bearing a nontransferable trimethylsilylmethyl group solves this problem. Thus, when mixed organozinc reagents of the

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[6] (a) Devasagayaraj, A.; Stüdemann, T.; Knochel, P. *Angew. Chem.* **1995**, *107*, 2952−54; *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2723−25. (b) Giovannini, R.; Stüdemann, T.; Dussin, G.; Knochel, P. *Angew. Chem.* **1998**, *110*, 2512−17; *Angew. Chem., Int. Ed.* **1998**, *37*, 2387−90. (c) Giovannini, R.; Stüdemann, T.; Devasagayaraj, A.; Dussin, G.; Knochel, P. *J. Org. Chem.* **1999**, *64*, 3544−53.

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[8] Knochel, P., Jones, P., Eds. *Organozinc Reagents: A Practical Approach*; Oxford University Press: New York, 1999.

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Scheme 1

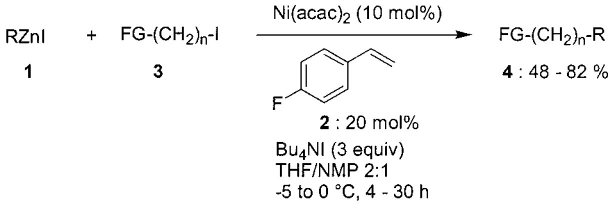
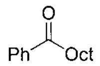
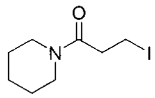
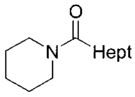
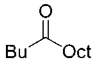
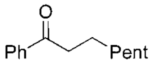
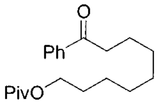


Table 1. Ni(0)-Catalyzed Cross-Coupling of Primary Alkyl Iodides 3a–e with Alkylzinc Iodides 1a–b in the Presence of Bu_4NI (3 equiv) and 2 (20 mol%) in THF/NMP

Entry	Alkylzinc iodide	Alkyl iodide	Reaction conditions (h, °C)	Product of type **4**	Yield (%)[a]
1	n-PentZnI **1a**	$PhCO(CH_2)_3I$ **3a**	16, -5	 **4a**	78 (82)[b]
2	**1a**	 **3b**	30, 0	 **4b**	62 (71)[b]
3	**1a**	$BuCO(CH_2)_3I$ **3c**	16, -5	 **4c**	52
4	**1a**	$EtO_2C(CH_2)_3I$ **3d**	16, -5	$OctCO_2Et$ **4d**	48
5	**1a**	$PhCOCH_2CH_2I$ **3e**	4, -5	 **4e**	57
6	$PivO(CH_2)_5ZnI$ **1b**	$PhCO(CH_2)_3I$ **3a**	10, -5	 **4f**	57 (78)[b]

[a] Isolated yield of analytically pure product. [b] Yield obtained by using 5 equiv of RZnI instead of 3 equiv.

Scheme 2

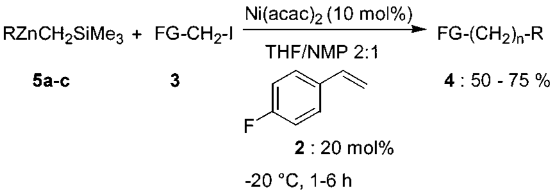
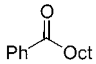
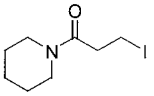
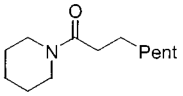
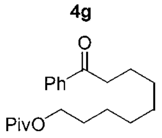
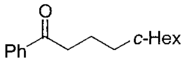


Table 2. Ni(0)-Catalyzed Cross-Coupling of Mixed Alkyl(TMSM)zincs 5a–c with Alkyl Iodides in the Presence of 2 (20 mol%) in THF/NMP

Entry	Zinc reagent	Alkyl iodide	Product of type **4**	Yield (%)[a]
1	*n*-PentZnTMSM **5a**	$PhCO(CH_2)_3I$ **3a**	 **4a**	74
2	**5a**	 **3b**	 **4b**	71
3	**5a**	$PhS(CH_2)_3I$ **3f**	PhS-Oct **4g**	75
4	$PivO(CH_2)_5ZnTMSM$ **5b**	**3a**	 **4f**	50[b]
5	*c*-HexZnTMSM **5c**	**3a**	 **4h**	65

[a] Isolated analytically pure products. [b] 4-trimethylsilylbutyl phenyl ketone is also isolated in 21% yield.

type $RZnCH_2SiMe_3$ (**5**)[9] are used, the cross-coupling with various alkyl iodides proceeds readily at −20 °C and does not require the use of Bu_4NI as a reaction promoter. Only the addition of 4-fluorostyrene (**2**) is necessary for the reaction to occur (Scheme 2 and Table 2).

The mixed zinc reagents $RZnCH_2SiMe_3$ (RZnTMSM, **5**) were prepared by reacting the corresponding alkylzinc iodide (RZnI) with commercially available Me_3SiCH_2Li. Thus, the reaction of pentyl trimethylsilylmethyl zinc with various functionalized alkyl iodides furnishes the expected cross-coupling products in 71−75% yields (entries 1−3 of Table 2). A functionalized zinc reagent like $PivO(CH_2)_5ZnTMSM$ (**5b**) reacts with 3-iodopropyl phenyl ketone (**3a**) and provides the cross-coupling product **4f** in 50% yield. In this case, the cross-coupling product with the TMSM group (phenyl trimethylsilyl ketone) is also isolated in 21% yield (entry 4). The secondary alkyl reagent cyclohexyl trimethylsilylmethyl zinc (**5c**) reacts smoothly with **3a**, affording the coupling product **4h** in 65% yield (entry 5). This result led us to examine in more detail the reaction of secondary dialkylzincs with alkyl iodides. With these more reactive zinc reagents, a fast cross-coupling occurs at −30 °C (16 h), furnishing the products **4h**−**m** in 56−73% yields. Due to the higher reactivity of secondary dialkylzincs compared to that of primary or secondary alkylzinc iodides, the use of Bu_4NI as an additive is unnecessary. The results of these cross-couplings are summarized in Table 3. Interestingly, di-*exo*-2-norbornylzinc **6**, obtained by the hydroboration of norbonene with Et_2BH and subsequent boron−zinc exchange[10] with *i*-Pr_2Zn, reacts with the iodoketone **3a** and provides diastereomerically enriched ketone **7** in 61% yield (Scheme 3), demonstrating that this nickel-catalyzed cross-coupling proceeds with high retention of configuration of the secondary zinc reagent.[11] Over 95% retention of configuration was observed, and the product **7** was obtained in an exo:endo ratio of >95:5. This indicates that this Ni-catalyzed cross-coupling proceeds with retention of configuration of the metalated carbon (>95% retention).[11c]

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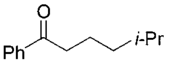
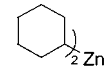
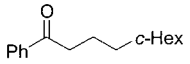
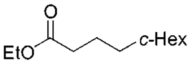
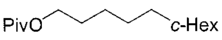
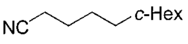
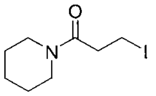
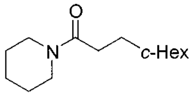
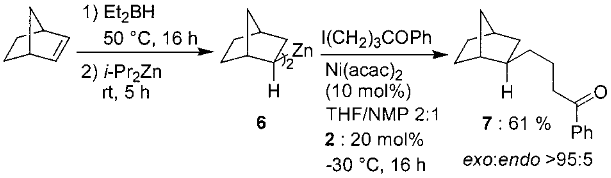
Table 3. Ni(0)-Catalyzed Cross-Coupling of Secondary Alkylzinc Iodides 1c–d with Alkyl Iodides in the Presence of 2 (20 mol%) in THF/NMP

Entry	Zinc reagent	Alkyl iodide	Product of type 4	Yield (%)[a]
1	$i\text{-}Pr_2Zn$ **1c**	$PhCO(CH_2)_3I$ **3a**	 **4i**	63
2	 **1d**	**3a**	 **4h**	69
3	**1d**	$EtO_2C(CH_2)_3I$ **3d**	 **4j**	61
4	**1d**	$PivO(CH_2)_5I$ **3h**	 **4k**	56
5	**1d**	$NC(CH_2)_4I$ **3g**	 **4l**	67
6	**1d**	 **3b**	 **4m**	73

[a] Isolated yield of analytically pure product.

Scheme 3



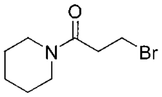
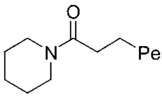
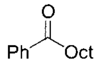
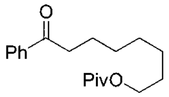
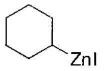
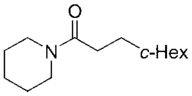
We have also examined the reactivity of alkyl bromides of type **8** and found that in the presence of Bu_4NI (3 equiv), the cross-coupling reaction takes place to furnish the desired product. As nucleophiles dialkylzincs such as $Pent_2Zn$ (entry 1 of Table 4), alkylzinc iodides such as pentylzinc iodide (**1a**; entries 2 and 3), or the functionalized alkylzinc reagent 4-pivaloyloxybutyl zinc iodide (**1e**; entry 4) have been used. Finally, a secondary alkylzinc iodide such as *c*-HexZnI (**1d**) aslo reacts, leading to the product **4m** in 63% yield (Scheme 4 and Table 4).

The side reactions in these nickel-catalyzed cross-couplings are mainly an iodine–zinc exchange reaction. No homocoupling product is observed.

This cross-coupling procedure can be successfully applied to alkyl iodides bearing an amino function with an unprotected NH group. Thus, the reaction of $Pent_2Zn$ with the amino acid derivative **9** and the oxazolidinone **10**[12] provides, under the standard reaction conditions, the expected products **11** and **12** in 56 and 60% yields, respectively (Scheme 5).

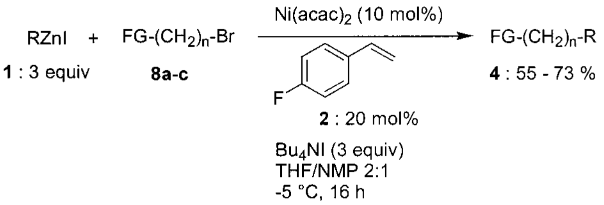
Whereas we have shown[6] that 4-fluorostyrene facilitates the reductive elimination of the intermediate Ni(II) complex $(R^1)(R^2)NiL_n$ by removing electron density from the metal center, the effect of Bu_4NI[13] is less clear.

Table 4. Ni(0)-Catalyzed Cross-Coupling of Functionalized Primary Alkyl Bromides with Various Zinc Organometallics in the Presence of Bu_4NI (3 equiv) and 2 (20 mol%) in THF/NMP

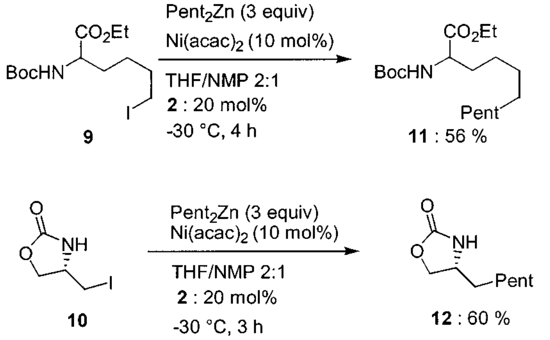
Entry	Zinc reagent	Alkyl bromide	Product of type **4**	Yield (%)[a]
1	$n\text{-}Pent_2Zn$[b]	$EtO_2C(CH_2)_3Br$ **8a**	$OctCO_2Et$ **4d**	55
2	n-PentZnI **1a**	 **8b**	 **4b**	69
3	**1a**	$PhCO(CH_2)_3Br$ **8c**	 **4a**	70
4	$PivO(CH_2)_4ZnI$ **1e**	**8c**	 **4n**	73
5	 **1d**	**8b**	 **4m**	63

[a] Isolated yields of analytically pure products. [b] Reaction temperature = −25 °C; Bu_4NI was omitted.

Scheme 4



Scheme 5



We noticed that an excess of this ammonium salt is necessary to achieve the optimum rate enhancement. The Bu_4NI-saturated reaction mixture has proven to be the best medium for this type of cross-coupling.[14] Concerning

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[12] Sibi, P.; Renhowe, P. A. *Tetrahedron Lett.* **1990**, *31*, 7407–10.

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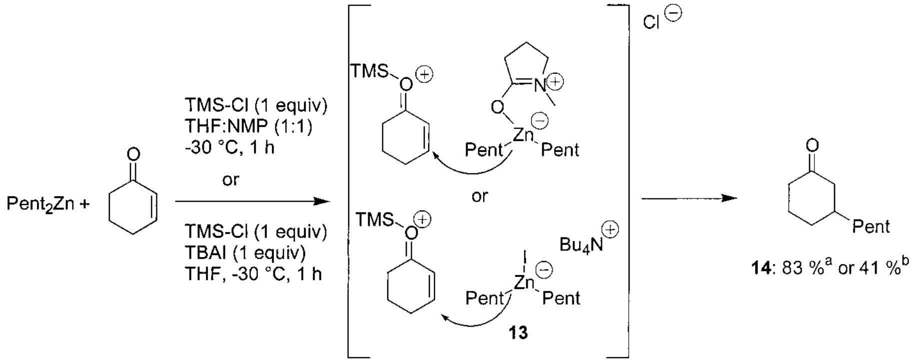
Scheme 6



^{a} With NMP as a cosolvent. ^{b} With TBAI, in the absence of NMP.

the mechanism of action of TBAI, the coordination of iodide to the alkylzinc iodide would possibly lead to a zincate of type **13** as an intermediate. This species should have an enhanced reactivity. To test this possibility, TBAI was used as an additive in the 1,4-addition reaction of dipentylzinc to cyclohexanone. Earlier experiments with this system had shown that NMP is needed as a cosolvent (THF/NMP 1:1) for the addition to take place.[15] In pure THF, no reaction occurs. However, when TBAI (1 equiv) was added, the addition reaction did take place in pure THF, although in lower yield (41%) than in the THF/NMP mixture, leading to the 1,4-addition product **14** (Scheme 6). Other possibilities like a change of the ionic strength of the medium or stabilization of a highly reactive low-valent nickel species may also be considered.

In summary, reaction conditions have been found allowing the cross-coupling of readily available functionalized alkylzinc halides with functionalized (and unfunctionalized) alkyl iodides. Further investigations are currently underway.

Experimental Section

General Methods. All reactions were carried out under an argon atmosphere in flame-dried glassware. THF was distilled under argon from sodium/benzophenone. NMP was distilled under argon from calcium hydride. Commercially available materials were used without further purification. Reactions were monitored by gas chromatography (GC) analysis of worked up reaction aliquots. Analytical thin-layer chromatography (TLC) was performed using Merck silica gel (60 F-254) plates (0.25 mm) precoated with a fluorescent indicator. Column chromatography was performed with 40−63 μm silica gel (Merck). GC analysis was performed on a bonded 5% phenylmethylpolysiloxane DB 5 capillary column (Megabore, 15 m, 0.53 mm i.d., 2.65 μm df). NMR spectra were recorded on a 200 or 300 MHz NMR spectrometer. Infrared spectroscopy was performed with a Spectrum 1000 Perkin-Elmer FT-IR spectrometer. The ionization method used for mass spectrometry was electron impact (EI, 70 eV). Elemental analyses were performed by the Microanalytical Service Laboratory of Universität München.

Starting Materials. The following starting materials were prepared according to literature procedures: 1-iodo-4-octanone (**3c**),[6c] 4-iodo-1-phenyl-1-butanone (**3a**),[16] 5-iodopentanenitrile (**3g**),[17] 3-iodo-1-piperidino-1-propanone (**3b**),[6c] 3-iodopropyl phenyl sulfide (**3f**),[18] 5-iodopentyl pivalate (**3h**),[19] 3-chloro-1-piperidino-1-propanone,[20] 3-iodo-1-piperidino-1-propanone.[21]

Preparation of Alkylzinc Iodides of Type 1 (Pentylzinc Iodide). A 25 mL two-necked flask equipped with a dropping funnel, a reflux condenser, and a stirring bar was charged with cut zinc foil (Merck) (1.77 g, 27 mmol), flame-dried, and flushed with argon. THF (1 mL) and 1,2-dibromoethane (51 mg, 0.27 mmol) were added, and the zinc was activated by being heated to reflux with a heat gun and then cooled to room temperature. This procedure was repeated until foam no longer formed as a result of the heating. The mixture was heated to 50 °C followed by dropwise addition of pentyl iodide (1.77 g, 9 mmol) in THF (4 mL). The mixture was kept at 50 °C until complete conversion was reached (checked by GC analysis, approximately 4 h).

Typical Procedure A: Nickel-Catalyzed Cross-Coupling between Primary Alkyl Iodides and Alkylzinc Iodides. Preparation of 1-Phenyl-1-octanone (4e). A dry and argon-flushed 10 mL two-necked flask was charged with Ni(acac)$_2$ (77 mg, 0.3 mmol). Dry THF (2 mL), NMP (1 mL), 3-iodo-1-phenyl-1-propanone (**3e**, 780 mg, 3 mmol), 4-fluorostyrene (74 mg, 0.6 mmol), and Bu$_4$NI (3.3 g, 9 mmol) were successively added at room temperature. The reaction mixture was cooled to −35 °C before the slow addition of a solution of pentylzinc iodide (4.5 mL, 2 M, 9 mmol). The reaction mixture was then allowed to warm to −5 °C. The conversion was complete in 16 h, after which time the reaction was quenched with saturated aqueous NH$_4$Cl solution (2 mL) and the mixture extracted with ether (4 × 50−75 mL). The combined organic phases were dried (MgSO$_4$) and the solvents removed in vacuo. Flash chromatography on silica gel (pentane/ether 20:1) furnished the cross-coupling product **4e** as a colorless oil (349 mg, 57%). IR (KBr): 2956 (s), 2856 (m), 1687 (s), 1449 (s), 1266 (m) cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.97 (d, J = 7.2 Hz, 2H), 7.56−7.42 (m, 3H), 2.95 (t, J = 7.5 Hz, 2H), 1.76−1.20 (m, 10H), 0.89 (t, J = 6.6, 3H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 200.8, 137.5, 133.2, 128.9, 128.4, 39.0, 31.9, 29.7, 29.5, 24.7, 23.6, 14.4. MS (EI, 70 eV): 204 (5), 133 (9), 120 (90), 105 (100), 77 (35). Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.52; H, 9.53. The products **4a**−**f** as well as **4m**,**n** were prepared according to this method.

1-Phenyl-1-nonanone (4a): From 4-iodo-1-phenyl-1-butanone (**3a**, 820 mg, 3 mmol) and pentylzinc iodide (6.0 mL, 1.5 M, 9 mmol). Reaction time: 16 h at −5 °C. Purification by flash chromatography (pentane/ether 20:1) yielded **4a** as a colorless oil (509 mg, 78%). IR (KBr): 2926 (s), 2855 (m), 1688

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(s), 1445 (m) cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$): δ 8.00−7.96 (m, 2H), 7.59−7.44 (m, 3H), 2.96 (t, J = 7.4 Hz, 2H), 1.79−1.68 (m, 6H), 1.31−1.17 (m, 4H), 0.92 (t, J = 7.4 Hz, 3H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 201.0, 137.5, 133.2, 128.9, 128.4, 39.3, 38.0, 37.5, 33.7, 27.1, 26.8, 22.1. MS (EI, 70 eV): 218 (6), 133 (8), 120 (73), 105 (100), 77 (18). Anal. Calcd for C$_{15}$H$_{22}$O: C, 82.52; H, 10.16. Found: C, 82.90; H, 10.38.

Alternatively, **4a** was prepared from 4-bromo-1-phenyl-1-butanone (**8c**, 681 mg, 3 mmol). Reaction time: 24 h at −5 °C (457 mg, 70%) (entry 3, Table 4).

1-Piperidino-1-octanone (4b): Prepared from 3-iodo-1-piperidino-1-propanone (**3b**, 798 mg, 3 mmol) and pentylzinc iodide (6.0 mL, 1.5 M in THF, 9 mmol). Reaction time: 16 h at −5 °C. Purification by flash chromatography (pentane/EtOAc 8:2) yielded **4b** as a colorless oil (392 mg, 62%). IR (KBr): 2930 (s), 2855 (m), 1644 (s), 1434 (m) cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$): δ 3.47 (bs, 2H), 3.32 (bs, 2H), 2.27−2.21 (m, 2H), 1.60−1.48 (m, 8H), 1.25−1.21 (m, 8H), 0.81 (t, J = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 171.9, 47.1, 43.0, 42.7, 33.9, 32.1, 29.9, 29.5, 27.0, 25.9, 25.0, 23.0, 14.4. MS (EI, 70 eV): 211 (7), 140 (41), 127 (100), 84 (41). Anal. Calcd for C$_{13}$H$_{25}$ON: C, 73.88; H, 11.92; N, 6.63. Found: C, 73.94; H, 11.86; N, 6.40.

Alternatively, **4b** was prepared from 3-bromo-1-piperidino-1-propanone (**8b**, 220 mg, 1 mmol). Reaction time: 16 h at 0 °C (145 mg, 69%) (entry 2, Table 4).

4-Tridecanone (4c): Prepared from 1-iodo-4-octanone (**3c**, 2.29 g, 9 mmol) and pentylzinc iodide (13.5 mL, 2 M in THF, 27 mmol). Reaction time: 16 h at −5 °C. Purification by flash chromatography (pentane/ether 20:1) yielded **4c** as a colorless oil (925 mg, 52%). IR (KBr): 2873 (s), 1716 (s), 1467 (m) cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$): δ 2.39 (t, J = 7.4 Hz, 4H), 1.57−1.52 (m, 4H), 1.33−1.26 (m, 12H), 0.92−0.84 (m, 6H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 212.0, 43.2, 42.9, 32.2, 29.7, 29.6, 29.5, 26.3, 24.2, 23.0, 22.7, 14.4, 14.2. MS (EI, 70 eV): 198 (6), 156 (10), 141 (72), 85 (85), 57 (100). Anal. Calcd for C$_{13}$H$_{26}$O: C, 78.72; H, 13.21. Found: C, 78.65; H, 13.31.

Ethyl Nonanoate (4d): Prepared from ethyl 4-iodobutanoate (**3d**, 726 mg, 3 mmol) and pentylzinc iodide (4.5 mL, 2 M in THF, 9 mmol). Reaction time: 16 h at −5 °C. Purification by flash chromatography (pentane/ether 20:1) yielded **4d** as a colorless oil (266 mg, 48%). IR (KBr): 2957 (m), 2928 (s), 2856 (m) 1739 (s) cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$): δ 4.10 (q, J = 7.2 Hz, 2H), 2.27 (t, J = 7.5 Hz, 2H), 1.60 (q, J = 7.2 Hz, 2H), 1.26−1.21 (m, 13H), 0.86 (t, J = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 172.5, 58.8, 33.0, 30.5, 27.9, 27.8, 27.8, 21.3, 16.3, 12.9, 12.7. MS (EI, 70 eV): 186 (4), 141 (39), 101 (60), 88 (100). Anal. Calcd for C$_{11}$H$_{22}$O$_2$: C, 78.72; H, 13.21. Found: C, 78.65; H, 13.31.

Alternatively, **4d** was prepared from ethyl 4-bromobutanoate (**8a**, 585 mg, 3 mmol) and dipentylzinc (1.2 mL, 5 M, 6 mmol) omitting Bu$_4$NI (typical procedure C). Reaction time: 16 h at −25 °C (102 mg, 55%) (entry 1, Table 4).

8-Oxo-8-phenyloctyl Pivalate (4f): Prepared from 4-iodo-1-phenyl-1-butanone (**3a**, 274 mg, 1 mmol) and {5-[(2,2-dimethylpropanoyl)oxy]-pentyl}zinc iodide (2.5 mL, 2 M in THF, 5 mmol). Reaction time: 16 h at −5 °C. Purification by flash chromatography (pentane/EtOAc 95:5) yielded **4f** as a colorless oil (250 mg, 78%). IR (KBr): 2933 (s), 2857 (m), 1728 (s) 1688 (s) cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.98−7.95 (m, 2H), 7.56−7.44 (m, 3H), 4.05 (t, J = 6.6 Hz, 2H), 2.97 (t, J = 7.4 Hz, 2H), 1.77−1.72 (m, 2H), 1.63−1.60 (m, 2H), 1.36 (m, 6H), 1.20 (s, 9H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 200.9, 179.6, 137.5, 133.2, 128.9, 128.4, 64.8, 39.1, 38.9, 29.7, 29.6, 29.5, 29.0, 27.6, 26.2, 24.7. MS (EI, 70 eV): 318 (3), 120 (88), 105 (100), 57 (28). Anal. Calcd for C$_{20}$H$_{30}$O$_3$: C, 75.43; H, 9.49. Found: C, 75.47; H, 9.32.

Alternatively, **4f** was prepared from 4-iodo-1-phenyl-1-butanone (**3a**, 820 mg, 3 mmol) and {5-[(2,2-dimethylpropanoyl)oxy]-pentyl}(TMSM)zinc (4.5 mL, 2 M in THF, 9 mmol) omitting Bu$_4$NI (typical procedure B). Reaction time: 6 h at −20 °C (474 mg, 50%) (entry 4, Table 2). By this reaction, additional 1-phenyl-4-(trimethylsilyl)-1-butanone was formed as a byproduct (147 mg, 21%). ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.95−7.90 (m, 2H), 7.60−7.46 (m, 3H), 2.97 (t, J = 7.2 Hz, 2H), 1.67−1.58 (m, 2H), 0.68 (t, J = 7.2 Hz, 2H), 0.00 (s, 9H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 198.9, 136.7, 133.2, 128.6, 127.8, 42.4, 18.7, 16.5, −2.0. MS (EI, 70 eV): 234 (3), 219 (44), 215 (72), 144 (35), 120 (100), 105 (43), 73 (87).[20]

1-(3-Cyclohexylpropanoyl)-piperidine (4m): Prepared from 3-bromo-1-piperidino-1-propanone (**8b**, 801 mg, 3 mmol) and cyclohexylzinc iodide (4.5 mL, 2 M in THF, 9 mmol). Reaction time: 16 h at −5 °C. Purification by flash chromatography (pentane/EtOAc 8:2) yielded **4m** as a colorless oil (421 mg, 63%). IR (KBr): 2922 (s), 2851 (m), 1644 (s) 1445 (m) cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$): δ 3.52−3.42 (m, 4H), 2.35−2.29 (m, 2H), 1.76−1.63 (m, 13H), 1.57−1.50 (m, 4H), 1.23−1.20 (m, 2H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 172.2, 47.1, 43.0, 37.9, 33.5, 33.5, 33.3, 31.4, 27.0, 27.0, 26.6, 26.6, 26.0, 25.0. MS (EI, 70 eV): 223 (3), 140 (25), 127 (100), 84 (18), 55 (10). Anal. Calcd for C$_{14}$H$_{25}$ON: C, 75.29; H, 11.28; N, 6.27. Found: C, 75.31; H, 11.16; N, 6.11.

7-Oxo-7-phenylheptyl pivalate (4n): Prepared from 4-bromo-1-phenyl-1-butanone (**8c**, 227 mg, 1 mmol) and {4-[(2,2-dimethylpropanoyl)oxy]-butyl}zinc iodide (2.5 mL, 2 M in THF, 5 mmol). Reaction time: 20 h at −5 °C. Purification by flash chromatography (pentane/EtOAc 95:5) yielded **4n** as a colorless oil (222 mg, 73%). IR (KBr): 2934 (s), 2859 (m), 1727 (s), 1688 (s), 1285 (s), 1157 (s) cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.89 (d, J = 6.9 Hz, 2H), 7.53−7.38 (m, 3H), 3.97 (t, J = 6.6 Hz, 2H), 2.89 (t, J = 7.5 Hz, 2H), 1.80−1.25 (m, 10H), 1.12 (s, 9H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 200.8, 179.0, 137.5, 133.3, 128.9, 128.4, 64.7, 39.1, 38.9, 29.6, 29.5, 29.0, 27.6, 26.2, 24.6. MS (EI, 70 eV): 304 (2), 120 (94), 105 (100), 57 (23). Anal. Calcd for C$_{19}$H$_{28}$O$_3$: C, 74.96; H, 9.27. Found: C, 74.99; H, 9.40.

Preparation of Mixed Alkyl(TMSM)zincs of Type 5 (Pentyl(TMSM)zinc). A 25 mL two-necked flask equipped with a stirring bar was flame-dried and flushed with argon. Pentylzinc iodide (4.5 mL, 2 M in THF, 9 mmol) was added and cooled to −40 °C before adding trimethylsilylmethyllithium (9 mL, 1 M, 9 mmol) dropwise over 5 min. The reaction was left for 1 h at −40 °C before being warmed to room temperature and then concentrated in vacuo until an approximately 2 M solution was obtained, which was used directly in the cross-coupling reaction.

Typical Procedure B: Nickel-Catalyzed Cross-Coupling between Primary Alkyl Iodides and Mixed Alkyl(TMSM)zincs. Preparation of 1-Phenyl-1-nonanone (4a). A dried and argon-flushed 10 mL two-necked flask was charged with Ni(acac)$_2$ (77 mg, 0.3 mmol). Dry THF (2 mL), NMP (1 mL), 4-iodo-1-phenyl-1-butanone (**3a**, 820 mg, 3 mmol), and 4-fluorostyrene (74 mg, 0.6 mmol) were added successively at room temperature. The reaction mixture was cooled to −60 °C before the slow addition of a solution of pentyl(TMSM)zinc (4.5 mL, 2 M in THF, 9 mmol). The reaction mixture was then allowed to warm to −20 °C. The conversion was complete in 1 h, after which time the reaction was quenched with saturated aqueous NH$_4$Cl solution (2 mL) and the mixture extracted with ether (4 × 50−75 mL). The combined organic phases were dried (MgSO$_4$) and the solvents removed in vacuo. Flash chromatography on silica gel (pentane/ether 20:1) furnished the cross-coupling product **4e** as a colorless oil (481 mg, 74%). The products **4a**,**b**,**f**−**h** were prepared according to this method.

Octyl Phenyl Sulfide (4 g): Prepared from 3-iodopropyl phenyl sulfide (**3f**, 556 mg, 2 mmol) and pentyl(TMSM)zinc iodide (2 mL, 2 M in THF, 4 mmol). Reaction time: 16 h at −20 °C. Purification by flash chromatography (pentane/ether 20:1) yielded **4g** as a colorless oil (300 mg, 71%). IR (KBr): 2957 (m), 2927 (s), 2855 (m), 1480 (w) cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.25−7.03 (m, 5H), 2.82 (t, J = 7.5 Hz, 2H), 1.59−1.51 (m, 2H), 1.35−1.31 (m, 2H), 1.21−1.10 (m, 6H), 0.80 (t, J = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 137.5, 129.2, 129.2, 126.0, 34.0, 32.2, 29.6, 29.3, 23.1, 14.5. MS (EI, 70 eV): 222 (55), 126 (26), 110 (100), 77 (9). Anal. Calcd for C$_{14}$H$_{22}$S: C, 75.61; H, 9.97; S, 14.42. Found: C, 75.82; H, 10.28; S, 14.41.

4-Cyclohexyl-1-phenyl-1-butanone (4h): Prepared from 4-iodo-1-phenyl-1-butanone (**3a**, 544 mg, 2 mmol) and pentyl(TMSM)zinc iodide (2 mL, 2 M in THF, 4 mmol). Reaction time: 5 h at −20 °C. Purification by flash chromatography (pentane/ether 20:1) yielded **4h** as a colorless oil (303 mg, 65%). IR (KBr): 2925 (s), 2849 (s), 1687 (s), 1448 (m) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.87−7.84 (m, 2H), 7.46−7.32 (m, 3H), 2.83 (t, $J = 7.5$ Hz, 2H), 1.70−1.53 (m, 4H), 1.18−1.02 (m, 2H), 0.81−0.77 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.8, 137.5, 128.9, 128.0, 39.3, 38.0, 37.5, 33.7, 33.7, 27.1, 26.8, 26.8, 22.7. MS (EI, 70 eV): 230 (8), 120 (100), 105 (71), 77 (28). Anal. Calcd for $C_{16}H_{22}O$: C, 83.43; H, 9.63. Found: C, 83.44; H, 9.85.

Preparation of Dinorbornylzinc (6). A 25 mL two-necked flask equipped with a stirring bar was flame-dried and flushed with argon. 2-Norbornene (376 mg, 4 mmol) was added and the flask degassed 3 times before the dropwise addition of diethylborane (1.6 mL, 7 M, 12 mmol) at room temperature. The reaction mixture was then left for 16 h at 50 °C. Excess diethylborane was distilled off (25 °C, 1 mmHg, 3 h). i-Pr_2Zn (2.4 mL, 5 M, 12 mmol) was added via syringe at room temperature and the resulting mixture stirred at room temperature for 5 h before excess i-Pr_2Zn was distilled off (25 °C, 1 mmHg, 2 h). The zinc reagent was taken up in THF (7 mL) and transferred to a dried and argon-flushed Schlenk flask; after centrifugation, the supernatant was concentrated in vacuo and used directly in the cross-coupling reaction.

Typical Procedure C: Nickel-Catalyzed Cross-Coupling between Primary Alkyl Iodides and Secondary Dialkylzincs. Preparation of 4-Bicyclo[2.2.1]hept-2-yl-1-phenyl-1-butanone (7). A dried and argon-flushed 10 mL two-necked flask was charged with $Ni(acac)_2$ (26 mg, 0.1 mmol). Dry THF (0.7 mL), NMP (0.3 mL), 4-iodo-1-phenyl-1-butanone (**3a**, 274 mg, 1 mmol), and 4-fluorostyrene (25 mg, 0.2 mmol) were added successively at room temperature. The reaction mixture was cooled to −60 °C before slow addition of a solution of dinorbornylzinc **(6)** (2 mL, 2 M in THF, 4 mmol). The reaction mixture was then allowed to warm to −15 °C. The conversion was complete in 16 h, after which time the reaction was quenched with saturated aqueous NH_4Cl solution (2 mL) and the mixture extracted with ether (4 × 50−75 mL). The combined organic phase was dried ($MgSO_4$) and the solvents removed in vacuo. Flash chromatography on silica gel (pentane/ether 20:1) furnished the cross-coupling product **7** as a colorless oil (146 mg, 61%, diastereomeric ratio > 95:5). IR (KBr): 2947 (s), 2868 (m), 1687 (s), 1449 (m) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.88−7.84 (m, 2H), 7.47−7.32 (m, 3H), 2.85 (t, $J = 7.5$ Hz, 2H), 2.10 (bs, 1H), 1.88 (bs, 1H), 1.64−1.59 (m, 2H), 1.39−0.94 (m, 11H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 199.4, 136.1, 131.8, 127.0, 41.1, 40.9, 37.8, 37.6, 36.2, 35.5, 34.3, 29.1, 27.8, 22.6. MS (EI, 70 eV): 242 (9), 133 (13), 120 (100), 105 (53). Anal. Calcd for $C_{17}H_{22}O$: C, 84.25; H, 9.15. Found: C, 83.98; H, 9.24. The stereochemistry of the product was determined by NOESY, HMBC, HMQC, COSY, and ^{1}H and ^{13}C NMR experiments. The observation of a NOE between one of the protons (1.5 ppm) of the one carbon bridge with the protons of the methylene group attached to the ring (1.2 ppm) clearly indicated that the exo product had been formed.

The products **4h−m** were prepared according to this method.

5-Methyl-1-phenyl-1-hexanone (4i): Prepared from 4-iodo-1-phenyl-1-butanone (**3a**, 274 mg, 1 mmol) and diisopropylzinc (0.55 mL, 3.7 M in THF, 2 mmol). Reaction time: 3 h at −30 °C. Purification by flash chromatography (pentane/ether 20:1) yielded **4i** as a colorless oil (121 mg, 63%). IR (KBr): 2955 (s), 2870 (m), 1687 (s), 1449 (m) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.99−7.96 (m, 2H), 7.57−7.45 (m, 3H), 2.96 (t, $J = 7.4$ Hz, 2H), 1.79−1.74 (m, 2H), 1.65−1.50 (m, 1H), 1.33−1.27 (m, 2H), 0.92 (d, $J = 3.3$ Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 201.0, 137.5, 133.2, 128.9, 128.4, 39.2, 39.0, 28.3, 22.9, 22.6. MS (EI, 70 eV): 190 (8), 133 (8), 120 (78), 105 (100), 77 (37). Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.53. Found: C, 81.92; H, 9.26.

Ethyl 4-Cyclohexylbutanoate (4j): Prepared from ethyl 4-iodobutanoate (**3d**, 726 mg, 3 mmol) and dicyclohexylzinc (7.5 mL, 0.8 M in THF, 6 mmol). Reaction time: 16 h at −30 °C. Purification by flash chromatography (pentane/ether 20:1) yielded **4j** as a colorless oil (351 mg, 61%). IR (KBr): 2955 (s), 2870 (m), 1687 (s), 1449 (m) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.06 (q, $J = 7.1$ Hz, 2H), 2.23−2.17 (m, 2H), 1.65−1.53 (m, 6H), 1.21−1.10 (m, 8H), 0.87 (t, $J = 7.1$ Hz, 3H), 0.81−0.79 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.3, 60.5, 37.7, 37.3, 35.6, 33.6, 27.0, 26.7, 22.7, 18.8, 14.6, 14.0. MS (EI, 70 eV): 198 (3), 155 (94), 135 (37), 101 (27), 88 (100). Anal. Calcd for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18. Found: C, 72.80; H, 10.96.

5-Cyclohexylpentyl Pivalate (4k): Prepared from 5-iodopentyl pivalate (**3h**, 894 mg, 3 mmol) and dicyclohexylzinc (7.5 mL, 0.8 M in THF, 6 mmol). Reaction time: 16 h at −20 °C. Purification by flash chromatography (pentane/ether 20:1) yielded **4k** as a colorless oil (425 mg, 56%). IR (KBr): 2924 (s), 2852 (m), 1731 (s), 1156 (s) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.97 (t, $J = 6.6$ Hz, 2H), 1.63−1.54 (m, 6H), 1.50−1.42 (m, 5H), 1.20−1.09 (m, 6H), 1.125 (s, 9H), 0.83−0.72 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 179.0, 64.8, 39.1, 38.7, 29.0, 27.6, 27.1, 26.8, 26.6. MS (EI, 70 eV): 254 (0), 152 (26), 124 (13), 103 (100), 96 (62), 57 (86). Anal. Calcd for $C_{16}H_{30}O_2$: C, 75.54; H, 11.89. Found: C, 75.77; H, 11.93.

5-Cyclohexylpentanenitrile (4l): Prepared from 5-iodopentanenitrile (**3f**, 624 mg, 3 mmol) and dicyclohexylzinc (7.5 mL, 0.8 M in THF, 6 mmol). Reaction time: 16 h at −20 °C. Purification by flash chromatography (pentane/ether 20:1) yielded **4l** as a colorless oil (330 mg, 67%). IR (KBr): 2924 (s), 2851 (s), 2246 (w), 1448 (m) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.26 (t, $J = 7.1$ Hz, 2H), 1.64−1.52 (m, 7H), 1.43−1.33 (m, 2H), 1.15−1.09 (m, 6H), 0.85−0.79 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 120.2, 37.8, 36.9, 33.2, 33.2, 27.0, 26.7, 26.7, 26.3, 26.0, 17.5. MS (EI, 70 eV): 164 (12), 136 (67), 110 (100), 83 (63), 55 (79). Anal. Calcd for $C_{11}H_{19}N$: C, 79.94; H, 11.59; N, 8.47. Found: C, 79.91; H, 11.08; N, 8.38.

4-Hexyl-1,3-oxazolidin-2-one (12): Prepared from 4-(iodomethyl)-1,3-oxazolidin-2-one (**10**, 340 mg, 1.5 mmol) and dipentylzinc (0.6 mL, 5 M in THF, 3 mmol). Reaction time: 3 h at −30 °C. Purification by flash chromatography (pentane/EtOAc 1:1) yielded **12** as a colorless oil (143 mg, 60%). IR (KBr): 3272 (m), 2956 (s), 2857 (s), 1754 (s) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.96 (bs, 1H), 4.43−4.37 (dt, $J = 8.4$ and 0.9 Hz, 1H), 3.95−3.90 (m, 1H), 3.81−3.76 (m, 1H), 1.51−1.47 (m, 2H), 0.83−0.79 (t, $J = 8.0$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.9, 70.7, 53.1, 37.7, 31.9, 29.3, 25.2, 23.1, 14.3. MS (EI, 70 eV): 154 (0), 86 (100), 58 (6). Anal. Calcd for $C_9H_{16}O_2N$: C, 63.13; H, 10.06; N, 8.18. Found: C, 63.20; H, 10.00; N, 8.12.

Ethyl 2-[*t*-Butoxycarbonyl)amino]undecanoate (11): Prepared from ethyl 2-[*t*-butoxycarbonyl)-amino]-6-iodohexanoate (**9**, 385 mg, 1 mmol) and dipentylzinc (0.4 mL, 5 M, 2 mmol). Reaction time: 4 h at −30 °C. Purification by flash chromatography (pentane/EtOAc 8:1) yielded **11** as a colorless oil (184 mg, 56%). IR (KBr): 3306 (m), 1745 (s), 1440 (m), 1403 (m), 1226 (s) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.95 (bd, 1H), 4.23−4.08 (m, 3H), 1.70−1.62 (m, 1H), 1.59−1.48 (m, 1H), 1.39 (s, 9H), 1.25−1.16 (m, 17H), 0.81 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.4, 155.8, 80.1, 61.5, 53.9, 42.7, 33.2, 32.2, 29.8, 29.7, 29.6, 29.6, 28.7, 23.0, 14.6, 14.4. MS (EI, 70 eV): 329 (2), 256 (42), 212 (76), 57 (100). Anal. Calcd for $C_{18}H_{35}O_4N$: C, 63.13; H, 10.06; N, 8.18. Found: C, 63.20; H, 10.00; N, 8.12.

2-[*t*-Butoxycarbonyl)amino]-6-iodohexanoate (9). A 250 mL flame-dried and argon-flushed flask containing LDA (60 mmol, 0.5 M in THF/hexane) was cooled to −78 °C before slow addition of ethyl 2-[*t*-butoxycarbonyl)amino]acetate (4.0 g, 20 mmol) in THF (70 mL). The mixture was allowed to warm to −60 °C, left for 1 h, and then cooled again to −78 °C before the slow addition of 4-chloro-1-iodobutane (17.4 g, 80 mmol). After complete addition, the reaction mixture was allowed to warm to room temperature overnight. The reaction was quenched with saturated NH_4Cl solution and the mixture extracted several times with EtOAc. Purification by flash chromatography (pentane/EtOAc 8:2) gave 2-[*t*-butoxycarbonyl)amino]-6-chlorohexanoate as a pale yellow oil (3.16 g, 54%). IR (KBr): 3306 (m), 1745 (s), 1440 (m), 1403 (m), 1226 (s) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.95 (bd, 1H), 4.28−4.08 (m, 3H), 3.46 (t, $J = 7.2$ Hz, 2H), 1.82−1.38 (m, 6H), 1.37 (s, 9H), 1.22 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.0, 155.7, 80.2, 61.7, 53.6, 44.9, 32.4, 32.2, 28.7, 22.9, 14.5. MS (EI, 70 eV): 293 (2), 258 (42), 212 (76), 57 (100). The alkyl chloride (2.5 g, 8.5 mmol) was taken up in acetone (30 mL), and NaI (12.6 g, 85 mmol) was added; then, the reaction was refluxed for 16 h. The solvent was distilled off in vacuo and the crude product taken up in EtOAc and washed with aqueous $Na_2S_20_3$, dried over $MgSO_4$, and concentrated. Purification by flash chromatography (pentane/EtOAc 8:2) gave the product as a pale yellow oil (2.87 g, 89%). IR (KBr): 3306 (m), 1745 (s), 1440 (m), 1403 (m), 1226 (s) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 4.95 (bd, 1H), 4.28−4.08 (m, 3H), 3.46 (t, $J = 7.2$ Hz, 2H), 1.82−1.38 (m, 6H), 1.38 (s, 9H), 1.22 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.0, 155.7, 80.3, 61.8, 53.6, 33.2, 32.1, 28.7, 26.5, 14.5, 6.6. MS (EI, 70 eV): 293 (2), 258 (42), 212 (76), 57 (100). Anal. Calcd for $C_{13}H_{24}O_4NI$: C, 40.53; H, 6.28; N, 3.64. Found: C, 40.33; H, 6.49; N, 3.65.

Synthesis of 3-Pentyl-cyclohexanone (14).[15] A 23 mL Schlenk flask charged with TBAI (738 mg, 2 mmol) and THF (2 mL) was cooled to −30 °C; then, cyclohexenone (192 mg, 2 mmol) and TMSCl (200 mg, 2 mmol) were added, followed by dipentylzinc (**3a**) (0.4 mL, 5.0 M, 2 mmol). The resulting mixture was stirred for 1 h at −30 °C, poured into aqueous 10% HCl solution (20 mL) in THF (20 mL), and stirred for 15 min. The reaction mixture was then extracted with ether, dried over $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography (pentane/diethyl ether 95:5) yielded **14** as a colorless oil (98 mg, 41%). ^1H NMR (300 MHz, $CDCl_3$): δ 2.37−1.80 (m, 9H), 1.13−1.20 (m, 8H), 0.81 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 211.0, 47.2, 40.5, 38.1, 35.6, 31.3, 30.6, 25.1, 24.3, 21.6, 13.0. MS (EI, 70 eV): 168 (11), 88 (100), 72 (22).

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Supporting Information Available: Copies of ^1H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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