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Ester Formation via Nickel-Catalyzed Reductive Coupling of Alkyl Halides with Chloroformates

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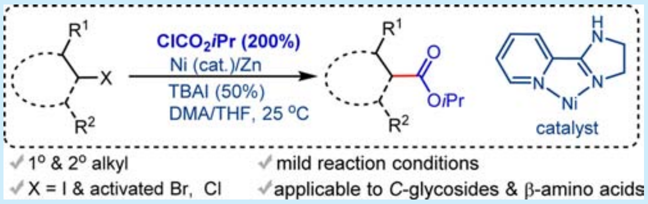
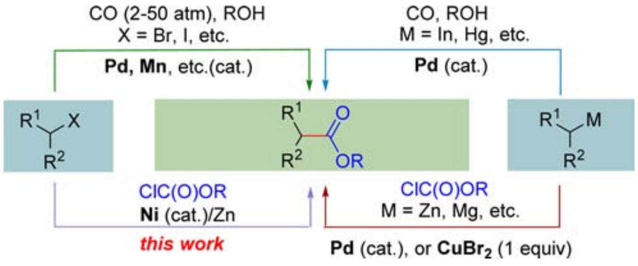
Supporting Information

ABSTRACT: The synthesis of alkyl esters from readily available alkyl halides and chloroformates was achieved for the first time using a mild Ni-catalyzed reductive coupling protocol. Unactivated primary and secondary alkyl iodides as well as glycosyl, benzyl, and aminomethyl halides were successfully employed to yield products in moderate to excellent yields with high functional group tolerance.



Alkyl acid esters are important structural motifs commonly found in bioactive natural products, pharmaceuticals, materials, and biofuels.[1] In addition to the textbook esterification of acid derivatives with alcohols, their preparation can be achieved through additions of alkyl-M (M = Mg, Zn, Li, etc.) to chloroformates or CO gas (M = In, Hg).[2−6] These reactions often require palladium catalysts, although a stoichiometric amount of $CuBr_2$ can promote the reaction of alkyl-Mg with chloroformates (Scheme 1).[3] Harsh alkyl nucleophiles appear to be inevitable for most cases. On the other hand, Pd- and Pt-catalyzed carbonylation of alkyl iodides under a CO atmosphere (usually high pressure) exemplifies a different protocol for ester formation that avoids prepreparation of organometallic reagents.[7−9] With the promotion of photo-irradiation, inexpensive metals (e.g., Cu, Mn, Co) can also catalyze such a process.[10,11] Herein we report the efficient construction of alkyl acid esters under mild, Ni-catalyzed reductive coupling conditions from both primary and secondary alkyl halides. The practicality of this method is manifested in the synthesis of α-C-glycosyl and amino esters.

Scheme 1. Transition-Metal-Catalyzed Ester Formation via Carbonylation and Coupling Strategies



In line with the recent progress in Ni-catalyzed reductive ketone, acid, and amide synthesis via the coupling of alkyl halides with acid derivatives, CO_2, and isocyanates,[12−16] we envisioned that direct coupling of alkyl halides with readily accessible chloroformates would be an efficient strategy to access the ester functional group. However, toward this end, the development of analogous conditions for ester synthesis proved to be more challenging. In fact, the complexities of these carboacylation transformations has been evidenced by their mechanistic distinctions. While a radical-chain process is involved in reductive ketone formation, insertion of CO_2 or isocyanates to an alkyl-Ni^I species is proposed for the production of acids and amides.[13f,15,16]

At the outset of this research, we examined the coupling between 4-iodo-1-tosylpiperidine (**1**) (limiting reagent) and methyl chloroformate. Initial attempts implementing previous methods used for the acylation of alkyl halides with acid derivatives provided the ester in only trace amounts.[13d−g] We were pleased to find that a combination of $Ni(COD)_2$/**3a**/Zn with TBAI as an additive in DMA/THF (7:3 v/v) was optimal. Under these conditions, the ester product (**2a**) was obtained in 82% yield (Table 1, entry 1), wherein commercially available isopropyl chloroformate proved to be a superior coupling partner (see **2b**−**d** in Figure 2). Upon removal of TBAI, the yield diminished slightly (entry 2). Hence TBAI may facilitate removal of the salts on the zinc surface or assist the homogeneity of the reaction mixture. Without $Ni(COD)_2$, no product was detected (entry 3). Other solvents and nickel sources (Table S1)[17] as well as ligands (**3b**−**d** and **4**−**8**, Figure 1; entries 4−12) and temperatures (entries 13 and 14) failed to improve the yield. Importantly, no product was observed without ligand **3a** (entry 15), and the use of 1.5 equiv of chloroformate resulted in 65% yield (entry 16). Finally, no reactions occurred when alkyl bromides were used, regardless of whether KI or NaI was added.

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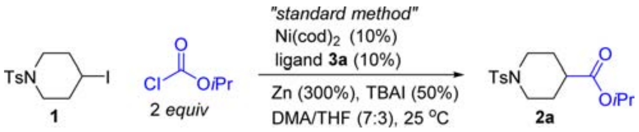
Table 1. Optimization of the Formation of 2



entry[a]	variation from the standard conditions	yield (%)[b]
1	none	82[c]
2	TBAI (0%)	74
3	without Ni(COD)$_2$	ND[d]
4	**3b** instead of **3a**	trace
5	**3c** instead of **3a**	61
6	**3d** instead of **3a**	60
7	**4** instead of **3a**	78
8	**5a** instead of **3a**	70
9	**5b** instead of **3a**	10
10	**6** instead of **3a**	ND[d]
11	**7** instead of **3a**	78
12	**8** instead of **3a**	63
13	40 °C	82
14	0 °C	82
15	without **3a**	ND[d]
16	1.5 equiv of ClC(O)O*i*Pr	65

[a] Reaction conditions: **1** (0.15 mmol), chloroformate (2 equiv), Ni (10 mol %), ligand (10 mol %), TBAI (50 mol %), Zn (3 equiv), DMA/THF (7:3 v/v, 1 mL). [b] NMR yields using 2,5-dimethylfuran as the internal reference. [c] Isolated yield. [d] Not detected by ^{1}H NMR analysis.

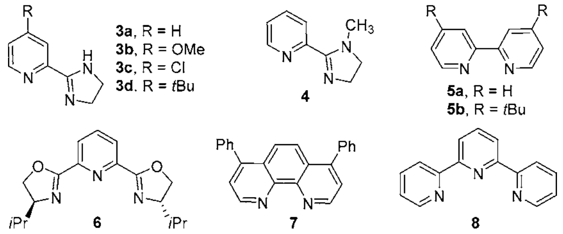


Figure 1. Structures of ligands.

Next, we examined the scope of alkyl iodides using the optimized conditions (Table 1, entry 1). The results are summarized in Figure 2. Both cyclic and open-chain secondary alkyl iodides were compatible, furnishing esters **9**–**22** in good to excellent yields. The sterically more hindered 6-iodoundecane afforded **16** in 70% yield. Primary alkyl iodides were also suited for this coupling protocol, as manifested in **23**–**26**. Furthermore, the mild reaction conditions tolerated a wide range of functional groups, including furyl, thienyl, and tosylamide.

The practicality of the ester-forming strategy was further manifested in the synthesis of C1-glycosyl esters (Figure 3). Moderate *α*-selectivity was shown for acetyl-protected glucoside **27** and galactoside **28**. Despite the propensity for benzylic substrates to undergo homocoupling, the use of activated 1-chloro-2,3-dihydro-1*H*-indene derivatives generated esters **29**–**31** in good yields. Installation of the ester functional group to phthamidyl-protected *α*-chloromethanamine was able to generate glycine methyl ester **32**, albeit in low yield. However, to the best of our knowledge, this is the first example of the synthesis of an *α*-amino acid using the reductive coupling protocol. Starting from their *α*-precursors, *β*-amino esters **33**–**37** were readily formed in good to excellent yields, wherein the iodo substrates were obtained from the ester precursor by reduction and iodination. Finally, **38** was achieved as a racemic mixture in good yield from its racemic iodo precursor.

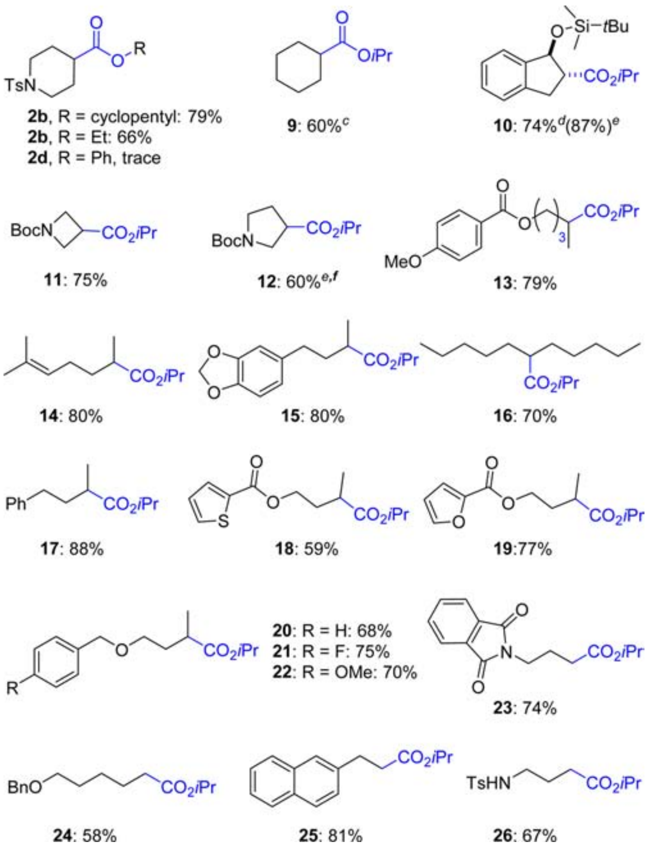


Figure 2. Scope of alkyl iodides. (a) Reaction conditions: as in Table 1, entry 1. (b) Isolated yields. (c) NMR yield using 2,5-dimethylfuran as the internal reference. (d) 3 equiv of chloroformate was used. (e) 4 equiv of chloroformate was used. (f) Without TBAI.

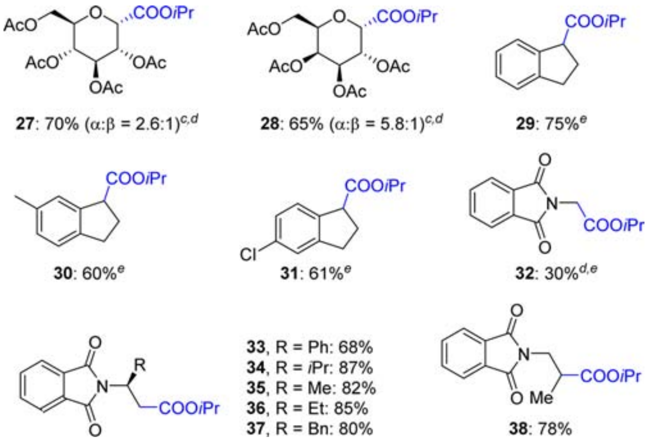
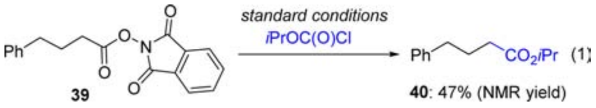


Figure 3. Coupling of activated alkyl halides and synthesis of *β*-amino acids. (a) Reaction conditions: as in Table 1, entry 1. (b) Isolated yields. (c) Glycosyl bromide was used. (d) **5a** was used as the ligand. (e) Benzyl chloride was used.

In accord with previous mechanistic studies, the radical nature of this method was verified by the synthesis of racemic ester **38** from its (*R*)-iodo precursor (87% ee) and by the ring-opening esterification of (iodomethyl)cyclopropane to yield isopropylpent-4-enoate in 30% yield.[17] Moreover, when *N*-hydroxyphthalimide ester **39** was subjected to the optimized reaction conditions, the transesterification product **40** was obtained in 40% yield, thus signifying the participation of alkyl radical via a possible Ni^{I}-mediated decarboxylative process (eq 1).[18,19] Although this result is indirectly related to alkyl iodides, both cases may accommodate an analogous mechanism.



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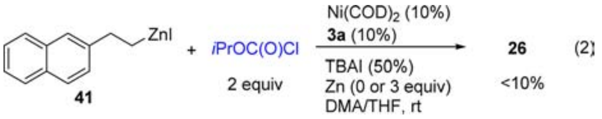
40: 47% (NMR yield)

Additional mechanistic studies excluded the possibility of an in situ Negishi mechanism. Exposure of alkylzinc reagent **41** to *i*PrOC(O)Cl under catalytic Ni conditions (eq 2) resulted in ester **26** in low yields both with and without Zn.[17]



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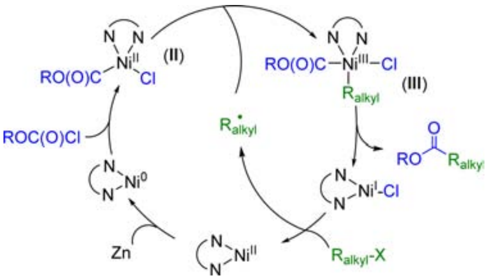
We then questioned whether the present ester formation event complies with a radical-chain mechanism analogous to the reductive ketone synthesis (Scheme 2). Interestingly, the key intermediate Bipy−Ni(Cl)−C(O)*i*Pr (**I**) engaged in the radical-chain process for ketone synthesis was stable in DMF (Figure 4),[13f] whereas Bipy−Ni(Cl)−C(O)O*i*Pr (**II-a**) and its analogs (**II-b** and **II-c**) arising from oxidative addition of chloroformate to Ni^0 decomposes instantly (Figure 4).[20,21]

Scheme 2. A Proposed Radical-Chain Catalytic Cycle



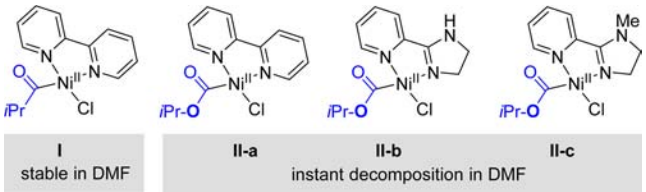
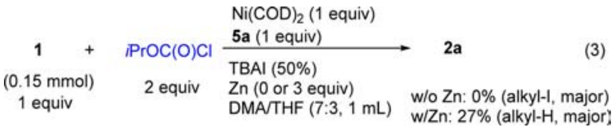
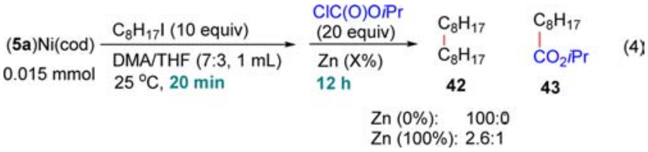


Figure 4. Stability of the proposed acyl intermediates in Ni-catalyzed ketone- and ester-forming methods.

Treatment of **1** with *i*PrOC(O)Cl in the presence of 1 equiv of Ni(COD)_2/**5a** but without Zn did not afford **2a**, and **1** was majorly recovered (eq 3), which may indicate that complex **II-a** formed but decomposed fast. With Zn, **2a** was obtained in 27% yield, wherein hydrodeiodination of **1** was observed as the major product (eq 3). Under the catalytic conditions, the good coupling yield of **2a** (70%; Table 1, entry 8) may arise from slow formation of complex **II-a** due to low concentrations of (**5a**)Ni^0, wherein decomposition of complex **II-a** may become less favored. As a result, complex **II** may have a long enough lifetime to trap escaped alkyl radical via a radical-chain process leading to *i*PrOC(O)−(L_n)Ni^{III}−alkyl (**III**) (Scheme 2).[22] The radical escape−rebound process is also supported by the experiments of esterification of 6-iodo-1-hexene under different Ni loadings.[23]



The results shown in eq 3 also indicated that oxidative addition of 2 equiv of chloroformate to Ni^0, resulting in complex **II**, is much more favored than that of 1 equiv of alkyl iodide leading to alkyl−(L_n)Ni^{II}−I species. However, stepwise reactions of (**5a**)Ni(COD) with *n*-octyl iodide followed by addition of chloroformate with or without Zn disclosed that the presence of Zn enabled a low ratio of product **43** to *n*-octyl dimerization product **42** (eq 4). Therefore, reduction of the alkyl-Ni^{II} precursor to give an alkyl−(L_n)Ni^{I} species that further reacts with chloroformate to produce the ester, although less likely, cannot be excluded at this time.[24,25]



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In summary, we have demonstrated that alkyl esters are readily accessible through reductive cross-electrophile coupling of alkyl iodides with isopropyl chloroformate under mild Ni-catalyzed conditions. This method tolerates a broad range of functional groups and displays an excellent substrate scope with application in the synthesis of amino esters and C1-glycosyl esters. The expansion of this method to new substrates and further mechanistic studies are currently underway.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03158.

> Detailed experimental procedures and characterization of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Sun, H. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 989. (b) Beller, H. R.; Lee, T. S.; Katz, L. *Nat. Prod. Rep.* **2015**, *32*, 1508. (c) Kamaly, N.; Yameen, B.; Wu, J.; Farokhzad, O. C. *Chem. Rev.* **2016**, *116*, 2602.

(2) (a) Yus, M.; Najera, C.; Chinchilla, R. *Sci. Synth.* **2006**, *20b*, 777. (b) Wu, X.-F.; Neumann, H.; Beller, M. *Chem. Rev.* **2013**, *113*, 1.

(3) RMgBr−CuBr−2LiBr: Bottalico, D.; Fiandanese, V.; Marchese, G.; Punzi, A. *Synlett* **2007**, *2007*, 974.

(4) R−Li: Moriya, K.; Didier, D.; Simon, M.; Hammann, J. M.; Berionni, G.; Karaghiosoff, K.; Zipse, H.; Mayr, H.; Knochel, P. *Angew. Chem., Int. Ed.* **2015**, *54*, 2754.

(5) Bn−Zn: Metzger, A.; Argyo, C.; Knochel, P. *Synthesis* **2010**, *2010*, 882.

(6) R−In: (a) Zhao, Y.; Jin, L.; Li, P.; Lei, A. *J. Am. Chem. Soc.* **2008**, *130*, 9429. R−Hg: (b) Baird, W. C., Jr.; Hartgerink, R. L.; Surridge, J. H. *J. Org. Chem.* **1985**, *50*, 4601.

(7) Sumino, S.; Fusano, A.; Fukuyama, T.; Ryu, I. *Acc. Chem. Res.* **2014**, *47*, 1563.

(8) Sargent, B. T.; Alexanian, E. J. *J. Am. Chem. Soc.* **2016**, *138*, 7520.

(9) Pt−RI/CO/H_2: Takeuchi, R.; Tsuji, Y.; Fujita, M.; Kondo, T.; Watanabe, Y. *J. Org. Chem.* **1989**, *54*, 1831.

(10) For an example of ambient light-mediated $Mn_2(CO)_{10}$-catalzyed radical cyclization/carbonylation of alkene-pendant alkyl iodides, see: McMahon, C. M.; Renn, M. S.; Alexanian, E. J. *Org. Lett.* **2016**, *18*, 4148.

(11) For additional examples of light-mediated inexpensive-metal-catalyzed carbonylation of alkyl halides, see: Cu: (a) Wang, H. W.; Jia, Y. P.; Gao, D. B.; Yin, J. M.; Zhou, G. Y.; Li, S. M. *Chin. Chem. Lett.* **2007**, *18*, 795. Co: (b) Cash, D.; Combs, A.; Dragojlovic, V. *Tetrahedron Lett.* **2004**, *45*, 1143. For additional examples using Cu-catalyzed carbonylative coupling of cycloalkanes, see: (c) Li, Y.; Dong, K.; Zhu, F.; Wang, Z.; Wu, X.-F. *Angew. Chem., Int. Ed.* **2016**, *55*, 7227. (d) Li, Y.; Zhu, F.; Wang, Z.; Wu, X.-F. *ACS Catal.* **2016**, *6*, 5561.

(12) For reviews of reductive coupling of two electrophiles, see: (a) Knappke, C. E. I.; Grupe, S.; Gärtner, D.; Corpet, M.; Gosmini, C.; Jacobi von Wangelin, A. *Chem. - Eur. J.* **2014**, *20*, 6828. (b) Everson, D. A.; Weix, D. J. *J. Org. Chem.* **2014**, *79*, 4793. (c) Moragas, T.; Correa, A.; Martin, R. *Chem. - Eur. J.* **2014**, *20*, 8242. (d) Weix, D. J. *Acc. Chem. Res.* **2015**, *48*, 1767. (e) Gu, J.; Wang, X.; Xue, W. C.; Gong, H. G. *Org. Chem. Front.* **2015**, *2*, 1411.

(13) For Ni-catalyzed reductive ketone synthesis, see: (a) Wotal, A. C.; Weix, D. J. *Org. Lett.* **2012**, *14*, 1476. (b) Wotal, A. C.; Ribson, R. D.; Weix, D. J. *Organometallics* **2014**, *33*, 5874. (c) Cherney, A. H.; Kadunce, N. T.; Reisman, S. E. *J. Am. Chem. Soc.* **2013**, *135*, 7442. (d) Wu, F.; Lu, W.; Qian, Q.; Ren, Q.; Gong, H. *Org. Lett.* **2012**, *14*, 3044. (e) Yin, H.; Zhao, C.; You, H.; Lin, Q.; Gong, H. *Chem. Commun.* **2012**, *48*, 7034. (f) Zhao, C.; Jia, X.; Wang, X.; Gong, H. *J. Am. Chem. Soc.* **2014**, *136*, 17645. (g) Jia, X.; Zhang, X.; Qian, Q.; Gong, H. *Chem. Commun.* **2015**, *51*, 10302.

(14) For photoredox/Ni dual catalytic ketone formation, see: (a) Le, C. C.; MacMillan, D. W. *J. Am. Chem. Soc.* **2015**, *137*, 11938. (b) Joe, C. L.; Doyle, A. G. *Angew. Chem., Int. Ed.* **2016**, *55*, 4040. (c) Amani, J.; Sodagar, E.; Molander, G. A. *Org. Lett.* **2016**, *18*, 732.

(15) For CO_2 trapping with alkyl halides and allylic acetates, see: (a) Liu, Y.; Cornella, J.; Martin, R. *J. Am. Chem. Soc.* **2014**, *136*, 11212. (b) Börjesson, M.; Moragas, T.; Martin, R. *J. Am. Chem. Soc.* **2016**, *138*, 7504.

(16) Serrano, E.; Martin, R. *Angew. Chem., Int. Ed.* **2016**, *55*, 11207.

(17) See the Supporting Information for details.

(18) Huihui, K. M. M.; Caputo, J. A.; Melchor, Z.; Olivares, A. M.; Spiewak, A. M.; Johnson, K. A.; DiBenedetto, T. A.; Kim, S.; Ackerman, L. K. G.; Weix, D. J. *J. Am. Chem. Soc.* **2016**, *138*, 5016.

(19) (a) Wang, J.; Qin, T.; Chen, T.-G.; Wimmer, L.; Edwards, J. T.; Cornella, J.; Vokits, B.; Shaw, S. A.; Baran, P. S. *Angew. Chem., Int. Ed.* **2016**, *55*, 9676. (b) Cornella, J.; Edwards, J. T.; Qin, T.; Kawamura, S.; Wang, J.; Pan, C.-M.; Gianatassio, R.; Schmidt, M. A.; Eastgate, M. D.; Baran, P. S. *J. Am. Chem. Soc.* **2016**, *138*, 2174.

(20) The Bipy−Ni(Cl)−C(O)OEt complex resulting from the reaction of Bipy−Ni(COD) with ethyl chloroformate was found to be thermally stable in the solid state. See: Seidel, W.; Raupach, L. Z. *Z. Chem.* **1988**, *28*, 414.

(21) Preparation of complex **II-a** was attempted following the procedure in ref 20. However, the isolated ochre solid turned green after overnight storage in a glovebox at rt. IR spectroscopy supported its decomposition. The ^{1}H NMR spectrum of the isolated solid in DMF-d_7 (even at −20 °C) was composed of characteristic peaks for *i*Pr-OH and paramagnetic peaks identical to those of (**5a**)$NiCl_2$, signifying complete decomposition (see the Supporting Information for details). Likewise, syntheses of **II-b** and **II-c** were attempted using the method in ref 20, but only complex mixtures were obtained in the DMF solutions.

(22) (a) Breitenfeld, J.; Ruiz, J.; Wodrich, M. D.; Hu, X. *J. Am. Chem. Soc.* **2013**, *135*, 12004. (b) Biswas, S.; Weix, D. J. *J. Am. Chem. Soc.* **2013**, *135*, 16192. (c) Schley, N. D.; Fu, G. C. *J. Am. Chem. Soc.* **2014**, *136*, 16588.

(23) Cyclization of 6-iodo-1-hexene with an increase in the Ni/**3a** catalyst loading from 2.5% to 15% resulted in a linear increase in the ratio of linear to 5-*exo*-cyclic esters, indicating that a radical escape−rebound mechanism may be operative (see the Supporting Information).

(24) Exposure of Ni^0 to excess alkyl iodide gives alkyl−Ni^{II}−I, which can be stable at low concentration (ref 22a). Also see: Yamamoto, T.; Kohara, T.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 2010.

(25) Jones, G. D.; Martin, J. L.; McFarland, C.; Allen, O. R.; Hall, R. E.; Haley, A. D.; Brandon, R. J.; Konovalova, T.; Desrochers, P. J.; Pulay, P.; Vicic, D. A. *J. Am. Chem. Soc.* **2006**, *128*, 13175.

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