

Linear-Selective Hydroarylation of Unactivated Terminal and Internal Olefins with Trifluoromethyl-Substituted Arenes

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S Supporting Information

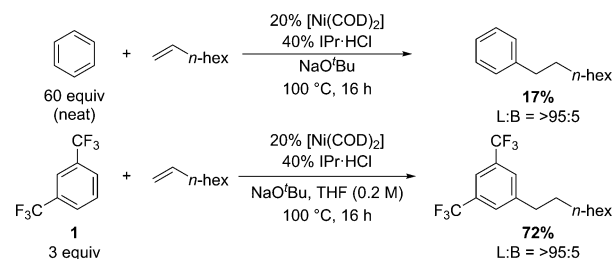
ABSTRACT: We report a series of hydroarylations of unactivated olefins with trifluoromethyl-substituted arenes that occur with high selectivity for the linear product without directing groups on the arene. We also show that hydroarylations occur with *internal*, acyclic olefins to yield linear alkylarene products. Experimental mechanistic data provide evidence for reversible formation of an alkyl-nickel-aryl intermediate and rate-determining reductive elimination to form the carbon-carbon bond. Labeling studies show that formation of terminal alkylarenes from internal alkenes occurs by initial establishment of an equilibrating mixture of alkene isomers, followed by addition of the arene to the terminal alkene. Computational (DFT) studies imply that the aryl C-H bond transfers to a coordinated alkene without oxidative addition and support the conclusion from experiment that reductive elimination is rate-determining and forms the anti-Markovnikov product. The reactions are inverse order in α -olefin; thus the catalytic reaction occurs, in part, because isomerization creates a low concentration of the reactant α -olefin.

The hydroarylation of olefins is the most direct method to prepare alkylarenes. Classical acid-catalyzed hydroarylations form branched alkylarene products, whereas metal-catalyzed hydroarylations could alter the regioselectivity and form linear alkylarenes. However, current metal-catalyzed hydroarylations that form linear products require directing groups,¹ occur with specific heteroarenes,² or occur with a modest preference for the linear over the branched product.³ The hydroarylation of unactivated alkenes by arenes with high selectivity for the linear products without directing groups has not been reported.⁴ We report nickel-catalyzed additions of the aryl C-H bonds on electron-poor aryl groups to terminal or *internal* alkenes to form the linear alkylarenes with selectivities approaching 20:1. Experimental and computational mechanistic data provide a detailed view into the factors controlling the rates and regioselectivity.

During our studies on Ni-catalyzed hydrogenolysis of aryl ethers,⁵ we discovered that a similar combination of nickel precursor Ni(COD)₂ and IPr carbene ligand (1,3-Bis(2,6-diisopropylphenyl)-1,3-dihydro-2H-imidazol-2-ylidene) cata-

lyzed the addition of benzene to 1-octene to form octylbenzene with a linear-to-branched selectivity of 95:5. Although the yield was <20%, the selectivity was much higher than that for any reported³ addition of a simple aryl C-H bond to an alkene (Scheme 1). Other carbene ligands formed less active catalysts for this reaction.⁶

Scheme 1. Development of Linear-Selective Hydroarylation with Unactivated Terminal Olefins



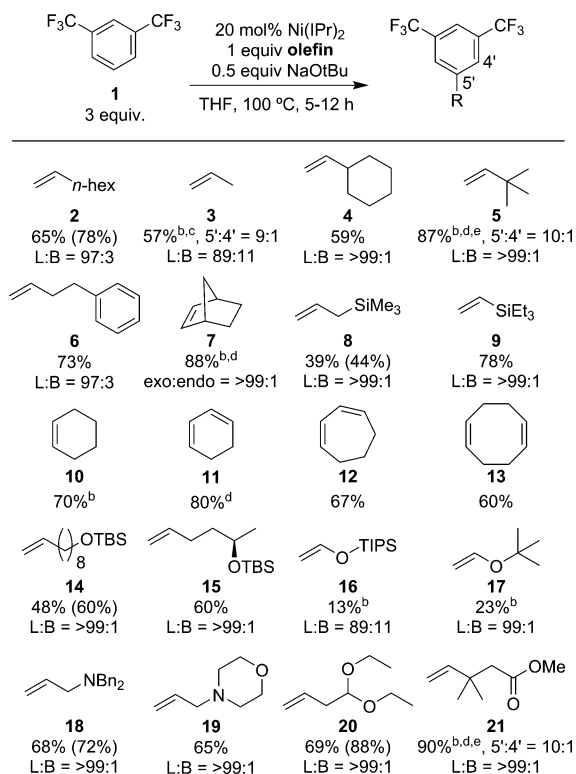
However, studies to identify more reactive arenes revealed that 1,3-bis(trifluoromethyl)benzene (**1**) reacted with 1-octene to give the linear product in 72% yield and a L:B selectivity >95:5 (Scheme 1).⁶ The regioselectivity at the arene appears to be dominated by steric factors, forming the product of hydroarylation at the least hindered position of the arene ring with >9:1 selectivity.

To avoid formation of side products from hydroarylation of COD, we examined reactions with precatalysts lacking alkene ligands. The combination of (TMEDA)Ni(CH₂TMS)₂ and IPr or Ni(IPr)₂ catalyzed the reaction but in lower yield and somewhat reduced L:B selectivity. However, reactions conducted with Ni(IPr)₂ as catalyst and 50 mol % NaOtBu additive formed the addition products in high yield, with high selectivity for the linear product and for alkylation at the least hindered position on the arene (L:B > 97:3).⁶

With these conditions, we examined the reactions of arene **1** with a range of olefins (Chart 1). Hydroarylation of propene (**3**), the least sterically biased alkene, resulted in good L:B selectivity (89:11). This selectivity is much higher than the 1.6:1 regioselectivity reported with previous catalysts.³ The scope of the reaction encompassed the hydroarylation of sterically bulky

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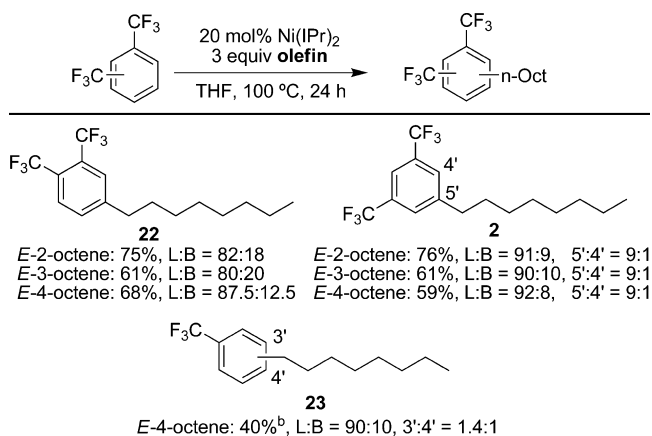
Chart 1. Hydroarylation of Olefins^a

^aReactions were performed with 0.33–0.5 mmol olefin. Isolated yields of combined isomers are reported, and GC or NMR yields are in parentheses. L:B ratios were determined by GC. ^bReaction was conducted without NaOtBu. ^c5 mol % Ni(IPr)₂. ^d10 mol % Ni(IPr)₂. ^e60 °C.

cyclohexyl- (4) and *tert*-butyl-substituted (5) alkenes to form anti-Markovnikov products in high yield as a single isomer. Reactions conducted with 4-phenyl-1-butene (6) occurred to form the product from intermolecular hydroarylation over the potential cyclic product from intramolecular hydroarylation. The reaction also occurred with strained and unstrained cyclic alkenes (10–13) giving the products from addition and isomerization of the remaining alkene to form the conjugated isomer of the product.

The reaction also occurred with olefins bearing a functional group in the allylic or vinylic position. Both allylic (8) and vinylic silanes (9) as well as primary (14) and secondary siloxyethers (15) yielded the linear hydroarylation product. Furthermore, allylic amines (18 and 19), acetals (20, masked aldehydes), and esters (21) reacted smoothly with excellent L:B ratio. While vinylic ethers (17) and vinyl silyl ethers (16) gave low yields, no hydroarylation was observed with allylic alcohols or allylic ethers.^{7,8}

In addition to the formation of linear alkylarenes from α -olefins, the nickel complex catalyzes the formation of linear alkylarenes from internal alkenes. Carbonylation reactions of internal alkenes to form terminal aldehyde or ester products are well-known,⁹ but few other reactions of internal alkenes give terminal products, and the reactions of arenes with internal, acyclic olefins to form linear products are limited to a single example in low yield.^{1d} Ni(IPr)₂ catalyzed the isomerization and hydroarylation of 3- and 4-octene to form linear products with yields and selectivities that are comparable to those from reactions of 1- and 2-octene (Chart 2). These reactions occur by

Chart 2. Hydroarylation of Internal Acyclic Olefins Generating Linear Products^{a,b}

^aReactions were performed with 0.15 mmol olefin. Yields and selectivities are averages from at least two experiments. Yields are for the major isomer as determined by GC. ^b30 equiv arene, the reported yields are for the combination of the isomers.

addition to the terminal alkene (*vide infra*), not by chain walking after insertion of the alkene into a metal-hydride, as occurs during carbonylations of internal alkenes.¹⁰

To understand the mechanism of this remarkably regioselective hydroarylation, we identified the catalyst resting state and conducted a series of kinetic studies and isotope labeling studies. We conducted these studies on the hydroarylation of norbornene to avoid complications from competing isomerization. The formation of metal complexes in solution was monitored by NMR spectroscopy using Ni(IPr)₂ possessing a ¹³C label at the carbene carbon.¹¹ The ¹³C NMR resonance of the carbene carbon was sensitive to the substituents on Ni.

Analysis of the reaction mixture by ¹H and ¹³C NMR spectroscopy indicated the presence of a single complex containing IPr when the conversion was <80%. The structure of the complex was identified as (IPr)Ni(norbornene)₂ (24) by independent synthesis, NMR spectroscopic analysis, and single-crystal X-ray diffraction (Figure 1). Computational studies by

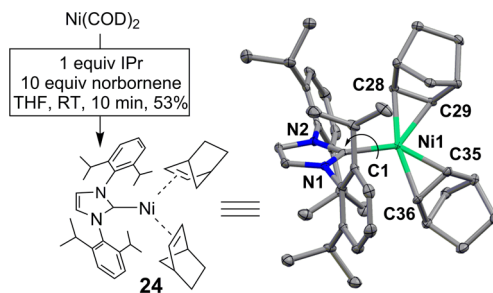


Figure 1. Synthesis of the resting state, complex 24, and ORTEP diagram of 24 showing 50% probability thermal ellipsoids. Hydrogen atoms are omitted for clarity.

DFT (*vide infra*) corroborate that the formation of the bis-olefin complex is thermodynamically favorable ($\Delta G = -4.1$ kcal mol⁻¹ for propene and Ni(IPr)₂, A).⁶

Having identified the resting state of the catalyst, we measured the reaction orders in substrates and ligand by the method of initial rates (up to 20% conversion by GC analysis). The

hydroarylation of norbornene by **1** is inverse first order in norbornene, first order in arene, and zeroth order in ligand.⁶

To assess whether C–H bond cleavage is irreversible or reversible, we conducted reactions with 5-deuterio-1,3-bis-(trifluoromethyl)-benzene. The reaction of this labeled arene with norbornene gave the product from syn addition of the C–D bond across the alkene (>98% D incorporation, Figure 2A). The kinetic isotope effects on the initial rate of two side-by-side reactions (conversion to 20%) of the deuterated and fully protiated arene was only 1.1 ± 0.1.

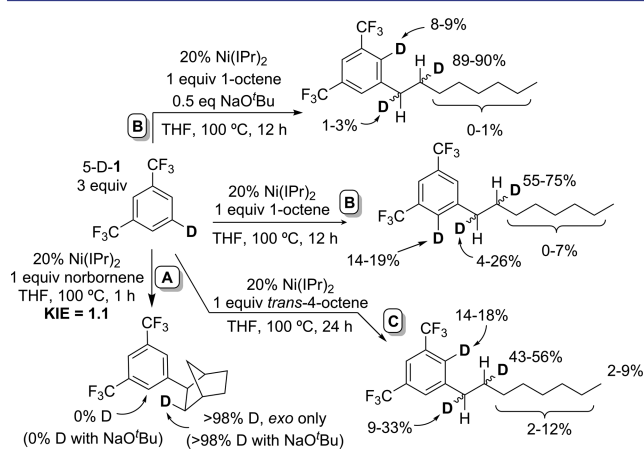


Figure 2. Deuterium incorporation in products of hydroarylation by deuterated **1**. Percentages refer to the integration ratio observed by ¹H and ²H NMR spectroscopy of isolated products.

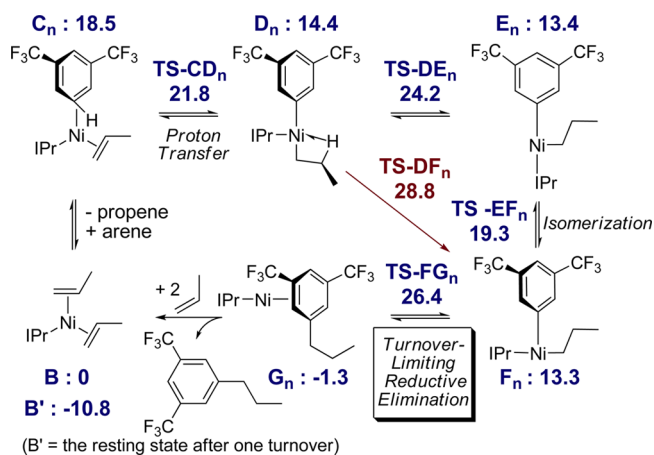
The hydroarylation of 1-octene by the deuterated arene resulted in complete transfer of the deuterium label predominantly to the β -position (Figure 2B). Hydroarylation of the internal alkene, 4-octene, by 5-D-**1** formed a product that also contained a majority of deuterium at the 2-position of the alkyl group (Figure 2C).¹²

Based on the above observations, we concluded that hydroarylation proceeds by a mechanism involving reversible formation of an alkylnickel aryl species, followed by rate-limiting C–C bond formation. Prior studies on the hydroarylation of alkynes suggested that the reactions of alkynes occur by the transfer of an aryl C–H bond to the bound alkyne without formation of an arylnickel hydride intermediate.¹³

These experimental mechanistic data and accompanying conclusions provided the foundation for computational studies to reveal the mode of C–H bond cleavage and the factors controlling regioselectivity. We computed the reaction of propene with 1,3-bis(trifluoromethyl)benzene. Scheme 2 shows the Gibbs energies at 373 K (kcal mol⁻¹) with solvent (THF) and dispersion (D3) corrections calculated by DFT-(PBE0).⁶ The overall ΔG for this reaction is –10.8 kcal/mol.

These calculations suggest that the C–H bond is cleaved by transfer of a proton from an arene bound through its C–H bond, **C_n** (Scheme 2), to the bound propene in a H-shift that is similar to the one described for the hydroarylation of alkynes catalyzed by Ni.¹³ The resulting alkylnickel aryl intermediate, **D_n**, which is stabilized by a β -C–H agostic interaction, contains the two hydrocarbyl groups *trans* to each other. This complex is computed to isomerize to a second T-shaped intermediate, **F_n**, in which Ni–C(aryl) and Ni–C(alkyl) bonds are mutually *cis* and able to undergo C–C bond-forming reductive elimination. This isomerization of T-shaped *d*⁸-ML₃ complexes occurs via Y-

Scheme 2. Proposed Catalytic Cycle with Calculated Free Energies in kcal mol⁻¹



shaped transition states (TSs).¹⁴ It is known that the energy of a Y-shaped *d*⁸-ML₃ structure increases with the σ -donating property of the group at the base of the Y.^{14b} A Y-shaped structure is also stabilized by a π -donor at the base of the Y.¹⁵ Consequently, the barrier for direct isomerization from **D_n** to **F_n**, with the alkyl group at the base of this structure, is significantly higher than the barrier for two consecutive isomerizations through **E_n**, with the aryl (TS-DE_n) and the IPr (TS-EF_n) groups at the base of the Y-shaped TSs, respectively (Scheme 2). The C–C bond-forming reductive elimination is computed to occur from **F_n** through TS-FG_n, and this TS lies at the highest energy on the catalytic cycle.¹⁶ Thus, reductive elimination is the turnover-limiting step of the overall process.¹⁷

Our computations indicate that an alternative pathway occurring by oxidative addition of the Ar–H bond, followed by migratory insertion of the olefin into the nickel-hydride bond is less favorable (Scheme S1).⁶

The C–C bond-forming reductive elimination is also the rate-determining step for the formation of the branched isomer (Scheme S2). Consequently the ratio of linear-to-branched products is determined by the difference in energy between the two corresponding transition states for reductive elimination. The calculated value of 1.1 kcal mol⁻¹ for propene translates at 373 K into a ratio of linear to branched products of 82:18, which agrees well with the experimentally observed ratio for **3** (Chart 1). The computations also are consistent with reversible transfer of the aryl-H/D bond to the olefin, which is consistent with the small KIE observed experimentally. Further consistent with experimental observations, the computational data indicate that the resting state will be the bis-olefin complex **B**. Spectroscopic features of an arene complex **G_n** are observed only after nearly complete conversion of the olefin.

Two mechanisms were evaluated for the conversion of internal olefins to give terminal products. First, the olefin could isomerize through a mechanism unrelated to that of the hydroarylation reaction (Figure 3A). In this case, the nickel would selectively coordinate the terminal olefin^{18,19} and favor hydroarylation of the terminal alkene. Alternatively, chain walking by a proton transfer from the arene to the internal olefin would result in a linear alkyl intermediate from an internal alkene (Figure 3B).²⁰ Heating 1-octene at 90 °C in the presence of Ni(IPr)₂ resulted in complete conversion of 1-octene to a combination of (IPr)Ni(1-octene)₂ and a mixture of internal olefins in 30 min. Thus, scenario A is kinetically feasible. Moreover, the results shown in

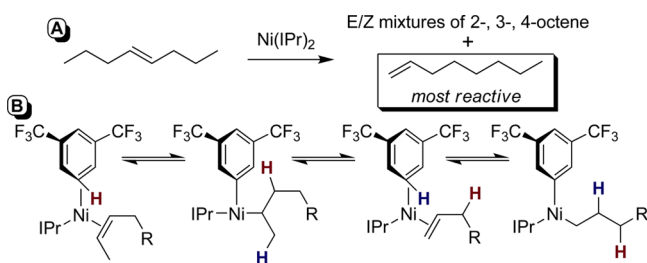


Figure 3. Possible scenarios for the formation of linear products by the hydroarylation of internal olefins.

scenario B indicate that scenario A is relevant to the catalytic reaction. If the reaction proceeds exclusively by scenario A, separate from hydroarylation, then the pattern of deuterium incorporation would be the same as that observed with reactions conducted with 1-octene (Figure 2B). If the reaction of the internal alkene were to occur by a chain-walking pathway, then deuterium would be incorporated at each carbon of the alkyl chain. We observed deuterium principally in the β - and α -position of the alkyl chain of the product with 4-octene (Figure 2C). This result is inconsistent with chain-walking as the major pathway for alkene isomerization²¹ and is consistent with rapid formation of a mixture of internal and terminal alkenes (scenario A in Figure 3).

In conclusion, we report a series of hydroarylations of unactivated olefins with high selectivity for the linear product without directing groups. These highly regioselective reactions include those of both terminal and internal alkenes to give terminal alkylarenes in high yields. Our combined experimental and computational studies reveal several aspects of the mechanism that make this reaction possible. First, the resting state of the catalyst during reactions of α -olefins contains two terminal alkenes, and one alkene dissociates reversibly prior to the turnover-limiting step; thus, isomerization of the terminal alkene to an equilibrium mixture of alkenes increases the reaction rate. Second, the reaction occurs without oxidative addition to form an unstable nickel hydride intermediate. Third, the high selectivity results from a lower barrier for reductive elimination to form linear alkylarenes, rather than a difference in stabilities of the linear vs branched alkyl complexes. Studies to understand the detailed mechanisms of isomerization with nickel complexes and to develop new catalysts for the addition of a wider scope of arenes with and without concomitant isomerization are ongoing.

■ ASSOCIATED CONTENT

Supporting Information

Full experimental protocols, characterization data for all new materials and computational details (list of coordinates of all calculated species in a .xyz file). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

- (1) (a) Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. *Nature* **1993**, *366*, 529. (b) Jun, C.-H.; Hong, J.-B.; Kim, Y.-H.; Chung, K.-Y. *Angew. Chem., Int. Ed.* **2000**, *39*, 3440. (c) Schinkel, M.; Marek, I.; Ackermann, L. *Angew. Chem., Int. Ed.* **2013**, *52*, 3977. (d) Lim, Y.-G.; Kang, J.-B.; Kim, Y. H. *J. Chem. Soc., Perkin Trans. I* **1996**, *0*, 2201. (e) Lenges, C. P.; Brookhart, M. *J. Am. Chem. Soc.* **1999**, *121*, 6616. (f) Jun, C.-H.; Moon, C. W.; Hong, J.-B.; Lim, S.-G.; Chung, K.-Y.; Kim, Y.-H. *Chem.—Eur. J.* **2002**, *8*, 485. (g) Ilies, L.; Chen, Q.; Zeng, X.; Nakamura, E. *J. Am. Chem. Soc.* **2011**, *133*, 5221. (h) Gao, K.; Yoshikai, N. *Angew. Chem., Int. Ed.* **2011**, *50*, 6888.
- (2) (a) Tan, K. L.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2002**, *124*, 13964. (b) Lewis, J. C.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 5332. (c) Nakao, Y.; Yamada, Y.; Kashiwara, N.; Hiyama, T. *J. Am. Chem. Soc.* **2010**, *132*, 13666.
- (3) (a) Matsumoto, T.; Taube, D. J.; Periana, R. A.; Taube, H.; Yoshida, H. *J. Am. Chem. Soc.* **2000**, *122*, 7414. (b) Lail, M.; Arrowood, B. N.; Gunnoe, T. B. *J. Am. Chem. Soc.* **2003**, *125*, 7506.
- (4) Nakao, Y.; Kashiwara, N.; Kanyiva, K. S.; Hiyama, T. *J. Am. Chem. Soc.* **2008**, *130*, 16170.
- (5) Sergeev, A. G.; Hartwig, J. F. *Science* **2011**, *332*, 439.
- (6) See the Supporting Information (SI) for details
- (7) For each alkene, different yields were observed with and without the presence of base. Hence, we report the higher of the two yields. Our current understanding is that the base inhibits isomerization. Further studies on the mechanistic effect of the base are ongoing.
- (8) So far, reactions with electron-neutral to electron-rich arenes containing typical functional groups, such as nitriles, esters, ketones, amides, and nitro groups, did not yield any hydroarylation product. An exception is 2-trifluoromethylpyridine (see SI).
- (9) (a) Seayad, A.; Ahmed, M.; Klein, H.; Jackstell, R.; Gross, T.; Beller, M. *Science* **2002**, *297*, 1676. (b) Jimenez Rodriguez, C.; Foster, D. F.; Eastham, G. R.; Cole-Hamilton, D. *Chem. Commun.* **2004**, 1720.
- (10) Orchin, M.; Rupilius, W. *Catal. Rev.* **1972**, *6*, 85.
- (11) Lara, P.; Rivada-Wheelaghan, O.; Conejero, S.; Poteau, R.; Philippot, K.; Chaudret, B. *Angew. Chem., Int. Ed.* **2011**, *50*, 12080.
- (12) No significant differences in deuterium incorporation were observed when altering the ratio of arene/olefin from 3:1 to 1:3. No product is formed in the presence of NaO^tBu with *trans*-4-octene. The incorporation of deuterium into the α -position is likely to occur from reversible H-shift of the terminal alkene during isomerization. Calculations showed that the isomerization of internal olefin following a pathway similar to that from C_n to E_n is lower in energy with the H of the arene than with the H of the isopropyl group of the ligand. Hence, the deuterium of the arene can be incorporated into the alkyl chain at various positions.
- (13) Guihaumé, J.; Halbert, S.; Eisenstein, O.; Perutz, R. N. *Organometallics* **2011**, *31*, 1300.
- (14) (a) Komiya, S.; Albright, T. A.; Hoffmann, R.; Kochi, J. K. *J. Am. Chem. Soc.* **1976**, *98*, 7255. (b) Tatsumi, K.; Hoffmann, R.; Yamamoto, A.; Stille, J. K. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 1857.
- (15) Riehl, J.-F.; Jean, Y.; Eisenstein, O.; Pélissier, M. *Organometallics* **1992**, *11*, 729.
- (16) Reductive elimination does not occur from E_n because the aryl group and the Ni–propyl bond are almost coplanar.
- (17) Jiang, Y. Y.; Li, Z.; Shi, J. *Organometallics* **2012**, *31*, 4356.
- (18) Hartley, F. R. *Chem. Rev.* **1973**, *73*, 163.
- (19) Coordination of two internal olefins (2-butene) in the bis-olefin complex is calculated to be less favorable by about 12 kcal mol⁻¹ than coordination of two terminal olefins (propene).
- (20) Vaidya, T.; Klimovica, K.; LaPointe, A. M.; Keresztes, I.; Lobkovsky, E. B.; Daugulis, O.; Coates, G. W. *J. Am. Chem. Soc.* **2014**, *136*, 7213.
- (21) Small amounts of deuterium (12% of the total deuterium on the product) are also observed farther along the alkyl chain. See ref 12.