

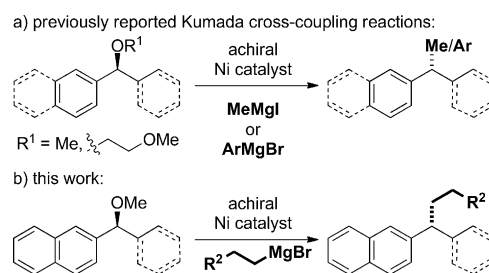
Stereospecific Nickel-Catalyzed Cross-Coupling Reactions of Alkyl Grignard Reagents and Identification of Selective Anti-Breast-Cancer Agents**

Ivelina M. Yonova, A. George Johnson, Charlotte A. Osborne, Curtis E. Moore, Naomi S. Morrisette, and Elizabeth R. Jarvo*

Abstract: Alkyl Grignard reagents that contain β -hydrogen atoms were used in a stereospecific nickel-catalyzed cross-coupling reaction to form $C(sp^3)-C(sp^3)$ bonds. Aryl Grignard reagents were also utilized to synthesize 1,1-diarylalkanes. Several compounds synthesized by this method exhibited selective inhibition of proliferation of MCF-7 breast cancer cells.

Alkyl-alkyl cross-coupling reactions have emerged as powerful transformations that provide a new disconnection for the synthesis of tertiary stereocenters that are difficult to construct using other methods.^[1,2] However, because of the inherent reactivity of alkyl metal intermediates, $C(sp^3)-C(sp^3)$ coupling reactions are significantly less common than their $C(sp^2)-C(sp^2)$ counterparts. In particular, alkyl metal intermediates are prone to β -hydride elimination, which results in non-productive pathways. Herein, we report nickel-catalyzed cross-coupling reactions of alkyl Grignard reagents that contain β -hydrogen atoms. This method was also utilized to prepare new compounds that display selective inhibition of breast cancer cell proliferation.

We have previously reported the stereospecific nickel-catalyzed Kumada cross-coupling of methylmagnesium bromide with benzylic ethers (Scheme 1 a).^[3,4] Furthermore, we were able to extend the utility of this reaction by employing



Scheme 1. Nickel-catalyzed Kumada cross-coupling reactions.

aryl magnesium reagents for the stereospecific synthesis of triarylmethanes.^[5] One class of nucleophiles that remained elusive comprises long-chain alkyl Grignard reagents (Scheme 1 b). These reagents perform poorly under our reported cross-coupling reaction conditions, as hydrogenolysis or elimination typically predominate. We hypothesized that these products result from β -hydride elimination of the organonickel intermediates, and that we could identify a system that favors the desired cross-coupling pathway by fine-tuning of the catalyst.

The bite angle and the steric and electronic environment of a ligand can have profound effects on the relative rates of the elementary steps in a catalytic cycle. We evaluated a series of catalysts (Table 1, entries 1–7) and determined that $[Ni(acac)_2]$ ($acac$ = acetylacetonate) in the presence of 1,2-bis(diphenylphosphino)ethane (dppe) afforded **2** as the major product in good conversion and modest enantioselectivity (entry 7).^[6] To improve the yield of the cross-coupling reaction, we systematically varied the ligand-to-metal stoichiometry. When the $dppe/[Ni(acac)_2]$ ratio was smaller than 2:1, the reaction showed little dependence on the ligand loading (entries 7 and 8). When more than two equivalents of dppe were used with respect to $[Ni(acac)_2]$, the desired product was not detected, and **1** was recovered quantitatively (entry 10). Interestingly, when a 2:1 ratio of $dppe/[Ni(acac)_2]$ was employed, the reaction gave highly variable results (entry 9); across seven experiments, four provided only recovered starting material, whereas three provided the desired product in >80% yield.^[7] We propose that when

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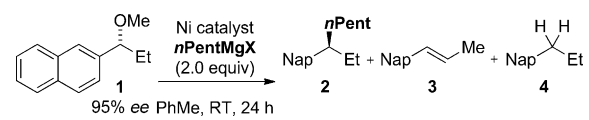
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Table 1: Optimization of the cross-coupling with the *n*-pentyl Grignard reagent.



Entry	Ni catalyst (mol %)	X	Yield 2 [%] ^[a]	<i>ee</i> 2 [%] ^[b]	<i>es</i> 2 [%] ^[c]	Yield 3 [%] ^[a]	Yield 4 [%] ^[a]
1	—	I	< 5 ^[d]	—	—	< 5 ^[d]	< 5 ^[d]
2	[Ni(acac) ₂] (10), no ligand	I	< 5 ^[d]	—	—	< 5 ^[d]	< 5 ^[d]
3	[Ni(acac) ₂] (10), <i>rac</i> -BINAP (10)	I	< 5 ^[d]	—	—	< 5 ^[d]	< 5 ^[d]
4	[Ni(acac) ₂] (10), DPEphos (10)	I	28	86	91	27	12
5	[Ni(acac) ₂] (10), PPh ₃ (10)	I	8	82	86	55	14
6	[Ni(acac) ₂] (10), dppp (10)	I	31	45	47	12	14
7	[Ni(acac) ₂] (10), dppe (10)	I	69	66	69	< 5	< 5
8	[Ni(acac) ₂] (10), dppe (15)	I	95	61	64	< 5	< 5
9	[Ni(acac) ₂] (10), dppe (20)	I	0–90 ^[e]	83 ^[f]	87 ^[f]	< 5	< 5
10	[Ni(acac) ₂] (10), dppe (22)	I	< 5 ^[d]	—	—	< 5 ^[d]	< 5 ^[d]
11	[Ni(cod) ₂] (10), dppe (10)	I	< 5 ^[d]	—	—	< 5 ^[d]	< 5 ^[d]
12	[Ni(dppe)Cl ₂] (10)	I	89	55	58	< 5	< 5
13	[Ni(dppe)Cl ₂] (10)	Cl	96	51	54	5	< 5
14	[Ni(dppe)Cl ₂] (10)	Br	95	91	96	< 5	< 5
15	[Ni(dppe)Cl ₂] (5)	Br	85	93	98	< 5	< 5
16	[Ni(dppe)Cl ₂] (2)	Br	97 ^[g]	96	> 99	< 5	< 5

[a] Determined by ¹H NMR analysis using PhSiMe₃ as an internal standard. [b] Determined by supercritical fluid chromatography (SFC) on a chiral stationary phase. [c] Enantiospecificity (*es*) = *ee*_{product}/*ee*_{starting material} × 100%. [d] Recovered and unreacted **1**. [e] Reaction was irreproducible: run 1: < 5% yield; run 2: < 5% yield; run 3: 90% yield, 85% *ee*, 89% *es*; run 4: < 5% yield; run 5: < 5% yield; run 6: 84% yield, 68% *ee*, 72% *es*; run 7: 90% yield, 94% *ee*, 99% *es*; [f] Average of runs 3, 6, and 7. [g] Yield of isolated product. BINAP = 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, DPEphos = bis[2-(diphenylphosphino)phenyl]-ether, dppp = 1,3-bis(diphenylphosphino)propane.

the ligand loading is ≥ 2:1, an inactive complex, [Ni(dppe)₂], is formed quantitatively, and the cross-coupling pathway is shut down. Consistent with this hypothesis, the use of [Ni(cod)₂] (cod = 1,5-cyclooctadiene) in the presence of dppe provided no product because of the rapid formation of the [Ni(dppe)₂] complex.^[8,9] To ensure strict control of the ligand-to-nickel ratio, we evaluated the complex [Ni(dppe)Cl₂]. The latter was a competent catalyst for the reaction affording **2** in good yield, albeit with slightly diminished enantiospecificity (entry 12). Furthermore, this nickel(II) salt is commercially available, inexpensive, and air- and moisture-stable.

To improve the enantiospecificity of the reaction, we investigated the importance of the identity of the organomagnesium reagent. Organomagnesium bromides proved to be superior to the respective chloride and iodide Grignard

reagents; the enantiospecificity improved from modest 58% *es* with *n*PentMgI to 96% *es* with *n*PentMgBr (entries 12–14). We next examined the impact of catalyst loading on the enantiospecificity, as in related transformations, our laboratory had observed an inverse correlation between catalyst loading and stereochemical fidelity.^[10] We hypothesized that, in analogy to palladium-catalyzed allylic^[11] and benzylic^[12] substitution reactions, the key π -benzyl nickel intermediate could be racemized by nucleophilic attack of a second nickel species (see below).^[13] We were pleased to see that lower catalyst loadings do provide higher enantiospecificity; employing only 2 mol % of [Ni(dppe)Cl₂] afforded the desired product in > 99% *es* without a drop in yield (entry 16).

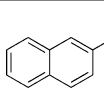
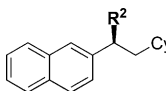
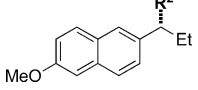
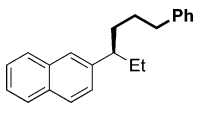
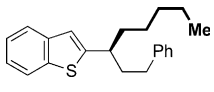
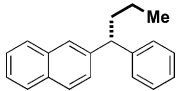
We designed a series of chiral benzylic ethers to determine the scope of the transformation (Table 2). Enantioenriched ethers can be prepared by several routes. For example, Corey–Bakshi–Shibata (CBS) reduction^[14] of the corresponding ketone or enantioselective alkylation^[15] or arylation^[16] of the requisite aldehyde typically provide robust strategies for their construction.^[17]

The reaction of each substrate and Grignard reagent was first evaluated under our standard reaction conditions employing 2 mol % of the catalyst. A range of primary alkyl Grignard reagents afforded the cross-coupled products in good yields and excellent enantiospecificities (entries 1–4). The cross-coupling reactions proceeded with high stereochemical fidelity and inversion at the stereogenic center.^[18] A trisubstituted olefin was well tolerated in the reaction, affording a product containing a convenient synthetic handle for further functionalization (entry 5). A substituent at the β -position of the alkyl magnesium reagent resulted in a low yield of product **11** owing to the formation of large amounts of elimination byproduct, but the reaction still proceeded with satisfactory enantiospecificity (entry 7). An electron-donating methoxy group on the naphthyl ring was well tolerated and did not result in a loss of stereospecificity (entries 8 and 9).

For challenging coupling reactions, we could typically improve enantiospecificity or yield by modifying catalyst loading and reaction temperature. For example, an electron-poor fluorinated alkyl magnesium reagent reacted sluggishly; increasing the catalyst loading to 10 mol % provided the corresponding product in good yield and high enantiospecificity (entry 6). A substrate that contains a heterocyclic moiety also required higher catalyst loading, presumably because of coordination to and deactivation of the catalyst (entry 11). For this substrate, addition of [Ni(dppe)Cl₂] in two portions over the course of the reaction permitted the use of higher catalyst loadings without compromising enantiospecificity. Diarylmethanol derivatives proved to be a more challenging class of substrates: reactions with primary alkyl Grignard reagents resulted in an increased amount of hydrogenolysis (21%) and low enantiospecificity (77% *es*).^[19] For diarylmethanol derivatives that are prone to racemization, lowering the temperature generally increased the enantiospecificity (entry 12, 91% *es*).

To investigate the generality of this method and evaluate its applicability to other classes of Grignard reagents, we

Table 2: Scope of the cross-coupling reaction with alkyl magnesium bromides.

$\text{Ar}-\text{CH}(\text{OMe})-\text{R}^1 \xrightarrow[\text{PhMe, RT, 24 h}]{[\text{Ni}(\text{dppe})\text{Cl}_2] (2 \text{ mol}\%), \text{R}^2\text{MgBr} (2 \text{ equiv})} \text{Ar}-\text{CH}(\text{R}^2)-\text{R}^1$						
Entry	Product			Yield [%] ^[a]	S.M. <i>ee</i> [%] ^[b]	Prod. <i>ee</i> [%] ^[b]
1		5		80	92	91
2		6	R ² = <i>n</i> Pr	93	97	97
3		7	R ² = <i>n</i> Pent	91	97	97
4		8	R ² = (CH ₂) ₃ Ph	88	97	97
5 ^[c]		9	R ² = 	81	97	97
6 ^[d]		10	R ² = (CH ₂) ₃ CF ₃	68	> 99	97
7		11	R ² = <i>i</i> Bu	40	97	90
8		12	R ² = <i>n</i> Pr	80	93	92
9		13	R ² = (CH ₂) ₃ Ph	88	93	93
10 ^[c]		14		93	97	97
11 ^[e]		15		54	99	96
12 ^[f]		16		67	> 99	91

[a] Yield of isolated product after column chromatography on silica gel. [b] Determined by SFC on a chiral stationary phase. [c] [Ni(dppe)Cl₂] (5 mol %). [d] [Ni(dppe)Cl₂] (10 mol %). [e] [Ni(dppe)Cl₂] was added in two aliquots of 5 mol %, see the Supporting Information for details. [f] 5 °C, 48 h; 2-benzyl-naphthalene formed as a byproduct (15 %). Cy = cyclohexyl, Prod. = product, S.M. = starting material.

chose to examine the use of aryl magnesium reagents as a strategy for the synthesis of chiral 1,1-diaryllkanes, which are pharmacophores that are found in a range of bioactive compounds.^[20–23] Our laboratory has previously developed the stereospecific cross-coupling of aryl Grignard reagents with benzhydryl alcohol derivatives to provide triarylmethanes.^[5] However, this method failed to afford the desired products in satisfactory yields with simple benzylic alcohol derivatives such as **1** and was therefore not amenable to the synthesis of 1,1-diaryllkanes. To address this shortcoming, we examined a variety of substituted aryl Grignard reagents (Table 3). Under standard reaction conditions, the cross-coupling proceeded in modest yield with significant formation of the byproduct from elimination.^[24] The efficiency of this process was improved when the overall reaction concentration was decreased 2.5 fold, which afforded **17** in 67 % yield, along

with the elimination byproduct in only 16 % yield (entry 1). Furthermore, the use of more than two equivalents of phenylmagnesium bromide was detrimental to the cross-coupling reaction.^[25] The electron-rich aniline- and anisole-derived organomagnesium reagents afforded the corresponding products in good yields and, in the case of **19**, with excellent stereospecificity (entries 2 and 3). Electron-deficient 4-fluorophenyl- and 2-thienylmagnesium bromides were also competent coupling partners for this reaction (entries 4 and 5). Electrophiles that contain benzofuran or benzothio-phenone moieties were tolerated in the cross-coupling, affording **24** and **25** in good yields and excellent stereospecificity.

During our initial optimization of the reaction and the development of the scope, we noted that increased enantio-specificity could be obtained at lower catalyst loadings (see above). We hypothesized that the loss of fidelity in the

Table 3: Scope of the cross-coupling reaction with aryl magnesium bromides.

		OMe Ar¹ R [Ni(dppe)Cl₂] Ar²MgBr (2 equiv) PhMe, RT, 24 h Ar¹ Ar² R 17–25					
Entry	Product		[Ni(dppe)Cl ₂] [mol %]	Yield [%] ^[a]	S.M. <i>ee</i> [%] ^[b]	Prod. <i>ee</i> [%] ^[b]	es [%]
1		17 R = H	2	67	> 99	91	92
2		18 R = NMe ₂	5	80	> 99	nd ^[c]	nd ^[c]
3		19 R = OMe	2	86 ^[d]	> 99	97	97
4		20 R = F	2	82 ^[d]	> 99	87	88
5		21	10	76	> 99	93	94
6		22	5	80	> 99	85	86
7		23	4	92 ^[d]	96	88	92
8		24	10	71	97	95	98
9 ^[e]		25	20	76	99	93	94

[a] Yield of isolated product after column chromatography on silica gel. [b] Determined by SFC on a chiral stationary phase. [c] Enantiomers could not be separated by SFC on a chiral stationary phase. [d] Calculated yield; see the Supporting Information for details. [e] [Ni(dppe)Cl₂] was added in two aliquots of 10 mol %, see the Supporting Information for details. nd = not determined, Prod. = product, S.M. = starting material.

transfer of stereochemical information resulted from racemization of the enantioenriched π -benzyl nickel intermediate (*S*)-**27** by reaction with a low-valent nickel species (Figure 1 a). This mechanism contrasts alternatives where stereochemical information is eroded during a competitive radical oxidative addition reaction or homolysis of the carbon–nickel bond in **27**.^[13,26] Consistent with our hypothesis, experiments performed in the presence of one equivalent of TEMPO afforded neither improvement nor erosion of the enantiospecificity of the reaction. We sought to obtain experimental evidence to further support or refute the bimolecular racemization mechanism. Based on our mechanistic hypothesis, the formation of the major and minor enantiomers should be first and second order with respect to catalyst concentration, respectively. Derivation of rate laws indicates that if that is the case, the ratio of the two enantiomers would be directly proportional to 1/[catalyst].^[27] Indeed, a plot of [(*S*)-**17**]/[(*R*)-**17**] versus 1/[Ni(dppe)Cl₂] yielded a good fit for a linear equation (Figure 1 b). The data are consistent with

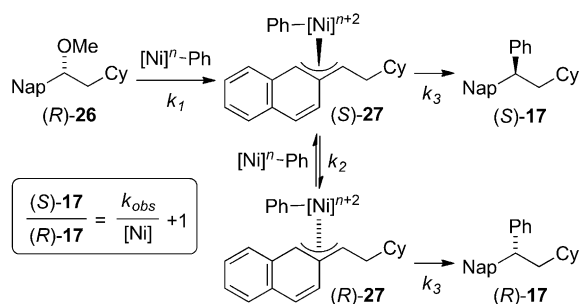
a mechanism where the formation of the minor enantiomer is second order with respect to catalyst concentration (Figure 1 a).

Having synthesized a variety of enantioenriched alkanes and diarylalkanes, we set out to evaluate these compounds for their biological activity. Compounds that contain the 1,1-diarylalkane scaffold have demonstrated broad bioactivity, including against breast cancer.^[21] The cross-coupling products in Tables 2 and 3 were tested for selective anti-breast-cancer activity against the MCF-7 breast cancer cell line relative to the normal MCF-10A stromal cell line using a proliferation-based procedure. Selected results of the broad compound screen are shown in Figure 2. Several compounds demonstrated selectivity for the inhibition of breast cancer cell proliferation; results were compared to those obtained with estrogen receptor antagonist faslodex (ICI 182,780).^[28] Thiophene-containing diarylalkane (+)-**21** inhibited MCF-7 cell proliferation with an EC₅₀ value of 5.3 μM (EC₅₀ = half maximal effective concentration). We observed that (–)-**21** (EC₅₀ = 6.5 μM) and the racemic mixture (EC₅₀ = 7.3 μM) were both nearly as efficacious as the (+) enantiomer. Interestingly, the structurally analogous diarylalkane **25** exhibited a similar level of inhibition. Control experiments confirmed that thio-

phene (**28**) and benzothiophene (**29**) did not inhibit cell growth. Furthermore, whereas replacing the thiophene moiety with different aryl groups, such as phenyl (**17**), *para*-methoxy (**19**), or *para*-fluoro (**20**) substituents, resulted in similar selective inhibition of cancer cell proliferation, compounds containing hydrocarbon chains (**9** and **7**) were much less potent. These results provide new lead compounds with selective inhibition of breast cancer cell growth.

In conclusion, we have developed a stereospecific nickel-catalyzed Kumada cross-coupling that tolerates Grignard reagents with extended alkyl chains. This catalytic system is also amenable to reactions of aryl and heteroaryl magnesium reagents for the synthesis of 1,1-diarylalkanes. Reactions typically proceeded with higher enantiospecificity at lower catalyst loadings, and mechanistic experiments are consistent with racemization of the π -benzyl nickel intermediate. Biological testing of compounds that were synthesized using this method identified several promising lead compounds that

a) proposed mechanism for racemization



b) plot of (S)-17/(R)-17 vs. 1/[Ni]

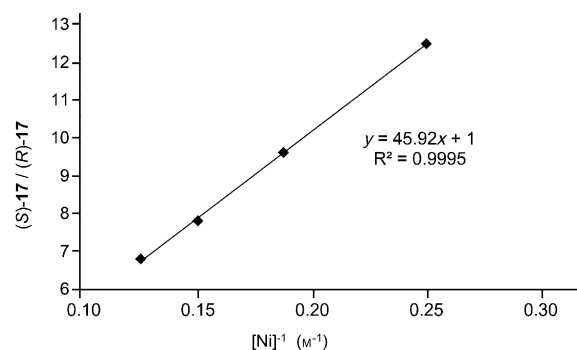


Figure 1. Nickel-catalyzed racemization of the π -benzyl nickel intermediate.

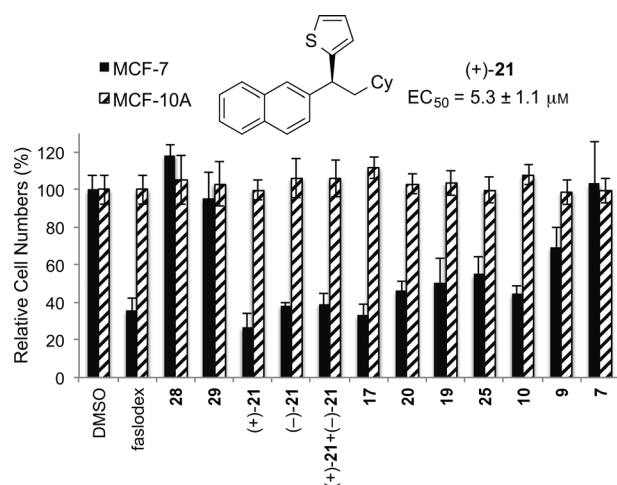


Figure 2. Anti-breast-cancer activity of selected compounds at a concentration of $10 \mu M$ screened against a breast cancer cell line (MCF-7) and a normal breast cell line (MCF-10A). Cell proliferation is represented as relative cell numbers after treatment; a low percentage indicates potent anti-cancer activity for that compound. All data are normalized to the DMSO vehicle control. DMSO = dimethyl sulfoxide.

exhibit selective inhibition of breast cancer cell proliferation in the low micromolar range.

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- [1] For reviews on asymmetric variants, see: a) E. C. Swift, E. R. Jarvo, *Tetrahedron* **2013**, 69, 5799–5817; b) B. L. H. Taylor, E. R. Jarvo, *Synlett* **2011**, 2761–2765; c) R. Jana, T. P. Pathak, M. S. Sigman, *Chem. Rev.* **2011**, 111, 1417–1492; d) F. Glorius, *Angew. Chem.* **2008**, 120, 8474–8476; *Angew. Chem. Int. Ed.* **2008**, 47, 8347–8349.
- [2] For a lead reference of stereoconvergent alkyl–alkyl cross-coupling, see: C. J. Cordier, R. J. Lundgren, G. C. Fu, *J. Am. Chem. Soc.* **2013**, 135, 10946–10949.
- [3] a) B. L. H. Taylor, E. C. Swift, J. D. Waetzig, E. R. Jarvo, *J. Am. Chem. Soc.* **2011**, 133, 389–391; b) M. A. Greene, I. M. Yonova, F. J. Williams, E. R. Jarvo, *Org. Lett.* **2012**, 14, 4293–4296.
- [4] For stereospecific Negishi couplings, see: H. M. Wisniewska, E. C. Swift, E. R. Jarvo, *J. Am. Chem. Soc.* **2013**, 135, 9083–9090.
- [5] a) B. L. H. Taylor, M. R. Harris, E. R. Jarvo, *Angew. Chem.* **2012**, 124, 7910–7913; *Angew. Chem. Int. Ed.* **2012**, 51, 7790–7793; for stereospecific Suzuki couplings of aryl boronic esters, see: b) M. R. Harris, L. E. Hanna, M. A. Greene, C. E. Moore, E. R. Jarvo, *J. Am. Chem. Soc.* **2013**, 135, 3303–3306; c) Q. Zhou, H. D. Srinivas, S. Dasgupta, M. P. Watson, *J. Am. Chem. Soc.* **2013**, 135, 3307–3310.
- [6] Nap = 2-naphthyl.
- [7] We hypothesize that a weighing error was responsible for the high variability in these small scale reactions; see: M. Wernerova, T. Hudlicky, *Synlett* **2010**, 2701–2707.
- [8] 31P NMR studies indicated formation of $[Ni(dppe)_2]$, a complex that is inactive in these cross-couplings (see the Supporting Information); for the characterization of $[Ni(dppe)_2]$, see: a) K. J. Fisher, E. C. Alyea, *Polyhedron* **1989**, 8, 13–15; for a similar observation, see: b) K.-i. Yamashita, H. Takeda, T. Kashiwabara, R. Hua, S. Shimada, M. Tanaka, *Tetrahedron Lett.* **2007**, 48, 6655–6659.
- [9] An alternative nickel(0) source, $[Ni(PPh_3)_4]$, afforded **6** in 73 % yield; see the Supporting Information.
- [10] B. L. H. Taylor, *Development of Nickel-Catalyzed Stereospecific Cross-Coupling Reactions*, University of California, Irvine, **2012**, Order No. 3540398. Ann Arbor: ProQuest. Web. 17 July **2013**.
- [11] a) S. I. Murahashi, Y. Taniguchi, Y. Imada, Y. Tanigawa, *J. Org. Chem.* **1989**, 54, 3292–3303; b) K. L. Granberg, J. E. Bäckvall, *J. Am. Chem. Soc.* **1992**, 114, 6858–6863.
- [12] J.-Y. Legros, M. Toffano, J.-C. Fiaud, *Tetrahedron* **1995**, 51, 3235–3246.
- [13] This mechanism was proposed and discounted in favor of a radical oxidative addition reaction to rationalize stereoablative reactions of benzylic bromides with nickel complexes; see: J. K. Stille, A. B. Cowell, *J. Organomet. Chem.* **1977**, 124, 253–261.
- [14] a) E. J. Corey, C. J. Helal, *Angew. Chem.* **1998**, 110, 2092–2118; *Angew. Chem. Int. Ed.* **1998**, 37, 1986–2012; b) “Reductions”: J. J. Li, C. Limberakis, D. A. Pflum in *Modern Organic Synthesis in the Laboratory: A Collection of Standard Experimental Procedures*, Oxford University Press, New York, **2007**, pp. 96–97.
- [15] a) R. Noyori, M. Kitamura, *Angew. Chem.* **1991**, 103, 34–55; *Angew. Chem. Int. Ed. Engl.* **1991**, 30, 49–69; b) F.-Y. Zhang, C.-W. Yip, C. Rong, A. S. C. Chan, *Tetrahedron: Asymmetry* **1997**, 8, 585–589.
- [16] a) C. Bolm, J. Rudolph, *J. Am. Chem. Soc.* **2002**, 124, 14850–14851; b) A. L. Braga, M. W. Paixao, B. Westermann, P. H. Schneider, L. A. Wessjohann, *J. Org. Chem.* **2008**, 73, 2879–2882.
- [17] The competing enantiomer conversion method can be used to assign the absolute configuration of secondary alcohols; see:

- A. J. Wagner, S. D. Rychnovsky, *J. Org. Chem.* **2013**, *78*, 4594–4598.
- [18] See the Supporting Information for details.
- [19] At room temperature, **16** was obtained in 71 % yield and 77 % *ee*, and 2-benzyl-naphthalene was formed in 21 % yield.
- [20] Representative examples: a) as ligands for nuclear receptors, see: M. Kainuma, J.-i. Kasuga, S. Hosoda, K.-i. Wakabayashi, A. Tanatani, K. Nagasawa, H. Miyachi, M. Makishima, Y. Hashimoto, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3213–3218; b) as combretastatin analogues for colon cancer, see: S. Messaoudi, A. Hamze, O. Provot, B. Tréguier, J. Rodrigo De Losada, J. Bignon, J.-M. Liu, J. Wdziejczak-Bakala, S. Thoret, J. Dubois, J.-D. Brion, M. Alami, *ChemMedChem* **2011**, *6*, 488–497; c) prostate cancer: Q. Z. Hu, L. N. Yin, C. Jagusch, U. E. Hille, R. W. Hartmann, *J. Med. Chem.* **2010**, *53*, 5049–5053; d) diabetes: R. M. Kim, E. R. Parmee, Q. Tan, C. Yang, A. R. Lins, U.S. Patent 12/227,030, May 11, **2007**.
- [21] For breast cancer, see: a) T. P. Pathak, K. M. Gligorich, B. E. Welm, M. S. Sigman, *J. Am. Chem. Soc.* **2010**, *132*, 7870–7871; b) T. P. Pathak, J. G. Osiak, R. M. Vaden, B. E. Welm, M. S. Sigman, *Tetrahedron* **2012**, *68*, 5203–5208.
- [22] For similar disconnections, see: a) A. López-Pérez, J. Adrio, J. C. Carretero, *Org. Lett.* **2009**, *11*, 5514–5517; b) D. Imao, B. W. Glasspoole, V. S. Laberge, C. M. Crudden, *J. Am. Chem. Soc.* **2009**, *131*, 5024–5025; c) J. Li, M. D. Burke, *J. Am. Chem. Soc.* **2011**, *133*, 13774–13777; d) P. Maity, D. M. Shacklady-McAtee, G. P. A. Yap, E. R. Sirianni, M. P. Watson, *J. Am. Chem. Soc.* **2013**, *135*, 280–285.
- [23] For representative alternative strategies for the enantioselective synthesis of 1,1-diarylalkanes, see Ref. [21a] and: a) V. Saini, L. Liao, Q. Wang, R. Jana, M. S. Sigman, *Org. Lett.* **2013**, *15*, 5008–5011; b) X. Wang, A. Guram, S. Caille, J. Hu, J. P. Preston, M. Ronk, S. Walker, *Org. Lett.* **2011**, *13*, 1881–1883; c) T. C. Fessard, S. P. Andrews, H. Motoyoshi, E. M. Carreira, *Angew. Chem.* **2007**, *119*, 9492–9495; *Angew. Chem. Int. Ed.* **2007**, *46*, 9331–9334.
- [24] **17** was formed in 54 % yield, 92 % *ee*, and 95 % *es*, along with the elimination byproduct in 34 % yield.
- [25] When PhMgBr (4 equiv) was used, **17** was obtained in 19 % yield, with 37 % unreacted starting material and 34 % elimination byproduct.
- [26] For evidence supporting a radical oxidative addition in cross-coupling reactions of alkyl halides, see: a) J. K. Kochi, *Pure Appl. Chem.* **1980**, *52*, 571–605; b) G. D. Jones, J. L. Martin, C. McFarland, O. R. Allen, R. E. Hall, A. D. Haley, R. J. Brandon, T. Kononova, P. J. Desrochers, P. Pulay, D. A. Vicić, *J. Am. Chem. Soc.* **2006**, *128*, 13175–13183; c) J. Choi, G. C. Fu, *J. Am. Chem. Soc.* **2012**, *134*, 9102–9105; d) X. Lin, D. L. Phillips, *J. Org. Chem.* **2008**, *73*, 3680–3688; for evidence of Ni–C bond homolysis after a polar oxidative addition, see: e) D. K. Nielsen, C.-Y. Huang, A. G. Doyle, *J. Am. Chem. Soc.* **2013**, *135*, 13605–13609.
- [27] For full details of the derivation, see the Supporting Information.
- [28] For discussions of faslodex and estrogen receptor antagonists, see: a) A. Howell, *Endocr.-Relat. Cancer* **2006**, *13*, 689–706; b) A. E. Wakeling, M. Dukes, J. Bowler, *Cancer Res.* **1991**, *51*, 3867–3873.