Cross-Coupling

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Synthesis of Enantioenriched Triarylmethanes by Stereospecific Cross-Coupling Reactions**

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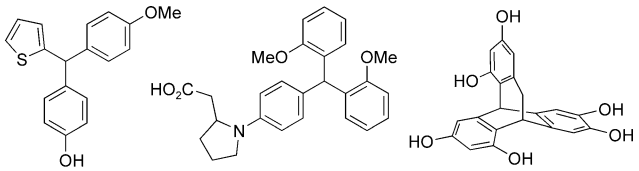
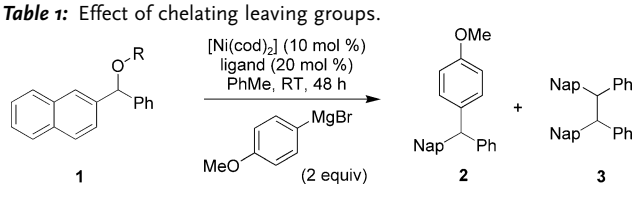
Triarylmethanes are attractive targets because of their applications in medicinal and materials chemistry.[1–7] For example, several triarylmethanes have emerged as promising pharmacological agents for treating cancer,[2] bacterial infection,[3] and diabetes (Scheme 1).[4] Triarylmethanes also have applications as dye precursors,[5] photochromic agents,[6] and reagents in material science.[7] The triarylmethine moiety can also be found as a core structure in natural products such as cassigarol B.[8] The classical approach to synthesize these compounds relies on Friedel–Crafts reactions.[9–12] Despite recent advances using chiral Brønsted acids and directed C–H activation reactions,[13,14] the asymmetric synthesis of triarylmethanes remains challenging. We envisioned an approach based on the stereospecific cross-coupling methodology recently developed in our laboratory.[15,16] Herein we describe the synthesis of enantioenriched triarylmethanes by cross-coupling reactions of diarylmethanol derivatives, which are easily prepared by a variety of asymmetric methods.[17]



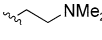
Scheme 1. Biologically relevant triarylmethanes.

At the outset, we found that direct application of our previously reported method was unsatisfactory for triarylmethane synthesis.[18] The reaction of methyl ether **1a** with an aryl Grignard reagent in the presence of $[Ni(cod)_2]$ and DPEphos provided triarylmethane **2** with low enantiospecificity (Table 1, entry 1).[19] All other ligands examined resulted in unacceptably low conversion of starting material **1a** (Table 1, entries 2–4).[20] The use of other catalysts, including those based on palladium and copper, did not lead to the desired reactivity.[21] We concluded that few catalysts are able to undergo efficient oxidative addition with **1a**. This limitation restricts our ability to optimize the catalyst toward reducing deleterious side reactions, which include racemization of the putative alkylnickel intermediate[22] and formation of products **3**, which are derived from homocoupling.[23] However, we considered that a substrate that was more active toward oxidative addition would overcome this limitation. We were encouraged to test this hypothesis because the use of certain catalysts led to reactions with promising

Table 1: Effect of chelating leaving groups.



1 2 3

Entry	Ether	R	Ligand	Yield **2** [%][a]	*es* **2** [%][b]	Yield **3** [%][a]
1[c,d]	(*S*)-**1a**	Me	DPEphos	56[e]	33	18[e,f]
2[d]	(±)-**1a**		*rac*-BINAP	<2	–	26
3[d]	(±)-**1a**		dppf	3	–	10
4[d]	(*S*)-**1a**		dppb	14	93	<2
5	(±)-**1b**		DPEphos	<2	–	<2
6[g]	(±)-**1c**		DPEphos	67	–	16
7	(*S*)-**1d**		DPEphos	69[e]	46	17[e,f]
8[d]	(*S*)-**1d**		dppb	67	93	3
9[h]	(*S*)-**1d**		dpppent	73	>99	<2
10[h]	(*S*)-**1d**		dpph	>95	>99	<2
11[h]	(*S*)-**1d**		dppo	84	>99	<2
12[h,i]	(±)-**1d**		$MePh_2P$	12	–	<2
13[h,i]	(*S*)-**1d**		Ph_3P	90	94	5

[a] Determined by ^1H NMR analysis using an internal standard ($PhSiMe_3$). [b] Enantiospecificity (*es*) = $ee_{product}/ee_{starting\ material} \times 100\%$. Determined by SFC chromatography using a chiral stationary phase. [c] 40 °C. [d] 5 mol% $[Ni(cod)_2]$, 10 mol% ligand. [e] Yield after chromatography. [f] Dimer **3** was isolated as a mixture of racemic and *meso* stereoisomers. [g] Enantiomers of (±)-**1c** are not separable by SFC chromatography using a chiral stationary phase. [h] $[Ni(acac)_2]$ substituted for $[Ni(cod)_2]$. [i] 40 mol% ligand. acac = acetylacetonate, cod = 1,5-cyclooctadiene, Nap = 2-naphthyl, definitions of ligands are given in Ref. [24].

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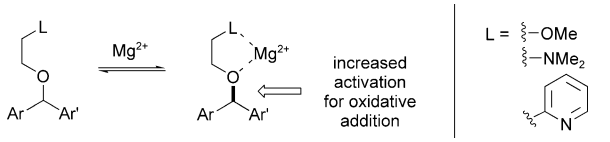
enantiospecificity, albeit the products were obtained in low yield (Table 1, entry 4).[24]

We considered activating the ether to accelerate the oxidative addition step, thus leading to reactions that could be promoted with a broad range of catalysts. We were attracted to the use of a directing group to increase the reaction rate,[25] as certain nickel-catalyzed cross-coupling reactions benefit from a strategically positioned functional group on the substrate.[26,27] For example, the presence of pendant carboxylates accelerate transmetalation of nickel thiolates during the cross-coupling of thioethers with arylzinc reagents.[28] We postulated that coordination of the ether to a magnesium Lewis acid would accelerate cleavage of the benzylic C–O bond (Scheme 2).[29] We designed ethers that contain pendant Lewis bases capable of magnesium-ion chelation. Importantly, this strategy would provide traceless activation of the substrate, as the directing group is excised during the reaction and is thus not present in the product.

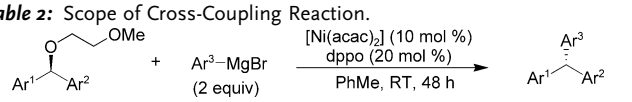


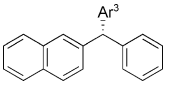
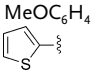
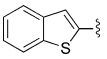
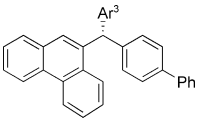
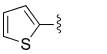
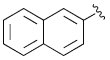
Scheme 2. Design of a chelating leaving group to activate C–O bonds toward oxidative addition

We were pleased to find that substrates **1c** and **1d**, which contain pendant dimethylamino and methoxy groups, respectively, were converted into product in improved yield compared to non-chelating substrate **1a** (Table 1, entries 6–7). In the presence of a range of ligands and either $[Ni(cod)_2]$ or $[Ni(acac)_2]$, methoxyethyl ether **1d** gave a high yield of product **2** and was therefore selected for further study. As found above, the use of DPEphos resulted in a reaction of low enantiospecificity and gave significant quantities of dimer **3** (Table 1, entry 7). However, the use of ligands in the bis(diphenylphosphino)alkane series gave reactions of very high enantiospecificity (Table 1, entries 8–11);[30] the use of the catalyst derived from $[Ni(acac)_2]$ and dpph led to complete conversion of **1d** into triarylmethane **2** with no detectable products derived from homocoupling (Table 1, entry 10). Triphenylphosphine was also an effective ligand for the cross-coupling reaction, although the enantiospecificity of the reaction is slightly lower (Table 1, entry 13). Bis(diphenylphosphino)alkanes were therefore selected as ligands for subsequent studies.

Having established optimal reaction conditions, we examined the scope of the reaction with respect to the aryl Grignard reagent (Table 2). In general, the reaction of substrates containing extended aromatic moieties proceed with very high enantiospecificity. Although the use of 2-methoxyethyl ether **1d** led to optimal yields of product, methyl ether **1a** underwent cross-coupling with a variety of Grignard reagents with high enantiospecificity and gave products in slightly lower yields.[31] For the majority of Grignard reagents examined, dppo was found to be the optimal ligand, although when *para*-methoxyphenylmagnesium bromide is used, dpph was the best ligand (Table 2, entry 3). Whereas the use many of the Grignard reagents work well in the presence of $[Ni(acac)_2]$, some gave better yields when $[Ni(cod)_2]$ was used (Table 2, entries 5 and 6); $[Ni(cod)_2]$ had a more general scope with respect to the Grignard reagent. We were pleased to find that the presence of a dimethylamino group was tolerated (Table 2, entry 4); thiophene and benzothiophene-based Grignard reagents were also tolerated (Table 2, entries 7 and 8). A phenanthrene-derived substrate also underwent cross-coupling, although the reaction was relatively slow, presumably owing to steric congestion in the product (Table 2, entries 9 and 10). Nevertheless, the reactions were highly enantiospecific, including the reaction where 2-naphthylmagnesium bromide was used as the Grignard reagent, although mild heating was required for this reaction to proceed.[32]

Table 2: Scope of Cross-Coupling Reaction.

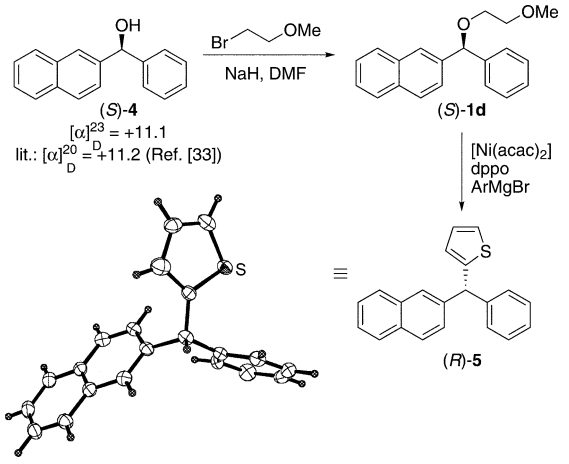


Entry	Product	Ar^3	Yield [%][a]	S.M.[b] *ee* [%]	Prod.[b] *ee* [%]	*es*[c] [%]
1		Ph	82	N/A	N/A	N/A
2		*p*-MeC_6H_4	86	93	91	98
3[d]		*p*-$MeOC_6H_4$	88	93	92	99
4		*p*-$(Me_2N)C_6H_4$	68	93	91	98
5[e,f]		*p*-FC_6H_4	92	93	91	98
6[e]		*m*-$MeOC_6H_4$	77	93	90	97
7			97	93	92	99
8[e,g]			83	93	87	94
9[e,f]			85	81	74	92
10[e,f,g]			56	81	69	85

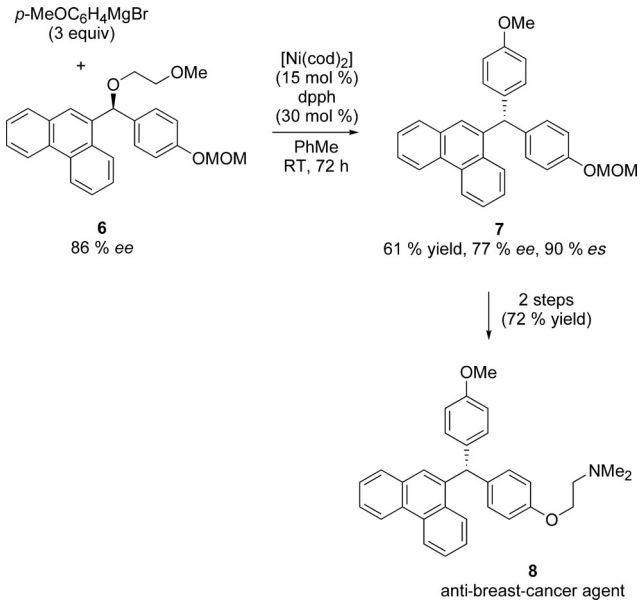
All data are averages of two experiments. [a] Yield after chromatography. [b] Determined by SFC chromatography using a chiral stationary phase. [c] Enantiospecificity (*es*) = $ee_{product}/ee_{starting\ material} \times 100\%$. [d] dpph was used in place of dppo. [e] $[Ni(cod)_2]$ was used in place of $[Ni(acac)_2]$. [f] Reaction run for 72 h. [g] Reaction run at 40 °C. N/A = not applicable, Prod. = product, S.M. = starting material.

The cross-coupling reaction proceeds with inversion of configuration at the methine carbon. The absolute configuration of the alcohol (*S*)-**4** was determined by comparison of the measured optical rotation to a literature value (Scheme 3).[33] After alkylation of (*S*)-**4** and cross-coupling of the resulting ether with 2-thienylmagnesium bromide, the configuration of the product, triarylmethane **5**, was determined to be *R* by X-ray crystallographic analysis.[34] This stereochemical outcome is consistent with an oxidative addition that occurs with inversion of configuration.[35]

To demonstrate the utility of the cross-coupling method, we synthesized an enantioenriched biologically active triarylmethane (Scheme 4). Racemic triarylmethane **8**, an analogue



Scheme 3. Determination of the stereochemistry associated with the cross-coupling reaction. For the X-ray structure of (*R*)-**5**, thermal ellipsoids are shown at 50% probability. DMF = *N*,*N*-dimethylformamide.



Scheme 4. Synthesis of an enantioenriched bioactive triarylmethane. MOM = methoxymethyl.

of tamoxifen, was reported to have anti-breast-cancer activity in the form of an IC_{50} value of 3.88 μM against MCF-7 breast cancer cells; promising activity in vivo was also demonstrated.[2] We prepared the enantioenriched ether **6** through asymmetric arylation followed by alkylation.[17d] Subjection of **6** to our cross-coupling reaction conditions gave triarylmethane **7** in good yield and enantiospecificity.[36] Deprotection and alkylation of **7** gave the target triarylmethane **8**. This approach is highly modular: a variety of aryl Grignard reagents can be used in the cross-coupling reaction and a variety of aminoalkyl groups can be appended in the last step to afford a library of enantioenriched analogues of **8**.

In summary, we have developed a nickel-catalyzed cross-coupling reaction for the synthesis of enantioenriched triarylmethanes. The substrates are diarylmethanol derivatives, which are easily synthesized by the asymmetric arylation of aldehydes. A variety of aryl Grignard reagents can be used in the cross-coupling reaction, which proceed with high enantiospecificity. The method was applied to the asymmetric synthesis of an anti-breast-cancer agent. Studies to further expand the scope of this reaction and elucidate the mechanism are underway.

Experimental Section

Representative procedure for cross-coupling reactions (Table 2, entry 1): In a glovebox, nickel(II) acetylacetonate (5.1 mg, 0.020 mmol, 0.10 equiv), 1,8-bis(diphenylphosphino)octane (19 mg, 0.040 mmol, 0.20 equiv), and PhMe (1.6 mL) were added to a 7 mL vial. The reaction mixture was stirred for 10 min and ether (±)-**1d** (58 mg, 0.20 mmol, 1.0 equiv) was added. The vial was removed from the glovebox and phenylmagnesium bromide (0.20 mL, 0.40 mmol, 2.0 M in Et_2O, 2.0 equiv) was added dropwise. The reaction mixture was stirred for 48 h before quenching with 2-propanol (1.5 mL). The solution was eluted through a plug of silica and concentrated in vacuo. The residue was purified by flash column chromatography through silica gel (0–3% Et_2O/pentane) to afford 2-benzhydrylnaphthalene as a white solid. First run: 50.3 mg (86%). Second run: 46.1 mg (79%).

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[19] Enantiospecificity (es) $= ee_{\text{product}}/ee_{\text{starting material}} \times 100\%$; see a) S. E. Denmark, T. Vogler, *Chem. Eur. J.* **2009**, *15*, 11737; b) S. E. Denmark, M. T. Burk, A. J. Hoover, *J. Am. Chem. Soc.* **2010**, *132*, 1232.

[20] Approximately 30 phosphine ligands were examined and the use of the majority resulted in no reaction. For example, starting material **1a** was recovered in $>90\%$ when the following ligands were used: xantphos (4,5-bis(diphenylphosphino)-9,9-dimethylxanthene), dppe (1,4-bis(diphenylphosphino)ethane), biphep (2,2′-bis(diphenylphosphino)-1,1′-biphenyl), tBu$_3$P, and Cy$_3$P, and davephos (2-dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl).

[21] See the Supporting Information for details.

[22] In the absence of nickel and ligand, no reaction occurs. The cause of decreased enantiospecificity is currently under investigation. We hypothesize that reversible homolysis of the Ni–C bond is competitive in certain reactions; this was suggested by Stille and Cowell: J. K. Stille, A. B. Cowell, *J. Organomet. Chem.* **1977**, *124*, 253.

[23] Homocoupling has been previously observed in palladium-catalyzed cross-coupling reactions of benzylic electrophiles; see Ref. [11b].

[24] Abbreviations: BINAP = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl, dppb = 1,4-bis(diphenylphosphino)butane; dpppent = 1,5-bis(diphenylphosphino)pentane; dpph = 1,6-bis(diphenylphosphino)hexane; dppo = 1,8-bis(diphenylphosphino)octane; dppf = 1,1′-bis(diphenylphosphino)ferrocene; DPEphos = bis(2-diphenylphosphinophenyl)ether.

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[30] dpppent has been used in the palladium-catalyzed cross-coupling of benzylic carbonates with arylboronic acids; see Ref. [11a].

[31] For example, methyl ether **1a** reacts with *meta*-methoxyphenylmagnesium bromide under the reaction conditions in Table 2, entry 6, to provide cross-coupling product in 63% yield and 99% *es*. See the Supporting Information for additional examples.

[32] The product in Table 2, entry 10 was isolated as a mixture of rotamers, as determined by ^{1}H NMR and ^{13}C NMR spectroscopy and mass spectrometry data. However, convergence of the rotamers was not observed in a variable-temperature ^{1}H NMR experiment. See the Supporting Information for details.

[33] F. Tjosaas, T. Anthonsen, E. E. Jacobsen, *ARKIVOC* **2008**, (6), 81.

[34] CCDC 881153 ((*R*)-**5**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[35] Reductive elimination at nickel catalysts occurs with retention of configuration: J. E. Bäckvall, O. S. Andell, *Organometallics* **1986**, *5*, 2350.

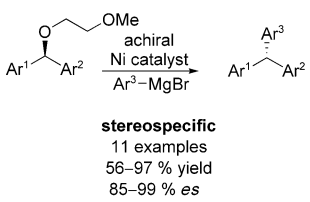
[36] In the absence of nickel and ligand, the reaction of **6** with *p*-MeOC$_6$H$_4$MgBr (3 equiv) gives triarylmethane **7** in 30% yield and 23% *ee* (29% *es*).

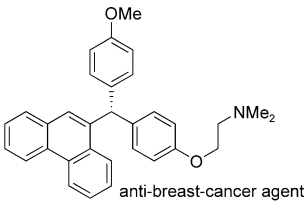
Communications

Cross-Coupling

B. L. H. Taylor, M. R. Harris, E. R. Jarvo* ——— ■■■■–■■■■

Synthesis of Enantioenriched Triarylmethanes by Stereospecific Cross-Coupling Reactions





Coupling with inversion: Chiral diarylmethanol derivatives undergo a stereospecific nickel-catalyzed cross-coupling reaction with aryl Grignard reagents (see scheme). The reaction proceeds with inversion of configuration and high enantiospecificity. The method has been applied to the asymmetric synthesis of a triarylmethane-based anti-cancer compound.