ORGANIC LETTERS

2012
Vol. 14, No. 16
4293–4296

Traceless Directing Group for Stereospecific Nickel-Catalyzed Alkyl–Alkyl Cross-Coupling Reactions

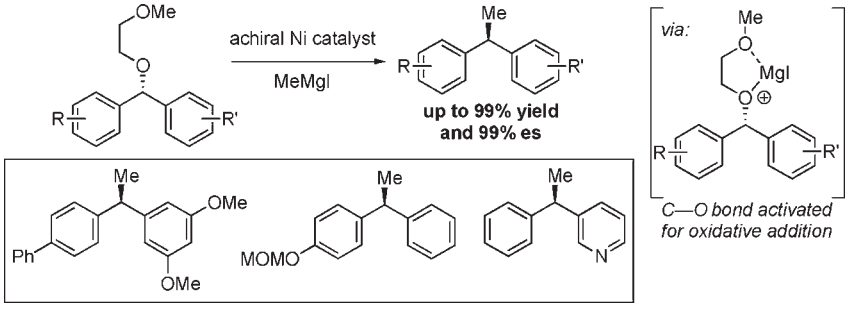
Margaret A. Greene, Ivelina M. Yonova, Florence J. Williams, and Elizabeth R. Jarvo*

Department of Chemistry, University of California, Irvine, California 92697-2025, United States

erjarvo@uci.edu

Received April 6, 2012

ABSTRACT



Stereospecific nickel-catalyzed cross-coupling reactions of benzylic 2-methoxyethyl ethers are reported for the preparation of enantioenriched 1,1-diarylethanes. The 2-methoxyethyl ether serves as a traceless directing group that accelerates cross-coupling. Chelation of magnesium ions is proposed to activate the benzylic C–O bond for oxidative addition.

Nickel-catalyzed alkyl–alkyl cross-coupling reactions are emerging as powerful new methods for the construction of tertiary stereogenic centers.[1] Our laboratory has reported stereospecific cross-coupling reactions of enantioenriched ethers as one approach to achieve such transformations.[2] The use of enantioenriched ethers in cross-coupling reactions is limited, however, by the difficulty of oxidative addition into sp^3 C–O bonds. In this communication we describe a new traceless directing group that accelerates oxidative addition reactions of less reactive electrophiles and application of this method toward synthesis of 1,1-diarylethanes containing a range of functional groups including N-heterocycles.

The field of transition metal catalysis is rich with examples where rate acceleration is afforded by strategically placed directing groups. In the context of nickel-catalyzed cross-coupling reactions, pendant ligands can increase the rate of reductive elimination by coordination to the nickel catalyst.[3,4] Pendant ligands can also accelerate transmetalation of nickel complexes after oxidative addition of C–S bonds by coordinating to the transmetalation partner.[5,6] Our previously reported stereospecific cross-coupling reactions required an adjacent extended aromatic ring to accelerate oxidative addition. Naphthylic ether **1** undergoes facile cross-coupling, likely due to participation of the extended aromatic ring, stabilizing the transition state for oxidative addition (Scheme 1a). In contrast, benzylic ether **2** provides a low yield under our reported reaction conditions (Table 1, entry 1).

(1) For reviews of stereospecific and stereoselective nickel-catalyzed alkyl–alkyl cross-coupling reactions, see: (a) Taylor, B. L. H.; Jarvo, E. R. *Synlett* **2011**, *19*, 2761. (b) Jana, R.; Pathak, T. P.; Sigman, M. S. *Chem. Rev.* **2011**, *111*, 1417. (c) Glorius, F. *Angew. Chem., Int. Ed.* **2008**, *47*, 8347.

(2) Taylor, B. L. H.; Swift, E. C.; Waetzig, J. D.; Jarvo, E. R. *J. Am. Chem. Soc.* **2011**, *133*, 389.

(3) Devasagayaraj, A.; Studemann, T.; Knochel, P. *Angew. Chem., Int. Ed.* **1995**, *34*, 2723. (b) Didiuk, M. T.; Morken, J. P.; Hoveyda, A. H. *Tetrahedron* **1996**, *54*, 1117.

(4) Interaction between the nickel catalyst and functional groups on the substrate are important during enantioselective nickel-catalyzed cross-coupling of alkyl halides. For a lead reference, see: Zhe, L.; Wilsily, A.; Fu, G. C. *J. Am. Chem. Soc.* **2011**, *133*, 8154.

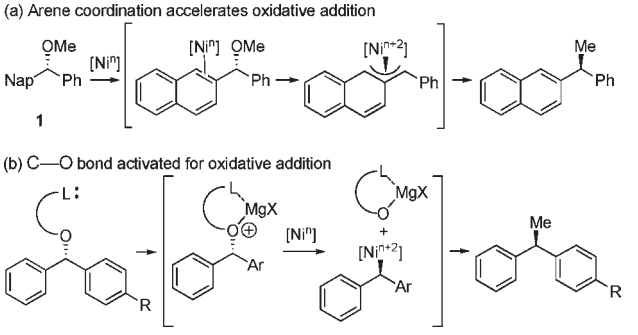
(5) (a) Srogl, J.; Liu, W.; Marshall, D.; Liebeskind, L. *J. Am. Chem. Soc.* **1999**, *121*, 9449. (b) Ni, Z. J.; Mei, N. W.; Shi, X.; Tzeng, Y. L.; Wang, M. C.; Luh, T. Y. *J. Org. Chem.* **1991**, *56*, 4035.

(6) For substrate-directed reactions of cuprates, see: Hanessian, S.; Thavonekham, B.; DeHoff, B. *J. Org. Chem.* **1989**, *54*, 5831.

10.1021/ol300891k
Published on Web 05/08/2012

To increase the reactivity of nonextended aromatic systems for cross-coupling, a new strategy was required. We developed a traceless directing group that would accelerate oxidative addition but not be present in the reaction products, by incorporating the directing group on the ether substituent (Scheme 1b). We envisioned that ethers that contain pendant ligands would chelate the magnesium salts present in the reaction mixture, thus activating the C–O bond for oxidative addition and accelerating the rate of the desired cross-coupling reaction. Unlike typical directed reactions where the directing functional group is present in the reaction product, this strategy allows for a wider substrate scope and precludes the necessity for further modification of the product to remove the directing group.[7]

Scheme 1. Traceless Directing Group Used To Accelerate Oxidative Addition



As a test application to determine the feasibility of this strategy, we targeted the enantiospecific synthesis of 1,1-diarylethanes (Figure 1). 1,1-Diarylalkanes are active against cancer, osteoporosis, smallpox, tuberculosis, and insomnia.[8] Furthermore, the diarylmethine pharmacophore is present in natural products and drugs including podophyllotoxin, peperomin B, kadangustin J, zoloft, tolterodine, lasofoxifene, and centchroman. Despite their promise, identification of new medicinal agents based on the 1,1-diarylalkane framework is held back because general methods for their enantioselective preparation do not exist. These compounds are typically prepared and tested for biological activity as racemic mixtures or are resolved using classical resolution by crystallization of diastereomeric salts. While there have been creative approaches to enantioselective syntheses of these compounds,[9] control of stereochemistry without directing groups that must later be removed remains a challenge.

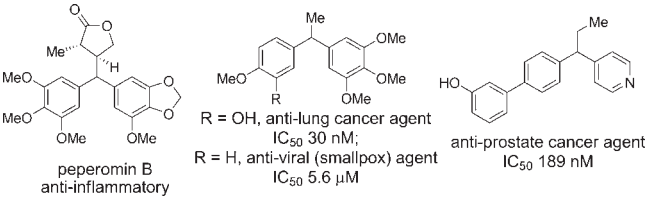


Figure 1. Bioactive diarylalkanes.

By starting with enantioenriched ethers and utilizing a traceless directing group for substrate activation, we envisioned a straightforward strategy for enantioselective synthesis of 1,1-diarylethanes. This methodology does not rely on steric bulk or electronic differentiation at the stereocenter because stereochemistry is set before the cross-coupling reaction, allowing diarylethanes with substitution far removed from the stereocenter to be synthesized in high enantiopurity.

We examined cross-coupling reactions of diphenyl carbinol derivatives to evaluate the influence of the ether substituent on the cross-coupling (Table 1). 2-Methoxyethyl ether **5** reacts more rapidly than methyl, MOM, or MEM ethers (cf. entries 1–4). These results are consistent with acceleration of oxidative addition by formation of an optimal five-membered ring chelate with magnesium salts (Scheme 1b).

Once we had identified a suitable directing group, we optimized the reaction conditions to further improve the yield of the desired product (Table 1). While other ligands were examined, DPEphos generally provided the highest yield (e.g., entries 4–6).[10] The precatalyst, $Ni(cod)_2$, could be replaced with more stable $Ni(acac)_2$ providing an improved yield (entry 7). Extending the reaction time to 48 h further improved the yield to 80% (entry 8).

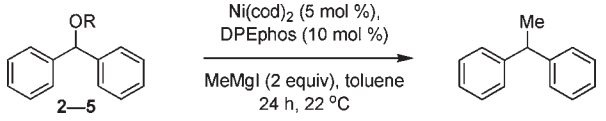
(7) For a representative example of an alternative type of traceless directing group, where a functional group is used first as a directing group and second as a leaving group, see: Wang, C.; Rakshit, S.; Glorius, F. *J. Am. Chem. Soc.* **2010**, *132*, 14006.

(8) (a) For a discussion, see: Kainuma, M.; Kasuga, J.-i.; Hosoda, S.; Wakabayashi, K.-i.; Tanatani, A.; Nagasawa, K.; Miyachi, H.; Makishima, M.; Hashimoto, Y. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3213. (b) Anti-lung cancer agent, see: Alami, M.; Messaoudi, S.; Hamze, A.; Provot, O.; Brion, J.-D.; Liu, J.-M.; Bignon, J.; Bakala, J. Patent WO/2009/147217 A1, Dec 10, 2009. (c) Anti-viral agent: Cheltsov, A. V.; Aoyagi, M.; Aleshin, A.; Yu, E. C.-W.; Gilliland, T.; Zhai, D.; Bobkov, A. A.; Reed, J. C.; Liddington, R. C.; Abagyan, R. *J. Med. Chem.* **2010**, *53*, 3899. (d) Anti-prostate cancer agent: Hu, Q. Z.; Yin, L. N.; Jagusch, C.; Hille, U. E.; Hartmann, R. W. *J. Med. Chem.* **2010**, *53*, 5049. (e) Messaoudi, S.; Hamze, A.; Provot, O.; Tréguier, B.; De Losada, J. R.; Bignon, J.; Liu, J.-M.; Wdzieczak-Bakala, J.; Thoret, S.; Dubois, J.; Brion, J.-D.; Alami, M. *Chem. Med. Chem.* **2011**, *6*, 488. (f) Shagufta; Srivastava, A. K.; Sharma, R.; Mishra, R.; Balapure, A. K.; Murthy, P. S. R.; Panda, G. *Bioorg. Med. Chem.* **2006**, *14*, 1497. (g) Pathak, T. P.; Gligorich, K. M.; Welm, B. E.; Sigman, M. S. *J. Am. Chem. Soc.* **2010**, *132*, 7870. (h) Moree, W. J.; Li, B. F.; Zamani-Kord, S.; Yu, J. H.; Coon, T.; Huang, C.; Marinkovic, D.; Tucci, F. C.; Malany, S.; Bradbury, M. J.; Hernandez, L. M.; Wen, J. Y.; Wang, H.; Hoare, S. R. J.; Petroski, R. E.; Jalali, K.; Yang, C.; Sacaan, A.; Madan, A.; Crowe, P. D.; Beaton, G. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 5874.

(9) For representative examples, see: (a) Hatanaka, Y.; Hiyama, T. *J. Am. Chem. Soc.* **1990**, *112*, 7793. (a) Wang, X.; Guram, A.; Caille, S.; Hu, J.; Preston, J. P.; Ronk, M.; Walker, S. *Org. Lett.* **2011**, *13*, 1881. (b) Imao, D.; Glasspoole, B. W.; Laberge, V. S.; Crudden, C. M. *J. Am. Chem. Soc.* **2009**, *131*, 5024. (c) Paquin, J.-F.; Defieber, C.; Stephenson, C. R. J.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127*, 10850. (d) Nave, S.; Sonawane, R. P.; Elford, T. G.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2010**, *132*, 17096. (e) Lewis, C. A.; Chiu, A.; Kubryk, M.; Balsells, J.; Pollard, D.; Esser, C. K.; Murry, J.; Reamer, R. A.; Hansen, K. B.; Miller, S. J. *J. Am. Chem. Soc.* **2006**, *128*, 16454. (f) Bolshan, Y.; Chen, C.-y.; Chilenski, J. R.; Gosselin, F.; Mathre, D. J.; O'Shea, P. D.; Roy, A.; Tillyer, R. D. *Org. Lett.* **2004**, *6*, 111. (g) Podhajsky, S. M.; Iwai, Y.; Cook-Sneathen, A.; Sigman, M. S. *Tetrahedron* **2011**, *67*, 4435.

(10) Alternative ligands, including Xantphos, *rac*-BINAP, dppb, and dppf provided < 5% product.

Table 1. Identification of Traceless Directing Group



entry	R	ligand	starting material (%)[a]	product (%)[a]
1	-CH_3, **2**	DPEphos	87	10
2	-CH_2OCH_3, **3**	DPEphos	80	16
3	**4**	DPEphos	70	10
4	-$(CH_2)_2OCH_3$, **5**	DPEphos	17	60
5	-$(CH_2)_2OCH_3$, **5**	BINAP	42	<5
6	-$(CH_2)_2OCH_3$, **5**	dppb	95	<5
7[b]	-$(CH_2)_2OCH_3$, **5**	DPEphos	5	73
8[b,c]	-$(CH_2)_2OCH_3$, **5**	DPEphos	<5	80

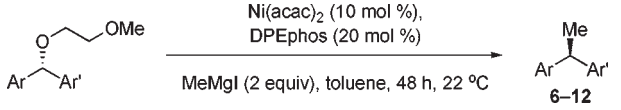
[a] Determined by ^{1}H NMR spectroscopy by comparison to internal standard (PhTMS). [b] $Ni(cod)_2$ replaced with $Ni(acac)_2$. [c] 48 h reaction time.

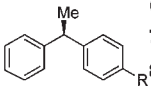
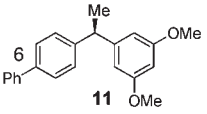
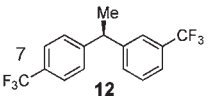
We designed a series of chiral substrates to test the enantiospecificity (es) of the reaction (Table 2).[11] Each substrate was prepared by enantioselective arylation of an aldehyde with the requisite boronic acid.[12] The nickel-catalyzed cross-coupling reaction is highly enantiospecific across a range of substitution patterns. As expected, cross-coupling proceeds with inversion at the stereogenic center.[13] For most substrates, the background reaction in the absence of nickel catalyst does not occur.[14]

To highlight the synthetic advantages of our method, our preliminary studies have focused on the synthesis of 1,1-diarylethanes where the arenes have similar steric properties and are only differentiated by distal substituents (e.g., products **6**–**10**). This type of tertiary stereocenter is very challenging to prepare using alternative methods. Electron-donating and electron-withdrawing groups[15] on the aromatic rings are well-tolerated (entries 2 and 3). A protected phenol (entry 4) and pendant alcohol (entry 5) are also competent substrates and provide functional group handles for further chemical modification of the products. Inclusion of a strong electron-donating *p*-OMe group provides a moderate yield of desired product **8** despite competitive dimerization of the starting material.[16] As anticipated, this method also provides access to compounds containing arenes with similar electronic properties. For example, compound **12** contains *m*- and *p*-CF_3 substituted arenes.

N-Heterocycles are another challenging class of compounds that we envisioned could undergo cross-coupling reactions using this traceless directing group strategy. N-Heterocyclic motifs are often present in biologically active compounds[17] and, therefore, represent an important set of targets. These substrates had proven recalcitrant under our original cross-coupling conditions: when substrates such as quinoline **13**, containing the simple methyl ether, are subjected to our previously reported reaction

Table 2. Scope of Cross-Coupling Reaction



entry	product (pdt)		yield (%)[a]	ether ee (%)[b]	pdt ee (%)[b]	es (%)[c]
1		**6**, R = Ph	68	87	85	98
2		**7**, R = CF_3	52 (61)	93	91	98
3[d]		**8**, R = OMe	57[e]	83	72	88
4		**9**, R = OMOM	65	92	90	98
5[f]		**10**, R = CH_2OH	64 (77)	91	80	88
6	 **11**		88	85	80	94
7	 **12**		50 (67)	96	nd[g]	nd

[a] Isolated yield after silica gel chromatography. Yields in parentheses are determined by NMR spectroscopy relative to an internal standard (PhTMS). [b] Determined by chiral SFC chromatography. [c] $100 \times ee_{product}/ee_{starting\ material}$. [d] 5% $Ni(cod)_2$, 10% DPEphos, 1.5 equiv of MeMgI. Average of four experiments. [e] 24% dimer product observed. [f] 15% $Ni(acac)_2$, 30% DPEphos, 3 equiv of MeMgI. [g] Enantiomers of product **12** were not separable by chiral SFC or GC.

(11) For definition of the term enantiospecificity (es), see: (a) Denmark, S. E.; Vogler, T. *Chem.–Eur. J.* **2009**, *15*, 11737. (b) Denmark, S. E.; Burk, M. T.; Hoover, A. J. *J. Am. Chem. Soc.* **2010**, *132*, 1232.

(12) (a) Bolm, C.; Rudolph, J. *J. Am. Chem. Soc.* **2002**, *124*, 14850. (b) Braga, A. L.; Paixão, M. W.; Westermann, B.; Schneider, P. H.; Wessjohan, L. A. *J. Org. Chem.* **2008**, *73*, 2879. (c) Moro, A. V.; Tiekink, E. R. T.; Zukerman-Schpector, J.; Lüdtke, D. S.; Correia, C. R. D. *Eur. J. Org. Chem.* **2010**, 3696.

(13) Comparison of optical rotations for synthesis of compound **8** to literature values demonstrates that the reaction proceeds with inversion at the stereogenic center. See Supporting Information for more detail.

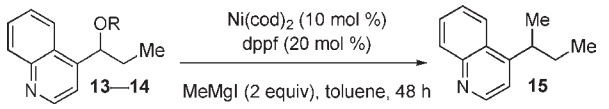
(14) For all substrates in Table 2, reactions run without nickel catalyst, in the presence and absence of phosphine ligand, provide < 5% product, except for entry 3 where 24% product **8** was observed.

(15) The yields of compounds **7** and **12** are high as measured by ^{1}H NMR spectroscopy; decreased isolated yields for these substrates are due to the challenging separation from starting material by silica gel column chromatography.

(16) 24% dimer observed. See Supporting Information for more information. The mechanism of formation of this dimer is under investigation. Related palladium-catalyzed cross-coupling of 1,1-diaryl-1-haloalkanes with aryl BF_3K salts also results in dimerization of starting material. See: Molander, G. A.; Elia, M. D. *J. Org. Chem.* **2006**, *71*, 9198.

(17) (a) Pathak, T. P.; Gligorich, K. M.; Welm, B. E.; Sigman, M. S. *J. Am. Chem. Soc.* **2010**, *132*, 7870. (b) Moree, W. J.; Li, B.-F.; Jovic, F.; Coon, T.; Yu, J.; Gross, R. S.; Tucci, F.; Marinkovic, D.; Zamani-Kord, S.; Malany, S.; Bradbury, M. J.; Hernandez, L. M.; O'Brien, Z.; Wen, J.; Wang, H.; Hoare, S. R. J.; Petroski, R. E.; Sacaan, A.; Madan, A.; Crowe, P. D.; Beaton, G. *J. Med. Chem.* **2009**, *52*, 5307. (c) Little, P. J.; Ryan, A. *J. Biochem. Pharmacol.* **1982**, *31*, 1795.

Table 3. Effect of Traceless Directing Group in Cross-Coupling Reactions of N-Heterocyclic Compounds



entry	R	temp (°C)	starting material (%)[a]	product (%)[a]
1	-CH_3, **13**	22	<5	<5
2	-CH_3, **13**	5	<5	18
3	-$(CH_2)_2OCH_3$, **14**	5	<5	50[b]
4[c]	-$(CH_2)_2OCH_3$, **14**	5	<5	62[b]

[a] Determined by ^{1}H NMR spectroscopy by comparison to internal standard (PhTMS). [b] Isolated yield after silica gel chromatography. [c] Slow addition of starting material.

conditions the rate of decomposition of starting material is much faster than that of product formation (Table 3, entry 1). Decreasing the reaction temperature provides a slight improvement in product distribution to afford quinoline **15** in 18% yield (entry 2). Employing the traceless directing group substantially improves the transformation and provides a 50% yield of the desired product (entry 3). We hypothesize that the 2-methoxyethyl ether accelerates oxidative addition, allowing the desired transformation to out-compete decomposition. Further optimization of the reaction conditions by slow addition of the starting material further suppressed decomposition pathways and afforded the desired product in 62% yield (entry 4).

A range of N-heterocyclic substrates react smoothly and with high levels of enantiospecificity under the optimized reaction conditions. Both 3- and 4-substituted quinolines underwent cross-coupling (Table 4, entries 1 and 2). Substituted pyridines are also well-tolerated and provided excellent yields (entries 3 and 4). Notably, substrates that contain a naphthalene ring in addition to the heteroaromatic ring are sufficiently reactive that the simple methyl ether **19** also provides desired product **18** in good yield.[18] This result is consistent with participation of the napthalene ring as shown in Scheme 1a.

In conclusion, we report a new traceless directing group that accelerates cross-coupling for unreactive oxidative addition partners. This strategy is demonstrated by developing new methods for nickel-catalyzed sp^3-sp^3 cross-coupling. Enantioenriched 1,1-diarylethanes are formed with high

(18) For more details, see the Supporting Information.

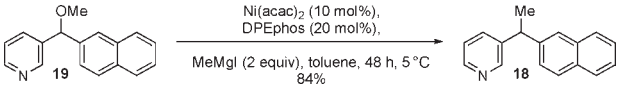
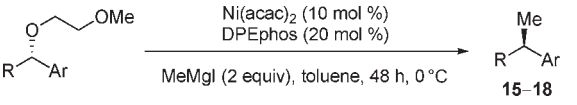
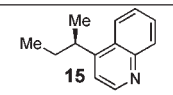
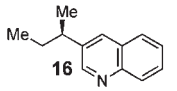
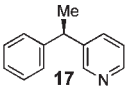
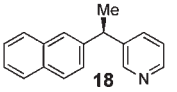


Table 4. Reactivity of N-Heterocyclic Compounds



entry	product	yield (%)[a]	ether ee (%)[b]	product ee (%)[b]	es (%)[c]
1[d]		50	82	80	98
2		75	71	nd[e]	nd
3		99	88	88	>99
4		98	96	88	92

[a] Isolated yield after silica gel chromatography. [b] Determined by chiral SFC chromatography. [c] 100 × $ee_{product}/ee_{starting\ material}$. [d] 10% $Ni(cod)_2$, 20% dppf, 5 °C. [e] Enantiomers of product **16** were not separable by chiral SFC or GC.

enantiospecificity, where the newly formed stereogenic center is flanked by arenes with similar steric and electronic properties. The use of the methoxyethyl ether as a directing group also promotes reactions of substrates containing sensitive N-heterocycles that did not provide the desired cross-coupling under our previously reported reaction conditions. Further expansion of the scope and elucidation of the mechanistic details of this reaction is an ongoing project in our group.

Acknowledgment. This work was supported by University of California, Cancer Research Coordinating Committee. We thank Frontier Scientific and Sigma-Aldrich for gifts of boronic acids and catalysts, respectively.

Note Added after ASAP Publication. There were errors in the version published ASAP May 8, 2012. Figure 1 was corrected. Reference 8 was rearranged for clarity, and two references to the work of Alami (8b and 8e) were added; the correct version reposted May 15, 2012.

Supporting Information Available. Experimental procedures and spectroscopic and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.