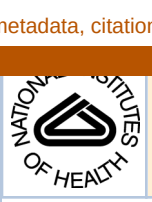

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Nickel-Catalyzed Enantioselective Cross-Couplings of Racemic Secondary Electrophiles that Bear an Oxygen Leaving Group

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Abstract

To date, effective nickel-catalyzed enantioselective cross-couplings of alkyl electrophiles that bear oxygen leaving groups have been limited to reactions of *allylic* alcohol derivatives with *Grignard* reagents. In this report, we establish that, in the presence of a nickel/pybox catalyst, a variety of racemic *propargylic* carbonates are suitable partners for asymmetric couplings with *organozinc* reagents. The method is compatible with an array of functional groups and uti-lizes commercially available catalyst components. The development of a versatile nickel-catalyzed enantioselective cross-coupling process for electrophiles that bear a leaving group other than a halide adds a significant new dimension to the scope of these reactions.

During the past several years, we have pursued the development of nickel-catalyzed asymmetric crosscoupling reactions of racemic secondary alkyl electrophiles.[1,2,3] Although both activated and unactivated electrophiles can serve as suitable coupling partners, our progress to date has been limited to substrates in which the leaving group is a halide. Of course, oxygen-based leaving groups are widely used in organic chemistry, and the conditions for their synthesis from alcohols can complement those employed for the genera-tion of halides (e.g., Brønsted-basic vs. Brønsted-acidic). We therefore sought to add a new dimension to our stereoconvergent cross-coupling reactions of alkyl electrophiles by developing a method that can utilize oxygen leaving groups. In this report, we de-scribe the achievement of this objective, specifically, nickel-catalyzed asymmetric Negishi reactions of racemic propargylic carbonates (eq 1).

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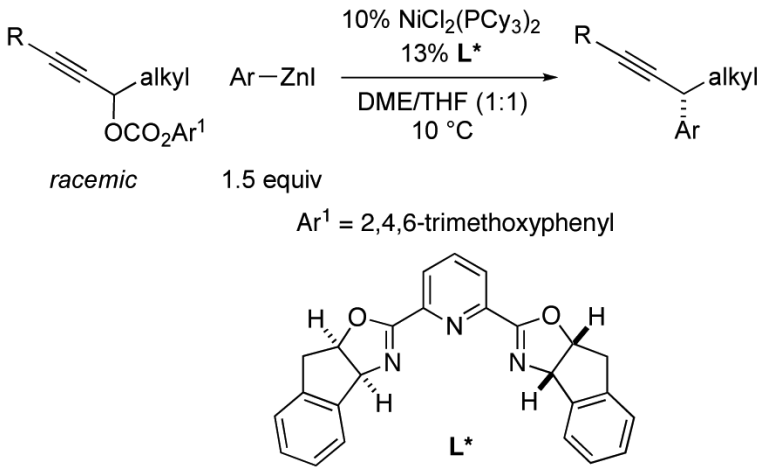
ASSOCIATED CONTENT

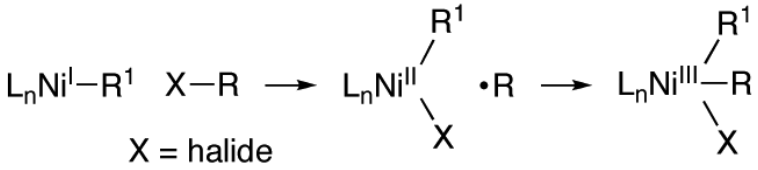
Supporting Information. Experimental procedures and compound characterization data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org



(1)

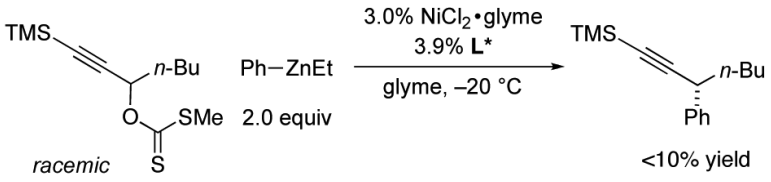
Oxygen leaving groups are widely employed in crosscoupling reactions of aryl electrophiles (C_{sp2}-O bond cleavage), including nickel-catalyzed carbon-carbon bond-forming processes.[4] In contrast, there are far fewer examples of corresponding nickel-catalyzed couplings of alkyl electrophiles (C_{sp3}-O bond cleavage), es-pecially secondary or tertiary electrophiles. Further-more, to the best of our knowledge, *enantioselective* reactions are limited to a rather narrow set of allylic electrophiles, and good ee's and yields are observed only with highly reactive Grignard reagents.[5]

We sought to expand the scope of such processes beyond allylic alcohol derivatives and beyond Grignard reagents as coupling partners. For some of the nickelcatalyzed cross-coupling methods that we have developed, we have hypothesized that oxidative addition proceeds through a two-step inner-sphere electron-transfer pathway, beginning with abstraction of the leaving group (X) by nickel (eq 2).[6,7] Because S_H2 reactions at oxygen are uncommon, we decided to pursue a Barton-McCombie-like approach[8] to achieving C-O bond cleavage, specifically, the use of acylated alcohols as substrates, which provides nickel with the oppor-tunity to initially interact with a carbon-heteroatom double bond and to cleave the target C-O bond in a subsequent step.



(2)

In view of the synthetic utility of alkynes,[9] we at-tempted to apply a method that we have developed for stereoconvergent Negishi reactions of propargylic halides[10] to the cross-coupling of an acylated propargylic alcohol (eq 3). Unfortunately, we obtained virtually none of the desired coupling product.

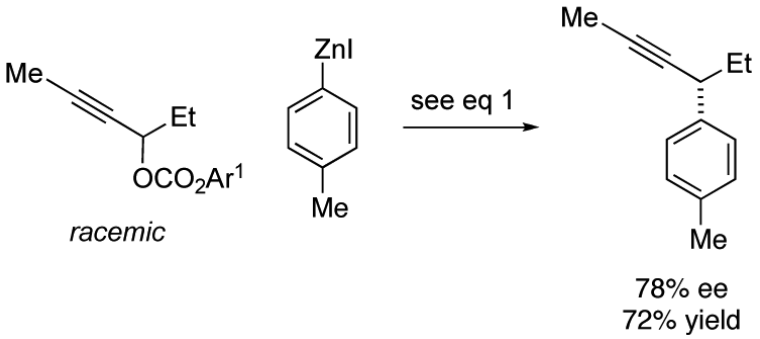


(3)

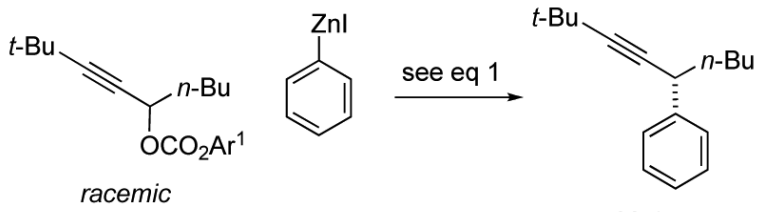
After considerable effort, we have developed a method that achieves enantioselective cross-couplings of propargylic electrophiles that bear an oxygen leaving group. As illustrated in Table 1, whereas a Negishi reaction of a propargylic xanthate proceeds with very modest ee and yield (entry 1), the corresponding carbonate couples with promising enantioselectivity (but still unsatisfactory yield; entry 2). Substitution of the methyl group of the carbonate with a phenyl group leads to a significant improvement in ee and product formation (entry 3), and, finally, the addition of electron-donating substituents to the 2, 4, and 6 positions of the aromatic ring results in a small enhancement in enantioselectivity and a substantial increase in yield (entries 4-6).

Table 2 provides a variety of examples of this new stereoconvergent cross-coupling of organozinc reagents with propargylic electrophiles via C-O bond cleavage.[11,12] Thus, an array of TMS-substituted propargylic carbonates couple with a range of arylzinc reagents, including ortho-,[13] meta-, and para-substituted nucleo-philes (entries 3-5). The method is compatible with a diverse set of functional groups, such as aryl methyl ethers (entries 3-5 and 9),[14] acetals (entries 8 and 12), silyl ethers (entry 9), esters (entry 10), aryl chlorides and fluorides (entry 10),[15] olefins (entry 11), alkyl chlorides (entry 12),[16] and a Boc-protected nitrogen heterocycle (entry 13). Both of the catalyst components ($NiCl_2(PCy_3)_2$ and **L***) are commercially available and air-stable.

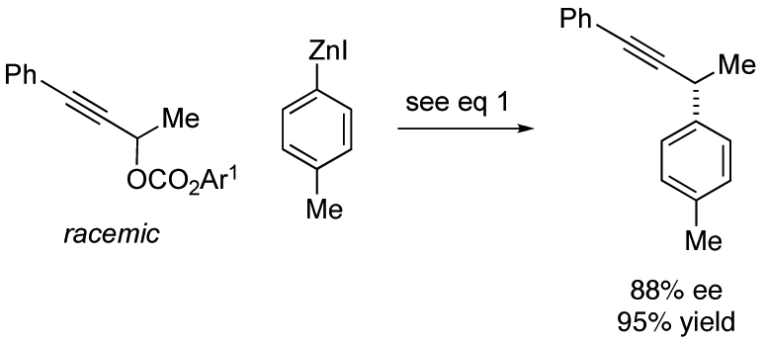
Although this method was optimized for asymmetric cross-couplings of readily deprotected TMS-substituted alkynes, we have determined that it can be applied without modification to other families of alkynes. Thus, regardless of whether the distal carbon of the propargylic carbonate bears a small or a large alkyl group, or an aromatic substituent, the stereoconvergent Negishi reaction proceeds with promising enantioselectivity and yield (eq 4-6).



(4)



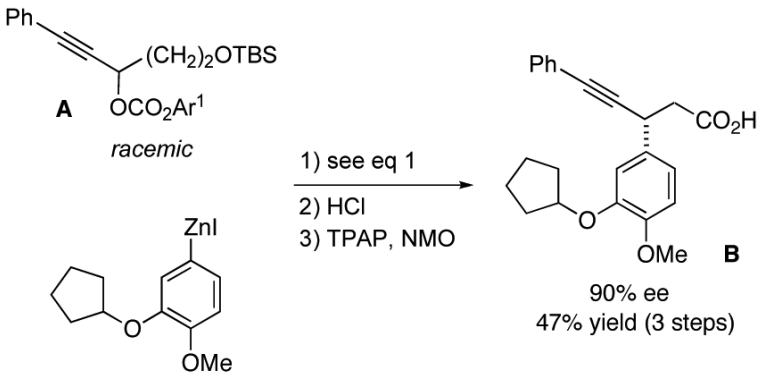
(5)



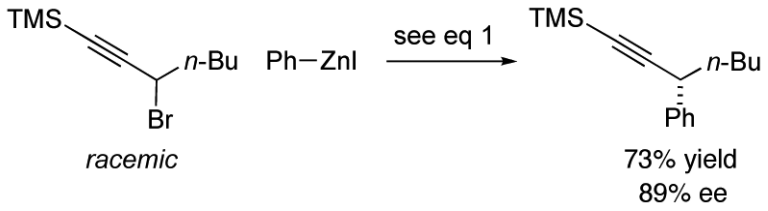
(6)

We have applied our method to the synthesis of alkyne **B**, which has potential utility for the treatment of allergic and inflammatory diseases.[17] Thus, on a gram-scale, a catalytic asymmetric Negishi cross-coupling of propargylic carbonate **A** with a functionalized arylzinc reagent, followed by desilylation and oxidation, fur-nishes the target alkyne in 90% ee and 47% overall yield (three steps; eq 7).

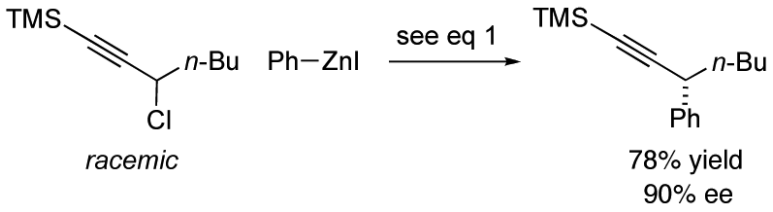
Although propargylic carbonates are not suitable cross-coupling partners (<2% ee and 5% yield) using our earlier procedure for Negishi reactions of propargylic bromides,[10] our new method *is* fairly versatile, effective not only for propargylic carbonates (Table 2), but, without modification, also for propargylic bromides and chlorides (eq 8 and eq 9).



(7)



(8)



(9)

In summary, with respect to nickel-catalyzed enantioselective cross-couplings of alkyl electrophiles that bear oxygen leaving groups, only reactions of a small set of *allylic* alcohol derivatives with *Grignard* reagents had previously been reported to proceed in good ee and yield. We have established that a diverse array of racemic *propargylic* carbonates are suitable coupling partners in nickel/pybox-catalyzed asymmetric *Negishi* reactions. The method is compatible with a range of functional groups and employs commercially available catalyst components. The development of a versatile nickel-catalyzed enantioselective cross-coupling process for electrophiles that bear a leaving group other than a halide adds a significant new dimension to the scope of these reactions. Further investigations into the use of non-halide leaving groups, as well as studies to eluci-date the mechanism of this transformation, are under-way.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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(2). For work by others, see: Caeiro J, Sestelo JP, Sarandeses LA. Chem. Eur. J. 2008; 14:741–746. [PubMed: 17929335]

(3). For reviews and leading references, see: (a) Rudolph A, Lautens M. Angew. Chem., Int. Ed. 2009; 48:2656–2670. (b) Glorius F. Angew. Chem., Int. Ed. 2008; 47:8347–8349.

(4). For a recent review with leading references, see: Rosen BM, Quasdorf KW, Wilson DA, Zhang N, Resmerita A-M, Garg NK. Percec, V. Chem. Rev. 2011; 111:1346–1416.

(5). Enantioselective coupling reactions of secondary allylic electrophiles: (a) Indolese AF, Consiglio G. Organometallics. 1994; 13:2230–2234. and references therein. (b) Nomura N, RajanBabu TV. Tetrahedron Lett. 1997; 38:1713–1716. (c) Gomez-Bengoa E, Heron NM, Didiuk MT, Luchaco CA, Hoveyda AH. J. Am. Chem. Soc. 1998; 120:7649–7650. (d) Nagel U, Nedden HG. Inorg. Chim. Acta. 1998; 269:34–42. (e) Chen H, Deng M-Z. J. Organomet. Chem. 2000; 603:189–193. (f) Chung K-G, Miyake Y, Uemura S. J. Chem. Soc., Perkin Trans. 2000; 1:15–18. Chung K-G, Miyake Y, Uemu-ra S. J. Chem. Soc., Perkin Trans. 2000; 1:2725–2729. (g) No-vak A, Fryatt R, Woodward S. Comptes Rendus Chimie. 2007; 10:206–212.

(6). For suggestions of radical intermediates in nickel-catalyzed cross-coupling reactions of unactivated alkyl electro-philes, see: (a) Suzuki: Zhou J, Fu GC. J. Am. Chem. Soc. 2004; 126:1340–1341. [PubMed: 14759182] (b) Hiyama: Powell DA, Fu GC. J. Am. Chem. Soc. 2004; 126:7788–7789. [PubMed: 15212521] (c) Reference 1a. We expect that the pathway for oxidative addition will depend on a variety of factors, including the ligand, the leaving group, and the nature of the electrophile (e.g., unactivated vs. activat-ed).

(7). For mechanistic proposals for Ni/terpyridine-catalyzed Negishi reactions of unactivated alkyl electrophiles, see: (a) Jones GD, Martin JL, McFarland C, Allen OR, Hall RE, Haley AD, Brandon RJ, Konovalova T, Desrochers PJ, Pulay P, Vicic DA. J. Am. Chem. Soc. 2006; 128:13175–13183. [PubMed: 17017797] Lin X, Phillips DL. J. Org. Chem. 2008; 73:3680–3688. [PubMed: 18410144]

(8). For a review and leading references, see: Mancuso J. Li JJ. Name Reactions for Homologations. 2009; 1:614–632.John Wiley & SonsHoboken, NJ

(9). For leading references to the chemistry of alkynes, see: (a) Science of Synthesis; Thomas EJ. Thieme. Stuttgart. 2008; 43 (b)Diederich F, Stang PJ, Tykwinski RR. Acetylene Chemistry. 2005Wiley-VCHNew York

(10). Smith SW, Fu GC. J. Am. Chem. Soc. 2008; 130:12645–12647. [PubMed: 18763769]

(11). Notes: (a) Under our standard reaction conditions: es-sentially no cross-coupling product (<2%) is formed in the absence of $NiCl_2(PCy_3)_2$, and very little (~5%) is generated in the absence of L*; a propargylic carbonate that includes a terminal alkyne is not a suitable substrate; an attempt to couple a hindered electrophile (alkyl = i-Pr) led to the formation of an allene; the corresponding propargylic iodide cross-couples in lower yield (<30%); there is no kinetic resolution of the propargylic carbonate during the course of a coupling reaction. (b) The cross-coupling illustrated in entry 2 of Table 2 proceeds in 91% ee and 48% yield (with 20% unreacted electrophile) in the presence of 5% $NiCl_2(PCy_3)_2$ and 6.5% L*. (c) In a preliminary study under related conditions, a benzylic carbonate couples with an arylzinc reagent in 64% ee and 72% yield.

(12). Using a nickel catalyst, but with a different leaving group (alkoxy), a different activating substituent (naphthyl and other extended aromatic), a different nucleophile (MeMgI), a different ligand (phosphine), etc., Jarvo has reported cross-couplings that proceed with inversion of stereochemistry: Taylor BLH, Swift EC, Waetzig JD, Jarvo ER. J. Am. Chem. Soc. 2011; 133:389–391. and references therein.

(13). In the case of asymmetric Negishi reactions of propargylic bromides (Reference 10), ortho-substituted arylzinc reagents are not suitable coupling partners (yield <40%).

(14). For examples of nickel-catalyzed cross-couplings of aryl methyl ethers, see Reference 4.

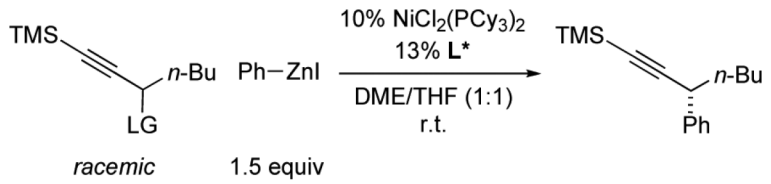
(15). For a recent report of nickel-catalyzed Negishi reactions of aryl chlorides, see: Liu N, Wang L, Wang Z-X. Chem. Commun. 2011:1598–1600.

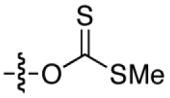
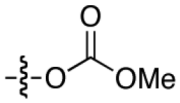
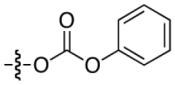
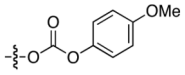
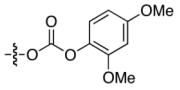
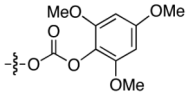
(16). For examples of nickel-catalyzed cross-couplings of unactivated primary alkyl chlorides, see: González-Bobes F, Fu GC. J. Am. Chem. Soc. 2006; 128:5360–5361. [PubMed: 16620105]

(17). Christensen, SB.; Karpinski, JM.; Frazee, JS. Substituted-Pent-4-Ynoic Acids. U.S. Patent 6,037,367. March 14. 2000

Table 1

The Impact of the Structure of the Oxygen Leaving Group on the Catalytic Asymmetric Cross-Coupling of a Propargylic Electrophile[a]



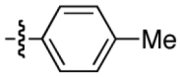
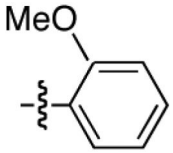
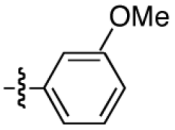
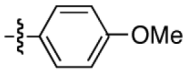
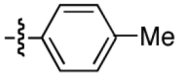
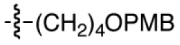
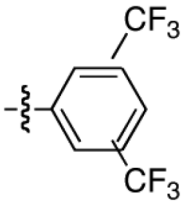
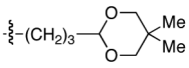
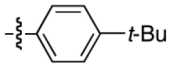
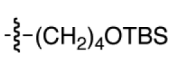
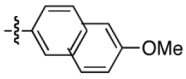
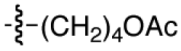
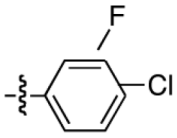
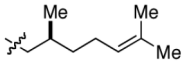
entry	LG	ee (%)	yield (%) [b]
1		8	24
2		60	9
3		85	33
4		88	53
5		89	56
6		90	83

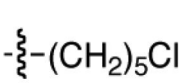
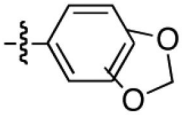
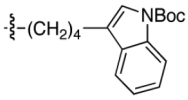
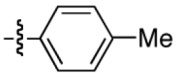
[a] All data are the average of two experiments.

[b] The yield was determined by GC analysis with the aid of a calibrated internal standard.

Table 2

Catalytic Asymmetric Cross-Couplings of TMS-Protected Racemic Propargylic Carbonates (for the reaction conditions, see eq 1, R = TMS)[a]

entry	alkyl	Ar	ee (%)	yield (%)[b]
1	Me		93	69
2	*n*-Bu	Ph	90	81
3	*n*-Bu		93	66
4	*n*-Bu		92	73
5	*n*-Bu		89	76
6	*i*-Bu		93	57
7			85	85
8			92	87
9			91	94
10			86	81
11		Ph	89[c]	79

entry	alkyl	Ar	ee (%)	yield (%)[b]
12			84	65
13			90	72

[a] All data are the average of two experiments.

[b] Yield of purified product.

[c] de.