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

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S *Supporting Information*

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 Communication, 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 utilizes 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 cross-coupling reactions of racemic secondary alkyl electrophiles.[1−3] 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 generation 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 Communication, we describe the achievement of this objective, specifically, nickel-catalyzed asymmetric Negishi reactions of racemic propargylic carbonates (eq 1).

Ar^1 = 2,4,6-trimethoxyphenyl
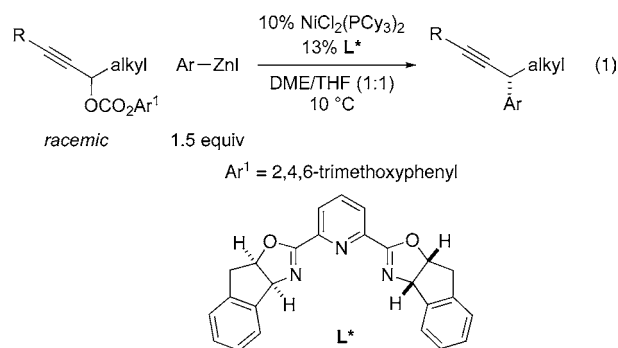
Oxygen leaving groups are widely employed in cross-coupling reactions of aryl electrophiles (C_{sp^2}−O bond

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_{sp^3}−O bond cleavage), especially secondary or tertiary electrophiles. Furthermore, 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 nickel-catalyzed 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]
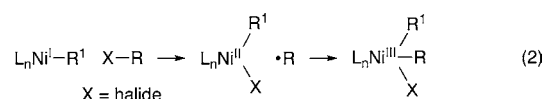
Because S_H2 reactions at oxygen are uncommon, we decided to pursue a Barton−McCombie-like approach[8] to achieving C−O bond cleavage, specifically, the use of acylated alcohols as substrates, which provides nickel with the opportunity to initially interact with a carbon−heteroatom double bond and to cleave the target C−O bond in a subsequent step.

In view of the synthetic utility of alkynes,[9] we attempted 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.
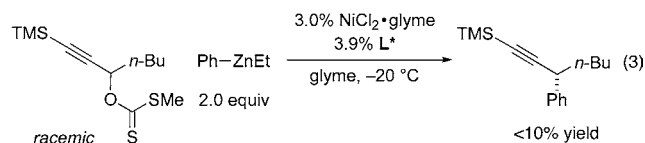
After considerable effort, we have developed a method that achieves enantioselective cross-couplings of propargylic electrophiles that bear an oxygen leaving group. As illustrated in Table 1, whereas a Negishi reaction of a propargylic xanthate proceeds with very modest ee and yield (entry 1), the corresponding 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

Table 1. 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	-O-C(=S)-SMe	8	24
2	-O-C(=O)-OMe	60	9
3	-O-C(=O)-O-Ph	85	33
4	-O-C(=O)-O-C₆H₄-OMe (para)	88	53
5	-O-C(=O)-O-C₆H₃(OMe)₂	89	56
6	-O-C(=O)-O-C₆H₂(OMe)₃	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.

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 nucleophiles (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 (NiCl₂(PCy₃)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 (eqs 4–6).

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

Table 2. Catalytic Asymmetric Cross-Couplings of TMS-Protected Racemic Propargylic Carbonates[a]

| entry	alkyl	Ar	ee (%)	yield (%)[b]
1	Me	C₆H₄-Me (para)	93	69
2	n-Bu	Ph	90	81
3	n-Bu	C₆H₄-OMe (ortho, MeO)	93	66
4	n-Bu	C₆H₄-OMe (meta)	92	73
5	n-Bu	C₆H₄-OMe (para)	89	76
6	i-Bu	C₆H₄-Me (para)	93	57
7	-(CH₂)₄OPMB	C₆H₃(CF₃)₂	85	85
8	-(CH₂)₃-(1,3-dioxane-Me₂)	C₆H₄-t-Bu (para)	92	87
9	-(CH₂)₄OTBS	naphthyl-OMe	91	94
10	-(CH₂)₄OAc	C₆H₃(F)(Cl)	86	81
11	(Me-branched olefin chain)	Ph	89[c]	79
12	-(CH₂)₅Cl	benzodioxole	84	65
13	-(CH₂)₄-indolyl-NBoc	C₆H₄-Me (para)	90	72

[a] All data are the average of two experiments. For reaction conditions, see eq 1 (R = TMS). [b] Yield of purified product. [c] de.

$$(4)$$

78% ee
72% yield

$$(5)$$

82% ee
62% yield

$$(6)$$

88% ee
95% yield
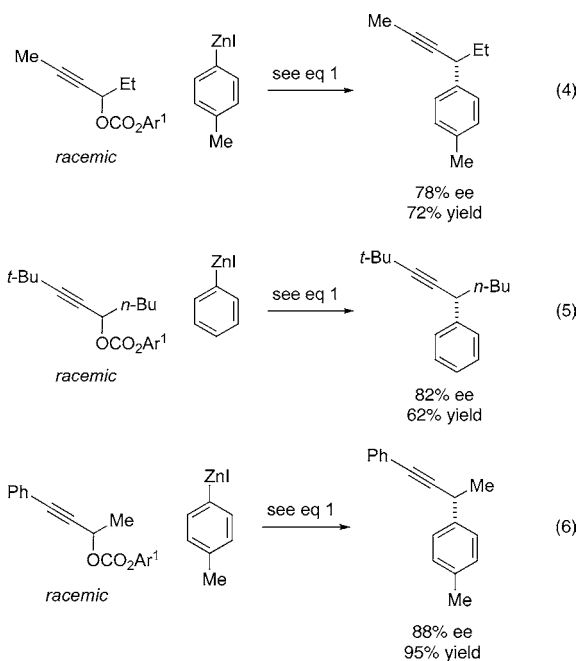
and oxidation, furnishes the target alkyne in 90% ee and 47% overall yield (three steps; eq 7).
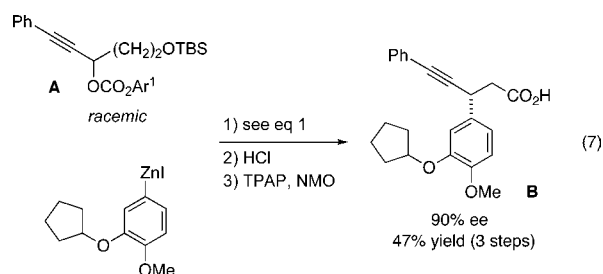
Although propargylic carbonates are not suitable cross-coupling partners (<2% ee and 5% yield) using our earlier procedure for Negishi reactions of propargylic bromides,[10] our new method *is* fairly versatile, effective not only for propargylic carbonates (Table 2), but, without modification, also for propargylic bromides and chlorides (eqs 8 and 9).
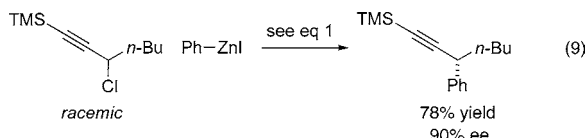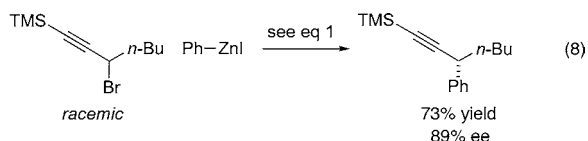
In summary, with respect to nickel-catalyzed enantioselective cross-couplings of alkyl electrophiles that bear oxygen leaving groups, only reactions of a small set of *allylic* alcohol derivatives with *Grignard* reagents had previously been reported to proceed in good ee and yield. We have established 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 elucidate the mechanism of this transformation, are underway.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and compound characterization data. 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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(11) Notes: (a) Under our standard reaction conditions: essentially 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, B. L. H.; Swift, E. C.; Waetzig, J. D.; Jarvo, E. R. *J. Am. Chem. Soc.* **2011**, *133*, 389−391 and references therein.

(13) In the case of asymmetric Negishi reactions of propargylic bromides (ref 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 ref 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.

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