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Nickel-Catalyzed Negishi Cross-Couplings of Secondary Nucleophiles with Secondary Propargylic Electrophiles at Room Temperature**

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In recent years, significant progress has been made in the development of metal-catalyzed cross-couplings of alkyl electrophiles.[1] A number of substantial challenges have not yet been met, including the coupling of sterically demanding partners. For example, we are not aware of reports of palladium- or nickel-catalyzed cross-couplings of secondary alkyl electrophiles with secondary organometallic nucleophiles.[2] Recognizing the importance of overcoming this limitation, we have recently turned our attention to addressing this deficiency. Due in part to the ease of synthesis and functional-group compatibility of alkylzinc reagents, we chose to focus our efforts on Negishi reactions.[3,4,5] In this communication, we describe the first nickel-based catalysts that achieve cross-couplings of secondary nucleophiles with secondary electrophiles [Eq. (1)].

(1)

As part of our initial investigation, we explored the Negishi reaction illustrated in Table 1.[6] Unfortunately, none of the methods that have previously been reported for cross-couplings of secondary alkyl electrophiles with primary alkylzinc reagents furnishes the desired product in substantial yield (<20%).[7,8] By optimizing the various reaction parameters, we were able to develop a catalyst system that achieves this Negishi cross-coupling with good efficiency at room temperature (89% yield; Table 1, entry 1).[9] In the absence of $\text{NiCl}_2\cdot\text{glyme}$ or terpyridine, essentially no carbon–carbon bond formation occurs (entries 2 or 3). If the bulky TIPS substituent is replaced with a smaller silyl or alkyl group, the yield of the cross-coupling

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decreases, due to the formation of a substantial amount of homocoupled electrophile (entries 4 and 5).[10] The other ligands, both bidentate and tridentate, that we have examined, are less useful than terpyridine (entries 6–8), as are solvents other than DMA (entries 9–11).

Our optimized method ($\text{NiCl}_2 \cdot \text{glyme}$ /terpyridine/DMA) can be applied to cross-couplings of a range of secondary propargylic bromides with secondary alkylzincs (Table 2). Esters, olefins (no E/Z isomerization), ethers, and carbamates are compatible with the reaction conditions. [11]

Although our primary objective was to develop a method for secondary–secondary cross-couplings, we were also interested in exploring the versatility of this catalyst. We have determined that, without modification, $\text{NiCl}_2 \cdot \text{glyme}$ /terpyridine/DMA can also be applied to Negishi reactions of less-hindered coupling partners, e.g., primary alkylzinc reagents with secondary/primary propargylic bromides (Table 3). Cross-couplings proceed in very good yield in the presence of an unactivated primary alkyl chloride, an ether, and an ester.[12]

If the alkyl group of the organozinc reagent is more hindered than cyclohexyl or isopropyl, the efficiency of $\text{NiCl}_2 \cdot \text{glyme}$ /terpyridine/DMA diminishes significantly (e.g., for entry 1 of Table 4: 20% yield). However, by replacing terpyridine with a related ligand, 2,6-bis(*N*-pyrazolyl)pyridine, and switching to THF as the solvent, the desired Negishi cross-coupling can be achieved in good yield (entry 1 of Table 4: 86% yield).[13,14] Functional groups such as alkynes, unactivated alkyl chlorides, and ethers are tolerated by this method (Table 4).[15]

We have determined that our coupling conditions can be employed not only for propargylic bromides, but also for propargylic chlorides (also at room temperature; [Eq. (2) and Eq. (3)]).

(2)

(3)

We have applied our method for secondary–secondary cross-couplings to the formal total synthesis of α -cembra-2,7,11-triene-4,6-diol (Scheme 1), a cembranoid diterpene with

antitumor activity that has been synthesized by Marshall[16] and by Thomas.[17] We envisioned that the isopropyl substituent could be installed by a Negishi reaction of propargylic bromide **1**, which can be generated from farnesyl acetate; indeed, using our Ni/terpyridine method, we were able to achieve the desired cross-coupling in 61% yield on a gram-scale. In preliminary studies, we have converted coupling product **2** into 14-membered macrocycle **3**, which served as an intermediate in the Thomas synthesis of α -cembra-2,7,11-triene-4,6-diol. [17,18]

In conclusion, we have developed the first method for secondary–secondary cross-couplings with a Group X catalyst, specifically a nickel-based system for coupling propargylic halides with alkylzinc reagents that proceeds under mild conditions (room temperature and no basic activators). Future efforts will focus on further expanding the scope of cross-coupling reactions of alkyl electrophiles.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

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2. Ready has reported copper-catalyzed couplings of secondary α -chloroketones with secondary alkylzinc reagents. He postulates that, unlike typical palladium- and nickel-catalyzed cross-couplings, these reactions proceed without oxidative addition of the electrophile to the catalyst. See: Malosh CF, Ready JM. *J Am Chem Soc* 2004;126:10240–10241. [PubMed: 15315425]
3. For a review of the Negishi reaction, see: Negishi, E-i; Hu, Q.; Huang, Z.; Wang, G.; Yin, N. *The Chemistry of Organozinc Compounds*. Rappoport, Z.; Marek, I., editors. Wiley; New York: 2006. Chapter 11
4. For pioneering studies of nickel-catalyzed Negishi reactions of alkyl electrophiles, see: (a) Devasagayaram A, Stüdemann T, Knochel P. *Angew Chem, Int Ed Engl* 1995;34:2723–2725. (b) Giovannini R, Stüdemann T, Devasagayaram A, Dussin G, Knochel P. *J Org Chem* 1999;64:3544–3553. [PubMed: 11674479]
5. For mechanistic studies of nickel-catalyzed Negishi reactions of alkyl electrophiles (including leading references), 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]. See also: Anderson TJ, Jones GD, Vicic DA. *J Am Chem Soc* 2004;126:8100–8101. [PubMed: 15225035] b) Lin X, Phillips DL. *J Org Chem* 2008;73:3680–3688. [PubMed: 18410144]
6. Palladium-catalyzed cross-coupling reactions of propargylic electrophiles with organometallic reagents typically provide the allene, rather than the alkyne, as the predominant product. See: a) Tsuji, J.; Mandai, T. *Metal-Catalyzed Cross-Coupling Reactions*. de Meijere, A.; Diederich, F., editors. Wiley–VCH; New York: 2004. Chapter 10 b) Ma S. *Eur J Org Chem* 2004:1175–1183. The regioselectivity of the corresponding nickel-catalyzed processes has not been well-studied.
7. For some recent examples, see: unactivated electrophiles: a) Zhou J, Fu GC. *J Am Chem Soc* 2003;125:14726–14727. [PubMed: 14640646]. activated electrophiles: b) Son S, Fu GC. *J Am Chem Soc* 2008;130:2756–2757. [PubMed: 18257579] Arp FO, Fu GC. *J Am Chem Soc* 2005;127:10482–10483. [PubMed: 16045323] Fischer C, Fu GC. *J Am Chem Soc* 2005;127:4594–4595. [PubMed: 15796523]
8. In addition, we explored previously reported methods for Negishi reactions of primary alkyl electrophiles. For example, see: a) Reference 5a. Jensen AE, Knochel P. *J Org Chem* 2002;67:79–85. [PubMed: 11777442]
9. For the use of Ni(cod)₂/terpyridine (and terpyridine derivatives) in THF as a catalyst for Negishi reactions of primary alkyl halides with primary alkylzinc reagents, see: a) Reference 5a. Jones GD,

McFarland C, Anderson TJ, Vivic DA. Chem Commun 2005:4211–4213. For the Negishi reaction depicted in Table 1, Vivic's procedure furnished the desired cross-coupling product in low yield (<20%).

10. Homocoupling of the propargylic halide to generate a bis(allene) or an allene–alkyne is the major side reaction. No other undesired product (e.g., from cross-coupling of the propargylic bromide with the organozinc reagent to form an allene, or from β -hydride elimination) has been identified. For all of the reactions that are reported in Tables 2–4, the starting propargylic halide has been consumed.
11. Notes: a) In the absence of $\text{NiCl}_2\cdot\text{glyme}$ or terpyridine, essentially no cross-coupling is observed, b) Organozinc iodides, rather than bromides, were employed due to ease of synthesis, c) Attempts to cross-couple an acetone-protected (i.e., $\text{R}=\text{CMe}_2\text{OH}$ in [Eq. (1)]) or an aryl-substituted alkyne were not successful. d) Under our standard conditions, Negishi reactions of hindered electrophiles (e.g., alkyl = *i*-Pr in Table 2) proceed in low yield, and unactivated alkyl chlorides are not suitable cross-coupling partners.
12. A Negishi cross-coupling of a primary propargylic bromide with a secondary alkylzinc reagent proceeded in low yield.
13. For the Negishi reaction illustrated in entry 1 of Table 4, the change in solvent (DMA $\rightarrow$ THF) and the change in ligand (terpyridine $\rightarrow$ 2,6-bis(*N*-pyrazolyl)pyridine) contribute comparably to the increase in yield (20% $\rightarrow$ 86%).
14. Vivic has reported that $\text{Ni}(\text{cod})_2/2,6\text{-bis}(N\text{-pyrazolyl})\text{pyridine}$ in THF catalyzes the Negishi coupling of a primary alkylzinc reagent with a primary alkyl bromide (45% yield) and with a primary alkyl iodide (67% yield): Reference 5a.
15. Notes: a) Under these conditions, *t*-BuZnI is not a suitable cross-coupling partner, b) For Negishi reactions of less-hindered alkylzinc reagents (e.g., those illustrated in Table 2), $\text{NiCl}_2\cdot\text{glyme}/2,6\text{-bis}(N\text{-pyrazolyl})\text{pyridine}/\text{THF}$ is not as effective as $\text{NiCl}_2\cdot\text{glyme}/\text{terpyridine}/\text{DMA}$.
16. Marshall JA, Robinson ED, Lebreton J. J Org Chem 1990;55:227–239.
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18. For additional details, see the Supporting Information.

Scheme 1.

Application of a secondary-secondary Negishi cross-coupling in a formal total synthesis of α -2,7,11-cembranetriene-4,6-diol.

Table 1

Negishi reactions of secondary nucleophiles with secondary propargylic electrophiles: Effect of reaction parameters.

$\text{TIPS-C}\equiv\text{C-CH(Br)-}n\text{-Bu}$ + IZn-Cyclohexyl (1.6 equiv)

$\xrightarrow[\text{DMA, r.t.}]{10\% \text{ NiCl}_2 \cdot \text{glyme}, 10\% \text{ terpyridine}}$

$\text{TIPS-C}\equiv\text{C-CH=C(Cyclohexyl)-}n\text{-Bu}$

"standard" conditions

	entryvariation from the “standard” conditions	yield (%)
1	none	89
2	no $\text{NiCl}_2 \cdot \text{glyme}$	<5
3	no terpyridine	<5
4	TMS, instead of TIPS	48
5	Me, instead of TIPS	15
6	bipyridine, instead of terpyridine	<5
7	isopropyl-pybox, instead of terpyridine	10
8	2,6-bis(<i>N</i> -pyrazolyl)pyridine, instead of terpyridine	62
9	THF, instead of DMA	11
10	DMF, instead of DMA	9
11	DMI, instead of DMA	4

The yield was determined by GC versus a calibrated internal standard. DMI = 1,3-dimethyl-2-imidazolidinone.

Table 2

Room-temperature Negishi reactions of secondary nucleophiles with secondary propargylic electrophiles.

		R^1-ZnI 1.6 equiv	10% $NiCl_2 \cdot gl$ 10% terpyridine DMA, r.t.
entry	R	alkyl		
1	TIPS	<i>n</i> -Bu		
2	TIPS

entry R

alkyl

3 TIPS

4 TIPS

n-Bu

entry R

alkyl

5 TIPS

Me

6 TIPS

entry R

alkyl

7 *t*-Bu 8 *t*-Bu

^aIsolated yield (average of two experiments).

Table 3

Negishi reactions of primary nucleophiles with secondary and primary propargylic electrophiles.

		$ \begin{array}{ccc} \text{TIPS} & & \text{TIPS} \\ \diagup & & \diagup \\ \text{C} \equiv \text{C} & \xrightarrow[\text{DMA, r.t.}]{\begin{array}{c} 10\% \text{ NiCl}_2 \cdot \text{glyme} \\ 10\% \text{ terpyridine} \end{array}} & \text{C} \equiv \text{C} \\ & & \\ \text{R}-\text{Br} & + \text{R}^1-\text{ZnBr} \text{ (1.6 equiv)} & \text{R}-\text{R}^1 \end{array} $	
entry	R	R ¹ -ZnBr	
1			
2			
3	H		

^aIsolated yield (average of two experiments).

Table 4

Room-temperature Negishi reactions of secondary nucleophiles with secondary propargylic electrophiles.

<div> <div> </div> </div>	
entry	alkyl
1	<i>n</i> -Bu
2
3

entry

alkyl

4

5

n-Bu

entry

alkyl

6

^a Isolated yield (average of two experiments).

^b Equiv of organozinc reagent: 3.0.