Homogeneous Catalysis

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

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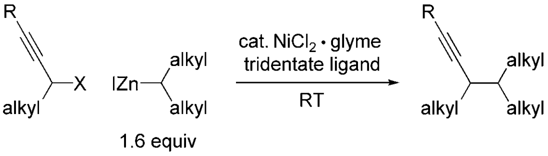
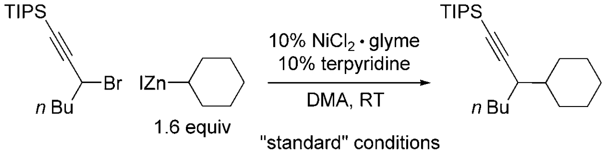
In recent years, significant progress has been made in the development of metal-catalyzed cross-couplings of alkyl electrophiles.[1] A number of substantial challenges have not yet been met, including the coupling of sterically demanding partners. For example, to our knowledge, palladium- or nickel-catalyzed cross-couplings of secondary alkyl electrophiles with secondary organometallic nucleophiles have not been reported.[2] Recognizing the importance of overcoming this limitation, we have recently turned our attention to addressing such deficiencies. The ease of synthesis and functional-group compatibility of alkylzinc reagents led us to focus our efforts on Negishi reactions.[3–5] Herein, we describe the first nickel-based catalysts for cross-couplings of secondary nucleophiles with secondary electrophiles [Eq. 1; X = Br, Cl].



(1)

As part of our initial investigation, we explored the Negishi reaction illustrated in Table 1.[6] Unfortunately, none of the previously reported methods for cross-couplings of secondary alkyl electrophiles with primary alkylzinc reagents furnished 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 $NiCl_2$·glyme or terpyridine, essentially no carbon–carbon bond formation occurs (Table 1, entries 2 and 3). If the bulky TIPS substituent is replaced with a smaller silyl or alkyl group, the yield of the cross-coupling decreases, as a result of the formation of a substantial amount of homocoupled electrophile (Table 1, entries 4 and 5).[10] The other ligands, both bidentate and tridentate, that we have examined are less useful than terpyridine (Table 1, entries 6–8), as are solvents other than *N*,*N*-dimethylacetamide (DMA; Table 1, entries 9–11).

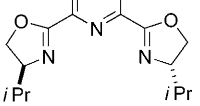
Table 1: Negishi reactions of secondary nucleophiles with secondary propargylic electrophiles: Effect of reaction parameters.



Entry	Variation from the “standard” conditions	Yield [%][a]
1	none	89
2	no $NiCl_2$·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(*N*-pyrazolyl)pyridine, instead of terpyridine	62
9	THF, instead of DMA	11
10	DMF, instead of DMA	9
11	DMI, instead of DMA	4

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

isopropyl pybox



Our optimized method ($NiCl_2$·glyme/terpyridine/DMA) can be applied to cross-couplings of a range of secondary propargylic bromides with secondary alkylzinc reagents (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, $NiCl_2$·glyme/terpyridine/DMA can also be applied to Negishi reactions of less-hindered coupling partners, for example, 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 $NiCl_2$·glyme/terpyridine/DMA diminishes significantly (e.g., Table 4, entry 1, L = terpyridine: 20 % yield). However, by replacing terpyridine with a related ligand, 2,6-bis(*N*-pyrazo-

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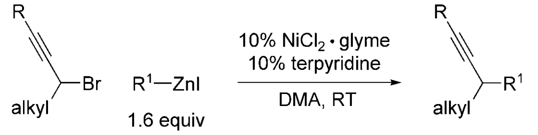
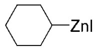
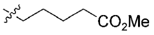
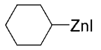
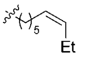
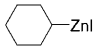
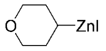
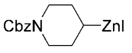
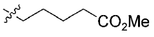
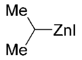
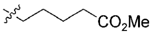
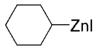
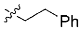
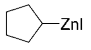
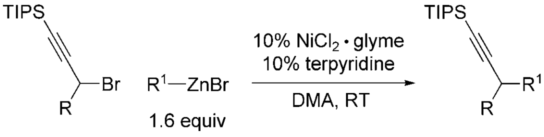
Table 2: Room-temperature Negishi reactions of secondary nucleophiles with secondary propargylic electrophiles.

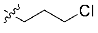
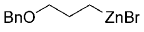
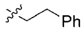
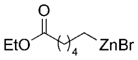
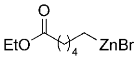


Entry	R	Alkyl	R^1–ZnI	Yield [%][a]
1	TIPS	*n*Bu		88
2	TIPS			72
3	TIPS			72
4	TIPS	*n*Bu		70
5	TIPS	Me		76
6	TIPS			63
7	*t*Bu			72
8	*t*Bu			73

[a] Yield of purified product (average of two experiments). Cbz = carbobenzyloxy.

Table 3: Negishi reactions of primary nucleophiles with secondary and primary propargylic electrophiles.

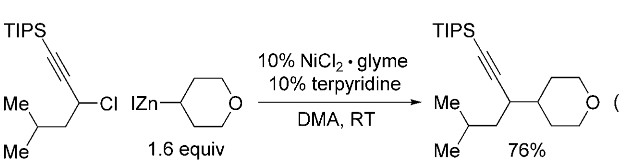


Entry	R	R^1–ZnBr	Yield [%][a]
1			97
2			96
3	H		90

[a] Yield of purified product (average of two experiments).

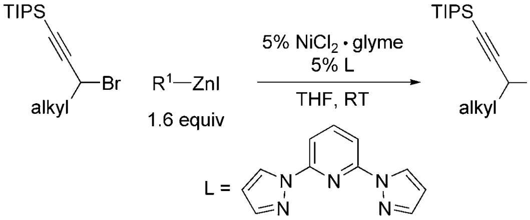
lyl)pyridine, and using THF as the solvent, the desired Negishi cross-coupling can be achieved in good yield (e.g., Table 4, entry 1: 86% yield).[13,14] Many functional groups, such as alkynes, unactivated alkyl chlorides, and ethers, are tolerated by this method (Table 4).[15]

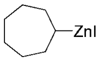
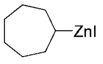
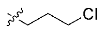
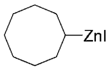
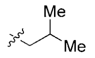
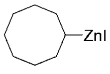
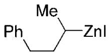
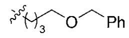
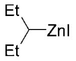
We have determined that our coupling conditions can be employed not only for propargylic bromides, but also for propargylic chlorides (also at room temperature; [Eqs. 2 and 3]).



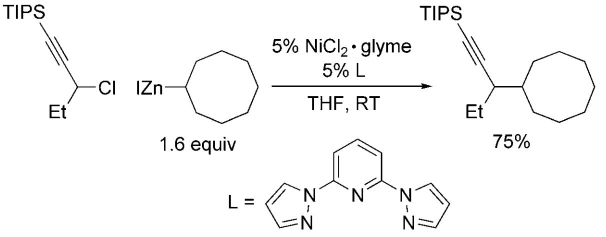
(2)

Table 4: Room-temperature Negishi reactions of secondary nucleophiles with secondary propargylic electrophiles.



Entry	Alkyl	R^1–ZnI	Yield [%][a]
1	*n*Bu		86
2			78
3			82
4			81
5	*n*Bu		76[b]
6			50[b]

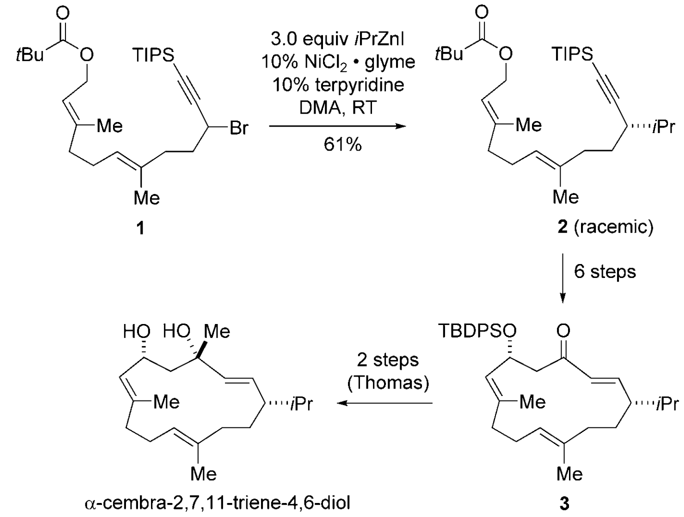
[a] Yield of purified product (average of two experiments). [b] Equivalents of organozinc reagent: 3.0.



(3)

We 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, which has been synthesized by the groups of Marshall[16] and 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 nickel/terpyridine method, we achieved the desired cross-coupling in 61% yield on a gram scale. In preliminary studies, we 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 10 transition-metal catalyst, specifically, a nickel-based system for coupling propargylic halides with alkylzinc reagents that proceeds under mild conditions (at room temperature and with no basic activators). Future efforts will focus on further



Scheme 1. Application of a secondary–secondary Negishi cross-coupling in a formal total synthesis of α-cembra-2,7,11-triene-4,6-diol. TBDPS = *tert*-butyldiphenylsilyl.

expanding the scope of cross-coupling reactions of alkyl electrophiles.

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[1] For reviews, see: a) A. C. Frisch, M. Beller, *Angew. Chem.* **2005**, *117*, 680 – 695; *Angew. Chem. Int. Ed.* **2005**, *44*, 674 – 688; b) M. R. Netherton, G. C. Fu, *Topics in Organometallic Chemistry: Palladium in Organic Synthesis* (Ed.: J. Tsuji), Springer, New York, **2005**, pp. 85 – 108; c) M. R. Netherton, G. C. Fu, *Adv. Synth. Catal.* **2004**, *346*, 1525 – 1532.

[2] Malosh and Ready reported copper-catalyzed couplings of secondary α-chloroketones with secondary alkylzinc reagents. It is postulated that, unlike typical palladium- and nickel-catalyzed cross-couplings, these reactions proceed without oxidative addition of the electrophile to the catalyst. See: C. F. Malosh, J. M. Ready, *J. Am. Chem. Soc.* **2004**, *126*, 10240 – 10241.

[3] For a review of the Negishi reaction, see: E.-i. Negishi, Q. Hu, Z. Huang, G. Wang, N. Yin in *The Chemistry of Organozinc Compounds* (Eds.: Z. Rappoport, I. Marek), Wiley, New York, **2006**, chap. 11.

[4] For pioneering studies of nickel-catalyzed Negishi reactions of alkyl electrophiles, see: a) A. Devasagayaraj, T. Stüdemann, P. Knochel, *Angew. Chem.* **1995**, *107*, 2952 – 2954; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2723 – 2725; b) R. Giovannini, T. Stüdemann, A. Devasagayaraj, G. Dussin, P. Knochel, *J. Org. Chem.* **1999**, *64*, 3544 – 3553.

[5] For mechanistic studies of nickel-catalyzed Negishi reactions of alkyl electrophiles, see: a) G. D. Jones, J. L. Martin, C. McFarland, O. R. Allen, R. E. Hall, A. D. Haley, R. J. Brandon, T. Konovalova, P. J. Desrochers, P. Pulay, D. A. Vicic, *J. Am. Chem. Soc.* **2006**, *128*, 13175 – 13183. See also: T. J. Anderson, G. D. Jones, D. A. Vicic, *J. Am. Chem. Soc.* **2004**, *126*, 8100 – 8101; b) X. Lin, D. L. Phillips, *J. Org. Chem.* **2008**, *73*, 3680 – 3688.

[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) J. Tsuji, T. Mandai in *Metal-Catalyzed Cross-Coupling Reactions* (Eds.: A. de Meijere, F. Diederich), Wiley-VCH, New York, **2004**, chap. 10; b) S. Ma, *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: a) unactivated electrophiles: J. Zhou, G. C. Fu, *J. Am. Chem. Soc.* **2003**, *125*, 14726 – 14727; b) activated electrophiles: S. Son, G. C. Fu, *J. Am. Chem. Soc.* **2008**, *130*, 2756 – 2757; F. O. Arp, G. C. Fu, *J. Am. Chem. Soc.* **2005**, *127*, 10482 – 10483; C. Fischer, G. C. Fu, *J. Am. Chem. Soc.* **2005**, *127*, 4594 – 4595.

[8] In addition, we explored previously reported methods for Negishi reactions of primary alkyl electrophiles. For example, see: a) Reference [5a]; b) A. E. Jensen, P. Knochel, *J. Org. Chem.* **2002**, *67*, 79 – 85.

[9] For the use of [Ni(cod)$_2$]/terpyridine (and terpyridine derivatives; cod = 1,5-cyclooctadiene) in THF as a catalyst for Negishi reactions of primary alkyl halides with primary alkylzinc reagents, see: a) Reference [5a]; b) G. D. Jones, C. McFarland, T. J. Anderson, D. A. Vicic, *Chem. Commun.* **2005**, 4211 – 4213. For the Negishi reaction depicted in Table 1, Vicic'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 is consumed.

[11] Notes: a) In the absence of NiCl$_2$·glyme or terpyridine, essentially no cross-coupling occurs; b) Organozinc iodides, rather than bromides, were employed owing to ease of synthesis; c) Attempts to cross-couple an acetone-protected (i.e., R = CMe$_2$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 Table 4, entry 1, the change in solvent (THF instead of DMA) and the change in ligand (2,6-bis(*N*-pyrazolyl)pyridine in place of terpyridine) contribute comparably to the increase in yield (20→86 %).

[14] Vicic et al have reported that [Ni(cod)$_2$]/2,6-bis(*N*-pyrazolyl)-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), NiCl$_2$·glyme/2,6-bis(*N*-pyrazolyl)pyridine/THF is not as effective as NiCl$_2$·glyme/terpyridine/DMA.

[16] J. A. Marshall, E. D. Robinson, J. Lebreton, *J. Org. Chem.* **1990**, *55*, 227 – 239.

[17] P. C. Astles, E. J. Thomas, *J. Chem. Soc. Perkin Trans. 1* **1997**, 845 – 856.

[18] For additional details, see the Supporting Information.