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Nickel-Catalyzed Asymmetric Negishi Cross-Couplings of Secondary Allylic Chlorides with Alkylzincs

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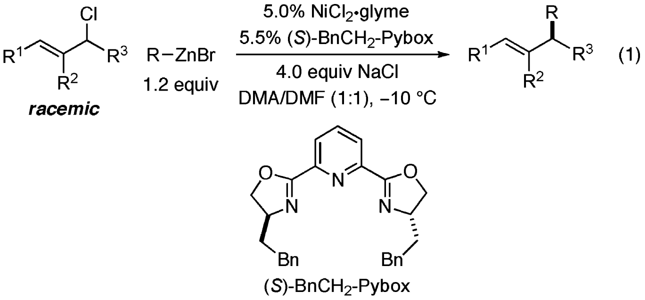
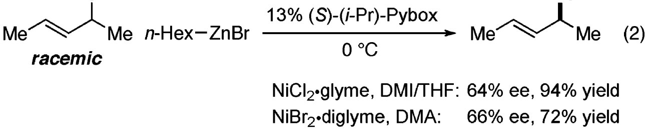
Metal-catalyzed enantioselective couplings of allylic electrophiles with carbon nucleophiles have been intensively studied,[1] with most of the investigations focused on palladium-catalyzed reactions of allylic esters/carbonates with enolates, copper-catalyzed couplings of primary allylic electrophiles with Grignard and diorganozinc reagents (S_N2' substitution),[2] and nickel-catalyzed reactions of certain allylic electrophiles with Grignard reagents.[3,4] Although powerful methods have been developed, there remains room for improvement, for example, processes that accommodate a broader range of nucleophiles and that display greater functional-group compatibility. In this report, we describe a versatile nickel-based catalyst for asymmetric couplings of racemic secondary allylic chlorides with readily available alkylzinc halides[5] (eq 1; DMA = *N*,*N*-dimethylacetamide), and we apply this method to a formal total synthesis of fluvirucinine A_1.

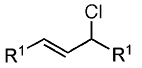
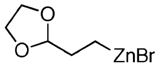
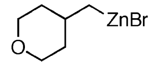
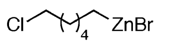
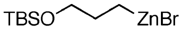
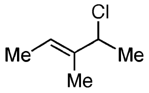
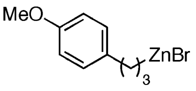


Previously, we have reported nickel-catalyzed enantioselective Negishi reactions of α-bromo amides and benzylic bromides with organozinc reagents.[6] Although the regioselectivity of the carbon−carbon bond-forming process was not a concern for these families of substrates, we anticipated that regioselectivity *would* be an issue for couplings of allylic electrophiles. To avoid this complication during our initial studies, we chose to examine the reaction of a "symmetrical" allylic halide. Under the conditions that we had developed for enantioselective Negishi couplings of α-bromo amides and benzylic bromides, we obtained promising results for an allylic electrophile (eq 2; DMI = 1,3-dimethyl-2-imidazolidinone).



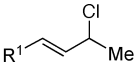
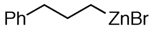
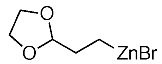
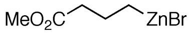
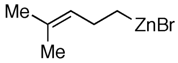
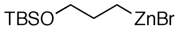
Through optimization studies, we were able to significantly improve the enantioselectivity of this Negishi cross-coupling reaction (87% ee, 95% yield; Table 1, entry 1).[7−9] The combination of a high ee and a high yield establishes that the process is stereoconvergent: the two enantiomers of the racemic substrate are transformed into the same enantiomer of the product with good stereoselectivity.

Table 1. Enantioselective Negishi Cross-Couplings of "Symmetrical" Allylic Chlorides with Alkylzinc Reagents (for the Reaction Conditions, See eq 1)

entry	allylic chloride	R−ZnBr	ee (%)	yield (%)[a]
1	 R^1 = Me	*n*-Hex−ZnBr	87	95[b]
2	Me		90	93
3[c]	*n*-Pr		85	81
4	*n*-Pr		79	81
5	*i*-Pr		69	57
6			98	54

All data are the average of two experiments. [a] Isolated yield. [b] The production is volatile. The yield was determined by GC versus an internal standard. [c] Solvent: DMA/DMF (9:1).

Table 2. Enantioselective Negishi Cross-Couplings of Unsymmetrical Allylic Chlorides with Alkylzinc Reagents (for the Reaction Conditions, See eq 1)

entry	allylic chloride	R−ZnBr	ee (%)	yield (%)[a]
1[b,c]	 R^1 = *n*-Bu		83	97
2[c]	*i*-Pr		84	95
3[c]	*t*-Bu		81	85
4	CO_2Et		96	86
5	$CONEt_2$	Et−ZnBr	91	57
6	CON(OMe)Me		93	91
7	$PO(OEt)_2$	*n*-Hex−ZnBr	90	63

All data are the average of two experiments. Regioselectivity, >20:1, except for entry 1. [a] Isolated yield. [b] Regioselectivity, 1.9:1; ee of the minor regioisomer, 88%. [c] The allylic chloride is a mixture of regioisomers.

As the steric demand of the R^1 substituent increases, the enantioselectivity of the cross-coupling decreases (Table 1, entries 1−5). Thus, good ee's are generally obtained if the group is unbranched (entries 1−4), but an erosion in stereoselection is observed for a hindered diisopropyl-substituted allylic chloride (entry 5). The Ni/Pybox catalyst can achieve an asymmetric Negishi

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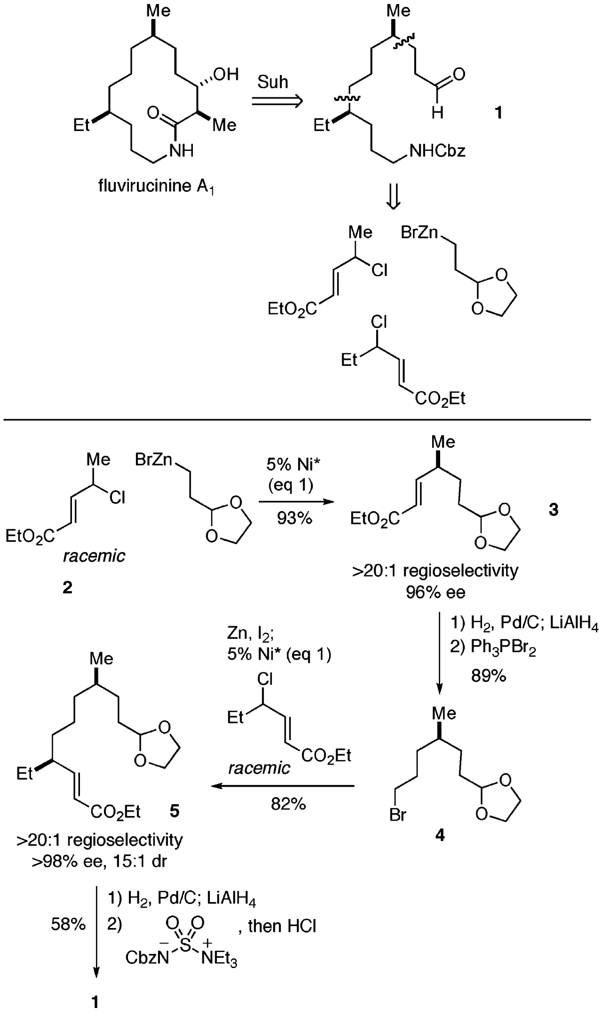
Scheme 1. Formal Total Synthesis of Fluvirucinine A_1 via Two Catalytic Asymmetric Negishi Reactions of Allylic Chlorides



reaction of a 1,2,3-trisubstituted allylic electrophile with excellent enantioselectivity (entry 6). An unactivated alkyl chloride is essentially inert to these conditions (entry 4).

Next, we turned our attention to enantioselective Negishi reactions of unsymmetrical allylic chlorides. Perhaps not surprisingly, the regioselection is only modest when the catalyst must differentiate between an *n*-butyl and a methyl group (1.9:1 selectivity in favor of reaction proximal to the methyl substituent; Table 2, entry 1); nevertheless, the ee's are substantial (major regioisomer, 83% ee; minor regioisomer, 88% ee), and the combined yield is excellent. For a variety of other electrophiles, the asymmetric Negishi couplings proceed with excellent regioselectivity (>20:1; entries 2−7).[10] Thus, an isopropyl/methyl- and a *t*-Bu/methyl-substituted allylic chloride undergo cross-coupling at the less hindered site with fairly good ee and in high yield (entries 2 and 3, respectively). Negishi reactions of conjugated electrophiles occur with a strong preference for carbon−carbon bond formation at the γ position and with excellent enantioselection (≥90% ee; entries 4−7).[11]

We have applied this nickel/Pybox-catalyzed asymmetric Negishi cross-coupling to a formal total synthesis of fluvirucinine A_1.[12] In 1999, Suh reported the first synthesis of this macrocycle, via aldehyde **1** (Scheme 1), which he generated in 16 steps through use of stoichiometric chiral-auxiliary chemistry introduced by Evans.[13] We have developed an eight-step catalytic enantioselective route to intermediate **1** wherein the two tertiary stereocenters are produced via asymmetric Negishi reactions of racemic secondary allylic chlorides. Thus, cross-coupling of chloride **2**, which is available in two steps from commercially available ethyl (*E*)-4-oxo-2-butenoate, provided compound **3** in excellent yield, regioselectivity, and ee. Reduction and then bromination furnished intermediate **4**, which was converted to the organozinc reagent and coupled with an allylic chloride to generate **5** in very good yield, regioselectivity, and stereoselectivity. A reduction/amination sequence then afforded target aldehyde **1**.

In summary, complementing previous advances in allylation chemistry, we have developed an effective nickel/Pybox catalyst for regioselective asymmetric Negishi cross-couplings of racemic secondary allylic chlorides with readily available organozinc halides. Furthermore, we have applied this method in two key steps of a formal total synthesis of fluvirucinine A_1. Additional studies of nickel-catalyzed coupling reactions of alkyl electrophiles are underway.

Acknowledgment. We thank Hong Shu for important preliminary studies. Support has been provided by the National Institutes of Health (National Institute of General Medical Sciences, Grant R01-GM62871), Merck Research Laboratories, and Novartis.

Supporting Information Available: 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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(1) For reviews, see: (a) Pfaltz, A.; Lautens, M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999; Vol. 2, Chapter 24. (b) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395−422. See also: Kar, A.; Argade, N. P. *Synthesis* **2005**, 2995−3022.

(2) For reviews, see: (a) Alexakis, A.; Malan, C.; Lea, L.; Tissot-Croset, K.; Polet, D.; Falciola, C. *Chimia* **2006**, *60*, 124−130. (b) Yorimitsu, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 4435−4439. Studies to date have focused largely on couplings of primary allylic electrophiles that generate terminal olefins (or, *symmetrical* secondary electrophiles). For reactions with organozinc reagents, use of RZnX has been reported to be problematic (for example, see: Dübner, F.; Knochel, P. *Angew. Chem., Int. Ed.* **1999**, *38*, 379−381 and Goldsmith, P. J.; Teat, S. J.; Woodward, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 2235−2237); instead, an excess of ZnR_2 (e.g., 2−6 equiv) is typically employed, resulting in the transfer of ≤25% of the available R groups.

(3) For example, see: (a) Consiglio, G.; Morandini, F.; Piccolo, O. *J. Chem. Soc., Chem. Commun.* **1983**, 112−114. (b) Gomez-Bengoa, E.; Heron, N. M.; Didiuk, M. T.; Luchaco, C. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1998**, *120*, 7649−7650.

(4) Progress with nucleophiles that exhibit greater functional-group tolerance has been relatively modest. For examples, see: (a) Chung, K.-G.; Miyake, Y.; Uemura, S. *J. Chem. Soc., Perkin Trans. 1* **2000**, 15−18. (b) Chen, H.; Deng, M.-Z. *J. Organomet. Chem.* **2000**, *603*, 189−193. (c) Novak, A.; Fryatt, R.; Woodward, S. *C. R. Chim.* **2007**, *10*, 206−212.

(5) Huo, S. *Org. Lett.* **2003**, *5*, 423−425.

(6) (a) Fischer, C.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 4594−4595. (b) Arp, F. O.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 10482−10483.

(7) The addition of NaCl has a pronounced effect on the rate of the cross-coupling, but little impact on the ee. Two of the possible roles of NaCl are to increase the ionic strength of the reaction mixture (the use of more polar solvents is generally advantageous) and to activate the organozinc reagent. For a review of halide effects in transition-metal catalysis, see: Fagnou, K.; Lautens, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 26−47.

(8) $BnCH_2$-Pybox can be prepared in two steps from homophenylalanine. Under otherwise identical conditions, commercially available *i*-Pr-Pybox furnishes 78% ee and 92% yield.

(9) Notes: (a) Under our standard conditions, if a simple allylic acetate or tosylate is employed as the electrophile, or if $NiCl_2$•glyme or the Pybox ligand is absent, then essentially no cross-coupling is observed; cross-couplings of certain *cyclic* allylic chlorides proceed in high ee but low yield; if R_2 is bulky (eq 1), coupling is inefficient. (b) For each Negishi reaction, the product is generated with >20:1 *E*:*Z* selectivity.

(10) The regioisomeric distribution of the cross-coupling product is independent of the regioisomeric composition of the allylic chloride (Table 2, entries 1−3). This contrasts with most copper-catalyzed reactions of allylic electrophiles, which exhibit a strong preference for formation of the regioisomer derived from S_N2' substitution (see ref 2).

(11) With a modified procedure, cross-couplings of aryl-substituted (R^1 = aryl, Table 2) allylic chlorides can be achieved in excellent ee and moderate yield (≥94% ee; see the Supporting Information).

(12) For applications of enantioselective metal-catalyzed allylations in total synthesis, see: Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921−2943.

(13) Suh, Y.-G.; Kim, S.-A.; Jung, J.-K.; Shin, D.-Y.; Min, K.-H.; Koo, B.-A.; Kim, H.-S. *Angew. Chem., Int. Ed.* **1999**, *38*, 3545−3547.

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