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Control of Vicinal Stereocenters through Nickel-Catalyzed Alkyl–Alkyl Cross-Coupling

*Xin Mu, Yu Shibata, Yusuke Makida, and Gregory C. Fu**

Abstract: *Vicinal stereocenters are found in many natural and unnatural compounds. Although metal-catalyzed cross-coupling reactions of unactivated alkyl electrophiles are emerging as a powerful tool in organic synthesis, there have been virtually no reports of processes that generate, much less control, vicinal stereocenters. In this investigation, we establish that a chiral nickel catalyst can mediate doubly stereoconvergent alkyl–alkyl cross-coupling, specifically, reactions of a racemic pyrrolidine-derived nucleophile with cyclic alkyl halides (as mixtures of stereoisomers) to produce vicinal stereocenters with very good stereoselectivity.*

The transition-metal-catalyzed cross-coupling of an alkyl nucleophile with an unactivated alkyl electrophile to generate an alkyl–alkyl bond is emerging as a powerful tool for the synthesis of organic molecules.[1] For many such processes, the challenge is two-fold: constructing the desired carbon–carbon bond and controlling the stereochemistry at one or both carbon atoms. Stereoconvergent reactions, wherein a catalyst converts a mixture of stereoisomeric substrates into a particular stereoisomer of the product, are attractive because such substrate mixtures are readily available (Figure 1). A number of methods for stereoconvergent metal-catalyzed alkyl–alkyl cross-coupling have been described that control the stereochemistry at one, but not both, of the carbon atoms of the new carbon–carbon bond (top of Figure 1).[1–3] In contrast, there are no examples of effective control of vicinal stereocenters in cross-coupling reactions of unactivated secondary electrophiles, owing to the difficulty of achieving bond formation,[4] much less stereoselectivity (maximum d.r. $<1.5{:}1$).[4d]

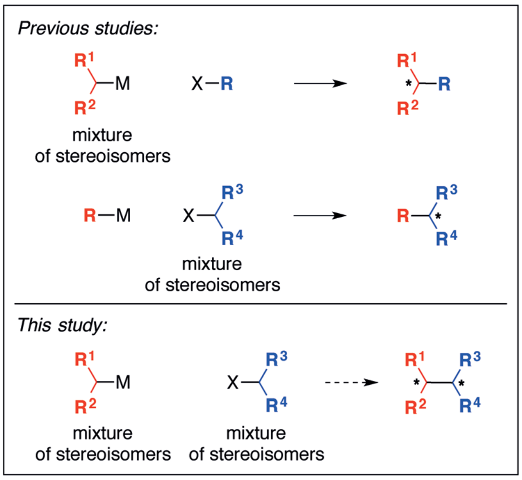
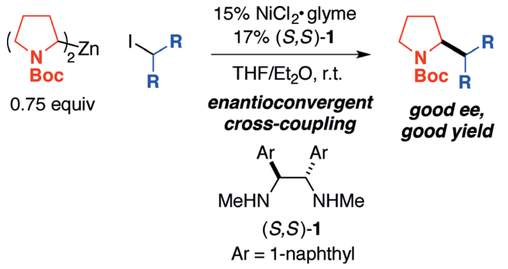


Figure 1. Stereoconvergent metal-catalyzed alkyl–alkyl cross-coupling.

Because pyrrolidine subunits are present in many natural and non-natural compounds,[5] a variety of methods for the asymmetric synthesis of chiral pyrrolidines have been described, including catalytic enantioselective processes.[6] For example, we have recently reported a nickel-catalyzed enantioconvergent cross-coupling of racemic[7] α-zincated *N*-Boc-pyrrolidine with an array of achiral secondary alkyl electrophiles [Eq. (1)].[2]



(1)

We decided to pursue the possibility that this method could provide control of vicinal stereocenters in alkyl–alkyl coupling. Specifically, we examined the cross-coupling of 2-zincated *N*-Boc-pyrrolidine with a 4-substituted cyclohexyl halide[8] (entry 1 of Table 1). Under our previously reported conditions,[2] we generated the coupling product with very good stereoselectivity (92% *ee*, 91:9 d.r.). Through the use of a different nickel source ($Ni(acac)_2$), we were able to obtain similar results while employing a smaller excess of the nucleophile (0.6 instead of 0.75 equiv of ZnR_2).[9] The *ee* and d.r. of the cross-coupling product remain constant throughout the course of the reaction.

This method produces good control of vicinal stereocenters[10] in alkyl–alkyl cross-coupling reactions of an array of achiral cyclohexyl and tetrahydropyranyl iodides (Table 1). For example, Negishi reactions of 4-monosubstituted coupling partners proceed with very good *ee* and diastereoselectivity with a sterically and electronically diverse set of substituents (Me, Et, *t*-Bu, CF_3, and Ph; Table 1, entries 1–5); except in the case of the methyl-substituted electrophile, essentially only one diastereomer is observed ($>99{:}1$). Furthermore, the alkyl–alkyl cross-coupling of a 4,4-disubstituted cyclohexyl iodide occurs with good stereoselectivity

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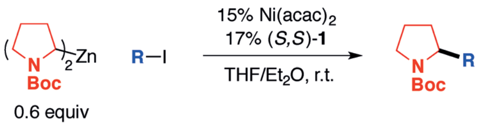
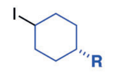
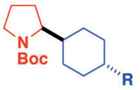
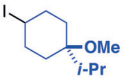
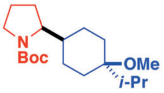
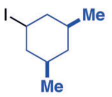
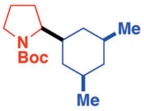
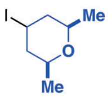
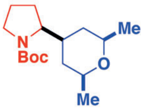
Table 1: Control of vicinal stereocenters: alkyl–alkyl cross-coupling of achiral electrophiles.[a]



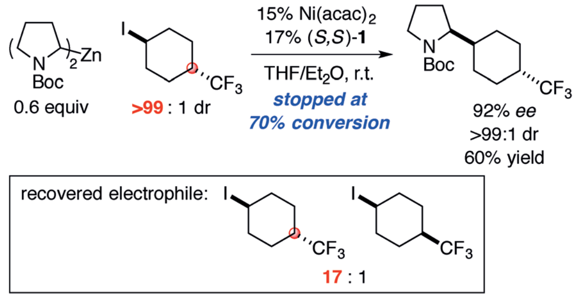
entry	R—I		product	*ee* [%][b]	dr[b]	yield [%][c]
						
	R	*cis*/*trans*				
1	Me	83 : 17		93	92 : 8	78
2	Et	87 : 13		93	>99 : 1	75
3	*t*-Bu	90 : 10		91	>99 : 1	82
4	CF_3	62 : 38		92	>99 : 1	82
5	Ph	91 : 9		91	>99 : 1	82
6	 >95 : 5 (*cis*/*trans*)			92	85 : 15	94
7	 67 : 33 (*cis*/*trans*)			92	>99 : 1	84
8	 82 : 18 (*cis*/*trans*)			91	>99 : 1	82

[a] All values are the average of two experiments. [b] Determined through GC, HPLC, and/or SFC analysis. [c] Yield of purified product.

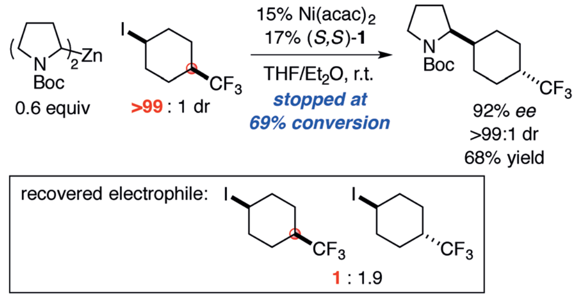
(entry 6). Finally, excellent control of the vicinal stereocenters is observed in Negishi reactions of 3,5-disubstituted electrophiles, including an oxygen heterocycle (entries 7 and 8).

Because high stereoselectivity and high yield can be obtained in the cross-coupling of a racemic nucleophile (i.e., prepared from racemic 2-lithio-*N*-Boc-pyrroline) with an electrophile that is an approximately 2:1 mixture of stereoisomers (entries 4 and 7 of Table 1), these Negishi reactions are doubly stereoconvergent (bottom of Figure 1). In the case of the stereogenic center on the pyrrolidine ring, the absolute stereochemistry is controlled by the chiral catalyst.[2] The stereochemistry at the other carbon atom of the new carbon–carbon bond is dependent upon the structure of the electrophile. We hypothesize that the nickel catalyst abstracts iodine from the electrophile,[11] which generates the same alkyl radical from either diastereomer of the alkyl iodide. In all cases in Table 1, the major stereoisomer of the product bears the new alkyl substituent in the thermodynamically favored equatorial position on the six-membered ring; this may be due to a kinetic preference during the reaction of the alkyl radical with nickel to form a nickel–carbon bond,[12] or to reversible nickel–carbon bond formation and stereochemistry-determining reductive elimination.[13]

By conducting the asymmetric cross-coupling with a single diastereomer of the alkyl iodide and stopping the reaction at partial conversion, we determined that the electrophile undergoes isomerization during the reaction [Eq. (2) and Eq. (3)]; in each case, the cross-coupling product is generated in 92 % *ee* and with > 99:1 d.r.). Possible mechanisms for this isomerization include halogen exchange through an S_N2 reaction (e.g., by zinc iodide that is generated during the cross-coupling) and reversible transfer of $I^\bullet$ from the alkyl iodide to the nickel catalyst. Because the two isomers of the electrophile do not interconvert in the presence of an iodide source (1 equiv ZnI_2 or TBAI; THF/Et_2O, RT, 48 h), we favor reversible iodine transfer between the alkyl radical and nickel as the more likely pathway.[14] Because the d.r. values of the alkyl iodides at partial conversion are different in [Eq. (2)] versus [Eq. (3)], this reversible iodine transfer appears not to occur rapidly relative to the cross-coupling.



(2)



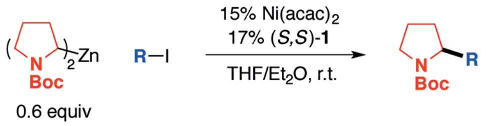
(3)

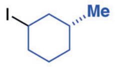
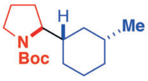
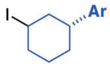
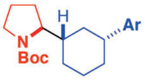
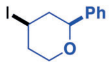
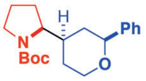
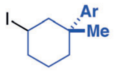
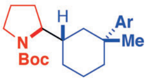
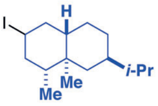
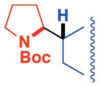
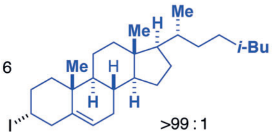
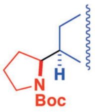
Not only achiral, but also chiral electrophiles serve as suitable substrates for this nickel-catalyzed stereoselective alkyl–alkyl cross-coupling, generating vicinal stereocenters with good selectivity (Table 2).[15] A 3-substituted carbocyclic or heterocyclic alkyl iodide reacts with high stereoselectivity to form the *cis*-1,3-disubstituted product (entries 1–3). Furthermore, coupling of a 3,3-disubstituted electrophile proceeds with good stereoselectivity (entry 4). Finally, bicyclic and polycyclic secondary alkyl iodides can be employed as cross-coupling partners (entries 5 and 6).

When the (*R*,*R*) rather than the (*S*,*S*) enantiomer of ligand **1** is used, similar stereoselectivity is generally observed, with the major products differing only in the stereochemistry at the position α to nitrogen (Table 1). This is consistent with control of that stereocenter by the chiral catalyst and control of the second stereocenter by the substrate.

In summary, alkyl–alkyl cross-coupling reactions have now been expanded to include an array of processes wherein vicinal stereocenters, rather than a single stereocenter, are controlled with high selectivity. In particular, a nickel/diamine

Table 2: Control of vicinal stereocenters: alkyl–alkyl cross-coupling of chiral electrophiles.[a]



entry	R—I	product	dr[b,c]	yield [%][c,d]
1	 90 : 10 (*cis*/*trans*)		97 : 3 (93 : 7)	81 (80)
2	 Ar = 4-BrC$_6$H$_4$ 83 : 17 (*cis*/*trans*)		94 : 6 (92 : 8)	60 (62)
3	 >99 : 1		96 : 4 (94 : 6)	90 (84)
4	 Ar = 4-ClC$_6$H$_4$ 50 : 50 (*cis*/*trans*)		86 : 14 (86 : 14)	65 (63)
5	 85 : 15 (*cis*/*trans*)		95 : 5 (94 : 6)	81 (80)
6	 >99 : 1		87 : 13 (68 : 32)	62 (52)

[a] The electrophilic coupling partners were applied at ≥99% *ee*, except for entry 4, where the coupling partner was present at 94% *ee*. [b] Determined through HPLC analysis; ratio (major stereoisomer):(sum of all other stereoisomers). [c] The values in parentheses are the data for (*R*,*R*)-**1**. [d] Yield of purified product.

catalyst mediates doubly stereoconvergent Negishi coupling of an alkylzinc reagent with an alkyl halide. With respect to the new carbon–carbon bond, the chiral catalyst controls the stereochemistry of the carbon that originates from the nucleophile, and the substrate controls the stereochemistry of the carbon that originates from the electrophile. Given the frequency with which vicinal stereocenters are encountered in organic molecules, we anticipate that the development of methods that achieve doubly stereoconvergent alkyl–alkyl bond formation will emerge as a highly active area of research in the coming years.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: alkylation · asymmetric synthesis · cross-coupling · nickel · zinc

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[4] a) E. Hohn, J. Pietruszka, *Adv. Synth. Catal.* **2004**, *346*, 863 – 866 (one example: cyclopropylboron reagent with cyclopropyl electrophile); b) P. Ren, O. Vechorkin, K. von Allmen, R. Scopelliti, X. Hu, *J. Am. Chem. Soc.* **2011**, *133*, 7084 – 7095 (one example: 7% yield); c) S. L. Zultanski, G. C. Fu, *J. Am. Chem. Soc.* **2011**, *133*, 15362 – 15364 (one example: cyclopropylboron reagent); d) C.-T. Yang, Z.-Q. Zhang, J. Liang, J.-H. Liu, X.-Y. Lu, H.-H. Chen, L. Liu, *J. Am. Chem. Soc.* **2012**, *134*, 11124 – 11127 (Grignard reagents as nucleophiles); e) Ref. [2] (nucleophile: α-zincated *N*-Boc-pyrrolidine).
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[6] For example: a) A. R. Brown, C. Uyeda, C. A. Brotherton, E. N. Jacobsen, *J. Am. Chem. Soc.* **2013**, *135*, 6747 – 6749; b) B. M. Trost, T. M. Lam, M. A. Herbage, *J. Am. Chem. Soc.* **2013**, *135*, 2459 – 2461.
[7] The organozinc reagent is prepared through lithiation with *s*-BuLi (no chiral additive) to generate a racemic organolithium reagent (RLi). Reaction with ZnI$_2$ affords a diorganozinc reagent (ZnR$_2$) that may bear homochiral or heterochiral substituents (R).
[8] Systematic studies of the use of an achiral catalyst to achieve diastereoselective cross-coupling of primary alkyl nucleophiles with cyclic alkyl electrophiles: a) P. M. Perez Garcia, T. Di Franco, A. Orsino, P. Ren, X. Hu, *Org. Lett.* **2012**, *14*, 4286 – 4289; b) H. Gong, R. Sinisi, M. R. Gagné, *J. Am. Chem. Soc.* **2007**, *129*, 1908 – 1909.
[9] Use of a lower catalyst loading (10% Ni(acac)$_2$/12% (*S*,*S*)-**1**) led to formation of the product in 92% *ee*, 93:7 d.r., and 85% yield.
[10] According to the IUPAC Compendium of Chemical Terminology (https://goldbook.iupac.org/S05980.html; accessed 21 February 2017), a stereogenic center is a "grouping of atoms consisting of a central atom and distinguishable ligands, such that

the interchange of any two of the substituents leads to a stereoisomer.”

[11] a) J. Zhou, G. C. Fu, *J. Am. Chem. Soc.* **2004**, *126*, 1340 – 1341; b) T. J. Anderson, G. D. Jones, D. A. Vicic, *J. Am. Chem. Soc.* **2004**, *126*, 8100 – 8101; c) N. D. Schley, G. C. Fu, *J. Am. Chem. Soc.* **2014**, *136*, 16588 – 16593.

[12] Capture of the 4-*t*-butylcyclohexyl radical often proceeds with poor to moderate stereoselectivity. For example: a) W. Damm, B. Giese, J. Hartung, T. Hasskerl, K. N. Houk, O. Hüter, H. Zipse, *J. Am. Chem. Soc.* **1992**, *114*, 4067 – 4079; b) J. O. Osby, S. W. Heinzman, B. Ganem, *J. Am. Chem. Soc.* **1986**, *108*, 67 – 72.

[13] For example: a) X. Lin, J. Sun, Y. Xi, D. Lin, *Organometallics* **2011**, *30*, 3284 – 3292; b) R. Fu, Ph.D. Thesis, California Institute of Technology, Pasadena, CA, **2014**, chap. 5; c) O. Gutierrez, J. C. Tellis, D. N. Primer, G. A. Molander, M. C. Kozlowski, *J. Am. Chem. Soc.* **2015**, *137*, 4896 – 4899.

[14] Examples of previous studies of the reversibility of halogen-atom transfer in nickel-catalyzed cross-coupling of unactivated alkyl halides: a) Ref. [4c] (Suzuki coupling; irreversible); b) Ref. [8a] (Kumada coupling; reversible).

[15] In preliminary studies under our standard conditions, very modest stereoselectivity was observed in cross-coupling of secondary alkyl electrophiles that are conformationally flexible.

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Communications

Asymmetric Synthesis

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G. C. Fu* ________ ■■■■–■■■■

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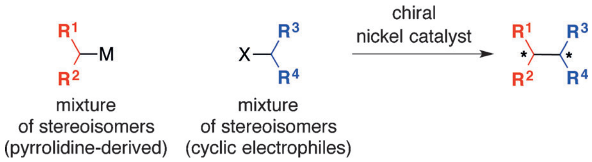

Side by side: A chiral nickel catalyst was found to mediate doubly stereoconvergent alkyl–alkyl cross-coupling, specifically, reactions of a racemic pyrrolidine-derived nucleophile with cyclic alkyl halides (as mixtures of stereoisomers) to produce vicinal stereocenters with very good stereoselectivity.