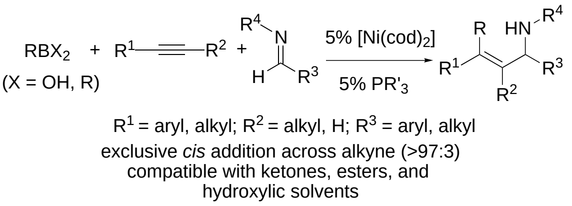
Ni-Catalyzed Multicomponent Reaction

Catalytic Three-Component Coupling of Alkynes, Imines, and Organoboron Reagents**

*Sejal J. Patel and Timothy F. Jamison**

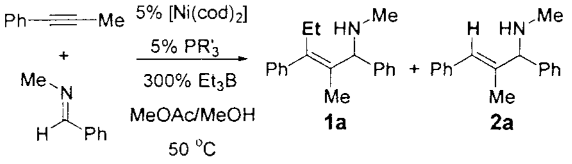
As part of our interest in selective, catalytic multicomponent reactions,[1] we report an unprecedented catalytic assembly of allylic amines from three simple precursors—alkynes, imines, and organoboron reagents (boronic acids or organoboranes). As allylic amines are key structural elements in a variety of important naturally occurring molecules[2] and pharmaceuticals[3] and are among the most versatile intermediates in the synthesis of other important molecules,[4] they have attracted much attention.[5] Previously, several Ni-catalyzed multicomponent coupling reactions involving additions to carbonyl compounds have been described.[1a,6] The process described herein is the first such example involving imines and also the first that utilizes boronic acids (Scheme 1).[7] Our preliminary investigations also support a mechanistic framework that accounts for the high selectivities observed in these reactions.



Scheme 1. Catalytic assembly of allylic amines from alkynes, imines, and organoboron reagents.

The markedly diminished electrophilicity of imines relative to aldehydes[8] presented significant challenges in our initial experiments. After extensive studies with different imines,[9] solvents,[10] and organometallic reagents,[11] we observed exceptional results when both organoboron reagents and hydroxylic solvents were employed.[12] Methanol in particular provided substantial increases in yield, and also displayed high selectivity for alkylative coupling product **1** over reductive coupling product **2** (Table 1).[13] Best results were obtained when methyl acetate was used as a cosolvent and electron-rich, tri-(*sec*-alkyl)-phosphane ligands were employed (Table 1, entries 3 and 4).[14] As summarized in Table 2, reactions involving internal alkynes with at least one alkyl substituent are typically highly selective, and nearly quantitative yields are observed in some cases (**1c** and **1f**). Imines derived from aliphatic aldehydes also undergo three-

Table 1: Ligand effects in catalytic three-component assembly of allylic amines.



Entry	PR'$_3$[a]	Yield [%]	**1a**:**2a**[b]	Regioselectivity[c]
1	Bu$_3$P	80	94:6	96:4
2	Bn$_3$P	72	97:3	93:7
3	Cy$_3$P	88	89:11	91:9
4	Cyp$_3$P	85	92:8	91:9
5	*t*Bu$_3$P	9	93:7	80:20
6	Ph$_3$P	34	95:5	91:9

[a] Cy$_3$P = (c-C$_6$H$_{11}$)$_3$P, Cyp$_3$P = (c-C$_5$H$_9$)$_3$P. [b] Ratio determined by ^{1}H NMR. [c] Regioselectivity of **1a** (determined by ^{1}H NMR).

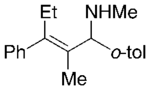
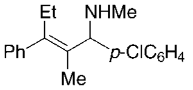
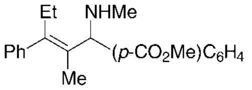
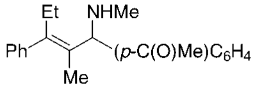
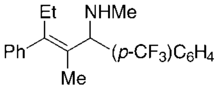
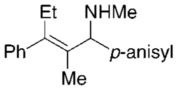
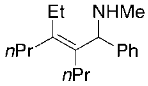
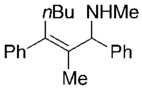
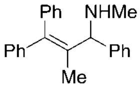
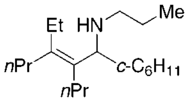
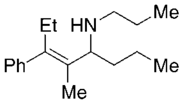
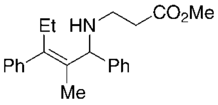
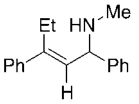
---

[*] Prof. Dr. T. F. Jamison, S. J. Patel
Department of Chemistry
Massachusetts Institute of Technology
Cambridge, MA 02139 (USA)
Fax: (+1) 617-258-7500
E-mail: tfj@mit.edu

[**] We thank the NIGMS (GM063755), the NSF (CAREER CHE-0134704), Merck Research Laboratories, Pfizer, Boehringer-Ingelheim, 3M, Johnson & Johnson, The Donors of the PRF, and MIT for generous financial support. NSF grants CHE-9809061 and DBI-9729592 and NIH grant 1S10RR13886-01 provided partial support for the MIT Department of Chemistry Instrumentation Facility (DCIF).

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

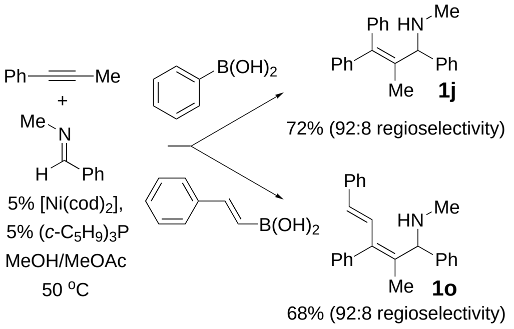
Table 2: Allylic amines prepared by catalytic three-component couplings of alkynes, imines, and organoboranes.[a]

	Product	Yield [%][b]	**1**:**2**[c]	Regio-selectivity[c,d]
1b		85	94:6	90:10
1c		95	96:4	90:10
1d		82	>96:4	90:10
1e		78	>96:4	91:9
1f		98	96:4	89:11
1g		64	86:14	91:9
1h		91	94:6	–
1i		70	90:10	91:9
1j		65	–	93:7
1k		52	>96:4	–
1l		30	90:10	91:9
1m		75	94:6	91:9
1n		35[e]	>95:5	>98:2

[a] [Ni(cod)$_2$] (5%) and (c-C_5H_9)$_3$P (5%) used in all cases. [b] Combined yield of alkylative (**1**) and reductive (**2**) coupling products. [c] Determined by ^{1}H NMR. [d] Regioselectivity of major product. [e] Reaction performed at 25 °C.

component coupling (**1k** and **1l**). Notably, esters (**1d** and **1m**) and ketones (**1e**) are tolerated, as are aryl chlorides (**1c**). Phenylacetylene affords trisubstituted allylic amine **1n** in moderate yield as a result of competitive cyclotrimerization of the alkyne under the reaction conditions.[15]

Of even greater significance is that both alkenylboronic and arylboronic acids are of equal or better efficacy in these reactions (Scheme 2). The scope and utility of this method is dramatically enhanced owing to the greater availability, stability, and functional group tolerance of boronic acids relative to organozinc reagents and organoboranes.[1a,6]

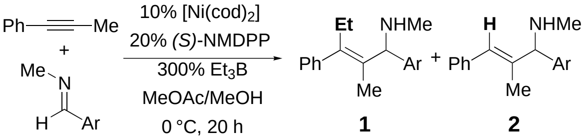


Scheme 2. Boronic acids in catalytic three-component couplings.

Contrasting mechanisms have been reported for Ni-catalyzed coupling reactions involving carbonyl compounds,[6,16] yet imines have to be studied in this regard. With the aim of eliminating some of the possible mechanistic frameworks, we conducted several catalytic couplings by using (*S*)-(+)-(neomenthyl)diphenylphosphane as a chiral phosphane. Most notably, we observed that the enantiomeric excess of the alkylative coupling product **1** is *identical* to that of the corresponding reductive coupling product **2** in every case (Table 3). In addition, in cases where the amount of the minor regioisomer of the reductive coupling product **2** is detectable in the unpurified product mixtures by ^{1}H NMR spectroscopy, the regioselectivity is also *identical* for coupling products **1** and **2**.

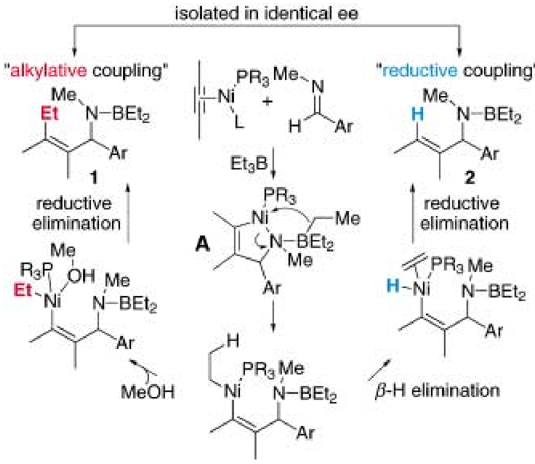
These findings are consistent with the mechanistic pathway shown in Scheme 3, in which enantioselectivity and regioselectivity are determined in the same step and *before* a common intermediate **A** partitions into two pathways to lead to either **1** or **2**. Furthermore, this mechanism accounts for the high selectivity for alkylative coupling (→**1**) imparted by methanol: occupation of coordination sites required for a β-H elimination step that would lead to reductive coupling (→**2**).[17] At this juncture, we have no direct evidence for azametallacyclopentene **A**; nevertheless, it is analogous to azametallacyclopentenes of early transition metals[5a–d] and related to oxametallacyclopentenes proposed for other Ni-catalyzed couplings of alkynes and aldehydes.[16]

Table 3: Enantioselectivities observed for alkylative (**1**) and reductive (**2**) coupling products by using (*S*)-(+)-(neomenthyl)diphenylphosphane ((*S*)-NMDPP).



Entry	Ar	*ee* **1** [%][a]	*ee* **2** [%][a]
1	Ph	41	42
2	*p*-ClC$_6$H$_4$	33	33
3	(*p*-CF$_3$)C$_6$H$_4$	40	39

[a] Enantiomeric excess determined for the corresponding acetamides (Ac_2O, Et_3N, cat. DMAP), Chiralcel OD column.



Scheme 3. A mechanistic framework for a novel Ni-catalyzed three-component coupling reaction that accounts for the selectivities observed.

In conclusion, the above catalytic transformation provides a significant amplification of molecular complexity and tolerates ketones, esters, and even unprotected hydroxy groups—three functional groups that are typically problematic in imine addition reactions.[18] Direct addition of the organoboron reagent to the imine is not observed,[19] and the mode of addition across the alkyne is exclusively *cis* ($>97:3$), thereby establishing the configuration of the double bond in the course of two carbon–carbon bond-forming events. Since the phosphane is involved in the enantio- and regioselectivity-determining steps, and methanol appears to be critical for catalytic turnover and for alkylative/reductive selectivity, efficient and highly selective asymmetric catalytic three-component coupling may be achieved by using chiral monodentate phosphanes with an appropriately placed hydroxy group. We are currently investigating ligands of this type and will report our findings of these and related studies in due course.

Experimental Section

General Procedure: The imine (1.0 mmol) and alkyne (0.40 mmol) were added to a solution of R_3B (0.60 mmol, 3 M in solvent specified), [Ni(cod)$_2$] (0.05 mmol), phosphane ligand (0.05 mmol), and MeOH (5 mL) and heated (50 °C) under Ar. Four equal portions of additional R_3B (4×0.60 mmol) and alkyne (4×0.40 mmol) were added over 4 h, and the solution was heated (50 °C) for 12 h. Concentration in vacuo and silica gel purification (hexanes/EtOAc) afforded the allylic amine products.

Received: November 13, 2002 [Z50542]

Keywords: alkynes · allylic amines · boronic acids · imines · nickel

---

[1] a) W.-S. Huang, J. Chan, T. F. Jamison, *Org. Lett.* **2000**, *2*, 4221; b) A. J. Skaggs, E. Y. Lin, T. F. Jamison, *Org. Lett.* **2002**, *4*, 2277.
[2] a) Microcystins: K. L. Reinhart, K.-i. Harada, M. Namikoshi, C. Chen, C. A. Harvis, M. H. G. Munro, J. W. Blunt, P. E. Mulligan, V. R. Beasley, A. M. Dahlem, W. W. Carmichael, *J. Am. Chem. Soc.* **1988**, *110*, 8557; b) motuporin: E. D. de Silva, D. E. Williams, R. J. Anderson, H. Klix, C. F. B. Holmes, T. M. Allen, *Tetrahedron Lett.* **1992**, *33*, 1561; c) cyclotheonamides: N. Fusetani, S. Matsunaga, H. Matsumoto, Y. Takebayashi, *J. Am. Chem. Soc.* **1990**, *112*, 7053; d) criamides: J. E. Coleman, E. D. de Silva, F. Kong, R. J. Andersen, T. M. Allen, *Tetrahedron* **1995**, *51*, 10653; e) leucascandrolide A: M. D'Ambrosio, A. Guerriero, C. Debitus, F. Pietra, *Helv. Chim. Acta* **1996**, *79*, 51.
[3] G. Petranyi, N. S. Ryder, A. Stütz, *Science* **1984**, *224*, 1239.
[4] Examples: a) K. Burgess, M. J. Ohlmeyer, *J. Org. Chem.* **1991**, *56*, 1027; b) M. Hagihara, N. J. Anthony, T. J. Stout, J. Clardy, S. L. Schreiber, *J. Am. Chem. Soc.* **1992**, *114*, 6568; c) E. Vedejs, M. Gringras, *J. Am. Chem. Soc.* **1994**, *116*, 579; d) T. A. Johnson, M. D. Curtis, P. Beak, *J. Am. Chem. Soc.* **2001**, *123*, 1004; e) Takasago process: R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, Wiley, New York, **1994**.
[5] Reductive coupling of alkynes and imines by using early transition metal complexes: a) S. L. Buchwald, B. T. Watson, M. W. Wannamaker, J. C. Dewan, *J. Am. Chem. Soc.* **1989**, *111*, 4486; b) M. Jensen, T. Livinghouse, *J. Am. Chem. Soc.* **1989**, *111*, 4495; c) K. Takai, S. Miwatashi, Y. Kataoka, K. Utimoto, *Chem. Lett.* **1992**, 99; d) Y. Gao, K. Harada, F. Sato, *Tetrahedron Lett.* **1995**, *36*, 5913; alkenylmetal additions to imines and related electrophiles: e) S. E. Denmark, N. Nakajima, O. J.-C. Nicaise, *J. Am. Chem. Soc.* **1994**, *116*, 8797; f) N. A. Petasis, I. A. Zavialov, *J. Am. Chem. Soc.* **1997**, *119*, 445; g) N. A. Petasis, I. A. Zavialov, *J. Am. Chem. Soc.* **1998**, *120*, 11798; h) R. A. Batey, D. B. MacKay, V. Santhakumar, *J. Am. Chem. Soc.* **1999**, *121*, 5075; i) P. Wipf, C. Kendall, C. R. J. Stephenson, *J. Am. Chem. Soc.* **2001**, *123*, 5122; j) review: M. Johannsen, K. A. Jørgensen, *Chem. Rev.* **1998**, *98*, 1689.
[6] a) Y. Sato, M. Takimoto, K. Hayashi, T. Katsuhara, K. Takagi, M. Mori, *J. Am. Chem. Soc.* **1994**, *116*, 9771; b) E. Oblinger, J. Montgomery, *J. Am. Chem. Soc.* **1997**, *119*, 9065; c) M. Kimura, A. Ezoe, K. Shibata, Y. Tamaru, *J. Am. Chem. Soc.* **1998**, *120*, 4033; d) J. Montgomery, *Acc. Chem. Res.* **2000**, *33*, 467, and references therein; e) S. Ikeda, *Acc. Chem. Res.* **2000**, *33*, 511, and references therein; f) Y. Ni, K. K. D. Amarasinghe, J. Montgomery, *Org. Lett.* **2002**, *4*, 1743.
[7] See references [5f–i] for other multicomponent couplings that afford allylic amines.
[8] a) S. Kobayashi, H. Ishitani, *Chem. Rev.* **1999**, *99*, 1069; b) P. Wipf, C. Kendall, *Org. Lett.* **2001**, *3*, 2773, and references therein.
[9] For example, more electrophilic imines (NSO_2R and $NP(O)Ph_2$) did not undergo coupling.
[10] Reactions with toluene, THF, hexanes, CH_3CN, or EtOAc as solvent gave mixtures of **1a** and **2a** in $<10\,\%$ yield.
[11] Et_2Zn, polymethylhydrosiloxane (PMHS), and Et_3SiH gave complex mixtures of undesired products corresponding to imine addition and/or reduction.
[12] M. Kimura, A. Ezoe, S. Tanaka, Y. Tamaru, *Angew. Chem.* **2001**, *113*, 3712; *Angew. Chem. Int. Ed.* **2001**, *40*, 3600.
[13] This phenomenon probably does not result from water, as substoichiometric, stoichiometric, or excess amounts depreciate yield. EtOH and *i*PrOH gave significantly lower yields.
[14] Reactions conducted with diphosphanes as ligands (BINAP, dppe, dppb) gave trace amounts of allylic amines.
[15] With 1-phenyl-2-(trimethylsilyl)acetylene, allylic amine **1n** is formed in 22 % yield (regioselectivity $>98:2$) under the standard reaction conditions.
[16] a) T. Tsuda, T. Kiyoi, T. Saegusa, *J. Org. Chem.* **1990**, *55*, 2554; b) Y. Sato, T. Takanashi, M. Mori, *Organometallics* **1999**, *18*, 4891; c) Y. Sato, N. Saito, M. Mori, *J. Am. Chem. Soc.* **2000**, *122*, 2371; d) S. K. Chowdhury, K. K. D. Amarasinghe, M. J. Heeg, J. Montgomery, *J. Am. Chem. Soc.* **2000**, *122*, 6775; e) K. K. D.

Amarasinghe, S. K. Chowdhury, M. J. Heeg, J. Montgomery, *Organometallics* **2001**, *20*, 370. See also Refs [6b, d].

[17] MeOH may also promote group transfer from B to Ni, in analogy to Suzuki reaction additives, but this hypothesis does not account for alkylative/reductive selectivity (i.e., **1** vs. **2**). Extended storage of Et_3B in MeOH results in formation of Et_2BOMe and $EtB(OMe)_2$ which, based on other experiments, do not undergo coupling reactions. See: K.-M. Chen, K. G. Gunderson, G. E. Hardtmann, K. Prasad, O. Repic, M. J. Shapiro, *Chem. Lett.* **1987**, *10*, 1923.

[18] The Strecker and Mannich reactions are also examples of this unusual functional group tolerance. For examples of imine additions in the presence of aldehydes, see: a) H. Nakamura, H. Iwama, Y. Yamamoto, *J. Am. Chem. Soc.* **1996**, *118*, 6641; b) S. Kobayashi, S. Nagayama, *J. Org. Chem.* **1997**, *62*, 232.

[19] K. Shibata, M. Kimura, K. Kojima, S. Tanaka, Y. Tamaru, *J. Organomet. Chem.* **2001**, *624*, 348. Also see references [5f–h].