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Regio- and Stereoselective Cross-Coupling of Substituted Olefins and Imines. A Convergent Stereoselective Synthesis of Saturated 1,5-Aminoalcohols and Substituted Piperidines

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The development of reactions that facilitate the syntheses of nitrogen-containing small molecules continues to be an intense area of research in organic chemistry. Whereas many powerful methods exist for the preparation of such targets, recent accomplishments in reductive coupling chemistry have provided new strategies of untapped potential for the convergent synthesis of secondary carbinolamines. To date, methods have been described for bimolecular alkyne−imine coupling that provide a convenient route to substituted allylic amines.[1] The corresponding cross-coupling reaction between internal olefins and imines represents a significantly more complex and potentially more powerful bond construction.[2] In addition to overcoming the lower reactivity of substituted olefins in bimolecular carbometalation reactions, a synthetically useful cross-coupling process must address the additional complexity that results from the need to simultaneously control site selectivity and diastereoselection in the carbon−carbon bond-forming event (**2**+**3** → **4**−**7**, Figure 1). The development of a synthetic method to accomplish the cross-coupling of internal olefins and imines in a regio- and stereoselective manner would represent a significant advance and provide a fundamentally new strategy for the synthesis of stereodefined secondary carbinolamines.

Here we describe a method for cross-coupling of aromatic imines with terminal, 1,1-disubstituted, (*E*)- and (*Z*)-disubstituted olefins. Additionally, we describe the use of this coupling reaction in single and double asymmetric synthesis, as well as define a novel route for convergent stereoselective synthesis of substituted piperidines.

Previously, we have described titanium alkoxide-mediated reactions for alkyne−alkyne,[3] alkyne−alkene,[4] and alkyne−imine[5] cross-coupling. These methods have provided a means to overcome the sluggish reactivity of highly substituted π-systems in reductive coupling chemistry and defined a means to control regioselection in bimolecular carbometalation that is independent of the differential steric environment around an unsymmetrically substituted alkyne or alkene. As depicted in Figure 2, the present study explores alkoxide-directed, titanium-mediated, reductive cross-coupling between homoallylic alkoxides **8** and imines **9** as a method for the synthesis of acyclic aminoalcohols (i.e., **10** or **12**) and substituted heterocycles (i.e., **11** or **13**). In contrast to established reductive cross-coupling reactions between alkynes and heterosubstituted π-systems (alkyne−aldehyde, alkyne−imine), this alkene−imine cross-coupling process is significantly more complex as the carbon−carbon bond formation proceeds with the simultaneous generation of two stereogenic sp^3 carbon centers.

To examine the potential of this proposed reaction pathway for regio- and diastereoselective C−C bond formation, a study was initiated to explore the reactivity of azametallacyclopropanes (generated in situ from aromatic imines) with homoallylic alkoxides of general structure **8**. As depicted in entry 1 of Table 1, deprotonation of homoallylic alcohol **14** (*n*-BuLi, Et_2O) and addition to a preformed azametallacyclopropane derived from imine **15** (Ti-

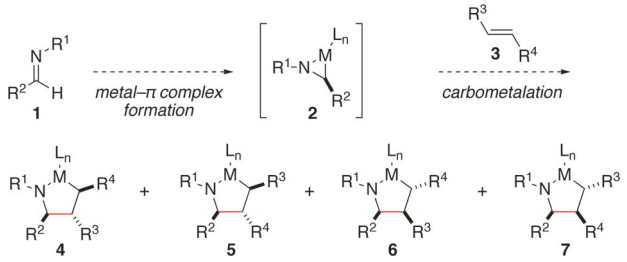

Figure 1. Bimolecular coupling of imines and substituted olefins via formation of azametallacyclopentanes.

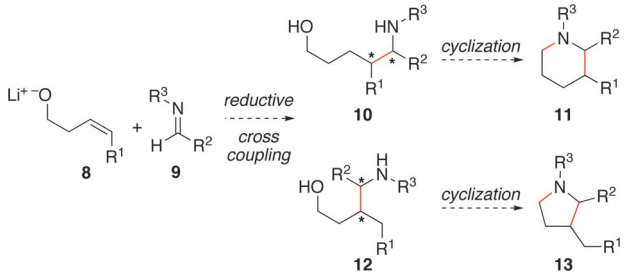

Figure 2. Cross-coupling of substituted olefins and imines—a potential pathway for the synthesis of aminoalcohols and substituted heterocycles.

(O*i*-Pr)$_4$, *c*-C_5H_9MgCl, Et_2O, −70 to −40 °C), followed by protonation of the presumed bicyclic azametallacyclopentane, resulted in formation of the 1,5-aminoalcohol **16** in 76% yield (rr ≥ 95:5). The success of this coupling reaction not only defines a convergent route to aminoalcohols but also provides a convenient means to access substituted piperidines. Treatment of 1,5-aminoalcohol **16** with PPh_3 and CCl_4 (reflux) resulted in the formation of the substituted piperidine **17** in 85% yield.[6]

More highly substituted olefins were well tolerated in this cross-coupling reaction. As illustrated in entry 2, coupling of the (*E*)-disubstituted homoallylic alcohol **18** with imine **15** provided the 4,5-*anti*-1,5-aminoalcohol **19** in 73% yield (dr ≥ 95:5; rr ≥ 95:5) and, on cyclization, the 2,3-*trans*-disubstituted piperidine **20** in 81% yield. Coupling of the related (*Z*)-disubstituted homoallylic alcohol **21** with imine **15** provided the 4,5-*anti*-1,5-aminoalcohol **22** in 63% yield (dr ≥ 95:5; rr ≥ 95:5) and, on cyclization, the 2,3-*trans*-disubstituted piperidine **23** in 77% yield (entry 3).

As depicted in Figure 3, the stereoconvergence observed in these coupling reactions can be rationalized by assuming preferential reaction by way of transition-state structures that avoid 1,2-steric interactions in a developing *cis*-fused bicyclo[3.3.0] ring system (**B** and **C**).[7,8]

The homoallylic alcohol **24**, bearing a 1,1-disubstituted olefin, was also an effective coupling partner with imine **15** providing the 1,3-*syn*-1,5-aminoalcohol product **25** in 67% yield (dr = 4:1; rr ≥ 95:5)[9] and, on cyclization, the corresponding 2,4-*trans*-disubstituted

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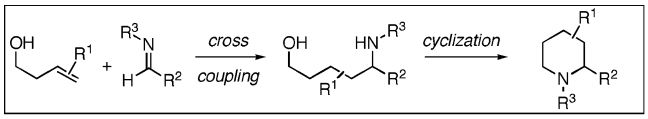
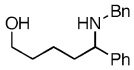
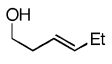
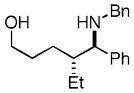
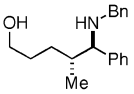
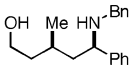
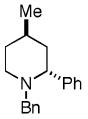
Table 1.



entry	homoallylic alcohol	imine	1,5-aminoalcohol[a]	yield (%)	rr	dr	piperidine[b] (yield)
1	 **14**	 **15**	 **16**	76	≥95:5	n/a	 **17** (85%)
2	 **18**	**15**	 **19**	73	≥95:5	≥95:5	 **20** (81%)
3	 **21**	**15**	 **22**	63	≥95:5	≥95:5	 **23** (77%)
4	 **24**	**15**	 **25**	67	≥95:5	4:1	 **26** (76%)

[a] Reaction conditions for cross-coupling: imine (1 equiv), Ti(O*i*-Pr)$_4$ (1.5 equiv), *c*-C_5H_9MgCl (3.0 equiv), Et_2O (−70 to −40 °C), then add alkoxide (1.5 equiv, −40 to −20 °C, 0 °C, or rt; see Supporting Information for details). [b] Reaction conditions for cyclization: PPh_3, imidazole, CCl_4, reflux.

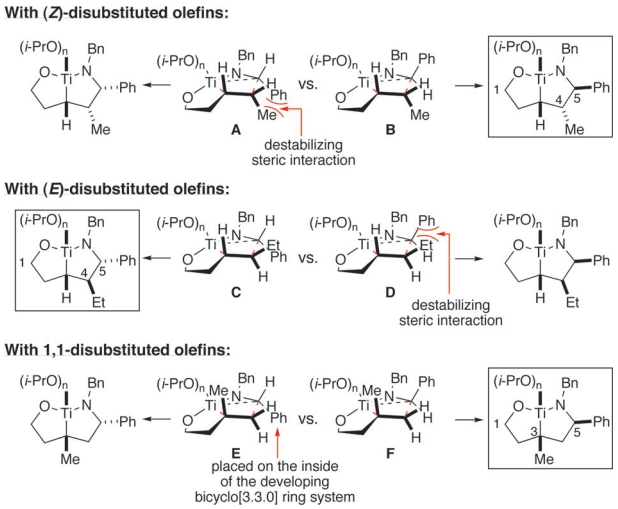
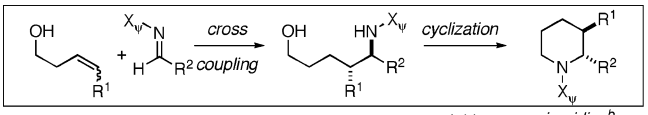


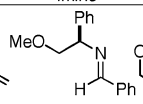
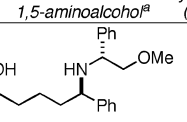
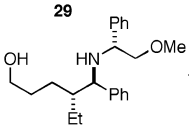
Figure 3. A model for stereoselection in imine−alkene cross-coupling.[7,8]

piperidine **26** in 76% yield. The stereoselectivity in this case is consistent with preferential progression through a transition-state geometry that has the phenyl substituent occupying a position outside the developing *cis*-fused bicyclo[3.3.0] ring system (**F** in Figure 3).[7,8]

Next, coupling reactions of achiral homoallylic alcohols with chiral imines were examined. As depicted in Table 2, coupling of homoallylic alcohols with chiral imine **28** proceeded in a generally efficient manner (61−83%).[10] Highest selectivities were observed in coupling reactions of the terminal- (**14**) and (*Z*)-disubstituted (**27**) olefins and provided products with dr ≥ 20:1 (entries 1 and 2). Cyclization of these 1,5-aminoalcohols (**29** and **31**) provides the corresponding substituted piperidines **30** and **32** with good efficiency (77 and 87% yield). Coupling of the (*E*)-disubstituted

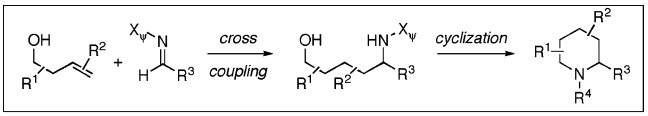
Table 2.

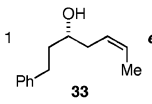
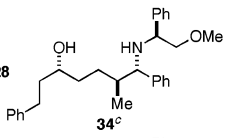
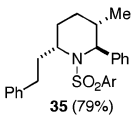
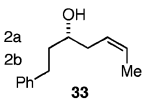
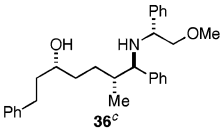
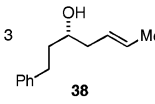
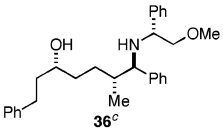
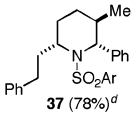
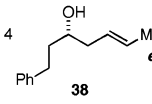
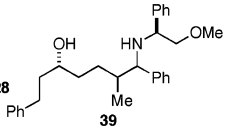


entry	homoallylic alcohol	imine	1,5-aminoalcohol[a]	yield (%)	dr	piperidine[b] (yield)
1	 **14**	 **28**	 **29**	83	24:1	 **30** (77%)
2	 **27**	**28**	 **31**	75	20:1	 **32** (87%)
3	 **18**	**28**	**31**	61	25:4:1	

[a] Reaction conditions for cross-coupling: imine (1 equiv), Ti(O*i*-Pr)$_4$ (1.5 equiv), *c*-C_5H_9MgCl (3.0 equiv), Et_2O (−60 to −30 °C), then add alkoxide (1.5 equiv, −30 to 0 °C or rt). [b] Reaction conditions for cyclization: For **30**: 2-NsCl, Et_3N, DMAP, CH_2Cl_2, rt. For **32**: MsCl, Et_3N, CH_2Cl_2, rt. R = CH(Ph)CH_2OMe.

Table 3.



entry	homoallylic alcohol	imine	1,5-aminoalcohol[a]	yield (%)	dr	piperidine[b] (yield)
1	 **33**	*ent*-**28**	 **34**[c]	76	≥50:1	 **35** (79%)
2a 2b	 **33**	**28**	 **36**[c]	30 85	4:1:1 6:3:1	
3	 **38**	**28**	 **36**[c]	88	35:4:1	 **37** (78%)[d]
4	 **38**	*ent*-**28**	 **39**	76	19:12:4:1	

[a] Reaction conditions for cross-coupling: imine (1 equiv), Ti(O*i*-Pr)$_4$ (1.5 equiv), *c*-C_5H_9MgCl (3.0 equiv), Et_2O (−60 to −30 °C), then add alkoxide (1.5 equiv, −30 to 0 °C (entries 1, 2a, 3, and 4) or rt (entry 2b)). [b] Reaction conditions for cyclization: (1) H_2 (1 atm), $Pd(OH)_2$, AcOH/MeOH (1:10 v/v), rt; (2) 2-NsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C to rt; (3) PPh_3, DIAD, THF, rt. Ar = 2-nitrophenyl. [c] Major diastereomer shown. [d] Cyclization of **36** to **37** was performed with the enantiomer of **36** (for data on *ent*-**37**, see Supporting Information).

olefin **18** with chiral imine **28** also led to aminoalcohol **31**, yet this product was obtained with levels of stereoselection (25:4:1) lower than that observed with the isomeric olefin **27**.

Cross-coupling reactions were also examined to determine the extent to which stereochemical matching and/or mismatching might occur in double diastereodifferentiating cases.[11] As illustrated in Table 3, coupling of the (*Z*)-homoallylic alcohol **33** with chiral imine *ent*-**28** furnished the 1,4-*anti*-1,5-*syn*-1,5-aminoalcohol **34** in

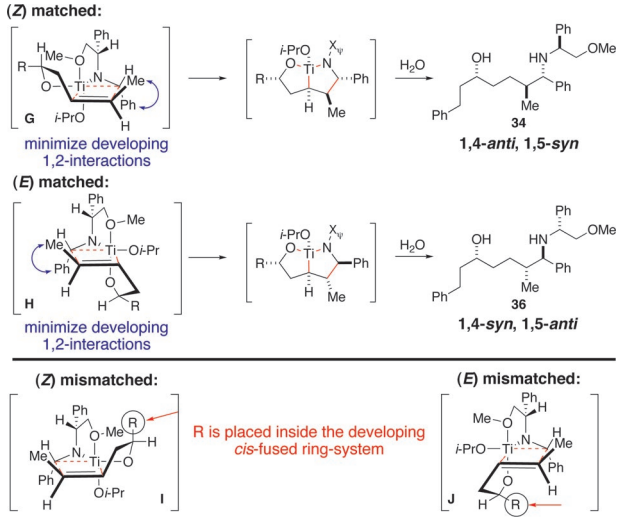


Figure 4. A model for stereoselection in the double asymmetric cross-coupling reactions of disubstituted olefins with chiral imines.

76% yield (dr ≥ 50:1), cyclization of which provided the 2,3-*trans*-2,6-*trans*-tetrasubstituted piperidine **35** (entry 1a). Coupling of the same homoallylic alcohol (**33**) with **28** proceeded with low conversion (30%) and provided a mixture of diastereomeric products (dr = 4:1:1; entry 2a). Although the efficiency of this coupling reaction can be increased on warming (entry 2b), the dr is affected. The disparate reactivity and selectivity observed defines a clearly matched (entry 1) and mismatched (entry 2) double asymmetric relationship in these coupling reactions.

The (*E*)-disubstituted homoallylic alcohol **38** displayed inverse double asymmetric behavior as compared to (*Z*)-disubstituted homoallylic alcohol **33**. As illustrated in entries 3 and 4, coupling of **38** with **28** represents a matched double asymmetric process (88% yield, dr = 35:4:1), whereas coupling of **38** with *ent*-**28** represents a mismatched double asymmetric reaction (dr = 19:12:4:1).

A preliminary empirical model to explain these double asymmetric reactions is proposed in Figure 4. The model is based on (1) diastereoselective coordination of the pendent methyl ether to the titanium center,[10] (2) intramolecular delivery of the olefin to the azametallacyclopropane,[3−5] (3) minimization of 1,2-interactions in the developing five-membered ring, and (4) positioning of the alkyl group (R) outside of the developing *cis*-fused ring system. The sum of these factors may contribute to defining matched double asymmetric reactions for the synthesis of either 1,4-*anti*-1,5-*syn* (**34**) or 1,4-*syn*-1,5-*anti* (**36**) aminoalcohols via transition-state geometries **G** and **H**.[7,8] On the basis of this empirical model, the mismatched double asymmetric reactions (Table 3, entries 2 and 4) may suffer from the requirement of placing the alkyl substituent (R) on the inside of the developing *cis*-fused ring system (**I** and **J**, Figure 4).

These double asymmetric cross-coupling reactions proceed with a great deal of variability in stereoselection that is dependent on the stereochemical relationship of the secondary alcohol, imine, and olefin. Interestingly, matched double asymmetric reactions can provide stereoselective access to either the 1,4-*anti*-1,5-*syn*-1,5-aminoalcohol or 1,4-*syn*-1,5-*anti*-1,5-aminoalcohol products and the corresponding tetrasubstituted piperidines **35** and **37**. The variability in the diastereomeric ratio of products observed in each of these matched double asymmetric coupling reactions is consistent with a stereoreinforcing[12] relationship based on olefin geometry: (*S,Z*)-homoallylic alcohol + *ent*-**28** is matched and benefits from a stereoreinforcing relationship with the (*Z*)-olefin, whereas (*S,E*)-homoallylic alcohol + **28** is also a matched double asymmetric reaction but there is a non-stereoreinforcing relationship with the (*E*)-olefin.

Overall, we report a titanium alkoxide-mediated reaction for regio- and stereoselective cross-coupling of substituted olefins and imines. The reported process provides convenient access to substituted 1,5-aminoalcohols and piperidines. Our studies focusing on simple diastereoselection have shown that this reaction is stereoconvergent with respect to olefin stereochemistry—both (*E*)- and (*Z*)-disubstituted homoallylic alcohols provide *anti*-products in coupling reactions with achiral imines. We have studied this reaction in both single and double asymmetric modes, have defined matched and mismatched double asymmetric relationships, and have shown a reversal of stereochemical matching/mismatching as a function of the olefin geometry of the chiral homoallylic alcohol. Research focused on further understanding the nature of stereoselection in this cross-coupling reaction, as well as application to the synthesis of complex heterocycles, is underway.

Acknowledgment. We gratefully acknowledge financial support of this work by the American Cancer Society (RSG-06-117-01), the American Chemical Society (PRF-45334-G1), the Arnold and Mabel Beckman Foundation, Boehringer Ingelheim, Eli Lilly & Co., the National Institutes of Health, NIGMS (GM80266), and Yale University.

Supporting Information Available: Experimental procedures and tabulated spectroscopic data for new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(2) For cross-coupling of zirconium−imine complexes and terminal olefins, see ref 1a.
(3) Ryan, J.; Micalizio, G. C. *J. Am. Chem. Soc.* **2006**, *128*, 2764−2764.
(4) Reichard, H. A.; Micalizio, G. C. *Angew. Chem., Int. Ed.* **2007**, *46*, 1440−1443.
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