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Stereoselective Cross-Coupling between Allylic Alcohols and Aldimines

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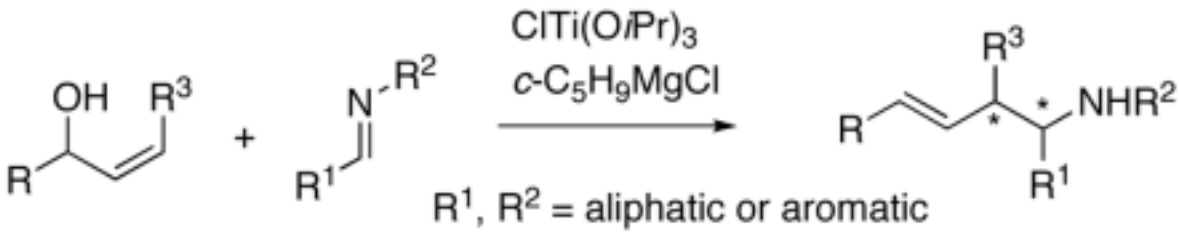
Abstract



A cross-coupling reaction between an allylic alcohol and an imine is described for stereoselective allylation of aromatic and aliphatic imines. This method provides operationally simple, enantioselective access to functionalized homoallylic amines. Particularly noteworthy is direct use of a functionalized allylic alcohol as an allylating reagent without pre-derivatization, which obviates the use of preformed organometallic reagents or activated imine derivatives.

Addition of organometallic reagents to imines provides a useful method for the stereoselective preparation of amines.[1] An enantioselective allylation/crotylation reaction to aldimines is a valuable tool in organic synthesis, as homoallylic amines are useful building blocks in natural product synthesis and medicinal chemistry.[2,3] Imines are less electrophilic than carbonyl groups, and addition of organometallic reagents to imines can be complicated by accompanying enolization, reduction, or dimerization.[4] This reactivity issue requires a judicious choice of an allylic metal reagent and/or activation of an imine by a suitable Lewis acid. Additionally, there is a paucity of convenient methods for generating functionalized allylic nucleophiles despite impressive advances in this field.[5] Direct use of an allylic alcohol as an allylating reagent is particularly attractive, as it obviates pre-derivatization of an allylic alcohol substrate. We report herein regio- and stereoselective cross-coupling between an allylic alcohol and an imine by the action of the Kulinkovich reagent.

A cross-coupling reaction between an allylic alcohol and a vinylsilane (or a styrene) was recently developed by use of the Kulinkovich reagent, in which directing effects of an allylic alkoxide were exploited via a temporary linker.[6,7] An imine was already shown by the Sato group to react with an alkyne–Kulinkovich reagent complex to afford an allylic amine.[8] Thus, we reasoned that the use of an aldimine in place of a vinylsilane could provide a new approach to regio- and stereoselectively preparing homoallylic amines. Our study began with the coupling reaction between 2-cyclohexen-1-ol and several imines **1a–h** (Table 1). Thus, coupling of 2-cyclohexen-1-ol and **1a** under previously reported conditions afforded

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Supporting Information Available Experimental details and spectroscopic data for key intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

homoallylic amine **2a** in 90% yield in >20:1 diastereoselectivity (entry 1). A broad scope with respect to imines (i.e., different R^1 and R^2) can be seen from entries 1–8: not only aromatic, but also aliphatic imines are amenable to cross-coupling. The resulting homoallylic amines **2a–h** were obtained as virtually single isomers. In the case of imine **1g** having an isopropyl branch, a 4:1 mixture of **2g** and the by-product (structure not shown) from addition of the cyclopentyl Grignard reagent to the imine was obtained (entry 7). This result could be attributed to steric effects.

Coupling of acyclic *Z*-allylic alcohols **3** and **4** with imines **1a–c,e** was next examined (Table 2). As was the case with cross-coupling with vinylsilanes or styrenes,[6] high levels of diastereocontrol was achieved to provide *E*-homoallylic amines **5a–c,e** and **6a–c,e**. Full compatibility with the presence of an allylic ether is clearly seen with allylic alcohol **4** (entries 5–8).

Complete chirality transfer was established by the use of enantiopure allylic alcohols **7–11** (Table 3). Coupling of (*S*)-**7** with **1a** and **1c** proceeded diastereo- and enantioselectively to afford amines **12** and **13** in 60% and 68% yield, respectively (entries 1 and 2). Similarly, **14** and **15** were obtained from **8** and **9**, respectively (entries 3 and 4). Comparative evaluation of *E*-allylic alcohols **10** and **11** was undertaken next for additional stereochemical studies. As expected by analogy to ethylation and cross-coupling with vinylsilanes,[6] these *E*-allylic alcohol substrates produced a mixture of two diastereomers: **10** gave a 1.3:1 separable mixture of **16** and **15** in 71% yield (entry 5), whereas a 1.2:1 mixture of **17** and **14** was obtained from **11** (entry 6). The unequivocal determination of the absolute and relative stereochemistry of the homoallylic amine products **12–17** was possible by these correlation studies, as well as an independent synthesis of **13**.[9]

The observed stereochemical outcome can be rationalized by formation of a temporary alkoxide tether and subsequent syn addition/syn β-elimination for the 1,3-transpositive cross-coupling reactions of acyclic and cyclic allylic alcohols. High diastereoselectivity displayed by *Z*-allylic alcohols is in accord with the involvement of conformer **A** to minimize $A^{(1,3)}$ strain (Scheme 1). The lack of selectivity for *E*-allylic alcohols and the attendant formation of both *E*- and *Z*-alkenes suggest the co-involvement of both conformers **B** and **C**.[6]

In conclusion, we have developed convenient cross-coupling reactions between allylic alcohols and imines for stereoselective allylation of aromatic and aliphatic imines. Particularly noteworthy is direct use of a functionalized allylic alcohol as an allylating reagent without pre-derivatization. This convenient method obviates the use of preformed organometallic reagents or activated imine derivatives.[10]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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9. (a) Amine 13 was independently prepared by the Claisen-Ireland rearrangement of the phenyl acetate of (*S*)-7, followed by the Curtius rearrangement, hydrolysis, and reductive amination with benzaldehyde. (b) The relative stereochemistry was also established by measurement of the key vicinal coupling constant of a tetrahydropyridine derived from 5c via allylation and ring-closing metathesis. (c) See Supporting Information for these stereochemical studies.

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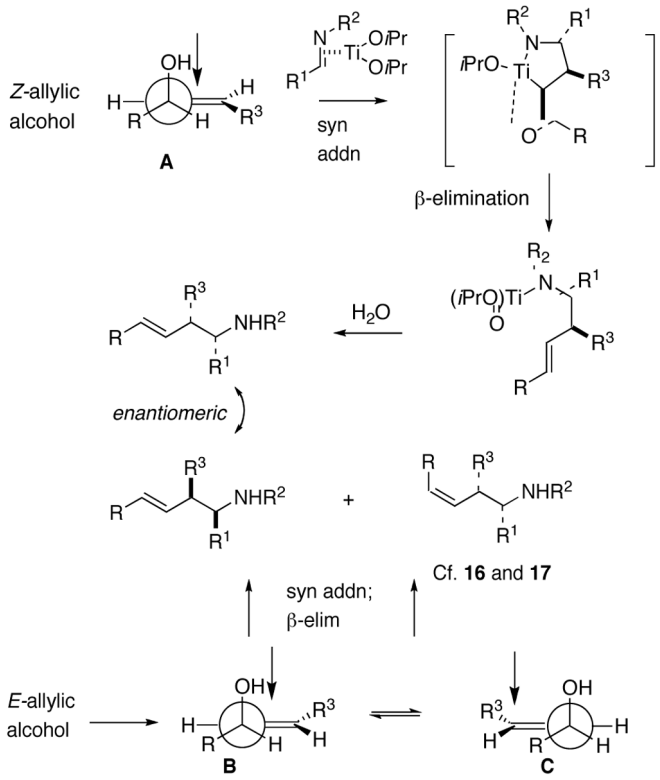
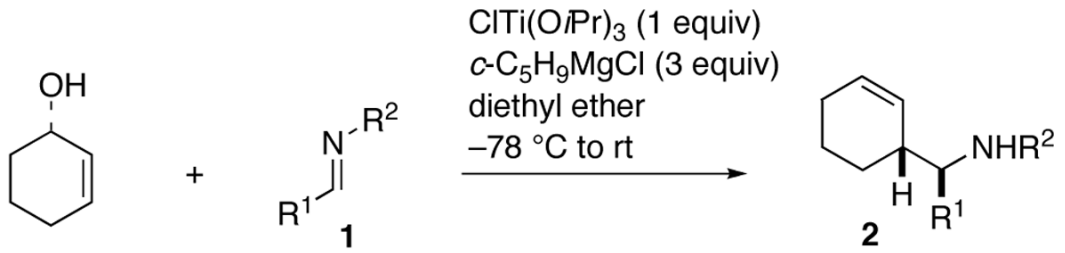


Scheme 1.

Table 1

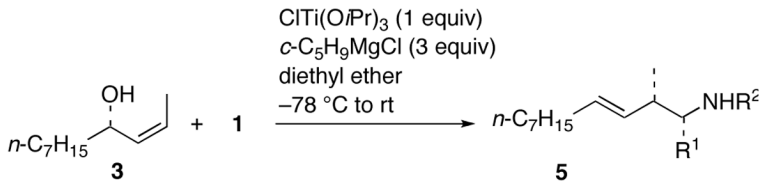
Cross-Coupling between 2-Cyclohexen-1-ol and Imines



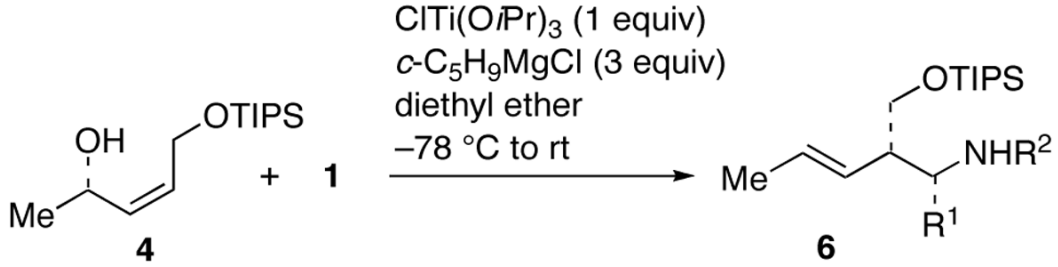
entry	imine	R^1	R^2	product	yield
1	**1a**	Ph	Ph	**2a**	90%
2	**1b**		*p*-$MeOC_6H_4$	**2b**	75%
3	**1c**		Bn	**2c**	78%
4	**1d**		CH_2-*o*-$MeOC_6H_4$	**2d**	69%
5	**1e**		*n*-Bu	**2e**	76%
6	**1f**	2-furyl	Bn	**2f**	55%
7	**1g**	*i*-Pr	Bn	**2g**	40%
8	**1h**	*n*-C_7H_{15}	Bn	**2h**	60%

Table 2

Cross-Coupling between (*Z*)-Allylic Alcohols and Imines



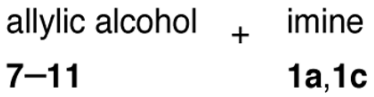
entry	imine	R_1	R_2	product	yield
1	**1a**	Ph	Ph	**5a**	78%
2	**1b**		*p*-$MeOC_6H_4$	**5b**	72%
3	**1c**		Bn	**5c**	74%
4	**1e**		*n*-Bu	**5e**	72%

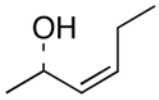
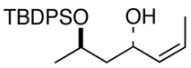
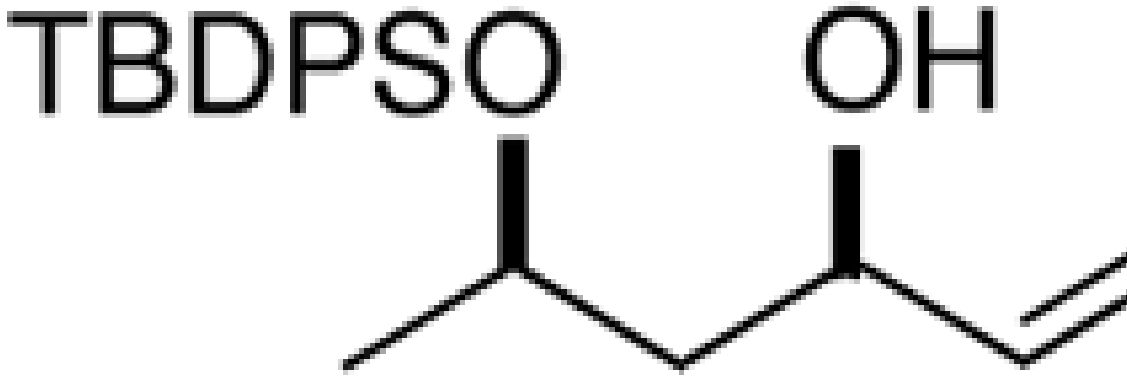
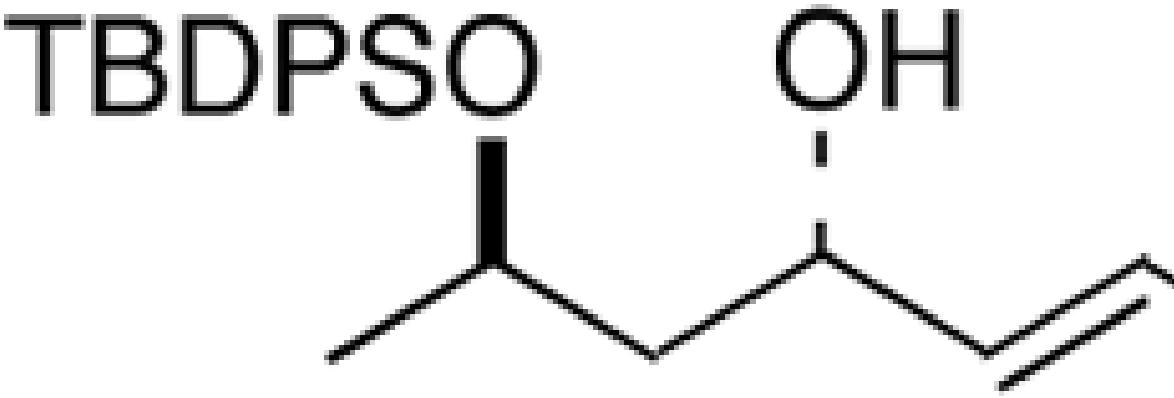


entry	imine	R^1	R^2	product	yield
5	**1a**	Ph	Ph	**6a**	62%
6	**1b**		*p*-$MeOC_6H_4$	**6b**	64%
7	**1c**		Bn	**6c**	68%
8	**1e**		*n*-Bu	**6e**	57%

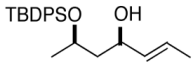
Table 3

Enantioselective Synthesis of Homoallylic Amines



entry	imine	allylic alcohol
1	**1a**	 (*S*)-**7**
2	**1c**	(*S*)-**7**
3	**1c**	 **8**
4	**1c**	 **9**
5	**1c**	 **10**

allylic alcohol **7–11** + imine **1a**,**1c**

entry	imine	allylic alcohol
6	**1c**	 **11**