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Cross-coupling of homoallylic alcohols with styrene

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ABSTRACT

A cross-coupling reaction between a homoallylic alcohol and styrene is described to broaden the scope of the titanium alkoxide tether-mediated coupling reactions. Particularly noteworthy is exceptional 1,3-diastereoselectivity by *o*-vinylanisole in coupling with a *Z*-homoallylic alcohol.

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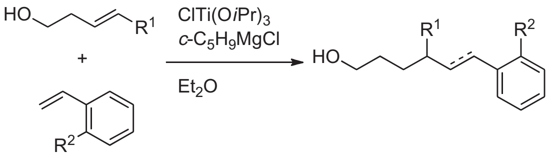
Despite impressive advances in transition metal-catalyzed C–C bond-forming reactions, an intermolecular cross-coupling of two unactivated alkenes stands as a challenging goal. Known examples typically involve the coupling of alkynes with polarized π-bonds (e.g., carbonyl groups or alkenes bearing electron-withdrawing groups).[1] As part of mechanistic and synthetic studies of the Kulinkovich cyclopropanation, we became interested in utilizing the Kulinkovich reagent in cross-coupling reactions, as well as cyclopropanation of carboxylic acid derivatives. The Kulinkovich reagent had been shown to be effective for regioselective homo-coupling of terminal olefins,[2,3] but selective cross-coupling proved to be a particularly difficult task. A convenient solution was subsequently found in in situ generation of a titanium alkoxide tether, which had first been developed for *trans*-dialkyl selective cyclopropanation of homoallylic alcohols.[4,5] Our laboratory and the Micalizio group reported cross-coupling of allylic alcohols with vinylsilanes or styrene,[6,7] followed by that with imines.[8–10] We report herein cross-coupling of homoallylic alcohols and styrene to broaden the scope of the titanium alkoxide tether-mediated coupling reactions (Eq 1).



(1)

Our study began with the coupling reaction between *E*- and *Z*-3-hexen-1-ol (*E*-**1** and *Z*-**1**) and styrene (Table 1). When a mixture of *E*-**1** and styrene was treated with the Kulinkovich reagent (generated under previously reported conditions for coupling reactions of allylic alcohols),[6,9] a 3:2 mixture of the coupling products **2** and **3** was isolated in 51% yield, along with unreacted starting alcohol (36%) (entry 1). Homo-dimerization products (not shown) of *E*-**1** and styrene were also isolated in 9% and 44% yields, respectively. A slightly higher conversion was possible by employing an excess of styrene (entry 2). However, an excess amount of the Kulinkovich reagent was deleterious due to competing formation of the cyclopentane adduct **4** (entry 5). The use of MeTi(O-*i*-Pr)$_3$ was not advantageous over that of ClTi(O-*i*-Pr)$_3$ (entry 3). The product ratio of **2** to **3** was dependent on reaction temperature and time, where **3** was believed to arise from β-hydride elimination of the presumed alkyltitanium intermediate (vide infra). When the reaction mixture was allowed to stand at room temperature for a longer period (15 h instead of 6 h), selective formation of **3** was observed (entry 4). The corresponding coupling reactions with *Z*-**1** were also examined, in which the reaction mixture was allowed to warm to room temperature to promote complete conversion to **3**. As shown in entries 6–9, the competing formation of the side product **4** was more pronounced.

With regard to selective preparation of **2** versus **3**, easy access to the latter product is readily available by allowing β-hydride elimination to proceed to completion at room temperature (Table 1, entry 4). On the other hand, formation of **2** was less straightforward, as it would require careful control of reaction variables, especially reaction temperatures. We sought a more convenient route to **2**. As a vacant coordination site is obligatory for β-hydride elimination, we hypothesized that the presence of a substituent capable of coordinating to the titanium metal, such as an *o*-alkoxy

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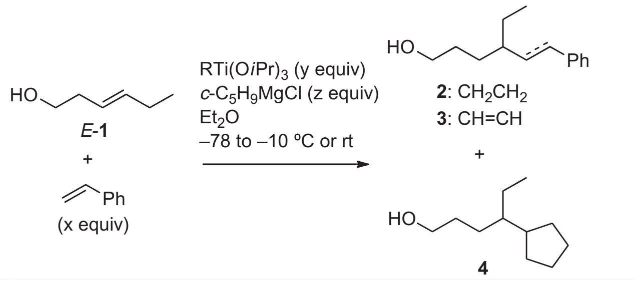
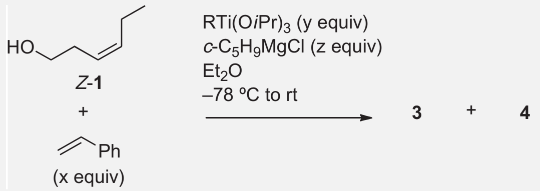
Table 1
Cross-coupling between *E*- & *Z*-**1** and styrene



Entry	R	x	y	z	**2 + 3**			**4**
1	Cl	1.1	1.0	3.0	51%	(69%)[a]	(3:2)[b]	Trace
2	Cl	1.4	1.0	3.0	69%	(78%)[a]	(7:3)[b]	Trace
3	Me	1.4	1.0	2.0	61%	(77%)[a]	(1:3)[b]	trace
4	Cl	1.4	1.0	3.0	65%	(74%)[a]	(0:1)[b,c]	Trace
5	Cl	1.4	2.0	5.0	36%		(1:0)[b,d]	30%

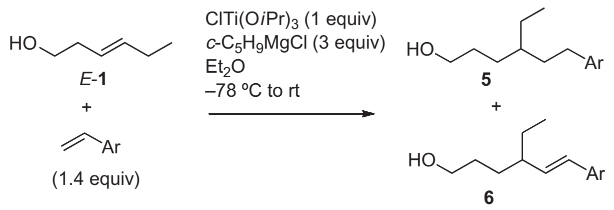


Entry	R	x	y	z	**3**	**4**
6	Cl	1.1	1.0	3.0	34% (40%)[a]	29% (35%)[a]
7	Cl	1.4	1.0	3.0	47% (60%)[a]	15% (19%)[a]
8	Me	1.1	1.0	2.0	44% (54%)[a]	14% (19%)[a]
9	Me	1.4	1.0	2.0	52% (62%)[a]	14% (17%)[a]

[a] Yields based on reacted starting material.
[b] Ratios of **2** to **3**.
[c] Allowed to stand at rt for a longer (15 h) period.
[d] Allowed to warm to −10 °C.

group, could prohibit β-hydride elimination. Toward this end, *o*-vinylanisole and other styrene derivatives were examined (Table 2). Indeed, coupling between *E*-**1** and *o*-vinylanisole under identical conditions afforded **5a** cleanly, free from **6a** (entry 1). Similarly, selective formation of **5b** was observed from 2,3-dimethoxystyrene (entry 2). Comparison with other examples (entries 3–7) provided additional evidence for chelation effects by an *o*-alkoxy substituent rather than electronic or steric effects.[11]

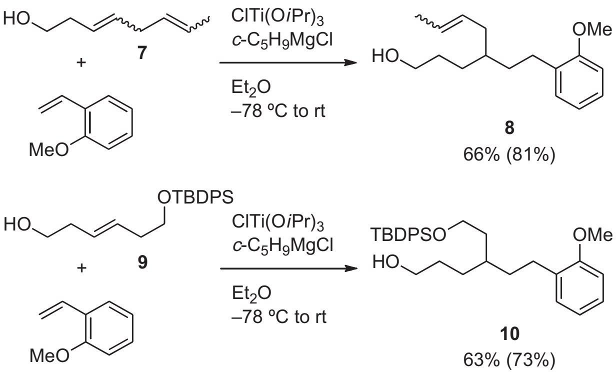
Table 2
Cross-coupling of substituted styrenes



Entry	Ar		**5a–h + 6a–h**
1	*o*-$\mathrm{MeOC_6H_4}$	**a**	68% (82%)[a] (1:0)[b]
2	2,3-$\mathrm{(MeO)_2C_6H_3}$	**b**	54% (69%)[a] (1:0)[b]
3	3,4-$\mathrm{(OCH_2O)C_6H_3}$	**c**	48% (65%)[a] (3:7)[b]
4	*p*-$\mathrm{MeOC_6H_4}$	**d**	52% (84%)[a] (3:7)[b]
5	*p*-$\mathrm{ClC_6H_4}$	**e**	63% (78%)[a] (3:7)[b]
6	*p*-$\mathrm{FC_6H_4}$	**f**	57% (78%)[a] (1:1)[b]
7	2-Naphthyl	**g**	47% (65%)[a] (1:1)[b]

[a] Yields based on reacted starting material.
[b] Ratios of **5** to **6**.

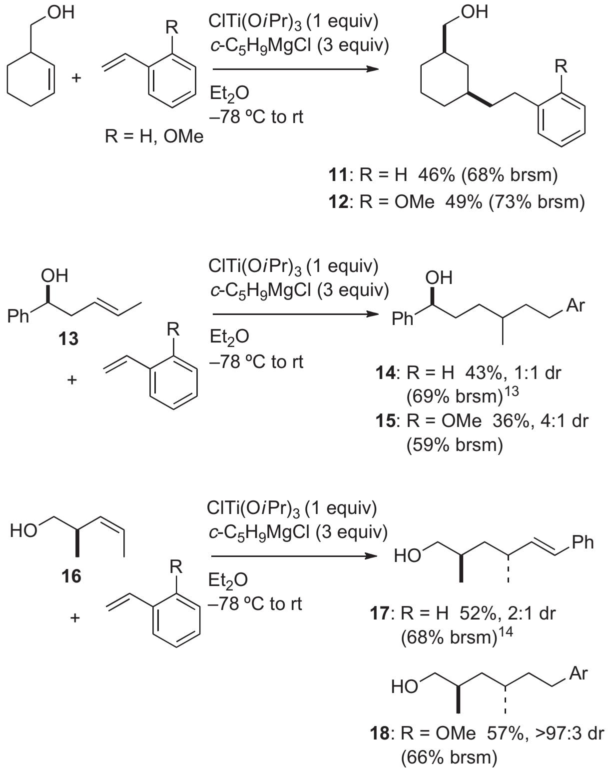
Common functional groups can be incorporated into homoallylic alcohol substrates. Two additional examples of alcohols bearing an allylic moiety and a siloxy group are shown in (Eq 2).[12]



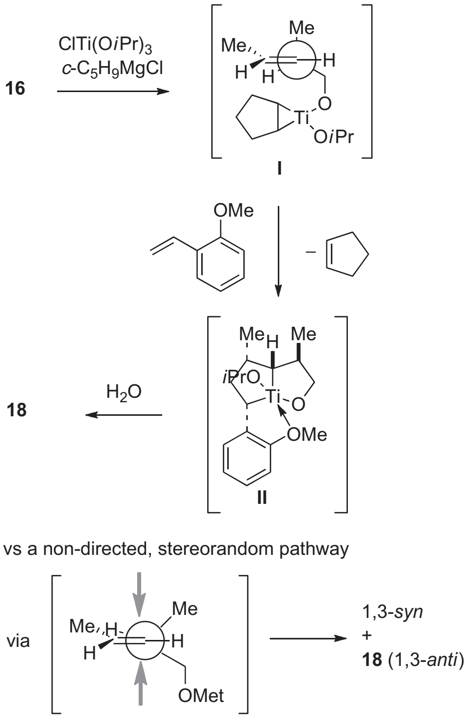
(2)

Our next investigation focused on diastereoselectivity of the coupling reactions of substituted homoallylic alcohols. Coupling of 3-(hydroxymethyl)cyclohexene[13] with styrene and *o*-vinylanisole afforded **11** and **12**, respectively, to corroborate *syn* addition (Scheme 1). Coupling of secondary alcohol **13** with styrene proceeded to provide **14** with no 1,4-stereoselectivity,[14] but that of *o*-vinylanisole gave **15** in 4:1 selectivity. The unexpected stereodirecting effect of the *o*-methoxy substituent was conspicuous in the coupling reactions of **16**, where **18** was obtained as a single isomer in marked improvement over 2:1 (*anti*:*syn*) selectivity for the formation of **17**.[15,16]

High 1,3-diastereoselectivity displayed by *Z*-homoallylic alcohol **16** is consistent with the involvement of conformer **I**, where 1,3-allylic strain is minimized, leading to stereoselective formation of the intermediate **II** (Scheme 2). At present, the nature of the directing effect by the *o*-methoxy substituent is unclear. Its predisposition to form a five-membered titanium chelate appears



Scheme 1.



Scheme 2.

to help disfavor a competing non-tethered (stereorandom) pathway, thus promoting alkoxide-tethered carbometalation, **I**→**II**.[17,18]

In summary, we have delineated a titanium alkoxide-directed cross-coupling reaction of homoallylic alcohols and styrenes. The use of *o*-vinylanisole is effective for not only prevention of β-hydride elimination but also stereocontrol; particularly noteworthy is exceptional 1,3-diastereoselectivity by *o*-vinylanisole in coupling with **16**. Optimization and studies to elucidate the origin of unique diastereocontrol by an *o*-alkoxy substituent of the styrene substrate are in progress.

Acknowledgment

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.08.054.

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11. (a) The product ratios given in Tables were determined by analysis of ^{1}H and ^{13}C NMR spectra. (b) Experimental procedures and spectral data are available in Supplementary Data.
12. (a) The yields in parenthesis are based on reacted starting material. (b) Comparable yields were also obtained for the corresponding coupling reactions of styrene.
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14. The coupling product **14** was obtained along with a varying amount of the corresponding dehydro compound (not shown for convenience). No attempt was made to maximize the β-elimination product.
15. The coupling product **17** was obtained along with a varying amount of the corresponding dihydro compound (not shown for convenience). The stereochemical determination was made by hydrogenation of the former to the latter and comparison of the spectral data with the known *syn* and *anti* isomers: (a) Brand, G. J.; Studte, C.; Breit, B. *Org. Lett.* **2009**, *11*, 4668–4670; The stereochemical assignment of **17** was further confirmed by its conversion (O$_3$; NaBH$_4$) to 2,4-dimethyl-1,5-pentandiol: (b) Fujita, K.; Mori, K. *Eur. J. Org. Chem.* **2001**, 493–502; (c) The stereochemistry of **18** was assigned by analogy to **17**.
16. The coupling product of **16** with an alkyne was also assigned 1,3-*anti* stereochemistry: Reichard, H. A.; Micalizio, G. C. *Angew. Chem., Int. Ed* **2007**, *46*, 1440–1443.
17. The five-membered titanium chelate could hinder an intermolecular cross-coupling by occupying a vacant coordination site necessary for carbometalation.
18. The titanium species are most likely to have an octahedral or trigonal bipyramidal geometry, but the remaining coordination sites are not indicated for convenience.