Asymmetric Catalysis

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Iridium-Catalyzed Enantioselective Allyl–Allylsilane Cross-Coupling**

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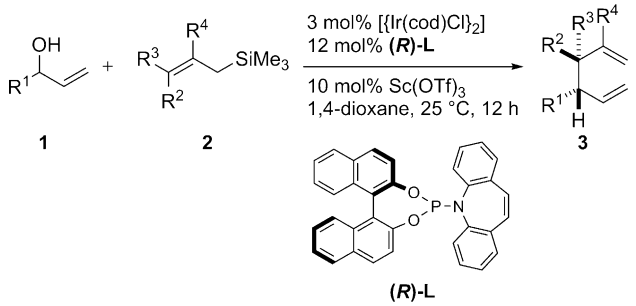
Abstract: *An enantioselective allyl–allylsilane cross-coupling involving racemic branched allylic alcohols and allylsilanes is reported. An iridium-(P,olefin) phosphoramidite complex enables the transformation with high regio- and stereoselectivity under operationally simple conditions. The utility of the coupling is demonstrated in a concise catalytic, enantioselective synthesis of a pyrethroid insecticide protrifenbute.*

Among the most important challenges in modern organic synthesis is the catalytic asymmetric formation of carbon–carbon bonds.[1] Of a particular importance is the asymmetric allyl–allyl cross-coupling between allyl–metal reagents and allylic electrophiles that provides a convenient synthetic route to enantioenriched chiral 1,5-dienes.[2] Although transition metal complexes of Pd, Cu, Au, and Ni have been reported to effect allyl–allyl cross-couplings over the years,[3] they can suffer from poor branched regioselectivity and enantioselectivity. Moreover, many of them rely on the use of toxic or reactive allyl–metal reactants such as organotin[3a,c] or Grignard[4] reagents, respectively. Herein, we report the development of the enantioselective cross-coupling reaction between racemic branched allylic alcohols and allylsilanes, catalyzed by an Ir-(P,olefin) complex (Scheme 1). The method provides facile access to various branched dienes and trienes in high yields and stereoselectivity following an operationally convenient protocol that does not require strict exclusion of moisture. In addition, the utility of this method is illustrated with an enantioselective synthesis of a pyrethroid insecticide protrifenbute.



Scheme 1. Iridium-catalyzed enantioselective allyl–allylsilane cross-coupling of racemic branched allylic alcohols with allylsilanes. cod = 1,5-cyclooctadiene; Tf = trifluoromethanesulfonyl.

Despite the value of enantioenriched chiral 1,5-dienes as versatile intermediates in organic synthesis, a high level of regio- and enantioselectivity in their preparation has only recently been documented. Pioneering work from the Morken group recently showcased the allyl–allyl cross-coupling between allylboronic acid esters and allylic carbonates in a process catalyzed by a Pd-chiral bisphosphine complex.[5] Additionally, a Cu-chiral phosphoramidite catalyst system for the preparation of branched chiral 1,5-dienes from allylic bromides and allyl Grignard reagents was disclosed by Feringa and co-workers.[4]

In recent years, there has been increasing interest in iridium-catalyzed allylic substitutions, as these are characterized by the preferred formation of branched products.[6] Hence, iridium-catalyzed allylations have emerged as a versatile tactic for the synthesis of chiral building blocks.[7] Recent applications underscore new strategic opportunities for target-oriented synthesis.[8–10] To this end, our group has been particularly interested in an approach that involves direct displacement of unactivated allylic alcohols in a highly step- and atom-economic manner.[11] A number of nucleophiles have been successfully employed for the highly regio- and stereoselective formation of carbon–heteroatom and carbon–carbon bonds.[8] As a part of ongoing efforts, we have recently reported a direct allyl–alkene coupling, wherein simple alkenes were efficiently coupled with an electrophilic allyl–iridium intermediate to deliver chiral 1,5-dienes.[9] This unique method circumvents the use of allyl–metal/metalloid reagents, rendering the reaction highly functional-group-tolerant with water as the only coproduct. However, the scope of the nucleophile in the reaction was restricted to 1,1-disubstituted olefins. Additionally, for certain olefin nucleophilic partners, mixtures of regioisomeric products were observed. Accordingly, this study was initiated with the aim of identifying alternative mild allylic nucleophiles that would significantly expand the range of accessible chiral 1,5-dienes.

Initial screening experiments revealed allylsilanes as promising nucleophiles. Thus, we were pleased to find that the test substrate 2-naphthylvinyl carbinol **1a** underwent a smooth reaction with **2a** in the presence of the chiral Ir/(***R***)-**L** catalyst and diphenyl phosphate in 1,2-dichloroethane to give diene **3a** in 70% yield and 99% *ee* with a branched (**3a**) to linear (**3a′**) ratio of 12:1 (Table 1, entry 2). It is noteworthy that the use of dialkylphosphates, which were efficient

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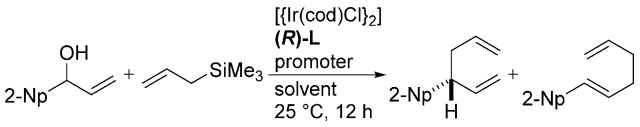
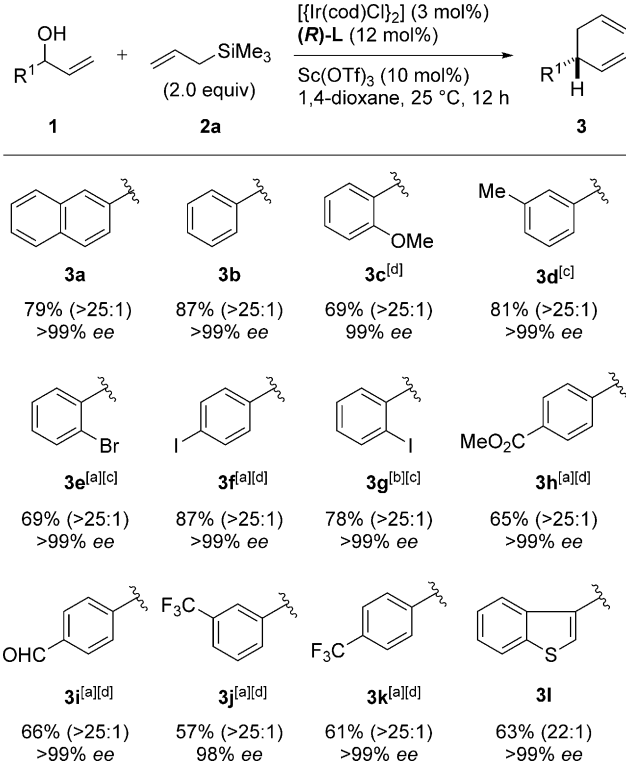
Table 1: Selected optimization studies for the allyl–allylsilane cross-coupling.[a]



1a **2a** **3a** **3a'**

Entry	Cat. [mol%]	**2a** [equiv]	Promoter (mol%)	Solvent	Yield [%][b]	B:L[c]	*ee* [%][d]
1	4	5	$(MeO)_2PO_2H$ (50)	DCE	< 5	–	–
2	4	5	$(PhO)_2PO_2H$ (50)	DCE	70	12:1	99
3	4	5	CF_3CO_2H (50)	DCE	69	6:1	98
4	4	5	CSA (50)	DCE	44	3:1	96
5	4	5	$(PhSO_2)_2NH$ (50)	DCE	60	> 25:1	99
6	4	5	$Zn(OTf)_2$ (20)	DCE	39	15:1	94
7	4	5	$Sc(OTf)_3$ (5)	DCE	79	11:1	99
8	4	2	$Sc(OTf)_3$ (5)	DCE	78	18:1	> 99
9	4	2	$Sc(OTf)_3$ (5)	dioxane	82	> 25:1	> 99
10	4	2	$Sc(OTf)_3$ (10)	dioxane	85	> 25:1	> 99
11	3	2	$Sc(OTf)_3$ (10)	dioxane	84	> 25:1	> 99

[a] Reaction conditions: **1a** (0.25 mmol, 1.0 equiv), $[\{Ir(cod)Cl\}_2]$, [Ir]/(***R***)-**L** = 1:2, solvent (0.5 mL), 25 °C, 12 h. [b] Determined by ^{1}H NMR analysis versus an internal standard (1,4-dinitrobenzene). [c] Ratio of branched (**3a**) to linear (**3a′**) products as determined by analysis of ^{1}H NMR spectra. [d] Determined by supercritical fluid chromatography (SFC) on a chiral stationary phase. Absolute configuration assigned by comparison with known compounds. 2-Np = 2-naphthyl; DCE = 1,2-dichloroethane; CSA = (±)-camphorsulfonic acid.



3a 79% (>25:1), >99% *ee*
3b 87% (>25:1), >99% *ee*
3c[d] 69% (>25:1), 99% *ee*
3d[c] 81% (>25:1), >99% *ee*
3e[a][c] 69% (>25:1), >99% *ee*
3f[a][d] 87% (>25:1), >99% *ee*
3g[b][c] 78% (>25:1), >99% *ee*
3h[a][d] 65% (>25:1), >99% *ee*
3i[a][d] 66% (>25:1), >99% *ee*
3j[a][d] 57% (>25:1), 98% *ee*
3k[a][d] 61% (>25:1), >99% *ee*
3l 63% (22:1), >99% *ee*

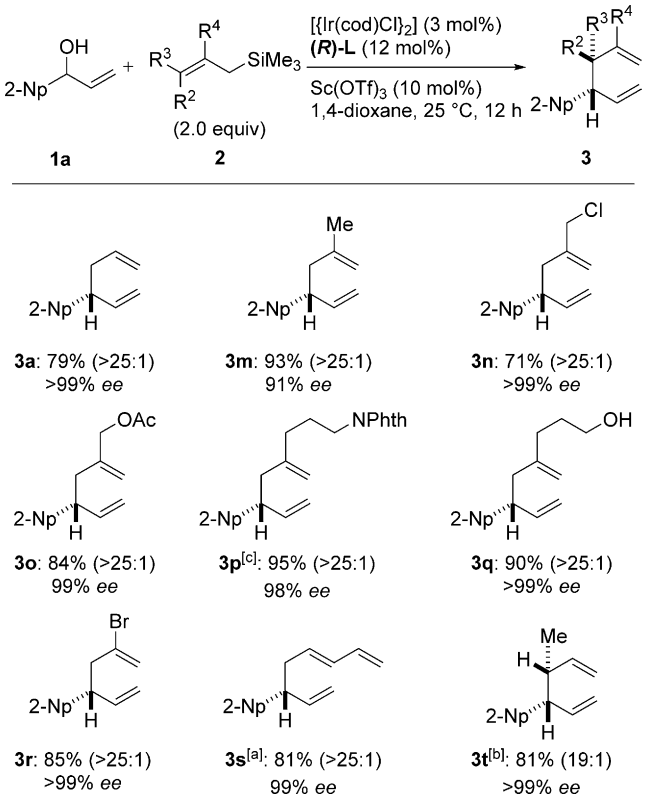
Scheme 2. Substrate scope of the enantioselective allyl–allylsilane cross-coupling. Unless otherwise noted, all reactions were performed on a 0.25 mmol scale under the standard conditions (see Table 1, entry 11). Yield of the isolated product after purification by chromatography on silica gel. Regioselectivity (reported in brackets) determined by analysis of ^{1}H NMR spectra. Enantiomeric excess determined by SFC on a chiral stationary phase. [a] 24 h reaction. [b] 72 h reaction. [c] Reaction conducted on gram-scale. [d] SFC analysis performed after derivatization.

promoters in the α-allylation of aldehydes,[8f] resulted in minimal conversion. We then turned our attention to the evaluation of the reaction parameters (see the Supporting Information for full details, Tables S1–S7).

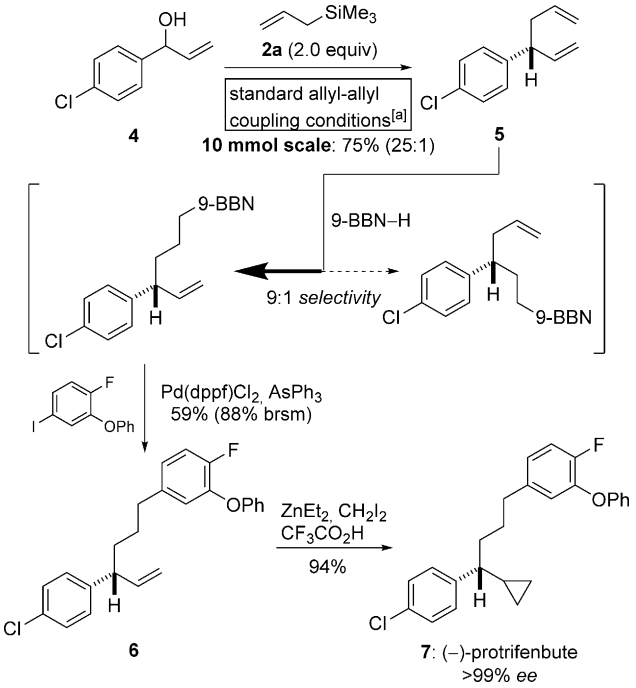
In contrast to our earlier work, in which Brønsted acids were optimal promoters for the activation of allylic alcohols in intermolecular allylic substitution reactions, a screening of various protic acids failed to lead to improved outcomes (Table 1, entries 3–5). Consequently, we examined the use of Lewis acids as cocatalysts. $Zn(OTf)_2$, which we had successfully employed in iridium-catalyzed intramolecular cyclizations,[10] was effective in delivering the product with good regio- and enantioselectivity, albeit with low conversion (Table 1, entry 6). The use of 5 mol% of $Sc(OTf)_3$ as promoter led to complete conversion, leading to product with high stereoselectivity and comparable regioselectivity (Table 1, entries 7 and 8). A series of experiments with various solvents revealed 1,4-dioxane as optimal (Table 1, entry 9). When the loading of $Sc(OTf)_3$ was increased to 10 mol%, some improvement in yield (Table 1, entry 10) was observed as well as a significantly increased substrate scope, as described below. Catalyst loading could be reduced to 3 mol% without noticeable deterioration in yield or selectivity (Table 1, entry 11).

Having identified the optimal conditions, the scope of allylic alcohols in the enantioselective allyl–allylsilane cross-coupling was evaluated using allyltrimethylsilane **2a** as summarized in Scheme 2. 2-naphthyl- (**3a**) and phenyl- (**3b**) vinyl carbinols underwent the reaction giving excellent isolated yields and enantioselectivity. Substrates with alkoxy (**3c**) and alkyl (**3d**) substituents proved to be good substrates for this process. A number of halogenated (**3e**–**3g**) aromatic substrates furnished the corresponding 1,5-dienes in good yields, > 25:1 regioisomeric ratio, and > 99% *ee*. Substrates incorporating electrophilic functional groups, such as ester (**3h**) and aldehyde (**3i**), could be employed. Other electronically demanding *m*- and *p*-CF_3 substitutions on the aromatic ring (**3j** and **3k**) were also tolerated. As can be expected, less reactive substrates such as halogen-, carbonyl-, and trifluoromethyl-substituted substrates required longer reaction times to achieve high conversion. The use of heteroaromatic substrates is showcased in the successful conversion of benzothiophenyl allylic alcohol **3l** to the corresponding diene. It warrants a mention that scalability and robustness of the cross-coupling is validated through gram-scale reactions with selected substrates (**3d**, **3e**, and **3g**). Aliphatic allylic alcohols did not undergo the described allyl–allylsilane cross-coupling.

We next explored the scope of the reaction with respect to the allylsilane component using **1a** as the electrophilic counterpart (Scheme 3). Substitutions at the internal carbon



Scheme 3. Scope of the enantioselective allyl–allylsilane cross-coupling with respect to allylsilanes. All reactions performed on a 0.25 mmol scale under the standard conditions (see Table 1, entry 8). The yield reported corresponds to isolated product after purification by chromatography on silica gel. The regioselectivity (reported in brackets) was determined by analysis of ^{1}H NMR spectra. The enantiomeric excess was determined by SFC on a chiral stationary phase. [a] 1-trimethylsilyl-2,4-pentadiene (5:1 = *E*:*Z*) was used as the nucleophile to give **3s** (16:1 = *E*:*Z*). [b] 4:1 diastereomeric ratio. The relative configuration was determined by X-ray crystallographic analysis. [c] SFC analysis performed after derivatization. NPhth = phthalimide.



Scheme 4. Enantioselective synthesis of (−)-protrifenbute (**7**). 9-BBN-H = 9-borabicyclo[3.3.1]nonane; dppf = 1,1′-bis(diphenylphosphino)ferrocene; brsm = based on recovered starting material. [a] 24 h reaction.

atom of the allylsilane were well tolerated. Corresponding products using methyl (**3m**), chloromethyl (**3n**), and acetoxymethyl (**3o**) substituents on the allylsilane were obtained in superb yields and excellent enantioselectivity. It is worth noting that 2-(chloromethyl)allyl-trimethylsilane (**2n**) and 2-(acetoxymethyl)allyl-trimethylsilane (**2o**), which are otherwise employed as trimethylenemethane (TMM) precursors in Pd-catalyzed allylic substitution reactions,[12] only behaved as allylnucleophiles under our conditions. Allylsilanes containing other functional groups such as protected amine (**3p**) and even free alcohol (**3q**) were shown to be good nucleophiles. Remarkably, the competitive allylic etherification in the presence of the hydroxy group was not observed. 2-Halo-allylsilane **3r** underwent the expected cross-coupling, and triene **3s** was obtained from the reaction when 1-trimethylsilyl-2,4-pentadiene was used. The reaction occurred exclusively at the terminal carbon of the conjugated allylsilane. Finally, when crotylsilane **3t** was used in the reaction, the product incorporating two vicinal stereogenic centers was obtained, displaying good diastereoselectivity and excellent enantiocontrol.[13]

The utility of this method is illustrated through a concise enantioselective synthesis of the pyrethroid insecticide protrifenbute (Scheme 4). Developed by the FMC Corporation, protrifenbute exhibits foliar larvicidal activity by targeting the ryanodine receptor and thus disrupting the Ca^{2+} balance.[14] When *p*-chlorophenylvinyl carbinol (**4**) was subjected to the allyl–allylsilane cross-coupling conditions described in this study, diene **5** was furnished in 75% yield and high regioselectivity (25:1 branched/linear). The reaction was also conducted on a larger scale (1.7 g, 10 mmol of **4**) with equally excellent results, further exemplifying the practical nature of the process.

If they are to be considered versatile building blocks, 1,5-dienes, such as **5**, present a challenge in chemoselectivity, as the selective manipulation of the alkenes would need to be addressed in any synthetic elaboration sequence. We were pleased to observe selective hydroboration of the homoallylic olefin in **5** and subsequent Suzuki cross-coupling to give **6**; analysis of the reaction mixture by ^{1}H NMR spectroscopy revealed that olefin hydroboration had proceeded in 9:1 chemoselectivity. Finally, treatment of **6** with zinc carbenoid[15] completed the synthesis of **7** in 94% yield and > 99% *ee*.

In summary, we have disclosed an enantioselective allyl–allylsilane cross-coupling reaction between unactivated racemic secondary allylic alcohols and allylsilanes to provide optically active 1,5-dienes. Salient features of the method are the observed excellent regio- and enantioselectivity, high functional group tolerance, and an operationally convenient protocol, using readily available and bench-stable allylsilanes as nucleophiles. Crotylsilane was also successfully employed, highlighting the potential of preparing products that incor-

porate two vicinal stereogenic centers with good diastereoselectivity. The practicality of the transformation was further demonstrated with gram-scale reactions with several substrates. Finally, we have demonstrated the use of the described cross-coupling reaction in the concise enantioselective preparation of the insecticide protrifenbute.

Experimental Section

General procedure: [{Ir(cod)Cl}$_2$] (5.1 mg, 7.5 μmol, 3 mol%) and phosphoramidite ligand **(*R*)-L** (15.2 mg, 30.0 μmol, 12 mol%) were dissolved in 1,4-dioxane (0.5 mL) in a screw-capped glass vial and vigorously stirred for 15 min under an N_2 atmosphere. To the resulting dark red solution, allylic alcohol **1** (0.25 mmol, 1.0 equiv), allyltrimethylsilane **2** (0.5 mmol, 2.0 equiv), and $Sc(OTf)_3$ (12.3 mg, 0.1 equiv) were sequentially added. The reaction vessel was briefly flushed with N_2, and the orange mixture was stirred at 25°C for 12 h. Upon complete consumption of the starting material, the reaction was filtered through a short pad of silica gel with CH_2Cl_2, concentrated, and then subjected to flash chromatography to afford the product.

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