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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
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Iridium-Catalyzed Enantioselective Allylic Vinylation

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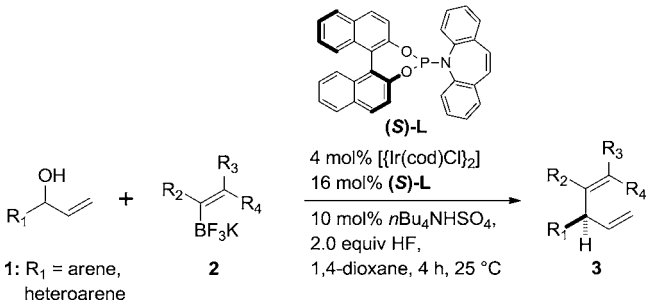
Supporting Information

ABSTRACT: The first example of Ir-catalyzed asymmetric substitution reaction with vinyl trifluoroborates is described. The direct reaction between branched, racemic allylic alcohols and potassium alkenyltrifluoroborates proceeded with high site selectivity and excellent enantioselectivity (up to 99%) mediated by an Ir-(P,olefin) complex. This method allows rapid access to various 1,4-dienes or trienes including the biologically active natural products (−)-nyasol and (−)-hinokiresinol.

Iridium-catalyzed allylic substitution constitutes a powerful method for the enantioselective formation of both carbon−heteroatom and carbon−carbon bonds.[1−3] Despite extensive studies and noteworthy advances in this field, several challenges remain to be addressed. Among these is the development of a method for enantioselective allylic vinylation. Herein we describe our efforts that led to the discovery of a highly enantioselective allylic substitution of unactivated allylic alcohols with potassium alkenyltrifluoroborates (Scheme 1).

Scheme 1. Ir-Catalyzed Enantioselective Vinylation



The resulting process relies on an operationally simple protocol that can be used to construct various dienes and polyenes with control over olefin geometry. Furthermore, the utility of this transformation is demonstrated by two-step enantioselective syntheses of norlignans (−)-nyasol and (−)-hinokiresinol, broad spectrum inhibitors of eicosanoid and nitric oxide production.

Despite significant developments in the field of asymmetric transition metal-catalyzed allylic substitution,[4] there have been only a few reports on vinylation. The recent pioneering work from the Hoveyda and Hayashi groups showcased the use of vinylaluminum and vinylboronic acid ester reagents in the displacement reaction of allylic phosphates in a Cu-catalyzed enantioselective substitution process.[5] We previously reported that direct allylic substitution of branched, racemic allylic alcohols with a variety of heteronucleophiles (amines, alcohols, thiols) proceeded with excellent branched-to-linear ratio and enantioselectivity in the presence of catalytic amounts of an Ir-(P,olefin) complex and Brønsted acids as activators.[6] Because these transformations involve direct displacement of the allylic alcohol, they display a high degree of atom economy.[7] Consequently, we have been interested in extending the scope of these Ir-catalyzed processes.

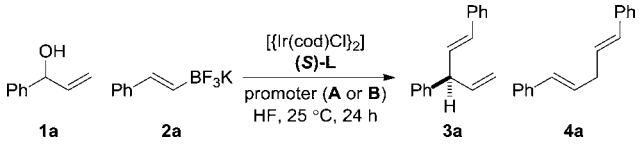
At the outset of our work, we focused on the identification of a suitable vinylic nucleophile that would readily participate in transfer to a putative allyl−Ir intermediate generated from the starting allylic alcohol. Considering that we have demonstrated that Brønsted acids can effect direct activation of allylic alcohols in Ir-catalyzed allylation reactions, we began our investigation by screening vinylboron reagents.[8] A screen of various styrylboron analogues with allylic alcohol **1a** under a variety of reaction conditions led to the identification of conditions wherein vinylated product **3a** is formed when potassium triflouroborate **2a** was used in combination with hydrofluoric acid (Table 1, entry 1; for full screening details see Supporting Information).[9] Thus, the best early result was obtained in the presence of di-*n*-butylphoshoric acid as promoter in acetone, delivering branched vinylated product **3a** in 24% yield and 99% ee with a branched (**3a**) to linear (**4a**) ratio greater than 50:1. Because of the low yields observed in the initial experiments, which we attributed to the noticeably poor solubility of potassium trifluoroborate **2a** in organic solvents, we prepared the corresponding tetra-*n*-butylammonium trifluoroborate analogue of **2a**.[10] This modification proved beneficial, resulting in an homogeneous reaction mixture and leading to a pronounced increase in yield (40% and 98% ee, Table 1, entry 2).

These observations prompted us to examine the use of potassium trifluoroborate **2a** in the presence of a phase transfer catalyst.[11] Specifically, we hypothesized that $n\mathrm{Bu_4NHSO_4}$ could play a dual role: first, as the phase transfer catalyst for potassium alkenyltrifluoroborates; and second, as the Brønsted acid activator for the allylic alcohols, since the pK_a of HSO_4^- is comparable to that of di-*n*-butylphoshoric acid (1.99 vs 1.72). Indeed, exposure of allylic alcohol **1a** to potassium styryltrifluoroborate **2a** in the presence of 50 mol % of $n\mathrm{Bu_4NHSO_4}$ led to formation of **2a** in 53% yield and 98% ee after 24 h at ambient temperature (Table 1, entry 3). The choice of solvent markedly influenced both yield and site selectivity. The use of MeCN, DME, or nitromethane as a solvent instead of acetone resulted in poor yields (31%, 22% and 40%, respectively) and lower branched/linear ratios (Table 1, entries 4−6). However,

Received: November 21, 2012
Published: December 21, 2012

   dx.doi.org/10.1021/ja311422z | J. Am. Chem. Soc. 2013, 135, 994−997

Table 1. Optimization of Ir-Catalyzed Allylic Vinylation[a]



entry	cat. (mol %)	2a (equiv)	promoter (equiv)[b]	solvent	yield (%)[c]	B:L[d]	ee (%)[e]
1	2	1.0	A (0.5)	acetone	24	>50:1	99
2	2	1.0[f]	A (0.5)	acetone	40	>50:1	98
3	2	1.0	B (0.5)	acetone	53	>50:1	98
4	2	1.0	B (0.5)	MeCN	31	0.7:1	97
5	2	1.0	B (0.5)	DME	22	20:1	97
6	2	1.0	B (0.5)	$MeNO_2$	40	0.6:1	97
7	2	1.0	B (0.5)	dioxane	60	>50:1	98
8	2	1.0	B (0.1)	dioxane	57	>50:1	99
9	3	2.0	B (0.1)	dioxane	75	>50:1	99
10	4	2.0	B (0.1)	dioxane	89	>50:1	99

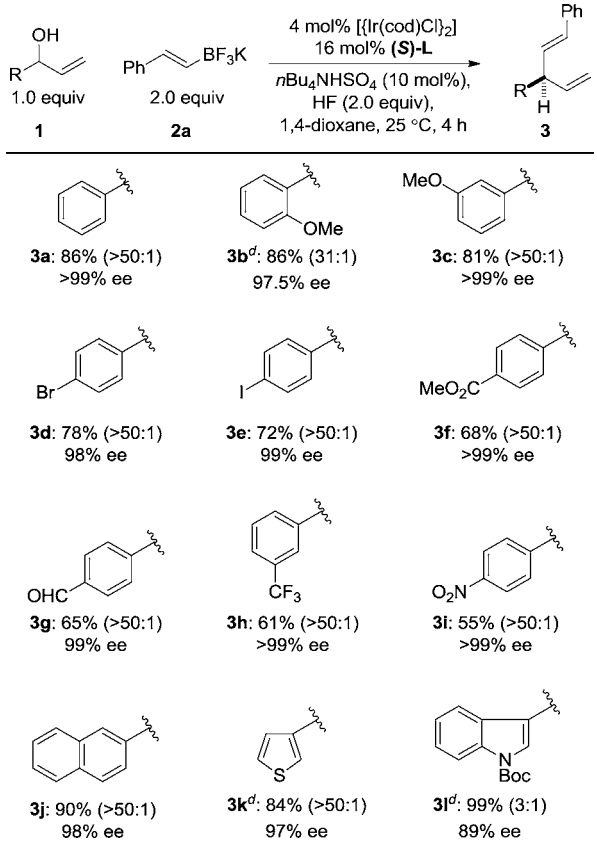
[a]Reaction conditions: **1a** (0.25 mmol, 1.0 equiv), [{Ir(cod)Cl}$_2$], [Ir]/(*S*)-**L** = 1:2, HF (50% aq, equimolar to **2a**), solvent (0.5 mL), 25 °C, 24 h. [b]A: di-*n*-butylphosphoric acid, B: nBu_4NHSO_4. [c]Determined by ^{1}H NMR integration relative to the internal standard. [d]Ratio of branched (**3a**) to linear (**4a**) determined by ^{1}H NMR integration. [e]Determined by SFC on a chiral stationary phase, absolute stereochemistry was assigned by comparison with known compound. [f]Tetra-*n*-butylammonium styryltrifluoroborate was used instead of **2a**.

a slightly better result was obtained in the case of 1,4-dioxane, which delivered the product in 60% yield and 98% ee (Table 1, entry 7). Importantly, reducing the amount of nBu_4NHSO_4 from 50 to 10 mol % had little effect on the reaction outcome (Table 1, entry 8). Additionally, we found that the reaction proceeded much more efficiently when the amounts of potassium styryltrifluoroborate **2a** and the Ir catalyst were increased (Table 1, entries 8–10). Thus, under optimized conditions, the reaction of allylic alcohol **1a** with 2.0 equiv of **2a** and aqueous HF afforded vinylated product **3a** in 89% yield and 99% ee (Table 1, entry 10). Finally, we noted that under these conditions the reaction was complete in 4 h.[12]

Having identified optimized reaction conditions for the enantioselective vinylation of allylic alcohols, we explored the substrate scope of this process by using potassium styryltrifluoroborate **2a**, as summarized in Table 2. Thus, a number of alkoxy-substituted (**3b** and **3c**) and halogenated (**3d** and **3e**) aromatics all furnished vinylated products in good yields and excellent enantioselectivities. Electrophilic functional groups, such as ester (**3f**) and aldehyde (**3g**), could be incorporated into the products without greatly affecting the overall efficiency of the allylic vinylation process. The tolerance of this reaction toward more electronically demanding substrates is demonstrated in the successful conversion of the *p*-NO_2 or *m*-CF_3-substituted aryl allylic alcohols (**3h** and **3i**), although a slight decrease in yield was observed. Furthermore, other aromatic and heteroaromatic systems could be successfully employed, as showcased with the example of naphthalene, thiophene and indole (**3j**–**3l**). Importantly, for vinylation of highly reactive allylic alcohols (**2b**, **2k**, **2l**), using 1.1 equiv of **2a** and HF was sufficient to achieve the full conversion. At the current level of development aliphatic allylic alcohols are not substrates for the substitution reaction of vinylboron reagents we describe.[13]

We next investigated the scope of potassium alkenyltrifluoroborates by using allylic alcohol **1a**, as depicted in Table 3. In addition to the standard styrylation (**3a**), the corresponding

Table 2. Substrate Scope of the Enantioselective Allylic Vinylation[a,b,c]



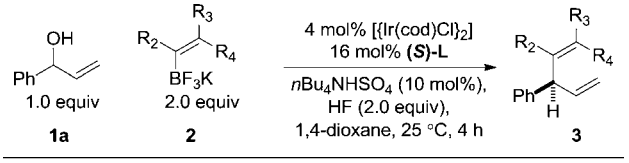
[a]Standard procedure: substrate **1** (0.25 mmol, 1.0 equiv), potassium styryltrifluoroborate **2a** (0.50 mmol, 2.0 equiv), [{Ir(cod)Cl}$_2$] (4 mol %), (*S*)-**L** (16 mol %), nBu_4NHSO_4 (10 mol %), HF (50% aq, 2.0 equiv), 1,4-dioxane (0.5 mL), 25 °C, 4 h. [b]Isolated yields after purification by flash chromatography. [c]Enantiomeric excess determined by SFC analysis on a chiral stationary phase, absolute stereochemistry was assigned by comparison with known compound. Ratio of branched to linear regioisomers in brackets. [d]1.1 equiv of **2a** and HF used.

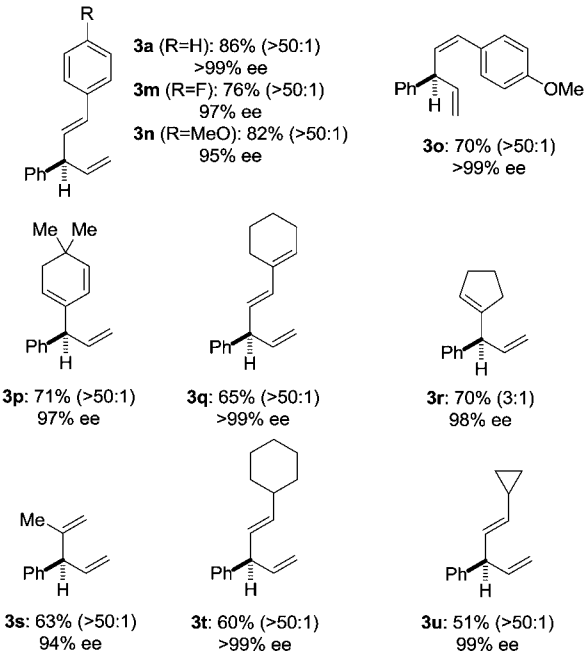
para-fluoro and *para*-methoxy substituted trifluoroborates delivered styrylated products **3m**–**3o** in comparable yields and selectivities. It is important to note that under the reaction conditions described, no potentially competitive olefin isomerization processes were observed, especially in the case of **3o**, where the corresponding vinylation proceeded with exclusive *cis* stereoselectivity. Gratifyingly, the Ir-catalyzed vinylation protocol is also suitable for enantioselective introduction of conjugated dienes, efficiently delivering polyene products (**3p** and **3q**). Furthermore, vinylation using a cyclic vinyltrifluoroborate could readily be achieved (**3r**), albeit with reduced site selectivity (3:1). Finally, the reaction proceeded as well with monosubstituted vinyltrifluoroborates, giving vinylated products (**3s**–**3u**) in good yields and excellent selectivities.

To further highlight the synthetic utility of the method, we applied this new catalytic vinylation reaction to the enantioselective synthesis of (−)-nyasol (**5**)[14] and (−)-hinokiresinol (**6**),[15] biologically potent inhibitors of eicosanoid and nitric oxide production. As illustrated in Scheme 2, exposure of allylic alcohol **1m** to either *cis*- or *trans*-*para*-methoxystyryltrifluoroborate (**2o** or **2n**, 1.1 equiv) under optimized vinylation conditions, followed by deprotection of the methoxy groups

dx.doi.org/10.1021/ja311422z | J. Am. Chem. Soc. 2013, 135, 994–997

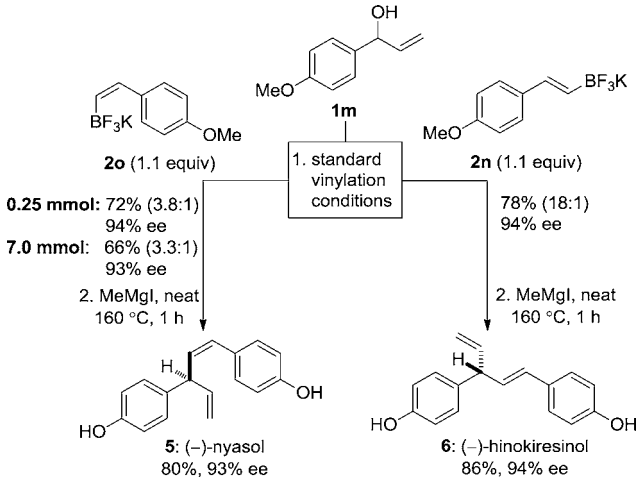
Table 3. Potassium Alkenyltrifluoroborates Scope of the Enantioselective Allylic Vinylation[a,b,c]





[a]All reactions were carried out on 0.25 mmol scale under the standard conditions (see Table 1 for details). [b]Isolated yields after purification by flash chromatography. [c]Enantiomeric excess determined by SFC analysis on a chiral stationary phase.

Scheme 2. Enantioselective Synthesis of (−)-Nyasol and (−)-Hinokiresinol



with MeMgI, rapidly furnished both natural products. Additionally, the enantioselective vinylation reaction in the case of (−)-nyasol (**5**) was also conducted on a larger scale (1.15 g, 7.0 mmol of **1m**) by using a reduced amount of catalyst (3 mol % of [{Ir(cod)Cl}$_2$]), technical grade solvent and open to air. We were pleased to observe only a slight decrease in yield, rendering this process practical and robust on a larger scale.

In summary, we have developed the first Ir-catalyzed enantioselective allylic substitution of racemic secondary alcohols, using a readily accessible potassium alkenyltrifluoroborates, to give optically active vinylated products. The method delivers products via user-friendly, scalable, open-flask conditions in high yields and excellent regio- and stereoselectivities. The synthetic value of this transformation has been demonstrated through concise and divergent syntheses of biologically active (−)-nyasol and (−)-hinokiresinol. It is noteworthy that vinylation represents a very atom-economical method that, unlike common alternatives, does not require any separate prior activation of allylic alcohols. Further studies regarding the development of related transformations and applications of our new methodology are ongoing and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for all reactions and products, including ^{1}H- and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This research was supported by the ETH Zürich and the Swiss National Science Foundation.

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