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Synthetic Methods

Cross-Metathesis/Isomerization/Allylboration Sequence for a Diastereoselective Synthesis of *Anti*-Homoallylic Alcohols from Allylbenzene Derivatives and Aldehydes

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Abstract: We describe a highly diastereoselective approach to *anti*-homoallylic alcohols from allylbenzene derivatives and aldehydes. The strategy is based on a cross-metathesis/isomerization/allylboration sequence catalyzed successively by ruthenium and iridium. This methodology provides another way to access this class of compounds, which leads to the preparation of hitherto-unknown homoallylic alcohols without the requirement to control the stereochemistry of the 1-alkenyl boronate intermediates. Our study towards an enantioselective version of this sequential reaction is also reported.

Introduction

Allylboration of aldehydes is probably one of the most popular and efficient methods for the preparation of functionalized homoallylic alcohols.[1] One of the main reasons for this success, besides simple implementation, is the predictable diastereocontrol of the allylation products via a six-membered transition state depending upon the stereochemistry of the starting allylboron reagent.[2] Numerous preparative methods of this structural class of reactants have been reported in the literature, most often with strict control of the geometry of the double bond to secure the construction of adjacent chiral centers in a highly diastereoselective manner.[3] However, in some cases, the low stability towards hydrolysis makes purification difficult and the necessity arises to devise reactions by simplifying experimental implementation and improving the resource efficiency (time, cost, etc.),[4] therefore other strategies have emerged to generate γ-substituted allylboron reagents in situ (with subsequent addition to carbonyl compounds).

For instance, with acyclic derivatives the 1,4-addition of an organometallic reagent to an alkenyl boronate with a γ-acetal group followed by an allylboration reaction stereoselectively furnished *anti*-diol derivatives.[5] Aggarwal and co-workers have developed a protocol that combines lithiated carbamates, vinyl boronic esters, and aldehydes to provide homoallylic alcohols with generally high diastereomeric and enantiomeric ratios.[6] The "one-pot" procedure can also be initiated by hydroboration of allenes with nonracemic Soderquist borane 10-TMS-9-borabicyclo[3.3.2]decane ([10-TMS-9-BBD-H]). The *Z* γ-substituted allylboranes generated reacted with aldehydes to give homoallylic alcohols with a modest-to-high diastereoselectivity in favor of the *syn* product.[7] A three-component procedure based on the hydroboration of propargyl bromide as the first step was also reported to give *anti*-homoallylic alcohols.[8] The cross-metathesis reaction of hindered olefins with pinacol allyl boronate followed by a subsequent allylboration led to the *anti* products with high selectivity.[9] A catalytic borylation–allylation approach with bis(pinacolato)diboron (B_2pin_2) as the boronate source has also been developed with different substrates.[10] For example, a "one-pot" procedure from *E*-allylic alcohols catalyzed by a palladium pincer complex was described to produce homoallylic alcohols with high *anti* selectivity.[11]

Among the catalytic reactions, which can be useful to generate allylboronates as transient intermediates, the double-bond isomerization of 1-alkenyl boronates has drawn the attention of several groups. 3-Alkoxy-1-alkenyl boronates were the first substrates studied with success, probably due to the presence of the oxygen-containing functionality.[12] However, the failed attempt of an intramolecular isomerization–allylboration sequence with various transition metals was described, which compromised the idea to develop a sequential reaction from this kind of alkenyl boronate.[13]

Since then, very few works have been published that describe the generalization of this reaction for other alkenyl boronates and integrate it into a sequential reaction for the synthesis of functionalized homoallylic alcohols. It was shown that a cationic rhodium(I) complex effectively catalyzed the olefin migration of 1-alkenyl boronates in 1,2-dichloroethane at reflux in the presence of aldehydes to give the corresponding allylation products.[14] However, the observed diastereoselectivity in favor of the *anti* product depends on the double-bond geometry of the starting materials. During the preparation of this manuscript, the same group described a new procedure that used a cationic iridium(I) complex under milder conditions

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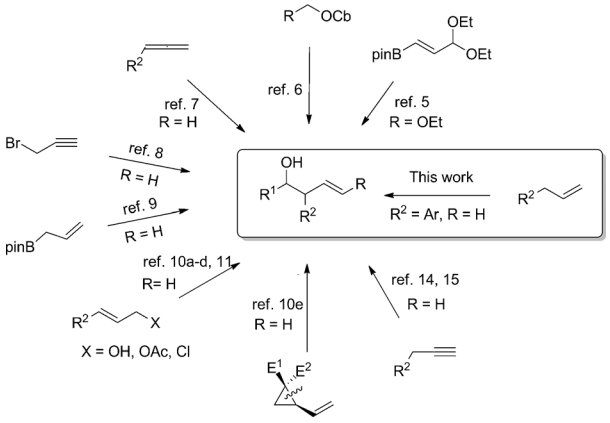
for the synthesis of *anti*-homoallylic alcohols.[15] In all cases, the stereodefined 1-alkenyl boronates were prepared by conventional hydroboration of the corresponding terminal alkynes.[14–16]

Taking into account that the accessibility of starting materials is an important consideration for the development of useful organic reactions, we envisaged the preparation of novel homoallylic alcohols from terminal alkenes and aldehydes based on a cross-metathesis/isomerization/allylboration sequence (Scheme 1). Moreover, due to the lower reactivity of



Scheme 1. Sequential reactions, including an allylboration step, for the preparation of acyclic homoallylic alcohols.

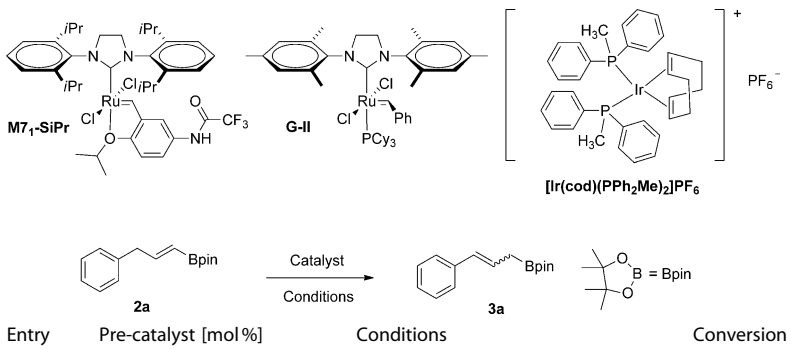
alkenes relative to terminal alkynes, this strategy should be more appropriate for the multistep synthesis of multifunctional products. Recently, we described a simple cross-metathesis procedure for the synthesis of 3-aryl-1-propenyl boronates, which are potentially good substrates for an isomerization reaction given their structural characteristics.[17] In this paper, we report our efforts devoted to the implementation of a three-component reaction of functionalized homoallylic alcohols from allyl benzene derivatives **1**, pinacol vinyl boronic ester **4**, and aldehydes. An activated iridium catalyst **[IrH$_2$(thf)$_2$(PPh$_2$Me)$_2$]PF$_6$** ([Ir])[18] was used for the olefin transposition reaction, which provides the allylboration products with high diastereoselectivity after the reaction with aldehydes. The selectivity is independent of the stereochemistry of the 1-alkenyl boronate precursors obtained by the cross-metathesis reaction. An asymmetric version of this new sequence that used a chiral Brønsted acid catalysis system was also explored with interesting results.

Results and Discussion

At the outset of the investigation, we initially compared the catalytic activity of different pre-catalysts for the isomerization of model substrate (*E*)-4,4,5,5-tetramethyl-2-(3-phenyl-propenyl)-[1,3,2]dioxaborolane (**2a**; Table 1). Compound **2a** can be easily prepared by esterification of the corresponding commercially available boronic acid.[14] Among the ruthenium pre-catalysts selected for this study, **M7$_1$-SIPr** was chosen for its ability to promote alkene isomerization in a 1,4-benzoquinone-free process.[19] With conventional heating, the desired product **3a** was only obtained when an excess of TMS vinyl ether (TMSO-ethene) was used to generate the likely ruthenium–hydride complex (Table 1, entries 1 and 2).[20] Although the stereoselectivity is completely in favor of the *E* isomer in MeOH under microwave irradiation (MWI), the conversion still remained modest (Table 1, entry 3). No improvement was obtained by changing the ruthenium pre-catalyst (**G-II** in place of **M7$_1$-SIPr**), but a loss of stereoselectivity was observed (Table 1, entry 4). The use of an iridium-mediated system increased the formation of the isomerized product. Catalyst **[Ir(cod)(PPh$_2$Me)$_2$]PF$_6$** (cod = 1,5-cyclooctadiene) activated by H_2 in THF gave superior results relative to the ruthenium metathesis pre-catalysts attempted, and the double-bond migration took place under milder conditions with high stereoselectivity (Table 1, entry 5).[21]

This catalytic procedure has proven compatible with the presence of an aldehyde in the reaction medium, which allows "one-pot" formation of the desired homoallylic alcohol from the alkenyl boronate **2a** (Scheme 2). Addition of 4-nitrobenzaldehyde (1 equiv) to **2a** (1 equiv) gave compound **5aa** (after purification) with an unoptimized yield of 60%. Only the *anti* diastereomer was observed, which confirmed the high stereoselectivity of the isomerization step in favor of the *E* isomer.[22] We were surprised that this high diastereoselectivity was main-

Table 1. Optimization of the isomerization methodology with different pre-catalysts.[a]



Entry	Pre-catalyst [mol%]	Conditions	Conversion [%][b]	*E*/*Z* **3a**[c]
1	**M7$_1$-SIPr** (10)	MeOH, reflux, 20 h	–	–
2	**M7$_1$-SIPr** (10)	TMSO-ethene CH_2Cl_2, reflux, 20 h	28	90:10
3	**M7$_1$-SIPr** (10)	MeOH, MWI, 70 °C, 80 W, 45 min.[d]	40	100:0
4	**G-II** (10)	MeOH, MWI, 70 °C, 80 W, 45 min.[d]	30	90:10
5	**[Ir(cod)(PPh$_2$Me)$_2$]PF$_6$** (3)	THF, rt, 2 h[e]	90	100:0

[a] All pre-catalysts were used without further treatment. [b] Conversion based on **2a**. [c] Determined by analysis of the ^{1}H NMR spectra of the product mixtures. [d] Reaction was carried out in the Explorer24 CEM reactor. [e] Hydrogen gas was gently bubbled into a solution of [Ir(cod)(PPh$_2$Me)$_2$]PF$_6$ (3 mol%) in THF (0.15 M) for around 2 min prior the addition of **2a** (0.20 mmol).

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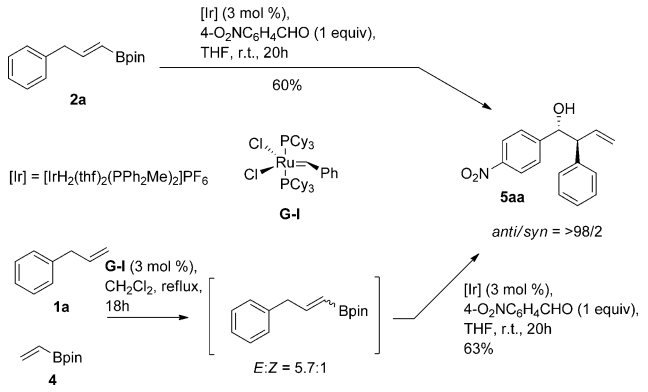
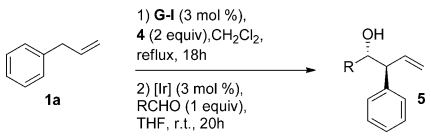
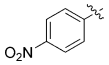
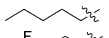
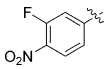


Scheme 2. Synthesis of **5aa** from **1a** by a cross-metathesis/isomerization/allylboration sequence with two different catalysts.

Table 2. Synthesis of *anti*-homoallylic alcohols **5** from allylbenzene **1a**.[a]



Entry	R	Product	Yield [%][b]	*Anti/syn*[c]
1		**5aa**	63	>98:2
2		**5ab**	60	>98:2
3		**5ac**	66	>98:2
4		**5ad**	70	>98:2
5		**5ae**	65	>98:2

[a] Reaction scale: **1a** (0.20 mmol), **4** (2 equiv), **G-I** (3 mol%) in CH_2Cl_2 (0.2 M); then RCHO (1 equiv), $[Ir(cod)(PPh_2Me)_2]PF_6$ (3 mol%) in THF (0.15 M). [b] Isolated yield of pure product **5**. [c] Determined by analysis of the ^1H NMR spectra of the product mixtures prior to purification.

tained when the double-bond geometry of the alkenyl boronate was not controlled. Indeed, the cross-metathesis reaction between allylbenzene **1a** and vinylboronic acid pinacol ester **4** in the presence of **G-I** led to the alkenyl boronate intermediate as a mixture of isomers ($E/Z = 5.7:1$).[17] After filtration of the Grubbs first-generation catalyst, this intermediate was used directly in the iridium-catalyzed isomerization–allylboration sequence to afford only the *anti*-homoallylic alcohol **5aa** in 63% yield.[23] This result provides real added value for the methodology relative to those previously described.[14,15]

The process also works well with aromatic and alkyl aldehydes to afford the *anti* products with yields of 60–70% (Table 2).[24]

We next explored the scope and limitations of this new diastereoselective approach for the synthesis of homoallylic alcohols by variation of the nature of the allylbenzene derivatives **1** (Figure 1).[25] In all cases, compounds **5** were synthesized with high diastereoselectivity (*anti/syn* = >98:2). The variation in the obtained yields can be mainly attributed to the allylboration step because the isomerization reaction is almost complete (>90%) in all cases.[26] The steric hindrance of the generated allylboronates (**5ca** versus **5da**), as well as the electron density on the C=O group of the aldehydes used in the allylation reaction [electron-deficient (**5fa**) versus electron-rich system (**5fb**)] have an influence on the yield of the reaction.

Taking into account that a substantial majority of these compounds are new, we took this opportunity to transform some of them into the corresponding α,β-unsaturated δ-lactones, a scaffold largely present in biologically active natural products.[27] Following a known synthetic approach for this class of compounds,[28] the homoallylic alcohols **5** were converted to acrylate esters **6a–e** with acryloyl chloride in presence of triethylamine. Subsequent ring-closing metathesis catalyzed by **M7$_1$-SIPr** afforded **7a–e** (Scheme 3).

We then turned our attention to an asymmetric version of this methodology. We studied different strategies, for instance the introduction of a chiral diol auxiliary on the boron atom.[29] Whatever chiral boronic ester **2** was used, the stereoselective isomerization reaction ($E/Z = >98:2$) was almost quantitative after 2 h, even with hindered camphor derivative **2d**.[30–31] After

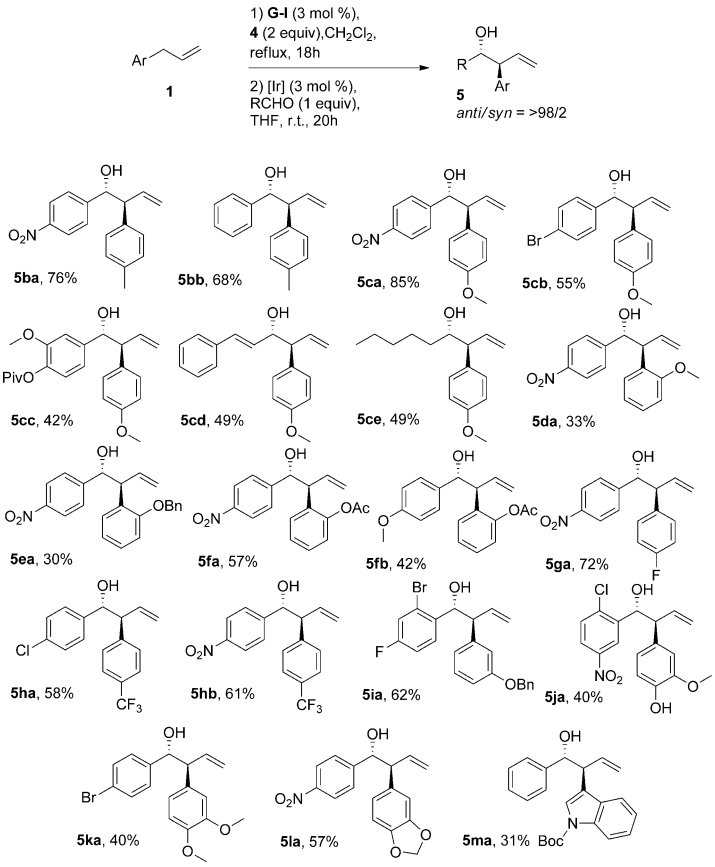


Figure 1. Synthesis of diversely functionalized *anti*-homoallylic alcohols **5**.

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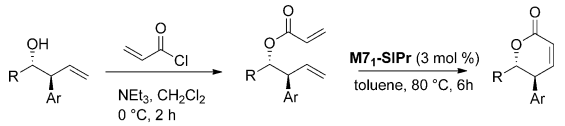
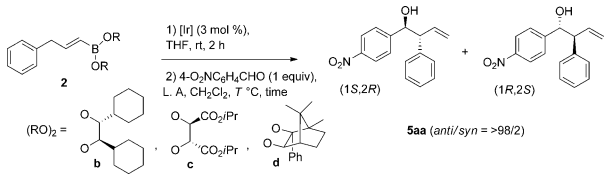


R = Ph, Ar = Ph	**6a**, 81%	**7a**, 93%
R = 4-BrC_6H_4, Ar = Ph	**6b**, 55%	**7b**, 80%
R = 4-$O_2NC_6H_4$, Ar = 4-FPh	**6c**, 76%	**7c**, 81%
R = 4-$O_2NC_6H_4$, Ar = 2-MeOPh	**6d**, 76%	**7d**, 60%
R = 2-Br-4-FC_6H_3, Ar = 3-BnOPh	**6e**, 46%	**7e**, 96%

Scheme 3. Synthesis of α,β-unsaturated δ-lactones from **5**.

evaporation of the solvent, a solution of 4-nitrobenzaldehyde in CH_2Cl_2 was added to the residue under typical conditions (low temperature) described in the literature for such chiral allylboronates.[32] In all cases, the allylated compound **5aa** was obtained with high diastereoselectivity (*anti*/*syn* = >98:2), the best enantiomeric ratio, measured by chiral HPLC, was found for the reaction with (*R*,*R*)-diisopropyl tartrate [(+)-DIPT] as a chiral auxiliary (Table 3, entry 2).[33] A disappointing enantiomeric excess (10% *ee*) was obtained with camphor-derived diol **2d**, by using a scandium-catalyzed protocol that has proven efficiency with crotylboronates (Table 3, entry 3).[34]

Table 3. Chiral allylboronates evaluated for an isomerization–allylboration sequence.[a]

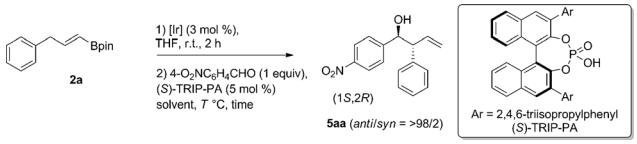


Entry	Boronate	LA[b]	*T* [°C]	Yield [%][c]	e.r. [%][d]	Absolute configuration[e]
1	**2b**	none	−78 to rt	60	50:50	–
2	**2c**	none	−78	54	16:84	(1*S*,2*R*)
3	**2d**	$Sc(OTf)_3$	−78	45	55:45	(1*R*,2*S*)

[a] Reaction scale: **2** (0.20 mmol), $[Ir(cod)(PPh_2Me)_2]PF_6$ (3 mol%) in THF (0.15 M), then aldehyde (1 equiv) in CH_2Cl_2 (0.15 M). [b] Lewis acid (10 mol%). [c] Isolated yield after flash chromatography. [d] Enantiomeric ratio (e.r.) measured by chiral HPLC. [e] Determined by analysis of the ^1H NMR spectra of the corresponding Mosher's esters.

Despite the encouraging result obtained from the tartrate-derived boronic ester, the air/moisture sensitivity of **2c**, as well as the low-temperature allylboration conditions, make development of a practical and general asymmetric cross- metathesis/isomerization/allylboration sequence more difficult. The enantioselective allylboration with the catalytic system described by Jain and Antilla seemed to be an appropriate alternative to alleviate the present drawbacks.[35] Indeed, the binaphthyl-derived chiral phosphoric acid (TRIP-PA; Table 4) promoted the allylboration reaction of pinacol-derived boronate esters with high enantioselectivity under mild conditions (even at room temperature) and has shown compatibility with different transition-metal catalysts in tandem reactions.[15,36]

Table 4. Optimization of an enantioselective isomerization–allylboration sequence.[a]



Entry	Solvent	*T* [°C]	*t* [h]	Yield [%][b]	*ee* [%][c]
1	toluene	0	24	52	74
2	CH_2Cl_2	0	24	43	68
3	toluene	−30	96	45	74

[a] Reaction scale: **2a** (0.20 mmol), $[Ir(cod)(PPh_2Me)_2]PF_6$ (3 mol%) in THF (0.15 M); then RCHO (1 equiv), (*S*)-TRIP-PA (5 mol%) in solvent (0.15 M). [b] Isolated yield after flash chromatography. [c] Determined by integration of the CF_3 signals of the diastereomeric Mosher's esters in the ^{19}F NMR spectra. Absolute configuration determined by analysis of the ^1H NMR spectra of the corresponding Mosher's esters.

In our case, the crude mixture from the iridium-catalyzed isomerization reaction of the *E* alkenyl boronate **2a** was used directly to optimize the allylboration reaction in the presence of (*S*)-TRIP-PA (5 mol%). A solution of 4-nitrobenzaldehyde (1 equiv) and **2a** (1 equiv) was added to the residue under a range of conditions (Table 4). From this small screening, we found that toluene was the most suitable solvent to perform this transformation at 0 °C in acceptable yield (Table 4, entry 1). Despite high diastereoselectivity in favor of the *anti* isomer, the observed enantioselectivity (74% *ee*) was not comparable to that obtained from alkenyl boronates with a terminal alkyl chain (up to 96% *ee*) as observed by Murakami.[15] In support of our result, Murakami and co-workers also described the preparation of homoallylic alcohol **5ab** (88% *ee*) from **2a** (1 equiv) and benzaldehyde (2 equiv) catalyzed by another cationic iridium(I) complex/chiral phosphoric acid system, which required a greater quantity of chiral TRIP (20 versus 5 mol%) coupled with a lower reaction temperature (−15 °C).[37] Based on these observations, we believe the enantioselectivity drop for this class of compounds can be attributed to the presence of the phenyl group which must be disturbed for preferential interaction between the allylboronate intermediate and the chiral phosphoric acid.[38]

Considering the good availability of the starting materials, we finally examined the application of this enantioselective catalytic process in a three-step sequence with a range of allylbenzene derivatives and aldehydes (Figure 2). After removal of the ruthenium catalyst by filtration, the crude product of the cross-metathesis reaction was engaged in an isomerization reaction, followed by the catalytic enantioselective allylboration without any purification steps. The unoptimized yields of isolated products **5** are acceptable for a three-step sequential reaction. In all cases, only one diastereomer was obtained and enantioselectivity (54–82%) was determined from the corresponding Mosher's esters.

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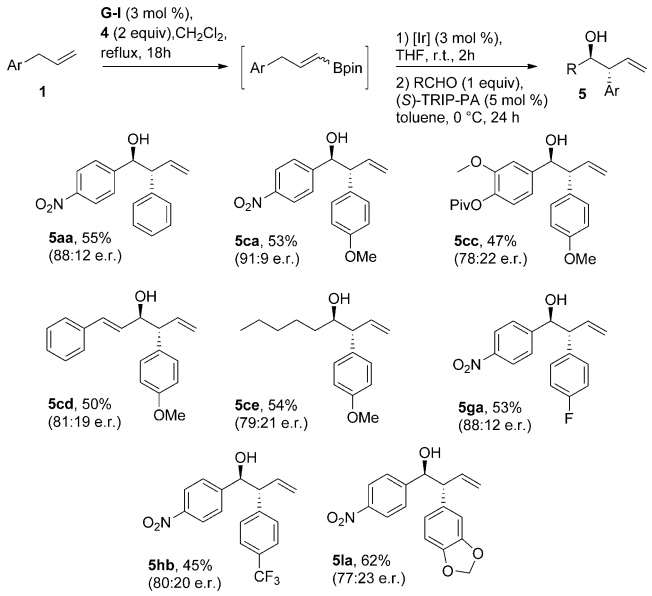

Figure 2. Asymmetric cross-metathesis/isomerization/allylboration sequence.

Conclusion

We report a diastereoselective, catalytic cross-metathesis/isomerization/allylboration sequence for the preparation of *anti*-homoallylic alcohols from allyl-substituted derivatives and aldehydes. The main advantages of this new three-step sequence are the accessibility of the starting materials relative to alkynes and the ability to obtain the homoallylic alcohols in a highly diastereoselective manner without structurally stereo-defined alkenyl boronates as transient intermediates. In our quest to develop an asymmetric version of this process, we found that the allylboration reaction catalyzed by a chiral phosphoric acid gave the best results. The enantioselectivity measured remained modest in all cases but, due to the unconventional structure of the allylboronates generated during the process, different conditions seem necessary to enhance it. Work underway in our laboratory is focused on this target.

Experimental Section

General procedure for the cross-metathesis/isomerization/allylboration sequence

Compound **4** (0.40 mmol) and catalyst **G-I** (3 mol%) were added successively to a solution of **1** (0.20 mmol) in dry CH_2Cl_2 (0.2 M) under an argon atmosphere. The resulting mixture was heated at reflux for 18 h. After this time, the solution was filtered through a short pad of silica and CH_2Cl_2 was removed under reduced pressure to afford the product **2**, which was used without further purification. A flask was charged with $[Ir(cod)(PPh_2Me_2)_2]PF_6$ (3 mol%) and flushed with argon. Anhydrous THF (0.15 M) was added. Dihydrogen was gently bubbled into the solution via a needle for around 2 min to give a light-yellow solution. The excess dihydrogen was then replaced with argon. A solution of crude **2** (0.20 mmol, 1.00 equiv) in dry THF (0.15 M) was immediately added to the solution that contained the catalyst, followed by aldehyde (0.20 mmol, 1.00 equiv). The mixture was allowed to stir at rt for 20 h. THF was then removed under reduced pressure and the residue was purified by column chromatography (cyclohexane/EtOAc) to afford the desired homoallylic alcohol **5**.

Acknowledgements

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Keywords: allylboration · catalysis · domino reactions · isomerization · metathesis

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[23] We observed a drop in the yield of the homoallylic alcohol **5aa** (42%) if the ruthenium catalyst was not removed by filtration through a short plug of silica in a Pasteur pipette after completion of the metathesis reaction.
[24] A slight excess of aldehyde (1.3 equiv) relative to **1a** can be employed to increase the yield (69% for **5ab**) but makes isolation of the final products more difficult.
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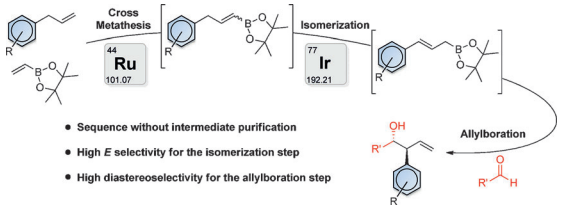

The ruthenium and iridium association: A complementary and alternative method for the synthesis of *anti*-homoallylic alcohols by a novel, highly diastereoselective, catalytic, three-component cross-metathesis/isomerization/allylboration reaction between allylbenzene derivatives, a vinyl boronate, and aldehydes has been achieved (see scheme).

Synthetic Methods

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Cross-Metathesis/Isomerization/Allylboration Sequence for a Diastereoselective Synthesis of *Anti*-Homoallylic Alcohols from Allylbenzene Derivatives and Aldehydes

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