



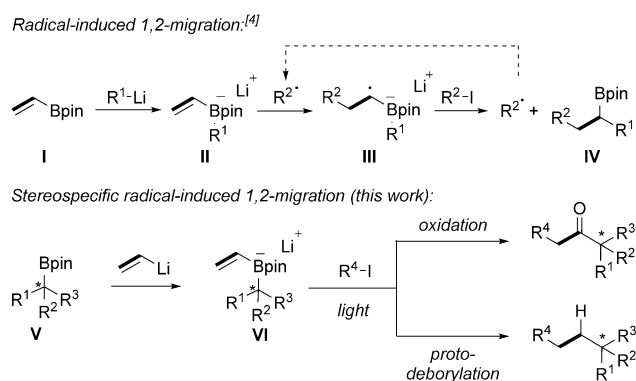
Synthesis of α -Chiral Ketones and Chiral Alkanes Using Radical Polar Crossover Reactions of Vinyl Boron Ate Complexes

Carolin Gerleve⁺, Marvin Kischkewitz⁺, and Armido Studer*⁺

Abstract: Vinyl boron ate complexes of enantioenriched secondary alkyl pinacolboronic esters undergo stereospecific radical-induced 1,2-migration in radical polar crossover reactions. In this three-component process various commercially available alkyl iodides act as radical precursors and light is used for chain initiation. Subsequent oxidation and protodeborylation leads to valuable α -chiral ketones and chiral alkanes, respectively, with excellent enantiopurity.

Vinylboronic esters and their boron ate complexes are highly valuable substrates for C–C bond formation in the Suzuki–Miyaura coupling.^[1] Moreover, vinyl boron ate complexes undergo 1,2-migration promoted by electrophilic halogenation^[2] or by electrophilic palladation in conjunctive cross couplings, as recently shown by Morken et al.^[3] Our laboratory and the group of Aggarwal independently demonstrated that in situ generated vinyl boron ate complexes **II** are efficient radical acceptors and that the corresponding radical anions **III** undergo a radical polar crossover reaction, inducing a 1,2-migration to provide secondary and tertiary alkyl boronic esters **IV** (Scheme 1).^[4] Aggarwal et al. further demonstrated that boron ate complexes of enantioenriched alkylboronic esters and furan-2-ylolithium undergo stereospecific 1,2-metalate rearrangements in the reaction with the trifluoromethyl radical.^[5] Importantly, such chiral secondary boronic esters are readily accessed by hydroboration,^[6] by the Matteson approach,^[7] and by reaction of boronic esters with Hoppe's enantioselectively lithiated carbamates.^[8]

We considered using in situ generated vinyl boron ate complexes **VI**, derived from enantioenriched boronic esters **V** and vinylolithium, in a radical polar crossover reaction with various alkyl iodides and report herein that this key transformation followed by oxidation offers a new route to α -chiral ketones. Such chiral moieties are widespread in natural products and the development of synthetic routes to access



Scheme 1. Synthesis of α -chiral ketones and chiral alkanes via radical-induced enantiospecific three-component coupling. Pin = pinacolate.

enantioenriched α,α -disubstituted ketones is therefore of great importance. Although many protocols for auxiliary-controlled asymmetric enolate reactions have been developed over the last decades,^[9] the direct asymmetric alkylation of ketones is still highly challenging^[10] and mostly transition-metal catalysts are required.^[11,12] In contrast, the protocol presented here proceeds without any transition metal, comprises the formation of two C–C bonds, and allows facile modular construction of α -chiral ketones using three different readily available components. Moreover, the intermediate boronic esters can be protodeborylated to provide the corresponding chiral alkanes.

For our initial studies we chose enantioenriched pinacol boronic ester **1a** ($R^1 = \text{Et}$, $R^2 = \text{CH}_2\text{CH}_2\text{Ph}$, Scheme 2). Its vinyl boron ate complex was readily generated by reaction with vinylolithium in diethyl ether at -78°C . Optimization with *tert*-butyl 2-iodoacetate as the C-radical precursor revealed that the chain is best initiated by light irradiation (Philips Master HPI-T plus, 400 W, see the Supporting Information). In the absence of light only traces of product **2a** were observed. Hence, after removal of the solvent the ate complex was reacted with *tert*-butyl 2-iodoacetate in acetonitrile under irradiation to provide the corresponding boronic ester as a 1:1 mixture of diastereoisomers. Without any purification and using standard oxidation reagents, the crude product boronic ester was then transformed into the corresponding α -chiral ketone **2a**, which was isolated in good overall yield (51%) and excellent enantiopurity, revealing that the radical-induced 1,2-alkyl migration occurred with complete stereospecificity (for a control experiment with the other enantiomer, see the Supporting Information).

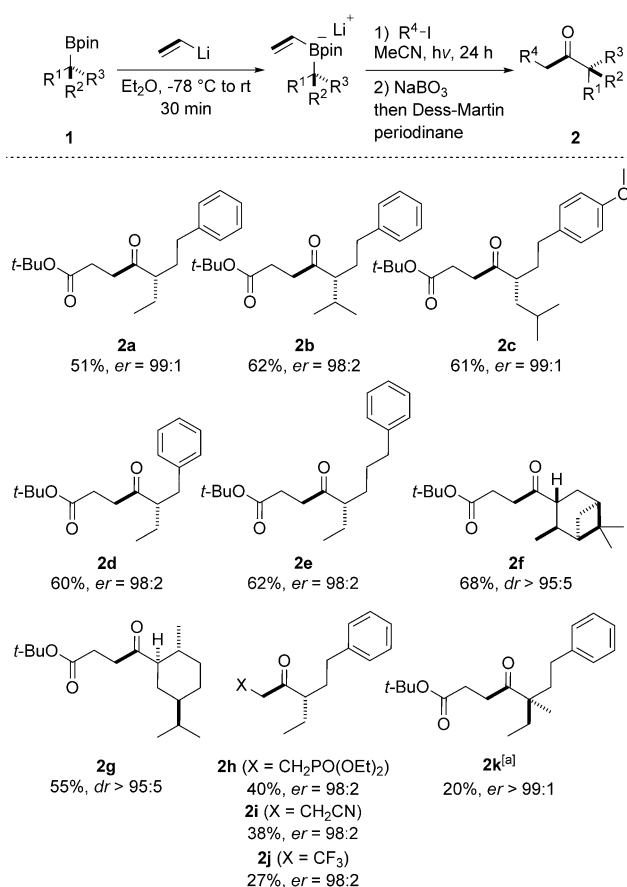
Under the optimized conditions, various enantioenriched secondary alkylboronic esters **1b–e** were tested in this sequence, keeping *tert*-butyl 2-iodoacetate as the reaction

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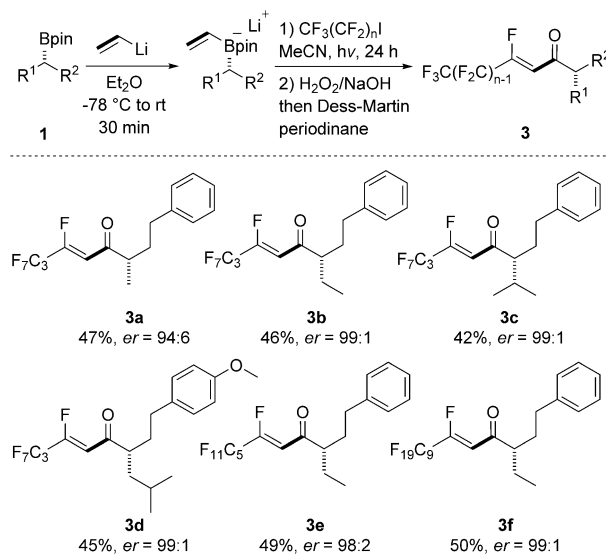


Scheme 2. Scope of the stereospecific three-component coupling/oxidation sequence. Yields correspond to yields of isolated products of the overall sequence. Conditions for the radical polar crossover reaction: **1** (0.30 mmol), vinyl lithium (0.39 mmol) in Et₂O (2.0 mL), alkyl iodide (1.5 mmol) in MeCN (2.0 mL). Conditions for oxidation: NaBO₃ (1.5 mmol), THF/H₂O (1:1, 20 mL), 4 h; Dess–Martin periodinane (0.75 mmol), CH₂Cl₂ (4 mL), 3 h. [a] Oxidation was conducted with H₂O₂/NaOH, see the Supporting Information.

partner. These cascades proceeded smoothly and the α -chiral ketones **2b–e** bearing different alkyl substituents at the α -position were isolated with high enantiopurity and good overall yield. Diastereoisomerically pure boronic ester **1f** derived from α -pinene and **1g** from the corresponding chloride (see the Supporting Information) provided the ketones **2f** and **2g** in 68% and 55% overall yield and complete diastereoselectivity as enantiomerically pure compounds. When we varied the C-radical precursor, we found that the commercial diethyl iodomethylphosphonate also performs in this sequence. Ketone **2h** was obtained in 40% overall yield and high enantiopurity. Furthermore, the method also allows the synthesis of α -chiral ketones bearing a nitrile or trifluoromethyl functionality at the β -position (see **2i**, **2j**) and a ketone bearing an all-carbon-substituted α -quaternary center was successfully prepared, albeit the yield was low (see **2k**).^[13]

Introducing fluorinated alkyl chains in organic compounds is of great importance, particularly in medicinal and agrochemical research.^[14] Therefore, we also tested commer-

cially available perfluoroalkyl iodides as C-radical precursors. The resulting α -perfluoroalkylated ketones are known to easily undergo dehydrofluorination^[15] to provide β -fluorinated Michael acceptors, which are useful building blocks to access fluoroalkylated heterocyclic compounds, such as pyrazoles, pyrimidines, and isoxazoles.^[16] Treatment of various enantioenriched vinyl boron ate complexes with perfluoroalkyl iodides under light irradiation and subsequent oxidation provided chiral α -perfluoroalkylated ketones that readily underwent HF elimination during purification by silica gel column chromatography to give the vinyl fluorides **3** (Scheme 3). The sequence comprising coupling of nonafluorobutyl iodide with four different boronic esters provided,



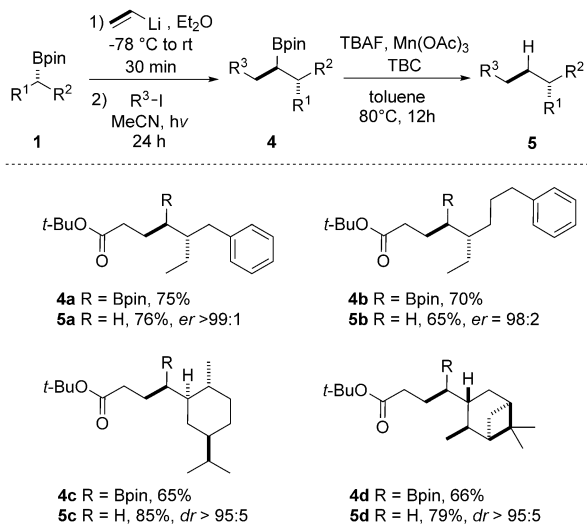
Scheme 3. Enantiospecific three-component coupling with subsequent oxidation to β -fluorinated Michael acceptors. Yields correspond to yields of isolated products of the overall sequence. Conditions for the radical polar crossover reaction: **1** (0.30 mmol), vinyl lithium (0.39 mmol) in Et₂O (2.0 mL), CF₃(CF₂)_nI (1.5 mmol) in MeCN (2.0 mL). Conditions for oxidation: H₂O₂/NaOH, 4 h; Dess–Martin periodinane (0.75 mmol), CH₂Cl₂ (4 mL), 3 h. Quantitative dehydrofluorination occurred during purification by column chromatography on silica gel.

after oxidation, fluorinated enones **3a–d** in moderate yields and excellent enantiopurities. As shown by the preparation of **3e** and **3f**, the sequence works also with similar efficiency for longer chain perfluoroalkyl iodides.

To further document the potential of the sequence, we extended the protocol to the construction of chiral *tert*-alkyl moieties using a protodeborylation reaction.^[17] The enantioselective construction of *tert*-alkyl centers that lack any nearby functionality to steer stereoselective build-up is challenging. Protodeborylation of the chiral secondary boronic esters obtained in the radical polar crossover reaction should open an approach to the targeted chiral *tert*-alkyl systems (see Scheme 1).

For these investigations we chose *tert*-butyl 2-iodoacetate as the C-radical precursor and four different boronic esters in combination with vinyl lithium. Whereas oxidation could be

performed directly on the crude boronic esters obtained in the radical polar crossover reaction (see above), protodeborylation required isolation of the intermediate boronic esters. The coupling of **1e** and **1f** with the iodoacetate gave **4a** and **4b** in 75% and 70% yield, respectively (Scheme 4). As expected,^[4] the chirality center in α -position to the B atom was not



Scheme 4. Stereospecific three-component coupling and subsequent protodeborylation. Yields correspond to yield of isolated products. Conditions for the radical polar crossover reaction: **1** (0.3 mmol), vinyl lithium (0.39 mmol) in Et₂O (2.0 mL), alkyl iodide (1.5 mmol) in MeCN (2.0 mL). Conditions for protodeborylation: TBAF·3 H₂O (0.18 mmol), Mn(OAc)₃ dihydrate (0.15 mmol), TBC (0.75 mmol) in toluene (0.7 mL).

controlled and the intermediate secondary alkyl boronic esters **4a** and **4b** were formed as mixtures of diastereoisomers (around 1:1, see the Supporting Information). However, this is not problematic since in the subsequent protodeborylation step this stereogenic center will be destroyed. Protodeborylation with *tert*-butylammonium fluoride (TBAF·3H₂O), manganese(III)acetate dihydrate, and 4-*tert*-butylcatechol (TBC) in toluene at 80 °C^[17c] provided **5a** and **5b** in good yields and excellent enantiopurities. Starting with natural-product-derived chiral boronic esters **1g** and **1h**, the sequence could be applied to the formation of the esters **5c** and **5d**.

In summary, we have reported a novel transition-metal-free process for the preparation of α -chiral ketones and for the construction of chiral *tert*-alkyl centers. The sequence comprises two sequential C–C bond formations including a radical-induced stereospecific 1,2-migration of a chiral secondary alkyl group using readily prepared vinyl boron ate complexes and commercial iodides as reaction components. Products obtained in this three-component radical polar crossover cascade are secondary alkyl boronic esters that are further transformed by either oxidation or protodeborylation to afford valuable α -chiral ketones, β -fluorinated enones, and linear or cyclic chiral alkanes in excellent enantiopurities.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: α -chiral ketones · boronic esters · protodeborylation · radical polar crossover reactions

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