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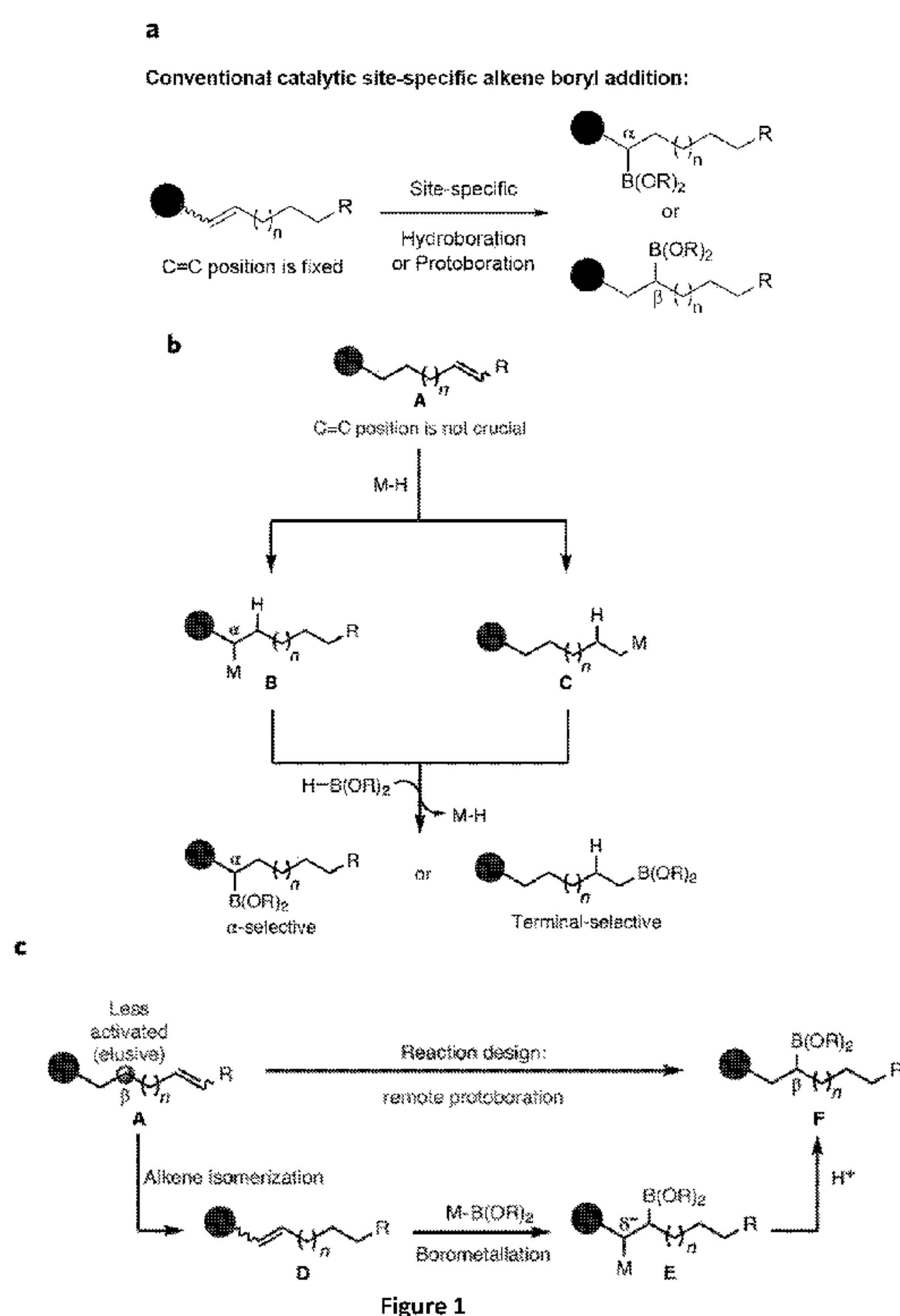
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(54) Title: METHODS OF BORYLATION AND USES THEREOF



(57) Abstract: The present invention relates, in general terms, to methods of borylation and uses thereof. In particular, the present invention provides a method of borylating an alkene compound by contacting the compound with a boron compound, a Fe pre-catalyst and a protic additive. The borylation occurs at a vicinal (β) position to an electron donating or electron withdrawing moiety of the compound.

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METHODS OF BORYLATION AND USES THEREOF

Technical Field

- 5 The present invention relates, in general terms, to methods of borylation and uses thereof.

Background

- 10 Boron-containing molecules are arguably one of the most versatile classes of compounds in chemical synthesis. Compared to other organometallic reagents, organoboronates are relatively stable, exceptionally functional group tolerant, and readily diversifiable to afford a broad range of synthetically valuable motifs through well-established C-B $\rightarrow$ C-X (e.g. X= C, N, O, halide) transformations. These desirable
15 attributes of organoboronates in part account for their role in drug discovery and their utility as indispensable precursors en route to diverse categories of chemical products ranging from small-molecule pharmaceuticals to functional polymeric materials.

- The extensive applicability of organoboron compounds has stimulated remarkable
20 developments leading to the discovery of catalysts and protocols that furnish C-B bonds through substitution reactions, nucleophilic additions to carbonyl derivatives, boryl additions across unsaturated C-C bonds, as well as borylation through C-H activation. An attractive and atom-economical approach for synthesis of aliphatic organoboron compounds involves catalytic hydroboration or protoboration of C=C bonds. Catalysts
25 containing either noble or base metals have been introduced to promote Markovnikov or anti-Markovnikov additions with good regioselectivities (Figure 1a). In recent years, there is growing interest in the development of remote borylations distant from the initial reactive site. Such transformations typically commence with a series of inter- or intramolecular hydride shifts involving a metal complex, engendering alkene
30 isomerization prior to reaction with a boryl reagent. Compared to conventional site-specific reactions, the location of the C=C bond within the substrate is no longer critical in remote functionalizations (Figure 1b). This strategy enhances practicality by allowing a wider set of alkenes or regioisomeric mixtures to be converted to value-added borylalkanes in a convergent and selective manner. Further, substrates are more easily
35 accessible and single metal-hydride species can be used. However, existing

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transformations are predominantly restricted to formal (sp³)C-H borylations at two common sites within an organic molecule: (i) the electronically activated α-carbon geminal to electron-withdrawing moieties including aryl-, heteroaryl and boryl units, or (ii) the sterically exposed terminal methyl groups. Selective boron introduction at other less activated carbons is a largely unresolved challenge, exacerbated by the presence of multiple sites of similar reactivity along a hydrocarbon chain.

Challenges in remote hydroboration includes that existing methods afford α-borylalkanes or 1-borylalkanes, stoichiometric borohydride reagent leads to fast hydrometallation/borylation, and it difficult to install boryl units at unactivated sites.

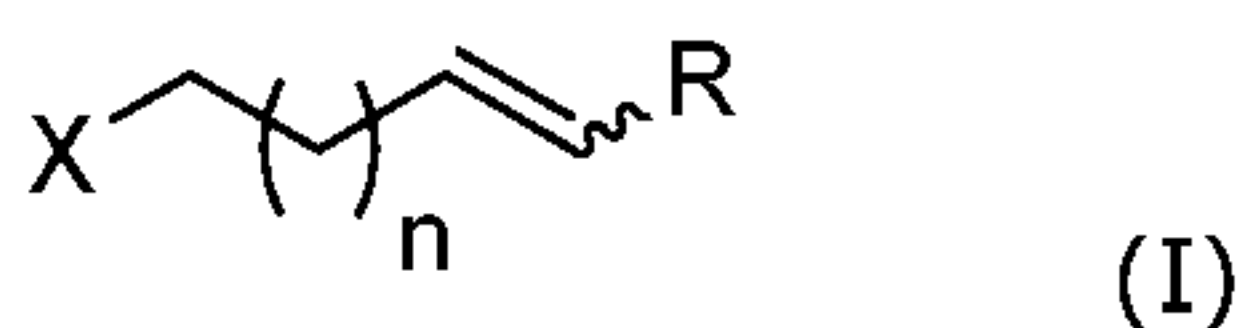
A general catalytic manifold that incorporates boryl groups at unactivated sites (e.g. β-position) in the absence of strong directing auxiliaries and offers complementarity to state-of-the-art methods remains to be conceived.

It would be desirable to overcome or ameliorate at least one of the above-described problems, or at least to provide a useful alternative.

Summary

The present invention is predicated on the understanding that remote hydroboration typically employs a stoichiometric borohydride reagent to generate a metal hydride species that promotes facile chain-walking, affording stabilized intermediates B or C, which subsequently undergo borylation to give α-borylalkanes or primary alkylboronates, respectively. The inventors have discovered that unactivated C-H bonds can be borylated. In this regard, the inventors have found that unactivated C-H bonds can be borylated by a synergistic hydrometallation and borometallation process.

The present invention provides a method of borylating a compound of Formula (I):



wherein X is selected from the group consisting of optionally substituted silyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted dioxyboronyl and B(pin);

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R is selected from the group consisting of H, halo, optionally substituted alkyl and optionally substituted cycloalkyl;

n is an integer selected from 0 to 10;

by contacting the compound of Formula (I) with:

- 5 i) a boron compound selected from the group consisting of bis(pinacolato)diboron, bis(neopentyl glycolato)diboron, bis(hexylene glycolato)diboron, 2,2'-bis-1,3,2-benzodioxaborole, 9-borabicyclo[3.3.1]nonane (9-BBN dimer), bis(2,4-dimethylpentane-2,4-glycolato)diboron, bis(butane-2,3-glycolato)diboron, the boron compound at
- 10 least stoichiometrically equivalent to the compound of Formula (I);
- ii) a Fe pre-catalyst; and
- iii) a protic additive;

wherein the borylation occurs at a vicinal (β) position to the X moiety of the compound of Formula (I) to give a compound of Formula (II):

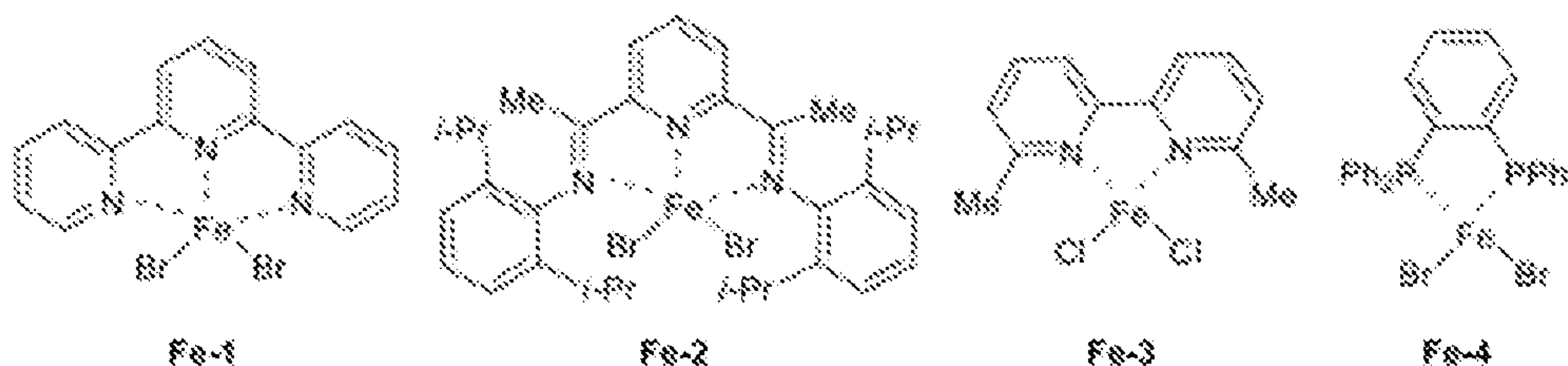


wherein X, R and n are as defined herein, and pin is pinacolyl.

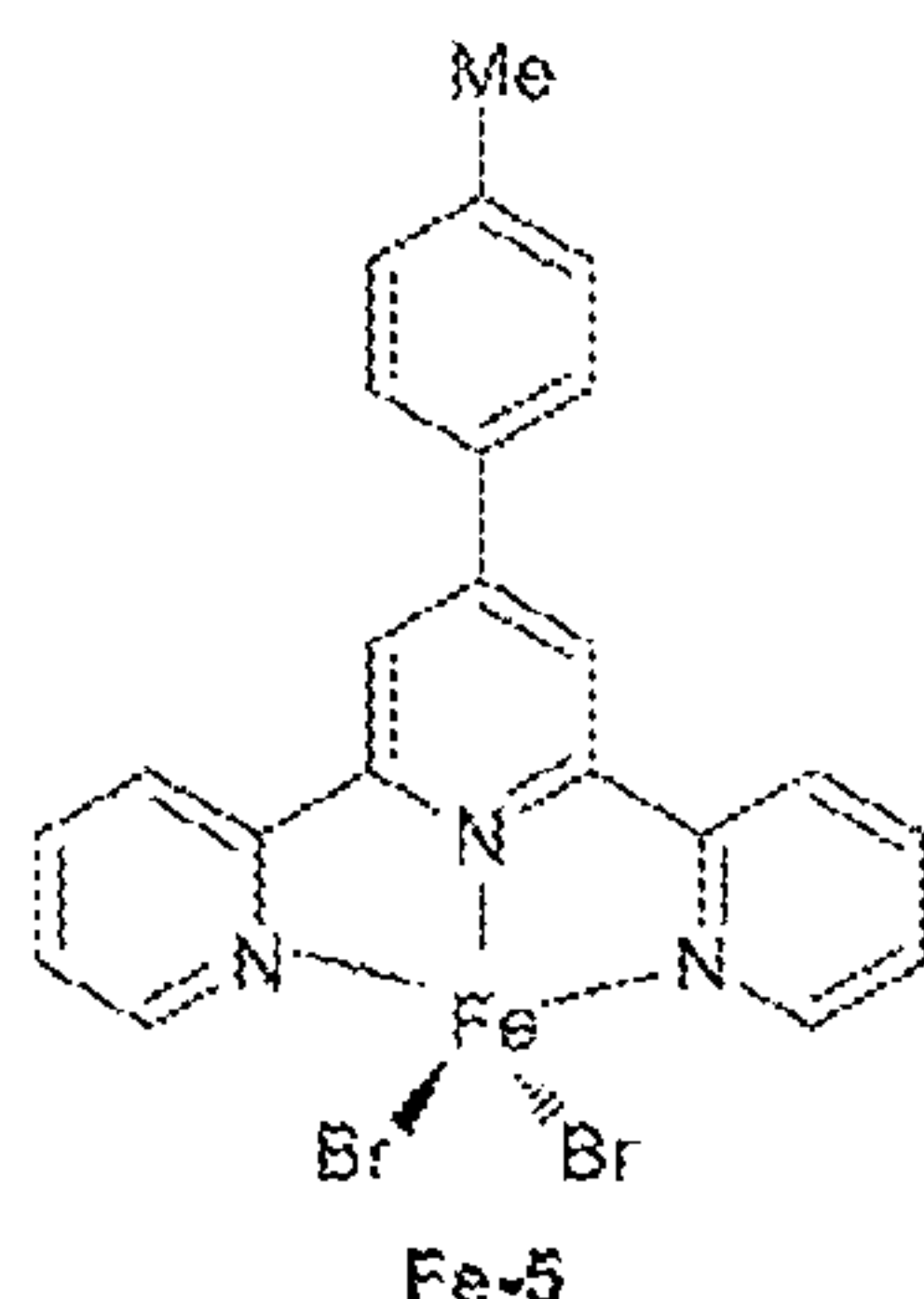
In some embodiments, the Fe pre-catalyst is selected from terpyridine-FeBr₂, FeBr₂, FeBr₃, Fe(OAc)₂, FeCl₂, FeCl₃, Fe(II) acetylacetonate, Fe(III) acetylacetonate, Fe(II) trifluoromethanesulfonate, tris(2,2,6,6-tetramethyl-3,5-heptanedionato)iron(III) and ferrous oxalate dehydrate.

20

In some embodiments, the Fe pre-catalyst is a Fe complex selected from



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In some embodiments, the Fe pre-catalyst is provided at at least 8 mol% to the compound of Formula (I).

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In some embodiments, the protic additive is present at less than 0.05 stoichiometric equivalence to the compound of Formula (I).

10 In other embodiments, the protic additive is generated *in situ* from a polar solvent and an alkali metal oxide.

In some embodiments, the polar solvent is a polar aprotic solvent.

15 In some embodiments, the polar solvent is dimethylacetamide (DMA), dimethylsulfoxide (DMSO), CH₃CN, N,N'-dimethylpropyleneurea (DMPU), dimethylformamide (DMF) or a mixture thereof.

In some embodiments, the alkali metal oxide is an at least stoichiometrically equivalent to the compound of Formula (I).

20

In some embodiments, the alkali metal oxide is selected from the group consisting of lithium tert-butoxide, lithium bis(trimethylsilyl)amide, lithium diisopropylamide, lithium trifluoromethanesulfonate, lithium methoxide, sodium benzenesulfinate, sodium phenolate, sodium methoxide, sodium tert-butoxide, potassium acetate, potassium carbonate, potassium fluoride, potassium tert-butoxide, potassium phosphate monobasic, potassium ethoxide and potassium phosphate tribasic.

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In some embodiments, the method further comprises a polar solvent, the polar solvent is a mixture of DMA and toluene in a volume ratio of 1:2.

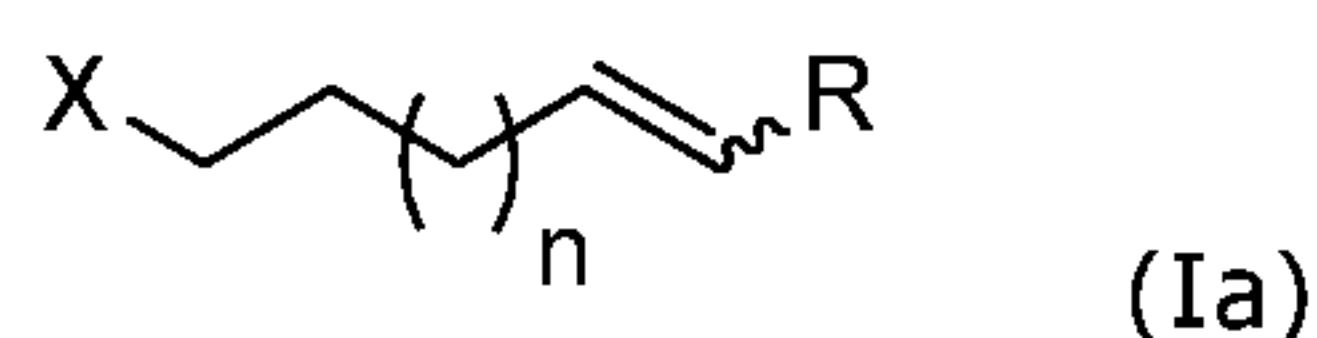
In other embodiments, the method is conducted at a temperature of at least 60 °C.

5

In other embodiments, the method further includes contacting the compound of Formula (I) with a protic reagent, the protic reagent being less than 0.25 stoichiometric equivalent to the compound of Formula (I).

- 10 In some embodiments, the protic reagent is t-butyl alcohol, methanol, ethanol, isopropyl alcohol (or any other alcohols), phenol, water and carboxylic acids.

In some embodiments, the compound of Formula (I) is a compound of Formula (Ia):



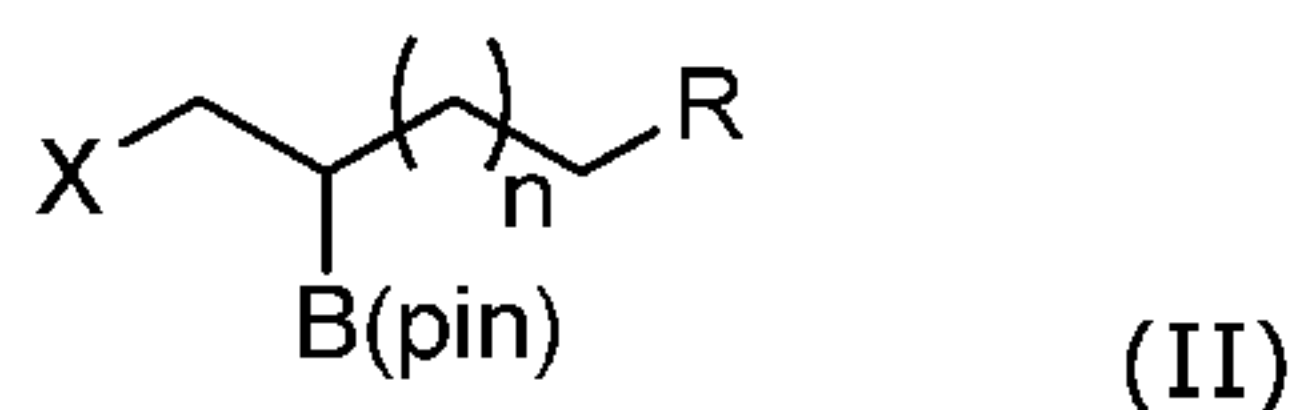
- 15 wherein X is selected from the group consisting of optionally substituted silyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted dioxyboronyl and B(pin);

R is selected from the group consisting of H, halo, optionally substituted alkyl and

- 20 optionally substituted cycloalkyl; and

n is an integer selected from 0 to 9.

In another aspect, the present invention provides a compound of Formula (II):



- 25 wherein pin is pinacolyl;

X is selected from the group consisting of optionally substituted silyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted dioxyboronyl;

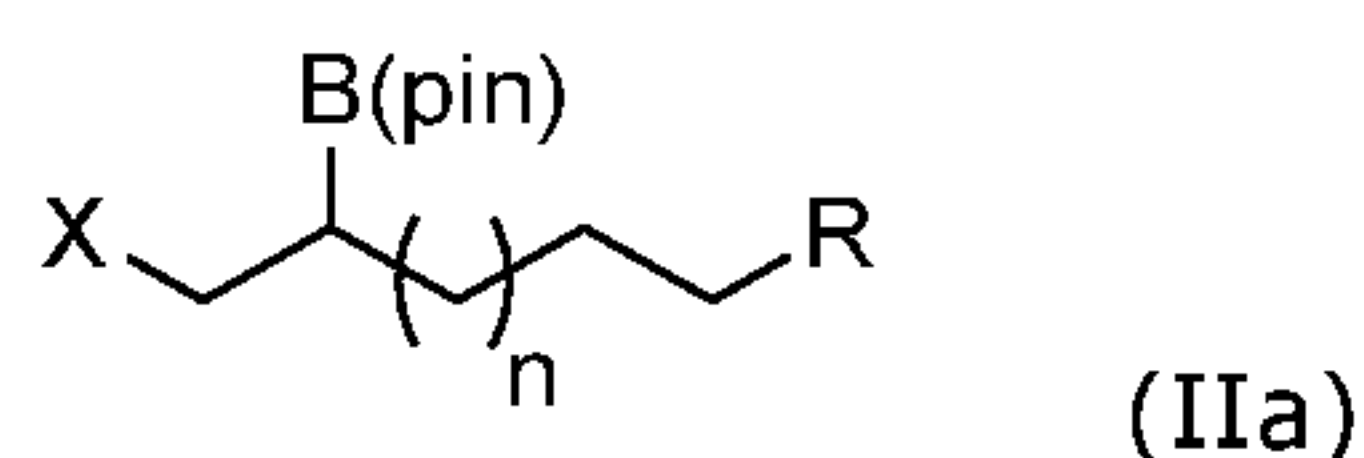
- 30 R is selected from the group consisting of H, halo, optionally substituted alkyl and optionally substituted cycloalkyl; and

n is an integer selected from 0 to 10.

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In some embodiments, the compound of Formula (II) has a chiral configuration about the borylated carbon (C_β).

- 5 In some embodiments, the compound of Formula (II) is a compound of Formula (IIa):



wherein X, R and n are as defined herein, and pin is pinacolyl.

Brief description of the drawings

10

Embodiments of the present invention will now be described, by way of non-limiting example, with reference to the drawings in which:

- 15 **Figure 1** illustrates (a) conventional catalytic site-specific alkene hydro- or protoborations, (b) tandem chain-walking/hydroboration compared to (c) remote borylation at unactivated C_β -H sites of the present invention;

Figure 2 illustrates the industrial applicability of exemplary organoboron compounds with (sp^3) C_β -B bonds (R, H or alkyl group; M, metal; X, halide; Ac, acetyl);

- 20 **Figure 3** presents embodiments of the present invention (a) with Fe-based compounds; (b) with addition of a protic reagent; and (c) with varying concentration of polar solvent (DMA);

Figure 4 illustrates (a) deuterium labelling experiments; and (b) kinetics studies of the reaction of **4a** under standard conditions over time; and

Figure 5 illustrates a proposed mechanism for catalytic remote protoboration.

- 25 **Figure 6** shows operando XANES and EXAFS measurements of Fe-1 and crude reaction mixture. a, FT-k² χ (R) Fe K-edge EXAFS of the catalyst Fe-1 and reaction mixture at different temperatures. Inset shows an enlarged view of peak II. b, The corresponding Fe K-edge EXAFS spectra. c, The corresponding normalized Fe K-edge XANES spectra. Insets show the enlarged pre-edge peaks and main peaks. RT, room temperature (22
30 °C); **Figure 7** shows that by using a single Fe-based catalytic manifold, alkene isomerization and/or proto-boryl addition can be controlled to selectively access various regioisomers of borylated products;

Figure 8 illustrates a proposed mechanism for Fe-catalyzed C=C bond migration; and

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Figure 9 shows a flowchart for isomerising alkene.

Detailed description

- 5 "Alkyl" refers to monovalent alkyl groups which may be straight chained or branched and preferably have from 1 to 10 carbon atoms or more preferably 1 to 6 carbon atoms. Examples of such alkyl groups include methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *n*-hexyl, and the like.
- 10 "Alkynyl" refers to alkynyl groups preferably having from 2 to 10 carbon atoms and more preferably 2 to 6 carbon atoms and having at least 1, and preferably from 1-2, carbon to carbon, triple bonds. Examples of alkynyl groups include ethynyl ($-\text{C}\equiv\text{CH}$), propargyl ($-\text{CH}_2\text{C}\equiv\text{CH}$), pent-2-ynyl ($-\text{CH}_2\text{C}\equiv\text{CCH}_2\text{-CH}_3$), and the like.
- 15 "Halo" or "halogen" refers to fluoro, chloro, bromo and iodo.
- "Aryl" refers to an unsaturated aromatic carbocyclic group having a single ring (eg. phenyl) or multiple condensed rings (eg. naphthyl or anthryl), preferably having
- 20 from 6 to 14 carbon atoms. Examples of aryl groups include phenyl, naphthyl and the like.
- "Heteroaryl" refers to a monovalent aromatic heterocyclic group which fulfils the Hückel criteria for aromaticity (ie. contains $4n + 2$ π electrons) and preferably has
- 25 from 2 to 10 carbon atoms and 1 to 4 heteroatoms selected from oxygen, nitrogen, selenium, and sulfur within the ring (and includes oxides of sulfur, selenium and nitrogen). Such heteroaryl groups can have a single ring (eg. pyridyl, pyrrolyl or N-oxides thereof or furyl) or multiple condensed rings (eg. indoliziny, benzoimidazolyl, coumarinyl, quinolinyl, isoquinolinyl or benzothienyl).
- 30 "Cycloalkyl" refers to cyclic alkyl groups having a single cyclic ring or multiple condensed rings, preferably incorporating 3 to 11 carbon atoms. Such cycloalkyl groups include, by way of example, single ring structures such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclooctyl, and the like, or multiple ring

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structures such as adamantanyl, indanyl, 1,2,3,4-tetrahydronaphthalenyl and the like.

"Heterocyclyl" refers to a monovalent saturated or unsaturated group having a single
5 ring or multiple condensed rings, preferably from 1 to 8 carbon atoms and from 1 to 4 hetero atoms selected from nitrogen, sulfur, oxygen, selenium or phosphorous within the ring. The most preferred heteroatom is nitrogen. It will be understood that where, for instance, an optionally substituted heterocyclyl which has one or more ring heteroatoms, the heterocyclyl group can be connected to the core
10 molecule of the compounds of the present invention, through a C-C or C-heteroatom bond, in particular a C-N bond.

Examples of heterocyclyl and heteroaryl groups include, but are not limited to, oxazole, pyrrole, imidazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, indolizine,
15 isoindole, indole, indazole, purine, quinolizine, isoquinoline, quinoline, phthalazine, naphthylpyridine, quinoxaline, quinazoline, cinnoline, pteridine, carbazole, carboline, phenanthridine, acridine, phenanthroline, isothiazole, phenazine, isoxazole, isothiazole, phenoxazine, phenothiazine, imidazolidine, imidazoline, piperidine, piperazine, indoline, phthalimide, 1,2,3,4-tetrahydroisoquinoline, 4,5,6,7-tetrahydrobenzo[b]thiophene,
20 thiazole, thiadiazoles, oxadiazole, oxatriazole, tetrazole, thiazolidine, thiophene, benzo[b]thiophene, morpholino, piperidinyl, pyrrolidine, tetrahydrofuranyl, triazole, and the like.

'Silyl' refers to a group connected to the core molecule by Si; i.e. $-\text{SiR}_3$, wherein R
25 can be any group. For example, each R can be independently selected from alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, heterocyclyl, and the like. Examples of silyl include, but are not limited to, trimethylsilyl, triethylsilyl, triisopropylsilyl, t-butyldimethylsilyl, t-butyldiphenylsilyl, methyldiphenylsilyl, and the like.

30 'Dioxybornyl' refers to a boronate ester group. The boronate ester group is preferentially connected to the core molecule by the boron atom, but can also be connected via any of the oxygen atom. Examples of boronate ester groups are 1,3,2-dioxaborolanyl, 1,3,2-benzodioxaborolyl, 4,4,5,5-tetramethyl-1,3,2-dioxaborolanyl and 2,2'-bi-1,3,2-dioxaborinanyl.

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Figure 1a and b shows some of the methodologies and results of the prior art. One way is by catalytic site-specific alkene boryl addition to obtain Markovnikov or anti-Markovnikov additions. Another way is by remote alkene boryl additions, in which the boryl moiety is selective for the terminal carbon or germinal (α) carbon to certain
5 electron-stabilising moieties. These methods enables borylations at remote sites irrespective of the C=C bond position, however these protocols are limited to functionalizations at typically more reactive α - or terminal C-H bonds.

In general, the present invention provides a method of borylation at unactivated sites
10 (for example, the β -position); i.e. a remote protoboration process (Figure 1c). In contrast to previous disclosures on remote hydroboration, a single catalyst system is used to promote C=C bond isomerization from **A** to an internal site in **D**, followed by regioselective metal-boryl addition and protonolysis to furnish the product.

15 As shown in Figure 1c, the inventors have found β -selective borylation can be obtained through tandem alkene isomerization followed by regioselective protoboration. This is advantageous compared to previous disclosures involving remote hydroboration where a metal-hydride catalytic species is primarily involved. Metal-hydride catalysed hydroboration is often anti-Markovnikov, which results in the hydrogen adding to the
20 least substituted carbon of the double bond. In the presence of an electron withdrawing group, the boron is added to the C adjacent to, for example, an aryl moiety; i.e. geminal (α) position. This limits the utility of the reaction. Further, a mixture of isomers is often obtained. Separation of such isomers may be difficult and require additional purification steps.

25

The inventors have found that site-selective β -borylation can be obtained by modulating the relative rates of alkene isomerization and borometallation/protonolysis. The inventors have further found that an effective catalytic system that promotes efficient alkene isomerization followed by regioselective protoboration allows for generation of
30 competing metal-hydride (for chain-walking) and metal-boryl (for boryl addition) species in the same vessel. Without wanting to be bound by theory, the inventors have postulated that for the successful implementation of remote protoboration, several conditions can be regulated (Figure 1c). (1) The appropriate catalytic species should be identified to effect chain-walking. A metal-hydride species (to promote chain-walking)
35 and a metal-boryl species (to effect protoboration), both of which can potentially

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compete for reaction with the alkene, can be regulated to co-exist in the same vessel. (2) Alkene isomerization from **A** to **D** can be faster than adventitious protoboration, which will otherwise lead to complex regioisomeric mixtures of borylated products. (3) The proton source can be judiciously selected to promote protonolysis of **E** to **F** but not
5 diminish the concentration of the metal-hydride species responsible for C=C bond migration. (4) Potential side pathways such as hydrogenation and diboration reactions can to be suppressed. In short, the two competing processes of hydrometallation and borometallation if carefully coordinated can result in a desired β -borylalkanes, which can serve as important intermediates to synthetically valuable organic building blocks
10 that enable access to numerous biologically active molecules of interest (Figure 2). In this regard, organoboron compounds can be versatile precursors to coveted building blocks that facilitate access to countless biologically active molecules.

In particular, an iron-catalysed method can overcome at least one of these challenges
15 to deliver remote protoboration, furnishing the desired borylated compounds in up to 85% yield and >98% β -selectivity.

Accordingly, the present invention provides a method of borylating a compound of Formula (I):



wherein X is selected from the group consisting of optionally substituted silyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted dioxyboronyl and B(pin);

25 R is selected from the group consisting of H, halo, optionally substituted alkyl and optionally substituted cycloalkyl;

n is an integer selected from 0 to 10;

by contacting the compound of Formula (I) with:

30 i) a boron compound selected from the group consisting of bis(pinacolato)diboron bis(neopentyl glycolato)diboron, bis(hexylene glycolato)diboron, 2,2'-bis-1,3,2-benzodioxaborole, 9-BBN dimer, bis(2,4-dimethylpentane-2,4-glycolato)diboron, bis(butane-2,3-glycolato)diboron, the boron compound at least stoichiometrically equivalent to compound of Formula (I);

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ii) a Fe pre-catalyst; and

iii) a protic additive;

wherein the borylation occurs at a vicinal (β) position to the X moiety of the compound of Formula (I) to give a compound of Formula (II):



wherein X, R and n are as defined herein, and pin is pinacolyl.

X can be an electron withdrawing group or an electron donating group. The inventors have found that regioselectivity at the vicinal position is provided by the metal-boryl species and accordingly, the electron influence of X is minimal.

10

In some embodiments, X is selected from the group consisting of optionally substituted silyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl. In other embodiments, X is selected from the group consisting of optionally substituted silyl, optionally substituted alkynyl, optionally substituted aryl, and optionally substituted heteroaryl. In other embodiments, X is selected from the group consisting of optionally substituted aryl, and optionally substituted heteroaryl.

15

20 In some embodiments, X is selected from the group consisting of optionally substituted silyl, optionally substituted C₂-C₈ alkynyl, optionally substituted C₃-C₈ cycloalkyl, optionally substituted C₃-C₈ heterocyclyl, optionally substituted C₆-C₁₂ aryl, and optionally substituted C₃-C₁₂ heteroaryl.

25 In some embodiments, X is selected from optionally substituted phenyl, optionally substituted indolyl, optionally substituted indenyl, optionally substituted furanyl, optionally substituted benzodioxolyl, optionally substituted naphthalenyl, optionally substituted cyclohexanyl, optionally substituted tetrahydropyranyl, and optionally substituted silyl.

30

As the electronic influence of X on the regioselectivity is minimal, the optional substituent can accordingly also be either electron donating or electron withdrawing. In

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some embodiments, the optional substituent at X is selected from halo, alkyl, alkoxy, heterocycloxy, cycloalkyl, heterocyclyl, aryl, heteroaryl and B(pin).

In some embodiments, R is selected from the group consisting of H, halo and optionally substituted alkyl. In other embodiments, R is selected from the group consisting of H, halo, optionally substituted C₁-C₆ alkyl and optionally substituted C₃-C₈ cycloalkyl. In other embodiments, R is selected from the group consisting of H, halo, C₁-C₆ alkyl and C₃-C₈ cycloalkyl.

10 As is shown in the examples, the alkene moiety can be positioned some distance away from the X moiety. In this regard, n is an integer selected from 0 to 10. In other embodiments, n can be from 0 to 9, 0 to 8, 0 to 7, 0 to 6, 0 to 5, 0 to 4, 0 to 3 or 0 to 2.

15 In some embodiments, the boron compound is selected from the group consisting of bis(pinacolato)diboron, bis(neopentyl glycolato)diboron, bis(hexylene glycolato)diboron, 2,2'-bis-1,3,2-benzodioxaborole, 9-borabicyclo[3.3.1]nonane (9-BBN dimer), bis(2,4-dimethylpentane-2,4-glycolato)diboron, and bis(butane-2,3-glycolato)diboron. In other embodiments, the boron compound is
20 bis(pinacolato)diboron.

In some embodiments, the boron compound is at least stoichiometrically equivalent to the compound of Formula (I). In other embodiments, the boron compound is at least 1.1 stoichiometrically equivalent to the compound of Formula (I), or at least 1.2, or at
25 least 1.3, or at least 1.4, or at least 1.5.

In some embodiments, the Fe pre-catalyst is provided at at least 8 mol% to the compound of Formula (I). In other embodiments, the Fe pre-catalyst is provided at at least 7 mol%, at least 6 mol%, at least 5 mol%, at least 4 mol%, at least 3 mol%, at
30 least 2 mol%, or at least 1 mol%.

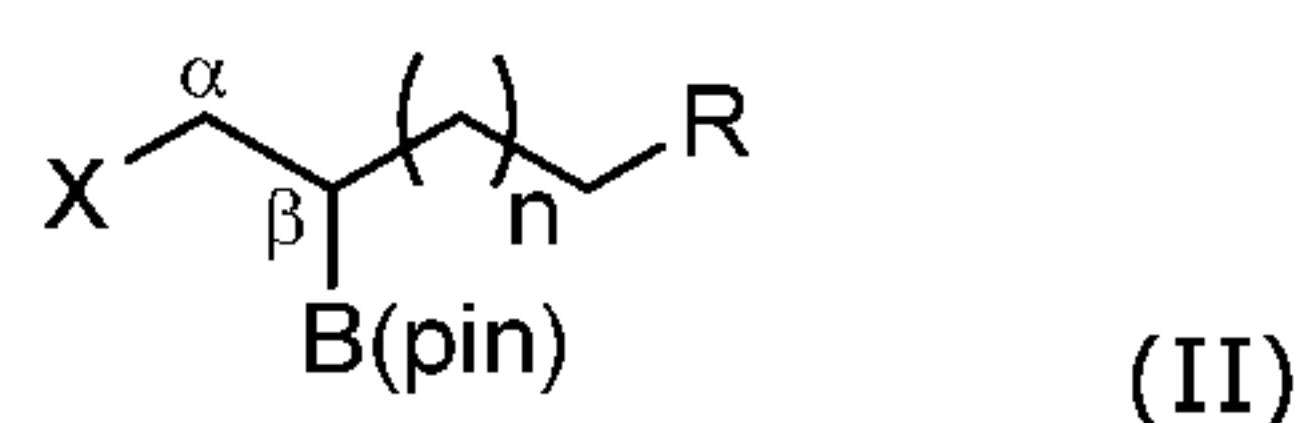
The advantage of the Fe pre-catalyst is two-fold. Firstly, the addition of a boron compound, for example, bis(pinacolato)diboron, and a Fe pre-catalyst (Fe compound) allows for the formation of a first Fe-B(pin) catalyst. This Fe-B(pin) catalyst is further
35 generated as a second Fe-H catalyst in the presence of compound of Formula (I). Figure

1-4 also unveil insights supporting a pathway that involves an in situ-generated Fe-hydride species. The Fe-H catalyst allows for the alkene isomerisation, of which the Fe-B(pin) catalyst then catalyses the protoboration. Monitoring the reaction of **4a** under standard conditions over time provided evidence that C=C bond migration occurs prior to the protoboration event (Figure 1-5). In the presence of a protic additive, a proton can be subsequently added to give a compound of Formula (II). In this regard, the Fe pre-catalyst serves to synergistically catalyse both alkene isomerisation and protoboration reactions.

10 As used herein, 'additive' refers to a substance added in small quantities to the mixture or composition. Accordingly, 'protic additive' refers to an additive that contains a labile H^+ ; i.e. a hydrogen atom bound to an oxygen (as in a hydroxyl group), a nitrogen (as in an amine group) or a fluorine (as in hydrogen fluoride).

15 In some embodiments, the protic additive is present at less than 0.05 stoichiometric equivalence to the compound of Formula (I). In other embodiments, the protic additive is present at less than 0.04, at less than 0.03, at less than 0.02, at less than 0.01, or at less than 0.005.

20 The inventors have found that alkene isomerisation is favoured towards the X moiety for generating an internal alkene that is stabilized by X. This results in the borylation at a vicinal (β) position to the X moiety of the compound of Formula (I) to give a compound of Formula (II):



25 wherein X, R and n are as defined herein, and pin is pinacolyl.

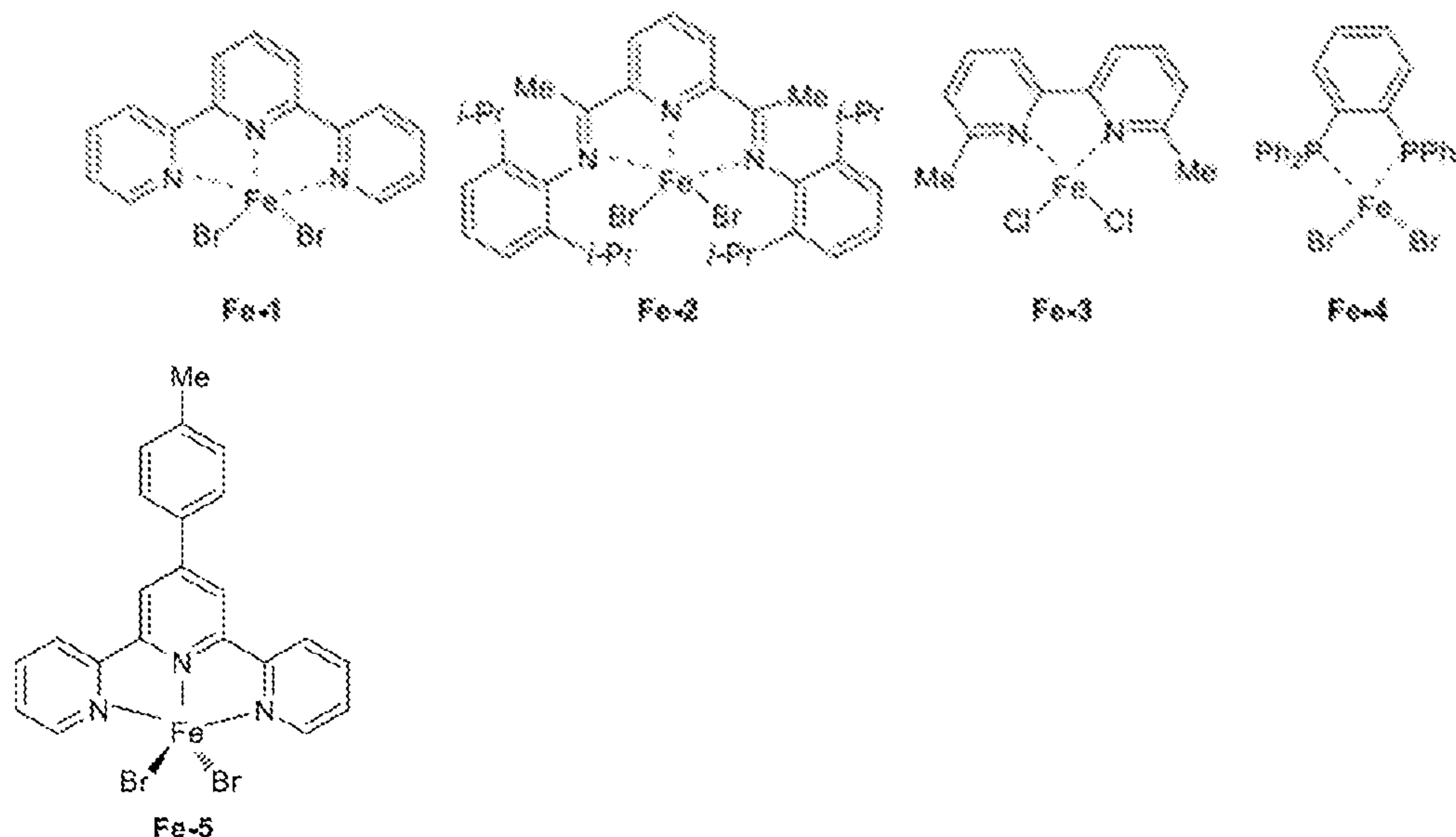
The inventors have found that addition of a boron compound, for example bis(pinacolato)diboron, and a Fe pre-catalyst (Fe compound) advantageously allows for a metal-hydride species (to promote chain-walking) and a metal-boryl species (to effect protoboration), both of which can potentially compete for reaction with the alkene, to be regulated such as to co-exist in the same vessel. Further advantageously, the catalytic reaction of alkene isomerization is faster than the reaction of protoboration, which allows for a good yield of the desired end product. Further advantageously, the

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addition of a protic additive, at less than stoichiometric equivalence, can further favour alkene isomerization over protoboration. This in turn allows for a high yield of the desired end product. Further, protonolysis of **C** to **D** (Figure 1b) can be promoted and at the same time not diminish the concentration of the metal-hydride species responsible for C=C bond migration. Potential side pathways such as hydrogenation and diboration reactions is also suppressed.

In some embodiments, the Fe pre-catalyst is selected from terpyridine-FeBr₂, FeBr₂, FeBr₃, Fe(OAc)₂, FeCl₂, FeCl₃, Fe(II) acetylacetonate, Fe(III) acetylacetonate, Fe(II) trifluoromethanesulfonate, tris(2,2,6,6-tetramethyl-3,5-heptanedionato)iron(III) and ferrous oxalate dehydrate. In other embodiments, the Fe pre-catalyst is selected from terpyridine-FeBr₂, FeBr₂, FeBr₃ and Fe(OAc)₂. In some embodiments, the Fe pre-catalyst is a Fe complex, for example terpyridine-FeBr₂.

15 In some embodiments, the Fe pre-catalyst is a Fe complex selected from



In some embodiments, the Fe pre-catalyst further comprises a ligand. For example, when the Fe pre-catalyst is selected from FeBr₂, FeBr₃, Fe(OAc)₂, FeCl₂, FeCl₃, Fe(II) acetylacetonate, Fe(III) acetylacetonate, Fe(II) trifluoromethanesulfonate, tris(2,2,6,6-tetramethyl-3,5-heptanedionato)iron(III) and ferrous oxalate dehydrate, an additional ligand can be added. The ligand can be a bulky ligand. For example, a bisphosphine

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ligand such as 1,1-Bis(diphenylphosphino)methane, 1,2-Bis(diphenylphosphino)ethane, 1,3-Bis(diphenylphosphino)propane, 1,2-Bis(diphenylphosphanyl)benzene, or 2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl can be added. In this way, a Fe complex can be generated *in situ*.

5

In some embodiments, the protic additive is selected from t-butyl alcohol, methanol, ethanol, isopropyl alcohol (or any other alcohols), phenol, water and carboxylic acids.

10 In some embodiments, the protic additive is added after the formation of the metal-hydride species and/or metal-boryl species. To this end, the protic additive can be added after the compound of Formula (I) has been contacted with the boron compound and iron pre-catalyst. For example, the protic additive can be added

15 In some embodiments, the protic additive is generated *in situ* from a polar solvent and an alkali metal oxide. Advantageously, the generation of the protic additive *in situ* delays protonolysis of the intermediate Fe-alkyl species in the presence of an alkoxide base without suppressing chain-walking.

20 As used herein, "alkali metal oxide" refers to alkali metals (group 1 elements) formed ionic oxides.

25 In some embodiments, the polar solvent is a polar aprotic solvent. Polar solvents have large dipole moments (aka "partial charges"); they contain bonds between atoms with very different electronegativities, such as oxygen and hydrogen. Polar aprotic solvents are generally solvents that lack an acidic hydrogen and consequently are not hydrogen bond donors. Polar aprotic solvents generally have intermediate dielectric constants and polarity. Polar aprotic solvent can have both high dielectric constants and high dipole moments. As used herein, polar solvents and polar aprotic solvents include solvent mixtures in which one component is a polar solvent or a polar aprotic solvent. Examples
30 of polar and/or polar aprotic solvents are, but not limited to, pyridine, ethyl acetate, dimethylformamide (DMF), HMPA, and dimethyl sulfoxide (DMSO), acetonitrile, dichloromethane (DCM), N-methylpyrrolidone, tetrahydrofuran (THF), acetone, propylene carbonate.

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In some embodiments, the polar solvent is dimethylacetamide (DMA), dimethylsulfoxide (DMSO), CH₃CN, N,N'-dimethylpropyleneurea (DMPU), dimethylformamide (DMF) or a mixture thereof. In other embodiments, the polar solvent is dimethylacetamide (DMA) or a mixture of DMA and toluene.

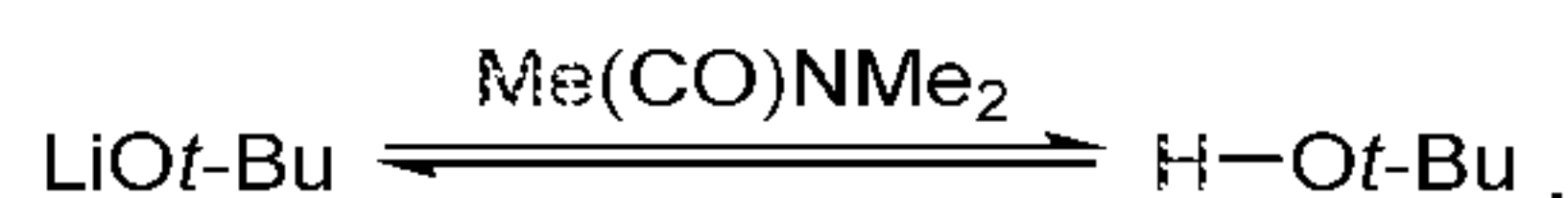
5

In other embodiments, the alkali metal oxide is an at least stoichiometrically equivalent amount of alkali metal oxide to the compound of Formula (I). In some embodiments, the alkali metal oxide is at least stoichiometrically equivalent to the compound of Formula (I). In other embodiments, the alkali metal oxide is at least 1.1
10 stoichiometrically equivalent to the compound of Formula (I), or at least 1.2, or at least 1.3, or at least 1.4, or at least 1.5.

In some embodiments, the alkali metal oxide is selected from the group consisting of lithium tert-butoxide, lithium bis(trimethylsilyl)amide, lithium diisopropylamide, lithium
15 trifluoromethanesulfonate, lithium methoxide, sodium benzenesulfinate, sodium phenolate, sodium methoxide, sodium tert-butoxide, potassium acetate, potassium carbonate, potassium fluoride, potassium tert-butoxide, potassium phosphate monobasic, potassium ethoxide and potassium phosphate tribasic. In other
20 embodiments, the alkali metal oxide is selected from the group consisting of lithium tert-butoxide, lithium bis(trimethylsilyl)amide, lithium diisopropylamide, lithium trifluoromethanesulfonate and lithium methoxide. In other embodiments, the alkali metal oxide is lithium tert-butoxide.

The protic additive can, for example, be generated *in situ* as follows:

25



It was found that a polar solvent (such as DMA) in the presence of an alkali metal oxide allows for remote protoboration, likely by promoting delayed protonolysis without inhibiting olefin isomerization (deuterium studies, Figure 4). It is believed that DMA can
30 act as a weak proton source, and by generating the proton source *in situ*, a low level of proton is maintained in the mixture such that potential side pathways such as hydrogenation and diboration reactions can also be suppressed. Advantageously, by selecting an appropriate solvent and/or alkali metal oxide, alkene isomerization may be further favoured over protoboration. This in turn allows for a high yield of the desired

- 17 -

end product. Further, protonolysis of **C** to **D** (Figure 1b) can be promoted and at the same time not diminish the concentration of the metal-hydride species responsible for C=C bond migration.

- 5 In this regard, by varying the amount of DMA, control over the protonation can be obtained. In some embodiments, the polar solvent is N,N-dimethylacetamide (DMA) or a mixture of DMA and toluene. In other embodiments, the solvent is a 1:2 ratio of DMA:toluene. In other embodiments, the solvent comprises 100% of DMA. In other
10 70%, or at least 60%, or at least 50%, or at least 40%, or at least 30%, or at least 20%, or at least 10%.

In some embodiments, the method is conducted at a temperature of at least 60 °C. In other embodiments, the temperature is at least 65 °C, at least 70 °C, at least 75 °C,
15 at least 80 °C, at least 90 °C or at least 100 °C.

In some embodiments, a protic reagent (high dielectric constants and high polarity) when added is found to be advantageous in that while C=C bond isomerization can be suppressed, the protic reagent can also suppress formation of undesirable diboration
20 products. As used herein, 'reagent' refers to a substance added at a substantive amount to a reaction.

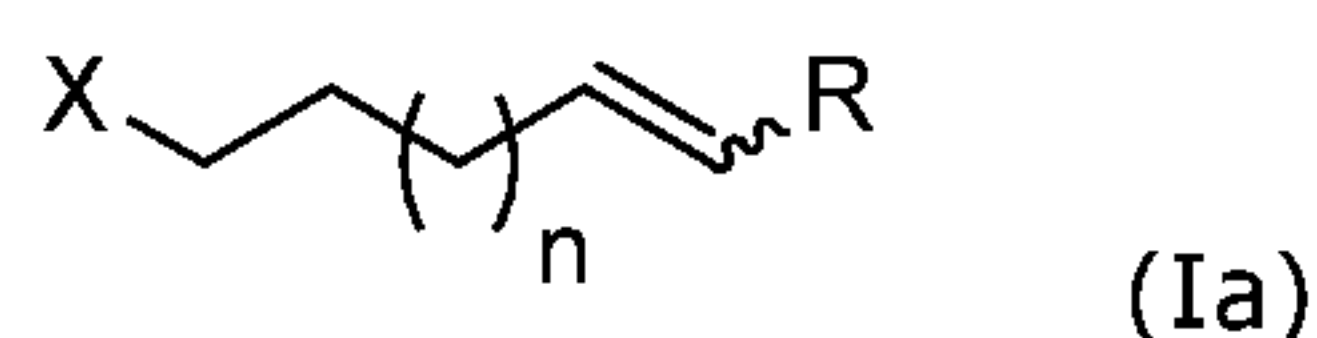
The inventors have found that when a protic reagent is added at a suitable amount, the advantage of suppression of diboration products outweighs the disadvantage of
25 suppression of C=C bond isomerisation. In this regard, in some embodiments, the method further includes contacting the compound of Formula (I) with less than 0.25 stoichiometric equivalent of a protic reagent. The protic reagent can be t-butyl alcohol, methanol, ethanol, isopropyl alcohol (or any other alcohols), phenol, water and carboxylic acids. In other embodiments, the protic reagent is t-butyl alcohol. In other
30 embodiments, less than 0.20 stoichiometric equivalent is added, or less than 0.15 stoichiometric equivalent is added, or less than 0.10 stoichiometric equivalent is added, or less than 0.05 stoichiometric equivalent is added.

The combination of the synergistic hydrometallation and borometallation reactions
35 allows for the remote borylation of unactivated C-H bond at the vicinal (β) position to

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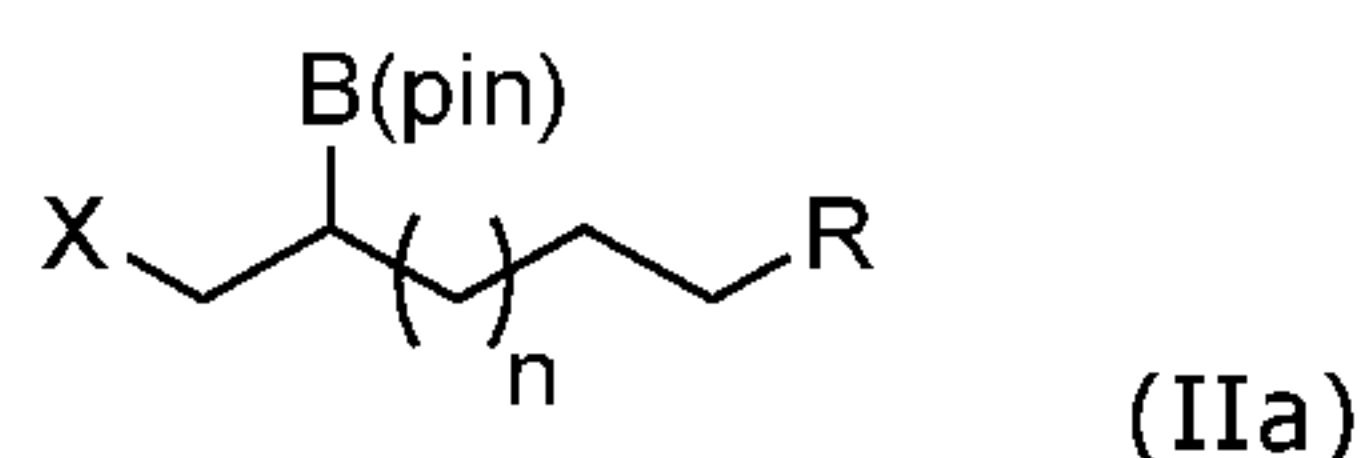
the X moiety of the compound of Formula (I). Because of the specificity of the reactions, and as elucidated in Figure 5, there can be stereochemistry at the borylated carbon (C_β). In this regard, in some embodiments, the compound of Formula (II) has a chiral configuration about the borylated carbon. The compound of Formula (II) can result in a racemic mixture, or a mixture which is enantiomeric rich in one form, or an enantiomeric pure compound.

In some embodiments, the compound of Formula (I) is a compound of Formula (Ia):



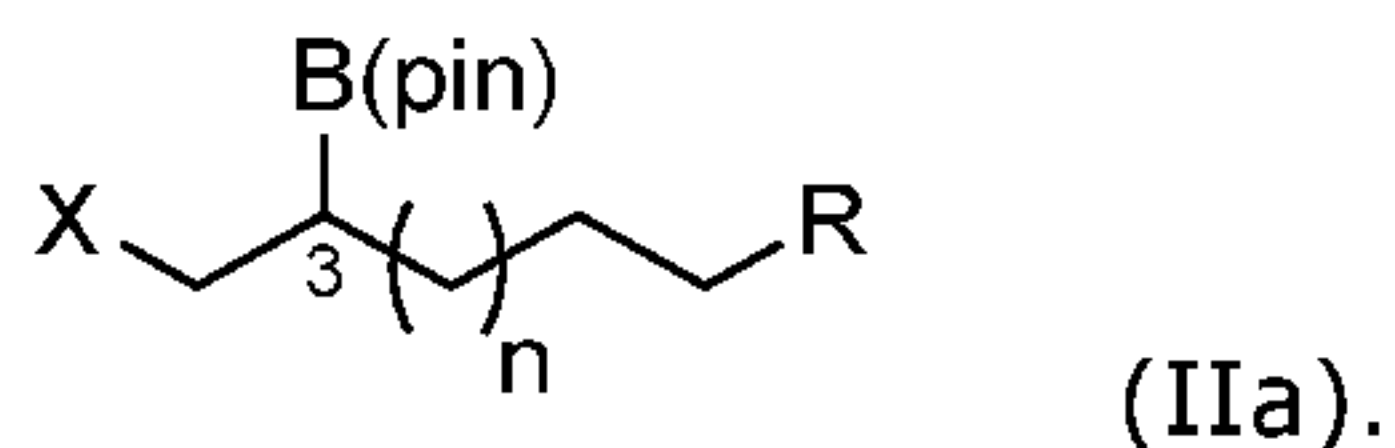
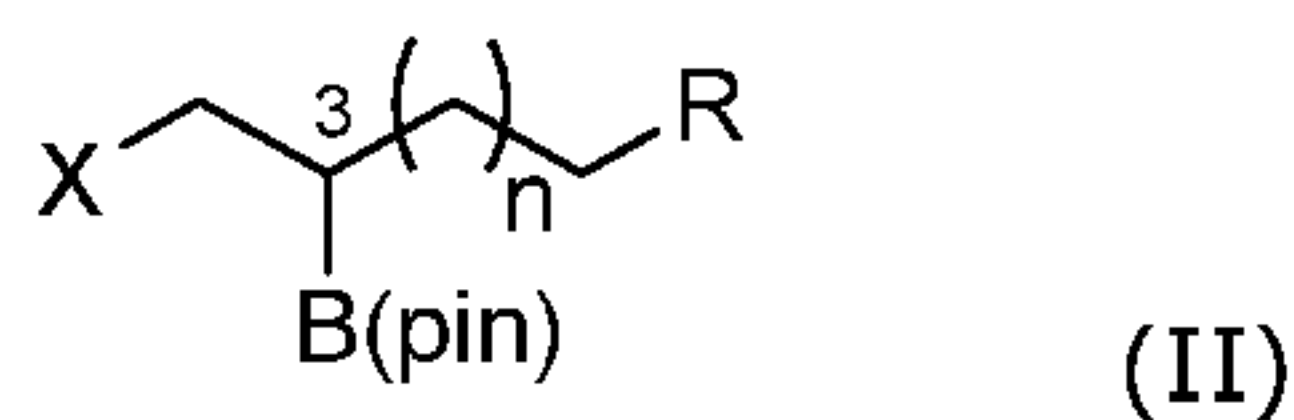
- wherein X is selected from the group consisting of optionally substituted silyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted dioxyboronyl and B(pin);
- R is selected from the group consisting of H, halo, optionally substituted alkyl and optionally substituted cycloalkyl; and
- n is an integer selected from 0 to 9.

Compounds of Formula (Ia) would thus give a compound of Formula (IIa):



- wherein X, R and n are as defined herein, and pin is pinacolyl.

In some embodiments, the borylation occurs at the 3' position (β position) of compound of Formula (II) and (IIa):



In some embodiments, a regioselective ratio (r.r.) of a compound of Formula (II) and/or (IIa) to a compound of other regioisomer (i.e. not at the 3' position) is at least about 70:30. In this regard, at least about 70% of the isomers obtainable is a compound of

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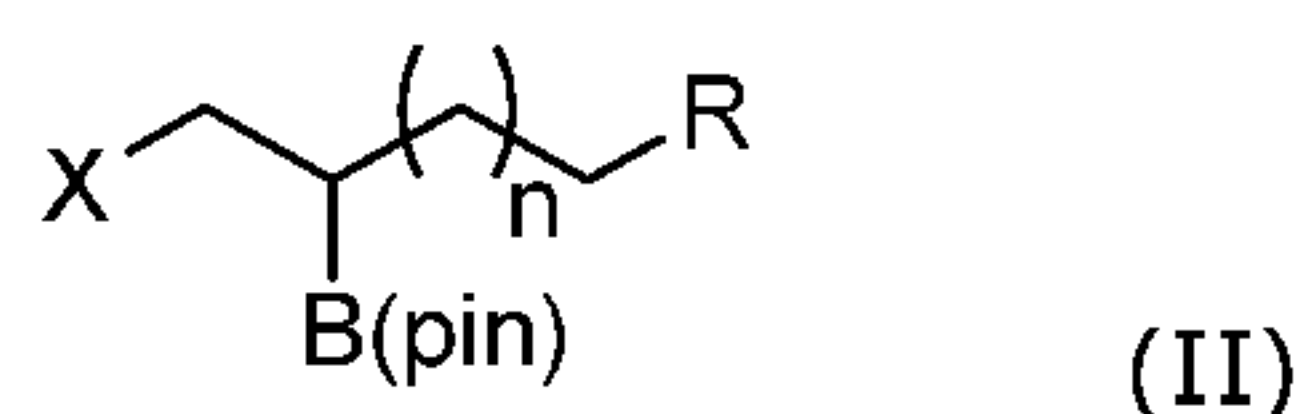
Formula (II) and/or (IIa). This is also referred to as β selectivity. In other embodiments, the r.r. is at least about 75:25, 80:20, 85:15, 90:10, or 95:5.

The present invention provide a method that allows for boron installation at typically unactivated sites β to an assortment of common functionalities. As illustrated in Figure 2 and in the examples, the ability to access β -borylalkanes by remote protoboration can simplify the way with which many molecules of interest are prepared. For example, lesser steps are required to produce a pharmaceutical compound, and the end product can be obtained at higher yield and higher stereospecificity. The presently disclosed method also allows for site-selective functionalizations of other unreactive C-H bonds that pervade an aliphatic hydrocarbon molecule, and accordingly allows for a route to access to currently productively unviable yet important compounds.

In a further aspect, one would appreciate that compounds of Formula (II) can be synthesized based on the method as disclosed herein, starting from compounds of Formula (I). In this regard, the present invention provides a method of preparing compounds of Formula (II).

In an aspect, the present invention discloses compounds of Formula (II) as prepared by the methods herein.

In another aspect, the present invention provides a compound of Formula (II):



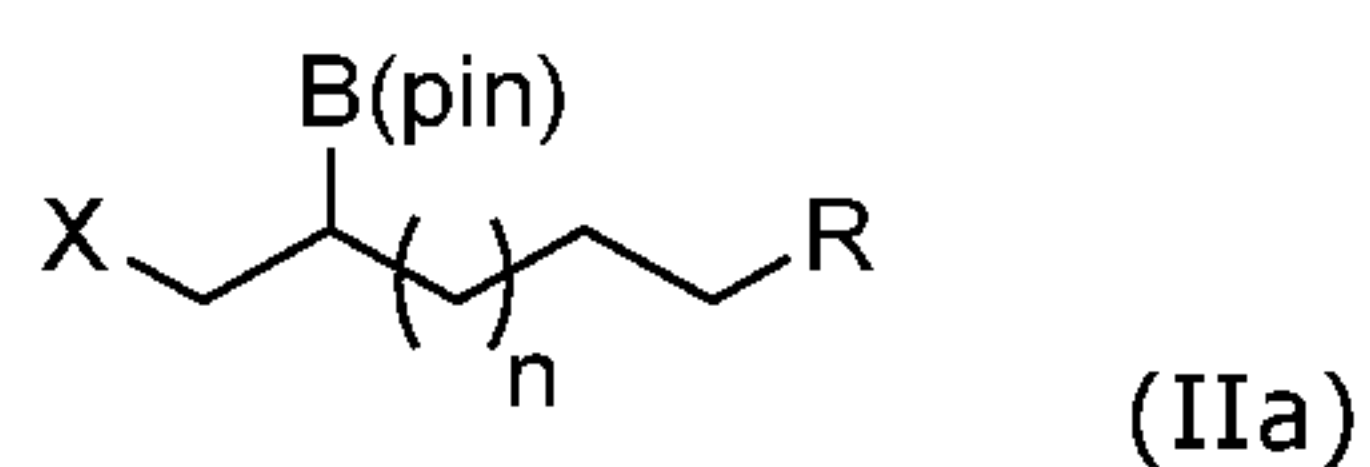
wherein pin is pinacolyl;

X is selected from the group consisting of optionally substituted silyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted dioxyboronyl and B(pin);

R is selected from the group consisting of H, halo, optionally substituted alkyl and optionally substituted cycloalkyl; and
n is an integer selected from 0 to 10.

In some embodiments, the compound of Formula (II) is a compound of Formula (IIa):

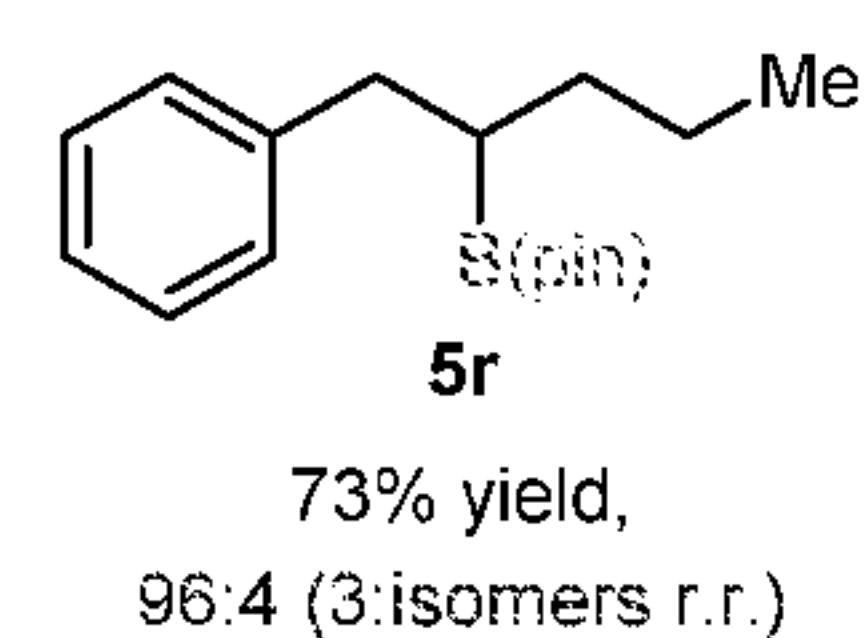
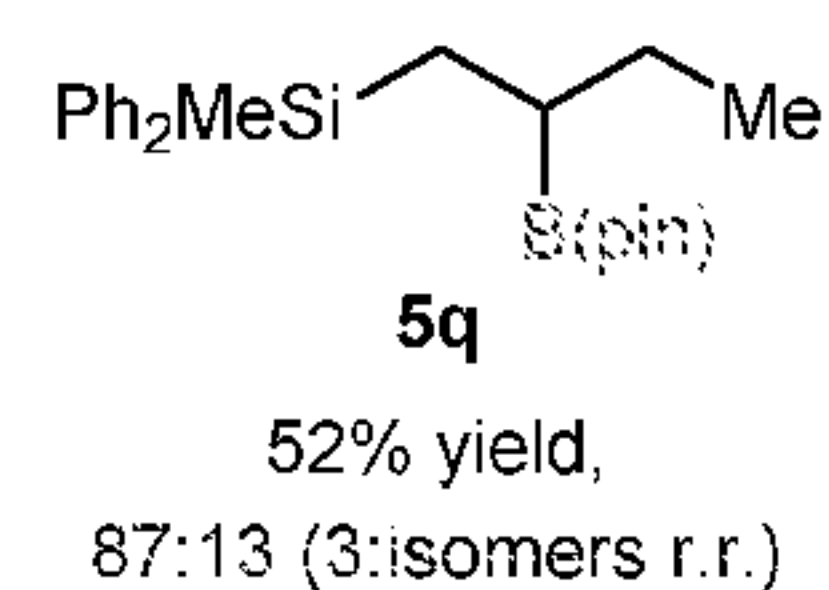
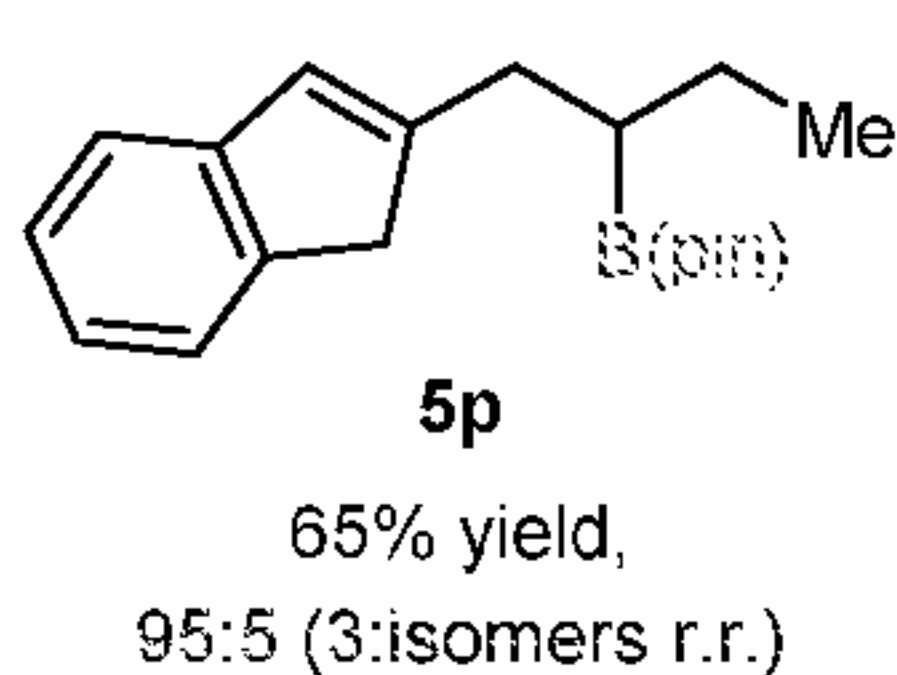
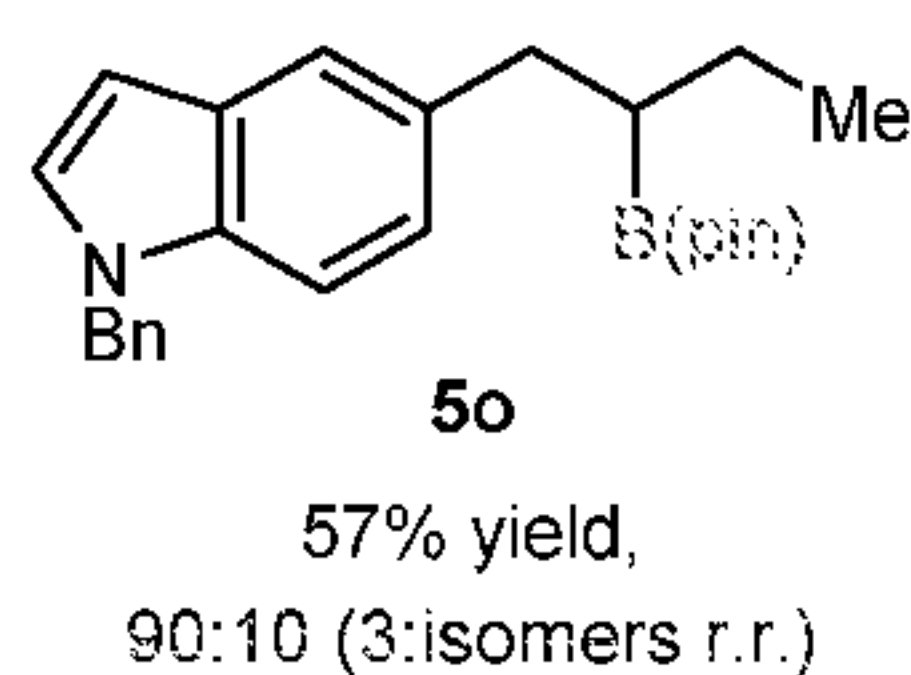
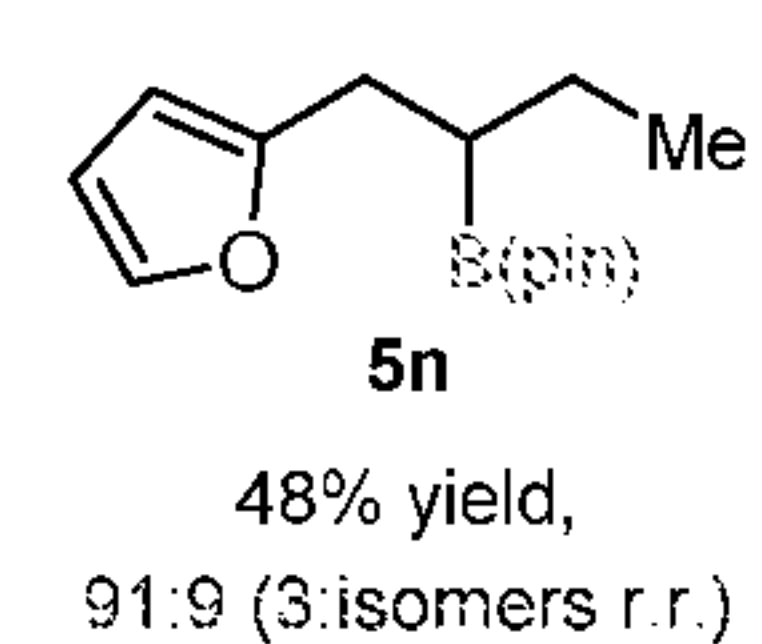
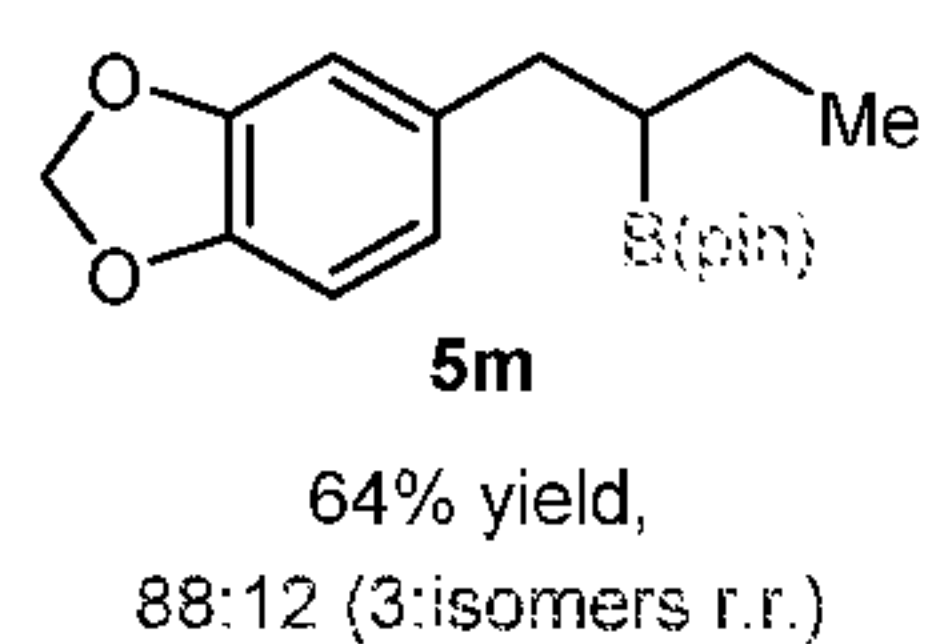
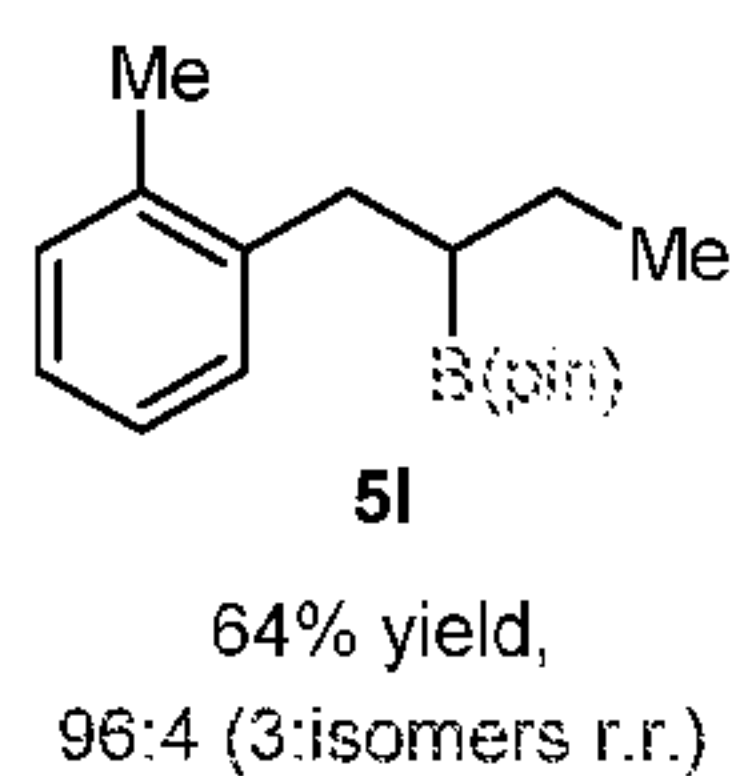
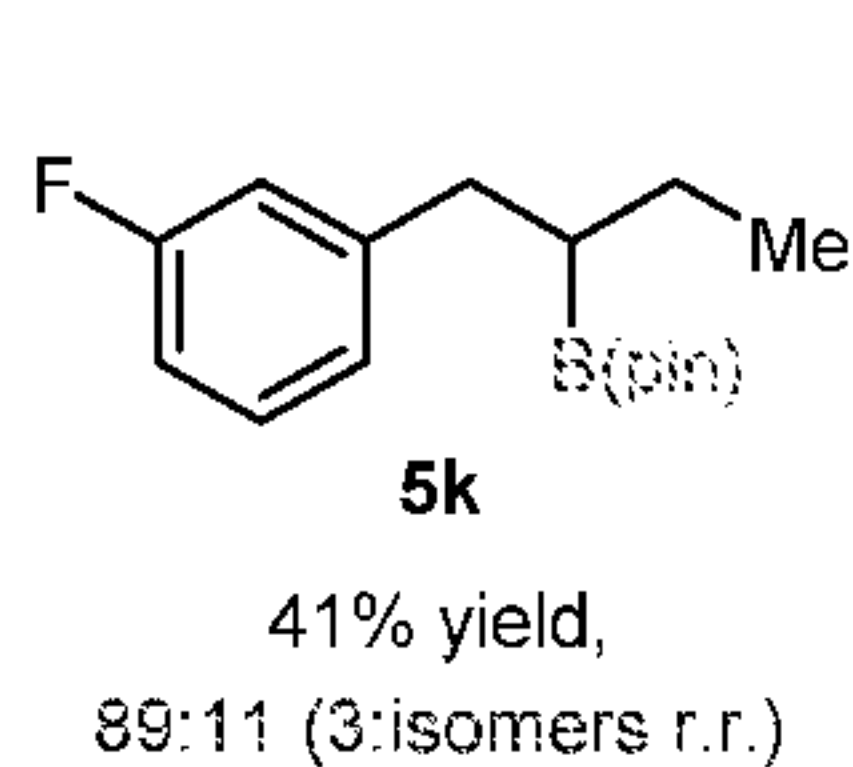
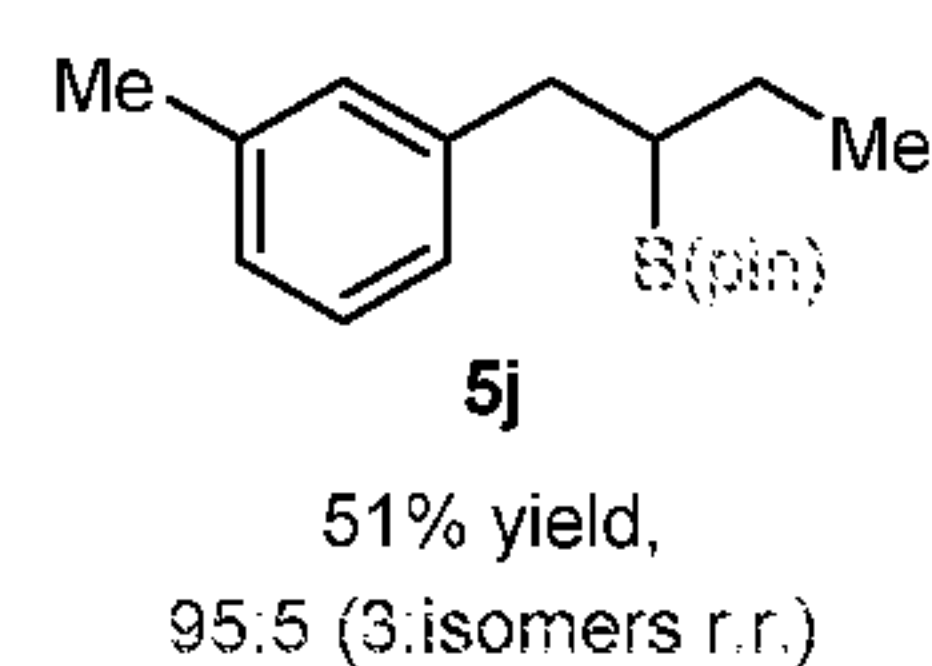
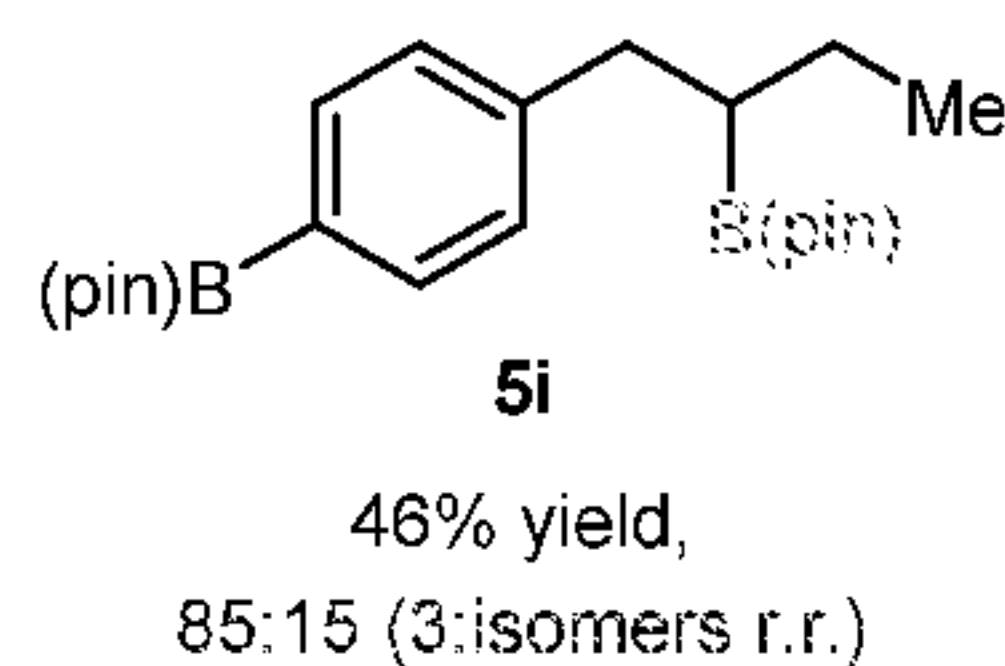
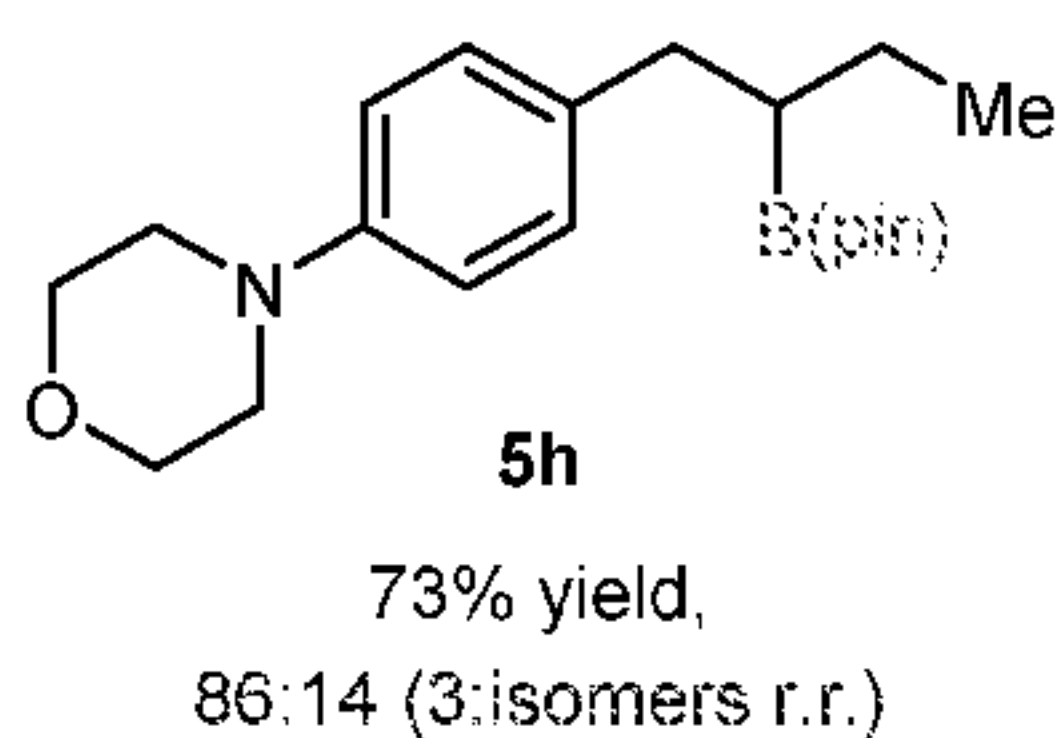
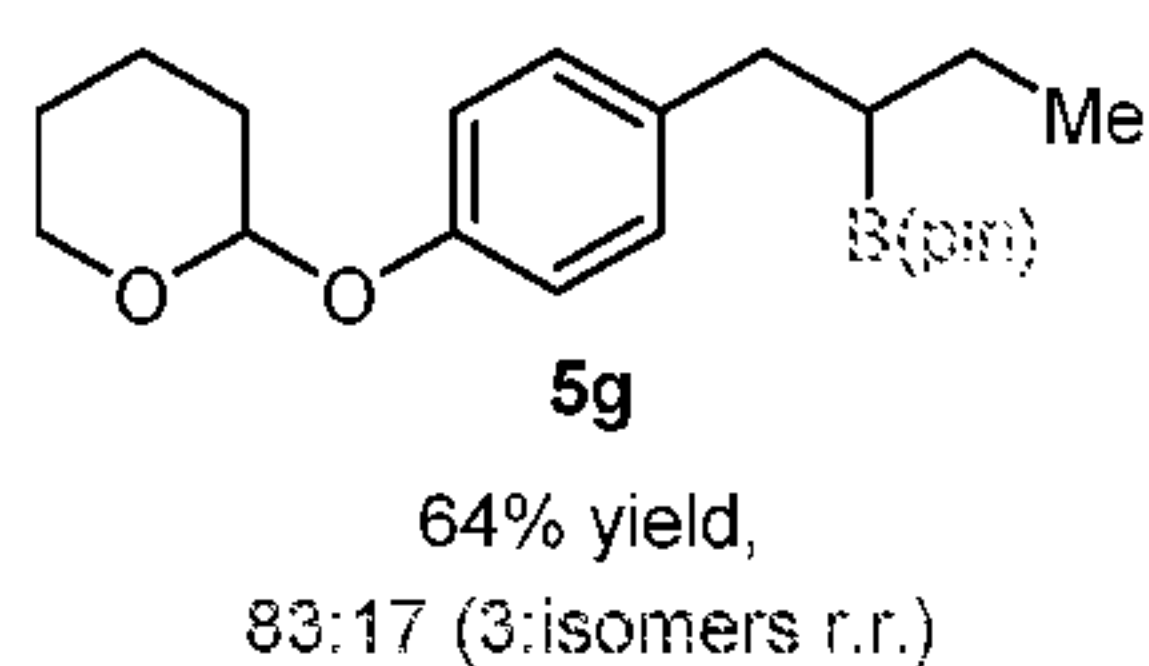
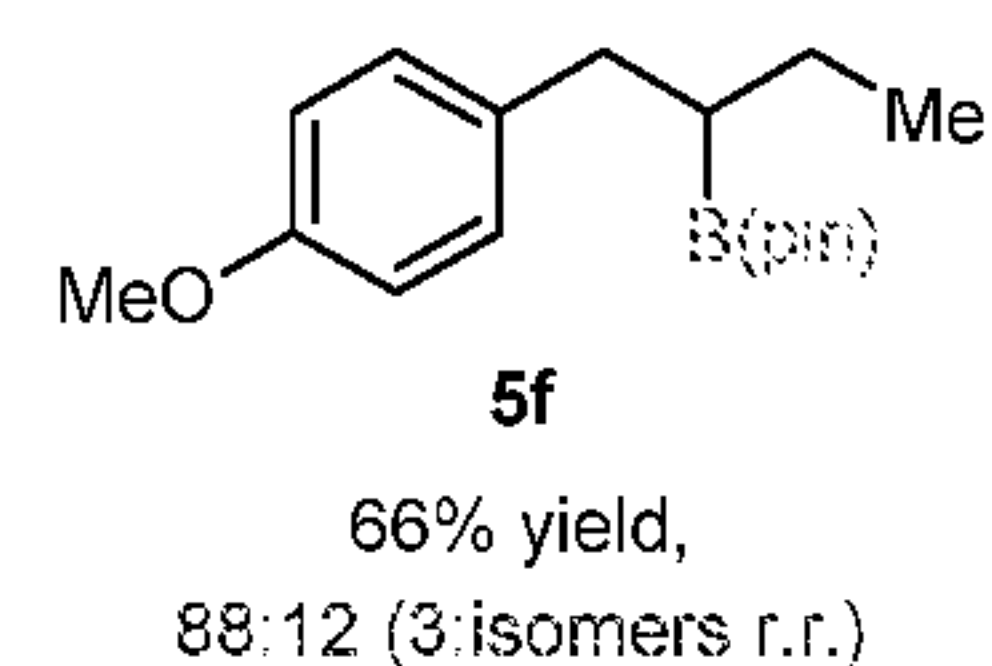
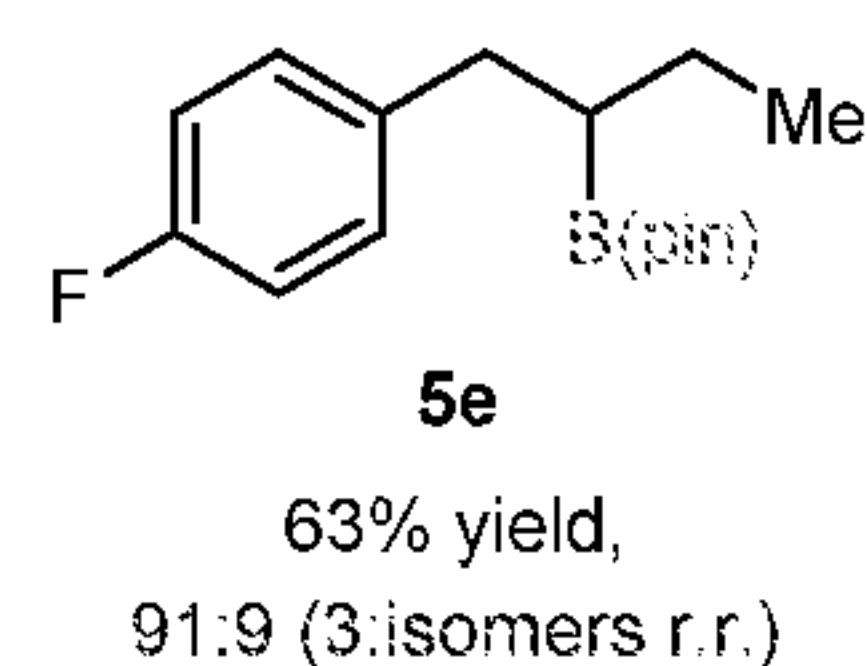
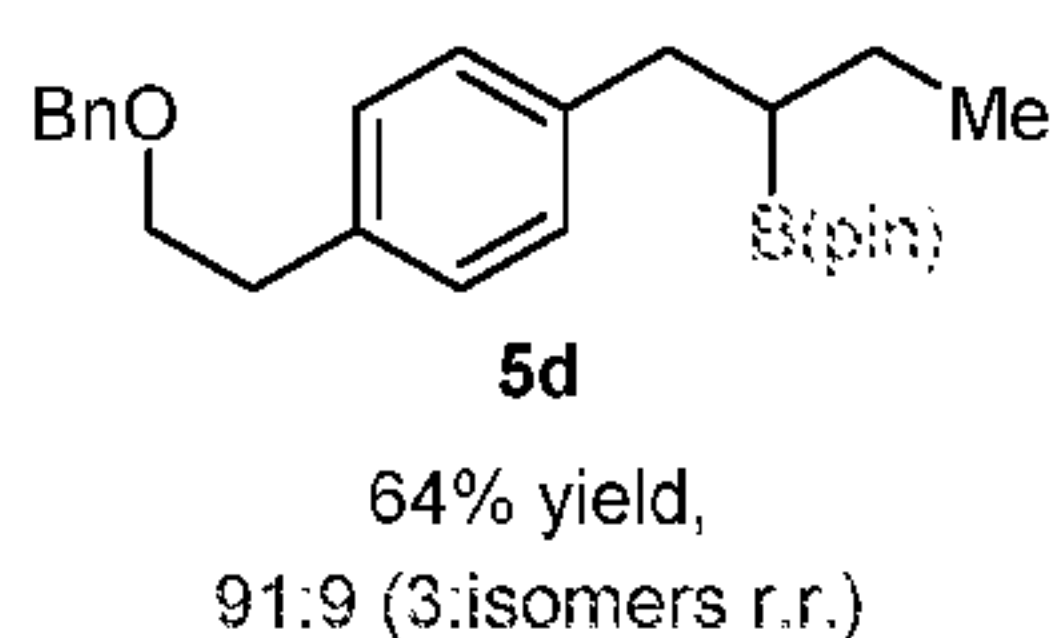
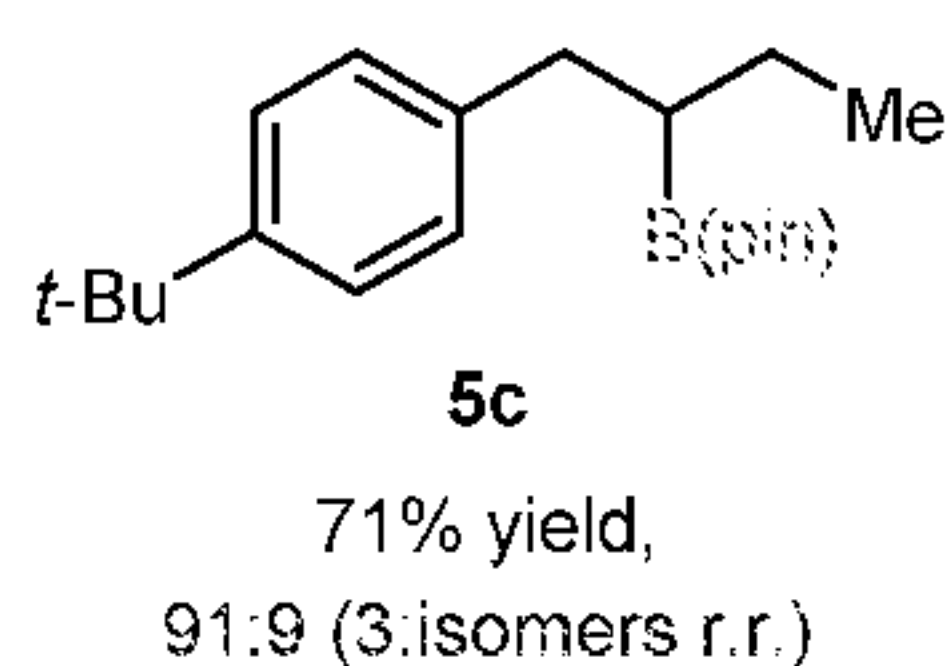
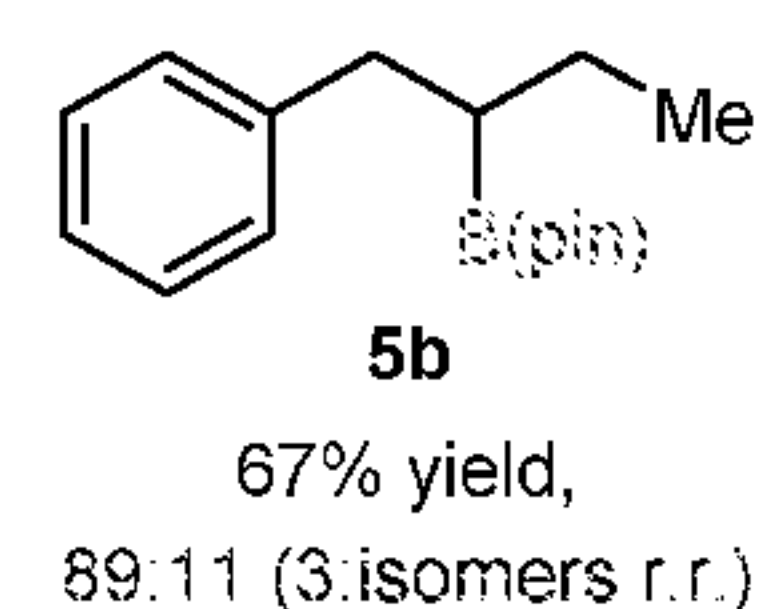
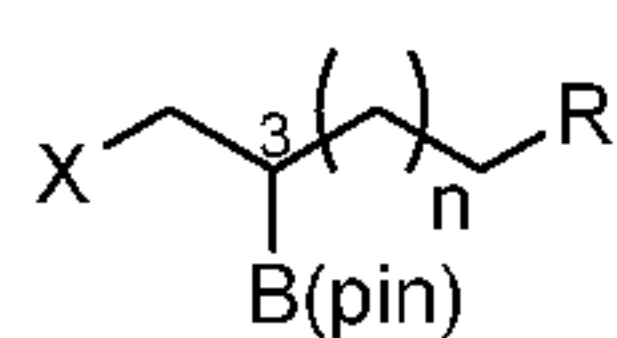
- 20 -



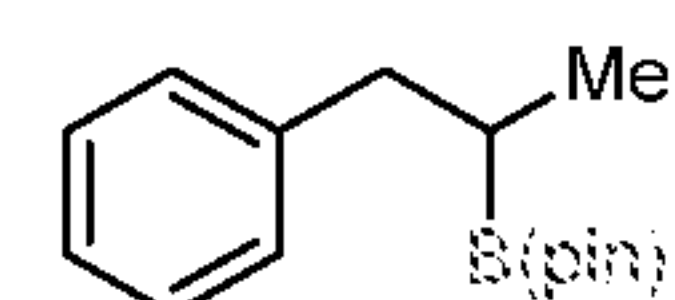
wherein X, R and n are as defined herein, and pin is pinacolyl.

Examples of compounds of Formula (II) and/or (IIa) are as follows:

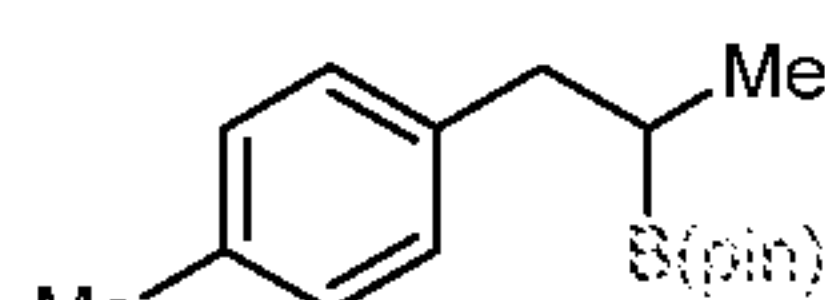
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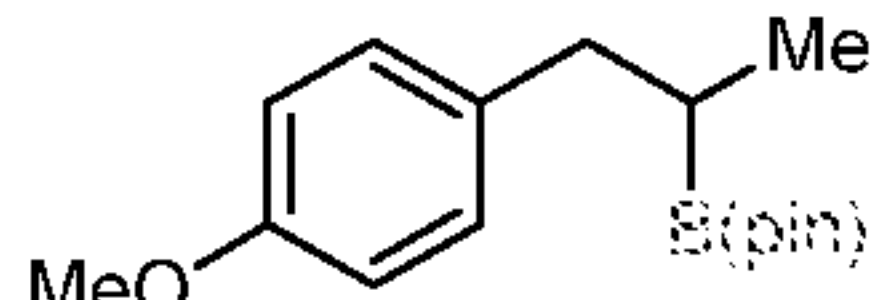
- 21 -

**7a**

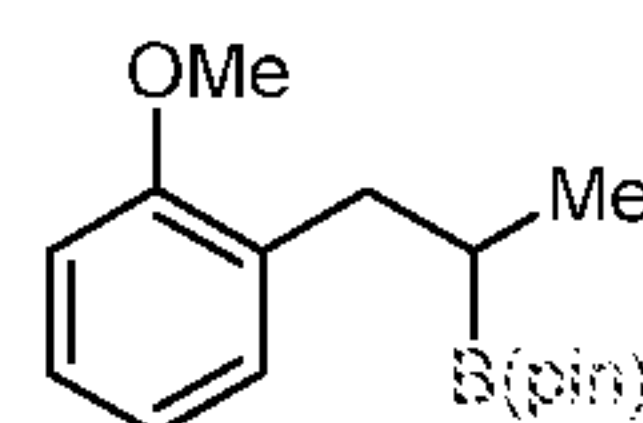
77% yield,
>98:2 (3:isomers r.r.)

**7b**

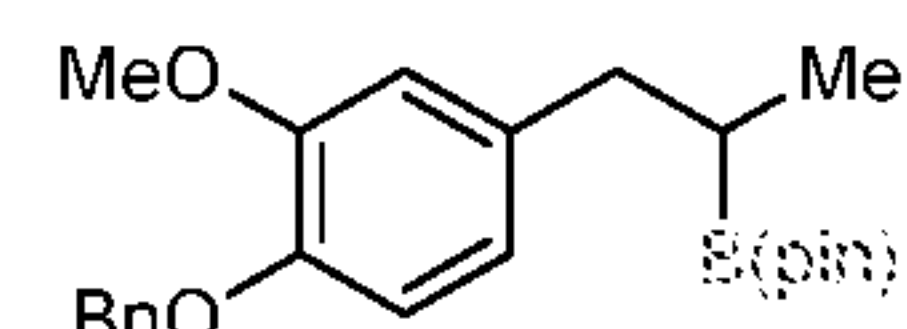
70% yield,
>98:2 (3:isomers r.r.)

**7c**

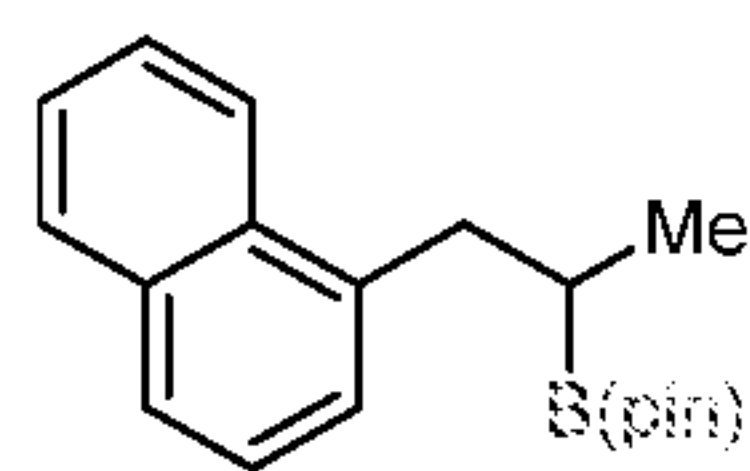
80% yield,
>98:2 (3:isomers r.r.)

**7d**

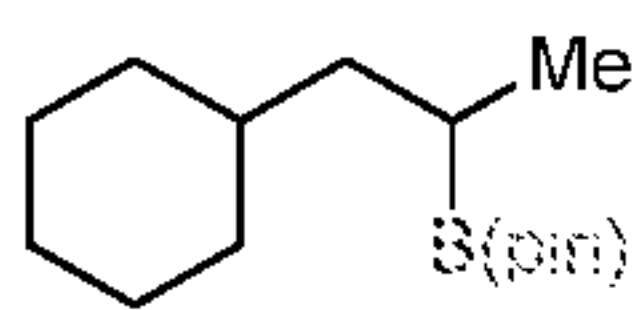
83% yield,
>98:2 (3:isomers r.r.)

**7e**

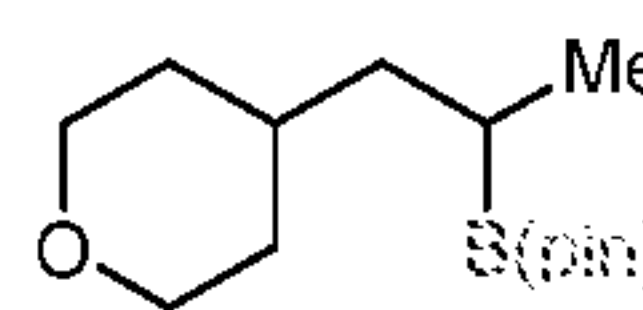
62% yield,
>98:2 (3:isomers r.r.)

**7f**

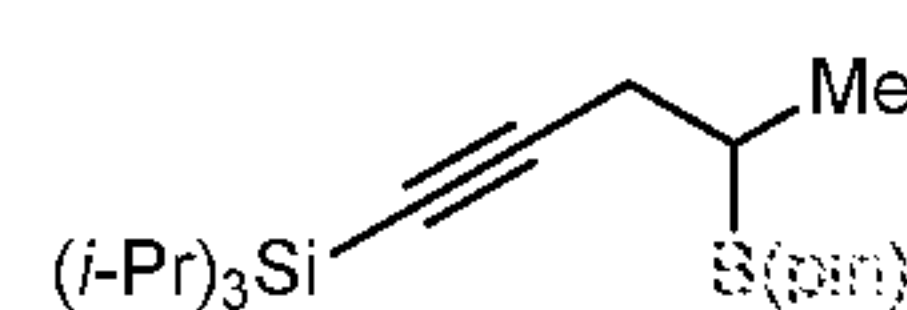
66% yield,
>98:2 (3:isomers r.r.)

**7g**

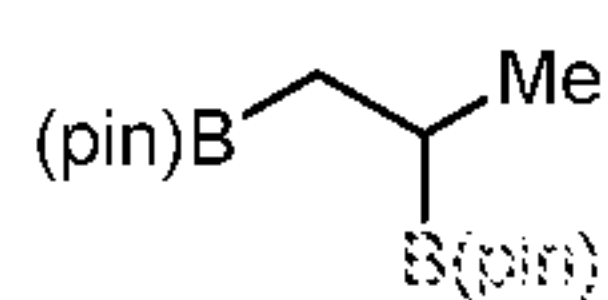
68% yield,
97:3 (3:isomers r.r.)

**7h**

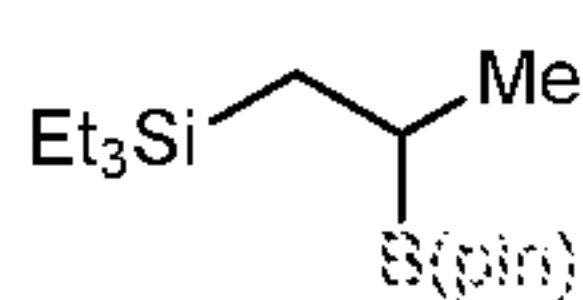
46% yield,
85:15 (3:isomers r.r.)

**7i**

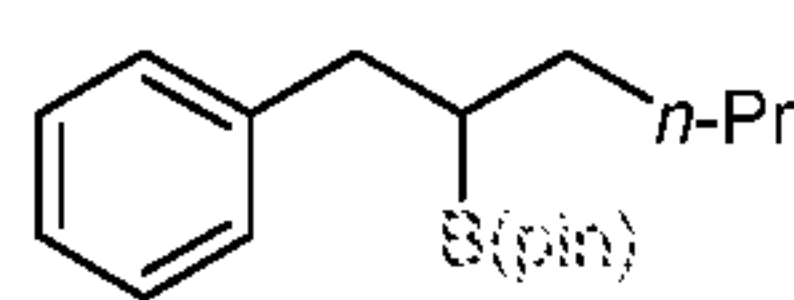
50% yield,
>98:2 (3:isomers r.r.)

**7j**

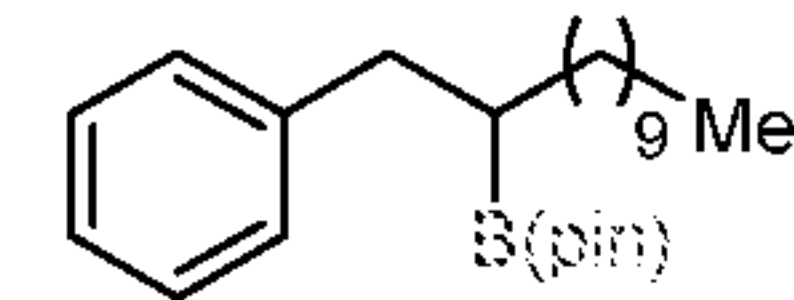
36% yield (47% yield),
>98:2 (3:isomers r.r.)

**7k**

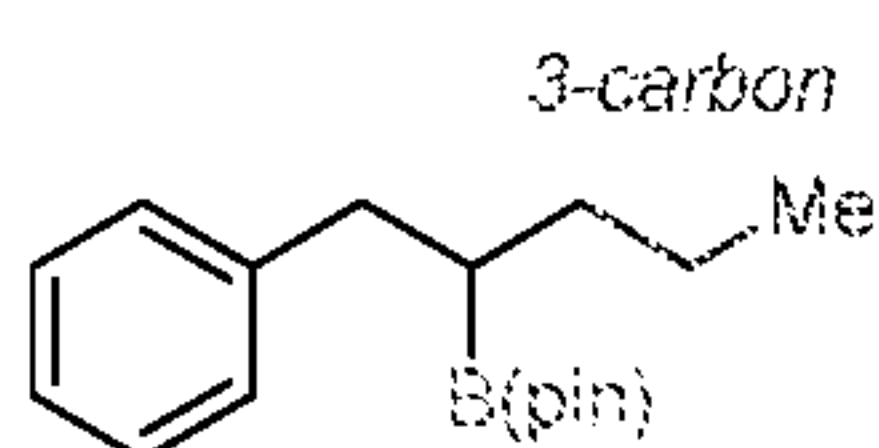
63% yield,
97:3 (3:isomers r.r.)

**7l**

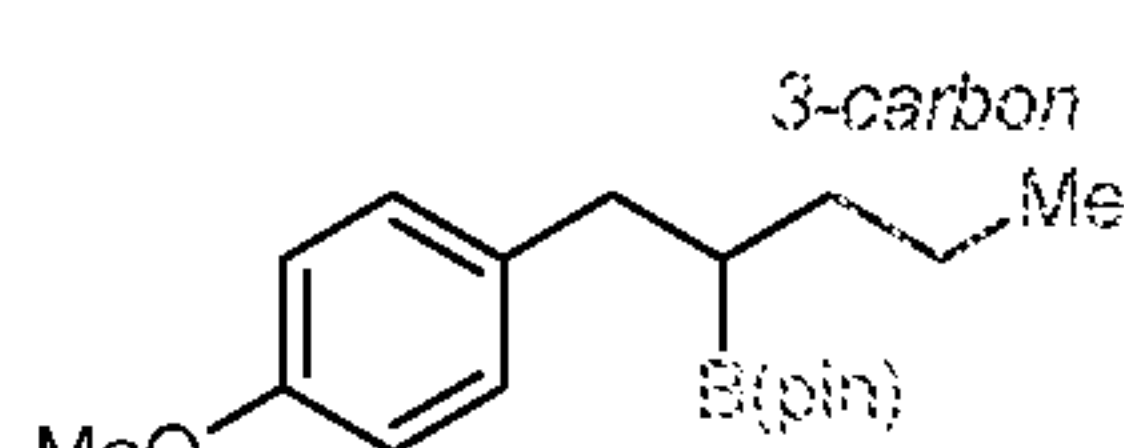
85% yield,
>98:2 (3:isomers r.r.)

**7m**

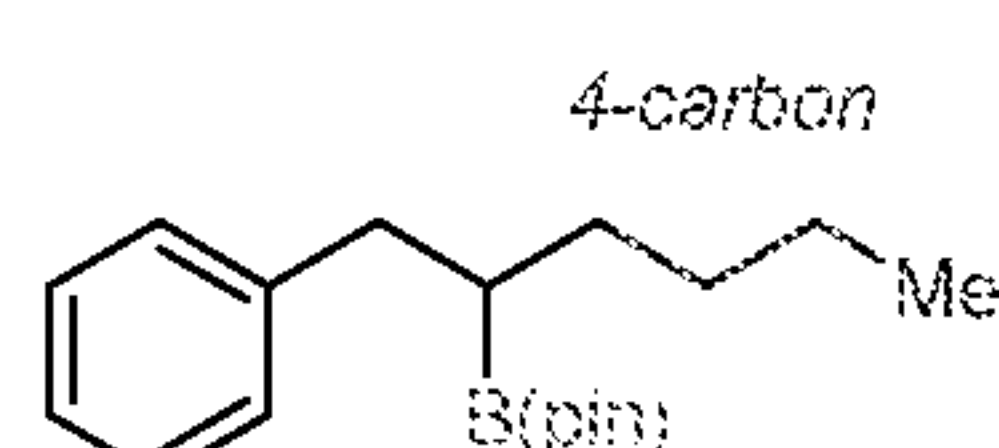
78% yield,
>98:2 (3:isomers r.r.)

**5r**

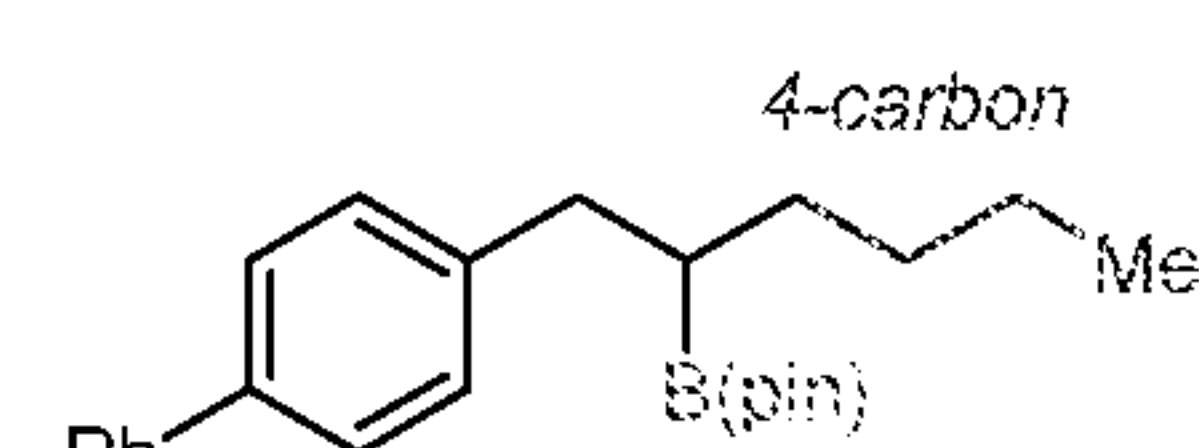
66% yield,
86:14 (3:isomers r.r.)

**9**

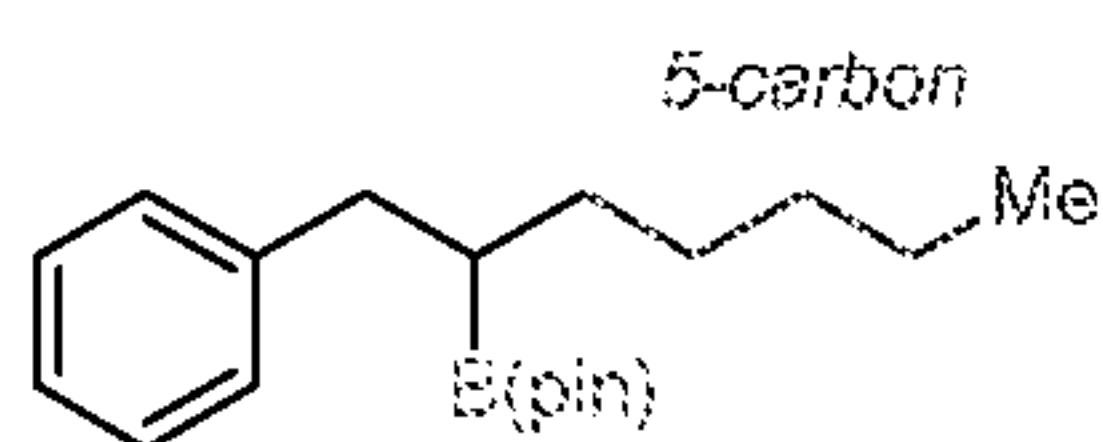
71% yield,
92:8 (3:isomers r.r.)

**7k**

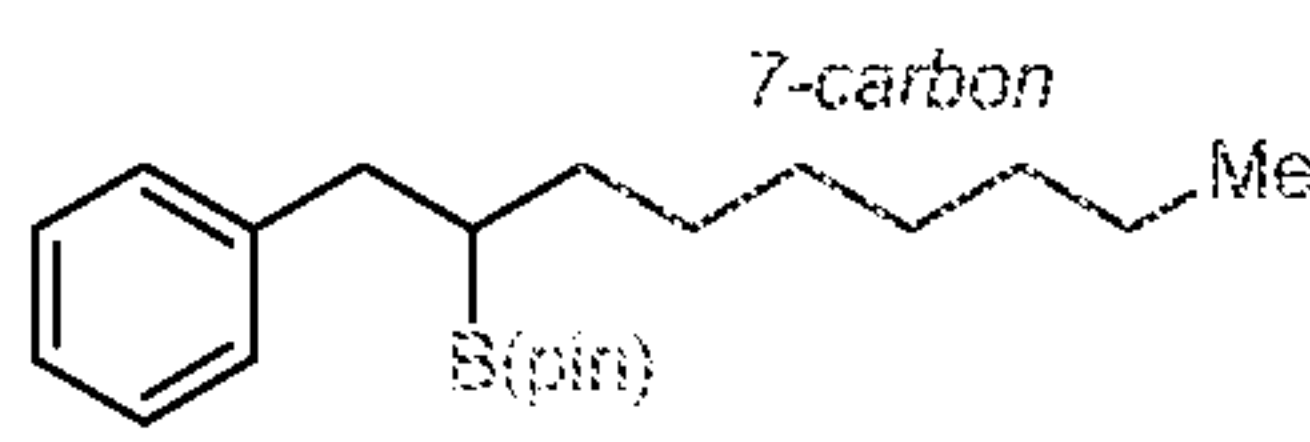
50% yield,
88:12 (3:isomers r.r.)

**10**

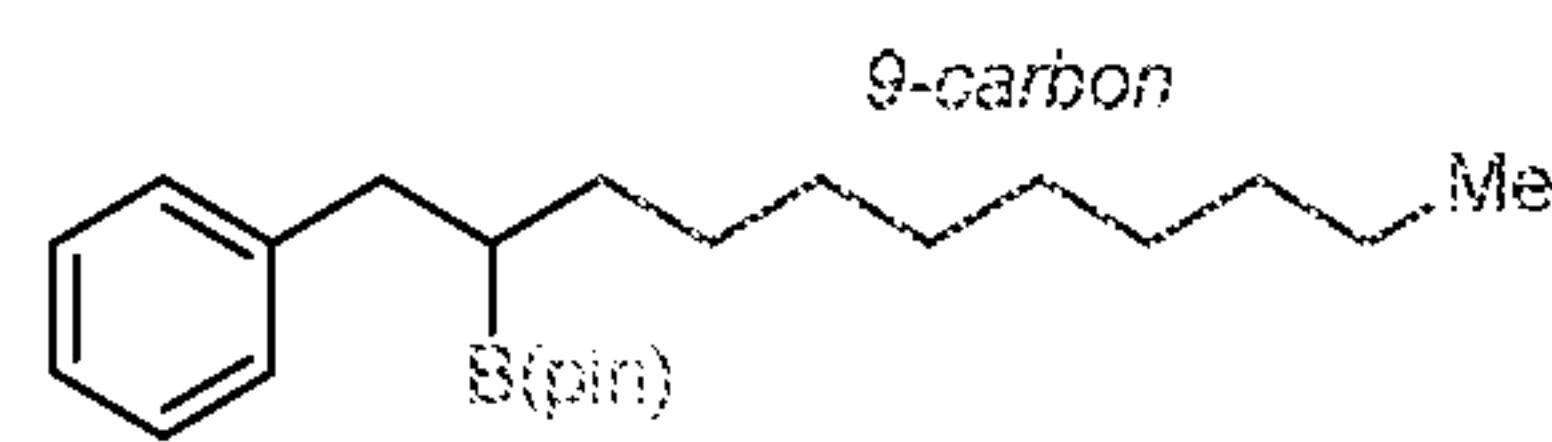
52% yield,
92:8 (3:isomers r.r.)

**11**

60% yield,
89:11 (3:isomers r.r.)

**12**

55% yield,
88:12 (3:isomers r.r.)

**13**

50% yield,
84:16 (3:isomers r.r.)

- 5 A detailed description of the workings of the invention is laid out below. The invention is described in relation to some embodiments and conditions for consistency to showcase the present invention. However, the skilled person would understand that the invention is not limited to such.

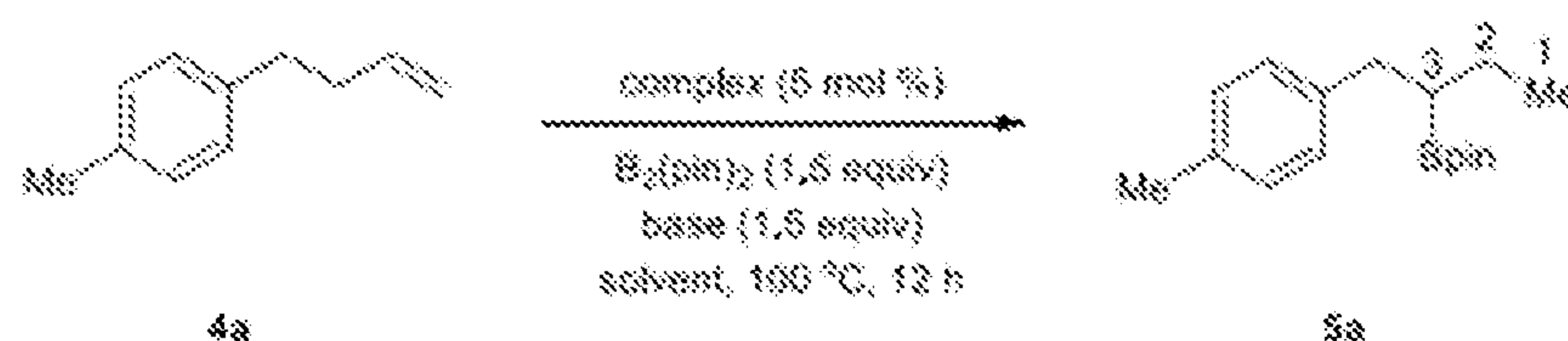
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Optimization Studies

With reference to Figure 3, studies were conducted with alkene **4a** using stoichiometric amounts of bis(pinacolato)diboron ($B_2(\text{pin})_2$; pin, pinacolato), lithium *tert*-butoxide and anhydrous *N,N*-dimethylacetamide (DMA; 0.4 M) as solvent under N_2 atmosphere (Figure 3i). A survey of representative base metal pre-catalysts (5 mol %) at 100 °C revealed that iron-based compounds and complexes were generally more efficient in promoting β -selective protoboration, whereas Cu-, Ni- and Co-based complexes either afforded olefin isomeric mixtures or gave poor conversions to 1- and 2-borylalkanes from site-specific protoboration (Table 1). Terpyridine- $FeBr_2$ complex **Fe-1** was found to be the pre-catalyst that furnishing the desired 3-borylalkane product **5a** with at least 85% β selectivity.

Table 1. Catalyst and solvent screening for homoallylic substrates

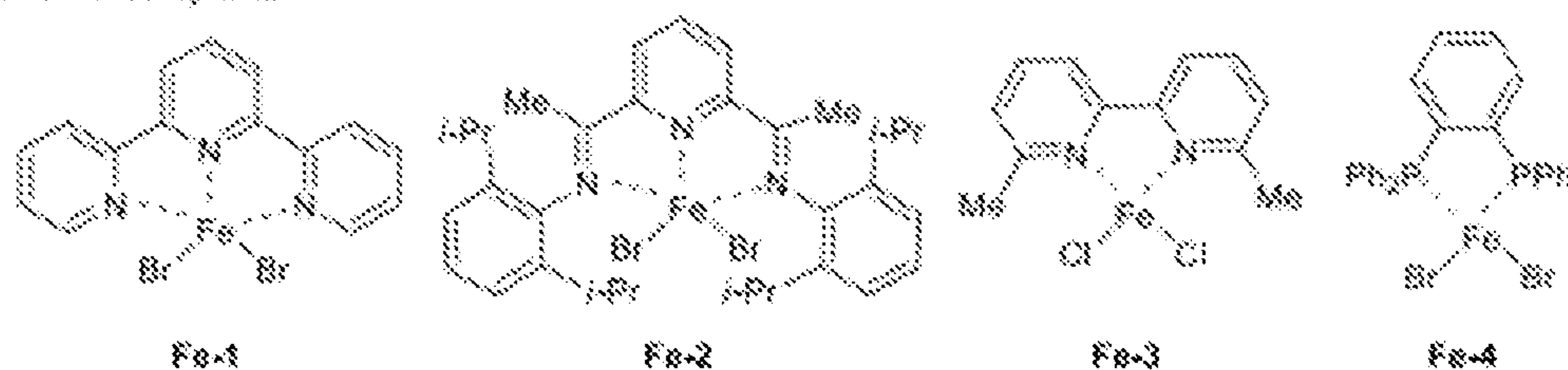
- 23 -



entry	complex	solvent	base	c.r. (3:2:1) ^b	GC yield (%) ^c
1	Fe-1	DMA	LiOt-Bu	88:10:4	89
2	Fe-2	DMA	LiOt-Bu	60:37:3	64
3	Fe-3	DMA	LiOt-Bu	64:32:4	85
4	Fe-4	DMA	LiOt-Bu	0:89:11	20
5	NiCl ₂ (DME)	DMA	LiOt-Bu	ND	trace ^d
6	SiMes-CuCl	DMA	LiOt-Bu	0:75:25	12 ^e
7	CoBr ₂	DMA	LiOt-Bu	ND	trace ^d
8	FeBr ₂	DMA	LiOt-Bu	79:19:2	73
9	FeBr ₂	DMA	LiOt-Bu	81:17:2	74
10	Fe(OAc) ₂	DMA	LiOt-Bu	78:19:3	73
11	<i>o</i> -C ₆ H ₅ Fe(CO) ₂	DMA	LiOt-Bu	0:24:76	30 ^f
12	Fe-1	DMA	NaOt-Bu	78:18:4	55
13	Fe-1	DMA	KOt-Bu	94:5:1	78 ^g
14	Fe-1	DMA	KF	ND	1 ^h
15	Fe-1	DMA	LiOMe	85:4:11	25 ⁱ
16	Fe-1	DMA	NaOPh	0:32:78	29 ^d
17	Fe-1	DMA	LiTMP	49:7:44	15 ^d
18	Fe-1	1,4-Dioxane	LiOt-Bu	78:22:0	10
19	Fe-1	DMF	LiOt-Bu	0:82:18	25
20	Fe-1	DMSO	LiOt-Bu	0:90:10	10
21	Fe-1	Toluene	LiOt-Bu	ND	trace ^d
22	Fe-1	DMA:Toluene = 1:2	LiOt-Bu	68:7:5	89(73)
23	Fe-1 ⁱ	DMA:Toluene = 1:2	LiOt-Bu	90:7:3	90(75)
24	Fe-1	DMA:DMSO = 1:2	LiOt-Bu	0:85:15	22 ^j
25	Fe-1	DMA:CF ₃ C ₆ H ₃ = 1:2	LiOt-Bu	69:30:11	57

^aReaction conditions: complex (5 mol %), **4a** (0.2 mmol), solvent (0.5 mL), N₂ atmosphere, ND, not determined.

^bc.r., determined by GC analysis. ^cConversion to product as determined by GC analysis with *n*-tridecane as internal standard. Values in parentheses are isolated yields. ^dRegioisomeric mixtures of **4a** obtained. ^e80% unreacted **4a** as determined by GC. ^f43% unreacted **4a** as determined by GC. ^g15% diboration side products obtained. ^hKOt-Bu is not optimal because β selectivities are not consistently high with other alkene substrates. ⁱ58% unreacted **4a** and 41% regioisomeric mixtures of **4a** obtained. ^jFe-1 was synthesized using 99,99% FeBr₂, 68% unreacted **4a** as determined by GC.



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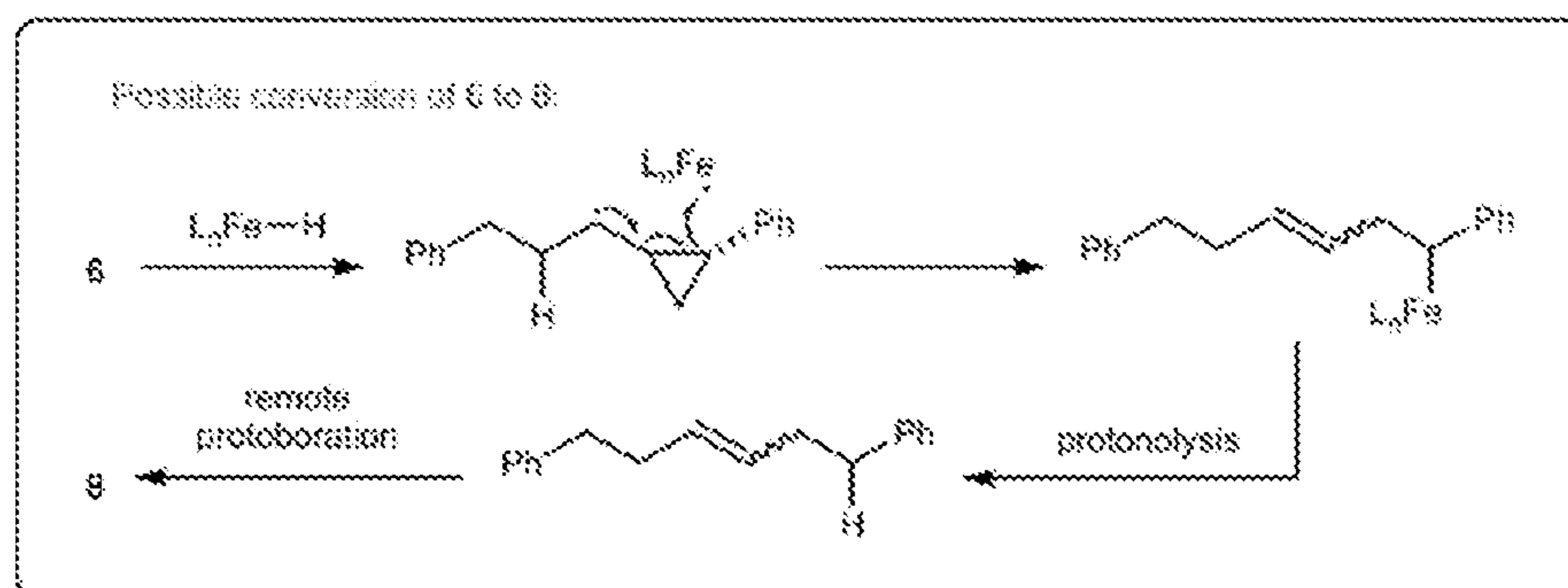
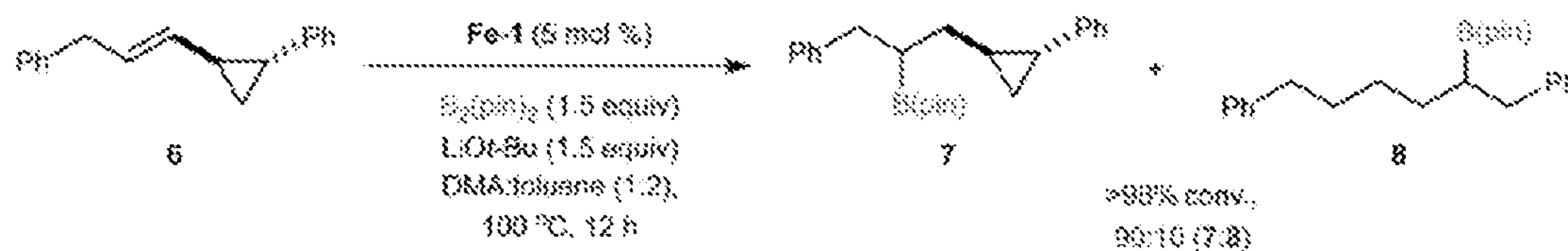
Changing the solvent or lowering the reaction temperature led to diminished efficiency and/or site selectivity. A temperature of at least 60 °C is advantageous. Less than 2% conversion of **4a** was observed in the absence of either Fe-1, boron compound such as B₂(pin)₂ or protic additive (base), highlighting that all components are necessary for chain-walking and/or proto-boryl addition to proceed. Less than 2% conversion to α-borylated product was detected in all experiments. Given the absence of a stoichiometric protic reagent (e.g. alcohol) which is typically employed under standard protoboration conditions, the results with **Fe-1** were somewhat intriguing. Control experiments by adding varied equivalents of *t*-BuOH to the system showed that the ratio of desired 3-borylalkane to other regioisomers diminishes as more alcohol is used (Figure 3ii). These observations suggest that the presence of excessive protons suppresses alkene isomerization by reacting with and lowering the concentration of Fe-hydride species required to promote chain-walking. Consequently, protoboration becomes more competitive giving rise to mixtures of borylated products. What is more, the results with DMA show that it may serve as a weak proton source by providing delayed release of *t*-BuOH (likely generated from adventitious deprotonation with LiOt-Bu) to promote protonolysis without inhibiting C=C bond migration. In line with this deliberation, further improvement in β selectivity by reducing DMA concentration was realized through a 1:2 DMA:toluene solvent mixture (0.4 M), and **5a** was isolated in 73% yield and 88% β selectivity (Fig. 3iii).

Role of solvent

The role of DMA as a proton source was ascertained through deuterium labelling studies with **4a** and *d*₃-DMA as solvent, where ¹H and ²D NMR analyses indicated deuterium scrambling across the hydrocarbon chain as a result of olefin deuteration (Figure 4a, top). Remote protoboration using **d-4b** as substrate shed important light into the mechanism of C=C bond isomerization (Figure 4b, bottom). The observations of deuterium scrambling across the entire hydrocarbon chain in product **d-5b** as well as the erosion of deuterium content led to a deduction that a free Fe-hydride species was generated through β-H elimination, (vs. intramolecular 1,3-hydride shift via a π-allyl intermediate) during the course of chain-walking. Intermolecular crossover between a deuterated and non-deuterated olefin was detected, lending further credence to the postulated formation of Fe-hydride in the catalytic system. Although olefin isomerization through hydrogen atom transfer (vs. Fe-hydride addition/ β-H elimination) cannot be

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completely ruled out, extended X-ray absorption fine structure (EXAFS) and radical clock experiments intimate that this pathway is less likely. Radical clock studies with cyclopropane-containing **6** intimate that olefin isomerization through a hydrogen atom transfer (HAT) pathway might also be competitive with iron-hydride addition- β -H elimination.



Time course study of the reaction of **4a** under the established conditions over 3 hours corroborated that alkene isomerization precedes protoboration (Figure 4b). Rapid conversion of **4a** to its olefin regioisomers **4a'** and **4a''** was observed within the first 15 minutes; the concentration of the latter diminished gradually over time as protoboration proceeded to deliver borylalkane **5a**. Control experiments showed that subjecting a 77:23 mixture of 1-boryl and 2-borylalkane regioisomers to the standard reaction conditions essentially led to complete recovery of the starting material, indicating that olefin borometallation/protonolysis is likely to be irreversible.

XANES and EXAFS studies

Operando X-ray absorption near-edge structure (XANES) and EXAFS measurements were performed of the same reaction mixture (i.e. **Fe-1**, alkene **4a**, $LiOt-Bu$, $B_2(pip)_2$ in DMA/toluene) at varying temperatures. The Fourier-transformed k_2 -weighted EXAFS spectrum of pure **Fe-1** complex in the mixed solvent (Figure 6) exhibited two characteristic peaks at 1.44 Å and 1.99 Å, which were assigned to the Fe-N ($R = 1.93$ Å) and Fe-Br ($R = 2.49$ Å) species and fitted with a coordination number of 5 ($3N+2Br$).

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The addition of LiOt-Bu to the reaction mixture at ambient temperature resulted in the disappearance of the Fe-Br peak and its pre-edge feature in the EXAFS and XANES spectra, respectively. Instead, a small shoulder at $\sim 1.6 \text{ \AA}$ from the Fe-O species ($R = 1.87 \text{ \AA}$) was observed owing to ligand exchange between Fe-Br and LiOt-Bu. This is supported by detailed EXAFS fitting, where the coordination of Fe evolved from 3N+2Br to 3N+2O (iron bisalkoxide).

Upon stepped heating of the reaction mixture from 22 °C to 90 °C to trigger remote protoboration, the intensity of first-shell peak I gradually increased together with an obvious shift in the second-shell peak (peak II) at $\sim 2.3 \text{ \AA}$. A similar phenomenon was detected in the pre-edge area and main peaks in the XANES spectra. The increase in first-shell peak intensity suggests a higher coordination number of Fe that could be attributed to the ligation and activation of **4a** by the organoiron species. During this process, dynamic ligand exchange from Fe-Ot-Bu to Fe-B(pin) to Fe-alkyl (and vice versa) could be taking place. The onset of such exchange could occur at at least 60 °C as substantiated by the shift to longer distance in the second-shell peak. This agrees with experimental observations that the alkene borylation only proceeded at at least 60 °C or above. The second-shell peak deviation might result from an elevated degree of steric encumberedness engendered by the reaction of iron bisalkoxide with bulky B₂(pin)₂ to afford iron-boryl and/or the activation of **4a** by the organoiron species that lead to ligands orienting away from the Fe center to minimize strain. The oxidation state of Fe was constant at +2 from the K-edge location in XANES spectra throughout the entire transformation (Figure 6c). Indirect evidence for the intermediacy of iron-boryl and iron-alkyl species could be derived from the conspicuous peak shift in second-shell atoms.

EPR studies

Electron paramagnetic resonance (EPR) experiments was conducted to analyze the reaction mixture (i.e. **Fe-1** or Fe(OAc)₂, alkene **4a**, LiOt-Bu, B₂(pin)₂ in DMA/toluene) at various temperatures, such as from 22 °C to 100 °C and at various times such as from 2 min to 60 min. Results showed that the originally EPR-silent reaction mixture at 22 °C produced detectable signals ($g = 2.003$) only upon heating to 60 °C and beyond, implying the formation of EPR-active species. At the onset of heating at 100 °C (optimal reaction temperature), EPR signals initially strengthened but gradually diminished

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beyond 10 min, culminating in a drastic reduction in signal intensity after 1 h. Taken together, these observations are somewhat congruent with experimental data and EXAFS measurements suggesting that remote protoboration preferentially occurred at 60 °C and above. Furthermore, since time course study indicated that alkene 4a rapidly converted to its regioisomers (4a' and 4a'') within the first 15 min as borylalkane 5a gradually accumulated over 3 h (Figure 4b), it is surmised that the observed EPR signals might largely arise from radical species formed during the course of HAT-dominated C=C bond transposition prior to the protoboration step. Control experiments also showed that (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) inhibited the reaction at ≥ 30 mol% loadings, and that a mixture of Fe-1, LiOt-Bu and B₂(pin)₂ in DMA/toluene at 100 °C (without 4a) was capable of quenching TEMPO. Further low-temperature experiments in combination with other spectroscopic studies are underway to provide more insights on the nature of the paramagnetic species generated in the reaction system.

Regardless of the Fe-based pre-catalyst being used (**Fe-1a** or Fe(OAc)₂), the signals observed at ambient temperature diminished/vanished and new peaks were obtained at the central field of 317 mT at 100 °C. This implies that a new organoiron species (or a mixture) was generated when the temperature was raised to 100 °C, albeit the nature of which cannot be unambiguously determined. Nonetheless, the EPR results highlight the appreciable changes in the reaction system upon heating and are congruent with XANES and EXAFS observations.

Proposed mechanism

Based on the acquired empirical data, a full mechanistic picture is proposed in Figure 5. The reaction begins with an initiation process that involves sequential addition of an in situ-generated iron(II)-boryl species **i** across alkene **ii**, followed by β -H elimination to afford the putative iron(II)-hydride species **iv** with concomitant release of by-product **iii** (detectable by GC analysis). Iron(II)-hydride **iv** then reacts with another molecule of **ii** to initiate C=C bond migration either through an iterative sequence of reversible and consecutive olefin insertion/ β -H elimination steps or by HAT. It is believed that the driving force for chain-walking is the eventual formation of the most stable disubstituted olefin **v** that subsequently undergoes regioselective *syn* borometallation to give Fe-alkyl **vi** (stabilization of electron density accumulation by α -substituent G and/or minimization

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of steric repulsion between B(pin) and G) in the presence of **i**. The *syn* nature of the iron-boryl addition process is established by diastereoselective deuteration experiments. The ensuing protonolysis with trace *t*-BuOH generated from adventitious deprotonation of DMA delivers the final product **vii** and turns over the catalytic cycle.

5 Delayed release of *t*-BuOH into the solution can be advantageous by allowing sufficient time for complete alkene isomerization from **ii** to **v** to occur before protoboration commences. A high proton concentration can interfere with chain-walking by reacting with the iron-hydride catalyst (releasing H₂), leading to premature boryl additions and poor site selectivities. Involvement of a catalytically active iron-boryl hydride species,

10 which has been proposed to promote formation of primary alkylboronates in site-specific alkene hydroboration (vs. secondary alkylboronates in this system), is unlikely.

Although XANES and EXAFS spectra reflected a statistically weighted average Fe(ii) oxidation state during the catalytic reaction, it is also possible that Fe(iii) and Fe(i)

15 species are involved, which might arise from the disproportionation of Fe(ii) intermediates.

Generality of method

The generality of the present invention was assessed with a variety of functionalized

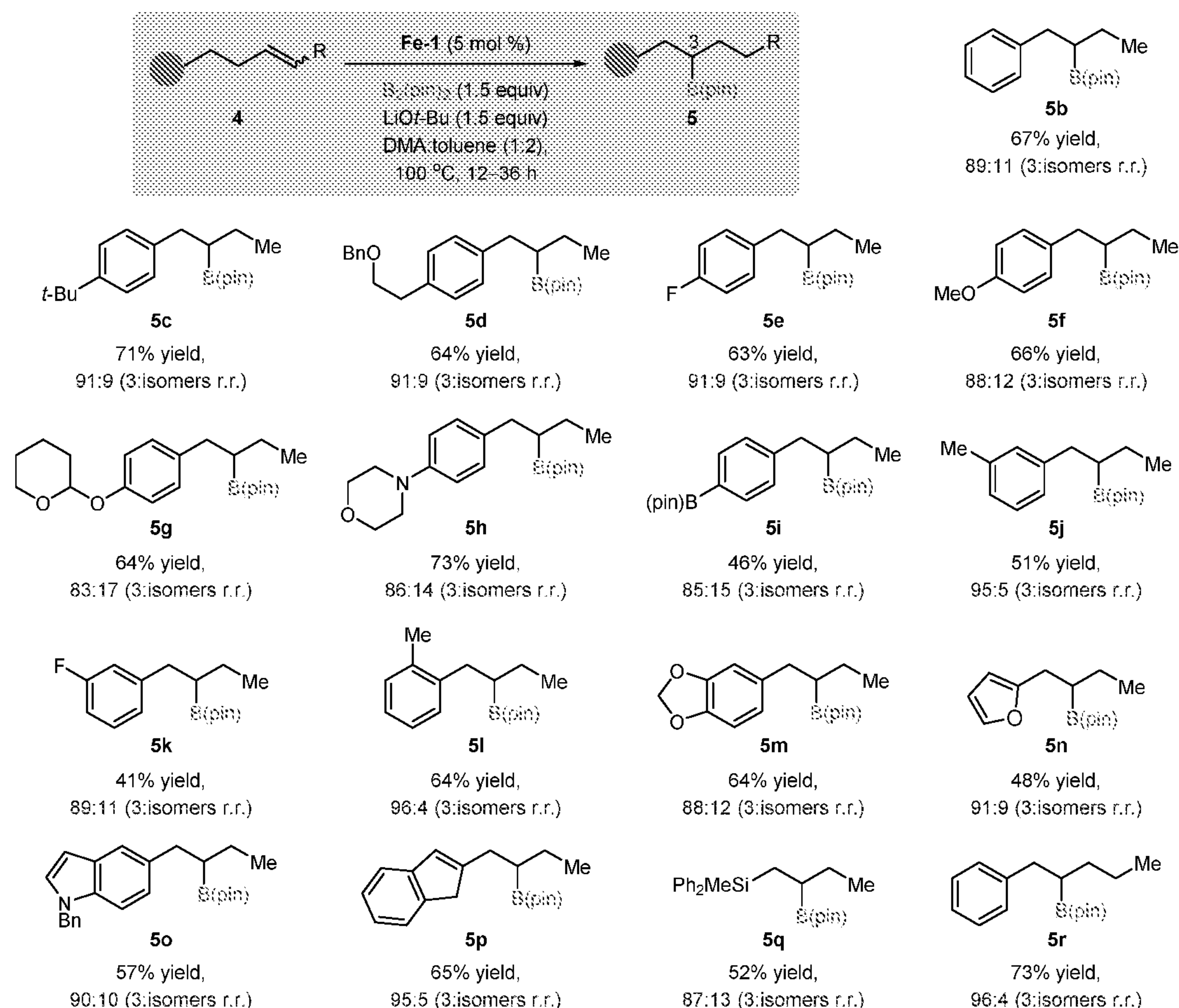
20 homoallylic substrates. The method is applicable to a range of allylic and homoallylic substrates bearing aryl, boryl, silyl, indenyl, carbocyclic and heterocyclic motifs. Transformations can be extended to internal alkenes (**5r**, **7l**, and **7m**); Fe(OAc)₂ was used in these cases. The reaction to afford **5m** was conducted in DMA. Table 2 shows that β -borylated compounds **5b-5r** were obtained in 41–74% yield and 83:15 to 96:4

25 regioisomeric ratios (β :other isomers). In most instances, use of DMA/toluene as the solvent consistently furnished superior site selectivities (versus pure DMA). Alkenes bearing aryl and heterocyclic substituents of different electronic and steric attributes are tolerated (**5b-5o**). Regioisomeric ratios are determined by analysis of ¹H NMR spectra of unpurified mixtures; yields are for isolated and purified products. Values in

30 parentheses are yields determined by GC analysis with *n*-tridecane as internal standard.

In particular, it was also found that β -selectivities could be further enhanced by replacing Fe-1 with 5 mol% of the complex derived from FeBr₂ and bulky bisphosphine ligands under otherwise standard conditions (for example, 85:15–88:12 to 93:7–95:5

35 regioisomeric ratios for **5f**, **5h** and **5i**).

Table 2. Examples of β -borylated compounds obtainable via the present invention

- 5 Allylic substrates are also effective in remote protoboration, affording the desired secondary borylalkanes **7a–7m** in up to 83% yield and >98% β selectivity (Table 3). For the synthesis of **7d** and **7e**, FeBr₂ was used. For the synthesis of **7f**, **7i** and **7j**, **Fe-1** was used. The reactions to afford **7g**, **7h** and **7k** were conducted in the presence of an additional 0.25 equiv *t*-BuOH. The reaction to afford **7j** was conducted for 6 h.
- 10 Ligand-free iron(II) acetate or iron(II) bromide were sometimes employed in these cases owing to slightly enhanced efficiency observed (vs. **Fe-1**). Control experiments revealed that allylic substrates react in similar fashion (alkene isomerization followed by protoboration) rather than direct site-specific protoboration. Employing DMA as the solvent and 80 °C was sufficient for optimal results (vs. DMA/toluene and 100 °C for two
- 15 C=C bond migrations in homoallylic derivatives). The transformations to access **7g**, **7h**

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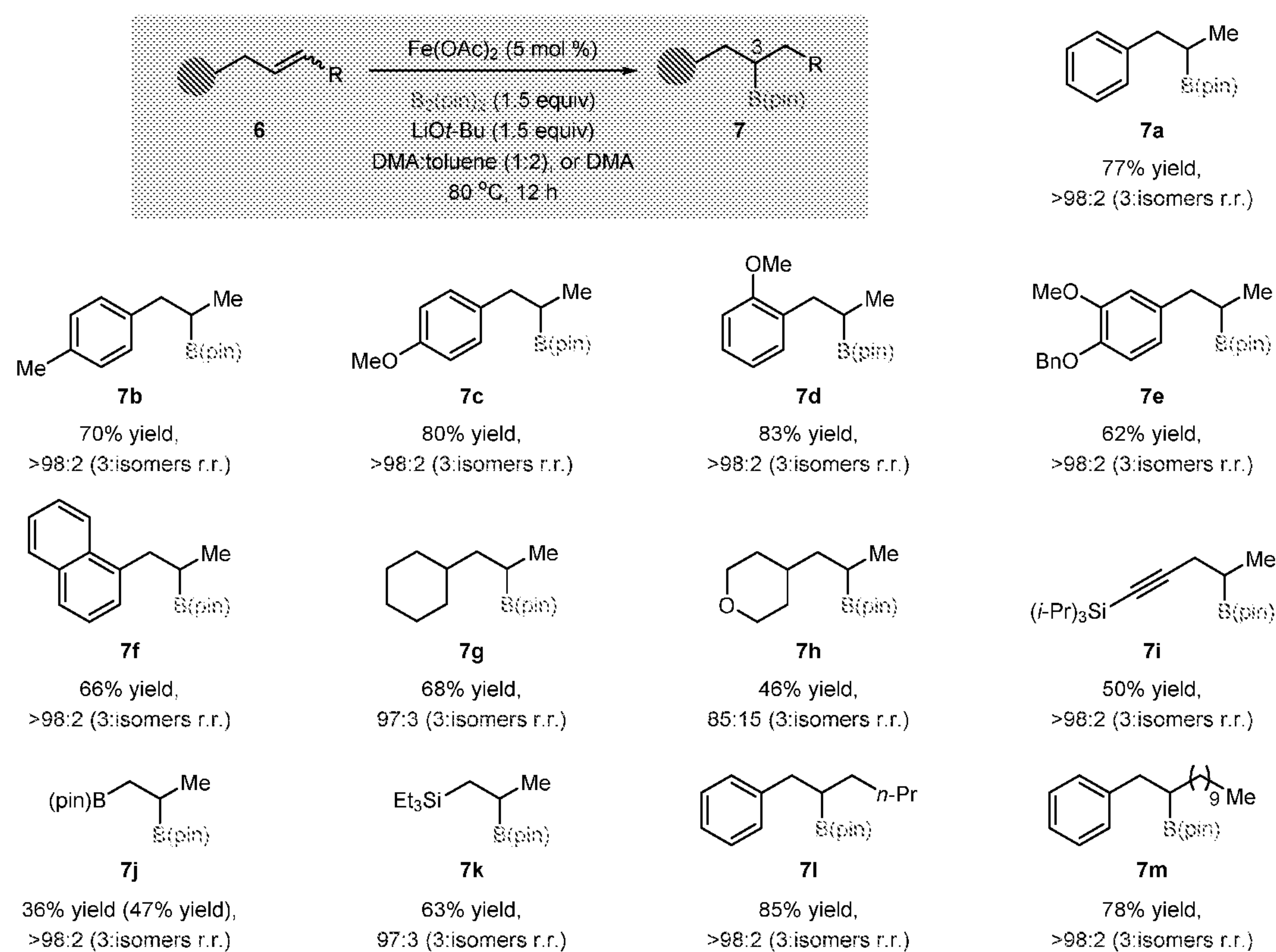
and **7j** can be carried out with an additional 0.25 equivalents of *t*-BuOH added to suppress formation of undesired diboration products (likely generated from adventitious reaction of **vi** with B₂(pin)₂) by accelerating protonolysis (**vi** → **vii**, Figure 5) without appreciably affecting site selectivity.

5

Besides aromatic entities, reactions are compatible with a cyclic olefin (**5p**; internal C=C bond remains intact), cycloalkyl group (**7g,h**), an alkyne (**7i**), a boronic ester (**7j**) as well as a silane (**5q, 7k**), underscoring the robustness of the present method. It merits mention that previously reported Fe-catalyzed hydroboration of alkyl-substituted olefins typically furnish primary alkylboronates through anti-Markovnikov additions. The catalytic protocol can also be extended to internal olefins (**5r, 7l,m**), such as 1,2-disubstituted internal olefins.

10

Table 3. Examples of β-borylated compounds obtainable via the present invention



15

Generality of method to long-chain alkenes

To challenge the limits of the protocol, a series of long-chain alkenes were subjected to remote protoboration (Table 4). Iron(II) acetate was found to give the best results (diminished yields and β -selectivities with Fe-1 or other iron-based complexes; Table 5). Across the board, β -borylalkanes were reliably obtained as the major regioisomer in $\geq 84\%$ site selectivity, demonstrating that alkene isomerization is similarly efficient across extended carbon skeletons (up to nine C=C bond migrations) prior to boryl addition.

Table 4. Boron incorporation at β -position regardless of alkene chain length

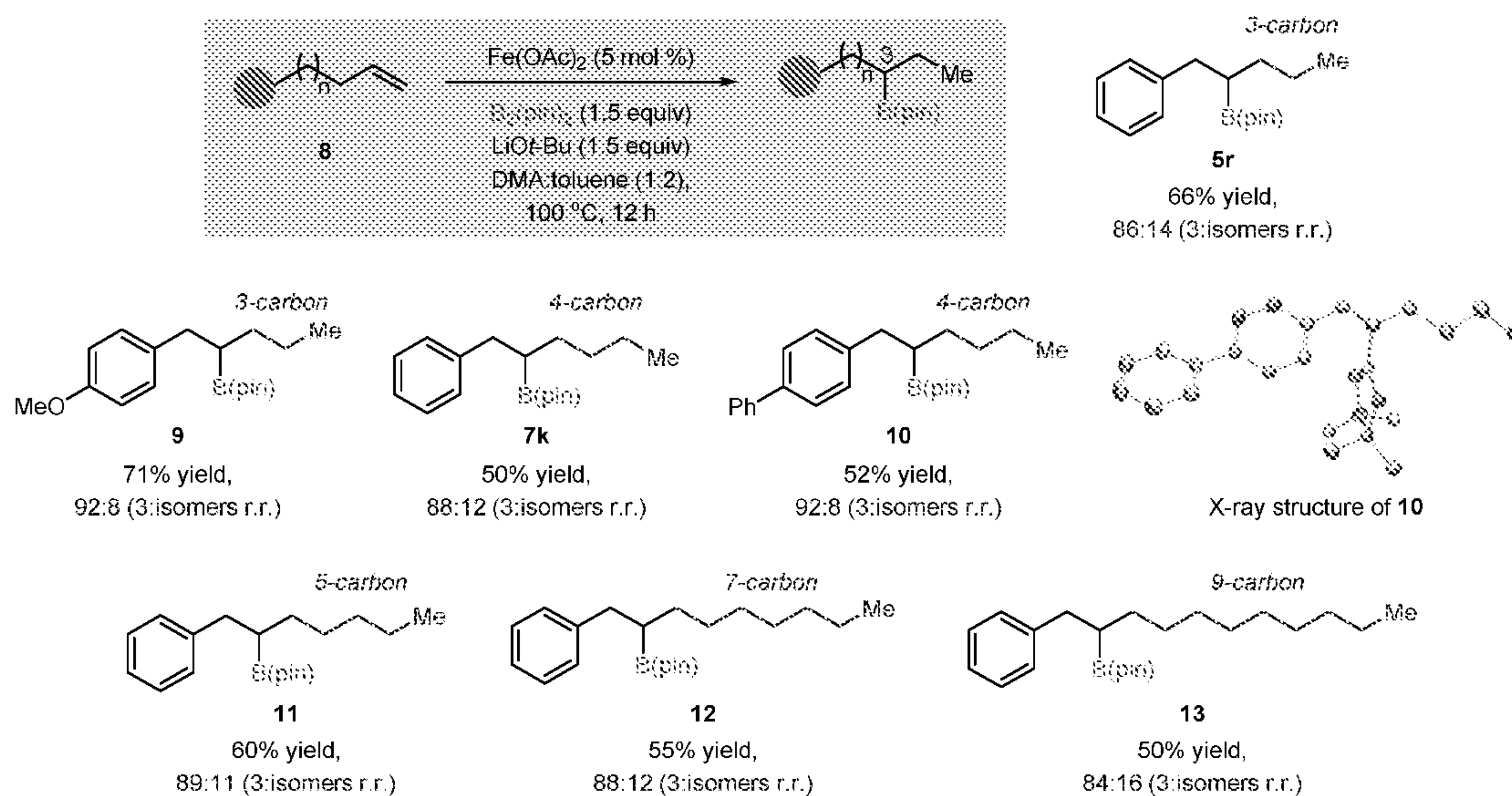
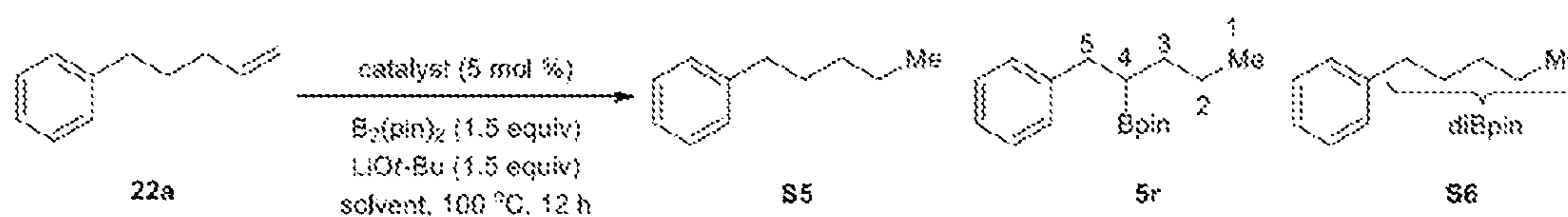


Table 5. Catalyst and solvent screening for bishomoallylic substrates^a

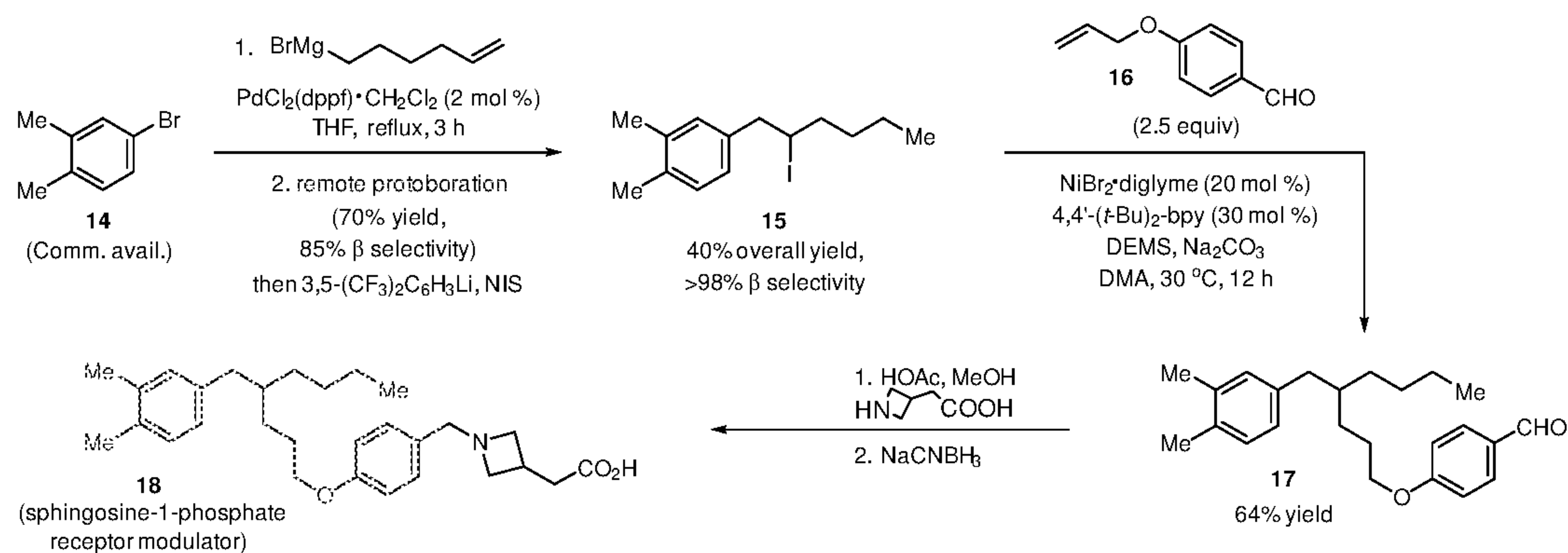


entry	catalyst	solvent	5s (%) ^a	5r (%) ^b (4:other isomers r.r.) ^c	56 (%) ^b	conv. (%) ^d
1	Fe-1	DMA	16	39 (27:12)	46	95
2	FeBr ₂	DMA	5	69 (47:22)	26	95
3	Fe(acac) ₃	DMA	5	57 (34:23)	38	95
4	FeCl ₂	DMA	6	64 (44:20)	30	95
5	FeBr ₃	DMA	7	62 (44:18)	31	95
6	Fe(OAc) ₂	DMA	5	79 (57:22)	16	98
7	Fe(OAc) ₂	DMA:toluene (1:2)	3	91 (78:13)	8	98

^aReaction conditions: catalyst (5 mol %), **22a** (0.2 mmol), solvent (0.5 mL), N₂ atmosphere. ^bConversion to product as determined by GC analysis with *n*-tridecane as internal standard. ^cr.r. determined by GC analysis. ^dTotal conversion of **22a** as determined by GC analysis.

Industrial applicability

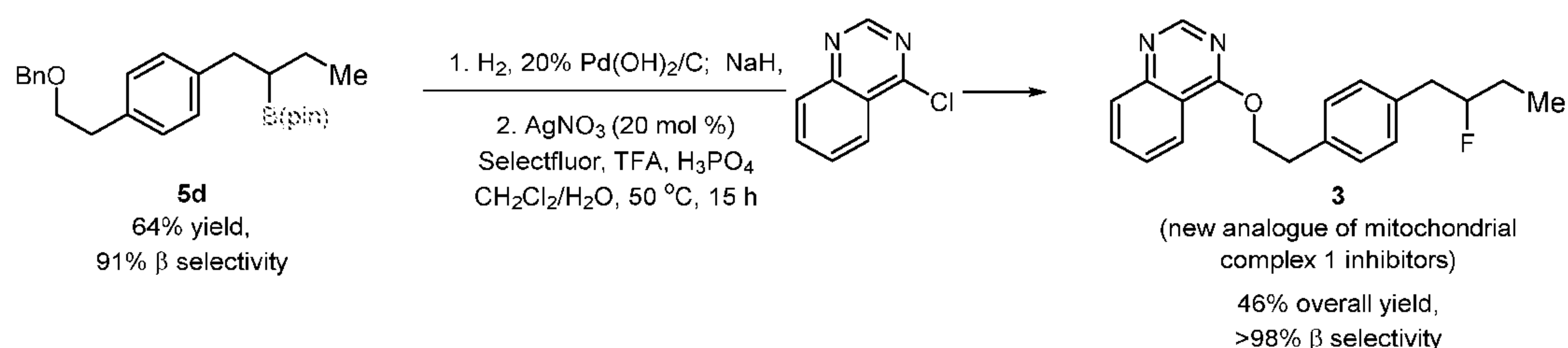
Utility of the present method is highlighted through concise synthesis of biologically
5 active compounds (Scheme 1). Remote protoboration of the terminal alkene derived
from commercially available **14** followed by iodination afforded iodide **15** in 40% overall
yield and >98% β selectivity. **17**, an intermediate used to access sphingosine-1-
phosphate receptor modulator **18**, was obtained after an additional catalytic
hydroalkylation in 64% yield. Overall, the four-step synthesis route offers a shorter and
10 complementary sequence compared to previously reported procedures. Regioisomeric
ratios are determined by analysis of ^1H NMR spectra of unpurified mixtures; yields are
for isolated and purified products. pin, pinacolato; dppf, 1,1'-
bis(diphenylphosphino)ferrocene; bpy, bipyridine; DEMS, diethoxymethylsilane; NIS,
N-iodosuccinimide.



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Scheme 1. Synthesis of sphingosine-1-phosphate receptor modulator

In another application (Scheme 2), boronate **5d** was subjected to deprotection/arylation followed by fluorination to furnish **3**, the β -fluoro analogue of previously disclosed mitochondrial complex 1 inhibitors, in 46% overall yield and >98% β selectivity. Notably, access to **3** facilitates screening of new F-containing therapeutic candidates for possible desirable properties, given that both the terminal organofluoride and β -fluoro derivative of **3** were found to be more potent than the parent non-fluorinated molecule. Selectfluor, 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate); TFA, trifluoroacetic acid

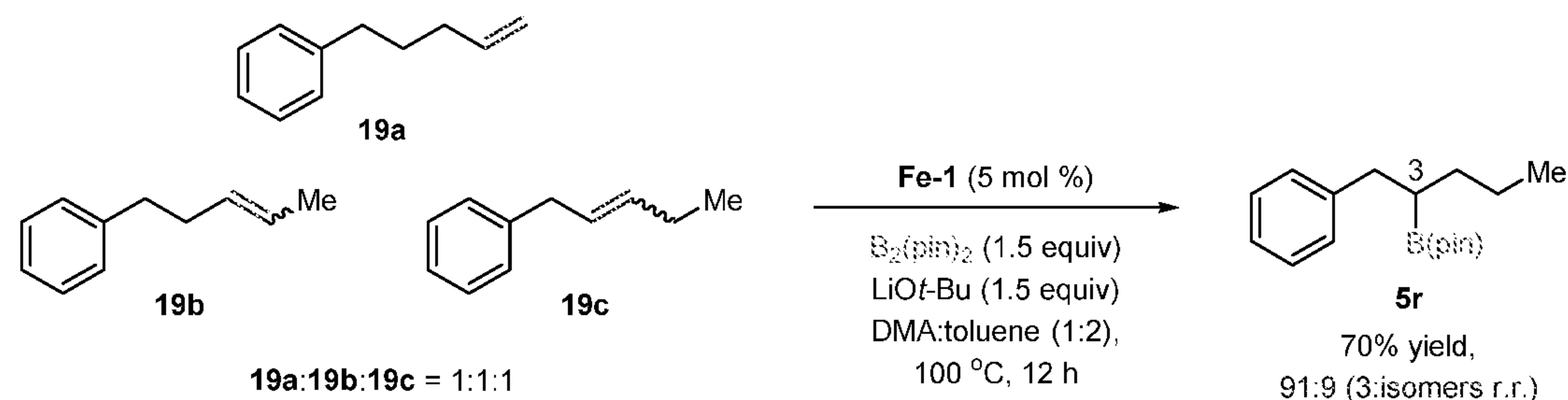


Scheme 2. Synthesis of mitochondrial complex 1 inhibitor

A corollary to the catalytic approach is the feasibility of implementing regioconvergent borylation, which would allow inexpensive chemical feedstock such as unrefined alkene isomers to be uniformly transformed to value-added products containing C_β -B stereogenic centers in a single step (Scheme 3). Treatment of a 1:1:1 regioisomeric mixture of alkenes **19a**, **19b** and **19c** with 5 mol % **Fe-1** under remote protoboration conditions afforded **5r** in 70% yield and 91% β selectivity. This is in contrast to site-specific boryl addition, where only one particular olefin regioisomer must be employed to afford a single borylated product. In addition to remote protoboration, through appropriate adjustment of the concentration of protic additive present to suppress $\text{C}=\text{C}$ bond migration, the Fe-catalysed method can be employed to deliver site-specific reactions (Fig. 7). Under standard conditions with 2.5 mol% **Fe-1** and 10 equiv. added t-BuOH in DMA, 1-borylalkane **23** could be selectively generated in 96% yield and 88:12 regioisomeric ratio (1/ other isomers). On the other hand, 2-borylalkane **24** was preferentially obtained (64% yield, 84% site selectivity) in the presence of 2.5 mol% of the Fe-based complex derived from FeBr_2 and neocuproine with 0.25 equiv. t-BuOH in

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DMA. Regiodivergent access to different organoboron isomers from one alkene substrate can thus be achieved with a single versatile catalytic system (Figure 7).



5 Scheme 3. Synthesis of C_β-B stereogenic centers

A general Fe-based catalytic platform that promotes robust and reliable boron installation at typically unactivated sites vicinal to an assortment of common functionalities is introduced herein. It was found that to successful β-borylation is to modulate the relative rates of competing hydrometallation and borometallation processes through controlling the concentration of the intermediate metal-hydride and metal-boryl species in the reaction mixture. Equally crucial is the discovery that DMA promotes delayed protonolysis of the intermediate Fe-alkyl species in the presence of an alkoxide base without suppressing chain-walking. By judicious tuning of reaction parameters to inhibit olefin transposition, the protocol is also amenable to site-specific borylations. The ability to access various borylalkane regioisomers with a single catalytic system is likely to have a notable impact on the way in which many molecules of interest are prepared. It is expected that the mechanistic principles derived from this work will find broad applicability in chemistry, and facilitate future efforts pertaining to site-selective functionalizations at other unreactive positions that pervade an aliphatic hydrocarbon molecule.

Method

Conversion and regioisomeric ratios are determined by GC analysis of unpurified mixtures. Yields are also determined for isolated and purified products.

General procedure for synthesis of alkene substrates: To a mixture of aryl bromide (1.0 equiv.) and [PdCl₂(dppf)·CH₂Cl₂] (dppf: bis(diphenylphosphino)ferrocene) (0.02 equiv.) in dried THF, a dried THF solution (1.0 mmol/mL) of R-MgBr (3.0 equiv.; prepared from

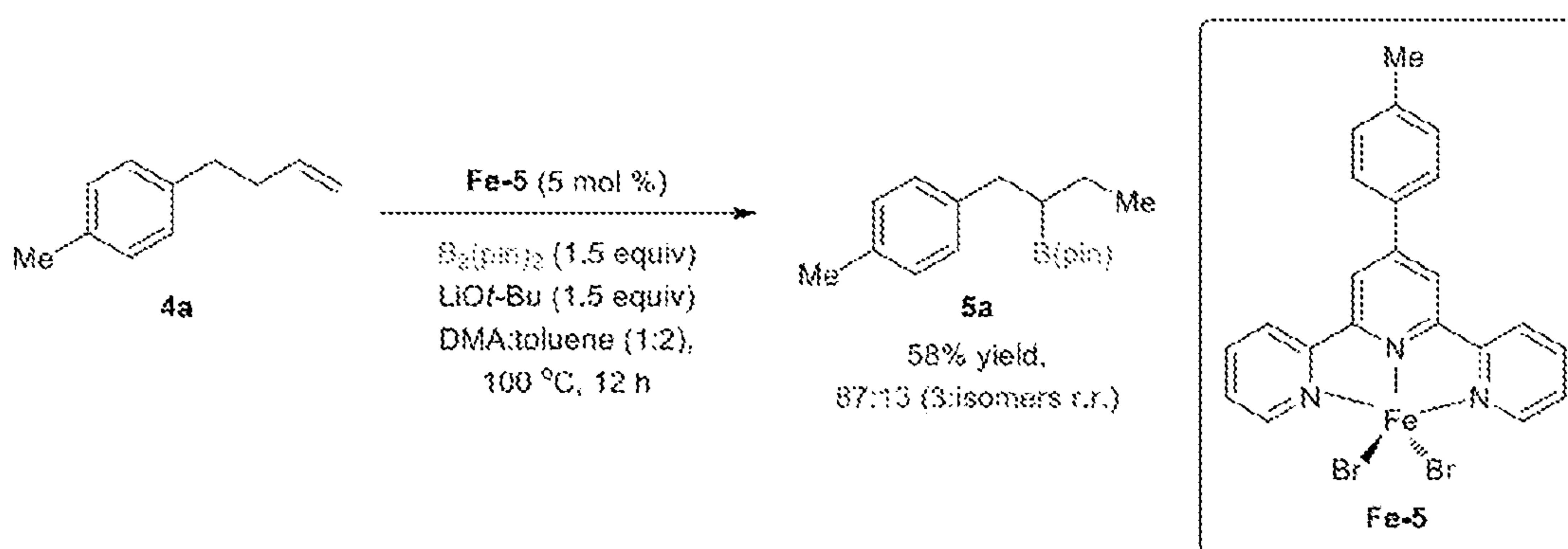
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magnesium and R-Br) was added dropwise at room temperature. The solution was then refluxed for 3 h. After removing the solvent under vacuum, dichloromethane was added and the mixture was washed with dilute aqueous NH_4Cl solution, dried over Na_2SO_4 , and concentrated in vacuo. The product was purified by column chromatography to afford the product.

General procedure for preparation of Fe-1: In a N_2 -filled glove box, an oven-dried 20 mL vial equipped with a magnetic stir bar was charged with FeBr_2 (215.0 mg, 1.0 mmol, 1.00 equiv), 2,2':6',2''-terpyridine (233.0 mg, 1.0 mmol, 1.00 equiv) and THF (10 mL), resulting in a dark red suspension. The vial was capped and the mixture was allowed to stir for 18 h at 22 °C. The residual red solid was washed with THF (5 mL x 2), Et_2O (5 mL x 2) and hexanes (5 mL x 2), and dried in vacuo. Either FeBr_2 (98%) or FeBr_2 (99.999%) may be used in the synthesis of Fe-1 without detectable difference in catalytic performance.

15

General β -Borylation Procedure: In a N_2 -filled glove box, an oven-dried 4 mL vial equipped with a magnetic stir bar was charged with Fe complex (5.0 mol %), LiOt-Bu (1.5 eq), B_2pin_2 (1.5 equiv.) and a solvent mixture of DMA (0.16 mL) and toluene (0.34 mL). The alkene substrate (0.20 mmol, 1.0 equiv.) was then added to the system via syringe and the reaction mixture was allowed to stir at 80°C or 100 °C for 12 h. After cooling to ambient temperature, purification was performed through silica gel chromatography.



25 **4,4,5,5-Tetramethyl-2-(1-(p-tolyl)butan-2-yl)-1,3,2-dioxaborolane (5a):** Based on the general procedure, **Fe-5** (5.4 mg, 0.01 mmol, 0.05 eq), LiOt-Bu (24.0 mg, 0.30 mmol, 1.5 eq) and $\text{B}_2(\text{pin})_2$ (76.2 mg, 0.30 mmol, 1.5 eq) were dissolved in a mixture of DMA

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(0.16 mL) and toluene (0.34 mL). Then, 4a (29.2 mg, 0.20 mmol, 1.0 eq) was sequentially added to the system via syringe and the reaction mixture was allowed to stir at 100 °C for 12 h. After cooling to ambient temperature, the resulting solution was purified by silica gel chromatography (hexanes:EtOAc = 98:2) to afford 5a (32.0 mg, 0.116 mmol, 58% yield) in 87:13 regioisomeric ratio (β :other isomers) as colorless oil.

4,4,5,5-Tetramethyl-2-(1-phenylbutan-2-yl)-1,3,2-dioxaborolane (5b): Based on the general procedure, Fe-1 (4.5 mg, 0.01 mmol, 0.05 eq), LiOt-Bu (24.0 mg, 0.30 mmol, 1.5 eq) and B₂(pin)₂ (76.2 mg, 0.30 mmol, 1.5 eq) were dissolved in a mixture of DMA (0.16 mL) and toluene (0.34 mL). Then, 4b (26.4 mg, 0.20 mmol, 1.0 eq) was sequentially added to the system via syringe and the reaction mixture was allowed to stir at 100 °C for 12 h. After cooling to ambient temperature, the resulting solution was purified by silica gel chromatography (hexanes:EtOAc = 98:2) to afford 5b (35.0 mg, 0.134 mmol, 67% yield) in 89:11 regioisomeric ratio (β :other isomers) as colorless oil.

¹H NMR (500 MHz, CDCl₃): isomer (major): δ 7.30 – 7.20 (m, 4H), 7.17 – 7.11 (m, 1H), 2.73 (dd, J = 13.6, 8.7 Hz, 1H), 2.66 (dd, J = 13.5, 7.7 Hz, 1H), 1.55 – 1.40 (m, 2H), 1.38 – 1.20 (m, 1H), 1.17 (s, 6H), 1.15 (s, 6H), 0.93 (t, J = 7.4 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃): δ 142.52, 128.98, 128.13, 125.65, 83.07, 37.18, 24.90, 24.84, 24.12, 13.70; ¹¹B NMR (160 MHz, CDCl₃): δ 34.02.

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2-(1-(4-(Tert-butyl)phenyl)butan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (5c): Based on the general procedure, Fe-1 (4.5 mg, 0.01 mmol, 0.05 eq), LiOt-Bu (24.0 mg, 0.30 mmol, 1.5 eq) and B₂(pin)₂ (76.2 mg, 0.30 mmol, 1.5 eq) were dissolved in a mixture of DMA (0.16 mL) and toluene (0.34 mL). Then, 4c (37.6 mg, 0.20 mmol, 1.0 eq) was sequentially added to the system via syringe and the reaction mixture was allowed to stir at 100 °C for 12 h. After cooling to ambient temperature, the resulting solution was purified by silica gel chromatography (hexanes:EtOAc = 98:2) to afford 5c (45.0 mg, 0.142 mmol, 71% yield) in 91:9 regioisomeric ratio (β :other isomers) as colorless oil.

¹H NMR (500 MHz, CDCl₃): isomer (major): δ 7.27 (d, J = 8.1 Hz, 2H), 7.14 (d, J = 8.2 Hz, 2H), 2.72 – 2.63 (m, 2H), 1.49 – 1.42 (m, 2H), 1.36 – 1.32 (m, 1H), 1.30 (s, 9H), 1.17 (s, 6H), 1.13 (s, 6H), 0.94 (t, J = 7.4 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃): δ 148.40, 139.39, 128.64, 124.99, 83.03, 36.66, 34.42, 31.55, 24.95, 24.78, 24.18, 13.76; ¹¹B NMR (160 MHz, CDCl₃): δ 34.24; HRMS (ESI) [M+Na]⁺ calcd for C₂₀H₃₃BNaO₂: 339.2469, found: 339.2467.

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2-(1-(4-(2-(Benzyloxy)ethyl)phenyl)butan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (5d): Based on the general procedure, Fe-1 (4.5 mg, 0.01 mmol, 0.05 eq), LiOt-Bu (24.0 mg, 0.30 mmol, 1.5 eq) and B₂(pin)₂ (76.2 mg, 0.30 mmol, 1.5 eq) were dissolved in a mixture of DMA (0.16 mL) and toluene (0.34 mL). Then, 4d (53.2 mg, 0.20 mmol, 1.0 eq) was sequentially added to the system via syringe and the reaction mixture was allowed to stir at 100 °C for 12 h. After cooling to ambient temperature, the resulting solution was purified by silica gel chromatography (hexanes:EtOAc = 98:2) to afford 5d (50.5 mg, 0.128 mmol, 64% yield) in 91:9 regioisomeric ratio (β:other isomers) as colorless oil. ¹H NMR (500 MHz, CDCl₃): isomer (major): δ 7.36 – 7.26 (m, 5H), 7.12 (q, J = 8.1 Hz, 4H), 4.53 (s, 2H), 3.66 (t, J = 7.3 Hz, 2H), 2.90 (t, J = 7.3 Hz, 2H), 2.71 (dd, J = 13.7, 8.5 Hz, 1H), 2.63 (dd, J = 13.7, 7.8 Hz, 1H), 1.55 – 1.35 (m, 2H), 1.32 – 1.28 (m, 1H), 1.18 (s, 6H), 1.15 (s, 6H), 0.94 (t, J = 7.4 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃): δ 140.34, 138.57, 136.07, 128.95, 128.69, 128.46, 127.73, 127.62, 83.06, 73.06, 71.63, 36.72, 36.09, 24.91, 24.83, 24.02, 13.70; ¹¹B NMR (160 MHz, CDCl₃): δ 34.81; HRMS (ESI) [M+Na]⁺ calcd for C₂₅H₃₅BNaO₃: 417.2576, found: 417.2589.

2-(1-(4-Fluorophenyl)butan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (5e): Based on the general procedure, Fe-1 (4.5 mg, 0.01 mmol, 0.05 eq), LiOt-Bu (24.0 mg, 0.30 mmol, 1.5 eq) and B₂(pin)₂ (76.2 mg, 0.30 mmol, 1.5 eq) were dissolved in a mixture of DMA (0.16 mL) and toluene (0.34 mL). Then, 4e (30.0 mg, 0.20 mmol, 1.0 eq) was sequentially added to the system via syringe and the reaction mixture was allowed to stir at 100 °C for 12 h. After cooling to ambient temperature, the resulting solution was purified by silica gel chromatography (hexanes:EtOAc = 98:2) to afford 5e (35.0 mg, 0.126 mmol, 63% yield) in 91:9 regioisomeric ratio (β:other isomers) as colorless oil. ¹H NMR (500 MHz, CDCl₃): isomer (major): δ 7.17 – 7.13 (m, 2H), 6.92 (t, J = 8.8 Hz, 2H), 2.68 (dd, J = 13.7, 8.9 Hz, 1H), 2.63 (dd, J = 13.8, 7.5 Hz, 1H), 1.47 – 1.40 (m, 2H), 1.27 (d, J = 7.9 Hz, 1H), 1.16 (s, 6H), 1.14 (s, 6H), 0.93 (t, J = 7.4 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃): δ 161.23 (d, J = 241.9 Hz), 138.15 (d, J = 3.1 Hz), 130.26 (d, J = 7.7 Hz), 114.80 (d, J = 20.9 Hz), 83.14, 36.39, 24.90, 24.86, 24.14, 13.67; ¹¹B NMR (160 MHz, CDCl₃): δ 34.30; ¹⁹F NMR (377 MHz, CDCl₃): δ -118.33; HRMS (EI) [M]⁺ calcd for C₁₆H₂₄BFO₂: 278.1853, found: 278.1856.

2-(1-(4-Methoxyphenyl)butan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (5f): Based on the general procedure, FeBr₂ (1.1 mg, 0.005 mmol, 0.05 eq), L1 (7.1 mg,

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0.006 mmol, 0.06 eq), LiOt-Bu (12.0 mg, 0.15 mmol, 1.5 eq) and B₂(pin)₂ (38.0 mg, 0.30 mmol, 1.5 eq) were dissolved in a mixture of DMA (0.05 mL) and toluene (0.20 mL). Then, 4f (16.2 mg, 0.10 mmol, 1.0 eq) was sequentially added to the system via syringe and the reaction mixture was allowed to stir at rt for 20 minute and then 100 °C for 12 h. After cooling to ambient temperature, the resulting solution was purified by silica gel chromatography (hexanes:EtOAc = 98:2) to afford 5f (21.0 mg, 0.072 mmol, 72% yield) in 94:6 regioisomeric ratio (β:other isomers) as colorless oil.

4,4,5,5-Tetramethyl-2-(1-(4-((tetrahydro-2H-pyran-2-yl)oxy)phenyl)butan-2-yl)-1,3,2-dioxaborolane (5g): Based on the general procedure, Fe-1 (4.5 mg, 0.01 mmol, 0.05 eq), LiOt-Bu (24.0 mg, 0.30 mmol, 1.5 eq) and B₂(pin)₂ (76.2 mg, 0.30 mmol, 1.5 eq) were dissolved in a mixture of DMA (0.16 mL) and toluene (0.34 mL). Then, 4g (46.4 mg, 0.20 mmol, 1.0 eq) was sequentially added to the system via syringe and the reaction mixture was allowed to stir at 100 °C for 12 h. After cooling to ambient temperature, the resulting solution was purified by silica gel chromatography (hexanes:EtOAc = 98:2) to afford 5g (46.1 mg, 0.128 mmol, 64% yield) in 90:10 regioisomeric ratio (β:other isomers) as colorless oil. ¹H NMR (500 MHz, CDCl₃): isomer (major): δ 7.10 (d, J = 8.2 Hz, 2H), 6.93 (d, J = 8.3 Hz, 2H), 5.35 (d, J = 3.3 Hz, 1H), 3.91 (t, J = 9.0 Hz, 1H), 3.57 (d, J = 10.1 Hz, 1H), 2.66 (dd, J = 13.5, 8.8 Hz, 1H), 2.59 (dd, J = 13.6, 7.8 Hz, 1H), 1.99 (d, J = 6.2 Hz, 1H), 1.84 (d, J = 4.0 Hz, 2H), 1.64 – 1.54 (m, 3H), 1.46 – 1.39 (m, 2H), 1.27 (d, J = 7.9 Hz, 1H), 1.17 (s, 6H), 1.14 (s, 6H), 0.92 (t, J = 7.3 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃): δ 155.16, 135.63, 129.77, 116.32, 96.72, 83.05, 62.16, 36.35, 30.58, 25.39, 24.93, 24.86, 24.05, 19.03, 13.73; ¹¹B NMR (160 MHz, CDCl₃): δ 34.58; HRMS (ESI) [M+Na]⁺ calcd for C₂₁H₃₃BNaO₄: 383.2368, found: 383.2374.

4-(4-(2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)butyl)phenyl)morpholine (5h): Based on the general procedure, FeBr₂ (1.1 mg, 0.005 mmol, 0.05 eq), L1 (7.1 mg, 0.006 mmol, 0.06 eq), LiOt-Bu (12.0 mg, 0.15 mmol, 1.5 eq) and B₂(pin)₂ (38.0 mg, 0.30 mmol, 1.5 eq) were dissolved in a mixture of DMA (0.05 mL) and toluene (0.20 mL). Then, 4h (22.0 mg, 0.10 mmol, 1.0 eq) was sequentially added to the system via syringe and the reaction mixture was allowed to stir at rt for 20 minute and then 100 °C for 12 h. After cooling to ambient temperature, the resulting solution was purified by silica gel chromatography (hexanes:EtOAc = 98:2) to afford 5h (27.0 mg, 0.078 mmol, 78% yield) in 95:5 regioisomeric ratio (β:other isomers) as colorless oil.

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4,4,5,5-Tetramethyl-2-(4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butyl)phenyl)-1,3,2-dioxaborolane (5i): Based on the general procedure, FeBr₂ (1.1 mg, 0.005 mmol, 0.05 eq), L1 (7.1 mg, 0.006 mmol, 0.06 eq), LiOt-Bu (12.0 mg, 0.15 mmol, 1.5 eq) and B₂(pin)₂ (38.0 mg, 0.30 mmol, 1.5 eq) were dissolved in a mixture of DMA (0.05 mL) and toluene (0.20 mL). Then, 4i (25.8 mg, 0.20 mmol, 1.0 eq) was sequentially added to the system via syringe and the reaction mixture was allowed to stir at 100 °C for 12 h. After cooling to ambient temperature, the resulting solution was purified by silica gel chromatography (hexanes:EtOAc = 95:5) to afford 5i (25.0 mg, 0.065 mmol, 65% yield) in 93:7 regioisomeric ratio (β:other isomers) as colorless oil.

4,4,5,5-Tetramethyl-2-(1-(m-tolyl)butan-2-yl)-1,3,2-dioxaborolane (5j): Based on the general procedure, Fe-1 (4.5 mg, 0.01 mmol, 0.05 eq), LiOt-Bu (24.0 mg, 0.30 mmol, 1.5 eq) and B₂(pin)₂ (76.2 mg, 0.30 mmol, 1.5 eq) were dissolved in a mixture of DMA (0.16 mL) and toluene (0.34 mL). Then, 4j (29.2 mg, 0.20 mmol, 1.0 eq) was sequentially added to the system via syringe and the reaction mixture was allowed to stir at 100 °C for 12 h. After cooling to ambient temperature, the resulting solution was purified by silica gel chromatography (hexanes:EtOAc = 98:2) to afford 5j (28.0 mg, 0.102 mmol, 51% yield) in 95:5 regioisomeric ratio (β:other isomers) as colorless oil.

¹H NMR (500 MHz, CDCl₃): isomer (major): δ 7.13 (t, J = 7.5 Hz, 1H), 7.03 (s, 1H), 6.98 (dd, J = 22.4, 7.5 Hz, 2H), 2.69 (dd, J = 13.6, 8.7 Hz, 1H), 2.63 (dd, J = 13.5, 7.5 Hz, 1H), 2.31 (s, 3H), 1.55 – 1.35 (m, 2H), 1.32 – 1.27 (m, 1H), 1.18 (s, 6H), 1.15 (s, 6H), 0.94 (t, J = 7.4 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃): δ 142.47, 137.52, 129.81, 128.03, 126.36, 126.03, 83.06, 37.14, 24.92, 24.86, 24.19, 21.51, 13.73; ¹¹B NMR (160 MHz, CDCl₃): δ 33.87; HRMS (ESI) [M+Na]⁺ calcd for C₁₇H₂₇BNaO₂: 297.1996, found: 297.1997.

2-(1-(3-Fluorophenyl)butan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (5k): Based on the general procedure, Fe-1 (4.5 mg, 0.01 mmol, 0.05 eq), LiOt-Bu (24.0 mg, 0.30 mmol, 1.5 eq) and B₂(pin)₂ (76.2 mg, 0.30 mmol, 1.5 eq) were dissolved in a mixture of DMA (0.16 mL) and toluene (0.34 mL). Then, 4k (30.0 mg, 0.20 mmol, 1.0 eq) was sequentially added to the system via syringe and the reaction mixture was allowed to stir at 100 °C for 12 h. After cooling to ambient temperature, the resulting solution was purified by silica gel chromatography (hexanes:EtOAc = 98:2) to afford 5k (23.0 mg, 0.082 mmol, 41% yield) in 89:11 regioisomeric ratio (β:other isomers) as

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- colorless oil. ^1H NMR (500 MHz, CDCl_3): isomer (major): δ 7.22 – 7.15 (m, 1H), 6.96 (t, J = 8.4 Hz, 1H), 6.94 – 6.87 (m, 1H), 6.85 – 6.75 (m, 1H), 2.71 (dd, J = 13.6, 8.9 Hz, 1H), 2.65 (dd, J = 13.6, 7.4 Hz, 1H), 1.49 – 1.38 (m, 2H), 1.31 – 1.25 (m, 1H), 1.18 (s, 6H), 1.15 (s, 6H), 0.93 (t, J = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3): δ 162.90 (d, J = 245.1 Hz), 145.26 (d, J = 7.1 Hz), 129.49 (d, J = 8.3 Hz), 124.64 (d, J = 2.6 Hz), 115.80 (d, J = 20.79 Hz), 112.49 (d, J = 21.04 Hz), 83.21, 36.95, 24.91, 24.87, 24.14, 13.64; ^{11}B NMR (160 MHz, CDCl_3): δ 34.34; ^{19}F NMR (377 MHz, CDCl_3): δ -114.49; HRMS (EI) $[\text{M}]^+$ calcd for $\text{C}_{16}\text{H}_{24}\text{BFO}_2$: 278.1853, found: 278.1851.
- 10 4,4,5,5-Tetramethyl-2-(1-(*o*-tolyl)butan-2-yl)-1,3,2-dioxaborolane (5l): Based on the general procedure, Fe-1 (4.5 mg, 0.01 mmol, 0.05 eq), LiOt-Bu (24.0 mg, 0.30 mmol, 1.5 eq) and $\text{B}_2(\text{pin})_2$ (76.2 mg, 0.30 mmol, 1.5 eq) were dissolved in a mixture of DMA (0.16 mL) and toluene (0.34 mL). Then, 4l (29.2 mg, 0.20 mmol, 1.0 eq) was sequentially added to the system via syringe and the reaction mixture was allowed to stir at 100 °C for 12 h. After cooling to ambient temperature, the resulting solution was purified by silica gel chromatography (hexanes:EtOAc = 98:2) to afford 5l (35.0 mg, 0.128 mmol, 64% yield) in 96:4 regioisomeric ratio (β :other isomers) as colorless oil. ^1H NMR (500 MHz, CDCl_3): isomer (major): δ 7.21 – 7.17 (m, 1H), 7.14 – 7.04 (m, 3H), 2.73 (dd, J = 13.9, 9.0 Hz, 1H), 2.64 (dd, J = 13.9, 7.2 Hz, 1H), 2.32 (s, 3H), 1.52 – 1.44 (m, 2H), 1.35 – 1.25 (m, 1H), 1.19 (s, 6H), 1.15 (s, 6H), 0.96 (t, J = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3): δ 140.70, 136.30, 130.13, 129.41, 125.76, 125.60, 83.08, 34.41, 24.98, 24.80, 24.60, 19.63, 13.83; ^{11}B NMR (160 MHz, CDCl_3): δ 34.26; HRMS (ESI) $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{17}\text{H}_{27}\text{BNaO}_2$: 297.1999, found: 297.2002
- 25 2-(1-(Benzo[d][1,3]dioxol-5-yl)butan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (5m): Based on the general procedure, Fe-1 (4.5 mg, 0.01 mmol, 0.05 eq), LiOt-Bu (24.0 mg, 0.30 mmol, 1.5 eq) and $\text{B}_2(\text{pin})_2$ (76.2 mg, 0.30 mmol, 1.5 eq) were dissolved in DMA (0.5 mL). Then, 4m (35.2 mg, 0.20 mmol, 1.0 eq) was sequentially added to the system via syringe and the reaction mixture was allowed to stir at 100 °C for 12 h. After cooling to ambient temperature, the resulting solution was purified by silica gel chromatography (hexanes:EtOAc = 98:2) to afford 5m (45.0 mg, 0.148 mmol, 74% yield) in 88:12 regioisomeric ratio (β :other isomers) as colorless oil. ^1H NMR (500 MHz, CDCl_3): isomer (major): δ 6.72 – 6.62 (m, 3H), 5.88 (s, 2H), 2.65 (dd, J = 13.7, 8.6 Hz, 1H), 2.57 (dd, J = 13.7, 7.6 Hz, 1H), 1.55 – 1.35 (m, 2H), 1.30 – 1.20 (m, 1H), 1.19 (s, 6H), 1.17 (s, 6H), 0.92 (t, J = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3): δ
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147.42, 145.49, 136.48, 121.68, 109.49, 107.93, 100.71, 83.11, 36.92, 24.95, 24.90, 24.00, 13.67; ^{11}B NMR (160 MHz, CDCl_3): δ 33.91; HRMS (ESI) $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{17}\text{H}_{25}\text{BNaO}_4$: 327.1738, found: 327.1743.

- 5 2-(1-(Furan-2-yl)butan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (5n): Based on the general procedure, Fe-1 (4.5 mg, 0.01 mmol, 0.05 eq), LiOt-Bu (24.0 mg, 0.30 mmol, 1.5 eq) and $\text{B}_2(\text{pin})_2$ (76.2 mg, 0.30 mmol, 1.5 eq) were dissolved in toluene (0.4 mL) Then, 4n (24.4 mg, 0.20 mmol, 1.0 eq) was sequentially added to the system via syringe and the reaction mixture was allowed to stir at 100 °C for 12 h. After cooling to ambient temperature, DMA (0.16 mL) was added to the system via syringe and the reaction mixture was allowed to stir at 100 °C for 12 h. After cooling to ambient temperature, the resulting solution was purified by silica gel chromatography (hexanes:EtOAc = 98:2) to afford 5n (24.0 mg, 0.096 mmol, 48% yield) in 91:9 regioisomeric ratio (β :other isomers) as colorless oil. ^1H NMR (500 MHz, CDCl_3): isomer (major): δ 7.26 (s, 1H), 6.24 (dd, J = 3.0, 1.9 Hz, 1H), 5.98 (dd, J = 3.1, 0.5 Hz, 1H), 2.75 (dd, J = 15.1, 8.8 Hz, 1H), 2.67 (dd, J = 15.2, 6.7 Hz, 1H), 1.51 – 1.40 (m, 2H), 1.36 – 1.30 (m, 1H), 1.20 (s, 12H), 0.93 (t, J = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3): δ 156.43, 140.64, 110.04, 105.17, 83.19, 29.29, 24.90, 24.87, 24.06, 13.54; ^{11}B NMR (160 MHz, CDCl_3): δ 34.27; HRMS (ESI) $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{14}\text{H}_{23}\text{BNaO}_3$: 273.1635, found: 273.1643.

- 1-Benzyl-5-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butyl)-1H-indole (5o): Based on the general procedure, Fe-1 (4.5 mg, 0.01 mmol, 0.05 eq), LiOt-Bu (24.0 mg, 0.30 mmol, 1.5 eq) and $\text{B}_2(\text{pin})_2$ (76.2 mg, 0.30 mmol, 1.5 eq) were dissolved in toluene (0.4 mL) Then, 4o (52.3 mg, 0.20 mmol, 1.0 eq) was sequentially added to the system via syringe and the reaction mixture was allowed to stir at 100 °C for 12 h. After cooling to ambient temperature, DMA (0.16 mL) was added to the system via syringe and the reaction mixture was allowed to stir at 100 °C for 12 h. After cooling to ambient temperature, the resulting solution was purified by silica gel chromatography (hexanes:EtOAc = 95:5) to afford 5o (44.4 mg, 0.114 mmol, 57% yield) in 90:10 regioisomeric ratio (β :other isomers) as colorless oil. ^1H NMR (500 MHz, CDCl_3): isomer (major): δ 7.48 (s, 1H), 7.31 – 7.24 (m, 3H), 7.18 – 7.02 (m, 5H), 6.47 (d, J = 3.0 Hz, 1H), 5.30 (s, 2H), 2.84 (dd, J = 13.6, 8.4 Hz, 1H), 2.76 (dd, J = 13.6, 7.8 Hz, 1H), 1.53 – 1.44 (m, 2H), 1.36 (dd, J = 8.7, 6.2 Hz, 1H), 1.18 (s, 6H), 1.13 (s, 6H), 0.95 (t, J = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3): δ 137.93, 135.06, 133.53, 128.85, 128.79,

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128.19, 127.58, 126.82, 123.33, 120.78, 109.29, 101.37, 82.97, 50.19, 37.23, 24.94, 24.86, 24.09, 13.81; ^{11}B NMR (160 MHz, CDCl_3): δ 35.02; HRMS (ESI) $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{25}\text{H}_{33}\text{BNO}_2$: 390.2599, found: 390.2589.

- 5 2-(1-(1H-inden-2-yl)butan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (5p): Based on the general procedure, Fe-1 (4.5 mg, 0.01 mmol, 0.05 eq), LiOt-Bu (24.0 mg, 0.30 mmol, 1.5 eq) and $\text{B}_2(\text{pin})_2$ (76.2 mg, 0.30 mmol, 1.5 eq) were dissolved in toluene (0.4 mL). Then, 4p (34.0 mg, 0.20 mmol, 1.0 eq) was sequentially added to the system via syringe and the reaction mixture was allowed to stir at 100 °C for 24 h. After cooling to ambient temperature, DMA (0.16 mL) was added to the system via syringe and the reaction mixture was allowed to stir at 100 °C for 12 h. After cooling to ambient temperature, the resulting solution was purified by silica gel chromatography (hexanes:EtOAc = 98:2) to afford 5p (39.0 mg, 0.130 mmol, 65% yield) in 95:5 regioisomeric ratio (β :other isomers) as colorless oil. ^1H NMR (500 MHz, CDCl_3): isomer (major): δ 7.37 (dd, J = 7.3, 0.6 Hz, 1H), 7.25 (d, J = 7.4 Hz, 1H), 7.20 (t, J = 7.0 Hz, 1H), 7.09 (td, J = 7.3, 1.2 Hz, 1H), 6.52 (d, J = 9.6 Hz, 1H), 3.31 (s, 2H), 2.63 (dd, J = 15.1, 8.9 Hz, 1H), 2.54 (dd, J = 15.0, 7.2 Hz, 1H), 1.60 – 1.40 (m, 2H), 1.32 (dd, J = 9.3, 6.5 Hz, 1H), 1.21 (s, 6H), 1.20 (s, 6H), 0.96 (t, J = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3): δ 150.91, 145.83, 143.37, 126.81, 126.22, 123.54, 123.44, 119.88, 83.16, 41.35, 32.67, 24.93, 24.90, 24.31, 13.71; ^{11}B NMR (160 MHz, CDCl_3): δ 34.21; HRMS (EI) $[\text{M}]^+$ calcd for $\text{C}_{19}\text{H}_{27}\text{BO}_2$: 298.2099, found: 298.2104.

- Methyldiphenyl(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butyl)silane (5q): Based on the general procedure, Fe-1 (4.5 mg, 0.01 mmol, 0.05 eq), LiOt-Bu (24.0 mg, 0.30 mmol, 1.5 eq) and $\text{B}_2(\text{pin})_2$ (76.2 mg, 0.30 mmol, 1.5 eq) were dissolved in toluene (0.4 mL). Then, 4q (50.4 mg, 0.20 mmol, 1.0 eq) was sequentially added to the system via syringe and the reaction mixture was allowed to stir at 100 °C for 24 h. After cooling to ambient temperature, DMA (0.16 mL) was added to the system via syringe and the reaction mixture was allowed to stir at 100 °C for 12 h. After cooling to ambient temperature, the resulting solution was purified by silica gel chromatography (hexanes:EtOAc = 98:2) to afford 5q (39.5 mg, 0.104 mmol, 52% yield) in 87:13 regioisomeric ratio (β :other isomers) as colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.55 – 7.52 (m, 4H), 7.37 – 7.32 (m, 6H), 1.43 (m, 2H), 1.26 – 1.20 (m, 2H), 1.17 (s, 6H), 1.16 (s, 6H), 1.10 (m, 1H), 0.86 (t, J = 7.4 Hz, 3H), 0.58 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 138.11, 138.04, 134.74, 134.68, 129.05, 127.82, 127.80, 83.03, 28.01,

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25.03, 24.87, 14.75, 13.41, -3.78; ^{11}B NMR (128 MHz, CDCl_3) δ 34.87; HRMS (ESI) $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{23}\text{H}_{33}\text{BNaO}_2\text{Si}$: 403.2239, found: 403.2237.

1-(Methyldiphenylsilyl)butan-2-ol (5q-OH): 5q (38.0 mg, 0.10 mmol, 1.0 eq) was dissolved in THF (1.0 mL) and H_2O (1.0 mL). Then, Sodium perborate tetrahydrate (61.2 mg, 0.40 mmol, 4.0 eq) was added to the system and the reaction mixture was allowed to stir at room temperature for 18 h. After removing the solvent under vacuum, EAOAc was added and the mixture was washed with H_2O , dried over Na_2SO_4 , and concentrated in vacuo. The mixture was purified by silica gel chromatography (hexanes:EtOAc = 95:5) to afford 5q-OH (24.3 mg, 0.09 mmol, 90% yield) as colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.60 – 7.51 (m, 4H), 7.41 – 7.32 (m, 6H), 3.90 – 3.60 (m, 1H), 1.51 – 1.38 (m, 5H), 0.89 (t, J = 7.4 Hz, 3H), 0.65 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 137.46, 137.24, 134.65, 134.63, 129.39, 128.07, 128.04, 71.14, 33.77, 23.75, 10.11, -3.26; HRMS (ESI) $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{17}\text{H}_{22}\text{NaOSi}$: 293.1332, found: 293.1337.

4,4,5,5-Tetramethyl-2-(1-phenylpentan-2-yl)-1,3,2-dioxaborolane (5r): Based on the general procedure, $\text{Fe}(\text{OAc})_2$ (1.7 mg, 0.01 mmol, 0.05 eq), LiOt-Bu (24.0 mg, 0.30 mmol, 1.5 eq) and $\text{B}_2(\text{pin})_2$ (76.2 mg, 0.30 mmol, 1.5 eq) were dissolved in a mixture of DMA (0.16 mL) and toluene (0.34 mL). Then, pent-3-en-1-ylbenzene (29.2 mg, 0.20 mmol, 1.0 eq) was sequentially added to the system via syringe and the reaction mixture was allowed to stir at 100 °C for 12 h. After cooling to ambient temperature, the resulting solution was purified by silica gel chromatography (hexanes:EtOAc = 98:2) to afford 5r (40.0 mg, 0.146 mmol, 73% yield) in 96:4 regioisomeric ratio (β :other isomers) as colorless oil. ^1H NMR (500 MHz, CDCl_3): isomer (major): δ 7.25 – 7.18 (m, 4H), 7.15 (dd, J = 5.1, 3.5 Hz, 1H), 2.75 – 2.63 (m, 2H), 1.43 – 1.31 (m, 5H), 1.17 (s, 6H), 1.13 (s, 6H), 0.89 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3): δ 142.54, 128.99, 128.14, 125.66, 83.06, 37.50, 33.64, 24.90, 24.84, 22.46, 14.52; ^{11}B NMR (160 MHz, CDCl_3): δ 34.31; HRMS (ESI) $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{17}\text{H}_{27}\text{BNaO}_2$: 297.1996, found: 297.1999.

4,4,5,5-Tetramethyl-2-(1-phenylpropan-2-yl)-1,3,2-dioxaborolane (7a): Based on the general procedure, $\text{Fe}(\text{OAc})_2$ (1.7 mg, 0.01 mmol, 0.05 eq), LiOt-Bu (24.0 mg, 0.30 mmol, 1.5 eq) and $\text{B}_2(\text{pin})_2$ (76.2 mg, 0.30 mmol, 1.5 eq) were dissolved in DMA (0.5 mL). Then, 6a (23.6 mg, 0.20 mmol, 1.0 eq) was sequentially added to the system via

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- syringe and the reaction mixture was allowed to stir at 80 °C for 12 h. After cooling to ambient temperature, the resulting solution was purified by silica gel chromatography (hexanes:EtOAc = 98:2) to afford 7a (38.0 mg, 0.154 mmol, 77% yield) as colorless oil. ¹H NMR (500 MHz, CDCl₃): δ 7.28 – 7.24 (m, 2H), 7.22 (t, J = 4.1 Hz, 2H), 7.19 – 7.14 (m, 1H), 2.83 (dd, J = 13.6, 7.5 Hz, 1H), 2.56 (dd, J = 13.6, 8.3 Hz, 1H), 1.43 – 1.35 (m, 1H), 1.21 (s, 6H), 1.20 (s, 6H), 0.99 (d, J = 7.4 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃): δ 142.48, 129.04, 128.13, 125.68, 83.12, 39.12, 24.85, 24.83, 15.32; ¹¹B NMR (160 MHz, CDCl₃): δ 34.48.
- 10 4,4,5,5-Tetramethyl-2-(1-(p-tolyl)propan-2-yl)-1,3,2-dioxaborolane (7b): 26 Based on the general procedure, Fe(OAc)₂ (1.7 mg, 0.01 mmol, 0.05 eq), LiOt-Bu (24.0 mg, 0.30 mmol, 1.5 eq) and B₂(pin)₂ (76.2 mg, 0.30 mmol, 1.5 eq) were dissolved in DMA (0.5 mL). Then, 6b (26.4 mg, 0.20 mmol, 1.0 eq) was sequentially added to the system via syringe and the reaction mixture was allowed to stir at 80 °C for 12 h. After cooling to ambient temperature, the resulting solution was purified by silica gel chromatography (hexanes:EtOAc = 98:2) to afford 7b (36.4 mg, 0.140 mmol, 70% yield) as colorless oil. ¹H NMR (500 MHz, CDCl₃): δ 7.14 – 7.00 (m, 4H), 2.79 (dd, J = 13.6, 7.3 Hz, 1H), 2.50 (dd, J = 13.6, 8.5 Hz, 1H), 2.31 (s, 3H), 1.39 – 1.32 (m, 1H), 1.21 (s, 6H), 1.20 (s, 6H), 0.96 (d, J = 7.4 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃): δ 139.35, 134.99, 128.90, 128.82, 83.09, 38.61, 24.86, 24.84, 21.11, 15.24; ¹¹B NMR (160 MHz, CDCl₃): δ 34.33.
- 15 2-(1-(4-Methoxyphenyl)propan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (7c): 27 Based on the general procedure, Fe(OAc)₂ (1.7 mg, 0.01 mmol, 0.05 eq), LiOt-Bu (24.0 mg, 0.30 mmol, 1.5 eq) and B₂(pin)₂ (76.2 mg, 0.30 mmol, 1.5 eq) were dissolved in DMA (0.5 mL). Then, 6c (29.6 mg, 0.20 mmol, 1.0 eq) was sequentially added to the system via syringe and the reaction mixture was allowed to stir at 80 °C for 12 h. After cooling to ambient temperature, the resulting solution was purified by silica gel chromatography (hexanes:EtOAc = 98:2) to afford 7c (44.5 mg, 0.160 mmol, 80% yield) as colorless oil. ¹H NMR (500 MHz, CDCl₃): δ 7.14 – 7.07 (m, 2H), 6.83 – 6.76 (m, 2H), 3.77 (s, 3H), 2.75 (dd, J = 13.7, 7.5 Hz, 1H), 2.55 – 2.44 (m, 1H), 1.37 – 1.31 (m, 1H), 1.20 (s, 6H), 1.19 (s, 6H), 0.96 (d, J = 7.4 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃): δ 157.77, 134.60, 129.89, 113.57, 83.07, 55.36, 38.20, 24.86, 24.83, 15.26; ¹¹B NMR (160 MHz, CDCl₃): δ 34.37.
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2-(1-(2-Methoxyphenyl)propan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (7d):
Based on the general procedure, FeBr₂ (2.2 mg, 0.01 mmol, 0.05 eq), LiOt-Bu (24.0 mg, 0.30 mmol, 1.5 eq) and B₂(pin)₂ (75.0 mg, 0.30 mmol, 1.5 eq) were dissolved in DMA (0.5 mL). Then, 6d (29.6 mg, 0.20 mmol, 1.0 eq) was sequentially added to the
5 system via syringe and the reaction mixture was allowed to stir at 80 °C for 12 h. After cooling to ambient temperature, the resulting solution was purified by silica gel chromatography (hexanes:EtOAc = 98:2) to afford 7d (46.0 mg, 0.166 mmol, 83% yield) as colorless oil. ¹H NMR (500 MHz, CDCl₃): δ 7.15 (m, 2H), 6.88 – 6.78 (m, 2H), 3.80 (s, 3H), 2.79 (dd, J = 13.6, 7.6 Hz, 1H), 2.58 (dd, J = 13.6, 8.4 Hz, 1H), 1.50 –
10 1.40 (m, 1H), 1.20 (s, 6H), 1.19 (s, 6H), 0.96 (d, J = 7.5 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃): δ 157.87, 130.84, 130.47, 126.85, 120.11, 110.27, 82.96, 55.32, 33.16, 24.85, 24.83, 15.50; ¹¹B NMR (160 MHz, CDCl₃): δ 34.21; HRMS (ESI) [M+Na]⁺ calcd for C₁₆H₂₅BNaO₃: 299.1792, found: 299.1785.

2-(1-(4-(Benzyloxy)-3-methoxyphenyl)propan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (7e): Based on the general procedure, FeBr₂ (2.2 mg, 0.01 mmol, 0.05 eq), LiOt-Bu (24.0 mg, 0.30 mmol, 1.5 eq) and B₂(pin)₂ (76.2 mg, 0.30 mmol, 1.5 eq) were dissolved in DMA (0.5 mL). Then, 6e (50.8 mg, 0.20 mmol, 1.0 eq) was sequentially added to the system via syringe and the reaction mixture was allowed to
20 stir at 80 °C for 12 h. After cooling to ambient temperature, the resulting solution was purified by silica gel chromatography (hexanes:EtOAc = 98:2) to afford 7e (46.0 mg, 0.124 mmol, 62% yield) as colorless oil. ¹H NMR (500 MHz, CDCl₃): δ 7.43 (d, J = 7.2 Hz, 2H), 7.35 (dd, J = 10.2, 4.8 Hz, 2H), 7.28 (dd, J = 8.4, 6.3 Hz, 1H), 6.81 – 6.73 (m, 2H), 6.67 (dd, J = 8.2, 1.8 Hz, 1H), 5.11 (s, 2H), 3.87 (s, 3H), 2.73 (dd, J = 13.7,
25 7.7 Hz, 1H), 2.49 (dd, J = 13.7, 8.2 Hz, 1H), 1.35 (dd, J = 15.3, 7.6 Hz, 1H), 1.18 (s, 6H), 1.17 (s, 6H), 0.97 (d, J = 7.4 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃): ¹³C NMR (126 MHz, CDCl₃) δ 149.52, 146.30, 137.69, 135.93, 128.56, 127.78, 127.41, 120.96, 114.34, 113.00, 83.08, 71.41, 56.05, 38.76, 24.84, 15.36; ¹¹B NMR (160 MHz, CDCl₃): δ 33.95; HRMS (ESI) [M+Na]⁺ calcd for C₂₃H₃₁BNaO₄: 405.2212, found: 405.2211.

4,4,5,5-Tetramethyl-2-(1-(naphthalen-1-yl)propan-2-yl)-1,3,2-dioxaborolane (7f): 26
Based on the general procedure, Fe-1 (3.7 mg, 0.01 mmol, 0.05 eq), LiOt-Bu (24.0 mg, 0.30 mmol, 1.5 eq) and B₂(pin)₂ (76.2 mg, 0.30 mmol, 1.5 eq) were dissolved in DMA (0.5 mL). Then, 6f (33.6 mg, 0.20 mmol, 1.0 eq) was sequentially added to the system
35 via syringe and the reaction mixture was allowed to stir at 80 °C for 12 h. After cooling

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to ambient temperature, the resulting solution was purified by silica gel chromatography (hexanes:EtOAc = 98:2) to afford 7f (39.0 mg, 0.132 mmol, 66% yield) as colorless oil. ¹H NMR (500 MHz, CDCl₃): δ 8.10 (d, J = 8.3 Hz, 1H), 7.87 – 7.81 (m, 1H), 7.70 (dd, J = 6.5, 2.9 Hz, 1H), 7.52 – 7.43 (m, 2H), 7.40 – 7.35 (m, 2H), 3.35 (dd, J = 14.0, 7.6 Hz, 1H), 2.95 (dd, J = 14.1, 8.2 Hz, 1H), 1.63 – 1.54 (m, 1H), 1.22 (s, 6H), 1.20 (s, 6H), 1.05 (d, J = 7.4 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃): δ 138.49, 134.04, 132.25, 128.75, 126.60, 126.54, 125.63, 125.38, 125.35, 124.36, 83.16, 36.04, 24.85, 15.83; ¹¹B NMR (160 MHz, CDCl₃): δ 34.48.

2-(1-Cyclohexylpropan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (7g): 28 Based on the general procedure, Fe(OAc)₂ (1.7 mg, 0.01 mmol, 0.05 eq), LiOt-Bu (24.0 mg, 0.30 mmol, 1.5 eq) and B₂(pin)₂ (76.2 mg, 0.30 mmol, 1.5 eq) were dissolved in DMA (0.5 mL). Then, 6g (24.8 mg, 0.20 mmol, 1.0 eq) and t-BuOH (3.7 mg, 0.05 mmol, 0.25 eq) were sequentially added to the system via syringe and the reaction mixture was allowed to stir at 80 °C for 12 h. After cooling to ambient temperature, the resulting solution was purified by silica gel chromatography (hexanes:EtOAc = 98:2) to afford 7g (33.5 mg, 0.136 mmol, 68% yield) in 97:3 regioisomeric ratio (β:other isomers) as colorless oil. ¹H NMR (500 MHz, CDCl₃): isomer (major): δ 1.80-1.50 (m, 5H), 1.34 (dd, J = 7.2, 5.0 Hz, 1H), 1.27– 1.24 (m, 1H), 1.23 (s, 12H), 1.20 – 1.06 (m, 5H), 0.93 (d, J = 7.1 Hz, 3H), 0.88 – 0.77 (m, 2H); ¹³C NMR (126 MHz, CDCl₃): δ 82.87, 40.94, 36.66, 33.82, 33.33, 26.90, 26.66, 26.60, 24.84, 15.85; ¹¹B NMR (160 MHz, CDCl₃): δ 34.69.

4,4,5,5-Tetramethyl-2-(1-(tetrahydro-2H-pyran-4-yl)propan-2-yl)-1,3,2-dioxaborolane (7h): 25 Based on the general procedure, Fe(OAc)₂ (3.4 mg, 0.02 mmol, 0.10 eq), LiOt-Bu (24.0 mg, 0.30 mmol, 1.5 eq) and B₂(pin)₂ (76.2 mg, 0.30 mmol, 1.5 eq) were dissolved in DMA (0.5 mL). Then, 6h (25.2 mg, 0.20 mmol, 1.0 eq) and t-BuOH (3.7 mg, 0.05 mmol, 0.25 eq) were sequentially added to the system via syringe and the reaction mixture was allowed to stir at 80 °C for 12 h. After cooling to ambient temperature, the resulting solution was purified by silica gel chromatography (hexanes:EtOAc = 98:2) to afford 7h (23.4 mg, 0.092 mmol, 46% yield) in 85:15 regioisomeric ratio (β:other isomers) as colorless oil. ¹H NMR (500 MHz, CDCl₃): isomer (major) : ¹H NMR (500 MHz, CDCl₃) δ 3.95 – 3.91 (m, 2H), 3.36 – 3.31 (m, 2H), 1.60 – 1.50 (m, 3H), 1.44 – 1.38 (m, 1H), 1.34 – 1.15 (m, 15H), 1.10 (dd, J = 14.9, 7.5 Hz, 1H), 0.94 (d, J = 7.3 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃): δ 83.01, 68.35, 40.28, 33.98,

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33.58, 33.13, 24.85, 15.73; ^{11}B NMR (160 MHz, CDCl_3): δ 34.55; HRMS (EI) $[\text{M}]^+$ calcd for $\text{C}_{14}\text{H}_{27}\text{BO}_3$: 254.2048, found: 254.2049.

Triisopropyl(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pent-1-yn-1-yl)silane

- 5 (7i): Based on the general procedure, Fe-1 (4.5 mg, 0.01 mmol, 0.05 eq), LiOt-Bu (24.0 mg, 0.30 mmol, 1.5 eq) and $\text{B}_2(\text{pin})_2$ (76.2 mg, 0.30 mmol, 1.5 eq) were dissolved in a mixture of DMA (0.16 mL) and toluene (0.34 mL). Then, 6i (44.4 mg, 0.20 mmol, 1.0 eq) was sequentially added to the system via syringe and the reaction mixture was allowed to stir at 80 °C for 12 h. After cooling to ambient temperature, the resulting
10 solution was purified by silica gel chromatography (hexanes:EtOAc = 98:2) to afford 7i (35.0 mg, 0.100 mmol, 50% yield) as colorless oil. ^1H NMR (500 MHz, CDCl_3): δ 2.38 (dd, J = 16.8, 6.2 Hz, 1H), 2.26 (dd, J = 16.8, 7.3 Hz, 1H), 1.23 (s, 12H), 1.10 – 0.99 (m, 25H); ^{13}C NMR (126 MHz, CDCl_3): δ 109.25, 83.32, 80.17, 24.91, 24.88, 23.24, 18.80, 14.97, 11.48; ^{11}B NMR (160 MHz, CDCl_3): δ 34.22; HRMS (ESI) $[\text{M}+\text{Na}]^+$ calcd
15 for $\text{C}_{20}\text{H}_{39}\text{BNaO}_2\text{Si}$: 373.2708, found: 373.2701.

- 2,2'-(Propane-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (7j): 29 Based on the general procedure, Fe-1 (4.5 mg, 0.01 mmol, 0.05 eq), LiOt-Bu (24.0 mg, 0.30 mmol, 1.5 eq) and $\text{B}_2(\text{pin})_2$ (76.2 mg, 0.30 mmol, 1.5 eq) were dissolved in a mixture
20 of DMA (0.16 mL) and toluene (0.34 mL). Then, 6j (33.6 mg, 0.20 mmol, 1.0 eq) was sequentially added to the system via syringe and the reaction mixture was allowed to stir at 80 °C for 6 h. After cooling to ambient temperature, the resulting solution was purified by silica gel chromatography (hexanes:EtOAc = 98:2) to afford 7j (21.3 mg, 0.072 mmol, 36% yield) as colorless oil. ^1H NMR (500 MHz, CDCl_3): δ 1.22 (s, 24H),
25 1.17 (t, J = 7.5 Hz, 1H), 0.99 (d, J = 7.4 Hz, 3H), 0.92 – 0.87 (m, 1H), 0.78 (dd, J = 15.9, 6.3 Hz, 1H); ^{13}C NMR (126 MHz, CDCl_3): δ 82.96, 82.94, 25.00, 24.96, 24.90, 24.85, 18.49; ^{11}B NMR (160 MHz, CDCl_3): δ 33.98.

- Triethyl(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propyl)silane (7k): Based on
30 the general procedure, $\text{Fe}(\text{OAc})_2$ (1.7 mg, 0.01 mmol, 0.05 eq), LiOt-Bu (24.0 mg, 0.30 mmol, 1.5 eq) and $\text{B}_2(\text{pin})_2$ (76.2 mg, 0.30 mmol, 1.5 eq) were dissolved in DMA (0.5 mL). Then, 6k (31.2 mg, 0.20 mmol, 1.0 eq) and t-BuOH (3.7 mg, 0.05 mmol, 0.25 eq) were sequentially added to the system via syringe and the reaction mixture was allowed to stir at 80 °C for 12 h. After cooling to ambient temperature, the resulting solution
35 was purified by silica gel chromatography (hexanes:EtOAc = 98:2) to afford 7k (36.0

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mg, 0.126 mmol, 63% yield) in 97:3 regioisomeric ratio (β :other isomers) as colorless oil. ^1H NMR (500 MHz, CDCl_3): isomer (major) : δ 1.23 (s, 12H), 1.10 – 1.04 (m, 1H), 1.04 – 0.98 (m, 3H), 0.92 (t, J = 7.9 Hz, 9H), 0.80 (dd, J = 14.8, 7.4 Hz, 1H), 0.51 (q, J = 7.9 Hz, 6H), 0.41 (dd, J = 14.8, 6.5 Hz, 1H); ^{13}C NMR (126 MHz, CDCl_3): δ 82.93, 24.95, 24.82, 19.84, 14.54, 7.67, 3.91; ^{11}B NMR (160 MHz, CDCl_3): δ 34.11; HRMS (EI) $[\text{M}-\text{C}_2\text{H}_5]^+$ calcd for $\text{C}_{13}\text{H}_{28}\text{BO}_2\text{Si}$: 255.1946, found: 255.1950

4,4,5,5-Tetramethyl-2-(1-phenylhexan-2-yl)-1,3,2-dioxaborolane (7l): Based on the general procedure, $\text{Fe}(\text{OAc})_2$ (1.7 mg, 0.01 mmol, 0.05 eq), LiOt-Bu (24.0 mg, 0.30 mmol, 1.5 eq) and $\text{B}_2(\text{pin})_2$ (76.2 mg, 0.30 mmol, 1.5 eq) were dissolved in DMA (0.5 mL). Then, 6l (32.0 mg, 0.20 mmol, 1.0 eq) was sequentially added to the system via syringe and the reaction mixture was allowed to stir at 80 °C for 12 h. After cooling to ambient temperature, the resulting solution was purified by silica gel chromatography (hexanes:EtOAc = 98:2) to afford 7l (49.0 mg, 0.170 mmol, 85% yield) as colorless oil. ^1H NMR (500 MHz, CDCl_3): δ 7.26 – 7.19 (m, 4H), 7.16 – 7.10 (m, 1H), 2.75 – 2.64 (m, 2H), 1.49 – 1.35 (m, 3H), 1.34 – 1.27 (m, 4H), 1.17 (s, 6H), 1.13 (s, 6H), 0.91 – 0.84 (m, 3H); ^{13}C NMR (126 MHz, CDCl_3): δ 142.53, 128.98, 128.13, 125.65, 83.05, 37.53, 31.55, 31.03, 24.89, 24.83, 23.04, 14.20; ^{11}B NMR (160 MHz, CDCl_3): δ 34.38; HRMS (ESI) $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{18}\text{H}_{29}\text{BNaO}_2$: 311.2156, found: 311.2149.

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4,4,5,5-Tetramethyl-2-(1-phenyltridecan-2-yl)-1,3,2-dioxaborolane (7m): Based on the general procedure, $\text{Fe}(\text{OAc})_2$ (1.7 mg, 0.01 mmol, 0.05 eq), LiOt-Bu (24.0 mg, 0.30 mmol, 1.5 eq) and $\text{B}_2(\text{pin})_2$ (76.2 mg, 0.30 mmol, 1.5 eq) were dissolved in DMA (0.5 mL). Then, 6m (51.7 mg, 0.20 mmol, 1.0 eq) was sequentially added to the system via syringe and the reaction mixture was allowed to stir at 80 °C for 12 h. After cooling to ambient temperature, the resulting solution was purified by silica gel chromatography (hexanes:EtOAc = 98:2) to afford 10m (58.0 mg, 0.156 mmol, 78% yield) as colorless oil. ^1H NMR (500 MHz, CDCl_3): δ 7.26 – 7.18 (m, 4H), 7.17 – 7.10 (m, 1H), 2.74 – 2.63 (m, 2H), 1.46 – 1.35 (m, 3H), 1.31 – 1.23 (m, 18H), 1.16 (s, 6H), 1.13 (s, 6H), 0.88 (t, J = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3): δ 142.55, 128.99, 128.13, 125.65, 83.06, 37.55, 32.07, 31.38, 29.98, 29.81, 29.80, 29.74, 29.71, 29.50, 29.30, 24.91, 24.84, 22.83, 14.26; ^{11}B NMR (160 MHz, CDCl_3): δ 33.83; HRMS (EI) $[\text{M}-\text{H}]^+$ calcd for $\text{C}_{24}\text{H}_{40}\text{BO}_2$: 371.3116, found: 371.3118.

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2-(1-(4-Methoxyphenyl)pentan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (9): Based on the general procedure, Fe(OAc)₂ (1.7 mg, 0.01 mmol, 0.05 eq), LiOt-Bu (24.0 mg, 0.30 mmol, 1.5 eq) and B₂(pin)₂ (76.2 mg, 0.30 mmol, 1.5 eq) were dissolved in a mixture of DMA (0.16 mL) and toluene (0.34 mL). Then, 1-methoxy-4-(pent-4-en-1-yl)benzene (35.2 mg, 0.20 mmol, 1.0 eq) was sequentially added to the system via syringe and the reaction mixture was allowed to stir at 100 °C for 12 h. After cooling to ambient temperature, the resulting solution was purified by silica gel chromatography (hexanes:EtOAc = 98:2) to afford 12 (43.2 mg, 0.142 mmol, 71% yield) in 92:8 regioisomeric ratio (β:other isomers) as colorless oil. ¹H NMR (500 MHz, CDCl₃): isomer (major): δ 7.11 (d, J = 8.5 Hz, 2H), 6.79 (d, J = 8.5 Hz, 2H), 3.77 (s, 3H), 2.65 (dd, J = 13.7, 8.4 Hz, 1H), 2.60 (dd, J = 13.7, 7.0 Hz, 1H), 1.42 – 1.28 (m, 5H), 1.17 (s, 6H), 1.14 (s, 6H), 0.88 (dd, J = 8.3, 5.4 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃): δ 157.72, 134.65, 129.84, 113.55, 83.02, 55.36, 36.56, 33.56, 24.90, 24.86, 22.46, 14.53; ¹¹B NMR (160 MHz, CDCl₃): δ 34.03; HRMS (ESI) [M+Na]⁺ calcd for C₁₈H₂₉BNaO₃: 327.2102, found: 327.2107.

4,4,5,5-Tetramethyl-2-(1-phenylhexan-2-yl)-1,3,2-dioxaborolane (7k): Based on the general procedure, Fe(OAc)₂ (1.7 mg, 0.01 mmol, 0.05 eq), LiOt-Bu (24.0 mg, 0.30 mmol, 1.5 eq) and B₂(pin)₂ (76.2 mg, 0.30 mmol, 1.5 eq) were dissolved in a mixture of DMA (0.16 mL) and toluene (0.34 mL). Then, hex-5-en-1-ylbenzene (32.0 mg, 0.20 mmol, 1.0 eq) was sequentially added to the system via syringe and the reaction mixture was allowed to stir at 100 °C for 12 h. After cooling to ambient temperature, the resulting solution was purified by silica gel chromatography (hexanes:EtOAc = 98:2) to afford 10l (29.0 mg, 0.100 mmol, 50% yield) in 88:12 regioisomeric ratio (β:other isomers) as colorless oil. ¹H NMR (500 MHz, CDCl₃): isomer (major): δ 7.25 – 7.18 (m, 4H), 7.16 – 7.12 (m, 1H), 2.75 – 2.64 (m, 2H), 1.48 – 1.25 (m, 7H), 1.16 (s, 6H), 1.13 (s, 6H), 0.87 (t, J = 7.1 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃): δ 142.55, 128.99, 128.13, 125.66, 83.06, 37.53, 31.55, 31.03, 24.90, 24.83, 23.04, 14.19; ¹¹B NMR (160 MHz, CDCl₃): δ 34.10; HRMS (ESI) [M+Na]⁺ calcd for C₁₈H₂₉BNaO₂: 311.2156, found: 311.2149.

2-(1-([1,1'-Biphenyl]-4-yl)hexan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (10): Based on the general procedure, Fe(OAc)₂ (1.7 mg, 0.01 mmol, 0.05 eq), LiOt-Bu (24.0 mg, 0.30 mmol, 1.5 eq) and B₂(pin)₂ (76.2 mg, 0.30 mmol, 1.5 eq) were dissolved in a mixture of DMA (0.16 mL) and toluene (0.34 mL). Then, 4-(hex-5-en-1-yl)-1,1'-

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biphenyl (47.2 mg, 0.20 mmol, 1.0 eq) was sequentially added to the system via syringe and the reaction mixture was allowed to stir at 100 °C for 12 h. After cooling to ambient temperature, the resulting solution was purified by silica gel chromatography (hexanes:EtOAc = 98:2) to afford 13 (38.0 mg, 0.104 mmol, 52% yield) in 92:8 regioisomeric ratio(β :other isomers) as colorless solid. ¹H NMR (500 MHz, CDCl₃): isomer (major): 7.58 (dd, J = 8.1, 0.9 Hz, 2H), 7.51 – 7.47 (m, 2H), 7.45 – 7.40 (m, 2H), 7.35 – 7.27 (m, 3H), 2.76 (dd, J = 12.4, 7.3 Hz, 1H), 2.72 (dd, J = 12.4, 6.0 Hz, 1H), 1.51 – 1.38 (m, 3H), 1.37 – 1.29 (m, 4H), 1.18 (s, 6H), 1.15 (s, 6H), 0.89 (t, J = 7.1 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃): δ 141.75, 141.43, 138.59, 129.41, 128.80, 127.08, 127.01, 126.88, 83.11, 37.16, 31.57, 31.08, 24.92, 24.85, 23.06, 14.21; ¹¹B NMR (160 MHz, CDCl₃): δ 34.80; HRMS (ESI) [M+Na]⁺ calcd for C₂₄H₃₃BNaO₂: 387.2466, found: 387.2463.

4,4,5,5-Tetramethyl-2-(1-phenylheptan-2-yl)-1,3,2-dioxaborolane (11): Based on the general procedure, Fe(OAc)₂ (1.7 mg, 0.01 mmol, 0.05 eq), LiOt-Bu (24.0 mg, 0.30 mmol, 1.5 eq) and B₂(pin)₂ (76.2 mg, 0.30 mmol, 1.5 eq) were dissolved in a mixture of DMA (0.16 mL) and toluene (0.34 mL). Then, hept-6-en-1-ylbenzene (34.8 mg, 0.20 mmol, 1.0 eq) was sequentially added to the system via syringe and the reaction mixture was allowed to stir at 100 °C for 12 h. After cooling to ambient temperature, the resulting solution was purified by silica gel chromatography (hexanes:EtOAc = 98:2) to afford 14 (36.0 mg, 0.120 mmol, 60% yield) in 89:11 regioisomeric ratio (β :other isomers) as colorless oil. ¹H NMR (500 MHz, CDCl₃): isomer (major): δ 7.26 – 7.16 (m, 4H), 7.16 – 7.12 (m, 1H), 2.74 – 2.63 (m, 2H), 1.46 – 1.25 (m, 9H), 1.16 (s, 6H), 1.13 (s, 6H), 0.87 (t, J = 6.9 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃): δ 142.55, 128.99, 128.13, 125.65, 83.06, 37.55, 32.20, 31.34, 28.97, 24.90, 24.84, 22.71, 14.18; ¹¹B NMR (160 MHz, CDCl₃): δ 34.40; HRMS (ESI) [M+Na]⁺ calcd for C₁₉H₃₁BNaO₂: 325.2313, found: 325.2321.

4,4,5,5-Tetramethyl-2-(1-phenylnonan-2-yl)-1,3,2-dioxaborolane (12): Based on the general procedure, Fe(OAc)₂ (1.7 mg, 0.01 mmol, 0.05 eq), LiOt-Bu (24.0 mg, 0.30 mmol, 1.5 eq) and B₂(pin)₂ (76.2 mg, 0.30 mmol, 1.5 eq) were dissolved in a mixture of DMA (0.16 mL) and toluene (0.34 mL). Then, non-8-en-1-ylbenzene (40.4 mg, 0.20 mmol, 1.0 eq) was sequentially added to the system via syringe and the reaction mixture was allowed to stir at 100 °C for 12 h. After cooling to ambient temperature, the resulting solution was purified by silica gel chromatography (hexanes:EtOAc = 98:2)

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to afford 15 (36 mg, 0.110 mmol, 55% yield) in 88:12 regioisomeric ratio (β :other isomers) as colorless oil. ^1H NMR (500 MHz, CDCl_3): isomer (major): δ 7.26 – 7.16 (m, 4H), 7.15 – 7.10 (m, 1H), 2.74 – 2.62 (m, 2H), 1.46 – 1.24 (m, 13H), 1.16 (s, 6H), 1.13 (s, 6H), 0.87 (t, J = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3): δ 142.55, 128.99, 128.14, 125.65, 83.06, 37.55, 31.96, 31.37, 29.94, 29.36, 29.30, 24.91, 24.84, 22.79, 14.25; ^{11}B NMR (160 MHz, CDCl_3): δ 34.60; HRMS (ESI) $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{21}\text{H}_{35}\text{BNaO}_2$: 353.2622, found: 353.2628.

4,4,5,5-Tetramethyl-2-(1-phenylundecan-2-yl)-1,3,2-dioxaborolane (13): Based on the general procedure, $\text{Fe}(\text{OAc})_2$ (1.7 mg, 0.01 mmol, 0.05 eq), LiOt-Bu (24.0 mg, 0.30 mmol, 1.5 eq) and $\text{B}_2(\text{pin})_2$ (76.2 mg, 0.30 mmol, 1.5 eq) were dissolved in a mixture of DMA (0.16 mL) and toluene (0.34 mL). Then, undec-10-en-1-ylbenzene (46.0 mg, 0.20 mmol, 1.0 eq) was sequentially added to the system via syringe and the reaction mixture was allowed to stir at 100 °C for 12 h. After cooling to ambient temperature, the resulting solution was purified by silica gel chromatography (hexanes:EtOAc = 98:2) to afford 16 (36.0 mg, 0.100 mmol, 50% yield) in 84:16 regioisomeric ratio (β :other isomers) as colorless oil. ^1H NMR (500 MHz, CDCl_3): isomer (major): δ 7.24 – 7.16 (m, 4H), 7.15 – 7.10 (m, 1H), 2.75 – 2.63 (m, 2H), 1.44 – 1.35 (m, 3H), 1.26 (t, J = 8.7 Hz, 14H), 1.16 (s, 6H), 1.13 (s, 6H), 0.88 (t, J = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3): δ 142.55, 128.99, 128.13, 125.65, 83.06, 37.55, 32.06, 31.38, 29.98, 29.71, 29.46, 29.30, 24.91, 24.84, 22.83, 14.25; ^{11}B NMR (160 MHz, CDCl_3): δ 34.60; HRMS (ESI) $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{23}\text{H}_{39}\text{BNaO}_2$: 381.2939, found: 381.2946.

4,4,5,5-Tetramethyl-2-(4-phenylbutyl)-1,3,2-dioxaborolane (23): Based on the general procedure, Fe-1 (2.3 mg, 0.005 mmol, 0.025 eq), LiOt-Bu (3.2 mg, 0.04 mmol, 0.2 eq) and $\text{B}_2(\text{pin})_2$ (76.2 mg, 0.30 mmol, 1.5 eq) were dissolved in a mixture of DMA (0.5 mL). Then, 4b (26.4 mg, 0.20 mmol, 1.0 eq) and $t\text{-BuOH}$ (148.2 mg, 2.0 mmol, 10.0 eq) were sequentially added to the system via syringe and the reaction mixture was allowed to stir at 100 °C for 12 h. After cooling to ambient temperature, the resulting solution was purified by silica gel chromatography (hexanes:EtOAc = 98:2) to afford 23 (50.0 mg, 0.192 mmol, 96% yield) in 88:12 regioisomeric ratio (1:other isomers) as colorless oil. The spectral data for this compound were identical to those previously reported. ^1H NMR (400 MHz, CDCl_3): isomer (major): δ 7.26 – 7.21 (m, 2H), 7.18 – 7.11 (m, 3H), 2.62 – 2.55 (m, 2H), 1.65 – 1.57 (m, 2H), 1.46 (dt, J = 15.2, 7.6 Hz, 2H), 1.22 (s, 12H), 0.80 (t, J = 7.8 Hz, 2H); ^{13}C NMR (101 MHz, CDCl_3): δ 143.04,

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128.51, 128.32, 125.62, 83.02, 35.90, 34.31, 24.95, 23.89; ^{11}B NMR (128 MHz, CDCl_3): δ 33.90.

4,4,5,5-Tetramethyl-2-(4-phenylbutan-2-yl)-1,3,2-dioxaborolane (24): Based on the
5 general procedure, FeBr_2 (1.1 mg, 0.005 mmol, 0.025 eq), 2,9-dimethyl-1,10-phenanthroline (1.3 mg, 0.006 mmol, 0.03 eq), LiOt-Bu (24.0 mg, 0.30 mmol, 1.5 eq) and $\text{B}_2(\text{pin})_2$ (76.2 mg, 0.30 mmol, 1.5 eq) were dissolved in a mixture of DMA (0.5 mL). Then, 4b (26.4 mg, 0.20 mmol, 1.0 eq) and $t\text{-BuOH}$ (3.7 mg, 0.05 mmol, 0.25 eq) were sequentially added to the system via syringe and the reaction mixture was allowed
10 to stir at 100 °C for 12 h. After cooling to ambient temperature, the resulting solution was purified by silica gel chromatography (hexanes:EtOAc = 98:2) to afford 24 (33.3 mg, 0.128 mmol, 64% yield) in 84:16 regioisomeric ratio (2:other isomers) as colorless oil. The spectral data for this compound were identical to those previously reported.
38 ^1H NMR (400 MHz, CDCl_3): isomer (major): δ 7.29 – 7.23 (m, 2H), 7.21 – 7.13 (m, 3H),
15 2.66 – 2.59 (m, 2H), 1.84 – 1.73 (m, 1H), 1.67 – 1.60 (m, 1H), 1.25 (s, 12H), 1.08 (m, J = 11.6, 6.4 Hz, 1H), 1.05 – 0.98 (m, 3H); ^{13}C NMR (101 MHz, CDCl_3): δ 143.23, 128.58, 128.33, 125.64, 83.03, 35.42, 24.94, 24.88, 15.55; ^{11}B NMR (128 MHz, CDCl_3): δ 34.34.

20 In corollary, alkene isomerization of alkene compounds can be obtained by in situ formation of an iron-hydride species which promotes olefin isomerization through sequential olefin insertion/ β -hydride elimination. Through this strategy, regiodivergent access to different products from one substrate can be facilitated, isomeric olefin mixtures commonly found in petroleum-derived feedstock can be transformed to a
25 single alkene product, and unsaturated moieties embedded within linear and heterocyclic biologically active entities can be obtained.

Alkenes are one of the most important and versatile functionalities in chemistry. Among the plethora of synthetic methods devised to install olefins, the transposition of an
30 existing C–C double bond giving rise to a new positional isomer represents an attractive atom-economical approach to access higher-value compounds with minimal skeletal modification and byproduct formation. To this end, metal-catalyzed alkene isomerization has emerged as a powerful strategy with far-reaching applications in the production of high-value chemicals (e.g., gasoline, polymers, fragrances, and
35 pharmaceuticals) across industry and academia. A vast number of C=C bond migration

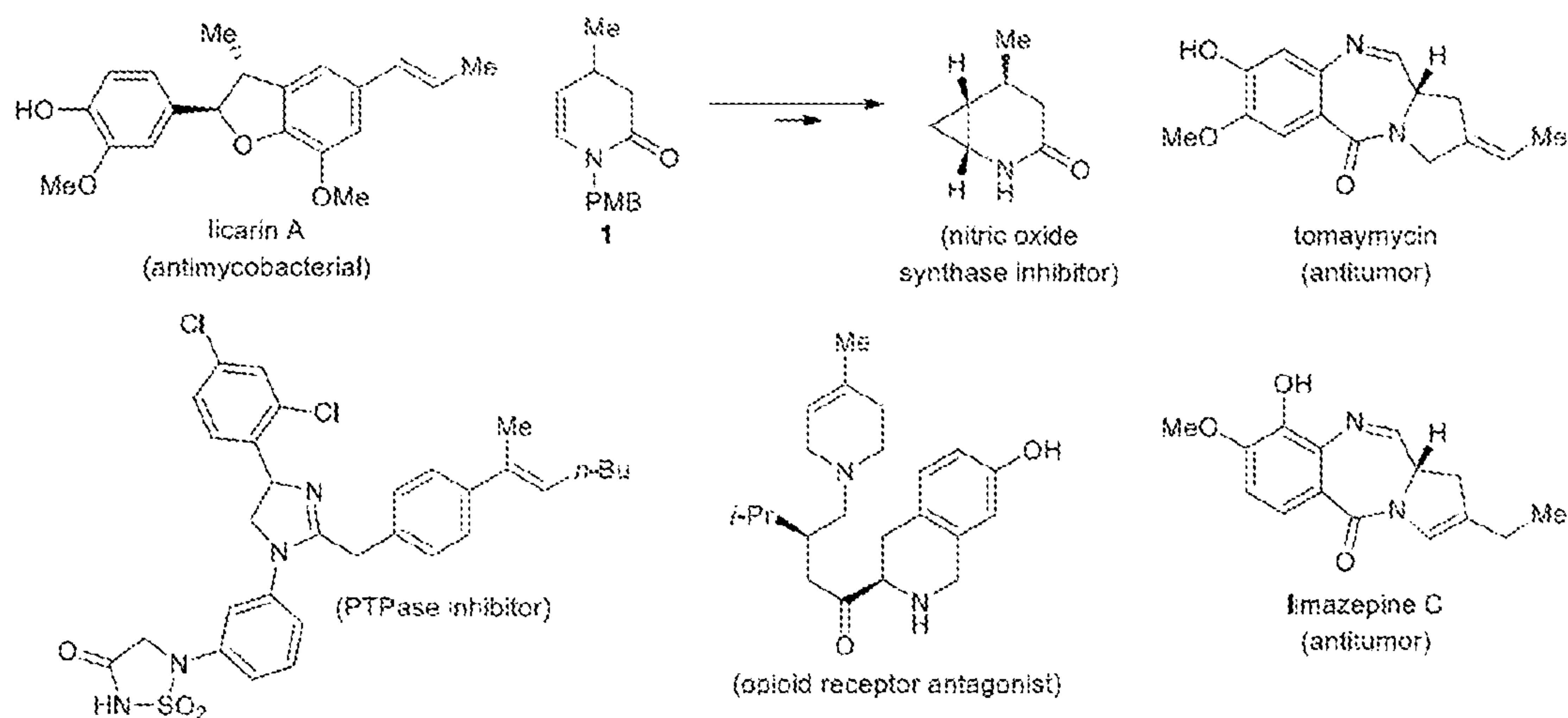
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protocols have been developed using catalysts derived from noble metals (e.g., Ir, Rh, Pd, and Ru) as well as base metals (e.g., Co, Ni, Fe, and Mo). A recent disclosure involving visible light/Co dual catalysis offers controllable isomerization of terminal alkenes to different regioisomers in the presence of suitable ligands. Despite the remarkable developments and merits associated with each of these transformations, enduring shortcomings remain to be addressed: (i) except for specific examples, most protocols either involve monoisomerizations (i.e., terminal alkenes to 2-alkenes) or isomerizations to the thermodynamically most stable internal alkene. Methods that offer both possibilities are scarce, and reported cases are limited to terminal alkenes. (ii) Tunable C=C bond transposition over multiple positions, which will provide regiodivergent access to different olefin positional isomers from one substrate, continues to be a formidable challenge. (iii) Conversion of regioisomeric alkene mixtures to a single olefin product, which is particularly useful for streamlining chemical synthesis, is yet to be implemented.

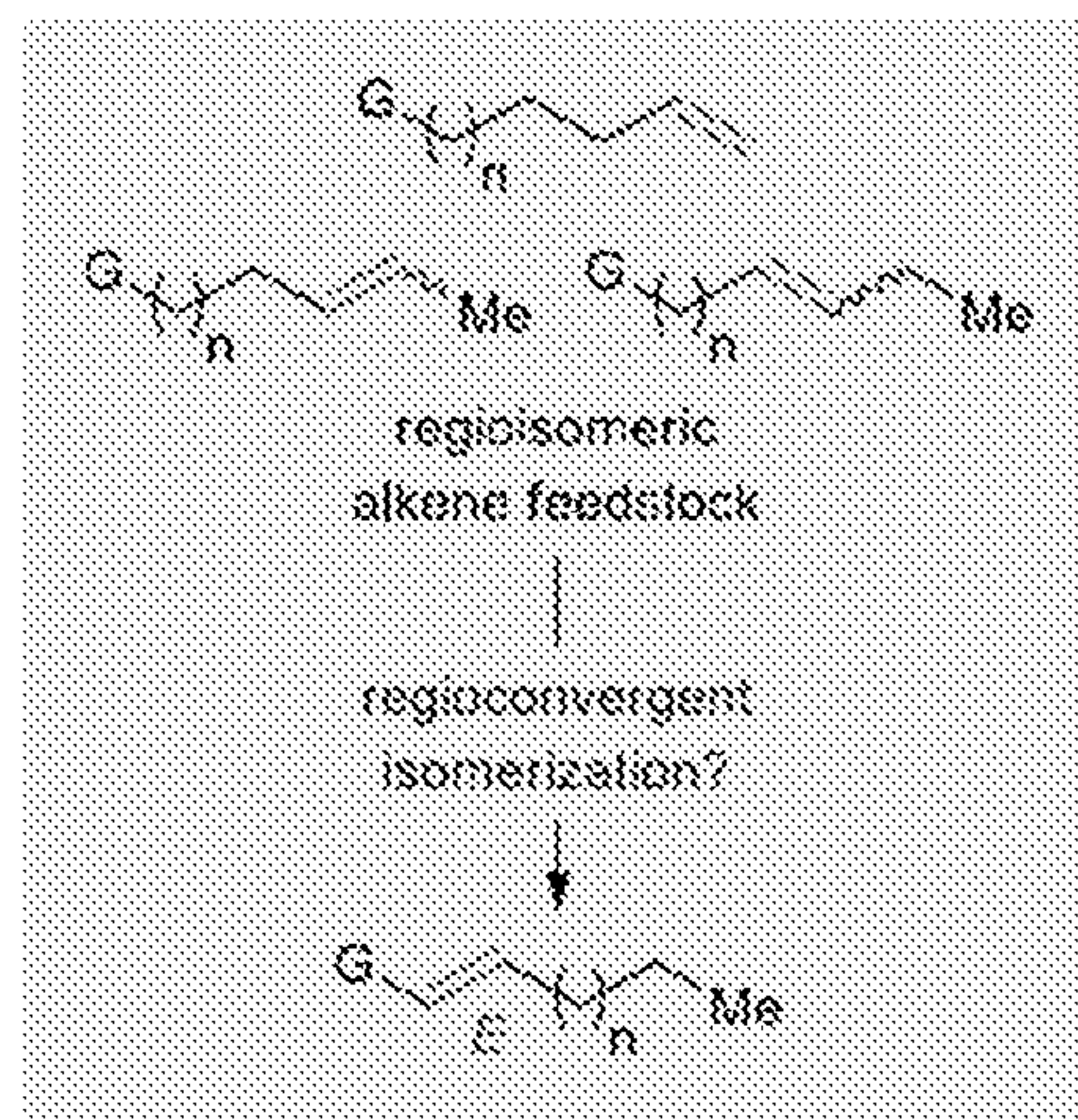
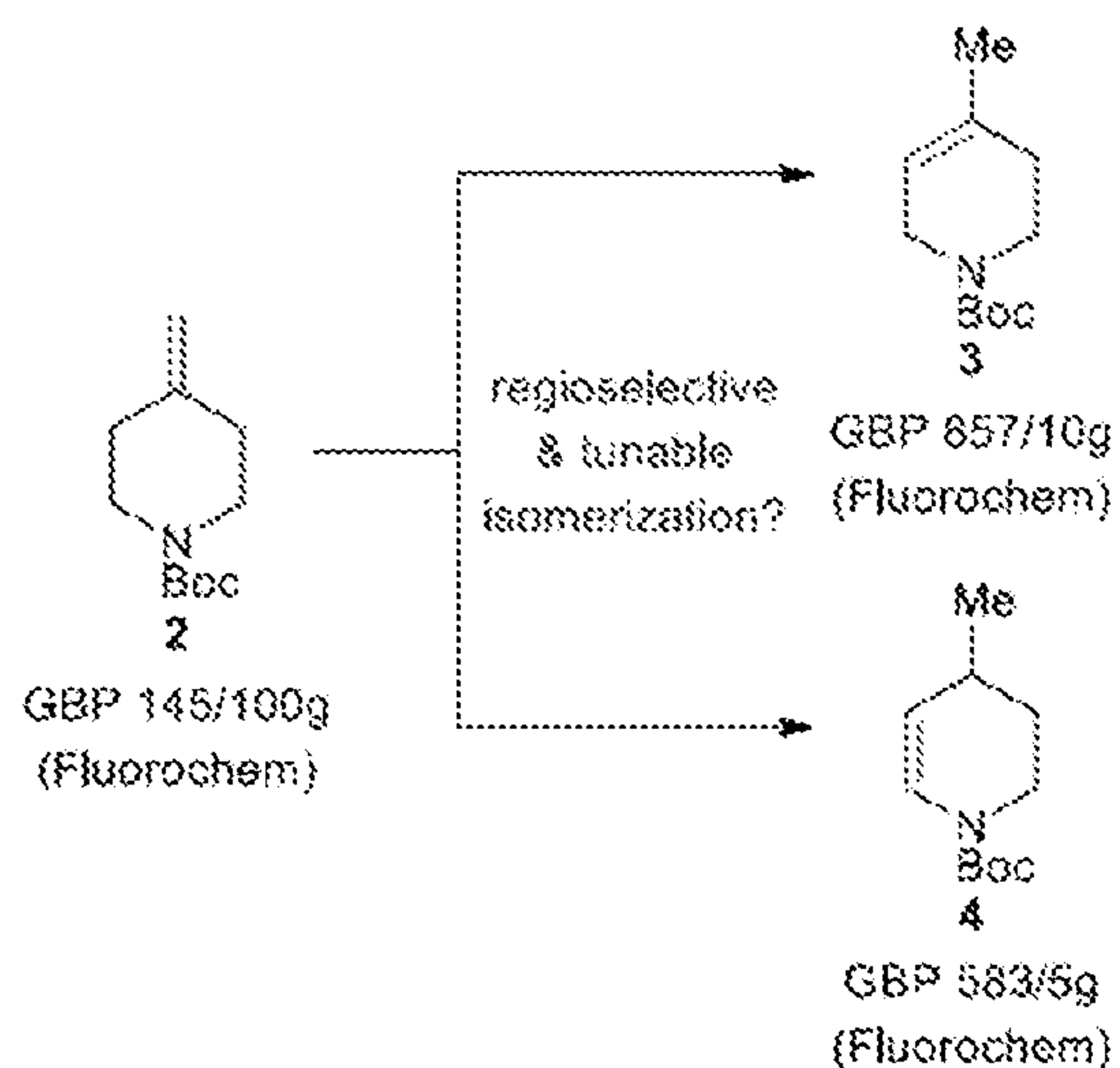
Iron is the most abundant nontoxic transition metal in the earth's crust (~6%) and is cheaper than other base metals. Added to these appealing traits is the commercial availability and ease of synthesis associated with iron-based complexes. Although iron catalysis had been previously examined for C=C bond transposition to access olefin products, the scope was largely limited to shifts over one position employing terminal alkene substrates. In light of the rising global demand for sustainable synthesis to reduce reliance on precious metals, it was sought to devise an operationally simple Fe-catalyzed protocol to facilitate tunable C=C bond migrations for the concise preparation of unsaturated motifs embedded within synthetically valuable bioactive entities (Scheme 4a). The new C=C bond isomerization manifold will be complementary to existing methods and may be leveraged to overcome longstanding challenges in alkene synthesis as highlighted in Scheme 4b.

Scheme 4a. Disubstituted and trisubstituted alkenes within biologically active compounds and their precursors

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Scheme 4b. Challenges in alkene synthesis and catalytic isomerization as a viable solution

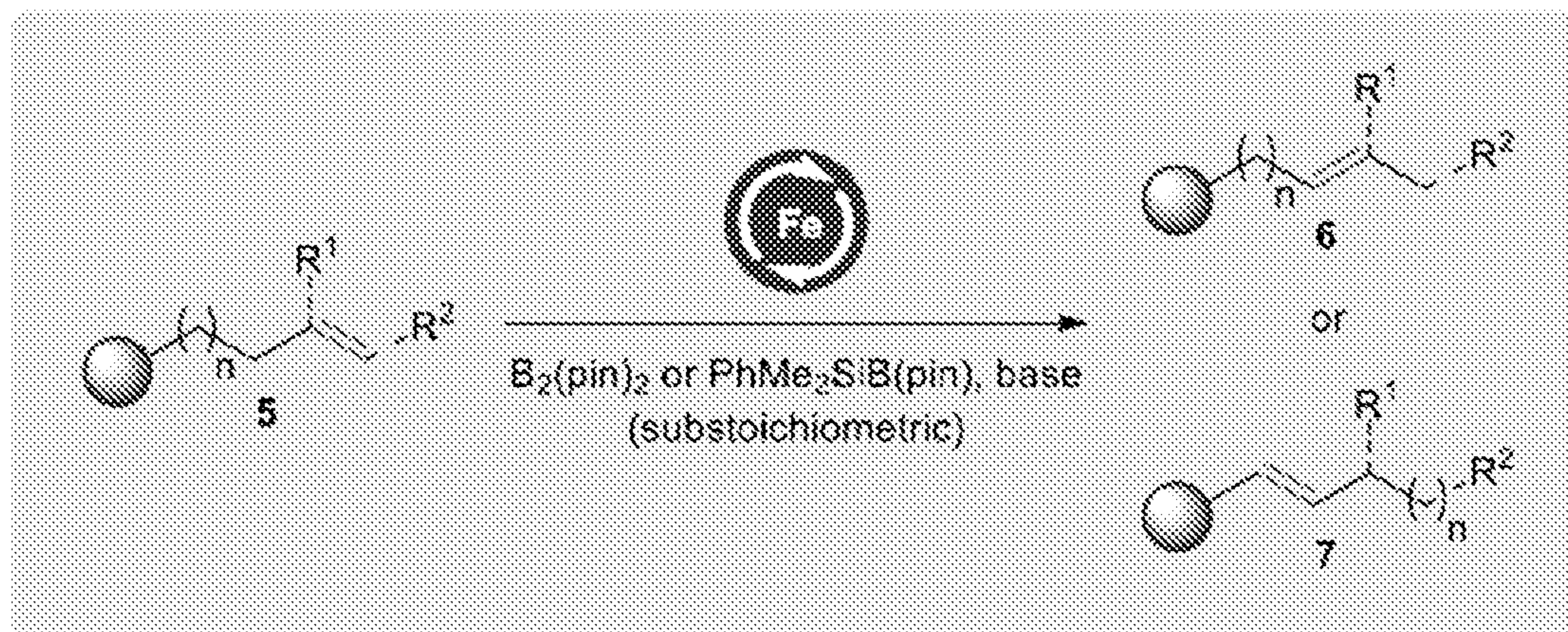


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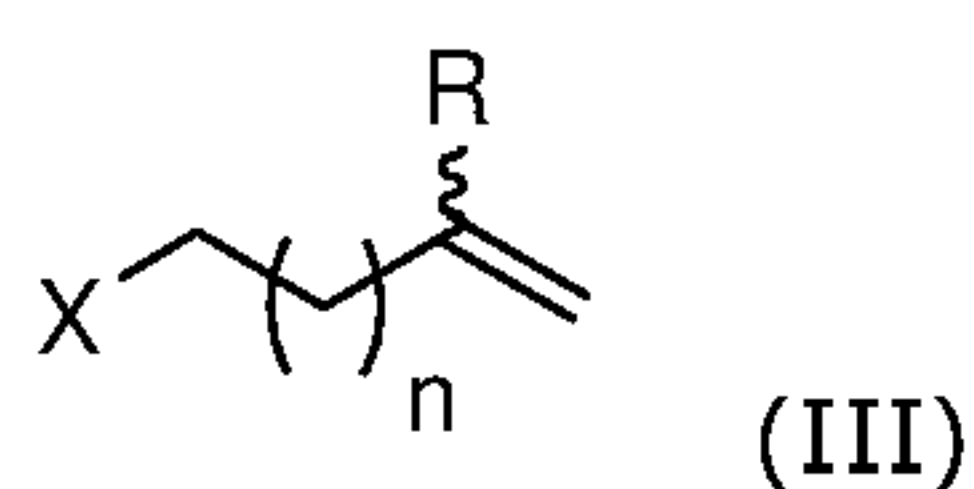
The present invention discloses a catalytic regime that accomplishes the regiodivergent conversion of inexpensive terminal and internal alkenes 5 (both cyclic and acyclic) to either 6 (over one position) or 7 (over multiple positions), as well as the regioconvergent transformation of isomeric olefin mixtures commonly found in unrefined raw materials from petroleum processing to value added isomerically pure products (Scheme 4c).

Scheme 4c. Tunable olefin transportation with a Fe-based catalyst converts unsaturated feedstock to higher-value alkenes

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The present invention provides a method of isomerising a compound of Formula (III):

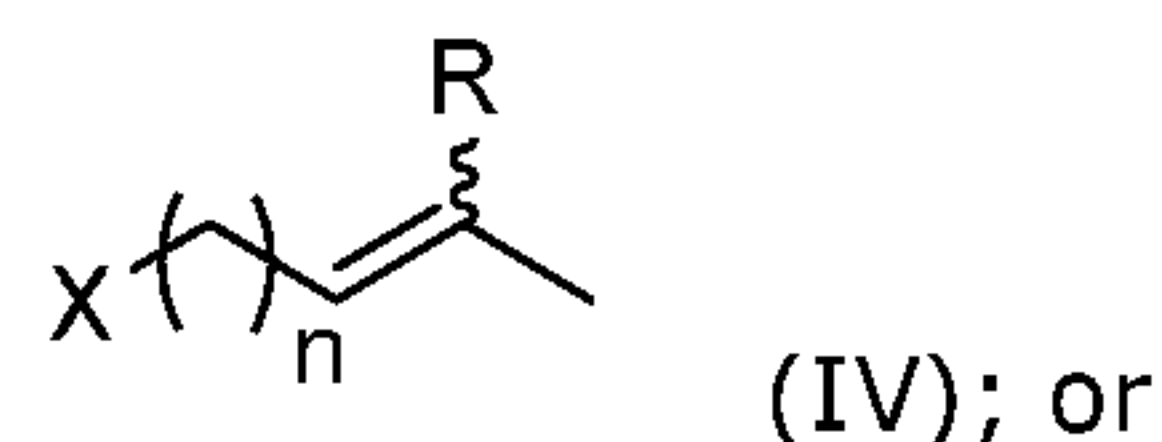


- 5 wherein X is selected from the group consisting of optionally substituted silyl, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl;
- R is selected from the group consisting of H, halo, optionally substituted alkyl and
- 10 optionally substituted cycloalkyl;
- or X and R together forms an optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted heterocyclyl, or optionally substituted heterocycloalkenyl;
- n is an integer selected from 0 to 10;
- 15 by contacting the compound of Formula (III) with:
- i) a boron compound selected from bis(pinacolato)diboron ($\text{B}_2(\text{pin})_2$), (dimethylphenylsilyl)boronic acid pinacol ester ($\text{PhMe}_2\text{SiB}(\text{pin})$), bis(neopentyl glycolate)diboron ($\text{Bis}(\text{NPG})\text{diboron}$) and bis(pinacolato)diboron ($\text{Bis}(\text{HG})\text{diboron}$);
 - 20 ii) a Fe catalyst selected from $[\text{Fe}(\text{bpy})_3][\text{FeBr}_4]$, $[(\text{bpy})\text{FeCl}_2]_2$, (6,6'-dimethyl-2,2'-bipyridine) FeCl_2 , (terpyridine) FeBr_2 , (neocuproine) FeBr_2 , FeBr_2 , FeCl_2 , $\text{Fe}(\text{acac})_2$ and $\text{Fe}(\text{OAc})_2$ optionally with (R)-(-)-5,5'-Bis[di(3,5-di-tert-butyl-4-methoxyphenyl)phosphino]-4,4'-bi-1,3-benzodioxole ((R)-DTBM-SEGPPOS); and

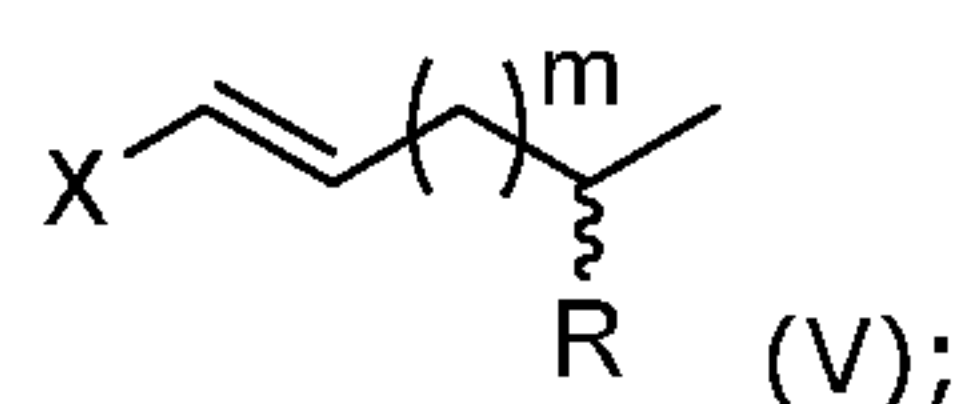
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iii) a base;

wherein the alkenyl moiety is isomerised over one position to give a compound of Formula (IV):



5 wherein the alkenyl moiety is isomerised over multiple position to give a compound of Formula (V):



wherein m is an integer selected from 0 to 9; and
X, R and n are as defined herein.

10

In some embodiments, the reaction is performed in an aprotic solvent.

In some embodiments, the Fe catalyst is added from about 0.5 mol% to about 30 mol% of compound of Formula (III).

15

In some embodiments, the boron compound is added from about 10 mol% to about 90 mol% of compound of Formula (III).

In some embodiments, the base is lithium tert-butoxide.

20

In some embodiments, the base is added from about 10 mol% to about 90 mol% of compound of Formula (III).

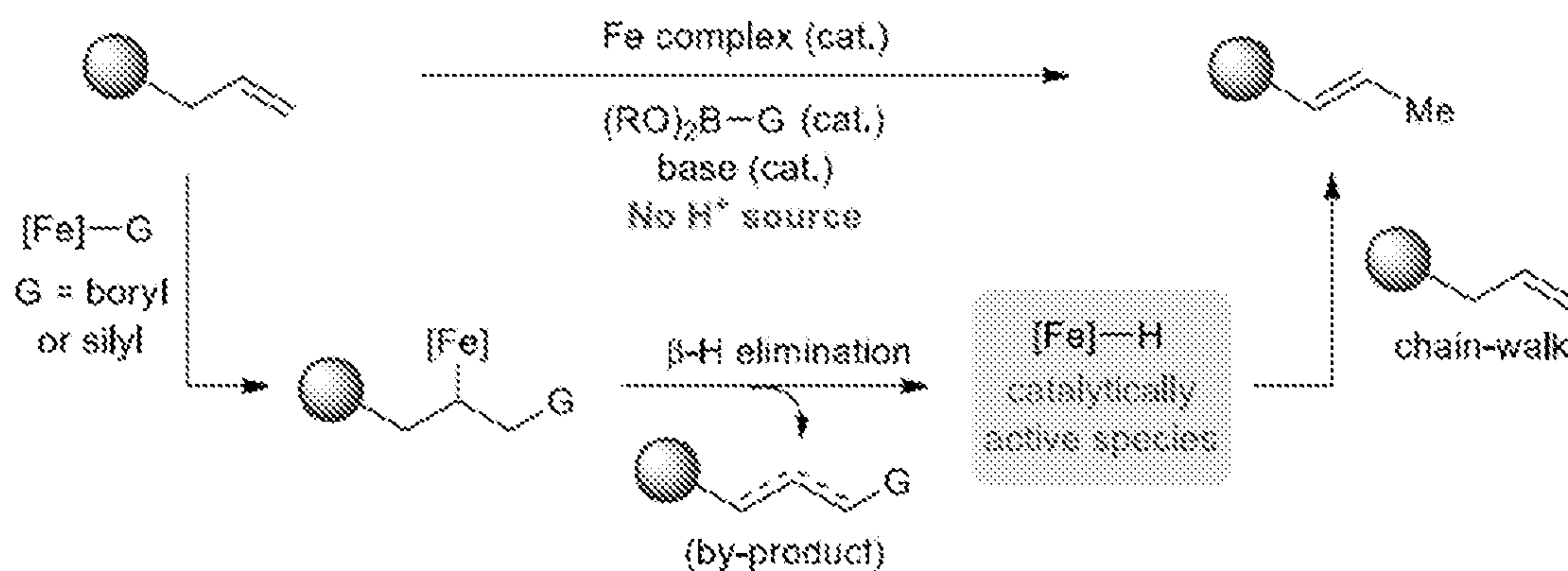
25 In some embodiments, the isomerised alkene (compound of Formula (IV) and/or compound of Formula (V)) has a E:Z isomeric ratio of about 60:40 to about 99:1.

Reaction Design and Mechanistic Studies. A survey of the Fe-catalyzed isomerization strategies reported to date showed that the C=C bond migration process could be triggered either by an intramolecular 1,3-hydride shift via a π -allyl intermediate or
30 through an olefin migratory insertion/ β -H elimination pathway involving an iron-hydride species generated from base/water additives. The present invention is predicated on

the understanding of the above borylation method and taking advantage of an Fe-based catalyst and stoichiometric amounts of a commercially available diboryl reagent/base to promote iron-boryl insertion followed by protonolysis of the resulting iron-alkyl complex.

- 5 It is speculated that in the absence of a protic source (thereby obviating protodemetalation), a diboryl (or silylboryl) reagent and base could be employed in catalytic or substoichiometric amounts to initiate formation of the putative iron-hydride species (from adventitious olefin iron-boryl addition/ β -H elimination) necessary for promoting C–C double bond transposition (Scheme 5a). The daunting challenge
- 10 remains whether appropriate Fe-based catalysts can be identified to promote site-selective isomerization (for both terminal and internal alkenes) to the desired location under conditions that completely suppress undesired boryl (or silyl) addition to the C=C bond.

- 15 Scheme 5a. Mechanistic basis for the generation of catalytic Fe-hydride species

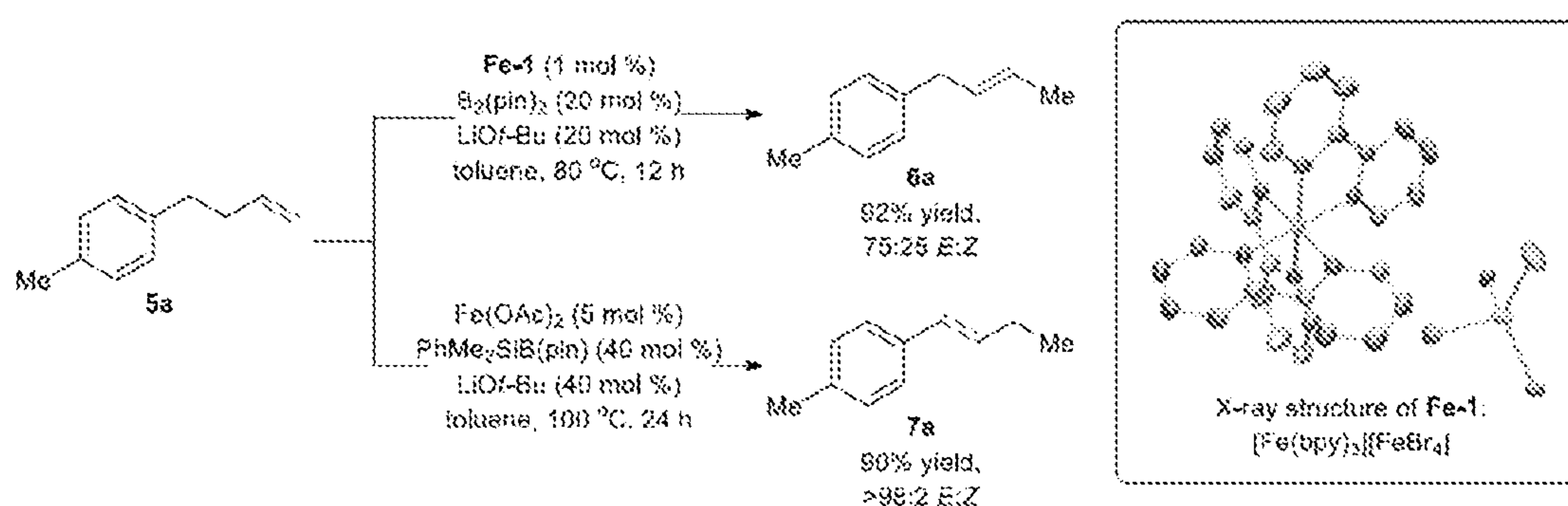


- After an extensive survey of various Fe(II)- and Fe(III)-based complexes, boryl reagents, bases, solvents, and temperature, it was found that, in some embodiments,
- 20 the monoisomerization of alkene 5a to 6a (obtained in 75:25 E:Z ratio) could be best achieved with 1 mol % of $[Fe(bpy)_3][FeBr_4]$ (Fe-1), 20 mol % of bis(pinacolato)diboron, and lithium tert-butoxide in toluene at 80 °C, furnishing the product in 92% isolated yield within 12 h (Scheme 5b, top). Fe-1 consists of a discrete $[Fe(bpy)_3]^{2+}$ cation and $[FeBr_4]^{2-}$ anion as ascertained by X-ray crystal structure analysis (recrystallization from
- 25 DME/DMA). No reaction was observed (>98% recovery of 5a) when Fe-1 was replaced with a separately synthesized $[Fe(bpy)_3]-[PF_6]_2$, while switching Fe-1 to $[Et_4N]_2[FeBr_4]$ under analogous conditions gave a mixture of unreacted 5a, 6a and over-isomerized 7a

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in 50:18:32 ratio. Although the role of each iron component in Fe-1 remains to be determined, these results imply that both components are required in promoting efficient and selective isomerizations over one position.

5 Scheme 5b. Development of conditions for Fe-catalysed regiodivergent alkene isomerisation

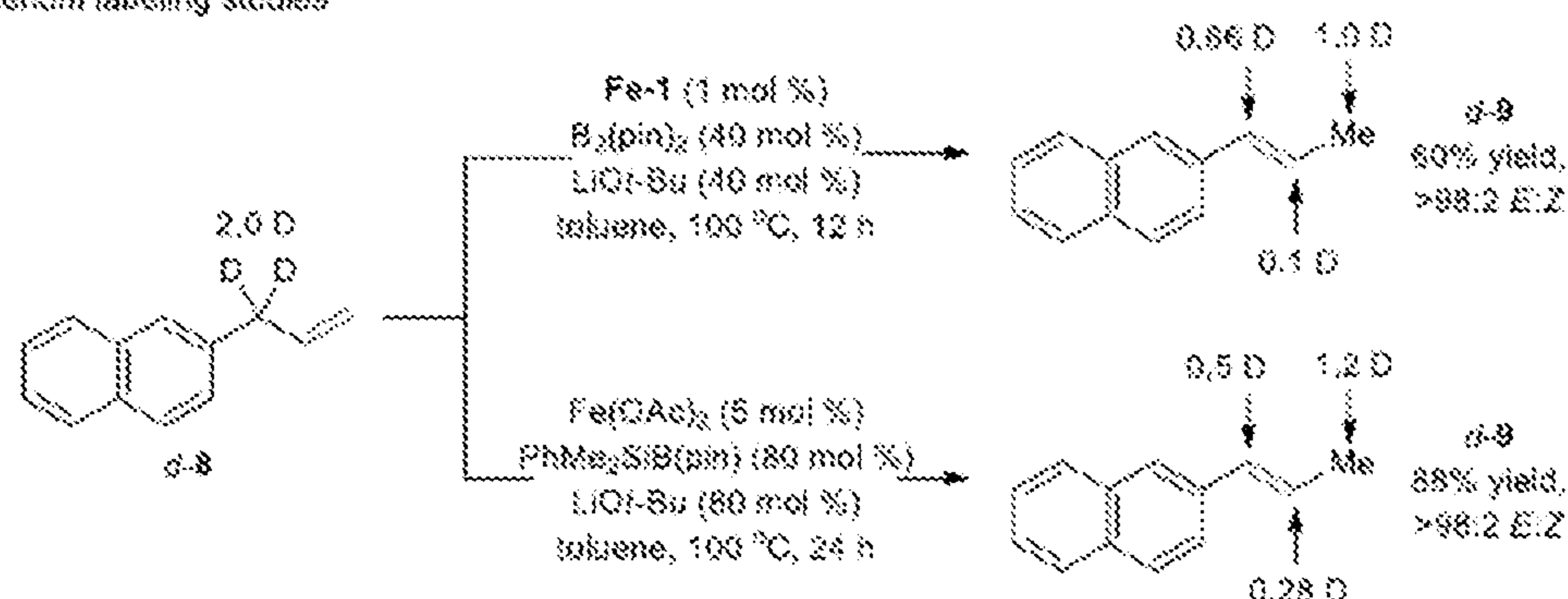


On the other hand, 5a could be converted to the thermodynamically most favored alkene 7a in 90% isolated yield as a single E isomer using 5 mol % of $\text{Fe}(\text{OAc})_2$, 40 mol % of (dimethylphenylsilyl)boronic acid pinacol ester, and lithium tert-butoxide in toluene at 100 °C for 24 h (Scheme 5b, bottom). In general, alkene isomerization was less efficient when Fe(III)-based salts or other solvents were used. Furthermore, in both conditions (Scheme 5b), trace amounts of the alkenyl boronate (or silane) initiation byproduct could be detected by GC analysis (cf. Scheme 5a). Attempts to access the iron-hydride catalytic species by using hydrosilanes led to a mixture of recovered 5a and its fully hydrogenated derivative.

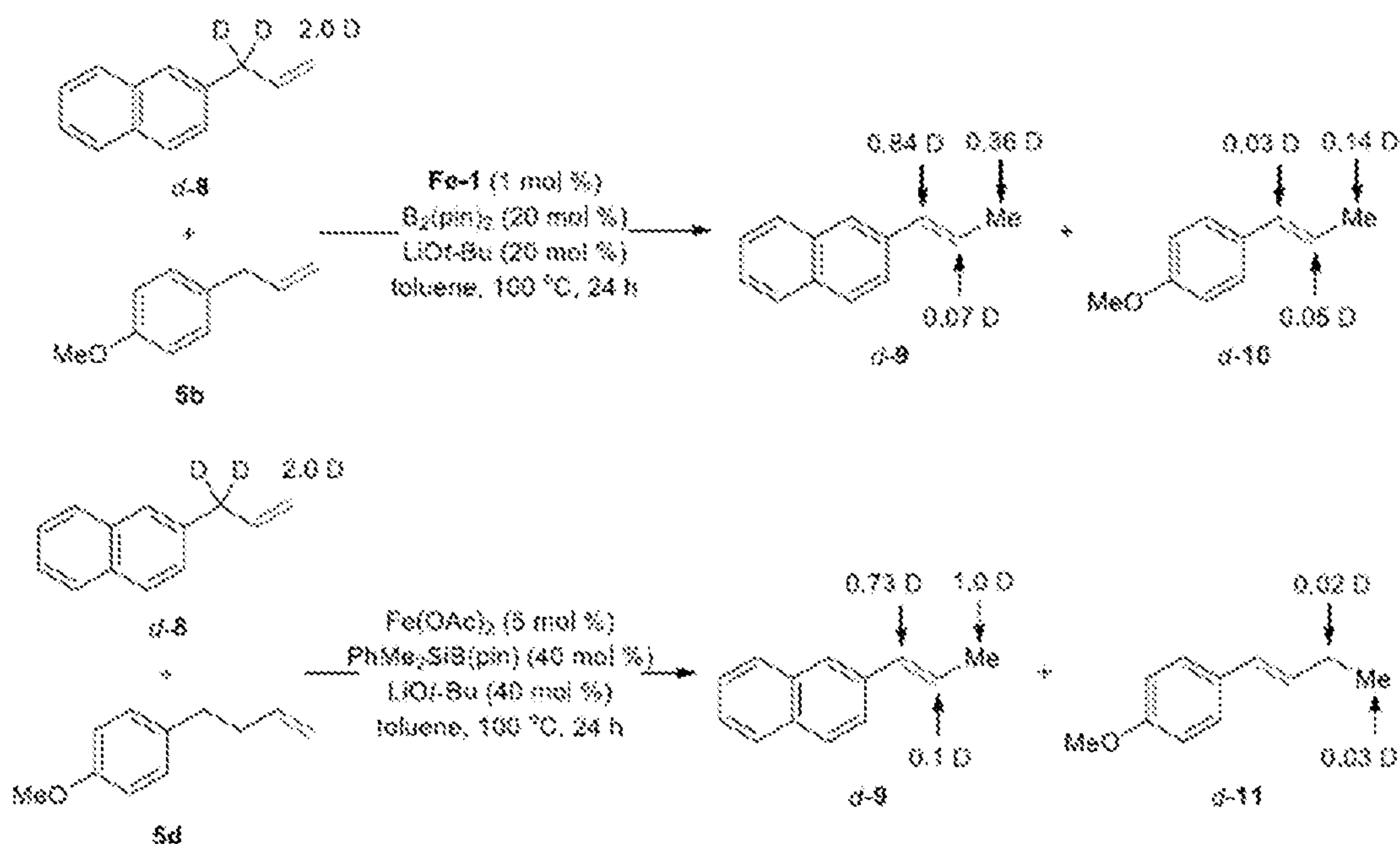
Further studies were conducted to gain insights into the operating mechanism of the Fe-catalyzed transformations (Scheme 6a). Olefin isomerization with d-8 resulted in deuterium scrambling across the entire hydrocarbon skeleton in d-9, suggesting formation of a free iron-hydride (deuteride) rather than a η -allyl species during the course of the reaction. This was substantiated by deuterium crossover experiments in which intermolecular crossover between d-8 and a nondeuterated alkene was detected in both catalytic systems (Scheme 6b), meaning that dissociation of the catalyst from the alkene occurs to a certain extent. The slight erosion of deuterium content was likely caused by adventitious reaction of a free Fe-deuteride species with moisture in the mixture.

Scheme 6. Mechanistic studies to probe the nature of alkene isomerisation

a) Deuterium labeling studies



b) Deuterium crossover studies



- 5 Given the surmised intermediacy of an iron-hydride complex, the question arises whether the latter could induce C=C bond transposition through one of these pathways: (a) iron-hydride addition/ β -H elimination or (b) metal-hydride hydrogen atom transfer (MHAT). Although isomerization studies with a vinylcyclopropane substrate led to 1,3-diene products, these results were inconclusive as ring-opening could also be attributed to nonradical processes. Analysis of the reaction mixture in both Fe-catalyzed systems by time- and temperature-dependent electron paramagnetic resonance (EPR) studies
- 10 showed no signals that would be expected to arise from radical species generated in a

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MHAT process. Control experiments with (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) or 5,5-dimethyl-1-pyrroline N-oxide (DMPO) also did not support the possibility of related radical intermediates.

5 On the basis of the aforementioned results, a plausible nonradical mechanism for the present transformation is proposed in Figure 8. It is believed that an initiation process involving adventitious formation of catalytic amounts of iron hydride IV (obtained from sequential addition of iron-boryl-(silyl) I to alkene II followed by β -H elimination with concomitant release of byproduct III) is needed to kick-start olefin isomerization. Iron-
10 hydride IV coordinates and reacts with another molecule of II by a series of migratory insertion/ β -H elimination steps, engendering migration of the C=C bond along the chain. Successful implementation of the current protocol relies on faster reaction between IV and II (vs reaction between I and II), consequently suppressing undesired formation of boryl/silyl adducts.

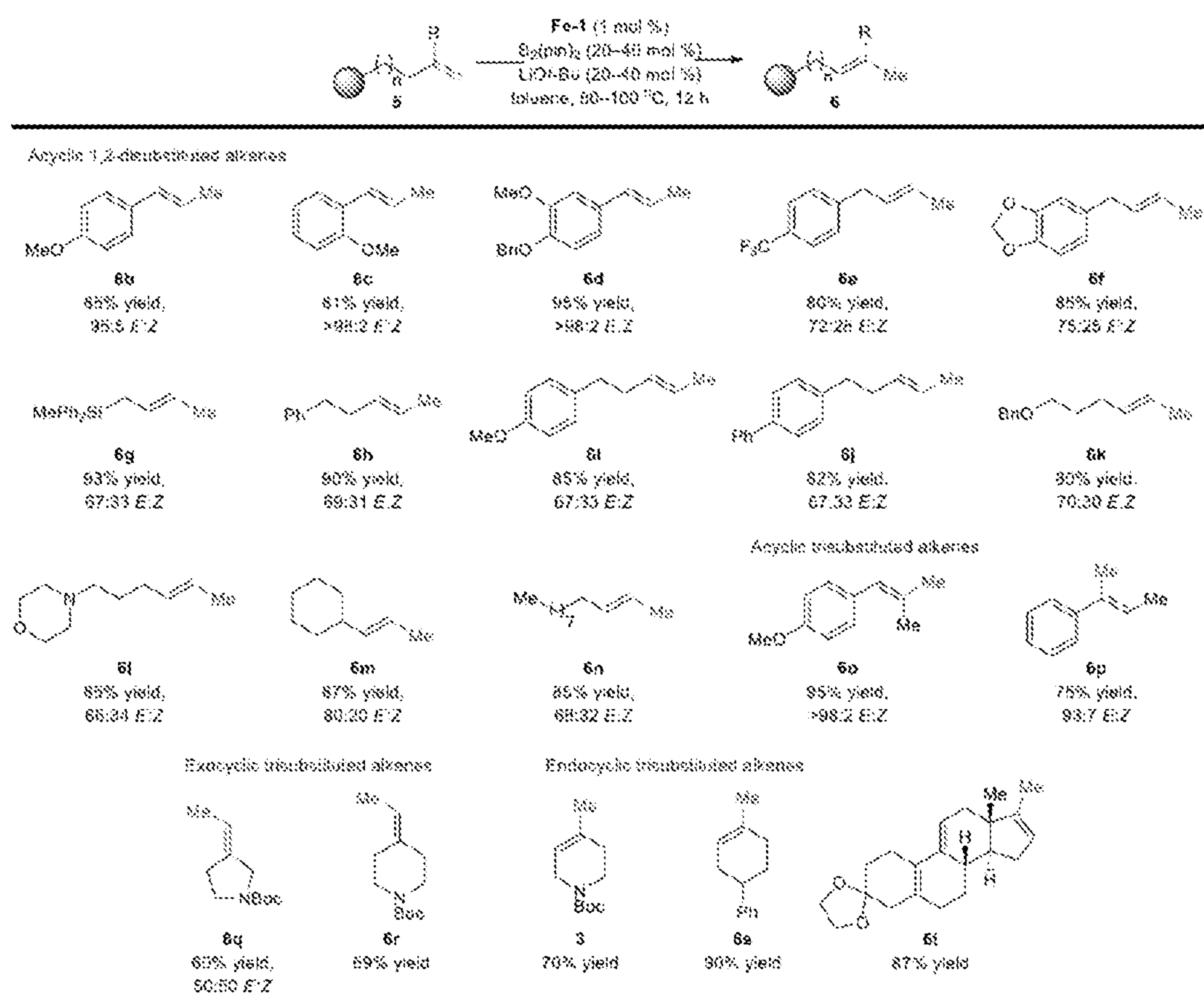
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The difference in reactivity profiles between the catalytic manifolds mediated by Fe-1 and Fe(OAc)₂ was evident from time course studies. In the presence of the organoiron species derived from the sterically encumbered and presumably less active Fe-1, Fe-olefin coordination could be weakened causing internal alkene V to completely dissociate
20 after a single migration. Conversely, under the conditions with ligand-less Fe(OAc)₂, chain-walking could continue to ultimately deliver the most stable olefin regioisomer VI. It appears that alkene isomerization using Fe(OAc)₂ may be thermodynamically driven. The E:Z ratios obtained for the products (cf. 5a and 6a in Scheme 5b) are probably influenced by steric effects arising from substituents of the incipient double bond during
25 the course of the reaction (i.e., greater steric repulsion results in higher E:Z ratios).

Scope and Applications of the Method. Conceiving a general catalytic isomerization protocol that is applicable to alkenes of different substitution patterns is a sought-after goal in chemistry. The inventors first examined a range of functionalized terminal
30 (monosubstituted and 1,1-disubstituted) olefins under monoisomerization conditions (Scheme 7). In general, single double-bond shifts could be accomplished with a variety of monosubstituted substrates bearing different carbon chain length and functional groups (e.g., arenes, ethers, amines, and silanes), furnishing 1,2-disubstituted olefins 6b–n in 78–95% yield. Styrenyl products 6b–d were obtained in $\geq 95\%$ E selectivities,
35 although nonaryl-substituted alkenes 6e–n could only be generated in moderate E:Z

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ratios. The method is also amenable to the synthesis of trisubstituted double bonds including linear olefins (6o–p) as well as exocyclic (6q–r) and endocyclic (3, 6s–t) products. Complete isomerization to an internal olefinic site was next assessed in Scheme 6. Transpositions over two positions could be effected with homoallylic arenes and heteroarenes bearing either electron-donating or electron-withdrawing substituents, furnishing β -ethylstyrenes 7b–j in 70–96% yield and >98:2 E:Z ratios.

Scheme 7. Isomerisation over one position with terminal olefins^a

- ^aYields are for isolated and purified products (E:Z mixtures). For 6b–d and 6o–p, the reactions were conducted with Fe(OAc)₂ (5 mol %), PhMe₂SiB(pin) (40 mol %), and LiOt-Bu (40 mol %) in toluene at 100 °C for 24 h. For 6m, yield was determined by GC analysis against internal standard. For 6q and 6r, the reactions were conducted with [(bpy)FeCl₂]₂ (Fe-2; 3–5 mol %), B₂(pin)₂ (40 mol %), and LiOt-Bu (40 mol %) in toluene at 100 °C for 24 h. For 3 and 6s, the reactions were conducted with (6,6'-dimethyl-2,2'-bipyridine)FeCl₂ (Fe-3; 5 mol %), B₂(pin)₂ (40 mol %), and LiOt-Bu (40

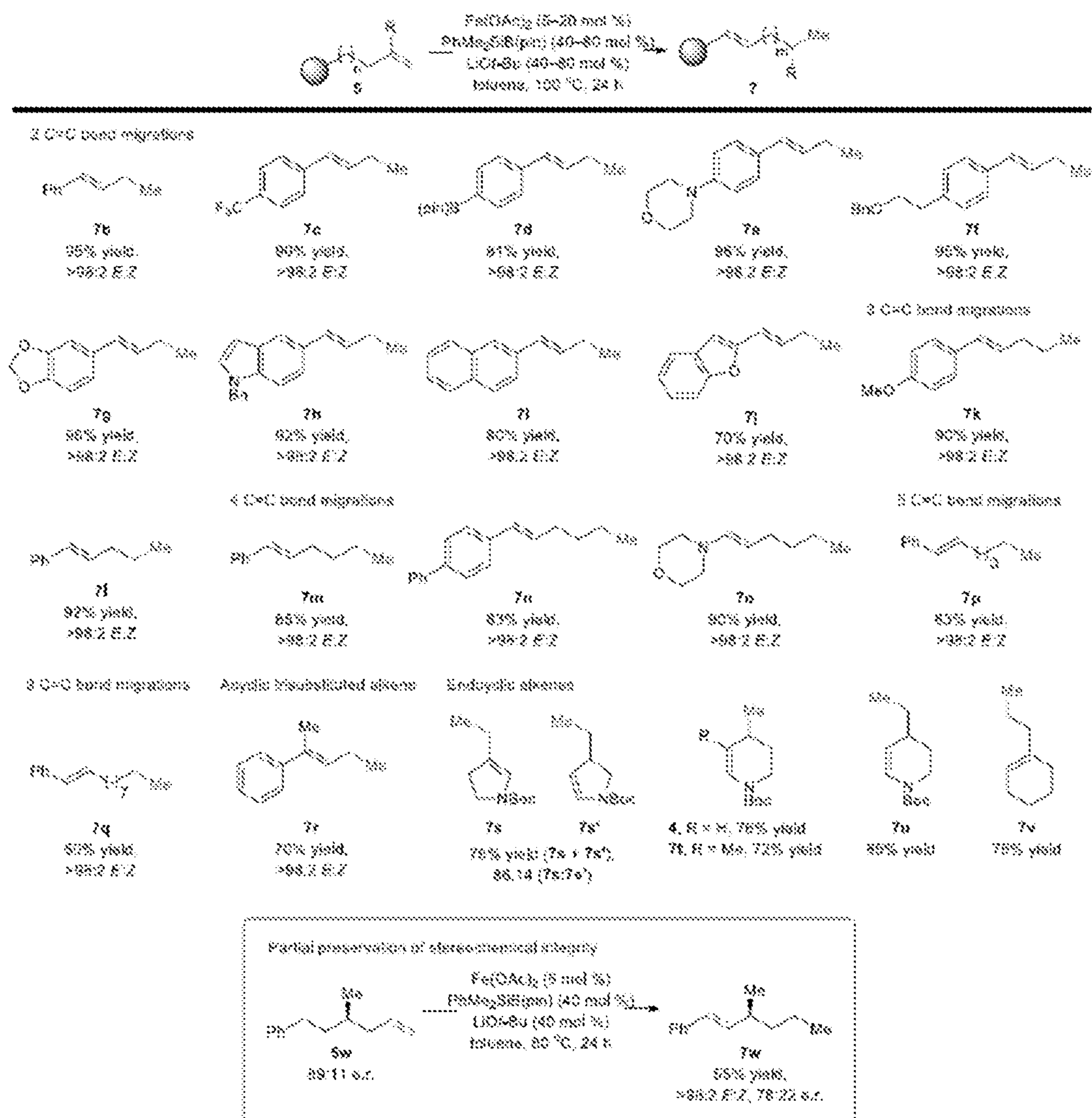
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mol %) in toluene at 100 °C for 24–36 h. For 6t, the reaction was conducted with Fe(OAc)₂ (5 mol %), B₂(pin)₂ (80 mol %), and LiOt-Bu (80 mol %) in toluene at 100 °C for 24 h.

- 5 Migrations over extended carbon skeletons were similarly efficient, affording the corresponding 1,2-disubstituted E alkenes 7k–q in up to 92% yield. Isomerization could be terminated by an amino group to deliver acid-labile E-enamine 7o in 90% yield. It is worth noting that the transformation leading to 7q (50% yield) features a transposition over nine C=C double bonds and compares favorably with a previous report (37% yield).
- 10 Trisubstituted alkenes (7r) could also be accessed through a double olefin migration. Synthesis of the endocyclic olefin 7v as well as pharmaceutically relevant five and six-membered heterocyclic building blocks containing enecarbamate moieties (4, 7s/7s', and 7t–u) by the Fe-catalyzed protocol is further testament to the robust versatility of the isomerization regime. The reaction with 5w containing a pre-existing stereogenic
- 15 center lent additional credence to the mechanistic proposal in Scheme 6. Under standard conditions, isomerization to 7w could proceed, albeit with considerable erosion in enantioselectivity at 100 °C (89:11 e.r. → 69:31 e.r.). By lowering the temperature to 80 °C, dissociation of the iron catalytic species from the alkene substrate is reduced, allowing stereochemical integrity to be partially retained (78:22 e.r.) during the chain-
- 20 walking process.

Scheme 8. Isomerisation over multiple C=C bonds with terminal olefins^a

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^aYields are for isolated and purified products. For 7j, the reaction was conducted with Fe(OAc)₂ (5 mol %), (R)-DTBM-SEGP_{HOS} (6 mol %), PhMe₂SiB(pin) (80 mol %), and LiOt-Bu (80 mol %) in toluene at 100 °C for 24 h. For 7s and 7u, B₂(pin)₂ was used instead of PhMe₂SiB(pin). For 7o and 7v, yields were determined by GC analysis against internal standard. For 7q, yield was determined by ¹H NMR analysis against the internal standard. For 7r, ~5% of inseparable alternative isomers were detected. A ratio of 7s and 7s' was determined by ¹H NMR analysis against the internal standard.

Besides terminal olefins, sterically more encumbered internal alkenes also served as effective substrates under these Fe-catalyzed conditions (Scheme 9a). Complete site-

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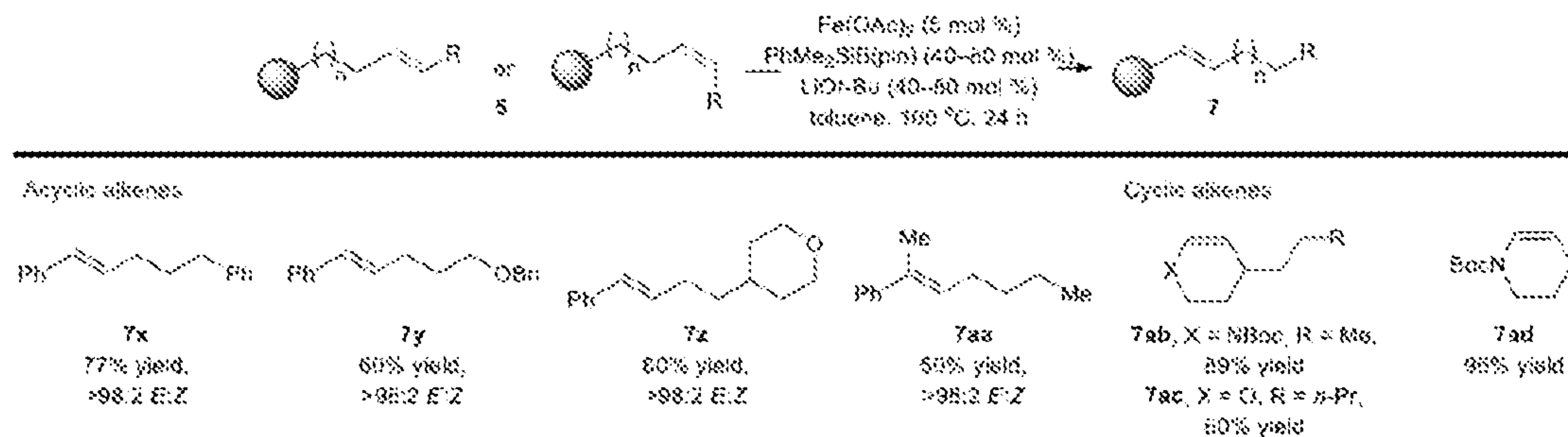
selective isomerization to presumably the most stable regioisomer proceeded to give disubstituted or trisubstituted styrenes, enecarbamates, and vinyl ethers 7x-ad in up to 96% yield. The example with 7ad demonstrates that endocyclic C=C bonds can also undergo transposition. However, selective single C=C bond migrations that afford 1,2-
5 dialkyl-substituted alkenes (vs using terminal olefins as substrates in Scheme 7) are difficult to control and pose complicating issues of over-isomerization.

The ability to react with both terminal and internal C=C double bonds offers an opportunity to integrate our catalytic platform for the transformation of abundant raw
10 materials derived from petroleum processing, such as unrefined isomeric olefin mixtures, to a single alkene product. Treatment of a 1:1:1 mixture of 6h (E:Z mixture), 12, and 13 (E:Z mixture) to standard isomerization conditions successfully furnished E-7l as the sole product in 75% yield (Scheme 9b). For comparison, repeating the reaction using conditions devised from a recent Ni-catalyzed disclosure only led to an inseparable
15 mixture of isomeric compounds. The corresponding Fe-catalyzed reaction of a complex mixture of isomeric 14, 15, and 16 cleanly delivered 7ab in 80% yield. These regioconvergent transformations represent a viable strategy for the streamlined value-enhancing conversion of inexpensive olefin feedstock to prized isomerically pure alkenes.

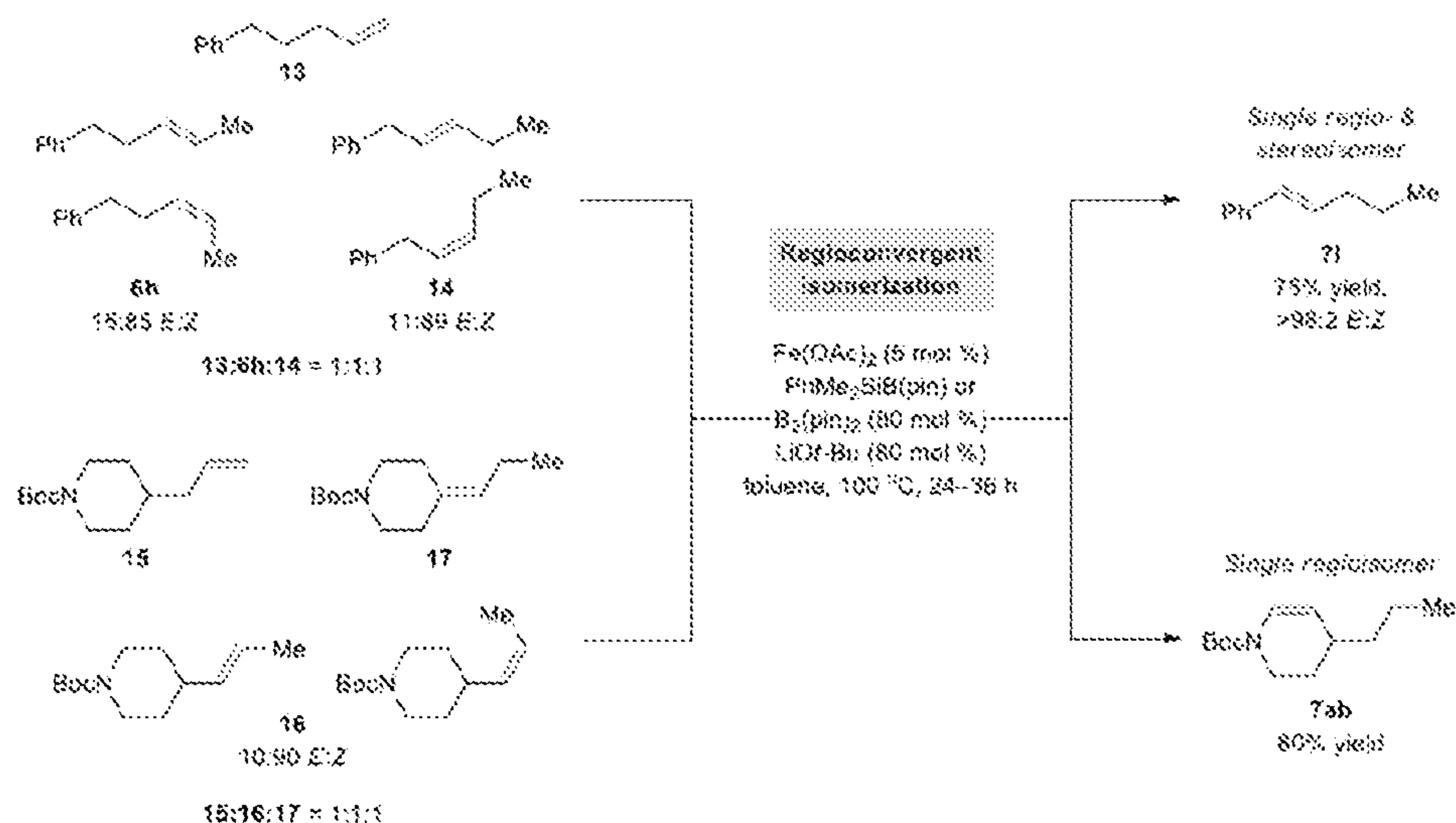
20 Scheme 9. Isomerisation with internal olefins and regioselective convergent and divergent reactions^a

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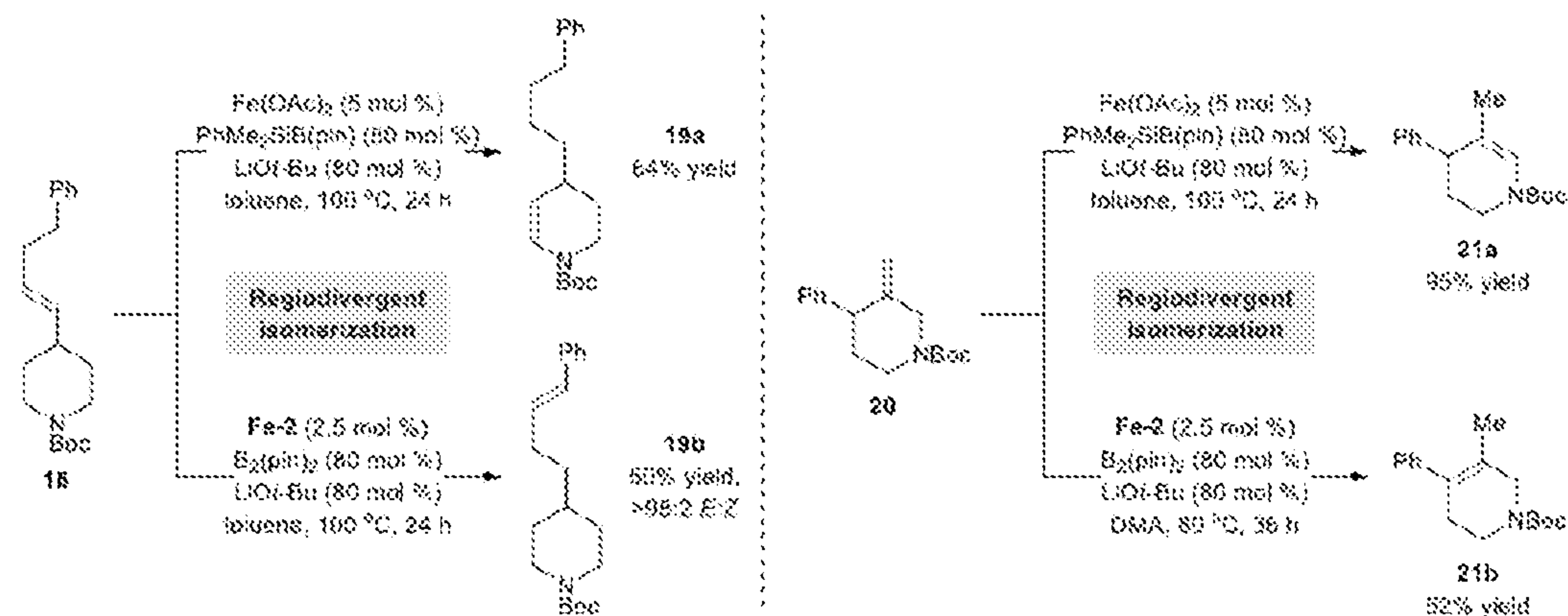
a) Isomerization with 1,2-disubstituted internal alkenes



b) Regioconvergent transformation of olefin mixtures to isomerically pure products



c) Regiodivergent alkene synthesis by catalytic isomerization

^aYields are for isolated and purified products

- 5 To further challenge the limits of our catalytic method, alkenes 18 and 20 were examined, each of which bears at least two possible sites that may serve to direct C=C

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bond migration (Scheme 9c). In the event, subjecting 18 to conditions promoted by ligand-free Fe(OAc)₂ predominantly afforded pure enecarbamate 19a in 64% yield (~12% 19b detected). Remarkably, by switching the Fe-based complex to the sterically more demanding [(bpy)FeCl₂]₂ (Fe-2), the direction of olefin transposition could be reversed and regioisomer 19b was obtained as the major product (~80% conversion, 50% yield) in >98% E selectivity. In a similar fashion, regiodivergent transformation of 20 to either 21a or 21b could be achieved with the established catalytic systems. 21a was isolated exclusively under standard conditions with Fe(OAc)₂ or Fe-1, whereas pure 21b was secured in 52% yield using Fe-2 as the catalyst (4:1 ratio of 21b:21a detected). Attempts to isomerize 20 to 21b by performing the reaction in the presence of alternative solvents or other Fe-based complexes under analogous conditions in DMA only led to unsatisfactory ratios of 21a and 21b.

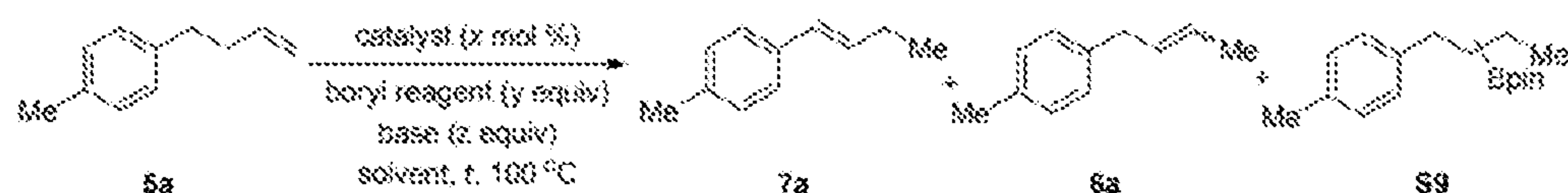
Density functional theory (DFT) calculations further revealed that the products (19a–b and 21a–b) are energetically more stable than the substrates (18 and 20, respectively) and the relative free energy difference between the products (i.e., 19a vs 19b and 21a vs 21b is ~3 kcal/mol. Our studies highlight the versatility of the present iron-based catalytic manifold in facilitating controllable and site-selective access to different alkene isomers from one substrate, thereby providing an important avenue to generate functional and structural diversity.

In conclusion, it is shown that the combination of a suitable iron-based catalyst with substoichiometric amounts of a commercially available boryl reagent and base enables tunable C=C bond transposition over one or multiple positions along the skeleton of an unsaturated hydrocarbon molecule. Transformations are robust and tolerant of a broad substrate class consisting of both terminal and internal olefins with various substitution patterns. Mechanistic investigations unveil an Fe-catalyzed olefin insertion/ β -H elimination process that is capable of facilitating site-selective migrations, including transformations of isomeric olefin mixtures to value-added isomerically pure products as well as tunable transpositions to different regioisomers. By virtue of such catalytic capacity coupled with the operational ease and availability of inexpensive organoiron complexes and reagents, it is believed that the present catalytic approach is a significant addition to an existing toolbox of metal-catalyzed olefin isomerization reactions for the preparation of high-value industrially relevant chemicals.

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Synthesis of Complex Fe-1

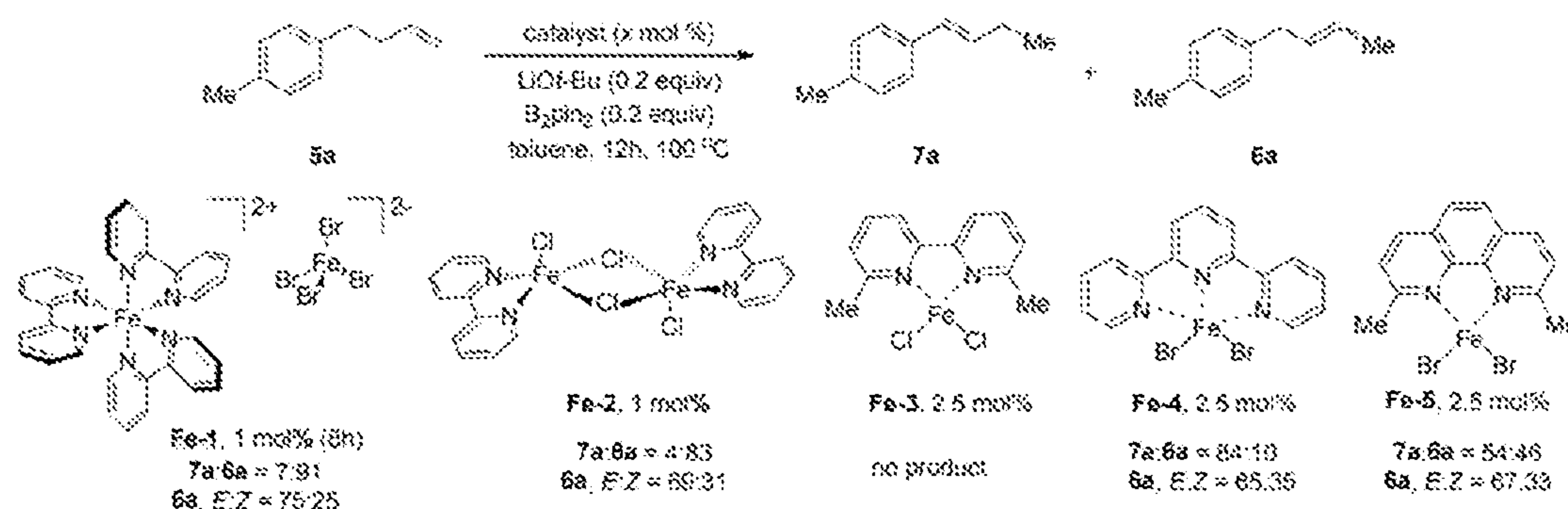
Anhydrous FeBr₂ (215.0 mg, 1.0 mmol, 1.00 eq), 2,2'-bipyridine (234.3 mg, 1.5 mmol, 1.5 eq) and CH₂Cl₂ (15 mL) were placed in a Schlenk tube. The reaction mixture was allowed to stir at rt for 18 h, after which a red powder precipitated. After removing the mother liquor, the residual red solid was washed with THF (5 mL, 2 times), Et₂O (10 mL) and hexanes (10 mL), and dried in vacuo.



entry	catalyst (x mol %)	boryl reagent (y equiv)	base (z equiv)	solvent	t (h)	yield (7a:8a:9a) % ^a	conv. (%) ^b
1	0	0	LiOt-Bu (0.4)	Toluene	24	-	<2
2	0	B ₂ pin ₂ (0.4)	LiOt-Bu (0.4)	Toluene	12	-	<2
3	Fe(OAc) ₂ (5)	0	LiOt-Bu (0.4)	Toluene	12	-	<2
4	Fe(OAc) ₂ (5)	B ₂ pin ₂ (0.4)	0	Toluene	12	-	<2
5	Fe(OAc) ₂ (5)	B ₂ pin ₂ (0.4)	LiOt-Bu (0.4)	Toluene	12	79:9:12	98
6	Fe(OAc) ₂ (5)	B ₂ pin ₂ (0.4)	LiOt-Bu (0.4)	DMF	12	34:12:17	63
7	Fe(OAc) ₂ (5)	B ₂ pin ₂ (0.4)	LiOt-Bu (0.4)	DME	12	54:12:34	98
8	Fe(OAc) ₂ (5)	B ₂ pin ₂ (0.4)	LiOt-Bu (0.4)	2-Me-THF	12	51:7:40	98
9	Fe(OAc) ₂ (5)	B ₂ pin ₂ (0.4)	LiOt-Bu (0.4)	1,4-Dioxane	12	71:9:20	98
10	Fe(OAc) ₂ (5)	B ₂ pin ₂ (0.4)	LiOt-Bu (0.4)	THF	12	59:10:30	98
11	Fe(OAc) ₂ (5)	Bis(NPG)diboron (0.4)	LiOt-Bu (0.4)	Toluene	12	58:16:23	98
12	Fe(OAc) ₂ (5)	Bis(HG)diboron (0.4)	LiOt-Bu (0.4)	Toluene	12	78:10:12	98
13	Fe(OAc) ₂ (5)	(TMS) ₂ (0.4)	LiOt-Bu (0.4)	Toluene	12	-	<2
14	Fe(OAc) ₂ (5)	PhMe ₂ SiB(pin) (0.4)	LiOt-Bu (0.4)	Toluene	12	84:14:0	98
15	Fe(OAc) ₂ (5) ^c	PhMe ₂ SiB(pin) (0.4)	LiOt-Bu (0.4)	Toluene	24	89:9:0	98
16	Fe(OAc) ₂ (5)	PhMe ₂ SiB(pin) (0.4)	LiOt-Bu (0.4)	Toluene	24	93:5:0	98
17	Fe(OAc) ₂ (5)	B ₂ pin ₂ (0.4)	KOt-Bu (0.4)	Toluene	12	11:3:13	27
18	Fe(OAc) ₂ (5)	B ₂ pin ₂ (0.4)	NaOt-Bu (0.4)	Toluene	12	11:3:16	30
19	Fe(OAc) ₂ (5)	B ₂ pin ₂ (0.4)	NaOPh (0.4)	Toluene	12	57:24:18	98
20	Fe(OAc) ₂ (5)	B ₂ pin ₂ (0.4)	NaOMe (0.4)	Toluene	12	59:26:15	92
21	Fe(OAc) ₂ (5)	B ₂ pin ₂ (0.4)	KF (0.4)	Toluene	12	-	<2
22	FeBr ₂ (5)	B ₂ pin ₂ (0.4)	LiOt-Bu (0.4)	Toluene	12	56:17:27	98
23	FeCl ₂ (5)	B ₂ pin ₂ (0.4)	LiOt-Bu (0.4)	Toluene	12	55:10:25	98
24	Fe(acac) ₃ (5)	B ₂ pin ₂ (0.4)	LiOt-Bu (0.4)	Toluene	12	3:0:20	23
25	Fe(acac) ₃ (5)	B ₂ pin ₂ (0.4)	LiOt-Bu (0.4)	Toluene	12	62:15:23	98
26	Fe-1 (1)	B ₂ pin ₂ (0.2)	LiOt-Bu (0.2)	Toluene	8	7:91:0	98
27	Fe-1 (1) ^c	B ₂ pin ₂ (0.2)	LiOt-Bu (0.2)	Toluene	12	4:94:0	98
28	Fe-2 (1)	B ₂ pin ₂ (0.2)	LiOt-Bu (0.2)	Toluene	8	4:83:3	90
29	Fe-3 (2.5)	B ₂ pin ₂ (0.2)	LiOt-Bu (0.2)	Toluene	8	0:0:10	10
30	Fe-4 (2.5)	B ₂ pin ₂ (0.2)	LiOt-Bu (0.2)	Toluene	8	64:10:5	98

^aReaction conditions: 5a (0.2 mmol), solvent (0.5 mL), N₂. ^bDetermined by GC analysis with *n*-tridecane as internal standard. ^c80 °C.

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Guide for selecting reaction conditions

- Reaction conditions may be selected according to Figure 9. B₂(pin)₂ is typically used for isomerizations over 1-position or multiple positions (for alkenes with R = nonaryl). In cases where adventitious olefin protoboration is observed (e.g. for alkenes with R = aryl), PhMe₂SiB(pin) may be used as the boryl reagent (due to less boryl or silyl addition side products). To drive complete migrations over extended carbon skeletons (n ≥ 4), higher loadings of Fe(OAc)₂ as well as boryl reagent/base may be needed. For exceptional cases where the aforementioned conditions still generate unsatisfactory results in reaction efficiency and/or site selectivity, other Fe-based complexes (e.g. Fe-2; [(bpy)FeCl₂]₂ and Fe-3; (6,6'- dimethyl-2,2'-bipyridine)FeCl₂) may be employed.

- General procedure A for isomerizing alkenes to thermodynamically stable isomers: In a N₂-filled glove box, an oven-dried 4 mL vial equipped with a magnetic stir bar was charged with Fe(OAc)₂ (0.01 mmol, 0.05 eq), LiOt-Bu (0.08 mmol, 0.4 eq), PhMe₂SiB(pin) (0.08 mmol, 0.4 eq) and toluene (0.5 mL). Then, the alkene substrate (0.20 mmol, 1.0 eq) was sequentially added to the system via syringe and the reaction mixture was allowed to stir at 100 °C for 24 h. After cooling to ambient temperature, the resulting mixture was purified by silica gel chromatography.

- General procedure B for isomerizing alkenes over one position: In a N₂-filled glove box, an oven-dried 4 mL vial equipped with a magnetic stir bar was charged with Fe-1 (0.002 mmol, 0.01 eq), Fe-2 (0.01 mmol, 0.05 eq) or Fe-3 (0.01 mmol, 0.05 eq), LiOt-Bu (0.04 mmol, 0.2 eq), B₂(pin)₂ (0.04 mmol, 0.2 eq) and toluene (0.5 mL). Then, the alkene substrate (0.20 mmol, 1.0 eq) was sequentially added to the system via syringe and the reaction mixture was allowed to stir at 80 °C or 100 °C for 24 h or 12 h. After cooling

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to ambient temperature, the resulting mixture was purified by silica gel chromatography.

5 It will be appreciated that many further modifications and permutations of various aspects of the described embodiments are possible. Accordingly, the described aspects are intended to embrace all such alterations, modifications, and variations that fall within the spirit and scope of the appended claims.

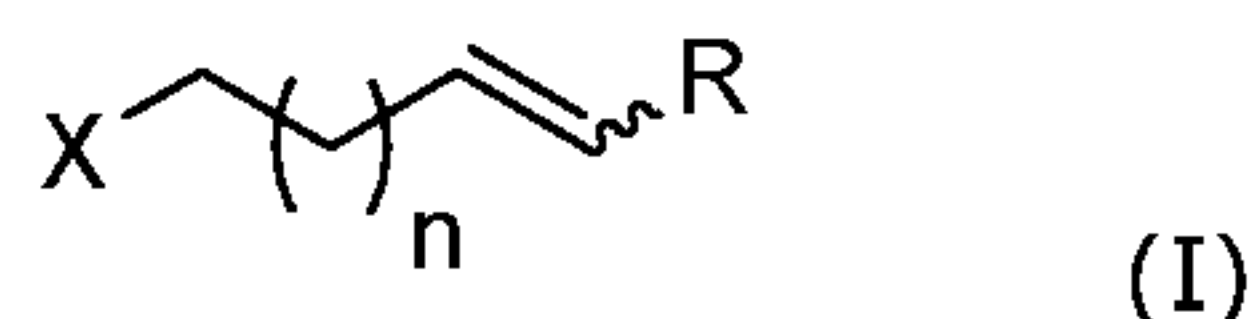
10 Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

15 The reference in this specification to any prior publication (or information derived from it), or to any matter which is known, is not, and should not be taken as an acknowledgment or admission or any form of suggestion that that prior publication (or information derived from it) or known matter forms part of the common general knowledge in the field of endeavour to which this specification relates.

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Claims

1. A method of borylating a compound of Formula (I):



5 wherein X is selected from the group consisting of optionally substituted silyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted dioxyboronyl and B(pin);

R is selected from the group consisting of H, halo, optionally substituted alkyl and
10 optionally substituted cycloalkyl;

n is an integer selected from 0 to 10;

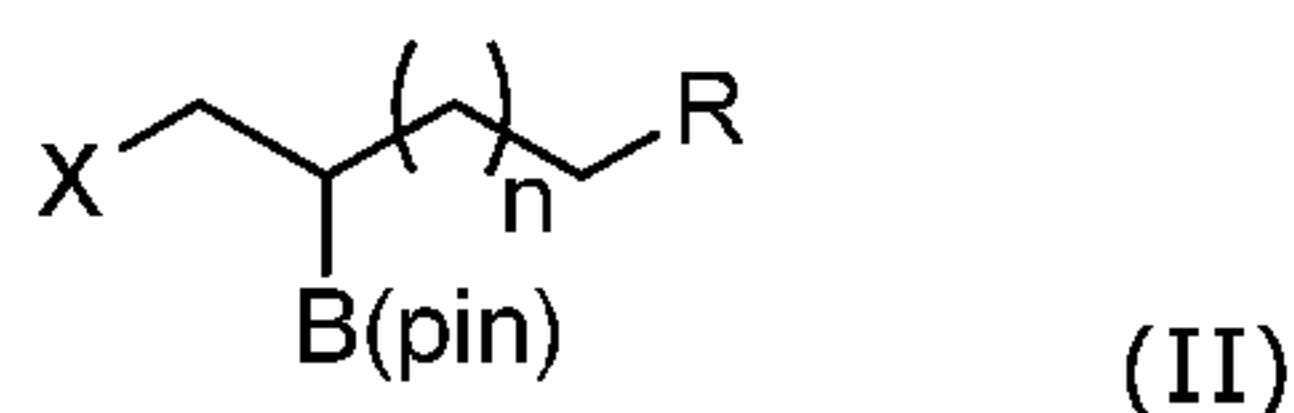
by contacting the compound of Formula (I) with:

i) a boron compound selected from the group consisting of
15 bis(pinacolato)diboron bis(neopentyl glycolato)diboron, bis(hexylene glycolato)diboron, 2,2'-bis-1,3,2-benzodioxaborole, 9-BBN dimer, bis(2,4-dimethylpentane-2,4-glycolato)diboron, and bis(butane-2,3-glycolato)diboron, the boron compound at least stoichiometrically equivalent to the compound of Formula (I);

ii) a Fe pre-catalyst; and

20 iii) a protic additive;

wherein the borylation occurs at a vicinal (β) position to the X moiety of the compound of Formula (I) to give a compound of Formula (II):



wherein X, R and n are as defined herein, and pin is pinacolyl.

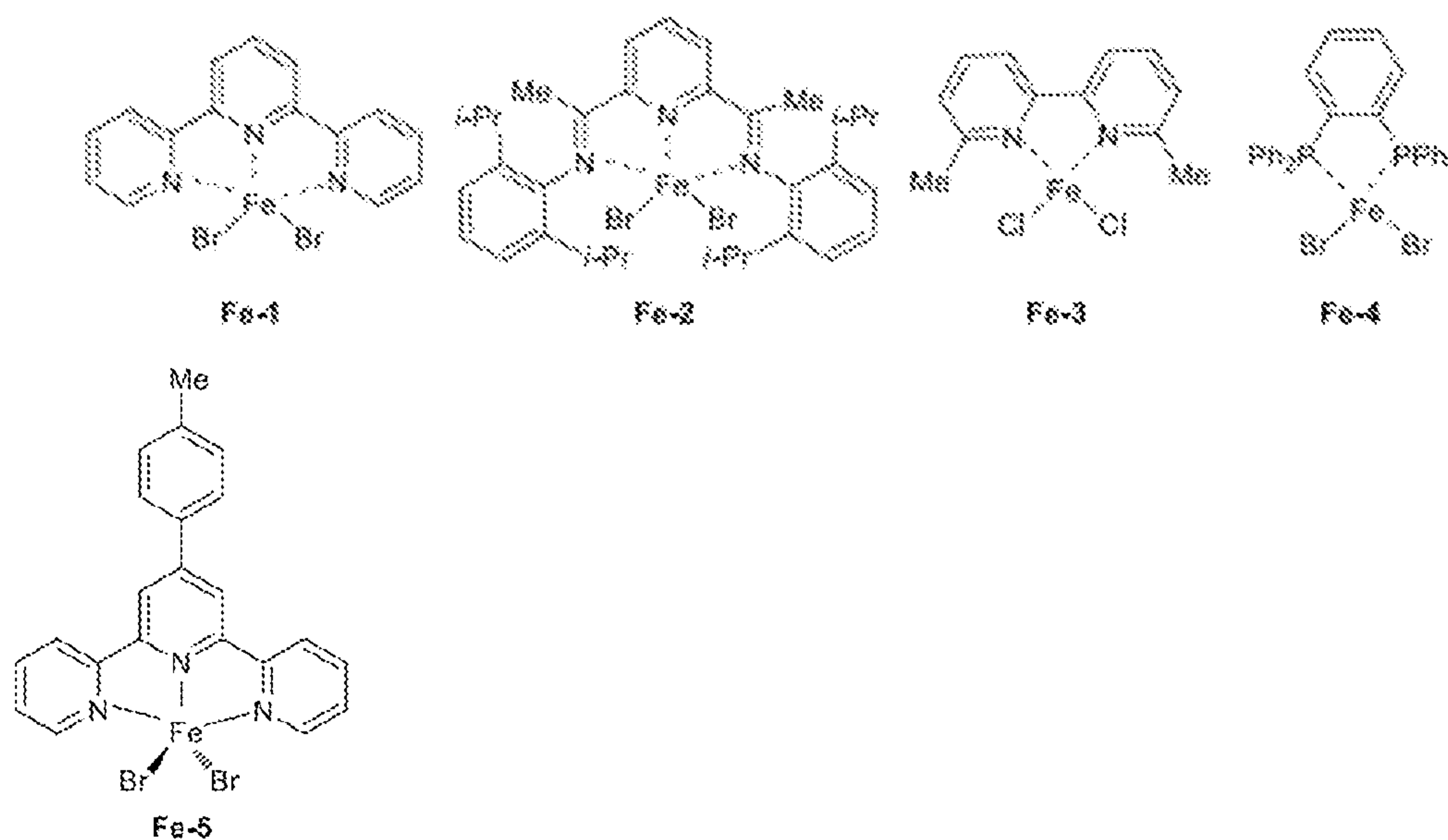
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2. The method according to claim 1, wherein the Fe pre-catalyst is selected from terpyridine-FeBr₂, FeBr₂, FeBr₃, Fe(OAc)₂, FeCl₂, FeCl₃, Fe(II) acetylacetonate, Fe(III) acetylacetonate, Fe(II) trifluoromethanesulfonate, tris(2,2,6,6-tetramethyl-3,5-heptanedionato)iron(III) and ferrous oxalate dehydrate.

30

3. The method according to claim 1, wherein the Fe pre-catalyst is a Fe complex selected from

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4. The method according to any one of claim 1 to 3, wherein the Fe pre-catalyst is
5 provided at at least 8 mol% to the compound of Formula (I).
5. The method according to any one of claim 1 to 4, wherein the protic additive is
present at less than 0.05 stoichiometric equivalence to the compound of Formula (I).
- 10 6. The method according to any one of claim 1 to 5, wherein the protic additive is
generated *in situ* from a polar solvent and an alkali metal oxide.
7. The method according to claim 6, wherein the polar solvent is a polar aprotic
solvent.
- 15 8. The method according to claim 6 or 7, wherein the polar solvent is
dimethylacetamide (DMA), dimethylsulfoxide (DMSO), CH₃CN, N,N'-
dimethylpropyleneurea (DMPU), dimethylformamide (DMF) or a mixture thereof.
- 20 9. The method according to claim 6, wherein the alkali metal oxide is at least
stoichiometrically equivalent to the compound of Formula (I) is added.

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10. The method according to claim 6 or 9, wherein the alkali metal oxide is selected from the group consisting of lithium tert-butoxide, lithium bis(trimethylsilyl)amide, lithium diisopropylamide, lithium trifluoromethanesulfonate, lithium methoxide, sodium benzenesulfinate, sodium phenolate, sodium methoxide, sodium tert-butoxide, potassium acetate, potassium carbonate, potassium fluoride, potassium tert-butoxide, potassium phosphate monobasic, potassium ethoxide and potassium phosphate tribasic.

11. The method according to any one of claims 1 to 10, further comprising a polar solvent, the polar solvent is a mixture of DMA and toluene in a volume ratio of 1:2.

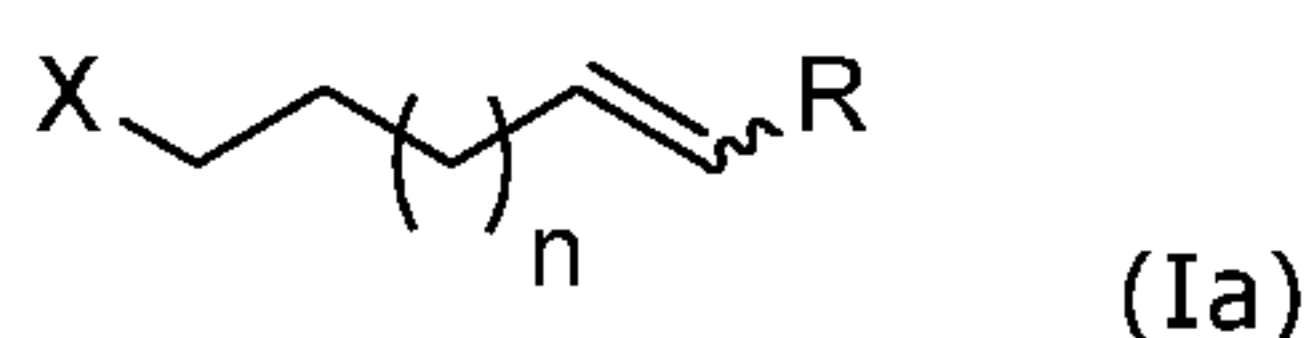
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12. The method according to any one of claims 1 to 11, the method being conducted at a temperature of at least 60 °C.

13. The method according to any one of claims 1 to 12, further including contacting the compound of Formula (I) with a protic reagent, the protic reagent being less than 0.25 stoichiometric equivalent to the compound of Formula (I).

14. The method according to claim 13, wherein the protic reagent is t-butyl alcohol, methanol, ethanol, isopropyl alcohol (or any other alcohols), phenol, water and carboxylic acids.

15. The method according to any one of claims 1 to 14, wherein the compound of Formula (I) is a compound of Formula (Ia):

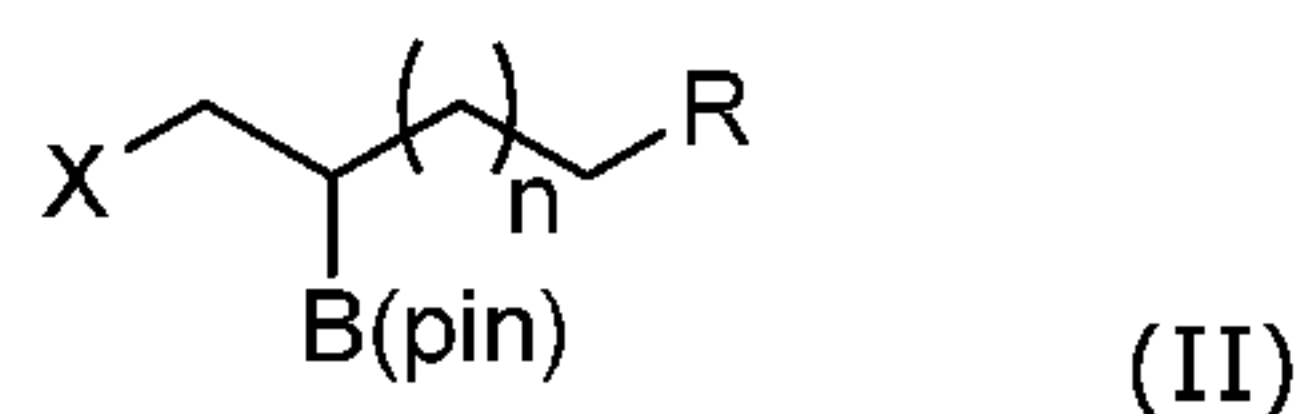


25 wherein X is selected from the group consisting of optionally substituted silyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted dioxyboronyl and B(pin);

R is selected from the group consisting of H, halo, optionally substituted alkyl and optionally substituted cycloalkyl; and
n is an integer selected from 0 to 9.

16. A compound of Formula (II):

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wherein pin is pinacolyl;

X is selected from the group consisting of optionally substituted silyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted dioxyboronyl;

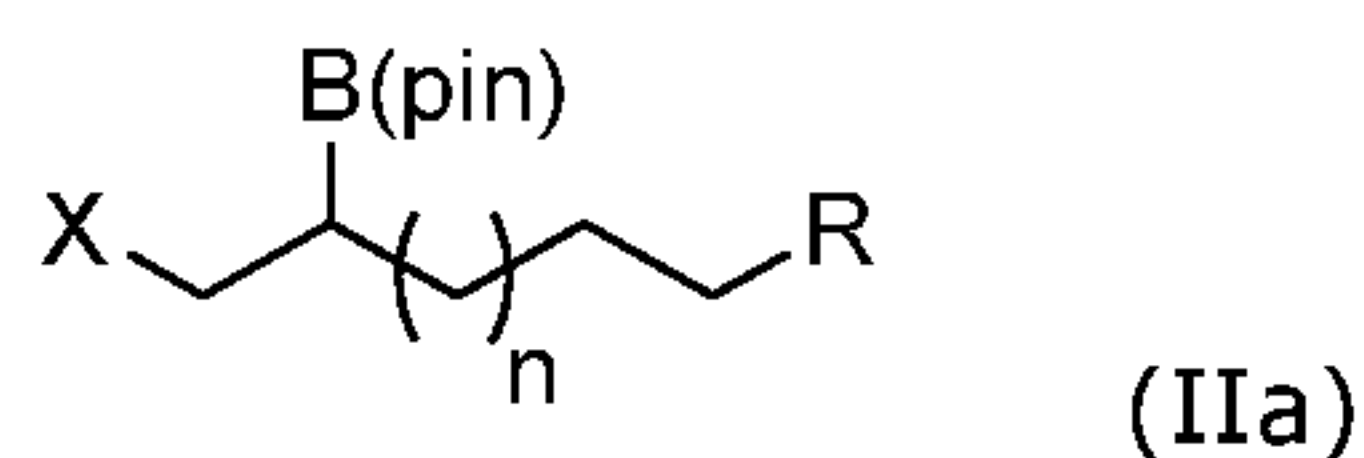
R is selected from the group consisting of H, halo, optionally substituted alkyl and optionally substituted cycloalkyl; and

n is an integer selected from 0 to 10.

10

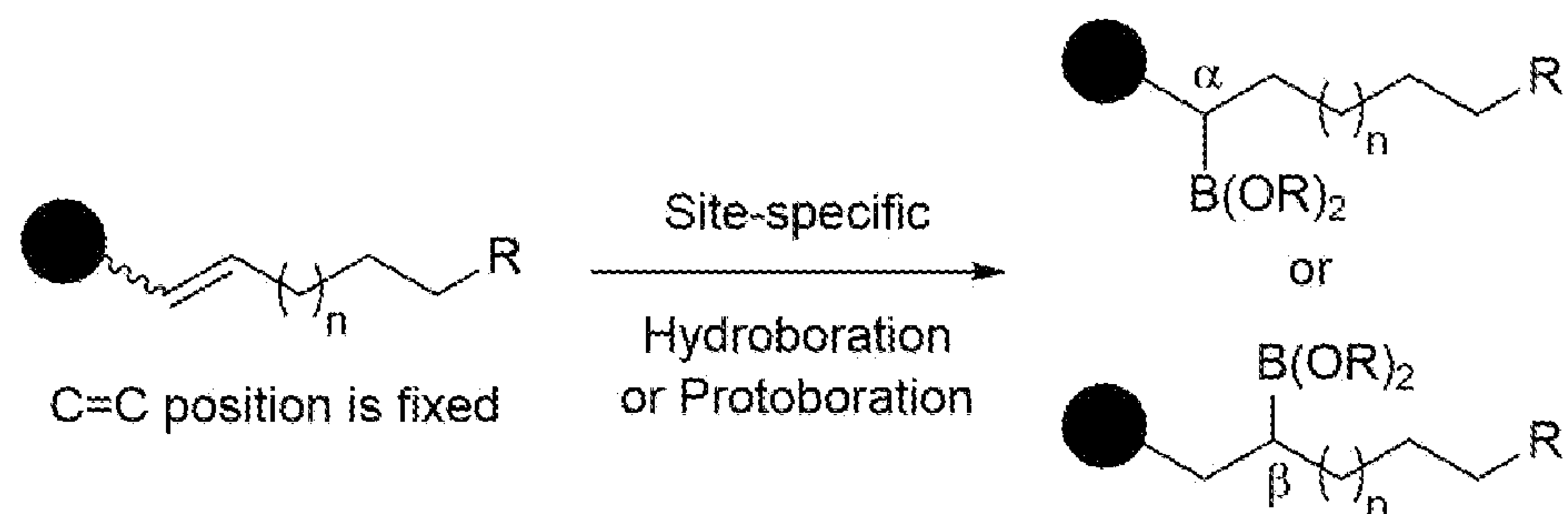
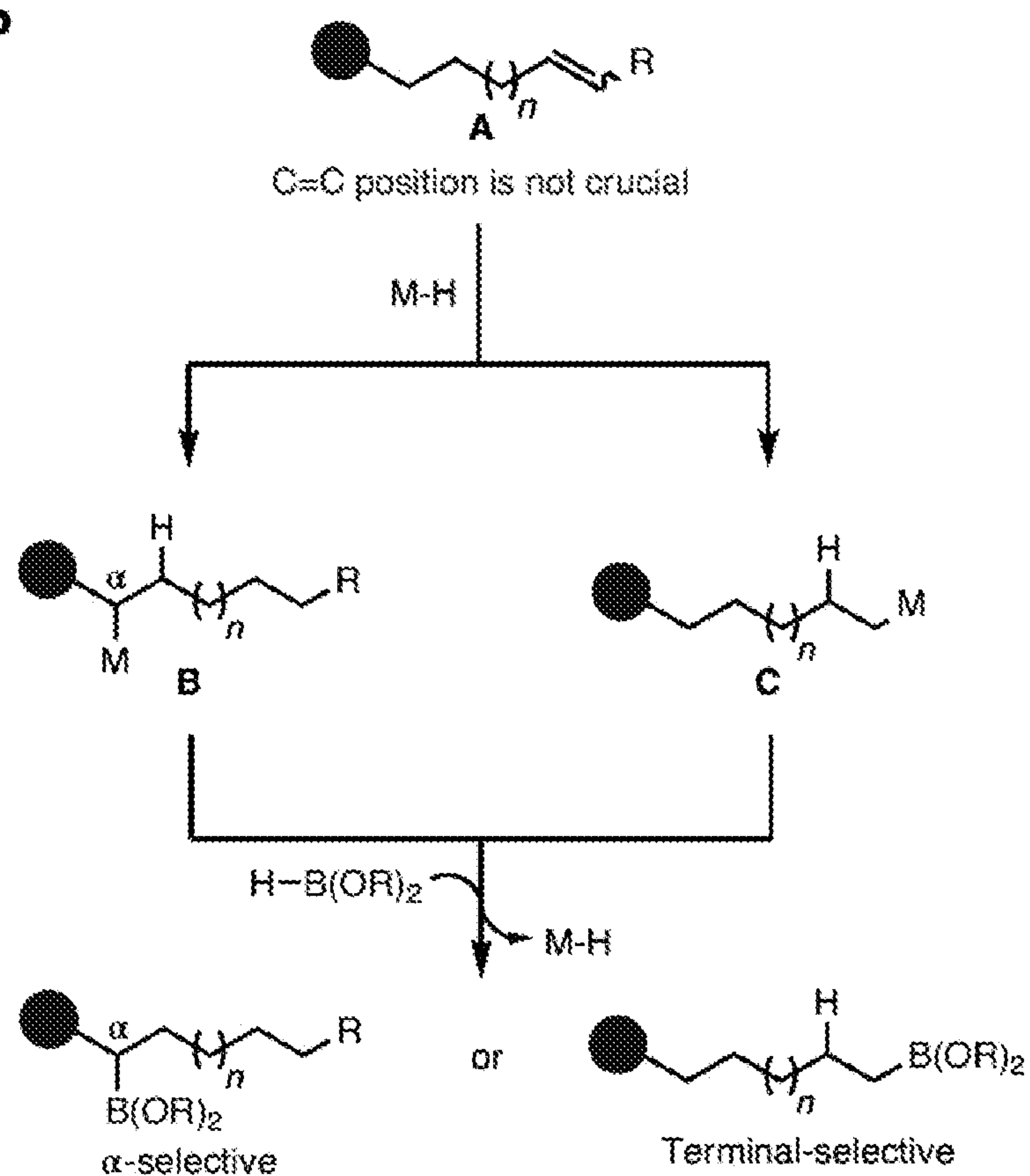
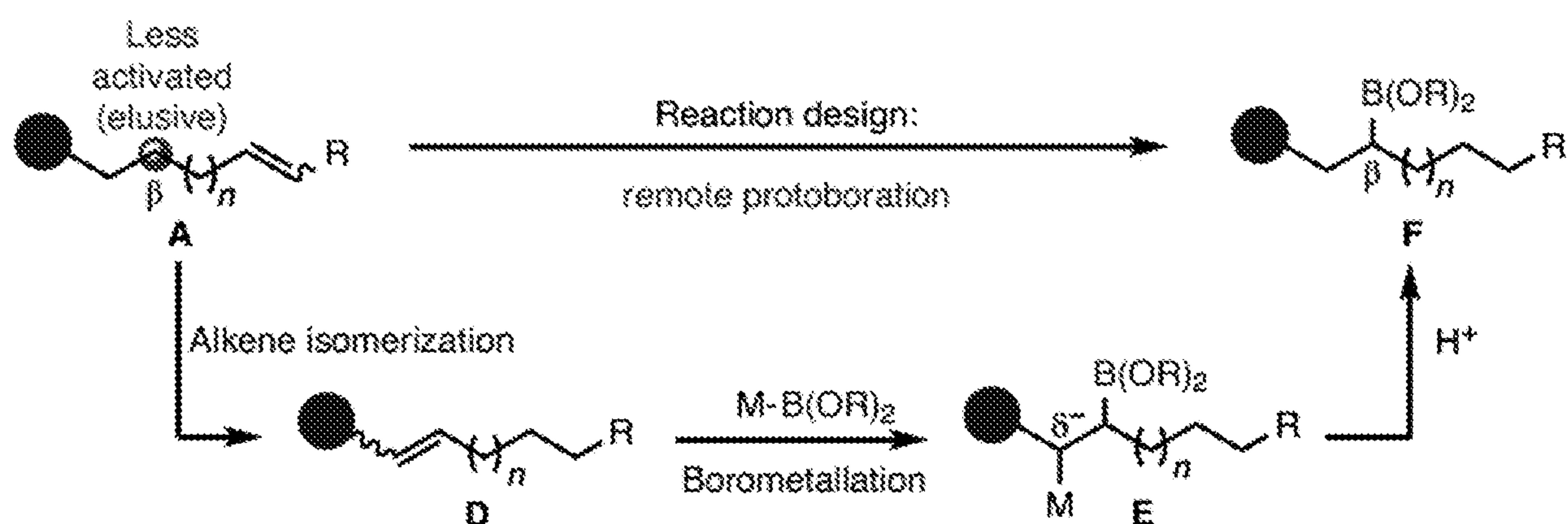
17. The compound of Formula (II) according to 16, wherein the compound has a chiral configuration about the borylated carbon.

18. The compound according to claim 16 or 17, the compound of Formula (II) is a compound of Formula (IIa):



wherein X, R and n are as defined herein, and pin is pinacolyl.

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a**Conventional catalytic site-specific alkene boryl addition:****b****c****Figure 1**

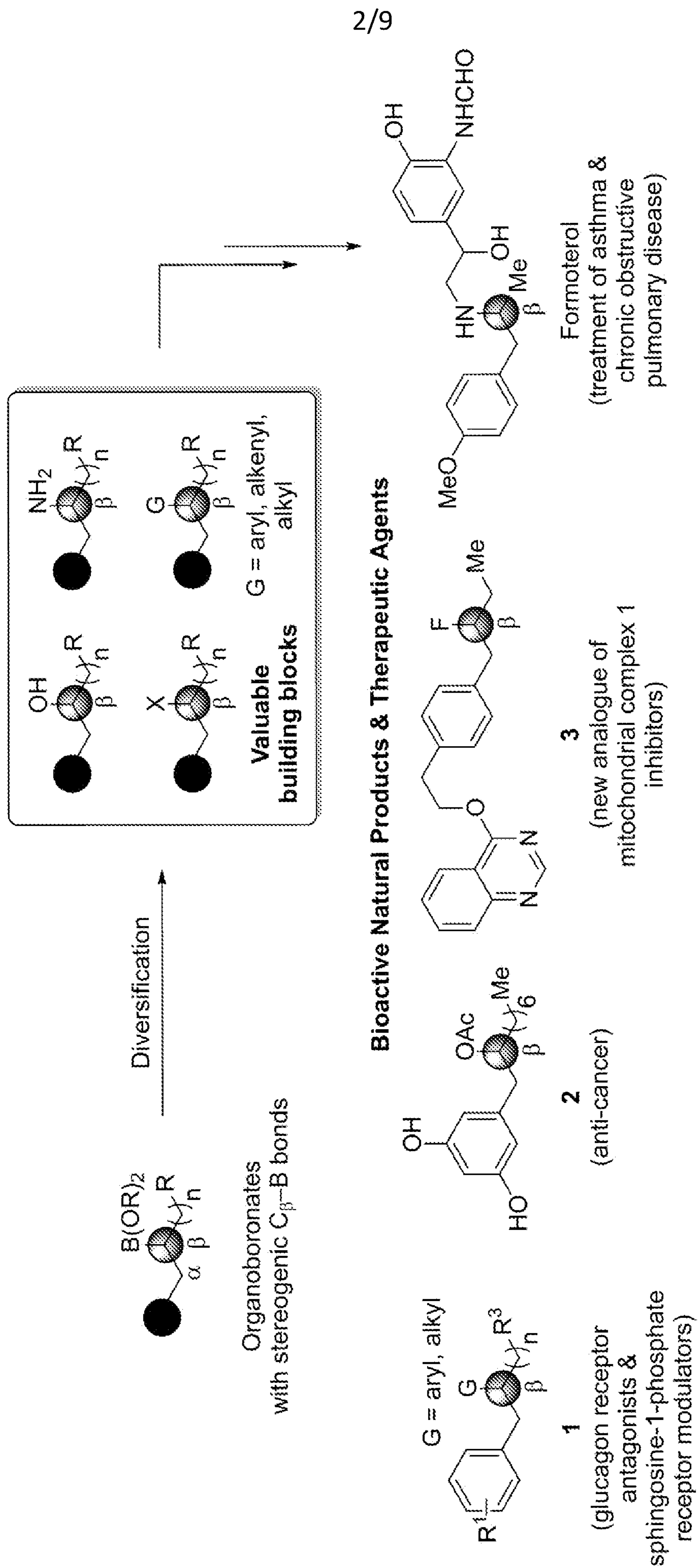
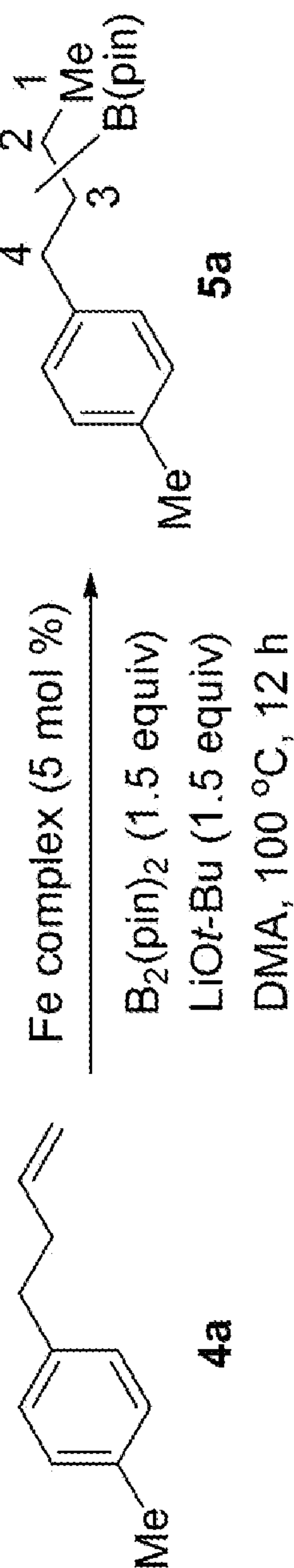


Figure 2

i. Effect of metal pre-catalyst:



with $\text{c-C}_8\text{H}_8\text{Fe}(\text{CO})_3$, 30% conv. to 5a , 0:24:76 (3:2:1 r.r.)	with FeBr_2 , 73% conv. to 5a , 79:19:2 (3:2:1 r.r.)	with FeBr_3 , 73% conv. to 5a , 81:17:2 (3:2:1 r.r.)	with Fe-1 , 89% conv. to 5a , 85:10:5 (3:2:1 r.r.)	<5% conv. to product with other Cu-, Co- or Ni-based pre-catalysts
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ii. Protic additive suppresses alkene isomerization:

iii. Enhancing site selectivity by reducing DMA concentration:

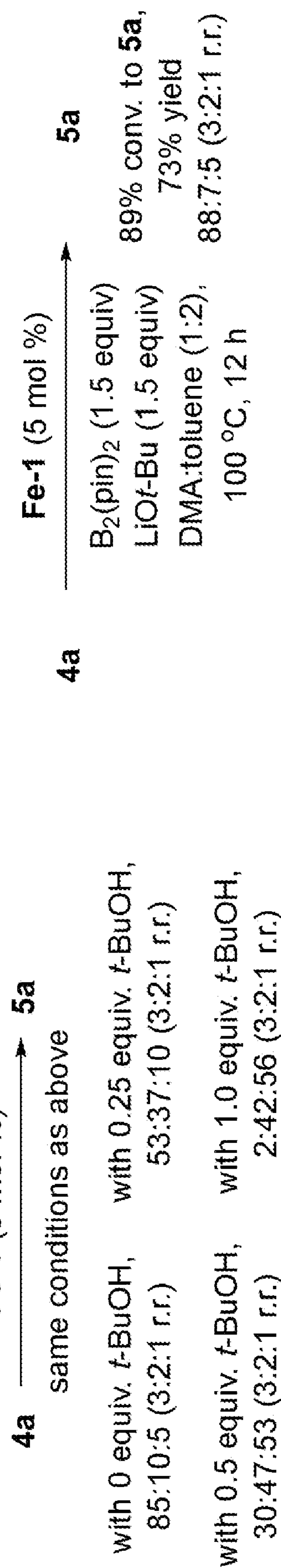
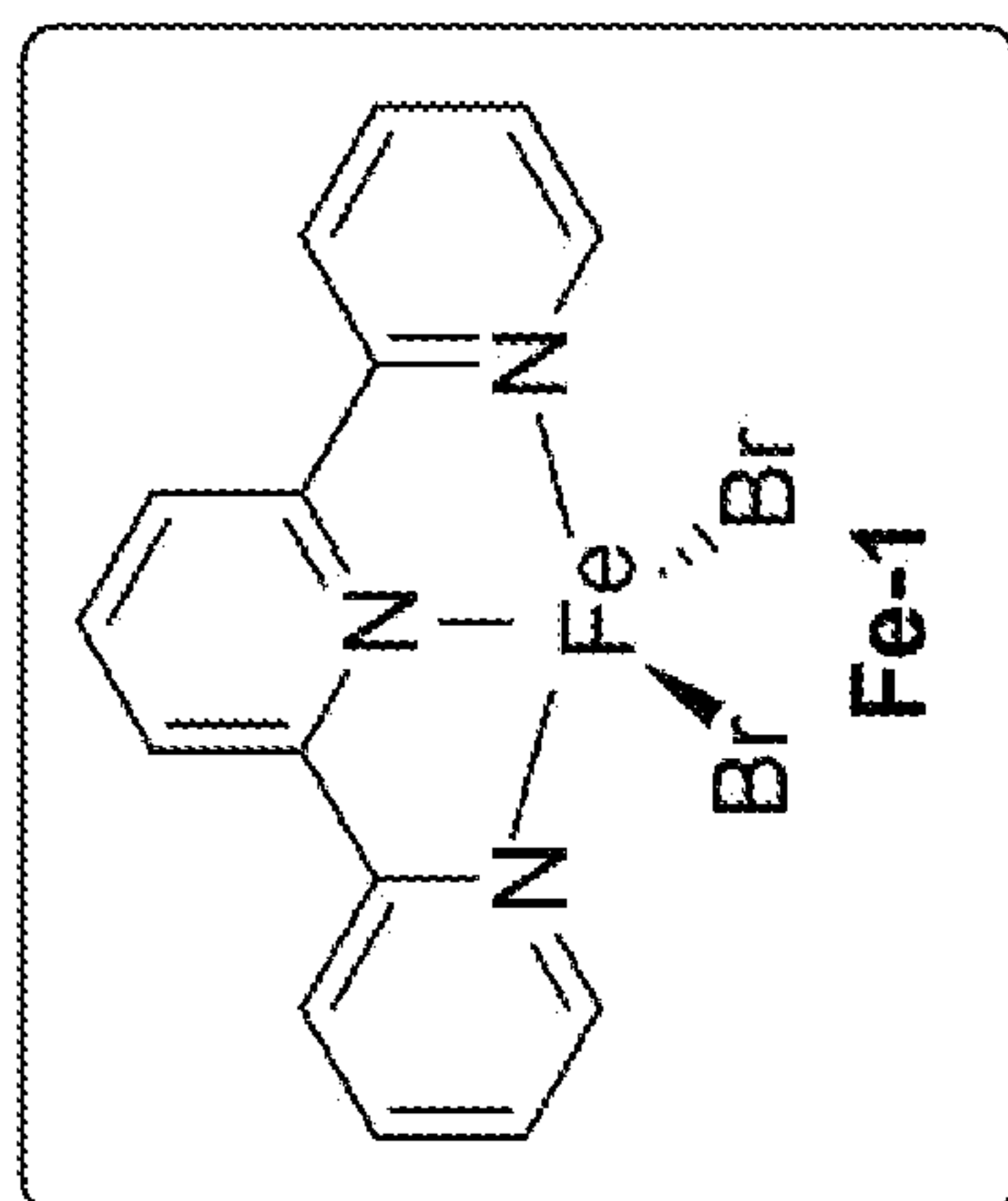


Figure 3



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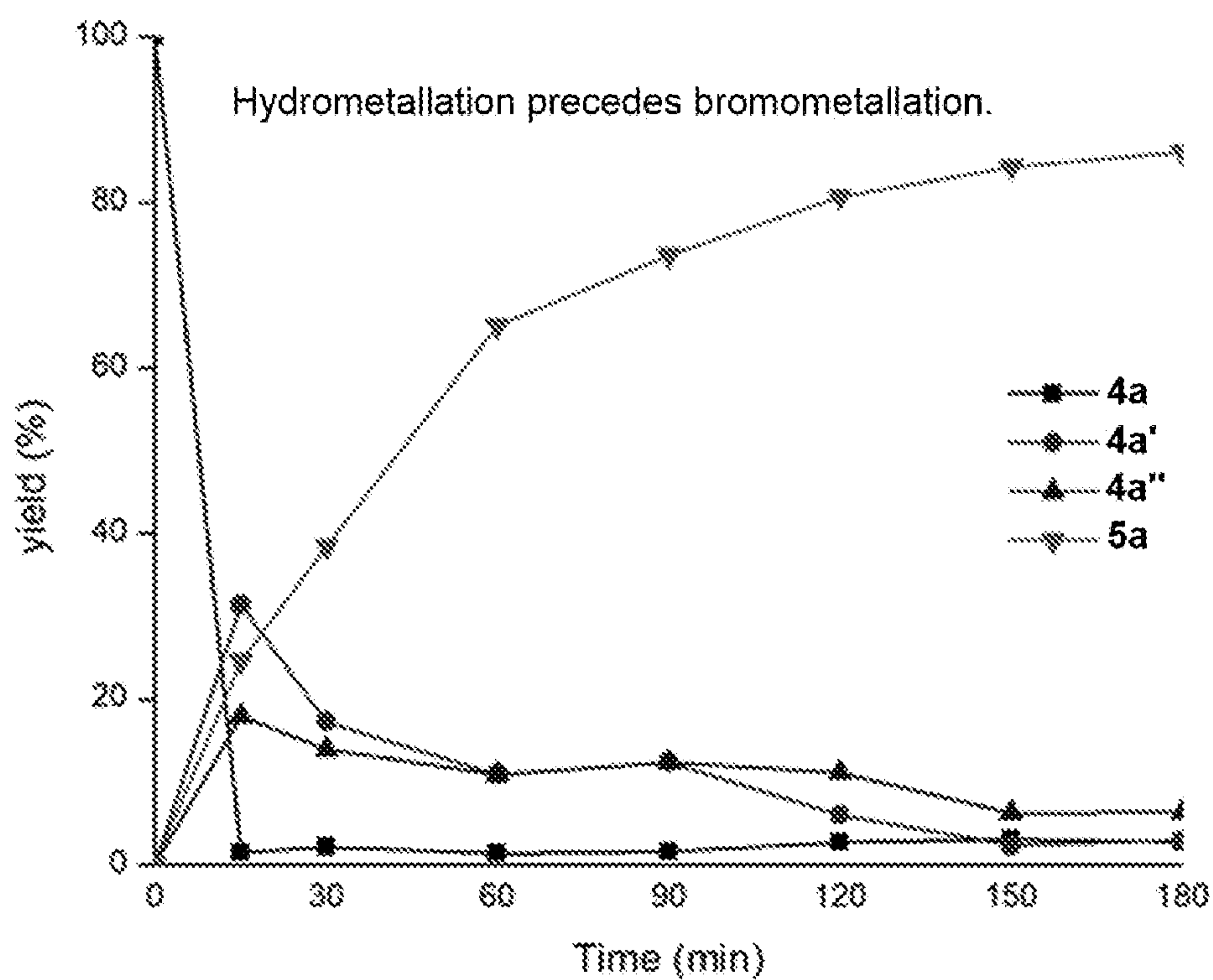
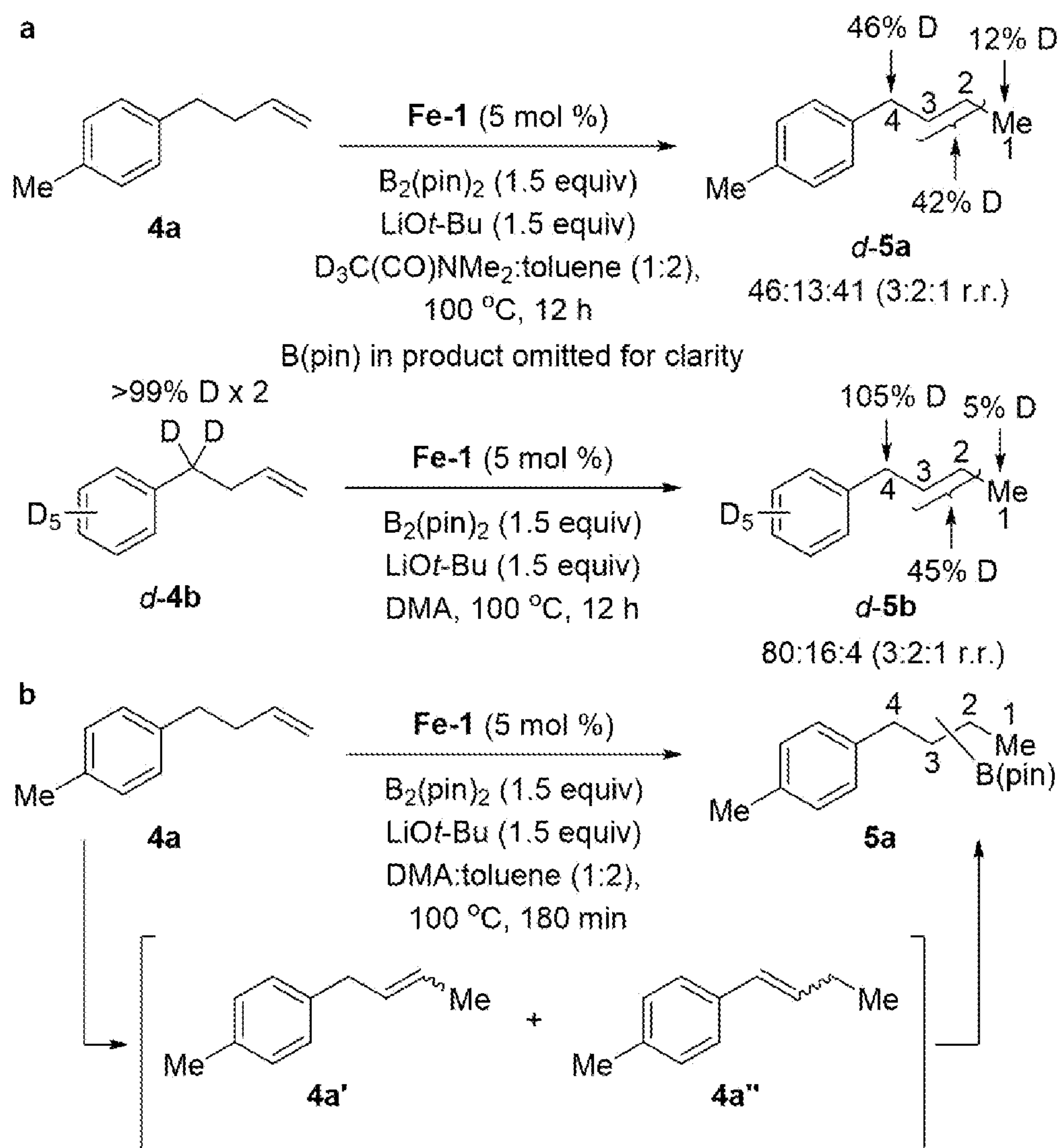


Figure 4

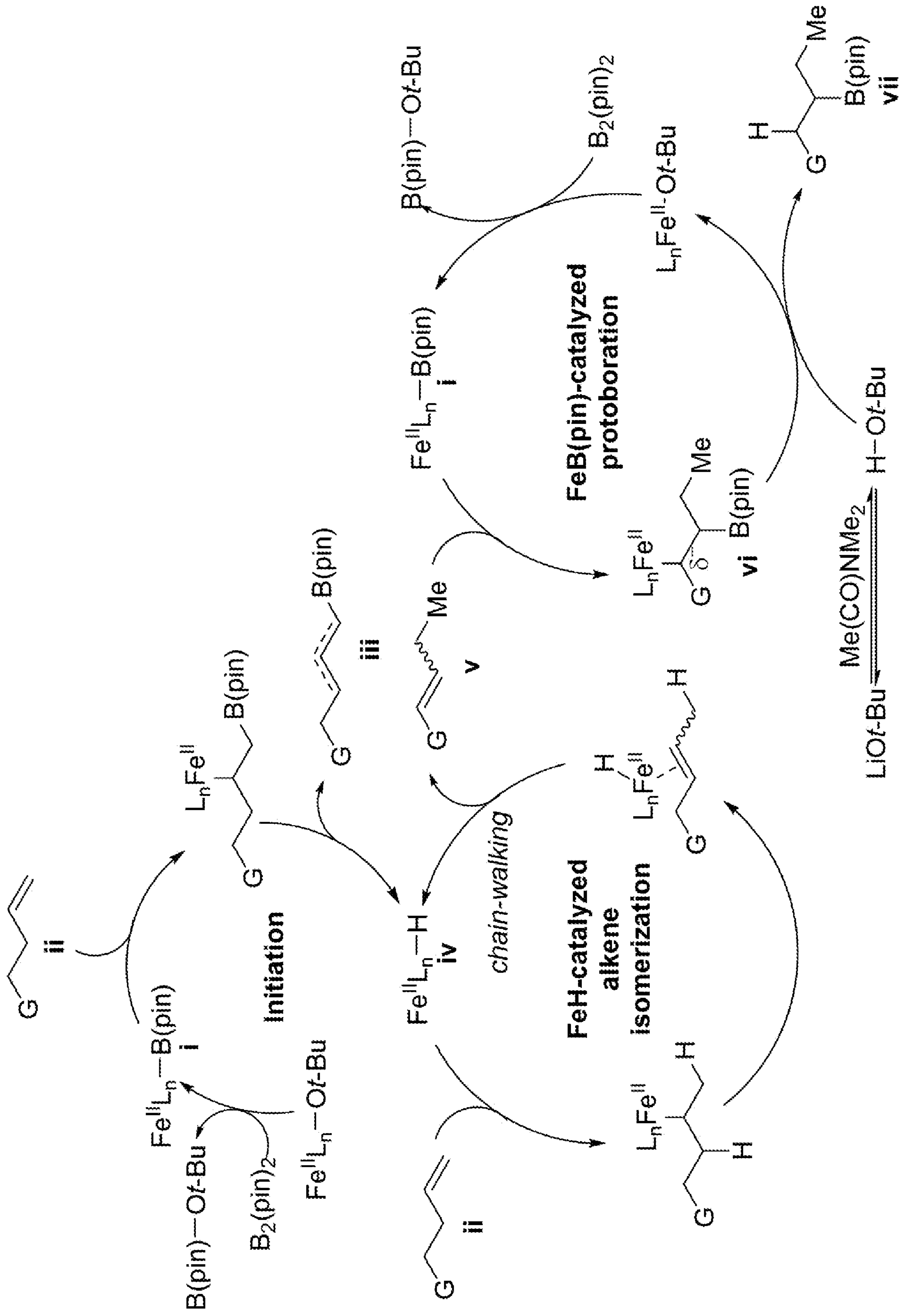


Figure 5

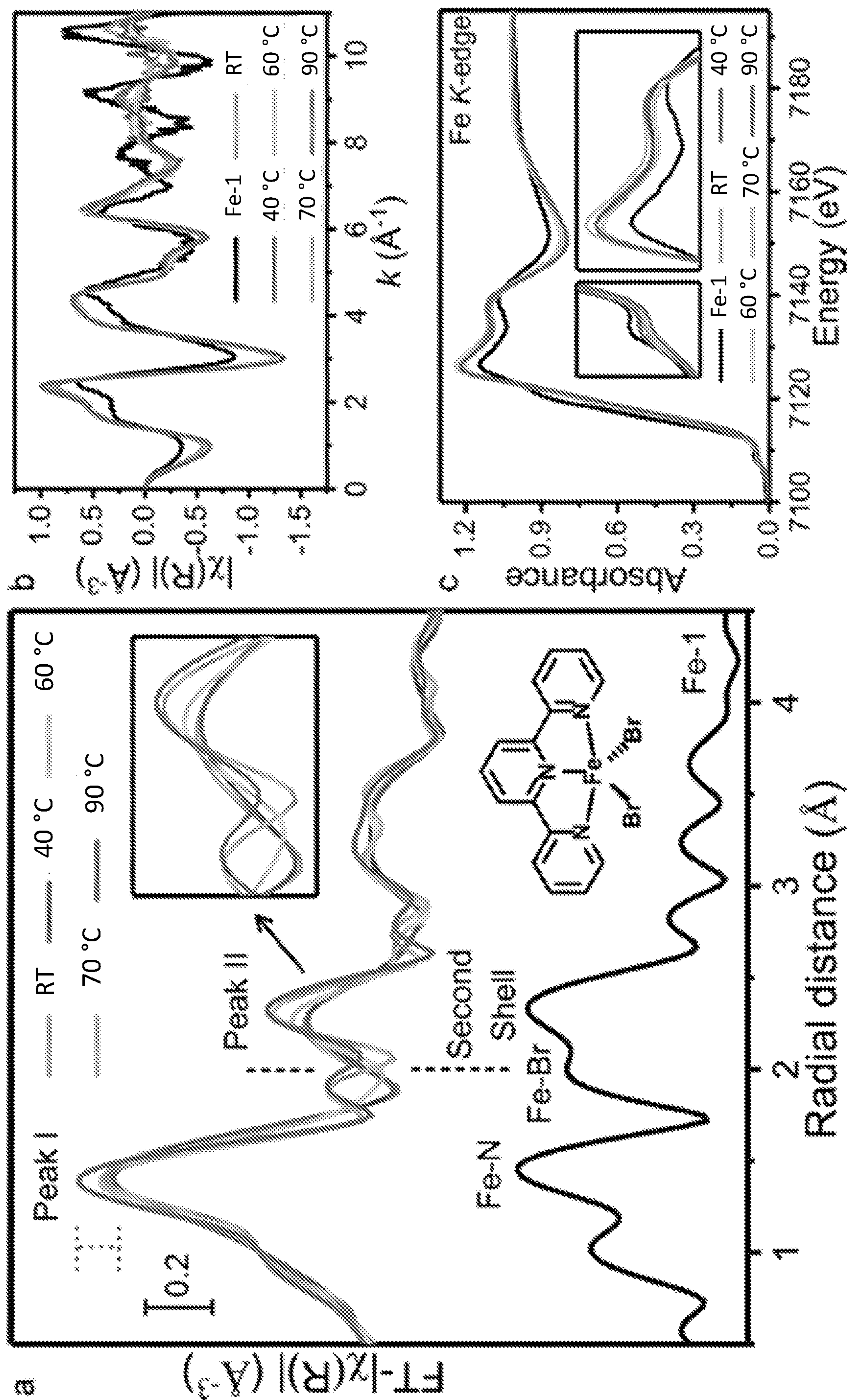


Figure 6

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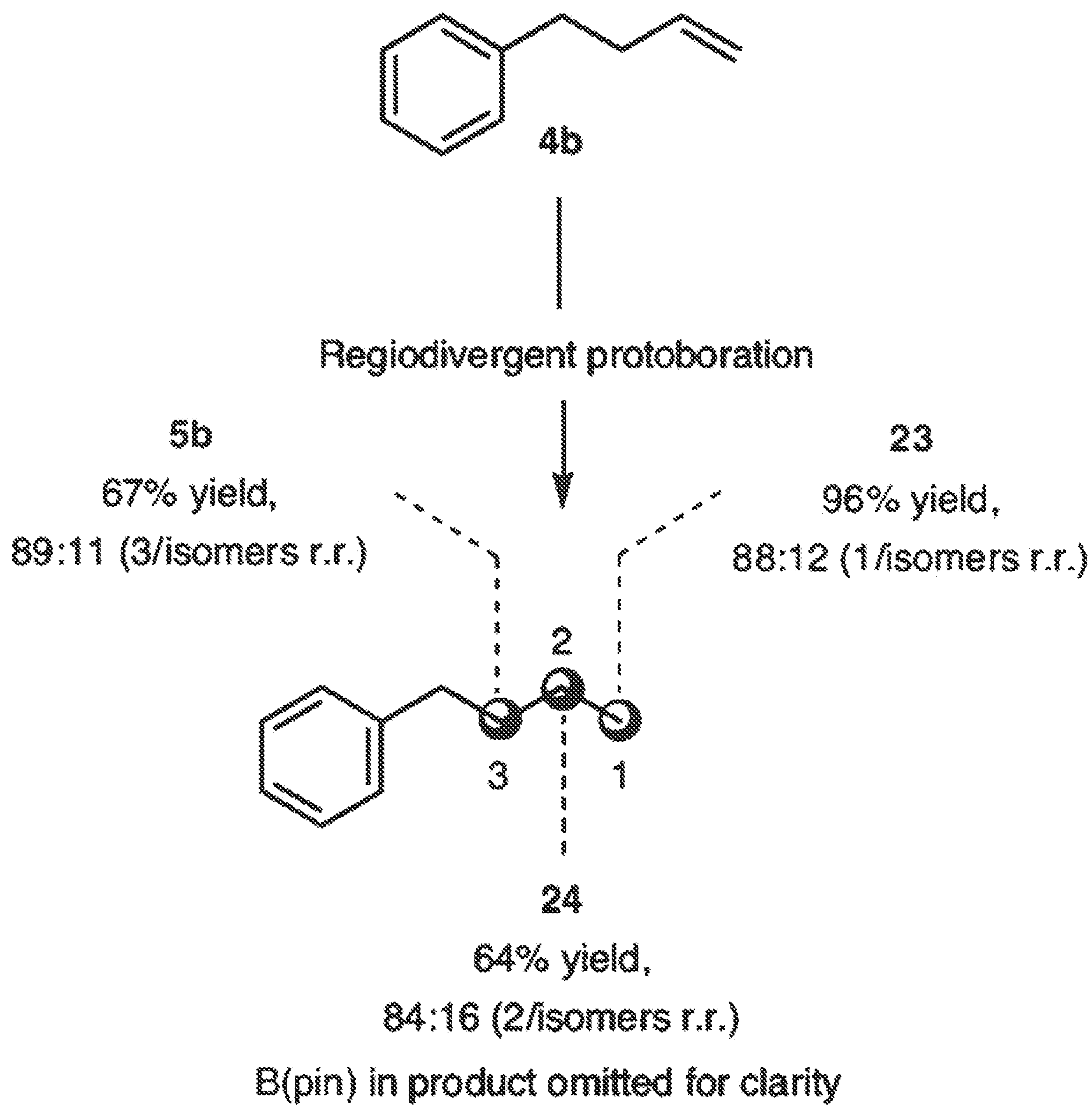


Figure 7

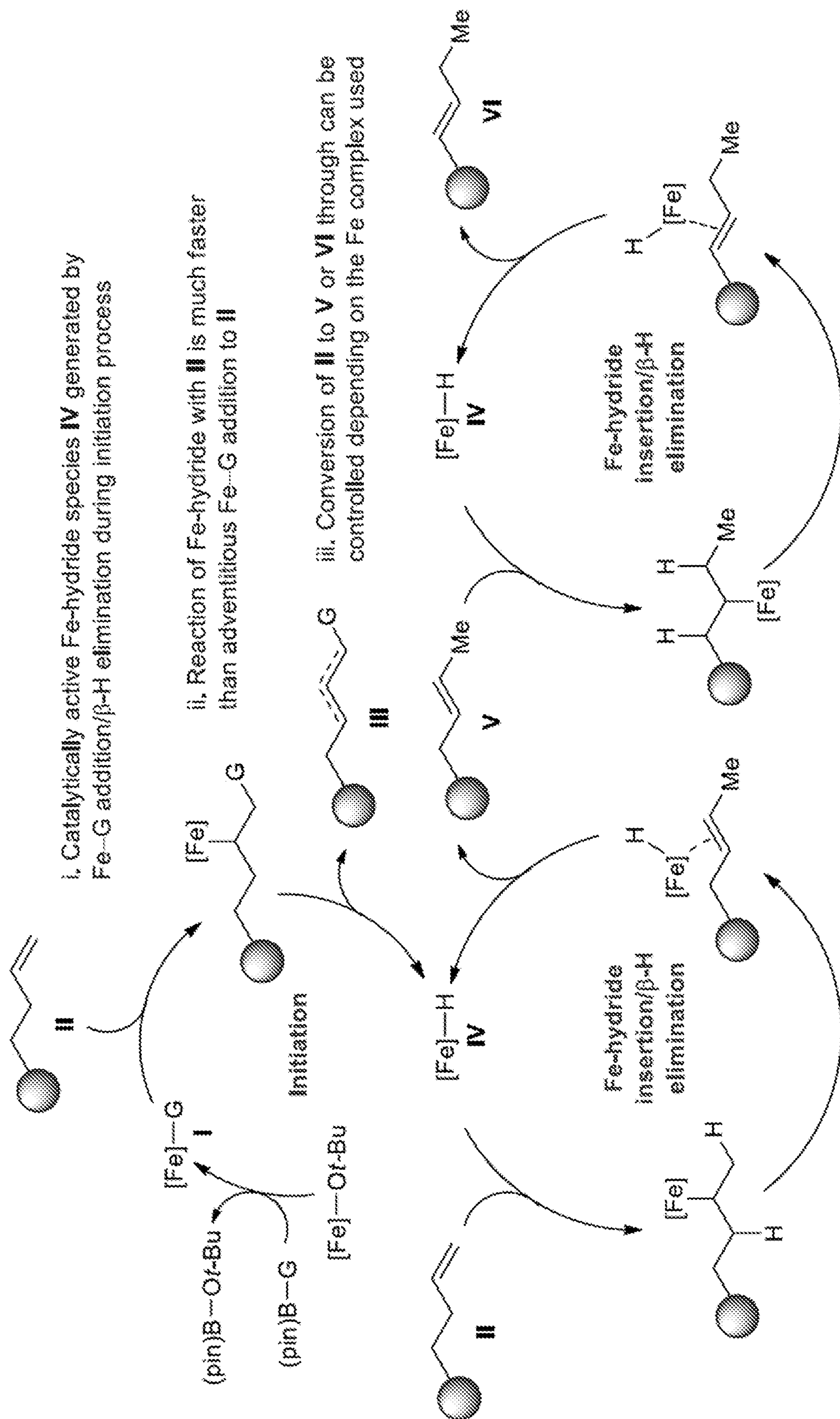


Figure 8

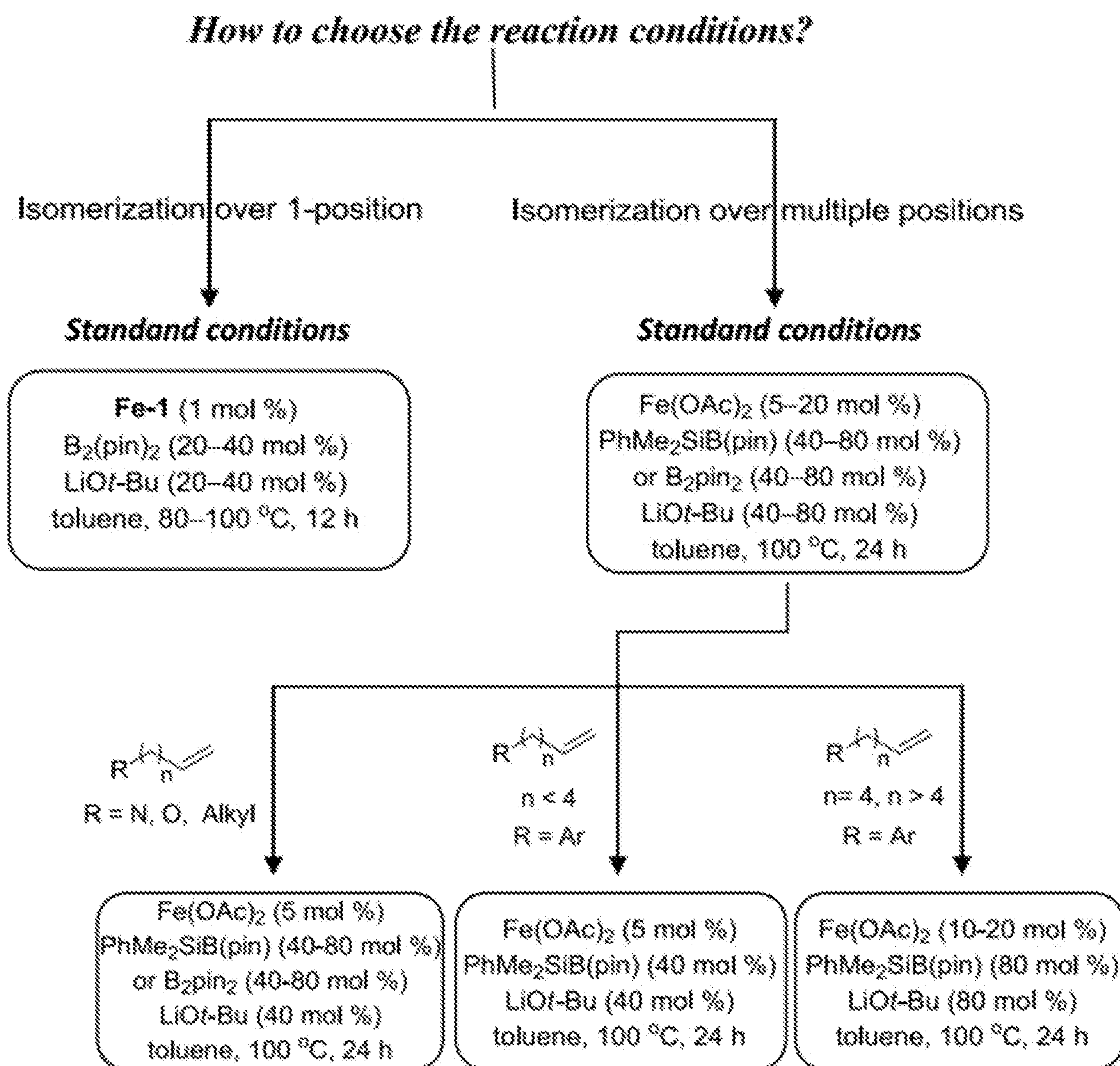


Figure 9

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SG2020/050606

A. CLASSIFICATION OF SUBJECT MATTER**C07F 5/02 (2006.01) C07B 35/08 (2006.01)**

According to International Patent Classification (IPC)

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS REGISTRY, CAPLUS & CASREACT: Chemical structural search of Formulae (I) and (II), alkene isomerization, hydroboration, and related terms

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	LIU, Y. ET AL., FeCl ₂ -catalyzed hydroboration of aryl alkenes with bis(pinacolato)diboron. <i>RSC Adv.</i> , 24 August 2015, Vol. 5, No. 90, pages 73705-73713	16-18
A	[Retrieved on 2021-01-20] <DOI: 10.1039/C5RA14869C> Compounds 3s, 3t, 3u and 3v in Table 3; Table 3; Scheme 1	1-15
X	Database Registry, Chemical Abstracts Services, CAS Registry Number: 2377758-27-3, Entered STN: 24/10/2019 2363038-60-0, Entered STN: 31/07/2019 2363036-50-2, Entered STN: 31/07/2019 2360552-58-3, Entered STN: 17/07/2019 2347425-06-1, Entered STN: 27/06/2019 2347424-91-1, Entered STN: 27/06/2019 2347424-84-2, Entered STN: 27/06/2019 2347424-52-4, Entered STN: 27/06/2019 [Retrieved on 2021-01-20 from STN]	16-18

☒ Further documents are listed in the continuation of Box C.☐ See patent family annex.

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

20/01/2021

(day/month/year)

Date of mailing of the international search report

21/01/2021

(day/month/year)

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/SG2020/050606

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	OGAWA, T. ET AL., Cobalt- and Iron-Catalyzed Isomerization–Hydroboration of Branched Alkenes: Terminal Hydroboration with Pinacolborane and 1,3,2-Diazaborolanes. <i>Organometallics</i> , 23 December 2016, Vol. 36, No. 2, pages 417-423 [Retrieved on 2021-01-20] <DOI: 10.1021/ACS.ORGANOMET.6B00823> Whole document, particularly, Schemes 1, 7 and 9	
P,X	YU, X. ET AL., Site-selective alkene borylation enabled by synergistic hydrometallation and borometallation. <i>Nature Catalysis</i> , 8 June 2020, Vol. 3, pages 585-592 [Retrieved on 2021-01-20] <DOI: 10.1038/S41929-020-0470-9> Whole document; and “Supplementary Table 1” on Page S3 of Supporting Information	1-18