COMMUNICATION

Regio- and stereoselective multisubstituted olefin synthesis *via* hydro/carboalumination of alkynes and subsequent iron-catalysed cross-coupling reaction with alkyl halides[†‡]

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A new synthetic route towards multisubstituted olefins, which are recurring core units in various pharmaceutical and bioactive compounds, was developed based on the direct cross coupling of alkenylaluminium reagents which were prepared *in situ* by the hydro- and carbometalation of alkynes, with non-activated alkyl halides in the presence of an iron catalyst. For the first time, alkenylaluminium reagents participated in an iron-catalysed cross-coupling reaction, following the activation of the aluminium reagents by a metal fluoride. The hydro- and carboalumination of alkynes and the subsequent cross-coupling reactions could be conducted in a one-pot manner and proceeded regio- and stereoselectively to give a variety of di-, tri-, and tetrasubstituted alkenes in good to excellent yields.

The development of regio- and stereoselective synthetic routes towards multisubstituted olefins, which are recurring core units in various pharmaceutical and bioactive compounds, has been a long-standing challenge in organic chemistry,[1] despite the numerous related methodologies that have been described.[2] Recently cross-coupling reactions have revealed their utility in olefin synthesis; amply demonstrated by their use in the synthesis of complex natural products.[3] A notable expedient approach in this regard is the hydro/carboalumination of alkynes and subsequent cross coupling with organic electrophiles in the presence of Pd or Ni catalysts (the Negishi protocol).[4] While this sequential protocol is particularly useful to couple alkenyl sp[2] carbon centres with other sp[2] carbon electrophiles, it has notable drawbacks. When alkyl (sp[3] carbon) electrophiles are employed, competing side reactions, such as β-hydride elimination which is inherently associated with Pd and Ni catalysts,[5] impair the cross coupling (Scheme 1a, path A).[6] Therefore, the introduction of an alkyl group usually requires a circuitous synthetic strategy: the alkenylaluminium reagent is converted to an alkenyl electrophile, e.g., alkenyl iodide, which is then cross coupled with alkyl zinc reagents in the presence of Pd or Ni catalysts.[3] In addition, alkylzinc reagents are typically prepared from alkyl halides with zinc metal (Scheme 1a, path B).[7] The direct cross coupling of *in situ* prepared alkenylaluminium with alkyl halides represents a straightforward method to achieve C_{sp2}–C_{sp3} bond formation for the synthesis of multisubstituted olefins, which has not been developed using conventional cross-coupling catalysts. We envisaged that iron-catalysed cross coupling of alkyl halides would be feasible for this purpose because of the excellent selectivity and reactivity of iron catalysts in the cross coupling of non-activated alkyl halides, regardless of the presence of β-hydrogens.[8–13] Herein, we describe that an iron catalyst enables the direct cross coupling of alkenyl aluminium reagents with alkyl halides in the presence of a metal

fluoride, and can be applied in the regio- and stereoselective synthesis of multisubstituted olefins (Scheme 1b).
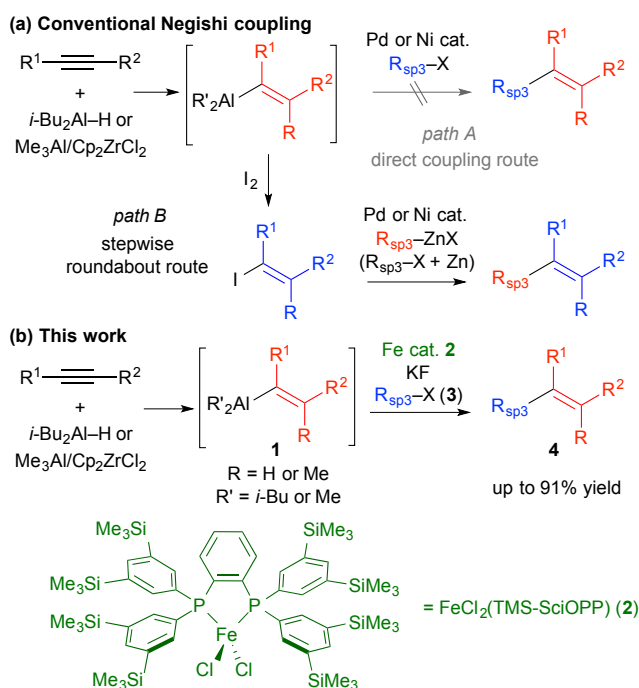
Scheme 1. Synthetic routes to stereodefined alkylsubstituted olefins via Negishi coupling.

We first examined the iron-catalysed cross coupling of alkenylaluminium reagent **1a**, which was prepared by the hydroalumination of 1-octyne with diisobutylaluminium hydride (DIBAL–H) as shown in Scheme 2. Reagent **1a**, generated *in situ*, was reacted with primary alkyl bromide **3a** in the presence of a catalytic amount of an Fe-bisphosphine complex, FeCl$_2$(TMS-SciOPP) **2**, which was previously reported to act as an efficient catalyst for the cross coupling of arylaluminium reagents.[11b] Under conditions developed previously for the coupling of arylaluminium reagents, the reaction of **1a** with **3a** gave the desired product in only 8% yield, albeit with high stereospecificity. In Negishi's original method for the Pd-catalysed cross coupling of alkenylaluminium reagents, it was observed that zinc salts were essential additives or co-catalysts to facilitate the cross coupling, as they form reactive organozinc or organozincate intermediates with the alkenylaluminium species.[4a,14] However, the addition of ZnCl$_2$ was totally ineffective here possibly due to the formation of an alkyl (isobutyl) zinc reagent, which may hamper the selective C$_{sp2}$–C$_{sp3}$ coupling due to the formation of over-reduced iron species.[15]
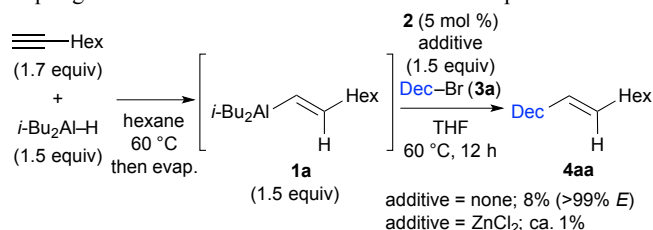
Scheme 2. Iron-catalysed cross coupling of 1-bromodecane **3a** with alkenylaluminium reagent **1a**, prepared by *in situ* hydroalumination.

These preliminary observations prompted us to identify a new activation method for alkenylaluminium reagents in iron-catalysed cross coupling. Although a variety of reported activation methods are available,[16] we envisioned that fluorides or alkoxides could directly activate the organoaluminium reagent *via* ate complex formation.[17] Moreover, we previously demonstrated that organoaluminate species participated efficiently in iron-catalysed cross-coupling reactions.[11c] Table 1 summarises the results of the additive screening. The addition of NaF, KF, and CsF improved the product yield significantly (entries 2–4), whilst LiF and MgF$_2$ had almost no effect on the reaction (entries 1 and 5). This is possibly

Table 1. Screening of additives.

| Entry | Additive | GC yield (%)[b] | | | RSM[b,c] |
		4aa (E/Z)	decane (5)	1-decene (6)	(%)
1	LiF	9 (>99% E)	8	12	66
2	NaF	38 (>99% E)	23	28	5
3	KF	76 (>99% E)[d]	9	10	0
4	CsF	30 (>99% E)	24	15	27
5	MgF$_2$	11 (>99% E)	8	20	56
6	KCl	12 (>99% E)	10	23	50
7	KBr	31 (>99% E)	34	25	5
8	t-BuOK	1 (>99% E)	0	9	85
9[e]	Bu$_4$NF	0	0	8	70
10[f]	none	8 (>99% E)	9	18	61

[a]Reactions were conducted for 3 h under the conditions described in Scheme 1. [b]Yields and ratios of stereoisomers were determined by GC analysis. [c]Recovery of the starting material **3a**. [d]Isolated yield. [e]1-Fluorodecane was obtained in ca. 20% yield. [f]Run for 12 h.

due to the strong bonding in the latter metal fluorides. Subsequently, the influence of the counter anion of a range of potassium salts was examined (entries 6–8). The product yield upon addition of KCl was almost the same as that without any additive (entry 6, 12% yield). The addition of *t*-BuOK decreased the catalytic activity (entry 8).[18] When Bu$_4$NF (TBAF) was used, the desired coupling reaction did not proceed (entry 9). Where cross-coupled product was obtained, the reactions proceeded in a stereospecific manner (entries 1–10), and the addition of KF resulted in the greatest yield of the coupling product (entry 3, 76% yield).[19] It should be noted that catalyst screening revealed that complex **2** facilitated the reaction most efficiently.[20]

The reactions with substituted alkenylaluminium reagents were examined under the optimised conditions. Substituted alkenylaluminium reagents were prepared *in situ* by hydroalumination or Zr-mediated carboalumination of terminal and internal alkynes,[4a–c] and were subsequently used in the iron-catalysed cross coupling with secondary alkyl bromide **3b** (Scheme 3). Alkenylaluminium reagents **1a** and **1b**, prepared by hydroalumination, were readily converted into the desired coupling products **4ab** and **4bb** in 91% (>99% *E*) and 86% (*E/Z* = 97/3) yield respectively (Scheme 3a). Reagents **1c** and **1d**, formed by carboalumination, also participated in the reaction to afford the desired multisubstituted olefins (86% and 19% yields respectively, Scheme 3b). Fortunately, the presence of concomitant zirconium species in the coupling reaction has no influence on the outcome of the reaction. Rate enhancement by KF was apparent regardless of the structure of the alkenylaluminum reagent used.[19] Reagent **1c** gave product **4cb** with high stereospecificity; however, reagent **1d** (*E/Z* = 80/20) gave product **4db** (*E/Z* = 70/30) with a slightly reduced stereoselectivity. This would be due to *E/Z* isomerisation of alkenylaluminum reagent under the coupling conditions.[21]
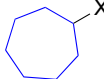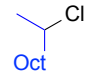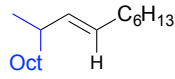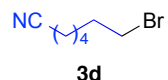

(a) Hydroalumination
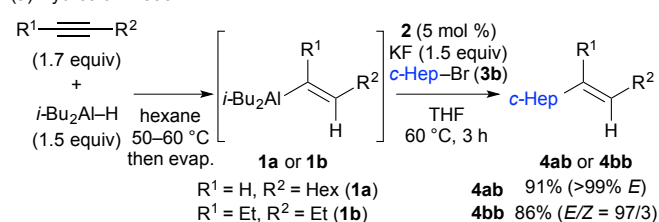
(b) Carboalumination
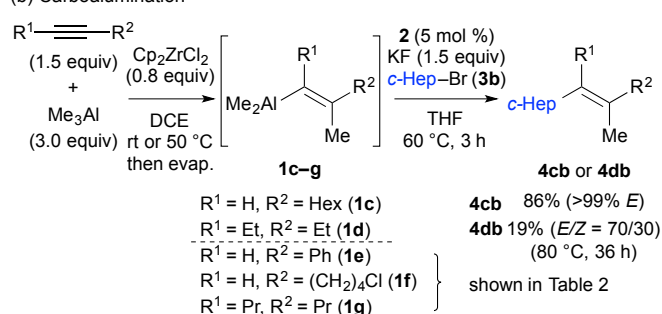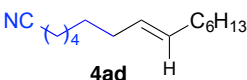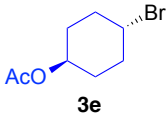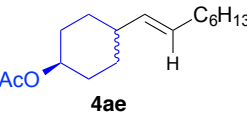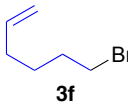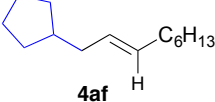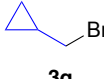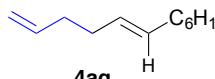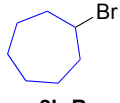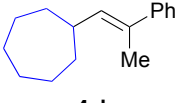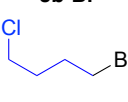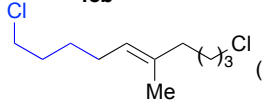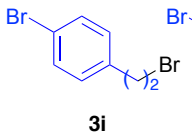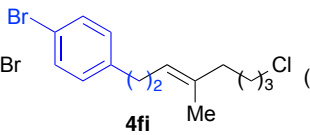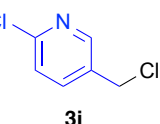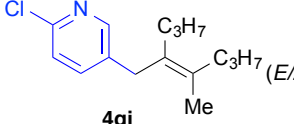
Scheme 3. The reaction of various alkenylaluminium reagents prepared by hydro/carboalumination.

Table 2 illustrates the scope of viable alkyl halide substrates in the coupling reaction. In entries 1–7, the reactivity of a range of primary alkyl halides was examined. 1-Iodo- and 1-bromodecane (**3a-I** and **3a-Br**) gave the desired coupling product **4aa** in 73% and 76% yields respectively (entries 1 and 2), whereas the reaction with the

corresponding chloride gave **4aa** in only 2% yield (entry 3). The reaction of 1-fluorodecane (**3a-F**) did not proceed at all (entry 4). The results highlight the opposing reactivity profile of the present coupling reaction from that of Friedel-Craft-type substitution reactions with organoaluminium reagents, where the more electronegative fluoride reacts smoothly.[22] Bromo- and chlorocycloheptane were successfully transformed into the desired product **4ab** in 91% and 88% yield respectively (entries 5 and 6). An acyclic secondary alkyl chloride also participated in the coupling reaction to afford product **4ac** in 86% yield (entry 7).

Table 2. Substrate Scope.

Entry[a]	Alkyl halide	Product	Isolated Yield (%)[b]
1	Dec—X	**4aa**	X = I 73 (>99% E)
2			X = Br 76[c] (>99% E)
3	**3a-I,Br,Cl,F**		X = Cl 2[c] (>99% E)
4			X = F 0
5	**3b-Br,Cl**	**4ab**	X = Br 91 (>99% E)
6			X = Cl 88[c] (>99% E)
7	**3c**	**4ac**	86 (>99% E)
8	**3d**	**4ad**	90 (>99% E)
9	**3e**	**4ae**	49 (>99% E) anti/syn = 58/42
10	**3f**	**4af**	46 (>99% E)
11	**3g**	**4ag**	17 (84)[c] (>99% E)
12	**3b-Br**	**4eb**	49 (>99% E)
13	**3h**	**4fh**	78 (>99% E)
14	**3i**	**4fi**	76 (>99% E)
15	**3j**	**4gj**	72 (E/Z = 64/36)

[a]See the Supporting Information for details of the reaction conditions for each entry. [b]The stereoisomeric ratio was determined by GC analysis. [c]Yield was

determined by ^{1}H NMR spectroscopic analysis using 1,1,2,2-tetrachloroethane as an internal standard.

The functional group compatibility of the organoaluminium reagents under the optimized conditions was demonstrated in the reaction of alkyl halides bearing nitrile (**3d**, 90% yield) and acetoxy groups (**3e**, 49% yield) as shown in entries 8 and 9. The observed stereochemical scrambling at the reaction centre of **3e** could be ascribed to the formation of alkyl radical intermediates, as in related coupling reactions.[8–13] Further evidence for an radical intermediate was provided by the reactions of 6-bromo-1-hexene **3f** and (bromomethyl)cyclopropane **3g**, which resulted in the formation of carbocycle product **4af** and ring-opening product **4ag** in 46% and 17% yields (84% spectroscopic yield) respectively (entries 10 and 11).

Various alkenylaluminium reagents (**1e–g**), prepared by Zr-catalysed carboalumination with Me₃Al, were subsequently employed in the reaction (entries 12–15). Alkylated (E)-styrene **4eb** was obtained in 49% yield from the reaction of β-styrylaluminium **1e** (entry 12). Olefins bearing halogens on their side chains can serve as versatile building blocks, and thus the chemoselectivity of the reaction was investigated by comparing substrates containing C_{sp3}–Br, C_{sp3}–Cl, and C_{sp2}–Br moieties; the reaction proceeded selectively at C_{sp3}–Br to provide desired olefins **4fh** and **4fi** in 78% and 76% yield respectively (entries 13 and 14). Finally, tetrasubstituted olefin **4gj**, bearing a coordinative pyridyl group, was obtained in 72% yield (E/Z = 64/36) (entry 15).[21] It should be noted the chloro group on the pyridyl group remained intact during the coupling reaction, showing again the preference of C_{sp3}–halogen bond cleavage.

In conclusion, we have demonstrated that multisubstituted olefins can be synthesised in a highly regio- and stereoselective manner via alkyne hydro/carboalumination and subsequent iron-catalysed cross coupling between the resulting alkenylaluminum species and non-activated alkyl halides. The use of KF as an additive to activate the alkenylaluminium reagents facilitates the unprecedented direct introduction of various alkyl side chains, thus reducing the steps of olefin synthesis in comparison with the one based on conventional Negishi protocol. We envisage that the present methodology based on the combination of an organoaluminum reagent and fluoride-promoted iron-catalysed cross coupling will provide facile access to multisubstituted olefins as well as an expedient synthetic method for natural or bioactive complex molecules bearing olefin frameworks.

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Notes and references

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19 For investigation of effect of KF, see Supporting Information.

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