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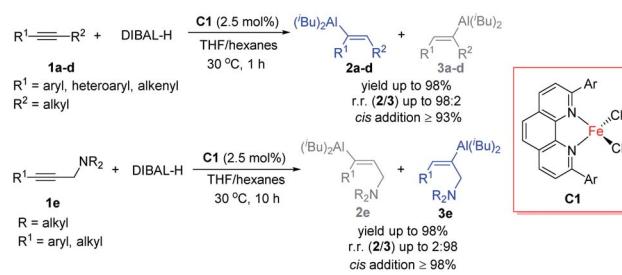
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Introduction

Iron catalysis attracts intensive attention mainly because of two reasons. First, because iron, which is the most abundant transition metal in the Earth's crust, is inexpensive and biocompatible, iron-catalysed organic reactions meet the requirements for green and sustainable chemistry. Second, the abundant valence states and variable spin states of iron provide opportunities to develop new reactions. Although research on iron-catalysed reactions has recently achieved significant progress, the activity and selectivity of iron catalysts are generally inferior to those of noble-metal catalysts.¹ The development of new iron-catalysed reactions, especially those in which iron catalysts exhibit superior activity or selectivity to other catalysts, is the key to promote iron catalysis.

Our group has a long-standing interest in the study of iron-catalysed reactions.² As part of this ongoing work, we herein report the first protocol for iron-catalysed hydroalumination reactions of alkynes with DIBAL-H (Scheme 1). By using 2,9-diaryl-1,10-phenanthroline iron complexes as catalysts, we

realized the hydroalumination of a diverse array of internal alkynes with specificity for *cis*-addition and with high regioselectivity. By subsequently employing the rich chemistry of the alkenylaluminum products,³ we efficiently synthesized a number of functionalized and unfunctionalized trisubstituted alkenes. The following aspects of this protocol distinguish it from previously reported catalytic methods of alkyne hydroalumination.^{4–6} First, the chemo- and regioselectivity were markedly better than those for previously reported catalysts under identical reaction conditions. Second, the protocol exhibited good functional group tolerance: substrates with alkenyl, halogen, hydroxy, amino, and acetal groups were successfully hydroaluminated. Third, using this protocol, we realized unprecedented amino-directed hydroalumination of internal alkynes, which enabled, for the first time, the selective



Scheme 1 Iron-catalysed hydroalumination of internal alkynes.

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cis-addition of aluminum to the alkyl side of aryl alkyl alkynes. Fourth, we achieved highly selective hydroalumination of conjugated alkynes to generate various new types of conjugated alkenylaluminums.

Results and discussion

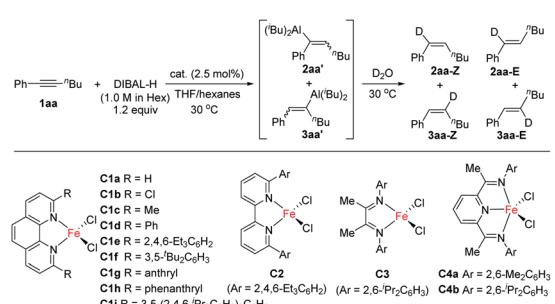
We initiated our study by using hex-1-yn-1-ylbenzene (**1aa**) as a model substrate and commercial DIBAL-H (1.0 M in hexanes) as the hydroalumination reagent (Table 1). Because of the high activity of the alkenylaluminum products, we determined the isolated yields and regioselectivities after hydrolysis with D_2O . First, we investigated various catalysts. When we used some transition-metal catalysts reported in the literature for hydroalumination of other alkynes, the reactions proceeded smoothly to achieve full conversion of the alkyne **1aa**, but the product yields and regioselectivities were unsatisfactory (entries 1–4). We attributed the poor yields mainly to two side reactions: over-

reduction and double bond isomerization. Next, we explored various iron catalysts. Although $FeCl_2$ exhibited low activity (entry 5), the addition of $N(sp^2)$ ligands markedly improved both the conversion and the regioselectivity. Systematic evaluation of ligands (entries 6–18) revealed that 2,9-diaryl-1,10-phenanthroline iron complexes effectively catalysed the reactions, with high selectivity for *cis*-addition products and moderate to high regioselectivity. When 2,9-dianthryl-substituted phenanthroline ligand **L1g** or 2,9-diphenanthrenyl-substituted phenanthroline ligand **L1h** was used, the regioselectivity reached 90% (entries 12 and 13). Because the coordinative THF may passivate DIBAL-H,⁷ the reaction without catalyst was totally inactive in the current study (entry 19).

We also systematically evaluated other reaction parameters (ESI Tables S2–S7†). When the iron catalyst, the ligand, or $FeCl_2$ was omitted under otherwise standard conditions (Table 1, entry 12), no reaction occurred, even at elevated temperature (Table S2†). More detailed ligand evaluation indicated that the monodentate phosphorus ligands, bidentate phosphorus ligands, and *N*-heterocyclic carbene ligands were inactive in the iron-catalysed alkyne hydroalumination; the other bidentate or tridentate *N*-ligands gave poor regioselectivities (Table S3†). These data clearly demonstrate the superiority of phenanthroline based ligands in this reaction. The conversion and regioselectivity were low when DIBAL-H was replaced with another hydroalumination reagent [Red-Al, $LiAlH_4$, $LiAlH(O^{'Bu})_3$, $HAICl_2 \cdot 2THF$, $Al(^3Bu)_3$, $Al(^3Bu)_2Cl$, or $AlEt_2Cl$, Table S4†]. The addition of organometallic reagents or a base as an additive exhibited a negative impact on yields and selectivities (Table S5†). The choice of solvent had an obvious effect on the reaction outcome. Only THF and other ether solvents gave good results, while all the other tested solvents decreased both yield and the regioselectivity (Table S6†). We suspect that THF was involved in the formation of the C–Al bond. When iron was replaced with cobalt, nickel, copper, manganese, gold, and palladium the yield or regioselectivity of the reaction dropped considerably (Table S7†).

Under the optimal conditions (Table 1, entry 12), we systematically investigated the substrate scope of the reaction (Scheme 2). First, we studied the effect of the substituent on the phenyl group of various aryl alkyl alkynes **1**. The tested substrates gave high yields of alkenes **2aa–2ap** in high regioselectivity with aluminum added at the aryl side of the alkynes (r.r. = 87 : 13 to 96 : 4) and excellent stereoselectivity (*Z/E* = 93 : 7 to >98 : 2). Substituents at the *meta* and *para* positions of the phenyl ring had little effect on the yield or selectivity, but substrates with an electron-donating methoxy group gave the highest regioselectivities (**2af** and **2am**). Substrates with *ortho*-substituents (**2an–2ap**) showed slightly better regioselectivities than most of the corresponding *meta*- or *para*-substituted compounds. When the phenyl ring was replaced with a fused aromatic ring system (naphthyl, **2ba**), a heteroaromatic ring (2-furanyl, **2bb**; 2-thiophenyl, **2bc**; 5-indolyl, **2bd**), or a ferrocenyl moiety (**2be**), the reaction also proceeded smoothly and afforded satisfactory results. Next, we investigated the effect of changing the alkyl group (R^2) with the R^1 group being a *para*-

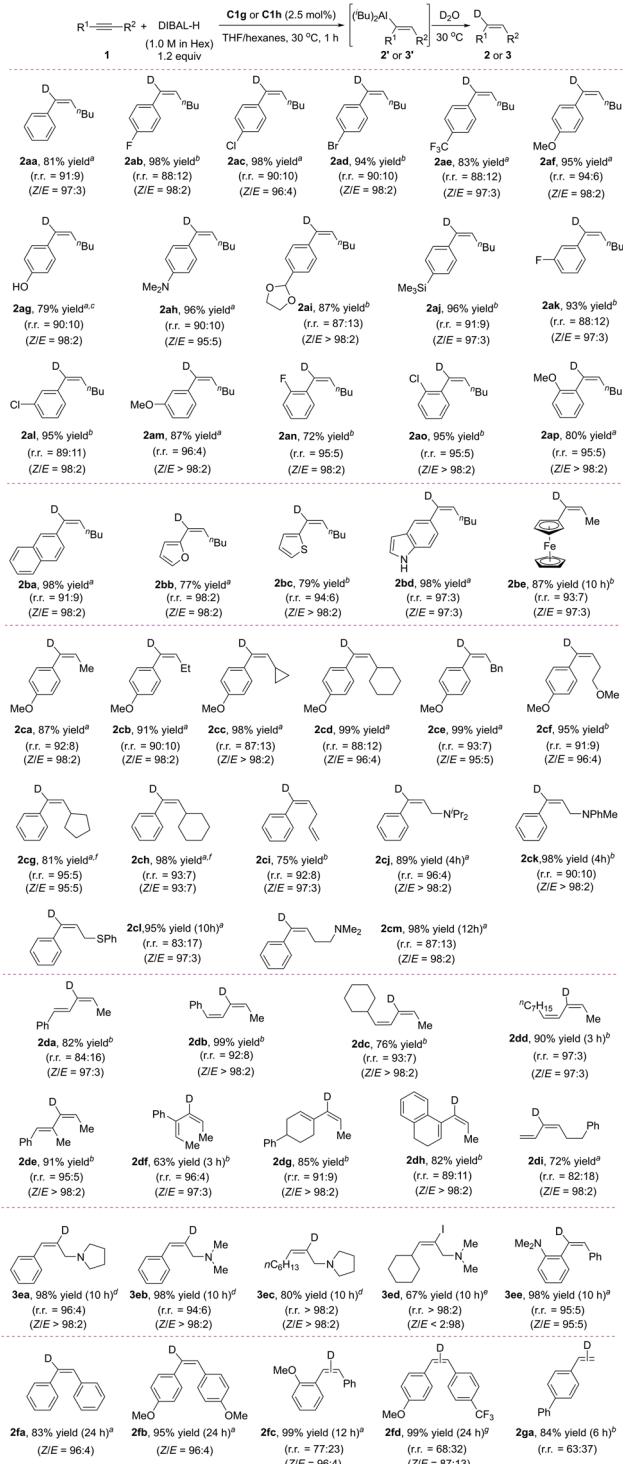
Table 1 Iron-catalysed hydroalumination of hex-1-yn-1-ylbenzene with DIBAL-H: optimization of reaction conditions



Entry ^a	Cat.	Conv. (%)	Yield (%)	r.r. (2aa/3aa)	<i>Z/E</i> (2aa)
1 ^b	Cp_2TiCl_2	45	40	81 : 19	98 : 2
2 ^b	Cp_2ZrCl_2	11	8	67 : 33	94 : 6
3 ^b	$Ni(PPh_3)_2Cl_2$	100	69	65 : 35	98 : 2
4 ^b	$Ni(dppp)Cl_2$	64	38	67 : 33	94 : 6
5	$FeCl_2$	7	5	56 : 44	88 : 12
6	C1a	26	21	75 : 25	98 : 2
7	C1b	52	36	76 : 24	98 : 2
8	C1c	99	69	69 : 31	98 : 2
9	C1d	100	94	73 : 27	97 : 3
10	C1e	100	84	71 : 29	98 : 2
11	C1f	100	97	85 : 15	98 : 2
12	C1g	100	81	91 : 9	97 : 3
13	C1h	100	91	90 : 10	98 : 2
14	C1i	70	54	88 : 12	87 : 13
15	C2	30	21	65 : 35	87 : 13
16	C3	11	5	55 : 45	92 : 8
17	C4a	100	94	69 : 31	97 : 3
18	C4b	81	48	60 : 40	94 : 6
19 ^c	None	Trace	ND	ND	ND

^a Reaction conditions: **1aa** (0.2 mmol), DIBAL-H (1.0 M in hexanes, 0.24 mmol), catalyst (2.5 mol%) in THF (1 mL) at rt (~ 30 °C). Conversion, yield, r.r. (regioisomeric ratio), and *Z/E* were determined by 1H NMR with 1,3,5-trimethoxybenzene as an internal standard after quenching with D_2O (30 °C, 30 min). ND, not detected. ^b 5 mol% catalyst was used. ^c The reaction was performed at rt and under reflux conditions.





Scheme 2 Iron-catalysed hydroalumination of internal alkynes: substrate scope. Reaction conditions: 1 (0.2 mmol), C1 (0.005 mmol, 2.5 mol%), DIBAL-H (1.0 M in hexanes, 0.24 mmol) in THF (1 mL) at 30 °C. Isolated yields were given. The r.r. and Z/E were determined by ¹H NMR after quenching with D₂O or I₂ (30 °C, 30 min). ^a C1g was used as catalyst. ^b C1h was used as catalyst. ^c 2.2 equiv. of DIBAL-H were used. ^d C1i was used as catalyst. ^e C1f was used as catalyst, and quenched with I₂. ^f HAlEt₂ (1.0 M in toluene, 0.24 mmol) in toluene (1 mL) at 30 °C.

methoxyphenyl (2ca–2cf) or a phenyl (2cg–2cm), respectively. The steric bulk of this group had little effect on the yield and selectivity of the reaction, which indicates that the regioselectivity was determined mainly by the aryl groups of the alkynes.

The reaction conditions were compatible with a range of functional groups: fluoride (2ab, 2ak, 2an), chloride (2ac, 2al, 2ao), bromide (2ad), trifluoromethyl (2ae), methoxy (2af, 2am, 2ap, 2ca–2cf), hydroxy (2ag), acetal (2ai), amino (2ah, 2cj, 2ck, 2cm), silyl (2aj) and thiophenyl (2cl). However, the functional groups of ester, amide, and nitro groups at the phenyl of the alkyne failed to give the desired products (data not shown). Notably, the chemoselectivity of the iron catalyst was very good: reaction of a substrate bearing an alkenyl group (2ci) was selective for the triple bond, leaving the double bond untouched. Taking advantage of this feature, we synthesized a series of novel conjugated dienyl aluminums 2da'–2di' from the corresponding conjugated enynes. As far as we know, the catalytic hydroalumination of conjugated enynes has not previously been reported. Noncatalytic hydroalumination reactions of conjugated enynes give poor yields⁸ or the products undergo further transformation under the reaction conditions.⁹

Interestingly, amino groups with little steric bulk and strong basicity could be used as directing groups to control the regioselectivity (3ea–3ee). For example, hydroalumination reactions of aryl- or alkyl-substituted propargylic amines bearing a tetrahydropyrrole or dimethylamino directing group specifically gave *cis*-addition products generated by addition of aluminum to the end of the triple bond attached to the amino group (3ea–3ee). This selectivity is completely different from that reported in the literature.^{5e,10} By using our hydroalumination protocol, we were able to add aluminum either to the alkyl end of aryl alkynes to afford 3ea and 3eb or to the amino-substituted alkyl end of alkyl alkynes to afford 3ec and 3ed. Similarly, by introducing a dimethylamino group at the *ortho* position of one of the aryl rings of a diaryl alkyne, we could selectively add aluminum to the amino-substituted aryl side of the triple bond to afford 3ee. Because a dimethylamino group can easily be transformed into other functional groups,¹¹ this protocol is expected to be useful for the synthesis of alkenes with three different aryl substituents. Using C1g as the catalyst, we also evaluated several symmetric and non-symmetric diaryl alkynes (1fa–1fd). The reactions of symmetric diaryl internal alkynes afford *cis*-addition products (2fa and 2fb) with high yields. The reactions of asymmetric diaryl internal alkynes also gave *cis*-addition products (2fc and 2fd) with high yields; however, only moderate regioselectivities were observed. In addition, the reaction with a terminal alkyne afforded a *cis*-addition product (2ga) with good yield but moderate regioselectivity.

As we did for aryl alkyl alkyne 1aa (Table 1, entries 1–4), we evaluated some typical Ti, Zr, and Ni catalysts^{3–5} in hydroalumination reactions of some of the other typical internal alkynes used in this study, including a vinyl alkyne (1ci), amino alkynes (1cj and 1ed), and a conjugated alkenyl alkyne (1de), and we compared the results with those obtained with our protocol (Table 2). These control experiments clearly showed that the iron catalyst was superior from activity, regioselectivity,

Table 2 Comparison of iron catalysts with other representative catalysts in hydroalumination reactions^a

Cat.	$\text{R}^1-\text{R}^2 + \text{DIBAL-H}$ (1.0 M in Hex) 1.2 equiv			
	$\xrightarrow[\text{THF/hexanes}]{\text{cat. (2.5 mol\%)}}$ 30°C			
	$\left[(\text{Bu})_2\text{Al} \begin{array}{c} \text{R}^1 \\ \diagup \\ \text{R}^2 \end{array} \right]$ $2' \text{ or } 3'$			
	2ci	2cj	2de	3ed
	Yield	Yield	Yield	Yield
	r.r.	r.r.	r.r.	r.r.
	Z/E	Z/E	Z/E	Z/E
[Fe]	75%	89%	91%	67%
	92 : 8	96 : 4	95 : 5	>98 : 2
	97 : 3	>98 : 2	>98 : 2	>98 : 2
[Ti]	19%	ND	17%	63%
	83 : 17	64 : 36	71 : 29	
	98 : 2	98 : 2	98 : 2	
[Zr]	ND	21%	ND	ND
	63 : 37			
	>98 : 2			
[Ni1]	93%	30%	79%	60%
	64 : 36	23 : 77	51 : 49	98 : 2
	97 : 3	65 : 35	81 : 19	84 : 16
[Ni2]	79%	29%	50%	58%
	53 : 47	9 : 91	60 : 40	98 : 2
	98 : 2	>98 : 2	95 : 5	60 : 40
None ^b	Messy	77%	25%	55%
	14 : 86	71 : 29	97 : 3	
	<2 : 98	20 : 80	3 : 97	

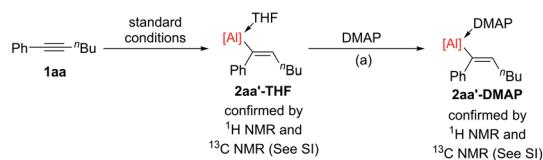
^a Reaction conditions: 1 (0.2 mmol), catalyst (0.005 mmol, 2.5 mol%), DIBAL-H (1.0 M in hexanes, 0.24 mmol) in THF (1 mL) at 30 °C. Isolated yields were given. The r.r. and Z/E were determined by ¹H NMR after quenching with D₂O or I₂ (30 °C, 30 min). [Fe] = C1g, C1h, or C1i, [Ti] = Cp₂TiCl₂, [Zr] = Cp₂ZrCl₂, [Ni1] = Ni(PPh₃)₂Cl₂, [Ni2] = Ni(dppe)Cl₂. ND = not detected. ^b Heated in hexanes at 50 °C for 12 h.

and stereoselectivity aspects, perhaps because of the unique steric and electronic structure of the phenanthroline iron complexes. These findings once again demonstrate that when an appropriate ligand is selected, iron catalysts can show activity and selectivity superior to that of other catalysts. Although the hydroalumination of alkynes with DIBAL-H could proceed in refluxing hexanes without catalysts,¹² the non-catalytic reactions of the above alkynes with DIBAL-H in refluxing hexanes generally exhibited poor yields and regioselectivities with opposite stereoselectivities (*trans*-addition as the major) compared to the iron catalysis (Table 2, bottom column).

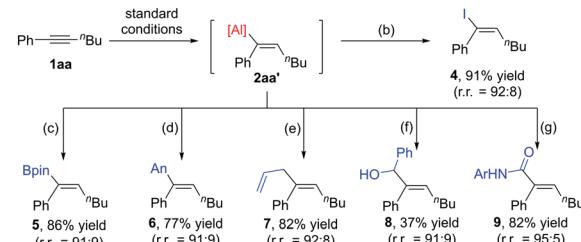
We were able to isolate alkenylaluminum-THF adduct 2aa'-THF in a glovebox and to determine its structure by NMR spectroscopy (Scheme 3a). In addition, 2aa'-THF could exchange the ligand with DMAP to generate alkenylaluminum-DMAP adduct 2aa'-DMAP, the structure of which was also determined by NMR spectroscopy.

Alkenylaluminum compounds are useful because their C-Al bonds readily undergo a variety of transformations. To

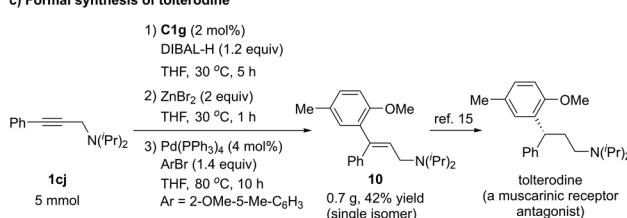
a) Characterization of the alkenylaluminium 2aa'



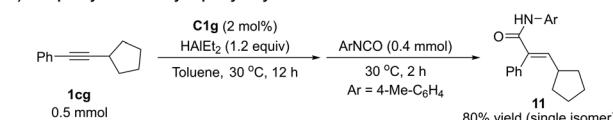
b) Transformations of hydroalumination product 2aa'



c) Formal synthesis of tolerodine



d) One-pot synthesis of cyclopentylacrylamide



Scheme 3 Characterization of a hydroalumination product and synthetic applications of iron-catalysed hydroalumination. Reaction conditions: ^a 1 equiv. of DMAP, 30 °C, 6 h. ^b 3 equiv. of I₂, 30 °C, 2 h. ^c 3 equiv. of ⁱPrOBpin, 80 °C, 24 h. ^d 1.1 equiv. of ZnBr₂, 1 h, 30 °C, then 4 mol% Pd(PPh₃)₄, 1.2 equiv. of 4-bromoanisole, 80 °C, 10 h. ^e 5 mol% CuCl, 3 equiv. of allyl bromide, 30 °C, 10 h. ^f 0.67 equiv. of PhCHO, 30 °C, 2 h. ^g 0.8 equiv. of ArNCO (*p*-tolyl isocyanate), 30 °C, 2 h.

demonstrate the utility of our protocol, we synthesized a number of trisubstituted alkenes by means of a one-pot procedure that combined iron-catalysed hydroalumination of internal alkyne 1aa with functionalization of the C-Al bond of alkenylaluminum product 2aa' (Scheme 3b). The alkenylaluminum 2aa' could easily transform into trisubstituted vinyl iodine 4 by capturing with iodine, and into vinylboronate 5 by capturing with ⁱPrOBpin. Alkenylaluminum 2aa' could also be easily converted into a vinylzinc compound, which underwent the Negishi coupling with 4-bromoanisole to give trisubstituted alkene 6. A copper-catalysed allylation reaction of 2aa' afforded diene 7.¹³ Alkenylaluminum 2aa' could be transformed into allylic alcohols 8 by carbonyl addition reactions with PhCHO and could be captured by *p*-tolyl isocyanate to afford α,β -unsaturated alkenylamide 9.¹⁴ In all these transformations, the olefin configurations were maintained.

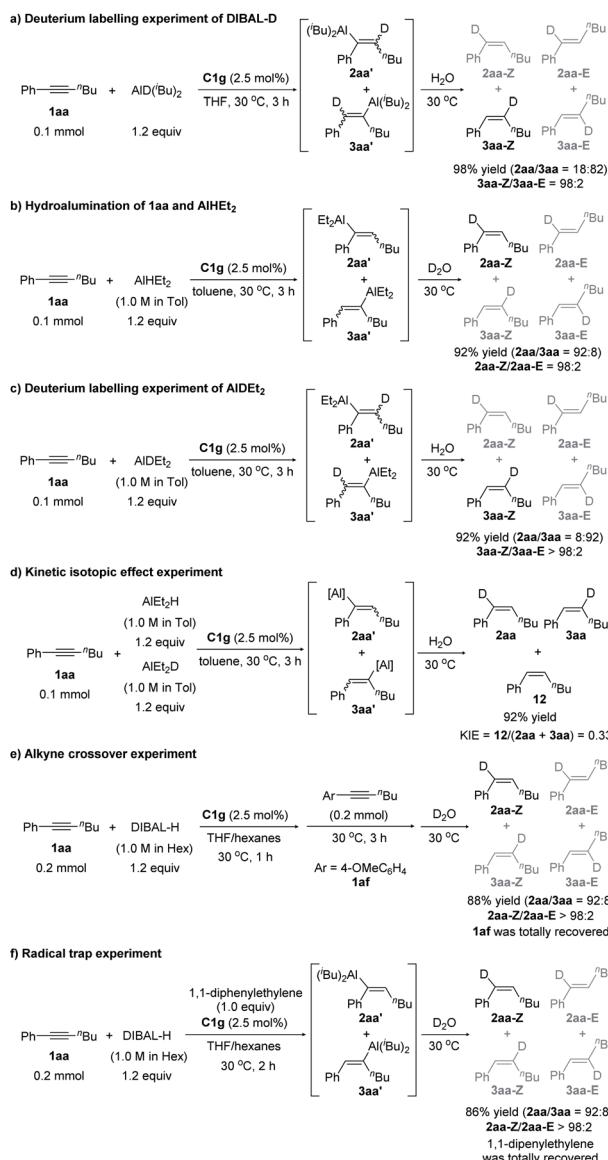
We also successfully used this hydroalumination protocol for the formal synthesis of a pharmaceutical compound (Scheme 3c). A C1g-catalysed gram-scale hydroalumination of propargylic amine 1cj following by trapping of the alkenylaluminum product with ZnBr₂ afforded trisubstituted vinylzinc,



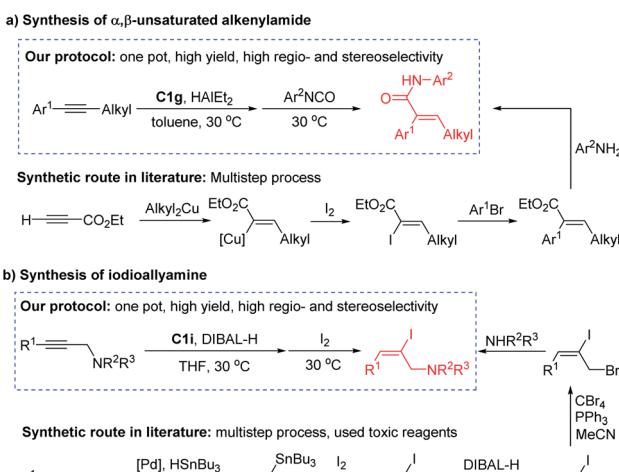
which underwent the Negishi coupling in one pot to generate a single isomer of trisubstituted allylic amines **10** in 42% overall yield. The alkene **10** is a key intermediate in the synthesis of the antimuscarinic drug tolterodine.¹⁵ We further prepared cyclopentylacrylamide **11** in one pot with high overall yield as a single isomer through the iron-catalysed hydroalumination of internal alkyne **1eg** and a following addition with isocyanate (Scheme 3d). The acrylamide **11** could be transformed into a glucokinase activator according to the reported procedure.¹⁶

It is worth mentioning that, compared with the synthetic routes reported in the literature, our hydroalumination protocol is more effective in synthesis of α,β -unsaturated alkenylamides and trisubstituted iodoallylamine with defined configuration (Scheme 4). The α,β -unsaturated alkenylamide is a useful building block for many bioactive compounds.¹⁶ The synthetic route to these compounds starting with ethyl propiolate comprises a four-step process of carbometalation, iodination, cross coupling, and amidation. In contrast, the iron-catalysed hydroalumination of easily available aryl-alkyl acetylene followed by addition of an isocyanate enabled a one-pot method to these important compounds (Scheme 4a). The trisubstituted iodoallylamine with defined configuration could be used to synthesize bioactive compounds, including the natural toxin product allopumiliotoxin-267A.¹⁷ However, the synthesis route of iodoallylamines in the literature involves multiple transformations of hydrostannation, iodination, reduction, bromination, and amination. The use of toxic organotin reagent and poor overall yield make this route less efficient. However, the protocol developed in this study enables a one-pot synthesis of trisubstituted iodoallylamine with high yield and high regioselectivity (Scheme 4b).

We next conducted a series of control experiments to gain some insight into the catalytic mechanism (Scheme 5). The reaction of alkyne **1aa** with DIBAL-D afforded deuterated products **2aa** and **3aa** in 98% yield (Scheme 5a), which clearly shows that the hydride of DIBAL-H other than the hydrogen of the isobutyl group transfers to the product. When HAlEt_2 was



Scheme 5 Control experiments.

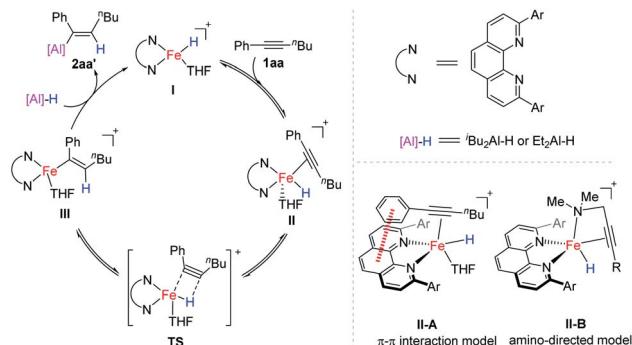


Scheme 4 Synthetic advantages of this protocol.

used, the chemo- and regioselectivity are similar to those of the reaction of DIBAL-H (Scheme 5b), which implies that the Al component might not be involved in the selectivity-determining step. The deuterium labelling experiment using DAIEt_2 gave similar results to those of DIBAL-D (Scheme 5c). The inverse KIE ($k_H/k_D = 0.33$) obtained in the competition experiments between DAIEt_2 and HAlEt_2 (Scheme 5d) indicates that the C–H bond formation is likely a fast-reversible step. At the end of the reaction of **1aa** and DIBAL-H, the addition of another internal alkyne **1af** could not afford crossover product **2af** (Scheme 5e), indicating that the whole reaction is irreversible. The addition of a radical scavenger, 1,1-diphenylethylene, had a neglectable effect on the outcomes of the model reaction of **1aa** and DIBAL-H (Scheme 5f), indicating that a radical pathway might not be an operative pathway.

Based on the above control experiments and by analogy to the related literature,^{1,2} we proposed a catalytic cycle of iron-





Scheme 6 A plausible catalytic cycle and regioselectivity determining models.

catalysed internal alkyne hydroalumination as shown in Scheme 6. Active $\text{Fe}(\text{II})\text{-H}$ complex **I** is generated by reducing a 2,9-diaryl-1,10-phenanthroline iron(II) complex with DIBAL-H through a similar pathway to that reported in the literature using other iron complexes.¹⁸ The migratory insertion of the C-C triple bond of alkyne **1aa** into the Fe-H bond through a transition state (**TS**) affords the alkenyl iron intermediate **III**. At the same time, the *cis*-addition can be expected in this inner-sphere migratory insertion step, which determines the stereoselectivity of the resulting alkene. The following transmetalation of alkenyl iron intermediate **III** with DIBAL-H produces the desired hydroalumination product and regenerated Fe-H catalyst **I**. The fact that the two aluminum hydride reagents, DIBAL-H and HAiEt_2 , give almost the same regional selectivity (Scheme 5b) indicates that the aluminum reagent might not participate in the step of hydride transfer (**II**-**III**). The remarkable ether solvent effect on the regioselectivity (Table S5†) indicates that these solvents might participate in the hydride transfer step by coordinating with the iron catalyst. Similar to our previous finding in an iron-catalysed hydro-silylation of olefins,^{2g} there may be significant $\pi-\pi$ interaction between the backbone of the 1,10-phenanthroline ligand and the aryl of the alkyne substrate, which leads the hydride to transfer to the alkyl substituent side of alkynes (as shown in the **II-A** model), and results in the observed regioselectivity. For the reactions with propargylic amines bearing a tetrahydropyrrole or dimethylamino as a directing group, the iron catalyst may coordinate with the amino group, direct the hydride transfer to the triple bond, and exhibit a unique regioselectivity (as shown in the **II-B** model). However, we cannot rule out the other pathways, including an $\text{Fe}(0)\text{-Fe}(\text{II})$ catalytic cycle, at the current stage. The more detailed mechanistic studies are still underway in our laboratory.

Conclusions

In conclusion, we have described herein the first protocol for iron-catalysed hydroalumination of internal alkynes. This mild, efficient, highly selective protocol is operationally simple and has a wide substrate scope and good functional group tolerance. Using commercially available DIBAL-H as the

hydroalumination reagent and readily available alkynes as substrates, we synthesized various new alkenylaluminum compounds, which could be easily converted to trisubstituted alkenes, including key intermediates in the synthesis of pharmaceutical compounds. Compared with catalysts reported in the literature, the iron catalysts developed in this study show superior activity, chemoselectivity, and regioselectivity, and they enabled unprecedented amino-directed hydroalumination reactions of internal alkynes. Our findings clearly demonstrate the potential of iron catalysts not only to replace precious metals but also, more importantly, to show superior performance.

Author contributions

S.-F. Z. supervised this study. S.-F. Z. and W.-T. L. conceived this work, designed the experiments, analyzed the data, and wrote the manuscript. W.-T. L., M.-Y. H., J.-W. X. and X.-Y. Z. conducted the experiments or analyzed the data. All authors have given approval to the final version of the manuscript.

Conflicts of interest

The authors declare no competing financial interest.

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