Keynote Article*

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Nickel catalysed coupling of allylamines and boronic acids

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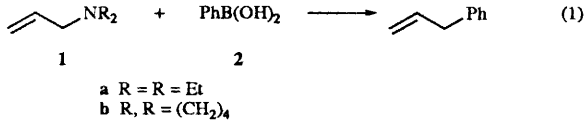
Allylamines function as substrates for cross-coupling with boronic acids in the presence of nickel(0) catalysts rather than palladium(0) catalysts. Aryl,- vinyl- and methyl-boronic acids function well. With vinyl derivatives, *E*-isomers couple more efficiently than *Z*-isomers and both fully retain the geometrical integrity. Methylations preferably employ the boronic esters like 2-methyl-1,3,2-benzodioxaborole or 2-methyl-1,3,2-dioxaborolane rather than methylboronic acid. The stereochemistry of the reaction involves a net inversion with respect to the allylamine. The regioselectivity is a function of ligand. Generally, sterically bulky donor phosphines promote new C–C bond formation at the less substituted position. Bidentate ligands, notably 1,1′-binaphthyl-2,2′-ylbis(diphenylphosphinite) (BINAPO), promote new C–C bond formation at the more substituted allyl terminus. The amines appear to be the preferred partner compared to allyl alcohols and esters with the boronic acids and give higher stereospecificity.

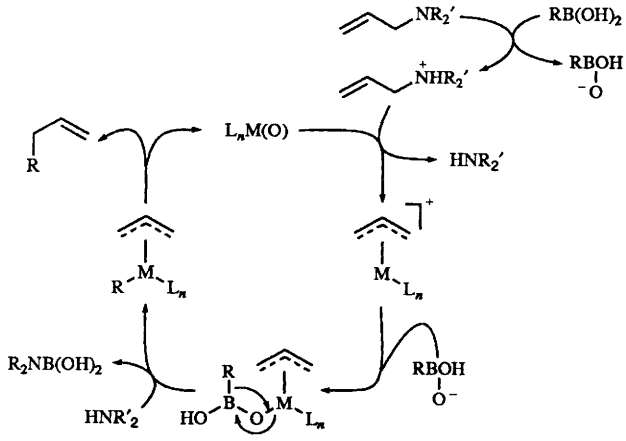
Introduction

Chemoselectivity in allylic alkylations depend upon the reactivity of the two partners. By using transition metals, allylic electrophiles which are relatively unreactive, such as allylic carboxylates, serve as adequate partners with 'soft' carbon nucleophiles, like anions derived from carbon acids of pK < 20, and heteroatom nucleophiles like amines, sulfinate, phosphinate, *etc.*[1] Extending the reaction to 'harder' carbon nucleophiles like alkyl, allyl, benzyl, vinyl and aryl *etc.* normally require organometallics of sufficient reactivity that chemoselectivity may be compromised. The well known ability of organoboranes to undergo transmetallation which allows them to participate in cross-couplings[2] and which stands in contrast to their normal lack of reactivity as a nucleophile induced us to consider their effectiveness in allylic alkylations.[3]

One of the limitations in the nucleophilic substitutions of allylic esters, especially in reactions with stronger nucleophiles, is acyl oxygen rather than alkyl oxygen cleavage. Use of leaving groups which lack this alternative cleavage mode removes this potential limitation. Considering the affinity of boron for nitrogen and the prospect that such amine coordination would increase the nucleophilicity of carbon bound to boron suggested the employment of allyl amines as substrates. While amines normally do not function as leaving groups in transition metal-catalysed reactions, the corresponding ammonium salts may.[4] Thus, boron coordination may activate the allylamine towards ionization. Furthermore, since boronic acids participate in cross-coupling in the presence of base, the use of a pro-leaving group which will depart after serving as a base such as an amine makes it an attractive possibility. Thus, Scheme 1 represents the proposed reaction. While the boronic acid is portrayed as a simple Bronsted acid, it could function as a Lewis acid whereby amine activation is achieved by coordination to boron. The resultant aminoboronate would then function in analogous fashion to the borate except that transfer of R would be facilitated by amine coordination. Another attractive feature of this strategy is the feasibility of utilizing water as a solvent—an environmentally desirable goal.

Before embarking on this program, a feasibility study was performed using a simple allylamine **1** and phenylboronic acid **2** as shown in eqn. (1). Utilizing tetrakis(triphenylphosphine)palladium **3** generated *in situ* from $Pd_2(dba)_3{\cdot}CHCl_3$ and triphenylphosphine gave no coupling in the absence of additional base. On the other hand, a 50% yield of allylbenzene arose upon sonicating at ambient temperature a solution of **1a, 2** in benzene and palladium catalyst with suspended powdered potassium hydroxide. Other solvents (*e.g.*, THF† < dioxane, DMSO,† MeCN *etc.*) and other bases (*e.g.*, NaOMe, NaOMe, Ag_2O, Ag_2CO_3, TlOEt, *etc.*) proved inferior. Sonication decreased the reaction time and homocoupling (*i.e.*, biphenyl formation) to <1% allowing the reaction to be performed at the stoichiometric 1:1 ratio of reactants. Changing the amine to the pyrrolidinyl derivative **1b** increased the yield to 61%. With the success of the pilot experiments, we turned to the synthesis of the α-allylated allylamines because of their expected higher reactivity than their regioisomers and their alkylations.





Scheme 1 Proposed allylation of 'hard' nucleophiles

Synthesis of allyl amines

While many methods are available for the synthesis of allylic amines including transition metal-catalysed allylation,[5] we focused on the convenience of generating α-alkylated allylamines by the addition of Grignard reagents to α-amino nitriles [eqn. (2) and Table 1].[6]

† THF = tetrahydrofuran, DMSO = dimethyl sulfoxide.

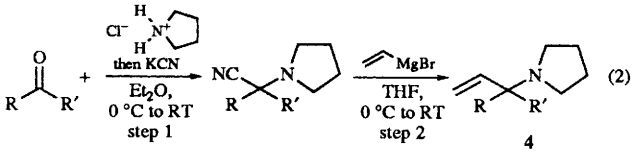
Table 1 Synthesis of α-alkylated allylamines

Entry	R	R^1	Yield (%) Step 1	Yield (%) Step 2	Compd.	Ref.
1	Me	H	89	82	**4a**	7*a*
2	Pr^i	H	87	85	**4b**	6*c*, 7*b*
3	Ph	H	83	57	**4c**	7*c*
4	Me	Me	95	68	**4d**	7*d*
5	—$(CH_2)_5$—		78	62	**4e**	7*e*

Table 2 Regioselectivity as function of ligand with 3-pyrrolidin-1-ylbut-1-ene

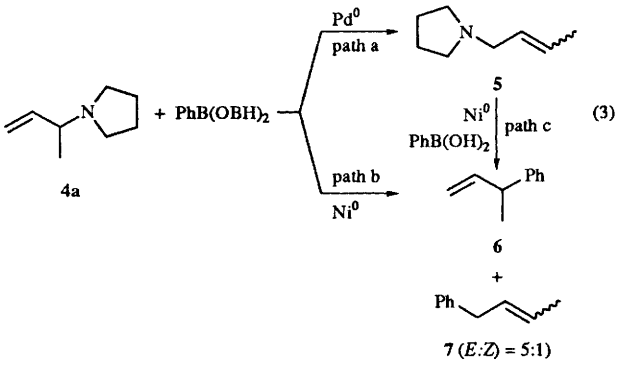
Entry	Ligand	Ratio **6**:**7**	Yield (%)	Entry	Ligand	Ratio **6**:**7**	Yield (%)
1	PPr^i_3	1:3.6	62	9	PPh_3	1.6:1	72
2	PBu_3	1:1.6	68	10	TFP	1.6:1	54
3	TTMPP	1:1.5	67	11	dppf	1.7:1	56
4	BBEDA	1:1.1	30	12	TPTP	1.8:1	68
5	TTPP	1.1:1	30	13	BINAP	2.1:1	63
6	$P(OPr^i)_3$	1.2:1	29	14	dppe	2.2:1	49
7	$P(c\text{-}C_6H_{11})_3$	1.5:1	53	15	dppb	2.6:1	65
8	$P(OPh)_3$	1.5:1	35	16	BINAPO	3.6:1	69

[a] All yields and ratios were determined by GC analysis using tetradecane as an internal standard. [b] Reaction performed by generating catalyst from 10 mol % [$Ni(COD)_2$] and 20–40 mol% ligand in benzene at reflux with 10 mol % KOH.



Arylation of allylamines

The allylamine **4a** when subjected to the coupling conditions shown in eqn. (1) in either benzene or THF gave only the rearranged allylamine **5**, slowly at room temperature (RT) and rapidly at the reflux temperature of THF [eqn. (3) path a].



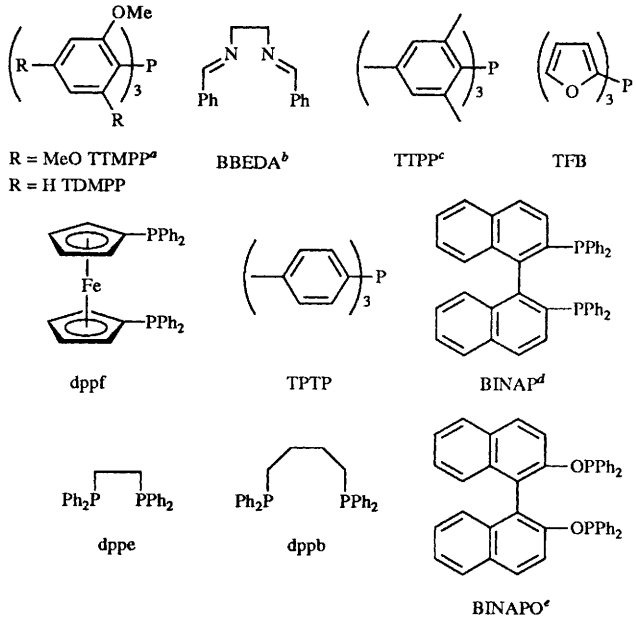


Chart 1 Ligands [a] Ref. 8*a*. [b] Ref. 8*b*. [c] Ref. 8*c*. [d] Ref. 8*d*. [e] Ref. 8*e*

Independent experiments confirmed the lack of reactivity of crotylamines like **5** under these conditions. On the other hand, a switch to tetrakis(triphenylphosphine)nickel (10 mol %) in benzene at reflux with 10 mol % potassium hydroxide gave a 64% yield of a 1.6:1 ratio of **6** and **7**, respectively. The nickel catalyst when generated *in situ* by treating $Ni(acac)_2$ with triethylaluminium (2.2 equiv.) and triphenylphosphine (4 equiv.) (both relative to nickel salt) improved the yield to 87% in toluene at reflux without any additional base required. In contrast to the situation with palladium catalysts, the allylically rearranged amine **5** under the same conditions gave 76% yield of the same products in the same ratio within experimental error. Thus, we did not discern whether any internal return of the amine competed with the coupling process.

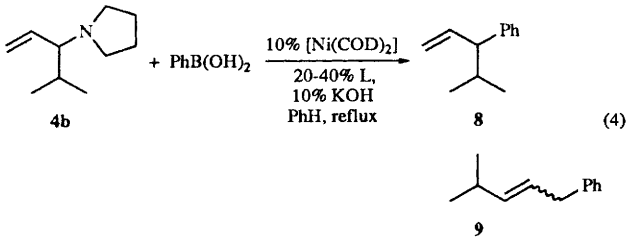
The unexpected regioselectivity wherein bond formation occurred preferentially at the more substituted terminus led us to probe the effect of ligands on the ratio of **6**:**7** for the reaction illustrated in eqn. (3), path b. The results are summarized in Table 2 and Chart 1. While no quantitative correlations arise with electronic or steric effects, some general trends emerge. Stronger donating ligands and sterically more demanding ones tend to favour bond formation at the less substituted position. On the other hand, sterically less demanding bidentate and electronically more accepting ligands favour bond formation at the more substituted allyl terminus.[9] Thus, the ratio can be inverted by switching from triisopropylphosphine favouring **7** to BINAPO favouring **6**.

A similar trend was observed with a sterically more

Table 3 Regioselectivity as function of ligand with 4-methyl-3-pyrrolidino-1-ylpent-1-ene

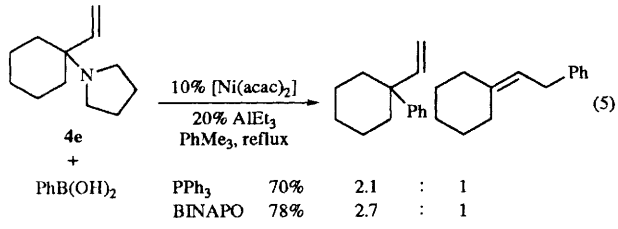
Entry	Ligand	Ratio **6**:**7**	Yield (%)	Entry	Ligand	Ratio **6**:**7**	Yield (%)
1	PPr^i_3	1:3.2	76	6	PPh_3	1.6:1	68
2	PBu_3	1:2.0	70	7	TPTP	1.7:1	76
3	TTMPP	1:1.5	60	8	dppf	1.7:1	56
4	TOMPP	1:1	41	9	dppb	2.8:1	65
5	$P(OPh)_3$	1.5:1	35	10	BINAPO	3.1:1	68

demanding allylamine partner as summarized in eqn. (4) and Table 3. Again, either regioisomer becomes available by



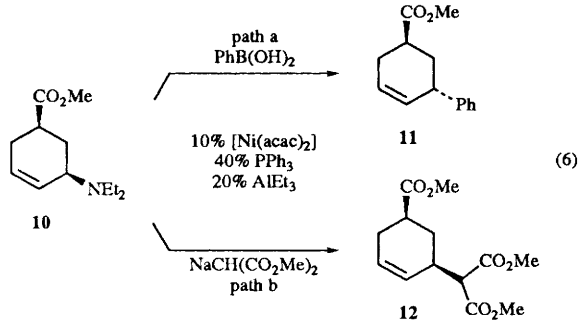
(4)

switching ligands from triisopropylphosphine to BINAPO. Creating a quaternary centre does not deter this preference although it is diminished somewhat as illustrated in eqn. (5)



(5)

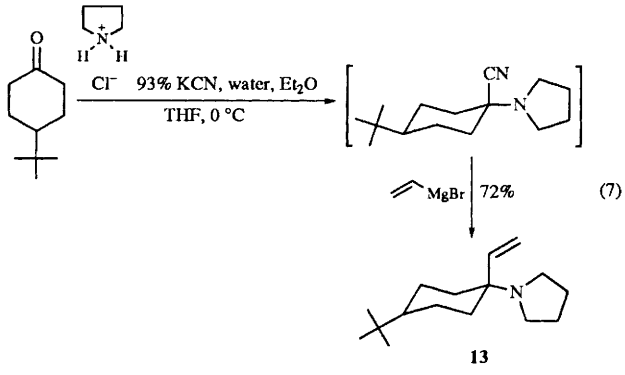
The stereochemical course of the process was probed with our 'standard' 5-methoxycarbonylcyclohexenyl system [10] which translates to allylamine **10** in this case. With phenylboronic acid, a single stereoisomer (> 100:1) which was assigned the *trans* stereochemistry **11** by comparison to an authentic sample resulted in 57% yield [eqn. (6), path a]. This stereochemistry is



(6)

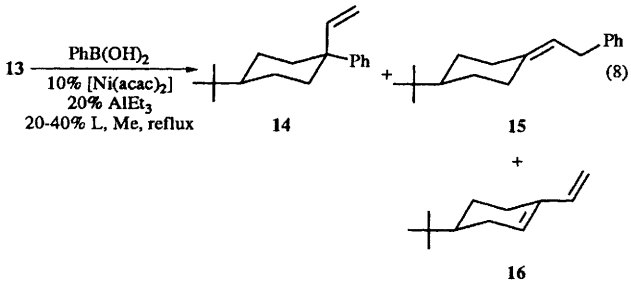
the reverse of that obtained from the reaction of soft nucleophiles with the corresponding ester [10] but in agreement with the stereochemistry of the reactions of phenylzinc chloride.[11] To demonstrate that the change of leaving group from ester to amine did not affect stereochemistry, we performed the reaction of **10** with a stabilized nucleophile which gave the 'expected' product of net retention **12** in 44% yield. To determine the relative reactivity of 'hard' and 'soft' nucleophiles,[1c,12] a competition experiment wherein equimolar amounts of phenylboronic acid and dimethyl sodiomalonate competed for 1 equiv. of **10** under the conditions of eqn. (6). Only **11** was obtained in 54% yield.[13]

The stereochemistry of addition to create a quaternary centre was probed with the 4-*tert*-butylcyclohexanone system as the substrate. Using the standard α-amino nitrile strategy, 4-*tert*-butylcyclohexanone was converted into a mixture of amino nitriles [diastereoisomer ratio (dr) 6:1]. Previous correlations[14] establish that the ^1H NMR shifts for the *tert*-butyl group correlate with the stereochemistry in which they are at lower field when the nitrile group is axial. In accord with this observation, the δ 0.88 shift for the major isomer compared to δ 0.845 for the minor one indicates the major isomer has the structure depicted. This stereochemistry is irrelevant however. Its reaction with vinylmagnesium bromide gives **13** as a single stereoisomer which was tentatively assigned the stereochemistry depicted in **13** [eqn. (7)]. Given that vinylmagnesium bromide



(7)

preferentially attacks 4-*tert*-butylcyclohexanone in an axial manner and that increasing the size of the ring heteroatom substituent should increase the bias for axial attack, axial addition of the Grignard reagent would be expected. Further, such a stereochemistry for addition of a Grignard reagent to an iminium ion derived from 4-*tert*-butylcyclohexanone has been reported.[14,16] Coupling of **13** with phenylboronic acid led to three products as illustrated in eqn. (8) and Table 4. The major



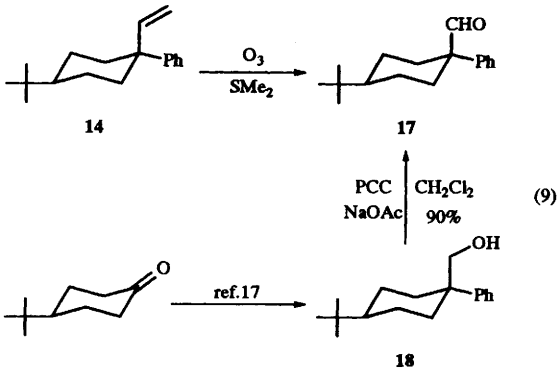
(8)

coupling product in all cases was **14** which was formed as a single diastereoisomer. The stereochemistry was proven by correlation of its ozonolysis product aldehyde **17** to an authentic sample prepared from the known alcohol **18**[17] which,

Table 4 Ligand effect on phenylation of 1-*tert*-butyl-4-pyrrolidin-1-yl-4-vinylcyclohexane

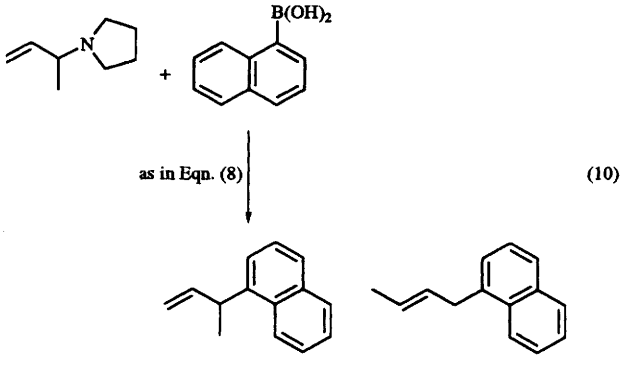
Entry	Ligand	Ratio L:Ni	Ratio **14**:**15**:**16**	Yield (%)
1	PPh_3	4	4.2:1:0.2	57
2	PPh_3	2	4.0:1:0.3	22[a]
3	$P(c\text{-}C_6H_{11})_3$	4	3.6:1:0.2	58
4	TOMPP	4	3.4:1:0.2	30
5	BINAPO	1	2.2:1:2.5	50
6	BINAPO	2	0:0:100	41

[a] Catalyst decomposed after 30 min.



in turn, was derived from 4-*tert*-butylcyclohexanone [eqn. (9)]. It appears this reaction proceeded with net retention of configuration.[18]

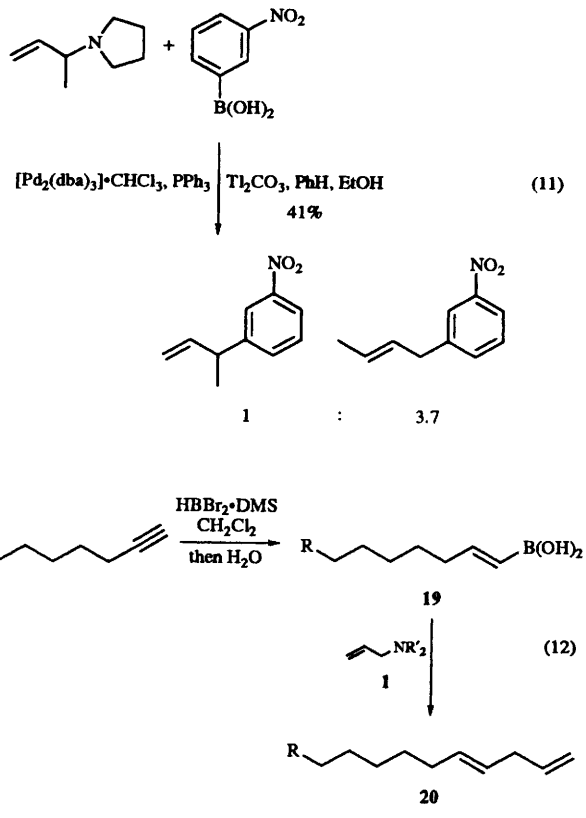
Variation of the aryl group was briefly examined. 1-Naphthylboronic acid[19] gave excellent yields of coupling products [eqn. (10)] with preference for coupling at the more



substituted position. On the other hand, our standard conditions led to poor results with 3-nitrophenylboronic acid. The best results employed palladium catalysts[20] which favoured attack at the less substituted allyl terminus [eqn. (11)].

Cross-coupling with other boronic acid derivatives

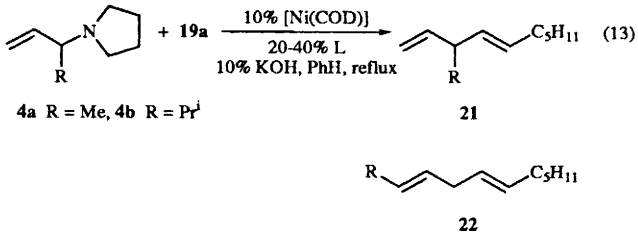
The ready availability of vinylboronic acids by hydroboration of alkynes with dibromoborane led us to investigate their participation as the nucleophilic partner in the nickel-catalysed cross-coupling reactions [eqn. (12)].[21] As previously noted, use of the pyrrolidine derivative gave better yields than the diethylamino substrate. The quality of the boronic acid affected the yield. For example, the vinylboronic acid **19c** gave only a 37% yield of **20c** if it was employed crude but a 69 and a 76%



	R	R′, R′	Catalyst	Yield (%)
(a)	H	Et, Et	$[Ni(PPh_3)_4]$, 10% KOH	45
(b)	H	$-(CH_2)_4-$	As in Eqn. (8)	72
(c)	C_5H_{10}	Et, Et	As in Eqn. (8)	See text

yield after one and two recrystallizations. The contaminants in the vinylboronic acid promoted simple protonation.

Vinylation exhibited the same regioselectivity as illustrated in eqn. (13) and Table 5 as the phenylation reaction. With both **4a**



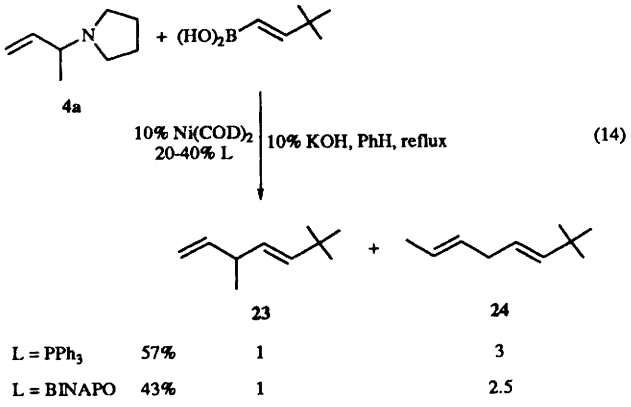
and **4b** either regioisomer could be made to dominate by switching from the sterically demanding donor ligands like triisopropylphosphine and TTMPP to BINAPO. In contrast to the phenylation, triphenylphosphine as ligand showed no regioselectivity. The choice of catalyst precursor had no effect on regioselectivity but generation of the catalyst *in situ* by reduction of $[Ni(acac)_2]$ did improve the yield (entry 3). Increasing the steric hindrance of the substituent on the vinylboronic acid changed the regioselectivity to favour attack at the less substituted allyl terminus to give **24** [eqn. (14)] rather than **23**.

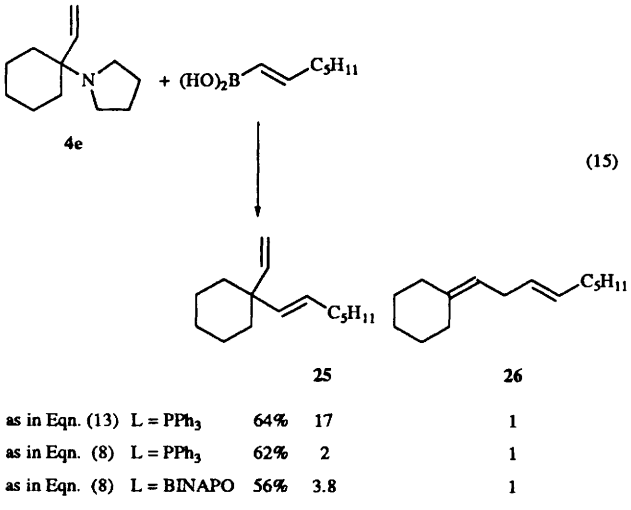
The choice of catalyst precursor did affect the regioselectivity with respect to formation of quaternary centres [eqn. (15)]. Use of $Ni(COD)_2$ strongly favoured formation of the quaternary product **25** even with triphenylphosphine as ligand. In this case, a small by-product arising from homocoupling of the

Table 5 Regioselectivity of vinylation

Entry	Substrate	Ligand	Ratio 21:22	Isolated yield (%)	Entry	Substrate	Ligand	Ratio 21:22	Isolated yield (%)
1	**4a**	PPr^i_3	1:4.1	52	7	**4a**	BINAPO	3.1:1	55
2	**4a**	TTMPP	1:3	53	8	**4b**	TTMPP	1:3.1	57[c]
3	**4a**	PPh_3	1:1	60, 71[a]	9	**4b**	PPh_3	1:1.2	55
4	**4a**	dppf	2.1:1	57	10	**4b**	PPh_3	1:1	65[b]
5	**4a**	dppe	2.2:1	49	11	**4b**	dppe	1.5:1	51
6	**4a**	BINAPO	2.5:1	68[b]	12	**4b**	BINAPO	2.2:1	56

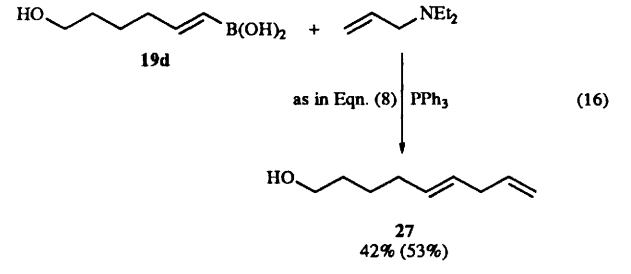
[a] Catalyst generated from 10% $[Ni(acac)_2]$ and 20% $AlEt_3$. [b] 20% $[Ni(CDD)_2]$ employed. [c] Yield determined by GC with tetradecane as internal standard.

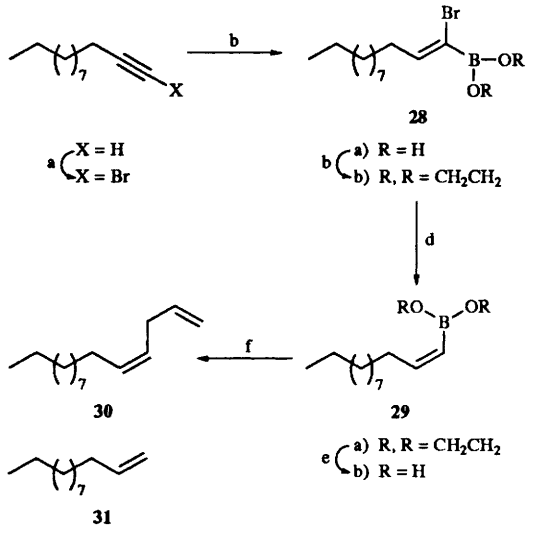




vinylboronic acid was also isolated. On the other hand, this selectivity decreased generating the active catalyst by *in situ* reduction of $[Ni(acac)_2]$ with triethylaluminum. We had not previously experienced such a dramatic dependence on the method of formation of the active catalyst and have no explanation for this sudden change.

Introducing a free hydroxy group on the boronic acid slows the addition but cross-coupling does succeed [eqn. (16)].[22] The





Scheme 2 Preparation and coupling of *cis*-vinylboronic acids

allylated product **27** was isolated in 42% yield along with 21% of recovered starting material. Thus, a 53% yield based upon recovered starting material was achieved in an 18 h reaction time in comparison to 5–10 h for complete consumption of starting material in most cases.

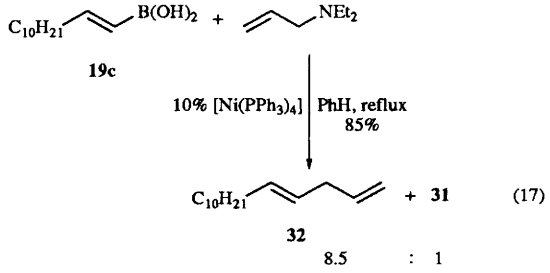
The olefin geometry also affected the process. Following a protocol derived from the work of Suzuki *et al.*[23] and Brown *et al.*[24], the bromoboronate ester **28** was prepared as outlined in Scheme 2. In contrast to their report, lithium triethylborohydride proved superior to potassium triisopropoxyborohydride for formation of **29a** which was hydrolysed during work-up to give **29b**. Purification proved easier by either chromatography or distillation at the stage of the boronic ester **29a** which reformed simply upon mixing ethylene glycol with crude boronic acid in pentane. Upon hydrolysis of purified boronic ester, *Z*-boronic acid formed a white solid that readily recrystallized from benzene. Cross-coupling of **29b** with allyldiethylamine [10% $[Ni(Ph_3P)_4]$, PhH, reflux] gave the cross-coupling product **30** with maintenance of olefin geometry but only as the minor product, the major product being the protonation product **31** (**30**:**31**, 1:11). On the other hand, reaction of the boronic ester **29a** gave the cross-coupling product **30** as the major product but still with considerable amounts of protonation (**30**:**31**, 1.7:1). On the other hand, the corresponding *E*-boronic acid gave the coupling product **32** with good selectivity and in good yield [eqn. (17)].

The extension of the reaction to methylations required the development of a suitable reagent. The insolubility of methylboronic acid **33**, readily available from its commercially available anhydride trimethylboroxine **34**,[25] led to the synthesis of the esters **35a, b** simply by allowing **34** to react with ethylene glycol[26] and catechol[27] respectively.[28] Palladium(0) catalysts showed no reactivity for cross-coupling with boronic

Table 6 Methylation of 1-pyrrolidin-1-yl-1-vinylcyclohexane[a]

Entry	Catalyst[b]	Ligand	Methylating agent	Ratio[c] **36**:**37**	Yield[d] (%)
1	A	PPh_3	**33**	2.5:1	37
2	A[e]	PPh_3	**33**	2.2:1	42
3	A	PPh_3	**34**	2.2:1	41
4	A	BINAPO	**34**	—	N.R.
5	A	PPh_3	**35a**	2.2:1	41
6	B[f]	PPh_3	**35a**	2.1:1	42 (57)
7	B[g]	PPh_3	**35a**	2.1:1	56 (65)
8	B[g,h]	BINAPO	**35a**	3.4:1	41
9	B[f]	PPh_3	**35b**	2.1:1	40
10	B[g]	PPh_3	**35b**	2:1	39

[a] All reactions were performed in benzene at 110 °C unless stated otherwise. [b] Catalyst A = 10% $[Ni(COD)_2]$ with 4P/Ni; B = 10% $[Ni(acac)_2]$ + 20% $AlEt_3$ with 4P/Ni. [c] Ratios determined by GC. [d] All yields are for isolated pure product except for those listed in parentheses which are yields determined by GC using tetradecane as an internal standard. [e] Triethylamine (1.5 equiv.) added. [f] Toluene employed as solvent at 110 °C. [g] No solvent at 110 °C. [h] 5% Catalyst employed.



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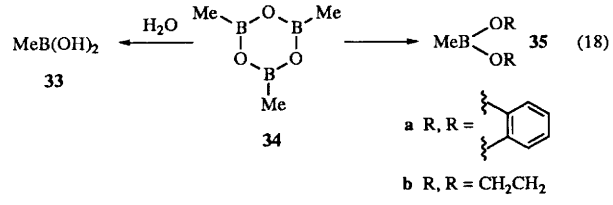
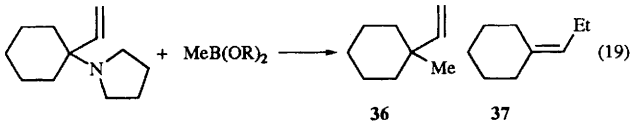


(18)

acid **33** whereas the nickel catalyst gave the desired coupling as illustrated in eqn. (19) and Table 6. It is highly likely that the



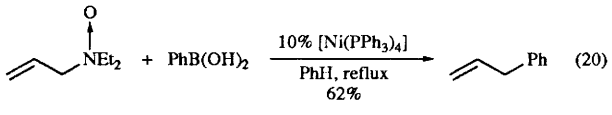
(19)

volatility of the products accounts for the modest yields of isolated purified product. Indeed, a comparison of GC and isolated yields in entries 6 and 7 support this contention. Nevertheless, trends are clear. All four methylating agents behave similarly but the catechol ester appears to give the best yield (entry 7). Use of triethylamine improves the reaction with methylboronic acid (entry 2) but stops reaction with the anhydride **34**. BINAPO serves as a suitable ligand only with the esters **35** with the normal enhancement of selectivity for alkylation at the more hindered allyl terminus (entry 8). The best conditions involve performing reactions neat–a protocol that also improves the turnover if the temperature range is kept in the range 100–120 °C.

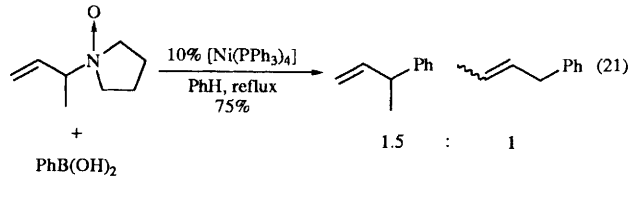
Discussion

The current results indicate that arylation, vinylation, and methylation of allylamines preferentially at the more substituted allyl terminus proceeds satisfactorily in the presence of a nickel catalyst. How the amine is activated as a leaving group in these reactions cannot be unequivocally attributed to the boronic acid serving as either a Bronsted or a Lewis acid. However, several observations support the latter. First, addition of base beyond that of the substrate is normally required. Since the increased basicity of the medium should diminish protonation of the substrate, a retardation rather than enhancement of the reaction would have been expected if Bronsted acidity was important. Second, boronic esters which can only serve as Lewis acids also participate as the nucleophilic partners. Third, the higher yields obtained with allylpyrrolidine compared to allyldiethylamines suggest the importance of steric accessibility of the nitrogen which should be more significant when the amine functions as a Lewis base than a Bronsted base. Comparison of leaving groups also addresses this issue. Acetate, carbonate, and even hydroxyl can participate whereas allyl chlorides and bromides do not. Furthermore, the amines are more reactive than the oxygen leaving groups. Clearly, there is no correlation with leaving group ability. There appears to be a correlation with the Lewis basicity with respect to boron as a Lewis acid.

To probe the role of base in promoting the cross-coupling, we explored the amine oxide leaving group with the notion that the liberated hydroxylamine might function in the same capacity. As shown in eqns. (20) and (21), reactions proceed well. Strikingly, no base is required in these couplings.

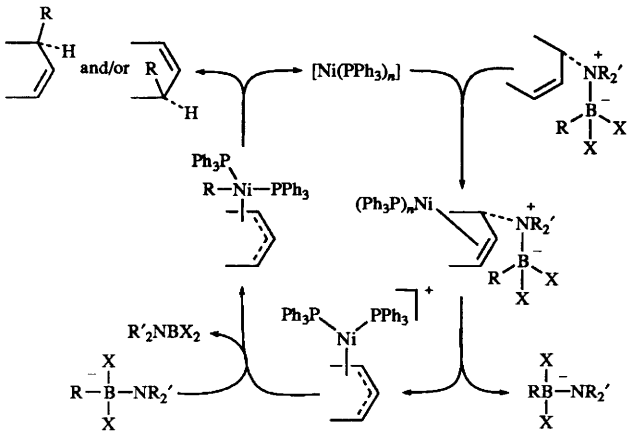


(20)



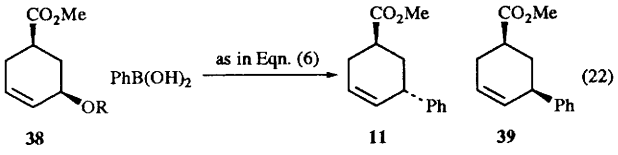
(21)

The stereochemistry indicates that the replacement of the C–N bond by a C–C bond occurs with net inversion of configuration. Extrapolating from the mechanism of palladium-catalysed reactions[10,12a] then leads to the mechanism depicted in Scheme 3. This rationale implies that the leaving group would influence the rate of the transmetallation step but would not influence the regioselectivity nor the stereochemistry of the reductive elimination.



Scheme 3 A mechanistic rationale

To probe the latter, the stereochemical bias for inversion of configuration was probed as a function of leaving group. In contrast to the allylamine **10** [eqn. (6)] which gave **11** with a 100:1 dr, the use of the acetate **38a** or alcohol **38b** gave a dr of 2–7:1 still favouring the product of net inversion **11** over net retention [eqn. (22)]. A reasonable explanation invokes



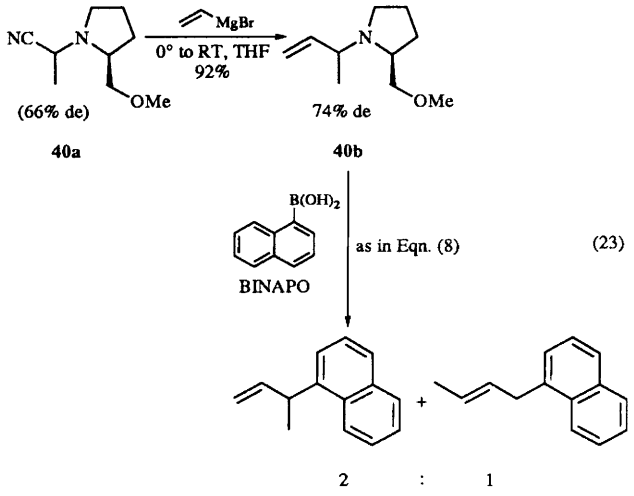
38

a R = Ac
b R = H

competition between loss of stereochemistry in the π-allylnickel intermediate and the rate of transmetallation from boron to nickel. With allylamine substrates, coordination of the leaving group to boron creates a more reactive transmetallating agent, thereby preventing loss of the stereochemical information of the starting material. On the other hand, the lack of such coordination to boron with the oxygen leaving groups allowed the loss of stereochemistry (such as by nickel-nickel substitution)[29] to compete with transmetallation and thereby diminished the diastereoselectivity. Further support for this interpretation arose from the observation that increasing the rate of the transmetallation in the case of **38b** by either increasing the concentration of phenylboronic acid or by adding potassium hydroxide to form an ate complex increased the diastereoselectivity from an initial ratio for **11**:**29** of 2:1 to 4.8:1 and 7:1, respectively.

The independence of the regioselectivity with respect to the leaving group was established in three ways. First, the positional identity of the leaving group in the starting material had no effect on the regioselectvity of the product [(eqn. (3)]. Second, changing the nature of the amine had no significant effect. Thus, the proline-derived leaving group as in **40b** [eqn. (23)] derived from the amino nitrile **40a** prepared in the usual fashion gave the same products in about the same ratio with BINAPO as ligand as with pyrrolidine as leaving group [eqn. (10)]. Likewise, the amine oxides [eqn. (21)] gave a similar product ratio as the amine [eqn. (3)]. Third, using substrates with oxygen-based leaving groups gave the same product ratios within experimental error as substrates with amine leaving groups.[30]

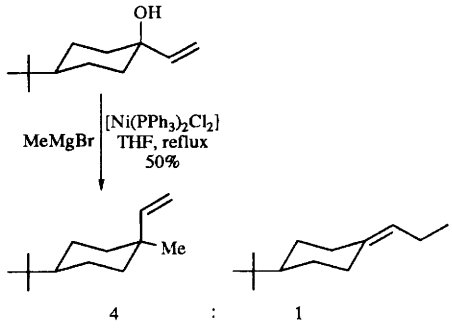
The total loss of stereochemistry in the arylation of **40b** also supports the intervention of π-allylnickel intermediates. First, if



40a **40b**

the leaving group was still involved during the coupling step, its being enantiomerically pure in the case of **40b** should have induced some asymmetry in the product-forming step. It did not. Second, since the α-methylallyl moiety was 74% enantiomerically pure, the absence of any stereoinduction requires the nickel to migrate from one enantiotopic face of the 1-methylallylnickel to the other either by π-σ-π internal migration or nickel-nickel substitution. Of the two paths, the former appears more important considering the complete loss of stereochemistry. The latter path, which is second order in nickel, would have been expected to have some stereochemical memory in the product considering the low concentration of nickel catalyst.

The regioselectivity of the process involves a more subtle interplay of effects. The electronic bias of π-allylmetal complexes wherein the more substituted terminus possesses the lower electron density favours attack of nucleophiles at that carbon.[31] Such a regioselectivity has been observed by Felkin in the nickel-catalysed methylation of allyl alcohols with Grignard reagents as illustrated in eqn. (24).[32] Steric effects oppose this



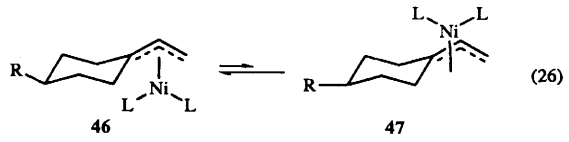
selectivity, preferentially delivering the nucleophile to the less substituted terminus. This competition between electronic and steric effects may account for the diminution of the regioselective bias towards coupling at the more substituted terminus in going from the methylallyl to isopropylallyl to 1, 1-pentamethyleneallyl systems [eqns. (3), (4) and (5)].

The effect of ligand on regioselectivity may be rationalized to some extent using this same competition. Electron-rich ligands highlighted by the trialkylphosphines favour attack at the less substituted position. Within a series, the sterically more hindered ligands also favour that bias. Thus, triisopropylphosphine has the highest selectivity for attack at the primary

position. In the electron-rich aryl series, the order TPTP < TTPP ~ TOMPP < TTMPP (see Chart 1) favouring attack at the less substituted position represents a balancing of the degree of electron donation and steric effects. Better acceptor ligands like the phosphites and TFP begin to favour attack at the more subsituted position since they magnify the differential charges on the allyl unit. The biggest change occurs upon switching from monodentate to bidentate ligands wherein attack invariably favours the more substituted position.

A possible explanation is outlined in eqn. (25). Transmetallation from boron to nickel should initially place the aryl (or alkenyl or methyl) group on an apical position as in **41**. If collapse to product is faster than equilibration, then the ratio of **44**:**45** reflects the kinetic ratio of formation of **41a**:**41b**. Assuming the π-allyl moiety preferentially spans apical-basal orientations, equilibration to **42** may occur. In this scenario wherein collapse of the set of **41a** and **42a** generates **44** and that of **41b** and **42b** generates **45** (assuming coupling occurs between apical-basal substituents), this ratio then depends upon the kinetic differences for the two sets of processes. Bidentate ligands like dppe should drive the equilibration to favour **42a** and **42b** which place these ligands in apical-basal orientations. The lower steric strain of **42a** compared to **42b** may then contribute to the enhanced selectivity for forming **44**. Combining the bidentate effect with increased acceptor properties in BINAPO accounts for the highest selectivity for coupling to the more subsituted terminus with this ligand. With monodentate ligands, a further complicating feature is ligand dissociation to **43** and the role of the latter in cross-coupling. Such ambiguity may account for some of the anomalies—most notably, tricyclohexylphosphine. Perhaps its high steric demand promotes ligand dissociation such that coupling occurs *via* **43** as well as *via* **41** and/or **42**.

The preference for equatorial attack noted here is in accord with other nickel-catalysed reactions.[32] It presumably reflects the steric preference for the nickel to form an equatorial complex as in **46** rather than an axial one as in **47** [eqn. (26)]. Since the aryl (or vinyl or methyl) group transfers from the nickel to carbon, the substituent adds to the same face of the π-allyl to which the metal is attached.



46 47 (26)

Conclusion

The present results expand the range of cross-coupling reactions to a new class of allylic derivatives, the amines. We had previously noted the ability of amines to function as leaving groups with Pd^0 if converted into ammonium ions upon protonation—a feature that subsequently has been extended to quaternized salts.[4] Indole served as a leaving group in a nickel-catalysed process.[34] However, amines have not been developed, in general, as leaving groups. Their effectiveness in conjunction with organoborane reagents is noteworthy.

Organoborane reagents represent excellent nucleophilic partners for cross-coupling in large part because of their excellent chemoselectivity and their effectiveness in transmetallation. For example, use of methylboronic acid and esters should prove more broadly applicable than the nickel-catalysed reactions of methylmagnesium halides with allyl alcohols. However, their employment in cross coupling reactions with allyl derivatives has, heretofore, been minimal. Furthermore, almost all of the reported results to date employ palladium catalysts. The results herein illustrate the effectiveness of nickel catalysts. After completion of our work, the nickel-catalysed coupling of allyl carbonates with arylborate esters has been reported.[35] We have independently established the effectiveness of nickel-catalysed cross-coupling of allyl acetates with boronic acids.[30] It is noteworthy that amines prove to be the best leaving group for the cross-coupling with boronic acids. Furthermore, enhanced diastereoselectivity is also observed with amine leaving groups compared to oxygen leaving groups. Thus, this new dimension to metal-catalysed allylation should prove a useful addition to our arsenal of synthetic reactions. Our related study on the couplings with allyl alcohols and esters will be reported in due course. While we have not extended our studies to aqueous media, the success of boronic acids in cross coupling under such conditions make such a prospect here likely as well.[36]

Experimental

General

Reactions were generally conducted under a postitive pressure of dry nitrogen within glassware which had been flame-dried under a stream of dry nitrogen. Reaction flasks were sealed with red rubber septa and were, unless otherwise mentioned, magnetically stirred. Anyhydrous solvents and reaction mixtures were transferred by oven-dried syringe or cannula. Flash chromatography employed E. Merck silica gel (Kisselgel 60, 230–400 mesh). Analytical TLC was performed with 0.2 mm coated commercial silica gel plates (E. Merck, DC-Plastikfolien, Kieselgel 60 F_{254}). ^1H NMR spectra were obtained and recorded from Gemini GEM-200 (200 MHz), Nicolet NT-300 (300 MHz) or Varian XL-400 (400 MHz) instruments, with TMS as internal standard. ^{13}C NMR spectra were recorded on a Nicolet NT-300 (75 MHz) or a Varian XL-400 (100 MHz) instrument. Chemical shifts are recorded in δ units, parts per million from the central peak of $CDCl_3$ (δ 77.0) as an internal reference; J values are recorded in Hz IR spectra were performed by the NIH Mass Spectral Facility at the School of Pharmacy, University of California-San Francisco on a Kratos MS-90 instrument with an ionizing current of 98 mA and an

Table 7 Experimental details for preparation of the amino nitriles

Entry	Aldehyde or ketone (*w*/g, mmol)	KCN (*w*/g, mmol)	Pyrrolidine (*w*/g, mmol)	Ether (*v*/cm^3)	Time (*t*/h)	Product (*w*/g, % yield)
1[a]	Acetaldehyde 88, 20	1.30, 20	1.42, 20	10	1	1.10, 89
2[a]	Isobutyraldehyde 1.44, 20	1.20, 20	1.42, 20	10	1	2.60, 87
3[a]	Benzaldehyde 4.24, 40	2.60, 40	2.84, 40	20	5	6.17, 83
4[a]	Acetone 2.32, 40	2.60, 40	2.84, 40	20	5	5.24, 95
5[a]	Cyclohexanone 3.92, 40	2.60, 40	2.84, 40	20	2	5.34, 78
6[b]	4-*tert*-Butylcyclohexanone 3.08, 20	1.30, 20	1.42, 20	10	2	4.37, 93
7[b]	Acetaldehyde 0.72, 16.3	0.90, 16.3	1.88, 16.3[c]	10	0.75	**40a**, 2.60, 96

[a] This compound has been previously reported (see Table 1). [b] The characterization data for this compound appears below. [c] (*S*)-2-Methoxymethylpyrrolidine (ref. 37) employed in this case.

ionizing voltage of 70 eV. Microanalyses were performed by M-H-W Laboratories, Phoenix, Arizona. Purity of compounds has also been verified chromatographically (GC, TLC, HPLC) and spectroscopically.

Preparation of amino nitriles

General Procedure: Pyrrolidine (2.84 g, 40 mmol) was acidified by 2 M hydrochloric acid and mixed with a solution of potassium cyanide (2.6 g, 40 mmol) in water (20 cm^3). The mixture was added slowly to a stirred solution of the appropriate aldehyde or ketone (40 mmol) in ether (20 cm^3) at 0 °C and then stirred vigorously for 2 h at RT. The ether layer was then separated, washed with brine (2 × 10 cm^3) and with water (2 × 10 cm^3) and then dried ($MgSO_4$). The crude product was then concentrated under reduced pressure and purified if required by distillation *in vacuo*. The experimental details for each run are summarized in Table 7.

(E)-1-tert-*Butyl*-4-*pyrrolidin*-1-*yl*-4-*vinylcyclohexane* **13**.—The diastereoisomeric ratio of 6:1 was determined by integrating the proton signals for the two isomers α to the nitrogen of the pyrrolidine at δ 2.75 for the major isomer and δ 2.65 for the minor isomer; mp 118–120 °C (recrystallized from benzene); ν_{max}(FT, film)/cm^{-1} 2217, 1480, 1467, 1394 and 1143; δ_H(200 MHz, $CDCl_3$) 2.75 (t, *J* 6, 4 H), 2.23 (d, *J* 11.8, 2 H), 1.82 (m, 6 H), 1.45 (m, 4 H), 1.0 (m, 1 H) and 0.88 (s, 9 H); δ_C(75 MHz, $CDCl_3$) 120.0, 63.3, 48.5, 47.3, 36.7, 32.5, 27.6, 24.2, 24.1, 23.8 and 20.8 [Found (HRMS): M, 234.2095. Calc. for $C_{15}H_{26}N_2$: *M*, 234.2095].

2-[(*S*)-2-*Methoxymethylpyrrolidin*-1-*yl*]*propionitrile* **40a**.—The de of 66% was determined by comparing the intensity of the signal for the proton α to the cyano group at δ 4.25 for the major isomer and δ 3.95 for the minor isomer; ν_{max}(FTIR, film)/cm^{-1} 2245, 1457 and 1106 cm^{-1}; δ_H(200 MHz, $CDCl_3$): mixture of diastereoisomers; main isomer: δ 4.25, (q, *J* 7, 1 H), 3.4 (s, 3 H), 3.4–3.2 (m, 2 H), 3.1 (m, 1 H), 2.9 (m, H), 2.5 (q, *J* 7.2, 1 H), 2.0–1.5 (m, 4 H) and 1.45 (d, *J* 7.6, 3 H); δ_C(75 MHz, $CDCl_3$) 119.2, 77.1, 61.4, 59.3, 49.7, 48.9, 27.9, 22.9 and 18.9 [Found (HRMS): M, 168.1253. Calc. for $C_9H_{16}N_2O$: *M*, 168.1262].

Preparation of allylamines

(a) From allyl bromides. The procedure of Cope using an allyl bromide and the amine was used to prepare allyldiethylamine **1a** [bp 111 °C at 760 mmHg (lit.,[38] bp 110–111 °C at 18 mmHg)] and *N*-but-2-enylpyrrolidine **5** [bp 42 °C at 15 mmHg (lit.,[39] bp 43–45 °C at 18 mmHg)].

(b) From allyl acetates. *Allylpyrrolidine*.—A solution of pyrrolidine (7.1 g, 100 mmol) in THF (20 cm^3) was added slowly to allyl acetate (5.0 g, 50 mmol) and tetrakis-(triphenylphosphine)palladium (0.568 g, 0.50 mmol) in THF (10 cm^3). After being heated at reflux for 3 h, the mixture was diluted with water (20 cm^3). Isolation of the product followed the protocol of Cope[38] in which precipitation of the hydrochloride salt was followed by its neutralization with potassium hydroxide. A diethyl ether solution of the crude product was dried ($MgSO_4$) and distilled to give the title compound (3.6 g, 65%), bp 132 °C at 760 mmHg (lit.,[40] bp 129 °C at 760 mmHg).

Methyl cis-5-*diethylaminocyclohex*-3-*enecarboxylate* **10**.[5c]—To a benzene (2 cm^3) suspension of 1 g of polymer-supported Pd^0 [a phosphinoylated polystyrene cross-linked with 1.8% divinylbenzene obtained from Aldrich and charged with 2 mol% Pd by stirring the polymer with tetrakis-(triphenylphosphine)palladium in benzene] was slowly added methyl *cis*-5-acetoxycyclohex-3-enecarboxylate (67 mg, 0.34 mmol) and diethylamine (74 mg, 1.02 mmol). After being heated at reflux for 48 h, the cooled reaction mixture was diluted with ether and filtered. The resultant solution was washed with aqueous sodium hydroxide (2 × 15 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure to afford the title compound (61 mg, 86%). GC analysis revealed a 14:1 mixture of the *cis* and *trans* isomers from which the pure *cis* could be isolated by preparative GC.

(c) From amino nitriles. *General procedure*.—To a solution of the amino nitriles (20 mmol) in THF (20 cm^3) under nitrogen, a solution of vinylmagnesium bromide (1 M in THF; 20 cm^3, 20 mmol) was added at 0 °C. The resulting mixture was stirred for 1–17 h at RT after which it was diluted with ether (50 cm^3) and washed with water (2 × 20 cm^3). The product was extracted with ether and the extract dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by distillation *in vacuo*. Table 8 summarizes the experimental details for each run.

3-Pyrrolidin-1-ylbut-1-ene **4a**[7a] ν_{max}(FTIR, $CDCl_3$)/cm^{-1} 1644, 1461, 1373 and 1135; δ_H(200 MHz, $CDCl_3$) 5.81 (ddd, *J* 17, 11, 6.2, 1 H), 5.15 (d, *J* 16.2, 1 H), 5.0 (d, *J* 10, 1 H), 2.7 (m, 1 H), 2.6 (m, 4 H), 1.8 (m, 4 H) and 1.2 (d, *J* 6.4, 3 H); δ_C(75 MHz, $CDCl_3$) 142.8, 114.9, 64.1, 52.3, 23.5 and 20.9.

4-Methyl-3-pyrrolidin-1-ylpent-1-ene **4b**[6c,7b] ν_{max}(FTIR, $CDCl_3$)/cm^{-1} 1640, 1461, 1385, 1367 and 1110; δ_H(200 MHz, $CDCl_3$) 5.7 (ddd, *J* 17, 10, 5.9, 1 H), 5.15 (d, *J* 10, 1 H), 5.05 (d, *J* 17, 1 H), 2.5 (m, 4 H), 2.25 (m, 2 H), 1.93 (m, 1 H), 1.7 (m, 4 H) and 0.85 (m, 6 H); δ_C(75 MHz, $CDCl_3$) 137.6, 117.8, 75.2, 52.1, 30.0, 23.3, 20.6 and 16.7.

3-Pyrrolidin-1-yl-3-phenylprop-1-ene **4c**[7c] δ_H(200 MHz, $CDCl_3$) 7.4–7.2 (m, 5 H), 6.0 (ddd, *J* 17, 10, 3, 1 H), 5.3 (bd, *J* 17, 1 H), 5.0 (br d, *J* 10, 1 H), 3.6 (d, *J* 8.5, 1 H), 2.6–2.3 (m, 4 H) and 1.8 (m, 4 H); δ_C(75 MHz, $CDCl_3$) 142.1, 129, 128.1, 127.6, 115.3, 75.6, 53.3 and 23.5.

3-Methyl-3-pyrrolidin-1-ylbut-1-ene **4d**[7d] ν_{max}(FTIR, $CDCl_3$)/cm^{-1} 1636, 1471, 1414, 1364 and 1177; δ_H(200 MHz, $CDCl_3$) 5.95 (dd, *J* 17, 6, 1 H), 5.05 (d, *J* 17, 1 H), 5.04 (d, *J* 10, 1 H), 2.6 (m, 4 H), 1.8 (m, 4 H) and 1.2 (s, 6 H); δ_C(75 MHz, $CDCl_3$) 144.5, 113.1, 56.5, 46.4, 24.5 and 24.0.

1-Pyrrolidin-1-yl-1-vinylcyclopentane **4e**[7e] ν_{max}(FTIR, $CDCl_3$)/cm^{-1} 1635, 1448, 1411, 1261 and 1119; δ_H(200 MHz,

Table 8 Experimental details for preparation of branched allylamines

Entry	Amino nitrile (*w*/g, mmol)	CH_2=CHMgBr (*v*/cm^3, mmol)	THF (*v*/cm^3)	Time/ (*t*/h)	Allylamine (*w*/g, % yield)
1	2-Pyrrolidin-1-ylpropionitrile 4.5, 36	47, 47	36	3	**4a**, 3.7, 82
2	3-Methyl-2-pyrrolidin-1-ylbutyronitrile 3.0, 19.8	22, 22	20	3	**4b**, 3.22, 85
3	2-Phenyl-2-pyrrolidin-1-ylacetonitrile 6.0, 32	40, 40	60	3.5	**4c**, 3.4, 57
4	2-Methyl-2-pyrrolidin-1-ylpropionitrile 5.0, 36	40, 40	50	3	**4d**, 3.4, 68
5	2-Pyrrolidin-1-ylcyclohexanecarbonitrile 2.7, 15	20, 20	20	3	**4e**, 1.8, 62
6	1-*tert*-Butyl-4-pyrrolidin-1-ylcyclohexanecarbonitrile 2.0, 8.6	13, 13	20	2	**13**, 1.4, 72
7	2-[(*S*)-2-methoxymethyl-pyrrolidin-1-yl]propionitrile 2.6, 15.4	20, 20	10	3	**40b**, 2.4, 92

$CDCl_3$) 5.9 (dd, *J* 17, 7, 1 H), 5.3 (dd, *J* 9.5, 1.5, 1 H), 5.0 (dd, *J* 17, 1.5, 1 H), 2.6 (m, 4 H), 1.8–1.5 (m, 10 H) and 1.35 (m, 4 H); δ_C(75 MHz, $CDCl_3$) 139.7, 116.0, 58.0, 48.3, 44.9, 36.7, 35.2, 25.1, 23.8, 23.5 and 22.4.

1-*tert*-Butyl-4-pyrrolidin-1-yl-4-vinylcyclohexane **13** ν_{max}(FTIR, film)/cm^{-1} 1630, 1477, 1446 and 1365; δ_H(200 MHz, $CDCl_3$) 5.9 (dd, *J* 17.8. 6.7, 1 H), 5.2 (dd, *J* 11, 1.8, 1 H), 5.0 (dd, *J* 17.7, 1.8, 1 H), 2.5 (t, *J* 6.6, 4 H), 1.9 (m, 2 H), 1.6–1.4 (m, 9 H), 1.2 (m, 2 H) and 0.9 (s, 9 H); δ_C(75 MHz, $CDCl_3$) 141.7, 113.3, 56.5, 48.4, 44.6, 35.4, 32.7, 27.9, 24.6 and 22.1 [Found (HRMS): M, 235.2291. Calc for $C_{16}H_{29}N$: *M*, 235.2300.]

3-[(S)-2-Methoxymethylpyrrolidin-1-yl]but-1-ene **40b:** $[\alpha]_D^{25}$ −44.96 10^{-1} deg cm^2 g^{-1} (*c* 2.52, $CHCl_3$); ν_{max}(FTIR, film)/cm^{-1} 1641, 1455, 1418, 1370, 1312, 1198 and 1115; δ_H(200 MHz, $CDCl_3$) 5.7 (m, 1 H), 5.1 (dm, *J* 13.2, 2 H), 3.3 (m, 5 H), 3.2 (m, 1 H), 2.9 (m, 2 H), 2.5 (q, *J* 6.5, 1 H), 1.7 (m, 4 H) and 1.2 (d, *J* 6.8, 3 H); δ_C(75 MHz, $CDCl_3$) 139.4, 116, 77.0, 59.5, 59.3, 49.0, 29.0, 23.6 and 20.3.

Preparation of 3-pyrrolidin-1-ylbut-1-ene N-oxide.—The standard protocol of Van Rheenan *et al.*[41] was used to oxidize 3-pyrrolidin-1-ylbut-1-ene (3 g, 24 mmol) with 30% aqueous hydrogen peroxide in acetic acid (5.2 cm^3) to give the title compound (2.2 g, 65%); δ_H(200 MHz, $CDCl_3$) 6.1–5.9 (m, 1 H), 5.55 (dd, *J* 17, 10, 2 H), 4.3–3.3 (m, 5 H), 2.5–2.0 (m, 4 H) and 1.6 (d, *J* 7, 3 H); δ_C(75 MHz, $CDCl_3$) 132.6, 124.7, 74.9, 65.4, 64.3, 21.7, 21.5 and 15.9 (Found: C. 68.2; H, 10.7; N, 9.7. Calc. for $C_8H_{15}NO$: C, 68.04; H, 10.70; N, 9.91%).

Preparation of boronic acids and esters

General. Phenylboronic acid and 3-nitrophenylboronic acid were purchased from Aldrich. The known 1-naphthylboronic acid,[19] methylboronic acid,[25,42] (*E*)-hept-1-enylboronic acid,[43] (*E*)-3,3-dimethylbut-1-enylboronic acid[19b,43a] and (*E*)-dodec-1-enylboronic acid[19b] were prepared by the literature methods.

Preparation of (*E*)-6-hydroxyhex-1-enylboronic acid 19d and its corresponding esters. (*a*) *Acid.*—Dibromoborane–dimethyl sulfide (1 M in dichloromethane; 17.5 cm^3, 17.5 mmol, 3 equiv.) was added slowly to a solution of 5-hydroxyhex-1-yne (0.50 g, 6.0 mmol) in dichloromethane (5 cm^3) at 0 °C. After completion of the addition, the ice-bath was removed and the solution allowed to warm to room temperature. After it had been stirred at this temperature for 30 min the reaction mixture was heated at reflux overnight (50 °C) and then poured slowly into a mixture of water–ether (1:1 mixture; 4 cm^3) at 0 °C. The mixture was stirred for 2 h after which the aqueous layer was separated and extracted with ether (2 × 10 cm^3). The combined ether layer and extracts were dried ($MgSO_4$) and evaporated under reduced pressure to afford the title compound as a pale yellow solid. Recrystallization of this from toluene (75%) gave the title acid **19d** as a white solid (0.56 g, 65%), mp 149 °C; ν_{max}(FTIR, $CDCl_3$)/cm^{-1} 3229, 2936, 1637, 1352, 1195 and 1161; δ_H($CDCl_3$) 6.4 (dt, *J* 18, 6, 1 H), 5.3 (d, *J* 18, 1 H), 3.2 (t, *J* 7, 2 H), 2.05 (m, 2 H) and 1.75 (m, 2 H). This compound was best characterized as its ethylene glycol derivative.

(*b*) *Ethylene glycol ester.*—A suspension of the above acid (280 mg, 1.95 mmol) and ethylene glycol (132 mg, 2.10 mmol) in pentane (5 cm^3) was stirred for 25 min at room temperature after which the reaction mixture was diluted with pentane. The pentane layer was then decanted, dried, and evaporated under reduced pressure to give 2-(6-hydroxyhex-1-enyl)-1,3,2-dioxaborolane; ν_{max}(FTIR, film)/cm^{-1} 1638, 1480, 1397, 1374, 1348, 1252, 1203 and 1025; δ_H(200 MHz, $CDCl_3$) 6.6 (dt, *J* 18, 6.4, 1 H), 5.5 (d, *J* 18, 1 H), 4.2 (s, 4 H), 3.4 (t, *J* 6.8, 2 H), 2.2 (m, 2 H), 1.8 (m, 2 H) and 1.55 (m, 2 H); δ_C (75 MHz, $CDCl_3$) 154.8, 65.8, 35.0, 33.7, 32.3 and 26.9 [Found (HRMS): M, 169.0869. Calc. for $C_8H_{15}BO_3$: *M*, 169.084 64].

(*c*) *Pinacol ester.*—This compound was prepared according to the above general procedure using 6-hydroxyhex-1-enylboronic acid (51 mg, 0.354 mmol) and pinacol (50 mg, 0.43 mmol) in pentane (1 cm^3). After a reaction period of 40 min followed by work-up, flash chromatography (hexane–ether, 3:1) gave the title compound (68 mg, 85% yield) as a clear oil; ν_{max}(FTIR, film)/cm^{-1} 1639, 1455, 1362, 1319 and 1145; δ_C(200 MHz, $CDCl_3$) 6.7 (dt, *J* 18, 6, 1 H), 5.4 (d, *J* 18, 1 H), 3.6 (td, *J* 6.3, 1.7, 2 H), 2.2 (m, 2 H), 1.9 (br s, 1 H), 1.55 (m, 4 H) and 1.2 (s, 12 H); δ_C(75 MHz, $CDCl_3$) 154.8, 83.4, 62.9, 35.7, 32.4 and 24.9 [Found (HRMS): M, 225.1505. Calc. for $C_{12}H_{23}BO_3$: *M*, 225.1505].

Preparation of (Z)-dodec-1-enylboronic acid 29b and esters. Dibromoborane–dimethyl sulfide (1 mol dm^{-3} in dichloromethane; 5 cm^3, 5 mmol) was added slowly to 1-bromododec-1-yne (1.0 g, 4.6 mmol) in dichloromethane (10 cm^3) at 0 °C. After completion of the addition, the mixture was stirred overnight at room temperature and then poured into a solution of water–ether (1:1; 10 cm^3) at 0 °C; the layers were then separated. The water layer was extracted with ether (2 × 8 cm^3) and the combined ether layer and extracts were dried ($MgSO_4$) before being concentrated under reduced pressure to afford 1-bromododec-1-enylboronic acid **28a** (1.16 g, 87%) as a pale yellow solid; ν_{max}(FTIR, pellet)/cm^{-1} 3300, 1629, 1471, 1361, 1303, 1166 and 1032; δ_H(200 MHz, $CDCl_3$) 6.9 (t, *J* 6.9, 1 H), 4.9 (br s, 2 H), 2.3 (q, *J* 7, 2 H), 1.5–1.2 (m, 16 H) and 0.9 (t, *J* 4, 3 H); δ_C(75 MHz, $CDCl_3$) 148.3, 33.0, 32.0, 29.8, 29.7, 29.6, 29.5, 27.9, 22.8 and 14.1. This product was used without further purification in the next step.

To a suspension of the above acid (1.15 g, 3.96 mmol) in pentane (10 cm^3) was added slowly at room temperature

ethylene glycol (0.295 g, 4.76 mmol); during the course of the reaction, the pale yellow solid slowly dissolved. After completion of the addition, the homogeneous reaction mixture was stirred at room temperature for 15 min. The pentane layer was then separated from the remaining ethylene glycol by vacuum withdrawal through a cannula and, after being dried ($MgSO_4$), was evaporated under reduced pressure to afford the corresponding ester **28b** (0.91 g, 73%) as a clear oil; ν_{max}(FTIR, pellet)/cm^{-1} 1632, 1397, 1372, 1332, 1227 and 1029; δ_H(200 MHz, $CDCl_3$) 6.9 (t, *J* 6.7, 1 H), 4.3 (s, 4 H), 2.3 (q, *J* 7, 2 H), 1.5–1.2 (m, 16 H) and 0.9 (t, *J* 6, 3 H); δ_C(50 MHz, $CDCl_3$) 151.0, 66.7, 32.5, 32.0, 29.8, 29.7, 29.6, 29.4, 27.9, 22.8 and 14.1 [Found (HRMS): M, 318.1173. Calc. for $C_{14}H_{26}BBrO_2$: *M*, 318.1188].

Lithium triethylborohydride (1 M in THF; 0.22 cm^3, 0.22 mmol) was added slowly to a solution of compound **28b** (69 mg, 0.2 mmol) in THF (0.5 cm^3) at 0 °C. [**CAUTION**: A violent reaction with appearance of fumes and bubbles in the reaction flask occurs.] After being stirred at room temperature overnight, the mixture was poured into ether–water (10:1; 2 cm^3) and the whole stirred at room temperature for 2 h. The layers were separated, and the water layer was extracted with ether (2 × 4 cm^3). The combined ether layer and extracts were dried ($MgSO_4$) and evaporated under reduced pressure to afford compound **29b** as a gummy yellow oil, purification of which by flash chromatography (hexane–ether, 1:1; R_F 0.56) gave a white solid (32 mg, 76%);[23] ν_{max}(FTIR, pellet)/cm^{-1} 3461, 3340, 1638, 1469, 1351, 1336, 1152 and 1036; δ_H(200 MHz, $CDCl_3$) 6.7 (dt, *J* 13.7, 7.5, 1 H), 5.45 (d, *J* 13.7, 1 H), 2.55 (q, *J* 7, 2 H), 1.3 (m, 16 H), 0.9 (t, *J* 6.4, 3 H); δ_C(75 MHz, $CDCl_3$) 159.7, 32.2, 29.9, 29.8, 29.6, 29.5, 22.9 and 14.3. This compound was best characterized as its ethylene glycol derivative.

Ethylene glycol (0.01 g, 0.175 mmol) was added slowly to a suspension of (*Z*)-dodec-1-enylboronic acid (31 mg, 0.146 mmol) in pentane (3 cm^3) at room temperature; during the course of the addition, the white solid slowly dissolved. After completion of the addition, the pentane layer was separated from the remaining ethylene glycol phase by decantation. The ethylene glycol phase was extracted with pentane (2 × 5 cm^3) and the combined pentane layer and extracts were then dried ($MgSO_4$) and subjected to rotary evaporation to afford the title compound (31 mg, 89%) as a pale brown oil. The crude product was purified by distillation (temperature of the oil bath 178 °C) in a microstill apparatus to afford **29a** as a colourless oil; ν_{max}(FTIR, film)/cm^{-1} 1629, 1421, 1394, 1269 and 1022; δ_H(200 MHz, $CDCl_3$) 6.5 (m, 1 H), 5.36 (d, *J* 13.6, 1 H), 4.23 (s, 4 H), 2.4 (q, *J* 7, 2 H), 1.3 (m, 16 H) and 0.9 (t, *J* 6.4, 3 H); δ_C(75 MHz, $CDCl_3$) 156.9, 65.7, 65.6, 32.7, 32.2, 29.9, 29.8, 29.7, 29.67, 29.6, 28.4, 22.9 and 14.3 [Found (HRMS): 238.2121. Calc. for $C_{14}H_{27}BO_2$: *M*, 238.2104].

Cross coupling reactions

General procedures *Method A*.—A mixture of pre-formed tetrakis(triphenylphosphine)palladium (29 mg, 0.025 mmol) or pre-formed tetrakis(triphenylphosphine)nickel (27 mg, 0.025 mmol), the allylic substrate (0.25 mmol), the boronic species (0.25 mmol) and the base (0.25–0.025 mmol) in the desired solvent (0.25–0.5 cm^3) was stirred at the reflux temperature or sonicated for 5–17 h. After completion of the reaction, the mixture was diluted with pentane (1.5 cm^3), filtered through a short pad of silica gel and evaporated under reduced pressure. Crude products were then purified by flash chromatography or distillation. Regioisomers were isolated by preparative gas chromatography.

Method B.—The allylamine (0.25 mmol), the boronic acid (0.275 mmol, 1.1 equiv.) and tetradecane (5 mg) were stirred for 10 min in benzene (0.1 cm^3) at room temperature at which point the appropriate ligand (0.1 mmol) was added. [Ni(cod)$_2$] (0.5 M solution in benzene; 0.5 cm^3, 0.025 mmol) was added and the mixture stirred for a further 10 min. Powdered potassium hydroxide (16.3 mg, 0.025 mmol) was then added and the resulting mixture heated at the reflux temperature for 3–10 h. Reactions were followed by GC. After completion of the reaction, the mixture was filtered through silica gel and submitted to flash chromatography to afford coupling products. Regioisomers were isolated by preparative gas chromatography.

Method C.—Triethylaluminum (1 M solution in hexane; 0.055 cm^3, 0.055 mmol) or diethylaluminium ethoxide (1.6 mol dm^{-3} solution in toluene; 0.034 cm^3, 0.055 mmol) was added slowly to [Ni(acac)$_2$] (6.4 mg, 0.025 mmol) and triphenylphosphine (26.2 mg, 0.1 mmol, 4 equiv.) in toluene (0.15 cm^3). The resulting mixture was stirred at 60 °C for 20 min after which it was transferred *via* a cannula to a mixture of the desired allylic substrate (0.025 mmol) and the boron compound (0.25–0.3 mmol) in toluene (0.1 cm^3) at 60 °C. After completion of the addition, the mixture was heated at reflux for 5–17 h. After completion of the reaction, the mixture was diluted with pentane (1.5 cm^3) or ether (1.5 cm^3), filtered through a short pad of silica gel and evaporated under reduced pressure. Crude products were then purified by flash chromatography or distillation. Regioisomers were isolated by preparative gas chromatography.

Method D.—Triethylaminium (1 M solution in hexane; 0.055 cm^3, 0.055 mmol) was added slowly to [Ni(acac)$_2$] (6.4 mg, 0.025 mmol) and triphenylphosphine (26.2 mg, 0.1 mmol, 4 equiv.) after which the hexane was evaporated under a strong stream of nitrogen (typically, the colour of the solid goes from green to brown–red after reduction). The allylic substrate (0.25 mmol) was then added to the residue along with the boronic acid (0.3–0.5 mmol, 1.2 to 2 equiv.) under a positive pressure of argon. The tube was then sealed and put in an oil-bath at 110–140 °C for 5–17 h. After completion of the reaction, the mixture was diluted with pentane (1–2 cm^3) and filtered through a short pad of silica gel to afford, after removal of the solvent under reduced pressure, the crude products. These were purified by flash chromatography or distillation. Regioisomers were isolated by preparative gas chromatography. The experimental details for each run are summarized in Table 9.

3-(3-Nitrophenyl)but-1-ene ν_{max}(FTIR, film)/cm^{-1} 1715, 1701, 1623 and 1532; δ_H(200 MHz, $CDCl_3$) 8.05 (d, *J* 6, 1 H), 7.85–7.40 (m, 3 H), 6.0 (ddd, *J* 17, 10.4, 4, 1 H), 5.13 (br d, *J* 10.4, 1 H), 5.11 (br d, *J* 17.0, 1 H), 3.6 (p, *J* 4, 1 H) and 1.4 (d, *J* 7, 3 H); δ_C(75 MHz, $CDCl_3$) 142.3, 134.3, 130.9, 129.8, 122.8, 122.3, 121.9, 115.2, 43.1 and 20.7 [Found (HRMS): M, 177.0789. Calc. for $C_{10}H_{11}NO_2$: *M*, 177.0789].

3-Naphthylbut-1-ene ν_{max}(FTIR, film)/cm^{-1} 1637, 1597, 1456, 1383 and 1111; δ_H(200 MHz, $CDCl_3$) 8.2–7.4 (m, 7 H), 6.2 (ddd, *J* 17, 11, 4, 1 H), 5.15 (d, *J* 17, 1 H), 5.14 (d, *J* 11, 1 H), 4.3 (m, 1 H) and 1.5 (d, *J* 7, 3 H); δ_C(75 MHz, $CDCl_3$) 143.5, 142.1, 132.1, 129.4, 127.3, 126.2, 126.1, 125.8, 124.2, 124.0, 114.4 and 20.4 [Found (HRMS): M, 182.1095. Calc. for $C_{14}H_{14}$: *M*, 182.1143].

1-Naphthylbut-2-ene (*cis*/*trans* mixture) ν_{max}(FTIR, film)/cm^{-1}: 1597, 1509, 1437, 1378, 1260, 1120, 1081 and 1016; δ_H(200 MHz, $CDCl_3$) 8.1–7.3 (m, 7 H), 5.75 (m, 1 H), 5.55 (m, 1 H), 3.8 (d, *J* 6, 2 H major) [(the minor is found at δ 3.84 (d, *J* 6, 2 H)] and 1.68 (d, *J* 6.4, 3 H); δ_C(75 MHz, $CDCl_3$) 137.7, 132.6, 130.1, 127.3, 127.2, 126.6, 126.2, 126.1, 126.0, 124.6 and 36.3 [Found (HRMS): M, 182.1132. Calc. for $C_{14}H_{14}$: *M*, 182.1143.].

1-[(*E*)-Hept-1-enyl]-1-vinylcyclohexane 25 ν_{max}(FTIR, film)/cm^{-1} 3690, 2930, 1602 and 1450; δ_H(200 MHz, $CDCl_3$) 5.7 (dd, *J* 17, 10, 1 H), 5.34 (dt, *J* 16, 6, 1 H), 5.26 (d, *J* 16, 1 H), 5.00 (d, *J* 17, 1 H), 4.99 (d, *J* 10, 1 H), 2.0 (m, 2 H), 1.6–1.2 (m, 16 H) and 0.9 (t, *J* 6, 3 H); δ_C(75 MHz, $CDCl_3$) 138.0, 129.1, 111.8,

Table 9 Experimental details for coupling reactions

Entry	Amine (*w*/mg, mmol)	Boronic acid (*w*/mg, mmol)	Method	Catalyst (*w*/mg, mmol)	Base or reducing agent (mmol)	Ligand (*w*/mg, mmol)	Solvent (*v*/cm^3)	Time (*t*/h)	Temp. (*T*/°C)	Product[a] (*w*/mg, % yield)
1	**1a** 28, 0.25	**2** 36.5, 0.275	A	[Pd (PPh_3)$_4$] 28.8, 0.025	KOH 0.025	NA	PhH 0.25	5	120	15, 50
2	**1a** 28, 0.25	**2** 36.5, 0.275	C	[Ni(acac)$_2$] 6.4, 0.025	$AlEt_3$ 0.055	PPh_3 26, 0.10	$PhMe_3$ 0.25	5	120	24, 80
3	**1a** *N* Oxide **33**, 0.25	**2** 36.5, 0.275	A	[Ni (PPh_3)$_4$] 27, .025	NA	NA	PhH 0.5	7	100	19, 62
4	**4a** 32, 0.25	**2** 36.5, 0.275	C	[Ni(acac)$_2$] 6.4, 0.025	$AlEt_3$ 0.055	PPh_3 26, 0.10	$PhMe_3$ 0.25	5	120	29, 87
5	**5** 32, 0.25	**2** 36.5, 0.275	C	[Ni(acac)$_2$] 6.4, 0.025	$AlEt_3$ 0.055	PPh_3 26, 0.10	$PhMe_3$ 0.25	5	120	29, 87
6	**4a** 32, 0.25	**2** 36.5, 0.275	C	[Ni(acac)$_2$] 6.4, 0.025	$AlEt_3$ 0.055	BINAPO 33, 0.05	$PhMe_3$ 0.25	17	60	23, 69[b]
7	**4a** 32, 0.25	**2** 36.5, 0.275	B	[Ni(COD)$_2$] 6.9, 0.025	KOH 0.025	$PPri_3$ 16, 0.10	PhH 0.5	24	60	20, 62[b]
8	**4b** 38, 0.25	**2** 36.5, 0.275	C	[Ni(acac)$_2$] 6.4, 0.025	$AlEt_3$ 0.055	PPh_3 26, 0.10	$PhMe_3$ 0.25	7	120	25, 68
9	**4b** 38, 0.25	**2** 36.5, 0.275	B	[Ni(COD)$_2$] 6.9, 0.025	KOH 0.025	$PPri_3$ 16, 0.10	PhH 0.5	24	60	28, 76[b]
10	**4b** 38, 0.25	**2** 36.5, 0.275	B	[Ni(COD)$_2$] 6.9, 0.025	KOH 0.025	BINAPO 66, 0.10	PhH 0.5	24	60	25, 68
11	**4e** 45, 0.25	**2** 35, 0.25	C	[Ni(acac)$_2$] 6.4, 0.025	$AlEt_3$ 0.055	PPh_3 26, 0.1	$PhMe_3$ 0.25	17	120	31, 70
12	**4e** 45, 0.25	**2** 35, 0.25	C	[Ni(acac)$_2$] 6.4, 0.025	$AlEt_3$ 0.055	BINAPO 66, 0.10	PhMe 0.25	17	120	36, 78
13	**10** 105, 0.50	**2** 70, 0.55	C	[Ni(acac)$_2$] 12.7, 0.05	$AlEt_3$ 0.11	PPh_3 52, 0.2	$PhMe_3$ 0.5	10	120	62, 57
14	**13** 117, 0.50	**2** 70, 0.55	C	[Ni(acac)$_2$] 12.7, 0.05	$AlEt_3$ 0.11	PPh_3 52, 0.2	$PhMe_3$ 0.5	17	120	69, 57
15	**4a** 62, 0.50	1-Naphthyl boronic acid 86, 0.55	C	[Ni(acac)$_2$] 12.7, 0.05	$AlEt_3$ 0.11	PPh_3 52, 0.2	$PhMe_3$ 0.5	17	120	73, 80
16	**4a** 62, 0.50	1-Naphthyl boronic acid 86, 0.55	C	[Ni(acac)$_2$] 12.7, 0.05	$AlEt_3$ 0.11	BINAPO 66, 0.10	$PhMe_3$ 0.5	17	100	69, 76
17	**4a** 32, 0.25	3-Nitrophenyl boronic acid 50, 0.3	A	[Pd_2 (dba)$_3$]·$CHCl_3$ 28, 0.025	Tl_2CO_3 0.05	PPh_3 26, 0.1	PhH[c] 0.2	17	60	18, 41
18	**1a** 56.5, 0.5	**19a** 74, 0.52	A	[Ni (PPh_3)$_4$] 55, 0.05	KOH 0.06	NA	PhH 1	3	60	32, 45
19	**1b** 55, 0.5	**19a** 74, 0.52	C	[Ni(acac)$_2$] 13, 0.05	$AlEt_3$ 0.11	PPh_3 52, 0.2	$PhMe_3$ 1	5	120	50, 72
20	**1a** 29, 0.25	**19c** 55, 0.26	C	[Ni(acac)$_2$] 6.5, 0.025	$AlEt_3$ 0.055	PPh_3 26, 0.1	$PhMe_3$ 0.5	17	120	40, 76
21	**4a** 32, 0.25	**19a** 37, 0.26	A	[Ni (PPh_3)$_4$] 27.5, 0.025	KOH 0.03	NA	PhH 0.5	17	60	23, 60
22	**4a** 32, 0.25	**19a** 37, 0.26	C	[Ni(acac)$_3$] 6.5, 0.025	$(C_2H_5)_3Al$ 0.055	PPh_3 26, 0.1	PhMe 0.5	17	120	27, 72
23	**4b** 39, 0.25	**19a** 3.7, 0.26	A	[Ni (PPh_3)$_4$] 55, 0.05	KOH 0.03	NA	PhH 0.5	17	60	30, 65
24	**4a** 32, 0.25	3,3-Dimethylbut-1-enylboronic acid 34, 0.26	A	[Ni (PPh_3)$_4$] 26.5, 0.025	KOH 0.03	NA	PhH 0.5	17	60	78, 57
25	**4e** 45, 0.25	**19a** 35, 0.25	B	[Ni(COD)$_2$] 6.9, 0.025	KOH 0.025	PPh_3 26, 0.1	PhH 0.5	24	60	33, 64
26	**4e** 45, 0.25	**19a** 37, 0.26	C	[Ni(acac)$_2$] 6.5, 0.025	$AlEt_3$ 0.055	PPh_3 26, 0.1	$PhMe_3$ 0.5	10	120	40, 62
27	**1a** 57, 0.25	**19d** 79.8, 0.6	C	[Ni(acac)$_2$] 13, 0.05	$AlEt_3$ 0.11	Ph_3P 52, 0.2	PhH 1	18	120	29, 42
28	**1a** 29, 0.25	**29b** 55, 0.26	C	[Ni(acac)$_2$] 6.5, 0.025	$AlEt_3$ 0.055	PPh_3 26, 0.1	PhH 0.5	17	120	15, 29[d]
29	**1a** 29, 0.25	**19c** 55, 0.26	C	[Ni(acac)$_2$] 6.5, 0.025	$AlEt_3$ 0.055	PPh_3 26, 0.1	$PhMe_3$ 0.5	17	120	40, 76[e]
30	**4e** 89.5, 0.5	**35a** 81, 0.59	D	[Ni(acac)$_2$] 13, 0.05	$AlEt_3$ 0.11	PPh_3 52, 0.2	Ph 1	17	110	69, 56

[a] For ratio of regioisomers, see text. All products are known compounds except for those for whom spectroscopic data is listed. [b] Yield determined by GC analysis. [c] Solvent includes 0.1 cm^3 of ethanol and 0.2 mL of water. [d] In addition, 7 mg (16% yield) of dodec-1-ene obtained. [e] In addition, 4 mg (9% yield) of dodec-1-ene obtained.

36.2, 33.0, 31.5, 29.5, 26.5, 22.6, 22.4 and 14.1 [Found (HRMS): M, 206.2041. Calc. for $C_{15}H_{26}$: 206.2034].

(*E*)-Non-3-enylidenecyclohexane **26** ν_{max}(FTIR, film)/cm^{-1} 1602 and 1447; δ_H(200 MHz, $CDCl_3$) 5.4 (m, 2 H), 5.06 (t, *J* 5, 1 H), 2.78 (t, *J* 5, 2 H), 2.2–1.9 (m, 9 H), 1.4–1.2 (m, 9 H) and 0.9 (t, *J* 5.5, 3 H); δ_C(75 MHz, $CDCl_3$) 131.0, 129.6, 119.8, 37.3, 32.7, 31.6, 30.5, 29.4, 28.8, 27.9, 27.2 and 12.2 [Found (HRMS): M, 206.2039. Calc. for $C_{15}H_{26}$: *M*, 206.2034].

(Z)-Pentadeca-1,4-diene **30** ν_{max}(FTIR, film)/cm^{-1} 1636, 1602, 1465, 1457 and 1216; δ_H(200 MHz, $CDCl_3$) 5.81 (m, 1 H), 5.42 (m, 2 H), 5.03 (d, *J* 17, 1 H), 4.98 (d, *J* 10, 1 H), 2.8 (t, *J* 6.6, 2 H), 2.0 (m, 2 H), 1.3 (m, 16 H) and 0.89 (t, *J* 6.5, 3 H); δ_C(75 MHz, $CDCl_3$) 137.80, 131.84, 127.12, 115.03, 32.15, 31.78, 29.85, 29.76, 29.57, 29.52, 27.36, 22.89 and 14.29 [Found (HRMS): 208.2185. Calc. for *M*, $C_{15}H_{28}$: 208.2191].

(E)-Pentadeca-1,4-diene **32** ν_{max}(FTIR, film)/cm^{-1} 1637, 1467 and 1434; δ_H(200 MHz, $CDCl_3$) 5.84 (ddt, *J* 16.8, 10.2, 6.4, 1 H), 5.42 (m, 2 H), 5.03 (dd, *J* 17.2, 1.5, 1 H), 4.98 (dd, *J* 10.2, 1.5, 1 H), 2.74 (t, *J* 6.5, 2 H), 2.0 (q, *J* 7, 2 H), 1.26 (m, 16 H) and 0.88 (t, *J* 6.3, 3 H); δ_C(75 MHz, $CDCl_3$) 138.16, 132.47, 128.08, 115.22, 37.01, 32.83, 32.15, 29.86, 29.75, 29.58, 29.41, 22.89 and 14.29 [Found (HRMS): M, 208.2185. Calc. for $C_{15}H_{28}$: *M*, 208.2191].

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