DOI: 10.1002/ejoc.201101305

The Development of Domino Reactions Incorporating the Heck Reaction: The Formation of N-Heterocycles

James E. Rixson,[a] Thomas Chaloner,[a] Charles H. Heath,[a] Lutz F. Tietze,[b] and Scott G. Stewart*[a]

Keywords: Domino reactions / Cascade reactions / Nitrogen heterocycles / Palladium / Homogeneous catalysis

The methodological development of a series of domino or cascade reactions affording a series of N-heterocycles is described. The rapid formation of these ring systems is in each case associated with the incorporation of a Heck reaction at either an early or a late stage of the domino process. A range of catalytic conditions and substrate modifications for optimisation of domino Tsuji–Trost/Heck, Buchwald–Hartwig/Heck and Heck/carbopalladation reaction sequences are reported.

Introduction

Recent developments in domino reaction chemistry have provided more effective methods for the synthesis of a range of complex ring systems and molecules. A domino reaction is defined as "the execution of two or more bond-forming transformations under identical reaction conditions, in which the latter transformations take place at the functionalities formed by the preceding transformation".[1] Such transformations are attractive to industry and research laboratories because of their potential for saving solvents, reagents, time and energy. Domino reactions have been useful in the preparation of complex molecules including several natural products.[2] Alternatively, one prime example of the potential for large-scale preparation of pharmaceuticals has been highlighted by Hayashi's group in their preparation of the anti-influenza drug (–)-oseltamivir phosphate (Tamiflu™).[3] In this synthesis, two single-pot domino processes are utilised, one incorporating a Michael/Horner–Wardsworth–Emmons reaction sequence.

In most cases the more realistic domino reactions are those in which all transformations occur under similar reaction conditions, such as domino reactions utilising two palladium-catalysed steps.

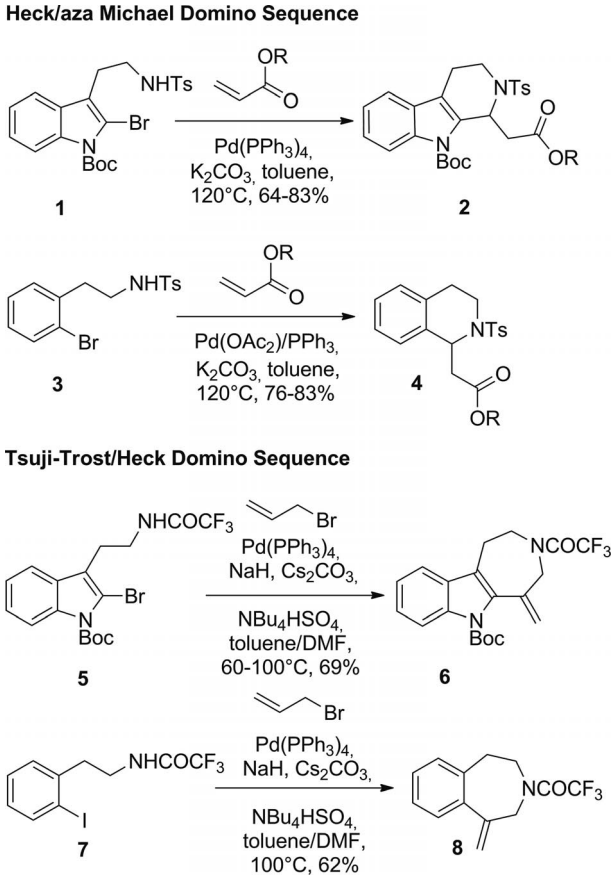
Reactions such as these have been useful in the production of biologically active molecules[1–2] such as scopadulcic acid A,[4] manzamine A,[5] biyouyanagin A[6] and α-tocopherol.[7] Likewise, a process in which a base-mediated step is combined with a palladium-catalysed step might also seem more promising, because bases are often used in conjunction with Pd-mediated cross-coupling reactions. Such palladium-catalysed domino reactions are becoming more frequently published and cited in the literature.[8]

Recently, studies within our group have focussed on domino reactions in which at least one step involves a palladium-catalysed Heck reaction. Recently we reported domino Heck/aza-Michael reactions based on rapid cross-coupling of the aryl halides **1** and **3** prior to any nucleophilic attack at carbon (Scheme 1). In these instances we were able to produce a range of tetrahydro-β-carbolines **2**, isoquinolines **4** and isoindolines, but not before careful consideration of the type of catalytic system.[9] By reversing the type of reaction order we also reported the use of a series of domino Tsuji–Trost/Heck reactions in the synthesis of the azepino[4,5-*b*]indoles **6** and 3-benzazepines **8** (Scheme 1), hence with nucleophilic addition processes in the early stages of the reaction sequences.[10] Because these domino reactions are assumed to go through two catalytic cycles they have also been described as pseudo-domino reactions.[11] As part of the fine tuning of the Tsuji–Trost/Heck domino reaction, a two-base system that utilises one base for each of the individual reactions was recognised as the most efficient. In our continuing studies we have sought to explore other possible domino reactions in combination with the Heck reaction to generate a new series of N-heterocycles.

In this report the indole, isoquinoline, benzazepine and azepinobenzindolizidine ring systems (Figure 1) were chosen as targets because of their prevalence in both pharma-

[a] The School of Biomedical, Biomolecular & Chemical Sciences, The University of Western Australia,
Crawley, WA 6009, Australia
Fax: +61-8-6488 1005
E-mail: sgs@cyllene.uwa.edu.au
[b] Institut für Organische und Biomolekulare Chemie der Georg-August-Universität Göttingen,
Tammannstraße 2, 37077 Göttingen, Germany

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201101305 or from the author.



Scheme 1. Domino Tsuji–Trost/Heck sequences and Heck/aza-Michael sequences in the formation of various N-heterocycles.

ceuticals and natural products. The indole ring system can be found in biologically active natural products such as vincristine and reserpine (**9**).[12] Likewise, laudanosine (**10**) is an excellent example of an isoquinoline natural product, but is simple in comparison with the structurally complex antitumour agent ecteinascidin 743.[13] The 3-benzazepine ring system is present in the cephalotaxus alkaloids[14] and in simpler entities such as lennoxamine (**11**), found in *Berberis darwinii*.[15] Efficient production of the N-heterocyclic cores of such compounds is paramount when investigating

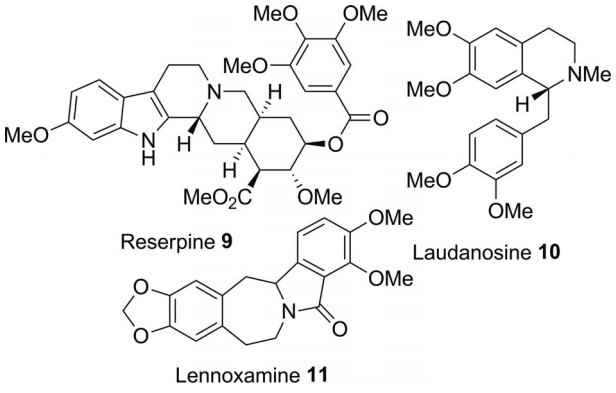


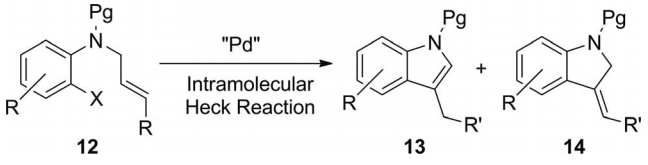
Figure 1. The natural products **9**, **10** and **11**, containing indole, isoquinoline, and benzazepine ring systems.

the production either of natural products for biological evaluation or of simpler analogues on an industrial scale. This paper investigates a range of palladium-mediated domino reactions incorporating the Heck reaction. These processes include Tsuji–Trost/Heck reaction sequences targeting indoles and tetrahydroisoquinolines, Buchwald–Hartwig/Heck reaction sequences applied in the synthesis of benzazepines, and Heck/carbopalladation reaction sequences for the synthesis of azepinobenzindolizidines.

Results and Discussion

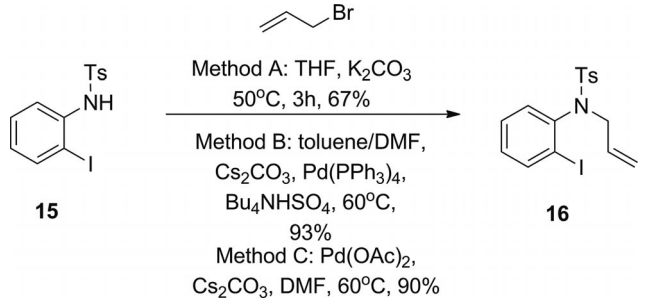
Domino Tsuji–Trost/Heck Reaction Combinations for the Synthesis of Indoles

The indole ring system has been prepared by numerous approaches, beginning with the Fischer indole synthesis[16] and followed by other comprehensive methods.[17] More recent methods utilising palladium catalysis have also been incorporated into successful synthetic programs,[18] some en route to biologically active compounds. In order to utilise our Tsuji–Trost/Heck domino approach towards this ring system we first sought an efficient method for the two individual reactions in this process. The 5-*exo*-*trig* intramolecular Heck reactions of the aryl halides **12** (Scheme 2), bearing amine tethers, have been reported by several groups with mixed success. These reactions depend on either the halide, the groups attached to the aromatic ring or the type of olefinic system.[19] In these reports the 5-*exo*-*trig* reactions predominate to afford the olefins **14**, which then normally aromatise upon further stirring or workup to form the sought after indole ring systems **13**.[20]



Scheme 2. Intramolecular Heck reactions in preparations of indoles.

The precursor **15** (Scheme 3) for our study could be prepared efficiently through simple tosylation of 2-iodoaniline. The tosyl group was chosen to provide an NH proton slightly more acidic than that in the trifluoroacetamide used previously in the group.[9a] The preparations of indoles

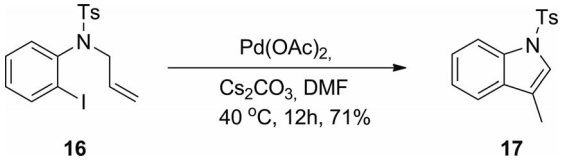


Scheme 3. Allylation of *N*-tosyl-2-iodoaniline (**15**).

through the initial allylation of **15** with allyl bromide was tested with and without the assistance of a palladium catalyst.[10a]

Modification of the base and solvent in each of the trial reactions revealed the optimum reaction system with the addition of a $Pd(PPh_3)_4$ catalyst (10 mol-%). As in our previous domino reaction methodology study with similar amines, allylation of compound **15** in the presence of the Pd catalyst (presumably through a π-allyl palladium intermediate) occurred at a much faster rate than the simple S_N2' reaction.[10a] DMF was also found to be an effective solvent for this Tsuji–Trost reaction, with complete conversion of the aryl iodide **15** into the olefin **16** (Scheme 3) achieved efficiently regardless of the allylating agent used. The increase in the rate of the Tsuji–Trost reaction in DMF might also be attributed to the role played by a high-polarity solvent in assisting dissociation of the bromide/chloride/acetate ion from the $L_2Pd(\eta^2)$ intermediate to form the reactive η^3-allyl cation complex, as reported previously.[21]

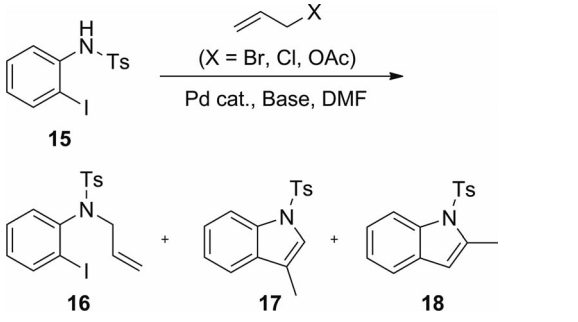
Once large quantities of the allyl sulfonamide **16** were to hand, the intramolecular Heck reaction was trialled as the eventual proposed second step of the domino reaction. The use of DMF as an effective solvent for the intramolecular Heck reaction was taken into account. A series of reactions with $Pd(PPh_3)_4$ and other common palladium-based catalysts were initially chosen.[22,23] *N*-Tosyl-3-methylindole (**17**, Scheme 4) was synthesised in a reasonable yield (71%) in the presence of $Pd(OAc)_2$ under phosphane-free Jeffery's conditions.[24] At this stage no attempts were made to investigate the Heck cyclisation reaction with more electron-rich phosphanes, as published by the groups of Fu and Buchwald; instead, optimisation of the domino process was examined.[25] During the course of our initial investigations, Beck's group proposed an allylation/Heck cyclisation sequence in a separate investigation involving aryl chlorides and use of the Buchwald ligand (up to 67% yield).[26] Although this work highlighted good process with aryl chlorides in reasonable yields and with moderate turnovers, we were wary of substrate scope and the use of the Buchwald ligands and possible competing C–N cross-coupling.



Scheme 4. Heck cyclisation of *N*-allyl-*N*-tosyl-2-iodoaniline (**16**).

After the successful investigation of the individual Tsuji–Trost and Heck reactions, the domino process was then attempted under a series of reaction conditions (Table 1). In the initial attempts, conditions leading to the formation of the intermediate **16** were maintained over a longer period, which led to small amounts of the domino product **17** being isolated (Table 1, Entries 1 and 2). In an effort to accelerate the secondary Heck reaction process, the catalytic system proposed by Fu [$Pd_2(dba)_3$·$CHCl_3$, $P(tBuP)_3HBF_4$ and Cs_2CO_3, Cy_2NMe][25a] was studied, but in this case the only domino product isolated was **18** (8%, Table 1, Entry 3). This phenomenon was attributed to a process in which an initial intermolecular Heck reaction occurred,[27] followed by a later CN coupling.[28] To test the possibility that there was a halide effect playing a part in the domino process, or more specifically the secondary Heck reaction, the allylating agent was changed to allyl chloride. (Entries 4 to 6, Table 1). This series of reactions confirmed this allylating agent to be superior in combination with $Pd(PPh_3)_4$ (10 mol-%) and triethylamine, but large amounts of the allylated sulfonamide **16** still remained. A change of allylating agent to allyl acetate produced moderate amounts of the domino product (26–34%) though not enough for a viable process. The bidentate dppf ligand was also used because of its potential to form an active (1:1) palladium bis-ligated precursor, but this reaction still only produced moderate amounts of both compounds **16** and **17**. In our case a breakthrough came on treatment of the aryl iodide **15** with the palladacycle **19** (Table 1, Entry 9) discovered by Herrmann and Beller.[29] This reaction showed complete consumption of the allyl product **16**, immediately detectable by tlc, and directly offered a new lead in the investigation of the domino process. The Herrmann–Beller catalyst **19** offers several advantages over the other catalytic systems pre-

Table 1. Initial investigation of Tsuji–Trost/Heck domino conditions with *N*-tosyl-2-iodoaniline (**15**).



	X[a]	Base	Catalyst[c]	Temp. [°C]	Add. reagent/ ligand	Yield [%] 16	17	18
1	Br	Cs_2CO_3	$Pd(OAc)_2$	60	–	90	<0.2	–
2	Br	Cs_2CO_3	$Pd(PPh_3)_4$	60	–	71	3	–
3	Br	Cs_2CO_3, Cy_2NMe	$Pd_2(dba)_3$·$CHCl_3$	80	$P(tBu)_3HBF_4$	81	–	8
4	Cl	Et_3N	$Pd(PPh_3)_4$	80	–	>45	48	–
5	Cl	Cs_2CO_3	$Pd(PPh_3)_4$	90–100	–	>70	22	–
6	Cl	Cs_2CO_3	$Pd(PPh_3)_4$	85–90	nBu_4NCl	<85	15	–
7	OAc	Cs_2CO_3	$Pd(PPh_3)_4$	75–80	–	<65	34	–
8	OAc	Cs_2CO_3	$Pd_2(dba)_3$·$CHCl_3$	70–90	dppf	21	31	–
9	OAc	Cy_2NMe	HB cat[b]	90–100	–	trace	26	16

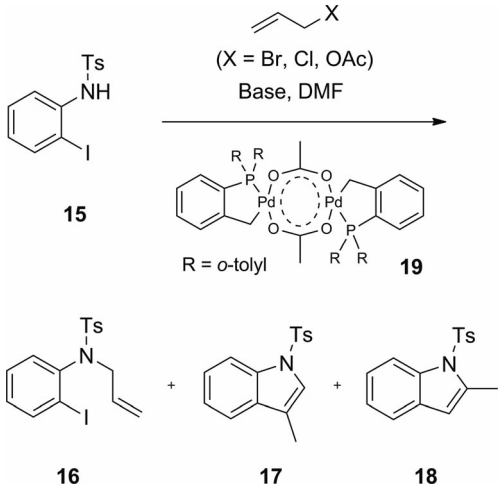
[a] In each reaction 1–2 equiv. of the allylating reagent were used. [b] The Herrmann–Beller (HB) catalyst is *trans*-bis(μ-acetato)-bis[*o*-(di-*o*-tolylphosphanyl)benzyl]dipalladium(II) (**19**) and was used at 5 mol-%. [c] All catalysts were used at 10 mol-% except **19** (5 mol-%).

viously investigated. This catalytic system allows reactions to be carried out at high temperatures without rapid catalyst decomposition and with a palladacycle considered a slow release precatalyst (SRPC), a clear advantage in intramolecular cross-coupling reactions.[30]

Additionally, it has been suggested that this catalyst follows an alternative $Pd^{(II/IV)}$ catalytic cycle rather than the traditional $Pd^{(0/II)}$ pathway, which could have distinct influences on the nature of the domino-type process in which both steps involve Pd.[29a,31] In the initial series of reactions conducted with the Herrmann–Beller palladacycle **19** (5 mol-%, Entries 1–4, Table 2) it is clear that the intermediate **16** was further consumed in the reaction except when allyl chloride was used (Entry 5, Table 2). It should be mentioned at this stage that the choice of Cy_2NMe was made because of its higher boiling point and that to date the use of this base in reactions in the presence of the Hermann–Beller palladacycle **19** is otherwise unreported. A change in the base to KOAc greatly improved the yield of the indole **17** but did not stop the formation of the isomeric product **18**. A change in the allylating agent from the allyl acetate to allyl bromide improved the yield of the desired indole **17** and almost eliminated the formation of its regioisomer **18**. This result can be attributed to allyl acetate being slightly more reactive in the intermolecular Heck reaction and possibly less reactive in the Tsuji–Trost reaction. The reaction with allyl chloride was selective for the allylated intermediate **16**, which is possibly attributable to the chloride ion hindering the initial stages of the Heck catalytic cycle.

On use of Cs_2CO_3 in combination with the HB catalyst (Entry 6, Table 2) an excellent yield of 86% of the desired indole was achieved, with this process also being repeatable on a larger scale. Additionally, to confirm that the HB catalyst was the active precursor species in this process an additional reaction was carried out with $Pd(OAc)_2$ and the P(*o*-tol)$_3$ ligand (Entry 7, Table 2). In this case only the intermediate **16** was generated.

Table 2. Investigation of the domino reaction with *N*-tosyl-2-iodoaniline (**15**) and the Herrmann–Beller catalyst.[a]

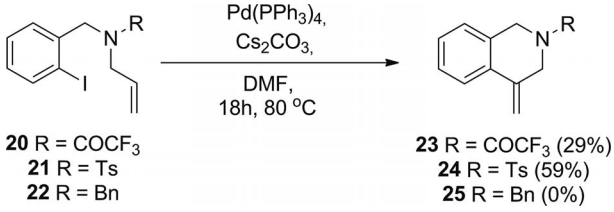


	X[b]	Base	Catalyst	Temp. [°C]	Add. ligand	Yield [%] 16	17	18
1	OAc	Cy_2NMe	HB[a]	90–100	–	trace	26	16
2	OAc	Cy_2NMe	HB[a]	120	–	trace	33	16
3	OAc	KOAc	HB[a]	120	–	trace	66	22
4	Br	KOAc	HB[a]	r.t. to 120	–	80	16	2
5	Cl	Cs_2CO_3	HB[a]	r.t. to 120	–	84	15	0.7
6	Br	Cs_2CO_3	HB[a]	r.t. to 120	–	trace	86	–
7	Br	KOAc	$Pd(OAc)_2$	70	P(*o*-tol)$_3$	> 90	–	–

[a] The Herrmann–Beller catalyst (HB) is *trans*-bis(μ-acetato)-bis[*o*-(di-*o*-tolylphosphanyl)benzyl]dipalladium(II) (**19**) and was used at 5 mol-%. [b] In each reaction 1–2 equiv. of the allylating reagent were used.

Domino Tsuji–Trost/Heck Reaction Combinations for the Synthesis of Tetrahydroisoquinolines

The synthesis of tetrahydroisoquinolines through intramolecular Heck reactions has been investigated by a few groups, but this process is in general far less reliable than the previously discussed formation of the indole ring system. Usually the product bearing the exocyclic double bond formed through a 6-*exo*-*trig* cyclisation predominates.[32] In previous reports, the second steps of our planned domino reaction sequences, intramolecular Heck reactions of allylated amines, often produce unwanted palladacycle intermediates. These intermediates, which have previously been isolated by Broggini and Balme, ultimately hinder β-hydride elimination and significantly lower the yields of the Heck reactions.[32] Therefore, because this was the second step in our proposed domino reaction sequence, we imagined that the yields of the tetrahydroisoquinoline might be lower than in the cases in which the indole ring system was targeted. In this context we deemed the protecting group on the nitrogen to be essential for potential improvement of the Heck reaction. To mirror the results from the earlier indole domino reactions, we investigated both trifluoroacetate and tosyl nitrogen-protecting groups, and hence prepared the compounds **20** and **21** (Scheme 5). Additionally, the benzyl protecting group was also trialled (compound **22**) for its possibly steric hindrance of the formation of stable and unwanted palladacycle intermediates, as observed by other groups, as well as for its potential to improve the rate of the allylation reaction.[32a,32b] The three protected amines (**20**–**22**) were prepared by standard allylation procedures (see the Exp. Section). Treatment of each of these olefins under identical catalytic conditions (Scheme 5), suggested that in this instance the toluenesulfonamide was the most

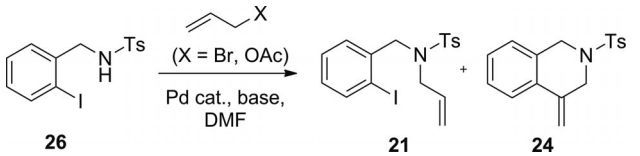


Scheme 5. Intramolecular Heck reactions of the olefins **20**–**22**.

reactive system for the intramolecular Heck reaction. Instability of compounds **20**–**22** was also evident in this process, with reasonable quantities of decomposition products being observed in these trials.

Investigations into the domino process were initiated by application of reaction conditions similar to those that had been successful in the indole ring formation (Entries 1 and 2, Table 3). In these cases we isolated only the allylated compound **21**, depending on the reaction time. Modification of the base or use of allyl acetate was unsuccessful in combination with the Hermann–Beller palladacycle (**19**). This was surprising, because we were anticipating that use of a system that would slowly release Pd^0 might possibly limit the formation of an unwanted intermediate amine palladacycle and improve the reaction yield. Interestingly in each of these cases, the starting material was consumed. Use of $Pd(PPh_3)_4$ (10 mol-%) as a catalyst (Table 3, Entries 6–9) seemed to result in rapid consumption of the starting material without significant mass return, suggesting either decomposition or precipitation of a Pd intermediate hindering the formation of tetrahydroisoquinoline **24**.

Table 3. Domino Tsuji–Trost/Heck reaction sequence with the *N*-tosyl-tetrahydroisoquinoline **26**.



26 **21** **24**

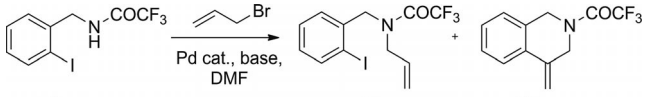
	X[a]	Base	Catalyst	Temp. [°C]	Additive	Add. ligand	Yield [%] **21**	**24**
1	Br	Cs_2CO_3	HB[b]	r.t. to 120		–	>90	–
2	Br	Cs_2CO_3	HB[b]	100		–	45	22
3	OAc	$CsCO_3$	HB[b]	120		–	15	–
4	OAc	KOAc	HB[b]	120		–	–	–
5	Br	Cs_2CO_3	HB[b]	50–90		–	–	–
6	Br	Et_3N	Pd $(PPh_3)_4$	60		–	6	–
7[c]	Cl	Et_3N	$Pd(PPh_3)_4$	80		–	48	–
8	OAc	Et_3N	$Pd(PPh_3)_4$	60		–	14	9
9[c]	OAc	Et_3N	$Pd(PPh_3)_4$	40–70[d]		–	–	–
10[c]	OAc	Et_3N	$Pd(OAc)_2$	40–80[d]		PPh_3	–	–
11	OAc	Et_3N	$Pd(OAc)_2$	45–80[d]	toluene	PPh_3	–	–
12	OAc	Cs_2CO_3	$Pd_2(dba)_3$·$CHCl_3$	50	4 equiv. base	P(*t*Bu)$_3$ HBF_4	<14	–
13	OAc	Cs_2CO_3	$Pd_2(dba)_3$·$CHCl_3$	45–80[d]		P(*t*Bu)$_3$ HBF_4	41	–
14	Br	Cs_2CO_3	$Pd_2(dba)_3$·$CHCl_3$	100	toluene	XPhos	–	–
15	Br	Cs_2CO_3	$Pd_2(dba)_3$·$CHCl_3$	100	toluene	Davephos	trace	–
16	Br	Cs_2CO_3	$Pd_2(dba)_3$·$CHCl_3$	100	toluene	XantPhos	–	–
17	Br	Cs_2CO_3	$Pd_2(dba)_3$·$CHCl_3$	100	toluene	dppf	–	–

[a] All reactions were completed in DMF, with 2 equiv. of the allylating agent. [b] Hermann–Beller catalyst (HB) is *trans*-bis(μ-acetato)-bis[*o*-(di-*o*-tolylphosphanyl)benzyl]dipalladium(II) (**19**) and was used at 5 mol-%. [c] In these reactions large quantities of the starting material **26** were also reisolated. [d] Reactions were held at the first temperature indicated for 5 h and then at the second temperature overnight.

At lower temperatures this catalyst seems to be much less active and either starting material remains or decomposition occurs. Alteration of the catalytic system to $Pd_2(dba)_3$ with a range of various electron-rich phosphanes, including Buchwald's bis-aryl phosphanes, also failed to improve the conversion of the sulfonamide **26** into the isoquinoline domino product **24** (Table 3, Entries 12–16). The most efficient process for this domino reaction was thus a 22% yield (Entry 2, Table 3) and so we decided to take a more drastic approach and to trial an alternative amine-protecting group.

We next investigated the trifluoroacetate moiety as a protecting group, similar to that utilised earlier in the domino reactions in the formation of 3-benzazepines and azepinoindoles.[10a] Initially we investigated the domino reaction under a range of reaction conditions, with use of $Pd(PPh_3)_4$ (10 mol-%) or HB catalyst (5 mol-%) (Entries 1–4, Table 4). The best conditions for the conversion of the amide **27** into compound **23** through a Tsuji–Trost/Heck reaction domino process was with use of $Pd(PPh_3)_4$ (10 mol-%) in DMF (49%).

Table 4. Domino Tsuji–Trost/Heck reaction sequence[a] to afford the *N*-trifluoroacetyl-tetrahydroisoquinoline **23**.



27 **20** **23**

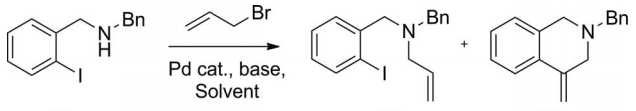
	Catalyst	Base	Temp. [°C]	Time [h]	Solvent	Yield [%] **20**	**23**
1	$Pd(PPh_3)_4$	Cs_2CO_3	80	18	DMF	0	49
2	HB[b]	Cs_2CO_3	80	18	DMF	0	19
3	$Pd(PPh_3)_4$	Cs_2CO_3	80	18	PhMe/ DMF (9:1)	0	27
4	$Pd(PPh_3)_4$	Cs_2CO_3	45	2.5	DMF	64	trace
5	$Pd(PPh_3)_4$ 1 mol-%	Cs_2CO_3	80	48	DMF	12	23
6	$Pd(PPh_3)_4$ + PPh_3 (100 mol-%)	Cs_2CO_3	80	18	DMF	0	52

[a] Pd (10 mol-%), solvent (2 mL) and allyl bromide (2 equiv.) unless stated otherwise. [b] The Hermann–Beller catalyst (HB) is *trans*-bis(μ-acetato)-bis[*o*-(di-*o*-tolylphosphanyl)benzyl]dipalladium(II) (**19**).

This yield was reasonable in view of the perceived complexity of the second intramolecular Heck reaction and the fact that it is incorporated as part of a domino process. At lower temperatures reasonable amounts of the allylated compound **20** were isolated in the absence of the tetrahydroisoquinoline **23**. A reduction in catalytic loading (Entry 5, Table 4), potentially to circumvent the rapid formation of any palladacycle intermediates, was also trialled. Similarly, the use of phosphane in excess, as reported by Balme's group, for the intermolecular Heck reaction was attempted in order to improve the yield of the domino product.[32b] In this case this set of reaction conditions (Entry 6, Table 4) was successful, with a yield of 52% of the domino product tetrahydroisoquinoline **23**, excellent considering the difficulty of the formation of these ring systems in Heck-type processes.

In the final example of this ring system we also investigated the domino reaction sequence with a benzyl-protected amine. Despite our poor result for the intramolecular Heck reaction we were in this case able to obtain some (21%) of the benzyl-protected tetrahydroisoquinoline **25** with use of the palladacycle **19**. In this example it was clear that the allyl species **22** was extremely unstable in the presence of a range of palladium catalysts and that this was the factor preventing reasonable conversion into the domino product. Reducing the catalytic loading (Entries 4 and 5, Table 5) had a dramatic effect on the initial Tsuji–Trost reaction, with large quantities of the starting material **28** remaining in the reaction mixtures.

Table 5. Domino Tsuji–Trost/Heck reaction sequence[a] to afford the *N*-benzyl-tetrahydroisoquinoline **25**.



28 **22** **25**

	Catalyst	Temp. [°C]	Time [h]	Solvent	Yield [%] **22**	**25**
1	$Pd(PPh_3)_4$	r.t. to 40–80[b]	20	DMF	23	12
2	$Pd(OAc)_2$	r.t. to 40–80[b]	20	DMF	25	8
3	HB[c]	r.t. to 40–80[b]	20	DMF	0	21
4	HB[c],[d]	80	20	PhMe	0	0
5	$Pd(OAc)_2$[c][d]	80	20	PhMe	0	0

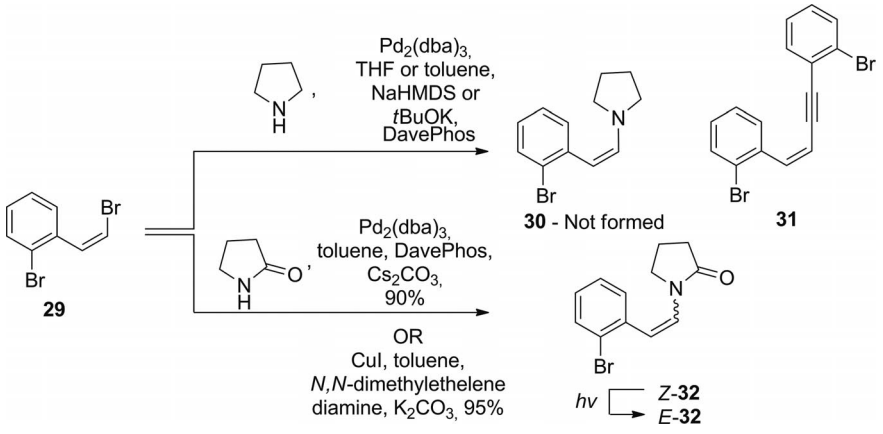
[a] Allyl bromide (2 equiv.) was used in each example. [b] Room temp. for 2 h, 40 °C for 1.5 h, 80 °C for 16 h. [c] The Hermann–Beller catalyst (HB) is *trans*-bis(μ-acetato)-bis[*o*-(di-*o*-tolylphosphanyl)benzyl]dipalladium(II) (**19**). [d] Pd catalyst (0.08 mol-%), and in these examples large amounts of the starting material **28** remained,.

Buchwald–Hartwig/Heck Reaction Sequence for the Synthesis of 3-Benzazepines

To expand the scope of domino reaction methodology involving Heck reactions, we also envisaged the incorporation of Buchwald–Hartwig cross-coupling reactions.[25b] The combination of these two reactions is extremely rare in the literature, possibly due to the need for ordered chemoselectivity for the two cross-coupling reactions, because they both utilise aryl and vinyl halides as their starting substrates. Substrate reactivity is vital, depending on whether the C–N cross-coupling is designed to occur as the first bond-forming process[33] or the second.[34] To construct a substrate for this domino reaction we prepared compound **29** (Scheme 6), bearing both an aryl and vinyl bromide. This compound has been employed in total syntheses[35] and in other domino-type processes.[36] Many of the reported domino processes involving this compound (and its derivatives) involve double C–N cross-coupling to afford indole N-heterocycles. Previously, in the case of C–C bond formation, this compound had shown some selectivity towards the vinyl bromide under palladium-catalysed reaction conditions.[35,37]

The dibromide **29** was prepared by transformation of *ortho*-bromobenzaldehyde into the 1,2-dibromovinyl compound, followed by nBu_3SnH reduction.[35] Additionally, a Wittig reaction process with the same starting material (*ortho*-bromobenzaldehyde) was effective in producing larger quantities of compound **29**, although a small degree of contamination with the *E*-isomer after chromatography was also observed.[36a,36b,38]

As part of the development of this domino reaction we initially investigated the chemoselectivity of a Buchwald–Hartwig reaction with the substrate **29**. For the C–N cross-coupling reaction we first sought a simple amine and so were attracted to pyrrolidine. Several reaction attempts with the ligands popularised by Buchwald only produced the dimeric compound **31** (Scheme 6),[39] together with a small amount of cyclic triyne. In this case it is assumed that compound **31** was formed through initial elimination of HBr and a subsequent Sonogashira-type reaction with a second molecule of the vinyl bromide **29** (Scheme 6). After this result, which had shown no indication of a C–N reaction, we required a slightly more reactive coupling partner that would react prior to the dimerisation of compound **29**. We thus considered the corresponding amide: pyrroldinone. A C–N cross-coupling reaction of this amide with $Pd_2(dba)_3{\cdot}CHCl_3$, DavePhos and Cs_2CO_3 afforded the desired



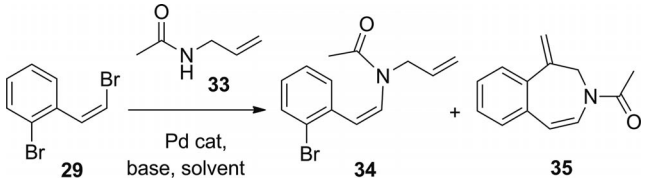
Scheme 6. C–N cross-coupling reactions of the dibromide **29**.

enamide (*Z*)-**32** (Scheme 6), in excellent yields (90%). Because the *Z* geometrical isomer was unstable, the light-promoted conversion into the *E* isomer was also carried out.[40] In this instance we were encouraged by the chemoselective nature of this reaction for the vinyl bromide over the aryl bromide. To investigate the copper variant of this reaction we also trialled the Ullmann–Goldberg reaction; in this instance treatment of **29** with pyrroldinone, CuI and *N*,*N*-dimethylethylenediamine furnished the required amide (*E*)-**32** in 95% yield.

Given the excellent chemoselective nature of the C–N cross-coupling of pyrrolidinone and the dibromo compound **29** we explored the possibility of also incorporating a vinyl (or olefinic) substituent in an amide of this type. Unfortunately, the corresponding amide (5-vinylpyrrolidin-2-one) was not commercially available and methods for the production of this compound are quite lengthy for a methodological study of this kind. In this case we decided upon the simpler compound **33** (Table 6), containing the two functionalities for C–N and C–C cross-coupling. Application of the conditions used for the original Buchwald–Hartwig cross-coupling reaction of pyrrolidinone to the reaction with *N*-allylacetamide (**33**) provided none of the desired domino product **35** or of the precursor **34** (Entry 1, Table 3). Increasing the amount of *N*-allylacetamide (**33**) to two equivalents (DavePhos, 10 mol-%), however, initiated the formation both of the domino product **35** and of the C–N cross-coupling precursor **34**. To test the rates of each of these single steps in the domino process the reaction was stopped after 2.5 hours and in this process a 35% yield of the C–N cross-coupling product **34** was obtained (Entry 3, Table 6), with only trace amounts of the domino product **35**. Increasing the amount of amide from 2 to 4 or 6 equiv. also improved the overall yield of the domino product **35** (Entries 4 and 5, Table 6). Under the last set of conditions a 50% yield of the domino product was achieved (Entry 5), but because of the impractical nature of using several equivalents of the amide an improved series of catalytic conditions were sought. Changing the base, solvent and Pd-to-ligand ratio (10 mol-% catalyst) also failed to have any significant influence on the reaction.

Modification of the biaryl ligand system was also investigated and in the case of SPhos (Entry 16, Table 6), containing two methoxy groups, the reaction proceeded in similar manner to when DavePhos was applied, with a 12% yield of the domino product **35**. Other Buchwald ligands (JohnPhos, XPhos, cyclohexyl JohnPhos and *tert*-butyl XPhos) unfortunately failed to initiate the domino process or to form any of the single C–N cross-coupling product, possibly indicating the need for an electron-donating group on the lower ring of the phosphane ligand. The key to improvement of the domino process was the use of an alternative ligand scaffold.[41] With a low Pd-to-ligand ratio (1:1 or 1:2) and the application of XantPhos (10 mol-%) this domino reaction was exceptional, with yields of the benzazepine **35** of 82 and 83%, respectively (Entries 23 and 24, Table 6). In our analysis the clear difference in yields with this ligand could be attributed to the wide bite angle of

Table 6. Investigations into domino Buchwald–Hartwig/Heck reaction sequences[a].



	Base	Amide (equiv.)	Ligand	Solvent	Pd [mol-%]	Pd/L ratio	Yield **34**	**35**
1	Cs_2CO_3	1	DavePhos	PhMe	10	2:1	0	0
2	Cs_2CO_3	2	DavePhos	PhMe	10	2:1	11	33
3[b]	Cs_2CO_3	2	DavePhos	PhMe	10	2:1	35	trace
4	Cs_2CO_3	4	DavePhos	PhMe	10	2:1	0	46
5	Cs_2CO_3	6	DavePhos	PhMe	10	2:1	0	50
6	K_3PO_4	2	DavePhos	PhMe	10	2:1	13	9
7[c]	*t*BuOK	2	DavePhos	PhMe	10	2:1	0	0
8	Cs_2CO_3	2	DavePhos	DMF	10	2:1	0	0
9	Cs_2CO_3	2	DavePhos	1,4- dioxane	10	2:1	0	17
10	Cs_2CO_3	2	DavePhos	PhMe	10	1:2	trace	trace
11	Cs_2CO_3	2	DavePhos	PhMe	10	1:1	trace	trace
12	Cs_2CO_3	2	DavePhos	PhMe	10	4:1	trace	19
13	Cs_2CO_3	2	DavePhos	PhMe	20	2:1	0	15
14	Cs_2CO_3	2	DavePhos	PhMe	5	2:1	7	9
15	Cs_2CO_3	2	JohnPhos	PhMe	10	2:1	0	0
16	Cs_2CO_3	2	SPhos	PhMe	10	2:1	15	12
17	Cs_2CO_3	2	XPhos	PhMe	10	2:1	trace	trace
18	Cs_2CO_3	2	cyclohexyl JohnPhos	PhMe	10	2:1	0	0
19	Cs_2CO_3	2	*tert*-butyl XPhos	PhMe	10	2:1	0	0
20	Cs_2CO_3	2	*o*-tol	PhMe	10	2:1	0	0
21	Cs_2CO_3	2	DavePhos	PhMe	10	2:1	0	0
22	Cs_2CO_3	2	XantPhos	PhMe	10	2:1	0	33
23	Cs_2CO_3	2	XantPhos	PhMe	10	1:1	0	82
24	Cs_2CO_3	2	XantPhos	PhMe	10	1:2	0	83

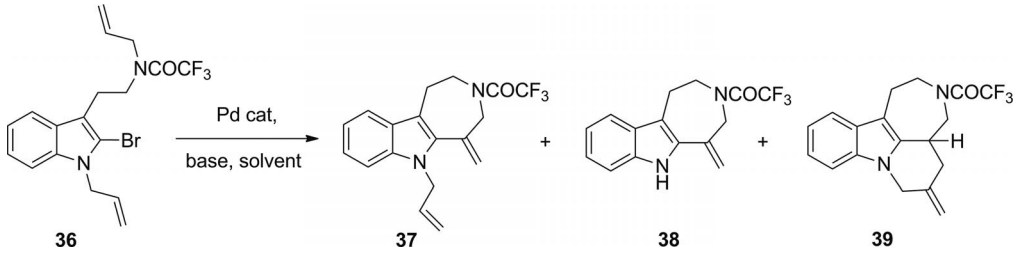
[a] All reactions were carried out at 100 °C with $Pd_2(dba)_3{\cdot}CHCl_3$ and the specified ligand. [b] Reaction was carried out for 2.5 h. [c] Reaction produced only the elimination product 2-bromoethynylbenzene.

XantPhos in relation to other ligands used for C–N cross-coupling.[42] In earlier studies by Hartwig, ligands with slightly smaller bite angles are proposed to be more reactive for aryl bromides.[43] Given that many of the studied reactions either go to completion or there is only a small amount of the allyl amide **34** remaining, it is assumed that the Heck reaction has the lower activation energy barrier of the two single-step processes. This was apparent when the olefin **34** was treated with $Pd(PPh_3)_4$ (10 mol-%) under standard Heck reaction conditions to afford a 73% yield of the desired 3-benzazepine **35**.

Domino Heck/Heck Carbopalladation to Azepinobenzindolizines

The original classification of a "Zipper" palladium-catalysed domino reaction is one of several general modes of domino carbopalladation, which has been described by sev-

Table 7. Domino Heck/carbopalladation reaction sequence to afford the tetracycle **39**.



36 **37** **38** **39**

Entry	Catalyst[a]	Base (equiv.)	Concentration	Solvent	Time	Ratio **37**/**39**	Isolated yields
1	$Pd(PPh_3)_4$	K_2CO_3 (1)	55 mmol L^{-1}	DMF	3 h	1:1	**37**:**39** 49%; **38** 40%
2	$Pd(PPh_3)_4$	K_2CO_3 (8)	97 mmol L^{-1}	DMF	5 h	1.00:0.88	**37**:**39** 52%; **38** 27%
3	$Pd(PPh_3)_4$	NBu_4OAc (2)	54 mmol L^{-1}	DMF	3 h	1.00:0.21	**37**:**39** 73%; **38** 0%
4	$Pd(PPh_3)_4$	NBu_4OAc (2)	56 mmol L^{-1}	DMF/PhMe 1:1	3 h	1.00:0.17	**37**:**39** 68%; **38** 0%
5	$Pd(PPh_3)_4$	NEt_3 (3)	80 mmol L^{-1}	DMF	21 h	1.00:1.18	**37**:**39** 57%; **38** 14%
6	$Pd(PPh_3)_4$	DBU (3)	89 mmol L^{-1}	DMF	24 h	1.00:0.41	**37**:**39** 43%; **38** 0%

[a] $Pd(PPh_3)_4$ was used at 10 mol-% loading for all reactions.

eral groups.[44] In 2009 we described a similar domino process for the bis-allyl compound **36** (Table 7), in which an initial Heck reaction of the allylacetamide group at the indole C2 position first produces the azepine ring, and a subsequent second Heck carbopalladation could occur with the indole allyl group to afford the azepino-benzindolizine ring system **39**. Unusually, the other possible reaction pathway involving the indole allyl group and the 2-bromoindole functionality forming the formation of a five-membered ring was not followed, possibly due to the more strained ring configuration.

In our original report of the reaction behaviour of the bisallylated indole **36** we isolated three compounds: the *N*-allylazepinoindole **37**, the azepino-indole **38** and the azepino-benzindolizidine **39** (Table 7). The products **37** and **39** presumably arise from a similar Pd intermediate, with the indoleazepine **37** resulting from immediate β-hydride elimination and the tetracycle **39** from additional carbopalladation. The last compound **38**, formed through deallylation, is the major obstacle in the production of the domino product **39**. Because the original reaction conditions had produced this mixture of three interesting compounds it seemed a useful method with which to probe the relative productiveness of the two different pathways leading to these compounds under a range of conditions. The N-heterocyclic ring system contained in compound **39** is of current interest because alkaloids with the same 6–5–7–6-membered ring system have been reported in the literature. Although this ring system is relativity rare, notable examples can be found; they include the chippiine indole alkaloids, the prototype compound of which, chippiine, was extracted from the African species *Tabernaemontana chippi*.[45] We were interested to see whether or not variation of the type of base would lead to changes in the **37**/**39** ratio, because the base is involved in the reductive elimination of the intramolecular Heck reaction.

Additionally, any base that would hinder the formation of the deallylated compound **36** would also be advantageous. Changes to the catalyst were not considered because of the high overall yields already obtained with $Pd(PPh_3)_4$. The original conditions (Entry 1, Table 7) gave a 1:1 ratio of the indoleazepine **37** and the tetracycle **39**, and with an increase in the equivalents of K_2CO_3 (Entry 2, Table 7) only a small change in the ratio of these two products was observed. The low solubility of K_2CO_3 in DMF, even at 100 °C, could explain why this excess base would have little effect on the reaction ratio outcome. To solve this problem we used NBu_4OAc, a more DMF-soluble base, (Entry 3, Table 7). Under these conditions none of the deallylated product was formed and furthermore the ratio was changed significantly in favour of the simpler azepinoindole **37**. This result, culminating in a 73% yield of the two desired compounds (**37** and **39**) was significant in view of the complexity of the process. Changing the solvent polarity (Entry 4, Table 7) again increased the ratio slightly in favour of the allyl azepinoindole **37**. Use of the organic base triethylamine (Entry 5, Table 7) gave the opposite result to NBu_4OAc, with the ratio changing slightly in favour of the tetracycle **39**, although some of the de-allylated product **38** was also produced. The stronger organic base DBU was also trialled, favouring the formation of the azepinoindole **37**. Unfortunately, we were not able to control the Heck reaction to give either **39** or **37** exclusively. It seems that the type of base had a distinctive influence on the reaction pathway, but there seems to be no distinction from inorganic to organic bases. It can be said from these trials, however, that more soluble bases lead either to less or to no formation of the deallylated product, which at least simplified the transformation to some degree.

The formation of **39** is unique amongst these reactions because in most cases the substrates are tailored to eliminate the possibility of premature β-hydride elimination.[46] The literature reports several other examples of palladium-catalysed domino reactions in which additional carbopalladation steps have occurred instead of β-hydride elimination.[47] In some cases deliberate efforts to control or suppress β-hydride elimination have been made, although these are still generally limited to isolated examples.[48]

Conclusions

We have designed a range of domino reactions incorporating the Heck reaction as one of the synthetic steps. Through these reactions we have efficiently produced a series of N-heterocycles including indoles, tetrahydroisoquinolines, 3-benzazepines and azepinobinzindolizidines. Through optimisation of the various reaction parameters for each of these domino reactions we have been able to achieve good to excellent yields in each of the domino processes by changing either the substrate or the catalytic system. These reaction examples represent a sound guide for use in production of the discussed N-heterocycles in more complex and highly functionalised systems.

Experimental Section

General Protocol: Starting materials and reagents were obtained from Sigma–Aldrich or Merck chemical companies. *trans*-Bis(μ-acetato)-bis[*o*-(di-*o*-tolylphosphanyl)benzyl]dipalladium(II) (HB catalyst, **19**) was prepared and purified by the procedure of Herrmann et al.[49] *N*-Methyldicyclohexylamine was distilled under reduced pressure and stored under argon. $Pd_2(dba)_3{\cdot}CHCl_3$[50] and $Pd(PPh_3)_4$[51] were prepared as described previously. Allyl chloride was distilled over $CaCl_2$ prior to use. All reactions were performed under argon and at ambient temperature unless stated otherwise. All solvents used in reactions were anhydrous unless noted otherwise. Anhydrous solvents were distilled from the appropriate drying agent[52] or acquired from a Pure Solv 5-Mid Solvent Purification System (Innovative Technology Inc.). ^1H and ^{13}C NMR spectra were acquired with Varian 300, Varian 400, Bruker AV 500 or Bruker AV 600 spectrometers and all signals (δ) are reported in parts per million (ppm). ^1H and ^{13}C assignments were made with the aid of DEPT, COSY, HSQC and HMBC sequences where appropriate. Chemical shifts were referenced to the residual (partially) undeuterated solvents and are reported in parts per million (ppm). Infrared spectra samples were prepared by the KBr disc method and samples were acquired with a Perkin–Elmer Spectrum One spectrometer at 2 cm^{-1} resolution. Melting points were recorded with a Reichart heated-stage microscope. The reported retention factors (R_f) were acquired by TLC performed on Merck silica gel (60 F_{254}) precoated aluminium sheets. Column chromatography was performed with silica gel 60 (0.04–0.063) supplied by Merck. Chromatography solvents were distilled prior to use. HPLC was performed with a Grace–Apollo 250 × 10 mm, 5 micron, C18 semi-preparative column coupled to a UV detector. The trifluoroacetamide **27** and the benzylamine **28** were prepared by standard literature procedures,[53] except that compound **28** was purified by column chromatography (EtOAc/hexane 1:19).

***N*-Tosyl-2-iodoaniline (15):** *N*-Tosyl-2-iodoaniline (**15**) was synthesised by a modification of the procedure of Larock and Zenner.[54] 2-Iodoaniline (1.98 g, 9.0 mmol) was added in one portion at ambient temperature to a magnetically stirred solution of *p*-toluenesulfonyl chloride (1.86 g, 9.8 mmol) in pyridine (5 mL). The resulting brown mixture was heated to 70 °C for 3 h and then allowed to cool to ambient temperature. Excess pyridine was removed under reduced pressure to give a brown solid. The solid was dissolved in CH_2Cl_2 (25 mL) and washed with water (3 × 5 mL), $CuSO_4$ (10 mL, 0.1 M in water) and brine (5 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to give a yellow solid. Flash column chromatography (EtOAc/hexane 1:9) afforded the protected aniline **15** (2.26 g, 67%) as a colourless solid. ^1H NMR and ^{13}C NMR spectroscopic data were consistent with those described in the literature.[54–55] R_f = 0.27 (EtOAc/hexane 1:9). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.66–7.61 (m, 4 H), 7.30 (ddd, J = 8.0, 8.0, 1.6 Hz, 1 H), 7.21 (XX′ part of AA′ XX′ system, 2 H), 6.82 (ddd, J = 8.0, 8.0, 1.6 Hz, 1 H), 6.80 (br s, 1 H), 2.38 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.4, 139.2, 137.6, 136.0, 129.8, 129.6, 127.6, 127.0, 122.6, 92.4, 21.7 (*C*H$_3$) ppm. IR: $\tilde{\nu}_{max}$ = (KBr) 3286 (N–H), 1474 [asymmetric S(=O)$_2$], 1394, 1330, 1158 [symmetric S(=O)$_2$] cm^{-1}. MS (EI): *m*/*z* (%) = 372.9 (79) $[M]^+$, 217.9 (41) $[M - C_7H_7SO_2]^+$, 155.0 (35) $[M - C_6H_5IN]^+$, 139.0 (25) $[M - C_6H_5INO]^+$, 91.0 (100) $[M\ C_6H_5INSO_2]^+$.

***N*-Allyl-*N*-tosyl-2-iodoaniline (16)**

Method A: K_2CO_3 (40 mg, 0.3 mmol) was added in one portion to a magnetically stirred solution of allyl bromide (0.1 mL, 1.2 mmol) and the aryl iodide **12** (109 mg, 0.3 mmol) in THF (2 mL). After this addition, the reaction mixture was heated to 50 °C for 4 h and then allowed to cool to room temperature. The resulting mixture was concentrated under reduced pressure, quenched with water (5 mL) and extracted with Et_2O (3 × 15 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to give a yellow oil. Flash chromatography (EtOAc/hexane 1:9) afforded the alkene **16** (81 mg, 67%) as a colourless oil.

Method B: $Pd(PPh_3)_4$ (31 mg, 0.03 mmol) was added to a magnetically stirred mixture of Cs_2CO_3 (187 mg, 0.57 mmol), nBu$_4$NHSO$_4$ (12 mg, 0.035 mmol), allyl bromide (0.05 mL, 0.6 mmol) and the aryl iodide **15** (101 mg, 0.27 mmol) in toluene/DMF (10:1, 1.65 mL). The resulting mixture was then heated to 60 °C for 18 h. The reaction mixture was concentrated under reduced pressure and the resulting crude oil was fused to silica gel. Flash chromatography (EtOAc/hexane 2:8) afforded the alkene **16** (104 mg, 93%) as a colourless oil. The spectroscopic data for this sample were consistent with those described in the literature.[23a] R_f = 0.34 (EtOAc/hexane 1:9). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.89 (dd, J = 8.0, 1.6 Hz, 1 H), 7.66 (AA′ part of AA′ XX′ system, 2 H), 7.29 (XX′ part of AA′ XX′ system, 2 H), 7.25 (ddd, J = 8.0, 8.0, 1.6 Hz, 1 H), 7.01 (ddd, J = 8.0, 8.0, 1.6 Hz, 1 H), 6.92 (dd, J = 8.0, 1.6 Hz, 1 H), 5.86 (m, 1 H), 5.03 (dtd, J = 8.9, 1.8, 1.2 Hz, 1 H), 4.97 (dtd, J = 17.2, 1.8, 1.2 Hz, 1 H), 4.22–4.08 (m, 2 H), 2.44 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.9, 141.3, 140.5, 136.6, 132.5, 131.1, 130.0, 129.7, 128.7, 128.3, 119.8 (CH=*C*H$_2$), 103.3 (CH=*C*H$_2$), 54.7 (*C*H$_2$), 21.7 (*C*H$_3$) ppm. IR (neat): $\tilde{\nu}_{max}$ = 3062 (C–H), 2922 (C–H), 2864 (C–H), 1595, 1465, 1353 [asymmetric S(=O)$_2$], 1164 [symmetric S(=O)$_2$] cm^{-1}. MS (EI^+): *m*/*z* (%) = 412.9 (20) $[M]^+$, 286 (42) $[M - I]^+$, 155 (39) $[M - C_6H_4INC_3H_5]^+$, 130 (100), 91 (48) $[M - C_6H_4INC_3H_5SO_2]^+$.

3-Methyl-*N*-tosylindole (17): $Pd(OAc)_2$ (8 mg, 0.036 mmol) was added to a stirred solution of Cs_2CO_3 (295 mg, 0.97 mmol), PPh_3 (9 mg, 0.036 mmol) and the alkene **16** (150 mg, 0.36 mmol) in DMF (1.5 mL). The reaction mixture was then heated to 40 °C for 12 h. The resulting mixture was allowed to cool to room temperature and extracted with EtOAc (100 mL). The organic layer was washed with water (5 × 5 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give a brown oil. Flash chromatography (EtOAc/hexane 1:19) afforded the indole **17** as a light brown solid (71%). R_f = 0.6 (EtOAc/hexane 2:8). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.98 (m, 1 H), 7.74 (AA′ part of AA′ XX′ system, 2 H), 7.45 (m, 1 H), 7.30 (m, 2 H), 7.23 (ddd, J = 8.0, 8.0, 0.8 Hz, 1 H), 7.19 (XX′ part of AA′ XX′ system, 2 H), 2.32 (s, 3 H), 2.24 (d, J = 1.6 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.8, 135.6, 135.4, 131.9, 129.9, 126.9, 124.7, 123.2, 123.1, 119.5, 118.7, 113.8, 21.7 (*C*H$_3$), 9.8 (*C*H$_3$) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 1445, 1364 [asymmet-

ric S(=O)$_2$], 1173 [symmetric S(=O)$_2$] cm^{-1}. MS (EI$^+$): *m*/*z* (%) = 285 (52) [M]$^+$, 130 (100) [M – $SO_2C_6H_4CH_3$]$^+$, 91 (18) [M – $C_9H_8NSO_2$]. Spectroscopic data for this sample were consistent with those described in the literature.[56]

Selected Reaction Procedures for Table 1. 3-Methyl-*N*-tosylindole (17)

Entry 1: $Pd(OAc)_2$ (11 mg, 0.049 mmol) was added to a magnetically stirred solution of Cs_2CO_3 (346 mg, 1.06 mmol), allyl bromide (0.05 mL, 0.7 mmol) and **15** (132 mg, 0.35 mmol) in DMF (2 mL). After this addition, the reaction mixture was stirred at room temperature for 16 h and then stirred at 60 °C for a further 5 h. The resulting mixture was allowed to cool to room temperature, diluted with EtOAc and then washed sequentially with water (5 × 1 mL) and brine. The organic layer was then dried ($MgSO_4$), concentrated under reduced pressure and fused to silica gel. Flash chromatography (EtOAc/hexane 1:19) afforded the alkene **16** (132 mg, 90%) and the indole **17** (2.2 mg, 0.2%).

Entry 3: $Pd_2(dba_3)$·$CHCl_3$ (17 mg, 0.016 mmol) was added to a magnetically stirred solution of Cs_2CO_3 (114 mg, 0.35 mmol), Cy_2NMe (0.08 mL, 0.38 mmol), P(*t*Bu)$_3$HBF (10 mg, 0.034 mmol), allyl bromide (0.06 mL, 0.7 mmol) and the aryl iodide **15** (119 mg, 0.32 mmol) in DMF (1 mL). The reaction mixture was stirred for 1 h at room temperature, heated to 80 °C over 30 min and then stirred at this temperature for 16 h. The resulting mixture was allowed to cool to room temperature, diluted with EtOAc and then washed sequentially with water (5 × 1 mL) and brine. The organic layer was then dried ($MgSO_4$), concentrated under reduced pressure and fused to silica gel. Flash chromatography (EtOAc/hexane 1:19) afforded the alkene **16** (107 mg, 81%) and the indole **18** (4 mg, 8%).

2-Methyl-*N*-tosylindole (18): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.16 (m, 1 H), 7.66 (AA′ part of AA′ XX′ system, 2 H), 7.52 (m, 1 H), 7.4 (m, 1 H), 7.29 (m, 1 H), 7.2 (XX′ part of AA′ XX′ system, 2 H), 6.34 (s, 1 H), 2.6 (s, 3 H), 2.35 (s, 3 H) ppm. Spectroscopic data for this sample were consistent with those described in the literature.[57]

Entry 4: $Pd(PPh_3)_4$ (32 mg, 0.028 mmol) was added to a magnetically stirred solution of triethylamine (0.06 mL, 0.83 mmol), allyl chloride (0.04 mL, 0.49 mmol) and the aryl iodide **15** (91.8 mg, 0.25 mmol) in DMF (3 mL). After this addition, the reaction mixture was degassed and stirred at room temperature for 1 h. Further allyl chloride (0.04 mL, 0.49 mmol) was added, after which the reaction mixture was heated to 80 °C and stirred for 16 h. The reaction mixture was allowed to cool to room temperature, diluted with EtOAc (20 mL) and then washed sequentially with water (5 × 1 mL) and brine. The organic layer was then dried ($MgSO_4$), concentrated under reduced pressure and fused to silica gel. Flash chromatography (EtOAc/hexane 1:19) afforded the alkene **16** (82 mg, 45%) and the indole **17** (34 mg, 48%).

Selected Reaction Procedures for Table 2

Entry 1: The Herrmann–Beller catalyst **19** (24 mg, 0.026 mmol) was added to a magnetically stirred solution of Cy_2NMe (0.14 mL, 0.66 mmol), allyl acetate (0.06 mL, 0.56 mmol) and the aryl iodide **15** (96.4 mg, 0.26 mmol) in DMF (4 mL). The reaction mixture was degassed and was then immediately heated to 100 °C and stirred at this temperature for 16 h. The reaction mixture was allowed to cool to room temperature, diluted with EtOAc (20 mL) and then washed sequentially with water (5 × 1 mL) and brine. The organic layer was then dried ($MgSO_4$), concentrated under reduced pressure and fused to silica gel. Flash chromatography (EtOAc/hexane 1:19) afforded the indoles **17** (19 mg, 26%) and **18** (16 mg, 16%).

Entry 2: The Herrmann–Beller catalyst **19** (54 mg, 0.058 mmol) was added to a magnetically stirred solution of Cy_2NMe (0.4 mL, 1.9 mmol) and **15** (201 mg, 0.54 mmol) in DMF (4 mL). The reaction mixture was degassed, allyl acetate (0.06 mL, 0.56 mmol) was added, and the mixture was immediately heated to 120 °C and stirred at this temperature for 16 h. The reaction mixture was allowed to cool to room temperature, diluted with EtOAc and then washed sequentially with water (5 × 1 mL) and brine (1 mL). The organic layer was then dried ($MgSO_4$), concentrated under reduced pressure and fused to silica gel. Flash chromatography (EtOAc/hexane 1:19) afforded the indoles **17** (50 mg, 33%) and **18** (24 mg, 16%).

Entry 6: The Herrmann–Beller catalyst **19** (52 mg, 0.055 mmol) was added to a magnetically stirred solution of Cs_2CO_3 (855 mg, 2.6 mmol) and the aryl iodide **15** (355 mg, 0.95 mmol) in DMF (10 mL). The reaction mixture was degassed and then treated with allyl bromide (0.125 mL, 1.43 mmol). After the addition, the reaction mixture was heated to 70 °C over 30 min and then stirred at 120 °C for 12 h. The resulting mixture was allowed to cool to room temperature, extracted with EtOAc (200 mL) and washed with water (5 × 5 mL) and brine (15 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure and the resulting oil was fused to silica gel. Flash chromatography (EtOAc/hexane 1:19) afforded the indole **17** (234 mg, 86%) as a colourless solid.

***N*-Allyl-2,2,2-trifluoro-*N*-(2-iodobenzyl)acetamide (20):** NaH (13 mg, 60% dispersed in mineral oil, 0.33 mmol) was added on one portion to a magnetically stirred solution of the trifluoroacetamide **27** (100 mg, 0.304 mmol) in DMF (2 mL). The mixture was stirred for 5 min before addition of allyl bromide (53 μL, 0.608 mmol). The resulting mixture was stirred at room temperature for 6 h before being concentrated under reduced pressure. The resulting residue was subjected to column chromatography (EtOAc/hexane 1:19) to give the alkene **20** as a colourless oil (98 mg, 0.265 mmol, 87%). R_f = 0.36 (EtOAc/hexane 1:19). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.87 (m, 1 H) 7.38 (m, 0.4 H) 7.34 (m, 0.6 H) 7.08 (m, 1 H) 7.01 (m, 1 H) 5.78 (m, 1 H) 5.31 (m, *J* = 10 Hz, 0.4 H) 5.28 (m, *J* = 10 Hz, 0.6 H) 5.25 (m, *J* = 18 Hz, 0.6 H) 5.18 (m, *J* = 18 Hz, 0.4 H) 4.68 (s, 0.6 H) 4.61 (s, 0.4 H) 3.97 (m, 2 H) ppm. ^{13}C NMR: δ = (125.8 MHz, $CDCl_3$) 157.8 (C=O), 157.5 (C=O), 140.02, 140.0, 137.3, 137.1, 131.5, 130.4, 129.8, 129.7, 128.9, 128.9, 128.1, 127.0, 119.9, 119.7, 98.8, 97.8, 55.2, 55.2, 53.7, 49.6, 49.6, 49.2 ppm. IR (thin film): $\tilde{\nu}_{max}$ = 3064 (C–H), 3014 (C–H), 2928 (C–H), 1697 (C=O), 1566, 1437, 1358, 1283, 1208 (C–F), 1143 (C–F), 1015, 749 cm^{-1}. MS (EI$^+$): *m*/*z* (%) = 370 (<1) [M + H]$^+$, 369 (<1) [M]$^+$, 328 (12) [M – allyl]$^+$, 243 (11), 242 (95) [M – I$^-$]$^+$, 217 (42), 86 (88), 84 (100). HRMS (EI$^+$): calcd. 368.9838 [M]$^+$; found 368.9846.

***N*-Allyl-*N*-(2-iodobenzyl)-4-methylbenzenesulfonamide (21):** NaH (13 mg, 60% dispersed in mineral oil, 0.33 mmol) was added in one portion to a magnetically stirred solution of the sulfonamide **26** (117 mg, 0.304 mmol) in DMF (2 mL). The resulting mixture was stirred for 5 min, treated with allyl bromide (53 μL, 0.608 mmol) and stirred at room temperature for a further 6 h, before being concentrated under reduced pressure. The resulting residue was subjected to column chromatography (EtOAc/hexane 1:19) to give the aryl iodide **21** as a colourless oil (121 mg, 0.283 mmol, 93%). R_f = 0.59 (EtOAc/hexane 2:8). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.8–7.73 (m, 3 H), 7.51 (dd, *J* = 7.6, 1.6 Hz, 1 H), 7.37–7.31 (m, 3 H), 6.96 (ddd, *J* = 7.6, 7.6, 1.6 Hz, 1 H), 5.55–5.44 (m, 1 H), 5.04 (m, 1 H), 5.0 (dtd, *J* = 8.0, 2.4, 1.2 Hz, 1 H), 4.35 (s, 2 H), 3.8 (d, *J* = 6.8 Hz, 2 H), 2.45 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$):

δ = 143.6, 139.4, 138.5, 137.1, 132.0, 130.0, 129.4, 129.3, 128.6, 127.4, 119.8, 98.2 (Ar-*C*I), 55.6 (*C*H_2), 51.1 (*C*H_2), 21.7 (*C*H_3) ppm. MS (EI$^+$): *m*/*z* (%) = 426.9 (31) [M]$^+$, 300.0 (41) [M – I]$^+$, 271.9 (100) [M – $SO_2C_6H_4CH_3$].

***N*-Benzyl-*N*-(2-iodobenzyl)prop-2-en-1-amine (22):** NaH (13 mg, 60% dispersed in mineral oil, 0.33 mmol) was added in one portion to a magnetically stirred solution of the benzylamine **28** (98 mg, 0.304 mmol) in DMF (2 mL). The resulting mixture was stirred for 5 min, treated with allyl bromide (53 μL, 0.608 mmol) and then stirred at room temperature for 6 h, before being concentrated under reduced pressure. The resulting residue was subjected to column chromatography (EtOAc/hexane 1:19) to give the alkene **22** as a colourless oil (85 mg, 0.234 mmol, 77%). R_f = 0.64 (EtOAc/hexane 1:19). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.83 (m, 1 H, ArH) 7.62 (m, 1 H, ArH), 7.40 (m, 2 H, ArH), 7.34 (m, 2 H, ArH), 7.33 (m, 1 H, ArH), 7.25 (m, 1 H, ArH), 6.95 (m, 1 H, ArH), 5.97 (m, 1 H, C*H*=CH_2), 5.25 (m, 1 H, C=C*H*$_2$), 5.19 (m, *J* = 10.0 Hz, 1 H, C=CH_2), 3.66 (s, 4 H, Ar-CH_2), 3.13 (d, *J* = 6.0 Hz, H_2C=CH-C*H*$_2$) ppm. ^{13}C NMR: δ = (125.8 MHz, $CDCl_3$) 141.8, 139.5, 139.4, 135.6, 130.2, 128.9, 128.6, 128.3, 128.2, 127.0, 117.7, 100.2 (Ar-I), 62.3, 57.9, 56.5 ppm. IR (thin film): $\tilde{\nu}_{max}$ = 3061 (C–H), 3027 (C–H), 3005 (C–H), 2976 (C–H), 2921 (C–H), 2796 (C–H), 2712 (C–H), 1698, 1642, 1562, 1494, 1454, 1455, 1258, 1012, 749 cm^{-1}. MS (EI$^+$): *m*/*z* (%) = 364 (7) [M + H]$^+$, 363 (33) [M]$^+$, 336 (29), 286 (19) 272 (35) [M – Bn]$^+$, 217 (62), 91 (100). HRMS (EI$^+$): calcd. 363.0484 [M]$^+$; found 363.0492.

2,2,2-Trifluoro-1-[4-methylene-3,4-dihydroisoquinolin-2(1*H*)-yl]-ethanone (23): $Pd(PPh_3)_4$ (16 mg, 0.0135 mmol) was added to a magnetically stirred solution of Cs_2CO_3 (88 mg, 0.27 mmol) and the allyl amide **20** (50 mg, 0.135) in DMF (1 mL). After this addition, the reaction mixture was heated to 80 °C and stirred for 16 h. The mixture was concentrated under reduced pressure and the residue was purified by flash chromatography (EtOAc/hexane 1:19) to give the isoquinoline **23** (9 mg, 29%) as a colourless oil. R_f = 0.27 (EtOAc/hexane 1:19), R_f = 0.27 (EtOAc/hexane 1:24). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.66 (m, 1 H, ArH), 7.31 (m, 2 H, ArH), 7.19 (m, 0.6 H, ArH) 7.15 (m, *J* = 1.0 Hz, 0.4 H, ArH), 5.68 (m, 0.4 H, =CH_2) 5.66 (s, 0.6 H, =CH_2), 5.27 (m, *J* = 1.0 Hz, 0.4 H, =CH_2), 5.18 (s, 0.6 H, =CH_2), 4.87 (s, 1.2 H, CH_2), 4.78 (s, 0.8 H, CH_2), 4.50 (s, 0.8 H, CH_2), 4.40 (s, 1.2 H, CH_2) ppm. ^{13}C NMR: δ = (125.8 MHz, $CDCl_3$), 155.9 (C=O), 155.6 (C=O), 132.5, 131.8, 131.5, 131.6, 128.9, 128.8, 128.1, 127.6, 126.7, 126.1, 124.5, 124.4, 116.6 (q, *J* = 1145 Hz, CF_3), 116.7 (q, *J* = 1145 Hz, CF_3), 111.4, 110.6, 50.2 (CH_2), 48.1 (CH_2), 48.0 (CH_2), 46.2 (CH_2) ppm. IR (thin film): $\tilde{\nu}_{max}$ = 2927 (C–H), 1694 (C=O), 1452, 1260, 1201 (C–F), 1177 (C–F), 1142 (C–F), 1009 cm^{-1}. MS (EI$^+$): *m*/*z* (%) = 241 (5) [M]$^+$, 219 (12), 131 (10), 86 (66). 84 (100). HRMS (EI$^+$): calcd. 241.0714 [M]$^+$; found 241.0720.

4-Methylene-2-[(4-methylphenyl)sulfonyl]-1,2,3,4-tetrahydroisoquinoline (24): $Pd(PPh_3)_4$ (26 mg, 0.023 mmol) was added to a magnetically stirred solution of Cs_2CO_3 (148 mg, 0.454 mmol) and the sulfonamide **21** (97 mg, 0.227 mmol) in DMF (1 mL). After the addition, the reaction mixture was heated to 80 °C and stirred overnight. The mixture was concentrated under reduced pressure and the residue was purified by column chromatography (EtOAc/hexane 1:4) to give the isoquinoline **24** (31 mg, 59%) as a white solid. R_f = 0.38 (EtOAc/hexane 2:8). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67 (AA′ part of AA′ XX′ system, 2 H), 7.55 (dd, *J* = 7.2, 1.6 Hz, 1 H), 7.33 (m, 1 H), 7.24 (XX′ part of AA′ XX′ system, 2 H), 7.19 (ddd, *J* = 7.2, 7.2, 1.6 Hz, 1 H), 7.05 (m, 1 H), 5.59 (s, 1 H), 5.1 (s, 1 H), 4.36 (s, 2 H), 4.0 (s, 2 H), 2.39 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.8, 136.6, 133.7, 129.7, 128.5, 128.1, 127.3, 126.7, 124.0, 110.1, 50.7 (*C*H_2), 48.8 (*C*H_2), 21.7 (*C*H_3) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 1346 [asymmetric S(=O)$_2$], 1166 [symmetric S(=O)$_2$], 1090 cm^{-1}. MS (EI$^+$): *m*/*z* (%) = 299.0 (10) [M]$^+$, 262.0 (13), 144.0 (83) [M – $SO_2C_6H_4CH_3$]$^+$, 143.0 (100). HRMS (EI$^+$): calcd. for $C_{17}H_{17}NO_2S$ [M]$^+$ 299.0980; found 299.0983.

Selected Reaction Procedures for Table 3

Entry 2: The Herrmann–Beller catalyst **19** (12 mg, 0.013 mmol) was added to a magnetically stirred solution of Cs_2CO_3 (252 mg, 0.775 mmol), the aryl iodide **26** (100 mg, 0.258 mmol) and allyl bromide (45 μL, 0.516 mmol) in DMF (2 mL). The resulting reaction mixture was then heated to 100 °C and stirred overnight. The mixture was concentrated under reduced pressure and the residue was purified by column chromatography (EtOAc/hexane 1:19 → EtOAc/hexane 1:4) to give the olefin **21** (53 mg, 48%) as a colourless oil [R_f = 0.18 (EtOAc/hexane 1:19)] and the tetrahydroisoquinoline **24** (18 mg, 23%) as a white solid [R_f = 0.38 (EtOAc/hexane 1:4)].

Entry 7: $Pd(PPh_3)_4$ (30 mg, 0.0258 mmol) was added to a magnetically stirred solution of NEt_3 (108 μL, 0.775 mmol), the aryl iodide **26** (100 mg, 0.258 mmol) and allyl chloride (42 μL, 0.516 mmol) in DMF (2 mL). The resulting reaction mixture was heated to 80 °C and stirred for 16 h. The mixture was concentrated under reduced pressure and the residue was purified by column chromatography (EtOAc/hexane 1:19 → EtOAc/hexane 1:4) to give the olefin **21** (53 mg, 0.124 mmol, 48%) as a colourless oil [R_f = 0.18 (EtOAc/hexane 1:19)] and the aryl iodide **26** (33 mg, 33%).

Entry 8: $Pd(PPh_3)_4$ (32 mg, 0.28 mmol) was added to a magnetically stirred solution of triethylamine (0.05 mL, 0.7 mmol), allyl acetate (0.06 mL, 0.56 mmol) and the aryl iodide **26** (100 mg, 0.26 mmol) in DMF (3 mL). The resulting reaction mixture was heated to 60 °C and stirred overnight. The reaction mixture was allowed to cool to room temperature, extracted with EtOAc (20 mL) and then washed sequentially with water (5 × 1 mL) and brine. The organic layer was then dried ($MgSO_4$), concentrated under reduced pressure and fused to silica gel. Flash chromatography (EtOAc/hexane 1:9) afforded the alkene **21** (16.4 mg, 14%) as a colourless oil and the isoquinoline **24** (7 mg, 9%) as a yellow solid.

Selected Reaction Procedures for Table 4

Entry 1: $Pd(PPh_3)_4$ (35 mg, 0.034 mmol) was added to a magnetically stirred solution of Cs_2CO_3 (297 mg, 0.912 mmol), the aryl iodide **27** (100 mg, 0.304 mmol) and allyl bromide (53 μL, 0.608) in DMF (2 mL). The resulting reaction mixture was heated to 80 °C and stirred for 16 h. The resulting mixture was concentrated under reduced pressure and the residue was purified by column chromatography (EtOAc/hexane 1:19) to give the tetrahydroisoquinoline **23** (36 mg, 49%) as a colourless oil. R_f = 0.27 (EtOAc/hexane 1:19).

Entry 5: $Pd(PPh_3)_4$ (3 mg, 0.003 mmol) was added to a magnetically stirred solution of Cs_2CO_3 (297 mg, 0.912 mmol), the aryl iodide **27** (100 mg, 0.304 mmol) and allyl bromide (53 μL, 0.608) in DMF (2 mL). After the addition, the reaction mixture was then heated to 80 °C and stirred for 16 h. The mixture was concentrated under reduced pressure and the residue was purified by column chromatography (EtOAc/hexane 1:19) to give alkene **20** (13 mg, 12%) as a colourless oil [R_f = (EtOAc/hexane 1:19)] and the isoquinoline **23** (17 mg, 23%) as a colourless oil [R_f = 0.27 (EtOAc/hexane 5%)].

Entry 6: $Pd(PPh_3)_4$ (35 mg, 0.034 mmol) was added to a magnetically stirred solution of Cs_2CO_3 (297 mg, 0.912 mmol), the aryl iodide **27** (100 mg, 0.304 mmol), PPh_3 (80 mg, 0.304 mmol) and allyl

bromide (53 μL, 0.608) in DMF (2 mL). The resulting reaction mixture was then heated to 80 °C and stirred for 16 h. The resulting mixture was concentrated under reduced pressure and the residue was purified by column chromatography (EtOAc/hexane 1:19) to give the isoquinoline **23** (38 mg, 52%) as a colourless oil [R_f = 0.27 (EtOAc/hexane 1:19)].

Selected Reaction Procedures for Table 5

Entry 3: The Herrmann–Beller catalyst **19** (15 mg, 0.015 mmol) was added to a magnetically stirred solution of Cs_2CO_3 (302 mg, 0.927 mmol), **28** (100 mg, 0.309 mmol) and allyl bromide (54 μL, 0.618 mmol) in DMF (2 mL). The resulting reaction mixture was then heated at 40 °C for 1.5 h and then to 80 °C and stirred for 16 h. The resulting mixture was concentrated under reduced pressure and the residue was purified by column chromatography (EtOAc/hexane 1:19) to give the tetrahydroisoquinoline **25** (15 mg, 21%) as a colourless oil. The spectroscopic data for this compound were identical to those previously reported.[58]

1-Bromo-2-[(*Z*)-2-bromovinyl]benzene (29)

Method A: A solution of PPh_3 (9.07 g, 34.6 mmol) in CH_2Cl_2 (30 mL) was added dropwise over 15 min to a magnetically stirred solution of CBr_4 (5.73 g, 17.3 mmol) in CH_2Cl_2 (30 mL), maintained at 0 °C. The reaction mixture was then allowed to warm to room temperature and stirred for 1 h before cooling to 0 °C. 2-Bromobenzaldehyde (1.00 mL, 8.65 mmol) in CH_2Cl_2 (30 mL) was added to the yellow-brown reaction mixture over 3 min and the resulting solution was allowed to warm to room temperature and stirred for a further 2 h. The resulting mixture was poured into hexane (400 mL) and filtered, and the residue was washed with hexane (2 × 50 mL). The filtrate was concentrated and purified by column chromatography (hexane) to afford 1-bromo-2-(2,2-dibromovinyl)benzene (2.69 g, 91%) as a pale yellow oil.[35] R_f = 0.66 (100% hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.60 (m, 1 H, Ar-H), 7.58 (m, 1 H, Ar-H), 7.51 (s, 1 H, 1′-H), 7.33 (m, 1 H, Ar-H), 7.20 (m, 1 H, Ar-H) ppm. ^{13}C NMR (125.8 MHz): δ = 136.7, 136.1 (C-2), 132.7, 130.4, 129.9, 127.2, 123.1 (C-1), 92.9 (C-2′) ppm. IR (thin film): $\tilde{\nu}$ = 3067 (C–H), 3019 (C–H), 2974 (C–H), 2863 (C–H), 1605, 1583, 1561, 1462, 2435, 1428, 1046, 1025 cm^{-1}. MS EI: *m*/*z* (%) = 344 (18) [M(^{81}Br$_3$)]$^+$, 342 (54) [M(^{81}Br$_2$^{79}Br$_1$)]$^+$, 340 (55) [M(^{81}Br$_1$^{79}Br$_2$)]$^+$, 338 (18) [M(^{79}Br$_3$)]$^+$, 263 (49) [M – Br]$^+$, 261 (100) [M – Br]$^+$, 259 (51) [M – Br]$^+$, 182 (72) [M – 2 Br]$^+$, 180 (73) [M – 2 Br]$^+$, 101 (34). HRMS EI: calculated for $C_8H_5Br_3$: 337.7941, found 337.7949.

nBu_3SnH (approx. 50%, 13.6 mL, 26 mmol) was added portionwise at room temperature over 5 h to a magnetically stirred solution of (*Z*)-1-bromo-2-(2-bromovinyl)benzene (8.90 g, 26.1 mmol) and $Pd(PPh_3)_4$ in toluene (150 mL), with monitoring of conversion by ^{1}H NMR. The mixture was stirred at room temperature for 16 h. The solvent was removed under reduced pressure and the resulting residue was purified by column chromatography (silica, hexane) to afford the (*Z*)-dibromostyrene **29** (4.22 g, 62%) as a colourless oil.[59] R_f = 0.63 (hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.78 (dd, *J* = 8.1, 1.8 Hz, 1 H, 6-H/3-H), 7.60 (dd, *J* = 7.8, 0.9 Hz, 1 H, 6-H/3-H), 7.34 ("dt", "*J*" = 7.8, 1.2 Hz, 1 H, 5-H/6-H), 7.21 (d, *J* = 8.1 Hz, 1 H, 1′-H), 7.19 (m, 1 H, 5-H/6-H), 6.59 (d, *J* = 8.1 Hz, 1 H, 2′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.3 (C-2), 132.8 (ArC), 132.5 (ArC), 130.7 (ArC), 127.7 (ArC), 127.0 (ArC), 123.9 (C-1), 109.5 (C-1′) ppm. IR (thin film): $\tilde{\nu}$ = 3070 (C–H), 3014 (C–H), 2921 (C–H), 1617, 1587, 1561, 1463, 1437, 1428, 1317 cm^{-1}. MS EI: *m*/*z* (%) = 262 (49) [M(^{81}Br$_1$^{79}Br$_1$)]$^+$, 260 (25) [M(^{79}Br$_2$)]$^+$, 183 (94) [M – Br]$^+$, 181 (98) [M – Br]$^+$, 102 (81), 93 (86), 84 (100). HRMS (EI) calculated for $C_8H_6Br_2$: 259.8836, found 259.8835.

Method B: (Bromomethyl)triphenylphosphonium bromide (8.28 g, 19.5 mmol) was added portionwise at –78 °C to a magnetically stirred solution of *t*BuOK (2.13 g, 19.0 mmol) in THF (50 mL) and the resulting mixture was stirred for 1.5 h. 2-Bromobenzaldehyde (3.0 g, 16.3 mmol) was added dropwise and the reaction mixture was stirred for 16 h, during which time the solution was allowed to warm from –78 °C to ambient temperature. The solution was diluted with hexane (30 mL) and filtered through a small celite pad with washing with hexane (150 mL). The filtrate was concentrated under reduced pressure and the resulting colourless oil was subjected to flash chromatography (hexane). The fractions corresponding to the olefinic product **29** were divided into three batches. Although the Z and *E* geometrical isomers could not be differentiated through visualisation by tlc the early fractions (R_f = 0.4) contained a *Z*/*E* ratio of 9.5:1 whereas the worst ratio fractions were 4.5:1. The combined mass was 3.1 g (72%). This method was a modification of the original procedure reported by Willis.[36a]

1-[(*Z*)-2-(2-Bromophenyl)vinyl]pyrrolidin-2-one [(*Z*)-32]: DavePhos (7.5 mg, 19 μmol) and $Pd_2(dba)_3$·$CHCl_3$ (20 mg, 19 μmol) were added in a single portion to a magnetically stirred solution of the dibromostyrene **29** (100 mg, 0.382 mmol), Cs_2CO_3 (414 mg, 1.14 mmol) and pyrrolidin-2-one (87 μL, 1.14 mmol) in toluene (0.4 mL). The resulting mixture was heated at 100 °C for 20 h. The resulting mixture was concentrated under reduced pressure and the residue was purified by column chromatography (EtOAc/hexane 1:4) to afford the *Z*-enamine **32** (92 mg, 90%) as a pale brown solid. R_f = 0.2 (ethyl acetate/hexane 20%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.55 (m, 1 H, 3-H/6-H), 7.29 (m, 1 H, 3-H/4-^{4}/5-H/6-H), 7.18 (m, 1 H, 3-H/4-H/5-H/6-H), 7.11 (m, 1 H, 4-H/5-H), 6.93 (d, *J* = 9.9 Hz, 1 H, 2′-H), 5.83 (d, *J* = 9.9 Hz, 1 H, 1′-H), 3.08 (t, *J* = 7.2 Hz, 2 H, 5′′-H), 2.39 (t, *J* = 8.1 Hz, 2 H, 3′′-H), 1.91 (m, 2 H, 4′′-H) ppm. Further characterisation was not achieved due to rapid isomerisation to the *E* isomer **32** under ambient light; see next procedure.

1-[(*E*)-2-(2-Bromophenyl)vinyl]pyrrolidin-2-one [(*E*)-32]: A solution of 1-[(*Z*)-2-(2-bromophenyl)vinyl]pyrrolidin-2-one [(*Z*)-**32**, 92 mg, 0.34 mmol] in $CDCl_3$ was left under ambient light and temperature for approximately 20 h. The solvent was removed under reduced pressure to afford (*E*)-**32** as a colourless solid, R_f = 0.16 (EtOAc/hexane 1:4). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.49 (d, *J* = 14.8 Hz, 1 H, 2′′-H), 7.47 (m, 1 H, 3-H/6-H), 7.45 (m, 1 H, 3-H/6-H), 7.17 ("dt", *J* = 8.6, 1.2 Hz, 1 H, 4-H/5-H), 6.97 ("dt", *J* = 8.0, 1.6 Hz, 1 H, 4-H/5-H), 6.13 (d, *J* = 14.8 Hz, 1 H, 2′′-H), 3.64 (t, *J* = 7.6 Hz, 2 H, 5-H′), 2.49 (t, *J* = 8 Hz, 2 H, 3′-H), 2.10 ("tt", *J* = 7.2 Hz, 2 H, 4′-H) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 173.7 (C-2′), 136.3, 133.0, 128.0, 127.7, 126.0, 125.6, 123.4, 110.6 (C-1′′), 45.4 (C-5′), 31.3 (C-3′), 17.5 (C-4′) ppm. IR (KBr): $\tilde{\nu}$ = 3074 (C–H), 2962 (C–H), 2930 (C–H), 2891 (C–H), 1700, 1637 (C=O), 1399 cm^{-1}. MS AP-CI: *m*/*z* (%) = 309 (90) [M(^{81}Br) + H + CH_3CN]$^+$, 307 (94) [M(^{79}Br) + H + CH_3CN]$^+$, (97) [M + H]$^+$, 268 (98) [M(^{81}Br) + H]$^+$, 266 (100) [M(^{81}Br) + H]. 187 (70) [M – Br]$^+$. HRMS FAB calculated for $C_{12}H_{12}N_1O_1Br_1$: 265.0102, found 265.0102.

3-Acetyl-1-methylene-2,3-dihydro-1*H*-3-benzazepine (35): $Pd(PPh_3)_4$ (10 mg, 0.008 mmol) was added to a magnetically stirred solution of the amide **34** (25 mg, 0.09 mmol) and K_2CO_3 (31 mg, 0.22 mmol) in DMF (0.5 mL). The resulting mixture was degassed and was then heated at 120 °C for 16 h. The resulting black mixture was diluted in ethyl acetate (5 mL) and washed with water (5 × 0.5 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude mixture was subjected to column chromatography (EtOAc/hexane 1:9) to give the

3-benzazepine **35** (13 mg, 73%) as a pale yellow oil; R_f = 0.17 (ethyl acetate/hexane 1:9). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.44 (m, J = 7.0 Hz, 1 H, H9), 7.25–7.22 (m, 2 H, 6-H, 7-H), 7.20 (m, 1 H, 8-H), 6.69 (d, J = 10.1 Hz, 1 H, 4-H), 5.74 (d, J = 10.1 Hz, 1 H, 5-H), 5.54 (s, 1 H, 3′-H), 5.41 (s, 1 H, 3′-H), 4.40 (s, 2 H, 2-H), 2.28 (s, 3 H, 4′-H) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 168.2 (*C*=O), 143.8 (C-1), 139.4 (C-1′), 132.4 (C-2′), 131.7 (C6), 128.0 (C7), 127.8 (C9), 127.3 (C4), 126.9 (C8), 117.4 (C-3′), 112.6 (C5), 46.6 (C-2), 22.4 (C-4′) ppm. IR (thin film): $\tilde{\nu}$ = 3059, 3010, 2925, 2853, 1732, 1674 (C=O), 1632 (C=O), 1455, 1387, 1334, 1238 cm^{-1}. MS (EI): *m*/*z* (%) = 200 (20) $[M + H]^+$, 199 (20) $[M]^+$, 158 (100). HRMS calculated for $C_{13}H_{13}NO$: 199.0997, found 199.0997.

Selected Reaction Procedures for Table 6

3-Acetyl-1-methylene-2,3-dihydro-1*H*-3-benzazepine (35)

Entry 2: $Pd_2(dba)_3$·$CHCl_3$ (28 mg, 27 mmol) was added to a magnetically stirred solution of the dibromostyrene **29** (143 mg, 0.545 mmol), the allyl acetamide **33** (108 mg, 1.09 mmol), Cs_2CO_3 (592 mg, 1.63 mmol) and DavePhos (10.7 mg, 27.3 μmol) in dry toluene (1 mL), and the mixture was heated at 100 °C for 20 h. The resulting mixture was concentrated under reduced pressure and the remaining residue was purified by column chromatography (EtOAc/hexane 1:10) to afford the 3-benzazepine **35** as a yellow oil (37 mg, 34%).

Entry 5: $Pd_2(dba)_3$·$CHCl_3$ (20 mg, 19 mmol) was added to a magnetically stirred solution of the dibromostyrene **29** (100 mg, 0.382 mmol), the allyl acetamide **33** (227 mg, 2.29 mmol), Cs_2CO_3 (373 mg, 1.15 mmol) and DavePhos (7.5 mg, 1.9 μmol) in dry toluene (1 mL), and the mixture was heated at 100 °C for 20 h. The resulting mixture was concentrated under reduced pressure and the remaining residue was purified by column chromatography (EtOAc/hexane 1:10) to afford the 3-benzazepine **35** as a yellow oil (37 mg, 34%).

Entry 23: $Pd_2(dba)_3$·$CHCl_3$ (20 mg, 19 μmol) was added to a magnetically stirred solution of the dibromostyrene **29** (100 mg, 0.382 mmol), the allyl acetamide **33** (76 mg, 0.76 mmol), Cs_2CO_3 (375 mg, 1.15 mmol) and XantPhos (22 mg, 38 μmol) in toluene (1 mL), and the mixture was heated at 100 °C for 20 h. The resulting mixture was concentrated under reduced pressure and the remaining residue was purified by column chromatography (EtOAc/hexane 1:10) to afford the 3-benzazepine **35** as a yellow oil (62 mg, 82%).

Entry 24: $Pd_2(dba)_3$·$CHCl_3$ (20 mg, 19 μmol) was added to a magnetically stirred solution of the dibromostyrene **29** (100 mg, 0.382 mmol), the allyl acetamide **33** (76 mg, 0.76 mmol), Cs_2CO_3 (375 mg, 1.15 mmol) and XantPhos (44 mg, 76 μmol) in dry toluene (1 mL), and the mixture was heated at 100 °C for 20 h. The resulting mixture was concentrated under reduced pressure and the remaining residue was purified by column chromatography (EtOAc/hexane 1:10) to afford the 3-benzazepine **35** as a yellow oil (63 mg, 83%).

(*Z*)-*N*-Allyl-*3*-(2-bromostyryl)acetamide (34): The intermediate **34** was highly unstable at room temperature, possibly due to geometrical isomerism. R_f = 0.19 (EtOAc/hexane 10%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.59 (m, 1 H, ArH), 7.32 (m, 1 H, ArH), 7.26 (m, 1 H, ArH), 7.14 (m, 1 H, ArH), 6.39 (d, J = 9.3 Hz, 1 H, Ar-CH=CH), 6.29 (d, J = 9.3 Hz, 1 H, Ar-CH=CH), 5.73 (m, 1 H, C*H*=CH_2), 5.11 (dd, J = 10.5, 1 Hz, 1 H, C=CH_2), 5.01 (dd, J = 17, 1 Hz, 1 H, C=CH_2), 3.99 (d, J = 6.5 Hz, 1 H, CH_2), 2.03 (s, 3 H, CH_3) ppm.

Selected Reaction Procedures for Table 7

6-Allyl-5-methylene-3-(trifluoroacetyl)-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole (37), 6-Methylene-3-(trifluoroacetyl)-2,3,4,4a,5,6-hexahydroazepino[3,4,5-*hi*]benz[*b*]indolizine (39), and 5-Methylene-3-(trifluoroacetyl)-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole (38)

Entry 3: The aryl bromide **36** (112 mg, 0.27 mmol) was placed in a flask fitted with a reflux condenser and containing a stirrer bar. NBu_4OAc (162 mg, 0.54 mmol) and $Pd(PPh_3)_4$ (31 mg, 0.027 mmol, 10 mol-%) were added and the flask was backfilled thrice with argon. DMF (5 mL) was added and the mixture was heated at 100 °C for 3 h, allowed to cool to room temperature and concentrated under reduced pressure. The crude material was subjected to flash chromatography (toluene/hexane 1:1→toluene). First to elute was an otherwise pure (1:0.21 by ^{1}H NMR) mixture of compounds **37** and **39** (66 mg, 73% combined, R_f = 0.6 in acetone/toluene 1:19). The mixture of the tricycle **37** and the tetracycle **39** could be separated by semipreparative HLPC (MeOH/H_2O 4:1, 4 mL min^{-1}) to give pure samples of both compounds.[10a]

Entry 5: The aryl bromide **36** (100 mg, 0.24 mmol) was placed in a flask fitted with a reflux condenser and containing a stirrer bar. $Pd(PPh_3)_4$ (28 mg, 0.024 mmol, 10 mol-%) was added and the flask was backfilled thrice with argon. DMF (3 mL) was followed by NEt_3 (101 mg, 3 equiv. mmol^{-1}) and the mixture was heated to 100 °C for 3 h. The reaction mixture was allowed to cool to room temperature and concentrated under reduced pressure. The crude material was subjected to flash chromatography (toluene/hexane 1:1 → toluene). First to elute was an otherwise pure (1:1.18 by ^{1}H NMR) mixture of compounds **37** and **39** (46 mg, 57% combined), R_f 0.6 (acetone/toluene 1:19). Second to elute was a sample of the indoleazepine **38** (10 mg, 14%). The mixture of the tricycle **37** and the tetracycle **39** could be separated by semipreparative HLPC (MeOH/H_2O 4:1, 4 mL min^{-1}) to give pure samples of both compounds.[10a]

Supporting Information (see footnote on the first page of this article): ^{1}H NMR, ^{13}C NMR data for compouds **20**–**24**, **32** and **35**.

Acknowledgments

The Alexander von Humboldt Foundation is gratefully acknowledged for a return fellowship to S. G. S. The authors would like to thank Prof. Emil Ghisalberti and Prof. George Koutsantonis for helpful discussions and the use of laboratory equipment. J. E. R. and C. H. H. are recipients of a University of Western Australia Post Graduate Scholarship (UPA) and Australian Postgraduate Scholarships (APA), respectively. The authors would also like to thank Dr. Lindsay Byrne for NMR assistance, Dr. Gavin Flematti for HPLC assistance and Dr. Tony Reeder for mass spectra acquisition.

[1] a) L. F. Tietze, G. Brasche, K. Gericke, *Domino Reactions in Organic Synthesis*, 1st ed., Wiley-VCH, Weinheim, **2006**; b) L. F. Tietze, A. Düfert, "Domino Reactions Involving Catalytic Enantioselective Conjugate Additions" in *Catalytic Asymmetric Conjugate Reactions* (Ed.: A. Cordova), Wiley-VCH, Weinheim, **2010**, p. 321–350; c) L. F. Tietze, A. Düfert, *Pure Appl. Chem.* **2010**, *82*, 1375–1392; d) L. F. Tietze, L. Levy, "The Mizoroki-Heck Reaction in Domino Processes" in *The Mizoroki-Heck Reaction* (Ed.: M. Oestreich), Wiley-VCH, Chichester, **2009**, p. 281–344; e) L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115–136.

[2] K. C. Nicolaou, D. J. Edmonds, P. G. Bulger, *Angew. Chem.* **2006**, *118*, 7292; *Angew. Chem. Int. Ed.* **2006**, *45*, 7134–7186.

[3] I. Hayato, S. Takaki, H. Yujiro, *Angew. Chem.* **2009**, *121*, 1330; *Angew. Chem. Int. Ed.* **2009**, *48*, 1304–1307.
[4] M. E. Fox, C. Li, J. P. Marino, L. E. Overman, *J. Am. Chem. Soc.* **1999**, *121*, 5467–5480.
[5] J. M. Humphrey, Y. Liao, A. Ali, T. Rein, Y.-L. Wong, H.-J. Chen, A. K. Courtney, S. F. Martin, *J. Am. Chem. Soc.* **2002**, *124*, 8584–8592.
[6] K. C. Nicolaou, T. R. Wu, D. Sarlah, D. M. Shaw, E. Rowcliffe, D. R. Burton, *J. Am. Chem. Soc.* **2008**, *130*, 11114–11121.
[7] L. F. Tietze, F. J. Stecker, K. Zinngrebe, M. Sommer, *Chem. Eur. J.* **2006**, *12*, 8770–8776.
[8] a) M. Blanchot, D. A. Candito, F. Larnaud, M. Lautens, *Org. Lett.* **2011**, *13*, 1486–1489; b) P. Thansandote, E. Chong, K.-O. Feldmann, M. Lautens, *J. Org. Chem.* **2010**, *75*, 3495–3498; c) M. Catellani, F. Frignani, A. Rangoni, *Angew. Chem.* **1997**, *109*, 142; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 119–122; d) K. M. Gericke, D. I. Chai, N. Bieler, M. Lautens, *Angew. Chem.* **2009**, *121*, 1475; *Angew. Chem. Int. Ed.* **2009**, *48*, 1447–1451; e) F. Zeng, H. Alper, *Org. Lett.* **2011**, *13*, 2868–2871; f) S. Yahiaoui, A. Fardost, A. Trejos, M. Larhed, *J. Org. Chem.* **2011**, *76*, 2433–2438; g) S. Inuki, A. Iwata, S. Oishi, N. Fujii, H. Ohno, *J. Org. Chem.* **2011**, *76*, 2072–2083; h) G. A. Salman, M. Hussain, V. Iaroshenko, A. Villinger, P. Langer, *Adv. Synth. Catal.* **2011**, *353*, 331–336; i) Y. Luo, X. Pan, J. Wu, *Org. Lett.* **2011**, *13*, 1150–1153; j) R. Liu, J. Zhang, *Adv. Synth. Catal.* **2011**, *353*, 36–40; k) Y. Hu, D. Ren, L. Zhang, X. Lin, J. Wan, *Eur. J. Org. Chem.* **2010**, 4454–4459; l) F. Zeng, H. Alper, *Org. Lett.* **2010**, *12*, 3642–3644; m) L. F. Tietze, S. Biller, T. Wolfram, *Synlett* **2010**, 2130,2132; n) B. Yucel, M. Noltemeyer, A. de Meijere, *Eur. J. Org. Chem.* **2008**, 1072–1078.
[9] a) D. L. Priebbenow, L. C. Henderson, F. M. Pfeffer, S. G. Stewart, *J. Org. Chem.* **2010**, *75*, 1787–1790; b) D. L. Priebbenow, S. G. Stewart, F. M. Pfeffer, *Org. Biomol. Chem.* **2011**, *9*, 1508–1515; c) D. L. Priebbenow, F. M. Pfeffer, S. G. Stewart, *Eur. J. Org. Chem.* **2011**, 1632–1635.
[10] a) S. G. Stewart, C. H. Heath, E. L. Ghisalberti, *Eur. J. Org. Chem.* **2009**, 1934–1943; b) L. F. Tietze, T. Redert, H. P. Bell, S. Hellkamp, L. M. Levy, *Chem. Eur. J.* **2008**, *14*, 2527–2535.
[11] G. Poli, G. Giambastiani, *J. Org. Chem.* **2002**, *67*, 9456–9459.
[12] F.-E. Chen, J. Huang, *Chem. Rev.* **2005**, *105*, 4671–4706.
[13] M. Chrzanowska, M. D. Rozwadowska, *Chem. Rev.* **2004**, *104*, 3341–3370.
[14] E. Valencia, A. J. Freyer, M. Shamma, V. Fajardo, *Tetrahedron Lett.* **1984**, *25*, 599–602.
[15] E. Valencia, I. Weiss, S. Firdous, A. J. Freyer, M. Shamma, A. Urzús, V. Fajardo, *Tetrahedron* **1984**, *40*, 3957–3962.
[16] a) E. Fischer, F. Jourdan, *Ber. Dtsch. Chem. Ges.* **1883**, *16*, 2241–2245; b) E. Fischer, O. Hess, *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 559–568.
[17] a) G. Bartoli, G. Palmieri, M. Bosco, R. Dalpozzo, *Tetrahedron Lett.* **1989**, *30*, 2129–2132; b) W. L. Andrew, D. Batcho, *Org. Synth.* **1990**, *7*, 34.
[18] a) S. Wagaw, B. H. Yang, S. L. Buchwald, *J. Am. Chem. Soc.* **1998**, *120*, 6621–6622; b) R. C. Larock, E. K. Yum, M. D. Refvik, *J. Org. Chem.* **1998**, *63*, 7652–7662; c) D. A. Candito, M. Lautens, *Org. Lett.* **2010**, *12*, 3312–3315; d) N. Halland, M. Nazare, J. Alonso, O. R'Kyek, A. Lindenschmidt, *Chem. Commun.* **2011**, *47*, 1042–1044.
[19] a) M. Mori, K. Chiba, Y. Ban, *Tetrahedron Lett.* **1977**, *18*, 1037–1040; b) T. Sakamoto, Y. Kondo, M. Uchiyama, H. Yamanaka, *J. Chem. Soc. Perkin Trans. 1* **1993**, 1941–1942; c) L. F. Tietze, T. Grote, *J. Org. Chem.* **1994**, *59*, 192–196; d) S. Cacchi, G. Fabrizi, *Chem. Rev.* **2011**, *111*, 215–283.
[20] a) S. Caddick, W. Kofie, *Tetrahedron Lett.* **2002**, *43*, 9347–9350; b) A. E. Sollewijn Gelpke, J. J. N. Veerman, M. Schreuder Goedheijt, P. C. J. Kamer, P. W. N. M. van Leeuwen, H. Hiemstra, *Tetrahedron* **1999**, *55*, 6657–6670; c) R. C. Larock, S. Babu, *Tetrahedron Lett.* **1987**, *28*, 5291–5294; d) J. T. Link, *The Intramolecular Heck Reaction*, John Wiley & Sons, New York, **2004**.
[21] L. A. Evans, N. Fey, J. N. Harvey, D. Hose, G. C. Lloyd-Jones, P. Murray, A. G. Orpen, R. Osborne, G. J. J. Owen-Smith, M. Purdie, *J. Am. Chem. Soc.* **2008**, *130*, 14471–14473.
[22] R. Odle, B. Blevins, M. Ratcliff, L. S. Hegedus, *J. Org. Chem.* **1980**, *45*, 2709–2710.
[23] a) X. Zhang, W. Zhang, H. Yang, *Asia-Pacific J. Chem. Eng.* **2009**, *4*, 821–825; b) H. S. Kim, H. S. Lee, S. H. Kim, J. N. Kim, *Tetrahedron Lett.* **2009**, *50*, 3154–3157.
[24] T. Jeffery, *J. Chem. Soc., Chem. Commun.* **1984**, 1287–1289.
[25] a) G. C. Fu, M. R. Netherton, *Org. Lett.* **2001**, *3*, 4295–4298; b) D. S. Surry, S. L. Buchwald, *Angew. Chem.* **2008**, *120*, 6438; *Angew. Chem. Int. Ed.* **2008**, *47*, 6338–6361.
[26] M. L. Weinrich, H. P. Beck, *Tetrahedron Lett.* **2009**, *50*, 6968–6972.
[27] B. Mariampillai, C. Herse, M. Lautens, *Org. Lett.* **2005**, *7*, 4745–4747.
[28] Another process in which an initial Heck reaction was followed by a Tsuji–Trost-type addition at the central carbon of a π-allyl species was also considered.
[29] a) W. A. Herrmann, C. Brossmer, K. Öfele, C.-P. Reisinger, T. Priermeier, M. Beller, H. Fischer, *Angew. Chem.* **1995**, *107*, 1989; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1844–1848; b) W. A. Herrmann, C. Brossmer, C.-P. Reisinger, T. H. Riermeier, K. Öfele, M. Beller, *Chem. Eur. J.* **1997**, *3*, 1357–1364.
[30] a) L. F. Tietze, S. G. Stewart, M. E. Polomska, A. Modi, A. Zeeck, *Chem. Eur. J.* **2004**, *10*, 5233–5242; b) L. F. Tietze, S. G. Stewart, M. E. Polomska, *Eur. J. Org. Chem.* **2005**, 1752–1759.
[31] B. L. Shaw, *New J. Chem.* **1998**, *22*, 77–79.
[32] a) E. M. Beccalli, G. Broggini, M. Martinelli, S. Sottocornola, *Synthesis* **2008**, 136–140; b) B. Clique, C.-H. Fabritius, C. Couturier, N. Monteiro, G. Balme, *Chem. Commun.* **2003**, 272–273; c) E. M. Beccalli, G. Broggini, M. Martinelli, N. Masciocchi, S. Sottocornola, *Org. Lett.* **2006**, *8*, 4521–4524; d) S. Gowrisankar, H. S. Lee, J. M. Kim, J. N. Kim, *Tetrahedron Lett.* **2008**, *49*, 1670–1673.
[33] a) B. José, M. A. Fernández, A. Fernando, V. Carlos, *Chem. Eur. J.* **2005**, *11*, 2276–2283; b) A. Fayol, Y.-Q. Fang, M. Lautens, *Org. Lett.* **2006**, *8*, 4203–4206.
[34] G. Battistuzzi, R. Bernini, S. Cacchi, I. De Salve, G. Fabrizi, *Adv. Synth. Catal.* **2007**, *349*, 297–302.
[35] L. F. Tietze, T. Nobel, M. Spescha, *J. Am. Chem. Soc.* **1998**, *120*, 8971–8977.
[36] a) M. C. Willis, G. N. Brace, T. J. K. Findlay, I. P. Holmes, *Adv. Synth. Catal.* **2006**, *348*, 851–856; b) A. J. Fletcher, M. N. Bax, M. C. Willis, *Chem. Commun.* **2007**, 4764–4766; c) A. C. Tadd, A. Matsuno, M. R. Fielding, M. C. Willis, *Org. Lett.* **2009**, *11*, 583–586.
[37] L. F. Tietze, R. Ferraccioli, *Synlett* **1998**, 145,146.
[38] C. Kuang, Q. Yang, H. Senboku, M. Tokuda, *Tetrahedron* **2005**, *61*, 4043–4052.
[39] M. Nishiura, Z. Hou, Y. Wakatsuki, T. Yamaki, T. Miyamoto, *J. Am. Chem. Soc.* **2003**, *125*, 1184–1185.
[40] Careful handling of compound (*Z*)-**32** is required for inital characterisation. If the *Z*-enamide **32** is left in ambient light for a resonable time is isomerises to the *E* product; see Exp. Section.
[41] G. Y. Gao, Y. Chen, X. P. Zhang, *J. Org. Chem.* **2003**, *68*, 6215–6221.
[42] M.-N. Birkholz, Z. Freixa, P. W. N. M. van Leeuwen, *Chem. Soc. Rev.* **2009**, *38*, 1099–1118.
[43] B. C. Hamann, J. F. Hartwig, *J. Am. Chem. Soc.* **1998**, *120*, 3694–3703.
[44] G. Poli, G. Giambastiani, A. Heumann, *Tetrahedron* **2000**, *56*, 5959–5989.
[45] T. A. Van Beek, V. Robert, A. B. Svendsen, *J. Nat. Prod.* **1985**, *48*, 400–423.
[46] a) E.-i. Negishi, C. Coperet, S. Ma, S.-Y. Liou, F. Liu, *Chem. Rev.* **1996**, *96*, 365–394; b) M. M. Abelman, L. E. Overman, *J. Am. Chem. Soc.* **1988**, *110*, 2328–2329; c) L. E. Overman, M. M. Abelman, D. J. Kucera, V. D. Tran, D. J. Ricca, *Pure*

Appl. Chem. **1992**, *64*, 1813–1819; d) B. M. Trost, Y. Shi, *J. Am. Chem. Soc.* **1991**, *113*, 701–703.
[47] a) C. H. Oh, C. Y. Rhim, J. H. Kang, A. Kim, B. S. Park, Y. Seo, *Tetrahedron Lett.* **1996**, *37*, 8875–8878; b) S. Schweizer, Z.-Z. Song, F. E. Meyer, P. J. Parsons, A. de Meijere, *Angew. Chem.* **1999**, *111*, 1550; *Angew. Chem. Int. Ed.* **1999**, *38*, 1452–1454.
[48] a) X. Lu, *Top. Catal.* **2005**, *35*, 73–86; b) L. Firmansjah, G. C. Fu, *J. Am. Chem. Soc.* **2007**, *129*, 11340–11341; c) B. Seashore-Ludlow, P. Somfai, *Org. Lett.* **2010**, *12*, 3732–3735.
[49] W. A. Herrmann, C. Brossmer, K. Ofele, C. Reisinger, T. P. M. Beller, H. Fischer, *Angew. Chem.* **1995**, *107*, 1989; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1844–1848.
[50] T. Ukai, H. Kawazura, Y. Ishii, J. J. Bonnet, J. A. Ibers, *J. Organomet. Chem.* **1974**, *65*, 253–266.
[51] D. R. Coulson, *Inorg. Synth.* **1972**, *13*, 121–123.
[52] W. Armarego, C. Chai, *Purification of Laboratory Chemicals*, 5th ed., Butterworth Heinemann, New York, **2003**.
[53] a) J. A. Miles, R. C. Grabiak, M. T. Beeny, *J. Org. Chem.* **1981**, *46*, 3486–3492; b) P. W. Jeffs, J. F. Hansen, G. A. Brine, *J. Org. Chem.* **1975**, *40*, 2883–2890.
[54] J. M. Zenner, R. C. Larock, *J. Org. Chem.* **1999**, *64*, 7312–7322.
[55] A. J. McCarroll, T. D. Bradshaw, A. D. Westwell, C. S. Matthews, M. F. G. Stevens, *J. Med. Chem.* **2007**, *50*, 1707–1710.
[56] a) R. Kuwano, M. Kashiwabara, K. Sato, T. Ito, K. Kaneda, Y. Ito, *Tetrahedron: Asymmetry* **2006**, *17*, 521–535; b) K. Okuma, T. Yasuda, I. Takeshita, K. Shioji, Y. Yokomori, *Tetrahedron* **2007**, *63*, 8250–8254.
[57] R. C. Larock, T. R. Hightower, L. A. Hasvold, K. P. Peterson, *J. Org. Chem.* **1996**, *61*, 3584–3585.
[58] R. Grigg, M. Kordes, *Eur. J. Org. Chem.* **2001**, 707–712.
[59] L. F. Tietze, T. Nöbel, M. Spescha, *J. Am. Chem. Soc.* **1998**, *120*, 8971–8977.

Received: September 8, 2011
Published Online: November 30, 2011

