Organic & Biomolecular Chemistry

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Cite this: *Org. Biomol. Chem.*, 2011, **9**, 1508

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PAPER

A general approach to *N*-heterocyclic scaffolds using domino Heck–aza-Michael reactions†

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Received 6th October 2010, Accepted 11th November 2010
DOI: 10.1039/c0ob00835d

Palladium-catalyzed domino Heck–aza-Michael reactions for the synthesis of a series of C1-substituted tetrahydro-β-carbolines, tetrahydroisoquinolines and isoindolines are described. The domino process involves the initial intermolecular Heck reaction of an aryl bromide with an electron deficient alkene, followed by an intramolecular aza-Michael reaction to form the new *N*-heterocycle in high yield.

Introduction

In the ongoing pursuit of environmentally friendly reaction processes, domino reactions have emerged as a powerful tool for synthetic chemists.[1,2] These domino processes generate a high level of molecular complexity in one efficient step, minimising solvent use, reagents, time and energy.[1] 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".[1,2] The more feasible domino reactions are those where all transformations occur under similar reaction conditions, for example, where each of the reaction steps is palladium-catalysed.[2–5] Likewise, because of the reliance of base in many Pd cross-coupling reactions, domino reactions involving both a Pd-catalysed and a base-initiated synthetic step are also plausible.

In spite of this possibility, the domino Heck–Michael methodology for the formation of heterocycles has not been widely reported.[6–8] Domino Heck–aza-Michael reactions have been applied to a series of unique benzo-fused sultams,[7] and isoindolinones using terminal alkene esters.[8] However, attempts to expand the scope of these methods to related substrates have proved problematic. Recently, our group has reported a domino Heck–aza-Michael reaction for the synthesis of a series of C1-substituted tetrahydro-β-carbolines.[9] Herein, we report that the scope of this novel domino process has been successfully expanded to include other *N*-heterocycles, namely tetrahydroisoquinolines and isoindolines.

The tetrahydro-β-carboline, tetrahydroisoquinoline and isoindoline scaffolds are all present in important biologically-active compounds. Tetrahydro-β-carbolines (THβCs or tryptolines) form the core of the antihypertensive agent reserpine (**1**) (Fig. 1), along with a range of other biologically-active natural products.[10–17] Likewise, the tetrahydroisoquinoline ring system forms the central part of a number of naturally-occurring alkaloids,[18–22] including the antitumor natural product quinocarcinol **2**.[23,24] In comparison, isoindoline-based natural products are not as prevalent. Nevertheless, this scaffold is found in a range of potential pharmaceutical agents,[25–28] such as compound **3** (Fig. 1), synthesized as a ligand for the melanocortin subtype-4 receptor (MC4R).[29]

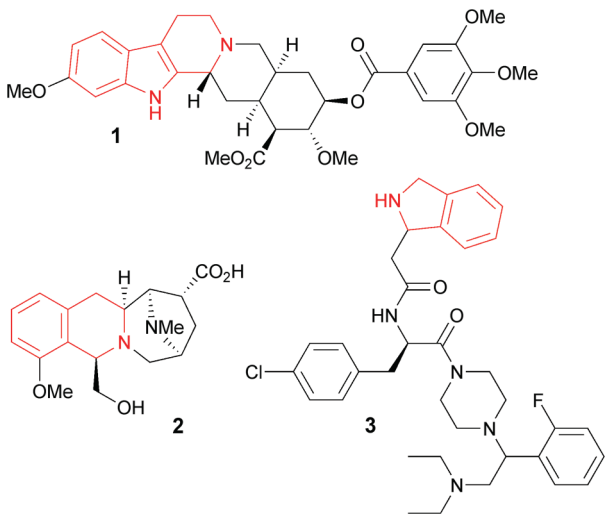

Fig. 1 Biologically-active compounds containing the tetrahydro-β-carboline (**1**), tetrahydroisoquinoline (**2**) and isoindoline (**3**) *N*-heterocyclic core.

As the importance of these classes of compounds grows in a medicinal chemistry setting, so does the focus on a general method for their synthetic preparation. Tetrahydro-β-carbolines and tetrahydroisoquinolines have traditionally been prepared by

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† Electronic supplementary information (ESI) available. ^{1}H and ^{13}C NMR spectra for compounds listed in the experimental section. See DOI: 10.1039/c0ob00835d

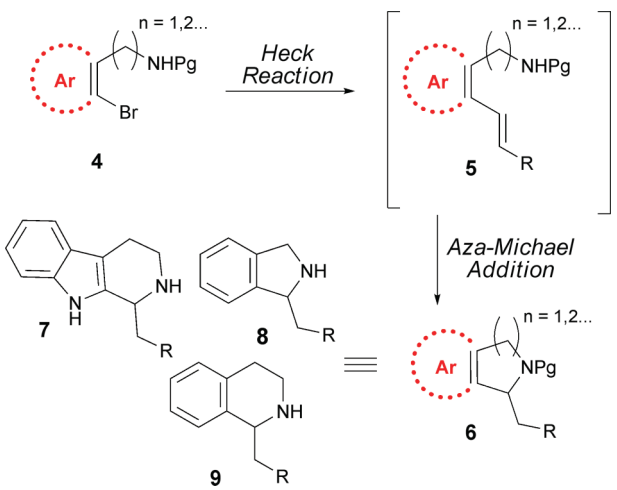
reacting tryptamine or phenethylamine with a suitable aldehyde; namely the Pictet–Spengler reaction.[30–34] Similarly, the Bischler–Napieralski reaction affords these ring systems through the cyclodehydration of an appropriately substituted amide.[32,35–39] Alternatives to the Pictet–Spengler or the Bischler–Napieralski reactions are limited. One of the most recent, the Ferracioli synthesis of tetrahydroisoquinolines, involves palladium-catalyzed *ortho*-alkylation/vinylation followed by an aza-Michael reaction.[40] Isoindolines substituted at the C1-position have also been accessed using an aryl radical cyclization of *N*-benzylenaminone esters.[41] More recently, 1,3-disubstituted isoindolines have been synthesized using a Brønsted acid-catalyzed 1,2-addition followed by an aza-Michael addition.[42]

A general approach to *N*-heterocycles using a domino Heck–aza-Michael strategy would complement existing methods and in some instances provide a more attractive option, for example, when suitable aldehydes for the Pictet–Spengler reaction are not readily available.[14,17,43] In order to be applied to a range of substrates, the domino process needs to occur under mild conditions using a readily available catalyst, base and with inexpensive electron deficient alkenes. As a wide range of suitable acrylates (such as acrolein, acrylonitrile, acrylic acid, *etc.*) are commercially available, the C1 functionality of the new heterocycle can be customised by appropriate alkene selection. To this end, we herein describe our recent efforts to expand our domino Heck–aza-Michael methodology from THβCs to include tetrahydroisoquinolines and isoindolines.

Results and discussion

In planning the Heck–aza-Michael domino process, a suitable halogenated aryl ring system for a rapid Heck reaction with an electron-withdrawn terminal alkene was sought. Aryl bromides **4** were selected due to the higher commercial cost of aryl iodides. Initial C–H activation was also envisaged but deemed to be too slow and less regioselective in the initial step of the domino sequence.[44]

The ring size of the newly formed *N*-heterocycle (compounds **7**–**9**, Scheme 1) is governed by the length of the alkyl chain connecting the amine to the aryl portion of starting material **4**. Similarly, the selection of a suitable protecting group for the tethered amine is important when considering the Michael addition step. An ideal protecting group would control the amine reactivity, avoiding the likelihood of an intermolecular 1,4-addition, prior to the Heck reaction.



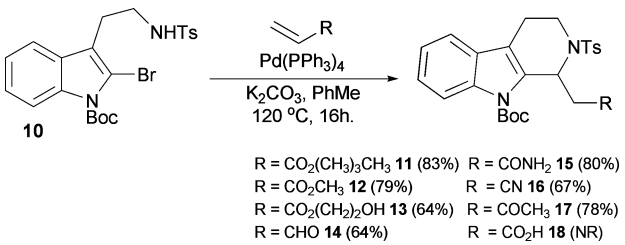
Scheme 1 Generic plan for the domino Heck–aza Michael reaction.

As the Heck reaction at the C2 position of substituted tryptamines is known from previous investigations within the group,[5] it was trialled first. Readily available *ortho*-halogenated benzylamines and phenethylamines were also identified as ideal substrates for this investigation, as the *ortho*-tethered amine is well positioned for the aza-Michael addition to form a new *N*-heterocycle, following the initial Heck reaction.

Tetrahydro-β-carbolines

The detailed optimisation of a domino Heck–aza-Michael reaction for the synthesis of tetrahydro-β-carbolines has previously been described by our group.[9] As the Heck reaction of 2-bromoindoles has been reported,[5,45,46] the limiting factor was the aza-Michael reaction. A key finding of our THβC investigation was that the tosyl protecting group of the tethered amine (superior to Boc, Ac and trifluoroacetyl) allowed the aza-Michael reaction to take place subsequent to the initial cross-coupling reaction. Following optimisation, the highest yields for the domino process between halogenated indole-*N*-Boc substrate **10** and butyl acrylate were obtained by using the $Pd(PPh_3)_4$, K_2CO_3 and toluene catalytic system.

The versatility of this domino Heck–aza-Michael reaction was then investigated using a number of suitably conjugated terminal alkenes (Scheme 2). The two-step domino process, forming a new 6-membered *N*-heterocycle, performed well for the alkenes employed, except in the case of acrylic acid, with isolated yields ranging from 64–83% (compounds **11**–**16**).‡ In addition to these previously reported scaffolds,[9] this domino process has now been expanded to include 3-buten-2-one, which afforded ketone-functionalised THβC **17** (78% yield). These tetrahydro-β-carboline scaffolds contain a series of C1 functionalities that allow for further synthetic manipulation and possible application as part of total syntheses.[9]



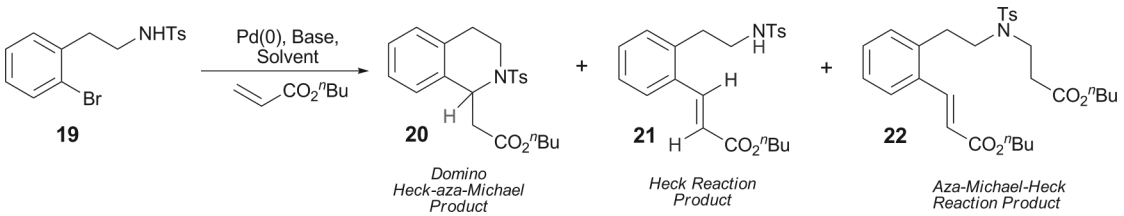
Scheme 2 The synthesis of tetrahydro-β-carbolines using a domino Heck–aza-Michael process.

Tetrahydroisoquinolines

Given the success of this initial series of domino reactions to generate tetrahydro-β-carbolines **7**, the synthesis of

‡ The unreactive nature of acrylic acid may be explained by the poor solubility of the corresponding carboxylate ion.

Table 1 Investigations into the domino reaction of aryl bromide **26**



Entry	Palladium catalyst[a] (10 mol%)	Base	Solvent	Major product[b]
1	$Pd(PPh_3)_4$	K_2CO_3	PhMe	**22**
2	$Pd(PPh_3)_4$	Na_2CO_3	PhMe	**21**
3	$Pd_2(dba)_3/P(^tBu)_3$	Cy_2NMe	PhMe	**21**
4	$Pd(OAc)_2/PPh_3$	NEt_3	PhMe	**21**
5	$Pd_2(dba)_3{\cdot}CHCl_3$	K_2CO_3	PhMe	NR[d]
6	$Pd(OAc)_2/PPh_3$	NEt_3	DMF	**21**
7	$Pd_2(dba)_3$/DavePhos	K_2CO_3	PhMe	**20** (79)[e]
8	$Pd(OAc)_2/PPh_3$	K_2CO_3	PhMe	**20** (80)[e]
9	Herrmann–Beller palladacycle[f]	Cy_2NMe	DMF–MeCN–H_2O[c]	**20** (67)[e]

[a] Palladium catalyst and ligand used in a 1 : 1 molar ratio. [b] As determined by ^{1}H NMR analysis of the crude reaction mixture. For immediate identification of product ratios in the ^{1}H NMR spectra δ: 5.46 (red), 4.60 (green), 7.84 (blue) and 6.28 (purple). [c] DMF–MeCN–H_2O (5 : 5 : 1). [d] NR = No reaction. [e] Yield (%). [f] The Herrmann–Beller catalyst is [*trans*-di-(μ-acetato)-bis[*ortho*-(di-*ortho*-tolylphosphino)benzyl]dipalladium(II)].

tetrahydroisoquinolines **9** using a domino Heck–aza-Michael reaction was investigated. As in the case of the THβCs, the tosyl (Ts) protecting group was employed to control amine nucleophilicity,[9] and the desired domino substrate (sulfonamide **19**) was prepared in 86% yield. Using this substrate, a series of trial reactions were carried out to determine if a domino Heck–aza-Michael process was feasible. These reactions were initially performed by treating aryl bromide **19** with butyl acrylate, a palladium catalyst, base and solvent in a pressure vessel, and heating to 120 °C for 16 h. The identification of the products (**20–22**) was performed by means of ^{1}H NMR spectroscopy of the crude reaction mixture (Table 1).

The ideal catalytic system for this domino process would *rapidly* produce Heck product **21**, with the base and solvent promoting the aza-Michael addition to form desired tetrahydroisoquinoline **20**, but not to an extent where intermolecular 1,4-nucleophilic addition of the acrylate occurs prior to the Heck reaction.

In the first attempt, the optimum conditions identified for the synthesis of THβCs ($Pd(PPh_3)_4$, K_2CO_3, PhMe; Table 1, entry 1) produced adduct **22** exclusively, *i.e.* the aza-Michael reaction is favoured but the Heck reaction is slow.

A number of alternative Pd catalysts ($Pd(PPh_3)_4$, $Pd_2(dba)_3/P(^tBu)_3$ and $Pd(OAc)_2/PPh_3$) combined with a range of bases (Table 1, entries 2–4) were subsequently trialled; however, only Heck adduct **21** was produced. It is apparent that whilst the Heck reaction was proceeding, the base used (Na_2CO_3, Cy_2NMe and NEt_3; Table 1, entries 2, 3 and 4, respectively) in each of these trials was not strong enough to induce either intra- or intermolecular aza-Michael addition, as only traces of these products were observed. From the previous work on THβCs, it is known that the aza-Michael process is sensitive to subtle variations in the base used. Again, for the synthesis of tetrahydroisoquinolines, slightly changing the base (*e.g.* from K_2CO_3 to Na_2CO_3; Table 1, entries 1 and 2) either facilitates or reduces the likelihood of the aza-Michael reaction. Of the bases trialled to this point (Table 1, entries 1–6), only K_2CO_3 was successful in enabling the aza-Michael reaction to occur (albeit intermolecularly).

To ensure rapid formation of the Heck adduct, the highly reactive and electron-rich $Pd_2(dba)_3$/DavePhos catalyst system, developed by Buchwald and Hartwig, was used in combination with K_2CO_3.[47]§ To our delight, this catalytic system furnished desired tetrahydroisoquinoline **20** in high yield (Table 1, entry 7).

Following further trials, other catalytic systems (Table 1, entries 8 and 9) also resulted in clean conversion of domino precursor **19** to tetrahydroisoquinoline **20**. These additional successes indicate that a judicious choice of base and solvent is crucial for promoting the desired aza-Michael cyclisation (compare Table 1, entries 4 and 8). In assessing each of these procedures, the $Pd(OAc)_2/PPh_3$ and K_2CO_3 in toluene catalytic system was deemed the most attractive due to its relatively low cost and commercial availability.

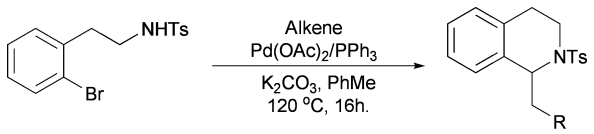
A range of acrylates were subject to this domino process to afford a series of C1-substituted tetrahydroisoquinolines **9** (Table 2). The resulting products from this series of reactions contain a range of functionalities, including ester, ketone and nitrile (Table 2, entries 1–5). In each of these cases, there seems to be no clear differentiation in the yield, suggesting that small differences in the electronics of each of these acrylates does not dramatically affect the domino process. Unfortunately, reactions attempted with both acrolein and acrylic acid did not furnish the desired tetrahydroisoquinolines, even though the reaction with acrolein had been successfully employed in a THβC domino Heck–aza-Michael reaction (Scheme 2).[9]

Isoindolines

With the successful development of domino Heck–aza-Michael reactions for the formation of two 6-membered *N*-heterocyclic

§ The possibility of a C–N cross-coupling was disregarded due to the strained ring system that would be generated as part of this process.

Table 2 Synthesis of a series of C1-substituted tetrahydroisoquinolines



19 20, 23-26

Entry	Alkene	R	Product	Yield (%)
1	Butyl acrylate	$CO_2{}^nBu$	**20**	80
2	Methyl acrylate	CO_2Me	**23**	83
3	2-Hydroxyethyl acrylate	$CO_2(CH_2)_2OH$	**24**	76
4	Acrylonitrile	CN	**25**	82
5	3-Buten-2-one	$COCH_3$	**26**	79
6	Acrylamide	$CONH_2$	**27**	Trace[a]
7	Acrolein	CHO	**28**	NR[b]
8	Acrylic acid	CO_2H	**29**	NR[b]

[a] Trace = less than 10%, as determined by ^{1}H NMR. [b] NR = No reaction.

systems, our attention turned to a third scaffold. To expand the scope of this methodology to include 5-membered *N*-heterocycles, an appropriately substituted benzylamine **30**, was prepared in 99% yield as a precursor to C1-substituted isoindolines **8**.

As with both the THβCs and tetrahydroisoquinolines, a range of conditions were evaluated for the preparation of the desired isoindoline **31** (Table 3). Bromosulfonamide **30**, butyl acrylate, a palladium catalyst, base and solvent were combined in a pressure vessel, and heated to 120 °C for 16 h. Following a simple work up, the major product was identified by ^{1}H NMR spectroscopy.

The first trial with tetrakis(triphenylphosphine) palladium ($Pd(PPh_3)_4$) afforded mixtures of the three predicted products, **31**, **32** and **33** (Table 3, entry 1). Repeating the reaction with $Pd(PPh_3)_4$ but changing the base and solvent (Table 3, entries 2–4) also proved unsuccessful. The highly active catalytic system of $Pd_2(dba)_3/P(^tBu)_3$ minimised the formation of aza-Michael–Heck product **33**; however, complete conversion of the Heck adduct to the desired isoindoline was not realised (Table 3, entry 5).[48]

A high yield of desired isoindoline **31** was observed when $Pd(OAc)_2/PPh_3$ and triethylamine were used in either toluene or DMF (Table 3, entries 8 and 9). The use of other highly active Pd catalysts also proved successful when teamed with an amine base in DMF. Again, it was apparent that a suitable base (in this case, an organic base rather than an inorganic base) was crucial to effect the desired cyclisation following the Heck reaction.

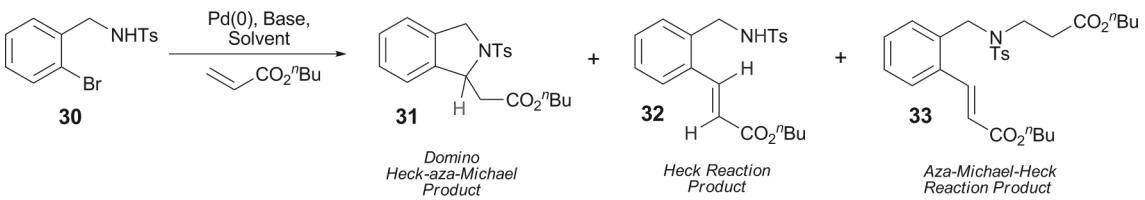
Even though the Pd_2dba_3/DavePhos catalytic system (Table 3, entry 10) provided isoindoline **31** in the highest yield, it was not significantly greater than that obtained when the $Pd(OAc)_2/PPh_3$ system was used (Table 3, entry 9). This latter system was subsequently used for the remainder of this investigation due to its low cost and commercial availability.

This optimized domino system was then used with a range of acrylates to afford a series of C1-substituted isoindolines (Table 4). The products synthesised contain a range of functionalities, including carboxylic acid, ester, ketone, amide and nitrile. This time, the use of acrylic acid resulted in the formation of isoindoline acetic acid **38**, presumably due to the increased solubility of the carboxylate ion in the triethylamine/DMF solvent system. Unfortunately, the use of acrolein[49] once again did not yield the desired isoindoline.

Conclusions

Following the successful development of a domino Heck–aza-Michael reaction for the synthesis of the tetrahydro-β-carbolines,[9]

Table 3 Preliminary investigations into the formation of isoindolines



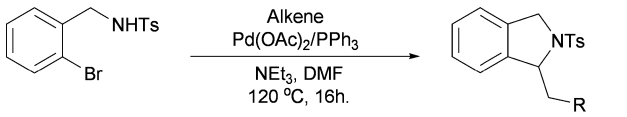
30 31 32 33

Domino Heck-aza-Michael Product *Heck Reaction Product* *Aza-Michael-Heck Reaction Product*

Entry	Palladium catalyst[a] (10 mol%)	Base	Solvent	Major product[b]
1	$Pd(PPh_3)_4$	K_2CO_3	PhMe	Mixture (**31**/**32**/**33**)
2	$Pd(PPh_3)_4$	Na_2CO_3	PhMe	Mixture (**31**/**32**/**33**)
3	$Pd(PPh_3)_4$	Cs_2CO_3	PhMe	NR[d]
4	$Pd(PPh_3)_4$	K_2CO_3	DMF	NR[d]
5	$Pd_2(dba)_3/P(^tBu)_3$	Cy_2NMe	PhMe	**31**/**32**
6	$Pd_2(dba)_3{\cdot}CHCl_3$	NEt_3	DMF	NR[d]
7	$Pd(OAc)_2/PPh_3$	K_2CO_3	PhMe	NR[d]
8	$Pd(OAc)_2/PPh_3$	NEt_3	PhMe	**31** (74)[e]
9	$Pd(OAc)_2/PPh_3$	NEt_3	DMF	**31** (77)[e]
10	$Pd_2(dba)_3$/DavePhos	Cy_2NMe	DMF	**31** (79)[e]
11	$Pd_2(dba)_3$/XPhos	Cy_2NMe	DMF	**31** (62)[e]
12	$Pd_2(dba)_3$/SPhos	Cy_2NMe	DMF	**31** (48)[e]
13	Herrmann–Beller palladacycle[f]	Cy_2NMe	DMF–MeCN–H_2O[c]	**31** (54)[e]

[a] Palladium and ligand used in a 1 : 1 molar ratio. [b] As determined by ^{1}H NMR analysis of the crude reaction mixture. For immediate identification of product ratios in the ^{1}H NMR spectra δ: 5.28 (red), 5.10 (green), 7.62 (blue) and 6.38 (purple). [c] DMF–MeCN–H_2O (5 : 5 : 1). [d] NR = No reaction. [e] Yield (%). [f] The Herrmann–Beller catalyst is [*trans*-di-(μ-acetato)-bis[*ortho*-(di-*ortho*-tolylphosphino)benzyl]-dipalladium(II)].

Table 4 Synthesis of a series of C1-substituted isoindolines



30 31, 35-39

Entry	Alkene	R	Product	Yield (%)
1	Butyl acrylate	$CO_2{}^nBu$	**31**	77
2	Methyl acrylate	CO_2Me	**34**	Unknown[a]
3	2-Hydroxyethyl acrylate	$CO_2(CH_2)_2OH$	**35**	84
4	Acrylamide	$CONH_2$	**36**	71
5	Acrylonitrile	CN	**37**	68
6	Acrylic acid	CO_2H	**38**	85
7	3-Buten-2-one	$COCH_3$	**39**	86
8	Acrolein	CHO	**40**	NR[b]

[a] This domino process also performed well using methyl acrylate; however, the isoindoline product could not be separated from the remaining starting material by column chromatography. [b] NR = No reaction.

the scope of this new methodology has been expanded to include the tetrahydroisoquinoline and isoindoline *N*-heterocyclic scaffolds. The key considerations of the domino Heck–aza-Michael methodology were identified as (i) the relatively quick formation of the Heck adduct (controlled through appropriate selection of Pd catalyst) and (ii) the nucleophilicity of the tethered amine (mediated through careful selection of the protecting group, base and solvent).

In determining the appropriate conditions for the Heck reaction, a palladium catalyst was required that facilitated a fast, high-yielding reaction between the aryl halide and the alkene in the presence of a mild base and a relatively non-polar solvent. It is important that the acrylate is consumed rapidly by the Heck process so that the intermolecular aza-Michael reaction cannot take place. For the Heck reaction at the indole 2-position, $Pd(PPh_3)_4$ afforded the highest yields. In the case of the benzyl- and phenethylamine aryl halides, the use of $Pd(OAc)_2/PPh_3$ proved optimal.

More importantly, an appropriate base is required; one that is able to sufficiently promote aza-Michael reaction, but not to the extent that it occurs before a high concentration of the Heck adduct is realised. Indeed, the outcome of reactions that were repeated, varying only the base used, ranged from a rapid intermolecular Michael reaction prior to the Heck reaction through to the desired domino Heck–aza-Michael process. For the synthesis of both THβCs and tetrahydroisoquinolines, K_2CO_3 was required to effect the cyclisation; however, in the case of the isoindolines, the new *N*-heterocycle formed in the presence of a milder amine base (either NEt_3 or Cy_2NMe).

Other parameters that could limit reaction progress included (i) the size of the *N*-heterocycle being formed, and (ii) the sterics associated with the Heck reaction and subsequent Michael addition. If the steric bulk of the proximal sulfonamide (benzylamine *vs.* phenethylamine) was a critical factor, the initial Heck reaction would be faster for the formation of compounds **11** and **20** over isoindoline **31**. Furthermore, for 5-membered isoindoline series **8**, a strained transition state in the Michael addition step may also hinder the progress of the domino reaction. Nevertheless, as little difference in the overall yields were observed for each of the domino processes studied herein, the role of ring size and sterics appears to be minor.

In conclusion, high yielding domino Heck–aza-Michael reactions to access C1-substituted tetrahydro-β-carbolines, tetrahydroisoquinolines and isoindolines have been successfully developed as a general approach to *N*-heterocycles. These reactions employ mild conditions, and readily available palladium catalysts and acrylates. The mild conditions described suggest this domino process may be applied to more complex substrates and key transformations in total syntheses. As indicated, the use of other highly active palladium catalysts may benefit the scope of this process and its functional group tolerance.

Experimental

General experimental

All proton (^{1}H NMR) and carbon (^{13}C NMR) spectra were recorded on a 270 MHz FT-NMR, 400 MHz FT-NMR or 300 MHz FT-NMR spectrometer as indicated. Samples were dissolved in deuterated chloroform ($CDCl_3$). Proton peaks are reported as follows: chemical shift δ (ppm) (multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integral, coupling constant J (Hz), assignment). Carbon peaks are reported as chemical shift δ (ppm). High resolution mass spectra (HRMS) were recorded on a TOF mass spectrometer with the following conditions: drying gas, nitrogen (7 mL min^{-1}, 350 °C); nebulizer gas, nitrogen (16 psi); capillary voltage, 4.0 kV; vaporizer temperature 350 °C; and cone voltage, 60 V. HPLC grade methanol was used as the mobile phase. Samples were dissolved in acetonitrile (less than 1 mg per mL). IR spectra were acquired on an FT-IR instrument using KBr discs and are reported in wave numbers (cm^{-1}). Column chromatography was performed using silica gel, 60 (70-230 mesh). Petroleum spirits (pet. sp) refers to the fraction boiling at 40–60 °C. All solvents used were AR grade. $Pd(PPh_3)_4$ was prepared according to a literature procedure.[50]

Full experimental details for the preparation of compounds **10**–**16** are described in an earlier communication.[9]

Specific experimental

(*R*,*S*)-2-(9-*tert*-Butoxycarbonyl-2-(*p*-toluenesulfonyl)-3,4-tetrahydro-1*H*-carbolin-1-yl)propan-2-one (17). A sealed tube containing 2-bromoindole **10** (300 mg, 0.61 mmol), $Pd(PPh_3)_4$ (70 mg, 10 mol%), K_2CO_3 (252 mg, 1.82 mmol) and 3-buten-2-one (51 mg, 0.73 mmol) in toluene (3 mL) was flushed with argon, then heated at 120 °C for 16 h. The reaction mixture was cooled to room temperature, filtered, and the solvent removed *in vacuo*. Purification by column chromatography (1 : 4 EtOAc : pet. sp.) afforded tetrahydro-β-carboline **17** as a pale yellow oil (228 mg, 0.47 mmol, 78%). FT-IR (ν, cm^{-1}, KBr) 1716vs, 1465, 1386, 1327, 1159, 698; ^{1}H NMR (270 MHz, $CDCl_3$, δ) 7.96 (dt, J = 0.9, 8.3 Hz, 1H), 7.61 (d, J = 8.3 Hz, 2H), 7.12–7.27 (m, 3H), 7.00 (dd, J = 0.6, 8.6 Hz, 2H), 6.23 (dd, J = 3.3, 10.6 Hz, 1H), 4.05 (dd, J = 6.5, 15.3 Hz, 1H), 3.38–3.50 (m, 1H), 3.08 (dd, J = 3.5, 14.2 Hz, 1H), 2.70 (dd, J = 10.6, 14.2 Hz, 1H), 2.41–2.58 (m, 2H), 2.35 (s, 3H), 2.14 (s, 3H), 1.73 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 206.0, 150.1, 143.5, 136.8, 135.2, 133.5, 129.1, 128.5, 127.0, 124.5, 122.8, 117.9, 115.6, 114.5, 84.8, 50.5, 48.8, 37.7, 29.2, 28.3, 21.2, 19.2;

HRMS-ESI (*m*/*z*) $[C_{26}H_{30}N_2O_5S + Na]^+$ calc. 505.1768, found 505.1790.

***N*-(2-Bromophenethyl)-*p*-toluenesulfonamide (19).** To a cooled solution (0 °C) of 2-bromophenethylamine (400 mg, 2.0 mmol) and triethylamine (242 mg, 2.4 mmol) in CH_2Cl_2 (10 mL) was added *p*-toluenesulfonyl chloride (420 mg, 2.2 mmol) in one portion. The reaction mixture was stirred for 2 h. at ambient temperature. The reaction mixture was then washed with HCl (1 M, 2 × 10 mL), NaOH (Aq. 5% w/w, 2 × 10 mL) and brine (10 mL). The organic layer was separated, dried ($MgSO_4$) and concentrated under reduced pressure to afford phenethylamine **19** as a colorless oil (624 mg, 1.76 mmol, 88%). FT-IR (*ν*, cm^{-1}, KBr) 3152, 1598, 1233, 1059, 754, 647; ^{1}H NMR (270 MHz, $CDCl_3$, *δ*) 7.69 (d, *J* = 8.4 Hz, 2H), 7.47 (dd, *J* = 1.2, 7.9 Hz, 1H), 7.26 (d, *J* = 8.1 Hz, 2H) 7.03–7.20 (m, 3H), 4.57 (brt, *J* = 6.2 Hz, 1H), 3.21 (q, *J* = 6.9 Hz, 2H), 2.90 (t, *J* = 7.2 Hz, 2H), 2.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, *δ*); 143.4, 137.1, 133.0, 131.1, 129.7, 129.0, 128.2, 127.7, 127.1, 124.4, 42.5, 36.3, 21.5; HRMS-ESI (*m*/*z*) $[C_{15}H_{16}BrNO_2S + Na]^+$ calc. 375.9977, found 375.9979.

General procedure A for tetrahydroisoquinoline formation

A sealed tube containing a 2-bromophenethylamine **19** (1.0 equiv.), $Pd(OAc)_2$ (10 mol%), PPh_3 (10 mol%), K_2CO_3 (3.0 equiv.) and alkene (1.2 equiv.) in toluene (3 mL) was flushed with argon and then heated at 120 °C for 16 h. The reaction mixture was cooled to room temperature, filtered, the solvent removed *in vacuo* and the crude product purified by column chromatography using the solvent system specified.

(*R*,*S*)-Butyl 2-(2-tosyl-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (20). General procedure A was followed using 2-bromophenethylamine **19** (100 mg, 0.28 mmol), butyl acrylate (44 mg, 0.34 mmol), $Pd(OAc)_2$ (6 mg, 10 mol%), PPh_3 (7 mg, 10 mol%), potassium carbonate (116 mg, 0.84 mmol) and toluene (3 mL). Purification by column chromatography (1 : 4 EtOAc : pet. sp.) afforded tetrahydroisoquinoline **20** as a pale yellow oil (90 mg, 0.22 mmol, 80%). FT-IR (*ν*, cm^{-1}, KBr) 2959, 1732, 1338, 1161, 1091, 756, 660, 548; ^{1}H NMR (270 MHz, $CDCl_3$, *δ*) 7.63 (d, *J* = 8.4 Hz, 2H), 7.14 (d, *J* = 7.9 Hz, 2H), 7.08–7.10 (m, 3H), 6.95 (m, 1H), 5.46 (t, *J* = 6.9 Hz, 1H), 4.04 (dt, *J* = 3.5, 6.7 Hz, 2H), 3.71–3.80 (m, 1H), 3.47–3.58 (m, 1H), 2.88 (dd, *J* = 7.2, 14.6 Hz, 1H), 2.63–2.74 (m, 3H), 2.32 (s, 3H), 1.58 (m, 2H), 1.32 (m, 2H), 0.90 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$, *δ*); 170.4, 143.3, 137.2, 135.5, 133.1, 129.5, 129.0, 127.3, 127.2, 126.7, 126.5, 64.8, 53.4, 43.6, 39.7, 30.6, 27.0, 21.5, 19.1, 13.8; HRMS-ESI (*m*/*z*) $[C_{22}H_{27}NO_4S + H]^+$ calc. 402.1734, found 402.1734.

(*R*,*S*)-Methyl 2-(2-tosyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-acetate (23). General procedure A was followed using 2-bromophenethylamine **19** (200 mg, 0.56 mmol), methyl acrylate (58 mg, 0.67 mmol), $Pd(OAc)_2$ (12 mg, 10 mol%), PPh_3 (14 mg, 10 mol%), potassium carbonate (232 mg, 1.68 mmol) and toluene (3 mL). Purification by column chromatography (1 : 9 EtOAc : pet. sp.) afforded tetrahydroisoquinoline **23** as a pale yellow oil (168 mg, 0.47 mmol, 83%). FT-IR (*ν*, cm^{-1}, KBr) 3464, 2924, 1744, 1333, 1158, 932, 750, 665, 546; ^{1}H NMR (270 MHz, $CDCl_3$, *δ*) 7.64 (d, *J* = 8.4 Hz, 2H), 7.14 (d, *J* = 7.9 Hz, 2H), 7.08–7.10 (m, 3H), 6.95 (m, 1H), 5.47 (t, *J* = 7.2 Hz, 1H), 3.77 (m, 1H), 3.65 (s, 3H), 3.53 (m, 1H), 2.90 (dd, *J* = 7.6, 14.6 Hz, 1H), 2.62–2.75 (m, 3H), 2.32 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$, *δ*); 170.7, 143.3, 137.2, 135.3, 133.1, 129.5, 129.1, 127.3, 127.2, 126.6, 126.5, 53.5, 52.0, 43.4, 39.7, 26.9, 21.5; HRMS-ESI (*m*/*z*) $[C_{19}H_{21}NO_4S + Na]^+$ calc. 382.1084, found 382.1080.

(*R*,*S*)-2-Hydroxyethyl 2-(2-tosyl-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (24). General procedure A was followed using 2-bromophenethylamine **19** (100 mg, 0.28 mmol), 2-hydroxyethyl acrylate (39 mg, 0.34 mmol), $Pd(OAc)_2$ (6 mg, 10 mol%), PPh_3 (7 mg, 10 mol%), potassium carbonate (116 mg, 0.84 mmol) and toluene (3 mL). Purification by column chromatography (2 : 3 EtOAc : pet. sp.) afforded tetrahydroisoquinoline **24** as a pale yellow oil (83 mg, 0.21 mmol, 76%). FT-IR (*ν*, cm^{-1}, KBr) 2924, 1737, 1597, 1336, 1158, 1091, 756, 659, 547; ^{1}H NMR (270 MHz, $CDCl_3$, *δ*) 7.61 (d, *J* = 8.4 Hz, 2H), 7.06–7.15 (m, 5H), 6.91 (m, 1H), 5.47 (t, *J* = 5.9 Hz, 1H), 4.21–4.31 (m, 2H), 3.71–3.78 (m, 2H), 3.50–3.59 (m, 2H), 2.91 (ddd, *J* = 1.5, 8.2, 14.8 Hz, 1H), 2.78 (dd, *J* = 5.7, 14.8 Hz, 1H), 2.60–2.65 (m, 2H), 2.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, *δ*); 170.0, 143.2, 137.1, 135.2, 133.0, 129.5, 129.0, 127.2, 127.1, 126.7, 126.6, 126.4, 62.5, 53.4, 43.3, 39.6, 26.7, 21.4; HRMS-ESI (*m*/*z*) $[C_{20}H_{23}NO_5S + Na]^+$ calc. 412.1189, found 412.1178.

(*R*,*S*)-2-(2-Tosyl-1,2,3,4-tetrahydroisoquinolin-1-yl)acetonitrile (25). General procedure A was followed using 2-bromophenethylamine **19** (100 mg, 0.28 mmol), acrylonitrile (18 mg, 0.34 mmol), $Pd(OAc)_2$ (6 mg, 10 mol%), PPh_3 (7 mg, 10 mol%), potassium carbonate (116 mg, 0.84 mmol) and toluene (3 mL). Purification by column chromatography (1 : 9 EtOAc : pet. sp.) afforded tetrahydroisoquinoline **25** as a pale yellow oil (75 mg, 0.23 mmol, 82%). FT-IR (*ν*, cm^{-1}, KBr) 2249, 1652, 1401, 1162, 1006, 862, 702, 548; ^{1}H NMR (270 MHz, $CDCl_3$, *δ*) 7.69 (d, *J* = 8.4 Hz, 2H), 7.13–7.22 (m, 5H), 7.07 (m, 1H), 5.17 (t, *J* = 5.7 Hz, 1H), 3.64–3.74 (m, 1H), 3.48–3.57 (m, 1H), 2.98 (dd, *J* = 4.0, 5.9 Hz, 2H), 2.64–2.92 (m, 2H), 2.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, *δ*); 144.1, 135.8, 134.1, 132.7, 130.0, 129.2, 128.2, 127.4, 127.1, 126.9, 117.3, 52.8, 41.1, 28.0, 27.7, 21.6; HRMS-ESI (*m*/*z*) $[C_{18}H_{18}N_2O_2S - H]^-$ calc. 325.1016, found 325.1009.

(*R*,*S*)-1-(2-Tosyl-1,2,3,4-tetrahydroisoquinolin-1-yl)propan-2-one (26). General procedure A was followed using 2-bromophenethylamine **19** (100 mg, 0.28 mmol), 3-buten-2-one (24 mg, 0.34 mmol), $Pd(OAc)_2$ (6 mg, 10 mol%), PPh_3 (7 mg, 10 mol%), potassium carbonate (116 mg, 0.84 mmol) and toluene (3 mL). Purification by column chromatography (1 : 9 EtOAc : pet. sp.) afforded tetrahydroisoquinoline **26** as a pale yellow oil (76 mg, 0.22 mmol, 79%). FT-IR (*ν*, cm^{-1}, KBr) 3412, 2924, 1713, 1597, 1335, 1159, 1091, 758, 663, 550; ^{1}H NMR (270 MHz, $CDCl_3$, *δ*) 7.63 (d, *J* = 8.2 Hz, 2H), 7.14 (d, *J* = 8.2 Hz, 2H), 7.07–7.09 (m, 3H), 6.94 (m, 1H), 5.50 (t, *J* = 6.2 Hz, 1H), 3.67–3.74 (m, 1H), 3.46–3.56 (m, 1H), 3.05 (dd, *J* = 5.9, 16 Hz, 1H), 2.82 (dd, *J* = 6.4, 16 Hz, 1H), 2.64–2.69 (m, 2H), 2.32 (s, 3H), 2.15 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, *δ*); 205.4, 143.4, 136.7, 136.2, 132.8, 129.5, 128.8, 127.2, 127.0, 126.7, 126.6, 52.7, 52.1, 40.1, 30.4, 27.2, 21.5; HRMS-ESI (*m*/*z*) $[C_{19}H_{21}NO_3S + Na]^+$ calc. 366.1134, found 366.1135.

***N*-(2-Bromobenzyl)-*p*-toluenesulfonamide (30).** To a cooled solution (0 °C) of 2-bromobenzylamine hydrochloride (400 mg, 1.80 mmol) and triethylamine (401 mg, 3.96 mmol) in CH_2Cl_2 (10 mL) was added *p*-toluenesulfonyl chloride (378 mg, 1.98 mmol)

in one portion. The reaction mixture was stirred for 2 h at ambient temperature. The reaction mixture was then washed with HCl (1 M, 2 × 10 mL), NaOH (aq. 5% w/w, 2 × 10 mL) and brine (10 mL). The organic layer was separated, dried ($MgSO_4$) and concentrated under reduced pressure to afford benzylamine **30** as a colorless oil (610 mg, 1.79 mmol, 99%). FT-IR (ν, cm^{-1}, KBr) 3087, 1622, 1159, 785, 667; ^1H NMR (270 MHz, $CDCl_3$, δ) 7.69 (d, J = 8.4 Hz, 2H), 7.43 (dd, J = 1.2, 7.9 Hz, 1H), 7.19–7.30 (m, 4H), 7.07 (dt, J = 1.7, 7.7 Hz, 1H), 5.11 (brt, J = 5.9 Hz, 1H), 4.21 (d, J = 6.2 Hz, 2H), 2.39 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ); 143.5, 136.9, 135.5, 132.8, 130.5, 129.6, 129.5, 127.7, 127.1, 123.5, 47.5, 21.5; HRMS-ESI (m/z) $[C_{14}H_{14}BrNO_2S - H]^-$ calc. 337.9856, found 337.9862.

General procedure B for isoindoline formation

A sealed tube containing a 2-bromobenzylamine **30** (1.0 equiv.), $Pd(OAc)_2$ (10 mol%), PPh_3 (10 mol%), triethylamine (3.0 equiv.) and alkene (1.2 equiv.) in DMF was flushed with argon and then heated at 120 °C for 16 h. The reaction mixture was cooled to room temperature, filtered, the solvent removed *in vacuo* and the crude product purified by column chromatography using the solvent system specified.

(*R*,*S*)-Butyl 2-(2-tosylisoindolin-1-yl)acetate (31). General procedure B was followed using 2-bromobenzylamine **30** (100 mg, 0.29 mmol), butyl acrylate (45 mg, 0.35 mmol), $Pd(OAc)_2$ (7 mg, 10 mol%), PPh_3 (8 mg, 10 mol%), triethylamine (88 mg, 0.87 mmol) and DMF (3 mL). Purification by column chromatography (1 : 9 EtOAc : pet. sp.) afforded isoindoline **31** as a pale yellow oil (86 mg, 0.22 mmol, 77%). FT-IR (ν, cm^{-1}, KBr) 3444, 2960, 1731, 1348, 1164, 1095, 666, 553; ^1H NMR (270 MHz, $CDCl_3$, δ) 7.75 (d, J = 8.2 Hz, 2H), 7.18–7.27 (m, 5H), 7.10–7.13 (m, 1H), 5.27 (m, J = 3.0, 3.7 Hz, 1H), 4.73(dd, J = 2.5, 13.8 Hz, 1H), 4.53 (d, J = 13.8 Hz, 1H), 4.09 (t, J = 6.7 Hz, 2H), 3.30 (dd, J = 3.9, 16.5 Hz, 1H), 2.86 (dd, J = 7.9, 16.5 Hz, 1H), 2.36 (s, 3H), 1.53–1.63 (m, 2H), 1.23–1.40 (m, 2H), 0.91 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ); 171.0, 143.7, 139.6, 135.5, 134.0, 129.8, 128.1, 127.9, 127.6, 122.7, 122.4, 64.6, 62.1, 53.9, 42.8, 30.6, 21.5, 19.1, 13.7; HRMS-ESI (m/z) $[C_{21}H_{25}NO_4S + Na]^+$ calc. 410.1397, found 410.1380.

(*R*,*S*)-2-Hydroxyethyl 2-(2-tosylisoindolin-1-yl)acetate (35). General procedure B was followed using 2-bromobenzylamine **30** (100 mg, 0.29 mmol), 2-hydroxyethyl acrylate (40 mg, 0.35 mmol), $Pd(OAc)_2$ (7 mg, 10 mol%), PPh_3 (8 mg, 10 mol%), triethylamine (88 mg, 0.87 mmol) and DMF (3 mL). Purification by column chromatography (2 : 3 EtOAc : pet. sp.) afforded isoindoline **35** as a pale yellow oil (91 mg, 0.24 mmol, 84%). FT-IR (ν, cm^{-1}, KBr) 3523, 2924, 1732, 1343, 1162, 1094, 754, 666, 555; ^1H NMR (270 MHz, $CDCl_3$, δ) 7.74 (d, J = 8.2 Hz, 2H), 7.19–7.28 (m, 5H), 7.09–7.16 (m, 1H), 5.31 (m, 1H), 4.73 (dd, J = 2.5, 14.1 Hz, 1H), 4.50 (d, J = 13.8 Hz, 1H), 4.32 (m, 1H), 4.19 (m, 1H), 3.81 (m, 2H), 3.17 (dd, J = 4.9, 15.8 Hz, 1H), 2.99 (dd, J = 5.9, 16.0 Hz, 1H), 2.36 (s, 3H), 2.33 (brt, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, δ); 171.1, 144.0, 139.3, 135.5, 133.8, 129.9, 128.3, 128.0, 127.6, 122.6, 122.5, 66.6, 62.3, 61.0, 53.9, 43.0, 21.5; HRMS-ESI (m/z) $[C_{19}H_{21}NO_5S + Na]^+$ calc. 398.1033, found 398.1024.

(*R*,*S*)-2-(2-Tosylisoindolin-1-yl)acetamide (36). General procedure B was followed using 2-bromobenzylamine **30** (100 mg, 0.29 mmol), acrylamide (25 mg, 0.35 mmol), $Pd(OAc)_2$ (7 mg, 10 mol%), PPh_3 (8 mg, 10 mol%), triethylamine (88 mg, 0.87 mmol) and DMF (3 mL). Purification by column chromatography (1 : 1 EtOAc : pet. sp.) afforded isoindoline **36** as a pale yellow oil (68 mg, 0.21 mmol, 71%). FT-IR (ν, cm^{-1}, KBr) 3419, 2924, 1682, 1330, 1162, 1093, 667; ^1H NMR (270 MHz, $CDCl_3$, δ) 7.75 (d, J = 8.2 Hz, 2H), 7.18–7.29 (m, 5H), 7.10–7.14 (m, 1H), 5.86 (brs, 1H), 5.40 (brs, 1H), 5.18 (m, J = 3.2, 3.9 Hz, 1H), 4.73 (dd, J = 2.0, 13.8 Hz, 1H), 4.53 (d, J = 13.8 Hz, 1H), 3.15 (dd, J = 3.7, 15.0 Hz, 1H), 2.90 (dd, J = 7.1, 15.0 Hz, 1H), 2.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ); 172.0, 144.2, 139.2, 135.0, 133.2, 130.1, 128.3, 128.2, 127.8, 123.3, 122.4, 62.6, 54.2, 43.7, 21.6; HRMS-ESI (m/z) $[C_{17}H_{18}N_2O_3S + H]^+$ calc. 331.1111, found 331.1126.

(*R*,*S*)-2-(2-Tosylisoindolin-1-yl)acetonitrile (37). General procedure B was followed using 2-bromobenzylamine **30** (100 mg, 0.29 mmol), acrylonitrile (18 mg, 0.35 mmol), $Pd(OAc)_2$ (7 mg, 10 mol%), PPh_3 (8 mg, 10 mol%), triethylamine (88 mg, 0.87 mmol) and DMF (3 mL). Purification by column chromatography (1 : 6 EtOAc : pet. sp.) afforded isoindoline **37** as a pale yellow oil (62 mg, 0.20 mmol, 68%). FT-IR (ν, cm^{-1}, KBr) 3429, 2361, 2254, 1352, 1350, 1160, 756, 664, 559; ^1H NMR (270 MHz, $CDCl_3$, δ) 7.76 (d, J = 8.2 Hz, 2H), 7.18–7.33 (m, 6H), 5.11 (m, 1H), 4.80 (dd, J = 2.7, 13.8 Hz, 1H), 4.55 (d, J = 13.8 Hz, 1H), 3.16 (s, 1H), 3.14 (d, J = 1.0 Hz, 1H), 2.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ); 144.4, 136.7, 135.8, 133.8, 130.1, 129.1, 128.4, 127.5, 122.9, 122.6, 116.7, 61.5, 53.9, 26.9, 21.5; HRMS-ESI (m/z) $[C_{17}H_{16}N_2O_2S + H]^+$ calc. 313.1005, found 313.1013.

(*R*,*S*)-2-(2-Tosylisoindolin-1-yl)acetic acid (38). General procedure B was followed using 2-bromobenzylamine **30** (100 mg. 0.29 mmol), acrylic acid (25 mg, 0.35 mmol), $Pd(OAc)_2$ (7 mg, 10 mol%), PPh_3 (8 mg, 10 mol%), triethylamine (88 mg, 0.87 mmol) and DMF (3 mL). Purification by column chromatography (3 : 1 EtOAc : pet. sp.) afforded isoindoline **38** as a pale yellow oil (82 mg, 0.25 mmol, 85%). FT-IR (ν, cm^{-1}, KBr) 3435 (vs), 2923, 1697, 1574, 1397, 1339, 1162, 1094, 666, 555; ^1H NMR (270 MHz, $CDCl_3$, δ) 7.75 (d, J = 8.2 Hz, 2H), 7.28 (d, J = 8.2 Hz, 2H), 7.18–7.22 (m, 3H), 7.10–7.13 (m, 1H), 5.28 (m, 1H), 4.73 (dd, J = 2.2, 13.9 Hz, 1H), 4.53 (d, J = 13.9 Hz, 1H), 3.39 (dd, J = 3.9, 16.5 Hz, 1H), 2.91 (dd, J = 7.9, 16.5 Hz, 1H), 2.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ); 176.5, 143.9, 139.2, 135.4, 133.8, 129.9, 128.3, 128.1, 127.6, 122.7, 122.5, 61.8, 53.9, 42.7, 21.5; HRMS-ESI (m/z) $[C_{17}H_{17}NO_4S + Na]^+$ calc. 354.0771, found 354.0759.

(*R*,*S*)-1-(2-Tosylisoindolin-1-yl)propan-2-one (39). General procedure B was followed using 2-bromobenzylamine **30** (100 mg, 0.29 mmol), 3-buten-2-one (24 mg, 0.35 mmol), $Pd(OAc)_2$ (7 mg, 10 mol%), PPh_3 (8 mg, 10 mol%), triethylamine (88 mg, 0.87 mmol) and DMF (3 mL). Purification by column chromatography (1 : 4 EtOAc : pet. sp.) afforded isoindoline **39** as a pale yellow oil (82 mg, 0.25 mmol, 86%). FT-IR (ν, cm^{-1}, KBr) 3448, 2923, 1714, 1342, 1161, 667, 559; ^1H NMR (270 MHz, $CDCl_3$, δ) 7.74 (d, J = 8.2 Hz, 2H), 7.28 (d, J = 7.9 Hz, 2H), 7.16–7.20 (m, 3H), 7.07–7.12 (m, 1H), 5.30 (m, 1H), 4.75 (dd, J = 2.4, 13.9 Hz, 1H), 4.50 (d, J = 13.9 Hz, 1H), 3.50 (dd, J = 3.4, 17.8 Hz, 1H), 2.99 (dd, J = 7.7, 18.0 Hz, 1H), 2.36 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 206.5, 143.8, 140.2, 135.1, 133.5, 129.9, 128.7, 128.0, 127.7, 122.9, 122.3, 61.1, 53.9, 52.2, 30.8, 21.5; HRMS-ESI (m/z) $[C_{18}H_{19}NO_3S + Na]^+$ calc. 352.0978, found 352.0993.

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