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PAPER

A tandem Heck–aza-Michael addition protocol for the one-pot synthesis of isoindolines from unprotected amines†

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A palladacycle-catalyzed tandem Heck-intramolecular aza-Michael reaction protocol has been developed for the one-pot synthesis of 1-substituted isoindolines from *N*-unprotected 2-bromobenzylamines and acrylates with high yields.

Introduction

Due to their widespread occurrence in nature, diverse biological activity and interesting chemical properties, isoindolines (**1**),[1] 1-substituted isoindolines (**2**),[2] 1,3-disubstituted isoindolines (**3**),[3] 3-substituted isoindolinones (**4**)[4] (Fig. 1) and their analogs are highly attractive organic compounds that have shown potential in organic synthesis and medicinal chemistry. Therefore, the development of new and highly efficient strategies for the generation of these intricate heterocyclic molecular architectures is of great interest and remains a preeminent goal in organic synthesis.

However, when compared to their congeners, access to 1- and 1,3-substituted isoindolines (**2**, **3**) has been hampered by the fact that very few synthetic methods have been developed for their synthesis. The access to 3-substituted isoindolinones *via* tandem oxidative C–H functionalization–aza Michael addition of benzamide was reported by Li *et al.*[5] using 4 mol% of [RhCp*Cl_2] in a sealed tube under nitrogen and by Falck and Zhu[6] using Pd(OAc)$_2$ with bathophenanthroline ligand. Fustero *et al*. reported the synthesis of 1-substituted isoindolines *via* aza-Michael addition using the *N*-protected amide (generated using the Hoveyda–Grubbs catalyst) with 20 mol% of diarylprolinols.[7] A metal-free one-pot Brønsted acid catalyzed Friedel–Crafts/base-catalyzed aza-Michael addition reaction of indoles with *N*-protected *N*-tosyliminoenoates using 10 mol% phosphoric acid catalyst leading to 1,3-isoindolines has been reported by Enders *et al*.[3d] Jarvo and Williams, and Pfeffer *et al.* had also reported methods that yield 1-substituted and 1,3-disubstituted isoindolines and related heterocycles from protected imines[8] and amines.[9] However, such methods usually require use of expensive starting materials/catalysts, high catalyst loadings and/or the requirement for protection of nitrogen with Cbz, Boc, Ts *etc.* The structural versatility of the isoindolines thus obtained was consequently limited, especially with respect to substituents on nitrogen, and extra chemical waste was inevitably generated during the protection–deprotection steps. Notable attempts to circumvent these issues include a Pd-catalyzed intramolecular α-arylation of α-amino acid esters reported by Buchwald and Gaertzen using biaryl based phosphines allowing incorporation of phenyl and methyl moieties on nitrogen (eqn (1))[2a] and a formal double arylation of azomethines with 10 mol% phosphoric acid catalysts reported recently by Gong *et al.* yielding disubstituted isoindolines (although no variation of substituent on nitrogen could be achieved) (eqn (2)).[10]

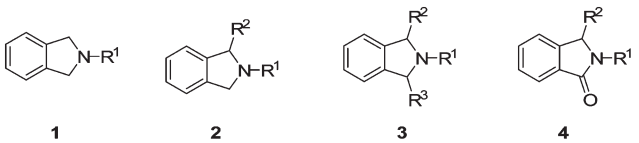

Fig. 1 Common isoindoline and isoindolinone scaffolds.

However, there is no precedent in the literature for the synthesis of 1-substituted isoindolines using easily accessible *unprotected* amines as substrates, a protocol that would also allow the incorporation of various substituents on the nitrogen atom. A major hindrance to the development of such a method is the fact that the electron deficient alkenes involved need to be consumed rapidly by the Heck process so as to avoid an intermolecular aza-Michael proceeding as the first step.

As efficient and versatile precatalysts, palladacycle **5** and its derivatives, (Fig. 2), have been extensively employed in the Heck reaction as well as in other coupling reactions.[11] Recently, we had reported the application of similar palladacycles in asymmetric hydrophosphination reactions[12] and in domino alkylation–cyclization protocols for indole synthesis.[13] We have also used palladacycle **7** as catalyst in a tandem allylic amination–allylation reaction for the one-pot synthesis of hitherto inaccessible 2-allylanilines.[14]

In line with our continuing interest in the catalytic application of these palladacycles, we herein investigate their efficacy in a

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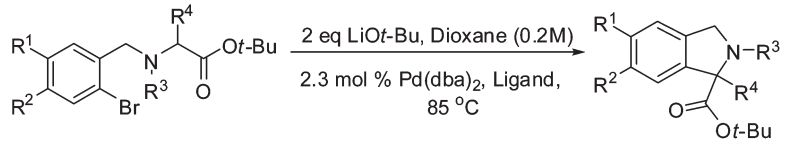
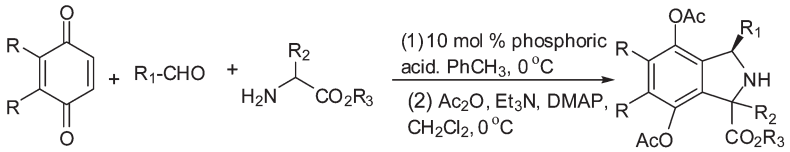


(1)



(2)

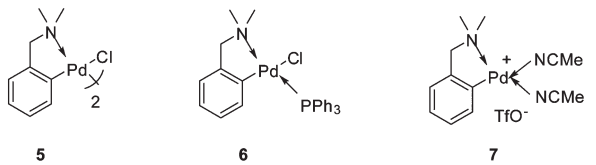


Fig. 2 Structures of palladacycles used in this study.

tandem Heck-intramolecular aza-Michael reaction sequence for the formation of isoindolines incorporating an ester substituent at the 1-position. The ester moiety is an attractive substituent because it can be easily transformed into other functionalities. This work also assumes significance in view of recent studies demonstrating that isoindolines can be easily converted into the corresponding isoindoles.[15]

Results and discussion

In order to test the feasibility of the protocol, 2-bromobenzylamine **8** (easily prepared *via* the reductive amination of 2-bromobenzaldehyde in good yields) was subjected to the tandem Heck reaction with acrylate **9** and a subsequent intramolecular aza-Michael addition (Table 1). The dimeric palladacycle **5** was employed as catalyst. Use of 2 mol% of **5** gave a higher yield and reactivity than 1 mol% (Table 1, entry 1 *vs.* entry 2). The addition of 20 mol% of tetrabutylammonium bromide accelerated the reaction rate and increased the conversions obtained for the final product (Table 1, entry 1 *vs.* entry 4).

No product however, was obtained when the reaction was conducted at 90 °C for 24 h in DMF (Table 1, entry 5) and 130 °C was found to be the optimum temperature. The presence of a triphenylphosphine ligand in complex **6** enhanced the activity and conversion rate drastically, and the reaction only required 12 h for completion instead of 24 h for complex **5** (Table 1, entry 6 *vs.* entry 3 and entry 7 *vs.* entry 4). The palladacycle complex **7**, which was efficient in our hands for the one-pot synthesis of 2-allylanilines, was, however, inefficient in this scenario (Table 1, entry 8). A detailed screening of solvents and bases indicated that DMF and $(n\text{-Bu})_4$NBr are best suited for this protocol. The choice of base is critical since it needs to help promote the intramolecular aza-Michael reaction but should not promote it to such an extent that an intermolecular aza-Michael takes precedence over the Heck process. With the optimum conditions established, we proceeded to screen various 2-bromobenzylamines with *tert*-butyl acrylate and good to high yields were achieved in all cases (Scheme 1).

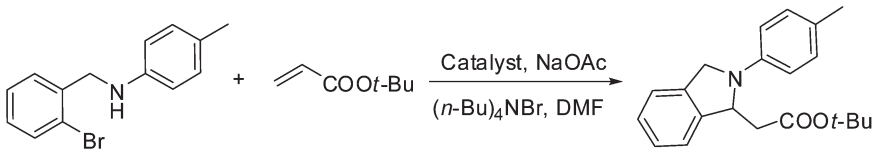
Significantly, the presence of electron-donating or electron-withdrawing moieties on the amines had no impact on the tandem Heck reaction–aza-Michael addition sequence (**10a–f** *vs.* **10g–h**). The presence of either *meta*- or *para*-substituent groups on the amines also had no significant effect on the yields and rates (**10a**, **10c**, **10f**, **10g**, **10h** *vs.* **10d**, **10e**). Furthermore, the reaction proceeded smoothly and provided good yields for 2-bromobenzylamines incorporating *tert*-butyl as the *N*-substituent. When compared to *tert*-butyl and *n*-butyl acrylates, relatively lower yields were observed for methyl and ethyl acrylates (**10j**, **10k**). This may be attributed to their relatively low boiling points. A good result was obtained for the use of acrylamides (**10m**). However, the aza-Michael addition occurred prior to the Heck reaction when more active terminal enones were used. A preliminary attempt to employ available chiral variants of the palladacycles[12,13] in an asymmetric version of this reaction did not yield satisfactory results in terms of enantioselectivity.

As aforementioned, the overall process for the formation of 1-substituted isoindolines from 2-bromobenzylamines and acrylates involves two general transformations: the Heck reaction and the aza-Michael addition. Thus, the overall reaction could either proceed *via* Heck reaction followed by an intramolecular aza-Michael addition (Path A, Scheme 2) or by an intermolecular aza-Michael addition followed by intramolecular arylation (Path B, Scheme 2). To obtain insights into the reaction mechanism, intermediate **11** (Scheme 3) was prepared *via* Heck reaction followed by reductive amination from the starting material 2-bromobenzaldehyde. When **11** was treated with 2 mol% of palladacycle **6** at the optimum conditions established previously, the 1-substituted isoindoline product was obtained. To gain a better mechanistic understanding of the palladacycle catalyzed aza-Michael addition, we conducted the controlled experiment for the intermediate **11** under the optimum conditions in the absence of **6** (Scheme 3).

The result showed that the aza-Michael addition was promoted to give the isoindoline only in the presence of palladacycle **6** (Scheme 3). Thus, it is clear that the formation of isoindoline followed a two step sequence consisting of a palladacycle-catalyzed Heck reaction followed by a palladacycle-catalyzed aza-Michael addition.

To ascertain the possibility for Path B occurring, compound **12** was prepared and subjected to the same reaction conditions. The results showed that no isoindoline product was formed (Scheme 4).

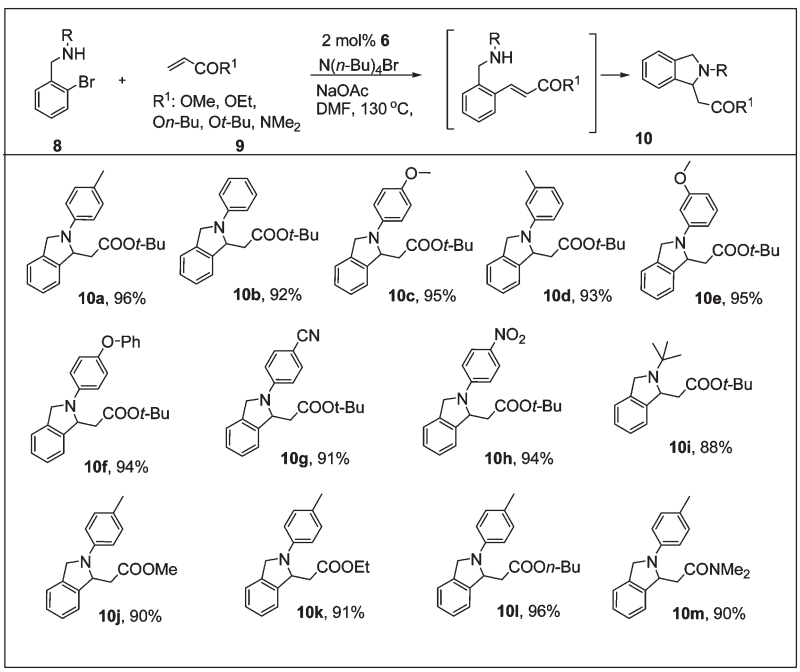
Table 1 Optimization of conditions[a]



8 9 10

Entry	Catalyst	Temp (°C)	Product yield[b] (%)
1	2 mol% **5**	130	95
2	1 mol% **5**	130	70
3[c]	2 mol% **5**	130	50
4[d]	2 mol% **5**	130	30
5	2 mol% **5**	90	N.R
6[c]	2 mol% **6**	130	96
7[d]	2 mol% **6**	130	75
8	2 mol% **7**	130	N.R

[a] Unless otherwise indicated, all reactions were performed using 2-bromobenzylamine (1 mmol), acrylate (1.2 mmol), catalyst (2 mol%), $(n\text{-Bu})_4$NBr (0.2 equiv) and NaOAc (1.4 equiv) in DMF (3 mL) for 24 h. [b] Isolated yield; [c] for 12 h. [d] Without $(n\text{-Bu})_4$NBr.



Scheme 1 Palladacycle-catalyzed one-pot tandem Heck reaction–aza-Michael addition protocol. Unless otherwise indicated, all reactions were performed at 130 °C using 2-bromobenzylamines (1 mmol), acrylates (1.2 mmol), catalyst (2 mol%), $(n\text{-Bu})_4$NBr (0.2 equiv) and NaOAc (1.4 equiv) in DMF (3 mL) for 12 h. Yields shown are isolated yields.

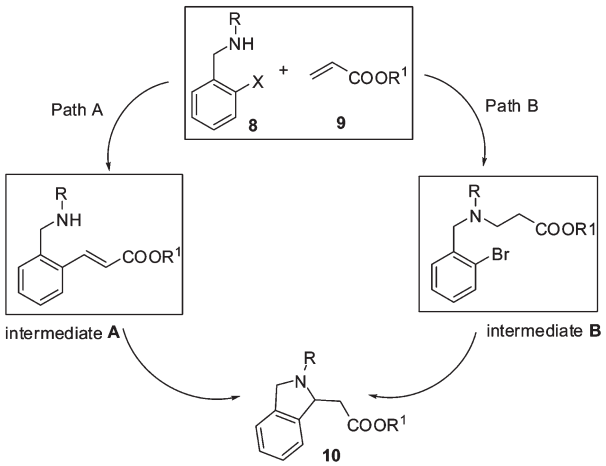
Conclusions

In conclusion, we have successfully developed a palladacycle-catalyzed tandem Heck–aza-Michael addition reaction at low catalyst loading for the one-pot synthesis of 1-substituted isoindolines. This protocol avoids the formation of chemical waste during the conventional protection and deprotection of amines by allowing the direct use of unprotected amines as starting materials. Furthermore it allows the incorporation of a wide range of substituents on the nitrogen atom of isoindolines, which has hitherto not been possible. Further studies on the scope of this novel process and the synthetic use of the heterocycles are currently underway.

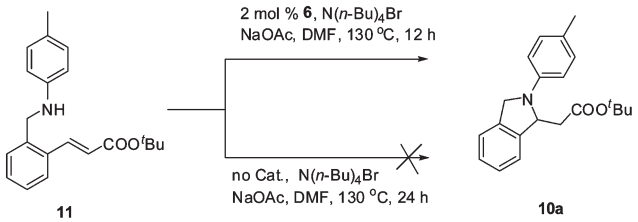
Experimental

General experimental

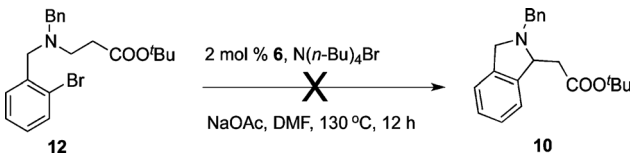
Unless otherwise stated, all reactions were performed under an argon atmosphere. Unless specified, all reagents and starting



Scheme 2 Plausible mechanistic pathways.



Scheme 3 Role of catalyst in the aza-Michael addition step (Path A).



Scheme 4 Intramolecular arylation of **12**.

materials were purchased from commercial sources and used as received. Solvents were purified following standard literature procedures. Analytical thin layer chromatography (TLC) was performed using pre-coated silica gel plate. Visualization was achieved by UV light (254 nm). Flash chromatography was performed using silica gel and a gradient solvent system (EtOAc: *n*-hexane as eluent). ^{1}H and ^{13}C NMR spectra were measured on 400 and 500 MHz spectrometers and the residual solvent peak was used as an internal reference: proton (chloroform δ 7.26), carbon (chloroform δ 77.0). Chemical shifts (ppm) were recorded with tetramethylsilane (TMS) as the internal reference standard. Multiplicities are given as: s (singlet), brs (broad singlet), d (doublet), t (triplet), dd (doublet of doublets) or m (multiplet). The number of protons (n) for a given resonance is indicated by nH and coupling constants are reported as a *J* value in Hz. High resolution mass spectra (HRMS) were obtained on a LC/HRMS mass spectrometer (Waters Q-Tof Premier Mass Spectrometer).

General procedure for the preparation of intermediates. To a solution of 2-bromobenzaldehyde (185 mg, 1 mmol) in ether (10 mL) was added amine (1.2 mmol) and anhydrous $MgSO_4$, and the mixture was stirred at room temperature for 12 h. After the aldehyde was converted completely, $MgSO_4$ was filtered off and the filtrate was concentrated and dissolved in MeOH (10 mL), the solution was treated with $NaBH_4$ (38 mg, 1 mmol) to give crude compound **8**. After standard work-up, the crude product was purified by column chromatography (Eluent: from Hex to EA–Hex = 1 : 30) to give the intermediate **8**.

Specific experimental

***N*-(2-Bromobenzyl)-4-methylaniline (8a).** Pale yellow solid; 95% (262 mg) isolated yield; mp: 58–60 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.57 (d, J = 7.9 Hz, 1H), 7.42 (d, J = 7.9 Hz, 1H), 7.25–7.28 (m, 1H), 7.12–7.15 (m, 1H), 7.00 (d, J = 8.1 Hz, 2H), 6.55 (d, J = 8.1 Hz, 2H), 4.39 (s, 2H), 4.08 (brs, 1H), 2.45 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ; 145.4, 138.4, 132.7, 129.7, 129.2, 128.6, 127.5, 126.9, 48.7, 20.4. HRMS (ESI): Calcd for $C_{14}H_{15}$ BrN (M^+ + H): 276.0388, found 276.0389.

***N*-(2-Bromobenzyl)aniline (8b).** Pale yellow oil; 94% (246 mg) isolated yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, J = 7.9 Hz, 1H), 7.42 (d, J = 7.6 Hz, 1H), 7.25–7.29 (m, 1H), 7.12–7.20 (m, 3H), 6.74 (t, J = 7.3 Hz, 1H), 6.63 (d, J = 8.1 Hz, 2H), 4.42 (s, 2H), 4.20 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ; 147.7, 138.2, 132.8, 129.3, 129.1, 128.7, 127.5, 123.2, 117.7, 112.9, 48.4; HRMS (ESI): Calcd for $C_{13}H_{13}$BrN (M^+ + H): 262.0231, found 262.0235.

***N*-(2-Bromobenzyl)-4-methoxyaniline (8c).** Pale yellow oil; 92% (269 mg) isolated yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.57 (d, J = 7.9 Hz, 1H), 7.41 (d, J = 7.6 Hz, 1H), 7.25–7.28 (m, 1H), 7.13 (t, J = 7.6 Hz, 1H), 6.78 (d, J = 8.4 Hz, 2H), 6.59 (d, J = 8.4 Hz, 2H), 4.37 (s, 2H), 3.97 (brs, 1H), 3.74 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ; 152.3, 141.9, 138.4, 132.8, 129.3, 128.6, 127.5, 123.3, 114.9, 114.2, 55.7, 49.3; HRMS (ESI): Calcd for $C_{14}H_{15}$BrNO (M^+ + H): 292.0337, found 292.0330.

***N*-(2-Bromobenzyl)-3-methylaniline (8d).** Pale yellow oil; 90% (249 mg) isolated yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (dd, J = 7.9, 1.1 Hz, 1H), 7.43 (dd, J = 7.6, 1.4 Hz, 1H), 7.29 (dd, J = 7.5, 1.1 Hz, 1H), 7.15 (td, J = 7.8, 1.7 Hz, 1H), 7.08 (t, J = 7.7 Hz, 1H), 4.41 (s, 2H), 4.12 (brs, 1H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.7, 139.1, 138.3, 132.7, 129.2, 129.1, 128.6, 127.5, 123.2, 118.7, 113.7, 110.0, 48.4, 21.6; HRMS (ESI): Calcd for $C_{14}H_{15}$BrN (M^+ + H): 276.0388, found 276.0391.

***N*-(2-Bromobenzyl)-3-methoxyaniline (8e).** Pale yellow oil; 92% (269 mg) isolated yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (dd, J = 7.9, 1.2 Hz, 1H), 7.41 (dd, J = 7.7, 1.5 Hz, 1H), 7.27 (td, J = 7.5, 1.2 Hz, 1H), 7.14 (td, J = 7.5, 1.5 Hz, 1H), 7.09 (t, J = 8.1 Hz, 1H), 6.30 (ddd, J = 8.2, 2.4, 0.8 Hz, 1H), 6.25 (ddd, J = 8.1, 2.2, 0.7 Hz, 1H), 6.18 (t, J = 2.3 Hz, 1H), 4.40 (s, 2H), 4.22 (brs, 1H), 3.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ; 160.8, 149.1, 138.1, 132.8, 130.0, 129.1, 128.7, 127.5, 123.2, 106.0, 102.8, 99.0, 55.1, 48.3; HRMS (ESI): Calcd for $C_{14}H_{15}$BrNO (M^+ + H): 292.0337, found 292.0338.

***N*-(2-Bromobenzyl)-4-phenoxyaniline (8f).** Pale yellow oil; 91% (322 mg) isolated yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (dd, J = 8.0, 1.2 Hz, 1H), 7.44 (dd, J = 7.6, 1.4 Hz, 1H), 7.25–7.31 (m, 3H), 7.15 (td, J = 7.8, 1.7 Hz, 1H), 6.99–7.03 (m, 1H), 6.88–6.94 (m, 4H), 6.60–6.62 (m, 2H), 4.40 (s, 2H), 4.13 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.9, 148.0, 144.3, 138.1, 132.8, 129.5, 129.2, 128.8, 127.6, 123.3, 122.0, 121.1, 117.2, 114.0, 49.0; HRMS (ESI): Calcd for $C_{19}H_{17}BrNO$ (M^+ + H): 354.0494, found 354.0493.

4-(2-Bromobenzylamino)benzonitrile (8g). Yellow solid; 90% (258 mg) isolated yield; mp: 111–113 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (d, J = 7.9 Hz, 1H), 7.39 (d, J = 8.6 Hz, 2H), 7.25–7.33 (m, 2H), 7.14–7.18 (m, 1H), 6.58 (d, J = 8.6 Hz, 2H), 4.84–4.85 (brs, 1H), 4.44 (d, J = 6.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ; 150.8, 136.5, 133.6, 133.0, 129.1, 128.8, 127.6, 123.2, 120.3, 111.4, 99.1, 47.5; HRMS (ESI): Calcd for $C_{14}H_{12}$ Br N_2 (M^+ + H): 287.0184, found 287.0181.

***N*-(2-Bromobenzyl)-4-nitroaniline (8h).** Yellow oil; 90% (276 mg) isolated yield; mp: 177–179 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (d, J = 9.2 Hz, 2H), 7.61 (d, J = 7.9 Hz, 1H), 7.27–7.33 (m, 2H), 7.17–7.21 (m, 1H), 6.57 (d, J = 9.2 Hz, 2H), 4.97 (brs, 1H), 4.51 (d, J = 6.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.7, 136.2, 133.2, 129.4, 129.0, 127.8, 126.4, 123.4, 111.5, 47.9. HRMS (ESI): Calcd for $C_{13}H_{12}$ Br N_2O_2 (M^+ + H): 307.0082, found 307.0085.

***N*-(2-Bromobenzyl)-2-methylpropan-2-amine (8i).** Pale yellow oil; 95% (230 mg) isolated yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (dd, J = 8.0, 0.8 Hz, 1H), 7.45 (dd, J = 7.6, 1.4 Hz, 1H), 7.27 (td, J = 7.6, 0.8 Hz, 1H), 7.09 (dd, J = 8.0, 1.4 Hz, 1H), 3.80 (s, 2H), 1.20 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ; 140.4, 132.7, 130.5, 128.4, 127.6, 124.0, 50.9, 47.3, 29.1; HRMS (ESI): Calcd for $C_{11}H_{17}BrN$ (M^+ + H): 242.0544, found 242.0543.

General procedure for the tandem Heck–aza-Michael addition reaction. A solution of **8** (1 mmol), **9** (1.2 mmol), N(nBu)$_4$Br (65 mg, 0.2 mmol), NaOAc (115 mg, 1.4 mmol) and catalyst **6** (11 mg, 0.02 mmol) in DMF (3 mL) was heated to 130 °C under argon for 12 h. Upon completion, the crude reaction mixture was poured into water (30 mL), the organic layer was extracted with dichloromethane (15 mL) and washed with water (3 × 5 mL), dried over anhydrous $MgSO_4$ and concentrated to give crude product. The residue was purified by column chromatography (Eluent: from Hex to EA–Hex = 1 : 30) to give product **10** in 88–96% yield.

Specific experimental

***tert*-Butyl 2-(2-*p*-tolylisoindolin-1-yl)acetate (10a).** Pale white solid; 95% (307 mg) isolated yield; mp: 73–75 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29–7.39 (m, 4H), 7.16 (d, J = 8.2 Hz, 2H), 6.70 (d, J = 8.2 Hz, 2H), 5.45 (d, J = 8.6 Hz, 1H), 4.76 (dd, J = 13.1, 2.9 Hz, 1H), 4.54 (d, J = 13.1 Hz, 1H), 3.06 (dd, J = 15.3, 2.4 Hz, 1H), 2.47 (dd, J = 15.3, 8.6 Hz, 1H), 2.30 (s, 3H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.0, 143.5, 141.7, 137.4, 130.0, 127.5, 127.2, 125.5, 122.7, 122.4, 112.3, 80.7, 60.2, 53.9, 39.8, 28.0, 20.3; HRMS (ESI): Calcd for $C_{21}H_{26}NO_2$ (M^+ + H): 324.1964, found 324.1967.

***tert*-Butyl 2-(2-phenylisoindolin-1-yl)acetate (10b).** Pale yellow oil; 92% (285 mg) isolated yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29–7.38 (m, 6H), 6.76–6.80 (m, 3H), 5.47 (d, J = 8.4 Hz, 1H), 4.77 (d, J = 13.2 Hz, 1H), 4.57 (d, J = 13.2 Hz, 1H), 3.05 (dd, J = 15.3, 1H), 2.48 (dd, J = 15.3, 8.6 Hz, 1H), 1.45 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.9, 145.6, 141.6, 137.2, 129.5, 127.5, 127.3, 122.7, 122.4, 116.4, 112.2, 80.7, 60.2, 53.8, 39.8, 28.0; HRMS (ESI): Calcd for $C_{20}H_{24}NO_2$ (M^+ + H): 310.1807, found 310.1812.

***tert*-Butyl 2-(2-(4-methoxyphenyl)isoindolin-1-yl)acetate (10c).** Pale white solid; 95% (322 mg) isolated yield; mp: 100–102 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30–7.36 (m, 4H), 6.94 (d, J = 8.9 Hz, 2H), 6.72 (d, J = 8.9 Hz, 2H), 5.40 (d, J = 8.6 Hz, 1H), 4.74 (dd, J = 13.0, 3.0 Hz, 1H), 4.50 (d, J = 13.0 Hz, 1H), 3.80 (s, 3H), 3.02 (dd, J = 15.2, 2.6 Hz, 1H), 2.45 (dd, J = 15.2, 8.7 Hz, 1H), 1.45 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.0, 151.3, 141.8, 140.3, 137.4, 127.4, 127.2, 122.6, 122.3, 115.2, 113.1, 80.7, 60.5, 55.8, 54.3, 39.8, 28.0; HRMS (ESI): Calcd for $C_{21}H_{26}NO_3$ (M^+ + H): 340.1913, found 340.1915.

***tert*-Butyl 2-(2-*m*-tolylisoindolin-1-yl)acetate (10d).** Pale yellow oil; 93% (300 mg) isolated yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27–7.37 (m, 4H), 7.19–7.23 (m, 1H), 6.57–6.61 (m, 3H), 5.44 (d, J = 8.6 Hz, 1H), 4.75 (dd, J = 13.2, 2.8 Hz, 1H), 4.55 (d, J = 13.2 Hz, 1H), 3.04 (dd, J = 15.2, 2.6 Hz, 1H), 2.45 (dd, J = 15.2, 8.6 Hz, 1H), 2.37 (s, 3H), 1.43 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.9, 145.7, 141.6, 139.2, 137.3, 129.3, 127.5, 127.2, 122.7, 122.4, 117.4, 113.0, 109.5, 80.7, 60.2, 53.9, 39.9, 28.0, 21.9; HRMS (ESI): Calcd for $C_{21}H_{26}NO_2$ (M^+ + H): 324.1964, found 324.1959.

***tert*-Butyl 2-(2-(3-methoxyphenyl)isoindolin-1-yl)acetate (10e).** Pale yellow oil; 95% (322 mg) isolated yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21–7.38 (m, 5H), 6.35–6.41 (m, 2H), 6.32 (s, 1H), 5.44 (d, J = 8.5 Hz, 1H), 4.74 (dd, J = 13.2, 2.7 Hz, 1H), 4.56 (d, J = 13.2 Hz, 1H), 3.85 (s, 3H), 3.06 (dd, J = 15.3, 2.7 Hz, 1H), 2.48 (dd, J = 15.3, 8.5 Hz, 1H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.8, 161.0, 146.9, 141.5, 137.1, 130.2, 127.5, 127.3, 122.6, 122.4, 105.4, 101.5, 98.7, 80.7, 60.3, 55.1, 53.9, 39.8, 28.0; HRMS (ESI): Calcd for $C_{21}H_{26}NO_3$ (M^+ + H): 340.1913, found 340.1924.

***tert*-Butyl 2-(2-(4-phenoxyphenyl)isoindolin-1-yl)acetate (10f).** Pale white solid; 94% (377 mg) isolated yield; mp: 94–97 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28–7.38 (m, 6H), 7.01–7.07 (m, 3H), 6.97 (d, J = 8.1 Hz, 2H), 6.74 (d, J = 8.9 Hz, 2H), 5.44 (d, J = 8.5 Hz, 1H), 4.77 (dd, J = 12.9, 2.8 Hz, 1H), 4.56 (d, J = 12.9 Hz, 1H), 3.04 (dd, J = 15.2, 2.7 Hz, 1H), 2.50 (dd, J = 15.2, 8.6 Hz, 1H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.8, 159.2, 147.0, 142.5, 141.6, 137.2, 129.5, 127.6, 127.3, 122.7, 122.4, 121.9, 121.5, 117.1, 113.0, 80.8, 60.5, 54.2, 39.8, 28.0; HRMS (ESI): Calcd for $C_{26}H_{28}NO_3$ (M^+ + H): 402.2069, found 402.2072.

***tert*-Butyl 2-(2-(4-cyanophenyl)isoindolin-1-yl)acetate (10g).** Pale yellow oil; 91% (304 mg) isolated yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.55 (d, J = 8.2 Hz, 2H), 7.32–7.36 (m, 4H), 6.71 (d, J = 8.2 Hz, 2H), 5.47 (d, J = 8.2 Hz, 1H),, 4.76 (d, J = 13.5 Hz, 1H), 4.60 (d, J = 13.1 Hz, 1H), 2.93 (dd, J = 15.0, 1.6 Hz, 1H), 2.53 (dd, J = 15.0, 8.2 Hz, 1H), 1.39 (s, 9H); ^{13}C

NMR (125 MHz, $CDCl_3$): δ 170.1, 148.3, 140.4, 136.0, 133.8, 128.1, 127.8, 122.7, 122.5, 120.5, 112.2, 98.3, 81.2, 60.4, 53.7, 39.6, 28.0; HRMS (ESI): Calcd for $C_{21}H_{23}N_2O_2$ (M^+ + H): 335.1760, found 335.1776.

***tert*-Butyl 2-(2-(4-nitrophenyl)isoindolin-1-yl)acetate (10h).** Yellow solid; 94% (333 mg) isolated yield; mp: 143–146 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19 (d, J = 9.3 Hz, 2H), 7.32–7.34 (m, 4H), 6.68 (d, J = 9.3 Hz, 2H), 5.50–5.53 (m, 1H), 4.81 (dd, J = 13.7, 2.2 Hz, 1H), 4.66 (d, J = 13.7 Hz, 1H), 2.95 (dd, J = 15.4, 2.9 Hz, 1H), 2.59 (dd, J = 15.4, 8.2 Hz, 1H), 1.38 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.9, 150.1, 140.1, 137.6, 135.7, 128.2, 127.9, 126.4, 122.7, 122.5, 111.1, 81.3, 60.7, 54.0, 39.6, 27.9; HRMS (ESI): Calcd for $C_{20}H_{23}N_2O_4$ (M^+ + H): 355.1658, found 355.1666.

***tert*-Butyl 2-(2-*tert*-butylisoindolin-1-yl)acetate (10i).** Pale yellow oil; 88% (255 mg) isolated yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.15–7.21 (m, 4H), 4.77 (d, J = 8.4 Hz, 1H), 4.13–4.24 (m, 2H), 2.76 (dd, J = 15.2, 2.7 Hz, 1H), 2.52 (dd, J = 15.2, 8.6 Hz, 1H), 1.42 (s, 9H), 1.14 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.4, 143.7, 139.8, 126.8, 126.7, 122.4, 121.9, 80.1, 61.0, 54.6, 53.3, 46.7, 28.1, 26.9; HRMS (ESI): Calcd for $C_{18}H_{28}NO_2$ (M^+ + H): 290.2120, found 290.2124.

Methyl 2-(2-*p*-tolylisoindolin-1-yl)acetate (10j). Pale yellow oil; 90% isolated yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28–7.34 (m, 4H), 7.13 (d, J = 8.3 Hz, 2H), 6.67 (d, J = 8.3 Hz, 2H), 5.46–5.49 (m, 1H), 4.75 (dd, J = 13.1, 3.1 Hz, 1H), 4.53 (d, J = 13.1 Hz, 1H), 3.72 (s, 3H), 3.15 (dd, J = 15.6, 2.9 Hz, 1H), 2.48 (dd, J = 15.6, 8.8 Hz, 1H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.1, 143.4, 141.5, 137.4, 130.1, 127.6, 127.3, 125.7, 122.5, 112.3, 60.0, 53.9, 51.7, 38.5, 20.3; HRMS (ESI): Calcd for $C_{18}H_{20}NO_2$ (M^+ + H): 282.1494, found 282.1497.

Ethyl 2-(2-*p*-tolylisoindolin-1-yl)acetate (10k). Pale yellow oil; 91% (253 mg) isolated yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27–7.33 (m, 4H), 7.13 (d, J = 8.1 Hz, 2H), 6.68 (d, J = 8.1 Hz, 2H), 5.46–5.48 (m, 1H), 4.75 (dd, J = 13.2, 2.7 Hz, 1H), 4.53 (d, J = 13.2 Hz, 1H), 4.18 (q, J = 7.2 Hz, 2H), 3.12 (dd, J = 15.5, 2.7 Hz, 1H), 2.48 (dd, J = 15.5, 8.9 Hz, 1H), 2.29 (s, 3H), 1.24 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.7, 143.4, 141.5, 137.4, 130.0, 127.3, 125.6, 122.5, 122.4, 112.3, 60.5, 60.0, 53.9, 38.7, 20.3, 14.2; HRMS (ESI): Calcd for $C_{19}H_{22}NO_2$ (M^+ + H): 296.1651, found 296.1657.

Butyl 2-(2-*p*-tolylisoindolin-1-yl)acetate (10l). Pale yellow oil; 96% (310 mg) isolated yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27–7.33 (m, 4H), 7.13 (d, J = 8.2 Hz, 2H), 6.68 (d, J = 8.2 Hz, 2H), 5.46–5.48 (m, 1H), 4.75 (dd, J = 13.1, 2.9 Hz, 1H), 4.53 (d, J = 13.1 Hz, 1H), 4.08–4.17 (m, 2H), 3.12 (dd, J = 15.5, 2.8 Hz, 1H), 2.49 (dd, J = 15.5, 8.9 Hz, 1H), 2.29 (s, 3H), 1.56–1.63 (m, 2H), 1.31–1.40 (m, 2H), 0.93 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.8, 143.4, 141.6, 137.4, 130.0, 127.6, 127.3, 125.6, 122.5, 122.4, 112.3, 64.4, 60.1, 53.9, 38.7, 30.6, 20.3, 19.1, 13.7; HRMS (ESI): Calcd for $C_{21}H_{26}NO_2$ (M^+ + H): 324.1964, found 324.1958.

***N*,*N*-Dimethyl-2-(2-*p*-tolylisoindolin-1-yl)acetamide (10m).** Pale yellow oil; 90% (265 mg) isolated yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (d, J = 6.9 Hz, 2H), 7.25–7.33 (m, 3H), 7.12 (d, J = 8.3 Hz, 2H), 6.68 (d, J = 8.3 Hz, 2H), 5.67–5.69 (m, 1H), 4.76 (dd, J = 13.2, 2.8 Hz, 1H), 4.54 (d, J = 13.2 Hz, 1H), 3.05 (dd, J = 15.8, 2.8 Hz, 1H), 3,00 (s, 3H), 2.81 (s, 3H), 2.46 (dd, J = 15.5, 9.0 Hz, 1H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.1, 143.6, 142.6, 137.1, 130.0, 127.34, 127.27, 125.4, 123.2, 122.3, 112.3, 60.3, 53.9, 37.8, 37.2, 35.3, 20.2; HRMS (ESI): Calcd for $C_{19}H_{22}N_2ONa$ (M^+ + Na): 317.1630, found 317.1642.

***tert*-Butyl 3-(2-((*p*-tolylamino)methyl)phenyl)acrylate (11).** Pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.94 (d, J = 15.8 Hz, 1H), 7.60 (d, J = 7.4 Hz, 1H), 7.42 (d, J = 6.9 Hz, 1H), 7.28–7.34 (m, 2H), 6.99 (d, J = 8.3 Hz, 2H), 6.55 (d, J = 8.3 Hz, 2H), 6.33 (d, J = 15.8 Hz, 1H), 4.41 (s, 2H), 3.81 (brs, 1H), 2.24 (s, 3H), 1.51 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.1, 145.6, 140.2, 138.2, 133.4, 129.9, 129.7, 128.9, 127.7, 127.0, 126.8, 122.2, 113.0, 80.6, 46.4, 28.1, 20.4. HRMS (ESI): Calcd for $C_{21}H_{26}NO_2$ (M^+ + H): 324.1964, found 324.1968.

***tert*-Butyl 3-(benzyl(2-bromobenzyl)amino)propanoate (12).** Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.17–7.31 (m, 9H), 3.53 (s, 4H), 2.74 (t, J = 8.0 Hz, 1H), 2.38 (t, J = 8.0 Hz, 1H), 1.38 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.0, 139.4, 128.8, 128.2, 126.9, 80.2, 58.0, 49.4, 33.9, 28.1. HRMS (ESI): Calcd for $C_{21}H_{27}$ Br NO_2 (M^+ + H): 404.1225, found 404.1219.

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