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Construction of 3-arylpropylamines using Heck arylations. The total synthesis of cinacalcet hydrochloride, alverine, and tolpropamine

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ABSTRACT

New synthetic routes toward the commercial drugs cinacalcet hydrochloride, alverine, and tolpropamine were developed using a Heck–Matsuda arylation as the key-step. Several reaction conditions were evaluated for the Heck–Matsuda reaction using allylamine derivatives and arenediazonium salts. For cinacalcet hydrochloride, *N*-formylamide provided the best result, furnishing the synthetic target in a very high overall yield (75% over five steps). For alverine, the best results were obtained using a double Heck–Matsuda strategy, providing alverine in an excellent overall yield (69%) from *N*-acetyl diallylamine in three steps. Tolpropamine was synthesized in a 46% yield over five steps using an efficient reductive Heck–Matsuda arylation between *p*-bromo-methylcinnamate with 3-chloro tolyldiazonium salt, generating the β,β-diaryl propionate that was converted to tolpropamine.

1. Introduction

The Heck reaction is a powerful and general synthetic method used to construct C–C bonds in a controlled fashion.[1] Its synthetic flexibility and compatibility with most organic functional groups make it one of the most explored reactions promoted by palladium.[2] Heck arylations employing arenediazonium salts instead of the conventional aryl halides or aryl triflates are usually known as Heck–Matsuda reactions, recognizing the first applications of arenediazonium salts by Matsuda in the late 1970s. Arenediazonium salts, particularly the tetrafluoroborates and hexafluorophosphates, are easy to prepare, thermally stable, and safe to work with in a regular organic laboratory. These diazonium salts make Heck arylations operationally easy, fast, green, and economical.[3] Furthermore, Heck–Matsuda reactions are typically carried out under mild, aerobic, and phosphine-free conditions.[4] In recent years, the Heck–Matsuda reaction has been extensively explored as a key step during the synthesis of several bioactive compounds, such as kavalactones,[5] (*R*)-tolterodine,[6] marinoquinoline A,[7] VPC01091,[8] pentabromopseudilin,[9] 3-arylindanone,[10] and others (Fig. 1).[11]

Recently, we have reported an efficient substrate-directed Heck reaction for the arylating allylic *O*-protected alcohols[12] and allylamine derivatives.[13] In these reactions, the regioselectivity is controlled by complexation between the cationic Pd(II) center and the carbonyl moiety on the substrate, providing arylated products with high stereo- and regioselectivities. Using this strategy, we completed the stereoselective synthesis of the bioactive aryl allylamines naftifine **4** and abamines **5** in good overall yields starting from allylamines (Scheme 1).

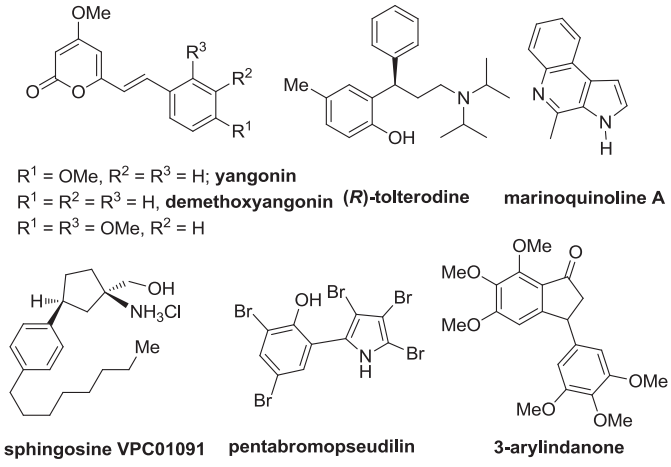

Fig. 1. Bioactive compounds synthesized using the Heck–Matsuda arylation.

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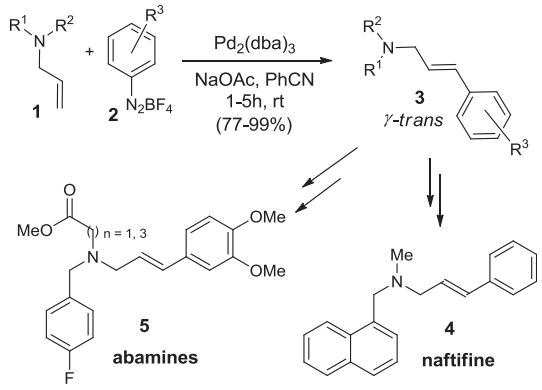
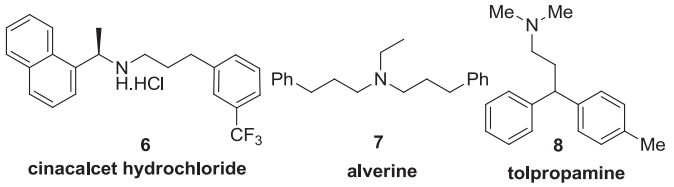


Scheme 1. Synthesis of naftifine **4** and abamines **5**.

Based on our previous success with this strategy and to further demonstrate the viability of substrate directed Heck–Matsuda arylations, we decided to apply the Heck–Matsuda arylation toward the synthesis of therapeutic compounds, highlighting its advantages and limitations (Scheme 2): cinacalcet hydrochloride **6**, alverine **7**, and tolpropamine **8**.



Scheme 2. Our synthetic targets.

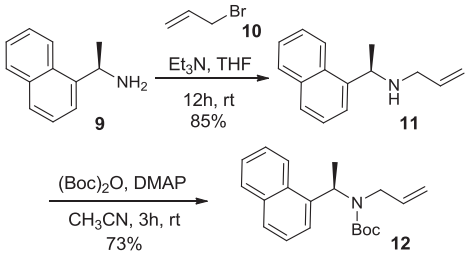
2. Results and discussion

2.1. Synthesis of cinacalcet hydrochloride 6

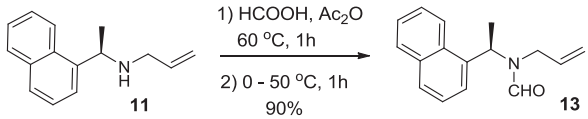
This compound is an attractive first target because it has a complex structure and proven medicinal use. This drug was the first member of the calcimimetic class approved by the United States Food and Drug Administration; this compound is marketed as Sensipar and Mimpara. Calcimimetics are a class of orally active drugs that decrease the secretion of the parathyroid hormone (PTH) by activating calcium receptors. Cinacalcet is used therapeutically to treat secondary hyperthyroidism in patients with chronic kidney disease after being submitted to dialysis and to treat elevated calcium levels in patients with parathyroid carcinoma.[14]

Several syntheses of cinacalcet hydrochloride **6** have already been described in the literature.[15] Classical approaches, such as the condensation of the amine with a carboxylic acid,[16] Suzuki and Heck-oxidative couplings,[17] as well as two large-scale approaches involving the Forster–Decker reaction[18] and Grignard reagent addition to a vinyl chloride.[19] The only Heck-based approach toward the synthesis of cinacalcet was described by Evans and co-workers, using a conventional Heck reaction between methyl acrylate and aryl bromide.[20]

We began our synthesis of cinacalcet hydrochloride **6** by generating the protected allylamines. Therefore, (*R*)-1-(naphthalen-1-yl)ethanamine **9** was treated with allyl bromide **10**, furnishing secondary amine **11** in 85% yield (Scheme 3). Subsequently, an N-protection with di-*tert*-butyl dicarbonate was carried out in acetonitrile at room temperature. *N*-Boc-protected **12** was isolated in 73% yield. To synthesize formylated allylamine **13**, the mixed anhydride was prepared from acetic anhydride and formaldehyde and added to secondary amine **11**. Formyl allylamine **13** was produced in 90% yield (Scheme 4).



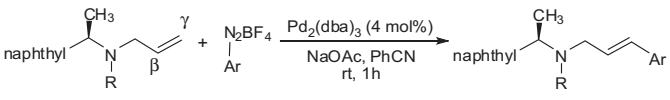
Scheme 3. Synthesis of protected allylamine **12**.



Scheme 4. Synthesis of *N*-formyl allylamine **13**.

Subsequently, these substrates were used in the Heck–Matsuda arylations (Table 1). First, *N*-Boc allylamine **12** (0.25 mmol) was treated with 3-trifluoromethyl benzenediazonium tetrafluoroborate **2a** (0.3 mmol) under our previously established conditions: $Pd_2(dba)_3$ (4 mol %) as the catalyst, NaOAc as the base, and benzonitrile as the solvent.[13] However, no Heck products were observed under these conditions (Table 1, entry 1). Next, we attempted the Heck–Matsuda reaction under the same conditions while using *N*-Boc-allylamine **12** and 4-methoxybenzenediazonium salt **2b**. This salt was chosen due to its higher thermal stability and the good results obtained with it during the Heck arylation of allylamide derivatives.[13] When salt **2b** was used, the corresponding product **14b** (γ-arylation, trans-isomer) was observed in good yields (80%) with an undesired internal β-arylated product (*trans*-γ-aryl/β-aryl ratio: 88/12, Table 1, entry 2). The successful arylation of **12** using methoxy substituted arenediazonium salt **2b** revealed that this slow Heck reaction allowed the 3-trifluoromethyl benzenediazonium salt **2a** to decompose. The decreased performance of olefin **12** was evident from the formation of the β-arylated adduct. The β-arylated product may form due to the steric hindrance caused by the *tert*-butyl and naphthylmethyl groups in the substrate; these groups most likely destabilize the proposed cyclic cationic palladium intermediate (Scheme 5). This hypothesis was confirmed when we combined less sterically demanding substrate **13** with diazonium salt **2a**. Corresponding adduct **14c** was isolated in 98% yield with complete regio- and stereocontrol favoring the γ-aryl, trans isomer (Table 1, entry 3).

Table 1
Heck arylation of allylamines **12** and **13**[a]



Entry	Allylamine	Ar	Yield (%)
1	**12**	3-$CF_3C_6H_4$, **2a**	**14a**, —
2	**12**	4-$OMeC_6H_4$, **2b**	**14b**, 80[b]
3	**13**	3-$CF_3C_6H_4$, **2a**	**14c**, 98

[a] The reaction was carried in air using an allylamine derivative (0.25 mmol), a diazonium salt (0.3 mmol), $Pd_2(dba)_3$ (4 mol %), and sodium acetate (3 equiv, 0.75 mmol, 0.061 g) dissolved in benzonitrile (1 mL) at room temperature for 1 h.
[b] This reaction provided two products that were difficult to separate (a single spot by TLC). The 88/12 ratio for the γ-*trans*/β-substituted products was determined using ^1H NMR analysis of the crude reaction mixture.

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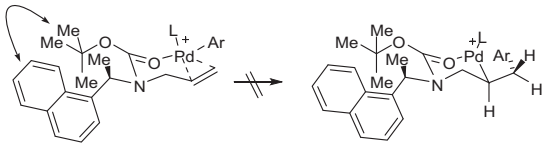
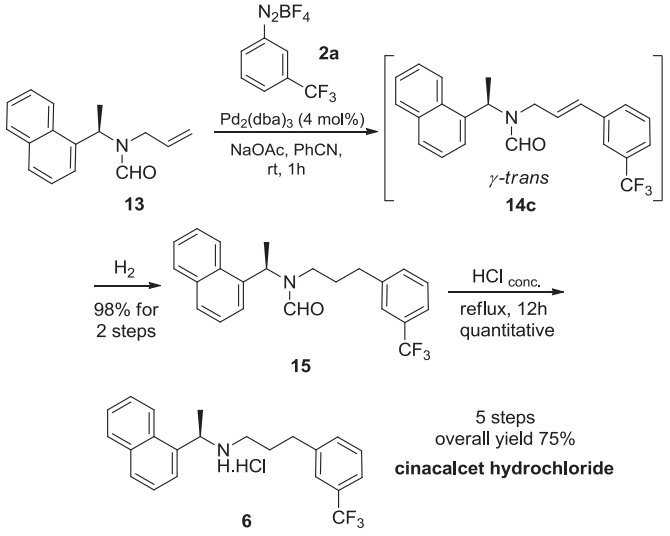


Scheme 5. Rationale for the lower regioselectivity during the arylation of *N*-Boc allylamine **12**.

After synthesizing the desired adduct, we carried out the Heck–Matsuda reaction followed by an in situ reduction of the double bond. Therefore, the Heck arylation was carried out under the usual conditions. When the arylation was complete, the system was purged with H_2 without changing the solvent or palladium catalyst. Gratifyingly, the expected reduction product **15** was obtained in 98% over the two steps (Scheme 6). Next, **15** was deformylated before the hydrochloride was formed using hydrochloric acid at reflux. Desired cinacalcet hydrochloride **6** was obtained in quantitative yield with an excellent overall yield (75%) over five steps (Scheme 6).



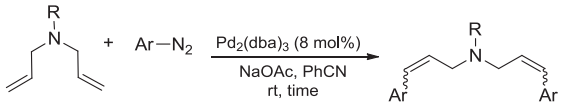
Scheme 6. Synthesis of cinacalcet hydrochloride **6**.

2.2. Synthesis of alverine 7

After completing the cinacalcet hydrochloride synthesis, we turned our attention toward alverine (**7**). Alverine is a relaxant for smooth muscle that is not under voluntary control, such as that found in the gut and uterus. For example, the drug may act directly in the gut muscle, causing it to relax while preventing muscle spasms in conditions, such as irritable bowel syndrome and diverticulitis.[21] The synthesis of alverine has been previously accomplished by alkylating secondary amines.[22] We envisioned a double substrate-directed Heck arylation with an allylamine derivative followed by an in situ hydrogenation to synthesize alverine.

Because the protecting group on nitrogen is one of the groups that complexes with the cationic palladium (II) species, the synthetic approach began with a brief evaluation of the *N*-protecting groups on the diallylamine moiety (Table 2). *N*-Boc diallylamine **16a** was tested first because the Boc group was easy to install and later remove. We decided to use the conditions optimized for cinacalcet, except that 2 equiv of the benzenediazonium salt **2c** and 8 mol % of the palladium catalyst were used (Table 2, entry 1). However, under these reaction conditions, Heck adducts were not observed. The reaction was subsequently carried out at 80 °C, but the desired Heck product was not observed (Table 2, entry 2). Similar to the procedure adopted during the cinacalcet synthesis,

Table 2
Heck arylations of **16a–c** with diazonium salts **2b,c**[a]

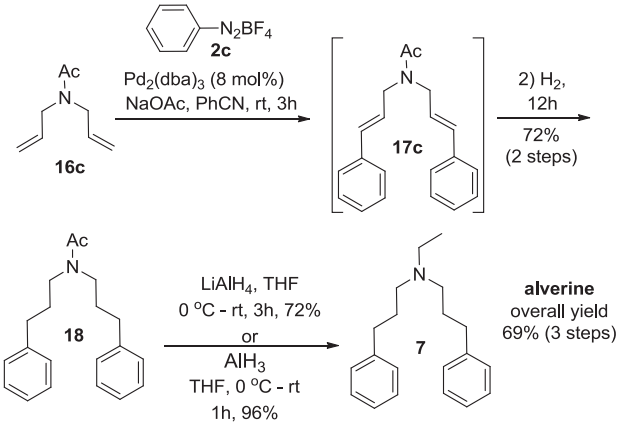


Entry	R	Ar	Compound, yield (%)	*trans*/*cis*
1	Boc, **16a**	C_6H_5, **2c**	**17a**, traces	—
2[b]	Boc, **16a**	C_6H_5, **2c**	**17a**, —	—
3	Boc, **16a**	4-OMeC_6H_4, **2b**	**17b**, 70[c]	84/16
4	CO_2Et, **16b**	4-OMeC_6H_4, **2b**	**17c**, complex mixture	—
5	Ac, **16c**	4-OMeC_6H_4, **2b**	**17d**, 68[d]	85/15
6	Ac, **16c**	C_6H_5, **2c**	**17e**, 85	87/13

[a] The reaction was carried under air, by using diallylamine derivative **16a–c** (0.25 mmol), diazonium salt (0.6 mmol), $Pd_2(dba)_3$ (8 mol %), sodium acetate (3 equiv, 0.75 mmol, 0.061 g), and benzonitrile (1 mL).
[b] The reaction was carried out at 80 °C.
[c] The monoarylated product was isolated in 25% yield.
[d] The triarylated product was isolated in 25% yield.

we investigated the Heck reaction with **2b**. To our satisfaction, the expected coupling product (**17b**) was obtained in 70% isolated yield with a *trans*/*cis* ratio of 84/16 (Table 2, entry 3).

Surprisingly, when using ethyl carbamate as the protecting group, **2b** did not furnish the expected Heck adduct (Table 2, entry 4). Due to these erratic results, we then decided to evaluate *N*-acetyl protected allylamide **16c** as a substrate for the Heck arylation. When **16c** was reacted with **2b**, the desired Heck product **17d** was produced in a reasonable 68% yield with a *trans*/*cis* ratio of 85/15 (Table 2, entry 5). Although the stereoselectivity issue is irrelevant in this case, it provides valuable information regarding the outcome of the Heck reaction. We were able to isolate a triarylated product in 25% yield with the adduct **17d**. Nevertheless, we applied the same reaction conditions used during the arylation of **16c** with **2c**. This time, the expected diarylated product **17e** was obtained in 85% yield with complete regiocontrol and good stereoselectivity favoring the *E* isomer (ratio *trans*/*cis* 87/13, Table 2, entry 6). The outcome provided by the allylamide **16c** was a bonus because this protecting group fit into our strategy to prepare alverine with an ethyl group on the nitrogen. After selecting the best substrate for the Heck reaction, we carried out the one-pot Heck reaction/hydrogenation. After the Heck arylation was complete, the system was purged with H_2 for 12 h at room temperature, similar to the procedure for cinacalcet, to provide **18** in 72% isolated yield over two steps (Scheme 7). Finally, the acetyl group was reduced using $LiAlH_4$ (72% yield) or AlH_3 (96% yield), generating alverine (**7**) in only three steps from **16c** in excellent overall yield (69%) (Scheme 7).



Scheme 7. Synthesis of alverine **7**.

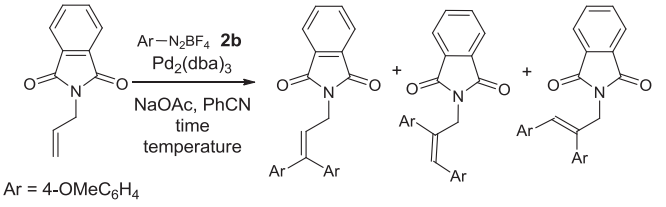
2.3. Synthesis of tolpropamine 8

Tolpropamine is an antihistamine and an antipruritic drug used to treat skin conditions, such as allergies and itching.[23] Previous syntheses relied on the Wittig reaction to obtain the 1-phenyl-1-(*p*-tolyl)ethane structure, followed by a hydroaminomethylation using rhodium catalysis.[24] However, this methodology does not enable enantioselective syntheses to be developed for this drug.

The synthesis of tolpropamine contained the challenging construction of a non-symmetrical diarylmethane moiety. Because a minor amount of triarylated product was present during the Heck arylation of olefin **16c** (not shown in Scheme 7), we initially proposed that the diarylation/hydrogenation of allyl phthalimide **19**, followed by deprotection/methylation would be somewhat straightforward. This strategy would also facilitate the stereoselective synthesis of tolpropamine.

We turned our attention toward the Heck diarylation of allyl phthalimide **19** using **2b** for the model reaction (Table 3). Again, this diazonium salt was chosen for its thermal stability and good reactivity.[13] Therefore, allyl phthalimide **19** (0.25 mmol) was treated with diazonium salt **2b** (1.0 mmol), using the previously established conditions: $Pd_2(dba)_3$ (8 mol %) and NaOAc, in benzonitrile at room temperature (Table 3, entry 1). Surprisingly, the γ-*trans*-monoarylated product was obtained as the major product in a 1.5/1.0 ratio of mono/diarylated products. The desired diarylated products were isolated in 39% yield as an isomeric mixture favoring γ,γ-diarylated adduct **20** (ratio **20**/**21**/**22**: 84/10/6).

Table 3
Heck–Matsuda diarylation of allyl phthalimide **19**[a]



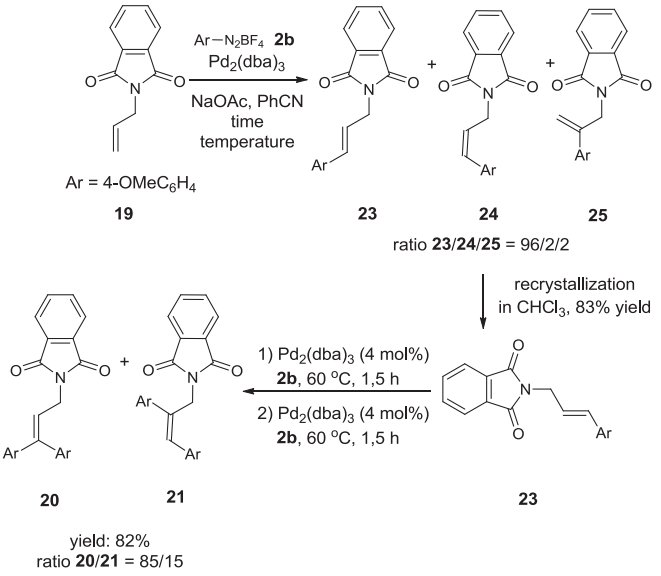
19 **20** **21** **22**

#	Equiv, **2b**	*T* (°C)/time	Diarylated yield (%)	Ratio **20**/**21**/**22**	Ratio mono/diarylated
1	4	rt/12 h	39	84/10/6	1.5/1.0
2	4	60/2 h	42	83/11/6	1.2/1.0
3	(1) 1.2	(1) rt/1 h	49	80/12/8	0.9/1.0
	(2) 1.2	(2) 45/3 h			
4	(1) 1.2	(1) rt/1 h	61	83/11/6	0.4/1.0
	(2) 1.2	(2) 60/3 h			
5	(1) 1.2	(1) rt/1 h	80	80/15/5	0/1.0
	(2) 1.2	(2) 60/1.5 h			
	(3) 1.2	(3) 60/1.5 h			
6	(1) 1.2	(1) rt/1 h	71	83/11/6	0/1.0
	(2) 1.2	(2) μW 60 °C/1 h			
	(3) 1.2	(3) μW 60 °C/1 h			

[a] The reaction was carried in air using allyl phthalimide **19** (0.25 mmol), 4-methoxybenzenediazonium tetrafluoroborate **2b**, $Pd_2(dba)_3$, and sodium acetate (3 equiv, 0.75 mmol, 0.061 g) dissolved in benzonitrile (2 mL). The progress of the reaction was monitored using the evolution of N_2. The yields refer to mixtures of the three isomers (a single spot by TLC). Compounds **20**–**22** were separated by preparative HPLC and fully characterized. The ratio between the regioisomers and the mono/diarylated products was based on the integrations of the appropriate signals in the ^1H NMR spectra. See the SD for further details.

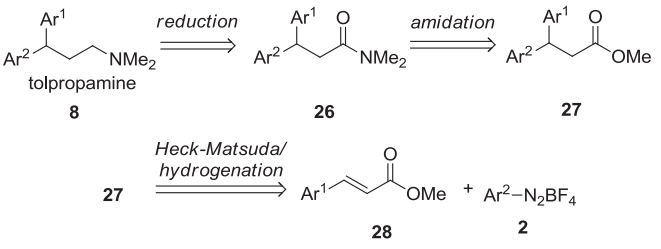
To increase the consumption of the monoarylated adduct, we carried out the reaction at 60 °C (Table 3, entry 2). After 2 h, the diazonium salt was completely consumed, but no significant improvements concerning the yields and product ratios were observed (Table 3, entry 2). Adding the diazonium salt and the $Pd_2(dba)_3$ portionwise (2×1.2 equiv; 2×2 mol %, respectively), at room temperature and then at 45 °C, slightly improved the yield of the diarylated product (Table 3, entry 3). Warming the reaction from 45 °C to 60 °C in the second step provided the diarylated products in 61% yield with a better mono/diarylated ratio (0.4/1.0) (Table 3, entry 4). The presence of the monoarylated adduct could be attributed to the decomposition of the diazonium salt under the reaction conditions; therefore, we decided to add the diazonium salt with the catalyst in three portions (Table 3, entry 5). Gratifyingly, we no longer observed the monoarylated product. The diarylated adducts were isolated in 80% yield as a complex mixture of compounds (**20**/**21**/**22** ratio of 80/15/5). Carrying out the reaction in a microwave reactor led to a slight decrease in yield but provided good selectivity (Table 3, entry 6).

Because the γ,γ-diarylated product **20** could not be obtained as a single compound and the isomeric mixture is difficult to separate, we envisioned a sequential arylation process as a viable alternative (Scheme 8). The Heck–Matsuda monoarylation of allyl phthalimide **19** afforded a mixture of monoarylated products (**23**–**25**) in a 96/2/2 ratio, from which the γ-trans isomer could be isolated in 83% yield after a recrystallization in chloroform. With **23** in hand, we carried out the second arylation as described in Scheme 8 to obtain the desired γ,γ-adduct **20** together with significant amounts of the β,γ adduct **21** (82% total yield in an 85:15 ratio).



Scheme 8. Synthesis of the diarylated adduct **20**.

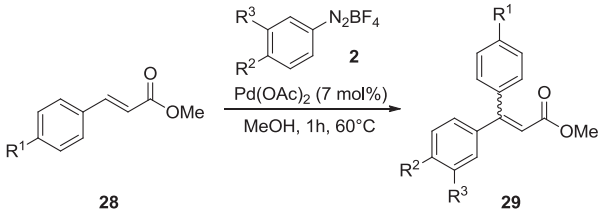
The modest regioselectivity of the second arylation step forced us to review our strategy toward synthesizing tolpropamine. Subsequently, we planned to synthesize tolpropamine using a reductive Heck–Matsuda arylation of methyl cinnamate (**28**) and arenediazonium salt **2**, followed by amidation and posterior reduction, as depicted in Scheme 9.



Scheme 9. Alternative strategy for the synthesis of tolpropamine.

We began the new route with a Heck arylation using commercially available **28a** with the *p*-tolyldiazonium salt under the optimized conditions: $Pd(OAc)_2$ (7 mol %) in methanol at 60 °C (Table 4, entry 1).[25] However, only traces of the desired Heck product **29a** were observed. When using NaOAc (2 equiv) as the base, the Heck adduct was isolated in 42% yield, favoring the *E*-isomer **29a**; therefore, base was essential for the reaction (Table 4, entry 2). Using 4 equiv of the *p*-tolyldiazonium salt led to an increase in the yield of **29a** (68%; Table 4, entry 3) but also a more complex reaction mixture. Changing the base to a substituted pyridine generated only trace amounts of the Heck adduct (Table 4, entry 4). Because the electronics of the reaction partners are also important for a successful Heck arylations, we evaluated different cinnamates and diazonium salts containing halogens; halogens may be easily removed later. When using 1.5 equiv of 4-bromobenzene diazonium salt and 4-methyl cinnamate **28b**, low conversion of starting material was observed (Table 4, entry 5). However, with methyl 4-bromocinnamate **28c** and 3-chloro-4-methylbenzenediazonium tetrafluoroborate, the corresponding Heck adducts were isolated in 60% yield with an *E*/*Z* ratio of 75:25 (Table 4, entry 6). Due to the good performance of the 3-chloro-4-methylbenzenediazonium salt, we carried out a reaction using this diazonium salt with methyl cinnamate **28a** using $CaCO_3$ as the base, providing **29d** in 88% yield with good stereoselectivity (*E*/*Z* ratio, 71:29, Table 4, entry 7). Notably, 4-bromo-cinnamate (**28c**) provided **29c** in 83% yield, strongly favoring the isomer *E* (*E*/*Z* ratio of 92:8, Table 3, entry 8).

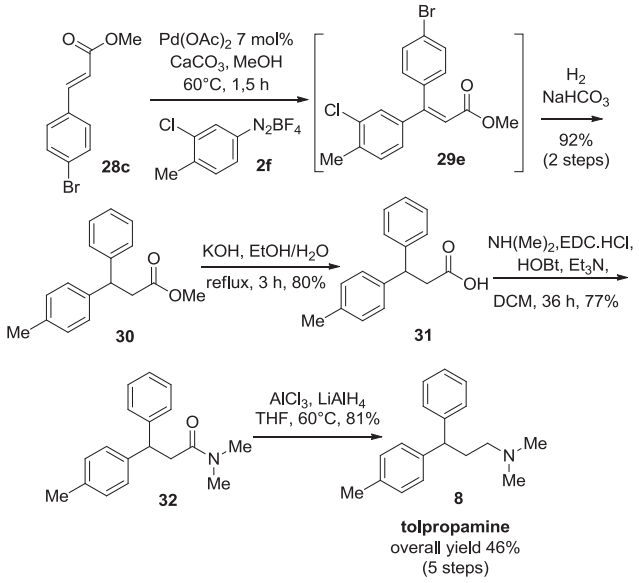
Table 4
Heck arylation of methyl cinnamates **28a**–**c**[a]



Entry	Base (equiv)	**2d**–**f** (equiv)	R^1	R^2	R^3	*E*/*Z*	Compound, yield (%)
1[b]	—	4, **2d**	H	Me	H	—	**29a**, trace
2	NaOAc (3)	2, **2d**	H	Me	H	100/0	**29a**, 42
3	NaOAc (3)	4, **2d**	H	Me	H	95/5	**29a**, 68
4	DTMPy (1)	1.5, **2d**	H	Me	H	—	**29a**, trace
5	NaOAc (3)	1.5, **2e**	Me	Br	H	—	**29b**, trace
6	NaOAc (3)	1.5, **2f**	Br	Me	Cl	75/25	**29c**, 60
7[c]	$CaCO_3$ (1)	1.5, **2f**	H	Me	Cl	71/29	**29d**, 88
8[c]	$CaCO_3$ (1)	1.5, **2f**	Br	Me	Cl	92/8	**29c**, 83

[a] Reactions performed in the presence of methyl cinnamate **28a**–**c** (0.25 mmol), arenediazonium salt **2d**–**f**, $Pd(OAc)_2$ (7 mol %), base, MeOH (5.0 mL) at 60 °C, during 1 h.
[b] The reaction was stirred during 2 h.
[c] The reaction was stirred for 1.5 h.

After establishing the best conditions to obtain the Heck–Matsuda adduct **29c** stereoselectively, we planned the racemic synthesis of tolpropamine **8** (Scheme 10). First, a Heck–Matsuda reaction was carried out to obtain **29c**, followed by hydrogenation in situ ($NaHCO_3$ was added before purging with H_2 at room temperature). This procedure provided dehalogenated and reduced adduct **30** in 92% yield using a one-pot procedure. Next, **30** was hydrolyzed using refluxing KOH to obtain the corresponding carboxylic acid **31** in 80% yield. The isolated carboxylic acid was treated with dimethylamine, EDC·HCl, and HOBt, to provide dimethylamide **32** in 77% yield. Finally, amide **32** was reduced with AlH_3 at 60 °C to complete the synthesis of tolpropamine (**8**) in 81% yield. Tolpropamine **8** was obtained in five steps in a 46% overall yield.



Scheme 10. Synthesis of tolpropamine **8**.

3. Conclusion

In summary, we describe an efficient, mild, and operationally simple room temperature Heck arylation in an open-flask using allylamine derivatives and methyl cinnamates with arenediazonium tetrafluoroborates. The Heck–Matsuda/hydrogenation reactions proceeded with superb regio- and stereochemical control to afford the corresponding arylated allylamine derivatives in good to excellent yields. Using this Heck–Matsuda method, new synthetic routes toward three commercial drugs (cinacalcet hydrochloride, alverine, and tolpropamine) were developed. For cinacalcet hydrochloride, the *N*-formylamide provided the best results, furnishing the synthetic target in 75% yield over five steps. For alverine, best results were obtained using a double Heck–Matsuda strategy that provided the product in 69% yield overall from *N*-acetyl diallylamine over three steps. The synthesis of tolpropamine was achieved in 46% yield over five steps and featured a reductive Heck arylation between *p*-bromo-methylcinnamate and 3-chloro tolyldiazonium salt; the resulting product, β,β-diaryl propionate, was converted to tolpropamine in a straightforward manner.

4. Experimental section

4.1. General

Proton nuclear magnetic resonance spectra (^{1}H NMR) were obtained at 250 MHz, 300 MHz, 400 MHz, 500 MHz and 600 MHz. The spectra were recorded in $CDCl_3$, DMSO-d_6, or MeOD solutions. The chemical shifts are reported in parts per million and referenced to the residual solvent peak or tetramethylsilane (TMS). The data are reported as follows: chemical shift (δ), multiplicity, coupling constant (J) in Hertz and integrated intensity. Carbon-13 nuclear magnetic resonance spectra (^{13}C NMR) were obtained at 62.5 MHz, 75 MHz, 100 MHz, 125 MHz, and 150 MHz. The spectra were recorded in $CDCl_3$ or DMSO-d_6 solutions. Abbreviations denoting the multiplicity of a particular signal include s (singlet), sl (singlet large), d (doublet), t (triplet), q (quartet), dd (double doublet), dt (double triplet), ddd (double double doublet), tdd (triple double doublet), and m (multiplet). The microwave reactions were conducted in a CEM Discover® Microwave synthesizer. The equipment consisted of a continuous, focused microwave-power delivery system with an operator-selected power output ranging from 0 to

300 W. The reactions were performed in glass vessels (capacity 10 mL) sealed with a septum. Temperature measurements were conducted using an infrared temperature sensor mounted in the reaction vessel. All experiments were performed with stirring using a rotating magnetic plate located below the floor of the microwave cavity with a Teflon-coated magnetic stir bar inside the vessel. All experiments were carried out with simultaneous cooling provided by passing compressed air through the microwave cavity while heating (option PowerMAX enabled). Column chromatography was performed using silica gel (230–400 mesh) following the method described by Still.[26] Thin layer chromatography (TLC) was performed using silica gel plates (GF_{254}, 0.25 mm thickness). For visualization, the TLC plates were either placed under ultraviolet light or stained with phosphomolybdic acid, followed by heating. Air- and moisture-sensitive reactions were conducted in flame- or oven-dried glassware equipped with a tightly fitted rubber septum under a positive atmosphere of dry argon. The reagents and solvents were handled using standard syringe techniques. Temperatures above room temperature were maintained using a mineral oil bath heated on a hotplate. All reagents purchased from commercial suppliers were used as received, except the reagents that were freshly distilled, as detailed in the Experimental section.

Some of the compounds synthesized by the Heck–Matsuda reaction of the allylic systems were mixtures of structural isomers that appeared as a single spot by TLC and were extremely difficult to separate by flash chromatography. These products were analyzed as mixtures and the ratios between their components were based on characteristic peaks belonging to each specific isomer in the ^{1}H NMR spectra. The reader should refer to the pure diarylated isomers **20**–**22** isolated by preparative HPLC and fully characterized as pure compounds. Their spectra appear in the Supplementary data section. When applicable, a reference is also made to the presence of rotamers, which are common when dealing with amides and formamides.

4.2. Synthesis of cinacalcet hydrochloride 6

*4.2.1. (R)-N-(1-(Naphthalen-1-yl)ethyl)prop-2-en-1-amine (**11**).*[27] Amine **9** (0.48 mL, 3.0 mmol), triethylamine (0.44 mL, 3.2 mmol), and THF (6.0 mL) were placed in a flame dried round-bottomed flask equipped with a magnetic stir bar under a nitrogen atmosphere. Next, allyl bromide **10** (0.26 mL, 0.3 mmol) was added dropwise. The system was stirred for 12 h before EtOAc (20 mL) was added. The reaction was washed with saturated $NaHCO_3$ (3×10 mL) and extracted; the combined organic layers were dried over $MgSO_4$. After filtration, the solvent was removed under reduced pressure to afford a yellow oil corresponding to (*R*)-*N*-(1-(naphthalen-1-yl)ethyl)prop-2-en-1-amine. The product was then purified by flash chromatography (hexanes/ethyl acetate 40:60 as the eluent, R_f=0.55) to provide compound **11** as a yellow oil. Yield: 0.53 g (85%). TLC stain: ultraviolet and ninhydrin. $[\alpha]_D^{20}$ +11.2 (*c* 2.03, MeOH). ^{1}H NMR: $CDCl_3$, 250 MHz, δ (ppm): 8.12 (d, *J*=7.6 Hz, 1H), 7.80–7.76 (m, 1H), 7.67–7.61 (m, 2H), 7.43–7.37 (m, 3H), 5.90 (ddt, J^1=17.0 Hz, J^2=10.4 Hz, J^3=6.5 Hz, 1H), 5.13–5.00 (m, 2H), 4.60 (q, *J*=6.5 Hz, 1H), 3.15–3.12 (m, 2H), 1.43 (d, *J*=6.5 Hz, 3H). ^{13}C NMR: $CDCl_3$, 62.5 MHz, δ (ppm): 140.8, 136.8, 133.7, 131.1, 128.7, 126.9, 125.4, 125.0, 122.7, 122.4, 115.4, 52.5, 50.1, 23.3.

*4.2.2. (R)-N-Allyl-N-(1-(naphthalen-1-yl)ethyl)formamide (**13**).* Acetic anhydride (141.0 mmol, 14 mL) and formic acid (142.0 mmol, 5.35 mL) were added to a flame dried round-bottomed flask equipped with a magnetic stir bar under a nitrogen atmosphere. The system was warmed to 60 °C and stirred for 1 h. Next, the system was cooled to 0 °C, and amine **11** was added (5.45 mmol, 1.15 g) dropwise. The reaction was warmed to 50 °C and stirred for another hour. Upon completion (TLC), the solvent was removed under reduced pressure to afford an oil residue. This reaction mixture was washed with saturated $NaHCO_3$ (3×30 mL) and dried over $MgSO_4$. After filtration, the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (hexanes/ethyl acetate 40:60 as eluent, R_f=0.70) to furnish compound **13** as a colorless oil. Yield: 1.17 g (90%). R_f=0.70. TLC stain: ultraviolet and iodine. $[\alpha]_D^{20}$ +122.8 (*c* 0.57, MeOH). ^{1}H NMR: $CDCl_3$, 250 MHz, 25 °C, δ (ppm) rotamers (The ^{1}H NMR shows the presence of two rotamers in a ratio of 0.34/0.66): 8.55 (s, 0.34H), 8.20 (s, 0.66H), 8.01–7.82 (m, 3H), 7.57–7.42 (m, 4H), 6.42 (q, *J*=7.0 Hz, 0.66H), 5.73–5.21 (m, 1.34H), 5.01–4.81 (m, 2H), 4.01–3.93 (m, 0.34H), 3.66–3.29 (m, 1.66H), 1.81 (d, *J*=7.0 Hz, 1H), 1.69 (d, *J*=7.0 Hz, 2H). ^{1}H NMR: DMSO-d_6, 500 MHz, 120 °C, δ (ppm): 8.36 (s, 1H), 8.05 (d, *J*=8.0 Hz, 1H), 7.94–7.86 (m, 2H), 7.64–7.48 (m, 4H), 5.95 (sl, 1H), 5.55–5.44 (m, 1H), 4.94–4.84 (m, 2H), 3.68 (s, 2H), 1.71 (d, *J*=6.8 Hz, 3H). ^{13}C NMR: DMSO-d_6, 125 MHz, 120 °C, δ (ppm): 162.4, 162.4, 135.5, 135.2, 134.7, 133.6, 133.3, 133.1, 131.2, 130.7, 128.7, 128.5, 128.4, 126.3, 125.6, 125.6, 125.0, 124.9, 124.3, 122.8, 122.6, 116.3, 116.1, 51.7, 45.4, 42.8, 19.7, 17.0.

*4.2.3. (R)-(E)-N-(1-(Naphthalen-1-yl)ethyl)-N-(3-(3-(trifluoromethyl)phenyl)allyl)formamide (**14c**).* To an open round-bottomed flask (or a test tube) equipped with a magnetic stir bar were added $Pd_2(dba)_3$ (4 mol %, 10 mg), sodium acetate (3 equiv, 0.75 mmol, 0.061 g), and benzonitrile (1.0 mL). To the resulting suspension was added allylamine derivative **13** (0.30 mmol, 0.071 g), followed by 3-(trifluoromethyl)benzenediazonium tetrafluoroborate (0.25 mmol, 0.065 g). The reaction was stirred at room temperature for 1 h. Subsequently, the reaction mixture was filtered through a plug of silica gel with ethyl acetate and concentrated under reduced pressure. The product was purified by flash chromatography (hexanes/ethyl acetate 60:40 as eluent, R_f=0.65) to provide the corresponding arylated product **14c** as a colorless oil. Yield: 0.091 g (98%). R_f=0.65. TLC stain: ultraviolet and phosphomolybdic acid. $[\alpha]_D^{20}$ +4.5 (*c* 0.42, MeOH). The ^{1}H NMR and ^{13}C NMR spectra show the presence of two rotamers in 0.40:0.60 ratio. ^{1}H NMR: $CDCl_3$, 250 MHz, 25 °C, δ (ppm): 8.62 (s, 0.4H), 8.26 (s, 0.6H), 8.0 (d, *J*=8.4 Hz, 0.6H), 7.91 (d, *J*=8.4 Hz, 0.4H), 7.81–7.74 (m, 2H), 7.59–7.38 (m, 5H), 7.30–7.25 (m, 1.2H), 7.15–7.12 (m, 0.8H), 7.01 (s, 1H), 6.47 (q, *J*=6.9 Hz, 0.6H), 6.01–5.87 (m, 1H), 5.74 (dt, *J*=6.4, 16.0 Hz, 0.4H), 5.56 (q, *J*=7.0 Hz, 0.4H), 5.40 (dt, *J*=6.4, 16.0 Hz, 0.6H), 4.17 (dd, *J*=5.7, 16.0 Hz, 0.4H), 3.71–3.61 (m, 1.6H), 1.82 (d, *J*=7.0 Hz, 1.2H), 1.71 (d, *J*=7.0 Hz, 1.8H). ^{1}H NMR: 500 MHz, DMSO-d_6, 120 °C, δ (ppm): 8.43 (sl, 1H), 8.09 (d, *J*=8.2 Hz, 1H), 7.83 (t, *J*=8.5 Hz, 2H), 7.67 (d, *J*=7.0 Hz, 1H), 7.56–7.38 (m, 5H), 7.27–7.21 (m, 2H), 6.18 (d, *J*=16.0 Hz, 1H), 6.00 (sl, 1H), 5.78–5.72 (m, 1H), 3.91–3.78 (m, 2H), 1.75 (d, *J*=6.7 Hz, 3H). ^{13}C NMR: 125 MHz, DMSO-d_6, 25 °C—rotamers, δ (ppm): 162.7, 162.6, 137.2, 137.0, 135.0, 134.8, 133.3, 133.1, 131.4, 130.9, 129.6, 129.4, 129.3, 129.0 (q, *J*=31.0 Hz, 1C), 128.9, 128.7, 128.5, 128.4, 127.5, 126.4, 125.6, 125.1, 125.1, 124.7 (q, *J*=272.0 Hz, 1C), 124.5, 123.6 (q, *J*=3.5 Hz, 1C), 122.9, 122.8, 121.9 (q, *J*=3.5 Hz, 1C), 51.6, 45.3, 44.6, 41.5, 19.5, 16.8. IR (film, cm^{-1}): 1666, 1512, 1395, 1331, 1164, 1124. MS (EI): 384 (M+1), 309, 230, 155. HRMS calcd for $C_{23}H_{21}F_3NO$: 384.1573. Found=384.1575.

*4.2.4. (R)-N-(1-(Naphthalen-1-yl)ethyl)-N-(3-(3-(trifluoromethyl)phenyl)propyl)formamide (**15**).* To an open round-bottomed flask (or a test tube) equipped with a magnetic stir bar were added $Pd_2(dba)_3$ (4 mol %, 10 mg), sodium acetate (3 equiv, 0.75 mmol, 0.061 g), and benzonitrile (1.0 mL). To the resulting suspension was added allylamine derivative **13** (0.30 mmol, 0.071 g), followed by 3-(trifluoromethyl)benzenediazonium tetrafluoroborate (0.25 mmol, 0.065 g). The reaction was stirred at room temperature for 1 h. Subsequently, the system was purged with hydrogen and left stirring with a balloon of H_2 for 12 h. Afterward, the reaction mixture was filtered through a plug of silica with ethyl acetate and

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concentrated under reduced pressure. The product was purified by flash chromatography (hexanes/ethyl acetate 60:40 as eluent, R_f=0.65) to provide arylated product **15** as a colorless oil. Yield: 0.092 g (98%). R_f=0.65. TLC stain: ultraviolet and phosphomolybdic acid. $[\alpha]_D^{20}$ +41.7 (*c* 0.55, MeOH). The ^{1}H NMR and ^{13}C NMR spectra show the presence of two rotamers in a 0.4:0.6 ratio. ^{1}H NMR: CD_3OD, 500 MHz, 25 °C, δ (ppm): 8.64 (s, 0.40H), 8.19 (s, 0.6H), 8.06–8.02 (m, 1H), 7.92–7.85 (m, 2H), 7.62 (d, *J*=7.2 Hz, 0.6H), 7.59–7.55 (m, 1H), 7.54–7.49 (m, 1.4H), 7.48–7.43 (m, 1H), 7.40–7.37 (m, 1H), 7.33–7.26 (m, 1H), 6.97–6.95 (m, 0.8H), 6.80–6.79 (m, 1.2H), 6.39 (q, *J*=7.0 Hz, 0.6H), 5.75 (q, *J*=7.0 Hz, 0.4H), 3.41–3.35 (m, 0.4H), 3.14 (dt, *J*=6.7, 14.7 Hz, 0.6H), 3.03 (dd, *J*=7.8, 14.7 Hz, 0.6H), 2.94–2.89 (m, 0.4H), 2.26–2.09 (m, 2H), 1.75 (d, *J*=7.0 Hz, 1.2H), 1.66 (d, *J*=7.0 Hz, 1.8H), 1.26–1.18 (m, 0.4H), 0.92–0.84 (m, 1.6H). The ^{1}H NMR and ^{13}C NMR spectra show the presence of two rotamers in 0.46:0.54ratio. ^{1}H NMR: DMSO-d_6, 500 MHz, 120 °C, δ (ppm): 8.61 (s, 0.46H), 8.21 (s, 0.54H), 8.09–8.05 (m, 1H), 7.92 (s, 1H), 7.87 (d, *J*=8.0 Hz, 1H), 7.63–7.37 (m, 6H), 7.18 (s, 1H), 7.04 (s, 1H), 6.29 (s, 0.54H), 5.68 (s, 0.46H), 3.29 (s, 0.46H), 3.06 (s, 0.54H), 2.31–2.26 (m, 2H), 1.72 (s, 1.38H), 1.63 (s, 1.62H), 1.26–1.12 (m, 2H). ^{13}C NMR: 125 MHz, DMSO-d_6, 25 °C—rotamers, δ (ppm)=165.5, 165.2, 144.0, 143.5, 135.9, 135.8, 135.4, 135.2, 133.4, 132.9, 132.8, 131.5 (q, *J*=31.0 Hz, 1C), 130.3, 130.2, 130.1, 129.9, 127.9, 127.8, 127.2, 127.1, 126.3, 126.1, 125.7, 125.7 (q, *J*=271.0 Hz, 1C), 125.6 (q, *J*=271.0 Hz, 1C), 125.6 (q. *J*=3.5 Hz, 1C), 124.2, 123.7, 123.6 (q, *J*=3.5 Hz, 1C), 54.4, 47.5, 44.6, 41.7, 33.8, 33.4, 33.1, 30.7, 20.0, 17.1. IR (film, cm^{-1}): 1665, 1329, 1163, 1122, 1073. MS (EI): 386 (M+1), 258, 232, 212, 155. HRMS calcd for $C_{23}H_{23}F_3NO$: 386.1732. Found=386.1729.

*4.2.5. (R)-N-(1-(Naphthalen-1-yl)ethyl)-3-(3-(trifluoromethyl)phenyl)propan-1-amine hydrochloride (**6**).*[28] To an open round-bottomed flask (or a test tube) equipped with a magnetic stir bar were added reduced adduct **15** (0.077 g, 0.2 mmol) and HCl (1.0 mL). Subsequently, the system was heated to reflux for 12 h. Afterward, the solvent was removed under reduced pressure to afford a reaction mixture that was purified by flash chromatography (ethyl acetate/methanol 90:10 as eluent, R_f=0.30) to provide product **6** as a white solid. Yield: 0.078 g (100%). R_f=0.30. TLC stain: ultraviolet and ninhydrin. $[\alpha]_D^{20}$ −27.4 (*c* 0.51, MeOH). ^{1}H NMR: CD_3OD, 600 MHz, δ (ppm): 8.18 (d, *J*=8.4 Hz, 1H), 7.95 (dd, *J*=3.7, 7.9 Hz, 2H), 7.77 (d, *J*=7.1 Hz, 1H), 7.65–7.56 (m, 3H), 7.45–7.36 (m, 4H), 5.38 (d, *J*=6.5 Hz, 1H), 3.11–3.06 (m, 1H), 2.90–2.85 (m, 1H), 2.70 (t, *J*=7.4 Hz, 2H), 2.04–2.02 (m, 2H), 1.80 (d, *J*=6.4 Hz, 3H). ^{13}C NMR: CD_3OD, 150 MHz, δ (ppm)=142.9, 135.5, 134.2, 133.2, 132.1, 131.8 (q, *J*=32.0 Hz, 1C), 131.0, 130.4, 128.5, 127.5, 126.6, 126.0 (q, *J*=272.0 Hz, 1C), 125.6 (q. *J*=3.5 Hz, 1C), 125.0 (q, *J*=3.5 Hz, 1C), 123.1, 54.2, 46.8, 33.2, 28.9, 20.2. MS (EI): 358 (M+1), 239, 204, 155, 122. HRMS calcd for $CH_{23}F_3N$: 358.1783. Found=358.1819.

4.3. Synthesis of alverine 7

*4.3.1. N,N-Bis(3-phenylpropyl)acetamide (**18**).*[29] To an open round-bottomed flask (or a test tube) equipped with a magnetic stir bar were added $Pd_2(dba)_3$ (8 mol %, 20 mg), sodium acetate (3 equiv, 0.75 mmol, 0.122 g), and benzonitrile (1.0 mL). To the resulting suspension was added allylamine derivative **16c** (0.25 mmol, 0.06 g) followed by benzenediazonium tetrafluoroborate (0.60 mmol, 0.114 g). The reaction was stirred at room temperature for 1 h. Subsequently, the system was purged with hydrogen and allowed to stir under this atmosphere for 12 h. The reaction mixture was filtered through a plug of silica gel with ethyl acetate and concentrated under reduced pressure. The product was purified by flash chromatography (hexanes/ethyl acetate 80:20 as eluent) to provide arylated product **18** as a colorless oil. Yield: 0.053 g (72%). R_f=0.53. TLC stain: ultraviolet and phosphomolybdic acid. ^{1}H NMR: $CDCl_3$, 250 MHz, 25 °C, δ (ppm): 7.31–7.12 (m, 10H), 3.34 (t, *J*=7.5 Hz, 2H), 3.17 (t, *J*=7.5 Hz, 2H), 2.58 (t, *J*=7.5 Hz, 4H), 1.96 (s, 3H), 1.90–1.77 (m, 4H). ^{13}C NMR: 62.5 MHz, $CDCl_3$, 25 °C, δ (ppm): 170.0, 141.4, 140.5, 128.3, 128.18, 128.11, 128.0, 126.0, 125.6, 47.9, 45.2, 33.1, 32.7, 30.0, 29.0, 21.3. MS (EI): 296 (M+1), 254, 136, 119, 91. HRMS calcd for $C_{20}H_{26}NO$: 296.2014. Found=296.2019.

*4.3.2. N-Ethyl-3-phenyl-N-(3-phenylpropyl)propan-1-amine (**7**).*[22] To a flame dried round-bottomed flask containing THF and a magnetic stir bar at 0 °C was added $AlCl_3$ (0.06 mmol, 0.008 g) under a nitrogen atmosphere. After 5 min, a solution of $LiAlH_4$ (0.2 mmol, 0.2 mL, 2.0 M in THF) was added dropwise. The reaction was then stirred for 10 min, followed by the addition of amide **18** (0.1 mmol, 0.029 g) in THF (1.0 mL). The system was warmed to room temperature and left to stir for 1.5 h. Next, a saturated $NaHCO_3$ solution (20 mL) was added, and the organic phase was extracted with EtOAc (3×20 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The product was purified by flash chromatography (hexanes/ethyl acetate 50:50 as eluent) to provide the arylated product **7** as a colorless oil. Yield: 0.026 g (96%). R_f=0.35. TLC stain: ultraviolet and phosphomolybdic acid. ^{1}H NMR: CD_3OD, 250 MHz, 25 °C, δ (ppm): 7.26–7.09 (m, 10H), 2.57–2.38 (m, 10H), 1.76–1.64 (m, 4H), 0.95 (t, *J*=7.1 Hz, 3H). ^{13}C NMR: 62.5 MHz, CD_3OD, 25 °C, δ (ppm): 143.2, 129.4, 129.3, 126.8, 53.6, 48.3, 34.7, 28.9, 11.5. MS (EI): 282 (M+1), 164, 119, 91. HRMS calcd for $C_{20}H_{28}N$: 282.2222. Found=282.2232.

4.4. Synthesis of tolpropamine 8

*4.4.1. 2-(3,3-Bis(4-methoxyphenyl)allyl)isoindoline-1,3-dione (**20**).* A flask was charged with allyl phthalimide **19** (0.25 mmol, 0.046 g), 4-methoxybenzenediazonium tetrafluoroborate **2b**, $Pd_2(dba)_3$, sodium acetate (3 equiv, 0.75 mmol, 0.061 g), and benzonitrile (2 mL). The reaction was left to stir, and the progress of the reaction was monitored by the evolution of N_2. After bubbling stopped, EtOAc (10 mL) was added. The reaction mixture was filtered through a plug of silica and concentrated under reduced pressure. The residue was purified by flash chromatography (hexanes/ethyl acetate as eluent, 7:1) to provide the corresponding aryl allylamines as a white solid (single spot on TLC). The yields refer to mixtures of the three isomers (a single spot on TLC). Compounds **20**–**22** were separated by preparative HPLC and fully characterized. The ratio of the regioisomers was based on the integrations of the appropriate signals in the ^{1}H NMR spectrum. See the SD for further details.

TLC stain: ultraviolet and $KMnO_4$. ^{1}H NMR: $CDCl_3$, 500 MHz, 25 °C, δ (ppm): 7.76–7.75 (m, 2H), 7.64–7.62 (m, 2H), 7.17 (d, *J*=8.5 Hz, 2H), 7.07 (d, *J*=8.5 Hz, 2H), 6.88 (d, *J*=8.5 Hz, 2H), 6.70 (d, *J*=8.5 Hz, 2H), 5.93 (t, *J*=6.5 Hz, 1H), 4.39 (d, *J*=6.5 Hz, 2H), 3.77 (s, 3H), 3.70 (s, 3H). ^{13}C NMR (ATP): 125 MHz, $CDCl_3$, 25 °C, δ (ppm): 168.0, 159.2, 158.9, 143.8, 134.5, 133.9, 132.4, 131.2, 131.0, 128.6, 123.1, 120.2, 113.7, 113.4, 55.2, 55.2, 37.7. MS (EI): 400 (M+1), 399 (M), 252, 237. HRMS calcd for $C_{25}H_{21}NO_4$=399.1471. Found=399.1455.

*4.4.2. (Z)-2-(2,3-Bis(4-methoxyphenyl)allyl)isoindoline-1,3-dione (**21**).* TLC stain: ultraviolet and $KMnO_4$. ^{1}H NMR: $CDCl_3$, 500 MHz, 25 °C, δ (ppm): 7.64–7.62 (m, 2H), 7.55–7.53 (m, 2H), 7.41 (d, *J*=8.5 Hz, 2H), 7.30 (d, *J*=8.5 Hz, 2H), 6.80 (d, *J*=8.5 Hz, 2H), 6.73–6.71 (m, 3H), 4.93 (d, *J*=1.0 Hz, 2H), 3.74 (s, 3H), 3.66 (s, 3H). ^{13}C NMR (ATP): 125 MHz, $CDCl_3$, 25 °C, δ (ppm): 168.1, 158.9, 158.4, 135.3, 133.7, 132.3, 131.8, 130.3, 129.8, 128.0, 123.0, 113.7, 113.6, 55.2, 55.1, 37.8. HRMS calcd for $C_{25}H_{21}NO_4$=399.1471. Found=399.1475.

*4.4.3. (E)-2-(2,3-Bis(4-methoxyphenyl)allyl)isoindoline-1,3-dione **22**.* TLC stain: ultraviolet and $KMnO_4$. ^{1}H NMR: $CDCl_3$,

500 MHz, 25 °C, δ (ppm): 7.74–7.72 (m, 2H), 7.63–7.61 (m, 2H), 7.09 (d, *J*=8.5 Hz, 2H), 6.82 (d, *J*=8.5 Hz, 2H), 6.73 (d, *J*=8.5 Hz, 2H), 6.63 (d, *J*=8.5 Hz, 2H), 6.49 (s, 1H), 4.56 (d, *J*=1.35 Hz, 2H), 3.70 (s, 3H), 3.64 (s, 3H). ^{13}C NMR (ATP): 125 MHz, $CDCl_3$, 25 °C, δ (ppm): 167.9, 158.8, 158.2, 134.0, 133.8, 131.9, 130.4, 130.3, 130.1, 129.0, 127.3, 123.2, 114.0, 113.2, 55.0, 55.0, 45.2. HRMS calcd for $C_{25}H_{21}NO_4$=399.1471. Found=399.1439.

*4.4.4. (E)-2-(3-(4-Fluorophenyl)allyl)isoindoline-1,3-dione (**23**).*[13] To a round-bottomed flask (or a test tube) were added $Pd_2(dba)_3$ (4 mol %, 10 mg), sodium acetate (3 equiv, 0.75 mmol, 0.061 g), and benzonitrile (1 mL). To the resulting suspension was added phthalyl allylamine **19** (1.2 equiv, 0.3 mmol) followed by 4-methoxybenzenediazonium tetrafluoroborate (0.25 mmol, 0.055 g). The reaction was stirred at room temperature, while the reaction progress was monitored by the evolution of N_2. After nitrogen bubbling stopped, the reaction mixture was filtered through a plug of silica gel and concentrated under reduced pressure. The product was purified by flash chromatography (hexanes/ethyl acetate as eluent) to provide the corresponding aryl allylamines (single spot on TLC). Yield: 0.063 g (91%). Ratio **23**/**24**/**25**=95/2/3 (single spot on TLC). ^{1}H NMR: $CDCl_3$, 250 MHz, δ (ppm): 7.88–7.85 (m, 2H), 7.74–7.71 (m, 2H), 7.34–7.29 (m, 2H), 7.00–6.94 (m, 2H), 6.64 (d, *J*=16.0 Hz, 1H), 6.22 (dt, J^1=16.0 Hz, J^2=6.5 Hz, 1H), 4.44 (dd, J^1=6.5 Hz, J^2=1.0 Hz, 2H). ^{13}C NMR: $CDCl_3$, 62.5 MHz, δ (ppm): 167.9, 162.4 (d, *J*=247.0 Hz, 1C), 134.0, 132.6, 132.4 (d, *J*=3.0 Hz, 1C), 132.1, 128.1 (d, *J*=8.0 Hz, 1C), 123.3, 122.4, 122.3, 115.6 (d, *J*=21 Hz, 1C), 39.5. MS (EI): 282 (M+1), 281 (M), 263, 148. HRMS calcd for $C_{17}H_{12}FNO_2$=281.0852. Found: 281.0850. The product was obtained as a white solid after purification by flash chromatography (hexanes/ethyl acetate 4:1 as eluent, R_f=0.51), mp 167–168 °C. The reaction was performed on a 5 mmol scale: 1.05 g of 4-fluorobenzenediazonium tetrafluoroborate, 6 mmol (1.121 g of allyl phthalimide), 0.2 mmol [0.2 g of $Pd_2(dba)_3$], 15 mmol (18.45 g of NaOAc) dissolved in 5 mL of PhCN were stirred for 1 h at room temperature. The yield was 91% (1.405 g) for the mixture of isomers (ratio **23**:**24**:**25**=96:2:2). The mixture was dissolved in $CHCl_3$ at 60 °C, and the trans isomer recrystallized in 83% yield upon cooling.

*4.4.5. (Z)-2-(3-(4-Methoxyphenyl)allyl)isoindoline-1,3-dione (**24**).* ^{1}H NMR: $CDCl_3$, 500 MHz, δ (ppm): 7.88–7.86 (m, 2H), 7.75–7.74 (m, 2H), 7.40–7.38 (m, 2H), 7.14 (t, *J*=8.5 Hz, 2H), 6.60 (d, *J*=11.0 Hz, 1H), 5.68 (dt, J^1=11.0 Hz, J^2=6.5 Hz, 1H), 4.57 (dd, J^1=6.5 Hz, J^2=1.5 Hz, 2H). ^{13}C NMR: $CDCl_3$, 125 MHz, δ (ppm): 168.0, 161.9 (d, *J*=247.0 Hz, 1C), 149.0, 147.0, 134.0, 132.2 (d, *J*=3.0 Hz, 1C), 132.0, 130.9, 130.4 (d, *J*=8.0 Hz, 1C), 125.7, 123.9, 115.3 (d, *J*=21.0 Hz, 1C), 36.3. MS (EI): 282 (M+1), 281 (M), 148, 134. HRMS calcd for $C_{17}H_{12}FNO_2$=281.0852. Found. 281.0844.

*4.4.6. 2-(2-(4-Methoxyphenyl)allyl)isoindoline-1,3-dione (**25**).*[13] ^{1}H NMR: $CDCl_3$, 500 MHz, δ (ppm): 7.87 (m, 2H), 7.75–7.73 (m, 2H), 7.50–7.47 (m, 2H), 7.04 (t, *J*=8.5 Hz, 2H), 5.41 (s, 1H), 5.20 (t, *J*=1.5 Hz, 1H), 4.70 (t, *J*=1.5 Hz, 2H). ^{13}C NMR: $CDCl_3$, 125 MHz, δ (ppm): 167.9, 162.5 (d, *J*=247.0 Hz, 1C), 141.5, 134.5 (d, *J*=3.0 Hz, 1C), 134.0, 131.9, 128.1 (d, *J*=8.0 Hz, 1C), 123.4, 115.3 (d, *J*=21.0 Hz, 1C), 114.25, 114.24, 41.5. MS (EI): 282 (M+1), 281 (M), 263, 160. HRMS calcd for $C_{17}H_{12}FNO_2$=281.0852. Found. 281.0856.

Compounds **23**–**25** were separated by preparative HPLC and fully characterized. The ratio between the regioisomers was based on the integrations of the appropriate signals in the ^{1}H NMR spectra.[13]

*4.4.7. (E)-Methyl 3-(4-bromophenyl)-3-(3-chloro-4-methylphenyl) acrylate (**29c**).* Cinnamate **28c** (0.48 g, 2.0 mmol), 3-chloro-4-methylbenzenediazonium tetrafluoroborate **2f** (0.72 g, 3.0 mmol), and MeOH (20 mL) were placed in a round-bottom flask equipped with a magnetic stir bar. Next, $Pd(OAc)_2$ (0.03 g, 0.14 mmol) and $CaCO_3$ (0.20 g, 2.0 mmol) were added. The system was stirred for 2 h; afterward, the mixture was concentrated, and H_2O was added (20 mL). The organic layer was extracted with EtOAc (3×20 mL). The combined organic layers were dried over $MgSO_4$ and evaporated under reduce pressure to afford a dark solid. The product was purified by flash chromatography (hexanes/ethyl acetate 95:5 as eluent) to furnish compound **29c** (*E*/*Z* stereoselectivity 92:8) as a white solid, mp: 119–121 °C. R_f=0.34. TLC stain: phosphomolybdic acid. ^{1}H NMR: $CDCl_3$, 400 MHz, 25 °C, δ (ppm): 7.52 (d, *J*=8.5 Hz, 2.5H), 7.25 (d, *J*=1.6 Hz, 1.5H), 7.18 (d, *J*=8.0 Hz, 1.5H), 7.07 (d, *J*=8.4 Hz, 3.5H), 6.34 (s, 1H), 3.63 (s, 3H), 2.37 (s, 3H). ^{13}C NMR: $CDCl_3$, 100 MHz, 25 °C, δ (ppm): 166.03, 154.50, 139.56, 137.74, 131.30, 130.98, 130.83, 128.67, 126.46, 122.79, 17.34, 51.45, 19.95. IR (film, cm^{-1}): 2044, 1719, 1623, 1487, 1431, 1358, 1257, 1153, 1053, 1053, 1012, 873, 828, 775, 687. HRMS calcd $C_{17}H_{15}BrClO_2$=364.9944. Found=364.9940. Structural determination of compound **29e** was performed using a NMR NOESY 1D experiment. Irradiating the vinylic hydrogen caused increases of 0.83% and 0.49% in the signals corresponding to the aromatic hydrogens at the 2 position of the ring bearing the methyl group.

*4.4.8. Methyl 3-phenyl-3-(p-tolyl)propanoate (**30**).* Cinnamate **28c** (0.48 g, 2.0 mmol), 3-chloro-4-methylbenzenediazonium tetrafluoroborate **2c** (0.72 g, 3.0 mmol), and MeOH (20 mL) were placed in a round-bottom flask equipped with a magnetic stir bar. Next, $Pd(OAc)_2$ (0.03 g, 0.14 mmol) and $CaCO_3$ (0.20 g, 2.0 mmol) were added. The system was stirred for 2 h before $NaHCO_3$ was added. The system was purged with H_2 and stirred until the reduction of the Heck–Matsuda product was complete. The mixture was concentrated under reduced pressure followed by addition of H_2O (20 mL). The mixture was extracted with EtOAc (3×20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated under reduce pressure. The crude product was purified by flash chromatography (hexanes/ethyl acetate 95:5 as eluent) to provide compound **30** as a yellow oil. Yield: 0.47 g (92%). R_f=0.28. TLC stain: phosphomolybdic acid. ^{1}H NMR: $CDCl_3$, 500 MHz, 25 °C, δ (ppm): 7.35–7.05 (m, 9H), 4.52 (t, *J*=7.9 Hz, 1H), 3.58 (s, 3H), 3.04 (d, *J*=7.9 Hz, 2H), 2.29 (s, 3H). ^{13}C NMR: $CDCl_3$, 125 MHz, 25 °C, δ (ppm): 172.3, 143.7, 140.5, 136.1, 129.3, 128.5, 127.6, 127.5, 126.5, 51.6, 46.6, 40.6, 21.0.

*4.4.9. 3-Phenyl-3-(p-tolyl)propanoic acid (**31**).* Ester **30** (0.15 g, 0.61 mmol) and KOH (0.27 g, 4.88 mmol) were added to H_2O/MeOH 1:4 (7.5 mL) in a round-bottomed flask equipped with a magnetic stir bar and a condenser. Next, the system was heated to reflux and left to stir for 3 h. Next, the system was cooled to room temperature and left to stir overnight. The reaction was concentrated under reduced pressure before 1 M HCl (20 mL) was added. The product was extracted with EtOAc (3×20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated under reduce pressure. The product was purified by flash chromatography (hexanes/ethyl acetate 90:10 as eluent) to give compound **31** as a white solid. Yield: 0.12 g (80%). R_f=0.28, TLC stain: phosphomolybdic acid. ^{1}H NMR: $CDCl_3$, 250 MHz, 25 °C, δ (ppm): 7.36–6.95 (m, 9H), 4.47 (t, *J*=7.8 Hz, 1H), 3.05 (d, *J*=7.9 Hz, 2H), 2.28 (s, 3H). ^{13}C NMR: $CDCl_3$, 62.5 MHz, 25 °C, δ (ppm): 177.3, 143.5, 140.2, 136.2, 129.3, 128.6, 127.5, 127.4, 126.5, 46.2, 40.3, 20.9.

*4.4.10. N,N-Dimethyl-3-phenyl-3-(p-tolyl)propanamide (**32**).* Carboxylic acid **31** (0.10 g, 0.43 mmol), dimethylamine (balloon), EDC·HCl (0.11 g, 0.65 mmol), HOBt (0.08 g, 0.65 mmol), DIPEA (0.17 mL, 1.29 mmol), and dry DCM (5 mL) were placed in a 25 mL dried flask and stirred for 36 h at room temperature. Afterward, the reaction mixture was diluted with brine (20 mL) and extracted with ethyl acetate (3×20 mL). The combined organic

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layers were dried over $MgSO_4$, filtered, and evaporated under vacuum. The residue was purified by flash column chromatography (hexanes/ethyl acetate 50:50 as eluent) to afford amide **32** as a yellow oil. R_f=0.28. TLC stain: phosphomolybdic acid. ^{1}H NMR: $CDCl_3$, 500 MHz, 25 °C, δ (ppm): 7.03–7.29 (m, 9H), 4.64 (t, J=7.5 Hz, 1H), 3.02 (d, J=7.5 Hz, 2H), 2.86 (s, 6H), 2.28 (s, 3H). ^{13}C NMR: $CDCl_3$, 125 MHz, 25 °C, δ (ppm): 170.3, 144.6, 141.3, 135.8, 129.2, 128.4, 127.8, 127.7, 126.3, 46.7, 39.3, 37.3, 35.6, 21.0.

*4.4.11. N,N-Dimethyl-3-phenyl-3-(p-tolyl)propan-1-amine (**8**).* To a flame dried round-bottomed flask containing THF (4 mL) and a magnetic stir bar, at 0 °C was added $AlCl_3$ (0.24 mmol, 0.03 g) under a nitrogen atmosphere. Next, 1.0 M $LiAlH_4$ in THF (8.4 mmol, 0.84 mL of) was added dropwise. Amide **32** was added, and the reaction mixture was heated at 60 °C for 2 h. Subsequently, 1 mL of a saturated NH_4Cl solution was added, followed by the dropwise addition of 10 mL of saturated $NaHCO_3$. The product was extracted with EtOAc (3×10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The product was purified by flash chromatography (hexanes/ethyl acetate, triethylamine 94:5:1 as eluent) to furnish compound **8** as a colorless oil. Yield: 81%. R_f=0.15. TLC stain: phosphomolybdic acid. ^{1}H NMR: CD_3OD, 250 MHz, 25 °C, δ (ppm): 7.34–6.94 (m, 9H), 3.88 (t, J=6.9 Hz, 1H), 2.31–2.13 (m, 10H), 1.91 (s, 3H). ^{13}C NMR: CD_3OD, 125 MHz, 25 °C, δ (ppm): 144.9, 141.6, 135.4, 128.7, 128.0, 127.3, 127.2, 125.8, 57.9, 48.8, 44.0, 32.7, 22.8, 19.6.

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Supplementary data

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