Brønsted AcidCatalyzed General Petasis Allylation and Isoprenylation of Unactivated Ketones

Brønsted Acid-Catalyzed General Petasis Allylation and Isoprenylation of Unactivated Ketones

Yang Zhou,[‡[a]] Zhen-Ni Zhao,[‡[a]] Yu-Long Zhang, [a] Jun Liu, [a] Quan Yuan, [a] Uwe Schneider*[b] and Yi-Yong Huang*[a]

Dedicated to Professor Albert S. C. Chan on the occasion of his 70th birthday

[a] Prof. Dr. Yi-Yong Huang
Department of Chemistry
School of Chemistry, Chemical Engineering and Life Science, Wuhan University of Technology
Wuhan 430070, China.
E-mail: huangyy@whut.edu.cn
[b] Dr. Uwe Schneider
EaStCHEM School of Chemistry
The University of Edinburgh
The King's Buildings, David Brewster Road, Edinburgh EH9 3FJ (UK)
E-mail: Uwe.Schneider@ed.ac.uk

Abstract: Brønsted acid-catalyzed general Petasis allylation and isoprenylation of unactivated ketones have been developed using *o*-hydroxyaniline and the corresponding pinacolyl boronic esters. This robust methodology has provided access to a broad variety of quaternary homoallylic amines and dienylamines in high yields, proved applicable to a gram-scale synthesis, and allowed the formation of a potentially bioactive quaternary homoallylic aminodiol.

Introduction

Nucleophilic allylation has been among the most studied C–C bond formations to transfer a synthetically useful allyl functional group. Compared with the well-established aldimine allylation to form tertiary homoallylic amines, the reaction using ketimines has remained a major challenge for their low electrophilicity.[1] However, this analogous reaction represents a convenient access to quaternary homoallylic amines,[2] which are key structural motifs in numerous biologically active molecules such as **I**,[3] **II**,[4] **III**,[5] and **IV**[6] (Figure 1). Therefore, diverse novel allylation strategies involving the use of ketimines have been devised to address the synthetic issues. To date, two main types of protocols involving ketimines have been documented: (1) The two-component allylation of isolated ketimines, where ketimines must be formed and purified prior to C–C bond formation. Recently, several allylation systems using a variety of stoichiometric metal or metalloid reagents[7] and metal catalysts[8] have been identified. (2) The three-component allylation of *in situ*-formed ketimines; either from the condensation of ketones and primary amines (Scheme 1),[9] or *via* other one-pot methods.[10] In contrast to the two-component approach, less progress has been achieved here although this more direct method can obviate the need for the pre-installation of moisture- and acid-sensitive ketimines.

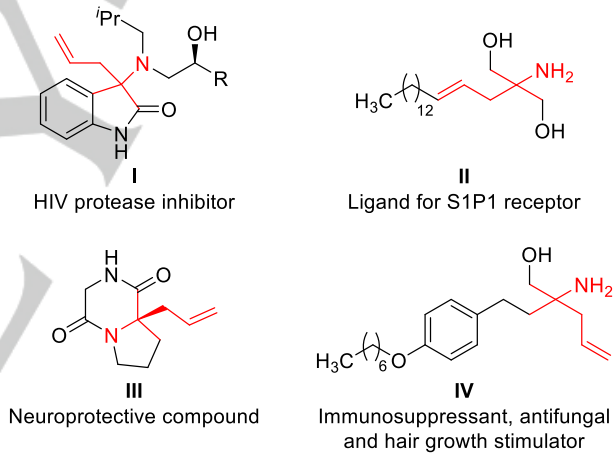
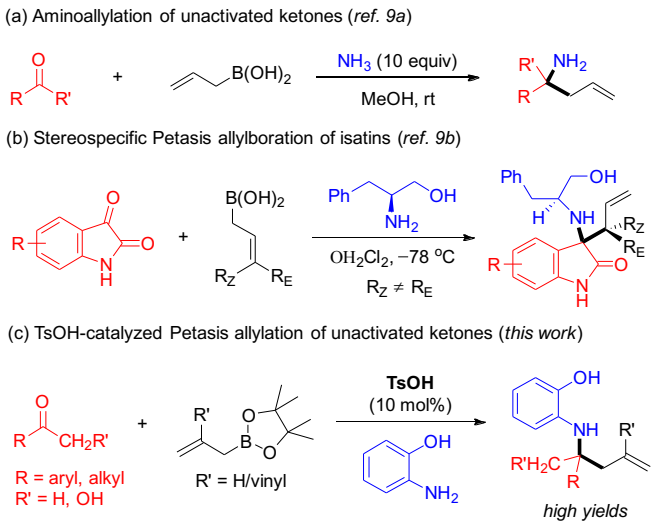


Figure 1. Selected bio-active molecules bearing quaternary homoallylamine motifs.

The Petasis allylboration of ketones[9] belonging to the second reaction type has remained scarce and underdeveloped, although the Petasis allylboration of aldehydes has been well established.[11] In 2005, inspired by the seminal work of Kobayashi's Petasis-type aminoallylation of aldehydes,[12] Thadani *et al.* accomplished the allylation and crotylation of *in situ*-formed *N*-unprotected ketimines using boronic acids in the presence of ammonia (Scheme 1a);[9a] however, a 10-fold excess of NH_3 had to be used. In 2017, Zhang *et al.* reported a diastereospecific Petasis allylboration of isatins using boronic acids in the presence of an optically pure primary aminoalcohol to give access to the corresponding products bearing two adjacent quaternary stereogenic centers (Scheme 1b);[9b] however, unfunctionalized ketones proved to be unreactive. In contrast to the corresponding boronic acids, cyclic allylboronic esters of the pinacol-type display a relatively high stability and thus a low reactivity.[13] Therefore, the challenge has been to activate these cyclic allylic boronic esters, unactivated ketones, and the corresponding *in situ*-formed ketimines in order to develop a general and robust Petasis allyl-

and isoprenylboration for the construction of highly functionalized quaternary amines (Scheme 1c). In this context, as part of our research interest in organoboron chemistry,[14] we report here a Brønsted acid-catalyzed Petasis allyl- and isoprenylboration of unactivated ketones by exploiting a neighboring hydroxyl group-activation strategy;[15] a derivative of compound **IV** (Figure 1) proved to be readily accessible as well.

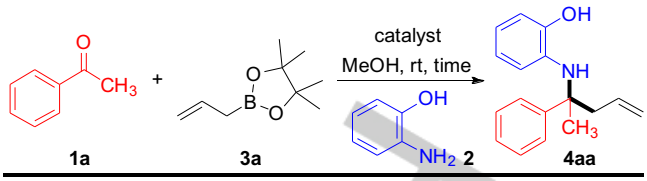


Scheme 1. Petasis allylborations of various ketones.

Results and Discussion

In our previous work, we have reported on the Petasis allylboration using aldehydes, a 1,2-aminoalcohol, and pinacolyl allylboronic ester.[14d,e] Accordingly, we sought to extend this methodology to the use of unactivated ketones (Table 1). However, the use of acetophenone (**1a**), *o*-hydroxyaniline (**2**; 1.2 equiv), and pinacolyl allylboronic ester (**3a**; 1.2 equiv) under the reported reaction conditions (rt, 48 h) gave the expected quaternary homoallylic amine **4aa** in only 18% yield (entry 1). This result may be attributed to both the sluggish *in situ*-generation and the low electrophilicity of the corresponding ketimine. As Brønsted acids have been shown to accelerate both imine formation and aldehyde allylboration,[16] several Brønsted acids (5 mol%) were screened (entries 2–4). *Para*-toluenesulfonic acid (TsOH) exhibited a slightly better performance than benzoic acid and camphorsulfonic acid (CSA); the yield of product **4aa** increased to 40% (entry 4). Subsequently, the loading effect of TsOH was examined (10–30 mol%; entries 5–7); the use of 10 mol% proved to be the best compromise (56% yield; entry 5). More importantly, the use of an increased amount of **3a** gave product **4aa** in 84% yield (1.5 equiv; entry 8). In contrast to our earlier work,[14d] the use of 4Å MS was not required (entry 9). Similarly, further increasing the amount of **3a** or conducting the reaction at 50 °C proved to be ineffective (entries 10–12). Finally, extending the reaction time led to a slight increase in the yield of product **4aa** (entries 13 and 14); the best compromise proved to be 96 h (90% yield; entry 14).

Table 1. Optimization of the Petasis allylation conditions.[a]



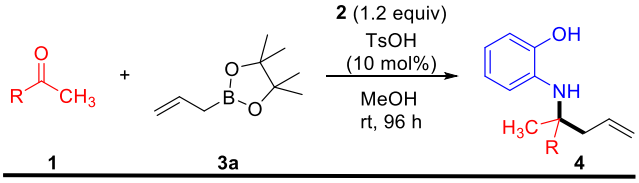
1a **3a** **2** **4aa**

entry	**3a**/equiv	catalyst/mol%	time/h	yield/%[b]
1	1.2	–	48	18
2	1.2	$PhCO_2H$/5	48	36
3[c]	1.2	CSA/5	48	38
4	1.2	TsOH/5	48	40
5	1.2	TsOH/10	48	56
6	1.2	TsOH/20	48	60
7	1.2	TsOH/30	48	51
8	1.5	TsOH/10	48	84
9[d]	1.5	TsOH/10	48	82
10	1.8	TsOH/10	48	85
11	2.0	TsOH/10	48	89
12[e]	1.5	TsOH/10	48	82
13	1.5	TsOH/10	72	86
14	1.5	TsOH/10	96	90

[a] Reaction conditions: **1a** (0.20 mmol), **2** (0.24 mmol), catalyst, MeOH (0.20 mL), rt, 2 h; **3a**, T, time. [b] Isolated yields. [c] Racemic product was obtained. [d] 4Å MS (50 mg) was used. [e] Run at 50 °C.

Next, the ketone scope was investigated under the optimized conditions (Table 1, entry 14). Various aromatic and aliphatic methyl ketones proved to be effective substrates (Table 2). The use of *para*-substituted aromatic ketones (Me, Hal, CF_3) gave the corresponding quaternary homoallylic amines **4ba–fa** in 70–87% yield (entries 2–6). Similar results were obtained for *meta*-substituted aromatic ketones (MeO, Me, Hal, CF_3); the corresponding products **4ga–la** were formed in 72–86% yield (entries 7–12). Similary, *meta*,*para*-disubstituted products **4ma** (Me) and **4na** (F) were obtained in 76% and 80% yield, respectively (entries 13 and 14). Furthermore, the use of *ortho*-substituted aromatic ketones (Me, Hal) and the 2-naphthyl derivative gave the corresponding products **4oa–ra** in 76–82% yield (entries 15–18). Notably, the synthesis of the quaternary aliphatic homoallylic amine **4sa** from ketone **1s** was achieved in 94% yield (entry 19).

Table 2. Ketone scope for the Petasis allylation.[a]



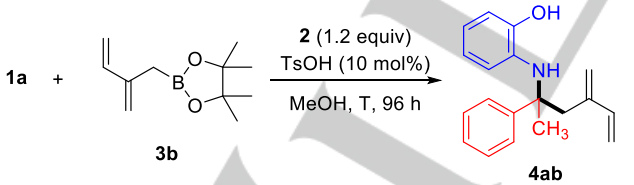
1 3a 4

entry	ketone (**1**)	product (**4**)	yield/%[b]
1	R = Ph (**1a**)	**4aa**	90
2	R = 4-Me-C_6H_4 (**1b**)	**4ba**	70
3	R = 4-F-C_6H_4 (**1c**)	**4ca**	75
4	R = 4-Cl-C_6H_4 (**1d**)	**4da**	79
5	R = 4-Br-C_6H_4 (**1e**)	**4ea**	87
6	R = 4-CF_3-C_6H_4 (**1f**)	**4fa**	70
7	R = 3-MeO-C_6H_4 (**1g**)	**4ga**	72
8	R = 3-Me-C_6H_4 (**1h**)	**4ha**	80
9	R = 3-F-C_6H_4 (**1i**)	**4ia**	86
10	R = 3-Cl-C_6H_4 (**1j**)	**4ja**	82
11	R = 3-Br-C_6H_4 (**1k**)	**4ka**	82
12	R = 3-CF_3-C_6H_4 (**1l**)	**4la**	80
13	R = 3,4-$(Me)_2$-C_6H_3(**1m**)	**4ma**	76
14	R = 3,4-$(F)_2$-C_6H_3 (**1n**)	**4na**	80
15	R = 2-Me-C_6H_4 (**1o**)	**4oa**	79
16	R = 2-F-C_6H_4 (**1p**)	**4pa**	82
17	R = 2-Cl-C_6H_4 (**1q**)	**4qa**	82
18	R = 2-naphthyl **(1r)**	**4ra**	76
19	R = *c*-hexyl (**1s**)	**4sa**	94

[a] Reaction conditions: **1** (0.20 mmol), **2** (0.24 mmol), TsOH (10 mol%), MeOH (0.20 mL), rt, 2 h; **3a** (0.30 mmol), rt, 96 h. [b] Isolated yield.

We also probed the versatility and robustness of this Petasis reaction by using isoprenylboronic ester **3b**,[14f] instead of **3a**, to access the corresponding quaternary dienylamine **4ba** (Table 3). Under the standard reaction conditions the expected product **4ba** was formed in 72% yield (entry 1); this result was slightly improved by conducting the experiment at 50 °C (75% yield; entry 2). A dilution of the reaction mixture (1 M) proved to be to somewhat effective (0.5–0.67 M; entries 3 and 4); the best compromise was observed at 0.67 M (82% yield; entry 3).

Table 3. Optimization of the Petasis isoprenylation conditions.[a]



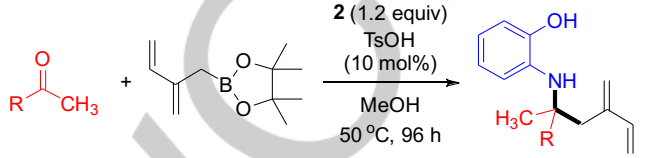
3b 4ab

entry	MeOH/mL	T/°C	yield/%[b]
1	0.2	rt	72
2	0.2	50	75
3	0.3	50	82
4	0.4	50	77

[a] Reaction conditions: **1a** (0.20 mmol), **2** (0.24 mmol), TsOH (10 mol%), MeOH, rt, 2 h; **3b** (0.30 mmol), T, 96 h. [b] Isolated yields.

Here again, the ketone scope was investigated under the optimized conditions (Table 3, entry 3). Various aromatic, heteroaromatic, and aliphatic methyl ketones proved to be effective substrates (Table 4). The use of *para*-substituted aromatic ketones provided quaternary dienylamines **4bb–fb** in 65–82% yield (entries 2–6). Similar results were observed for *meta*-, *meta*,*para*-di-, and *ortho*-substituted aromatic ketones; the corresponding products **4gb–qb** were formed in 60–77% yield (entries 7–17). Importantly, the quaternary aliphatic target compound **4sb** was generated in 89% yield (entry 18). Finally, the use of 1-naphthyl and 3-pyridyl derivatives gave the corresponding products **4tb** and **4ub** in 76% and 90% yield, respectively (entries 19 and 20). These data highlight the generality of this Petasis methodology in terms of unactivated ketones.

Table 4. Ketone scope for the Petasis isoprenylation.[a]



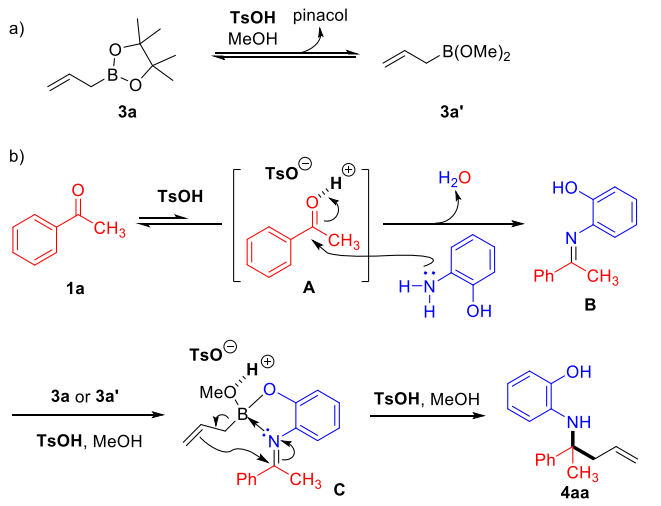
1 3b 4

entry	ketone (**1**)	product (**4**)	yield/%[b]
1	R = Ph (**1a**)	**4ab**	82
2	R = 4-Me-C_6H_4 (**1b**)	**4bb**	65
3	R = 4-F-C_6H_4 (**1c**)	**4cb**	73
4	R = 4-Cl-C_6H_4 (**1d**)	**4db**	77
5	R = 4-Br-C_6H_4 (**1e**)	**4eb**	82
6	R = 4-CF_3-C_6H_4 (**1f**)	**4fb**	81
7	R = 3-MeO-C_6H_4 (**1g**)	**4gb**	72
8	R = 3-Me-C_6H_4 (**1h**)	**4hb**	60
9	R = 3-F-C_6H_4 (**1i**)	**4ib**	73
10	R = 3-Cl-C_6H_4 (**1j**)	**4jb**	76
11	R = 3-Br-C_6H_4 (**1k**)	**4kb**	77
12	R = 3-CF_3-C_6H_4 (**1l**)	**4lb**	75
13	R = 3,4-$(Me)_2$-C_6H_3 (**1m**)	**4mb**	61
14	R = 3,4-$(F)_2$-C_6H_3 (**1n**)	**4nb**	75
15	R = 2-Me-C_6H_4 (**1o**)	**4ob**	63
16	R = 2-F-C_6H_4 (**1p**)	**4pb**	68
17	R = 2-Cl-C_6H_4 (**1q**)	**4qb**	70
18	R = *c*-hexyl (**1s**)	**4sb**	89
19	R = 1-naphthyl **(1t)**	**4tb**	75
20	R = 3-pyridyl (**1u**)	**4ub**	90

[a] Reaction conditions: **1** (0.20 mmol), **2** (0.24 mmol), TsOH (10 mol%), MeOH (0.30 mL), rt, 2 h; **3b** (0.30 mmol), 50 °C, 96 h. [b] Isolated yield.

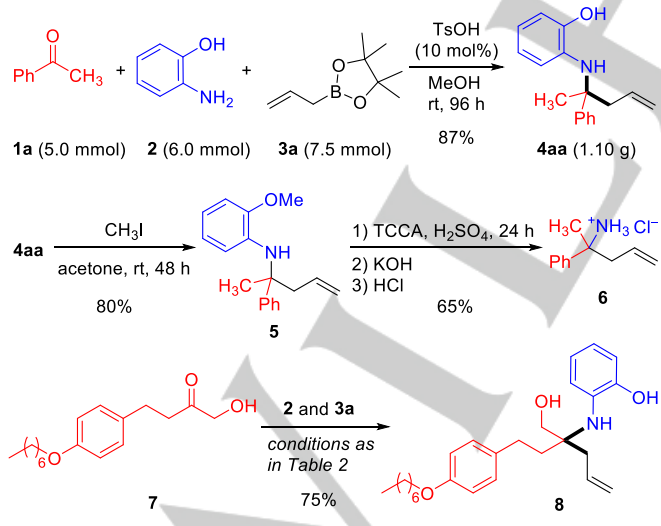
The *para*-toluenesulfonic acid catalyst is proposed to promote these Petasis reactions in distinct ways (Scheme 2). First, TsOH may enable ligand exchange processes[17] at boron between cyclic allylboronic ester **3a** and MeOH (excess) to generate *in situ* the more reactive[13] acyclic allylboronic ester **3a'** (Scheme 2a); or an acyclic hybrid (not displayed).[17] Second, the protonation of the oxygen atom of ketone **1a** by TsOH would increase substantially the carbonyl electrophilicity (**A**; Scheme 2b); such fast pre-equilibrium would result in a facilitated nucleophilic addition of aniline **2** and thus a more effective condensation to form *in situ* the corresponding ketimine **B**. Third, a TsOH-promoted ligand exchange at boron between **3a** or **3a'** and bidentate species **B** would lead to boron–ate complex **C** and thus a cyclic transition state for C–C bond formation (Scheme 2b);[17] in **C**, a basic oxygen atom is likely protonated by TsOH increasing the Lewis acidity of the adjacent boron atom[16] to favor the B←N interaction and thus

the ketimine allylation. Finally, TsOH should promote the B–O(Ar) bond hydrolysis to give product **4aa**.



Scheme 2. Possible roles of TsOH in the Petasis allylation.

In order to demonstrate the practicality and utility of this Petasis methodology, we first attempted a gram-scale synthesis (Scheme 3); gratifyingly, quaternary homoallylic amine **4aa** was obtained in 87% yield. Next, **4aa** underwent smooth *O*-methylation to give aromatic ether **5**, which was treated with trichloroisocyanuric acid (TCCA) in H_2SO_4[18] to form the corresponding *N*-deprotected quaternary homoallylic amine as its ammonium chloride salt **6** in 65% yield. In addition, when the aliphatic α-hydroxyketone **7** (see SI) was used the corresponding quaternary homoallylic aminodiol **8**, a derivative of biologically active compound **IV**,[6] was formed in 75% yield.



Scheme 3. Synthetic utility of the developed Petasis allylation.

Conclusion

In summary, we have developed Brønsted acid-catalyzed Petasis allylation and isoprenylation of unactivated ketones using *o*-hydroxyaniline and the corresponding cyclic boronic esters to give various quaternary homoallylic amines and dienylamines in high yields. Plausible roles of the TsOH catalyst include the promotion of: ligand exchange processes at boron; the *in situ* ketimine generation; the C–C bond formation through the activation of a boron–ate intermediate. This general and robust methodology has proved applicable to a gram-scale synthesis and the formation of a complex, potentially bioactive quaternary homoallylic aminodiol. Further studies towards an asymmetric version of these processes involving the use of α-, β-, and γ-substituted allylic boronates are ongoing in our laboratory.

Experimental Section

General Information. All reactions involving air-sensitive compounds were performed in oven-dried glassware by using standard Schlenk techniques. All reactions were monitored by TLC, and TLC analysis was performed by illumination with a UV lamp (254 nm). Flash column chromatography was carried out using silica gel of 200–300 mesh; preparative thin-layer chromatography (PTLC) was conducted using silica gel GF254. NMR spectroscopy was performed using a Bruker Avance 500 instrument (^{1}H NMR: 500 MHz; ^{13}C NMR: 126 MHz; ^{19}F NMR: 471 MHz). In ^{1}H NMR spectra, chemical shifts were reported in ppm downfield from internal TMS with the solvent resonance as the internal standard ($CDCl_3$, δ = 7.26 ppm). In ^{13}C NMR spectra, chemical shifts were reported in ppm downfield from TMS with the solvent resonance as the internal standard ($CDCl_3$, δ = 77.2 ppm). Infrared spectra were recorded on a NICOLET FT/IR-200 spectrometer. High resolution MS (ESI-orbitrap) were obtained on a Thermo Fisher Q Exactive Mass Spectrometer.

General procedure for the Petasis reactions with pinacolyl allylboronic ester (3a): A solution of the corresponding ketone **1** (0.20 mmol), *o*-hydroxyaniline (**2**; 0.24 mmol, 1.2 equiv), and TsOH (0.02 mmol, 10 mol%) was stirred in MeOH (0.2 mL) at rt for 2 h. Pinacolyl allylboronic ester (**3a**; 0.30 mmol, 1.5 equiv) was added, and the mixture was stirred at rt for 96 h prior to purification by preparative thin-layer chromatography on silica gel to give the corresponding product **4a**.

Analytical data of compounds 4ca, 4ga, 4ha, 4ka and 4la:

2-((2-(4-fluorophenyl)pent-4-en-2-yl)amino)phenol (4ca): Brown oil, 40.5 mg, 75% yield, R_f = 0.50 (PE/EA = 10:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49–7.38 (m, 2H), 7.08–6.97 (m, 2H), 6.76–6.67 (m, 1H), 6.63–6.51 (m, 2H), 6.14–6.01 (m, 1H), 5.74–5.60 (m, 1H), 5.16–5.10 (m, 2H), 2.67 (dd, *J* = 13.5, 7.0 Hz, 1H), 2.58 (dd, *J* = 13.5, 7.0 Hz, 1H), 1.62 (s, 3H) ppm; *signals for O–H and N–H were not observed*. ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.58 (d, *J* = 244.8 Hz), 144.70, 142.31, 133.96, 133.31, 127.77 (d, *J* = 7.8 Hz), 120.81, 119.30, 118.01, 116.64, 115.16 (d, *J* = 21.0 Hz), 114.25, 57.54, 48.57, 25.49 ppm. ^{19}F NMR (471 MHz, $CDCl_3$) δ –117.08 ppm. IR (neat): ν = 3421, 2976, 1609, 1511, 1444, 1264, 1166, 1101, 918, 816, 701 cm^{-1}. HRMS (ESI; m/z): $[M–H]^-$ calcd for $C_{17}H_{17}FNO^-$, 270.1299, found: 270.1297.

2-((2-(3-methoxyphenyl)pent-4-en-2-yl)amino)phenol (4ga): Brown oil, 40.6 mg, 72% yield, R_f = 0.48 (PE/EA = 10:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (d, *J* = 7.5 Hz, 1H), 7.16–7.04 (m, 2H), 6.83 (dd, *J* = 7.5, 2.5 Hz, 1H), 6.78–6.50 (m, 3H), 6.19–6.18 (m, 1H), 5.84–5.64 (m, 1H), 5.16 (d, *J* = 13.0 Hz, 2H), 3.82 (s, 3H), 2.72 (dd, *J* = 13.5, 7.5 Hz, 1H), 2.63 (dd, *J* = 13.5, 7.5 Hz, 1H), 1.64 (s, 3H) ppm; *signals for O–H and N–H were not observed*. ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.78, 148.66, 145.09, 133.96, 133.59, 129.40, 120.76, 119.06, 118.55, 118.26, 117.30, 114.15, 112.43, 111.41, 57.92, 55.25, 48.30, 25.41 ppm. IR (neat): ν = 3423, 1607, 1512, 1433, 1260, 1043, 918, 748 cm^{-1}. HRMS (ESI; m/z): $[M–H]^-$ calcd for $C_{18}H_{20}NO_2^-$, 282.1499, found: 282.1495.

2-((2-(*m*-tolyl)pent-4-en-2-yl)amino)phenol (4ha): Brown oil, 42.6 mg, 80% yield, R_f = 0.49 (PE/EA = 10:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–7.31 (m, 2H), 7.28 (d, *J* = 7.5 Hz, 1H), 7.11 (d, *J* = 7.5 Hz, 1H), 6.84–6.16 (m, 4H), 5.85–5.64 (m, 2H), 5.19 (d, *J* = 3.5 Hz, 1H), 5.16 (s, 1H), 2.74 (dd, *J* = 13.5, 7.5 Hz, 1H), 2.65 (dd, *J* = 13.5, 7.5 Hz, 1H), 2.40 (s, 3H), 1.65 (s, 3H) ppm; *signals for O–H and N–H were not observed*. ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.74, 145.27, 137.94, 133.99, 133.74, 128.30, 127.24, 126.70, 123.13, 120.71, 118.97, 118.32, 117.52, 114.15, 57.88, 48.30, 25.43, 21.76 ppm. IR (neat): ν = 3419, 2977, 1607, 1511, 1444, 1262, 1185,1099, 917, 742 cm^{-1}. HRMS (ESI; m/z): $[M–H]^-$ calcd for $C_{18}H_{20}NO^-$, 266.1550, found: 266.1546.

2-((2-(3-bromophenyl)pent-4-en-2-yl)amino)phenol (4ka): Brown oil, 54.1 mg, 82% yield, R_f = 0.50 (PE/EA = 10:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (s, 1H), 7.43 (d, *J* = 7.5 Hz, 1H), 7.39 (d, *J* = 7.5 Hz, 1H), 7.21 (t, *J* = 8.0 Hz, 1H), 6.84–6.04 (m, 4H), 5.77–5.61 (m, 1H), 5.24–5.03 (m, 2H), 2.69 (dd, *J* = 13.5, 7.5 Hz, 1H), 2.58 (dd, *J* = 13.5, 7.5 Hz, 1H), 1.62 (s, 3H) ppm; *signals for O–H and N–H were not observed*. ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.43, 144.63, 133.79, 133.02, 130.06, 129.67, 129.22, 124.89, 122.83, 120.90, 119.55, 118.12, 116.64, 114.29, 57.70, 48.22, 25.36 ppm. IR (neat): ν = 3443, 2360 ,1637, 1511, 1443, 1251, 1206, 997, 749 cm^{-1}. HRMS (ESI; m/z): $[M–H]^–$ calcd for $C_{17}H_{17}BrNO^–$, 330.0499, found: 330.0496.

2-((2-(3-(trifluoromethyl)phenyl)pent-4-en-2-yl)amino)phenol (4la): Brown oil, 51.2 mg, 80% yield, R_f = 0.53 (PE/EA = 10:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62–7.56 (m, 4H), 6.80–6.66 (m, 1H), 6.61–6.49 (m, 2H), 6.14–5.96 (m, 1H), 5.72–5.62 (m, 1H), 5.22–5.02 (m, 2H), 2.70 (dd, *J* = 13.5, 7.5 Hz, 1H), 2.60 (dd, *J* = 13.5, 7.5 Hz, 1H), 1.66 (s, 3H) ppm; *signals for O–H and N–H were not observed*. ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.97, 144.51, 133.77, 132.83, 130.79 (q, *J* = 32.0 Hz), 129.74, 128.94, 124.33 (q, *J* = 272.3 Hz), 123.47 (q, *J* = 3.6 Hz), 122.77 (q, *J* = 3.5 Hz), 120.90, 119.72, 118.06, 116.38, 114.31, 57.81, 48.18, 25.46 ppm. ^{19}F NMR (471 MHz, $CDCl_3$) δ –62.36 (s, 3F) ppm. IR (neat): ν = 3450, 2360 ,1637, 1511, 1331, 1262, 1124, 1073, 748 cm^{-1}. HRMS (ESI; m/z): $[M–H]^–$ calcd for $C_{18}H_{17}F_3NO^–$, 320.1267, found: 320.1263.

General procedure for the Petasis reactions with pinacolyl isoprenylboronic ester (3b): A solution of the corresponding ketone **1** (0.20 mmol), *o*-hydroxyaniline (**2**; 0.24 mmol, 1.2 equiv), and TsOH (0.02 mmol, 10 mol%) was stirred in MeOH (0.2 mL) at rt for 2 h. Pinacolyl isoprenylboronic ester (**3b**; 0.30 mmol, 1.5 equiv) was added, and the mixture was stirred at 50 °C for 96 h prior to the purification by preparative thin-layer chromatography on silica gel to give the corresponding product **4b**.

Analytical data of compounds 4ab, 4fb, 4jb, 4kb and 4qb:

2-((4-methylene-2-phenylhex-5-en-2-yl)amino)phenol (4ab): Brown oil, 45.6 mg, 82% yield, R_f = 0.49 (PE/EA = 10:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (d, *J* = 7.5 Hz, 2H), 7.35 (t, *J* = 7.5 Hz, 2H), 7.30–7.21 (m, 1H), 6.76–6.67 (m, 1H), 6.60–6.48 (m, 2H), 6.39 (dd, *J* = 17.5, 10.5 Hz, 1H), 6.11 (d, *J* = 7.0 Hz, 1H), 5.28 (d, *J* = 17.5 Hz, 1H), 5.25 (s, 1H), 5.05 (d, *J* = 10.5 Hz, 1H), 4.84 (s, 1H), 2.85 (d, *J* = 13.5 Hz, 1H), 2.78 (d, *J* = 13.5 Hz, 1H), 1.63 (s, 3H) ppm; *signals for O–H and N–H were not observed*. ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.80, 145.24, 141.98, 140.04, 133.99, 128.42, 126.49, 126.24, 120.67, 120.34, 118.10, 117.18, 114.19, 113.95, 58.70, 44.82, 25.11 ppm. IR (neat): ν = 3410, 2977, 1606, 1511, 1445, 1375, 1264, 992, 905, 742 cm^{-1}. HRMS (ESI; m/z): $[M–H]^–$ calcd for $C_{19}H_{20}NO^–$, 278.1550, found: 278.1547.

2-((4-methylene-2-(4-(trifluoromethyl)phenyl)hex-5-en-2-yl)amino)phenol (4fb): Brown oil, 56.1 mg, 81% yield, R_f = 0.52 (PE/EA = 10:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66–7.56 (m, 4H), 6.77–6.48 (m, 3H), 6.36 (dd, *J* = 17.5, 11.0 Hz, 1H), 6.03–5.95 (m, 1H), 5.24 (s, 1H), 5.23 (d, *J* = 17.5 Hz, 1H), 5.04 (d, *J* = 11.0 Hz, 1H), 4.81 (s, 1H), 2.82 (d, *J* = 13.5 Hz, 1H), 2.77 (d, *J* = 13.5 Hz, 1H), 1.67 (s, 3H) ppm; *signals for O–H and N–H were not observed*. ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.89, 144.49, 141.42, 139.76, 133.84, 128.79 (q, *J* = 32.4 Hz), 126.75, 125.39 (q, *J* = 3.8 Hz), 124.33 (q, *J* = 274.7 Hz), 120.85, 120.68, 117.80, 116.16, 114.34, 114.11, 58.61, 44.83, 25.18 ppm. ^{19}F NMR (471 MHz, $CDCl_3$) δ –62.26 (s, 3F) ppm. IR (neat): ν = 3413, 2976, 1608, 1511, 1327, 1262, 1164, 1122, 905, 841, 749 cm^{-1}. HRMS (ESI; m/z): $[M–H]^–$ calcd for $C_{20}H_{19}F_3NO^–$, 346.1424, found: 346.1419.

2-((2-(3-chlorophenyl)-4-methylenehex-5-en-2-yl)amino)phenol (4jb): Brown oil, 47.5 mg, 76% yield, R_f = 0.50 (PE/EA = 10:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (s, 1H), 7.40 (d, *J* = 7.5 Hz, 1H), 7.28–7.21 (m, 2H), 6.71 (d, *J* = 5.2 Hz, 1H), 6.63–6.45 (m, 2H), 6.36 (dd, *J* = 17.5, 11.0 Hz, 1H), 6.06 (d, *J* = 6.3 Hz, 1H), 5.25 (d, *J* = 17.5 Hz, 1H), 5.24 (s, 1H), 5.04 (d, *J* = 11.0 Hz, 1H), 4.82 (s, 1H), 2.80 (d, *J* = 13.5 Hz, 1H), 2.73 (d, *J* = 13.5 Hz, 1H), 1.61 (s, 3H) ppm; *signals for O–H and N–H were not observed*. ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.17, 144.77, 141.58, 139.82, 134.42, 133.84, 129.70, 126.71, 126.57, 124.62, 120.83, 120.59, 117.97, 116.57, 114.30, 114.10, 58.52, 44.88, 24.99 ppm. IR (neat): ν = 3414, 2969, 1592, 1511, 1375, 1263, 1095, 903, 748 cm^{-1}. HRMS (ESI; m/z): $[M–H]^–$ calcd for $C_{19}H_{19}ClNO^–$, 312.1161, found: 312.1156.

2-((2-(3-bromophenyl)-4-methylenehex-5-en-2-yl)amino)phenol (4kb): Brown oil, 54.8 mg, 77% yield, R_f = 0.50 (PE/EA = 10:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (t, *J* = 2.0 Hz, 1H), 7.47–7.35 (m, 2H), 7.20 (t, *J* = 8.0 Hz, 1H), 6.77–6.49 (m, 3H), 6.36 (dd, *J* = 17.5, 11.0 Hz, 1H), 6.11–5.99 (m, 1H), 5.25 (d, *J* = 17.5 Hz, 1H), 5.24 (s, 1H), 5.05 (d, *J* = 11.0 Hz, 1H), 4.83 (s, 1H), 2.80 (d, *J* = 13.5 Hz, 1H), 2.73 (d, *J* = 13.5 Hz, 1H), 1.61 (s, 3H) ppm; *signals for O–H and N–H were not observed*. ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.46, 144.77, 141.56, 139.80, 133.82, 130.01, 129.65, 129.43, 125.11, 122.76, 120.84, 120.60, 117.99, 116.60, 114.30, 114.12, 58.49, 44.92, 24.99 ppm. IR (neat): ν = 3413, 2977, 1607, 1511, 1374, 1262, 994, 903, 743 cm^{-1}. HRMS (ESI; m/z): $[M–H]^–$ calcd for $C_{19}H_{19}BrNO^–$, 356.0656, found: 356.0652.

2-((2-(2-chlorophenyl)-4-methylenehex-5-en-2-yl)amino)phenol (4qb): Brown oil, 43.7 mg, 70% yield, R_f = 0.49 (PE/EA = 10:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43–7.37 (m, 2H), 7.24–7.18 (m, 2H), 6.86–6.69 (m, 2H), 6.51 (t, *J* = 7.5 Hz, 1H), 6.36 (dd, *J* = 17.5, 11.0 Hz, 1H), 6.18 (d, *J* = 7.5 Hz, 1H), 5.36 (d, *J* = 17.5 Hz, 1H), 5.20 (s, 1H), 5.04 (d, *J* = 11.0 Hz, 1H), 4.83 (s, 1H), 3.19 (d, *J* = 13.5 Hz, 1H), 3.02 (d, *J* = 13.5 Hz, 1H), 1.62 (s, 3H) ppm; *signals for O–H and N–H were not observed*. ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.29, 142.42, 142.30, 140.12, 132.54, 132.21, 131.97, 130.16, 128.41, 126.94, 121.68, 120.69, 120.19, 119.99, 114.04, 113.95, 60.61, 41.82, 24.51 ppm. IR (neat): ν = 3413, 2980, 1607, 1511, 1375, 1261, 1095, 903, 831, 749 cm^{-1}. HRMS (ESI; m/z): $[M–H]^–$ calcd for $C_{19}H_{19}ClNO^–$, 312.1161, found: 312.1157.

2-((1-(4-(heptyloxy)phenyl)-3-(hydroxymethyl)hex-5-en-3-yl)amino)phenol (8): A solution of ketone **5** (55.6 mg, 0.20 mmol), *o*-hydroxyaniline (**2**; 26.3 mg, 0.24 mmol, 1.2 equiv), and TsOH (4.2 mg, 0.02 mmol, 10 mol%) in MeOH (0.2 mL) was stirred at rt for 2 h. Pinacolyl allylboronic ester (**3a**; 50.4 mg, 0.30 mmol, 1.5 equiv) was added, and the mixture was stirred at rt for 96 h prior to purification by flash column chromatography on silica gel (PE/EA = 3:1) to give **8** as a yellow oil (61.7 mg, 75% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13–6.66 (m, 8H), 6.02–5.83 (m, 1H), 5.33–5.13 (m, 2H), 3.91 (t, *J* = 6.6 Hz, 2H), 3.52 (s, 2H), 2.78–2.52 (m, 2H), 2.50–2.30 (m, 2H), 1.88–1.64 (m, 4H), 1.50–1.39 (m, 2H), 1.40–1.26 (m, 6H), 0.89 (t, *J* = 6.8 Hz, 3H) ppm; *signals for O–H (2x) and N–H were not observed*. ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.40, 150.27, 133.91, 133.29, 131.88, 129.11, 124.43, 123.60, 120.67, 118.93, 115.48, 114.53, 68.06, 65.59, 60.51, 38.79, 36.14, 31.81, 29.33, 29.09, 28.59, 26.03, 22.63, 14.11 ppm. IR (neat): ν = 3854, 3748, 2928, 2858, 1607, 1510, 1491, 1242, 1176, 1032, 824, 747 cm^{-1}. HRMS (ESI; m/z): $[M+H]^+$ calcd for $C_{26}H_{38}NO_3^+$, 412.2846, found: 412.2845.

Acknowledgements

We thank the National Natural Science Foundation of China (21772151), the Natural Science Foundation of Hubei Province (2018CFA084), and the Wuhan Morning Light Plan of Youth Science and Technology (2017050304010314) for the financial support of this investigation.

Keywords: allylation • functionalised aminophenols • isoprenylation • Petasis reaction • quaternary homoallylic amines

[1] a) O. Riant, J. Hannedouche, *Org. Biomol. Chem.* **2007***, 5,* 873–888*;* b) M. Shibasaki, M. Kanai, *Chem. Rev.* **2008**, *108*, 2853–2873; c) S. Kobayashi, Y. Mori, J. S. Fossey, M. M. Salter, *Chem. Rev.* **2011**, *111*, 2626–2704; d) M. Yus, J. C. González–Gómez, F. Foubelo, *Chem. Rev.* **2011**, *111*, 7774–7854; e) H.-X. Huo, J. R. Duvall, M.-Y. Huang, R. Hong, *Org. Chem. Front.* **2014**, *1*, 303–320; f) C. Diner, K. J. Szabó, *J. Am. Chem. Soc.* **2017**, *139*, 2–14; g) D. Kumar, S. R. Vemula, N. Balasubramanian, G. R. Cook, *Acc. Chem. Res.* **2016**, *49*, 2169–2178.

[2] *Umpolung* allylation of imines: a) X.-H. Huo, R. He, J.-K. Fu, J.-C. Zhang, G.-Q. Yang, W.-B. Zhang, *J. Am. Chem. Soc.* **2017**, *139*, 9819–9822; b) X.-H. Huo, J.-C. Zhang, J.-K. Fu, R. He, W.-B. Zhang, *J. Am. Chem. Soc.* **2018**, *140*, 2080–2084; c) L. Wei, Q. Zhu, S.-M. Xu, X. Chang, C.-J. Wang, *J. Am. Chem. Soc.* **2018**, *140*, 1508–1513; d) C. Shen, R.-Q. Wang, L. Wei, Z.-F. Wang, H.-Y. Tao, C.-J. Wang, *Org. Lett.* **2019**, *21*, 6940–6945; e) Y.-W. Wang, L.-F. Deng, X. Zhang, D.-W. Niu, *Org. Lett.* **2019**, *21*, 6951–6956; amination of α-allyl ketones: f) T. Takeda, M. Terada, *J. Am. Chem. Soc.* **2013**, *135*, 15306–15309; (g) B. M. Trost, J.

S. Tracy, E. Y. Lin, *ACS Catal.* **2019**, *9*, 1584–1594; (h) B. M. Trost, J. S. Tracy, T. Saget, *Chem. Sci.* **2018**, *9*, 2975–2980.

[3] A. K. Ghosh, G. Schiltz, R. S. Perali, S. Leshchenko, S. Kay, D. E. Walters, Y. Koh, K. Maedad, H. Mitsuyad, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1869–1873.

[4] S. S. Schilson, P. Keul, R. S. Shaikh, M. Schaefers, B. Levkau, G. Haufe, *Bioorg. Med. Chem.* **2015**, *23*, 1011–1026.

[5] L. I. Glass, M. J. Bickerdike, M. F. Snape, P. P. De Cogram, WO patent 2015013397, **2015**.

[6] F. Tetsuro, A. Kunitomo, K. Toshiyuki, K. Masatoshi, C. Kenji, T. Koji, M. Tadashi, US patent 5948820A, **1999**.

[7] a) D. A. Cogan, G.-C. Liu, J. Ellman, *Tetrahedron* **1999,** *55*, 8883–8904; b) J. A. Ellman, T. D. Owens, T. P. Tang, *Acc. Chem. Res.* **2002**, *35*, 984–995; c) R. Berger, K. Duff, J. L. Leighton, *J. Am. Chem. Soc.* **2004**, *126*, 5686–5687; d) P. M. A. Rabbat, S. C. Valdez, J. L. Leighton, *Org. Lett.* **2006**, *8*, 6119–6121. (e) N. R. Perl, J. L. Leighton, *Org. Lett.* **2007**, *9*, 3699–3701; f) E. Canales, E. Hernandez, J. A. Soderquist, *J. Am. Chem. Soc.* **2006**, *128*, 8712–8713; g) J. L.-Y. Chen, V. K. Aggarwal, *Angew. Chem.* ***2014****, 126*, 11172–11176; *Angew. Chem. Int. Ed.* **2014**, *53*, 10992–10996; h) X.-W. Sun, M.-H. Xu, G.-Q. Lin, *Org. Lett.* **2006**, *8*, 4979–4982; i) J. A. Sirvent, F. Foubelo, M. Yus, *Chem. Commun.* **2012**, *48*, 2543–2545.

[8] a) R. Wada, T. Shibuguchi, S. Makino, K. Oisaki, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2006**, *128*, 7687–7691; b) D. Li, Y. Park, W. Yoon, H. Yun, J. Yun, *Org. Lett.* **2019**, *21*, 9699–9703; c) Y.-F. Luo, H. B. Hepburn, N. Chotsaeng, H. W. Lam, *Angew. Chem.* **2012***, 124*, 8434–8438; *Angew. Chem. Int. Ed.* **2012**, *51*, 8309–8313; d) H. B. Hepburn, N. Chotsaeng, Y.-F. Luo, H. W. Lam, *Synthesis* **2013**, *45*, 2649–2661; e) H. B. Hepburn, H. W. Lam, *Angew. Chem.* **2014***, 126*, 11789–11794; *Angew. Chem. Int. Ed.* **2014**, *53*, 11605–11610; f) Z.-Y. Cao, Y. Zhang, C.-B. Ji, J. Zhou, *Org. Lett.* **2011**, *13*, 6398–6401; g) S. Nakamura, K. Hyodo, M. Nakamura, D. Nakane, H. Masuda, *Chem. Eur. J.* **2013**, *19*, 7304–7309; h) J. Wang, Q.-X. Zhang, B.-Y. Zhou, C. Yang, X. Li, J.-P. Cheng, *iScience* **2019**, *16*, 511–523.

[9] a) B. Dhudshia, J. Tiburcio, A. N. Thadani, *Chem. Commun.* **2005**, 5551–5553; b) Q.-Y. Tan, X.-Q. Wang, Y. Xiong, Z.-M. Zhao, L. Li, P. Tang, M. Zhang, *Angew. Chem.* **2012***, 129*, 4907–4911; *Angew. Chem. Int. Ed.* **2017**, *56*, 4829–4833; c) N. Y. Kuznetsov, R. M. Tikhov, T. V. Strelkova, Y. N. Bubnov, *Org. Lett.* **2018**, *20*, 3549–3552.

[10] a) H. Jang, F. Romiti, S. Torker, A. H. Hoveyda, *Nat. Chem.* **2017**, *9*, 1269–1275; b) S. Pramanik, R. R. Reddy, P. Ghorai, *Org. Lett.* **2015**, *17*, 1393–1396; c) S. Pramanik, P. Ghorai, *Chem. Commun.* **2012**, *48*, 1820–1822; d) A.-L. Lu, D.-F. Huang, K.-H. Wang, Y.-P. Su, J.-Y. Ma, Y.-L. Xu, Y.-L. Hu, *Synthesis* **2016**, *48*, 293–301; e) D. Vasu, A. L. Fuentes de Arriba, J. A. Leitch, A. de Gombert, D. J. Dixon, *Chem. Sci.* **2019**, *10*, 3401–3407.

[11] a) P. Wu, M. Givskov, T. E. Nielsen, *Chem. Rev.* **2019**, *119*, 11245–11290; b) N. R. Candeias, F. Montalbano, P. M. S. D. Cal, P. M. P. Gois, *Chem. Rev.* **2010**, *110*, 6169–6193; c) T. R. Ramadhar, R. A. Batey, *Synthesis* **2011**, *9*, 1321–1346.

[12] a) M. Sugiura, K. Hirano, S. Kobayashi, *J. Am. Chem. Soc.* **2004**, *126*, 7182–7183; b) S. Kobayashi, K. Hirano, M. Sugiura, *Chem. Commun.* **2005**, *1*, 104–106.

[13] a) H. C. Brown, U. S. Racherla, P. J. Pellechia, *J. Org. Chem.* **1990**, *55*, 1869–1874; b) C. D. Roy, H. C. Brown, *J. Organomet. Chem.* **2007**, *692*, 784–790.

[14] a) X. Yang, S. J. Kalita, S. Maheshuni, Y.-Y. Huang, *Coord. Chem. Rev.* **2019**, *392*, 35–48; b) Y.-Y. Huang, C. Cai, X. Yang, Z.-C. Lv, U. Schneider, *ACS Catal.* **2016**, *6*, 5747–5763; c) Y.-Y. Huang, X. Yang, Z.-C. Lv, C. Cai, C. Kai, Y. Pei, Y. Feng, *Angew. Chem.* **2015***, 127*, 7407–7410; *Angew. Chem. Int. Ed*. **2015**, *54*, 7299–7302; d) X. Yang, Z.-H. Cao, Y. Zhou, F. Cheng, Z.-W. Lin, Z. Ou, Y. Yuan, Y.-Y. Huang, *Org. Lett*. **2018**, *20*, 2585–2589; e) Z.-W. Lin, Y. Zhou, Z.-N. Zhao, Y. Zhao, J. Liu, Y.-Y. Huang, *Org. Chem. Front*. **2019**, *6*, 751–755; f) Y.-L. Zhang, B.-J. He, Y.-W. Xie, Y.-H. Wang, Y.-L. Wang, Y.-C. Shen, Y.-Y. Huang, *Adv. Synth. Catal.* **2019**, *361*, 3074–3079; g) X. Yang, S. Pang, F. Cheng, Y. Zhang, Y.-W. Lin, Q. Yuan, F.-L. Zhang, Y.-Y. Huang, *J. Org. Chem*. **2017**, *82*, 10388–10397.

[15] a) R. K. Chambers, N. Chaipukdee, T. Thaima, K. Kanokmedhakul, S. G. Pyne, *Eur. J. Org. Chem.* **2016**, *2016*, 3765–3772; b) D. E. Carrera, *Chem. Commun.* **2017**, *53*, 11185–11188; c) Y. Yamaoka, H. Miyabe, Y. Takemoto, *J. Am. Chem. Soc.* **2007**, 129, 6686-6687; d) W.-Y. Han, Z.-J. Wu, X.-M. Zhang, W.-C. Yuan, *Org. Lett.* **2012**, *14*, 976–979; e) T. Thaima, S. G. Pyne, *Org. Lett.* **2015**, *17*, 778–781; f) F. Liepouri, G. Bernasconi, N. A. Petasis, *Org. Lett.* **2015**, *17*, 1628–1631; g) A. Das, R. Alam, L. Eriksson, K. J. Szabó, *Org. Lett.* **2014**, *16*, 3808–3811; h) L. Li, Z. Yang, J. Yang, Q.-Z. Zhang, Q.-Y. Tan, C.-H. Zhang, M. Zhang, *J. Org. Chem*. **2019**, *84*, 1605–1613.

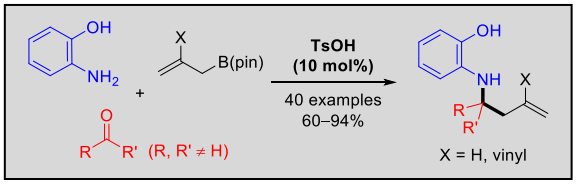
[16] a) S. H. Yu, M. J. Ferguson, R. McDonald, D. G. Hall, *J. Am. Chem. Soc.* **2005**, *127*, 12808–12809; b) P. Jain, J. C. Antilla, *J. Am. Chem. Soc.* **2010**, *132*, 11884–11886.

[17] a) S. Lou, P. N. Moquist, S. E. Schaus, *J. Am. Chem. Soc.* **2007**, *129*, 15398–15404; b) R. S. Paton, J. M. Goodman, S. C. Pellegrinet, *Org. Lett.* **2009**, *11*, 37–40; c) D. S. Barnett, P. N. Moquist, S. E. Schaus. *Angew. Chem. Int. Ed.* **2009**, *48*, 8679–8682.

[18] J. M. M. Verkade, L. J. C. van Hemert, P. J. L. M. Quaedflieg, P. L. Alsters, F. L. van Delfta, F. P. J. T. Rutjes. *Tetrahedron Lett.* **2006**, *47*, 8109–8113.

Entry for the Table of Contents

Insert graphic for Table of Contents here. ((Please ensure your graphic is in **one** of following formats))



Brønsted acid-catalyzed general Petasis allylation and isoprenylation of unactivated ketones have been developed giving access to various quaternary homoallylic amines and dienylamines.