JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

Ruthenium Hydride/Brønsted Acid-Catalyzed Tandem Isomerization/*N*-Acyliminium Cyclization Sequence for the Synthesis of Tetrahydro-*β*-carbolines

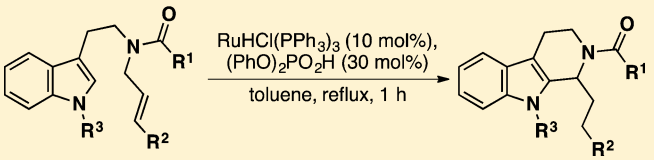
Casper L. Hansen,[†] Janie W. Clausen,[†] Ragnhild G. Ohm,[†] Erhad Ascic,[†] Sebastian T. Le Quement,[†] David Tanner,[†] and Thomas E. Nielsen*[,†,‡]

[†]Department of Chemistry, Technical University of Denmark, DK-2800 Kgs. Lyngby, Denmark

[‡]Singapore Centre on Environmental Life Sciences Engineering, Nanyang Technological University, Singapore 637551, Singapore

Supporting Information

ABSTRACT: This paper describes an efficient tandem sequence for the synthesis of 1,2,3,4-tetrahydro-*β*-carbolines (THBCs) relying on a ruthenium hydride/Brønsted acid-catalyzed isomerization of allylic amides to *N*-acyliminium ion intermediates which are trapped by a tethered indole nucleophile. The methodology provides not only a convenient "aldehyde-free" alternative to the classical Pictet–Spengler reaction but also attractive possibilities for total synthesis, including rapid generation of molecular complexity and formation of quaternary stereogenic centers. TBHCs can also be accessed by harnessing the Suzuki cross-coupling reaction to the isomerization/*N*-acyliminium cyclization sequence. Finally, diastereo- and enantioselective versions of the title reaction have been examined using substrate control (with dr >15: 1) and asymmetric catalysis (ee up to 57%), respectively.



INTRODUCTION

The 1,2,3,4-tetrahydro-*β*-carboline (THBC) ring system is a key motif in a multitude of biologically and pharmacologically significant alkaloids that provide a variety of challenges to organic synthesis (Figure 1).[1]

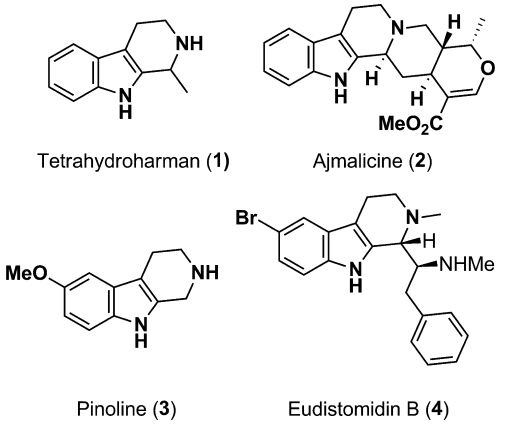


Figure 1. Some THBC-containing natural products.

The classical route to THBCs is the venerable Pictet–Spengler reaction, involving the condensation of tryptamines and aldehydes in the presence of protic or Lewis acids.[2] Since its initial disclosure in 1911,[3] the Pictet–Spengler reaction has been the subject of much fine-tuning and now includes diastereo- and enantioselective versions,[2] along with metal-catalyzed variations[4] that rely on the isomerization of *N*-allylic systems to generate reactive iminium intermediates.[5,6] For example, our laboratory[4a] celebrated the Pictet–Spengler centenary with a ruthenium-catalyzed tandem sequence which efficiently transformed simple tryptamine derivatives into indolizinoindoles via *N*-acyliminium intermediates (Figure 2).

The reaction cascade was initiated by ruthenium alkylidene-catalyzed RCM of dienes **5** to give lactams **6** and **7**, which in the case of the five-membered ring (n = 0), formed the reactive *N*-acyliminium species **10** via successive tautomerizations. Trapping of **10** by a tethered indole nucleophile completed the Pictet–Spengler variant with formation of tetracycle **11**. The sequence was successful only if the double bond formed in the RCM step was in conjugation with the lactam carbonyl,[4a,7] as no further conversion of lactams **6** (n = 1, 2) was seen upon treatment with ruthenium alkylidene catalysts.

Subsequently, we found that the metal-catalyzed isomerization of allylic amines to *N*-alkyliminium ions allowed an "aldehyde-free" variation on the classical Pictet–Spengler theme, the starting materials **12** (where R^1 is typically benzyl) being readily available from tryptamines via *N*-allylation (Scheme 1).[4b]

In these initial studies, it was not possible to form structurally related *N*-acyliminium ions from *N*-acylated allylic amines using Wilkinson's catalyst and a range of other catalysts, so we decided to look for alternatives. Related work by Sorimachi and Terada demonstrated the ruthenium hydride/Brønsted acid-catalyzed isomerization of protected allylamines to reactive *N*-

Received: October 7, 2013
Published: November 1, 2013

   dx.doi.org/10.1021/jo402192s | J. Org. Chem. 2013, 78, 12545–12565

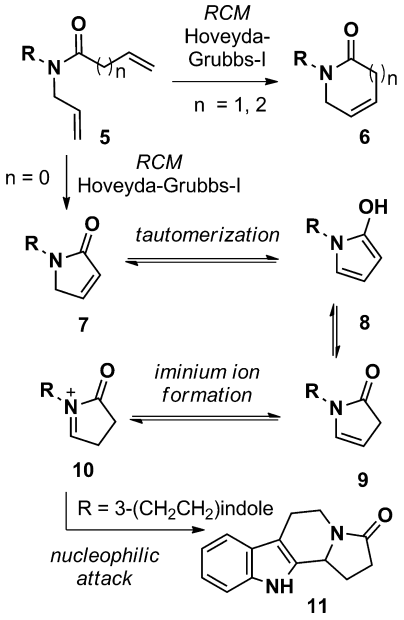
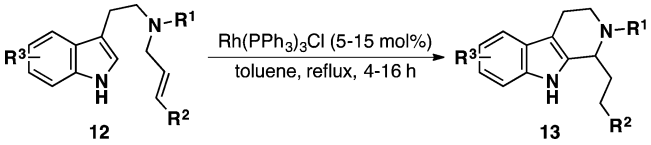


Figure 2. Proposed mechanism for the formation of indolizinoindoles via RCM, tautomerization, and *N*-acyliminium ion formation.[4a,7]

Scheme 1. Metal-Catalyzed Synthesis of THBCs[4b]

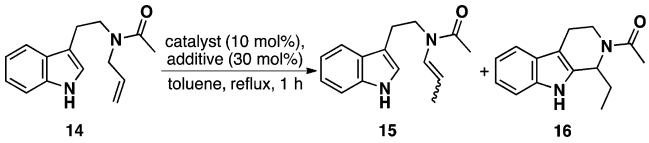


acyliminium ions which were then trapped in Friedel–Crafts-type reactions with electron-rich aromatics.[8] The high electrophilicity of the *N*-acyliminium species is also a major advantage of the reaction sequence shown in Figure 2, but the structural requirements to allow the tautomerization process obviously limit the scope of this methodology. Since the chemistry depicted in Scheme 1 is potentially a much more general approach for the rapid generation of molecular complexity, we decided to make a thorough investigation of related tandem isomerization/cyclization reactions involving *N*-acyliminium ions.

RESULTS AND DISCUSSION

Preliminary investigations were conducted on a simple model system, allylic amide **14** (Table 1), and, as we expected, the generation of the *N*-acyliminium ion proved to be the most challenging feature of the reaction sequence. Wilkinson's catalyst, which had previously proven highly efficient in facilitating the isomerization of the double bond in allylic amines,[4b] unfortunately showed no reactivity toward the acylated allylamine **14**, and the same negative result was obtained with $RhCl_3$ (Table 1, entries 3–5). However, we were delighted to find that the ruthenium hydride catalyst $RuHCl(CO)(PPh_3)_3$ very efficiently promoted the isomerization to the enamide (Table 1, entry 6). The presence of a strong Brønsted or Lewis acid proved vital for the transformation of the enamide **15** to the THBC **16** (Table 1, entries 7, 13, 15, and 17–20). In the absence of any metal catalyst (Table 1, entry 1) and with only catalytic amounts of acids such as $(PhO)_2PO_2H$ (Table 1, entry 2), no conversion of starting material was detected, which shows that both the metal

Table 1. Metal/Acid-Catalyzed Synthesis of THBC 16



entry	catalyst	additive	ratio of **14**:**15**:**16** *a,b*
1	none		1:0:0
2	none	$(PhO)_2PO_2H$	1:0:0
3	$Rh(PPh_3)_3Cl$		1:0:0
4	$RhCl_3$		1:0:0[c]
5	$RhCl_3$		1:0:0
6	$RuHCl(CO)(PPh_3)_3$		0:1:0
7	$RuHCl(CO)(PPh_3)^3$	$(PhO)_2PO_2H$	0:0:1
8	Grubbs-II		0:1:0[d]
9	$[Ir(cod)(PPh2Me)_2]PF_6$		1:0:0[d]
10	$[Ir(cod)(PPh2Me)_2]PF_6$	$(PhO)_2PO_2H$	1:0:0[d]
11	$RuHCl(CO)(PPh_3)_3$	HCO_2H	0:1:0
12	$RuHCl(CO)(PPh_3)_3$	AcOH	0:1:0
13	$RuHCl(CO)(PPh_3)_3$	TFA	1:0:3
14	$RuHCl(CO)(PPh_3)_3$	$B(OH)_3$	0:1:0
15	$RuHCl(CO)(PPh_3)_3$	$BF_3{\cdot}OEt_2$	0:0:1
16	$RuHCl(CO)(PPh_3)_3$	$Ti(O\text{-}iPr)_4$	0:1:0
17	$RuHCl(CO)(PPh_3)_3$	$Cu(OTf)_2$	0:0:1
18	$RuHCl(CO)(PPh_3)_3$	TfOH	0:0:1
19	$RuHCl(CO)(PPh_3)_3$	TsOH	0:0:1
20	$RuHCl(CO)(PPh_3)_3$	$(2,4\text{-}(NO_2)_2)C_6H_3SO_3H$	0:0:1

[a]Determined by RP-HPLC (215 nm). [b]Reaction mixtures were clean (>85% of **14**, **15**, and **16** in the reaction mixture) unless stated differently. [c]Solvent: *n*-PrOH. [d]Reaction temperature: 60 °C; complex reaction mixture.

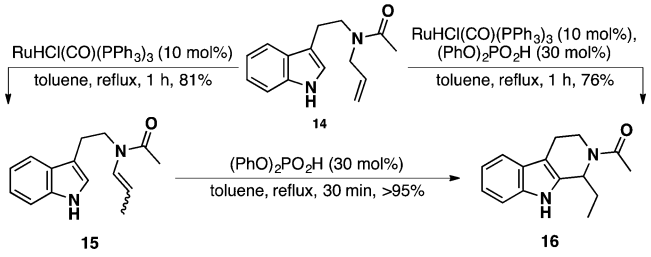
complex and the acid are necessary, but not sufficient, components of the overall catalytic transformation. The combination of $RuHCl(CO)(PPh_3)_3$ together with the phosphoric acid $(PhO)_2PO_2H$ proved to be most efficient and was chosen for further experiments. High reaction temperature (refluxing toluene) proved necessary, as experiments run at lower temperatures (e.g., 80 °C) gave mixtures of starting material **14**, enamide **15**, and THBC **16** after 41 h.

The results collected in Table 1 thus provided the opportunity to control the outcome of the reaction to be either the enamide **15** (81% isolated yield) or the THBC **16** (76% isolated yield) from amide **14**. Furthermore, it was possible to convert the isolated enamide **15** to THBC **16** in quantitative yield by treatment with catalytic amounts of acid (Scheme 2).

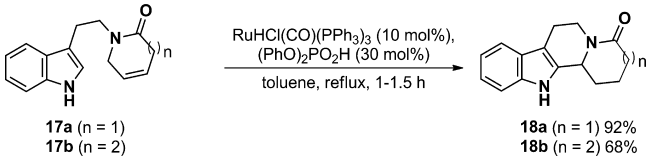
With the optimized reaction conditions in hand, the methodology was tested on the cyclic allylic amides **17a** and **17b**, and the tetracyclic THBCs **18a** and **18b** were isolated in good to excellent yields (92% and 68%, respectively, Scheme 3). These gratifying results showed that the generation of *N*-acyliminium ions occurs via isomerization and not tautomerization, thus significantly extending the scope of the chemistry shown in Figure 2. We believe that the present methodology provides a powerful tool for the target-oriented synthesis of complex molecules, including important natural products (Figure 1).

dx.doi.org/10.1021/jo402192s | J. Org. Chem. 2013, 78, 12545–12565

Scheme 2. Mechanistic Investigations of the Tandem Isomerization/Iminium Cyclization

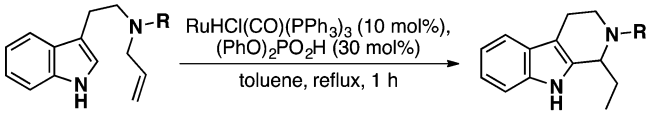


Scheme 3. Ru Hydride/Brønsted Acid-Catalyzed Synthesis of Tetracyclic THBCs



The scope of the reaction was then investigated, with focus on the influence of the electron-withdrawing *N*-substituent (Table 2). In most cases, the desired THBCs were isolated in high yields (70–96%), and the electronic properties of the amide did indeed prove to be important. When the *N*-substituent was a chloroacetyl group, the THBC **20f** was isolated (Table 2, entry 6) in 82% yield, whereas with more strongly electron-withdrawing groups (R = trichloroacetyl or trifluoroacetyl), the isomerization stopped at the enamide stage (Table 2, entries 7 and 8).

Table 2. Ru Hydride/Brønsted Acid-Catalyzed Synthesis of THBCs: Effect of the *N*-Substituent

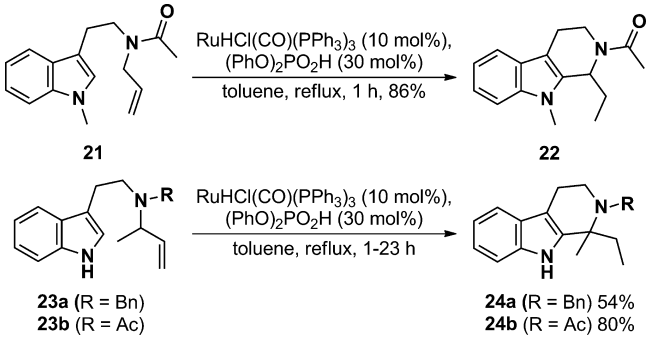


entry	substrate	R	product, yield[a] (%)
1	**19a**	$C(O)C_6H_{13}$	**20a**, 93
2	**19b**	C(O)Ph	**20b**, 93
3	**19c**	$C(O)(4\text{-}OMe)C_6H_4$	**20c**, 70
4	**19d**	$C(O)(4\text{-}NO_2)C_6H_4$	**20d**, 96
5	**19e**	C(O)OMe	**20e**, 93
6	**19f**	$C(O)CH_2Cl$	**20f**, 82
7	**19g**	$C(O)CCl_3$	**20g**, –[b,c]
8	**19h**	$C(O)CF_3$	**20h**, –[c,d]
9	**19i**	Boc	**20i**, 95
10	**19j**	Fmoc	**20j**, 82
11	**19k**	$P(O)(PhO)_2$	**20k**, 88
12	**19l**	S(O)*t*-Bu	**20l**, –[c,e]
13	**19m**	$S(O)_2Ph$	**20m**, 86
14	**19n**	C(O)NHPh	**20n**, –[c,e]
15	**19o**	$C(S)NH(4\text{-}NO_2)C_6H_4$	**20o**, –[c,e]

[a]Isolated yield after flash column chromatography. [b]Yield of enamide: 52%. [c]Reaction time: 23 h. [d]Yield of enamide: 87%. [e]No conversion of starting material.

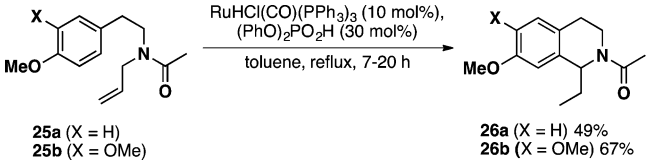
The methodology proved highly tolerant, and standard protecting groups such as Boc and Fmoc (Table 2, entries 9 and 10), as well as phosphoramidate (Table 2, entry 11) and sulfonamide (Table 2, entry 13), all survived. However, no conversion of starting material was observed with sulfinamide **19l** (Table 2, entry 12). Not unexpectedly, the urea **19n** and thiourea **19o** substrates (Table 2, entries 14 and 15) also proved to be recalcitrant, as they presumably function as metal catalyst scavengers.[9] Furthermore, an *N*-substituted indole **21** and two α-methylated allylic compounds (**23a** and **23b**) were successfully converted to the corresponding THBCs in good yields (Scheme 4, no acid was required for the formation of **24a**). The ease of formation of a quaternary stereocenter is noteworthy in the last two cases, and we shall return to the question of stereoselectivity later in this paper.

Scheme 4. Ru Hydride/Brønsted Acid-Catalyzed Synthesis of THBCs: *N*-Substituted Indole and Formation of Quaternary Centers



When applying the reaction conditions to other electron-rich aromatics, the 1,2,3,4-tetrahydroisoquinolines[10] **26a** and **26b** were isolated in moderate yields (49–67%, Scheme 5). In both cases, varying amounts of deallylated starting material were also isolated (9–19%).

Scheme 5. Ru Hydride/Brønsted Acid-Catalyzed Synthesis of 1,2,3,4-Tetrahydroisoquinolines



TANDEM SUZUKI CROSS-COUPLING/ISOMERIZATION/IMINIUM CYCLIZATION

Having recently demonstrated a tandem Tsuji–Trost allylation/isomerization/iminium cyclization sequence,[4b] we wished to explore the possibility of harnessing the isomerization/iminium cyclization cascade to other powerful catalytic transformations, our first choice being the Suzuki cross-coupling reaction (Figure 3).[11−13]

Upon variation of the reaction parameters (catalyst type and loading, ligand, base, solvent, temperature, and reaction time),[14] the best result was obtained using a combination of $Pd_2(dba)_3$, P(*t*-Bu)$_3$, and KF in THF. The Suzuki cross-coupling was carried out at room temperature for 24 h, whereupon toluene was added and the reaction mixture was heated at reflux for 24 h. THBC **32** was isolated in 18% yield (Scheme 6). This was increased slightly to 20% isolated yield

dx.doi.org/10.1021/jo402192s | J. Org. Chem. 2013, 78, 12545−12565

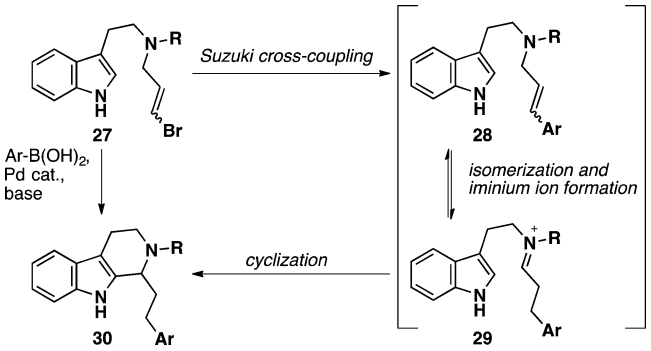
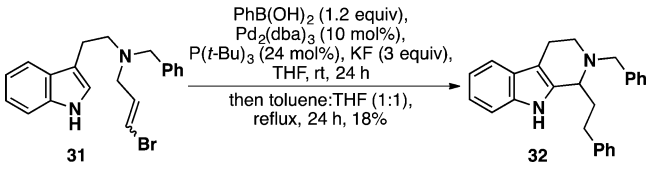


Figure 3. Strategy for the tandem Suzuki cross-coupling/isomerization/iminium cyclization.

with the addition of Wilkinson's catalyst (15 mol %) together with the toluene.

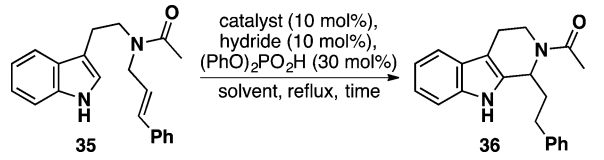
Scheme 6. Synthesis of THBC 32 via a Tandem Pd-Catalyzed Suzuki Cross-Coupling/Isomerization/Iminium Cyclization Sequence



The optimization experiments revealed that full conversion of the starting material occurred under the Suzuki conditions, implying that the low overall yields were due to problems later in the tandem sequence. Therefore, a stepwise synthesis of the desired THBCs was chosen for the next phase of the study. Based on previous experience,[4b] we performed a catalyst screen[14] for optimization of the transformation of the Suzuki products, and once again the combination of a ruthenium hydride catalyst with a phosphoric acid proved to be the most efficient system, i.e., 10 mol % of $RuHCl(CO)(PPh_3)_3$ and 30 mol % of $(PhO)_2PO_2H$ at 115 °C.[14] When bromide **31** was subjected to a range of commercially available boronic acids, using the optimized conditions, the Suzuki products were isolated in moderate yields (49–65%, Table 3). Generally, the bromide **31** was converted into the desired products **33a–k**, but also variable amounts of the diene resulting from homocoupling of **31** were obtained. For boronic acids containing a heterocycle (except furan) or a nitrogen or sulfur atom as a substituent on the aromatic ring, the Suzuki cross-coupling failed.[14] The relative reactivity of the (*E*)- and (*Z*)-alkenes was tested, but no significant difference in the reaction time was observed.[14] Generally, the desired THBCs could be isolated in quite moderate yields (38–71%, Table 3).

In order to expand the methodology of the Suzuki products into the *N*-acyl version of the isomerization/iminium cyclization sequence, amide **35** was exposed to the usual reaction conditions for the ruthenium hydride/Brønsted acid-catalyzed cyclization, providing a reaction mixture of starting amide **35** and THBC **36** of 92:8 (Table 4, entry 1). This was

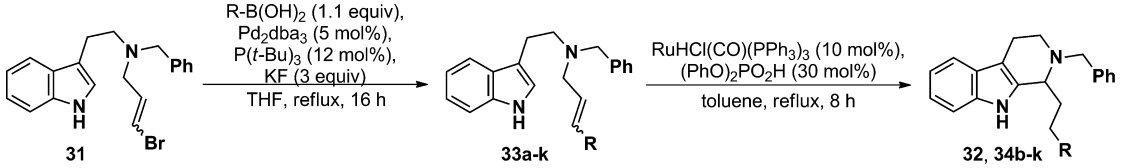
Table 4. Screening of Reaction Conditions for the Synthesis of THBC 36



entry	catalyst	solvent	hydride	time (h)	ratio **35**:**36** *a,b*
1	$RuHCl(CO)(PPh_3)_3$	toluene		22	92:8
2	$RuH_2(CO)(PPh_3)_3$	toluene		7	49:51
3	$RuHCl(CO)(PPh_3)_3$	toluene	$NaBH_4$	24	75:25
4	$RuHCl(CO)(PPh_3)_3$	*m*-xylene		31	0:100
5	$RuHCl(CO)(PPh_3)_3$	*m*-xylene	$NaBH_4$	3.5	0:100[c]

[a]Determined by RP-HPLC (215 nm). [b]Product mixtures were generally very clean (>85% of **35** and **36** in the reaction mixture). [c]Isolated yield 81%.

Table 3. Suzuki Cross-Coupling and Ru Hydride/Brønsted Acid-Catalyzed Synthesis of THBCs



entry	R	substrate, yield of cross coupling[a] (%)	product, yield of isomerization/iminium cyclization[a] (%)
1	Ph	**33a**, 65	**32**, 71
2	$(4\text{-Me})C_6H_4$	**33b**, 63	**34b**, 59
3	$(3\text{-Me})C_6H_4$	**33c**, 66	**34c**, 60
4	$(3,4\text{-}(OMe)_2)C_6H_3$	**33d**, 57	**34d**, 49
5	$(4\text{-}NO_2)C_6H_4$	**33e**, 49	**34e**, 60
6	$(3\text{-}NO_2)C_6H_4$	**33f**, 50	**34f**, 71
7	$(4\text{-}CF_3)C_6H_4$	**33g**, 59	**34g**, 53
8	$(4\text{-F})C_6H_4$	**33h**, 53	**34h**, 67
9	(6-OMe)-2-naphthyl	**33i**, 58	**34i**, 53
10	2-furyl	**33j**, 54	**34j**, 38
11	(*E*)-styryl	**33k**, 50	**34k**, 40

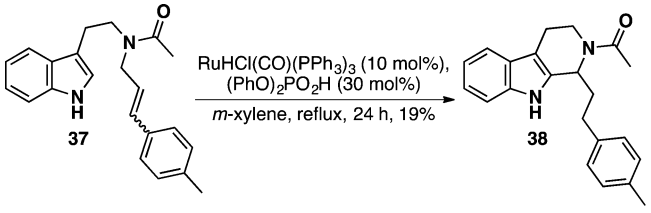
[a]Isolated yield after flash column chromatography.

dx.doi.org/10.1021/jo402192s | J. Org. Chem. 2013, 78, 12545–12565

improved to a ratio of 49:51 by using a ruthenium dihydride catalyst (Table 4, entry 2). However, this catalyst proved to be unstable toward storage, prompting the use of its in situ formation.[15] By addition of sodium borohydride (10 mol %) to the $RuHCl(CO)(PPh_3)_3$ catalyst and increasing the reaction temperature, full conversion of the starting amide **35** was obtained (Table 4, entry 5) and the product was isolated in a very good 81% yield. Other sources of hydride were investigated, such as DIBAL-H, $NaBH(OAc)_3$, and n-Bu_4NBH_4, but all proved less efficient than $NaBH_4$.

However, when the reaction conditions were applied to other Suzuki products, it quickly became obvious that full conversion of the allylic amides was difficult to achieve, as illustrated in Scheme 7, where THBC **38** was isolated in 19% yield, and no further optimization studies were conducted.[14]

Scheme 7. Ru Hydride/Brønsted Acid-Catalyzed Synthesis of THBC 38

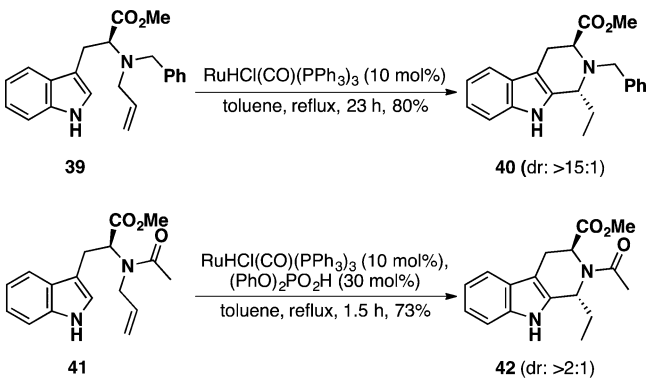


STEREOSELECTIVE SYNTHESIS

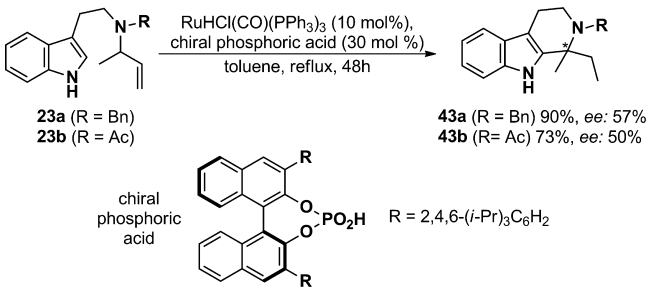
Several examples of diastereo- and enantioselective versions of Pictet–Spengler-type reactions have been reported.[2] The Cook group has observed that L-tryptophan esters can be used as directing groups in a substrate-controlled diastereoselective version of the classical Pictet–Spengler reaction.[2,16] When the substrates derived from L-tryptophan (**39** and **41**) were exposed to our isomerization/iminium cyclization sequence, the nature of the *N*-substituent proved important for the diastereoselectivity. When the substituent was benzyl, the THBC **40** was isolated in good yield (80%) and high dr (>15:1) was obtained, but when the substituent was acetyl (**42**) low dr (>2:1) was observed. In both cases, the thermodynamically more stable *trans* isomer was isolated (Scheme 8).[2,16]

In 1998, Nakagawa[17] reported the first enantioselective version of the Pictet–Spengler reaction using stoichiometric amounts of a chiral boron reagent. In 2004, Jacobsen[18] described the first catalytic enantioselective Pictet–Spengler reaction using a chiral thiourea catalyst, and in 2006, List[19] presented an enantioselective version using catalytic amounts of chiral phosphoric acids. Since chiral phosphoric acids have proved to be especially valuable as organocatalysts in combination with a metal catalyst,[20] it was decided to pursue an enantioselective version of the metal-catalyzed isomerization/iminium cyclization sequence. Our standard substrate, amide **14**, was exposed to many different reaction conditions, and the highest obtained ee was 18% by use of $RuHCl(CO)(PPh_3)_3$ as catalyst together with a chiral phosphoric acid.[14] You and co-workers[4c] have recently presented an enantioselective version of the RCM/isomerization/Pictet–Spengler cascade reaction catalyzed by a ruthenium alkylidene catalyst and a chiral phosphoric acid and showed that the steric bulk of the substituent adjacent to the nitrogen in the allylic system was crucial for the high enantioselectivity. In our preliminary investigation, the allylic compounds **23a** and **23b** were treated with $RuHCl(CO)(PPh_3)_3$ and a chiral phosphoric acid, affording the THBCs **43a** and **43b** in high yields (90% and 73%, respectively) and moderate enantioselectivities (57% and 50% ee, respectively, Scheme 9).

Scheme 8. Diastereoselective Substrate-Controlled Synthesis of THBCs



Scheme 9. Enantioselective Synthesis of THBC 43a and 43



CONCLUSION

In summary, we have developed an extension of our previous work on the RCM/isomerization/*N*-acyliminium cyclization sequence for the synthesis of TBHCs. The methodology relies on a ruthenium hydride/Brønsted acid-catalyzed isomerization for the formation of *N*-acyliminium ions, which are trapped by a tethered indole nucleophile. This approach represents an attractive alternative to the classical Pictet–Spengler reaction and also has great potential for applications in total synthesis. A tandem Suzuki cross-coupling/isomerization/iminium cyclization sequence was also examined, which generally was less efficient for the synthesis of THBC derivatives. Substrate-controlled stereoselective synthesis employing L-tryptophan derivatives gave modest to excellent diastereoselectivity, depending on the electronic nature of the *N*-substituent. Finally, an enantioselective version of the tandem process with a chiral phosphoric acid gave enantioselectivities of up to 57% ee, the best results being obtained for reactions in which a quaternary stereogenic center was formed.[21]

EXPERIMENTAL SECTION

General Experimental Methods. Unless otherwise stated, all reactions were run under an argon atmosphere. The glassware was dried over a Bunsen flame under vacuum before contact with any of the reactants or solvents. All flasks were equipped with a rubber septum, through which transport of chemicals, to or from the flask, was performed by use of needle-tipped syringes. All reactions were monitored by thin-layer chromatography (TLC), reversed-phase high-

dx.doi.org/10.1021/jo402192s | J. Org. Chem. 2013, 78, 12545–12565

performance liquid chromatography (RP-HPLC), and/or reversed-phase ultraperformance liquid chromatography mass spectrometry (RP-UPLC/MS).

All solvents were of HPLC quality or purified using an Innovative Technology PureSolv MD7 System. All commercially available reagents were used without further purification. In vacuo evaporation of solvents was performed using a rotary evaporator connected to a membrane pump at various temperatures.

All new compounds were characterized by melting point (mp), TLC, RP-HPLC, IR, ^{1}H NMR and ^{13}C NMR, MS (ESI), and HRMS (ESI), and whenever appropriate, optical rotation. Known compounds were characterized by TLC, RP-HPLC, ^{1}H NMR and ^{13}C NMR, and MS alone. Analytical TLC was conducted using Merck aluminum sheets covered with silica gel C-60 F_{254}. The plates were either visualized under UV light or stained by dipping in a developing agent followed by heating. $KMnO_4$ (3 g in H_2O (300 mL) along with K_2CO_3 (20 g) and 5% aqueous NaOH (5 mL)) and/or phosphomolybdic acid (PMA) (10 g in 200 mL of EtOH) were used as developing agents. Flash chromatography was performed using glass columns packed with Matrex 60 Å silica gel (35−70 μm particles), as stationary phase. The liquid phase is specified in the experimental procedures. Analytical HPLC was conducted using a Symmetry C-18 column (*d* 2.5 μm, 4.6 × 75 mm, column temp 25 °C flow 1 mL/min) with detection at 215 and 254 nm. Eluents A (0.1% TFA in H_2O) and B (0.1% TFA in MeCN) were used in a linear gradient (100% A to 100% B) in a run time of 13 min. Analytical chiral RP-HPLC was conducted on a CHIRALCEL OD-H column (*d* 5 μm, 4.6 × 250 mm, column temp 25 °C, flow 1 mL/min) using a constant eluent system (*i*-PrOH/hexane; 1:19) in a run time of 60 min.

The chemical shifts (δ) are reported in parts per million (ppm) and the coupling constants (*J*) in Hz. Usually, DMSO-d_6 and $CDCl_3$ were used as the solvent, and signal positions were measured relative to the signal for DMSO (δ 2.50 ppm for ^{1}H NMR and δ 39.43 ppm for ^{13}C NMR) and $CHCl_3$ (δ 7.26 ppm for ^{1}H NMR and δ 77.36 ppm for ^{13}C NMR). All measurements of optical rotation was conducted at approximately 20 °C, and the concentrations, *c*, are given in g/mL.

Analytical LC/MS (ESI) analysis was conducted on an AQUITY UPLC BEH C-18 column (*d* 1.7 μm, 2.1 × 50 mm; column temp 65 °C; flow: 0.6 mL/min). Eluents A (0.1% HCO_2H in H_2O) and B (0.1% HCO_2H in MeCN) were used in a linear gradient (5% B to 100% B) in a total run time of 2.6 min. The LC system was coupled to a SQD mass spectrometer. Analytical LC/HRMS (ESI) analysis was performed on an Luna C-18 column (*d* 3 μm, 2.1 × 50 mm; column temp 40 °C; flow: 0.4 mL/min). Eluents A (0.1% HCO_2H in H_2O) and B (0.1% HCO_2H in MeCN) were used in a linear gradient (20% B to 100% B) in a total run time of 15 min. The LC system was coupled to a Micromass LCT orthogonal time-of-flight mass spectrometer equipped with a Lock Mass probe operating in positive electrospray mode.

General Procedure I. Acylation of secondary amines A.

*N-Allyl-N-acetyltryptamine (**14**).* In a round-bottomed flask fitted with a magnetic stirring bar, acetyl chloride (183 mg, 165 μL, 2.33 mmol) was added to a stirred solution of *N*-allyltryptamine[4a] (405 mg, 2.02 mmol) and Et_3N (246 mg, 165 μL, 2.43 mmol) in CH_2Cl_2 (8 mL) at 0 °C. The reaction mixture was stirred at 0 °C and was monitored by TLC. Upon full conversion of the amine (5 min), the reaction was quenched with H_2O (10 mL). The reaction mixture was transferred to a separatory funnel with CH_2Cl_2 (10 mL). The organic layer was separated, and the aqueous phase was further extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layers were dried over Na_2SO_4 and evaporated to dryness in vacuo to give the title compound as a brown solid (481 mg, >95%): mp 74−76 °C; R_f = 0.30 (EtOAc; UV, $KMnO_4$); HPLC purity >95% (t_R = 7.56 min); IR (neat) cm^{-1} 3257, 2918, 1615, 1455, 1434, 1414, 1281; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.78 (s, 0.5H), 8.61 (s, 0.5H), 7.65 (d, *J* = 7.3 Hz, 0.5H), 7.56 (d, *J* = 7.3 Hz, 0.5H), 7.40−7.33 (m, 1H), 7.23−7.06 (m, 2H), 6.98 (dd, *J* = 9.2, 2.3 Hz, 1H), 5.90−5.58 (m, 1H), 5.24−4.95 (m, 2H), 4.05 (d, *J* = 5.9 Hz, 1H), 3.77 (dt, *J* = 4.7, 1.7 Hz, 1H), 3.65 (dd, *J* = 8.4, 6.8 Hz, 1H), 3.55 (dd, *J* = 8.2, 6.6 Hz, 1H), 3.02 (q, *J* = 7.3 Hz, 1H), 2.94 (q, *J* = 7.3 Hz, 1H), 2.10 (s, 1.5H), 1.96 (s, 1.5H), rotamers; ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2/170.9, 136.6/136.6, 133.8/133.2, 127.7/127.3, 122.7/122.4, 122.3/122.1, 119.7/119.4, 119.0/118.4, 117.4/116.7, 113.3/112.1, 111.8/111.5, 52.0/48.9, 48.2, 47.5, 24.9/24.0, 21.9/21.6, rotamers; HRMS (ESI) *m*/*z* calcd for $C_{15}H_{19}N_2O$ [M + H]$^+$ 243.1497, found 243.1493.

*N-Prop-1-en-1-yl-N-acetyltryptamine (**15**).* In a Schlenk tube fitted with a magnetic stirring bar and a reflux condenser, **14** (300 mg, 1.24 mmol) and $RuHCl(CO)(PPh_3)_3$ (118 mg, 0.12 mmol) were dissolved in toluene (12.4 mL). The reaction mixture was stirred at reflux, and progress was followed by TLC. Upon full conversion of the starting material (1 h), the reaction mixture was evaporated to dryness in vacuo. The residue was purified by flash column chromatography on silica gel (Et_3N/EtOAc/heptane 1:49:50) to give the title compound as a white solid (244 mg, 81%): mp 103−105 °C; R_f = 0.20 (EtOAc/heptane (1:1); UV, $KMnO_4$); HPLC purity >95% (t_R = 7.33 min); IR (neat) cm^{-1} 3208, 3186, 2919, 2875, 1623, 1411, 1261, 1103; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39 (s, 0.3H), 8.27 (s, 0.7H), 7.71 (d, *J* = 8.2 Hz, 0.7H), 7.58 (d, *J* = 7.6 Hz, 0.3H), 7.40−7.29 (m, 1H), 7.27−7.10 (m, 2H), 7.04 (d, *J* = 2.3 Hz, 0.7H), 6.97 (d, *J* = 2.3 Hz, 0.3H), 6.49 (dd, *J* = 13.9, 1.5 Hz, 1H), 5.21 (dq, *J* = 13.4, 6.6 Hz, 1H), 3.96−3.83 (m, 1.4H), 3.83−3.73 (m, 0.6H), 3.13−2.93 (m, 2H), 2.22 (s, 2H), 1.91 (s, 13H), 1.80 (dd, *J* = 6.6, 1.5 Hz, 1H), 1.76 (dd, *J* = 6.6, 1.5 Hz, 2H), rotamers; ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.3, 136.5, 128.7, 127.7/126.1, 122.7/122.4, 122.3/122.11, 119.8/118.4, 119.5/119.1, 113.3/111.8, 111.5, 108.5/106.7, 46.7/44.3, 23.5/23.0, 22.6/22.2, 15.9, rotamers; HRMS (ESI) *m*/*z* calcd for $C_{15}H_{19}N_2O$ [M + H]$^+$ 243.1497, found 243.1494.

General Procedure II. Formation of THBCs via tandem isomerization/*N*-acylimimium ion cyclization sequence.

*THBC **16**.* In a Schlenk tube fitted with a magnetic stirring bar and a reflux condenser, **14** (200 mg, 0.83 mmol), $RuHCl(CO)(PPh_3)_3$ (78.8 mg, 0.083 mmol), and $(PhO)_2PO_2H$ (62 mg, 0.35 mmol) were dissolved in toluene (8.3 mL). The reaction mixture was stirred at reflux, and progress was followed by TLC. Upon full conversion of the starting material (1 h), the reaction mixture was evaporated to dryness in vacuo. The residue was purified by flash column chromatography on silica gel (Et_3N/EtOAc/heptane 1:49:50) to give the title compound as a white powder (152 mg, 76%): mp 193−194 °C; R_f = 0.14 (EtOAc/heptane (1:1); UV, $KMnO_4$); HPLC purity >95% (t_R = 6.91 min); IR (neat) cm^{-1} 3245, 2968, 2929, 1633, 1614, 1448, 1425; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.78 (s, 0.8H), 8.49 (s, 0.2H), 7.47 (d, *J* = 7.5 Hz, 1H), 7.37−7.28 (m, 1H), 7.20−7.05 (m, 2H), 5.75 (dd, *J* = 8.8, 5.4 Hz, 1H), 4.09−3.94 (m, 1H), 3.51 (ddd, *J* = 14.1, 10.7, 5.7 Hz, 1H), 2.82 (dd, *J* = 11.0, 4.4 Hz, 2H), 2.28 (s, 2.4H), 2.19 (s, 0.6H), 2.03−1.60 (m, 2H), 1.10 (t, *J* = 7.5 Hz, 0.6H), 1.01 (t, *J* = 7.4 Hz, 2.4H), rotamers; ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.2, 136.4, 135.0/133.9, 126.9, 122.2/121.8, 119.9/119.6, 118.6/118.1, 111.4/111.2, 109.4/107.4, 55.7/50.6, 41.4/36.3, 28.7/27.8, 22.4, 22.3/21.3, 11.3/11.0, rotamers; HRMS (ESI) *m*/*z* calcd for $C_{15}H_{19}N_2O$ [M + H]$^+$ 243.1497, found 243.1491.

*THBC **16** from N-Prop-1-en-1-yl-N-acetyltryptamine (**15**).* In a Schlenk tube fitted with a magnetic stirring bar and a reflux condenser, **15** (50 mg, 0.21 mmol) and $(PhO)_2PO_2H$ (15.5 mg, 0.062 mmol) were dissolved in toluene (2.1 mL). The reaction mixture was stirred at reflux, and the reaction progress was monitored by TLC. Upon full conversion of the starting material (30 min), the reaction mixture was evaporated to dryness in vacuo. The residue was taken up in satd $NaHCO_3$ (aq) (15 mL) and CH_2Cl_2 (15 mL). The organic layer was separated, and the aqueous phase was further extracted with CH_2Cl_2 (15 mL). The combined organic layers were dried over Na_2SO_4 and evaporated to dryness in vacuo to give the title compound as a white powder (49 mg, >95%).

*1-(2-(1H-Indol-3-yl)ethyl)-3,6-dihydropyridin-2(1H)-one (**17a**).* In a round-bottomed flask fitted with a magnetic stirring bar, 3-butenoic acid (316 mg, 329 μL, 2.12 mmol), DCC (356 mg, 1.72 mmol), and *N*-hydroxysuccinimide were dissolved in CH_2Cl_2 (10 mL). The reaction mixture was stirred at rt for 4 h, whereupon *N*-allyltryptamine was added. The solution was stirred overnight, whereupon the reaction mixture was filtered through a pad of Celite, which was washed with Et_2O (3 × 25 mL) to remove the precipitated *N*,*N*′-dicyclohexylurea.

dx.doi.org/10.1021/jo402192s | J. Org. Chem. 2013, 78, 12545−12565

The organic layer was washed with 1 M HCl (aq) (25 mL), satd $NaHCO_3$ (aq) (25 mL), and brine (25 mL). The organic layer was dried over $MgSO_4$ and evaporated to dryness in vacuo. The residue was purified by flash column chromatography on silica gel (Et_3N/EtOAc/heptane 1:49:50), to give *N*-allyl-*N*-3-butenoyltryptamine as a clear oil (212 mg, 53%): R_f = 0.26 (EtOAc/heptane (1:1); UV, $KMnO_4$); HPLC purity >95% (t_R = 7.42 min); IR (neat) cm^{-1} 3223, 3054, 2918, 1769, 1607, 1433, 1244, 912, 743; ^1H NMR (300 MHz, $CDCl_3$) δ 8.18 (s, 0.5H), 8.09 (s, 0.5H), 7.67 (d, J = 7.8 Hz, 0.5H), 7.57 (d, J = 7.8 Hz, 0.5H), 7.37 (t, J = 8.3 Hz, 1H), 7.23−7.07 (m, 2H), 7.01 (dd, J = 12.6, 2.3 Hz, 1H), 6.11−5.65 (m, 2H), 5.21−5.04 (m, 3.5H), 4.95 (dq, J = 17.2, 1.6 Hz, 0.5H), 4.06 (d, J = 6.0 Hz, 1H), 3.81 (dt, J = 4.7, 1.7 Hz, 1H), 3.72−3.49 (m, 2H), 3.13 (dt, J = 6.6, 1.5 Hz, 1H), 3.06−2.95 (m, 3H), rotamers; ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.4,/171.2, 151.7, 136.6/133.9, 133.4/132.2, 127.8/127.4, 122.6/122.5, 122.3/122.3, 120.0/119.7, 119.2/118.6, 118.0/117.9, 117.5/117.0, 113.7/112.5, 111.7/111.4, 51.3/48.3, 48.0/47.6, 38.9/38.76, 25.9/25.0, rotamers; HRMS (ESI) m/z calcd for $C_{17}H_{21}N_2O$ $[M + H]^+$ 269.1654, found 269.1654.

In a Schlenk tube fitted with a magnetic stirring bar, *N*-allyl-*N*-3-butenoyltryptamine (150 mg, 0.56 mmol) and Grubbs second-generation catalyst (47.5 mg, 0.056 mmol) were dissolved in toluene (5.6 mL). The reaction mixture was stirred at 50 °C and was monitored by TLC. Upon full conversion of the starting material (1 h), the reaction mixture was evaporated to dryness in vacuo. The residue was purified by flash column chromatography on silica gel (Et_3N/EtOAc 1:99) to give the title compound as a gray-green solid (68 mg, 51%). Analytical data are in accordance with those previously reported:[22] R_f = 0.28 (Et_3N/EtOAc (1:99) ; UV, $KMnO_4$); HPLC purity >95% (t_R = 6.26 min); ^1H NMR (300 MHz, $CDCl_3$) δ 8.41 (s, 1H), 7.67 (d, J = 7.3 Hz, 1H), 7.37 (dd, J = 8.0, 0.9 Hz, 1H), 7.22−7.15 (m, 1H), 7.12 (ddd, J = 8.1, 7.1, 1.2 Hz, 1H) 7.03 (br s, 1H), 5.80−5.69 (m, 1H), 5.68−5.59 (m, 1H), 3.84 (tdd, J = 4.9, 3.0, 2.0 Hz, 2H), (dd, J = 8.2, 6.9 Hz, 2H), 3.08 (dd, J = 8.5, 6.6 Hz, 2H), 3.00 (tdd, J = 5.1, 3.4, 1.9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.4, 136.6, 127.7, 122.8, 122.4, 122.2, 121.2, 119.6, 119.0, 113.2, 111.6, 49.9, 48.1, 32.6, 23.2; MS (ESI) m/z calcd for $C_{15}H_{17}N_2O$ $[M + H]^+$ 241.1, found 241.2.

1-(2-(1H-Indol-3-yl)ethyl)-1,3,4,7-tetrahydro-2H-azepin-2-one (17b). In a round-bottomed flask fitted with a magnetic stirring bar, 4-pentenoyl chloride (259 mg, 241 μL, 2.18 mmol) was added to a stirred solution of *N*-allyltryptamine (380 mg, 1.90 mmol) and Et_3N (230 mg, 218 μL, 2.28 mmol) in CH_2Cl_2 (12 mL) at 0 °C. The reaction was stirred at 0 °C and was followed by TLC. Upon full conversion of the amine (5 min), the reaction was quenched with H_2O (20 mL). The reaction mixture was transferred to a separatory funnel with CH_2Cl_2 (20 mL). The organic layer was separated, and the aqueous phase was further extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were dried over Na_2SO_4 and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel (Et_3N/EtOAc/heptane 1:49:50) to give *N*-allyl-*N*-4-pentenoyltryptamine as a yellow oil (458 mg, 85%): R_f = 0.31 (EtOAc/heptane (1:1); HPLC purity >95% (t_R = 7.97 min); IR (neat) cm^{-1} 3271, 1617, 1416, 1339, 1224; ^1H NMR (300 MHz, $CDCl_3$) δ 8.37 (s, 0.5H), 8.26 (s, 0.5H), 7.69−7.62 (m, 0.5H), 7.61−7.54 (m, 0.5H), 7.41−7.33 (m, 0.5H), 7.25−7.07 (m, 2H), 7.00 (dd, J = 10.5, 2.3 Hz, 1H), 5.98−5.64 (m, 2H), 5.24−5.06 (m, 2H), 5.06−4.87 (m, 2H), 4.06 (d, J = 5.9 Hz, 1H), 3.81 (dt, J = 4.7, 1.7 Hz, 1H), 3.65 (dd, J = 8.6, 6.8 Hz, 1H), 3.57 (dd, J = 8.2, 6.6 Hz, 1H), 3.08−2.96 (m, 2H), 2.49−2.38 (m, 2H), 2.34−2.24 (m, 2H), rotamers; ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.7/172.5, 138.0/137.8, 136.6/136.6, 134.0/133.4, 127.8/127.3, 122.5, 122.3/122.2, 119.9/119.6, 119.1/118.5, 117.3/116.8, 115.4/115.4, 113.6/112.4, 111.8/111.5, 51.1/48.4, 48.0/47.7, 32.7/32.5, 29.7/29.6, 25.1/24.0, rotamers; MS (ESI) m/z calcd for $C_{17}H_{22}N_2O$ $[M + H]^+$ 283.1810, found 283.1810.

In a Schlenk tube fitted with a magnetic stirring bar, *N*-allyl-*N*-4-pentenoyltryptamine (150 mg, 0.53 mmol) and Grubbs second-generation catalyst (45.0 mg, 0.053 mmol) were dissolved in toluene (5.3 mL). The reaction mixture was stirred at 50 °C and was followed by TLC. Upon full conversion of the starting material (1 h), the reaction mixture was evaporated to dryness in vacuo. The residue was purified by flash column chromatography on silica gel (EtOAc) to give the title compound as a green oil (119 mg, 88%): R_f = 0.28 (EtOAc; UV, $KMnO_4$); HPLC purity >95% (t_R = 6.64 min); IR (neat) cm^{-1} 3233, 1623, 1489, 1458, 1431; ^1H NMR (300 MHz, $CDCl_3$) δ 8.77 (s, 1H), 7.66 (d, J = 7.5 Hz, 1H), 7.35 (d, J = 7.8 Hz, 1H), 7.18 (td, J =7.5, 1.2 Hz 1H), 7.12 (td, J = 7.5, 1.1 Hz, 1H), 6.97 (s, 1H), 5.74−5.54 (m, 2H), 3.80−3.70 (m, 4H), 2.99 (t, J = 7.8 Hz 2H), 2.83−2.64 (t, J = 6.6 Hz 2H), 2.43−2.33 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.8, 136.6, 131.4, 127.6, 124.7, 122.6, 121.9, 119.3, 118.8, 112.9, 111.6, 49.8, 47.1, 34.0, 25.3, 24.5; HRMS (ESI) m/z calcd for $C_{16}H_{19}N_2O$ $[M + H]^+$ 255.1497, found 255.1491.

THBC 18a. Following general procedure II, the reaction of **17a** (50 mg, 0.21 mmol), $RuHCl(CO)(PPh_3)_3$ (19.9 mg, 0.021 mmol), and $(PhO)_2PO_2H$ (15.6 mg, 0. 062 mmol) gave, after purification by flash column chromatography on silica gel (Et_3N/EtOAc 1:99), the title compound as a white solid (46 mg, 92%). Analytical data are in accordance with those previously reported:[23] R_f = 0.13 (Et_3N/EtOAc (1:99); UV, $KMnO_4$); HPLC purity >95% (t_R = 6.11 min); ^1H NMR (300 MHz, $CDCl_3$) δ 8.18 (s, 1H), 7.51 (d, J = 7.4 Hz, 1H), 7.34 (dd, J = 7.6, 1.2 Hz, 1H), 7.18 (td, J = 7.2, 1.2 Hz, 1H), 7.15−7.09 (td, J = 7.5,1.2 Hz, 1H), 5.22−5.13 (m, 1H), 4.82−4.74 (m, 1H), 2.93−2.73 (m, 3H), 2.67−2.30 (m, 3H), 2.03−1.66 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6, 136.5, 133.7, 127.2, 122.4, 120.1, 118.7, 111.3, 109.9, 54.7, 40.5, 32.8, 29.4, 21.4, 19.7; MS (ESI) m/z calcd for $C_{15}H_{17}N_2O$ $[M + H]^+$ 241.1, found 241.2.

THBC 18b. Following general procedure II, the reaction of **17b** (90 mg, 0.35 mmol), $RuHCl(CO)(PPh_3)_3$ (33.8 mg, 0.035 mmol), and $(PhO)_2PO_2H$ (26.6 mg, 0.11 mmol) gave, after purification by flash column chromatography on silica gel (Et_3N/EtOAc 1:99), the title compound as a light brown solid (61 mg, 68%): mp 141−145 °C; R_f = 0.31 (EtOAc; UV, $KMnO_4$); HPLC purity 78% (t_R = 6.70 min); IR (neat) cm^{-1} 3154, 2921, 1614, 1428, 1355, 1299, 1187, 1174; ^1H NMR (300 MHz, $CDCl_3$) δ 8.63 (s, 05H), 8.31 (s, 0.5H), 7.70−7.60 (m, 0.5H), 7.51 (d, J = 7.4 Hz, 0.5H), 7.39−7.30 (m, 1H), 7.23−7.07 (m, 1.5H), 7.03 (d, J = 2.4 Hz, 0.5H), 6.20 (dt, J = 12.1, 5.1 Hz, 0.5H), 6.03 (dt, J = 12.0, 1.5 Hz, 0.5H), 5.00−4.89 (m, 1H), 3.87−3.68 (m, 1H), 3.33−3.25 (m, 1H), 3.13−2.92 (m, 1H), 2.91−2.70 (m, 2H), 2.68−2.57 (m, 1H), 2.34−2.13 (m, 1H), 2.10−1.51 (m, 4H), rotamers; ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.8/168.9, 138.5/136.7, 133.3, 127.3/126.8, 122.4, 122.3/122.2, 119.9/119.6, 119.0/118.6, 111.5/111.3, 54.7/54.6, 49.6/48.4, 38.0/36.9, 33.7/29.3, 28.8/28.3, 24.6, 23.8/21.2, rotamers; HRMS (ESI) m/z calcd for $C_{16}H_{19}N_2O$ $[M + H]^+$ 255.1497, found 255.1497.

General Procedure III. Acylation of secondary amines B.

N-Allyl-N-hepanoyltryptamine (19a). In a round-bottomed flask fitted with a magnetic stirring bar, heptanoyl chloride (316 mg, 329 μL, 2.12 mmol) was added to a stirred solution of *N*-allyltryptamine (370 mg, 1.85 mmol) and Et_3N (224 mg, 309 μL, 2.22 mmol) in CH_2Cl_2 (14 mL) at 0 °C. The solution was stirred at 0 °C, and the reaction was monitored by TLC. Upon full conversion of the amine (5 min), the reaction was quenched with H_2O (20 mL). The reaction mixture was transferred to a separatory funnel with CH_2Cl_2 (20 mL). The organic layer was separated, and the aqueous phase was further extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were dried over Na_2SO_4 and evaporated to dryness in vacuo. The residue was purified by flash column chromatography on silica gel (Et_3N/EtOAc/heptane 1:34:65) to give the title compound as a white solid (469 mg, 81%): mp 85−86 °C; R_f = 0.17 (EtOAc/heptane (7:13); UV, $KMnO_4$); HPLC purity >95% (t_R = 9.25 min); IR (neat) cm^{-1} 3219, 2928, 1610, 1454, 1439, 1171; ^1H NMR (300 MHz, $CDCl_3$) δ 8.60 (s, 0.5H), 8.45 (s, 0.5H), 7.67 (d, J = 7.8 Hz, 0.5H), 7.58 (d, J = 7.7 Hz, 0.5H), 7.40−7.33 (m, 1H), 7.24−7.05 (m, 2H), 6.98 (dd, J = 8.5, 2.3 Hz, 1H), 5.91−5.61 (m, 1H), 5.24−5.09 (m, 2H), 4.07 (d, J = 5.9 Hz, 1H), 3.81 (d, J = 4.8 Hz, 1H), 3.65 (dd, J = 8.6, 6.8 Hz, 1H), 3.58 (dd, J = 8.2, 6.6 Hz, 1H), 3.02 (dd, J = 14.6, 6.3 Hz, 2H), 2.31 (t, J = 7.8 Hz 1H), 2.19 (t, J = 7.5 Hz. 1H), 1.74−1.64 (m, 1H), 1.61−1.49 (m, 1H), 1.45−1.14 (m, 6H), 1.00−0.80 (m, 3H), rotamers; ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.7/173.6, 136.7/136.6, 134.1/133.6, 127.8/127.4, 122.6/122.4, 122.4/122.1, 119.7/119.5,

dx.doi.org/10.1021/jo402192s | J. Org. Chem. 2013, 78, 12545−12565

119.1/118.5, 117.2/116.7, 113.5/112.3, 111.8/111.5, 51.2/48.3, 48.1/47.6, 33.5/33.2, 32.0,/31.9, 29.5/29.4, 25.7/25.7, 25.1/24.0, 22.9/22.8, 14.4/14.4, rotamers; MS (ESI) m/z calcd for $C_{20}H_{29}N_2O$ $[M + H]^+$ 313.2280, found 313.2269.

*N-Allyl-N-benzoyltryptamine (**19b**).* Following general procedure III, the reaction of *N*-allyltryptamine (390 mg, 1.95 mmol), benzoyl chloride (315 mg, 260 μL, 2.24 mmol), and Et_3N (236 mg, 326 μL, 2.34 mmol) gave, after purification by flash column chromatography on silica gel (Et_3N/EtOAc/heptane 1:49:50), the title compound as a white solid (528 mg, 89%): mp 124−126 °C; R_f = 0.30 (EtOAc/heptane (1:1) UV, $KMnO_4$); HPLC purity >95% (t_R = 7.98 min); IR (neat) cm^{-1} 3186, 2929, 2877, 1573, 1450, 1298; ^1H NMR (300 MHz, $CDCl_3$) δ 8.37 (s, 1H), 7.62 (d, J = 7.4 Hz, 0.5H), 7.41−6.98 (m, 8H), 6.93−6.83 (m, 1H), 6.68 (s, 0.5H), 6.02−5.71 (m, 0.5H), 5.71−5.43 (m, 0.5H), 5.34−4.90 (m, 2H), 4.18 (d, J = 5.2 Hz, 1H), 3.72 (t, J = 7.4 Hz, 1H), 3.65 (d, J = 4.3 Hz, 1H), 3.43 (t, J = 7.2 Hz 1H), 3.08 (t, J = 7.3 Hz, 1H), 2.82 (t, J = 7.2 Hz, 1H), rotamers; ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4/172.2, 136.9, 136.6, 133.8/133.7, 129.8/129.5, 128.7, 126.8, 126.7, 122.65 122.2, 119.5, 119.1/118.5, 117.8, 113.3/112.0, 111.6, 52.7/49.4, 47.7/46.3, 25.0/23.5, rotamers; MS (ESI) m/z calcd for $C_{20}H_{21}N_2O$ $[M + H]^+$ 305.2, found 305.4.

*N-Allyl-N-(4-methoxy)benzoyltryptamine (**19c**).* Following general procedure III, the reaction of *N*-allyltryptamine (155 mg, 0.77 mmol), 4-methoxybenzoyl (152 mg, 120 μL, 0.89 mmol), and Et_3N (94 mg, 130 μL, 0.93 mmol) gave, after purification by flash column chromatography on silica gel (Et_3N/EtOAc/heptane 1:49:50), the title compound as a white powder (212 mg, 82%): mp 114−116 °C; R_f = 0.22 (EtOAc/heptane (1:1) UV, $KMnO_4$); HPLC purity >95% (t_R = 7.89 min); IR (neat) cm^{-1} 3186, 2927, 1603, 1439, 1246; ^1H NMR (500 MHz, $CDCl_3$) δ 8.86 (s, 1H), 7.53−6.62 (m, 9H), 5.85 (d, J = 131.1 Hz, 1H), 5.42−5.05 (m, 2H), 4.28 (br s, 1H) 3.81 (s, 3H), 3.67−3.52 (m, 1H), 3.34−2.87 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 160.7, 136.6, 133.8, 128.9, 128.6, 127.6, 122.6, 121.9, 119.2, 118.9, 117.6, 113.8, 112.9, 111.6, 55.5, 52.7, 49.5, 47.8, 46.6, 24.8, 23.4; MS (ESI) m/z calcd for $C_{21}H_{23}N_2O_2$ $[M + H]^+$ 335.1760, found 335.1765.

*N-Allyl-N-(4-nitro)benzoyltryptamine (**19d**).* Following general procedure III, the reaction of *N*-allyltryptamine (175 mg, 0.87 mmol), 4-nitrobenzoyl (187 mg, 1.00 mmol), and Et_3N (106 mg, μL, 1.05 mmol) gave, after purification by flash column chromatography on silica gel ($E_{t3}N$/EtOAc/heptane 1:49:50), the title compound as a yellow powder (108 mg, 72%): mp 115−117 °C; R_f = 0.24 (EtOAc/heptane (1:1) UV, $KMnO_4$); HPLC purity >95% (t_R = 8.01 min); IR (neat) cm^{-1} 3181, 2924, 1599, 1523, 1430, 1335; ^1H NMR (300 MHz, $CDCl_3$) δ 8.23 (d, J = 8.6 Hz, 1H), 8.15 (s, 1H), 7.85 (d, J = 8.6 Hz, 0.5H), 7.70 (d, J = 7.5 Hz, 1H), 7.50 (d, J = 8.7 Hz, 1H), 7.36 (dd, J = 14.2, 8.2 Hz, 1H), 7.27−7.07 (m, 2H), 6.97 (d, J = 8.5 Hz, 1.5H), 6.87 (t, J = 7.3 Hz, 1H), 6−04−5.91 (m, 0.5H), 5.79−5.45 (m, 0.5H), 5.43−5.27 (m, 1H), 5.22 (d, J = 10.4 Hz, 0.5H), 5.13 (d, J = 17.1 Hz, 0.5H), 4.29 (d, J = 6.0 Hz, 1H), 3.83 (t, J = 7.5 Hz, 1H), 3.66 (d, J = 4.9 Hz, 1H), 3.55 (t, J = 6.5 Hz, 1H), 3.19 (t, J = 7.4 Hz, 1H), 2.91 (t, J = 6.5 Hz, 1H), rotamers; ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1/169.9, 148.4/147.7, 142.9/142.2, 136.5/136.5, 133.0/132.9, 127.7/127.4, 124.9/123.4, 122.9/122.5, 122.4/122.3, 119.6/119.6, 118.9/118.5, 118.2/117.9, 112.8, 111.7/111.3, 52.4/48.8, 47.3/46.6, 24.3/23.4, rotamers; HRMS (ESI) m/z calcd for $C_{20}H_{20}N_3O_3$ $[M + H]^+$ 350.1505, found 350.1504.

*Methyl (2-(1H-Indol-3-yl)ethyl)(allyl)carbamate (**19e**).* Following general procedure I, the reaction of *N*-allyltryptamine (285 mg, 1.42 mmol), methyl chloroformate (187 mg, 127 μL, 1.71 mmol), and Et_3N (173 mg, 238 μL, 1.42 mmol) gave, after aqueous workup, the title compound as a yellow powder (108 mg, 89%): mp 81−83 °C; R_f = 0.34 (EtOAc/heptane (1:1) UV, $KMnO_4$); HPLC purity >95% (t_R = 7.82 min); IR (neat) cm^{-1} 3309, 2925,1679, 1474, 1456, 1434, 1404, 1338, 1233; ^1H NMR (300 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.54 (br s, 1H), 7.28 (d, J = 7.9 Hz, 1H), 7.09 (dt, J = 21.0, 7.0 Hz, 2H), 6.93 (br s, 1H), 5.70 (br s, 1H), 5.05 (d, J = 11.0 Hz, 2H), 3.77 (d, J = 15.8 Hz, 2H), 3.64 (s, 3H), 3.45 (br s, 2H), 2.93 (br s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.2, 136.6, 134.0, 127.5, 122.3, 122.0, 119.3, 118.8, 117.1/116.6, 112.84, 111.52, 52.8, 50.4/50.1, 48.3/47.3, 24.8/24.2, rotamers; MS (ESI) m/z calcd for $C_{15}H_{19}N_2O_2$ $[M + H]^+$ 259.1447, found 259.1446.

*N-Allyl-N-(chloroacetyl)tryptamine (**19f**).* Following general procedure I, the reaction of *N*-allyltryptamine (70 mg, 0.35 mmol), chloroacetyl chloride (45 mg, 32 μL, 0.40 mmol), and Et_3N (42 mg, 59 μL, 0.42 mmol) gave, after aqueous workup, the title compound as a brown oil (92 mg, 95%): R_f = 0.09 (EtOAc/heptane (1:3); UV, $KMnO_4$); HPLC purity >95% (t_R = 7.45 min); IR (neat) cm^{-1} 3294, 2918, 1637, 1456, 1418, 742; ^1H NMR (300 MHz, $CDCl_3$) δ 8.49 (s, 0.5H), 8.35 (s, 0.5H), 7.57 (d, J = 7.7 Hz, 0.5H), 7.47 (d, J = 7.7 Hz, 0.5H), 7.37−7.21 (t, J = 5.1 Hz, 1H), 7.22−6.97 (m, 2H), 6.93 (d, J = 1.9 Hz, 0.5H), 6.88 (d, J = 2.3 Hz, 0.5H), 5.80−5.58 (m, 1H), 5.19−4.98 (m, 2H), 3.97 (s, 2H), 3.71 (dt, J = 4.9, 1.6 Hz, 1H), 3.64−3.40 (m, 3H), 3.00−2.91 (m, 2H), rotamers; ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1/167.0, 136.6, 132.9/132.8, 127.6/127.0, 122.9/122.6, 122.2, 120.0/119.6, 118.9/117.4 118.3/117.9, 112.8/111.9, 112.7/111.61, 51.5/38.1, 48.5/48.4, 41.8/41.2, 24.8/23.6, rotamers; HRMS (ESI) m/z calcd for $C_{15}H_{17}ClN_2NaO$ $[M + Na]^+$ 299.0927, found 299.0925.

*N-Allyl-N-(trichloroacetyl)tryptamine (**19g**).* Following general procedure I, the reaction of *N*-allyltryptamine (125 mg, 0.62 mmol), trichloroacetyl chloride (131 mg, 80 μL, 0.72 mmol), and Et_3N (76 mg, 105 μL, 0.75 mmol) gave, after aqueous workup, the title compound as a brown oil (202 mg, 94%): R_f = 0.31 (EtOAc/heptane (1:3); UV, $KMnO_4$) HPLC purity >95% (t_R = 9.32 min); IR (neat) cm^{-1} 3357, 3317, 2960, 2931, 1662, 1415, 1218, 811; ^1H NMR (300 MHz, $CDCl_3$) δ 8.44 (s, 0.3H), 8.36 (s, 0.7H), 7.69 (d, J = 7.7 Hz, 0.7H), 7.58 (d, J = 7.3 Hz, 0.3H), 7.38 (d, J = 7.9 Hz, 1H), 7.25−7.11 (m, 2H), 7.02 (d, J = 2.3 Hz, 1H), 6.07−5.66 (m, 1H), 5.40−5.07 (m, 2H), 4.18 (d, J = 5.5 Hz, 2H), 4.01 (t, J = 7.5 Hz, 0.6H), 3.68 (t, J = 13H), 3.29−2.99 (m, 2H), rotamers; ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.0/160.5, 136.5, 132.4/131.8, 127.5/127.2, 122.7, 122.3, 119.7/119.6, 119.0, 118.6/118.3, 112.5, 111.6, 93.51, 53.4/49.4, 45.9, 24.2/22.6, rotamers; MS (ESI) m/z calcd for $C_{15}H_{16}N_2OCl_3$ $[M + H]^+$ 345.0328, found 345.0300.

*N-Allyl-N-(trifluoroacetyl)tryptamine (**19h**).* In a round-bottomed flask fitted with a magnetic stirring bar, TFAA (1.15 g, 63 μL, 5.49 mmol) was added to a stirred solution of *N*-allyltryptamine (275 mg, 1.37 mmol) in CH_2Cl_2 (14 mL) at 0 °C. The reaction mixture was stirred at 0 °C and was monitored by TLC. Upon full conversion of the amine (4 h), the reaction was quenched with satd $NaHCO_3$ (aq) (10 mL). The reaction mixture was transferred to a separatory funnel, and the organic layer was separated. The aqueous phase was further extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with H_2O (10 mL), dried over Na_2SO_4, and evaporated to dryness in vacuo to give the title compound as a brown solid (373 mg, 92%): R_f = 0.48 (EtOAc/heptane (1:1) UV, $KMnO_4$); HPLC purity >95% (t_R = 8.61 min); IR (neat) cm^{-1} 3320, 1673, 1455, 1342, 1196, 1179, 1142, 1099; 3^1H NMR (300 MHz, $CDCl_3$) δ 8.22 (s, 0.5H), 8.16 (s, 0.5H), 7.56 (d, J = 7.8 Hz, 0.5H), 7.47 (d, J = 7.8 Hz, 0.5H), 7.32−7.22 (m, 1H), 7.18−7.00 (m, 2H), 6.91 (dd, J = 4.2, 2.4 Hz, 1H), 5.78−5.54 (m, 1H), 5.15 (td, J = 10.4, 1.2 Hz, 1H), 5.11−4.99 (m, 1H), 4.01 (d, J = 5.9 Hz, 1H), 3.75 (d, J = 5.7 Hz, 1H), 3.73 (t, J = 7.8 Hz, 2H), 3.06−2.88 (t, J = 7.8 Hz 2H), rotamers; ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.4/156.9, 136.6, 132.3/131.5, 127.5/127.2, 122.6/122.5, 122.5/122.5, 112.0/119.8, 119.4, 119.0/118.9, 118.5, 112.5, 111.8/111.6, 51.1/49.8, 48.2/48.0, 25.3/23.0, rotamers; HRMS (ESI) m/z calcd for $C_{15}H_{16}F_3N_2O$ $[M + H]^+$ 297.1215, found 297.1216.

*N-Allyl-N-Boc-tryptamine (**19i**).* In a round-bottomed flask fitted with a magnetic stirring bar, Boc_2O (432 mg, 1.98 mmol) was added to a stirred solution of *N*-allyltryptamine (330 mg, 1.65 mmol) and Et_3N (233 mg, 322 μL, 2.31 mmol) in CH_2Cl_2 (7 mL) at 0 °C. The solution was stirred at 0 °C, and the reaction was followed by TLC. Upon full conversion of the amine (5 min), the reaction mixture was evaporated to dryness in vacuo. The residue was purified by flash column chromatography on silica gel (Et_3N/EtOAc/heptane 1:24:75), to give the title compound as a yellow oil (438 mg, 88%): R_f = 0.16 (EtOAc/heptane (1:3); UV, $KMnO_4$); HPLC purity >95% (t_R = 9.18 min); IR (neat) cm^{-1} 3305, 1662, 1477, 1416, 1248; ^1H NMR (300 MHz, $CDCl_3$) δ 8.23 (s, 1H), 7.64 (d, J = 7.7 Hz, 1H), 7.36 (d, J = 8.0

Hz, 1H), 7.20 (t, J = 7.4 Hz, 1H), 7.13 (t, J = 7.4 Hz, 1H), 6.99 (s, 1H), 5.86−5.73 (m, 1H), 5.12 (d, J = 13.9 Hz, 2H), 3.86 (br s, 2H), 3.49 (br s, 2H), 3.00 (br s, 2H), 1.45 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.9, 136.6, 134.6, 127.7, 122.3, 122.1, 119.4, 118.9, 116.7, 113.4, 111.5, 79.8, 49.8, 47.6, 28.9, 24.7; HRMS (ESI) m/z calcd for $C_{18}H_{24}N_2NaO_2$ $[M + Na]^+$ 323.1735, found 323.1735.

*N-Allyl-N-Fmoc-tryptamine (**19j**).* In a round-bottomed flask fitted with a magnetic stirring bar, FmocCl (267 mg, 1.03 mmol) was added to a stirred solution of *N*-allyltryptamine (207 mg, 1.03 mmol) and K_2CO_3 (186 mg, 1.34 mmol) in CH_2Cl_2/H_2O (1:1, 20 mL) at rt. The reaction mixture was stirred at rt and was monitored by TLC. Upon full conversion of the amine (30 min), the organic layer was separated. The organic layer was washed with satd $NaHCO_3$ (aq) (10 mL), 0.1 M HCl (aq) (10 mL), H_2O (5 mL), and brine (5 mL). The organic layer was dried over Na_2SO_4 and evaporated to dryness in vacuo to give the title compound as brown solid (361 mg, 83%): R_f = 0.21 (EtOAc/heptane (1:3); UV, $KMnO_4$); HPLC purity 91% (t_R = 10.11 min); IR (neat) cm^{-1} 3187, 3049, 2919, 1606, 1447, 727; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.77−7.62 (m, 2H), 7.53 (t, J = 7.6 Hz, 2H), 7.46−7.17 (m, 7H), 7.16−6.81 (m, 2H), 5.82−5.42 (m, 1H), 5.12−4.86 (m, 2H), 4.40 (t, J = 10.0 Hz, 2H), 4.27−4.02 (m, 1H), 3.83−3.61 (m, 2H), 3.60−3.25 (dt J = 43.8, 1.8 Hz, 2H), 2.83 (dt, J = 65.6, 7.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.5/156.3, 144.4, 141.7, 136.5, 134.0, 127.9/127.9, 127.4/127.4, 125.3/125.2, 125.0, 122.3/122.2, 120.4/120.3, 119.7, 119.7/119.0, 117.3/116.8, 111.5, 67.5/67.2, 65.5, 50.7/50.5, 47.8, 24.7/24.3, rotamers; MS (ESI) m/z calcd for $C_{28}H_{26}N_2NaO_2$ $[M + Na]^+$ 445.1892, found 445.1862.

*Diphenyl (2-(1H-Indol-3-yl)ethyl)(allyl)phosphoramidate (**19k**).* Following general procedure III, the reaction of *N*-allyltryptamine (245 mg, 1.22 mmol), diphenyl chloridophosphate (378 mg, 1.41 mmol), and Et_3N (149 mg, 205 μL, 1.47 mmol) gave, after purification by flash column chromatography on silica gel (Et_3N/EtOAc/heptane 1:24:75), the title compound as an off-white solid (345 mg, 65%): mp 108−109 °C; R_f = 0.07 (EtOAc/heptane (1:3); HPLC purity >95% (t_R = 9.47 min); IR (neat) cm^{-1} 3263, 2922, 1591, 1485, 1456, 1314, 1246, 1170, 923; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.49 (d, J = 7.8 Hz, 1H), 7.30−7.22 (m, 5H), 7.22−7.16 (m, 5H), 7.14−7.00 (m, 3H), 6.84 (d, J = 2.3 Hz, 1H), 5.56 (ddt, J = 16.3, 10.0, 6.4 Hz, 1H), 5.18−4.95 (m, 2H), 3.79 (dd, J = 11.2, 6.4 Hz, 2H), 3.48−3.27 (m, 2H), 2.94−2.64 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.2/151.1, 136.5, 134.6/134.5, 129.9, 127.5, 125.1, 122.3/122.2, 120.5/120.4, 119.5, 118.9, 118.7, 112.9, 111.5, 49.3/49.3, 46.4/46.3, 24.7/24.7, rotamers; HRMS (ESI) m/z calcd for $C_{25}H_{26}N_2O_3P$ $[M + H]^+$ 433.1681, found 433.1679.

*N-Allyl-N-tert-butylsulfinamide−Tryptamine (**19l**).* In a round-bottomed flask fitted with a magnetic stirring bar, *tert*-butylsulfinyl chloride (61 mg, 54 μL, 0.44 mmol) was added to a stirred suspension of *N*-allyltryptamine (87 mg, 0.44 mmol) and K_2CO_3 (73 mg, 0.53 mmol) in CH_2Cl_2 (2 mL) at 0 °C. The reaction mixture was stirred overnight at rt, whereupon EtOAc (20 mL) and H_2O (20 mL) were added. The reaction mixture was transferred to a separatory funnel, the organic layer was separated, and the aqueous phase was further extracted with EtOAc (2 × 20 mL). The combined organic layers were dried over Na_2SO_4 and evaporated to dryness in vacuo. The residue was purified by flash column chromatography on silica gel (Et_3N/MeOH/CH_2Cl_2 1:5:95), to give the title compound as a yellow oil (104 mg, 79%): R_f = 0.45 (MeOH/CH_2Cl_2 (1:9); PMA, UV); HPLC purity >95% (Rt = 8.11 min); IR (neat) cm^{-1} 3245, 2923, 2862, 1455, 1356, 1049, 929, 737. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.58 (dd, J = 7.8, 0.7 Hz, 1H), 7.36 (d, J = 8.0 Hz, 1H), 7.15 (dtd, J = 7.8, 7.1, 1.2 Hz, 2H), 7.01 (d, J = 2.3 Hz, 1H), 5.95−5.81 (m, 1H), 5.27 (ddd, J = 11.6, 6.6, 1.5 Hz, 2H), 4.12 (q, J = 7.1 Hz, 1H), 3.93 (dd, J = 15.9, 5.7 Hz, 1H), 3.52 (dd, J = 16.0, 6.8 Hz, 1H), 3.36 (ddd, J = 9.3, 6.7, 4.7 Hz, 2H), 3.13−2.93 (m, 2H), 2.05 (s, 1H), 1.66 (s, 0.5H), 1.21 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.4, 135.0, 127.4, 122.5, 122.0, 119.3, 118.7, 118.2, 112.8, 111.4, 58.1, 54.5, 50.0, 49.5, 43.9, 24.7, 23.3. HRMS (ESI) m/z calcd for $C_{17}H_{24}N_2NaOS$ $[M + Na]^+$ 327.1507, found 327.1502.

*N-Allyl-N-benzenesulfonamide−Tryptamine (**19m**).* Following general procedure III, the reaction of *N*-allyltryptamine (280 mg, 1.40 mmol), benzenesulfonyl chloride (2.84 mg, 205 μL 1.61 mmol), and Et_3N (171 mg, 236 μL, 1.69 mmol) gave, after purification by flash column chromatography on silica gel (Et_3N/EtOAc/heptane 1:24:75), the title compound as an off-white solid (383 mg, 81%): mp 107−108 °C; R_f = 0.10 (EtOAc/heptane (1:3); UV, $KMnO_4$); HPLC purity >95% (t_R = 8.83 min); IR (neat) cm^{-1} 3398, 1446, 1327, 1160, 1089; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.74 (d, J = 8.1 Hz, 2H), 7.49−7.42 (m, 2H), 7.38 (t, J = 7.6 Hz, 1H), 7.26 (dd, J = 8.0, 0.8 Hz, 1H), 7.15−6.95 (m, 1H), 6.89 (d, J = 1.9 Hz, 1H), 5.71−5.39 (m, 1H), 5.16−4.92 (m, 2H), 3.78 (d, J = 6.4 Hz, 2H), 3.34 (dd, J = 9.5, 6.5 Hz, 2H), 2.94 (dd, J = 9.5, 6.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.4, 136.5, 133.5, 132.8, 129.4, 127.5, 127.3, 122.4, 122.3, 119.7, 119.3, 118.9, 112.7, 111.6, 51.4, 48.2, 25.4; HRMS (ESI) m/z calcd for $C_{19}H_{21}N_2O_2S$ $[M + H]^+$ 341.1324, found 341.1324.

*1-(2-(1H-Indol-3-yl)ethyl)-1-allyl-3-phenylurea (**19n**).* In a round-bottomed flask fitted with a magnetic stirring bar, isocyanatobenzene (146 mg, 133 μL, 1.22 mmol) was added to a stirred solution of *N*-allyltryptamine (175 mg, 1.85 mmol) in CH_2Cl_2 (4 mL) at 0 °C. The reaction mixture was stirred at 0 °C and was monitored by TLC. Upon full conversion of the amine (5 min), the reaction mixture was evaporated to dryness in vacuo. The residue was purified by flash column chromatography on silica gel (Et_3N/EtOAc/heptane 1:49:50), to give the title compound as an off-white solid (246 mg, 88%): mp 134−136 °C; R_f = 0.32 (EtOAc/heptane (1:1); UV, $KMnO_4$); HPLC purity >95% (t_R = 8.61 min); IR (neat) cm^{-1} 3371, 3217, 2931, 1619, 1593, 1519, 1496, 1434, 1334, 1232; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.51 (s, 1H), 7.72−7.64 (m, 1H), 7.40 (dt, J = 8.1, 0.9 Hz, 1H), 7.31−7.22 (m, 1), 7.21−7.14 (m, 1H), 7.14−7.06 (m, 2H), 6.96−6.84 (m, 1H), 6.77 (d, J = 2.3 Hz, 1H), 6.63 (d, J = 7.8 Hz, 2H), 5.91 (ddt, J = 17.2, 10.2, 5.6 Hz, 1H), 5.80 (s, 1H), 5.30 (dq, J = 12.4, 1.6 Hz, 1H), 5.25 (dd, J = 5.4, 1.5 Hz, 1H), 4.00 (dt, J = 5.5, 1.4 Hz, 2H), 3.66 (t, J = 6.4 Hz, 2H), 3.03 (t, J = 6.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.6, 139.3, 137.0, 134.5, 128.9, 126.5, 123.9, 122.6, 122.5, 120.1, 119.4, 118.2, 117.4, 112.4, 111.5, 49.9, 48.2, 24.7; MS (ESI) m/z calcd for $C_{20}H_{22}N_3O$ $[M + H]^+$ 320.1763, found 320.1755.

*1-(2-(1H-Indol-3-yl)ethyl)-1-allyl-3-(4-nitrophenyl)thiourea (**19o**).* In a round-bottomed flask fitted with a magnetic stirring bar, 4-nitrophenyl isothiocyanate (220 mg, 1.22 mmol) was added to a stirred solution of *N*-allyltryptamine (175 mg, 1.85 mmol) in CH_2Cl_2 (4 mL) at 0 °C. The solution was stirred at 0 °C, and the reaction was monitored by TLC. Upon full conversion of the amine (5 min), the reaction mixture was evaporated to dryness in vacuo. The residue was purified by flash column chromatography on silica gel (Et_3N/EtOAc/heptane 1:49:50) to give the title compound as an orange powder (322 mg, >95%): R_f = 0.14 (EtOAc/heptane (1:1); UV, $KMnO_4$); HPLC purity >95% (t_R = 8.83 min); IR (neat) cm^{-1} 3389, 1597, 1538, 1502, 1329, 1294, 1219, 1107; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.46 (s, 1H), 7.90 (d, J = 8.7 Hz, 2H), 7.69 (d, J = 7.8 Hz, 1H), 7.44 (d, J = 8.2 Hz, 1H), 7.30 (t, J = 7.2 Hz, 1H), 7.18 (ddd, J = 7.9, 7.1, 1.0 Hz, 1H), 7.02 (d, J = 1.3 Hz, 1H), 6.69 (br s, 3H), 6.01 (dq, J = 10.8, 5.6 Hz, 1H), 5.40−5.36 (m, 1H), 5.33 (dd, J = 10.8, 1.2 Hz, 1H), 4.49 (br s, 2H), 3.99 (t, J = 5.6 Hz, 2H), 3.19 (t, J = 6.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.6, 146.1, 143.1, 136.8, 132.2, 126.4, 124.3, 124.0, 123.3, 121.9, 120.9, 118.9, 118.5, 112.3, 111.5, 54.4, 46.3, 23.8; MS (ESI) m/z calcd for $C_{20}H_{21}N_4O_2S$ $[M + H]^+$ 381.1385, found 381.1381.

*THBC **20a**.* Following general procedure II, the reaction of **19a** (200 mg, 0.64 mmol), $RuHCl(CO)(PPh_3)_3$ (61.1 mg, 0.064 mmol) and $(PhO)_2PO_2H$ (48.0 mg, 0.19 mmol) gave, after purification by flash column chromatography on silica gel (Et_3N/EtOAc/heptane 1:34:65), the title compound as a light solid (186 mg, 93%): mp 47−50 °C; R_f = 0.14 (EtOAc/heptane (7:13) ; UV, $KMnO_4$); HPLC purity >95% (t_R = 9.60 min); IR (neat) cm^{-1} 3271, 2927, 1613, 1450, 1425; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.52−7.42 (m, 1H), 7.33 (d, J = 7.9 Hz, 1H), 7.12 (ddd, J = 14.8, 13.8, 6.5 Hz, 2H), 5.75 (dd, J = 8.7, 5.7 Hz, 1H), 4.13−4.02 (m, 1H), 3.48 (ddd, J = 14.0, 10.3, 5.8 Hz, 1H), 2.89−2.76 (m, 2H), 2.60−2.26 (m, 2), 2.01−1.57 (m, 5H), 1.48−1.22 (m, 6H), 1.03 (t, J = 7.4 Hz, 3H), 0.90 (t, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 136.5, 135.3, 126.8, 121.6, 119.3, 117.9, 111.5, 106.9, 50.6, 40.5, 34.1, 31.9, 29.5, 27.7, 25.9, 22.8, 22.5,

dx.doi.org/10.1021/jo402192s | J. Org. Chem. 2013, 78, 12545−12565

14.3, 10.9; HRMS (ESI) m/z calcd for $C_{20}H_{29}N_2O$ $[M + H]^+$ 313.2280, found 313.2272.

THBC ***20b.*** Following general procedure II, the reaction of **19b** (100 mg, 0.33 mmol), $RuHCl(CO)(PPh_3)_3$ (30.4 mg, 0.033 mmol) and $(PhO)_2PO_2H$ (24.7 mg, 0.099 mmol) gave, after purification by flash column chromatography on silica gel (Et_3N/EtOAc/heptane 1:49:5), the title compound as a white powder (93 mg, 93%): mp 87−90 °C; R_f = 0.41 (EtOAc/heptane (1:1); UV, $KMnO_4$); HPLC purity >95% (t_R = 8.45 min); IR (neat) cm^{-1} 3243, 1608, 1430, 1301, 1233; ^1H NMR (300 MHz, $CDCl_3$) δ 8.43 (s, 1H), 7.50−7.34 (m, 6H), 7.30 (d, J = 7.8 Hz, 1H), 7.17−7.06 (m, 2H), 5.88 (t, J = 7.1 Hz 1H), 3.94 (dd, J = 13.6, 5.1 Hz, 1H), 3.49 (ddd, J = 13.8, 11.8, 4.6 Hz, 1H), 2.94−2.75 (m, 1H), 2.69 (dd, J = 15.4, 3.6 Hz, 1H), 2.25−1.76 (m, 2H), 1.16 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7, 137.1, 136.4, 134.6, 129.9, 129.0, 126.9, 126.7, 122.0, 119.7, 118.2, 111. 5, 107.3, 51.0, 42.4, 28.1, 22.7, 11.2; HRMS (ESI) m/z calcd for $C_{20}H_{21}N_2O$ $[M + H]^+$ 305.1654, found 305.1648.

THBC ***20c.*** Following general procedure II, the reaction of **19c** (150 mg, 0.45 mmol), $RuHCl(CO)(PPh_3)_3$ (42.8 mg, 0.045 mmol), and $(PhO)_2PO_2H$ (33.7 mg, 0.13 mmol) gave, after purification by flash column chromatography on silica gel (Et_3N/EtOAc/heptane 1:49:50), the title compound as an off-white solid (105 mg, 70%): mp 206−208 °C; R_f = 0.14 (EtOAc/heptane (4:6); UV, $KMnO_4$); HPLC purity >95% (t_R = 8.41 min); IR (neat) cm^{-1} 3242, 2927, 1602, 1571, 1426, 1250, 1181; ^1H NMR (300 MHz, $CDCl_3$) δ 8.56 (s, 1H), 7.40−7.30 (m, 3H), 7.22−7.16 (m, 1H), 7.09−6.97 (m, 2H), 6.88 (d, J = 8.3 Hz, 2H), 5.76 (t, J = 6.6 Hz, 1H), 3.95 (d, J = 9.1 Hz, 1H), 3.78 (s, 3H), 3.42 (t, J = 8.5 Hz, 1H), 2.79−2,55 (m, 2H), 2.04−1.69 (m,, 2H), 1.04 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCL_3$) δ 171.5, 160.9, 160.8, 136.4, 134.7, 129.3, 128.8, 122.0, 119.8, 118.2, 114.2, 111.4, 107.5, 55.7, 51.1, 42.5, 28.1, 22.7, 11.2; MS (ESI) m/z calcd for $C_{21}H_{23}N_2O_2$ $[M + H]^+$ 335.1760, found 335.1776.

THBC ***20d.*** Following general procedure II, the reaction of **19d** (80 mg, 0.23 mmol), $RuHCl(CO)(PPh_3)_3$ (21.8 mg, 0.023 mmol), and $(PhO)_2PO_2H$ (17.2 mg, 0.069 mmol) gave, after purification by flash column chromatography on silica gel (Et_3N/EtOAc/heptane 1:49:50), the title compound as a white solid (77 mg, >95%): mp 201−202 °C; R_f = 0.31 (EtOAc/heptane (1:1); UV, $KMnO_4$); HPLC purity >95% (t_R = 8.51 min); IR (neat) cm^{-1} 3272, 2975, 1612, 1594, 1495, 1431, 1342; ^1H NMR (300 MHz, $CDCl_3$) δ 8.41 (s, 1H), 8.31 (d, J = 8.7 Hz, 2H), 7.59 (d, J = 8.7 Hz, 2H), 7.46 (d, J = 7.4 Hz, 1H), 7.31 (d, J = 7.7 Hz, 1H), 7.15 (dtd, J = 18.5, 7.2, 1.2 Hz, 2H), 5.82 (dd, J = 8.3, 5.8 Hz, 1H), 3.75 (dd, J = 13.9, 3.7 Hz, 1H), 3.53 (ddd, J = 13.9, 10.9, 5.2 Hz, 1H), 2.93−2.61 (m, 2H), 2.21−1.80 (m, 2H), 1.15 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.3, 148.6, 143.1, 136.4, 133.9, 127.8, 126.8, 124.4, 122.8, 120.0, 118.3, 111.4, 107.2, 51.2, 42.4, 28.1, 22.6, 11.2; MS (ESI) m/z calcd for $C_{20}H_{20}N_3O_3$ $[M + H]^+$ 350.1505, found 350.1504.

THBC ***20e.*** Following general procedure II, the reaction of **19e** (200 mg, 0.70 mmol), $RuHCl(CO)(PPh_3)_3$ (66.8 mg, 0.070 mmol), and $(PhO)_2PO_2H$ (52.6 mg, 0.21 mmol) gave, after purification by flash column chromatography on silica gel (Et_3N/EtOAc/heptane 1:39:60), the title compound as an off-white solid (186 mg, 93%): mp 67−70 °C; R_f = 0.33 (EtOAc/heptane (4:6); UV, $KMnO_4$); HPLC purity >95% (t_R = 8.06 min); IR (neat) cm^{-1} 3295, 2964, 2930, 16781, 1446, 1408, 1229; ^1H NMR (300 MHz, $CDCl_3$) δ 8.41 (s, 0.6H), 8.17 (s, 0.4H), 7.50 (d, J = 7.0 Hz, 1H), 7.36−7.27 (m, 1H), 7.24−7.02 (m, 2H), 5.31 (br s, 0.6H), 5.14 (br s, 0.4H), 4.58 (d, J = 9.3 Hz, 0.4H), 4.37 (dd, J = 13.5, 4.3 Hz, 0.6H), 3.82 (s, 3H), 3.33−3.12 (m, 1H), 2.95−2.80 (m, 1H), 2.72 (dd, J = 15.2, 3.4 Hz, 1H), 2.01−1.74 (m, 2H), 1.07 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.1, 136.3, 134.8, 127.0, 121.9, 119.6, 118.3, 111.2, 108.1, 53.2, 38.9, 27.9, 21.8, 21.4, 11.0; MS (ESI) m/z calcd for $C_{15}H_{19}N_2O_2$ $[M + H]^+$ 259.1447, found 259.1456.

THBC ***20f.*** Following general procedure II, the reaction of **19a** (50 mg, 0.18 mmol), $RuHCl(CO)(PPh_3)_3$ (17.2 mg, 0.018 mmol), and $(PhO)_2PO_2H$ (13.6 mg, 0.054 mmol) gave, after purification by flash column chromatography on silica gel (EtOAc/heptane 32:68), the title compound as a light brown solid (41 mg, 82%): mp 192−194 °C; R_f = 0.18 (EtOAc/heptane (32:68); UV, $KMnO_4$); HPLC purity >95% (t_R = 7.72 min); IR (neat) cm^{-1} 3245, 2967, 2917, 1959, 1638, 1620, 1454, 1433; ^1H NMR (300 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.46 (d, J = 7.7 Hz, 1H), 7.34 (d, J = 7.8 Hz, 1H), 7.22−7.03 (m, 2H), 5.66 (dd, J = 8.3, 5.5 Hz, 1H), 4.22 (s, 2H), 4.19−4.02 (m, 1H), 3.12−2.72 (m, 1H), 2.16−1.78 (m, 2H), 1.05 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4, 136.3, 134.1, 126.8, 122.3, 119.9, 118.3, 111.4, 107.6, 51.4, 41.9, 41.0, 28.0, 22.6, 11.1; HRMS (ESI) m/z calcd for $C_{15}H_{18}N_2OCl$ $[M + H]^+$ 277.1108, found 277.1102.

N-Prop-1-en-1-yl-N-(trichlorocetyl)tryptamine ***(20g).*** In a Schlenk tube fitted with a magnetic stirring bar and a reflux condenser, **19g** (60 mg, 0.17 mmol), $RuHCl(CO)(PPh_3)_3$ (16.6 mg, 0.017 mmol), and $(PhO)_2PO_2H$ (13.0 mg, 0.052 mmol) were dissolved in toluene (1.74 mL). The reaction was stirred at reflux and was followed by TLC. After 23 h of stirring, the reaction mixture was evaporated in vacuo. The residue was purified by flash column chromatography on silica gel (EtOAc/heptane 1:4), to give the title compound a brown oil (131 mg, 87%): R_f = 0.21 (EtOAc/heptane (1:4); UV, $KMnO_4$); HPLC purity 94% (t_R = 9.76 min); IR (neat) cm^{-1} 3339, 1653, 1428, 1256, 812, 739; ^1H NMR (300 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.71 (d, J = 7.4 Hz, 1H), 7.38 (d, J = 7.9 Hz, 1H), 7.22 (td, J = 7.5, 1.2 Hz 1H), 7.15 (td, J = 7.5, 1.2 Hz 1H, 1H), 7.07 (d, J = 2.3 Hz, 1H), 6.99 (dd, J = 13.9, 1.5 Hz, 1H), 5.50−5.34 (m, 1H), 4.00 (t, J = 6.3 Hz, 2H), 3.11 (t, J = 7.8 Hz, 2H), 1.76 (d, J = 6.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.8, 140.3, 136.5, 127.7, 127.6, 122.5, 122.3, 119.9, 119.2, 113.0, 112.8, 111.5, 93.5, 41.6, 22.9, 15.9; HRMS (ESI) m/z calcd for $C_{15}H_{16}Cl_3N_2O$ $[M + H]^+$ 345.0328, found 345.0329.

N-Prop-1-en-1-yl-N-(trifluoroacetyl)tryptamine ***(20h).*** In a Schlenk tube fitted with a magnetic stirring bar and a reflux condenser, **19h** (150 mg, 0.51 mmol), $RuHCl(CO)(PPh_3)_3$ (38.0 mg, 0.15 mmol), and $(PhO)_2PO_2H$ (38.0 mg, 0.15 mmol) were dissolved in toluene (5.1 mL). The reaction was stirred at reflux and was followed by TLC. After 23 h of stirring, the reaction mixture was evaporated in vacuo. The residue was purified by flash column chromatography on silica gel (Et_3N/EtOAc/heptane 1:24:75), to give the title compound a light brown solid (131 mg, 87%): mp 55− 58 °C; R_f = 0.21 (EtOAc/heptane (1:3); UV, $KMnO_4$); HPLC purity >95% (t_R = 8.92 min); IR (neat) cm^{-1} 3361, 1680, 1665, 1190, 1144; ^1H NMR (300 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.69 (d, J = 7.7 Hz, 1H), 7.38 (d, J = 7.5 Hz, 1H), 7.27−7.13 (m, 2H), 7.06 (d, J = 2.4 Hz, 1H), 6.54−6.41 (dp, J = 13.8, 1.8 Hz 1H), 5.56−5.40 (m, 1H), 3.99−3.90 (m, 2H), 3.15−3.04 (m, 2H), 1.76 (dd, J = 6.7, 1.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.0/155.5, 136.6, 127.6, 125.7, 122.6, 122.5/122.4, 119.9, 119.0, 116.1, 112.6/112.5, 111.6, 47.2, 22.9, 15.7, rotamers; HRMS (ESI) m/z calcd for $C_{15}H_{16}F_3N_2O$ $[M + H]^+$ 297.1215, found 297.1210.

THBC ***20i.*** Following general procedure II, the reaction of **19i** (200 mg, 0.67 mmol), $RuHCl(CO)(PPh_3)_3$ (63.5 mg, 0.067 mmol), and $(PhO)_2PO_2H$ (50.0 mg, 0.20 mmol) gave, after purification by flash column chromatography on silica gel (EtOAc/heptane 1:4), the title compound as a light yellow solid (190 mg, 95%): mp 183−184 °C; R_f = 0.31 (EtOAc/heptane (1:4); UV, $KMnO_4$); HPLC purity >95% (t_R = 9.47 min); IR (neat) cm^{-1} 3262, 1661, 1460, 1417, 1379, 1233, 1156; ^1H NMR (300 MHz, $CDCl_3$) δ 8.66 (s, 0.5H), 8.17 (s, 0.5H), 7.52 (d, J = 7.3 Hz, 1H), 7.35−7.28 (m, 1H), 7.22−7.04 (m, 2H), 5.33 (br s, 0.5H), 5.14 (br s, 0.5H), 4.57 (d, J = 9.3 Hz, 0.5H), 4.36 (d, J = 9.6 Hz, 0.5H), 3.29−3.05 (m, 1H), 2.95−2.81 (m, 1H), 2.79−2.65 (m, 1H), 2.00−1.76 (m, 2H), 1.58 (s, 9H), 1.20−0.99 (m, 3H), rotamers; ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.8/155.4, 136.3, 135.3/134.8, 127.1, 121.9/121.7, 119.7/119.5, 118.4/118.2, 111.2, 109.0/108.2, 80.19, 53.2/52.4, 39.1/37.89, 28.8, 28.3/28.90, 21.9/21.6, 11.3/11.0, rotamers; HRMS (ESI) m/z calcd for $C_{18}H_{24}N_2O_2Na$ $[M + Na]^+$ 323.1735, found 323.1728.

THBC ***20j.*** Following general procedure II, the reaction of **19j** (200 mg, 0.47 mmol), $RuHCl(CO)(PPh_3)_3$ (45.2 mg, 0.047 mmol), and $(PhO)_2PO_2H$ (35.5 mg, 0.14 mmol) gave, after purification by flash column chromatography on silica gel (Et_3N/EtOAc/heptane 1:24:75), the title compound as a brown oil (16 3 mg, 82%): R_f = 0.24 (EtOAc/heptane (1:3); UV, $KMnO_4$); HPLC purity 94% (t_R = 10.39 min); IR (neat) cm^{-1} 3252, 3063, 2964, 2930, 1770, 1471, 1226, 1023, 727; ^1H NMR (300 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.76−7.61 (m, 2H), 7.60−7.12 (m, 10H), 7.10−6.96 (m, 2H), 5.18 (t, J = 6.7 Hz, 1H), 4.70−

4.30 (m, 1H), 4.29−3.97 (m, 1H), 3.26−2.91 (m, 1H), 2.73−2.40 (m, 2H), 1.89−1.41 (m, 2H), 0.93 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.3/156.1, 144.3, 141.7, 136.2, 134.7/134.1, 128.0/127.9, 127.4/127.4, 127.1, 125.2/125.0, 122.1, 120.4/120.3, 119.8, 118.5/118.3, 111.2/111.1, 109.1/108.3, 67.8/65.5, 53.2/47.7, 39.0/38.8, 32.2, 28.1/28.0, 23.0/21.9, 14.5/11.0, rotamers; MS (ESI) m/z calcd for $C_{28}H_{27}N_2O_2$ $[M + H]^+$ 423.2073, found 423.2068.

THBC ***20k***. Following general procedure II, the reaction of **19k** (200 mg, 0.46 mmol), $RuHCl(CO)(PPh_3)_3$ (44.1 mg, 0.046 mmol), and $(PhO)_2PO_2H$ (34 mg, 0.19 mmol) gave, after purification by flash column chromatography on silica gel (Et_3N/EtOAc/heptane 1:34:65), the title compound as a brown solid (186 mg, 93%): mp 194−195 °C; R_f = 0.18 (Et_3N/EtOAc/heptane (1:34:65); UV, $KMnO_4$); HPLC purity >95% (t_R = 9.76 min); IR (neat) cm^{-1} 3243, 1590, 1487, 1243, 1214, 1187, 1138, 925; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.83 (s, 1H), 7.37−7.37 (m, 6H), 7.22−7.10 (m, 6H), 7.05 (t, J = 7.5 Hz, 1H), 6.95 (t, J = 7.4 Hz, 1H), 4.73 (td, J = 8.8, 4.5 Hz, 1H), 3.97−3.84 (m, 1H), 3.47−3.16 (m, 1H), 2.64 (d, J = 5.0 Hz, 2H), 1.93−1.55 (m, 2H), 0.82 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 150.7/150.6, 150.2/150.1, 135.5, 134.6/134.5, 129.7/129.7, 126.3, 125.1, 124.7, 120.8, 120.4/120.4, 119.5/119.5, 118.3, 117.6, 111.0, 106.1, 54.8, 52.8/52.7, 27.7/27.7, 21.0, 10.5, rotamer MS (ESI) m/z calcd for $C_{25}H_{26}N_2O_3P$ $[M + H]^+$ 433.1681, found 433.1648.

THBC ***20m***. Following general procedure II, the reaction of **19m** (200 mg, 0.59 mmol), $RuHCl(CO)(PPh_3)_3$ (56.0 mg, 0.059 mmol), and $(PhO)_2PO_2H$ (44 mg, 0.18 mmol) gave, after purification by flash column chromatography on silica gel (Et_3N/EtOAc/heptane 1:34:65), the title compound as white crystals (171 mg, 81%): mp 133−135 °C; R_f = 0.28 (EtOAc/heptane (1:4); UV, $KMnO_4$); HPLC purity >95% (t_R = 8.74 min); IR (neat) cm^{-1} 3362; 2967, 2932, 1446, 1352, 1303, 1158, 1091; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.74−7.62 (m, 2H), 7.33−7.24 (m, 1H), 7.23−7.14 (m, 4H), 7.07−6.99 (m, 1H), 6.99−6.90 (m, 1H), 5.02 (dd, J = 8.6, 5.0 Hz, 1H), 4.05 (dd, J = 14.8, 5.6 Hz, 1H), 3.32 (ddd, J = 14.8, 12.0, 4.7 Hz, 1H), 2.40 (dd, J = 15.8, 4.0 Hz, 1H), 2.30−2.14 (m, 1H), 1.93−1.60 (m, 2H), 1.02 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.3, 136.1, 133.3, 132.8, 129.2, 127.0, 126.8, 122.2, 119.7, 118.3, 111.2, 107.7, 55.0, 40.0, 29.2, 20.0, 11.2; HRMS (ESI) m/z calcd for $C_{19}H_{21}N_2O_2S$ $[M + H]^+$ 341.1324, found 341.1323.

N-Allyl-N-acetyl-1-methyltryptamine ***(21)***. In a round-bottomed flask fitted with a magnetic stirring bar, acetic anhydride (1.65 g, 1.53 mL, 16.2 mmol) was added to a stirred solution of 1-methyltryptamine[24] (1.41 g, 8.09 mmol) and pyridine (1.92 g, 1.96 mL, 24.28 mmol) in CH_2Cl_2 (33 mL) at 0 °C. The reaction mixture was stirred at 0 °C, and progress was followed by TLC. Upon full conversion of the starting material (5 min), the reaction was quenched with H_2O (25 mL) and transferred to a separatory funnel. The organic layer was separated, and the aqueous phase was further extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were dried over Na_2SO_4 and evaporated to dryness in vacuo. The residue was purified by flash column chromatography on silica gel (EtOAc), to give *N*-acetyl-1-methyltryptamine as an off-white solid (1.46 g, 83%). Analytical data are in accordance with those previously reported:[25] R_f = 0.17 (EtOAc; UV, $KMnO_4$); HPLC purity 84% (t_R = 6.04 min); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62−7.56 (m, 1H), 7.34−7.29 (m, 1H), 7.29−7.21 (m, 1H), 7.12 (ddd, J = 8.0, 6.8, 1.2 Hz, 1H), 6.89 (s, 1H), 5.64 (br s, 1H), 3.76 (s, 3H), 3.58 (dd, J = 12.6, 6.6 Hz, 2H), 2.95 (dd, J = 11.4, 5.0 Hz, 2H), 1.92 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 137.4, 128.1, 127.1, 122.1, 119.3, 119.12 111.7, 109.6, 40.3, 33.0, 25.5, 23.7; MS (ESI) m/z calcd for $C_{13}H_{17}N_2O$ $[M + Na]^+$ 217.1, found 217.1.

In round-bottomed flask fitted with a magnetic stirring bar, NaH (44.4 mg, 1.85 mmol) was added to a stirred solution of *N*-acetyl-1-methyltryptamine (200 mg, 0.92 mmol) in DMF (5 mL) at 0 °C. The reaction mixture was allowed to reach rt and stirred for 30 min, whereupon allyl bromide (447 mg, 320 μL, 3.70) was added. The reaction temperature was raised to 50 °C, and the progress of the reaction was followed by TLC. Upon full conversion of starting material (45 min), the reaction mixture was evaporated to dryness in vacuo. The residue was taken up in H_2O (10 mL) and CH_2Cl_2 (10 mL) and transferred to a separatory funnel. The organic layer was isolated, and the aqueous phase was further extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over Na_2SO_4 and evaporated to dryness in vacuo. The residue was purified by flash column chromatography on silica gel (EtOAc/heptane 1:1) to give the title compound as a light yellow oil (184 mg, 74%): R_f = 0.14 (EtOAc/heptane (1:1); UV, $KMnO_4$); HPLC purity >95% (t_R = 7.45 min); IR (neat) cm^{-1} 2950, 1634, 1471, 1415, 737; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (d, J = 7.8 Hz, 0.5H), 7.44 (d, J = 7.8 Hz, 0.5H), 7.23−7.08 (m, 2H), 7.07−6.67 (m, 1H), 6.76 (d, J = 11.1 Hz, 1H), 5.82−5.50 (m, 1H), 5.09−4.96 (m, 2H), 3.94 (d, J = 5.5 Hz, 1H), 3.70−3.65 (m, 1H), 3.62 (dd, J = 4.4, 1.6 Hz, 3H), 3.51 (t, J = 7.6 Hz, 1H), 3.42 (t, J = 7.5 Hz, 1H), 2.89 (dd, J = 14.5, 7.2 Hz, 2H), 1.99 (d, J = 1.7 Hz, 1.5H), 1.90 (d, J = 1.7 Hz, 1.5H), rotamers; ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9/169.5, 136.4, 132.8/132.2, 127.1/126.6, 126.1/125.9, 121.0/120.7, 118.2/118.1, 118.0/117.5, 116.2/115.6, 111.0/109.8, 108.6/108.4, 50.9/48.0, 47.1/46.5, 31.8/31.8, 23.7/22.8, 20.8/20.5, rotamers; HRMS (ESI) m/z calcd for $C_{16}H_{21}N_2O$ $[M + H]^+$ 257.1654, found 257.1654.

THBC ***22***. Following general procedure II, the reaction of **21** (100 mg, 0.39 mmol), $RuHCl(CO)(PPh_3)_3$ (37.2 mg, 0.039 mmol) and $(PhO)_2PO_2H$ (29.3 mg, 0.12 mmol) gave, after purification by flash column chromatography on silica gel (EtOAc/heptane 1:1), the title compound as a light yellow oil (86 mg, 86%): R_f = 0.18 (EtOAc/heptane (1:1); UV, $KMnO_4$); HPLC purity >95% (t_R = 7.49 min); IR (neat) cm^{-1} 2966, 2931, 1637 1420 733; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (t, J = 6.3 Hz, 1H), 7.18 (d, J = 7.1 Hz, 1H), 7.11 (d, J = 5.9 Hz, 1H), 7.05−6.99 (m, 1H), 5.76−5.67 (m, 1H), 3.89 (d, J = 10.1 Hz, 1H), 3.57 (s, 3H), 3.52−3.33 (m, 1H), 2.86−2.58 (m, 2H), 2.13 (s, 1H), 1.91−1.59 (m, 2H), 1.02−0.92 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 137.4, 136.7, 126.5, 121.6, 119.4, 118.2, 109.2, 106.4, 49.0, 40.3, 30.2, 27.3, 22.2, 22.0, 11.05; HRMS (ESI) m/z calcd for $C_{16}H_{21}N_2O$ $[M + H]^+$ 257.1654, found 257.1646.

N-Benzyl-N-2-but-3-enyltryptamine ***(23a)***. In a round-bottomed flask fitted with a magnetic stirring bar, 3-(2-bromoethyl)indole (283 mg, 1.26 mmol) was added to a stirred suspension of K_2CO_3 (222 mg, 1.60 mmol) and *N*-benzylbut-3-en-2-amine[26] (185 mg, 1.15 mmol) in DMF (6 mL). The reaction mixture was heated to 60 °C and was monitored by TLC. Upon full conversion of the starting material (23 h), the reaction mixture was evaporated to dryness in vacuo. The residue was taken up in CH_2Cl_2 (15 mL) and H_2O (12 mL) and transferred to a separatory funnel. The organic layer was separated, and the aqueous phase was further extracted with CH_2Cl_2 (4 × 15 mL). The combined organic layers were dried over Na_2SO_4 and evaporated to dryness in vacuo. The residue was purified by flash column chromatography on silica gel (Et_3N/EtOAc/heptane 1:24:75) to give the title compound as a brown solid oil (221 mg, 60%): mp 52−58 °C R_f = 0.21 (Et_3N/EtOAc/heptane (1:24:75); UV, $KMnO_4$); HPLC purity >95% (t_R = 6.37 min); IR (neat) cm^{-1} 3411, 3146, 3061, 2967, 2920, 2849, 1495, 1127, 734; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (s, 1H), 7.36 (d, J = 7.8 Hz, 1H), 7.30 (d, J = 7.4 Hz, 2H), 7.24−7.09 (m, 4H), 7.09−7.01 (m, 1H), 7.00−6.92 (m, 1H), 6.75 (d, J = 2.0 Hz, 1H), 5.81 (ddd, J = 17.1, 10.8, 6.4 Hz, 1H), 5.08−4.93 (m, 2H), 3.64 (d, J = 14.1 Hz, 1H), 3.57 (d, J = 14.1 Hz, 1H), 3.32 (p, J = 6.6 Hz, 1H), 2.84−2.73 (m, 2H), 2.73−2.59 (m, 2H), 1.07 (d, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.3, 140.7, 136.4, 128.9, 128.5, 127.9, 126.9, 122.1, 121.8, 119.4, 119.2, 115.5, 115.0, 111.3, 57.5, 55.0, 50.9, 25.0, 15.9; HRMS (ESI) m/z calcd for $C_{21}H_{25}N_2$ $[M + H]^+$ 305.2018, found 305.2017.

N-Acetyl-N-2-but-3-enyltryptamine ***(23b)***. In a round-bottomed flask fitted with a magnetic stirring bar, 3-chloro-1-butene (622 mg, 691 μL, 6.87 mmol) was added to a stirred suspension of K_2CO_3 (1.04 g, 7.49 mmol) and tryptamine (1.00 g, 6.24 mmol) in DMF (30 mL). The reaction was heated to 60 °C and stirred for 4 days, whereupon the reaction mixture evaporated in vacuo. The residue was taken up in CH_2Cl_2 (150 mL) and H_2O (150 mL) and transferred to a separatory funnel. The organic layer was separated and the aqueous phase was further extracted with CH_2Cl_2 (2 × 150 mL). The combined organic layers were dried over Na_2SO_4 and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel (Et_3N/

heptane/EtOAc 1:24:75) to give *N*-2-but-3-enyltryptamine as a brown solid (468 mg, 18%): mp 65−67 °C R_f = 0.11 (Et_3N/heptane/EtOAc (1:24:75); UV, $KMnO_4$); HPLC purity >95% (t_R = 5.10 min); IR (neat) cm^{-1} 3411, 3050, 2972, 2917, 2854, 1452, 1101; ^1H NMR (300 MHz, $CDCl_3$) δ 8.18 (s, 1H), 7.55 (d, J = 7.7 Hz, 1H), 7.27 (d, J = 7.8 Hz, 1H), 7.18−7.08 (m, 1H), 7.08−6.99 (m, 1H), 6.94 (d, J = 1.6 Hz, 1H), 5.69−5.51 (m, 1H), 5.05−4.89 (m, 2H), 3.12 (p, J = 6.7 Hz, 1H), 2.97−2.75 (m, 4H), 1.38 (br s, 1H), 1.05 (dt, J = 6.1, 2.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.8, 136.7, 127.7, 122.3, 122.2, 119.5, 119.2, 114.9, 114.1, 111.5, 57.0, 47.7, 26.3, 22.0; HRMS (ESI) m/z calcd for $C_{14}H_{19}N_2$ $[M + H]^+$ 215.1548, found 215.1548.

Following general procedure I, the reaction of *N*-2-but-3-enyltryptamine (55 mg, 0.26 mmol), acetyl chloride (23 mg, 21 μL, 0.30 mmol), and Et_3N (31 mg, 23 μL, 0.31 mmol) gave, after aqueous workup, the title compound as a brown oil (108 mg, 89%): R_f = 0.08 (EtOAc/heptane (1:1); UV, $KMnO_4$); HPLC purity >95% (t_R = 7.09 min); IR (neat) cm^{-1} 3180, 2968, 2927, 1604, 1447, 1415, 1103; ^1H NMR (300 MHz, $CDCl_3$) δ 8.69 (s, 0.5H), 8.47 (s, 0.5H), 7.72 (d, J = 7.7 Hz, 0.5H), 7.56 (d, J = 7.8 Hz, 0.5H), 7.37 (dd, J = 10.6, 8.4 Hz, 1H), 7.24−7.06 (m, 2H), 7.00 (d, J = 1.8 Hz, 1H), 6.05−5.78 (m, 1H), 5.33−5.15 (m, 2H), 5.12−5.05 (m, 0.5H), 4.49−4.40 (m, 0.5H), 3.60 (ddd, J = 13.2, 11.5, 5.0 Hz, 0.5H), 3.44 (dd, J = 10.0, 6.2 Hz, 1H), 3.33 (ddd, J = 13.2, 11.2, 5.4 Hz, 0.5H), 3.17−3.05 (m, 0.5H), 3.05−2.92 (m, 1.5H), 2.21 (s, 1.5H), 2.16 (s, 1.5H), 1.36 (t, J = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1/171.0, 139.0/138.3, 136.6/136.6, 127.8/127.3, 122.4/122.3, 122.3/122.0, 119.7/119.4, 119.3/118.6, 116.2, 113.8/112.6, 111.8/111.5, 55.6/51.3, 46.1/43.9, 27.3/25.4, 22.5/22.3, 18.3/17.1; HRMS (ESI) m/z calcd for $C_{16}H_{21}N_2O$ $[M + H]^+$ 257.1654, found 257.1647.

THBC ***24a***. In a Schlenk tube fitted with a magnetic stirring bar and a reflux condenser, **23a** (76 mg, 0.25 mmol) and $RuHCl(CO)(PPh_3)_3$ (12 mg, 0.012 mmol) were dissolved in toluene (2.5 mL). The reaction mixture was stirred at reflux, and progress was followed by TLC. Upon full conversion of the starting material (1 h), the reaction mixture was evaporated to dryness in vacuo. The residue was purified by flash column chromatography on silica gel (Et_3N/EtOAc/heptane 1:19:80), to give the title compound as a brown solid (41 mg, 54%): mp 83−85 °C; R_f = 0.33 (Et_3N/EtOAc/heptane (1:19:80); UV, $KMnO_4$); HPLC purity >95% (t_R = 6.40 min); IR (neat) cm^{-1} 3409, 1964, 2929, 2800, 142, 1318, 1164, 734; ^1H NMR (300 MHz,$CDCl_3$) δ 7.64 (s, 1H), 7.52−7.46 (m, 3H), 7.41−7.32 (m, 3H), 7.32−7.27 (m, 1H), 7.15 (dddd, J = 14.5, 8.3, 7.1, 1.3 Hz, 2H, 4.09 (d, J = 14.3 Hz, 1H), 3.43 (d, J = 14.3 Hz, 1H), 2.95−2.88 (m, 1H), 2.79−2.72 (m, 2H), 2.67−2.58 (m, 1H), 2.13 (dq, J = 14.5, 7.3 Hz, 1H), 1.74 (dq, J = 14.6, 7.3 Hz, 1H), 1.43 (s, 4H), 0.83 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.4, 139.1, 136.3, 128.6, 128.4, 127.6, 126.9, 121.5, 119.5, 118.4, 110.9, 110.4, 58.6, 54.7, 52.5, 44.1, 31.8, 22.1, 21.7; HRMS (ESI) m/z calcd for $C_{21}H_{25}N_2$ $[M + H]^+$ 305.2018, found 305.2014.

THBC ***24b***. Following general procedure II, the reaction of **23b** (45 mg, 0.18 mmol), $RuHCl(CO)(PPh_3)_3$ (17 mg, 0.018 mmol), and $(PhO)_2PO_2H$ (13 mg, 0.053 mmol) gave, after purification by flash column chromatography on silica gel (EtOAc/heptane 1:3), the title compound a light brown oil (38 mg, 84%): R_f = 0.21 (EtOAc/heptane (1:3); UV, $KMnO_4$); HPLC purity >95% (t_R = 6.70 min); IR (neat) cm^{-1}3281, 2973, 2932, 1631, 1524, 1436, 1367, 1297; ^1H NMR (300 MHz, $CDCl_3$) δ 7.97 (s, 0.7H), 7.90 (s, 0.3H), 7.49 (dd, J = 11.5, 7.8 Hz, 1H), 7.22 (dt, J = 10.5, 4.7 Hz, 1H), 7.13−6.69 (m, 2H), 5.76 (dt, J = 15.4, 6.9 Hz, 1H), 5.55−5.36 (m, 1H), 3.45 (q, J = 6.5 Hz, 2H), 2.95 (t, J = 6.8 Hz, 1.4H), 2.79 (t, J = 6.7 Hz, 0.6H), 2.05−1.93 (m, 3H), 1.82−1.73 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4/170.3, 138.9/135.3, 136.1/135.6, 129.3/128.6, 128.3/127.8, 122.3/122.1, 119.9/119.8, 118.9/118.8, 111.1/110.92, 109.5/108.6, 40.6/40.1, 25.1/25.0, 24.9/23.7, 16.7, 15.7, 14.4; HRMS (ESI) m/z calcd for $C_{16}H_{21}N_2O$ $[M + H]^+$ 257.1654, found 257.1654.

N-Acetyl-N-allyl-2-((4-methoxy)phenyl)ethanamine (***25a***). In a round-bottomed flask fitted with a magnetic stirring bar, 4-methoxyphenethyl bromide (200 mg, 145 μL, 0.93 mmol) was added in portions to a stirred suspension of K_2CO_3 (17 mg, 1.19 mmol) in allylamine (1.53 g, 2.0 mL, 26.7 mmol) over 30 min. The reaction mixture was stirred at rt overnight and then filtered through a pad of Celite, which was washed with CH_2Cl_2 (2 × 15 mL). The filtrate was evaporated to dryness in vacuo, and the residue was purified by flash column chromatography on silica gel (Et_3N/MeOH/CH_2Cl_2 1:10:89), to give *N*-allyl-2-((4-methoxy)phenyl)ethanamine as a yellow oil (141 mg, 71%): R_f = 0.13 (MeOH/CH_2Cl_2 (1:9); UV, PMA); HPLC purity >95% (t_R = 4.63 min); ^1H NMR (300 MHz, $CDCl_3$) δ 7.13 (d, J = 8.3 Hz, 2H), 6.87−6.80 (m, 2H), 5.89 (ddt, J = 22.5, 10.2, 6.0 Hz, 1H), 5.13 (ddd, J = 17.5, 9.6, 5.9 Hz, 2H), 3.79 (s, 3H), 3.29−3.24 (m, 2H), 2.89−2.82 (m, 2H), 2.80−2.73 (m, 2H), 1.72 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.0, 136.7, 131.9, 129.6, 115.9, 113.8, 55.2, 52.3, 50.7, 35.4; MS (ESI) m/z calcd for $C_{13}H_{20}N_2O$ $[M + H]^+$ 192.1, found 192.2.

In a round-bottomed flask fitted with a magnetic stirring bar, acetic anhydride (71.4 mg, 66 μL, 0.70 mmol) was added to a stirred solution of *N*-allyl-2-((4-methoxy)phenyl)ethanamine (133 mg, 0.69 mmol) and Et_3N (70.4 mg, 97 μL, 0.70 mmol) in CH_2Cl_2 (3.5 mL) at 0 °C. The reaction mixture was stirred at 0 °C, and progress was followed by TLC. Upon full conversion of the amine (10 min), the reaction was quenched with H_2O (8 mL). The reaction mixture was transferred to a separatory funnel, and the organic layer was separated. The aqueous phase was further extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried over $MgSO_4$ and evaporated to dryness in vacuo to give the title compound as an orange oil (150 mg, 93%): R_f = 0.58 (MeOH/CH_2Cl_2 (1:9); UV, PMA); HPLC purity >95% (t_R = 6.75 min); IR (neat) cm^{-1} 2933, 2836, 1637, 1511, 1414, 1243, 822; ^1H NMR (300 MHz, $CDCl_3$) δ 7.14−7.02 (m, 2H), 6.87−6.78 (m, 2H), 5.84−5.63 (m, 1H), 5.20−5.05 (m, 2H), 3.98 (t, J = 5.7 Hz, 1H), 3.76 (s, 3H), 3.71 (dt, J = 4.7, 1.7 Hz, 1H), 3.52−3.37 (m, 2H), 2.83−2.72 (m, 2H), 2.05 (s, 1.5H), 1.92 (s, 1.5H), rotamers; ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 158.4,158.1, 133.6, 132.9, 131.4, 130.2, 129.8, 129.8, 117.1, 116.5, 114.2, 113.9, 55.3, 55.3, 51.8, 49.9, 48.3, 47.8, 34.2, 33.3, 21.6, 21.3, rotamers; HRMS (ESI) m/z calcd for $C_{14}H_{20}NO_2$ $[M + H]^+$ 234.1494, found 234.1491.

N-Acetyl-N-allyl-2-((3,4-dimethoxy)phenyl)ethanamine (***25b***). In a round-bottomed flask fitted with a magnetic stirring bar, 3,4-dimethoxyphenethyl bromide (221 mg, 0.90 mmol) was added in portions to a stirred suspension of K_2CO_3 (16 mg, 1.12 mmol) in allylamine (1.53 g, 2.0 mL, 26.7 mmol) over 30 min. The reaction was stirred at rt overnight, whereupon the reaction mixture was filtered through a pad of Celite, which was washed with CH_2Cl_2 (2 × 15 mL). The filtrate was then evaporated in vacuo. The residue was then purified by flash column chromatography on silica gel (Et_3N/MeOH/CH_2Cl_2 1:10:89), to *N*-allyl-2-((3,4-dimethoxy)phenyl)ethanamine as a yellow oil (139 mg, 70%): R_f = 0.16 (MeOH/CH_2Cl_2 (1:9); UV, PMA); HPLC purity 83% (t_R = 4.33 min); ^1H NMR (300 MHz, $CDCl_3$) δ 6.84−6.67 (m, 3H), 5.91 (ddt, J = 16.4, 10.3, 6.1 Hz, 1H), 5.26−5.08 (m, 2H), 3.87 (s, 3H), 3.86 (s, 3H), 3.30 (dt, J = 6.1, 1.4 Hz, 2H), 2.93−2.77 (m, 2H), 2.64 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.1, 147.7, 134.5, 131.8, 120.7, 118.2, 112.1, 111.5, 56.0, 56.0, 51.8, 50.1, 35.1; MS (ESI) m/z calcd for $C_{13}H_{20}N_2O$ $[M + H]^+$ 222.1, found 222.2.

In a round-bottomed flask fitted with a magnetic stirring bar, acetic anhydride (60.5 mg, 56 μL, 0.61 mmol) was added to a stirred solution of *N*-allyl-2-((3,4-dimethoxy)phenyl)ethanamine (130 mg, 0.59 mmol) and Et_3N (59.5 mg, 82 μL, 0.59 mmol) in CH_2Cl_2 (3.5 mL) at 0 °C. The reaction was stirred at 0 °C and was followed by TLC. Upon full conversion of the amine (10 min), the reaction was quenched with H_2O (8 mL). The reaction mixture was transferred to a separatory funnel, and the organic layer was separated. The aqueous phase was further extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried over $MgSO_4$ and evaporated in vacuo to give the title compound as an orange oil (145 mg, 93%): R_f = 0.58 (MeOH/CH_2Cl_2 (1:9); UV, PMA); HPLC purity >95% (t_R = 6.26 min); IR (neat) cm^{-1} 3484, 2935, 2835, 1634, 1514, 1234, 1026; ^1H NMR (300 MHz, $CDCl_3$) δ 6.83−6.60 (m, 3H), 5.83−5.61 (m,1H), 5.19−5.03 (m, 2H), 3.96 (d, J = 5.9 Hz, 0.5H), 3.84 (s, 3H), 3.82 (s, 3H), 3.75 −3.66 (m, 1.5H), 3.53−3.38 (m, 2H), 2.76 (dt, J = 7.0, 5.9 Hz, 2H), 2.04 (s, 2H), 1.91 (s, 1H), rotamers; ^{13}NMR (75 MHz, $CDCl_3$) δ 170.8, 170.3, 149.1, 148.9, 147.9, 147.5, 133.6, 132.9, 131.9,

130.8, 120.8, 120.7, 117.1, 116.5, 112.0, 111.9, 111.4, 111.2, 55.9, 55.9, 51.8, 49.8, 48.3, 47.8, 34.6, 33.8, 21.6,21.3, rotamers; HRMS (ESI) *m/z* calcd for $C_{15}H_{22}NO_3$ $[M + H]^+$ 264.1600, found 264.1598.

1,2,3,4-Tetrahydroquinoline ***26a***. Following general procedure II, the reaction of **25a** (115 mg, 0.50 mmol), $RuHCl(CO)(PPh_3)_3$ (44.6 mg, 0.48 mmol), and $(PhO)_2PO_2H$ (36.6 mg, 0.15 mmol) gave, after purification by flash column chromatography on silica gel (EtOAc/heptane 1:1), the title compound as a white solid (56.6 mg, 49%): R_f = 0.59 ($MeOH/CH_2Cl_2$ (1:9); UV, PMA); HPLC purity >95% (t_R = 7.55 min); IR (neat) cm^{-1} 3306, 2933, 1644, 1511, 1243; ^1H NMR (300 MHz, $CDCl_3$) δ 7.22−7.04 (m, 2H), 6.89−6.08 (m, 1H), 6.44 (dd, *J* = 13.9, 1.6 Hz, 0.5H), 5.12 (dp, *J* = 13.4, 6.7 Hz, 0.5H), 3.79 (s, 3H), 3.77−3.71 (m, 1H), 3.70−3.61 (m, 1H), 3.48 (dd, *J* = 12.8, 6.7 Hz, 1H), 2.78 (ddd, *J* = 11.6, 10.8, 6.5 Hz, 2H), 2.47 (ddd, *J* = 14.7, 7.4, 1.4 Hz, 1H), 2.17 (s, 1.5H), 2.01−1.90 (m, 1.5H), 1.76 (ddd, J = 10.8, 1.6 Hz, 2H), 1.14−1.08 (m, 1H), rotamers; ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 168.8, 158.6, 158.4, 158.3, 131.2, 130.4, 130.0, 129.9, 129.8, 129.8, 128.5, 125.9, 114.3, 114.1, 114.1, 114.0, 107.9, 106.2, 55.4, 47.7, 45.0, 41.0, 34.8, 32.8, 32.3, 22.4, 22.1, 15.8, 15.8, rotamers; MS (ESI) *m/z* calcd for $C_{14}H_{20}NO_2$ $[M + H]^+$ 234.1489, found 234.1502.

1,2,3,4-Tetrahydroquinoline ***26b***. Following general procedure II, the reaction of **25b** (116 mg, 0.44 mmol), $RuHCl(CO)(PPh_3)_3$ (38.2 mg, 0.041 mmol), and $(PhO)_2PO_2H$ (34.0 mg, 0.14 mmol) gave, after purification by flash column chromatography on silica gel (MeOH/CH_2Cl_2; 1:49), the title compound as a white solid (77.1 mg, 67%): R_f = 0.33 ($MeOH/CH_2Cl_2$ (1:19); UV, PMA); HPLC purity >95% (t_R = 5.90 min); IR (neat) cm^{-1} 2934, 1631, 1516, 1436, 1119; ^1H NMR (300 MHz, $CDCl_3$) δ 76.62−6.56 (m, 2H), 5.45 (dd, *J* = 8.5, 6.2 Hz, 0.5 H), 4.68−4.56 (m, 0.8H), 3.84−3.82 (m, 6H), 3.81−3.72 (m, 0.8H), 3.53 (ddd, *J* = 13.6, 10.4, 5.2 Hz, 0.7H), 3.08−2.57 (m, 2.8H), 2.19 (s, 3H), 1.93−1.70 (m, 2H), 0.97 (dt, *J* = 22.3, 7.4, 3H Hz, 3H), rotamers; ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 148.1, 147.8, 147.7, 147.5, 126.3, 125.1, 111.7, 111.2, 110.5, 109.8, 60.5, 58.8, 56.2, 56.1, 56.0, 55.4, 53.8, 40.9, 35.5, 30.2, 29.5, 28.7, 27.7, 21.7, 14.4, 11.4, 11.1, rotamers; HRMS (ESI) *m/z* calcd for $C_{15}H_{22}NO_3$ $[M + H]^+$ 264.1600, found 264.1595.

General Procedure IV. Alkylation of secondary amines.

*N-Benzyl-N-3-bromoprop-2-enyl-1-tryptamine (****31****).* In a round-bottomed flask fitted with a magnetic stirring bar, 3-bromoallyl bromide (878 mg, 439 μL, 4.39 mmol) was added to a stirred suspension of *N*-benzyltryptamine[27] (1.00 g, 4.00 mmol) and K_2CO_3 (1.657 g, 11.98 mmol) in DMF (12 mL). The reaction mixture was stirred at room temperature, and progress was followed by TLC. Upon full conversion of the amine (30 min), the reaction mixture was evaporated to dryness in vacuo. The residue was taken up in H_2O (50 mL) and CH_2Cl_2 (65 mL) and transferred to a separatory funnel. The organic layer was isolated, and the aqueous phase was further extracted with CH_2Cl_2 (65 mL). The combined organic layers were dried over $MgSO_4$ and evaporated to dryness in vacuo. The residue was purified by flash column chromatography on silica gel ($Et_3N/MeOH/CH_2Cl_2$, 1:1:98) to give the title compound as a yellow oil (regioisomeric mixture, 1.36 g, 92%): R_f = 0.32, 0.36 (EtOAc/heptane (3:7); UV, $KMnO_4$); HPLC purity > 95% (t_R = 6.41 min); IR (neat) cm^{-1} 3417, 3057, 2806, 1619, 1493, 1454, 1338, 1287, 1112, 1011, 736, 697, 422; ^1H NMR (300 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.52 (dd, *J* = 7.8, 0.5 Hz, 1H), 7.42−7.25 (m, 6H), 7.25−7.17 (m, 1H), 7.12 (dddd, *J* = 8.0, 7.0, 3.7, 1.1 Hz, 1H), 7.00−6.96 (m, 1H), 6.38−6.17 (m, 2H), 3.74 (d, *J* = 11.3 Hz, 2H), 3.48−3.41 (m, 1H), 3.19 (dd, *J* = 6.3, 0.7 Hz, 1H), 3.07−2.93 (m, 2H), 2.92−2.81 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.3, 129.1, 128.9, 128.4, 127.6, 127.2 (two signals), 122.1, 122.0 (two signals), 121.7, 119.3 (two signals), 119.0, 118.9, 111.2 (two signals), 58.7, 58.2, 55.3, 54.4, 54.1, 52.8, 23.4, 23.1; HRMS (ESI) *m/z* calcd for $C_{20}H_{21}BrN_2$ $[M + H]^+$ 369.0966 found 369.0954.

THBC ***32****, Tandem Reaction.* In a Schlenk tube fitted with a magnetic stirring bar and a reflux condenser, phenylboronic acid (36.3 mg, 0.29 mmol), $Pd_2(dba)_3$ (12.4 mg, 0.014 mmol), and KF (47.2 mg, 0.81 mmol) were added to a stirred solution of **31** (100 mg, 0.27 mmol) and P(*t*-Bu)$_3$ (6.6 mg, 7.9 μL, 0.032 mmol) in THF (271 μL). The reaction mixture was stirred overnight at rt, whereupon toluene (271 μL) was added and the solution was stirred at reflux for 16 h. The reaction mixture was diluted with CH_2Cl_2 (20 mL) and filtered through a pad of Celite, which was washed with CH_2Cl_2 (2 × 20 mL). The filtrate was concentrated in vacuo, and the residue was purified by flash column chromatography ($Et_3N/MeOH/CH_2Cl_2$, 1:1:98) to give the title compound as a yellow oil (18 mg, 18%). Analytical data are in accordance with those previously reported:[4b] R_f = 0.36 (EtOAc/heptane (1:4); UV, $KMnO_4$); HPLC purity 87% (t_R = 7.34 min); ^1H NMR (300 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.52 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.47−7.07 (m, 13H), 3.80 (d, *J* = 4.0 Hz, 2H), 3.70 (dd, *J* = 8.1, 4.4 Hz, 1H), 3.35−3.22 (m, 1H), 3.04−2.55 (m, 5H), 2.22−1.97 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.6, 139.9, 135.9, 135.2, 129.1, 128.6, 128.5, 128.4, 127.3, 127.1, 125.8, 121.4, 119.3, 118.1, 110.8, 107.9, 57.4, 56.2, 44.7, 36.5, 32.4, 17.9; MS (ESI) *m/z* calcd for $C_{26}H_{26}N_2$ $[M + H]^+$ 367.2, found 367.2.

THBC ***32****, Tandem Reaction.* In a Schlenk tube fitted with a magnetic stirring bar and a reflux condenser phenylboronic acid (36.3 mg, 0.29 mmol), $Pd_2(dba)_3$ (12.4 mg, 0.014 mmol), and KF (47.2 mg, 0.81 mmol) were added to a stirred solution of **31** (100 mg, 0.27 mmol) and P(*t*-Bu)$_3$ (6.6 mg, 7.9 μL, 0.032 mmol) in THF (271 μL). The reaction mixture was stirred overnight at rt, whereupon toluene (271 μL) and $Rh(PPh_3)_3Cl$ (22.5 mg, 0.024 mmol) were added, and the reaction mixture was stirred for additional 3 days at reflux, whereupon it was diluted with CH_2Cl_2 (20 mL) and filtered through a pad of Celite, which was washed with CH_2Cl_2 (2 × 20 mL). The filtrate was concentrated to dryness in vacuo, and the residue was purified by flash column chromatography ($Et_3N/MeOH/CH_2Cl_2$, 1:1:98) to give the title compound as a yellow oil (20 mg, 20%).

General Procedure V. Suzuki cross-coupling of allylic amines.

*N-Benzyl-N-3-phenylprop-2-enyl-1-tryptamine (****33a****).* In a Schlenk tube fitted with a magnetic stirring bar and a reflux condenser, phenylboronic acid (109. mg, 0.894 mmol), $Pd_2(dba)_3$ (37.2 mg, 0.041 mmol), and KF (142 mg, 2.44 mmol) were added to a stirred solution of **29** (300 mg, 0.812 mmol) and P(*t*-Bu)$_3$ (19.7 mg, 23.6 μL, 0.097 mmol) in THF (812 μL). The reaction mixture was stirred overnight at reflux, whereupon it was diluted with CH_2Cl_2 (30 mL) and filtered through a pad of Celite, which was washed with CH_2Cl_2 (2 × 30 mL). The filtrate was concentrated in vacuo, and the residue was purified by flash column chromatography ($Et_3N/MeOH/CH_2Cl_2$, 1:1:98) and then (Et_3N/EtOAc/heptane, 1:50:50) to give the title compound as a yellow oil (mixture of cis−trans isomers (3:2), 193 mg, 65%): R_f = 0.30 (EtOAc/heptane, (3:7); UV, $KMnO_4$); HPLC purity > 95% (t_R = 7.24 and 7.30 min); IR (neat) cm^{-1} 3425, 3025, 2921, 1494, 1454, 1354, 1114, 739, 698; ^1H NMR (300 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.58−7.02 (m, 14H), 6.93 (dd, *J* = 11.1, 2.2 Hz, 1H), 6.63 (d, *J* = 11.0 Hz, 0.6H), 6.56 (d, *J* = 15.7 Hz, 0.4H), 6.35 (dt, *J* = 15.9, 6.5 Hz, 0.4H), 6.01−5.88 (m, 0.6H), 3.77 (d, *J* = 17.3 Hz, 2H), 3.54 (dd, *J* = 6.4, 1.9 Hz, 1H), 3.45−3.36 (m, 1H), 3.10−2.79 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.8, 139.7, 137.5 (two signals), 136.4 (two signals), 132.7 (two signals), 131.4, 130.9, 129.3 (two signals), 129.2, 128.8, 128.5 (two signals), 128.4, 128.0, 127.8, 127.6, 127.2, 127.1 (two signals), 126.6, 122.1, 121.8, 121.7, 119.4 (two signals), 119.2 (two signals), 114.8, 111.3 (two signals), 58.7, 58.6, 56.6, 54.6, 54.4, 51.8, 23.3, 23.2; HRMS (ESI) */z* calcd for $C_{26}H_{26}N_2$ $[M + H]^+$ 367.2174, found 367.2169.

*N-Benzyl-N-3-(p-tolyl)prop-2-enyl-1-tryptamine (****33b****).* Following general procedure V, the reaction of **31** (200 mg, 0.54 mmol), *p*-tolylboronic acid (81.0 mg, 0.60 mmol), $Pd_2(dba)_3$ (24.8 mg, 0.027 mmol), P(*t*-Bu)$_3$ (13.1 mg, 15.8 μL, 0.065 mmol), and KF (94.4 mg, 1.63 mmol) gave, after flash column chromatography ($Et_3N/MeOH/CH_2Cl_2$, 1:2:97) and then (Et_3N/EtOAc/heptane, 1:50:50), the title compound as a brown oil (mixture of cis−trans isomers (3:2), 130 mg, 63%): R_f = 0.31 (EtOAc/heptane (3:7); UV, $KMnO_4$); HPLC purity 92% (t_R = 8.60 and 8.68 min); IR (neat) cm^{-1} 3421, 3025, 2921, 1608, 1512, 1493, 1455, 1356, 1116, 738, 699; ^1H NMR (300 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.55−7.27 (m, 9H), 7.22−7.05 (m, 4H), 6.94 (dd, *J* = 10.3, 2.3 Hz, 1H), 6.60 (d, *J* = 11.9 Hz, 0.6H), 6.53 (d, *J* = 16.1 Hz, 0.4H), 6.30 (dt, *J* = 15.8, 6.6 Hz, 0.4H), 5.94−5.85 (m, 0.6H), 3.78 (d, *J* = 15.4 Hz, 2H), 3.56 (dd, *J* = 6.4, 1.8 Hz, 1H), 3.41 (d, *J* = 6.0 Hz, 1H), 3.05−2.83 (m, 4H), 2.37 (d, *J* = 3.2 Hz, 3H); ^{13}C NMR (75

MHz, $CDCl_3$) δ 138.9, 138.3, 137.9 (two signals), 136.1 (two signals), 134.3, 132.9, 131.0, 130.8, 130.6 (two signals), 130.6, 130.0, 129.3, 128.7 (two signals), 128.0, 123.6, 123.3 (two signals), 120.9, 120.8, 120.7, 116.2, 112.8 (two signals), 60.2, 60.0, 58.0, 56.0, 55.8, 53.3, 24.7, 24.6, 23.0; HRMS (ESI) m/z calcd for $C_{27}H_{28}N_2$ $[M + H]^+$ 381.2331, found 381.2323.

*N-Benzyl-N-3-(m-tolyl)prop-2-enyl-1-tryptamine (**33c**).* Following general procedure V, the reaction of **31** (300 mg, 0.81 mmol), *m*-tolylboronic acid (122 mg, 0.89 mmol), $Pd_2(dba)_3$ (37.2 mg, 0.041 mmol), P(*t*-Bu)$_3$ (19.7 mg, 23.6 μL, 0.097 mmol), and KF (142 mg, 2.44 mmol) gave, after flash column chromatography (Et_3N/MeOH/CH_2Cl_2, 1:2:97) and then (Et_3N/EtOAc/heptane, 1:50:50), the title compound as a brown oil (mixture of cis−trans isomers (3:2), 203 mg, 66%): R_f = 0.32 (EtOAc/heptane (3:7); UV, $KMnO_4$); HPLC purity 92% (t_R = 7.59 and 7.66 min); IR (neat) cm^{-1} 3419, 3026, 2918, 1602, 1493, 1454, 1355, 1092, 738, 697; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.74−7.21 (m, 13H), 7.11 (dd, *J* = 11.8, 1.5 Hz, 1H), 6.77 (d, *J* = 12.0 Hz, 0.6H), 6.69 (d, *J* = 16.1 Hz, 0.4H), 6.51 (dt, *J* = 15.3, 6.2 Hz, 0.4H), 6.09 (dt, *J* = 12.2, 6.1 Hz, 0.6H), 3.94 (d, *J* = 15.0 Hz, 2H), 3.72 (d, *J* = 6.4 Hz, 1H), 3.57 (d, *J* = 6.5 Hz, 1H), 3.24−2.99 (m, 4H), 2.54 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.8, 139.7, 138.3, 137.9, 137.4 (two signals), 136.4 (two signals), 132.8, 131.5, 130.6, 129.9, 129.3, 128.7, 128.5 (two signals), 128.4, 128.3, 127.9, 127.8, 127.7, 127.3, 127.1 (two signals), 126.3, 123.7, 122.1 (two signals), 121.8, 121.7, 119.4 (two signals), 119.2, 114.8, 111.3 (two signals), 58.7, 58.6, 56.5, 54.5, 54.4, 51.8, 23.3, 23.2, 21.8, 21.7; HRMS (ESI) m/z calcd for $C_{27}H_{28}N_2$ $[M + H]^+$ 381.2331, found 381.2319.

*N-Benzyl-N-3-(3,4-dimethoxyphenyl)prop-2-enyl-1-tryptamine (**33d**).* Following general procedure V, the reaction of **31** (300 mg, 0.81 mmol), 3,4-dimethoxyphenylboronic acid (163 mg, 0.89 mmol), $Pd_2(dba)_3$ (37.2 mg, 0.041 mmol), P(*t*-Bu)$_3$ (19.7 mg, 23.6 μL, 0.097 mmol), and KF (142 mg, 2.437 mmol) gave, after flash column chromatography (Et_3N/MeOH/CH_2Cl_2, 1:1:98) and then (Et_3N/EtOAc/heptane, 1:50:50), the title compound as a light brown oil (mixture of cis−trans isomers (2:3), 196 mg, 57%): R_f = 0.21 (EtOAc/heptane (1:1); UV, $KMnO_4$); HPLC purity > 95% (t_R = 6.96 min); IR (neat) cm^{-1} 3373, 2932, 2833, 1601, 1512, 1454, 1337, 1256, 1137, 1023, 737, 698; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.57−7.24 (m, 8H), 7.22−7.14 (m, 1H), 7.13−7.01 (m, 1H), 6.98−6.88 (m, 2H), 6.86−6.78 (m, 2H), 6.56 (d, *J* = 10.6 Hz, 0.4H), 6.48 (d, *J* = 15.4 Hz, 0.6H), 6.20 (dt, *J* = 15.8, 6.6 Hz, 0.6H), 5.90−5.81 (m, 0.4H), 3.90 (d, *J* = 2.7 Hz, 6H), 3.85 (s, 1H), 3.77 (d, *J* = 12.7 Hz, 2H), 3.54 (dd, *J* = 6.4, 1.8 Hz, 1H), 3.39 (d, *J* = 5.7 Hz, 1H), 3.04−2.85 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.1, 148.7, 148.6, 148.1, 139.8, 139.6, 136.4, 136.3, 132.3, 131.0, 130.5, 130.4, 129.4, 129.2, 128.4 (two signals), 127.7, 127.1, 125.9, 122.0, 121.8, 121.7 (two signals), 119.6, 119.3, 119.2, 119.1, 119.0, 114.7, 112.4, 111.2, 111.0, 108.8, 58.6, 56.6, 56.1, 56.0 (two signals), 54.4, 54.3, 51.8, 23.2, 23.1; HRMS (ESI) m/z calcd for $C_{28}H_{30}N_2O_2$ $[M + H]^+$ 427.2386, found 427.2383.

*N-Benzyl-N-3-(4-nitrophenyl)prop-2-enyl-1-tryptamine (**33e**).* Following general procedure V, the reaction of **31** (200 mg, 0.54 mmol), 4-nitrophenylboronic acid (99 mg, 0.60 mmol), $Pd_2(dba)_3$ (258 mg, 0.027 mmol), P(*t*-Bu)$_3$ (13.1 mg, 15.8 μL, 0.065 mmol), and KF (94 mg, 1.63 mmol) gave, after flash column chromatography (Et_3N/CH_2Cl_2, 1:99) and then (Et_3N/EtOAc/heptane, 1:50:50), the title compound as a yellow oil (mixture of cis−trans isomers (1:1), 110 mg, 49%): R_f = 0.33 (EtOAc/heptane (1:1); UV, $KMnO_4$); HPLC purity 88% (t_R = 7.16 and 7.25 min); IR (neat) cm^{-1} 3416, 2802, 1594, 1511, 1454, 1337, 1107, 856, 736, 697; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.48 (dd, *J* = 11.7, 7.9 Hz, 1H), 7.42−7.13 (m, 9H), 7.11−6.89 (m, 4H), 6.54 (d, *J* = 11.2 Hz, 0.5H), 6.47 (d, *J* = 15.7 Hz, 0.5H), 6.21 (dt, *J* = 15.9, 6.5 Hz, 0.5H), 5.94−5.84 (m, 0.5H), 3.74 (d, *J* = 16.4 Hz, 2H), 3.45 (dd, *J* = 6.5, 1.8 Hz, 1H), 3.35 (d, *J* = 6.5 Hz, 1H), 3.05−2.79 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.0, 163.5, 160.8, 160.3, 139.8, 139.6, 136.5, 136.4, 133.6 (two signals), 133.5 (two signals), 131.4, 130.8, 130.7 (two signals), 130.4, 129.3, 129.2, 128.5 (two signals), 128.0, 127.9, 127.8 (two signals), 127.2, 122.1, 121.8, 121.7, 119.4 (two signals), 119.2, 119.1, 115.8, 115.5, 115.4, 115.1, 114.8 (two signals), 111.3 (two signals), 58.7 (two signals), 56.5, 54.6, 54.4, 51.6, 45.4, 23.4, 23.2; HRMS (ESI) m/z calcd for $C_{26}H_{25}N_3O_2$ $[M + H]^+$ 412.2025, found 412.2025.

*N-Benzyl-N-3-(3-nitrophenyl)prop-2-enyl-1-tryptamine (**33f**).* Following general procedure V, the reaction of **31** (250 mg, 0.68 mmol), 3-nitrophenylboronic acid (124 mg, 0.75 mmol), $Pd_2(dba)_3$ (31.0 mg, 0.034 mmol), P(*t*-Bu)$_3$ (16.4 mg, 19.7 μL, 0.081 mmol), and KF (118 mg, 2.03 mmol) gave, after flash column chromatography (Et_3N/CH_2Cl_2, 1:99) and then (Et_3N/EtOAc/heptane, 1:50:50), the title compound as a yellow oil (mixture of cis−trans isomers (2:3), 138 mg, 50%): R_f = 0.34 (EtOAc/heptane (1:1); UV, $KMnO_4$); HPLC purity > 95% (t_R = 7.12 and 7.23 min); IR (neat) cm^{-1} 3421, 2921, 1526, 1455, 1349, 740; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12−7.98 (m, 2H), 7.93 (d, *J* = 10.1 Hz, 1H), 7.55−7.18 (m, 9H), 7.18−7.09 (m, 1H), 7.08−6.97 (m, 1H), 6.93 (dd, *J* = 12.6, 2.3 Hz, 1H), 6.56 (d, *J* = 11.6 Hz, 0.4H), 6.48 (d, *J* = 17.1 Hz, 0.6H), 6.35 (dt, *J* = 15.9, 6.1 Hz, 0.4H), 6.08−5.97 (m, 0.6H), 3.72 (d, *J* = 17.4 Hz, 2H), 3.43 (dd, *J* = 6.5, 1.8 Hz, 1H), 3.33 (dd, *J* = 6.1, 1.0 Hz, 1H), 3.01−2.77 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.6, 148.2, 139.6, 139.2, 139.0, 138.8, 136.3 (two signals), 134.9, 133.7, 132.1, 131.8, 129.8, 129.4, 129.1 (two signals), 129.0, 128.4, 128.3, 127.6 (two signals), 127.1, 123.7, 122.0, 121.9, 121.7 (two signals), 121.6, 120.9, 119.2, 118.9 (two signals), 114.5, 114.4, 111.2 (two signals), 58.6 (two signals), 56.1, 54.5 (two signals), 54.4, 51.5, 23.4, 23.1; HRMS (ESI) m/z calcd for $C_{26}H_{25}N_3O_2$ $[M + H]^+$ 412.2025, found 412.2023.

*N-Benzyl-N-3-(4-(trifluoromethyl)phenyl)prop-2-enyl-1-tryptamine (**33g**).* Following general procedure V, the reaction of **31** (300 mg, 0.81 mmol), 4-(trifluoromethyl)phenylboronic acid (170 mg, 0.89 mmol), $Pd_2(dba)_3$ (37.2 mg, 0.041 mmol), P(*t*-Bu)$_3$ (19.7 mg, 23.6 μL, 0.097 mmol), and KF (142 mg, 2.44 mmol) gave after flash column chromatography (Et_3N/MeOH/CH_2Cl_2, 1:1:98), the title compound as a brown oil (mixture of cis−trans isomers (3:2), 208 mg, 59%): R_f = 0.26 (EtOAc/heptane (3:7); UV, $KMnO_4$); HPLC purity > 95% (t_R = 7.78 and 7.87 min); IR (neat) cm^{-1} 3249, 3058, 3027, 2923, 2803, 1615, 1455, 1323, 1163, 1116, 1066, 1025, 853, 739, 699;; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.61−6.92 (m, 14H), 6.62 (d, *J* = 11.0 Hz, 0.6H), 6.55 (d, *J* = 13.6 Hz, 0.4H), 6.40 (dt, *J* = 15.8, 6.1 Hz, 0.4H), 6.10−5.98 (m, 0.6H), 3.76 (d, *J* = 19.7 Hz, 2H), 3.48 (d, *J* = 6.5 Hz, 1H), 3.40 (d, *J* = 6.3 Hz, 1H), 3.08−2.82 (m, 4H).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.8, 139.6, 139.4, 136.3 (two signals), 133.0, 131.1, 130.9, 130.0, 129.2, 129.1, 129.0, 128.4, 128.3, 127.6, 127.1, 126.5, 125.6, 125.5, 125.2 (two signals), 125.1, 122.0, 121.7, 121.6, 119.3 (two signals), 119.0, 118.9, 58.6, 56.3, 54.5, 54.4, 51.5, 23.3, 23.1; HRMS (ESI) m/z calcd for $C_{27}H_{25}F_3N_2$ $[M + H]^+$ 435.2048, found 435.2047.

*N-Benzyl-N-3-(4-fluorophenyl)prop-2-enyl-1-tryptamine (**33h**).* Following general procedure V, the reaction of **31** (300 mg, 0.81 mmol), 4-fluorophenylboronic acid (124 mg, 0.89 mmol), $Pd_2(dba)_3$ (37.2 mg, 0.041 mmol), P(*t*-Bu)$_3$ (19.7 mg, 23.6 μL, 0.097 mmol), and KF (144 mg, 2.44 mmol) gave, after flash column chromatography (Et_3N/MeOH/CH_2Cl_2, 1:1:98) and then (Et_3N/EtOAc/heptane, 1:50:50), the title compound as a brown oil (mixture of cis−trans isomers (1:1), 164 mg, 53%): R_f = 0.20 (EtOAc/heptane (3:7); UV, $KMnO_4$); HPLC purity > 95% (t_R = 7.31 and 7.38 min); IR (neat) cm^{-1} 3417, 3027, 2801, 1600, 1506, 1454, 1338, 1223, 1157, 1092, 1011, 968, 842, 735, 697, 422; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.57−6.92 (m, 14H), 6.57 (d, *J* = 10.8 Hz, 0.5H), 6.50 (d, *J* = 15.7 Hz, 0.5H), 6.24 (dt, *J* = 15.9, 6.5 Hz, 0.5H), 5.99−5.84 (m, 0.5H), 3.77 (d, *J* = 16.4 Hz, 2H), 3.48 (dd, *J* = 6.5, 1.8 Hz, 1H), 3.39 (d, *J* = 6.5 Hz, 1H), 3.08−2.82 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.9, 163.4, 160.6, 160.1, 139.7, 139.4, 136.3 (two signals), 133.5, 133.4 (two signals), 133.3, 131.2, 130.7, 130.6, 130.5, 130.2, 129.1 (two signals), 128.4, 128.3, 127.9, 127.8, 127.7, 127.6, 127.0, 122.0, 121.7, 121.6, 119.3, 119.2, 119.0 (two signals), 115.6, 115.4, 115.2, 115.0, 114.6 (two signals), 111.2 (two signals), 58.6, 58.5, 56.3, 54.4, 54.2, 51.4, 45.3, 23.2, 23.1; HRMS (ESI) m/z calcd for $C_{26}H_{25}FN_2$ $[M + H]^+$ 385.2080, found 385.2079.

*N-Benzyl-N-3-(6-methoxynaphthalen-2-yl)prop-2-enyl-1-tryptamine (**33i**).* Following general procedure V, the reaction of **31** (300 mg, 0.81 mmol), 6-methoxy-2-naphthaleneboronic acid (181 mg, 0.89 mmol), $Pd_2(dba)_3$ (37.2 mg, 0.041 mmol), P(*t*-Bu)$_3$ (19.7 mg, 23.6

μL, 0.097 mmol), and KF (142 mg, 2.44 mmol) gave, after flash column chromatography (Et_3N/MeOH/CH_2Cl_2, 1:2:97) and then (Et_3N/EtOAc/heptane, 1:50:50), the title compound as a light brown oil (mixture of cis−trans isomers (1:1), 209 mg, 58%): R_f = 0.27 (EtOAc/heptane (3:7); UV, $KMnO_4$); HPLC purity 94% (t_R = 7.81 and 7.87 min); IR (neat) cm^{-1} 3418, 2933, 1732, 1627, 1600, 1482, 1454, 1388, 1264, 1164, 1118, 1028, 968, 853, 807, 736, 698, 473, 423; ^1H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, J = 10.0 Hz, 1H), 7.75−7.03 (m, 15H), 6.94 (dd, J = 18.7, 2.3 Hz, 1H), 6.75 (d, J = 11.7 Hz, 0.5H), 6.68 (d, J = 15.8 Hz, 0.5H), 6.42 (dt, J = 15.9, 6.5 Hz, 0.5H), 6.04−5.94 (m, 0.5H), 3.94 (d, J = 2.4 Hz, 3H), 3.79 (d, J = 18.5 Hz, 2H), 3.64 (dd, J = 6.4, 1.8 Hz, 1H), 3.45 (dd, J = 6.5, 0.9 Hz, 1H), 3.11−3.01 (m, 1H), 3.00−2.83 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.0, 157.9, 139.9, 139.8, 136.4 (two signals), 134.2, 133.6, 132.9 (two signals), 132.7, 131.5, 130.6, 129.8, 129.7, 129.3, 128.9, 128.5 (two signals), 128.1, 127.9 (two signals), 127.4, 127.3, 127.1 (two signals), 126.7, 126.1, 124.5, 122.1 (two signals), 121.8, 121.7, 119.4, 119.3, 119.2 (two signals), 114.8, 111.3, 106.1, 105.9, 58.7, 58.6, 56.7, 55.6 (two signals), 54.7, 54.5, 54.4, 51.9, 50.1, 23.4, 23.2; HRMS (ESI) m/z calcd for $C_{31}H_{30}N_2O$ $[M + H]^+$ 447.2436, found 447.2435.

*N-Benzyl-N-3-(furan-2-yl)prop-2-enyl-1-tryptamine (**33j**).* Following general procedure V, the reaction of **31** (200 mg, 0.54 mmol), 2-furanylboronic acid (676 mg, 0.60 mmol), $Pd_2(dba)_3$ (25 mg, 0.027 mmol), P(*t*-Bu)$_3$ (13.1 mg, 15.8 μL, 0.065 mmol), and KF (95 mg, 1.63 mmol) gave, after flash column chromatography (Et_3N/MeOH/CH_2Cl_2, 1:1:98) and then (Et_3N/EtOAc/heptane, 1:50:50), the title compound as a light brown oil (mixture of cis−trans isomers (1:1), 105 mg, 54%): R_f = 0.28 (EtOAc/heptane (3:7); UV, $KMnO_4$); HPLC purity > 95% (t_R = 6.93 min); IR (neat) cm^{-1} 3416, 3027, 2802, 1601, 1491, 1454, 1338, 1111, 1011, 963, 921, 730, 697, 593, 423; ^1H NMR (300 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.52 (td, J = 7.8, 0.5 Hz, 1H), 7.46−7.27 (m, 7H), 7.24−7.16 (m, 1H), 7.14−7.05 (m, 1H), 6.96 (dd, J = 4.6, 2.3 Hz, 1H), 6.46−6.28 (m, 2.5H), 6.24 (dd, J = 14.0, 3.3 Hz, 1H), 5.81 (dt, J = 12.3, 6.3 Hz, 0.5H), 3.80 (d, J = 5.8 Hz, 2H), 3.71 (dd, J = 6.3, 1.9 Hz, 1H), 3.38 (d, J = 6.0 Hz, 1H), 3.08−2.97 (m, 2H), 2.97−2.86 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.0, 152.9, 141.9, 141.8, 139.6, 136.3, 129.2, 129.0, 128.5, 128.3 (two signals), 127.7, 127.0 (two signals), 126.4, 121.9, 121.7, 121.6, 121.0, 119.2, 119.0 (two signals), 118.7, 114.6 (two signals), 111.3, 111.1, 110.0, 107.2, 58.7, 58.3, 55.9, 54.6, 54.5, 54.2, 52.4, 23.3, 23.1; MS (ESI) m/z calcd for $C_{24}H_{24}N_2O$ $[M + H]^+$ 357.2, found 357.3; HRMS (ESI) m/z calcd for $C_{24}H_{24}N_2O$ $[M + H]^+$ 357.1967, found 357.1958.

*N-Benzyl-N-5-phenylpenta-2,4-dienyl-1-tryptamine (**33k**).* Following general procedure V, the reaction of **31** (400 mg, 1.083 mmol), *trans*-2-phenylvinylboronic acid (176.3 mg, 1.191 mmol), $Pd_2(dba)_3$ (99.2 mg, 0.108 mmol), P(*t*-Bu)$_3$ (53 mg, 63.1 μL, 0.26 mmol), and KF (189 mg, 3.25 mmol) gave, after flash column chromatography (Et_3N/MeOH/CH_2Cl_2, 1:1:98), the title compound as a dark brown oil (mixture of cis−trans isomers (1:1), 211 mg, 50%): R_f = 0.28 (EtOAc/heptane (3:7); UV, $KMnO_4$); IR (neat) cm^{-1} 3420, 3057, 3025, 2918, 2801, 1597, 1493, 1454, 1337, 1091, 988, 907, 735, 691, 422; HPLC purity > 95% (t_R = 7.73 min; ^1H NMR (300 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.48−7.38 (m, 1H), 7.34−7.17 (m, 9H), 7.17−7.11 (m, 2H), 7.08 (dd, J = 12.7, 5.6 Hz, 1H), 7.01−6.94 (m, 1H), 6.91 (dd, J = 11.2, 1.0 Hz, 0.5H), 6.85 (t, J = 2.3 Hz, 1H), 6.70 (dd, J = 15.5, 10.4 Hz, 0.5H), 6.42 (dd, J = 20.0, 15.6 Hz, 1H), 6.34−6.17 (m, 1H), 5.89−5.76 (m, 0.5H), 5.61 (dt, J = 11.0, 7.0 Hz, 0.5H), 3.64 (d, J = 2.3 Hz, 2H), 3.35 (dd, J = 7.1, 1.3 Hz, 1H), 3.21 (d, J = 6.6 Hz, 1H), 2.96−2.72 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.7, 139.6, 137.5, 137.4, 136.3, 136.2, 133.3, 133.1, 132.1, 131.6, 131.5, 129.5, 129.2, 129.1, 128.8, 128.7, 128.4, 127.7, 127.6, 127.5, 127.0, 126.6, 126.4, 124.3, 122.0, 121.9, 121.6, 119.3, 119.0, 118.9, 114.6, 111.2, 58.4 (two signals), 56.0, 54.4, 54.2, 50.8, 23.3, 23.2; HRMS (ESI) m/z calcd for $C_{28}H_{28}N_2$ $[M + H]^+$ 393.2331, found 393.2322.

General Procedure (VI). Synthesis of THBCs via isomerization/iminium cyclization of Suzuki products.

*THBC **32**.* In a Schlenk tube fitted with a magnetic stirring bar and a reflux condenser, **33a** (150 mg, 0.41 mmol), $RuHCl(CO)(PPh_3)_3$ (39.1 mg, 0.041 mmol), and $(PhO)_2PO_2H$ (30.7 mg, 0.12 mmo) were dissolved in toluene (4.1 mL). The reaction mixture was stirred at reflux, and progress was followed by TLC. Upon full conversion of the starting material (8 h), the reaction mixture was evaporated to dryness in vacuo. The residue was purified by flash column chromatography on silica gel (Et_3N/EtOAc/heptane, 1:10:90) to give the title compound as a yellow oil (106 mg, 71%). Analytical data are in accordance with those previously reported:[4b] R_f = 0.36 (EtOAc/heptane (1:4); UV, $KMnO_4$); HPLC purity 87% (t_R = 7.34 min); ^1H NMR (300 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.52 (dd, J = 7.7, 1.3 Hz, 1H), 7.47−7.07 (m, 13H), 3.80 (d, J = 4.0 Hz, 2H), 3.70 (dd, J = 8.1, 4.4 Hz, 1H), 3.35−3.22 (m, 1H), 3.04−2.55 (m, 5H), 2.22−1.97 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.6, 139.9, 135.9, 135.2, 129.1, 128.6, 128.5, 128.4, 127.3, 127.1, 125.8, 121.4, 119.3, 118.1, 110.8, 107.9, 57.4, 56.2, 44.7, 36.5, 32.4, 17.9; MS (ESI) m/z calcd for $C_{26}H_{26}N_2$ $[M + H]^+$ 367.2, found 367.2.

*THBC **34b**.* Following general procedure VI, the reaction of **33b** (80 mg, 0.21 mmol), $RuHCl(CO)(PPh_3)_3$ (20.1 mg, 0.021 mmol) and $(PhO)_2PO_2H$ (15.8 mg, 0.063 mmol) gave, after flash column chromatography (Et_3N/EtOAc/heptane, 1:10:90), the title compound as a yellow oil (47 mg, 59%): R_f = 0.37 (EtOAc/heptane, (1:4); UV, $KMnO_4$); HPLC purity 95%, (t_R = 7.61 min); IR (neat) cm^{-1} 3403, 3231, 3055, 3025, 2922, 2842, 1514, 1493, 1452, 1300, 1113, 1024, 1006, 814, 735, 697; ^1H NMR (300 MHz, $CDCl_3$) δ 7.68 (s, 1H), 7.44−7.38 (m, 1H), 7.36−7.30 (m, 2H), 7.30−7.14 (m, 4H), 7.03 (m, 3H), 6.99−6.94 (m, 2H), 6.88 (d, J = 8.0 Hz, 1H), 3.68 (d, J = 4.9 Hz, 1H), 3.56 (dd, J = 8.0, 4.4 Hz, 1H), 3.22−3.10 (m, 1H), 2.92−2.74 (m, 2H), 2.73−2.43 (m, 4H), 2.21 (d, J = 5.1 Hz, 3H), 2.10−1.83 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.9, 139.5, 135.9, 135.3, 135.2, 129.2, 129.1, 128.5, 128.4, 127.4, 127.1, 121.4, 119.3, 118.1, 110.8, 107.9, 57.4, 56.2, 44.6, 36.6, 31.9, 21.1, 17.9; HRMS (ESI) m/z calcd for $C_{27}H_{28}N_2$ $[M + H]^+$ 381.2331, found 381.2327.

*THBC **34c**.* Following general procedure VI, the reaction of **33c** (150 mg, 0.394 mmol), $RuHCl(CO)(PPh_3)_3$ (37.6 mg, 0.039 mmol), and $(PhO)_2PO_2H$ (29.6 mg, 0.12 mmol) gave, after flash column chromatography (Et_3N/EtOAc/heptane, 1:10:90), the title compound as a yellow oil (90 mg, 60%): R_f = 0.37 (EtOAc/heptane (1:4); UV, $KMnO_4$); HPLC purity > 95%, (t_R = 7.62 min); IR (neat) cm^{-1} 3249, 3026, 2936, 1606, 1452, 1300, 1025, 1006, 908, 732, 697; ^1H NMR (300 MHz, $CDCl_3$) δ 7.52 (s, 1H), 7.48−7.39 (m, 1H), 7.39−7.32 (m, 2H), 7.32−7.21 (m, 4H), 7.15−7.00 (m, 3H), 7.00−6.88 (m, 2H), 6.81 (d, J = 6.5 Hz, 1H), 3.71 (d, J = 3.8 Hz, 1H), 3.65−3.55 (m, 1H), 3.27−3.13 (m, 1H), 2.99−2.80 (m, 2H), 2.80−2.46 (m, 4H), 2.23 (d, J = 5.7 Hz, 3H), 2.13−1.86 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.6, 139.9, 138.0, 135.9, 135.3, 129.4, 129.1, 128.4, 127.1, 126.5, 125.6, 121.3, 119.2, 118.1, 110.8, 107.9, 57.4, 56.2, 44.7, 36.5, 32.3, 21.5, 18.0; HRMS (ESI) m/z calcd for $C_{27}H_{28}N_2$ $[M + H]^+$ 381.2331, found 381.2334.

*THBC **34d**.* Following general procedure VI, the reaction of **33d** (150 mg, 0.35 mmol), $RuHCl(CO)(PPh_3)_3$ (33.6 mg, 0.035 mmol), and $(PhO)_2PO_2H$ (26.4 mg, 0.11 mmol) gave, after flash column chromatography (Et_3N/EtOAc/heptane, 1:25:75), the title compound as an off-white solid (74 mg, 49%): mp 77−79 °C; R_f = 0.26 (EtOAc/heptane (3:7); UV, $KMnO_4$); HPLC purity > 95%, (t_R = 6.98 min); IR (neat) cm^{-1} 3362, 3057, 3027, 3001, 2933, 2835, 1590, 1512, 1450, 1259, 1232, 1138, 1025, 907, 733, 697; ^1H NMR (300 MHz, $CDCl_3$) δ 7.62 (s, 1H), 7.56−7.51 (m, 1H), 7.45 (dd, J = 8.1, 1.5 Hz, 2H), 7.42−7.26 (m, 5H), 7.20−7.09 (m, 2H), 6.76 (d, J = 8.1 Hz, 1H), 6.67 (d, J = 1.9 Hz, 1H), 6.62 (dd, J = 8.1, 2.0 Hz, 1H), 3.86 (s, 3H), 3.80 (s, 3H), 3.69 (dd, J = 8.2, 4.4 Hz, 1H), 3.35−3.23 (m, 1H), 3.06−2.86 (m, 2H), 2.84−2.55 (m, 4H), 2.21−1.94 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.9, 147.6, 140.0, 135.9, 135.2, 135.1, 129.0, 128.4, 127.4, 127.1, 121.5, 120.3, 119.4, 118.2, 111.9, 111.3, 110.8, 108.1, 57.4, 56.3, 56.0, 55.9, 44.6, 36.7, 32.0, 17.9; HRMS (ESI) m/z calcd for $C_{28}H_{30}N_2O_2$ $[M + H]^+$ 427.2386, found 427.2375.

*THBC **34e**.* Following general procedure VI, the reaction of **33e** (75 mg, 0.182 mmol), $RuHCl(CO)(PPh_3)_3$ (17.4 mg, 0.018 mmol), and $(PhO)_2PO_2H$ (13.7 mg, 0.055 mmol) gave, after flash column chromatography (Et_3N/EtOAc/heptane, 1:25:75), the title compound as a yellow oil (45 mg, 60%). Analytical data are in accordance with those previously reported:[4b] R_f = 0.36 (EtOAc/heptane (3:7); UV, $KMnO_4$); HPLC purity > 95%, (t_R =7.30 min); ^1H NMR (300 MHz,

dx.doi.org/10.1021/jo402192s | J. Org. Chem. 2013, 78, 12545−12565

$CDCl_3$) δ 8.06−7.98 (m, 2H), 7.65 (d, J = 9.4 Hz, 1H), 7.54−7.48 (m, 1H), 7.43−7.25 (m, 6H), 7.19−7.05 (m, 4H), 3.77 (s, 2H), 3.64 (dd, J = 8.7, 3.9 Hz, 1H), 3.33−3.21 (m, 1H), 3.06−2.95 (m, 1H), 2.95−2.68 (m, 3H), 2.66−2.54 (m, 1H), 2.19−1.92 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.8, 146.2, 139.8, 136.0, 134.5, 129.3, 129.2, 128.5, 127.4, 127.3, 123.7, 121.8, 119.6, 118.3, 110.9, 108.6, 57.6, 55.6, 45.2, 36.0, 32.1, 18.0; HRMS (ESI) m/z calcd for $C_{26}H_{25}N_3O_2$ $[M + H]^+$ 412.2025, found 412.2014.

THBC ***34f***. Following general procedure VI, the reaction of **33f** (80 mg, 0.194 mmol), $RuHCl(CO)(PPh_3)_3$ (18.6 mg, 0.019 mmol), and $(PhO)_2PO_2H$ (14.6 mg, 0.058 mmol) gave, after flash column chromatography (Et_3N/EtOAc/heptane, 1:25:75), the title compound as a yellow oil (57 mg, 71%): R_f = 0.34 (EtOAc/heptane (3:7); UV, $KMnO_4$); HPLC purity > 95%, (t_R = 7.30 min); IR (neat) cm^{-1} 3406, 3246, 3059, 3028, 2927, 2843, 1522, 1451, 1346, 1024, 805, 731, 696; ^{1}H NMR (300 MHz, $CDCl_3$) 7.94−7.84 (m, 2H), 7.78 (s, 1H), 7.43 (dd, J = 7.9, 1.0 Hz, 1H), 7.35−7.17 (m, 8H), 7.10−6.97 (m, 2H), 3.69 (d, J = 2.9 Hz, 2H), 3.64−3.55 (m, 1H), 3.18 (ddd, J = 12.3, 8.6, 5.2 Hz, 1H), 2.95−2.75 (m, 3H), 2.74−2.60 (m, 1H), 2.58−2.47 (m, 1H), 2.09−1.88 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.3, 144.7, 144.6, 139.7, 136.0, 135.0, 134.6, 129.3, 129.2, 128.5, 127.3, 127.2, 123.3, 121.6, 121.0, 119.5, 118.2, 110.9, 108.4, 57.6, 56.0, 45.1, 35.9, 31.9, 18.1; HRMS (ESI) m/z calcd for $C_{26}H_{25}N_3O_2$ $[M + H]^+$ 412.2025, found 412.2025.

THBC ***34g***. Following general procedure VI, the reaction of **33g** (150 mg, 0.35 mmol), $RuHCl(CO)(PPh_3)_3$ (32.9 mg, 0.035 mmol), and $(PhO)_2PO_2H$ (25.9 mg, 0.10 mmol) gave, after flash column chromatography (Et_3N/EtOAc/heptane, 1:10:90), the title compound as a yellow oil (80 mg, 53%): R_f = 0.31 (EtOAc/heptane (1:4); UV, $KMnO_4$); IR (neat) cm^{-1} 3407, 3258, 3059, 3029, 2938, 2844, 1617, 1452, 1322, 1160, 1115, 1066, 1018, 825, 731, 697; HPLC purity > 95%, (t_R = 7.86 min); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (d, J = 8.2 Hz, 1H), 7.46−7.12 (m, 9H), 7.10−6.96 (m, 4H), 3.67 (d, J = 9.5 Hz, 2H), 3.61−3.49 (m, 1H), 3.27−3.09 (m, 1H), 2.96−2.58 (m, 4H), 2.58−2.44 (m, 1H), 2.10−1.81 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.9, 139.8, 136.1, 136.0, 134.8, 129.3, 129.2, 128.9, 128.8, 128.5, 128.5, 127.2, 127.1, 125.3, 121.6, 119.5, 118.2, 110.9, 108.3, 57.5, 55.8, 54.6, 44.9, 36.2, 32.1, 18.0; HRMS (ESI) m/z calcd for $C_{27}H_{25}F_3N_2$ $[M + H]^+$ 435.2048, found 435.2042.

THBC ***34h***. Following general procedure VI, the reaction of **33h** (100 mg, 0.26 mmol), $RuHCl(CO)(PPh_3)_3$ (24.8 mg, 0.026 mmol), and $(PhO)_2PO_2H$ (19.5 mg, 0.078 mmol) gave, after flash column chromatography (Et_3N/EtOAc/heptane, 1:25:75), the title compound as a brown oil (67 mg, 67%): R_f = 0.33 (EtOAc/heptane (1:4); UV, $KMnO_4$); HPLC purity > 95%, (t_R = 7.39 min); IR (neat) cm^{-1} 3403, 3230, 3060, 2936, 2842, 1600, 1508, 1452, 1300, 1218, 1156, 1024, 823, 736, 697; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.46−7.38 (m, 1H), 7.35−7.15 (m, 6H), 7.09−6.97 (m, 2H), 6.93−6.87 (m, 2H), 6.85−6.78 (m, 2H), 3.68 (s, 2H), 3.56 (dd, J = 8.4, 4.2 Hz, 1H), 3.24−3.10 (m, 1H), 2.94−2.75 (m, 2H), 2.73−2.44 (m, 3H), 2.08−1.80 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.8, 159.6, 139.9, 138.2, 138.1, 136.0, 135.1, 129.9, 129.8, 129.2, 128.4, 127.3, 127.1, 121.4, 119.3, 118.1, 115.2, 115.0, 110.9, 108.0, 57.4, 55.9, 44.8, 36.6, 31.4, 17.9; HRMS (ESI) m/z calcd for $C_{26}H_{25}FN_2$ $[M + H]^+$ 385.2080, found 385.2079.

THBC ***34i***. Following general procedure VI, the reaction of **33i** (150 mg, 0.336 mmol), $RuHCl(CO)(PPh_3)_3$ (32.1 mg, 0.034 mmol), and $(PhO)_2PO_2H$ (25.2 mg, 0.10 mmol) gave, after flash column chromatography (Et_3N/EtOAc/heptane, 1:25:75), the title compound as a yellow oil (80 mg, 53%): R_f = 0.25 (EtOAc/heptane (1:4); UV, $KMnO_4$); HPLC purity > 95%, (t_R = 7.83 min); IR (neat) cm^{-1} 3231, 3056, 2936, 1604, 1483, 1452, 1389, 1264, 1228, 1157, 1118, 1025, 908, 852, 813, 730, 697, 475; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.52 (t, J = 8.7 Hz, 2H), 7.44−7.39 (m, 1H), 7.38−7.22 (m, 6H), 7.17−7.09 (m, 2H), 7.07−6.96 (m, 4H), 3.80 (s, 3H), 3.69 (d, J = 1.8 Hz, 2H), 3.60 (dd, J = 8.3, 4.1 Hz, 1H), 3.26−3.15 (m, 1H), 2.96−2.66 (m, 4H), 2.50 (ddd, J = 15.0, 4.4, 2.5 Hz, 1H), 2.16−1.89 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.2, 140.0, 137.8, 135.9, 135.3, 133.0, 129.2, 129.1, 129.0, 128.4, 128.0, 127.3, 127.1, 126.9, 126.4, 121.3, 119.2, 118.7, 118.1, 110.8, 107.9, 105.7, 57.4, 56.0, 55.4, 44.7, 36.5, 32.2, 17.9; HRMS (ESI) m/z calcd for $C_{31}H_{30}N_2O$ $[M + H]^+$ 447.2436, found 447.2434.

THBC ***34j***. Following general procedure VI, the reaction of **33j** (80 mg, 0.224 mmol), $RuHCl(CO)(PPh_3)_3$ (21.4 mg, 0.022 mmol), and $(PhO)_2PO_2H$ (16.8 mg, 0.067 mmol) gave, after flash column chromatography (Et_3N/EtOAc/heptane, 1:25:75), the title compound as a brown oil (30 mg, 38%): R_f = 0.35 (EtOAc/heptane (1:4); UV, $KMnO_4$); HPLC purity 93%, (t_R = 7.62 min); IR (neat) cm^{-1} 3407, 3028, 2927, 1597, 1493, 1452, 1299, 1144, 1112, 1073, 1006, 730, 697, 598, 462; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70−7.64 (m, 1H), 7.53 (dd, J = 7.8, 1.2 Hz, 1H), 7.44−7.27 (m, 7H), 7.22−7.08 (m, 2H), 6.26 (dd, J = 3.1, 1.9 Hz, 1H), 5.85 (dd, J = 3.1, 0.8 Hz, 1H), 3.78 (s, 2H), 3.67 (t, J = 6.5 Hz, 1H), 3.26 (ddd, J = 14.6, 10.3, 5.0 Hz, 1H), 3.03−2.85 (m, 2H), 2.80 (dd, J = 13.9, 7.3 Hz, 2H), 2.65−2.53 (m, 1H), 2.13−2.06 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.2, 141.1, 140.0, 136.1, 135.1, 129.3, 128.5, 127.5, 127.3, 121.7, 119.6, 118.3, 111.0, 110.4, 108.4, 105.3, 57.6, 56.0, 44.6, 33.2, 24.9, 18.0; HRMS (ESI) m/z calcd for $C_{24}H_{24}N_2O$ $[M + H]^+$ 357.1967, found 357.1974.

THBC ***34k***. Following general procedure VI, the reaction of **33k** (100 mg, 0.255 mmol), $RuHCl(CO)(PPh_3)_3$) (24.3 mg, 0.026 mmol), and $(PhO)_2PO_2H$ (19.1 mg, 0.076 mmol) gave, after flash column chromatography (Et_3N/EtOAc/heptane, 1:10:90), the title compound as a yellow oil (40 mg, 40%): HPLC purity 83%, (t_R = 7.71 min); R_f = 0.35 (EtOAc/heptane (1:4); UV, $KMnO_4$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (s, 1H), 7.46−7.40 (m, 2H), 7.38−6.93 (m, 10H), 6.17 (d, J = 15.9 Hz, 1H), 6.02 (dt, J = 15.8, 6.8 Hz, 1H), 3.71−3.56 (m, 2H), 3.31−3.09 (m, 2H), 2.95−2.75 (m, 2H), 2.55−2.42 (m, 2H), 2.32−2.19 (m, 1H), 1.98−1.82 (m, 1), 1.74 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.0, 137.8, 135.9, 135.3, 130.8, 130.3, 129.2, 128.6, 128.4, 128.3, 127.2, 127.0, 126.0, 121.6, 119.5, 118.2, 110.8, 108.1, 57.5, 55.7, 44.8, 34.5, 29.6, 17.9; IR (neat) cm^{-1} 3415, 3057, 3025, 2924, 2844, 1600, 1493, 1451, 1299, 1154, 964, 734, 695, 460; HRMS (ESI) m/z calcd for $C_{28}H_{28}N_2$ $[M + H]^+$ 393.2331, found 393.2334.

General Procedure VII. Acetylation of secondary amines.

*(E)-N-Acetyl-N-3-phenylprop-2-enyl-1-tryptamine (**35**).* In a round-bottomed flask fitted with a magnetic stirring bar, acetic anhydride (659 mg, 610 μL, 6.45 mmol) was added to a stirred solution of (*E*)-*N*-3-phenylprop-2-enyl-1-tryptamine (1.78 g, 6.44 mmol) and Et_3N (652 mg, 898 μL, 6.44 mmol) in CH_2Cl_2 (17 mL) at 0 °C. The reaction mixture was stirred at 0 °C, and the progress was followed by TLC. Upon full conversion of the amine (10 min), the reaction was quenched with H_2O (17 mL). The reaction mixture was transferred to a separatory funnel, and the organic layer was separated. The aqueous phase was further extracted with CH_2Cl_2 (2 × 25 mL). The combined organic layers were dried over $MgSO_4$ and evaporated to dryness in vacuo. The residue was purified by flash column chromatography on silica gel (Et_3N/heptane/EtOAc 1:40:60) to afford the title compound as an off-white solid (1.42 mg, 69%): mp 92−93.0 °C; R_f = 0.43 (MeOH/CH_2Cl_2 (1:9); PMA,UV); HPLC purity >95% (t_R = 8.04 min); IR (neat) cm^{-1} 3214, 3048, 2923, 1606, 1449, 1350, 970, 737. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (d, J = 25.5 Hz, 1H), 7.65 (d, J = 7.8 Hz, 0.5H), 7.56 (d, J = 7.8 Hz, 0.5H), 7.41−7.07 (m, 8H), 7.01 (d, J = 18.5 Hz, 1H), 6.42 (dd, J = 23.8, 16.0 Hz, 1H), 6.19 (dt, J = 15.8, 6.5 Hz, 0.5H), 6.03 (dt, J = 15.9, 5.4 Hz, 0.5H), 4.18 (d, J = 6.3 Hz, 1H), 3.92 (d, J = 4.2 Hz, 1H), 3.77 (m, 1H), 3.61 (t, J = 7.3 Hz, 1H), 3.06 (dd, J = 14.9, 7.6 Hz, 2H), 2.17 (s, 1.5H), 2.00 (s, 1.5H), rotamers; ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 170.9, 136.7, 136.4, 133.0, 131.9, 129.2, 128.8, 128.7, 128.0, 127.8, 126.5, 125.1, 124.3, 122.4, 122.2, 119.8, 119.5, 119.0, 118.4, 113.4, 112.2, 111.6, 111.3, 54.6, 51.6, 48.7, 47.8, 47.3, 24.8, 23.8, 21.9, 21.4, rotamers; HRMS (ESI) m/z calcd for $C_{21}H_{23}N_2O$ $[M + H]^+$ 319.1810, found 319.1806.

THBC ***36***. In a Schlenk tube fitted with a magnetic stirring bar and a reflux condenser, (*E*)-*N*-acetyl-*N*-3-phenylprop-2-enyl-1-tryptamine (91.8 mg, 0.29 mmol), $RuHCl(CO)(PPh_3)_3$ (15.2 mg, 0.016 mmol), $(PhO)_2PO_2H$ (21.3 mg, 0. 085 mmol), and $NaBH_4$ (1.3 mg, 0.033 mmol) were dissolved in *m*-xylene (2.93 mL). The reaction mixture was stirred at reflux, and was followed by RP-UPLC/MS. Upon full conversion of the starting material (5 h), the reaction mixture was evaporated to dryness in vacuo. The residue was purified by flash

dx.doi.org/10.1021/jo402192s | J. Org. Chem. 2013, 78, 12545−12565

column chromatography on silica gel (heptane/EtOAc 1:4) to give the title compound as a pale pink solid (74.2 mg, 81%): mp 78−79 °C; R_f = 0.56 (pure EtOAc; UV, PMA); HPLC purity >95% (t_R = 8.32 min); IR (neat) cm^{-1} 3260, 2919, 1614, 1422, 739; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (s, 0.7H), 7.46 (d, J = 7.6 Hz, 0.9H), 7.35−7.22 (m, 3.7H), 7.22−7.07 (m, 4.7H), 5.87 (dd, J = 8.6, 5.4 Hz, 0.8H), 5.01−4.92 (m, 0.3H), 3.97 (dd, J = 9.8, 6.5 Hz, 0.8H), 3.58−3.43 (m, 0.9H), 2.92−2.65 (m, 4.1H), 2.25 (s, 2.8H), 2.22−2.02 (m, 2.4H), rotamers; ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 141.6, 136.2, 134.3, 128.9, 128.6, 128.4, 128.4, 126.6, 126.1, 122.3, 122.0, 119.9, 119.6, 118.5, 118.0, 111.2, 107.5, 49.5, 41.3, 37.0, 36.2, 32.7, 22.1, 22.0, 21.8, 21.0, rotamers; HRMS (ESI) m/z calcd for $C_{21}H_{23}N_2O$ $[M + H]^+$ 319.1810, found 319.1805.

General Procedure VIII. Suzuki cross-coupling reactions of allylic amides.

N-Acetyl-N-3-(p-tolyl)prop-2-enyl-1-tryptamine (37). In a Schlenk tube fitted with a magnetic stirring bar and a reflux condenser, P(t-Bu)$_3$ (1.0 M in THF, 60 μL) was added to a stirred solution of *N*-acetyl-*N*-3-bromoprop-2-enyl-1-tryptamine (123 mg, 0.38 mmol), *p*-tolylboronic acid (67 mg, 0.50 mmol), $Pd_2(dba)_3$ (19.7 mg, 0.022 mmol), and KF (86 mg, 1.48 mmol) in degassed THF (380 μL). The reaction mixture was stirred overnight and monitored by RP-UPLC/MS. Upon full conversion of the bromide (2.5 h), the reaction mixture was filtered through a pad of Celite, which was washed with CH_2Cl_2 (2 × 15 mL). The filtrate was concentrated to dryness in vacuo, and the residue was purified by flash column chromatography (Et_3N/MeOH/CH_2Cl_2, 1:1:98) to give the title compound as an orange oil (120 mg, 94%): R_f = 0.45 (MeOH/CH_2Cl_2 (1:9); PMA, UV); HPLC purity >95% (t_R = 8.43 min); IR (neat) cm^{-1} 3174, 2921, 1607, 1450, 969, 725; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.58−8.30 (m, 1H), 7.64 (d, J = 7.8 Hz, 0.4H), 7.55 (d, J = 7.8 Hz, 0.4H), 7.38−7.30 (m, 1.2H), 7.26−6.89 (m, 6.5H), 6.94 (d, J = 2.2 Hz, 0.5H), 6.59 (t, J = 12.0 Hz, 0.25H), 6.38 (dd, J = 23.8, 15.9 Hz, 0.8H), 6.12 (dt, J = 15.8, 6.5 Hz, 0.4H), 5.97 (dt, J = 15.9, 5.5 Hz, 0.4H), 5.67−5.49 (m, 0.25H), 4.40 (dd, J = 6.4, 1.8 Hz, 0.2H), 4.19−4.10 (m, 1H), 3.75−3.53, (m, 2H), 3.11−2.93 (m, 2H), 2.37 (d, J = 2.1 Hz, 0.8H), 2.32 (s, 2.4H), 2.14 (s, 1.2H), 1.98 (t, J = 9.5 Hz, 2H), rotamers; ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 170.8, 170.7, 170.7, 137.9, 137.6, 137.4, 137.0, 136.4, 136.4, 133.9, 133.7, 133.4, 133.2, 132.7, 132.0, 131.7, 131.7, 130.0, 129.4, 129.4, 129.2, 129.1, 128.9, 128.8, 128.1, 127.6, 127.5, 127.3, 127.1, 127.0, 126.7, 126.4, 126.4, 126.3, 124.0, 123.2, 122.5, 122.4, 122.2, 122.1, 122.0, 121.9, 119.6, 119.5, 119.4, 119.3, 118.9, 118.8, 118.3, 118.2, 115.4, 113.2, 113.0, 112.0, 111.9, 111.6, 111.5, 111.3, 111.2, 51.6, 49.2, 48.6, 47.7, 47.2, 43.4, 29.1, 24.8, 24.6, 23.8, 23.6, 22.1, 21.9, 21.5, 21.4, 21.3, 21.3, rotamers; HRMS (ESI) m/z calcd for $C_{22}H_{25}N_2O$ $[M + H]^+$ 333.1967, found 333.1962.

General Procedure IX. Synthesis of THBCs via isomerization/*N*-acyliminium cyclization of Suzuki products.

THBC 38. In a Schlenk tube fitted with a magnetic stirring bar and a reflux condenser, **37** (54.6 mg, 0.17 mmol), $RuHCl(CO)(PPh_3)_3$ (22.3 mg, 0.024 mmol), and $(PhO)_2PO_2H$ (12.9 mg, 0.52 mmol) were dissolved in *m*-xylene (1.65 mL). The reaction mixture was stirred at reflux, and progress was followed by RP-UPLC/MS. After 24 h, the reaction mixture was evaporated to dryness in vacuo. The residue was purified by flash column chromatography on silica gel (heptane/EtOAc 2:3) to give the title compound as a yellow oil (10.6 mg, 19%): R_f = 0.14 (MeOH/CH_2Cl_2 (1:9); UV, PMA); HPLC purity 85% (t_R = 8.71 min); IR (neat) cm^{-1} 3273, 2923, 1618, 1447, 1167; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.56−7.43 (m, 2H), 7.43−7.01 (m, 6H), 5.83 (dd, J = 13.4, 6.4 Hz, 1H), 5.04−4.86 (m, 0.4H), 4.12 (q, J = 7.2 Hz, 1H), 3.97 (dd, J = 12.9, 3.5 Hz, 1H), 3.50 (ddd, J = 14.1, 10.4, 5.8 Hz, 1H), 2.94−2.60 (m, 6H), 2.31 (s, 3H), 2.21 (s, 3H), rotamers; ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 138.1, 135.9, 129.4, 128.4, 122.3, 119.9, 118.1, 111.2, 107.6, 50.1, 41.6, 36.3, 32.3, 22.0, 21.2, rotamers; HRMS (ESI) m/z calcd for $C_{22}H_{25}N_2O$ $[M + H]^+$ 333.1967, found 333.1962.

L-Tryptophan-N-allyl-N-benzyl Methyl Ester (39). In a round-bottomed flask fitted with a magnetic stirring bar, allyl bromide (189 mg, 125 μL, 1.56 mmol) was added to a stirred suspension of L-tryptophan-*N*-benzyl methyl ester[28] (240 mg, 0.78 mmol) and K_2CO_3 (323 mg, 15.6 mmol) in DMF (4 mL). The reaction mixture was stirred at rt, and progress was followed by TLC. Upon full conversion of the starting material (18 h), the reaction mixture was evaporated to dryness in vacuo. The residue was taken up in CH_2Cl_2 (30 mL) and H_2O (20 mL) and transferred to a separatory funnel. The organic layer was separated, and the aqueous phase was further extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried over Na_2SO_4 and evaporated to dryness in vacuo. The residue was purified by flash column chromatography on silica gel (Et_3N/EtOAc/heptane 1:24:75) to give the title compound as a yellow oil (206 mg, 76%): R_f = 0.19 (EtOAc/heptane (1:3); UV, $KMnO_4$); HPLC purity 89% (t_R = 6.79 min); IR (neat) cm^{-1} 3410, 2949, 1726, 1455, 1164, 737; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.42−7.37 (m, 1H), 7.33 (dt, J = 8.1, 0.9 Hz, 1H), 7.31−7.22 (m, 6H), 7.18 (ddd, J = 8.3, 7.0, 1.2 Hz, 1H), 7.06 (ddd, J = 8.0, 7.1, 1.1 Hz, 1H), 6.97 (d, J = 2.3 Hz, 1H), 5.82 (dddd, J = 17.5, 10.1, 7.6, 4.8 Hz, 1H), 5.24 (dd, J = 17.2, 1.2 Hz, 1H), 5.13 (d, J = 10.1 Hz, 1H), 4.06 (d, J = 14.1 Hz, 1H), 3.86 (dd, J = 9.0, 5.9 Hz, 1H), 3.67 (s, 3H), 3.60 (d, J = 14.1 Hz, 1H), 3.52−3.43 (m, 1H), 3.35 (ddd, J = 14.3, 9.0, 0.6 Hz, 1H), 3.21−3.00 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5, 140.1, 136.8, 136.4, 129.0, 128.5, 127.8, 127.1, 123.0, 122.1, 119.5, 119.0, 117.7, 112.6, 111.3, 62.6, 54.8, 54.0, 51.3, 26.3; $[\alpha]^{20}_D$ −20.0 (c 0.0026, CH_2Cl_2); HRMS (ESI) m/z calcd for $C_{22}H_{25}N_2O_2$ $[M + H]^+$ 349.1916, found 349.1915.

THBC 40. In a Schlenk tube fitted with a magnetic stirring bar and a reflux condenser, **39** (60 mg, 0.17 mmol) and $RuHCl(CO)(PPh_3)_3$ (16.4 mg, 0.0127 mmol) were dissolved in toluene (1.7 mL). The reaction mixture was stirred at reflux, and progress was followed by TLC. When the starting material was fully converted (23 h), the reaction mixture was evaporated to dryness in vacuo. The residue was purified by flash column chromatography on silica gel (Et_3N/EtOAc/heptane 1:24:75) to give the title compound as a brown oil (48 mg, 80%), diastereomeric ratio: >15:1; R_f = 0.29 (Et_3N/EtOAc/heptane (1:24:75); UV, $KMnO_4$); HPLC purity 92% (t_R = 6.95 min); IR (neat) cm^{-1} 3391, 2953, 2931, 1731, 1543, 1437, 1264, 1217, 1172, 697; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.55 (d, J = 7.6 Hz, 1H), 7.42 (d, J = 7.4 Hz, 2H), 7.33 (dd, J = 14.3, 7.2 Hz, 3H), 7.29−7.24 (m, 1H), 7.24−7.11 (m, 2H), 4.04 (dd, J = 8.2, 5.1 Hz, 1H), 3.96−3.90 (m, 2H), 3.89 (s, 1H), 3.74 (s, 3H), 3.17 (dd, J = 15.7, 8.3 Hz, 1H), 3.04 (dd, J = 15.7, 5.1 Hz, 1H), 1.95−1.72 (m, 2H), 0.90 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1, 140.0, 136.4, 135.4, 129.2, 128.5, 127.3, 121.9, 119.7, 118.4, 111.1, 107.6, 57.1, 57.0, 53.8, 52.1, 49.9, 27.5, 22.0, 10.3; $[\alpha]^{20}_D$ +48.2 (c: 0.079, CH_2Cl_2); HRMS (ESI) m/z calcd for $C_{22}H_{25}N_2O_2$ $[M + H]^+$ 349.1916, found 349.1913.

L-Tryptophan-N-allyl-N-acetyl Methyl Ester (41). Following general procedure III, the reaction of L-tryptophan-*N*-allyl methyl ester[4a] (165 mg, 0.64 mmol), acetyl chloride (58 mg, 52 μL, 0.73 mmol), and Et_3N (78 mg, 107 μL, 0.77 mmol) gave, after purification by flash column chromatography on silica gel (EtOAc/heptane 1:1), the title compound as a clear oil (119 mg, 62%): R_f = 0.14 (EtOAc/heptane (1:1); UV, $KMnO_4$); HPLC purity >95% (t_R = 6.80 min); IR (neat) cm^{-1} 3295, 2950, 1736, 1627, 1439, 1224,741; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.79 (s, 0.2H), 8.68 (s, 0.8H), 7.58 (d [app. dt], J = 7.8 Hz, 1H), 7.38−7.34 (m, 1H), 7.23−7.08 (m, 2H), 7.02 (d, J = 2.3 Hz, 0.8H), 6.97 (d, J = 2.4 Hz, 0.2H), 5.88 (ddt, J = 16.1, 10.2, 6.0 Hz, 0.2H), 5.55 (ddt, J = 17.2, 10.3, 5.5 Hz, 0.8H), 5.15 (ddd, J = 5.1, 3.3, 1.5 Hz, 0.4H), 5.06 (ddd, J = 10.1, 5.8, 1.4 Hz, 1.6H), 4.69 (dd, J = 9.4, 5.8 Hz, 1H), 3.70 (s, 3H), 3.56−3.29 (m, 2H), 2.05 (s, 2.4H), 1.81 (s, 0.6H), rotamers; ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8/171.5, 136.5, 134.2/133.3, 127.6/127.0, 123.9/123.1, 122.3/122.1, 119.8/119.6, 118.6/118.0, 117.7/117.0, 112.0/111.7, 111.6/110.1, 61.2/59.7, 52.4/51.9, 46.1, 32.1, 25.7/25.0, rotamers; $[\alpha]^{20}_D$ −28.0 (c 0.0015, CH_2Cl_2); HRMS (ESI) m/z calcd for $C_{17}H_{21}N_2O_3$ $[M + H]^+$ 301.1552, found 301.1552.

THBC 42. Following general procedure II, the reaction of **41** (40 mg, 0.13 mmol), $RuHCl(CO)(PPh_3)_3$ (12.7 mg, 0.013 mmol), and $(PhO)_2PO_2H$ (10.0 mg, 0.040 mmol) gave, after purification by flash column chromatography on silica gel (EtOAc/heptane 1:1), the title compound as a light brown solid (29 mg, 73%, diastereomeric ratio:

dx.doi.org/10.1021/jo402192s | J. Org. Chem. 2013, 78, 12545−12565

>2:1): mp 141−145 °C; R_f = 0.31 (EtOAc/heptane (1:1); UV, $KMnO_4$); HPLC purity 89% (t_R = 6.91 min); IR (neat) cm^{-1} 3313, 2931, 1735, 1629, 1423, 1333, 1268, 1219, 1162; ^1H NMR (500 MHz, $CDCl_3$) δ 8.30 (s, 0.0.67H), 8.20 (s, 0.33H), 7.50 (t, J = 7.2 Hz, 1H), 7.32 (d, J = 7.8 Hz, 1H), 7.16 (dd, J = 13.9, 6.8 Hz, 1H), 7.12 (dd, J = 14.0, 6.7 Hz, 1H), 4.90 (dd, J = 8.3, 5.8 Hz, 0.67H), 4.84 (dd, J = 4.9, 2.2 Hz, 0.33H), 4.24 (dd, J = 9.6, 4.4 Hz, 0.67H), 4.12 (q, J = 7.1 Hz, 0.33H), 3.73 (s, 2H), 3.51 (s, 1H), 3.32 (dd, J = 15.7, 9.7 Hz, 0.75H), 3.18 (dd, J = 15.3, 5.0 Hz, 0.5H), 3.04 (dd, J = 15.7, 4.4 Hz, 0.75H), 2.18 (s, 2H), 2.16 (s, 1H), 2.04−1.85 (m, 2H), 1.26 (t, J = 7.2 Hz, 1H), 1.16 (t, J = 7.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8/172.5, 171.8/171.2, 136.5/136.4, 135.3/134.3, 126.9/126.4, 122.6/122.0, 120.2/119.9, 118.7/118.2, 111.4/111.3, 108.9/106.1, 58.2/57.3, 53.8/52.5, 53.3/53.1, 28.9, 24.5/23.8, 22.8/22.4, 11.0/8.9, rotamers; $[\alpha]^{20}_D$ −48.2 (c 0.013, CH_2Cl_2) HRMS (ESI) m/z calcd for $C_{17}H_{21}N_2O_3$ $[M + H]^+$ 301.1552, found 301.1546.

N-3-Bromoprop-2-enyl-1-tryptamine. In a round-bottomed flask fitted with a magnetic stirring bar, 1,3-dibromo-1-propene (830 mg, 415 μL, 4.15 mmol) dissolved in DMF (2 mL) was added dropwise to a stirred suspension of tryptamine (5.06 g, 31.6 mmol) and K_2CO_3 (666 mg, 4.81 mmol) in DMF (12 mL) at 0 °C. The reaction was stirred at rt overnight, whereupon CH_2Cl_2 (50 mL) and H_2O (50 mL) were added. The mixture was transferred to a separatory funnel. The organic layer was separated, washed with H_2O (3 × 50 mL), dried over $MgSO_4$, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel (Et_3N/heptane/EtOAc 1:10:70) to give the title compound as a brown oil (1.03 g, 89%): R_f = 0.27 ($MeOH/CH_2Cl_2$ (1:9); PMA, UV); HPLC purity 91% (Rt = 5.41, 5.46 min); IR (neat) cm^{-1} 3408, 2916, 2841, 1619, 1454, 738. 1H NMR (300 MHz, $CDCl_3$) δ 8.13−8.01 (m, 1H), 7.65−7.61 (m, 1H), 7.40−7.36 (m, 1H), 7.23−7.09 (m, 3H), 7.07−7.05 (m, 1H), 6.28−6.18 (m, 2H), 3.67 (q, J = 6.4 Hz, 1H), 3.46 (d, J = 4.9 Hz, 1H), 3.24 (d, J = 5.1 Hz, 1H), 3.04−2.95 (m, 2H), 2.88 (s, 1H), 1.91 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.5, 135.6, 132.4, 127.4, 122.2, 119.5, 118.9, 111.3, 110.0, 107.7, 55.4, 51.2, 49.1, 48.2, 25.6, rotamers; HRMS (ESI) m/z calcd for $C_{13}H_{16}N_2Br$ $[M + H]^+$ 279.0497, found 279.0499.

*(E)-N-Benzyl-N-3-phenylprop-2-enyl-1-tryptamine (**SI1**).* Following general procedure IV, the reaction of *(E)-N*-3-phenylprop-2-enyl-1-tryptamine[4b] (1.20 g, 4.34 mmol), benzyl bromide (570 μL, 817 mg, 4.78 mmol), and K_2CO_3 (1.80 g, 13.03 mmol) gave, after flash column chromatography ($Et_3N/MeOH/CH_2Cl_2$, 1:2:97), the title compound as a yellow oil (1.08 g, 68%). Analytical data are in accordance with those previously reported:[4b] R_f = 0.32 (EtOAc/heptane (3:7); UV, $KMnO_4$); HPLC purity > 95% (t_R = 7.15 min); ^1H NMR (300 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.56 (dd, J = 6.7, 6.1 Hz, 1H), 7.50−7.25 (m, 11H), 7.21 (tt, J = 2.8, 1.4 Hz, 1H), 7.10 (dd, J = 11.5, 1.3 Hz, 1H), 6.96 (t, J = 2.4 Hz, 1H), 6.66−6.54 (m, 1H), 6.45−6.33 (m, 1H), 3.83 (s, 2H), 3.44 (dd, J = 6.5, 1.1 Hz, 2H), 3.12−2.89 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.6, 137.3, 136.3, 132.5, 129.1, 128.6, 128.4, 127.8, 127.6, 127.4, 127.0, 126.4, 121.9, 121.7, 119.2, 119.0, 114.5, 111.2, 58.4, 56.4, 54.2, 23.1; MS (ESI) m/z calcd for $C_{26}H_{26}N_2$ $[M + H]^+$ 367.2, found 367.2.

*N-Acetyl-N-3-bromoprop-2-enyl-1-tryptamine (**SI2**).* Following general procedure VII, the reaction of *N*-3-bromoprop-2-enyl-1-tryptamine (1.08 g, 3.87 mmol), acetic anhydride (394 mg, 365 μL, 3.86 mmol), and Et_3N (392 mg, 540 μL, 3.87 mmol) gave, after purification by flash column chromatography on silica gel ($MeOH/CH_2Cl_2$; 2:98), the title compound as an orange solid (1.16 g, 93%): mp 75−76 °C; R_f = 0.50 ($MeOH/CH_2Cl_2$ (1:9); PMA, UV); HPLC purity >95% (t_R = 7.26 min); IR (neat) cm^{-1} 3176, 2922, 1606, 1480, 1277, 730; ^1H NMR (300 MHz, $CDCl_3$) δ 8.13 (m, 1H), 7.69−7.53 (m, 1H), 7.41−7.34 (t, J = 7.1 Hz, 1H), 7.25−7.10 (m, 2H), 7.06−6.98 (m, 1H), 6.37−6.30 (m, 0.6H), 6.26−6.18 (m, 0.8H), 6.12−6.00 (m, 0.5H), 4.24 (dd, J = 6.5, 1.2 Hz, 0.8H), 3.99 (dd, J = 6.0, 1.7 Hz, 0.5H), 3.93 (m, 0.5H), 3.70−3.62 (m,1H), 3.61−3.54 (m, 1.5H), 3.09−2.98 (m, 2.3H), 2.12 (s, 0.75H), 2.10 (s, 0.5H), 1.95 (s, 0.9H), 1.93 (s, 1.1H), 1.75 (s, 0.9H), rotamers; ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 170.7, 136.4, 133.1, 132.6, 131.2, 130.7, 127.2, 122.5, 122.5, 122.4, 122.3, 122.2, 122.1, 119.9, 119.8, 119.6, 119.6, 119.0, 118.9, 118.4, 118.3, 112.3, 112.1, 111.6, 111.5, 111.4, 111.3, 110.4, 108.6, 108.2, 51.3, 49.7, 49.1, 48.9, 47.5, 47.3, 47.2, 44.9, 25.0, 24.8, 23.8, 23.7, 22.1, 21.9, 21.4, 21.3, rotamers; HRMS (ESI) m/z calcd for $C_{15}H_{18}N_2OBr$ $[M + H]^+$ 321.0603, found 321.0597.

*N-Acetyl-N-3-phenylprop-2-enyl-1-tryptamine (**SI3**).* Following general procedure VIII, the reaction of *N*-acetyl-*N*-3-bromoprop-2-enyl-1-tryptamine (103 mg, 0.32 mmol), phenylboronic acid (56 mg, 0.46 mmol), $Pd_2(dba)_3$ (14 mg, 0.015 mmol), P(*t*-Bu)$_3$ (1.0 M in THF, 20 μL), and KF (68 mg, 1.16 mmol) gave, after flash column chromatography ($Et_3N/MeOH/CH_2Cl_2$, 1:1:98), the title compound as a brown oil (92 mg, 91%): R_f = 0.43 ($MeOH/CH_2Cl_2$ (1:9); PMA, UV); HPLC purity >95% (t_R = 8.06 min); IR (neat) cm^{-1} 3268, 2925, 1611, 1454, 739; ^1H NMR (300 MHz, $CDCl_3$) δ 8.32 (m, 0.8H), 7.69−6.81 (m, 10H), 6.64 (t, J = 18.0 Hz, 0.4H), 6.42 (dd, J = 23.7, 15.8 Hz, 0.6H), 6.19 (dt, J = 15.8, 6.5 Hz, 0.3H), 6.03 (dt, J = 15.9, 5.4 Hz, 0.3H), 5.71−5.54 (m, 0.4H), 4.40 (dd, J = 6.5, 1.6 Hz, 0.4H), 4.13 (ddd, J = 10.0, 7.1, 4.4 Hz, 1H), 3.92 (d, J = 4.0 Hz, 0.6H), 3.66 (ddd, J = 17.3, 14.9, 7.5 Hz, 1.6H), 3.55−3.42 (m, 0.5H), 3.06 (dd, J = 15.0, 8.0 Hz, 1H), 3.01−2.93 (m, 0.5H), 2.89−2.82 (m, 0.5H), 2.16 (s, 0.8H), 2.02 (dt, J = 16.3, 8.0 Hz, 2.4H), 1.26 (t, J = 7.0 Hz, 0.6H), rotamers; ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 170.9, 170.8, 136.7, 136.6, 136.4, 136.3, 136.2, 134.1, 132.9, 132.2, 131.9, 131.8, 129.0, 128.9, 128.8, 128.7, 128.6, 128.5, 128.0, 127.9, 127.8, 127.6, 127.3, 127.1, 126.5, 126.5, 125.0, 124.3, 122.4, 122.4, 122.3, 122.2, 122.1, 122.0, 119.7, 119.6, 119.5, 119.4, 118.9, 118.8, 118.4, 118.3, 113.3, 112.1, 112.0, 111.6, 111.5, 111.3, 111.2, 51.6, 49.2, 48.7, 47.7, 47.6, 47.3, 47.2, 43.4, 24.8, 24.6, 23.8, 23.6, 21.9, 21.4, 21.4, rotamers; HRMS (ESI) m/z calcd for $C_{21}H_{23}N_2O$ $[M + H]^+$ 319.1810, found 319.1806.

*N-Acetyl-N-3-(m-tolyl)prop-2-enyl-1-tryptamine (**SI4**).* Following general procedure VIII, the reaction of *N*-acetyl-*N*-3-bromoprop-2-enyl-1-tryptamine (90 mg, 0.28 mmol), *m*-tolylboronic acid (52 mg, 0.38 mmol), $Pd_2(dba)_3$ (13.2 mg, 0.014 mmol), P(*t*-Bu)$_3$ (1.0 M in THF, 40 μL), and KF (61 mg, 1.05 mmol) gave, after flash column chromatography ($Et_3N/MeOH/CH_2Cl_2$, 1:1:98), the title compound as an orange oil (89 mg, 96%); R_f = 0.54 ($MeOH/CH_2Cl_2$ (1:9), PMA, UV); HPLC purity >95% (t_R = 8.46 min); IR (neat) cm^{-1} 3247, 2921, 1619, 1454, 737; ^1H NMR (300 MHz, $CDCl_3$) δ 8.23−8.02 (m, 0.8H), 7.65 (d, J = 7.9 Hz, 0.2H), 7.56 (d, J = 7.9 Hz, 0.2H), 7.50 (d, J = 7.8 Hz, 0.3H), 7.40−7.31 (m, 1.4H), 7.29−7.02 (m, 6H), 7.00−6.91 (m, 1H), 6.87 (s, 0.3H), 6.60 (t, J = 12.4 Hz, 0.6H), 6.47−6.31 (m, 0.4H), 6.24−6.13 (m, 0.2H), 6.07−5.97 (m, 0.2H), 5.70−5.52 (m, 0.6H), 4.40 (dd, J = 6.5, 1.8 Hz, 0.6H), 4.17 (d, J = 5.9 Hz, 0.4H), 4.11 (dd, J = 6.2, 2.0 Hz, 0.6H), 3.91 (d, J = 3.7 Hz, 0.5H), 3.74−3.56 (m, 1.6H), 3.50−3.44 (m, 0.7H), 3.05 (dd, J = 15.0, 7.5 Hz, 1H), 3.00−2.93 (m, 0.7H), 2.90−2.83 (m, 0.7H), 2.37 (s, 2H), 2.33 (s, 1.4H), 2.15 (s, 0.8H), 2.01 (s, 1H), 1.99 (s, 0.7H), 1.98 (s, 1H), 1.46 (s, 1H), 1.42 (s, 1H), rotamers; ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 170.7, 170.7, 170.6, 138.3, 138.2, 138.1, 138.0, 136.6, 136.6, 136.5, 136.4, 136.4, 136.2, 136.1, 132.9, 132.2, 131.9, 131.9, 129.7, 129.6, 128.8, 128.7, 128.6, 128.6, 128.4, 128.4, 128.3, 128.0, 127.9, 127.5, 127.2, 127.2, 127.1, 127.1, 126.0, 125.9, 125.0, 124.1, 123.7, 123.6, 122.5, 122.4, 122.2, 122.2, 122.0, 121.9, 119.6, 119.5, 119.4, 119.3, 118.9, 118.8, 118.3, 118.3, 113.3, 113.1, 112.1, 112.0, 111.6, 111.5, 111.4, 111.3, 54.5, 51.6, 49.2, 48.6, 47.6, 47.2, 43.3, 29.2, 27.2, 24.8, 24.6, 23.8, 23.7, 22.0, 21.6, 21.5, 21.4, rotamers; HRMS (ESI) m/z calcd for $C_{22}H_{25}N_2O$ $[M + H]^+$ 333.1967, found 333.1964.

*N-Acetyl-N-3-(o-tolyl)prop-2-enyl-1-tryptamine (**SI5**).* Following general procedure VIII, the reaction of *N*-acetyl-*N*-3-bromoprop-2-enyl-1-tryptamine (90 mg, 0.28 mmol), *o*-tolylboronic acid (49 mg, 0.36 mmol), $Pd_2(dba)_3$ (16.5 mg, 0.018 mmol), P(t-Bu)$_3$ (1.0 M in THF, 40 μL), and KF (61 mg, 1.05 mmol) gave, after flash column chromatography ($Et_3N/MeOH/CH_2Cl_2$, 1:1:98), the title compound as an orange oil (56 mg, 60%): R_f = 0.46 ($MeOH/CH_2Cl_2$ (1:9); PMA, UV); HPLC purity >95% (t_R = 8.38 min); IR (neat) cm^{-1} 3256, 2923, 1616, 1455, 738; ^1H NMR (300 MHz, $CDCl_3$) δ 8.35 (t, J = 34.1 Hz, 1H), 7.67 (d, J = 7.8 Hz, 0.25H), 7.58 (d, J = 7.8 Hz, 0.25H), 7.49 (d, J = 7.8 Hz, 0.3H), 7.45−7.31 (m, 1.5H), 7.27−6.91 (m, 6H), 6.83 (d, J = 2.1 Hz, 0.3H), 6.75−6.65 (m, 0.8H), 6.08 (dt, J = 15.7, 6.6 Hz, 0.2H), 5.92 (dt, J = 15.7, 5.5 Hz, 0.2H), 5.73 (ddt, J = 27.4, 11.4,

dx.doi.org/10.1021/jo402192s | J. Org. Chem. 2013, 78, 12545−12565

6.6 Hz, 0.5H), 4.29−4.19 (m, 1H), 4.01−3.92 (m, 1H), 3.77−3.69 (m, 0.5H), 3.66−3.59 (m, 1H), 3.43 (dd, J = 8.5, 6.6 Hz, 0.5H), 3.08 (dd, J = 14.9, 7.4 Hz, 1H), 2.94 (t, J = 8.1 Hz, 0.5H), 2.80 (t, J = 8.1 Hz, 0.5H), 2.33 (s, 0.5H), 2.30 (s, 0.5H), 2.28 (s, 1H), 2.26 (s, 0.5H), 2.18 (s, 0.5H), 2.00 (d, J = 4.4 Hz, 1.5H), 1.95 (s, 0.8H), rotamers; ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 170.7, 170.6, 170.6, 136.4, 136.3, 135.8, 135.6, 135.5, 135.4, 135.1, 131.6, 131.3, 131.0, 130.7, 130.4, 130.4, 130.3, 130.1, 129.9, 129.3, 129.1, 128.4, 127.9, 127.7, 127.6, 127.5, 127.1, 127.1, 126.5, 126.3, 126.2, 125.8, 125.8, 125.7, 122.4, 122.3, 122.2, 122.1, 122.0, 119.6, 119.6, 119.4, 119.3, 118.9, 118.8, 118.3, 118.2, 113.3, 113.1, 112.1, 112.0, 111.6, 111.5, 111.3, 111.2, 54.5, 51.8, 49.8, 49.1, 48.6, 47.9, 47.2, 46.9, 43.0, 29.1, 27.2, 24.9, 24.5, 23.9, 23.6, 21.9, 21.8, 21.5, 21.4, 20.1, 20.0, 19.9, rotamers; HRMS (ESI) m/z calcd for $C_{22}H_{25}N_2O$ $[M + H]^+$ 333.1967, found 333.1960.

N-Acetyl-N-3-(3,5-dimethoxyphenyl)prop-2-enyl-1-tryptamine (**SI6**). Following general procedure VIII, the reaction of *N*-acetyl-*N*-3-bromoprop-2-enyl-1-tryptamine (96 mg, 0.30 mmol), 3,5-dimethoxyphenylboronic acid (70 mg, 0.39 mmol), $Pd_2(dba)_3$ (13.1 mg, 0.014 mmol), P(*t*-Bu)$_3$ (1.0 M in THF, 40 μL), and KF (59.3 mg, 1.02 mmol) gave, after flash column chromatography (Et_3N/MeOH/CH_2Cl_2, 1:1:98), the title compound as an orange solid (101 mg, 90%): mp 116−117 °C; R_f = 0.48 (MeOH/CH_2Cl_2 (1:9), PMA, UV); HPLC purity >95% (t_R = 7.94, 7.95, 7.96 min); IR (neat) cm^{-1} 3233, 2930, 1589, 1419, 1152, 735; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.61 (m, 0.9H), 7.65 (d, J = 7.8 Hz, 0.2H), 7.54 (dd, J = 16.6, 7.8 Hz, 0.5H), 7.41−7.31 (m, 1.2H), 7.24−6.86 (m, 3H), 6.63−6.32 (m, 3H), 6.28 (d, J = 2.2 Hz, 0.6H), 6.24−6.13 (m, 0.3H), 6.09−5.98 (m, 0.2H), 5.72−5.53 (m, 0.5H), 4.39 (dd, J = 6.5, 1.7 Hz, 0.5H), 4.17 (d, J = 6.2 Hz, 0.5H), 4.10 (dd, J = 6.3, 1.9 Hz, 0.5H), 3.00 (d, J = 3.9 Hz, 0.4H), 3.78 (s, 6H), 3.76− 3 0.68 (m, 0.7H), 3.60−3.56 (m, 1H), 3.52−3.42 (m, 0.6H), 3.11−2.84 (m, 2H), 2.16 (s, 0.7H), 2.03 (s, 0.8H), 1.99 (d, J = 4.2 Hz, 1.5H), rotamers; ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 170.8, 170.6, 161.0, 161.0, 160.8, 160.7, 138.7, 138.6, 138.2, 138.0, 136.4, 136.3, 132.8, 132.1, 131.8, 131.6, 129.3, 128.5, 127.5, 127.1, 127.1, 125.7, 124.9, 122.5, 122.4, 122.2, 122.2, 122.1, 122.0, 121.9, 119.6, 119.5, 119.4, 119.3, 118.9, 118.8, 118.3, 118.3, 113.2, 113.1, 112.0, 112.0, 111.6, 111.5, 111.4, 111.2, 107.0, 107.0, 104.5, 104.5, 100.3, 100.2, 99.5, 55.5, 54.5, 51.4, 49.3, 48.7, 47.6, 47.6, 47.2, 43.5, 29.1, 24.8, 24.6, 23.8, 23.6, 22.0, 21.9, 21.5, 21.4, rotamers; HRMS (ESI) m/z calcd for $C_{23}H_{27}N_2O_3$ $[M + H]^+$ 379.2022, found 379.2021.

N-Acetyl-N-3-(4-nitrophenyl)prop-2-enyl-1-tryptamine (**SI7**). Following general procedure VIII, the reaction of *N*-acetyl-*N*-3-bromoprop-2-enyl-1-tryptamine (87 mg, 0.27 mmol), 4-nitrophenylboronic acid (59.7 mg, 0.36 mmol), $Pd_2(dba)_3$ (19.6 mg, 0.021 mmol), P(*t*-Bu)$_3$ (1.0 M in THF, 40 μL), and KF (64.1 mg, 1.10 mmol) gave, after flash column chromatography (Et_3N/MeOH/CH_2Cl_2, 1:1:98), the title compound as an orange solid (76.1 mg, 77%): mp 116−117 °C; R_f = 0.50 (MeOH/CH_2Cl_2 (1:9), PMA, UV); HPLC purity >95% (t_R = 7.85, 7.92 min); IR (neat) cm^{-1} 3246, 2925, 1622, 1512, 1338, 738; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 (d, *J* = 19.1 Hz, 0.8H), 8.19−8.10 (m, 1.9H), 7.62 (d, *J* = 7.9 Hz, 0.2H), 7.55 (d, *J* = 7.8 Hz, 0.3H), 7.47−7.27 (m, 3H), 7.25−7.09 (m, 2H), 7.09−6.98 (m, 1H), 6.96−6.88 (m, 0.4H), 6.60 (d, *J* = 11.7 Hz, 0.5H), 6.48−6.28 (m, 0.8H), 6.17 (dt, *J* = 16.0, 5.1 Hz, 0.3H), 5.86−5.67 (m, 0.5H), 4.30−4.14 (m, 1H), 4.00−3.90 (m, 0.8H), 3.73 (t, *J* = 7.3 Hz, 0.5H), 3.62 (td, *J* = 7.1, 3.8 Hz, 1H), 3.55−3.47 (m, 0.7H), 3.07 (dd, *J* = 14.1, 6.8 Hz, 1H), 2.94 (dt, *J* = 21.2, 7.1 Hz, 1H), 2.14 (s, 0.6H), 2.03 (s, 1H), 2.01 (s, 0.9H), rotamers; ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 170.8, 143.2, 136.4, 132.8, 132.0, 130.4, 130.2, 130.1, 129.7, 129.5, 129.4, 127.0, 127.0, 124.1, 124.1, 123.8, 123.7, 122.5, 122.4, 122.3, 122.2, 119.8, 119.7, 119.6, 119.5, 118.8, 118.6, 118.3, 118.1, 111.7, 111.6, 111.4, 54.6, 51.4, 49.3, 49.1, 47.8, 47.5, 44.0, 27.2, 25.1, 23.9, 22.0, 22.0, 21.4, 21.4, rotamers; HRMS (ESI) m/z calcd for $C_{21}H_{22}N_3O_3$ $[M + H]^+$ 364.1661, found 364.1657.

N-Acetyl-N-3-(3-nitrophenyl)prop-2-enyl-1-tryptamine (**SI8**). Following general procedure VIII, the reaction of *N*-acetyl-*N*-3-bromoprop-2-enyl-1-tryptamine (82 mg, 0.26 mmol), 3-nitrophenylboronic acid (55 mg, 0.33 mmol), $Pd_2(dba)_3$ (13.4 mg, 0.015 mmol), P(*t*-Bu)$_3$ (1.0 M in THF, 40 μL), and KF (62 mg, 1.07 mmol) gave, after flash column chromatography (Et_3N/MeOH/CH_2Cl_2, 1:1:98), the title compound as an orange solid (77 mg, 78%): mp 124−125 °C; R_f = 0.48 (MeOH/CH_2Cl_2 (1:9); PMA, UV); HPLC purity >95% (t_R = 7.80, 7.91 min); IR (neat) cm^{-1} 3283, 2919, 1615, 1627, 1347, 749; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.35 (t, *J* = 29.5 Hz, 0.9H), 8.17−7.99 (m, 1.6H), 7.88−7.84 (m, 0.2H), 7.65−7.53 (m, 0.8H), 7.51−7.28 (m, 3H), 7.24−6.88 (m, 3H), 6.58 (dd, *J* = 11.7, 4.8 Hz, 0.5H), 6.47−6.22 (m, 0.7H), 6.09 (dt, *J* = 16.0, 5.2 Hz, 0.2H), 5.89−5.65 (m, 0.6H), 4.26 (dd, *J* = 6.4, 1.9 Hz, 0.7H), 4.17 (d, *J* = 5.7 Hz, 0.5H), 3.95 (ddd, *J* = 6.7, 5.7, 1.8 Hz, 0.8H), 3.73 (t, *J* = 7.2 Hz, 0.4H), 3.63 (td, *J* = 7.2, 3.3 Hz, 1H), 3.52 (t, *J* = 7.2 Hz, 0.8H), 3.07 (dd, J = 14.6, 7.2 Hz, 1H), 2.97 (t, *J* = 7.3 Hz, 0.5H), 2.90 (t, *J* = 7.2 Hz, 0.7H), 2.15 (s, 0.6H), 2.03 (dd, J8.0, 4.7 = Hz, 2H), rotamers; ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 170.8, 170.5, 148.6, 148.2, 138.5, 138.1, 138.0, 137.4, 136.5, 136.4, 134.8, 134.6, 132.4, 132.2, 131.9, 131.1, 130.1, 129.7, 129.6, 129.5, 129.3, 129.3, 129.2, 128.6, 128.0, 127.5, 127.3, 127.1, 126.9, 123.4, 123.2, 122.5, 122.4, 122.4, 122.3, 122.2, 122.1, 121.1, 120.9, 119.7, 119.6, 119.5, 119.4, 118.8, 118.5, 118.3, 118.0, 113.2, 113.0, 112.0, 111.8, 111.7, 111.5, 111.4, 111.3, 54.5, 51.4, 49.3, 49.0, 47.7, 47.5, 47.2, 43.8, 27.2, 27.1, 25.0, 25.0, 23.9, 23.8, 22.0, 21.9, 21.4, 21.4, rotamers; HRMS (ESI) m/z calcd for $C_{21}H_{22}N_3O_3$ $[M + H]^+$ 364.1661, found 364.1658.

N-Acetyl-N-3-(4-(trifluoromethyl)phenyl)prop-2-enyl-1-tryptamine (**SI9**). Following general procedure VIII, the reaction of *N*-acetyl-*N*-3-bromoprop-2-enyl-1-tryptamine (107 mg, 0.33 mmol), 4-(trifluoromethyl)phenylboronic acid (79 mg, 0.41 mmol), $Pd_2(dba)_3$ (18.2 mg, 0.019 mmol), P(*t*-Bu)$_3$ (1.0 M in THF, 50 μL), and KF (74 mg, 1.27 mmol) gave, after flash column chromatography (Et_3N/MeOH/CH_2Cl_2, 1:1:98), the title compound as an orange oil (106 mg, 82%): R_f = 0.59 (MeOH/CH_2Cl_2 (1:9); PMA, UV); HPLC purity >95% (t_R = 8.66, 8.72 min); IR (neat) cm^{-1} 3271, 2927, 1614, 1322, 1110, 1065, 738; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (t, *J* = 24.2 Hz, 0.9H), 7.66−7.52 (m, 2H), 7.49 −6.91 (m, 7.4H), 6.87 (s, 0.3H), 6.66−6.56 (m, 0.6H), 6.47−6.33 (m, 0.4H), 6.32−6.22 (m, 0.6H), 6.15−6.05 (m, 0.2H), 5.81−5.63 (m, 0.6H), 4.30 (dd, *J* = 6.5, 1.8 Hz, 0.8H), 4.17 (d, *J* = 6.2 Hz, 0.5H), 4.01 (dd, *J* = 6.3, 1.9 Hz, 0.6H), 3.93 (d, *J* = 4.2 Hz, 0.4H), 3.72 (t, *J* = 7.3 Hz, 0.4H), 3.62 (td, *J* = 7.5, 2.8 Hz, 1H), 3.48 (t, *J* = 4.5 Hz, 0.8H), 3.06 (q, *J* = 14.6, 7.4 Hz, 1H), 2,97 (t, *J* = 7.5 Hz, 0.6H), 2.88 (t, *J* = 7.5 Hz, 0.8H), 2.14 (s, 0.7H), 2.02 (s, 0.9H), 2.01 (s, 0.7H), 1.99 (s, 1H), rotamers; ^{13}C NMR (75 MHz, $CDCl_3$) δ 1 171.1, 171.0, 170.9, 170.6, 140.3, 139.7, 136.5, 136.5, 131.3, 131.2, 130.9, 130.4, 130.4, 129.2, 129.1, 128.1, 127.7, 127.6, 127.4, 127.2, 127.1, 126.7, 125.7, 125.7, 125.6, 125.6, 125.5, 125.5, 125.4, 122.5, 122.5, 122.5, 122.4 (d, J_{C-F} = 17.5 Hz), 122.3 (d, J_{C-F} = 22.7 Hz), 122.2, 122.2, 119.8, 119.8, 119.6, 119.5, 118.9, 118.8, 118.4, 118.2, 113.4, 113.2, 112.2, 112.1, 111.7, 111.6, 111.5, 111.4, 88.0, 54.7, 51.5, 49.4, 49.0, 47.8, 47.7, 47.5, 47.3, 43.8, 27.3, 25.1, 24.9, 24.0, 23.8, 22.1, 21.5, 21.5, rotamers; HRMS (ESI) m/z calcd for $C_{22}H_{22}N_2OF_3$ $[M + H]^+$ 387.1679, found 387.1699.

N-Acetyl-N-3-(4-fluorophenyl)prop-2-enyl-1-tryptamine (**SI10**). Following general procedure VIII, the reaction of *N*-acetyl-*N*-3-bromoprop-2-enyl-1-tryptamine (93 mg, 0.29 mmol), 4-fluorophenylboronic acid (45 mg, 0.32 mmol), $Pd_2(dba)_3$ (13.3 mg, 0.015 mmol), P(*t*-Bu)$_3$ (1.0 M in THF, 40 μL), and KF (60 mg, 1.03 mmol) gave, after flash column chromatography (Et_3N/MeOH/CH_2Cl_2, 1:1:98), the title compound as a brown oil (78 mg, 80%): R_f = 0.53 (MeOH/CH_2Cl_2 (1:9); PMA, UV); HPLC purity 89% (t_R = 8.09 min); IR (neat) cm^{-1} 3270, 2925, 1615, 1454, 1224, 738; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.71−8.44 (m, 1H), 7.70−7.53 (m, 0.7H), 7.48 (d, *J* = 7.9 Hz, 0.2H), 7.41−7.32 (m, 1.2H), 7.32−6.92 (m, 6H), 6.87 (d, *J* = 2.2 Hz, 0.2H), 6.57 (dd, *J* = 11.3, 9.5 Hz, 0.3H), 6.44−6.28 (m, 0.6H), 6.21 (q, *J* = 13.5, 6.5 Hz, 0.2H), 6.11 (t, *J* = 6.4 Hz, 0.1H), 6.04 (dt, *J* = 7.2, 6.3 Hz, 0.2H), 5.93 (dt, *J* = 15.8, 5.4 Hz, 0.2H), 5.70−5.52 (m, 0.3H), 4.33 (dd, *J* = 6.4, 1.8 Hz, 0.3H), 4.25 (dd, *J* = 6.5, 1.3 Hz, 0.4H), 4.14 (t, *J* = 7.1 Hz, 0.5H), 4.04 (dd, *J* = 6.2, 1.9 Hz,0.3H), 3.98 (dd, *J* = 6.1, 1.8 Hz, 0.3H), 3.90 (dd, J = 5.4, 1.5 Hz, 0.4H), 3.76−3.52 (m, 1.8H), 3.51−3.43 (m, 0.4H), 3.12−2.93 (m, 2H), 2.87 (t, *J* = 8.1 Hz, 0.5H), 2.15 (s, 0.5H), 2.13 (s, 0.4H), 2.05 (s, 0.3H), 2.03−1.97 (m, 1.5H), 1.92 (s, 0.5H), rotamers; ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 170.9, 170.8, 170.7, 170.6, 136.4, 131.5, 131.1, 130.9, 130.6 (d, J_{C-F} = 1.6 Hz), 130.6, 130.5, 130.5, 130.4 (d, J_{C-F} = 8.0 Hz), 128.8,

dx.doi.org/10.1021/jo402192s | J. Org. Chem. 2013, 78, 12545−12565

128.0, 128.0, 127.9 (d, J_{C-F} = 1.2 Hz), 127.5, 127.4, 127.1 (d, J_{C-F} = 2.6 Hz), 127.0, 124.8 (d, J_{C-F} = 2.2 Hz), 124.1 (d, J_{C-F} = 2.1 Hz), 122.5 (d, J_{C-F} = 5.0 Hz), 122.4, 122.3, 122.2, 122.2, 122.0, 121.9, 119.5, 119.5, 119.5 (d, J_{C-F} = 3.9 Hz), 119.3, 119.3, 118.8, 118.8, 118.6, 118.3, 118.3, 118.1, 115.8, 115.7, 115.6, 115.5, 115.3 (d, J_{C-F} = 14.2 Hz), 115.2, 113.1, 112.9, 112.9, 111.9, 111.8, 111.8, 111.6 (d, J_{C-F} = 7.7 Hz, 111.5, 111.3 (d, J_{C-F} = 3.7 Hz), 111.3, 110.4, 110.4, 54.5, 51.4, 49.7, 49.2, 49.0, 48.7, 47.6, 47.5, 47.2, 44.9, 43.4, 29.1, 27.2, 24.9, 24.8, 24.7, 23.8, 23.7, 22.0, 21.9, 21.4, 21.4, 21.3, 14.3, rotamers; HRMS (ESI) m/z calcd for $C_{21}H_{22}FN_2O$ $[M + H]^+$ 337.1716, found 337.1712.

*N-Acetyl-N-3-(6-methoxynaphthalen-2-yl)prop-2-enyl-1-tryptamine (**SI11**).* Following general procedure VIII, the reaction of *N*-acetyl-*N*-3-bromoprop-2-enyl-1-tryptamine (72 mg, 0.22 mmol), 4-(trifluoromethyl)phenylboronic acid (56 mg, 0.28 mmol), $Pd_2(dba)_3$ (11.2 mg, 0.011 mmol), P(*t*-Bu)$_3$ (1.0 M in THF, 30 μL), and KF (54 mg, 0.93 mmol) gave, after flash column chromatography (Et_3N/MeOH/CH_2Cl_2, 1:1:98), the title compound as an orange solid (84 mg, 95%): mp 94−96 °C; R_f = 0.53 (MeOH/CH_2Cl_2 (1:9); PMA, UV); HPLC purity >95% (t_R = 8.71 min). IR (neat) cm^{-1} 3185, 2925, 1610, 1482, 1257, 732; ^1H NMR (300 MHz, $CDCl_3$) δ 8.82−8.37 (m, 1H), 7.76−7.63 (m, 2.3H), 7.63−7.49 (m, 1.3H), 7.49−7.43 (m, 0.8H), 7.40−7.05 (m, 6H), 7.04−6.85 (m, 1.4H), 6.80−6.68 (m, 0.9H), 6.61−6.44 (m, 0.5H), 6.32−6.20 (m, 0.2H), 6.13−6.03 (m, 0.2H), 5.77−5.56 (m, 0.6H), 4.48 (dd, J = 6.4, 1.7 Hz, 0.6H), 4.21 (d, J = 6.3 Hz, 0.4H), 4.18−4.12 (m, 0.6H), 3.94 (s, 0.9H), 3.93 (s, 1H), 3.90 (d, J = 1.0 Hz, 1H), 3.74 (t, J = 6.9 Hz, 0.5H), 3.69−3.58 (m, 1.1H), 3.49−3.42 (m, 0.7H), 3.13−3.01 (m, 0.9H), 2.97 (t, J = 8.1 Hz, 0.6H), 2.83 (t, J = 8.1 Hz, 0.6H), 2.17 (s, 0.6H), 2.02 (s, 0.7H), 2.00 (s, 0.6H) 1.98 (s, 0.8H), rotamers; ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 170.8, 170.6, 158.1, 157.9, 157.9, 157.8, 136.5, 136.4, 136.3, 136.3, 134.3, 134.2, 133.7, 133.6, 132.9, 132.1, 132.1, 131.9, 131.9, 131.6, 131.4, 129.7, 129.6, 129.6, 129.0, 128.9, 128.8, 128.6, 128.6, 127.7, 127.6, 127.5, 127.3, 127.2, 127.1, 127.1, 127.0, 126.9, 126.8, 126.4, 126.2, 124.4, 124.2, 124.0, 123.6, 122.5, 122.4, 122.3, 122.1, 122.0, 121.9, 121.8, 119.5, 119.4, 119.3, 119.2, 119.1, 118.8, 118.7, 118.3, 118.1, 113.1, 113.0, 111.9, 111.8, 111.7, 111.5, 111.4, 111.3, 105.9, 105.7, 55.4, 55.4, 55.4, 51.6, 49.2, 48.7, 47.8, 47.7, 47.2, 43.4, 31.6, 31.5, 29.1, 29.0, 27.2, 24.8, 24.6, 23.8, 23.6, 21.9, 21.4, 21.4, rotamers; HRMS (ESI) m/z calcd for $C_{26}H_{27}N_2O_2$ $[M + H]^+$ 399.2067, found 399.2094.

*N-Acetyl-N-3-(furan-2-yl)prop-2-enyl-1-tryptamine (**SI12**).* Following general procedure VIII, the reaction of *N*-acetyl-*N*-3-bromoprop-2-enyl-1-tryptamine (72 mg, 0.23 mmol), 2-furylboronic acid (40 mg, 0.35 mmol), $Pd_2(dba)_3$ (11.5 mg, 0.015 mmol), P(*t*-Bu)$_3$ (1.0 M in THF, 40 μL), and KF (44 mg, 0.76 mmol) gave, after flash column chromatography (Et_3N/MeOH/CH_2Cl_2, 1:1:98), the title compound as a brown oil (57 mg, 82%): R_f = 0.32 (MeOH/CH_2Cl_2 (1:9); PMA, UV); HPLC purity 89% (t_R = 7.53 min,); IR (neat) cm^{-1} 3255, 2924, 1616, 1419, 735; ^1H NMR (300 MHz, $CDCl_3$) δ 8.68−8.42 (m, 1H), 7.69−7.53 (m, 1H), 7.46 (d, J = 7.9 Hz, 0.3H), 7.41−7.32 (m, 1.7H), 7.23−6.97 (m, 3H), 6.97 (d, J = 2.3 Hz, 0.3H), 6.94 (d, J = 2.3 Hz, 0.2H), 6.41 (dd, J = 3.3, 1.8 Hz, 0.3H), 6.36 (dt, J = 3.4, 1.7 Hz, 0.4H), 6.34−6.31 (m, 0.2H), 6.31−6.06 (m, 2H), 6.03 (dd, J = 6.6, 3.7 Hz, 0.2H), 5.97 (t, J = 5.1 Hz, 0.1H), 5.52 (dt, J = 11.8, 6.7 Hz, 0.2H), 5.44−5.36 (m, 0.2H), 4.58 (dd, J = 6.8, 1.7 Hz, 0.4H), 4.35 (dd, J = 6.2, 2.0 Hz, 0.4H), 4.24 (dd, J = 6.5, 1.3 Hz, 0.2H), 4.14 (d, J = 6.0 Hz, 0.6H), 3.98 (dd, J = 6.0, 1.8 Hz, 0.1H), 3.88 (dd, J = 5.1, 1.5 Hz, 0.6H), 3.74−3.63 (m, 1.2H), 3.62−3.52 (m, 1.3H), 3.04 (dd, J = 15.0, 7.4 Hz, 2.5H), 2.14−2.10 (m, 1.5H), 1.97 (s, 1.4H), 1.92 (s, 0.3H), rotamers; ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 170.8, 170.7, 152.7, 152.3, 152.3, 151.9, 142.6, 142.3, 142.2, 142.1, 136.5, 136.4, 131.1, 127.6, 127.1, 126.3, 125.6, 123.9, 123.0, 122.6, 122.5, 122.5, 122.2, 122.1, 122.0, 121.9, 121.0, 119.9, 119.6, 119.5, 119.3, 119.3, 119.1, 119.0, 118.8, 118.3, 113.2, 113.2, 112.1, 112.0, 111.6, 111.6, 111.5, 111.4, 111.3, 111.0, 110.6, 110.4, 108.4, 107.9, 51.1, 49.8, 49.7, 49.5, 49.1, 48.8, 48.4, 47.4, 47.3, 47.2, 44.9, 44.3, 39.6, 38.9, 29.2, 27.2, 24.8, 24.8, 24.8, 23.8, 23.7, 22.1, 21.9, 21.4, 21.3, rotamers; HRMS (ESI) m/z calcd for $C_{19}H_{21}N_2O_2$ $[M + H]^+$ 309.1603, found 309.1599.

*N-Acetyl-N-5-phenylpenta-2,4-dienyl-1-tryptamine (**SI13**).* Following general procedure VIII, the reaction of *N*-acetyl-*N*-3-bromoprop-2-enyl-1-tryptamine (86 mg, 0.27 mmol), *trans*-2-phenylvinylboronic acid (49 mg, 0.33 mmol), $Pd_2(dba)_3$ (11.0 mg, 0.012 mmol), P(*t*-Bu)$_3$ (1.0 M in THF, 40 μL), and KF (58 mg, 0.99 mmol) gave, after flash column the title compound as a brown oil: R_f = 0.44 (MeOH/CH_2Cl_2 (1:9); PMA, UV); HPLC purity 91% (t_R = 8.53, 8.59 min); IR (neat) cm^{-1} 3255, 3025, 2925, 1615, 1419, 988, 729; ^1H NMR (300 MHz, $CDCl_3$) δ 8.44−8.24 (m, 1H), 7.66 (dd, J = 7.8, 4.3 Hz, 0.5H), 7.58 (dd, J = 7.6, 4.9 Hz, 0.6H), 7.44−7.28 (m, 5H), 7.25−6.97 (m, 4H), 6.88−6.70 (m, 0.7H), 6.70−6.58 (m, 0.6H), 6.54 (d, J = 5.7 Hz, 0.3H), 6.49 (d, J = 5.7 Hz, 0.2H), 6.40−6.15 (m, 1H), 5.85−5.74 (m, 0.3H), 5.65 (dt, J = 15.1, 5.4 Hz, 0.3H), 5.54 (dt, J = 10.9, 7.4 Hz, 0.3H), 5.44−5.34 (m, 0.2H), 4.31 (d, J = 6.3 Hz, 0.5H), 4.13 (d, J = 6.5 Hz, 0.5H), 4.03 (dd, J = 6.9, 1.6 Hz, 0.4H), 3.86 (d, J = 4.5 Hz,0.5H), 3.69 (t, J = 6.9 Hz, 1H), 3.62−3.56 (m, 1H), 3.11−3.02 (m, 2H), 2.16 (s, 0.6H), 2.14 (s, 0.7H), 2.00 (s, 0.7H), 1.99 (s, 0.6H), rotamers; ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 170.7, 137.2, 137.1, 137.0, 136.8, 136.4, 135.2, 134.5, 133.2, 133.1, 132.5, 132.1, 131.9, 131.6, 129.2, 128.8, 128.8, 128.8, 128.7, 128.3, 128.2, 128.2, 128.0, 127.9, 127.7, 127.7, 127.6, 127.1, 126.7, 126.7, 126.5, 126.5, 123.2, 122.4, 122.3, 122.2, 122.2, 122.1, 119.7, 119,7, 119.5, 119.4, 118.9, 118.8, 118.4, 118.3, 113.4, 113.3, 112.1, 111.6, 111.6, 111.3, 54.5, 51.3, 48.9, 48.7, 47.3, 47.3, 47.0, 42.5, 24.9, 24.8, 23.8, 23.8, 22.1, 21.9, 21.5, rotamers; HRMS (ESI) m/z calcd for $C_{23}H_{25}N_2O$ $[M + H]^+$ 345.1967, found 345.1961.

*THBC **SI14**.* Following general procedure IX, the reaction of **SI4** (69.6 mg, 0.21 mmol), RuHCl(CO)(PPh_3)$_3$ (28.0 mg, 0.030 mmol), and $(PhO)_2PO_2H$ (15.4 mg, 0. 062 mmol) gave, after purification by flash column chromatography on silica gel (heptane/EtOAc 2:3), the title compound as an orange oil (20.8 mg, 30%): R_f = 0.47 (MeOH/CH_2Cl_2 (1:9); UV, PMA); HPLC purity 94% (t_R = 8.78 min); IR (neat) cm^{-1} 3404, 3274, 2926, 1616, 1449, 1167; ^1H NMR (300 MHz, $CDCl_3$) δ 7.74 (s, 1H), 7.45 (d, J = 8.1 Hz, 1H), 7.29 (d, J = 7.9 Hz, 1H), 7.23−7.08 (m, 4H), 7.07−6.99 (m, 4H), 5.84 (dd, J = 6.0, 1.8 Hz, 1H), 5.01−4.90 (m, 0.4H), 3.97 (d, J = 13.7 Hz, 1H), 3.61−3.47 (m, 1H), 2.82 (dd, J = 10.7, 5.8 Hz, 4H), 2.71 (dd, J = 18.6, 10.4 Hz, 1H), 2.33 (s, 3H), 2.28 (s, 3H), 2.26−2.10 (m, 4H), rotamers; ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1, 141.0, 138.4, 136.1, 133.4, 129.3, 129.2, 128.6, 127.1, 126.5, 125.4, 122.4, 120.2, 119.9, 118.2, 111.2, 107.5, 50.3, 41.6, 36.2, 32.6, 22.0, 21.5, 20.9, rotamers; HRMS (ESI) m/z calcd for $C_{22}H_{25}N_2O$ $[M + H]^+$ 333.1967, found 333.1964.

*THBC **SI15**.* Following general procedure IX, the reaction of **SI5** (78.1 mg, 0.21 mmol), RuHCl(CO)(PPh_3)$_3$ (20.4 mg, 0.022 mmol), and $(PhO)_2PO_2H$ (17.0 mg, 0. 068 mmol) gave, after purification by flash column chromatography on silica gel (heptane/EtOAc 2:3), the title compound as an orange oil (16.9 mg, 22%): R_f = 0.47 (MeOH/CH_2Cl_2 (1:9); UV, PMA); HPLC purity 82% (t_R = 8.71 min); IR (neat) cm^{-1} 3400, 2940, 1594, 1149; ^1H NMR (300 MHz, $CDCl_3$) δ7.80 (s, 1H), 7.46 (d, J = 7.3 Hz, 1H), 7.30 (d, J = 7.9 Hz, 1H), 7.23−7.07 (m, 2H), 6.43−6.30 (m, 3H), 5.84 (t, J = 6.8 Hz, 1H), 4.97 (m, 0.4H), 3.99 (d, J = 14.4 Hz, 1H), 3.78 (s, 6H), 3.61−3.46 (m, 1H), 2.87−2.60 (m, 5H), 2.29 (s, 3H), 2.24−2.09 (m, 3H), rotamers; ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1, 161.1, 143.6, 136.1, 133.3, 126.5, 122.4, 120.0, 118.2, 111.2, 107.6, 106.5, 106.4, 98.5, 55.5, 55.5, 50.0, 41.6, 35.8, 32.8, 22.0, 21.1, rotamers; HRMS (ESI) m/z calcd for $C_{23}H_{27}N_2O_3$ $[M + H]^+$ 379.2022, found 379.2017.

*THBC **SI16**.* Following general procedure IX, the reaction of **SI6** (90.0 mg, 0.25 mmol), RuHCl(CO)(PPh_3)$_3$ (34.4 mg, 0.037 mmol), and $(PhO)_2PO_2H$ (19.2 mg, 0. 077 mmol) gave, after purification by flash column chromatography on silica gel (heptane/EtOAc 2:3), the title compound as an orange oil (14.4 mg, 14%): R_f = 0.47 (MeOH/CH_2Cl_2 (1:9); UV, PMA); HPLC purity >95% (t_R = 8.24 min); IR (neat) cm^{-1} 3285, 2849, 1625, 1518, 1343, 700; ^{1} H NMR (300 MHz, $CDCl_3$): δ 8.24 (s, 0.5H), 8.18−8.13 (m, 0.5H), 8.04 (d, J = 8.6 Hz, 1.3H), 7.47 (d, J = 7.5 Hz, 1.3H), 7.39−7.24 (m, 4.3H), 7.15 (ddd, J = 15.0, 13.6, 6.1 Hz, 2H), 5.89−5.79 (m, 0.9H), 5.05−4.95 (m, 0.1H), 3.99 (t, J = 12.0 Hz, 0.8H), 3.51 (dd, J = 13.9, 10.4 Hz, 1.2H), 3.36−3.21 (m, 0.5H), 2.95−2.70 (m, 3.5H), 2.34−2.06 (m, 5H), rotamers; ^{13} C NMR (75 MHz, $CDCl_3$): δ 170.7, 149.3, 147.9, 146.5, 136.2,

dx.doi.org/10.1021/jo402192s | J. Org. Chem. 2013, 78, 12545−12565

133.5, 129.3, 123.8, 122.3, 119.9, 118.2, 111.3, 107.9, 49.2, 41.3, 35.6, 32.5, 22.1, 21.8. HRMS (ESI) m/z calcd for $C_{21}H_{22}N_3O_3$ $[M + H]^+$ 364.1661, found 364.1653.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and characterization of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: ten@kemi.dtu.dk.

Author Contributions

All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The Technical University of Denmark, Lundbeck Foundation, and the DSF Center for Antimicrobial Research (CAR) are gratefully acknowledged for financial support. We thank Mette Ishoey for valuable discussions and writing assistance.

■ REFERENCES

(1) For recent reviews on THBCs, see: (a) Cao, R.; Peng, W.; Wang, Z.; Xu, A. *Curr. Med. Chem.* **2007**, *14*, 479−500. (b) El-Sayed, M.; Verpoorte, R. *Phytochem. Rev.* **2007**, *6*, 277−305. (c) Chen, F.-E.; Huang, J. *Chem. Rev.* **2005**, *105*, 4671−4706. (d) Kam, T.-S.; Sim, K.-M. *Phytochemistry* **1998**, *47*, 145−147.

(2) For selected reviews on the Pictet−Spengler reaction, see: (a) Stöckigt, J.; Antonchick, A. P.; Wu, F.; Waldmann, H. *Angew. Chem., Int. Ed.* **2011**, *50*, 8538−8564. (b) Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797−1842. (c) Nielsen, T. E.; Diness, F.; Meldal, M. *Curr. Opin. Drug. Discov. Devel.* **2003**, *6*, 801−814.

(3) Pictet, A.; Spengler, T. *Ber. Dtsch. Chem. Ges.* **1911**, *44*, 2030−2036.

(4) (a) Ascic, E.; Jensen, J. F.; Nielsen, T. E. *Angew. Chem., Int. Ed.* **2011**, *50*, 5188−5191. (b) Ascic, E.; Hansen, C. L.; Le Quement, S. T.; Nielsen, T. E. *Chem. Commun.* **2012**, *48*, 3345−3347. (c) Cai, Q.; Liang, X.-W.; Wang, S.-G.; Zhang, J.-W.; Zhang, X.; You, S.-L. *Org. Lett.* **2012**, *14*, 5022−5025. (d) Cai, Q.; Liang, X.-W.; Wang, S.-G.; You, S.-L *Org. Biomol. Chem.* **2013**, *11*, 1602−1605.

(5) For selected reviews on metal-catalyzed isomerization of double bonds, see: (a) Krompiec, S.; Krompiec, M.; Penczek, R.; Ignasiak, H. *Coord. Chem. Rev.* **2008**, *252*, 1819−1841. (b) Alcaide, B.; Almendros, P.; Luna, A. *Chem. Rev.* **2009**, *49*, 3817−3858. (c) Donohoe, T. J.; O'Riorden, T. J. C.; Rosa, C. P. *Angew. Chem., Int. Ed.* **2009**, *48*, 1014−1017.

(6) For reviews on iminium ion cyclization, see: (a) Maryanoff, B. E.; Zhang, H.-C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431−1628. (b) Royer, J.; Bonin, M.; Micouin, L. *Chem, Rev.* **2004**, *104* (2311), 2352. (c) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, 3817−3856. (d) Le Quement, S. T.; Petersen, R.; Meldal, M.; Nielsen, T. E. *Biopolymers* **2010**, *94*, 242−256.

(7) Petersen, M. T.; Nielsen, T. E. *Org. Lett.* **2013**, *15*, 1986−1989.

(8) Sorimachi, K.; Terada, M. *J. Am. Chem. Soc.* **2008**, *130*, 14452−14453.

(9) For examples of urea/thiourea metal scavengers, see: (a) Zuo, G.; Muhammed, M. *React. Polym.* **1995**, *24*, 165−181. (b) Fleming, C. A.; Cromberge, G. *J. S. Afr. Inst. Min. Metall.* **1984**, *84*, 125−137.

(10) For selected reviews on 1,2,3,4-tetrahydroquinolines, see: Scott, J. D.; Williams, R. M. *Chem. Rev.* **2002**, *102*, 1669−1730. (b) Chrzanowska, M.; Rozwadowska, M. D. *Chem. Rev.* **2004**, *104*, 3341−3370.

(11) For selected reviews on the Suzuki cross-coupling, see: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483. (b) Casalnuovo, A. L.; Calabrese, J. C. *J. Am. Chem. Soc.* **1990**, *112*, 4324−4330. (c) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020−4028.

(12) For selected review on tandem catalysis, see: Wasilke, J.-C.; Obrey, S. J.; Baker, R. T.; Bazan, G. C. *Chem. Rev.* **2005**, *105*, 1001−1020.

(13) For examples of tandem processing involving Suzuki couplings, see: (a) Wang, W.-Y.; Sun, L.-L.; Deng, C.-L.; Tang, R.-Y.; Zhang, X.-G. *Synthesis* **2013**, *45*, 118−126. (b) Liu, T.-P.; Xing, C.-H.; Hu, Q.-S. *Angew. Chem., Int. Ed.* **2010**, *49*, 2909−2912. (c) Shu, W.; Jia, G.; Ma, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 2788−2791.

(14) See the Supporting Information for details.

(15) For examples of in situ formation of ruthenium hydride catalyst, see: (a) Kumobayashi, H.; Akutaqawa, S.; Otsuka, S. *J. Am. Chem. Soc.* **1978**, *12*, 3949−3959. (b) Bressy, C.; Memant, C.; Piva, O. *Synlett* **2005**, *16*, 577−582. (c) Nielsen, S. D.; Ruhland, T.; Resmussen, L. K. *Synlett* **2007**, *18*, 443−446.

(16) (a) Deng, L.; Czerwinski, K. M.; Cook, J. M. *Tetrahedron Lett.* **1991**, *32*, 175−178. (b) Czerwinski, K. M.; Deng, L.; Cook, J. M. *Tetrahedron Lett.* **1992**, *33*, 4721−4724. (c) Cox, E. D.; Hamaker, L. K.; Li, J.; Yu, P.; Czerwinski, K. M.; Deng, L.; Cook, J. M; Watson, H.; Krawiec, J. *Org. Chem.* **1997**, *62*, 44−61. (d) Ungemach, F.; DiPierro, M.; Weber, R.; Cook, J. M. *J. Org. Chem.* **1981**, *46*, 164−168. (e) Soerens, D.; Sandrin, J.; Ungemach, F.; Mokry, P.; Wu, G. S.; Yamanaka, E.; Hutchins, L.; DiPierro, M.; Cook, J. M. *J. Org. Chem.* **1979**, *44*, 535−545.

(17) Yamada, H.; Kawate, T.; Matsumizu, M.; Nishida, A.; Yamaguchi, K.; Nakagawa, M. *J. Org. Chem.* **1998**, *63*, 6348−6353.

(18) Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 10558−10559.

(19) Seayad, J.; Seayad, A. M.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 1086−1087.

(20) For selected reviews on the combination of chiral phosphoric acids and metal catalysts, see: (a) Shao, Z.; Zhang, H. *Chem. Soc. Rev.* **2009**, *38*, 2745−2755. (b) Rueping, M.; Koenigs, R. M.; Atodiresei, I. *Chem.—Eur. J.* **2010**, *16*, 9350−9365. (c) Zhong, C.; Shi, X. *Eur. J. Org. Chem.* **2010**, 2999−3025.

(21) While this manuscript was in preparation, a related report focusing on the isomerization of protected allylic amines in an enantioselective Pictet−Spengler-type reaction catalyzed by a ruthenium catalyst and a Brønsted acid was published; see: Toda, Y.; Terada, M. *Synlett* **2013**, *24*, 752−756.

(22) Nakagawa, M.; Kiuchi, M.; Obi, M.; Tonozuka, M.; Kobayashi, K.; Hino, T.; Ban, Y. *Chem. Pharm. Bull.* **1975**, *23*, 304−312.

(23) Airiau, E.; Girard, N.; Mann, A.; Salvadori, J.; Taddei, M. *Org. Lett.* **2009**, *11*, 5314−5317.

(24) Lygin, A. V.; Meijere, A. D. *Eur. J. Org. Chem.* **2009**, *30*, 5138−5141.

(25) Righi, M.; Topi, F.; Bartolucci, S.; Deldini, A.; Piersanti, G.; Spadoni, G. *J. Org. Chem.* **2012**, *77*, 6351−6357.

(26) Duboyk, I.; Watson, I. D. G.; Yudin, A. K. *J. Am. Chem. Soc.* **2007**, *129*, 14172−14173.

(27) Martin, D. B. C.; Vanderwal, C. D. *J. Am. Chem. Soc.* **2009**, *131*, 3472−3473.

(28) Li, J.; Wang, T.; Yu, P.; Peterson, A.; Weber, R.; Soerens, D.; Grubisha, D.; Bennett, D.; Cook, J. M. *J. Am. Chem. Soc.* **1999**, *121*, 2998−7010.